FACULTY OF MEDICINE

SCHOOL OF MEDICAL SCIENCES

DEPARTMENT OF PHARMACOLOGY

PHAR 3101

Rational Drug Design

COURSE OUTLINE

SESSION 2, 2010

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PHAR3101 Course Information

Rational Drug Design (PHAR3101) is a 3rd year Science Course worth Six Units of Credit (6 UOC). The course is usually undertaken as part of a major in Pharmacology for the Bachelor of Science or Bachelor of Medical Sciences. The course will build on the information you have gained in Pharmacology (PHAR2011, PHAR3102 & PHAR3251) and Physiology (PHSL2101 & PHSL2201).

OBJECTIVES OF THE COURSE

This course will explore the process of drug development, from lead discovery to final drug registration. It will present drug development as a process involving target selection, lead discovery using computer-based methods and combinatorial chemistry/high-throughput screening. Safety evaluation, bioavailability, clinical trials, and the essentials of patent law will also be discussed. Along the way you will learn about molecular recognition, computer-aided drug design, and toxicology as applied to the development of new medicines

COURSE CO-ORDINATOR and LECTURERS:

Course Coordinator:
A/Prof. Renate Griffith
Rm M206 Wallace Wurth Building ph: 9385 1912
Consultation times: Wednesday 11-12am

Students wishing to see course coordinator outside consultation times should make an appointment *via* email.

Lecturers in this course:

Dr Trudie Binder	w.binder@unsw.edu.au
A/Prof. Renate Griffith	r.griffith@unsw.edu.au
Prof. Peter Gunning	p.gunning@unsw.edu.au
Dr Nicole Jones	n.jones@unsw.edu.au
Dr John Langlands	j.langlands@.unsw.edu.au
Dr Trevor Lewis	t.lewis@unsw.edu.au
Dr Lu Liu	lu.liu@unsw.edu.au
A/Prof. Laurence Wakelin	l.wakelin@unsw.edu.au

COURSE STRUCTURE and TEACHING STRATEGIES

Learning activities occur on the following days and times:

- Lectures: Tuesday 11-12 am, Wednesday 12-1 pm; **Weeks 1-12**
- Tutorials: Thursday 11-12 am or* Wednesday 5-6 pm; **Weeks 2-13**
- Practicals: Monday 10-1; **Weeks 2-6, 8-10, 12+13**
- *: Once enrolled in one of the two sessions, students cannot change.

Students are expected to attend all scheduled activities for their full duration (2 hours of lectures per week and up to 4 hours of practical and tutorial sessions per week). Students are reminded that UNSW recommends that a 6 units-of-credit course should involve about 125-150 hours of study and learning activities. The formal learning activities are approximately 60 hours throughout the semester and students are expected (and strongly recommended) to do at least the same number of hours of additional study.

Lectures will provide you with the concepts and theory essential for understanding the processes involved in drug development. To assist in the development of research and analytical skills practical classes and tutorials will be held. These classes and tutorials allow students to engage in a more interactive form of learning than is possible in the lectures. The

skills you will learn in practical classes are relevant to your development as professional scientists.

APPROACH TO LEARNING AND TEACHING

The learning and teaching philosophy underpinning this course is centred on student learning and aims to create an environment which interests, challenges, and enthuses students. The teaching is designed to be relevant and engaging in order to prepare students for future careers.

Although the primary source of information for this course is the material covered in lectures, tutorials, and practical classes, effective learning can be enhanced through self-directed use of other resources such as textbooks and Web based sources. Your practical classes will be directly related to the lectures and it is essential to prepare for practical classes before attendance. It is up to you to ensure you perform well in each part of the course; preparing for classes; completing assignments; studying for exams and seeking assistance to clarify your understanding.

STUDENT LEARNING OUTCOMES

PHAR3101 will develop those attributes that the Faculty of Science has identified as important for a Science Graduate to attain. These include; skills, qualities, understanding and attitudes that promote lifelong learning that students should acquire during their university experience.

Graduate Attributes

A. Research, inquiry and analytical thinking abilities
B. The capability and motivation for intellectual development
C. Ethical, social and professional understanding
D. Effective communication
E. Teamwork, collaborative and management skills
F. Information Literacy – the skills to locate, evaluate and use relevant information.

On completion of this course students should:

1. be able to describe the process of drug discovery and development
2. be able to discuss the challenges faced in each step of the drug discovery process
3. have gained a basic knowledge of computational methods used in drug discovery
4. be able to organise information into a clear report
5. be able to demonstrate their ability to work in teams and communicate scientific information effectively

ASSESSMENT PROCEDURES

- Progress exam (45 min duration): short and long answer questions **10%**
- Practical assessment (1 report) **10%**
- Practical assessment (1 exercise) **5%**
- Group assignment (10% for each individual's report) and synopsis (5%) **15%**
- End of session examination (2 hours duration): short and long answer q. **60%**
  (50% on lectures and tutorials, 10% on practicals)

The *practicals and tutorials* are provided to support lecture material and practise analytical skills. The practical classes and tutorials help you to develop graduate attributes A, C, D & E. During the practical course you will be required to submit a written report covering three of the practical sessions. The report itself should be in the form of a scientific communication comprising aims, results and discussion (see in separate practical notes). Reports must be

as concise as possible, and are limited to a maximum of 4 pages of writing (excluding tables, figures and computer traces). **The report will be due Friday, October 8 (week 11)**. For the Visualisation practical, **brief written answers to questions will be required by Friday, August 20 (week 5)**. Written assessment tasks must be accompanied by a signed plagiarism form and placed in the locked box in room MG14, Wallace Wurth building. The report also has to be submitted electronically *via* Blackboard, through Turnitin. A penalty will apply for late submissions (10% per day). Material covered in the Practical Classes will be examined.

Students will work in teams to research the drug discovery process of a given drug. They will submit an *individual written report* and a *group synopsis* on their findings by Monday, October 18 (week 13). This assessment task will allow you to develop your research, information literacy, communication and time management skills, as well as allowing you to demonstrate your ability to work in a team and collaborate successfully (Graduate attributes A, D, E &F). The marking criteria and instructions are on pages 17 to 22. Written assessment tasks must be accompanied by a signed plagiarism form and placed in the locked box in room MG14. They also have to be submitted electronically *via* Blackboard, through Turnitin. A penalty will apply for late submissions (10% per day).

