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A CRISPR response to pandemics?

Exploring the ethics of genetically engineering the human immune system

Federico Germani, Sebastian Wäscher & Nikola Biller-Andorno*

In 1881, Louis Pasteur proved the "germ theory of disease", namely that microorganisms are responsible for causing a range of diseases. Following Pasteur's and Robert Koch's groundbreaking work on pathogens, further research during the 20th century elucidated how the immune system fends off disease-causing microorganisms from a molecular perspective.

The COVID-19 pandemic has again focused scientific and public attention on immunology not the least owing to the race of employing vaccines to halt the spread of the virus. Although most countries have now started vaccination programs to immunize a large part of the world's population, the process will take time, vaccines may not be available to everyone, and a number of unresolved issues remain including the potential contagiousness of vaccinated individuals and the duration of protection (Polack *et al*, 2020).

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It would therefore be extremely helpful from a public health perspective—and indeed lifesaving for those with elevated risk of developing severe course of the disease—if we could boost the human immune system by other means to better fight off SARS-CoV-2 and possibly other viruses. Recent studies showing that some individuals may be less susceptible to contract severe COVID-19 depending on their genetic status support such visions (COVID-19 Host Genetics Initiative, 2020). This could eventually inspire research projects on gene therapy with the aim of generally enhancing immunity against viral infections.

The idea of genetically enhancing the human immune response is not new and spread from academic circles to policymakers and the general public even before the pandemic, when He Jiankui announced in November 2018 the birth of genetically edited twins who, he claimed, were resistant to HIV. The public outcry was massive, not only because He violated standards of methodological rigor and research ethics, but also because of fundamental doubts about the wisdom and legitimacy of human germline manipulation (Schleidgen *et al*, 2020).

Somatic gene therapy has been met with a less categorical rejection, but it has also been confronted with skepticism when major setbacks or untoward events occurred, such as the death of Jesse Gelsinger during an early clinical trial for gene therapy in 1999. Nonetheless, given the drastic impact the current pandemic has on so many lives, there may be a motivation to put concerns aside. In fact, even if we managed to get rid of COVID-19 owing to vaccines—or at least to keep its infectiousness and mortality low—another virus will appear sooner or later; an improved resistance to viral pathogens—including coronaviruses—would be an important asset.

Interventions to boost the immune system could in fact make use of either germline gene editing, as has been the case of the Chinese twins, or through somatic gene editing. The first requires time and only the next generation would potentially benefit while the latter could be immediately applied and theoretically used to deal with the ongoing COVID-19 pandemic.

Safety and efficacy

Somatic gene therapy involves the integration of corrective DNA via plasmids to temporary bypass mutations, small RNA interference to block the expression of target genes, or potentially the replacement of a mutated gene with a functional copy. It refers to applications in any type of cell, with the exclusion of germ cells as genetic manipulations could otherwise be inherited by the offspring. The downside of approaches with no stable integration of genetic material into the host genome is that patients require multiple treatments. While stable integration could permanently cure genetic diseases, this approach raises additional concerns as it can cause cancer due to random insertional mutagenesis.

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Recent advancements in CRISPR/Cas9 technology could come to a rescue as specific integration can be attained, even though concerns remain for potential off-target effects due to integrations at multiple loci in the genome. Other concerns include the potential of these therapies to unwittingly influence the germline, thus transmitting gene modifications to the following

Institute of Biomedical Ethics and History of Medicine (IBME), University of Zurich, Zurich, Switzerland
*Corresponding author. E-mail: biller-andorno@ibme.uzh.ch
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generation. In addition, the viral vectors used to carry genetic information to the target cells can elicit inflammatory responses and can dampen the effectiveness of the therapy (Goswami *et al,* 2019).

Despite its great potential for treating monogenic hereditary diseases, gene therapy is currently not actively pursued as a potential treatment or preventive tool against infectious diseases such as COVID-19. In fact, such therapies would require a deeper understanding of the disease, and in particular the role of the genetic background for associated predisposition to infection and severity, and the cell types affected by the virus.

