

AVACTA GROUP LTD

UPDATE II: PART II

04.06.2020

Ticker: AVCT.L
Price (p): 150.0
Shares in issue (m): 248.8
Market cap. (£m): 373.2

Introduction

This note follows on from Part I of our Update Note (2) on Avacta Group, viewable here:

<https://aimchaos.files.wordpress.com/2020/05/avacta-group-update-ii-part-i.pdf>

All notes on Avacta Group viewable here:

<https://aimchaos.com/>

On 15 May, Avacta announced that its Affimer reagents that bind to the SARS-CoV-2 virus' spike protein (that are being used to develop its two types of antigen test) also block the interaction between said spike protein and a receptor found on human cells, called ACE2, to which the virus spike protein binds in order to infect cells. This opens up the potential for developing an Affimer-based neutralising therapy for SARS-CoV-2, the virus that causes the coronavirus disease (which is itself known as 'COVID-19').

Neutralising therapies can be used either to treat already infected patients, by limiting disease progression; or as a prophylactic, providing temporary passive immunity to those most at risk of exposure to the virus, such as healthcare workers.

There are numerous neutralising therapies for SARS-CoV-2 currently being developed worldwide, with hundreds of millions of dollars having been invested in them. These are primarily antibody-based therapies. In a similar vein to antigen testing, we believe that an *Affimer*-based neutralising therapy could offer numerous advantages over an antibody-based neutralising therapy, both clinically and commercially.

In its announcement on 15 May, Avacta essentially declared an open invite to Big Pharma, seeking a partner with the resources to fast-track the development of an Affimer-based neutralising therapy. Given the substantial commercial interest being shown in the space at present, we feel that it is possible that the Company could secure a partner in the coming weeks.

On 23 May, we published the first instalment of a three-part Update Note on Avacta Group ('Avacta'). It focussed on the point-of-care antigen testing market for SARS-CoV-2, and on Avacta's work within this market.

This second instalment of the Update Note examines *neutralising therapies*. Firstly, we explore what a neutralising therapy is, how it works, and the developments achieved in this therapeutics submarket to date. We then examine how a neutralising therapy could be used in the war against the COVID-19 pandemic, and the players already developing such therapies. Finally, we examine how Avacta is well positioned to potentially develop an Affimer-based neutralising therapy for SARS-CoV-2 with a major partner.

In the third and final instalment of the Update Note, we will provide a detailed valuation analysis and updated Investment Thesis for Avacta, which will also consider the £48m equity placing and updated strategy announced by the Company today. We intend to publish the final instalment within the next two weeks.

An Introduction to Neutralising Antibody Therapies

A neutralising antibody (‘NAb’) is an antibody that defends a cell from a pathogen or infectious particle by neutralising any effect it has biologically. After neutralisation, the infectious particle is no longer infectious or pathogenic. By binding specifically to surface structures on an infectious particle (such as the spike proteins on a coronavirus particle), neutralising antibodies prevent the particle from interacting with target host cells that it otherwise would infect and destroy.

NABs can be used both as a treatment, and as a form of passive immunisation, for infectious diseases. As a treatment, NABs can limit the progression of the disease in an already-infected patient. As a prophylactic (or ‘passive vaccine’), they can prevent infection for those most at-risk to the virus, such as healthcare workers, the elderly and those with underlying health conditions.

Antibodies are found in plasma, one of the four main components of blood besides red blood cells, white blood cells and platelets. The concept of convalescent plasma (‘CP’) therapy dates back to the end of the 19th century, when the transfer of plasma from an individual that had recovered from a certain disease, to a sick or unprotected individual, was examined in animal studies (specifically, in treating diphtheria and tetanus). Indeed, at the turn of the century, CP therapy was being used in the hospital setting to reduce mortality during diphtheria outbreaks. In 1918, during the influenza pandemic (more commonly known as the Spanish Flu), CP therapy was used to successfully treat acutely ill patients.

In the latter half of the 20th century, CP therapy was refined: numerous polyclonal antibody (‘pAb’) treatments were developed that targeted either prevention of viral infections or treatment of bacterial toxin related diseases. pAbs are collections of antibodies that target the same pathogen but bind to different epitopes (the part of an antigen that is recognised by the antibody). pAbs are obtained from a collection of different plasma cells of human donors or animals that have been exposed to the antigen. By using pAbs (antibodies that bind to multiple epitopes), a treatment is still effective even if the virus mutates and one of the epitopes changes in structure. However, because of the nature of the production, treatment with polyclonal antibodies suffers from batch to batch variation and low antibody concentration.

A breakthrough in the potential for NAb therapies came in the 1980s, with the discovery of a method of large-scale production of *monoclonal* antibodies (‘mAb’). mAbs are ‘synthetic’ antibodies that are made by identical immune cells, that are themselves clones of a unique parent cell. mAbs bind to the same epitope as one another; that is to say, they have *monovalent affinity*. This gives them a high specificity (thus minimal cross-reactivity). The aforementioned method of production, namely *hybridoma technology*, also ensures very high consistency and scalability in comparison to pAb production. mAb production technology has been refined further in the new millennium, with several alternative production methods developed such as *phage display* (this particular method generates *recombinant* mAbs – it does not require the use of animals).

As of December 2019, 79 therapeutic mAbs had been approved by the US’ Food & Drug Administration (‘FDA’), and 690 more were in clinical trials. Therapeutic mAbs have dramatically improved the treatment of cancer, multiple sclerosis, cardiovascular disease and psoriasis, amongst many other diseases. The global mAb market was valued at \$115bn in 2018, with the top eight therapeutic mAbs each generating revenue of over \$5 billion (the cumulative total for those top eight best sellers was \$66.4bn).¹

However, only a handful of those 79 therapeutic mAbs are for infectious disease indications, i.e. are NAb therapies. Amongst these are palivizumab (branded Synagis), a treatment for respiratory syncytial virus (RSV) that was approved in 1998; and raxibacumab (branded ABthrax), a treatment for inhaled anthrax that was approved in 2012. In August 2014, an experimental treatment for Ebola, named ZMapp, was given to two patients under the FDA’s ‘compassionate use’ regulation, despite having not gone through clinical trials at the time. Although it seemed to be effective on both patients, a 2019 clinical study determined that ZMapp was ineffective against Ebola compared to two other treatments. To date, it still has not been granted FDA approval.

