



Faculty of Medicine
School of Medical Sciences

SOMS3232

Cellular Mechanisms of Health and Disease

COURSE OUTLINE

SESSION 3, 2019

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Please read this manual/outline in conjunction with the following pages on the [School of Medical Sciences website](#):

- [Advice for Students](#)
- [Learning Resources](#)

(or see "STUDENTS" tab at medicalsciences.med.unsw.edu.au)

SOMS3232 Course Information

This course in molecular medicine bridges the gap between the fundamental sciences of cell biology/biochemistry/immunology and their therapeutic applications. It conveys the dynamic process of scientific discovery in areas of research strengths in biomedicine at UNSW by a focus on novel techniques bringing about paradigm shifts in our understanding of cell function and our ability to diagnose and treat diseases. Students will engage closely with researchers, and will develop a range of skills to prepare them for research-oriented careers in academia and industry.

OBJECTIVES OF THE COURSE

The primary aim of the course is to teach students some of the molecular and cellular processes that drive normal cell function and how subtle changes can lead to a range of common diseases. These concepts will be presented in the context of cutting-edge research to highlight how research outcomes can inform development of technologies, drugs and clinical practice ("bench to bedside").

Secondly, the aim is to convey the recent transformation of biomedical research to a quantitative discipline, the incorporation of approaches from the physical sciences (biophysics, chemistry, mathematics, engineering) and the invention of new methodologies that have opened new fields (e.g. transgenic animals, gene editing, imaging and microscopy). Overall the course is designed to raise the students' curiosity about how a cell works, what the big questions are, how these can be addressed experimentally and how these discoveries relate to our understanding of human health and disease. Lecturers will be tasked to convey the excitement of cutting edge research including its challenges and controversies. Interaction between the lecturer and the students is desired to facilitate critical thinking.

COURSE CO-ORDINATOR and LECTURERS

Course Coordinator:

Till Böcking till.boecking@unsw.edu.au
ph: 9385 1179

Students wishing to see the course coordinators should make an appointment *via* email.

Lecturers in this course:

Edna Hardeman	e.hardeman@unsw.edu.au
Peter Gunning	p.gunning@unsw.edu.au
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John Lock	john.lock@unsw.edu.au

COURSE STRUCTURE and TEACHING STRATEGIES

Learning activities occur on the following days and times:

- Research seminars: Thursdays 15:00-17:00
- Collaborative Learning Session (Journal Club): Thursdays 13:00-15:00
- Practical component (lab embedment): to be negotiated

Students are expected to attend all scheduled activities for their full duration (2 hours of research seminars per week, 2 hours of collaborative learning sessions per week, negotiated practical component). Students are reminded that UNSW recommends that a 6 units-of-credit course should involve about 150 hours of study and learning activities. The formal learning activities are approximately 60 hours throughout the term and students are expected (and strongly recommended) to allocate 90 hours of additional study.

Research seminars will provide you with the concepts and theory essential for an understanding of the cellular and molecular basis of human health. To assist in the development of research and analytical skills practical classes and collaborative learning sessions will be held. These sessions allow students to engage in a more interactive form of learning than is possible in the research seminars. The skills you will learn in practical classes are relevant to your development as professional scientists.

RESOURCES

Journal articles and web-based resources are available electronically via links on the course Moodle page.

See also medsciences.med.unsw.edu.au/students/undergraduate/learning-resources

STUDENT LEARNING OUTCOMES

On completion of this course students should be able to:

1. Describe the molecular and cellular mechanisms that underlie a range of common diseases such as cancer, metabolic disorders and immune diseases.
2. Analyse the process of scientific research and the appraise the role of transforming technologies in advancing our knowledge
3. Understand strategies for translation of research into technologies and treatments
4. Analyse scientific literature, integrate and contrast scientific data from different sources to synthesise new models and hypotheses; participate in scientific discussions.
5. Use reflective practice to integrate knowledge, skills and experience of scientific research

COURSE EVALUATION AND DEVELOPMENT

Course evaluation will be conducted using myExperience. Student feedback is taken seriously, and continual improvements are made to the course based, in part, on such feedback.

