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CDRI
LUCKNOW

Central Drug Research Institute

Chattar Manzil Palace, M.G. Marg, Lucknow-226001

www.cdriindia.org

With compliments from:

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Director
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Lucknow

Annual Report
2007-2008

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THE CHARTER

- **Development of new drugs and diagnostics**
- **Cellular and molecular studies to understand disease processes and reproductive physiology**
- **Development of contraceptive agents and devices**
- **Systematic evaluation of medicinal properties of natural products**
- **Development of technology for drugs, intermediates and biologicals**
- **Dissemination of information in the field of drug research, development and production**
- **Consultancy and development of technical manpower**

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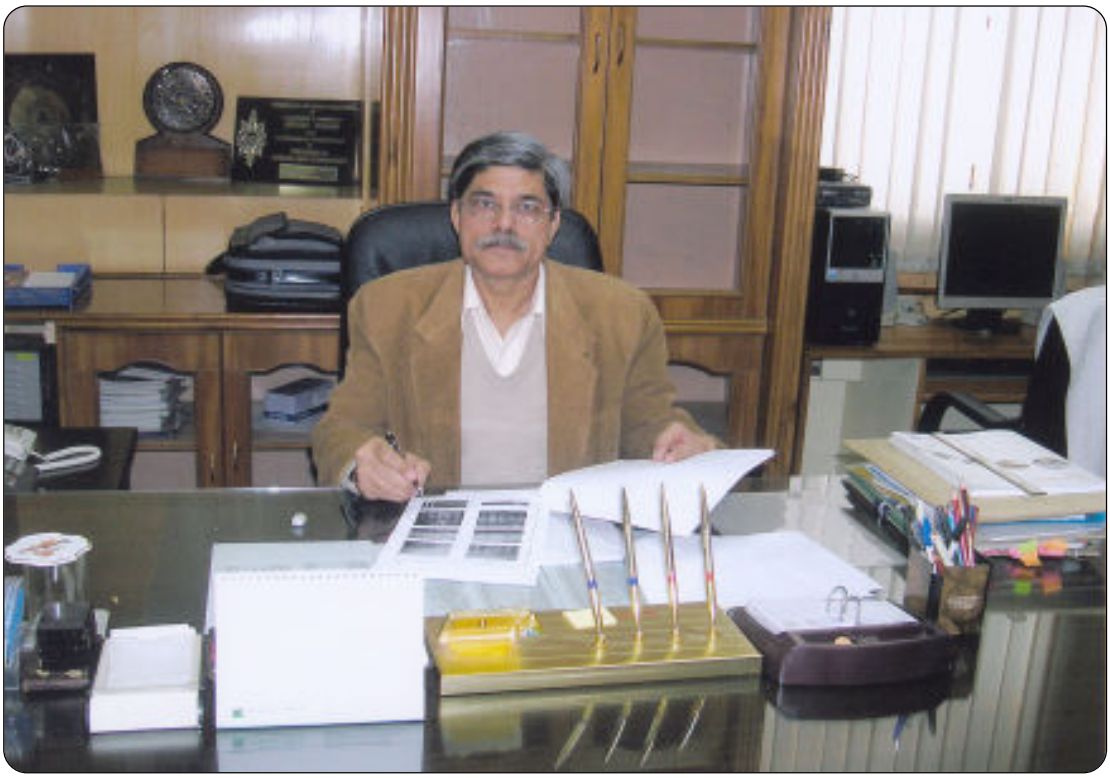
From the Director's Desk



Through the last five decades, CDRI has built a unique model for drug research in India - having everything under one roof, from synthesis, screening, development studies, process up-scaling to clinical studies. This model has stood the test of time on its own merits and strengths built through sustained efforts of our scientists and staff, thus setting great traditions in science, institutional culture and work ethics. With an increasing number of academic and research institutions and pharma companies making forays in drug research in the country and the paradigm shift in drug R&D approaches, the scenario has brought new challenges in recent years. The capabilities and strengths have to now match global regulatory standards and cut down the cost and time of drug discovery and development. These challenges can be faced only through the synergy of creative thinking, joint programs, collaborations and linkages within and with outside institutions and pharma industry.

The first recourse to enhance our competitiveness and global impact is through strengthening of S&T infrastructure and facilities, introduction of innovative and trained youngsters, quality systems and adoption of high standards in science and efficiency at all levels. Laying down of the foundation stone of the institute's New Campus at Sitapur Road in Lucknow by the Honourable Minister of Science & Technology and Earth Sciences, Mr. Kapil Sibal, was an important step in carving the future of CDRI. This has speeded up the process of campus development so that our scientists could occupy their benches with state-of-the-art facilities and fulfill the requirements of quality systems and best practices at the earliest. Thus, this year laid foundations of "future CDRI on global platform". Dr. C. M. Gupta made some of the

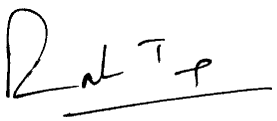
richest contributions to CDRI and superannuated on August 31st, 2007, after steering the institute as Director for ten years.

The institute's research focus has been in disease areas relevant to national needs. Resurgence of infectious diseases like malaria and tuberculosis with new dimensions of complexities like drug resistance and compromised immunity are new challenges that CDRI will address during the XI Five Year Plan in the *'New drug development program on parasitic diseases'* as a supra-institutional flagship program. The institute's greater stress on tropical infections will accelerate progress towards developing more affordable drugs for poorer economies. Combating parasitic infections has been a strength of this institute, as is evident from the presence of two drugs in market (**E-Mal** and **Aablaquin**) and a process technology for a generic drug (**Artemether**) in commercial production. Two new anti-malarial products (**99/411** & **97/78**) made further advances through this year. For tuberculosis, a test Kit for early diagnosis of infection is expected to be marketed shortly. A collaboration was initiated with Drugs for Neglected Diseases Initiative (DNDi) of WHO for development of new chemotherapeutic agents for Trypanosomiasis in larger global interest. CDRI was invited to join another international program for drug development against malaria and leishmania under the UNICEF/UNDP/World Bank/WHO programme for Research & Training in Tropical Diseases.

The year witnessed operationalization of in-house anticancer screening facility using cell lines from ATCC covering activity against cancer of pancreas, ovary, prostate, colon, breast, lung and cervical cancers. The institute's regulatory studies set-up (pharmacology, toxicology, pharmacokinetics, quality control & standardization and toxicology) is a major strength and a valuable resource for the nation. This was strengthened further by commissioning of two BSL-3 facilities for tuberculosis research and by nearly completing the preparations for the establishment of GLP laboratories in several divisions in the institute. During the year, the institute carried out regulatory toxicology for not only in-house candidate drugs but also several outside bioactives received under the CSIR network project and from industry. I invite academia, industry and foreign clients to avail these facilities and the immense knowledgebase available at CDRI through collaborations.

Institute's newly acquired capability in structural biology is reflected by a significant milestone achieved through structure elucidation of the potential target protein, peptidyl-tRNA hydrolase from *M. tuberculosis* H37RV in solution by NMR spectroscopy. The institute's basket of products in pipeline comprises an assortment of products in different stages of development. Some of the recently developed candidate drugs are **CDR-134D123** (antihyperglycemic), **CDR 99/373** (antiresorptive), **CDR-123F194** (antihyperglycemic), **puffer fish oil** (antihyperlipidemic) and **NP1** (osteogenic). Most of these products have already captured the attention of pharma companies.

A recent report by the Third World Academy of Sciences on CDRI, under their series *'Excellence in Science: Profiles of Research Institutions in Developing Countries'* published during the year, is a tribute to this institute. I look forward to many more accolades in the coming years.



(Rakesh Tuli)

SIGNIFICANT ACHIEVEMENTS

Significant Achievements

The year witnessed all round progress of CDRI. The R&D programs, contract research, partnership with industry and S&T services made impressive advances. Dr. C.M. Gupta laid down the office as Director CDRI. Some other senior scientists who retired this year on superannuation were: Dr. Vinod Bihari, Dr. K.P. Madhusudanan, Dr. Chandan Singh, Dr. S.C. Agarwal, Dr. Satyawan Singh, etc. Dr. Rakesh Tuli, Director, National Botanical Research Institute, Lucknow took over the additional charge as Director of the Institute on September 1, 2007. The Institute continued its competitive efforts in promoting the available leads on candidate drug molecules, standardized fractions, identification of new hits, development of new screens, molecular basis of disease progression and drug action, regulatory studies and new partnerships with industry. Earlier, on August 4, 2007, Honorable Union Minister of Science & Technology, Mr. Kapil Sibal laid the foundation stone of New Campus at Sitapur Road. The construction work has made good progress as the staff of CDRI look forward to move their laboratories into a world-class facility for drug research. A brief summary of the salient features of the work done during the year is presented below:

1. Business Development and Contract Research

Collaborations continued with national and international research organizations and academic institutions. A research agreement was signed with DNDi, Geneva for development of new chemotherapeutic agents for Human African Trypanosomiasis. Yet another agreement, in the area of Leishmaniasis, is under discussions. IPCA Laboratories, Mumbai, a leader in antimalarial drugs in India, entered into a collaborative agreement with the Institute for further development of compound 99/411, a promising synthetic substitute, developed at CDRI, as a preferable substitute to Artemisnin. Toxicity studies on another antimalarial candidate compound 97/78 were carried out under a sponsored project with IPCA and the compound was found to be safe. Its Phase I clinical trials will be initiated soon at PGIMER, Chandigarh. An extended collaborative agreement with Duphar Interferan Limited, Mumbai was executed to further extend Phase III clinical trials at different centers in respect of PICROLIV, a hepatoprotective agent. The institute received permission from Institutional Animal Ethics Committee and Committee on the Prevention, Control and Supervision on Experimental Animals for conducting 28 days toxicity studies, in respect of Herbal Medicament (for treatment of cerebral stroke) in Rhesus Monkey, in collaboration with Themis Medicare, Mumbai. Ranbaxy Labs sought consultation for creating a facility for polypeptide synthesis at their R&D center at Gurgaon. A material transfer agreement for providing pET28b CFP-10 expression vector was executed with Indian Immunological Limited, Hyderabad for the development of diagnostic kits for tuberculosis in animals.

A novel formulation of compound 80/574 (a hypolipidaemic) with atorvastatin, which exhibited

better synergistic lipid lowering activity, continued to be of interest to Cadila Pharma. Discussions with several large pharma companies are near finalization for collaborative development of a synthetic molecule 99/373 (anti-resorptive), CDR-134D123 (antidiabetic and antidyslipedmic), Centchroman (non-steroidal female contraceptive) and *Bacopa monniera* extract (memory enhancer). Phase I clinical trials were permitted for the compound 99/373. CDR-134D123 is to be taken up for multiple dose phase I studies. The other two products - Centchroman and *Bacopa monniera* extract are already in the market.

2. Progress in R&D Activities

2.1 Clinical Trials & Pharmacokinetic Studies

The clinical studies continued on 9 candidate products, which are in different phases of drug development. Drugs Controller of India (DCGI) cleared CONSAP, a contraceptive cream of herbal origin, for human use. This product is expected to be extremely beneficial in our family planning endeavor as it has good contraceptive efficacy, product acceptability by women and is devoid of any undesirable side effects. Multicentric clinical trials for efficacy of Arteether (blood schizonticidal) in 235 children suffering from *P. falciparum* malaria concluded at 5 centers and the dossier is under submission to DCGI. Safety evaluations in G6-PD deficient cases in respect of the compound 80/83 (anti-relapse antimalarial) were conducted in Thailand. It was observed that its safety profile was better than primaquine. Phase III clinical trials continued on Picroliv (hepatoprotective) and 80/574 (hypolipidemic) and the data analysis is in progress.

Pharmacokinetic and metabolic studies were undertaken on 7 candidate products. Bio-analytical method development and pilot PK studies were undertaken on 4 anti-thrombotic compounds.

2.2 Pre-clinical Safety Evaluation and Regulatory Toxicology

Regulatory Toxicity studies have been carried out on the Institute's as well as on outside products. Institute's candidate drugs, CDR 267F018, 97/78, 99/373 and CDR 134/F194 were evaluated for their preclinical safety profiles. Amongst the products from outside agencies, evaluated for safety, were AP76P, AP 20am 14, AP20am 15, AP20 am 16, Kajjali Yoga, Ras Sindoor, Vasant Kusumakar and ICB014P04A002. In addition to this, several basic research studies were also conducted, which included testing teratogenecity potential of Cyclophosphamide and Mitomycin-C at the platform of Metabonomics using NMR. This was planned with an idea to develop a testing system which should not be time and cost intensive and also requires lesser number of animals (rats/mice). A pilot study was also conducted to test renal toxicity using biofluids (urine) on the same platform. Furthermore, Single nucleotide polymorphism (SNP) diseases and standardization of initial parameters for neurotoxicity study were also accomplished. Also the setting up of a laboratory for immunotoxicity studies of compounds has also been completed and standardization of various parameters and studies in this regard is under progress.

2.3 Biological Screening

A new in-house facility for screening of *in vitro* anticancer activity was established. The facility became operational and the assays are being performed for pancreas, ovary, prostrate, colon, breast, lung and cervical cancers. A large number of marine extracts were screened using this facility and the active ones are being followed up. The DST-Dabur project on anticancer drug development has been concluded. Leads, thus generated, were exploited and modified by synthesizing several chemical compounds.

High throughput screening for anti-trypanosoma activity was undertaken under a DNDi

sponsored project. Over 7500 molecules were screened using pentamidine as standard drug and the active ones are being perused further. The HTS facility was used for screening of over 2400 new samples for anti-TB activity. Based upon the screening results and follow-up studies, 4 molecules exhibited variable degree of clearance of infection.

2.4 Cardiovascular, Central Nervous System & other Disorders

Synthesis and screening of new synthetic molecules and natural products as anti-hypertensive, anti-stroke and anti-thrombotic agents continued during the year. One compound had significant anti-stroke activity and is being followed up. Anti-stroke potential of some genomic extracts was studied wherein Gugulipid and Withanolide A were found to have significant activity and could serve as important anti-stroke agents. An animal model for myocardial infarction by the ligation of left anterior descending coronary artery was standardized in rats. As hypertension is a major risk factor for acute stroke, the neuroprotective role of AT1 receptor blocker Candesartan was assessed in focal cerebral ischemia model in rats and the study suggests that Candesartan may impart neuroprotection by reducing oxidative stress.

In the studies related to CNS, the effect of antidementia drugs, tacrine and donepezil, on biochemical markers of oxidative stress in brain was studied in STZ induced experimental model of dementia in mice. The results indicated that both the compounds suppress oxidative stress. Exposing rat glioma cell lines with lipopolysaccharide and estimating release of various inflammatory mediators established an *in vitro* model for neuroinflammation. Biological screening of synthetic compounds and natural products for Anti-dementia, anti-anxiety, anti-depression and appetite suppression activities continued and those found active are being perused further for optimization of activity. During the year, 7 compounds showed promising anti-inflammatory activity while significant anti-ulcer activity was observed in one extract under CSIR coordinated project. Two synthetic compounds exhibited significant anti-hyperglycemic activity in mice model and are being followed up. Antidyslipidemic effect of the compound 80/574 combined with atorvastatin was monitored in high fat diet fed hamsters and was found to be more effective than the effect of individual effective doses.

2.5 Filariasis

Compound S-005-116 was moderately active in both *B. malayi/M. coucha* and jird models. An albendazole formulation ALB-1+DEC produced prolonged mf suppression (68-95%) till day 90 of treatment. However, ALB-1+ IVM produced better sterilization of female *B. malayi*. The two fractions (F004 and F005) and a pure compound K009 of CDRI plant 4613 were adulticidal *in vitro* at 15.6 and 7.8 mg/ml *in vitro*. CDR-332A001 and AU2-357A001 at 250 mg/kg x 5 days, p.o. and Crude and fraction/sub-fractions of CSM-0012P04 and RJM-0069P03 revealed adulticidal activity on *B. malayi* in rodents. Fraction F004 of CDR-332 was highly active *in vitro*. Doxycycline at 25 mg/kg, i.p. killed all peritoneal micro- and macro-filariae within 15-30 days causing absolute female sterility. The recombinant *B. malayi* myosin (BmAF-Myo) offered significant protection against L3 challenge and was found to be immunologically Th1 inducer. *In vitro* culture of L3, adult male, female or Mf with mouse splenocytes revealed that adult worms and mf cause cellular hyporesponsiveness, adult and L3 principally induce pro-inflammatory responses while mf elicited mixed Th1/Th2. *B. malayi* B14 fraction eliminated >65% of adult parasites from the peritoneal cavity of host via NO production. Molecular cloning *of B. malayi* hexokinase (1.7 Kb), its over-expression and enzyme kinetics revealed BmHk to be a tetramer with a subunit molecular mass of 72 kDa and C.D. analysis done. Antibody raised in rabbit to pure hexokinase reacted with BmHk in ELISA/blot. Molecular cloning and

overexpression of *B. malayi* L3 DEAD box RNA Helicase was done, it reacted with IgG of all the categories of bancroftian subjects in blots and ATP utilization assay showed that dsRNA was the preferential substrate for the enzyme RNA Helicase. Immunoscreening of *B. malayi* lgt11 cDNA expression library with rabbit antibodies raised against circulating filarial antigen led to isolation of four cDNA clones and insert from one of these (Bm-6) was sub cloned in pGEM-T, sequenced, showed homology to *B. pahangi* and *Loa loa* antigens.

2.6 Leishmaniasis

Over 1200 synthetic compounds and marine extracts were screened against *L. donovani* infection and a sizeable number were found to be active *in vitro*. Based upon the leads from the results of *in vitro* screening, 10 synthetic compounds were evaluated *in vivo* against *L. donovani* in hamsters and one compound exhibited 92% inhibition in parasite multiplication and was selected for further optimization. Three materials - one from plant 4666K004 and two synthetic compounds (antifolate DHFR analogues: S-004-931 & S-007-1058) have shown more than 80% inhibition in parasite multiplication when tested *in vivo*.

Enhanced and stable expression of GFP in *L. donovani* clinical isolates was achieved by integrating GFP gene into the parasite genome at downstream of the 18s rRNA promoter region. These parasites expressed high levels of GFP in the absence of G418 drug pressure for more than 12 months.

The immunomodulatory F2 fraction (68-97.4 kDa) and its four sub-fractions of soluble *L. donovani* proteins, which have shown significant prophylactic efficacy, were characterized by 1-DE, 2DE and MALDI-TOF which revealed that out of total 18 proteins that have been identified major immunostimulatory proteins were Elongation factor-2, p45, Heat shock protein (HSP)-70, HSP-83, aldolase, enolase, triosephasphate isomerase, disulfideisomerase and calreticulin.

Leishmania actin has been over-expressed in insect cell system by generating recombinant baulovirus and is being characterized biochemically. In order to explore function of actin network in Leishmania, gene knockout experiments of various actin binding proteins viz. coronin, cofilin and myosin have been performed. Knocking out of coronin led to improper cytokinesis and coronin null cells do not survive. Gene knockout studies with leishmania ADF/cofilin homologue revealed essential roles in the flagellar motility function. The depletion of ADF/cofilin hampered flagellar growth and beating.

Squalene synthase was purified under denaturating conditions for the production of antibodies in rabbit and partial purification was done in soluble form using Q-sepharose column chromatography. Triose Phasphate Isomerase (TIM) cloned in pGEMT vector was further subcloned in pET 43.1a(+) to get protein in soluble form and was over expressed and purified by Ni-NTA affinity chromatography using 6 x His tag on vector. Antibodies were raised against purified Fusion tagged rLdTIM in rabbit for Immunological studies.

Based on biochemical studies, molecular modeling and docking strategy of Pteridine reductase 1 together with biological activity *in vitro* and *in vivo* led to identification of 2 out of 10 inhibitors of potential therapeutic value necessary assist the structure based development of novel antileishmanial drugs.

Conformational stability of recombinant Trypanothione reductase in presence of urea and guanidinium hydrochloride was studied. Biochemical characterization and molecular modeling of recombinant dipeptidyl carboxypeptidase was carried out.

2.7 Malaria

Drug combination studies employing identified endoperoxide compounds CDRI 97/78 and CDRI 99/411 in combination with antimalarial drugs have been successful in optimizing regimens providing total parasite clearance with two to four fold lower doses of the individual components in the rodent model. Biochemical characterization of transketolase, as a novel enzyme target for drug development, has been undertaken. *P. falciparum* transketolase gene was cloned, expressed and purified protein so obtained is being characterized. Studies on induction of oxidative stress in *P. falciparum* malaria have suggested that bilirubin, through the development of oxidative stress, induces *P. falciparum* cell death and that the malaria parasite lacks an HO system probably to protect itself from bilirubin-induced cell death as a second line of defense. Studies have been initiated on expression and characterization of *P. cynomolgi* CSP and MSP proteins with a view to explore their potential for immunoprophylaxis againt vivax malaria. Molecular studies with *P. falciparum* apicoplast have led to the characterization of *P. falciparum* gyrase subunits in terms of their structure and function and their targeting to the apicoplast was confirmed. Inhibition of PfGyrB activity by novobiocin was characterized *in vitro*. The apicoplast-encoded translation elongation factor EF-Tu was characterized for its nucleotide binding and GTPase activity. Additionally, the nucleotide exchange reaction mediated by the nuclear-encoded putative apicoplast EF-Ts was assayed. Additionally, interaction between apicoplast encoded SufB and imported SufC was observed *in vitro*. The role of human genetic factors in determining individual responses to *P. falciparum* malaria were studied in the context of SNPs in genes encoding cytokines and adhesion and immune regulatory molecules. The distribution of SNP frequencies across Indian populations and correlation of individual SNPs with cytokine levels and disease severity was established.

2.8 Microbial Infections

Upregulated genes of *M. tuberculosis* belonging to fatty acid metabolism, membrane transport, nitric oxide defence and PE_PGRS/PPE family were identified during residence in lungs of mice/*ex vivo* and in hypoxia condition using IVET approach, proteome and transcript analysis by microarray and subsequent validation by Real Time PCR. Genes for AHAS of *M. tuberculosis* cloned and over expressed *E. coli*. Few inhibitors of ICL of *M. tuberculosis* and synthetic compounds with antitubercular activity (MIC 0.79 µg/ml) were identified. Resuscitation of dormant mycobacteria by Rpf proteins from *Micrococcus luteus* and *M. tuberculosis* demonstrated *in vitro* and *in vivo* in mice using *M. fortuitum* as model. Interacting partners of Rpf, Eis (Rv2416c) and Erp (Rv3810) proteins identified on *M. tuberculosis* genome using bacterial and yeast two hybrid systems. Novel (calcium dependent) PKC isoforms phosphorylated during the invasive process of macrophages with pathogenic mycobacteria have been shown and 18 differentially expressed proteins of the *M. tuberculosis* at sub lethal concentrations of isoniazid and rifampicin identified. A recombinant *M. aurum* for screening of FAS-II pathway inhibitors constructed. 24 clones for *C. albicans* and 2 for *A. fumigatus from* fresh fusion experiments with GPI anchored protein of *C. albicans* as well as metabolic proteins of *A. fumigatus* identified. Proteome analysis of amphotericin B resistant *C. albicans* revealed three proteins which were over expressed.

2.9 Natural Products

Chemical and pharmacological investigations on Indian medicinal plants continued during the year. Significant anti-hyperglycemic activity was observed in ethanolic and purified extracts of several plants in streptozotocin induced diabetic rats. Isolation and characterization of chemical compounds from these materials is in progress. Regulatory pharmacology and toxicity studies related to CDR 134F194 (anti-hyperglycemic),

which is in pre clinical phase, have been completed. Several compounds were isolated from the chloroform and n-hexane fractions of the plant 1020 (anti-osteoporotic) and 5 of them exhibited promising osteogenic activity. Of these, 3 compounds were synthesized and activity was reconfirmed. Dose dependent analgesic and anti-inflammatory activities were observed in 2 pure compounds isolated from the plant 4406. Chemical transformation of natural products continued during the year with a view of lead optimization.

2.10 Newer Approaches in Drug Design and Discovery

During this period the crystal structures of the *M. tuberculosis* Feast/Famine regulatory protein and complexes with a variety of amino acid effectors have been solved. Secondly, Crystal structures of Lysine e-amino transferase (LAT) from *M.tuberculosis* and some mutants have been solved in a variety of enzyme states and complexes with substrates followed by identification of two novel inhibitors of the enzyme by virtual screening.

Structure-based investigations and development of computational predictive models for structure-activity relationship studies including molecular docking and CoMFA and CoMSIA 3D-QSAR studies were carried out on Pyrrolidine Carboxamide inhibitors as anti-mycobacterial agents and human mitotic kinesin Eg5 inhibitors as anti-cancer agents. The results provided clear guidelines and reasonably good activity predictions for novel inhibitor design.

We have achieved a significant milestone by solving structure of the potential drug target protein peptidyl-tRNA hydrolase from *M. tuberculosis* H37Rv (MtPth) in solution by NMR spectroscopy. Our results highlight the dynamic interaction of the protein with its substrate peptidyl-tRNA.

During this period, studies on two proteins namely *Plasmodium falciparum* glutathione S-transferase and *Toxoplasma gondii* Ferredoxin-$NADP^+$ Reductase (TgFNR) have been completed and the results demonstrate the significance of electrostatic interactions both in stabilization of native conformation and maintenance of structural cooperativity particularly in TgFNR.

During this period, 20 new compounds were synthesized and evaluated for PTP inhibition *in vitro*. Some of the compounds have shown significant inhibition (>70 % at 10 μM) of PTP-1β enzyme. Furthermore, 28 new compounds were synthesized as DPPIV inhibitors one of the compounds was found to be most potent with Ki, 1.0 μ mole. A mild and efficient protocol for the Pictet–Spengler reaction in water using an acid catalyst has been developed and a number of tetrahydro-ß-carboline compounds were synthesized in high yields and purity.

2.11 Reproductive Health Research

Designing, synthesis and bio-evaluation of new synthetic molecules / isolates from natural resources for development of male / female contraceptives continued this year also. Screening of these materials as anti-osteoporosis agents led to identification of one synthetic compound and two natural products and follow-up studies are in progress. In the follow up studies related to 99/373, its binding affinity studies with Raloxifene, Tamoxifene and Centchroman are in progress. Crude extract of NP-1, led to the isolation of 26 pure compounds of which 5 were active *in vitro*. A pharmaceutical composition 'OsteoAnabol' has been derived from an Indian medicinal plant for the management, prevention and treatment of bone disorders. Four pure compounds isolated from this plant exhibit differential modes of action in osteoblasts. The potent non-detergent spermicide S-003-296 caused total inhibition of conception at 200 μg dose when evaluated for contraceptive activity in rats. In our endeavor to design more effective, safer and cost effective molecules for Benign Prostatic Hyperplasia, 21 compounds were screened and 9 compounds exhibited promising activity in rat model.

2.12 Technology Development

2.12.1 Chemical Technology

Pilot-scale preparation of CDRI candidate drugs was undertaken. Two antimalarial compounds 97/78 and 99/411 were synthesized and submitted to Pharmaceutics Division for quality control studies. Several antidiabetic fractions of CDR-134 were prepared in large scale and supplied for further studies. Herbal Medicament, for treatment of cerebral stroke, was also prepared in additional amounts. An improved and cost effective process for Centchroman was developed at bench scale and an Indian patent has been filed.

2.12.2 Fermentation Technology

Studies related to Fermentation Technology continued during the year. A *Streptomyces* strain (M4) was isolated from soil samples and it exhibited good broad-spectrum antibacterial activity. Two antifungal compounds were isolated from the fermented broth and cell extracts of *Streptomyces triostinicus*. Structure elucidation of these compounds is in progress. A fungus, *Talaromyces wortmanni* MTCC 8802, was isolated from soil dwelling termite and it exhibited strong broad-spectrum antifungal and antitumor activities. Studies on stereochemistry of the compound wortmannin, isolated from this organism, are in progress. Studies related to generation of monoclonal antibodies against *C. albicans* and *A. fumigatus* are continuing. Fusion experiments for the development of hybridomas were carried out with GP1 anchored proteins of these fungi. Resulting hybridoma clones were screened with ELISA and western blotting and positive clones have been identified and subjected to single cell cloning. Characterization of resulting monoclonal antibodies is in progress.

2.12.3 Pharmaceutical Technology

Development of drug delivery systems being one of the major objects of the project, product development of inhalable microparticles containing two antitubercular drugs was carried out. Final formulation, intended for clinical trials, was standardized and its storage stability was demonstrated to be 2 years under ambient conditions. Development of non-ionic surfactant based formulations of cyclosporine continued and bioavailability experiments were conducted and were found to be 1.73 times better than the marketed product Neoral. Studies related to delivery system for septic shock, ultra thin polyelectrolyte microreservoir, etc. are progressing well. Quality control and stability studies on 2 natural products and 2 synthetic compounds were completed during the reporting period.

3. Publications & Patents

During the year the Institute published over 225 research papers in various national and international periodicals and contributed several papers and poster presentations in different seminars/symposia and conferences. The average impact factor increased considerably over the last few years. The success of Institute's innovative approaches is well reflected in filing of 16 foreign and 6 Indian patents and grant of 16 foreign and 8 Indian patents.

4. Technical Services Provided

Sophisticated Analytical Instrumentation Center (SAIF) and National Laboratory Animal Center continued to provide their services to the scientists, academic institutions, industrial houses, etc. SAIF analyzed over 9590 external and 23720 internal samples for various spectral analyses catering to the needs of around 1100 users. Over 800 grids of samples were analyzed for Transmission Electron Microscopy. The National Laboratory Animal Center supplied over 48000 animals for research and testing to different projects of the Institute and other organizations. Documentation & Library Services Division continued to publish current awareness bulletins viz. Drugs & Pharmaceuticals – Industry Highlights and Drugs & Pharmaceuticals

– R&D Highlights. Technical queries, received from clients, were promptly attended to. The Institute continued to provide *in vitro* and *in vivo* biological screening facilities to different organizations within the country.

5. Human Resource Development

The Institute gave top priority to provide training and exposure to its staff in the use of management approaches, tools and latest techniques. During the year, 27 staff members were deputed for various training programs held at Human Resource Development Center, Ghaziabad. Six employees were deputed to attend the Awareness Program on Right to Information Act held at NBRI, Lucknow and 2 scientists were trained at Administrative Staff College of India, Hyderabad and 1 scientist at National Institute for Research in Reproductive Health, Mumbai. During the year, 45 research fellows and a backlog of 23 students submitted their thesis and many of them were awarded Ph.D. The Institute continued to conduct the Advance Technology Training Program, for scientists and technical persons, mainly from industry besides training to foreigners under bilateral cooperation with different countries and international agencies and training to sponsored students from academic institutions and ad-hoc short-term training for academia and industry. During the year, 274 university/college sponsored students were imparted training.

6. Events/Seminars/Symposia

6.1 CDRI Annual Day

The 56th Annual Day of the Institute was celebrated on February 17, 2007. Prof. N.K. Ganguly, Director General, ICMR, New Delhi was the Chief Guest and Prof. R.P. Singh, Vice Chancellor, Lucknow University presided in the event. Dr. C.M. Gupta, Director presented an account of the achievements made during the year. Staff members completing 25 years of their service were awarded a memento and a certificate of honor. Incentive Awards for papers published in biological sciences having an impact factor 5 or above were given to 5 scientists. In chemical sciences, 10 scientists were awarded whose papers were published in journals having an impact factor of 3.5 or above. For foreign patents granted, 4 scientists were given the Incentive award.

6.2 Mellanby Memorial Lecture

The 32nd Mellanby Memorial Lecture was delivered by Dr. Lalji Singh, Director, Center for Cellular and Molecular Biology, Hyderabad on February 17, 2007 on the topic: *What is Human Life*? The function was presided over by Prof. N.K. Ganguly, Director General, ICMR, New Delhi.

6.3 Current Trends on Drug Discovery Research

An international symposium *Current Trends in Drug Discovery Research* (CTDDR) was organized at CDRI from 17-21 February 2007. Prof. N.K. Ganguly, Director General, ICMR delivered the inaugural address while Dr. Toshio Fujita, Kyoto University, Japan delivered the keynote lecture on 'SAR-Omics'. Several scientific dignitaries attended the symposium. Dr. C.M. Gupta, Director, CDRI welcomed the audience and emphasized that drug R&D institutions are influenced by advancements in science frontiers, introduction of new instruments/tools and techniques, changes in regulatory requirements and the market forces.

6.4 Dr. B. Mukerji Memorial Lecture

The 10th Dr. B. Mukerji Memorial Lecture was delivered on 27th February 2007. This lecture was held in the memory of Late Dr. Bishnupada Mukerji, the first Indian Director of CDRI. The guest speaker was Dr. Kanury V.S. Rao, Head, Immunology Group, International Center for Genetic Engineering & Biotechnology, New Delhi. The topic of his presentation was *Plasticity of the Intracellular Signaling Network*. The event was

presided over by Dr. Nitya Nand, Former Director of the Institute.

6.5 CSIR Program on Youth for Leadership in Science

The two-day *CSIR Program on Youth for Leadership in Science* was organized twice in the Institute on 13-14 March 2007 and December 27-28, 2007. Under this program, meritorious students of Uttar Pradesh who secure more than 80% marks in their board examinations at High School level and had opted for CDRI. Overall, a total of 21 students from different colleges participated in the two programs.

6.6 Conference "Atherosclerosis in Hypertension, Diabetes and Coronary Artery Disease"

A conference of the Indian Society of Hypertension and international symposium Atherosclerosis in Hypertension, Diabetes and Coronary Artery Disease was organized on March 15 – 16, 2007. Dr. Nimal Hettiaratchy, Regional Director, UNICEF delivered the inaugural address.

6.7 Symposium "Organic Chemistry and Drug Research"

A symposium "Organic Chemistry and Drug Research" was organized on June 28, 2007 in the honor of the superannuating senior scientist Dr. Chandan Singh. Prof. H. Ila, Prof. Y.D. Vankar, Dr. S.K. Puri and Dr. Chandan Singh delivered lectures on the occasion. Dr. Nitya Nand, Former Director, CDRI presided over the function.

6.8 National Symposium "Structural Biology – Interfacing Drug Research"

A one day symposium "Structural Biology – Interfacing Drug Research" was organized to honor Dr. C.M. Gupta, who relinquished his office on August 31, 2007. Prof. S.W. Akhtar, Vice Chancellor, Integral University, Lucknow was the chief guest for the event. Dr. Nitya Nand, former Director, CDRI, presided over the function. Prof. Kanury V.S. Rao, Dr. D. Saulanke and Prof. Kasturi Datta, were among those who presented their views on the occasion. Dr. Vinod Bhakuni, Head, Molecular and Structural Biology Division, CDRI proposed a vote of thank as the organizing secretary of the symposium.

6.9 CSIR Foundation Day

Four Lucknow based CSIR laboratories – Central Drug Research Institute, National Botanical Research Institute, Industrial Toxicology Research Center and Central Institute of Medicinal and Aromatic Plants jointly celebrated the CSIR Foundation Day on 26 September 2007. An exhibition, highlighting major achievements of these CSIR laboratories was inaugurated by Dr. V.P. Kamboj, Former Director, CDRI. Institute was open for general public and students from schools and colleges on this occasion. Staff members, who completed 25 years of their continuous service in CSIR, were felicitated by the Director, Dr. Rakesh Tuli. Children of CDRI staff members, who had excelled in science subjects, sports and essay competitions, etc. were suitably awarded by Dr. Kamboj and Dr. (Mrs.) Madhu Tuli. The Foundation Day Lecture *"What can we learn from insect society"* was delivered by Prof. Raghavendra Gadagkar, Sir J.C. Bose National Fellow, Center for Ecological Sciences, Indian Institute of Science, Bangalore. Prof. S.S. Agarwal, Former Director, SGPGI, Lucknow presided over the function.

7. Honors and Awards

Several CDRI scientists were awarded by different bodies for their meritorious work and achievements in the field of drug research. Dr. Rakesh Tuli, Director was the recipient of J.C. Bose Fellowship and the Science Counsellor Award – 2007 from Indian Society of Health, Environment, Education and Research. Dr. Anup Kumar Misra and Dr. Atul Goel were awarded Ramanna Fellowship Award in 2007 by Department of

Science and Technology, New Delhi. Dr. Goel was selected for the Dr. Ghanshyam Srivastava Memorial Award – 2007 to be given by Indian Chemical Society, Kolkata. Dr. Vinod Bhakuni was elected the Fellow of National Academy of Science. Dr. C. Nath was elected the Fellow of Indian Pharmacological Society. Dr. Rakesh Shukla was given the S.B. Pandey Oration Award – 2007 by Indian Pharmacological Society and he continued to be the Treasurer of Indian Academy of Neurosciences, Lucknow Branch. Dr. Neena Goyal, Dr. Madhur Ray and Dr. J.K. Saxena were the recipients of Best Poster Awards for their respective research papers. Dr. Atul Kumar was conferred upon the OPPI Scientist Award 2007. One of our research students Mr. Ashutosh was conferred upon the M.B. Mirza Award at Annual Conference of Indian Society for Parasitology held at Visakhapatanam.

Section : I

PROGRESS IN RESEARCH PROJECTS

REGULATORY STUDIES

1. Area: Clinical Trials and Pharmacokinetic Studies

(Coordinator : Dr. O.P. Asthana)

Clinical studies on candidate drugs continued this year. A total of 9 candidate drugs were undertaken for different phases of clinical studies. Pharmacokinetic studies were undertaken on 7 candidate drugs. This section covers progress in studies carried on different drugs.

1.1 Clinical trials of candidate drugs/products

1.2 Pharmacokinetic and metabolic studies of synthetic compounds and natural products

1.1 Clinical trials of candidate drugs/ products

1.1.1 Consap (Contraceptive cream)

Product acceptability studies concluded. The overall observations are that though carried out under the supervision of a specialist, there are clear positive signals regarding the advantage of this product. The product was able to generate positive feedback from a section of the volunteer users as well as the administering doctors. Right from elements like its herbal origin, a purely ladies contraceptive etc., the product has been able to garner a good opinion regarding its contraceptive efficacy, near absence of side effects, pleasure inducement, etc. Despite the difficult elements like restriction on douching, measured usage and also the task of woman in convincing her partner to use this product. As is for any other contraceptive product, a full acceptance across a section of users is rare. Hence with these indications we can conclude that a certain section of fertile population will find this product acceptable. It, however, needs a clear communication regarding its contraceptive efficacy and till the time of awareness levels are created, it may be supplied through gynecologists or through a dispensary for restricted use. This will enable the users to be clearly briefed regarding the usage of the product. DCG(I) cleared the cream for use.

1.1.2 Arteether (Blood schizontocidal agent)

Multicentric clinical trials for efficacy in 235 children suffering from *P. falciparum* malaria concluded at five centers viz. Dibrugarh, Guwahati, Rourkela, Jabalpur and Jodhpur. Draft of the Dossier is ready for submission to DCG(I).

1.1.3 Compound 80/53 (Antirelapse antimalarial)

Independently undertaken clinical trials for safety evaluation in G6-PD deficient cases in Thailand provided evidence of its better safety profile than primaquine.

1.1.4 Picroliv (Hepatoprotective agent)

Placebo controlled, double blind, non cross over Phase III clinical trials are in progress at KGMU,

Lucknow for evaluation of Hepatoprotective activity of Picroliv in patients of tuberculosis receiving MDT. So far, a total of 78 patients of tuberculosis, included in the trial, were subjected to interim analysis. After opening the codes, they were divided into two groups based on random allocation of treatment i.e. placebo or Picroliv. In placebo group 36 patients (19 males, 17 females, mean age 28.33±9.66 years) where as in Picroliv treated group 42 patients (11 males, 31 females, mean age 26.86±11.57) were included in the study.

In placebo treated group, 21 patients completed six months study, 7 patients completed 5 months study and 8 patients completed 3-4 months study. While in Picroliv treated group, 20 patients completed six months study, 12 patients completed 5 month study and 10 patients completed 3-4 month study. All these patients were monitored and evaluated on clinical parameters (fever, cough, expectoration, loss of appetite, loss of weight, pain in abdomen, recurrent diarrhoea, vomiting, swelling in neck or groin: graded as - = to absent + = 0-0.5, ++ = 0.51 – 1.0, +++ = 1.1-1.5, ++++ = 1.6-2.0, +++++ = 2.1-2.5, ++++++ = 2.6-3.0; clinical signs like temperature, pulse, BP, lymphadenopathy, splenomegaly, hepatomegaly and radiological signs) and laboratory parameters including biochemical parameters (serum urea, creatinin, total protein, albumin, bilirubin, SGOT, SGPT, and ALP), hematological parameters (Hb, TLC, Polymorphs, Lymphocytes, Eosinophils, Monocytes, RBC count, Platelet count, ESR) were determined before treatment and periodically during allocated treatment.

Interim analysis of the study revealed that clinical recovery of tuberculosis patients was faster in patients treated with Picroliv in comparison to patients receiving Placebo treatment. Liver function test performed before and during treatment revealed no appreciable difference in both the groups i.e. Placebo v/s Picroliv. Adverse events were also monitored during the trial and no major side effects were reported with the Picroliv treatment when compared to the Placebo therapy. The trial is still continuing and as the number of patients in both the treatment groups is very small, definite conclusions cannot be drawn at present.

1.1.5 CT-1 (Antidiabetic agent)

Exploratory clinical trials showed promising results. Available data has been reviewed and discussed with NPIL for future course of action.

1.1.6 Compound 80/574 (Hypolipidemic agent)

Phase III Multicentric clinical trials concluded at SGPGI and KGMU, Lucknow, Seth GSMC, Mumbai and PGIMER, Chandigarh. Data compilation is in progress.

1.1.7 CDR134D123 (Antihyperglycaemic agent)

Single dose Phase I clinical studies completed and the product was found safe. Phase I multiple dose tolerance studies were initiated at Seth GSMC, Mumbai and the first case has been enrolled in this study in December 2007.

1.1.8 Compound 97/78 (Antimalarial)

Dossier containing preclinical data and protocol and CRF for phase I clinical trial submitted to DCG(I). Phase I clinical trial permission obtained from DCG(I) in 2007.

1.1.9 Compound 99/373 (Antiosteoporotic)

Dossier containing preclinical data and protocol and CRF for phase I clinical trial was submitted to DCG(I). Phase I clinical trial permission obtained from DCG(I) in 2007.

1.1.10 Dossiers on IND filed with DCG(I) to seek permission for Phase I clinical trial

- Puffer fish oil (Antihyperlipidemic)
- CDR 134F194 (Antihyperglycemic)

1.2 Pharmacokinetic and metabolic studies of synthetic compounds and natural products

1.2.1 Compound 99/373 (Antiosteoporotic)

- Tissue distribution studies in GI tract (stomach, small intestine and large intestine).
- Biliary excretion studies in SD Rats.
- Toxicokinetic studies in male and female rhesus monkeys.

1.2.2 Compound 99/411 (Antimalarial)

Multiple dose PK studies in male and female monkeys by oral route.

1.2.3 Compound 80/574 (Antihyperlipidemic agent)

Drug-drug interaction studies with:

- Atorvastatin
- Azetimibe
- Phenofibrate
- Piperine

1.2.4 Compound S-002-853

Metabolic stability and interspecies profiling with liver microsomes of :

- Mice
- Rat
- Monkey

1.2.5 Compound S-002-857

Metabolic stability and interspecies profiling with liver microsomes of :

- Mice
- Rat
- Monkey

1.2.6 CDR134F194 (Antidiabetic and antidyslipidemic)

Toxicokinetic studies in male and female rhesus monkeys.

1.2.7 Plant 1020 (NP-1: Antiosteoporotic-osteogenic)

- LCMS/MS analytical Method Development for marker compound K051, K052, K054, K080, K082 and K095.
- Finger printing and absolute quantification of marker compound K051, K052, K054, K080, K082 and K095 in crude extract and n-butanol fraction.

1.2.8 New Leads: Bio-analytical method development and pilot PK studies

a. Bio-analytical method development of four anti-thrombotic compounds:
   - S-000-20
   - S-001-556
   - S-002-329
   - S-002-333

b. Pilot PK studies of four anti-thrombotic compounds in NZ rabbits:
   - S-000-20
   - S-001-556
   - S-002-329
   - S-002-333

1.2.9 Bio-Marker of bone metabolism (De-oxypyrodinoline and pyrodinoline): (Osteoporosis)

More than 300 urine samples from treated group and control were analyzed for DPD and PYD for correlation of anti-osteoporotic activity of test compounds.

2. Area: Preclinical Safety Evaluation and Regulatory Toxicity

(Coordinator: Dr. O.P. Asthana)

The studies carried out under this project had three major objectives:

I. Toxicology profiling of candidate drugs according to internationally accepted methods for studying local, systemic, reproductive, genetic toxicity and other special toxicity if required.

II. In addition to various basic research, deployment of alternative test systems which can be less or non cost and time intensive and can also reduce, refine or replace the use of animals in toxicity testing.

III. To provide vital information(s) on safety/mechanism of toxicity/metabolism of drugs.

2.1 Regulatory studies:

1	CDR 267/F018	10 day DRF study in rat by oral route
		28 day toxicity study in rat by oral route
2	97/78	28 day toxicity study in rhesus monkey by oral route
3	AP76P	1- Dose toxicity study in rat by oral route
		10 day DRF study in rat by oral route
4	AP20am 14	1- Dose toxicity study in rat by oral route
5	AP20am 15	- do -
6	AP20am 16	- do -
7	Kajjali Yoga	- do -
8	Ras Sindoor	- do -
9	Vasant Kusumakar	- do -

10	ICB014P04A002	28 day toxicity study in rat by oral route
11	99/373	28 day toxicity study in rhesus monkey by oral route
12	99/373	28 day toxicity study in rat by oral route (NOAEL Study)
13	CDR134/F0194	28 day toxicity study in rhesus monkey by oral route
14	99/411	28 day toxicity study in rat by oral router
		28 day toxicity study in rat by oral route (NOAEL Study)
15	99/373	Male fertility study in rat
16	CDR 134/F194	- do -
17	99/411	- do -
18	99/373	Ames Test (Mutagenicity)
19	CDR 267/F018	- do -
20	AP20am-14	- do -
21	AP20am-15	- do -
22	AP20am-16	- do -
23	99/411	- do -
24	CDR 134/F194	- do -

2.1 Experimental toxicology works completed / continued

- Testing teratogenecity potential of Cyclophosphamide and Mitomycin-C in rats at the platform of Metabonomics using NMR. This was planned with an idea to develop a testing system which should not be time and cost intensive and also requires lesser number of animals (rats/mice).
- Study to test renal toxicity using biofluids (urine) on the same platform.
- Signature profiling of differentially expressed genes in mice following administration of 8-aminoquinoline derivatives.
- Association of polymorphisms in selected DNA repair and drug metabolizing genes with the risk of breast cancer.
- Identification of nuclear and mitochondrial DNA mutations involved in Progressive External Ophthalmoplegia.
- *In vivo* gene expression studies in mice following flavonoid administration.
- Toxicity and gene expression profiling by co-exposure of certain antimalarials.

- Association of DNA repair gene polymorphisms and identification of gene expression signatures associated with the susceptibility of Squamous Cell Carcinoma of the Head and Neck.
- Association of selected genes and identification of gene expression signatures in Chronic Periodontitis.
- Development of *in vitro* and *in vivo* models for screening of novel compounds for treating diabetes and dyslipidemia.
- Single Nucleotide Polymorphism (SNP) and diseases.
- Establishment and standardization of in vitro hepatotoxicity test system.
- Studies were conducted using INH as reference compound for evaluating the validity of HEP-G2 cells as a test system for screening hepatotoxic potential of candidate drugs.

PROJECT AREA STUDIES

1. Area: Biological Screening

(Coordinator: Dr. Sudhir K. Sinha)

The main objectives of this project area are: (a) anti-TB screening, (b) anti-cancer screening (c) high-throughput screening (HTS) and (d) development of new screening models.

1.1 Tuberculosis

1.2 Cancer

1.3 Trypanosomiasis

1.4 Solubility analysis of CDRI's chemical library

1.1 Tuberculosis

1.1.1 Screening

Over two thousand four hundred new samples (1549 extracts from terrestrial flora and microbes, 504 extracts from marine flora and fauna, and 351 synthetic molecules) were screened for their anti-TB activity. Design of new synthetic molecules was based on the chemical structure of 'hits' identified during previous screening campaigns, with the view to generate and optimize novel 'leads'.

