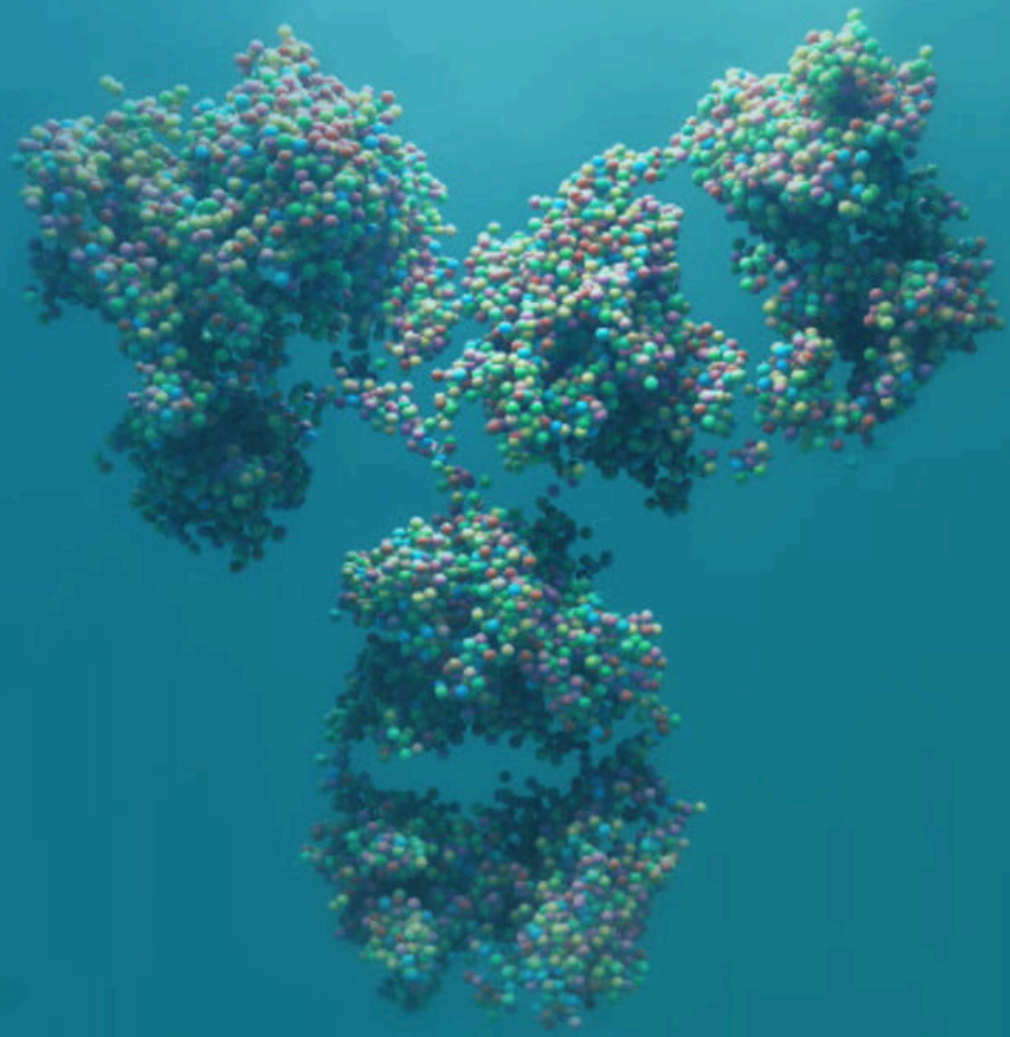
Antibody Engineering & Therapeutics 2021: The Rewind

Top highlights from the week

Antibody Engineering & Therapeutics

AbCellera



Introduction

In December 2021, the **Antibody Engineering & Therapeutics** hybrid conference took place in San Diego, with a digital experience option for those who couldn't join.

Sessions exploring topics across antibody-based drug production were led by 135+ speakers from around the industry.

The comprehensive program, created in conjunction with the Antibody Society, boasted fascinating insights shared by the likes of **Kristian Andersen** (Scripps Research), **James Wells** (UCSF), **Aviv Regev** (Genentech Research & Early Development) and many more.

Join us as we take a look back at the highlights from the week, including the most captivating keynotes, the scientific poster presentation hall and reflective insights from AbCellera.

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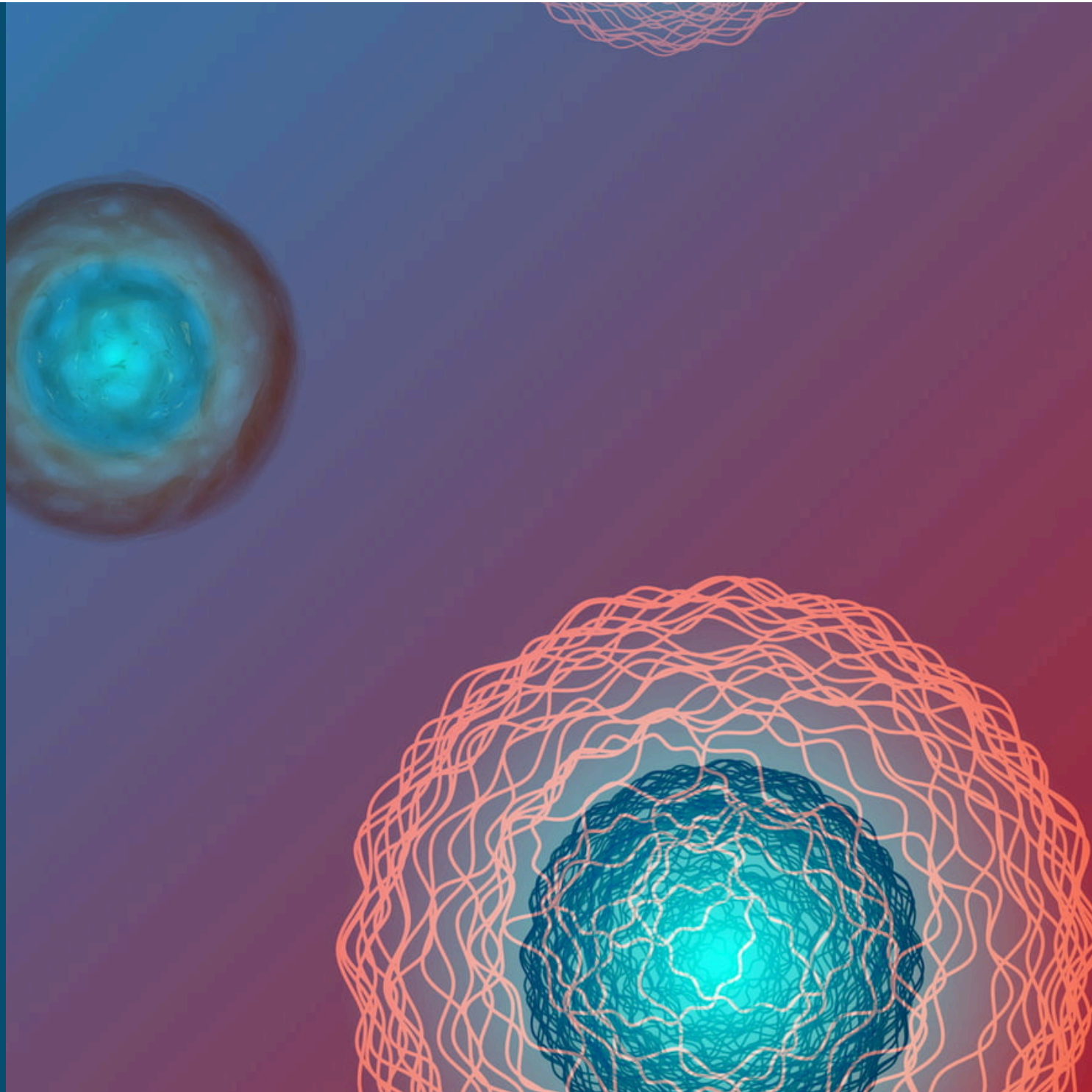
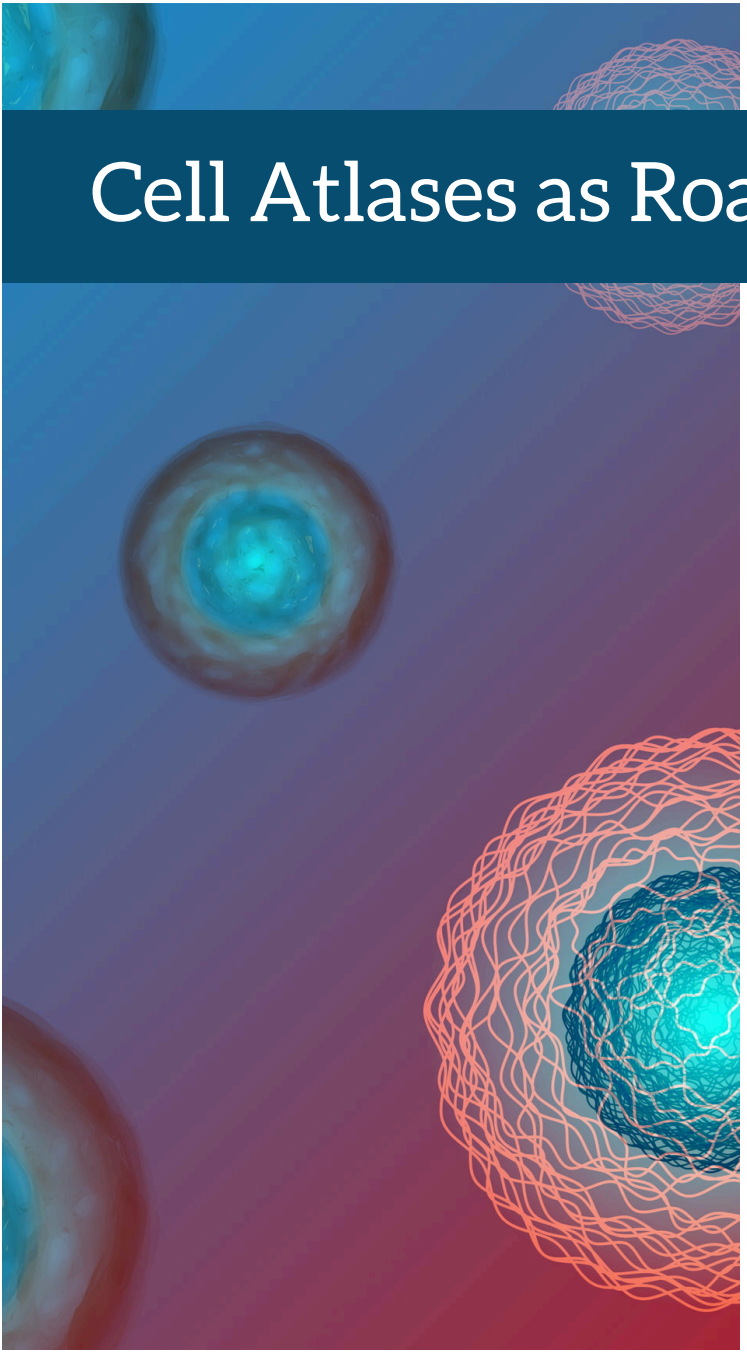
Cell Atlases as Roadmaps in Health and Disease

Understanding cell-specific cellular networks: a presentation by Dr Aviv Regev at Genentech Research and Early Development



Cell Atlases as Roadmaps in Health and Disease



Single-cell genomics is a revolutionary technology able to unveil cell types, differentiation status, gene programs, physical location, and cell interactions in space. **Dr Aviv Regev**, Executive Vice President at Genentech Research and Early Development delivered a comprehensive summary of her group's research during the conference.

