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A 21st-century approach to age-old problems: the ascension of biologics in clinical therapeutics

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Small organic molecules have been the pharmaceutical mainstay of the developed world for some time. However, in recent years, advances within the fields of genomics and proteomics have strengthened and given rise to new biologic therapies. Protein therapies, such as monoclonal antibodies and peptide drugs, have provided patients with pharmaceuticals that offer a higher level of selectivity and effectiveness that would be otherwise undeliverable within the realm of small organics. In addition to protein therapies, DNA-based therapy, such as RNA interference (RNAi) and gene therapy, have gained renewed interest within modern medicine and are potentially poised for a comeback within the biotechnology industry. As we discuss here, the advantages of such therapies continue to accumulate and have kept the biologic market strong.

Until recently, small organic molecules (SOMs) have been the cornerstone for pharmacotherapy. Although this has continued into the 21st century, advances in the fields of genomics and proteomics are beginning to bear fruit with the rise of biological drugs. Since the discovery of non-SOMs, strides have been taken to increase the knowledge, understanding, and potential applications of biologic-based therapies. This initiative was boosted with completion of the Human Genome Project in 2001 [1], which provided the basis for gathering information on molecular drug targets that could be mutated or blocked *via* nucleotide-directed therapies. In terms of protein-based therapies, both recombinant and synthetic methods have advanced greatly through the utilization of newly introduced techniques of the late 20th and early 21st centuries, including novel mass spectrometry techniques, genome-wide scanning methodologies, and the production of humanized and chimeric antibodies. However, the transition from academic to industrial research, as well as difficulties with large-scale production, have created significant hurdles in bringing the clinical benefits of biologic therapeutic research to light.

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A brief history of small molecule drugs

SOM drugs have had a continual impact on the wellbeing of society. Numerous ancient civilizations documented the medicinal use of plants or mineral extracts, and the practice of extracting active botanics for medicinal therapeutics became a common practice world-wide in several civilizations, with some of these still commonplace as pharmaceuticals. One prominent example of this is acetylsalicylic acid, more generally known as aspirin. The origins of aspirin are natural extract taken from the bark of the willow tree [2]. Although an effective antipyretic and pain reliever, in botanical form salicylic acid causes irritation to mucous membranes because of its acidity. Hence, only as recently as 1893, when Felix Hoffmann acetylated salicylic acid, did aspirin become a marketable oral drug. Aspirin is now one of the most commonly used therapies in the world for pain relief, and its original developer, Bayer, grosses nearly €400 million annually from aspirin sales alone [3]. This is an excellent example of the use of natural products to make reliable and profitable therapeutics, and provided a template for commercial drug development during the 20th and now the 21st century.

SOMs have several advantages when considering their potential for drug discovery and development, including: uncomplicated and economical synthesis and/or production, desirable pharmacokinetic characteristics, and a track record for therapeutic success.

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Hence, the transition from small molecule drug development, to biologic molecule development, has been both technically and fiscally difficult. Indeed, many major pharmaceutical companies continue to find success by focusing their research on modulating and/or combining older drugs with the intention of improving what is already known to work. This is also evident in the continued focus on 'Me Too' drugs, where introduction of the initial lead compound is rapidly followed by similar-acting molecules of the same class [e.g., Viagra® (Pfizer), Cialis® (Eli Lilly) and Levitra®/Vivanza® (Bayer Pharmaceuticals, GlaxoSmithKline, and Schering-Plough)]. By contrast, only a small percentage of the resources of a manufacturer are allocated to the discovery and development of new chemical entities (NCEs) [4]. Ease of manufacture, known effectiveness, and oral formulations are all factors contributing to the attractive business model of 'Me Too' drugs, in turn diverting attention away from novel biologics.

Despite the remarkable success of the SOM market, SOM pipelines have recently experienced several problems, including a lack of good methodologies for truly predictive novel drug design; inability to eliminate off-target effects because of selectivity rather than specificity for receptors and targets, and the high failure rate of clinical trials because of imperfect preclinical predictivity. Combined, these hurdles have contributed to a thinning of drug pipelines across all major areas of medicine. A highly competitive market for similarly acting drugs further compounds this. Given that it is now accepted that most of the 'low-hanging fruit' has been identified, and biologic-based therapies are on a continual path to progression, a paradigm shift towards the development of more specific biological entities is occurring.

