5. Specifications for an educational scenario on the topic "Workings and malfunctions of human Immunological memory"

5.1. Introduction to the module

This topic sheds light onto the concepts of long-lasting immunological memory and protective immunity, to simplify and improve the understanding of a challenging subject such as Immunology. Educators and students of ages 12 – 15 years old (preferably 15-years of age), are therefore given the opportunity to expand their knowledge by learning about important concepts in Immunology, such as the innate and adaptive arms of the human immune system and the cellular components involved in the establishment of immune memory and the interactions that bring about protective immunity and preventing re-infections. An insight is also given on how immune memory is independent of the frequency or persistence of re-infection, being a long-lasting feature involving both specialised cells of the adaptive and innate immune systems, but also depending on all the rest of the cells of the human body.

Using differentiated instructions to teach immunological concepts related to immunity against infections to a diverse group of learners, of various ages, provides a comprehensive learning module designed to expose high school students to immunological concepts related to the immune memory mechanisms. Such mechanisms are in place to minimise and preventing the spreading of disease and cause of epidemics and possible pandemics. The present learning scenario uses active hands- and minds-on teaching strategies, where students are also introduced to the consequences following malfunction of immune memory mechanisms.

This module includes and proposes the following:

Activity 1: Flipped-classroom activity introducing primary and secondary innate and adaptive immune memory.

Activity 2: In-class short presentation of collaborative work on a selected topic involving immune memory.

Activity 3: Building concept maps of the events leading to established innate and adaptive immune memory.

5.2. Expected student prior knowledge

Students should have a basic Cell Biology knowledge of the characteristics and the Variety of living organisms, including:

- ✓ knowledge and ability to describe the common features shown by eukaryotic organisms (i.e., animals, fungi and protoctists, and prokaryotic organisms such as bacteria),
- ✓ an understanding of the term pathogen and know that pathogens may include fungi, bacteria, protoctists or viruses,
- ✓ knowledge of structures within living organisms and their associated functions (i.e., the bone marrow enclosed withing the spinal cord comprises the lymphopoietic organ of the human body, lymphoid tissues such as the thymus gland and peripheral lymph nodes are organs where immune cells differentiate and develop into specialised cells) including levels of cell organisation, cell structure, biological molecules (including proteins, enzymes, DNA, RNA),
- ✓ an understanding of the different ways of transport of substances in and out of living cells, with emphasis on receptor-mediated transport processes.
- ✓ an understanding of cell membrane features such as the presence of surface bound receptors that can be associated with cell-to-cell interactions, or receptor mediated antigen binding and presentation, (i.e., T-cell and B-cell receptors, the Major-Histocompatibility-Complex, MHC, found on all cells of the body an associated with the presentation of internal and external antigens) etc.

5.3. Expected outcomes

Learns will have the opportunity to acquire new knowledge and enhance their understanding, about:

- ✓ The two arms of the immune system: the innate immune responses are non-specific and general against groups of pathogens, whereas the adaptive immune responses are highly specific against given structural motifs of a given pathogen,
- ✓ The cellular and molecular components of each arm of the immune system: this includes the cells and molecules involved in innate and adaptive responses,
- ✓ The interactions between the immune cells and molecules: chemical and molecular interactions including, signalling, activation, proliferation, differentiation processes, to trigger immune memory mechanisms and protection against re-infection,
- ✓ The problems arising from malfunctions in immune memory: such issues may lead to lack of protection and in some case the trigger and initiation of autoimmune disease, whereby the immune system turns against its own cells and molecules.

Learners will also acquire the use of transferable skills such as critical thinking, problem solving, analysis, reasoning, interpretation, adaptive learning, creativity, continuous learning, self-direction, responsibility, perseverance, self-regulation (metacognition, forethought, and reflection), integrity, self-monitoring, self-evaluation, self-reinforcement, and apply all these qualities to their everyday life within their community.

5.4. Relation to other topics

This module could complement the teaching of the existing general curriculum in biology that focuses on the immune system. The activities included are designed to give students the opportunity to explore, learn, and peer teach concepts related to more specialised functions of the immune leading to immunological memory to past infections. The specific assignments are geared toward a general biology course, but the strategies are applicable for higher-level biology classes (A-level, undergraduate classes) if the content is scaled up appropriately. The order in which these activities should be applied follows a scaffolding approach where students uncover new knowledge at each activity level and then use it to bridge their understanding to new learning.

5.5. Pedagogical methods utilised in the teaching of this module

The objective linked to this module is to help students build on prior learning and develop further skills and attitudes. Meanwhile, the current knowledge of their educators is also enhanced, enabling them to present the given module in a way that is relevant to their students' needs.

A range of different pedagogical methods are implemented through all different activities, catering for a broad range of different learners. The current learning module is based on the pedagogical approach of inquiry-based learning, where students are encouraged to ask questions and complete research while learning various concepts of basic immunology associated with immunological memory. In this way, individual learners acquire the skills necessary to develop their own understanding, as well as question themselves and group members in a constructive way.

The initial flip-class room activity investigates primary versus secondary innate and adaptive immunity, whereby students are asked to watch a series of related online videos and are given a set of pre-lesson questions that they are to complete prior to the actual lesson. This provides an excellent tool that improves tremendously the in-class time with their educator, making the delivery of a lesson more productive. The additional workload imposed by the pre-class activities is worthwhile, as it helps students in their understanding through reinforcement of pre-class material in class, allowing them to adapt an incremental work ethic as opposed to memorising and cramming of information. Additionally, the student responses are used by the educator to provide whole-class feedback and to better focus the in-class plan on the collective needs of the students, transforming the classroom from educator-dominated to student-centered, allowing for bidirectional constructive feedback, creating thus an information loop where in-class and outside-of-class work is highly connected allowing for exploration, collaboration, and interaction among students, while the educator is consistently given feedback of the level of their understanding.

The in-class short collaborative presentation activity follows the “peer instruction” active learning strategy where students are given a narrow list of topics and asked to sign up for a topic of their choice, prepare and present this to their class or in small groups. This approach is particularly useful as this will involve the breaking down of the presented topic into smaller parts, and each student groups will be presenting information about a different part. This approach helps the students to associate cells and molecules and their interactive processes, with different people, therefore acting as an aide memoire for their benefit. This approach also encourages interaction and trust-building between students, being especially important at a time where a portion of learning may take place online while students will be researching on their selected topics.

The final learning activity of building a concept map of the events leading to established innate and adaptive immune memory comes to sum up the previous activities, providing students with a framework within which to organize their newly acquired knowledge, without becoming overwhelmed from all the information involved. This learning technique is particularly well-suited for teaching challenging topic such as immunology-based topics, as students must master an impressive number of new words and concepts in a short period of time. Assigning concept maps after studying a chapter that is particularly jargon-heavy is quite successful and works well in-class group and individual activities, as well as a take home study tool. Assigning students to work on creating concept maps in groups of three or four, also decreases the grading burden, allowing the educator to give more thoughtful feedback to their students, but it also allows students the benefits of discussing with each other what belongs where, and why, and how processes can be interlinked. Thus, in the process of constructing the map, the students are highly engaged in peer-instruction and metacognition learning.

5.6. Background science

5.6.1. What is immunological memory?

Immunological memory is an important evolutionary feature that improves host survival upon re-infection with pathogens. This means that immune cells of the human body can retain memory of past infectious agents and their associated antigens and responds fast and efficiently to any reencounters.