The *progress examination* will be held during the first lecture session in week 6, on the 24th of August. This exam will give you feedback on how you are succeeding in the course. The *progress examination* and *end of session examination* will test not only your knowledge of the process of drug design and development but also your ability to apply the knowledge you have acquired from multiple lectures to drug development scenarios. The examination will be in the format of short and long answer questions. The questions will be based on the material covered in the lectures, practical classes and tutorials. Material covered prior to the progress exam may be again examined in the final exam. The examinations will address graduate attributes A and B. The end of session examination will be held during the official examination period.

TEXTBOOK AND READING LIST

Recommended Primary Text:

- Drug Discovery and Development; Technology in Transition. HP Rang. Elsevier Ltd 1st edition 2006.

This textbook will be available at the UNSW bookshop.

Additional reading suitable as Secondary Resources:

- A Pharmacology Primer. Theory, Applications, and Methods. T. P. Kenakin. 3rd Edition Elsevier, 2009.
- An introduction to medicinal chemistry. G. L. Patrick. 4th Edition Oxford UK, Oxford University Press, 2009.
- Medicinal chemistry: an introduction. G. Thomas. Chichester UK: John Wiley, 2000.
- Textbook of Drug Design. Krogsgaard-Larsen, Liljefors and Madsen (Editors), Taylor and Francis, London UK, 2002.
- Drug Discovery Handbook S.C. Gad (Editor) Wiley-Interscience Hoboken USA, 2005.

These textbooks are available from the UNSW library.

Other Resources:

The following electronic journals are accessible *via* the UNSW library.

- Nature Reviews: Drug Discovery. In particular the Article series
- Drug discovery and development
- Drug discovery today.
- Science online special “Drug discovery” http://www.sciencemag.org/sciext/drugdisc/

Links to additional articles of interest will be placed on the course pages on Blackboard.

COURSE EVALUATION AND DEVELOPMENT

Each year feedback is sought from students about the courses offered in the Department of Pharmacology and continual improvements are made based on this feedback. The Course and Teaching Evaluation and Improvement [CATEI] Process of UNSW is the way in which student feedback is evaluated and significant changes to the course will be communicated to subsequent cohorts of students. A staff-student liaison group will also be set up and students will be invited to become class representatives to seek feedback from their colleagues and meet with academic staff to discuss any issues that arise. Several improvements to PHAR3101 have been made based on feedback given in 2006 to 2009. These changes include: a new textbook, increased tutorial support and changes to lecture and practical content. Two new practicals have been introduced for 2010.

GENERAL INFORMATION

The Department of Pharmacology is part of the School of Medical Sciences and is within the Faculty of Medicine. It is located on the lower ground, ground, 2nd and 3rd floors of the Wallace Wurth building. General inquiries can be made at the School of Medical Sciences Student enquires counter, located on the Ground Floor of the Biosciences building (G27). Office hours are 9.00 am - 5:00 pm.

Professor Margaret Morris is Head of Department and appointments may be made through the Administrative Assistants in Room MG14, Wallace Wurth building.

The School of Medical Sciences conducts an honours program. The Honours program is coordinated by Dr Patsie Polly, Room 508, Wallace Wurth building (ph: 9385 2924). Any students considering an Honours year should discuss the requirements with the coordinator. Outstanding students may be considered for scholarships offered by the University and School and these are offered annually.

Postgraduate research degrees
The Department of Pharmacology offers students the opportunity to enter into the following graduate program:

Doctorate (***Ph.D)***: In Pharmacology. For further information contact the co-ordinator Dr Pascal Carrive (p.carrive@unsw.edu.au)

Departmental Vacation Scholarships: The Department of Pharmacology supports several summer vacation scholarships each year to enable good students to undertake short research projects within the department. For further details contact the Administrative Officer.

The School Teaching Administrator
Ms Carmen Robinson is able to provide additional information on any courses offered by the School. Student enquires counter, located on the Ground Floor of the Biosciences building (G27). Ph: 9385 2464. Email: Carmen.Robinson@unsw.edu.au

OFFICIAL COMMUNICATION BY EMAIL

All students in the course PHAR3101 are advised that email is now the official means by which the School of Medical Sciences at UNSW will communicate with you. All email messages will be sent to your official UNSW email address (e.g. z1234567@student.unsw.edu.au) and, if you do not wish to use the University email system, you MUST arrange for your official mail to be forwarded to your chosen address. The University recommends that you check your mail at least every other day. Facilities for checking email are available in the School of Medical Sciences and in the University library.
When contacting a lecturer with a query, it is essential that the following information is provided as a minimum: student name, student number, course number, course name.

ATTENDANCE REQUIREMENTS

Attendance at practical classes is compulsory, and must be recorded in the class roll ON THE DAY OF THE CLASS. It is your responsibility to ensure that the demonstrator records your attendance and no discussions will be entered into after the completion of the class. Satisfactory completion of the work set for each class is essential. It should be noted that non-attendance for other than documented medical or other serious reasons, or unsatisfactory performance, **for more than 1 practical class during the session** may result in an additional practical assessment exam or ineligibility to pass the course.

BEHAVIOUR IN PRACTICAL CLASSES

The practical class is an opportunity for students to develop graduate attribute C by behaving in an ethical, socially responsible and professional manner within the practical class.

- Punctual arrival is expected.
- Turn off mobile phones before entering the class.
- A lab coat must be worn to practical classes in weeks 4-6, 8, and 12+13.
- Enclosed shoes are compulsory for all practicals.

Information on relevant Occupational Health and Safety policies and expectations will be provided in the practical notes, as outlined at http://www.hr.unsw.edu.au/ohswc/ohs/ohs_policies.html.

Students must take due care with biological and hazardous material and make sure all equipment is left clean and functional. Those who don't adhere to these basic laboratory rules will be marked absent.

