Greg Winter

The inventor of humanized monoclonal antibodies and cofounder of Cambridge Antibody Technology, Greg Winter, muses on the future of antibody therapeutics and UK life science innovation.

Though currently in vogue, monoclonal antibodies (mAbs) took a long time to earn their present status. They were initially hailed as 'magic bullets,' but the excitement soon abated with the realization that immunogenicity problems compromised the use of rodent mAbs. Through the use of protein-engineering approaches, first to humanize rodent mAbs and later to make human antibodies, Greg Winter and his collaborators helped facilitate the transition from rodent mAbs to the therapeutic antibodies in use today, such as Campath-1H, Herceptin, Avastin and Humira. In 1989, Winter cofounded Cambridge Antibody Technology

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and later went on to establish Domantis; his latest venture is Bicycle Therapeutics (Cambridge, UK), where he is attempting to produce small antibody mimics with covalently bonded hydrophobic cores.

Why did it take so long for pharma to recognize the value of mAbs?

Gregory Winter: Several companies like Genentech, Celltech and Behringwerke believed in antibodies. But large pharma didn't really believe; they were suspicious because of the earlier hopes that hadn't been realized. In particular they wanted evidence that antibodies could be given for a prolonged treatment—much longer than for a rodent antibody. Also, antibodies weren't the kind of drug that they were used to dealing with; it was out of their comfort zone, so they left it to biotechs. It was probably the prospect of making money that changed their attitudes, when in the mid-90s the first engineered antibodies received [US Food and Drug Administration] approval and started to sell.

With the rise of biosimilars, what do prospects look like for innovator companies focusing on mAbs, their fragments and antibody-like scaffolds?

GW: The rise of biosimilars will depend on the attitude of various regulatory bodies, and market pressures, and that's difficult to predict. But biosimilars will be pushed hard by innovators making differentiated, and better, products. For instance, the addition of extra power to antibodies, whether it's cytotoxic drugs, effector functions or enhanced pharmacokinetics, will give an edge over biosimilars, as will the use of bispecifics. Using combinations of antibodies to proven drug targets is particularly attractive. For example, given there is angiogenesis in rheumatoid joints, it may be advantageous to combine an anti-tumor necrosis factor-α antibody [like Humira] for rheumatoid arthritis with an anti-vascular endothelial growth factor antibody [like Avastin] that inhibits angiogenesis. An implication is that the chances of making a blockbuster may become less as differentiation starts splitting up the market. I also expect to see increasing use of smaller antibodies: fragments with, for example, appendages that could extend their serum half-life.

In what directions do you anticipate future mAb therapies going?

GW: I can see at least two directions for the technologies. For antibodies with a very long half-life in serum (as may be possible to achieve by mutation of the binding site for the recycling receptor), or where the biological response is prolonged, it is possible to envisage injections once a year or every 6 months, rather than a daily pill. That's got to be a lot more convenient and efficient. Amgen's denosumab is already injected every 6 months. Another route is to make antibodies much smaller, to penetrate the tissues more effectively. With the startup Bicycle Therapeutics we are trying to make tiny antibody mimics with binding and effector activities, that can be cut and pasted together just as in antibodies. Perhaps these can be made orally available.

As a founder of three companies, who remains in academia, what do you consider to be the best way of translating academic discoveries?

GW: Dream while (just) keeping your feet on the ground. More specifically, from discovery to translation, keep an eye on the big picture as well as the nitty-gritty details, and be lucky! I was lucky, as the [Laboratory of Molecular Biology] with its block grant gave me *carte blanche* for getting on with my work without distinguishing between pure and applied science. It would have been very difficult to have made my inventions on classic grant funding (it would have been seen as too applied) or on industry money (it would have been seen as too early, and anyway most companies weren't interested in antibodies at the beginning). I immersed myself fully in the process of translation and was lucky because the whole antibody field was about to expand greatly; with hindsight it was like pushing on an open door, but at the time it didn't feel like that.

To what extent is UK life science innovation under threat?

GW: It is under serious threat. Life science innovation is an international business; the UK is in competition with the rest of the world. We do have good scientists here, but they are not that well paid, and we will certainly lose them if they can't get the money to do their science here, or if the bureaucracy involved in running a scientific group continues to expand. We are also seeing a reduction in the number of pharmaceutical jobs in the UK. That's very worrying, especially for the message it gives. If it is thought that the UK pharmaceutical industry is on the slide, it could become a self-fulfilling prophecy, and difficult to reverse. If we can't hold onto our academic stars and our pharmaceutical industry, we are in danger of losing life science innovation and the industries of the future.