Map-making in a hurry

*** IMPORTANT - this blog article is intended to illustrate how one particular corner of the scientific community responded to the COVID-19 crisis: nothing in here is intended to be taken as any kind of medical advice. If you need treatment, please consult your own physician ***

Much has changed since I last put fingers to keyboard to write one of these blog posts. The COVID-19 pandemic has caused drastic changes in the way we live and work, in this country, in the hope of containing its spread while work proceeds on treatments and on attempts to develop an effective vaccine. The sign-off at the bottom will not say 'Edinburgh' as it usually does because, like so many other people, I am now working from home. But the momentum built at IUPHAR on trying to identify a rational strategy for tackling COVID-19 has continued to build. We have had numerous video conferences, amongst ourselves and with international partners, most notably senior members of the Chinese Pharmacological Society who have been fighting this disease since the beginning. They led the development and running of the first clinical trials, conducted under very difficult circumstances with terrified patients and, often, very frightened doctors. They were the first to witness what this disease can do to a community. They were also the first to mourn colleagues whose drive to heal others, before the nature of the danger was understood, exposed them fatally to the virus. Words cannot express how grateful I am that these far-away colleagues found time to join our conference calls and to advise us on everything that they found.

One of the main points of the conferences, and of the many hours of study that took place between them, was to determine a sensible set of priorities for testing existing drugs and developing new against COVID-19 (against both the virus that causes it, and against the unhelpful aspects of the body's response). IUPHAR, being constituted under WHO and UNESCO, is in a position to carry some influence, so bringing some clarity from as much sold data as exists felt like an important duty. Steve Alexander, of the University of Nottingham, chairs the Nomenclature Committee of IUPHAR (which does much more than that name suggests) and took on the task of coordinating a document to summarize all of this. Entitled *A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development*, the document was released publicly, pre-peer review, on a pre-print server. It has now been accepted for formal peer reviewed publication in the British Journal of Pharmacology, one of a small set of journals through which NC-IUPHAR publishes various reports.

From the beginning of the outbreak, there has been more talk in the general press about vaccines than drugs, but we strongly believe drug development should not be neglected, for three reasons. The first is that there is no vaccine yet, but some drugs are here now. The second is that there may be no vaccine; while we hope as much as anyone that one will be developed, attempts to make one for SARS-CoV itself were not conspicuously successful. The third is that vaccines are generally useful only against one specific virus while drugs can often be useful against a whole family of them. SARS-CoV-2 is not the first coronavirus to cause us problems; there was coronavirus pandemic in the late 19th Century, and in the 21st Century we have had SARS, MERS and now COVID-19. The fact that a standard nomenclature for outbreaks has been developed (COronaVirus Infections Disease {year}) is a clear indication that nobody assumes that this one will be the last, especially if humans continue to have such terrible biosecurity around wildlife. Having broad-spectrum anti-coronavirus drugs, and drugs that prevent unhelpful immune over-activations, will help.

In our document, to avoid making a confusing list of drugs, we organized approaches to drug development according to particular stages in the viral life-cycle and in the host response. Going through everything we said in the paper would not be appropriate for a blog post (you can see the paper itself by clicking in the URL in the links section). The key point is that it is much too early for anything in the report to be based on sound, large, bias-free clinical trials (against COVID-19), and the point is to try to give advice for those trials. Our task was therefore identifying what data there are from lab studies of COVID-19, and human clinical trials for other diseases, and making what we hope were intelligent guesses about which approaches for COVID-19 look most promising. For example, for existing drugs, we thought

- RNA synthesis by the virus is a very promising target: remdesivir is a potentially valuable existing drug that should be added to larger scale trials; this area is ripe for future drug development.
- viral proteinases are promising targets; velpatasvir and ledipasvir might be worth adding to a trial. As with HIV, combinations of drugs may work much better than single drugs used alone.
- For patients that produce too little response, interferon 1β may be useful; timing is probably critical.
- There is only weak in vitro evidence to support weak bases such as chloroquine being

especially useful in real patients, despite current strong lobbying by enthusiasts (and chroloquine has well-known cardiovascular dangers).

- lisinopril and similar ACE inhibitors are unlikely to make any difference to viral entry.

The field is moving very fast, of course, and it will be interesting to see the results of clinical trials when they come out. At the moment, there is a large (some would say ridiculous) number of different clinical trials running, most of them too small to detect anything but a massive effect. This division of effort is a natural symptom of everyone wanting to do something useful, and also of the very restricted timing to plan something properly. Some very large trials are being planned, though, including two in the UK, on in England targeting mainly the virus and one based here in Edinburgh targeting mainly the host response. The USA also has plans for larger trials.

It will be interesting to look back at this roadmap in months to come, and see what we called righy, what we missed, and where we turned out to be completely wrong.

Jamie Davies, East Lothian, April 2020

Links
The *Rational Roadmap* paper:
https://bpspubs.onlinelibrary.wiley.com/doi/abs/10.1111/bph.15094