Objective	Response
› Describe and characterise B and T cell deficiencies (e.g. XLA, Hyper IgM, DiGeorge) and SCID	B cells immunodeficiencies include: X linked agammaglobulemia (XLA) and Hyper IgM syndrome. T cell immunodeficiencies include Wiskott-Aldrich Syndrome, Familial Hemophagocytic Lymphohistocytosis (FHL), Epidermodysplasia Verrcuiformis, DiGeorges Syndrome and Bare Lymphocyte Syndrome. Deficiency in both B, T and NK cells (most of adaptive immune system) is known as severe combined immunodeficienciy (SCID). B CELL IMMUNODEFICIENCIES **X linked agammaglobulemia (XLA):** Caused by mutation in the gene econding for **Bruton's Tyrosine Kinase (Btk)**, resulting in inability for pre-B cells to make a complete BCR, leading to pre-B cell apoptosis. Block in B cell production leads to lack of antibody production altogether. These inidivudals will be suseptible to pyrogenic bacteria. Treatment: intravenous Ig Therapy. **Hyper IgM syndrome:** Associated with absence of isotype switching, having no IgG or IgA, detecting a high increase in IgM serum as compensation. These patients are more suseptible to streptococci and pneumocystis carinii. Treatment: intravenous Ig Therapy. Two main types, X linked hyper IgM syndrome, **a mutation in CD40L**, which blocks isotype swithcing, affinity maturation and cellular differentiation into plasma and memory cells. Furthermore, this affects activation of DC and macrophages. **Hyper IgM syndrome type 2, AID deficiency,** autosomal recessive disorder, a mutation in activation-induced cytidine deaminase, which causes inability for affinity maturation and isotype switching to occur. This does not affect activation of macrophages and DC since it does not affect the CD40:CD40L, it only impacts the inability for random mutations to occur in the germinal center when B cells need to be proliferated. Both X linked hyper IgM syndrome and Type 2 syndrome will cause an abundance of igM to be produced. There are other types of hyper IgM syndromes which include selective IgA immunodeficiency, which causes patients to have mucosal areas with no IgA. Another type will be common variable immunodeficiency (CVID), which indicates a defect in one or more genes affecting B cell growth or stimulation, present with variable reductions in IgG and IgA, with varying levles of disease and presents later in life. T CELL IMMUNODEFICIENCIES **Wiskott-Aldrich Syndrome**: X-linked genetic defect in **WAS protein** which induces actin polyermization and redistribution of lymphoid cells upon TCR activation-- as needed for cytotoxicity, including release of perforin and granzyme. Fuirthermore, this inhibits the formation of immunological synpases hence the immune communcation between T cells and other immune cells become weaker. Characterised by thrombocytopenia: low platelet count, suseptibility to bruising and hemmorage, imparied T cell function and low Ig levels. Leads to normal T cell count in thymus but decreased in periphery. **Familial Hemophagocytic Lymphohistocytosis (FHL)**: Autosomal recessive disease that causes l**ack of perforin in CD8+ T cells** due to a missense mutation, affecting cytotoxic secretions and polyclonal CD8+ T cell accumulation in lymph nodes. This leads to uncontrolled T cell activation and a cytokine storm-- **progressive inflammation** which is lethal unless immunosurpressant is used. **Epidermodysplasia Verrcuiformis**: Abnormal suseptiblity to HPV infection due to mutation in **EVER1 and EVER2** genes involved in **zinc homeostasis in lymphocytes.** Causes defective T cell immunity and cutaneous warts in HPV infection. **DiGeorges Syndrome:** Deletion of up to 30 genes in **chromosome 22,** occurs randomly during fetal development in pregnancy, causing congential heart disease, facial abnormalities due to a mutation in **tbx1** which causes thymic epithelium development failure -- defect in T cell maturation. **Bare Lymphocyte Syndrome:** Two types, **MHC I and MHCII deficiency**, known as **BARE** lymphocyte syndrome 1 and 2. 1: mutation in tap 1 and 2, causes defects in CD8 immune rsponses due to inability of loading peptide antigens onto MHC I in ER lumen, and accumulation of MHC I in the ER. 2: Mutation in one of four genes that leads to expression of Class II transactivators **(CIITA, RFXANK, RFX5, RFXAP), resulting in failed positive sleection in the thymus** (reduced T helper cells as only MHC I is used in DP positive selection to ensure TCR ersponds to self MHC class) which results in little to no expression of MHC II in all professional APCs, causing severe and recurrent infection. **Severe combined immunodeficienciy (SCID):** Two types, **X linked SCID and Autosomal recessive SCID.** X linked causes a mutation in common gamma chain used in cytokine receptors **CD132**, causes defect in receptors for **IL-2, 7 4, 9, 15, 21**. These are important for lymphocyte maturation, causing patients to lack functional B, T and NK cells. Autosomal recessive, a mutation in either **JAK3, Adenosine deaminase (ADA) or RAG**. JAK3 mutation mediates downstream singalling after cytokines bind y-chain receptor, resembling X-linked SCID. ADA mutation causes defective adenosine deaminase, which breaks down **purines** as a toxic intermediate within the cell, without this enzyme, lymphocytes will die of **progressive lymphoneia**. RAG mutation disables VDJ recombination in lymphocyrtes resulting in complete lack of B cells and T cells due to inability to form receptors. Does not affect NK cells as they dont require RAG.
