Making CRISPR hype more of a reality

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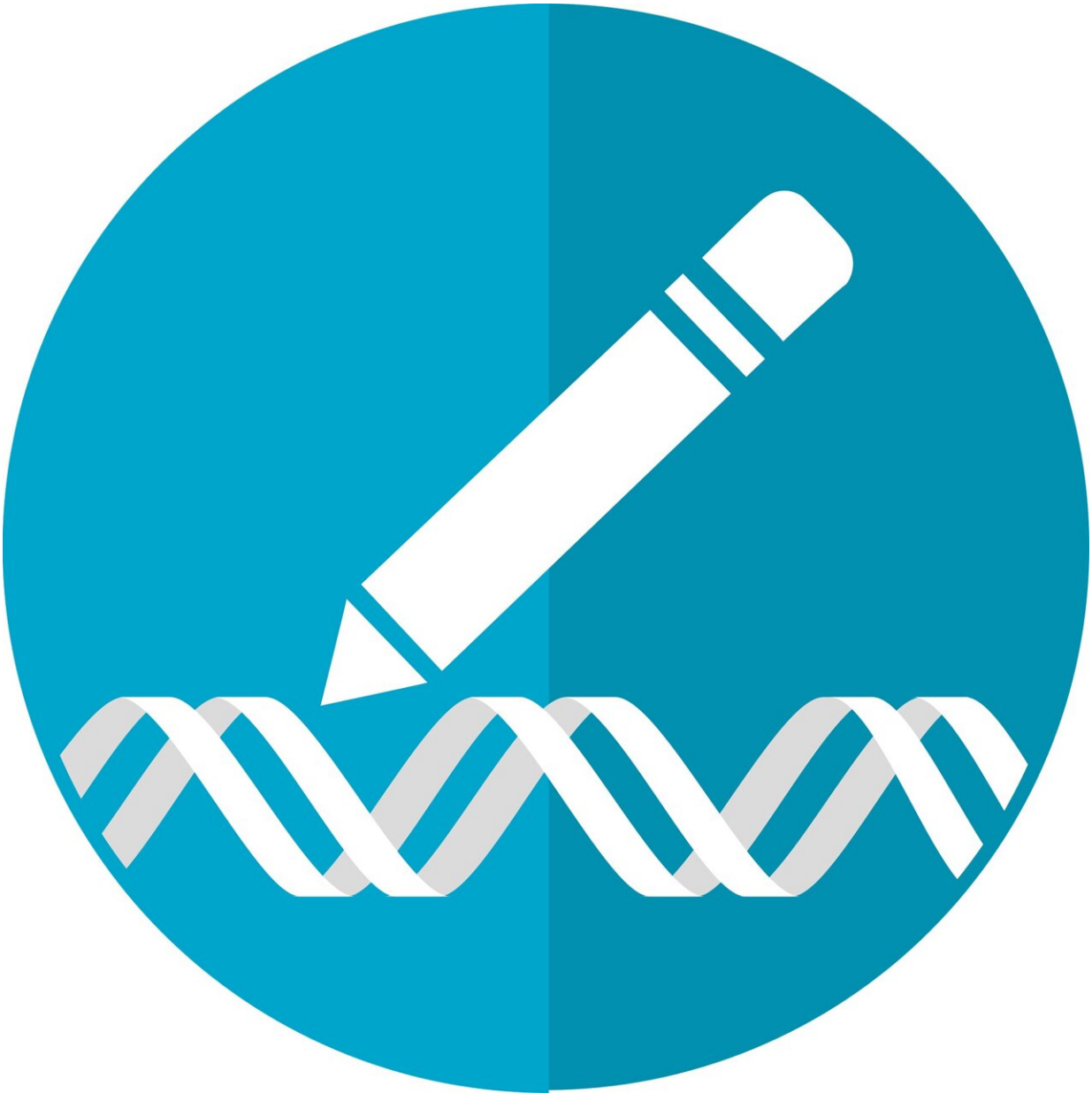

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This year, we celebrate 10 years of genome editing with CRISPR. The system is often referred to as molecular scissors, and this designation is quite accurate for its first applications. These short 10 years were marked by stunningly swift development and a great promise to cure thousands of genetic diseases with relative ease—with a single treatment dose that specifically corrects disease-causing DNA mutations in the body's cells. Sickle cell anemia and muscular dystrophy are two such diseases. And indeed, a decade later, we are now delivering on that promise in the form of many therapies currently being tested in human clinical trials.