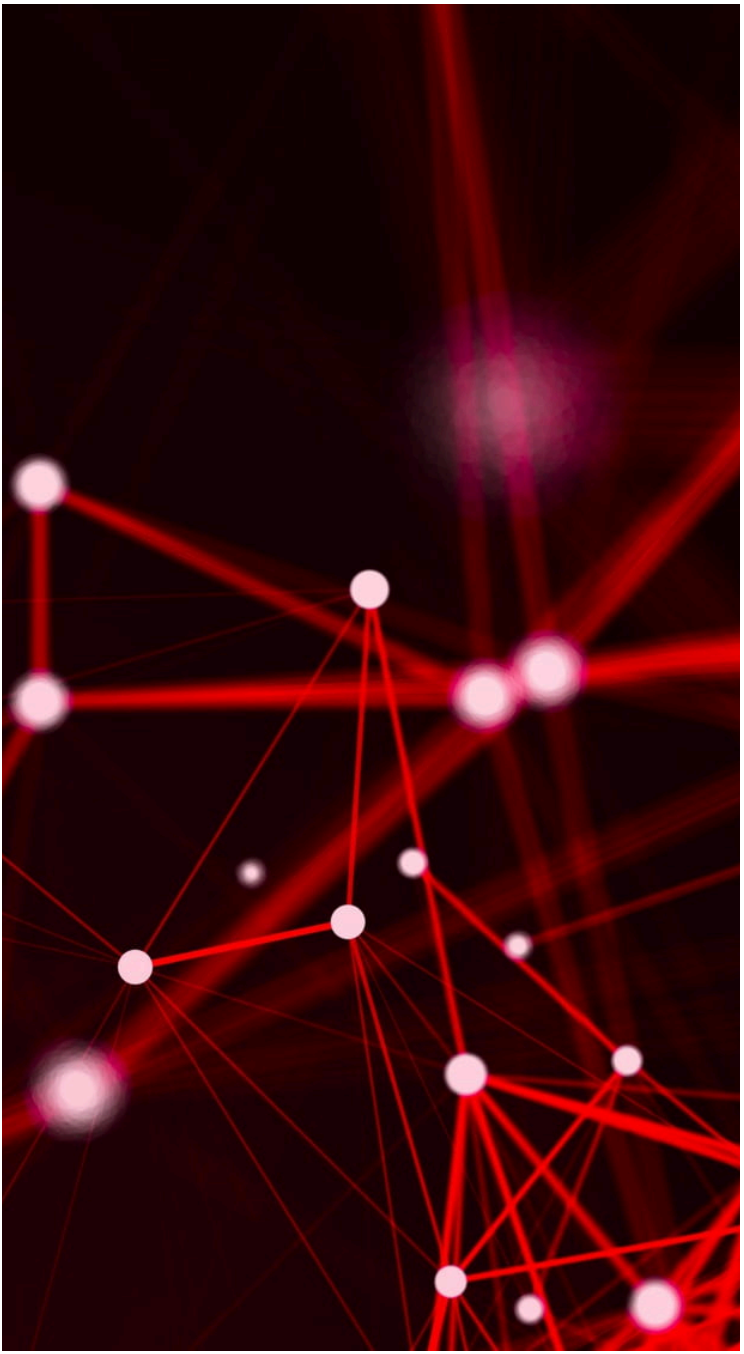
She postulated that single-cell genomics can help to unveil new relationships between the genotype and phenotype, and ultimately enhance our understanding of diseases. To illustrate her point, she first outlined her use of single-cell genomics to elucidate the cellular basis of a complex genetic disease, ulcerative colitis (UC), a form of irritable bowel syndrome (IBS).

Single-cell atlas of ulcerative colitis sheds light on cell-specific cellular networks

Genome-wide association studies (GWASes) previously identified multiple loci linked to IBS. However, the cellular faction of the variants or the mechanism of action of the variants remains unknown.

To address this problem, Dr Smillie from Dr Regev's lab created a single-cell atlas of the healthy and ulcerative colitis (UC) colonic mucosa (Smillie et al., 2018, bioarXiv).

Through sequencing of 251,133 cells from 17 patients with UC and 10 healthy biopsies, scPhere deep-learning algorithm separated the cells into epithelial, stroma, and immune cells.



> "There is a need for more comprehensive cell atlases, because of the techniques used to recover cells used for downstream sequencing"

The study demonstrated a change of cellular profile, an enrichment in M-like stromal cells, and expansion of inflammatory fibroblasts in UC compared to healthy tissue.

Dr Regev's group next looked into the enrichment of specific GWAS genes in certain cellular populations (Smillie et al., 2019, Cell). They found that specific GWAS genes are enriched in M-like cells in UC.

A connectome analysis between cells identified a change in cellular networks in UC, driven by GWAS genes and cell types enriched in such genes acting as hubs of decompartmentalization. Dr Regev highlighted that most UC-risk genes are only expressed in specific mucosal cells, which may be lacking in their research (Drokhlyansky et al., Cell 2020).

There is a need for more comprehensive cell atlases, because of the techniques used to recover cells used for downstream sequencing. Dr Regev's lab developed such techniques, named RAISIN-Seq (nuclei + ribosomes) and MIRCL-Seq (label-free rare cell enrichment).

Dr Drokhlyansky combined the two methods to construct an enhanced single-cell atlas, unraveling additional genes constricted to new cell types related to enteric neuropathies and extra-intestinal disorders with gastrointestinal dysmotility, such as Parkinson's disease.

Dr Regev suggested that this technique could be used to study conditions that are CNS-related, but affect neurons outside of the CNS, posing barriers to their current research. She highlighted the need to have comprehensive catalogs of diseases available.

scLinker: towards the understanding of pathways and cellular programs with scRNA-Seq

In the second part of her talk, Dr Regev focused on the potential use of single-cell sequencing for understanding cellular programs and the ways genes relate to each other.

To illustrate her point, Dr Regev introduced gene C1org106 commonly expressed in enterocytes (Smillie et al., 2019, Cell).

By studying C1org106 co-expression signatures, Dr Regev's group found that C1org106 expression was found to vary across tight junction enterocytes, suggesting the gene's potential new function.

Related to intercellular co-expression variability, Dr Regev's group studied co-expressing of C1org106 within the cells, finding that 10 meta-modules span over 50% of GWAS-implicated IBD risk genes.

Dr Regev next asked whether causal genes for the risk regions could be identified. Smillie et al. (2019) found that single-cell expression and co-expression help nominate causal genes in associated regions, identifying concrete disease-related cellular programs.

Dr Regev's lab created a scLinker technique to be able to identify cell programs from GWAS studies combined with scRNA-Seq sequencing (Jagadeesh et al., 2021, BioarXiv).

Using the technique, Dr Regev found that pathway-related programs can be found in UC, and also Alzheimer's disease and multiple sclerosis. Using the analysis, IBD heritability cell programs could be found across monocytes and fibroblasts.

Deciphering multicellular programs with the use of genetic perturbations

Building upon cell programs, Dr Regev explained that the focus of her lab was next on 'multi-cellular programs' (Jerby et al., 2020, BioarXiv) as cells need to coordinate cell-type specific response across tissues.

Jerby and Regev et al. (2020, bioarXiv) developed a two-step approach for sequencing called Dialogue, that allows inference of multicellular programs. Dialogue can be applied onto dissociated tissues, including the single-cell atlas of healthy and UC colonic mucosa.

Jerby and Regev identified IBD-associated multicellular program across T cells, epithelial cells and macrophages using the scRNA-Seq and Dialogue.

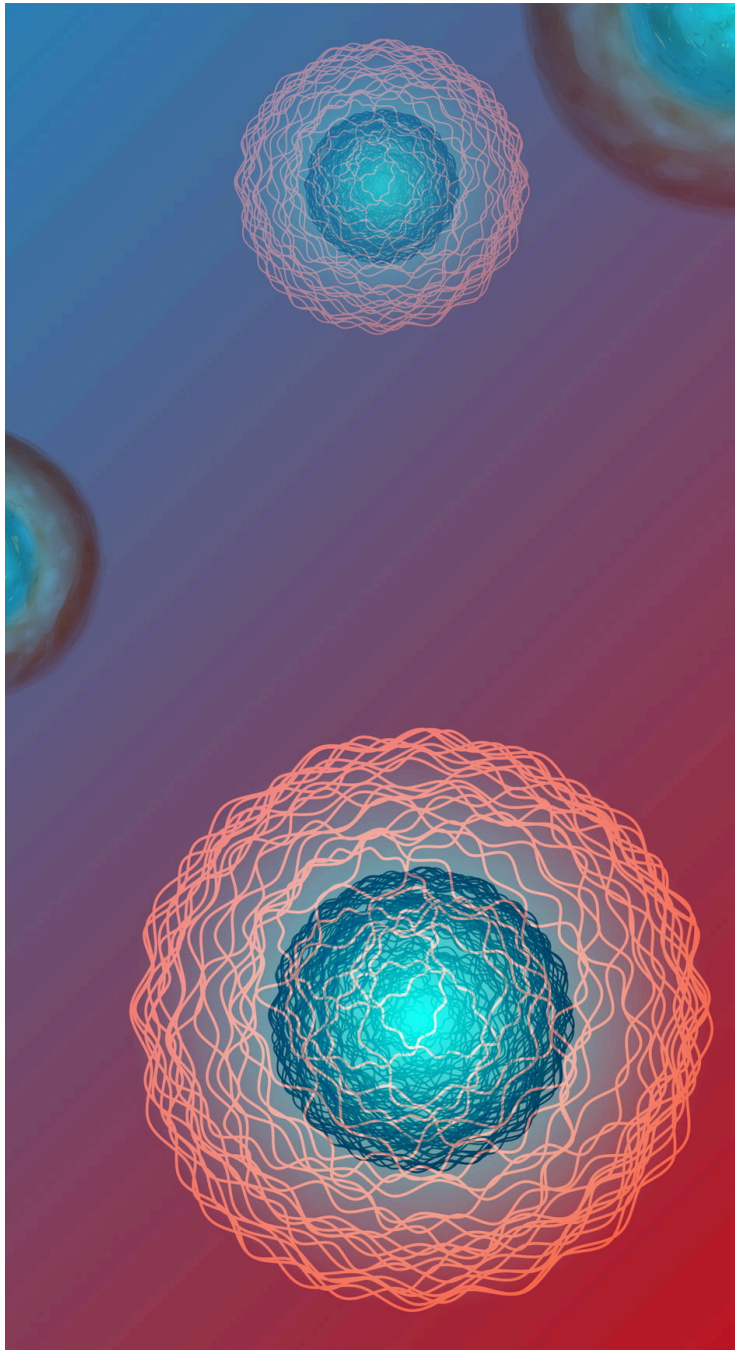
In the last part of her talk, Dr Regev focused on using genetic perturbations to decipher cellular function. Dr Regev's lab used Perturb-Seq technique of engineered perturbations, by combining single-cell RNA-Seq with CRISPR-Cas9 engineering (Dixit and Parnas et al., Cell, 2016).

Using computational analyses, Dr Regev was able to identify transcription factor modules controlling five cellular programs in dendritic cells treated with lipopolysaccharides.

Another use of Perturb-Seq was to study gain-of-function coding variants in cancer. Dr Regev's lab investigated p53 and KRAS variants, including common missense mutations.

To conclude her talk, Dr Regev summarized that Perturb-Seq is a family of methods that couples pooled perturbation with a high content readout that can be applied to one or multiple perturbations per cell and can be applied in a variety of contexts.

This includes in vivo or in organoids, and in combination with other techniques such as genome-wide and interactions screens.



Untangling Pandemics in a Data-driven World

Origins, variants and vaccines: a keynote presentation by Prof Kristian Andersen at Scripps Research

Untangling Pandemics in a Data-driven World

Prof Kristian Andersen from Scripps Research delivered an engaging talk focused on the evolution of SARS-CoV-2. Prof Andersen's lab uses genomic epidemiology approaches in his lab, sequencing viruses including Ebola, Zika and SARS-CoV-2. SARS-CoV-2 has been the main priority of Prof Andersen's research over the past year.

By taking samples from SARS-CoV-2 patients from different outbreak populations, Prof Andersen's group was able to build phylogenetic trees outlining the connectedness of the virus in the community.

