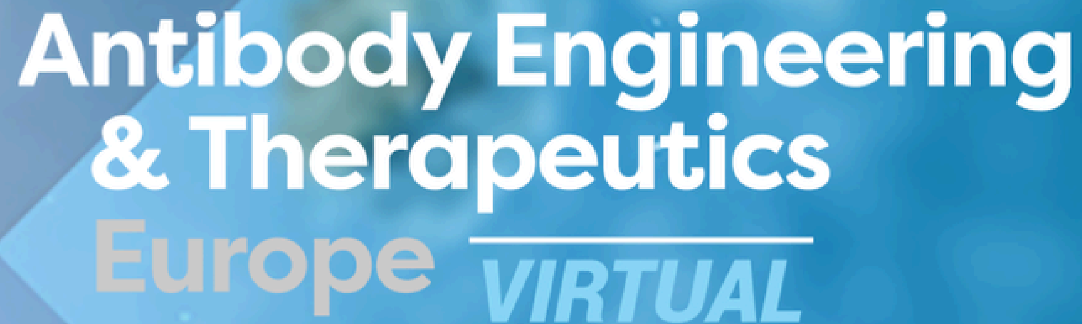
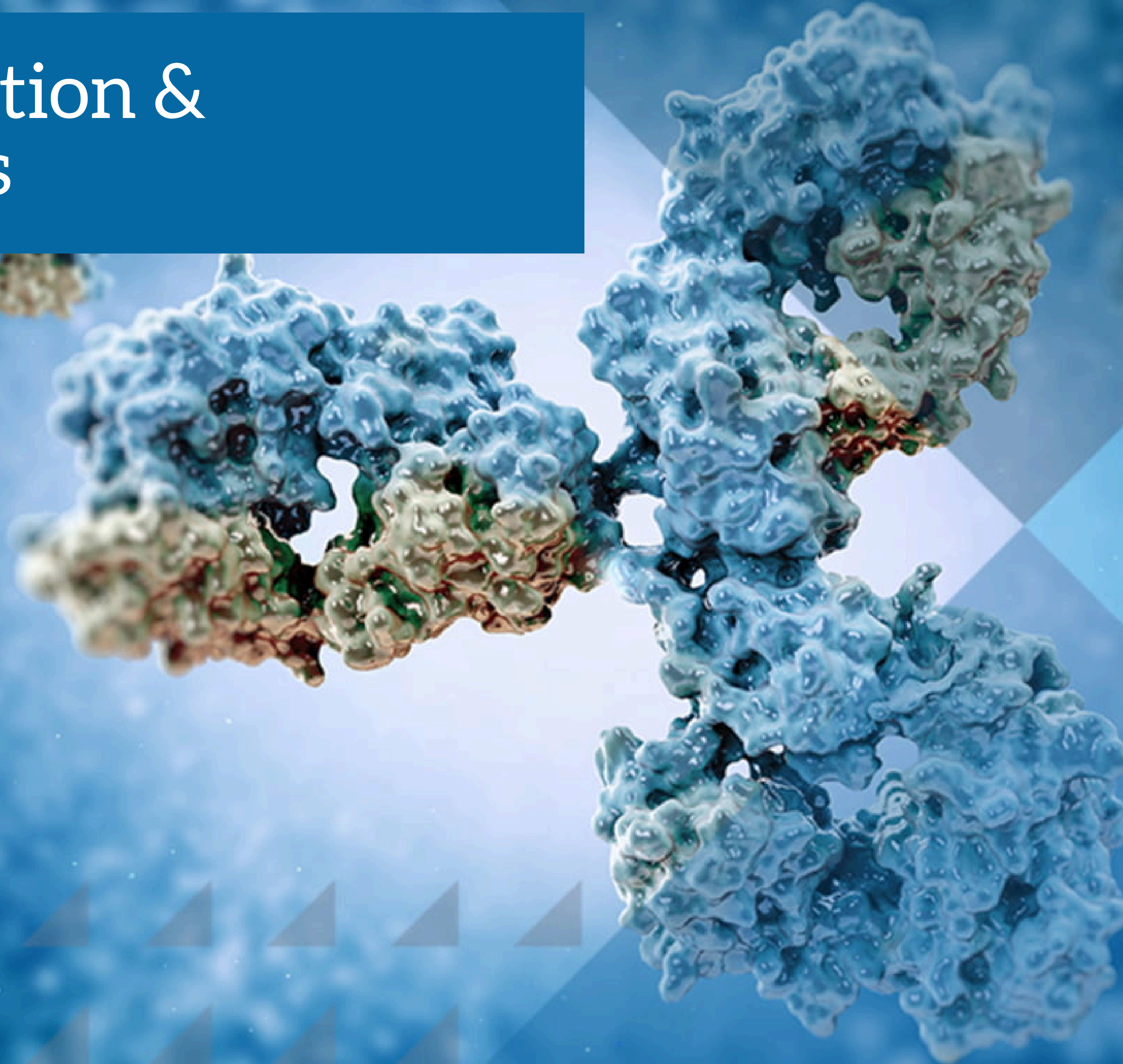


Post-Event Report: Antibody Engineering & Therapeutics Europe

Executive summary, panel discussions, poster winners and selected sessions on-demand

Antibody Engineering & Therapeutics

Introduction & Contents



Welcome...

Over the course of four days on 24 – 27 August 2020, Antibody Engineering & Therapeutics Europe Virtual, run by Informa Connect in conjunction with The Antibody Society, featured a range of industry leading keynotes, live panel discussions and hot topic roundtables, over 50 on-demand sessions and 20 online posters.

In this post-event report we have gathered together some of the highlights from the week, including summaries of the keynotes and hottest discussions, The Antibody Society student/post doc poster competition winners, and full on-demand recordings of selected sessions.

Whether you joined us for the event and are looking for a summary of the week, or else want to see what you missed out on, this is a great summary of the week and will hopefully whet your appetite for Antibody Engineering & Therapeutics US Virtual on December 14-16, 2020.

Sincerely,
Michael Keenan, Project Manager and Producer, Informa Connect

Contents

p5. Key Themes of the Week

An executive summary of the four key themes addressed in the keynotes across the week, including COVID-19, cancer treatments, nanobodies and cytotoxic T cells.

p.13 Hot Topic Discussion: COVID-19 Antibodies

One of the most popular sessions of the week was a hot topic discussion around COVID-19 antibodies. Here we explore some of the key themes that came from the panel.

p.16 Panel Discussion: Antibody Discovery and Developability

Six industry leaders including Dr John McCafferty and Dr Andrew Bradbury discussed antibody discovery and developability as well as engineering aspects of COVID-19 antibodies.

p.20 The Antibody Society Student/Post Doc Poster Competition Award Winners

Read the posters and watch presentations from the two winners, on reagentless fluorescence immunosensors and multiple paratope states that can differ in VH-VL domain orientations.

p.25 Selected Sessions On-Demand

Watch four full recordings of sessions from across the week from Twist, BioCytogen, AbCellera and Berkeley Lights.

Key Themes of the Week

Executive summary

Across 50+ sessions and discussions the hottest topics in the antibody engineering and therapeutics industry in 2020 were explored.

From antibody discovery and developability, to advances in the latest technologies such as computational and machine learning, to, of course, engineering of COVID-19 antibodies.

Here University of Cambridge biochemist writer and entrepreneur Silvia Hnatova offers a summary of the key themes addressed in the keynotes.