ASSESSMENT PROCEDURES

- ePortfolio/reflective journal **30%**
- Literature Oral Presentations **35%**
- Project Assignment **35%**

ePortfolio/reflective journal

Students will be required to keep a reflective journal. Entries will be guided by the material (online) and a set of questions. The entry for each topic in the course will consist of a combination of (a) questions on the online material prior to the corresponding research seminar and (b) reflection on the topic after the research seminar. Feedback will be provided by peers and academics. Peers will read and comment on each other's posts. Assessment will be based on the following components:

(1) Participation: Posting of weekly entries answering the assigned questions and comments by due date.

(2) Content: Understanding of the topic, scientifically sound response, appropriate references.

Literature Oral Presentations (Journal Club)

Students present a summary and analysis of research articles. Students will be assigned a journal articles chosen by the guest lecturer/course convenor. The presentation should highlight the main research question, key result(s) and conclusions as well as implications for research translation. The presentation (20 min + 10 min questions) will be held using slides (power point or similar format) for the entire class during the seminar component of the course. The presentation and subsequent class discussion will be moderated by the lecturer. Feedback will be provided by academics and peers. Criteria for Assessment: 1. CLARITY AND STRUCTURE: Oral presentation was clear, well-structured and illustrated and easily understood. 2. TIMING: Appropriate weight given to different aspects within the allocated time frame. 3. UNDERSTANDING: Presenter appeared to have a good understanding of the topic: able to answer audience questions clearly. 4. STIMULATED LEARNING: Presentation was interesting; significant issues and answered questions were highlighted.

Project Assignment

Groups of students will be teamed up with a postgraduate student in the laboratories of lecturers. The group will be given a research question and will be tasked to design an experimental plan that can address this question. This is to be worked out in the team, whereby the students can discuss their ideas with the postgraduate student they are teamed up with. The student team will then prepare a poster of their proposed experiment. The poster should cover the following aspects: (1) Introduction/background to the research problem. (2) Experimental design, including choice of techniques. (3) Discussion of how data should be analysed and interpreted. (4) Expected outcomes. The posters will be presented in a dedicated seminar at the end of the course whereby the students have to defend their proposal.

GENERAL INFORMATION

Attendance Requirements

For details on the Policy on Class Attendance and Absence see [Advice for Students](#) and the [Policy on Class Attendance and Absence](#).

Practical Classes

Groups of students will be assigned to the laboratories of lecturers participating in the course, where they will be teamed up with a postgraduate student. After a short introduction to the research focus of the lab from the group leader, the postgraduate student will show the students the laboratory and introduce them to the main techniques and experimental approaches used in the research. The team will then work on a project assignment related to the laboratory placement (see above).

Special Consideration

Please see [UNSW-Special Consideration](#) and [Student Advice-Special Consideration](#)

See: [Student-Advice-Reviews and Appeals](#)

Student Support Services

See: [Student Advice-Student support services](#).

Academic Integrity and Plagiarism

The [UNSW Student Code](#) outlines the standard of conduct expected of students with respect to their academic integrity and plagiarism.

More details of what constitutes plagiarism can be found [here](#)

RESEARCH SEMINAR OUTLINES

Cancer I: Mechanisms underlying cell architecture: the actin cytoskeleton

Edna Hardeman, School of Medical Sciences, UNSW

The architecture of all cells underpins their function and is altered significantly in cancer. One of the challenges in biology has been to understand how cell architecture is assembled and regulated. Three major polymer systems are used in human cells to provide architectural specificity: microfilaments, intermediate filaments and microtubules. These three systems provide overlapping functional properties and collaborate to satisfy the architectural demands of the cell. The microfilaments are thin filaments, around 8nm in diameter, composed of a core polymer of actin. These microfilaments not only provide architectural information but also support most if not all functions in the cell. There are 2-3 versions (isoforms) of actin present in mammalian cells, that operate by recruiting specific 'actin binding proteins' such as the motor proteins myosin to carry out a particular function.