Prof Andersen, together with his collaborators and the San Diego Epidemiology and Research for COVID Health, studied early in the pandemic the level of SARS-CoV-2 transmission in the community.

This was done using miniaturized PCR testing and large-scale sequencing. The work resulted in critical computational infrastructure, including iVar and oubreak.info tools.

Applying the learnings from SARS-CoV-1 to SARS-CoV-2

In the first part of his talk, Prof Andersen explained the emergence of SARS-CoV-2 in the human population. Using computational estimates (virological.org), Prof Andersen estimated retrospectively the start of the pandemic, which correlates quite well with the first known cases being documented in Wuhan in early December 2019.

He then compared SARS-CoV-2 to SARS-CoV-1 that originated in November 2002 in Guangdong, China. Similar to SARS-CoV-2, SARS-CoV-1 was associated with the wet markets, and virus' reservoirs were suspected as bats.

> "Prof Andersen posed the question of whether the original host may have been missed and whether the sources of SARS-CoV-1 and SARS-CoV-2 may have been identical."

Original hosts of SARS-CoV-1 were thought to be civets and raccoon dogs. Prof Andersen highlighted that a lot of information for the evolution of both viruses is still unknown.

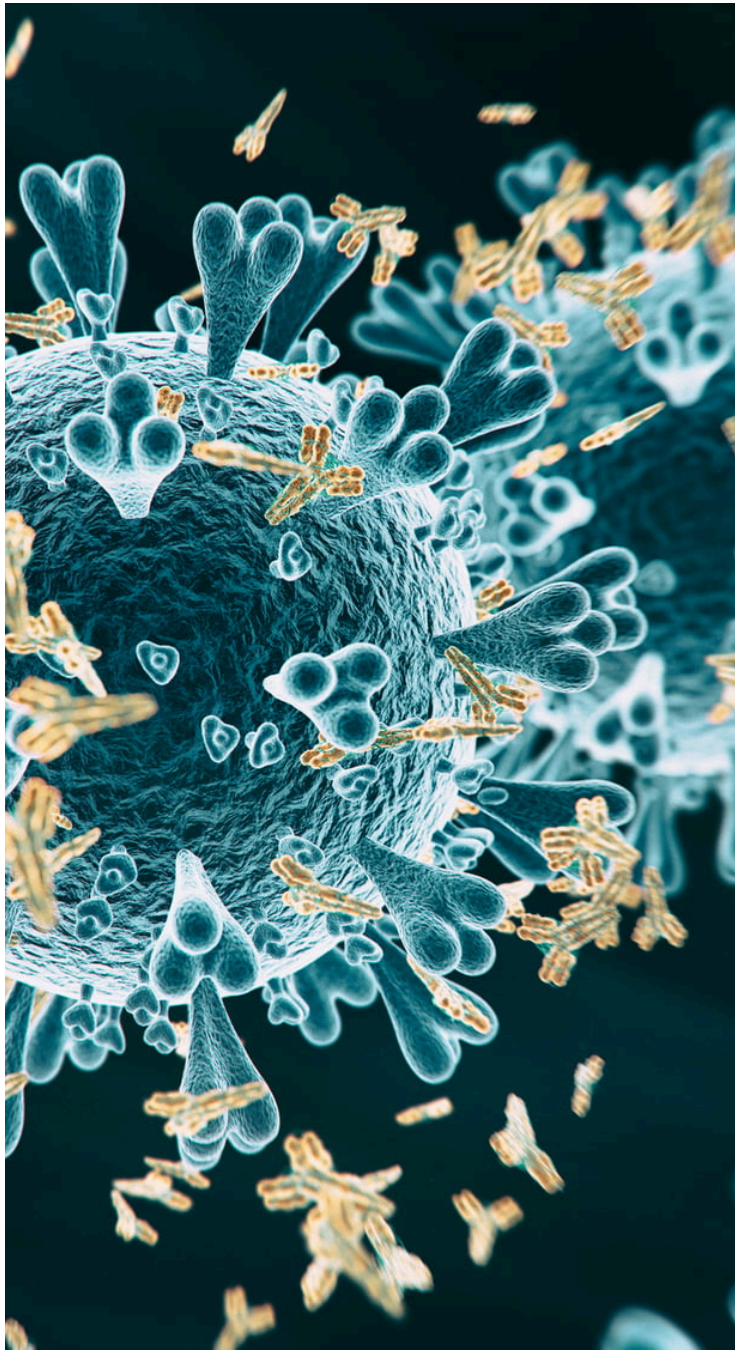
SARS-CoV-1 was found on farms in Hubei in civets, which were phylogenetically closer to the human cases, closer than the SARS-CoV-1 cases found in market animals.

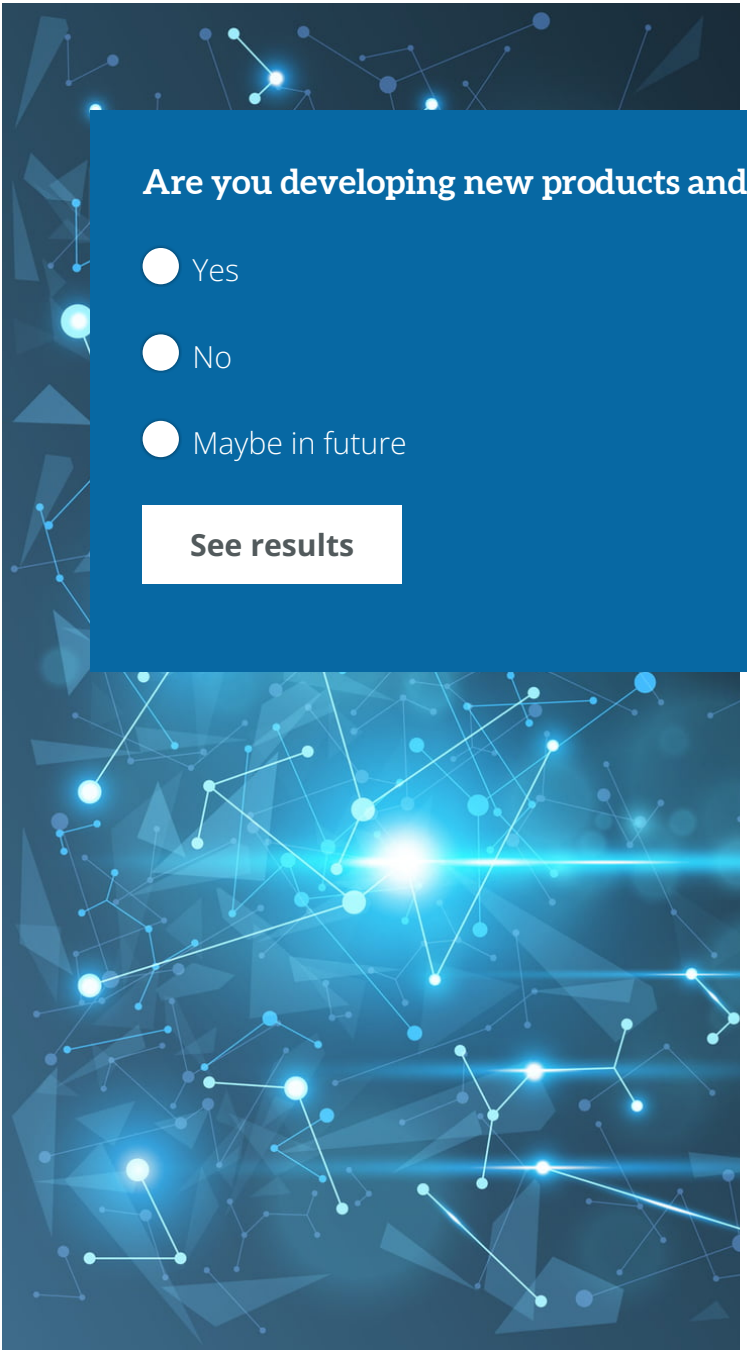
Prof Andersen posed the question of whether the original host may have been missed and whether the sources of SARS-CoV-1 and SARS-CoV-2 may have been identical. He noted that there was a tight clustering of SARS-CoV-2 cases within the market, associated with animal sales.

Explaining the evolution of SARS-CoV-2, Prof Andersen highlighted that the original human cases were clustered around the Wuhan market, including early excess pneumonia deaths.

Extrapolating the knowledge of SARS-CoV-1 onto SARS-CoV-2, Prof Andersen described the emergence of coronaviruses in the human population.

Coronaviruses occasionally emerge in the human population, though most of them end up not causing serious disease. The family of coronaviruses, sarbecoviruses are widespread across Southeast Asia, correlating with the reservoirs of horseshoe bats.





In contrast to other zoonotic viruses, Prof Andersen noted that SARS-CoV-2 had since its emergence unusual epidemiological status. It was highly transmissible but, at the same time, it can cause severe disease.

Prof Anderson hypothesized that this may be due to two key features of SARS-CoV-2. SARS-CoV-2 has a polybasic cleavage site, that allows the processing of the spike protein into two subunits, facilitating faster and more widespread infection.

SARS-CoV-2 also has a receptor-binding domain to ACE-2 protein in human lungs (Andersen et al., Nature Medicine, 2020), facilitating efficient binding to human cells.

Ultra-rapid displacement of SARS-CoV-2 lineages and the need for urgent action

In the second part of the talk, Prof Andersen talked about the evolution of SARS-CoV-2 over the past couple of years.

He explained that the fast evolutionary trajectory of SARS-CoV-2 meant that there was an ultra-rapid displacement of lineages taking place, as Delta variant displaced Alpha, and Omicron displaced Delta.

The speed of the displacements was illustrated using rapid Omicron rise in South Africa. Prof Anderson pointed out that the steepness of Omicron cases rise is much steeper than Beta or Delta, though it is not known why.

He hypothesized that a part of the steep rise may be a faster immune escape rate, causing breakthrough infections in a population previously exposed to Delta. Omicron has at least 20 new mutations in its spike protein compared to other SARS-CoV-2 variants.

Based on the information presented, Prof Andersen continued his talk hypothesizing how bad the Omicron outbreaks could become in the future. The difficulty with estimating Omicron outbreaks is that it emerged recently, and more data is needed.

The difficulty with the Omicron variant is that the entire world may be susceptible to Omicron, because the immunity from previous infection or vaccination may not be as effective as against the older variants.