¹ <https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z/tables/2>

The success of alternative methods to combat infectious disease, notably cost-effective vaccines and anti-viral small molecules, partially explains the lack of approved therapeutic mAbs for infectious disease indications. Of the aforementioned 690 mAbs in clinical trials as at end 2019, only 35 (~5%) were anti-viral therapeutics.² Indications that *are* being focussed upon are those viral diseases either without available vaccines (such as Ebola, HIV, SARS and MERS) or without effective anti-viral drugs (such as rabies and influenza).

To quote an article from March 2006 in the journal, *Nature Reviews Drug Discovery*:³

So far, most monoclonal antibodies have been developed for treating cancer or immunological diseases. However, the global spread of infections such as West Nile and corona viruses, and the need to address the potential threat of bioterrorism, has boosted public interest in, and government support of, counter-measures for infectious diseases. The attractive features of monoclonal antibodies, such as high specificity and effective recruitment of the immune system, would seem to make them excellent candidates as anti-infective agents.

The SARS-CoV-2 pandemic of 2020 has driven that *public interest in, and government support of, countermeasures* to a level that the authors of the above article would likely have considered implausible back in 2006. Yet multiple billions of dollars have been invested in over a hundred potential vaccines under development for the virus worldwide, by governments and the private sector alike. Even so, in the most optimistic of scenarios widespread administration of a successfully developed vaccine might not occur until the latter half of next year.

Consequently, interest – and investment – in the development of *neutralising therapies* (which are predominantly mAb-based) has exploded in the past several months. As we explore in the next section, NAbs can (theoretically, at least) be developed more quickly than a vaccine, and thus could prove to be a critical weapon in our arsenal in the war against the SARS-CoV-2 pandemic.

² <https://www.antibodysociety.org/covid-19/>

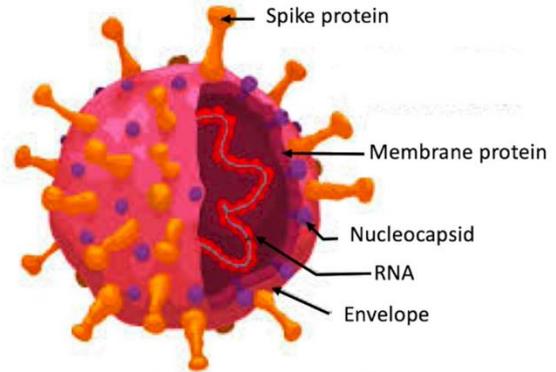
³ <https://pubmed.ncbi.nlm.nih.gov/16518372/>

A Neutralising Therapy for SARS-CoV-2

SARS-CoV-2: the infection process⁴

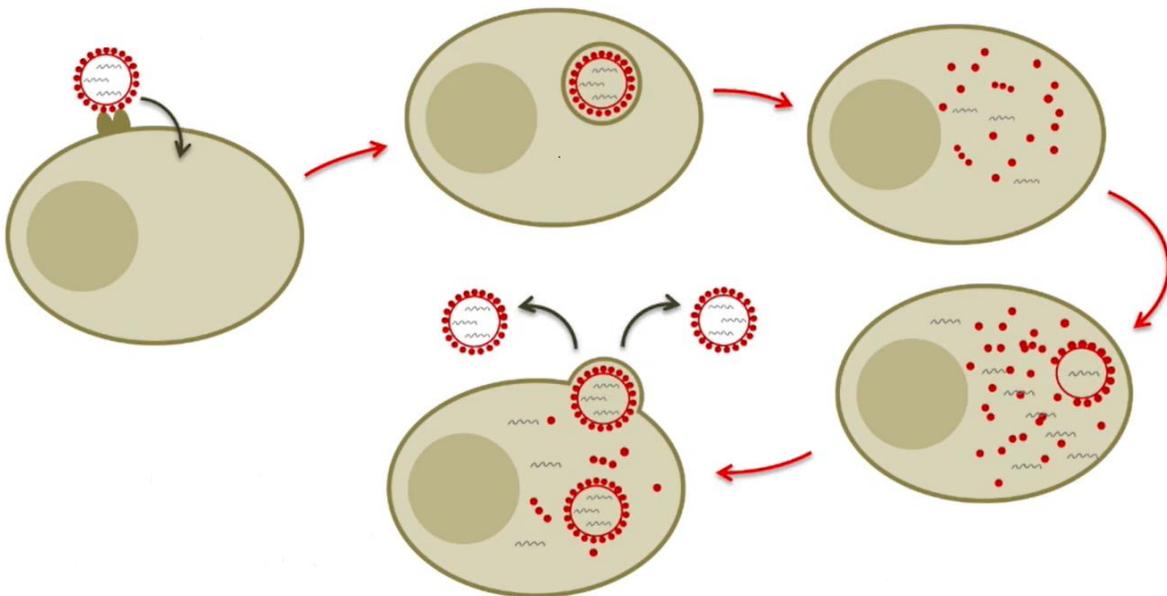
An antigen is a molecule (usually a protein) that is specific to a pathogen and is normally found on the pathogen's surface. In the case of SARS-CoV-2, the antigens are the spike proteins on the outside of the coronavirus structure and the nucleocapsid proteins embedded on its surface. As we detail below, these spike proteins – of which there are approximately one hundred on each particle – are integral to the virus' infection process. They are ideally suited to latch onto a certain enzyme on the surfaces of throat and lung cells, slip into them via endocytosis and then proceed to replicate themselves millions of times.

Exhibit 1: coronavirus structure



In short, SARS-CoV-2 thrives by transforming the human cells that it has infected into virus 'super-factories' that subsequently generate multiple more virus particles: these new particles then burst out of the super-factory cell to seek out more cells to infect. Below, we summarise the steps in the infection process.

Exhibit 2: the infection process for SARS-CoV-2



In the first image, the virus particle binds to the healthy human cell (such as a lung epithelial cell). Specifically, the spike proteins on the surface of the virus bind to a receptor on the human cell called ACE2 (see Exhibit 3, p.5, for a detailed image).