An antigen is basically a molecular structure that can stimulate an immune response. It is important to note that not all molecular structures are antigens, as many will not activate the immune system against them. Immune memory provides a characteristic acknowledged within both the innate and adaptive cellular barriers of the human immune system. Although the mechanisms and properties through which innate and adaptive immune memory induction occur are distinct, their combined effects improve host defence towards pathogenic intruders. Initially, immunological memory was tightly connected to the actions of the cells of the adaptive arm of the immune system, which includes the B and T cell populations. However, since 2013, innate immune memory, otherwise termed "trained immunity", has been explored during vaccine adjuvant development (Vasiliakos P. J., 2013, Basto P. A., et al., 2014, Töpfer E. et al., 2015) and has been acknowledged as an important supportive component of the protection provided by the cellular adaptive barrier.

This topic reviews the main effector components of the human immune system and provides a clear insight to how the two arms of the immune system collaborate to bring about immunological memory to all past but also newly emerging invaders.

5.6.2. The cell players of Immune memory.

The human immune system is comprised by a distinct population of cells along with a vast number of molecular components that all work together to orchestrate an effective protection against any foreign entity that enters the human body. To ensure understanding of all the complicated interactions and mechanisms that take place during an immune response to bring about immune memory, one needs to become familiar with the very basics of immunology.

Starting from fundamental knowledge, all the cells of the human immune system are generated in the bone marrow from progenitor stem cells (Figure 1), some of which develop and differentiate locally, whereas others that require unique environmental conditions migrate to other tissue of the human body to do so. A helpful example is that of B and T lymphocytes, with the latter migrating to the thymus

gland to develop and differentiate into mature, specialized T cell populations that can respond to non-self-antigens. There are two main lineages from which immune cells are derived, these being the myeloid and lymphoid progenitors from which innate and adaptive immune cells, respectively, arise (Figure 1). The cells of the innate immune arm are derived from myeloid progenitor cells, the most important being:

- mast cells, mainly associated with responses to allergens
- myeloblasts, including:
    - monocytes that give rise to macrophages and dendritic cells, these being the major antigen presenting cells of the immune system, and mediators of the adaptive immune arm,
    - eosinophils and basophils, mainly associated with parasitic infections,
    - neutrophils, important phagocytic cells involved in the elimination of bacteria and fungi.

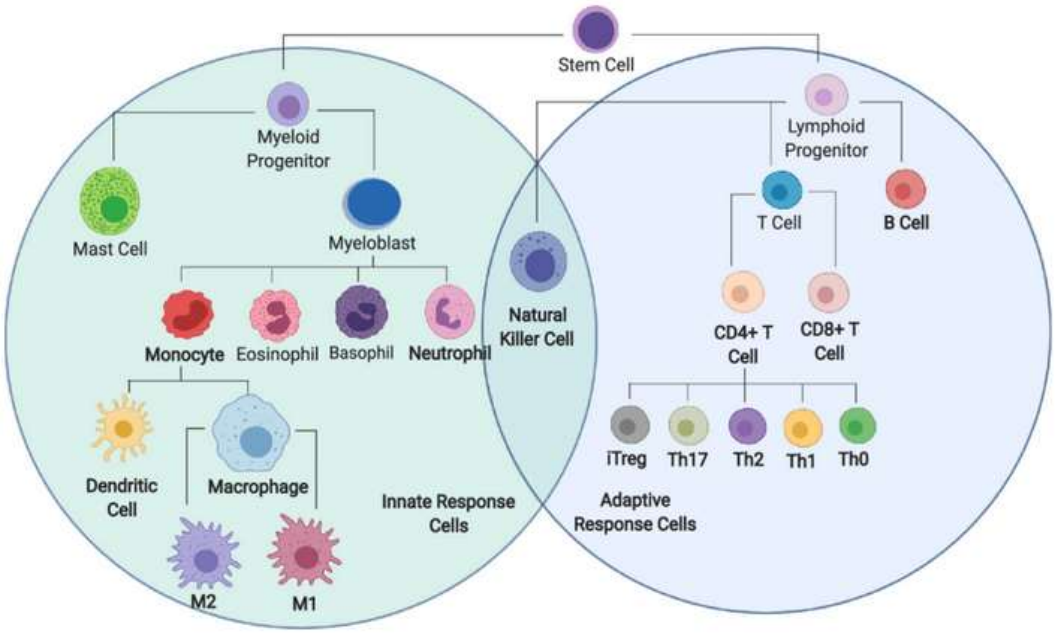


Figure 1: Representation of cells of the immune system.
Immune cells are derived from hematopoietic stem cells in the bone marrow and differentiate into lymphoid and myeloid progenitors that further branch out to differentiate into more specific cell types associated with adaptive and innate immunity. (Figure taken from Torang A., et al., 2019)

The cells of the adaptive immune arm include the T and B lymphocytes, both assigned to pathogen-specific responses and initially linked to long term immunological memory. To our current knowledge, both innate and adaptive immune cells comprise important mediator of immune memory and this topic examines both categories, to explain how memory is implemented and how this can sometimes malfunction to results in re-infection and possible development of disease.

Each immune cell serves a given purpose, this being either auxiliary or specific. However, immune memory is associated with specificity to a given pathogen and is directed against both external and internal molecular pathogen-associated structures, i.e., external surface molecules and/or internal genetic material. Lymphocytic cells of the immune adaptive arm have evolved to directly identify specific pathogen-associated molecular motifs via specialised receptor molecules expressed on their cellular membrane. Activation of B lymphocytes via their B-cell receptor (BCR) leads to the secretion of pathogen-specific antibodies. In a similar way, activation of T lymphocytes via their T-cell receptor (TCR) leads to direct cytotoxic elimination of pathogen and/or the initiation of orchestrated T-cell-mediated responses against it, involving both adaptive and innate arms of the immune system (Figure

2). The action of both B lymphocytes and innate cells is directed against specific external molecular pathogenic motifs, whereas the T lymphocyte-associated immunity is mostly directed towards internal molecular pathogenic motifs (Figure 3), that are exposed following pathogen internatisation, processing and presentation by specialised antigen-presenting cells, such as macrophages, dendritic cells, and organ/tissue specific epithelial and endothelial cells. It is important to note that phagocytic cells are equipped with specialised receptors, known as Toll-like-receptors (TLRs) that are expressed both on their cell membrane but also within their cell cytoplasm and involved in the identification and binding to conserved (unchanged) pathogen-associated motifs. This feature enables phagocytic cells to "remember" conserved molecular patterns expressed by a variety of pathogens, an ability that has been acquired through evolution and continuous exposure to pathogens.

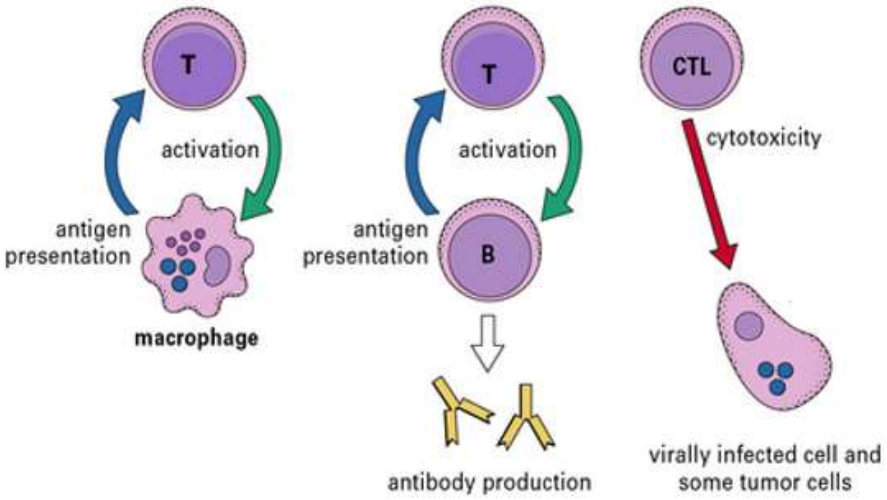


Figure 2: T lymphocyte orchestrated immune response against pathogen.
T lymphocytes can be specifically activated, via their pathogen specific TCR, by a specialised antigen presenting cell (APCs) such as macrophages and dendritic cells, presenting them with the exact specific pathogen antigenic motif, highly compatible to their TCR. An activated T lymphocyte will in turn secrete specific cytokines enhancing the action of antigen presenting cells, as well as the activation of pathogen-specific B lymphocytes and the secretion of pathogen-specific antibodies. Additionally, pathogen-specific cytotoxic T lymphocytes can directly identify and eliminate pathogen via their toxic secretions.