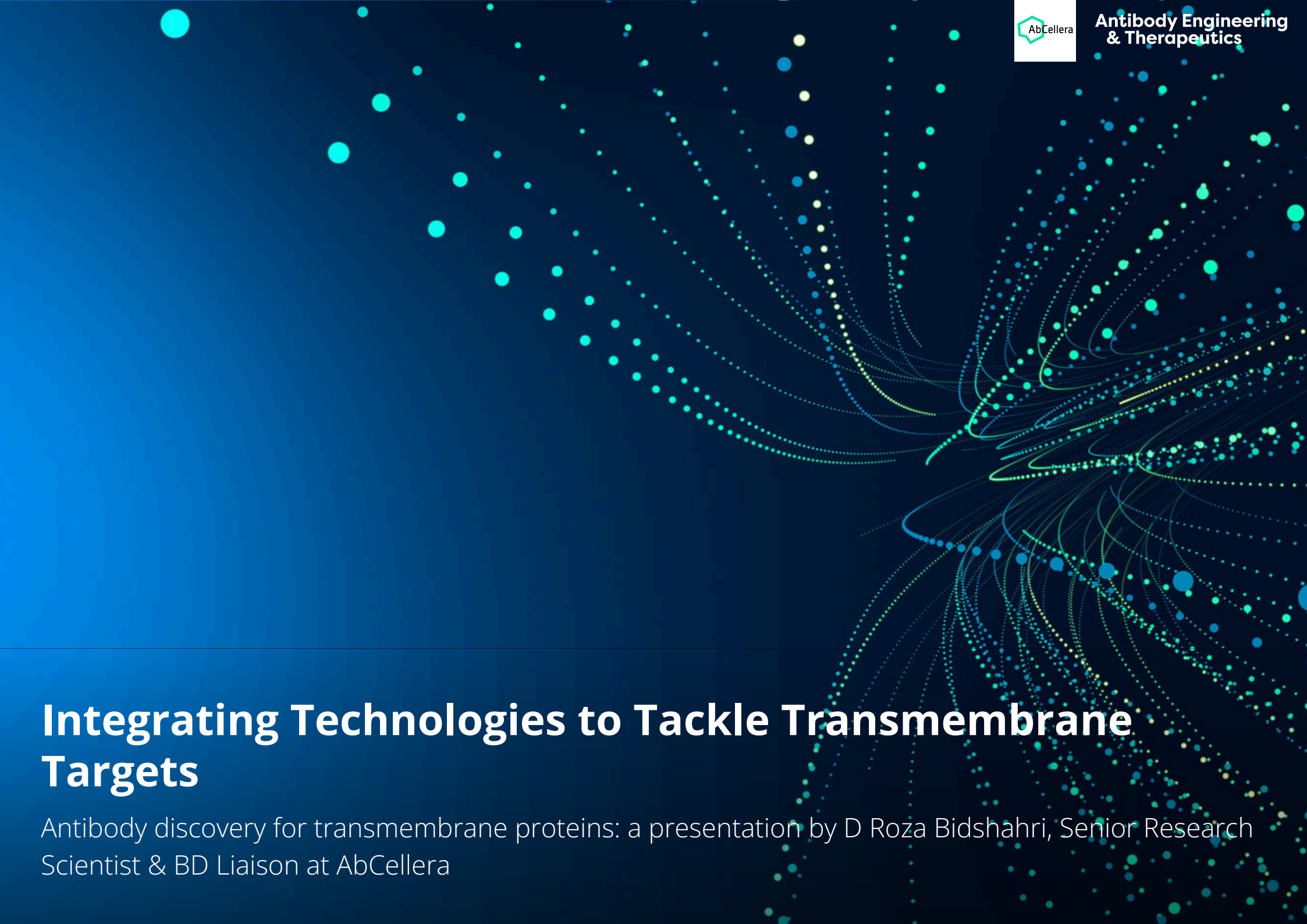
Booster vaccines protect to some extent against Omicron variant, though the issue of waning immunity will remain. Prof Anderson concluded that this is something expected in the evolution of the pandemic.

"The difficulty with estimating Omicron outbreaks is that it emerged recently, and more data is needed."

Prof Anderson concluded his talk by highlighting that the world's response to SARS-CoV-2 needs to improve, and not just by focusing on decreasing the death rate, but mainly the incidence rate.

The more we constrict the mutational supply to SARS-CoV-2, the better our response to SARS-CoV-2 will become, limiting new reservoirs and evolution of the virus.

He cautioned against our lack of knowledge about SARS-CoV-2 and its biological and evolutionary limits and stressed the importance of learning from our past mistakes.



Integrating Technologies to Tackle Transmembrane Targets

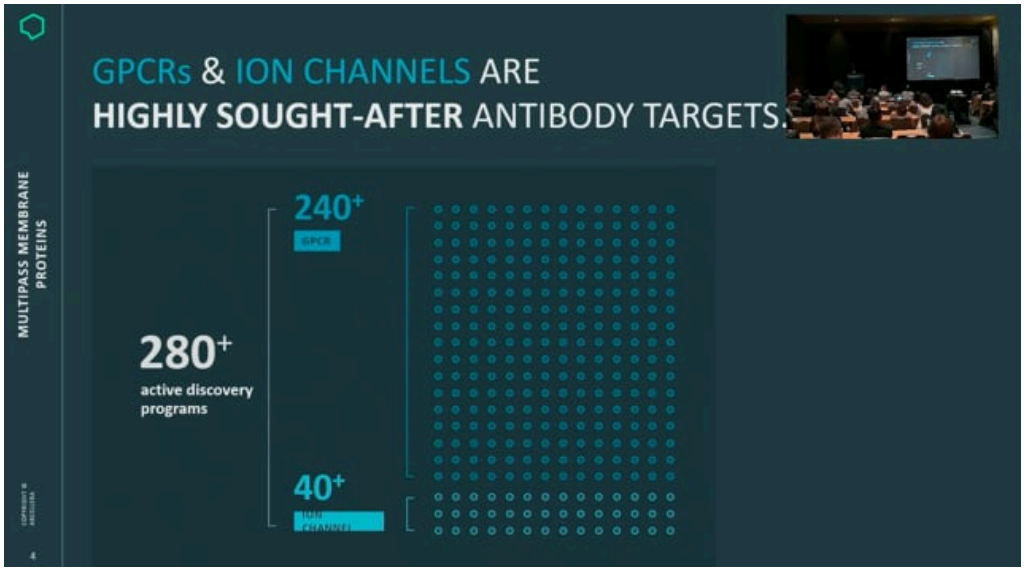
Antibody discovery for transmembrane proteins: a presentation by D Roza Bidshahri, Senior Research Scientist & BD Liaison at AbCellera

Integrating Technologies to Tackle Transmembrane Targets

GPCRs and ion channels are highly sought-after drug targets, but of the ~300 well-validated opportunities, only two antibody drugs have been approved.

AbCellera's technology tackles the biggest challenges limiting antibody discovery for transmembrane proteins: producing antigens, driving antibody responses, and finding hits.

Optimized immunization strategies, single-cell screening technologies, and hyper-scale data science leads to hundreds of hits, and by integrating Tetrahymena — a natural membrane protein factory — we're driving powerful solutions to unlock these targets.

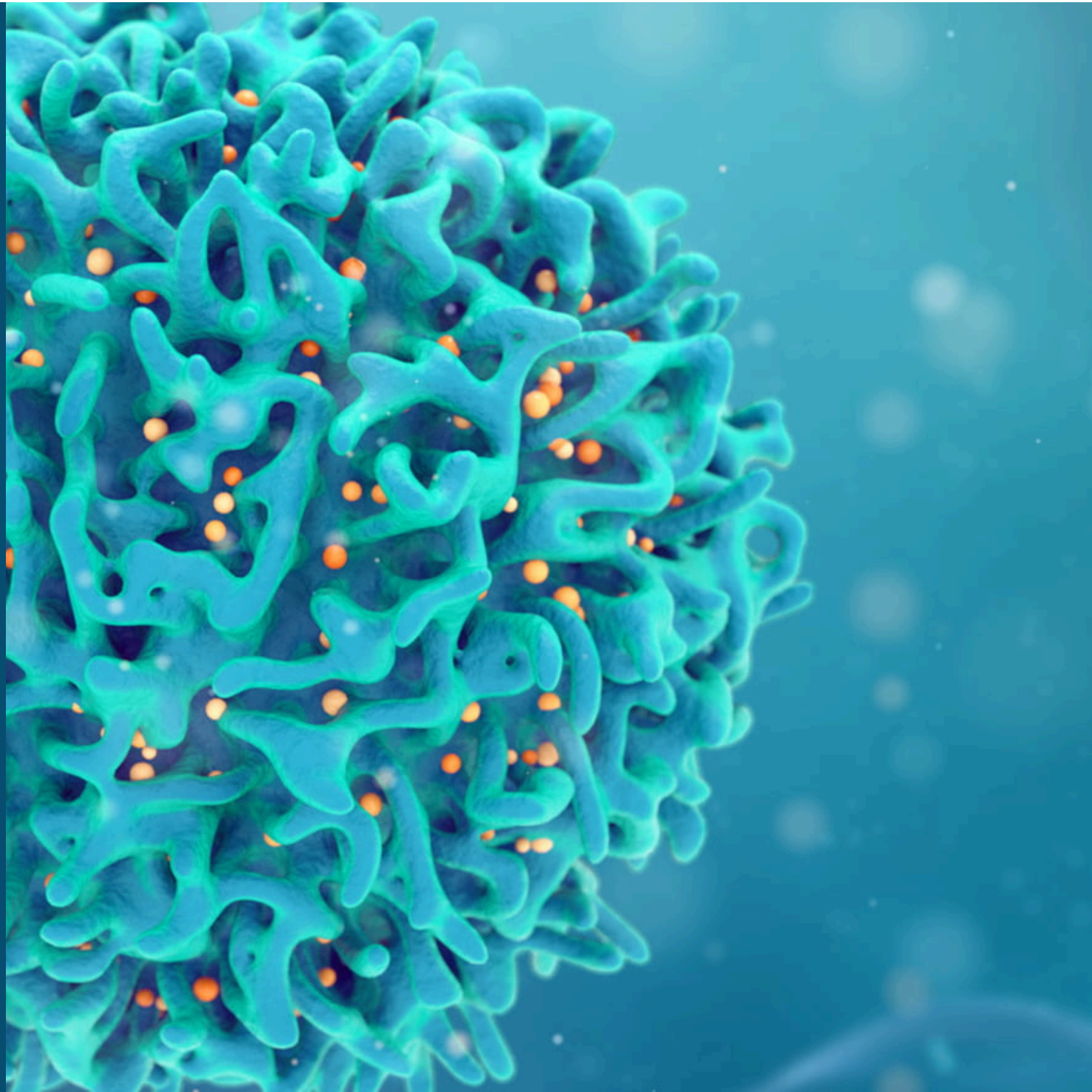


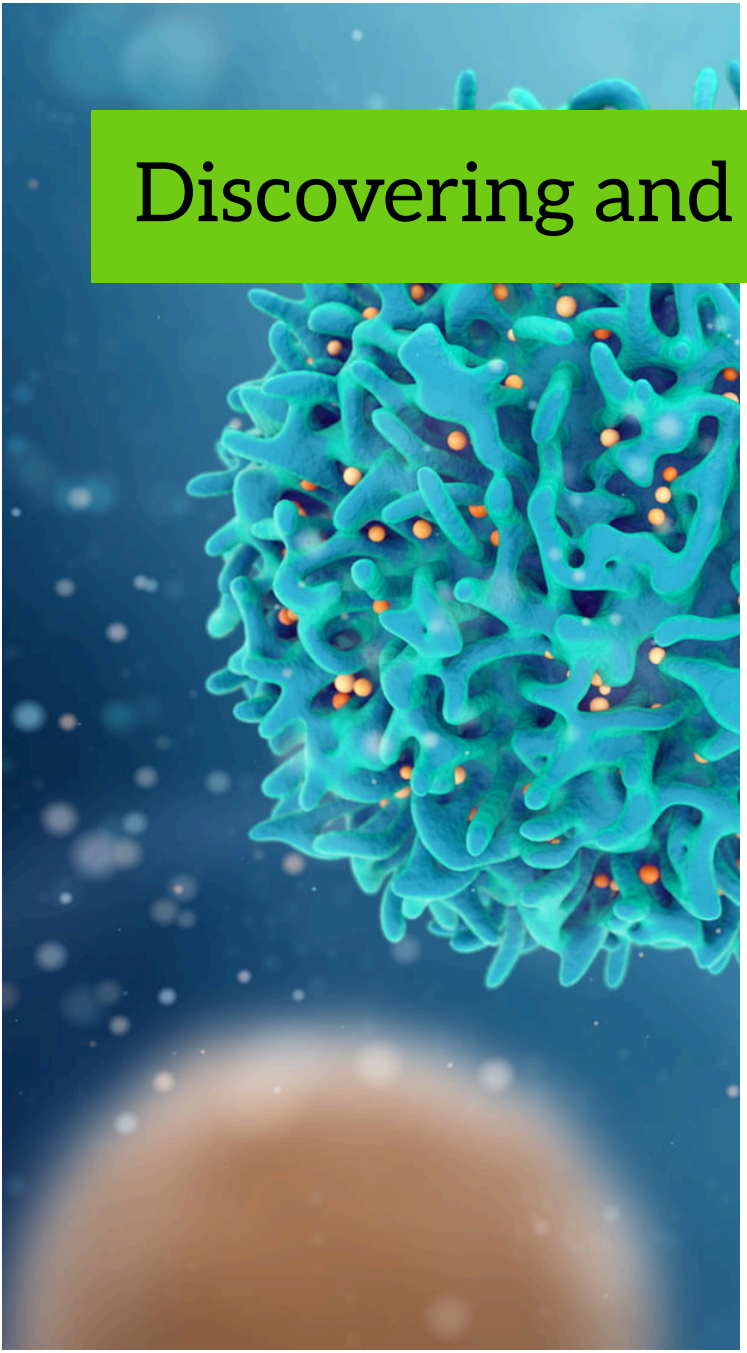
Learn more at abcellera.com

Click here to watch the full video

Discovering and Targeting Neo-epitopes in Cancer

Proteomics and antigen discovery: a keynote presentation by Prof Jim Wells at University of California





Discovering and Targeting Neo-epitopes in Cancer

A fascinating presentation about neo-epitopes and proteolytic landscape in cancer was delivered by **Prof Jim Wells** from the University of California San Francisco.

