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Central Drug Research Institute
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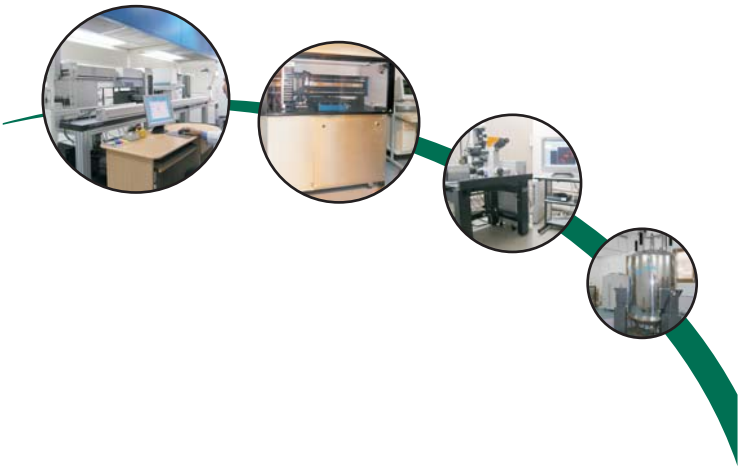

Central Drug Research Institute
Post Box Number 173, Lucknow-226001
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With compliments from :

Dr. C.M. Gupta, *FNA, FASc, FNASc*
Director
Central Drug Research Institute
Lucknow

वार्षिक प्रतिवेदन

ANNUAL REPORT

2006-2007

केन्द्रीय औषधि अनुसंधान संस्थान, लखनऊ

CENTRAL DRUG RESEARCH INSTITUTE

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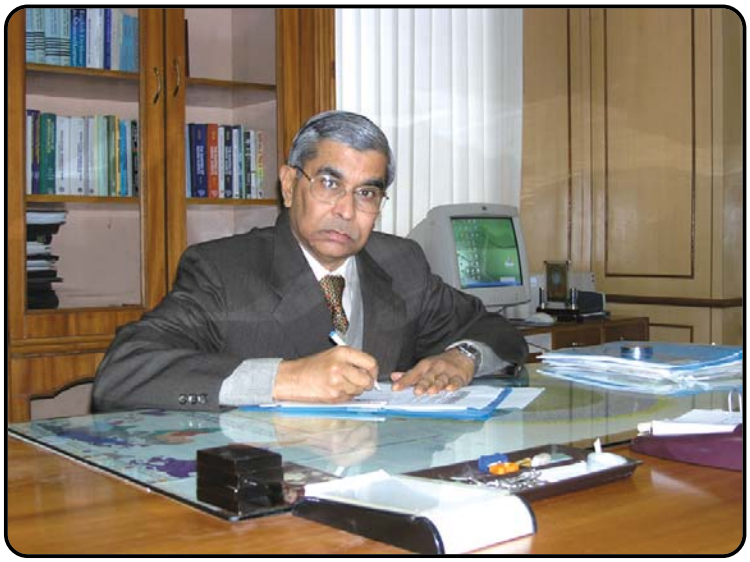
THE CHARTER

- 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.

Contents

From the Director's Desk



Drug R&D institutions are influenced by advancements in science frontiers, introduction of new instrumentations/tools/techniques, changes in regulatory requirements and the market forces. The consequences of failure to effectively understand and deal with these forces can create void in S&T strengths and capability, can cause failure in regulatory compliance, can lead to inability to fulfill market demands and thus seriously jeopardize the very existence of an organization. We therefore need to closely monitor on almost continuos basis these influences and update and upgrade on all fronts.

Our timely efforts to consolidate our scientific and innovative capacities in the last few years have visibly improved our research quality and innovation capacity. While research quality is marked by increasing number of publications in high impact journals, large number of patents in India and abroad are indicative of our increased innovative strength, which has culminated into an impressive pipeline of products in development in not only those therapeutic areas which this institute is conventionally known for but also new disease area like osteoporosis. Among various products under development are antihyperglycemics, antidiabetics, antimalarials, etc. some being of herbal origin.

There is ardent need to promote professionalism at all levels and quickly build up cohesive project teams by building trust and by awarding those who make this effort instead of those who boast of solitary performance. At CDRI we have had one or more of these management related problems and aim to handle them far more effectively in the near future. Another front that we have lacked is quality certification of our major regulatory facilities, which is long overdue.

We are seriously lacking on business development front. The current business activity principally relies on those approaching us instead of ourselves aggressively selling our projects, capacities, products in pipeline (or those ready on shelf) to potential national and international customers. Though we have had growing net-worked projects within CSIR, some under CDRI-industry, and others funded by national agencies, the national pharma companies need to be reaped in for larger collaborations. Among existing projects with the industry are DST/DRF project on anticancer compound development and DST/IPCA project on new antimalarial compounds development. The existing opportunities in international collaboration through joint projects, such as those funded by various international agencies, needs to be exploited. On this front I would expect much intensive activity.

Over all, during the year 2006-07, the institute has made several significant achievements presented in detail separately. However, I consider these only a means of subsistence. The true party will start only when some of our pipeline products reach commercialization as major drugs.

(C.M. Gupta)

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SIGNIFICANT ACHIEVEMENTS

Significant Achievements

Over the last few years acquisition of latest research tools and techniques, which are currently used by international pharma in drug research and development, together with the CDRI's decades old conventional strengths in research, have improved the institute's overall research quality and led to generation of useful data on new leads and products under development, besides attracting brilliant scholars for pursuing their research endeavors. In this backdrop, the year 2006-07, has been a productive year on most fronts. An account of some of the most prominent achievements across its broad-based activities are summarized below:

1. Business Development Output

The Institute continued to pursue its long-standing open door policy to encourage business cooperation with public and private industry and national and international research organizations and academia. Industry continued to show its confidence in the institute's products. Several companies have approached the institute showing their interests in pipeline products. As a result, several secrecy agreements have been signed and findings shared with the interested companies. The industry has been particularly interested in new leads and candidate drugs under development, namely CDR-134F194, CDR-267F018, NP-1, S-002-853, S-002-857and compound 99-411. The year witnessed cooperation with Ranbaxy, IPCA, Indigene Pharmaceutical and Satsang Rasaishana Mandir. The institute also outsourced facilities existing in a company for mechanism of action study of one of its products under development.

The institute continued to generate funding by submitting new projects to funding agencies and pursued existing sponsored projects. During the year, projects supported by MOH, DBT, DST, MoES, ICMR, CSIR, DRDO, ICAR, NMITLI and IFCPAR Indo-French program were in operation. During the year the Institute's total ECF through business linkages and contract research is expected to achieve a mark of Rs. 1300 lakhs by March 2007.

2. Progress in R&D Programs

The achievements made under R&D programs can be broadly classified under drug development and drug discovery.

2.1 Drug Development Studies

2.1.1 Clinical studies

The licensee firm Hindustan Latex conducted a product acceptability study on CONSAP (contraceptive cream) at Chennai and Cochin and found that the product was acceptable and convenient to use by women volunteers. Its plant origin attracted them to use it, and by using it, both women and men found the sexual experience pleasurable.

The antimalarial drug Arteether continued its multicentric efficacy studies in Dibrugarh, Rourkela, Jabalpur, Jodhpur and Guwahati completing so far 234 cases, and data

compilation has since commenced. Capsules of the other antimalarial drug, compound 80/53, were sent to Thailand for safety evaluation in G6-PD deficient cases suffering from malaria. The findings reported by Thai researchers confirm efficacy and safety of compound 80/53.

Phase III multicentric clinical trials on compound 80/574 (hypolipidemic) have been initiated at SGPGI and KGMU, Lucknow; PGI, Chandigarh; and Seth G.S. Medical College, Mumbai, and this trial, besides pharmacokinetic studies, are in progress.

Clinical studies to evaluate efficacy of Picroliv (hepatoprotective) in alcoholic cirrhosis and in tuberculosis patients on MDT have been carried out at three centres (Seth G.S Medical College, T.N. Medical College, & KG's Medical University).

Exploratory double blind clinical trials carried out on CT-1(anti-diabetic) in a total of 55 patients, at KGMU, Lucknow, have been concluded. The findings reveal statistically significant reduction in total serum proteins, SGOT, SGPT in CT-1 treated patients.

Among other products under clinical studies, CDR-134D123 (antihyperglycemic) has completed Phase I single dose double blind studies in healthy volunteers, and protocols for Phase I studies on compound 97/78 (antimalarial), as per GCP guidelines, have been developed.

2.1.2 Regulatory toxicity studies

Regulatory toxicity studies were carried out on inhouse products and outside products, besides some basic and applied toxicity studies. CDRI products 99/411, 97/78, herbal medicament, CDR-267F018, CDR-134F194 were evaluated for generating their safety profiles. Industry sponsored products were evaluated under contract research. Experimental studies carried out included hepatotoxic effects of isoniazid with special reference to oxidative stress and apoptosis using hepatoma cell line (Hep-G2), nephrotoxic effects of cisplatin, amphotericin B and gentamycin by using renal cortical slices, primary cell cultures and renal cell lines, and teratogenicity potential of cyclophosphamide and synthetic compounds was carried out by measuring biochemical changes in an *in vitro* system.

2.1.3 Pharmacokinetic studies

Pharmacokinetic evaluations (PK) were carried out on three candidate drugs 97/78 (antimalarial), S-002-853 (antidiabetic) and 99-373 (anti-osteoporotic).

Multiple dose PK studies on compound 97/78 and its metabolite in rhesus monkeys revealed insignificant plasma accumulation. Further, metabolite stability and CYP profile suggest involvement of CYP3A4 in its metabolism.

Tissue distribution profile of compound 99/373 and its two major metabolites in rat liver, lung, spleen and kidney has been established. Urinary excretion studies have revealed excretion of the compound and its metabolite in conjugated form.

Plasma pharmacokinetic studies of antidiabetic compound S-002-853 are in progress. Active S-isomer of this compound showed good systemic exposure with long elimination half-life.

2.1.4 Technology development

Efforts have been carried out to develop appropriate technologies-chemical, fermentation and pharmaceutical-for institute's

55th Annual Day Celebrations of CDRI in progress. Seated on the dais (R to L) are : Dr. C.M. Gupta, Director, CDRI, Prof. Asis Datta, Director, National Centre for Plant Genome Research, Prof. N.K. Ganguly, Director General, ICMR and Dr. O.P. Asthana.

Prof. Asis Datta, Director, National Centre for Plant Genome Research, New Delhi and Dr. C.M. Gupta, Director, CDRI releasing the CDRI Annual Report 2005-06 on 55th Annual Day Celebrations.

Recipients of CDRI Incentive Award - 2006 pose with Prof. N.K. Ganguly, Director General, ICMR and Dr. C.M. Gupta, Director, CDRI.

Prof. Asis Datta, Director, National Centre for Plant Genome Research, New Delhi (seated second from left) getting ready to deliver the 31st Sir Edward Mellanby Memorial Oration. Also seen in the picture are : Dr. O.P. Asthana, Prof. N.K. Ganguly and Dr. C.M. Gupta.

The newly acquired Jeol Accutof Direct Analysis in Real Time (DART) Mass Spectrometer in the SAIF.

New X-ray facility for primates.

Feed pelleting unit for preparation of animal diet.

Dr. Vinod Bhakuni receiving the Shanti Swarup Award in Biological Sciences from Honorable Prime Minister of India Dr. Man Mohan Singh. Also seen in the picture are Honorable Mr. Kapil Sibal, Union Minister of Science and Technology and Dr. R.A. Mashellkar, Former D.G., CSIR.

Dr. Sohail Akhtar receiving the CSIR Young Scientist Award -2006 from Honorable Kapil Sibal, Union Minister of Science and Technology. On the right is Dr. R.A. Mashelkar, Former D.G., CSIR.

Dr. Sohail Akhtar with his Young Scientist Award-2006 given by National Academy of Sciences, India.

candidate drugs and sponsored products, and several products have been produced in required quantities in order to allow further studies.

An improved process of **simvastatin** with lesser number of steps, which also allows reactant recovery and recycling, has been developed at bench scale. A 5-step improved process for the synthesis of **sertraline hydrochloride** developed at bench scale avoids the use of hazardous titanium tetrachloride. Scaling up processes for **paroxetine hydrochloride** (antidepressant) is in progress. The in-house products prepared for further studies were compound 99/411 (110 g) and Picroliv (9 kg).

Some cultures derived from soil samples have been characterized as *Talaromyces assiutensis* MTCC 7582 and *Streptomyces capoamus* MTCC 8123 and have shown strong antifungal activity against unicellular and filamentous fungi. Chemical characterization of the active compound produced by cultures is in progress. Studies on hydroxylation of compound **80/574** with the help of *Aspergillus ochraceus* is continued and its derivatives are under pharmacokinetic evaluation. Experiments related to long-term preservation of microbial cultures by freeze-drying and their maintenance are continued. Preserved cultures are checked at regular intervals for their purity, potency and viability.

Quality control and stability studies on several candidate drugs are continued, besides using HPLC methods for proper resolution of starting materials and for separation of chiral preparation. Efforts for development of novel delivery systems have led to progress on several fronts: preparation of nanometer emulsion for albendazole, studies on new formulation of inhalable biodegradable microparticles containing antitubercular drugs, and surfactant vesicles containing cyclosporin, etc.

2.2 Drug Discovery Research

Drug discovery efforts comprised basic studies to find out novel targets on one hand and natural products / synthetic compounds screening, the lead optimization, and other required studies on the other hand. During the year 21 new terrestrial plants and 12 new marine flora & fauna samples were collected and documented. A record number of 1749 new synthetic molecules were prepared. The compounds and extracts were evaluated for various primary and follow up biological screenings under different disease oriented research programs. A summary of significant achievements under different areas is presented below:

2.2.1 Biological screening

The project focus is on anti-TB and anti-cancer screening using both conventional and HTS based tools, on anti-leishmanial screening and botanical screening (CSIR-Procter & Gamble) using entirely HTS tools. Out of three hundred thirty eight compounds screened against *M. tuberculosis* H37Rv, two compounds were found active *in vitro* with none showing toxicity towards Vero cells or mouse bone marrow derived macrophages. On screening in mice, 2 compounds showed variable degree of infection clearance in spleen and lungs. The level of activity of these molecules was reconfirmed and further evaluations are underway. The mouse bone marrow model of TB has been developed and adopted in routine use.

Under the project on anticancer drug emphasis was focused on chemistry based lead optimization. Hit molecules of 4 chemical classes

were short listed and from hit molecules approximately 70 new analogs were synthesized and subjected to advanced screening using 8 cancer cell lines.

To screen out poor candidate drugs based on their rapid clearance or conversion to toxic metabolites by cytochrome P450 enzymes, a metabolic profiling assay using five Cyp enzymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2 and CYP2C19) commonly involved in drug metabolism, have been developed and subsequently used for screening of 10 lead molecules.

2.2.2 Newer approaches in drug discovery and design

To capitalise on newer approaches now available for drug discovery an integrated environment for informatics systems, computational chemistry and molecular modeling is in operation at the institute to facilitate and enhance drug design and discovery in different target therapeutic areas. Structure-based investigations and computational predictive models for structure-activity relationship studies including molecular docking and CoMFA and CoMSIA studies were applied on diaryloxy methano phenanthrene analogues as anti-tubercular agents, on 4-thiazolidinones as HIV-1 RT inhibitors and on human mitotic kinesin Eg5 inhibitors as anti-cancer agents. The results provided clear guidelines and reasonably good activity predictions for designing novel inhibitors. A rational evaluation of a series of *R* and *S* amino acid derived, 3-substituted 1,4-benzodiazepin-2-ones as anti-ischaemic agents has been carried out by molecular modeling and docking studies. Some of these compounds have shown promising neuronal protection activity.

Interaction and assembly of the leucine zipper peptide (LZP), its single alanine substituted analog, and double alanine-substituted analogs to human red blood and *E. coli* cells as a model system were studied. Fluorescence resonance energy transfer and gel electrophoresis experiments revealed the differences among the amino acids in their assembly onto the live human RBC and in their oligomeric states in zwitterionic lipid vesicles and human RBC ghost membrane. The findings have disclosed that assembly of these peptides in human RBC and *E. coli* is pivotal in determining their lytic activity against the corresponding cells.

Studies on the design and synthesis of thiazolidinone as HIV-RT inhibitors continued and several compounds were synthesized and the biological activity evaluation is in progress. Crystallization and 3D X-ray intensity data collection of 43 compounds of biological and structural importance were completed. Structure determinations and refinements of 32 compounds were completed. A significant milestone in the structure determination of the potential drug target viz. peptidyl-tRNA hydrolase from *M. tuberculosis* H37Rv in solution by NMR spectroscopy was achieved. Significant progress was also made in characterization of CFP-10 and ESAT-6 T-cell antigens of *M. tuberculosis* H37Rv.

2.2.3 CNS/CVS & other disorders

Neuroprotective effect of herbal medicament (HM) was investigated with respect to cytochrome C translocation and caspase dependent death pathway leading to necrosis and/or apoptosis. HM was found to exert its neuroprotective effects by acting at multiple targets in the signaling pathways that are activated in ischaemic and neuro-degenerative brain diseases. It appears to be a

Prof. J. Triggle, State University of New York at Buffalo, USA lights the lamp to mark the inauguration of the 10th International Conference Drug Discovery: Perspectives and Challenges.

A view of the 10th International Conference on Drug Discovery : Perspectives and Challenges. Seated on the dais (R to L) are : Dr. C.M. Gupta, Director, CDRI, Prof. D.P. Singh, Vice Chancellor, Dr. H.S. Hour University, Sagar, Prof. D.J. Triggle, State University of New York at Buffalo, USA.

Galaxy of the scientists during the International Satellite Symposium on Medicinal Plants and Functional Foods in the Management of Diabetes, Obesity and Cardiovascular Diseases.

Dr. R.A. Mashelkar, Former D.G., CSIR looks over the model of the proposed building of new CDRI campus.

Dr. R.A. Mashelkar, Former D.G., CSIR visits the site of the proposed new CDRI.

View of the 9th Dr. B. Mukerji Memorial Lecture function. Seated on the dais (R to L) are : Dr. C.M. Gupta, Director, CDRI, Prof. K. Muniyappa, Chairman, Department of Biochemistry, Indian Institute of Science, Bangalore, Dr. S.S. Agarwal, Former Director, SGPGI, Lucknow and Dr. Zaka Imam, Deputy Director, CDRI.

Dr. C.M. Gupta, Director, CDRI felicitating Prof. K. Muniyappa, Chairman, Department of Biochemistry, Indian Institute of Science, Bangalore for delivering the 9th Dr. B. Mukerji Memorial Lecture.

A view of the dignitaries presents on the occasion of 10th Dr. C.R. Krishna Murti Memorial Oration. Seated from (R to L) are : Dr. C.M. Gupta, Director, CDRI, Prof. N.K. Ganguly, Director General, ICMR, Mr. C.K. Ram Chandran, Dr. G.G. Sanwal and Dr. J.K. Saxena.

Dr. C.M. Gupta, Director, CDRI felicitating Prof. N.K. Ganguly, Director General, ICMR for delivering the 10th Dr. C.R. Krishna Murti Memorial Oration.

promising agent for the treatment of cerebral stroke. Studies on memory enhancing activity of Gugulipid have shown significant improvement in memory deficit induced by either scopolamine or streptozotocin in Morris water maze test in mice.

Essential safety pharmacology studies of three candidate drugs CDR-134D123; 99-411; Lysostaphin cream and Lysostaphin gel have been undertaken for their effect on cardiovascular, respiratory and CNS parameters in rats, rabbits and mice.

2.2.4 Filariasis

In immunological studies, SDS-PAGE and western blotting of *Wolbachia* intact and bacteria depleted *B. malayi* adult parasite were carried out with WSP serum and three antigens (66, 39, 27 kD) were recognized in intact worm antigen. *Wolbachia* (endo-symbiotic bacteria) were found to play an important role in development of host tissue inflammatory reaction in jirds infected with *B. malayi* during prepotency. Studies related to establishment of antifilarial efficacy of DEC with antibiotic tetracycline demonstrate that prior killing of *Wolbachia* has beneficial effect on the efficacy of standard antifilarial drugs. The immunological characterization of recombinant myosin was carried out in Balb/c mice. Efforts are in progress to produce polyclonal antibodies against purified fraction of *S. cervi* antigen that will be used for molecular characterization of filarial circulating antigen.

Biochemical and molecular studies on filarial parasites included purification of two isoforms of acetyl cholinesterase and polyclonal antibodies raised against those. In order to clone the filarial AchE gene, specific primers were designed based on conserved sequences of AchE from related parasites. PCR amplification was done using cDNA library and genomic DNA. Cloning was carried out in pGEMT vector and the sequencing of the gene inserts is underway. Hexokinase gene of *B. malayi* was cloned, protein expressed and purified to a single band of 72 kDa on SDS-PAGE.

2.2.5 Leishmania

Development of new screening models based on reporter gene is under way. *Leishmania* cell lines expressing green fluorescent protein without any drug pressure were constructed by integrating the GFP- containing construct downstream of promoter of 18S ribosomal RNA gene into the genome of *L. donovani* clinical isolates. Luciferase tagged *L. donovani* promastigotes were transformed into axenic amastigotes and their suitability for screening of antileishmanial compounds is underway. Studies related to cloning, over expression and characterizations of *L. donovani* drug targets viz. serine hydroxymethyl transferase, squalene synthase, triose phosphate isomerase, trypanothione reductase, dipeptidyl carboxypeptidase and glycosylphosphatidylinositol transferase-1 are progressing well. Biochemical properties and structure-modeling studies of *Leishmania donovani* pteridine reductase 1 were performed to reveal the active site features important for ligand binding and to guide inhibitor designing. Structure based drug design on homology model, based on recombinant pteridine reductase enzyme of *Leishmania donovani*, has enabled identification of inhibitors some of which have been tested *in vitro* and found to be inhibiting the enzyme in a target based assay.

Studies on actin network of *L. donovani*, through characterization of various actin-binding proteins, have revealed its involvement in various cell biological processes. Actin deploymerizing factor (ADF/cofilin) homologue

of *L. donovani* has been seen to play a role in cell development, maturation and infectivity. Over-expression of this protein in *L. donovani* has increased chemotaxis significantly whereas decreased promastigote interactions with peritoneal macrophages. *L. donovani* coronin (F-actin binding protein) gene deletion has shown defects in cytokinesis during cell division cycle. Preliminary experiments with recombinant *L. donovani* actin have shown that it forms filaments and bundles *in vitro*. An actin-related protein, which is close to ARP6 of yeast localizes predominantly in the nucleus and seems to play a role in chromatin remodeling process in promastigotes. Findings so far have collectively increased the research interests and are being perceived as a potential drug target in *L. donovani*. Use of micro-array technology enabled identification of important biochemical pathways for use as drug targets. One target viz. long chain fatty acyl Co-A ligase gene has been sequenced. Detection of the endogenous copy of this gene by southern blotting and transcript by northern blotting are underway.

2.2.6 Malaria

The curative response with synthetic compound 99/411 was established earlier in *P. yoelii* - Swiss mice model and against *P. cynomolgi* rhesus monkey model. Further studies with this compound have demonstrated efficacy in single and double dose against the rodent model and also in simian model.

As a follow-up on immunoprophylaxis studies with recombinant MSP-1 protein against simian malaria model, twenty-nine monoclonal antibodies were characterized for their epitope specificity. These monoclonals have been categorized in six groups on the basis of their reactivities with *P. cynomolgi* and *P.vivax* conformational and linear epitopes of MSP-1 antigen. Biochemical studies primarily focussed on molecular characterization of a putative choline kinase and transketolase from *P. falciparum* to identify novel enzyme targets for antimalarial drug development. Molecular studies continued with *P. falciparum* apicoplast and replication machinery has been characterized in terms of DNA protein interaction at replication origin. Studies have also been initiated on transcriptional machinery operative within the apicoplast. Analyses of genotype data of 4 genes, correlated with malaria susceptibility from 56 Indian sub-populations infected from *P. falciparum* were carried out. The results have revealed that extensive sub-population specific variations in allele frequency of several SNPs. *P. falciparum* malaria patient samples collected from endemic and non-endemic regions of India are being analysed for SNP association with disease severity as well as cytokine profiles.

2.2.7 Microbial infections

A murine infection model of latency with *M. fortuitum* has been developed to investigate virulence factors, pathogenesis and to screen mutants defective in persistence. Two mutants defective in persistence have been isolated. The *tol*C gene of *Vibrio cholerae* was cloned. The ORF encoding TolC protein plays an important role in regulating tolerance to osmolarity in small intestine. The gene has been overexpressed in *E. coli* using T7 expression vector. Work related to pathogenesis and development of a knockout of *tol*C is in progress.

The role of Rv3878, which is deleted in BCG vaccine strain, was found associated with enhanced hydrophobicity and biofilm formation. Rapid suscitation factors of *M. tuberculosis* were cloned and demonstrated to resuscitate the dormant cells in nutrient deprived condition. A recombinant *M. aurum* for screening of FASII pathway inhibitors has

A view of symposium Hypertension Update. Seated on the dais (L to R) are:
Prof. Ashok Chandra, Professor, Medicine, KGMU, Prof. V.S. Narain, Professor, Cardiology, KGMU, Dr. O.P. Asthana and Dr. A. Ghatak.

Dr. Naibedya Chattopadhyay addresses the audience during the symposium on Current Advances in Endocrinology. Seen in the picture (R to L) are : Dr. Nitya Nand, Former Director, CDRI, Dr. M.M. Singh, the superannuating Deputy Director, CDRI, Dr. V.P. Kamboj, Former Director, CDRI and Dr. Vinod Bihari, Scientist G, CDRI.

Dr. Amit Misra, Scientist, Pharmaceutics Division delivering his presentation in the program "Faculty Training/Motivation & Adoption of the Colleges". Seated on the dais (L to R) are: Dr. D.N. Upadhyay, Dr. A.K. Goel and Dr. Zaka Imam.

A view of the teachers and students participating in the program "Faculty Training/Motivation & Adoption of Colleges".

Dr. C.M. Gupta, Director, CDRI & ITRC delivering his presentation in the CSIR Foundation Day Celebration Function. Seated on the dais are: (L to R) are : Dr. S.P.S. Khanuja, Director, CIMAP, Dr. R. Tuli, Director, NBRI, Prof. R.B. Singh, Member, National Commission of Farmers, New Delhi and Prof. M. Vijayan, Professor Emeritus, Indian Institute of Science, Bangalore.

A view of the awardees completing 25 years of service during CSIR Foundation Day. Seen on the dais (R to L) are: Dr. C.M. Gupta, Director, CDRI, Mr. Sudhir Kumar, Principal Secretary, Department of Food and Civil Supplies, Govt. of U.P., Prof. M. Vijayan, Professor Emeritus, Indian Institute of Science, Bangalore and Dr. O.P. Asthana, Deputy Director, CDRI.

Mrs. Savita Gupta inaugurates the exhibition on occasion of CSIR Foundation Day at CDRI.

Mrs. Savita Gupta poses with the office bearers and awardees of the annual prize distribution function of CDRI Club.

been constructed and being evaluated. Role of Rv2416c (Eis) in modulation of immune response was demonstrated. Few interacting partners of Erp (Rv3910) in host have been identified by Yeast Two Hybrid method.

Phosphorylation of PKC isoforms appears to be induced by direct interaction of mycobacteria with macrophages rather using cytokines as mediators. The exposure of healthy volunteers from TB endemic area to *M. tuberculosis* was confirmed by elevated serum antibody levels and *in vitro* lymphocyte proliferation *M. tuberculosis* antigens.

2.2.8 Natural products

Twelve new plant extracts were prepared, extracted and submitted for biological screening besides continued evaluation of previously identified plants and marine extracts. Fifteen new derivatives of K009 from the plant 3247 (antihyperglycemic) were prepared and 4 of them had better activity profile than the parent compound. One novel compound from 4674 (antihyperglycemic), a rare stigmasterol glycoside derivative has been isolated. The plant 4601 (antileishmanial) yielded eight berbarine alkaloids out of which 2 are reported to be new and have exhibited antileishmanial and immunomodulatory activities *in-vitro* . Their structures have been elucidated by spectroscopic and degradation studies. Promising osteogenic activity has been reported in 5 pure compounds isolated from the plant 1020. From the roots of plant 4406, ten compounds of various classes have been isolated out of which 2 have shown significant anti-inflammatory and analgesic activities in dose dependant manner.

2.2.9 Reproductive health research

Out of several substituted phenanthrene derivatives with basic amino side chains, synthesized to search for new anticancer breast agents, one has shown appreciable activity comparable to tamoxifen.

Design, synthesis, characterization and evaluation of novel non-detergent spermicides has led to the discovery of two compounds which were 25 times more potent spermicides than nonoxynol-9. Stability studies on medicated condoms coated with *Sapindus* saponins indicated that the product was stable upto one year from the date of manufacture.

3. Publications and Patents

A total of 194 research papers were published in reputed national and international journals which is consistent with the quality improvement evident from increase in average impact factor over last few years. Filing patents continued to receive major thrust. This year, a total of 50 patents were filed (19 in India and 31 abroad). During the year 25 patents were granted, 12 in India and 13 abroad.

4. Technical Services

The Institute's Library continued to provide services to its users. Apart from the online subscription of all journals from 11 publishers, these services were extended to another 8 journals viz. Cell, EMBO Journal, Journal of Biological Chemistry, Nature, Nature Biotechnology, Nature Cell Biology, Nature Medicine and Science. During the year of report, CDRI acquired one-year access of Beilstein Cross Fire through MDL Discovery Gate. Beilstein Cross Fire is of immense help for searching chemical structure based information such as synthesis, reactions and properties of molecules. A sub-structure search is also possible.

The Institute continued to provide the *in vitro* and *in vivo* screening facilities to the outside users on payment basis. CDRI Library received recognition from national

and international organizations. Publication of periodicals viz. **Drugs and Pharmaceuticals-Industry Highlights** (monthly), **Drugs and Pharmaceuticals - Current R&D Highlights** and **Ocean Drugs Alert** (quarterly) were carried out regularly.

5. Human Resource Development

Under the CSIR Human Resource Development Centre, training in RTI Act-2005 was provided to concerned officials (Dr. Zaka Imam, Dr. A.K. Goel and Mr. B.D. Vashisth). Dr Imam also attended the FICCI-DST joint 2nd Global Conference and Exhibition **India R&D 2006 - "Mind to Market"** from 4-6 December 2006.

Training and exposure of institute staff received top priority. As many as 10 staff members were deputed for different training programs and conferences: Dr. K.R. Arya, 'Pharmacognostical Evaluation of Medicinal Plant Samples and Quality Control Measures', Dr. (Ms.) Poonam Singh, 'Good Laboratory Practices and Regulatory Issues'; Dr. S.K. Rath, 'RNAi and Viral Vectors in Gene Knock Down', 'Project Management Techniques and Practices', Dr. S.K. Rath, Dr. Ashok Singh & Dr. Amit Kumar Misra, 'Statistical Methods in the Analysis of SNP Marker Data', Naseem Ahmed Siddiqui, & Mr. Kalyan Mitra, V.K. Bajpai, 'General Management for Senior Scientists', Kalyan Mitra,'Cross-sectioning of biological tissue for electron microscopy'.

Several workshops were held to train staff: Multivariate Analysis and Drug Research Data (29.11.06) for introducing multivariate data analysis, chemometrics concepts, methods and their applications in drug research.

In order to promote Hindi in official working, a **Hindi Workshop** was organized (27 & 28 December 2006). 150 State and central government offices of Lucknow participated in the workshop under the auspices of Town Official Language Implementation Committee.

6. Seminars / Symposia / Lectures

The 31st Sir Edward Mellanby Memorial Oration '*Winning of Disease and Hunger: Chasing a Dream*' was delivered by Prof. Asis Datta, Director, National Centre for Plant Genome Research, New Delhi, on 17 February, 2006. Prof. K. Muniyappa, Chairman, Department of Biochemistry, Indian Institute of Science, Bangalore, delivered 9th Dr. B. Mukerji Memorial Lecture on '*Telomere Length Maintenance as a Target for Anticancer Drug Discovery*'. The *10th International Conference Drug Discovery: Perspective and Challenges* (including symposium on infectious diseases) was organized on 24-25 February 2006. The event was jointly organized by Indian Society of Chemists & Biologists India and University of Toronto, Canada. Large number of renowned scientists from several countries participated in the program. The keynote address '*Medicines Discovery in the 21st Century: For What and For Whom*?' was delivered by Prof. J. Triggle, State University of New York at Buffalo, USA. Prof. D.P. Singh, Vice Chancellor, Dr. H.S. Gour University, Sagar and President, Indian Society of Chemists & Biologists India delivered the Presidential Address. An International Satellite Symposium on *Medicinal Plants and Functional Foods in the Management of Diabetes, Obesity and Cardiovascular Diseases* was organized on 26th February 2006, in which a large number of scientists from all over the world participated.

The *10th Dr. C.R. Krishnamurthy Memorial Oration 'Indian Health and Development Index in 2050'* was delivered under the Society of Biological Chemists (India), Lucknow Chapter, on 7th March 2006 by Prof. N.K. Ganguly,

Mr. Ali Kausar explaining the CDRI achievements and facilities in the Indian Science Congress held at Hyderabad.

Dr. R.C. Tripathi explaining CDRI facilities to the participants in Bangalore-Bio 2006 exhibition.

Dr. B. Joshi, Chief Executive, Economic and Management Consultants, Lucknow delivering his lecture "Managing Creativity for Quality Innovation".

56वीं अर्ध–वार्षिक बैठक के अवसर पर नराकास, लखनऊ के सदस्य कर्यालयों के प्रतिनिधियों एवं अधिकारियें को संबोधत करते हुए संस्थान के प्रशासन नियंत्रक श्री बी0डी0 वशिष्ठ।

बैठक के अवसर पर उत्कृष्ट राजभाषा कार्यान्वयन हेतु पुरस्कृत विभिन्न कार्यालयों के सदस्यगण।

Director General, Indian Council of Medical Research, New Delhi. The Society conferred upon six researchers from the country Young Scientists Awards.

On the occasion of World Hypertension Day on 15th May, 2006, a half-day symposium *Hypertension Update* was organized by Indian Society of Hypertension. A symposium on *Current Advances in Endocrinology* was held on 28th August 2006.

The **CSIR Foundation Day** was celebrated on 26th September 2006 jointly by all the Lucknow based CSIR laboratories (viz. CDRI, ITRC, NBRI and CIMAP). On this occasion, an exhibition of these laboratories' major achievements, organized at ITRC, was inaugurated by Mr. Sudhir Kumar, IAS, Principal Secretary, Department of Food and Civil Supplies, Govt. of UP. The highlights of the event were a lecture by Prof. M. Vijayan, Indian Institute of Science, Bangalore, presidential address by Prof. R.B. Singh, Member, National Commission of Farmers, New Delhi, and award of certificates and mementoes to the staff who completed 25 years of their continuous service in CDRI/CSIR. Besides, as a part of this event, institute's scientists delivered lectures in various schools of Lucknow and held quiz competitions. Suitable prizes were distributed amongst the children who won prizes in various events.

A seminar *Project Management in R&D Organizations: Introduction, Quantitative Tools and Techniques & Selected Case Studies* was organized on 17th November 2006 in which all principal investigators of CDRI projects and scientists participated. Dr. Sushil Kumar, Associate Professor, Operations Management Group, Indian Institute of Management delivered a thought provoking lecture followed by an interactive discussion.

A half-day seminar *Nucleofactor Technology : A New Revolution in Gene Transfer & Silencing in Primary Cells* took place on 28th November 2006, which dealt with a newly developed technique called nucleofactor technology; the technology allows for direct delivery of DNA, siRNA and micro RNA of interest, directly to nucleus thereby facilitating its expression remarkably over the currently available technology and helps in high throughput screening.

7. Exhibitions

During the year 2006, Institute participated and displayed its achievements and facilities in the following exhibitions and events:

- Indian Science Congress, Hyderabad (3-5 January 2006);
- CSIR Exhibition-cum-Fair on Rural Technology, Jais, Raibareilly (18-22 February 2006);
- Science & Technology Exhibition, Deoria (12-14 April 2006);
- Bangalore-Bio 2006, Bangalore (3-5 June 2006);
- CSIR Foundation Day – 2006, ITRC, Lucknow (26 September 2006);
- CSIR Exhibition on Rural Technology, Deoghar, Jharkhand (27-31 October 2006);
- Global Health Care Conference and Exhibition: Promoting Partnership, New Delhi (15-16 January 2007).

8. Training Programs Conducted

Under the CSIR scheme for Excellence in Science for an Innovative India for promoting interaction of science students with different laboratories and motivating brilliant students to adopt science as a career, a program Faculty Training/Motivation and Adoption of Colleges was organized on 26th September 2006. Faculty members and students of science stream visited

the exhibition and interacted with scientists. Dr. Amit Mishra delivered a thought provoking interactive popular science lecture, which marked the inauguration of the event. Thereafter the students were exposed to the roving exhibition on major achievements of CSIR laboratories at ITRC. In continuation of the program, several scientists delivered lectures on popular science topics in the identified three adopted government inter colleges of Lucknow.

9. Administrative Reforms

An intranet commenced operation as a portal of institutional information sharing useful information among staff and management. Some other steps have been taken to optimize the functioning of the Institute. Botany Division was provided more working space to enable them reorganize and maintain records, plant materials and voucher specimens. The tissue and cell culture facility was segregated out from Animal House as a separate Tissue & Cell Culture Unit and Dr. A.K. Balapure was made as the unit incharge.

With a view to strengthen the on-line literature search capabilities of research staff, additional internet connectivity and computers were provided to all the research scientists during the year.

The institute catered to the obligations under RTI-2005 by promptly supplying information to applicants within the specified time limits.

10. Honours and Awards

Several scientists and staff members were honoured for their contributions. Among scientists who received various awards were: Dr. Vinod Bhakuni (Shanti Swaroop Bhatnagar Award - 2006 in Biological Sciences (CSIR) and P.B. Rama Rao Memorial Award - 2006 (Society of Biological Chemists); Dr. Md. Sohail Akhtar (CSIR Young Scientist Award – 2006 and Young Scientist Award from National Academy of Sciences, India); Dr. S.K. Puri (Dr. B.N. Singh Memorial Oration Award - 2005 from Indian Society of Parasitology); Dr. A. Ghatak (Triveni Devi Ram Sahai Award – 2005 by Indian Medical Association); Dr. (Ms.) Madhu Dikshit (N.S. Bhalla Oration – 2006 by Indian Pharmacological Society); Dr. Atul Kumar (CDRI Annual Day Incentive Award 2006); Dr S. K. Rath (Raman Research Fellowship - 2007-08) and Dr. Anup Kumar Misra (DST Ramanna Fellowship).

Dr. R.P. Tripathi (Most Cited Paper 2003-2006 Award by Elsivier Ltd., UK); Ms. Anuradha Kalani (Best Poster Award at 17th National Congress of Parasitology); Ms. Preeti Bajpai (Prof. M.B. Mirza Award for Best Research Publications - 2005 from Indian Society for Parasitology); Ms. Preeti Dohare (Best Paper Award at Neuroscience Meeting "Neurodegeneration and Neuroprotection", IICB, Kolkata).

Dr. Ram Raghubir was elected as Senior Vice President, Indian Pharmacological Society for the year 2005; Dr. S.B. Katti was appointed as Adjunct Visiting Professor in Department of Pharmaceutical Sciences, MAHE, Manipal; Dr. (Ms.) Madhur Ray was elected as Treasurer of Indian Society of Hypertension 2003-06 & Indian Academy of Neurosciences, Lucknow Branch.

11. Sports, Cultural and Miscellaneous Activities

CDRI indoor sports team participated in the Shanti Swaroop Bhatnagar Memorial Tournament held at National Metallurgical Laboratory, Jamshedpur and won several prizes in different events viz. Badminton, Chess and Carrom. Mrs. A.P. Deb (Endocrinology Division) and Mrs. Harjeet Kaur (Bill Section) became CSIR National Champions in Ladies Carrom.

PROGRESS IN RESEARCH PROJECTS

REGULATORY STUDIES

1. Clinical Trials & Pharmacokinetic Studies

Coordinator : Dr. O.P. Asthana

Clinical studies on candidate drugs continued this year. A total of 8 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 CONSAP (Contraceptive cream)

Before undertaking post marketing surveillance program, a pilot study to evaluate the product acceptability was undertaken at the initiative of Hindustan Latex Limited. It was seen that with continued usage, more users found the CONSAP cream to be convenient and acceptable. Use acceptability at Chennai exhibited that women from 43% in round 1 escalated to 57% in round 3. At the end of third round, 60% of the women volunteering for CONSAP cream use, felt that the product is a very convenient method for contraception. In Cochin, at least 50% volunteers felt the product to be very convenient and got attracted to use because of its plant origin. There were some dropouts due to various reasons but overall safety was good as except <5% cases complained of transient burning and irritation, tolerability was good. On the behavioral front, an increasing number of women and men found the sexual experience to be pleasurable.

1.2 Arteether (Blood schizontocidal agent)

Multicentric clinical trials continued for antimalarial efficacy in children suffering from *P. falciparum* malaria at Dibrugarh, Rourkela, Jabalpur, Jodhpur and Guwahati. So far, 234 cases completed the study and now data compilation is in progress.

1.3 Compound 80-53 (Antirelapse antimalarial)

500 capsules were sent to Thailand for clinical trials for safety evaluation in G6-PD deficient cases suffering from malaria. Data published by Thai group confirms the efficacy as well as safety of compound 80-53. It also shows its advantage over primaquine in G6-PD deficient cases [Reference: Safety and tolerability of elubaquine (CDRI 80-53) for treatment of *Plasmodium vivax*) malaria in Thailand, S. Krusood et. al., Korean Journal of Parasitology, **44(3)**, 221-228, September 2006].

1.4 Picroliv (Hepatoprotective)

1.4.1 Clinical trials in patients of tuberculosis receiving MDT and in patients suffering from alcoholic cirrhosis are in progress at 3 centers i.e. Seth G.S. Medical College, T.N. Medical College, Mumbai and KGMU, Lucknow.

