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The Danger of False Promises and Hopes in the New Age of Science: The Case of Gene and Cell Therapy

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Abstract

A broad palette of proposals aiming at therapeutic gene manipulation and stem-cell therapy have been made until now, but approved applications are still scarce in numbers, especially when compared to the number of resources invested. Also, risky interventions get to be conducted relying solely upon expert opinion and patient agreement. The lay public is generally benevolent towards novel medical biotechnologies. However, exaggerated promises and involving human subjects in unreliable research protocols might erode people's trust, while being open and honest about the eventual imperfections and complications of scientific work should maintain the public's appreciation and attract long-term support.

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THE DANGER OF FALSE PROMISES AND HOPES IN THE NEW AGE OF SCIENCE: THE CASE OF GENE AND CELL THERAPY

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INTRODUCTION

The field of modern medical biotechnologies developed rapidly in terms of gaining attention and support, as well as in producing scientific literature and generating ethical debates. Also, a lot of valuable applications were established. Still, many medical tools that were initially acclaimed as most promising seem to have trouble in finding their way into the real world. Gene and cell therapy represent some of the most prominent examples. Decades of investments and efforts have resulted in few clinical applications, some of them ephemeral, so that in spite of the enthusiastic discourses still present in the public and academic media we got to a point where the “promises and hurdles” of these fields might seem totally imbalanced.

GENE AND CELL THERAPY IN THE REAL WORLD

During the last few decades, therapeutic gene manipulation has been suggested for and attempted to various extents in cancer, several types of immunodeficiencies, Alzheimer, Parkinson and Huntington diseases, muscular spinal atrophy, cystic fibrosis, retinopathies, as well as diabetes, cardiac failure, and others. Stem-cell therapy was also proposed for a

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wide range of conditions, many of them common with gene therapy targets.

In gene therapy, nucleic acids are introduced into the organism in order to prevent or treat a disease. They enter the cells by means of a carrier that is either a vector derived from a virus (lentivirus, poxvirus, adenovirus, adeno-associated virus, retrovirus, human foamy virus, herpes virus a. o.) or one of the molecular complexes or polymers proposed for use in gene therapy (e. g. liposomes, chitosan derivatives, poly(L-lysine), poly(ethylenimine) derivatives a. o.).² In order to obtain significant results, a substantial distribution of the delivered gene and persistence of its functioning should be ensured, which is very difficult as many gene carriers do not travel adequately through tissues and are subsequently lost. Also, they are not welcomed by the immune system, nor are the transgene or its product. Another significant problem is the risk of insertional mutagenesis posed by certain classes of carriers. The highly risky side of gene therapy research was tragically illustrated by the death of Jesse Gelsinger (1999) due to a violent systemic inflammatory response to the administered vector,³ and the development of leukemia in four out of nine children treated for SCID (2003).⁴ Improvements in vector design led to some better results,⁵ but the difficulties are far from being overcome.

It was said that gene therapy had traversed a “hype cycle,” comprising the over-enthusiasm elicited by its potential, the despair generated by its serious side-effects and the realism attached to improvements that might lead to success; it was also said that it might get again into another comparable sequence of events.⁶ Indeed, the development of gene editing techniques stormed the enthusiasm of researchers. However, the supposedly revolutionary DNA modifying CRISPR-Cas 9 system and its

² Y. K. Sung and S. W. Kim, “Recent advances in the development of gene delivery systems,” *Biomaterials Research* 12 (2019): 23-28.

³ S. E. Raper et al., “Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer,” *Molecular Genetics Metabolism* 80 (2003): 148–158.

⁴ M. P. McCormack and T. H. Rabbitts, “Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency,” *The New England Journal of Medicine* 350 (2004): 913–922.

⁵ C. E. Dunbar et al., “Gene therapy comes of age,” *Science* 359 (2018): 1-10.

⁶ W. F. Kaemmerer, “How will the field of gene therapy survive its success?” *Bioengineering & Translational Medicine* 3 (2018): 166–177.

derivatives also pose lots of problems. The drawbacks of Cas 9 employment are significant – difficulties related to delivery into the cell, low efficiency of the enzyme itself and of the cellular repair processes,⁷ toxicity mediated via a p53 mechanism,⁸ and the completely undesirable capacity of the enzyme to induce unintended modifications in the DNA not only by off-target effects but also through its on-target activity.⁹ Other tools considered promising, the CRISPR-Cas derived cytosine base editors (CBEs) were shown to induce a high rate of off-target modifications in mouse models,¹⁰ as well as off-target DNA edits and extensive transcriptome-wide RNA cytosine deamination in human cells, generating missense, nonsense, splice site, 5' UTR, and 3' UTR mutations, effects that their discoverers tried to alleviate by further engineering of the CBE.¹¹ In short, all the examined molecular editors generate unintended, potentially dangerous modifications into the DNA, and other side effects.

