COVID-19 and the Chemical Biology Community

The spread of COVID-19 has been declared a pandemic and we as a global community are watching as hot spots of this illness emerge across not only countries but continents. As the situation has progressed, the focus of scientists and their ability to undertake most experiments has been limited to facilitate physical distancing. Still, research addressing varied aspects of diagnosing, treating, and mitigating spread of COVID-19 is not only continuing but accelerating with the goal of reducing loss of life. Chemical biologists have integral contributions to make: Chemical tools can address challenges in biology, which is what is required to understand and mitigate SARS-CoV-2. Given that Italy is now under tremendous stress from COVID-19, we asked an Italian scientist to discuss the strategies that academic and industrial labs in Italy are pursuing to limit the impact of the virus both on their research and on society. We hope that this perspective along with that of our Chinese colleagues will provide insight into the important scientific advancements and the human aspects of advancing science in the face of a rapidly growing pandemic.

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When the others become us: a chemist's perspective of the COVID-19 outbreak in Italy

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The situation in northern Italy

Epicentre of the current epidemic in Italy, the Lombardy region is fighting a hard battle against an invisible enemy, the propagation of SARS-CoV-2. At the time of writing (17th March 2020)[1] the region registers more than half (51%) of the total national confirmed cases (31.506) with a mortality rate at almost 8%. It is especially concerning in general, and for me personally, the situation in the province of Bergamo with almost 4000 cases (3993) and many fatalities (460, almost 12%), where two small towns not far from where I was born and raised are paying a brutal toll. Of little comfort is the knowledge that the majority of infected people (up to 80%) is likely asymptomatic and goes by undetected, as revealed by a study conducted on the small village of *Vo' Euganeo* (not far from Padua), where all the 3000 residents have been tested after lockdown. [2] These results mirror those recently published by Li and co-workers.[3]

Figure 1. Art work acknowledging the incredible work carried out by all the medical staff, affixed on the wall of the *Papa Giovanni XXIII* Hospital in Bergamo, the Italian province with the highest infection rate and the highest death toll so far (credit: Franco Rivolli Art and LP GRAFICA S.r.l.).

Teaching and academic research in Milan

This balance and the constant sound of the ambulance sirens is weighing heavily on our minds when thinking about keep doing science. At the University of Milan, where I work, from the 24th of February we have been caught up in a crescendo of restrictive measures, at first stopping on-site lectures and then locking research labs two weeks later. Even professors and assistant professors have been discouraged from accessing the site for preparing or carrying out on-line teaching: please do it from home. Only essential in-person activities, such as refills of cryogenic gases to NMR instruments, are currently authorized in our department.

Chemistry courses are more effectively taught in the classroom, where the classical chalk and blackboard approach is paired with a direct interaction with the students. The many teaching labs we usually implement consolidate hands-on the knowledge acquired. This winning combination has been cut by the impending safety requirements, shifting toe-learning alone. This resulted in many colleagues being elbows-deep in the last minute preparation of the on-line version of their courses. On the other hand, for the few fortunate enough to have completed their teaching duties the past semester, this might be a good time to write those papers that were laying unfinished on our desks, or to finally catch up with the recent literature.

From the research point of view, while computational studies can continue from home, even if with a few mishaps here and there in the remote access to servers or software licences, all wet-lab experiments are on

hold, and presumably will be for (at least) one (or more) months. This of course leads to personal concerns about being able to fulfil the commitment made upon receiving both national and European funding. Not less worrying is that the must of social distancing, if long lasting, would negatively impinge on the intrinsically collective nature of research groups. Returning to business as usual might not be as straightforward as one might think. As a society, especially for the younger generations, a useful lesson would be realizing that social media cannot fully substitute human contact and face-to-face talking.

Recent efforts against COVID-19

In this increasingly surreal situation, I am pleased to ascertain that the Italian ability of "*fare di necessità virtù"*, *i.e.* making lemonade out of the lemons life gives you, is still undisputed, as testified by the number of initiatives carried out by the local and national scientific community and by the private sector.

