Dr. B R Ambedkar Center for Biomedical Research
Faculty of Science
University of Delhi

SYLLABUS FOR Ph.D. COURSE WORK

The center in keeping with its inter-disciplinary nature offers the following syllabus for the Ph.D. Course work. There are a total of four papers that each student has to clear. Paper I (Research Methodology), Paper II (Tools and Techniques in Biomedical Research) and Paper III (Writing a Research proposal) are compulsory. In Paper IV a student can opt for any two modules.

Overview of the Papers:

The Research Methodology paper has been designed to inculcate a scientific temperament in the student and introduce the basic requirements for being a good and motivated researcher. Emphasis is laid on the need to identify a challenging research topic following an extensive literature survey. Learning how to design simple and complicated experiments, the need for reproducibility, analyses of the data obtained and its significance in moving forward follows this. In parallel, the student is also trained to follow ethical guidelines, display scientific integrity; identify conflict of interest and plagiarism issues while writing scientific documents.

The Paper on Tools and Techniques in Biomedical Research focuses on the principles, scope and applications of routine and advanced techniques the student is likely to use in his/her research. This will prepare the student to keep in mind the scope and limitations of each technique that will be useful in designing experiments and interpreting the data.

The Paper on Writing a Research Proposal, prepares the students for writing grant proposals that will be extremely useful following the successful completion of the Ph.D. With a number of post-doctoral fellowships now being offered by leading National and International funding agencies this paper will be beneficial to him/her.

The Advanced Modules Paper with an array of modules is in keeping with the inter-disciplinary nature of ACBR. A student can opt for any two. Any student is welcome to attend the courses of other modules as well but will be evaluated on his/her choice of the modules opted at the start of the semester.

Course structure and evaluation criteria:

All the papers will be evaluated at the end of each semester and include internal assessment. The individual teachers as per their chosen criteria will decide the internal assessment. A written

exam will be held for Papers I, II and IV. For Paper III (Writing a Research Proposal) the student will have to submit a project proposal and defend the same in the form of power-point presentation.

The student has to score at least 50% marks in each paper to qualify the same.

Program Structure

PAPER NO.	Paper Title	End-semester Examination	Internal Assessment
PHBS-I	**Research Methodology**	**50 Marks (July-December)**	**50 Marks (July-December)**
PHBS-II	**Tools and Techniques in Biomedical Research**	**70 Marks (July-December)**	**30 Marks (July-December)**
PHBS-III	**Writing a Research Proposal**	**70 Marks (January-June)**	**30 Marks (January-June)**
PHBS-IV	**Advanced Modules (any two)**	**70 Marks (January-June)**	**30 Marks (January-June)**

PHBS-I: Research Methodology

Research Methodology: An Introduction

Objectives and motivation in research, Approaches to scientific research- Issues and concerns related to scientific investigation; lack of exclusivity of methods of research; Merging of various approaches in practice of scientific research

Literature Search and managing research outcomes

Introduction to peer-reviewed and open access journals, E-journals and E-books. Citation of papers; Search of research articles via subject and author index. Common search engines for literature- NCBI, Scopus, Google Scholar, Scirus, SciFinder. Systematic literature search. The importance of reliability of retrieved data; source evaluation. Formulating key word(s)based query to retrieve appropriate data, Managing personal reference database.

Defining a Research Problem

Identifying gaps in knowledge through literature mining, identifying area of societal need like health/technology/anticipated crisis such as epidemic, energy, water. Elements for outlining a research problem. Developing an approach strategy, feasibility testing.

This unit will have extensive classroom discussion, and students' participation through formulation of pilot projects to illustrate identification of research problems.

Designing of Experiment: Strategies, Planning and Analysis

Selection of research topic and its national and international scenario. Techniques involved in research plan using an illustration, Defining Standard Operating Protocols (SOPs), Research Conditions, Repeatability, reproducibility and reliability of results, Accuracy and Precision, Significant figures with reference to numerical data, Errors and uncertainty analysis. Types of errors: Gross error, systematic error, random error, Statistical analysis of data.

