

Healthcare industry BW

The growing significance of peptide therapeutics

The therapeutic use of peptides lags behind that of proteins. And there are good reasons for this. However, it seems that this is beginning to change and that peptide therapeutics are growing in significance. As a matter of fact, peptides have become rather popular candidates for drugs.

There is a rich source of peptide therapeutics; they can be mined from a variety of unicellular and multicellular organisms as well as from recombinant and chemical libraries. Peptides offer a chemical diversity greater than that of any other class of biological molecule. Closely related analogues increase the diversity still further.

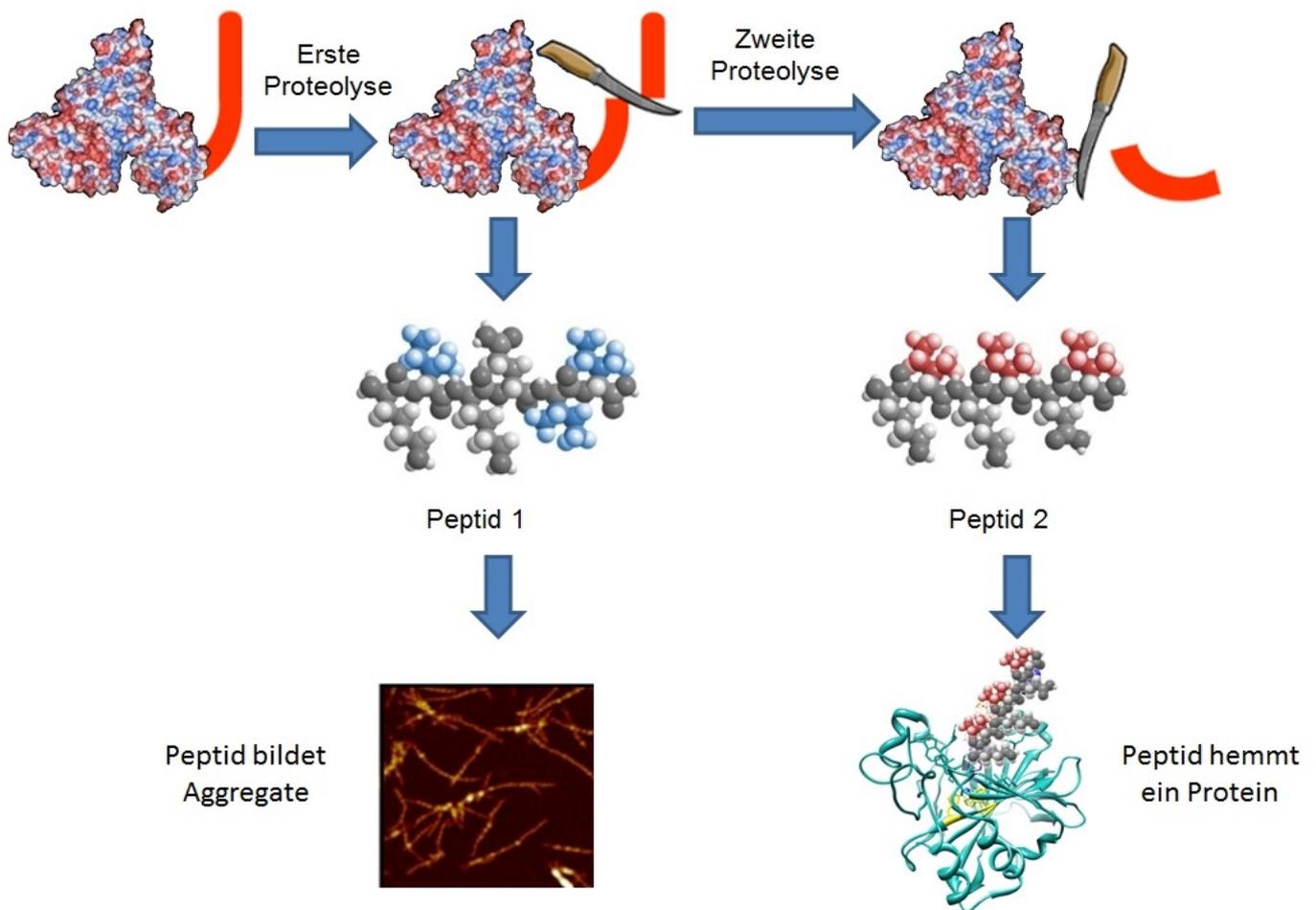
Many challenges

“The use of peptides as drugs is associated with many challenges,” says Tanja Weil, a chemist with many years of pharmaceutical experience. Many researchers share Weil’s opinion. The list of challenges is rather long. Challenge number one: peptides need to be delivered via injection because oral administration would lead to their degradation in the digestive tract. Challenge number two: they have a short half-life because they are quickly broken down by proteolytic enzymes in the digestive tract. Challenge number three: they are relatively quickly cleared from the blood circulation by the liver and kidneys. Challenge number four: their hydrophilic nature prevents them to a large extent from getting past physiological obstacles. Challenge number five: their pronounced conformational flexibility sometimes leads to a lack of selectivity, the activation of different cell structures and adverse effects.

Bioactive, specific and non-immunogenic



Prof. Tanja Weil has recently joined the Faculty of Chemistry at the University of Ulm
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Proteases create a structural and functional variety of peptides that most likely hide some surprise or other.
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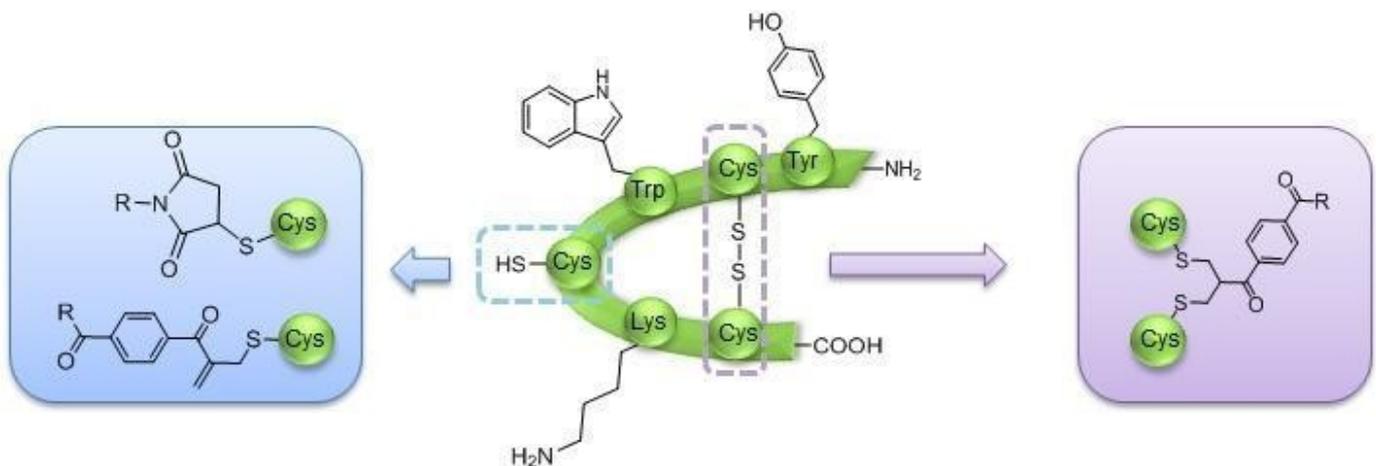
