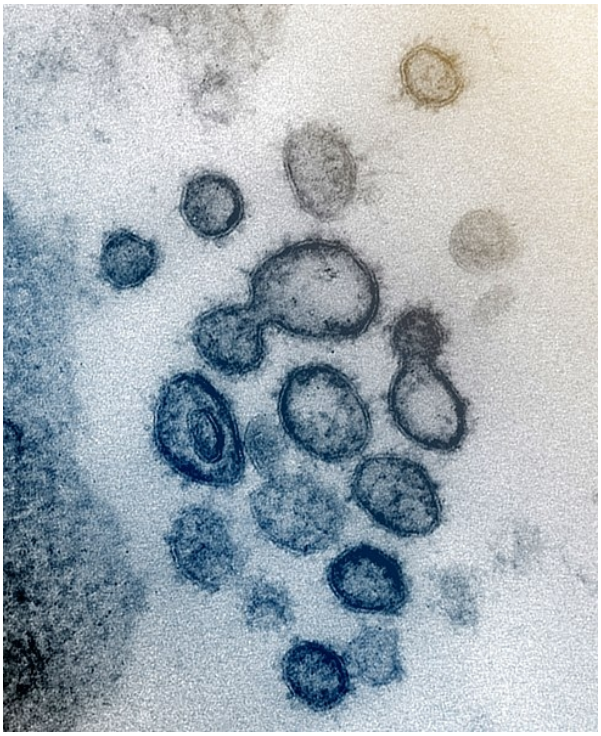
COVID-19: making a small contribution

Unusually for these blogs, the title of this one has no silly pun or whimsical start, because it is about something serious that has already caused loss and grief, and the response to it is currently (Friday 13th March) causing much disruption and fear in continental Europe. I am writing, of course, about the outbreak of coronavirus SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), and about the modest but I hope useful role this group is playing in the fight against it.



SARS-CoV-2, image from NIAID Rocky Mountain Laboratories (RML), U.S. NIH, Public domain. Source https://commons.wikimedia.org/wiki/File:SARS-CoV-2_49534370233.jpg

There are several ways of tackling a viral outbreak. For an infection that is spread from person-to-person, rather than only from animal reservoirs to people, the first is to try to prevent its spread by public health interventions. This means identifying those infected and those at risk of having been infected, and isolating them from the rest of the population so that the infection does not spread. If actions can be taken quickly enough, and if people are willing to cooperate, this can work very well. Sometimes, though, the virus spreads faster than containment and public health measures can at best control the rate of spreading and help at least some people avoid infection. This is, broadly, the current status with SARS-CoV-2.

The most effective way of controlling viral spread that cannot be contained physically is to vaccinate the population, especially the population that has not yet been exposed to the virus. Vaccination primes the immune system so that, in most people, the virus will be killed before it is passed on to someone else. At a population level, this confers 'herd immunity'; the people still susceptible are few and far between so that the virus cannot pass efficiently between them. Unfortunately, vaccine development takes time. By the standards of previous outbreaks, the development of vaccines to SARS-CoV-2 has been astonishingly fast but the first trials are likely to

take place only about 5 months after the initial outbreak, and it will still be more than a year before vaccination can be rolled out generally.

The other, very important weapon against viruses is having a means to treat an infection. This is valuable at all stages, partly to halt or slow a spread and partly to treat people who have been infected and who are developing a serious form of the disease. The most effective treatments usually involve drugs, whether conventional small-molecule types or large 'biologic' molecules such as antibodies. In most fields of medicine, drug development is an infamously slow process, so how can something useful be made available rapidly for an emergency?

Most progress in finding useful drugs depends on mechanistic understanding of a virus; what it is, how it adheres to and detects human cells, what molecules it contains, and how these molecules work. Viruses evolve, just like any organism, so they have various evolutionary relatives more or less closely related. In particular, even when two even distantly viruses are divergent in many aspects, they may still rely on highly conserved active sites of enzymes, such as proteinases, to run core aspects of their biology. Careful study of the gene structure of the new virus (obtained within days - brilliantly done China!), and the predicted protein structures, can highlight similarities to viruses against which we already have useful drugs. These similarities can be confirmed by structural studies of pure viral proteins and of the interaction of the drugs with these. When we are lucky, there will be an existing drug that can be used 'off the shelf' and have at least some helpful effect, an example of 'drug re-purposing'. Small variations in that drug can often be made quickly (indeed, they may still exist from the development process of that drug years ago), and one of these might be even better although it will not yet be approved for human use. But rapid trials and approvals can result in doctors having a better drug than the original, in some months' time.