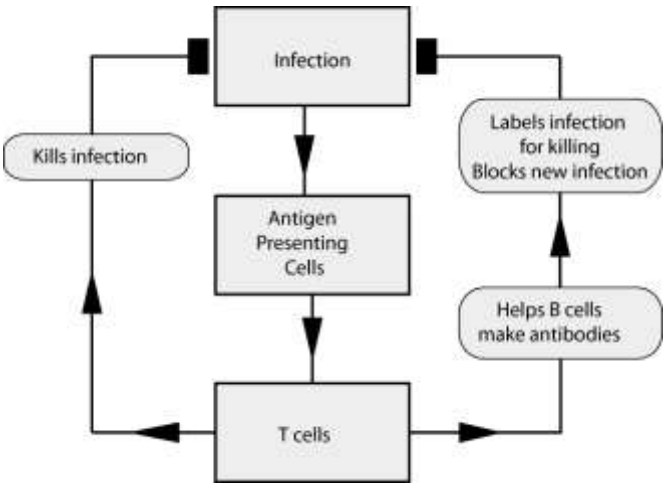


Figure 3: **The adaptive immune response to infection**

Infection, detected by APCs, triggers specific T lymphocytes that co-ordinate killing and antibody production, which stop the infection. (Diagram taken from Nicholson B., 2016)

5.6.3. Activation of immune memory following re-exposure to pathogen.

As already mentioned, immune memory is the ability of the immune system to quickly and specifically recognise an antigen that the body has previously encountered and initiate an analogous immune response against it. Generally, memory responses are rapid secondary, and tertiary subsequent responses to this same antigen, or very similar forms of it. To understand immune memory, one would first need to understand what a primary immune response is. A primary immune response is regarded as the outcome following the first encounter of an organism with a pathogen, and it primarily involves the initial non-specific actions of the chemical and cellular innate barriers of the body's immune system, followed by more efficient and specific immune responses of the adaptive system.

Non-specific innate memory:

The complement system is composed of about 20 proteins that circulate in the blood and tissue fluids and provides an essential feature that complements the action of innate immune responses. Most of its proteins are normally inactive, but in response to recognition of molecular features expressed on microorganisms, these proteins become sequentially activated in an enzyme cascade where the activation of one protein enzymatically cleaves and activates the next protein in the cascade, resulting in the targeted killing of bacteria. Additionally, complement components will flag and give away pathogens, thus enhancing the phagocytic action of macrophages and neutrophils that patrol sites of usual pathogen entry. These phagocytes engulf and digest flagged pathogen, that they can also identify via TLRs expressed on their cell surface. The combined actions of the complement and the innate immune cells is almost immediate and only requires up to twelve hours to ensure control of pathogen invasion.

Studies show that innate memory is achieved via TLR-pattern-recognition, and molecular mechanisms underlying its establishment show strong involvement of transcriptional and epigenetic reprogramming of innate cells, including histone acetylation, methylation, and modulation of miRNAs, which can be shaped by environmentally induced metabolic changes (Saeed S., et al., 2014). The fact that most cells of the human body express TLRs on their surface indicates that innate memory is not a privilege attributed only to immune cells. In fact, epithelial stem cells have been also shown to retain memory of previous inflammatory challenges by displaying an enhanced wound healing capacity upon skin damage (Naik S., et al., 2017) providing scientists with important proof that innate memory is not restricted to immune cells, and that most components of the body can remember past "events of invasion".

Highly Specific adaptive memory:

In situations whereby the innate arm of the immune system is unable to establish control following the entry of a pathogen, an inflammatory response takes place during which phagocytes as well as pathogen infected cells secrete a variety of soluble chemical factors, known as chemokines and cytokines, that are respectively associated with the recruitment and activation of adaptive memory cells (T and B lymphocytes). One comes to question from where these pathogen-specific memory cells originated. At this point it is important to note that all sites of the human body are drained by the lymphatic system, that allows for antigen presenting cells (APCs) to travel to peripheral lymph nodes where they get to present encountered antigens to pathogen-specific T and B lymphocytes. Additionally, antigen can also enter peripheral lymph nodes, where it is captured by local APCs and presented to adaptive cells within the node. Figure 4 provides a diagrammatic summary of the stages following antigen entry and the launching of a specific immune response against it. A typical lymph node is divided into areas of naïve T and B cells. T cells are initially presented with antigen by incoming or local APCs, these being of macrophage or dendritic cell origin. These T lymphocytes possess TCRs that firmly binds to the antigen presented to them in context with the Major Histocompatibility Complex-II (MHC) molecule, expressed on the surface of any APC. Upon interactive binding, a T cell becomes successfully activated and in turn enables the activation of a naive antigen-specific B cell, that is located at adjacent germinal centers within the lymph node's architectural structure. Note that cells need to directly interact with each other, at the barriers of the different regions of the lymph node, and their activation is also facilitated by the secretion of various essential cytokines.

In continuation, an activated B cell will undergo somatic hyper-mutation and re-structuring of their BCR (also known as surface bound antibody receptor) to ensure maximum compatibility (affinity) to the antigen that was presented to them, and will differentiate into a:

- short-lived plasma cells, released into circulation and maintained for a several weeks, producing and secreting antigen-specific antibodies,
- long-lived plasma cells, deposited in the bone marrow throughout life and recruited during memory responses, and
- memory B cells, acting as surveillance cells that circulate throughout the body in a quiescent state until specific antigen is re-encountered and triggers a potent secondary immune response.

These memory B cells respond to antigen much faster (within less than 12h), requiring lower amounts of antigen, and can even be induced in its absence by soluble cytokines secreted by other cells at a site of inflammation, in part because their BCR is already localized on rafts on their cell membrane. Subsequently, just like naïve B cells (these being cells that have not encountered their antigen yet), memory B cells can ingest antigen and express it onto their cell surface, presenting this to helper T cells, receiving thus activation and the ability to undergo expansion and differentiation into antibody producing plasma cells.

Just like memory B cells, T cells also can retain specific memory to incoming pathogens. These memory T cells can thus cut short the 'stealth phase' of pathogen replication that occurs before the initiation of antiviral responses, and mediate extremely potent effector responses, providing thus strong protection upon re-infection, even in the absence of neutralizing antibody.