Key Themes of the Week - Executive Summary

1. Anti-SARS-CoV2 antibodies in development

Dr Janice M. Reichert, Executive Director of The Antibody Society, delivered the keynote presentation *Antibodies to Watch in a Pandemic*. The talk was divided into two parts: anti-SARS-CoV-2 antibodies being developed and the general trends for antibody approvals.

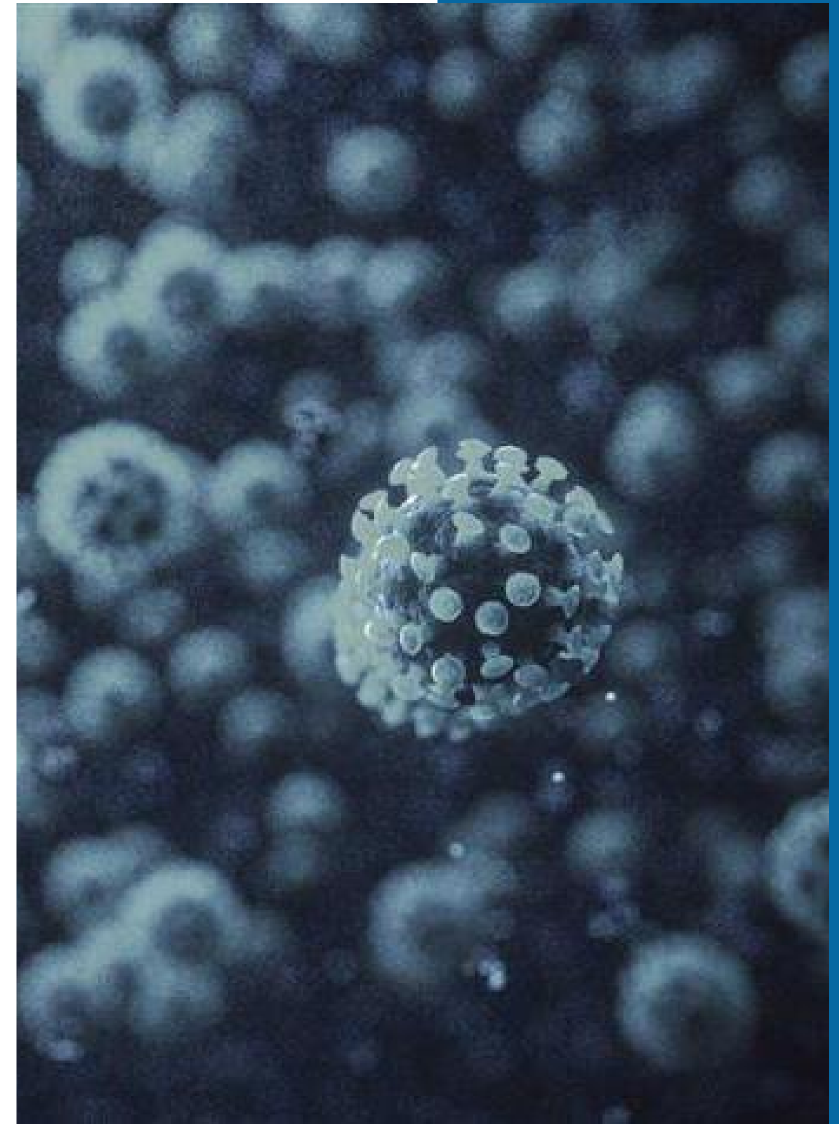
At the time of presenting (27 Aug 2020), two types of anti-SARS-CoV-2 antibodies have been granted regulatory approvals or are anticipated to gain approvals: repurposed antibodies and novel antibodies. Out of the existing antibodies, Dr Reichert identified common pathways being targeted: interleukin-6 or the receptor, GM-CF or the receptor, CS/a or the receptor. Most advanced antibodies are in Phase 2 or Phase 3 trials. Examples of antibodies authorized for therapy in COVID-19 patients are: levilimab (trade name Ilsira) registered for the treatment of patients with severe COVID-19 in Russia, itolizumab (trade name Alzumab) registered for the treatment of cytokine release syndrome in COVID-19 patients in India. Dr Reichert presented seven antibodies that are marketed for COVID-19 use in late-stage trials or in studies, that include the highly publicised remdesivir. She highlighted that the FDA can allow the use of 'unauthorized drugs for prevention, treatment of

> "The year 2020 will likely be ground-breaking in the number of antibodies obtaining regulatory approval"

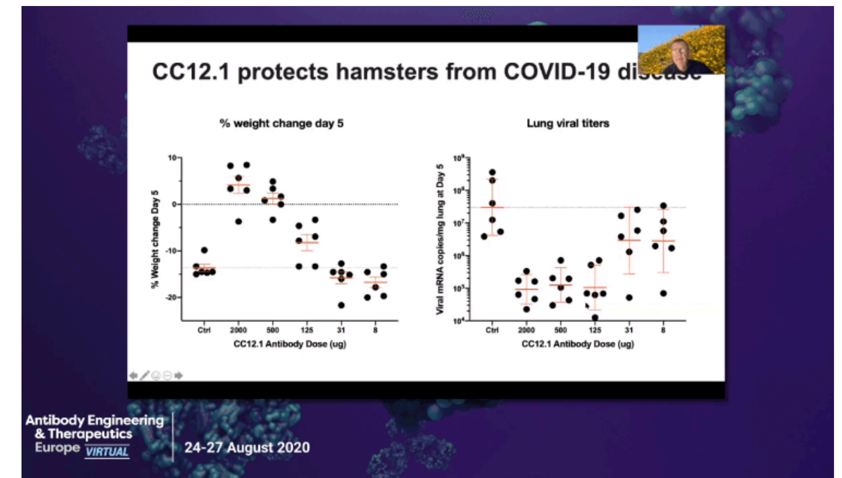
diagnosis of severe or life-threatening conditions, such as SARS-CoV-2'.

The highlight of the talk were anti-SARS-CoV-2 antibodies that are being tracked for use in COVID-19 patients. These represent ~100 small molecules, most of them mAb-based therapeutics. The most advanced anti-SARS-CoV-2 mAbs in Phase 2/3 trials include molecules developed by AbCellera and Eli Lilly and Company, and Regeneron. The completion dates for these antibodies are set in 2020/2021. Dr Reichert pointed out the strategy by Regeneron to roll several antibodies into clinical trials that have different ways of administration: one mAbs being administered intravenously and another subcutaneously. An intriguing part of the talk was focus on ostrich, cow and swine-derived anti-SARS-CoV-2 proteins. A recombinant ACE2, even though not antibody-based, was highlighted as a 'trap' protein that Dr Rechert is intrigued to compare to traditional mAbs in development. Overall, around '20 companies plan to progress anti-SARS-CoV-2 molecules into the clinic by the end of 2020', Dr Reichert said. She introduced an online tracker used for summarizing the latest developments in COVID-19 antibodies.