Stem cells are able to differentiate into various types of cells and, for therapeutic purposes, they are supposed to be transplanted into the diseased organism. The undesirable aspects of their employment are linked to immune rejection, the risk of tumor development due to incomplete reprogramming in the cell population, difficulties in tissue targeting, retention and functional integration.¹² Human embryonic stem cells are also subject to intense ethical debates, as their obtainment requires the destruction of the embryos. The development of induced pluripotent stem cells (iPS), i.e. cells from adult sources that are re-programmed into an embryonic-like state, was regarded as a significant

⁷ W. J. Dai et al., “CRISPR-Cas9 for *in vivo* gene therapy: promise and hurdles,” *Molecular Therapy—Nucleic Acids* 5 (2016): 1-4.

⁸ R. J. Ihry et al., “p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells,” *Nature Medicine* 24 (2018): 939-946.

⁹ M. Kosicki, K. Tomberg, and A. Bradley. “Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements,” *Nature Biotechnology* 36 (2018): 765-771.

¹⁰ E. Zuo et al., “Cytosine base editor generates substantial off-target single-nucleotide variants in mouse embryos,” *Science* 364 (2019): 289-292.

¹¹ J. Grünwald et al., “Transcriptome-wide off-target RNA editing induced by CRISPR-guided DNA base editors,” *Nature* 568 (2019): 433-453.

¹² G. Cossu et al., “Lancet Commission: Stem cells and regenerative medicine,” *Lancet* 391 (2018): 883-910.

step in the field¹³ and elicited over-enthusiasm, unfortunately not supported by the subsequent results.

Ex-vivo gene therapy that combines gene and cell therapy by using autologous genetically modified cells might represent a better approach and seems to have been successfully applied in treating some maladies.

The first gene therapy product ever marketed was Gendicine®, a vector bearing the gene encoding for the p53 tumour-suppressor. It received the Chinese authorities' endorsement in 2003 and it is, together with Oncorine®, another Chinese gene therapy drug, pretty controversial.¹⁴

In the USA, the Federal Drug Agency (FDA) has a current (as of 2019) number of seventeen “cellular and gene therapy products” approved.¹⁵

About half of them are cord blood preparations containing hematopoietic progenitor cells, a “classic” in cell therapy, further improved. As for the other products, MACI® (2016) is a scaffold type product bearing autologous cells, intended for the repair of cartilage defects of the knee¹⁶; GINTUIT® is another cellularized scaffold product, designed for topical oral use¹⁷; PROVENGE® (2010) is to be prepared with autologous CD54+ cells, activated, being advised as immunotherapy for metastatic prostate cancer¹⁸; LAVIV® (2018) is an autologous cell preparation advised for nasolabial fold wrinkles.¹⁹ Two products make use of genetically modified cells – KYMRIA® (2017) is to be prepared from CD-19-directed genetically modified autologous T-cells and is

¹³ H. Inoue et al., “iPS cells: a game changer for future medicine.” *The EMBO Journal* 33 (2014): 409-417.

¹⁴ G. Ma et al., “Gene medicine for cancer treatment: commercially available medicine and accumulated clinical data in China”. *Drug design, Development and Therapy*, 2 (2009): 115–122.

¹⁵ FDA. *Approved Cellular and Gene Therapy Products* <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products> (accessed September 29, 2019).

¹⁶ FDA. *Package Insert, MACI®* www.fda.gov/media/101914/download (accessed September 29, 2019).

¹⁷ FDA. *Package Insert GINTUIT*, www.fda.gov/media/83264/download (accessed September 29, 2019).

¹⁸ FDA. *Package Insert and Patient Information PROVENGE®*, www.fda.gov/media/78511/download (accessed September 29, 2019).

