Outline of the MIMS lecture course

Important note: This information is provided at the beginning of the year for your guidance and that of your supervisors. It is not intended to be a comprehensive list of contents. Lecturers will all issue their own handouts and may vary the topics and the order in which they are presented.

Michaelmas Term: Metabolism in Health and Disease

Giles Yeo: Prologue: Diabetes mellitus as a metabolic disease (2)

The aim of the Prologue is to illustrate the molecular basis of medicine, to anticipate the main topics covered in the first term's lectures and to introduce terminology, within the context of diabetes as a common metabolic disease.

Lecture 1

- Case studies, illustrating typical presentation of diabetes.
- Definition of diabetes in terms of hyperglycaemia; diagnosis by glucose tolerance test.
- Classification, causes and treatment of type 1 (juvenile) and type 2 (maturity onset) diabetes; other forms of diabetes; diabetes in animals.
- Historical perspective on Banting and Best and the discovery of insulin.
- Acute manifestation of diabetes as a metabolic problem reflecting lack of insulin action.
- Long term complications of diabetes resulting from chronic hyperglycaemia
- Statistics on prevalence of diabetes and obesity and cost implications for health care.

Lecture 2

- Structure of insulin, as an example of a small protein.
- Carbohydrates and lipids as fuels; metabolic pathways for their oxidation.
- Introduction to regulation of metabolic pathways by cellular energy charge or hormonal signals; allosteric regulation and covalent modification of enzymes.
- Insulin biosynthesis and secretion.
- Actions of insulin on carbohydrate, lipid and protein metabolism.
- Insulin receptors and glucose transporters as examples of membrane proteins.
- Introduction to mechanism of insulin action & signalling via protein kinase cascades.
- Obesity, insulin resistance and type 2 diabetes; why is insulin action impaired by obesity?

Helen Mott: Introduction to macromolecules: protein structure and enzyme catalysis (6)

After an introduction to macromolecules, the lectures concern understanding of the structure of proteins and how the structure governs the function. We will study examples of the structures of medically relevant proteins and enzymes. We will then focus on enzymes, studying how they catalyse reactions and how this activity is controlled.

Lecture 1: Introduction to macromolecules.

- Sugars, nucleic acids and proteins and their building blocks

Lectures 2-3: Protein structure and function

- The levels of protein structure.
- Peptide bond formation.
- The structure of a protein is determined by the amino acid sequence.
- Forces that hold protein structures together.
- Fibrous and globular proteins.
- **Case study** - antibody structure and function.
- The role of prosthetic groups and cofactors.
- **Case study** - how protein structure leads to function in haemoglobin.
- Membrane proteins.
- Methods for studying macromolecules.
- Prediction of function from sequence information.
- Protein misfolding and disease

Lectures 4-6: Enzyme function and control

- Energetics of enzyme-catalysed reactions
- Catalysis of a reaction by transition state stabilisation.
- How the structure of an enzyme active site causes catalysis.
- Enzyme mechanisms
- **Case study** – development of HIV protease inhibitors.
- Classification and characterisation of enzymes.
- Michaelis-Menten kinetics.
- Enzyme inhibition
- Alteration of activity by covalent modification.
- Allosteric control and conformational change.
- Cooperativity of multimeric enzymes.
- Case study – development of influenza drugs.

Bill Broadhurst (lecture 1)**, Kathryn Lilley (lectures 2-4), Florian Hollfelder** (lectures 5-7)**, and Giles Yeo** (lecture 8): Bioenergetics and metabolism

The metabolic fates of glucose and fat after feeding

- Importance of blood glucose concentration and insulin.
- Cameos of fuel economies of gut, liver, muscle, adipose tissue, brain.
- Uptake of glucose and its conversion to fuel stores.
- Glycolysis.
- Formation of acetyl-CoA from pyruvate.
- Biosynthesis of fatty acids from acetyl-CoA.
- Biosynthesis of triacylglycerols (‘fat’).
- Digestion of dietary fat: formation and fate of chylomicrons.
- Role of other lipoproteins in transferring triacylglycerol from liver to adipose tissue.

The fuelling of muscle contraction by carbohydrate and lipids

- Mobilisation of glycogen: glycogenolysis.
- Fates of pyruvate: reduction to lactate (anaerobic) and oxidation to CO_2 (aerobic)
- Mobilisation of triacylglycerol: lipolysis.
- Fatty acid transport to muscle and β-oxidation to acetyl-CoA.
- Citric acid cycle and oxidation of acetyl-CoA to complete carbohydrate and fat oxidation.
- Formation and use of ketone bodies.