In the second image, the virus particle has moved *inside* the human cell via the process of endocytosis. The particle then breaks open, releasing the viral RNA – which is the blueprint for all the components of the virus.

⁴ Data and images predominantly sourced from Company website, www.avacta.com

At this point, the virus has essentially commandeered the cell. The ‘viral super-factory’ comes into play: the human cell uses the viral RNA information and its own cellular machinery to produce the various virus components in large quantities. These components then instinctively assemble together to form whole new virus particles.

In the final image of Exhibit 2, we see these multiple new virus particles emerge from the cell. They will go on to seek out and infect more healthy cells.

Neutralising therapy for SARS-CoV-2: the mechanics

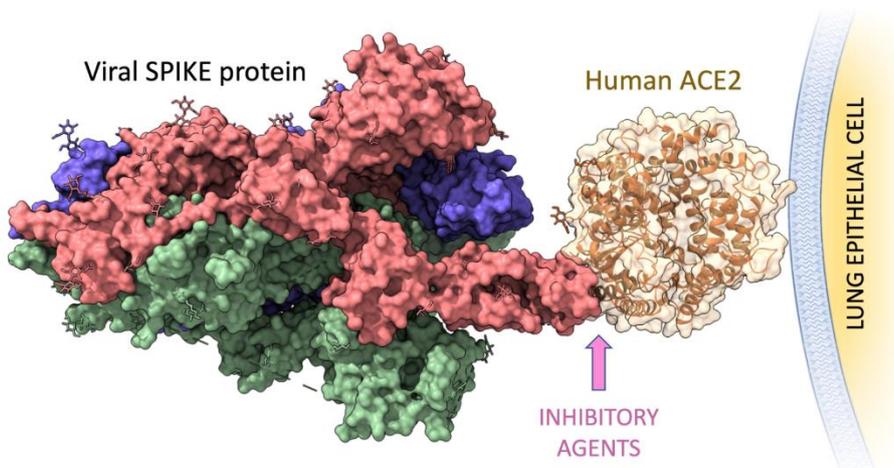
The presence of the antigens on the surface of the virus particle (i.e. the spike proteins) catalyses the human immune system to generate antibodies that will subsequently neutralise the virus. These antibodies bind to the spike proteins, thus prohibiting the spikes from binding to the ACE2 receptors on healthy cells – ultimately preventing the process of endocytosis. Moreover, the human immune system acts against *already infected* cells via a martyrdom strategy: infected cells effectively sacrifice themselves by displaying distress signals for cytotoxic T-cells, which swiftly detect and kill them.

However, as the world now knows, the immune systems of the elderly and those with underlying health conditions (such as asthma, diabetes and heart disease) are sometimes not strong enough to mount these two necessary lines of defence to fight off the virus. Antibodies, and especially T-cells, are not generated quickly enough or in sufficient quantities.

The basic concept of a *neutralising therapy* is to supercharge the innate antibody response, both in speed and in strength. A therapeutic is injected or infused into the patient, which contains one or more types of antibody (or antibody mimetic, such as Affimers) that binds specifically to the spike proteins of the virus particles. This much more rapidly neutralises the virus than would otherwise have been the case, had the natural immune system been left to fend for itself. [It takes a week minimum, and often at least two, for the body to start generating antibodies in meaningful quantities against a new pathogen.]

To date, only antibodies (either polyclonal or monoclonal) have been used as the inhibitory agent in neutralising therapies.

Exhibit 3: blocking the binding between the spike protein and ACE2



Neutralising therapy for SARS-CoV-2 as a prophylactic or as a treatment

A neutralising therapy can be used as a prophylactic which, by definition, is a medication or a treatment designed and used to prevent a disease from occurring. It is a form of *passive* immunisation, as opposed to vaccination, which is a form of *active* immunisation. The latter consists of priming the innate immune system to mount a defence when necessary: a vaccine introduces certain molecules from the pathogen in question (usually the antigens, such as the spike proteins on a coronavirus particle) to the human immune system. This trains the immune system to develop specific antibodies to the virus, whilst ensuring the virus cannot replicate and cause disease.

There are several clinical advantages of a neutralising therapy (passive immunity) over a vaccination (active immunity):

- Neutralising therapies provide immunity immediately after dosage. Vaccination only becomes effective after two weeks minimum, once the immune system has had sufficient time to learn to generate the specific antibodies. This often results in a vaccination programme requiring multiple doses over a period of weeks.
- Neutralising therapies are equally effective in all classes of patients, including the elderly and those with weakened immune systems – as although they operate in tandem with the immune system, they by no means *rely* on it. Conversely, ample recent research has verified that vaccines (in general) have reduced efficacy in the elderly.⁵

However, neutralising therapies have a number of downsides:

- The immunity they bestow on patients is temporary. For example, Synagis provides infants with immunity to RSV for only a month, following each dose.
- They are generally much more expensive than vaccines (as a result of the usage of monoclonal antibodies in neutralising therapies, which are expensive to manufacture). In the UK for example, the price of a vaccine averages around £100 per dose;⁶ each dose of Synagis costs over £1,000.⁷
- Neutralising therapies must be administered via either infusion or injection. This significantly reduces the potential for the therapy to be used en masse across the population.

A neutralising therapy can also be used for treating an already infected patient, by preventing the disease from spreading further and thus giving the innate immune system the opportunity to destroy existing infected cells with T-cells. As with the prophylactic use case, two key benefits of using a neutralising therapy as a treatment are: i) its very rapid onset of action; and ii) its efficacy is not diminished by a weaker innate immune system.

⁵ e.g. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778733/>

⁶ <https://travelvaccination.co.uk/vaccinations/>

⁷ <https://www.ncbi.nlm.nih.gov/books/NBK109540/>

Neutralising therapies under development for SARS-CoV-2

Incredibly, China's state-owned medical products maker, China National Biotec Group, had developed a convalescent plasma ("CP") therapy for COVID-19 patients as early as mid-February. The company had achieved this by collecting plasma from a number of recovered patients: the treatment had been used on over ten critically ill patients, whose conditions had all improved within 24 hours. In its latest treatment guideline (updated in February) China's National Health Commission listed CP therapy among the treatment measures for critically ill patients.