¹⁹ FDA. *Package Insert and Patient Information Sheet, LAVIV®* www.fda.gov/media/80838/download (accessed September 29, 2019).

recommended for the treatment of certain types of leukemia and lymphoma, refractory or relapsed²⁰; YESCARTA® (2017) is also an autologous genetically modified T cells-based therapeutic product for lymphoma.²¹ Three other products consist in gene therapies: IMLYGIC® (initially approved in 2015) contains a genetically modified virus used for local therapy in recurrent melanoma²²; LUXTURNA® (2017) is a gene therapy product employing an adeno-associated virus vector designed for the treatment of retinal dystrophy due to a biallelic RPE65 mutation, bearing a warning for serious adverse effects such as cataract, retinal tear, and maculopathy²³; ZOLGENSMA® (2019) uses an adeno-associated virus vector for the treatment of spinal muscular atrophy with bi-allelic mutations in the SMN1 gene and it bears a warning of acute serious liver injury as well as the mention that its safety and effectiveness in the case of repeat administration have not been evaluated.²⁴

In Europe, medicines based on genes, tissue or cells are named “advanced therapy medicinal products (AMTPs)” and have to be approved by The European Medicines Agency (EMA). So far, the EMA has approved ten products, out of which four have already been withdrawn. The cell therapies in use comprise Alofisel® (2018), that contains allogeneic mesenchymal adult stem cells and is recommended for perianal fistulas²⁵; Spherox® (2017), a preparation of expanded autologous chondrocytes and self-synthesized extracellular matrix advised for articular cartilage defects²⁶; Holoclar® (2015), employed in ocular burns, that contains autologous corneal epithelial cells expanded

²⁰ FDA. *Package Insert, KYMRLAH™* <https://www.fda.gov/media/107296/download> (accessed September 29, 2019).

²¹ FDA. *Package Insert YESCARTA™* <https://www.fda.gov/media/108377/download> (accessed September 29, 2019).

²² FDA. *Package Insert IMLYGIC* <https://www.fda.gov/media/94129/download> (accessed September 29, 2019).

²³ FDA. *Package insert LUXTURNA* <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna> (accessed September 29, 2019).

²⁴ FDA. *Package Insert ZOLGENSMA®* <https://www.fda.gov/media/126109/download> (accessed September 29, 2019).

²⁵ EMA. *Product information Alofisel* https://www.ema.europa.eu/en/documents/product-information/alofisel-epar-product-information_en.pdf (accessed September 29, 2019).

²⁶ EMA. *Product information Spherox* www.ema.europa.eu/en/documents/product-information/spherox-epar-product-information_en.pdf (accessed September 29, 2019).

*ex vivo*²⁷. Genetically modified preparations in use include Strimvelis[®], Zalmoxis[®] and Imlygic[®]. Strimvelis (2016) is a preparation of autologous CD34⁺ cells modified with a retroviral vector containing the human ADA cDNA sequence designed for the treatment of the severe combined immunodeficiency ADA-SCID; it exhibits as adverse effects a series of autoimmune disorders.²⁸ Zalmoxis (2016) is prepared from allogeneic T cells genetically modified with a retroviral vector encoding for two genes of interest and is recommended as adjunctive treatment in haploidentical hematopoietic stem cell transplantation in patients with blood cancer. Zalmoxis has notable adverse effects such as neoplasm, immune system disorders, and hepatic failure.²⁹ Glybera[®] (alipogene tiparvec), known as the most expensive drug in the world, left the market in 2017, after five years from the initial approval. Glybera was a complex product, containing a human gene (LPL, encoding for lipoprotein lipase), packed into a chimeric vector derived from adeno-associated virus serotype 1, bearing the cytomegalovirus (CMV) promoter, a hepatitis virus posttranscriptional regulatory element and some adeno-associated virus serotype 2 derived inverted terminal repeat.³⁰ ChondroCelect[®] (2009), an autologous cell preparation advised for cartilage repair, is another product that is no longer authorized, as requested by the marketing authorisation holder.³¹ So is Provenge[®]³², while the authorisation of Maci expired following the holder's decision not to pursue its renewal.³³

Some oligonucleotidic preparations were also approved either by the FDA or by the FDA and the EMA, but they had a complicated market route and/or significant side effects, which made them not very attractive, with the possible exception of Spinraza[®], developed for spinal

²⁷ EMA. *Product information Holoclar*, www.ema.europa.eu/en/documents/product-information/holoclar-epar-product-information_en.pdf (accessed September 29, 2019).

²⁸ EMA. *Product information Strimvelis*, www.ema.europa.eu/en/documents/product-information/stirimvelis-epar-product-information_en.pdf (accessed Sept. 29, 2019).

²⁹ EMA. *Product information Zalmoxis*, www.ema.europa.eu/en/documents/product-information/zalmoxis-epar-product-information_en.pdf (accessed September 29, 2019).

³⁰ EMA. *Product information Glybera*, www.ema.europa.eu/en/documents/product-information/glybera-epar-product-information_en.pdf (accessed September 29, 2019).

³¹ EMA. *ChondroCelect*, www.ema.europa.eu/en/medicines/human/EPAR/chondrocelect (accessed September 29, 2019).

