

Raising the bar on the **BIOLOGICS** potential

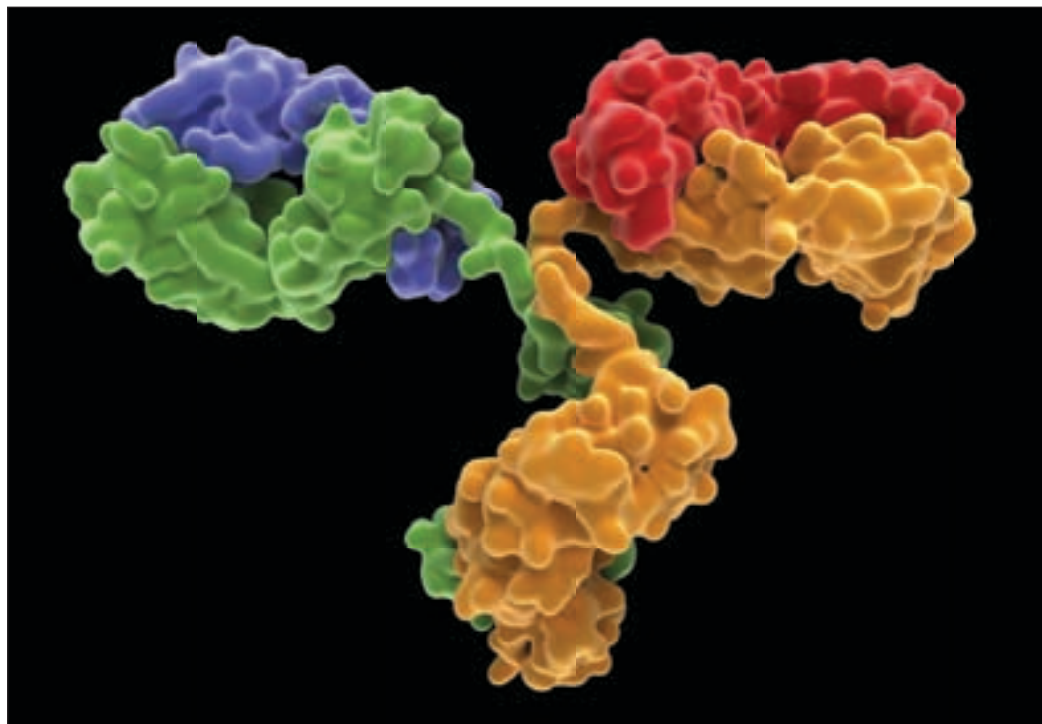
In the quest for safe, efficacious and profitable therapies, pharma research is changing. There is continued pressure to fill the drug pipeline and, at the same time, globalisation of personalised medicines is complex, expensive and requires a significant time commitment. With budgets being tight and time scarce, outsourcing has become more common. Additionally, risk, perception and regulation have limited the adoption of biologics, biosimilars and biobetters, as small molecules and synthetic drugs have been the traditional therapeutic standard. Fortunately, innovative biological therapeutic tools and technologies are now proven to be viable, highly effective, low risk and safe. The strides made to reduce therapeutic toxicity, increase patient safety and enhance efficacy, along with the increased financial ROI for biologicals, have provided the foundation and the right incentive for pharma moving toward these therapies. Several other factors, such as automation, are imperative to the success as they bring particular benefits to streamline the path towards better biologicals development, production and regulatory body approvals, including parallel development of companion diagnostics. The time is right; the technologies are ready and the rewards are sweet.

Targeted biological therapies have transformed pharmaceutical research and treatment. Of all therapies, including chemically-derived small molecules and synthetic drugs, biological drugs produced by living systems represent the largest class of drugs currently under development by the biotechnology and biopharmaceutical industries¹. Despite the fact that small molecule drugs still continue to dominate the majority of the US Food and Drug Administration (FDA)-approved therapies, advances in technology and increases in our knowledge of subcellular processes in relation to multiple disease states have exponentially increased biomarker identification and therapeutic targets for protein-based biologics.