Methods in Biomedical Research

To illustratively discuss Clinical Research, Ethical issues in clinical research, Epidemiology: (classical examples of epidemiological studies such as leprosy, twin studies), Good clinical research methodology

Laboratory and Safety Practices

Biosafety; Introduction to occupational health and safety (chemical, biological and radiation), awareness about handling toxic laboratory chemicals, pathogenic microorganisms, and their safe disposal. Idea about labels and Material Safety Data Sheet (MSDS), safety equipment and procedures, Fire extinguishers, First aid kit.

Research Ethics and Intellectual Property

Research and scientific writing ethics, plagiarism, concept of peer-review, conflict of interest, research misconduct. Illustrations of violation of ethical conduct. Introduction to IPR (Patent, trademarks, copyright, trade secrets), Importance of academia-industry interaction, Marketing of research outcome.

Scientific Documentation

Significance of report writing, steps in report writing, Types of report: Decision-oriented (Technical) and Survey-based report. Guidelines for reviewing draft report format, typing instructions, citing references with examples.
Writing a scientific paper; structuring a manuscript, data representation for effective communication. Discussions on Journals relevant to Biomedical research and their paper writing patterns could be discussed.

SUGGESTED READINGS:

1. Research in Education (2005) 10th ed., Best, J.W. and Kahn, J.V., Prentice Hall of India Pvt. Ltd. (ISBN-13: 978-0205458400)

2. At the Bench: A Laboratory Navigator (2005) Barker, K., Cold Spring Harbor Laboratory Press (New York). ISBN: 978-087969708-2.

3. Research Methodology - Methods and Techniques (2004) 2nd ed., Kothari C.R., New Age International Publishers. (ISBN-13 / EAN: 9788122415223)

4. Research Methodology: A Step by Step Guide for Beginners (2010) 3rd ed., Kumar R., Pearson Education. (ISBN-13: 978-1849203012)

5. The Craft of Research (Guides to writing, editing and publishing) (2008), Booth, W.C., Colomb, G.G., Williams, J.M., University of Chicago Press, 2008. (ISBN-13: 978-0226065663)

PHBS-II: Tools And Techniques in Biomedical Research

Spectroscopic techniques and their biomedical application
Absorption Spectroscopy: UV-Vis and IR spectroscopy- Beer's Lambert's Law, Hook's Law, Instrumentation, Application in quantitation of Protein and Nucleic acid samples

Circular Dichroism Spectroscopy- Cotton effect and Basic principle, instrument, Application in elucidation of protein secondary structure

Fluorescence spectroscopy- Principle, Instrument, Stoke's shift, fluorophores- extrinsic and intrinsic, various type of probes, Application in biomolecule quantitation. Basic principle of FRET (Fluorescence Resonance transfer)

NMR - Basic principle, Instrument, Sample preparation, [^{1}H] NMR analysis, troubleshooting **with its biomedical application**

Mass spectroscopic techniques- Basic principle and EI, Instrument, calculate m/z, MALDI-TOF instrument and principle.

Chromatographic techniques: HPLC, FLPC, RPLC, and *Gel chromatography:* protein, DNA and RNA purification and separation by PAGE, SDS PAGE, and Agarose gel electrophoresis, Sample preparation and trouble shooting.

1. **Centrifugation**: Principle and different types of centrifugation- differential, density gradient and equilibrium.

2. **Radioactivity:** Basic principle, various labels and their energy, radioactivity decay, Concentration vs specific activity, biomedical application, biosafety

3. **Microscopic techniques and its biomedical application**: bright field, dark field, phase contrast, confocal, fluorescence, electron microscopy, infrared and ultraviolet microscopy. Sample preparation and trouble-shooting.

4. **Flow cytometry**-Basic Principle, Instrument, Sample preparation and quantitation and trouble-shooting and biomedical application of flow cytometry.