Control of fuel storage and oxidation

- The interplay of insulin and the catabolic hormones glucagon and adrenaline.
- Principles of metabolic control.
- Control of glycogen synthesis and breakdown.
- Control of fatty acid and triacylglycerol synthesis.
- Interplay of short-term acute control and longer-term adaptive control.
- Control of lipolysis in adipose tissue.
- Control of glycolysis and citric acid cycle.
- Amphibolic role of citric acid cycle.

Fasting and gluconeogenesis; aspects of amino acid metabolism

- Fuel needs of the brain and how it is met in fasting by liver making glucose and ketone bodies.
- Amino acids in gluconeogenesis and ketogenesis.
- Control of gluconeogenesis.
- Ketosis and diabetes.
- Overview of metabolic roles of amino acids and of amino acid catabolism.
- The importance of aminotransferases and glutamate dehydrogenase.
- The urea cycle.

Mitochondrial respiration and oxidative phosphorylation

- ATP couples exergonic catabolism to endergonic anabolism.
- How oxidation is coupled to phosphorylation by mitochondria.
- Overview of the electron-transport chain.
- Some comments on individual redox cofactors.
- Experimental background to the ordering of the electron-transport chain.
- Structure and function of the complexes of the electron-transport chain.
- How the proton motive force drives the ATP synthase to make ATP.
- How the proton motive force drives transport in and out of mitochondria.

Sarah Lummis: Membrane dynamics and function; signalling by hormones (5)

Lecture 1: Protein trafficking, secretion and endocytosis.

- Secretion and endocytosis.
- Importance of protein trafficking for maintenance and synthesis of intracellular structures.

- The diabetes context: insulin synthesis and secretion.
- Structure of the endoplasmic reticulum, Golgi apparatus and plasma membrane, emphasising their dynamic nature and interrelationship.
- **Secretion**: Concept of targeting sequences. Consideration of organelle-specific targeting, protein processing, role of cytoskeleton and motor proteins. Outline of molecular events in secretion.
- **Endocytosis**: Pinocytosis and endocytosis in coated pits leading to lysosomes or recycling to plasma membrane. Example of LDL receptors.

Lectures 2-5: Hormonal signalling

- Recognition of water-soluble hormones by surface receptors generates a signal inside the cell. The lectures will give an understanding of the key elements of the nature of some of the signals, how they are generated and removed, and how the cell interprets them as a part of its function.
- The three basic types of receptor, how they work and why: ligand-gated ion channels, G-protein coupled (7 transmembrane domain), and tyrosine kinase.
- The role of trimeric G-proteins in signal transduction, illustrated by control of adenylyl cyclase activity to produce the 2nd messenger cyclic AMP. Actions of cyclic AMP to illustrate protein phosphorylation as a transducing mechanism.
- Simple introduction to cyclic GMP and nitric oxide.
- Hormonal activation of phosphoinositide hydrolysis and elevation of Ca^{2+} concentration by inositol trisphosphate.
- Action of diacylglycerol to activate protein kinase C.
- Phosphatidylinositol 3,4,5-trisphosphate as another lipid second messenger.
- A brief outline of Ca^{2+} regulation and its importance as a 2nd messenger.
- The operation of tyrosine kinase receptors, illustrated by the (typical) PDGF receptor and the insulin receptor.
- Receptor families and the concept of more complex signal transduction cascades involving protein kinases. A complex signal transduction cascade exemplified by the pathway from the insulin receptor to the stimulation of glycogen synthesis.

There will be a revision lecture in Easter Term.

Helen Mott: Proteins and molecular recognition (2)

The aim of these lectures is to understand how molecules interact with one another within the cell. We will consider the basic principles of molecular recognition, focusing on examples from growth factor response pathways. We will then go on to see how knowledge of protein structure and function helps to develop inhibitors that act as drug molecules

Lecture 1: Principles of molecular recognition

- How the structure of a protein allows it to perform molecular recognition.
- Bond formation in recognition.
- Conformational changes and reversible covalent modification.
- Protein-protein and protein-DNA recognition in growth factor response pathways

- Measuring binding affinities and finding new interactions

Lecture 2: Principles of drug design

- Design of enzyme inhibitors as drug molecules.
- How monoclonal antibodies are produced experimentally.
- Use of monoclonal antibodies in cancer therapy.

Giles Yeo: Epilogue (1)

I will use the opportunity to tie together the information covered in the PBL, and will discuss the obesity epidemic: a major threat to public health.

We also have a brief look at leptin and mechanisms regulating appetite and energy expenditure.

Lent Term: The Genome in Health and Disease

Trevor Littlewood: Prologue: Cancer as a molecular disease (1)

The lectures provide a general introduction to cancer and the types of molecules that are involved.