Over the last decade, global economic decline has driven the pharmaceutical industry to re-evaluate its business model and revise discovery processes. This has created a large paradigm shift in the way pharma approaches drug discovery. New therapeutic entities (NTEs) have been on the decline, however pressure remains to fill the ever-increasing drug pipeline in order to remain competitive. Globalisation of personalised medicine is emerging as a major consideration. Pharma is now focusing on expanding scientific exploration with better targets and more efficacious therapies, while still finding ways to emphasise big profits for shareholders. Outsourcing arose as a consequence of pharma companies thinking differently about time and

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Antibody molecule. Molecular structure of a monoclonal human immunoglobulin (IgG2a). IgG antibodies are composed of two long heavy chains and two shorter light chains. This antibody adopts a T-shape: the arms of the T make up the Fab or antigen binding region, while the base part or Fc region plays a role in interacting with the immune system. Under the name of Denosumab this type of human monoclonal antibody is used for the treatment of osteoporosis, treatment-induced bone loss and bone metastases. *Image courtesy of Alfred Pasieka/ Science Photo Library*



expense allocations. By outsourcing one or more stages of the drug path, from discovery through human trials, pharma companies reap the benefit of dedicated expertise without incurring the overhead. Now, pharma companies are thinking differently about the types of therapeutics to fill their product and profit pipelines and, interestingly, a significant majority of pipelined drugs are coming from small companies, who collaborate and grant licensing agreements with large pharmaceutical companies. Some of the major pharma players with blockbuster biologicals include AbbVie, Roche, Sanofi, Janssen and Pfizer. This shift has accompanied better compound enrolment into clinical trials as well, which translates to more effective and generally safer therapies compared to traditional chemically-derived small molecules.

As history shows, there is no ‘silver bullet’ cure or single method for success. Biological medicines represent a mainstay to current therapies for a multitude of diseases. However, as they are more structurally complex in nature and hypersensitive to manufacturing conditions, they are difficult to characterise and produce. They inherently exhibit physiochemical differences, and any change in manufacturing could potentially result in a significant variation in not only the processes (ie purification methods) used for biological production, but also to differences in the product characteristics for quality, such as stability and structure². Similarly, any

change in quality also affects function, including therapeutic efficacy, immune response, patient tolerance and outcome. Thus, finding the ‘needle in the haystack’, and manufacturing biologicals while meeting the needs of globalisation requirements involves significant time and financial resources. Small companies, academics and contract research organisations (CROs) alike are now interfacing in the biologicals sector of the market where they are quickly progressing the industry by combining their technical expertise and sharing their knowledge of biology and chemistry with the clinicians in a collaborative model.

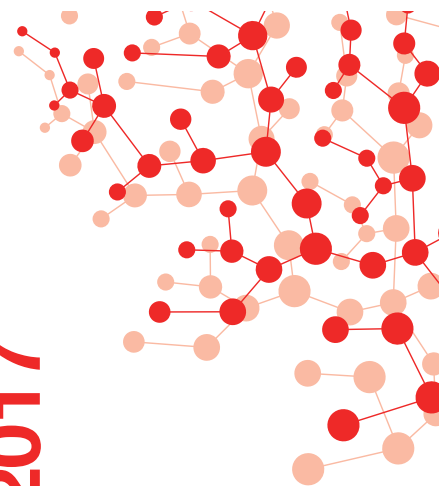
The area of monoclonal antibodies (mAbs) has significantly grown for drug discovery research and development. As biologics have considerable therapeutic specificity and benefits, some believe that these biological pharmaceuticals may be the greatest among all human medicines. Biotherapeutics have shown to have extremely high potency and target biomarkers responsible for pathology and disease, which makes it very attractive from a patient perspective, as dosing is lower than traditional therapies. This, in turn, translates to lower toxicity and reduced potential for side-effects, since the proteins do not show any mammalian pharmacological activity once metabolised into fragments by the human body. The majority of the fragments also do not display any residue signature of the active substance. Moreover, the high

potency also allows for increased profits because of higher yield manufacturing, which makes it advantageous from an environmental standpoint as well.

Renewed focus has been placed on biologics, biosimilars and biobetters. While biological therapies are much more expensive than chemically-derived compounds, they are largely considered by clinicians and payers to be worth their cost, assuming that patients can receive them and attain their desired clinical outcome. Many users taking biological therapies have previously failed conventional therapies and do not have any other therapeutic option. Biological therapies have been established in the European Union (EU) for almost two decades, while in the United States it has taken longer for these therapies to take hold. In fact, only 2% of the US population is using biological therapies, even though 40% of prescription drug spending is dedicated to biologics³. At the same time, profit margins are low and during a five-year period from 2004 to 2009, expenses exceeded sales for biologics. Where once this therapeutic avenue was limited by lack of education, abundant data, robust methods and the issues mentioned above,

regulatory compliance and specific guidance on biologics is also continuously changing, making the development and manufacturing model more complex. However, due to increased competition and demand for biologics and biosimilars, biomanufacturing and bioreactor technologies have grown dramatically in current good manufacturing practice (cGMP) manufacturing. Advancements in new processing systems and cellular systems, such as 3D and induced pluripotent stem cell (iPSC) cultures and screenings, have allowed researchers to better understand and determine specificity of the biological agents. Now, technologies and modelling tools have matured from theory to viable implementation, where industrial production has increased flexibility and reduced costs and is expected to increase by more than 300% in the next five years³.