5. **Living organisms as tool for research**
   A. Bacteria: *Handling of bacteria:* laminar flow hoods its principle and SOP, preparation of culture media for bacterial propagation, sterilization and disinfection, identification of contamination and its prevention, bacterial growth curve, transformation, competent cell preparation, disposal of bacterial culture and media.

B. **In-vitro cell culture:** *concept of cell culture:* isolation of cell, maintaining cells in culture medium, cell line contamination and its detection, *manipulation of cell culture*: passage and transfection, sterilization of culture room, disposal of cell culture and media, application of cell culture.

6. **Bio-statistical tools for data analysis**: Introduction to Mean, mode, median, mean deviation, Standard deviation, coefficient of variation. Correlation (Karl Passions, Co-efficient of correlation, Rank correlation) and Regression analysis, taking suitable examples from biological data. Probability: Theorems on probability, Binomial and normal distribution. Methods of Sampling of biological data and analysis using various tests of significance for small and large samples (AVONA and post-hoc analysis).

PHBS-III: Writing a Research Proposal

Under this course, each student will write a project proposal and defend it through presentation. The student will collect the relevant literature, collate the information and write a research proposal with proper incorporation of references using appropriate software like Reference Manager or EndNote or Mendeley on a topic of mutual interest of the mentor.

The student will identify a problem on which he/she would be able to work, identify the scope of research on the chosen topic and will frame the objectives to be addressed in the project through a work plan.

The student will write the standard operating protocols (SOPs) and identify requirement for equipment and reagents. Each student will be required to make a presentation and defend the proposed project including literature available, objective sought and work plan as described above.

PHBS-IV – ADVANCED MODULES (Opt any two)

A. Methods in Enzyme kinetics, Ligand binding and protein Structure

Enzyme kinetics:
Introduction to enzyme catalysis, Michaelis-Menten relations, enzyme assay methods, specific activity estimation, determination of Activation energy, Determination of inhibition mechanisms, Determination of enzymatic parameters (K_m, k_{cat}, V_{max}).

Ligand binding:
Introduction to ligand, concept of stoichiometry of binding, common instruments used to study ligand binding (ITC, SPR and FRET): principle and method of analysis binding curves, Methods for determination of binding constants and other thermodynamic parameters, Determination of number of binding sites

Protein Structure:
Concept of native and denatured state, common tools use to address protein structure (UV-vis, Fluorescence spectroscopy, CD, FTIR, NMR, X-ray etc.) (Principle and applications), Protein denaturation, Different mode and Mechanisms of denaturation, Understanding and analysis of melting curves, Tools commonly use to monitor protein denaturation (Optical methods and DSC) co-solutes and their interaction with native protein

B. Computational and Molecular Modeling Method

1. Basic bioinformatics: Databases, sequences, sequence alignment-pair wise/multiple, global/local protein family, domain, sequence conservation.

2. Basic structural elements of protein and nucleic acids- Primary, secondary and tertiary structures of the proteins and DNA, super secondary structure, hairpin, beta-beta units, beta-alpha unit etc. nucleic acid structures.

3. Analysis of 3D Structures: Adding hydrogens, analyzing H-bonds, analyzing cavities, analysis of atomic contacts etc.

4. Structural modeling and secondary structure prediction: Structure prediction in ID space, *scoring function*: force fields, knowledge based potentials, surface area based function, searching procedures: grid search, *Monte carlo* algorithm, genetic algorithm, *Building*

Models- homology models, fold recognition, Ab initio methods, modeling side chain conformation, rotamer libraries.

5. Molecular docking- Protein-protein docking, protein-ligand docking.

6. Molecular motions: Energy minimization methods and conformational sampling and optimization (grid search, steepest descent, conjugate gradient), molecular dynamics.

