

**Accademia Nazionale dei Lincei
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Animal experiments needed in Italy to fight the COVID-19 battle

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The search for effective treatments against SARS-COV-2, the coronavirus responsible for the COVID-19 pandemic, is engaging thousands of researchers from around the world. Essential tools to fight this battle are specific drugs and vaccines, which are not yet available. Research in the field, however, is neither simple nor rapid. Prior to human testing, new drugs and vaccines must be validated to make sure that therapy effects occur without concomitant toxicity. Drugs are usually chosen based on their *in vitro* effects on isolated cells, then investigated in appropriate animal models. Direct analysis of drugs and vaccines in humans would not only be unethical, but also very risky (1). Studies for COVID-19 were started in mice, the animal most frequently employed for the development of new drugs. However, mice infected with SARS-COV-2 failed to exhibit pneumonia, typical of COVID-19 in humans. Consequently, attempts have been initiated with other species, including very expensive animals such as ferrets and monkeys.

Recently, however, the low SARS-COV-2 sensitivity of mice with respect to humans has been shown to depend on the virus receptor. In humans, the virus attack follows it binding to the ACE2 receptor, exposed at the plasma membrane of target cells, the epithelial cells of lungs and endothelial cells of vessels. Mice are virus-resistant because their ACE2 receptor is different from the corresponding human receptor. However, mice that are injected with the gene of human ACE2 receptor become sensitive to the virus, developing pneumonia upon infection. This approach is not innovative. A variety of genetically modified mice are in fact already available. Therefore, transgenic mice, including immunodeficient mice, are excellent models for the analysis of drugs and other COVID-19 treatments. Interestingly, immunodeficient mice can be injected with cells from different species, including human cells. Genetically modified mice can thus be employed to

analyze drugs as new animal models. When approved, the drug studies on mice are followed by human studies according to the traditional clinical trial procedures.

At this point, new drugs validated in mice and proved to be safe and effective also in humans can be applied to the patients. Unfortunately, animal experiments in Italy are more complex than in other countries. Years ago, Italy's Legislative Decree 26/2014 amended several aspects of Italian animal research by removing a part of the European directive (2010/63), in which research conditions are laid out for the Member States. Among other problems, the Italian Decree introduced a heavy bureaucratic process (many months and extra money are required to start a new project!) and the ban on various types of experiments. Until now, the Government has temporarily suspended a few aspects of the Decree. However, this suspension will expire at the end of this year. At the moment, therefore, animal research on COVID-19 animal models is extremely difficult in our Country. The Health Committee of the Accademia dei Lincei makes an urgent request to the Italian Government and Parliament to completely eliminate, without further delays, both the absurd bureaucracy and prohibitions of some experiments. Italian researchers should be free to compete with their European colleagues for the discovery of drugs against COVID-19 and other diseases for which no cure is available.

1. Jiang S. Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees. *Nature* 579: 321, 2020.