Adaptive Immune Receptors: Structural Modelling and Immunoinformatics
5th April 2024, Lady Margaret Hall, University of Oxford

Full Agenda with Abstracts

08:00-09:00, Monson Room
Registration with Refreshments

09:00-09:10, Simpkins Lee Lecture Theatre
Opening Remarks

09:10-10:00, Simpkins Lee Lecture Theatre
OPENING KEYNOTE
Harnessing AI to Advance Biotherapeutics: From Structure to Affinity Prediction
Professor Charlotte Deane (University of Oxford)

Antibodies are cornerstone immune system players, vital for vaccine responses and emerging as powerful biotherapeutics. However, traditional development can be lengthy and expensive, exceeding $1 billion.

This talk explores how cutting-edge computational methods, particularly machine learning, hold immense promise for revolutionizing biotherapeutics development. I will showcase our pioneering tools ranging from rapid, accurate structure prediction to binding affinity forecasting, highlighting both their potential and current limitations.

10:00-10:30, Monson Room
Morning Break with Refreshments

10:30-11:05, Simpkins Lee Lecture Theatre
Generative deep learning models for protein design
Dr. Joe Watson (University of Washington)

De novo protein design seeks to learn the underlying principles of protein folding from natural proteins and to subsequently apply them to generate novel proteins with programmable functions. In recent years, there have been significant and concomitant advances in both our abilities to learn from protein structural data (AlphaFold2, RoseTTAFold) and in generative deep-learning methods in other fields (image and text generation). In this talk, I will discuss our recent work building upon these advances, in which we trained a generative neural network for de novo protein design; RoseTTAFold Diffusion (RFdiffusion). I will focus on the applications of RFdiffusion for designing protein-protein interactions, describing the characterization of hundreds of functional designed binders, followed by recent advances where we have extended RFdiffusion to design anatomically-accurate de novo nanobodies and antibodies.

11:05-11:40, Simpkins Lee Lecture Theatre

Modelling Conformational Dynamics of Antibodies - Consequences for Biophysical Properties

Dr. Monica Fernández-Quintero (Scripps Institute)

Describing an antibody's binding site using only one single static structure limits the understanding of the antibody's function. To improve antibody structure prediction and to take the strongly correlated loop and interface movements into account, antibody paratopes should be described as interconverting states in solution. Therefore, the definition of kinetically and functionally relevant states can be successfully used to improve the accuracy and enhance the understanding of antibody-antigen recognition. Accounting for the high conformational diversity of antibodies by considering them as conformational ensembles can additionally advance the antibody development process, as the identification of potential liabilities and optimization of biophysical properties, such as hydrophobicity and electrostatics, can be facilitated. Even the low population states, that occur more frequently near hydrophobic surfaces, can contribute to understand processes such as aggregation or chemical modifications. In fact, these interactions with hydrophobic surfaces can result in a population shift towards more hydrophobic conformations, which are more likely to aggregate. In addition, we also test state-of-the art structure prediction tools, emphasize the importance of reliable protein structure models, in terms of structural and physical accuracies and the influence of predicted antibody structures on biophysical properties and recognition. Furthermore, we also discuss the abilities of AlphaFold2 to predict ensembles of the immunoglobulin binding site and how these findings align with available experimental structural information and ensembles from molecular dynamics simulations.

11:40-12:00, Simpkins Lee Lecture Theatre

Using integrative structural biology to develop more powerful immunostimulatory antibodies

Isabel Elliot (University of Southampton)

Immunostimulatory antibodies (ISAs) represent a promising strategy for cancer immunotherapy. By activating co-stimulatory molecules expressed on immune cells, such as tumour necrosis factor receptors (TNFRs), ISAs can enhance the immune response towards tumours, resulting in powerful anti-cancer effects. However, to develop more effective therapeutics, we need a deeper understanding of the structure-function relationship behind agonistic activity. Antibodies comprise two antigen-binding domains linked to an effector domain through a disulfide-containing hinge. There are four isotypes of human (h)IgG, and previous work has shown that hIgG2 antibodies can deliver strong agonistic activity for ISAs, due to their unique hinge disulfide arrangement. Using a series of hIgG2 cysteine-to-serine exchange mutations in the hinge of a clinically-relevant ISA targeting TNFR CD40, strong activity was associated with restricted global antibody flexibility through the formation of a disulfide 'cross-over' in the hinge. To extend these findings, we investigated other ISAs targeting different TNFRs and also whether further hinge restriction would provide augmented agonism. New variants were characterised in a host of biophysical, biochemical and cellular assays to ascertain binding properties and activity. Subsequently, X-ray crystallography (with anomalous scattering) was performed to determine hinge disulfide location. Flexibility and conformation were then assessed using small angle X-ray scattering (SAXS). Structural information was integrated with molecular dynamics simulations and SAXS-guided ensemble reweighting approaches to characterise the link between conformational dynamics and agonistic activity. Together, these orthogonal and complementary approaches provide a rational means to develop more powerful ISAs to deliver more effective anti-cancer treatments.