Moreover, an unprecedented global plasma industry collaboration – the COVIg-19 Plasma Alliance – is driving the rapid development of a CP therapy for COVID-19. The Alliance is led by Japan's biopharmaceutical giant, Takeda, and by global biotherapeutics leader, CSL Behring, and counts eight other leading plasma companies in its ranks.

The Alliance is developing a single, unbranded anti-SARS-CoV-2 polyclonal hyperimmune immunoglobulin medicine (i.e. a CP therapy) with the potential to treat individuals with serious complications from COVID-19. The collaboration is leveraging leading-edge expertise and work programmes that the members already have underway. Experts from the Alliance are collaborating across key aspects such as plasma collections, clinical trial development and manufacturing.

The Alliance is also supported by global organisations outside of the plasma industry, including Microsoft and Uber Health. These companies are assisting in the collection of convalescent plasma from donors, which is key to the successful development of a CP therapy. [For example, Uber Health has agreed to donate 25,000 round-trip rides to transport potentially eligible donors to and from plasma collection centres.]

On 26 May, The Alliance launched a new campaign, "The Fight Is In Us", to seek to mobilise tens of thousands of people in the US who have recovered from COVID-19 to donate their blood plasma.

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The transfusion of convalescent plasma from patients who have recovered from the virus, to treat critically ill patients, is not in our view a truly scalable or sustainable solution to the war against the pandemic. However, the success of CP therapy in China already, coupled with the ongoing efforts of the Takeda / CSL consortium, *do* demonstrate the potential for, and indeed clinical interest in, neutralising therapies as a whole.

There are reportedly over one hundred recombinant protein-based (i.e. antibody *and* antibody mimetic) COVID-19 interventions in pre-clinical development.⁸ One collaboration has commenced a Phase I clinical trial, and at least 14 other developers of neutralising therapies also intend to commence clinical trials before end 2020. Below, we detail those who we believe to be the standout names.

Amgen (NASDAQ:AMGN) and Adaptive Biotechnologies Corp (NASDAQ:ADPT)⁹

On 2 April, the two US companies – multinational biopharmaceuticals company Amgen, and biotechnology business Adaptive – announced a partnership to "*discover and develop fully human neutralising antibodies targeting SARS-CoV-2. The mutually exclusive collaboration brings together Adaptive's proprietary immune medicine platform for the identification of virus-neutralising antibodies with Amgen's expertise in immunology and novel antibody therapy development.*"

The financial details of the agreement had not been finalised at the time of the announcement, nor have they since been disclosed. Moreover, since the announcement of the partnership over two months ago, the partners have still not announced that they have discovered and validated the mAbs that they are screening for.

⁸ <https://www.antibodysociety.org/covid-19/>

⁹ <http://investors.amgen.com/news-releases/news-release-details/amgen-and-adaptive-biotechnologies-announce-strategic>

AstraZeneca (LON:AZN)¹⁰

On 8 April, British-Swedish multinational pharmaceutical company, AstraZeneca, announced that it was “*joining forces with government and academia with the aim of discovering novel coronavirus-neutralising antibodies. Harnessing internal expertise and via new collaborations, the aim is to identify monoclonal antibodies that have the potential to recognise, bind to and neutralise the SARS-CoV-2 virus.*”

In addition to having over 50 of its own experts working internally on the programme, AstraZeneca has partnered with a number of institutions to fast-track its efforts, including: the Chinese Academy of Sciences (China); Vanderbilt University Medical Center (US); the United States Army Medical Research Institute of Infectious Diseases; and the University of Maryland School of Medicine.

As with Amgen and Adaptive, AstraZeneca is yet to announce that it has sourced NAbs specific to SARS-CoV-2.

Celltrion (KRX:068270)¹¹

Celltrion is a South Korean biopharmaceutical company with a market capitalisation of approximately \$25 billion. On 23 March, it announced that it was developing a NAb therapy for SARS-CoV-2. It had identified the library of antibodies sourced from the blood of recovered patients in Korea, which it had successfully screened by mid-April, discovering fourteen powerful neutralising antibodies against SARS-CoV-2. Pre-clinical trials (mice and non-human primates) commenced shortly afterwards.

On 1 June, the company announced positive pre-clinical results, with its treatment candidate demonstrating a 100-fold reduction in viral load of SARS-CoV-2, as well as improvement in lung lesions. It intends to commence first in-human clinical trials next month.

Following the announcement, Celltrion’s market capitalisation increased by ~£1.6 billion that day.

Eli Lilly (NYSE:LLY) and AbCellera Biologics (private)¹²

On 12 March, Lilly and AbCellera announced that they had entered into an agreement to co-develop antibody products for the treatment and prevention of COVID-19. Lilly is a US multinational pharmaceutical company. AbCellera is a privately held company specialising in monoclonal antibody discovery for therapeutics.

The collaboration will “*leverage AbCellera’s rapid pandemic response platform, developed under the DARPA Pandemic Prevention Platform (P3) Program, and Lilly’s global capabilities for rapid development, manufacturing and distribution of therapeutic antibodies.*”

On 3 May, AbCellera announced it had “*received a commitment of up to \$175.6 million in support from the Government of Canada’s Strategic Innovation Fund... to expand efforts related to the discovery of antibodies for use in drugs to treat COVID-19, and to build technology and manufacturing infrastructure for antibody therapies against future pandemic threats.*”

On 27 May, AbCellera closed a \$105m Series B equity raise (valuation undisclosed) with investors including Viking Global Investors, Peter Thiel and Lilly. The funding will be used to “*expand AbCellera’s capacity and invest in technologies that complement and extend its proprietary antibody discovery engine.*”

On 1 June, Lilly commenced its Phase I study of LY-CoV555, the lead antibody from its collaboration with AbCellera, by dosing its first patients at major medical centres in the US. The study is a “*randomized, placebo-controlled, double-blind Phase 1 trial that aims to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LY-CoV555, following a single dose administered to participants hospitalised for COVID-19.*”

¹⁰ <https://www.astrazeneca.com/media-centre/articles/2020/researching-antibodies-to-target-covid-19.html>

¹¹ <https://www.celltrion.com/en-us/pr/newslist>

¹² <https://www.lilly.com/news/press-releases>

Results for Phase I are anticipated by the end of June. If successful, the next phase of testing will examine LY-CoV555 in non-hospitalised COVID-19 patients. Lilly “*also plans to study the drug in a preventative setting, focussing on vulnerable patient populations who historically are not optimal candidates for vaccines.*”

Lilly’s goal is to have several hundred thousand doses available by the end of 2020.

