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Application of CRISPR–Cas in Ageing and Health Equity

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Abstract: The recent advances in CRISPR-Cas technology have shown great potential in tackling age-related diseases and pathologies. However, older people from disadvantaged groups are less likely to have access to this technology compared to those from the more advantaged background. In particular, research shows that older people from certain minority groups may have concerns about participating in CRISPR-Cas-related research due to mistrust of this technology. This may lead to the underrepresentation of certain minority groups in the research, hence affecting the effectiveness of the CRISPR-Cas-related treatment. CRISPR-Cas may also have limited applications for the poor and those who live in less developed regions where this technology is either too expensive or not available. We urge governments to address the issue of equitable access to CRISPR-Cas technology by involving underrepresented groups in research, improving the ethical diversity in genomics databases, and reducing financial barriers to accessing the technology.

Keywords: CRISPR–Cas, Ageing, Health Equity, Accessibility.

Researchers have developed new gene therapies to help to slow down the ageing process or tackle age-related pathologies, such as neurodegenerative disorders, cancers, and other metabolic diseases. In particular, CRISPR–Cas (clustered regularly interspaced short palindromic repeats and CRISPR-associated genes), a potent gene-editing tool, has demonstrated the potential in correcting some of these ageing-related pathologies by ameliorating symptoms or curing diseases. Although advances in gene-based therapies and treatments provide opportunities for personalized medicine, disadvantaged older people may not benefit from these advances due to access barriers or affordability issues. The purpose of this paper is twofold: firstly, it seeks to provide a review of current applications of CRISPR–Cas in ageing; secondly, it discusses the potential issues in equitable access to this technology among older people.

One of the most common applications of CRISPR–Cas system is to treat age-related diseases. CRISPR–Cas works as a gene-editing tool in

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correcting gene-mediated age-related pathology, which can be used to delete target genes and correct gene mutations. Clinically it has been translated to medicines or therapies for Alzheimer's disease or other neurodegenerative diseases (Jo et al., 2015) and reducing gene-targeting inflammatory molecule production to treat metabolic or inflammatory diseases (Jing et al., 2015), and in some cases, treating cancer (Kim et al., 2017). Another application of the CRISPR-Cas9 system is to offer a new novel approach to understanding anti-ageing research on ageing-related genes and pathologies. For instance, researchers found that the CRISPR-Cas9 system contributes to identifying genes that could affect cellular senescence where cells cease multiplying but continue to trigger inflammation and induce cell death (Wang et al., 2021). Liu et al. (2019) used a CRISPR-Cas9–based screen to find several gene deficiencies connecting to cellular senescence bypass, and these associated genes could be used to initiate or facilitate senescence. CRISPR-Cas9 also works as a tool by allowing the manipulation of gene function and regulation in traditional models of ageing and informing research on ageing processes such as cellular senescence and telomeric attrition - the loss of protective caps of chromosomes (Haston, et al., 2020). The potential application of CRISPR-Cas in anti-ageing practice involves interventions in DNA repair pathways and the ageing process. Li, et al. (2020) found that CRISPR is able to allow the correction of anomalous genetic functions, which may allow people to age without significant decreases in quality of life (Adli, 2018). Wang et al. (2021) found that genome-editing therapy using the CRISPR-Cas9 system offers a new approach to slow the progression of ageing. Hutchinson-Gilford progeria, a genetic disorder, provides an ideal ageing model for researchers to target molecular drivers of ageing (Salk Institute, 2019). Beyret et al. (2019) successfully developed a CRISPR/Cas9 genome-editing therapy to decelerate the process of ageing among progeria mice. These technological breakthroughs shed light on seeking new interventions to suppress ageing progress for human beings.

Although CRISPR-Cas9 can potentially benefit all communities, a number of barriers to equitable participation in and benefit from this technology exist. First, minority groups have barriers to equal participation in research. Racial and ethnic minorities and disabled people may have experienced unequal treatment in research and received inferior care (Benz, et al., 2011). This may be worse among older people due to potential functional decline and low motivation for participating in research. The disadvantaged groups may have concerns about the potential misuse of this technology in genetic enhancement to further increase health disparities and unjust resource allocation (Hildebrandt and Marron, 2018). The mistrust of research among older or minority populations may lead to an underrepresentation of certain minority groups in genomics databases. An example of this lack of diversity of populations is the Genome-wide

Association Studies Catalogue where the African respondents only represent 3 per cent of the total sample (Popejoy and Fullerton, 2016).

Second, if the underrepresented population becomes an issue in genomic research, the lack of ethnically diverse groups in datasets may also impede scientists' capacities to understand the full genetic diversity spectrum, which may hamstring clinical care (Sirugo, et al., 2019). Considering the genetic differences, the gene therapy treatment, which is yielded from datasets lacking ethnic diversity, may be less effective, or even unsafe for certain populations (Popejoy and Fullerton, 2016). Likewise, it may also result in a higher risk of misunderstanding genetic variations and misdiagnosis for certain groups. This is exemplified by the mistakes in classifying benign hypertrophic cardiomyopathy variants as pathogenic among black Americans (Manrai et al., 2016). There are also significant racial differences in hypertrophic cardiomyopathy variants (Torii et al., 2017). Involving more ethical populations in these studies would prevent this misclassification and these misclassification reports highlight the need for sequencing populations across multiple ancestry backgrounds (Manrai et al., 2016).

Third, there could also be potential inequalities in terms of the affordability of this technology among older people. The costs for gene medicine or therapies can be hefty for ordinary people when the technology becomes commercially available because older people often have greater health and long-term care needs but are also poorer due to being over the working age (Abdi, et al., 2020). This issue may be even more pronounced among those older people from low- and middle-income countries or living in rural areas where such technologies may not be available or are less developed. (Etieyibo, 2012).

To sum up, in order to ensure equable access to the application of CRISPR–Cas, it is imperative to involve underrepresented groups in the research, improve the ethical diversity in genomics databases, and to reduce financial barriers to accessing the technology locally and globally. We also urge governments to take actions to address equity issues by establishing a sound, ethical, and equitable governance system of this technology (World Health Organization, 2022).

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