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BIOTECHNOLOGY:
A CROSS-DISCIPLINARY RESPONSE TO THE ONGOING COVID-19 PANDEMIC

The 2020 outbreak of the SARS-CoV-2 pandemic has had a major impact on most aspects of our lives. The whole scientific community, both in the academic and in the industrial setting, has shown a tremendous ability to join forces, mobilize and act quickly in the search for possible solutions. This massive response builds on years of research in the fields of, not only immunology and virology, but also cancer research, biotechnology, molecular biology and genetics. We wouldn't be seeing vaccines and therapeutic antibodies nearing the end of the clinical trials so fast if not for the enormous base of interdisciplinary knowledge accumulated over many years and a very efficient biotech-ecosystem built by biotechnology and pharma companies together with academic research units. The most advanced solutions that we might see reaching the market before the end of the year are therapeutic monoclonal antibodies based on decades of research, and vaccines based on disruptive technologies that borrow from genetic medicine and even investigational anti-cancer therapies.

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ANTIBODIES: UNPRECEDENTED SPEED AND EFFICACY GAINED FROM DECADES OF EXPERIENCE

The combined technological advancements of the last 30 years have provided an opportunity to quickly isolate, develop and produce monoclonal antibodies as a complementary approach to vaccine development. SARS-CoV-2-neutralizing antibodies have been generated using practically every available method of antibody discovery available in academia and industry. The most well-characterized and highly potent antibodies have come from the single-cell cloning of B cells isolated from the immune system of convalescent patients or from humanized mice.

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Monoclonal antibodies, the single largest class of biologic therapeutics, are one of the most powerful tools in modern medicine. Nowadays, more than 100 FDA-approved antibodies are transforming the way doctors treat and prevent cancer and autoimmune and infectious diseases[1]. In 2019, seven out of the ten best-selling drugs were monoclonal antibodies for cancer and autoimmune diseases[2]. The first therapeutic monoclonal antibody – for preventing kidney transplant rejection – was OKT3-approved in 1986. A few years later, it was followed by abciximab, which inhibits platelet aggregation in cardiovascular diseases (1994) and the first oncology antibody: its anti-CD20 (rituximab), approved for lymphoma in 1997. That marked the beginning of the so-called precision-medicine era and the longstanding domination of the antibody market by oncology products until kinase inhibitors and cell therapy completed the picture. If 7 out 10 best selling drugs were antibodies in 2019, the majority of them was still in oncology setting (4 out of this 7)[3]. Over time, large-scale production has revolutionized the market. Since the 1980s, the manufacturing yield has improved from tens of milligrams to over 3 grams per litre, thanks to cell-line engineering, the usage of easily scalable suspension cell cultures and more efficient purification[4]. The estimated cost of goods has shifted from approximately $300 per gram of antibody to as low as $20, provided production is carried out in a large facility producing approximately 10 tons per year[5]. Nowadays, there are at least 25 plants capable of fulfilling this criterion, while the total installed monoclonal antibody production base has exceeded 3 million litres worldwide. The bioreactors are readily adaptable to produce any type of recombinant antibody, targeting diseases from cancer to viral infections.

Antibodies can be used as prophylaxis, as therapeutic agent and for passive immunization when the vaccine for a viral disease is unavailable, as in the case of respiratory syncytial virus (RSV). SARS-CoV-2-neutralizing monoclonal antibodies have entered clinical trials with unprecedented speed – by the spring of 2020, more than 50 groups had established antibody programmes, thanks to the advanced antibody discovery platforms available throughout the biotech industry[6]. Preclinical studies have accelerated threefold relative to what had been typical for antibody therapeutics[7]. One way of discovering these antibodies was to screen the immune cells from convalescent patients: Eli Lilly's collaborator AbCellera has sequenced the genomes from over 5 million different B cells, seeking those that produced neutralizing antibodies. This effort led to over 500 unique antibody sequence candidates, which were then tested in vitro to find the most efficacious ones – which are now being evaluated in phase-3 clinical trials. Another approach was applied by Regeneron, whose method was based mainly on using the genetic code of the virus as a starting point, producing specific viral proteins in the laboratory and immunizing mice for antibody production. The major advancement of this approach is to use specific genetically engineered mice with a fully human immune system and able to produce human antibodies, which can proceed much faster than murine antibodies to the clinical trial, without the need for any additional genetic engineering step (humanization) before they can be safely tested on patients. The major targets of those antibodies were the S protein and its receptor-binding domain (RBD), as neutralizing antibodies to them have been shown to effectively inhibit the virus binding to the host receptors in the laboratory.