PRACTICAL CLASSES

The experimental procedure for each practical is given in separate practical notes. Students are required to familiarise themselves with the experimental procedure before attending each class.

In the interests of safety, special attention should be paid to any precautionary measures recommended in the notes. If any accidents or incidents occur they should be reported immediately to the demonstrator in charge of the class who will record the incident and recommend what further action is required.

Animal Experimentation

The procedures used in the laboratory classes involving *the use of animals* have been approved by Animal Care and Ethics Committee (registration number ACEC10/71A). All experiments undertaken in the Department of Pharmacology adhere to the NHMRC code of conduct for animal experimentation.

NOTICEBOARDS

Noticeboards for this course can be found on the 2nd floor of the Wallace Wurth building. Current timetables and information relevant to you will be displayed here and on the course page on Blackboard. It is your responsibility to check these regularly.

WWW TEACHING RESOURCES

The Department of Pharmacology has chosen to use the University's central Blackboard service to provide teaching materials for all of its courses.

- To access these materials, either point your browser to the TeLT gateway (http://telt.unsw.edu.au/) or go to the School's home page at: http://medicalsciences.med.unsw.edu.au/ then select "Current Students" from the menu bar and click on UNSW Blackboard Learning, under "Quicklinks" in the left column.
- Log in using your zPass (zStudentNo. and password).
- After logging on to Blackboard, look for the course PHAR3101. You should have access to it if you are properly enrolled.

You can make use of Lectopia (formerly ilectures) recordings taken of the lectures that are available on Blackboard. Lecture notes will also be made available on Blackboard before each lecture. It is recommended that students print these out and bring them to the lecture, so they can annotate them and make their additional own notes during the lecture.

HANDWRITING

Students whose writing is difficult to read will disadvantage themselves in their written assessment. Make every effort to write clearly and legibly. Do not use your own abbreviations.

STUDENT RIGHTS AND RESPONSIBILITIES

Refer to Student Central @:
https://my.unsw.edu.au/student/academiclife/StudentCentralKensington.html.
Student equity and diversity issues can be addressed *via* Student Equity Officers (Disability) in the Student Equity and Diversity Unit (9385 4734).

MISSED ASSESSMENT ITEMS

If in any circumstances you unavoidably miss an examination, progress exam or cannot hand in an assessment task on time, **you must inform the course coordinator and you must lodge a special consideration request**, supported by a medical certificate or other documentation to Student Central (see web address above) within **3 DAYS**.
Your request for consideration will be assessed and a deferred exam may be granted. You cannot assume you will be granted supplementary assessment.
If necessary, a supplementary final examination will be held. It is intended that supplementary exams for the School of Medical Sciences in Semester 2, 2010 will be held in the week commencing Monday 7th December 2010. Normally, if you miss an exam (without valid reasons) you will be given an absent fail. If you arrive late for an exam, no time extension will be granted. It is your responsibility to check timetables and ensure that you arrive with sufficient time.

MISSED PRACTICAL CLASSES

Students who miss practical classes due to illness or for other reasons must submit a copy of medical certificates or other acceptable documentation to the course coordinator in Room M206. **Certificates should be lodged no more than 3 days after an absence.**

SPECIAL CONSIDERATION

Please note the following Statement regarding Special Consideration.

If you believe that your performance in a course, either during session or in an examination, has been adversely affected by sickness or for any other reason, you should notify the Registrar and ask for special consideration in the determination of your results. Such

requests should be made as soon as practicable after the problem occurs. ***Applications made more than three days after an examination in a course will only be considered in exceptional circumstances****.*

*When submitting a request for special consideration you should provide all possible supporting evidence (eg medical certificates) together with your registration number and enrolment details. Consideration request forms are available from Student Central. In exceptional circumstances further assessment may be given****. If you believe you might be eligible for further assessment on these grounds, you should contact the Course Coordinator as soon as possible.***

REPEATING STUDENTS

Practical class exemptions may be granted to repeat students but students **must** check with the course co-ordinator whether they have exemption **prior** to their first practical class. All students must be familiar with the material covered in the practical classes.

STUDENT SUPPORT

Those students who have a disability that requires some adjustment in their teaching or learning environment are encouraged to discuss their study needs with the course coordinator prior to, or at the commencement of, their course. Issues to be discussed may include access to materials, signers or note-takers, the provision of services and additional exam and assessment arrangements. Early notification is essential to enable any necessary adjustments to be made. Further information for students with disabilities is available at http://www.studentequity.unsw.edu.au/disabil.html

APPEAL PROCEDURES

Refer to Student Central @:
https://my.unsw.edu.au/student/academiclife/StudentCentralKensington.html

GRIEVANCE RESOLUTION OFFICER

In case you have any problems or grievances about the course, you should try to resolve it with the Course Organizer (A/Prof. Renate Griffith ph:9385 1912) or the Head of Department (Prof Margaret Morris ph: 9385 1560). If the grievance cannot be resolved in this way, you should contact the School of Medical Sciences Grievance Officer, Dr P.Pandey (9385 2483, P.Pandey@unsw.edu.au)

PLAGIARISM

The School of Medical Sciences will not tolerate plagiarism in submitted written work. The University regards this as academic misconduct. Evidence of plagiarism in submitted assignments, etc. will be thoroughly investigated and may be penalised by the award of a score of zero for the assessable work. Evidence of plagiarism may result in a record being made in the Central Plagiarism Register and the Faculty Students Ethics Officer being notified.

