Drug
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Innovative vaccine platforms

How modern vaccine development is shaping the fight against latent viruses

Memory B cell antibody-based treatments

Understanding how these cells can aid in fighting cancer

AI in drug discovery

The importance of integrating AI into drug development

Biotherapeutic trends

Exploring recent developments in early biopharmaceutical research

Q&A

Emerging trends in biotherapeutic development

The COVID-19 pandemic has placed a spotlight on the discovery and development of biotherapeutics, for both the treatment and prevention of diseases. In this article, industry experts discuss the emerging trends they see in biotherapeutic development and how they predict the field will evolve in the near future.

Dr Molly Gibson

Chief Strategy and Innovation Officer at Generate Biomedicines

Molly is Co-Founder and Chief Innovation Officer of Generate Biomedicines, a Flagship Pioneering company. She oversees corporate, platform and data strategy and a group that explores applications of the company's generative biology platform. Prior to joining Flagship, Molly led computational biology at Kaleido Biosciences and she received a PhD in computational and systems biology from Washington University in Saint Louis.

What is the vision for Generate Biomedicines?

Our vision is to leverage artificial intelligence (AI) to instantly generate medicines that treat and cure humanity's most intractable diseases. This is an incredibly ambitious vision, but with machine learning, we can move from an era of random trial-and-error drug discovery to one that is much more intentional.

How can machine learning and AI technologies enable discovery?

AI and machine learning can impact all parts of the drug discovery and development pipeline, from lead generation to optimisation. If you could, for an antibody, for example, pick an epitope on a target and generate a molecule directly to that epitope, you could transform this process. For current lead optimisation, oftentimes iterative rounds of optimising for one parameter are done without considering another parameter, making it a long and laborious process. AI can help avoid this.

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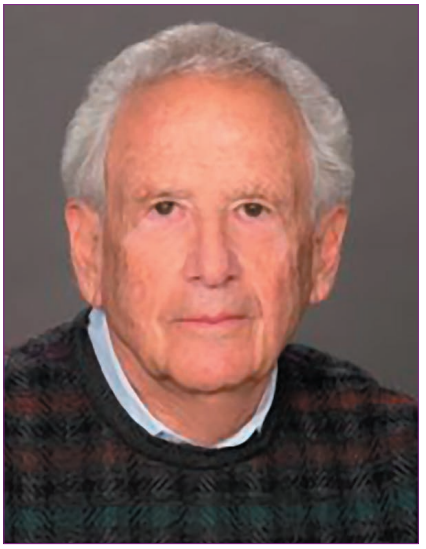
Can you describe a particular discovery or development workflow?

We were able to generate evidence of femtomolar antibodies, which is incredibly rare. We were able to generate, or create, them in about one and a half months total; traditional methods would take around a year.

We can generate *de novo* antibodies to specific epitopes and have been able to generate antibodies to the SARS-CoV-2 receptor binding domain, where we can look at regions of that binding domain that are more conserved across all variants of concern.

How do you see AI and machine learning evolving within biotherapeutic development?

We are just starting to realise the potential of AI and machine learning in drug discovery and development. We have the algorithms, data and experimental technologies that can truly feed machine learning, which we combine with our wet lab capabilities for our unique integrated platform. Discovery is no longer going to be the right word to even describe it. Soon we will be able to engineer what we need based on knowledge and principles that machines have learned, allowing us to have a much more intentional programmable future in medicine.



Dr Gary Cohen

Professor of Microbiology at the University of Pennsylvania

Gary is a Professor at the University of Pennsylvania. The overall goal of his research is to understand the molecular events that mediate the entry process of HSV into mammalian cells and promote its pathogenesis in its human host. A major focus of this research has been on key cellular receptors and the HSV glycoproteins. These studies have enabled application of basic knowledge to a more translational goal, ie, to develop a prophylactic human HSV vaccine using mRNA coding for both virion fusion and immune modulating proteins. A project in the works!

What is your lab's overall mission?

The overall goal is to understand the molecular events that mediate herpes simplex virus (HSV) entry into mammalian cells, creating an atmosphere to promote pathogenesis. I am interested in these events and the effect of infection, understanding the mechanism of entry and devising counterproductive events – including for the development of vaccines.