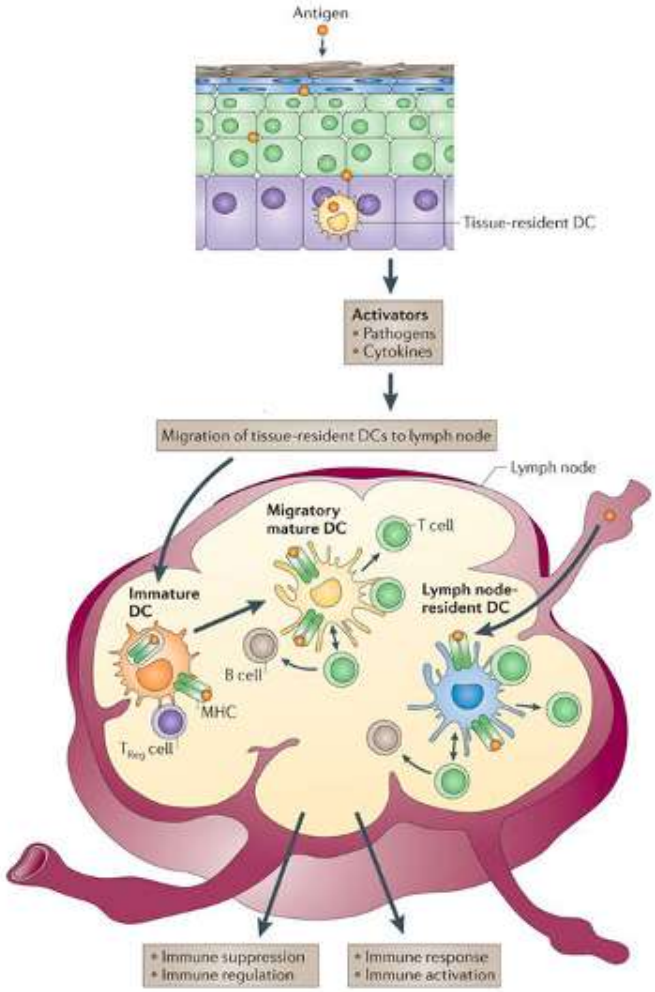


Figure 4: Launching an immune response against an incoming pathogen.

Antigens can enter lymph nodes via the lymphatics, where the antigen is captured by lymph node-resident DCs and macrophages or via tissue-resident DCs and macrophages that in turn migrate to local lymph nodes. DCs and macrophages display antigens in the context of major histocompatibility (MHC) class I and MHC class II molecules or in the context of non-classical CD1 molecules, which allow the selection of rare antigen-specific T lymphocytes (NK T cells). Activated T cells drive DCs towards their terminal maturation, which induces further expansion and differentiation of T lymphocytes into effector T cells.

(Figure from Palucka K., et al., 2012)

5.6.4. Immune Memory is long-lasting.

Protective immunity is defined as the resistance to re-infection, following natural exposure to an infectious agent, or artificial exposure via vaccination. It is therefore a consequence of both innate and adaptive immunity, operating through the epigenetic changes occurring in most cells of the human body and the clonal selection of T and B lymphocytes, respectively. Protective immunity does not depend only on preformed antibody and armed effector T cells. It also depends on the establishment of a population of T and B lymphocytes that mediate long-lived immunological memory, and the given capacity of these cells to respond rapidly to re-exposure to the same antigen or newly altered antigen, that can be also transferred to naive recipients.

Memory T and B lymphocytes can be distinguished by changes in specialised receptor genes, these being their TCR and BCR respectively, due of somatic hyper-mutation, and secondary and subsequent immune responses are characterized by cells expressing surface receptors with increasing affinity for the given antigen. This is termed affinity maturation and summarised in Figure 5. Additionally, memory B lymphocytes will also give rise to antibodies with a similar increasing affinity towards the specific antigen during secondary and subsequent responses (Figure 6). It is important to note that protective immunity does not depend on, nor maintains itself through the numerous re-exposures or persistence of the same pathogen. This is most clear in examples of individuals who were themselves previously exposed to a given infectious agent and are therefore immune. Their memory is not dependent on repeated exposure to infection because of contacts with other infected individuals.

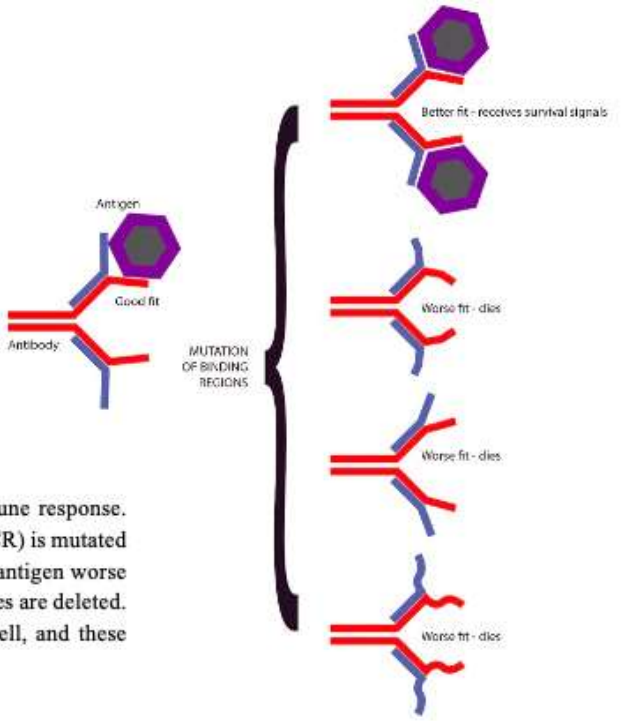


Figure 5: Affinity maturation.

Antibodies that fit the best are selected early in the immune response. The antibody receptor otherwise termed B-cell receptor (BCR) is mutated within daughter B-cells. Many of these mutations bind the antigen worse than the parent antibody, and cells producing these antibodies are deleted. Some antibodies bind the antigen better than the parent cell, and these cells are positively selected.

This was established by observations made on remote island populations, where a virus such as measles would cause an epidemic, infecting all people living on the island at that time, after which the virus seemed to have disappeared for many years. On re-introduction from outside the island, the virus would not affect the original population but causes disease in those people born since the first epidemic that have not been previously exposed to measles. Vaccination provides a means of ensuring that those circulating memory cells are updated to the new "versions" of a pathogen, while been given a head start to undergo somatic hyper-mutation to maintain their alertness to future pathogen encounters.

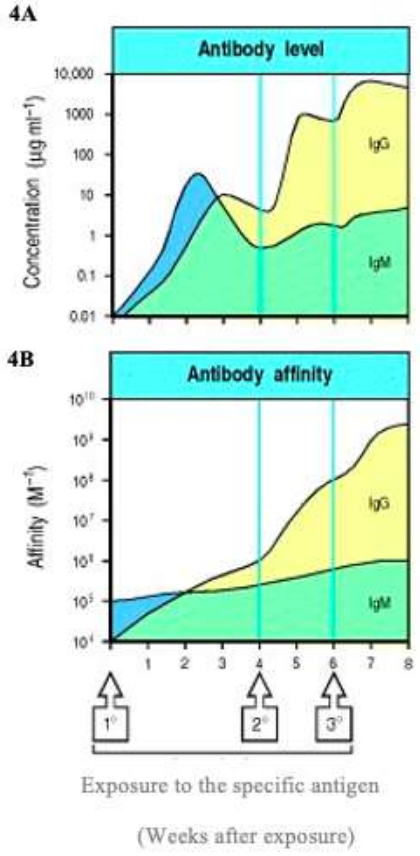


Figure 6: Both antibody affinity and the amount of antibody generated increase with subsequent exposure to the same pathogen-related antigen.

Graph 4A shows the increase in the concentration of antibody with increasing time after primary, followed by secondary and tertiary, exposure (immunisation or natural re-exposure) to the same pathogen-related antigen; Graph 4B shows the increase in the affinity (strength with which an antibody binds it compatible antigen) of the antibodies produced following each exposure. This increase in affinity is seen largely in IgG antibody (as well as in IgA and IgE, which are not shown) coming from mature B cells that have undergone isotype switching (have changed antibody class from IgD which is the initial membrane bound antibody seen on naïve B cells, to either IgG, IgM, IgA or IgE) and somatic hyper-mutation (changes in the gene locus associated with the fragment of antigen binding region of an antibody) to yield higher-affinity antibodies. Although some affinity maturation occurs in the primary antibody response, most arises in later responses to repeated antigen exposure.

(Figure taken from, Janeway C. A. Jr., Travers P., Walport M., et al., 2001)

5.6.5. Malfunctions to Immunological memory.

When an antigen is encountered more than once, the adaptive immune response to each subsequent encounter is faster and more effective. This is a crucial feature of protective immunity, also known as immunological memory, and it is specific towards a particular antigen, as well as long-lived. As previously mentioned in subsection 6.4, immunological memory involves both the adaptive and innate arms of the human immune system, but also involves the trained memory of most cells of the human body.

For an immune system to be effective it must be able to interpret changes in the environment around it and respond appropriately, by solving various issues arising (Nicholson L. B., 2016). For instance, our whole existence depends on the ability of our immune system to be able to discriminate against self and non-self-antigens. The inability to do so efficiently may lead to all sorts of issues like autoimmunity and the development of cancer. Flexibility is another characteristic of an effective immune system, allowing adaptation to strange environmental changes to effectively tackle issues such as infections and cancer that may arise at any point during cell renewal processes and can lead to the development of random unpredictable mutations that will transform a normal cell into a cancer cell. Infectious agents replicate much more rapidly than their hosts and can change their appearance to allow evasion of recognition mechanisms. An effective immune system must be alert and able to always cope with such unpredictability.

One other important feature of the human immune system is its ability to manage infections, and this is achieved through the development of protective barriers. For a pathogen to gain entry it must first breach the innate anatomical and chemical barriers that cover and protect all entries to the human body. When pathogens succeed in penetrating these defences, seeking to cause harm or co-existence with the host organism, they pose many threats, from quiet co-existence to full-blown cell destruction and death. However, the most significant feature of an immune response is the ability to retain memory of previous infections. This both protects from re-infection and limits the spread of infection within a community.

Immune memory can be long-lasting and decays so slowly, with a half-life of approximately 3000 years, which goes well beyond life-long protection.

Rarely, but frequently, individuals are born without an effective immune system. This arises when uncommon mutations prevent immune cells from maturing, and in such cases, individuals have a very limited life expectancy. Less dangerous, but still severe, are mutations that cripple a particular arm of the immune system. There are also situations that an immune system is partly defective, for instance, individuals whose complement proteins do not operate suffer from repeated infections, or those with deficiencies in the action of their natural killer cells are highly susceptible to herpes-virus infections, those who have macrophages that cannot digest bacteria that they encounter develop recurrent abscesses and so on. The importance of efficient innate immune responses is to slow infections down, giving the rest of the immune system time to catch up, readapt and respond appropriately. Such malfunctions of innate immune response will cause "auto-inflammatory" diseases, often manifesting as spontaneous spells of illness and fever.

All above mentioned situations may lead to a defective trained-innate memory. Most common though are defects that arise in B lymphocytes, the cells solely responsible for the production of antibodies. These conditions are often X-linked, meaning that they are encoded on the female X chromosome and therefore are more common in men rather than women. There are also situations that a "stronger-responding" immune memory may lead to complications such as autoimmunity. This is observed in situations involving infections that contain cross-reactive antigens, i.e., pathogen-related antigens that mimic self-antigens, and where tissue damage is caused as immune memory is built against such cross-reactive antigens, therefore posing a threat against the organism's own organs and tissues.

5.7. Educators' implementation guide

The three activities within this learning module have been designed to provide educators and their students with the opportunity to explore, research, learn, reflect and peer teach concepts related to the general knowledge regarding innate and adaptive immune responses, the cellular and chemical components comprising each arm of immune system and how these components come to interact as to bring about immune memory and resistance to re-infection. Students are allowed to explore and understand possible undesirable outcomes of malfunctions in immune memory leading to repeated re-infections and likely outcomes of autoimmunity. The proposed learning activities are geared toward the topic of immunity, which comprises part of a general biology class for students between the age range of 12-15 year, but these proposed strategies are applicable for higher A-level, and undergraduate level biology courses if the content is scaled up. The order in which these activities should be applied follows a scaffolding approach where students acquire new knowledge at each level via performing their own research to present their peers with new concepts, and then use this to bridge their understanding to new learning.
This section includes all three proposed learning activities and descriptions of how these could be implemented as an extension to the general biology topics taught at the different stages of lower secondary education. These include:

- a Flipped-classroom activity introducing primary and secondary innate and adaptive immune memory,
- an in-class short presentation of collaborative work on a selected topic involving immune memory,
- the building of concept maps of the events leading to established innate and adaptive immune memory.

All three activities will ensure that students achieve a basic understanding of the different components of the immune system that are associate with immune memory and how these interact with each other to bring about fast and effective memory responses following re-encounter with the same or mutated pathogens.

5.7.1. Flipped-classroom activity: introducing primary and secondary innate and adaptive immune memory.

Learning and understanding immunology require the engagement of educators and students with new vocabulary and some examples of challenging biological concepts. Stranford A. S. et al., (2020) have found that biology students who regularly spend time before class dealing with new terminology and challenging concepts come to class more prepared to ask interesting, good questions, practice their skills, and apply their self-acquired new knowledge in higher-level thinking endeavours. Students participating in well-designed, pre-class preparation activities, results in being more productive during their class experiences when presented the given topic by their educator. Furthermore, the Flipped-classroom approach aids students in their understanding of challenging concepts, through the reinforcement of pre-class material in class, and helps to entrain an incremental work ethic as opposed to the usual cramming observed amongst young learners.

In this first learning activity, students are provided with a series of online video links to watch prior their actual class introduction, related to the concepts of immune memory. This constitutes their preparation for answering questions shortly before class, where they are requested to submit their answers to these pre-class questions online, 24 hours prior to the class meeting (Stranford et al., 2020). The student responses are used by the educator to provide whole-class feedback and to better focus the in-class plan on the collective needs of their students, transforming their classroom from educator-dominated to student-centred (Simkins S. M. M. et al., 2010). In this way, bidirectional feedback occurs to suitably address the material that is delivered, generating an ideal feedback loop where in-class and outside-of-class work is highly connected, and where the educator is consistently aware of the level of student engagement and understanding. The learning activity assignments can vary, from questions that probe basic vocabulary or the application of concepts, to real-world problems or queries about the assigned online videos. It is ideal to include questions that highlight common confusion and misconception so for the educator to be able to diffuse any issues during the actual delivery of the topic. Examples of such are provided in the section that follows.

Activity 1: Flipped-classroom activity introducing primary and secondary innate and adaptive immune memory.	
Learning objectives	Students will: ➢ Learn about the two arms of an effective immune system, innate and adaptive, ➢ learn about the cellular and molecular components of each arm, ➢ be able to identify the important cellular and molecular components in each, ➢ be able to identify and recall the function of each of these components and how they come to interact to bring about immune memory and prevent reinfection, ➢ be able to explain in simple terms how immune memory arises following primary exposure to a pathogen and how this takes over following future exposure to the same or similar forms of pathogen.
Time requirements	➢ Students are provided with three online video links to watch, a day prior to their introduction to this activity. Each video is approximately 9-minutes long, requiring from the students approximately 30-minutes time to watch. ➢ After watching the related series of online videos, students are requested to answer a series of targeted questions and submit their answers online prior to their next day's lesson. This should take no longer than 15 minutes. ➢ The educator needs to prepare an online questioner for their students, following a selection of the suggested questions found within this activity.

	These could be in the form of multiple choice or structured questions or a combination of both. Students should be provided with these questions 24h prior to their classroom activity.
Description of activity sequence / Educator's Instructions	➢ The educator asks all students to watch at home a series of three online video links or listen to a podcast (**DER5**: https://www.exploratorium.edu/audio/drama-immune-system). All these explain the concept of innate and adaptive immunity, how the arms of innate and adaptive immunity work together to protect against infection and how immune memory is established to prevent re-infection. ➢ The educator prepares a series of questions that will allow them to assess their students' level of outside-classroom learning and understanding on the given topic. ➢ The educator constructs their lesson plan based on the student needs arising from the outcome of their assessment. **Examples of pre-class questions that can be used for this activity**: For 1st online video: Emergency immune response 1. (True/False) Innate immunity involves soluble products and is a part of humoral (antibody-associated) immunity, while adaptive immunity involves the work of B and T cells, or cell-mediated immunity. Please provide a brief rationale for your choice. 2. (True/False) Adaptive immunity is engaged during both a primary and a secondary immune response. Please provide a brief rationale of your choice. 3. (True/False) All antibodies produced during an immune response can stop a virus from entering the bodies epithelial cells. Please provide a brief rationale of your choice. 4. (Optional) Do you have any questions from this part of the viewing preparation for class? Please be as specific as possible. For 2nd online video: Do cells remember? 1. (True/False) Immune memory is only linked to the adaptive immune system, which includes T and B cells. Please provide a brief rationale of your choice. * For this question students will not be aware on the memory mechanisms of the innate immune system. This can be introduced by the educator as part of their lesson planning. 2. (True/False) Adaptive immune memory requires the combined action of both memory T and B cells. Please provide a brief rationale of your choice. 3. (True/False) Immune memory can be only achieved through the concept of vaccination, using either fractions of a virus or an attenuated (weak form) of this virus. Please provide a brief rationale of your choice. 4. (Optional) Do you have any questions from this part of the viewing preparation for class? Please be as specific as possible. For 3rd online video: Why do immune systems forget? 8. (True/False) The immune system of elderly people forgets of past infections. Please provide a brief rationale of your choice. 9. (True/False) Immune memory is short lived and needs continuous boosting. Please provide a brief rationale of your choice. 10. (True/False) Viruses can escape immune memory by mutating their genetic makeup. Please provide a brief rationale of your choice. 11. (Optional) Do you have any questions from this part of the viewing preparation for class? Please be as specific as possible.

Materials required	Electronic device (iPad, personal laptop, other smart device) that will allow internet access.
Learning Objects (LO) / **Digital Educational Resources (DER)**	From the website of British Society of Immunology: ➢ Online Video 1: Emergency response **DER6**: https://www.youtube.com/watch?v=g_RZWDBFJjI ➢ Online Video 2: How do cell remember? **DER7**: https://www.youtube.com/watch?v=IUEWpHAbAGE ➢ Online Video 3: Why do immune systems forget? **DER8**: https://www.youtube.com/watch?v=kN0WROnxaCg ➢ Other online useful links: **LO3**: https://www.playfactile.com/ **LO4**: https://www.gingerlabs.com/ **DER9**: https://www.khanacademy.org/science/high-school-biology/hs-human-body-systems/hs-the-immune-system/a/intro-to-viruses **DER10**: https://www.exploratorium.edu/search/immunity **DER5**: https://www.exploratorium.edu/audio/drama-immune-system
Assessment/evaluation of learning outcomes	➢ Student groups are asked to answer a series of pre-class questions and provide a simple explanation of the rationale for their choice of response. ➢ Student answers are assessed by their educator prior to the introduction of the topic allowing them to assess the level of learning and understanding during this outside-classroom activity. ➢ The educator can plan their teaching of the topic, focusing more on the challenges and needs of their students.

5.7.2. In-class short presentation of collaborative work on a selected topic involving immune memory.

This learning activity, that continues from the previous Flipped-classroom activity, requires that the lesson time is divided into sections, with the educator sharing some in-class presenting time with their students. For instance, the educator might set the stage for the topic to be presented entirely by their students, who shall be in groups and given some of the material to deliver to their peers. Sometimes, the educator will need to interfere to emphasize the main points that have been made by each student group and offer a summary of conclusions. This approach is particularly useful when the subject involves presenting information in the form of a sequence of similar, but slightly different cells and molecules or events occurring during immune memory mechanisms. When student groups are responsible for different parts of the lesson the perceived "sameness" of the material is broken up, helping the students to associate cells, molecules, and biochemical events with different people, and acting as an aide memoire (Stranford A. S. et al., 2020).
The educator could introduce the overall concept of innate and adaptive immunity and then delved into a discussion of how cell members of the two arms of the immune system work together to bring about immune memory. Student groups can then take up the story and present their selected subtopics sharing their acquired knowledge with the rest of the class, referring to concepts of:

- Components of the innate immune system
- Components of the adaptive immune system
- Primary immune response against first encounter with a pathogen
- Secondary immune response following re-infection
- The time span of immune memory to an invading pathogen

Designing and delivering these mini lectures gives the students (usually much needed) additional experience and confidence that they have grasped the newly acquired knowledge, that are able to present to a group of peers. Students should be introduced to different presenting approaches to demonstrate their acquired learning towards the given topic, including preparation of a poster, use of short video, structuring of lists, diagrams, and other creative approaches, other than just PowerPoint presentations that most times are misused by students who get carried away by mechanically copying and pasting information of the internet. This will also help the educator to assess the individual and overall level of understanding of their students.

Activity 2: In-class short presentation of collaborative work on a selected topic involving immune memory.	
Learning objectives	Students will: ➢ Learn how to perform their own research on their chosen topic and prepare for it before they enter the classroom. ➢ Learn to summarise and present important facts regarding immune memory. ➢ Will be able to develop a skill set for effective presentation and communication of their acquired knowledge.
Time requirements	➢ Student groups should be given a week to prepare for their chosen presentation topics, allowing for required communication and collaboration with their peers.
Description of activity sequence / Educator's Instructions	The educator should provide their students with a list of topics to choose from and to prepare short 5–10-minute presentations (poster, lists, diagrams, video, etc.) The topics provided to students should be relevant to the previous activity, focusing on the mediators of innate and adaptive immunity and how are these collaborate and are associated with the establishment of immune memory. Examples of topic presentations could include: 1. Introducing the cells and molecules of the innate immune system 2. The cells and molecules of the adaptive immune system: how these are involved in primary immune responses. 3. Innate immunity and emergency responses 4. Primary versus secondary immune response 5. Innate versus adaptive immune response 6. Immune memory is linked to secondary response 7. The innate immune response and how this adds to the establishment of immune memory.
Materials required	Each student group is to decide on the method of delivering their presentation, therefore this part should be left open to them to choose the material, equipment required, or the approach that they would like to follow for their presentation.
Learning Objects (LO) / Digital Educational Resources (DER)	Online links that could be send to students: ➢ Fighting infection by clonal selection: **DER11:** https://youtu.be/HUSDvSknIgI ➢ Immune encounters: **DER12:** https://www.immunology.org/sites/default/files/Immune%20Encounters.pdf

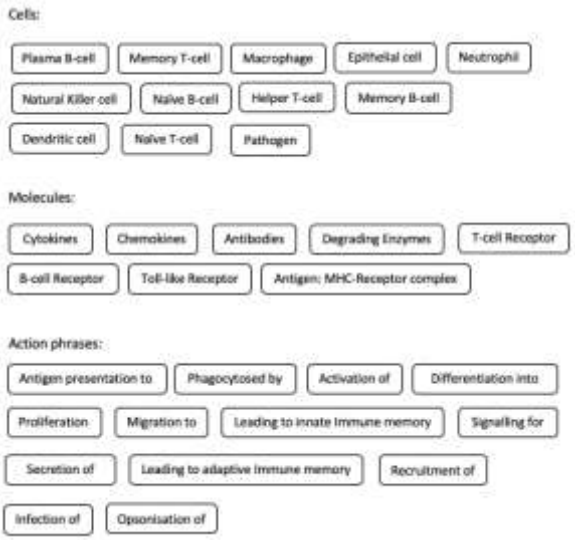
	➢ Educational illustrations: **LO5:** https://www.immunology.org/public-information/immunology-related-activities-and-resources/infectious-educational-illustrations
Assessment/evaluation of learning outcomes	➢ Student presentations are assessed by their educator prior to the lesson allowing them to assess the lever of learning and understanding during this outside-classroom preparation activity. ➢ The educator can prepare a series of questions to assess the level of understanding of their students following each group's presentation. ➢ Following assessment of the presenting material, all groups are asked to collaborate to come up with one final presentation that they are to present during a science forum organised at their local school community, including peers, teachers, parents and selected academic specialists in the fields, leading to an open discussion on the topic.

5.7.3. Building concept maps of the events leading to established innate and adaptive immune memory.

When studying any discipline for the first-time students lack cognitive tools that they could use to "manage" the new facts and ideas they encounter. Lacking a framework within which to organize their new acquired knowledge, students can become overwhelmed and feel like they are swaying in a sea of unrelated facts. The use of concept maps has always been a first-time challenge to most students, but in fact, mastering the correct use of this approach is proven to be extremely helpful in students being able to synthase and model their recently gained knowledge, to merit continued use in science related classes. A concept map typically represents each idea, for instance an organ such as the lymph node, a cell such as a lymphocyte, or a secreted molecule such as an antibody, as a shape, joined to other shapes by lines that indicate the conceptual connection between them. These lines can be labelled with phrases that are used to describe the relationship between the linked shapes. For example:

1. an epithelial cell infected with a viral pathogen
2. will secrete appropriate chemokines
3. to signal for the recruitment of neutrophils
4. and macrophages to the side of infection,
5. which would in turn phagocytose the pathogen
6. and present to antigen-specific memory T helper cells
7. that would activate antigen-specific memory B cells
8. to secrete antigen specific antibody.

This provides a single chain of events following infection with pathogen (Figure 7). Such a technique is particularly well-suited for teaching challenging concepts to students, such as immune memory, that include various cells, molecules, and difficult terminology. Students could be provided with a list of term from which they could select the most appropriate terms to generate their concept maps.

Activity 3: Building concept maps of the events leading to established innate and adaptive immune memory.	
Learning objectives	Students will: ➢ Be able to manage their newly acquired knowledge from previous activities 1 and 2 into a simple structured concept map, summarising the main points. ➢ Be able choose correct terms and action phrases from a list to construct their own concept maps of innate and adaptive immune memory responses against re-invading pathogen, following subsequent re-infection or/and vaccination. ➢ Develop collaborative and communication skills as they will have to work within groups.
Time requirements	➢ This could be a 30-minute classroom activity. Students can be provided with the list of terms to either copy or cut out and use to construct their concept maps.
Description of activity sequence / Educator's Instructions	The educator should provide their students with a list of terms and action phrases to use to construct their concept maps. For example:  1. Students are asked to colour the terms and action phrases of the innate and adaptive immune memory with a different colour. 2. Arrows connecting terms of the same arm of immune system (i.e., innate components) should be in the same colour as that initially selected. Arrows interconnecting innate with adaptive immune memory components should be drawn with a different colour. 3. Completed concept maps can be displayed withing the classroom, allowing peer review and discussion.
Materials required	➢ Printed lists of terms and action phrases ➢ Scissors ➢ Colour pencils/pens ➢ A3 Cartons ➢ Glue / sticky tape
Learning Objects (LO) / **Digital Educational Resources (DER)**	➢ Fighting infection by clonal selection: **DER11**: https://youtu.be/HUSDvSknIgI ➢ Immune encounters: **DER12**: https://www.immunology.org/sites/default/files/Immune%20Encounters.pdf ➢ Educational illustrations: **LO5**: https://www.immunology.org/public-information/immunology-related-activities-and-resources/infectious-educational-illustrations

Assessment/evaluation of learning outcomes	➢ Educator can visually assess the understanding of their students.

5.8. References

Basto A. P., and Leitao A., (2014) Targeting TLR2 for vaccine development, Journal of Immunology Research, Vol. 2014, https://doi.org/10.1155/2014/619410.

Janeway C. A. Jr., Travers P., Walport M., et al., (2001), New York: Garland Science, https://www.ncbi.nlm.nih.gov/books/NBK27158/.

Naik S., Larsen S. B., Gomez N. C., Alaverdyan K., Sendoel A., Yuan S., et al., (2017) Inflammatory memory sensitizes skin epithelial stem cells to tissue damage, Nature https://doi.org/10.1038/nature24271.

Nicholson L. B., (2016) The immune system, Essays Biochem., Vol. 60, pp:275-301, https://dx.doi.org/10.1042%2FEBC20160017.

Palucka K., and Banchereau J., (2012) Cancer immunotherapy via dendritic cells, Nat Rev Cancer, Vol. 12, pp: 265-277, http://dx.doi.org/10.1038/nrc3258.

Saeed S., Quintin J., Kerstens H. H. D., Rao N. A., Aghajanirefah A., Matarese F., et al., (2014) Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity, Science, https://doi.org/10.1126/science.1251086.

Simkins S. M. M., (2010) Just-in-Time Teaching: Across the Disciplines, Across the Academy. Sterling, VA: Stylus Publishing.

Stranford S. A., Owen J. A., Mercer F., and Pollock R. R., (2020) Active Learning and Technology Approaches for Teaching Immunology to Undergraduate Students, Front. Public Health, Vol 8, pp: 114, 10.3389/fpubh.2020.00114.

Töpfer E., Boraschi D., and Italiani P., (2015) Innate Immune Memory: The Latest Frontier of Adjuvanticity, Journal of Immunology Research, Vol. 2015, https://doi.org/10.1155/2015/478408

Torang A., Gupta P., and KlinkeII D. J., (2019) An elastic-net logistic regression approach to generate classifiers and gene signatures for types of immune cells and T helper cell subsets, BMC Bioinformatics, Vol. 20, pp: 433, https://doi.org/10.1186/s12859-019-2994-z.

Vasilakos J. P., and Tomai M. A., (2013) The use of Toll-like receptor 7/8 agonists as vaccine adjuvant, *Expert Review of Vaccines*, Vol. 12, pp. 809–819, https://doi.org/10.1586/14760584.2013.811208.

5.9. Educational Scenario Impact Assessment Questionnaire

Context: Basic knowledge of long-lasting immunological memory and protective immunity provides an essential means of simplifying and improving the understanding of challenging topics such as the spreading of communicable disease and prevention of pandemics. The topic of "Workings and malfunctions of human Immunological memory" provides educators and their students with the opportunity to expand their existing knowledge by learning about important concepts in Immunology, including the innate and adaptive arms of the human immune system, the cellular components involved in the establishment of immune memory, and the interactions that bring about protective immunity and preventing re-infections. The topic clarifies how immune memory is independent of the frequency or persistence of re-infection, being a long-lasting feature involving both specialised cells of the adaptive and innate immune systems, that also depends on all the rest of the cells of the human body. High school

students are therefore exposed to immunological concepts related to the immune memory mechanisms in place to minimise and prevent the spreading of disease, preventing thus the occurrence of epidemics and possible pandemics.

Additional information: the topic is provided in the specifications of an educational scenario of the "Workings and malfunctions of human Immunological memory".

The questions that follow provide and assessment for the impact of the given learning scenario on the knowledge acquired and skills acquired by the students throughout the teaching of this topic and the effect of this topic on their beliefs, attitude, and behaviour.

As part of acquired knowledge students can:	
1. Identify immunological memory and its importance in ensuring survival upon reinfection.	1.1. What is immune memory? A. The ability of immune cells to retain memory of past infectious agents and their associated antigens and respond fast. B. The ability of immune cells to retain memory of past infectious agents and their associated antigens and respond slow. C. The initial ability of immune cells to respond to new infectious agents and their associated antigens and respond fast. 1.2. An antigen: A. is a molecular structure that will always stimulate an immune response B. is a molecular structure that will sometimes stimulate an immune response C. is a molecular structure that will never stimulate an immune response 1.3. An effective immune response against a pathogen is achieved: A. by the combined action of both acquired innate and adaptive immune memory. B. primarily by the acquired adaptive immune memory C. primarily by the acquired innate immune memory
2. Recognize the key cell players of immune memory	2.1. Which comprise cells of the adaptive immune system, involved with specialised responses against specific antigens? A. T cells and B cells B. T cells, B cells and macrophages C. Macrophages 2.2. Immune memory is: A. Specific to a given pathogen B. General to all pathogens C. General to a group of pathogens 2.3. Immune memory is brought about by: A. The direct action of pathogen-specific antibodies only B. The direct action of pathogen-specific antibodies and pathogen-specific cells C. The direct action of pathogen-specific cells only 2.4. Phagocytic cells can also remember past pathogens by identifying: A. Conserved molecular structures on the surface of a groups of pathogens. B. Conserved molecular structures on the surface of a specific pathogen only C. Altered molecular structures on the surface of a group of pathogens.
3. Understanding how immune memory is	3.1. Immune memory can be: A. Innate

activated and brought about	B. Adaptive C. Both 3.2. Which of the following is true about innate immune memory? A. innate memory involves immune cells and other body cells B. innate memory is restricted to immune cells only C. innate memory is restricted to body cells only 3.3. Antibodies responsible for bringing about immune memory are secreted by which type of cell: A. B cells B. T cells C. Macrophages 3.4. Immune memory to incoming pathogens begins: A. the lymph nodes that are local to the side of infection B. the bone marrow C. the blood circulation 3.5. Immune memory is: A. Long lasting B. Temporary C. Does not exist
4. Understanding the issues of immune memory malfunctions	4.1. Which is not considered an immune memory malfunction? A. Hypercholestolaemia B. Autoimmune disease C. Natural killer deficiency
As part of skills being gained/developed students can:	
1. Identify the two main arms of the immune system involved in immunological memory and their cellular and molecular components	1.1. Immune memory depends on: A. The innate arm B. The adaptive arm C. Both the innate and adaptive arm 1.2. Innate immune memory involves the action of: A. Macrophages/ dendritic cells/ epithelial cells B. Macrophages/ B cells/ epithelial cells C. B cells/ T cells/ epithelial cells 1.3. Cells involved in adaptive immune memory include: A. B and T cells B. B cells only C. T cells only 1.4. Specific immune memory involves the: A. Secretion of pathogen specific antibodies by B cells and the specific direct killing by T cells B. Secretion of pathogen specific antibodies by B cells and the specific direct killing by phagocytic cells C. Secretion of non-specific antibodies by B cells and the specific direct killing by T cells
2. Identify and recall the function of each of the components of the immune system and how they come to interact to bring about	2.1. The cells of the innate immune system include: A. Macrophages, dendritic cells, Natural Killer cells, basophils, eosinophils, neutrophils B. Macrophages, dendritic cells, Natural Killer cells, basophils, eosinophils, B cells C. Macrophages, dendritic cells, Natural Killer cells, basophils, T cells, B cells

immune memory and prevent reinfection	2.2. The cells of the immune system responsible to produce pathogen specific antibodies are: A. B cells B. T cells C. Macrophages 2.3. The complement system is a component of the innate immune system, composed by 20-proteins that can: A. Stick to the pathogens surface and promote the targeted killing of a pathogen B. Activate the cells of the adaptive immune system C. Are expressed on the surface of immune cells 2.4. Toll-like receptors are involved in immune memory and are found on the surface of: A. All cells of the body B. Only on macrophages and dendritic cells C. Only on B and T cells 2.5. Immune memory to a specific pathogen is: A. Long lasting throughout lifetime B. Short lived and up to 6 months C. Short lived and up to a few weeks
3. Identify that immune memory arises following primary exposure to a pathogen and this results in faster and stronger immune responses to the same pathogen.	3.1. Following primary exposure to a pathogen, re-exposure will result in: A. Faster and stronger immune responses B. Slower and weaker immune responses C. Slower and weaker immune responses
4. Perform own research on their chosen topic regarding immune memory, learn to summarise and present important facts regarding immune memory.	4.1. I feel able to identify scientific sources to use in my research 1) strongly disagree… 5) strongly agree. 4.2. I feel confident to prepare a poster/power point presentation of my chosen topic involving immune memory. 1) strongly disagree… 5) strongly agree 4.3. I can confidently summarise the important facts related to immune memory and present these to my peers 1) strongly disagree… 5) strongly agree
5. Demonstrate understanding and being able to describe the series of events leading to immune memory towards re-encounter with pathogen.	5.1 I can understand the steps following re-encounter with the same pathogen, and how these can lead to faster and stronger responses as a result to immune memory. 1) true... 5) false. 5.2 I can outline and describe briefly these steps leading to immune memory responses following a second exposure to the same pathogen. 1) true... 5) false

6. Development of research, collaborative, and communication skills	6.1 I feel able to identify scientific sources relevant to the consent of immune memory. 1) strongly disagree… 5) strongly agree. 6.2 I know the main sources to consult about immune memory. 1) strongly disagree… 5) strongly agree. 6.3 To find scientific information about immune memory I should consult the following sources. A. researchers, scientific publications, WHO and CDC data bases. B. newspapers, google, YouTube C. friends, journalists, Facebook, other social media. 6.4 I feel able to identify the main problems my community faces when it comes to understanding difficult concepts such as immune memory and how this is the outcome of less severe symptoms following re-exposure to a pathogen. 1) false… 5) true. 6.5 I feel capable of proposing actions that address how to promote immune memory, either using effective vaccination, or testing for pre-existing memory following natural infection. 1) true... 5) false.
As part of Beliefs, Attitudes and Behaviour, there are no correct or incorrect answers; we are only interested in knowing the students' perspective on the topic introduced.	
1. Believes that is important to contribute to global efforts for tackling future pandemics.	1.1. My acquired knowledge and understanding of immune memory will increase the chances of success of the global efforts for preventing a future pandemic. 1) strongly disagree… 5) strongly agree. 1.2. I am physically capable of adopting actions (i.e., school, community presentations) that contribute to the efforts of increasing awareness about immune memory and how this is achieved and can help in decreasing the spread of disease that could lead to future pandemics (i.e., vaccination strategies, testing for specific immune memory against a specific pathogen etc.). 1) extremely unlikely... 5) extremely likely. 1.3. My family and friends think that I should adopt actions that contribute to increase awareness about immune memory and add to the global efforts for tackling future pandemics. 1) Extremely unlikely... 5) Extremely likely.
2. Believes that learning about immune memory and that the human immune system responds fast and effectively to even the most powerful viruses following re-exposure can lead to positive outcomes at the community level when it comes to evaluating severity levels.	2.1. To learn about how immune memory works and how this could help in protecting people from severe symptoms and prevent the uncontrolled spreading of a disease, will lead to positive outcomes at my community. 1) strongly disagree… 5) strongly agree. 2.2. My community thinks that increasing awareness about difficult concepts such as that of immune memory and its contribution to lowering disease severity, will bring positive outcomes. 1) Extremely unlikely... 5) Extremely likely.
3. Has intention to perform sustainable behaviours in his/her lifestyle.	3.1. I will try to update myself with current information regarding highly contagious virus variants. 1) Extremely unlikely... 5) Extremely likely.

	3.2. I plan to update myself about updated versions of vaccines available for communicable diseases. 1) Strongly disagree... 5) Strongly agree. 3.3. I plan to enforce my immune memory to current communicable diseases by being up to date with my vaccinations. 1) Strongly disagree... 5) Strongly agree.
4. Attitude toward learning about how immune memory works and its implications towards controlling the severity of a communicable disease.	4.1. For me to achieve such knowledge is: Harmful : : : : : : beneficial Pleasant : : : : : : unpleasant Good : : : : : : bad Worthless : : : : : : valuable Enjoyable : : : : : : unenjoyable