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The COVID-19 immunology masterclass enters its fourth year

By Daniel M. Altmann

Immunologists have made great strides in COVID-19 research and therapies. However, now is not the time to be complacent and sit back on our laurels.

It seems unthinkable that our interaction with SARS-CoV-2 now enters its fourth year. The human cost has been devastating and, literally, uncountable. Yet this has also been the period in which all those decades of basic immunology research came to be stress tested in the heat of battle and came through, at pace, more effective than any might have dared predict. This has been evident in every sphere, from the refinement and multimillion-scale production of lateral flow tests and the therapeutic monoclonal antibodies, to effective vaccines across the diverse platforms exemplified by the AstraZeneca, Pfizer, Moderna and Novavax vaccines, among scores of others. For the most part, the vaccine technologies that have been widely adopted had never before been licensed for general use and never produced and rolled out at anything approaching this scale, yet they elicited neutralizing antibody titers and T cell response frequencies far beyond expectations. These levels of immunity in turn fuelled unanticipated protective efficacy. Immunologists around the globe should give themselves a collective pat on the back for the many millions of lives saved, the pandemic slowed (if not yet beaten), and the health services rescued from meltdown. Lightning-speed progress of course was not just in these most explicit deliverables, but in the huge advances in decoding COVID-19 human immunology. The SARS-CoV-2 immunology dataset rapidly overtook our knowledge of most other human pathogens that had been studied for decades. Yet, lest we sink into self-congratulatory immunological hubris, there are huge and self-evident caveats to our pride in these achievements.

The victories salvaged a desperate situation, but the insights gained have been superficial, imperfect and rushed, and have barely scratched the surface of our immunological nous and the job that we could do, given the time, will, ingenuity and funding. Consider the huge gulf between where we are now and where we could be, given sufficient application of our collective immunology brain wattage. We face a massive translational research agenda if this job is to be properly completed. We remain firmly stuck in the phase that Mary Poppins might have described as "well begun is half done". In this regard, having enjoyed a period of détente and mutual respect between scientists and policy makers, we now again face segregation into rival tribes: the short attention spans, COVID-19 revisionism and 'move along, there's nothing to see here' attitude of our global leaders threatens the laser focus that the scientists will need if we are to avoid endemic bedding-in of massively elevated mortality along with a lasting worldwide burden of disability imposed by more than 150 million cases of long COVID. How did 'endemic' — the term used in infectious disease to describe our relentless struggle in the relationship with our greatest scourges of HIV, tuberculosis and malaria — come to be re-appropriated to mean some form of victory over COVID-19? If we now meet the COVID challenge poorly and throw in the towel, historians may puzzle over our ineptitude for centuries to come.

Entering year four, the situation is that many parts of the world have received upwards of three vaccine doses. Meanwhile, we have yet to overcome the political, legal and technological barriers that mean a third of the planet are yet to receive a single dose. Even in the parts fortunate enough to be offered the boosters that look so critical for the cross-protective antibody levels to keep Omicron subvariants at bay, we are in uncharted territory. In terms of rapid antibody waning, reliance on frequent, repeated mRNA boosters appear to be yielding diminishing returns. Policymakers are wont to declare 'it's simple now like flu — you'll just queue up each year for your annual jab'. These are words that should strike all aspirational immunologists with both horror and mystification: what on earth should best be in that 'simple jab', and how will we ensure it does the job better than we currently achieve? As a community, we collectively know enough about long-term resident memory (mucosal and otherwise), adjuvant design and affinity maturation to be doing so much better, if only given the chance. Head-to-head trials to compare modalities and find those with genuine response durability would be rewarding, yet it is hard to imagine the train being slowed to allow these to proceed. Meanwhile, many initiatives to investigate transmission blocking through intranasal delivery of mucosal vaccines are underway, so long as we retain sufficient momentum and traction to get them into use. Then there is the fraught question of variant chasing. We find ourselves in a place where the approaches are delivering results — witness the compelling real-life data on protection from bivalent vaccine boosting against severe or fatal outcome after BA.5 infection. Yet, is there an immunology professor out there who can fully justify how and why, in the face of nearly four years of diverse spike sequence immune imprinting, the solution of choice might be to inject a bivalent preparation pairing a variant sequence spike somewhat related to the currently prevalent sequences, together with the ancestral sequence last seen on the planet in early 2020? This is a combination that is further shaping B and T cell receptor repertoires, but we lack the data to know if this carries us in a long-term advantageous direction or not. Many teams around the world have been working hard on the structural biology of those neutralizing epitopes that are highly conserved between coronavirus sequences and, potentially, variant future proofed. Once again, though, we can only channel these into use if there is common will to aim higher and do better.

The other topic within this throwing down of the gauntlet to immunology researchers and funders is the huge challenge of long COVID, often correctly referred to as the 'pandemic within the pandemic'. We cannot accurately count how many on the planet have experienced COVID-19 infection, but estimate that around one-tenth suffer persistent symptoms — the lives of a significant minority of these remain changed at three and half years and counting. This is a

disease process that is destroying lives and has potential to destroy health services and damage economies, imposing a societal disease burden as large as that of rheumatic or cardiac disease. Most agree that defining an etiology, whatever the mix of autoimmunity, immunopathology, endotheliitis, viral persistence and hypercoagulation, lies within the remit of immunologists. Given the huge successes over past decades of translational immunology across areas from cancer to autoimmune disease, there is reason for optimism that with knowledge of long-COVID mechanisms, the well-stocked immunology toolkit would have the wherewithal to supply solutions. We just need the resources to fight this next battle.

So, as immunologists return to the day job and rightly go back to the countless research questions that occupied us prior to the end of 2019, let us also keep reminding ourselves of the only half-done COVID-19 job and the need for us, with the help of appropriate funding, to now show what can be achieved if we really let rip with all that hard-fought immunological knowledge.

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Competing interests
D.A has received honoraria for consultancies with AstraZeneca, Pfizer and Oxford Immunotec, and is co-author of The Long Covid Handbook (Penguin Books).