Clinical isolates

Especially active have been, of course, the institutions voted primarily to the study of infectious diseases. After isolating (29th Jan) and diagnosing (30th Jan) the first two cases of COVID-19 in the country (two Chinese tourists arrived in Rome), researchers at the National Institute for Infectious Diseases (INMI) *Spallanzani* had promptly isolated the viral strain 3 days later (2nd Feb).[4] The patients have been treated with an experimental antiviral, Remdesivir, that is under development for Ebola and Marburg infections. The drug was administered "for compassionate use", giving the current lack for specific authorizations, and the couple was declared officially cured on Feb 26th. Other clinical isolates from Italian patients have been obtained both at the *Luigi Sacco* Hospital, which is also a research campus for the University of Milan (Department of Biomedical and Clinical sciences), and at the *S. Raffaele* Hospital (3rd - 4th March). These isolates and their genome sequencing are the foundation on which to start our quest for effective drugs and, likely on a longer time-frame, for vaccines.

Clinical trials

The two most promising repurposed drugs that have been used during the current emergency are now entering legitimate clinical trials for COVID-19, as follows.

The Italian Drug Association (AIFA) and Gilead have recently announced that Italy will take part to two Phase III clinical trials that will allow to assess the efficacy and safety of the experimental drug Remdesivir in COVID-19 patients.[5] As mentioned above, this drug is currently being administered "for compassionate use" for emergency treatment of COVID-19 patients in critical conditions that do not have alternative therapeutic options.

Tocilizumab, a monoclonal antibody developed for treating rheumatoid arthritis, was first used to treat some COVID-19 patients in Naples. It inhibits the receptor of IL-6, likely damping the effect of the *cytokine storms* (*i.e.* massive release of pro-inflammatory cytokines that over-stimulates the immune system) observed in the more severe cases. Today, AIFA swiftly authorized the beginning of a clinical trial,[6] involving many hospitals

in Italy, that was made possible also by Roche committing to supply the drug for free for the whole emergency duration.

Phylogenetic analysis of SARS-CoV-2

Even before the appearance of COVID-19 cases in Italy, the group led by Prof. Zehender at the University of Milan, performed a temporal reconstruction of the SARS-CoV-2 phylogeny.[7] The results suggest that the epidemic originated between October and November 2019, few weeks before the identification of the first cases. We now know that this is spot on, since the first confirmed case reported has been fixed at Nov 17th.[8] Analysis of the reproduction number *R* of the virus (*i.e.* the number of secondary cases induced by a single infected individual) increased in December 2019, leading to the current pandemic. R usually decreases on the course of an epidemic, due to the reduced number of susceptible individuals, but in this case the increase might be due to the acquisition of a more efficient human-to-human transmission trait (*i.e.* via the now *in*famous droplets).

