Biotherapeutics News & Views

CREDOS

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FEATURE

Fully human antibodies for therapeutic application – a promise fulfilled from great expectations?

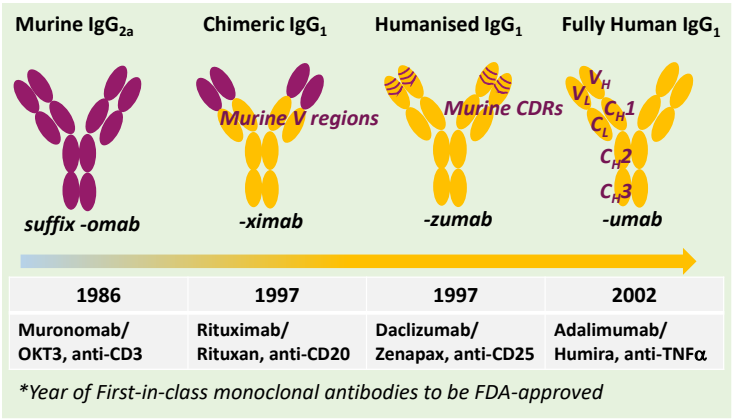
It is now 15 years since the FDA approved the first fully human monoclonal antibody (adalimumab, Humira®), heralding a new era in biotherapeutics. Fast forward to 2017, has their promise been realised? In this first issue of *Biotherapeutics News and Views*, **Emma Campbell[1] and Charles Owen[2]** review the evolution of this burgeoning field of drug discovery.

Currently over 30 monoclonal antibodies (mAbs) have been FDA approved, of which 11 are fully human and 14 are derived from humanization. With many more in clinical development, they account for an increasing percentage of the FDA's New Therapeutic Biological Products. Sales growth in the mAb sector has grown hugely from ~$39 bn in 2008 to $75 bn in 2013 and estimated to be $125 bn by 2020 (*Ecker et al MAbs. 2015; 7(1): 9–14*).

The first therapeutic mAb, muronomab/OKT3, was approved in 1986 and developed using hybridoma technology. However, as a wholly mouse protein its repeated use in patients was limited by a strong immunogenic response. Replacement of the conserved, constant (C) regions with human IgG sequences (whilst retaining the target-binding murine variable (V) regions) reflected efforts to address this problem. Since these 'chimeric' proteins are ~65-70% human, immuno-genicity is reduced thus increasing serum half-life. Furthermore, grafting of only the critical murine target-binding domains (complementarity determining regions, CDRs) onto human mAbs produced 'humanized' therapies with ~95% human sequences. However, these can be costly and time-consuming to engineer.

The development of fully human antibodies (hu mAbs) came to fruition in the 1990s through the availability of key platform technologies. Transgenic mice expressing hu mAb genes, where endogenous mouse genes were silenced, enabled hu mAbs to be generated against an immunised target by traditional hybridoma means. Generally, a high success rate moving into the clinic was observed, possibly reflecting the stability selection that *in vivo* immunisation confers. In fact, hu mAbs approved up to the end of 2010 were almost exclusively generated from these mice (adalimumab aside). However, Big Pharma's acquisition of the leading transgenics (Medarex's platforms by Bristol Myers-Squibb in 2009, whilst Amgen bought Abgenix's XenoMouse in 2005), forced companies to either go down the time-consuming path of developing their own version of these mice or alternatively focus on phage-display technologies. These *in vitro* selection systems represent vast libraries of synthetic human mAb fragments (Fab, Fv or scFv) 'displayed' by fusion to phage coat proteins. Having benefited from improvements over time (with respect to numbers, quality and diversity of repertoire), they are now able to give rise to at least 10^{12} distinct hu mAbs. This enables rapid selection of candidates with high affinity against a predetermined set of criteria (e.g. affinity, selectivity, species cross-reactivity). Unsurprising, this has now emerged as the mainstay of hu mAb identification. Of note, the expiry of two key patents in the 2000s (Boss/Cabilly), which claimed processes for recombinant mAb production, led the way for a less licence-complex field in general (although Cabilly continuation patents do not expire in US until 2018).

Today's therapeutic mAbs have significantly mitigated the risk of immunogenicity. However, some can still elicit human anti-human antibody (HAHA) responses. This can lead to altered clinical efficacy, especially where the immunogenicity arises from the CDRs. That said, several marketed hu mAbs induce detectable immune responses which, although variable between patients, is also generally tolerable (*Harding et al, MAbs. 2010; 2(3): 256–265*). A trend for more extensive engineering within the C regions can address other inherent risk factors (e.g. potential T cell epitopes, glycosylation patterns) and offers opportunities to alter IgG receptor-mediated effector functions (e.g. cell killing) depending on therapeutic requirements.



**Year of First-in-class monoclonal antibodies to be FDA-approved*

Hu mAbs have undoubtedly fulfilled their promise of being safe and efficacious therapies, rapidly generated (through phage display) to meet a desired product profile. This has enabled a raft of novel therapeutic targets to be addressed over the last few years, particularly for chronic inflammatory and oncological indications. These medicines will increasingly have their rightful place in the clinic, continuing to shape the evolution of biotherapeutics in the future.

