The potential impact of COVID-19 on therapeutic research worldwide

Michael Spedding
Secretary General IUPHAR

Therapeutic research and healthcare will be profoundly changed by the SARS-CoV-2 virus, in multiple ways. Although, at the time of writing (June 2020) it is still unclear whether the virus will continue to prevent scientific congresses, and will continue to spread worldwide, it has already changed the way medical research is perceived by the public. Priorities have shifted massively. Some of these changes will be very long-lasting, hopefully, because lessons from the first SARS epidemic, were not fully enacted to prepare the world for the different menace of SARS-CoV-2. Even if there is not a second wave of SARS-CoV-2, we will continue to be menaced by future viral outbreaks, and also by epidemics of bacteria which are fully antibiotic resistant, where little is being done, particularly to limit antibiotic use in farming.

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By definition, an article such as this is forward-looking, therefore speculative. The article is written in three parts, first as secretary-general of the International Union of Basic and Clinical Pharmacology (IUPHAR), describing how the world of pharmacology has responded to the crisis, second, as a drug-discovery scientist how the science which has come out from the successive coronavirus outbreaks will change future research, and finally, how science itself, and scientific advice, may give us a last chance to advance changes in society and health care.

IUPHAR and the response of the world's pharmacology societies

The arrival of the COVID-19 epidemic not only coincided with, but also accelerated, IUPHAR changing its governance procedures to be more interactive with the world's pharmacological societies. The IUPHAR website (https://iuphar.org/) shows how the societies have spread information and supplied expert advice to their respective governments. The nomenclature committee of IUPHAR (NC-IUPHAR) has issued a roadmap for targeting drugs at SARS-CoV2 and COVID19 (https://guidetopharmacology.org), and kept a list of the drug targets, and drugs in development. The clinical division has issued guidelines for drug development for COVID-19 (https://iuphar.org/) and we have held a review meeting of the Chinese experience for treating COVID-19, which is also on the web site. IUPHAR is a non-governmental organisation (NGO) to WHO.

Now that many scientists are working remotely from their laboratories, and students are working from home, authoritative web sites are critical and NC-IUPHAR has developed the IUPHAR/BPS guidetopharmacology.org which lists all the drug targets in the human genome. This is the web-based culmination of NC-IUPHAR's 30 years of development in order to structure modern pharmacology, starting from 5 expert subcommittees in 1992

to >100 now, which represents the efforts of >700 expert scientists. NC-IUPHAR has published 130 authoritative reviews on receptors, ion channels and enzymes, with an H-index of 90. All scientists are invited to use it, and also to contribute to it, in a feed-forward, expert-reviewed knowledgebase, which contrasts with the scientifically-embarrassing posturing over chloroquine and its derivatives as therapy for COVID-19. Quality control is obtained by having NC-IUPHAR meetings every six months which validate data, publications, and also explore new areas with invited experts. Subcommittees must contain the main experts – but also scientists with divergent views, so controversy is open and direct. Meetings are therefore lively but controlled. Industrial scientists are welcome, but balance is controlled by a quality control in that any finding has to be independently verified. The first chair was Paul Vanhoutte, then Bob Ruffolo, I was secretary then chair from 1992-2014 and Steve Alexander chair from 2014. Development of the web site by the curators (based at Edinburgh in Professor Jamie Davies lab) has been facilitated by two major grants from the Wellcome foundation, and now from the British Pharmacological Society, but this is a worldwide resource.

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COVID-19 has taught us the critical interplay between pharmacology and immunology. Fortunately NC-IUPHAR had the foresight to gain a major Wellcome grant to produce the https://www.guidetoimmunopharmacology.org/ database listing all the immunological drug targets, a key interface for the future. IUPHAR also signed a memorandum of understanding with the International Union of Immunological Sciences (IUIS) furthering immunopharmacology. Thus IUPHAR's free on-line pharmacology education project (PEP) directly links to immunopaedia https://www.pharmacologyeducation.org/pharmacology/immunopharmacology. Thus both basic pharmacology and immunology education are only a click away. IUPHAR welcomes initiatives with other societies to expand these sites, and also to have web sites in languages other than English. Furthermore, we try to expand into new healthcare areas, having obtained a grant from the Medicines for Malaria Venture, backed by Blll Gates, for https://www.guidetomalariapharmacology.org/. Pharmacological societies can have IUPHAR as a partner in obtaining grants about critical health care issues.

