Modern Chemistry & Applications
ISSN: 2329-6798

Sun, Mod Chem appl 2013, 1:1
DOI: 10.4172/2329-6798.1000e103

Editorial Open Access

Peptide-Based Drug Development

Lichun Sun*

Department of Medicine, Peptide Research Laboratories, Tulane Health Sciences Center, New Orleans, LA 70112-2699, USA

Editorial

With the number of small molecule-based drug candidates in clinical trials and approved drugs for the market decreasing, scientists from the pharmaceutical industry and academia are giving more attention to peptides or other bioactive drugs. Peptide drugs, especially the short synthetic and long-acting ones, are quickly increasing in the global market while advances in such fields as chemical synthesis and peptide formulation having been made in recent decades.

Significance and the Increasing Market

Peptides are involved in a variety of physiological and pathological processes and play very important roles in modulating various cell functions. Peptide drugs have been successfully applied in treating certain human diseases. For instance, Goserelin (a synthetic gonadotropin-releasing hormone analog, marketed as Zoladex) is applied to treating breast cancer and prostate cancer. Glatiramer acetate (a synthetic peptide with four amino acids, Copaxone) is used for multiple sclerosis and Exenatide (a synthetic glucagon-like peptide-1 analog, Byetta) for type 2 diabetes. The synthetic somatostatin analogs such as octreotide (Sandostatin) and lanreotide (Somatuline) are the most common drugs used in treating neuroendocrine tumors while conventional chemotherapy and radiotherapy have very limited effects. In the commercial market, there is no lack of blockbuster peptide drugs generating more than $1 billion in annual sales, such as Lupron, Zoladex, Copaxone and Sandostatin [1]. Copaxone revenues from the Teva 2012 Reports (Third Quarter) [http://www.tevapharm.com] were even estimated to be around $4 billion in 2012. Unfortunatly, the annual sales of all the approved peptide drugs are only about 20 billion US dollars. This is just a small amount (approximately 2%) of the huge drug market. However, the approval rate for peptide drugs may be twice as high as that for small molecules [2]. The peptide drug market is also growing twice as fast in the worldwide drug market [3]. Currently, there are around 60-70 approved peptide drugs in the global market, with 100-200 more in clinical trials, 400-600 more in pre-clinical studies [2,3] and possibly hundreds to thousands more on the laboratory bench. With the barriers having been broken, it will be open season for peptide drugs and their hunters for the future.

Advantages and Disadvantages

Compared to the small molecules that dominate the worldwide drug market, with advantages such as small size, low cost and low price, oral availability, ready synthesis, membrane-penetrating ability and stability, peptides are at a disadvantage [2-6]. However, peptides are still small compared to large molecules such as proteins and antibodies. Due to this smaller size, peptides can be readily synthesized, optimized, evaluated and do not cause serious immune responses. Peptides are potent and could be metabolically cleaved and rapidly cleared from body. Peptides do not accumulate in specific organs and this can minimize their toxic side effects. In contrast, small molecules are not selective and can accumulate in specific organs such as the kidney and liver, resulting in severe toxic side effects. To be more stable, peptides could be modified or made as a cyclic peptide pro-drug. The cost of making peptides is dropping as production scale and efficiency is rising with progress in synthesizer, synthesis- and purification strategies etc. being made [2,6,7]. Almost half of the marketed drugs target the G protein-coupled receptors (GPCRs) [8], many of which have natural peptide ligands. Thus, these peptide ligands could be modified to be more stable and long-acting analogs with high binding affinity and high receptor subtype-specific selectivity. For instance, natural somatostatin targets all five somatostatin receptor (SSTR) subtypes, but the synthetic analogs octreotide and lanreotide are SSTR2-preferential, while the analog L797,591 is SSTR1-preferential and BIM23268 is SSTR5-preferential [9]. The real darkside that peptides have is poor oral availability, mainly due to the fact that peptides can be readily degraded and pass poorly through the intestinal mucosa [2,5,10]. However, there are some optional administration routes such as injection delivery, nasal delivery, sublingual and pulmonary delivery. Also, for good or bad, peptides are unable to cross the blood-brain barrier [6].