> ***The overall goal is to understand the molecular events that mediate herpes simplex virus (HSV) entry into mammalian cells, creating an atmosphere to promote pathogenesis***

How has that mission evolved due to COVID-19?

COVID-19 and HSV are related because the vaccine that we are associated with in a collaboration with Dr Harvey Friedman and Dr Drew Weissman involved messenger RNA (mRNA). Clearly, the COVID-19 pandemic and the generation of an mRNA vaccine presages an HSV vaccine; in fact, Moderna has recently announced they are investigating an mRNA HSV vaccine.

What are some of the new tools enabling vaccine research?

We can use a high-throughput surface plasmon resonance (SPR) machine on multiple samples and have recently started using a new SPR machine in the lab.

To make an effective vaccine, focusing on just one protein and its interaction with the receptor is not sufficient. It is best to understand each one of the events that take place between the glycoproteins and cellular receptor. This can be done by developing large panels of monoclonal antibodies (mAbs), looking at each of the proteins and the panels of mAbs, directed at each one to produce what is essentially an antigenic map of the glycoproteins. Then we can place each one of the epitopes on the three-dimensional (3D) structure of the glycoprotein and relate structure to function.

New technologies are allowing us to make these antigen maps, to take the mAbs, place them into communities, »

understand their relationship and then place them on the 3D structure of the protein. If you can do that, you can put it into an ongoing picture and try to make a story of fusion, allowing you to develop vaccine candidates rationally.

What other emerging trends are there?

I think old fashioned Phase I, II and III has now been truncated into a much more rational approach to develop vaccines. The stage has been cleared for moving forward, rapidly and confidently, into new vaccines.

Dr Erica Ollmann Saphire

Professor at La Jolla Institute for Immunology (LJI)

Erica is a professor in LJI's Center for Infectious Disease and Vaccine Research and the Director of the Coronavirus Immunotherapy Consortium (CoVIC), which united academics, non-profits, small and large biotechs and major corporations from around the globe to identify antibody therapeutics for COVID-19. Erica received her PhD degree in 2000 from Scripps Research and joined as an Assistant Professor in 2003, where she then became a full Professor in 2012. In 2019, she joined LJI.

Could you provide some detail about the programmes at LJI now that you are CEO?

We have a variety of initiatives. One is in women's health that builds on new research; there are a number of immune genes encoded on the X chromosome and females and males have different gene expression patterns, meaning an immune response in a female can vary from that in a male.

Another is against viral pandemics. We are headquartering a global programme to compare the world's antibody therapeutics against SARS-CoV-2. The consortium has antibodies resistant to every variant that has emerged and that are more potent than current commercially available ones.

We also have other programmes to understand the immune response against infectious diseases like tuberculosis, rabies, Ebola viruses, dengue and measles and in development of immunogens and antibody therapeutics.

> *We are headquartering a global programme to compare the world's antibody therapeutics against SARS-CoV-2*

How can partnerships impact the discovery of new medicines?

The coronavirus consortium I am heading up includes around 75 different partners and provides access to a multidisciplinary battery of assays that a lot of these companies would not otherwise have access to.

We are discovering human antibodies for a variety of drug applications and would like to partner to move these to the clinic. We have an additional longstanding relationship with Kyowa Kirin that supports joint projects.

Are there any new technologies enabling your work around COVID-19 variant analysis?

We are doing a lot of cryo-EM. This ability to rapidly solve structures has helped us get a roadmap for therapeutics against SARS-CoV-2 variants. We also now have an instrument for single B-cell discovery that has let us rapidly go from a survivor's arm to a novel mAb in a matter of days and the consortium has been accelerated by high-throughput competition analysis with SPR.

What are the most exciting emerging trends in biotherapeutic development?

Understanding how to best harness the power and precision of the immune response. There is a chance to make therapies for conditions that were previously incurable. We have reached a point now with the wealth of the data and bioinformatics at LJI that means we can drill down to understand the mechanisms of disease and markers of disease. If we understand these, we have the opportunity to prevent and treat disease – not just let it happen to us and our families but advance the technologies we need to preserve health.

Dr Andrew Bradbury

Founder and Chief Scientific Officer at Specifica

Andrew is Chief Scientific Officer of Specifica. He trained in medicine at the Universities of Oxford and London and received his PhD from the University of Cambridge. He has worked in the fields of antibody library generation and engineering for almost 40 years. Specifica's mission is to enable companies developing therapeutic antibodies with the world's best antibody discovery platform.