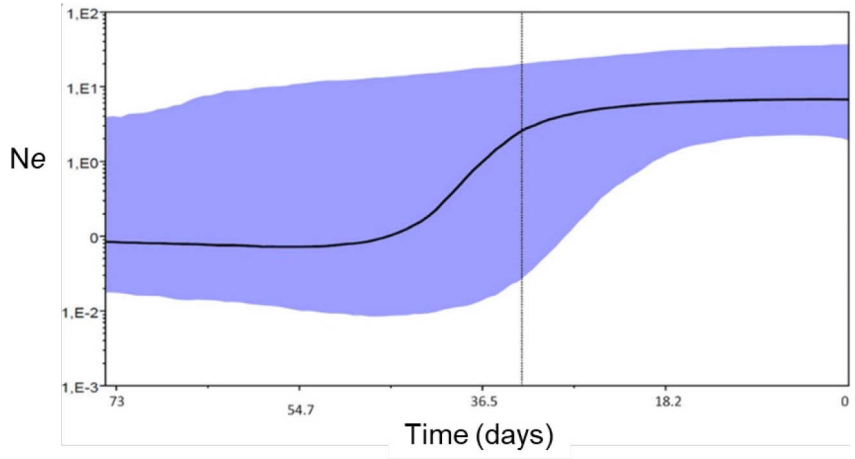

Figure 2. Bayesian skyline plot of the SARS-CoV-2 outbreak.[7] N*e* is the effective population size; Time 0 = 30th of January 2020, then 18.2 days, 36.5 days, 54.7 days, and 73 days before. The thick solid line represents the median value of the estimates, and the blue area the 95% HPD (higher posterior density interval, *i.e.* credible interval). It is apparent the rapid increase in the number of infections in the second half of December 2019.

Has the majority of the population already come into contact with SARS-CoV-2?

This is the fundamental question that two colleagues of the University of Milan, Prof. Bollati and Dr. Milani, are trying to answer. They designed a study to determine whether a large cohort of asymptomatic people already have circulating antibodies against the virus, both short-term response and memory antibodies. In parallel volunteers will be tested for the presence in the respiratory tract of the virus itself. This will allow in the first place to understand if the virus had been circulating long before the outbreak of the epidemic (allowing the immune system to generate a long-term immune response in some individuals) and, secondly, to cross-check the results of swabs and detect false negatives. The results will need to be interpreted cautiously. Indeed, viral RNA quantification is an established diagnostic tool but the interpretation of the presence of specific antibodies is still under debate, as it is currently unknown whether they will confer long

term immunity against future infections. The protocol for safe samples collection (timing of individual appointments and access to the dedicate location) has been designed in collaboration with the Italian Association of Blood Donors (AVIS). The call for voluntary participation to all the people working at the university registered more than 1500 adhesions in less than 24 hours. The study, named UNICORN (UNIversity against CORoNavirus), is funded by the University of Milan, has already obtained the ethics committee approval and is ready to start as soon as citizens' mobility restrictions will be lifted.

Development of more rapid diagnostic tools

It is apparent that quick and reliable tests for positivity to SARS-CoV-2 are of paramount importance for identifying infected individuals and break the contagion propagation chain. Current analysis methods rely on the amplification of viral genetic material isolated from the patient sample (generally a nasopharyngeal swab) that takes altogether 6 to 7 hours. This takes into account the lengthy careful preparation of dangerous samples in a P3 facility followed by a pushed PCR protocol.

An Italian multinational company, DiaSorin has developed a much quicker analytical solution that will allow to obtain a viral positivity answer in 60 minutes.[9] The company completed, in collaboration with the abovementioned *Spallanzani* Institute and the *S. Matteo* Hospital in Pavia, all the necessary tests and obtained the EU and the FDA-EUA (Emergency Use Authorization) approval[10]. The test was developed taking into account 150 viral sequences deposited in worldwide databases, in order to detect all the currently known variants and minimize false negative results. Compatibly with the necessary production scale-up, this represents a strong asset for the quick analysis of samples directly at POC (point of care).

The escalation of this pandemic found the world utterly unprepared to face it as a united front, as the situation would require for maximum contagion containment efficacy. Italy found itself instead as the unfortunate western pioneer of this fight. As a country, we are still days (?) away from the peak and we have already paid a steep price as it is.

To conclude on a more auspicious note, the Innovative Medicines Initiative (IMI), a big private-public partnership in the life sciences, launched their 21st call putting on the table 45M € for collaborative projects of public and private institutions to fight against COVID-19.[11] They are looking for proposal that will develop antivirals and therapeutics for the current or future outbreaks or rapid diagnostic tools for the detection of asymptomatic carriers and symptomatic infected individuals.

Despite the many scientific efforts described here and the titanic efforts of our doctors and nurses, the only truly effective "vaccine" we have available at the moment is social distancing, so #staysafe #stayhome #iorestoacasa.

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