Vibha Tandon

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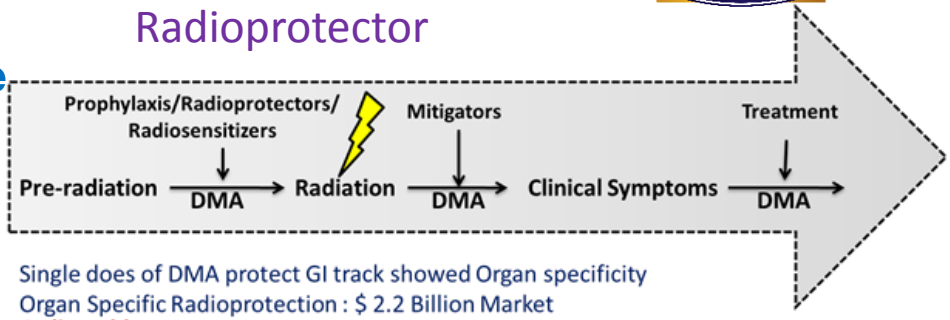
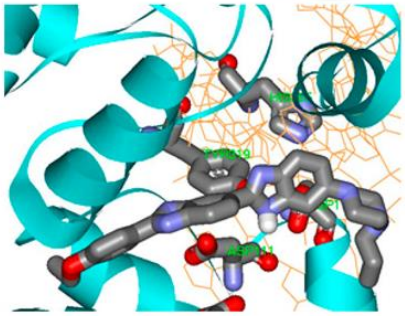
Special Center for Molecular Medicine
Jawaharlal Nehru University

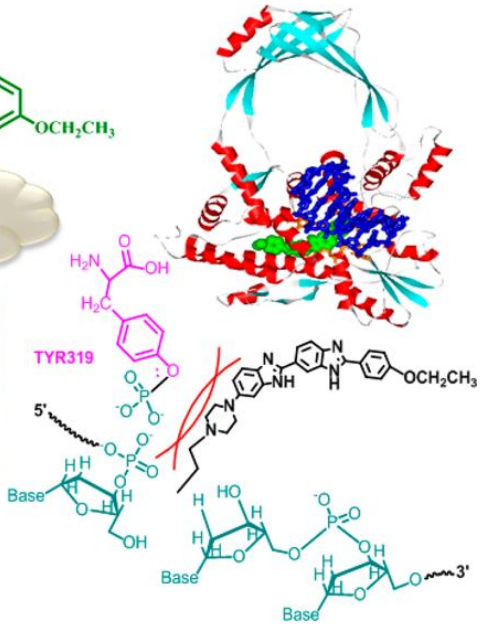
Radioprotector



Single does of DMA protect GI track showed Organ specificity
Organ Specific Radioprotection : $ 2.2 Billion Market
Deliverables : DMA can be given Orally, IV , IP or SC mode
A formulation need to be developed to convert in tablet.



Antibacterial Activity



Research experience: 28 years ,
Teaching experience : 20 years
Ph.D. Students guided : 19
M.Sc. Dissertation : 70
Publications : 76 Books : 03
Administrative experience : Chief Proctor, Coordinator DST PURSE ,JNU, Chairperson SCMM
Chairperson DST –WoS A Scheme

Hand Holding with Industry

IND Filing and Clinical Trial

Anthem BioSciences

&

PACT & Health LLC

In DU and JNU interacted with 5000 Students at Masters level

Prof Vibha Tandon
Jawaharlal Nehru University

SWOT Analysis of III-M Jammu

Strengths (S):

- An institute with a legacy
- Intellectual capital , Leading in research
- Diverse Research Areas , Inter-disciplinary research
- Strong research grants and government funding
- Digital information and resource medium
- Patents and research projects
- Establishing digital traditional knowledge
- Skill development through research
- Equal opportunity provider, especially to the students from most backward areas.
- International, national collaborations , Industry collaborations
- In-house research facilities such as CIF, GLP compliance Animal house, cGMP facility, pk –pd facility
- Herberium, 600 plants repository , QCQA , extraction Unit , formulation unit , Licence to manufacture , Technology business incubator
- high quality of faculty with experience in foreign laboratories
- Lot of farming land is available

Weaknesses (W)

- Under-utilization of laboratory resources
- Identifying the research priorities
- Emphasis on international linkage and collaborations
- Low provision of incentivizing and rewarding innovators
- Low commercialization of patents on global scale
- Policy crunches
- Accountability of extension education activities
- Low no of Ph D students , researchers in labs
- Phytopharmaceutical part is neglected
- Facilites does not have accredition
- Structural biology Program Missing
- Direct Involvement of Clinicians in drug discovery prog

Opportunity (O)

- Reorganize scientific manpower vis-à-vis mandate
- Prioritization of research in Natural Product
- Inter- and Intra- laboratory collaborations
- Fast pace of commercialization of IP
- Establishment of CoE
- Technoglobalism
- Opportunities for International exposure to the students and faculties

Threats (T)

- Intellectual vacuum Identifying the research priorities
- Career stability leading to personality clashes affecting Research progress
- Loss of Natural Product Chemist & Chemistry
- Under-utilization and judicious use of infrastructure
- Lack of training and mapping
- Low commercialization of patents on global scale
- Loss of patented, but un-commercialized technologies
- Demography of IIIM Jammu , Harsh Condition
- Local Disturbance , last mile connectivity
- Post corona threats ,changes
- Gender Bias ,Gender Inequality
- Lack of Funds to maintain the facilty , Less revenue

Overall Picture & Background of IIIM

1941: Drug Research Laboratory (DRL) and Drug Manufacturing Unit (Baramulla) in J&K

Established by Sir R.N. Chopra

1957: Laboratory was formally taken over by CSIR and renamed as:

Regional Research Laboratory (RRL)

2007: Renamed as Indian Institute of Integrative Medicine (IIIM)

Vision & Mandate

- Internationally competitive Center of Natural Products driven drug discovery, integrating modern biology with chemistry
- Bridging expertise gap for IND-enabling studies (GLP/GMP) & clinical development of NCEs and phytopharmaceutical drugs
- Sustainable harnessing of natural resources (MAPs and extremophilic microorganisms) from J&K
- Creating a viable ecosystem in J&K for integrating rural economy with businesses

