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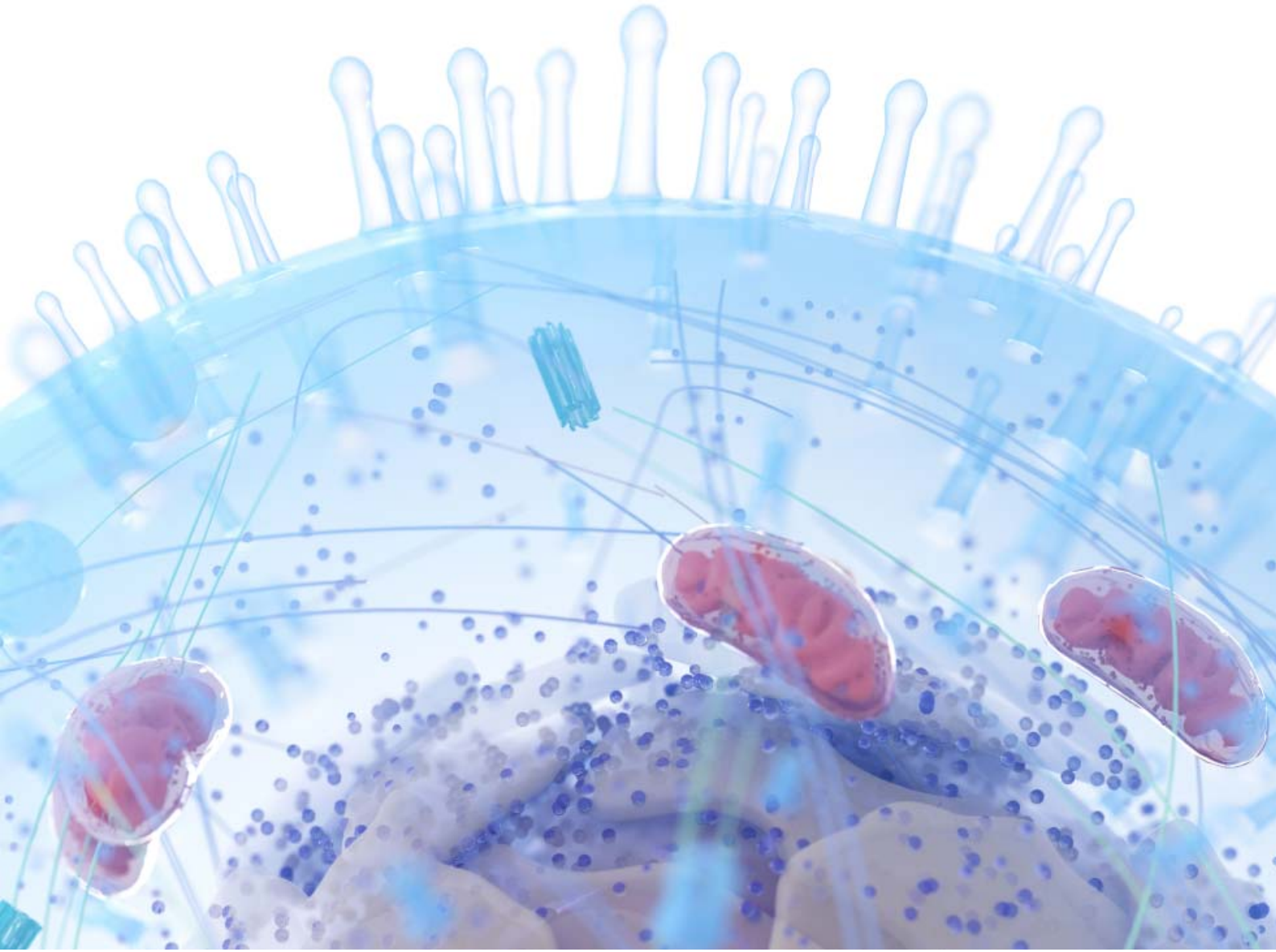


Deal Watch in the Time of COVID-19

By Sharon Finch and Jill Ogden, Medius Associates Ltd

In signing off on our monthly Deal Watch articles, it was always intended that the Medius team would write the occasional special interest article; and with a huge number of collaborations and partnerships establishing across the world to address the COVID-19 pandemic, this certainly seems to be an appropriate moment. A caveat applies here though, as the news is breaking so quickly in this very fluid situation, this article will certainly date as new partnerships are announced and scientific break throughs advance the campaign to manage and control the impact of this devastating coronavirus.

