RAPID RESEARCH IN COVID-19 PROGRAMME

Re-positioning of drug-discovery approaches to develop point-of-care diagnostic tests for COVID-19

AIMS

- Point-of-care (PoC) tests are urgently needed to accelerate clinical decision-making and reduce the workload of test laboratories. In this study, drug discovery approaches that revolutionise cancer therapy were re-positioned to generate the building blocks of next generation PoC diagnostics, combining academic and commercial expertise. As a by-product of this research we also wanted to determine if we could/would generated some potent anti-Covid drugs too.

KEY FINDINGS

- To try and better understand this technology it may be necessary to think first about how a vaccine works. When we are vaccinated the human immune response generates antibodies to the vaccine. The immune system is a sophisticated set of cells and other components in the body that help mammals to fight diseases. For simplicity, in this setting a disease can be simplified as an infection. An infection tends to be caused by bacteria, fungi or viruses which take over and eventually kill cells within our bodies. If a vaccine is successful then the antibodies generated are often called “neutralising”. Antibodies work by recognising a disease-causing infection and binding specifically to them in the same way a key fits into a particular lock and no other. When an antibody binds to a virus for example the presence of the antibody makes the virus “seen” by the rest of our immune system which is activated to destroy it and reverse the infection. Elasmogen and the Scottish Biologics Facility (a biologic is a large drug manipulated from a natural origin and differs from most drugs that are made by chemistry) both maintain collections of over 100 billion different biologic drugs. One particular aspect of the drug-collections that are held by the SBF and Elasmogen is that they mimic the function of antibodies that we have in our bodies. Both organisations use the very

latest genetic engineering techniques such diverse and large drug collections, and have the capacity to go looking within these collections for antibody-like molecule drugs that can recognise and neutralise a Covid-19 virus. The two different drug collections are slightly different in their origins and the Elasmogen collection in particular is unique to this Scottish company and has been the source of some exciting neutralising drugs against cancer. The SBF and Elasmogen have isolated from their drug-collections a total of 80+ unique antibody-like binders (specific recognition) to 4 key Covid-19 proteins. And whilst a virus is quite a simple structure it is still made up of several different protein components that when they are all put together (like a lego toy) they make a live virus. One of the key sub-structures on a Covid-19 virus, that has been discussed endlessly and in great detail in almost every news briefing over the last 10 months, and is seen in every photo of the virus on TV, is the so called spike protein. It is called a spike protein because it looks like a series of spikes coming off the main spherical body of the virus. At the outside end of this spike (away from the virus core) there is a very specialised protein known as the "Receptor Binding Domain (RBD)". It is via this protein that the virus recognises human cells and causes infection. Neutralising antibodies to Covid-19 often cover up this particular RBD protein and stop it interacting with human cells blocking infection before the rest of the immune system can come along and destroy the virus. The 80+ different binders to Covid-19 recognise three different proteins of the virus. One sub-group recognise the Spike and the RBD region and 2 sub-groups recognise structural building blocks of the virus (between the Spikes). These binders (a bit like antibodies) can be used to design diagnostic and therapeutic strategies for the disease and are a unique resource across Scotland and significant parts of the world. By using drug discovery approaches we have been able to isolate both the binders and the genes that encodes these binders – this is key to fast-tracking validation and manufacture of diagnostic kits or drugs.

- One of the structural viral proteins is called 3a and is a target protein possibly overlooked by other groups but is increasingly becoming more important in the overall biology of the virus and could be present in a number of bodily fluids making it an interesting diagnostic target and possible marker to identify patients that are likely to deteriorate quickly if they become infected and is also a possible marker for or drug target for long Covid.
- The use of clever binder formats means that we have achieved affinities in the picomolar range (can "see" a few drops in an Olympic swimming pool) that, in theory, will be sensitive enough to find the virus in a saliva sample in around 30 min as a dip-stick "pregnancy" test (now with our diagnostic kit collaborators)

- With additional collaborators in the US we have also shown that the Spike binders could be excellent drugs in their own right, outperforming other binder (antibody) drugs in early testing
- By making the binders available to others we have successfully engaged with a number of academic and commercial partners with MTAs in place to make the most effective binders available to them. Collaborators are in the UK, USA and soon to be India.

WHAT DID THE STUDY INVOLVE?

- We successfully identified, sourced samples (from across the globe) and screened four different Covid-19 proteins including the biologically important (for infection) S1 spike protein and its receptor binding domain –RBD (how it infects human cells) and two proteins which are highly suitable for diagnostic markers for the disease (Nucleocapsid and 3a protein). We used two distinct biologics (large molecule) drug platforms to identify all of these targets.
- To summarise we isolated a total of 17 S1 binders, 24 RBD binders, 30 N binders and 12 3a binders. This appears to compare favourably with the Covid-19 assets produced by a very small number of research groups worldwide. The Spike-binders from the unique Elasmogen platform cannot be isolated from any other source and the 3a binders also appear to be unique to our program.
- We ranked and characterised this portfolio determining how sensitive and potent they might be as diagnostics or therapeutics, where exactly they recognise the target proteins and the ability of the Spike protein binders to neutralise infections. From this work we have identified around 15 binders that show exceptional binding to all four target proteins.
- We have also identified from this 15 a number of paired binders that will be ideal for super-sensitive diagnostic assay development and are making these available to diagnostic kit collaborators in order to improve on the availability of diagnostic tests.
- We have re-formatted lead binders to further increase their diagnostic and therapeutic potency.
- We are actively promoting access to these binders to academic and commercial groups around the world and ensuring and encouraging open and transparent data sharing.
- The project has been featured in the media following several press releases from the company Elasmogen, from the University of Aberdeen and by Opportunity North East, an economic development organisation based in Aberdeen.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