Core competence

- Chemistry and medicinal chemistry of natural products from plants and microbes.
- *In vitro* & *in vivo* pharmacology (infection, cancer, rheumatoid arthritis and neurodegeneration)
- Fermentation based Industrial technologies
- Phytopharmaceutical drug development (GAP GLP GMP GCP)
- Captive cultivation and agro-technology packages of high value cash crops (med and aromatic plants)
- ~ 60 Scientists and 120 Ph. D. Students

IIIM campus at Srinagar

Experimental farm – Chatha (Jammu)

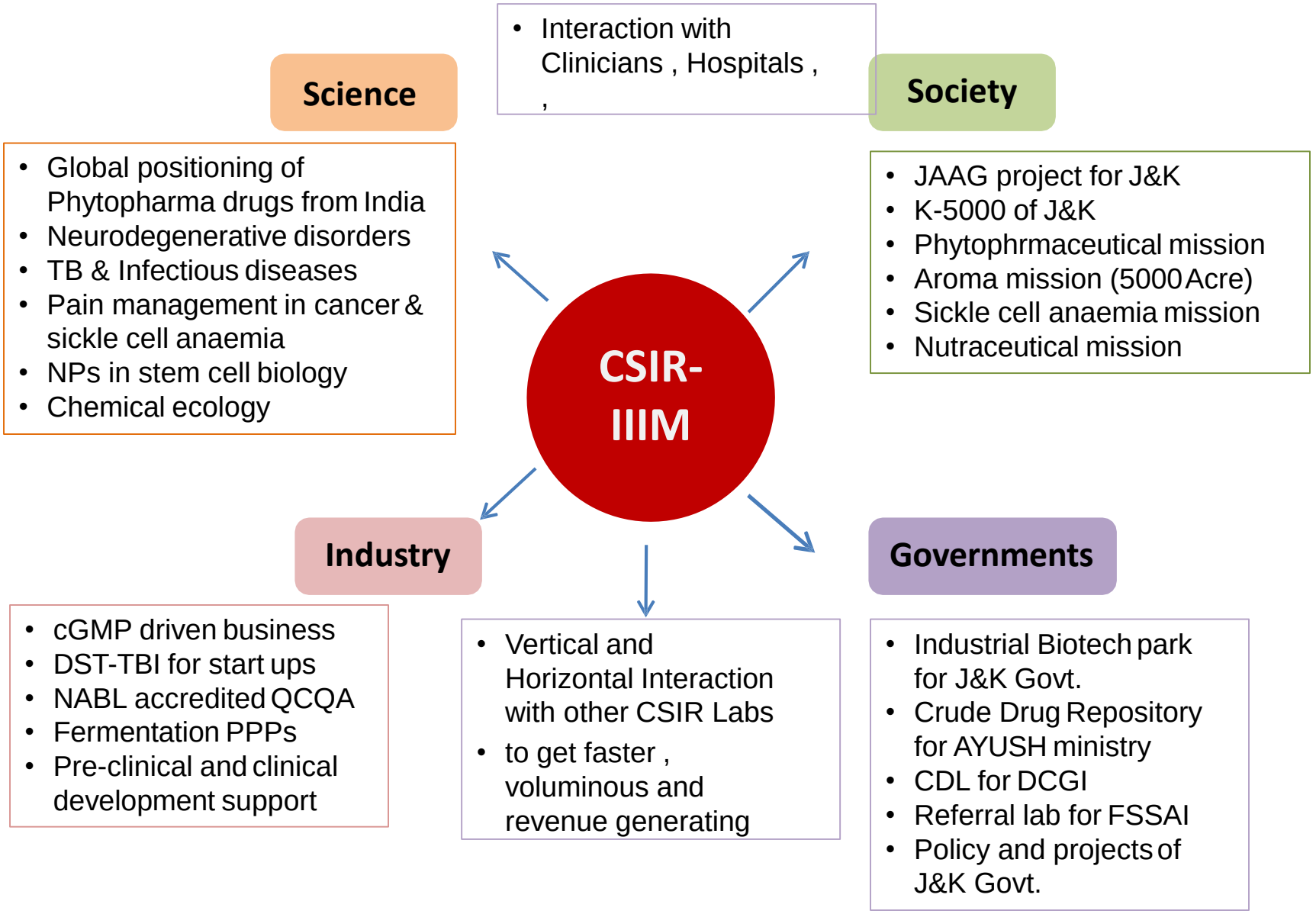
Experimental farm – Bonera (Kashmir)

Experimental farm – Verinag(Kashmir)

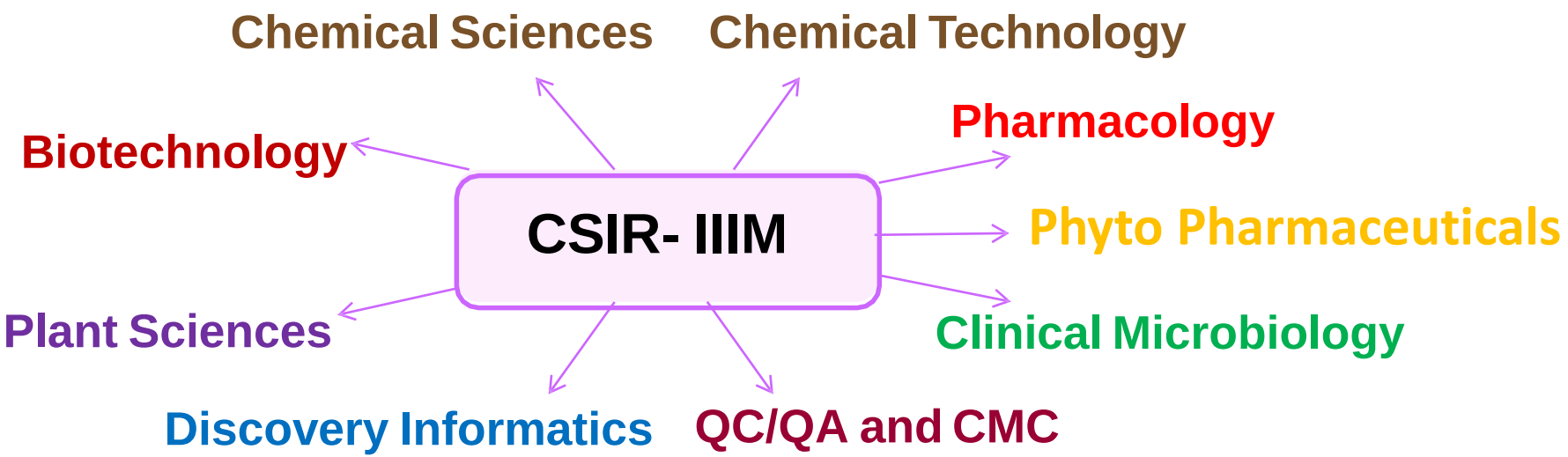
Experimental farm – Yarika (Kashmir)