While the general strategies of success for globalising biotherapeutics have left biologics with a short-term, patented option, pharma is continuing to focus on long-term strategies for sustainable growth and the development of biosimilars and biobetters, complementing existing products and



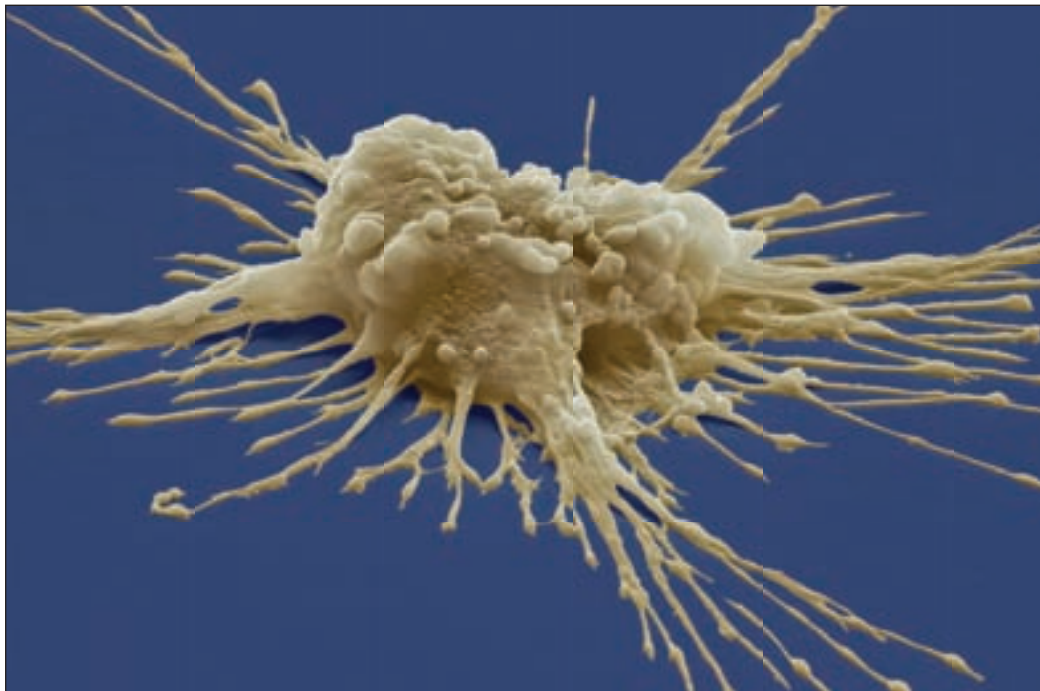
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Pluripotent stem cell. Coloured scanning electron micrograph (SEM) of a pluripotent stem cell derived from a macrophage white blood cell. Magnification: x4000 when printed at 10 centimetres wide. Image courtesy of Steve Gschmeissner/ Science Photo Library



meeting pipeline requirements. Physicians and patients are crucial to the future adoption of biological therapies as each party is vital to the discussion and global attitude. Likewise, the regulatory approval process for biologics, biosimilars and biobetters, requires significant data support from each stage of development, including physicochemical characteristics combined with a considerable functional comparison evaluation. Each biological therapy seeking approval is assessed on an individual basis, by a specific agency, which may prevent a global release if two agencies disagree on the approval of the biologic therapy under investigation. Several key recommendations for biologics have been identified to augment global development and co-ordination, which include: (a) comprehensive clinical trials to identify any differences between biological therapies (ie biologics vs biosimilars); (b) European Medical Agency (EMA), World Health Organization (WHO) and the FDA guidance on regulatory elements and approval processes guidelines to ensure the safety along the biological product therapeutic cycle; (c) continued education for healthcare professionals on basic scientific principles for the biomanufacturing processes and pharmacovigilance reports for biologicals that have been licensed for use. As biosimilars emerge into the market, the FDA is currently demanding Phase III clinical trials that can be extensive and costly in order to approve the therapy for use, while they

do not require this level of additional studies for generic drugs. As a biologic, biosimilar or biobetter is tested for the clinical trial programme, pharmacokinetic (PK) analysis, clinical efficacy and safety, as well as immunogenicity are assessed with the aim of demonstrating its effectiveness and similarity between the biologic originator and biosimilar or biobetter. By definition, a biosimilar should behave identically and show the same pharmacological activity to that of the biologic originator. However, regulatory agencies have issued new requirements and advice, suggesting that the clinical trials should be tailored to testing whether the product can be considered a biosimilar and demonstrate the similarity of its activity in order to detect any sort of important clinical differences. Thus, most companies strive for the biologic that can overcome immunogenicity, time-sensitivity and decay, as well as prove clinical effectiveness in treatment. This reduces global risk along the value chain, from manufacturers, CROs and clinicians, all the way to patients^{2,3}.