Forty eight synthetic molecules were active *in vitro* against *Mycobacterium tuberculosis* $H_{37}Rv$. Thirty actives had a minimum inhibitory concentration (MIC) of ≤ 1.56 µg/ml and the remaining 18 had a MIC of ≤ 3.12 µg/ml. Twenty nine of the actives did not show *in vitro* cytotoxicity towards Vero cells or mouse bone marrow derived macrophages. Fourteen non-toxic active molecules (having a MIC of ≤ 1.56 µg/ml) were further evaluated using the *ex vivo* mouse macrophage model of TB. The readouts were (i) microscopy following acid-fast staining of intracellular bacilli *(M. tuberculosis)* and (ii) counting of colony forming units (CFUs) of bacilli following culture of lysates of infected macrophage on agar-based medium. In this assay, 7 molecules belonging to 3 different chemical classes showed a potency comparable with that of the standard anti-TB drugs isoniazid or rifampicin. These were subjected to *in vivo* screening in the mouse model of TB.

Four out of 7 molecules which were tested *in vivo* showed a variable degree of clearance of infection, as determined by mean survival time and bacterial load in the lungs of infected mice. The activity of two molecules (of different chemical class) was reconfirmed by repeat assays. One of them showed an enhancement of 9 days in mean survival time and 10-fold reduction in bacterial load in the lungs. The gastric stability of this molecule

was checked by treating it with simulated gastric juice and monitoring the outcome by HPLC. Some loss in its quantity, as evident from a reduced HPLC peak, was attributable to the acid-labile nature of the molecule. Efforts are underway to enhance the gastric stability of the molecule through 'enteric' coating.

1.1.2 Development of new screens

Efforts were directed at development of protocols for 'mode of action' studies on molecules which show a significant anti-TB activity. Assays pertaining to the effect of a drug candidate on biosynthesis of macromolecules (lipids, protein, DNA and RNA) by *M. tuberculosis* are based on incorporation of radio-labeled precursors (^{14}C Acetate for lipids, ^{3}H Thymidine for DNA, ^{3}H Uracil for RNA and ^{3}H Leucine for proteins) during the metabolism of bacteria. The assay for DNA biosynthesis has been standardized.

1.2 Cancer

A new in-house facility for screening of natural and synthetic molecules for their anti-cancer activity was established during this year. The facility has become operational and presently *in vitro* assays are being performed using cell lines (procured from American Type Culture Collection) for pancreas, ovary, prostrate, colon, breast, lung and cervical cancers. Standard cell viability based protocol using an indicator dye (MTT) is being followed.

Two hundred sixty four marine extracts were screened for their anti-cancer activity. Initially, solubility of the extracts in aqueous medium was determined by laser nephelometry (described below) and only the soluble extracts were bioevaluated. Samples showing ≥ 80% growth inhibition (at 50 µg/ml concentration) of cancer cells were considered as 'hits' and were categorized according to their selective cytotoxicity towards certain cancer types as well as Vero cells (used as a non-cancer control). Out of 62 hits which were active against 5 cancer cell lines, only 12 were selected for further evaluation. The remaining 50 extracts were toxic for all cancer types and/or for Vero cells, which indicated the 'non-specific' nature of their activity. Out of the 12 selected extracts, 2 were active against 3 cancer types (oral, lung and ovary/pancreas), 5 against 2 cancer types (from oral, prostate, ovary, lung and pancreas), and 5 against a single cancer type (4 for oral and 1 for ovary).

The ongoing DST-Dabur project on cancer drug development came to an end. During the current year, emphasis was laid on chemistry-based lead generation and optimization. 'Hits' belonging to 4 chemical classes (active against oral, colon, pancreas and ovary cancers) were short listed and over 40 new analogs were synthesized at CDRI. Further screening of these molecules will be taken up by our new in-house facility.

1.3 Trypanosomiasis

HTS for anti-trypanosoma activity of the synthetic compound library of CDRI is being pursued under a project sponsored by "Drugs for Neglected Diseases Initiative (DNDI)". The assay procedure is based on determination of viability of the parasites *in vitro* using Alamar Blue as an indicator dye. Petamidine was used as a standard drug for the assay. Approximately 7500 molecules were screened at a fixed concentration (1 µg/ml) and were considered as 'hits' if they reduced the parasite viability by at least 50%. The total number of hits was around 5% of all molecules. Categorization of hits under different chemical classes (to remove those belonging to certain undesirable classes) and screening for their non-specific cytotoxicity, if any, is underway.

Determination of 50% inhibitory concentrations (IC_{50}) of hits, by way of screening of their serial dilutions, is also underway.

1.4 Solubility analysis of CDRI's chemical library

For *in vitro* screening assays, solubility of test molecules in aqueous solvents (buffers/culture media) is an important consideration. Molecules that are insoluble are not suitable for *in vitro* screens. With this view, 7104 compounds of CDRI's chemical library (synthesized after 1980) were subjected to a laser nephelometry based procedure for solubility determination. Phosphate buffered saline (PBS) was used as a solvent and sucrose was used a standard (soluble) compound, as per recommended procedures. All compounds were screened at 25 µg/ml concentration. Compounds showing values (laser light diffraction units) more than twice that of the sucrose solution were considered as insoluble. By this criterion, 1883 (26.5%) molecules turned out to be 'insoluble'.

2. Area: Cardiovascular, Central Nervous System and Other Disorders

(Coordinator: Dr. Ram Raghubir)

The research activity pursued under the above project includes design, synthesis and development of new drugs for various diseases of Cardiovascular System (stroke, thrombosis and hypertension), Central Nervous System (dementia and stress) and other disorders (diabetes, lipid disorders, inflammation, and gastric ulcers). The project area also covers regulatory pharmacological studies of the candidate drugs. Development of suitable better and predictable screening models for evaluation of plant and marine extracts, fractions and synthetic compounds. Besides, neuro-chemical and molecular investigations are also persuaded for developing newer molecular targets for drug discovery and analyzing the possible mechanism(s) of action of newer drugs. Developing new target based assays is of prime concern which may eventually help in the development of new target based drugs.

2.1 Cardiovascular System

2.1.1 Development of anti-hypertensive agents

Total 96 synthetic, marine substances and plant extracts were screened for antihypertensive activity in anaesthetized SHR rats. None of these showed any promising effect.

2.1.2 Development of anti-stroke agents

A total of 31 compounds were screened for anti-stroke activity using embolic and filament model of middle cerebral artery occlusion in rat. One compound and its series was identified as having significant anti-stroke activity. The efficacy, therapeutic window were evaluated.

2.1.3 Development of anti-thrombotic agents

Total 24 test substances and 55 fractions were tested at a dose of 30 µM/kg (po) in mice against collagen + adrenaline induced thrombosis and increase in the bleeding time. Seven compounds exhibited appreciable protection against thrombosis.

2.1.4 Preclinical studies for stroke therapy

Effect of compound S-005-1000 was evaluated in middle cerebral artery occlusion model in rats

for its efficacy and therapeutic time window by ip route. Compound S-005-1000 ameliorated the infarct and edema volume and neurological deficit significantly in dose dependent manner. It also ameliorated significantly the infarct and edema volume and neurological deficit evaluated 24 hrs post ischemia. Further, its effect was seen with the lowest dose given 3 hrs post ischemia. A significant attenuation in flowcytometric analysis of intra neuronal levels of reactive oxygen species, calcium, nitric oxide, mitochondrial membrane potential, peroxynitrite and apoptosis was observed. The compound had no significant effect on blood pressure in spontaneously hypertensive rat. Pretreatment of all the series of compounds were evaluated in heart challenged to ischemia. None of the compounds evaluated had anti-ischemic activity. Compound S-005-1000 has no per-se effect on the heart and blood pressure. The results showed compound S-005-1000 significantly reduced infarct volume, improved neurological deficit and reduced the brain edema in a dose-dependent manner. It seems the compound S-005-1000 is a potent neuroprotectant.

2.1.5 Anti-stroke potential of some natural products

The anti-stroke potential of Gugulipid suspension and Withanolide A, Withoferin and Withanone single molecules of *Withania somnifera* were tested in Rat Middle Cerebral Artery Occlusion (MCAO) model. Male SD rats were subjected to MCAO for 2 hours ischemia, followed by 24 hours of reperfusion. Cerebral damage was assessed by subjecting the rats to neurobehavioural studies on 10-point scale. Blood samples were withdrawn to estimate the levels of GSH, MDA and SOD. Further, rats were sacrificed and brain was removed in chilled condition and infarct area was determined using TTC stained brain sections, by Biovis Image Analyzer.

In another set of experiment, rats were divided into three groups and each of the *W. somnifera* molecules viz. Withanolide A, Withoferin and Withanone were administered 6 hour post-reperfusion at 50 mg/kg, p.o. in ischemic rats. Among the three molecules Withanolide A was found to be most effective on all parameters and reduced the infarct size by about 90% indicating its potent antistroke potential.

Gugulipid suspension was administered at three different doses (25, 37.5 and 50 mg/kg, p.o.) 6 hour post-reperfusion in MCAO model. It significantly reduced the neurological deficit and ameliorated the levels of GSH, MDA and SOD. The infarct size was also significantly reduced in a dose dependent manner. Hence, Gugulipid and Withanolide are significantly active and could serve as important anti-stroke agents.

2.1.6 Animal model of intravascular thrombosis

Topical application of ferric chloride ($FeCl_3$) in various concentrations on the carotid artery of male SD rats led to the occlusion and complete cessation of arterial blood flow. Total time to occlusion (TTO) was measured for each concentration and was represented as time elapsed between application of ferric chloride to the time taken for the vessel occlusion, which was monitored by a blood flow meter. Application of a piece of Whatman paper, saturated with 20% $FeCl_3$ blocked the carotid artery within 13.6±1 min in a reproducible manner. Anti-platelet drugs (aspirin, ticlopidine and clopidogrel) and anticoagulants (heparin and warfarin) were evaluated in this model at clinically used doses. Aspirin (30mg/kg, po, 1h and 3 days) and ticlopidine (200mg/kg, po, 2h) did not prolong the TTO in comparison to the control while, a significant increase was observed following 3 days of treatment with ticlopidine (200mg/kg) or clopidogrel (30mg/kg, po 4h and 30mg/kg, po, 3 days) consistently increased TTO. Heparin (10U/kg, 30U/kg & 100U/kg, iv) on the other hand increased TTO in a dose dependent manner (18±2, 22±4 and 37±17min respectively). TTO in warfarin

(0.1mg/kg, po; or 0.3mg/kg, po, once for 5 days) treated groups was 66±26 and 120±0min respectively. The model thus seems to be a suitable animal model for predicting the efficacy of anti-thrombotic agents.

2.1.7 Myocardial infarction model in rats

An animal model for myocardial infarction (MI) by the ligation of left anterior descending (LAD) coronary artery was standardized in anesthetized Sprague-Dawley male rats. A prominent infarct zone in the myocardium of rats was observed after 24 h and scar formation after three weeks. The hemodynamic parameters showed a significant decrease in heart rate and blood pressure with time after inducing MI. Serum levels of CK-MB and LDH reached their peak levels at 7th day after MI, and then declined gradually reaching their normal levels by 13 weeks. The histological examination of the infarcted myocardium at different time points showed a prominent infarcted area, infiltration of neutrophils and fibrosis. The TTC staining showed approximately 20% infarct (TTC negative myocardial area) in all experimental animals while control animals exhibited uniform deep red colored TTC staining with no sign of infarction.

2.1.8 Basic studies in CVS

2.1.8.1 Hyperlipidemic hamster as a model to study Athero-thrombosis

Atherosclerosis is an inflammatory disease characterized by intense immunological activity, increased oxidative stress, decreased NO production, endothelial dysfunction, apoptosis, fibrosis and platelet hyperaggregability. Atherothrombosis was evaluated in three months high fat diet (HFD) (3% cholesterol +15% saturated fat) fed Golden Syrian hamster (FIB strain). HFD induced hyperlipidemia as confirmed by increase in plasma lipids and lipid deposition in aorta (Oil red O staining). Atherothrombotic potential was evaluated by measuring platelet adhesion (on collagen coated surface), coagulation parameter [prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen time (FT)], whole blood aggregation (induced by ADP 10µM, Collagen 2.5µg/ml and Thrombin 0.64µg/ml), as well as ferric chloride ($FeCl_3$ 10% solution) induced thrombosis. Increased level of total cholesterol ($p<0.001$), HDL ($p<0.01$), LDL ($p<0.01$), TGs ($p<0.05$) and lipid stained area showed well developed hyperlipidemic condition and lipid deposition after HFD treatment. The significant reduction in PT ($p<0.001$), aPTT, ($p<0.01$), and FT ($p<0.01$) exhibited hypercoagulability of the blood in HFD group. Significant increase in thrombin (0.64 µg/ml) induced whole blood aggregation ($p<0.05$) reflected increase in thrombin generation and hypercoagulability of blood in HFD group. No change was however observed in TT, collagen and ADP induced whole blood aggregation, $FeCl_3$ induced thrombosis and platelet adhesion in high fat fed group (comparison in matched controls). The results obtained reflect hypercoagulability of blood (platelet activation and increased activity of extrinsic/intrinsic coagulation pathways) in hyperlipidemic conditions suggesting that Golden Syrian hamsters could be a useful model to investigate thrombotic and atherosclerotic changes.

2.1.8.2 Involvement of nitric oxide in monocyte differentiation and macrophage foam cell formation

Monocyte derived macrophages are important for atherosclerosis due to their role in inflammation and accumulation of modified lipids to form foam cells. Involvement of nitric oxide (NO) in macrophage differentiation and foam cell formation has been investigated in THP cell line.

Low density lipoprotein (LDL), mildly and extensively oxidized LDL (M-OX-LDL and E-OX-LDL) were prepared by differential ultra centrifugation and copper sulfate mediated oxidation. THP-1 floating monocytic cells differentiated into adherent macrophage like cells

on PMA treatment. Status of NO was measured in terms of cellular nitrite content (Griess reagent), NO (DAF-2DA dye and Flow cytometry) and NOS expression (Western blotting). NO levels were significantly increased (~ 3 folds) in PMA differentiated THP-1 cells as compared to undifferentiated control. PMA differentiated cells treated with E-OX-LDL for 24,48,72 hrs showed significant foam cell formation at 48 hrs in comparison to respective control (~2 fold) or M-OX-LDL (~1.5 fold) treated cells. Differentiated THP cells were treated with LPS (1µg/ml, 1, 2, 4, 8 and 12 hours,), E-OX-LDL (40µg/ml, 48 hrs) or both. A significant increase in NO levels of undifferentiated (~2 fold) and differentiated cells (~1.5 folds) at 12 hrs of LPS treatment was observed. A significant increase in NO levels was observed in differentiated THP-1 cells treated with E-OX-LDL (~25%). However, simultaneous treatment of E-OX-LDL and then LPS did not alter the NO levels significantly (~21%). Results indicate involvement of NO in monocyte differentiation, macrophage foam cell formation and inflammation.

2.1.8.3 Studies on rat and human neutrophils

a. Studies on rat neutrophils following LPS treatment

Neutrophils are the forerunners to sites of inflammation. Lipopolysaccharide (LPS), an endotoxin, induces local and systemic inflammatory response. An air pouch model of inflammation was used to assess the alteration in free radical and nitric oxide generation among the infiltrated cells following LPS challenge.

An air pouch was produced on the dorsal surface of male SD rats (150-200g) by subcutaneous injection of 20 ml sterile air. On 6th day, 10µg LPS or vehicle was injected into the pouch and subsequently after 4 hours Hank's Balanced Salt Solution was injected at the same site to collect infiltrated cells. Neutrophils from the pouch exudate and from peripheral blood were isolated. Nitrite content and myeloperoxidase (MPO) activity were estimated in the plasma, pouch exudate, peripheral neutrophils and pouch cells. Nitrite content was increased significantly in LPS treated infiltrated pouch cell (1.75 ± 0.3 vs 6.44 ± 0.5 nmole/10^6cells, $p<0.01$) as well as in pouch supernatant (70.13 ± 6.5 vs140 ± 10.6 nmole/ml, $p<0.005$), while MPO activity was increased significantly only in the pouch cells (110.00 ± 13.9 vs159.00 ± 1.7 mM/min/10^6cells, $p<0.05$). Free radical generation was also augmented by two fold in the infiltrated cells. No significant change was observed in the above mentioned parameters in peripheral neutrophils and plasma following LPS challenge. LPS challenge thus seems to induce infiltration of activated neutrophils at the inflammatory site as indicated by enhanced NO production, oxidative burst and MPO activity, but does not affect the peripheral neutrophil repertoire.

b. Studies on NO during neutrophil maturation

Abnormalities in neutrophil maturation might lead to acute or chronic myeloid leukaemia (CML). Nitric Oxide (NO) has been recognized as an important modulator of cell survival, maturation and differentiation. Levels of NO in the bone marrow cells from control and CML patients were explored. Since uncontrolled proliferation is found in leukaemia without differentiation, effect of NO donor (SNP 1µM-1mM) and NOS inhibitor (L-NAME 1mM) on cell cycle in rat neutrophil precursors by using Propidium iodide and BrdU staining during their culture for 24 hrs was also investigated. Cells were isolated from rat and human bone marrow by Percoll density gradient and the purity was confirmed by Giemsa staining and CD markers. Three bands were obtained: band 3 rich in myeloblasts/promyelocytes, band 2 rich in myelocytes/metamyelocytes and band 1 rich in band cells/segmented neutrophils. Level of intracellular NO was assessed with the help of florescent probe DAF-2DA in CD11b, CD15 and

CD16 positive cells according to maturation stages, which was highest in band 1 and lowest in band 3. Total nitrite and NOS activity also exhibited the similar pattern in rat marrow cells. Free radical generation as measured by DCF-2DA was found to be increased with maturation. CML patients exhibited comparatively less DAF-2DA fluorescence in band 3 as compared to band 1. SNP treated cells exhibited an increase in apoptosis (6±1.5 Vs 14±2 %), while viable cells showed a marginal increase in the S phase in band 2 and band 3 (10±1 Vs 16±4 %). L-NAME, however, decreased apoptosis of the cells (6±1.5 Vs 2 ± 0.7%) without any significant modulation in the stages of cell cycle.

c. Regulation neutrophil free radical generation by NO

Nitric Oxide (NO), a pleotropic molecule, has been recognized as a mediator and regulator of inflammatory responses. Acute response to infection is initiated by neutrophils, by releasing antimicrobial peptides, proteases and by producing reactive oxygen species (ROS). Incubation of human neutrophils with NO donors, sodium nitroprusside (SNP) or S-nitroso-N-acetyl-penicillamine (SNAP) led to the formation of ROS and RNS. To investigate the role of NOS, NADPH oxidase and MPO in NO mediated free radical formation; human PMNs were treated with free radical scavenger (N-acetyl cysteine) NOS inhibitors (diphenyleneiodonium chloride, 7-nitroindazole), NADPH oxidase inhibitor (diphenyleneiodonium chloride, apocynin) and MPO inhibitor (4-aminobenzoic acid hydrazide). NO mediated free radical formation was prevented in the presence of free radical scavenger, NOS and MPO inhibitors but not in case of NADPH Oxidase inhibitor suggesting the possible role of NOS and MPO. To further confirm the independence of NADPH oxidase in NO mediated free radical generation studies were done in promyelocytes, a neutrophil precursor cell that lack NADPH oxidase and in cytokineplasts. NO mediated free radical formation was augmented in both promyelocytes and cytokineplasts suggesting the role of NOS in free radical generation. The migration of p47 subunit of NADPH-oxidase in response to SNAP towards the plasma membrane could not be observed, thus excluding involvement of NADPH oxidase in NO mediated free radical generation. It is thus proposed that NO mediated free radical formation was dependent on the NO synthase (NOS) uncoupling and MPO derived free radicals, but independent of NADPH-oxidase.

d. NOS distribution in human eosinophils

High labeling of nNOS was localized in granules, which was strikingly different from iNOS which was equally distributed in the cytoplasmic and granular compartments in human eosinophils, while in rat, iNOS was the predominant isoform and mainly present in eosinophilic granules and cytoplasm. eNOS though sparingly observed was mainly confined to the cytosolic compartment in both rat and human. Differences in localization of NOS isoforms possibly indicate towards a differential mode of catalysis as offered by these isoforms in generating NO also implicating diverse means of regulation imposed upon them.

2.1.8.4 Influence of various risk factors on estradiol induced cardiac electrophysiological alterations

It has been suggested that estrogen may influence the duration of cardiac repolarization. Thus we investigated influence of estradiol on ventricular repolarization within the physiological concentration range of this hormone by intracellular recording technique. It caused dose dependent prolongation of repolarisation phase of cardiac action potential. We also evaluated the influence of various risk factors such as electrolyte imbalance (hypomagnesemia and hypokaelemia), gender difference, pacing frequency, ischemia reperfusion insult on APD prolongation property of estradiol.

Only gender difference, high pacing frequency (reverse use dependent manner) amplified adverse electrophysiological effect of this female sex hormone.

2.1.8.5 Evaluation of cardiac adverse effect of arsenic trioxide on myocardium

Arsenic trioxide (ATO/ As_2O_3) is a new promising regimen for patients with a relapse of acute promyelocytic leukemia (APL), but causes frequently life threatening arrhythmias. In the present study using electrophysiological method, we showed the dose dependent effect of ATO on electrically driven cardiac action potential from papillary muscle of guinea pig. It caused significant prolongation of action potential duration at various levels of repolarization, conduction delay and increased triangulation, which is a novel marker for proarrhythmic potential of a compound. We also found electrolyte imbalance (hypomagnesaemia and hypokaelemia) to cause amplification of the adverse effect of ATO. Since ion channels of repolarization phase of action potential are targets of ATO, we used some ion channel modulators such as choline, minoxidil, nifedipine and verapamil to see whether they can antagonize electrophysiological alterations caused by ATO. None of them worked except choline which showed some protective effect. *In vivo* experiments, administration of ATO by intraperitoneal route to animals for 10 days caused myocardial disorganization, interstitial edema and infiltration of inflammatory cells in heart. We also screened efficacy of vitamin C against ATO induced histopathological alteration. Besides, administration of ATO for 10 days caused significant increase in serum creatine kinase isoenzyme, lactate dehydrogenase, glutathione peroxidase and reduced glutathione. Unfortunately the exact molecular mechanism of cardiovascular adverse effect due to ATO exposure has not been fully elucidated except alteration on ion channel. To evaluate cytotoxic effect of ATO on cardiac myocytes, primary culture of cardiac myocytes were treated with different doses of ATO for various periods. Cardiac toxicity was assessed by monitoring cell viability, mitochondrial and DNA integrity, apoptosis and ROS generation. Results showed ATO exposure caused ROS generation, calcium overload, apoptosis and altered mitochondrial integrity in cardiac cells in dose and duration dependent manner. None of the groups showed DNA fragmentation. We conclude that ATO causes significant cardiac adverse effect and suggest that cardiac function should be monitored during treatment with ATO.

2.1.8.6 Studies on cerebral stroke

The pathophysiology of cerebral stroke with certain molecular targets like caspases, PARP, neurotrophins, calcineurin NMDA, glutamate uptake inhibitors, Endoplasmic reticulum and AT receptor blockers were studied to understand the disease process and identify targets for developing novel drug candidates.

a. Focal cerebral ischemia induced apoptosis in diabetes is mediated by Caspase-3 and AIF

Diabetes plays a major role in development and pathogenesis of cerebral stroke through a myriad of molecular mechanisms. Efforts were made to delineate the role of key cell death signaling elements in aggravation of ischemic/reperfusion (I/R) injury in diabetes.

The cerebral ischemia was induced in STZ-diabetic male SD rats using MCAO. After 1.0 h of ischemia, CBF was restored and brain damage was evaluated at 3.0, 6.0, 12 and 24 h post-reperfusion by measuring infarct size. Cellular changes were differentiated with H&E and TUNEL staining. The molecular alterations include ROS, mitochondrial potential and protein expression were analysed using flow cytometry, western blotting and immunocytochemistry.

The I/R injury resulted in the marked increase in neurological deficit and infarct size with increasing I/R time points in diabetics. The cellular morphology exhibited marked apoptotic cell death, besides necrosis. At nuclear level, these changes were comprised of DNA fragmentation, nuclear condensation and apoptotic body formation. The DNA damage led early increase in poly(ADP-ribose) polymerase-1, which seems to cause release of apoptosis inducing factor (AIF), leading to noncaspase-dependent apoptosis. These observed changes seem to have direct correlation with the release of cytochrome c and AIF from mitochondria as revealed by altered ROS generation. Cytochrome c activates caspase-3 and that caspase-3 activation together with AIF aggravates cellular damage in diabetes. Based on these results, it may be concluded that diabetes activate apoptotic cell death pathway(s) and that interplay of these exacerbate the brain damage following cerebral ischemia.

b. Focal cerebral ischemia is associated with oxidative stress induced altered prossesing of neurotrophins

The role of oxidative stress (OS) in cerebral ischemia/reperfusion (I/R) induced altered processing of NTs and the role of p^{75NTR} in mediating apoptotic cell death following their activation via proNTs was investigated. Since proteolytic cleavage is one of the crucial mechanisms which determine the intracellular and extracellular processing of mature neurotrophins (mNTs) form proNT and promotes their neuronal growth, maintenance and survival responses. Altered processing may lead to enhanced levels of proNTs, which promotes apoptosis through p^{75NTR} activation.

Male SD rats were subjected to middle cerebral artery occlusion for 1hr followed by 3, 6, 12 and 24hr reperfusion. OS was measured by estimating the levels of GSH, MDA, SOD-1 and SOD-2. Differential expression of neuroserpin (Nsp) which is involved in the conversion of proNTs to mNTs and their eventual degradation respectively. The altered processing of NGF and BDNF was studied using western blot and RT-PCR. TUNEL and co-immunolabelling techniques were employed to identify apoptosis and activation of p^{75NTR} via proNTs, respectively, Pre-treatment with Thiotic acid significantly ameliorated the level of GSH, MDA, SOD-1 and SOD-2 and reduced the number of TUNEL positive cells. Expression levels of TNF-α, Nsp, MMP-9 were significantly increased following I/R injury with a concomitant increase in the levels of proNGF and proBDNF in striatum and cortex, which were significantly reversed by TA Pre-treatment. It seems, OS plays a major role in mediating I/R injury induced altered levels of proNGF and proBDNF and seems to promotes apoptosis through the activation of p^{75NTR}.

c. Role of endoplasmic reticulum stress during cerebral ischemia/reperfusion

Endoplasmic reticulum (ER) stress is a consequence of accumulation of unfolded/misfolded proteins within its lumen. ER is emerging as an important source of apoptotic signaling as ER stress induced apoptosis is associated with a range of diseases including neurodegenerative disorders, diabetes, cerebral ischemia etc. Prolonged ER stress accompanied by failure of adaptive response seems to result in apoptotic cell death. Caspase-12 is the key player for the ER stress induced apoptotic cell death programme. However, the precise molecular mechanism of ER stress induced apoptotic cell death is not yet clear. The events of apoptotic regulatory machinery in cerebral ischemia/reperfusion (I/R) induced ER stress analyzed with a view to identify the molecular switch of apoptosis. Focal cerebral ischemia was induced in male SD male rats by using middle cerebral artery occlusion (2h) followed by varying time intervals of reperfusion. We have observed the enhanced expression of GRP78, CHOP and ATF-4 (hallmarks of ER stress) and TUNEL positivity, a marker for DNA fragmentation in affected brain regions at varying time intervals of reperfusion. These

findings strongly support the induction of ER stress and apoptosis as a consequence of I/R. Further, the co-localization of caspase-12 immunoflourescence with TUNEL staining indicates that caspase-12 appears to be associated with apoptotic cell death. Moreover, western blot analysis of subcellular fractions revealed that pro-caspase-12 (~55kDa) was processed into its active form and was found predominantly in the microsomal as well as in cytosolic fractions of striatum and cortex but in a low amount in the hippocampus of rats subjected to I/R. The caspase-12 activation peaked at 2h ischemia followed by 6h-24h of reperfusion. Interestingly, co-immunoprecipitation studies at 6h and 24h reperfusion revealed that tumor necrosis factor receptor-associated factor-2 (TRAF-2) an adaptor protein, was associated with caspase-12. Furthermore, inositol requiring enzyme-1β, an ER transmembrane protein kinase and ER stress sensor was also associated with caspase-12 at the above time points of I/R. It seems that these interactions are crucial for the activation of caspase-12 and further down stream signaling. These findings would further help to precisely understand the I/R induced ER stress mediated cell death signaling.

d. Role of NF_K-B in cerebral ischemia reperfusion

The search for effective neuroprotectants against ischemic insult is a key area of research in the field of cerebral stroke. Melatonin, a potent antioxidant, has shown to provide significant protection in various animal models of cerebral ischemia/reperfusion. Efforts were made to analyze the possible mechanisms by which melatonin confers protection against injury induced by cerebral stroke. As the transcription factor NF kappa B is important in regulating proteins involved in preventing apoptosis as well as in regulating molecules responsible for induction of inflammation, both of which are crucial in the outcome of ischemia, we have studied the effect of melatonin on NF kappa B activation. There was no significant change in the level of NF kappa B p65 in the nuclear fraction of cortex and striatum in melatonin treated rats.

e. Alteration in calcineurin activtty following cerebral ischemia/ reperfusion

The alterations in the CaN activity have been implicated in the pathogenesis of various neurological diseases. However the precise molecular mechanism of calcineurin regulation following I/R is still poorly understood. Therefore the present study was undertaken to elucidate the possible mechanisms involved in the down regulation of CaN following cerebral I/R. Male Sprague Dawley rats were subjected to 2h Ischemia followed by 0h, 3h, 12h & 24h of reperfusion. Neurological deficit (ND), GSH, MDA, SOD levels and cerebral infarct area was measured to assess the oxidative stress and brain damage. CaN phosphatase activity was measured using RII peptide as a substratre in the I/R affected brain regions. Gene expression levels of Can A, SOD-1, SOD-2 and Bcl-2 were analysed by using RT-PCR. Increased level of MDA and depletion of GSH stores following I/R clearly indicates oxidative stress. Calcineurin activity as well as gene expression has shown significant alterations in cortex as well as in striatum, whereas there was no significant change in hippocampus following I/R. Moreover, transcriptional upregulation of Bcl-2, SOD1 and SOD2 genes further supports the notion of calcineurin inactivation by oxidative stress. The study strongly supports the notion that oxidative stress and Bcl-2, a well known antiapoptotic and antioxidant molecule, might regulate the activity of calcineurin following cerebral I/R injury. This downregulation may be a net effect of several pathways including increased ROS which may cleave the active site of the enzyme rendering it into an inactive form or may be due to sequestration of CaN by Bcl-2.

f. Studies on the expression of NMDA receptor subunits following cerebral ischemia/reperfusion injury

Since its inception, the excitotoxic theory has been the centre of attraction in developing targets for cerebral ischemia. According to this, excessive glutamate is released from the pre-synaptic neurons due to persistent depolarization following cerebral ischemia. This overactivates the NMDA receptors on postsynaptic neurons, causing massive influx of Ca^{2+} leading to excitotoxicity, which culminates in the cell death. We have investigated the altered expression of NR1 & NR2b subunits of NMDA receptors in cerebral cortex of rats at various time points i.e. 1/0, 1/2, 1/4, 1/6, 1/12, 1/24 hours of cerebral ischemia /reperfusion injury. Western blot analysis of ischemic brain tissue showed an increase in NR1 subunit expression, which was maximum at 4-6 hours of reperfusion but declined to its basal level at 24hours post reperfusion. However, the NR2b subunit expression did not yield any significant result except at the 6 hour post reperfusion. Hence, it may be concluded that the altered expression of selective NMDA subunits may play a significant role in cerebral ischemia/ reperfusion injury.

g. Glutamate transporters: recent targets for neuroprotection

Glutamate induced excitotoxicity and ionic imbalance are the major early events of ischemic brain stress, which mediates injury at cellular and at the sub-cellular levels in neurons, astrocytes, microglia, oligodendrocytes and vascular elements. In order to protect brain cells from glutamate excitotoxicity, glutamate transporters may be of use to sequester it from the extracellular space.

The role of glutamate transporters GLT-1 was analysedin glutamate homeostasis following cerebral ischemia /reperfusion (I/R) injury. Western blot analysis showed that the expression of GLT-1 increased in early hours and subsequently decreased post 24h of reperfusion following 1 hour of ischemia in cortex while in striatum a significant decrease was observed in late hours of I/R injury. Pretreatment with ceftriaxone, a beta lactum antibiotic acting through GLT-1, showed a significant decrease in infarct area following 1/24 h of I/R injury. Efforts are on to unravel the role of glutamate transporters and their modulation by various pharmacological agents to unearth new neuroprotective strategies for prevention of stroke.

h. Neuroprotective role of AT1 receptor blockers in focal cerebral ischemia

Hypertension is a major risk factor for acute stroke. Neuroprotective role of AT1 receptor blocker Candesartan was assessed in model of focal cerebral ischemia in rat. Candesartan was given two hours prior to induction of ischemia for one hour and then at 24 hours post reperfusion for seven days. It reduced infarct area after cerebral ischemia. Neurological deficit was also improved by its treatment. Effect of this treatment has also been studied on reactive oxygen species. The study shows that besides producing antihypertensive effect, Candesartan may impart neuroprotection by reducing oxidative stress.

i. Role of NADPH oxidase in cerebral ischemia/reperfusion injury

Oxidative stress plays a detrimental role in progression of damage due to cerebral stroke. NADPH oxidase plays a pivotal role in the oxidative stress. We have examined the role of oxidative stress on cerebral damage following focal ischemia by studying oxidative stress parameters like GSH, MDA, SOD and reactive oxygen species at varying time points of reperfusion at 0hr, 3hr, 6hr, 12hr, 24hr, 168hr and 360hr after 1hr ischemia. Expression of different subunits NADPH oxidase (gp91 and p47) and cell survival/death signaling molecules like ERK and JNK was also studied at these time points.

Markers of oxidative stress increased following cerebral ischemia/reperfusion injury at 3, 6 and 12hr

and then began to decline at 24hr, 168hr and 360hr. Expression of different subunits of NADPH oxidase (gp91 and p47) also increased following cerebral ischemia/reperfusion injury and peaked at 12hrs. Identification of time points of markers of oxidative stress following cerebral ischemia/reperfusion will help in targeting intervention of antioxidative therapy at appropriate time.

2.2 Central Nervous System

2.2.1 Drug development

2.2.1.1 CSIR-Network programme

- **Anti-dementia**: 29 new samples were tested on scopolamine induced dementia in passive avoidance test in mice.
- **Anti-Anxiety activity:** 18 compounds were screened for anti anxiety activity using Elevated Plus Maze test in mice and none of them were found to be active.
- **Discovery Groups:** Samples of discovery groups (4) were evaluated in detail for anti-dementia potential on STZ (icv) model of dementia.
- **Anti-depression**: 23 samples were tested by swimming despair test in mice.

2.2.1.2 NMTILI [Ashvagandha]

Samples tested for CNS, memory and anti-depression activity, 2 samples showed significant anti-amnesic activity.

2.2.1.3 Appetite suppressants

Eleven synthetic compounds have been tested for appetite suppressants in scheduled fed rats at the dose of 20 µmol/kg, p.o. None showed significant activity.

2.2.2 Basic studies in CNS

2.2.2.1 Role of insulin in learning and memory functions in rodents

The effect of intracerebroventricular (ICV) injection of Streptozotocin (STZ) on expression of insulin receptors (IRs) was seen in the brain areas of SD rats. Rats were treated with ICV STZ (3mg/kg) bilaterally twice, on day 1 and day 3. Memory function was evaluated by Morris water maze test. Insulin receptor was analyzed by western blotting. The memory test was started on day 14 from 1st ICV injection of STZ and the rats were sacrificed on day 21 for estimation of insulin receptors in different rat brain areas: hypothalamus, hippocampus, cerebral cortex and cerebellum. In Morris water maze test the latency time to reach platform in ICV STZ treated group was significantly higher than control and vehicle (artificial CSF) trained, which indicates memory improvement. IR protein expression was found to be significantly increased in hypothalamus of trained group as compared to control whereas significant decrease was found in hypothalamus, hippocampus and cerebral cortex of STZ treated rats in comparison to control. The results indicate the involvement of brain IR in memory functions.

2.2.2.2 Standardization of IR protein expression studies in different regions of hippocampus in SD rat

Hippocampus region of the brain is mainly responsible in regulating the memory processes of the brain. The IR protein expression was studied by western blotting in different areas - CA1, DG and CA3 of hippocampus in control SD rat. In dentate gyrus (DG), the IR protein expression level was found higher in comparison to CA1 and CA3. Further studies are under progress to correlate IR in hippocampus with learning and memory functions.

2.2.2.3 Study on oxidative stress in rat brain areas

In vitro study was done on homogenates of different brain regions - striatum, mid brain, frontal cortex and hippocampus of adult male SD rats to compare the sensitivity of rat brain areas to oxidative stress. Effect of melatonin (antioxidant)

and nimesulide (Cyclooxygenase-2 inhibitor) was observed against oxidative stress induced by neurotoxins - LPS (lipopolysaccharide) and rotenone. Reduced Glutathione (GSH) as a marker of oxidative stress and malondialdehyde (MDA) an index of lipid peroxidation was estimated in homogenates of different brain regions. The brain areas showed different patterns of susceptibility to oxidative damage in relation to generation of free radicals as well as protection from antioxidant. These results indicate that sensitivity to oxidative stress of different brain areas may not be similar. Such variability in brain areas to respond against oxidative stress might be an important factor in free radical induced area specific neurodegeneration.

2.2.2.4 Effect of antidementia drugs on oxidative stress in icv streptozotocin induced model of dementia

The effect of antidementia drugs, tacrine and donepezil, on biochemical markers of oxidative stress, glutathione (GSH) and malondialdehyde (MDA) and acetylcholinesterase activity in the brain was studied in streptozotocin-induced experimental model of dementia in mice. Both tacrine- and donepezil-treated mice showed a significant improvement in streptozotocin (i.c.) induced memory impairment in Morris water maze test. Streptozotocin (i.c.) administration caused a significant decrease in GSH and increase in MDA in the brain as compared to control, indicating a state of oxidative stress in the brain of streptozotocin (i.c.) treated mice. Treatment in streptozotocin (i.c.) per treated mice with tacrine or donepezil did not cause significant changes in GSH and MDA levels in the brain as compared to control. Streptozotocin treated mice had raised acetylcholinesterase activity in the brain while there was a significant decrease in brain acetylcholinesterase activity in tacrine- and donepezil treated streptozotocin (i.c.) mice. Thus, results indicate that tacrine and donepezil, beside inhibition of acetylcholinesterase, may also suppress oxidative stress.

2.2.2.5 Standardization of LPS model of neuroinflammation

The model of neuroinflammation has been standardized by icv administration of LPS in SD rats. The LPS dissolved in 20 µl of artificial CSF and the effect had been studied 24 hrs after LPS administration. At 100 µg dose there was high mortality. The parameters studied were GSH, MDA, IL-1β, TNF- α, AChE activity in both DS and SS fraction in the Striatum, Cerebral Cortex, Hippocampus and Hypothalamus of rat brain. LPS 50 µg, icv of was selected for time dependent studies i.e. 4 hrs, 24 hrs, 48 hrs and 96 hrs after LPS. Results indicate that acute injection of LPS (50 µg, icv) is causing its neurotoxic effects at 24hr.

2.2.2.6 Study the effect of LPS on memory test

Effect of LPS was studied on Streptozotocin induced dementia in Morris Water Maze test. Rats have been trained for 5 days for complete learning after that LPS injection. No alteration in memory and learning was observed up to 15 days.

2.2.2.7 Study the effect of antidementia drug donepezil in LPS induced neuroinflammation

The effect of antidementia drug donepezil (2.5-10 mg/kg, po) was studied in the LPS induced model of neuroinflammation. The parameters studied are GSH, MDA, IL-1β, TNF- α, AChE activity in both DS and SS fraction. The brain regions studied were Striatum (Str), Cerebral Cortex (CC), Hippocampus (HP) and Hypothalamus (HT). Only the highest dose of donepezil i.e 10 mg/kg was found to be effective for normalizing GSH, whereas MDA, TNF-α, IL-1β and AChE activity in both DS and SS fraction were found to be attenuated in dose dependant manner.

2.2.2.8 Effect NOS and COX inhibitors on LPS induced oxidative stress

LPS produced significant elevation in the level of malondialdehyde and nitric oxide with a

reduction of reduced glutathione (GSH) in all brain regions of rats, whereas MPO significantly increased in cerebral cortex, hippocampus, thalamus and medulla. Pretreatment of indomethacin, celecoxib, L-NAME and curcumin significantly ameliorated the oxidative stress induced by LPS by reducing levels of MDA, restoring GSH content and normalizing the NO and MPO levels in the brain. The study showed that the COX and NOS inhibitors regulate the increased free radical generation during infections and LPS-induced oxidative stress.

2.2.2.9 *In vitro* studies on neuroinflammation

In vitro model for neuroinflammation has been established by exposing rat glioma cell line (C6) with Lipopolysaccharide (LPS) in different concentrations and by estimating the release of various inflammatory mediators released by activated C6 cells. Non cytotoxic concentration of LPS was assed by MTT assay on C6 cell line, which was up to 800 µg/ml. LPS was found suitable at 10 µg/ml dose to generate reactive oxygen species 160% measured by DCF-DA dye, Glutathione deficit 68%, increased NO production 3700%, increased COX-2 expression 6 fold and increased GFAP (Glial fibrillry acidic protein) expression 1.5 fold. Gugulipid dose dependently (3.12, 6.25, 12.5 µg/ml) reverts LPS induced changes in rat glioma cell line (C6) suggesting its potential role in treatment of neuroinflammation.

2.2.2.10 Role of serotonergic receptors in anxiety and depression

Various models of depression (tail suspension test, amphetamine potentiation test) and anxiety (elevated plus maze) have been standardised in mice and studied the effect of fluoxetine, a selective serotonin reuptake inhibitor, which increases serotonin levels at the synaptic cleft in these models and evaluated changes in their behaviour profile. Acute treatment of fluoxetine potentiates amphetamine induced hyperactivity and also shows anti-depressant effects against these depression models. However, it fails to show significant anxiolytic effect. Further work is in progress to evaluate the role of 5-HT1A receptor by modulating its action with specific agonist and antagonist treatment.

2.2.2.11 Alteration in dopamine receptor (D-1) density during stressful situations

In order to elucidate the role of dopaminergic receptors involved in stress induced alterations, we perform receptor binding studies of D-1 in two important dopaminergic rich brain regions i.e. striatum and cortex. Thus we aimed to evaluate possible alterations in the D-1 receptor density (B_{max}) and affinity (Kd) on exposure of acute stress (150 Minutes immobilization). Acute stress (AS) procedure resulted in a significant 25% increase in D-1 receptor density in striatum and a 43% decrease in cortex. In chronic unpredictable stress (CUS) there is a significant 60% increase in D-1 receptor density in striatum and 62% decrease in cortex. However, AS and CUS did not influence the binding affinities (Kd values) in any brain region.

2.2.2.12 Glucocorticoid receptor (GR) expression profile in hippocampus and cortex of rat brain under different stress models

In order to elucidate the effect of stress models on glucocorticoid receptor (GR) expression in brain we performed western blot analysis of cytosolic fraction of GR in hippocampus and cortex regions. We found a significant decrease of GR expression in both regions during chronic unpredictable stress (CUS). However acute stress (AS) and chronic stress (CS) did not show significant influence on GR expression (density) and thus suggesting that during CUS, persistent increase in corticosterone might down regulate the GR expression in these two stress sensitive brain regions.

2.3 Other disorders

2.3.1 Development of anti-inflammatory agents

A total of 27 compounds, 2 plant extracts and 5 samples of *Withania somnifera* have been evaluated for anti-inflammatory activity in carraginin induced paw oedema model in rats. Seven compounds showed promising activity.

2.3.2 Development of anti-ulcer agents

Total 29 crude extracts were screened for anti-ulcer and anti-anxiety activity and one of them showed anti-ulcer activity.

2.3.3 Elucidation of molecular mechanism of AP76P (WGI 76P) in gastric ulcer healing

Effect of AP76P on the expression of TNF-α, IL-1β and Vascular Endothelial Growth Factor (VEGF) against chronic ulcer healing in rats (10 days treatment) by RT-PCR and Western Blot analysis was observed. On administration of AP76P for 10days, we observed a downregulation in expression of TNF-α and upregulation of the growth factor VEGF in ulcerated tissues. Whereas, it remained ineffective in regulation of IL-1β induced in the ulcerated tissues. Further confirmatory studies are in progress in order to evaluate its mechanism of action.

2.3.4 Anti-ulcer activity of ICB-014-P04-A002

ICB-014-P04-A002 has showed significant anti-ulcer activity against different gastric and duodenal ulcer models in comparison to standard anti-ulcer drug, Omeprazole. It has been identified for IND filing.

2.3.5 Anti-ulcer activity of RBH08321P01

RBH08321P01 showed significant anti-ulcer activity in Cold Restraint Ulcer, Aspirin induced, Alcohol induced and Histamine induced gastric and duodenal ulcers. Further studies with the fractions of RBH08321P01 will be conducted.

2.3.6 Role of PPAR-γ in gastric ulcer healing

Role of PPAR-γ in regulation of gastrointestinal inflammation induced by ulcer have been confirmed by downregulation of mRNA expression of TNF-α and IL-1β and inhibition of translocation of NF-KB to the nuclear fraction in ulcerated tissues by pioglitazone (40mg/kg, p.o.) treatment. The effect of pioglitazone on expression of growth factors involved in ulcer healing was investigated. A number of different growth factors including Epidermal Growth Factor (EGF), basic Fibroblast Growth Factor (bFGF), Platelet Derived Growth Factor (PDGF), Trefoil Peptides (TP), Hepatocyte Growth Factor (HGF) and Vascular Endothelial Growth Factor (VEGF) have been implicated in the process of cell proliferation and restitution at the ulcer margin and in the formation of granulation tissue at the ulcer base. Of these, VEGF is a key regulatory factor of the angiogenic process. Significant increase in the VEGF protein expression on treatment with pioglitazone was observed. Thus pioglitazone might accelerate ulcer healing process via stimulation of angiogenesis. Other growth factors involved are yet to be determined.

2.3.7 Effect of melatonin against experimental reflux oesophagitis

In our preliminary studies we have observed a dose dependent effect of melatonin against reflux esophagitis. At a dose of 20 mg/kg melatonin showed significant protective effect in comparison to standard drug Omeprazole. Further, we have observed the effect of melatonin on lipid peroxidation, Glutathione levels (GSH), Superoxide Dismutase (SOD) activity in reflux esophagitis. Administration of melatonin decreased lipid peroxidation and increased GSH levels and SOD activity resulting in protective effects mediated against reflux esophagitis. This effect shown by melatonin may be due to its free radical scavenging

properties. Further work is being continued to evaluate the effect of melatonin against pro-inflammatory cytokines induced by reflux esophagitis.

2.3.8 Development of antidiabetic agents

2.3.8.1 *In vitro* activity (target based screening)

Total 66 synthetic compounds were evaluated for *in vitro* protein tyrosine phosphatase-1β inhibitory activity. Only four compounds S-005-941, S-005-559, S-005-560 and S-005-561 showed more than 50% inhibition in 100 μM dose. Out of 21 synthetic compounds, screened for DPP-IV inhibitory activity, two compounds, S-007-63 and S-007-64 showed more than 50% inhibition at 10 μM concentration. Similarly, 37 compounds for α glucosidase inhibition, 32 for glucose-6-phosphatase inhibition and 17 compounds for glycogen phosphorylase inhibitory activity were evaluated. None of them were found to have any significant activity.

2.3.8.2 *In vivo* activity

A total of 73 compounds were evaluated for antihyperglycaemic activity in sucrose loaded rat model at 100 mg/kg dose levels and two of them S-006-1634 and S-006-1635 showed promising antihyperglycemic activity.

2.3.9 Development of antidyslipidemic agents

2.3.9.1 Follow up studies of CDR-267 and CDR-269

These leads will undergo product development including chemical fractionation, isolation of single molecules, dose titration and comparison with reference drugs.

2.4 Safety Pharmacological Studies

Safety Pharmacological profile of candidate drugs PFO and 99/411 have been completed. IND filing and Safety Regulatory and Toxicology studies of WGI 76P (Batch no. 18) are under progress.

3. Area: Filariasis

(Coordinator: Dr. Shailja Bhattacharya)

Lymphatic filariasis has been and still is a major public health problem in India. The disease though is not fatal, but in chronic state, it is disabling and a cause of social stigma. Development of a macrofilaricide and/or female worm-sterilizing agent is today's urgent need. The project is being pursued with the objective to develop orally active macrofilaricides and female worm sterilizing agents, to define biochemical and immunological functions of parasites and host and to utilize genomic information in the identification of molecular targets for in vitro screening and *rational design of potential antifilarials and also to understand pathogenesis of the disease.*

3.1 Development of macrofilaricidal agents

3.2 Immunological studies on filariasis

3.3 Molecular cloning and characterization of *Brugia malayi* enzymes/proteins

3.1 Development of macrofilaricidal agents

3.1.1 Synthetic agents

Of 13 synthetic products tested against adult *B. malayi in vitro*, 3 compounds were found to be active.