Cancer epidemiology and tumour development

- Changes in cancer incidence and mortality in the UK and worldwide
- The causes of cancer
- Cancers occur in many distinct forms but are characterised by common features – the hallmarks of cancer
- The process of tumour development: vascularisation, invasion and metastasis.
- Cancer is primarily a genetic disease.
- The relevance of DNA repair mechanisms in cancer
- Introduction to the classes of genes that promote cancer (oncogenes) and those that are involved in suppressing tumour development (tumour suppressors). A small number of examples will be discussed to illustrate the common principles of their molecular functions.

Luca Pellegrini: Organisation, replication and repair of genomes (5)

Lecture 1: Organisation of DNA in the genome

- DNA is the genetic material.
- Chemistry and structure of the DNA double helix.
- Dimensions and scale of the DNA double helix.
- How do you fit 2 metres of DNA into a 10 micron diameter nucleus?
- Different levels of compaction.

- Nucleosomes, nuclear scaffold, chromosomes.

Lecture 2: How DNA is replicated

- The double helix as a template. Semiconservative replication.
- DNA polymerases, requirement for substrates, primers and template.
- Ensuring accuracy – proof reading.
- Discontinuous replication and Okazaki fragments.
- Origins of replication – the replication fork.
- How genomes are replicated.
- The problem of linear chromosomes and the solution – telomeres.
- Centromeres.
- Sequencing DNA – classical methods and massively parallel sequencing.
- Polymerase chain reaction.

Lectures 3-4: Information content of DNA

- What is a gene?
- What is gene expression – cDNA libraries and microarrays?
- The human and other genome projects – genomic libraries, sequencing and sequence assembly.
- How many genes make a human?
- Differing sizes of genomes.
- Not all DNA encodes genes.
- Junk DNA?
- Repetitive DNA, microsatellites, hypervariability and fingerprints.
- Mobile genetic elements.

Lecture 5: Change and constancy of DNA

- DNA modifications and epigenetics.
- Mutations and how they arise.
- DNA damage and its consequences.
- Mechanisms of DNA repair.
- DNA repair and cancer.
- How DNA rearrangements can be a good thing.

Eric Miska: Transcription, translation and control (5)

Lecture 1: Transcription in prokaryotes and its control

- Course overview – The Central Dogma
- What is a gene? What is mRNA?
- Basic mechanism of RNA synthesis (transcription)
- Regulation of transcription
- The lac repressor and the catabolite activator protein (CAP)
- Antibiotics that inhibit prokaryotic transcription

Lecture 2: Transcription in eukaryotes and its control

- RNA Polymerases

- Eukaryotic promoters and upstream regulatory elements
- Regulation of transcription
    - Roles of chromatin
    - Enhancers and response elements
    - Tissue-specific and developmentally regulated transcription factors
- Transcription factors and cancer – cFos/c-Jun, p53

Lecture 3: Pre-mRNA processing – from pre-RNA to mature mRNA

- 'Polishing' pre-mRNA
    - 5' Capping
    - Termination and polyadenylation
- RNA splicing
    - Alternative splicing
    - Anomalous splicing and cancer – Wilms tumour
- Making cDNA and genomic libraries

Lecture 4: Translation – Protein synthesis

- Control of mRNA stability
- Genetic code
- tRNA structure and charging with amino acids
- Ribosomes and polysomes: structure and function
- Initiation of translation

Lecture 5: Translation continued – elongation, termination, degradation

- Elongation
- Control and termination of translation
- Antibiotics that target the translational machinery
- Protein degradation – the lysosome and the proteasome, ubiquitin.
- Gene expression studies, arrays and cancer
- MicroRNA, siRNA and RNAi.

Elizabeth Murchison (lectures 1-4) and **Christine Farr** (lectures 5-8): Genetics in human and animal medicine (8)

The aim of these lectures is to introduce you to genetics in human and animal health, including a framework for cancer genetics, and will focus on many of the basic principles and concepts which form the foundation for understanding genetics in the clinic and in biomedical research today.

Lecture 1: Introduction to medical and veterinary genetics

- Introduction to the course
- Chromosomes and the structure of the genome
- Mutations and mutational mechanisms
- The germline and inheritance
- Genetic diseases and germline evolution
- Single gene disorders and complex genetic diseases

Lecture 2: Genetic disease mechanisms

- Chromosomal disorders and diagnosis
- Single nucleotide variants and disease
- Diseases caused by splicing defects
- Repeat tract expansion diseases
- Mitochondrial diseases
- Finding disease-causing mutations: linkage studies
- Genetic diagnosis
- Gene therapy and germline modification

Lecture 3: De novo germline mutations and somatic mutations

- De novo mutations and developmental disorders
- Exome and whole genome sequencing
- Mosaicism and somatic mutations
- Chimerism

Lecture 4: Cancer genetics

- Somatic evolution of cancer – overview
- Driver and passenger mutations
- Cancer genes
- Germline genetic variation and inherited cancer risk
- Types of somatic mutation
- Mutation signatures
- Epigenetic changes in cancer
- Viruses and cancer
- Transmissible cancers