What is Plagiarism?
Plagiarism is the presentation of the thoughts or work of another as one's own.* Examples include:

- direct duplication of the thoughts or work of another, including by copying material, ideas or concepts from a book, article, report or other written document (whether published or unpublished), composition, artwork, design, drawing, circuitry, computer program or software, web site, Internet, other electronic resource, or another person's assignment without appropriate acknowledgement;
- paraphrasing another person's work with very minor changes keeping the meaning, form and/or progression of ideas of the original;
- piecing together sections of the work of others into a new whole;
- presenting an assessment item as independent work when it has been produced in whole or part in collusion with other people, for example, another student or a tutor; and
- claiming credit for a proportion a work contributed to a group assessment item that is greater than that actually contributed.†
- For the purposes of this policy, submitting an assessment item that has already been submitted for academic credit elsewhere may be considered plagiarism.
- Knowingly permitting your work to be copied by another student may also be considered to be plagiarism.
- Note that an assessment item produced in oral, not written, form, or involving live presentation, may similarly contain plagiarised material.
- The inclusion of the thoughts or work of another with attribution appropriate to the academic discipline does *not* amount to plagiarism.
- The Learning Centre website is the main repository for resources for staff and students on plagiarism and academic honesty. These resources can be located *via*: www.lc.unsw.edu.au/plagiarism

The Learning Centre also provides substantial educational written materials, workshops, and tutorials to aid students, for example, in:

- correct referencing practices;
- paraphrasing, summarising, essay writing, and time management;
- appropriate use of, and attribution for, a range of materials including text, images, formulae and concepts.

Individual assistance is available on request from The Learning Centre.

Students are also reminded that careful time management is an important part of study and one of the identified causes of plagiarism is poor time management. Students should allow sufficient time for research, drafting, and the proper referencing of sources in preparing all assessment items.

* Based on a document proposed to the University of Newcastle by the St James Ethics Centre. Used with kind permission from the University of Newcastle
† Adapted with kind permission from the University of Melbourne.

RATIONAL DRUG DESIGN
LECTURE and PRACTICAL OUTLINES

The course timetable is appended at the end of these outlines (p. 15) and can also be found on Blackboard.

The course is divided into 6 main themes covering the drug development process from bench to bedside.

1. Introduction to Drug Design and Development
2. Target Selection and Validation
3. Lead Identification and Modification
4. Computer-Aided Drug Design
5. Drug Delivery
6. Pre-clinical and Clinical Testing

1. Introduction to Drug Design and Development

Drug Discovery as a Process

This lecture stresses the important realisation that drug discovery is a lengthy, expensive, and complicated process, that requires the collaboration of a large number of research scientists with skills ranging from computational and structural chemistry, through synthetic organic chemistry, molecular cell biology, genomics, proteomics, physiology, pharmacology, toxicology, and clinical biochemistry, amongst others.

Target Identification and Validation

In this lecture the role of genomics and bioinformatics in target selection and drug design and development will be explored. The use of genetic approaches to identify target candidates such as the mapping of disease loci, genomics and proteomics will be covered. Also covered will be the role of bioinformatics in the analysis of nucleic acid sequence, protein sequence and structure, expression databases and functional pathway data contained in databases.

Structure Determination

A fundamental requirement of rational drug design is knowledge of the 3-dimensional structure of the receptor, generally a protein, sometimes a nucleic acid, occasionally a protein-nucleic acid complex. In this lecture we will explore the experimental methods available for determining these structures, focussing on X-ray crystallography, NMR spectroscopy, and the computational force fields that are used to refine such structures. These force fields are also important for determining ligand conformations and the energies of ligand-receptor binding – topics that will be taken up in later lectures.

Molecular Modelling Practical: Visualisation

Students will learn how to use molecular visualisation software to examine protein structures, protein/ligand interactions, and DNA/ligand interactions pertinent to structure-based drug design.

2. Target Selection and Validation

Targets: DNA

DNA, messenger RNA, and ribosomal RNA are important molecular targets for cancer, viral, and microbial chemotherapy. Drugs that bind to these targets inhibit DNA replication, the transcription of mRNA, and its translation into proteins. In this lecture we will focus on how structure-based approaches have been applied to the rational design of DNA groove binding

agents that recognise specific nucleotide sequences, and how this provides the opportunity for the development of gene-specific inhibitors of transcription – a holy grail of many molecular pharmacologists.

Drug Target Validation

Validation of a drug target involves the demonstration that successful 'targeting' will indeed produce the desired outcomes. Experimental approaches to validation increasingly use genetic manipulation of the target to identify the functional consequences of compromising the target. In this interactive lecture validation approaches will be presented with practical examples of both strengths and weaknesses intrinsic to current approaches.

Target Validation and Drug Validation Practicals

Practical 1: Target Validation will use siRNA to test the role of a specific tropomyosin to regulate cancer cell growth. Each student team will get to fix and stain cells treated with various siRNAs to estimate impact on cell colony forming capacity. The students will count cell colonies by eye in a 6 chamber plate.
Practical 2: Drug Validation will use the same methodology to generate a dose response curve for cell colony formation after exposure to a lead compound. Members of each team will also evaluate the impact of the drug on the intracellular target by viewing on their computer screen cell images displaying different parts of the cell cytoarchitecture. Students will count cells which have intact actin filaments and intact microtubules.

Targets: RNA

In the “Targets: DNA” lecture we focussed on DNA-binding agents that specifically inhibit the transcription of designated genes, here, in the “Targets: RNA” lecture we will consider the development of agents that selectively block mRNA so as to inhibit gene expression at the level of translation. We will discuss three different approaches: (1) the development of anti-sense oligonucleotides, (2) the design of ribozymes that selectively cleave designated mRNAs, and (3) the use of small inhibitory RNAs, known as siRNAs, in post-transcriptional gene silencing.

Targets: Receptors

Over 50% of all current drug targets are receptors and the majority of these receptors are membrane proteins. The role of the major families of both soluble and membrane bound receptors as drug targets will be examined. Newly identified receptor families and their potential as drug targets will also be discussed. The lecture will cover the challenges faced in the drug design and development process when transmembrane receptors are the target; including receptor selectivity, the difficulty in obtaining crystal structures for membrane proteins and performing high throughput screening.

Targets: Ion Channels

Ion channels are a large and important class of drug targets, which encompasses ligand-gated ion channels, voltage-gated ion channels, osmolyte or mechanosensitive channels and gap junction channels. This topic will explore why ion channels are a good target, the main mechanisms by which drugs can act on ion channels, the structural information currently available on ion channels and the techniques available for the screening of drug action.

Targets: Enzymes

Many cellular process involved in disease are mediated or controlled by the specific action of enzymes. A number of disease processes can therefore be reduced or eliminated by manipulating the activity of specific enzymes. This lecture will briefly outline how selected enzymes are identified as drug targets and then validated. Examples of how several drugs exert their therapeutic effects by interacting with these enzymes will also be given.

