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Therapeutic Peptides: Regulatory Challenges and Future Direction

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Introduction

Peptide therapeutics have continued to be an innovative strategy for developing biopharmaceutical pipelines and diagnostics tools. Peptide therapeutic is still an untapped innovative area because of the challenges associated with lack of oral bioavailability, cell permeability; and lack of regulatory guidance for manufacturing. This article covers (a) regulatory challenges in peptide-based drug discovery and development, and (b) future direction for peptide-based drugs.

Discussion

Therapeutic peptides are endogenous ligands that are efficacious and safe. Because of the safety and efficacy advantage, the attrition rate of peptides over small molecules are exceptionally low. Twenty-five percent of peptide-based clinical candidate that enters the clinical trial make it to market. This is more than two times higher than small molecules because of its unpredictable safety profile. The Food and Drug Administration (FDA) has approved more than one hundred peptides including peptidomimetics based drugs for marketing. The commercial successes of peptide therapeutics have been seen in metabolic diseases and for peptide drugs acting on extracellular targets such as GPCR.

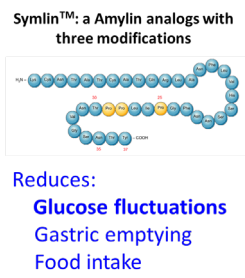

Fig. 1. Amylin is a 37 amino acid peptide co-secreted with Insulin.

Approximately thirty plus peptides are in Phase 2 and Phase 3 clinical studies; and those have commercially potential for sale for billions of dollars. Even with the successful Phase 2 and Phase 3 clinical studies results, the regulatory approval process for peptides is not straight forward as we may think. For example, regulatory process for approval of SymlinPen® (Figure 1) for treatment of Type I and Type 2 diabetes took almost 3-5 years. After the first review of Symlin New Drug Application (NDA), FDA responded as 'Not Approved" for concern that it may cause hypoglycemia when taken with Insulin. Amylin pharmaceutical addressed the regulatory concern by careful statistical analysis of the data and resubmitted the application. The FDA responded as "Approvable" and asked to provide the dose titration in combination with Insulin at multiple time points. Amylin pahrmaceuticals performed the studies and resubmitted the application, and this time (in 2005) FDA approved the SymylinPen™ for both Type 1 and Type 2 diabetic patients.

Persistence, hard work, and belief in science ultimately paid off

In recent years, the FDA has denied the approval of drugs because of Manufacturing issues. The FDA and the EMA are paying close attention to Chemistry, Manufacturing and Control (CMC). The FDA recently provided CMC guidance that covers five peptide drug products: glucagon, liraglutide,

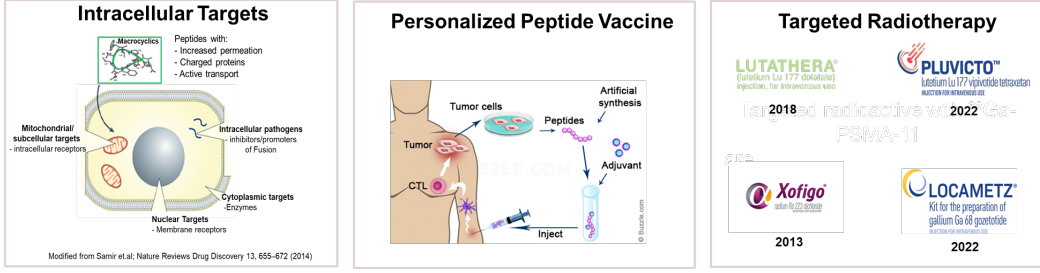

Fig 2. Foresight for therapeutic peptide for oncology.

nesiritide, teriparatide, and teduglutide. The regulators recommend identifying and characterizing all impurities present at levels between 0.10% and 0.5%, including their potential immunogenicity. In-silico and cell-based immunogenicity assessments are good enough. The ICH guideline suggests the process-related impurities or product-related impurities must be differentiated. The development of accelerated stability indicating analytical methods are critical to analyze impurity profiling. In addition, regulators require to evaluate extractable and leachable impurities and sterility testing for the Container Closure system. A total quality system management is required.

The assessment of quality risk in manufacturing is required, early in the process development, by Quality by Design (QbD) and Failure Modes and Effects Analysis (FMEA) for the smooth approval of the peptide-based drug [1].