Eli Lilly (NYSE:LLY) and Shanghai Junshi Biosciences (HKG:1877)¹³

On 4 May, Lilly formed a second partnership to develop NAb therapies for the prevention and treatment of COVID-19, with Junshi, a China-based biopharmaceutical company specializing in discovery, development and commercialisation of novel therapies. Junshi has already engineered multiple NABs, which are recombinant, fully human monoclonal neutralising antibodies that are specific to the SARS-CoV-2 spike proteins. It is expected that the collaboration’s lead asset, JS016, will enter Phase I trials later this month in the US.

Molecular Partners (SWX:MOLN)¹⁴

Swiss-based Molecular Partners AG is a clinical-stage biotech company developing its proprietary DARPin® therapeutics platform. This platform can generate a new class of custom-built protein therapeutics based on natural binding proteins that open a new dimension of multi-functionality and multi-target specificity in drug design. The DARPin® platform is – like Avacta’s Affimer technology – an *antibody mimetic*.

On 20 April, Molecular announced that it was initiating an Anti-COVID-19 Therapeutic Program. The company had identified multiple potent monospecific DARPin® proteins which neutralise samples of the SARS-CoV-2 virus. It has engineered these proteins into tri-specific antiviral candidates that target three parts of the viral spike protein. It stated: “*multi-specific inhibition represents a differentiated approach to treating COVID-19, offering potentially greater therapeutic efficacy and reduced potential for the development of viral drug resistance... Preliminary data indicate that multispecific DARPin® molecules show synergistic antiviral activity, exceeding the activity of their constituent parts.*”

On 7 May, Molecular announced that it had completed candidate construction: two candidates demonstrated “*extremely robust antiviral activity*” in in-vitro testing. These candidates have now been progressed into in-vivo testing (pre-clinical studies in mice and non-human primates). Molecular intends to initiate a Phase I trial in the second half of this year.

Regeneron Pharmaceuticals (NASDAQ:REGN)¹⁵

Regeneron is a US biotechnology company which engages in the discovery, invention, development, manufacture, and commercialisation of medicines. Founded in 1988, Regeneron sells seven medicines that it has developed in-house, with a further 29 currently undergoing clinical trials. One of Regeneron’s core technology platforms is VelocImmune®, which uses unique genetically-humanized mice to produce optimized fully-human antibodies and bispecific antibodies.

As early as 4 February, Regeneron announced an expanded agreement with the U.S. Department of Health and Human Services (‘HHS’) to develop new treatments against SARS-CoV-2 (the company had already been collaborating with HHS in developing other NAB treatments, such as Regeneron’s investigational Ebola treatment REGN-EB3).

On 17 March, Regeneron stated that it had isolated hundreds of virus-neutralising, fully human antibodies from the company’s VelocImmune® mice, which had been genetically-modified to have a human immune system. The company had also “*isolated antibodies from humans who have recovered from COVID-19, in order to maximize the pool of potentially potent antibodies. From this large pool of candidates, Regeneron will select the top two antibodies for a ‘cocktail’ treatment... Using a multi-antibody approach allows for targeting of different parts of the virus and may help protect against multiple viral variants.*”

¹³ <https://www.lilly.com/news/press-releases>

¹⁴ <https://www.molecularpartners.com/news/press-releases/>

¹⁵ <https://newsroom.regeneron.com/press-releases>

Regeneron intends to commence a Phase I trial for its novel antibody cocktail, REGN-COV2, later this month, and has set itself a goal of producing hundreds of thousands of prophylactic doses per month “*by the end of summer.*”

SAB Biotherapeutics (private) and CSL Behring (subsidiary of CSL (ASX:CSL))¹⁶

SAB is a US-based clinical-stage, biopharmaceutical company advancing a new class of immunotherapies using its proprietary DiversitAb™ platform. DiversitAb™ is capable of naturally and rapidly producing large amounts of targeted, fully human polyclonal antibodies. It uses genetically engineered cattle to achieve this, thus negating the need for human donors. CSL Behring is a global leader in the plasma protein biotherapies industry and is a subsidiary of ASX-listed biotechnology giant, CSL Limited. [As discussed on p.7, CSL is also a co-leader of the COVIg-19 Plasma Alliance, which is driving the rapid development of a CP therapy for COVID-19.]

On 8 April, SAB and CSL Behring announced their partnership “*to combat the coronavirus pandemic with the rapid development of SAB-185, a COVID-19 therapeutic candidate on track for clinical evaluation by early summer.*”

On 28 May, the partners confirmed that in-vitro work on SAB-185 had been successful and that it had commenced clinical manufacturing of the therapeutic candidate with a view to taking it into human trials in “*early summer.*”

Sorrento Therapeutics (NASDAQ:SRNE)¹⁷

Sorrento is a clinical stage biopharmaceuticals company that develops therapies for cancer, autoimmune, inflammatory, and neurodegenerative diseases. One of its core platform technologies, the G-MAB™ fully human antibody library, has enabled it to screen billions of antibodies in order to identify those that bind to the SARS-CoV-2 spike protein (or even subunits of it). Using this technology, it is developing no less than six potential coronavirus antiviral therapies and vaccines.

On 15 May, Sorrento announced that one antibody in particular, STI-1499, “*demonstrated 100% inhibition of SARS-CoV-2 virus infection in an in-vitro virus infection experiment at a very low antibody concentration.*”

One of the therapeutics that Sorrento intends to develop is an “*antibody cocktail product*”, that is to say a NAb therapy that includes multiple monoclonal antibodies. The rationale for this is that it could remain effective even if virus mutations were to render *one* of the types of antibody in the therapy ineffective.

Sorrento’s STI-1499 antibody will likely be the first antibody in this antibody cocktail (named COVI-SHIELD™). It is also expected to be developed as a stand-alone therapy (this second programme is named COVI-GUARD™).