³² EMA. *Provenge*, www.ema.europa.eu/en/medicines/human/EPAR/provenge,

³³ EMA. *Maci*, www.ema.europa.eu/en/medicines/human/EPAR/maci (accessed September 29, 2019).

muscular atrophy.³⁴ Other products were approved in the Philippines (Rexin-G[®], an antitumoral), and Russia (Neovasculgen[®], for arterial diseases).³⁵

THE DANGER OF FALSE PROMISES AND HOPES

The biological hurdles in gene and cell therapies were presented above on the short. Also, a series of practical issues interfere with cell and gene therapy products manufacturing – their development is difficult, requiring an unusual trial design, the production process and the quality control are highly demanding, regulations are complex and may vary across countries, and some developers, as well as the insurance companies, feel that reimbursement might represent a serious challenge.³⁶

Unfortunately, over-enthusiasm led to less accuracy in experimentation so that now, as some authors put it, “The literature is replete with instances of therapeutic interventions pursued on the basis of expert opinion and patient acceptance that ultimately proved ineffective or harmful when studied in well-controlled trials comparing them with the standard of care.”³⁷ And, in spite of all evidence and signaled dangers, exaggerated optimism persists. In a comprehensive review from 2015, Trounson and McDonald expressed their confidence that there will be “many stem cell products that will meet the criteria for registered products in the established regulatory systems over the next 5 years”³⁸ – even though the paper listed lots of running experiments, trials

³⁴ C. A. Stein and D. Castanotto, “FDA-Approved oligonucleotide therapies in 2017,” *Molecular Therapy* 25 (2017): 1069-1075.

³⁵ R. Goswami et al., “Gene therapy leaves a vicious cycle,” *Frontiers in Oncology* 9 (2019): 1-25.

³⁶ W. F. Kaemmerer, “How will the field of gene therapy survive its success?” *Bioengineering & Translational Medicine* 3 (2018): 166–177. M. T. R. ten Ham et al., “Challenges in advanced therapy medicinal product development: A survey among companies in Europe,” *Molecular Therapy: Methods & Clinical Development* 11 (2018): 121-130. J. F. Barlow, M. Yang, and J. R. Teagarden, “Are payers ready, willing, and able to provide access to new durable gene therapies?” *Value in Health*; 22 (2019): 642–647. J. Spoor, E. Croft, and A. Walker, “Regeneration X: The payer perspective on gene therapy,” *British Journal of Healthcare Management*, 23 (2017): 158-166.

³⁷ P. W. Marks, C. M. Witten, and R. M. Califf, “Clarifying stem-cell therapy’s benefits and risks,” *The New England Journal of Medicine* 376 (2017): 1007-1009.

³⁸ A. Trounson and C. McDonald, “Stem Cell Therapies in Clinical Trials: Progress and Challenges,” *Cell Stem Cell* 17 (2015): 11-22.

involving only a handful of subjects from which even less experienced a positive outcome, not always stable, and other not too convincing examples of progress in stem cells research. Anyway, the fifth year has begun, and their optimism had not proven to be substantiated yet, whilst the only truly reliable application of cell therapy continues to be the long-established hematopoietic stem cell transplantation.

Inflated optimism regarding cell and gene therapies seems to be shared by some officials: “We anticipate that by 2020 we will be receiving more than 200 INDs³⁹ per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products.”⁴⁰ What does such a positive estimate rely upon? Around 2,900 gene therapy clinical trials were registered from 1989 till 2018.⁴¹ Still, as shown above, only a few products were approved for actual therapeutic use, with some of them rapidly leaving the market.

It is true that the industry has recently known a serious infusion of capital. Data collected by the Alliance for Regenerative Medicine show that in 2018 there were “906 Regenerative Medicine Companies worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers” – 484 based in North America, 241 in Europe and Israel, 142 in Asia and the remaining in Oceania and South America, with the total level of financing in the industry reaching 13.3 billion US dollars in 2018 (73% increase from 2017), from which 9.7 billion were invested in gene-based therapies (64% increase from the previous year).⁴²

³⁹ Investigational New Drug – the item described as such and also the procedure by which FDA allows an experimental drug to be shipped from state to state and used in clinical trials. See FDA. *Investigational New Drug (IND) Application* www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application (accessed Oct. 8, 2019).

⁴⁰ FDA, *Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies* www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics (accessed October 8, 2019).

⁴¹ Journal of Gene Medicine, Gene Therapy Clinical Trials Worldwide Provided by the Journal of Gene Medicine www.abedia.com/wiley/years.php (accessed October 8, 2019).

