

The "laboratory origin hypothesis" of SARS-CoV-2 has recently gained additional consideration. The main driver justifying this assumption is represented by the so-called "gain of function" (GOF), a process resulting in the acquirement of new phenotypic/behavioural features, due to the manipulations of the viral genetic make-up artificially made in the laboratory. Within this framework, there is a question of crucial relevance: is the "laboratory of virology" or, more precisely, was the "Institute of Virology of Wuhan" the site where SARS-CoV-2 originated, based upon a GOF-related process involving one or more "cousin" coronaviruses? And, still noteworthy, may a GOF-associated process also occur in nature, with one or more viral "genetic/molecular signatures" testifying its development (which would also apply to artificial/laboratory conditions)? In this respect, it should be adequately emphasized that the SARS-CoV-2 genome is made of approximately 30,000 nucleotides, with each viral replication cycle implying the occurrence of an average of 1 mutation/10,000 bases. There are, of course, different types of mutations, some "silent", some "non-silent", some "disadvantageous" (against which "purifying, or negative selection" operates), some other ones "advantageous" (against/ toward which "Darwinian, or positive selection" operates). Just to make a long story short, following the aforementioned mutational events, SARS-CoV-2 could have originated under natural conditions from a coronavirus "ancestor" (RA-TG13) sharing with it over 96% genetic homology and originally infecting *Rhinolophus affinis* bats. Further mutations of the SARS-CoV-2 genetic make-up could have led the virus to develop a growing number of "variants of concern" (VOC), such as the "English" (recently renamed "alfa" by the World Health Organization), the "South African (recently renamed "beta"), the "Brazilian" (recently renamed "gamma"), and the "Indian" (recently renamed "delta") VOC. Indeed, these (and other ones) are called "variants of concern" on the basis of their higher binding affinity to the ACE-2 viral cell receptor and/or of their worrisome ability to elude the host's antibody-based immune response elicited both by the infection and by the anti-SARS-CoV-2 vaccination. Additional genomic mutations could lead SARS-CoV-2 to infect, in the coming future, new animal species alongside those which have already been recognized as susceptible to both natural and experimental infection. In this regard, mink is the only species (apart from the human one) in which SARS-CoV-2, once acquired from man (viral spillover), has been proven - in intensive mink herds from The Netherlands and Denmark - to undergo a series of mutational events leading to a viral strain subsequently re-transmitted to humans (viral spillback). As a matter of fact, the genetic background of the latter SARS-CoV-2 isolate (named "cluster 5"), harbouring the "Y453F" mutation within the viral "spike protein's receptor-binding domain" (S-RBD), was different from the viral strain originally caught from the minks' breeders, keepers and/or caregivers. In consideration of the above, why not taking into serious account the possibility of vaccinating (also) animals against SARS-CoV-2, with special emphasis on those living in close contact with humans and, overall, on intensely bred species, such as minks and pigs? Indeed, by encountering more and more susceptible (and non-immunized) animal hosts along its way, the possibility that SARS-CoV-2 will continue to mutate - independently from the human mass vaccination campaign currently underway - should be adequately emphasized. To this aim, a simultaneous "One Health" and "evidence-based" approach should be utilized, the former of which reminds us that human, animal, and environmental health are tightly and mutually connected to each other.

(F: G. Di Guardo, Science Advances, June 14, 2021)

