Antibody–drug conjugates: the success of failure

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As a young scientist, I was interested in antibody–drug conjugates (ADCs) because of my background in immunochemistry and previous experience in the development of antibody derivatives. I was asked to participate in a project involving the conjugation of cytotoxic drugs to monoclonal antibodies that specifically recognized tumor-associated antigens. The idea was based on a concept originally advanced by Paul Ehrlich, to create a magic bullet for cancer treatment, long before such tools became available. Many different toxic substances were available as the payload, most of which had already been used in chemotherapy, albeit with the risk of serious adverse effects due to their nonspecific activity. Chemotherapy needed to be aggressive and oncologists managed a fine line between the quantitative eradication of tumor cells and the serious impact of adverse effects. The study was financed by the European Community under the framework program Europe Against Cancer (1987–2000) and its mission was clear. Little had changed 16 years after the signing of the National Cancer Act (1971), which US President Richard Nixon often referred to as “the war on cancer”, despite dramatic improvements in certain areas of cancer therapy. In the meantime, however, basic research had helped to create a better understanding of cancer biology, improved diagnostics and tumor-associated surface proteins that were thought to be ‘undruggable’ came under scrutiny for targeted therapies.

My professor, a highly recognized expert in his subject, warned me to stay away from the project because the products I had in mind were heterogeneous populations of closely related compounds rather than a defined chemical structure. Such populations would not crystallize and were therefore regarded as chemically dubious. Analytical characterization was supposed to be difficult and nobody would help me reproduce my work. Fortunately, I did find a good assistant to help me. Also, because I had already crossed the red line by working with antibodies, which tend to show microheterogeneous characteristics even without further modification, I went ahead and investigated ways to couple toxins to antibodies using random, as well as site-specific linkages involving stable and cleavable covalent bonds.

The concept was that antibodies would deliver the toxic payload to malignant primary cells or metastases, and would be taken up by endocytosis. The toxic conjugate would then be released from the antibody within the lysosomal degradation pathway, killing the target cells via a phenomenon known today as apoptosis. Our favored drugs were the streptomycetes metabolites neocarcinostatin and bleomycin, both of which introduce double-strand breaks into DNA and were therefore known as ‘radiomimetics’ [1]. Along with our EU partners, we enthusiastically developed in vitro and in vivo models to prove the efficacy of our concept and – to cut a long story short – we failed. The small worldwide community working on similar...
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concepts, but using toxic proteins (such as gelonin, ricin A chain orphtheria toxin) or small molecules such as methotrexate, also failed. We all failed because, despite generating promising results, these first-generation concepts followed a monocausal approach that used artificial models and underestimated the versatility of tumor metabolism, as well as pharmacokinetic requirements.

We were unable to take advantage of all options during the project, including a new class of compounds that were so toxic that a single molecule can kill a cell, again by inducing DNA strand breaks. Interestingly, these supertoxic compounds gave rise to a new first-in-class type of immunoconjugate some 10 years later, which were described as ADCs [2,3]. The first approval was gemtuzumabozogamicin (marketed by Wyeth as Mylotarg®), an anti-CD33 antibody derivatized with calicheamicin. This was approved by the US FDA under their orphan drug program in 2000 for the treatment of acute myelogenous leukemia. Mylotarg was withdrawn from the US market in June 2010 at the request of the FDA because of its toxicity, although it is still marketed in some other jurisdictions [101].

More recently, two improved ADC products have entered the market. In February 2013, the FDA approved trastuzumabemtansine (Kadycla®), a Genentech product indicated for HER2-positive breast cancer, which uses the same antibody component as Herceptin® conjugated to the anti-mitotic agent mertansine (also known as DM1). In May 2013, the FDA approved brentuximabvedotin (Adcetris®), a Takeda product indicated for the treatment of certain types of lymphoma, which combines an anti-CD30 antibody and up to five molecules of the antimitotic agent monomethylauristatin E. Both products stem from the two most prominent ADC platforms of Immunogen and Seattle Genetics, which are collaborating with a number of leading pharmaceutical and biotechnology companies. A further 74 ADC candidates are currently in development, among which 70% are in preclinical or early clinical development (Phase I). Given normal attrition rates, we appear to be anticipating a wave of second-generation ADC products over the next few years incorporating secondary metabolites such as mertansine and auristatin that are significantly more potent than traditional chemotherapeutics. Further improvements have been achieved with the development of heterobifunctional coupling agents that generate stable linkers and keep the payload attached to the antibody in the bloodstream and control its release and activation once inside the target cell.

It is certainly good news that the regulators appear well prepared to handle the approval process for ADCs and clear responsibilities for the various compounds of the final drug, that is, the antibody, the linker, the drug substance and the overall product [4]. As with unfunctionalized monoclonal antibodies, comparability requirements are critical and the reproducibility of the manufacturing process plays a central role. The coupling of the cytotoxic agent may add another layer of microheterogeneity that must be considered as part of the characterization and release process, but site-specific conjugation may soon provide an advanced technical solution to this problem. It is important to understand that ADCs are highly toxic substances that can presently be handled by only a few specialized contract manufacturers. There are specific segregation requirements and the risks of cross-contamination need to be assessed. Integrated production concepts are being discussed, and single-use manufacturing solutions that offer complete containment seem to provide a good starting point for some of these challenges. With many of the development obstacles solved, ADCs look like they are here to stay. There is now a strong demand for this class of biopharmaceuticals to fulfill the next level of medical treatment.

To complete the picture, therapeutic monoclonal antibodies also failed to make a significant medical impact when they were first developed in the 1970s [5]. Their advent gave rise to various new tools in biomedical research and created an expectation that antibodies would provide an immediate and major breakthrough in the treatment of cancer, but then a number of drawbacks were identified and confidence was shaken. Monoclonal antibodies survived in niches, as research and diagnostic reagents, and as therapeutics for highly specific indications. In 1986, the launch of the murine anti-CD3 antibody OKT3, indicated for the prevention of transplant rejection, was followed by a 9-year hiatus in further approvals. During this time,

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the entire industry matured and adopted a more pharmacogenomics-driven approach, novel formats were developed leading to chimeric, humanized and eventually fully human recombinant antibodies. This resulted in a spectacular renaissance similar to the one that seems to be unfolding for ADCs. Monoclonal antibodies today represent the fastest-growing segment of the biopharmaceuticals market with sales of more than US$50 million predicted for 2013, corresponding to a manufacturing scale of more than 20 tonnes. They include today’s top-selling drug adalimumab (HUMIRA®) produced by AbbVie and indicated for arthritis (market US$9 billion) and today’s most expensive drug eculizumab (Soliris®) produced by Alexion and indicated for paroxysmal nocturnal hemoglobinuria ($1.5 billion). But this is the tip of the iceberg, since the majority of drug development candidates are also antibody-related molecules, this suggests the best is yet to come. Future concepts will include biobetter versions of established monoclonal antibodies that can achieve their full potential by conjugation with toxic payloads to fight diseases that are otherwise inaccessible to therapeutic approaches. The lesson learned is that early failures are rarely, if ever, indicative of the future potential of novel therapeutic concepts.

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