- The collaboration between SBF and Elasmogen has produced a world class panel of new binders to important viral proteins that can become the unique building blocks of diagnostic kits and even new drugs to treat the disease. In addition, these binders have the potential to be used by others to unlock new knowledge about the biology of the virus and we are actively encouraging this collaborative research.
- When the program of work began we did not know whether the advantages seen for the Elasmogen technology, when developing drugs to treat cancers, would translate across to the diagnosis and treatment of Covid-19. All the early indicators would suggest (both from our data and data from collaborators in the UK and US) that the Elasmogen binders "see" the virus when present at very low levels and are able to block infection despite being only 1/10th the size of complex and costly to produce antibodies (given for example to President Trump). The small size and robust nature of the Elasmogen binders could facilitate the rapid and cost-effective development of novel therapeutic approaches (subject to funding).
- A clever choice of diagnostic target (that has not been considered or was overlooked by many Groups) is called the 3a protein. This can now be recognised with super-sensitive binders from the SBF platform. These 3a binders far exceed the activity of any other antibodies anywhere in the world (that we aware of) to this particular target.
- Having generated a broad panel of quality building blocks it is now down to our collaborators to translate them into new diagnostics or therapeutics. For this to happen we have actively promoted access to our portfolio of binders and we have a growing list of "premier league" collaborators keen to access the materials form this programme. The sad reality for therapeutics is that some approaches may now slow as funding is now exhausted. In a world where we still don't know if a vaccine will work effectively (and for everyone) the passive immunisation treatments offered by Elasmogen's therapy options could be a life-saving alternative.

WHAT IMPACT COULD THE FINDINGS HAVE?

- The most immediate benefit from this research would be the conversion of some of our binders into point of care diagnostics. These "pregnancy" tests could deliver a result in as little as 15 – 30 min (from saliva) and could be used by less skilled operators in all current settings including: hospitals, care-homes, airports etc. They would also be ideal as a cost-effective test for a developing world settings delivered through our partners in counties in crisis, such as India, where it is the rural and poorest communities that are suffering the most.

- Whilst not a main objective of the original work we did always wonder if the potency of the Elasmogen platform (seen for cancer) would translate into this setting too. We now have data to confirm that this is indeed the case and we have three binders at least that look to be exciting therapeutic options with a potency in head to head laboratory studies that is superior to other drugs that are already heading towards clinical acceptance.

- The use of 3a protein as a marker of disease may prove useful not just as an indicator of infection but as a predictive indicator of the severity of disease and long COVID. This second "disease severity" hypothesis would require additional studies beyond the scope of this research.

- Our binders are being used in a number of labs across the UK and globally. We intend to further promote access to them through our networks our websites and *via* the presentation of early data sets. The outcomes from these collaborative studies are more difficult to predict but we anticipate diagnostic, therapeutic and academic applications.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- We will use all of the normal channels to promote the outcomes of our research including: publications (first as a patent where necessary), conferences, bio-partnering meetings, professional social media accounts such as our twitter and LinkedIn. One of the great advantages of working as a large team is that we have twice the routes and channels to exploit *via* Elasmogen and the SBF through the University.

- We will of course, and when appropriate, follow up our initial press stories. We have had help here from Opportunity North East the local development agency. Elasmogen employs professional consultants to help deliver the maximum impact from this effort working alongside the University's Communication team.

CONCLUSION

- In biotech terms the progress that has been made in a few short months is nothing short of miraculous. All this has been achieved with the relatively modest and welcomed investment from Scottish Government supplemented with in kind cash and effort from both Elasmogen and the University of Aberdeen's Scottish Biologics Facility. Where our budgets are a few hundred thousand pounds, similar efforts across the globe are funded with $100 M.

- We have successfully generated an impressive portfolio (80 +), high-sensitivity, potent, building blocks required to produce next-generation diagnostic (and therapeutic) products that rivals the quality of anything produced anywhere in the world. We have modified to optimise their activity and have made them available to a growing number of premier league collaborators.

- Our concerns now are that the urgency driven progress we have experienced over the last 6 months will now lose momentum as the assets are developed by others and we are exploring further funding routes to continue the development in Scotland.

RESEARCH TEAM & CONTACT

NAME or NAMES	Email address
Professor Andy Porter (Director SBF) Dr Soumya Palliyil (Head of Research, SBF) Dr Caroline Barelle (CEO, Elasmogen Ltd)	a.porter@abdn.ac.uk soumya.palliyil@abdn.ac.uk caroline.barelle@elasmogen.com
Address The Liberty Building Foresterhill Health Campus Aberdeen AB25 2ZP	Phone number 07968175791 07793601366 07979222029

ADDITIONAL INFORMATION: The Project finished on 31st October 2020 and collaborative work to take the outputs forward is actively continuing. The project was supported by an award of £223,676 from the Chief Scientist Office and an in kind contribution from Elasmogen of approx. £150k.