Compound S-005-116 (100 mg/kg i.p. x 5 days) was moderately active in both *B. malayi/ Mastomys coucha* and jird models. Compounds S-005-898 and 771 at 100mg/kg, i.p. x 5 days did not exert desirable activity against adult worms in mastomys, thus not followed further.

3.1.2 Natural products

3.1.2.1 Plant extracts

Of the 6 CDRI plant extracts evaluated for antifilarial efficacy against *B. malayi* in mastomys, one plant 4726-A001 showed adulticidal action even on repeat testing at 62.5 µg/ml.

Twenty two CDRI new plant extracts were evaluated for antifilarial efficacy against *B. malayi* in *M. coucha* at 1 gm/kg, p.o. x 5 days. Extract Nos. 4701, 4708, 4712, 4673, 4717 showed adulticidal efficacy, 4713 revealed low microfilaricidal action (>53%) in *B. malayi* infected mastomys while the rest were inactive.

Two fractions of plant 4613 (F004 and F005) were effective *in vitro* against adult *B. malayi* showing LC_{100} of 15.6 µg/ml. Of the ten pure compounds isolated from this plant, K009 was found most effective *in vitro* showing LC_{100} of 7.8 µg/ml followed by K017.

3.1.2.2 Marine extracts

A total of 678 new marine extracts were tested *in vitro* against adult female *B. malayi* at 62.5 µg/ml conc., out of which 50 samples were found active using the motility and MTT assay. Repeat testing confirmed activity in 25 samples while 19 still await confirmation. The active extracts would be further evaluated to short list the most active ones for further follow-up.

The crude extract CDR-332-A001, at 300 mg/kg, orally x 5 days caused 41.1% adulticidal efficacy against *B. malayi* in mastomys. The other *in vitro* picked up extract AU2-357A001 also exerted almost similar macrofilaricidal action (43.3%) with no noticeable microfilaricidal or sterilization efficacy.

3.1.2.3 Bioactive molecules from traditional preparations

a. *In vitro* antifilarial activity of plant products against *B. malayi* adult worms

None of the 1609 samples received under this project demonstrated *in vitro* antifilarial activity on *B. malayi* adults at 62.5 µg/ml conc.

b. Follow-up studies on antifilarial activity of active plant products *in vivo*

Adulticidal activities of crude samples and fraction/sub-fractions of CSM0012P04 and RJM0069P03 were confirmed in *B. malayi-M. coucha* model and the findings were further validated in *B. malayi-jird* model. Experiments with crude extract and fraction of another active extract (NBR010P04) are in progress.

3.1.2.4 Antifilarial efficacy of ALB-1 + ivermectin against *B. malayi-M. coucha* system

An albendazole formulation, ALB-1 (200 mg/kg, p.o.x5 days) given with DEC (25 mg/kg, i.p.x5 days) produced prolonged mf suppression (68-95%) till day 90 of treatment with no additive adulticidal effect. ALB-1+ IVM produced better sterilizing effect on female worms than ALB-1 or IVM alone.

3.1.2.5 Wolbachia as antifilarial drug target

Tetracycline killed a good proportion of various developing larval stages of B. malayi in peritoneal cavity of jirds at 200 mg/kg when fed orally for 7/14 days. Recovered larval stages (which survived) showed poor development up to the adult stage on transfer to naive jirds and female worms lacked developing eggs/embryos. Doxycycline was highly effective in killing peritoneal micro- and macrofilariae with mf disappearing within 15 days with total female worm sterilization and 50/100% adult worm killing in 15/30 days at 25 mg/kg. The lower doses are being tried further. Tetracycline at much higher dose demonstrated inferior efficacy that too in 90 days.

3.2 Immunological studies on filariasis

3.2.1 Immunological characterization of recombinant myosin (BmAF-Myo) in rodent host

We have earlier reported on the purification of the recombinant *B. malayi* myosin by Ni-NTA column and the recombinant protein was found to offer protection against *B. malayi* infective larval challenge demonstrating ~78% reduced microfilarial density and ~58.8% decrease in adult worm establishment in mastomys. To characterize the recombinant protein further, Balb/c mice were vaccinated with purified BmAF-Myo (20 µg/animal) with Freund's complete/incomplete (FCA/FIA) adjuvant on days 0, 14 and 21.

The immunized mice displayed higher antigen-specific cellular proliferation and nitric oxide (NO) production with marked antibody-mediated cellular adherence to microfilariae. The animals also developed higher level (~128 fold) of antibodies to recombinant protein with predominance of IgG1, IgG2a, IgG2b and IgA isotype and low IgG3 and IgM levels. BmAF-Myo vaccination led to

increased production of Th1 cytokines (IFN-γ and TNF-α) *in vitro* within 24/48 h while Th2 cytokines like IL-4, IL-6, IL-10 remained at low level in both vaccinated and control groups. There was significant expansion of B cells (CD19), $CD4^+$ T helper cells, CD8a cytotoxic T cells and NK cells associated with increased expression of CD80/86 in vaccinated animals. No significant difference could be observed in the proportion of CD30 cells, a known Th2 cell surface marker. The findings thus revealed that *B. malayi* myosin predominantly elicits a Th1 immune response in Balb/c which possibly protects against a homologous infective larval challenge.

Further studies have been initiated on increasing the immunization efficiency of BmAF-Myo by using its liposomal formulation and human compatible adjuvants.

3.2.2 Characterization of identified inflammation-modulating molecules of *B. malayi* adults

B14 fraction appears to possess molecules that eliminate a good percentage (>65%) of adult parasites from the peritoneal cavity of host via NO production. Another fraction B6 when tested with sera of different categories of human bancroftian subjects and rodent host mastomys infected with *B. malayi* revealed predominant reactivity with IgG2 and IgG3 in clinical cases and IgG1 and IgG2a in chronic experimental infection.

3.2.3 Protective efficacy of liposomised BmAFII against establishment of *B. malayi* infection in *M. coucha*

Animals have been immunized with liposomized preparation of protective fraction of adult *B. malayi* (BmAFII) and subsequently challenged with L_3. Microfilaraemia in the tail blood of these animals is being monitored since day 90 post L3 challenge.

3.2.4 Development and establishment of *Leishmania donovani* in hamsters pre- and post-exposure to different life stages of filarial parasites

We previously reported that *B. malayi* L_3 were capable of inhibiting progression of leishmania infection in hamsters. Hamsters were exposed to *B. malayi* adult worms/mf and *L. donovani* infection either simultaneously or one infection before the other to see the effect of one infection on the susceptibility of the host to other infection. Results showed that the development of *L. donovani* infection is affected by adult filarial worms but not by mf. Filarial infection was not affected by *L. donovani* infection.

3.2.5 Cross protectivity of identified filarial antigen fraction (BmAFII) against leishmanial challenge

BmAFII fraction of *B. malayi* inhibited the progression of *L. donovani* infection in hamsters. Immunological responses of the host supported the findings.

3.2.6 Immune-interaction of *B. malayi* live-parasite stages with murine splenocytes

Different life-stages of *B. malayi* (infective larvae, adult male, female, microfilariae) were co-cultured with the host splenocytes *in vitro* in culture plates using inserts. The live infective larvae-lymphocytes co-culture caused marked lymphoproliferation while live female worm or microfilariae induced cellular hyporesponsiveness. All the live stages led to increased $CD4^+/CD8^+$ T cell expression. Live adult parasites of both sexes and infective larvae induced the release of proinflammatory Th1 cytokines (IFNγ/TNF-α) while microfilarial stages induced both Th1/Th2 cytokine responses. The incubation of all the live life-stages caused increased cellular oxidative burst except the male worm. The findings thus indicate that adult worms and mf stage appear to be responsible for cellular hyporesponsiveness as

observed in case of human microfilaraemic carriers. The adult worms and infective larvae principally induce pro-inflammatory immune responses while mf elicits both Th1/Th2 responses.

3.3 Molecular cloning and characterization of *B. malayi* enzymes/proteins

3.3.1 Filarial acetylcholinesterase

Acetylcholinesterase (AchE), an important enzyme of neuromuscular transmission, is found in many species of helminth parasites including filarial parasites. Earlier this enzyme from filarial parasite (pAchE) was partially purified, the two isozymes were separated and immunochemically characterized using specific substrates, inhibitors and polyclonal antibodies. Polyclonal antibodies produced in rabbits against purified pAchE1 and pAchE2 isoforms showed significant reactivity with *S. cervi* and *B. malayi* AchE but not with the host enzyme but could not differentiate the two isozymes. Monoclonal antibodies were also generated and one of these strongly inhibited the activity of parasite AchE, but could not differentiate the two isozymes of *S. cervi* AchE suggesting that both the isozymes are immunochemically similar, but different from the host enzyme.

In order to clone the filarial AchE gene, different set of degenerate primer were designed from the conserved sequences of AchE from related organisms and inserts of 0.8 kb and 0.6 kb were obtained with *S. cervi* genomic DNA as template. The *S. cervi* AchE gene fragments were cloned in pGEM-T plasmid vector. Efforts were also made to identify the full length AchE gene and primers were designed from the C terminal region of the known AchE sequences and 1.8 kb insert was amplified. The cloning and sequencing of the probable full length AchE gene is underway.

3.3.2 Molecular cloning and characterization of *B. malayi* hexokinase

Hexokinase (ATP: D-hexose-6-phosphotransferase, EC 2.7.1.1.) is key regulatory enzyme of glycolytic pathway. The product of catalysis, glucose-6-phosphate (G6P), also serves as a precursor for pentose phosphate pathway which yields NADPH and pentose sugars. Hexokinases can be distinguished based upon their molecular weight and sensitivity to inhibition by the product G6P. A full-length cDNA sequence derived from the 3' RACE and EST of *B. malayi* was cloned, sequenced and showed homology with *C. elegans* and *H. contortus* hexokinases. Further transformation, colony PCR screening and restriction showed a 1.7 Kb fragment. The cloned product was expressed in BL-21 (DE3) Rosetta cells. The kinetic properties of the expressed protein were studied. It phosphorylated glucose, fructose, maltose at different Km values and was strongly inhibited by various inhibitors but insensitive to glucose-6-phosphate. ADP noncompetitively inhibited the activity while PPi exhibited mixed inhibition. K_m values for substrates glucose, fructose, ATP indicated preferential utilization of glucose. The enzyme showed optimum activity at pH 8.4, temperature 40 °C and significantly inhibited by its various inhibitors viz., mannoheptulose, glucosamine, N-acetyl glucosamine, and PPi. The sulfhydral group inhibitors pCMB (p-chloromercuribenzoate), NEM (N-ethylmaleimide) and metal chelators viz., o-phenanthrolene and EDTA proved to be strong inhibitors of the enzyme. The inhibition by NEM and pCMB indicate the requirement of –SH group for the enzyme activity. Zymogram analysis was performed to validate the hexokinase activity of recombinant BmHk. Polyclonal antibodies against purified hexokinase were successfully raised in rabbit and the specificity of anti-BmHk antibodies was confirmed by ELISA and Western immunoblotting. The structural integrity and helix content of the recombinant protein was determined

by C.D. analysis. BmHk was a tetramer protein with a subunit molecular mass of 72 kDa and contained 37% α-helix and 26% β sheet.

3.3.3 Purification of cDNA Clones of *B. malayi* coding for infective larval stage proteins/enzymes

To identify and purify immunodominant antigens of human filarial species, immunoscreening of larval stage cDNA library of *B. malayi* was carried out. The hyperimmune serum was raised in *M. coucha* by vaccinating with 25 krads irradiated live infective larvae. The 6 clones obtained in primary screening were purified by repeated screening for further sequencing. NCBI BLASTn homology was searched with recently released *B. malayi* draft genome. The accession numbers were taken for these six cDNA clones, which showed similarity with different proteins viz. (1) *B. malayi* ribosomal protein S23 mRNA, complete cds, 510 bp, Accession No. DQ327712, (2) *B. malayi* clone rBmL3 immunogenic protein-like mRNA sequence, 1372 bp, Accession No. DQ464237, (3) *B. malayi* exonuclease/endonuclease/phosphatase family protein, Accession No. EU344984 (4) *B. malayi* L3SXP antigen mRNA, complete cds, 745 bp, Accession No. EF375724, (5) *B. malayi* allergen protein, Accession No. DQ327712 and (6) *B. malayi* super family II DNA/RNA helicase-like mRNA, complete cds, 1160 bp, Accession No. EF409381.

One of these clones, *B. malayi* DEAD box RNA Helicase was sub-cloned into expression vector and optimal expression was observed on 10% SDS-PAGE. Western blot with anti-His antibody confirmed the expression of protein. Cross-reactivity was checked by western blot with bancroftian human sera. ATP utilization assay was performed using this enzyme. It was found that dsRNA was the preferential substrate for the enzyme RNA Helicase. Further studies on characterization of this enzyme are underway.

3.3.4 Isolation of *S. cervi* antigen(s) equivalent to filarial circulating antigen

S. cervi antigen equivalent to circulating filarial antigen was purified by column chromatography and polyclonal antibodies raised in rabbit. Affinity purified IgG fraction from immune rabbit serum reacted strongly with *S. cervi* purified antigen, *W. bancrofti* Mf antigen, filarial circulating antigen and used for immunoscreening of *B. malayi* lgt11 cDNA expression library. Four cDNA clones (Bm-1, Bm-3, Bm-6, Bm-7) were picked up which on PCR amplification and agarose gel electrophoresis contained 0.7, 0.6, 1.5 and 0.4 kb inserts. The Bm-6 cDNA insert (1.5 kb insert) was cloned in pGEM-T sequencing vector and sequencing was done. The BLAST analysis showed homology to *B. pahangi* and *Loa loa* antigens. Attempts are in progress to get the complete sequence of Bm-6 cDNA clone and express the protein.

4. Area: Leishmaniasis

(Coordinator: Dr. Anuradha Dubey)

Visceral Leishmaniasis (VL) is a chronic and infectious disease which often becomes epidemic and leads to a heavy loss of human lives in many parts of the world, including India. In the face of new challenges of drug resistance, treatment failures, occurrence of relapses and convergence of HIV related VL cases, there is an urgent need to search for new and better alternatives of chemotherapy. Our program, therefore, envisages screening of synthetic compounds as well as extracts from plants and marine sources for antileishmanial activity, development of diagnostic kit of high specificity and sensitivity, studies in molecular mechanism of virulence and drug resistance and search for newer specific biochemical and molecular targets.

4.1 Development of potential antileishmanial agents

4.2 Development of reporter gene based screening models/assay system

4.3 Immunobiological studies

4.4 Cloning, over expression and characterization of *Leishmania donovani* drug targets

4.1 Development of potential antileishmanial agents

4.1.1 Antileishmanial screening

Novel synthetic moieties representing several prototypes viz. quinolines, quinoline derivatives, chromanochalcones, aryl chalcones, terpenyl, chalcones, pyrimidines, styryl pyrimidines, triazines, β-carbolinetriazines, aplysinopsin derivatives, indole derivatives, quinazolines, benzylidene derivatives, indolyl bisphosphonates and benzo cycloalkyl azoles derivatives (imidazoles and triazoles) were synthesized during the year for their evaluation against *in vitro* and *in vivo* experimental models.

A total of 707 agents were screened against *L. donovani* infection. of the 181 synthetic compounds screened *in vitro* against promastigotes, 117 compounds were found active at 10 µg/ml. Amongst these, 44 were found cytotoxic. Of the rest 73 nontoxic compounds, 31 have shown significant activity at 10 µg/ml concentration against intracellular amastigotes (80-100 % inhibition in parasite multiplication).

Of the 526 marine extracts, 10 extracts were active at 10 µg/ml concentration against promastigotes. Of these, only 3 extracts have shown promise against intracellular amastigotes. On the basis of sensitivity index (SI) 4 highly active extracts and 2 moderately active extracts were identified for *in vivo* trial in hamster model.

Based on leads from *in vitro* screening results and also compounds/plant extracts received directly for *in vivo* evaluation, a total of 10 synthetic compounds representing three different prototypes were evaluated *in vivo* against *L. donovani* / hamster model. Of these, 5 have shown moderate activity (53-62% inhibition) and one exhibiting 92% inhibition in parasite multiplication was selected for further optimization. Out of 16 plant extracts, 4 crude extracts have shown promise *in vivo*.

4.1.2 Follow up studies with active antileishmanial agents

A pure compound of plant 4666K004 have been reported to possess >80% antileishmanial activity. Several morphological and biochemical parameters were assessed to confirm the putative pathway responsible for death of *L. donovani* on treatment with this pure compound. It was found that 4666K004 is mediating apoptosis-like cell death in Leishmania parasite via loss of mitochondrial transmembrane potential. Various assays like exposure of phosphotidylserine, tunnel assay, DNA fragmentation confirmed our observation. Further studies are ongoing on target site of this compound.

4.2 Development of reporter gene based screening models/assay system

4.2.1 Stable Green Fluorescent Protein (GFP) Transfectants

Enhanced and stable expression of GFP in *L. donovani* clinical isolates was achieved by integrating GFP gene into the parasite genome at downstream of the 18S rRNA promoter region. These parasites expressed high levels of GFP in the absence of G418 drug pressure as no decrease in fluorescent intensity was observed in the absence of G418 for more than 12 months. These promastigotes were transformed into axenic amastigotes and they too express GFP gene. The application of these transfected parasite lines in the development of antileishmanial drug screening assays using Fluorescence Activated Cell Sorting (FACS) and 96-well microplate fluorometer is being explored.

4.2.2 Axenic amastigotes of *L. donovani* cells expressing luciferase reporter gene

Luciferase tagged *L. donovani* promastigotes were transformed in to axenic amastigotes in cell free medium. These axenic amstigotes also express luciferase gene. The transgenic amastigotes were tested for their sensitivity to sodium stibogluconate, SbIII, pentamidine and amphotericin B under *in vitro* condition and compared with that of promastigotes. The amastigote were found more sensitive than promastigotes towards these drugs except amphotericin B. Luciferase tagged *L. donovani* axenic amastigotes also maintained their infectivity to macrophages.

4.3 Immunobiological studies

4.3.1 Identification of Th1 stimulatory proteins for immunoprophylactic potential

The immunomodulatory F2 fraction (68-97.4 kDa) and its four sub fractions of soluble *L. donovani* proteins were characterized by 2D & MALDI-TOF. Lymphoproliferative responses of these 4 sub fractions, which were found to exhibit positive reactions against cured hamster lymphocytes, were further validated against cured/ exposed VL patients. These subfractions were assessed for their prophylactic potential either individually or in pooled form in combination with BCG against *L. donovani* challenge in hamsters. Interestingly, significant prophylactic efficacy was obtained in hamster vaccinated with pooled subfractions and generated considerably good cellular responses as compared to the individual subfractions. Further characterization of these subfractions by 1-DE and MALDI-TOF-MS revealed that out of total 18 proteins that have been identified five were hypothetical/unknown proteins. Other major immunostimulatory proteins

were Elongation factor-2, p45, Heat shock protein (HSP)-70, HSP-83, Aldolase, Enolase, Triosephosphate isomerase, Disulfideisomerase and Calreticulin.

4.3.2 Proteophosphoglycan of *L. donovani*

A partial gene (1.5 kb) of Proteophosphoglycan (PPG3) of *L. donovani* has been amplified using the primers of PPG 3 gene of *L. major*. The gene was sequenced, cloned in mammalian expression vector and expressed in BHK cells.

4.4 Cloning, over expression and characterization of *L. donovani* drug targets

4.4.1 Squalene Synthase (SSN)

Squalene Synthase (SSN) enzyme of sterol biosynthesis pathway is an attractive target. LdSSN has been cloned and confirmed by nucleotide sequencing. This was further sub cloned in expression vector pET-23a (+), transformed in E. coli host BL21 (DE3). Various parameters like IPTG concentrations, incubation temperatures, growth temperatures were optimized. Western analysis of recombinant protein with anti-his antibodies revealed a sharp band at 47 KD. The hydropathy plot revealed that the amino acids from 405-414 were highly hydrophobic in nature and therefore tend to bury inside the tertiary structure, thus taking the his tag inside and making it unavailable to bind with Ni-NTA matrix. Hence DNA of SSN-pGEMT was digested with NdeI and HindIII, ligated with pET28a(+) and transformed in E. coli expression hosts. SDS PAGE analysis and western with anti his antibodies confirmed the positive clone SSN-pET28a. Protein was purified from inclusion bodies in denaturating conditions by Ni-NTA spin columns for immunizing rabbits to generate antibodies against Squalene synthase.

4.4.2 Triose Phosphate Isomerase (TIM)

For over expression of TIM the complete ORF was subcloned in *E. coli* expression vector pET-23a (+), various parameters were standardized viz. *E. coli* host strains, IPTG concentrations, incubation temperatures before and after induction to get protein in soluble/active form. The whole amount of protein was found in inclusion bodies, so further studies were carried out to get the protein in soluble form by using *E. coli* rosetta cells but were unable to get protein in soluble form. LdTIM was sub cloned in pET- 43.1a (+) vector to obtain protein in soluble form. After optimizing the various parameters i.e. pH, temperature, IPTG concentration etc. the 50% soluble TIM was obtained at 0.1 mM IPTG induction with cells grown at 18°C. The protein was purified by using 6 x His of expression vector.

4.4.3 Trypanothione Reductase (LdTR)

Folding stability of recombinant trypanothione reductase was studied in presence of chemical purtubants. Chemical denaturants induced enzyme activity loss before any noticeable change in secondary structure. Interestingly, LdTR exhibited resistance to urea-induced denaturation with an intact active site disulfide. Further, the loss in secondary structure was found reversible to a significant extent.

4.4.4 Dipeptidyl carboxypeptidase (DCP)

Biochemical characterization and molecular modeling of recombinant LdDCP revealed that in contrast to angiotensin converting enzyme (ACE), NaCl significantly inhibit LdTR activity. Some divalent cations like Zn^{++} exhibited inhibitory effect on the enzyme while Ca^{++} had some stimulatory effect. Further, 3D model of LdDCP was constructed by means of comparative modeling using *E. coli* DCP as a template and compared with angiotensin convertion enzyme. Docking studies were carried out with captopril and compared with EcDCP and ACE.

4.4.5 Pteridine Reductase (PTR1)

The enzyme pteridine reductase 1 (PTR1) of *L. donovani* acts as a metabolic bypass for drugs targeting dihydrofolate reductase (DHFR), therefore, for successful antifolate chemotherapy to be developed against *Leishmania,* it must target both enzyme activities. *Leishmania* cells overexpressing PTR1 tagged at the N-terminal with green fluorescent protein were established to screen for proprietary dihydropyrimidone derivatives of DHFR specificity synthesized in our laboratory. A cell permeable molecule with impressive antileishmanial *in vitro* and *in vivo* oral activity was identified. Structure activity relationship based on homology model drawn on our recombinant enzyme established the highly selective inhibition of the enzyme by this inhibitor which was also confirmed by recombinant enzyme inhibition assay. It was seen that the leishmanicidal effect of this inhibitor is triggered by programmed cell death. Oligonucleosomal DNA fragmentation observed in Leishmania parasites as a result of induction by this inhibitor, is regulated by noncaspase proteases of the proteasome.

4.4.6 Actin network in *Leishmania* parasites

Actin is a highly conserved and indispensable cytoskeletal protein among eukaryotes and is known to regulate cellular physiology. Trypanosomatid actin however, possessed various peculiar structural and functional divergences which makes it an attractive therapeutic candidate. The studies on actin network of *L. donovani,* through characterization of actin and various actin binding proteins have revealed its role in cell division and motility. Purified recombinant *Leishmania* actin showed capacity to cycle monomer to polymer (G- to F-actin) and vice-versa and the polymers possess bundling propensity. The purified recombinant *Leishmania* actin did not respond to various classical tools such as phallotoxins, latrunculin, cytochalasin and DNaseI and hydrolyses ATP, significantly faster than mammalian actin. Apart from actin various actin binding proteins have also been studied which are supposed to regulate actin dynamics in these cells. It was demonstrated by gene knockout methodology that depletion of coronin (F-actin binding protein) results in improper cytokinesis and coronin null cells do not survive. Gene knockout studies with *Leishmania* ADF/cofilin homologue revealed essential roles in the flagellar motility function. The depletion of ADF/cofilin hampered flagellar growth and beating. Thus these findings demonstrated that actin in association with various binding partners is involved in various essential cell biological processes and therefore can be perceived as a potential drug target.

5. Area: Malaria

(Coordinator: Dr. S.K. Puri)

Malaria is a major health problem in many tropical countries, including India. Inspite of tremendous gains witnessed in biomedical research during 20th century, malaria continues to provide barriers to the global health community. The global problem of malaria is largely due to the emergence of parasite resistance to limited armamentarium of antimalarial drugs. The progress in our understanding of mechanism of action and resistance to traditional drugs, the emergence of artemisinins as one of the most important antimalarial class of compounds and determination of the genome sequence of malaria parasite promise a more optimistic future for antimalarial drug development. The focus of our research program is aimed towards development of novel, orally effective chemotherapeutic agents for treatment of drug resistant malaria; exploration of suitable drug combinations with available agents; validation of novel parasite-specific drug targets as a result of an improved understanding of the parasite biology and characterization of drug resistant parasites and SNP's linked to disease endemicity.

5.1 Chemotherapy of malaria

5.1.1 Synthesis and screening

Novel synthetic moieties comprising 662 compounds representing several prototypes viz. trioxanes, β-carbolines, aryl-amides, substituted quinolines, substituted triazines, substituted pyrimidines, peptide deformylase inhibitors, chalcones, thiazolidinones, lactone derivatives, lupeole derivatives, and urea / thiourea derivatives were synthesized during the year for evaluation against *in vitro* or *in vivo* experimental malaria models. In addition, 35 extracts/fractions from natural sources were prepared and evaluated for antimalarial activity.

5.1.1.1 Screening against *Plasmodium falciparum in vitro*

A total of 392 new synthetic compounds were screened against *P. falciparum* (strain 3D7) *in vitro* at various concentrations ranging between 50 ng/ml to 50 µg/ml. The screening protocol was designed to select chemical moieties exhibiting inhibition in maturation of ring stage parasites into

the schizont stage (MIC) during 36-40 hour incubation period. Compounds exhibiting activity at 1 µg/ml or lower concentrations were selected for *in vivo* evaluation. In addition a microfluorimetric assay employing SYBR Green nucleic acid dye was established to perform concentration response profile for active molecules. This assay has been standardized for use in lieu of previously employed radioactive- precursor-uptake based assay. A number of novel compounds representing 4-amino-thiourease quinolines, triazino-quinolines, quinolino-β-carboline derivatives, 4-amino-quinoline-triazines, 4-amino-quinoline- alkyl diamides, 9-anilino-acridine-triazines and thiazolidinione analogues have been identified with MIC below 0.1 µg/ml. Screening of several urea derivative compounds yielded novel quinoline urea and quinazoline urea compounds with MIC in the range of 0.25 to 0.5 µg/ml. Screening of 625 samples representing marine fauna against *in vitro* model did not yield any promising lead. In addition, nearly 1470 samples of natural origin were evaluated under a CSIR coordinated network programme and 2 plant extracts showing schizont maturation inhibition at 10 µg/ml concentration were identified for follow up.

5.1.2 Screening against *Plasmodium yoelii* - (N-67) Swiss mice model

A total of 34 synthetic compounds identified after activity response against *P. falciparum in vitro* were evaluated against chloroquine resistant *P. yoelii* (N-67) – Swiss mice model. These compounds represented four different prototypes viz. β-carbolines, 6-ureido-quinolines, quinazoline urea derivatives and quinoline triazines. Though none of these agents provided total clearance of parasites, some of the compounds exhibiting above 85% parasite clearance after 4 day treatment regimen were selected for further optimization. None of the 7 plant extracts evaluated against the same model showed any promising activity.

5.1.3 Screening against *P. yoelii* - (MDR) Swiss mice model

Screening of new peroxide generating derivatives was continued and 260 new compounds were screened at 96mg/kgx4 day, both p.o. and i.m. routes, against multi-drug resistant model *P. yoelii* in Swiss mice. Compounds exhibiting curative response during the 28 day observation period were revalidated and assayed at lower doses. Several novel trioxanes showing curative efficacy in a 24 mg/kg and 12 mg/kg x 4 day regimen were identified as the promising leads for follow up studies.

5.1.4 Follow up studies with compound 99/411

Synthetic endoperoxide compound 99/411 had been shown earlier to exhibit curative activity at 24 mg/kg dose in 4 dose regimen against *P. yoelii* - Swiss mice model and at 20 mg/kg dose in 5 day regimen against *P. cynomolgi*-rhesus monkey model. Our recent studies with this compound employing shorter regimen have established curative activity with 20 mg/kg x 3 days against *P. cynomolgi* - rhesus monkey model.

5.1.5 Combination chemotherapy

Drug combinations studies have been continued against *P. yoelii*- Swiss mice model employing combinations of identified endoperoxide compounds with two antimalarial drugs piperaquine and lumefantrine. An overview of the recent clinical trials has revealed that these two antimalarials have been extensively employed as partner drugs with available artemisinine derivatives. The isobologram plots of the ED_{90} responses after administration in combination with 97/78 and 99/411 points towards an additive action of such combinations. Observations on monitoring the curative response with such combinations have been successful in optimizing regimens providing total parasite clearance with two to four fold lower doses of the individual components. The curative response has also been obtained in combination studies with short duration regimens.

5.1.6 Arteether resistant rodent malaria model

A strain of rodent malaria parasite *P. vinckei* showing experimentally induced (>25 fold) stable resistance to arteether had been selected previously. In our attempts to understand the mechanism by which malaria parasites become resistant to arteether, a comparative estimation on status of anti-oxidant enzymes in parasite preparations from sensitive and arteether resistant rodent parasites had been made and studies had shown a marked increase in the levels of reduced glutathione in parasite preparations from resistant strain. Glutathione (GSH) is known to play a role in protection of cells against oxidative stress. Glutathione also has a role in degradation of non - polymerized heme in the food vacuole during intracellular growth of malaria parasites. We had earlier observed that GSH levels are higher in arteether resistant isolated parasites as well as whole blood samples as compared to those in arteether sensitive parasites. Concurrently we have also observed that hemozoin content in arteether sensitive parasites is more than the arteether resistant parasites, thereby showing an inverse relationship between the GSH level and the hemozoin content. In the resistant parasites the decreased hemozoin production is associated with increased GSH levels. Hence it is tempting to hypothesize that arteether resistance is associated with a shift from polymerization of heme into hemozoin to GSH mediated disposal of heme in rodent model. This has been experimentally validated by treatment of resistant parasites' infected mice with buthionine sulfoximine (BSO, a specific inhibitor of GSH synthesis) which leads to a marked increase in the hemozoin production and depletion of intracellular GSH in concentration dependent manner. Administration of BSO concurrently with arteether also suppresses the growth of arteether resistant parasites *in vivo*. The effect of BSO in modulating the infection profile with arteether resistant parasites and in the increased production of hemozoin could be related to inhibition of GSH synthesis in resistant parasites.

5.2 Immunology of malaria

5.2.1 Merozoite surface protein-1 and circumsporozoite protein of *P. vivax* and *P. cynomolgi*

Plasmodium vivax is the second most important disease causing malaria parasite of humans, but the major lacuna with evaluation of vaccines against *P. vivax* is that there is no *in vitro* culture system and the *in vivo* method requires a highly specialized monkey malaria model. *P. cynomolgi bastianelli,* a parasite of rhesus monkeys, has been shown to be closely related to *P. vivax* and the two parasites share a similar clinical course of infection, a reticulocyte-specific preferential invasion, presence of Schuffner's dots on infected erythrocytes, a dormant liver hypnozoite stage and a similar genomic GC content. In our previous studies, we have evaluated the *P. cynomolgi* rhesus monkey model system for demonstrating the protective potential of *P. vivax* MSP1-42 kD recombinant antigen and monkeys immunized with *vivax* and *cynomolgi* MSP1-42 kD antigens had shown significant reduction in parasite burden. These findings suggest that *P. cynomolgi* rhesus monkey model can be used to evaluate the protective efficacy of prime vaccine candidates of *P. vivax* having high homology with *P. cynomolgi* such as the circumsporozoite protein (CSP) and the merozoite surface protein1 (MSP1-42). Earlier we have produced monoclonal antibodies (MoAb) against the conformational epitopes of *P. cynomolgi* and *P. vivax* MSP1 antigen. The epitope mapping revealed common as well as specific conformational and linear epitopes of *P. vivax* and *P. cynomolgi* MSP-1 antigen.

Efforts on further characterization of the target epitopes of these monoclonal antibodies were directed towards cloning the gene inserts of $MSP1_{42}$ and $MSP1_{19}$ of *P. cynomolgi* B. PCR amplification of MSP1 (42 and 19 kDa) gene was performed using specific primers and *P. cynomolgi* B genomic DNA. The PCR products from *P. cynomolgi* B MSP1 (42 and 19) were cloned in pGEM-T Easy vector. The

sequencing of the *P. cynomolgi* B $MSP1_{42}$ and $MSP1_{19}$ DNA clones was done and BLAST analysis revealed that the amplified fragments are of *P. cynomolgi* B $MSP1_{42}$ and $MSP1_{19}$. The cloned fragment of *P. cynomolgi* B $MSP1_{42}$ was excised using BamH1 and HindIII restriction enzymes and cloned in expression vector (pTriEx4) at BamH1 and HindIII site. The recombinant fragment was expressed using IPTG and fusion protein of 60 kD was obtained. The optimum conditions for expression of $MSP1_{42}$ protein were standardized and maximum expression was obtained at 0.1 mM IPTG at 25-30°C. Studies to purify, refold and characterize the *P. cynomolgi* $MSP1_{42}$ recombinant protein and express $MSP1_{19}$ proteins are in progress.

The *P. cynomolgi* B CSP gene fragment was PCR amplifed using CSP specific primers and *P. cynomolgi* B genomic DNA, and a PCR fragment of 1.3 kb was obtained. The *P. cynomolgi* B CSP (1.3 kb) gene fragments was cloned in pGEM-T Easy vector and sequenced to confirm the identity by BLAST analysis. Efforts are underway to express the *P. cynomolgi* B CSP gene.

5.3 Biochemistry of malaria

5.3.1 Cloning and expression of transketolase of *P. falciparum*

Transketolase (TK EC 2.2.1.1) is the key enzyme of non-oxidative segment of Pentose Phosphate Pathway, which normally transfers two carbon unit from xylulose-5-phosphate to ribose-5-phosphate or erythrose-4-phosphate generating glyceraldehyde-3-phosphate (G3P), sedoheptulose-7-phosphate and fructose-6-phosphate (F6P) in the process. Recent studies have suggested that this enzyme has chemotherapeutic potentials for developing novel drugs. The transketolase gene was cloned in TOPOT7-NT cloning and expression vector and transformed in DH5β cells. TOPOT7-PfTk construct was transformed in BL21 DE3 Rosetta cells for expression of protein. The expressed protein was purified by affinity chromatography on Ni-NTA column and ammonium sulphate precipitation. The molecular mass of purified protein was found to be 70 kDa. The native molecular mass of purified protein was found to be 418 kDa by size exclusion chromatography indicating hexameric nature of protein. Polyclonal antibodies against purified transketolase were raised in rabbit and specificity of anti-PfTk antibodies was confirmed by ELISA and Western immunoblotting. The purified protein was biochemically characterized and it utilized fructose-6-phosphate and hydroxypyruvate as substrate. The transketolase inhibitor viz, p-hydroxyphenylpyruvate,-SH group inhibitors (pCMB, NEM) and metal chelators (EDTA, o-phenanthrolene) significantly inhibited the enzyme activity. The inhibition by NEM and pCMB indicated involvement of –SH group in enzyme activity. A homology model of *P. falciparum* transketolase was built based on the crystal structure of homologue transketolase of *S. cerevisae*. Superposition of PfTk homology model on template revealed close structural resemblance of modeled PfTk with template. The structural integrity and helix content of the recombinant protein was determined by C.D. analysis.

5.3.2 Bilirubin mediated inhibition of *P. falciparum* growth through augmentation of oxidative stress

Free heme is very toxic for malaria parasite because it generates highly reactive hydroxyl radicals to cause oxidative damage. Detoxification of free heme by the heme oxygenase (HO) system is a very common phenomenon by which free heme is catabolized to form bilirubin as an end product. Interestingly, the malaria parasite, *P. falciparum,* lacks an HO system, and it forms hemozoin, mainly to detoxify free heme. Our studies have shown that bilirubin significantly induces oxidative stress in the parasite as evident from the increased formation of lipid peroxide, decrease in glutathione content, and increased formation of H_2O_2 and OH^-. Bilirubin

can effectively inhibit hemozoin formation also. Furthermore, results indicate that bilirubin inhibits parasite growth and induces caspase-like protease activity, up-regulates the expression of apoptosis-related protein (Gene ID PFI0450c), and reduces the mitochondrial membrane potential. Scavengers of OH^- such as mannitol, as well as the spin trap alpha-phenyl-n-tert-butylnitrone, effectively protect the parasite from bilirubin-induced oxidative stress and growth inhibition. These findings suggest that bilirubin, through the development of oxidative stress, induces *P. falciparum* cell death and that the malaria parasite lacks an HO system probably to protect itself from bilirubin-induced cell death as a second line of defense.

5.4 Molecular biology of malaria

5.4.1 Identification and analysis of proteins involved in *P. falciparum* apicoplast DNA replication

Nuclear-encoded *P. falciparum* homologs of *E. coli* gyrase A and gyrase B subunits were analysed for their role in replication of the apicoplast genome. Our earlier studies with the plastid-like organelle in *P. falciparum,* the apicoplast, have dealt with the expression and purification of recombinant PfGyraseB (~115 kDa) and determination of ATPase activity of PfGyrB (K_m, ~120 µM; K_{cat}, ~0.024 sec^{-1}), enhancement of PfGyrB ATPase activity in the presence of DNA and inhibition of ATPase activity by novobiocin, characterization of inhibition of parasite growth by novobiocin in culture, reduction of apicoplast/nuclear DNA ratio in the presence of novobiocin indicating apicoplast DNA replication as the site of action of the drug, expression and purification of the cleavage and religation domain of PfGyrA, generation of antibodies against PfGyrA and PfGyrB and detection of uncleaved and processed forms of PfGyrB and processed form of PfGyrA in *P. falciparum* lysates, immuno-localization of PfGyrB in the apicoplast and molecular modeling of PfGyrA and PfGyrB to understand drug action and inhibition profiles. Although replication of the apicoplast genome is a validated drug target, the proteins involved in the replication process are only partially characterized. We analyzed DNA-protein interactions at a plDNA replication ori region and identified a nuclear-encoded DnaJ homolog that binds directly to ori elements of the plDNA molecule with high affinity. The PfDnaJ homolog, identified after MALDI-TOF analysis and peptide mass fingerprinting, was cloned and expressed as a recombinant protein in *E. coli.* Recombinant PfDnaJ also bound the ori sequence with high affinity. Inhibition of binding with anti-PfDnaJ antibodies confirmed identity of the protein in DNA-binding experiments with organellar protein fractions. The DNA-binding domain of the ~69 kDa PfDnaJ lay within the N-terminal 38 kDa region that carries DnaJ signature motifs. In contrast to PfDnaJ in parasite organellar fractions, the recombinant protein interacted with DNA in a sequence non-specific manner. The protein was detected in parasite lysates and localized in the apicoplast by immunofluorescence confocal microscopy. Our results suggest a role for PfDnaJ in replication/repair of the apicoplast genome.

5.4.2 Functional analysis of proteins putatively involved in apicoplast-specific pathways

Studies on three additional putative apicoplast-targeted proteins were initiated. Nuclear genes annotated as prokaryotic translation elongation factor EF-Ts and [Fe-S] complexation protein SufC have predicted interacting partners encoded by the apicoplast genome. The current annotations are based on sequence identity and lack functional confirmation. Moreover, apicoplast translation is a validated drug target while the Sufs may play a critical role in maintaining oxidative potential of the apicoplast. We also analysed function of the hypothetical protein PFI0230c that exhibits homology with histone like DNA-binding protein

(HU) of bacteria and *Toxoplasma gondii*. Its possible role in nucleoid organization and/or DNA replication is of interest. The following progress was made in these programmes:

(i) EF-Ts: Translation elongation factor Tu (EF-Tu) is encoded by the apicoplast while its predicted interacting partner, EF-Ts, is nuclear-encoded. We have previously localized EF-Tu in the apicoplast and studied the effect of the prokaryotic translation inhibitor, thiostrepton, on apicoplast EF-Tu levels. In order to analyse PfEF-Tu and PfEF-Ts interaction, the gene encoding PfEF-Ts has been PCR-amplified from parasite cDNA and cloned into the pGEX-KG vector. GST-tagged mature protein (65 kDa) has been expressed in soluble form in *E.coli* and purified by affinity chromatography. Cleaved, processed EF-Ts has been obtained. Specific antibodies have been generated against PfEF-Ts. These recognize a ~46 kDa full-length form as well as a ~39 kDa processed form (after cleavage of signal and transit peptide) in parasite lysates indicating that the predicted apicoplast-targeting sequence is cleaved *in vivo*. Recombinant EF-Tu has also been expressed as a fusion protein with GST. The GTP-binding and GTPase activity of apicoplast EF-Tu has been assayed and the nucleotide exchange reaction mediated by EF-Ts has been observed by fluorimetry using Mant-GDP. Interactions between EF-Tu and EF-Ts have also been observed by co-elution of the two proteins on affinity columns. The ability of apicoplast EF-Ts to mediate nucleotide exchange on *E. coli* EF-Tu has been investigated.

(ii) SufC: The suf operon of *E. coli* comprises six genes and is involved in iron metabolism/ assembly of [Fe-S] clusters/oxidative stress response. Components of a similar system have been identified in *P. falciparum* and are likely to function in the apicoplast. While the sufB homolog (ycf24) is encoded by the apicoplast genome, homologs of the other components of this pathway are nuclear-encoded. We initiated studies on two interacting components of this pathway-SufB and SufC. The region of the *P. falciparum* sufC gene encoding the predicted processed protein has been PCR-amplified and cloned in the pQE30 vector. Soluble mature protein (29 kDa) has been obtained and purified by Ni-NTA chromatography. The ATPase activity of recombinant SufC has been characterized. The enzyme exhibits a hyperbolic dependence on ATP concentration, follows Michaelis-Menten kinetics, and hydrolyzes ATP with a K_m of ~21 μM and K_{cat} of ~0.052 sec^{-1}. An internal portion of SufB, the predicted interacting partner of SufC, encoded by the apicoplast genome has also been expressed. Interaction between the two Sufs has been investigated by their co-elution from affinity columns.

(iii) Hypothetical protein PFI0230c that exhibits similarity with histone-like DNA-binding protein (HU) of bacteria has been identified. The *P. falciparum* protein has 31.3 % identity (55% similarity) with the *T. gondii* Hu protein and 31.3% identity (71% similarity) with the Chloribium histone-like DNA-binding factor. The protein carries predicted apicoplast-targeting elements. Recombinant 14 kDa protein has been expressed in *E. coli* and dimeric and tetrameric forms of the protein have been observed in solution. Antibodies against PfHU recognize the protein in parasite lysates with maximal expression observed in the schizont stage.The recombinant protein is capable of binding supercoiled DNA and linear DNA with greater affinity for the former. PfHU condenses DNA *in vitro* at a protein/DNA mass ratio ~10. Overexpression of PfHU in *E. coli* results in condensation of bacterial DNA visible as tight dot-like structures in a fluorescence microscope. The targeting and binding of PfHU to the apicoplast is indicated by ChIP assay using anti-PfHUAbs. Apicoplast-specific DNA sequences are immunoprecipitated and amplified in the assay while no signal is observed for parasite nuclear DNA.

5.4.3 Analysis of SNPs related to susceptibility/resistance to *P. falciparum* malaria in populations across India and case-control studies for genotype-disease association in *P. falciparum* endemic and non-endemic regions in India

Fifty five subpopulations (>1850 samples) of different linguistic lineages, geographical regions of habitat, and ethnicity have been analysed. Data from SNPs of 10 genes related to susceptibility/ resistance to *P. falciparum* malaria in other world populations has been obtained in phase 1 and phase 2 (genotype analysis carried out by Sequenom mass array). Differentiating SNPs have been identified and their frequency maps have indicated interesting correlates with disease endemicity. Further, F_{st} analysis carried out using data from five malaria-related SNPs, indicated that a population in the Terai belt exhibits maximal genic variation. Interestingly, this population is known to be resistant to malaria. Extension of this F_{st} analysis to include larger number of SNPs from other genes, previously correlated with malaria in other world populations, identified populations from the eastern endemicity belt as highly differentiated from other populations of the country.

We have initiated case-control studies for determining disease association of specific SNPs with severity of *P. falciparum* malaria in India. Samples of patients and ethnically-matched controls have been collected from field surveys and hospitals in Uttar Pradesh (non-endemic region), Chhattisgarh and Orissa (endemic regions). Initial genotyping of candidate SNPs and cytokine and CR1 level analysis in patients and controls followed by association statistics has indicated interesting variations from reports from other countries. SNPs of the TNF-α enhancer/promoter and the FcãRIIa exon4 G/A R131H SNP were examined for possible association with severity of *P. falciparum* malaria in individuals from a malaria-endemic and a non-endemic region of India. Frequency distribution of FcãRIIa R131H and TNF-α promoter/enhancer SNPs, including a novel TNF-α –76 T>A SNP, analysed in populations across India was used to plan a control panel for combined analysis of patient and control samples from the two regions. Individuals carrying minor alleles of the TNF-α -1031 T>C and -863 C>A SNPs as well as those homozygous for the haplotype CACGG (-1031C, -863A, -857C, -308G, -238G) had enhanced plasma TNF-α levels. Additionally, minor alleles of –1031 and –863 SNPs and the CCCGG haplotype were associated with increased susceptibility to severe malaria.

The high-affinity IgG2 binding FcãRIIa 131H allele was significantly associated with protection from disease manifestation, with stronger association observed in the malaria non-endemic region. Higher frequency of the FcãRIIa AA genotype in populations from *P. falciparum*-endemic and 'high risk' areas of the country is suggestive of selection due to malaria.

Regulatory and coding region SNPs of cytokines IL4, IL12β, IL13, adhesion molecules ICAM-1, PECAM-1, CD-36 and the complement receptor CR1 have been genotyped and their distribution and association with disease has been investigated.

6. Area: Microbial Infections

(Coordinator: Dr. Ranjana Srivastava)

The objective of the project area covers the development of vaccines for cholera and tuberculosis, development of rapid molecular screens for drug screening, screening of synthetic compounds and natural products for antitubercular, antifungal, antibacterial and antiviral activity, development of diagnostics for tuberculosis infection, construction of mycobacterial vectors, novel antigens and drug targets, basic studies on mycobacterial, bacterial and fungal proteins and virulence genes.

6.1 Cholera

The recombinant TolC (VC1565) protein of *Vibrio cholerae* was over expressed and purified in sufficient quantities to generate crystals of the protein for determination of 3-D structure. Variation in incubation conditions have not yielded positive results and hence will continue in the current year.

The regulatory mechanism of regulatory elements VC0973 and VC0974 on virulence determinants of *V. cholerae* by transcriptional analysis is under investigation.

6.2 Tuberculosis

6.2.1 Evaluation of synthetic compounds and extracts for *in vitro* activity against *M. tuberculosis*

The synthetic compounds (in house) (66), marine extracts/ fractions (39) and natural extracts (3) were tested for antitubercular activity by agar dilution method and radiometric BACTEC system using *M. tuberculosis* H37Rv as test strain. 2 fractions of a marine extract were found to be active at 50 and 100 µg/ml respectively. Out of 66 synthetic compounds, 18 were identified having activity in range of 0.79 - 6.25 µg/ml against *M. tuberculosis* H37Rv. Cytotoxicity of the active molecules was tested in Vero cells, mouse and human macrophage cell line.

6.2.2 Identification of genes of *M. tuberculosis* upregulated during residence in lungs of infected mice

The genes of *M. tuberculosis* upregulated during residence in lungs of infected mice were identified in an *in vivo* expression system based on kanamycin resistance from a promoter library of *M. tuberculosis* constructed in a promoter trap shuttle vector pLL192 (constructed in lab) containing an artificial bicistronic operon composed of promoterless green fluorescent protein gene followed by kanamycin resistance gene. 20 genes

belonging to fatty acids metabolism, membrane transport, nitric oxide defence and PE_PGRS/PPE family were identified. Real Time PCR analysis using RNA isolated from *M. tuberculosis* grown *in vitro* and from the lungs, confirmed upregulation of genes from 2 to 20-fold *in vivo* compared to growth *in vitro*.