Many of the advancements for biologics, biosimilars and biobetters have been due to oncology research. Fifty biosimilars are in the pipeline for the US development programme for biosimilars, and the EU has approximately 20 biosimilars approved and effective in the market for cancer therapy^{4,5}. However, four of the main biological therapies, namely Erbitux[®] (cetuximab), Rituxan[®] (rituximab), Herceptin[®] (trastuzumab) and

Avastin® (bevacizumab), are ending their patent lifespan by 2020, which is spurring the development of several biosimilar and biobetter therapies⁵. However, unlike generics, biologicals are large and complex proteins that cannot be precisely replicated, which are in stark contrast to small-molecule drugs. Additionally, high expectations are being placed on the safety and efficacy of biosimilars and biobetters⁶. Therefore, the notion of a generic equivalent cannot be applied to biologicals.

Another technology that has revolutionised the biological drug pipeline is automation. Recent state-of-the-art systems allows for increased throughput, streamlined workflows, enhanced reproducibility and decreased variability compared to manual methods. Additionally, reagent and material costs can be reduced when miniaturising and automating 3D methods, while minimal hands-on time frees users to focus on other laboratory tasks. Finally, automation also monitors and tracks the entire process from R&D, through scale-up and on to manufacturing. The concept on an integrated automation facility has been adapted and applied to each of those areas of R&D, screening, scale-up, manufacturing and even in the clinical setting. Robust automated systems are already known in compound screening, characterisation and development to increase throughput and reduce time and variability.

What may not be readily apparent is how these automated systems can facilitate standardisation and control across the global project and throughout the project lifetimes. First, document and data control via laboratory information management systems (LIMS) is a way for automatic information transfer between all of the integrated systems in the automated process. Additionally, systems can be set up for parallel development (ie companion diagnostics) for precision medicine. Similarly, systems can be standardised as a single platform across all global sites, with pre-set workflows to reduce variability and errors, to enable easy data comparison and consolidation. Automation also allows facilities to do more with less for high throughput parallel processing of multiple disparate samples or assays at once for drug screening, development, testing and monitoring. Ultimately, by incorporating automated workflows across global projects, CROs can help their clients to bring effective products to market efficiently.

Looking ahead, production of biotherapies in human cell lines is growing. While some are still under development in multiple therapeutic areas, several of the products are currently approved for clinical use. Human expression systems are well

developed and accomplish equal efficiency to other cell lines for the production of proteins. The future holds such promise with new technological advancements and continued research investments to better optimise human cell lines for a more sophisticated product collection strategy in order to become one of the standard platforms for the production of biological therapies. Additionally, pharmacists will play a critical role in the biosimilar adoption into healthcare. While the framework has already been set, practical considerations still remain for pharmacists regarding biosimilars. These include manufacturer attributes, product labelling, interchangeability, substitution, therapeutic drug monitoring, logistics of product use and payer reimbursement⁷. Thus, by understanding the evolving regulatory guidelines, the principles of biosimilar and biobetter development will bridge the gap between the pharmacists making informed decisions regarding chemical formulary inclusion, and healthcare providers and patients understanding the practical benefits. Additionally, the data from the clinical trials will provide increased confidence in biologic originator compared to the biosimilar. Taken together, this will be good news for pharma companies which develop successful, patent obtained, biologics to reap the high revenue benefits for longer.

Biologics are the wave of the therapeutic future. From a clinical perspective, these biopharmaceuticals can offer reduced therapeutic toxicity, better tolerance to increase patient safety and enhance efficacy for improved patient outcomes. They can be targeted for personalised medicine initiatives. From a business perspective, biologics offer increased opportunities with reduced risks compared to chemically-derived small molecules. And they can lock out generic threats to improve or extend revenue over the product lifecycle. Thus, the future for drug discovery and development will continue to be a diverse industry, which is less constrained by the limitations of large pharma, but that good science is the only essential requirement. The time is right; the technologies are ready, and the rewards are sweet, and the healthcare industry is finally catching up. **DDW**

Dr Michael Mouradian received a doctorate in biochemistry at the University of Nevada Reno, followed by a postdoctoral fellowship at the Medical College of Wisconsin. With a career-spanning focus on cancer research, he currently serves as Scientific Leader for drug discovery applications at Hamilton Robotics in Reno, NV.

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