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Scope for innovation in immunotherapy from the financial market's point of view

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In the vast area of immunotherapies, the development of monoclonal antibodies as a therapeutic concept emerged as a quantum leap out of the area of traditional vaccines (Köhler and Milstein).[1] In vitro selection and optimisation made it possible to elaborate a single biological molecule from the molecular plethora of an individual adaptive immune response and to utilize such a cloned antibody repeatedly in a generalized fashion whenever the therapeutic indication is given to humans.

At present, some 25 therapeutic monoclonal antibodies are currently being marketed in oncology, exceeding sales of USD20bn in 2011. A total of about 270 antibodies are currently in phase II and III clinical development. Working on the assumption of usually lower attrition rates for antibody candidates, we expect approximately 120 of these 270 antibodies to be finally approved. This poses some key questions. What level of differentiation is required so that the coming new antibody drugs can command premium pricing when members of the founding generation become generic and inexpensive? What will global demand for antibody drugs be in view of the rising buying power in emerging pharmaceutical ('pharmerging') markets, but which is still not comparable with that of developed ones? What would the next quantum leaps be that might potentially push antibody technology on to a next level by disruptive innovation? Presentations given at the Phacilitate Immunotherapy Leaders' Forum 2012 (9–11 May in Barcelona) reflected on these questions and provided some stimulating perspectives.

Looming Biosimilar Monoclonals—Challenges and Opportunities

The successful launch of a first series of monoclonal antibodies represented the first major wave of the biotech era. It saw innovative therapies being established to treat cancer and chronic inflammatory diseases. Monoclonals turned out to be the novel class of biologics which promised, a few years later, to become means for the pharmaceutical industry to steer clear of another looming 'patent cliff' related to their small-molecule drugs, one that was forecast to materialize from 2009. As a result, the P/E ratios the stock market was willing to pay for shares of pharmaceutical companies more than halved to ca.9× from above 20× before 2005. During this same period of decaying earnings quality, these traditional pharmaceutical companies began to enter the arena of biologics as a defensive move, selectively acquiring or entering into strategic partnerships with companies specialized in discovering and developing monoclonal antibodies. Their intention was to secure a share of the future market projected to be dominated by these innovative macro-molecules. Moreover, their strategic M&A decisions were also driven by the assumption that entry barriers to biologics were high as a regulatory path, particularly, for biosimilar antibodies was not imaginable and manufacturing was believed to be prohibitively costly, with the upshot that competitors with less powerful muscles would not be able to enter the field.

The halcyon days when fancifully upbeat prospects were being predicted for monoclonals started to fade soon after. This overlapped with a decline in such M&A activities as regulatory barriers for approvability of biosimilars started to fall in Europe. It became clear it would only be a matter of time before the almost USD 60 min in sales of the some 45 biologics facing patent expiry by 2015 would become vulnerable to generic substitution in the coming years. Of these sales, ca. USD 20 min are forecast to stem from some 13 monoclonal antibodies and/or FC-fusion proteins: a first one saw its patent expiring back in 2010, with others set to follow in increasing numbers from 2012. Following the dawn of monoclonals and a growing number of other biologics entering the market as well, manufacturing capacity was massively expanded from 2007, be it by originators, traditional custom manufacturing organisations (CMOs) or new players entering the field. In the area of monoclonal antibodies, market research firms and business development units of various industry players uniformly forecast a quasi-linear increase in bulk masses of monoclonal antibodies to be manufactured, starting at some 18 tonnes in 2009 to reach about 80t by 2020, to which some 10t of biosimilar antibodies would come on top in that year. As many more manufacturers started to compete for delivering these bulk quantities than had originally been active, excess capacity built up, a situation that has been becoming increasingly aggravated as (1) fermentation yields are forecast to improve potentially by approximately 5- to 10-fold over the coming

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eight years [Lonza is forecasting 10 g/L would be achievable for commercial production by 2020], and (2) novel antibody drugs on their own or particularly following conjugation with drugs or radionuclides are likely to become more potent by one to two orders of magnitude than their forerunners. In the aftermath of this manufacturing capacity accumulated in excess, competition for orders to fill the meanwhile cheap and under-exploited capacity became fierce. Eventually, custom manufacturers of biologics saw their margins decline from 2007. This can be seen for Bachem, a global leader in custom manufacturing of peptides, and was reported from 2009 by Lonza, the leading custom manufacturer of biologics coming with very high molecular weight, e.g., antibodies or other recombinant proteins. Following in the footsteps of Novartis' Sandoz, the Teva/Lonza alliance was the second to enter the arena of biosimilars as a major player, but more rivals have appeared since, e.g., Celltrion/Hospira and a series of other alliances of smaller players announcing themselves since 2010. We expect some of these alliances formed between a manufacturer and a distributor to profit from a situation where no major capital spending on capacity will be needed anymore, but where clinical R&D costs are more likely to become critical for determining returns on investment.