6.2.3 Identification of proteins of *Mycobacterium bovis* BCG expressed during adaptation to anaerobic non-replicating persistence

M. bovis BCG was adapted *in vitro* from aerobic growth to a state of anaerobic non replicating persistence characterized by non dividing cells, low metabolic activity, sensitivity to metranidazole and <1% dissolved oxygen. Proteome analysis of differentially expressed mycobacterial proteins during adaptation to anaerobic non replicating persistence by two-dimensional gel electrophoresis, mass spectrometry, and database searching, revealed 34 proteins, out of these 28 proteins showed either unique or increased expression and 6 proteins were downregulated. The identity and expression of proteins were confirmed by DNA microarray covering all known transcripts of *M. tuberculosis* H37Rv genome. These proteins are those involved in fatty acid oxidation, intermediary metabolism and respiratory pathways of mycobacteria, suggesting their role in persistence.

6.2.4 Identification of genes of *M. tuberculosis* upregulated during anaerobic persistence by fluorescence and kanamycin resistance selection

In vivo Expression Technology (IVET) was applied to identify upregulated genes in an *in vitro* simulated condition of anaerobic persistence likely to be encountered by the pathogen in lung granulomas. A promoter library of *M. tuberculosis* constructed in plasmid pLL192 was subjected to hypoxic condition (dissolved oxygen <1%) in a controlled fermenter to monitor differential expression of mycobacterial promoters in aerobic and hypoxia conditions. On the basis of green fluorescent protein fluorescence and kanamycin resistance, the upregulated promoters were selected, identified by nucleotide sequence and the expression levels of genes belonging to the identified promoters were then individually confirmed by Real Time PCR analysis.

6.2.5 Role of suscitation factor (Rpf) genes in resuscitation of dormancy in mycobacteria

The *rpf* genes of *M. tuberculosis* and *Micrococcus luteus* were cloned and expressed in *E. coli*. The recombinant proteins were able to resuscitate the aged, dormant BCG cells generated during extended stationary phase. Gene expression changes were followed from stationary phase through the transition to resuscitation phase by whole genome expression profiling by microarray and proteome analysis. *M. tuberculosis* H37Rv microarray were custom designed using multiple 60 oligonucleotides covering all known transcripts of *M. tuberculosis* H37Rv genome. Array was designed at Genotypic Technology (P) Ltd. using Agilient Technologies e-Array platform. Genes highly upregulated (upto 40 fold) are being validated by Real Time PCR.

A bacterial two hybrid system based on interaction-mediated reconstitution of the adenylate cyclase activity in *E. coli* has been adopted to identify interacting partners of Rpf proteins in *M. tuberculosis*. Three *M. tuberculosis* proteins have been identified which show positive interaction with Rpf protein of *M. tuberculosis* and *M. luteus*. The genes have been cloned and over expressed in *E. coli* for further interaction analysis of Rpf with purified proteins.

The role of Rpf in reactivation of nonreplicating persistent (NRP) bacilli in *M. fortuitum* - murine latency model (developed in lab) is being investigated. The expression of *rpf* genes was found

to interfere with the onset of non replicating persistent (NRP) state *in vitro* as well as in mice.

6.2.6 Drug targets

The genes of AHAS, a key enzyme in the pathway to the biosynthesis of the Branched chain amino acids (BCAAs) from *M. tuberculosis* along with selected genes expressed during persistence and *in vivo* infection as probable drug targets were cloned and overexpressed in *E. coli*. The knock out mutants of these genes in *M. tuberculosis* are being constructed by allele exchange and intron mediated gene disruption methods. *In silico* methods were used to design inhibitors of ICL enzyme of *M. tuberculosis*. Few molecules have been identified which inhibit the enzyme activity of recombinant ICL enzyme (cloned from *M. tuberculosis* and expressed in *E. coli*) and growth of *M. tuberculosis*.

6.2.7 Biology of interaction between macrophages and *M. tuberculosis*

Eis (Rv2416c) and Erp (Rv3810) are reported to enhance the virulence of *M. tuberculosis* in macrophages. Yeast Two Hybrid method has been adopted to explore the interacting partners of Eis and Erp proteins in host. Using human macrophage and *M. tuberculosis* library cDNA, interacting partners of these two proteins have been identified and are being confirmed by co-immuno precipitations. Analysis of the data is under progress.

6.2.8 Interaction of macrophage PKCs with Serine Threonine Kinases of mycobacteria

Study on expression of different isoforms of PKCs during interaction of macrophage with pathogenic and non-pathogenic mycobacteria revealed that novel (calcium independent) PKC iosforms are phosphorylated during the invasive process. The studies show that pKnG of mycobacteria has direct correlation with PKC alpha of macrophages.

6.2.9 Elucidation of mechanism of action of anti-tuberculosis molecules through proteomics

The proteomic data on known drugs rifampicin and isoniazid are being explored to define a pathway specific stimulon or proteomic signatures which might prove useful in identifying novel drugs that act within or without that pathway. The proteomic signature of the effect of sub lethal concentrations of isonizaid and rifampicin on the proteome of *M. tuberculosis* is being analyzed by two dimensional gel electrophoresis. Based on 2-D gel electrophoresis and peptide mass mapping using MALDI-mass spectrometry, 18 differentially expressed proteins of the bacillus have so far been identified.

6.2.10 Construction of recombinant *M. aurum* for screening of FASII pathway inhibitors and expression of Sigma Factor in different mycobacterial species

A recombinant mycobacterial strain carrying H37Rv kas operon promoter in fusion with *E. coli* lacZ gene has been reconstructed that shows induced synthesis of reporter molecule after inhibition of FAS-II pathway by specific inhibitors.

Comparative analysis of the *M. tuberculosis* (H37Rv) and *M. aurum* kas operon promoters is in progress. Presence of *sigF* gene in *M. smegmatis* and its expression at different stages of growth is being investigated.

6.3 Fungal Infection

6.3.1 *In vitro* and *in vivo* evaluation of compounds

A total of 707 (synthetic 342, marine 316, and plants 49) compounds/extracts were evaluated for *in vitro* antifungal and antibacterial activity. Eight synthetic compounds (MIC 0.01-25 µg/ml), three marine extracts (MIC 1.9-62.3 µg/ml), and four plant extracts/fractions (MIC 7.8-25 µg/ml) were

found active against *Candida albicans, C. parapsilosis* (ATCC 22019), *Cryptococcus neoformans, Sporothrix schenckii, Aspergillus fumigatus* and *Trichophyton mentagrophytes*. The marine extract NIT-204 A001 (100 mg/kg p.o. x 7 days) and the synthetic compound NCL-19 (50 mg/kg p.o. x 7 days) were found active *in vivo* against *C. albicans* infection (i.v) in mice and reduced the CFU load in kidney significantly.

6.3.2 Generation of monoclonal antibodies against *C. albicans* and *A. fumigutus*

Eight new sequences of dodeca-peptides based on CDRs and their flanking regions were identified with the help of "Predicted Antigenic Peptides' software and synthesized for evaluation of activity against *C. albicans*. 24 clones for *C. albicans* and 2 for *Aspergillus fumigatus* from fresh fusion experiments with GPI anchored protein (HF puyridime extracted cell wall) of *C. albicans* as well as metabolic proteins of *Aspergillus fumigatus* have been identified.

Strains of *C. albicans* (ATCC 10231) resistant to amphotericin B, fluoconazole and 5-flucytosine were isolated showing enhanced MIC 400 µg/ml against fluconazole (original MIC 6.25 µg/ml) and 5-fllucytosine (original MIC 3.12 µg/ml) and 62.5 µg/ml against amphotericin B (original MIC 0.02µg/ml). The microscopic examination revealed distinct morphological differences between control and resistant strains. 2-D gel electrophoresis analysis of amphotericin B resistant strain revealed 3 proteins which were over expressed in resistant strain. These proteins were identified through MALDI-MS and MASCOT data base search with a significance level of >65%.

The amphotericin B resistant strain was studied for spheroplast formation and regeneration in order to study protein expression during cell wall formation in the presence of amphotericin B. Western blotting with polyclonal sera (against lyticase treated cell wall) highlighted a protein whose expression varied with the concentration of amphotericin B. Identification and characterization of this protein is under progress.

6.4 Viral Infection

120 marine extracts were tested for *in vitro* activity against Japanese encephalitis (JE) virus in Vero cells. The *in vitro* antiviral activity of extracts was determined as inhibition of viral cytopathic effect in Vero cells infected with Japanese encephalitis virus. Three fractions of an active extract showed 100 % CPE inhibition at 7.8 µg/ml.

7. Area: Natural Products

(Coordinator: Dr. Rakesh Maurya)

Chemical and pharmacological investigation of Indian medicinal plants and marine flora/fauna for isolation of active constituents to obtain new therapeutic agents.

7.1 Bioactivities of medicinal plants

7.2 Modification of natural products

7.1 Bioactivities of medicinal plants

7.1.1 Antihyperglycaemic/ Antidyslipidemic activity

7.1.1.1 Plant 4554: Antihyperglycaemic

Ethanolic extract (C002) and aqueous extract (C003) were evaluated for antihyperglycaemic activity in sucrose loaded rat model at 250 mg/kg p.o. dose level; the percent antihyperglycaemic activity was calculated to be around 13.5 and 34.4 respectively.

The aqueous extract (C003) was evaluated for antihyperglycaemic activity in STZ-S model at 250 mg/kg p.o. dose level, the percent antihyperglycaemic activity was calculated to be around 25.1 (5h) and 24.3 (24h); Four compounds have been isolated.

7.1.1.2 Plant 4699: Antihyperglycaemic

Ethanolic extract (A001) showed significant antihyperglycaemic activity in sucrose loaded rats (28.8%) and streptozotocin-induced diabetic rats (16.5% at 5h; 22.5% at 24h) models, at 250 mg/kg p.o. dose levels.

7.1.1.3 Plant 4665: Antihyperglycemic

Ethanolic extract (A001) showed significant activity of 21.2% at the dose of 250 mg/kg. Isolation of the compounds from the active extract is in progress.

7.1.1.4 Plant 4499: Antihyperglycemic

Twelve derivatives of active compound K027 from 4499 were synthesised and evaluated for their antihyperglycemic activity. Amongst these, two compounds, S-006-1634 and S-006-1635 showed glucose lowering of 15.7% and 18.2% respectively at 100 mg/kg in STZ-S model.

7.1.1.5 Plant 4698: Antidyslipidemic

Ethanolic extract (A001) at 500 mg/kg dose, was found to reduced serum cholesterol by 27%, serum LDL and TG were decreased by 33% and 49 %, respectively. Therefore, ethanolic extract was fractionated into four fractions; F002, F003, F004 and F005. Fractions F002 and F005 were found to be active.

7.1.1.6 Plant 4655: Antidyslipidemic

Ethanolic extract (A001) and its four fractions (F002, F003, F004, F005) have been evaluated for antidyslipidemic activity. The activity is localized in hexane fraction (F002). 3 Diterpenes (K005, K008, K009) have been isolated from active fraction F002. 6 Alkaloids (K016-K021) have been isolated and characterized from fraction F003. K021 is under evaluation for antistroke activity.

7.1.1.7 Plant 4049: Antidyslipidemic

Ethanolic extract (C002) showed good antidyslipidemic activity with the respective lowering of 70% (TG), 20% (TC), 27% (Gly) with increase in HDL (16%) and HDL/TC (48%) at the dose of 500 mg/kg. One new compound, alongwith two known compounds have been isolated from the extract.

7.1.1.8 Plant 4714: Antidyslipidemic

Ethanolic extract (A001) was found to lower the lipid profile by 38% (TG), 23% (TC) and 30% increase in HDL/TC ratio at the dose of 100 mg/kg. Further fractions showed antidyslipidemic activity in two fractions (F002 and F004).

7.1.1.9 CDR-134F194: Antihyperglycemic

CDR-134F194, which is in the preclinical phase, the regulatory pharmacology and toxicity studies have been completed.

7.1.1.10 CDR-324: Antihyperglycemic

Ethanolic extract (A001) showed promising activity in SLM and STZ-S models at 250 mg/kg dose. Isolation of compounds from active fraction is in progress.

7.1.1.11 CDR-150: Antihyperglycemic

Antidiabetic activity was reconfirmed in the extracts C003 and C004 prepared from the repeat collections. Isolation of compounds from active fraction is in progress.

7.1.2 Anti-stress activity

7.1.2.1 Plant 38: Anti-stress

Five derivatives were prepared from active compound K116, a compound previously isolated from n-butanol fraction (F005). Three derivatives were found to be effective in normalizing all parameters of acute stress (hyperglycemia, increased corticosterone, CK and adrenal hypertrophy) and hence will be further studied in chronic unpredictable stress model.

7.1.2.2 Plant 2659: Anti-stress

Four new compounds K037, K044, K080 and K092 were isolated, from the n-butanol fraction of plant 2659. Only one compound was found to be effective in reverting the alteration induced in acute stress model.

7.1.3 Antiulcer activity

7.1.3.1 Plant 4483: Antiulcer

Ethanolic extract (C002) was studied against different ulcer models and showed significant antiulcer activity. Activity guided fractionation and isolation is in progress.

7.1.4 Antiparasitic activity

7.1.4.1 Plant 4601: Antileishmanial

Two alkaloids have been isolated and identified from the stems of 4601 plant. These compounds are under antileishmanial activity testing.

7.1.4.2 Plant 4666: Antileishmanial

Ethanolic extract (A001) showed promising activity in vivo at the dose of 500 mg/kg x 5 p.o. The active extract was fractionated into chloroform (F002) and aqueous fraction (F003). F003 was found to be active and from this active fraction, two active compounds, K004 and K006 were isolated along with two inactive compounds, K005 and K007. K004 and K006 depicted significant

percent inhibition at 100 mg/kg. The K004 has been studied for its mode of action and dose-dependency. It induced apoptosis like cell death without affecting the host cells by targeting DNA topoisomerase with no cytotoxic effects.

7.1.4.3 Plant 4613: Antifilarial

Different class of compounds (seven) were isolated and characterized. These compounds are under bioevaluation.

7.1.5 Anti-osteoporotic activity

7.1.5.1 Plant 1020: Anti-osteoporotic

Ethanol extract and n-butanol fraction of plant 1020 showed promising osteogenic activity. 8 Compounds from chloroform fraction 16 compounds have been isolated from n-butanol fraction. These compounds were evaluated for anti-osteoporotic activity and five compounds were found to show promising osteogenic activity. The three active compounds have been synthesized and activity was reconfirmed.

Extracts of leaves, flowers, seeds and twigs of plant 1020 were evaluated only leaves extract showed weak osteogenic activity.

7.1.5.2 Plant 914: Anti-osteoporotic

Ethanol extract (C002) administered to overiectomized (OVX) rats showed improvement in BMD. Activity guided isolation is under progress.

7.1.6 Anticancer activity

7.1.6.1 CDR 350: Anticancer

Ethanol extract (A001) showed anticancer breast activity (60 % inhibition at 10 µg/ml in MCF-7 cell line). Ethanol extract (A001) was fractionated in to F002 (Hexane), F003 (Chloroform), F004 (n-Butanol) and F005 (Aqueous) fractions. 6 New and 4 known compounds were isolated from active fraction (F002). New compounds K027 and K028 showed significant activity in different cancer cell lines.

7.1.6.2 Plant 4698: Anticancer

Ethanol extract A001 has shown antibreast cancer activity. Its four fractions (F002, F003, F004 and F005) are under bioevaluation.

7.1.6.3 Plant 4655: Anticancer

Six alkaloids (K016-K021) have been isolated and characterized from chloroform fraction (F003) for anticancer activity testing. Ten new benzocoumarin derivatives were prepared for anti-breast cancer activity and 2 compounds showed significant activity comparable to Tamoxifen.

7.1.7 Antistroke Activity

7.1.7.1 Plant 4400 and 4705: Antistroke

Ethanol extracts of plant 4400A001 and 4705A001 showed significant antistroke activity, isolation of compounds are in progress.

7.1.8 Anti-inflammatory activity

7.1.8.1 Plant 4406: Anti-inflammatory

Two compounds (K021 and K023) showed dose dependant analgesic and anti-inflammatory activities.

7.2 Modification of natural products

Transformation of solanesol (antidiabetic), lupeol (antimalarial), seselin (antithrombotic) and psorlene continued. Four compounds derived from lupeol and a psorlene derived tetrahydro β-carbolin (S-006-837) have shown inhibition at 10 µg/ml and 2 µg/ml *in-vitro* against *Plasmodium falciparum* respectively. Compound derived from seselin (S-001-556) was prepared for detailed antithrombotic evaluation.

8. Area: Newer Approaches in Drug Design and Discovery

(Coordinator: Dr. S.B. Katti)

The project area envisages exploring and exploiting emerging technologies like structural biology, in silico design and x-ray crystallography towards lead generation and optimization of drug like molecules. Structural studies on small and macromolecules and identification of druggable targets

8.1 Studies on protein folding

8.1.1 *Plasmodium falciparum* glutathione S-transferase

The malarial parasite *P. falciparum* possesses only one typical glutathione S-transferase. This enzyme, PfGST, cannot be assigned to any of the known GST classes and represents a most interesting target for antimalarial drug development. PfGST is present as a tetramer in solution and dissociates into dimers in the presence of GSH. Using size exclusion chromatography and protein cross-linking as well as fluorescence and CD spectroscopy in combination with enzyme activity assays we studied this unique feature of PfGST in detail. Our data indicate that the dimer – and not the tetramer – is the active form of PfGST, and that substrate saturation is directly paralleled by dissociation of the tetramer. As observed after removal of GSH, this dissociation is a reversible process indicating that the dimer-tetramer equilibrium of PfGST is defined by the surrounding GSH concentration. Our results contrast with previous studies, which proposed that GSH binds to the inactive dimeric enzyme converting it into active dimer. Neither the presence of GSSG, nor of H_2O_2 or ferriprotoporphyrin IX influence this equilibrium indicating that it is not a redox-dependent process but solely depends on the availability of GSH. We show that the PfGST tetramer has significantly higher stability against pH changes and GdnHCl denaturation when compared with the dimer. Since the dimerization does not cause major alterations in the secondary

or tertiary structure of PfGST the enhanced stability of the tetramer is likely to be due to stronger ionic interactions existing in it. PfGST is the first GST for which a regulation of quaternary structure and activity by GSH has been demonstrated.

8.1.2 *Toxoplasma gondii* Ferredoxin-NADP$^+$ Reductase (TgFNR): Role of ionic interactions in stabilization of native conformation and structural cooperativity

The apicoplast and the proteins present therein are parasite-specific targets for chemotherapy of apicomplexan parasites. Ferredoxin-NADP$^+$ reductase (FNR) is an important enzyme present in the apicoplast of *T. gondii* that operates as a general electron switch at the bifurcation step of many different electron transfer pathways. In spite of its importance as drug target not much structural information on the enzyme is available. Using fluorescence and CD spectroscopy in combination with enzyme activity measurement and size exclusion chromatography we studied the pH dependent changes in structural properties and inter-domain interactions in TgFNR to understand the interactions responsible for stabilization of native conformation and structural cooperativity in the enzyme. Under physiological conditions, TgFNR is stabilized in an open conformation. Strong interactions exist between the NADP$^+$- and FAD-binding domains thus making the enzyme a structurally cooperative molecule under these conditions. The inter-domain interactions also enhance the stability of the FAD-binding domain. The open conformation of the native enzyme was found to be essential for its optimum functioning, as induction of compactness/rigidity lead to decrease in the functional activity. Under acidic conditions (pH about 4), the inter-domain interactions present in native TgFNR were lost and the enzyme became structurally non-cooperative. The pH induced structural modification in the NADP$^+$ binding domain, more precisely compaction of the conformation, leading to loss of inter-domain interactions is probably the underlying reason for loss of structural cooperativity in the enzyme molecule under acidic conditions. The studies demonstrate the significance of electrostatic interactions both in stabilization of native conformation and maintenance of structural cooperativity in TgFNR.

8.2 X-ray crystallographic studies

The primary objective of this programme is cloning, over-expression, purification and biochemical characterization of select proteins from pathogenic sources. X-ray crystal structures of the proteins are then used in *in-silico* approaches to identify potential inhibitors which are then subsequently verified by *in vitro* assays. Co-crystal structures with identified inhibitors would enable further lead optimization. During this period the crystal structures of the *M. tuberculosis* Feast/ Famine regulatory protein and complexes with a variety of amino acid effectors have been solved. The structures suggest novel regulatory mechanisms in this protein. The protein is a novel drug target against persistence. Secondly, Crystal structures of Lysine e-amino transferase (LAT) from *M. tuberculosis* and some mutants have been solved in a variety of enzyme states and complexes with substrates. This enzyme is reportedly more than 40-fold upregulated in the latent/persistent stage of *M. tuberculosis*. The structures have revealed the basis for the reaction specificity of the enzyme. Mutational analysis has identified key residues essential for enzyme activity. Two novel inhibitors of the enzyme have been identified by virtual screening. Crystal structures of the 35kD co-factor binding domain of *M. tuberculosis* LigA earlier reported from this laboratory has been used to identify novel inhibitors viz. tetracyclic indoles with specificity for LigA over human DNA ligase I.

8.2.1 Small molecule X-ray crystallographic studies

Crystallization and 3D- X-ray data collection of 32 compounds of biological and structural importance were done. Structure determinations and refinements of 25 compounds were completed. Structure analysis of eight pyrazolo[3,4-d]pyrimidine molecules were performed in order to study weak non-covalent interactions. The studies showed the presence of both intra- as well as intermolecular interactions of the types p…p, C-H…p, S….Ar. and C-H…N. The X-ray crystallographic studies of five pyran-2-one derivatives were performed and they showed the presence of weaker hydrogen bonding interactions apart from van der Waals interactions. The confirmation and conformational studies of two carbohydrate-derived molecules were performed and they also showed the presence of weaker hydrogen bonding.

8.3 Computational biology and bioinformatics in drug discovery

A vibrant program to provide integrated environment for informatics systems, computational chemistry and molecular modeling and to facilitate drug design and discovery in different target therapeutic areas is the major endeavor of this project area. A large part of theoretical efforts are focused on understanding more about how biology works at molecular level, to develop 3-D molecular models of proteins-protein/ligand complexes and exploit the structural information for the identification and design of novel inhibitors.

8.3.1 Prioritizing structure based virtual screening hits using structure interaction fingerprints to identify novel inhibitors of different drug targets from *M. tuberculosis*

In continuation of our efforts to identify new chemical entities endowed with activity against *M. tuberculosis,* we have employed an integrated approach to prioritize target specific anti-tubercular compounds using ligand and structure-based virtual screening and subsequently, we have employed structure interaction fingerprints to prioritize the leads. We are using five well known anti-tubercular targets to validate our approach. Structure interaction fingerprints were used to examine conserved interactions across the five proteins considered in this study. These conserved interactions can be used to understand critical determinant for inhibitor binding and selectivity and to prioritize leads from virtual screening. The degree of conservation of interactions in five protein-inhibitor complexes was determined by exploring the frequency of contacts at each residue position for each of the five protein targets.

8.3.2 Development of computational predictive models

Structure-based investigations and development of computational predictive models for structure-activity relationship studies including molecular docking and CoMFA and CoMSIA 3D-QSAR studies were carried out on Pyrrolidine Carboxamide inhibitors as antimycobacterial agents and human mitotic kinesin Eg5 inhibitors as anticancer agents. The results provided clear guidelines and reasonably good activity predictions for novel inhibitors design.

We have also demonstrated, using molecular modeling studies that a new series of 4,5-dihydronaphthofurans and dibenzofurans, possess good inhibitory activity against PTP1B. Our molecular docking studies show that the hydroxy and the carbomethoxy functionalities at the adjacent positions on dibenzofuran scaffold are crucial for inhibitory activity as they are involved in a number of H-bond interactions with important residues in the PTP1B binding site. A series of dibenzofurans demonstrated good inhibition against PTP1B and are useful candidates as leads for the development of potential antihyperglycemic agents. Further studies in this area are currently in progress.

8.4 Structural genomics of *M. tuberculosis* proteins using NMR spectroscopy

We have achieved a significant milestone by solving structure of the potential drug target protein peptidyl-tRNA hydrolase from *M. tuberculosis* H37Rv (MtPth) in solution by NMR spectroscopy. We have assigned ~2100 NOEs derived from ^{15}N-edited NOESY-HSQC and ^{13}C-edited NOESY-HSQC experiments and have used the distance constraints, dihedral angle constraints, and hydrogen bond constraints to generate an ensemble of 40 structures using the software CYANA-1.0.5. This ensemble of 40 structures represents the solution structure of MtPth and has been deposited in PDB under ID 2JRC. Parallely, we have measured the amide ^{15}N T1, T2 and ^{15}N{^{1}H} heteronuclear NOE and have used these parameters for detailed dynamic analysis of the protein. Our results highlight the dynamic interaction of the protein with its substrate peptidyl-tRNA.

We have preformed analysis of complex formation and immune response for CFP-10 and ESAT-6 T-cell antigens of *M. tuberculosis* H37Rv. This study will be very useful for introducing beneficial mutations into recombinant BCG vaccines which will improve its efficacy. We have identified inhibitors of chorismate mutase (Rv1885c) from *M. tuberculosis* H37Rv.

8.5 Structural and function studies of proteins, antimicrobial peptides and design of peptide inhibitors

Recently, we have been working on the role of an amphipathic leucine zipper motif found in melittin. Results showed that the substitution of heptadic leucine(s) by single or double alanine residue(s) appreciably reduced the cytotoxic activity of melittin without affecting its antibacterial activity. Moreover, we designed novel antibacterial peptides on the basis of classical amphipathic leucine zipper sequence with or without alanine substitution at 'a' and/or 'd' position of the heptad repeat, which showed remarkable variation in hemolytic activity against human red blood cells but exhibited similar antibacterial activity. However, despite these studies still it is not clear whether the leucine zipper sequences possess a general role in controlling the cytotoxicity in antimicrobial peptides. With a goal to understand the general structural and functional roles of heptad repeats in the antimicrobial peptide family, two small stretches of heptad repeat sequences at both N- and C- terminal of two cathelicidin-derived antimicrobial peptides of bovine origin (BMAPs) have been identified. Cathelicidin-derived peptides exhibit a diverse range of lytic activity against Gram-negative and Gram-positive bacteria, parasites and enveloped viruses and considered as potential lead molecules for developing antimicrobial agents. The selected cathelicidin-derived bovine antimicrobial peptides possess broad-spectrum antimicrobial activity and also lyse normal human cells like red blood cells and neutrophils. In order to investigate the basis of cytotoxic activities in these bovine antimicrobial peptides and also to understand the roles of the identified heptad repeat stretches, both the wild type peptides and their several analogs were synthesized and characterized after substituting the amino acids at 'a' and/or 'd' positions of the heptad repeats of the peptides by alanine. The alanine-substituted analogs exhibited significantly reduced cytotoxicity against the human red blood cells and murine 3T3 cells compared to the respective wild type peptides. Interestingly, these analogs showed comparable lytic activity against the selected Gram (+)ve and (-)ve bacteria to the respective wild type peptides. The results further revealed that each of the wild type peptides and their respective analogs showed similar localization, assembly onto these bacteria and induced comparable permeability in them. However, only the wild type peptide but not its analogs assembled and localized onto the hRBCs and 3T3 cells and permeabilized them. Combining

our previous results the present data indicated a possible general role of the heptad repeats in maintaining assembly of the antimicrobial peptides in mammalian cells and their cytotoxicity. Our results also showed the evaluation of structural and functional roles of a phenylalanine zipper sequence in an antimicrobial peptide for the first time.

8.6 Synthesis of combinatorial libraries

8.6.1 Synthesis of tetrahydro-ß-carbolines via Pictet–Spengler reaction

A mild and efficient protocol for the Pictet–Spengler reaction in water using an acid catalyst has been developed. The condensation of tryptophan, tryptamine, and N_b-benzyl tryptophan with different aldehydes having both electron-withdrawing and -donating substituents in the presence of a catalytic amount of TFA in water furnished tetrahydro-ß-carbolines in good isolated yields. A salient feature of the water mediated Pictet–Spengler reaction is the general trend observed during the condensation of Trp-OMe and aryl/aliphatic aldehydes furnishing diastereomeric mixtures with a preference for the cis-isomer. This has been extended to deactivated heterosystems. The Pictet-Spengler reaction generally involves condensation of an β-aromatic amine attached to electron-rich aromatic rings with aldehydes leading. Recently, we developed a modified strategy wherein, aromatic amines originating from activated heterocyclic rings represented second generation substrates for the Pictet-Spengler reaction. During the course of endo cyclization with our modified substrates, we observed that 1) the cyclizations occurred with a wide variety of aldehydes having both electron-donating and withdrawing substituents and 2) the rate of Pictet-Spengler reaction in substrates (Second generation) with aryl amine was faster than the conventional Pictet-Spengler reaction substrates (First generation) having aliphatic amine. The faster rate of reaction for aryl amine substrates can be attributed to the enhanced electrophilicity of the resulting imines that has been documented as the driving force for endo cyclization. This led us to envisage that owing to the enhanced electrophilicity of the imine derived from aryl amine, the cyclization can be affected even when aryl amine is linked to a deactivated heterocyclic ring. Accordingly, we designed and synthesized substrate with an aryl amine originating from a deactivated quinoxaline ring. The reaction of this substrate with aromatic aldehydes in general, furnished imine with sufficient electrophilicity that triggered endo cyclization even in the presence of a deactivated nucleophile.

In continuation of our studies on the application of aryl amine substrates for the Pictet-Spengler reaction, we have further examined the efficacy of our modified approach on bicyclic substrates with aryl amine originating from carbon of the bicyclic ring. Initially we selected imidazopyridines and imidazothiazoles as bicyclic substrates and converted them into Pictet-Spengler substrates by allowing aryl amines to originate in a manner to facilitate endo cyclization when treated with alddehydes. The reaction of the substrates with a variety of aromatic aldehydes in general, furnished polycyclic skeletons based on azoles and pyridines hitherto not reported.

8.6.2 Cu-$FeCl_3$-mediated one-pot multi-component reaction leading to N-aryl/alkyl triazoles in water

A concise, convenient and mild route for the one-pot syntheses of N-aryl/alkyltriazoles in water has been developed. The methodology involved three-component reaction comprising phenyl acetylene, sodium azide and aryl/alkyl halide catalyzed by Cu (I) species generated *in situ* by a redox reaction between $FeCl_3$ and copper metal. Prominent features of the methodology are: 1) incorporation of aryl fluoride to generate N-aryl triazoles whose reports are rather scarce, 2) use of water as reaction medium, and 3) avoidance of hazardous aryl azide as a reactant.

8.7 Novel methodologies for peptide design and synthesis

During this period we have been working on the design and synthesis of peptidominetics for type-2 diabetes. Diabetes is a chronic metabolic syndrome caused by insulin deficiency that affects millions of people world wide. The disease is marked by the insufficient secretion of insulin or development of resistance to insulin. The long-term effects of elevated blood sugar (hyperglycemia) include damage to the eyes, heart, feet, kidneys, nerves and blood vessels. This clearly highlights the urgent need for novel chemotherapeutic agents for the treatment of diabetes. Therefore we have chosen protein tyrosine phosphatease-1β (PTP1β), dipeptidyl peptidase (DPP-IV) and peroxisome proliferator-activated receptors-gamma (PPAR-γ) as targets for the development of novel antidiabetic agents. The progress of work during the period of report is as follows.

8.7.1 Peptidomimetcs as selective inhibitors of PTP-1γ

Protein tyrosine phosphatases (PTPs) belong to a growing family of enzymes which are involved in the regulation of a variety of cellular events. The current estimate is that humans have as many as 1000 phosphatase genes and many show high selectivity and specificity. PTP1B is a cytosolic phosphatase consisting of a single catalytic domain which is considered to be a receptor-like PTP. Recent studies showed that PTP-1γ attenuates insulin signaling by catalyzing dephosphorylation of insulin receptors (IRs). By inhibiting this enzyme selectively the insulin receptors can be maintained in its active form. Therefore, PTP-1γ has emerged as an attractive target for the development of drugs for type-2 diabetes. We have been working on the lead optimization of a dipeptide by developing peptidomimetics to improve its potency and selectivity. During this period 20 new compounds were synthesized and evaluated for PTP inhibition *in vitro*. Some of the compounds have shown significant inhibition (>70 % at 10 μM) of PTP-1γ enzyme.

8.7.2 DPP-IV inhibitors as potential antidiabetic agents

GLP-1 is an incretin hormone released from the L-cells in the intestine upon food intake and stimulates insulin secretion from the beta-cells in the pancreas. It is also reported that the GLP-1 helps to regenerate the degenerated beta cells in the pancreas. GLP-1 is rapidly degraded *in vivo* through the action of dipeptidyl peptidase IV (DPP-IV), to give the inactive form of GLP-1. Dipeptidyl peptidase IV (DPP-IV) is a widely distributed serine protease. It has been demonstrated that selectively inhibiting the DPP-IV results in the protection of GLP-1 from its degradation thereby enhanced insulinotropic activity. Therefore, DPP-IV is an excellent target for development of drugs in the management of type-2 diabetes. DPP-IV is a highly specific aminopeptidase that cleaves Xaa-Pro and modification of pro to pyrolidine result in the antagonistic activity. Therefore, we have chosen Xaa-prolidide as prototype for the lead optimization by designing several peptidomimetics. During this period 28 new compounds were synthesized. These compounds are being evaluated for their inhibition activity *in vitro.*

8.7.3 Synthesis of PPAR-γ agonist

The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor supergene family that play a central role in the regulation of the storage and catabolism of dietary fats. The three subtypes of peroxisome proliferator-activated receptors bind to fatty acids and fatty acid metabolites and regulate the expression of genes involved in the transport, metabolism and buffering

of these ligands within the cells. PPAR-γ is an important target for the development of antidiabetic agents. However, this class of compounds exhibit liver toxicity. We have designed several molecules with objective to minimize the toxicity and simultaneously improve the activity. During this year, 11 new compounds have been synthesized and the biological activity evaluation is in progress, some of the compounds have been found to show ~20% glucose lowering in animal experiments.

9. Area: Reproductive Health Research

(Coordinator: Dr. Naibedya Chattopadhyay)

Design and synthesize novel molecules/isolate from natural sources and bioevaluate them for generating new leads and to develop them as female or male contraceptives, spermicides with anti-STI properties, agents for the management of post-menopausal osteoporosis and other endocrine disorders; evaluate traditional remedies for fertility regulation and endocrine disorders; understand mode of action of promising agents and undertake basic research to generate new knowledge on female and male reproductive endocrinology relevant to fertility regulation.

9.1 Development of anti-osteoporosis agents

As a recently started programme, much progress has been made in short span of time in identifying and developing putative anti-osteoporosis agents from CDRI. Given the discontinuation of hormone replacement-/estrogen replacement therapy due to adverse cardio-vascular side effects, lead compounds/agents from CDRI has been given particular attention to be devoid of estrogen agonistic activity.

9.1.1 Screening

Screening of osteogenic/bone anabolic agents is a major area of research. We focus in rationale drug design targeting various bone anabolic events and key molecules associated with the events. We use osteoblast mineralization as the assay for biological screening. We also undertake screening of India's rich source of traditional and ethno-traditional knowledge base to screen natural extracts (terrestrial plants/marine flora and fauna) for the possible bone forming/healing actions. Our goals are to localize and identify the active ingredients of the active natural product and use those as leads in order to synthesize novel compounds by computer-aided drug design, chemi-informatics and combichem.

In past few years, we identified one synthetic and two natural products having anti-osteoporotic activity. All three are undergoing development.

9.1.2 Follow-up studies: Compound 99/373

9.1.2.1 Effect of 99/373 on estrogen signaling; comparison with Raloxifene: Study in rat uterus

The binding affinity of 99/373, Raloxifene, Tamoxifene and Centchroman with cytosolic and membrane ERs was studied in rat uterus. Results revealed that Raloxifene, Tamoxifene and Centchroman competed with E_2 for binding to membrane ERs in a similar manner as they did with cytosolic ERs, although with a considerably low efficiency. Among the SERMs tested, Raloxifene showed maximum RBA for membrane ERs followed by Centchroman and Tamoxifen whereas 99/373 was least effective (<0.01%). 99/373 did not compete with E_2 for binding to uterine cytosolic or membrane estrogen receptor.

Further, studies were undertaken to evaluate the binding affinity of metabolites of 99/373 for uterine estrogen receptor in vitro and the effect on ER binding capacity and PR expression in rat uterus with a view to explore its estrogenic potential at uterine level as compared to SERM raloxifene. Results revealed that 99/373 and its metabolites did not bind to uterine estrogen receptor. It did not induce ER binding capacity in ovariectomized rat uteri; but interestingly, it antagonized E_2-induced ER binding when given for three days. The results were comparable to raloxifene. In ovariectomized rat uterus, it down regulates PR expression as observed at mRNA level. These results indicate the lack of estrogenic response at uterine level by 99/373 as compared to that exerted by Raloxifene.

9.1.2.2 Stability studies of 99/373

The validated HPLC-UV assay method was developed and applied to determine the compound concentration in rat serum, urine and feces. The compound was found to be chemically stable for 12 months at 50^0 and 60^0 C. Luminal stability study in Simulated Gastric and Simulated Intestinal Fluids (SGF & SIF) showed that the compound is stable in both acidic and basic pH. In vitro protein binding was found to be moderate 60.5 ± 3.2%).

Metabolic studies on 99/373 were conducted using hepatic S9 fraction. Compound was metabolized completely within 60 min with rat S-9 fraction. Two metabolites (M1 and M2) could be detected and identified.

9.1.2.3 Preclinical pharmacokinetic studies with 99/373

Pre-clinical pharmacokinetic studies were carried out in male Sprague Dawley rats after a single 10-mg/kg oral dose. The parent could be monitored up to a period of 4 h post dosing where as the metabolites could be detected up to 8-10 h. Tissue distribution studies revealed that comparatively higher levels of the 99-373, M-1 and M-2 are detected in liver, lung, brain, gastro-intestinal tract, spleen and kidney.

The compound could be monitored up to 120 h in feces and the maximum amount of the dose was excreted by 24 h. The % cumulative amount excreted was 10.02 ± 4.94. Biliary excretion studies revealed excretion of parent and the two metabolites through bile also.

9.1.2.4 Toxicity studies with 99/373 in monkeys

Healthy, young adult rhesus monkeys, selected after initial screening their general health and body weights, were employed in the study. They were randomly assigned to three treatment groups, each consisting of 3 male and 3 female animals. A fourth group comprising of an equal number of animals served as control. Compound 99/373 at the dose levels of 95, 190 and 375 mg/kg suspended in 1% gum acacia was given daily by oral route to the animals belonging to treatment groups for a period of 28 days. Controls were treated with equal volumes of 1% aqueous gum acacia in an identical manner. No abnormality related to nature or dose of compound was observed up to the dose of 375 mg/kg under the conditions of exposure employed in this 28 days toxicity study. All these studies were

performed as per the OECD and DCGI guidelines for respective toxicity studies undertaken.

9.1.3 Follow-up studies: NP-1

9.1.3.1 Mode of action studies

Studies have led to the isolation of twenty-six pure compounds from NP-1 crude extract. Of these, five were found to be the most active based on in vitro proliferation and mineralization assays. Osteoblast cells were treated with all the five pure NP-1 pure compounds for 24h at varying concentrations and BrdU incorporation was measured which is directly proportional to cell proliferation. BrdU cell proliferation assay revealed K051 to be the most active of all the five isolates. Measurement of ALP activity after treatment of osteoblast cells for 48h in presence of varying concentrations of pure NP-1 compounds revealed K095 and K080 to be the most active. In vitro mineralization assay assessed by alizarin staining and Von Kossa staining after culturing osteoblast cells for 21d at concentration 10^{-10}M of all pure compounds each also revealed K095 and K080 to be the most potent. Further, in osteoblast cells pretreated with MAPK pathway inhibitors and followed by compound treatment for 48h, ALP activity increased by pure compounds K095 and K080 was abolished in presence of p38MAPK pathway inhibitor. K095 also induced the phosphorylation of p38 antibody. NP-1 pure compounds also inhibited apoptosis induced by serum deprivation is osteoblast cells as assessed by Hoechst staining. Besides, anti-osteoclastogenic effect of K095 has also been found. Studies are ongoing to investigate the mode of action of other NP-1 pure compounds.

9.1.3.2 Evaluation of proliferative action on MCF-7 and Ishikawa cells by MTT assay

NP-1 pure compounds did not show any proliferative effect in MCF-7 cell lines at concentrations ranging from 10^{-10} to 10^{-6}M as assessed by MTT cell viability assay. Similar effect was found in Ishikawa cell line, except K052, which was mildly estrogenic at 10^{-6}M concentration, by MTT cell viability assay. In comparison, there was a marked increase in proliferation of both MCF-7 and Ishikawa cells in case of estradiol. Findings show lack of proliferative effect of NP-1 pure compounds on these cells.

9.1.3.3 Evaluation of osteoblast differentiation and mineralization of K095 analogs

Six analogs of K095 were submitted. These were evaluated in osteoblast cultures for ALP activity. After treatment for 48h, ALP activity was quantified. Of these S006-1709, S006-1710, S006-1711, S006-1712, S006-1713 were found to be active, while S006-1714 was found to be inactive. Out of the five active compounds, S006-1709 is the most potent in stimulating osteoblast differentiation and mineralization in addition to being anti-osteoclastogenic.

9.1.4 'Osteo Juvenate' from an Indian medicinal plant

A pharmaceutical composition designated as "Osteo Juvenate" for the management or prevention or treatment of bone disorders have been derived from an Indian medicinal plant. Bone sparing and bone forming activities have been revealed in vitro and in vivo in the alcoholic extract and its fraction as well as in isolated pure compounds. Four pure compounds isolated from the plant exhibit differential modes of action in osteoblasts, all toward bone formation, making these compounds as potent anabolic agents for bone loss disorders.

9.2 Development of anti-proliferative agents against breast cancer

During this period, total fifty synthetic compounds were screened for anti-proliferative activity in MCF-7 cells in vitro using MTT assay with tamoxifen as positive control. Out of these

three synthetic compounds (S005-989, S005-991, S005-1118) showed anti-proliferative activity by inducing apoptosis. None of these three compounds exhibited non-specific cytotoxicity in normal cells when assessed *in vitro* in primary osteoblast cells, HEK-293 and vero cell line using MTT and LDH release assay. In addition, none of these compounds exhibit estrogenic or anti-estrogenic effects in both *in vitro* and *in vivo* assays.

When these three lead molecules were evaluated in DMBA-induced mammary tumor model for their therapeutic efficacy, S005-989 showed *in vivo* efficacy in preliminary studies. Further studies are going on for characterizing their efficacy *in vivo.*

9.3 Development of anti-implantation and early post-implantation interceptive agents

9.3.1 Screening

Twenty seven synthetic compounds and 30 extract of natural products including plant extract and marine flora/fauna were tested for anti-implantation-cum-early post-implantation interceptive activity in adult female Sprague-Dawley rats when administered on days 1-5/1-7 post-coitum by the oral route. Of these three synthetic compounds were found active and taken for follow-up studies and there MED has been determined while others were found to be inactive.

9.4 Contraceptives for the male and spermicides

Eight synthetic compounds and 17 natural products were evaluated for spermicidal activity in vitro by Sander Cramer assay using live human sperm. However, none exhibited any detectable spermicidal activity.

9.4.1 Follow-up with promising spermicide

Potent, non-detergent spermicide S-003-296 was evaluated for contraceptive activity in a rat model. The compound was instilled through the cervix into the uterus of proestrous rat at 400, 200, 100 and 50 µg/animal and cohabited with adult male rats of proven fertility. The compound caused total inhibition of conception at 200 µg dose.

9.5 Development of anti-STI agents

9.5.1 Screening

Twenty-five synthetic compounds and nine natural products were evaluated for anti-trichomonas activity *in vitro* using *Trichomonas vaginalis* cell culture. Of these, six compounds were found to have promising anti-STI activity. The marketed drug Metronidazole was used as reference standards. However, none of the natural products exhibited any promising activity.

9.5.2 Carbodithioic acid esters of SSRI antidepressants, a novel class of anti-STI spermicides

Carbodithioic acid esters of 1-phenyl-1-{(4-trifluoromethyl) phenoxy} N-methyl propyl amine have been prepared by replacing the methylamino function in aminopropane chain with carbodithioic acid ester group and by adding various S-2-hydroxypropyl ester of dialkyl carbodithioic acid at 3-methylamino group. Some of these compounds showed spermicidal, antifungal and anti-Trichomonas activities**.** The study revealed that incorporation of carbodithioic acid residue directly into 1-phenyl-1-{(4-trifluoromethyl) phenoxy} N-methyl propyl amine structure leads to compounds with better antifungal and anti-Trichomonas activities, and N-methyl-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl] carbodithioic acid S-(2-pyrrolidino-ethyl) ester has shown better profile than both 1-phenyl-1-{(4-trifluoromethyl) phenoxy)} N-methyl propyl amine and nonoxynol-9. Further lead optimization may yield a potent dual-function spermicide.

9.6 Development of agents for the management of Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common disorder of aging men that is often accompanied by lower urinary tract symptoms (LUTS). Historically, surgery was the only widely accepted management option for BPH. Of late, medical therapy with 5α- reductase inhibitors (e.g. finasteride) and β-blockers (e.g. tamsulosin) is being preferred as effective and non-invasive method for the management of BPH. However, the need for indefinite therapy to maintain improvement is often associated with long-term side effects, cost and compliance issues. In an endeavour to design novel molecules that could serve as more effective, safer and cost effective options for BPH management, synthesis and evaluation of 21 chemical structures was taken up. In the *in vivo* test model utilizing rat, 9 compounds showed promising activity by effectively reducing prostatic weights. Finasteride was used as positive control.

Phytotherapy is also increasingly being practiced as a safe approach to BPH management. Using rat as the test model and finasteride as positive control, we discovered promising activity in two common plant seed extracts. The activity in one of these seed extracts was confirmed in repeat tests.

10. Area: Technology Development

(Coordinator: Dr. A.K. Saxena)

The research activity pursued under this area includes chemical technology, fermentation technology and pharmaceutical technology. Development/improvement of processes for CDRI candidate drugs, synthetic compounds, natural products, development/improvement of the processes for known drugs/ intermediates, search for novel bioactive agents, development of antibacterial compounds through microbial sources, novel antifungal compounds from active microorganisms, bio-transformations, studies on enzymes such as ß-galactosidase, protease, lipase etc., bioreactors and biocatalysts processing, quality control and pre-formulation studies of candidate drugs and development of drug delivery systems are the major activities of this area.

10.1 Sub Area: Chemical Technology
Coordinator: Dr. A.K. Saxena

10.2 Sub Area: Fermentation Technology
Coordinator: Dr. C.K.M. Tripathi

10.3 Sub Area: Pharmaceutical Technology
Coordinator: Dr. A.K. Dwivedi

10.1 Chemical Technology

10.1.1 Large scale preparation of CDRI candidate Drugs

10.1.1.1 Synthetic Compounds

10.1.1.1.1 Compound 99/411 (Antimalarial)

29g of the compound 99/411 was prepared and supplied to Pharmaceutics division.

10.1.1.1.2 Compound 97/78 (Antimalarial)

50g of the compound 97/78 was prepared and supplied to Pharmaceutics division.

10.1.1.2 Natural Products

10.1.1.2.1 Herbal Medicament (for treatment of cerebral stroke)

550g of the hexane extract was prepared and supplied to Pharmaceutics division.

10.1.1.2.2 CDR-134 BS-479-C (Antidiabetic)

441g Ethyl acetate fraction has been prepared and supplied.

10.1.1.2.3 CDR-134 BS-481 (Antidiabetic)

2.07 kg ethyl acetate fraction was prepared and supplied.

10.1.1.2.4 CDR-134 BS-430-C (Antidiabetic)

7 Kg alcohol fraction has been prepared and supplied.

10.1.2 Synthesis of known drugs and intermediates

10.1.2.1 Centchroman (antifertility)

An improved, cost effective process for antifertility drug Centchroman was developed at bench scale. An Indian patent has been filed.

10.2 Fermentation Technology

10.2.1 Screening of microbial cultures for antibacterial compounds

There is growing need for novel antimicrobial agents as the existing antimicrobials remain ineffective for certain infectious diseases. The rapid emergence of Multi Drug Resistant (MDR) pathogen necessitates the search for effective alternative antimicrobials. Microbial products, like other natural products, are rich source of drug lead compounds and continue to provide greater chemical/structural diversity showing activity against wide range of assay targets.

A *Streptomyces* strain (M4), showing broad spectrum antibacterial activity, was isolated from the soil samples. Morphological and 16S rRNA homology studies demonstrated that the strain showed maximum closeness with *Streptomyces triostinicus* NBRC 13836 (98% gene sequence similarity). From the fermented broth of the culture four antibacterial compounds were purified. All four compounds belong to the same chemical class, as the presence of phenoxazone ring was confirmed by UV, ^{1}H and ^{13}C NMR spectra. Two compounds were chemically characterized as Actinomycin V and D. One of the antibacterial compounds with 1273 molecular weight appears to be a new form of actinomycin. Studies on chemical characterization of other compounds are in progress.

