European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2021; 25: 2830-2833

Letter to the Editor

Comment on the article by Zaami S, et al. "CRISPR-based techniques: Cas9, Cas13 and their applications in the era of COVID-19". Eur Rev Med Pharmacol Sci 2021; 25 (3): 1752-1761

Dear Editor,

We have carefully perused the letter titled "CRISPR-based techniques: Cas9, Cas13 and their applications in the era of COVID-19" published in the European Review for Medical and Pharmacological Sciences journal[1].

The Authors have concluded that application of clinical practices ought to be conducted in adherence to the highest standards of ethics, safety and the rule of law designed to safeguard those vital aspects. Such warnings must be heeded, we believe, if we are to preserve the very fabric of our society in an ethically sustainable way. Nonetheless, the high standards which have been outlined and stressed by the Authors are nothing but a reflection of philosophical values and priorities that appear to be slowly changing; some could view it as a positive evolution, some others may view it as a degeneration, but it is hard to deny that such a shift has been slowly unfolding. First and foremost, we refer to the notion of health care as a means to preserve physical and mental well-being; nowadays, the underlying notion of "preserving" is often conflated with "improving" or "enhancing", and that association encompasses the notion of preventing, whenever technically possible, "unfit" individuals from even being born. Hence, that enhancement is poised to be carried out at the genetic level, as enhancement technologies are perfected, and their scope widened. The availability of CRISPR-Cas9 genome editing techniques has ignited a spirited debate centered around human enhancement for purposes other than medical and therapeutic ones[2,3]. For instance, the maximization of human performance has long been the target of military research, for the purpose of bridging the gap between major warfare innovations and the human physical, mental and intellectual limitations[4,5]. Interestingly, several schools of thought subscribe to a set of ethical-philosophical principles that most of us are likely to find extreme and provocative: genetically editing humans long before birth is desirable and maybe, even morally imperative. Prominent bioethicist Julian Savulescu is in that respect a distinguished advocate, and he has gone so far as to posit a way to genetically edit behavioral characteristics in order to prevent criminal behaviors, arguing that intervening in eliminating the criminal tendency of future children is morally and ethically justifiable[6]. That path would be pursued at the embryonic level: according to the contentious "Principle of Procreative Beneficence", parents would be morally obliged to discard an embryo with potential criminal genes and at the same time choose the embryos that have the most favorable genes for himself and for society[7]. After all, techniques such as preimplantation genetic diagnosis and screening have become rather widespread, along with the development of assisted reproduction techniques (ARTs)[8], which have been regulated by each country with varying degrees of restriction due to the legal, moral and ethical challenges[9,10] they entail. This principle naturally evolves into the notion that the new genome-editing technologies should become available for use on a large scale, thus producing beneficial enhancements for millions of people, at least potentially. That is however bound to give rise to a quandary of major magnitude: should germline editing and genetic enhancement be not only advisable, but made legally mandatory? What could keep governments from pro-

Corresponding Author: Alessandro Del Rio, MD; e-mail: alessandrodelrio70@gmail.com

