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King in the kingdom of uncertainty

Monoclonal antibodies (mAbs) are not good drugs, at least they are not good drugs in any conventional sense. Many of the fundamental qualities of mAbs are just the sort of characteristics that used to make pharmaceutical manufacturers run a mile.

Most fundamentally, they are biological molecules and hence intrinsically complicated. The average IgG has 1,300 chiral centers and thus $2^{1,300}$ enantiomers. No sane medicinal chemist would touch them, so it is just as well they are produced biologically. That, of course, brings its own problems. It takes approximately twice the time and costs twice as much to work up mAbs to clinical-grade material compared with small molecules. Biological production systems are prone to synthetic variability with the result that a mAb—like any 'pure' protein—contains in addition to its major molecular type, a complex mixture of isomers, splice variants, truncated versions and so forth. Again, that variation within 'the composition of matter' does not matter as long as the overall composition is the same in the current batch as it was in the batch that received regulatory approval. And that can be achieved by ensuring that the production method is identical each time through rigorous control and monitoring. Naturally, mAbs are tightly regulated: the product itself, the batch-to-batch process and the manufacturing plant are all highly scrutinized.

Not only is it terribly complicated to produce mAbs, they are difficult to use, too. Maintaining the integrity of large glycoproteins on storage is not straightforward, and they obviously cannot be administered orally. Furthermore, once they are in the body they take 5–7 days to reach their targets given their large girth relative to the average pore size in endothelium. In addition, although the severe problems of low efficacy and toxicity seen with early rodent-derived mAbs therapies have been largely overcome by, er well, not using rodent antibodies, humanized and even human mAbs retain the immunogenicity of a large recombinant biological entity.

In short, mAbs are large and clunky, difficult to make and difficult to use. And if that were not enough, every nuance of production or fragmentation or chimerization or molecular remodeling has been, it seems, invented by different people. The production vectors, the splice sites, the domain structures and the algorithms for making human-like proteins are owned by different companies and require distinct licenses: just the sort of retiarius of intellectual property of which pharmaceutical companies normally fight shy.

But if mAbs are such a nightmare, why is so much effort being invested into R&D (as illustrated by the reviews and articles in this focus issue) and, according to the most recent estimate by the Tufts Center for the Study of Drug Development, why are there now over 350 mAb-based medicines in clinical trials, three times the number a decade ago? Why is it that most major pharmaceutical firms—companies not known primarily for their spirit of madcap adventure—are not only in-licensing mAbs like crazy but also building substantial internal portfolios of mAbs? And why is it that Biogen Idec—still smarting from its voluntary suspension in February of Tysabri (a mAb for the treatment of multiple sclerosis) leapt at the beginning of August into a $660-million deal with Protein Design Labs to develop and commercialize three mAbs for multiple sclerosis, cancer and autoimmune disease?

The answer, of course, is that mAbs have one saving grace that overrides all their deficiencies, and from which many advantages flow. It is their exquisite specificity, their ability to home in on a particular target, that has carved out a highly profitable niche for them as second/third-line therapies in cancer or primary treatments in certain viral diseases. Rituxan, Remicade, Herceptin and Synagis, for example, are billion-dollar-plus blockbusters. Like an elephant doing needlepoint, mAbs are capable of an exquisite precision that belies their size: they bind in a very predictable way to very specific antigens.

That doesn't sound like much—especially given all their undrug-like qualities, but these days, any element of certainty looks like a haven in a storm of risk. And it is their predictability that really endears mAbs to the pharmaceutical industry.

From the outset, their binding characteristics are known. Antibodies can be readily labeled to demonstrate in animal or early human studies precisely where they localize. The path to humanized or human antibodies is technically complex and littered with potential royalty leaks, but it is well trodden and the costs are standard items. The passage of mAbs through clinical trials is reliable: according to Tufts, attrition rates are significantly lower than for small molecules (p. 1073).

Where mAbs have produced unpleasant surprises in the clinic, it is usually because of insufficient grasp of the biology of the target antigen, especially in murky, relatively unexplored areas. The molecular explanation for Tysabri's toxicity is not yet known but bookmakers versed in the molecular arts are laying shorts odds that by blocking $\alpha_4\beta_1$ integrin so well, Tysabri restricts immune cell migration, thereby allowing the previously dormant polyomavirus JC license to wreak havoc in the brain. Even the most specific mAb will be doomed if its antigen target moonlights in processes unrelated to the target indication that are crucial for normal function.

That said, as knowledge grows and preclinical screening can be carried out against all extracellular targets in a wider range of tissues, mAbs' attrition rates could become even lower. And, the fact that whole mAbs are large and cannot reach deep crevices or into intracellular sites may even be an advantage in the context of our fragmented understanding of human biology: in comparison, smaller molecules (e.g., chemical entities, or mAb fragments for that matter) may penetrate all sorts of nooks and crannies in which they might cause problems.

In a commercial environment where, as Merck will attest, any huge pharma company can be threatened by rare adverse events associated with even the best of its molecules, lumbering molecules that do one job really well, which can travel a convoluted but well-trodden path to the market, and which don't go nosing around in places where they are not wanted are starting to look very backable. It is in this kingdom of uncertainty that the mAb reigns supreme.