It is interesting to note that many of the deals are coming together very rapidly and the focus appears to be on achieving a viable scientific outcome rather than impressing the shareholders with big biodollar headlines; consequently, very few press releases actually disclose financial terms. Indeed, several companies, for example GSK, clearly note that there is no expectation of any profit from the COVID-19 vaccines.

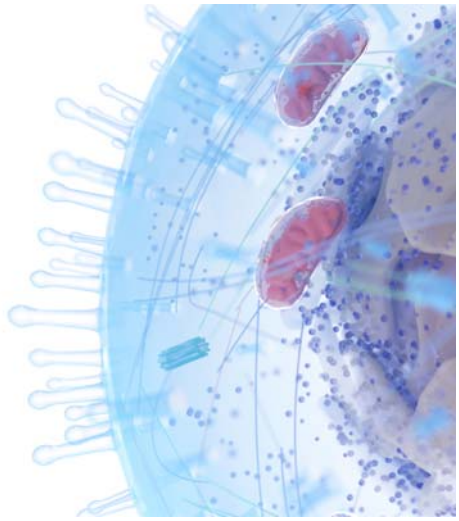
Major players

Most of the big pharma companies have stepped up to the challenge in various ways either in forming collaborations (such as GSK with Sanofi to advance vaccine work as quickly as possible) or by donating supplies of key products; for example, Sandoz and Sanofi with hydroxychloroquine. Other companies are making financial donations to COVID-19 relief funds (e.g. AbbVie $35m, Merck & Co $30m, Pfizer $40m, J&J $50m, Novartis $20m), whereas others are very specifically stating that sales of any COVID-19 vaccines will be on a not for profit basis (J&J / BARDA).

Against this backdrop, some companies are likely to do well and others not so well in terms of revenues from product sales. With individuals reluctant to attend hospitals and GPs there has been a massive shift towards telehealth. Furthermore, with the sales force unable to visit doctors, companies such as J&J, Merck & Co and Pfizer have indicated that there will be a negative impact on sales revenues for Q2. Merck has predicted a $2.1bn hit in revenues and J&J a $7bn cut in sales forecast. In addition, several companies have indicated that certain product launches will be delayed, for example Bluebird Bio's Zynteglo (autologous CD34+ cells encoding βA-T87Q-globin gene) gene therapy for transfusion-dependent beta -thalassaemia, Biogen's Spinraza (nusinersen) in spinal muscular atrophy and Celgene's Zeposia (ozanimod) in relapsing remitting multiple sclerosis. As these are all highly priced products, delay at this time of intense pressure on health care budgets seems quite appropriate.

Regulatory aspects

As for other areas of the industry, there is an upside as well as a downside in the regulatory field. The big news was the issue of an emergency use authorisation (EUA) by the FDA for Gilead's remdesivir for the treatment of COVID-19 in hospitalised patients with severe disease; the recent clinical data have shown a shortening time to recovery in some patients although earlier studies were less conclusive. Japan has also approved remdesivir under an exceptional approval pathway.



"I have never seen a moment so rich in collaboration, ingenuity and acts of bravery. Public health authorities, private sector companies, research universities, governments and, most of all, the heroes on the front lines of care are mobilizing in ways that current generations have never before witnessed."
Chairman & CEO Alex Gorsky, Johnson & Johnson

The FDA EUA fast track has also been deployed to secure approvals for diagnostic tests in 24 hours from receipt of data. An example of this was Roche's antibody test Elecsys® designed to determine if a patient has been exposed to the SARS-CoV-2 virus and has developed antibodies. There is immense political and social pressure to get tests, vaccines and therapies widely available as quickly as possible and the system appears to be working.

On the downside however, for non-COVID-19 therapies, there may be a considerable negative impact on clinical studies, indeed IQVIA has reported that 80% of clinical trial sites are currently inaccessible. It is currently difficult to anticipate an early return to routine hospital appointments and clinics, although it remains a matter of concern that non-COVID-19 patients may be at risk.

New sources of innovation

Managing the pandemic has highlighted the need for innovative support for every aspect of healthcare but help has come from some unexpected sources. Companies such as Dyson and Gtech answered the call for assistance with the provision of ventilators working on a new design, the CoVent. Similarly, Mercedes F1 joined Project Pitlane and University College London (UCL) scientists to develop a breathing aid (Continuous Positive Airway Pressure (CPAP) devices) for the NHS.