Experimental farm – Stakna ,Leh , Ladakh

Connection with key stakeholders



Organization of R&D groups



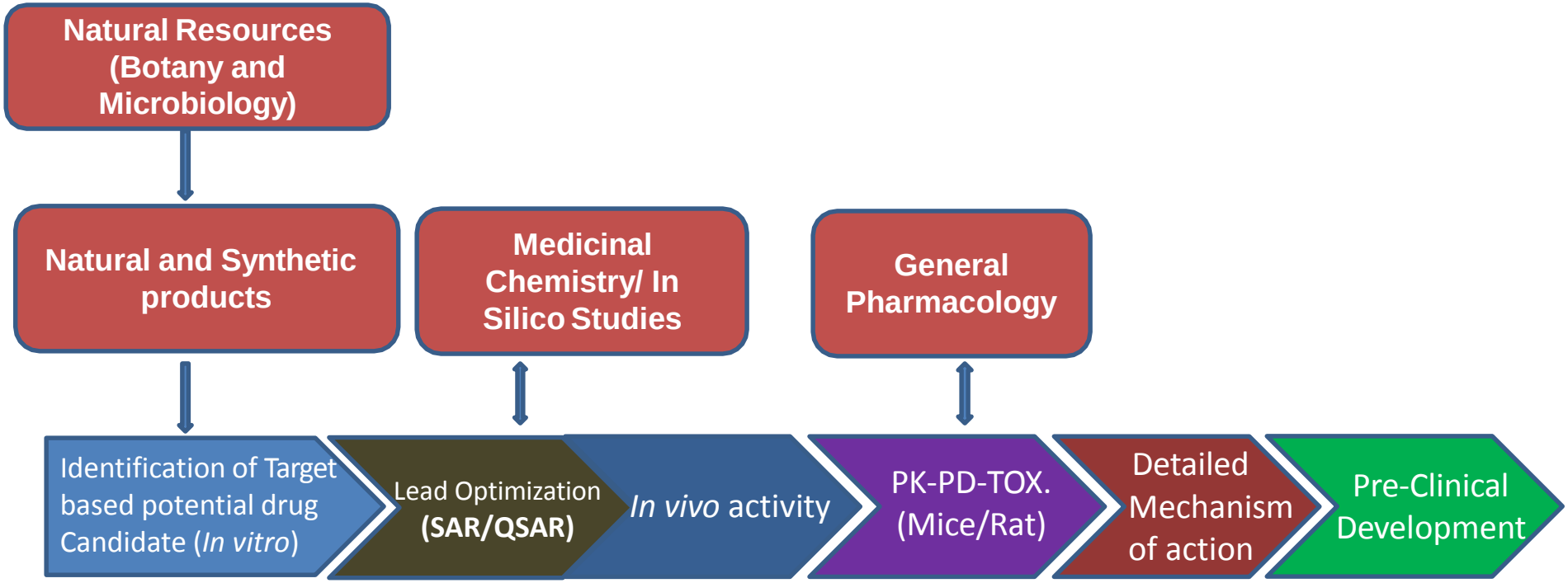
- **Cancer**
- **Inflammation**
- **Alzheimer**
- **Drug resistant infections**

- **Cardiovascular Diseases ,**
- **Chronic Respiratory Diseases**
- **Iron Deficiency Anemia Malnutrition**
- **Pain (Neuropathic, Cancer and Sickle Cell Anaemia)**
- **Positioning of natural products for management of neurodegenerative diseases (Alzheimer's, Depression)**
- **Understanding transport mechanism of secondary metabolites in plants**

Missing Direct Affiliation to Clinics and Hospitals to get patient Samples and critical feed back from Clinicians on IIIM drug development program

Target Driven Drug Discovery from Natural Products

Overview of Drug Discovery at IIIM



My Suggestions

1. Bulk Drug Synthesis
2. Biopharma Mission of DBT
3. Make in India

New Research Centre of CSIR-IIIM at Stakna, Leh, Ladakh

CSIR-IIIM

Total land area : 40 acres

Altitude : 3500 m asl

Temperature range : -30°C to 35°C

Rainfall : 10.3 cm (annual)

2.5 acres nursery of aromatic crops developed in 2018

Some important medicinal plants of Leh

Arnebia guttata

Hippophae rhamnoides

Rhodiola himalensis

Lepidium latifolium

- **Scientific validation of drugs from Sowa-Rigpa system of medicine**
- **Survey, inventorization of bio resources from the region**
- **Chemical ecology studies (counterpart of Yellowstone National Park in India)**
- **Captive cultivation of high altitude medicinal, aromatic and nutraceutical plants from Leh and Kargil**
- **Human resource training of young educated population**

