The majority of vertebrate hormones, as well as growth factors and several neurotransmitters, are short peptides, typically having fewer than 100 amino acids [Hutchinson et al., 2017]. Scores of peptide hormones and their cellular receptors are implicated in nearly all aspects of human physiology and pathophysiology, thus making them drug candidates. Presently, only a few peptides are used as therapeutics in their natural form, most notably insulin and erythropoietin, while others are in clinical trials, for example, nasal oxytocin as treatment for autism spectrum disorders [Parker et al., 2017]. However, similarly to all peptides, peptide hormones are not suitable for oral administration, being rapidly degraded by the gastrointestinal system, which necessitates their administration by intramuscular injection, or as nasal sprays, for therapeutic use, limiting their utility as therapeutics [Varamini and Toth, 2016]. Peptide mimetics, non-peptide compounds that mimic or modulate the action of natural peptides, have the potential to circumvent this barrier and be suitable for oral administration. Notable successful examples for such peptide mimetic drugs and drug candidates are briefly discussed in this editorial.

Presently, the share of peptide mimetics among Food and Drug Administration (FDA)-approved drugs is rather small compared with major drug classes such as therapeutics targeting enzymes, G-protein coupled receptors (GPCRs), or growth-factor receptors [Dimitrov, 2012]. The current theme issue of Drug Development Research includes several reviews on novel approaches for designing therapeutically viable peptide mimetics suitable for oral administration. Readers are referred to the comprehensive review by Marshall and Ballante in this issue, discussing novel strategies for designing type III peptide mimetics, that is, peptide mimetics having unique templates that position the necessary functional epitopes for serving as topographical mimetics [Marshall and Ballante, 2017]. In another research overview in this issue, Justin Holub discusses general aspects encountered during the development of miniature proteins as therapeutics, in particular, including epitopes that facilitate endosomal escape for improving bioavailability [Holub, 2017]. Further reviews in this issue discuss specific examples for peptide mimetic drug development.

NEWLY APPROVED PEPTIDE MIMETICS

Out of 15 New Molecular Entity (NME) applications approved by the FDA as therapeutics during fiscal year 2016 [CDER New Molecular Entity (NME) and Original Biologic Approvals Calendar Year, 2016], only a single drug, Venetoclax (Venclexta), can be viewed as a true peptidomimetic. Venetoclax is an orally bioavailable Bcl-2 homology domain 3 (BH3) mimic that acts as a Bcl-2 inhibitor with an indication for treating chronic lymphocytic leukemia (CLL) patients that relapsed or were refractory to previous treatments [Roberts et al., 2017]. Another 2016 FDA approval is for a modified peptide, Lixisenatide (Adlyxin). However, while based on a naturally occurring peptide, the latter is a modified peptide acting as a glucagon-like peptide-1 (GLP-1) receptor agonist intended for treating type-2 diabetes. As such, it is an injectable drug [McCarty et al., 2017]. Further GLP-1 agonists are in various stages of development, as reviewed in this issue [McBrayer and Tal-Gan, 2017].

FORTHCOMING PEPTIDE MIMETICS

In coming years, further peptide mimetics currently undergoing preclinical studies may join the short list of FDA-approved peptide mimetics. A few examples
are described below for illustrating the diverse potential of peptide mimetics as oral therapeutics.

**Defensin Mimetics**

Defensins are short peptides constituting part of the innate immune response, present in oral mucosa and the enteric system and functioning as host defense peptides against bacteria, as well as some fungi and viruses. Defensins therefore play key role in managing the human microbiome in health and disease [Sankaran-Walters et al., 2017]. Defensin mimetics are thus gaining interest as antibiotics. For example, a synthetic lipid defensin mimetic was protective in an in vivo sepsis animal model [Varney et al., 2013]. Antifungal defensin mimetics were proposed for treating oral candidiasis [Ryan et al., 2014]. Considering the escalating global worries surrounding antibiotic resistance [Nathan and Cars, 2014; Crofts et al., 2017], defensin mimetics are attractive drug candidates.

**Formyl Peptide Receptor Ligands**

Formyl peptide receptors (FPRs) are GPCRs encoded in humans by three distinct genes that play key role in inflammatory processes. FPRs are typically activated by N-formyl oligopeptides released by tissue bacteria, and recruit circulating blood leukocytes. Non-peptide FPR ligands (both agonists and antagonists) are therefore of interest as therapeutics for boosting the innate immunity for host defense against microbial pathogens, or for inhibiting dysregulated immune responses, such as, during stroke-mediated ischemia/reperfusion brain injury [Stepniewski and Filipek, 2015]. For example, synthetic FPR antagonists were shown to reduce ischemia/reperfusion injury in mouse stroke model [Smith et al., 2005]. Recently, several phenylacetamido-substituted heterocycles were described as potent FPR agonists [Vergelli et al., 2017].

**Brain-Derived Neurotrophic Factor Mimetics**

A small peptide mimetic of brain-derived neurotrophic factor (BDNF), cyclo-dPAKKR, was shown to promote peripheral myelination and proposed as therapeutic for multiple sclerosis and other peripheral demyelinating diseases [Xiao et al., 2013]. Another BDNF-mimetic, tricyclic dimeric peptide 6 (TDP6), was proposed for the same purpose [Wong et al., 2014]. However, these BDNF mimetics are unlikely to have good oral bioavailability due to their peptide nature. BDNF mimetics with improved oral bioavailability appear to have a potential as neuropsychiatric drugs for conditions associated with reduced BDNF levels, in particular for major depressive disorder [Allen et al., 2015; Jiang et al., 2017; Zhou et al., 2017].