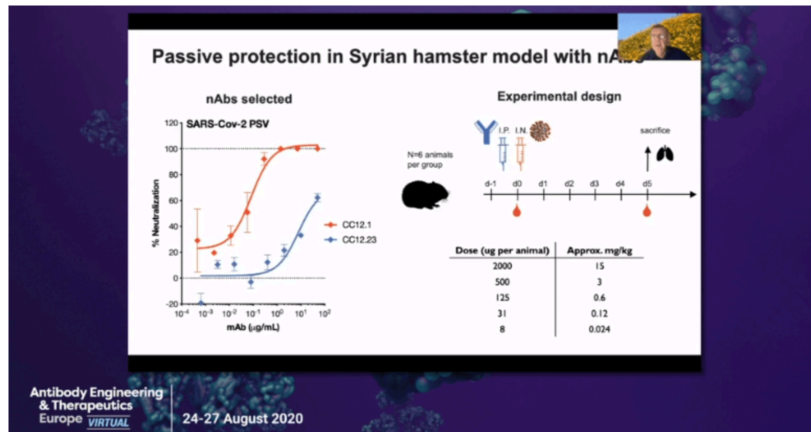
In the second part of the talk, Dr Reichert pointed out the increasing yearly trends of the number of antibodies gaining regulatory approval. The year 2020 will likely be ground-breaking in the number of antibodies obtaining regulatory approval, she highlighted. In addition to five already approved antibodies, at the end of July, there were eight other antibodies in review, three of which were expected to be improved by the end of August. She wrapped up the talk saying that 'projections into 2020 look good' and that she 'hopes that we have a record year in 2020 for the number of antibodies being approved'. Dr Reichert closed the keynote session by praising the global efforts for developing COVID-19 therapeutics.



2. Neutralizing anti-SARS-CoV2 antibodies



Prof Dennis Burton from the Department of Immunology & Microbiology at Scripps Research Ragon Institute described his path towards the discovery of neutralizing antibodies (nAbs) to SARS-CoV-2, published by Rogers et al. (2020) in Science. His group recruited a cohort of COVID-19 patients to look at neutralizing and eventually monoclonal antibodies. The purpose was to set up neutralization assays to look at recombinant antibodies, isolate them and validate their activity in vivo in mice. For this, Prof Burton and his group developed neutralization assays for SARS-CoV-2. They obtained serum and PBMCs from mild to severe COVID-19 survivors near the symptom onset. They sorted around 2,018 IgGs from B cells from three donors. The majority of antibodies contained S spike, RBD and BG505 respectively. The binding of the antibodies, including the ACE2 binding, was confirmed via ELISA assays.



Prof Burton described the fascinating discovery of highly potent monoclonal antibodies against SARS-CoV-2. The antibody epitopes were binned to discover that most mAbs bind to RBD-A, RBD0B and S-A, respectively. The most potent mAbs are those directed against RBD-A, Dr Burton said, and they have very low levels of somatic hypermutation. Dr Burton described how he selected two neutralizing antibodies for validation in Syrian hamster model, in varying doses. Upon the administration of each of the two selected nAbs, hamsters are protected against COVID-19 showing significantly lower viral titers at higher antibody concentrations. Dr Burton pointed out that it is 'possible to generate escape variants' to account for potential resistance of the virus to the antibodies, by generating a cocktail of antibodies. Dr Burton concluded that 'RBD-A ACE2 binding site should be of major focus' for the development of neutralizing antibodies and COVID-19 vaccines.

3. Antibodies in cancer treatment

Multiple intriguing talks touched upon the latest developments in cancer immunotherapies.

Prof Jeanette Leusen, Head of Immunotherapy group at University Medical Center Utrecht and Founder and CSO of TigaTx that engineers IgA as cancer therapeutics, delivered a fascinating keynote lecture on the role of neutrophils in the fight against cancer. She explained that myeloid derived suppressor cells (PMN-MDSCs) are the main obstacle to immunotherapy. PMN-MDSCs are indicators of poor prognosis because of their ability to suppress CD4 and CD8 T cells and induce suppressor macrophages. Prof Leusen aims to redesign PMN-MDSCs to activate appropriate cells, instead of suppressing them. She demonstrated her fascinating results leveraging IgA for inducing killing of cancer cells in in vitro assays. Prof Leusen explained that IgA, 'the most produced antibody in our immune system', induces activation of neutrophils via FcR activation. The question was, according to Prof Leusen, 'whether it would work in vivo'. Her group injected IgA1 into mice that resulted in decreased tumour volume in A431 lung metastasis SCID model. She explained the choice of IgA2 as opposed to IgA1 for therapeutic applications, as IgA2 had no association with Berger's disease.

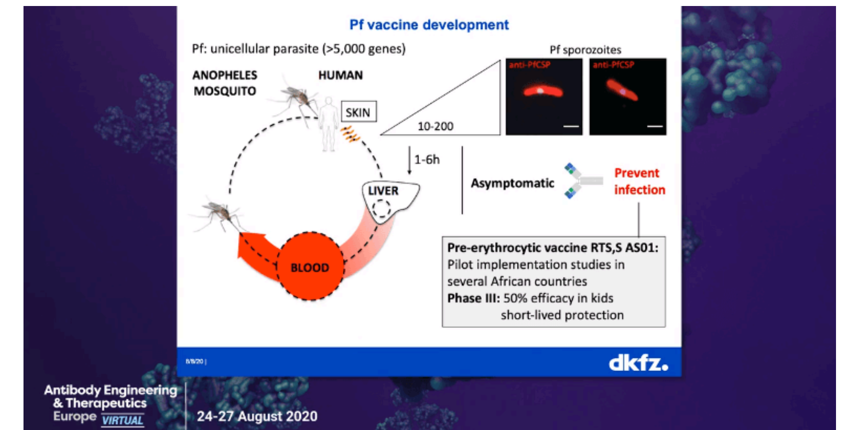
Prof Leusen pointed out at the main challenge of therapeutic applications of IgA: short half-life. In addition to the half-life that is 'around 15 hours' for IgA in mice, she highlighted several other challenges for clinical use of IgAs and her strategies for overcoming them: the presence of a receptor and manufacturing issues, among others. Prof Leusen engineered several IgA molecules to resolve the challenges, leading to the successful IgA3.0 molecule that solves manufacturing, production and stability issues. The strategy used to increase the half-life of the protein was to attach an albumin domain to the molecule. IgA3.0 was demonstrated to work efficiently in vivo in mice, reducing tumour progression. Prof Leusen concluded her talk with the clinical potential for IgA3.0, that could be used for the atreatment of neuroblastoma. She said that IgA3.0 could be an 'alternative to dinutuximab that is FDA-approved but has a very severe side effect (neuropathic pain)', because of diminished binding to neuronal receptors. This was

validated in vivo in mice: IgA bound to neurons but did not activate nociceptors, and successfully reached the tumour in mice.

Prof Sergio Quezada from the UCL Cancer Institute discussed his progress in the research of anti CTLA-4 antibodies. His research showed that reengineered anti CD25 antibodies deplete Tregs, in contrast to previous research that showed that anti CD25 antibodies fail to boost the activity of immunotherapies. In combination with anti PD-1, anti CD25 antibodies contributed to the rejection of established tumours, in eleven out of fourteen mice models.