⁴² M. Ruffin and L. Scull, March 28, 2019, *Sector Overview. Gene Therapy for Rare Disorders*, ARM, 2019, https://alliancerm.org/wpcontent/uploads/2019/03/ARM-Gene-Therapy-for-Rare-Disorders_FINAL.pdf (accessed September 29, 2019).

Yet, this cannot account as a decisive indicator since some of the obstacles encountered by gene and cell therapy are intrinsic to how organisms are built, so that largely the same problems accompany their development despite decades of efforts.

In the US, where the majority of the polls have been conducted, the public is benevolent towards gene therapy, especially when intended for severe conditions, while people are ethically alert, wondering about properly informing the subjects, psychological and medical side effects, heritability of modifications, therapeutic applications versus enhancement, resource allocation and potential discrimination.⁴³ Mentioning risk in terms of potential negative side effects and the danger of eugenics to lay people asked about their opinion on CRISPR-Cas9 technology had an impact, but the respondents generally remained in favor of pursuing with research in the field⁴⁴. Therapeutic editing seems to be supported by the public, both in Europe and the US, while enhancement does not gain the same endorsement⁴⁵; also, interventions in adults are judged as more morally acceptable than interfering with the embryo or the germline.⁴⁶

Still, it seems that public support of genetic modifications in humans decreased over time,⁴⁷ a similar decline being noticed in Europe with respect to the use of biotechnologies, even if medical.⁴⁸ Could it be related to inappropriate discourse elements eroding people's trust, as "Overhyped promises and exaggerated predictions of the impacts of genetic engineering raised not only hopes, but also suspicion, concerns

⁴³ J. M. Robillard et al., "Prevailing public perceptions of the ethics of gene therapy," *Human Gene Therapy* 25 (2014): 1-7.

⁴⁴ S.M. Weisberg, D. Badgio, and A. Chatterjee, "A CRISPR New World: Attitudes in the Public toward Innovations in Human Genetic Modification," *Frontiers in Public Health* 5 (2017): 1-9.

⁴⁵ G. Gaskell et al., "Public views on gene editing and its uses," *Nature Biotechnology* 35 (2017): 1021-1023.

⁴⁶ R. J. Blendon, M. T. Gorski, and J. M. Benson, "The Public and the Gene-Editing Revolution," *The New England Journal of Medicine* 374 (2016): 1406-1411. D. A. Scheufele et al., "U.S. attitudes on human genome editing," *Science* 11 (2017): 553-554.

⁴⁷ L. Guertin, R McGuire, and A. Torres, "Public Perception of Human Applications of CRISPR Gene Editing," 2018, https://web.wpi.edu/Pubs/E-project/Available/E-project-042618-095556/unrestricted/CRISPR_full_draft.FINAL3.0.pdf (accessed September 29, 2019).

⁴⁸ G. Gaskell et al., "Biotechnology and the European public," *Nature Biotechnology* 18 (2000): 935-938.

and anxiety”⁴⁹? Or does the public feel not betrayed but just tired of vain promises? This remains to be established, especially as on the other hand certain data indicate that at least part of the public feels that there is a right to try unregulated therapies.⁵⁰ Speaking of this hypothetical right, it should be mentioned that in 2014 The European Court of Human Rights denied a citizen’s request to access on behalf of his daughter an unproven stem cell procedure, as it was revealed that the so-called “therapy” was not actually qualifying even for compassionate use, i.e. the use of an unapproved drug when there is no better alternative,⁵¹ which is worrisome, in the context when some countries have adopted Compassionate Use Programmes.⁵²

What should be done under the circumstances?

The 2018 Lancet Commission on stem cells and regenerative medicine underlines that “The current gap between public expectations and the realities of translating regenerative technologies threatens regenerative medicine’s social ‘license to operate’” and asks for stronger regulations, more rigorous publication policies and more responsibility for public dialogue on behalf of researchers and funders.⁵³

Scientists should try to communicate better with lay people as social partners entitled to information and decision, as some official documents have already stated.⁵⁴ There is a need for developing the required attitude and skills. Some studies revealed that with regard to advanced medical developments (such as stem cells research and the entire topic of regenerative medicine) the larger public has in mind specific concrete aspects pertaining to costs, risks, responsibility and liability, while scientists need to develop their awareness with respect to the same issues

⁴⁹ H. Gottweis, “Gene therapy and the public: a matter of trust,” *Gene Therapy* 9 (2002): 667.

⁵⁰ L. Riva et al., “Unproven stem cell therapies: is it my right to try?”, *Annali dell’Istituto Superiore di Sanità* 55 (2019): 179-185.

