THE FOUNDATION FOR SCIENCE AND TECHNOLOGY

LECTURE/DISCUSSION SUMMARY

The antibody revolution; turning inventions into medicines and companies

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Chair: **The Earl of Selborne GBE FRS**
Chairman, The Foundation for Science and Technology

Speakers: **Sir Greg Winter CBE FRS FMedSci**
Master Elect, Trinity College, Cambridge and MRC Laboratory of Molecular Biology

Panel Members: **Sir John Savill FMedSci FRSE**
Chief Executive, Medical Research Council
Dr Neil Brewis
Vice-President of Research, Biopharm R&D, GSK

SIR GREG WINTER summarized the consequences of the antibody revolution. Not only had it delivered a great change in diagnosis and treatment of diseases, but its development had shown how inventions could be carried through into commercial success with sales of $50bn a year avoiding the "valley of death" - the failure to secure sufficient funds to develop inventions commercially. The UK had played a major role in the research and development of therapeutic antibodies, and its economy had substantially benefited.

Therapeutic antibodies had a wide and increasing use in treating immune disorders, such as bowel, head and neck cancers, leukemia, and immune disorders, such as osteoporosis, and arthritis which had traditionally been treated by chemical methods. By 2010, antibodies were in the top 10 of drugs sold – Enbrel sales were $6.8 billion, Humira $6.5 billion, Remicade $5.8 billion - and would soon occupy the top three places in global sales.

The immune system produces large numbers of antibodies to repel foreign invaders. The task was to produce individual or monoclonal antibodies which would deliver reproducible results without side effects. The advantages of antibodies over chemical therapeutic treatments were great - their high target specificity and affinity, their low off target toxicity, their long term half life and their killing mechanisms. But they were not universally applicable - they were not effective for some cancers.

Although it had been known for many years that it should be possible to block inappropriate immune response, it was not until 1975 that it was discovered how to isolate and reproduce monoclonal antibodies, developed from mice spleen. But uses were limited, because of the reaction of human tissue to mice antibodies. But it was in 1986 that he and his colleagues in the Laboratory of Molecular Biology (LMB) pioneered a technique for "humanising" mouse monoclonal antibodies. This made them more suitable for human medical use, for such conditions as osteopathy, rheumatoid arthritis, and breast cancer.

However, in order for antibodies to be used clinically and sold commercially, a package had to be developed to isolate the necessary antibody from the 100m or so produced. This called for protein engineering. Finally in 2003, the LMB and the Scripps Research Institute developed a particular technique of producing antibodies with specific and demonstrable impact. A MRC spin out company - Cambridge Antibody Technologies - launched the first fully human monoclonal antibody drug - Humira - for rheumatoid arthritis.

The UK contribution to research and development had been large. But of the 29 products now on the market only seven had UK input. This showed that our technological development had not carried through to full commercial reward. Some of the reasons lay in the lack of interest by the National Research Development Corporation (NRDC) to patent the original mouse antibody. When the "humanized" mouse monoclonal antibodies were developed and commercialised by a spinout Celltech and Genentech had patents but the rights to future developments, were retained by the MRC. This enabled further research on humanized antibodies to be carried on, leading to Humira and other developments, which were patented. The work was carried out in the MRC Collaborative Centre, which worked with company partners and led to successful treatment for further conditions. By 2010 the sales of Actemra had reached

$435m and $1,000m for Tysabri. The final development of human antibodies, fully and exclusively patented, led to the setting up of Cambridge Antibody Technology (CAT) and the exploitation of Humira. CAT's characteristics were core science and intellectual property, funding from investors and deal income, good business and scientific management, and a sound business plan.

He emphasized that monoclonal antibodies had come from blue skies research - no one, at the start, had worked on the research because of its potential commercial or other benefits. The time scale had been long – ten years. The success of the translation from research to commercial sales lay in an understanding of the need to evaluate and protect IP; working to establish the clinical impact of products in collaboration with industry, and of developing realistic business plans. Venture capitalists were not a necessary part of the development. But it was clear that public subsidy was necessary; the LMB could not have continued its work without it. The benefits to the MRC were substantial. In 2005 the rights to Humira were sold for $100m and in 2006 Cambridge Antibody Technology was sold to AstraZenica for $702m.

SIR JOHN SAVILL said that, for him, the great benefit of the antibody revolution was the benefit it brought to patients and healthcare. But, the benefit to the UK economy was also of great value. Sir Greg's presentation had showed how MRC research benefited the economy. He endorsed the Government's "Strategy for Life Sciences" and saw the future as working in partnership with industry and understanding how to combine intellectual protection, through patents and licensing, and with free access to data.

The MRC commercial revenue was £15.1m in 2002/2003 and by 2011/2012 it had risen to £75.2m. The revenue was now included in their expenditure limits. It had enabled the MRC to build the new LMB building in Cambridge. MRC Technology had led to eighteen start-ups and twelve leading drugs on the market. MRC Technology had generated over £500m of income for the MRC and more than £40bn of sales for industry.