1.4.2 Evaluation of hepatoprotective Effects of Picroliv in patients with alcoholic cirrhosis

The work is being carried out at Seth G.S. Medical College, Mumbai under the supervision of Prof. Nilima Kshirsagar. Thirty-six patients screened, 19 patients have been recruited in the study. Ten patients completed the study period of 6 months. 4 patients were withdrawn due to non-compliance of protocol, 4 cases dropped out and 1 patient expired during the study.

1.4.3 Evaluation of hepatoprotective effects of Picroliv in patients of tuberculosis on AKT

This work is also being carried out at Seth G.S. Medical College, Mumbai under the supervision of Prof. Nilima Kshirsagar. A total of 264 TB patients were screened, out of which 143 enrolled for the study so far. Sixty-two patients have completed the study period of 6 months. 13 patients are on going at present (n=6, completed 5 months treatment, n=4 completed 4 months treatment, 2 patients completed 3 months treatment and 1 patient completed 1 month treatment). 42 patients have dropped-out of the study or withdrawn.

1.4.4 Evaluation of hepatoprotective effects of Picroliv in patients of alcoholic cirrhosis

These studies are being carried out at T.N. Medical College, Mumbai under the supervision of Dr. Urmila Thatte. Thirty-four patients are enrolled in the study. Of these, only 10 cases have completed the study, 18 patients dropped out and 4 were withdrawn from the study while 2 cases are continuing with the trials.

1.4.5 Evaluation of hepatoprotective effects of Picroliv in patients of tuberculosis on MDT

The studies are in progress in collaboration with Prof. Rajendra Prasad at KGMU, Lucknow. So far, 32 patients have completed the 6 months study. 45 cases are currently in the various stages of follow-up while 174 cases did not complete the 6 months follow-up. Detailed mid-term analysis of this double blind study will be undertaken shortly.

1.5 CT-1 (Antidiabetic)

Exploratory double blind clinical trials were concluded at KGMU, Lucknow under supervision of Prof. C.G. Agarwal. A total of 150 patients were screened, 105 enrolled in this study and total of 55 patients (22 on placebo and 33 on CT-1) completed the trial as per protocol. HbA1C reduction was found to be 0.52% (p=0.0001). Data has been reviewed and

discussed with NPIL for future course of action. Statistically significant decrease in total serum proteins, SGOT and SGPT was observed in CT-1 treated patients.

1.6 Compound 80-574 (Hypolipidemic)

Phase III double blind multicentric clinical trials in patients of hyperlipidemia have been initiated at SGPGI, Lucknow, KGMU, Lucknow, PGIMER, Chandigarh and Seth G.S. Medical College, Mumbai. A total of 281 patients have been screened at four centers. Of these, a total of 66 patients have been randomized and allocated treatment (Atovastatin/CDRI compound 80-574) is being given. Clinical trials and pharmacokinetic studies are in progress.

1.7 CDR-134D123 (Antihyperglycemic)

Phase I single dose (0.5 to 7.5 g.) double blind tolerance studies completed in 31 healthy human volunteers. Data compilation has been done. Ethical approval is awaited for initiating Phase I multiple dose tolerance study at Seth G.S. Medical College, Mumbai.

1.8 Compound 97-78 (Antimalarial)

Protocol and case record form as per GCP guidelines for phase I clinical trials has been developed in collaboration with Department of Pharmacology, PGIMER, Chandigarh. In addition to this, protocol for human pharmacokinetic studies has also been developed jointly.

1.9 Pharmacokinetic and metabolic studies of synthetic compounds

1.9.1 97-78 (Antimalarial)

- Metabolic stability and kinetics of metabolism was investigated with rat liver S-9 and microsomal fraction.
- Multiple dose pharmacokinetic studies of antimalarial 97-78 and its *in vivo* metabolite 97-63 were performed in male rhesus monkeys following oral administration.
- 28-Day repeat dose toxicokinetic studies were performed in male and female rhesus monkeys. Doses used were 20, 40, 60, 80 and 100 mg/kg (60 mg/kg d-1 to d 10; 80 mg/kg d 11 to d 20 and 100 mg/kg d 21 to d 30; n=2 in each group in male and female monkeys).

1.9.2 S-002-853 (Anti-diabetic)

Pharmacokinetic studies of compound S-002-853 as isomeric mixture and as its S-isomer were carried out in male *SD* rats following oral (40 mg/kg and 25 mg/kg respectively) and intravenous (10 mg/kg and 2.5 mg/kg) doses respectively.

1.9.3 99-373 (Anti-osteoporotic)

- Pharmacokinetic studies of 99-373 in male rats were done after intravenous dose of 2.5 mg/kg.
- Pharmacokinetic study of 99-373 was done in female SD rats after 10 mg/kg oral dosing.
- Serum protein binding study of 99-373 was carried out at four concentrations (0.1, 1, 5 and 10 µg/ml) using charcoal adsorption method.

- Excretion studies of 99-373 were carried out in male and female SD rats after administration of 10 mg/kg by oral route.
- The *in vivo* absorption from gastrointestinal tract was studied using portal-venous concentration difference method after a single 10 mg/kg oral dose of the compound in female *Sprague Dawley* rats.
- Tissue distribution of 99-373 was studied after a single 10 mg/kg oral dose in female *Sprague Dawley* rats. The parent and the two major metabolites were detected in lung, liver, spleen, kidney, brain and GIT.
- Pharmacokinetics of 99-373 was studied in male and female rabbits after oral dose of 6 mg/kg body weight.
- *In vivo* metabolites of 99-373 in female SD rat's urine were detected and characterized by HPLC-UV. Four putative metabolites were synthesized. These putative metabolites were resolved by HPLC-UV in urine samples and further confirmed by LC-MS/MS.

1.9.4 80-574 (Anti-hyperlipidemic)

- Metabolic stability and kinetics of metabolism was investigated with rat liver S-9 and microsomal fraction.
- Single dose preclinical pharmacokinetic studies of compound 80-574 were carried out in male NZ rabbits after oral (20, 40, 80 mg/kg) and intravenous (3 mg/kg) administrations by serial sampling approach.
- Dose escalation pharmacokinetic of HP-β-CD complex of 80-574 by oral route was carried out in male SD rats at 18, 25, 36 and 72 mg/kg dose levels.

1.10 Pharmacokinetic and Metabolic Studies of Natural Products

1.10.1 Picroliv (Hepatoprotective)

Preclinical pharmacokinetics of Picroliv preparation was carried out in male NZ rabbit at a dose of 100 mg/kg. Pharmacokinetic parameters were calculated from the plasma concentration time profile of Picroside-1 and Kutokoside by non compartmental model approach.

1.10.2 Turmeric oil (Herbal Medicament)

Oral pharmacokinetic of Herbal Medicament (HM) was carried out in rat (N=3) at a dose of 250 mg/kg. Pharmacokinetic parameters were calculated from the plasma concentration time profile of the marker components by non compartmental model approach.

1.11 Drug targeting to bone: Bio-distribution of Lovastatin to bone

- A sensitive HMG-CoA reductase enzyme inhibition radioassay, which detects net inhibitory activity that is inherently present in biological samples after lovastatin administration, was standardized for determination of active inhibitor concentration in plasma, liver and bone tissues. The assay procedure was optimized for different experimental protocols and fully validated for linearity, accuracy, precision, specificity, recovery and stability. The sensitivity of assay method was found to be 1 ng/ml in all the matrices studied. Parallelism was also evaluated to verify that other active inhibitors in the samples behave similarly to lovastatin acid.

- The distribution of lovastatin equivalents in plasma, liver and bone was studied after oral (20 mg/kg) and intravenous (1 mg/kg) administration of lovastatin to female *Sprague Dawley* rats.
- The bone-sparing effect of lovastatin was also evaluated *in vitro* and *in vivo*. Its effect on PTH induced bone resorption, ovariectomy-induced increase in body weight, serum total cholesterol and biochemical markers of bone metabolism, PYD and DPD, in urine was also studied.
- Lovastatin-conjugate was synthesized in order to target lovastatin specifically to bone. The pharmacokinetic parameters of lovastatin equivalents in bone were significantly improved after conjugate administration as compared to lovastatin administration. This not only resulted in sustained release of lovastatin from conjugate at the site of action i.e. bone, but also dramatically reduced ovariectomy induced markers of bone metabolism and increased the bone mineral density.

2. Preclinical Safety Evaluation and Regulatory Toxicity

Coordinator: Dr. Sudhir Srivastava

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

I. Toxicological profiling of candidate drugs according to internationally accepted methods for studying local, systemic, reproductive and genetic toxicity, and

II. Deployment of alternative test systems that will reduce, refine or replace the use of animals in toxicity testing, and provide vital information on safety/mechanism of toxicity/metabolism of drugs.

2.1 Regulatory studies

99-411	1-Dose toxicity study in rat, 10-Days DRF toxicity study in rat.
CDR-267F018	1-Dose toxicity study in rat, 10 Days DRF toxicity study in rat.
r-Lysostaphin (cream formulation)	1-Dose toxicity study in rat and rabbit, 28 Days toxicity study in rat and rabbit.
r-Lysostaphin (Pure)	1–Dose Biocompatibility study in rat.
97-78	28 Days toxicity study in monkey, Teratogenecity study in rat and rabbit Male fertility study in rat.
MA 1596 (Maharishi Ayurveda)	1-Dose study in rat and mice.
Herbal medicament	28 Days study in rat.
CDR-134 F194	28 Days toxicity study in monkey.
AP76P	1-Dose toxicity study in rat.
AP20am14	1-Dose toxicity study in rat.
Kajjali Yoga	1-Dose toxicity study in rat.

2.2 Experimental toxicology work

1. Evaluation of hepatotoxic effects of isoniazid with special reference to oxidative stress and apoptosis using hepatoma cell line (Hep-G2).
2. Evaluation of nephrotoxic effects of cisplatin, amphotericin B and Gentamycin, using renal cortical slices, primary cell cultures and renal cell lines.
3. Teratogenicity of cyclophosphamide: Biochemical changes in an *in vitro* system.
4. Detecting teratogenecity potential of compounds by NMR based metabonomics.
5. Microarray based evaluation of hepatotoxicity of acetaminophen and primaquine.

2.3 Other studies in planning

1. Microarray and SiRNA Based mechanism of toxicity studies.
2. Working in compliance to the OECD principles of GLP.

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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) anticancer screening (c) high-throughput screening and (d) development of new screening models.

1.1 Tuberculosis - Screening

Three hundred thirty eight new compounds, submitted during the year, were screened against *M. tuberculosis* $H_{37}R_v$. Thirty three of these molecules were found active *in vitro* [24 having minimum inhibitory concentration (MIC) < 3.12 µg/ml and 9 with MIC < 6.25 µg/ml], with no *in* vitro toxicity towards Vero cells or mouse bone marrow derived macrophages. Seven non-toxic active molecules were evaluated using macrophage model of TB at their 5x and 10x MIC. The readouts were (a) microscopy following acid-fast staining and (b) counting of colony forming units (CFUs) of *M. tuberculosis* following cultures on agar-based medium. Four molecules, which showed potency equivalent to standard drugs isoniazid and rifampicin in this assay, were subjected to *in vivo* screening in the mouse model of TB. Two molecules were found toxic to mice while remaining 2 showed variable degree of clearance of infection, as determined by estimating survival time and bacterial load in spleen and lungs. The level of activity of both these molecules was reconfirmed. Further evaluation is underway.

1.2 Development of new screening models

The mouse bone marrow model of TB was developed and adopted as routine practice. It mimics growth environment in natural infection. It also demonstrates ability of a candidate molecule to penetrate host cell and phagocytic vacuole, bacilli residing within the vacuole and reach the desired drug target. In addition, mouse macrophages were also used for *in vitro* cytotoxicity assays, which in a sample survey, showed higher sensitivity than Vero cells in terms of toxicity manifestation.

1.3 Cancer

The project on cancer drug development is being pursued in collaboration with the industry

partner Dabur. During the current year, emphasis was on chemistry based lead optimization. 'Hit' molecules, belonging to 4 chemical classes, were short listed and approximately 70 new analogs of selected hit molecules were synthesized at CDRI and submitted for advanced screening (using 8 cancer cell lines- pancreas, ovary, prostate, breast, colon, lung, leukemia and oral).

1.4 Leishmaniasis

In the first phase of antileishmanial high-throughput screening (HTS) using a luciferase construct of *L. donovani* promastigote produced 'in house', over 6000 molecules of the Institute's chemical library (synthesized prior to 1980) were screened. The assay was standardized using antileishmanial drugs Pentamidine, Amphotericin B and Miltefosine. In the second phase of HTS, 4456 molecules (synthesized after 1980) were evaluated. After eliminating active molecules, which were toxic to Vero cells and mouse bone-marrow macrophages *in vitro*, 25 molecules have been selected as hits (MIC < 1.5 µg/ml). The chemical classes of hits have been determined. Selected molecules will be evaluated against amastigotes using the hamster macrophage model.

1.5 High-throughput screening of botanicals for the identification of skin and hair bio-actives

The HTS laboratory of CDRI is a partner lab in this CSIR – Procter & Gamble (P&G) joint project that is funded by P&G, USA. The lab will perform screening assays for the target enzymes – Cycloxygenase (COX)-1 and –2, using plant materials provided by other partner CSIR institutes. A total of 247 samples (183 extracts and 64 fractions) have been screened. After reconfirmation, 14 samples have shown significant inhibition of COX enzymes.

1.6 Metabolic profiling of selected leads using cytochrome P450 assays

Cytochromes are major catalysts for oxidative metabolism of hydrophobic chemicals. Compounds that are turned over rapidly or that are converted to toxic products by these enzymes are poor drug candidates. Metabolism of drugs by P450 enzymes influences drug clearance, toxicity, activation, and in some cases, adverse interaction with other drugs. Five Cyp enzymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2 and CYP2C19) are most commonly involved in drug metabolism. We have working assays for all the 5 enzymes and have screened 10 lead molecules, produced by CDRI, using these assays.

2. Area: Cardiovascular, Central Nervous System & 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, impaired wounds, inflammation, allergy including asthma and 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 Herbal Medicament (HM) as an anti-stroke agent

The preclinical work of HM was completed and detailed report was given to Themis Medicare, Ltd., Mumbai. Cadila Zydus, Ahemdabad, will do large animal toxicity studies on HM.

2.1.2 Anti-stroke activity

A total of 57 compounds were screened for antistroke activity. One compound was significantly active.

2.1.3 The mechanism involved in the neuroprotective action of HM in rats

Neuroprotective effect of HM was investigated with respect to cytochrome C translocation and Caspase dependent death pathway leading to necrosis and/or apoptosis. Rats subjected to cerebral ischemia by occlusion for 2h of middle cerebral artery followed by 24h of reflow. HM was administered either before or after ischaemic reflow and up to 6h after ischemia. Evaluations were carried out at 24h. The study showed that the cerebral lesion and TUNEL-positive cells in the ischaemic penumbra zone were significantly reduced. Immuno-reactivity of endothelial, neuronal and

inducible nitric oxide synthase, cytochrome C translocation, p53 expression and Caspase 3 activation was significantly attenuated by HM as compared to IR. Attenuation of behavioral deficit has further complemented these cytoprotective effects of HM. The therapeutic window with HM is at least 6h. HM appears to exert its neuroprotective effects by acting at multiple targets in the signaling pathways that are activated in ischaemic and neuro-degenerative brain diseases. It appears to be a promising agent not only for the treatment of cerebral stroke but also in the treatment of other disorders associated with chronic inflammation and oxidative stress.

2.1.4 Neuroprotective action of curcumin in rat focal embolic model of cerebral stroke

Neuroprotective role of curcumin in a clinically relevant model of focal cerebral ischemia was studied. Cerebral thromboembolism is the most common type of acute stroke. Focal cerebral ischemia was induced in rats by occluding middle cerebral artery (MCA) with preformed clots of 3 ml. Curcumin was administered 300 mg/kg ip after 4 hr of clot implant. The rats were scored at 48 h after surgery for neurobehavioral activity using neurological deficit, rotarod and open field activity. The effect of curcumin on brain infracts volume, edema volume, reactive oxygen species (ROS), myeloperoxidase (MPO) level and plasma nitrite content was studied in middle cerebral artery occluded rats. There was increase in infract volume, edema, ROS, MPO and plasma nitrite level in MCAO group when compared with sham. The rats of MCAO+curcumin group showed significant reduction in infarct, edema volume, ROS, MPO and plasma nitrite level. The neurobehavioral assessment further strengthened the above biochemical data, there by indicating delayed post-administration of curcumin is neuroprotective in embolic stroke model.

2.1.5 Development of anti-thrombotic agents

Total 65 test agents were tested at a dose of 30 µM/kg (po) in mice against collagen and adrenaline induced thrombosis and increase in the bleeding time. In addition, 7 fractions of marine organisms were also tested at 50 and 100 mg/kg dose.

2.1.6 Follow up studies on identified anti-thrombotic compounds

CDRI compounds (S-001-556, S-000-20, S-002-329 and S-002-333) were found to be promising in preliminary anti-thrombotic screening models. Follow up studies on platelet aggregation profile and coagulation parameter revealed their different mechanism of action.

Present study was conducted to assess the efficacy profile of these compounds against various thrombosis models in rats and mice. Hardened RBCs induced thrombotic challenge, arachidonic acid induced thrombosis in mice, arteriovenous shunt model and ferric chloride induced thrombosis in rats was used. S-001-556 conferred 20-40% protection against hardened RBCs induced thrombotic challenge and 20-30% protection against arachidonic acid induced thrombosis in mice. Moreover, significant reduction in thrombus weight was observed in arteriovenous shunt model. However, it did not increase TTO in ferric chloride induced thrombosis model significantly. S-000-20 conferred 10-15% protection against hardened RBCs induced thrombotic challenge and about 30% protection against arachidonic acid induced thrombotic challenge in mice. S-000-20 significantly inhibited thrombin generation

induced by ADP and collagen *in vitro*. Moreover, significant reduction in thrombus weight was observed in arteriovenous shunt model. S-002-329 conferred 10-15% protection against hardened RBCs induced thrombotic challenge and about 20% protection against arachidonic acid induced thrombotic challenge in mice. Moreover, it significantly reduced thrombus weight in arteriovenous shunt model. S-002-333 conferred 40% protection against hardened RBCs induced thrombotic challenge and about 30% protection against arachidonic acid induced thrombotic challenge mice. Moreover, it inhibited thrombus formation in arteriovenous shunt model.

2.1.7 Development of anti-hypertensive agents

Twelve synthetic compounds from CDRI were tested at 5, 10 and 25 mg/kg intravenously. Among them, 3 exhibited anti-hypertensive activity. A total of 170 marine substances and 10 plant extracts have been evaluated for antihypertensive activity in anaesthetized rats on polygraph. None of these showed any promising effect.

2.1.8 Anti ischaemic activity

8 compounds were screened but none was found significantly active.

2.1.9 Basic Studies in CVS

2.1.9.1 Studies on cerebral stroke

Studies were extended to understand pathophysiology of cerebral stroke at cellular and molecular level to identify novel targets for developing newer and novel anti-stroke molecules. These include role of NFK-B, AIF, Calcineurin, Caspases, PARP, HSPs and neurotrophins.

(a) Temporal progression of cellular damage in cerebral ischemia

Focal cerebral ischemia was induced in male Sprague Dawley rats for 2 hours by middle cerebral artery occlusion (MCAO) followed by reperfusion (R) for the period of 0 hrs, 4 hrs, 8 hrs, 12 hrs and 24 hrs. The degree of cell damage was assessed by MDA in blood serum followed by delineation of the infarct size by TTC staining. There was significant increase in the neurological score i.e. >5 and MDA was significantly increased at 4 hrs, 12 hrs and 24 hrs of reperfusion. The infarct arc significantly increased from 3.22±2.99 to 78.56±3.90 mm^2 exponentially from 2/0 hrs to 2/24hrs of I/R.

The nature of cell death was analyzed by hematoxylin and eosin which showed a greater number of necrotic neurons at early reperfusion time points, followed by an increase in the number of apoptotic neurons beyond 8 hrs of reperfusion in striatal and cortical regions of the brain. Furthermore, TUNEL positive cells were observed which showed a significant increase from 28.0%to 66.5% in the striatal region and 23.0% to 78.0% in the cortical region from 2/0 hrs to 2/24 hrs of I/R.

These studies indicate that I/R injury of varying time points lead to massive damage of the striatal and cortical regions of the brain, resulting in the motor deficit.

(b) Altered expression of HSP70 and Bax/Bcl-2 proteins in cerebral ischemia reperfusion injury

The nature of cell death analyzed by hematoxylin and eosin showed greater number of necrotic neurons in the striatum as compared to the cortex. DNA fragmentation studies revealed a significant increase in TUNEL positive cells from 59.0% to 78.0% in the cortical

region and 59.0% to 66.4% in the striatal region from 8 to 24 hrs of reperfusion respectively. Moreover, Bax/Bcl-2 ratio was more in the cortical region as compared to the striatum. It is accompanied by significant increase from 127.0% to 149.4% in the cortical region and significant decrease in the HSP70 protein expression from 69.0% to 45.0% in the striatal region from 8 hrs to 24 hrs of reperfusion respectively.

These results clearly indicate that HSP70 was unable to rescue the cells due to its inhibition at later reperfusion time points from necrosis/apoptosis in striatum. However, increased expression of HSP70 and Bax in the cortical regions seems to reflect a significant apoptotic damage in the cortex as compared to striatum, which mostly undergoes necrotic type of cell death in focal cerebral ischemia.

(c) Role of neurotrophins and their receptors in Focal cerebral ischemia

Male Sprague Dawley rats were subjected to middle cerebral artery occlusion (I) for 1 h and different time intervals of reperfusion (R). It showed ND>6. Further, biochemical (MDA and GSH), histochemical (HE, CV and TUNEL) and western blot (SOD1 and SOD2). Gene expressions of NTs and their receptors (TrkA, TrkB and p75) were studied using RT-PCR technique, whereas protein expressions of pro-NGF and pro-BDNF were also studied using western blotting (WB). Time dependent elevation of MDA levels, reduction in GSH, SOD1 (in cytosol) and SOD2 (in mitochondria) levels and gradual increase in the apoptotic vs. necrotic cells ratio in striatum and cortex during reperfusion are indicative of I/R-induced necrosis at early and apoptosis at later time points. In RT-PCR and WB studies, we found that mRNA levels of NGF and BDNF increased gradually in striatum and cortex, but up-regulation of this gene doesn't seem to get translated into active ligands due to I/R stress. Though, significant increase was found in pro-NGF and pro-BDNF protein expressions in striatum and cortex but not in hippocampus. Interestingly, it was established that elevation in the mRNA levels of p75 and activation of its downstream signaling molecule (pJNK) at similar time points and brain regions. It is apparent from the above findings that as a consequence of I/R injury pro-NTs up-regulates and may mediate apoptotic cell death through p75 receptors.

(d) Modulation of apoptosis by calcineurin during cerebral ischemia

Sprague Dawley rats (250±10 g) were subjected to 2 h ischemia followed by 0 h, 3 h, 12 h and 24 h of reperfusion using MCAO. Neurological deficit (ND), blood GSH and MDA levels were measured to assess the oxidative stress and extent of brain damage. CaN expression studies were done by western blotting in cortex and striatum. The area of infarction was quantified in TTC stained brain slices. The progression of cell death following I/R stress was assessed in the cortical and striatal brain regions by cresyl echt violet and haematoxylin eosin staining as well as by apoptosis detection assay (TUNEL). These results indicate that CaN upregulation seems to aggravate ischemic cell damage. This is further supported by neuroprotective action of FK-506, a well-known CaN inhibitor. Hence, this molecule may play a central role in the progression of cell death particularly apoptosis in I/R injury. Further, the studies on intracellular localization and interaction of CaN with different death inducing and death suppressing molecules may help to provide new insight into the pathogenesis of cerebral ischemia.

(e) Modulation of calcineurin (PP2B) following I/ R injury

Efforts were made on understanding the modulation of CaN following different time points of ischemia/reperfusion (I/R) injury. Sprague Dawley rats were subjected to 2 h I followed by 0 h, 3 h, 6 h, 12 h and 24 h of reperfusion. Neurological deficit (ND), GSH and MDA levels and area of infarction were measured to assess the oxidative stress and brain damage. Calcineurin (CaN) phosphatase activity was measured using RII peptide as a substratre, whereas CaN expression profile was assessed by western blotting in hippocampal, striatal as well as in cortical brain regions. Increased level of MDA and depletion of GSH stores following I/R clearly demonstrated the lipid peroxidation due to oxidative stress. Calcineurin expression and its activity profile suggest that 2/6 h and 2/12 h I/R time points are crucial for the I/R mediated cell death. FK-506, a well known CaN inhibitor shows neuroprotective effect indicating that this molecule plays a central role in the progression of cell death following I/R injury. This CaN seems to interfere in the development and progression of ischemic brain damage. However, a proper understanding of CaN interaction with different death inducing or death suppressing molecules may be helpful in exploiting the potential of this molecule as a new therapeutic target.

(f) ER stress and cerebral ischemia

Transient focal cerebral ischemia (2 h) was produced by middle cerebral artery occlusion in SD rats followed by different time intervals of reperfusion. The expression pattern of GRP78 (an ER-stress marker) and caspase-12 (an ER resident pro-apoptotic protein), caspase-7 and TRAF-2 were analysed by western blotting and/or immuno-histochemistry. Terminal deoxynulceotidyl transferase-mediated DNA nick end labeling (TUNEL) was performed to detect DNA fragmentation. TUNEL/double immuno-flourescent staining of caspase-12 was performed to clarify whether caspase-12 is associated with cell death. Enhanced expression of GRP78 and TUNEL positive cells in various brain regions support induction of ER stress and apoptosis as a consequence of I/R. Moreover, TUNEL/double immunoflourescence staining indicates that caspase-12 might be associated with apoptotic cell death. Both the pro (55kDa) and active form (42KDa) of caspase-12 were observed predominantly in the microsomal fractions of striatum, cortex and hippocampal regions. Presence of active caspase (42 KDa) only in the cytosolic fraction suggests that activated caspase-12 translocates from the ER to the cytosol. Thus present study confirmed the translocation of cytosolic procaspase-7 to the ER at the time of caspase-12 cleavage. On the other hand, TRAF-2 was also upregulated in both microsomal and cytosolic fractions. These findings collectively demonstrate that ER stress may play a key role in I/R injury induced cell death signaling pathways.

(g) Role of NF_K-B in cerebral ischemia

MMP-9 levels in the ischemic hemisphere as detected by zymography in PDTC a NFk-B inhibitor treated animals were higher by 170%. Fluorimetric estimation of Evans blue dye also showed relative increase in its permeability across BBB in the left hemisphere in PDTC treated MCAO rats by 135% as compared to control MCAO rats. NF_K-B has been found to regulate MMP-9 transcription, and it is a major enzyme responsible for BBB disruption and its expression is increased in transient focal ischemia leading to breakdown of BBB. It was expected that PDTC, a NF_K-B inhibitor, might

alleviate post ischemic BBB disruption. But the results indicate that PDTC exacerbates BBB leakage. This may be because PDTC, besides inhibiting NF_K-B, activates the transcription factor AP-1, which seems to upregulate MMP expression. It may be concluded that the NF_K-B inhibitor PDTC does not seem to protect post-ischemic BBB damage.

(h) Diabetes and cerebral ischemia

Neurological deficits were more pronounced in the diabetic animals subjected to MCAO. SOD level was reduced at 1/3 h I/R, which seems to recover later suggesting the involvement of enhanced oxidative stress at early hours of I/R injury in diabetic group. The DNA damage in terms of disorderly splitted fragments was detected clearly as smear in affected brain tissue of diabetics indicative of necrosis. Further, enhanced PARP expression and H&E staining supported the dominance of necrosis in diabetic group. Thus the present study suggests that necrosis predominantly plays a major role in enhancing brain damage in diabetic rats which seems to be due to increased oxidative stress and over expression of PARP.

(i) Role of apoptosis in exaggerating brain damage in diabetic stroke

The effect of varying degree of cerebral ischemia/reperfusion (I/R) ranging 0.5 h, 1.0 h and 2.0 h of ischemia and 24 h of reperfusion was examined at each time point on cellular damage in STZ-diabetic rats. An increasing order of I/R tends to cause pronounced decrease in neurological function, depletion of endogenous antioxidant GSH and significant increase in lipid peroxidation by-product malondialdehyde (MDA) as measured in the blood of diabetic ischemic rats as compared to normoglycemic ones. Moreover, 2,3,5-triphenyl tetrazolium chloride (TTC) clearly demonstrated infarction at 0.5 h/24 h of I/R in diabetic but not in normoglycemic rats. Further, the infarct size at each time point was comparatively larger with increasing I/R injury in diabetic rats as compared to normoglycemic ischemic subjects.

The cellular alterations visualized with haematoxylin and eosin (H&E) staining revealed that besides necrotic changes, cells exhibited features of apoptotic damage. Further, the density of apoptotic cell was more pronounced in diabetic animals, as demonstrated by TUNEL positive brain cells. The immunoflourescence detection of active caspase-3 and apoptosis inducing factor (AIF) translocation to cytosol and nucleus further delineated the role of apoptotic cell damage following I/R stress in diabetes. The striatal tissue was greatly affected followed by cortex and hippocampal nuclei in diabetics as compared to control during varying I/R insults.

(j) Role of sodium influx in patho-mechanism of cerebral ischemia in gerbil model

An attempt was made to elucidate role of sodium influx in the initiation of ischaemic events and subsequent interdependent pathways leading to neuronal death after 24 h of reflow in bilateral common carotid occlusion (BCCAO) model of transient (5 min.) global ischemia. Monensin (a sodium ionophore) or tetrodotoxin (a sodium channel opener) (TTX), (10 mg/kg i.p. 30 min prior to ischemia) was given to gerbil. In this study, we showed that the nesting behavior and spatial mapping was impaired after ischaemic insult and TTX could significantly ameliorate the injury. Better nesting score and attenuation in spatial mapping was observed in IR-TTX treated group. Cerebral infarct was reduced by TTX in cerebral cortex was performed in gerbil brain cryosections. Our results showed decrement in immunoreactivity

of endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), inducible nitric oxide synthase (iNOS), cytochrome c and p53 expression by TTX, which was intensified by monensin as compared to IR sections. Cell death visualization by the terminal deoxyribonucleotidyl transferase-mediated dUTP nick end (TUNEL) labeling confirmed apoptotic cells in cerebral cortices of IR sections which was less in TTX treated sections. In the neurons the total nitrate/nitrite (NOx) level, peroxynitrite, calcium load and apoptotic population were estimated. Our results show that after 24 h NOx, peroxynitrite levels, calcium load and apoptotic population were significantly attenuated by TTX and augmented by monensin more than ischemia reperfusion (I/R) groups. Monensin worsens the ischaemic-induced injury in most of the parameter studied. TTX, fast sodium channel blocker, offered neuroprotection by attenuating behavioral and structural parameters.

(k) Effect of iNOS inhibitor, l-w-(1-aminoethyl) lysine (l-nil) against global ischemia in gerbil

Since NO involvement has been implicated in the neuronal damage. The present study, was undertaken to investigate the neuroprotective effect of an iNOS inhibitor, NIL on global cerebral ischemia. Global cerebral ischemia-reperfusion (IR) injury was produced by 5 min occlusion of both common carotid arteries followed by reperfusion of 24 h in the adult male Mongolian gerbils. The extent of injury was assessed behaviorally by measuring neurological functions, locomotor activity, motor coordination test and by cellular apoptosis, cellular death by TUNEL staining and expressional pattern of endothelial, neuronal and iNOS forms of nitric oxide synthase(NOS). NIL (10 mg kg, i.p., administered 5 and half hour after ischemia) treatment did not improve the neurological functions but increased the hyper locomotion and memory impairment in IR challenged gerbils. The n and iNOS expression was reduced where as eNOS was increased, a significant rise of NO was observed. NOS levels at 2, 4, 6, 8, 12 and 24 h of ischemia was observed. A sharp rise at 6 h was observed. An independent mode of apoptosis was also observed with rise in p53 expression caused by global IR injury These results suggest that as neuronal survival were unchanged or augmented by NIL given at 6 h after ischemia evaluated at 24 h. A specific iNOS inhibitor has failed to be effective neuroprotective agent for global cerebral ischemia.

2.1.9.2 Elucidation of atherosclerosis phenomenon

The objective of the proposed study was to elucidate the mechanisms involved in the development of atherosclerosis. Since platelets and macrophages play an important role in the above phenomena, understanding their signaling mechanisms will help to decipher the mechanism of the disease. The proposed studies were undertaken, a) Golden Syrian hamster model of atherosclerosis and b) Induction of differentiation and macrophage foam cell formation in human monocytic-macrophage cell line THP-1. In a high fat diet induced model of atherosclerosis, male Golden Syrian hamsters were fed either commercially available standard chow diet (control) or the high fat atherogenic diet (Research Diet Inc, NJ, USA.) containing Fat (23.3%), Fructose (172.8%), coconut oil (177.5%) and cholesterol (12.5%). Preliminary observations indicate the occurrence of fatty streaks in the aortic arch and thoracic aorta of hamsters fed with high fat diet for 10 weeks. Even after 20 weeks of feeding, advanced lesions were not observed. However, in another model

of atherosclerosis, ApoE knock out mice, animals developed significant lesions on a normal chow diet when compared with the control animals.

Tyrosine phosphorylation of platelet proteins was analyzed by phosphor blotting. Significant difference in the tyrosine phosphorylation pattern was observed between the control and high fat fed hamsters. Role of phosphatase in the above observation is also speculated on the basis that phosphorylation patterns were different in the presence of phosphatase inhibitors, sodium fluoride and sodium orthovanadate.

To assess the role of monocytes derived macrophages in atherosclerosis, human THP-1 cells were differentiated with 200 nM of PMA for 72 hours. For LDL treatment of these cells, LDL isolation was done from the plasma of healthy individuals. LDL was prepared by sequential ultracentrifugation. The appropriateness of the preparation was validated by oil O red staining and agarose gel electrophoresis. The electrophoretic mobility of the isolated lipopoprotein was 0.3ìm $s^{-1}CMV^{-1}$. The LDL isolated was oxidized by the standard copper oxidation method, dialyzed and concentrated. The oxidized LDL (Ox LDL) electrophoretic mobility was ~2 times more than that of native LDL. Oxidation of LDL was also evident from the ~4 fold increase in the TBARs reactivity assessed by standard MDA estimation protocol.

PMA differentiated THP cells were treated with 40µg/ml of oxidized LDL for 2 days. PMA+oxidized LDL treated cells differentiated more than the cells treated with PMA alone. These initial observations indicate that modified lipids have an important role in macrophage differentiation and thus might contribute to atherosclerotic lesion development.

2.1.9.3 Studies on rat and human neutrophils with reference to modulation of hemostasis

Nitric oxide (NO) modulates diverse functions of peripheral blood cells bearing both physiological and pathological implications. NO as a ubiquitous signal transducer influences several physiological immune functions of neutrophils (PMNs). Besides neutrophils have a vast ascorbate storage which is supportive of NOS catalysis apart from its vital role in counteracting oxidative stress. The objective of the present studies was to evaluate NO mediated modulation of neutrophil functions under hypertensive conditions in spontaneously hypertensive rats, during ascorbate deficiency in scorbutic guinea pig models, and in LPS treated rats. In addition role of NO in rats PMNs maturation as well NOS distribution in human blood cells has also been investigated.

2.1.9.4 Studies on scorbutic guinea pigs, hypertensive and LPS treated rats

Previous observations have recorded that ascorbate deficiency causes a down regulation in NOS catalysis and thereby NO production from neutrophils attributed to the destabilization of tetrahydrobiopterin amongst the scorbutic guinea pigs. NO and free radical generation potential, phagocytosis, apoptosis, immunolabelling of surface markers, mitochondrial transmembrane potential loss, intracellular calcium mobilization was ascertained by flowcytometry studies. Expression profile of pro-inflammatory cytokines and nNOS isoforms was done by RT-PCR analysis. MPO activity was evaluated by spectrophotometric methods and total nitrite content was quantified by Griess methods following cadmium reduction and $HgCl_2$ treatment. We also evidenced that decreased NO

generation correlates with a compromised oxidative burst potential and hence presumable non-effective combat against pathogenic intrusion. Now the putative pathway leading to a trigger for NOS and NADPH catalysis offered by ascorbate seems to occur due to mobilization of intracellular calcium pools, subsequently causing activation of PKC in this process. Neutrophils from scorbutic guinea pigs are more prone to apoptosis and furthermore ascorbate enhances the apoptotic clearance of activated neutrophils *in vitro* following phagocytosis by triggering the mitochondrial pathway. MPO content in neutrophils from scorbutic group is found to be much higher and thus there could be a difference in extent of maturation of the peripheral blood neutrophils too, which needs to be ascertained.

Neutrophils from spontaneously hypertensive rats (SHR) were found to be in a more activated state evaluated in terms of surface expression of CD11b and capable of robust oxidative burst in comparison to the normotensive sex and age matched Wistar rats. To further explore the role of NOS in pathological conditions expression of NOS isoform was checked in hypertensive rats. Neutrophils from SHR showed a marked augmentation in the expression of pro-inflammatory iNOS, IL-1β and thereby NO generation potential. We did not observe a significant alteration in expression profile of TNF-α and GTP cyclohydrolase. Simultaneous enhancement in oxidative burst and NOS activity subsequently contributes to the generation of $ONOO^-$ and hence limits the concentration of vasodilatory NO in circulation among SHR. Moreover, increase in NOS activity positively influences the respiratory burst potential among neutrophils from the SHR group since it is partially dependent on NOS catalysis as well as external and intracellular calcium resources. The rate of spontaneous apoptosis in neutrophils from the hypertensive group was found to be slower which could be attributed to the high level of sustained NO production in neutrophils from the hypertensive group. On the whole the activated neutrophils in peripheral circulation of SHR contribute to predispose them to oxidative stress and pro-inflammatory conditions further complicating the adversities of hypertensive disorder.

LPS treatment (1 mg/kg) was given to rats intraperitoneally and expression of NOS isoforms was explored. No change was observed in peripheral and peritoneal PMNs in control and treated animals but total nitrite was found to be higher in plasma, suggesting that due to mRNA instability no change was observed at expression level while marked difference was observed in terms of nitric oxide generation.

2.1.9.5 NOS distribution in human blood cells

The present study was undertaken to investigate the expression pattern (RT-PCR) and localization (immunogold microscopy) of different isoforms of nitric oxide synthases (nNOS, iNOS and eNOS) in human PMNs and in other blood cells. RT-PCR products showed expression of house keeping gene GAPDH in all blood cells like RBC, platelet and PMNs while iNOS was only found in the PMNs, while the expression other NOS isoforms could not be seen in platelets, RBC and WBC by using self designed primers. High expression of iNOS was evident in PMNs and also in RBCs. eNOS protein was mainly found in PMNs, monocytes and lymphocytes. NOS isoforms in PMNs were localized to the nucleus, azurophilic granules, and plasma membrane and in the cytoplasm.

2.1.9.6 Studies on NO during neutrophil maturation

Since NO plays an important role in the regulation of various functions of neutrophils (PMNs), we have undertaken a study to explore the presence of nitric oxide synthase (NOS) during PMNs maturation. In bone marrow (BM) PMNs mature in six stages: myeloblast (MBs), promyelocytes (PMs), myelocytes (MCs), metamyelocytes (MMs), band cells (BCs) and segmented neutrophils. Neutrophil precursor cells at different stages were isolated from BM by using Percoll density gradient. Three bands were obtained which were confirmed by Giemsa staining and by the presence of granular marker, myeloperoxidase (MPO). Cell cycle analysis of these cells by flowcytometry showed maximum cells in S-phase cells in band-3 as compared to band 1 cells, in which maximum cells were in G1/G0 phase. Level of NO in these cells was measured by a probe DAF-2DA, which augmented with the maturation of neutrophils. Total nitrite (NO_2^- and NO_3^-) and NOS activity was also estimated to confirm DAF results and exhibited similar pattern of increase with PMNs maturation. Basal and fMLP, PMA, bacteria, and SNP stimulated ROS generation was assessed by using DCF-DA, the basal level of ROS was found highest in case of band 3, while stimulated response was augmented from immature to mature neutrophils. Phagocytosis by the neutrophil and precursor cells was analyzed by using FITC labeled bacteria, which exhibited minimal response by immature precursors in contrast to the mature cells.

2.1.9.7 Regulation neutrophil free radical generation by NO

Neutrophils play a key role in host-defense mechanisms against invading pathogens, using their capacity to migrate, engulf microorganisms and produce toxic radicals. NADPH-oxidase (NOX), xanthine oxidase (XO), myeloperoxidase (MPO), cyclooxygenase (COX), electron transport chain (ETS) and nitric oxide synthase (NOS) are the major players to generate superoxide radicals (O_2^-)/ hydrogen peroxide (H_2O_2). Neutrophils lack XO and have very scanty number of mitochondria. Previous work from our lab has shown that nitric oxide (NO) modulates neutrophil NOX and NO is documented to affect the entire above mentioned enzyme systems. The present study addresses to detangle the "NO, MPO, NOS and NOX" (One molecule, rest enzymes, is it OK) in neutrophils. Flowcytometry, H_2O_2 assay, and dityrosine measurement were used to study the free radical generation, while MPO activity was assessed spectrophotometrically. Activation of MAP Kinases (p38 MAPK, ERK) was analysed by phospho blotting and flow cytometer based bead assay. Calcium was also estimated by a fluorimetric method. SNP and SNAP (10 mM to 1 mM) in a concentration and time dependent manner augmented the free radical generation as assessed by DCF-DA, without adversely affecting the cell viability. NO also led to the release of MPO and protein. The response seems to be mediated by MPO, which was activated/ released by peroxynitrite, a process involving calcium, kinases (p38 MAPK, ERK), and cytoskeleton, as interventions preventing the modulation of these parameters blocked or attenuated NO mediated responses. The results obtained suggest that addition of NO to the neutrophil suspension leads to the uncoupling of nitric oxide synthase, generating O_2^-, and H_2O_2 and subsequently peroxynitrite, which is utilized by MPO to form hypochlorous acid (HOCl). HOCl reacts with nitrite (NO_2^-), a NO metabolite to generate nitryl chloride (NO_2Cl), a potent oxidant and nitrating agent. NO thus seems to participate in the neutrophils mediated microbial killing and inflammation.