› Discuss the possible treatment options for immunodeficiences	Can be treated in four ways, **Antibiotics**, **Intravenous immunoglobulin injection**, **Enzyme replacement** and **bone marrow transplant**. **Antibiotics** can treat chronic infections but wil have associated cytotoxicity and selection of resistant mutants. I **Intravenous immunoglublin** injections can treat x Linked agammaglobulemia and hyper IgM syndrome, but patients have to repeatdely go and get treatment given half life of antibodies, and is costly. **Enzyme replacement** can help patients with ADA, such as using gene therapy to aid the inability to produce adenosine deaminase. **Bone marrow transplants** can help SCID but has risks of grafting and host disease inoculation if the bone marrow of the donor has had viral infection which cannot be cleared by the SCID patient during transplant adaptation.

› Discuss the stimuli, immune mechanisms and effectors associated with immune hypersensitivities (type I-IV)	**Type I**: immediate hypersensitivity, IgE, mast cells and lipid mediators. **Type II**: antibody mediated, IgG against cell-bound or extracellular matrix antigen such as complement. Categorized by injuries caused of **activation** of **Ab binding** mechanisms, or Ab binding to **receptors** or proteins that **interfers** with their function (**graves disease)**. An example is **Rhesus**, where maternal IgG antibodies attack fetus RBC due to Rhesus antigens present on the fetal blood cells. This acts like tissue rejection, and as the baby is birthed, the blood will seep into the mothers body to which teh body can develop immunological memory and clearance for the next child. To treat this, the mother must be injected with **anti Rh antibodies** which will disallow the mother to mount a strong immune response to the Rh antigen for it to not atack the second baby with time -- no immunolgical memory produced to "foreign Rh antigne." This can also occur with penicillin allergy, where the penicin binds to our self antigen to alter it, where the immune system will begin to attack our own altered antigen cells via binding of antibodies. **Type III:** immune complex, IgM and IgG immune complex deposition. Categorized by having too many antigens and not enough clearance-- usually at initial stages of infection. This could also occur if there are too many self-antigens. During the course of an infection, Ab are gradually produced where antibody to antigen ratio will increase as time goes. In initial stages, when antigens are not cleared, and antibody affintiy is low, complement opsonization is also low, the antigens can be deposited on cell vessel walls which increase in concentration over time. Release of C3a C5a will cause tissue damage via neutrophil and mast **cell degranulation**, macrophage **cytokine** release, **platete** activation and **vasoactive amines** which increase vasuclar permeability. The damage done via this mechanism is by immune complexes clogging up vessels causing **vasculitis (Blood), glumerulonephritis (kidey) or arthritis (joint).** **Type IV**: delayed type hypersensitivity, CD4 T cell mediated delayed type hypersensitivity (can be CD8).