3. Lead Identification and Modification

Biological Assays: Lead Identification and High-throughput Screening

Before computational drug discovery was introduced drugs were discovered by chance in a trial- and error-manner. The introduction of new technologies, such as high throughput screening (HTS) can experimentally test hundreds of thousands of compounds a day, which have resulted in a more successful identification of promising drug candidates or reduced drug development costs. The outline of the lectures:

- Lead identification: the new technologies eg. genomics, combinatorial chemistry and HTS used to search new compounds
- Lead optimization: HTS used for validation runs; laboratory biological assays for testing binding properties, activities and selectivity of new compounds.

Lead Identification and Screening Practical: Radioligand Binding

Radioligand binding experiments are easy to perform, and provide useful data in many fields, including drug screening for lead compound identification. Through the analysis of the raw binding data obtained from COS-7 cell line expressing the human β_2 adrenoceptor, students will gain an understanding of the concepts of kinetic, saturation and competition binding, and will learn to apply various data analytical methods for addressing different binding parameters, eg. the dissociation constant (K_D) and maximum binding capacity (B_{max}) of a radioligand; IC_{50} and inhibitory constants (K_I) of competitors.

Lead Modification Practical: Structure Activity Relationships

This practical will explore the relationship between the structure of a compound and its activity. Using the contraction/relaxation of guinea-pig trachea as the screening assay, drug discovery teams (groups of 3-4 students) will test a lead compound and several compounds based on the lead compound to determine their biological activity.
In the class the following week the data generated will be analysed and the effect of the substituents and stereochemistry of the compounds on activity will be examined.

Combinatorial Chemistry

The last 15 years has seen a revolution in medicinal chemistry, with the introduction of combinatorial methods of general organic synthesis. These approaches make it possible to generate tens of thousands of compounds in a few days, in a form suitable for evaluation in high-throughput biological assays. In this lecture we will review the two principal approaches to these methods: the use of parallel array synthesis, and the split-and-mix approach of library synthesis. We will focus on the logical structure of combinatorial libraries, rather than the specific chemical methodologies.

4. Computer-Aided Drug Design

Molecular Modelling

Computer-aided drug design methods are widely used today in academic and industrial environments. This lecture will explain the basics on how the structures of molecules can be entered into a computer and manipulated *in silico*. This includes methods for geometry optimisation, molecular dynamics simulation, and conformational searching.

Ligand-based Drug Design

To improve the properties of a potential drug, structure activity relationships are established to identify structural moieties that contribute to the binding and activity of a compound. Computational methods will be discussed in this lecture which can be used to model and predict these properties, and to screen databases for new leads. These methods include quantitative structure-activity relationship (QSAR) and pharmacophore determination. A pharmacophore defines the structural features and geometry of a drug that impart biological activity.

Structure-based Drug Design

Where the detailed three-dimensional structure of the protein target is available, so called structure-based computer-aided drug design methods can be utilised to identify and modify lead compounds. If the protein structure is not available, then computer models, based on structures of similar proteins, can be prepared and are suitable for structure-based drug design. This lecture will introduce structure-based drug design and protein modelling methods.

Molecular Modelling Practical

This practical will use the same software the students have already become familiar with in the Visualisation practical. This time, the emphasis will be on exploring the structure and properties of small, drug-like molecules, including conformational models and superimpositions.

5. Drug Delivery

Bioavailability

Pharmacokinetics is the study of what the body does to a drug once it is within the body. A clinically important outcome of the body's treatment of a drug is how much drug is finally available in the body to bind to its intended therapeutic target (bioavailability). A brief outline will be given in this lecture on how ADME processes (Absorption, Distribution, Metabolism and Excretion) impact on a drug's bioavailability.

Pro-drugs and Drug Delivery

An inactive derivative of a known active drug may be called a prodrug and requires transformation within the body in order to release the active drug. Prodrugs can provide improved physiochemical properties such as solubility and enhanced delivery characteristics and / or therapeutic effect. This lecture outlines barriers to drug action, pro-drugs as drug delivery systems, and the application of pharmacokinetics and pharmacodynamics in drug delivery.

6. Pre-Clinical and Clinical testing

Pre-clinical Toxicology: *In Vitro*

From this lecture students will understand:

- the role of *in vitro* toxicity tests in establishing the safety of new drugs
- *in vitro* toxicity tests required by the world's regulatory bodies; tests for genotoxicity, cytotoxicity and others as required by chemical class
- the theory and methodology underlying various *in vitro* toxicology tests
- the role of Good Laboratory Practice in performing these tests

Pre-clinical Toxicology: *In Vivo*

From this lecture students will understand:

- the role of *in vivo* toxicity tests in establishing the safety of new drugs
- *in vivo* toxicity tests required by the world's regulatory bodies; genotoxicity, acute and short-term toxicity tests, tests for carcinogenic potential, Q-T prolongation and others as required by chemical class.
- the theory and methodology underlying various *in vivo* toxicology tests
- the ethics of *in vivo* toxicity testing and the potential for replacement by *in vitro* models

Pre-clinical Toxicology Practical: Ames Test

Chemicals which damage or mutate DNA and chromosomes are called mutagens. Damage to genetic material may lead to unregulated, cancerous growth of cells and tissues; indeed 80% of known carcinogens (cancer-causing chemicals) are also mutagens. Therefore one of the early, key tests performed on new chemicals or pharmaceuticals is a test for mutagenicity. The standard *in vitro* test for mutagenicity is known as the Ames test, named for its' inventor Professor Bruce Ames. It is a bacterial reverse mutation assay. In this practical specifically developed, mutant strains of *Salmonella typhimurium* are used, which are unable to synthesize the essential amino acid histidine. Thus the *S. typhimurium* strains will only grow in medium including histidine as an added supplement. Mutagenic chemicals damage the bacterial DNA, causing the strains to revert (reverse-mutate) to the 'wild-type' state in which growth is independent of histidine. In the practical the *S. typhimurium* strain TA98 will be grown in culture with a growth-limiting concentration of histidine. Various test chemicals will be added to the cultures to assess their mutagenic potential. The number of bacterial colonies which form on the culture plates indicates the growth rate; the greater the number of colonies, the greater the mutagenic potential of the chemical.