Other philanthropic efforts to support innovation have come from the Wellcome Trust which put out a call to secure $8bn of funding. The $8bn is intended to be deployed as follows: $2bn on vaccine development, $1.5bn on advancing therapeutics and $4.5bn to support diagnostics, manufacturing and other tasks to help the world eradicate COVID-19. Wellcome highlighted CEPI* and the COVID-19 Therapeutics Accelerator among the groups that need more cash. The COVID-19 Therapeutics Accelerator has been set up with the specific aim of bringing pharma companies and academic institutions into coordinated research programmes to emulate CEPI. It is coordinated by the Bill & Melinda Gates Foundation, Wellcome, and Mastercard.

It is a testament to this extraordinary spirit of collaboration that Google and Apple, normally close competitors, announced a joint effort to enable the use of Bluetooth technology to help governments construct a contact tracing platform.

Diagnostic testing

The policy on diagnostic antigen testing for the presence of COVID-19 has proved quite controversial and the practice has varied from country to country but an effective testing regime is considered critical to enable a return to a more normal life style. A huge number of companies and organisations have been involved in developing and conducting tests. As seen across the entire healthcare landscape, partnerships have been key; in the UK GSK, AstraZeneca and the University of Cambridge formed a joint collaboration to boost testing. A new laboratory was set up in Cambridge to be used for high throughput screening for COVID-19 testing and to explore the use of alternative reagents to help overcome supply shortages. For the majority of antigen tests it can take up to several days for an individual to receive their results, however Abbott has developed a test that can deliver a result in approximately 15 minutes and this obtained FDA EUA status on 27th March. However it was recently reported that the FDA is currently reviewing reports that this test has returned a small number of false negative results.

Diagnostic companies are also ploughing huge investment into the development of reliable COVID-19 antibody tests to map how widely populations have been infected. For example Roche has invested $459m into antibody test production. Its Elecsys anti-SARS-CoV-2 antibody test has now been approved in Europe and the US.

**Coalition for Epidemic Preparedness Innovations (CEPI) is an Oslo based not for profit organisation*

Therapeutics

Companies have been exploring repurposing of existing products as well as novel approaches to treating COVID-19 patients. The quick fit is of course to dig deep into existing compound libraries as well as reviewing marketed products to determine if any could be repurposed beyond their current indications. Different approaches include looking at existing antivirals, kinase inhibitors and antibodies with possible utility in either prevention or treatment of secondary complications associated with COVID-19, such as the cytokine storm seen in some patients. While the majority of this repurposing work is not necessarily via collaborative partnerships, even the big pharma cannot completely go it alone and manufacturing alliances are being developed (see section below). Some examples of the drug repurposing work that is under way are noted in Table 1.

Table 1: Repurposing candidates

Company	Product	Original indication	Status
Gilead	remdesivir	Ebola	broad-spectrum antiviral nucleotide analogue, approved in US, Japan
Fujifilm	Avigan (favipiravir)	influenza	antiviral, phase 3
AstraZeneca	Farxiga (dapaglifozin)	type 2 diabetes	SGLT2 inhibitor, phase 3
AstraZeneca	Calquence (acalabrutinib)	haematological malignancies	Bruton's tyrosine kinase (BTK) inhibitor, phase 2
J&J	Imbruvica (ibrutinib)	haematological malignancies	BTK inhibitor, phase 2
Novartis/Incyte	Jakafi (ruxolitinib)	myelofibrosis	JAK 1 / JAK 2 tyrosine kinase inhibitor, phase 3
Eli Lilly	Olumiant (baricitinib)	rheumatoid arthritis	JAK 1 / JAK 2 tyrosine kinase inhibitor, phase 2
Roche	Activase (alteplase)	stroke	fibrinolytic agent, phase 2
Alexion	Soliris (eculizumab)	PNH	complement inhibitor, phase 2
Genentech	Actemra (tocilizumab)	inflammatory conditions	interleukin-6 (IL-6) antibody, phase 3
EUSA Pharma	Sylvant (siltuximab)	Castleman's disease	IL-6 antibody, phase 2
Regeneron/ Sanofi	Kevzara (sarilumab)	rheumatoid arthritis	IL-6 antibody, phase 2/3
Eli Lilly	LY3127804	oncology indications	antibody against angiopoietin 2 (Ang2), phase 2
GSK	otilimab	rheumatoid arthritis	antibody against granulocyte macrophage colony stimulating factor (GM-CSF), phase 2
Synairgen	SNG001		inhaled formulation of interferon beta-1a (IFNβ1), phase 2

PNH paroxysmal nocturnal haemoglobinuria

In addition to the examples illustrated in Table 1 other big pharma companies such as AbbVie and Pfizer have programmes to investigate the potential to repurpose existing antiviral and other classes of drug candidates to tackle COVID-19. There are also publications proposing the evaluation of antibodies to tumour necrosis factor (TNF) to prevent the acute inflammatory reactions seen in some of the patients hospitalised with COVID-19 thereby avoiding the need for intensive care support.