In cancer, it is pivotal to understand how cell surface proteins change in response to different oncogenes.

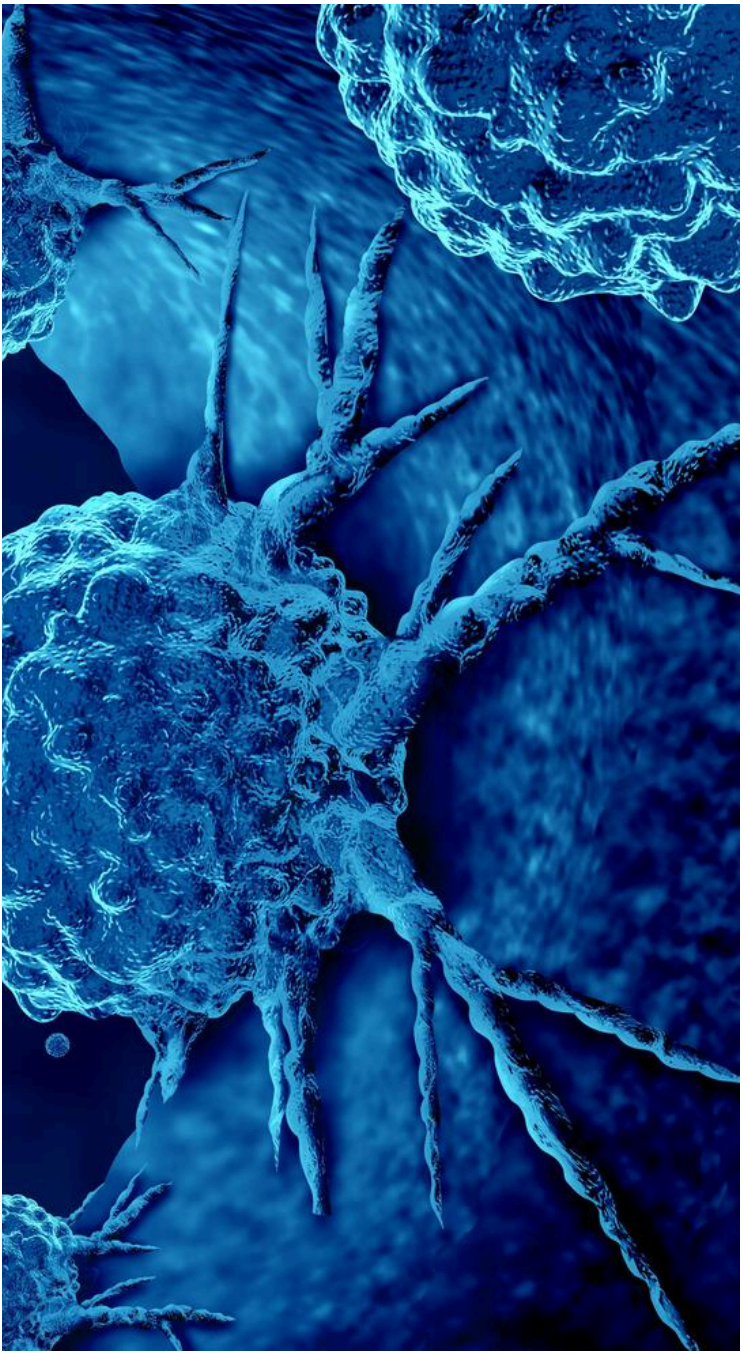
Prof Wells addressed this by creating a proteomics platform to find oncogene-specific antigens and antibodies (Leung et al., 2020, PNAS). The platform enables antigen discovery and specificity testing of final antibodies to find potential therapeutics.

Proteolytic cleavage sites as potential cancer therapeutics

In addition to understanding expression levels of cell surface proteins during different stages of cancer, Prof Wells' lab is interested in neo-epitopes and their correlation with cell surface epitopes.

Some examples of such neo-epitopes include MHC-peptide complexes or extracellular post-translational modifications (PTMs; Douglass and Zhou et al., 2021).

Prof Wells is particularly interested in proteolysis, a prominent extracellular PTM, playing role in a number of cell processes, such as angiogenesis, growth, survival, or metastasis. Prof Wells' lab focused on the discovery of proteolytic cleavage sites and their targeting for



potential therapeutics.

The group developed a method for the identification of proteolytic cleavage sites, using a caspase digestion strategy (Mahrus et al., 2008 Cell). The results from the project were released via a database of caspase cleavage points (wellslab.ucsf.edu/degrabase).

The cleaved form of the CDCP1 protein is upregulated in pancreatic cancer cells

Applying subtiligase at the cell surfaces strategy (Weeks et al., 2021, PNAS), Dr Weeks from Prof Wells' lab succeeded in labeling cell-surface proteins. Dr Weeks engineered the subtiligase to make it more successful in labeling the N-terminus of cell surface proteins.

Using an improved technology coupled with LC-MS mass spectrometry, Dr Shaefer labeled proteolytic neo-epitopes, allowing Prof Wells' lab to examine ectodomain cleavage events in neo-epitopes. The lab team identified numerous ectodomain cleavage events in the N-termini.

Comparing the cell surface proteolysis to expression levels of cell surface proteins in cancer, Prof Wells claimed to find that oncogenes change proteolysis rate.

Comparing common and unique proteolytic events between KRAS G12V mutation and Her2, some of the events were shared but several were unique to the individual oncogenes. One of the proteins identified through the analysis of proteolytic events was the protein CDCP1, found highly upregulated in pancreatic cancer cells.

Dr Zhou and Dr Lim from Prof Wells' lab next looked into CDCP1 cleavage in pancreatic cancer cell model lines and found an abundance of cleaved CDCP1 in some pancreatic cancer cell lines.

Prof Wells highlighted that the cleaved form of CDCP1 is only present in cancerous cells, and therefore his lab focused on developing

antibodies against CDCP1, cleaved and full-length forms, as potential cancer therapeutic.

The development of antibodies was done using a differential selection strategy following affinity maturation, raising antibodies against cleaved and full-length CDCP1.

Prof Wells' lab then raised mouse-specific antibodies against CDCP1 forms to study the toxicity of antibodies in mice. Mice treated with cleaved form anti-CDCP1 antibodies tolerated the antibody well, but those mice treated with full-length anti-CDCP1 antibodies lost ~10% body weight following a few days of treatment.

Using mice with Fc1245 tumors, the anti-CDCP1 antibody treatment seemed promising in slowing down tumor volume growth.

The results from the anti-CDCP1 antibody experiments were so encouraging, that Prof Wells' lab next looked into raising antibodies against targets that are both upregulated in cancer cells and have proteolytic events in them. This work is currently ongoing.

> "The cleaved form of CDCP1 is only present in cancerous cells, and therefore Wells' lab focused on developing antibodies against CDCP1 as potential cancer therapeutic"

MHC-peptide complexes as selective therapeutic targets

In the second part of his talk, Prof Wells outlined his work on MHC-peptide targets for engineering BiTes and CAR-T cells. MHC-peptides are important for recognition by cytotoxic T cells, enabling engineering for cytotoxic T-cell recruitment in cancer.

The work in Prof Wells' lab (Dr Rettko and Dr Kirkemo) focused on engineering peptide-HLA complexes that would be secreted by cells, enabling targeting by cytotoxic T cells.

Dr Rettko and Dr Kirkemo from Prof Wells' lab identified specific HLA.A:02.01 peptides using an HLA Fc-fusion workflow and investigated these in hypoxic PDAC cells. Hypoxia is a typical tumor state, whereas normoxia refers to normal levels of oxygen.

By comparing immunopeptidome of hypoxic and normoxic pancreatic cells (MiaPaCa2), Prof Wells' lab identified 99 peptides over-represented in hypoxia and is now raising antibodies to 4 of these hypoxic pMHC targets. Dr Rettko next used a differential screening strategy to identify antibodies selective to MHC-peptide complexes.

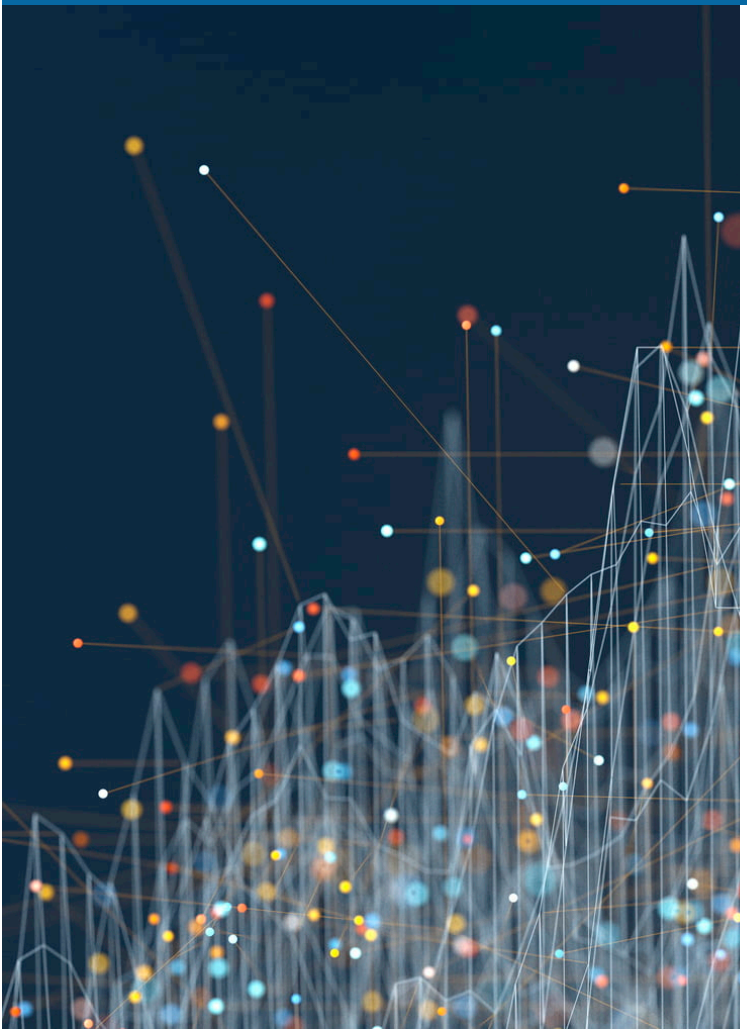
Secreted MHC-peptide immunopeptidomics allows profiling of specific MHC-1 alleles, and the approach used by Prof Wells' lab allows to pair peptides with specific MHC.

They also built a platform for building and characterizing antibodies to specific MHC-peptide complexes, which has been applied to state-specific cell conditions such as hypoxia, MEKi, and specific oncogenes.