The conundrum has been to explain how actin filaments, with so few isoforms, can be involved in so many diverse cellular functions. Surprisingly, this has only been solved recently. It was discovered that most microfilaments of human cells (and indeed all metazoans) are composed of two polymers, actin and tropomyosin, which wrap around each other. There are many isoforms of tropomyosin - over 40 in human cells - that have fundamentally different functional properties. It is the specific isoform of tropomyosin wrapped around an actin filament that provides the cellular functional 'post code' to the filament and decides which actin binding protein(s) can interact with the actin. We will discuss how choice of experimental system, genetic technology and improvements in imaging contributed to this transformation of our thinking.

Cancer II: Targeting the actin cytoskeleton in cancer: how tropomyosin provided an unexpected opportunity

Peter Gunning, School of Medical Sciences, UNSW

The involvement of the actin cytoskeleton in cell proliferation and migration makes it an attractive anti-cancer target. Many drugs have been developed which target the assembly of actin into filaments and several of these have progressed to pre-clinical trials in animal models. Unfortunately, all anti-actin drugs have failed because of their impact on the contraction of the heart. This could, perhaps, have been predicted because the actin in the cancer cell is almost identical to the actin used for contraction of the heart. Alternative strategies have therefore been employed in many laboratories throughout the world. These have focussed on the targeting of actin binding proteins and signalling molecules and have thus far proved disappointing. In contrast, the targeting of the major tropomyosin isoform found in cancer cells has shown promise and has proved to be well tolerated in pre-clinical animal models.

The targeting of tropomyosin has the advantage that the major cancer cell tropomyosin isoform is structurally different to the tropomyosin isoform in the human heart. This facilitated the development of drugs that target cancer cells but avoid any cardiac impact. Furthermore, the anti-tropomyosin drugs synergise with anti-microtubule drugs which are among the most

widely used anti-cancer drugs. We will discuss how our understanding of fundamental biological processes informs our approach to human health and drug development and the weaknesses inherent in limited knowledge. We will also cover the interface between protein structure and drug design and the revolution in drug development in the last 5 years.

Immunity I: T cell receptor function – from first principles to synthetic biology

Jesse Goyette, EMBL Australia Node in Single Molecule Science

Katharina Gaus, EMBL Australia Node in Single Molecule Science

T cell decision making. T cells migrate through tissues continuously monitoring for infection or neoplastic transformation (cancerous cells). To carry out this function T cells use a specialised surface receptor, the T cell receptor (TCR), to sample antigens presented on major histocompatibility complex (MHC) molecules. When activated through the TCR, T cells can lyse infected cells, secrete cytokines, and perform other effector functions that collectively allow them to initiate and regulate immune responses. Critically, T cells must be insensitive to self-antigens, which are constantly presented at high levels on MHCs, and exquisitely sensitive to foreign antigens that are often presented at very low levels. This ability to discriminate between self and non-self is central to adaptive immunity and consequences of a failure to discriminate lead to autoimmunity, uncontrolled infection or cancer. In this module we will explore how T cells use their TCR to make the decision to respond to cells they encounter or remain quiescent.

CAR receptors. We now understand the molecular mechanisms of T cell activation to the point where we can create synthetic T cell receptors, called 'chimeric antigen receptors' (CARs) that react to antigens which would otherwise not be recognisable. This has been used clinically in a strategy that involves isolating T cells from a cancer patient, rewiring them with a CAR recognising a cancer-specific antigen and returning them to the patient. Results from haematological cancers have been exciting and since the seminal work of Carl June the field has expanded rapidly. We will discuss the design principles involved in engineering CAR receptors, their clinical potential and active areas of future research.

Immunity II: Immune cell search and kill strategies

Maté Biro, EMBL Australia Node in Single Molecule Science, SoMS, UNSW

The main immune cells responsible for antitumor activity are Cytotoxic T cells (CTLs). CTL can migrate rapidly and with striking versatility in a continuous search for cells to subdue. They constitutively patrol organs for cognate antigen and typically migrate using an elongated and polarised shape with a dynamic leading edge and a uropod at the rear. T cells are however able to adopt diverse migration modes depending on both extra- and intracellular cues. In order to reach their target cells, circulating CTL must first cross the endothelial barrier and then negotiate the complex interstitial space within the tumour microenvironment. Burgeoning immunotherapies against cancers attempt to harness the capacity of these T cells to navigate various barriers and organs to reach the tumour and then effectively engage and kill their targets, yet little is known of the cellular forces that underpin their movements and interactions.