Challenges

There are still some challenges for us to be able to bring a peptide to commercial drug status and to expand the peptide drug market despite more peptides that have been sucessfully brought to market. The oral drug administration route is the most convenient and comfortable way, but is the most difficult challenge for peptide drugs. The poor oral bioavailability limits the commercial applications of these drugs. Peptides are easily degraded and have difficultly passing through the intestinal mucosa. Gastric acid in the stomach and peptidases in the blood could easily chop peptides into single amino acids while poor permeability blocks intestinal absorption [5]. Also, different administration routes could affect the peptides' pharmacokinetics and biological activity [11]. Compared to cheap and small molecules, the production cost and the market price are still high for commercializing a peptide drug besides costing more to synthesize longer peptides than shorter ones. There are some other challenges, like the stability of recombinant peptides (recombinant peptides may be reasily digested by enzymes in body), peptide antigenicity (peptide antigenicity may result in immune responses) and production scales (different production scales may require a completely different technology for synthesis and purification). We also need to consider the challenges in searching and identifying novel peptides and the associated technologies. All these show us there is a long way to go before peptides fit well with commercial requirements.

Perspectives

Despite the many challenges we face, the advances made in the fields of peptide drug development give us more confidence and more willingness to develope novel peptide-based therapeutics. The new phage display technology now is used for peptide discovery. This is completely different from the traditional way and may open a new

***Corresponding author:** Lichun Sun, Department of Medicine, Peptide Research Laboratories, Tulane Health Sciences Center, New Orleans, LA 70112-2699, USA, Tel: 504-988-1179; Fax: 504-988-3586; E-mail: lsun@tulane.edu

Received December 13, 2012; **Accepted** December 17, 2012; **Published** December 19, 2012

Citation: Sun L (2013) Peptide-Based Drug Development. Mod Chem appl 1:e103. doi:10.4172/2329-6798.1000e103

window for finding completely new peptide drugs. Also, bioinformatics and systematic biological approaches help us search for potential peptide drug candidates based on the knowledge and data we have. The development of a new generation of peptide-based vaccines may provide a whole new market [2,12]. The progress achieved with new synthesizer, synthetic and purifying strategies will continue to improve the production scales with high peptide quality and directly result in a cutoff of the manufacturing cost. The production scales are directly associated with the commercial cost. For instance, the cost per gram (g) may drop down 10 times when the production scale increases from 300-500 g to 50-100 kg [7]. People from industry are considering further increasing production scales up to multi-100 kgs or over [2]. Following that, the cost will steadly go down to a new low. On the other hand, certain peptides have been developed as receptor-specifc drug delivery carriers and are broadly used to deliver various bioactive compounds to target sites. This strategy could significantly increase drug internalization and efficacy [13-15]. Due to low permeability being the major barrier for oral peptide delivery, the progress in this field will promise us a bright future. Nanoparticles as a promising drug delivery carrier have been relied on and applied to conjugation with peptides to increase peptide uptaken and efficacy and to overcome the limits of the peptides [16,17]. Meanwhile, a family of cell-penetrating peptides (CPPs) such as penetratin, M918 and TP10 [5,18] have been found able to pass through cell membrane with high efficiency and less membrane damage [5,18]. This characteristic could be used to deliver peptide drugs through cell membranes to overcome poor oral peptide bioavailability [5].

Due to the severe toxic side effects of small molecules, the advances in receptor-targeted therapeutics in which peptides and mAbs are used as receptor-specific drug delivery carriers is catching scientists' interests. Many peptides target the family of GPCRs, some of which are aberrantly expressed in some specific diseased cells/tissues [6]. These peptides, especially the chemically modified and long-acting peptide analogs, have been used as drug delivery carriers to couple the small molecule drugs at the N- or C-terminus to form new drug-peptide conjugates. The new conjugates could bind to specific GPCR members on the cell surface and deliver drugs into target cells. More examples come from cancer treatments due to many cancer cells highly expressing certain GPCRs, such as SSTR2 and GRPR. These receptor-specific conjugates such as AN215, AN238 and JF-10-81 display much more potent and specific anti-tumor efficacy while reducing toxic side effects and multi-drug resistance [9,13,14]. This kind of receptor-targeted therapeutics has been named as a new generation approach. These synthetic peptides, used as delivery carriers, also have been widely used to couple with siRNAs, oligoDNAs, oligoPNAs, other peptides, to deliver them into target cells, and thus increase their internalization and efficacy [15,19-21].