10.2.2 Screening of microbial cultures for antifungal compounds

10.2.2.1 Polyene antifungal compounds

Two antifungal compounds were isolated and purified from the fermented broth and cell extracts of *S. triostinicus*. Both the compounds are polyene in nature (molecular weight 1430 and 1331) and show activity against unicellular and filamentous fungi. *S. triostinicus* is not reported to produce antifungal antibiotics. However, *S. triostinicus*, produces antibacterial quinoxaline antibiotics (chromolactones) which is of higher molecular weight. Work on structure elucidation of these compounds is in progress.

10.2.2.2 Cell wall active antifungals

The increasing incidence of life-threatening fungal infections has driven the search for new, broad-spectrum fungicidal agents that can be used for treatment and prophylaxis in immunocompromised patients. Microbial natural product inhibitors of fungal cell wall components such as chitin, 1,3-d-glucan and cell wall proteins are the most extensively studied targets for the development of novel antifungal agents. Chitin is the second most abundant carbohydrate polymer in nature, and is a major structural polysaccharide of fungi. For the isolation of fungal cell wall active microorganisms yeast cells were used as the only substrate and two actinomycte cultures, *Streptomyces halstedii* (accession no. MTCC 6817) and *Streptomyces annulatus* (accession no. MTCC 6818) were isolated. Fermented broth of these isolates showed antifungal and chitinase activity. Studies on purification and characterization of the chitinases and other active metabolites produced are in progress.

10.2.2.3 Fungal PI 3 Kinase Inhibitor

A fungus, *Talaromyces wortmanni* MTCC 8802, was isolated from termite dwelling soil and showed strong broad-spectrum antifungal activity against unicellular and filamentous fungi. Intracellular

antibiotic produced by this organism was purified and characterized as wortmannin. Studies of the stereochemistry of the compound is in progress. This antibiotic inhibits fungal PI 3 Kinase enzyme and exhibits antitumor activity as well.

10.2.3 Heparinase production

10.2.3.1 Enzymatic depolymerization of heparin to produce Low Molecular Weight Heparins (LMWHs) – anticoagulants

Heparin, a linear highly sulfated glycosaminoglycan (HSGAGs) produced by mast cells, is a widely used clinical anticoagulant and is one of the first biopolymeric drugs and one of the few carbohydrate drugs. LMWHs are derived from unfractionated heparin via controlled chemical or enzymatic depolymerization, while retaining the antithrombotic activity of heparin. Heparinases from *Flavobacterium heparinum* are enzymatic tools that have been used for the generation of LMWH (5000–8000 Da) and ultra-LMWH (3000 Da). Heparinase production by other microbial sources is reported. Heparinases have other important clinical applications such as monitoring of heparin levels in blood and neutralization of heparin in blood. In addition, heparinases are potent inhibitors of neovascularization and angiogenesis.

10.2.3.2 Screening and isolation of heparinase producing cultures

Cultures capable of utilizing heparin, as an inducer, for heparinase production were isolated by method of selective / enrichment culturing. The microorganisms isolated by enrichment culturing method were screened for heparinase production in a liquid medium and their growth kinetics as well as heparinase production kinetics was monitored. Two heparinase producing microbial cultures have been isolated and one of the strains has been characterized as *Aspergillus flavus* (accession no. MTCC 8654) by morphological, biochemical and rRNA homology studies. The Internal Transcribed Spacer region (ITS) and D1/D2 domain of 26S ribosomal RNA was sequenced using ABI sequencing kit on 3010xls model sequencer at Microbial Type Culture Collection (MTCC), IMTECH, Chandigarh, India. Pair-wise sequence alignment of partial 26S rRNA gene sequence was performed to identify closely related homologs with the help of BLAST search tool available at NCBI webserver. Phylogenetic tree was constructed to predict the species level characterization of the studied isolate through distance method based web-tool namely, CLUSTALW. The other strain, a gram negative cocci, has been submitted for complete 16S rRNA sequencing at MTCC, Chandigarh.

10.2.3.3 Optimization of heparinase production by *A. flavus*

The effect of different carbon and nitrogen sources on growth and heparinase production was assayed by replacement experiments. Nutrient components found to significantly influence heparinase production by single-dimensional search were incorporated in the production medium and their interaction effects were optimized by Plackett Burman Design (PBD), central composite design (CCD) and response surface methodology (RSM) to determine the optimum level of the key variables. Heparin, ammonium nitrate and chitin were identified as the significant nutrients controlling heparinase production.

10.2.3.4 Purification and characterization of heparinase

Heparinase has been purified to homogeneity as determined by SDS-PAGE and HPLC. Its native molecular weight is ~24 KDa as determined by mass spectroscopy. The kinetic constant of purified heparinase with 20 to 300µM heparin as substrate has been determined. Michaelis-Menten constants were determined using a Lineweaver-Burk plot. The Km and V max of heparinase towards heparin were calculated. Effects of pH, temperature, divalent metals and NaCl concentration on heparinase activity have been determined.

10.2.3.5 Depolymerization of heparin

Free and immobilized whole cells were deployed for deheparinization of heparins and conditions were standardized for the production of LMWHs. Heparin concentration, nature of buffer, aeration and kind of bioreactor significantly influenced the depolymerization processes. With free cells, initial rate of deheparinization was faster. 60-65% deheparinization was achieved in 5 hours with acrylamide and agarose immobilized cells in the first use. Stability of the entrapped cells was maintained up to four reuses. Mixture of oligosaccharides (LMWHs) obtained after deheparinization was fractionated by sephadex G25 fine gel permeation chromatography using 0.2 M NaCl as eluent. Further purification, characterization and pharmacological evaluation of the LMWHs produced is in progress.

10.2.4 Monoclonal antibodies

10.2.4.1 Generation of monoclonal antibodies against *C. albicans* and *A. fumigatus*

Further work on monoclonal antibody NE5 generated earlier against *C. albicans* cell wall protein was continued. Ten dodeca-peptides synthesized (based on the CDR sequence and their flanking regions) earlier did not exhibit any MIC up to 50 mg/ml. Eight new sequences of dodeca-peptides based on CDRs and their flanking regions were identified with the help of 'Predicted Antigenic Peptides' software and synthesized. The peptides have been subjected to anti-*Candida* activity *in vitro*.

Four hybridoma clones (single cell clones, 1A1, 1A2, 1C1, and 1C2) generated earlier against mycelial cell wall proteins were used for the development of ascites in Balb/C mice. The ascites fluid for all the four hybridomas was collected and the antibody titer was determined in the supernatant (OD>0.5) and confirmed through western blot. These hybridomas as well as the ascites fluids have been cryopreserved for further studies.

Fresh fusion experiments for the development of hybridomas were carried out with GPI anchored proteins (HF pyridine extracted cell wall) of *C. albicans* as well as metabolic proteins of *A. fumigatus*. The resulting hybridoma clones were screened with ELISA and western blotting. Positive clones (24 for *C. albicans* and 2 for *A. fumigatus*) were identified and subjected to single cell cloning. Characterization of resulting monoclonal antibodies is under progress.

10.2.4.2 Developing drug resistant strains of *C. albicans*

A strain of *C. albicans* (ATCC 10231) was exposed to graded concentrations of amphotericin B, fluconazole and 5-flucytosine to develop resistant strains. The resulting strains exhibited enhanced MIC 400 mg/ml against fluconazole (original MIC 6.25 mg/ml) as well as 5-flucytosine (original MIC 3.12 mg/ml), and 62.5 mg/ml against amphotericin B (original MIC 0.02 mg/ml). Amphotericin B resistance was further confirmed by Time Kill Assay at different MICs (2X, 1X and 0.5X) keeping wild type strain of *C. albicans* (ATCC 10231) as control. Microscopic studies showed distinct morphological differences. The strain exhibiting resistance to amphotericin B was subjected to protein analysis where 3 proteins were over expressed. These proteins were identified through MALDI-MS and MASCOT data base search with a significance level of >65%.

The resulting amphotericin B resistant strain was studied for spheroplast formation and regeneration in order to study protein expression during cell wall formation in the presence of amphotericin B. Western blotting with polyclonal sera (against lyticase treated cell wall) highlighted a protein whose expression varied with the concentration of amphotericin B. Identification and characterization of this protein is under progress.

10.3 Pharmaceutical Technology

10.3.1 Development of drug delivery systems

10.3.1.1 Biodegradable microparticles of antitubercular drugs

Product development of inhalable microparticles containing two antitubercular drugs continued in collaboration with M/S Lupin Laboratories Ltd. under NMITLI. The final formulation intended for clinical trials was standardized. Its storage stability was demonstrated for a period of 2 years under ambient conditions. Pharmacokinetics of incorporated drugs after administration as dry powder inhalation to mice and monkeys were established. A 90-day repeat dose inhalation safety/toxicity in monkeys is in progress, and an Investigational New Drug Application is expected to be submitted by March 2008.

10.3.1.2 A rational delivery system for Testosterone

A computation model of hormones secreted episodically by the male hypothalamo-pituitary-gonad axis, as reported earlier, was refined to include the effects of long-term deprivation of episodic gonadotropin-releasing hormone (GnRH). The model predicted that such deprivation would lead to abrogation of the secretion of luteinizing hormone (LH). Episodic GnRH was suppressed for periods lasting up to 14 weeks by transdermal systems capable of pulsatile delivery of testosterone. Rats were used to examine whether such suppression of GnRH would lead to apoptosis of pituitary gonadotrophes and arrest of spermatogenesis. Histological findings confirmed that suppression of episodic GnRH by episodic exogenous testosterone led to pituitary gonadotrophe apoptosis and arrest of spermatogenesis in the rat.

10.3.1.3 Delivery system for cyclosporine

The work on development of nonionic surfactant based formulations of cyclosporine continued and many other formulations were developed and tested for bioavailability study in rats. The relative bioavailability of Bilosomal formulation was found to be 1.73 times compared to marketed product Neoral while microemulsion based formulation showed almost equi-biovailability with respect to Neoral.

10.3.1.4 Delivery system for septic shock

Chitosan based (SE-CH) and Chylomicron mimicking nanoemulsion (CM) were prepared loaded with ciprofloxacin. The payload efficiency of ciprofloxacin in these formulations was improved (from 30% to 75%) by preparing ciprofloxacin ionic complexes with oppositely charged surfactants. The prepared emulsion was optimized and characterized for Zeta potential, size and size distribution, encapsulation efficiency *in-vitro* release profile and cell viability. The effect of these formulations on LPS induced cellular binding was studied using flow cytometry. It has been observed that both SE-chitosan based and Chylomicron mimicking nanoemulsion has ability to alter LPS binding with cells (J 774 macrophages) however the chitosan based nanoemulsion was more effective which is anticipated to reduce LPS mediated lethal cascading events. When studied for LPS induced ROS generation the SE-CH and CM reduced the generation ROS three and 1.5 times respectively. Further evaluation is in progress.

10.3.1.5 Ultrathin polyelectrolyte micro-reservoir based drug delivery

Microreservoirs of polyelectrolytes have been prepared by taking $CaCO_3$ as core and coated with alternatively charged polymer combination like Poly(allylamine hydrochloride) and polystyrene sulfonate (F1); Chitosan and Sodium alginate (F2) etc. These systems were optimized, characterized and evaluated for delivery of macromolecule taking

BSA as model molecule. The entrapment of BSA was found to be more than 70% in both formulations and the release was well controlled and showing nearly 52 % in 24 hors in both cases. Further optimization of formulation is in progress.

10.3.2 Starch nanoparticles ligand conjugates for cancer targeting

Starch nanoparticles (200-300 nm) were prepared and coupled with various ligands i.e. folic acid, transferrin. These NPs conjugates are intended for targeting the specific receptor reported to be over expressed on some cancer cells. Incorporation of cytotoxic agents in these NPs conjugates and further development towards the selective targeting is in progress.

10.3.3 Quality control and stability studies

Quality control and stability studies on Herbal Medicament, CDR-134F194, S-002-853 and 99-411 were conducted. HPLC methods for S-001-556, S-007-867, S-002-853 (R) and S-002-853 (S) isomers, 1020/K052, 1020/K054 1020/K080 were developed.

Section : II

RESEARCH OUTPUT & OTHER ACTIVITIES

1. Publications

2006

1. Arya KR and Agarwal SC. Indigenous therapeutic uses of some selected medicinal plants of Western Himalaya and their biological activities for modern medicines.

   J. Econ.Tax. Bot 30 (Suppl.), 184-196

2. Arya KR and Agarwal SC. Conservation of threatened medicinal plants through cultivation in Uttaranchal state.

   Ethnobotany 18, 77- 86

3. Mishra DK and Agarwal SC. Medicinal plants of Maharashtra state: Importance in modern drug therapeutics and their international trade.

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4. Pandey Gyanendra and Saxena AK. 3D-QSAR Studies on protein tyrosine phosphatase 1β inhibitors: Comparison of the quality and predictivity among 3D QSAR models obtained from different conformer based alignment.

   J. Chem. Inf. Model 46, 2579-2590

5. Saxena M, Gaur S, Prathipati P and Saxena AK. Synthesis of some substituted pyrazinopyridoindoles and 3D QSAR studies along with related compounds: Piperazines, piperidines, pyrazinoisoquinolines, and diphenhydramine, and its semi-rigid analogs as antihistamines (H1).

   Bioorganic and Medicinal Chemistry 14, 8249-8258

6. Seth P K, Dikshit M, Khanna VK and Dalal PK. Alterations in selected biochemical parameters in platelets and polymorphnuclear leucocytes in depression and schizophrenia.

   Int J Neuropsychopharmacology 9, S207-S207

2007

7. Agnihotri Geetanjali, Mandal Pintu Kumar and Misra Anup Kumar. Concise synthesis of two trisaccharide analogs related to the glycone constituent of phanoside, a novel insulin releasing natural product.

   Tetrahedron 63, 7240-7245

8. Agrawal H, Kumar A, Bal NC, Siddiqi MI and Arora A. Ligand based virtual screening and biological evaluation of inhibitors of chorismate mutase (Rv1885c) from *Mycobacterium tuberculosis* $H_{37}R_v$.

   Bioorganic & Medicinal Chemistry Letters 17, 3053-3058

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J. Enzyme Inhib Med Chem 22, 327-342

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Genetics 177, 1487-1497

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Biochemical and Biophysical Research Communications 353, 286-292

14. Kumar Amit, Singh Fateh V and Goel Atul. A regioselective palladium-free protocol for accessing unsymmetrical biaryls through ring transformation of 6-aryl-α-pyrones.

Tetrahedron Letters 48, 7283-7286

15. Anand Aparna, Roy Abhijeet Deb, Chakrabarty Ruchika, Saxena Anil K and Roy Raja. Investigation of the barrier to the rotation of carbamate and amide C–N bonds in antidepressant (6aR*,11bS*)-7-[carbobenzyloxy-l-alanyl]-2-[(4-methylphenyl sulfonyl]-1,2,3,4,6,6a,7,11b,2,12a(S)-decahydropyrazino[2',1':6,1]pyrido[3,4-b]indole by dynamic NMR and molecular mechanics.

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16. Ashutosh, Sundar Shyam and Goyal Neena. Molecular mechanisms of antimony resistance in Leishmania.

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17. Avasthi Kamlakar, Farooq Sheikh M, Bal Chandralata, Kumar Rishi, Tewari Ashish K and Maulik Prakas R. Design and synthesis of pyrazolo [3,4-d]pyrimidine and triazolo[4,5-d]pyrimidine based dissymmetrical 'Leonard linker' compounds: ^{1}H NMR and crystallographic evidence for folded conformation due to arene interactions.

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2. Patents

1.	**Patents Filed Abroad**	**16**
2.	**Patents Filed in India**	**06**
3.	**Patents Granted Abroad**	**16**
4.	**Patents Granted in India**	**08**

1 Patents Filed Abroad

1. **PCT Patent Appl. No.:** PCT/IN07/00375 **Filing Date:** 30/08/2007
Title: **Novel 6-(1-aryl ethyl)-1, 2, 4-trioxanes, useful as antimalarial agents and a process for the preparation thereof**
Inventors: Chandan Singh, Ajit Shankar Singh & Sunil Kumar Puri
Supporting Staff: Shashi Rostagi, Akhilesh Kumar Srivastav & Kamlesh Singh

2. **US Patent Appl. No.:** 11/842674 **Filing Date:** 21/08/2007
Title: **2-Alkyl/aryl sulphonyl-1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acid esters /amides as antithrombotic agents**
Inventors: Stuti Gaur, Zeeshan Fatima, Ansuman Dixit, Zahid Ali, William Rascan Surin, Kapil Kapoor, Kanta Bhatuni, Mohd. Salim Ansari, Madhu Dikshit & Anil Kumar Saxena
Supporting Staff: Arimardan Singh Kushwaha & Dayanand Vishwakarma

3. **PCT Patent Appl. No.:** PCT/IN07/00326 **Filing Date:** 2/8/2007
Title: **Antidiabetic and antidyslipidemic activities of S-(+)-7-[3 N-substituted amino-2-hydroxypropoxy] flavones**
Inventors: Ram Pratap, Himanshu Singh, Alok Kumar Verma, Amar Bahadur Singh, Priti Tiwari, Mukesh Srivastava & Arvind Kumar Srivastava
Supporting Staff: Krishna Kumar Chaudhari & Suresh Yadav

4. **US Patent Appl. No.:** 11/812251 **Filing Date:** 15/6/2007

Title: **Substituted mercapto phenyl naphthyl methane derivatives as SERM for the prevention and treatment of osteoporosis and other estrogen dependent disorders and as contraceptives**

Inventors: Sangita, Atul Kumar, Man Mohan Singh, Girish Kumar Jain, Puvvada Sri Ramchandra Murthy & Suprabhat Ray

Supporting Staff: Vasi Ahmad, A.H. Ansari, Mohini Chhabra & Govind Keshari

5. **South African Patent Appl. No.:** 2007/06835 **Filing Date:** 29/5/2007

Title: **Synergistic combination kits of α, β-arteether, sulfadoxin and pyrimethamine for the treatment of severe/multi-drug resistant cerebral malaria**

Inventors: Renu Tripathi, Sunil Kumar Puri, Jagdishwar Sahai Srivastava, Satyawan Singh, Omkar Prasad Asthana & Anil Kumar Dwivedi

6. **Mexican Patent Appl. No.:** MX/A/2007/006181 **Filing Date:** 22/5/2007

Title: **A process for heterologous expression and large scale production of functionally active enzyme trypanothione reductase of *Leishmania donovani* in prokaryotic system**

Inventors: Neena Goyal & Mukul Kumar Mittal

7. **Brazilian Patent Appl. No.:** PI0419069-6 **Filing Date:** 17/5/2007

Title: **A process for heterologous expression and large scale production of functionally active enzyme trypanothione reductase of *Leishmania donovani* in prokaryotic system**

Inventors: Neena Goyal & Mukul Kumar Mittal

8. **European Patent Appl. No.:** 05718507.6 **Filing Date:** 14/5/2007

Title: **Oxy substituted flavones/chalcones as antihyperglycemic and antidyslipidemic agents**

Inventors: Ram Pratap, Mavurapu Satyanarayana, Chandeshwar Nath, Ram Raghubir, Anju Puri, Ramesh Chander, Priti Tiwari & Brajendra Kumar Tripathi

9. **South African Patent Appl. No.:** 2007/03783 **Filing Date:** 10/5/2007

Title: **A process for heterologous expression and large scale production of functionally active enzyme trypanothione reductase of *Leishmania donovani* in prokaryotic system**

Inventors: Neena Goyal & Mukul Kumar Mittal

10. **Japanese Patent Appl. No.:** 0356NF2004/JP **Filing Date:** 13/04/2007
Title: **Oxy substituted flavones/chalcones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayana, Chandeshwar Nath, Ram Raghubir, Anju Puri, Ramesh Chander, Priti Tiwari & Brajendra Kumar Tripathi

11. **Canadian Patent Appl. No.:** 0356NF2004/CA **Filing Date:** 12/04/2007
Title: **Oxy substituted flavones/chalcones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayana, Chandeshwar Nath, Ram Raghubir, Anju Puri, Ramesh Chander, Priti Tiwari & Brajendra Kumar Tripathi

12. **US Patent Appl. No.:** 11/688359 **Filing Date:** 20/03/2007
Title: **Naturally occurring coumarins and their precursors as acetycholine esterase inhibitors**
Inventors: Janaswamy Madhusudhana Rao, B. Chinaraju, P.V. Srinivas, K.S. Babu, Jhillu Singh Yadav, K.V. Raghavan, H.K. Singh & Chandishwar Nath

13. **PCT Patent Appl. No.:** PCT/IB07/00686 **Filing Date:** 19/03/2007
Title: **Naturally occurring coumarins and their precursors as acetycholine esterase inhibitors**
Inventors: Janaswamy Madhusudhana Rao, B. Chinaraju, P.V. Srinivas, K.S. Babu, Jhillu Singh Yadav, K.V. Raghavan, H.K. Singh & Chandishwar Nath

14. **US Patent Appl. No.:** 11/684559 **Filing Date:** 09/03/2007
Title: **Biodegradable, inhalable microparticles containing anti-tubercular drugs**
Inventors: Himadri Sen, Suryakumar, Rakesh Sinha, Rolee Sharma & Pavan Muttil

15. **US Patent Appl. No.:** 11/684562 **Filing Date:** 09/03/2007
Title: **Biodegradable, inhalable microparticles containing anti-tubercular drugs**
Inventors: Himadri Sen, Suryakumar, Rakesh Sinha, Rolee Sharma & Pavan Muttil

16. **PCT Patent Appl. No.:** PCT/IB07/00468 **Filing Date:** 27/02/2007
Title: **Antiosteoporosis activity of *Butea* species**
Inventors: Rakesh Maurya, Geetu Singh, Pandruvada Subramanyam Narayana Murthy, Sandhya Mehrotra, Divya Singh, Biju Bhargavan & Man Mohan Singh

2 Patents Filed in India

1. **Patent Appl. No.:** 2639DEL2007 **Filing Date:** 17/12/2007
Title: **An improved process for preparation of trans-3,4-diarylchroman**
Inventor: Devi Prasad Sahu
Supporting Staff: Atma Prakash Dwivedi

2. **Patent Appl. No.:** 2456DEL2007 **Filing Date:** 26/11/2007
Title: **5-[Trimethoxy phenyl] -1-thiomethyl -N-arylamino-penta-1,4-dien-3-ones**
Inventors: Shivaji Narayanrao Suryawanshi, Suman Gupta, Nishi & Sushmita Pandey
Supporting Staff: Manju

3. **Patent Appl. No.:** 1523DEL2007 **Filing Date:** 18/7/2007
Title: **Novel cyclopropa[a]naphthalenes for the treatment of neurocerebrovascular disorders**
Inventors: Atul Goel, Fateh Veer Singh, Puja Garg, Preeti Dohare & Madhur Ray

4. **Patent Appl. No.:** 1417DEL2007 **Filing Date:** 3/7/ 2007
Title: **Synthesis of N-[2-alkyl-6-(3-substituted phenyl-ureido)-quinolin-4-yl]-acetamide and benzamide derivatives useful as antiprotozoal and antibacterial agents**
Inventors: Sanjay Batra, Zehra Tusi, Sudharshan Madapa, Kum Kum Srivastava, Renu Tripathi, Sunil Kumar Puri, Gaddam Balakrishna Shiva Keshava, Praveen Kumar Shukla, Asuthosh Kumar, Mohammad Imran Siddiqi, Ravi Shankar Prasad Singh, Anil Gaikwad, Jayanta Sarkar, Sudhir Sinha, Wahjuddin & Girish Kumar Jain

5. **Patent Appl. No.:** 0735DEL2006 **Filing Date:** 19/03/2007
Title: **A pharmaceutical composition useful as acetycholineesterase inhibitors**
Inventors: Janaswamy Madhusudhana Rao, B. Chinaraju, P.V. Srinivas, K.S. Babu, Jhillu Singh Yadav, K.V. Raghavan, H.K. Singh & Chandishwar Nath

6. **Patent Appl. No.:** 0280DEL2007 **Filing Date:** 13/2/2007
Title: **Novel substituted bis-1, 2, 4-trioxanes, useful as antimalarial agents and a process for the preparation thereof**
Inventors: Chandan Singh, Ved Prakash & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi, Akhilesh Srivastava & Kamlesh Singh

3 Patents Granted Abroad

1.

US Pat. No.:	7250446	**Grant Date:**	31/7/2007
Patent Appl. No.:	10/809845	**Filing Date:**	26/03/2004
Title:	**Novel mercaptophenyl naphthyl methane compounds and synthesis thereof**		
Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray, Puvvada Sri Ramachandra Murthy & Girish Kumar Jain		
Supporting Staff:	Vasi Ahmad, A.H. Ansari, Mohini Chhabra & Govind Keshari		

2.

European Pat. No:	1034794	**Grant Date:**	30/05/2007
Patent Appl. No.:	99301912.4	**Filing Date:**	12/03/1999
Title:	**Formulation of dihydroartemisinin for the control of wide spectrum of malaria**		
Inventors:	D C Jain, R S Bhakuni, R P Sharma, Sushil Kumar & Guru Prakash Dutta		

3.

German Pat. No.:	DE69836020T2	**Grant Date:**	10/5/2007
Patent Appl. No.:	98890317.5	**Filing Date:**	29/10/1998
Title:	**Composition useful for the early diagnosis of visceral leishmaniasis and a process for preparing the same**		
Inventors:	Girish Kumar Jain, Suman Tiwari, Suman Gupta & Jagdish Chandra Katiyar		

4.

US Pat. No.:	7183291	**Grant Date:**	27/02/2007
Patent Appl. No.:	09/316313	**Filing Date:**	21/05/1999
Title:	**Use of primaquine derivative N'-ethylidinotetrahydrofuran-2-one)- N'-(6-methyl-8-quinodinyl) 1-4-pentane diamine as gametocidal agent**		
Inventors:	Ram Pratap, Amiya Prasad Bhaduri, Harsh Pati Thapaliyal, Sunil Kumar Puri, Guru Prasad Dutta, Anil Kumar Dwivedi, Satyawan Singh, Pratima Srivastava, Vikas Chandra Pandey, Sudhir Srivastava, Shio Kumar Singh, Ram Chandra Gupta & Jagdishwar Sahai Srivastava		

5.

Great Britain Pat. No.:	2412373	**Grant Date:**	21/02/2007
Patent Appl. No.:	0514808.5	**Filing Date:**	20/07/2005
Title:	**An improved process for the synthesis of guggulsterones: A pharmacologically active constituent of gugulipid**		
Inventors:	Ram Pratap, Dharmendra Pratap Singh, Raghwendra Pal & Satyawan Singh		

6.	**Chinese Pat. No.:**	01800744.9	**Grant Date:**	14/02/2007
	Patent Appl. No.:	01800744.9	**Filing Date:**	30/11/2001
	Title:	**Linker based solid support for peptide and small molecule organic synthesis**		
	Inventors:	Wahajul Haq & Seturam Bandhacharya Katti		
	Supporting Staff	Krishna M. Shukla		
7.	**European Pat. No.:**	1348714	**Grant Date:**	03/01/2007
	Patent Appl. No.:	02-252133.0	**Filing Date:**	25/03/2002
	Title:	**A process for the preparation of polypeptide useful as antiallergic, antiasthmatic and anticomplementary agent**		
	Inventors:	B. Kundu, S.K Khare, R. Singh, Amarnath, P.P. Gupta , G.K. Patnaik & A. Kapil		
	Supporting Staff	Ramjeet		
8.	**European Pat. No.:**	1174152B1	**Grant Date:**	20/12/2006
	Patent Appl. No.:	0030267.47	**Filing Date:**	31/03/2000
	Title:	**Inclusion complexes of a high potent opioid peptide, pharmaceutical compositions and method of treatment**		
	Inventors:	Anil Kumar Dwivedi, Madhu Khanna, Wahajul Haq, Ram Raghubir, Sudhir Srivastava, P S R Murty, O P Asthana, J S Srivastava & Satyawan Singh		
9.	**OA Pat. No.:**	13318	**Grant Date:**	29/12/2006
	Patent Appl. No.:	1200600134	**Filing Date:**	22/10/2003
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Surya Kumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
10.	**European Pat. No.:**	0997734	**Grant Date:**	20/12/2006
	Patent Appl. No.:	98890317.5	**Filing Date:**	29/10/1998
	Title:	**Composition useful for the early diagnosis of visceral leishmaniasis and a process for preparing the same**		
	Inventors:	Girish Kumar Jain, S. Tiwari, Suman Gupta & J.C. Katiyar		
11.	**European Pat. No.:**	EP1104768B1	**Grant Date:**	29/11/2006
	Patent Appl. No.:	99309700.5	**Filing Date:**	02/12/1999
	Title:	**Polypeptides useful for diagnosis of *Aspergillus fumigatus* and a process of preparing the same**		
	Inventors:	Puranam U Sarma, Taruna Madan, Priyanka Priyadarsiny, Seturan B Katti & Wahajul Haq		

12.	**European Pat. No.:**	1692101	**Grant Date:**	23/09/2006
	Patent Appl. No.:	03780487.9	**Filing Date:**	17/11/2005
	Title:	**Substituted mercapto phenyl naphthyl methane derivatives as SERM for the prevention and treatment of osteoporosis and other estrogen dependent disorders and as contraceptives**		
	Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray, Puvvada Sri Ramachandra Murthy & Girish Kumar Jain		
	Supporting Staff	Vasi Ahmad, A.H. Ansari, Mohini Chhabra & Govind Keshri		
13.	**European Pat. No.:**	1263800	**Grant Date:**	11/09/2006
	Patent Appl. No.:	01906091.2	**Filing Date:**	04/01/2001
	Title:	**Linker based solid support for peptide and small molecule organic synthesis**		
	Inventors:	Wahajul Haq & Seturam Bandhacharya Katti		
	Supporting Staff	Krishna M. Shukla		
14.	**European Pat. No.:**	913397	**Grant Date:**	05/07/2006
	Patent Appl. No.:	97308391.8	**Filing Date:**	22/10/1997
	Title:	**Methods for preparing 1-[4-arylpiperazine-1-yl]-3-[2-oxopyrrolidin/piperidin-1-yl]propanes**		
	Inventors:	Neelima Sinha, Sanjay Jain, Anil Kumar Saxena, Nitya Anand, Ram Mohan Saxena, Mangal Prasad Dubey, (Late) Gyanendra Kumar Patnaik & Madhur Ray		
15.	**Japanese Pat. No.:**	3686281	**Grant Date:**	10/06/2005
	Patent Appl. No.:	11-114004	**Filing Date:**	18/03/1999
	Title:	**Formulation of dihydroartemisinin for the control of wide spectrum of malaria**		
	Inventors:	D C Jain, R S Bhakuni, R P Sharma, Sushil Kumar & Guru Prakash Dutta		
16.	**US Pat. No.:**	6855347	**Grant Date:**	15/02/2005
	Patent Appl. No.:	10/103738	**Filing Date:**	25/03/2002
	Title:	**New herbal composition for treating gastric ulcer**		
	Inventors:	Janaswamy Madhusudhana Rao, Upparapally Sampathkumar, Boggavarapu Subrahmanya Sastry, Jhillu Singh Yadav, Kondapuram Vijaya Raghavan, Gautam Palit, Deepak Rai, Panniyampally Madhavankutty Varier, Trikovil Sankaran Muraleedharan & Kollath Muraleedharan		
	Supporting Staff:	Dwarka Nath Bhalla, Tarunlata Seth, Mohammad Saleem Ansari		

4 Patents Granted In India

1. **Patent No.:** 211247 **Grant Date:** 23/10/2007
Patent Appl. No.: 1095DEL2000 **Filing Date:** 30/11/2000
Title: **A formulation of α-β arteetether useful for the treatment of wide spectrum multi drug resistant malaria through rectal route**
Inventors: Guru Prakash Dutta, Dharam Chand Jain, Ranjendra Singh Bhakuni, Sudhanshu Saxena, Sangeeta Dhawan, Suman Preet Singh Khanuja, Sushil Kumar, Renu Tripathi, Aseem Umesh, Nuzhat Kamal, Anil Kumar Dwivedi & Satyawan Singh

2. **Patent No.:** 211244 **Grant Date:** 23/10/2007
Patent Appl. No.: 0212DEL2000 **Filing Date:** 09/03/2000
Title: **Novel ether derivatives of dihydro artimisinin as antimalarials**
Inventors: Chandan Singh, Rani Kanchan & Sunil Kumar Puri

3. **Patent No.:** 197502 **Grant Date:** 08/10/2007
Patent Appl. No.: 0767DEL2000 **Filing Date:** 29/08/2000
Title: **Diaryl naphthyl methane derivatives**
Inventors: Neeta Srivastava, Arvind Grover, Sangeeta, Atul Kumar, Man Mohan Singh, Janak Dulari Dhar & Suprabhat Ray

4. **Patent No.:** 199829 **Grant Date:** 28/09/2007
Patent Appl. No.: 0998DEL2002 **Filing Date:** 30/09/2002
Title: **A process for the preparation of novel N^1, N,N-diglycosylated diaminoalcohols useful in chemotherapy of tubercular infections**
Inventors: Rama Pati Tripathi, Vinod Kumar Tiwari, Neetu Tiwari, Ranjana Srivastava, Anil Kumar Srivastava, Vinita Chaturvedi, Kishore Kumar Srivastava, Sudhir Sinha & Brahm Shankar Srivastava
Supporting Staff: V.K. Maurya

5. **Patent No.:** 191696 **Grant Date:** 26/8/2004
Patent Appl. No.: 0236DEL1999 **Filing Date:** 12/2/1999
Title: **A process for the preparation of a dihydro artemisinin formulation useful for the control of wide spectrum of malaria**
Inventors: Dharam Chand Jain, Rajendra Singh Bhakuni, Ram Prakash Sharma, Sushil Kumar & Guru Prakash Dutta

6. **Patent No.:** 189314 **Grant Date:** 23/01/2004
Patent Appl. No.: 0746DEL1998 **Filing Date:** 24/03/1998
Title: **A process for the preparation of a novel synthetic peptide epitope useful for diagnosis of aspergillosis**
Inventors: P U Sarma, T Madan, Seturam Bandhacharya Katti, Wahajul Haq & P Priyadarsiny

7.	**Patent No.:**	189176	**Grant Date:**	10/10/2003
	Patent Appl. No.:	0752DEL1998	**Filing Date:**	24/03/1998
	Title:	**A process for the preparation of a novel synthetic peptide epitope useful for diagnosis of aspergillosis**		
	Inventors:	P U Sarma, T Madan, Seturam Bandhacharya Katti, Wahajul Haq & P Priyadarsiny		
8.	**Patent No.:**	188957	**Grant Date:**	19/09/2003
	Patent Appl. No.:	0751DEL1998	**Filing Date:**	24/03/1998
	Title:	**A process for the preparation of a novel synthetic peptide epitope useful for diagnosis of aspergillosis**		
	Inventors:	P U Sarma, T Madan, Seturam Bandhacharya Katti, Wahajul Haq & P Priyadarsiny		

3. Papers Presented in Conferences

2006

NRC-2006: Paradigm Shift Through Governance, Lucknow (4-5 March)

ICT & Healthcare: For better networked governance. G. Sharma, D. Tripathi, D. Awasthi & R.K. Sharma

All India Seminar on Frontier Areas of Chemical Engineering: Strategies for Future, Lucknow (18-19 March)

Information resources and tools for kinetics simulation of biochemical pathways. M. Abbas & R.K. Sharma.

New technologies (Nano & Bio): Drug development and delivery. R.K. Sharma.

International Symposium on Recent Advances in Steroid Biochemistry and Molecular Biology, Tyrol, Austria (1-3 June).

Modulation of AP-1 mediated estrogenic response by ormeloxifene in rat uterus. A. Daverey, S. Awasthi & A. Dwivedi

8th World Congress of Gynecology and Obstetrics, Kuala Lumpur, Malaysia (5-10 November).

A demonstration of $\alpha_v\beta_3$ integrin's involvement in implantation by *in vitro* and *in vivo* studies in rats. P.K. Mehrotra, K.R. Srinivasan, S. Kitchlu & A. Dwivedi

Indo-US CCNP, Hyderabad (13-14 November)

Antidyslipidemic profile of semi-synthetic furano-flavonoids. T. Khaliq, T. Narender, A. Puri & R. Chander.

PPTase profile of natural and semi-synthetic alkaliod amides. Shweta, T. Narender, P. Tiwari, A.K. Srtivastava, S.C. Agarwal & K. Raj.

International Symposium on New Frontiers in Tuberculosis Research, New Delhi (4-6 December)

Identification and evaluation of *Mycobacterium smegmatis* as a surrogate screen for selecting molecules active against drug resistant *Mycobacterium tuberculosis*. V. Chaturvedi.

International Conference on Multivariate Statistical Methods in the 21st Century, Kolkata (28-29 December)

Statistical challenges and limitations in analyzing ^{1}H NMR metbonomics data. M. Abbas, M. Srivastava & R.K. Sharma.

2007

36th National Seminar on Crystallography, Chennai (22-24 January)

X-ray crystallographic and docking studies of synthetic tricyclic compounds. G.P. Yadav, R. Nainavat, K. Hajela & P.R. Maulik.

33rd Indian Immunology Society Conference, New Delhi (28–31 January)

Characterization of specific and cross-reactive epitopes of merozoite surface protein 1 of *Plasmodium vivax* and *Plasmodium cynomolgi*. D.C. Kaushal & N. A. Kaushal.

Crude extract of *Piper betle* L. induces apoptosis-like death in *Leishmania donovani* promastigotes. P. Misra, M. Samant, S.K. Gupta, A. Kumar, N. Kumar & A. Dube.

Generation and characterization of monoclonal antibodies specific to filarial acetylcholinesterase. N.A. Kaushal, S.K. Singh & D.C. Kaushal.

Genomic fingerprinting of sodium stibogluconate (SSG) sensitive and resistant strains of *Leishmania donovani* through amplified fragment length polymorphism. A. Kumar, M. Samant, A.K. Shasney & A. Dube.

Growth inhibitory and immunostimulatory effect of *Piper betle* L. (betelvine) against *Leishmania donovani* infection. N. Singh, S. Gupta, A. Kumar, P. Misra, N. Kumar & A. Dube.

Proteophosphoglycans (PPGs) are differentially expressed in sodium stibogluconate (SSG) sensitive and resistant clinical isolates of Indian kala-azar. M. Samant, A. Kumar, N. Singh & A. Dube.

The recombinant myosin of adult *Brugia malayi* imparts significant protection against *homologous* infective larval challenge in rodent model. S. Vedi, A. Dangi, R. Sahoo, S.K. Verma, J. K. Saxena & S.M. Bhattacharya.

XXX All India Cell Biology Conference and Symposium on Molecules to Compartments: Cross Talks and Networks, New Delhi (2-4 February)

Characterization of kas opeon upstream regulatory regions of $H_{37}R_v$ and *Mycobacterium aurum*. R. K. Biswas, N. Gupta & B. N. Singh.

Expression analysis of sigma factor F in *Mycobacterium smegmatis*. A.K. Singh, R.K. Biswas & B.N.Singh.

Facile synthesis of 2-spiro (3-aryl-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran) -2'-(5',5'-dimethylcyclohexane-1',3'-diones) under Hantzsch reaction conditions. S.K. Giri, V.Varshney, S. Kumar & D.P. Sahu.

Highly rapid approach to donor-acceptor 1,2,3-triarylarenes, fluorenes and fluorenones with blue, green, yellow light tuning. M. Dixit & A. Goel.

Synthesis of quinolines from Baylis-Hillman derivatives. S. Madapa & S. Batra.

Annual Conference of Association of Physicians of India APICON 2007, Goa (15-18 February)

A new bio-marker for predicting cardiovascular risk : Lipoprotein sub-fractions by NMR. A. Ghatak, R. Khanna, C.G. Agarwal, A. Chandra, S. Mehrotra, J.K. Saxena, M. Chandra & R. Roy.

National Conference on Redefining Governance through IT, Lucknow (17-18 February)

A statistical tool for risk assessment and decision support for health services. M. Abbas, M. Srivastava, M. Mathur & S. Kumar.

3rd International Symposium on Current Trends in Drug Discovery Research, Lucknow (17-21 February)

Antioxidant and antidyslipidemic activities of different fractions of *Pongamia pinnata* fruits. G. Bhatia, A. Puri, R. Maurya, P.P. Yadav, M. Khan, A.K. Khanna & J.K. Saxena.

Antidyslipidemic action of gemfibrozil and cholestryamine in dyslipidemic diabetic hamster model. M.M. Khan, R. Saxena, A. Puri, A.K. Khanna, R. Chander & J.K. Saxena.

Antidyslipidemic profile of naturally occuring 4-hydroxy-pipecolic acid in db/db mice model. Shweta, T. Narender, A. Singh & A.K. Srivastava.

Antioxidant profile of naturally occuring furano-flavonoids. T. Khaliq, Shweta, T. Narender & G. Bhatia.

Combinatorial and conventional synthesis of glycohybrid molecules as new class of antitubercular agents. V.Chaturvedi.

Hamsters co-infected with *Leishmania donovani* and *Brugia malayi*: Host responses. S. Gupta, S. Dixit, R.L. Gaur, Nishi, S. Palne & P.K. Murthy.

Molecular docking and 3-D QSAR studies of human mitotic kinesin Eg5 inhibitors. A. Kumar, U. Saquib & M. I. Siddiqi.

Substituted urea/thiourea derived from fluoxetine as potent appetite suppressant. K. Bhandari, N. Srinivas, L. Sharma, S. Srivastava, A. Nath & C. Nath.

Synthesis and post-coital contraceptive of some tetrazolyl indole derivatives. U.S. Singh, R. Shankar, M.M. Singh, G. Keshri, G.P. Yadav, P.R. Maulick & K. Hajela.

Synthesis of oligosaccharide fragments corresponding to the exopolysaccharide released by *Streptococcus macedonicus* Sc 136. P. Tiwari & A. K. Misra**.**

Synthesis of some novel conformationally constrained tricyclic compounds as potential estrogen receptor agonist/antagonist. R. Shankar, A.K. Jha, U.S. Singh, G. Keshri, A. Dwivedi, A.K. Balapure, M.M. Singh & K. Hajela.

Synthesis and antitubercular activity of nucleoside analogs based on purines and L-ascorbic acid. N. Singh, N. Dwivedi, M. Misra, & R.P. Tripathi.

L-ascorbic acid in organic synthesis: An ecofriendly and facile synthesis of 4-vinyl-1, 4-dihydropyridine. Surendra S. Bisht.

11th ISCB International Conference on Advances in Drug Discovery Research, Aurangabad (24 - 26 February)

Antidyslipidemic activity of terrestrial plants. S.K. Maurya, A.K. Srivastava & O.P. Asthana.

Characterization of hexokinase from filarial parasite. A.R. Singh, A.M. Kayastha, L.M. Tripathi & J.K. Saxena.

Characterization of thioredoxin reductase a potent chemotherapeutic target of filarial parasites. S. Joshi, Ravi, Naresh & J. K. Saxena.

Cloning, sequencing and characterization of SRRG-1 gene of *Leishmania donovani*. Ravinder, Ashutosh, S. Sundar & N. Goyal.

Derivatisation of aplysinopsin to generate lead for antimicrobial activity. S. Porwal, P.M.S. Chauhan & S. Gupta.

Design, synthesis, ^{1}H NMR and X-ray crystallographic study on pyrazolo[3,4-*d*]-pyrimidine core based dissymmetrical "Leonard/propylene linker" compounds for studying arene-arene interactions in flexible compounds. Amantullah, K. Avasthi, R. Kumar & P. R. Maulik.

Folding stability of trypanothione reducatse from *Leishmania donovani*. S. Rai, M. K. Mittal, M. Owis & N. Goyal.

Friedel-Crafts heteroarylation of arenes and heteroarenes: a facile entry to 4-(hetero)aryl substituted quinazolines and quinolines. S. Kumar & D.P. Sahu.

Immunochemical characterization of *Setaria cervi* microfilarial antigen. Kalani, N.A. Kaushal & D.C. Kaushal.

In vitro antleishmanial activity of few naturally occurring and synthetic chalcones. S. Palne, Nishi, Shweta, S. Gupta & T. Narender.

In vitro cultivation of *Plasmodium falciparum*: Protein profile of parasites grown in RPMI and RPNI modified media with human and animal sera. S. Singh, P. Singh, S.K. Puri & K. Srivastava.

Isolation and molecular characterization of filarial acetylcholinesterase. S.K.Singh, N.A. Kaushal & D.C. Kaushal.

Studies on biochemical basis of arteether resistance in a rodent malaria model. R. Chandra, L.M. Tripathi, J.K. Saxena & S.K. Puri.

Studies on reductive cleavage of isooxazolines. V. Varshney & D.P. Sahu.

Synthesis and antimalarial activity of new 1, 2, 3-trisubstituted tetrahydro-â-carbolines. R. Kumar, K. Srivastava, S.K. Puri & P.M.S. Chauhan.

Synthesis and evaluation of antimalarial activity of 4-aminoquinoline triazine derivatives. A. Kumar, K. Srivastava, S.K. Puri & P.M.S. Chauhan.

Synthesis of 2,4,6-trisubstituted pyrimidines and triazine heterocycles as antileishmanial agents. N. Sunduru, A. Agarwal, S.B. Katiyar, Nishi, N. Goyal, S. Gupta & P.M.S.Chauhan.

Synthesis, molecular docking and PTP-1B inhibitory activity of functionalized naphthofurans and dibenzofurans. A. Kumar, M. Dixit, A.K. Srivastava & A. Goel.

Unexplored potential of bisindole alkaloids as antileishmanial agents. L. Gupta, A. Talwar, P.M.S. Chauhan & S. Gupta.

An efficient synthesis of tetramic acid derivatives with extended conjugation from *L*-ascorbic acid. Biswajit K. Singh.

Synthesis and antitubercular activity of substituted phenylmethyl and pyridylmethyl amines. Nisha Saxena, R.P. Tripathi.

BPCON-2007 and International Symposium on Atherosclerosis in Hypertension Diabetes and Coronary Heart Disease, Lucknow (15-16 March)

Effect of some medicinal plants on lipid levels in high fructose and high fed hamsters. S.K. Maurya, S.P. Srivastava, O.P. Asthana & A.K. Srivastava.

Lipid dysregulation in high fructose and high fat diet fed hamsters and rats. S.P. Srivastava, S.K. Maurya, A.K. Srivastava & O.P. Asthana.

Non-pharmacological management of hypertension. A. Ghatak.

National Seminar on Theoretical and Applied Bayesian Methodologies, Varanasi (17-18 March)

Preprocessing, feature selection and classifier design in bioinformatics with emphasis on Naïve Bayes. M. Abbas & M. Srivastava.

All India Seminar on Cyber Crimes and Security Challenges, Lucknow (13-15 April)

Protection of organization's sensitive information against insider attacks. M. Abbas & R.K.Sharma.

Security and patch management. R.K. Sharma & M. Abbas.

International Conference on Strategic Management for Firms in Developing Countries, Bombay (10-12 May)

Cause related marketing : A strategic tool for marketer. Naseem Ahmed Siddiqui.

Indo-GermanWorkshop, Heidelberg Germany (12-14 July)

Antileishmanial potential of a marine sponge *Haliclona exigua* (Krikpatrick) against experimental visceral *Leishmania*sis. A. Dube, N. Singh, A. Saxena & V. Lakshmi.

Chemotherapy of leishmaniasis: Synthesis and bioevaluation of terpenyl pyrimidines as antileishmanial agents. N. Chandra, S. Pandey, Nishi, S.N. Suryawanshi & S. Gupta.

Effect of CDRI 99/373 and ormeloxifene on 7,12-dimethylbenz(a) anthracene induced mammary tumor in rats. P. S. R. Murthy, R. Mishra, S. Gupta & P. K. Murthy.

Hamsters co-infected with *Leishmania donovani* and *Brugia malayi*: Host responses. S. Gupta , S. Dixit, R.L. Gaur, Nishi, S. Palne & P.K. Murthy.

Synthesis and antileishmanial profile of some new terpenyl labdane derivatives. S.Pandey, Nishi, S.N. Suryawanshi & S. Gupta.

Environmental Parasitology and Community Health Care Initiatives, Agra (13-15 October)

Safety assessment of drugs for human use. R.K.Singh, T. Agarwal & P. S. Soam.

The combination toxicity of azathioprine, isoniazid and rifampicine in bone marrow of rabbits. R.K. Singh & P. Yadav.

Toxicity evaluation of antiretroviral drug-azidothymidine for community health care. R.K. Singh, P. S. Soam & Tripti Agarwal.

e-Cheminfo Interaction Meeting on Latest Advances in Drug Discovery & Development, Pennsylvania, USA (15-19 October)

Biochemical and *in silico* characterization of dipeptidylcarboxypeptidase from *Leishmania donovani*: a potential drug target for antileishmanial drug discovery. M.S. Baig, Ashutosh, M.I. Siddiqui & N. Goyal.

