MOLECULAR VIROLOGY

MODULE NUMBER: BIO00021H

ORGANISER: Prof Norman J Maitland

VERSION: Provisional Autumn term 2012

SUBJECT COMMITTEE: MBB

ASSESSMENT: Closed examination.

SUMMARY: Much of our knowledge of normal gene expression in mammalian cells has been derived by extrapolation from data obtained with virus infections. This course aims to investigate the molecular mechanisms by which animal viruses can subvert gene control in infected cells. The course progressively deals with the molecular details of the infection process as they are known and in the latter four lectures applies this to known biological situations including virally induced cancers, acquired immune deficiency syndrome and the use of viruses as potential gene transfer agents for gene therapy.

AIMS: To provide a sound background in both viral disease and use of viruses as biological agents. To broaden understanding of molecular processes in animal cells, as exploited by viruses.

PREREQUISITES: Module 0220403 Immunology, Biochemistry, basic biology and molecular cell biology.

SYNOPSIS: Mammalian viruses are responsible for a high proportion of morbidity and mortality in the animal and human populations. We will explore in detail the remarkable diversity of molecular mechanisms whereby mammalian viruses can reproduce their genetic material within cells. The course stresses the different mechanisms of viral gene replication and transcription and the limitations placed upon viruses by the types of cells that they can infect. Since viruses are obligate parasites, they must employ host cell mechanisms for replication, and have served as excellent models for the molecular processes which occur in mammalian cells.

Using these interactions as a framework, the specific life cycles of a number of well understood viruses including SV40, human herpes viruses and human retroviruses will be discussed in some detail. Account will be taken of the importance of the molecular factors in designing gene cloning and transfer vectors based on the mammalian viruses which offer a unique opportunity to target genes to specific host cells. There will be therefore be overlap in this area with other lecture courses including Applied Molecular Genetics and Eukaryotic Gene Expression.

Finally, the links between a number of human viruses, including human retroviruses and human papillomaviruses, with human cancer will be discussed in some detail. Virally induced cancers may constitute a large portion of cancers in the third world and in contrast to environmentally induced cancers, should be readily preventable by appropriate vaccination. Here there will inevitably be some overlap with the Cancer and the Cell Cycle course, but the emphasis in 726 will remain on the viral, rather than the cellular contribution to carcinogenesis.
Learning outcomes are below on a lecture by lecture basis. The lectures will follow approximately the following programme in 2012:-

**Lecture 1 (NJM)**

An overview of mammalian viruses stressing their importance in human disease.

1. The diversity of mammalian viruses, transmission patterns, methods of combating virus infection.
2. Diversity of virus structure: protein capsids in most but not all cases. More sophisticated viruses have membranes surrounding the protein capsid.
3. Diversity of viral genomes present within the capsid, comprising double and single stranded DNA +/- and double stranded RNA and hybrid DNA RNA.
4. Emergent virus infections, such as Nipah virus, Ebola virus.
5. Topicality in terms of new viruses such as TT virus, the Astroviruses, Blue Tongue, Foot and Mouth Disease.
6. Mechanisms of virus evolution and diversification, emphasising the major differences between DNA and RNA viruses.

**Lecture 2 (NJM)**

Lecture 2 focuses on the life cycle of animal viruses:-

2. A general scheme into which most animal viruses can be plugged, to discuss logically their interactions with the host cell.
3. The genome problem in viruses – how do viruses with very different nucleic acid genomes achieve replication within the confines of normal cellular processes? Example: paroviruses.
4. Virus attachment via both receptors and non specific mechanisms with particular emphasis on endocytosis and endosome release. Receptor mechanisms (Example: Picornaviruses). The potential for inhibition of attachment.
5. Example of viral attachment: Influenza virus and the importance of haemagglutinin and neuraminidase genes in defining infectivity. The ability of ‘flu to re-assort its genome.
6. A structural approach to influenza virus variability, through the detailed knowledge of the haemagglutinin protein.
7. The importance of the flu fusion peptide and its structural variability under acidic conditions.

**Lecture 3 (RT)**

Viral Structure and Function:-

1. The principle of genetic economy as a biological reason for the occurrence of symmetry in viruses.
2. Classification of virus structure in terms of T-numbers, including examples of viruses outside the T-number classification.
3. Different mechanisms of genome packaging.
4. Virus assembly.
5. The roles of autostery and allostery in RNA virus assembly.
6. Structural transitions in viruses important for infection.

Lecture 4 (NJM)

Viral life cycles at single cell, tissue and whole body levels.

1. The differences between early and late synthesis in virus infectious cycles and the importance of genome replication as the boundary between these two phases. Example: SV40.
2. Mutant types to study viral protein function. Example: SV40 T antigen, a multi functional protein involved in both transcription and replication control.
3. The coding problem in small viruses Example SV40 early proteins, late proteins, the usage of multiple reading frames and bi-directional transcription from a common core promoter in the SV40 genome.
4. The whole body response to virus infections and how the immune system can combat them, leading to a overall non-permissive interaction.
5. Evolved multiple immune evasion systems which permit viral infection in the presence of a powerful immune response.
6. The classical and alternative complement responses against virus infection.