Proposed New Research Centre of CSIR-IIIM at Ladakh

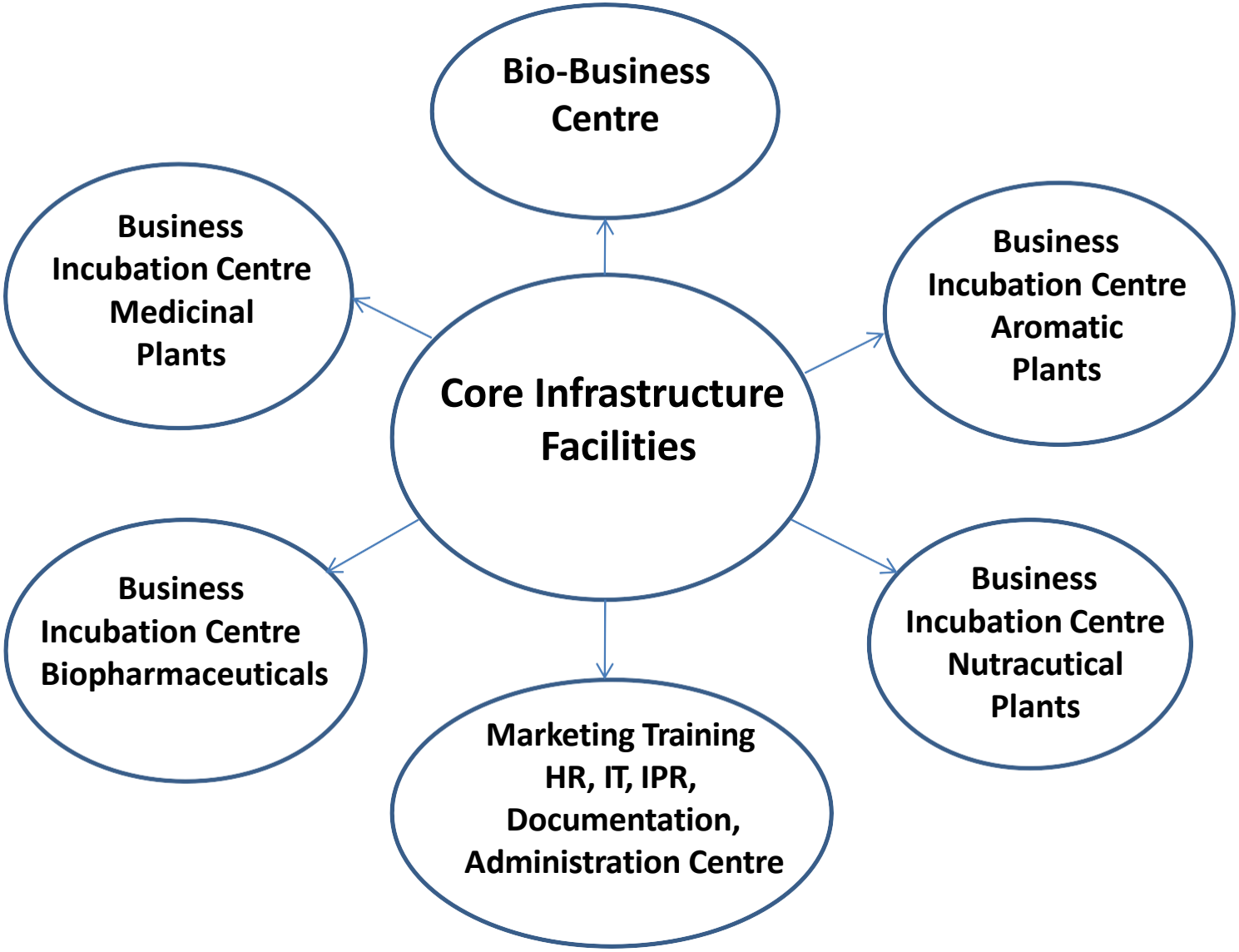
To create laboratory and experimental farm in this unique area (Leh and Kargil) of J&K enabling scientific research and employment generation

- Scientific validation of drugs from Sowa-Rigpa system of medicine
- Survey, inventorization of bio resources from the region
- Chemical ecology studies (counterpart of Yellowstone National Park in India)
- Captive cultivation of high altitude medicinal, aromatic and nutraceutical plants from Leh and Kargil
- Human resource training of young educated population

Land has been allotted in favour of IIIM in Leh

Layout plan of the Biotechnology Parks

CSIR-IIIM



Creation of Industrial Biotech Parks

- at
- Jammu and Srinagar
- with enabling infrastructure and incubator for

- Medicinal plants, Aroma products, Nutraceuticals, Therapeutic proteins, Antibodies, Hormones, Growth factors, Antibiotics, Bio-generics etc.

Highlights of bio-prospection (medicinal plants and microbes) and plant biology

Bio-prospection of plant species

Bio-prospection of microbial species

Biotechnology of plant secondary metabolism

Biotechnology of plant secondary metabolism in *Dysoxylum binectariferum*

Systems level analysis of *Coleus forskohlii*: Identification & Expression of CYPs

Bio-prospection of microbial species IIIM Microbial Repository

Unraveling the regulatory pathway of apocarotenoids biosynthesis in *Crocus sativus*

Plant based expression system for therapeutic proteins

CSIR-IIIM

Chemical Sciences Resource - Summary

I.

Procured Drug like Compounds : 80,000 compounds Code: IE000001 – IE080000		
Chembridge Library	ChemDiv Library	New Library
20,000 compounds	**30,000 compounds**	**30,000 compounds**

II.

Institute's Natural Product Repository: 664 compounds Code: IN00001 – IN00664
Pure Natural Compounds (Source: Plants & Microbes)
664 compounds

III.

Institute's Synthetic Compound Repository: 2172 compounds Code: IS00001 – IS02172
2172 compounds

Highlights of Natural Product Chemistry, Medicinal Chemistry and Chemical Biology

Procured drug like compound Natural Product Repository

Institute Synthetic Compound Repository ~ 2000 compounds

Institute natural Product Repository

Medicinal Chemistry towards development of Pre-clinical Candidates

Fascaplysin based anti-cancer NCEs

Non-planar analogs of fascaplysin:

Profile of D-ring opened analogs: IIIM-985 and IIIM-986

Rohutikine based anti-cancer NCEs: CDK inhibitor IIIM-290

Isoform-selective PI3K-alpha inhibitors

Preclinical and Clinical Development of Cannabis based Phytopharmaceutical leads

Highlights of Pharmacology and Pre-Clinical Development

Alzheimer's Disease and Strategies to challenge it

Anti infective screening

Medicinal Chemistry for Stem Cell Biology and Regenerative Medicine (MEDCHEM

Nurturing a new Pan-CSIR drug pipe line: high Intensity preclinical, clinical studies on lead candidates (CSIR-DPL)

Pancreatic Cancer

Oncology , Bioenhancers , Arthritis, Tuberculosis

Phytopharmaceuticals.