2.1.9.8 Effect of haloperidol on papillary muscles

The effect of haloperidol, an antipsychotic drug on electrically driven action potential of G. pig papillary muscle was investigated. The influence of various physiological and pharmacological factors on haloperidol induced prolongation ventricular repolarization was investigated. APD prolongation property of haloperidol accelerated in hypokalemia.

2.2 Central nervous system

2.2.1 Gugulipid as memory enhancer

Pre- as well as post-treatment of Gugulipid showed significant improvement in memory deficit induced by either scopolamine or streptozotocin (ic) in Morris water maze test in mice. Chronic treatment (14 days) of Gugulipid (50 mg/kg, po) caused significant decrease in AChE activity, low level of MDA and high concentration of GSH in brain following STZ (ic) as compared to vehicle administration in STZ (ic) treated mice. The study demonstrated that Gugulipid has significant protective affect against streptozotocin induced memory deficits model of dementia that can be attributed to anti-oxidant property of Gugulipid. These observations suggest Gugulipid as a potential anti-dementic drug.

2.2.2 Development of receptor binding technique for evaluation of atypical anti-psychotics

The facility for *in vitro* screening of test compounds using receptors binding assay has been established. The binding affinity of test compounds to D2 dopamine receptor was studied in striatal membranes, in competition with [^{3}H]-spiperone. In addition, atypical profile test compounds were also evaluated for the affinity to inhibit [^{3}H]-ketanserin binding to 5-HT2A serotonergic receptors in cortical membranes.

2.2.3 Anti-dementia

30 Synthetic compounds were tested on scopolamine induced dementia in passive avoidance test in mice. Significant activity was found in 6 compounds. The activity is being confirmed.

2.2.4 Anti-obesity

Twelve synthetic compounds were tested on scheduled fed rat at the dose of 20µM/kg, po. None were found active. One marine product CDR-347A001 was tested on scheduled fed rat at the dose of 250 mg/kg po, but showed no significant activity.

2.2.5 Anti-stress activity

Six compounds were screened for anti-stress effect in different stress models in rodents. Among them, one of these significantly attenuated the stress-induced perturbations in acute stress model in rats.

2.2.6 Studies on Ashvagandha

11 Samples were tested for CNS, memory and anti-depression activity. Two samples showed significant memory enhancing activity. The antioxidant effect of genomic extract of Ashvagandha was observed in the rotenone induced degrenulation model in rat and neuroprotective effective MCAO model only one extract offer significant protection.

2.2.7 Basic Studies in CNS

2.2.7.1 Pharmacological and biological correlates of different natures of stress

In the ongoing studies on stress research, evaluation of the role of corticosterone in various

stress-induced alterations in homeostais is under process. In these studies, we elucidated the peripheral markers dependent differentially on levels of corticosterone. Subjecting adrenalecto-mised animals to acute and chronic stress regimens, we observed that plasma glucose changes are dependent whereas alteration in creatine kinase level is independent of corticosterone. Further studies to elucidate the role of corticosterone, in changes in levels of monoamines at different regions of the brain, are under progress.

2.2.7.2 Role of insulin in learning and memory functions in rodents

(a) Effect of peripheral and icv insulin on central insulin receptor, neurotrans-mitters, AChE activity and oxidative stress

Effect of centrally (ICV) and peripherally (ip) administered insulin, was studied on central insulin receptor (IR) level (WB), neurotransmitters - NE, DA and 5-HT level by HPLC cholinergic activity – acetyl cholinesterase (AChE) activity, and biochemical parameters for oxidative stress - reduced glutathione and malondialdehyde, in rat brain areas - hypothalamus, hippocampus, cerebral cortex and cerebellum. Level of central IR and neurotransmitters were found unaltered by central and peripheral insulin administration. AChE activity was not significantly influenced by peripherally administered insulin whereas central insulin administration had shown significant decrease in AChE activity in Detergent Soluble fraction (G4 isoform) of brain regions except hypothalamus. Levels of reduced glutathione and malondialdehyde were also affected only by icv insulin. Thus, results indicate that cholinergic system and oxidative stress may be more susceptible to centrally administered insulin as compared to peripherally administered insulin.

(b) Study on central insulin receptor in Passive avoidance

Effect of anti dementia drug-donepezil (5 mg/kg,po), insulin (0.5 and 1 unit/kg, ip) and melatonin (10 and 20 mg/kg, po) on central insulin receptor (IR) and AChE activity was studied in scopolamine induced amnesia model in mice to find out the involvement of central IR in learning and memory tested by passive avoidance task. Food was allowed to animal after insulin administration to maintain euglycemic state. All the drugs attenuated scopolamine induced amnesia. In control trained mice central IR level remained unchanged as compared to non-trained animals. Level of insulin receptor was found significantly increased with melatonin in hypothalamus, hippocampus, and cerebral cortex while with donepezil only in cerebral cortex in scopolamine treated mice. Melatonin and donepezil did not affect IR in cerebellum. IR was not affected by insulin in any area. Insulin, melatonin and donepezil mainly in hippocampus region inhibited AChE activity. Thus, the study indicates the possibility of involvement of central IR along with increased cholinergic activity in hippocampus in anti-amnesic effect of melatonin and donepezil. Further studies on role of central IR in memory functions are under progress.

2.2.7.3 Basic studies on neuroinflammation

Tacrine, rivastigmine and donepezil were studied on neuro-inflammation induced by intraperitoneal administration of lipopolysaccharide (LPS) in mice. LPS significantly increased the level of IL-2 in all the brain areas while enhancement of AChE activity varied in brain areas. It was found that

administration of tacrine, rivastigmine and donepezil in mice significantly attenuated the LPS induced increased levels of IL-2 along with the significant reduction of AChE activity. This study indicate that cholinesterase inhibitor anti-dementia drugs are effective against LPS induced neuroinflammation that may be linked to enhanced cholinergic activity.

2.2.7.4 Effect of chronic unpredictable stress

Pro-inflammatory cytokines IL2 and IL6 level in mice was significantly increased during chronic unpredictable stress. *Panax quinquifolium* showed normalizing effect on the increased brain IL-2 and IL-6 levels due to chronic unpredictable stress.

2.2.7.5 Evaluation of role of central histaminergic system in anxiety disorder

Central histaminergic system is reported to mediate behavioural, hormonal and physiological homeostasis of living organisms. We evaluated the effect of activation of central histaminergic system in anxiety conditions using elevated plus maze test in mice and elucidated the role of different histaminergic receptors mediating such effects. Peripheral administration of L-histidine (LH) significantly decreased the exploration time in open arms and percentage of number of entries into open arms of elevated plus maze in a dose dependant manner, indicating anxiogenesis effect of activation of central histaminergic system. Further, such effects of central histamine were significantly attenuated by pretreatment with pyrilamine (H1 receptor antagonist) in a dose dependant manner. However, pretreatment with either zolantidine (H2 receptor antagonist) or thioperamide (H3 receptor antagonist) failed to attenuate the LH induced anxiogenesis. Our results indicate that anxiogenic effects of central histaminergic system appeared to be mediated prominently by activation of H1 receptors.

2.2.7.6 Study on activation of central histaminergic system in amphetamine induced hyperactivity model in mice

We evaluated the effect of L-histidine (LH), precursor of histamine, on amphetamine (AMP) induced elevation in horizontal activity and stereotypy of animals. Intraperitoneal administration of LH significantly attenuated the AMP induced hyperactivity in a dose dependant manner. Further, effects of LH are blocked by pretreatment with pyrilamine or thioperamide, H1 and H3 receptor antagonists respectively. In line with behavioral observations, LH significantly inhibited the AMP induced elevation in levels of monoamines in cortex and striatal regions of the brain. Neurochemical observations clearly indicated the prominent effect of LH on release of dopamine followed by serotonin in both the regions and lack of effect on levels of noradrenaline. In addition, neurochemical effects of LH are significantly blocked by pretreatment with pyrilamine or thioperamide as observed in behavioral studies. All these observations clearly indicated that central histaminergic system has negative regulatory effect on dopaminergic system activated by AMP, which is mediated by H1 and H3 receptors.

2.3 Other disorders

2.3.1 Anti-ulcer activity

Effect of gamma irradiated granular sample of an antiulcer agent was studied against cold

restraint induced ulcer (CRU) and alcohol induced ulcer model and found to be effective in both the models.

2.3.2 Development of anti-inflammatory agents

A total of 55 compounds, 3 plant extracts and 14 samples oh *Withenia somnifera* have been evaluated for anti-inflammatory activity in carraginin induced paw oedema model in rats. Seven compounds showed promising activity. Ibuprofen at 100 mg/kg (po) was used as standard drug and it showed 62% activity.

2.3.3 Development of anti-allergic/anti-asthmatic compounds

Twelve compounds were subjected to antihistaminic activity evaluation by Co PI assay. Two compounds showed significant histamine blocking activity comparable to reference drug cetrizine. Five plant fractions of plant code No. 4533 were tested for antiallergic/anti-asthmatic activity in rats, one plant fraction showed significant activity at the dose of 50 mg/kg (po) in comparison to standard drug disodium-chromoglycate at 50 mg/kg (ip).

2.3.4 Bio-evaluation of antidiabetic activity

A total of 51 synthetic compounds were screened for antihyperglycemic activity in sucrose loaded rat model and out of which 13 compounds showed antihyperglycemic activity at 100 mg/kg dose levels. All the compounds, except S-005-1089, also showed significant lowering in blood glucose profile of sucrose-challenged low dosed streptozotocin-induced diabetic rats at this dose level. ED_{50} of compound S-006-1084 is about 10.55 mg/kg in sucrose challenged streptozotocin-induced diabetic rats. The antidiabetic activity profile in db/db mice is being determined for further follow-up studies.

2.3.5 Effect of antidiabetic compounds on carbohydrate metabolism

The candidate antidiabetic compounds i.e. S-001-469, S-002-853 and S-002-857 were orally fed at 100 mg/kg dose level to the streptozotocin-induced diabetic for a period of 25 days and the activities of various regulatory enzymes of carbohydrate metabolism were measured in order to elucidate their mode of action. The treated animals showed declined activities of glucose-6-phosphatase, fructose-1, 6-bisphosphatase and phosphoenolpyruvate carboxykinase and increased activities of glucokinase, phosphofructokinase, pyruvate kinase and lactate dehydrogenase in liver, kidney and muscle tissues. The pyruvate kinase activity was found decreased in liver and muscle tissues of STZ-induced diabetic rats treated either with S-002-853, S-002-857 or S-001-469. The treated animals showed increased phosphofructokinase activity in liver and muscle tissues but had no effect on counterpart from renal tissue. Both S-002-853 and S-002-857 increased 2-^{3}H-deoxyglucose uptake in 3T3 L1 cells in a dose dependent manner and no cytotoxic effects against 3T3L1 and L-6 muscle cells were observed upto 10 µg/ml concentration.

2.3.6 Follow up studies for hypolipidemic activity

Activity was confirmed in CDR-150C003, and C004. However, fractions F005, F006, F007 and F008 were inactive. Among the fractions tested of CDR-134, D234 and D245 were active, but D246 was not active. Crude extract of CDR-333A001 was found to be active at 5 g/kg dose.

Three fractions of this marine product were however not found to be active in high fat diet fed hyperlipidemic hamster model.

2.3.7 Effect of CDRI compounds on action potential duration

The compound S-002-853 (racemic) caused dose dependent prolongation of cardiac action potential duration significantly. It caused 24% of increase in AP duration at the concentration of 6.4 μM. This result reflects this compound has tendency to induce arrhythmia.

2.3.8 Basic Studies: Role of ppARγ receptors in gastric ulcer healing

Peroxisone proliferators activated receptors-gamma (PPARγ) belongs to the family nuclear receptors and has been found to play a vital role in regulation of inflammation. We are studying the involvement of PPARγ in the control of healing of gastric ulcers. Our studies showed that pioglitazone, a PPARγ agonist, significantly healed the acetic acid induced gastric ulcers in a dose dependant manner by inhibiting the generation of pro-inflammatory cytokines like IL-1β and TNF- which are up-regulated in the course of ulceration. Western blot analysis and RT-PCR observations confirmed a significant decrease in the expression profile of PPARγ in course of ulceration which was been restored to normal levels by pioglitazone treatment, which signifies the involvement of PPARγ receptors in gastric ulcer healing. Molecular mechanisms involved in such effects mediated by PPARγ are under evaluation.

2.4 Safety pharmacological studies

Essential safety pharmacology studies of candidate drugs (CDR-134D123; 99/411; Lysostaphin cream and Lysostaphin gel) have been evaluated for their effect on cardiovascular, respiratory and CNS parameters in rats, rabbits and mice respectively as per Appendix III of Schedule Y gazette dated 20th January 2005. While final reports for a Dabur compound DRF-7295; CD R-267F018; CDR-134D123F194; 99-373 and 97-78 were submitted during this period.

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 is disabling and a cause of social stigma. Development of a macrofilaricide and/or female worm-sterilizing agent is todays 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 New Antifilarial Agents

3.2 Immunological Studies

3.3 Biochemical and Molecular Studies.

3.1 Development of antifilarial agents

3.1.1 Preparation and screening of synthetic compounds and natural products *in vitro* and *in vivo*

3.1.1.1 *In vitro* and *in vivo* antifilarial activity of CDRI plant extracts

Twenty-six new CDRI plant extracts were tested in mastomys against *B. malayi in vivo*. Two of them, 4665 and 4664, showed macrofilaricidal (50-60%) activity.

3.1.1.2 *In vitro* antifilarial activity of marine extracts against *B. malayi* adult worms

A total of 78 extracts received from various participating laboratories under DOD project were tested for *in vitro* antifilarial efficacy. Two extracts CDR-332A001 and AU2-357A001 showed activity at 31.25 µg/ml. Of the four fractions of CDR-332, one was found most effective showing LC_{100} of <15.6 µg/ml.

3.1.1.3 Network COR-0023 project

A total of 2583 samples were received under network project COR-0023. Of these, 2168 were screened against adult worms of *B. malayi in vitro*. However, none was picked up for *in vivo* evaluation. Combination of a plant extract (which has shown moderate adulticidal activity) with DEC did not enhance the adulticidal activity.

3.1.1.4 Follow-up studies

(a) Antifilarial activity of crude extract of *Piper betle* and its fractions against *B. malayi* in mastomys

PBL-ALC, the crude alcoholic extract of *Piper betle* of Bangla Mahoba variety received from NBRI, Lucknow, contained moderate

macrofilaricidal action (47.0%) against *B. malayi in vivo* at 100 mg/kg when given orally for 15 alternate days. Hexane and chloroform fractions when administered i.p. for 15 alternate days (spread over a period of 1 month) exerted between 31 and 38% macrofilaricidal action with 30-50% sterilization of surviving female worms. Chloroform fraction by oral route of administration at the same dose level given for 5 days was also equally effective. The fractions would now be tested using a longer treatment schedule.

(b) Confirmation of antifilarial activity of plant extract 4665 against *B. malayi* in mastomys

The crude extract of plant 4665 when administered orally at 1 gm/kg, for 5 consecutive days, did not exert significant macrofilaricidal activity. The extract would now be tested using a longer schedule of treatment.

(c) Antifilarial activity of a fraction of marine extract CDR-332F004 against *B. malayi* in mastomys

The F004 fraction of marine extract CDR-332A001 when administered orally at 250 mg/kg for 5 consecutive days exerted ~40% macrofilaricidal activity. The extract would now be tested using a different schedule of treatment.

(d) Antifilarial activity of albendazole formulation against *B. malayi* in mastomys

Micro emulsion formulation of albendazole (ALB-1) which was reported to show better female sterilizing potential over pure albendazole or its marketed tablet in *B. malayi-M. coucha* system was also found to exhibit some antifilarial activity in *B. malayi*-jird system.

Experiments related to establishment of efficacy of albendazole in combination with DEC suggest that it produced a significant suppression of microfilaraemia as compared to ALB-1 alone. However, ALB-1 and ALB-1+DEC produced identical female worm sterilization.

(e) Antifilarial activity of compounds received from VCRC, Pondichery

Two compounds received from VCRC, Pondichery were also evaluated *in vivo* against *B. malayi* and VCRC PF-19 revealed moderate macrofilaricidal action (45%) at 50 mg/kg, i.p.x 5 days while the other one VCRC PF-210 has been evaluated at a low dose of 1 mg/kg but was found inactive.

3.2 Immunological studies

3.2.1 Proteomic studies with filarial parasites: Effect of killing of *Wolbachia*

SDS-PAGE and western blotting of *Wolbachia* intact and bacteria depleted *B. malayi* adult parasite extract when reacted with WSP serum, 66, 39, 27 kD antigens were recognized in intact worm antigen but not in *Wolbachia* depleted (by long-term tetracycline treatment) worms. The *Wolbachia* intact and bacteria depleted adult *B. malayi* antigens were analysed by 2-D gel electrophoresis. *Wolbachia* depletion led to disappearance or under expression of several of the protein spots in both low as well as high molecular weight region while few spots showed over expression in 2D gels. These protein spots would be further characterized.

3.2.2 Effect of *Wolbachia* depletion on filarial pathological manifestations

Mastomys coucha and *Meriones unguiculatus* subcutaneously infected with *B. malayi* were histologically examined for inflammatory pathogenesis in different tissues harbored by the adult parasites (lungs, lymph nodes, heart and

testes) at two different time periods of infection (pre-patent and post-patent). All the tissues were paraffin embedded, serially microtome sectioned and haematoxylin / eosin stained. Large number of mononuclear phagocyte cells forming a granuloma-like structure were found accumulated around the hyalinising adult parasites in the lung tissues of pre-patent hosts. The cells mainly consisted of neutrophils, eosinophils, macrophages and lymphocytes. These reactions were more intense in *Meriones unguiculatus* than *Mastomys coucha*. On the other hand, none of the tissues taken out from the patent host demonstrated any kind of pathological reactions around the parasites which were live. Only mild lymphangieactasia was observed in the lymph nodes of *Mastomys coucha*.

As the antibiotic treatment schedule required for complete depletion of *Wolbachia* bacteria from adult *B. malayi* is 90/120 days attempts were made to induce inflammatory reactions around sepharose beads coated with filarial antigen. Thus, sepharose beads were coated with *Wolbachia* depleted and *Wolbachia* intact *B. malayi* adult worm soluble antigen (BmA) which were allowed to get imbolized in the lungs of *Meriones* infected with *B. malayi*. The lung tissue sections of the animals receiving the antigen coated beads revealed accumulation of large number of mononuclear phagocytic cells forming multilayer around *Wolbachia* intact BmA antigen coated beads. The inflammatory cellular accumulation was found to be significantly reduced around the *Wolbachia* depleted BmA antigen coated beads indicating the involvement of *Wolbachia* derived molecules in inflammatory pathogenesis associated with filariasis.

3.2.3 Effect of pretreatment with tetracycline on antifilarial efficacy of DEC

The antifilarial efficacy exerted by tetracycline requires a very long treatment schedule of about 90-120 days which not only is clinically impractical but also results into toxic effects of the antibiotic. Since tetracycline kills *Wolbachia* in filariids, the efficacy of standard filaricide DEC was evaluated in animals, which had prior, received oral antibiotic treatment (200 mg/kg x 40 days). DEC was administered midway at the dose of 100 mg/kg, orally for 5 consecutive days starting on day 40 (the last day of antibiotic treatment) in *Mastomys coucha*. The antibiotic treatment schedule for 40 days was unable to exert any significant antifilarial efficacy, whereas, DEC therapy in the pretreated host led to almost total clearance of circulating microfilariae along with >70% adulticidal and 83% embryo static efficacy, which was markedly higher than that of DEC alone. The study thus demonstrates that prior killing of *Wolbachia* has beneficial effect on the efficacy of standard antifilarial drugs.

3.2.4 Immunoprophylactic studies with recombinant myosin

The expressed myosin of *B. malayi* was purified to a single band. The recombinant myosin of *B. malayi* reacted with the antibodies present in the sera of mastomys infected with *B. malayi* and mastomys immunized with recombinant myosin but not with uninfected normal mastomys in blots. This protein also showed reactivity with human bancroftian serum whether collected from endemic normal patients, microfilaraemic carriers or symptomatic MF+ve or MF-ve individuals but not with the serum collected from subjects living in nonendemic area. Mastomys were immunized

with recombinant myosin and challenged with the infective larvae as reported earlier. Microfilaraemia was found to be suppressed in the animals immunized with rMyosin. Myosin led to >60% reduction in the establishment of adult *B. malayi* demonstrating significant protection against the challenged larvae. In addition, the established female parasites revealed marked sterilization.

The immunological characterization of recombinant myosin was carried out in Balb/c mice. Splenocytes from mice immunized with recombinant protein showed enhanced ConA induced as well as myosin induced lymphocyte proliferation, increased ROI content as detected by FACS using DCF-DA, as also the NO production from peritoneal macrophages of immunized animals. Both inflammatory cytokines e.g. TNF-α and IFN-γ levels were also found to be significantly higher in vaccinated animals as compared to the adjuvant or normal controls. The Th2 cytokines like IL-4 and Il-10 remained unaffected. The levels of IL-1beta and IL-6 were, however, not affected. The CD3+/CD4+ and CD3+/CD8+ cell counts were also found enhanced in the vaccinated group. However, the CD8+ increase was not significant while CD19+ counts were rather decreased.

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

Immunization of animals with inflammation-modulating fraction B6 (54.3-67.8kDa) of *B. malayi* prevented the adult worm survival by 77%. The fraction induced up regulation of NO, pro-inflammatory cytokines (TNF-α and IL-6) release, CMI and antibodies (IgM predominant) and downregulation of IL-10. Further, it induced 100% degranulation of mast cells. The results indicate that the fraction has pro-inflammatory molecules. Further characterization and identification of B6 fraction would be carried out by 2D and MALDI-TOF.

3.2.6 Cellular interaction between different life cycle stages of *B. malayi* and host lymphocytes when co-cultured *in vitro*

Lymphoproliferative response of sensitized splenocytes to live L3, mf and male as well as female adult *B. malayi* parasites differed greatly from that of the corresponding crude parasite soluble somatic antigen *in vitro*. Attempts would further be made to analyze the T and B cell responsiveness when co-cultured in the presence of various life stages of *B. malayi*.

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

The crude somatic extract from *S. cervi* adults was prepared, subjected to heat treatment and the supernatant obtained was used for isolation of antigen equivalent to filarial circulating antigen. The supernatant was fractionated on DEAE-Sephacel column followed by Sephacryl S-500 column chromatography. The purified fraction showed 1-2 protein bands on SDS-PAGE. The purified fraction also showed high reactivity with filarial patient sera. Efforts are in progress to produce polyclonal antibodies against purified fraction that will be used for molecular characterization of filarial circulating antigen.

3.2.8 Immunomodulatory activity of PBL ALC

The alcoholic extract of *Piper betle* demonstrated strong immunostimulatory property by significantly affecting various

humoral and cell mediated immune parameters of mice when given orally at 100, 30 and 10 mg/kg, for 14 consecutive days. Of the different fractions, n-hexane fraction showed remarkable increase in PFC, HA titre, DTH, T and B cell proliferation as also in the Nitric oxide release by macrophages. The chloroform fraction was less effective. The study demonstrates for the first time that *Piper betle* leaves possess strong immunostimulant properties, which appear to primarily reside in the hexane fraction.

3.2.9 Filariasis and leishmaniasis in experimental animals - Impact of co-infection

Hamsters were infected with various life stages (mf/L_3/adult worms) of *B. malayi* before or after amastigote inoculation or simultaneously with both the parasite species. The development and progression of *L. donovani* in animals was markedly inhibited by pre – and post-exposure to *B. malayi* L_3, but simultaneously infected animals showed almost identical parasite burden as compared to infection with leishmania alone. However, development of L_3 was not affected in coinfected animals. On the other hand, coinfection with mf or adult parasites with leishmania influenced the status of each other. Confirmation of these findings is in progress.

3.2.10 NMITLI project on pharmacological and genomic investigations on *Withania somnifera* - Evaluation of immunomodulatory activity

Various chemotypes of plant *Withania somnifera* were evaluated for immunomodulatory activity in Balb/c mice. Of the active chemotypes, two (NMITLI 25R and NMITLI 2R) were selected based on the wide spectrum of immunomodulatory properties stimulating both humoral and cellular arms of the host immune response. Former was most active at 100 mg/kg, p.o.x14 days while latter was effective at much lower dose of 10 mg/kg. The two chemotypes have been selected for confirmation and reconfirmation studies at various log doses.

3.3 Biochemical and molecular studies

3.3.1 Polyclonal antibodies against two isoforms of acetyl cholinesterase

The two isoforms of *S. cervi* AchE (pAchE1 and pAchE2) were purified using Con-A affinity column and preparative polyacrylamid gel. The reactivities of *S. cervi* AchE isoforms were tested with monoclonal antibodies produced against ScAchE. Both the isoforms showed significantly high ELISA reactivity with anti-AchE monoclonal antibody.

One monoclonal recognized both AchE isoforms in immunoblotting under non-reducing conditions. Polyclonal antibodies against these purified pAchE1 and pAchE2 isoforms were produced by immunizing the rabbits. The immune rabbit sera showed high antibody titre in ELISA and will be used for the characterization of filarial AchE isoforms.

3.3.2 Cloning of gene coding for filarial acetyl cholinesterase

In order to clone the filarial AchE gene, specific primers were designed based on conserved sequences of AchE from related parasites. PCR amplification was done using *B. malayi* and *W. bancrofti* cDNA library and *S. cervi* genomic DNA. Out of different set of

primers tried for the PCR amplification, different sizes of PCR products were obtained. *B. malayi* and W. *bancrofti* cDNA gave 0.8 kb PCR product and 2 PCR products (1, 0.6 kb) were observed with *S. cervi* genomic DNA. The PCR products were purified and cloned in pGEMT vector. The presence of inserts in different clones was verified by isolating the plasmid followed by restriction digestion. The sequencing of these gene inserts is underway.

3.3.3 Cloning and characterization of hexokinase from *B. malayi*

The hexokinase gene was amplified from EST of *B. malayi* using specific primers by PCR. The product was used for semi-nested PCR using *B. malayi* specific primers and 3′ adaptor primer. The 1400 bp product was cloned in TOPO-TA cloning vector and sequenced. A full length cDNA sequence was derived from the 3′ RACE and EST of *B. malayi*. Specific primers were designed to amplify DNA which produced a 1701 bp PCR product. The product was cloned in TOPO-TA cloning vector and sequenced. The BLAST analysis showed homology with *C. elegance* and *H. contortus* hexokinases. The cloned product was transformed in DH5α cells and screened through colony PCR and restriction enzyme analysis. A 1.7 kb DNA fragment was obtained which was cloned in pTriEx-4-Bm-Hk plasmid, transformed in BL21 (DE3) Rosetta cells and induced with 1mM IPTG. The expressed protein showed a band of 72 kDa on SDS-PAGE gel. The expression of recombinant protein was finally confirmed by western blotting using anti-HIS antibody. The protein was purified by affinity chromatography. The kinetic properties of the purified protein were studied.

3.3.4 Immunoscreening of L_3 cDNA library of *B. malayi*

Hyperimmune L_3 resistant serum was raised using Cobalt-60 irradiated *B. malayi* L_3 in Balb/c mice. Immunoscreening of the cDNA expression library of *B. malayi* L_3 with this resistant mouse serum led to identification of 10 immunoreactive dominant positive plaques, which were picked up. Five of these ten cDNA clones were purified by repeated screening and sequenced. The NCBI accession numbers taken for two of these clones are : i) DQ 464237 ($rBmL_3$) for 1.3 kb immunogenic protein and ii) DQ 327712 (ribosomal protein S23 mRNA 535 bp). Partial nucleotide sequencing of three other clones has also been done and clone MD3 was found to code for SXP *Brugia malayi* antigen (100% identity); clone MD8 coding for *C. elegans* Helicase super family C-terminal domain (71% identity) while clone MD9 coded for *Loa loa* 15kda repetitive antigen (100% identity). The remaining five clones are under purification.

4. Area : Leishmaniasis

Coordinator: Dr. (Ms.) 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 new antileishmanial agents

A total of 332 agents (CDRI synthetic compounds 141, plant and marine extracts 55, DOD samples 127 and extracts from CSIR co-ordinated project 9) were screened against *L. donovani* infection. Of the 141 synthetic compounds screened *in vitro* against promastigotes by luciferase assay, 90 compounds were found active at 10 µg/ml. Of the 127 DOD compounds, nine extracts were active at 50 µg/ml concentration.

Forty-one compounds were tested against amastigotes at 10 µg/ml concentration. Amongst them, 17 compounds were found active (80-100% inhibition in parasite multiplication). Rest of the compounds showed cytotoxicity at 5 µg/ml concentration. Lower concentrations are under trial. Two DOD extracts have shown activity at 10 µg/ml concentration and 8 extracts were found active at 50 µg/ml concentration.

Amongst the 17 compounds tried in hamster model, two compounds (S-006-72 and S-006-253) have shown 70-80% inhibition in parasite multiplication.

Out of 50 plant extracts, 4 extracts were found active (>80%) when screened *in vitro* against promastigotes and macrophage-amastigote system. Similarly, out of 5 marine products, 2 crude extracts and their fractions and /or pure compounds viz. CDR-332A001, CDR-332A002 and CDR-292K007 have shown promise in *in vitro* screens.

Amongst the 13 plant extracts and 3 marine products tested in hamster model at a dose of 500 mg/kg x 5, nine (six plant and three marine) crude extracts and their fractions/pure compounds have shown 70-80% efficacy. These are under detailed study for optimization of dose activity response.

4.2 Development of screening models

4.2.1 Stable Green Fluorescent Protein transfected *Leishmania* cell lines

Leishmania cell lines that strongly and stably express GFP without any drug pressure were constructed by integrating the GFP-containing construct downstream of promoter of 18S ribosomal RNA gene into the genome of *L. donovani* clinical isolates. Each of the drug sensitive and resistant isolate was integrated with GFP at the 18S ribosomal promoter locus of the parasites. These stable lines have shown high and consistent levels of GFP expression in the absence of selective drug pressure as observed by epifluorescence microscopy and flow cytometry. There has been no decrease in GFP expression in transfected parasites till day 60 post transfection. These stable integrants are being tried for screening of standard antileishmanial drugs and several plant extracts/marine products. Standardization of protocols for high throughput screening of large library of new chemical entities and natural products is underway. In an attempt to develop *in vivo* model for antileishmanial screening, syrian golden hamsters have been infected with these stable lines. The outcome of infection and stability of GFP expression are under investigation.

4.2.2 Development of 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. Suitability of these axenic amastigotes for *in vitro* screening of antileishmanials is under way.

4.3 Immunobiological studies

4.3.1 Identification of Th1 stimulatory proteins for immunoprophylactic potential

F2 fraction (68-97.4 kDa) and its immunostimulatory sub fractions (4) were characterized by 2D and 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. Vaccination studies with these four sub fractions have been initiated in naïve hamsters.

4.3.2 Proteophosphoglycan of *L. donovani*

PPG3 gene of 1.6 kb of *L.donovani* has been amplified using the primers of PPG 3 gene of *L.major*. This has been further cloned and sequenced. The expression of this fragment is underway.

4.4 Biochemical and molecular mechanisms of drug resistance

Resistance to antimonials has become a clinical threat in the treatment of visceral leishmaniasis. Drug efflux, known to be the primary mechanism of resistance in laboratory

mutants was however, not frequently found to be present in the clinical isolates used in our present study. In one of the resistant isolates, R5 gene (PG1) was earlier identified which was implicated in antimony resistance. Using antibody raised against (PG1) recombinant protein, confocal microscopy showed its localization on the parasite membrane indicating towards alteration of pellicular plasma membrane of the parasite as a mechanism of resistance. No efflux pump activity could be detected in the same isolate. Detection of increased MRP pump activity in another resistant isolate 2039 along with increased GCS expression in this isolate as compared to R5, indicated drug efflux to be the primary mechanism of resistance in 2039. Further, effect of some inhibitors was studied on rhodamine 123 and calcein AM uptake and efflux. No significant difference was observed between sensitive and resistant isolates in the efflux of both drugs. These findings indicate that resistance in the field is not the outcome of one mechanism but may be multifactorial.

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

4.5.1 Serine hydroxymethyl transferase

Serine hydroxymethyltransferase (SHMT) is a PLP dependent enzyme that catalyses the interconversion of serine to glycine with tetrahydrofolate serving as the one carbon acceptor. This enzyme is component of thymidylate cycle. The SHMT activity has been described in number of trypanosomatids but the enzyme has not been over expressed and purified. SHMT has been cloned, over expressed in homologous and heterologous system. The studies on biochemical, immune localization and biophysical characterization of recombinant protein have been completed.

Enzyme kinetic studies were carried with recombinant SHMT. Km and V_{max} of *Leishmania donovani* SHMT substrates were determined and found comparable to the SHMT from other sources. In order to understand the mechanism of ligand binding and the interaction between the substrates and lSHMT, a three-dimensional (3D) homology model of lSHMT was made based on the x-ray crystallographic structure of the human cytosolic SHMT (hSHMT) (PDB code 1BJ4). The overall stereo chemical quality of the lSHMT was assessed against the published hSHMT structure solved by x-ray crystallography. Starting with this model, a flexible substrate docking study is performed and comparison between the substrate binding to our model and that of crystallographic hSHMT revealed some key differences in substrate interaction that could be exploited for rational design of selective inhibitors against lSHMT.

4.5.2 Squalene synthase

The enzymes of sterol biosynthesis pathway are attractive targets for the specific treatment of leishmaniasis as the etiological agents for the disease require endogenous ergosterol and other alkylated sterols for growth and survival and are unable to use the abundant supply of cholesterol present in the mammalian host.

Squalene synthase (SQS, EC 2.5.1.21), a major enzyme in the sterol biosynthetic pathway, catalyses an unusual head to head reductive dimerization of two molecules of farnesyl-pyrophosphate (FPP) in a two-step reaction to form squalene. Farnesyl diphosphate (FPP) serves as a metabolic intermediate in the formation of sterols, dolichols, ubiquinones and farnesylated proteins.

Squalene synthase gene of *Leishmania donovani* was PCR amplified, amplicon was cloned, and confirmed for sequence homology (accession no. AM229310).

4.5.3 Triose phosphate isomerase

Triose Phosphate Isomerase (TIM) is a key enzyme of the glycolytic pathway that interconverts glyceraldehyde 3-phosphate to dihydroxyacetone phosphate. The TIM has been cloned and characterized in number of trypansomatids but the purification of recombinant enzyme has not been reported till date in *Leishmania* species. The gene that encodes for Triose Phosphate Isomerase from *Leishmania donovani* was cloned in pGEMT vector and sequenced (Accession number DQ649411). The sequence analysis shows 49.2%, 66.7 %, 88.10% identity with Human, *Trypansoma cruzi* and *Leishmania mexicana* respectively. A glutamic acid residue (168) is involved in the catalytic mechanism. The sequence around the active site residue is perfectly conserved in all known TIM's. Over-expression and purification of TIM for biochemical and biophysical characterization is underway.

4.5.4 Trypanothione reductase (LdTR)

Effect of guanidine hydrochloride (GdnHCl), SDS and urea was studied for leishmanial trypanothione reductase enzyme activity. GdnHCl has marked effect on the activity of LdTR than urea. Urea at 5M concentration caused 100% loss of enzyme activity while only 100mM GdnHCl was required for the same effect. This may be due to strong denaturant property of GdnHCl. In the process of de-naturation, the loss in enzyme activity was observed before any detectable change in secondary structure of protein.

4.5.5 Dipeptidyl carboxypeptidase (DCP)

This enzyme has been over expressed in *E. coli*. Recombinant DCP is highly unstable. In order to enhance the stability, the effect of glycerol was investigated at 40^0C. Glycerol, as stabilizer, enhanced the stability of recombinant leishmanial dipeptidyl carboxypeptidase (DCP) up to 7 days at 4^oC. Three-dimensional (3D) model of LdDCP was constructed by means of comparative modeling using *E. coli* DCP as a template. The two proteins have a similar architecture with 25 alpha helix.

4.5.6 Glycosylphosphatidylinositol transferase-1 (GPI-1)

Complete open reading frame of leishmanial GPI-1 was cloned. Partial sequencing of 5′ and 3′ end confirmed the presence of right clone.

4.5.7 Structure based modeling to identify inhibitors targeting PTR1

Biochemical properties and structure-modeling studies of *Leishmania donovani* pteridine reductase 1 were performed to reveal the active site features important for ligand binding and to guide inhibitor designing. This is an NADPH dependent short-chain reductase (SDR) responsible for the salvage of pterins in the protozoan parasite *Leishmania*. It represents a target for the development of improved therapies for infections caused by the parasite. This enzyme has a role in pteridine metabolism as well as in antifolate resistance. PTR1 was cloned from *L. donovani* field isolate in pET28a$^+$ expression vector and expressed as recombinant protein in *E. coli* host. Further, its biochemical properties have been determined and molecular modeling and docking studies were carried out with the substrate (biopterin) and known antifolate inhibitor methotrexate (MTX). The

recombinant enzyme displayed optimal pteridine reductase activity at pH 4.8 and (Ki= 1.246 µM) was obtained for MTX. The drug sensitivity assay using GFP transfected promastigotes shows that level of MTX resistance is higher in the *L. donovani* field isolate used in this study. This may be due to higher activity of PTR1 in the field isolate. The molecular modeling and docking studies with MTX, reveals that the pteridine ring of MTX binds in the same orientation as observed for the biopterin. However pABA group and glutamyl tail of MTX are relatively flexible and not contribute that much to enzyme inhibition. We hypothesized that smaller entity like pterin moiety may bind effectively to the active site and will be used for the development of pharmacophores. This information, together with model-building experiments based on biopterin and methotrexate-containing structures, has enabled to deduce a plausible geometry for binding of pteridine ring and explain some degree of transition state stabilization.

Structure based drug design on our homology model based on recombinant pteridine reductase enzyme of *Leishmania donovani* has enabled identification of inhibitors some of which have been tested *in vitro* and found to be inhibiting the enzyme in a target based assay.

4.5.8 Actin network in *Leishmania* parasites

Actin network is indispensable for the survival of any eukaryotic organism. *Leishmania* has long been assumed to have no role and presence of actin in it. Our recent report for the presence of abundant actin in *Leishmania* has uncovered the facts regarding an essential element in these parasites. This study includes elaborate analyses of actin network and its role in *Leishmania* parasites. Many regulatory/ actin binding proteins that alter network composition, stability and functional parameters for the cell have been planned to analyze in order to explore function of actin network in *Leishmania* parasites. *Leishmania* actin was over-expressed in insect cell expression system using baculoviral vector and demonstrated partial purification of the same. Further standardization experiments are in progress.

4.5.9 Biochemical characterization of *Leishmania* Actin Depolymerising Factor (ADF)

Leishmania ADF/cofilin depolymerizes rabbit muscle actin (α-actin) as well as β-actin in mammalian cell lines. It is independent of alteration in pH from 6.0-8.5. It was demonstrated that Leish-ADF/cofilin binds *Leishmania* actin in *Leishmania* cell lysates. Leish-ADF/cofilin preferentially binds with ADP-Actin and forms stable 1:1 complex with rabbit muscle G-actin. Biochemical analyses of actin depolymerizing protein (ADF / cofilin) from *Leishmania* shows that it alters the actin dynamics *in-vitro* as well as *in-vivo*. *Leish*-ADF overexpression has further shown to reduce invasion process of promastigotes by perhaps modulation in the compassion of membrane rafts. These transfectants have also shown 3-4 times increase in chemotaxis. Further analyses are underway.

4.5.10 Analysis of *Leishmania* Actin Related Protein (ARP)

One of the actin-related proteins was demonstrated to localize mainly in nucleus, especially with euchromatin and also shown this interaction biochemically by ChIP assay.

4.5.11 Creation of coronin knockout

After the analysis of coronin actin interaction in filamentous structures of actin, various deletion mutants have been created to characterize different functional motifs and their roles in actin filament interaction. Coronin gene is being attempted to be knocked off from *L.donovani*. For the same, various DNA constructs have been designed, cloning and selection of coro$^{-/+}$ and coro$^{-/-}$ are under progress. For biochemical analyses of *Leishmania* coronin with actin, both the actin and coronin has been cloned in baculovirus-insect cell expression system. Both of these proteins have been expressed for preliminary expression analysis and are now in the process of pure recombinant virus selection for large-scale purification.

4.5.12 Identification of new drug targets using microarray technology

Use of microarray technology enabled identification of important biochemical pathways for use as drug targets. One target viz. long chain fatty acyl Co-A ligase gene has been sequenced. Detection of the endogenous copy of this gene by southern blotting and transcript by northern blotting is underway.

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; characterization of enzyme markers for drug resistant parasites; and validation of novel parasite-specific drug targets as a result of an improved understanding of the parasite biology.

5.1 Chemotherapy of malaria

5.1.1 Synthesis and screening

Novel synthetic moieties comprising 592 compounds representing several prototypes viz. peroxides, β-carbolines, amides, substituted quinolines, substituted triazines, substituted pyrimidines, indoles, chalcones, thiazolidinones, lupeole derivatives and urea derivatives were synthesized during the year for evaluation against *in vitro* or *in vivo* experimental malaria models. In addition, 130 extracts/ fractions from natural sources were prepared and evaluated for antimalarial activity.

5.1.1.1 Screening against *P. falciparum in vitro*

A total of 460 new synthetic compounds were screened against *Plasmodium falciparum* (strain NF 54 / 3D7) *in vitro* at various concentrations ranging between 100 ng/ml to 50 µg/ml. The screening protocol employed incubation of ring stage parasites with designated concentrations of the test agent for 36-40 hours under defined environment *in vitro.* The moieties exhibiting total parasite maturation inhibition (MIC) at <2 µg/ml were identified for evaluation against *in vivo* models. In addition concentration response profile for active molecules was determined employing hypoxanthine uptake assay. Screening of

several urea derivative compounds yielded novel 6-ureido-quinolines with MIC in the range of 0.25 to 1 µg/ml. Several new compounds representing quinoline-triazines, acridine-triazines, tetrahydro-pyrimidine and amide derivatives have also been identified. SAR studies with thiazolidinione and guanidine analogues have also resulted in selection of a few novel analogues inhibiting parasite maturation at below 1 µg/ml concentration. Evaluation of 110 samples representing marine fauna against *in vitro* model did not yield any promising lead. In addition, nearly 2500 samples of natural origin were evaluated under a CSIR coordinated network program and 5 plant extracts showing schizont maturation inhibition at 10 µg/ml concentration were identified for follow up.