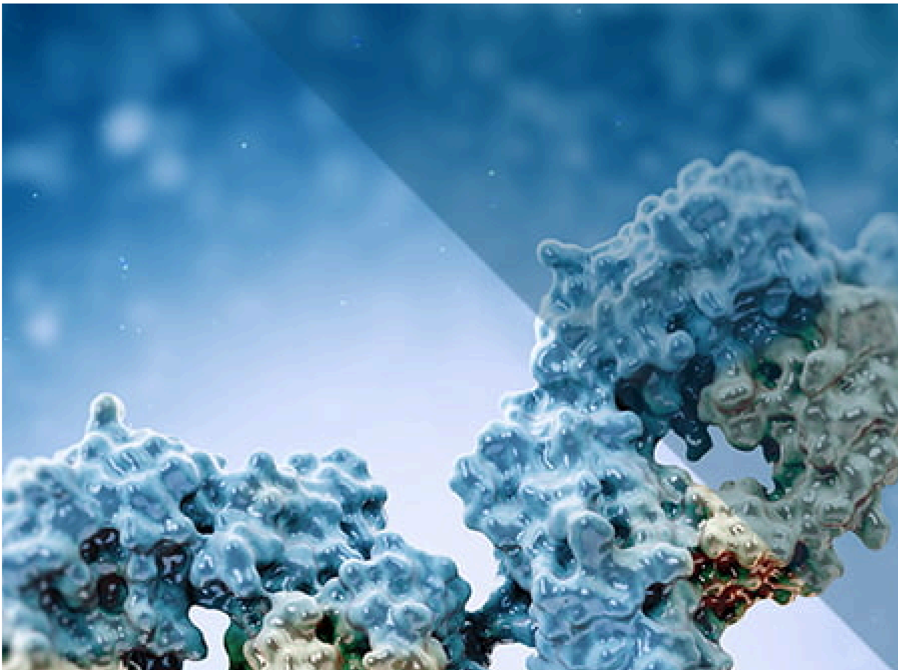
Prof Quezada described his path towards developing clinical-grade anti CD25 antibodies. The strategy was to deplete Tregs without blocking IL2 receptors, to enhance the immune response. Prof Quezada developed such anti CD25 antibody, that after a single dose administration achieved a complete response in mice. This led to the development of the first human anti CD25 with non-interleukin blocking activity (CD25NIB, RG6292) that was acquired by Roche. RG6292 preferentially depleted Tregs in PBMCs in human tumour samples, including lung cancer and colorectal carcinoma, and activated effector T cells in humanized mouse models. Prof Quezada concluded the talk by highlighting that RG6292 is now in Phase I of clinical trials conducted by Roche, awaiting efficacy results.

Prof Hedda Wardemann, Head of Division of B Cell Immunology at the German Cancer Research Center, delivered a fascinating talk about how we can leverage our understanding of B cells to induce a potent B cell response via vaccination. Prof Wardemann focuses on the B cell response to Plasmodium falciparum. She highlighted that there is only one vaccine that succeeded in Phase III trials: the pre-erythrocytic RTS,S vaccine that is being trailed in African countries. Because the efficacy is only 50%, the hope is that improved design will improve efficacy,



The Human B Cell Response to a Repetitive Malaria Parasite Protein - Hedda Wardemann, Professor and Head, Division of B Cell Immunology - German Cancer Research Center

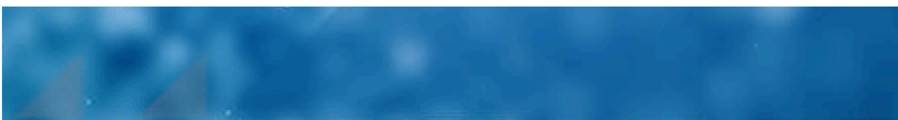
she said. The RTS,S vaccine targets the circumsporozoite protein (CSP) and Prof Wardemann specializes in the human anti-PfCSP antibody response. Her group generated a library of anti-CSP B cell antibodies and compared their strength. Some of them showed good immunization response, with the most potent antibodies being low-mutated or unmutated antibodies that accumulated in the host after multiple parasite exposures.



Most of the CSP antibodies were encoded by a specific gene combination and encoded antibodies with short motifs. 'These antibodies were detected in three out of the eight donors we observed', Prof Wardemann highlighted. She pointed out at the VH3-33 gene segment being the most prominent among the anti CSP antibodies. Because the motif encodes tryptophan, Prof Wardemann hypothesised that this motif may facilitate binding against CSP. She tested this by mutating the tryptophan residue to arginine or lysine, strongly reducing the binding strength to CSP.

Prof Wardemann highlighted that for clinical use of anti CSP antibodies, we need to consider parasite's inhibitory activity of the antibodies. She closed the talk summarising that all potent CSP antibodies target the central repeat including the junction of the protein, that epitope cross-reactivity is associated with high affinity and that most potent PfCSP antibodies recognize a conserved epitope. She suggests that to develop CSP vaccine, 'the quality of anti-repeat response can be improved by promoting germinal center reactions and affinity maturation'.

> “
> The quality of anti-repeat response can be improved by promoting germinal center reactions and affinity maturation."
>
> Prof Hedda Wardemann, Head of Division of B Cell Immunology at the German Cancer Research Center



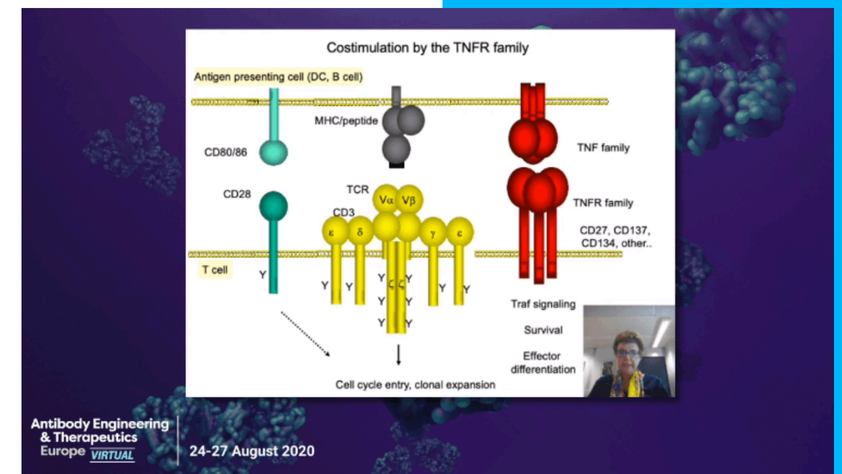
4. Nanobodies and cytotoxic T cells

Prof Serge Muyldermans from the Vrije Universiteit Brussel discussed nanobodies and their clinical applications. Thanks to harbouring camel blood, Vrije Universiteit Brussel was able to conduct strong research using camel antibodies, leading to several spinoffs working on nanobodies.