Lecture 5 (NJM)

The complex life cycles of larger viruses

1. A more complex example of temporal control in a DNA virus: human adenoviruses.
2. Viral recombination resulting in hybrid viruses: new species?
3. The diversity and number of viruses in the herpes virus group: Grouping of the herpes viruses into alpha, beta and gamma herpes viruses.
4. Pathogenesis of herpes viruses including herpes simplex virus, varicella-zoster virus, cytomegalovirus.
5. The life cycle of herpes simplex virus based on the standard protocol developed in earlier lectures: The importance of herpes virus gene regulation including immediate early, early and late gene expression.
6. Herpes simplex virus latency as a mechanism of persistence in neurons. Potential mechanisms of latency and recurrence in herpes simplex virus.

Lecture 6 (FM)

Human retroviruses: HTLV and HIV:-

1. The historical basis and discovery of HIV and HTLV.
3. The different HIV receptor types. Use of different receptors to allow HIV to infect different human cell types, leading to widespread infection.
5. The complex capsid structure in immature and mature types of lentiviruses: virus attachment and entry.
6. HIV life cycle.
7. Expression control of human retroviruses. Comparison between HTLV and HIV and the control elements resident within the long terminal repeat (LTR) of the retroviruses.
8. Anti HIV therapies. New drugs available and in development, potential drug targets.

Lecture 7 (CL)
Human papillomaviruses and Cancer:-

2. The relationship between HPV sequence conservation and disease type: the concept of high risk papillomaviruses for cancer. The unusual distribution of certain types of human papillomavirus eg the butchers wart (HPV 7).
3. The genome of human papillomavirus type 16. The usage of multiple reading frames on the 8kb genome to encode more proteins than expected.
4. A general account of the functions of the different human papillomavirus proteins.
5. The role of the papillomavirus E1 protein as a replicator of the virus genome.
6. The E2 protein, its multi functional nature, activity as a DNA binding transcription and replication factor, existence as a dimer. The function and biology of the E6 and E7 protein. HPV oncogenes.
7. The role of human papillomaviruses in cervical, oral and some other types of cancers. Integration of the HPV genome and its consequences.
8. Cervical cancer screening and vaccination against genital HPV types.

Lecture 8 (NJM)
Virus Pathogenesis:-

1. Types of viruses implicated in human cancers and the criteria (Koch’s postulates) which must be fulfilled in order to prove an association.
2. Experimental viral carcinogenesis: first steps in a proof of a causal relationship
3. Hepatitis virus: its extremely high incidence and the close link between hepatitis incidence patterns worldwide and hepatocellular carcinoma.
4. Retrovirus mediated cell transformation in vitro. The different types of transforming retroviruses.
5. XMRV: a virus in search of a disease
6. How viruses cause human cancer: Epstein Barr virus
7. Susceptibility and resistance: Interferon, a cellular antiviral response
8. Susceptibility and resistance: Small molecule inhibitors of viral infections

Lecture 9 (NJM)

Viruses as vectors for gene therapy:-

1. A framework to decide on the effectiveness of viruses as gene transfer vectors for gene therapy.
2. Non viral methods of gene transfer into mammalian cells including the use of hybrid systems and basic protein conjugates such as transferrin.
3. How to generate a recombinant virus.
5. Gene Therapy: viral vectors in common use.
6. Baculoviruses (insect viruses) as tools in molecular biology: Baculoviruses, as sources of high levels of protein for molecular biology studies: the ability of insect viruses to infect but not to grow in human cells.
7. Safety and ethical aspects of human gene therapy.

RECOMMENDED READING:

Cann, A.J. Principles of Molecular Virology. (4th edition). Harcourt Brace & Company Ltd. (This is the basic text book for the course and covers many of the topics to be discussed).


N.B. Detailed lecture notes including reprints of articles fundamental to the understanding of the course are available for consultation at the end of each lecture, and will be placed on Blackboard if possible.

LECTURES AND ORGANISATION:
Prof Maitland - 9 lectures, each one to two hours (maximum)

STUDENT WORKLOAD:
Lectures: 9 hours or more
Total contact hours: 9 hours or more
Private study: up to 27 hours

PRIVATE STUDY: If all the required papers are to be consulted then considerable extra reading is required, however a good basic knowledge can be gained from study of the provided lecture notes which are as comprehensive as possible. I encourage the students to listen during the lectures and provide notes on the slides with substantial detail for them to consult in their own time. All lectures are updated
annually, and are available the week of the lecture on Blackboard. Key references and any changes in programme are also recorded there.