In addition to reviewing their existing portfolios for drugs which may have potential to combat the various facets of COVID -19 disease, many companies have initiated programmes to develop new therapeutic candidates. This has proved to be a rich source of new partnerships targeting multiple approaches covering many types of technologies, from small molecules and antibody based therapeutics to RNAi. However as mentioned above, there is very little information on the financial terms of the deals signed.

Of the small companies, Vir Biotechnology a US biotech with an infectious disease focus has been particularly active in deal making to tackle COVID-19, using its various technology platforms. Its numerous partnerships include a collaboration with GSK to identify new antiviral antibodies that could be used as options in the treatment of COVID-19. The companies plan to proceed directly into a phase 2 clinical trial within the next few months. Vir's share price has increased over 150% since the beginning of 2020.

Some selected examples of new partnerships to develop therapeutics to treat COVID-19 are noted in Table 2.

Table 2: Partnerships to develop therapeutics to treat COVID-19

Companies/ Partners	Comments
AbCellera Biologics / Lilly	Co-development of antibodies
Adaptive Biotechnologies / Amgen	Discovery/ development of neutralising antibodies targeting SARS-CoV-2
AstraZeneca	R&D into novel antibodies with various government and academic partners
Vir Biotechnology / Biogen	Development and clinical manufacturing of antibodies
Vir Biotechnology / GSK	Development of existing and identification of new antiviral antibodies; GSK makes $250m equity investment in Vir at 10% premium to share price
Xencor/ Vir Biotechnology	Technology licence for non-exclusive access to Xencor's Xtend™ Fc technology to extend the half-life of novel antibodies
Vir Biotechnology / Alnylam	RNAi therapeutics targeting SARS-CoV-2
Mabpharm / Sorrento Therapeutics	Development of ACE-MAB fusion protein that binds to the spike protein of the SARS-CoV-2 virus; Sorrento has US and European rights

Plasma therapy

In another example of cross industry co-operation, the consortium led by Takeda and CSL Behring (aka CoVIg Plasma Alliance) is working on the development of an immunoglobulin which could provide passive immunity for seriously ill patients. As all of these companies already operate plasma collection networks this enables them to source the virus-neutralising antibodies required for the drug development. It is hoped that the plasma treatment will go into clinical trials in the summer.

Vaccines

Vaccines remain the great white hope in being able to control COVID-19. The Economist recently reported that there are 86 vaccines in development covering a range of different approaches: subunit, RNA, recombinant vector, DNA, inactivated virus. Not surprisingly there has been huge activity in terms of partnerships for both research and production.

Plasma-derived therapies	
Takeda/ CSL Behring/ Octapharma/ LFB/ Biotest/ Bio Products Laboratory	Collaboration between plasma manufacturers to produce polyclonal hyperimmune immunoglobulins to treat serious complications from COVID-19
Grifols/ BARDA	Production of hyperimmune immunoglobulins to treat COVID-19

The two largest vaccine companies GSK and Sanofi have combined forces to develop an adjuvanted COVID-19 vaccine, which is expected to enter clinical trials in the second half of 2020 with vaccine availability anticipated by the second half of 2021. While GSK is also collaborating with the University of Queensland, Clover Biopharmaceuticals and Xiamen Innovax Biotech, Sanofi is working with Translate amongst others.

David B. Weiner, Wistar Institute's Vaccine and Immunology Center:

"This is not about competition….. we are all in this together."

In looking at vaccine manufacture, Moderna has tied up with Lonza with the aim of delivering 1 billion units. J&J has placed two manufacturing deals, firstly with Emergent and subsequently with Catalent and AstraZeneca has brought its development and manufacturing capabilities to a collaboration with Oxford University and The Jenner Institute.

In a classic biotech / big pharma deal BioNTech signed up with Pfizer for its mRNA vaccine for COVID-19. The deal has a headline value of $748m, with a $185m upfront payment of cash ($72m) and equity ($113m) with $563m in milestones. Pfizer will initially pay the full developmental costs of the vaccine, but BioNTech will reimburse Pfizer for 50% of the development costs during commercialisation. Phase 1 testing has already been started in the US. If the development goes to plan, the scale up of vaccine production should reach hundreds of millions of doses in 2021.

