

Molecules to Malady 2018

B Cell Module

<u>PID</u>	<ul style="list-style-type: none"> >350 rare chronic disorders • produce normal immune response impaired • recurrent/severe/unusual/persistent/run-in-familiy infections • not caused by other diseases/treatments/toxins (=2°) • mostly genetic disorders – monogenetic usually • most diagnosed <1 yr old - can affect any age/gender - ↑ early developmental stage affected => ↑ severe/younger children affected 	
<u>Antibody Deficiencies</u>	<ul style="list-style-type: none"> • humoral immunity lost (some/completely) • cellular immunity intact • include <ul style="list-style-type: none"> - XLA (X-linked agammaglobulinaemia) - CVID (common variable immunodeficiency) - HIGM (hyper IgM syndromes) 	<ul style="list-style-type: none"> • Majority of PID is antibody disorders
<u>CID (Combined Immunodeficiencies)</u>	<ul style="list-style-type: none"> • humoral and cellular immunity lost • include <ul style="list-style-type: none"> - SCID (severe CID) 	<ul style="list-style-type: none"> • CD4 T cells help B cells • Defects in T cells only can be SCID
<u>Treatment of PID</u>	<ul style="list-style-type: none"> • depends on severity of PID 1) most severe forms, SCID, XLA => replace the whole immune system using <ul style="list-style-type: none"> - HSCT/BMT/PBSC/UCST - gene therapy 2) some Ab exist, HIGM, CVID, XLP => replace Ab using <ul style="list-style-type: none"> - IVIG/SCIG - HSCT/gene therapy require immunosuppression to prevent GVHD (Graft vs Host Disease) 	<p>IVIG</p> <ul style="list-style-type: none"> • pooled human sera (>100) • broad-spectrum, all IgG subclasses • 400~600 mg/Kg/month • 2~4 hrs • 5g/L at trough <p>SCIG</p> <ul style="list-style-type: none"> • wk/2wk • abdomen, thigh, f.arm • 100~150 mg/Kg • no adverse • avoid peak/trough
<u>SCID</u>	<p>fatal PID with</p> <ul style="list-style-type: none"> • T and B cell function lost • recurrent viral/fungal/bacterial infections – lethal early • 20 genes account for 90% SCID cases 	<ul style="list-style-type: none"> • 1:200,000 birth worldwide (NBS suggest 1:50,000) • 0~6 babies in Australia per year
<u>SCID Genes</u>	<ul style="list-style-type: none"> • ADA (encode adenosine deaminase) – no T/B/NK • DCLRE1C (encode RAG1/2, Artemis) – no T/B • IL2RG/JAK3 (encode γc chain) – no T/NK • IL7R (encode IL7Rα) – no T 	<ul style="list-style-type: none"> • IL2RG/JAK3 SCID is X-linked • γc chain is common cytokine receptor

