Panel Discussion on PEPTIDES

In this Monographic issue on Oligonucleotides & Peptides we have foreseen a Panel discussion on Peptides involving companies linked to their synthesis. In the next few pages the reader will have an update on the status of progress reached by peptide synthesis and technologies, the high quality achieved, the regulatory and therapeutical application hurdles such as bioavailability and what the future holds and where peptides are aiming at (for example Personalised medicines).

The following Players have joined this initiative:

PANELISTS

Daniel Bourgin, *Business Development*
Dr. Reddy's Custom Pharma Services (CPS)

Frank Otto Gombert, *Managing Director*
Gombert Pharma Research Solutions

Elisabetta Bianchi, *Director Peptide Chemistry*
IRBM S.p.A.

Robert Hagopian, *Director, Business Development*
PolyPeptide Group

Daniel Bourgin, *Business Development*
Dr. Reddy's Custom Pharma Services (CPS)

What has been the most important progress in peptide synthesis and technologies during the last 3 years?
The most important progress in peptide synthesis has probably been achieved in the manufacture of long peptides in an improved quality. For industrial scale production most of the progress originated from more sophisticated engineering such as automation paired with QbD methods such as monitoring and simulating single steps in the elongation step of a peptide on the resin and in the down-stream processes. The waste stream handling in upstream and downstream processes is still a challenge and represents a significant cost factor in the production.
Further progress was made by using microwave assisted solid phase synthesis which is a promising technology to significantly reduce the production cycle and has the potential to reduce production costs and therefore makes peptide production more economical.
We've also seen progress in the formulation of peptides. Technologies such as nanoencapsulated peptides are used to control the release of the active ingredients and will make it possible to further replace injections by oral delivery.

What do we have to expect for the costs of goods perspective in the future?
Industrial solid phase peptide production on commercial scale is still expensive. To make peptide products more attractive, especially in regulated markets and as generics, the efforts are focused on the development of processes, which provide higher yield by avoiding deletion, repetition and other side reactions during the elongation of the peptide chain on the resin. There will also be a need for the development of novel coupling agents that are more efficient and recyclable combined with further recycling of solvents generated in the downstream process an approach which reduces the costs, but also makes the production more sustainable.

What are the hurdles with respect to a broader application as therapeutics?
The application of peptides as therapeutics requires mostly the injection of a buffered solution. The longevity of peptides is rather short in the blood stream and digestive system due to the rapid degradation by proteolytic enzymes. Several technologies are investigated to enhance the lifetime in the organism and to reach the target by penetrating the physiological barrier due to the peptides hydrophilicity. Highlights have been reported in the following areas:

- Different formulation: There is a push to develop orally applicable peptides e.g. Insulin by encapsulating the peptide into engineered liposomes.
- PEGylation of peptides to enhance stability in the plasma and to reduce excretion through the kidneys. Today there are 14 PEGylated peptides on the market.
- Nanotechnology which makes it possible to encapsulation the peptide into multi-layer capsules to control the release at the target site.

How do next generation peptide therapeutics look like?
The main therapeutic areas of peptides are cancer, metabolic diseases, and diabetes. The future will show that peptides also have the potential to meet unmet needs - especially for diseases which are affecting the immune system or the central nervous system.

To enhance the longevity of peptides in the organism and higher concentration at the target site, we will see more and more peptide-mimetics bearing unnatural amino acid. Very promising in this respect are also peptide conjugation derivatives such as combinations of peptides with small molecules, fatty acids or polyethylene glycol chains. Another emerging class are Peptide Nucleic Acid (PNA's) which are a combination of nucleic acids with a peptide back bone to expand the range of application.
There is also a trend towards more oral applications due to different drug formulation technologies e.g. nanoparticles (encapsulation in multi-layer capsules) combined with enzyme inhibitors to control the release and half-life of the peptide API.