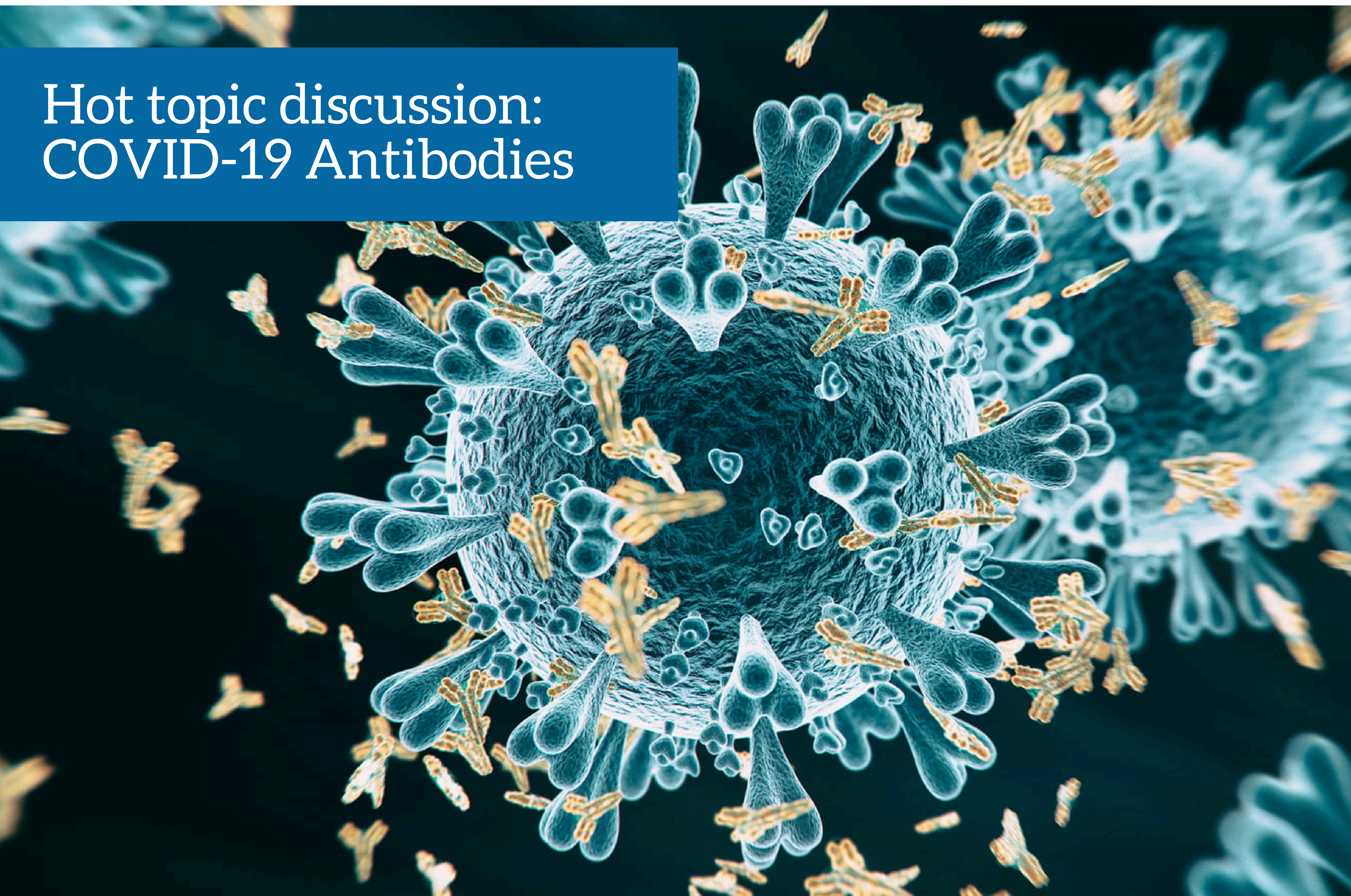
Prof Muyldermans told an interesting story about how blood from healthy and trypanosoma-infected camels was shipped to the university, establishing the research on IgG antibodies in dromedary. Efforts focused on cloning specific domains of the IgG antibodies could produce smaller antibodies, via library generation and nanobody selection. Prof Muyldermans then present several use cases of nanobodies and finally, target applications. Nanobody-facilitated tumour radiolysis and CAR-T cell therapy belong among the candidates for nanobody applications, using their small size, high affinity and specificity.

Prof Jannie Borst, Head of Department of Immunohematology and Blood Transfusion at the Leiden University Medical School introduced the cytotoxic T cells as potential means of targeting cancer immunotherapy during her Keynote Presentation on TNF Receptor Targeting. She is interested in stimulating T cell response via checkpoint inhibitors, to promote a cytotoxic response in cancer. She highlighted PD-1 as a target for promoting T cell response: PD-1 can inhibit both TCR and CD28 signalling.

She studied TNF receptors in mice and concluded that different receptors and ligands act sequentially to promote CTL survival in lymphoid and non-lymphoid tissues. She argued that a combination of CD27 agonism and PD-1 blockade is the most prospective cancer therapy, that her group is exploring in clinical trials as a multimodal cancer treatment.



TNF Receptor Targeting in Cancer Immunotherapy - Jannie Borst, PhD Head, Department of Immunohematology and Blood Transfusion - Leiden University Medical School



Hot topic discussion: COVID-19 Antibodies

Hot topic discussion: COVID-19 Antibodies

One of the most popular sessions of the week was a hot topic discussion around COVID-19 antibodies. Here we explore some of the key themes that came from the panel featuring:

- Prof Charlotte Deane, Professor of Structural Bioinformatics, University of Oxford
- Prof Dennis Burton, Professor and Chairman at the Department of Immunology & Microbiology, The Scripps Research Institute
- Dr Joseph Jardine, Director of Product Discovery and Optimization, International AIDS Vaccine Initiative
- Dr Devin Sok, Director of Antibody Discovery and Development, International AIDS Vaccine Initiative

---

The hot topic discussion was a fascinating discussion among the specialists on the front of COVID-19 antibody research. Prof Deane opened the discussion by highlighting that most of the innovation grants awarded for COVID-19 antibody research in the UK study the antibody response to vaccine administration. She emphasised that antibody therapeutics remain the least explored area of research despite the need of 'a combination of vaccine and antibody therapeutics' for overcoming COVID-19. Prof Deane and Prof Burton agreed that antibody therapeutics is so far the least popular treatment in clinical trials, discussing the reports of doctors about low efficiency. Dr Jardine protested saying that 'convalescent trials rarely looked at people with bad outcomes', because 'in general, you tend to look at people who do better' that could have led to the reporting of negative outcomes in patients. Dr Sok agreed in the debate that there 'has not been any indication that the antibodies could be linked to enhanced respiratory disease'. There was a technical discussion on Fc receptor binding knockout design and whether this could resolve the safety concerns.

Dr Jardine then discussed 'what will happen in the next 6 months' of COVID-19 therapeutics research. He outlined that any future

strategies will depend on the outcomes of the major vaccine trials, highlighting that evidence for 'passive antibody transfer having a positive effect'. Dr Jardine discussed the prospects of monoclonal antibodies, saying 'there is good evidence it will work', even though the antibodies would have to be administered multiple times. Dr Sok agreed, 'he thinks antibodies will be needed' regardless of whether a vaccine will be successful. Prof Deane brought a good point, saying that antibodies will be needed in parallel to vaccine approaches, because vaccines would have to be administered to the majority of the population for the approach to work. Prof Burton pointed at the expenses of antibody manufacturing, posing a question of 'what is feasible'. Dr Jardine contributed to the discussion highlighting that the global efforts to make treatment more accessible could solve the universal problem of scalability of any monoclonal antibody therapeutics. Dr Sok agreed that the global use of an antibody therapeutic would be unprecedented, putting pressure on making the antibody accessible and feasible. His opinion was that having multiple companies will be very important to meet the global demand and to bring the cost of antibody therapeutics down. Dr Sok pointed out that the susceptibility of the elderly and immunocompromised people would make them the best candidates for prophylaxis treatment.

Prof Burton asked the panel 'how far should we go in the engineering of the antibodies?' Dr Jardine responded that the major advantage of engineering antibodies would be that they would be able to cover different mutations of the virus. There was then a discussion of various technical aspects of antibody engineering, that could aid the overall design. Questions from the audience highlighted several other potential issues with antibodies, for example how much the host immune response could contribute to a response to the virus in parallel to antibodies, whether antibodies could enhance or also inhibit host's immune response and questions about the overall safety of monoclonal antibodies.