Rheumatoid Arthritis Module

<u>Arthritis</u>	<ul style="list-style-type: none"> umbrella term that denotes joint diseases >100 types (95% due to osteoarthritis, RA, gout) prevalence 9% in Australia <ul style="list-style-type: none"> ↑ with age ↑ in indigenous people 	<ul style="list-style-type: none"> <1% under 35yr, 35% over 80yr
<u>Rheumatoid Arthritis</u>	<ul style="list-style-type: none"> chronic inflammatory autoimmune disease of unknown cause articular manifestations dominant feature systemic extra-articular complications progressive disability reduced life expectancy (~10yr) 1:1000 max incidence per year 0.5~1% prevalence globally in adult Caucasian popn 2~3 times ↑ common in female peak age of onset 40~70 	<ul style="list-style-type: none"> significant socioeconomic costs associated with RA corresponding to menopausal stage
<u>Clinical Features of RA</u>	<ul style="list-style-type: none"> synovitis <ul style="list-style-type: none"> 1° manifestation pannus erosion of bone/cartilage/peri-articular structures osteoporosis (more fragile bone) inflamm cells in subintima (fibroblast/macrophage) => hypertrophy of synoviocytes => swollen joint articular manifestations <ol style="list-style-type: none"> insidious onset (wks/months) <ul style="list-style-type: none"> morning stiffness >1hr gel if inactive pain and swelling intermediate (days/wks) acute (days) 	
<u>Articular Manifestations</u>	<ul style="list-style-type: none"> symmetrical small joints usually affected MCP, PIP, wrist, knee, MTP characteristic deformities 	<ul style="list-style-type: none"> larger joints affected means longer symptoms
<u>Characteristic Deformities (Hand)</u>	<ol style="list-style-type: none"> radial (lateral) wrist deviation MCP swelling/subluxation/ulnar deviation Z deformity = fixed flex/sublex of MCP + fixed hyperext of PIP Boutonniere = fixed flex of PIP + fixed hyperext of DIP <ul style="list-style-type: none"> extensor tendon (dorsal) rupture with inflamm -> force protrusion of PIP Swan neck = fixed h.ext of PIP + fixed flex of DIP <ul style="list-style-type: none"> flexor tendon (palmar) rupture & slide sideways lateral bands sublux dorsally at PIP tendon shortening at DIP PIP fusiform swelling 	

Muscular Dystrophy Module

<u>Muscle</u>	<ul style="list-style-type: none"> • Shortening of muscles moves joints • Muscle tissue enables motion and maintenance of posture • Muscle tissue also generates heat 	
<u>Terminology</u>	<ul style="list-style-type: none"> • Myopathies = disorders of muscle • Congenital myopathies = genetic disorders of muscle contractile apparatus <ul style="list-style-type: none"> - characteristic pathological changes are static • Muscular dystrophies = genetic disorders of muscle supporting structures <ul style="list-style-type: none"> - usually progressive - pathology characterised by degeneration & regeneration of muscle fibres 	
<u>Skeletal Muscle</u>	<ul style="list-style-type: none"> • attached to bone • striated • vary in function & structure <ul style="list-style-type: none"> - variable colour depending on myoglobin content - variable speed in contraction - variable metabolic processes 	<ul style="list-style-type: none"> • Fibres contain alternating light & dark bands perpendicular to their long axes
<u>Structure of Skeletal Muscle</u>	<ul style="list-style-type: none"> • Muscle belly is made up of muscle fibres • Muscle fibre consists of sarcolemma <ul style="list-style-type: none"> - contains myofibrils and sarcoplasm - multinuclear - grouped into fasciculi • Fibres within each fasciculi are surrounded by endomysium • Each fasciculus is surrounded by perimysium 	<ul style="list-style-type: none"> • Myofibrils and sarcoplasm make up the contractile components of muscle
<u>Substructure of Skeletal Muscle</u>	<ul style="list-style-type: none"> • Each myofibril is divided into sacromeres • Sacromere is the smallest contractile unit <ul style="list-style-type: none"> - I band is aligned actin filaments - A band is aligned myosin and actin filaments 	<ul style="list-style-type: none"> • Sacromeres are repeated along the length of muscle fibres
<u>Myofibrils</u>	<ul style="list-style-type: none"> • have sarcoplasm => contains glycogen, fat particles, enzymes & mitochondria • have 2 myofilaments running parallel => actin & myosin <ul style="list-style-type: none"> - Myosin has tiny globular heads => form cross-bridges & muscle action - Actin, tropomyosin and troponin are thin filaments 	
<u>Muscle Contraction</u>	<ul style="list-style-type: none"> • occurs by sliding filaments <ul style="list-style-type: none"> - At rest tropomyosin covers myosin binding sites (of actin) - Ca^{+} binds to troponin => alters tropomyosin structure - Myosin heads bind to actin => forms cross-bridges - ADP & P_i are released => generates sliding movement of actin - New ATP binds to myosin head & cross-bridge breaks • is caused by release of ACh by motor neurons <ul style="list-style-type: none"> - ACh binds to nACh receptor => causes Na^{+} influx & action potential initiation in muscle - Muscle AP travels along T tubules & reach to SR (sarcoplasmic reticulum) => allow Ca^{+} flow into sacromere 	