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About Credos Consulting

The discovery and development of biological therapeutics is a specialist activity requiring specific skills and experience. CREDOS is a leading source of technical expertise and consulting services for antibody and protein-based therapeutic discovery and development.

We work with a diverse range of clients across disciplines from early discovery to late development of biological therapeutics.

Our consulting services include:-

- Strategic leadership and technical expertise across all disciplines supporting the discovery and development of biotherapeutics.*
- Distillation of development plans for a range of biotherapeutic projects (e.g. antibodies, recombinant proteins, novel-scaffolds, biosimilars) and where alternative routes of administration are needed.
- Independent experts and consultants offering tailored solutions to address bespoke project needs, including derailed projects.
- Individual consultations on an hourly/daily basis for short or longer-term projects.
- Virtual teams of experts to support and lead more complex or challenging projects including project management skills.
- Due diligence opportunities/risk assessments.
- Life cycle management of biologics portfolio.
- Training to address gaps in drug discovery knowledge within your organisation, tailored to your specific needs.

Our consultant network. CREDOS brings together a network of multidisciplinary experts, each with a track record of successful biotherapeutic drug discovery and development. With at least 10 years hands-on experience in a wide range of projects, they each bring a pre-emptive approach to identifying and providing solutions to potential hurdles. Our consultants are leading experts in their respective fields and have contributed to numerous original scientific publications and reviews, industry white papers, and Advisory panels.

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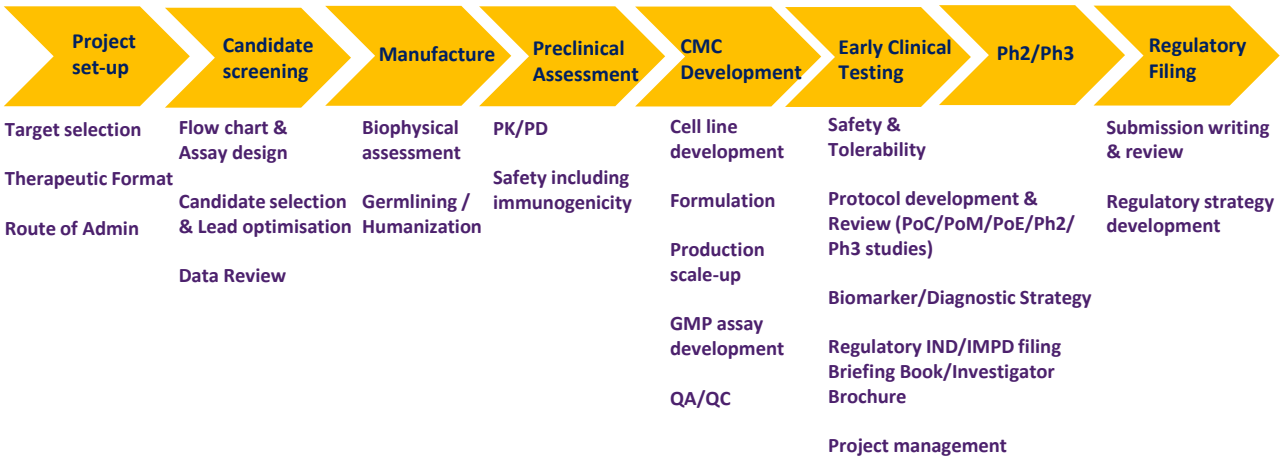
*CREDOS expertise across all disciplines supporting biotherapeutic drug discovery



Key News & Deals

- Sanofi has paid €120m ($126m) upfront and committed up to €495m more for a stake in AstraZeneca's MEDI8898 mAb against respiratory syncytial virus (RSV).
- Celgene acquired Delinia with a deal of $300m upfront and $475m in milestones down the line. Celgene boosts its inflammation and immunology pipeline with the addition of Delinia's lead program DEL106, a new IL-2 mutein/Fc fusion protein designed to preferentially upregulate regulatory T cells.
- TG Therapeutics announced positive results from a Phase 3 clinical trial, GENUINE, assessing TG-1101 (ublituximab) plus ibrutinib [AbbVie's (NYSE:ABBV) Imbruvica®] in treatment-experienced, high-risk chronic lymphocytic leukaemia (CLL) patients. The study met its primary endpoint of overall response rate (ORR) compared to ibrutinib alone. Specifically, in the treated population the ORR was 80% for TG-1101 plus ibrutinib versus 47% for ibrutinib alone.
- Seattle Genetics (NASDAQ:SGEN) will resume two Phase 1 clinical trials assessing vadastuximab talirine (VT) (SGN-CD33A) in patients with acute myeloid leukaemia (AML) after the FDA removed the clinical hold instituted in December following a comprehensive data analysis from over 300 patients treated to date. The agency took action after six patients developed liver toxicity, including four fatalities.

Diary

- *Protein & Antibody Global Congress July 10-11th London*
- *PEGS Europe November 13-17th Lisbon, Portugal*