Parallel to the development of the first such therapies, scientists have further evolved genome editing technologies. Recently developed molecular CRISPR tools have little in common with molecular scissors and are poised to make medical applications even safer.

Let's take a brief look back: "first generation" CRISPR genetic scissors dock at specific sites in the genome and cut the DNA molecule. The cell generates short, arbitrary mutations at the break site to, for example, disrupt gene function. However, unintended genetic alterations to the cell are possible, and the scope of diseases treatable with this methodology are relatively small. An ill-intended cut in the genome might manifest itself as a trigger for cancer decades later. Additionally, these scissors cause DNA damage, and such damage is inherently toxic and potentially lethal for cells. Stem cells, a primary target for clinical uses of CRISPR, react particularly sensitively to DNA damage.

A broad application of this first generation of CRISPR in humans is therefore not entirely risk-free. This is also a major reason why scientists have developed molecular tools to generate genomic modifications without using scissors.

In the past few years, researchers across the globe have developed a host of such "next generation" CRISPR technologies. A more appropriate analogy for these innovative systems would that be of a molecular taxi. Such platforms can be used to shuttle, for example, specialized proteins to specific destinations in the genome. These proteins can directly change the DNA code without the same deleterious consequences caused by scissors.

Reduced toxicity

Not only does this approach reduce toxicity for cells, but it also vastly expands the range of treatable genetic diseases. Instead of simply cutting a gene to render it non-functional, these CRISPR genome editors1 can be used to correct individual genetic mutations to restore gene function. It is estimated that more than 100,000 DNA mutations in our genome cause disease, a vast majority of which could be treated with such new technologies.

Next generation genome editing systems are expected to be used in human trials for the first time later this year. An American biotech company recently received approval to begin human trials to cure sickle cell disease and beta-thalassemia.2 Treatments for high cholesterol and a form of blindness are also on the verge of moving into humans as well, not to mention the plethora of projects to treat a range of genetic disorders that are currently being tested in animals and could one day benefit humans. In all cases, these diseases can be cured by reverting the mutated genetic code back to the "normal" sequence, reversions which were not possible with the traditional CRISPR scissor-based approach.

One-time therapy

CRISPR-based technologies have an enormous upside. Today, patients

suffering from hemophilia need multiple infusions per week. A CRISPR treatment, on the other hand, would ideally take place once, and the cells modified with CRISPR would persist for the rest of the patient's life.

This also means, however, that once the treatment has been started, it can no longer be discontinued. But would you choose a treatment where you can never stop taking the drug? This question arises with CRISPR-based therapies.

Safety concerns about unintended editing have mostly, but not entirely, been alleviated with next generation CRISPR molecular taxis. It must be stressed that the first generation treatments currently being clinically tested have underwent extensive studies to determine and limit detrimental effects. Nevertheless, the safety of CRISPR-based systems must be kept in mind. It is important that the long-term safety profiles of CRISPR technologies are established, and therefore I expect the first CRISPR-treated patients will be monitored for life.

A cure for previously uncurable diseases

Given all the safety considerations, one must also consider the therapeutic alternatives. Take progeria for example, a genetic disease in which children rapidly age and medication only exists to marginally extend lifespan. A next generation CRISPR technology currently under development has the potential to revolutionize progeria therapy: it doubled the lifespan in mouse models. For a fatal disease like progeria, for which there is no or inadequate therapy, many patients are likely to opt for a CRISPR treatment, even if there is some residual risk of potentially negative outcomes in the long term.

The speed at which CRISPR technologies have advanced over the past decade has been tremendous. Regulatory agencies, which are required to assess the safety of these technologies, have sometimes failed to keep up

with this pace. Urgently needed guidelines for the approval of the new technologies are not yet mature. This must change. There is a great need for action on the part of the regulatory authorities.

The first decade of CRISPR has brought immense potential, rapid technological development, and the first patients treated. As we look to the next 10 years, both first and next generation CRISPR systems are poised to deliver on its potential and provide life-long cures to patients of both rare and more common genetic disorders.

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