Cystic Fibrosis Module

<u>Introduction (Lecture 1)</u>	<ol style="list-style-type: none"> 1) Common inherited disorder 2) Variable severity 3) No cure 4) Treatment increase lifespan 5) Death due to respiratory/cardiac complications 6) Multiple system affected 7) All affected by production of excessively thick & dehydrated mucus 8) Failure of salt (Cl⁻) and water transport by epithelial cells lining ducts
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<1> Common Inherited Disorder (Lecture 2)

<u>CFTR Gene</u>	<ul style="list-style-type: none"> • Gene responsible for CF identified by <ul style="list-style-type: none"> - Positional cloning - Fundamental defect => cAMP-mediated regulation of Cl⁻ transport - Linkage analysis => map to chromosome 7q31.2 • CFTR gene <ul style="list-style-type: none"> - 190kb DNA, 27 exons - Codes for an ion channel protein 	<ul style="list-style-type: none"> • Gene names are written in italics • The ion channel protein coded by CFTR = CF transmembrane conductance regulator = CFTR protein
<u>CFTR Protein</u>	<ul style="list-style-type: none"> • 170kD, 1480 amino acids • Member of ABC superfamily • Gated chloride channel protein • Ions diffuse down concentration gradient • Regulated by cAMP-dependent phosphorylation • Expressed in epithelial cells (apical membrane) in wide variety of tissues 	<ul style="list-style-type: none"> • ABC = ATP-binding cassette superfamily of membrane transporters
<u>CFTR Protein Function</u>	<ul style="list-style-type: none"> • Regulates anion (mostly Cl⁻ and HCO₃⁻) transport • Regulates mucociliary clearance • Have a role in immunity and inflammation 	
<u>CFTR Protein Structure</u>	<ul style="list-style-type: none"> • Five domain <ol style="list-style-type: none"> 1) Two membrane spanning domains (MSD 1 and 2) => form channel 2) Two nucleotide-binding domains (NBD 1 and 2) => bind & hydrolyse ATP 3) Regulatory (R) domain => phosphorylated by cAMP dependent protein kinase • Activation of CFTR channel relies on phosphorylation <ol style="list-style-type: none"> 1) Closed state = de-phosphorylated state 2) One ATP molecule is permanently bound 3) 2nd ATP binding trigger opening of the channel via phosphorylation of NBD • CFTR protein interacts with other proteins <ul style="list-style-type: none"> - C-terminal anchored to cytoskeleton & kept close to other proteins - Which influence CFTR functions such as: <ul style="list-style-type: none"> ○ conductance ○ regulation of other channels ○ signal transduction ○ localisation at apical plasma membrane 	