moting better health in people yet to be born or, to put it rather bluntly, prevent certain "adverse" genes from making future citizens unhealthy[11] or maladjusted within society[12]? Supporters of such techniques have drawn a parallel with vaccination programs, which prevent viruses from triggering life-threatening diseases: they contend that interventions designed to stave off illnesses, whether virus-induced or genetic, have a social, moral, philosophical and even economic value, considering the potential reduction in health care costs such an approach would produce over time[13]. That takes on even greater significance in the current SARS-CoV-2 pandemic under which we have been struggling for over a year; many researchers have been looking into genome editing to counter future pandemics such as the current brutal healthcare crisis that has plagued and besieged almost every nation in the world. In that respect, not only could CRISPR techniques be implemented to disable viruses by altering their genetic code, but also to edit human genes in order to enhance their resistance to infection[14]. A potential COVID-19 therapy based on CRISPR-Cas13 for termed Prophylactic Antiviral CRISPR in human cells (PAC-MAN) has been looked into as a means to inhibit SARS-CoV-2, with a study proving degradation of genomic sequences of SARS-CoV-2 and influenza A virus (IAV) in human lung epithelial cells[15]. The potential such methods hold in the long terms is considerable; there is in fact no denying that the pandemic has laid bare a brutal reality: most countries across the world are not adequately equipped to handle unexpected, massive strain on healthcare systems, and that has led to ethically daunting decisions such as selecting patients who should get prioritized access to intensive care units[16,17]. In addition, COVID-19 patients are not the only ones being heavily impacted: a significant number of patients with cancers or cardiovascular conditions, for example, have been cut off from treatments or diagnosis in a timely fashion. Psychological repercussions such as fear, anxiety, and severe stress have impacted people all over the world, worsening latent psychiatric and psychological disorders and exacerbating addiction issues[18]. Hence, new preventive and therapeutic approaches based on genome editing could prove invaluable in terms of sparing millions of people horrific sufferings and death, although this strategy may face demanding challenges for approval in human clinical trials. Cancer research using genome-based techniques has also shown great promise. New prognostic tools such as non-coding RNAs are already available and have a proven value in some types of cancer[19,20]. Furthermore, some have looked into ways, for example, to target cells that play a pivotal role in the body's immune response, the T cells[21]. Such trials have involved the genetic alteration of T cells via gene transfer in order to "guide" them to target cells of interest and have focused on tailoring T cells for adoptive cell transfer (ACT) for cancer[22]. Several trials are also being conducted aimed at genome editing T cells in cancer patients for the ultimate purpose of heightening anti-tumour immunity[23,24]. It is worth noting, however, that such gene editing practices differ from germline editing in that they target non-reproductive cells: such changes are therefore not heritable, which makes them rather less controversial. Still, some predict that germline editing[25] could become more effective at optimizing T-cell functioning[26]. It is hard to see, in our view, what moral objection could be raised against the prospect of curing diseases that cause millions of casualties or disabilities worldwide every year. That being said, the sheer magnitude of the moral dilemmas posed by genome editing calls for a well-balanced, thoroughly devised and enacted set of precautionary and regulatory measures. While outlining such rules, it is of utmost importance to take into account complexities such as the moral status of the embryo and the rights of genetically modified individuals, who had no say in what was imposed on them by the will of other humans rather than by nature. There is a rather general consensus that any intervention entailing major risks, which may not be properly offset by the expected benefits, is unacceptable[27].