12:00-12:45, Monson Room
Lunch

12:45-14:00, Olga Pocock Room
Poster Session

14:00-14:35, Simpkins Lee Lecture Theatre
Using *in silico* approaches to accelerate engineering in the ImmTAX platform
Dr Paula Dobrinić (Immunocore)

Traditional experimental approaches to T cell receptor (TCR) discovery and therapeutic engineering have led to successful drug candidates and the first TCR bispecific to show a survival benefit. Our soluble TCR platform delivered precision engineered ImmTAX molecules targeting cancer, infected or self-reactive cells. However, identifying an optimal TCR and affinity engineering to achieve specific and potent on-target activity is a resource- and time-consuming process. Using in silico approaches can significantly accelerate TCR engineering but requires large, high-quality datasets. We developed high throughput paired chain NGS methods to generate large sequence datasets from TCR display libraries. Leveraging this sequence data augmented with our TCR-pHLA structure database is allowing us to expand our understanding of affinity-based selection and specificity, contributing to more efficient lead discovery and engineering.

14:35-14:55, Simpkins Lee Lecture Theatre
Limits on Inferring T-cell Specificity from Partial Information
James Henderson (University College London)

A key challenge in modern molecular biology is to map the amino acid sequence of a protein to its observed biological function. To perform this mapping we must identify sequence features that are informative about function. We present a theoretical framework to quantify the amount of information (in bits) that T cell receptor (TCR) features contain about antigen specificity. We identify informative features by analyzing their degree of conservation among antigen-specific receptors relative to null expectations. We demonstrate that our statistical approach provides measures of information that bound how accurately TCR co-specificity can be predicted from partial feature sets. We find that TCR specificity synergistically depends on all hypervariable regions of the TCR, and we highlight how this limits inferences that can be drawn from bulk-sequenced repertoires about the completeness of thymic negative selection. We anticipate that our framework will provide useful guides for developing machine learning models and for optimizing TCR specificity for cell therapies. The proposed coincidence-based information theoretic measures might furthermore be relevant in other fields.

14:55-15:30, Monson Room
Afternoon Break with Refreshments

15:30-15:50, Simpkins Lee Lecture Theatre

Biophysical cartography of the native and human-engineered antibody landscapes quantifies the plasticity of antibody developability

Dr. Habib Bashour (University of Oslo)

Designing effective monoclonal antibody (mAb) therapeutics faces a multi-parameter optimization challenge known as "developability", which reflects an antibody's ability to progress through development stages based on its physicochemical properties. While natural antibodies may provide valuable guidance for mAb selection, we lack a comprehensive understanding of natural developability parameter (DP) plasticity (redundancy, predictability, sensitivity) and how the DP landscapes of human-engineered and natural antibodies relate to one another. These gaps hinder fundamental developability profile cartography. To chart natural and engineered DP landscapes, we computed 40 sequence- and 46 structure-based DPs of over two million native and human-engineered single-chain antibody sequences. We found lower redundancy among structure-based compared to sequence-based DPs. Sequence DP sensitivity to single amino acid substitutions varied by antibody region and DP, and structure DP values varied across the conformational ensemble of antibody structures. Sequence DPs were more predictable than structure-based ones across different machine-learning tasks and embeddings, indicating a constrained sequence-based design space. Human-engineered antibodies were localized within the developability and sequence landscapes of natural antibodies, suggesting that human-engineered antibodies explore mere subspaces of the natural one. Our work quantifies the plasticity of antibody developability, providing a fundamental resource for multi-parameter therapeutic mAb design.

15:50-16:25, Simpkins Lee Lecture Theatre

Computational strategies for antibody discovery and multi-trait optimization

Dr. Pietro Sormanni (University of Cambridge)

De novo design methods promise a cheaper and faster route to antibody discovery, while enabling the targeting of predetermined epitopes and the parallel screening of multiple biophysical properties. I will present recent advances to design antibodies targeting structured epitopes, to humanise nanobodies, and to simultaneously increase stability and solubility.

16:25-17:15, Simpkins Lee Lecture Theatre

CLOSING KEYNOTE

Predicting antibody developability using interpretable machine learning

Professor Peter Tessier (University of Michigan)

The development, delivery, and efficacy of therapeutic antibodies are strongly influenced by three types of molecular interactions mediated by their variable regions. These include affinity (antibody/antigen) interactions that govern their therapeutic activity and two types of non-affinity interactions, namely off-target interactions that negatively impact bioavailability and pharmacokinetics as well as repulsive self-interactions that positively impact formulation stability and reduce viscosity in concentrated formulations. It is difficult to achieve optimal combinations of these three types of molecular interactions given the competing goals of attractive on-target interactions, a lack of off-target interactions, and repulsive self-interactions. We have developed interpretable machine learning models for identifying clinical-stage mAbs with optimal combinations of low off-target binding in physiological conditions and low self-association in common formulation

conditions, and demonstrate that these co-optimal antibodies display favorable in vitro (formulation) and in vivo (pharmacokinetic) properties. These models also enable the accurate prediction of mutations in antibody variable regions that co-optimize affinity and non-affinity interactions, which we demonstrate for multiple clinical-stage antibodies with unique combinations of suboptimal non-affinity interactions. Our findings can be readily implemented to optimize antibody candidates for diverse therapeutic applications.

17:15-17:30, Simpkins Lee Lecture Theatre
Closing remarks, end of conference.