We will cover various aspects of immune cell-mediated antitumour responses, from the cell-intrinsic cytoskeletal machinery driving motility to the sensing of extracellular cues and population level search strategies, as well as killing mechanisms upon target encounter and engagement.

Immunity III: Molecular arms race between host cells and HIV

Till Böcking, EMBL Australia Node in Single Molecule Science, SoMS, UNSW

David Jacques, EMBL Australia Node in Single Molecule Science, SoMS, UNSW

Stuart Turville, Kirby Institute UNSW

We will summarise the basic life cycle of the human lentivirus Human immunodeficiency virus type 1 (HIV-1), from the point of cellular attachment/fusion, reverse transcription, integration and subsequent viral assembly. We will further map how our immune system has evolved to counter the passage of lentiviruses through the expression of various restriction factors and in turn how lentiviral genomes have evolved to respond to each restriction. Our discussion will highlight how basic science has enabled breakthroughs in medicine:

(1) What is the role of structural biology and new imaging technologies in providing drugs for treating HIV infection and answering question about the molecular arms race between host and virus?

(2) How can lentiviruses can be harnessed for gene delivery? We will outline the power of genetic manipulation using technologies like CRISPR in targeting disease states. We will further outline how elements of HIV used in gene delivery may in turn represent the most promising efforts towards a HIV cure.

Genetics I: Careers beyond research — taking the next step

Bennett Shum, EMBL Australia Node in Single Molecule Science, SOMS, UNSW

Traditional career paths for science graduates are typically centred on academic research-based activities. However, in Australia where research funding is becoming increasingly difficult to secure, the goal of becoming a laboratory research leader is becoming less of a reality for many junior scientists. Advances in scientific discovery and technological innovation offer abundant career opportunities for scientists in non-academic research settings. However the pathways to securing non-academic careers are not often explored in traditional scientific training. The aim of this research seminar series is to provide students with awareness of alternate career paths outside of academic research, and to introduce concepts, skills, and processes that increase likelihood of success when working in the corporate sector. By studying a real-world case study of developing an Australian-first new genetic preventive health test using next-generation DNA sequencing, we take a practical examination of using scientific thinking and training in the application of entrepreneurship and commercialisation of scientific discoveries. Areas such as Leadership, Communication, New Product Development, and other skills and processes useful for advancing a scientific

career beyond academic research are explored. The implications of the rapidly evolving shift of science towards 'big data' for future scientists are also considered.

Genetics II: The complex life of messenger RNA

James Halstead, School of Medical Sciences, UNSW

The human genome project was declared complete in April 2003. It is astonishing then, that 16 years later, we are still not clear on how many genes make up a person (estimates range from ~20,000 - ~50,000). Why is this such a hard question to answer? And why does it matter? One key factor is that the RNA transcribed from the genome is far more varied than previously thought possible, and this continues to challenge our view of what defines a gene. This lecture focuses on this phenomenon.

In the first half we'll explore the different modes of regulation that biology employs to generate varied mRNAs from one DNA sequence, and how this changes cell behaviour. As we consider these mechanisms we will encounter a fundamental biological question: how many different mRNAs (and thus peptides) does the genome encode? We will discuss the mechanisms that allow the cell to 'pick and choose' which mRNAs to make and how this can go wrong in diseases, particularly in cancer. Finally we will investigate mRNA biology as a frontier of therapy. We will explore how microRNAs, despite their immense potential, turned out to be ineffective therapeutic agents, and how different aspects of mRNA biology are now providing unexpected cancer treatments.

In the second part, we will address the different techniques that have been used to illuminate mRNA biology, from historical approaches to early questions, to cutting-edge tools employing single molecule microscopy and next-generation sequencing. We will explore the latest models that these tools have driven, from gene bursts to stochastic gene expression. To end we will consider the growth of mRNA biology as a field, and ask how we can best answer the (many) questions that remain unanswered.