In such circumstances, we believe the area of biologics will undergo massive polarization. We ultimately expect to see novel drugs with disruptive technology coming at a premium price as opposed to biosimilars offered at the cost of manufacturing plus a mark-up for marketing and sales. Before we ultimately reach this end-game, we believe that the market for immunotherapeutics is going to divide into four major segments: bio-similars; bio-mimics; bio-betters; bio-innovators [i.e., the advent of antibody drug conjugates (ADCs), a topic that was one of the main threads at this year's Phacilitate Immunotherapy Leaders' Forum, in our opinion, represents the current culmination of innovation in immunotherapy]. This trend is not only the upshot of looming patent expiries for the founding generation of immunotherapeutics, but is also attributable to the major R&D boost biomedicine has enjoyed thanks to revenue streams coming from these now aging mega-blockbusters. Furthermore, emerging nations' growing wealth is leading to expanding demand for modern, possibly also cutting-edge drugs including biologics. This scenario of robust growth in emerging markets is being mirrored, to a large extent, in the Western world as pending health-care reforms, particularly in the US, look set to make such drugs affordable in future to social classes who, so far, have had no access to them.

In a next step, such a global scenario could very soon lead to further polarization along the innovation scale, and could sideline or even make redundant the numerous bio-mimics and a few bio-betters if they constitute only incremental innovation at best or do not share features of disruptive innovation as seen, in contrast, the most with ADCs or radio-conjugates or bi- and multi-specific antibody-related molecules. At best, we would see certain niches emerging over the coming years that would still be worth being filled by bio-betters, like antibodies from Xencor with engineered Fc-portions, *BITE* molecules from Micromet/Amgen or *Nanobodies* from Ablynx, to just name a few. These bio-betters would still come with features that could share aspects of disruptive innovation, as we see with ADCs today as the most extreme culmination to date, but they would no longer offer the promise of capturing those sizeable market shares they were originally conceived for. As for bio-mimics (i.e., biologics with a different molecular composition than their originators, but going for the same molecular target), these might then be considered as remnants from the early era of venture-capital-financed biotechs that had to go for established, de-risked drug targets at a time when the possibility of biosimilars arriving some day on the market was considered a fanciful and foolhardy idea.

Roche is possibly unique in the sense that the Basle group managed to integrate the sequence of innovation along the entire chain of antibody generations, in particular those targeting Her2-positive breast cancer. It entered into an alliance with the Indian Emcure to distribute Roche's *Herceptin* and *Rituxan/MabThera* under an Indian brand, pricing it at a level at least affordable for a larger part of the local population than would have been the case for these drugs at current prices. On the next higher level from actually bringing a genuinely bio-identical to the mass market, Roche secured, through collaboration with Halozyme, the development and potential launch of a subcutaneous formulation of *Herceptin* and *Rituxan/MabThera* based on the addition of hyaluronidase: this could be seen as a bio-better version of the original intravenous infusion and allowing patients to tolerate the large-volume drug much better when injected into the skin. Moving one more step up the innovation scale, Roche is developing antibodies against the traditional CD20 and EGFR *(*epidermal growth factor receptor) target, but now with antibodies that show the promise of being more effective as they carry engineered FC-portions based on the GlycArt technology. Lastly, the ADC, trastuzumab-emtansine (T-DM1), is found right at the top of the innovation ladder. It promises to combine substantially increased efficacy with a massively improved safety and tolerability profile when compared with a traditional combination of a cytotoxic and a targeted drug (e.g., docetaxel plus trastuzumab or capecitabine plus lapatinib). With such a thorough offering of distinct variants of biologics for Her2-positive breast or stomach cancers, Roche is positioned to address the global market of these cancer indications while taking into consideration the relative buying power of these patients. As such, we assume Roche is a perfectly well positioned player in the Chinese market where the incidence of Chinese patients suffering from Her2-positive stomach cancer comes close to that of patients suffering from Her2-positive breast cancer in Europe, even though only a smaller number of them are as wealthy.

Selected Examples For Potential Innovators in Antibody Technology

As for *Nanobodies*, Dr Hilde Revets, Senior Research Fellow (Ablynx), presented the technology of these single variable domain antibodies (derived from heavy-chain only antibodies of camelidae) for their straightforward manufacturing and engineering flexibility including multispecificity. Furthermore, it can capitalise through this technology on the flexibility for formatting to deliver improvements in terms of extending half-life and penetration of inflamed or tumor tissue.