- Pain (Neuropathic, Cancer and Sickle Cell Anaemia)
- Positioning natural products for management of neurodegenerative diseases (Alzheimer's, Depression)
- Hair follicle biology and translation
- Biotransformation of drugs and metabolites using human cytochrome p450 cloned in yeast system
- Understanding transport mechanism of secondary metabolites in plants (ABC transporters)
- Protein drug conjugates

IIIM Societal Contributions throughout India

Rural prosperity and job creation in J&K

Catalyzing Rural Empowerment through Cultivation, Processing, Value Addition and Marketing of Aromatic Plants

Establishment of demonstration farms of aroma cash crops in district Kupwara of Kashmir Valley (K-5000)

CSIR- Sickle Cell Anaemia Mission

Phytopharmaceutical Mission Verticals

Sub divided into following verticals (CIMAP, IHBT, IIIM, CDRI, IICB, NEIST, NBRI, URDIP)

- **Vertical A: Captive cultivation of selected medicinal plants.**

Production of Quality Planting Material (QPM)/ Post harvest management package for 21 and Agrotechnology package for 16 medicinal plants.

- **Vertical B: Captive cultivation of selected high value rare, engendered and threatened (RET) medicinal plant species**

Creation of gene bank of RET species, their phytochemical evaluation for identifying elite populations (15 medicinal plants).Developing protocols for macro/ micro-propagation of 29 medicinal plants

- **Vertical C: Technology packages for production of GMP grade medicinal plant extracts for export markets.**

Developing improved process for the production of GMP extracts with defined CMC for 15 medicinal plants for global markets.

- **Vertical D: Phytopharmaceutical development from important medicinal plants**

DCG(I) guidelines

- *Cassia occidentalis* (CDRI) - glucocorticoid-induced osteoporosis (GIO)
- *Murraya koenigii* (IICB) - ovarian cancer/cancer stem cell
- *Dysoxylum binectariferum* (IIIM) - rheumatoid arthritis
- *Picrorhiza* (IHBT & CDRI) - Non Alcoholic Fatty Liver Diseases (NAFLD)

AYUSH guidelines

- *Glycyrrhiza glabra* rich extract (CIMAP) - diabetes related complications
- *Cissampelos pareira* (IHBT) - anti-venom formulation
- *Tinospora coridfolia* (CDRI) - cognitive impairments in CNS disorders
- *Bergenia ciliata* (IIIM) - pain in rheumatoid arthritis

Industrial collaboration and outlicensing

- ✓ Approval for legal captive cultivation of Cannabis accorded to IIIM (First in India)
- ✓ Preparation of clinical grade raw material
- ✓ Isolation of marker compounds and standardization of analytical procedures for phyto-cannabinoid analysis
- ✓ Clinical development of phytocannabinoid based product development for different disease areas

To develop CBD-THC based phytopharmaceutical product for pain management in Indian territory following DCGI guidelines

Investigation of Pancharishta

Nutraceutical for Brain Health

Service support for Regulatory system (DCGI & AYUSH) and Pharma Industry

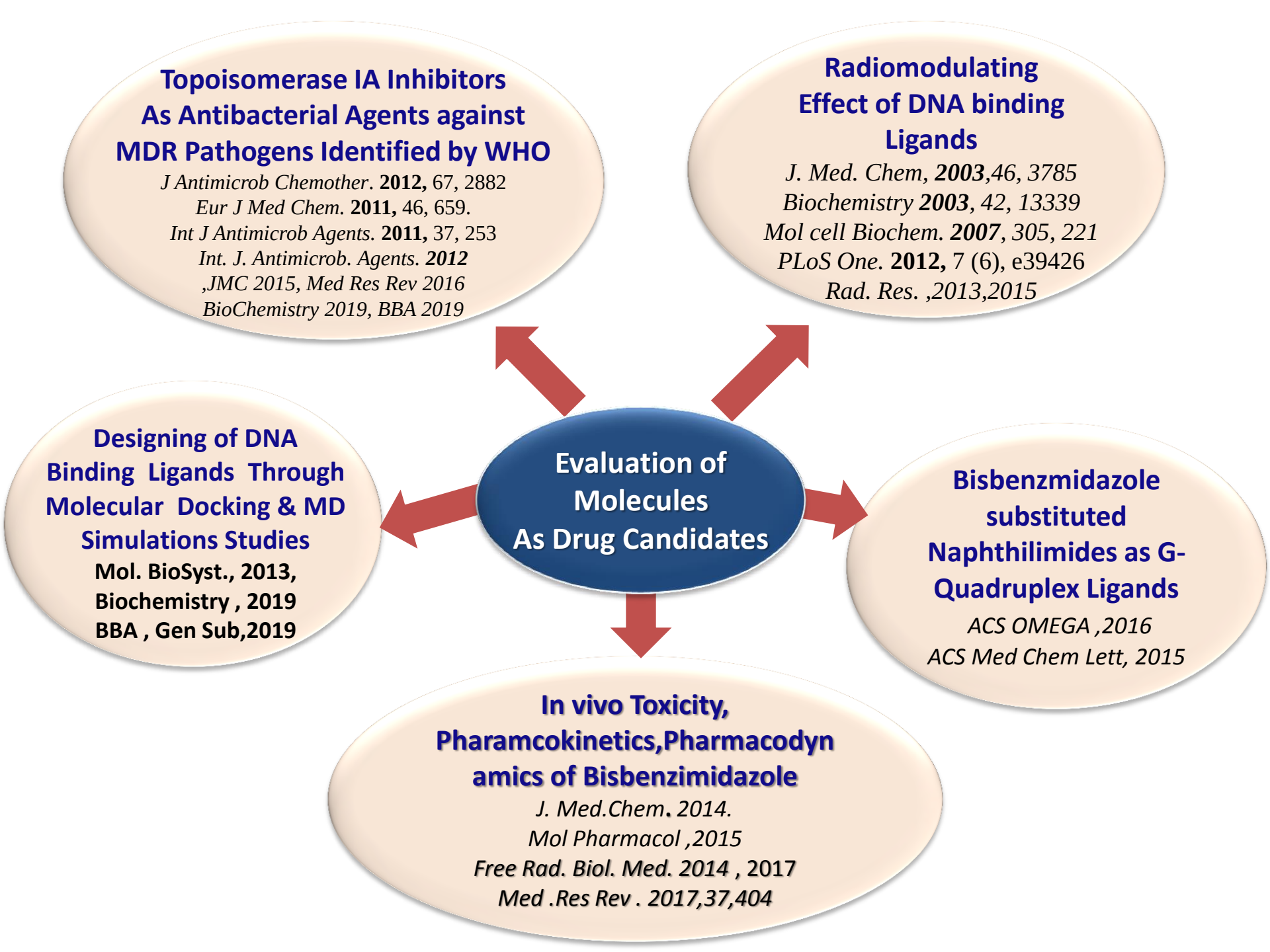
- Designated as the first CDL in India for phytopharma drugs by DCGI in 2016 for (i)data audit & verification of IND filings in India; (ii) testing samples from different state govts and (iii) drugs imported into India.