> “There has not been any indication that the antibodies could be linked to enhanced respiratory disease."
>
> Dr Devin Sok, Director of Antibody Discovery and Development, International AIDS Vaccine Initiative

Panel discussion: Antibody Discovery and Developability

Panel discussion: Antibody Discovery and Developability

Across the week there were a number of fascinating panel discussions. Here we explore some of the key themes that came from a discussion on antibody discovery and developability featuring:

- Dr Andrew Bradbury, Chief Scientific Officer at Specifica
- Tushar Jain, Principal Scientist at Adimab
- Dr Lucy Ahmed, Postdoctoral Fellow at Boehringer Ingelheim Pharmaceuticals
- Tileli Amimeur, Senior Data Scientist at Just-Evotec Biologics
- Dr John McCafferty, CSO at Iontas
- Dr Jordan Dimitrov, Scientist at the Department of Immunology at INSERM - Centre de Recherche des Cordeliers

---

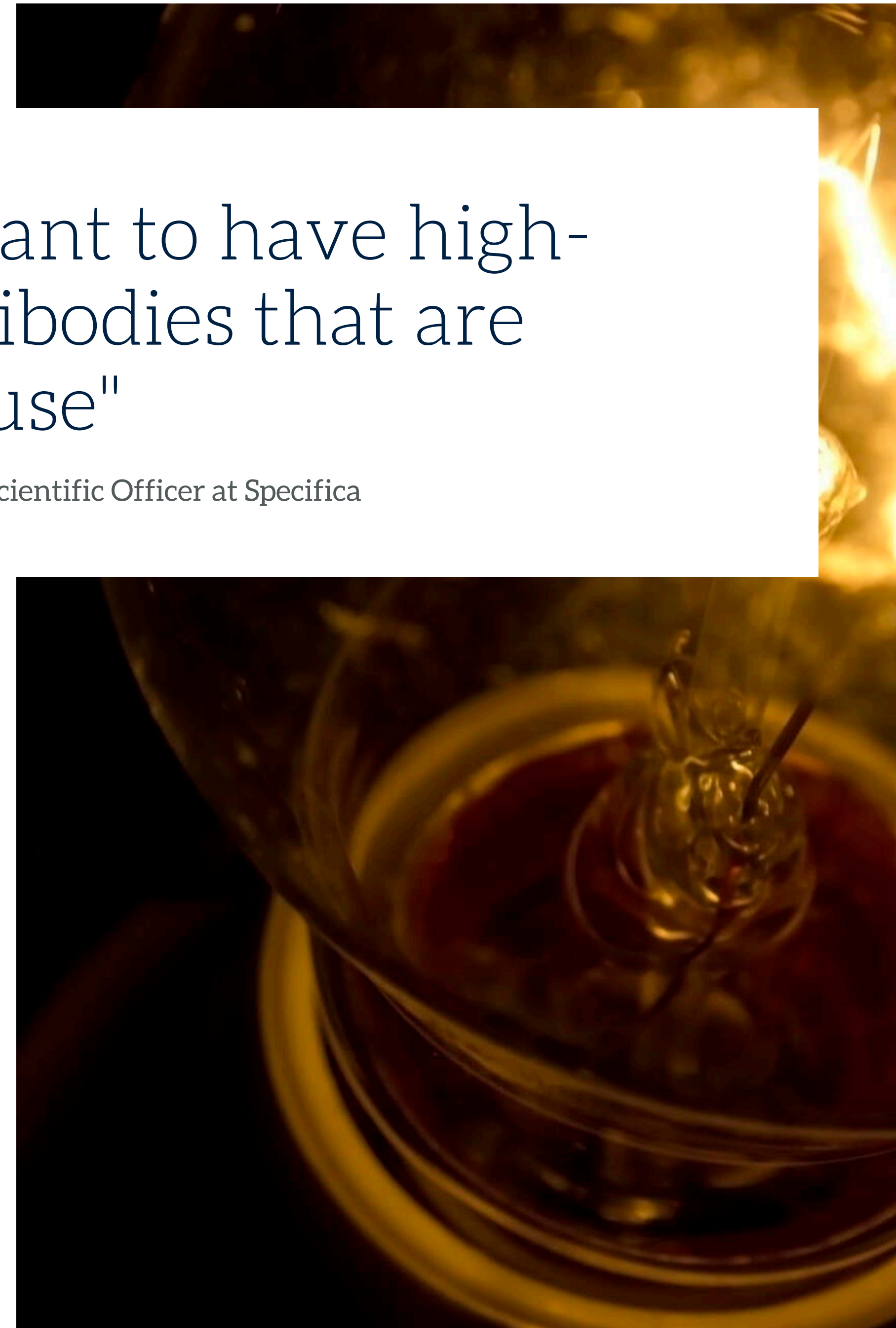
This very technical discussion focused on the engineering aspects of COVID-19 antibodies, supported by opinions of the leaders in the field. Dr Bradbury opened the discussion by asking participants about their approaches to antibody design and the role of AI. Tileli Amimeur explained that the 'whole AI approach is entirely sequence-based', explaining the role of AI in antibody engineering saying that 'we need a lot of data for the approach to work'. She summarized her approach as depending on the generation of the data, to be able to answer the antibody design questions better. Tushar Jain explained the challenges of publishing huge datasets of sequences in a public domain. Tileli Amimeur elaborated his point adding that the public datasets usually lack negative examples, that 'would enable us to learn'. There was a technical discussion sparked by the audience questions on general antibody design in silico, with Tushar Jain concluding that a parallel design approach testing affinity and specificity would be very useful. Dr Dimitrov

disagreed saying that antibody design is a 'case-by-case' problem, saying that antibody cannot be designed based on a single parameter only. Dr Bradbury asked the panel whether any blood proteins could modify antibody function. Dr Dimitrov replied that there are many reasons for hemolysis and that they are trying to understand the process. Dr Bradbury asked if there are any examples of changes of antibody specificity following hem exposure, with Dr Dimitrov explaining that hem exposure does not affect antibody binding.

The panel discussion was followed by an intriguing exchange between Dr Bradbury and Dr McCafferty, who discussed their experience in COVID-19 antibody design and their vision of future COVID-19 treatments. They agreed that it is important to keep as many as possible antibodies in the clinical trials, to have the most chances to beat the virus. Dr McCafferty highlighted that once a vaccinated patient is COVID-19 positive, the antibodies will be needed because the vaccine will no longer be useful. Dr McCafferty and Dr Bradbury agreed on the ideal future vision for COVID-19 therapy. If a patient would test positive for COVID-19 test, a dose of neutralizing antibody could be administered immediately. Through his research, Dr McCafferty highlighted that

> “We don't want to have high-affinity antibodies that are difficult to use"
>
> Dr Andrew Bradbury, Chief Scientific Officer at Specifica

by using mRNA from convalescent plasma donors, they obtained a library of potent neutralizing antibodies within two months. Unfortunately, his research was thrown into unknown charters because the that UK funding was withdrawn at short notice, due to the existence of cheaper antibodies being



repurposed for COVID-19. Dr McCafferty is hopeful that a new partner could help to bring the neutralizing antibodies into the clinic.

Dr Bradbury and Dr McCafferty then discussed the success of different neutralizing antibodies. This prompted a technical discussion about motif design in the 3-53 gene that encodes the immunoglobulin heavy-chain variable region, that was previously shown to target the spike protein of COVID-19.

Dr McCafferty outlined that the problem with selecting higher affinity antibodies might generate 'stickier' antibodies. He said that through his research, he learned that some paratopic residues have a higher affinity. Dr Bradbury elaborated on the point explaining that the 'the stability is increased by virtue of interaction, preventing the antibody from falling apart'. They concluded that 'we don't want to have high-affinity antibodies that are difficult to use'.

