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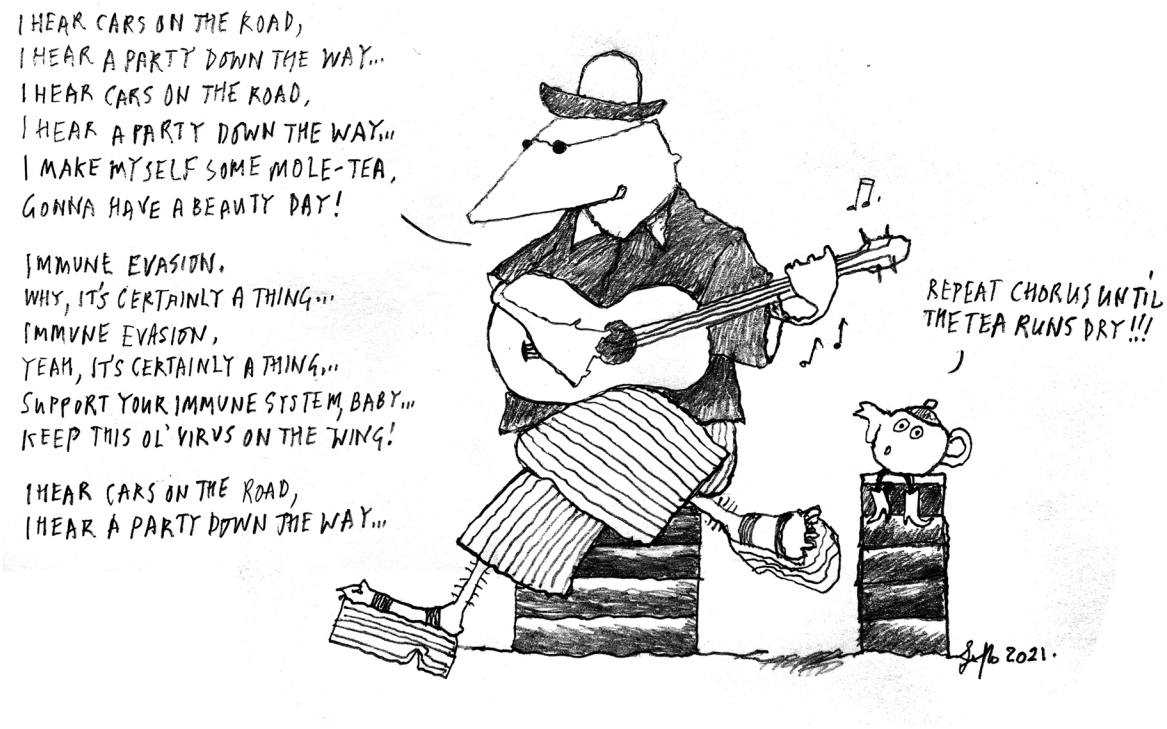
STICKY WICKET

Corona XL – listen

Mole



Original artwork by Pete Jeffs – www.peterjeffsart.com

Listen! I hear cars on the road. I hear a party down the way. I hear people in restaurants and bars (bars!). I hear music on the breeze. Where I am, the world is opening up, and the sounds of it are all around. I hope that's true where you are, too. *Listen*!

But of course, it isn't the case everywhere. We are far from done with this Terrible Pandemic, much as we'd like to see it in the rear-view mirror. In my country, the one with the actual President rather than a Batman villain (the old, campy Batman villains, like the Penguin, not the new psychopaths, who win Academy Awards for the actors who portray them), we still have outbreaks, hospitalizations, and deaths among the unvaccinated. And in the world at large, the TP still rampages, and the race against time continues.

Listen! We are being warned, repeatedly, that new variants are rising, and pose a demonstrable threat. While coronaviruses do not mutate quickly, all viruses mutate. It's evolution. That could be a game show: It's Evolution! "You know the rules, the fittest survive to reproduce, and that's all there is to it! Let's meet our first contestant!"

Here's the thing. When a microbe infects a range of hosts, it is selected in the most prominent of them (because it is present in larger numbers in these primary hosts). The *Legionella* bacteria infects many different amoebae and can infect us. My friend, Professor Goshawk brilliantly showed that Legionella can dispense with a large swath of its genome and still grow in human macrophages, because these genetic elements are critical for growth in different single-celled eukaryotes that are tougher than our cells. Legionella does not need us – there are more than enough amoeba to go around. But when we become a primary host, the game of 'It's Evolution' is staged in us, and sure enough, Sars-CoV2 is evolving to infect and transmit with higher efficiency in humans. We have seen this in real time: the spike protein in some variants binds with higher affinity to its Ace2 receptor than did the original Sars-CoV2. Even if these mutations were to decrease its affinity for Ace2 in, say, bats, there are more than enough of us to go around.

