UNISA

Future Industries Institute:

Mass Spectrometry and Proteomics Facility

PhD Projects - 2021

ADVANCING PROTEIN THERAPEUTIC DEVELOPMENT

Background

The use of monoclonal antibodies and recombinant versions of proteins as therapeutics, referred to as biologics, has changed the pharmaceutical landscape. It is anticipated that more than 70% of new drug approvals will be biologics by 2025, with seven of the ten best-selling treatments being protein based. The growth in protein-based therapies requires cutting-edge analytical tools to ensure the final product is of high quality, safe, and effective. CSL, a world-leader in protein-based therapeutics, continuously develops and adopts analytical strategies to support new research to better understand disease progression and identify new drug candidates. This involves investment into research on new analytics to provide important information for developing new therapies and ensure progression through the drug discovery pipeline. CSL, working with the University of South Australia and Karlsruhe Institute of Technology, have defined specific projects focused on creating new approaches to support drug discovery and development.

Project 1: Streamlined high-throughput analytical automation to support downstream process development and characterization studies

Objectives: Utilise novel and emerging at-line/on-line technologies to maximise sample throughput to provide comprehensive data set and faster assay turnaround to facilitate rapid downstream process development decision making.

Anticipated outcomes: A fully integrated automation stack with at-line/on-line analytics (*e.g.* protein concentration, impurities, aggregates, truncation, and charge variants) for high-throughput downstream purification screening support. Current CSL analytical throughput is not able to support design of experiment (DOE) type of downstream process development using robo-columns. This project will assess emerging new technologies that is able to deliver robust high-throughput analytical methods, for instance, ion mobility mass spectrometry (MS), chip-based impurity screening, size exclusion, dynamic light scattering, etc. The chosen analytical method will be inter-connected with Tecan robo-column by a mobile mechanic arm for at-line analysis. The developed automation platform will be of significant interest to all biopharma companies for rapid screening of different purification conditions, streamlining the Purification Process Development allowing the team to make informed forward processing decisions.

This PhD project will be in collaboration with CSL in Melbourne and 1/3 of the 3yeras PhD project will be conducted at CSL's research facility.

Eligibility

Domestic students are welcome to apply. Applicants must meet the eligibility requirements for a research degree program at the University of South Australia.
How to apply: Research Training Program domestic (RTPd) Scholarship

Applications now open until 31 October.
*All applications and supporting evidence must be submitted by **31 October**.*
Please apply early to allow us time to review your application and request any additional information required.

Apply online HERE

Please reference Supervisor: Professor Peter Hoffmann and your chosen project in your application. If you have any specific questions about the project(s) please email Professor Peter Hoffmann
Peter.Hoffmann@unisa.edu.au or Dr Mark Condina Mark.Condina@unisa.edu.au

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Project 2: PAT Spectroscopic and MS techniques for high throughput product characterisation for recombinant protein products

Objectives: Develop and establish a suitable process analytical toolbox (PAT) based on a combination of High-performance liquid chromatography (HPLC), spectroscopy and mass spectrometry (MS)- based monitoring of critical quality attributes (CQAs) in order to drive process development for recombinant protein products.

Anticipated outcomes: From a regulatory standpoint it is important to assure that pharmaceutical processes are always controlled to ensure the therapeutic achieves a defined quality level. In biopharma, PAT has been recommended by the FDA since 2004 to manage production by monitoring and controlling processes to ensure a high-quality final product. PAT typically combines HPLC and spectroscopy data with chemometric analyses to obtain and analyse relevant information of the process and product quality, such as monitoring CQAs. By using PAT, critical decisions and process adjustments can be made in (near) real-time. The project will establish a high throughput and PAT suitable toolbox based on a combination of UV/Vis absorption, FTIR, MS and Raman spectroscopy for characterisation of CQAs. The approach will be specific for recombinantly expressed protein products, focusing on adoption of MS strategies, such as liquid chromatography (LC) coupled to high-resolution MS for monitoring quality attributes during production. Integration of MS data as part of a PAT requires a dedicated effort to ensure output is compiled in a way that can be incorporated and assessed in conjunction with other analytical strategies. High quality spectroscopic and MS data will be generated using potential therapeutic candidates provided by CSL. Mechanistic models developed from the analytical approaches used will support the learning process of artificial neural networks (ANNs), to generate hybrid or meta-models for simplification of root cause investigations and improve process understanding. The project builds on expertise of Professor Hubbuch for PAT development, UniSA for spectroscopy, MS, and data analytics, and CSL for implementation to support recombinant protein products.

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Project 3: PAT Spectroscopic and MS techniques for high throughput product characterisation for plasma derived products

Objectives: Develop and establish a suitable process analytical toolbox (PAT) based on a combination of High-performance liquid chromatography (HPLC), spectroscopy and mass spectrometry (MS)- based monitoring of critical quality attributes (CQAs) in order to drive process development for plasma-derived protein products.

Anticipated outcomes: The project will establish a high throughput and PAT suitable toolbox based on a combination of UV/Vis absorption, FTIR, MS and Raman spectroscopy for characterisation of CQAs for plasma derived protein products. The approach will be specific for plasm-derived products, focusing on adoption of MS strategies, such as liquid chromatography (LC) Multiple Reaction Monitoring (MRM) MS quantitation strategy of proteins in human plasma fractions, to monitor plasma fractionation process performance. This integrated PAT approach will replace conventional biochemical approaches for targeted protein quantitation of plasma fractions. The data compiled from the mechanistic models developed from the analytical approaches used will support the learning process of artificial neural networks (ANNs), to generate hybrid or meta-models for simplification of root cause investigations and improve process understanding. The project builds on expertise of Professor Hubbuch for PAT development, UniSA for spectroscopy, MS, and data analytics, and CSL for implementation to support plasma-derived protein products.

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Project 4: Pushing the boundaries of high-throughput quantification by mass-spectrometry in tissue

Analytical measurements of any kind should be sensitive, fast, accurate and reproducible. To achieve the most sensitive measurement, lengthy sample preparation and complex analysis might be necessary. Both are not compatible with high throughput applications. Although Matrix-assisted laser desorption/ionization (MALDI) Time OF Flight (TOF)-Mass Spectrometry (MS) can acquire data as fast as 10 ms/sample, it is currently underperforming as a high-throughput technology. Additionally, you can use MALDI TOF-MS as well as MALDI Quadrupole (Q) TOF-MS for Mass Spectrometry Imaging (MSI) where intensities of molecules are measured with spatial resolution and intensity maps/images can be created with the long-term aim of absolute quantification. To develop this enabling technology of MALDI MS and MSI, innovative sample preparation protocols, matrixes and data analysis will be developed, which will disrupt the current status quo. This project will have a transformative impact on multiple research areas, such as monitoring of drug candidates for the pharmaceutical industry, mapping and quantifying environmental exposures to humans, plants and animals and quantifying small molecules/metabolites in tissue.

The successful applicant will apply the developed high throughput MALDI MS and MALDI MSI technology to cancer tissue treated with therapeutic candidates to monitor distribution in the tissue. The approach will have applications for monitoring multiple analytes across tissue, such as for use in pharmaceutical and/ot environmental contaminant monitoring for human, mouse or plant tissues.

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