7. Drug design- Docking, virtual screening, QSAR, ADMET, drug likeliness etc.

C. Introduction to tools of Genomics Research

1. Generation of disease models for Biomedical Research.
   Transgenic animals, targeted Knock-out and knock-in, Cre-lox and CRSPR-Cas system, Design of knock-down through siRNA/RNAi

2. Assessment of genetic manipulation: example PCR, RT-PCR, qPCR, LAMP

3. Introduction to New Generation Sequencing methods.

4. Transcriptomics: Microarray,RNA-sequencing, exome sequencing, exome Chip,

5. Tools for epigenome analysis: DNA methylation analysis, Chromatin Immuno-precipitation (ChIP), ChIP-sequencing, Approaches to long range interaction in the genome.

D. Introduction to Tools of Proteomics Research

1. Methods of protein analysis: Different types of Gel electrophoresis, substrate gel electrophoresis, ELISA, EMSA, Western Blot.

2. Co-Immunoprecipitation, Yeast Two hybrid: experimental design and strategy, read-outs, and trouble-shooting Applications and its limitations.

3. Proteome analysis: 2D-PAGE, Mass spectroscopy for protein: principle, sample preparation handling and trouble-shooting, Orbitrap Mass analyser.

4. Introduction to software used for proteomics data analyses.

5. Concept of Metabolomics and Lipidomics and their applications.

E. **Techniques in translational Research**

1. Prokaryotic and eukaryotic organisms as model. (OPT ANY ONE)

a) Guide for the selection of appropriate microorganism as model organism-Bacteria, basic maintenance and propagation and storage, methods to identify species by sequencing, disease model based on prokaryotes.

b) Guide for the selection of appropriate eukaryotic organism as model organisms e.g. Yeast, *C. elegans*, Drosophila, Mouse, Rat based disease-models.

c) Mouse and rat as research tools: Animals and their welfare, basic animal handling, breeding and maintenance, understanding of animal behavior, use of anesthesia and analgesia, Euthanasia, Sample size and statistical analysis, administration of drug and animal waste disposal, contamination and infection.

d) Research ethics for animal and human use for experiments: animal and human welfare in research, justification of research, skill of personnel conducting the research, *experimental procedures and its rationale:* choice of biological fluid withdrawal and route of drug administration.

2. **Techniques in translational research (OPT ANY ONE)**

a) **Techniques in physiology:** ECG- basic cardiology and analysis of ECG, General organization of brain-receptors, neuro-transmitters and analysis of EEG, General muscle physiology and EMG analyses.

b) **Techniques in Behavioral pharmacology and toxicology:** Acute toxicity, LD_{50}, ADMET studies, behavioral test for cognition and motor function.

c) **Techniques in Immunology:** ELISA, immunizations, antibody generation in small animals. Techniques to study innate immune responses, use of FACS, MACS, RNAi and real time lime lapse video microscopy to study immune activation/inhibition in 4-dimensions.

F. Essential Paradigm in Medicinal Chemistry Research

1. Basic principles of Medicinal chemistry –Biochemical reactions relating to organic reactions, endogenous ligand and their role in drug design, serendipity in new drug discovery.
2. Concepts in drug targeting: Pathology of diseases e.g. PD, Alzheimer and Cancer, molecular pathways for identification of target for drug design.
3. Strategies for lead discovery-Lead identification and modification: Hammett equation, Hansch postulates and extension of Hansch equation, SAR and QSAR.
4. Ligand based drug discovery: Conventional methods and High Through put screening of the virtual libraries. Structure based drug design- *Classical methods and In-silico tools*.
5. Pharmacophore and the Factors modulating the pharmacophore.
6. Theories of drug and receptor (biomolecule) interactions.
7. Factors influencing drug receptor interactions.
8. Pharmacokinetics and drug metabolism and factors influencing drug metabolism.
9. Modulation of drug like properties of compounds.
10. Measure the binding of agonist and antagonist with receptor and Enzyme kinetics to calculate substrate binding.
11. Example of existing drug and their design strategies: drug acting on receptors and DNA.
12. Methods of Drug Discovery to Improve pharmacokinetic profile.