“For pharmaceutical researchers peptides used to be a ‘no go’ area,” says Weil. However, the bias against peptides as pharmaceutical agents has changed and important advantages have come to the fore. Despite their disadvantages, peptides have several advantages over small molecule drugs. They are naturally occurring biologics and hence safer than synthetic drugs and have a greater efficacy, selectivity and specificity. Peptides possess bioactivities that are of major interest for drug discovery; peptides, peptide fragments, amino acids or proteins control and coordinate most physiological processes. In contrast to synthetic substances, peptides are degraded into their component proteinogenic amino acids without leading to toxic metabolites. Tanja Weil believes that this is the reason why the bias against peptides as pharmaceutical agents is fading. In addition, a disadvantage can also be an advantage: although short half-lives make peptide drugs costly on the one hand, the advantage of short half-lives is that peptide drugs are associated with less accumulation in the body, thereby reducing the risks that might arise from their degradation products. Compared with larger proteins and antibodies, peptides can penetrate further into tissue. Moreover, they are generally less immunogenic than recombinant proteins and antibodies. In addition, they are associated with lower manufacturing costs, higher activity and greater stability (they can be stored at room temperature). Many therapeutic peptides are derived from natural proteins or polypeptides and tend to interact with membrane proteins. Usually, tiny quantities of peptides are sufficient to activate or deactivate the target receptors. Only a handful of peptide antagonists that compromise ligand-receptor interactions have been placed on the market. In general, peptide antagonists need to occupy more than half of the targeted receptors in order to exert their effect; peptide agonists can do so by occupying as little as five to 20 percent.

