Titre: Translating the genomics revolution: the need for an international gene therapy consortium for monogenic diseases
Title:

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Date: 2013

Type: Article de revue / Article

Référence: Tremblay, J. P., Xiao, X., Aartsma-Rus, A., Barbas, C., Blau, H. M., Bogdanove, A. J., Boycott, K., Braun, S., Breakefield, X. O., Bueren, J. A., Buschmann, M. D., Byrne, B. J., Calos, M., Cathomen, T., Chamberlain, J., Chuah, M., Cornetta, K., Davies, K. E., Dickson, J. G., ... Gao, G. (2013). Translating the genomics revolution: the need for an international gene therapy consortium for monogenic diseases. Molecular Therapy, 21(2), 266-268. https://doi.org/10.1038/mt.2013.4
Citation:

Titre de la revue: Molecular Therapy (vol. 21, no. 2)
Journal Title:

Translating the Genomics Revolution: The Need for an International Gene Therapy Consortium for Monogenic Diseases

To the editor:

Over the past decade, gene therapy has been successfully used to treat several monogenic disorders, and it shows promise for treating diseases of more complex etiology. In addition, the recent development of induced pluripotent stem cells now opens the possibility of transplanting genetically corrected autologous cells.[1,2] Very recently, the European Medicines Agency approved the first gene therapy treatment in the Western world.[3] The substantial progress over the preceding decades arguably portends the development of gene therapies for most monogenic diseases. Given this remarkable opportunity, we are proposing the creation of an International Gene Therapy Consortium for Monogenic Diseases. This consortium would facilitate coordination of the production and availability of a variety of vectors, oligonucleotides, and recombinant proteins—including zinc-finger nucleases and Tal effector nucleases—as well as support the development of suitable animal models, preclinical studies, and clinical trials. Financial resources should be developed so as to attract collaborations from the private sector to boost the development of a gene therapy industry, similar to the way the Apollo project to explore the moon stimulated growth of the space and computer industries in the 1960s. In this century, a similar concerted effort will be required to develop effective treatments and even cures of diseases here on Earth!

A model for such a consortium can be found in the field of genomics. Advances in genomics have been rapid, owing in large part to the formation of international consortia such as the Human Genome and the ENCODE (Encyclopedia of DNA Elements) projects. These consortia have been awarded large budgets by various government agencies that have permitted intense collaboration among scientists as well as engagement of industry for the development of supporting technologies. The funding made available for these projects contrasts sharply with the relatively limited budgets that have been available for gene therapy research. Typically, most gene therapy researchers work as small teams on a specific disease with a relatively small budget. Moreover, the funding for gene therapy research tends to be piecemeal, with part coming from private foundations supported by patients, parents, and friends. Although these small groups can provide proof of concept for a gene therapy approach in cell and animal models, they generally lack the expertise and funding to efficiently translate their strategies to a clinical trial.

The fragmentation of gene therapy research efforts and the limited funding thus present significant hurdles for clinical translation. The establishment of an international gene therapy consortium would allow these small groups to tap into broader expertise and infrastructure, increasing the likelihood of a potentially beneficial treatment moving to clinical trials. There are already smaller consortia that can serve as examples. Indeed, European Union–sponsored collaborative networks in Europe have demonstrated the advantages of consortia-fostered collaboration among basic scientists, clinical investigators, industry, patient organizations and regulatory authorities. This format of collaboration and interactive multidisciplinary networks is ideally suited to address the various challenges of this multifaceted field. Consequently, such a concerted effort is much more cost-effective. One such group, the Transatlantic Gene Therapy Consortium, has successfully developed gene therapy strategies and trials predominantly for rare hematologic and immunologic diseases. In the EU Seventh Framework Programme, two pan-European translational projects have been funded, one focusing on neurological and neurodegenerative diseases (NEUROMICS), the other on rare diseases of the kidney (EuRenOmics). In the United States, the Rare Diseases Clinical Research Network was funded by the National Institutes of Health and the Office for Rare Diseases Research in order to facilitate collaboration among experts in many types of rare diseases. The FORGE Canada project, a national consortium of clinicians and scientists, is using next-generation sequencing technology to identify genes responsible for 200 rare pediatric-onset disorders and investigate their molecular etiology. The International Rare Diseases Research Consortium (IRDiRC), launched in April 2011, aims to foster international collaboration, maximizing resources and coordinating efforts in rare-diseases research. Worldwide sharing of information, data, and samples is currently hampered by the absence of an exhaustive rare-disease classification, standard terms of reference, common ontologies, and harmonized regulatory requirements. The IRDiRC has two main objectives to achieve by the year 2020: to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases. The group will next develop the scientific and policy framework to guide research activities and foster collaboration among the stakeholders to systematically explore the opportunities to accelerate the development of diagnostics and therapies for rare diseases. However, it should be emphasized that currently the majority of the 200 therapies sought by this consortium are based on the use of small molecules rather than on gene and/or cell therapy.

We believe that there is a need for a larger gene therapy consortium, with a larger budget, to focus on developing definitive gene and cell therapy treatments for most monogenic hereditary diseases over the next 20 years. This consortium will permit the development of focused areas of expertise. A major impediment to the commercialization of gene therapy for rare diseases lies in the lack of a sound business model for companies owing to the small number of patients, the fact that a single

treatment can cure a patient for life, and the requirements for long-term evaluation by federal agencies. As recently suggested, public funds could be used to pay for centralized manufacturing facilities and to subsidize enterprises with the necessary expertise, as has been done for vaccines.[4] A worldwide consortium would also facilitate the assembly of larger cohorts of patients with specific rare diseases, which are present in very small numbers in individual countries; this would allow for more robust clinical trial designs. Finally, a gene therapy consortium could facilitate long-term evaluation of integration sites and adverse events so as to better track the safety of new therapies. The creation of an International Gene Therapy Consortium for Monogenic Diseases would thus be, for these diseases, the first concrete step toward the personalized medicine that genomic research makes possible. It should be emphasized that some of these diseases (e.g., sickle cell disease and β-thalassemia) affect millions of peoples.

Like mankind's quest to travel to the moon in the 1960s, this proposal represents a grand challenge, but we have a societal obligation to the rare-disease community to collaborate and build the infrastructure to meet it. With an international consortium in place, it is more likely that therapies will be established that help patients not only in the developed world but also in less developed parts of our planet. Importantly, current scientific developments make this a timely challenge, and, in the long term, gene therapies for these diseases should become cost-effective. Just as we witnessed with the Human Genome Project, the technologies to correct the human genome will progress over the years with the appropriate incentives, generating a boost for the new knowledge-based economy. The time to take this step is now.

The scientists and directors of foundations or patient associations that would like to support the creation of such a consortium are invited to e-mail Jacques P. Tremblay at Jacques-P.Tremblay@crchul.ulaval.ca.

doi:10.1038/mt.2013.4

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REFERENCES

1. Takahashi, K and Yamanaka, S (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**: 663–676.
2. Gurdon, JB, Byrne, JA and Simonsson, S (2003). Nuclear reprogramming and stem cell creation. *Proc Natl Acad Sci USA* **100** (suppl. 1): 11819–11822.
3. Gaudet, D, Méthot, J, Déry, S, Brisson, D, Essiembre, C, Tremblay, G *et al.* (2012). Efficacy and long-term safety of alipogene tiparvovec (AAV1-LPL(S447X)) gene therapy for lipoprotein lipase deficiency: an open-label trial. *Gene Ther*, e-pub ahead of print 21 June 2012.
4. Mavilio, F (2012). Gene therapies need new development models. *Nature* **490**: 7.