Viruses infect human cells by binding to them and being drawn into them, typically by a process called endocytosis. Some (glyco)protein on the surface of the virus will have a high affinity for a specific human surface protein, and that is how it sticks. Identification of this human protein is very useful, because anything that can inhibit the interaction between it and the virus will interfere with the virus' ability to infect cells. In the case of SARS-CoV-2, as in SARS-CoV of the early 2000s, the high affinity receptor seems to be a human cell surface-associated enzyme, ACE2 (well done McLellan group, in Texas, for the speed at which you discovered this!). As it turns out, ACE1 and ACE2 have been subject to a lot of pharmacological research for the unrelated reason that they play

a role in setting blood concentrations of the blood pressure-regulator, angiotensin. This means that there are experimental drugs that bind to ACE2 and which may, possibly, be useful in interfering with the ability of the virus to do so.

Some drug interventions depend not so much on the biology of the virus as the biology of the host's response to it. There are predictions from artificial intelligence algorithms that the anti-inflammatory drug baricitinib will inhibit endocytosis, which might impede the entry of SARS-CoV-2 in to cells. Many of the most dangerous symptoms of a serious SARS-CoV-2 infection arise, paradoxically, from the immune response itself. Inflammatory reactions in the lungs, for example, cause accumulation of fluid (oedema) in the tissues, making breathing difficult. The antibody bevacizumab is a potent inhibitor of one of the signalling pathways thought to cause lung oedema in COVID-19, and a clinical trial (NCT04275414) is beginning to test whether this drug is helpful in severe cases of COVID-19.

As knowledge of SARS-CoV-2 and the response to it increases, there may be many more possibilities for re-purposing existing drugs or research compounds, and all of this work is moving much faster than old-fashioned publications. That's where we come in. In previous blog posts (eg *And today we have Naming of Parts*), I have mentioned this lab's work in constructing, curating and maintaining the *Guide to PHARMACOLOGY* database for IUPHAR (the International Union of Basic and Clinical Pharmacology) and BPS (British Pharmacological Society) respectively (see Links). IUPHAR, with its global reach and independence, is widely regarded as a trusted source of information. It has therefore been encouraged by various national medical societies and labs to try to keep track of these developments, filtering information for probable reliability. This last part is important; normal search engines cannot tell the difference between real pharmacology and snake-oil selling, and everything is much too urgent to wait for the classical scholarly check of peer-reviewed publication. The work of curators and their advisors is therefore critical.

We (and "we" really means my valued lab members Elena Faccenda and Simon Harding, aided by Jane Armstrong, Adam Pawson) have therefore set up a new page of the database, dedicated to pharmacology against SARS-CoV-2/ COVID-19, with links to other data sources on the key molecules. The contents draw on the knowledge of a much larger set of people in IUPHAR committees, and from the virology and immunology communities. The database is open to anyone to read (at https://www.guidetopharmacology.org/coronavirus.jsp) and, while only the curators can

write to it (to stop snake-oil salesmen and conspiracy theorists populating it with nonsense), anyone can write to the curators to draw attention to new data and to make sensible suggestions.

A screenshot of the top of our new page (which carries on down to the data themselves).

It's interesting working in an area that is moving faster than traditional scholarly communication can move, and that is full of information with much less certainty than would usually be tolerated, because of the urgency of the situation. It will be interesting to look back, when the current emergency is over and SARS-CoV-2 has settled down to be an annual minor (at a population level) nuisance, as I assume it will when herd immunity has been attained, to see how well this rapid-communication science did compared to the conventional model. Perhaps we will be left wondering whether the delays in the conventional systems are so necessary, and whether more science in general can be done effectively this fast-and-informal way.

Jamie Davies, Edinburgh, March 2020

Links
Guide to Pharmacology main page: https://www.guidetopharmacology.org/
New Coronavirus page: https://www.guidetopharmacology.org/coronavirus.jsp
IUPHAR: https://iuphar.org/
BPS: https://www.bps.ac.uk/
SARS-CoV-2 Wikipedia page:
https://en.wikipedia.org/wiki/Severe_acute_respiratory_syndrome_coronavirus_2