5.1.1.2 Screening against *P. yoelii* - (N-67) Swiss mice model

Based on leads from *in vitro P. falciparum* screening results, a total of 41 synthetic compounds representing five different prototypes were evaluated against chloroquine resistant *P. yoelii* (strain N-67) Swiss mice model. Though none of these agents provided total clearance of parasites, a few compounds exhibiting above 70% parasite clearance after 4 day regimen were selected for further optimization. None of the 12 plant extracts evaluated against the same model showed any promising activity.

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

Lead optimization studies with synthetic peroxide generating derivatives were continued and 128 new compounds were screened at 96 mg/kgx4 day, both p.o. and i.m. routes, against multi-drug resistant model *P. yoelii* in Swiss mice. Several of the active compounds were also evaluated at lower doses. Four new orally active saturated trioxanes showing curative efficacy in a 24 mg/kg x 4 day regimen were identified as the promising lead for follow up studies.

5.1.2 Follow up studies with compound 99-411

Synthetic endoperoxide compound 99-411 had been recorded earlier to exhibit curative activity at 24 mg/kg dose in 4 days 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 regimens have established curative response with 48 mg/kg in two doses and 96 mg/kg in single dose against the rodent model. Initial studies in two monkeys have also demonstrated curative response with 20 mg/kg x 3 days against *P. cynomolgi*. Revalidation studies are in progress.

5.1.3 Combination chemotherapy

Drug combinations studies have been conducted against *Plasmodium yoelii*- Swiss mice model employing combinations of identified endoperoxides 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. Studies are underway to optimize a suitable drug combination.

5.1.4 Arteether resistant rodent malaria model

A strain of rodent malaria parasite *P. vinckei* showing experimentally induced (>12 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 has been made, since generation of carbon centered free radicals is believed to be involved in antimalarial action of this class of compounds. Our studies have shown a marked increase in the levels of reduced glutathione in parasite preparations from resistant strain, which presumably would counteract the formation of alkoxy radicals from arteether thereby decreasing its potency against resistant parasites. A 3.5 fold increase in catalase and a 2 fold increase in glutathione reductase and G-6-PDH activities has also been recorded. We have observed no significant alterations in the activity of glutathione S transferase in resistant parasites. In addition, the SDS-PAGE analysis of parasite proteins from the two preparations has shown presence of additional 37 and 79 kDa protein bands in preparations from the resistant parasites while 25 kDa and 42kDa protein bands localized in sensitive parasites were not observed in resistant parasites. Immunochemical analysis of these proteins is proposed to be undertaken.

5.2 Immunology of malaria

5.2.1 Monoclonal antibodies against *P. vivax* and *P. cynomolgi* B merozoite surface protein-1

The merozoite surface protein-1 (MSP1) of malaria parasites has been shown to be protective in a wide range of host-parasite systems. In our previous study, we have evaluated the *P. cynomolgi* rhesus monkey model for testing the protective potential of *P. vivax* MSP1-42 kDa antigen and monkeys immunized with vivax and cynomolgi MSP1-42 kD antigens showed significant reduction in parasite burden. Earlier we have produced monoclonal antibodies (Moab) against the conformational epitopes of *P. cynomolgi and P. vivax* MSP1 antigen. Total of twenty-nine monoclonal antibodies, produced earlier against *P. vivax* and *P. cynomolgi* MSP-1 antigen, were characterized for their epitope specificity. The monoclonals were divided into six categories on the basis of their reactivities with *P. vivax* and *P. cynomolgi* conformational and linear epitopes of MSP-1 antigens. Out of 11 monoclonals specific to *P. vivax* MSP1, 3 monoclonals were against the conformational epitope and 8 against the linear epitopes. Three monoclonals (two against conformational and one against linear epitope) were specific to *P. cynomolgi* MSP-1 antigen. Out of 15 monoclonals common between these two parasites (*P. vivax* and *P. cynomolgi*), 9 monoclonals were against the conformational and six against linear epitope. The epitope mapping revealed a total of 12 epitopes (7 conformational and 5 were linear) on *P. vivax* and *P. cynomolgi* MSP-1 antigen. Out of the 7 conformational epitopes, 1 epitope was specific to *P. vivax*, 1 specific to *P. cynomolgi* and 5 epitopes were common between these two parasites. Among the 5 linear epitopes, 2 epitopes were specific to *P. vivax*, 1 specific to *P. cynomolgi* and 2 epitopes were common between these two parasites.

5.2.2 Studies on DNA vaccine encoding circumsporozoite protein and merozoite surface protein-1 of *P. vivax* and *P. cynomolgi* B

Genomic DNA was isolated from *P. cynomolgi* B parasites and PCR amplification of CSP and MSP1 (42 and 19kDa) gene was done using specific primers. CSP specific primers gave a PCR fragment of 1.3 kb and MSP1 primers gave 1.2 kb and 0.4 kb fragments with *P. cynomolgi B* DNA. PCR products were run on

preparative gel and inserts were purified using gel extraction kit from Sigma and PCR products from *P. cynomolgi* B CSP, MSP1 (42 and 19) were cloned in pGM-T Easy vector. Plasmids digested with EcoR1 were run on agarose gel electrophoresis to identify the insert. The sequencing of these inserts is in progress.

5.3 Biochemistry of malaria

5.3.1 Molecular characterization of a putative choline kinase from the human malaria parasite *P. falciparum*

With a view to identify novel enzyme targets for antimalarial drug development, studies continued towards characterization of choline kinase enzyme from the human malaria parasite *P. falciparum*. Generation of phosphocholine by choline kinase is important for phosphatidylcholine biosynthesis via Kennedy pathway. Choline kinase is the first enzyme in Kennedy pathway (CDP-choline pathway) for the biosynthesis of most essential phospholipid phosphatidylcholine in *P. falciparum*. In addition, choline kinase also plays a pivotal role in trapping essential polar head group choline inside the malaria parasite. Inhibition of choline kinase is postulated to inhibit parasite membrane biosynthesis during the growth of intra-erythrocytic parasite stages and hence may serve as a target for antimalarial chemotherapy. Recently, *P. falciparum* choline kinase (PfCK) has been cloned, over-expressed and purified. But the function of this enzyme in parasite growth and survival has not been evaluated owing to lack of suitable inhibitor. Purified recombinant PfCK enabled us to identify an inhibitor of PfCK, hexadecyltrimethylammonium bromide (HDTAB), which has very close structural resemblance to hexadecylphosphocholine (miltefosin), the well known anti-proliferative and antileishmanial drug. HDTAB dose dependently inhibited PfCK and offered very potent antimalarial activity *in vitro* against *P. falciparum*. Moreover, HDTAB exhibited moderate antimalarial activity *in vivo* against a strain of rodent malaria parasite *P. yoelii* (N-67 strain). During *in vitro* studies, we observed that parasites at trophozoite and schizont stages were found particularly sensitive to HDTAB. The stage specific antimalarial effect of HDTAB correlated well with the expression pattern of PfCK in *P. falciparum*, which was observed by RT-PCR and immunofluorescence microscopy. Further, antimalarial activity of HDTAB paralleled with the decrease in phosphatidylcholine content, which was found to correlate with the decreased phoshocholine generation. These results suggest that inhibition of choline kinase by HDTAB led to decreased phosphocholine, which in turn causes decrease in phosphatidylcholine biosynthesis resulting in death of the parasite. Since choline kinase plays a vital role for growth and multiplication of *P. falciparum* during intra-erythrocytic stages, this well characterized PfCK would be exploited for developing target specific assay model for screening of new choline kinase inhibitors as potential antimalarial.

5.3.2 Cloning and expression of transketolase of *Plasmodium falciparum*

Pentose phosphate pathway has a significant role in antioxidant defense and nucleic acid synthesis. Transketolase is an important key enzyme of pentose pathway regulating the synthesis of NADPH/ATP and ribose-5-phosphate and has chemotherapeutic potential. Specific primers were designed from the ORF sequence of the transketolase gene. These primers were used to amplify transketolase gene from genomic DNA of *P. falciparum*. The size of PCR product as determined on 1% agarose gel was found to be 1900 bp. The

sequence of the product showed homology with putative transketolase gene. The gene was cloned in TOPO-T7/NY cloning and expression vector and transformed in DH5 cells. TOPO-17Tk construct was transformed in B1-21 (DE3) Rosetta cells for expression of protein.

Expression of recombinant protein was checked at various concentrations. It was found to be maximally induced at 1mM IPG concentration at 18°C for 20 hrs. Expression of protein was confirmed by western blotting using anti-His antibodies. The transketolase was purified by affinity chromatography and ammonium sulfate fractionation. The molecular mass of the expressed protein was found to be 70 kDa. The native molecular mass of expressed protein was 418 kDa indicating the hexameric nature of the protein. Further studies to characterize the protein are in progress.

5.3.3 Thioredoxin reductase from *P. yoelii*

The thioredoxin system consists of NADPH dependent disulphide oxidoreductase TrxR and small protein thioredoxin. This system is responsible for several reductive reactions within the cell and thioredoxin is regarded as the general redox messenger that interacts with variety of proteins. Thioredoxin possesses a typical Gly Pro Cys active size motif. In the oxidized state, cystine residues form a disulphide, which is reduced by TrxR.Thioredoxin system has many functions in the cell. Thioredoxin reductase from isolated *P. yoelii* parasites has been purified by ammonium sulphate fractionation and kinetic properties of the purified enzyme are being studied.

5.4 Molecular biology of malaria

A plastid-like organelle in *P. falciparum*, the apicoplast, has been the focus of study. Characterization of the replication machinery of apicoplast DNA has been carried out in terms of *ori* identification and characterization of DNA-protein interactions at replication origins. Nuclear-encoded gyrase subunits that are imported into the apicoplast have been partially characterised and their sensitivity to drugs that inhibit prokaryotic gyrases has been assessed. Another nuclear-encoded protein that interacts with apicoplast DNA *ori* has been identified. In continuation of our work on apicoplast translation, elongation factor Ts has been expressed in *E.coli* and interaction of plastid EF-Tu and the imported EF-Ts molecules is being investigated.

Studies have also been initiated on the transcription machinery operative within the apicoplast with the aim to understand the mechanism of transcriptional regulation. The organelle is likely to utilise α_2, β, β′-DNA dependent RNA polymerase that is homologous to that of cyanobacteria and eubacteria and recombinant expression of these subunits is underway.

Analysis of human genetic factors that may contribute to the severity of *P. falciparum* infection in the Indian population has been undertaken. Genotype data for 4 genes correlated with malaria susceptibility has been generated for 56 sub-populations of India in the first phase of analysis while SNP typing for 9 other genes is underway. Our results have revealed extensive sub-population-specific variations in allele frequency of several SNPs. *P. falciparum* malaria patient samples, collected from endemic and non-endemic regions of India, are being analysed for SNP association with disease severity as well as cytokine profiles.

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 antituberculosis, antifungal and antibacterial 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 *tol*C gene of *V. cholerae* was cloned. The ORF encoding TolC protein plays an important role in regulating tolerance to osmolarity in small intestine. The gene has been overexpressed in *E. coli* using T7 expression vector. A knockout of *tol*C will be created in the current year to investigate its role in pathogenesis.

6.2 Tuberculosis

6.2.1 Evaluation of synthetic compounds for *in vitro* activity against *M. tuberculosis* by radiometric BACTEC technique

Synthetic compounds, prepared at the Institute, were screened against *M. tuberculosis* $H_{37}R_v$. One of the compounds was found active against *M. tuberculosis* $H_{37}R_v$ (<6.25 µg/ ml) was also active in the *in vivo* murine *fortuitum* model. The compound is thus active against both tubercular and NTM infections and provides an active lead.

6.2.2 Elucidation of the localization and function of Rv3878 of *Mycobacterium tuberculosis*

The ORF Rv3878 originally selected from *M. tuberculosis* expression library using *in vivo* induced antigen technology, was overexpressed in *E. coli* and the protein encoded by Rv3878 was purified. CD spectroscopy revealed that it is a molten globule. The protein is synthesized in cytoplasm and localized at one or both poles of the cell. It is found in almost all the species of mycobacteria. It is an outer membrane associated protein and appears colocalized with genomic DNA. BCG overproducing Rv3878 displays change in cell and colony morphology and enhanced hydrophobicity. It appears that it might be involved in aggregation of cells and biofilm formation.

6.2.3 Identification of proteins differentially expressed in viable non-replicating persisting *Mycobacteria*

Having standardized *in vitro* hypoxia model of persistence, the proteome of BCG harvested from persistent state was compared with that of actively dividing wild type cells by two dimensional gel electrophoresis, mass spectrometry, MALDI-TOFF- MS. At least 35 proteins were picked up and their identity is being finalized.

6.2.4 Generation of murine infection model for latency

A murine infection model was developed which can maintain a persistent non-replicating population of pathogenic mycobacteria *M. fortuitum* in latent state. The dexamathasone treatment resulted in immunocompromised mice causing reactivation of latent bacilli as evident from rise in CFU in kidney, reappearance of disease symptoms, rise in metabolism and change in drug susceptibility profile. The model has been used to study pathogenesis, identify virulence factors, isolate mutants defective in persistence and can be reliably used in screening of drugs active against replicating and nonpersistent *fortuitum* and other NTM. An attenuated mutant, defective in virulence and persistence, was generated by transposon mutagenesis and *in vivo* screening in above mice model. The mutant produced very mild and delayed symptoms upon infection in mice. The gene disrupted by transposon has been identified by nucleotide sequencing and has a homologue in *M. tuberculosis* with 100% identity.

6.2.5 Cloning, expression and role of rapid suscitation factor (Rpf) genes in resuscitation of dormancy in *Mycobacteria*

In vitro extended stationary phase culture of *M. bovis* BCG representing dormant/ latent state of bacilli was optimized to generate viable but non-culturable state (VBNC). The cells could be resuscitated by addition of Rpf protein from *Micrococcus luteus* and *M. tuberculosis* (cloned recombinant protein). The protein expression profiling during the dormant and resuscitated phase is being attempted by proteome analysis to identify differentially regulated proteins during resuscitation phase.

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

A recombinant *M. aurum* strain has been created which shows the increased expression of lacZ following the administration of FAS-II pathway inhibiting drugs in the microbe. Further studies towards the evaluation of the screen system and its exclusivity for the given mechanism are in progress.

The alternative Sigma Factor F orthologs from different mycobacterial species have been cloned for expression analysis.

6.2.7 Biology of interaction between human macrophages and *Mycobacterium tuberculosis*

The exposure of the donors (10 healthy volunteers from TB endemic area) to *M. tuberculosis* was confirmed by elevated serum antibody levels and *in vitro* lymphocyte proliferation *M. tuberculosis* antigens. The donor

group fell into two categories - low and high resisters of their macrophages to kill phagocytosed *M. tuberculosis*. Opsonized *M. tuberculosis* with complement deficient (heat inactivated) serum prior to *in vitro* infection of macrophages led to lower CFU counts compared to unopsonized bacilli in both donors. TNF alpha and IL12 levels in the culture supernatants of infected macrophages were significantly raised in high resisters as compared to low resisters.

6.2.8 Studies on interaction of mycobacterial Eis and hspX with macrophages

Eis (Enhanced Intracellular Survival), Rv2416c, of *Mycobacterium tuberculosis* $H_{37}R_v$ is reported to enhance intracellular survival of *M. smegmatis* within macrophages. The biophysical and biochemical characterization of this protein were done. The results suggest that Eis play a role in modulation of immune response. Stimulation of PBMCs with Eis recombinant protein of *M. tuberculosis* inhibited ConA mediated T-cell proliferation *in vitro*. Treatment of PBMCs with Eis inhibits ERK1/2, JAK pathway and subsequent production of TNF-α and IL-4. Increased production of IFN-γ and IL-10 indicated that immunity in response to Eis treatment was skewed away from a protective TH1 response and Eis disturbed the cross regulation of T-cells.

Exported repetitive protein (Erp, Rv 3910) is reported to enhance the virulence of *M. tuberculosis* in macrophages. How does this protein achieve this enhanced virulence is not known. It is tempting to speculate that Erp might be interacting with the host proteins in macrophages. Therefore, Yeast Two-Hybrid method was employed to explore the interacting partners of Erp in host. Few interacting partners have been identified and the analysis of data is under study.

6.2.9 Direct and indirect mechanisms of protein kinase C phosphorylation by *Mycobacteria*

Expression of different isoforms of PKCs during direct interaction of mcrophage with pathogenic and non-pathogenic mycobacteria has been analyzed. Human macrophage (THP-1) cells were incubated with *Mycobacterium bovis* BCG, *M. tuberculosis* H37Ra, *M. tuberculosis* H37Rv and *M. smegmatis*. The results showed that phosphorylation of PKC α and β was unaltered, while un-phosphorylated proteins were deactivated by H37Rv treatment. PKC δ, μ and θ were phosphorylated by both types of mycobacteria. No change was observed either in expression or in phosphorylation of PKC ζ/λ proteins. To see the modulation of PKCs by indirect mechanism, *M. tuberculosis* immunized serum was used to treat mouse macrophages (J774A.1). PKC α was activated while there was a little increase in phosphorylated protein in serum treated cells. PKC ξ were increased in serum treated cells while phosphorylation was unaltered. There was no apparent change in phosphorylated or un-phosphorylated proteins of PKC δ, μ, θ The data strongly suggest that novel (calcium independent) PKC isoforms are phosphorylated during the invasive process. Moreover, mycobacteria induce phosphorylation by direct interaction rather using cytokines as mediators.

6.3 Fungal infection

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

A total of 537 (synthetic 226, marine 258 and plant 53) compounds/extracts were evaluated for *in vitro* antifungal and

antibacterial activity. Six synthetic compounds were found to be active against bacteria and fungi tested (MIC 1.56 - 12.5 µg/ml) whereas one marine extract NIT-118A001 exhibited mild antifungal activity.

Marine extract NIT-130A001 was evaluated *in vivo* against *C. albicans* (iv) infection in mice. The extract (100 mg/kg p.o. x 7 days) could reduce 43% CFU load in kidney tissue of infected mice compared to standard drug fluconazole (50 mg/kg p.o. x 7 days) where 93.4% reduction in CFU was observed.

6.3.2 Synergy of synthetic peptide with known antifungals

There has been a marked expansion in the knowledge of new antifungal peptides. A novel dodecapeptide H-Arg-Trp-Trp-Arg-D-Trp-DPhe-Ile-D-Phe-His-Trp-Arg-Trp-NH2 derived from previously described nonapeptide and synthesized by combinatorial approach was studied in combination with antifungals such as amphotericin B, flucytosine and fluconazole by checkerboard and time kill assay to obtain their dynamic pictures with respect to time. The best synergistic activity was observed with a combination of peptide and fluconazole followed by flucytosine.

6.3.3 Molecular diagnosis of fungal infections

Diagnosis of mycotic keratitis from corneal scrapings was attempted by PCR amplification using fungal specific primers of large subunit region. The amplified products were analyzed by single stranded conformation polymorphism (SSCP) for species identification. The DNA samples from corneal scrapings of 7 out of 12 patients were successfully amplified using fungal specific primer pair LROR and LR7 and their similarity dissimilarity were established by Jaccard's coefficient. The causal fungi were identified as *Aspergillus flavus, Alternaria tenussima, Fusarium lichenicola, F. solani and Candida parapsilosis.*

6.3.4 Monoclonal antibodies

6.3.4.1 *Aspergillus fumigatus*

Three monoclonal antibodies (designated as MAb-7, MAb-B, and MAb-C) were identified which exhibited a potent inhibitory activity against *A. fumigatus* and caused a significant reduction in the number of CFU compared to controls (without any MAb) and their binding with mycelium and swollen conidia could be demonstrated by immuno-flourescence. Thirteen immunodominant proteins including those against which, these MAbs were produced were identified by using MALDI-TOF-MS.

6.3.4.2 *Candida albicans*

Based on the nucleotide sequence of light chain of monoclonal antibody NE5, amino acid chain and CDRs of antibody was predicted. Ten dodeca peptides were synthesized based on the CDR sequence and their flanking regions. However, none of the ten peptides showed any significant binding with antigen.

6.4 Viral infections

Fifty-five marine extracts were screened for activity against JE virus *in vitro* using vero cells. Five extracts showed inhibition (50-75%) at concentrations ranging from 31.2 to 62.5 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 Drugs from Medicinal Plants

7.2 Modification of Natural Products

7.3 General Screening of Terrestrial Plants and Marine Flora/Fauna for Antihyperglycemic /Antidyslipidemic Activities.

7.1 Drugs from medicinal plants

7.1.1 Antihyperglycemic/ antidyslipidemic activity

7.1.1.1 Plant 4554 (Antihyperglycemic)

Ethanolic extract (C002) and aqueous extract (C003) were evaluated in STZ-S model at 250 mg/kg p.o. Aqueous extract (C003) showed significant activity. Repeat extract has been prepared from 9.0 kg plant material for further studies.

7.1.1.2 Plant 3247 (Antihyperglycemic)

Fifteen new derivatives of active compound K009 have been prepared. Out of these, 4 have shown better activity than parent compound K009.

7.1.1.3 Plant 4674 (Antihyperglycemic)

Extract (A001) has been submitted for antidiabetic activity testing. One novel compound and a rare stigmasterol glycoside derivative have been isolated.

7.1.1.4 Plant 4655 (Antidyslipidemic/ anti-hyperglycemic)

Extract (A001) and its four fractions (F002 to F005) have been evaluated for antidyslipidemic activity. The activity is localized in hexane fraction (F002). Three diterpenes (K004, K006 and K008) and three alkaloids (K016, K017 and K020) have been isolated so far. Ethanolic extract (A001) has also shown antihyperglycemic activity in SLM model. Compound K163 has shown anticancer activity also.

7.1.1.5 Plant 4574 (Antidyslipidemic)

Ethanolic extract (C003) and three fractions (F004 to F006) were evaluated for antidyslipidemic activity. From the active chloroform fraction (F004), three compounds (K017-K019) were isolated. K017 and K019 showed antidyslipidemic activity. Five derivatives of K017 and K019 showed antioxidant activity.

7.1.1.6 CDR-267 (Antihyperglycaemic)

Extraction and fractionation from repeat collection (15 kg) was carried out. Six pure

compounds were isolated from fraction (F018). Three compounds (K029, K030 and K031) have shown antihyperglycemic activity in STZ-S model at 100 mg/kg p.o. dose.

7.1.2 Antistress activity

7.1.2.1 Plant 38 (Antiulcer)

Antiulcerogenic activity of ethanolic extract was studied against cold restraint, asprin, alcohol, pyloric ligation induced gastric ulcer models in rats and histamine induced duodenal ulcer in guinea pig and ulcer healing activity in acetic acid induced chronic ulcer model. We found that ethanolic extract decreased the incidence of ulcer and also enhanced the healing of ulcers. Therefore, it possesses potent antiulcerogenic as well as healing properties. 12 Compounds have been isolated from n-BuOH active fraction and 1 from chloroform fraction. Pure compounds K099, K114, K116, K117 and K171 were found to be effective in reverting the alteration induced in acute and chronic unpredictable stress model. Four new compounds K118, K119, K161 and K164 were isolated and their biological activity testing is in progress.

7.1.2.2 Plant 2659 (Antioxidant)

Evaluation of anti-stress and anti-oxidant activity of 2659 in plasma and brain regions of rats subjected to chronic unpredictable stress in rats. Ethanolic extract (200 mg/kg, p.o.) has normalized the stress-induced alterations, reduced lipid peroxidation and changes in antioxidant enzymes in plasma and different areas of brain. 11 compounds have been isolated from n-butanol fraction. The plant has also shown promising memory enhancing activity in Morris Water Maze Test model. Pure compounds K014, K015 and K019 were found to be effective in reverting the alteration induced in acute and chronic unpredictable stress model. Four new compounds K037, K044, K080 and K092 were isolated and activity testing is in progress.

7.1.3 Antiparasitic activity

7.1.3.1 Plant 4601(Antileishmanial)

Eight berbarine alkaloids have been isolated and identified from the stems. 2 Compounds are reported to be new. The structure has been elucidated by spectroscopic and degradation studies. This novel compound exhibited *in-vitro* antileishmanial and immunomodulatory activities as it enhanced Nitric Oxide (NO) production and provided resistance against infection established in peritoneal macrophages by the protozoan parasite *Leishmania donovani*.

7.1.3.2 Plant 4666 (Antileishmanial)

Ethanolic extract (A001) showed antileishmanial activity both *in vitro* and *in vivo* (80% at the dose of 500 mg/kg in hamsters). Three compounds (K004, K005 and K006) were isolated from chloroform insoluble fraction and evaluated. Two compounds K004 and K006 have shown *in vivo* antileishmanial activity (60-80%) at the dose of 100 mg/kg in hamsters.

7.1.4 Anti-osteoporotic activity

Extracts and fractions from five plants 1020, 4404, 4455, 4617 and 4627 were evaluated. Only ethanolic extract and *n*-butanol fraction of plant 1020 showed promising osteogenic activity. 8 Compounds (K084, K090, K095, K103, K105, K113, K115 and sitosterol) from chloroform fraction 16 compounds (K010, K035, K039, K040, K051, K052, K053, K054, K064, K080, K082, K098, K111, K130, K135 and sitosterol glucoside) have been isolated from n-butanol fraction. These compounds were evaluated and only five compounds (K051, K052, K054, K080 and K095) were found to show promising osteogenic activity.

7.1.5 Anticancer activity

7.1.5.1 Plant 4539 (Anticancer)

Compound (K056) showed *in-vivo* anti-breast cancer activity at the dose of 10 mg/kg. Four new derivatives of compound K056 have been prepared to evaluate anti-breast cancer activity.

7.1.5.2 Plant No. 4690 (Anticancer)

Extract (A001) has shown anti-breast cancer activity. Its four fractions (F002, F003, F004 and F005) have been submitted for activity testing. Eight compounds (K023 to K028 and K030 to K031) have been isolated from hexane fraction (F002). Four compounds (K027, K028, K030 and K031) are new. Their bio-evaluations are in progress.

7.1.5.3 Plant No. 4698 (Anticancer)

Ethanolic extract A001 has shown anti-breast cancer activity. Its four fractions (F002, F003, F004 and F005) are under bio-evaluation.

7.1.5.4 Plant No. 1260 (Anticancer)

Nine compounds (K021 to K029) were isolated from ethyl acetate extract of plant 1260. One compound (K021) has shown anti-breast cancer and glycogen phosphorylase inhibitor activities.

7.1.6 Plant 4406 (Analgesic)

From roots of plant 4406, ten compounds of various classes have been isolated from chloroform fraction (F003). Compounds K023 and K024 have shown significant anti-inflammatory and analgesic activities in dose dependant manner. These findings may help in understanding the mechanism of action of this traditional plant leading to control activated mast cells on inflammatory conditions like arthritis.

7.2 Modification of natural products

Ten new benzocoumarin derivatives (S-006-1551 to S-006-1560) have been synthesized and are under evaluation for anticancer activity.

7.3 General screening of terrestrial plants and marine flora/fauna for antihyperglycemic/antidyslipidemic activities

Twelve new plant extracts (4701 to 4712) were prepared and submitted for activity testing.

A total of around 36 new plant extracts and 60 new marine extracts were evaluated for antihyperglycemic activity in sucrose loaded rat model. Out of these, four plant extracts i.e. 4693A001, 4697A001, 4701A001 and 4702A001 and two marine extracts CDR-269A001 and CDR-333A001 showed significant improvement on glucose tolerance post sucrose load at 250 mg/kg dose levels in normoglycaemic rats. A pure compound isolated from plant 4554 viz. K037 showed significant antihyperglycemic activity in all the three models i.e. sucrose loaded rats, streptozotocin-induced diabetic rats and db/db mice. Its ED_{50} was determined to be around 25 mg/kg in sucrose-challenged streptozotocin-induced diabetic mice. The extract prepared from the recollected marine sample CDR-150 showed promising antihyperglycemic activity in both sucrose loaded and streptozotocin-induced diabetic rats.

8. Area: Newer Approaches in Drug Design and Discovery

Coordinator: Dr. S. B. Katti

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

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

Very little is known how the assembly of membrane-active, naturally occurring or designed antimicrobial peptides in different prokaryotic and eukaryotic cells influences their lytic activity against the respective cells. Also, often the biological activities of these membrane-active antimicrobial peptides are explained by studying their interactions with model lipid membrane, which only roughly mimic the eukaryotic and prokaryotic membrane. All these observations led us to study the interaction and assembly of the leucine zipper peptide (LZP) and one of its single alanine–substituted analog (SASA) and double alanine-substituted analogs (DASA) to human red blood and *E. coli* cells as a model system. The LZP, SASA and DASA bound to *E. coli* cells with equal affinity and also permeablized and damaged them to a similar extent. Interestingly, LZP bound to hRBCs with highest affinity followed by the SASA and DASA respectively and the same trend was observed when the peptides permeabilized or damaged hRBC membrane. Fluorescence resonance energy transfer and gel electrophoresis experiments revealed the differences among the LZP, SASA and DASA in their assembly onto the live hRBCs and in their oligomeric states in zwitterionic lipid vesicles and hRBC ghost membrane. However, all three peptides assembled and oligomerized

to a similar extent in live *E. coli* cells and in negatively charged lipid vesicles or in *E. coli* spheroplasts. The findings disclose that assembly of these peptides in hRBCs and *E. coli* is pivotal in determining their lytic activity against the corresponding cells.

Also recently we have found that a wild type peptide, H-205 derived from the amino acid region 205-234 of *E. coli* toxin hemolysin E can inhibit the cytotoxic activity of the protein. Interestingly, the designed mutants of the peptide did not inhibit the activity of the protein. Detailed structural and functional studies have been carried out in order to understand the basis of inhibition of hemolytic activity of HlyE by H-205. Flow cytometric studies with annexin-V-FITC staining after the treatment of hRBCs with either protein or protein/peptide complex suggested that H-205 inhibited the hemolysin E-induced damage of membrane organization of hRBCs. Tryptophan fluorescence and circular dichroism studies showed that H-205 induced aggregation in HlyE, which is accompanied by the enhancement of appreciable helical structure.

8.2 Synthesis of combinatorial libraries

8.2.1 Bicyclic substrates for the Pictet-Spengler reaction

Based on our new concept for Pictet-Spengler reaction involving an aryl amine attached to an activated heterocyclic ring, we extended the strategy to bicyclic substrates: imidazopyridine and imidazothiazole. The studies led to formation of N-rich new polycyclic skeletons: triaza-benzofluorenes and pentalenona-phthalene hitherto not reported in the literature in high yields and purities. This is in contrast to the traditionally used aliphatic amine derived substrates (tryptamine and imidazoles) and aryl amine derived second-generation substrates reported earlier by us, that are based on an activated monocyclic heterosystems.

8.2.2 Synthesis of fused polycyclic nitrogen-containing heterocycles via cascade cyclization

In view of our continued interest in the development of novel antimalarial agents derived from natural products, we were interested in the synthesis and screening of β-carboline derivatives. However, during our attempts to synthesize these compounds, an unusual fused polycyclic nitrogen-containing heterocycles via cascade cyclizations was obtained as a byproduct. Since latter had strong resemblance to yohimbane skeleton, we developed method to obtain this class of compounds in high yields. The methodology involves condensation of 1-(2-aminophenyl)-9H-β-carboline-3-carboxylic acid amide with isothiocyanates followed by *in situ* treatment of the resulting thioureas with $HgCl_2$. The one-pot cascade cyclization leads to interesting changes in molecular structure and an increase in molecular complexity.

8.3 Novel methodologies for peptide design and synthesis

During this period, we carried out investigations on two important areas. These are design and synthesis of peptidominetic for type-2 diabetes and synthesis of thiazolidinone as HIV-RT inhibitors.

8.3.1 Design and synthesis of peptidominetic for type-2 diabetes

Diabetes mellitus is a metabolic disorder that affects millions of people worldwide. The

insufficient secretion of insulin or development of resistance to the insulin is the leading cause of diabetes. 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 of novel chemotherapeutic agents for the treatment of diabetes. Therefore, we have chosen protein tyrosine phosphatease-1-β (PTP1β), dipeptidyl peptidase (DPP-IV) and peroxisome proliferator-activated receptors-γ (PPAR-γ) as targets for the development of novel antidiabetic agents.

8.3.1.1 Peptidomimetcs as selective inhibitors of PTP1β

It is well known that PTP1β 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-1β 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, 19 new compounds were made and some of them have shown significant inhibition of PTP enzyme.

8.3.1.2 DPP-IV inhibitors as 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 β-cells in the pancreas. It is also reported that the GLP-1 helps to regenerate the degenerated β 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, this 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 peptidomimetic compounds. During this period, seven compounds were synthesized. The *in vitro* model for the DPP-IV enzyme assay has been standardized.

8.3.1.3 Synthesis of PPAR-γ agonist

Peroxisome proliferator activated receptors-γ is an important target for the development of antidiabetic agents. However, these classes of compounds exhibit liver toxicity. We have designed several molecules with objective to minimize the toxicity and simultaneously improve the activity. During this period, nine compounds have been synthesized and the biological activity evaluation is in progress.

8.3.2 Thiazolidinones as potent HIV-RT inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1 RT are an important part of currently available anti-HIV therapies because of their diversity and specificity in targeting this enzyme. However, the efficacy of NNRTIs is seriously hampered by the emergence of mutant viral strains. Therefore, it is imperative to look for new chemical entities having broad-spectrum activity against a variety of clinically relevant mutant RT enzymes with minimal cytotoxicity. During this period, a detailed QSAR and docking

studies were carried out on 4-thiazolidinone skeleton. Based on these predictions, thirty-three compounds were synthesized and evaluated for HIV-RT inhibitory activity by the enzyme as well as cell based assay protocols. Four compounds from this series emerged as the most potent compounds with EC_{50} values in the range of 22-28 nM in MT-4 and in CEM cell lines with a selectivity index as high as up to >10,000. Further, these compounds were also found to be two times more active than Nevirapine (EC_{50}=44 nM, selectivity index >370) in CEM cells. These results validate the robustness of the QSAR and modeling predictions.

8.4 X-ray crystallographic studies (small molecule crystallography)

Crystallization and 3D- X-ray intensity data collection of 43 compounds of biological and structural importance were completed. Structure determinations and refinements of 32 compounds were completed. Structure analysis of eight pyrazolo [3,4-*d*] pyrimidine molecules was performed in order to study weak non-covalent interactions, which showed the presence of both the intra- as well as inter-molecular interactions of the types π…π, C-H…π, S…. Ar and C-H…N. Confirmations of structures of two compounds from natural sources were performed by x-ray crystallographic studies. The x-ray crystallographic studies of seven pyran-2-one derivatives were performed and they showed the presence of weaker hydrogen bonding interactions apart from vander Waals interactions.

8.4.1 Cloning, over-expression, purification and biochemical characterization

X-ray crystal structures of the proteins are used in *in-silico* approaches to identify potential inhibitors, which are then subsequently verified by *in vitro* assays. Co-crystal structures with identified molecules are expected to help in improving the efficacy of the inhibitors. With this objective, a few druggable target proteins have been studied. Crystal structures of Lysine e-amino transferase (LAT) from *M. tuberculosis* 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. We have earlier solved crystal structures of the 35kD co-factor-binding domain of *M.tuberculosis* LigA and this structure has been used to identify novel inhibitors for the drug target. Novel class of inhibitors, *viz*. tetracyclic indoles have been identified with specificity for LigA over human DNA ligase I. We have also solved the crystal structures of the *M. tuberculosis* Feast/Famine regulatory protein and these structures are being analyzed to understand the structural basis for its transcriptional regulatory action.

8.5 Studies on protein folding

8.5.1 Differential effect of cations on functional and structural properties of *Mycobacterium tuberculosis* α-isopropylamate synthase

α-Isopropylmalate synthase (MtαIPMS), an enzyme that catalyzes the first committed step in the leucine biosynthetic pathway of *Mycobacterium tuberculosis* is a potential drug target for the anti-tuberculosis drug. Structural studies with divalent cations demonstrated that Zn^{2+} interacts specifically with the TIM barrel domain and induces loss of its secondary structure whereas, Mg^{2+} and K^{+} had no significant effect on the enzyme structure. This differential effect of divalent cations on the

MtaIPMS structure is the underlying mechanism for the cation induced differential modulation of functional activity of the enzyme. The functional and structural studies demonstrated that the differential effect of various cations studied showed that the a functionally active folded fragment of the enzyme was obtained by limited proteolysis of MtαIPMS using α-chymotrypsin. This fragment, corresponding to the amino acid residues Arg47 to Phe457 of the full-length protein was named TIM barrel domain. It was stabilized as a functionally active (about 12 % activity) dimer. Unlike the MtαIPMS, which is activated by Mg^{2+} and K^{+} and inhibited by L-leucine, the TIM barrel domain was activated by K^{+} only and not inhibited by L-leucine. These results for the first time demonstrated that the C-terminal domain of the MtαIPMS is essential for the optimal activity of the catalytic TIM barrel domain, as well as for Mg^{2+} induced activation and L-leucine induced inhibition of the enzyme. An important observation was that Mg^{2+} ions induced co-operativity in the otherwise non-cooperative MtαIPMS molecule thus establishing interaction between the regulatory and the catalytic domain of the enzyme which in turn might result in modulation of the functional activity of the catalytic domain.

8.5.2 Hyaluronate lyase: Insight into modulation of functional activity by non-catalytic domain

Hyaluronate lyases (HLs) cleave hyaluronan and certain other chondroitin / chondroitin sulfates. Although native HL from *Streptococcus agalactiae* is composed of four domains but it finally stabilizes after autocatalytic conversion as 92kDa enzyme composed of N-terminal spacer, middle- and C-terminal domain. These three domains are found to be independent folding/unfolding units of the enzyme. Comparative structural and functional studies using the enzyme and its various fragments/domains suggest a relatively insignificant role of the N-terminal spacer domain in the 92kDa enzyme. Functional studies demonstrate that α-domain is the catalytic domain. However, independently it shows only a maximum of about 10 % of the activity of the 92kDa enzyme whereas its complex with C-terminal domain *in vitro* shows a significant enhancement (about 6 fold) in the activity. It has been previously proposed that C-terminal domain modulates the enzymatic activity of HLs. In addition, one of the possible roles for calcium ions was suggested to induce conformational changes in the enzyme loops making HL more suitable for catalysis. However, we observed that calcium ions do not interact with the enzyme and its role actually is in modulating the hyaluronan conformation and not in the functional regulation of enzyme.

8.6 Structural genomics of *Mycobacterium tuberculosis* proteins using NMR spectroscopy

We have achieved a significant milestone in the structure determination of the potential drug target protein viz. peptidyl-tRNA hydrolase from *M. tuberculosis* H37Rv (MtPth) in solution by NMR spectroscopy. NMR assignment of backbone and side-chains for ^{1}H, ^{13}C, and ^{15}N resonances for ^{13}C, ^{15}N-labeled MtPth have been completed and deposited in BMRB. We have already assigned ~1000 NOEs derived from ^{15}N-edited NOESY-HSQC experiment. Parallel to this, we have calculated a model structure with 1.3 A rmsd based on ~1700 theoretical NOEs. We are currently in the process of assigning ~700 NOEs from the ^{13}C-edited NOESY-HSQC experiment.

Significant progress was also made in characterization of CFP-10 and ESAT-6 T-cell antigens of *M. tuberculosis* H37Rv. A comprehensive study on complex formation, interaction with phospholipid membranes, mutational analysis of ESAT-6, thermodynamic stability and biochemical stability was completed. Mutational analysis of CFP-10 along similar lines is being pursued currently. This study will be very useful for introducing beneficial mutations into recombinant BCG vaccines, which are expected to improve its efficacy.

8.7 Drug target development using *in silico* biology

8.7.1 Computational biology and bio-informatics in drug discovery

A vibrant program to provide integrated environment for informatics systems, computational chemistry and molecular modeling and to facilitate and enhance drug design and discovery in different target therapeutic areas is the major endeavor of this project area. Some of the significant achievements during the year include:

(a) Identification of potent and selective inhibitors of *M. tuberculosis* chorismate mutase with low K_i values, by a ligand-based virtual screening approach. The structural models for these leads in the chorismate mutase-binding site will facilitate further medicinal chemistry efforts targeting this protein.

(b) 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 extended on diaryloxy methano phenanthrene analogues as anti-tuberculosis agents, 4-thiazolidinones as potent HIV-1 RT inhibitors and human mitotic kinesin Eg5 inhibitors as anti-cancer agents. The results provided clear guidelines and reasonably good activity predictions for designing the novel inhibitors.

8.7.2 *In silico* target identification

In this study, we have used an integrated approach towards the identification of novel drug targets of *Mycobacterium tuberculosis* for inhibitor design. A comparative metabolic pathway analysis of the host *H. sapiens* and the pathogen *M. tuberculosis* for the identification of unique pathways was done. Though sequence similarity greater than 25% implies homology, we have adopted a stringent measure of listing out only those enzymes which have no similarity (or negligible similarity above the *e*-value threshold of 0.005) to the host proteins as potential targets. We have then used other approaches like choke point analysis, essentiality and damage analysis for the identification of drug targets. These approaches were successful in listing out many targets from the *M. tuberculosis* proteome, which are involved in vital aspects of the pathogen's metabolism and cell wall biosynthesis.

A rational evaluation of a series of *R* and *S* amino acid derived, 3-substituted 1,4-benzodiazepin-2-ones as an anti-ischaemic agents was done by molecular modeling and docking studies. This study complementing the *in vitro* evaluation of anti-ischaemic activity of this series of compounds, some of them showing promising neuronal protection activity, indicates an interesting new possibility of utilization of 1,4-benzodiazepin-2-one derived compounds as anti-ischaemic agents.