⁵¹ E. Rial-Sebbag and A. Blasimme, “The European Court of Human Rights ‘Ruling on Unproven Stem Cell Therapies: A Missed Opportunity?’” *Stem Cells and Development* 23 (2014): 39-43.

⁵² L. Riva et al., “Unproven stem cell therapies: is it my right to try?”, *Annali dell’Istituto Superiore di Sanità* 55 (2019): 179.

⁵³ G. Cossu et al., “Lancet Commission: Stem cells and regenerative medicine,” *Lancet* 391 (2018): 883-910.

⁵⁴ European Commission. *Science and Society Action Plan*, 2002. ec.europa.eu/research/swafs/pdf/pub_gender_equality/ss_ap_en.pdf (accessed Sept. 29, 2019). UNESCO. *Recommendation on Science and Scientific Researchers*, 2018. www.unesco.org/wp-content/uploads/2018/11/263618e.pdf (accessed Sept. 29, 2019).

and the social consequences of their work, in general, as well as their interest and availability for science communication, that should also be stimulated by the society.⁵⁵

In any case, exaggeration in assumptions about the potential of rising approaches in medicine should be avoided and the difficulties encountered honestly presented. Not only such an attitude should be ethically imperative, but it might have become a necessary safety measure. There is more than one sort of false promise and some are more dangerous than others.

CONCLUSIONS

In the field of gene and cells therapies, over-enthusiasm had some undesirable consequences. The potential benefits of such approaches were exaggerated and the necessary small steps procedures that incorporate the appropriate safety measures tend on occasions to be eluded. This might indeed threaten regenerative medicine's social "license to operate," as the 2018 Lancet Commission observed.

In the New Age of Science, scientists should be careful about promises and about inducing hopes, as false promises deceive, and false hopes might get to hurt people. Researchers should be permanently aware of the fact that certain developments exert a fascination that can make people vulnerable as it can be easily exploited by rogue scientists and/or other sorts of "confidence artists."

Being open and honest when communicating about the complications that accompany research in modern biotechnologies can maintain the public's appreciation and attract long-term support, while exaggerations and half-truths might exert the opposite effect.

⁵⁵ R. Shineha et al., "A Comparative Analysis of Attitudes on Communication toward Stem Cell Research and Regenerative Medicine between the Public and the Scientific Community," *Stem Cells Transl Med* 7 (2018): 251-257. R. Shineha et al., "Science communication in regenerative medicine: Implications for the role of academic society and science policy," *Regen Ther.* 7 (2017): 89-97.

REFERENCES

- Barlow, Jane F., and Mo Yang, J. Russell Teagarden. "Are payers ready, willing, and able to provide access to new durable gene therapies?" *Value in Health* 22 (2019): 642–647.
- Blendon, Robert J., and Mary T. Gorski, John M. Benson. "The Public and the Gene-Editing Revolution." *The New England Journal of Medicine* 374 (2016): 1406-1411.
- Cossu, Giulio, and Martin Birchall, Tracey Brown, Paolo De Coppi, Emily Culme-Seymour, Sahra Gibbon, Julian Hitchcock et al. "Lancet Commission: Stem cells and regenerative medicine." *Lancet* 391 (2018): 883-910.
- Dai, Wei-Jing, and Li-Yao Zhu, Zhong-Yi Yan, Yong Xu, Qi-Long Wang, Xiao-Jie Lu. "CRISPR-Cas9 for in vivo gene therapy: promise and hurdles." *Molecular Therapy—Nucleic Acids* 5 (2016): 1-4.
- Dunbar, Cynthia E., and Katherine A. High, J. Keith Joung, Donald B. Kohn, Keiya Ozawa, Michel Sadelain. "Gene therapy comes of age." *Science* 359 (2018): 1-10.
- EMA. ChondroCelect. www.ema.europa.eu/en/medicines/human/EPAR/chondrocelect (accessed September 29, 2019).
- EMA. Maci www.ema.europa.eu/en/medicines/human/EPAR/maci (accessed September 29, 2019).
- EMA. Product information Alofisel. www.ema.europa.eu/en/documents/product-information/alofisel-epar-product-information_en.pdf (accessed September 29, 2019).
- EMA. Product information Glybera. www.ema.europa.eu/en/documents/product-information/glybera-epar-product-information_en.pdf (accessed September 29, 2019).
- EMA. Product information Holoclar. www.ema.europa.eu/en/documents/product-information/holoclar-epar-product-information_en.pdf (accessed September 29, 2019).
- EMA. Product information Spherox. www.ema.europa.eu/en/documents/product-information/spherox-epar-product-information_en.pdf (accessed September 29, 2019).
- EMA. Product information Strimvelis. www.ema.europa.eu/en/documents/product-information/strimvelis-epar-product-information_en.pdf (accessed September 29, 2019).