Vir Biotechnology (NASDAQ:VIR) and GlaxoSmithKline (LON:GSK)¹⁸

Vir is a clinical-stage immunology company focussed on immune approaches to treating and preventing serious infectious diseases. It has four proprietary platforms, with its most advanced being its *Antibody Platform*. This enables the identification of rare antibodies from survivors that have the potential to treat and prevent rapidly evolving and/or previously untreatable pathogens, via direct pathogen neutralisation and immune system stimulation.

GSK is a British multinational pharmaceutical company that operates three global businesses, namely: Pharmaceuticals; Vaccines; and Consumer Healthcare. In 2019 GSK was the eight largest pharmaceuticals business in the world, by revenue.

¹⁶ <https://sabbiotherapeutics.com/news/>

¹⁷ <https://investors.sorrentotherapeutics.com/news-releases>

¹⁸ <https://investors.vir.bio/press-releases>

On 12 February, Vir announced that it had identified two antibodies that bind to the spike protein of the SARS-CoV-2 virus particle. On 6 April, the company entered into a major partnership with GSK. The collaboration will use Vir's proprietary monoclonal antibody platform technology to accelerate existing, and identify new, anti-viral antibodies; will leverage GSK's expertise in functional genomics; and combine both their capabilities in CRISPR screening and artificial intelligence. In tandem with the partnership, GSK invested \$250m in Vir (at a 10% premium to the prevailing share price) for a 6% equity stake.

For the partnership's NAb programme, Vir has entered into various manufacturing agreements with each of Samsung Biologics, Biogen and WuXi Biologics.

Vir and GSK intend to move directly into Phase II clinical trials between July and September.

Other notable players developing neutralising therapies for SARS-CoV-2:

- ***Brii Biosciences*** (focussing on monoclonal antibodies)
- ***Systemmune*** (focussing on an ACE2 protein mimetic)
- ***Vanderbilt University Medical Centre*** (focussing on monoclonal antibodies)
- ***YUMAB*** (focussing on monoclonal antibodies)

Out of the above-mentioned players we feel that, owing to the sheer depth of both their resources and their experience and expertise in NAb therapies, the three standout candidates are the Eli Lilly / AbCellera collaboration; Regeneron; and the Vir / GSK collaboration. Indeed, these three are already the nearest to commencing human trials (with the first one already having done so).

An Affimer-based Neutralising Therapy for SARS-CoV-2?

Already-generated Affimer reagents found to block the virus' interaction with ACE2

On 15 May, Avacta announced that it had discovered that several of its Affimer reagents that bind to the SARS-CoV-2 virus' spike protein (which will be used to develop its two types of antigen test), also block the interaction between said spike protein and ACE2.

As we have seen in the preceding pages with other biotech companies developing primarily antibody-based therapies, this discovery opens up for Avacta the potential for developing an Affimer-based neutralising therapy for SARS-CoV-2. To quote CEO Alastair Smith:

“This is a very exciting development in the COVID-19 programme. It only took four weeks to generate more than fifty Affimer reagents that bind the SARS-CoV-2 virus spike protein and amongst those we now know that there are neutralising Affimers that block the interaction with a key human cell surface receptor, raising the potential for a therapy to prevent infection...”

There is significant potential for a therapy that could help prevent infection and limit the progression of the disease, providing immediate benefit to patients. With a large and well-resourced partner, a neutralising Affimer therapy could potentially be developed more quickly than a vaccine and we believe that the likelihood of success would be high.”

The potential advantages of using Affimers instead of antibodies in neutralising therapies

There are reportedly over one hundred recombinant protein-based (i.e. antibody *and* antibody mimetic) COVID-19 interventions in pre-clinical development. One collaboration has already commenced a Phase I clinical trial, and at least 14 other developers of neutralising therapies also intend to commence clinical trials before end 2020.

Why would Avacta seek to develop an Affimer-based neutralising therapy for SARS-CoV-2 in such a competitive space? After all, its business model is founded upon targeting uncrowded therapeutics markets, or those therapeutics that Affimers can *significantly* improve, in comparison to antibodies. Why would a “large and well-resourced partner” be interested in collaborating with Avacta, instead of the 100+ biotech companies out there that are developing – or indeed have already developed – monoclonal antibody equivalents?

In fact, we believe that there are numerous reasons why an Affimer-based neutralising therapy might possess numerous advantages over a NAb therapy, both clinically and commercially. We would remind readers that Affimer molecules are engineered non-antibody binding proteins, designed to mimic – but also *enhance* – the molecular characteristics of monoclonal antibodies (‘mAb’). In short, Affimer proteins were developed and commercialised *specifically* to address a number of the shortcomings of mAbs, for use both in therapeutic applications and in reagents and diagnostics. With that in mind, our readers should already begin to perceive how it is highly feasible that some of those engineered enhancements of Affimers over mAbs might lend themselves to creating a clinically and/or commercially superior neutralising therapy. Below, we detail those enhancements and advantages that we believe could be the most pertinent:

1) Rapid discovery and validation process

Affimers are small, single domain proteins derived from the cystatin family of cysteine protease inhibitors. Two scaffolds, both based on cystatins, have been developed:

- The first is a mammalian scaffold – specifically, of human origin, based on the naturally occurring human protease inhibitor, Stefin A. It is ideal for therapeutic applications such as a neutralising therapy.
- The second is a plant scaffold – specifically, based on a consensus sequence of Cystatin A from a number of plant species. It is ideal for use in reagents and diagnostics.

For each of these, the Company has two highly complex phage display libraries each containing more than 10 billion Affimer proteins. These ‘synthetic libraries’ can be screened for certain Affimers that bind to specific targets using an in-vitro phage display process (i.e. a simple laboratory technique). As Avacta recently demonstrated in sourcing Affimers specific to the SARS-CoV-2 spike protein, the screening / discovery timeframe can be as little as *four weeks*.

mAbs, on the other hand, are primarily produced via hybridoma technology (which involves immunizing an animal (usually a mouse) multiple times with a specific antigen, and subsequently extracting the B cells from the spleen). It takes several months at least to cultivate and harvest the B cells from the immunized animals.

[More recently, antibody phage display technology using human naïve antibody gene libraries (in a similar manner to Affimer screening / discovery) has been used to generate recombinant mAbs – and thus does not require the use of animals. The phage display screening / discovery timeframe for recombinant mAbs is similar to that of Affimers.]