Listen! Many very smart people are talking about the fear that a variant will emerge that renders our vaccinated status irrelevant. That is a very scary idea – and not fun-scary, like a horror flick, but scary-scary, like nuclear fallout (actually, I don't find most horror films fun-scary; I find good films immersive, and if they are scary, I'm immersed in fear; and if I'm not immersed, I don't enjoy any film – that's just me. Then again, I did love Shawn of the Dead, but I don't think that was supposed to be scary, not like 'Dumb and Dumber'. Maybe that wasn't supposed to be scary either, but it terrified me. What were we talking about? Oh, right. Focus, Mole). Immune evasion.

It's worth talking about this. Many of the smart people who talk about immune evasion don't know very much about the immune response (despite being very smart – intelligence is not the same thing as knowledge). So, let's talk about the immune response. The vast amount of literature on anti-viral vaccination concentrates on antibodies. Hopefully, you know what an antibody is (if you don't, please go look it up – we need to be on the same page here). When we are vaccinated, say, with the spike protein of CoV2 (which is

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what all of the approved vaccines use), we generate antibodies to the portions of the molecule that are exposed to water. We do this because we have B lymphocytes, and each B lymphocyte generated in our bone marrow has a different receptor for 'stuff that might be out there' (how this happens, this Generation of Diversity, is a really great molecular trick, but again, we don't have to go there. You probably already know about this, because you're not only intelligent, but also very well informed). If the B cell happens to 'see' what its receptor binds, and if there are additional signals (which we will get to), the B cell proliferates and now secretes a soluble form of its unique receptor in the form of an antibody. So, when we are vaccinated with the CoV2 spike protein, we make a lot (a lot a lot) of different antibodies that bind to the exposed bits of the spike protein in different ways. So, if the virus mutates its spike protein so that one (or a few) of these antibodies no longer bind, there are many, many others that still do. The virus would have to change very dramatically to evade antibody binding (and that isn't what we should worry about, because coronaviruses do not change in this way).

When the antibodies bind to the spike protein on the actual virus, they do various things (these vary with the class of antibody, but we again don't have to go there. And you may already know about antibody classes, because YAVWI). First, they can neutralize the virus by preventing its binding to the Ace2 receptor on our cells. And this is where the changes to CoV2 do make a difference, because when the spike protein mutates to increase its affinity for its receptor, it can outcompete the antibodies and infect the cell. This is what we mean when we say that vaccine-induced antibodies are X% less effective in neutralizing a variant. But it is a numbers game – if our antibodies are 50% less effective against the variant, we just need more antibody to neutralize it, and actually, we have way, way more than the needed levels. Sure, if our antibody levels fall significantly, the variant might infect us (and there was some concern that this would happen, and would raise the requirement for boosters, but we now have reason to believe that this is not going to happen for most of us for a long time). So, we seem to be good. But antibodies do not work only by neutralization; they also do other things. One of these is to activate an enzymatic cascade called Complement, which can strip the virus of its coat lipids. Another is to bring the virus to cells that engulf the virus and bath it in noxious agents to kill it. At this point, we do not know the extent to which these additional antibody mechanisms protect us from CoV2, but it's good to know that we have backups in play.

And vaccines do not only activate B cells, they also activate T cells, and T cells are very different beasts. Some T cells function to instruct the B cells whose receptors bind to the vaccine protein to go ahead and make antibodies (nearly all vaccines of any type activate these T cells, which is why we make the antibodies). But all of the approved vaccines also activate another type of T cell, whose function is to kill virally infected cells before they can make more virus. Unlike B cells, the receptors on T cells recognize small peptides derived from the vaccine protein (in this case, from the spike protein). And different T cells recognize different peptides in different ways. While a mutation in the virus protein might evade one of the T cells, it won't matter at all to another one. Now, there is some emerging evidence that in some individuals the T cell response is restricted to a few peptides, but even then these are different among different individuals. The virus has another trick it can do, which is to vary the bits of the peptides that bind to the molecule that 'presents' the peptide to the T cell, but this molecule is so variable in the human population that even if a virus manages this trick (which would only happen in the most common human form, present in about 30% of people of European descent), the other alleles will still do the job (we have a bunch of these presentation molecules). In other words, it is really, really hard for a virus to mutate to evade immune responses.

Listen! So, I think we're going to be okay, *if* we can manage to get most people vaccinated, and not only in our own countries. But, and this is a huge *but* (not to be confused with my own, large butt), there are a lot of viruses out there that are ready to jump to humans. Will we learn from what we have just been through and be better prepared?

And in the meantime, we really do have to get the vaccines to people, and when we do, convince them to take them. This morning I read some advice for those of us who are trying to convince the hesitant. Many such people have concerns, and hurling facts and statistics at them doesn't help to convince them. It turns out that it is much more effective to listen to their concerns and answer their questions. Work with them to explore their sources (usually online) that raised their concerns, and help to manage the misinformation, discuss the consequences of vaccination and the lack thereof, and talk about how, if they get infected, they themselves can be the source of the next variant. So, yes, it's about listening, after all.

Listen!