Frank Otto Gombert, *Managing Director*
GPRS - Gombert Pharma Research Solutions

What has been the most important progress in peptide synthesis and technologies during the last 3 years?
The invention (WO20150929) of the water soluble Fmoc-group "Smoc" by the team of Prof. Kolmar from the TU Darmstadt, DE will certainly reduce the burden of volatile organic compound usage during the automated solid-phase peptide synthesis. The full potential of this new protecting group is awaiting broader market validation.
A more efficient purification method for SPPS cleaved peptides – in terms of time and solvent usage – is available through the introduction of new traceless catch-and-release chemistry (Journal of Peptide Science 25, e3136 2019) by the group of Prof. Seitz in Berlin, DE. The introduction of synthetic scaffolds to perform chemical reactions "Rink et al. Chemistry - A European Journal 25, 1665, 2019." by the group of Franziska Thoma in Göttingen, DE will open the path to synthetic enzyme like reaction catalysis.
Combinations of biotechnological methods with chemical synthesis and modifications is another fast-developing research area. In particular three aspects are important: 1. synthetic amino acids are used in bacterial expression systems to incorporate unnatural amino acids or reengineer synthetic pathways. 2. High throughput expression and screening are used to generate structures of 1st hits, which are then synthetically validated and further optimized. 3. Bacterial, phage or ribosomal display methods with final chemical synthetic steps are applied to the expression product or used to modify obtained peptides or peptidomimetic constructs.

What do we have to expect for the costs of goods perspective in the future?
There are two parts to consider over the value chain. First the building blocks introduced to the peptide synthesis. The market of the standard 20 genetically encoded amino acids is fully functional and I do not expect significant changes here. New protecting groups, unnatural amino acids or new coupling reagents will put some pressure on prices of established products, potentially increasing the costs of the final product until they run out of patent protection. The second part of the value chain includes the synthesis and purification infrastructure for research peptides as well as for clinical trials preparations (CMC). In this part I see a huge potential for improvement in terms of total costs, time, quality and certified documentation. The synthesis planning, automation and purification robots and methods are still not fully integrated. The team with a clever idea for a software platform to do it, might be the champion of the future.

The quality aspect is getting more attention, as well as keeping to agreed time lines. In Europe consumers are nowadays willing to pay more for these 2 important selling points. Cheaper is in the very end not advantageous.

What can we foresee from the regulatory bodies in the years to come?
I have the impression that they are getting more open and flexible for new types of therapies. They have realized that they have to provide an independent service for all stake holders in the approval of new drug, diagnostics and medical product and devices. I hope that besides the established medical key option leaders, independent skilled experts from pharma research, chemical manufacturing organizations and patient organizations are more often included in guiding the evaluation process for new approvals.

What are the hurdles with respect to a broader application as therapeutics?
Peptide therapeutics have the big advantage of being highly selective - as biologics - compared to small molecules. Thus, they have a significant higher success rate in passing clinical phases to market entry. Their drawback is the low permeability through gut epithelial and most other cell membranes. Medicinal chemistry research should focus on this, e.g. by systematically elaborating the structural and physico-chemical properties to facilitate membrane permeability, improve with suitable formulations, invent new cell permeability enhancers or permeability chaperones.

How do next generation peptide therapeutics look like?
Cyclic and macrocyclic. This leads to a significant improvement of the in-vitro ADMET properties and the pharmacokinetic profile. The solid-phase peptide synthesis and native chemical ligation technologies are rapidly improving. Thus, I foresee that chemical synthesis of mini-proteins (51 to 100 amino acids) and proteins (>100 amino acids) will be competitive compared to biotechnological processes very soon. Protein-mimetics and domain-mimetics could be the new stars.

Elisabetta Bianchi, *Director Peptide Chemistry*
IRBM S.p.A.