Bi-specific antibodies in the format of kappa/lambda-bodies were presented by Dr Krzysztof Masternak, Head of Biology (NovImmune). This format is based on a natural, fully human immunoglobulin G (IgG) where a common heavy chain is combined with one kappa and one lambda light chain expressed from a proprietary tri-cistronic vector. The light chain diversity was mentioned as being sufficient to achieve specificity. When it comes to manufacturing, the company is currently trying to move it up from 25- to 100-L scale (1.7 g/L yield in semi-stable pools expected to increase to > 3 g/L for stable cell lines). Kappa/lambda heterodimers are found at more than 40% of total IgG in stable CHO cell lines and reported to come with good thermal and storage stability. The pharmacokinetic profile in mice is similar to that of a human monoclonal antibody (ca. 14 d).

Principles of dual variable domain (DVD) IgG antibodies were presented by Dr Tariq Ghayur, Senior Principal Scientist and Research Fellow (Abbott Laboratories). Essentially, two pairs of variable domains are combined on top of the invariable domain distal to the FC-portion. This modular architecture, permutated by the type of linkers chosen or the orientation (outer vs. inner), the pairing of the variable domains and, finally, the overall tertiary structure, opens up the possibility of blocking two or more disease mechanisms simultaneously, recruiting immune effector cells to eliminate tumor cells or other types of site-specific targeting. DVD molecules can be expressed at around 1 g/l, show an aggregation behavior comparable to other biologics and appropriate serum half-life up to 15 d.

Dr Philip Howard, Head of Targeted Therapeutics (Spirogen), reported on the development of potent pyrrolobenzodiazepine agents (PBDs) both as monotherapeutics and as part of ADCs. PBD dimers are minor groove binders of DNA while not causing significant distortion of the DNA molecule. As these molecules provoke cell-cycle arrest without inducing considerable DNA repair activity efficient enough to remove the DNA adduct, these molecules promise to become valid alternatives to traditional cytotoxics following development of resistance or if tumors were to relapse following ADC therapy based on agents blocking assembly of microtubules, like maytansine, auristatin and calicheamicin. PBD dimers cross-link DNA in a sequence-selective fashion, which blocks DNA replication and causes cell-cycle arrest at the G2/M transition, followed by apoptosis. The SG2000/SJG136 molecule is in a phase II trial for cisplatin-refractory ovarian cancer; a phase II leukemia trial is in preparation in the UK. A next generation of PBD dimers has been developed for ADCs. The free drug potency of this novel family of compounds is at least an order of magnitude higher than that of the three types of cytotoxics currently used for ADCs (maytansine, auristatin and calicheamicin). Spirogen has collaborations ongoing with Seattle Genetics and Genentech to develop such PBD-ADCs in tumor models.

Outlook

There are currently incongruent trends, interests and expectations that are being exploited by companies developing drugs as well as by custom manufacturers to satisfy the needs of patients. A multi-polarized space is emerging: divergent trajectories are originating from biologics moving toward bio-similars, bio-mimics, bio-betters and bio-innovators. The financial market is currently undecided, if not clueless, as to who will emerge as the winners in this space characterized by highly heterogeneous product offerings. On the one hand, several European countries are bogged down in the sovereign debt crisis; on the other hand, emerging markets are seeing their buying power mount as their economies become ever stronger. Financial markets are either in limbo or riveted to the sidelines, as evidenced by the low valuation levels of big pharma and biotech companies. For this to change, we believe that breakthroughs will be necessary in R&D for immunotherapies to regain some traction (as demonstrated by fast uptake of product sales following approval) or drug companies will be forced to come up on their own with innovative pharmacoecomonic proposals to regain the trust of financial markets.

On these grounds, the future of biologics will not only be influenced by a consolidating health-care sector, with bio-betters becoming marginalized and bio-mimics possibly becoming side-lined even more, but also by, literally speaking, 'molecular consolidation'. We presume that drug development will strive to combine several effector functions into a single pluri-versatile molecule. We expect such innovation will initially come in the form of the arrival of ADCs, followed by radio conjugates. The disruptive side to this innovation is that commonalities in treating certain malignancies, e.g., the need for a specifically targeted drug used together with a cytotoxic or radiotherapeutic—depending on the susceptibility of the tumor—are established as a combination in a single molecule. As we have learned, such an intramolecular combination of two therapeutic principles has proved to be worth pursuing based on the efficacy, safety and tolerability outcomes reached so far in pivotal trials for Adcetris and T-DM1. In the area of angiogenesis and inflammation, such a combinatorial approach is moving within reach with the development of bi- and multi-specific antibody-like molecules. Their advantage lies in simultaneously and selectively collecting and draining those key effector molecules out of a cocktail of ligands that are driving the progression of a given disease. When it comes to bi-specific antibodies that mediate, for instance, the recruitment of critical immune cells to the effector site, potential hurdles could still arise in trying to establish an appropriate therapeutic window between alleviating potential systemic side effects while maintaining the promising high effectiveness of targeted cell recruitment. Whatever, in the end, the various novel therapeutic approaches turn out to be, they would make it possible to set new therapeutic standards, recalibrate the health-care system for long-term outcomes to be fulfilled going forward, meet patients' needs and, ultimately, propel medicine forward.

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