Impact Objectives

- Create a library of structurally diverse proteins, which can be studied from a microscopic and macroscopic viewpoint in different environments to obtain a comprehensive dataset
- Train PhD students in the biophysical and structural characterisation of proteins, thus creating a strong intersectoral network between academic and industrial sectors
- Ultimately improve healthcare due to more robust formulation development processes and at the same time improve the cost-effectiveness of biologics

Developing a library of proteins for drug research

The abundance of protein drugs on the market shows there is an increasing demand for knowledge within the formulation of biologics, as Professor Pernille Harris, Principal Investigator and Coordinator of the Protein-excipient Interactions and Protein-Protein Interactions in formulation (PIPPI) project explains. The project will extend the medicinal industry’s knowledge on protein formulation and lead in future drug development. Having the edge in knowledge on protein formulation will lower the risk of failure and increase the likelihood of better and more convenient dosage forms (for example, suitable for home treatment instead of hospitalisation). Overall, industry and academia in the EU will benefit from a large pool of highly skilled researchers and research groups.

One intrinsic area of focus is training PhD students in the biophysical and structural characterisation of proteins in a pharmaceutical setting. They will create a strong intersectoral network between academic and industrial sectors. They will be key opinion leaders of the future. Scientifically, the aims are to create a representative library of structurally diverse proteins, and through a systematic study of their microscopic and macroscopic behaviour in different environments, we will obtain a comprehensive dataset. We will create a database enabling how to best predict protein stability on a minimum number of experiments and guide how to select the best experiments. We will bring biophysical understanding and characterisation tools for formulation of biologics to the next level.

Who comprises the PIPPI consortium?

Partners in the PIPPI consortium have been selected to comprise a diverse set of scientific and industrial skills. Their selection is not based wholly on their strong CVs, but because of their high scientific level and innovative approach to scientific questions. This includes the industrial partners that are known to be excellent scientific collaborators with a serious commitment to training young researchers.

The academic partners include: Günther Peters and myself, Department of Chemistry, Technical University of Denmark (DTU); Robin Curtis, Alexander Golovanov, Alain Pluen, Jim Warwicker and Jeremy Derrick, University of Manchester, UK; Wolfgang Frieß and Gerhard Winter, Ludwig-Maximilians-Universität München, Germany; Mikael Lund, Lund University, Sweden; Åsmund Rinnan, University of Copenhagen, Denmark; and Marjolein Thunnissen, MAXIV Laboratory, Sweden. The industrial partners include: Shahid Uddin and Chris van der Walle, MedImmune; Werner Streicher and Allan Nørgaard, Novozymes; Dierk Roessner, Wyatt Technology Europe; Philipp Baaske, NanoTemper Technologies; Kishore Ravuri, F. Hoffmann-La Roche; and Jan Petersen, Danish National Metrology Institute.

What are the key aims of the PIPPI project and what does it hope to achieve?

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Who will benefit from the research?

There will be widespread benefits across academia, industry and the wider public. Global academic research is likely to take a big step forward due to the unprecedented amount of coherent biophysical data that will be made available by the consortium. For industry, it will deliver the ability to recognise the potential values of biophysical techniques normally used only in academia. They will also gain an understanding of which of the currently used high throughput techniques add more value to the drug development process. For society, it will improve healthcare due to more robust formulation development processes, and at the same time, improve the cost-effectiveness of biologics. It will also allow the European Union (EU) to build on its strong pharmaceutical industry and take the lead in future drug development. Having the edge in knowledge on protein formulation will lower the risk of failure and increase the likelihood of better and more convenient dosage forms (for example, suitable for home treatment instead of hospitalisation). Overall, industry and academia in the EU will benefit from a large pool of highly skilled researchers and research groups.

Why do so few universities in Europe have formulation of biologics as a subject?

Except for a few examples, the use of biologics is a relatively new field within the medicinal industry. Traditionally, the big pharma industry is focused on small molecules, and teaching in academia, as well as public funding, are often driven by industrial opportunities. In society, it is recognised that protein drugs are more expensive and difficult to develop and less convenient for the patient, whereas it is not acknowledged that at the same time, biologics are often safer, with fewer side-effects and are much more precise in their mechanism of action and efficacious in treatment of diseases compared to small molecule-based drugs.
Paving the way for protein-based drugs

There is a constant pressure to develop safer and more effective medicines, which has resulted in a shift in interest by the pharmaceutical industry towards protein-based drugs. To improve our understanding of these drugs, the PIPPI research project will develop a representative library of structurally diverse proteins.