Clinical Trials

The regulation of therapeutic products and the phases (I-IV) of clinical trial that a drug must pass through before registration will be covered in this lecture.

Clinical Trial Design

This lecture will cover clinical trial design. The components of clinical trial design to be discussed will be: aims, design, controls and placebo, blinds, randomisation procedures, sample size, statistics, endpoints and ethics (ethics will be covered later in the course).

Ethics of Human and Animal Experimentation

Testing of drugs in animals and humans is under strict regulation to limit any harm and distress to the research subjects. In this lecture we will discuss the ethical conduct of biomedical research, including the policies governing biomedical and animal research in Australia. The role of institutional human ethic committees and what constitutes informed consent will be discussed. The general principles for the care and use of animals for scientific purposes and the 3 R's, replacement, reduction and refinement will be covered and the role of institutional animal ethics committees will be covered.

Intellectual Property

The basic principles underlying the protection of intellectual property will be discussed, focussing on the legal issues relevant to the patenting of pharmaceutical agents. We will discuss the types of patents available and what can be protected, the notions of disclosure, prior art, innovation, challenges, and what needs to be included in a patent application.

Commercial Considerations of Drug Development

The lecture will cover commercial considerations in drug development from target discovery, indication selection and lead identification, through safety assessments, clinical trials and marketing. It will look at what drives decisions (Go/No-Go), time-scales, program planning issues and the interactive perspectives of different groups in small through to large pharma companies.

Wk		Practical Mon 10-1 WW204	Lecture 1 Tue 11-12 WWLG02	Lecture 2 Wed 12-1 WWLG02	Tutorial-2 time slots; Thu 11-12 WWLG03, Wed 5-6 WWLG02
1	19/7		Introduction & course overview/ Drug discovery as a process R. Griffith/L. Wakelin	Target identification and validation R. Griffith	
2	26/7	Assessment in RDD R.Griffith	Structure determination L. Wakelin	Targets - DNA L. Wakelin	Drug target validation (interactive lecture) P. Gunning
3	2/8	Visualisation of drug-target interactions R. Griffith	Targets - RNA L. Wakelin	Targets – receptors R. Griffith	Nucleic acids as targets L. Wakelin
4	9/8	Target Validation P. Gunning	Targets – ion channels T. Lewis	Targets – enzymes R. Griffith	Targets R.Griffith
5	16/8	Drug Validation P. Gunning	Biological assays: lead identification L. Liu	Biological assays: high-throughput screening L. Liu	Students to meet for groupwork in tutorial rooms R. Griffith (office)
6	23/8	Lead identification and screening: radioligand binding L.Liu	**Test**	Combinatorial chemistry L. Wakelin	Student directed tutorial L. Wakelin
7	30/8		Molecular modelling R. Griffith	Ligand-based drug design R. Griffith	Student directed tutorial L. Wakelin
	6/9	**Mid-semester break**	**Mid-semester break**	**Mid-semester break**	**Mid-semester break**
8	13/9	Lead modification: SAR L. Liu	Structure-based drug design R. Griffith	Bioavailability R. Griffith	Lead identification & screening L. Liu
9	20/9	Lead modification: SAR data analysis L. Liu/R. Griffith	Pro-drugs and drug delivery T. Binder	Pre-clinical toxicology – *in vitro* J. Langlands	Computer methods R. Griffith
10	27/9	Molecular Modelling R. Griffith	Pre-clinical toxicology – *in vivo* J. Langlands	Clinical trials J. Langlands	Computer-aided drug design R. Griffith
11	4/10	**Holiday**	Clinical trial design J. Langlands	Ethics of human and animal experimentation N. Jones	Drug discovery as a process R. Griffith
12	11/10	Preclinical toxicology: Ames test 1 J. Langlands	Intellectual property L. Wakelin	Commercial considerations of drug development J. Langlands	Clinical trial design J. Langlands
13	18/10	Preclinical tox.:Ames test 2 J. Langlands			Exam preparation R. Griffith

Group assignment due Monday, week 13. Lab report due Friday, week 11. Visualisation exercise report due Friday, week 5.

Group Assignment

Each group will research the drug design and development process of a given drug and present the information in the form of four individual reports (1000 words each) and a group synopsis (500 words).

The group will comprise of four members. Each member will research one stage of the drug design and development process. These stages are: (A) Target Selection, (B) Lead Discovery, (C) Preclinical Development and (D) Clinical Trials.

Individual report

- The group as a whole needs to decide which person will research each of the four stages of drug design.
- Each team member will write an individual report on their stage of the drug design and development process.
- The word limit is 1000 words, excluding tables, figures legends and references.
- The report should be referenced using in-text referencing in the style of the British Journal of Pharmacology.
- Written assessment tasks must be accompanied by a signed plagiarism form and placed in the locked box in room MG14. An electronic version must also be submitted *via* Blackboard.
- The report must be accompanied by the signed Group Members – Evaluation form (p. 22).
- The report is to be submitted by 5pm on the 18th of October, 2010. A penalty will apply for late submissions.

Synopsis

- The group will produce a written synopsis of the drug design and development process of their drug, covering the journey that the drug took from bench to bedside.
- The word limit is 500 words, excluding tables, figures legends and references.
- The synopsis should be referenced using in-text referencing in the style of the British Journal of Pharmacology.
- Written assessment tasks must be accompanied by a signed plagiarism form (signed by all group members) and placed in the locked box in room MG14. The front cover should indicate which student researched each stage. An electronic version must also be submitted *via* Blackboard.
- The synopsis is to be submitted by 5pm on the 18th of October, 2010. A penalty will apply for late submissions.