9. Area: Reproductive Health Research

Coordinator: Dr. Naibedya Chattopadhyay

Design and synthesis of novel molecules/isolates 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; to understand mode of action of promising agents and to 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 program, much progress has been made in identifying and developing putative anti-osteoporosis agents from CDRI. Given the discontinuation of hormone replacement/estrogen replacement therapy due to adverse cardiovascular side effects, lead compounds/agents from CDRI have received particular attention to be devoid of estrogenic activity.

9.1.1 Screening

Fourteen synthetic and eighteen natural extracts (terrestrial plants/marine flora and fauna) were tested for their potential mitogenic effect on calvarial osteoblasts by MTT assay. One synthetic compound and one natural extract were found to be active.

9.1.2 Follow-up studies: compound 99-373

9.1.2.1 Molecular mechanism of osteoclastogenesis

To resorb bone, osteoclasts must form a sealing zone by generating a ring structure made of F-actin, which corresponds exactly to clear zones in bone-resorbing osteoclasts. Actin ring formation precedes resorption and is a functional marker of activated osteoclasts. Therefore, finding drugs that disturb the integrity of the actin ring could be a useful approach to therapy

to slow bone resorption. Compound 99-373 inhibited RANKL-induced actin ring formation in osteoclasts derived from bone marrow cell differentiation. This effect of 99-373 was concentration-dependent from 1.0 to 5.0 µM.

9.1.2.2 Testing for estrogenic activity

Estrogen receptors (ER) α and α were cloned and expressed in mammalian cells. i.e., COS-1 cells. Expressed receptors were characterized for estradiol binding activity and estradiol-induced transcriptional activity. Transcriptional activation of both the ER isoforms under the influence of SERMs, as assessed using luciferase reporter construct containing ERE consensus sequences, revealed that 7-hydroxy centchroman showed potent estrogen antagonistic activity for ERα than for ERβ. Compound 99-373, a potential anti-resorptive agent, also suppressed transactivation of estrogen receptors although it does not bind to ERs. This effect of 99-373 appears to be due to down regulation of ERs induced via different pathway.

Using expression of estrogen responsive genes, whereas raloxifene and tamoxifen acted as ER antagonists in Ishikawa cell line, 99-373 at 1 µM concentration did not. Expression levels of CAT-D, cmyc and IGF-1 were highest in estradiol treated samples. While centchroman exerted ER antagonistic effect in MCF-7 cell line, compound 99-373 did not show any estrogenic activity in MCF-7 cell line at 1 µM concentration. In case of Ishikawa cell line, expression levels of ER responsive genes were significantly high in tamoxifen treated samples and were almost comparable to estradiol treated samples. No such partial agonistic effect was observed with compound 99-373, raloxifene or centchroman.

9.1.2.3 Pharmacokinetic studies

The compound was found to be chemically stable for 12 months at 50°C and 60°C. Luminal stability study in Simulated Gastric and Simulated Intestinal Fluids (SGF and SIF) showed that the compound was stable in both acidic and basic pH. *In vitro* protein binding was found to be moderate. In pre-clinical pharmacokinetic studies undertaken in adult Sprague Dawley rats treated with a single 10 mg/kg oral dose of compound 99-373, the compound exhibited multiple C_{max} and low systemic bioavailability. Two metabolites were identified in serum. *In vitro* metabolic studies with liver S-9 fraction revealed that it was metabolised fast and two metabolites, as identified *in vivo*, were obtained.

Using rat hepatic S9 fraction, compound 99-373 was completely metabolized within 60 min. and two metabolites were detected and identified. After single 10 mg/kg oral dose of the compound in male Sprague-Dawley rats, compound as well as the two metabolites were detected. The parent compound was monitored up to 4 h post dosing, whereas the metabolites were detected up to 8-10 h with t_{max} being achieved between 0.25-0.5 h. AUC for the parent compound and metabolites M1 and M2 was 39.11, 359.00 and 168.00, respectively whereas the MRT were found to be 1.8, 3.43 and 3 h, respectively. The compound could be monitored for upto 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%.

9.1.3 Follow-up studies: NP-1

9.1.3.1 Effect on bone mineral density (BMD) in growing rats

Oral administration of NP-1 at 1 g/kg daily dose administered orally for 30 consecutive days

to 30-day old intact female Sprague-Dawley rats induced marked increase in BMD in lumbar vertebrae (L1 - L4), tibia (global, proximal and tibio-fibular separation point) as well as femur (global and mid-shaft) bones, without exhibiting any effect on change in body weight. There was also no effect on uterine weight, suggesting lack of any estrogen agonistic activity of the extract at the uterine level when administered at this dose/schedule. The increase in BMD in femur neck was comparatively of lower order. Further studies on effect at lower (500 mg/kg/day) dose of the extract are in progress.

9.1.3.2 Testing for estrogenic activity

NP-1 at its osteogenic (0.05% and 0.1%) concentrations did not show any proliferative effect on Ishikawa or MCF-7 cell lines. 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 on these cells and thus confirm absence any estrogenic effect of NP-1 on these cell lines. In addition, NP-1 was evaluated in ovariectomized immature rat bioassay following once daily oral administration for three consecutive days, showed no significant uterotrophic activity. E2 was used as positive control.

9.1.3.3 Expression analysis of marker genes

Single oral administration of NP-1 (1000 mg/kg) increased level of osterix, but not that of collagen-I, in calvariae of immature rats at 48 h of treatment. By 72 h post-treatment, however, more than 5-fold increase in collagen-I and osteocalcin transcript levels was observed in calvariae of NP-1 treated rats, demonstrating potential role of NP-1 in osteoblast maturation and mineralization. Substantial reduction in transcript levels of Cathepsin K and RANK was also observed in this study, suggesting possible osteoclast inhibitory effect of NP-1.

9.1.3.4 Osteogenic activity in fractions of NP-1

Five pure fractions out of twenty-six fractions were tested *in vitro* for their osteogenic activities. Significant osteogenic activity was observed as assessed by increased osteoblast proliferation, differentiation and mineralization.

9.2 Development of agents for anti-cancer breast

9.2.1 Screening

Twenty synthetic compounds and seventeen natural products were screened for anti-proliferative activity in MCF-7 cells *in vitro* using MTT assay with tamoxifen as positive control. Out of these, seven synthetic compounds and two natural products showed anti-proliferative activity in breast cancer cell line. All active compounds were screened for induction of apoptosis using nuclear staining and also subjected to estrogenicity and anti-estrogenicity profiling in order to exclude its hormone-like side effects. Anti-proliferative but non-estrogenic compounds were also screened for *in vitro* cytotoxicity in normal cell lines. Compounds showing anti-proliferative activity *in vitro* and devoid of non-estrogenic activity are undergoing trial in DMBA-induced rat mammary tumor model.

9.2.2 Estrogenicity profile of promising lead molecules in mammary and endometrial carcinoma cell lines

This study was aimed to compare the effect of promising lead molecules on estrogen receptor (ER) responsive genes in mammary (MCF-7) and endometrial (Ishikawa) carcinoma cell lines using tamoxifen and raloxifene as reference standards. Using MCF-7 cell line, maximum expression of all the three ER

responsive genes i.e., CAT-D, cMyc and IGF-1 was observed in estradiol treated cultures. In comparison, raloxifene, tamoxifen as well as centchroman exhibited ER antagonistic response. These results are complementary with those observed by Shang and Brown (Shang Y and Brown M., Molecular determinants for the tissue specificity of SERMs, Science, **295**, 2465-2468, 2002). In studies on Ishikawa cell line, while tamoxifen acted as an estrogen agonist with expression levels of all ER responsive genes almost comparable to that of estradiol treated samples thus implicating it in endometrial cancer, no such agonistic effect was observed in raloxifene or centchroman treated cultures.

9.2.3 Substituted phenanthrenes with basic amino side chains: A new series of anti-breast cancer agents

In the course of search for new anti-cancer breast agents, substituted phenanthrenes with basic amino side chains were synthesized and some of them showed remarkable antiproliferative activity against ER-positive MCF-7 cell line with IC_{50} in the range of 3.53–22.25 μM. One of the compounds showed anticancer activity in 7,12-dimethylbenz[a]anthracene (DMBA) induced hormone-dependent mammary tumor in rat and the activity was comparable to that shown by tamoxifen.

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

9.3.1 Screening

21 synthetic compounds and 43 extracts of natural product including marine flora and 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* (p.c.) by the oral route. Of these, two synthetic compounds were found active and taken for follow-up studies and their MED has been determined.

9.3.2 Relative Binding Affinity (RBA) to estrogen receptors

A total of 10 synthetic compounds, synthesized as possible estrogen receptor modulators, were evaluated for their relative binding affinity to rat uterine cytosolic estrogen receptors using *in vitro* competitive binding assay. Of these, compounds S-005-107 and S-005-565 showed RBA of <0.1%, compounds S-005-108, S-005-276, S-005-277, S-005-278 showed RBA of 0.1%, compound S-005-278 showed RBA of 1%, while the remaining compounds were found to be inactive with RBA of <0.001% of estradiol-17β.

9.3.3 Follow-up studies with ormeloxifene on uterine expression of estrogen receptor a and b in pseudopregnant rats

Studies were undertaken to explore the effect of ormeloxifene (Orm) on expression of estrogen receptors α and β with a view to explore the role of ER α/β during decidualization and also to explore the mechanism of antideciduogenic activity of the molecule. Immunohistochemical studies revealed that both ER subtypes were expressed in uterus as observed on day 6, 7, and 8 of pseudopregnancy. However, the ERβ subtype expression was highest on day 8. Results were also correlated with western blot analysis. Orm when given at 1.25 mg/kg dose prior to decidual induction, did not alter the expression of ERα, however, ERβ was significantly reduced under

the influence of Orm. The study suggests the role of ERβ subtype during the decidualization and the downregulation of ERβ may be one of the factors responsible for inhibition of decidualization by ormeloxifene.

9.3.4 Demonstration of $\alpha_v\beta_3$ expression as a marker of uterine receptivity in rat

To investigate the expression of $\alpha_v\beta_3$ integrin in rat endometrial epithelial cells (EEC) in order to establish it as the marker of uterine receptivity, the expression of $\alpha_v\beta_3$ was studied at the protein level in rat EEC by immunocytochemistry and flow-cytometry. Immunocytochemical study showed cell surface staining of both α_v and β_3 subunits in EEC isolated from day 4 and day 5 p.c., but the intensity of staining for both the subunits was high in EEC of day 5 p.c. as compared to the cells of day 4 p.c. Flow-cytometric study also showed a very high expression of $\alpha_v\beta_3$ in EEC of day 5 p.c. as compared to the cells of day 4 p.c. and non-pregnant animals. Poor expression of $\alpha_v\beta_3$ integrin in EEC of non-pregnant animals is due to the non-receptivity of endometrial epithelium to blastocyst implantation. The inference of this study is that the $\alpha_v\beta_3$ integrin is highly expressed in EEC during implantation window (day 5 p.c.) and therefore it holds good promise to be a vital marker of uterine receptivity in rat.

9.4 Contraceptives for the male and spermicides

9.4.1 Screening for spermicidal activity

Seven out of 9 synthetic compounds, evaluated for spermicidal activity *in vitro* by Sander Cramer assay using live human sperm, exhibited moderate activity. However, none of the 21 natural products exhibited any detectable spermicidal activity *in vitro*. CDRI compounds/ plant products were also screened for using a microplate-based *in vitro* sperm hyaluronidase inhibition activity. Fourteen synthetic compounds were tested using this assay, however, none of the compounds showed activities at 100 µg/ml.

9.4.2 Novel disulphide esters of carbothioic acid as potent, non-detergent spermicides with low toxicity to *Lactobacillus* and HeLa cells *in vitro*

The design, synthesis, characterization and evaluation of novel series of non-detergent spermicides has led to the discovery of two unique disulphide esters of carbothioic acid that were ~25 times more potent spermicides than nonoxynol-9 (N-9). Normal human spermatozoa were used to assess the spermicidal activity (Sander–Cramer Assay), the effect on sperm-membrane integrity [hypo-osmotic swelling test (HOST)], supravital staining and scanning electron microscopy and the induction of apoptosis (FITC Annexin-V and JC-1 labelling using flow cytometry) by the new class of compounds. HeLa and *Lactobacillus* cultures were used to assess the cytotoxicity of compounds and their compatibility to normal vaginal flora, respectively. The new compounds exhibited a strong spermicidal activity [minimum effective concentration (MEC) = 0.002%], which was ~25 times more potent than that of N-9 and *Sapindus* saponins (MEC = 0.05%). As compared with surfactants, they were found to be safer at MEC towards the growth and survival of *Lactobacilli* and HeLa cells *in vitro* and to have a milder effect on sperm plasma membrane. At EC_{50} both induced apoptosis in sperm cells as characterized by increased labelling with Annexin-V and decreased polarization of sperm mitochondria. Preliminary studies have revealed

that in sharp contrast to the non-specific surfactant action of N-9, new non-detergent spermicides have a highly potent, mechanism-based, detrimental action on human sperm. The unique ability of these molecules to selectively kill sperm and spare *Lactobacilli* and HeLa cells at MEC values much lower than that required for N-9 indicates their potential as superior ingredients for formulation into microbicidal contraceptives.

9.4.3 Reversible anti spermatogenic agents targeting rat testicular germ cell type(s)

Spermatogenesis goes through very critically and precisely balanced ratios of germ cells with diverse DNA ploidies (1C, 2C and 4C). Antispermatogenic agents that reversibly interrupt spermatogenesis may have a contraceptive relevance. To study the precise mechanism of action of antispermatogenic agents and identify the germ cell type(s) targeted by various agents *in vivo*, spermatogenic cells with diverse DNA ploidies were measured in rat testis during treatment and recovery with compounds 1-formyl, 4-dichloroacetyl piperazine (CDRI-drug), gossypol and estradiol, using Flow Cytometry. Treatment with CDRI-drug resulted in a significant and rapid drop in 1C population with a concomitant and parallel rise in 2C population. In gossypol-treated animals 1C peak disappeared gradually and the arrest was seen predominantly at 2C stage and partially at 4C stage. At the end of the treatment most of the germ cells were arrested at 2C stage. Estradiol affected spermatogenesis differently with 1C population falling in complement to rise in both 2C and 4C peaks. Germ cells were mainly arrested at the 4C stage after the treatment. The data suggest that germ cells fail to enter meiosis in CDRI-drug treated rats. Few cells entering meiosis do not complete the cell division and remain arrested at 4C stage. However, in case of estradiol and gossypol, the meiotic 4C cells become incapable of further differentiation into haploid cells. The population of various germ cell types in the testis of recovery-group animals indicated that spermatogenesis resumes substantially in case of estradiol treatment and partially in case of treatment with the other two agents.

9.4.4 Medicated condoms

Stability studies performed with medicated condoms coated with the herbal spermicide (*Sapindus* saponins) indicated that the product was stable up to one year of manufacture. This study is being performed in collaboration with M/s. Hindustan Latex Limited, Chennai.

9.5 Development of anti-STI agents

9.5.1 Screening

Twenty-one synthetic compounds were evaluated for anti-trichomonas activity *in vitro* using *Trichomonas vaginalis* cell culture. The test agents were dissolved in DMSO/methanol (final conc.: 0.1%) and diluted with the culture medium. Of these, five compounds bearing numbers S-002-381, S-002-894, S-003-163, S-004-1278 and S-004-1279 significantly decreased cell numbers and motility of the parasite with MEC of 10-22 µM concentration. Almost all the parasites were found dead at 25-30 µM concentration. These compounds as evidenced by Trypan blue staining. The marketed drugs Metronidazole (MEC: 6.3 µM) and Tinidazole (MEC: 5.0 µM) were used as reference standards.

9.5.2 Follow-up studies: Anti-*trichomonas activity* of two synthetic compounds

Two synthetic compounds C-1274 and C-757 were found to be effective anti-

trichomonas agent at 15 µg/ml and 20 µg/ml, respectively. These compounds do not show any cytotoxic effect on host cells, which was determined by MTT cytotoxic assay and reduction potential by JC-1 flurochrome dye. The effect of the compounds on the local vaginal flora was seen on *Lactobacillus*, and these compounds were found to be much less toxic as compared N-9, a well known commercially available spermicidal. C-1274 and C-757 on treatment for 17 hr were found to effectively inhibit the cytoadherence of *T. vaginalis* to HeLa cervical cells, which is the primary step for initiation of infection. Also, C-1274 has comparatively inhibitory effect on cysteine proteases while C-757 does not have any effect on cysteine proteinases. As hemolytic activity is an important phenomenon of virulence, effect on the hemolytic activity of parasites was studied. It was found that C-1274 inhibited the hemolytic activity to 50% on treatment for 24 hr while C-757 inhibited on treatment for 36 hr. C-1274 and C-757 were also studied for their effect on inflammatory responsive cells. RAW264.7 macrophage cells on interaction with *T. vaginalis* were found to have increased level of TNF-α on treatment with C-1274 and C-757 as compared to control RAW 264.7 cells interacting with *T. vaginalis*.

9.5.3 Anti-*trichomonas activity* of CONSAP

Trichomoniasis is an important sexually transmitted disease (STD) caused by the protozoan *Trichomonas vaginalis* and has been associated with with increased HIV incidence. Classical treatment involves drugs of nitroimidazole family, which are toxic and are associated with side effects. Moreover, resistance to these classical drugs is on the rise, thus emphasizing the need for development of effective novel anti-*trichomonas* agents. Saponins, a component of the herbal local contraceptive CONSAP, exhibit *in vitro* spermicidal activity at a concentration of 0.05%. Using *in vitro* susceptibility assay, the minimum lethal concentration of *Sapindus* saponins for *Trichomonas vaginalis* (0.005%) was found to be ten-folds lower than that of its effective spermicidal concentration (0.05%). *T. vaginalis* adheres to cervical epithelial cells through adhesins and cysteine proteinases. Using cytoadherence assay, saponins were found to inhibit the ability of parasites to adhere to HeLa cells by ~50%. Substrate gel electrophoresis analysis has shown that 2 hour treatment of parasites with the saponins decreases proteolytic activity of the parasite's cysteine proteinases. Hemolytic activity of the parasites was also diminished on treatment with saponins for 3 hours. Saponins at the concentration of 0.005% significantly reduced expression level of parasite specific genes TvCP2 and AP65. Saponins also inhibited the host immune evasion effect of *T. vaginalis*, as evidenced by consistent up-regulation of IL-8 up to six hours in HeLa cells incubated with the saponin treated parasites. Preliminary scanning electron microscopic studies have indicated that treatment of parasites with the saponins decreased their phagocytic ability, which complements well with the observed decrease in hemolytic activity of parasites after saponin treatment.

9.5.4 Spermicidal and anti-*trichomonas* activities of certain SSRI anti-depressants

This study investigated spermicidal and anti-*Trichomonas* activity of certain SSRI antidepressants with a view to generate new leads for development of dual-function spermicidal contraceptives, which is an urgent global need. Fluoxetine, Sertraline and

Fluvoxamine exhibited both spermicidal and anti-*trichomonas* activities *in vitro*, whereas Paroxetine and Citalopram showed only the spermicidal activity. Fluoxetine exhibited better activity profile than the other antidepressant drugs with its spermicidal and anti-trichomonas activities being comparable to the OTC contraceptive Nonoxynol-9. The non-detergent nature of Fluoxetine and a much superior spermicidal ED_{50} value may add considerably to its merit as a candidate for microbicidal contraceptive. Thus, the antidepressants exhibiting both spermicidal and antitrichomonas activities might provide useful leads for the development of novel, dual-function spermicidal contraceptives.

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 α-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 improvements is often associated with long-term side effects, costs and compliance issues. Phytotherapy is increasingly being practiced as the safest approach to BPH management. Using rat as the test model and finasteride as positive control, we have discovered promising activity in two common plant seed extracts. The studies are in progress to validate these natural products for their further development as effective, innocuous and economical method for BPH management. One synthetic compound evaluated in this model did not exhibit any detectable activity.

10. Area: Technology Development

Coordinator: Dr. Vinod Bihari

Development of appropriate technology for production of Institute's candidate drugs, generic drugs, drug intermediates and biochemicals.

The development of commercially viable technology of drugs and drug intermediates is one of the key activities in the launching of new drugs. An appropriate environment friendly technology is the only solution to successful commercialization of a new and generic drug compatible with international standards, viz. ISO 9000 and ISO 14000. Development of know-how of drugs through sponsored as well as collaborative projects, has been the regular activity of Technology Development area.

10.1 Sub Area: Chemical Technology

Coordinator: Dr. Chandan Singh

10.2 Sub Area: Fermentation Technology

Coordinator: Dr. Vinod Bihari

10.3 Sub Area: Pharmaceutical Technology

Coordinator: Dr. Satyawan Singh

10.1 Sub Area: Chemical Technology

10.1.1 Compound 99-411 (Antimalarial)

110 g. of the compound 99-411 was prepared and supplied to Pharmaceutics Division.

10.1.2 Picroliv (Hepatoprotective)

A total of 9.1 kg of the required material was supplied to Pharmaceutics Division.

10.1.3 Generic Drugs

(a) Simvastatin (Hypolipidemic)

An improved process of Simvastatin was developed at bench scale. The highlight of the process includes lesser number of steps, recovery and recycling of some reactant utilized.

(b) Sertraline Hydrochloride (Antidepressant)

A 5-step improved process for the synthesis of Sertraline hydrochloride was developed and carried out at bench scale, avoiding the use of hazardous reagent like titanium tetrachloride. The reductive amination step was carried out at room temperature and low pressure.

(c) Paroxetine Hydrochloride (Antidepressant)

A novel 8-step process was envisaged with a view to avoid the use of hazardous lithium

aluminium hydride and hydrogenation step. First three steps have been carried out.

10.2 Sub Area : Fermentation Technology

10.2.1 Screening of microbial cultures for antibacterial compounds

Novel bioactives and lead drug molecules are being continuously discovered from natural sources. Exploration/exploitation of vast microbial diversity for this purpose is one of the networked projects being currently pursued in many laboratories. Hundreds of microbial cultures were isolated from the soil samples collected from remote areas witnessing diversified geological/ecological conditions and tested for antibacterial/antifungal activities. Cultures showing broad-spectrum antimicrobial activity were cultivated in optimum fermentation conditions for production, purification, isolation and characterization of the active compound. Precise taxonomic/molecular characterization of the producer strains/organism is essential. Active cultures were subjected to 16S rRNA gene sequencing at MTCC, IMTECH, Chandigarh and identified as *Streptomyces griseoruber* MTCC 8121 and *S. sindenensis* MTCC 8122. The active compound produced by *S. sindenensis* has been characterized as actinomycin D. Improvement of this strain was attempted by UV irradiation and a mutant showing substantially enhanced antibiotic yield has been isolated. *S. sindenensis* was not reported earlier to produce actinomycin D.

10.2.2 Search for novel antifungal compounds from microbial source

Active cultures showing strong antifungal activity have been characterized as *Talaromyces assiutensis* MTCC 7582 and *Streptomyces capoamus* MTCC 8123. These cultures are active against unicellular and filamentous fungi. Chemical characterization of the active compound, produced by this culture, is in progress. Other active compounds are at different stages of purification and characterization.

10.2.3 Production of low molecular weight heparins (LMWHs) by the enzyme heparinases produced from microbial sources

Commercial availability of effective and safe natural antithrombotic agents for clinical applications is very much required. Heparinases are microbially produced inducible enzymes that degrade heparins to generate LMWHs, which act as anticoagulant and antithrombotic agent. Bacterium *Pedobacter heparinus* NRRL B-14731 was obtained and heparinase activity of the culture was confirmed. This strain will be used as a reference strain. A heparinase producing fungus has been isolated from the soil sample. The culture produces intracellular as well as extracellular heparinase during late log phase of growth in complex protein digest medium with heparin as inducer. Enzyme production, deheparinization and LMWHs production with the type and isolated strain is being studied.

10.2.4 Biocatalysis

Innovative application of microbial cells as biocatalysts to accomplish various biochemical reactions for producing drugs/drug intermediates is a major growing area of biotechnology.

10.2.4.1 Hydrolysis of Lactose

β-galactosidase enzyme is commercially used for hydrolyzing milk lactose to glucose as many humans lack this enzyme and cannot

consume raw milk. Whole and immobilized cells of the yeast *Kluyveromyces lactis* were used to hydrolyse lactose under various conditions and the process was optimized. Attempts were made to hydrolyse milk lactose also in column reactors with considerable success.

10.2.4.2 Production of L-phenylacetyl carbinol (L-PAC)

L-phenylacetyl carbinol, an intermediate substrate to prepare L-ephedrine, is a biotransformation product of benzaldehyde. The biocatalytic conversion is accomplished by a yeast strain of *Saccharomyces cerevisiae* and efficiency of the process is dependent on the use of carbon source and reaction conditions. By manipulating carbon source, its concentration and biotransformation conditions, L-PAC of higher purity was obtained.

10.2.5 Biotransformation

Studies on hydroxylation of 80-574 compound with the help of *Aspergillus ochraceus* was continued and derivatized products were subjected to pharmacokinetic evaluation as well as for the synthesis of other intermediates in collaboration with the scientists of Chemistry group.

10.2.6 Culture maintenance

Long-term preservation by freeze-drying and maintenance of microbial cultures was continued. At regular intervals purity, potency and viability of the preserved/maintained cultures was checked.

10.3 Sub Area: Pharmaceutical Technology

10.3.1 Development of drug delivery systems

10.3.1.1 Novel formulation of albendazole

A nanometer-range emulsion containing albendazole was prepared and was found to be active against *Brugia malayi* in the Mastomys and Jird models.

10.3.1.2 Biodegradable microparticles of antitubercular drugs

Product development of inhalable microparticles containing two antitubercular drugs was continued in collaboration with M/S Lupin Laboratories Ltd. under NMITLI. Stability issues required a change in the formulation and fresh stability studies were initiated. Efficacy and toxicity evaluations of new formulation were also initiated and are showing encouraging results.

10.3.1.3 Delivery of Glucagon likes peptide-1 (GLP-1)

Experiments continued on a micro- or nano-particulate delivery system incorporating GLP-1. The peptide was synthesized and purified. Efforts are underway to produce a stable formulation as the peptide shows rapid denaturation.

10.3.1.4 Delivery system for cyclosporin

Novel surfactant vesicles containing cyclosporin (CsA) have been prepared by incorporating bile salt as integral component. The formulation showed improvement in absorption and reduction in efflux of CsA when studied through *in vitro* everted sac *in situ*

(intestinal segment of rat) method. The developed formulation showed almost 1.6 times increase in bioavailability compared to marketed formulation while it was 6 times compared to control when studied in rats.

10.3.1.5 Delivery system for septic shock

Novel emulsion based formulations have been prepared by incorporating cationic charge with chitosan. The cell viability with these formulations were found to be more than 90%. The formulation showed marked reduction in nitrite release as compared to free lipopolysaccharide.

10.3.2 Quality control and stability studies

Quality control and stability studies on Herbal Medicament, 109K022, CDR-134F194, CDR-267F018, S-002-853 and 99-411 are continuing. HPLC method for S-005-141 with proper resolution of the starting materials and HPLC method for chiral separation of S-002-853 was developed.

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RESEARCH OUTPUT & OTHER ACTIVITIES

II. Publications

2005

1. Katiyar SB, Bansal Iti, Saxena JK & Chauhan PMS. Synthesis of 2,4,6-trisubstituted pyrimidine derivatives as a new class of antimalarial topoisomerase inhibitors.

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3. Sondhi SM, Goyal RN, Lahoti AM, Singh N, Shukla R & Raghubir Ram. Synthesis and biological evaluation of 2-thio pyrimidine derivatives.

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8. Agnihotri Geetanjali & Misra Anup Kumar. Facile synthesis of pyruvate ketals of carbohydrates.

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9. Agnihotri Geetanjali & Misra Anup Kumar. Synthesis of a di- and a trisaccharide related to the O-antigen of *Escherichia coli* O83:K24:H31.

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14. Akhtar MS, Krishnan MY & Bhakuni Vinod. Insight into the mechanism of action of hyaluronate lyase: Role of C-terminal domain and Ca^{++} in the functional regulation of enzyme.

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191. Tripathi Sarvind Mani & Ravishankar Ramachandran. Direct evidence for a Glutamate switch necessary for substrate recognition: Crystal structures of Lysine α-aminotransferase (Rv3290c) from *Mycobacterium tuberculosis* H37Rv.

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III. Patents

1.	**Patents Filed in India**	**19**
2.	**Patents Filed Abroad**	**31**
3.	**Patents Granted in India**	**12**
4.	**Patents Granted Abroad**	**13**

Patents Filed in India

1. **Patent Appl. No.:** 3516DEL2005 **Filing Date:** 30/12/2005
Title: **Novel spiro 1,2,4-trioxanes**
Inventors: Chandan Singh, Heetika Malik & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi, Akhilesh K. Srivastava & Kamlesh Kumar Singh

2. **Patent Appl. No.:** 0123DEL2006 **Filing Date:** 07/12/2006
Title: **A process for screening of anti-leishmanial compounds using *Leishmania donovan*i cell lines expressing luciferase reporter gene**
Inventors: Neena Goyal & Ashutosh

3. **Patent Appl. No.:** 0391DEL2006 **Filing Date:** 13/02/2006
Title: **Novel ester derivatives of dihydroartemisinin**
Inventors: Chandan Singh, Sandeep Chaudhary & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi, Akhilesh Kumar Srivastava & Kamlesh Kumar Singh

4. **Patent Appl. No.:** 0523DEL2006 **Filing Date:** 28/02/2006
Title: **Intravaginal gel composition and method for early termination of pregnancy**
Inventors: Satyawan B. Jadhav, Rabi Sankar Bhatta, Man Mohan Singh & Girish Kumar Jain
Supporting Staff: Mohini Chhabra

5. **Patent Appl. No.:** 0529DEL2006 **Filing Date:** 07/12/2006
Title: **5-[2-(2,6,6-Trimethyl-cyclohex-2-enyl)-ethenyl]-isoxazoles**
Inventors: Shivaji Narayanrao Suryavanshi, Suman Gupta, Ramesh & Naveen Chandra
Supporting Staff: Manju & Shiveram

6. **Patent Appl. No.:** 0528DEL2006 **Filing Date:** 28/02/2006
Title: **Isolation and synthesis of novel furano and pyranoflavonoids as antidiabetic agents**
Inventors: Rakesh Maurya, Atul Goel, Tadigoppula Narender, Arvind Kumar Srivastava, Anil Kumar Rastogi, Suresh Chandra Agarwal, S.M. Rajendran, Chandishwar Nath, Ram Raghubir, Mukesh Srivastava, Prem Prakash Yadav, Shweta, Manish Dixit, Priti Tiwari & Brajendra Kumar Tripathi
Supporting Staff: S.C. Tiwari, Suresh Yadav, H.C.Verma, G.P. Singh & J.K. Joshi

7. **Patent Appl. No.:** 0525DEL2006 **Filing Date:** 28/02/2006
Title: **Synthesis and antibacterial activity of novel erythromycin derivatives**
Inventors: Wahajul Haq, Deepa Pandey, Chandra Kant Mani Tripathi & Seturam Bandacharya Katti
Supporting Staff: Bikram Banerjee

8. **Patent Appl. No.:** 0533DEL2006 **Filing Date:** 28/02/2006
Title: **C-3 alkyl or arylalkyl substituted 2,3-dideoxy glucopyranosides and a process for preparation thereof**
Inventors: Ram Sagar, Mohd. Saquib, Arun Kumar Shaw, Anil Nilkanth Gaikwad, Sudhir Kumar Sinha, Anil Srivastava, Vinita Chaturvedi, Manju Yashoda Krishnan, Ranjana Srivastava & Brahm Shanker Srivastava
Supporting Staff: Anup Kishore Pandey & Ajay Singh Verma

9. **Patent Appl. No.:** 0522DEL2006 **Filing Date:** 28/02/2006
Title: **Antiosteoporosis activity of *Butea* species**
Inventors: Rakesh Maurya, Geetu Singh, Pandruvada Subramanya Narayana Murthy, Sandhya Mehrotra, Divya Singh, Biju Bhargavan & Man Mohan Singh
Supporting Staff: J.K. Joshi

10. **Patent Appl. No.:** 0524DEL2006 **Filing Date:** 28/02/2006
Title: **A process for the isolation of a standardized antiulcer fraction from the fruits of *Xylocarpus granatum* Koen. and its use as an antiulcer drug**
Inventors: Vijai Lakshmi, Rajesh Kumar, Poonam Gupta, Poonam Dharmani, Gautam Palit & Mahendra Nath Srivastava
Supporting Staff: Hirday Ram Misra, Naveen Prakash Misra & Madhusudan Bhol

11. **Patent Appl. No.:** 0611DEL2006 **Filing Date:** 08/03/2006
Title: **Novel naphtho [1,2-d] oxazole derivatives as agent for treatment or prophylaxis of non insulin dependent diabetes and related metabolic disorders**
Inventors: Pervez Ahmad, Priti Tiwari, Brajendra Kumar Tripathi, Arvind Kumar Srivastava & Atul Kumar
Supporting Staff: Janak Chand Ranjan

12. **Patent Appl. No.:** 0610DEL2006 **Filing Date:** 08/03/2006
Title: **Novel glycosyl ureides useful as inhibitors of NAD^+ DNA ligase from *M. tuberculosis***
Inventors: Rama Pati Tripathi, Neetu Tewari, Sandeep Srivastava & Ravishankar

13. **Patent Appl. No.:** 0609DEL2006 **Filing Date:** 08/03/2006
Title: **Novel glycosyl -D-fructose derivatives as antihyperlipidemic agent**
Inventors: Anup Kumar Misra, Pallavi Tiwari, Anju Puri, Ramesh Chander & Geetika Bhatia
Supporting Staff: Sant Ram & Noor Jehan

14. **Patent Appl. No.:** 0671DEL2006 **Filing Date:** 07/12/2006
Title: **Novel 4-nitrobuatnoates, their acid derivatives and salts thereof**
Inventors: Ranjana Srivastava, Brahm Shanker Srivastava, Manish Kumar Gupta, Rama Pati Tripathi, Neetu Tiwari, Diksha Katiyar & Ravishankar Ramchandran
Supporting Staff: D.K. Tripathi

15. **Patent Appl. No.:** 0842DEL2006 **Filing Date:** 28/03/2006
Title: **Composition and methods of nonionic surfactant based vesicular formulation for improved delivery of cyclosporine**
Inventors: Prabhat Ranjan Mishra, Vure Prasad, Anil Kumar Dwivedi & Satyawan Singh

16. **Patent Appl. No.:** 1803DEL2006 **Filing Date:** 09/08/2006
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, Anil Kumar Dwivedi, Satyawan Singh, Pratima Srivastava, Shio Kumar Singh, Chandishwar Nath & Ram Raghubir
Supporting Staff: Krishna Kumar Chaudhari & Suresh Yadav

17. **Patent Appl. No.:** 1937DEL2006 **Filing Date:** 30/08/2006
Title: **A process for the isolation of standardized antidiarrhoeal fraction and its active compounds from the fruit seed coat of *Xylocarpus granatum* Koen. and its use thereof**
Inventors: Vijai Lakshmi, Ajet Saxena, Satyawan Singh, Raghwendra Pal, Sudhir Srivastava, Mahendra Nath Srivastava & Ram Raghubir
Supporting Staff: Naveen Prakash Misra, Hirday Ram Misra, Suresh Chandra, Tarun Lata, R.R. Gupta & Tika Ram

18. **Patent Appl. No.:** 2158DEL2006 **Filing Date:** 26/09/2006
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 Rastogi, Akhilesh Kumar Srivastava & Kamlesh Singh

19. **Patent Appl. No.:** 2157DEL2006 **Filing Date:** 26/09/2006
Title: **Novel hydroxy functionalized adamantyl substituted 6-arylvinyl-1,2,4-trioxanes and their hemisuccinates, useful as antimalarial agents and a process for the preparation thereof**
Inventors: Chandan Singh, Sunil Kumar Puri & Upasana Sharma
Supporting Staff: Akhilesh Kumar Srivastava, Shashi Rastogi & K.K. Singh

Patents Filed Abroad

1. **US Patent Appl. No.:** 11/210567 DIV **Filing Date:** 24/08/2005
Title: **Herbal medicament for treatment of cerebro-vascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhry

2. **Canadian Patent Appl. No.:** 2524568 **Filing Date:** 02/11/2005
Title: **Mercapto-phenyl-naphthyl methane derivatives and preparation thereof**
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 Keshri

3.	**European 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, other estrogen dependent or independent disorders and for regularity of fertility**		
	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 Keshri		
4.	**Chinese Patent Appl. No.:**	200380110327.4	**Filing Date:**	29/11/2005
	Title:	**Substituted mercapto-phenyl-naphthyl methane derivatives as SERM for the prevention and treatment of osteoporosis, other estrogen dependent or independent disorders and for regularity of fertility**		
	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 Keshri		
5.	**Canadian Patent Appl. No.:**	0559NF2002/CA	**Filing Date:**	17/03/2006
	Title:	**Novel (3R,4R)- trans 3,4-diaryl chroman derivatives useful in fertility regulation and the prevention or treatment of estrogen related diseases or syndromes**		
	Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray & Girish Kumar Jain		
	Supporting Staff:	Vasi Ahmed		
6.	**European Patent Appl. No.:**	03748468.0	**Filing Date:**	24/03/2006
	Title:	**Novel (3R, 4R)- trans 3,4-diaryl chroman derivatives useful in fertility regulation and the prevention or treatment of estrogen related diseases or syndromes**		
	Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray & Girish Kumar Jain		
	Supporting Staff:	Vasi Ahmed		

7.	**Japanese Patent Appl. No.:**	0559NF2002/JP	**Filing Date:**	24/03/2006
	Title:	**Novel (3R,4R)- trans 3,4-diaryl chroman derivatives useful in fertility regulation and the prevention or treatment of estrogen related diseases or syndromes**		
	Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray & Girish Kumar Jain		
	Supporting Staff:	Vasi Ahmed		
8.	**Chinese Patent Appl. No.:**	0559NF2002/CN	**Filing Date:**	24/03/2006
	Title:	**Novel (3R, 4R)- trans 3,4-diaryl chroman derivatives useful in fertility regulation and the prevention or treatment of estrogen related diseases or syndromes**		
	Inventors:	Sangita, Atul Kumar, Man Mohan Singh, Suprabhat Ray & Girish Kumar Jain		
	Supporting Staff:	Vasi Ahmed		
9.	**Indonesian Patent Appl. No.:**	WO200601094	**Filing Date:**	24/04/2006
	Title:	**Biodegradable, inhalable microparticles containing anti tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
10.	**Philippines Patent Appl. No.:**	0365NF2003/PH	**Filing Date:**	24/04/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
11.	**South African Pat.Appl. No.:**	2006/3526	**Filing Date:**	24/04/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
12.	**Brazilian Patent Appl. No.:**	PI03185621	**Filing Date:**	25/04/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		

13.	**Bangladesh Pat. Appl. No.:**	105/2006	**Filing Date:**	27/04/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
14.	**Japanese Patent Appl. No.:**	2005-509828	**Filing Date:**	27/04/2006
	Title:	**Novel herbal composition for the treatment of gastric ulcer**		
	Inventors:	Janswamy Madhusudanan Rao, Upparapalli Sampathkumar, Boggavarapu Subrahmanya Sastry, Jhillu Singh Yadav, Kondapuram Vijaya Raghavan, Gautam Palit, Madhu Dikshit, Deepak Rai, P.M.Varier, T.S. Murleedharan & K Murleedharan		
	Supporting Staff:	Dwarkanath Bhalla, Tarunlata Seth & Mohammed Saleem Ansari		
15.	**Chinese Patent Appl. No.:**	200380110617.9	**Filing Date:**	28/04/2006
	Title:	**Novel herbal composition for the treatment of gastric ulcer**		
	Inventors:	Janswamy Madhusudanan Rao, Upparapalli Sampathkumar, Boggavarapu Subrahmanya Sastry, Jhillu Singh Yadav, Kondapuram Vijaya Raghvan, Gautam Palit, Madhu Dikshit, Deepak Rai, P.M.Varier, T.S. Murleedharan & K Murleedharan		
	Supporting Staff:	Dwarkanath Bhalla, Tarunlata Seth & Mohammed Saleem Ansari		
16.	**Chinese Patent Appl. No.:**	200380110723.7	**Filing Date:**	19/05/2006
	Title:	**α-Substituted naphthyloxy-ω-substituted alkyl/aryl amino-substituted alkane derivatives as agents for the treatment or prophylaxis of diabetes and related metabolic disorders**		
	Inventors:	Devdutt Chaturvedi, Atul Kumar, Reema Rastogi, Arvind Srivastava, Priti Tiwari, Rehan Ahmed, Ramesh Chander, Anju Puri, Geetika Bhatia, Farhan Rizvi, Anil Kumar Rastogi & Suprabhat Ray		
	Supporting Staff:	Vasi Ahmed, Ashok Kumar Khanna & Suresh Yadav		
17.	**Russian Federation Patent Appl. No.:**	200600801	**Filing Date:**	19/05/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		

18.	**Eurasia Patent Appl. No.:**	2006008001	**Filing Date:**	19/05/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
19.	**Viet Nam Patent Appl. No.:**	1-2006-00797	**Filing Date:**	22/05/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
20.	**Chinese Patent Appl. No.:**	200380110741.5	**Filing Date:**	25/05/2006
	Title:	**Biodegradable, inhalable microparticles containing anti-tubercular drugs**		
	Inventors:	Himadri Sen, Suryakumar Jayanthi, Rakesh Sinha, Rolee Sharma & Pavan Muttil		
21.	**European Patent Appl. No.:**	03769719.0	**Filing Date:**	26/05/2006
	Title:	**Novel herbal composition for the treatment of gastric ulcer**		
	Inventors:	Janswamy Madhusudanan Rao, Upparapalli Sampathkumar, Boggavarapu Subrahmanya Sastry, Jhillu Singh Yadav, Kondapuram Vijaya Raghavan, Gautam Palit, Madhu Dikshit, Deepak Rai, P.M.Varier, T.S. Murleedharan & K Murleedharan		
	Supporting Staff:	Dwarkanath Bhalla, Tarunlata Seth & Mohammed Saleem Ansari		
22.	**European Patent Appl. No.:**	03818933.8-2103	**Filing Date:**	31/05/2006
	Title:	**α-Substituted naphthyloxy-ω-substituted alkyl/aryl amino-substituted alkane derivatives as agents for the treatment or prophylaxis of diabetes and related metabolic disorders**		
	Inventors:	Devdutt Chaturvedi, Atul Kumar, Reema Rastogi, Arvind Srivastava, Priti Tiwari, Rehan Ahmed, Ramesh Chander, Anju Puri, Geetika Bhatia, Farhan Rizvi, Anil Kumar Rastogi & Suprabhat Ray		
	Supporting Staff:	Vasi Ahmed, Ashok Kumar Khanna & Suresh Yadav		