Antibody Engineering & Therapeutics US
VIRTUAL
December 14-16, 2020
Annual Meeting of the ANTIBODY SOCIETY
THE #1 ANTIBODY ENGINEERING CONFERENCE FOR ACCELERATING NEXT GENERATION ANTIBODIES TO COMMERCIAL SUCCESS
KEYNOTES SHARE PERSPECTIVES TO FAST-TRACK YOUR R&D
The Structural Basis of Neutralization by Antibodies Against Viral Fusion Proteins
Pamela Bjorkman Ph.D.
David Baltimore Professor of Biology and Biological Engineering, CALTECH
Engineering Bispecific Antibodies as Therapeutics: Utilizing Intrinsic Heavy/Light Chain Pairing Preferences and Mitigating High Viscosity
Paul J. Carter, Ph.D.
Genentech Fellow, Department of Antibody Engineering, GENENTECH, INC.
Characterizing Polyclonal Antibody Responses Using Single Particle Electron Microscopy
Andrew Ward, Ph.D.
Professor, Department of Integrative Structural and Computational Biology, THE SCRIPPS RESEARCH INSTITUTE
Prepare for the Conference in Advance by Attending this Pre-Conference Virtual Training Course
INTRODUCTION TO ANTIBODY ENGINEERING
December 8-10, 2020 (2 hours per day)
Conveniently Scheduled for Both North American and European Time Zones at 11:00 am- 1:00pm EST • 5:00pm – 7:00pm CET • 8:00am-10:00 PST
Brought to you by informa connect
www.AntibodyEng.com

The Antibody Society Student/Post Doc Poster Competition Award Winners

View the posters and watch a presentation of each by the winners

Poster - Click to expand

Development of Reagentless Fluorescence Immunosensors for Continuous Analyte Monitoring

Christian Fercher

ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Australian Institute for Bioengineering and Nanotechnology, The University of Queensland

Find out more or contact at www.cbns.org.au.

Fluorescence-based immunodiagnostics are an emerging field in biosensor development and exhibit several advantages over traditional detection methods. While various affinity biosensors have been developed to generate a fluorescence signal upon sensing varying analyte concentrations, reagentless, reversible and continuous monitoring of complex biological samples remains challenging. Here, we aimed to genetically engineer biosensors based on single-chain antibody fragments (scFv) that are site-specifically labelled with environmentally sensitive fluorescent unnatural amino acids (UAA).

A rational design approach resulted in quantifiable

analyte-dependent changes in peak fluorescence emission wavelength and enabled antigen detection in vitro. Incorporation of a polarity indicator in proximity of the antigen binding interface generated a titratable wavelength blueshift, resulting in nanomolar detection limits. In order to ensure continuous analyte monitoring, scFv candidates with fast binding and dissociation kinetics were selected from a CDR mutant library employing a directed evolution phage display biopanning approach coupled to subsequent high-throughput affinity screening. Initial rankings were further refined towards rapid dissociation kinetics using bio-layer interferometry (BLI) and surface plasmon resonance (SPR).

The most promising candidates were expressed, purified and tested for their potential to detect varying concentrations of the target antigen in a continuous microfluidics-based assay. Variations of dissociation kinetics within an order of magnitude were achieved without compromising specificity of the antibody fragments. This approach is generally applicable to numerous antibody/antigen combinations and currently awaits integration in a wide range of assay platforms for specific one-step protein quantification in complex samples.

Presentation - click to watch

Antibodies exhibit multiple paratope states that can differ in VH-VL domain orientations

Monica Fernández-Quintero

Department of General, Inorganic and Theoretical Chemistry,
University of Innsbruck, Austria

Find out more at liedllab.org or email Monica.Fernandez-Quintero@uibk.ac.at

In contrast to this prevalent static view of the binding interface we demonstrate a dynamic perspective not only of the paratope but of whole Fvs and Fabs. We show that antibodies exist as ensembles of paratope states. These paratope states are defined by a characteristic combination of CDR loop conformations and interdomain orientations. They interconvert into each other in the micro-to-millisecond timescale by correlated loop and interdomain rearrangements. We demonstrate that crystal packing effects can distort the paratope state and thus result in misleading X-ray structures. By advancing the repertoire of cutting-edge simulation techniques, for the first time we achieve a complete description of conformations, thermodynamics and kinetics of the whole binding paratope in solution.

Poster - Click to expand

These findings have broad implications in the field of antibody design and in the development of biotherapeutics as they provide a new paradigm in the understanding of CDR binding loop states, antibody-antigen recognition, relative VH and VL interface angles and elbow-angle distributions and their respective dynamics. Preliminary findings are already published in six manuscripts, but a considerable number of further publications is upcoming.

Presentation - click to watch

These upcoming publications will also address issues like inter-loop correlation and the relationship of Fv-interface dynamics with loop rearrangements:

- Characterizing the Diversity of the CDR-H3 Loop Conformational Ensembles in Relationship to Antibody Binding Properties, Monica L. Fernández-Quintero, Johannes R. Loeffler, Johannes Kraml, Anna S. Kamenik, Klaus R. Liedl, Frontiers in Immunology 9 (2018) 3065
- CDR-H3 Loop Ensemble in Solution — Conformational Sélection upon Antibody Binding, Monica L. Fernández-Quintero, Johannes Kraml, Guy Georges, Klaus R. Liedl, mAbs 11 (2019) 1077
- Transitions of CDR-L3 Loop Canonical Cluster Conformations on the Micro-to-Millisecond Timescale, Monica L. Fernández-Quintero, Barbara A. Math, Johannes R. Loeffler, Klaus R. Liedl, Frontiers in Immunology 10 (2019) 2652
- Antibody humanization—the influence of the antibody framework on the CDR-H3 loop ensemble in solution, Monica L. Fernández-Quintero, Martin C. Heiss, Klaus R. Liedl, Protein Engineering, Design and Selection 32 (2019) 411
- VH-VL interdomain dynamics observed by computer simulations and NMR, Monica L. Fernández-Quintero, Valentin J. Hoerschinger, Leonida M. Lamp, Alexander Bujotzek, Guy Georges, Klaus R. Liedl, Proteins: Structure, Function, and Bioinformatics (2020) early view DOI: 10.1002/prot.25872
- Antibody CDR Loops as Ensembles in Solution vs. Canonical Clusters from X-ray structures, Monica L. Fernández-Quintero, Martin C. Heiss, Nancy D. Pomarici, Barbara A. Math, Klaus R. Liedl, mAbs 12 (2020) in press DOI: 10.1080/19420862.2020.1744328

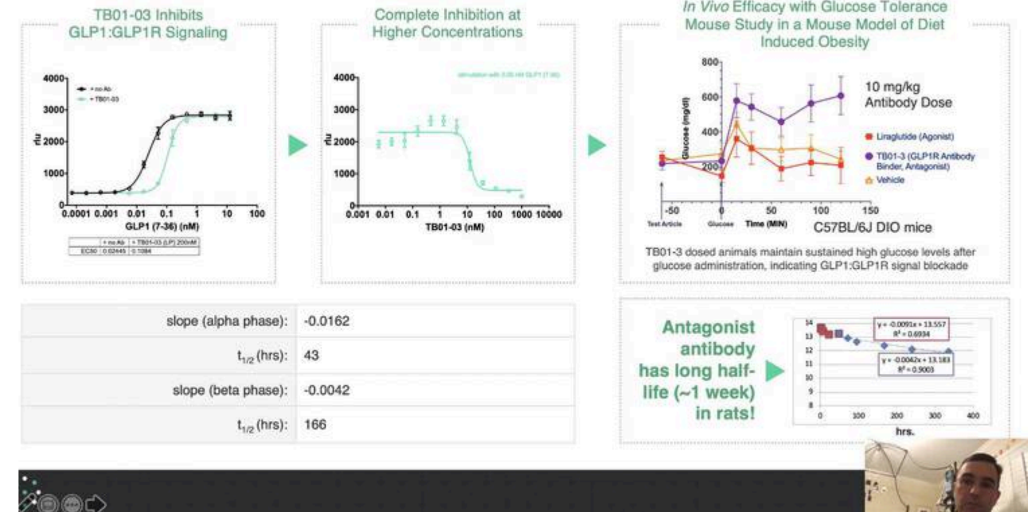
Selected Sessions On-Demand

Watch full recordings of sessions from across the week

Synthetic DNA Technologies Enable Antibody Discovery and Optimization

Aaron Sato, PhD
Chief Scientific Officer, Biopharma,
Twist Bioscience

Presentation - Click to Watch



Utilizing its proprietary DNA technology to write synthetic libraries, Twist Biopharma, a division of Twist Bioscience, provides the biotechnology industry with an end-to-end antibody discovery and optimization solution.