DR BREWIS shared Sir John's emphasis on the benefits of the antibody revolution for health care. He stressed, however, the complexity and expense of bringing new drugs to market. There were many more failures than success, and it was clear that companies could not now work in isolation in developing new products. They needed to work in collaboration with academia and with other companies, both small and large. They already do this with some success, but there was still more to be done. Companies had a duty to promote research and should be willing to share equipment and expertise to promote the development of a vibrant life sciences sector.

He emphasized the importance of the human factor in research and development. There was a danger that academics, researchers and industry pursued their own lines in isolation because they did not share ideas. It was important that they worked near each other so that a critical mass of those interested could know and work with each other. Such clusters would also enable scientists to move from one field to another without disruption to families and home.

In the following discussion, a number of speakers were concerned about how the balance between open access to data, which would allow researchers to collaborate and use information, and the need to protect intellectual property for exclusive use in order for commercial success, and profits, to be achieved. There was no universal solution for this problem - it had to be dealt with case-by-case. But, the crucial point was, that if commercial success were to be maintained on the basis of exploitation of existing research, whether patented or not, it had to be through the development of new ways of using the research - of "tweaking" it , through an understanding of its potentialities. An example might be the development of a "super antibody". The difficulty of protecting IP internationally, with today's communication technology was already great. In any case patents would run out and it was important that companies concentrated on the next set of research breakthroughs, not on the last. Health data should always be made available in anonymised form for research for the benefit of all future patients.

Speakers also questioned the way in which universities exploited their research and encouraged their staff to set up start up companies. There was too great a concentration on securing income for the university, and not enough on looking at the ultimate impact of the technology. Moreover, because researchers setting up start up companies still continue in their academic posts, they lacked the ability to do two very different jobs - run a company and continue research. This system was contrasted with the MIT system where researchers who wanted to exploit their research through a start-up were required to choose - either they left and ran the company or they stayed in post. The advantage was that they could then become serial inventors and work on other issues if they stayed. Crucial to this was the status and drive of the MIT technology transfer office - who knew how to find capital, recruit CEOs and develop business plans.

Speakers were concerned about the translation process. Was industry now more prepared to work with blue skies research? The pharmaceutical industry might well be, because it understood the speed with which new developments came about, and how (as with antibodies) existing commercial success could be undermined. Indeed, they now understood the need for research which led to disruptive technologies, which might transform the market. But it was important for researchers to understand that they need to present a package of research which would have scale and impact. It was no use just suggesting potential. There was a need for leadership in academia, to motivate researchers and help them understand commercial reality, from funders, to drive research forward, and from industry to seize opportunities. A missing link was, however, intermediate institutions between research and commerciality - such as Technology Enterprise Companies.

Regulation and delay were a problem, particularly for small companies who needed to do small scale tests. Was a solution to set up centres of excellence, where regulations could be relaxed? The government hoped to make regulation more proportionate to risk, but there would always be resistance to allowing treatments which did not have full regulatory approval.

Speakers also questioned whether antibody therapeutics would continue to lead the field. Was there not a possibility that vaccines might turn out to be future treatment leaders. This was doubted. Self creating antibodies were dangerous and uncontrollable; every person would have a different reaction.

There were 5,000 rare diseases which could only be treated at enormous cost per individual. How could such patients be helped? The cost would come down if the treatment for a rare disease became applicable to a wider range of conditions. There was a great potential to learn from them the special cases of rare diseases. What we needed to do was to understand the biology behind the disease and use the basic understanding of disease to see if treatments for other conditions can apply to the rare disease.

Useful web links:

The Prime Minister's speech on life sciences and opening up the NHS:
www.number10.gov.uk/news/pm-speech-on-life-sciences-and-opening-up-the-nhs/

The Science and Universities Minister's speech on "Our Hi-Tech Future":
www.bis.gov.uk/news/speeches/david-willetts-policy-exchange-britain-best-place-science-2012

The history of the development of monoclonal antibodies
www.mrc.ac.uk/Achievementsimpact/Storiesofimpact/Therapeuticantibodies/index.htm

AstraZeneca
www.astrazeneca.co.uk

The Foundation for Science and Technology
www.foundation.org.uk

GlaxoSmithKline
www.gsk.com

Medical Research Council
www.mrc.ac.uk

MRC Laboratory for Molecular Biology
www.mrc-lmb.cam.ac.uk

MRC Technology
www.mrctechnology.org

Office for Life Sciences, Department for Business, Innovation and Skills
www.bis.gov.uk/ols

Pfizer UK
www.pfizer.co.uk

The Royal Society
www.royalsociety.org

The Wellcome Trust
www.wellcome.ac.uk

Sir Geoffrey Chipperfield KCB