With the increase of approved peptide-based drugs and the advance in peptide-associated technologies, we believe that peptide-based drug therapeutics will become more significant and will open up more commercial opportunities for treating human diseases. Especially, this promising future could be enhanced once one day the challenge of poor oral delivery is broken through.

References

1. Reichert J (2010) Development Trends for Peptide Therapeutics (2010 Report Summary). Peptide Therapeutics Foundation: 1-10.
2. Lax R (2010) The Future of Peptide Development in the Pharmaceutical Industry. PharManufacturing: The International Peptide Review: 10-15.
3. Bellmann-Sickert K, Beck-Sickinger AG (2010) Peptide drugs to target G protein-coupled receptors. Trends Pharmacol Sci 31: 434-441.
4. Edwards CM, Cohen MA, Bloom SR (1999) Peptides as drugs. QJM 92: 1-4.
5. Khafagy el-S, Morishita M (2012) Oral biodrug delivery using cell-penetrating peptide. Adv Drug Deliv Rev 64: 531-539.
6. Reubi JC (2003) Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 24: 389-427.
7. Marx V (2005) Watching Peptide Drugs Grow up. C&EN 83: 17-24.
8. Rozenfeld R, Devi LA (2011) Exploring a role for heteromerization in GPCR signalling specificity. Biochem J 433: 11-18.
9. Sun LC, Coy DH (2011) Somatostatin receptor-targeted anti-cancer therapy. Curr Drug Deliv 8: 2-10.
10. Mahato RI, Narang AS, Thoma L, Miller DD (2003) Emerging trends in oral delivery of peptide and protein drugs. Crit Rev Ther Drug Carrier Syst 20: 153-214.
11. Grant M, Leone-Bay A (2012) Peptide therapeutics: it's all in the delivery. Ther Deliv 3: 981-996.
12. Yamada A, Sasada T, Noguchi M, Itoh K (2012) Next-generation peptide vaccines for advanced cancer. Cancer Sci.
13. Keller G, Schally AV, Nagy A, Baker B, Halmos G, et al. (2006) Effective therapy of experimental human malignant melanomas with a targeted cytotoxic somatostatin analogue without induction of multi-drug resistance proteins. Int J Oncol 28: 1507-1513.
14. Engel JB, Schally AV, Halmos G, Baker B, Nagy A, et al. (2005) Targeted cytotoxic bombesin analog AN-215 effectively inhibits experimental human breast cancers with a low induction of multi-drug resistance proteins. Endocr Relat Cancer 12: 999-1009.
15. Sun LC, Coy HD (2008) Cytotoxic conjugates of peptide hormones for cancer chemotherapy. Drugs of the Future 33: 217-223.
16. Silva AL, Rosalia RA, Sazak A, Carstens MG, Ossendorp F, et al. (2012) Optimization of encapsulation of a synthetic long peptide in PLGA nanoparticles: Low-burst release is crucial for efficient CD8(+) T cell activation. Eur J Pharm Biopharm.
17. Dombu CY, Betbeder D (2013) Airway delivery of peptides and proteins using nanoparticles. Biomaterials 34: 516-525.
18. Madani F, Lindberg S, Langel U, Futaki S, Gräslund A (2011) Mechanisms of cellular uptake of cell-penetrating peptides. J Biophys 2011: 414729.
19. Sun L, Fuselier JA, Murphy WA, Coy DH (2002) Antisense peptide nucleic acids conjugated to somatostatin analogs and targeted at the n-myc oncogene display enhanced cytotoxity to human neuroblastoma IMR32 cells expressing somatostatin receptors. Peptides 23: 1557-1565.
20. Nakagawa O, Ming X, Huang L, Juliano RL (2010) Targeted intracellular delivery of antisense oligonucleotides via conjugation with small-molecule ligands. J Am Chem Soc 132: 8848-8849.
21. Kubo T, Yanagihara K, Sato Y, Morita Y, Seyama T (2012) Enhancement of gene silencing effect and membrane permeability by Peptide-conjugated 27-nucleotide small interfering RNA. Molecules 17: 11089-11102.