An increasing number of peptide drugs is being placed on the market

Many of the peptide drugs on the market are peptide hormones or peptide derivatives that stimulate hormone action. The number of peptide drugs being placed on the market has been increasing since 2000. A highlight and temporary peak was in 2012 when six peptide drugs were placed on the American market and five on the European market. However, one of the drugs was withdrawn from the American market in 2013. An injectable GLP-1R agonist (lixisenatide) was approved by the European Commission for the treatment of type 2 diabetes in 2013; a synthetic peptide hormone (afamelanotide) with the ability to prevent the occurrence of skin cancers is currently undergoing EMA review and results are expected by mid-2014. As early as in 2006, a recombinant human parathyroid hormone (Preotact) with the potential to prevent vertebral fracture in postmenopausal women was placed on the market.

Around a dozen or so peptide drugs are currently undergoing advanced clinical testing. The peptide therapeutics that are already on the market target a broad range of indications and are administered either intravenously, subcutaneously, by inhalation and even orally (linaclotide). The majority of the 120 peptide drugs that are currently undergoing clinical testing target indications in oncology and infectious diseases. More than 50% of all peptide drug candidates target a single target structure and about 10% target microbes. The most frequent targets of peptide drugs are membrane proteins, especially G protein-coupled receptors (almost 40% according to Kaspar/Reichert) that reside in the outer cell membrane and transfer external signals into the interior of the cells. Peptides undergoing clinical phase II testing frequently have a wide range of structural changes (e.g. they are linked to lipids or PEG). The fact that peptides represent around half of all drug candidates in phase I clinical testing over the last two years is seen as evidence of the growing importance of peptide drugs for the treatment of human disease.

Improving stability and function



According to Weil, cysteine is perfect for stabilizing and functionalizing peptides.
 © Weil/Uni Ulm

“The oral administration of peptides is still a ‘Holy Grail’ of pharmaceutical research,” says Weil, also highlighting that new technologies have succeeded in breaking down the barrier to using peptide drugs. The pharmaceutical industry is working hard to find solutions that allow the oral administration of insulin in such a way that it is not rapidly degraded in the gastrointestinal tract. However, all attempts are still experimental and no marketable product is in sight. Many researchers are working on optimising the delivery of the drug and Tanja Weil is convinced that the cooperation

between medical doctors and scientists, which also involves the use of high-throughput omics technologies (e.g. proteomics, metabolomics), has led to considerable progress in peptide research.