VACCINES: DISRUPTIVE TECHNOLOGIES SHORTEN THE TIME FROM DISCOVERY TO CLINIC

At the time of writing this article, there were 47 candidate vaccines in clinical studies and a further 155 in preclinical evaluation[8]. The idea of vaccination is to safely expose the body to a virus or viral parts so that the immune system creates a defence mechanism against it. Some innovative solutions go even one step further, resulting in the vaccine itself being temporarily produced inside a human body. So far, the most promising and fastest-progressing in clinic are the vaccine candidates based on RNA and viral vector platforms. In these approaches, the instruction of how to produce a specific viral protein is delivered to the human body, which uses its own natural mechanisms to synthesise a piece of the virus in order to "train" the immune system. RNA vaccines were originally developed as anti-cancer therapeutic vaccines, many of which are still undergoing clinical trials. Alternatively to RNA, DNA can be also used to instruct the body on how to safely make pieces of virus that are meant to immunize against the real infection. Several companies are using adeno-associated viral (AAV) vectors to deliver genetic instructions for the SARS-CoV-2 to spike protein into human cells. The same technology is used in gene therapies, where any defect in the production of a single protein is corrected with the provision of instructions on how to produce a healthy version of it. Two such therapies have so far been approved: Luxturna, for congenital blindness, and Zolgensma, for spinal muscular atrophy.

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The most advanced SARS-CoV-2 vaccine candidates have been developed by companies working on therapeutic anti-cancer vaccines. With a developed RNA production platform, such vaccines can be made substantially faster than conventional systems. In the case of traditional vaccines using inactivated or attenuated viral particles, or recombinant proteins, product-specific manufacturing processes have to be developed, optimized, validated and approved for production – a more time-consuming process. On the other hand, the agility of the RNA and AAV platforms allows for the rapid production and testing of

multiple vaccine variants, which are agnostic to the disease target and do not require the need for major process modification or re-validation. The production of new vaccine candidates can thus be achieved around 10 times faster. Moderna demonstrated the power of the RNA platform when the company proceeded from genetic sequence information of the virus to producing – in only 42 days – its first batch of clinical-grade vaccine material to be tested on humans. Shattock Group at Imperial College London generated a prototype RNA vaccine candidate in 2 weeks, after the selection of the genetic sequence of the spike protein[9]. Nonetheless, one must keep in mind that, despite the numerous production and affordability advantages, the RNA platform still remains unproven, with no commercial vaccine developed using this technology to date.

Given that RNA vaccine production processes are two-to-three orders of magnitude smaller than conventional vaccine production, they can be built much quicker and with a fraction of the capital needed for establishing the traditional process[9]. Multiple companies are scaling up their production facilities to provide cumulative worldwide capacity of close to 9 billion doses by the end of next year and more than 900 million doses before the end of this year[10]. Provided clinical trials deliver positive outcomes, most of the vaccines that reach the market this year will be based on RNA technology platforms (Moderna, and Pfizer with BioNtech), closely followed by DNA-encoded vaccines (AstraZeneca and JnJ). While the phase-3 clinical trials are still underway, Pfizer with BioNtech has proposed to supply up to 100 million doses of their mRNA vaccine candidate by the end of 2020 and approximately 1.3 billion next year, pending clinical success and regulatory authorization of the investigational candidate. Moderna expects to have approximately 20 million doses ready to ship by the end of this year and up to a billion doses next year, equivalent to 500 million full vaccination courses. AstraZeneca's DNA-encoded vaccine candidate will be produced in 2 billion doses, 700 million of which are expected to be ready by December.

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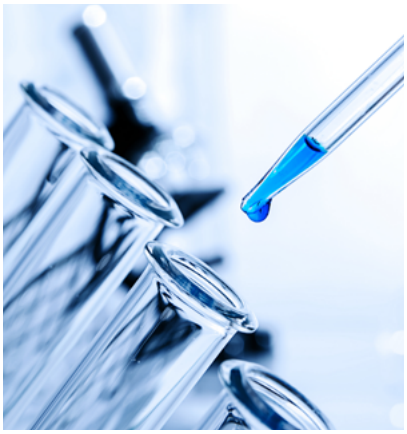
With this article, we would like to emphasize that research on infectious diseases and possible solutions to a pandemic cannot be seen as an isolated discipline. Multiple-platform technologies such as monoclonal antibody discovery, gene therapy and RNA manufacturing have all contributed to the preclinical development of therapeutics and vaccines at an unprecedented speed. Thanks to groundbreaking technologies, combined with an installed broad biotech ecosystem and the efforts of scientists across many different fields, we now have a much better chance than ever before to design and mass-produce at an acceptable price multiple therapeutics and vaccines bringing a solution to the pandemic.



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