Podcast Episode 9: Current status of gene therapy in regenerative medicine

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Teaser

Hey everyone! Welcome to the new episode of the Life Extension Podcast – technology & magic, society & business. In the traditional medical system we take pharmacological drugs against diseases, drugs which improve symptoms, but don't heal. This is going to change through regenerative medicines, of which gene therapy is an important part. You should continue listening to this short episode, if you want to be informed about the promises and current status of gene therapies. I will mention the newest technological breakthroughs, incl CAR-T cell treatment against cancer, the CRISPR/Cas9 gene editing tool, and the gene delivery system through genetically engineered viruses. I will compare business models of traditional big Pharma and regenerative medicine, and I will touch on impacts on the public health system. Last I will point out the role of magical beliefs in an area so much determined by psychological drives of aging people on the one side, and mystifying expert knowledge on the other side.

Introduction

This episode is about the current status of gene therapies in regenerative medicine. Gene therapy is the transfer of genetic materials into a patient's cells or into cell cultures in the laboratory, in order to manipulate gene expression. Gene therapy acts by deactivating or replacing defective genes, or by adding new genes to treat a disease.

The original focus of gene therapy was on the treatment of inherited disorders such as sickle cell anaemia and hemophilia, or rare disease conditions which were considered easy targets. But the field has now increasingly shifted to the enormous future market of regenerative medicine. Together with stem cell therapies, gene therapies promise to cure age-related diseases, such as cancer, cardiovascular disease, renal disease, neurodegenerative diseases, etc, all being chronical diseases which so far were deemed to be not curable. They are also those disease conditions most people die of. As such diseases are part of the natural aging process, gene therapy together with cell therapy are at the moment our best chance not only to treat the most common diseases but to actually live longer.

Only three gene therapy products have been approved by FDA and EMA (FDA 2021, Cynober 2020), all of them very recently. Among them Yescarta by Gilead Science and Kymriah by Novartis are both treating leukemia and were developed based on the new CAR-T cell technology, which I will explain further down.

The third approved gene therapy product is Luxturna by Spark Therapeutics. It treats retina dystrophy, a condition leading to vision loss, which is caused by a hereditary genetic mutation. This gene therapy delivers a normal copy of a faulty gene to retinal cells through a virus vector. Retinal cells then start to produce a missing protein, ultimately leading to restored vision.

These newly approved gene therapies are just the beginning of an expected flow of new gene therapy products. Until then many clinical trials of gene therapies are ongoing, however, and some patients have the opportunity to enroll in those trials already.

Technologies/tools

There are three new technologies I want to point out, helping us to understand the current status of gene therapies. Among them the gene-editing tool Crispr/Cas9, the gene delivery system through vectors, and CAR-T cells.

The Crispr/Cas9 gene editing tool provides precision and speed to gene editing. CRISPR is part of the immune system of bacteria to protect them against viral infections. It has the capability to identify and break specific areas in the genome. This system is being used by scientists together with the Cas9 enzyme to precisely identify and edit areas in the DNA. As an example, using that method scientists were able to screen thousands of human genes for their contribution to cellular senescence, and then succeeded to identify one of them, kat7, as a likely candidate for causing aging. After inactivating that same gene in mice cells, it was found that mice experienced 25% longer life spans (Pollard 2021). In another example, Crispr/Cas9 was successfully infused into a monkey designed to deactivate a single gene causing high LDL cholesterol (Musunuru et al 2021). Experiments such as this show the capability of the gene editing tool, but also that for itself it is not the solution yet. Many more insights into interconnected molecular pathways in the cell need to be gained before mechanisms are really understood and therapy against aging could be envisaged.

Next to gene editing, gene delivery technology is crucial for successful gene therapy. Altered genes are transferred into targeted tissue cells trough a vector, a sort of carrying vessel capable to insert gene materials from the laboratory into host cells. Those vectors are in most cases genetically engineered viruses due to their natural ability to enter cells, as well as bacteria, or physical and chemical methods.

I also want to mention here CAR-T cell therapy, which is a newly developed technology with high promises for the treatment of cancer. A viral vector is genetically engineered to induce a patient's T-cells to build an antigen receptor. T-cells are such enabled to connect to targeted cancer cells and destroy them. Through this procedure T-cells are in fact being reprogrammed by adding genetic material from outside the patient's own DNA. That is why CAR is the abbreviation for chimeric antigen receptor. The beauty of this procedure is that one treatment should last forever, because the patient's immune system will remember that cancer type. CAR-T cell procedures however are not mature yet, as they still lead to serious side-effects, and a lot of work is currently focused on improving the method (Sterner 2021).

All of these new technologies are crucial to design gene therapies, but they are still just at the beginning of their development.

Gene-therapy based antiaging cocktails

Due to the interconnected nature of age-related diseases, it became clear that gene therapy for a single disease condition does often not result in a better outlook for health span. Antiaging gene therapies for simultaneous treatment of several age-related diseases has therefore been tested on mouse models. Researchers found that the administration of several gene treatments within one single formulation was able to create synergies by treating a variety of age-related diseases at the same time, such as obesity, type 2 diabetes, renal failure, and heart failure (Davidsohn 2020). Aim of this type of research is to develop antiaging cocktails based on gene therapy treating several disease conditions at the same time. However, interconnectedness of disease conditions and multiple gene pathways involved makes an understanding of precise molecular mechanism even more complex, with potentially adverse effects on approval procedures through regulatory institutions.