There are two key areas in peptide therapeutics that need immediate attention to make a significant impact on the commercial scale. One is the development of technology for alternative peptide drug delivery routes, and the other is discovery and development focused on the oncology therapeutic areas.

Delivery Routes for Peptides: Peptides are being delivered via the invasive parenteral route; however, several non-invasive delivery routes, such as nasal, buccal, transdermal, and pulmonary, have been investigated, particularly for chronically administered drugs [2]. Peptide drug molecules are not delivered orally because of its poor aqueous solubility and poor membrane permeability in the gastrointestinal (G.I.) tract, leading to unacceptably low oral bioavailability. The oral route is a better option because of its patient-friendly delivery and increase in the drug's therapeutic value. However, a few peptide drugs are approved for oral delivery, but they are intended for the G.I. restricted therapeutic targets, e.g., Linaclotide (Linzess®). Several biotech and large pharma are investing in developing the technologies for oral delivery of peptides, and most recently Semaglutide, RYBELSUS®) for lowered blood sugar and body weight. Implantable technologies can facilitate the delivery of a controlled drug concentration to a patient by controlling the rate of drug release. Considerable progress has been made toward developing various implantable technologies to deliver drugs via intracranial, intrathecal, or intravaginal routes [3]. However, the most promising developments have been in intraocular and subcutaneous implants. These implantable technologies may contain therapeutic agents in nanomaterial formulations of non-bioabsorbable and biodegradable polymers.

Therapeutic Peptides for Oncology: On the discovery front, understanding and exploration of intracellular targets are critical for the next wave of peptide therapeutics for cancer treatment. For example, modulation of protein-protein interaction by peptides MDM2/p53 for HCV, cytoplasmic targets such as kinases involved in pathways like JNK1 for inflammation, nuclear targets receptors such as transcription factors, AP-1, mitochondrial and subcellular targets, heat shock proteins. Macrocyclic peptides of 10-15 aa possess cell-penetrating properties and could be a good modality to achieve the goals. Target specificity for these peptides is still a challenge though.

Personalized neoantigen vaccines came into play very recently; after diagnosis, biopsies are done on the patient's tumor on both cancerous and normal tissues. A set of most immunogenic antigen sequences are then identified using differential bioinformatics tools and AI approaches. These peptides are then manufactured and formulated with immunoadjuvant before administering to the patient, and immune responses are monitored. GAPVAC, a consortium of eight organizations in Europe, is developing GAPVC-101, a mixture of four peptides for newly diagnosed patients with glioblastoma.

Targeted Radiopharmaceuticals drugs raise hopes for treating cancer [4]. In 2018, Lutathera®, a radioactive ^{177}Lu-DOTATATE was approved for neuroendocrine tumor treatment. It is a Somatostatin-targeted theragnostic. In 2022, the FDA approved, Pluvicto^{TM}, ^{177}Lu PSMA-617 to treat metastatic castration-resistant prostate cancer. LOCAMETZ®, Ga 68 Gozetotide, a kit for preparing PET Imaging in PSMA, Prostate Cancer. The FDA designates Pluvicto as brake through therapy. Both these drugs were conjugated to the beta-emitting radioisotope Lutetium-177. Bayer received approval for Xofigo® (radium Ra 223 dichloride) in 2013 as a new treatment for Castration-Resistant Prostate Cancer with Bone Metastases. Xofigo is not a radioconjugate but a straight ^{223}Radium dichloride for prostate cancer. ^{223}Ra – Radium dichloride is a calcium mimic, localizes in areas of bone mineralization (i.e., bone metastases). Xofigo is an alpha-emitting radiopharmaceuticals.

It is believed alpha-targeted radiopharmaceuticals can provide a powerful new treatment option for all stages of solid tumor cancers, including breast, lung, liver, ovarian, bladder, and colorectal

cancer. Alpha particle therapy includes a highly localized large particle, He nuclei and tissue exposure are very narrow100 μm range and covers only a 2-10 cell radius thus killing only tumor cells and irreversibly brakes both double-strand DNA. In clinical use, patients are shielded by just a paper, with limited risk of exposure to family and doctors. On the other hand, current beta particle therapy, beta particle radiates energy to ~1 cm radius, with Linear Energy Transfer LET of 0.2keV/mm, covering 10-1200 cells thus killing healthy cells and immune cells in addition to tumor cells and brakes only a single strand of the DNA. This requires extensive lead shielding and patient sequestration. Often requires an in-patient stay in the hospital for several days (Figure 2).

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