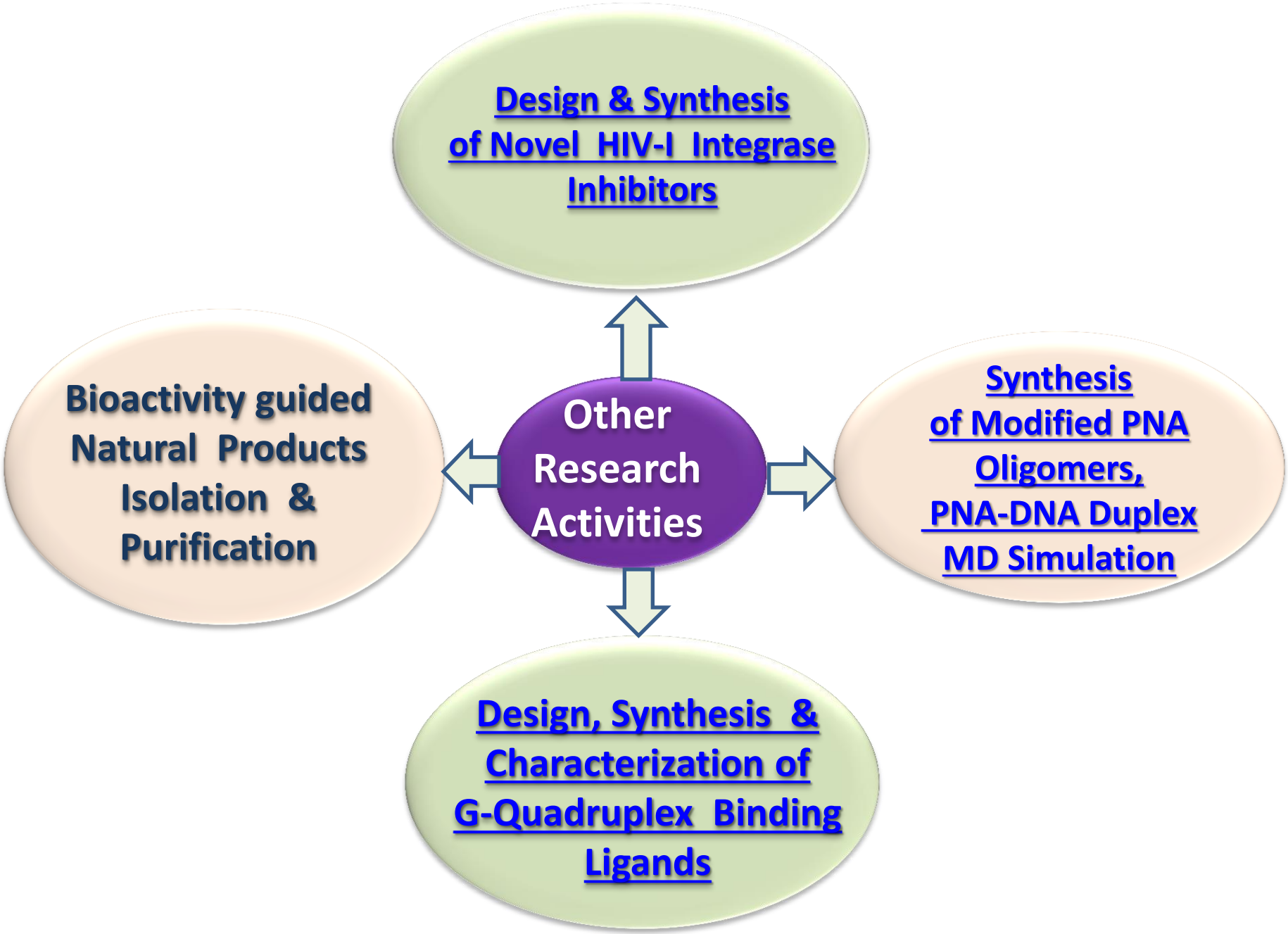
- Drug Testing Laboratory (DTL) at IIIM : A collaborative initiative of IIIM & CTR for testing of Cosmetics Pharmaceuticals (Capsules, tablets, syrups, injectables)

- Regional Raw Drug Repository (RRDR) Centre (Himalayan region) at IIIM, Jammu- being sponsored by NMPB: To act as an accredited reference library for authentication of raw drugs from i) Uttarakhand, ii) Himachal Pradesh and iii) Jammu & Kashmir

- IIIM Jammu designated as referral laboratory for FSSAI in 2016 for food products for commercial testing.

- GOI, Ministry of Health & Family Welfare, Department of Ayush, Approved CSIR-IIIM, Jammu under rule 160 (A-J) Drug & Cosmetic Rules, 1945 as Ayush commercial Ayush drug testing in the year 2010.


Topoisomerase IA Inhibitors As Antibacterial Agents against MDR Pathogens Identified by WHO
J Antimicrob Chemother. 2012, 67, 2882
Eur J Med Chem. 2011, 46, 659.
Int J Antimicrob Agents. 2011, 37, 253
Int. J. Antimicrob. Agents. 2012
,JMC 2015, Med Res Rev 2016
BioChemistry 2019, BBA 2019
Radiomodulating Effect of DNA binding Ligands
J. Med. Chem, 2003,46, 3785
Biochemistry 2003, 42, 13339
Mol cell Biochem. 2007, 305, 221
PLoS One. 2012, 7 (6), e39426
Rad. Res. ,2013,2015
Designing of DNA Binding Ligands Through Molecular Docking & MD Simulations Studies
Mol. BioSyst., 2013,
Biochemistry , 2019
BBA , Gen Sub,2019
Evaluation of Molecules As Drug Candidates
Bisbenzmidazole substituted Naphthilimides as G-Quadruplex Ligands
ACS OMEGA ,2016
ACS Med Chem Lett, 2015
In vivo Toxicity, Pharamcokinetics,Pharmacodynamics of Bisbenzimidazole
J. Med.Chem. 2014.
Mol Pharmacol ,2015
Free Rad. Biol. Med. 2014 , 2017
Med .Res Rev . 2017,37,404