Lecture 5: Sex-chromosomes, sex-linked inheritance and X inactivation

- Sex chromosomes
- Sex-linked disorders
- X inactivation
- Introduction to epigenetics
- Epigenetic modifications and genome function

Lecture 6: Epigenetics in health and disease

- Mendelian epigenetic disorders
- Genomic imprinting and imprinted disorders
- Gene-environment interactions and disease – non-genetic inheritance
- Twin studies
- Mitochondrial disease

Lecture 7: Introduction to evolution and population genetics

- Hardy-Weinberg equilibrium
- Allele-frequencies in populations
- Founder effects and bottlenecks
- Selection
- Genetic variants in populations

- Genetic selection and livestock breeding

There will be a revision lecture in Easter Term.

Philip Zegerman: Cell Cycle and Cell Death (4)

Lecture 1:

- Why should you care about cell division?
- The phases and checkpoints of the cell cycle overview
- How is the cell cycle controlled?
- How do cells start to cycle?
- How does this go wrong in cancers?

Lecture 2:

- How do cells initiate DNA replication?
- How do cells segregate chromosomes?
- Checkpoints ensure that replication and segregation go to completion
- What happens when replication/segregation go wrong?
- Most chemotherapies work by inhibiting replication and/or mitosis

Lecture 3:

- Cell Death and why you should care about it
- Apoptosis
- Caspase activation mechanisms
- Intrinsic and Extrinsic cell death pathway

Lecture 4:

- Apoptosis and cancer
- Apoptosis and chemotherapies

Trevor Littlewood: Epilogue: Molecular biology of cancer (1)

Cancer genes: oncogenes and tumour suppressor genes

- What are oncogenes and tumour suppressor genes and where do they operate in biological processes?
- Oncogenes – discovery, mechanisms and consequences of “activation”
- Oncogene cooperation in tumorigenesis
- Tumour suppressor genes – their discovery and the consequences of loss of function
- The molecular basis of the inheritance of genetic predisposition to cancer.

Prof. Alun Williams: A lecture on nutrition (1)

Easter Term: Translating Biochemistry and Genetics to the Clinic

TBC: Imaging Biology in the Cancer Patient (2)

Our growing understanding of the molecular basis of cancer is allowing the design of new clinical imaging methods that provide early disease detection, that give prognostic information and that can detect early treatment response to guide therapy in individual patients. These lectures will outline the physical principles of these methods and show how they can be used to interrogate specific aspects of tumour cell biology in the cancer patient.

Parallel lecture (1):

Prof. Nick Wareham: Nutrition and Preventive Medicine (for the medics)

A look at translating science into treatment and prevention in the diabetes clinic. To consider how the classification of diabetes is driven by the tools that we have available to sub-divide the phenotype into different sub-groups. To illustrate how the study of biology at a molecular level is fundamental to dividing disease groups into specific sub-types and to tailoring effective therapy to individual diagnoses. To discuss the potential for genetic and molecular science to further stratify disease and provide insights into tailored treatment and prevention.

TBC: Clinical Aspects of Energy Metabolism in Small Animals (for the vets)

This lecture will help you realise the importance of an understanding of nutrition and energy metabolism in the clinical setting in dogs and cats. We will discuss a couple of real cases: a Labrador being tube-fed in our ICU after a pharyngeal stick injury and a very overweight cat with a urinary obstruction. We will use these to compare and contrast energy metabolism in a critical care situation or for controlled weight loss. By the end of the lecture, you will understand how basal energy requirements change in hospitalised animals and overweight animals; understand the changes in relative contribution of fat, carbohydrate and protein to energy metabolism in hospitalised anorexic animals (‘accelerated starvation’) and how this differs between dogs and cats and appreciate why fat cats, but not dogs, are predisposed to potentially fatal hepatic lipidosis if starved.

Christine Farr and/or Elizabeth Murchison: Genetics revision session and preparation for exams (1)

Revision session and preparation for exams – your choice of topics

The purpose of this lecture is to review specific topics that you will choose from the previous genetics lectures, in preparation for the examination. During the Lent term and

Easter break, students are encouraged to contact the lecturer if there is a specific area that they would like to see covered in this session.

Sarah Lummis: "Membrane dynamics and function; signalling by hormones" revision session and preparation for exams (1)

Revision session and preparation for exams – your choice of topics

The purpose of this lecture is to review specific topics that you will choose from the previous membrane dynamics and function lectures, in preparation for the examination. During the Lent term and Easter break, students are encouraged to contact the lecturer if there is a specific area that they would like to see covered in this session.

Daniel Nietlispach: Exam strategy and data handling preparation session (1)

Revision session and preparation for exams delivered by the Course Organiser