Protein-based therapy

Protein biologics have been gradually positioning themselves as serious contenders in the modern drug market. Late 20th-century advancements in proteomics and immunology contributed strongly to the development of protein- and peptide-based therapies [5,6]. The selectivity of monoclonal antibodies (Mabs) has been a major positive force for bringing protein-based therapeutics to the forefront of novel drug development. This is illustrated by the US Food and Drug Administration's (FDA) list of recently approved or in-trial drugs for the years 2012 and 2011, where five out of 14 (35%) new biologic license approvals (BLAs) were Mabs, accounting for approximately 9% of all therapeutics for those years [7]. Ten years earlier, Mabs only accounted for approximately 3.5% of the drug market and 16% of BLAs [7]. Also of interest, the rise of biological drugs has been most apparent in disease states where discovery and development of SOMs have repeatedly failed to resolve the diseases, such as for cancer and Alzheimer's disease.

Monoclonal antibodies

Despite the success of early protein-based therapeutics, such as insulin or hirudin, protein-based therapies had not until recently been able to surpass SOMs in terms of sales and profitability. The bottleneck of mass production was caused by extraction techniques for proteins too difficult to synthesize. However, advances during the later 20th and 21st centuries have helped bring protein and smaller peptide-based products closer to the forefront of therapeutics in terms of commercial viability, reflected in the efforts of Frederick Sanger (peptide sequencing) [8], Pehr Edman (peptide sequencing) [9], Bruce Merrifield (peptide synthesis) [10], John Fenn (mass spectrometry) [11], Koichi Tanaka (mass spectrometry) [12], Franz Hillenkamp and Michael Karas (mass spectrometry) [13], Paul Berg (recombinant synthesis) [14], and eventually Gregory Winter, who produced the first humanized and fully human antibodies during the 1980s, leading to the development of Herceptin® (Trastuzumab; Genentech/Roche) and Avastin® (Bevacizumab; Genentech/Roche) (among others) [15].

Antibodies did not become competitors within the SOM market until the 1970s, when it was discovered that the risk of anaphylactic response (compared with the original diphtheria vaccine made in horses) could be reduced by fusing activated B cells isolated from mice with human myeloma cells that produced a single line of antibodies [16]. The fused cells were deemed hybridomas and their product Mabs. Mabs have led at the forefront of biological therapeutics because of their epitope specificity. This specificity addresses an age-old problem in drug therapeutics: namely that most organic molecules are highly selective, but seldom specific, conferring dose-dependent off-target effects. Subsequently, hundreds of Mab therapies are either in clinical trials or already in the marketplace for many conditions, although they have found most success in diseases with a strong genetic component, such as certain cancers, cystic fibrosis, and neurodegenerative diseases [17]. These drugs have had strong therapeutic success with a concurrent lack of major adverse effects and high return on investment for their developers.

Peptide drugs

Whereas antibody therapies are well established and increasingly popular, a rising category of biologic therapy is the smaller (<50 amino acids) peptide-based drugs. Peptides, similar to Mabs, provide an array of possibilities in terms of selectivity, are easily and inexpensively synthesized, and are often slightly more stable than the larger protein-based biologics, such as insulin [18]. To date, the major barrier in the development of peptide drugs has been their oral absorption [19]. Recently, novel lipid and chemical delivery systems have been developed that are making peptide-based therapeutics increasingly viable. Some examples of successful or future potential peptide drugs include: the conotoxin-derived morphine alternative Prialt®/Ziconotide/ω-conotoxin MVIIA (Jazz Pharmaceuticals) [20]; the NMDA-modulating potential antidepressant GLYX13 (Naurex Inc.) [21]; the gp41-binding HIV entry inhibitor T-20 or Enfuvirtide [22]; and (iii) the antibiotic peptide ColyMycin® (colistin/polymyxin E; JHP Pharmaceuticals) [23].

Peptide-based drugs, similar to that of their larger antibody-based cousins, are unique in that they have a high ability for selective targeting because of innate analogy to the receptors of the body. Unlike SOMs, it has been postulated that peptides have a higher potential to mimic the natural communication systems of an organism, conferring lower risk of toxicity compared with SOMs [19]. In fact, approximately 20% of peptide drugs come to market after surviving clinical trials, in comparison to only 10% for SOMs [23]. This relatively high success rate has contributed to the re-evaluation and renewed enthusiasm for peptide-based therapeutics (and other biologics) within the pharmaceutical sector [19].

Most current efforts focus on the development of orally active peptide-based drugs, with laboratories (both academic and

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