Assessment

- The report and synopsis will be worth 15% of your total grade, 10% for the report and 5% for the synopsis.
- The report and the synopsis will be assessed by one of the members of the PHAR3101 lecturing staff (see attached forms).
- You will also give a peer/self assessment of the members of your group (see form on p. 22). **Important: the peer/self assessment will be used to modulate the marks given to each individual for the group synopsis, if a team member has not contributed fully to the group assignment.**

STAGES OF DRUG DESIGN AND DEVELOPMENT PROCESS

A. Target Selection:
In "Target selection" you should cover the information that the drug design and development team needed to know to start the process *i.e.* the disease they want to treat, what is the patho-physiological basis of it, why was the target chosen (are there other possible targets), what is known about the target (*i.e.* structure, signalling pathways etc), what physiological processes is the target involved in.

B. Lead discovery:
Lead discovery is the next step in the process and includes topics such as lead discovery, lead modification, rational drug design (*i.e.* pharmacophores and QSAR) and screening assays. To research this stage you will need to search for information on the compounds that lead to the final development of your drug of interest.

C. Pre-clinical development:
Pre-clinical development includes a comprehensive account of *in vitro* and *in vivo* studies conducted on your drug. These will include studies in animal models of disease states. Your research should cover how the studies were done, what the drug was compared to *i.e.* placebo or current treatment and the results of these studies. This stage of development also includes toxicology studies and non-human pharmacokinetics and metabolism studies

D. Clinical trials:
The journey from bench to bedside of your drug will end with clinical trials. It may be difficult to find any information on phase 1 and 2 trials as they are often not published. However you may find information on the pharmacokinetics of the drug (this information is generated in phase 1 and sometimes phase 2 trials). This section should summarise what trials were done, what were they comparing (*i.e.* drug *vs.* placebo or drug *vs.* current treatment), the types of patients recruited (*i.e*. the diseases they had, sometimes the one drug is trialled in the treatment of a few different conditions/syndromes etc.), and what were the outcomes (*i.e.* was the drug 10 times better, the same but with fewer side effects etc.), what side effects were reported in the trials. Make sure you only include trials prior to the registration of the drug; often more trials are done post registration for other indications.

INDIVIDUAL REPORT MARKING CRITERIA PHAR3101 S2 2010

Student name/number:_____

Group number & Drug:_____

Stage of the drug design and development process:

(A) Target Selection ☐

(B) Lead Discovery ☐

(C) Preclinical development ☐

(D) Clinical trials ☐

SECTION	COMPONENT PARTS	COMMENTS
Content & structure		
Introduction		
The introduction gives an overview of the whole Stage	**Orientation to topic**. ▪The topic and why it is of interest? **Clearly stated purpose.** ▪ What is the overall purpose of the paper.. **Outline-preview** ▪ How is the report going to be organised? **/5**	
Body of Essay		
Background information	**Clearly introduce**- the pharmacological issues, methods and procedures that related to this stage of the drug design and development process and how it relates to the overall development process. **/30**	
Evaluation of the issues identified from the sources	**Critical evaluation** of the key issues identified and supported by your chosen sources. ▪A balanced and logical presentation that explores the steps taken, challenges faced and outcomes achieved to progress your drug through this phase of the drug design and development process. **/30**	
End of Essay		
Conclusion	**Re-state key findings** and how they relate to the overall drug design and development process. **/10**	

INDIVIDUAL REPORT MARKING CRITERIA PHAR3101 S2 2010

Student name/number:_____

Group number & Drug:_____

Stage of the drug design and development process:

(A) Target Selection ☐

(B) Lead Discovery ☐

(C) Preclinical development ☐

(D) Clinical trials ☐

SECTION	COMPONENT PARTS	COMMENTS
Writing Conventions		
	Overall readability- ▪Sentence structure-correct grammar and word usage. ▪Sentences and paragraphs well connected. ▪Discipline specific – appropriate vocabulary-use of formal not oral language. ▪Has been proof read **/10**	
	Support –sources-evidence BJP **–** ▪**In-text citations and reference list follow conventions.** ▪**Relevant information selected.** **/10**	
Formatting		
	Title page: Course name & number, Topic, student names and numbers, date. **Assignment Presentation:** ▪Neat, margins, 1.5 spacing, 12 point font. Simple staple. Page numbering **/2**	
	Word Limit- ▪1000 words (1000/ stage 4000 total) **/3**	

Additional comments:

Content & Structure: /75

Writing Conventions & Formatting: /25

Total: /100

SYNOPSIS MARKING CRITERIA PHAR3101 S2 2010

Group number & Drug:_____

SECTION	COMPONENT PARTS	COMMENTS
Content & structure		
	Orientation to topic. ▪The topic and why it is of interest? **Clearly stated purpose.** ▪ What is the overall purpose of the paper. **Outline-preview** ▪ How is the report going to be organised? **/5**	
	Clearly introduce- the pharmacological issues, methods and procedures that related to the drug design and development process. **/35**	
	Critical evaluation of the key issues identified and supported by your chosen sources. ▪A balanced and logical presentation that explores the steps taken, challenges faced and outcomes achieved to progress your drug through the drug design and development process. **/35**	
Writing conventions & formatting		
	As for the individual assignment (see page 20) (Word limit is 500) **/25**	

Additional comments:

Content & Structure: /75

Writing Conventions & Formatting: /25

Total: /100

Group Members - Evaluation Form

Group number/drug name _____

Instructions: Use this form to evaluate the members of your group. Write the name of each group member, including yourself, on top of one of the columns, then assign a score of 0 to 10 (0 being the lowest grade, 10 the highest) to each group member for each criterion. Because each group member has different strengths and weaknesses, the scores you assign will differ. At the bottom of this sheet, write down any comments you wish to make, and sign the form.
This form has to be submitted with your individual report.

Criterion	Group Members			
Regularly attends meetings				
Is prepared at meetings				
Meets deadlines				
Contributes good ideas				
Effort given to researching subject				
Submits high-quality work				
Listens to other members				
Gives constructive feedback				
Responds to constructive feedback				
Overall assessment of this person's contribution				
Total (/100)				

Examples of Past Exam Questions:

Short answer questions
Allow 10 minutes to answer each of these questions. Typically, a choice of 6 questions is given, with students required to answer 4 questions. If more than 4 questions are answered, only the first 4 are marked.