Design & Synthesis of Novel HIV-I Integrase Inhibitors
Bioactivity guided Natural Products Isolation & Purification
Other Research Activities
Synthesis of Modified PNA Oligomers, PNA-DNA Duplex MD Simulation
Design, Synthesis & Characterization of G-Quadruplex Binding Ligands

My Strength

- Trained as chemical biologist , synthesis of Nucleic Acids ,Peptides and their functional and biological characterization . Design and characterization of small molecules against a specific drug target for a particular disease.
- Worked extensively on Radiotherapy in Cancer, Antibiotic development against a novel drug target Topoisomerase IA
- Cloning , Expression of Proteins/enzymes , Single , double and triple mutant generation of Proteins
- Omics of Mammalian Cells and Bacterial Cells . Evaluation of Single Cell Omics for treatment of head & neck cancer patients in India.

Two Major Research Projects

Area of expertise of Prof. Vibha Tandon: Chemical Biology, Radiation Biology, Cell Signalling ,

Working on two major projects on Drug Development

1. **DEVELOPMENT OF PPEF (SMALL MOLECULE)TARGETING BACTERIAL TOPOISOMERASE IA TO COMBAT THE ANTIMICROBIAL RESISTANCE (AMR)**

Salient discoveries include a) design of selective bacterial topoisomerase I inhibitor , which do not inhibit human topoisomerase nor DNA gyrase; and b) PPEF reduces significant bacterial load reduction for both gram-negative *E. coli* and gram-positive *S. aureus* (MRSA,VRSA) strains in Neutropenic thigh model and Systemic infection model in mice. C) These compounds showed inhibition of few ESKAPE strains and WHO priority strains of 2019. d) Active against MDR bacteria.

- The Development of PPEF as antibacterial agent has reached to TLR 5 stage.
- Societal Relevance : Development of Therapeutic Agent against Pathogens
- **DBT has sanctioned a project in mission mode under AMR call where JNU, IIT Mumbai , UDCT Mumbai and Anthem Biosciences will participate to take it to human clinical trial.**

2. Development of DMA as Radioprotector to protect Normal Cells during Radiation Therapy of Cancer.

Prof. Tandon and her co-workers synthesized a library of benzimidazoles and then screened them as Free radical quencher and radiomodulator. In vitro studies showed that DMA a benzimidazole, a DNA minor groove binder and non-toxic free radical scavenging radioprotector offered better radioprotection to normal human lung fibroblast over human lung carcinoma. Mechanistic studies revealed that DMA exerts its radioprotective activity in intestine through activation of Akt/PKB which in turn activates NFkB signaling. Interestingly, tumor tissue investigation in small animal models suggested that DMA + Radiation condition did not increase either NFkB or pAkt level in intestine. Pk, PD, Bioavailability & toxicity studies suggested that DMA has a good therapeutic potential and specifically protects normal cells over tumor cells.

- The Development of Radioprotector has reached to TLR 6 stage.
- Societal Relevance : Development of Radioprotectors for protection of normal cells during radiotherapy of cancer cells.
- **BIRAC has approved under PACE/CRS/AIR call to develop it for Radiotherapy of Head & Neck Cancer patients.**

Project1 ; Development of PPEF (Small Molecule)Targeting Bacterial Topoisomerase IA to Combat the Antimicrobial Resistance

Work Done So Far

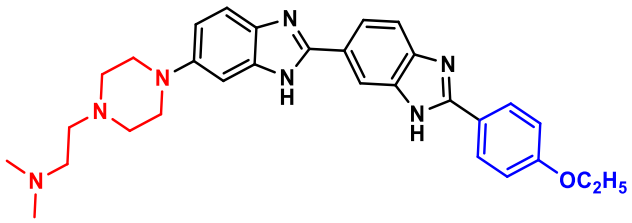
Novel benzimidazole PPEF showed inhibition of 150 clinical E. coli strains and 80 gram-negative and positive clinical strains.
PPEF inhibits Topoisomerase IA. PPEF binds traps the topoisomerase IA PPEF binds near acidic triad at the active site of enzyme.
PPEF showed 2 and 4 log reduction in bacterial infection in Septicaemia and Neutropenic thigh model in mice

PPEF does not inhibit gyrase and human topoisomerase .
It accumulates ~20 min into bacteria and efflux out slowly .
Treatment with PPEF does not induce mutation in target enzyme at gene level.
PPEF showed lower binding with mutant protein having mutation at active site (DDE motif).

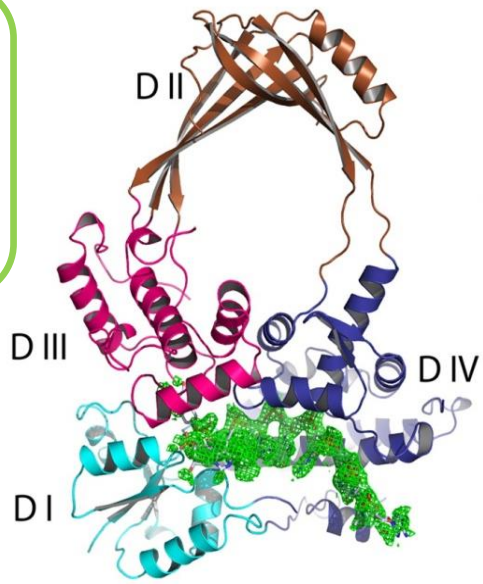
Biochemistry. 2019, 58(6):809-817.
Sci Rep. 2017, 7:44419.
Med Res Rev. 2017, 37(2):404-438.
J Med Chem. 2014, 57(12):5238-57.
J Antimicrob Chemother. 2012,67(12):2882-91.
Int J Antimicrob Agents. 2010, 35(2):186-90.