Molecular modeling and docking analysis of human α-glucosidase enzyme: A construction towards the development of antidiabetic agents. U. Saquib, A. Kumar & M.I. Siddiqui.

19th National Congress of Parasitology, Visakhapatnam (26-28 October)

Antileishmanial activity of novel substituted azoles. S.Palne, N. Srinivas, Nishi, N. Goyal, K. Bhandari & S. Gupta.

Antileishmanial efficacy of an 8-aminoquinoline drug- Elubaquine. S. Gupta, Nishi, S. Palne & S.K. Puri.

Bangla Mahoba (*Piper betle* L.): The immunomodulatory activity of the crude extract and its various fractions in mice. V. K. Soni, M. Singh, R. Sahoo, A. Dangi, S. Tewari, N. Kumar & S.M. Bhattacharya.

Bilirubin induces apoptosis like death in *Plasmodium falciparum* through the augmentation of oxidative stress. S. Kumar, S. K. Puri & U. Bandopadhyay.

Brugia malayi: Cloning and characterization of hexokinase. A.R. Singh, R. Arya, S. Joshi, A.M. Kayastha & J.K. Saxena.

Cloning, expression and purification of *P. falciparum* transketolase. S. Joshi, A.R. Singh, P.C. Misra & J.K. Saxena.

Depletion of endosymbiont bacteria *Wolbachia* from filarial parasite (*Brugia malayi*) leads to altered proteomic pattern of parasite apart from modifying the host's parasitological, immunological and inflammatory responses. P. Bajpai, S. Shakya & S.M. Bhattacharya.

Evaluation of mechanisms contributing towards antileishmanial activity of anilino-(2-bromophenyl) acetonitrile. S. Mishra & S. Gupta.

Glutathione synthetase inhibitor reverses resistance to arteether in rodent malaria model. R.Chandra, A. Kushwaha & S.K. Puri.

Immune responses of the rodent host to liposomised BmAFII filarial antigen. M.K. Sahoo, S. K. Joseph, S.K. Verma, M. Owais & P.K. Murthy.

In vitro cultivation of *Plasmodium falciparum*: optimization of a new cell based fluorescence assay using modified medium. S. Singh, S. K. Puri & K. Srivastava.

Involvement of cytochrome P450 enzyme in antimalarial drug resistance. A. Rizvi, J.K. Saxena, S.K.Pandey & R. Tripathi.

Particulate fraction of adult *Brugia malayi* imparts protection against infective larval challenge in rodent host. S. Shakya, V.K. Soni, S.Vedi, P. Bajpai & S.M. Bhattacharya.

Possible alternative of human serum for continuous culture of *Plasmodium falciparum.* S.K.Pandey, A. Rizvi & R. Tripathi.

Studies on the efficacy of lumefantrine, piperaquine and mefloquine in combination with arteether against drug resistant rodent malaria model. A. Kushwaha & S.K. Puri.

W*olbachia:* an antifilarial drug target. S.M. Bhattacharya, A. Dangi & P. Bajpai.

40th Annual Conference of the Indian Pharmacological Society, Mohali (1-3 November)

Anti-ulcer effect of ethanolic extract of *Withania coagulans* in experimental models of peptic ulcer in rats. G. Palit**,** S. Lahiri & R. Maurya.

Hexose uptake stimulatory effect of pongamol and karanjin from *Pongamia pinnata* on L6 myotubes. A.K. Tamrakar, P.P. Yadav, R. Maurya & A.K. Srivastava.

The 55th Fall Conference of the Korean Association of Immunobiologists, Seol, Korea (8-9, November)

Induction of mucosal immunity by intra-nasal immunization in rabbits against challenge of *Vibrio cholerae* by recombinant toxin co-regulated pilus and cholera toxin B subunit protein vaccine. Juthika Kundu, Rupa Majumdar, Ranjana Srivastava and Brahm S. Srivastava.

25th Biennial Conference of Indian Association of Leprologists, Kanpur (19-21 November)

Semi–quantitative detection of *Mycobacterium leprae* antigens in skin scrapings: Suitability as a laboratory aid for field diagnosis of leprosy. V. Chaturvedi.

39th Conference of Endocrine Society of India, Tirupati (29 November – 2 December)

Non-steroidal anti-estrogens in combination with 5á-reductase inhibitor effectively reduce prostate size in rats: novel approach for management of benign prostatic hyperplasia. R. Kumar, V. Verma, J.P. Maikhuri & G. Gupta.

Silver Jubilee Conference of Indian Society for Medical Statistics, Manipal (30 November - 2 December)

Nearest centroid classification methods in bioinformatics. M. Abbas & M. Srivastava.

Role of principle component analysis techniques in bioinformatics. M. Srivastava & M. Abbas.

Standard clustering techniques revisited in bioinformatics era. M. Abbas & M. Srivastava.

International Tropical Ecology Congress, Dehradun (2-5 December)

Threatened medicinal plant diversity of Uttrakhand Himalaya: sustainable utilization in drug development programme. K.R. Arya, D.K. Mishra & R.K. Sharma**.**

18th All India Congress of Zoology & National Seminar on Current Issues on Applied Zoology and Environmental Sciences, Lucknow (7-9 December)

A new class of antifilarial agents: 2-Sulfanyl-5-methyl-3,4-dihydropyrimidines. P. K. Murthy, B.K. Singh, M. Mishra, N. Saxena, R.L. Gaur, G.P. Yadav, P.R. Maulik, M.K. Sahoo & R.P. Triapthi.

Bone marrow toxicity assessment of antiosteoporetic drug alendronate. R.K. Singh, V. Joshi & M.R. Priya.

Current developments in treatment and control of lymphatic filariasis. S.M. Bhattacharya.

Identification, isolation and expression of a novel RNA helicase from lymphatic filarial parasite *Brugia malayi.* M. Singh, K.K. Srivastava & S.M. Bhattacharya.

In vivo and *in vitro* toxicity assessment of chloramphenicol in HepG2 cell line & Sprague Dawley rats. R.K. Singh, A. Mishra, N. Tiwari & S. Purohit.

In vivo toxicity evaluation of chloramphenicol in charles fosters rats. R.K. Singh & S.K. Singh.

In vitro cultivation of *Brugia malayi* and iron supplemented experimental hosts's era. K. Srivastava, P.K. Murthy & S.M. Bhattacharya.

Stable freeze dried antigen from *Leishmania donovani* promastigotes for serodiagnosis of kala-azar by direct agglutination test (DAT). S. Gupta, S. Mishra & G.K. Jain.

Terpenyl pyrimidines as antileishmanial agent. S. Gupta, N. Chandra, S.R. Palne, N. Goyal & S.N. Suryawanshi.

Breeding and weight gain in Rat (*Rattus norvagicus*) of Sprague Dawley strain used in biomedical studies. A.K. Srivastava.

Annual Congress of the Society of Andrology, New Delhi (15-16 December)

An *in vitro* toxicity assessment of male antifertility drug- RISUG. R.K. Singh, J. P. Singh, S. Pandey & M.R. Priya.

First Annual Meeting of the Cytometry Society, Lucknow (17-18 December)

Recombinant myosin of Lymphatic filarial parasite *Brugia malayi* induces predominant Th1 immune response which protects rodents against homologous infective larval challenge. S. Vedi, A. Dangi & S.M. Bhattacharya.

59th Indian Pharmaceutical Congress, Varanasi (20-23 December)

Comparison of immune responses elicited by the Hepatitis B surface antigen adsorbed or encapsulated in poly (lactic acid) microparticles. S.Vinay, P.K. Murthy & D. Kohli.

Comparison of immune responses elicited by the Hepatitis B surface antigen adsorbed or encapsulated in poly (lactic- acid) macroparticles. V. Saini, P.K. Murthy & D. Kohli.

Biopesticide Conference - 2007, Palayamkottai (28-30 December)

Notable biopesticide keystone species of some wild plants of western ghats, India. S. M. Rajendran.

3rd Symposium on Current Advances in Molecular Biochemistry: Applications in Health, Environment and Agriculture, Lucknow (28-30 December)

Characterization of *P. falciparum* transketolase. S. Joshi, A.R. Singh, P.C. Misra & J.K. Saxena.

Cloning and expression profiling of Rv3291c (a probable transcription factor) involved in persistence/ latency. S.Kaur, B.S. Srivastava & R. Srivastava.

Cloning, expression and purification of acetohydroxyacid synthase (AHAS) genes of *M. tuberculosis* $H_{37}R_v$. V. Singh, D. Chandra & R. Srivastava.

Construction of 3D homology model of dipeptidylcarboxypeptidase from *Leishmania donovani*: A molecular model for inhibitor design. M.S. Baig, Ashutosh, M.I. Siddiqui & N. Goyal.

Role of autocrine growth factor in the resuscitation of non-culturable cells in *Mycobacterium smegmatis*. R.K.Gupta & R. Srivastava.

Urea and GdmCl induced denaturation and refolding of trypanothione reductase. S. Rai & N. Goyal.

2008

Annual Conference of Association of Physicians of India APICON, Kochi (10-14 January)

Nuclear magnetic resonance studies of lipoproteins : A novel bio-marker for cardiovascular disease risk prediction. A Ghatak, R. Khanna, C.G. Agarwal, A. Chandra, S. Mehrotra, J.K. Saxena, M. Chandra & R. Roy.

4. Inter-Agency Linkages

Title	Funding Agency	Principal Investigator
Reproductive health research programme	Ministry of Health & Family Welfare, Govt. of India	Director, CDRI
National project on development of potential drugs from the ocean	Ministry of Earth Sciences, Govt. of India	Director, CDRI
Sophisticated Analytical Instrument Facility (SAIF)	Department of Science & Technology, Govt. of India	Director, CDRI
Golden triangle partnership scheme for validation of traditional ayurvedic drugs and development of new drugs	CSIR/AYUSH/ICMR	Dr. Ram Raghubir
An approach towards exploration of mechanism of drug nonresponsiveness to Sb (V) in field isolates of *Leishmania donovani*	Department of Biotechnology, Govt. of India	Dr. Neena Goyal
Role of rapid suscitation promoting factors (Rpf) in wake up of dormancy in *Mycobacterium tuberculosis*	-do-	Dr. Ranjana Srivastava
Leishmania target antigens from promastigotes and amastigotes: Identification on experimental visceral leishmaniasis	-do-	Dr. Anuradha Dubey
Solution structure of *Mycobacterium tuberculosis, E.coli* and *Homo sapiens* peptidyl-tRNA hydrolase by NMR spectroscopy	-do-	Dr. Ashish Arora
Structure based drug design of inhibitors targeting recombinant pteridine reductase 1 from *Leishmania donovani* clinical isolate	-do-	Dr. Neeloo Singh
Cloning, expression and characterisation of filarial acetylcholine esterase	-do-	Dr. N.A. Kaushal

Correlation of single nucleotide polymorphism in gene encoding cytokines and adhesion and immune regulatory molecules with severity of *P. falciparum* malaria in Uttar Pradesh	-do-	Dr. Saman Habib
Evaluation of *Mycobacterium* as an immunomodulator for the management of visceral leishmaniasis and as an adjunct to antileishmanial vaccine/drug	-do-	Dr. Anuradha Dubey
Up-gradation of the CDRI project on design, synthesis and development of new molecules against MDR tuberculosis to a DBT centre of excellence of TB drug discovery	-do-	Dr. Sudhir Sinha
Studies on neutrophil nitric oxide synthase: Isolation, molecular characterisation and identification of interacting proteins	-do-	Dr. Madhu Dikshit
New inhibitor design/drug development using novel protein targets: NAD+ dependent DNA ligases and feast/famine regulatory proteins from *M. tuberculosis*	-do-	Dr R. Ravishankar
Studies on the structure and functions of actin cytoskeletal network in *Leishmania donovani*	-do-	Dr. C.M. Gupta
Anti-osteoclastogenic effect of 99/373 and its mode of action	-do-	Dr. N. Chattopadhyay
Studies on the modulation of neutrophil free radical generation and nitro oxide synthesis by calcium, reactive nitro and oxygen species	Department of Science & Technology, Govt. of India	Dr. Madhu Dikshit
Identification and characterization of stage specific gene(s) of *Leishmania donovani* using genomic microarray	-do-	Dr. Neena Goyal
Study of viable non-replicating persistent mycobacteria and identification of genes expressed during latency	-do-	Dr. B.S. Srivastava
Diversity oriented organic synthesis of small but smart molecules in drug discovery research	-do-	Dr. G. Panda
Isolation and characterisation of proteo-phosphoglycans of *Leishmania donovani*	-do-	Dr. Anuradha Dube
Studies on synthesis of cyclic compounds using Baylis-Hillman chemistry	-do-	Dr. Sanjay Batra

Expansion of facilities in national centre for pharmacokinetic and metabolic studies	-do-	Dr. G.K. Jain
Identification and elucidation of novel signaling pathways involved in monocyte/macrophage activation, migration, differentiation, proliferation and death during dyslipidemia and atherosclerosis	-do-	Dr. M.K. Barthwal
Establishing national facility for regulatory pharmacology and toxicology	-do- (PRDSF)	Director, CDRI
Design and synthesis of PPAR- α, γ modulators as antihyperglycemic agents	-do- (SERC Fast Track)	Dr. Atul Goel
A mechanistic approach towards improvement in oral bioavailability with special reference to cyclosporine	-do-	Dr. P.R. Mishra
Synthesis of biologically active resin glycosides and evaluation of their anticancer properties	-do-	Dr. B. Mukhopadhyay
Synthesis of heptasaccharide motifs found in the cell wall of *Mycobacterium gordonae* towards the preparation of carbohydrate vaccine against *Mycobacteria*	-do- (Ramanna Fellowship)	Dr. Anup Kumar Misra
Molecular diversity- oriented synthesis of aromatic scaffolds through ring transformation strategy	-do-	Dr. Atul Goel
Computer aided drug design and synthesis of antihistamines	-do- (Women Scientist Scheme)	Dr. M. Saxena
Synthesis of some heterocyclic compounds containing amidoalkyl groups for their antiviral and antifungal activities	-do-	Dr. Z. Tusi
Osteoporosis in Indian women and men : Diagnosis using bone mineral density and biochemical markers of bone turnover	-do-	Dr. Anu Makker
Genome wide approaches to assess the involvement of Cyp1A1 polymorphism in Indian breast cancer patients and the effect of resveratol on cyclophosphamide induced gene expression profile of MCF-7 cell line	-do-	Dr. Neetu Singh
Identification and development of novel anticancer agents: Extended work plan for lead optimization and drug candidate selection	DST/DABUR	Dr. S. Sinha

Lead optimization and development of new orally active antimalarial peroxides	DST/IPCA	Dr. Chandan Singh
Search for the cell wall and membrane protein(s) of *Candida albicans* to be used as target molecule	Indian Council of Medical Research, Govt. of India	Dr. P.K. Shukla
Development of new chemotherapeutic agents and drug combinations for the multi-drug resistant/service malaria treatment	-do-	Dr. Renu Tripathi
Synthesis of monosaccharide derivatives as potential antimycobacterial agents	-do-	Dr. A.K. Shaw
Design and synthesis of novel SERMs for the management of osteoporosis and other estrogen related disorders	-do-	Dr. G. Panda
Target based design and synthesis of novel compounds for treating diabetes and dyslipidemia	-do-	Dr. Atul Goel
Syntheses of antimalarial agents and their combinatorial chemistry	-do-	Dr. P.M.S. Chauhan
Development of antiulcer drug from Indian medicinal plant *Tectona grandis*	-do-	Dr. G. Palit
Osteoporosis and development of novel antiosteoporosis agents	-do- (Emeritus Scientist Scheme)	Dr. M.M. Singh
Development of new chemotherapeutic agents for Human African Tripanosomiasis (HAT)	DNDi, Geneva	Dr. Renu Tripathi
Carbohydrate based aminoaclohols and acids: Development of new chiral ligands for potential application in defence	DRDO	Dr. R.P. Tripathi
Pharmacological and genomic investigations on *Withania somnifera* - An Indian medicinal plant	NMITLI (CSIR)	Dr. S. Bhattacharya
Development of biodegradable micro-particles containing antitubercular drug for delivery of dry powder inhalation	-do-	Dr. Amit Mishra
Improved genome annotation through a combination of machine learning and experimental methods: *Plasmodium falciparum* as a case study	-do-	Dr. Saman Habib
High-throughput screening of botanicals for the identification of skin and hair bioactives	Proctor & Gamble, USA (RRL/NCL)	Dr. S. Sinha
Mode of action of Artemisinin based antimalarial drugs	Uttar Pradesh Council of Science & Technology	Dr. J.K. Saxena

5. R & D/Technical Facilities and Services

1. Sophisticated Analytical Instrument Facility

Over 9590 external and 23720 internal samples were analysed by the division. There were 677 users from universities/colleges, 45 users from research laboratories, 8 users from industries, and 364 internal users. Over 550 grids of internal samples and 250 grids of external samples were analysed for Transmission Electron Microscopy. About 320 stubs of internal samples and 104 stubs of external samples were analysed for Scanning Electron Microscopy.

Instrumentation division continued to provide repair, maintenance and upkeep of sophisticated analytical, biomedical, electronics and laboratory instruments and maintained uninterrupted smooth power supply to all the divisions of the institute. In cases of non availability of imported components, equivalent indigenous substitutes were installed to ensure the smooth functioning of instruments. Specifications and technical evaluations were also prepared for procurement of new equipments.

2. Biological screening of outside samples

The institute provided *in vitro* and *in vivo* biological screening facilities to R&D institutions, Universities, academic organisations and industrial houses within the country.

3. National Laboratory Animal Center

3.1 Services provided

a) The Center supplied of laboratory animals for research and testing purposes to the CDRI projects as well as other government and profit making private institutions. Month wise supply of animals from January 2007 to November 2007 is shown below:

Month	Mouse	Rat	Hamster	Mastomys	Gerbil	G. pigs	Rabbit	Total
January	1996	1882	570	85	65	170	19	4787
February	1652	1917	617	130	60	170	26	4572
March	2544	2269	483	60	50	16	41	5463
April	1827	1961	406	70	80	76	13	4433
May	1814	1631	401	105	75	115	26	4167
June	2094	1487	425	150	95	60	14	4325
July	1972	1649	450	30	70	241	-	4412
August	1767	1285	570	125	110	260	05	4122
September	1571	1577	446	100	115	200	04	4013
October	1513	1539	495	85	85	240	19	3976
November	1668	1495	370	120	40	200	10	3903
Grand Total	**20418**	**18692**	**5233**	**1060**	**845**	**1748**	**177**	**48173**

Apart from health monitoring and quality control of animals through microbiological, parasitological and hematological screenings and genetic and production profiles of animals, following jobs were completed in the National Laboratory Animal Centre:

➢	Microbiological monitoring of animals through screening of fecal, blood, urine samples as well as from the representative live and dead animals	:	877
➢	Parasitological screening of animals through stool and skin scrapings	:	336
➢	Hematological monitoring through blood examination	:	410
➢	Non-human primates tuberculin testing (through PPD) performed	:	164
➢	Non-human primates chest radiographies undertaken	:	15
➢	Non-human primates maintained under rehabilitation.	:	24

4. Documentation and library services

CDRI Library continued to receive recognition from national and international organizations. These include:

- WHO Collaborating Centre on Drug Information for South-East Asian Region
- User Centre for Biotechnology System Network under Department of Biotechnology, Govt. of India
- National Marine Data Centre by Department of Ocean Development, Govt. of India and
- Nodal Centre for Lucknow Special Libraries Consortium (LUSLIC).

The present collection of Library has 21796 books, 68388 bound volumes of the periodicals and 246 subscribed periodicals. All activities of the department are fully computerized and confirm to the norms of e-governance. Publication of periodicals viz. **Drugs and Pharmaceuticals - Industry Highlights (**monthly**), Drugs and Pharmaceuticals - Current R&D Highlights and Ocean Drugs Alert (**quarterly**)** continued. Subscribers and peers largely appreciated the contents of these publications. Library manages, updates and maintains the Website of the Institute.

6. Human Resource Development

1. Trainining Programmes/Workshops Attended By CDRI Staff

Name of the Scientist	Title of the training programme/ workshop	Place	Date
Dr. R.K. Sharma	Workshop on information security management system	HRDC, Ghaziabad	26 Feb. – 1 Mar., 2007
Dr. D.K. Dikshit	Workshop on information security management system	HRDC, Ghaziabad	26 Feb. – 1 Mar., 2007
Dr. Anand P. Kulkarni	Workshop on towards a more customer responsive CSIR	HRDC, Ghaziabad	14-15 Mar., 2007
Dr. S.R. Kulkarni	Workshop on US & European patent issues directed to pharmaceuticals'	HRDC, Ghaziabad	22-25 Mar., 2007
Mr. Vinay Tripathi	Workshop on US & European patent issues directed to pharmaceuticals	HRDC, Ghaziabad	22-25 Mar., 2007
Mr. N.S. Rana	Training programme on service tax act	HRDC, Ghaziabad	16-17 Apr., 2007
Mr. U.S. Rawat	Training programme on service tax act	HRDC, Ghaziabad	16-17 Apr., 2007
Ms. Sarika	Induction training programme	HRDC, Ghaziabad	30 Apr. - 5 May, 2007
Ms. Smrati Bhaduria	Induction training programme	HRDC, Ghaziabad	30 Apr. - 5 May, 2007

Dr. Sanjay Batra	Training programme on enhancement of managerial efficiency for scientists	HRDC, Ghaziabad	4-8 June, 2007
Dr. A. Ghatak	Workshop on clinical trials an important component of innovation chain in new drug development	HRDC, Ghaziabad	21-22 June, 2007
Dr. O.P. Asthana	Workshop on clinical trials an important component of innovation chain in new drug development	HRDC, Ghaziabad	21-22 June, 2007
Shri R.P. Tripathi	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Shri A.K. Chauhan	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Shri Prasenjit Mitra	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Shri SuniL Kumar	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Shri Ramesh Singh	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Dr. A.K.Goel	Awareness programme on RTI	NBRI, Lucknow	9-10 Jul., 2007
Dr.(Ms.) Kanchan Hajela	Programme on leadership for senior women scientists	ASCI, Hyderabad	23-27 Jul., 2007
Dr. R.S. Bhatta	Training programme on crafting effective S&T communications	HRDC, Ghaziabad	3-4 Aug., 2007
Dr. Arun K. Trivedi	Training programme on crafting effective S&T communications	HRDC, Ghaziabad	3-4 Aug., 2007
Mr. Vinay Tripathi	Three-day programme on leveraging intellectual property for business development at HRDC, Ghaziabad	HRDC, Ghaziabad	6-8 Aug., 2007
Dr. Praveen Kumar Dubey	Induction training programme	HRDC, Ghaziabad	20-25 Aug.,2007
Dr. Akhilesh Kumar Jain	Induction training programme	HRDC, Ghaziabad	20-25 Aug.,2007
Dr. Sripathi Rao Kulkarni	Induction training programme	HRDC, Ghaziabad	20-25 Aug.,2007

Dr. Anil K. Gaikwad	Research methodologies and stastical methods	HRDC, Ghaziabad	17-20 Sept.,2007
Mr. N.A. Siddiqui	Training programme on service tax act	HRDC, Ghaziabad	27-28 Sept.,2007
Dr. A.K. Dwivedi	Training Programme on drafting of patent applicantions, patent prosecution and litigation	HRDC, Ghaziabad	8-10 Oct., 2007
Dr. D.N. Upadhyay	Workshop on strategic management of human capital	HRDC, Ghaziabad	12-14 Oct., 2007
Mr. N.S. Rana	DST sponsored technology commercialization programme for senior scientists	ASCI, Hyderabad	22 Oct-2 Nov., 2007
Mr. Prem Prakash	Workshop on project management techniques and practices	HRDC, Ghaziabad.	24-26 Oct., 2007
Dr. Ram Raghubir	Workshop on project management techniques and practices	HRDC, Ghaziabad.	24-26 Oct., 2007
Dr. S.B. Katti	Workshop on to develop India-specific action plan to implement strategies for linking sexual and reproductive health and HIV/AIDS programme	National Institute for Research in Reproductive Health, Mumbai	20-22 Nov., 2007
Dr.(Mrs.) Ranjana Srivastava	Intrapreneurship development programme	HRDC, Ghaziabad.	7-12 Jan., 2008
Dr. Sudhir Sinha	Workshop on CSIR leadership development programme	HRDC, Ghaziabad	17-29 Feb., 2008
Dr. (Mrs.) Anila Dwivedi	Training programme on monitoring as a management tool	HRDC, Ghaziabad	21-22 Jan., 2008

2. Ph.D. Programme

2.1 Ph.D.s submitted/awarded during 2007

Name of the Research Fellow	University	Title/guide
Abhijeet Deb Roy	JNU, New Delhi	NMR based mechanistic evaluation in synthesizing analogues of bioactive molecules: Preferentially anticancer agents./ Dr. Raja Roy
Akshya Kumar Meher	JNU, New Delhi	Biophysical and biochemical characterization of ESAT-6, CFP-10 and ESAT-6-CFP-10 complex from *Mycobacterium tuberculosis* H37Rv. / Dr. Ashish Arora
Alka Saxena	JNU, New Delhi	Studies with *Mycobacterium bovis* BCG on biology of persistent/latent mycobacteria. / Dr. B.S. Srivasatava
Ambrish Kumar	JNU, New Delhi	Investigation of the regulation of transcription and replication of the *Plasmodium falciparum* apicoplast genome. / Dr. Saman Habib
Anshuman Dixit	JNU, New Delhi	Molecular modeling, pharmacophore mapping and design of thrombin receptor antagonists. / Dr. A.K. Saxena
Ashok Singh	JNU, New Delhi	Analysis of single nucleotide polymorphisms (SNPs) in C100RF-2(PEO1) and N-methylepurine DNA glycosylase (MPG) in selected Indian sub populations. / Dr. S.K. Rath
Biswajit Saha	Dr. BRA University, Agra	Combinatorial synthesis of heterocyclic molecules of biological significance/Dr. B. Kundu
CS Blesson	JNU, New Delhi	Studies on the regulation of steroid receptor and cofactor expression during implantation in rat uterus./ Dr. Anila Dwivedi
Fateh Veer Singh	JNU, New Delhi	Molecular target oriented synthesis of potential antidiabetic agents. / Dr. Atul Goel
Himanshu Agrawal	JNU, New Delhi	Identification and characterization of chorismate mutase from *Mycobacterium tuberculosis* H37Rv. / Dr. Ashish Arora
Jitendra Kumar Misra	HNB Garhwal University, Srinagar, Garhwal	Quest for potential biodynamic agents./ Dr. Gautam Panda

Madhumita Chatterjee	JNU, New Delhi	Role of ascorbic acid in nitric oxide mediated modulation of polymorphonuclear leukocyte functions. / Dr. Madhu Dikshit
Mithu Guha	JNU, New Delhi	Studies on oxidative stress in liver during malaria./ Dr. Uday Bandhopadhyay
Namrata Manhas	JNU, New Delhi	Studies on heat shock proteins and apoptotic molecules in cerebral ischemia/ Dr. Ram Raghubir
Naresh Chandra Bal	JNU, New Delhi	Biophysical and biochemical characterization of peptidyl-t RNA hydrolase from *Mycobacterium tuberculosis*./Dr. Ashish Arora
Narmata Dwivedi	CSJMU, Kanpur	Synthetic studies in carbohydrate scaffolds and development of new antitubercular agents. / Dr. R.P. Tripathi
Nasib Singh	JNU, New Delhi	Studies on the application of green fluorescent protien transfected *Leishmania donovani* for antileishmanial screening. / Dr. Anuradha Dube
Neeta Gupta	JNU, New Delhi	Characterization of upstream regulatory sequences of *kas*A operon involved in fatty acid synthesis type II (FAS-II) pathway in *Mycobacterium tuberculosis.* / Dr. B.N. Singh
Pallavi Tiwari	Banaras Hindu University, Baranasi, India	Synthetic studies on carbohydrate derived biodynamic molecules**. /** Dr. Anup Kumar Misra (CDRI) and Prof. R.M. Singh (BHU).
Parul Misra	JNU, New Delhi	Structural and functional characterization of hyaluronate lyase (HYLP2) from *Streptococcus pyogenes* bacteriophage 10403. / Dr. Vinod Bhakuni
Prasad Vure	JNU, New Delhi	Nonioinic surfactant based delivery systems bearing cyclosporine as the model drug./ Dr. P.R. Mishra
Rabi Sankar Bhatta	JNU, New Delhi	Bio-availability enhancement for a highly effective anti-hyperlipidemic agent "16-Dehydropregnenolone" and the evaluation of its drug-drug interaction potential / Dr. G.K. Jain

Rajeev Mishra	CSJMU, Kanpur	Modulation of mammary and liver carcinogenic by certain synthetic and plant products. / Dr. P.S.R. Murthy
Rajiv Kumar Jain	JNU, New Delhi	Target sites of human sperm for novel, nondetergent spermicidal molecules useful as prophylactic contraceptives with dual protection. / Dr. Gopal Gupta
Rajiv Lochan Gaur	CSJMU, Kanpur	Characterization of antigen molecules of *Brugia malayi* identified by sera of anitifilarial treated host in relation to parasitological and immunological responses. / Dr. Kalpana Murthy
Ramendra Pratap	Dr. RML Avadh University, Faziabad	Design and synthesis of PPAR gama anatagonists as antihyperglycemic agents. / Dr. V.J. Ram
Ramesh Chandra	JNU, New Delhi	Characterization, sub-cellular localization and functional analysis of actin binding proteins(s) in Leishmania. / Dr. C.M. Gupta
Ravi Kumar Lella	Dr. BRA University, Agra	Characterization of Eis protein [Rv 2416c] of *Mycobacterium tuberculosis* H37Rv. / Dr. J.K. Saxena
Ruchika Yogesh	BHU, Varanasi	Synthesis and structure activity relationships of biologically active molecules. / Dr. A.K. Saxena
Sandeep Chaudhary	JNU, New Deddlhi	Artemisinin analogues: Synthesis, chemistry and antimalarial assessment. / Dr. Chandan Singh
Sanjeev Noel	JNU, New Delhi	Differential gene expression in mice liver following acute exposure to 8-aminoquinoline derivatives. / Dr. S.K. Rath
Satyananda Patel	JNU, New Delhi	Characterization of neutrophil nitric oxide synthase: Role of nitric oxide in modulating neturophi functions/ Dr. Madhu Dikshit
Satyendra Singh Suryavanshi	JNU, New Delhi	Pharmacokinetic studies of 16-dehydropregnenolone, a hypolipidemic agent. /Dr. G.K. Jain
Shabih Raza	JNU, New Delhi	Characterization, sub-cellular localization and functional analysis of actin-related proteins(s) in Leishmania. / Dr. C.M. Gupta

Shraddha Kumari	Devi Ahilya Vishwavidyalaya	Studies on vaccination strategies against experimental Leishmaniasis. / Dr. Anuradha Dube
Shweta	Dr. BRA University, Agra	Chemical investigation of *Aegle marmelos* and *Crotolaria medicaginea* and synthesis of flavonoids and their biological activity./ Dr. Rakesh Maurya
Shyam Sunder Verma	Dr. RML Avadh University, Faizabad	Synthetic studies in carbohydrate based structure: Development of antimalarial agents/ Dr. R.P. Tripathi
Soniya Malhotra	JNU, New Delhi	Structural and functional studies on *Streptococcus pyrogenes* bacteriophage hyaluronidase. / Dr. Vinod Bhakuni
Swati Gupta	Dr. Hari Singh Gaur Vishwavidhyalyay, Sagar	Development and evaluation of targeted chemotherapy for Leishmaniasis. / Dr. Anuradha Dube
Tanvir Khaliq	Dr. BRA University, Agra	Chemical investigation of *Peganum harmala* and *Indigofera tinctoria*. / Dr. Rakesh Maurya
Upasana Sharma	Lucknow University, Lucknow	Building on leads from natural products: Synthesis of novel antimalarial agents. / Dr. Chandan Singh
Vandana Praveen	Lucknow University	Production of antimicrobial metabolites by various micro-organisms isolated from natural environments./ Dr. C.K.M. Tripathi
Vikas Srivastava	JNU, New Delhi	Identification of *in vivo* induced genes of *Mycobacterium tuberculosis* H37Rv using IVET approach. / Dr. Ranjana Srivastava
William Rasican Surin	JNU, New Delhi	Biochemical studies on thrombosis and its modulation by anti-thrombotic drugs. / Dr. Madhu Dikshit
Zeeshan Fatima	Dr. BRA University, Agra	Synthesis, QSAR and molecular modeling studies on antialzheimers and cardio protective agents. / Dr. A.K. Saxena

2.2 Ph.D.s submitted/awarded during 2006

Name of the Research Fellow	University	Title/guide
Ashok Kumar Chaturvedi	JNU, New Delhi	Proteome analysis of cellwall antigens of *Aspergillus fumigatus* and role of MAbs in immunotherapeutics. / Dr. P.K. Shukla
Amrendra Kumar Roy	CSJMU, Kanpur	Synthesis of isoxazole derivatives as possible antithrombotic agents./ Dr. Sanjay Batra
Deepa Pandey	Dr. BRA University, Agra	Design and synthesis of macrolide derived antibacterials and peptides as immunomodulators. / Dr. W. Haq
Geetu Singh	Dr. BRA University, Agra	Phytochemical investigation of *Butea monosperma* and *Cissus quadrangularis*. / Dr. Rakash Maurya
K.R. Srinivasan	Jamia Hamdard, New Delhi	Role of cell adhesion molecules, the integrins in uterine receptivity to implantation: Experssion studies in rat endometrial cells. / Dr. P.K. Mehrotra
Neeraj Shakya	Lucknow University, Lucknow	Design, synthesis and QSAR studies on β3 adrenergic receptor agonist and acetylcholine estrase inhibitiors. / Dr. A.K. Saxena
Pranav Kumar	JNU, New Delhi	Pteridine reductase 1 (PTR) as target fro antifolate chemotherapy against *Leishmania donovani*. / Dr. Neeloo Singh
Prasoon Gupta	Dr. BRA University, Agra	Phytochemical investigation of medicinal plants in search of bioactive natural products./ Dr. Rakesh Maurya
Pravej Akhtar	JNU, New Delhi	Molecular characterization of immunodominant antigens of *Mycobacterium tuberculosis* H37Rv. / Dr. Ranjana Srivastava
Preeti Bajpai	Dr. BRA University, Agra	Improved strategies for the development of antifilarial agents and reversal of immunopathological lesions in rodent host infected with sudperiodic human filarrid *Brugia malayi*. / Dr. Shailja Bhattacharya
Priti Tiwari	Lucknow University, Lucknow	Exploration of biochemical and molecular mechanisms of antidiabetic action of novel natural products. / Dr. Arvind Srivastava

Puja Garg	Lucknow University, Lucknow	Pathomachanism of cerebral ischemia: Role of NO and its immunomodulators/ Dr. Madhur Ray
Rit Vatsyayan	JNU, New Delhi	Characterization of *Leishmania donovani* proteins involved in metabolic pathway. / Dr. Uma Roy
Rumana Ahmad	Lucknow University, Lucknow	Molecular biology and biochemical studies an glutathione-S-transferase(s) from malarial parasites and filarial worms. / Dr. Arvind Srivastava
Sangeeta Aswal	JNU, New Delhi	Synthesis of flexible bicyclic nitrogenous heterocycles, their X-ray crystallographic studies and biological activities./ Dr. Kamlakar Avasthi
Sanjay Kumar	JNU, New Delhi	Studies on heme-induced oxidative stress and antioxidant- defense system in malaria parasite. / Dr. Uday Bandhopadhyay
Sathiamoorthy B.	Dr. RML Avadh University, Faizabad	Phytochemical investigation of biologically active plants. / Dr. Rakesh Maurya
Shagufta	Lucknow University, Lucknow	Design and synthesis of antiestrogens for contraception, osteoporosis and management of other estrogen related disorders./Dr. Gautam Panda
Sharda Prasad Yadav	JNU, New Delhi	Identification and characterization of important structural and function elements of a porforming toxin Hemolysin E, isolated from a pathogenic strain of *Escherichia coli*./ Dr. Jimut Kant Ghosh
Sheikh Mohd. Farooq	Kashmir University, Kashmir	Design, synthesis and chemistry of flexible models based on pyrazolo [3,4-d] pyrimidines and releated compounds for understanding aromatic stacking interactions./ Dr. K. Awasthi
Shipra Srivastava	Dr. BRA University, Agra	Design and synthesis of some potential antiobesity agents / Dr. Kalpana Bhandari
STVS Kiran Babu	Dr. BRA University, Agra	Search for novel dual-function spermicides/ Dr. V.L. Sharma
Vinay Choubey	Jadavpur University	Analysis of a putative gene from *Plasmodium falciparum* having sequence homology with choline kinase with a view to explore its chemotherapeutic potential. / Dr. Uday Bandhopadhyay

2.3 MD Thesis submitted/awarded

Name	University/College	Title/Guide
Smita Govila	Saraswati Dental College & Hospital, Lucknow	A stereo microscopic study evaluating the uniformity and adaptability of guttaflow paste to root canal walls as compared to conventional laterally condensed Gutta Percha using AH^+ as a filler – an *ex vivo* study./ Dr. neeraj Sinha
Ramesh Bharti	KGDU, Lucknow	Peroxide penetration into the pulp chamber from newer bleaching products: An *in vitro* study/ Dr. J.K. Saxena
Akhilesh Kumar	CSMMU, Lucknow	A clinical study of metabolic syndrome in schizophrenia and bipolar disorder. / Dr. J.S. Srivastava
Sarvesh Singh	CSMMU, Lucknow	Study on effect of melatonin in experimental gastro-esophageal reflux disease in rats. / Dr. Gautam Palit

3. Training to sponsored personnel

Under this programme, the Institute conducted the "*Advance Technology Training Programme*" for scientists and technical persons, mainly from industry; training to foreigners under bilateral cooperation with different countries and international agencies; training to sponsored students from academic institutions and ad-hoc short-term training for academia and industry.

3.1 Training under cooperation with Indian universities

Under the training programme, 15 students from Birla Institute of Technology and Science (BITS), Pilani, were provided six months training on monthly stipend.

3.2 Training under cooperation with Indian Academy of Science

Under the programme, 4 students were provided two months training under the cooperation with Indian Academy of Science, Bangalore.

3.3 Adhoc training

Following industry and academia sponsored personnel were trained in Medicinal & Process Chemistry, Toxicology, Pharmaceutics, Parasitology, SAIF, Molecular & Structural Biology, Microbiology and Laboratory Animals divisions of the Institute.

Dr. Chanderesh
PI Industries Ltd.
Udai Sagar Road, Udaipur

Dr. G. Sudhandiran
University of Madras,
Chennai

Dr. Nafeesa Siddiqui
M.P. Council of Science &
Technology, Bhopal

Dr. Shaheen A. Ansari
Bharat Immunological & Biological
Corporation, Bulandsahar

Dr. Shalini Singh
Bareilly College, Bareilly

Mr. Amit Kumar
Bharat Immunological & Biological
Corporation, Bulandsahar

Mr. Avik Mazumdar
D.R.D.E.,
Gwalior

Mr. Pramod Sairkar
M.P. Council of Science &
Technology, Bhopal

Mr. Praveen Kumar Paliwal
PI Industries Ltd.
Udai Sagar Road, Udaipur

Mr. Shubhranshu Gupta
Jawaharlal Nehru Centre for Advanced
Scientific Research Bangalore

Mr. Suresh Kumar
Integral University, Lucknow

Mr. Zameer Ansar
Integral University, Lucknow

Ms. Anapama Tamt
Hindustan Liver Limited, Bangalore

3.4 Following university sponsored students were imparted training

Name of University/College	Name of the Student(s)	Division
A.P.S. University, Rewa	Neha Vaghel	Molecular & Structural Biology
Acharya Nagarjuna University, Guntur, A.P.	A.D.V. Janardhan	Toxicology
Alagappa University, Karaikudi	R. Ajeetha Jeevanathi	Endocrinology
Allahabad Agricultural Institute, Allahabad	Jyoti Tiwari	Toxicology
	Tripti Pandey	Molecular & Structural Biology
	Nilay Mitash	Microbiology
	Neha Kumari	Parasitology
	Amrita Srivstava	Microbiology
Allahabad University, Allahabad	Swati Dwivedi	Biochemistry
	Sunita Yadav	-do-
Amity Institute of Biotechnology, Noida	Sonam Shashmata	Fermentation Technology
	Shrish Mishra	-do-
	Neha Singh	Endocrinology
	Anupama Rajput	Fermentation Technology
	Shivika Rai	Parasitology
	Deepika Gupta	Pharmaceutics
	Shambhavi Pandey	Toxicology
	Sandeep Mann	Laboratory Animals
	Kanishka Gupta	Pharmacology
	Deepanshi Dhar	Microbiology
	Shruti Pandey	Molecular & Structural Biology
	Molika Gupta	Endocrinology
Andhra University, Visakhapatnam	Sanghamitra Purohit	Toxicology
Annamalai University, Annamalai	Santosht Kirtane	Pharmacokinetics & Metabolism & Metabolism
	Vipin Kumar Singh	Pharmaceutics
	Himani Awasthi	-do-
	Shivendra Singh	-do-
	Sandeep Kumar Singh	Toxicology
Avadh University, Faizabad	Anju Srivastava	Fermentation Technology
	Priyanka Singh	Toxicology
	Amber Riaz	Biochemistry
	Richa Srivastava	Parasitology
Ayya Nadar Janaki Ammal College, Sirakasi	P. Sankareswari	Toxicology
	Sudha Pannusamy	Toxicology
	R. Selva Bharathi	Endocrinology

Banaras Hindu University, Varanasi	Shome Sarkar Bhuniya	Medicinal & Process Chemistry
Banasthali Vidyapith Rajasthan	Sonika Jain	Medicinal & Process Chemistry
	Arti Dwivedi	Toxicology
	Shikha Jain	-do-
	Bhawana Singh	Molecular & Structural Biology
	Swati Jain	Toxicology
	Neha Paliwal	Molecular & Structural Biology
	Priyanka Tiwari	Medicinal & Process Chemistry
	Arti Bhardwaj	-do-
	Jyotsana	-do-
	Ritu Chug	-do-
	Pallavi Hajela	Pharmacokinetics & Metabolism
	Megha Joshi	Medicinal & Process Chemistry
	Tooba Shamail	-do-
	Sonal Rastogi	-do-
	Charu Mahawar	-do-
	Anju Yadav	-do-
	Anuradha	-do-
	Deepika Parashar	-do-
	Chandrarupinee	-do-
	Deepti Mishra	-do-
	S. Shilpa	-do-
	Priyanka Chitranshi	-do-
	Jyotsana Jha	-do-
	Anchal Misra	-do-
	Sushma Yadav	-do-
	Neha Srivastava	Fermentation Technology
	Apeksha Srivastava	Documentation & Library
	Vini Fariya	Biochemistry
	Nidhi Shrivastava	-do-
	Mansi Kulshrestha	Fermentation Technology
	Nalinee Pathak	Toxicology
Barkatullah University, Bhopal	Rameshwar Tiwari	Biochemistry
Bharathidasan University, Tiruchirappali	R. Dilmal Krishnanj	Pharmaceutics
	Queenteen Adai	Biochemistry
	Kala Mory R.	
	C. Sofia	Medicinal & Process Chemistry
BIMC College of Life Science, Gwalior	Kirti Srivastava	Toxicology
	Renu Yadav	Biochemistry
Birla Institute of Technology, Mesra, Ranchi	Surbhi Bhargava	Microbiology

Brahamanand College, Kanpur	Anupreeta Sharma	Toxicology
	Anamika Pandey	-do-
	Seema Sachan	Parasitology
Bundelkhand University, Jhansi	Parul Nigam	Biochemistry
	Pallavi Singh	Drug Target Discovery & Development
	Manu Singhal	Molecular & Structural Biology
	Tanvi Saxena	Pharmacokinetics & Metabolism
	Dhirendra Pandey	Endocrinology
	Shalini Shukla	Toxicology
	Shiv Vardan Singh	Parasitology
	Sweta Misra	Pharmacology
	Vikash Yadav	Molecular & Structural Biology
C.C.S. University, Meerut	Rishu Kumar Mittal	Fermentation Technology
	Shweta Srivastava	Drug Target Discovery & Development
	Vikrant Kumar	Biochemistry
C.M.S. College of Science & Commerce, Coimbatore	Mohnnapriya R.	Toxicology
	Suji S. Pillai	Medicinal & Process Chemistry
C.S.J.M. University, Kanpur	Archna Singh	-do-
	Anubhav Rastogi	-do-
	Ankita Jain	-do-
	Rakhi Gupta	Toxicology
	Rakhi Gupta	Molecular & Structural Biology
	Ruchika Saxena	Fermentation Technology
	Garima Singh	Molecular & Structural Biology
	Reetika Chaurasia	Fermentation Technology
	Kritika Srivstava	Documentation & Library
	Rshi Parihar	Molecular & Structural Biology
	Sandeep Kumar Vishwakarma	Documentation & Library
	Rana Rais	Fermentation Technology
	Neha Kashyap	-do-
	Pushpsheel Shukla	Toxicology
Career College, Bhopal	Neha Singh	Fermentation Technology
Chinmaya College of Science, BHEL, Haridwar	Surbhi Jain	Toxicology
College of Life Sciences, Gwalior	Ritu Agarwal	Biochemistry
College of Pharmaceutical Science, Berhampur	Pramdeep Bagga	Pharmaceutics

D.D.U. Gorakhpur University, Gorakhpur	Sweta Singh	Toxicology
	Amrita Shalini Robert	Biochemistry
	Anubha Srivastava	Medicinal & Process Chemistry
D.N.R. College P.G. Course, Bhimavaram	Tangadu Naveen Kumar	Toxicology
	P. Sowmya	-do-
D.S.B. Campus Kumaun University, Nainital	Mohd. Suhail Javed	Medicinal & Process Chemistry
Dayanand Girls College, Kanpur	Pragya Dwivedi	Biochemistry
	Shweta Shukla	-do-
Devi Ahilya Vishwavidyalaya , Indore	Shubra Gupta	Fermentation Technology
	Yashumati Ratan	Medicinal & Process Chemistry
Dolphin (P.G.) Institute of Biomedical Science, Dehradun	Neha Tiwari	Biochemistry
	Chanda Jain	Laboratory Animals
	Kiritka Prakash	Biochemistry
	Manish Dev Sharma	Fermentation Technology
Dr. B. R. Ambedkar University, Agra	Pooja Yadav	Toxicology
	Jeevan Verma	Pharmaceutics
	Dheeraj Upadhyay	-do-
Dr. G.R. Damodaran College of Science, Coimbatore	G. Vanijinayaki	Molecular & Structural Biology
	R. Sridhar	-do-
Dr. H.S. Gaur University, Sagar	Manoj Nahar	Parasitology
	Priyanka Jain	Medicinal & Process Chemistry
G.B. Pant Engineering College, Pauri, Garhwal	Mukesh Mahajan	Medicinal & Process Chemistry
G.B. Pant University, Pant Nagar	Upasana Pawar	Molecular & Structural Biology
	Samlesh Kumar Tiwari	Laboratory Animals
	Mukesh Mahagari	Medicinal & Process Chemistry
Gandhi Institute of Biological Science, Orissa	Bimal Kumar	Parasitology
	Meeralini Khatua	-do-
Government Model Science College, Jabalpur	Saraswati Dubey	SAIF
Govt. Dungar College Bikaner	HemendraSingh Bhandari	SAIF
Govt. M.H. College, Jabalpur	Rashmi Tripathi	Parasitology
Guru Nanak Dev University, Amritsar	Tanu Chandra	Laboratory Animal
	Sadhna Pandey	Fermentation Technology