In summary, the faster screening / discovery / validation process for neutralising Affimers (using phage display) than for neutralising mAbs (using hybridoma) provides a distinct commercial advantage. Specifically with regards to SARS-CoV-2, this would be particularly important in the case of wholesale mutations to the virus’ spike proteins, as this would require a complete redevelopment of the neutralising therapy.

2) Simple, cheap, consistent and ethical manufacturing process

Commercial-scale production of mAbs involves an in-vivo or in-vitro procedure, or combinations of both. Once the target mAbs have been identified via hybridoma or phage display, they are then cloned into high-yield expression vectors. These vectors are subsequently introduced into expression hosts (such as bacteria, yeast, or mammalian) to generate mAbs on a large scale. It is important to note that mAbs produced in mammalian cells are heterogeneous, as a result of post-translational modifications (‘PTM’). PTMs can occur during mAb production, purification or storage. PTMs can have wide-ranging effects on potency and immunogenicity of antibodies used in therapeutics and diagnostics, as they cause product variability. As such, characterisation of PTM patterns is a complex and time-consuming part of biopharmaceutical development and production.

Like mAb production, *Affimer* production also uses bacterial expression hosts, specifically *E. coli* (a type of bacteria normally found in the lower intestines of mammals). However, the Affimer scaffold is much simpler than the average mAb:

- It is a simple monomeric protein (the structures of mAbs are more complex)
- It is 10x smaller than the average mAb
- It does not have PTMs

Thus Affimers can be produced extremely cheaply and rapidly, in comparison to mAbs.

Specifically with regards to SARS-CoV-2: the simple, rapid – and critically, *cheap* – manufacturing process for Affimers provides another distinct commercial advantage over mAbs when considering the use of either one in a neutralising therapy.

3) Size and versatility of Affimers offers two key *clinical* advantages over mAbs

The small size and monomeric structure of Affimers make them much more soluble than mAbs. This ensures that Affimers can be present in much higher concentrations in therapeutics than mAbs can be.

In considering the optimal neutralising therapy for SARS-CoV-2, one should be able to recognize that such a therapy would contain sufficient Affimers, mAbs, etc. to bind to *all* of the protein spikes on the surfaces of *all* of the virus particles in the patient. This would immediately result in *complete* neutralisation of the virus.

To achieve this, a mammoth quantity of Affimers, mAbs, etc. would be required in the neutralising therapy. Accordingly, the substantially higher solubility of Affimers over mAbs (brought about size and structure differences between the two) would offer a distinct clinical advantage to an *Affimer*-based neutralising therapy.

Separately, the monomeric structure of Affimers makes them highly flexible: they can be easily chained together into dimers, trimers or even larger polymers. This enables the construction of multi-specific therapies that bind to multiple targets. It is much more difficult to conjoin multiple mAbs in this way.

It is unlikely that SARS-CoV-2 will experience a wholesale mutation. However, minor mutations have, as has already been widely reported, occurred across the globe. The spike proteins on the surface of the virus particle are one such area where mutation has occurred.¹⁹ Most mutations of RNA viruses are deleterious: consequently, the majority of viruses with mutations die out. But some mutations provide selective advantages to the virus: these mutated strains tend to flourish and spread rapidly

The optimal neutralising therapy for SARS-CoV-2 would not only bind to *all* of the spikes on the virus particle, but would also bind to *multiple sites* on each spike. Thus if a minor mutation to the spike protein were to occur, and one of the binding proteins of the neutralising therapy were weakened or rendered inert, the therapy would remain effective (although of course not 100%): the other types of protein in the therapy would still be effective in binding to those sites on the spikes that are *not* mutated.

A polymeric Affimer molecule that could bind to, for example, *three* different sites on the spike protein of the coronavirus particle, would hold a significant clinical advantage over a mAb neutralising therapy, as it would offer a much greater degree of protection to the therapy against mutation. The in-vitro work of Molecular Partners in developing such a polymeric neutralising therapy using its own antibody mimetic, DARPin® proteins, provides powerful evidence of this potential significant clinical advantage.²⁰

Considerations for a potential major partner in developing an Affimer-based neutralising therapy

We have detailed above how an Affimer-based neutralising therapy could provide significant advantages over a neutralising antibody ('NAb') therapy. An Affimer-based therapy could be faster to develop and – once developed – cheaper to manufacture. We would remind readers that NAb therapies are expensive: for example, Synagis – which provides infants with immunity to RSV – costs over £,1,000 in the UK *per dose*. Each dose provides immunity for only a month. A significant reduction in manufacturing costs of the key component of the therapy (i.e. the neutralising protein – the mAb or the Affimer) could thus prove highly compelling to a potential partner from a commercial perspective.

Clinically speaking, the advantages of Affimers over mAbs in both solubility, and flexible formatting, could also be highly attractive to a potential partner – as an Affimer-based neutralising therapy could be first-in-class.

So then, why hasn't Big Pharma already jumped at the opportunity to secure the rights to Avacta's Affimers? There is one crucial reason: *Affimers have not yet been tested in man*. Avacta has not yet brought *any* Affimer-based therapeutic into human trials. As such, the clinical safety and efficacy profile of the protein scaffold is unknown. It is a big ask for Big Pharma to commit \$100m+ to fast-tracking a novel therapeutic for a disease so globally significant as COVID-19, which demands unprecedented urgency – on a technology platform that has not yet been proved to work in humans.

Of course, all the pre-clinical data for Affimers generated over the past decade are highly promising and indicative that the technology will work in man. Indeed, three of Avacta's major therapeutics partners (Moderna, ADC Therapeutics and LG Chem) have committed a cumulative total of over \$500m in upfront and milestone payments to Avacta (and are also paying for all R&D costs incurred by Avacta in these collaborations), in return

¹⁹ <https://www.biorxiv.org/content/10.1101/2020.05.04.075911v1.full.pdf>

²⁰ <https://www.molecularpartners.com/molecular-partners-confirms-ultra-potent-inhibition-of-sars-cov-2-live-virus-by-anti-covid-19-darpin-candidates/>

for licensing certain Affimers for use in various therapeutics they are each developing. These are substantial commitments from global leading biotech and pharma names and provide us with a very high level of confidence that Affimers will prove to have a very good clinical safety and efficacy profile.