CHARACTERISING BIOLOGICS

To overcome this difficulty in characterising biological sciences, scientists in the field of structural biology, biophysics, protein formulation and stability have formed the Protein-Experient Interactions and Protein-Protein Interactions in formulation (PIPPPI) project, to use an interdisciplinary approach to systematically map physicochemical properties of biologics, formulation conditions and protein stability. The main objective of this consortium is to provide a new generation of innovative and entrepreneurial researchers who will develop methodologies, tools and databases to guide the robust formulation of biologics. ‘Understanding the molecular mechanisms behind protein stability and solubility is difficult and complex, but it is not recognised as such,’ Penline Harris, Associate Professor in the Department of Chemistry at the Technical University of Denmark (DTU), and Principal Investigator for PIPPI explains. ‘Therefore, little training and general understanding is available in the community. The combined efforts in the consortium will provide the necessary molecular understanding to guide the development of future biologics.’

Also, technologies in many non-pharmaceutical industries are based on protein science, and for a sustainable future, the world requires these up-coming technologies in fields such as bioethanol, biocatalysis, biopolymers and bioagriculture.’ Harris explains that if the knowledge of how the formulation affects the protein structure and behaviour increases, then this fundamental understanding will guide the choice of formulations that are more likely to be correct on the first try. This will decrease the time it takes for the protein to reach the market and hence the patients. ‘In the PIPPI project we are investigating many proteins under many conditions using a diverse set of techniques,’ she continues. ‘Therefore, our main challenge is to utilise all results coherently. We are getting interesting results and those results give rise to new interesting questions that cannot be all investigated in-depth within the time limit of the current grant.’

DEVELOPING PROTEIN LIBRARIES

During the project, researchers will select a protein library, which will be characterised systematically using current state-of-the-art excipients. On the microscopic level, the molecular interactions will be examined using advanced experimental and in-silico techniques. On the macroscopic level, the critical formulation properties such as shelf life stability and phase behaviour will be assessed: ‘All the results will be collected in a database that will contain comprehensive data of protein structure, self-interactions and interactions with state-of-the-art excipients, protein stability and behaviour,’ Harris adds. ‘The database will enable the consortium to use modern data treatment of large datasets to link the results from the different studies and provide novel and in-depth insight into important protein properties that govern protein stability. The consortium is highly-skilled and covers the required expertise and innovation power to catalyse this scientific field and set it in motion.’

The programme will collect a large, comprehensive, coherent dataset on several proteins, where all data will be publicly available in a database. ‘We will treat the complete dataset using a Big Data approach with statistical data-driven analysis,’ Harris continues. ‘I am confident that we will make the first small, but crucial step towards a scientific revolution within this scientific field with an approach similar to the one seen with the large human genome projects.’

PARTNER PARTICIPATION

In addition, PIPPI will generate 15 highly skilled young researchers with a comprehensive knowledge of research in academia and in industry. They will have obtained training in protein formulation. Alongside DTU, there are five other partners – University of Manchester, UK; Ludwig-Maximilians-Universität München, Germany; Lund University, Sweden; University of Copenhagen, Denmark; and MAXIV Laboratory, Sweden – that form a strong academic partnership.

Alexander Colovano of the University of Manchester explains that he has been keen to participate in PIPPI because the consortium gives unprecedented access to a wide range of biopharmaceutically-relevant protein models, and brings together a wide range of techniques to look at the behaviour of these from different perspectives, collating all the information together and making sense of it all. ‘If we recall an ancient parable of the blind men and an elephant, when several men were touching and exploring different parts of the same elephant, they which they have never seen before, and later disagreeing with each other what the elephant is – in a way we are in the same position, looking at the same thing from different perspectives,’ Colovano explains. ‘What, however, differentiates us from these old men is there are more of us exploring the same elephant, and more importantly, we do it systematically and talk to each other.’