**Apolipoprotein A-I Mimetics**

Apolipoprotein A-I (apoA-I) mimetics are gaining interest as potential LDL-cholesterol lowering drugs, however, a key issue for their development remains their restricted bioavailability [Rosenbaum et al., 2015]. Nanolipid particles containing multivalent peptide mimetics of apolipoprotein A-I reduced plasma LDL-cholesterol levels by up to 40% in mice following chronic oral administration and were proposed as atherosclerosis therapeutics [Leman et al., 2014; Zhao et al., 2014]. However, a recent report casts doubts on lowering LDL-cholesterol mode of action by apoA-I mimetics, reporting a discordance between the selective in vitro and in vivo functional properties of seven apoA-I mimetic peptides [Ditiatkovski et al., 2017].

**SMALL PROTEIN MIMETICS?**

Below three proteins are described that deserve consideration for the development of future peptide mimetics owing to their documented biological activities. While these examples concern proteins rather than peptides, the therapeutic potential of proteins may be retained by short peptides derived from crucial protein epitopes and knowledge on tertiary protein structure [Shoji-Kawata et al., 2013; Yannakakis et al., 2017]. Hence, once short peptides that maintain the biological activity of such proteins are identified, designing and testing synthetic peptide mimetics is a logical subsequent step for obtaining satisfactory oral bioavailability.

**Tissue Inhibitor of Metalloproteinases 2**

A recent study has received extensive media coverage as the long-sought “rejuvenating drug” [Castellano et al., 2017]. Using a mouse model of senescence the authors showed that tissue inhibitor of metalloproteinases 2 (TIMP2), a blood-borne metalloproteinase inhibitor protein enriched in human umbilical cord plasma and until the present studied mostly for its documented anti-metastatic potency in cancer, is responsible for the increased synaptic plasticity and improved cognition mediated in aged mice by human umbilical cord plasma. Moreover, these authors showed that recombinant TIMP2 entered the mouse brain and produced cognitive enhancement following intravenous injection [Castellano et al., 2017]. As TIMP2 is known to possess anti-angiogenic activity, and low TIMP2 levels are correlated with tumor
metastasis [Yang et al., 2015], TIMP2 mimetics have a potential as both cancer and neurodegenerative disease therapeutics. While orally active TIMP2 mimetics remain to be reported, matrix metalloproteinase (MMP) inhibitors have since long gained attention as tentative therapeutics [Levy et al., 1998; Liu and Khalil, 2017]. Until small TIMP2 mimetics are available, studies should focus on examining currently known synthetic MMP inhibitors for finding those exhibiting similar pharmacological profiles to TIMP2 while retaining good oral bioavailability; such compounds seem to have exceptional market potential.

**Insulin-like Growth Factor 1 and IGF Binding Protein 2**

Low endogenous availability or resistance to the action of insulin-like growth factor 1 (IGF1), a key growth factor affecting virtually all human tissues, have been the subject of numerous studies. IGF1 has been implicated in the pathophysiology of bipolar disorder, as well as in the efficacy of lithium as first-line bipolar disorder therapeutic [Squassina et al., 2013; Milanesi et al., 2015; da Silva et al., 2017]. The main brain-expressed protein carrier of IGF1 is IGF binding protein 2 (IGFBP2), known to enhance the action of IGF1, for which reduced levels were recently reported in bipolar disorder patients compared with healthy controls as well as with major depressive disorder patients [Milanesi et al., 2017]. While further studies are required for elucidating the roles of IGF1 and IGFBP2 in bipolar disorder pathophysiology, IGF1 and/or IGFBP2 mimetics, if capable of entering the brain, may have a potential as bipolar disorder therapeutics. Low bioavailability and resistance to IGF1 were also suggested to be involved in Alzheimer’s disease [Trueba-Sáiz et al., 2013; Liu et al., 2016; Trueba-Sáiz et al., 2017]. Thus, IGF1 and/or IGFBP2 mimetics may also have a potential as early stage Alzheimer’s therapeutics.

**CONCLUSION**

The majority of marketed drugs target cellular, microbial, or viral proteins. In human cells, each protein is part of a large interactome protein network [Muraticioglu et al., 2015; Spurrell et al., 2016]. Some members of such protein networks are short secreted peptides, or have short epitopes that may be mimicked by peptides, so that they can serve as template for designing peptide mimetics. The scientific literature includes many examples for peptide mimetics, while only a handful have made it to the list of FDA-approved drugs. Given the central role of peptides in endocrinology and intercellular interactions, including between host and pathogens, an untapped potential exists for the development of novel peptide mimetic drugs. Better knowledge on protein tertiary structure and on functional protein epitopes taking part in protein-protein interactions will be crucial for discovering new peptide mimetics. High-resolution X-ray crystallography studies and powerful protein-folding prediction software tools will be essential for achieving this goal. This knowledge is not around the corner; huge research investments will be required. The author’s personal view is that, as a fast-forward optimistic projection, peptide mimetics could become among the best therapeutics for future generations.

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