- EMA. Product information Zalmoxis. www.ema.europa.eu/en/documents/product-information/zalmoxis-epar-product-information_en.pdf (accessed September 29, 2019).
- EMA. Provenge. www.ema.europa.eu/en/medicines/human/EPAR/provenge (accessed September 29, 2019).
- European Commission. Science and Society Action Plan, 2002. https://ec.europa.eu/research/swafs/pdf/pub_gender_equality/ss_ap_en.pdf (accessed September 29, 2019).
- FDA. “Approved Cellular and Gene Therapy Products.” <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products> (accessed September 29, 2019)
- FDA. Investigational New Drug (IND) Application. www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application (accessed October 8, 2019).
- FDA. Package Insert and Patient Information PROVENGE®. <https://www.fda.gov/media/78511/download> (accessed September 29, 2019).
- FDA. Package Insert and Patient Information Sheet, LAVIV®. www.fda.gov/media/80838/download (accessed Sept. 29, 2019)
- FDA. Package Insert GINTUIT. www.fda.gov/media/83264/download (accessed September 29, 2019).
- FDA. Package insert-LUXTURNA. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/luxturna> (accessed September 29, 2019).
- FDA. Package Insert YESCARTA™. www.fda.gov/media/108377/download (accessed September 29, 2019).
- FDA. Package Insert ZOLGENSMA®. www.fda.gov/media/126109/download (accessed September 29, 2019).
- FDA. Package Insert, IMLYGIC. www.fda.gov/media/94129/download (accessed September 29, 2019).
- FDA. Package Insert, KYMRIA™. www.fda.gov/media/107296/download (accessed September 29, 2019)
- FDA. Package Insert, MACI®. www.fda.gov/media/101914/download (accessed September 29, 2019).
- FDA. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of

- safe and effective cell and gene therapies. www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics (accessed October 8, 2019).
- Gaskell, George, and Imre Bard, Agnes Allansdottir, Rui Vieira da Cunha, Peter Eduard, Juergen Hampel, Elisabeth Hildt, et al. “Public views on gene editing and its uses.” *Nature Biotechnology* 35 (2017): 1021-1023.
- Gaskell, George, and Nick Allum, Martin Bauer, John Durant, Agnes Allansdottir, Heinz Bonfadelli, Daniel Boy, et al. “Biotechnology and the European public.” *Nature Biotechnology* 18 (2000): 935–938.
- Goswami, Reena, and Gayatri Subramanian, Liliya Silayeva, Isabelle Newkirk, Deborah Doctor, Karan Chawla, Saurabh Chattopadhyay, Dhyana Chandra, Nageswararao Chilukuri, and Venkaiah Betapudi. “Gene therapy leaves a vicious cycle.” *Frontiers in Oncology* 9 (2019): 1-25.
- Gottweis, H. “Gene therapy and the public: a matter of trust.” *Gene Therapy* 9 (2002): 667–669.
- Grünewald, Julian, and Ronghao Zhou, Sara P. Garcia, Sowmya Iyer, Caleb A. Lareau, Martin J. Aryee, and J. Keith Joung. “Transcriptome-wide off-target RNA editing induced by CRISPR-guided DNA base editors.” *Nature* 568 (2019): 433-453.
- Guertin, Lauren Robert McGuire, and Alessandra Torres. *Public Perception of Human Applications of CRISPR Gene Editing*. 2018. https://web.wpi.edu/Pubs/E-project/Available/E-project-042618-095556/unrestricted/CRISPR_full_draft.FINAL3.0.pdf (accessed September 29, 2019).
- Ihry, Robert J., and Kathleen A. Worringer, Max R. Salick, Elizabeth Frias, Daniel Ho, Craig Theriault, Sravya Kommineni et al. “p53 inhibits CRISPR–Cas9 engineering in human pluripotent stem cells.” *Nature Medicine* 24 (2018): 939–946.
- Inoue, Haruhisa, and Naoki Nagata, Hiromi Kurokawa, Shinya Yamanaka. “iPS cells: a game changer for future medicine.” *The EMBO Journal* 33 (2014): 409-417.
- Kaemmerer, William F. “How will the field of gene therapy survive its success?” *Bioengineering & Translational Medicine* 3 (2018): 166–177.
- Kosicki, Michael, and Kärt Tomberg, Allan Bradley. “Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements.” *Nature Biotechnology* 36 (2018): 765-771.