This solution includes (1) a panel of highly diverse synthetic naïve antibody phage display libraries, (2) several target class specific antibody phage display libraries focused on difficult-to-drug targets, (3) a Twist Antibody Optimization (TAO) platform for antibody affinity and developability optimization and (4) a high-throughput antibody expression service.

Amplifying Antibody Diversity: Single-cell Screening Combined with Repertoire Sequencing from Humanized Mice

Sherie Duncan, PhD
Senior Manager Programs and Partnerships
AbCellera

Presentation - Click to Watch

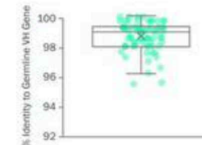
IDENTIFIED HUNDREDS OF UNIQUE ANTIBODIES

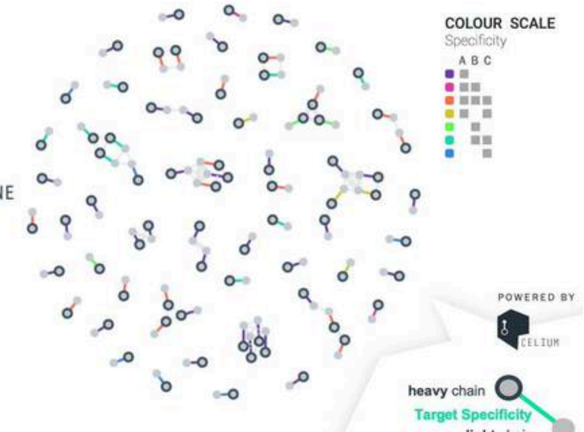
540,000 SINGLE CELLS

421 HITS (0.08% frequency)

75 UNIQUE ANTIBODIES

44 CLONAL FAMILIES
17 VH GENES
95-100% HC ID TO GERMLINE





We identified hundreds of target-specific antibodies using high-throughput single-cell screening from humanized mice. To reveal greater diversity, we sequenced the immunoglobulin repertoire of immunized animals and superimposed validated single-cell-derived sequences using bioinformatics to reconstruct clonal trees.

This versatile approach dramatically expands the total available number of fully human, in vivo-generated antibodies against any therapeutic target.

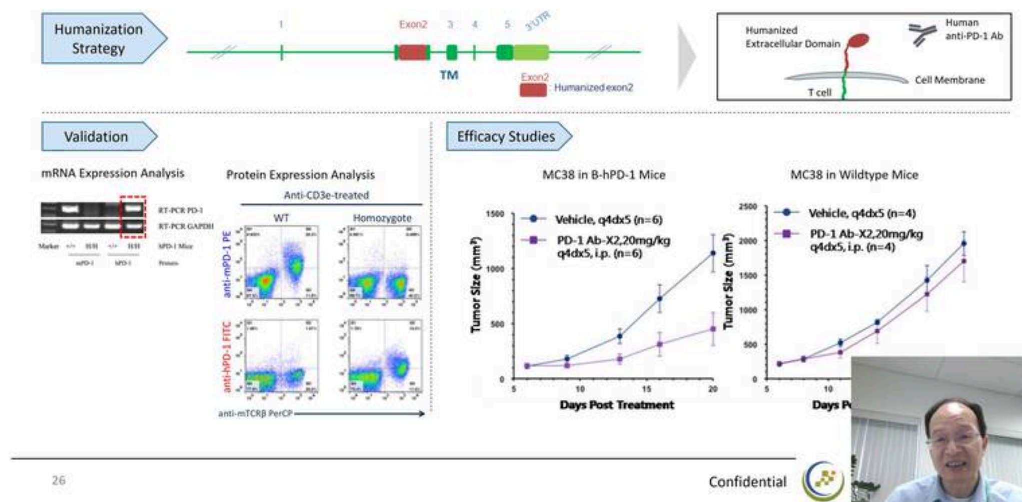
Accelerating Therapeutic Antibody Discovery with Three Distinct Humanized Mouse Models

Qingcong Lin, PhD
Chief Executive Officer
Biocytogen Boston Corp.

Biocytogen has recently developed RenMab™ Mouse, which is a transgenic mouse with human germline Ig heavy chain and kappa light chain regions in lieu of those in the wild-type mouse, allowing for rapid generation of fully-human antibodies. Created with chromosome engineering technology, the RenMab™ Mouse has demonstrated no significant abnormality when compared to wild-type mice, with cell profiles, B-cell development, and immune repertoire all indistinguishable from normal. The RenMab™ Mouse has demonstrated robust immune responses to various antigens, subsequently producing antibody hits with strong functionalities, high antigen-specific affinities, and highly diverse sequences and epitopes.

Presentation - Click to Watch

Case 1. Humanized PD-1 Mice (B-hPD-1) Can Be Used for α–hPD-1 In Vivo Efficacy Evaluation

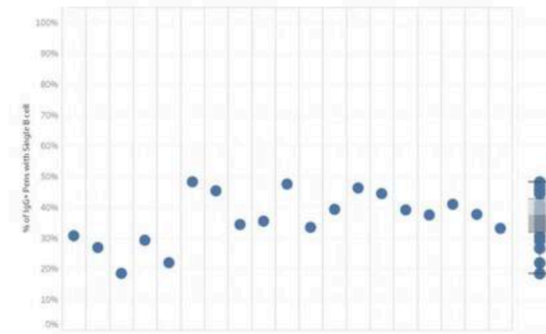


To identify leads from the antibody hits derived from RenMab immunization, Biocytogen has created a catalog of target-humanized mouse models, allowing for researchers to conduct high throughput antibody hit screening. Lastly, to further select for candidates with best clinical translation potential, Biocytogen offers immune-cell humanized mouse models for use in preclinical efficacy and toxicity evaluation. Combining the aforementioned three humanized mouse models, Biocytogen is soon to offer an integrated-technology platform to both generate and screen for therapeutic antibodies, accelerating the process from target validation to IND application.

Reaching the High-Hanging Fruit: Accessing Broad B cell Diversity to Select Better Lead Candidates in Under 1 Week

Anupam Singhal, PhD
Product Manager, Antibody Therapeutic
Berkeley Lights, Inc.

Presentation - Click to Watch



Traditional technologies are unable to screen the entire B cell repertoire. As a result, antibody therapies have only been developed against simple targets with limited success for more difficult targets such as GPCRs and ion channels. Plasma B Discovery on the Beacon® optofluidic system enables discovery of antibodies against more difficult targets by accessing broad B cell diversity to discover thousands of hits and down-select lead candidates in less than 1 week.

Join us at Antibody Engineering & Therapeutics US Virtual on December 14-16, 2020

informaconnect.com/antibody-engineering-therapeutics

Antibody Engineering
& Therapeutics
Europe VIRTUAL

24 - 27 AUGUST 2020