Pandemics Module

<1> HIV

<u>Retrovirus of Lentiviridae Family</u>	<ul style="list-style-type: none"> • 3 main genes: gag, pol, env • plus regulatory proteins: tat, rev, vpr, vpu, vif, nef • gag: structural proteins <ul style="list-style-type: none"> - p17 matrix => icosahedral - p24 capsid => protection - p7 nucleocapsid => inside nucleus, coat RNA • pol: viral enzymes <ul style="list-style-type: none"> - p66/51 RT (reverse transcriptase) - p32 integrase - p11 protease • env: envelope glycoproteins <ul style="list-style-type: none"> - gp120 => cell attachment - gp41 => transmembr fusion domain 	<ul style="list-style-type: none"> • Regulatory proteins allow few tricks for virus • Retrovirus: "backward" RNA -> DNA - These viruses circulated for centuries and a lot of animals affected (sheep, horse, cow, cat, primates) - Cross-species transmission of HIV occurred in 1930s - HIV-1 = SIVcpz (chimpanzee) - HIV-2 = SIVsm (sooty mangabey)
<u>8 Things to Know for Lentiviruses</u>	<ul style="list-style-type: none"> • slow disease - long-lived • 80~130 nm size (small) • capsid symmetry: icosahedral • envelope • diploid linear 10kb +ve sense ssRNA • replicate in nucleus • assemble in cytoplasm at memb • AIDS, neurologic, arthritis, pneumonia 	<ul style="list-style-type: none"> • Diploid means two copies of single stranded RNA
<u>HIV Clades</u>	<ul style="list-style-type: none"> • a lot of HIV strains exist • strains/clade determined by similarity of seq/genetic code • different strains in different regions of the world <ul style="list-style-type: none"> - which is why making vaccine is difficult 	
<u>Life Cycle of HIV</u>	<ol style="list-style-type: none"> 1) gp120 bind CD4 => conformation change of gp120 2) gp120 bind chemokine co-receptor 3) gp41 allow fusion 4) RNA enter 5) RT produce DNA and DNA integrates into host genome 6) DNA transcription -> RNA -> translation 7) assembly, budding, maturation, new virion! <ul style="list-style-type: none"> • virus cross mucosa memb within hours • local expansion within 4 days (infected T cells) • virus go to lymph node/blood within weeks 	<ul style="list-style-type: none"> • Integration is common for retrovirus • Integration is why we don't have cure for HIV ("We live with them and their DNA")

Neuro-degeneration (ND) Module

<Lecture 1> Introduction: 8 Things to Remember

<u><1> Single Etiology Model Doesn't Work</u>	<ul style="list-style-type: none"> • Make model • We can model only aspects of ND <ul style="list-style-type: none"> - Mutation in SOD1 is associated with familial MND but - Mutation in SOD1 affects sensory neurons in dogs - The difference in gene expression between human & dog sensory neurons can point to key mechanisms 	<ul style="list-style-type: none"> • Risk factors => disease onset => active disease => failed organ • MND is motor neuron disease
<u><2> Risk and End Stages Are Different Entities</u>		
<u><3> What Constitutes "x" Disease Is Constantly Changing</u>		
<u><4> Clinical Signs Tell You the Anatomical Pathology</u>	<ul style="list-style-type: none"> • Phenotype tells which brain region is injured & hence which cells are injured <ul style="list-style-type: none"> - Increased reflexes & weakness/paralyses indicate that upper motor neurons are affected - Loss of reflexes & fasciculation indicate lower motor neurons 	<ul style="list-style-type: none"> • Different cell types are due to gene expression which gives biochemistry, morphology & energy demands
<u><5> Similar Cells Have Similar Disease Susceptibility</u>	<ul style="list-style-type: none"> • Similar neurons have common embryology/transmitters/morphology/gene expression => thus similar risk to diseases 	
<u><6> Each ND Affects a System of Cells</u>	<ul style="list-style-type: none"> • Both PD and AD have dementia but • dementia of PD have frontal cortex/executive dementia <ul style="list-style-type: none"> - attention, executive function & impulsivity • dementia of AD have posterior cortex/ammestic dementia <ul style="list-style-type: none"> - attention, memory & language - 15% of PD have amnesic dementia & increased $A\beta$ levels 	
<u><7> Each ND Tends to Have a Specific Misbehaving Protein</u>	<ul style="list-style-type: none"> • AD (Alzheimer) -> $A\beta$ • PD (Parkinsons) -> α-synuclein • dementia with LBody -> α-synuclein • progressive supranvelear palsy -> Tau • fronto-temporal dementia -> Tau & TDP43 	<ul style="list-style-type: none"> • We can say they are "signiture proteins"
<u><8> ND Progresses</u>	<ul style="list-style-type: none"> • All NDs spread to neighbouring neurons <ul style="list-style-type: none"> - Infantile ND causes severe gene abnormalities - Young onset ND causes less severe gene abnormalities or increased expression of late onset genes - Late onset ND is the conventionally held ND and have common features: <ul style="list-style-type: none"> ○ have energetic component ○ inclusion formation: autophagy, misfolding & lysosome disturbance ○ axon transport problems & terminal dieback 	