NOTES FOR THIS REVISION DOCUMENT:

- This revision document contains a concise summary of EVERY lecture. They are NOT in the order in which they were given, but rather grouped into a more logical order (e.g. MHC and genetics, primary and secondary immunodeficiencies lectures grouped together). But ALL lectures are in here.
- Summaries are divided into 'key facts' (KFs), then Short-Answer Questions (SAQs) and flashcards made by myself.
- Good luck! ☺

LECTURES COVERED:

LECTURE 2 (13/08/19): MHC & Genetics of Immunological Disease .....

LECTURE 3 (14/08/19): Immunity to Infection 1 – viruses and immune evasion .....

LECTURE 4 (21/08/19): Immunity to Infection 2 – EC bacteria and immune evasion..

LECTURE 5 (27/08/19): Immunity to Infection 3 – IC bacteria and immune evasion ..

LECTURE 6 (28/08/19): Immunity to Infection 4 – parasites and immune evasion.....

LECTURE 7 (04/09/19): Vaccination and novel vaccine approaches.....

LECTURE 8 (10/09/19): Acquired Immunodeficiency – HIV/AIDS.....

LECTURE 9 (11/09/19): Molecular Basis of Primary Immunodeficiencies.....

LECTURE 10 (18/09/19): Self-tolerance and autoimmunity .....

LECTURE 11 (24/09/19): Autoimmune diseases .....

LECTURE 12 (25/09/19): Nervous System Immunology .....

LECTURE 13 (09/10/19): Transplantation Immunology .....

LECTURE 14 (15/10/19): Imaging of the immune system.....

LECTURE 15 (16/10/19): Tumour Immunology.....

LECTURE 16 (23/10/19): Cancer Immunotherapy.....

LECTURE 17 (29/10/19): Mucosal Immunology.....

LECTURE 18 (30/10/19): Allergic Diseases.....

<u>IMMU KEY FACT SUMMARIES:</u>

L2 KF: MHC and genetics

HLA background:

- Many genetic associations revolve around the Human Leukocyte Antigen (HLA) system – has a role in predisposing us to AI disease, and our ability to control infections.
- HLA is the locus on chromosome 6 in humans. Involved in MHC I, II and the complement system. Three main regions within locus:
    - Class I – encodes 3 x classical loci, HLA-A, B and C with varying antigen specificities (+ some non-classical molecules).
    - Class II – encodes 3 x classical loci, HLA-DR, DP and DQ with varying antigen specificities (+ non-classical DM and DO - involved in lysosomes and delivery to MHC II).
    - Class III – encodes complement factors and TNF-a.
- T cell responses are MHC-restricted – can only respond to own MHC presenting a foreign peptide.

- MHC I basics: heavy chain and B2 microglobulin, PBC made of alpha 1 and alpha 2 regions (variable), fits 6-16 AA peptide, B2 invariant region (CD8 binding site), expressed by all nucleated cells.
- MHC II basics: two chains – alpha and beta. PBC is made of alpha 1 and beta 1 – open cleft that fits 30 AA peptide. Expressed constitutively on APCs (DC, macro, B cells) and can be INDUCED on other cells via IFN-y. Invariant region a2 binds to CD4.

Types of genetic defects:

- Can look at genetic defects in two ways:
    - How many genes affected: Both monogenic defects (Mendelian inheritance, single gene mutation e.g. X-linked, AR, AD) and polygenic defects (cumulative effects of SNPs in multiple genes) are heritable.
    - Outcome spectrum: Genetic defects can range from a global deficiency (absent T/B cells), to a single defect (lose a type of T cell, become susceptible to a single class of pathogen as in MSMD), to a major allele, to polygenic (many genes affected).
- Monogenic defects and changes to the immune response:
    - Single gene defects can alter the IR, and lead to absent or non-functional proteins.
    - Mendelian inheritance – AR or X-linked.
    - Can cause a primary immunodeficiency (heritable immune disorder).
    - Example 1: global deficiency – absent T or B cells
        - T cell deficiency can be due to absent common gamma chain of IL-2 receptor – diagnosed as SCID.
        - Patients suffer from severe infections, many pathogens.
    - Example 2: susceptibility to a particular class of microbe
        - Can get MSMD (Mendelian Susceptibility to Mycobacterial Infections) due to a deficiency in IFNy or IL-12 signalling.
        - Severe disease due to non-tuberculous environmental mycobacterium, e.g. M avium. Not susceptible to a whole range, as in SCID, but just to one class.
- Polygenic defects and changes to the immune response:
    - Cumulative effects of gene mutations/allelic variation in multiple genes can affect the IR
    - Can lead to a non-functional protein or a subtle change in function.
    - Mendelian inheritance, but more complex because the phenotype requires the effects of multiple variants
    - Example 1: require SNP in both genes to lose function (AR) or if protein acts as a dominant negative mutant

Studying polygenic defects:

- Family Association Studies:
    - Risk of disease associated with inheritance of allele or gene locus from a parent
    - Acts like a Quantitative Trait Locus (QLT) – this is a gene defect whose frequency correlates with presence in population
- Case-Control studies:
    - Assembled 'cases' - people suffering from a particular disorder (vaccine response, AI, allergic disease, infection risk), AND controls, and measured the frequency of genes/gene loci in 2 groups. HLA is the obvious candidate for study.
    - This is based on the assumption that a gene product is associated with variation in IR.
- Genome Wide Association Studies (GWAS):
    - Risk of disease is associated with variations in SNPs across WHOLE genome – stat tests performed to determine risk – can ID multiple genetic loci responsible.
- Can identify sequence variation in the human genome by a variety of mechanisms. Often will find a block of variants OR variants separated by a recombination hotspot, associated with disease.
- Can ID SNPs using PCR or gene chips (first prove association then perform fine mapping of individual gene) then compare thousands of SNPs in case-control studies.

- Can use GWAS to survey the whole genome and ID regions of chromosomes associated with disease – regions where variation explodes.

Particular diseases:

- MHC has been shown to be a crucial player in many disorders (AI, infection, allergy, drug response) through case control studies
- Ankylosing spondylitis (hunchback) = B27 allele → increases disease risk by 100-200
- Diabetes = DR4/3
- Hypothyroidism = DR2
- Rheumatoid Arthritis = DR4
- SLE = DR3

L2 SAQs:

1. **Compare MHC I and II function**
2. **What are the different ways of looking at mutations?**
3. **Compare monogenic defects and polygenic defects**
4. **What are 3 ways in which we can study polygenic defects**
5. **What can analysis of HLA polymorphisms indicate?**
6. **What are some gene associations between T1D and RA?**