Potential of gene therapy for SARS-CoV-2

Recent studies indicate that there is a genetic susceptibility to COVID-19, although only limited data are available. Two gene clusters, one on chromosome 3 and one on chromosome 9, were identified as risk loci for respiratory failure after infection with SARS-CoV-2 (Severe Covid-19 GWAS Group *et al*, 2020). The first one includes several genes that have not been studied in the context of COVID-19, whereas the latter coincides with the ABO blood group locus. Interestingly, an association of the blood type with the severity of the disease had already been shown for SARS (Cheng *et al,* 2005).

The viral spike (S) glycoproteins are affine to the human angiotensin-converting enzyme 2 (ACE2) and provide the mechanism of entry into the target cell. This is followed by the cleavage of the S glycoprotein by the host cell's transmembrane protease, serine 2 (TMPRSS2), which is fundamental for the release of viral RNA into the cell, with the consequent production and dissemination of new viruses. Polymorphisms in both *ACE2* and *TMPRSS2* have been identified to be relevant for susceptibility to SARS-CoV-2, providing a rationale for editing of these candidates genes (Hou *et al,* 2020). Another gene of interest is *TRIM55*, which encodes for the ubiquitin E3 ligase tripartite motif containing 55 and plays a possible role in the inflammatory response in the lungs following infection with SARS in mice (Gralinski *et al,* 2015). In this context, other genes of interest are involved in the antiviral and proinflammatory response or influence the replication of the virus. This includes cyclophilins, which have been shown to play a fundamental role for Human Coronavirus 229E infections (von Brunn *et al,* 2015).

Still, we currently do not have a good understanding of the genes and variants associated with coronavirus infections. Nonetheless, somatic gene editing to treat or prevent severe COVID-19 seems a viable option in principle, if further research validates the candidate genes that have been identified, and independent groups replicate the findings. It is however unlikely that such research, along with safety and efficacy requirements, will be carried out in a short time, although strategies to fight against COVID-19 could be beneficial to fend off other coronaviruses, and, by extension, other viral infections that may challenge us in the future.

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Finally, it is important to consider the risk/benefit profile of future therapies to enhance immunity, to better understand when these applications are truly necessary and when not. As discussed, our current understanding of the genetic factors that determine whether our immune defenses can successfully fend off pathogens is poor. Furthermore, a growing body of evidence suggests that immunity intermingles with and affects other fundamental processes, such as cell growth or reproduction. These processes respond to intrinsic and extrinsic factors and collectively mount a cohesive and precise biological response. For instance, various studies have shown that the innate immune response decreases the effectiveness of other processes, such as reproduction or growth, when the organism is faced with an infection. This appears to be true in plants (Lozano-Duran & Zipfel, 2015), animals (Soler *et al,* 2003), and humans (Urlacher *et al,* 2018). The molecular pathways involved in these processes are well established in plants, but the molecular understanding of these interactions remains poor in animals.

In summary, we do not have a clear picture of the biological costs of an enhanced immune response, nor a proper understanding of the genetic factors determining predisposition to pathogenic infections. We also need to understand how any manipulation might affect our health beyond immunity. This is of particular relevance for germline editing, but it is nonetheless important for somatic gene editing applications, as interactions between pathways involved in immunity and cell growth for instance need to be studied both systemically and in the context of specific tissues.

Access and autonomy

Once the biological and technical problems are solved to ensure the safety of somatic gene editing to enhance the immune response against viral infections, a host of ethical and societal questions will require answers. The first question is access to treatment—an issue which is currently being discussed for COVID-19 vaccination programs. A risk is that these therapies might become available only for a small, privileged fraction of the population, further increasing gaps in health status and life expectancy and giving those enhanced more freedom and more choices during a pandemic.

This could be prevented by allowing immune-enhancement campaigns only during a pandemic. These campaigns could be used as preventive or therapeutic measures against a specific pathogen, rather than to potentiate immunity in general. For example, early determination of the mortality rate stratified for age and comorbidities, as well as the evaluation of epidemiological parameters, could help to define who should be prioritized for treatment. Generally, defining eligibility and priority criteria will help prevent inappropriate use of somatic gene editing to enhance the human immune response.