What has been the most important progress in peptide synthesis and technologies during the last 3 years?
The most important contribution in this field has been the clear emergence and establishment of various screening technologies that can provide macrocycle peptide leads to nominally target any protein-protein interactions in a similar way to antibody therapeutics. Among these technologies, a few years ago the old phage display platform was revisited and combined with macro-cyclization chemistries to generate libraries of macrocyclic peptides. Even more powerful are the emerging new encoded *in vitro* display technologies that enable the incorporation of a plethora of non-natural amino acids in the context of macrocyclic peptide libraries. Among these discovery techniques, mRNA display can be used to screen huge libraries of macrocyclic peptides changing the paradigm of lead identification for challenging targets such as protein-protein interactions.

What do we have to expect for the costs of goods perspective in the future?
One could expect an increase in the cost of goods based on the presence of non-natural amino acids incorporated into most peptide leads identified by *in vitro* display technologies. However incorporation within the peptide lead of non-natural amino acids and its sequence engineering with chemical constraints and other modifications are key strategies to improve receptor potency and specificity, half-life, and stability resulting in a much lower dose needed for *in vivo* efficacy. Moreover, most recent approaches take advantage of advancements in chromatography and mass spectrometry for the identification of *in vivo* peptide metabolites. Medicinal chemistry approaches can then be applied to modify and stabilize the lead. So whilst the cost of goods might tend to be higher due to challenges in the number of chemical modifications introduced within a peptide lead these chemical improvements should indeed translate to a lower therapeutic cost due to a much reduced dose needed for an optimized product.

What can we foresee from the regulatory bodies in the years to come?
For peptide and protein therapeutic development, there is certainly a need for guidelines for validated methodologies for the assessment of the immunogenicity potential of novel therapeutics but also, most importantly, for the pseudo-allergic potential mediated by mast cell activation. I would expect that these key issues will soon be addressed by the regulatory agencies to guarantee development of safer peptide and protein therapeutics.

What are the hurdles with respect to a broader application as therapeutics?
One of the main obstacles for a broader application of peptides as therapeutics is oral bioavailability. Oral delivery is still viewed as greatly attractive to support patient compliance for indications where chronic therapy is required for most therapeutic areas. So many efforts are devoted to address the issue of oral bioavailability by increasing peptide drug stability in the GI tract and by formulating peptides with compounds that act as enhancers for permeability. The strategies described so far for gastrointestinal delivery, although promising, have been only marginally successful with bioavailabilities in the order of 1%. Another very promising area comes from research in the chemical engineering field with the appearance of a few fascinating reports on ingestible devices for oral delivery of macromolecules in the GI tract. I am expecting incredible breakthroughs in the field of oral bioavailability from these various approaches.

How do next generation peptide therapeutics look like?
I would anticipate that next generation therapeutics will be typically derived through direct evolution of large combinatorial libraries with screening processes amenable to therapeutically target intracellular processes and most likely they will incorporate a large degree of chemical complexity with multiple chemical constraints and conjugation moieties.

Robert Hagopian, *Director, Business Development* - PolyPeptide Group

What has been the most important progress in peptide synthesis and technologies during the last 3 years?
Advances related to equipment automation in peptide synthesis in recent years will shape the future of peptide manufacture. This will benefit both from an efficiency and from an overall cost of manufacture. Another area to note is related to advances in analytical chemistry, which will certainly allow for improved peptide characterization, especially for impurities identification as applied to the related CMC section of a regulatory filing.

What do we have to expect for the costs of goods perspective in the future?
As indicated above, advances in automation will certainly impact costs favorably. While this may be the case from a manufacturing stand point, the changes in regulatory landscape as related to impurity identification above a certain low threshold, for peptides, may actually have an opposite impact on cost. This will especially be true for longer, more complex peptides.

What can we foresee from the regulatory bodies in the years to come?
As indicated above, and based on recent publications, tighter specifications related to impurities identification are anticipated from the regulatory bodies for peptides.

How do next generation peptide therapeutics look like?
We may be already living part of the next generation of peptide therapeutics: NeoAntigens and the personalized medicines. Based on ongoing reports, this should be a breakthrough both from a conceptual stand point as well as from a regulatory stand point. Only time will tell the success level of these potentially potent therapeutics. We may only be seeing the beginning…