Gurukul Kangari University, Haridwar	Astha Singh	Endocrinology
Gwalior Institute for Computer Technology & Science, Gwalior	Manjari Dwivedi	Fermentation Technology
Gyan Vihar School of P.G. Studies, Jaipur	Khusbhu Sharma	Toxicology
	Rajnesh Kumar	-do-
	Reena Rawal	-do-
	Piar Chand	Medicinal & Process Chemistry
	Abhishek Raj Agarwal	Fermentation Technology
	Heena Tiwari	Endocrinology
	Vijay Verma	Toxicology
	Garima Dubey	-do-
	Neha Anand	-do-
	Arpan Kaul	Medicinal & Process Chemistry
H.N.B. Garhwal University, Garhwal	Nishant	Biochemistry
Hindustan College of Art & Science, Kalambakkam	Shubham Misra	Molecular & Structural Biology
I.P. College, Bulandshaher	Amit Kumar Sharma	Parasitology
I.T.S. Paramedical College, Ghaziabad	Rahul Kumar Mourya	Medicinal & Process Chemistry
	Vineeta Singh	Biochemistry
	Varun Agarwal	Molecular & Structural Biology
Indira Gandhi Institute of Pharmaceutical	Ajay Kumar	Medicinal & Process Chemistry
Sciences, Bhubaneswar, Orrisa	Bipin Bihari	-do-
Institute of Allied Sciences & Computer Applications, Gwalior	Gagan Jain	Endocrinology
Institute of Engineering & Technology, Lucknow	Vivek Srivastava	Molecular & Structural Biology
	Mohd. Tabish Qidwai	-do-
	Keerti Gupta	Pharmaceutics
	Vaibhav Misra	-do-
Institute of Technology & Science, Ghaziabad	Jayendra Maurya	Medicinal & Process Chemistry
Integral University, Lucknow	Prashant Singh Chauhan	Endocrinology
	Rashmi Singh	Molecular & Structural Biology
	Mahvish	Fermentation Technology
	Khushboo Ambreen	Molecular & Structural Biology
	Sheeba Afreen	Biochemistry

	Amreen Iqbal	Fermentation Technology
	Tajalli Ilm Chandel	Molecular & Structural Biology
	Nazreen Fatima	Microbiology
	Sonali Dubey	Parasitology
	Sweta Prasad	Toxicology
	Ankita Tiwari	Microbiology
	Abha Verma	Medicinal & Process Chemistry
	Vikash Kushwaha	Fermentation Technology
	Bhawna Rupani	Library
	Divya Singh	Molecular & Structural Biology
International College, Jaipur	Runjhun Mathur	Fermentation Technology
Janta College, Bakewar (Etawah)	Gaurav Chaudhary	Fermentation Technology
	Rahul Shivahre	-do-
	Ratna Prabha	Parasitology
Jiwaji Univeristy, Gwalior	Pooja Bhadoriya	Microbiology
	Shubhra Singh	Toxicology
Kamla Raja Girls P.G. College Gwalior	Sapna Agarwal	Fermentation Technology
Kanak Manjari Institute of Pharmaceutical Science, Orissa	Pinki Verma	Pharmacology
	Kirti Gupta	Medicinal & Process Chemistry
	Vinay Kumar Thakur	-do-
Kanguradu Arts Science College, Coimbatore	Tharani Murugavehu	Molecular & Structural Biology
Lord Budha Institute of Technology & Science College, Kota	Pratishtha Sharma	Laboratory Animal
	Swati Tyagi	Toxicology
Lucknow University, Lucknow	Rati Tandon	Endocrinology
	Iram Fatima	Parasitology
	Meenal Gupta	-do-
	Reena Kumari	-do-
	Vishwa Deepak Tripathi	Medicinal & Process Chemistry
M.B. Khalsa College, Indore	Anjita Kashyap	Biochemistry
M.L.K. (P.G.) College, Balrampur	Amar Chand	Pharmaceutics
Madanlal Sukhadia University, Jaipur	Rahul Tyagi	Laboratory Animal
	Rajhans Tyagi	Toxicology
	Neeraj Verma	Molecular & Structural Biology
Maharishi Arvind Institute of Engineering & Technology, Jaipur	Vishakha Joshi	Toxicology

Meerut Institute of Engineering & Technology, Meerut	Shaswal KansaL	Pharmaceutics
MJP Rohilkhand University, Bareilly	Akanksha Mishra	Biochemistry
Modern Institute of Technology, Rishikesh	Ritu Saini	Parasitology
Modi Institute of Management of Technology, Rajasthan	Savita Prashar	Molecular & Structural Biology
Muthayamal College of Art & Science, Tamil Nadu	Deepika Gavvala	Fermentation Technology
Nehru Art & Science College, Coimbatore	Deepa Alex	Endocrinology
	Betty Teena Thomas	-do-
	Shinti Achamma George	-do-
Nirma University, Ahemadabad	Rabadia Nishat Vithal Bhai	Medicinal & Process Chemistry
	Viral Devmurari	-do-
	Jagat Kumar Upadhyay	-do-
Northern India Engineering College, Lucknow	Samidhi Lal	Medicinal & Process Chemistry
	Gaurav Garg	-do-
	Shikha Shrivastva	-do-
	Mukesh Masand	-do-
Orissa University of Agriculture & Technology, Bhubaneswar	Bineta Biswajeeta Raout	Molecular & Structural Biology
P.V.K.K. P.G. College, Anantapur	R. Bharathi	SAIF
Patna University, Patna	Prema Kashyap	Biochemistry
Pondicherry University, Pondicherry	Arti Singh	Toxicology
PSG College of Art & Science, Coimbatore	R. Dinesh	Endocrinology
	K. Venkatasub-ramaniam	Parasitology
Pt. J.N.M. Medical College, Raipur	Shilpi Halder	Toxicology
Punjab Technical University, New Delhi	Arpit Khanna	Biochemistry
Punjab Technical University, New Delhi	Arif jamal Siddiqui	Parasitology
R.C. Patel College of Pharmacy, Maharashtra	Balaramnavar Vishalsinh Maharisirh	Medicinal & Process Chemistry
Rajeev Gandhi College, Bhopal	Animesh Mathur	Parasitology
	Megha Ahirwar	-do-

Rajiv Gandhi Proudyogiki Vishvidyalaya, Bhopal	Shiwal Kumar Singh	Microbiology
Sai (P.G.) Institute of Paramedical & Allied Science, Garhwal	Pushpa Prasad	Biochemistry
	Rashmi Umaro	-do-
	Ankur Bishnoi	Fermentation Technology
Sambalpur University, Orissa	Rajlaxmi Mishra	Pharmacology
Sanjay Gandhi Post Graduate College, Meerut	Narendra Kumar	Microbiology
Sastra University, Thanjavur	Nitin Chitranshi	Molecular & Structural Biology
Seedling Academy of Design & Management, Jaipur	Tripty Agarwal	Toxicology
	Payal Singh	-do-
	Shuit Mathur	Molecular & Structural Biology
	Akshima Agrawal	Toxicology
	Neha Mathur	-do-
	Himanshu Bhatanagar	Anti. T.B. Screening Unit
	Varun Sharma	Laboratory Animals
	Sakshi Saxena	-do-
	Juhi Saxena	Pharmacology
	Deepak Bhaskar	Molecular & Structural Biology
Seemanta Institute of Pharmaceutics Science, Orissa	Debarjan Sen	Medicinal & Process Chemistry
Sri Krinshnadevaraya University, Anantapur	K. Zabiulla	Molecular & Structural Biology
SRM Collage of Pharmacy, Katlankula	Chandra Shekhar	SAIF
St. Thomas College, Bhilai, Chhatisgarh	Ozhathil Lijo Cherian	Microbiology
Study center for Biochemistry, Rewa	Smita Verma	Endocrinology
Subhash Chandra Bose College, Gwalior	Sweta Srivastava	Fermentation Technology
T. John Collage, Bangalore	V. Divya	Toxicology
Thapar Institute of Engineering & Technology, Patiala	Sneha Agarwal	Toxicology
Ultra College of Pharmacy, Madurai	Saket Singh Chandel	Pharmacology
V.B.S. Purvanchal University, Jaunpur	Vandana Singh	Microbiology

Vellore Institute of Technology, Vellore	Subhandu Chakraborty	Medicinal & Process Chemistry
	Rajat Pandey	Toxicology
	Shweta Mishra	SAIF
	Kavita Kakkar	Microbiology
	Anjan Kumar Nayak	Medicinal & Process Chemistry
	Pawan Kumar	-do-
	S. Surya Dilip	-do-
	Jagan Mohan Paluru	-do-
	Sangram Keshari Saraf	-do-
	Pratap Paritala	-do-
	Ashutosh Kumar	Microbiology
Vikram University, Ujjain	Nidhi Jain	Molecular & Structural Biology
Vinayaka Missions College, Salem	Praveen Bansal	Pharmacology

7. Lectures Delivered

Name of the Scientist	Title of the Lecture	Place/Date
Dr. K.P. Madhusudanan	Direct analysis in real time (DART) – A new ionization technique.	CDRI, Lucknow (27.09.07)
	Direct analysis in real time (DART) – A new ionization technique.	National Institute for Interdesciplinary Science & Technology, Trivandrum (27.04.07)
	Applications of direct analysis in real time (DART) –A new ionization technique.	NIO, Goa (25.03.07)
Dr. A.K. Saxena	Rational drug design in substituted arylpiperazines.	Institut für Chemie Abteilung Organische Chemie Universität, Rostock, Germany (17.09.07)
	QSAR & molecular modeling studies on substituted pyrazinopyridoindoles and related compounds as potential antihistamines (H_1).	Universität Erlangen-Nürnberg, Erlangen, Germany (13.09.07)
	Design and synthesis of octa/ decahydropyrazinopyridoindoles as potential antipsychotic agents.	Technische Universitat, Dressden, Germany (11.09.07)
	Chemistry and pharmacology of octahydropyrazinopyridoindoles and related compounds.	Georg-August-University Göttingen, Germany (07.09.07)
	Internet resources in GPCR modeling.	Leninsky Prospekt, Moscow (01.09.07)
	The concept proposal.	URDIP, Pune (30.06.07)
	Global warming and public health: Role of drug discovery research.	Kumaun University, Nainital (08.06.07)

	An introduction to drug discovery & development.	SMS College, Chandausi (16.04.07)
	Application of 2D & 3D QSAR in rational drug design (Part III).	Lucknow University, Lucknow (16.03.07)
	Basic principles & methodologies of 2D & 3D QSARs (Parts I & II).	Lucknow University, Lucknow (15.03.07)
	Basics and applications of 2D & 3D QSAR in antihistamines.	Saurashtra University, Rajkot (03.01.07)
	Design, synthesis & SAR in substituted octahydropyridoindoles for their antipsychotic activity.	Saurashtra University, Rajkot (02.01.07)
Dr. G. Palit	Development of anti gastric ulcer drug: strategies and future prospects.	Jadavpur University, Kolkata (14.07.07)
Dr. O.P. Asthana	R&D programme & achievements of CDRI.	CDRI, Lucknow (28.12.07)
	Management of *P. falciparum* malaria with focus on E-mal, á/â Arteether, a success story from CDRI/CIMAP-THEMIS Medicare Ltd, India.	ACCRA, Ghana (29.11.07)
	CDRI, an institutional profile with focus on R&D capabilities and achievements.	CDRI, Lucknow (07.11.07)
	Integrating with diverse inputs: reaching the unreached.	CSIR Headquarters, New Delhi (11.09.07)
	Profile of CDRI Compound 97/78, an IND for *P. falciparum* malaria.	ICMR Headquarters, New Delhi (02.06.07)
	Achievements of CDRI with reference to drug development programme.	CDRI, Lucknow (14.03.07)
	Phase-III and Phase-IV clinical trials in reference to clinical trials with CDRI drugs.	PGIMER, Chandigarh (20.02.07)
Dr. Ram Raghubir	Marine-Biota: A rich source of novel drug candidates.	NIPER, Chandigarh (03.11.07)
	Molecular targets in cerebral stroke.	ITRC, Lucknow (30.07.07)
Dr. S.B. Katti	DNA microarray: Enabling technology in drug discovery	MCPS, Manipal (15.11.07)
	Structural investigation on peptide coupling reagents	MCPS, Manipal (15.11.07)

Dr. R. K. Sharma	An introduction to biotechnology and Web resources.	Biotech Park, Lucknow (10.11.07)
	Biological database and bioinformatics: a case study.	SGPGI, Lucknow (1.12.07)
	Introduction to biological databases.	SGPGI, Lucknow (1-2.12.07)
	Bioinformatics & drug development.	ACS Bio-informatics, Lucknow (29.04.07)
	Genome analysis: Tools, technologies and case studies.	AMU, Aligarh (24-25.02.07)
	Genome analysis: Statistical & visualisation tools.	AMU, Aligarh (24-25.02.07)
	Genome-phylogenetics and sequence alignment.	AMU, Aligarh (24-25.02.07)
	Protein structure prediction.	AMU, Aligarh (24-25.02.07)
Dr. Kamalakar Awasthi	Pyrazolo[3,4-d]pyrimidine core : A versatile heterocycle for studying 'arene interactions' in flexible compounds.	Welcom Hotel Rama International, Aurangabad (24.02.07)
Dr. J. K. Saxena	Parasitic enzymes as potential targets for antiparasitic . drug development	Lucknow University, Lucknow (29.12.07)
	DNA topoisomerases as effective chemotherapeutic targets for development of new antifilarial compounds.	Lucknow University, Lucknow (08.12.07)
	Parasitic enzymes as chemotherapeutic targets for antiparasitic drug discovery.	Dr B.R. Ambedkar Marathwada University, Aurangabad (25.02.07)
Dr. J.S. Srivastava	Therapeutic misconception.	St. John's Medical College, Bangalore (18.09.07)
	Bioethics initiative at CDRI.	University of Toronto (28.05.07)
	Ethical issues in clinical research.	PGIMER, Chandigarh (20.02.07)
	Biomedical ethics.	KGMU, Lucknow (09.02.07)

Dr. C. Nath	Targets for the development of anti-dementia drugs.	AIIMS, New Delhi (19.11.07)
	Evaluation of young Spontaneously Hypertensive rats as a model of attention deficit hyperactivity disorder.	NIPER, Chandigarh (03.11.07)
	Neuropharmacology of memory functions and disorders.	CSMMU, Lucknow (24.08.07)
Dr. Madhu Dikshit	Free radical generation and neutrophil extracellular trap formation by nitric oxide.	SGPGI, Lucknow (17-22.12.07)
	New drug development for cardiovascular activities at CDRI: basic studies on neutrophils and aortic rings.	Sree Chitra Institute for Medical Sciences & Technology, Trivandrum (17.11.07)
	Molecular, biochemical and pharmacological strategies for new drug development in CVS.	DRDO, Gwalior (10-11.09.07)
	Nitric oxide mediated signaling in neutrophils: Modulation of free radical generation and apoptosis.	JNU, New Delhi (10 -14.02.07)
	Methodologies for the assessment of free radical generation from neutrophils: Use of flow cytometry.	Amrita Institute of Medical Sciences, Cochin (4-5.01.07)
	Nitric oxide mediated signaling and modulation of neutrophil free radical generation.	Fariyas, Lonavala (8 -11.01.07)
Dr. A. K. Dwivedi	Purification of the compounds by Prep HPLC.	Pesticides India, Udaipur (05.10.07)
Dr. M. Abbas	Statistical analysis and modeling of data in post-genomic era.	CDRI, Lucknow (20.09.07)
	Theoretical and computational aspects of bioinformatics.	CDRI, Lucknow (05.09.07)

Dr. Naibedya Chattopadhyay	Biology of calcium-sensing receptor.	North Bengal University, Siliguri (12.12.07)
	Preventive to therapeutic transition of phytoestrogens as anti-osteoporotic agents: Are we there yet?	Sri Venkateswara Institute of Medical Sciences, Tirupati (02.12.07)
	CaSR mutations. *Meet the Professor session.*	Sri Venkateswara Institute of Medical Sciences, Tirupati (30.11.07)
	Discovery and physiology of calcium-sensing receptor.	AIIMS, New Delhi (29.09.07)
	Role of calcium-sensing receptor in bone biology.	Nutrition Foundation of India, New Delhi (01.08.07)
	Role of a cell surface cation-sensing receptor in the regulation of chemokine secretion and chemotaxis in gonadotropin releasing hormone secreting neuron.	BHU, Varanasi (27.02.07)
Dr. Sudhir Sinha	Fundamentals of proteomics	CIMAP, Lucknow (07.12.07)
	Proteomic approach for identification of new drug targets and vaccine candidates against mycobacterial diseases.	Kanpur University, Kanpur (20.11.07)
	Determinants of immunity against tuberculosis in a TB endemic setting.	AIIMS, New Delhi (30.01.07)
Dr. Madhur Ray	Neurodegeneration and neuroprotection.	IICB, Kolkata (08.01.07)
Dr. Neeraj Sinha	An outline for safety evaluation of ayurvedic medicines with emphasis on Bhasmas.	BHU, Varanasi (30-31.10.07)
	GLP – Practical aspects.	CDRI, Lucknow (18.09.07)
	Testing of reproductive toxicity of candidate drugs.	CDRI, Lucknow (18.09.07)
	Santan virupita (Birth Defects/ Teratogenicity.	CDRI, Lucknow (27-28.09.07)
	NMR based metabonomics.	Biotech Park, Lucknow (30.06.07)
	NMR based metabonomics-A platform for toxicology and teratological studies.	ICCMRT, Lucknow (29.04.07)
	Lead exposure and reproductive health.	NGRI, Hyderabad (06.04.07)
	Safety evaluation of ayurvedic medicines/compounds.	Goaplabandhu Ayurveda Mahavidyalaya, Puri (09.01.08)
	WHO guidelines on research in herbal and herbomineral drugs.	Goaplabandhu Ayurveda Mahavidyalaya, Puri (09.01.08)

Dr. R. P. Tripathi	Carbohydrates: A natural gift for new chemotherapeutics.	Gorakhpur University, Gorakhpur (21.06.2007)
	Explorations in medicinal chemistry with simple sugars	Delhi University, Delhi (27.11.2007)
Dr. Wahajul Haq	Chemistry of peptides.	Ranbaxy Laboratories Ltd., Gurgaon (08.05.07)
	Peptide-oligonucleotide conjugates: Synthesis and applications.	BHU, Varanasi (24.03.07)
	Novel strategies for vaccine construct towards enhanced immunogenicity and HIV recognition.	Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (25.02.07)
Dr. P.M.S. Chauhan	Combinatorial chemistry: A new tools in drug discovery.	Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (26.02.06)
Mr. Vinay Tripathi	Intellectual property rights and related issues.	CDRI, Lucknow (27.09.07)
Dr. A.K. Shaw	Stereoselective syntheses and application of highly functionalized carbohydrate derived tetrahydrofurans.	BHU, Varanasi (24.03.07)
	Studies on glycal derived 2,3-epoxy alcohols and their application towards syntheses of trisubstituted. THF derivatives	Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (26.02.07)
Dr. Neena Goyal	DNA microarray: A tool to explore mechanism of drug resistance in Leishmania.	CDRI, Lucknow (20.12.07)
	DNA microarray as a tool for drug development against Leishmania.	ITRC, Lucknow (19.11.07)
Dr. P.R. Maulik	Crystallography with 1D, 2D and 3D crystals.	University of Madras, Chennai (23.01.07)
Dr. S.K. Rath	Single nucleotide polymorphism and disease association.	Utkal University, Bhubaneshwar (10.02.07)
	Single nucleotide polymorphism and diseases.	JNMMC, Raipur (09.02.07)
Dr. Amit Misra	Design and process considerations for ayurvedic nanomaterials.	Biotech Park, Lucknow (22.12.07)
	Apoptosis induction by microparticle drug delivery system in infected macrophages.	Grand Maratha Sheraton, Mumbai (14.02.07)

Dr. R.K. Singh	Molecular toxicity of male antifertility drugs.	NIH & FW, New Delhi (15.12.07)
	Molecular haematotoxicity of drugs & vaccines.	LU, Lucknow (08.12.07)
	Molecular toxicology of chemicals	Hebbal Veterinary College Bangalore. (06.10.07)
Dr. Gautam Panda	Synthesis of α-amino acid based chiral privileged heterocycles and their pharmacological evaluation	Ludwig-Maximilians-Universität, Germany (13/06/07)
	- do -	Universität Regensburg, Germany (14/06/07)
	- do -	University of Leiden, The Netherlands (06/06/07)
	- do -	University of Düsseldorf, Germany (18/06/07)
Dr. T. Narender	Biologically active lead molecules from the Indian medicinal plants.	Acharya Nagarjuna University, Guntur (10.02.07)
Dr. Charu Sharma	Principles and applications of bioinformatics in biotechnology.	Biotech Park, Lucknow (11.12.07)
	Structural bioinformatics.	Biotech Park, Lucknow (08.06.07)
Dr. Imran Siddiqui	Protein 3-D structure prediction.	SGPGI, Lucknow (02.12.07)
	Bioinformatics and *insilico* drug discovery.	Biotech Park, Lucknow (13.09.07)
	Computer-aided drug design : From molecular interactions to molecular docking.	Biotech Park, Lucknow (22.06.07)
	Computer-aided drug design : From molecular interactions to molecular docking.	Biotech Park, Lucknow (08.06.07)
	Bioinformatics and *in silico* drug discovery.	ICCMRT, Lucknow (29.04.07)
	Bioinformatics and *in silico* drug discovery.	Integral University, Lucknow (29.03.07)
	Bioinformatics and *in silico* drug discovery.	Biotech Park, Lucknow (15.02.07)

Dr. Manoj K. Barthwal	Models to study atherosclerosis.	Sree Chitra Institute for Medical Sciences & Technology Trivandrum (18.11.07)
Dr. Shakil Ahmed	A protein similar to Rb binding protein 2 at the crossroad of chromatin and DNA damage checkpoint pathway.	IMTECH, Chandigarh (26.07.07)
Dr. Mukesh Srivastava	Experimental design, testing and regression in drug research.	CDRI, Lucknow (19.09.07)
Dr. Sripathi Rao Kulkarni	Intellectual property rights and related issues.	CDRI, Lucknow (28.09.07)
	Introduction to intellectual property rights.	CDRI, Lucknow (18.05.07)

8. Distinguished Visitors/ Lectures

Dr. Lalji Singh Director Center for Cellular and Molecular Biology Hyderabad.	32nd Sir Edward Mellanby Memorial Lecture "What is human life?"	17.2.07
Dr. Sabyasachi Sanyal Center for Biotechnology Department of Bio-sciences & Nutrition Karolinska Institute Sweden.	Involvement of co repressor complex subunit GPS2 in transcriptional pathways governing bile acid biosynthesis in humans.	22.2.07
Dr. Kanury V.S. Rao, Head, Immunology Group, International Center for Genetic Engineering & Biotechnology New Delhi.	10th Dr. B. Mukerji Memorial Lecture "Plasticity of the Intracellular Signaling Network."	27.2.07
Dr. Surender Kharbanda Assistant Professor Dana Farber Cancer Institute Harvard Medical School, AccuraGen.	Oncology drug development using novel technology and unique platform of targets.	20.3.07
Dr. Ashwinikumar A. Raut Department of Clinical Pharmacology T.N. Medical College, Mumbai.	Ayurveda and rheumatology.	26.3.07
Dr. Debendra Kumar Mohapatra Division of Organic Chemistry National Chemical Laboratory, Pune.	Asymmetric total synthesis of biologically active complex natural products and designed molecules.	26.3.07
Prof. Sandeep Kumar Department of Surgery K.G. Medical University, Lucknow.	Endocrinological regulation of benign breast disorders.	10.4.07

Dr. Devki Nandan Assistant Professor Department of Medicine University of British Colombia Vancouver, Canada.	Regulation of macrophage cell signaling by intracellular pathogens : Leishmania as a paradigm.	26.4.07
Prof. Susheel Durani Indian Institute of Technology, Mumbai.	Book of life in language of God : What about the grammars.	2.7.07
Dr. Raghava Reddy Kethiri Department Chemie Technische Universität Dresden Bergstrasse 66,01069 Dresden, Germany	Transition metals in the synthesis of pharmacologically active carbazole alkaloids.	7.8.07
Dr. Patricia K.A. Mongini Hospital of Joint Disease, New York University Medical Centre, USA	Role of innate immunity and autocine in human B-cell colonal expansion	14.8.07
Prof. K.P. Chang Rosalind Franklin Institute of Medical Sciences, Chicago, USA	Leishmaniac jihad: Let the evils fight the devils.	24.10.07
Mr. John E. Croft Marine Research and Development Consultant, New Zealand	Natural healthcare products from the sea with special focus on New Zealand: Green lipped mussel for treatment of arthritis.	20.11.07
Dr. Saleem A. Khan University of Pittsburgh School of Medicine Pittsburg, USA	Intron mediated gene disruption for functional analysis.	27.11.07
Prof. Subhash C. Pandey Department of Psychiatry, University of Illinois, Chicago, USA	Activity regulated cytoskeleton (Arc) protein, spines and alcohol addiction.	3.12.07
Prof. Sanghamitra Raha Crystallography and Molecular Biology Division Saha Institute of Nuclear Physics Kolkata	Reversal of the anti-apoptotic conditions prevailing in chronic stress and malignancy by Resveratrol.	30.1.08

9. Membership of Committees/Boards

Dr. Rakesh Tuli

Member, Executive Council, The National Academy of Sciences, Allahabad;
President, Institute of Ethnobiology, Gwalior;
President, International Society of Environmental Botanists, Lucknow;
Member, Executive Committee, Environmental Mutagen Society of India;
Vice President, Executive Committee, Uttar Pradesh Association for Science and Technology Advancement;
Member, Genetic Engineering Advisory Committee, Ministry of Environment & Forests;
Member, Review Committee on Genetic Manipulation, Department of Biotechnology;
Member, Bureau of Indian Standards, Govt. of India;
Member, Research Advisory Committee, Indian Institute of Sugarcane Research, Lucknow;
Member, Research Council, National Institute of Science Communication and Information Resources (NISCAIR), New Delhi;
Member, Research Council, Central Drug Research Institute, Lucknow;
Chairman, Local Advisory Committee, Regional Science Centre, Lucknow;
Member, Uttar Pradesh State Biodiversity Board;
Member, Editorial Board, Proc. (Biological Sciences), National Academy of Sciences, India;
Member, Advisory Committee/Management Board of Lucknow Zoological Garden;
Expert Member and Examiner for Ph.D. and Postgraduate Degrees in Biotechnology and Botany in Indian Agricultural Research Institute, Jawahar Lal Nehru University, Banaras Hindu University, Lucknow University, Guwahati University, Punjab University, Meerut University, S.G.P.G.I. Medical Sciences, Indian Institute of Technology (Kharagpur), etc;
Member/Chairman, Assessment, Selection and Screening Committees for academic positions under CSIR, ICAR, ASRB, DBT & DST;
Member, Committees of DST, DBT, DAE, CSIR, ICAR, Indo-French Centre, European Communities, Rajiv Gandhi Institute of Contemporary Studies;
Chairman, Advisory Committee / Peer Group of Experts, Central Research Institute of Unani Medicine, Lucknow;

Member, Task Force, Agricultural Biotechnology, Department of Biotechnology, New Delhi;
Member, Task Force, Biopesticide and Crop Management, Department of Biotechnology, New Delhi;
Member, Task Force, Improvement of Fibre Crops, Department of Biotechnology, New Delhi;
Member, Task Force, Reinvigorating Indian Agriculture through S&T, Department of Science & Technology;
Member, Joint Working Group, Referral Centres for Detection of Genetically Modified Foods under PFA Act, Department of Biotechnology, New Delhi;
Member, Inter Departmental Plant Variety Registration Implementation, Protection of Plant Varieties and Farmer's Rights Authority, New Delhi;
Member, Editorial Board, Medicinal & Aromatic Plants Abstracts (MAPA), NISCAIR;
Member, Editorial Board, Indian Journal of Biotechnology, NISCAIR;
Member, Editorial Board, Indian Journal of Experimental Biology, NISCAIR.

Dr. C.M. Gupta

President, Society of Biological Chemists (India);
President, Uttar Pradesh Association for Scientific and Technology Advancement;
Chairman, Joint National Committee for Biochemistry & Molecular Biology and Microbiological Science;
Chairman, DBT Reconstituted Review Committee on Genetic Manipulation;
Chairman, DST Expert Committee, Pharmaceutical Research & Development Support Fund;
Chairman, Committee of Ministry of Chemicals & Fertilizers for Granting Exemption from Price Control under DPCO, 95;
Chairman, Scientific Advisory Committee, Tuberculosis Research Centre (ICMR), Chennai;
Chairman, Scientific Advisory Committee, National Institute for Research in Reproductive Health (ICMR), Mumbai;
Chairman, Nagar Rajbhasha Samiti, Lucknow;
Member, Scientific Advisory Committee of Drugs for Neglected Diseases Initiative (DNDI), Geneva;
Member, ASSOCHAM Pharmaceuticals Committee;
Member, FICCI Pharmaceuticals Committee;
Member, CII National Pharmaceutical Committee;
Member, Medical Biotechnology Development Board of DBT;
Member, Promotions and Assessment Committee, Indian Institute of Science, Bangalore;
Member, Drug Development Promotion Board, Govt. of India;
Member, ICMR Scientific Advisory Board;
Member, Governing Body, National Centre for Cell Science;

Member, Scientific Advisory Committee, AIDS Research Institute (ICMR), Pune;
Member, Scientific Advisory Committee, National Center for Cell Science, Pune;
Member, Scientific Advisory Committee, National Institute of Immunology, New Delhi;
Member, DBT Biotechnology Research and Promotion Committee;
Member, Academic Council, Jawaharlal Nehru University, New Delhi;
Member, Executive Council, Jawaharlal Nehru University, New Delhi;
Member, Governing Body, Institute of Clinical Research, Dehradun & Mumbai;
Member, Drugs Technical Advisory Board;
Member, Board of Directors of Bharat Immunologicals & Biologicals Corporation Ltd.;
Member, DST Project Advisory Committee in the Area of Health Sciences;
Member, Fellowship Scrutiny Committee, National Academy of Sciences, India;
Member, Research Council, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow;
Member, Research Council, Post Graduate Institute of Medical Education and Research, Chandigarh;
Member, Editorial Board, Indian Journal of Biophysics;
Member, Editorial Board, Medicinal and Aromatic Plants Abstracts.

Dr. Vinod Bihari

Member, Board of Studies for M.Sc. (Biotechnology), V.B.S. Purvanchal University, Jaunpur;
Member, Core Group on Biotechnology, Council of Science & Technology, U.P., Lucknow;
Member, Adhoc Expert Committee for Project Evaluation of TDB;
Chairman, Expert Committee for Biotechnology, Council of Science & Technology, U.P.;
Member, Research Degree Committee for Biotechnology and Bioinformatics, U.P. Technical University, Lucknow;
Member of Project Monitoring Committee of Technology Development Board, New Delhi;
Member, Board of Studies for Biochemical Engineering, BHU, Varanasi;
Chairman, Expert Committee of Biotechnology, Council of Science & Technology, U.P. (2006-07);
Member, Research Degree Committee of Biotechnology and Bioinformatics of U.P. Technical University, Lucknow (2006-08);
Core Member of CSIR's Assessment Committee of RAB for area Biosciences & Biotechnology;
Member, Management Council, ITRC, Lucknow (2007-09);
Nominated as DBT representative in the Institutional Bio-safety Committee (IBSC) of CIMAP, Lucknow (2007-10).

Dr. K.P. Madhusudanan	Member, Editorial Board, Journal of Mass Spectrometry, John Wiley & Sons, UK.
Dr. Zaka Imam	Member, Editorial Board, CDRI Annual Report 2007- 08; Member, Editorial Board, International Journal of Health Technology & Management, Inter Science Enterprises Ltd., UK; Member, Management Council, CDRI.
Dr. S.C. Agarwal	Member, Governing Body, Institute of Ethnobiology, Jiwaji University, Gwalior; Member, Editorial Board, Ocean Drugs Alert Bulletin, CDRI, Lucknow.
Dr. Satyawan Singh	Member, Drugs Panel for New Drugs Manufacturing Licenses, Directorate of Medical & Health Services, U.P.; Member, Drugs and Pharmaceutical Working Group, Udyog Bandhu, UP.; Member, Ecomark Technical Committee, Central Pollution Control Board, Ministry of Environment & Forests, New Delhi.
Dr. P.K. Roy	Chief Editor, Drugs and Pharmaceuticals - Industry Highlights; Chief Editor, Drugs and Pharmaceuticals - Current R&D Highlights; Chairman, Lucknow Special Libraries Consortium.
Dr. A.K. Saxena	Member, Board of International Charitable Foundations (Scientific Partnership) Coordinating Board, Russia; Member, Editorial Board of the International Journal Medicinal Chemistry Research; UGC Nominee, Department of Chemistry, Saurastra University, Rajkot; UGC Nominee, Department of Chemistry, A. P. S University, Rewa; Patent Evaluator, Current Drugs Ltd., U.K.; Secretary, QSAR Society of India; Member, American Chemical Society, USA; Life Member, Indian Chemical Society; Life Member, Indian Association of Medicinal Chemists; Member, Board of Directors, American Bibliography Inc. USA.; Life Member, UP Association for Science and Technology Advancement.
Dr. Ranjana Srivastava	Member, Task Force on "Biotech Products and Process Development", DBT; Editor, Indian Journal of Microbiology; Member, Microbial Prospecting, National Bioresource Development Board, DBT; Member, IBSC, ITRC, Lucknow; DBT Nominee, IBSC, IITR, IIT, Kanpur; Convener, IBSC, CDRI; DBT Nominee, IBSC, IITR, Lucknow; Member, Doctoral Committee, SGPGI, Lucknow.

Dr. O.P. Asthana

Member, Scientific Advisory Committee of NLAC, National Institute of Nutrition (ICMR), Hyderabad (2001-2007);
Member, Panel of Project Reviewers, UPCST;
Member, Panel of Project Reviewers, DST, Govt. of India;
Member, Panel of Referees, Indian J. Biotechnology (NISCOM);
Member, Selection Committee, CDRI, Lucknow;
Member, Selection Committee, NEERI, Nagpur;
Member, Selection Committee,CSIO, Chandigarh;
Medical Ethics Committee, CDRI, Lucknow;
Member, Medical Ethics Committee, U.P. Biotechpark, Lucknow;
Member, Medical Ethics Committee, Era Medical College, Lucknow;
Member, Medical Ethics Committee, ITRC, Lucknow;
Member, Panel of Referees, Indian Journal of Biotechnology;
Chairman, Selection Committee, CEERI, Pilani;
Member, Selection Committee, ITRC, Lucknow;
Invited Faculty Member, Institute of Clinical Research (India), New Delhi;
Member, Selection Committee, University of Delhi;
Member, Selection Committee, UPDPL, Lucknow;
Member, Management Council, CDRI.

Dr. Ram Raghubir

Secretary, Indian Pharmacological Society (Lucknow Branch);
Member, National Steering Committee, MoES Project: Drugs from the sea, New Delhi;
Member, Master's & Doctoral Committee, SGPGIMS, Lucknow, IVRI, Izatnagar, Delhi University, Delhi, Jiwaji University, Gwalior, BITS, Ranchi and NDAUST, Faizabad;
Chairman, Ocean Drug Alert, CDRI, Lucknow;
Member, Editorial Board, Drugs & Pharmaceuticals, Current R&D Highlights;
Member, Editorial Board, Annals of Neurosciences;
Member, Animal Ethics Committee, CDRI, Lucknow.

Dr. Gautam Palit

Member, Project Review Committee, Department of Scientific & Industrial Research (DSIR), DST, New Delhi;
Member, Fellowship Expert Group Committee, Indian Council of Medical Research (ICMR), New Delhi;
Member, Ethics Advisory Committee, CDRI, Lucknow;
Member, Institutional Ethics Committee, Vivekananda Polyclinic & Institute of Medical Sciences, Lucknow;
Member, Task Force – CSIR co-ordinated programme on bioactive substances from plant sources – Anti-ulcer and anti-anxiety activity;
Member, Board of Examiner, Jadavpur University, Kolkata, University of Calcutta, Kolkata, and Aligarh University, Aligarh.

Dr. R.K. Sharma	Member, Editorial Board "Ocean Drugs Alert" (2006-2007), CDRI, Lucknow; Member, Computer Society of India, Chennai; Member, Indian Society of Authors, New Delhi; Member, Euro-India GRID; Member, Bioinformatics. Org.; Member, Proteomics-Genomics.net; Member, Indian Phytopathological Society, New Delhi.
Dr. S.K. Puri	Member, Editorial Board, Journal of Parasitic Diseases; Member, Executive Committee, Indian Society for Parasitology; Member, Steering Committee, DNDI sponsored Pan Asian Network for Drugs for Neglected Diseases from Natural Sources; Member, Institutional Animal Ethics Committee, Indian Animal Suppliers, Lucknow.
Dr. C. Nath	Member, Documentation & Library Committee, CDRI; Member, Staff Welfare Committee, CDRI; Member, Animal Ethic Committee, ITRC; Member, Review Committee, ITRC; Member, Discovery Groups (Anti-dementia & Anti-psychotics), CSIR-Coordinated Programme.
Dr. Sudhir Srivastava	Life Member, National Academy of Sciences, Allahabad, India; Life Member, Society of Toxicology, India; Life Member, Indian Medical Association; Fellow, German Academic Exchange Service, Bonn, Germany; Home Grown Technology (HGT) Project Activity Monitoring Committee, TIFAC; Member, Histochemical Society, Washington; Life Member, UP Association of Science and Technology.
Dr. Shailja Bhattacharya	Member, Scientific Advisory Committee (SAC), VCRC, Pondicherry; Member, Academic Council of JNU, Delhi; Member, Cytometry Society of India; Honorary Advisor, German Academic Exchange Services (DAAD). Member, Management Council, CDRI.
Dr. Ashim Ghatak	Member, Adjudicating Committee, Indian Pharmacology Society for Awards & Orations; Member, Assessment Committee, NML, Jamshedpur; Elected Secretary General, Indian Society of Hypertension; Member, National Expert Panel on Lathyrism, Ministry of Agriculture, Govt. of India; Member, Doctoral Committee, SGPGIMS, Lucknow.
Dr. J. S. Srivastava	Member, Ethics Committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI), Lucknow; Member, Ethics Committee of King George Medical University, Lucknow; Member Secretary – Medical Ethics Committee of CDRI, Lucknow.

Dr. V. K. Bajpai	Member, Editorial Board, E.M.S.I. Bulletin, Kanpur.
Dr. G. K. Jain	Member, ISTAG & ISTAD, CSIR; Member, Official Side of the Local Council of CSIR, Adoption of Central Civil Services Rules, 1993 & for Establishment of Joint Consultative Machinery.
Dr. Rajendra Prasad	Life Member, UP Association for Advancement of Science & Technology; Member, Editorial Board, CDRI Annual Report 2007- 08.
Dr. A. K. Dwivedi	Member, Drugs Panel for New Drugs Manufacturing Licenses, Directorate of Medical & Health Services, U.P.; Life Member, UP Association for Advancement of Science & Technology; Life Member, Indian Pharmaceutical Association; Member, Expert Committee, Dr. B. R. Ambedkar University, Agra; Joint Secretary, Indian Society of Chemists and Biologists. Lucknow.
Dr. M. Dikshit	Member, Project Advisory Committee – ICMR; Member, Project Advisory Committee – DST; Member, Project Advisory Committee – SGPGI.
Dr. A.K. Goel	Executive Editor, Ocean Drugs Alert Bulletin; Executive Editor, CDRI Annual Report 2007- 08.
Dr. M. Abbas	Institutional Animal Ethics Committee, CDRI; Member, Task Force, MoES Project; Member, CDRI Editorial Board, Drugs and Pharmaceutical Industry Highlights, CDRI.
Dr. Uma Roy	Expert Member, Research Degree Committee, CSJM University, Kanpur.
Dr. Rakesh Shukla	Member, Course Coordinator: CDRI-JNU Ph.D program;
Dr. J.K. Saxena	Member, Expert Committee, B. Tech. Indian Institute of Technology, Roorkee; Member, Agriculture Research Service Examination Board; Expert, Department of Biochemistry, Lucknow University, Lucknow; Expert, School of Biotechnology, BHU, Varanasi; Member, IVRI, Izatnagar, Expert Committee; Member, Expert Committee for Chemical and Pharmaceutical Sciences, UPCST, Lucknow; Member, Animal House Committee, CDRI; Member, Quality Assurance Unit, CDRI; Member, Expert Committee Sai Institute of Paramedical Research Institute, Dehradun.
Dr. Sudhir Sinha	Coordinator, CSIR Networked Project, Molecular Biology of Selected Pathogens for Developing Drug Targets.

Dr. Naibedya Chattopadhyay	Member, National Scientific Advisory Council, American Federation for Aging Research; Member, Editorial Board, The Open Physiology Journal.
Dr. D.C. Kaushal	Member, Editorial board of Journal of Parasitic Diseases; Member, Editorial Board Current R & D Highlights, CDRI, Lucknow; Member, Research Degree Committee of Microbiology for PhD of Ram Manohar Lohia Avadh University, Faizabad.
Dr. G. Bhatia	Member, Indian Society of Atherosclerosis.
Dr. Vinod Bhakuni	DST Program Advisory Committee in Life Sciences; DBT Expert Committee on SiRNA; DBT-Post Doctoral Fellowship Committee.
Dr. R.P. Tripathi	Life Member, Association of Carbohydrate Chemists and Technologists of India; Executive Member, Association of Carbohydrate Chemists and Technologists of India.
Dr. A.K. Balapure	Member, Executive Committee, Indian Pharmacological Society.
Mr. Vinay Tripathi	Member, Ocean Drugs Alert Bulletin; Member, CDRI Annual Report 2007- 08.
Dr. Madhur Ray	Member, International Brain Research Organization; Member, International Society for Neurochemistry; Member, Asia Pacific Society for Neurochemistry; Member, Society of Medicines Research.
Dr. A.K. Srivastava	Member, Infectious Diseases Biology, Department of Biotechnology, Government of India, New Delhi.
Dr. D.S. Upadhyay	Member, CPCSEA Sub-Committee for Rehabilitation of Laboratory Animals; Member, Livestock Feeds, Equipment & System, Sectional Committee, FAD, Bureau of Indian Standards, New Delhi; Member, Veterinary Council of India; Member, Institutional Animal Ethics Committee, IVRI, Izatnagar; Member, Institutional Animal Ethics Committee, CIMAP, Lucknow; Member, Institutional Animal Ethics Committee, Animal Husbandry Department, Uttar Pradesh, Lucknow; Member, Institutional Animal Ethics Committee, CDRI Lucknow; Member, Institutional Animal Ethics Committee, ITRC Lucknow; Member, Institutional Animal Ethics Committee CIMAP Lucknow; Member, Institutional Animal Ethics Committee Integral University Lucknow; Member, CSIR Nominee, National Institute of Animal Welfare (AWBI) U.P. Veterinary Council; Life Member, Society for Advancement of Electrochemical Science & Technology.

Dr. Neeraj Sinha	Life Member, Society of Toxicology, India; Life Member, ISCA; Life Member, Laboratory Animal Science Association of India; Life Member, Indian Society of Cell Biology; Life Member, National Academy of Science, Allahabad.
Dr. R.C. Tripathi	Member, Editorial Board, CDRI Annual Report 2007- 08; Member, Research Board of Advisors, American Bibliographical Institute.
Dr. P.K. Shukla	Associate Editor, Asian Journal of Biochemistry, USA.; Member, Editorial Board, Research Journal of Biological Sciences, Medwell Online.
Dr. D. N. Upadhyay	Life Member, Society for Advancement of Electrochemical Science & Technology; Member, Editorial Board, CDRI Annual Report 2007- 08.
Dr. M.N. Srivastava	Editorial Board Ocean Drugs Alert, CDRI, Lucknow.
Dr. (Mrs.) Neena Goyal	Member, Doctoral Committee, ITRC, Lucknow.
Dr. N. A. Kaushal	Reviewer, Journal of Experimental Parasitology.
Dr. A. K. Srivastava	Life Member, UP Association of Science and Technology; Life Member, Indian Society of Parasitology.
Dr. Sharad Sharma	Member, Core Committee, National GLP Compliance Monitoring Authority.
Dr. Jawahar Lal	Life Member, Indian Society of Chemists and Biologists.
Mr. S.M. Rajendran	Member, Executive Council Society of Ethnobotanists, NBRI, Lucknow; Member, Organizing Committee, Silver Jubilee Symposium on Ethnobotany in the New Millennium, NBRI, Lucknow; Member, Editorial Board, Phytotaxonomy, NBRI, Lucknow.
Mr. P. Prakash	Expert Member, Board of Studies for B.Pharm. course, V.B.S. Purvanchal University, Jaunpur; Life Member, UP Association for Advancement of Science & Technology; Life Member, Indian Pharmaceutical Association; Member, Editorial Board, CDRI Annual Report 2007- 08.
Dr. S.K. Rath	Member, Board of Examiners for D.Sc., University of Allahabad; Life Member, ISCB; Life Member and Treasurer; EMSI; Life Member, ADNAT.
Dr. Amit Misra	Life Member, Indian Pharmaceutical Association; Member, Controlled Release Society, Indian Chapter; Founder Member, Indian Nanoscience Society; Member, Consultative Committee appointed by the Principal Scientific Advisor, Govt. of India, on Drug Discovery and Delivery.

Dr. (Mrs.) Kumkum Srivasatava	Life Member, Society of Biological Chemists, India, Bangalore.
Dr. Atul Goel	Member, Chemical Research Society of India.
Dr. R. K. Singh	Life Member, Society of Toxicology, India; Life Member, Indian Society for the Study of Reproduction and Fertility, Mumbai, India; Life Member, International Society of Applied Biology, India; Life Member, Society for Reproductive Biology and Comparative Endocrinology, Chennai; Life Member, Laboratory Animal Science Association of India, CDRI, Lucknow; Life Member, National Academy of Science, Allahabad.
Dr. Gautam Panda	UP Association for Science and Technology, UP, India; Chemical Research Society of India, Bangalore, India.
Dr. P. R. Mishra	Member, Advisory Board, IIPC, Bilaspur University; Life Member, Indian Pharmaceutical Association; Founder Member, Indian Nanoscience Society; Member, Expert Committee, Jamia Hamdard, New Delhi; Member, Expert Committee, Bilaspur University.
Dr. Shakil Ahmed	DBT representative on the IBSC constituted at the Faculty of Agriculture Sciences, Aligarh Muslim University, Aligarh.
Dr. Akhilesh Tamrakar	Life Member, Society for Biological Chemists.
Dr. Dhananjay Hansda	Life Member, Indian Association of Veterinary Microbiologists, Immunologists, and Specialists in Infectious Diseases; Life Member, West Bengal Veterinary Council; Life Member, Scientist and Engineering wing, Rajayoga Education and Research Foundation, Pandav Bhawan, Mt. Abu, Rajasthan, India.
Dr. Anand P. Kulkarni	Associate Editor, CDRI Annual Report 2007- 08.
Dr. Sripathi Rao Kulkarni	Life Member, Association of Microbiologists of India; Member, Editorial Board, CDRI Annual Report 2007- 08.
Mr. Naseem Ahmed Siddiqui	Member, All India Management Association, New Delhi.
Mr. Janki Prasad	Associate Member, Institution of Engineers (India); Member, Indian Institute of Chemical Engineers, Kolkata.

10. Visits Abroad

Dr. C.M. Gupta	***Geneva, Switerzerland***, To participate in the Next Scientific Advisory Committee Meeting (3-4 May, 2007).
Dr. A.K. Saxena	***Russia,*** To participate and deliver an invited lecture in 14th International Symposium on Computational Methods in Toxicology and Pharmacology: Integrating Internet Reseources (1-6 September, 2007);
	Germany, To deliver a invited lecture in Germany (6-23 September, 2007).
Dr. O.P. Asthana	***Accra, Ghana,*** To deliver a lecture on "Management of *Falciparum* Malaria with E-mal" (23 November-2 December, 2007).
Dr. Naibedya Chattopadhyay	***Lisbon, Portugal,*** To attend a meeting on Flavonoids and Osteoporosis (12-14 February, 2007).
Dr. Neeraj Sinha	***Germany,*** For 3 weeks under INSA/DFG International Collaboration/ Exchange Programme 2007-2008.
Dr. S.K. Puri	***China,*** To attend Pan-Asian Network for Neglected Diseases (4- 6 June, 2007).
Dr. J.S. Srivastava	***Toronto, Canada***, To participate in MH. Sc. (Bioethics) International Graduate Reunion and Joint Ethics Conference, (28 May - 03 June, 2007).
Dr. S.K. Rath	***Baltimore, USA,*** Raman Research Fellowship, (13 August 2007-12 February 2008)
Dr. Gautam Panda	***Germany,*** INSA, DFG Exchange Programme (28 March - 27 June, 2007).
Dr. T. Narender	***California, USA,*** BOYSCAST Fellowship 2006-07 (30 March, 2007 - 29 March, 2008)**.**
Dr. Brijesh Kumar	***Tokyo, Japan,*** To attend training and technical discussions concerning JEOL Instrument (29 January - 2 February, 2007).
Mr. Sanjeev Kanojiya	***Tokyo, Japan,*** To attend training and technical discussions concerning JEOL Instrument (29 January - 2 February, 2007).
Dr. Smrati Bhadauria	***New York, USA,*** For 3 months post doctoral training in the area of Cell Stress and Cancer Biology (9 August, 2007-9 November, 2007).