23.	**Sri Lanka Patent Appl. No.:**	14131	**Filing Date:**	20/06/2006	
	Title:	**Improved process for isolation of *bisvittoside D* from sea cucumber**			
	Inventors:	Vijai Lakshmi, Ajet Saxena, Kartikay Pandey, Kunnath Padmanabhan Madhusudanan, Deepak Raina, Mahendra Nath Srivastava, Zafar Kamal Khan, Pooja Jain, Gopal Gupta & Janak Dulari Dhar			
	Supporting Staff:	J.P. Maikhuri			
24.	**Sri Lanka Patent Appl. No.:**	14128	**Filing Date:**	20/06/2006	
	Title:	**Process for isolation of saponin disogenin penta glicoside**			
	Inventors:	Vijai Lakshmi, Kartikay Pandey, Raja Roy, Bhawani Shankar Joshi, Kunnath Padmanabhan Madhusudanan, Ramesh Chandra, Arvind Kumar Srivastava, Deepak Raina & Anil Kumar Rastogi			
25.	**PCT Patent Appl. No.:**	PCT/IB06/01897	**Filing Date:**	10/07/2006	
	Title:	**Novel spiro 1,2,4 trioxanes as antimalarial agents and a process for the preparation thereof**			
	Inventors:	Chandan Singh, Heetika Malik & Sunil Kumar Puri			
	Supporting Staff:	Shashi Rastogi, Akhilesh K. Srivastava & Kamelesh K. Singh			
26.	**British Patent Appl. No.:**	0614760.7	**Filing Date:**	25/07/2006	
	Title:	**Novel N-aryloxypropanolyl-N^1-phenethyl-urea**			
	Inventors:	Kalpana Bhandari, Shipra Srivastava & Chandeshwar Nath			
	Supporting Staff:	Anoop Kumar Srivastava, Ram Pati Maurya & Vishwabhar Nath			
27.	**US Patent Appl. No.:**	0151NF2005/US	**Filing Date:**	01/09/2006	
	Title:	**Novel spiro 1,2,4 trioxanes as antimalarial agents and a process for the preparation thereof**			
	Inventors:	Chandan Singh, Heetika Malik & Sunil Kumar Puri			
	Supporting Staff:	Shashi Rastogi, Akhilesh K. Srivastava & Kamelesh K. Singh			
28.	**PCT Patent Appl. No.:**	PCT/IB06/02462	**Filing Date:**	07/09/2006	
	Title:	**A process for the isolation of an antidiabetic and antihyperlipidimic fraction from the fruits of *Xylocarpus granatum*, a mangrove plant**			
	Inventors:	Vijai Lakshmi, Ajet Saxena, Rajesh Kumar, Raghwendra Pal, Satyawan Singh, Arvind Kumar Srivastava, Preeti Tiwari, Deepak Raina, Anil Kumar Rastogi, Sudhir Srivastava, Mahendra Nath Srivastava, Ramesh Chandra, Anju Puri, Ram Raghubir, Poonam Gupta, Narender Tadigoppula Brijendra Kumar Tripathi			
	Supporting Staff:	Hriday Ram Mishra, Naveen Prakash Mishra, Mukesh Srivastava, Suresh Chandra Tripathi, Teeka Ram, R.R. Gupta, Ganesh S. Sonker, Raja Krishna Purshottam, Ganga Ram Bhatt, Suresh Yadav & Subhash Chandra Tripathi			

29. **US Patent Appl. No.:** 11/09/2006 **Filing Date:** 11/09/2006
Title: **A process for the isolation of an antidiabetic and antihyperlipidimic fraction from the fruits of *Xylocarpus granatum*, a mangrove plant**
Inventors: Vijai Lakshmi, Ajet Saxena, Rajesh Kumar, Raghwendra Pal, Satyawan Singh, Arvind Kumar Srivastava, Preeti Tiwari, Deepak Raina, Anil Kumar Rastogi, Sudhir Srivastava, Mahendra Nath Srivastava, Ramesh Chandra, Anju Puri, Ram Raghubir, Poonam Gupta, Narender Tadigoppula & Brijendra Kumar Tripathi
Supporting Staff: Hriday Ram Mishra, Naveen Prakash Mishra, Mukesh Srivastava, Suresh Chandra Tripathi, Teeka Ram, R.R. Gupta, Ganesh S. Sonker, Raja Krishna Purshottam, Ganga Ram Bhatt, Suresh Yadav & Subhash Chandra Tripathi

30. **US Patent Appl. No.:** 10806078 **Filing Date:** 22/03/2004
Title: **Isolation of bivittoside-D from sea cucumber and activity thereof**
Inventors: Vijai Lakshmi, Ajet Saxena, Kartikay Pandey, Kunnath Padmanabhan Madhusudanan, Mahendra Nath Srivastava, Zafar Kamal Khan, Pooja Jain, Gopal Gupta & Janak Dulari Dhar
Supporting Staff: J.P. Maikhuri

31. **PCT Patent Appl. No.:** PCT/IN03/000456 **Filing Date:** 31/12/2003
Title: **Isolation of bivittoside-D from sea cucumber and activity thereof**
Inventors: Vijai Lakshmi, Ajet Saxena, Kartikay Pandey, Kunnath Padmanabhan Madhusudanan, Mahendra Nath Srivastava, Zafar Kamal Khan, Pooja Jain, Gopal Gupta & Janak Dulari Dhar
Supporting Staff: J.P. Maikhuri

Patents Granted In India

1.	**Patent No.:**	193304	**Grant Date:**	16/12/2005
	Patent Appl. No.:	2302DEL1995	**Filing Date:**	13/12/1995
	Title:	**Use of pregnane compound as hypolipidemic drug**		
	Inventors:	Ram Pratap , Ram Chandra Gupta , Narendra Kumar Kapoor, Ramesh Chander, Ashok Kumar Khanna, Asheem Ghatak, Omkar Prasad Asthana, Swarn Nityanand, Sukh Dev & Nitya Nand		
2.	**Patent No.:**	193544	**Grant Date:**	13/01/2006
	Patent Appl. No.:	1207DEL2001	**Filing Date:**	29/11/2001
	Title:	**A process for the preparation of novel combinational library of 3 and 30-substituted lup-20(29)-ene useful as antimalarial agents**		
	Inventors:	Misbah Alam Farooq Biabani, Thangathirupathi Srinivasan, Sunil Kumar Puri, Kanwal Raj & Bijoy Kundu Anil Kumar Srivastava		
3.	**Patent No.:**	192965	**Grant Date:**	20/01/2006
	Patent Appl. No.:	0898DEL2000	**Filing Date:**	06/10/2000
	Title:	**An improved process for the preparation of 2-pyridyl -2,8-bis-(trifluromethyl)-4-quinolyl ketone**		
	Inventor:	Devi Prasad Sahu		
4.	**Patent No.:**	192963	**Grant Date:**	20/01/2006
	Patent Appl. No.:	1303DEL2001	**Filing Date:**	31/12/2001
	Title:	**Substituted 1,2,4-trioxanes useful as antimalarial agents and a process for the preparation thereof**		
	Inventors:	Chandan Singh, Pallavi Tiwari & Sunil Kumar Puri		
	Supporting Staff:	Shashi Rastogi & Akhilesh Kumar Srivastava		
5.	**Patent No.:**	194227	**Grant Date:**	20/01/2006
	Patent Appl. No.:	3157DEL1998	**Filing Date:**	28/10/1998
	Title:	**A process for the preparation of a novel device useful for the delivery of physiologically active substances or nutrients**		
	Inventors:	Satyawan Singh, Madhu Khanna & Anil Kumar Dwivedi		
6.	**Patent No.:**	194984	**Grant Date:**	17/03/2006
	Patent Appl. No.:	1272DEL2001	**Filing Date:**	24/12/2001
	Title:	**A process for the preparation of novel combinational library of 3-substituted amino-3-glycosylated propanoate useful as antifungal and antibacterial agents**		
	Inventors:	Rama Pati Tripathi, Bijoy Kundu, Praveen Kumar Shukla, Sudhir Sinha, Ranjana Srivastava, Kishore Kumar Srivastava, Vinita Chaturvedi, Anil Srivastava & Brahm Shankar Srivastava		
	Supporting Staff:	Vinod Kumar Maurya		

7.	**Patent No.:**	195684	**Grant Date:**	21/04/2006
	Patent Appl. No.:	0162DEL2002	**Filing Date:**	28/02/2002
	Title:	**An improved process for preparation of penta-substituted pyridines**		
	Inventors:	Devi Prasad Sahu, Hiralal Sharma & Abdul Haq Ansari		
8.	**Patent No.:**	195817	**Grant Date:**	21/04/2006
	Patent Appl. No.:	1227DEL2002	**Filing Date:**	09/12/2002
	Title:	**A process for the preparation of chiral centpropazine**		
	Inventors:	Devi Prasad Sahu, Sri Nivas Rastogi, Kamlesh Chandra Agarwal & Ram Raghubir		
9.	**Patent No.:**	195824	**Grant Date:**	21/04/2006
	Patent Appl. No.:	0297DEL2002	**Filing Date:**	26/03/2002
	Title:	**Novel substituted-1,2,4-trioxanes, useful as antimalarial agents**		
	Inventors:	Chandan Singh, Pallvi Tiwari & Sunil Kumar Puri		
10.	**Patent No.:**	196956	**Grant Date:**	23/06/2006
	Patent Appl. No.:	1274DEL2001	**Filing Date:**	24/12/2001
	Title:	**A novel combinational library of 3-substituted amino-3-glycosylated propanamides useful as antifungal and antibacterial agents**		
	Inventors:	Rama Pati Tripathi, Praveen Kumar Shukla, Sudhir Sinha, Ranjana Srivastava, Kishore Kumar Srivastava, Vinita Chaturvedi, Anil Srivastava & Brahm Shankar Srivastava		
	Supporting Staff:	Vinod Kumar Maurya		
11.	**Patent No.:**	196914	**Grant Date:**	04/08/2006
	Patent Appl. No.:	1226DEL2002	**Filing Date:**	09/12/2002
	Title:	**A process for resolution of R-and S-centpropazine**		
	Inventors:	Devi Prasad Sahu, Sri Nivas Rastogi & Kamlesh Chandra Agarwal		
12.	**Patent No.:**	199556	**Grant Date:**	06/10/2006
	Patent Appl. No.:	0264DEL2002	**Filing Date:**	20/03/2002
	Title:	**A process for the preparation of novel combinational library of N^1-glycosylated and N^3- substituted ureas and thioureas**		
	Inventors:	Rama Pati Tripathi, Vinod Kumar Tiwari, Neetu Tiwari, Ranjana Srivastava, Anil Srivastava, Vinita Chaturvedi, Kishore Kumar Srivastava, Sudhir Sinha & Brahm Shankar Srivastava		
	Supporting Staff:	Vinod Kumar Maurya		

Patents Granted Abroad

1.	**Lithuania Pat. No.:**	5284	**Grant Date:**	25/11/2005
	Patent Appl. No.:	2004-060	**Filing Date:**	02/07/2004
	Title:	**Herbal medicament for treatment of cerebro-vascular disorders**		
	Inventors:	Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna		
	Supporting Staff:	Jharna Arun & Madhuri Chaudhry		
2.	**South African Pat. No:**	2004/4648	**Grant Date:**	30/11/2005
	Patent Appl. No.:	2004/4648	**Filing Date:**	11/06/2004
	Title:	**Herbal medicament for treatment of cerebro-vascular disorders**		
	Inventors:	Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna		
	Supporting Staff:	Jharna Arun & Madhuri Chaudhry		
3.	**European Pat. No.:**	1224938	**Grant Date:**	14/12/2005
	Patent Appl. No.:	01300257.1	**Filing Date:**	12/01/2001
	Title:	**Novel uses of gugulipid: as cognition enhancer, anti-hyperglycemic and for dermal conditions**		
	Inventors:	Ram Pratap, Raghvandra Pal, Satyawan Singh, Girja Shankar, Kapil Kapoor, Chandishwar Nath, Hemant Kumar Singh, Deepak Raina, Arvind Kumar Srivastava, Anil Kumar Rastogi, P.S.R. Murthy, Sudhir Srivastava, Onkar Prasad Asthana, Narendra Singh & Nitya Nand		
4.	**ARIPO Pat. No.:**	AP1546	**Grant Date:**	13/01/2006
	Patent Appl. No.:	AP/P/2003/02772	**Filing Date:**	28/03/2003
	title:	**Novel 6-[(cycloalkylphenyl) vinyl] -1,2,4-trioxanes useful as antimalarial agents**		
	Inventors:	Chandan Singh, Pallavi Tiwari & Sunil Kumar Puri		
	Supporting Staff:	Shashi Rastogi & Akhilesh Kumar Srivastava		
5.	**US Pat. No.:**	6991814	**Grant Date:**	31/01/2006
	Patent Appl. No.:	10/319373	**Filing Date:**	13/12/2002
	Title:	**Herbal medicament for treatment of cerebro-vascular disorders**		
	Inventors:	Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna		
	Supporting Staff:	Jharna Arun & Madhuri Chaudhry		
6.	**Latvia Pat. No.:**	13250	**Grant Date:**	20/02/2006
	Patent Appl. No.:	P-04-78	**Filing Date:**	13/07/2004
	Title:	**Herbal medicament for treatment of cerebro-vascular disorders**		
	Inventors:	Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna		
	Supporting Staff:	Jharna Arun & Madhuri Chaudhry		

7.	**Israel Pat. No.:**	126852	**Grant Date:**	06/05/2006
	Patent Appl. No.:	126852	**Filing Date:**	02/11/1998
	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		
8.	**Eurasian Pat. No.:**	007067	**Grant Date:**	30/06/2006
	Patent Appl. No.:	200400807	**Filing Date:**	13/07/2004
	Title:	**Herbal medicament for treatment of cerebro-vascular disorders**		
	Inventors:	Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna		
	Supporting Staff:	Jharna Arun & Madhuri Chaudhry		
9.	**US Pat. No.:**	7071226	**Grant Date:**	04/07/2006
	Patent Appl. No.:	11/023905	**Filing Date:**	28/12/2004
	Title:	**Amino functionalized 1,2,4-trioxanes useful as antimalarial agents and process for preparation thereof**		
	Inventors:	Chandan Singh, Heetika Malik & Sunil Kumar Puri		
	Supporting Staff:	Shashi Rastogi, Akhilesh K. Srivastava & Kamelesh K. Singh		
10.	**German Pat. No.:**	0913397	**Grant Date:**	05/07/2006
	Patent Appl. No.:	97308381.9	**Filing Date:**	22/10/1997
	Title:	**A process for the synthesis of 1-(4-arylpiperazine-1-yl) -3-(2-oxopyrrolidin-1-yl) propanes**		
	Inventors:	Neelima Sinha, Sanjay Jain, Anil Kumar Saxena, Nitya Anand, Ram Mohan Saxena, Mangal Prasad Dubey & Gyanendra Kumar Patnaik		
11.	**US Pat. No.:**	7081465	**Grant Date:**	25/07/2006
	Patent Appl. No.:	10/693098	**Filing Date:**	27/10/2003
	Title:	**α-Substituted naphthyloxy-ω-substituted alkyl/aryl amino-substituted alkane derivatives as agents for the treatment or prophylaxis of diabetes and related metabolic disorders**		
	Inventors:	Devdutt Chaturvedi, Atul Kumar, Reema Rastogi, Arvind Srivastava, Priti Tiwari, Rehan Ahmed, Ramesh Chander, Anju Puri, Geetika Bhatia, Farhan Rizvi, Anil Kumar Rastogi & Suprabhat Ray		
	Supporting Staff:	Vasi Ahmed, Ashok Kumar Khanna & Suresh Yadav		
12.	**European Pat. No.:**	945462	**Grant Date:**	02/08/2006
	Patent Appl. No.:	98302287.2	**Filing Date:**	25/03/1998
	Title:	***Mycobacterium tuberculosis* specific DNA fragment (probe)**		
	Inventors:	Ranjana Srivastava, Deepak Kumar & Brahm Shanker Srivastava		
13.	**US Pat. No.:**	7160866	**Grant Date:**	09/01/2007
	Patent Appl. No.:	10806065	**Filing Date:**	22/03/2004
	Title:	**Isolation of tigogenin pentaglycoside from *Chlorophytum nimonii***		
	Inventors:	Vijai Lakshmi, Kartikay Pandey, Raja Roy, Bhawani Shankar Joshi, Kunnath Padmanabhan Madhusudanan, Ramesh Chander, Arvind Kumar Srivastava, Deepak Raina & Anil Kumar Rastogi		

IV. Papers Presented In Conferences

2005

Annual Conference of Indian Society of Hypertension ISHCON 2005, New Delhi (12-13 November)

A study of plasma homocysteine levels in ischemic strokes. A. Ghatak, L.K. Jha, C.G. Agarwal, A.K. Vaish, A. Agarwal, S. Mehrotra, A. K. Srivastava & M. Chandra.

2006

58th Indian Pharmaceutical Congress, Mumbai (1-7 Jaunary)

QSAR studies on benzoylaminobenzoic acid derivatives as inhibitors of β–ketoacyl-acyl carrier protein synthesis III. S. Singh, K.L. Soni, M.K. Gupta, Y.S. Prabhakar & S.G. Kaskhedikar.

International Symposium on Organic Chemistry – Today and Tomorrow, Bangalore (4-7 January)

New synthetic strategy for preparing naturally occurring and biologically relevant oxygen heterocycles. M. Dixit & A. Goel.

Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry & Chemical Biology (CSIR-ACS-OCCB-2006), Pune (6-9 January)

3D QSAR analysis of cis –tetra- & hexa-hydropthalazinones as PBE-4 inhibitiors. A. Dixit & A.K. Saxena.

Amino steroids as antimalarial agents. U. Sharma, S.K. Puri & C. Singh.

Aminopyridazine derivatives as acetylcholinesterase inhibitors – An assessment with multi-model QSAR studies. M.K. Gupta, Y.S. Prabhakar & W. Sippl.

Functionally congested bi-aryls and tetra-aryls through carbanion-induced ring transformation of 2-pyranones. F.V. Singh & A. Goel.

Insights into the hydrogenolysis of 3-(2-nitrophenyl)- isoxazoles and 3-(nitro substituted pheny1)-2-isoxazolines. V. Singh & S. Batra.

Novel orally active C-10α ester analogues of dihydroartemisinin as antimalarials. S. Chaudhary, S.K. Puri & C. Singh.

Synthesis of 1,2,4-trioxepanes via photo-oxygenation of homoallylic alcohols. S. Pandey, N. Srivastava, M. Sharma & C. Singh.

Synthetic utility of allylamines for the synthesis of nitrogen containing heterocycles. R. Pathak & S. Batra.

Topological and topographical descriptors in modeling the non steroidal estrogen receptor ligands. Y.S. Prabhakar, M.K. Gupta & W. Sippl.

Indo-Italian Workshop on Chemistry & Biology of Antioxidants, New Delhi (8-9 January)

Mycobacterium tuberculosis NAD+ - dependent ligase is selectively inhibited by glycosylamines as compared to human DNA ligase. N. Tiwari, N. Dwivedi, R.P. Tripathi, Sandeep, Divya & R. Ravishankar.

An attempt towards the synthesis of novel glycosides phenolics: Development of new chemotherapeutics. N. Saxena.

National Conference on Immunology in Health and Disease, Chhatrapati Sahuji Maharaj University, Kanpur (12-13 January)

Diagnosis of Human Filariasis. S. Bhattacharya.

Joint Annual Meeting of International Society of Heart Research & International Academy of Cardiovascular Sciences, Chennai (12-14 January)

Drug induced QT interval prolongation: A potential threat to new drug discovery programme. K.G. Raghu.

29th All India Cell Biology Conference and Symposium on Gene to Genome: Environment and Chemical Interaction, Lucknow (17-20 January)

A recombinant mycobacterial strain sensing the disruption of FASII elongation pathways as a rational based drug screen system. N. Gupta & B.N. Singh.

Induction of apoptosis in MCF-7 and MDA MB-231 human breast cancer cells by antiestrogens centchroman. M. Nigam, V. Ranjan, S. Srivastava, R. Sharma & A.K. Balapure.

Mechanism of molecular iodine induced cell death in breast carcinoma cells. A. Srivastava, M. Tiwari, R.A. Sinha, A. Kumar, A.K. Balapure, V.K. Bajpai, R. Sharma, K. Mitra & M. M. Godbole.

Signature profile of differentially expressed genes in mice liver following acute exposure to carbon tetrachloride. S. Noel, S. Sharma & S. K. Rath.

Single nucleotide polymorphism (SNP) analysis of gene 2′3′-cyclic nucleotide 3′-phosphodiesterase (CNP) in representative human sub population of India. A.K. Mitra, A. Singh & S.K. Rath.

Single nucleotide polymorphism (SNP) analysis of gene C10ORF2 (PEO1) in representative human sub-population of India. A. Singh, A.K. Mitra & S. K. Rath.

10th ISMAS Triennial International Symposium on Mass Spectrometry, Munnar (28 January-1 February)

Tandem mass spectra of ammonium ion, metal ion and ligated metal ion adducts of thioglycosides, glycosyl sulfoxides and glycosyl sulfones. B. Kumar, S. Kanojiya, G. Agnihotri, A.K. Misra & K.P. Madhusudanan.

Effect of metal cationization on substituted deoxysugars by electrospray ionization tandem mass spectrometry. S. Kanojiya, B. Kumar, R. Sagar, Mohd. Saquib, A. K. Shaw & K.P. Madhusudanan.

2nd International Symposium on Drug Discovery and Process Research, Belgaum (10-12 February)

Chimeric 4-aminoquinolines as antimalarial agents. V.R. Solomon, W. Haq, S.K. Puri, K. Srivastava & S.B. Katti.

Synthesis and antibacterial properties of thiazolidinone tethered erythromycins. D. Pandey, S.B. Katti, W. Haq & C.K.M. Tripathi.

Current Trends in Drug Discovery Research Conference, Lucknow (17-21 February)

The relative contribution of apoptosis in exaggerating brain damage in diabetic stroke. S. L. Mehta & R. Raghubir.

3rd Hands on Training Workshop on Methods in Gene Analysis from Molecular Cloning to Bioinformatics, Gwalior (20 February-11 March)

Genomics driven approach to design a model antimycobacterial screen system that senses the mechanism disruption of FAS-II elongation pathway. N. Gupta & B.N. Singh.

International Congress on Gamete Biology: Emerging Frontiers in Fertility and Contraceptive Development, New Delhi (22-25 February)

A novel, non- detergent, potent spermicide with low toxicity to normal vaginal flora (*Lactobacillus*) and human cervical (HeLa) cells *in vitro*: promising replacement for N-9. R.K. Jain, V.L. Sharma & G. Gupta.

Symposium on Frontiers in Reproduction: Concepts and Applications in Genomic Era & 16th Annual Meeting of the Indian Society for the Study of Reproduction and Fertility, Karnal (23-25 February)

Effect of ormeloxifene on ER expression during pre-implantation period in rat endometrium. C.S. Blesson, G. Kharkwal, A. Daverey & A. Dwivedi.

Involvement of αvβ3 integrin during implantation in rat. K.R. Srinivasan, S. Kitchlu, S.K. Jain, P.K. Mehrotra & A. Dwivedi.

10th International Conference of ISCB on Drug Discovery Perspectives and Challenges, Lucknow (24-26 February)

1-Aryloxy-2-substituted aminomethyltetra-hydronaphthalenes as selective and potent appetite suppressants. S. Srivastava, G. Shankar & C. Nath.

A multicomponent reaction : Efficiently furnishing phenylmethylene-2-thiohydantoin with some unusual consequences. S. Porwal, R. Kumar, P.R. Maulik & P.M.S. Chauhan.

A semi parametric approach to outlier detection in NMR data of metabolites. M. Srivastava, M. Abbas, R. Roy & A. Pandey.

Design, synthesis and biological evaluation of peptidomimetic inhibitions of protein tyrosine phosphatase-1β. A. Sharma, W. Haq, A.K. Srivastava & S.B. Katti

Dipeptide linked loganin as an immunostimulant. A. Bhardwaj, R. Sahu, U. Singh, W. Haq, K. Raj, Anju Puri & L.M. Tripathi.

Effect of centchroman co-administration on pharmacokinetics of metformin, an anti-diabetic agent. J. Lal & G.K. Jain.

Enhanced dose dependent lipolytic activity of WY14643 in dyslipidemic diabetic hamster. G. Bhatia, A. Puri, R. Chander, A. K. Khanna, J. K. Saxena, R. Pal & A.K. Saxena.

Facile synthesis of pyrazolo[3,4-d]pyrimidine and pyrimido [4,5-d]pyrimidin-4-one derivatives. R. Kumar, S.B. Katiyar, A. Kumar & P.M.S. Chauhan.

Immunomodulatory activity of loganin based dipeptide. A. Bhardwaj, R. Sahu, U. Singh, W. Haq, K. Raj, Anju Puri & L.M. Tripathi.

In vitro cultivation of *Plasmodium falciparum* in modified media with various sera supplements. K. Srivastava, S. Singh, P.Singh & S. K. Puri.

In vitro cultivation of *Plasmodium falciparum*: Studies with modified media supplemented with albumax and hypoxanthine. S. Singh, P. Singh, S.K. Puri & K. Srivastava.

Lipid lowering activity of *Anthocephalus indicus* (Kadam). A.K. Khanna, V. Kumar, M. M. Khan, R. Chander, K. Jawed, J. K. Saxena & R. K. Singh.

Pharmacokinetic studies on CDRI 85/92 (an antiulcer pharmacophore) and its ester form as pro-drug. P. Srivastava & J. Lal.

Role of glutathione redox system in resistance to antimalarial drug arteether. R. Chandra, L. M. Tripathi, J. K. Saxena & S. K. Puri.

Saponins: Potential as contraceptive microbiocide. P. Tiwari, D. Singh, K. Mitra & M.M. Singh.

Synthesis and antileishmanial profile of some novel terpenyl pyrimidone derivatives. S. Pandey, S.N. Suryavanshi & S. Gupta.

Synthesis and antileishmanial profile of some novel pyridyl/ dipyridoyl alkanes. S. Pandey, M. Verma, Ramesh, Nishi, S.N. Suryavanshi & S. Gupta.

Synthesis and biological evaluation of coscinamide and synthetic analogues. L. Gupta, A. Talwar & P.M.S. Chauhan.

Synthesis of 2-[3,5-substituted pyrazol-1-yl]-4,6-trisubstituted triazine derivatives as antimalarial agents. N. Sundru, S.B. Katiyar, K. Srivastava, S.K. Puri, & P.M.S. Chauhan.

Synthesis of 4-amino-3-cyanopyrimidine derivatives as antiparasitic agents. A. Kumar & P.M.S. Chauhan.

Annual Conference of ISHG on Human Genomics & Public Health, New Delhi (27 February- 1 March)

Polymorphisms in the transcriptional regulatory region of TNF – α in Indian subpopulations. S. Sinha, S. Mishra & S. Habib.

Proceedings of 8th FIMSA/IIS Advanced Immunology Course, New Delhi (1-5 March)

Prophylactic potential of culture-derived secreted and excreted soluble exogenous antigens from recent field isolate of *Leishmania donovani* infected hamsters. A. Kumar & A. Dube.

International Conference on Molecules to Materials-2006, Longowal, Punjab (4-5 March)

Synthesis of glycosyl heteocycles as potential chemotherapeutic agents. V.K. Tiwari & R.P. Tripathi.

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

A general framework for the analysis of NMR data in biotechnology. M. Srivastava, M. Abbas & R. Roy.

Techniques and tools for biochemical kinetics simulation. M. Abbas, M. Srivastava & R.K. Sharma.

National Symposium on Designing the Molecular World Through Chemistry, Varanasi (22-24 March)

Development of glycosyl mercaptans as new class of antitubercular agents. V.K. Tiwari & R.P. Tripathi.

DBU assisted aldol type reaction and elimination: an expeditious synthesis of glycosyl 1,3-dienes via glycosylated β–hydroxy esters. S.S. Verma, N. Dwivedi, B.K. Singh & R.P. Tripathi.

L-Ascorbic Acid in organic synthesis: DBU-catalysed one-pot synthesis of tetramic acid derivatives from 5,6-O-isopropylidene ascorbic acid. B.K. Singh, N. Dwivedi, S.S. Verma & R.P. Tripathi.

14th International Society for Magnetic Resonance in Medicine Meeting, Washington USA (6-12 May)

A quantitative study of various metabolites in breast tumors by *in-vitro:* Proton MR

spectroscopy and its statistical evaluation. A. Pandey, P. Ramakant, S. Kumar, A. Srivastava, M. Srivastava & R. Roy.

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

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

Conference on Drug Development for the Third World, International Centre for Theoretical Physics, Italy (5-9 June)

Molecular docking and 3D-QSAR studies on 4- thiazolidinones as HIV-1 RT inhibitors. M. I. Siddiqi, R.K. Rawat, A. Kumar & S.B. Katti.

International Seminar on Present Trends and Future Prospects of Angiosperm Systematics and XVI Annual Conference of IAAT, Pune (4-6 October)

Some new additions to the flora of Tamil Nadu, India. S.M. Rajendran & S.C. Agarwal.

Workshop on Pharmaceutical and Biotech Product Development & Clinical Research, New Delhi (26-28 October)

The need for a world class regulatory environment in India. O.P. Asthana.

INDO-US Conference on New Bioactive Molecules in Pharmaceutical Research, Hyderabad (13-14 November)

One pot synthesis of bioactive isoflavones. H. Singh & Ram Pratap.

A facile synthesis of Homoflavones. J. Gupta & Ram Pratap.

18th National Congress of Parasitology, Kolkata (22-24 November)

Bangla mahoba – The immunomodulatory activity of the crude extract and its various fractions in mice. M. Singh, R. Sahoo, A. Dangi, S. Tewari, N. Kumar & S. Bhattacharya.

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

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

Therapeutic efficacy of crude extract and fractions of *Tinospora sinensis* Merr against *Leishmania donovani*. N. Singh, P. Gupta, K. Samant, A. Kumar, R. Maurya & A. Dube.

Unraveling drug resistance mechanisms in *Leishmania donovani* clinical isolates. N. Singh.

33rd Annual Conference of Association of Clinical Biochemists of India, Pune (23-26 November)

Lipid lowering and anti-oxidant activity of *Anthocephalus indicus* (Kadam) in hyperlipidemic rats. V. Kumar, A.K. Khanna, M. M. Khan, S. Singh, R. Chander, F. Mahdi, J. K. Saxena & R. K. Singh.

20th Carbohydrate Conference, Lucknow (24-26 November)

Synthesis of glycosyl amino esters as possible inhibitors of DNA-topoismerase4 II. A.K. Srivastava & R.P. Tripathi.

Synthesis of glyophenolics as inhibitors of glycosidase. N. Saxena & R.P. Tripathi.

32nd Annual Conference of Indian Immunology Society, Chandigarh, (24-27 November)

Monoclonal antibodies against merozoite surface protein 1 of *Plasmodium vivax*. D.C. Kaushal & N.A. Kaushal.

Molecular characterization of acetylcholin-esterase from filarial parasites. N.A. Kaushal, S.K. Singh & D.C. Kaushal.

21st Symposium on Recent Development in Carbohydrate Chemistry, New Delhi (26-29 November)

Synthesis and antitubercular activity of novel purine derivatives of 2,3-di-O-alkyl-6-deoxy-L-ascorbic acid and 4,5-didehydro-5, 6-dideoxy-L-ascorbic acid. N. Dwivedi & R.P. Tripathi.

Synthesis of oligosaccharides containing galactofuranose. A.K. Misra.

Synthesis of oligaosaccharides: Methodology development, total synthesis and applications. B. Mukhopadhyay, S. Dasgupta, B. Roy, V.K. Rajput & A.D. Roy.

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

Activation and phosphorylation of macrophage specific protein kinase C by pathogenic and non-pathogenic mycobacteria. S.K. Chaurasia & K.K. Srivastava.

Expression and regulation of rpf genes in mycobacteria. A. Yadav, B.S. Srivastava & R. Srivastava.

Identification of macrophage specific mycobacterium tuberculosis genes by green fluorescent protein and kanamycin resistance selection. V. Srivastava, C. Rouanet, R. Srivastava, B. Ramalingam, C. Locht & B.S. Srivastava.

Identification of *Mycobacterium tuberculosis* genes expressed in anaerobic viable non-replicating persistent state. A. Saxena, B.S. Srivastava & R. Srivastava.

Mechanism of isoniazide resistance in *Mycobacterium aurum*. A. Goel & R. Srivastava.

Phylogenetic coservation and expression analysis of sigma factor F in fast growing mycobacterial species. A.K. Singh, R.K. Biswas & B.N. Singh.

EMBO Workshop on Human Evolution and Disease, Hyderabad (5-7 December)

Association of Cyp1A1 polymorphisms with breast cancer: A case control study. N. Singh, A.K. Mitra, V.K. Garg, A. Agarwal, M. Sharma, R. Chaturvedi & S.K. Rath.

Society for Biological Chemists, New Delhi (9-11 December)

Proteomic approach for identification and characterization of novel immunostimulatory proteins from soluble antigens of *Leishmania donovani* promastigotes. S.K. Gupta, B.S. Sisodia, S. Sinha, K. Hajela, S. Naik, A. K. Shasany & A. Dube.

NBRC Conference, New Delhi (13-15 December)

Modulation of calcineurin (PP2B) following I/R injury. A. Gusain, N.V. Prasuja, I.K. Patro & R. Raghubir.

Cerebral ischemia/reperfusion induced ER stress leading to activation and translocation of caspase-12. N.V. Prasuja, A. Gusain & R. Raghubir.

Temporal progression of cellular damage in cerebral ischemia/reperfusion injury. N. Manhas & R. Raghubir.

2nd International Conference of Heterocyclic Chemistry, Jaipur (16-19 December)

Design and synthesis of peptidomimetic inhibitors of protein tyrosine phosphatase-1b (ptp-1b) for the development of anti-diabetic agents. A. Sharma, W. Haq, A. Srivastava, A.K. Tamarkar & S.B. Katti.

Design and synthesis of dpp-iv inhibitors as anti-diabetic agents. N. Sethi, W. Haq & S.B. Katti.

Design and synthesis of a new class of thiazolidine-4-ones as PPAR-γ agonists. S. Raza, W. Haq & S.B. Katti.

EMBO International Workshop on Developmental Mechanisms and Disease Models, Kanpur (16-20 December)

Identification of a protein interacting with a replication initiation site of the apicoplast genome of *Plasmodium falciparum*. A. Kumar & S. Habib.

24th Annual Conference on Indian Academy of Neurosciences, Lucknow (18-20 December)

Calcineurin seems to modulate apoptosis during cerebral ischemia/reperfusion in rats. A. Gusain, N.V. Prasuja, I.K. Patro & R. Raghubir.

Focal cerebral ischemia-induced altered expression of neurotrophins and their receptors. R. Sharma & R. Raghubir.

Altered expression of hsp70 and bax/bc12 proteins in cerebral ischemia-reperfusion injury. N. Manhas & R. Rghubir.

39th Annual Conferece of the Indian Pharmacological Society, Jaipur(21-23 December)

The NFk-B inhibitor PDTC may increase post-ischemic blood brain barrier damage. A. Desai, N. Singh & R. Raghubir.

2007

30th All India Cell Biology Conference, Delhi (2-4 February)

Association of base excision repair gene polymorphisms with breast cancer risk. A.K. Singh, N. Singh, V.K Garg, A. Agarwal, M. Sharma, R. Chaturvedi & S.K. Rath.

V. Inter-Agency Linkages

Title	Funding Agency	Principal Investigator
Reproductive Health Research Program	Ministry of Health & Family Welfare, Govt. of India	Director, CDRI
Sophisticated Analytical Instrument Facility	Department of Science & Technology, Govt. of India	Director, CDRI
National Project on Development of Potential Drugs from the Ocean	Ministry of Earth Sciences, Govt. of India	Director, CDRI
Development of National Laboratory Animal Centre-X FYP	Department of Biotechnology, Govt. of India	Director, CDRI
Distributed Information Sub Center	-do-	Dr. P.K. Roy
Development of Anti-osteoporotic Agents from Indian Medicinal Plants	-do-	Director, CDRI
An Approach Towards Exploration of Mechanism of Drug Non-responsiveness to SbV in Field Isolates of *Leishmania donovani*	-do-	Dr. Neena Goyal
Role of Rapid Suscitation Promoting Factors (Rpf) in Wake Up of Dormancy in *Mycobacterium tuberculosis*	-do-	Dr. R. Srivastava
Leishmania Target Antigens from Promastigotes and Amastigotes: Identification on Experimental Visceral Leishmaniasis	-do-	Dr. A. Dubey
Solution Structure of *M. tuberculosis*, *E. coli* and *H. sapiens* Peptidyl-tRNA Hydrolase by NMR Spectroscopy	-do-	Dr. A. Arora

Evaluation of *Mycobacterium* as an Immunomodulator for the Management of Visceral Leishmaniasis and as an Adjunct to Antileishmanial Vaccine/Drug	-do-	Dr. A. 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. S. Sinha
Structure Based Drug Design of Inhibitors Targeting Recombinant Pteridine Reductase 1 from *Leishmania donovani* Clinical Isolates	-do-	Dr. N. Singh
Studies on neutrophil nitric oxide synthase : Isolation, molecular characterization and identification of interacting proteins	-do-	Dr. M. Dikshit
Cloning, Expression and Characterization of Filarial Acetyl Cholinesterase	-do-	Dr. N.A. Kaushal
Correlation of Single Nucleotide Polymorphism in Gene Encoding Cytokines & Adhesion & Immune Regulatory Molecules with Severity of *P. falciparum* Malaria in UP	-do-	Dr. S. Habib
Design and Synthesis of C-glycoside Mimics of Anti-inflammatory Agents	Department of Science and Technology, Govt. of India	Dr. A.K. Misra
Design and Development of Tissue Selective Anti-estrogens	-do-	Dr. G. Panda
Studies on the Chemistry of Baylis - Hilman Reaction of Substituted Isoxazole Carboxaldehydes	-do-	Dr. S. Batra
Studies on the Modulation of Neutrophil Free Radical Generation and Nitric Oxide Synthesis by Calcium, Reactive Nitro and Oxygen Species	-do-	Dr. M. Dikshit
Investigation on the Structure Function Relationship of a Novel *E. coli* Toxin Hemolysis E, a Potential Virulent Factor	-do-	Dr. J.K. Ghosh

Identification and Characterization of Stage Specific Gene(s) of *Leishmania donovani* Using Genomic Microarray	-do-	Dr. N. Goyal
Study of Viable Non-replicating Persistent *Mycobacteria* and Identification of Genes Expression During Latency	-do-	Dr. B.S. Srivastava
Establishing National Facility for Regulatory Pharmacology and Toxicology	-do-	Director, CDRI
Isolation and Characterization of Proteophosphoglycans of *Leishmania donovani*	-do-	Dr. A. Dubey
Studies on Syntheses of Cyclic Compounds using Baylis-Hillman Chemistry	-do-	Dr. S. Batra
Diversity Oriented Organic Synthesis of Small but Smart Molecules in Drug Discovery Research	-do-	Dr. G. Panda
Design and Synthesis of PPAR-α, γ-Modulators as Antihyperglycemic Agents	-do- (SERC Fast Track)	Dr. Atul Goel
Synthesis of Biologically Active Resin Glycosides and Evaluation of their Anticancer Properties	-do- (SERC Fast Track)	Dr. B. Mukhopadhyay
A Mechanistic Approach Towards Improvement in Oral Bioavailability with Special Reference to Cyclosporine	-do- (SERC Fast Track)	Dr. P.R. Mishra
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- (Women Scientist Scheme)	Dr. Z. Tusi
Osteoporosis in Indian Women and Men: Diagnosis Using Bone Mineral Density and Biochemical Markers of Bone Turnover	-do- (Women Scientist Scheme)	Dr. A. 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	-do- (Women Scientist Scheme)	Dr. Neetu Singh

Identification and Development of Novel Anticancer Agents: Extended Work Plan for Lead Optimization and Drug Candidate Selection	DST/DABUR (DRF)	Dr. S. Sinha
Lead Optimization and Development of New Orally Active Antimalarial Peroxides	DST/IPCA LAB	Dr. C. Singh
Plasmodium falciparum Apicoplast ORF470: Investigation of Structure-Function Relationship	Indian Council of Medical Research, New Delhi	Dr. S. Habib
Design and Synthesis of Novel SERM's for the Management of Osteoporosis and Other Estrogen Related Disorders	-do-	Dr. G. Panda
Pharmacokinetic Studies of Herbal Medicines	-do-	Dr. R.C. Gupta
Search for the Cell Wall and Membrane Protein(s) of *Candida albicans* to be used as Target Molecules	-do-	Dr. P.K. Shukla
Development of Anti-ulcer Drug from Indian Medicinal Plant *Tectona grandis*	-do-	Dr. G. Palit
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 Anti-mycobacterial Agents	-do-	Dr. A.K. Shaw
Osteoporosis and Development of Novel Anti-osteoporosis Agents	ICMR (Emeritus Scientist Scheme)	Dr. M.M. Singh
Sending a Wake Up Call to Dormant Cells of *Mycobacterium tuberculosis:* Identification of Signal Proteins and Receptors	CSIR- (New Idea Fund)	Dr. R. Srivastava
Golden Triangle Partnership Scheme for Validation of Traditional Ayurvedic Drugs and Development of New Drugs	CSIR/AYUSH/ICMR	Dr. R. Raghubir

Synthesis and Biological Evaluation of Solanesol Derivatives as Novel Bioactive Substances	Indian Council of Agricultural Research, New Delhi	Dr. K. Raj
Biotoxins and Other Bioactive Substances from Marine Organisms	-do-	Dr. T. Narender
Carbohydrate Based Amino Alcohols and Acids: Development of New Chiral Ligands for Potential Application in Defence	DRDO	Dr. R.P. Tripathi
Compound 97-78: 28 Day Repeat Dose Toxicity Study in Rhesus Monkey by Oral Route	M/S IPCA Laboratories Ltd., Mumbai	Dr. S. Srivastava
Latent *M. tuberculosis*: Therapeutic Component	NMITLI	Dr. S. Sinha
Development of Novel Biotech Therapeutic Molecule Lysostaphin	-do-	Director, CDRI
Development of Oral Herbal Formulation for Treatment of Psoriasis: A Clinical and Scientific Challenge	-do-	Dr. R. Raghubir
Development of Biodegradable Microparticles Containing Anti-Tubercular Drug for Delivery of Dry Powder Inhalation	-do-	Dr. Amit Misra
Pharmacological and Genomic Investigations on *Withania somnifera* – An Indian Medicinal Plant	-do-	Dr. S. Bhattacharya
Improved Genome Annotation Through a Combination of Machine Learning and Experimental Methods: *Plasmodium falciparum* as a Case Study	-do-	Dr. S. Habib
Mode of Action of Artemisinin Based Antimalarial Drugs	UPCST	Dr. J.K. Saxena

VI. R & D / Technical Facilities & Services

1. Sophisticated Analytical Instrument Facility

Over 10980 external and 23080 internal samples were analysed at the Institute by the Division. There were 640 external users and 270 internal users. Over 1240 samples and 4260 grids were prepared for TEM analysis and 320 samples were analysed on SEM. Around 144 slides were examined by Confocal Microscopy.