› To describe the molecular and cellular interactions of the two phases of type I hypersensitivities (sensitization and response)	The **two phases** in type I hypersensitivty is **sensitization** and **response**. **Sensitization** is when DC picks up antigen in low doses and induces a Th2 response via IL-4 and IL-13 release to induce CD4 cells, interacting with B cells to secrete IgE agianst the antigen that is picked up. This is in response to allergens, which can be inhaled or ingested, inhaled are highly soluble and ingested are slowly degraded. Usually intoruced in doses less than 1 microgram. **Response** can be **local** or **systemic**, although systemic respoonses are rare. **Local response**: Mast cells bind IgE via **FceR** receptors which secrete active compounds as effector functions -- inducing local inflammation, such as secretion of **preformed mediators, histamine,** which causes blood vessel dilation and increased permeability. Followed by secretion of **lipid mediators** which are prostaglandins **and leukotrienes** which play a role in bloodfllow, chemotaxis, pain and fever. As well as cytokine secretion of IL-3.4.5 and 13. Can lead to **rhinitis**, **bronchoconstriction** or conjuctivitis. **Systemic response**: depending on which tissue mast cells are activated in, the system will complement the response when mast cell becomes activated. In the GI tract, it will result in increased fluid flow and peristalsis, introducing symtpoms such as diarrhea and vomiting. In airways, it will cause decrease in diameter and increase in mucus secretion, causing wheezing and coughing, production of **phlegm**. In **blood,** it will result in increease blood flow and permeability, as well as increased migtration of cells, proteins, lymph flow and effector responses. Dissemination of this repsonse can ultimately lead to **anaphylaxis**.
› To describe the different mechanisms that cause immediate and late responses in type I hypersensitivity	Type I **immediate responses** happens within minutes, characterized on skin and usually histamine is preformed and readily metabolised. This causes **wheal and flare**, which wheal means localised swelling, and flare means blood vessls dilate to engorge with blood. This will cause redness due to vasodilation, stop selling due to leakage of plasma from venules, and dependent of IgE levels released at the time. **Late respoonse** happens within hours or days, where cells infiltrate the area causing sustained edema, swelling and smooth muscle contraction-- a result of migration of **neutrophils**, **Th2** cells and **esinophils**.
› To describe the molecular and cellular interactions of the two phases of type IV hypersensitivities (sensitization and response)	Type IV hypersensitivty requires the use of **adaptive** immune system and occurs around 24 to 72 hours after infection. Sensitization: requires priming of an adaptive immune system where antigen is taken in skin or mucosal areas, drained to lymph node via DC carrige, priming T cells which elicits **response**: migrate to effector sites, and clearance of antigens.
› The apply understanding of the immunological hypersensitivity reactions to explain immunopathology	Immunopathology associated with type II hypersensitivity-- Rhesus and penicillin allergy. Three key types of immunopathology is associated with type IV hypersensitivty, contact with pentadecacatechol, tuberculosis and celiac disease (gluten). **Poison ivy** (**pentadecacetechol**): Skin comes in cotnact, DC migrates, T cells beocme specific to **the** hapten compound. Reactivation will cause Th1 cells to induce local infammatory response. **Tuberculosis** (**Mantoux test**): Injection of **PDD** and checking after 48 hours to test for hypersensitivty response to tb antigen due to stimulation of gamma interferons by T cells. **Tuberculosis**: formation of granulomas is a type of delayed hypersensitivty where Th1 cells release IFN as a means to activate macrophages but it cannot digest TB-- hence granulomas form to try and contain disease. **Celiac disease**: allergy to gluten is due to allergic reaction to gliadin, occurs in Europe. Patients are **DQ2** or **DQ8** positive (**HLA subtype for MHC II)**. **Tissue transglutaminase (tTg)** usually digests glutamine into glutamic acid (highly negative and has high affinity to DQ MHC II 2 or 8) on gliadin, which has a negative charge and binds to **HLADQ2** or **HLADQ8**, eliciting **TCR** immune respoinse via **CD4**. Causes **Villous atrophy** which is swollen vili and inability to absorb things in the gut.
› To understand and explain the mechanism(s) of antibody mediated autoimmune disease	Antibody mediated autoimmune diseases are defined as type **II hypersnesitivty**. It occurs when our antibodies binds to self antigen and cause damage, this is a form of binding to **cell-associated epitopes**. This causes injury due to activation of effector mechanisms such as the complement cascade, or causes antibodies to bind to receptors or proteins as a result of over activation or inhibition of normal function. This is seen in **graves disease** as well as **myasthenia gravis.**

› To understand and explain the mechanism(s) of cell-mediated autoimmune disease	Cell-mediated autoimmune disease are defined as type IV hypersensitivty. This occurs when **naive T cells become activated based on a self antigen** and begins to differentiate into Th which contributes to antibody secretion towards the same self atnigen. Examples of this would be **IDDM** and **Multiple sclerosis**.