“In Ulm, we have access to a large number of peptides with a huge chemical diversity. So the chance of matching a peptide to a physiological target is quite good. Peptides are interesting drug candidates because they carry numerous functional groups that can be altered chemically. We are therefore able to synthesize peptides that nature is unable to produce and that have improved properties,” summarizes the chemist from Ulm.

Weil uses the amino acid cysteine as an example to explain why peptides have become popular targets of drug discovery approaches. Cysteine is a sulphur-containing natural amino acid. Cysteines can form disulphide bonds, thereby boosting their stability. “This is chemistry par excellence,” says Weil explaining that it is possible to induce a particular reaction between an organic molecule and a cysteine molecule. When incorporated at a particular site, cysteine also has the ability to connect peptides with each other. Weil believes that this approach has the potential to produce a functional protein in vitro. Although the ability to create an enzyme in the test tube is still a pipe dream, the potential is no doubt there.

Optimizing makes progress

Weil believes that some peptide optimization strategies have already achieved a certain maturity: for example, animal experiments are being carried out with encapsulated peptide drugs which are expected to survive the journey through the digestive tract. It has been shown that mesoporous silica particles are suitable for encapsulating peptides and subsequently releasing them into the blood. Other approaches involve the attachment of polymers such as polyethylene glycol groups to peptide drugs (PEGylation). Here, polymers that do not adsorb very well to plasma proteins are used; the drugs remain longer in the blood and can reach suitable cellular surface receptors.

Other researchers concentrate on approaches focused on increasing peptide stability by adding residues that are not so easily recognized by enzymes. It has been shown that the proteolytic degradation of peptide drugs can be slowed down by substituting L-type amino acids with D-type amino acids which are less susceptible to proteolytic degradation and therefore effective for longer. Only recently, research groups led by Münch, Kirchhoff and Weil succeeded in identifying and characterizing a peptide that forms visible aggregates and considerably improves the transport of viruses into cells. This approach might also be of interest for application in gene therapy. “There are some highly promising approaches, including here in Ulm. Research in this area has made greater progress than research related to the oral bioavailability of the peptide drugs,” says Weil.

New stars among biologics?

Biologics such as peptides are gaining in importance due to their high specificity and biological activity, especially given that small molecule drugs are expensive, often produce toxic metabolites and are associated with unwanted interactions.

Due to the availability of advanced optimization strategies, peptide drugs have meanwhile become an attractive substance class that is suitable for producing semi-synthetic drugs for treating CNS (Vlieghe, 54) and other diseases. Peptide drugs are already being tested for their efficacy in treating cancer and inflammation as well as for their potential as antibiotic and enzyme inhibitors. Antimicrobial peptides are predicted to have a great future.

The search for active drug ingredients in nature is not a new idea in itself, what is new is that

researchers are looking for them in human body fluids. "This approach might be a good choice as their isolation and purification is usually rather difficult," says Weil. It goes without saying that peptides produced by the human body have a toxicological profile that is far removed from that of exogenous substances that are extracted from sponges or of cytotoxic substances derived from tree bark.

Researchers from Ulm and elsewhere are of the opinion that the degradome, i.e. all proteins degraded by proteolytical enzymes, is not biological waste and not a hazard. This is because the large number of proteases (> 500) that cut proteins into peptide fragments could potentially be altered under pathological conditions. In addition, there is growing evidence that some of the cleavage products of larger proteins have a specific, and sometimes unexpected, reaction against human pathogens.

It seems likely that the human organism harbours important peptide immune modulators and effectors. A dozen therapeutically interesting peptides with antimicrobial and anti- or proviral activity have been identified in human peptide libraries (Münch, Ständker, 15). Not all peptides isolated from body fluids are worth developing into drug leads. However, the researchers from Ulm are happy about any new finding they make as they hope that insights into the regulation of cells and the uptake of peptide drugs into cells will improve their current knowledge and potentially also lead to the discovery of completely new mechanisms of action and defence.

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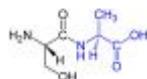
31-Mar-2014

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Peptides – diverse molecules of life