Cancer III: Reprogramming of metabolism in cancer

Nigel Turner, School of Medical Sciences, UNSW

Metabolic reprogramming is now well established as a critical aberration facilitating the growth and proliferation of many cancers. While the initial description of altered metabolism in cancer cells was made over 90 years ago by the famous biochemist Otto Warburg, the last 2 decades has seen an explosion of research in this field, with a compelling body of evidence now showing that signalling pathways that drive oncogenesis also trigger major alterations in nutrient uptake and metabolism, and that several cancers can be directly caused by mutations in specific metabolic enzymes. In addition to changes in metabolism at the level of the tumour, strong links have also emerged between metabolic diseases, such as obesity and diabetes, and cancer prevalence, severity and disease progression. This extensive interplay between oncogenic signalling and intermediary metabolism has raised the possibility that targeting metabolic pathways may be an exciting therapeutic approach for preventing and treating cancer. This research seminar will explore some of the key findings

in this field, the technologies that have greatly advanced this area of study and the latest developments in targeting metabolism for cancer therapy.

Cancer IV: From a challenge to an opportunity: emerging research strategies making sense of heterogeneity in cancer cell migration

John Lock, School of Medical Sciences, UNSW

More than 90% of cancer-induced mortality is caused by the spread of cancer cells from primary to secondary sites. This process, called metastasis, is driven by cancer cell migration. As throughout cancer biology, a key challenge in understanding and preventing cancer cell migration lies in the heterogeneity of this phenomenon.

We will first address the discovery that cancer cells can migrate using several distinctive 'modalities'. This behavioural heterogeneity is coupled to, and emerges from, heterogeneity in the organisation of the molecular systems underlying migration. These directly include the cytoskeleton, cell-cell and cell-matrix adhesions, polarity regulators, protein trafficking pathways and numerous signalling networks, to name but a few. We will consider the challenges that behavioural and organisational heterogeneity pose to researchers trying to understand and therapeutically target cancer cell migration.

In the second part, we will explore new imaging-based research strategies that aim to convert heterogeneity in cancer cell migration from a research challenge to an opportunity for deeper insight and therapeutic efficacy. Focusing on multidisciplinary 'Systems Microscopy' approaches integrating experimental automation, quantitative imaging, image analysis and statistics, we will see how experimentally induced (e.g. RNAi / CRISPR) as well as spontaneous cellular heterogeneity can be used to delineate correlative and causal links governing cell migration. We will consider the advantages offered by quantitative imaging in these and similar research contexts, and finally envisage future developments in this fast-moving research field.

TIMETABLE

Week	Day	Month	Journal Club (13:00-15:00)	Research seminar (15:00-17:00)
1	19	September	Introduction to SOMS3232 (Böcking)	Cancer I: Cytoskeleton (Hardeman)
2	26	September	Cancer I (Hardeman)	Cancer II: Cancer drug development (Gunning)
3	3	October	Cancer II (Gunning)	Immunity I: T cell activation (Goyette)
4	10	October	Immunity I (Goyette)	Immunity II: Immune search and kill (Biro)
5	17	October	Immunity II (Biro)	Immunity III: HIV infection (Böcking/Jacques/Turville)
6	24	October	Immunity III (Jacques/Böcking)	Genetics I: Diagnostics and start-ups (Shum)
7	31	October	Immunity III (Turville/Böcking)	Genetics II: Gene expression (Halstead)
8	7	November	Genetics II (Halstead)	Cancer III: Metabolic reprogramming (Turner)
9	14	November	Cancer III (Turner)	Cancer IV: Systems biology (Lock)
10	21	November	Posters (Böcking)	Posters (Böcking)

ASSESSMENT TASKS

Task	Due date		Assessment	
<i>ePortfolio</i>	<i>Entry</i>	<i>Comments</i>	<i>Participation</i>	<i>Content</i>
Cancer II	25-Sep	2-Oct	all	Stream A&B
Immunity I	2-Oct	9-Oct	all	Stream C
Immunity II	9-Oct	16-Oct	all	Stream D
Immunity III	16-Oct	30-Oct	all	Stream A&B
Genetics II	30-Oct	6-Nov	all	Stream C
Cancer III	6-Nov	13-Nov	all	Stream D
Cancer IV	13-Nov	20-Nov	all	-
<i>Literature Oral Assignment</i>	to be allocated to groups		marking of group presentation from lecturers	
<i>Project Assignment (Poster)</i>	21-Nov		peer marking of group presentations	
			individual participation marks from lecturers	