Hopes & magic

Research in genetics and the development of gene therapies takes much more time than was originally expected, namely after the human genome was decoded in the year 2000. During the last 2 decades we have learned that genetic mechanisms are more complex than thought. Taking into account the enormous expectations scientists and businesses are putting into gene therapies, not that much has been achieved so far (Mackenzie 2021). No wonder then that players in the industry as well as potential users are becoming impatient. Hopes for gene therapies as a solution for uncurable diseases is getting sky high, which creates favourable market conditions for magic pills. As a result, any research result on the treatment of aging not totally negative is often being transformed to very positive and amplified by public media, often supported by business interests, to satisfy expectations of the audience.

In this way the identification of a gene which seems in some way to be more related to the aging process than other genes is immediately interpreted as a therapeutic possibility to delay aging. No questions are asked why that gene exists in the DNA in the first place, and if it may not have other important functions as well, making its deletion perhaps an unwise proposition. The complexities are left to the scientists, while the consumer is happy with the magical outlook on a longer life in the future.

The US company Libella Therapeutics recently made headlines in professional circles due to an innovative approach, offering pay and play participation to enrol in a clinical trial involving the lengthening of telomeres in human chromosomes, while promising to reverse aging by 20 years. Identical trials were announced to be conducted to test the therapy on Alzheimer and on critical limb ischemia. The location of the trial is Columbia, outside of jurisdiction of the FDA, and the price tag for enrolment is USD 1mil. Clear purpose was to avoid strict regulation of FDA and to fund the clinical trial. Results are not published yet (Libella 2019; NIH Clinical trials). This approach has been criticized by some for the reason of avoiding the FDA and the unusual fee (Linese unknown date). But more importantly, the claim that increasing telomere length will lead to slower aging, has been contested (Kuo et al 2019). But again, people with high hopes and little time can always be found to participate.

Recently the FDA published a warning against self-administration of gene therapies by using do-it-yourself kits available in the illegal market (FDA 2017). Apparently, sellers of these kits are promising, and buyers are desiring magic of some kind, based on hope, but without much understanding of what gene therapy is actually doing.

Market/business

Gene therapy as part of the field of regenerative medicine is just at the beginning. Traditional pharmaceutical companies don't seem to be highly involved yet, however, although big pharma's business model of developing chemical drugs fighting disease symptoms is threatened to become ultimately replaced by regenerative medicine, which promises to actually heal diseases. So far traditional pharmacological approaches to slow down aging are still being undertaken by many players in the pharmaceutical industry, although efficacy appears doubtful (Magalhaes 2017). While important growth in the gene therapy market is predicted, big pharma is entering the market selectively through inorganic strategic acquisitions (Parada 2020). The problem of conventional pharmaceutical companies is that their value chains differ in important ways from regenerative medicine. This starts with approval procedures and the protection of intellectual property rights, which are still in the process of social negotiation. Safety and efficacy, but also ethical concerns, and the fundamental question, if a genetic

product can be protected at all, stand at the forefront of the discussion. Recently, Novartis was forced by NGOs to withdraw a European patent application for Kymriah, because CAR T-cell treatments could be considered a medical procedure, and not a drug (Doctors of the World 2019). Furthermore, the development of gene and cell therapies are more complex than of chemical drugs and carry more financial risks. And last, conventional drugs are manufactured, sold, transported, stored, and administered as discreet products. Gene therapies on the other hand are more like protocols involving clinical facilities and laboratories near each patient. Pharmaceutical companies may be forced to change their business models if they want to switch from conventional drugs to regenerative medicine. Another important issue to be solved before gene treatments will be made available to patients is the reimbursement through the healthcare system (Neis-Beeckmann 2018). The question of how much society is ultimately prepared to pay for increased longevity of individual members has been hardly discussed in public. Costs of the health care system in industrial countries are already spiraling due to their aging populations. We don't know yet, if regenerative medicine is leading to further cost increases, or possibly to reductions, as claimed by Aubrey de Grey among other transhumanists.

Conclusion for the patient/consumer

Gene therapy, often together with cell therapy, has huge potential to prolong life span and reduce suffering from age-related diseases. For most people, this is probably the best bet to delay their own death in comfort. Unfortunately, progress to deliver such therapies to patients is often not fast enough, although this inconvenient truth is often being deliberately mystified by industry players looking for fresh funding. Molecular mechanisms in cells are highly complex, making the design of gene therapies complicated. Scientists also need to further optimize tools and treatment protocols. Then clinical trials and regulatory approval add many years of work. Even when a therapy is finally safe, effective, approved, and negotiated with health insurance providers, roll-out to patients via medical clinics will take even more time. People who are running out of time sometimes need to make a hard decision: accept the fate that we all must die anyway, or look out for opportunities to gain access to unproven, early-stage therapies. In case you had to choose, what would you do?

The attraction of magic is greatest in times of disruption – and which disruption could be more significant than facing death or cognitive decay. The magic potion thrives in the space between our inner drives of fear and greed. People who are resigned to the fact of aging and dying will rather try to cultivate a perspective of wisdom, somehow pretending to turn a bad into a good thing. Others may however be attracted by magical promises. As we know by now, science and magic are not that different, but it is still important to select carefully and avoid the charlatans.

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