Project at TLR 5 Stage

PPEF



2-(4-(2'-(4-ethoxyphenyl)-1*H*,3'*H*-[2,5'-bibenzo[*d*]imidazol]-6-yl)piperazin-1-yl)-*N*,*N*-dimethylethan-1-amine



E. coli Topoisomerase IA

Future Work

To determine binding site of PPEF at Topoisomerase and elucidate mechanism of Inhibition by X-ray crystallography.
To study the effect of benzimidazole on the genome and transcriptome of Bacteria to find out new drug targets
Development of bioenhanced and targeted DDS for oral and IV delivery of PPEF

To study the effect of PPEF on WHO reported priority pathogens (*A. baumannii, Enterobacteriaceae* spp. *E. faecium*, *S. aureus, S. typhi S. pneumonia*, *Shigella* spp) & *E. coli* (ESBL producing Strain).

To Study ADME and Toxicity
To Study In-vivo efficacy with oral delivery - SMEDDS; ED_{50} study for lead molecule
In-vivo efficacy using Intravenous delivery system
In situ nano technology; ED_{50} study for lead molecule
Validate GMP synthesis and GLP Toxicity studies

Novelty, Feasibility and IP Strategy

Novel Molecule, Solid, Stable, Long shelf life, Salt formation and formulation is possible, Bioavailability is good, Synthesis can be upscaled upto kilogram level , Huge market for antibiotics

Novel drug target : Topoisomerase IA, Target druggable, No mutations reported
Molecule is targeting topoisomerase IA of bacteria but not humans , Cost effective

1. PCT Application Filing No: PCT/IN2017/000013

   Title: "Broad spectrum antibacterial activity of novel Bisbenzimidazole targeting topoisomerase IA and synergistic composition of Bisbenzimidazole with efflux pump inhibitors against pathogenic bacteria"

   Date of Filing: 20/01/2017, RO/IN (Delhi).

2. Indian Filing no. 201611002627

   Title: "Broad spectrum antibacterial activity of novel Bisbenzimidazole targeting topoisomerase IA and synergistic composition of Bisbenzimidazole with efflux pump inhibitors against pathogenic bacteria"
   Date of Filing: 23/01/2016, Delhi.

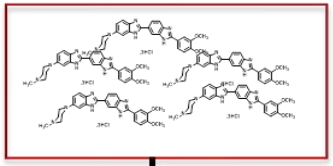
3. US Application No.: 16/072,018

   Title: Broad Spectrum antibacterial activity of Novel Bisbenzimidazoles targeting topoisomerase IA and the synergistic composition of Bisbenzimidazole with efflux pump inhibitors against Pathogenic Bacteria
   Date of filing : January 20, 2017

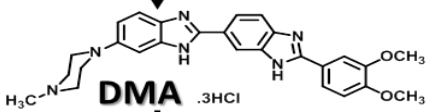
4. Canada Application No. **3,011,672**

   Title: Broad spectrum antibacterial activity of novel bisbenzimidazoles targeting topoisomerase IA and the synergistic composition of bisbenzimidazole with efflux pump inhibitors against pathogenic bacteria
   Date of filing : January 20, 2017

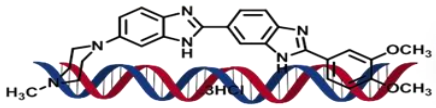
Project 2: Development of DMA as Radioprotector to protect Normal Cells during Radiation Therapy of Cancer



Bisbenzimidazole Library

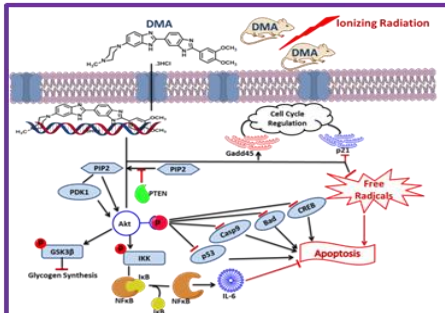


Free Radical Scavenging

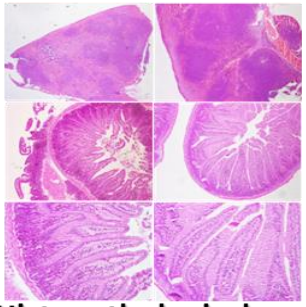


DNA minor groove Binder (AT specific)

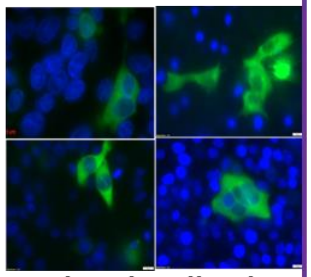
In vivo & vitro Radioprotection work



Mechanism of action



Histopathological study



Nuclear localization

Differential Radioprotection Normal v/s Tumor

Comprehensive toxicological & pharmacological data

Akt & NFκB Knockdown mice for further validation of mechanism of action

Bisbenzimidazole library Synthesis

⇩

Bisbenzimidazole library Screening for potent radioprotector

⇩ Stage I

Maximum tolerated dose & toxicity of agent

⇩ Stage II

Radioprotective/Mitigative effect in vivo & vitro in both normal & tumor

Histopathological study

⇩

Identification of Mechanism of action, if any

⇩ Stage III

Comprehensive toxicological & pharmacological data on ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity profiles)

⇩ Stage IV

Clinical Investigation

Novelty, Feasibility and IP Strategy

Novel Molecules Solid , Formulations can be made , Oral or other mode of actions.

1. US Patent Granted : US 10, 016,515 B2 , Date of Patent : Jul 10, 2018.

Title of the invention:

DMA, a Bisbenzimidazole, confers radioprotection to the intestine via AKT/NFkB dual pathway activation. Inventors name: Vibha Tandon, SCMM, JNU.

Brief description of the Invention:

- **DMA, a benzimidazole acts as a radio protector. It exerts radio protective activity through activation of Akt/PKB pathway that in turn activates NfkB signaling in normal tissue/Cells. However tumor tissue investigation suggested that DMA+ radiation condition did not increase either NfkB or pAkt level, suggesting it specially protects normal cells over tumor cells.**

2. Filed in Canada application no. 2,937,241, Pending for examinations.

3. Indian Patent No: 241650, Patent application No 32/DEL/2003
Title: The process for the synthesis of benzimidazoles and its derivations.
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4. European Patent No: 1590332 European patent application no. 03815133.8
PCT International patent application no.PCT/IN03/00301
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