Peptide Synthesis For Personalized Medicine

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Peptide Synthesis Overview

Current life style has produced an increase in the incidence of several chronic diseases, including cardiovascular conditions and diabetes (Bloom et al, 2012). Medical advances, on the other hand, have increased life expectancy, and the longer life span has been accompanied by the need to confront the issues of the senior population (Alzheimer’s, dementia and cancer are a few of the medical conditions faced by the elderly). One of the consequences of these changes is an increase in healthcare cost, to the point that current healthcare systems may not be able to sustain the cost for an aging population much longer (Lehnert et al, 2011). Modern medicine focuses on the treatment of a disease, but changing this paradigm may offer a solution to the ever increasing medical cost: the development of personalized medicine, meaning the development of diagnosis and treatment techniques tailored to every patient’s needs, might help in making medicine more effective, efficient and cost effective (Phillips et al, 2013). Also of notice is that the current pharmaceutical development is finding it harder and harder to get new drugs into the market, due to the high cost and long development times (Lowman et al, 2012). While traditional drug developments have decreased in the last few years, the entry of therapeutic peptides into the market has actually increased. Synthetized peptides can be designed according to every individual needs. Modern peptide synthesis methods have made it possible to surpass the limitations that made peptides unsuitable for medical use in the past, and chemical synthesis methods have made it possible for peptides to be produced at a large scale, in a way that’s fit for industrial needs (Albericio & Kruger, 2012).

Personalized Medicine

Human beings are incredibly complex beings. Every person is the result of around 210 different cell types, 35,000 genes and over 10 million proteins. Cells can communicate
among them, forming networks and systems, reinforcing the notion that human beings are indeed very complex organisms (Flood & Carson, 2013). Besides this complexity, human beings are also highly variable. Differences among individuals can come from genetic factors; as differences in genetic sequences in the form of mutations, single nucleotide polymorphisms (SNPs) or alternative splicing; or from protein factors, as the existence of isoforms or post-translational variations. Human being also differ in other noticeable traits as age and gender (Durham, 1991). These differences have an impact in health and disease: the idea that one efficacious drug can treat a specific disease in any individual has been questioned (Hamburg & Collins, 2010).

Personalized medicine aims to take into account both the complexity of human physiology and the variability among individuals. Its goal is to create practices and products tailored to the needs of every individual patient. These ideas are nothing new: China has performed personalized medicine for over 3,000 years, in the form of a specific treatment for every patient based on individual diagnosis. In the western world, Hippocrates was already arguing in favor of personalized medicine more than 2000 years ago (Steele, 2009). Nowadays, modern medicine is in need of change. While the standard and efficacy of healthcare has dramatically increased over the last century in many parts of the world, so has its cost, to the point where it will soon become unsustainable for Western economies. Current medicine aims to treat a disease on the onset, while personalized medicine looks to the possibility of identifying and treating a condition before it develops clinical symptoms, perhaps by treating it at a molecular level. This approach not only is better for a patient from a medical point of view, it also potentially involves a significant cost reduction, becoming a sustainable alternative (Weston & Hood, 2004).

Personalized medicine seeks to classify every disease into classes and subclasses; it aims to create disease subtypes, which can help in the optimization of therapies. Its goal is to create a molecular characterization for every pathological condition. It also considers every patient’s unique molecular and biochemical profile, as well as individual physiology. Hopefully, this approach will lead to earlier intervention and a more specific treatment designed accordingly to every patient’s biochemistry (Chan & Ginsburg, 2011).
The development of personalized medicine requires the understanding of every patient’s fundamental biology. This includes a deep understanding at the DNA, RNA and protein level. Genome sequencing, for example, has allowed the discovery of pointed mutations for several pathological conditions. Genomics, proteomics and metabolomics offer opportunities for pharmaceutical development, particularly related to personalized medicine (Ginsburg & McCarthy, 2001).

Peptides in personalized medicine

Nowadays, the cost of developing a new drug is both time-consuming and very expensive. The investment into research and development has increased, however, medical innovations are actually declining. Besides, the efficacy of therapeutic drugs for conditions as cancer and cardiovascular diseases has not improved in the last years (Lowman et al, 2012). These realities have created the need to explore new alternatives. Peptides emerge then as an attractive form of potential new therapeutic component, especially with the goal of personalized medicine in mind.

