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Non-protein biologic therapeutics

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While the therapeutic biologics are dominated by therapeutic proteins, particularly monoclonal antibodies, a wide range of non-protein therapeutic biologics are rapidly gaining ground both in clinical studies and approved products. Many of these first-in-class therapies provide novel treatment modalities and address previously untreatable conditions or undruggable targets. In particular, novel treatments for rare genetic disorders and qualitatively different oncology therapeutics have been approved in the last two years. This review discusses recent advances in peptide, nucleic acid, carbohydrate, vaccine, and cell-based therapies as well as the manufacturing and commercialization challenges associated with these novel therapeutics.

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Introduction

While protein therapeutics and monoclonal antibodies, in particular, are still the dominant biological therapeutics approved and in clinical pipelines [1•,2], a wide range of novel molecular and cellular therapies may revolutionize health care in upcoming decades. Perhaps most notable are the recent US Food and Drug Administration (FDA) approvals of two chimeric antigen receptor (CAR) T-cell therapies, Kymriah (tisagenlecleucel) for pediatric and young adult patients with a form of acute lymphoblastic leukemia on August 30, 2017 (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm) and Yescarta (axicabtagene ciloleucel) to treat adult patients with diffuse large B-cell lymphoma, the most common type of non-Hodgkins lymphoma on October 18, 2017 (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm). In addition to CAR T-cell therapies, novel biologics include peptides, a wide range of nucleic acids used to both inhibit and augment biological process, carbohydrates, viruses, and cells for regenerative medicine applications. While it is impossible to group all of the novel therapeutics into a few categories, two themes do stand out, immunomodulation (which is also significant in recent and emerging antibody therapeutics) and the rise of nucleic acid therapeutics. In this review, I discuss recent non-protein biologic approvals, molecules in the preclinical and clinical pipelines, and some of the manufacturing challenges in going from clinical to production scale for widespread adoption of these therapies. Production of small molecule therapeutics by metabolic engineering, particularly natural products and antibiotics, has been reviewed extensively in a previous issue of this journal [3–8], and will not be discussed in this review.

Peptides

Peptides, in general, are considered to be chains of amino acids less than ~50 residues, though the actual definition depends on whether it is defined by a market research company, a regulatory agency, or a contract manufacturer. Peptides are most commonly chemically synthesized, though some are extracted from natural sources (see for example [9]) while others are produced by recombinant DNA technology, generally in bacteria or yeast. A large number of naturally occurring peptides are synthesized nonribosomally by nonribosomal peptide synthetases. These naturally occurring peptides (or their derivatives) include the immunosuppressant cyclosporine A, the antibiotic daptomycin, and the anticancer drug, bleomycin A2 [10].

Approximately 70 peptide therapeutics have been approved as of 2016, with an average of 2–3 new approvals per year [11]. A recently developed database, THPdb, provides a list of all US FDA approved protein and peptide therapeutics [12•]. There are approximately 140 peptides in clinical trials and more than 500 in preclinical studies [13••]. Peptides can be broadly grouped into three categories, therapeutic peptides, which exert some desired biological activity, immunogenic peptides that are used (possibly in conjunction with antigen-presenting cells) to raise an immune response against an infectious or oncologic target, and cell penetrating peptides (CPP) that are used as carriers to deliver a protein, nucleic acid, or small-molecule drug inside a cellular target, although other types of peptides can also be used as targeting molecules to deliver a drug cargo.

Peptides straddle the space between small molecules and protein therapeutics, having a much lower production cost than recombinant proteins, but providing access to

targets that are considered undruggable by small molecules such as protein–protein interactions [14•], and having greater permeability than large protein therapeutics. However, peptides also suffer from a number of limitations including chemical and physical instability and short half-lives [13••]. To increase the half-lives, a number of modifications are often made to the peptides including sequence modification to reduce the risk of proteolysis, PEGylation and cyclization, including the formation of bicylic peptides [14•].