Hence, it stands to reason that therapies applied to individuals who cannot grant or refuse their informed consent are only ethically tenable and justifiable if the benefits to be expected are the survival or the well-being of those yet to be born. That is the case with vaccinations, corrective surgeries and the like[28]. Besides, unique human identities have to be preserved: therapies which may lead to the modification or selective destruction of individuals or of their identities are ethically unjustifiable. Therefore, regulatory frameworks specifically tailored to genome editing ought to be aimed at preventing uncontrolled advances in such techniques from hijacking our deeply-held core values, public health, freedom from suffering and the common good, while discussing how far to take scientific innovations.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Zaami S, Piergentili R, Marinelli E, Montanari Vergallo G. Commentary - CRISPR-based techniques: Cas9, Cas13 and their applications in the era of COVID-19. Eur Rev Med Pharmacol Sci 2021; 25: 1752-1761.
2) Batzir NA, Tovin A, Hendel A. Therapeutic genome editing and its potential enhancement through CRISPR guide RNA and Cas9 modifications. Pediatr Endocrinol Rev 2017; 14: 353-363.
3) Marinelli S, Del Rio A. Beginning of life ethics at the dawn of a new era of genome editing: are bioethical precepts and fast-evolving biotechnologies irreconcilable? Clin Ter 2020; 171: e407-e411.
4) Ayanoğlu FB, Elçin AE, Elçin YM. Bioethical issues in genome editing by CRISPR-Cas9 technology. Turk J Biol 2020; 44: 110-120.
5) Greene M, Master Z. Ethical issues of using CRISPR technologies for research on military enhancement. J Bioeth Inq 2018; 15: 327-335.
6) Savulescu J, Hemsley M, Newson A, Foddy B. Behavioural genetics: why eugenic selection is preferable to enhancement. J Appl Philos 2006; 23: 157-171.
7) Macpherson I, Roqué MV, Segarra I. Ethical challenges of germline genetic enhancement. Front Genet 2019; 10: 767.
8) Napoletano S, Del Rio A. Reproductive medicine between advancement and ethics. Clin Ter 2018; 169: e108-e109.
9) Pashkov V, Lyfar A. Assisted reproductive technologies: the problems of legal enforcement. Wiad Lek 2018; 71: 1066-1070.
10) Montanari Vergallo G, Zaami S, Bruti V, Signore F. How the legislation in medically assisted procreation has evolved in Italy. Med Law 2017; 36: 5-2.
11) So D, Kleiderman E, Touré SB, Joly Y. Disease resistance and the definition of genetic enhancement. Front Genet 2017; 8: 40.
12) Kanaris C. Foetal surgery and using in utero therapies to reduce the degree of disability after birth. Could it be morally defensible or even morally required? Med Health Care Philos 2017; 20: 131-146.
13) Hendriks S, Giesbertz NAA, Bredenoord AL, Repping S. Reasons for being in favour of or against genome modification: a survey of the Dutch general public. Hum Reprod Open 2018; 2018: hoy008.
14) Kumar P, Malik YS, Ganesh B, Rahangdale S, Saurabh S, Natesan S, Srivastava A, Sharun K, Yatoo MI, Tiwari R, Singh RK, Dhama K. CRISPR-Cas system: an approach with potentials for COVID-19 diagnosis and therapeutics. Front Cell Infect Microbiol 2020; 10: 576875.
15) Abbott TR, Dhamdhere G, Liu Y, Lin X, Goudy L, Zeng L, Chemparathy A, Chmura S, Heaton NS, Debs R, Pande T, Endy D, La Russa MF, Lewis DB, Qi LS. Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and Influenza. Cell 2020; 181: 865-876.e12.
16) Marinelli E, Busardò FP, Zaami S. Intensive and pharmacological care in times of COVID-19: A "special ethics" for emergency? BMC Med Ethics 2020; 21: 117.
17) Robert R, Kentish-Barnes N, Boyer A, Laurent A, Azoulay E, Reignier J. Ethical dilemmas due to the Covid-19 pandemic. Ann Intensive Care 2020; 10: 84.
18) Di Trana A, Carlier J, Berretta P, Zaami S, Ricci G. Consequences of COVID-19 lockdown on the misuse and marketing of addictive substances and new psychoactive substances. Front Psychiatry 2020; 11: 584462.
19) de Oliveira JC, Oliveira LC, Mathias C, Pedroso GA, Lemos DS, Salviano-Silva A, Jucoski TS, Lobo-Alves SC, Zambalde EP, Cipolla GA, Gradia DF. Long non-coding RNAs in cancer: another layer of complexity. J Gene Med 2019; 21: e3065.
20) Vallone C, Rigon G, Gulia C, Baffa A, Votino R, Morosetti G, Zaami S, Briganti V, Catania F, Gaffi M, Nucciotti R, Costantini FM, Piergentili R, Putignani L, Signore F. Non-coding RNAs and endometrial cancer. Genes (Basel) 2018; 9: 187.
21) Azangou-Khyavy M, Ghasemi M, Khanali J, Boroomand-Saboor M, Jamalkhah M, Soleimani M, Kiani J. CRISPR/Cas: from tumor gene editing to T cell-based immunotherapy of cancer. Front Immunol 2020; 11: 2062.
22) Hirakawa MP, Krishnakumar R, Timlin JA, Carney JP, Butler KS. Gene editing and CRISPR in the clinic: current and future perspectives. Biosci Rep 2020; 40: BSR20200127.

23) Zhang X, Cheng C, Sun W, Wang H. Engineering T cells using CRISPR/Cas9 for cancer therapy. Methods Mol Biol 2020; 2115: 419-433.

24) Akram F, Ikram Ul Haq, Ahmed Z, Khan H, Ali MS. CRISPR-Cas9, a promising therapeutic tool for cancer therapy: A Review. Protein Pept Lett. 2020; 27: 931-944.

25) Miri SM, Tafsiri E, Cho WCS, Ghaemi A. CRISPR-Cas, a robust gene-editing technology in the era of modern cancer immunotherapy. Cancer Cell Int. 2020 Sep 15; 20: 456. doi: 10.1186/s12935-020-01546-8. Erratum in: Cancer Cell Int. 2020; 20: 521.

26) Singh N, Shi J, June CH, Ruella M. Genome-editing technologies in adoptive T cell immunotherapy for cancer. Curr Hematol Malig Rep 2017; 12: 522-529.

27) Delaney JJ. Possible people, complaints, and the distinction between genetic planning and genetic engineering. J Med Ethics 2011; 37: 410-414.

28) Hendrix KS, Sturm LA, Zimet GD, Meslin EM. Ethics and childhood vaccination policy in the United States. Am J Public Health 2016; 106: 273-278.

A. Del Rio, F. Negro, F. Umani Ronchi

Department of Anatomical Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy