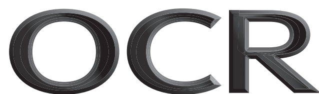


Oxford Cambridge and RSA

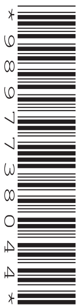
For issue on or after: 13 March 2023

A Level Biology B (Advancing Biology)

H422/02 Scientific literacy in biology

Advance Notice Article

To prepare candidates for the examination taken on Friday 16 June 2023 – Morning



INSTRUCTIONS
- Before the exam, read this article carefully and study the content of the learning outcomes for A Level Biology B (Advancing Biology).
- You can ask your teacher for advice and discuss this article with others in your class.
- You can investigate the topic of this article yourself using any resources available to you.
- Do **not** take this copy of the article or any notes into the exam.

INFORMATION
- A clean copy of this article will be given to you with the question paper.
- In the exam you will answer questions on this article. The questions are worth 20–25 marks.
- This document has **4** pages.

ADVICE
- In the exam you won't have time to read this article in full but you should refer to it in your answers.

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Development of therapeutic antibodies for the treatment of disease

The specific immune response involves the production of antibodies against pathogenic antigens. Clonal selection results in a population of B cells that produce these antibodies. Many different clones of B cells are produced in a normal immune response, and each clone is specific to different antigens. This is known as a polyclonal response, and the antibodies produced are known as polyclonal antibodies.

Monoclonal antibodies (mAbs), on the other hand, are produced by cloning one original B cell. The hybridoma technique for producing monoclonal antibodies was developed by George Kohler and Cesar Milstein, working at the MRC Laboratory of Molecular Biology in Cambridge. By fusing a single B cell with a myeloma (cancer) cell, the hybrid cell gains the ability to divide rapidly, allowing large numbers of identical antibody-producing cells to be grown in culture. Originally, mAbs were produced from mouse cells. These mouse mAbs have been used for many years in basic research and in diagnostic tests such as pregnancy test kits.

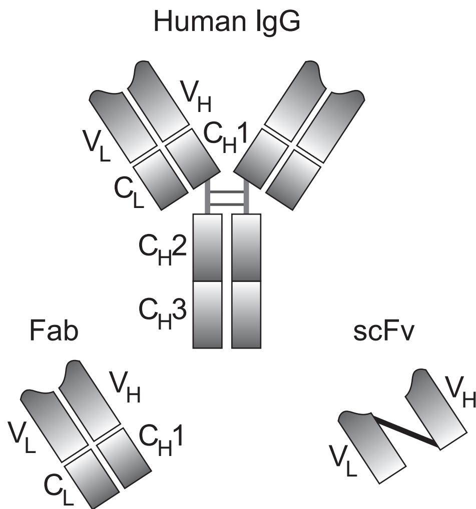
More recently, however, mAbs have been used in clinical applications to treat, rather than simply diagnose, disease. These are known as therapeutic mAbs. In 2018, six of the top ten best-selling drugs worldwide were mAbs. Hundreds of therapeutic mAbs have been studied in clinical trials, and 79 of these had been approved for use as medicines by the end of 2019. Almost half of the approved therapeutic mAbs are for the treatment of cancer.

Problems exist with the use of therapeutic mAbs from mouse cells: they cause a rapid human anti-mouse antibody (HAMA) response. This leads to removal of the mouse mAbs from the blood and can also lead to allergic reactions. To avoid these problems with mouse mAbs, Greg Winter, also working at the MRC Laboratory of Molecular Biology, developed a technique known as CDR grafting to humanise the mAbs. This method uses genetic engineering to graft the antigen-binding portion (variable region, or CDR) of a mouse antibody onto the constant region of a human antibody. In this way, mAbs can be produced that contain much less mouse protein and, therefore, pose less risk of a HAMA response. An example of a widely used humanised mAb is the drug Herceptin, which is used in the treatment of breast cancer.

A subsequent development, known as phage display, created a library of human immunoglobulin G (IgG) genes inserted into a type of virus known as a bacteriophage (phage for short). The variable regions of heavy (V_H) and light (V_L) antibody (IgG) chains are encoded by different genes. The constant region of these antibodies is encoded by a small number of genes. Therefore, it was possible to combine different variable region genes with constant region genes to produce millions of different antibody fragments. Fab fragments consist of the whole of the light chain, the variable region of the heavy chain (V_H) and the first part of the constant region of the heavy chain (C_{H1}). scFv fragments are even smaller and consist of only the variable light chain (V_L) and the variable heavy chain (V_H). Fragments expressed in a phage display can be screened for the required specificity.

Fig. 1 shows the structure of Fab and scFv fragments in comparison to a human IgG molecule.

Fig. 1



The phage display method removed the need for immunisation of mice and the production of hybridomas. It also enabled the production of fully human antibodies. The first approved therapeutic mAb produced using phage display was adalimumab, which is approved to treat inflammatory diseases, such as rheumatoid and psoriatic arthritis, Crohn's disease, and psoriasis. Adalimumab is now the world's best-selling pharmaceutical drug.

Development of new mAbs by these recent methods can take many months, even years. A quicker method is being developed that involves the use of flow cytometry to isolate single B cells that produce a required antibody. The speed of this technique is proving useful as a way of obtaining neutralising antibodies with the potential to treat viral or bacterial infections (e.g. HIV, zika virus, and anthrax, caused by *Bacillus anthracis*). However, therapeutic mAbs produced using flow cytometry are yet to be approved to treat these infections in patients.

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