What are the emerging trends in biotherapeutic development?

I think antibodies are going to continue to be extremely popular,

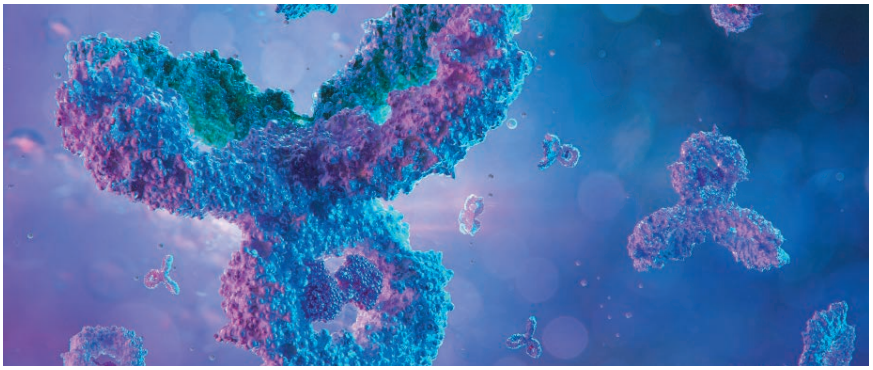
with different antibody formats, such as bispecifics, drug conjugates and so on. However, high-quality antibodies are going to be key.

Where do you see developmental technologies heading in the future?

I think we will see an increased application of bioinformatic methods, AI and machine learning. People are likely going to continue to try and generate antibodies *de novo* using these methods. In five years, these processes will be quite validated, in my opinion. Although until that happens, *in vitro* methods will continue to be essential.

What are some of the areas addressed by the Gen3 Specifica platform?

Our platform is agnostic in terms of the diseases treated; what we are trying to do is generate antibody libraries in which antibodies with liabilities have been completely eliminated and have been successful with this. The first step is to start with good complementarity-determining regions (CDRs), as opposed to CDRs where you randomly change amino acids. In our case, we start with real CDRs from sequenced antibodies, from which we eliminate all those containing known sequence liabilities and others we have identified. Eventually, we end up with a population of CDRs that fold and function well within the scaffold into which they are inserted and that have no sequence liabilities.



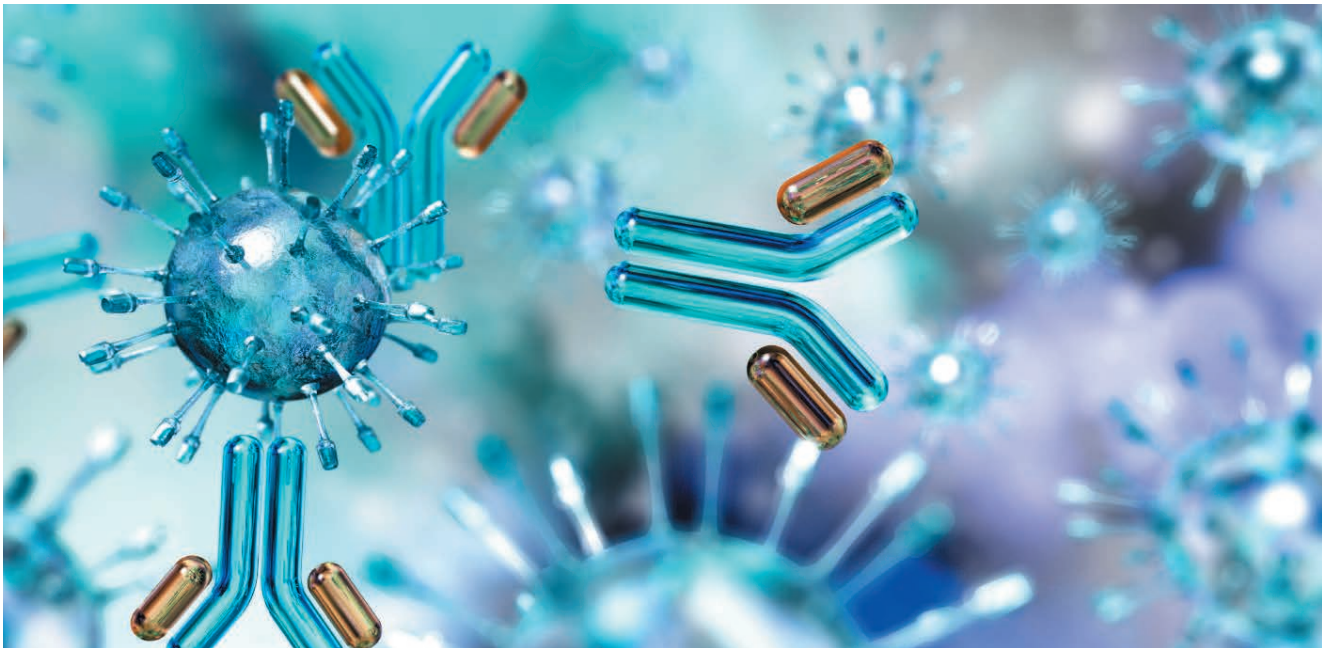
> *I think we will see an increased application of bioinformatic methods, AI and machine learning*