Peptides are molecules found in between typical small molecules and larger proteins. Their basic unit consists on aminoacids linked by peptide bonds. Their size is limited, up to 100 residues (Rode, 1999). Traditionally, several limitations have been identified in the use of peptides for medical treatment: They lack the ability to be bioavailable when consumed orally, their hydrophilicity makes it hard for them to cross biological membranes, they are efficiently cleared by the liver and the kidney, inside the human body their half life is short due to the presence of proteases. These limitations have made the use of peptides unfit for medical development; however, recent technological advances have made their use in diagnostics and therapeutics a possibility. Currently, technology allows for peptides to be modified: the chemical incorporation of sugar or salts into the peptide structure helps increase their solubility and in vivo stability, the use of surfactants have enhanced their transport across membranes. Other strategies that aim to increase peptide’s naturally short half-life include the use of protease inhibitors and the incorporation of the peptide into nano carriers (Fonseca, Pereira & Kelley 2009). In short, current biotechnology has made it possible for peptides to become efficacious and safe drugs.
The use of peptides in medicine is currently on the rise: In 2011 there were between 500 and 600 peptides in pre-clinical phases; in 2012, 11 peptides arrived to the market considering the USA and Europe (Uhlig et al, 2014). Besides, proteomics is considered to be the next step in personalized cancer treatment. One example is immunotherapy, in which the patients’ own immune system is used to attack cancer cells. Peptides can be used in order to elicit an effective immune response: a peptide is designed, and then it’s given subcutaneously to the patient. The immune system creates a response against the peptide and against tumor cells. Peptides can be designed specifically for every individual in a form of modern personalized medicine, as it’s been done for prostate cancer (Noguchi et al, 2012).

**Peptide Synthesis Mechanisms**

Recent technological advances have helped in the potential use of peptides for medical uses. Several methods are currently available for peptide synthesis, including: chemical synthesis, recombinant DNA technologies, cell-free expression systems (also known as *in vitro* translation), and the use of transgenic plants and animals (Bodanszky, 2012).

Chemical synthesis consists on uniting the carboxyl group (C-terminus) of one aminoacid to the amino groups (N-terminus) of the next aminoacid. In order to prevent the occurrence of an unplanned reaction, groups are usually chemically protected. Peptide chemical synthesis can be distinguished in three: liquid phase synthesis, solid phase synthesis and hybrid approaches, the last one combining the first two.

**Liquid phase peptide synthesis**

Liquid phase synthesis is the first developed method for synthetic protein synthesis. In the laboratory, this form of synthesis has been mostly replaced by solid-phase synthesis; however, liquid phase synthesis is especially well suited for the production of
small to medium sized peptides. Besides, it remains useful for large-scale production of peptides. In liquid synthesis each aminoacid is added to the polypeptitic chain through a chemical reaction that occurs in aqueous solution. After each aminoacid is added, the product needs to be removed from the reaction solution, making this method slow and laborious. Besides, this approach requires another chemical group to protect the C-terminus of the first amino acid (Bayer, 1972).

Solid phase peptide synthesis

Solid phase peptide synthesis allows the production of large, complex peptides and it’s the preferred method for peptide synthesis in the modern laboratory. It allows the incorporation of unnatural aminoacids and the modification of the peptide backbone. This technique consists on the covalent attachment of an aminoacid by its free C terminal to a solid phase that contains free amino residues. This aminoacid has a chemically protected C terminal, which is subsequently deprotected in order to add a new aminoacid. After every residue, a washing step is performed in order to remove excess reagent. This cycle of deprotection, washing, coupling and washing is repeated until the final synthetic peptide is created (Merrifield, 1963).
Concluding Remarks

Modern technologies have made it possible for peptide synthesis to be used in a therapeutic matter. Besides, personalized medicine is emerging as an attractive alternative for making medicine more efficient. The use of personalized peptides is already being used in the development of cancer therapies, and its use in a personalized manner could be increased in the near future.

References