› To describe the immunological basis of diabetes mellitus, Graves disease, Myasthenia gravis, SLE and Multiple sclerosis	**Graves disease:** Occurs in the thyroid. An example of **Type II** hypersensitivty. In normal functions, the pituatiary gland secretes **TSH** which acts on the thyroid to induce thyroid hormone release, where the hromones feed back to the pitutary for negative feeedback. In graves disease, autoimmune B cells will produce antibodies to TSH receptor binding to thyroid gland, causing over-production off thyroid hormones. Downstream, this will cause the **shut down of TSH** production altogether, and cause **excessive thyroid hormone production**. This will cause **hyperrthyroidism**. **Myasthenia gravis:** Occurs at the neuromuscular junction. An example of **Type II h**ypersensitivty. In a normal neuromuscular junction, acetylcholine vesicles are released into the synapse to deposit acetylcholine for muscle contraction. This disease causes **antibodies** to be bound to **actylcholine receptors** to cause **internatilization** and **destruction** of the acetylcholine **receptors** which causes **loss of muslce contraction**. Furthermore, binding of antibodies will attract compelemnt to form **MAC** complex and damage neruons. **SLE- Systemic lupus erythermatosus:** Found systemically. An example of **Type III** hypersensitivty. Explicit triggering event unknown, buit induced by **hyper-reactive B cells and T cells** which produuces antibodies against our own nuclei and DNA which causes **complement activation and deposition**. Presnece of Anti-DNA antibodty deposition in kdiney, characterized by rash on face-- triggered by sun exposure to release nucleating cells which antibodies can respond to. **Multiple Sclerosis:** Found in the brain. An example of **Type IV** hypersensitivty. Polygenic degerenative disorder of the CNS, trigger unknown, but autoimmune T cells such as Th1, Th17, associated with eliciting damage and inflammation, activated by **microglial cells** found in the brain as antigen presentation. Destroys **myelin sheath** found on axons degrading functioanlity of neurons. Further characterized by activation of B cells and complement. Damage of brain is significant to a point where inidivudal cannot repair the system. Individuals with **HLA-DR15 and HLA-DQ6** as assoicated with this disease. **Additional- IDDM, Type I dependent diabetes mellitus:** Found in the pancreas (beta cells). An example of **Type IV** hypersensitivity. Characterized by **CD4 and CD8** activation towards pancreatic beta cells which produce **insulin, destroying these cells.** Occurs more frequently in indiviudals who have **HLA-DR3-DQ2 and DR4-DQ8**. Characterized by macrophage accumulation around beta cells, retention of **alpha cells**, and infalmation in pancreas destroying Beta cells. *Recalling Th1 cell ativation causes downstream release of chemokines, IFN-y, TNF-a and IL-3 to mediate damage. Th1 release of **chemokines**: recruit macrophages to site of antigen deposition**, IFN-y** induces expression of vascular adhesion, activates macrophages and release of inflammatory medators. **TNF-a** causes local tissue destruction and expression of adhesion molecules in blood vessels, **IL-3** stimulates monocyte production by bone marrow stem cells.
› To describe how autoreactive-antibodies may be generated	Generation of autoreactive antobides are as follows: **DC** comes in contact with self antigen after **trauma** or **microbial infection** and presents it. DC activates a naive **T cell** on a self antigen basis, proviidng co-stimulation and **activation**. **Autoreactive** B cells also pick up the self atnigen from periphery, comes in contact with a T cells specific for the same peptide intiating B cell differentiation, releasing self antigen specific antibody, where the antibodies can bind to release of self peptides causing more self injury and **tissue damage**. Although we all have presenece of self reactive TCR and BCR as a result of clonal selection and retention of semi-self reactive cells, these don't always cause autoimmuntiy as these cells could be anergic -- high threshold, or surrpessed by Treg, or found in areas that will not be exposed to antigens which will trigger autoimmunity unless trauma occurs. As an example: **sympathetic opthlamia** is when trauma in the eye activvates self-reactive antigens in **prievliged sites**.