The goal is to start with a diverse 'problem free' library where developability issues do not arise downstream; we never use donors twice, so that each library we provide is exclusive and unique.

Which areas of therapeutic development do your technologies enable?

The more stringent the engineering, expression or downstream modification of the antibody is, the more important that the antibodies are developable, which our library enables.

If you are producing antibody-drug conjugates (ADCs) and you are putting something onto an antibody that might damage its functionality, then you want to start off with as functional an antibody up front, both in terms of antigen binding, but also in terms of developability. You do not want the addition of some chemical moiety to then cause the antibody to aggregate; that is what our platform prevents. »



Dr Bryan Jones
Senior Research Fellow at
Eli Lilly & Company

Bryan is currently a Senior Research fellow at Eli Lilly & Company, located at the Lilly BioTechnology Center in San Diego, California. He received his PhD in chemistry from Pennsylvania State University and completed post-doctoral research at the University of Washington. Throughout his time at Lilly, his research has focused on the biochemical aspects of antibody discovery and engineering, including leading efforts to develop new technologies aimed to improve antibody discovery capabilities.

What is your lab's mission?

The role of my group is in supporting our antibody discovery and engineering efforts from a biochemistry perspective. Our group here, as part of the BioTechnology Discovery Research organisation of Lilly, provides a range of capabilities ranging from molecule expression and purification to analytical and biophysical characterisation, where we focus on the binding properties of antibodies and their biophysical properties that are related to aspects such as pharmacology, manufacturing and formulation.

> ***From an antibody discovery perspective, the approaches we took to deliver therapeutic antibodies rapidly to patients relied on an array of capabilities that have been built over time – so called 'platform' technologies***

What are some new technologies critical to your success?

From an antibody discovery perspective, the approaches we took to deliver therapeutic antibodies rapidly to patients relied on an array of capabilities that have been built over time – so called 'platform' technologies. For instance, we relied on computational methods to help predict potential risks with antibodies to prioritise which to focus on initially. We took advantage of higher-throughput processes to make and perform initial characterisation of a relatively large number of antibodies, for example, automation-enabled expression and purification and binding property data, in addition to other functional characterisation like neutralisation assays.

How do you see the development of therapeutic antibodies changing in the future?

I suspect that like in all areas of drug discovery, continued improvement in the ability to discover antibodies to a particular target will enable the expansion of types of targets, including more challenging classes such as G protein-coupled receptors (GPCRs) and ion channels.

What are some of the opportunities to further therapeutic discovery?

I think that in addition to expanding the target space, there is opportunity in trying to take advantage of the properties of antibodies, such as their affinity and specificity to enable other treatment modalities, akin to ADCs. That might enable antibodies to target other therapeutics to specific tissues or cells, or maybe expanding the use of ADCs beyond the oncology setting.