A newly acquired Joel Accut of Direct Analysis in Real Time (DART) Mass Speetrometer was installed in the Division and became functional w.e.f. 19.12.06. The instrument can analyse samples without any sample preparation or solvents.

The Instrumentation Division continued to provide repair, maintenance and upkeep facilities of sophisticated analytical, biomedical, electronic and laboratory instruments to all divisions/sections of the Institute. In cases of non-availability of imported components, equivalent indigenous substitutes were installed to ensure the smooth functioning of instrument. Specifications and technical evaluations were also prepared for procurement of new equipments.

2. Biological screening of outside samples

The Institute continued to provide the *in vitro* and *in vivo* screening facilities to the users on payment basis. As per the practice in past, these facilities were provided to R&D institutions, Universities and industrial organizations. In view of the implementation of Right to Information Act – 2005, terms for providing these services were reorganized so as to rule out problems associated with the denial of service. Further, mould growth test was performed on aircraft accessories for Hindustan Aeronautics Ltd., Lucknow.

3. Digital designing of panels

CDRI provided designing facility of exhibition display of charts / panels to ITRC, NBRI, CSIR and Ministry of Earth Science. A total of 55 panels were prepared for CSIR Foundation Day Celebrations, CSIR Exhibition-cum-Fair on Rural Technology, Jais, Raibareilly and 10 display panels for Ministry of Earth Science, New Delhi.

4. National Laboratory Animal Center

During the year, cell lines supplied include: MCF-7, MDA MB-231, MDA MB-453, L-929, VERO C-1008, J744A.1, 3T3 L1, HEK 293, L-6, THP-1, RAW 264.7, Hep G-2, T47-D, PC-12, MG-63, SHSY 5Y, C-6, PDC cell lines maintained. A total of 222 flasks of various cell lines were supplied in the Institute under various projects and 6 flasks were sold outside to M/S Eastern Medikit Ltd., Gurgaon, Haryana and M/S Shriram Institute for Industrial Research, Delhi.

Further, a total of 47135 animals were supplied for research usage. Month wise supply

of animals from January 2006 to November 2006 is shown below:

Months	Mice	Rat	Hamster	Mastomys	Gerbil	Guinea pigs	Rabbit	Total
January	1968	1704	446	105	60	66	06	4355
February	1567	1144	376	75	65	26	15	3268
March	1844	1998	291	90	65	59	28	4375
April	1576	1324	362	105	111	57	08	3543
May	2474	1960	342	165	60	96	22	5119
June	2174	1430	357	150	30	80	97	4318
July	1985	1326	282	130	71	142	68	4004
August	1797	1518	348	160	40	105	15	3983
September	2819	1842	365	110	50	240	6	5432
October	1920	1245	149	150	45	140	9	3658
November	1753	1808	1031	50	50	165	23	4880
Grand Total	**21877**	**17499**	**4349**	**1290**	**647**	**1176**	**297**	**47135**

Further, following jobs were completed in the National Laboratory Animal Center:

- Cell lines maintained 18
- Cell lines supplied 228
- Health monitoring of animals through sample screening 750
- Microbiological monitoring undertaken 895
- Genetic profiling of animals using biochemical markers 15
- Non-human primates procured for experimentation 124
- Monkeys under rehabilitation and breeding 30
- Tuberculin testing of monkeys conducted 126
- Chest radiography of monkeys performed 96
- New animal breeding lines developed 6 strains belonging to 4 species

5. Documentation and Library Services

CDRI Library continued to receive recognition from national and international organizations. These include: (i) National Information Center for Drugs and Pharmaceuticals from Department of Scientific and Industrial Research, Govt. of India (ii) WHO Collaborating Centre on Drug Information for South-East Asian Region (iii) User Centre for Biotechnology System Network under Department of Biotechnology, Govt. of India (iv) National Marine Data Centre by Department of Ocean Development, Govt. of India and (v) Nodal Centre for Lucknow Special Libraries Consortium (LUSLIC). The present collection of Library has 21601 books, 65923 bound volumes of the periodicals and 253 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 to be carried out regularly. Subscribers and peers largely appreciated the contents of these publications. Library manages, updates and maintains the Website of the Institute.

VII. Human Resource Development

1. Ph.D. Programme

1.1 Following students were awarded the Ph.D. degree

Name	University	Title/Guide
A.R. Subramanian	BITS, Pillani	NMR structural aspects in biological systems: Analysis in leishmaniasis, tuberculosis and meningitis/ Dr. Raja Roy
Amol Kavishwar	JNU, New Delhi	Proteome-wide generation of monoclonal antibodies against cell wall proteins of *Candida albicans* and their use as immunotherapeutics/ Dr. P.K. Shukla
Bhasir Ahmed Bhat	JNU, New Delhi	Synthesis of antidiabetic and hypolipidemic compounds/ Dr. D.P. Sahu
Diksha Katiyar	RML, Faizabad	Synthetic studies in heterocyclic and sugar derivatives: Development of potential chemotherapeutic agents/ Dr. R.P. Tripathi
Gyanedra Singh	JNU, New Delhi	An *in vitro* approach assessing teratogenicity of compounds by using whole rat embryo culture/ Dr. Neeraj Sinha
Manish Kumar	JNU, New Delhi	rDNA based approach for identification of fungi and early diagnosis of mycotic keratitis/ Dr. P.K. Shukla
Neeraj Shakya	Lucknow	Design, synthesis and QSAR studies on β_3-adrenergic receptor agonists and acetylcholinesterase inhibitors/ Dr. A.K. Saxena
Neetu Tewari	RML, Faizabad	Synthetic studies in glycohybrid molecules: Development of new class of antitubercular agents/ Dr. R.P. Tripathi
Parvez Akhtar	JNU, New Delhi	Molecular characterization of immunodominant antigen Rv3303c of *Mycobacterium tuberculosis* H37Rv/ Dr. Ranjana Srivastava
Philip Parthipati	JNU, New Delhi	Computer aided drug design: 3D QSAR and molecular modelling studies on β_3-AR agonists and α1-AR antagonists/ Dr. A.K. Saxena
Sushma Chaubey	JNU, New Delhi	Investigations into the roles of hypothetical apicoplast encoded proteins of *Plasmodium falciparum*/ Dr. Saman Habib

1.2 Following students have submitted their thesis for the award of Ph.D. degree

A.N. Gaikwad	JNU, New Delhi	Studies on cellular, molecular and therapeutic aspects of interaction between human macrophages and *Mycobacterium tuberculosis* in a tuberculosis endemic setting / Dr. S. Sinha
Ashok Kumar Chaturvedi	JNU, New Delhi	Proteome analysis of cell wall antigens of *Aspergillus fumigatus* and role of MAbs in immunotherapeutics/ Dr. P.K. Shukla
B.K. Agrawal	CSJM, Kanpur	Investigation of degradation kinetics: Isolation and characterization of degradation products of CDRI candidate drug/ Dr. G.K. Jain
Geetanjali Agnihotri	H.N.B., Garhwal	Synthetic studies towards carbohydrate derived molecules of biological importance/ Dr. A. K. Misra
Hema Kothari	JNU, New Delhi	Differential gene expression between sensitive and resitant *Leishmania donovani* clinical isolates by microarray / Dr. Neelo Singh
Manish K. Gupta	JNU, New Delhi	Molecular characterization of immunodominant antigen Rv3878 of *Mycobacterium tuberculosis* H37Rv/ Dr. Ranjana Srivastava
Naveen Chandra	Lucknow	Studies toward the synthesis and bio-evaluation of novel bioactive natural products/ Dr. S.N. Suryawanshi
Pavan Muttil	JNU, New Delhi	Targeted delivery of inhalable microparticles for pulmonary tuberculosis/ Dr. Amit Misra
R.P. Singh	JNU, New Delhi	Pharmacokinetics of novel trioxane antimalarials/ Dr. R.C. Gupta
Satish Kumar	H.N.B., Garhwal	Chemical investigation of some important medicinal plants and chemical modification of phytochemicals/ Dr. K. Raj
Satyawan B. Jadhav	JNU, New Delhi	Drug targeting to bone/ Dr. G.K. Jain
Saurabh Dixit	CSJM, Kanpur	Studies on identification and characterization of *Brugia malayi* antigens of inflammatory potential/ Dr. (Mrs) P.K. Murthy

1.3 MD

Aparajita Singh	KGMU, Lucknow	Plasma and placental levels of oxidative stress parameters in preeclampsia and eclampsia/ Dr. J.K. Saxena, Dr. A. Ghatak
Ramesh Bharti	KGMU, Lucknow	Peroxide penetration into the pulp chamber from newer bleaching products: an *in vitro* study/ Dr. J.K. Saxena
Roopali Khanna	KGMU, Lucknow	A study of lipoprotein subfraction by nuclear magnetic resonance in ischemic heart disease/ Dr. J.K. Saxena, Dr. A. Ghatak, Dr. Raja Roy
Vivek Sharma	KGMU, Lucknow	Assessment of comprehension of informed consent for clinical research in patients of bipolar mania/ Dr. J.S. Srivastava

2. 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; and training to sponsored students from academic institutions with which the Institute has signed MOU and ad-hoc short-term training for academia and industry.

2.1 International training

Dr. Gilbert Arthur, Department of Biochemistry and Medical Science, University of Manitoba, Canada was trained in the Medicinal & Process Chemistry Division.

2.2 Training under co-operation with Indian universities

Under the training of students from Birla Institute of Technology and Science, Pilani, six months training was provided to 14 students on monthly stipend.

2.3 Adhoc training

The following industry and academia sponsored personnel were trained in the Division of Medicinal & Process Chemistry, SAIF and New Target Drug Development divisions of the Institute.

Ms. Kamna Nanda
Ranbaxy Research Laboratories
Gurgaon.

Mr. Vimal Bansal
Ranbaxy Research Laboratories
Gurgaon.

Dr. Anjani Kumar Tiwari
Defence Research & Development Organization
New Delhi.

Dr. Madhuri Singhal
Govt. Girl's Post Graduate College
Bhopal.

Ms. Meeta Khanna
Bareilly College
Bareilly.

Mr. Nishant Misra
Bareilly College
Bareilly.

Ms. Sultana Razia Laskar
Defence Research Laboratory
DRDO, Tezpur
Assam.

Mr. Vikas Jain
C.S.J.M. University,
Kanpur.

2.4 Following university sponsored students were imparted training in various divisions of the Institute:

Name of University/College	Name of Student(s)	Division
A.P.S. University, Rewa	Om Prakash Dwivedi	Fermentation Technology
Allahabad Agricultural Institute, Allahabad	Tanuj Shukla	Biochemistry
	Ghazala Firdaus	-do-
	Alok Ranjan	-do-
	Manisha	-do-
	Arti Rai	-do-
	Moazzam Naqi Naqvi	Microbiology
	Naviedita Jaiswal	-do-
	Supriya Upadhyaya	-do-
	Rohan Tripathi	Molecular & Structural Biology
	Madhu Priya Pandey	-do-
	Nidhi Upadhyay	-do-
	Tripti Pandey	-do-
	Somesh Singh	-do-
	Pooja Goswami	Parasitology
Allahabad University, Allahabad	Charu Dwivedi	Fermentation Technology
	Anshu Singh	Laboratory Animals
Amity Institute of Biotechnology, Noida	Ajit Nigam	Biochemistry
	Vandana Tandasi	Endocrinology
	Ruchi Singh	Fermentation Technology
	Manjul Tripathi	-do-
	Vishal Shukla	-do-
	Anupama Rajput	Microbiology
	Ritika Singh	Parasitology
	Sneha	Pharmacology
Annamalai University, Chennai	Prashantam Tiwari	Laboratory Animals
	Ratnesh K. Sharma	Microbiology
	Ayush Sharma	Molecular & Structural Biology
	Santosh Kirtane	Pharmacokinetics

Annie Besant College of Engineering & Management, Lucknow	Nidhi Pandey	Microbiology
Apex Institute of Management & Science, Jaipur	Ashok Kumar Chhipa	Laboratory Animals
	Meghwala Goyal	Parasitology
	Monika Agrawal	-do-
Arulmigeh Kalasalingam College of Pharmacy, Tamil Nadu	Abhishek Soni	Pharmaceutics
Banaras Hindu University, Varanasi	Gyan Prakash Modi	Medicinal & Process Chemistry
	Richa Singh	Pharmacology
Bramhanand Degree College, Kanpur	Pratibha Chaturvedi	Biochemistry
Banasthali Vidyapith, Rajasthan	Garima Sharma	Documentation & Library Services
	Meenakshi Sharma	-do-
	Nishi Agarwal	-do-
	Priyankd Mishra	Fermentation Technology
	Shweta Kumari	-do-
	Swapnil	-do-
	Meha Srivastava	-do-
	Neha Agarwal	Medicinal & Process Chemistry
	Itti Bhist	-do-
	Yoshita Paliwal	-do-
	Neha Paliwal	-do-
	Mansi	-do-
	Divya	-do-
	Parul Agarwal	-do-
	Sudeepa Sharma	-do-
	Chhaya Verma	-do-
	Nidhi Tibrwal	-do-
	Arpita Srivastava	-do-
	Rachana Rani	-do-
	Anjali Kevlani	-do-
	Suman Rani	-do-
	Nisha Pundir	-do-
	Shipra Poddar	-do-

	Richa Sharma	-do-
	Ashu Gupta	-do-
	Neetu Punia	-do-
	Ruchi Khandelwal	-do-
	Shalini Agarwal	-do-
	Anju Singh	Molecular & Structural Biology
	Divya Durgapal	-do-
	Rashi Mehrotra	-do-
	Konika Gupta	-do-
	Deepshikha Tripathi	-do-
	Madumita Singh	Parasitology
	Swati Jain	Toxicology
	Shikha Jain	-do-
Bareilly Collage, Bareilly	Lalita Pathak	Biochemistry
Barkatullah University, Bhopal	Ajay Kumar Pandey	Biochemistry
	Parmanand Malvi	-do-
Bhoj Mahavidyalaya, Bhopal	Sumit S. Choudhary	-do-
Bhupal Nobles P.G. College, Udaipur	Virbhadra Singh	Laboratory Animals
Birla Institute of Technology, Mesra, Ranchi	Urmila Saxena	Fermentation Technology
	Kuldeep Kumar Roy	Medicinal & Process Chemistry
	Pankag Agarwal	-do-
	Vishal Singh	Pharmacology
	Hemant Kumar	-do-
	Arshyaya C. Rath	-do-
	Ravi Prakash Rao	-do-
	A. K. Chaudhary	-do-
Bishop Herber College, Tiruchirapalli	Blesson Philip	Laboratory Animalss
Brahmanand College, Kanpur	Isha Singh	Toxicology

Bundelkhand University, Jhansi	Nikhil Srivastava	Biochemistry
	Preeti Yadav	-do-
	Kundan K. Chaubey	-do-
	Avinash Kumar	Endocrinology
	Bhavana Gangwar	Fermentation Technology
	Tanvi Saxena	-do-
	Raginee Niranjan	Medicinal & Process Chemistry
	Sanjeev Kumar Shukla	Parasitology
	Vardan Singh	-do-
	Avineesh Kumar	Toxicology
	Gaurav Singh	-do-
	Naina Srivastava	-do-
	Rashmi Srtivastava	-do-
C. S. J. M. University, Kanpur	Richa Verma	Biochemistry
	Sandhya Rajput	-do-
	Reshu Tewari	-do-
	Mayank Baranwal	-do-
	Anita	Fermentation Technology
	Puneeta Yadav	-do-
	Priya Khare	Laboratory Animals
	Alka Yadav	Microbiology
	Divya Verma	Molecular & Structural Biology
	S. S. Bhadouriya	-do-
	Shaziya Javed	-do-
	Saurabh Shukla	-do-
	Akancha Rathore	-do-
	Mohammad Tauqeer	-do-
	Shalini Srivastava	-do-
	Vijaya Dubey	Pharmaceutics
	Manbhavni Verma	Toxicology
	Shashi Kala	-do-
	Bhumika Arora	-do-

Chinmaya College of Science, Haridwar	Avankita Misra	Microbiology
College of Pharmaceutical Sciences, Berhampur	Sanjukta Das	Biochemistry
College of Life Science, Gwalior	Shradha Porwal	-do-
	Smita Chaurasia	Toxicology
D.A.V. College, Kanpur	Akhilesh Singh	Biochemistry
Dayanand Girls College, Kanpur	Jyoti	Laboratory Animals
Dhanalakshmi Srinivasan College of Arts & Science for Women, Perambudur	J. Seeja	Medicinal & Process Chemistry
	K. Umayal	-do-
Dr. H. S. Gour Vishwavidyalaya, Sagar	Swati Gupta	Parasitology
	Vinay Sinay	-do-
	Nitin Kumar Jain	Pharmaceutics
	Mandakini Jain	Pharmacokinetics
Dr. R. M. L. Avadh University, Faizabad	Chakarpani Tripathi	Toxicology
Feroze Gandhi College, Raibareli	Tanvee Tripathi	Medicinal & Process Chemistry
	Supriya Singh	-do-
	Pooja Srivastava	Molecular & Structural Biology
	Saloni Mishra	-do-
G.S.V.M. Medical College, Kanpur	Pooja Tripathi	Biochemistry
	Ruchi Katiyar	-do-
Gandhi Institute of Biological Sciences, Orissa	Sonali Tripathi	Parasitology
	Bibhudatta Mohaty	Toxicology
Goa University, Goa	Vaishali Satpute	Endocrinology
Gorakhpur University, Gorakhpur	Pratigya Tiwari	Laboratory Animals
Gujarat University, Gujarat	Arpit Srivastava	Biochemistry
Guru Jambheshwar University, Hisar	Akansha Jalota	Parasitology
Guru Nanak Dev University, Amritsar	Harshita Chaudhary	-do-

Gyan Vihar P.G. Studies, Jaipur	Sapna Sharma	Fermentation Technology
	R. Narmadha	Toxicology
	Farah Amir	-do-
	Baby Kumari	-do-
Gopabandhu Ayurveda Mahavidyalaya, Orissa	Amit Sinha	Parasitology
H.N.B. Garhwal University, Srinagar	Abhishek Trigunaite	-do-
Holy Cross College, Triuchirapalli	Prisila Dulcy Charles	Endocrinology
I.E.T. Biotechnology Institute, Rajasthan	Deepti Arya	Biochemistry
I. P. College, Bulandshahar	Alka Rani	Endocrinology
Indian Institute of Technology, Bombay	Preetha Sashi	Pharmacokinetics
Institute of Applied Medicines & Research, Ghaziabad	Shalu Chaudhary	Fermentation Technology
Institute of Engineering & Technology , Lucknow	Rubha Saxena	Molecular & Structural Biology
	Upasana Yadav	-do-
	Suchit Swaroop	Pharmacokinetics
Institute of Engineering Technology and Biotechnology, Alwar	Shuchi Chaudhary	Biochemistry
Integral University, Lucknow	Nadiya Siddiqui	Fermentation Technology
	Sadaf Waheed	-do-
	Shweta Prasad	Toxicology
Janta College, Bakewar	Jetan Chauhan	Laboratory Animals
	Asana Pal	-do-
	Shikha Sharma	Parasitology
	Nishi Shukla	-do-
	Nao Jyoti K Gupta	-do-
	Durgesh Dubey	-do-
	Sadhvi Tiwari	-do-
	Shilki Vishnoi	-do-

Jiwaji University, Gwalior	Ankita Dhami	Biochemistry
	Rajendra Singh Tomar	Fermentation Technology
	Mohd. Murtaza Mehdi	Microbiology
Kanak Manjari Institute of Pharmaceutical Science, Rourkela	Hari Narayan Kushwaha	Molecular & Structural Biology
	Durga Garg	Pharmaceutics
	Banashree Nath	-do-
	Anuja Pandey	-do-
Kanya Gurukala Mahavidyalaya, Hardwar	Namita Pant	Fermentation Technology
Kumaun University, Nainital	Syed Farquan Ahmad	-do-
Lucknow University, Lucknow	Ashish Rai	Medicinal & Process Chemistry
	Amal Pandya	-do-
	Nehal Akhtar	Molecular & Structural Biology
	Jyotsana Thapar	SAIF
Maharishi Dayanand Saraswati University, Ajmer	Tanushree Dangi	Parasitology
Majhigariani Institute of Technology & Science, Gwalior	Avantika Singh	Medicinal & Process Chemistry
Mahatma Gandhi Gramodaya Vishwavidyalaya, Chitrakoot, Satna	Priyanka Gupta	-do-
Mahatma Jyoti Rao Phule P.G. Mahila Mahavidyalaya, Jaipur	Ritu Sachdeva	Parasitology
Mahatma Jyoti Phuley Shaiksanik Parisar, Nagpur	Shashikant B. Bagade	Pharmacology
Madhav Institute of Technology Sciences , Rayagada, Orissa	Ruchi Sahu	Molecular & Structural Biology
Manipal College of Pharmaceutical Sciences, Manipal	Sumeet Kumar Verma	Medicinal & Process Chemistry
	V. V. Changediya	Parasitology
Meerut Institute of Engineering & Technology, Meerut	Katya Singh	-do-
Modi Institute of Management & Technology, Kota	Anju Rani	Toxicology
Modi College of Arts, Science & Commerce, Rajasthan	Pallavi	Biochemistry
	Madhvi Srivsastava	Microbiology

Mahatma Gandhi University, Kerla	Sijumon Kunjachan	Pharmaceutics
Narendra Dev University of Agricultural & Technology, Faizabad	Anuj Kumar Singh	Pharmacology
	Vinay Mishra	-do-
	Govind K Yadav	-do-
National Institute of Ayurveda, Jaipur	Rachana Narula	Medicinal & Process Chemistry
Northern India Engineering College, Lucknow	Neha Mathur	-do-
Orissa University of Agricultural & Technology, Bhubaneswar	Pabitra Mohan Behera	-do-
P. P. N. College, Kanpur	Bhavana Yadav	Pharmacology
Pt. Ravishankar Shukla University, Raipur	Nidhi Singh	Fermentation Technology
Punjab University, Patiala	Gulshan Thakur	Toxicology
R.B.S. College, Agra	Kirti Saxena	Biochemistry
Rajiv Gandhi College, Satna	Shaily Mishra	Laboratory Animals
Rajiv Gandhi College, Bhopal	Megha Bhargava	Biochemistry
Rajiv Gandhi Institute, Pune	Shweta Samant	Toxicology
Rajiv Gandhi Proudyogiki Vishwavidyalaya, Bhopal	Pooja Singh	Biochemistry
	Jadhav Prakash Ashok	Pharmaceutics
Ramswaroop College of Engineering & Management, Lucknow	Kashif Ahmed	Technical Information, Industrial Liaison & Planning
S.B.S. P.G. Institute of Biomedical Science & Research, Dehradun	Namita Verma	Biochemistry
	Nidhi Srivastava	Molecular & Structural Biology
Sadhu Vaswani College, Bhopal	Priyanka Srivsastava	Microbiology
Saifia College of Science & Education, Bhopal	Ashutosh Pandey	Biochemistry
	Dinesh Tripathi	Molecular & Structural Biology
Sai Institute of Paramedical & Allied Science, Dehradun	Archana Pal	Biochemistry
	Pooja Verma	-do-
	Mamta Negi	-do-
	Amit sharma	-do-
	Priyanka Sharma	-do-
	Gajendra B. Singh	Pharmacology
	Preeti Bhatnagar	-do-
	Laxmi Negi	-do-

Sardar Patel University, Gujarat	Divya Gupta	Fermentation Technology
Seedling Academy, Jaipur	Saurabh Mathur	Biochemistry
	Apoorv Saxena	-do-
Seemanta Institute of Pharmaceutical Science, Orissa	P. Ayash Kumar	Medicinal & Process Chemistry
	Debanjan Sen	-do-
Shri G.S. Institute of Technology & Science, Indore	Pankaj Pandey	-do-
Shri Guru Ram Rai Institute of Technology & Science, Patel Nagar, Dehradun	Ratendra Kumar	Pharmacology
Shri Krishnadev Arya University, Anantapur	G. Srinivas	Molecular & Structural Biology
Sophia College, Gwalior	Nitin Kumar	Laboratory Animals
St. John's College, Agra	Pallavi Chauhan	Pharmaceutics
St. Joseph's College, Triuchirapalli	Deepa Arul Priya J.	Biochemistry
	W. Bridegl Jeyatha	Endocrinology
Utkal University, Bhubaneshwar	Prasant Kumar Biswal	Pharmacology
	Manoja Kumar Brahma	-do-
	Namita Khanna	Toxicology
V.B.S. Purvanchal University, Jaunpur	Rajendra Prasad	Laboratory Animals
Vellore Institute of Technology Deemed University, Vellore	Chacko Lirin	Medicinal & Process Chemistry
	Noopur Dwivedi	-do-
	Chandrani Mitra	-do-
	Sandip Chakraborty	-do-
Vellore Institute of Technology, Vellore	Monisha Mishra	Biochemistry
	Rashmi Rekha	Endocrinology
	Shilpy Sinha	Laboratory Animals
Vinayka Mission's College of Pharmacy, Salem	Sadanand R Mallurwar	Pharmacokinetics
	Vijay Kumar Kale	Parasitology

VIII. Lectures Delivered

Dr. C.M. Gupta	Drug discovery and development: An overview	CIMAP, Lucknow (28.10.06)
	Some newer insights into the structure and function of actin cytoskeleton in Leishmania	JNU, New Delhi (08.12.06)
Dr. K.P. Madhusudanan	Applications of GCMS in essential oil chemistry	Essential Oil Association of India, Kanpur (29.03.06)
Dr. O.P. Asthana	CONSAP cream: Preclinical and clinical evaluation and future plan	Convention Centre, New Delhi (11.10.06)
	Requirements of animal house	CRI (Ayurveda), Gwalior (26.08.06)
	Drug development: Indian perspective	Biotech Park, Lucknow (23.08.06)
Dr. Zaka Imam	CDRI drug discovery innovation chain: Towards fulfilling millennium development goals and sustainable development	Saskatoon, Canada (06.08.06)
Dr. Chandan Singh	Synthesis, biology and chemistry of new antimalarial 1,2,4-trioxanes	CDRI, Lucknow (24.02.06)
	Orally active 1,2,4-trioxanes	Delhi University, Delhi (01.12.06)
Dr. D.P. Sahu	Transitional metal nanocluster catalyzed processes, perspective and future challenges	The Institute of Engineers, Lucknow (19.03.06)
Dr. Naibedya Chattopadhyay	Strategies to study dys-regulated cells in rheumatoid arthritis	SGPGIMS, Lucknow (14.10.06)

Dr. A.K. Saxena	Computer aided drug design: Integration of ligand- and structure-based approaches	KLE Educational Institution, Belgaum (10.02.06)
	Computer aided drug design: Pharmacophore modeling and Synthesis of β3-AR agonists	CDRI, Lucknow (24.02.06)
	Drug discovery research: Lead identification and optimization (ligand based drug design)	IPHMR, New Delhi (10.03.06)
	Drug discovery research: Modern trends	India International Centre, New Delhi (26.05.06)
	Recent trends in discovery and development of pharmaceuticals	Integral University, Lucknow (27.11.06)
Dr. Sudhir Srivastava	Approach and design of toxicity studies: Regulatory considerations	CDRI, Lucknow (08.11.06)
	An overview of special toxicity studies	CDRI, Lucknow (10.11.06)
	Toxicity testing of biopharmaceuticals	CDRI, Lucknow (23.11.06)
Dr. Ram Raghubir	Overview of ICMR advanced centre for drug development from natural products	B.L. Nair Hospital, Mumbai (22.11.06)
	Defining molecular targets: Cerebral ischemia for optimizing neuroprotection	ITRC, Lucknow (18.12.06)
	Marine natural products as novel drugs	SMS Medical College, Jaipur (21.12.06)
Dr. S. K. Puri	The scourge of malaria	Spring Dale School, Lucknow (20.09.06)
	Perspectives in malaria chemotherapy	IICB, Kolkata (23.11.06)

Dr. J.S. Srivastava	Ethics in medical research	KGMU, Lucknow (01.09.06)
	Informed consent	KGMU, Lucknow (12.09.06)
	Bioethics in clinical research	KGMU, Lucknow (18.12.06)
Dr. (Mrs.) Ranjana Srivastava	Tuberculosis: Understanding the enemy	AIIMS, New Delhi (27.03.06)
	VNTR polymorphism and regulation of gene expression in *Mycobacterium tuberculosis*	IISc, Bangalore (5.06.06)
	Development of murine infection model for latency and reactivation	ICGEB, New Delhi (04.12.06)
	How unsafe, the bacteria	ITRC, Lucknow
Dr. Jawahar Lal	Role of pharmacokinetics in drug development	CDRI, Lucknow (09.10.06)
Dr. Pratima Srivastava	Heme and drug metabolism in malaria	CDRI, Lucknow (11.10.06)
	Drug metabolism and disposition	CDRI, Lucknow (21.11.06)
Dr. S. K. Singh	Animal and human pharmacokinetics in drug development	CDRI, Lucknow (10.10.06)
Dr. (Mrs.) Shailja Bhattacharya	Major parasitic diseases of India and their management	St. Anjani's Public High School, Lucknow (15.09.06)
	Diagnosis of human filariasis	CSJM University, Kanpur (12.01.06)
Dr. (Mrs.) Anuradha Dube	Proteophosphoglycans of *Leishmania donovani*	Melbourne, Australia (28.03.06)

Dr. Raja Roy	T1 and T2 relaxation	Manipal University, Manipal (22.05.06)
	MRI: Basic principles	Manipal University, Manipal (23.05.06)
	Basic principles of 2D NMR in liquids	Manipal University, Manipal (24.05.06)
	Contrast agents and molecular imaging	Manipal University, Manipal (26.05.06)
	Applications of NMR in chemistry leading to biological applications	Manipal University, Manipal (27.05.06)
	FT NMR spectroscopy and its application	DMSRDE, Kanpur (29.11.06)
Dr. Sudhir Sinha	Principles and applications of proteomics: A case study	ITRC, Lucknow (31.01.06)
Dr. S.B. Katti	Anti-HIV therapies: An overview	MAHE, Manipal (23.10.06)
	Design and synthesis of novel antimalarial agents from 4-aminoquinoline	MAHE, Manipal (23.10.06)
Dr. Atul Goel	Design and synthesis of PPAR-α,γ modulators as antihyperglycemic agents	SMIT, Sikkim (20.11.06)
Dr. Y.S. Prabhakar	Feature selection – A challenge in modeling studies	Allahabad Agriculture Institute, Allahabad (17.11.06)
Dr. R.P. Tripathi	Synthesis of glycohybrid molecules: Development of new chemotherapeutic agents	Delhi University, Delhi (08.01.06)
	Development of new generation of antitubercular agents	BHU, Varanasi (24.03.06)
	Tuberculosis: New drug development	Rennes University, France (13.06.06)
	Potential of simple sugars in chemistry and medicinal chemistry	BHU, Varanasi (30.09.06)
	Exploration in medicinal chemistry with simple sugars	Delhi University, Delhi (27.11.06)

Dr. P.M.S. Chauhan	Combinatorial chemistry: A new tool in drug research	Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (25.09.06)
	Trends in anti-parasitic chemotherapy	Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (26.09.06)
Dr. Saman Habib	IGVD: Understanding population sub-structure, disease factors and drug response in the diverse Indian population	Taipei, Taiwan (03.03.06)
	Understanding apicoplast DNA replication: DNA-protein interactions at replication origins	ICGEB, New Delhi (29.11.06)
Dr. U. Bandyopadhyay	Important tools in proteomics with special references to ELISA: Western blot and their application in biomedical research	SGPGI, Lucknow (23.09.06)
Dr. Imran Siddiqui	Role of computers in bioinformatics	Biotech Park, Lucknow (08.02.06)
	Bioinformatics in drug development	Biotech Park, Lucknow (22.08.06)
	Molecular modeling tools and techniques	Biotech Park, Lucknow (24.08.06)
Dr. Ashish Arora	Analysis of proteins using NMR spectroscopy	INSAS-Delhi Chapter (18.08.06)
	Functional and structural studies on peptidyl-tRNA hydrolase from *M. tuberculosis* H37Rv	Mumbai (15.10.06)
Dr. M. Abbas	Bioinformatics: Introduction, need, applications, advantages and limitations	CDRI, Lucknow (07.08.06)
	Statistical analysis and modeling of data in post-genomic era	CDRI, Lucknow (31.08.06)

Dr. Mukesh Srivastava	Hypothesis testing and regression in drug development	CDRI, Lucknow (11.08.06)
Dr. D.S. Upadhyay	Behaviour of laboratory animals	Forestry Training Institute, Kanpur (09.11.06)
Dr. Anil Balapure	Overview of preclinical research in *in vitro* studies	Reliance Life Sciences Pvt. Ltd., Navi Mumbai (04.08.06)
Dr. Madhu Dikshit	Ascorbate mediated modulation of redox signaling: Actions beyond antioxidant	INMAS, New Delhi (04.09.06)
	Signal transduction-II	KGMU, Lucknow (30.06.06)
	Signal transduction-I	KGMU, Lucknow (07.07.06)
	Intravascular thrombosis: Prevention by herbal drugs and spices	Delhi University, Delhi (09.12.2006)
Dr. G. Palit	Role of molecular biology in drug discovery	K.M. College of Pharmacy, Madurai (30.01.06)
	Neuroprotection in cerebral ischemia: The facts – need for fresh approaches	CDRI, Lucknow (29.03.06)
	Peptic ulcer disease: Evaluation of anti-ulcer compound from preclinical to clinical stage	Himalaya Institute of Medical Sciences, Dehradun (12.04.06)
	Pharmacological approaches for evaluation of drugs for behavioural disorders	KGMU, Lucknow (28.07.06)
	Exploring natural products as a source of new drugs for peptic ulcer disease	IICT, Hyderabad (14.11.06)
	The neuroprotective action of herbal medicament against cerebral ischemia is associated with the prevention of delayed death in rats	University of Delhi, New Delhi (09.12.06)
	Exploring natural products as a source of new drugs for peptic ulcer disease	University of Delhi, New Delhi (10.12.06)

Dr. C. Nath	Herbal preparations as memory enhancer	ITRC, Lucknow (12.06.06)
Dr. Rakesh Shukla	Biochemical and immunological mediators of inflammation: An update	DIPSAR, New Delhi (17.03.05)
	Cytokines and inflammation and update	DIPSAR, New Delhi (2.6.06)
Dr. Neeraj Sinha	Assay for detection of apoptosis in fishes	National Bureau of Fish Genetic Resources, Lucknow (21.02.06)
	Teratogenicity of cyclophosphamide: biochemical changes in *in vitro* system	Jiwaji University, Gwalior (09.10.06)
	Toxicology and its role in drug development	City Montessori School, Lucknow (24.09.06)
	GLP: Practical aspects	CDRI, Lucknow (30.08.06)
	Testing for reproductive toxicity of candidate drugs	CDRI, Lucknow (21.11.06)
Dr. Sharad Sharma	Key features of different types of toxicity studies	CDRI, Lucknow (09.11.06)
Dr. S.K. Rath	Importance of SNP databases in genomics and proteomics based drug development	Biotech Park, Lucknow (19.05.06)
	Drug toxicity	Regional Science Centre, Lucknow (16.11.06)
Dr. Poonam Singh	Biological decolorization and degradation of azo dyes	Lady Doak College, Madurai (27.11.06)
Dr. (Mrs.) P. Kalpana Murthy	Immunomodulatory parasite molecules in lymphatic filariasis	CSJM University, Kanpur (11.01.06)
Dr. K.K. Srivastava	Genesis of pathogenic and non-pathogenic *Mycobacteria*	G.B. Pant Agriculture University, Pantnagar (26.06.06)
	Recombinant DNA technology	Regional Science Centre, Lucknow (13.11.06)

Dr. B.N. Singh	An approach to bioinformatics and its usefulness in human molecular genetics	Jiwaji University, Gwalior (28.07.06)
	Gene expression analysis using *in silico* methods and high throughput approaches	Jiwaji University, Gwalior (28.07.06)
	Human genome	Regional Science Centre, Lucknow (14.11.06)
Dr. J.K. Saxena	An overview of chemotherapeutic targets for anti-parasitic drug discovery	CDRI, Lucknow (24.02.06)
Dr. Amit Misra	Immunization by transdermal electroporation	University Institute of Chemical Technology, Mumbai (10.11.06)
	Inhalable microparticles induce serendipitous activation of lung macrophages infected with *Mycobacterium tuberculosis*	Mumbai (11.11.06)
Dr. Man Mohan Singh	Bone turnover in relation to estrogen deficiency, ageing and induced discontinuity defect and its management	King George's University of Dental Sciences, Lucknow (20.07.06)
Mr. Vinay Tripathi	Intellectual property rights: An overview	CDRI, Lucknow (27.11.06)
Dr. A.K. Dwivedi	HPTLC: A versatile tool for the analysis	Udaipur (11.7.06)

IX. Distinguished Visitors / Lectures

Prof. Asis Datta Director National Centre for Plant Genome Research New Delhi.	**31st Sir Edward Mellanby Memorial Oration "Winning of Disease and Hunger: Chasing a Dream".**	17.2.06
Prof. N.K. Ganguly Director General Indian Council of Medical Research New Delhi.	**(i) Presidential Address in the 55th Annual Day Celebrations.** **(ii) 10th Dr. C.R. Krishna Memorial Oration "Indian Health and Development Index in 2050".**	17.2.06 7.3.06
Prof. K. Muniyappa Chairman Dept. of Biochemistry Indian Institute of Science Bangalore.	**9th Dr. B. Mukerji Memorial Lecture "Telomere Length Maintenance as a Target for Anticancer Drug Discovery".**	28.2.06
Prof. S.S. Agarwal Former Director SGPGI Lucknow.	**Presidential Address in the 9th Dr. B. Mukerji Memorial Lecture.**	28.2.06
Prof. D.P. Singh Vice Chancellor Dr. H.S. Gour University Sagar.	**Presidential Address in the Symposium "Drug Discovery: Perspective and Challenges".**	24.2.06
Prof. David J. Triggle State University of New York at Buffalo New York USA.	**Medicines Discovery in the 21st Century: "For What and For Whom?"**	24.2.06
Dr. Robert A. Field University of East Anglia Norwich United Kingdom.	**Chemical and Enzymatic Tools for Carbohydrate Chemistry: Underpinning Antimicrobial Drug Discovery.**	24.2.06

Dr. Ulrich Jordis Institute fur Angewandte Synthesechemie Austria.	**Synthesis of Second Generation Galanthamine Type Antialzheimer Drugs.**	24.2.06
Dr. Vladimir Vuksan St. Michael Hospital University of Toranto Canada.	**(i) A Revolutionary Discovery That Can Change Path of Diabetes and Cardiovascular Drugs.**	24.2.06
	(ii) Clinical Models for Medicinal Herbs and Functional Foods in the Management of Diabetes, Obesity and Cardiovascular Diseases.	26.2.06
Dr. Wafaa M. Abdou National Research Centre, Dokki Cairo Egypt.	**Biophosphonates and Related Structural Classes for Bone Resorption Disorder.**	24.2.06
Dr. Srinivas Nanduri Dr. Reddy's Laboratories Ltd. Hyderabad India.	**Andrographolide: A Versatile Starting Material for the Generation of Novel, Structurally Diverse and Biologically Potent Molecule.**	24.2.06
Dr. A. Geronikaki University of Thessaloniki Greece.	**Novel 2-Thiazolylamino-5-Arylidenthiazole-4-ones with COX Inhibitory Activity.**	24.2.06
Dr. Sreedhara Swamy Matrix Laboratories Ltd. Hyderabad.	**New Targets and Therapeutic Strategies for Type 2 Diabetes.**	24.2.06
Dr. Simon L. Croft Drugs for Neglected Diseases Initiative Geneva Switzerland.	**Discovery and Development of Drugs for Leishmaniasis.**	25.2.06
Dr. Paolo La Clla University of Cagliari Italy.	**NM283, the First Nucleoside Analog with Selective Anti-HCV Activity. Phase II b Clinical Trial Results.**	25.2.06
Dr. Chung Man Chin University of Sao Paulo State Brazil.	**Prodrug Design Strategy to Improve Chemotherapeutic Drug Effectiveness.**	25.2.06