Building an academic / pharma / government consortium J&J started its research early back in January through its Janssen division which formed a partnership with the Rega Institute for Medical Research, University of Leuven. From this base the company has identified a lead vaccine candidate with two backups. The agreement with BARDA followed - a headline $1bn partnership for vaccine and antiviral research and development.

Selected COVID-19 vaccine development programmes and partnerships*

Companies/ Partners	Status	Comments
Beijing Institute of Biological Products/ Wuhan Institute of Biological Products	P1	Inactivated coronavirus
BioNTech/ Pfizer	P1	mRNA vaccine
CanSino Biologics/ Beijing Institute of Biotechnology	P2	Adenovirus-based vaccine
Clover Biopharmaceuticals/ GSK	PC	Protein-based vaccine with adjuvant
CureVac	PC	mRNA vaccine
GSK/ Sanofi	PC	Protein-based antigen with adjuvant
Imperial College, London	PC	Self-amplifying RNA (saRNA) vaccine
Inovio Pharmaceuticals	P1	DNA plasmid vaccine
J&J/ BARDA	PC	Adenovirus-based vaccine, $420m funding from BARDA
Moderna/ BARDA	P1	Lipid nanoparticle (LNP)-encapsulated mRNA vaccine, $483m funding from BARDA
Shenzhen Geno-Immune Medical Institute	P1	Lentiviral vector-based vaccine containing synthetic mini-gene
Sinovac	P1	Inactivated coronavirus with adjuvant
The Jenner Institute, University of Oxford/ AstraZeneca	P1	Adenovirus-based vaccine
Translate Bio/ Sanofi	PC	mRNA vaccine

**Source: WHO, company websites*
BARDA, Biomedical Advanced Research and Development Authority

In addition to all of the above partnerships, CEPI has been kick starting the biotech and academic community by making grants to companies such as Moderna and also Inovio which received $9m to support pre-clinical and clinical research. Inovio was also the recipient of a $5m grant from the Bill & Melinda Gates Foundation. The biggest grant award however of $384m went to Novavax for scale up of the production of its nanoparticle vaccine combined with an adjuvant. Other grant recipients include CureVac, the University of Hong Kong, Oxford University, the University of Queensland and a group led by Institut Pasteur.

Manufacture and Supply

Scaling up and cost effective supply of both vaccines and therapeutics is very much centre stage in terms of managing this pandemic. No sooner had Gilead secured its authorisation for remdesivir than the call went out for partners to assist with manufacture and supply. Gilead then quickly put in place contracts with Cipla, Mylan, Ferozsons Laboratories, Hetero Labs and Jubilant Lifesciences to assist with manufacture. Under the agreements which share manufacturing know-how, no royalties are due to Gilead until WHO calls the pandemic over or until another therapy is approved.

Looking more broadly, there may also be a move to reshore / repatriate manufacture of essential products such as PPE by national governments as the coronavirus crisis has shown up clear weaknesses in supply chains.

Summary

It is clear that the current global economic uncertainty that has occurred in the wake of the pandemic will have a major impact on the industry for the rest of 2020, but on the plus side there has been an upturn in the reputation of the pharma industry. This positive light may, however, dim if the industry is seen to overcharge for vaccines or therapies. The price of remdesivir has yet to be set but the benefit is a 31% faster recovery, a possible saving of 4 hospital days. There are press reports that a course of treatment might cost ~$4,500 but this is unconfirmed.

It is difficult to predict what longer term impact the intense focus of R&D efforts in the search for COVID-19 vaccines and therapies will have for other non-antiviral therapies. Hitherto oncology has been the dominant therapeutic field for many companies' R&D budgets but this may well change. This specific focus may also have implications for availability of investment capital for biotech companies with a non-anti-infective portfolio.

Looking more broadly, those companies which are currently carrying high levels of debt may also be at risk with a lowering of company valuations and potential trade sales of failing businesses. In addition, there may be further mergers and acquisitions by cash rich businesses which are best able to weather the storm. Challenging times for us all.

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Sharon Finch, the founder of Medius, has extensive business development experience working both in industry and for over 20 years with Medius. Sharon works primarily on partner searches, due diligence and transactions. She is the Editor of the Business Development and Licensing Journal and is the Course Director for the PLG MSc in Pharmaceutical Business Development & Licensing run by the University of Manchester.

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