- Ma, Guangyu, and Hideaki Shimada, Kenzo Hiroshima, Yuji Tada, Nobuo Suzuki, Masatoshi Tagawa. "Gene medicine for cancer treatment: commercially available medicine and accumulated clinical data in China." *Drug design, Development and Therapy* 2 (2009): 115–122.
- Marks, Peter W., and Celia M. Witten, Robert M. Califf. "Clarifying stem-cell therapy's benefits and risks." *The New England Journal of Medicine* 376 (2017): 1007-1009.
- McCormack, Mathew P., and Terence H. Rabbitts. "Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency." *The New England Journal of Medicine* 350 (2004): 913–922.
- Raper, Steven E., and Narendra Chirmule, Frank S. Lee, Nelson A. Wivel, Adam Bagg, Guang-ping Gao, James M. Wilson, Mark L. Batshaw. "Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer." *Molecular Genetics Metabolism* 80 (2003): 148–158.
- Rial-Sebbag, Emmanuelle, and Alessandro Blasimme. "The European Court of Human Rights 'Ruling on Unproven Stem Cell Therapies: A Missed Opportunity?" *Stem Cells and Development* 23 (2014): 39-43.
- Riva, Luciana, and Laura Campanozzi, Massimiliano Vitali, Giovanna Ricci Vittoradolfo Tambone. "Unproven stem cell therapies: is it my right to try?" *Annali dell'Istituto Superiore di Sanità* 55 (2019): 179-185.
- Robillard, Julie M., and Dylan Roskams-Edris, Boris Kuzeljevic, Judy Illes. "Prevailing public perceptions of the ethics of gene therapy." *Human Gene Therapy* 25 (2014): 1-7.
- Ruffin, Morrie, and Lyndsey Scull. *Sector Overview. Gene Therapy for Rare Disorders* (2019). https://alliancerm.org/wp-content/uploads/2019/03/ARM-Gene-Therapy-for-Rare-Disorders_FINAL.pdf (accessed September 29, 2019).
- Scheufele, Dietram A., and Michael A. Xenos, Emily L. Howell, Kathleen M. Rose, Dominique Brossard, Bruce W. Hardy. "U.S. attitudes on human genome editing." *Science* 11 (2017): 553-554.
- Shineha, Ryuma, and Yusuke Inoue, Tsunakuni Ikka, Atsuo Kishimoto, Yoshimi Yashiro. "A Comparative Analysis of Attitudes on Communication toward Stem Cell Research and Regenerative Medicine between the Public and the Scientific Community." *Stem Cells Translational Medicine* 7 (2018): 251-257.

- Shineha, Ryuma, and Yusuke Inoue, Tsunakuni Ikka, Atsuo Kishimoto, Yoshimi Yashiro. "Science communication in regenerative medicine: Implications for the role of academic society and science policy." *Regenerative Therapy* 7 (2017): 89-97.
- Spoons, John, and Eleanor Croft, Andrew Walker. "Regeneration X: The payer perspective on gene therapy." *British Journal of Healthcare Management* 23 (2017): 158-166.
- Stein, Cy A. and Daniela Castanotto. "FDA-Approved oligonucleotide therapies in 2017." *Molecular Therapy* 25 (2017): 1069-1075.
- Sung, Yong K. and S. W. Kim. "Recent advances in the development of gene delivery systems." *Biomaterials Research* 12 (2019): 23-28.
- Ten Ham, Renske M.T., and Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G.M. Leufkens, Olaf H. Klungel. "Challenges in advanced therapy medicinal product development: A survey among companies in Europe." *Molecular Therapy: Methods & Clinical Development* 11 (2018): 121-130.
- The Journal of Gene Medicine. Gene Therapy Clinical Trials Worldwide Provided by the Journal of Gene Medicine www.abedia.com/wiley/years.php (accessed October 8, 2019).
- Trounson Alan, and Courtney McDonald. "Stem Cell Therapies in Clinical Trials: Progress and Challenges." *Cell Stem Cell* 17 (2015): 11-22.
- UNESCO. Recommendation on Science and Scientific Researchers, 2018. www.unesco.se/wp-content/uploads/2018/11/263618e.pdf (accessed September 29, 2019).
- Weisberg, Steven M., and Daniel Badgio, Anjan Chatterjee. "A CRISPR New World: Attitudes in the Public toward Innovations in Human Genetic Modification." *Frontiers in Public Health* 5 (2017): 1- 9.
- Zuo, Erwei, Yidi Sun, Wu Wei, Tanglong Yuan, Wenqin Ying, Hao Sun, Liyun Yuan, et al. "Cytosine base editor generates substantial off-target single-nucleotide variants in mouse embryos." *Science* 364 (2019): 289-292.