Dr. Alireza Foroumadi Tehran University of Medical Sciences Iran.	**Synthesis and Structure Activity Relationship of Novel Quinolones Against Gram Positive Bacteria.**	25.2.06
Dr. Michael Collins CEM Corporation USA.	**Scale up with Microwave.**	25.2.06
Dr. Virendra Sondhi Managing Director Ayush Herbs Inc., Bellevue Washington USA.	**Clinical Studies with Indian Herbs and Plants: Management of Diabetes and Cardiovascular Diseases.**	26.2.06
Dr. Cyril W.C. Kendall St. Michael Hospital University of Toronto Canada.	**(i) Clinical Studies with Evaluating Role of Low Glycemic Index, Fruits, Vegetables and Consumer Products in the Management of Cardiovascular Disease Risk Factors.**	26.2.06
	(ii) The Portfolio Diet: Potential of Functional Foods to Maximize Cardiovascular Disease Risk Factor Reduction.	26.2.06
Dr. Carmen Tamayo Flora Inc. Washington USA.	**Clinical Trial Development of Complex Herbal Products.**	26.2.06
Dr. Pierre S. Haddad University of Montreal Canada.	**Antidiabetic Properties of Cree Traditional Medicine: An *in-vitro* Bioassay.**	26.2.06
Dr. Amit Agarwal Director (R&D) Natural Remedies Pvt. Ltd. Bangalore.	**Use of Bioassays in Antidiabetic Research: in-vitro Study**	26.2.06
Dr. Harpal Buttar Therapeutics Products Directorate Ottawa Canada.	**Pharmacokinetic and Pharmacodynamic Changes Induced by the Combined Use of Prescription Drugs with Herbal and Dietry Products.**	26.2.06

Prof. Y.C. Awasthi Department of Biochemistry & Molecular Biology University of Texas USA.	**Stress Response Signaling – Some Novel Concepts.**	24.3.06
Prof. Ashok Chandra King George's Medical University Lucknow.	**Overview and Hypertension in Elderly.**	15.5.06
Prof. V.S. Narain King George's Medical University Lucknow.	**Reappraisal of Hypertension Management.**	15.5.06
Dr. Nitin Deshmukh Senior Product Manager Labindia Instruments Pvt. Ltd. Thane.	**Recent Advances in Real Time PCR Technology.**	14.6.06
Dr. Sheetij Dutta Scientist Walter Reed Army Research Institute, USA.	**Antigenic Escape in Malaria: Implications for Vaccine Design.**	14.6.06
Dr. H.N. Dutta Deputy Director National Physical Laboratory New Delhi.	**Antarctica: A Land of Enormous Promises.**	27.6.06
Prof. H.S. Sharma Department of Surgical Sciences Uppsala University Sweden.	**Alteration in Blood Brain Barrier Function by Morphine and Methamphetamine.**	28.6.06
Dr. Vinod K. Goel Senior Advisor World Bank New Delhi.	**Meeting with CDRI Scientists.**	28.6.06
Dr. Reiner Westermier GE Healthcare Biosciences Munich Germany.	**Current Proteomics.**	29.6.06

Dr. Stephan Poetsch GE Healthcare Biosciences Munich Germany.	**DIGE – An Overview.**	29.6.06
Prof. M.M. Godbole Sanjay Gandhi P G Institute of Medical Sciences Lucknow.	**Thyroid Hormone Deficiency Mediated Cell Death During Neurogenesis.**	28.8.06
Dr. R. Goswami All India Institute of Medical Sciences New Delhi.	**Sporadic Idiopathic Hypoparathyroidism: Newer Aspects.**	28.8.06
Dr. A. Mithal President ISBMR New Delhi.	**New Perspectives on Vitamin D and Bone Health.**	28.8.06
Prof. O.D. Gulati Emeritus Scientist National Academy of Neurosciences New Delhi.	**Advances in Cardiovascular Pharmacology.**	31.8.06
Mr. Sudhir Kumar IAS & Principal Secretary Food & Civil Supplies Govt. of UP Lucknow.	**Chief Guest, CSIR Foundation Day Celebrations.**	26.9.06
Prof. M. Vijayan Professor Emeritus Indian Institute of Science Bangalore.	**CSIR Foundation Day Lecture.**	26.9.06
Ms. Marian Schuegraf Science Counselor Embassy of the Federal Republic of Germany New Delhi.	**Meeting with CDRI Scientists.**	16.11.06

Dr. Sushil Kumar Associate Professor Operations Management Group Indian Institute of Management Lucknow.	**Chief Guest Speaker, Seminar on Management in R&D Organizations.**	17.11.06
Dr. Klaus Peter-Rehorn Export Manager Amaxa Biosystems, GmbH Germany.	**Nucleofactor Technology – A New Revolution in Gene Transfer & Silencing in Primary Cells.**	28.11.06
Mr. Suresh Kumar CAMO Software India Pvt. Ltd. Bangalore.	**Guest Speaker, Workshop on Multivariate Analysis and Drug Research Data.**	29.11.06
Dr. B. Joshi Chief Executive Economic and Management Consultants Lucknow.	**Managing Creativity for Quality Innovation.**	28.12.06
Dr. Mukesh Verma Programme Director & Acting Chief Analytical Epidemiology Research Branch Division of Cancer Control & Population Sciences National Cancer Institute, NIH USA.	**Cancer Biomarkers.**	19.1.07

X. Membership of Committees / Boards

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. Tech. in Biochemical Engineering, IT, BHU, Varanasi; 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.
Dr. K. P. Madhusudanan	Member, Editorial Board, Journal of Mass Spectrometry, John Wiley & Sons, UK.
Dr. Zaka Imam	Member, Editorial Board, CDRI Annual Report 2006-07; Member, Editorial Board, International Journal of Health Technology & Management, Inter Science Enterprises Ltd., UK.
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, International Journal of Medicinal Chemistry Research; Member, Board of Directors, American Bibliography Inc. USA; UGC Nominee, Advisory Committee, Special Assistance Programme, Department of Chemistry, Saurastra University, Rajkot; UGC Nominee, Advisory Committee, Special Assistance Programme, 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; Life Member, UP Association for Science and Technology Advancement.
Dr. Ranjana Srivastava	Member DBT Task Force, Biotech Products and Process Development; Convener, IBSC, CDRI; DBT Nominee, IBSC, IIT, Kanpur; DBT Nominee, IBSC, ITRC, Lucknow; Member, Doctoral Committee, SGPGI, Lucknow.
Dr. O.P. Asthana	Member, Scientific Advisory Committee, National Institute of Nutrition, Hyderabad; Member, Panel of Project Reviewers, UPCST; Member, Panel of Project Reviewers, DST; Member, Panel of Referees, Indian Journal of Biotechnology;

	Member, Panel of Referees, Indian J. Biotechnology (NISCOM); Member Selection Committee (Gr. I, II & III), CDRI, Lucknow; Member, Selection Committee (Gr. III), NEERI, Nagpur; Chairman, Selection Committee (Gr. II), CEERI, Pilani; Member, Selection Committee (Gr. III), ITRC, Lucknow; Invited Faculty Member, Institute of Clinical Research (India), New Delhi; Member, Selection Committee, University of Delhi; Member, Selection Committee, UPDPL, Lucknow.
Dr. Ram Raghubir	Secretary, Indian Pharmacological Society (Lucknow Branch); Member, Steering Committee, MoES Project: Drugs from the Sea, New Delhi; Chairman, Ocean Drugs Alert; Member, Editorial Board, Indian Journal of Pharmacology; Member, Doctoral Committee, SGPGIMS, Lucknow, IVRI Izatnagar, Delhi University, Jiwaji University, Gwalior; Member, Editorial Board, Drugs and Pharmaceuticals, Current R&D Highlights.
Dr. S.K. Puri	Member, Steering Committee, DNDi Sponsored Pan Asian Network for Drugs for Neglected Diseases from Natural Substances; Member, Institutional Animals Ethics Committee, Indian Animal Supplier, Lucknow.
Dr. Gautam Palit	Member, Institutional Ethics Committee at Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow; Member, Project Review Committee, Department of Scientific and Industrial Research, New Delhi; Member, Ethics Advisory Committee, CDRI, Lucknow; Member, Task Force, CSIR Co-ordinated Programme on Bioactive Substances from Plant Sources- Anti-ulcer and Antianxiety Activity; Member, Advisory Committee, Seminar on Clinical Research, Kolkata; Member, Selection Committee, ITRC & CIMAP, Lucknow and RRL, Jammu; Member, Board of Examiners, Jadavpur University, Kolkata; Member, Internal Review Committee, Lucknow.

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. C. Nath	Chairman, Assessment Committee, ITRC, Lucknow; Member, Animal Ethics Committee, ITRC; Member, Library Committee, CDRI; Member, Editorial Board, Ocean Drugs Alert.
Dr. Shailja Bhattacharya	Member, DAAD Advisory Committee, Indo-German Relations; President, Society of Biological Chemists, India; Fellow, Indian Society of Parasitology.
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. R.K. Sharma	Member, Editorial Board, Ocean Drugs Alert.
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. D.C. Kaushal	Member, Editorial Board, Journal of Parasitic Diseases; Member, Research Degree Committee (Microbiology), Ram Manohar Lohia Avadh University, Faizabad.
Dr. J.S. Srivastava	Member, Ethics Committee, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Member, Ethics Committee, KGMU, Lucknow.
Dr. Rajendra Prasad	Life Member, UP Association for Advancement of Science & Technology; Member, Editorial Board, CDRI Annual Report 2006-07.

Dr. A.K. Srivastava	Member, Infectious Diseases Biology, Department of Biotechnology, Government of India, New Delhi.
Dr. A.K. Balapure	Member, Executive Committee, Indian Pharmacological Society.
Dr. A.K. Dwivedi	Member, Expert Committee, Dr. B.R. Ambedkar University, Agra; Life Member, UP Association for Advancement of Science & Technology; Life Member, Indian Pharmaceutical Association; Member, Expert Committee, Kakatiya University, Warangal.
Dr. A.K. Goel	Executive Editor, Ocean Drugs Alert Bulletin; Executive Editor, CDRI Annual Report 2006-07.
Dr. R.P. Tripathi	Life Member, Association of Carbohydrate Chemists and Technologists of India.
Dr. M.N. Srivastava	Member, Editorial Board, Ocean Drugs Alert Bulletin.
Dr. R.C. Tripathi	Member, Editorial Board, CDRI Annual Report 2006-07; Member, Research Board of Advisors, American Bibliographical Institute.
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. M. Abbas	Member, Institutional Ethics Committee, CDRI; Member, Task Force, MoES Project, CDRI; Member, Editorial Board, Drugs & Pharmaceuticals Industry Highlights, CDRI.
Dr. A.K. Srivastava	Life Member, UP Association of Science and Technology; Life Member, Indian Society of Parasitology; Member, Animal House Working Committee, CDRI, Lucknow.

Dr. D. Hansda	Life Member, Indian Association of Veterinary Microbiologists, Immunologists and Specialists in Infectious Diseases; Life Member, W. B. Veterinary Council under Veterinary Council of India.
Dr. D.N. Upadhyay	Life Member, Society for Advancement of Electrochemical Science & Technology; Member, Editorial Board, CDRI Annual Report 2006-07.
Dr. G. Bhatia	Member, Indian Society of Atherosclerosis.
Dr. Gautam Panda	Member, UP Association for Science and Technology, UP, India; Member, Chemical Research Society of India, Bangalore, India.
Mr. Janki Prasad	Associate Member, Institution of Engineers (India); Member, Indian Institute of Chemical Engineers, Kolkata.
Dr. J.K. Saxena	Member, Expert Committee, IIT, Roorkee; Expert, M.Sc. Examinations, Department of Biochemistry, Lucknow University, Lucknow; Expert, School of Biotechnology, BHU, Varanasi; Member, Expert Committee, IVRI, Izatnagar; Member, Expert Committee, Chemical and Pharmaceutical Sciences, UPCST, Lucknow.
Dr. P.R. Mishra	Member, Advisory Board, IIPC, Bilaspur University.
Dr. Jawahar Lal	Life Member, Indian Society of Chemists and Biologists.
Dr. Kumkum Srivasatava	Life Member, Society of Biological Chemists, India, Bangalore.
Dr. M. Dikshit	Member, Editorial Board, Indian Journal of Pharmacology; Member, Editorial Board, National Academy of Sciences India; Member, Editorial Board, Drugs & Pharmaceutical Industry Highlights; Member, Doctoral Committee, SGPGIMS & ITRC, Lucknow.
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. V.G.M. Nair	Member, Editorial Board, CDRI Annual Report 2006-07.

Dr. Vinod Bhakuni	Member, DST, PAC; Member, DBT, Post Doctoral Committee; Joint Secretary, 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.
Dr. N.A. Kaushal	Reviewer, Journal of Experimental Parasitology.
Dr. Neena Goyal	Member, Doctoral Committee, ITRC, Lucknow.
Mr. Vinay Tripathi	Member, Ocean Drugs Alert Bulletin; Member, CDRI Annual Report 2006-07.
Dr. Rakesh Shukla	Vice President, Indian Pharmacological Society; Treasurer, Indian Society of Hypertension; Course Co-ordinator, CDRI-JNU Ph.D. Programme; Reviewer, Indian Journal of Pharmacology.
Dr. S.K. Rath	Member, CSIR Committee for Use of Alternative Animal Models; Member, Doctoral Committee, ITRC, Lucknow; Member, Expert Committee for Genotoxicity of RISU, ICMR; Life Member, ISCB; Life Member and Treasurer; EMSI; Member, Project Review Committee, Department of Science and Technology, New Delhi; Member, Board of Examiners, University of Allahabad; Member, Institutional Animal Ethics Committee, University of Allahabad; Life Member, ADNAT.
Dr. Sharad Sharma	Member, Core Committee, National GLP Compliance Monitoring Authority.
Dr. Sudhir Sinha	Coordinator, CSIR Networked Project, Molecular Biology of Selected Pathogens for Developing Drug Targets.
Dr. Uma Roy	Expert Member, Research Degree Committee, CSJM University, Kanpur.

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; Member, Faculty Training, Motivation and Adoption of Schools and Colleges by CSIR.
Dr. P.K. Shukla	Joint Secretary, International Society of Applied Biology, India; Member, Editorial Board, Asian Journal of Biochemistry, Academic Journals Inc., USA.
Dr. P.Y. Guru	Member, Core Group for Designating Primate Breeding Facility of IRR, Mumbai at Sasunawghar, Thane District, (Maharashtra); Institutional Animal Ethics Committee, ITRC, Lucknow; Member, Institutional Animal Ethics Committee, Homeopathic Drug Research Institute (HDRI), Lucknow; Member, Institutional Animal Ethics Committee, of Era's Medical College, Lucknow; Member, Institutional Animal Ethics Committee, Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow Faculty Member of CDRI-JNU Course on Biotechnology and Drug Development; CPCSEA Nominee in IAEC of Indian Animal Supplier, Lucknow; CPCSEA Nominee in IAEC of Development of Biotechnology, Lucknow University, Lucknow; CPCSEA Nominee in IAEC of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh; CPCSEA Nominee in IAEC of IVRI Mukteshwar Campus, Distt. Nainital; CPCSEA Nominee in IAEC of Biological Products Institute, Directorate of Animal Husbandry, Lucknow.
Mr. Naseem Ahmed Siddiqui	Member, All India Management Association, New Delhi.

XI. Visits Abroad

Dr. C. M. Gupta	***Geneva***, To participate in meeting "Scientific Advisory Committee of Drugs for Neglected Diseases" (3-5 May 2006).
Dr. Zaka Imam	***Canada***, To attend 18th WAITRO Biennial Congress 2006 (7-10 August 2006).
Dr. A.K. Saxena	***Russia***, To participate in the 3rd International Conference on Chemistry & Biological Activity of Nitrogen Containing Heterocycles (22-25 June 2006);
	Germany, Resumption of Alexander Von Humblot Fellowship (25 June-25 July 2006).
Dr. Sudhir Srivastava	***China***, Member, CSIR Delegation (13-21 March 2006);
	Brazil, To attend meeting "WHO/TDR Network of GLP Trainees" (4-9 June 2006).
Dr. S. K. Puri	***Japan***, *DNDi* To attend Pan-Asian Network to Screen New Drugs Against Neglected Diseases (15-17 May 2006);
	Malaysia, To attend in the *DNDi* Pan-Asian Network Steering Committee and Natural Substances – Drug Discovery and Development for Neglected Diseases (3-6 December 2006).
Dr. J. S. Srivastava	***Thailand***, To attend GLP Course for Potential TDR Clinical Monitor (18-26 August 2006).
Dr. (Mrs.) Anuradha Dube	***Australia***, DBT Visiting Associateship (23 March-20 June 2006).
Dr. (Mrs.) Saman Habib	***Taiwan***, To attend 2nd Indo-Taiwan Joint Workshop on Functional Genomics (3-5 March 2006).
Dr. (Mrs.) V. Lakshmi	***China***, INSA-CAS Bilateral Exchange Programme (28 March - 10 April 2006).
Dr. (Mrs.) Renu Tripathi	***Japan***, *DNDi* To attend Pan-Asian Network to Screen New Drugs Against Neglected Diseases (15-17 May 2006).
Dr. R.P. Tripathi	***France***, INSA Exchange Programme (29 May-1 July 2006).
Dr. Mohammad Imran Siddqui	***Trieste, Italy***, To attend conference on Drug Development for the Third World (5-9 June 2006).
Mrs. Ankita Pandey	***USA***, To participate in 14th ISMRM Scientific Meeting (6-12 May 2006).

XII. Honours & Awards

This year several scientists of this Institute received honours and awards for their outstanding performance/contributions in their fields.

Dr. R. Raghubir	Elected as Senior Vice President, Indian Pharmacological Society 2005.
Dr. S.B. Katti	Appointed as Adjunct Visiting Professor in Department of Pharmaceutical Sciences, MAHE, Manipal (April 2006 to March 2008).
Dr. S.K. Puri	Dr. B.N. Singh Memorial Oration Award – 2005 from Indian Society of Parasitology.
Dr. A. Ghatak	Triveni Devi Ram Sahai Award of the Year 2005.
Dr. Vinod Bhakuni	Shanti Swaroop Bhatnagar Award 2006 in Biological Sciences (CSIR); P.B. Rama Rao Memorial Award 2006 from Society of Biological Chemists.
Dr. (Ms.) Madhu Dikshit	N.S. Bhalla Oration, Indian Pharmacological Society 2006.
Dr. (Ms.) M. Ray	Treasurer, Indian Society of Hypertension 2003-06; Treasurer, Indian Academy of Neurosciences, Lucknow Branch.
Dr. R.P. Tripathi	Most Cited Paper 2003-2006 Award by Elsivier Ltd., UK.
Dr. Md. Sohail Akhtar	Young Scientist Award – 2006 (CSIR); Young Scientist Award (National Academy of Sciences, India).
Dr. Atul Kumar	CDRI Annual Day Incentive Award 2006.
Dr. S.K. Rath	Raman Research Fellowship 2007-08.
Dr. Anup Kumar Misra	Ramanna Fellowship of DST.
Ms. Anuradha Kalani	Best Poster Award at 17th National Congress of Parasitology at Dibrugarh.
Ms. Preeti Bajpai	Prof. M.B. Mirza Award for Best Research Publications – 2005 from Indian Society of Parasitology.

XIII. Budget

2006-07 (Sanctioned Estimates)*

Heads		(Rs in Lakhs)
(a) Recurring		
Pay & Allowances		1688.00
Contingencies		170.000
HRD		4.000
Maintenance		130.000
Staff Quarter Maintenance		12.000
Chemicals & Consumables		225.000
	Sub-Total	**2229.000**
(b) Capital		
Equipments and Office Equipments		102.500
Furniture and Fittings		4.00
Library Books & Journals		190.00
Staff quarters		35.410
	Sub-Total	**331.910**
(c) Network Projects		6483.567
	Grand Total	**9044.477**

*Including Network Projects

2005-06 (Actual Expenditure)#

Heads		(Rs in Lakhs)
(a) Recurring		
Pay & Allowances		1604.403
Contingencies		175.205
HRD		4.000
Maintenance		140.030
Staff Quarter Maintenance		11.948
Chemicals & Consumables		238.495
	Sub-Total	**2174.081**
(b) Capital		
Works & Services		21.347
Equipments		95.248
Furniture and Fittings		7.460
Library Books & Journals		206.755
Models & Exhibits		1.000
	Sub-Total	**331.810**
(c) Network Projects		811.432
	Grand Total	**3317.323**

#Including Network Projects & LRF.

XIV. Research Council

(2004 - 2006)

Chairman

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

Members

Dr. Sudarshan K. Arora
President R & D
Lupin Ltd. (Research Park)
46 A / 47 A, Village Nande, Taluka Mulshi
Pune.

Dr. Sandeep K. Basu
Director
National Institute of Immunology
Aruna Asaf Ali Marg
New Delhi - 110 067.

Dr. A. Surolia
Department of Molecular Biophysics Unit
Indian Institute of Science
Bangalore - 560 012.

Dr. M.G. Deo
Visiting Professor
School of Health Sciences
University of Pune
C-13, Kubera Gulshan Apartment, D.P. Road,
Aundh
Pune - 411 007.

Prof. S.K. Brahmachari
Director
Institute of Genomics and Integrative Biology
University Campus, Mall Road
New Delhi - 110 007.

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

Secretary
Department of Biotechnology
Block 2, CGO Complex
Lodi Road
New Delhi - 110 003.

Dr. Y.K. Gupta
Former Director
Industrial Toxicology Research Centre
Lucknow - 226 001.

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

Dr. O.P. Agarwal
Former Head, RDPD
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.

XV. Management Council

(1.7.2005 to 30.6.2007)

Chairman

Dr. C.M. Gupta
Director
Central Drug Research Institute
Lucknow.

Members

Dr. G.N. Qazi
Director
Regional Research Laboratory
Jammu.

Dr. K.P. Madhusudanan
Scientist G
CDRI.

Dr. D.K. Dikshit
Scientist F
CDRI.

Dr. Zaka Imam
Scientist F
CDRI.

Dr. (Ms.) Kalpana Murthy
Scientist F
CDRI.

Mr. Anil Gaikwad
Scientist B
CDRI.

Mr. Rajendra Srivastava
CDRI.

Finance & Accounts Officer
CDRI.

Member - Secretary

Controller of Administration
CDRI.

XVI. The Staff

Director
C.M. Gupta, M.Sc., Ph.D. (Agra), FNA, FASc., FNASc.

R & D DIVISIONS/UNITS

BIOCHEMISTRY

Scientists Group IV(4)
J.K. Saxena, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*
Uma Roy, M.Sc., Ph.D. (Kanpur)
Gitika Bhatia, M.Sc., Ph.D. (Agra), (MOH & FW Scheme)
A.K. Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientist Group IV(3)
Neena Goyal, M.Sc. (Lucknow), Ph.D. (Agra)

Scientists Group IV(2)
P.K.S. Visen, M.Sc. (Meerut), Ph.D. (Kanpur)
Anju Puri, M.Sc. (Kanpur), Ph.D. (Lucknow)

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

Group III(6)
S.M. Kaul, M.Sc. (Lucknow), Ph.D. (Kanpur)
M.M. Khan, M.Sc., Ph.D. (Kanpur)

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

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

BOTANY

Scientist Group IV(5)
S.C. Agarwal, M.Sc., Ph.D. (Lucknow), *In-charge*

Scientists Group IV(3)
M.N. Srivastava, M.Sc. (Kanpur), Ph.D. (Lucknow)
S.M. Rajendran, M.Sc. (Madurai Kamaraj)

Scientist Group IV(2)
K.R. Arya, M.Sc. (Kumaon), Ph.D. (Kanpur)

Scientist Group IV(1)
D.K. Mishra, M.Sc. (Vidyasagar), Ph.D. (Pune)

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

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

Group III(5)
O.S. Tiwari, M.Sc. (Lucknow), Ph.D. (Faizabad) [Retired on 28/02/2006]

DRUG TARGET DISCOVERY AND DEVELOPMENT

Scientist Group IV(4)
Sudhir K. Sinha, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*

Scientist Group IV(3)
Neeloo Singh, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(2)
Charu Sharma, M.Sc. (Lucknow), Ph.D. (Chandigarh)
Uday Bandyopadhyay, M.Sc. (Kolkata), Ph.D. (Jadavpur) [Resigned on 01/12/2006]

Scientists Group IV(1)
Anil N. Gaikwad, M.S.(Pharm.) (NIPER, Chandigarh)
Jayant Sarkar, M.V.Sc., Ph.D. (IVRI)

Group III(6)
Sidheshwar Gupta, B.Sc.

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

ENDOCRINOLOGY

Scientists Group IV(5)
Naibedya Chattopadhyay, M.Sc. (Calcutta), Ph.D. (Lucknow), *In-Charge*
M.M. Singh, M.Sc., Ph.D., D.Sc. (Lucknow), FNASc, [Retired on 31/08/2006]

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

Scientists Group IV(3)
Anila Dwivedi, M.Sc. (Lucknow), Ph.D. (Kanpur)
Gopal Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)
F.W. Bansode, M.Sc. (Nagpur), Ph.D. (Udaipur)

Scientists Group IV(2)
Shobha R. Srivastava, M.Sc. (Bombay) [Retired on 31/12/2006]

Scientist Group IV(1)
Divya Singh, M.Sc. (Lucknow), Ph.D. (Lucknow)
Ritu Trivedi, M.Sc. (Lucknow), Ph.D. (SGPGI)
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)

Group III(6)
Rukmani Agarwal, B.Sc.

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

Group III(4)
Mohini Chhabra, B.Sc., C.L.Sc.
Shakti Kitchlu, M.Sc. (Kanpur)
Balvir Singh, M.Sc. (Rohilkhand)

FERMENTATION TECHNOLOGY

Scientist Group IV(6)
Vinod Bihari, M.Tech. (Kanpur), Ph.D. (I.I.T., Delhi), *In-Charge*

Scientists Group IV(4)
A.K. Misra, M.Tech., Ph.D. (Kanpur) [Retired on 31/08/2006]
C.K.M. Tripathi, M.Sc., Ph.D. (BHU)
Banani Sur, Ph.D. (Utkal)

Scientist Group IV(3)
P.K. Shukla, M.Sc. (Lucknow), Ph.D. (Kanpur)

Group III(6)
A.K. Joshi, M.Sc. (Kumaon)

Group III(5)
Shyamendra Mehrotra, B.Sc.
Bikram Banerjee, B.Sc.
M.K. Srivastava, M.Sc. (Sagar)

Group III(4)
Malkhan Singh, B.Sc.
M. Prakash, Dip. Mech. Engg.
Agney Lal, B.Sc.

MEDICINAL AND PROCESS CHEMISTRY DIVISION

Scientists Group IV(5)
Chandan Singh, M.Sc. (Kurukshetra), Ph.D. (Pune), *In-Charge*
A.K. Saxena, M.Sc., Ph.D. (Meerut)
D.P. Sahu, M.E. (Chem. Engg.) (S.I.T., USA), Ph.D., (IIT, Kharagpur)
D.K. Dikshit, M.Sc., Ph.D. (Lucknow)
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)

Scientists Group IV(4)
V.K. Sharma, M.Sc. (Jabalpur), Ph.D. (Faizabad)
Kalpana Bhandari, M.Sc., Ph.D. (Lucknow)
Rakesh Maurya, M.Sc., Ph.D. (Varanasi)
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)

Scientists Group IV(3)
V.L. Sharma, M.Sc., Ph.D. (Lucknow)
Pradeep Kumar, M.Sc. (Kanpur)
Atul Kumar, M.Sc., Ph.D. (Lucknow)

Scientists Group IV(2)
Sanjay Batra, M.Sc., Ph.D. (Meerut)
Anup K. Misra, M.Sc. (Calcutta), Ph.D. (Jadavpur)
Atul Goel, M.Sc., Ph.D. (Lucknow)
Gautam Panda, M.Sc. (IIT, Khargpur), Ph.D. (Hyderabad)
T.G. Narender, M.Sc., Ph.D. (Kakatiya University)
Sashidhara K.V., M.Sc. (MS Univ.), Ph.D. (Avadh)
Balaram Mukhyopadhyaya, M.Sc. (Burdwan), Ph.D. (Jadhavapur)
Susanta Sekhar Adhikari, M.Sc. (Kharagpur), Ph.D. (Osmania) [Resigned on 31.1.07]

Scientists Group IV(1)
Prem Prakash Yadav, M.Sc. (Allahabad), Ph.D. (Avadh)
Vijay Kumar Goel, M.Sc. (Meerut), Ph.D. (AIIMS) [Resigned on 19/07/2006]

Group III(6)
A.H. Ansari, B.Sc. [Retired on 30/06/2006]
R.K. Asthana, M.Sc. (Agra)
S.P. Vishnoi, M.Sc., Ph.D. (Meerut)
A.K. Srivastava, B.Sc.

Group III(5)
Janki Prasad, M. Tech. (BHU)
S.C. Tripathi
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.

Group III(4)
Pramod Kumar, M.Sc. (Bundelkhand)
Deepali Pandey, B.Sc.
A.S. Kushwaha, B.Sc.

MICROBIOLOGY

Scientist Group IV(5)
Ranjana Srivastava, M.Sc., Ph.D. (Kanpur), *In-Charge*

Scientist Group IV(4)
D.C. Kaushal, M.Sc. (Pantnagar), Ph.D. (Kanpur)

Scientists Group IV(3)
K.K. Srivastava, M.Sc., Ph.D. (Kanpur)

Scientist Group IV(2)
B.N. Singh, M.Sc., Ph.D. (BHU)

Group III (7)
M. Kazim, M.Sc., Ph.D. (Lucknow)

Group III (6)
A.P. Singh, M.Sc. (Lucknow)
M. N. Joshi, M.Sc., Ph.D. (Agra)

Group III (5)
Reeta Singh, M.Sc., Ph.D. (Kanpur)

MOLECULAR & STRUCTURAL BIOLOGY DIVISION

Scientists Group IV(4)
Vinod Bhakuni, M.Sc., Ph.D. (Lucknow), FASc, FNASc, *In-Charge*
P.R. Moulick, 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)
J. Venkatesh Pratap, M.Sc., Ph.D. (IISc, Bangalore)

Scientists Group IV(2)
Jimut Kanti Ghosh, M.Sc., Ph.D. (Kalyani, Calcutta)
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)
Philip Prathipati, M.Sc. (Pondicherry), Ph.D. (JNU) [Resigned on 21/12/2006]
Sushma Chaubey, M.Sc. (BHU), Ph.D. (JNU)

Group III(4)
R.K. Srivastava, B.Sc.
J.P. Srivastava, B.Sc., LL.B.

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)

Scientists Group IV(4)
L.M. Tripathi, M.Sc. (Kumaon), Ph.D. (Awadh) [Retired on 31/10/2006]
Anuradha Dubey, M.Sc. (Lucknow), Ph.D. (Kanpur)
Suman Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(3)
N.A. Kaushal, M.Sc. (Lucknow), Ph.D. (Kanpur)
Renu Tripathi, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(2)
Kumkum Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)
S. Rajakumar, M.Sc. (Madras)

Group III(6)
S.C. Nigam, M.Sc., Ph.D. (Kanpur)

Group III(5)
A.K. Roy, M.Sc. (Kanpur)

Group III(4)
R.N. Lal, M.Sc. (Agra)

PHARMACEUTICS

Scientist Group IV(5)
Satyawan Singh, M.Pharm., Ph.D. (Banaras), *In-Charge*

Scientists Group IV(4)
Raghwendra Pal, M.Sc., Ph.D. (Lucknow)
A.K. Dwivedi, M.Sc., Ph.D. (Agra)

Scientists Group IV(3)
Prem Prakash, M. Pharm. (BHU)
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)
Praveen Dubey, M.Pharm., Ph.D. (Sagar)
Akhilesh Kumar Jain, M.Pharm. (Sagar)

Group III(5)
Madhuri Chaudhry, M.Sc. (Lucknow)

PHARMACOKINETICS & METABOLISM

Scientist Group IV(5)
G.K. Jain, M.Sc. (Rewa), Ph.D. (Kanpur), *In-Charge*

Scientists Group IV(3)
S.K. Singh, M.Sc. (Patna), Ph.D. (IIT, Kanpur)
Jawahar Lal, M. Pharm., Ph.D. (BHU)

Scientist Group IV(2)
Pratima Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur) [Resigned on 29/12/2006]

Scientists Group IV(1)
R.S. Bhatta, M. Pharm. (Nagpur)
M. Wahajuddin, M.S. (Pharm.)
Pharmacoinformatics (NIPER)
R.S.P. Singh, M. Pharm. (BITS Pilani)

Group III(5)
S.K. Pandey, M.Sc. (Kanpur)

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*

Scientists Group IV(4)
Rakesh Shukla, M.Sc., Ph.D. (Lucknow)
Madhu Dikshit, M.Sc., Ph.D. (Kanpur) *(Unit In-charge, Cardiovascular Pharmacology Unit)*
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), *(Cardiovasular Pharmacology Unit)*
Manoj Barthwal, M.Sc., Ph.D. (Lucknow)

Scientists Group IV(1)
Vijay Kumar Kuchibholta, M. Pharma. (Andhra)
Kashif Haneef, M.Sc. (Hamdard)

Group III(7)
G.P. Singh, M.Sc. (Kanpur)

Group III(6)
Urmila Sharma, B.Sc.
M.S. Ansari, B.Sc.

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.

Group III(4)
C.P. Pandey, M.Sc. (Chandigarh)

TOXICOLOGY

Scientist Group IV(5)
Sudhir Srivastava, M.B.B.S., M.D. (Lucknow), *In-Charge*

Scientist Group IV(4)
Neeraj Sinha, M.Sc., Ph.D., D.Sc. (Kanpur)

Scientists Group IV(3)
P.S.R. Murthy, M.Sc. (Nagpur), Ph.D. (Kanpur) [Retired on 30/04/2006]
Sharad Sharma, M.B.B.S., M.D. (Kanpur)
S.K. Rath, M.Sc. (Utkal), Ph.D. (BHU)

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)
Sarika Singh, M.Sc. (Lucknow)
Poonam Singh, M.Sc. (CSJMU)

Group III(6)
S.K. Mathur, M.Sc. (Lucknow), B.M.S.
S.K. Srivastava, M.Sc. (Bombay)

Group III(4)
P.K. Agnihotri, M.Sc. (Lucknow), Ph.D. (Kanpur)
S. M. Verma, B.Sc.
Sadan Kumar, M.Sc. (Bihar)

ANTITUBERCULAR SCREENING UNIT

Scientists Group IV(3)
Anil Srivastava, M.Sc., Ph.D. (Kanpur) [Retired on 30/09/2006]
Vinita Chaturvedi, M.Sc., Ph.D. (Agra)

Scientist Group IV(1)
Y.K. Manju, M.Sc. (Calicut)

CLINICAL PHARMACOLOGY UNIT (CDRI), SETH G.S. MEDICAL COLLEGE, MUMBAI

Scientist Group IV(2)
N.K. Desai, M.Sc., Ph.D. (Bombay)

TECHNICAL INFRASTRUCTURE DIVISIONS / SECTIONS

ACADEMIC AFFAIRS UNIT

Scientists Group IV(4)
Alka Singh, M.Sc., Ph.D. (Rajasthan)
Sheela Ghoshal, M.Sc. (Burdwan), Ph.D. (Kanpur)

BIOMETRY AND STATISTICS

Scientist Group IV(4)
M. Abbas, M.Sc. (IIT, Kanpur), Ph.D. (IIT, Bombay), *In-Charge*

Group III(5)
Mukesh Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)

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.

DOCUMENTATION & LIBRARY

Scientists Group IV(5)
P.K. Roy, M.Sc., Ph.D. (Gauhati), *In-Charge*
R.K. Sharma, M.Sc., Ph.D. (Agra)
Sheela Tandon, M.Sc., Ph.D. (Agra)

Scientists Group IV(4)
A.K. Srivastava, B. Tech. (Bangalore)
N.N. Mehrotra, M.Sc. (Pantnagar), Ph.D. (AIIMS, New Delhi)
S.K. Mallik, M.A. (JNU), B.L.ISc. (IGNOU)
Shyamala Saxena, M.Sc. (Tirupati), B.L.Sc. (Lucknow)

Group III(6)
Seema Mehrotra, M.Sc. (Lucknow)

Group III(5)
V.K. Vohra, B.Sc.
W.F. Rahman, M.A. (Rohailkhand), B.L.Isc, (IGNOU)
A.K. Verma, M.A. (Eco.), L.L.B, Dip. Comp. Sc. (Lucknow)
J.A. Zaidi, M.Sc. (Aligarh), B.L.Isc. (IGNOU)
Sanjay Kumar, M.L.ISc (IGNOU)

DRAWING AND PHOTOMICROGRAPHY

Group III(6)
Ali Kausar, B.F.A. (Lucknow), *In-Charge*

Group III(5)
G.C. Gupta, B.Sc.
R.M. Pathak, B.F.A. (Comm. Arts)
Group III(4)
R.N.S. Londhe, GD Art (Comm.), Art Teachers Dip.

INSTRUMENTATION

Scientist Group IV(5)
Ravinder Singh, B.E. (Allahabad)

Scientist Group IV(3)
N.K. Agarwal M.Sc. (Calcutta)

Group III(6)
Usha Kapil, I.Sc., Dip Electronic Engg.

LABORATORY ANIMALS

Scientists Group IV(4)
D.S. Upadhyay, M.V.Sc. (Pantnagar), Ph.D. (Izatnagar), *In-Charge*
P.Y. Guru, M.Sc. (Indore) [Voluntary Retirement on 02/09/2006]

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)

Group III(5)
S.N.A. Rizvi, M.Sc. (Lucknow)
A.K. Bhargava, B.Sc.

Group III(4)
Karunesh Rai, M.Sc. (Lucknow)

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY

Scientist Group IV(6)
K.P. Madhusudanan, M.Sc., Ph.D. (Kerala), FNASc, *In-Charge*

Scientists Group IV(5)
V.K. Bajpai, M.Sc., Ph.D. (Kanpur)
G.R. Bhatt, M.Sc. (Meerut)

Scientist Group IV(4)
Raja Roy, M.Sc. (Lucknow), Ph.D. (Meerut), FNASc

Scientist Group IV(3)
Brijesh Kumar, M.Sc., Ph.D. (Awadh)

Scientists Group IV(1)
Ankita Trivedi, M.Sc. (Kanpur), M.Phil. (Delhi)
Sanjeev Kanojiya, M.Sc. (Jabalpur)
Mitra Kalyan, M.Sc. (Culcutta)

Group III(6)
Prakash Narain, M.Sc. (Lucknow)
Abha Arya, B.Sc., B.Ed. (Kumaun)
H.M. Gauniyal, M.Sc. (Garhwal)

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)

Group III(4)
Sunil Kumar, B.Sc. (Lucknow)
R.K. Purushottam, B.Sc. (Lucknow)

TECHNICAL INFORMATION, INDUSTRIAL LIAISON & PLANNING

Scientists Group IV(5)
Zaka Imam, M.Sc., M.Phil., Ph.D. (Aligarh), *In-Charge*
Rajendra Prasad, M.Sc., Ph.D. (Lucknow)

Scientists Group IV(4)
A.K. Goel, M.Sc., Ph.D. (Lucknow)
V.G. Mohanan Nair, M.Sc. (Kerala), Ph.D. (Kurukshetra)
Vinay Tripathi, M.Sc., M.B.A. (AMU), P.G. Dip. in S&T (Pilani)
N.S. Rana, M.Sc. (Kumoun)

Scientists Group IV(3)
D.N. Upadhyay, M.Sc., Ph.D. (Gorakhpur)
R.C. Tripathi, M.Sc. (Kanpur), Ph.D. (Lucknow)

Scientists Group IV(1)
Anand P. Kulkarni, M.Sc. (Karnataka), Ph.D. (Mysore)
Naseem Ahmed Siddiqui, M.B.A. (Rohilkhand)
Sripathi Rao S. Kulkarni, M.Sc. (SRTMU, Nanded) Ph.D. (JNTU, Hyderabad), P.G. Dip. in Patents Law (NALSAR, Hyderabad)

Group III(6)
Shri Ram, B.Sc., LL.B.

TISSUE AND CELL CULTURE UNIT

Scientist Group IV(4)
A.K. Balapure, M.Sc., Ph.D. (Lucknow), *Unit In-Charge*

Group III(5)
Ramesh Sharma, M.Sc., Ph.D. (Kanpur)

LABORATORY ENGINEERING SERVICES

Group III(7)
Parvez Mahmood, B.Sc. Engineering (Civil)

Group III(5)
Manoj Kumar, B.Sc. Engineering (Civil)
Kamal Jain, B.E. (Electrical), MBA (Marketing)

Group III(4)
A. Dayal, Diploma (Mechanical)

ADMINISTRATION

B.D. Vashisth, M.A. (Kurukshetra), *Controller of Administration*
U.S. Rawat, *Controller of Finance & Accounts*
A.K. Dwivedi, *Finance & Accounts Officer*
Gopal Chand, *Store & Purchase Officer*
Raza Hussain, *Section Officer (G)* [Retired on 31/12/2006]
Krishna Kumar, *Section Officer (G)*
Madhuranjan Pandey, *Section Officer (G)*
Biranchi Sarang, *Section Officer (G)*
I.B. Dixit, M. Sc. (Lucknow), *Section Officer (F&A)*
Ankeshwar Misra, *Section Officer (F&A)*
A. K. Chauhan, *Section Officer (F&A)*
Kailash Singh, *Section Officer (F&A)*
Shekhar Sarkar, *Section Officer (Store & Purchase)*
Prasanjeet Mitra, *Section Officer (Store & Purchase)*
Prafful Kumar, *Section Officer (Store & Purchase)*

Senior Hindi Officer
V.N. Tiwari, M.A., Ph.D. (BHU)

Senior Security Officer
R.S. Deswal, B.Sc., LL.B.

Private Secretaries
G.M. Nair [Expired on 22/09/2006]
H.K. Khulve
G.M. Dayal, B.Sc., D.P.A.
K.L. Gupta, B.A.