However, this approach would risk dividing citizens in classes with different rights based on whether they underwent treatment; those who did could have privileges such as the possibility to circulate freely, meet people, travel, or have dinner in a restaurant, while the others remain in lockdown or quarantine. This is not a far-fetched scenario as several governments have already discussed such a system of sizeable rights based on "immunity certificates" during the first COVID-19 wave.

Autonomy is another key issue. It concerns the right to decide for oneself whether or not to use a therapy or intervention and inherently comes with the variable and subjective assessment of the dangers posed by a given pathogen. Mandatory vaccinations have remained controversial even for pathogens that ravaged humanity before the advent of vaccines. For new pathogens, of which we do not initially understand the harmfulness, this proves to be especially difficult. Although there is currently unanimous consensus that COVID-19 is a disease that requires global and coordinated efforts, there is no consensus on whether vaccinations should be mandatory and for whom (Bowen, 2020). There are also controversies around more or less subtle ways of using nudges, incentives, or social pressure to make people get vaccinated. Such strategies might arise similarly for gene therapy as treated individuals would be less likely to fall severely ill, they might pose less of an infection risk to others and could continue serving even in exposed jobs, for instance, as healthcare professionals.

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Even if genetic immunity enhancement eventually proved to be safe, effective, and possibly superior to vaccines—which may have limited protection or require frequent boosts—it is hard to imagine it could become mandatory. However, in societies that linked immune status to privileges, individuals could feel incentivized or even compelled to undergo treatment. If and how autonomous choice can be maintained under such circumstances remains a largely unresolved question.

Addressing challenges from an ethical perspective

The challenges concerning the use of somatic gene editing to enhance the human immune response relate to technical, biological, social, and policy concerns, and all need to be addressed from an ethical perspective before applications can be considered in the context of a pandemic or other global health problems.

Technical concerns include the possibility of random or undesired integration of exogenous DNA sequences in the genome; the undesired integration of genetic material in the germline; the toxicity of viral vectors and the immune response they elicit. Biological concerns include the poor understanding of the genetic background that determines the efficacy and effectiveness of the immune response to various pathogens; the lack of comprehensive data and the validation of individual polymorphisms in candidate genes; the lack of proper and complete understanding of how immunity influences other fundamental biological process, and the biological costs of enhancement.

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Social and policy concerns include the current lack of proper guidance to define when immune enhancement might be considered appropriate depending on the harms and risks of the intervention and the dangerousness of the pathogenic threat; the warranty that applications will be made fairly available to all individuals, regardless of their socio- economic status; and the lack of communication tools and regulatory safeguards that allow citizens to make informed choices whether to use or not to use these applications.

Time is of the essence during a pandemic, and we believe there will not be enough time during the ongoing COVID-19 pandemic to consider a gene therapy-based strategy in order to protect the population from infection. Nonetheless, this approach could help to prevent future pandemics and fend off endemic pathogenic diseases, with COVID-19 possibly falling in this category if current efforts will not be effective as hoped.

Genetic manipulation might open up interesting perspectives, but we should not rush to applications before having solved ethical problems regarding safety, effectiveness, access and autonomy. Finally, scientists and policymakers must not forget the importance of public trust when it comes to biomedical applications, including human gene editing (Riggan *et al,* 2019). Given the prevalence of fake news and misinformation on social media and their effect on public opinion, this could undermine scientific and medical efforts and dampen the effectiveness of global health responses. Thus, the discussion about limitations and strengths of new therapeutic approaches—such as somatic gene editing and its potential to enhance our immune system—should be transparent and understandable for citizens, and societal debate should commence long before new technology becomes available for use. In light of the fast turnover of scientific discoveries in this field, and the desperate need to defend ourselves from pathogenic diseases, we should start discussing the implications of gene editing for enhancing the human immune response now, and do so by involving media, policymakers and the general public.

Conflict of interest

The authors declare that they have no conflict of interest.

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