How science will change after COVID-19

The epidemic has shown the fragility of human healthcare, even in countries which spend massively. It reminds us that pandemics happen and cannot be predicted. Nevertheless, the SARS and MERS epidemics were warnings, and greater heed should have been taken of them. Furthermore, considerable harm has been made by non-scientific touting of 'medical advances' which are unjustified. There now more than 2000 clinical trials listed in ClinicalTrials.gov https://clinicaltrials.gov/ct2/results?cond=COVID-19 with more than 200 targeting hydroxychloroquine. This is unsustainable because the epidemic is limited in time by confinement, so it is possible that at the end of it we will still not have a definitive answer as to the correct drugs to use. In this respect, IUPHAR has produced guidelines for clinical trials, but Governmental and WHO priorities must be given (as in India) because clinical resources must be prioritised if progress is to be made in such emergencies.

Viral pharmacology is complicated and simple *in vitro* tests of viral replication insufficient to advance drugs into the clinic. Yet there are virtually no reliable animal models for the unique pharmacology of COVID-19. Furthermore, the closure of laboratories not working directly on SARS-CoV-2 has been very serious, particularly as the virus uses many host cell mechanisms to replicate (see below) and research has stopped on these mechanisms. Stopping all 'non-essential' research will prove to have been a very wasteful idea, as building up stocks on transgenic animals for other

critical diseases, for example, may take years. Already, patient groups with rare and severe diseases feel left behind, as the research that they fund has been stopped to prevent SARS-CoV-2 spreading.

What will happen in the future? First, the public now appreciates drug research, and Harris polls (https://theharrispoll.com/) have shown that the pharmaceutical industry has lost much of its negative image. The societal costs of ignoring drug research have been made clear. Collaboration to produce vaccines has been real and this trend will probably continue, and is needed if cures are to be found for the common diseases (Alzheimer's, amyotrophic lateral sclerosis, ALS, etc.) which have resisted therapy to now. Viral pharmacology will come into its own. COVID-19 has a totally novel clinical profile and phenotypical screening must make a comeback. My industrial PhD supervisor, Roy Brittain, was head of the first Glaxo pharmacology group and discovered drugs which have sold for >650 billion£, cumulatively, 40-50 years ago, when we knew very little of what we know now: this was achieved by phenotypical screening using analytical pharmacology techniques, where the only variable was the drug, in a pathophysiological setting. Modern pharmacology techniques can do this now but in totally novel ways. High throughput metabolomics can give new insights and potential therapies into diseases such as ALS (Henriques et al., 2015, 2017, 2018, Bouscary et al, 2019), because sugar and lipid chemistry is so complicated (but essential) that it can only be addressed properly by metabolomics: genomic techniques are blind to these changes except for identifying the rare diseases caused by enzyme mutations. Furthermore, viruses use host receptors and enzymes to multiply and spread, which can also be assessed by metabolomics. The symptoms of COVID-19 are also exacerbated by ageing, but human ageing and performance decline is quite different from other animals, and this has been underestimated by pharma research (Noakes and Spedding, 2012): this may change post CoVID-19.

The pharmacology of rare diseases will continue apace, but we now realise that common diseases, such as schizophrenia, may be consequent to environmental impact on brains which have a myriad of mutations, or copy number variations: all of which affect neuronal plasticity to different extents (Artigas et al, 2017). There are so many molecular causes, that this common disease, may have a myriad of molecular triggers, impossible to target individually so drugs must target directly the brain circuits which are at risk, downstream. Again, phenotypical screening is important.

The future of scientific meetings is in doubt, depending on a second wave of infection, but the advantages of teleconferencing have been made clear. This will change the way scientists will work, for ever.

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How scientific advice will change society

The failure to take on board scientific advice early on has had an immense impact on the overall death rates between countries and the total viral load in a particular country. This failing has been evident and scientists must act quickly to ensure that science continues to be seen as a critical human endeavor, and an excellent career path for young people.

Michael Spedding
Secretary General IUPHAR;
President, Spedding Research Solutions SAS,
6 Rue Ampere, Le Vesinet, 78110, France.
0033637059188.
Michael@speddingresearchsolutions.fr

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