11. Honours & Awards

Dr. Rakesh Tuli	◆ J.C. Bose Fellowship; ◆ Science Counsellor Award – 2007 by Indian Society of Health, Environment, Education & Research.
Dr. Vinod Bhakuni	◆ Fellow of National Academy of Science (FNA).
Dr. C. Nath	◆ Fellow of Indian Pharmacological Society (FIPS).
Dr. Rakesh Shukla	◆ Elected Vice President of Indian Pharmacological Society; ◆ S.B. Pandey Oration Award - 2007 by Indian Pharmacological Society; ◆ Treasurer, Indian Academy of Neurosciences, Lucknow Branch.
Dr. Madhur Ray	◆ Award for best paper "The anti-apoptogenic activity of Herbal medicament in transient focal ischemia in rat brain." Presented at International Symposium on "Neurodegeneration and Neuroprotection.
Dr. Anup Kumar Misra	◆ Ramanna Fellowship Award by DST**.**
Dr. Atul Goel	◆ Ramanna Fellowship Award by DST; ◆ Selected for Dr. Ghanshyam Srivastava Memorial Award - 2007 by Indian Chemical Society, Kolkata.
Dr. Atul Kumar	◆ Organization of Pharmaceutical Producers of India (OPPI) Scientist Award- 2007.
J.K. Saxena	◆ Best Poster Award for the paper entitled "Cloning, expression and purification of *P. falciparum* transketolase". Presented at 19th National Congress of Parasitology, Visakhapatnam.
N. Goyal	◆ Best Poster Award for the paper entitled "Folding stability of trypanothione reducatse from *Leishmania donovani.*" Presented in International Conference on Advances in Drug Discovery Research held at Aurangabad, Feb.24-26, 2007.
Ashutosh (Ph.D. Student)	◆ M. B. Mirza Award at Annual Conference of Indian Society for Parasitology, Vishkhapatanum.

Budget

2007-08 (Sanctioned Estimates)

	Heads	(Rs in lakhs)
(a)	***Recurring***	
	Pay & Allowances	1691.500
	Contingencies	180.000
	HRD	4.000
	Maintenance	140.000
	Staff Quarter Maintenance	12.000
	Chemicals & Consumables	350.000
	Sub-Total	**2377.500**
(b)	***Capital***	
	Works & Services	11.000
	Equipments and Office Equipments	655.000
	Furniture and Fittings	3.000
	Library Books & Journals	200.000
	Staff Quarters	24.175
	Infrastructure, Renovation & Refurbishing (ICT)	38.492
	Sub-Total	**931.667**
(c)	Network Projects	3153.000
	Grand Total	**6462.167**

2006-07 (Actual Expenditure)[#]

	Heads	(Rs in lakhs)
(a)	***Recurring***	
	Pay & Allowances	1704.167
	Contingencies	185.302
	HRD	3.782
	Maintenance	148.343
	Staff Quarter Maintenance	14.985
	Chemicals & Consumables	412.386
	Sub-Total	**2468.965**

(b)	***Capital***	
	Equipments	215.039
	Furniture and Fittings	4.692
	Library Books & Journals	215.003
	Infrastructure, Renovation & Refurbishing (ICT)	152.773
	Infrastructure, Renovation & Refurbishing (Construction)	36.873
	Staff Quarter (Construction)	55.302
	Sub-Total	**679.682**
(c)	Network Projects	720.593
	Grand Total	**3869.240**

[#]Including LRF, C/F 2005-06

Research Council

(April 2007 – March 2010)

Chairman

Prof. N.K. Ganguly
Director General
Indian Council of Medical Research
Ansari Nagar, New Delhi - 110 029.

Members

Dr. A. Surolia
Director
National Institute of Immunology
Aruna Asaf Ali Marg, New Delhi - 110 067.

Dr. T.P. Singh
Professor and Head
Department of Biophysics
All India Institute of Medical Sciences
Ansari Nagar, New Delhi – 110 029.

Dr. Y.K. Gupta
Professor, Department of Pharmacology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi – 110 029.

Dr. M.D. Nair
Former Vice President, SPIC Pharmaceuticals
A-11 Sagarika No. 15, 3rd Seaward Road
Valmiki Nagar, Thiruvanmiyur, Chennai-600 041.

Prof. K. Muniyappa
Head, Department of Biochemistry
Indian Institute of Science
Bangalore – 560 012.

Dr. M. Venkateswarlu
Drug Controller General (India)
Directorate General of Health Sciences
Ministry of Health and Family Welfare
Nirman Bhawan, New Delhi – 110 011.

Dr. K.P. Mohankumar
Scientist
Indian Institute of Chemical Biology
4, Raja S.C. Mullick Road, Jadavpur
Kolkatta – 700 032.

Dr. Rakesh Tuli
Director
Central Drug Research Institute
Lucknow – 226 001.

Dr. C.M. Gupta
Former Director
Central Drug Research Institute
Lucknow - 226 001.

The Head
R&D Planning Division
Council of Scientific & Industrial Research
Rafi Marg, New Delhi - 110 001.

Secretary

Dr. S.B. Katti
Scientist F
Central Drug Research Institute
Lucknow - 226 001.

Management Council

(July 2007 – June 2009)

Chairman

Dr. Rakesh Tuli
Director
Central Drug Research Institute
Lucknow – 226 001.

Members

Dr. Tapan Chakrabarti
Scientist G
IMT, Chandigarh.

Dr. Zaka Imam
Scientist F
CDRI.

Dr. O.P. Asthana
Scientist F
CDRI.

Dr. (Smt.) Shailaja Bhattacharya
Scientist F
CDRI.

Dr. (Smt.) Saman Habib
Scientist EI
CDRI.

Dr. Amogh Sahasrabuddhe
Scientist B
CDRI.

Controller of Finance & Accounts
CDRI.

Member – Secretary

Controller of Administration
CDRI.

The Staff

Director
Dr. Rakesh Tuli, M.Sc. (Pantnagar), Ph.D. (Gujarat)
C.M. Gupta, M.Sc., Ph.D. (Agra), FNA, FASc., FNASc. [Retired on 31/08/2007]

R & D DIVISIONS/UNITS

BIOCHEMISTRY

Scientists Group IV (5)
J.K. Saxena, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*
Uma Roy, M.Sc., Ph.D. (Kanpur)

Scientists Group IV (4)
Gitika Bhatia, M.Sc., Ph.D. (Agra), (MOH & FW Scheme)
A.K. Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)
Neena Goyal, M.Sc. (Lucknow), Ph.D. (Agra)

Scientist Group IV (3)
Anju Puri, M.Sc. (Kanpur), Ph.D. (Lucknow)

Scientist Group IV (1)
A.K. Tamrakar, M.Sc., Ph.D. (Jiwaji)

Technical Officer Group III (6)
M.M. Khan, M.Sc., Ph.D. (Kanpur)

Technical Officer Group III (5)
A.K. Khanna, M.Sc. (Lucknow), Ph.D. (Kanpur)

Technical Officer Group III (4)
B. Maity, M.Sc. (Kanpur), Ph.D. (Rohilkhand)

Technical Assistants Group III (1)
Rima Ray Sarkar
Ishbal Ahmad

Technical Assistants Group II (4)
Suresh Yadav
B.R. Yadav

Technical Assistant Group II (3)
Ram Pal Rawat, B.Sc., LL.B

Helpers Group I (4)
Ramesh Chandra
Noor Jehan

BOTANY

Scientists Group IV (5)
R.K. Sharma, M.Sc., Ph.D. (Agra), *In-Charge*
S.C. Agarwal, M.Sc., Ph.D. (Lucknow) [Retired on 31/07/2007]

Scientist Group IV (4)
M.N. Srivastava, M.Sc. (Kanpur), Ph.D. (Lucknow)

Scientist Group IV (3)
S.M. Rajendran, M.Sc. (Madurai Kamaraj), Ph.D. (Lucknow)

Scientists Group IV (2)
K.R. Arya, M.Sc. (Kumaon), Ph.D. (Kanpur)
D.K. Mishra, M.Sc. (Vidyasagar), Ph.D. (Pune)

Technical Assistant Group III (1)
Savita Tripathi

Technical Assistant Group II (5)
J.K. Joshi, B.Sc.

Helpers Group I (4)
Devi Dutt
K. K. Yadav
Maiku Lal Lodh
Jeewan Ram
Makhan Lal
Satya Narain
Gopi

Helper Group I (2)
R.C. Maurya

Helpers Group I (1)
N.K. Khanduri
Lakhana Devi

Sr. Steno (ACP)
Gehani J.

CLINICAL & EXPERIMENTAL MEDICINE

Scientists Group IV (5)
O.P. Asthana, M.B.B.S., D.C.H., M.D. (Lucknow), FNASc., *In-Charge*
S.P.S. Gaur, M.B.B.S., M.D. (Lucknow)
J.S. Srivastava, M.B.B.S., M.D. (Lucknow), D.M. (PGIMER), M.H.Sc. (Toronto)
A. Ghatak, M.B.B.S., M.D. (Lucknow), FICP

Technical Officer Group III (6)
A.K. Nigam, M.Sc. (Kanpur)

Technical Assistant Group III (1)
Shail Singh, M.Sc. (Jabalpur)

Technical Assistant Group II (5)
J.R. Gupta

Technical Assistants Group II (4)
H.S. Dubey
Kishori Lal

Helper Group I (3)
Umesh Kumar

DRUG TARGET DISCOVERY AND DEVELOPMENT

Scientist Group IV (5)
Sudhir K. Sinha, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*

Scientist Group IV (4)
Neeloo Singh, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV (3)
Vinita Chaturvedi, M.Sc., Ph.D. (Agra)
Sabyasachi Sanyal, M.Sc. (Viswabharati), Ph.D. (CNU, South Korea)

Scientists Group IV (2)
Charu Sharma, M.Sc. (Lucknow), Ph.D. (Chandigarh)
Arun Kumar Trivedi, M.Sc. (Varanasi), Ph.D. (Ludwik Maximillians)

Scientists Group IV (1)
Y.K. Manju, M.Sc. (Calicut), Ph.D. (Thiruvananthapuram) [on EOL from 16/07/2007 to 15/07/2008]
Anil N. Gaikwad, M.S.(Pharm.) (NIPER, Chandigarh), Ph.D. (JNU)
Jayant Sarkar, M.V.Sc., Ph.D. (IVRI)

Technical Officer Group III (6)
Sidheshwar Gupta, B.Sc. [Retired on 30/11/2007]

Technical Officer Group III (5)
S.L. Verma, B.Sc.

Technical Assistants Group III (1)
Ajay Singh Verma, M.Sc. (Aligarh)
Shyam Singh, M.Sc. (Agra)

Technical Assistants Group II (4)
Lal Hori
Chandramool

Technical Assistant Group II (3)
B.P. Yadav

ENDOCRINOLOGY

Scientist Group IV (5)
Naibedya Chattopadhyay, M.Sc. (Calcutta), Ph.D. (SGPGIMS), *In-Charge*

Scientists Group IV (4)
Archana Srivastav, M.Sc., Ph.D. (Lucknow)
Govind Keshri, M.Sc. (Lucknow), Ph.D. (Agra)
Anila Dwivedi, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV (3)
Gopal Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)
F.W. Bansode, M.Sc. (Nagpur), Ph.D. (Udaipur)
Durga Prasad Mishra, M.Sc. (Karnal), Ph.D. (Delhi)

Scientist Group IV (2)
Rajender Singh, M.Sc. (Amritsar), Ph.D. (JNU)

Scientists Group IV (1)
Divya Singh, M.Sc. (Lucknow), Ph.D. (Lucknow)
Ritu Trivedi, M.Sc. (Lucknow), Ph.D. (SGPGIMS)
Hemant Kumar Bid, M.Sc. (Avadh), Ph.D. (Kanpur)
Konwar Rituraj, M.V.Sc., Ph.D. (IVRI)
Geetanjali Mishra, M.Sc (Lucknow), Ph.D. (Lucknow) [Resigned on 03/08/2007]

Technical Officer Group III (6)
Rukmani Agarwal, B.Sc. [Retired on 31/01/2008]

Technical Officers Group III (5)
P.K. Dasgupta, B.Sc.
J.P. Maikhuri, M.Sc. (Garhwal), Ph.D. (Jamia Hamdard)

Technical Officers Group III (4)
Mohini Chhabra, B.Sc., CLSc.
Shakti Kitchlu, M.Sc. (Kanpur)
Balvir Singh, M.Sc. (Rohilkhand)

Technical Assistants Group III (1)
Lakshma Nayak V.
Preeti

Technical Assistant Group II (5)
A.P. Dev

Technical Assistants Group II (4)
P.C. Patni
P.K. Bhattacharya
T. Firdaus, B.Sc.
Kanak Lata, B.Sc.

Technical Assistants Group II (3)
Chattar Pal
Geet Kumar Nagar, B.Sc.

Helpers Group I (4)
Prakash
N.P. Misra
B.P. Mirsa
R.G. Pandey

Helper Group I (2)
Mahesh Chandra Tewari

Helpers Group I (1)
Ram Karan
Jagdish Prasad

FERMENTATION TECHNOLOGY

Scientist Group IV (6)
Vinod Bihari, M.Tech. (Kanpur),
Ph.D. (I.I.T., Delhi), [Retired on 31/12/2007]

Scientist Group IV (5)
C.K.M. Tripathi, M.Sc., Ph.D. (BHU), *In-Charge*

Scientists Group IV (4)
Banani Sur, Ph.D. (Utkal)
[Retired on 31/12/2007]
P.K. Shukla, M.Sc. (Lucknow), Ph.D. (Kanpur)

Technical Officer Group III (6)
A.K. Joshi, M.Sc. (Kumaon)

Technical Officers Group III (5)
Shyamendra Mehrotra, B.Sc.
Bikram Banerjee, B.Sc.
M.K. Srivastava, M.Sc. (Sagar)

Technical Officers Group III (4)
Malkhan Singh, B.Sc.
M. Prakash, Dip. Mech. Engg.
[Transferred to NAL, Bangalore]
Agney Lal, B.Sc.

Technical Assistants Group II (4)
A.K. Pandey
Kishan Singh

Technical Assistant Group II (3)
O.P. Gupta

Helpers Group I (4)
A.N. Dixit
Lakshmi Prasad

Private Secretary
H.K. Khulve

MEDICINAL AND PROCESS CHEMISTRY

Scientist Group IV (6)
Chandan Singh, M.Sc. (Kurukshetra), Ph.D.
(Pune), [Retired on 30/06/2007]

Scientists Group IV (5)
A.K. Saxena, M.Sc., Ph.D. (Meerut), *In-Charge*
D.P. Sahu, M.E. (Chem. Engg.) (S.I.T., USA),
Ph.D., (IIT, Kharagpur)
Kanwal Raj, M.Sc., Ph.D. (Lucknow)
S.B. Katti, M. Pharm., Ph.D. (Mysore)
Bijoy Kundu, M.Sc., Ph.D. (Kanpur)
Ram Pratap, M.Sc., Ph.D. (BHU)
K.C. Agarwal, M.Sc., Ph.D. (Lucknow)
S.N. Suryawanshi, M.Sc., Ph.D. (Pune)
Kamlakar Avasthi, M.Sc., Ph.D. (Lucknow)
Rakesh Maurya, M.Sc., Ph.D. (Varanasi)

Scientists Group IV (4)
V.K. Sharma, M.Sc. (Jabalpur), Ph.D. (Faizabad)
[Retired on 30/11/2007]
Kalpana Bhandari, M.Sc., Ph.D. (Lucknow)
Vijay Lakshmi, M.Sc., Ph.D. (Allahabad)
Kanchan Hajela, M.Sc., Ph.D. (Lucknow)
R.P. Tripathi, M.Sc. (Gorakhpur), M. Phil, Ph.D.
(Delhi)
W. Haq, M.Sc., Ph.D. (Lucknow)
Y.S. Prabhakar, M.Sc. (Vishakhapatnam), Ph.D.
(Pilani)
Arun K. Shaw, M.Sc., Ph.D. (Calcutta)
P.M.S. Chauhan, M.Sc., Ph.D. (Agra)
V.L. Sharma, M.Sc., Ph.D. (Lucknow)

Scientists Group IV (3)
Pradeep Kumar, M.Sc. (Kanpur)
Atul Kumar, M.Sc., Ph.D. (Lucknow)
Sanjay Batra, M.Sc., Ph.D. (Meerut)
Anup K. Misra, M.Sc. (Calcutta), Ph.D. (Jadavpur)
Atul Goel, M.Sc., Ph.D. (Lucknow)

Scientists Group IV (2)
Gautam Panda, M.Sc. (IIT, Khargpur), Ph.D. (Hyderabad)
T.G. Narender, M.Sc., Ph.D. (Kakatiya)
Sashidhara K.V., M.Sc. (MS Univ.), Ph.D. (Avadh)
Balaram Mukhyopadhyaya, M.Sc. (Burdwan), Ph.D. (Jadhavapur) [Resigned on 31/12/2007]

Scientist Group IV (1)
Prem Prakash Yadav, M.Sc. (Allahabad), Ph.D. (Avadh)

Technical Officers Group III (6)
R.K. Asthana, M.Sc. (Agra)
S.P. Vishnoi, M.Sc., Ph.D. (Meerut)
A.K. Srivastava, B.Sc. [Retired on 31/07/2007]

Technical Officers Group III (5)
S.C. Tripathi, B.Sc.
Janki Prasad, M. Tech. (BHU)
Keshav Prasad, AMIE, M. Tech. (BHU)
Suresh Chandra, B.Sc.
S.P.S. Bhandari, M.Sc. Ph.D. (Avadh)
A.K. Mandwal, M.Sc., Ph.D. (Avadh)
S.K. Kakaji, B.Sc.
Vasi Ahmed, B.Sc.
P.N. Rai, Dip. Mech. Engg.
Zahid Ali, B.Sc., L.LB.
Tara Rawat, B.Sc.

Technical Officers Group III (4)
Deepali Pandey, B.Sc.
A.S. Kushwaha, B.Sc.

Technical Assistants Group III (1)
K. S. Anil Kumar, PGDCA, M.Sc. (Bharathiar)
Atma Prakash Dwivedi
Vidisha Sharma
Ashok Kumar Sharma, B.Sc., D.ChE, A.M.I.E.
Surya Pratap Singh
Tahseen Akhtar

Technical Assistants Group II (5)
Preeti Rastogi, M.Sc. (Gorakhpur)
Ahmad Zaheer (Glass Blowing)

Technical Assistants Group II (4)
V.K. Maurya
Ram Sant
Raju Arora, B.Sc.
Mithilesh Sharma, M.Sc. (Lucknow)
Shashi Rastogi, M.Sc. (Lucknow)
Radha Rani Gupta, B.Sc.
Ramjeet, B.Sc., P.G.D. Comp.Sc.
A.K. Srivastava, M.Sc.

Technical Assistants Group II (3)
Veena Mehrotra, M.Sc. (Lucknow)
Akhilesh Kumar Srivastava, B.Sc., Ayurved Ratan, L.T.
K. M. Shukla, B.Sc.
Rajesh Kumar, B.Sc.
D.N. Vishwakarma
Kumar Rajesh
Tika Ram

Technical Assistants Group II (2)
Ram Lakhan
Manju, B.Sc.

Technical Assistants Group II (1)
A.K. Pandey
H.R. Misra
N.P. Misra
Krishna Kumar
Satish Chandra Tiwari

Helpers Group I (4)
Ram Sanehi
G.S. Sonkar
M.S. Bhol
J.C. Rajan

Helper Group I (2)
Satish Chandra

Sr. Steno
Renuka Mushran

Sr. Steno (H)
Avadhesh Kumar

MICROBIOLOGY

Scientist Group IV (5)
Ranjana Srivastava, M.Sc., Ph.D. (Kanpur), *In-Charge*

Scientists Group IV (4)
D.C. Kaushal, M.Sc. (Pantnagar), Ph.D. (Kanpur)
K.K. Srivastava, M.Sc., Ph.D. (Kanpur)

Scientist Group IV (2)
B.N. Singh, M.Sc., Ph.D. (BHU)

Technical Officer Group III (7)
M. Kazim, M.Sc., Ph.D. (Lucknow) [Retired on 31/10/2007]

Technical Officers Group III (6)
A.P. Singh, M.Sc. (Lucknow)
M.N. Joshi, M.Sc., Ph.D. (Agra)

Technical Officer Group III (5)
Reeta Singh, M.Sc., Ph.D. (Kanpur)

Technical Assistant Group III (1)
Sandeep Kumar Sharma

Technical Assistants Group II (3)
Ram Kumar Misra [Retired on 31/12/2007]
P.D. Misra
Nuzhat Kamal, B.Sc.
D.K. Tripathi, M.Sc. (Avadh), B.Ed.

Helpers Group I (4)
Ram Murti Gupta [Retired on 31/10/2007]
Tulsa Devi [Retired on 31/07/2007]
J.C. Pant
U.C. Pandey

Helpers Group I (1)
Ravi Shankar Misra
Ram Prakash

MOLECULAR & STRUCTURAL BIOLOGY

Scientists Group IV (4)
Vinod Bhakuni, M.Sc., Ph.D. (Lucknow), FNA, FASc, FNASc, *In-Charge*
P.R. Maulik, M.Sc., Ph.D. (Calcutta)

Scientists Group IV (3)
Ashish Arora, M.Sc. (Jaipur), Ph.D. (Chandigarh)
Ravishankar, R., M.Sc., Ph.D. (IISc., Bangalore)
Saman Habib, M.Sc. (Delhi), Ph.D. (NII)
Jimut Kanti Ghosh, M.Sc., Ph.D. (Kalyani, Calcutta)
J. Venkatesh Pratap, M.Sc., Ph.D. (IISc, Bangalore)

Scientists Group IV (2)
Mohammad Imran Siddiqi, M.Sc. Ph.D. (AIIMS)
Shakil Ahmed, M.Sc. (Aligarh), Ph.D. (Punjab)

Scientists Group IV (1)
Amogh Anant Sahasrabuddhe, M.Sc. (Kanpur), Ph.D. (JNU)
Mohammad Sohail Akhtar, M.Sc. (Calicut), Ph.D. (JNU) [on EOL from 16/07/22007 to 31/05/2008]
Sushma Chaubey, M.Sc. (BHU), Ph.D. (JNU) [Resigned on 5/10/2007]

Technical Officers Group III (4)
R.K. Srivastava, B.Sc.
J.P. Srivastava, B.Sc., LL.B.

Technical Assistants Group III (1)
Ruchir Kant, M.Sc. (Lucknow)
Anupam Jain, M.Sc. (Agra)

Technical Assistant Group II (3)
Ram Radhey Shyam

PARASITOLOGY

Scientists Group IV (5)
S.K. Puri, M.Sc., Ph.D. (Punjab), *In-Charge*
Shailja Bhattacharya, M.Sc., Ph.D. (Kanpur)
P.K. Murthy, M.Sc. (Lucknow), Ph.D. (Kanpur)
Anuradha Dube, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV (4)
Suman Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)
Renu Tripathi, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV (3)
N.A. Kaushal, M.Sc. (Lucknow), Ph.D. (Kanpur)
Kumkum Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientist Group IV (2)
S. Rajakumar, M.Sc. (Madras)

Technical Officer Group III (6)
S.C. Nigam, M.Sc., Ph.D. (Kanpur)

Technical Officer Group III (5)
A.K. Roy, M.Sc. (Kanpur)

Technical Officer Group III (4)
R.N. Lal, M.Sc. (Agra)

Technical Assistants Group II (5)
V.K. Bose
R.S. Dubey

Technical Assistants Group II (4)
Ram Dayal
Ravi Kumar Mehra

Technical Assistant Group II (3)
K.K. Singh, M.Sc. (Kanpur)

Technical Assistant Group II (1)
A.K. Singh

Helper Group I (4)
Saheb Prasad

Helper Group I (1)
Prem Babu

Attendant
Om Prakash
Ram Das

Sr. Steno (ACP)
T. S. Sashi Kumar

PHARMACEUTICS

Scientists Group IV (5)
A.K. Dwivedi, M.Sc., Ph.D. (Agra), *In-Charge*
Satyawan Singh, M.Pharm., Ph.D. (Banaras)
[Retired on 30/06/2007]

Scientist Group IV (4)
Raghwendra Pal, M.Sc., Ph.D. (Lucknow)
[Voluntary retirement on 01/07/2007]

Scientist Group IV (3)
Amit Misra, M. Pharm. (Delhi), Ph.D. (JNU)

Scientists Group IV (2)
Prabhat Ranjan Mishra, M.Pharm., Ph.D. (Sagar)
Manish Kumar Chourasia, M.Pharm., Ph.D. (Sagar) [On EOL from 27/08/2007 to 26/08/09]
Praveen Dubey, M.Pharm., Ph.D. (Sagar)
[Resigned on 10/12/2007]
Akhilesh Kumar Jain, M.Pharm. (Sagar), Ph. D. (Jamia Hamdard)

Technical Officer Group III (5)
Madhuri Chaudhry, M.Sc. (Lucknow)

Technical Assistant Group II (4)
Bhatnagar S. K., B.Sc.

Helper Group I (4)
Ghanshyam

Helper Group I (1)
Ram Kumar

PHARMACOKINETICS & METABOLISM

Scientist Group IV (5)
G.K. Jain, M.Sc. (Rewa), Ph.D. (Kanpur), *In-Charge*

Scientist Group IV (4)
S.K. Singh, M.Sc. (Patna), Ph.D. (IIT, Kanpur)

Scientist Group IV (3)
Jawahar Lal, M. Pharm., Ph.D. (BHU)

Scientists Group IV (1)
R.S. Bhatta, M. Pharm. (Nagpur)
Wahajuddin, M.S. (Pharm.) (NIPER)
R.S.P. Singh, M. Pharm. (BITS Pilani)

Technical Officer Group III (5)
S.K. Pandey, M.Sc. (Kanpur)

Technical Assistant Group II (3)
Narendra Kumar, B.Sc., L.T.

Technical Assistant Group II (1)
Akhilesh Kumar

Helper Group I (4)
Shiv Lal

Helpers Group I (1)
Ram Bhajan Shukla
Ram Sunder Lal
Pankaj Sengupta

Sr. Steno
Nandita Pandey

PHARMACOLOGY

Scientists Group IV (5)
Ram Raghubir, M.V.Sc., Ph.D. (Agra), *In-Charge*
G. Palit, M.B.B.S., M.D. (Lucknow), (*Unit In-charge, Neuropharmacology Unit*)
C. Nath, M.B.B.S., M.D. (Lucknow), (*Neuropharmacology Unit*)
Madhu Dikshit, M.Sc., Ph.D. (Kanpur) *(Unit In-charge, Cardiovascular Pharmacology Unit)*
Rakesh Shukla, M.Sc., Ph.D. (Lucknow)

Scientist Group IV (4)
M. Ray, M.Sc., Ph.D. (Lucknow)

Scientist Group IV (3)
Amar Nath, M.Sc. (Lucknow)

Scientists Group IV (2)
K.G. Raghu, M.Sc. (Calicut), Ph.D. (Saurashtra)
Kapil Kapoor, M.B.B.S., M.D. (Lucknow), Ph.D. (The Netherlands), [Resigned on 24/10/2007]
Manoj Barthwal, M.Sc., Ph.D. (Lucknow)

Scientist Group IV (1)
Kashif Haneef, M.Sc. (Hamdard)

Technical Officers Group III (6)
G.P. Singh, M.Sc. (Kanpur)
Urmila Sharma, B.Sc. [Retired on 30/11/2007]
M.S. Ansari, B.Sc.

Technical Officers Group III (5)
Kanta Bhutani, M.Sc. (Kanpur)
Jharna Arun, B.Sc.
T.L. Seth, B.Sc.
S. Sengupta, B.Sc.
V.S. Nigam, B.Sc. (MOH Scheme)
M.L. Bhatnagar, B.Sc.

Technical Officer Group III (4)
C.P. Pandey, M.Sc. (Chandigarh)

Technical Assistants Group III (1)
Jawaid Sultana
Sheeba Saji Samuel
Sachi Bharti

Technical Assistant Group II (5)
O.P. Pandey

Technical Assistants Group II (3)
Bhushan Bharti, B.Sc., NCVT. Diploma
Ramesh Chandra, M.Sc., (Kanpur)
Shailendra Mohan, M.Sc., (Kanpur)

Technical Assistants Group II (2)
H.C. Verma
Anil Kumar Verma, B.Sc.

Jr. Steno
Varun Kumar Pathak

TOXICOLOGY

Scientist Group IV (5)
Sudhir Srivastava, M.B.B.S., M.D. (Lucknow), [Voluntary retirement on 01/10/2007]

Scientist Group IV (4)
Neeraj Sinha, M.Sc., Ph.D., D.Sc. (Kanpur)

Scientists Group IV (3)
Sharad Sharma, M.B.B.S., M.D. (Kanpur)
S.K. Rath, M.Sc. (Utkal), Ph.D. (BHU) [On deputation from 10/08/2007 to 10/02/2008]

Scientists Group IV (2)
R.K. Singh, M.Sc., Ph.D. (Lucknow)
R.K. Tripathi, M.Sc., Ph.D. (Kanpur)

Scientists Group IV (1)
Smrati Bhadauria, M.Sc. (Jiwaji) [On EOL from 7/8/2007 to 19/11/2007]
Sarika Singh, M.Sc. (Lucknow)
Poonam Singh, M.Sc. (CSJMU)

Technical Officers Group III (6)
S.K. Mathur, M.Sc. (Lucknow), B.M.S. [Retired on 31/07/2007]
S.K. Srivastava, M.Sc. (Bombay)

Technical Officer Group III (5)
S.M. Verma, B.Sc.

Technical Officers Group III (4)
P.K. Agnihotri,
M.Sc. (Lucknow), Ph.D. (Kanpur)
Sadan Kumar, M.Sc. (Bihar)

Technical Assistants Group III (1)
Neeti Sagar, M.Sc. (Lucknow)
Anurag Kumar Srivastava

Technical Assistant Group II (3)
Anupma, B.Sc.

Helpers Group I (4)
Mahabir
R.K. Sarkar
V.K. Samant
Shree Krishan

Helper Group I (1)
Ram Kumar

CLINICAL PHARMACOLOGY UNIT (CDRI), SETH G.S. MEDICAL COLLEGE, MUMBAI

Scientist Group IV (2)
N.K. Desai, M.Sc., Ph.D. (Bombay)

Technical Assistant Group III (1)
N.A. Rajwade

Technical Assistant Group II (4)
P.S. Acharya

Technical Assistant Group II (2)
Vijal J. Ashar

Helper Group I (4)
R.B. Pawar

TECHNICAL INFRASTRUCTURE DIVISIONS / UNITS

BIOMETRY AND STATISTICS

Scientist Group IV (5)
M. Abbas, M.Sc. (IIT, Kanpur), Ph.D. (IIT, Bombay), *In-Charge*

Technical Officer Group III (5)
Mukesh Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)

Technical Assistant Group II (3)
Negi M. P. S., B.Sc., PGDCA

Helper Group I (2)
Savitri Devi

CSIR DISPENSARY

Medical Officers Group III (7)
K.K. Arora, M.B.B.S., M.D., *In-Charge,*
D.K. Bhateja, M.B.B.S., M.D.

Medical Officer Group III (6)
Asha Negi, M.B.B.S., M.D.

Technical Assistants Group II (5)
Nandita Dhar
H.U. Khan
Subramaniam M.

Helper Group I (3)
S.K. Paswan

Gp-'C' Cdr-D
Sundari

DOCUMENTATION & LIBRARY

Scientists Group IV (5)
P.K. Roy, M.Sc., Ph.D. (Gauhati), *In-Charge*
Sheela Tandon, M.Sc., Ph.D. (Agra)
A.K. Srivastava, B. Tech. (Bangalore)
Shyamala Saxena, M.Sc. (Tirupati), B.L.Sc. (Lucknow)
S.K. Mallik, M.A. (JNU), B.L.I.Sc. (IGNOU)

Scientist Group IV (4)
N.N. Mehrotra, M.Sc. (Pantnagar), Ph.D. (AIIMS) [On deputation from 17/04/2007]

Technical Officer Group III (6)
Seema Mehrotra, M.Sc. (Lucknow)

Technical Officers Group III (5)
V.K. Vohra, B.Sc.
W.F. Rahman, M.A. (Rohailkhand), B.L.I.Sc, (IGNOU)
A.K. Verma, M.A., L.L.B, Dip. Comp. Sc. (Lucknow)
J.A. Zaidi, M.Sc. (Aligarh), B.L.Isc. (IGNOU)
Sanjay Kumar, M.L.I.Sc. (IGNOU)

Technical Assistant Group III (2)
Ramesh Chandra Gupta

Technical Assistants Group II (4)
B. K. Sethi
Nazir Akbar

Technical Assistant Group II (3)
Y.C. Pandey

Helpers Group I (4)
Mohd Moen
S. Islam
Rasheed Ahmad

Helper Group I (1)
Deepayan

Asstt. (G) GR. I
M.K. Thapar

DRAWING AND PHOTOGRAPHY

Technical Officer Group III (6)
Ali Kausar, B.F.A. (Lucknow), *In-Charge*

Technical Officers Group III (5)
G.C. Gupta, B.Sc.
R.M. Pathak, B.F.A. (Comm. Arts)

Technical Officer Group III (4)
R.N.S. Londhe, GD Art (Comm.),
Art Teachers Dip.

Helper Group I (3)
Basanti Mukherjee

INSTRUMENTATION

Scientist Group IV (5)
Ravinder Singh, B.E. (Allahabad)

Scientist Group IV (4)
N.K. Agarwal, M.Sc. (Calcutta)

Technical Officer Group III (6)
Usha Kapil, I.Sc., Dip Electronic Engg.

Technical Assistant Group III (2)
Sanjay Kumar

Technical Assistants Group II (4)
Laxmi Narain
Kamal Singh

DIVISION OF LABORATORY ANIMALS

Scientist Group IV (4)
D.S. Upadhyay, M.V.Sc. (Pantnagar),
Ph.D. (Izatnagar), *In-Charge*

Scientist Group IV (3)
A.K. Srivastava, M.Sc., Ph.D. (Lucknow)

Scientists Group IV (1)
Dhananjoy Hansda, M.V.Sc. (IVRI)
Shanker Dayal, M.V.Sc. (IVRI),
[Resigned on 26/07/2007]
Dr. P. Nagarajan, B.V.Sc., M.Sc. (Manipal)

Technical Officers Group III (5)
S.N.A. Rizvi, M.Sc. (Lucknow)
A.K. Bhargava, B.Sc.

Technical Officer Group III (4)
Karunesh Rai, M.Sc. (Lucknow)

Technical Assistant Group II (5)
Baldev Singh

Technical Assistants Group II (4)
Ram Avatar
Ravinder Singh, M.Sc. (Kanpur)
A.K. Dubey

Technical Assistants Group II (3)
S.R. Yadav
Deep Mala Misra
Ravi Kumar Shukla
Sanjeev Kumar Saxena, B.Sc.

Technical Assistants Group II (2)
Narendra Kumar, B.A.
Dinesh Kumar, B.A.
Pradeep Tirkey

Helpers Group I (4)
P.B. Thapa
Babu
S.K. Varma
Asharfi Lal
M.H. Khan
Ahrar
Gaffar Ali
Singh Vikram
M.D. Kushwaha

Wazahtullah
R.P. Maurya
Singh Bhim
G.K. Sharma
O.P. Verma
V.B.L. Srivastava
Shiv Pal Singh
T. B. Thapa
Dilip Kumar
Mohd. Saleem
Hari Lal

Helper Group I (1)
Changa Lal

Jr. Steno (H)
Raj Kumar

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY

Scientist Group IV (6)
K.P. Madhusudanan, M.Sc., Ph.D. (Kerala), FNASc, [Retired on 30/09/2007]

Scientist Group IV (5)
D.K. Dikshit, M.Sc., Ph.D. (Lucknow), *In-charge*

Scientist Group IV (5)
G.R. Bhatt, M.Sc. (Meerut) [Retired on 31/05/2007]

Scientist Group IV (4)
Raja Roy, M.Sc. (Lucknow), Ph.D. (Meerut), FNASc, [On deputation from 16/04/2007]

Scientist Group IV (3)
Brijesh Kumar, M.Sc., Ph.D. (Awadh)

Scientists Group IV (1)
Sanjeev Kanojiya, M.Sc. (Jabalpur)
Sanjeev Kumar Shukla, M.Sc., Ph.D. (Kanpur)

Technical Officers Group III (6)
Prakash Narain, M.Sc. (Lucknow)
H.M. Gauniyal, M.Sc. (Garhwal)
Abdul Hafees, M.Sc. [Retired on 30/09/2007]

Technical Officers Group III (5)
A.L. Vishwakarma, M.Sc. (Kanpur)
Rakesh Khanna, B.Sc., A.I.C. (Calcutta)
A. Vohra, B.Sc., M.A. (Lucknow)
A.K. Sinha, M.Sc. (Kanpur)
A.K. Sircar, B.Sc., B.A. (Lucknow)

Technical Officers Group III (4)
Sunil Kumar, B.Sc. (Lucknow)
R.K. Purushottam, B.Sc. (Lucknow)
Pramod Kumar, M.Sc. (Bundelkhand)

Technical Assistant Group III (1)
Binod Kumar Saw

Technical Assistant Group II (5)
R. K. Varma

Technical Assistants Group II (4)
Radhey Krishna, B.Sc.
Abdul Haleem
Sandeep Sengupta, B.Sc.
Ashok Pandey, B.Sc.

Technical Assistants Group II (3)
Madhu Chaturvedi
S.A. Singh, B.Sc.
Vashundhara Madhwar, B.A.

Helper Group I (4)
S.K. Manjhi

Helper Group I (1)
Mansoor Ali

Asstt. (G) GR. I
V.K. Kanal

TECHNICAL INFORMATION, INDUSTRIAL LIAISON & PLANNING

Scientists Group IV (5)
Zaka Imam, M.Sc., M.Phil., Ph.D. (Aligarh), *In-Charge*
A.K. Goel, M.Sc., Ph.D. (Lucknow)

Scientists Group IV (4)
V.G. Mohanan Nair, M.Sc. (Kerala), Ph.D. (Kurukshetra) [Transferred on 04/10/2007]
Vinay Tripathi, M.Sc., M.B.A. (AMU), P.G. Dip. in S&T (Pilani)
R.C. Tripathi, M.Sc. (Kanpur), Ph.D. (Lucknow)
D.N. Upadhyay, M.Sc., Ph.D. (Gorakhpur)

Scientist Group IV (3)
Prem Prakash, M. Pharm. (BHU)

Scientists Group IV (1)
Anand P. Kulkarni, M.Sc. (Karnataka), Ph.D. (Mysore)
Sripathi Rao S. Kulkarni, M.Sc. (SRTMU, Nanded) Ph.D. (JNTU, Hyderabad), P.G. Dip. in Patents Law (NALSAR, Hyderabad)

Technical Officer Group III (6)
Shri Ram, B.Sc., LL.B.

Technical Assistants Group II (4)
Krishna Prasad, B.Sc.
Chandrika Singh, B.Sc. P.P.L., LL.B.

Helpers Group I (4)
V.P. Srivastava
Madho Singh
Kamlesh

Sr. Steno (ACP)
Manoshi Chatterji

Jr. Steno (H)
Jitendra Patel

ACADEMIC AFFAIRS UNIT

Scientist Group IV (5)
Alka Singh, M.Sc., Ph.D. (Rajasthan)

Scientist Group IV (4)
Sheela Ghoshal, M.Sc. (Burdwan), Ph.D. (Kanpur)

BUSINESS MANAGEMENT UNIT

Scientist Group IV (5)
Rajendra Prasad, M.Sc., Ph.D. (Lucknow), *Unit In-Charge*

Scientist Group IV (4)
N.S. Rana, M.Sc. (Kumoun)

Scientist Group IV (1)
Naseem Ahmed Siddiqui, M.B.A. (Rohilkhand)

ELECTRON MICROSCOPY UNIT

Scientist Group IV (5)
V.K. Bajpai, M.Sc., Ph.D. (Kanpur), *Unit In-Charge*

Scientist Group IV (1)
Kalyan Mitra, M.Sc. (Culcutta)

Technical Officer Group III (6)
Abha Arya, B.Sc., B.Ed. (Kumaun)

Technical Assistants Group III (1)
Kavita Singh, M.Sc. Ph.D. (Lucknow)
Manish Singh, M.Sc. (Allahabad)

Technical Assistant Group II (3)
Madhuli Srivastava, B.A.

INFORMATION TECHNOLOGY UNIT

Scientist Group IV (4)
Kural, BE (BIT, MESRA), *Unit In-Charge*

Technical Assistant Group III (2)
Ajay Kumar Maurya, MCA (Purvanchal)

TISSUE AND CELL CULTURE UNIT

Scientist Group IV (4)
A.K. Balapure, M.Sc., Ph.D. (Lucknow),
Unit In-Charge

Technical Officer Group III (5)
Ramesh Sharma, M.Sc., Ph.D. (Kanpur)

LABORATORY ENGINEERING SERVICES

Senior Superintending Engineer Group III (7)
Parvez Mahmood, B.Sc. Engineering (Civil)

Executive Engineers Group III (5)
Manoj Kumar, B.Sc. Engineering (Civil)
Kamal Jain, B.E. (Electrical), MBA (Marketing)

Technical Officer Group III (4)
A. Dayal, Diploma (Mechanical)

Junior Engineers Group III (2)
Jai Prakash
Sidho Hembrom
D.K. Vishwakarma
Mohit Kumar Shukla

Technical Assistants Group II (5)
Khan Abdul Jabbar
Sayeed Mohammad
A.K. Tewari
B.P. Sunwar
S.R. Shukla
E.A. Bhatti

Technical Assistants Group II (4)
Om Prakash
K.K. Kaul
A.K. Sonkar
S.K. Biswas
V.K. Misra
M.S. Verma
S.K. Kar
Radhey Lal
Ramakant Ram
Mahindra Singh

Technical Assistants Group II (3)
Naseem Mohammad
Radhey Shyam
Harish Kumar
Vijay Kumar
Pradhan Basudev
Verma Kamal Kishore
Ramesh Kunwar
G.C. Roy
Arun Kumar Srivastava
Swapan Karmi
S.S. Bhakuni

Technical Assistants Group II (2)
Rajesh Chand Dwivedi
Ram Karan Ram

Technical Assistant Group II (1)
Bhagwan Singh Pokhariya

Helpers Group I (4)
A.N. Rabbani
Popinder Singh
Ramanuj
Ram Ajure
Hussain Taqvi
Kandhai Lal
S.K. Bhattacharya
Munna Lal
T.P. Pathak
S.K. Yadav
A.K. Misra
Lallu
R. K. Yadav
Raju
Mahabir Prasad

Raj Kishore
N.K. Mudgal
Shiv Giri
Bishan Singh
Om Prakash
Rama
Iftikhar Ahmad
Ganeshi Prasad
Siya Ram
Garibe
Ram Lal
Roy Shankar

Helpers Group I (3)
Z.U. Beg
Om Prakash
Phool Chand
Ramesh Chandra
Darshan Lal

Helpers Group I (2)
Tara Chand
Hari Om Garg
Raju Vishwakarma
J.S. Singh
Ram Autar
Mohd. Irfan
Dhirendra Misra
Sandeep Roy

Asstt. (G) GR. I
N.K. Checker
A.G. Khan

Helper
Tansen

ADMINISTRATION

Controller of Administration
B.D. Vashisth, M.A. (Kurukshetra)

Administrative Officer
L.R. Arya,

COA OFFICE

Private Secretary to COA
G.M. Dayal
Sumit Srivastava

Helpers Group I (4)
Maiku Lal
Sohan Lal

DIRECTOR'S OFFICE

Private Secretary to Director
Kanhaiya Lal

Sr. Steno (ACP)
Sunita Chopra

Technical Assistant Group II (3)
R.C. Samanta

Helper Group I (1)
Nand Kishore

Helper Group D
Ram Swarth Prasad Rai

ESTABLISHMENT I

Section Officer (G)
Sunil Kumar

Asstt. (G) Group I
Sachin Mehrotra
Krishna Raj Singh
B. K. Shukla

Asstt. (G) Group II
Smriti Srivastava
Saju P. Nair
Reena Bisaria

Jr. Steno (H)
Mohd. Sufiyan

Helper Group I (3)
Vinod Kumar

Helper Group-'C' Cadre-D
Manju Yadav

Helper Group D
Ram Kumar

ESTABLISHMENT II

Asstt. (G) Group I
Ramesh Singh
B. K. Pillai
Rashmi Srivastava

Sr. Steno
Vinod Kumar Yadav

Asstt. (G) Group II
Aparna Bajpai
Dilip Kumr Sen
Lata Bhatia
Rani
Neena Raizada
Madan Chandra

Asstt. (G) Group III
Mohd. Irfan

Helper Group I (3)
Shanti Devi

Helper Group I (1)
Mohd. Saleem

GENERAL SECTION

Asstt. (G) Group I
Birendra Singh
Kailash Chandra

Proj. Asstt.
Masood Sahab

Sr. Steno
Seema Rani Srivastava

Asstt. (G) Group II
Gangadin Yadav
Rajendra Prasad
Ajai Shukla

Technical Assistant Group II (2)
K.K. Kashyap
Shakeel Ahmad Khan

Driver
Chote Lal
Prem Chand
Daya Shankar Singh

Helper Group I (3)
Kishori Kumari
Mohd Islam

Helper Group D
Kalpanath Sharma

Helper Group-'C' Cadre-D
Munna

BILL SECTION

Section Officer (G)
Madhuranjan Pandey

Asstt. (G) Group I
H.K. Johar
Valsala G. Nair
Hem Chandra
Rama Dhawan
Harsh Bahadur
Vivek Bajpai
Dilip Kumar (Cash)

Asstt. (G) Group II
Naseem Imam

Helper Group I (1)
Vinod Kumar Sharma
Lalji Prasad

VIGILENCE

Asstt. (G) Group I
C.P. Nawani
Chandra Kant Kaushik

Asstt. (G) Group II
Tez Singh

Sr. Steno
P.S. Padmini

Helper Group I (3)
Bhagwanti Devi

RECORDS

Section Officer (G)
Biranchi Sarang

Asstt. (G) Group II
S.K. Pandey

Helper Group I (3)
Ved Prakash Misra

HINDI SECTION

Senior Hindi Officer
V.N. Tiwari, M.A., Ph.D. (BHU)

Senior Translator (Hindi)
Mrs. Neelam Srivastava

Jr. Steno (Hindi)
Anil Kumar

FINANCE & ACCOUNTS

Controller of Finance & Accounts
U.S. Rawat

Finance & Accounts Officer
A.K. Dwivedi

Section Officers (F&A)
I.B. Dixit
A.K. Chauhan
Ankeshwar Misra
Kailash Singh

Private Secretary
V.P. Singh

Asstt. (F&A) Group I
R.P. Tripathi
S.L. Gupta
Nitu Kumari
Viresh
Mahesh Babu
R.C. Bisht
Ajitha Nair

Asstt. (F&A) Group II (ACP)
Sashidharan Radha
U.K. Tewari

Asstt. (F&A) Group II
D.K. Khare
Mahendra Kumar
Sanjay Kumar
Tahseen Talat

Asstt. (F&A) Group III
S.A. Siddiqui
Chandrashekhar

Helper Group I (1)
Vikramaditya

Helper Group D
Mohd. Firoz

STORES & PURCHASE

Stores & Purchase Officer
Thomas T. Kuriakose

Section Officers (Store & Purchase)
Shekhar Sarcar
Prasenjeet Mitra
Prafful Kumar

Asstt. (S&P) Group I
A.K. Govil
A.K. Misra
P.S. Chauhan
G.C. Dwivedi
Arun Wadhera

Asstt. (S&P) Group II (ACP)
K.K. Mishra

Asstt. (S&P) Group II
M.C. Verma
H.B. Neolia
R.C. Dwivedi

Asstt. (S&P) Group III
G.P. Tripathi
Vandana Parwani
Shree Kant
Kanchan Bala
Shakuntala Singh

Asstt. (G) Group III
Shail Tewari

Sr. Steno (ACP)
K.P. Ballaney

Helpers Group I (4)
Dan Singh
Krishan Kumar
Rama Shukla

Attendant
Hardwari

SECURITIES

Senior Security Officer
R.S. Deswal, B.Sc., LL.B.

Security Guard Group D
Chakrasen Singh

CDRI CANTEEN

Manager
J.P. Sati

Asstt. Manager
R.S. Tewari

Count Sales (ACP)
Shiv Prasad

Count Clerk (ACP)
Ram Jeeyawan Tewari
Y.K. Singh

Cook (ACP)
Man Bahadur

Asstt. Halwai
Uma Shanker Tewari

Bearer
Dil Bahadur
Ganga Ram Yadav
Rajender
Kripa Shanker
Sukh Deo Prasad

S/Man
Raj Kumar

W/Boy
Ram Murat
Dinesh Pal Singh

CDRI
LUCKNOW

Central Drug Research Institute
Chattar Manzil Palace, M.G. Marg, Lucknow-226001

www.cdriindia.org