Therapeutic peptides

Metabolic diseases such as diabetes and obesity and oncology are the most common targets for therapeutic peptides. In particular, glucagon-like peptide-1 agonists have been widely investigated as potential therapeutics [13••,15]. However, peptides are currently under investigation as potential therapies to treat many other conditions including pain [16], neurodegenerative diseases [17,18], and allergic disorders [19]. Of particular note is the use of peptides as antimicrobial agents [20]. With the rise in antibiotic-resistant bacteria, new classes of therapeutics will be necessary to treat infectious disease. Antimicrobial peptides (AMPs) directly kill bacteria, but also have immunomodulatory activity to boost host cell defenses including stimulation of chemotaxis, promotion of immune cell differentiation, and initiation of adaptive immunity [21••]. Moreover, it is expected that widespread resistance to AMPs will not occur as AMPs address multiple low affinity targets rather than the single high affinity target addressed by traditional antibiotics.

Immunogenic peptides

Recent clinical studies have demonstrated the role that the immune system plays in tumor suppression and mechanisms for tumor evasion of these immune defenses [22•]. To boost immune recognition, immunization with tumor specific antigens (TSAs) has been proposed, either alone or in conjunction with dendritic cells, the most potent of the antigen-presenting cells (APCs). Recently, a large number of TSAs have been identified, including antigens deriving from somatic mutations in oncogenes or tumor suppressor genes (e.g. RAS, BCR/ABL, BRCA1,2, HER2,3 and P53). In addition to oncologic vaccines, peptides are currently under investigation as vaccines for infectious diseases, including HIV and influenza [23]. Potential advantages over whole-organism vaccines include reduced side effects, greater stability and better manufacturing control. However, reduced immunogenicity of peptides compared with whole organisms necessitates careful design of delivery mechanisms and adjuvants to achieve the desired immune response.

Cell-penetrating peptides

CPPs were first identified as part of cell-penetrating proteins in the late 1980s and 1990s [24••] from HIV (trans-activator of transcription, TAT) or *Drosophila melanogaster* (homeodomain of Antennapedia). Further studies defined the specific peptides within these proteins that were necessary for penetration. Subsequently, hundreds of peptides with translocation capacities were identified. CPPs typically contain 5–30 amino acids and can pass through tissue and cell membranes via energy-dependent or energy-independent mechanisms with no interactions with specific receptors. Cell penetrating peptides can be used to bring in a wide range of cargoes including proteins, peptides, DNA, siRNA, and small-molecule drugs, either through covalent conjugation or formation of non-covalent complexes [25,26]. The mechanisms by which CCPs translocate vary widely and have been recently reviewed by Guidotti *et al.* [24••] A wide range of clinical trials (many ongoing) have employed CCPs for a variety of indications including hearing loss, cancer, ischemia and pain management, but to date, none have been approved. A more recent application is the use of CPPs coupled with site-specific nucleases (e.g. zinc finger nucleases, CRISPR) as a mechanism for gene editing for gene therapy applications [26], potentially addressing one of the critical challenges in gene therapy.

Nucleic acids

Nucleic acid therapies have been in the offing for nearly 40 years, with the promises of antisense oligonucleotides to inhibit aberrant biological processes and gene therapy to cure genetic defects. Nucleic acid-based therapeutics include antisense oligonucleotides, interfering double-stranded RNA (RNAi) and aptamers, generally used to inhibit expression, and nucleic acid vaccines and gene replacement therapy, in which the nucleic acid is used as a template for gene expression [27•]. In 2016, these drugs appeared poised to finally come into their own with the approval of two first-in-class antisense RNA drugs, Sarepta Therapeutics' Exondys 51 (eteplirsen) to treat Duchenne muscular dystrophy and Biogen/Ionis's Spinraza (nusinersen) to treat spinal muscular atrophy, both rare genetic disorders [1]. Currently 18 companies are developing antisense therapies with ~130 clinical trials; 16 companies are developing RNAi therapies with 28 clinical trials, and 7 are developing aptamer-based therapies with 10 clinical trials ongoing [28]. Nucleic acids therapeutics have suffered from two major limitations throughout their development, stability and delivery. Nucleic acids and RNA, in particular, are subject to nuclease digestion, which initially necessitated large quantities of nucleic acids to be delivered to have a pharmacological effect. Critical modifications, including changing from a phosphodiester backbone to a phosphorothioate (PS) backbone (Figure 1a) combined with sugar (primarily at the 2′ site, Figure 1b) and nucleotide modifications have improved stability, increased trafficking by reducing the net charge, and significantly increased affinity of oligonucleotides for their targets, increasing the utility of these molecules [29,30••,31]. Alternative modifications substitute a neutral phosphorodiamidate morpholino

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