Even so, it *will* be a gamble for Big Pharma to partner with Avacta in developing an Affimer-based neutralising therapy for SARS-CoV-2.

Our opinion is that someone will take the risk. Our rationale for this is simple: so great is the scale of funding being thrown into the war against the pandemic, and so serious and urgent is the need for developing a neutralising therapy, that a major pharma player will be willing to bear the (in our view, low) risk of Affimers ‘failing’ in man, especially given that an Affimer-based neutralising therapy could be first-in-class.

The Benefits for Avacta in Developing a Neutralising Therapy for SARS-CoV-2

We do not include the development and commercialisation of an Affimer-based neutralising therapy for SARS-CoV-2 in our valuation modelling. If Avacta secures a major partner who will take charge of, and finance, the development programme, we will consider it a major bonus for the Company. We detail below the key benefits for Avacta were a major partner indeed to be secured and a neutralising therapy for SARS-CoV-2 successfully developed and commercialised.

1) *An immediate, and potentially very substantial, upfront payment from the partner*

As we explained in our original Investment Thesis (p.16): so long as the Affimer technology remains at a pre-clinical stage (i.e. it has not successfully completed a Phase I human trial), upfront payments from a commercial partner to Avacta will be in the region of 1% to 2% of the total potential value of the collaboration. However, once the first Phase I human trial has been completed – which fundamentally proves the safety profile of the platform technology – upfront payments will increase to 10% to 15% of the total potential value of collaborations.

However, we are in unprecedented times. For example, there is talk of successfully developing a vaccine for SARS-CoV-2, from scratch, in 12 months. Normally, vaccine development for a new virus would span 5-10 years. The urgency of the pandemic has catalysed an unparalleled level of funding from both private and public sectors across the globe, into vaccines, treatments, diagnostics and PPE. This funding has been directed both into products under development, and into scaling up production of existing products in use.

We will provide our financial modelling for a potential Affimer-based neutralising therapy in Part III of this Update Note, but now for illustrative purposes only, we would suggest that any deal could be worth as much as several hundred million dollars to Avacta in upfront and milestone payments. We would also suggest that, owing to the unprecedented situation as detailed above, the upfront payment component of the total deal value could be closer to the 10% to 15% mark, despite being at a pre-clinical stage. Furthermore, the majority of the remaining 85% to 90% of the deal value would likely be paid out much more quickly than it would in other, similar stage collaborations that Avacta is already part of (such as its partnership with ADC Therapeutics). Finally, a single digit royalty stream for Avacta would also commence immediately upon successful commercialisation of the therapy.

GSK's \$250m equity injection into Vir (at a premium to the prevailing share price), primarily to fund the accelerated development of Vir's NAb therapy, is a useful comparator in understanding the potential commercial value that Big Pharma is attributing to neutralising therapies for SARS-CoV-2.

2) *Establishes the Affimer platform as the go-to for developing future neutralising therapies*

As we discussed on pp.2-3, neutralising therapies have been a relative backwater of medicine in recent times. The COVID-19 pandemic has brought the space sharply back into focus. Were Avacta and a partner to successfully develop and commercialise an effective neutralising therapy for SARS-CoV-2, the Affimer platform could become the go-to technology for rapidly developing neutralising therapies in the event of future pandemics, acts of bioterrorism, etc.

3) *A fast-track to validating the clinical safety and efficacy profile of the Affimer technology*

Needless to say, successfully developing and commercialising an effective neutralising therapy for SARS-CoV-2 would, by definition, mean that Affimers are safe and effective in man. At present, Avacta intends to commence its first ever Phase I trial involving Affimers next year (either in the form of a monotherapy, a bispecific therapy, or a TMAC drug conjugate). Top line data readout might be available by the end of the year.

However, in the event of a partnership with Big Pharma for the development of a neutralising therapy, a Phase I trial would most likely occur in H2 *this year*. As such, it would bring forward the all-important value

inflection point for Avacta – securing clinical validation of its Affimer platform – by at least 12 months. Moreover, the partner would almost certainly be fully funding the Phase I trial.

4) Showcasing Avacta’s antibody mimetic, the Affimer technology, to a global audience

A successfully developed neutralising therapy for SARS-CoV-2 would draw the eyes of industry participants, the investment community and indeed mainstream media to Avacta, from all across the globe. The Company’s Affimer platform would stand in the world’s limelight. Just consider how extensively the mainstream media has covered the ups and downs of Gilead’s remdesivir throughout the pandemic.

Antibody mimetic platforms are becoming increasingly sought after: as we examine on pp.21-23 of our Investment Thesis, Ablynx, the owner of a competing antibody mimetic named *Nanobody*, was acquired in June 2018 by global pharmaceutical company Sanofi for a total equity value of **€3.9 billion**, paid in cash. It is important to note that there was a bidding war for Ablynx, which indicates that there are other tier one players still in the hunt for antibody mimetics such as Avacta’s Affimer technology.

5) Bringing Avacta’s therapeutics pipeline to the attention of the global investment community

In our Investment Thesis, we analyse Avacta’s cancer therapies under development: its multi-specific immunotherapies; its reformulated, targeted chemotherapies; and its Affimer-based drug conjugates. In the paper, we provide our rationale as to why we feel that these therapeutics have the potential to genuinely change the landscape of the cancer treatment market.

Investors drawn to Avacta because of its collaboration with Big Pharma on a neutralising therapy for SARS-CoV-2, would not *only* examine the Company’s Affimer platform, but would analyse other aspects of the business, including its pre|CISION platform and its hybrid TMAC platform. For us, the potential upside residing within the Company’s assets and projects focussed on oncology, dwarfs that of all of its (potential) COVID-19 projects. We believe that most new investors will likewise perceive this and realise that there is immense upside potential for Avacta’s valuation, regardless of its COVID-19-specific workstreams.

Disclosure

The author of this paper, Myles McNulty, is a private investor. He and his family hold 0.9% of the ordinary shares of Avacta Group.

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Myles McNulty has no business relationship with Avacta or with any other company mentioned in this paper, and has received no compensation from any party for writing it.

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