Applications of Machine Learning and Informatics in Antibody and Protein Research

Humanized antibodies and computational screening: a keynote presentation by Prof Charlotte Deane at Oxford University

Applications of Machine Learning and Informatics in Antibody and Protein Research



Prof Charlotte Deane from Oxford University commenced her talk on machine learning in antibody and protein research by explaining data and the databases developed in her lab: Observed Antibody Space (Olsen et al, 2021), Structural Antibody Database (Schneider et al., 2021) and Thera-SAbDab (Raybould et al., 2020), a self-updating database of immunotherapeutic variable domain sequences and the CoV-AbDab, the Coronavirus Antibody Database, a database of all antibodies shown to bind to SARS-CoV-2.

Hu-mAb database – computational solution to improve the immunogenicity profile of antibody therapeutics

Talking about humanization, Prof Deane outlined the issues with current therapeutics, 50% of which are currently derived from non-human sources.

Non-human antibodies can potentially result in a harmful immune response in patients (immunogenicity) and therefore, it is important to humanize antibody therapeutics for safety and efficacy purposes. Currently, the humanization process is typically carried out experimentally, in a largely trial-and-error process.

Prof Deane presented a potential solution to finding humanized antibodies, a Hu-mAb database of humanized antibodies that uses random forest machine learning (ML) models built with over 65 million human and non-human sequences from the Observed Antibody Space database.

There are separate models for each human V gene type available in the Hu-mAb database. Prof Deane explained that feeding the ML models a sequence trying to predict whether a sequence is human or not is not a difficult task, and the prediction achieves a very high AUC-ROC (area under the curve of the receiver-operator curve), suggesting a very good performance.

Compared to other published models, the Hu-mAb model has a surprisingly good performance.

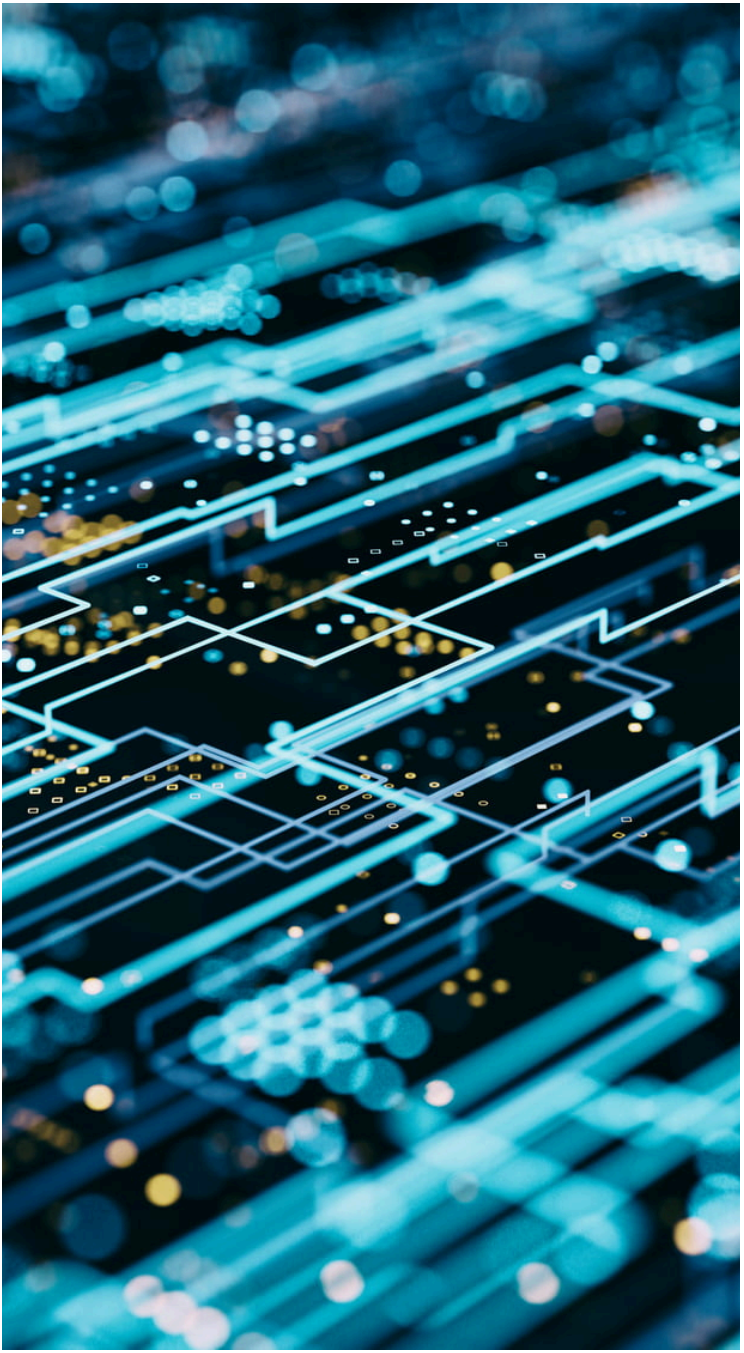
The next step of testing was testing whether Hu-mAb is able to distinguish human, humanized, chimeric, or mouse known therapeutics. Hu-mAb performed well on human and humanized antibodies, though not as well on the chimeric antibodies.

Therapeutic sequences classified as human by the Hu-mAb model tend to have low immunogenicity levels, while sequences classified as not human as more immunogenic.

The ultimate goal was to convert Hu-mAb into a humanization database so that the models could suggest the optimal humanized sequence with the lowest immunogenicity.

Prof Deane tested Hu-mAb on 25 humanized sequences that demonstrated low immunogenicity and for which the precursor sequences were available (murine, rat or rabbit).

The results suggested that 77-85% of mutations suggested by Hu-mAb to humanize the antibodies were similar to those made experimentally, and 58-59% of the mutations suggested were indeed made experimentally.



The comparison of Hu-mAb results with experimental humanization, therefore, demonstrates a good agreement but greater efficiency.

Hu-mAb proposes fewer mutations to the VH-VL interface making the orientation and therefore binding properties more likely to be preserved, leading to a greater likelihood of preserving antibody structure and function.

In summary, in addition to being able to accurately predict whether an antibody is human or not, Hu-mAb can also be used to evaluate and improve the immunogenicity profiles of antibodu sequences.

Computational screening of antibody therapeutics as means to improve their design

Prof Deane was next interested in adding structural information to the Hu-mAb database, to improve its prediction abilities. Adding full structural annotation of BCR data led to building a Human Antibody Model Library, that would describe the structural variability of human antibody space.

The library contains BCR data from approximately 500 healthy individuals, with sequences from unpaired naive and memory IgM molecules sourced from peripheral blood, bone marrow, and spleen. Using computational models, the sequences were reduced to ~20,000 structurally diverse antibodies that were possible to be modeled accurately.

To enable better design of therapeutic antibodies in conjunction with the Human Antibody Model Library, Prof Deane's group developed the Therapeutic Antibody Profiler, to

reduce developability issues such as poor stability or high levels of aggregation.

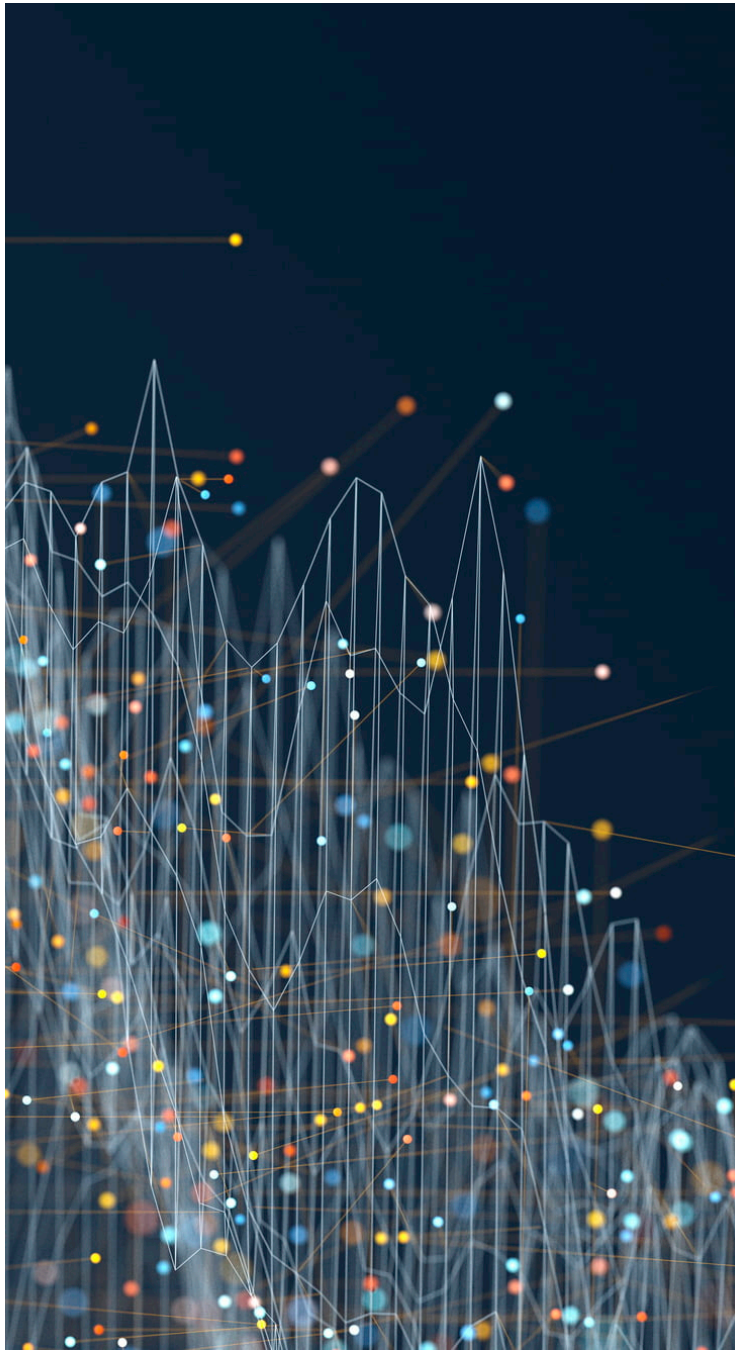
The Profiler was built using variable domain structure of 137 post-Phase I clinical-stage antibody therapeutics and validated two datasets of MedImmune developability failures (Jain et al., 2017 PNAS). The profiler is automatically updated with source data, enabling continuous prediction improvements.

Building on the success of the Profiler, Prof Deane presented a virtual screening tool of a model antibody library using deep learning, named Dlab (Schneider et al., 2021, Bioinformatics). The Dlab works using convoluted neural nets to predict whether an antibody will bind or not bind to the target peptide.

When tested on identifying binders amongst 50 non-binders, Dlab enriched in the top 20% binders amongst the non-binders. As the availability of data increases, virtual screening for libraries may become more and more prominent, identifying potential starting points for antibody therapeutics.

In the last part of her Talk, Prof Deane introduced ABlooper, a model improving the speed and quality of structural models of antibodies (Abanades et al., 2021). ABlooper uses equivariant graph neural networks to give predictions of complementarity-determining regions, and it also provides an estimate of the accuracy of the prediction.

ABlooper is very fast and it takes under five seconds to perform predictions on hundreds of structures. Compared to the benchmark tools, ABlooper does not perform significantly better than other prediction models. However, it offers a prediction on how good the prediction might be.