1. You have discovered a drug that shows *in vitro* activity, and you now wish to conduct whole animal experiments using several routes of administration that may require surgical intervention.
What are the **THREE** guiding principles underpinning the use of animals for scientific purposes that you need to consider when preparing your submission to the institutional ethics committee? Give examples of how you would achieve these.

2. List **FIVE** limitations to drug action. Using examples, describe a drug delivery strategy to overcome **ONE** of these.

3. High-throughput screening techniques used in the generation of 'hit' and 'lead' compounds can be loosely divided into two categories; biochemical assays and cell-based assays. Give an example of each category, and briefly discuss the relative advantages and disadvantages of each category.

4. Choose **TWO** of the techniques listed below and for each:
(a) Briefly describe the technique and
(b) Describe how the technique could be used for Target Selection, Lead Discovery or Lead Development.
a. Linkage Analysis
b. Virtual Screening
c. Homology Modelling
d. Common Module Profiling
e. Common Pathway Scanning

5. Discuss the **THREE** clinical rationales for using enzyme inhibition as a therapeutic approach. Include in your answer examples of drugs and the disease/disorder treated.

6. You have developed a novel series of DNA-binding cancer drugs that are dual poisons of the enzymes topoisomerase I and topoisomerase II. Several drugs that individually target these enzymes are currently used clinically.
Describe the process by which you would secure a full patent on your invention, pointing out the situations and events that would limit or disqualify your application.

7. Clinical trials are an important phase of the drug design and development process.
a. List the different phases of clinical trial and for each phase describe:
(i) the objectives of the phase
(ii) the type of subjects enrolled and
(iii) sample size used
b. List the regulatory authorities that monitor the conduct of clinical trials and approval/ documentation that must be obtained before a trial can start in Australia.

8. With regard to the oral bioavailability of a drug:
a. List the **FIVE** possible physico-chemical and structural properties of a drug that can be manipulated to enhance bioavailability.
b. For **TWO** of these properties briefly describe;
(i) a definition
(ii) how it affects bioavailability
(iii) its method of calculation or measurement.

Long answer questions
Allow 30 minutes to answer each of these questions. Typically, a choice of 4 questions is given, with students required to answer 2 questions. If more than 2 questions are answered, only the first 2 are marked.

1. Three principal tests are used to determine the genotoxicity of a pharmaceutical, the Ames test, the chromosome aberration test, and the micronucleus test. For **EACH ONE** of these tests, describe:
a. the specific purpose of the test, i.e. what it is designed to demonstrate
b. the basic method of the test, including whether the test is conducted *in vitro* or *in vivo*, the types of cells involved, what the data consist of, and how a positive or negative result is determined.

2. DNA and soluble enzymes make drug targets that lend themselves to the development of lead compounds by the application of structure-based approaches. Discuss the methods used to determine the 3-dimensional structure of such targets, their strengths and weaknesses, and indicate how the structural information may be used for rational drug design. Illustrate your answer with practical examples discussed in your lectures.

3. Discuss combinatorial chemistry approaches to lead discovery, focusing on its basic principles. What are the main benefits and drawbacks of the approach, and how can its use be exploited in a cost-effective manner? In what situations may this be the only practical way of proceeding?

4. Give an overview of the drug discovery process, from target selection through to the filing of a clinical trial exemption scheme application. In your essay include; the challenges faced and techniques/technology used to facilitate the progression of the drug discovery process through each stage.

5. Your company currently has an α_1-adrenergic receptor antagonist in clinical development for the treatment of hypertension. The compound is called Bepelowosin. The pre-clinical and Phase I-II clinical studies have not indicated any adverse reactions. In Phase II studies it was found that 20 µg twice a day was more effective than placebo in lowering blood pressure. You now wish to design a Phase III trial to compare Bepelowosin to Losartan, an angiotensin II receptor antagonist that is currently used in the treatment of hypertension.
Prepare a report (in essay form) for your project team outlining the design of the trial. Include your recommendations for the: location, objectives, subject population, inclusion/exclusion criteria, controls, blinding, design, randomisation, sample size and end-points of the trial.

6. PAR is a newly identified nuclear receptor. It has been shown to play a role in pancreatic cancer. You have chosen PAR as your target for the rational design of a drug to treat pancreatic cancer. No crystal structures exist for PAR. Searches of various databases have generated the following information:
PAR shares homology with the oestrogen receptor (ER), peroxisome proliferator-activated receptor γ(PPARγ), and the progesterone receptor (PR). PAR has 14 % sequence similarity with the ER, 35 % sequence similarity with the PPARγ, and 28 % sequence similarity with the PR.

Answer the following EIGHT parts:

(i) Describe the difference between homology and sequence similarity

(ii) Which of the above receptors would you choose to base your homology model of PAR on? What are your reasons for making this choice?

(iii) Describe the steps involved in building an homology model

(iv) You have carried out a virtual screen by docking a library of compounds onto your homology model of the PAR receptor. You are searching for drug-like molecules that you will subsequently screen *in vitro*. The Table below shows the "hits" from your virtual screen.
Which of the "hits" from this screen meet "Lipinski's rule of five" for drug-like molecules?

Compound	Log P	Molecular Weight	Hydrogen bond donor	Hydrogen bond acceptor
1	5.2	367	5	10
2	6	285	3	7
3	4.8	333	4	8
4	2.6	510	2	5
5	3.4	580	4	3
6	5.2	287	6	5
7	2	495	3	6
8	1.8	158	6	2
9	1.1	275	3	4
10	4.9	380	2	11

The "hits" from your docking study have been tested *in vitro* for affinity and potency. These data were then used to generate a Quantitative Structure Activity Relationship (QSAR) according to the Hansch equation:

$$\log (1/C) = x\log P + y\sigma + zMR$$

(i) **C, log P, σ** and **MR**, the constants in the Hansch equation, are measures of what properties of the drug?

(ii) What is the relationship between log P and the *in vivo* activity of a compound?

(iii) Of the drug-like molecules from your virtual screen, which one is less likely to have CNS side effects? Explain the rationale behind your choice.

(iv) What characteristics of your lead compound can be optimised by the use of QSAR?