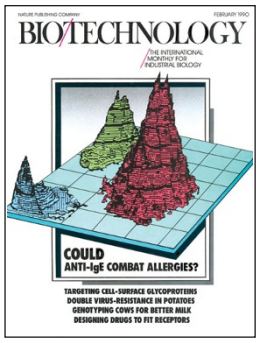
nature biotechnology

A piece of history



Sometimes there are occasions when blowing your own horn is not only irresistible but appropriate as well. This is one of them. On June 20, 2003, the US Food and Drug Administration (FDA), following the unanimous opinion of an expert advisory panel, approved a new asthma treatment—a highly specific anti-IgE, humanized monoclonal antibody to be marketed under the trade name Xolair. In February of 1990, *Bio/Technology* (as *Nature Biotechnology* was then known) published a paper by Tse Wen Chang and coworkers of Tanox Biosystems and Johns Hopkins University School of Medicine that is the cornerstone scientific finding on which this approval rests (*Bio/Technology* **8**, 122–126, 1990). We were so impressed by the inherent rationality of the approach, and the cleanness of the experimental results, that we featured the paper on the cover (reprinted above) and wrote a commentary on its scientific merits and possible therapeutic implications (*Bio/Technology* **8**, 96, 1990). Much of what we wrote reappeared as early third-millennium media transformations in the fusillade of attention Xolair's approval garnered, all of which noted that it is the first drug to target the root cause of the allergic response, and not the symptoms.

It does this, as published in these pages almost 13 years ago, by having binding specificities for IgE (the dispensable immunoglobulin responsible for most forms of allergy) that exclude the possibility of cross-linking antibodies bound at the surface of mast cells and basophiles. This cross-linking property of anti-IgE antibodies is what makes them such potent pseudo-allergens, and it was perhaps the reason they were not generally considered at the time as being potential frameworks that could be rationally remodeled using the powers of monoclonal antibody technology. What Chang and his colleagues reasoned, completely correctly, was that since IgEs also interact with the B cells that produce them, as well as being free in the blood, there should be epitopes available that could be exploited to prevent the interaction of IgE with the allergic-response-provoking cells—effectively removing the unwanted antibody from the circulatory system—and in the best case scenario, actually downregulate IgE-producing B cells by complement and antibody-mediated cytolysis. The paper they published demonstrated convincingly that monoclonal antibody populations of the required binding affinities and avidities could be obtained. In the intervening years, a large amount of clinical data has accumulated proving that Xolair is a safe and effective pharmaceutical, bearing out all the previous predictions.

So much for the irresistible. The appropriateness of our horn blowing is that it also sounds a number of object lessons for biotechnology in general. The most important perhaps is that it should call our attention to the difference between 'fad, fashion and flavor of the month' and fundamentally sound reasoning. At the time the Chang paper was submitted, for example, interleukin-4 modulation was the current most flavorful approach for attacking IgE-producing B cells. But good ideas have a curious way of recycling in the biotechnology universe. Despite being relegated in the early nineties to the septic tank along with Centoxin, Centocor's rushed and failed antisepsis antibody, monoclonal antibodies are not nearly as highly discounted today as they were a decade ago.

Finally, we are reminded of both the paradox and parable involving Achilles and a tortoise, and have every hope that Xolair will prove as successful in the real world of asthma sufferers as it has been in the thoughtful, and sometimes infinitely slow-seeming process of getting its chance.

Number crunching

This year's meeting of the US Biotechnology Industry Organization (BIO) held in Washington, DC, at the end of June was the largest biotechnology industry gabfest ever. According to BIO, 16,234 registrants and 1,268 exhibits crammed into 2.3 million square feet of space (roughly six city blocks). Attendees included no less than one president of the United States, nine US state governors and 29 formal international delegations from around the world, all participating in an ulcer-popping profusion of free lunches and hospitality receptions.

But BIO's most shocking statistic is that biotechnology is no longer an upstart industry: in 2002, it employed 194,600 people in the US—more than the toy and sporting goods industries. The question is, does biotech continue to be more entrepreneurial than industries where racket heads with more ping and dolls that precisely mimic human bodily functions are the pinnacles of innovation?

Back in 1993, when 1,400 attended the inaugural meeting in Research Triangle, NC, BIO was a networking opportunity; a chance for those from the US industry's 1,272 companies to share triumphs and tragedies and do new business together. But in 2003, even though more than twice as many people are employed in US biotech, there are only 200 more companies—a surprisingly low number considering the hundreds of billions of dollars ploughed in over the past decade.

Biotechnology is now a mature sector with large companies offering steady employment not only to scientists and entrepreneurs, but also clinical trial coordinators, regulatory professionals, reimbursement specialists, marketing/sales personnel, accounting/tax experts, consultants, PR agents and lawyers (to name a few). But despite the overabundance of regional development agencies and delegations at BIO, the industry that launched a thousand companies is unlikely to be launching a thousand more anytime soon. Today, venture capital not only is much more stringent and selective about the types of startups it will finance, but also has many lucrative opportunities in the growing number of late-stage companies.