From complexity to clarity: integrating antibody discovery technologies to create confidence at every step

A whitepaper by AbCellera

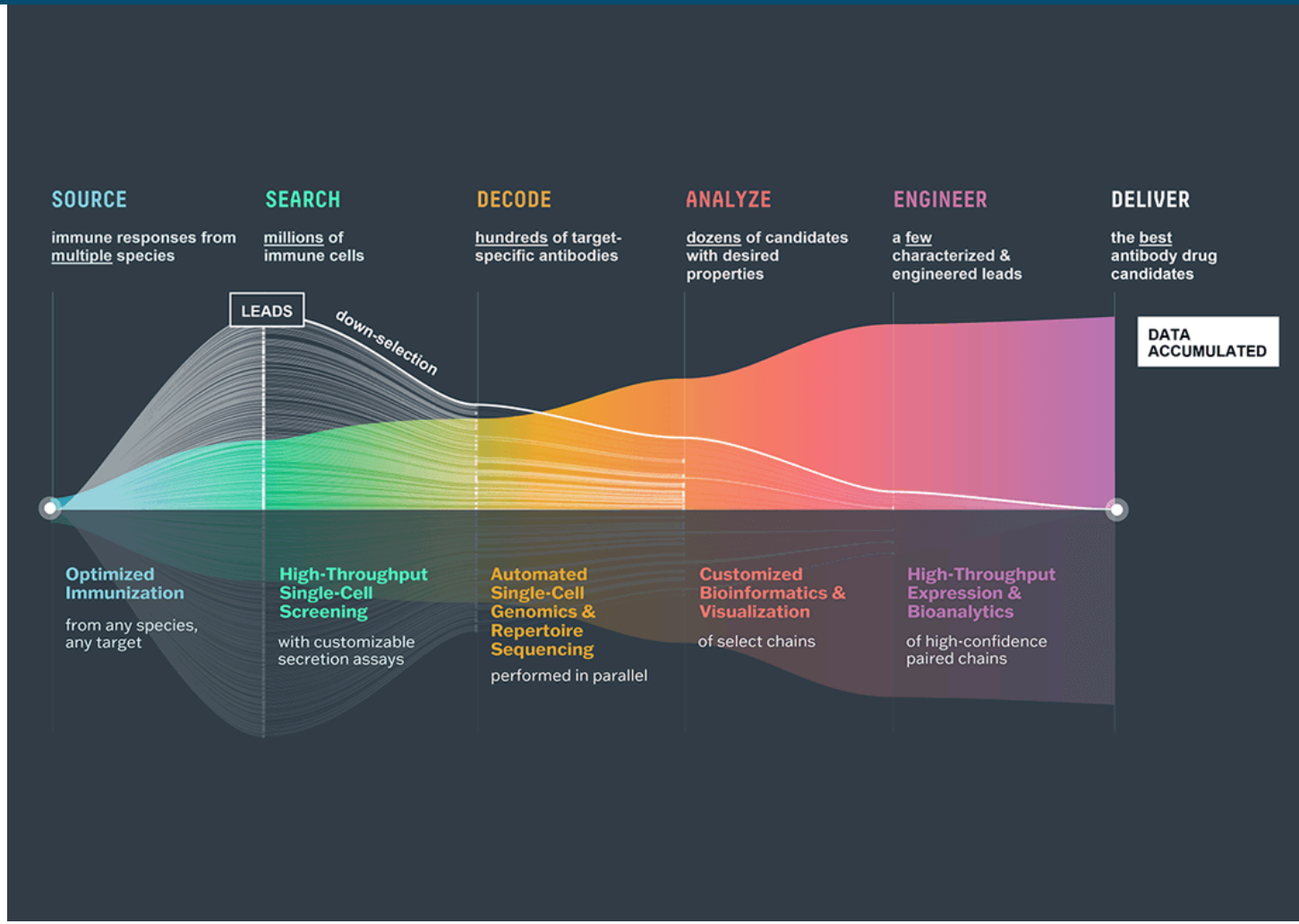
From complexity to clarity: integrating antibody discovery technologies to create confidence at every step

Natural immune systems provide vast databases of potential antibody drugs, but mining them for the most promising candidates rapidly generates large volumes of data.

Fragmented approaches to antibody discovery fail to fully integrate these multidimensional datasets, limiting actionable insights.

Finding the best antibodies requires optimized technologies at every step, but the value of each step is only fully realized when executed as part of a streamlined, end-to-end system.

At AbCellera, we're helping our partners bring better antibodies to patients faster with complex data integration and interlocking technologies that **optimize every step with a compounding effect on the entire process.**

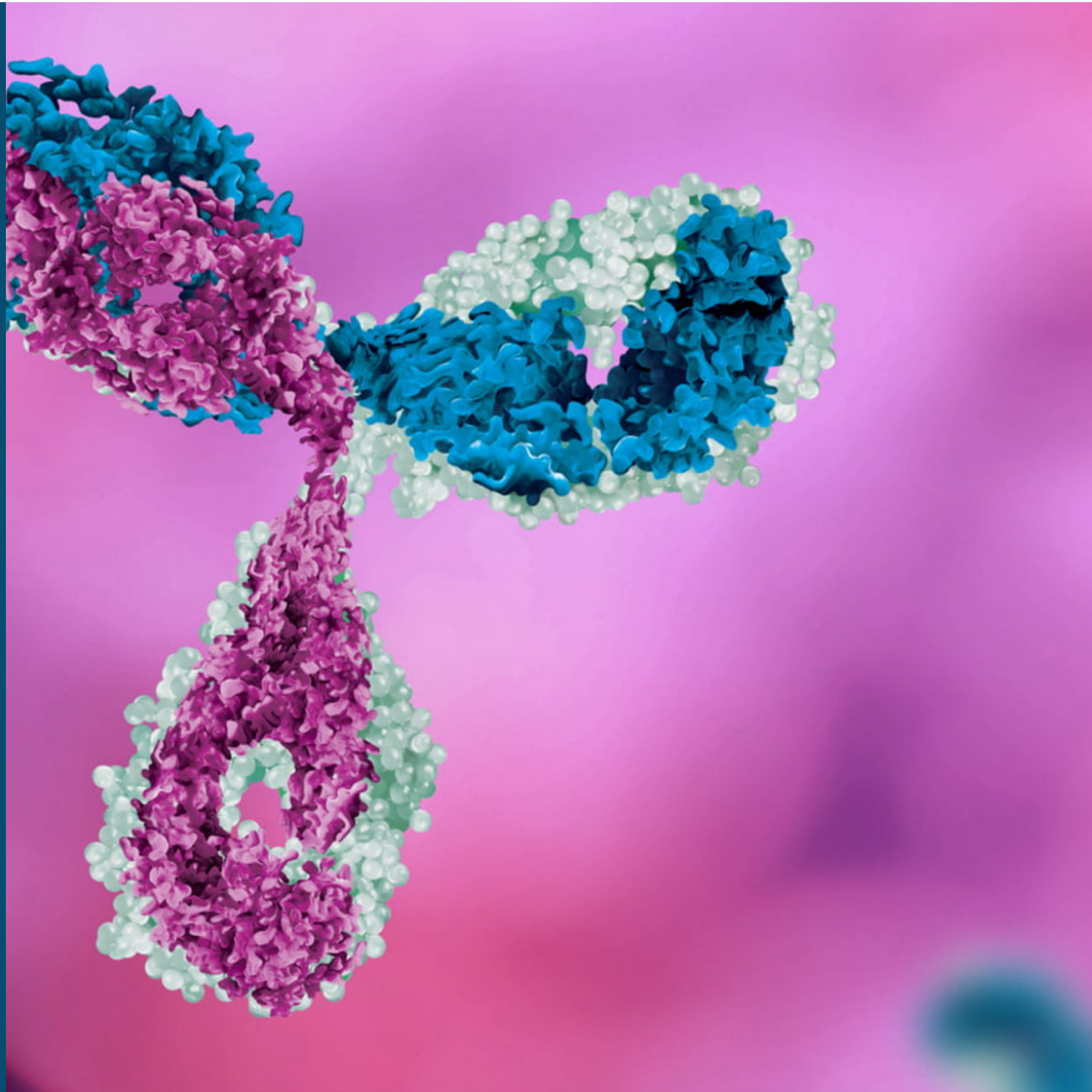


	DISCOVERY CHALLENGES	ABCELLERA'S SOLUTION
SOURCE	**Limited target** protein for immunizations and **limited antibody** titers make it difficult to **generate a source of high-quality antibodies**	**Optimize** target input and **maximize** antibody output with: • TetraExpress™ technology for hard-to-make proteins • Proprietary immunization methods • Protocols for breaking tolerance
SEARCH	**Conventional technologies** are **limited** in their ability to **deeply search** natural antibody responses, resulting in **limited leads** for downstream analyses	Start with **more data upfront** with multiplexed bead- and cell-based assays, including: • Binding assays: affinity, specificity, cross-reactivity • Functional assays: ligand-blocking, internalization, T cell activation
DECODE	**Limited access** to the diversity needed to find the best candidates leads to **limited diversity** for antibody drug candidates	**Expand the diversity** of antibody databases with integrated: • Single B-cell sequencing • High-throughput RepSeq technology
ANALYZE	**Challenges in collecting, standardizing,** and **storing** multidimensional antibody datasets leads to **limited insights** to guide lead selection	Validate **complex, multidimensional** antibody datasets and **select the best of the best** with: • High-throughput analytics and antibody characterization • Celium™, proprietary data visualization and computational software
ENGINEER	**Limited technologies** for antibody optimization **limit abilities** to **fine-tune** the **functionality** of fit-for-purpose formats	**Combine any two** antibodies and **fine-tune function** with: • OrthoMab™, a clinically-validated bispecifics platform

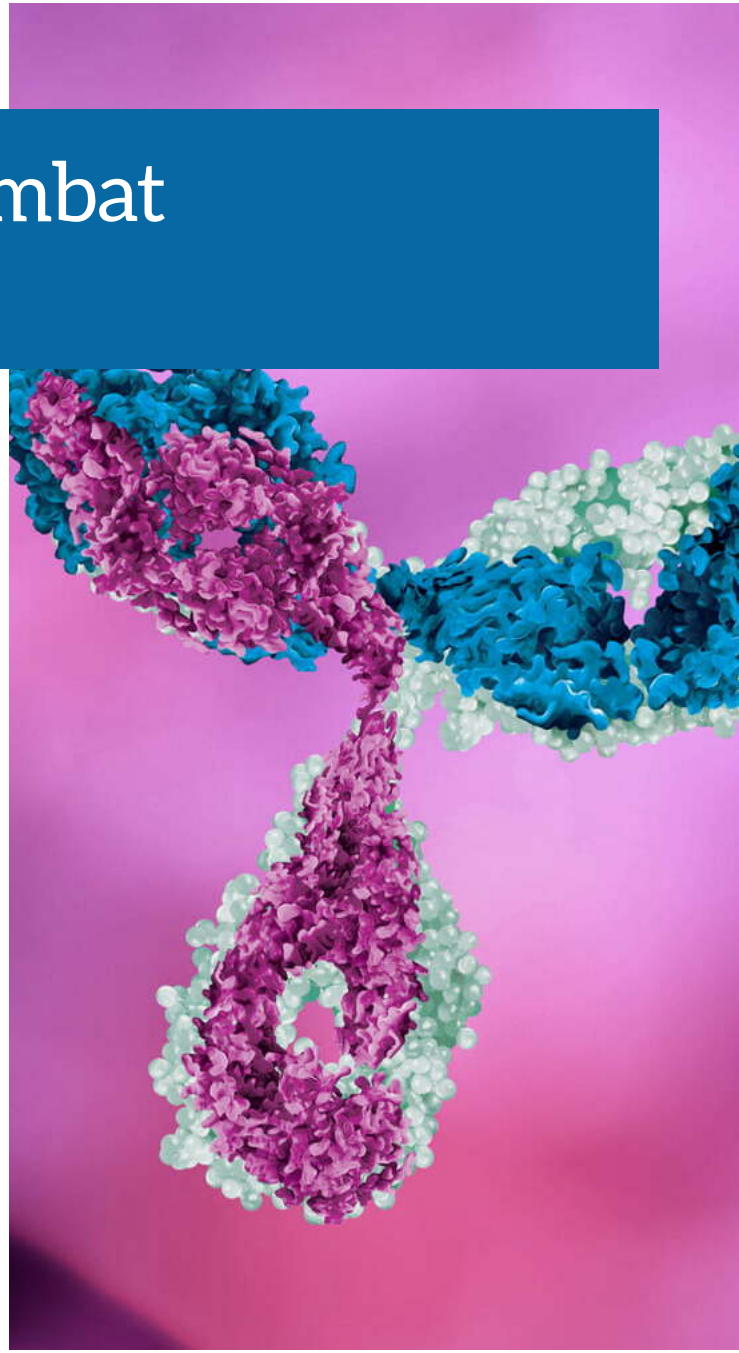
Learn more at abcellera.com.