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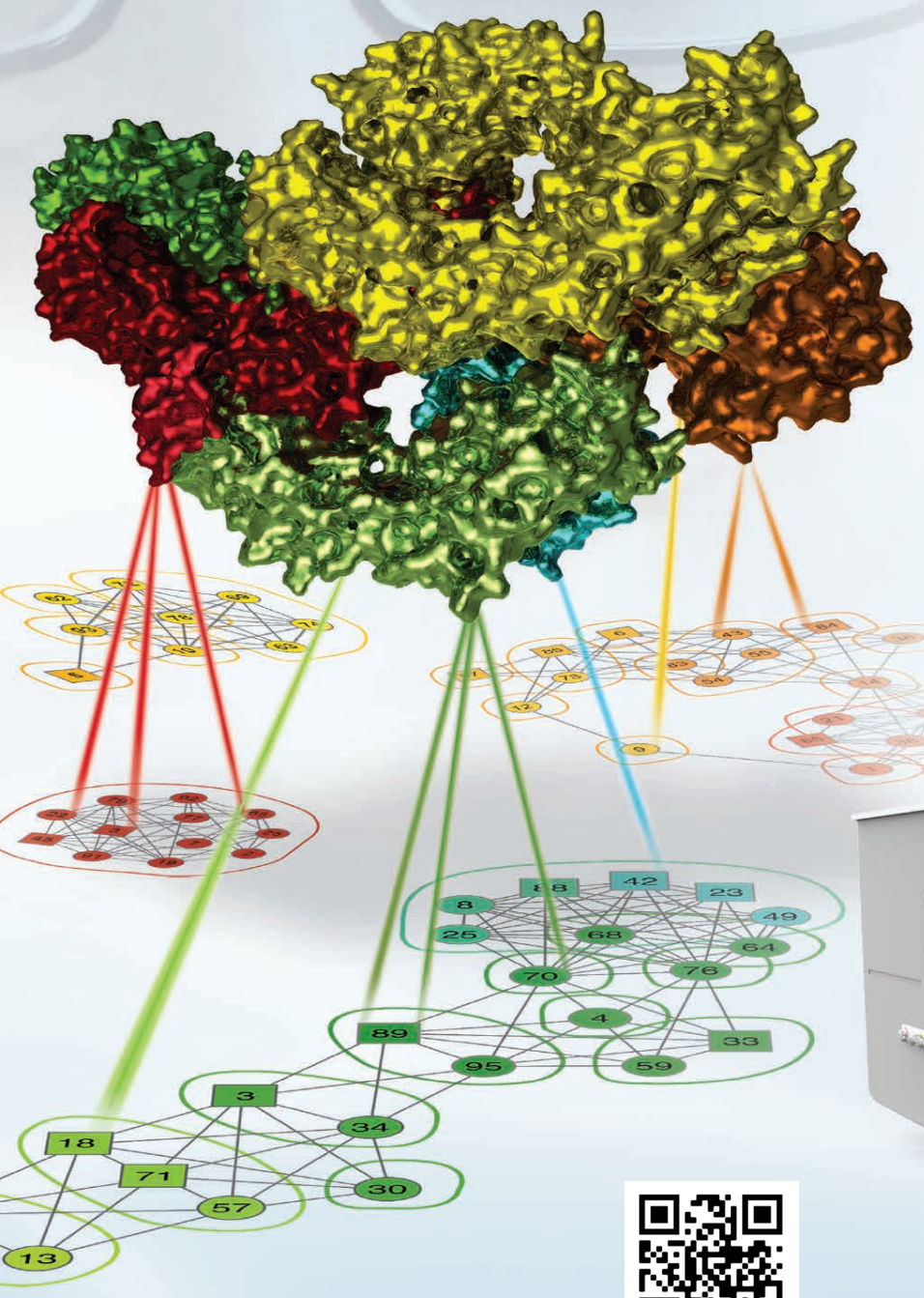

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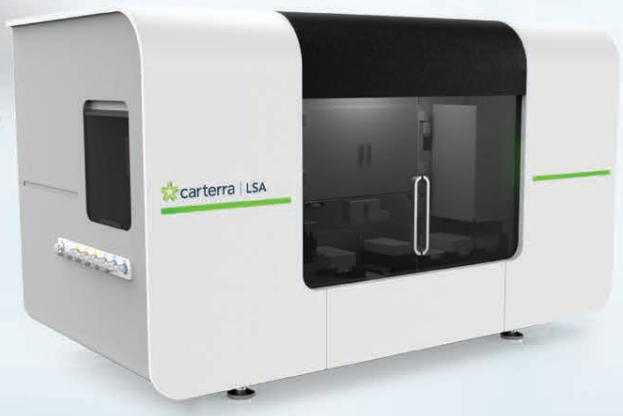

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