Broadly Neutralizing Antibodies to Combat Antigenically Diverse Viruses

Targeting future variants: a keynote presentation by Dr Laura Walker at Adimab, LLC



Broadly Neutralizing Antibodies to Combat Antigenically Diverse Viruses



Dr Laura Walker, Senior Director of Antibody Sciences at Adimab, LLC., discussed her work on engineering antibodies to fight rapidly emerging diseases.

Currently, neutralizing antibodies have a range of applications in prophylaxis, therapy, and vaccine design in HIV-1, ebolavirus, and SARS-CoV-2.

However, the challenge of emerging diseases is a rapid emergence and the current 'proactive' approaches to the emerging viruses are too slow to prevent a pandemic.

For example, the monoclonal antibodies to SARS-CoV-2 have been abandoned despite the much more rapid development than usual.

An alternative approach would be a 'preemptive' approach that could work against a broad spectrum of viruses and diseases. For instance, had there been a pan-coronavirus vaccine available prior to the SARS-CoV-2, there would be a tool available to use when the pandemic emerged.

Broadly neutralizing antibodies (bNAbs) as elite neutralizers

A strategy for the development of broadly neutralizing antibodies (bNAbs) is to target conserved epitopes on viral envelope proteins, against for example HIV-1 or influenza. Over the past few years, advances in large-scale donor screening followed by FACS screening and single-cell technologies led to the

identification of bNAbs to many viral pathogens.

Illustrating her point with an example, Dr Walker explained that only a handful of bNAbs had been identified that broadly neutralized HIV, none of which had been very potent.

However, following large-scale donor screening, a small subset of HIV patients was found to develop highly potent bNAbs to HIV, called elite neutralizers. A collaboration with Theraclone Biosciences allowed screening memory B cells directly for neutralization, screening potential IgGs for neutralization.

Dr Walker identified PG9 and PG16 antibodies that had a remarkable breadth and potency to target HIV (Walker et al., Science, 2009). Building upon Dr Walker's work, dozens of HIV bNAbs have been identified to date, revealing multiple targets for vaccine design. Currently, HIV-1 bNAbs are being explored in both treatment and prevention.

bNAbs could target future emerging variants of the same virus

In the second part of her talk, Dr Walker focused on ebolavirus species. There are 6 ebolavirus species and each treatment/ measure is species-specific, meaning that it would not work against another ebolavirus species.

Broadly neutralizing anti-ebolavirus antibodies must target conserved surfaces on the GP protein. Dr Walker's group developed a workflow for the identification and engineering of a pan-ebolavirus antibody cocktail (MBP134).

This was done by taking samples from ebolavirus survivor PBMCs, followed by single B cell cloning and isolation of bNAbs that would bind to the GP protein. The resulting molecule MBP134 is in Phase 1 clinical trials.

MBP134 shows a neutralizing activity against a novel, divergent ebolavirus, Bombali virus (Wec

et al., 2019, Cell Host Microbe). This is of proof-of-principle that bNAbs could work against future emerging antibodies.

bNAbs and the potential for a pan-coronavirus vaccine

In the final part of her talk, Dr Walker talked about her work on coronaviruses. Novel coronaviruses will likely emerge in the future, highlighting the need for pan-neutralizing coronavirus vaccines.

The difficulty with SARS-CoV-2 is that there is a continuous emergence of new variants that escape common classes of neutralizing antibodies, due to the escape mutations affecting the spike protein.

Many of the antibodies isolated until now that are in clinical stages or EUA authorized target common epitopes and fail to neutralize other coronavirus variants. Dr Walker suggested that inherent features of broadly neutralizing antibodies should offer a high barrier to resistance.

Dr Walker's group obtained blood samples from a convalescent SARS donor, and through single B cell sorting, antibodies that would demonstrate cross-neutralizing activity were isolated. 3 of the 7 antibodies were affinity matured, increasing the neutralization potency of the antibodies, leading to three potential therapeutic candidates.

The antibodies were Fc modified to extend their half-life and two of the antibodies were demonstrated to show broad and potent neutralizing in vitro activity across diverse SARS-related coronaviruses.

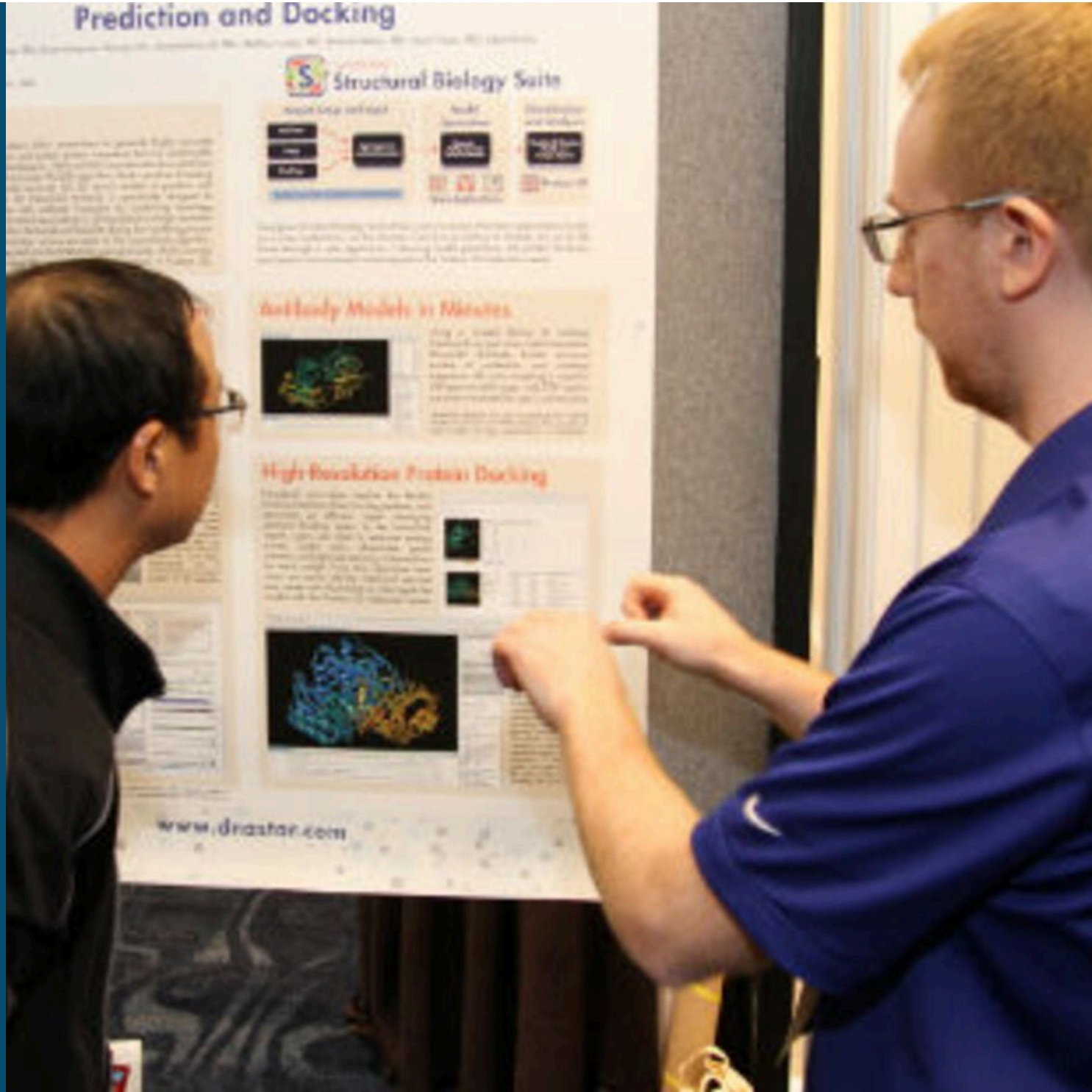
Typically, bNAbs target epitopes distinct from those recognized by commonly elicited antibodies, enabling a pan-coronavirus neutralizing activity. bNAbs maintain neutralizing activity against Alpha, Beta, Gamma, and Delta SARS-CoV-2 variants of concern (Dejnirattisai et al., Cell 2021, Liu et al., Cell 2021).

Out of these, many bNAbs maintain some of their activity against the Omicron variant, unlike the monoclonal antibodies that were developed in the early stages of the pandemic.

The bNAbs identified by Dr Walker's group is now in clinical trials and their pharmacokinetics and potential for prolonged protection are being assessed. bNAbs could potentially become platforms for a pan-SARS vaccine design.

Scientific Posters

A look back at the live and virtual poster presentations at the event



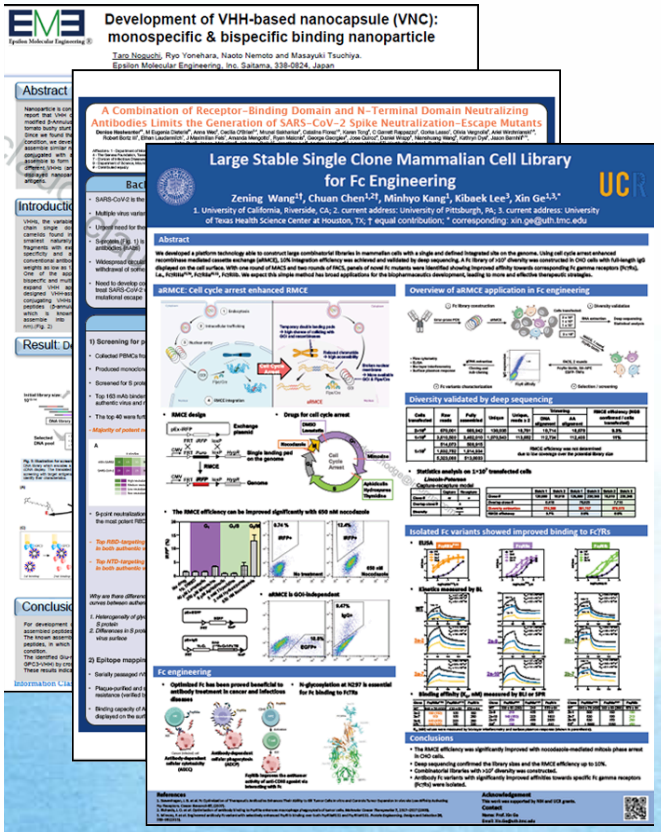
Scientific Poster Presentations

Throughout the course of the event, more than 70 scientific posters featured in the virtual poster presentation area and live poster presentation hall in San Diego. A range of organizations showcased their latest research in the biggest ever poster gallery at the event.

The posters covered a range of topics including:

- **High-Throughput Antibody Discovery and Engineering: Driving Innovation Towards 0-Day Discovery**
- **Machine Learning for Antibody and Protein Engineering**
- **Engineering the Fc Region for Therapeutics**
- **Single Domain Antibodies, Repertoire, Engineering and Applications**
- **Vaccines and Antibodies to SARS-CoV-2: Dealing with Antigenic Variation**

Find out about poster presentations at Antibody Engineering & Therapeutics Europe 2022.



Take our quick poll on the next page...

What topic would you be MOST interested in seeing a poster presentation about?

- ○ Novel Therapeutic Targets and Non-Cancer Indications
- ○ Engineering the Fc Region for Therapeutics
- ○ Vaccines and Antibodies to SARS-CoV-2: Dealing with Antigenic Variation
- ○ Intratumoral Immunotherapy Administration
- ○ Engineered Cytokines for Cancer Immunotherapy
- ○ Antibody Library Design, Selection and Screening
- ○ Single Domain Antibodies, Repertoire, Engineering and Applications
- ○ Advances with CAR-effectors
- ○ Targeted Drug Conjugates
- ○ Machine Learning for Antibody and Protein Engineering

See results

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