Gene therapy: back on track?

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Gene therapy is the use of genetic information to correct a genetic defect or provide new functions to human cells. The twenty-first century started with seminal clinical studies showing that transplantation of genetically corrected cells, or direct gene delivery to patients, could cure severe genetic defects such as immunodeficiencies or haemophilia. Unfortunately, they were soon followed by reports indicating that the genetic vectors might cause systemic inflammatory responses, immune rejection of genetically corrected cells and insertional oncogenesis, with severe and sometimes fatal consequences (Porteus *et al*, 2006). The side effects soon obscured the therapeutic successes in the media as well as in the perception of the scientific community and, thus, gene therapy was described as a dangerous technology that didn't deliver on the expectations it had raised. US and European regulatory authorities responded unevenly, asking for more preclinical studies or imposing moratoria on the use of 'oncogenic' vectors.

The combination of skepticism, bad press and mixed government reactions threw the field into recession. The uncertainty about the consequences of tighter regulations discouraged scientists from embarking on new clinical trials and scared investors and the biotechnology industry away from the field. Leading industrial players either closed their operations or redirected their efforts away from gene therapy, effectively depriving the field of resources and competencies necessary for its technological development.

Much of this negative perception was unfounded. Despite the setbacks, gene therapy has made steady and consistent progress towards true clinical efficacy. In the last 20 months, a series of high-profile clinical studies reported success in correcting inherited forms of retinal degeneration (Bainbridge *et al*, 2008; Maguire *et al*, 2008), severe combined immunodeficiency (SCID; Hacein-Bey-Abina *et al*, 2008; Aiuti *et al*, 2009) and adrenoleukodystrophy

(Cartier *et al*, 2009), as well as in enabling bone marrow transplantation from mismatched donors in the therapy of leukaemia (Ciceri *et al*, 2009). Retrospectively, it was unrealistic to expect from genetic medicine what no other therapeutic intervention has ever provided in the history of medicine: efficacy without side effects. In the case of SCID, a patient without a fully histocompatible donor has a higher chance of being cured by gene therapy than by bone marrow transplantation, and a better chance of survival even taking the oncogenic risks into account. Furthermore, the gene therapy community offered a spectacular example of how scientific knowledge and technology can be put to work to understand the causes of severe adverse events, design new vectors and develop tools and models to predict their safety and efficacy. As an added benefit, these efforts brought new basic knowledge on virus-host interactions and on the biology and dynamics of human somatic stem cells.

Is gene therapy back on track? Maybe not yet—and this time not because of faulty vectors or poor knowledge. The real threats to the field—and indeed to all cell-based therapies—are now over-regulation and lack of resources. Regulatory agencies are asking for an enormous, unprecedented amount of preclinical data and post-treatment monitoring in order to authorize a trial, even when preclinical models are lacking or uninformative, and patients have no therapeutic alternatives. As for any other experimental therapy, a correct risk/benefit evaluation should be the major criterion for authorizing a treatment. Applying a different standard to gene therapy is unfair, delays or discourages its development and ultimately affects the right of patients to have access to efficacious treatments in due time. Unfortunately, risks cannot be assessed without clinical investigation. Excellent animal models failed to predict insertional oncogenesis or immune rejections as risk factors for SCID and haemophilia.

To make matters worse, cell and gene therapeutics must now be produced under the rules developed for chemical drugs—the so-called good manufacturing practices—and only in establishments built and operated with industry-like standards certified by government agencies. Such facilities are too demanding for academic centres to operate and too expensive for public granting agencies and charities to fund, which is preventing innovative, investigator-driven clinical trials from being carried out with the speed and flexibility that has always characterized experimental medicine. Many scientists argue that genetically modified cells are individualized, 'orphan' therapies that are somewhere in between drugs and organ transplants and should be regulated accordingly, particularly in the early phases of clinical development. Over-regulation is creating an unprecedented challenge: scientific innovation is becoming too difficult to translate into therapies, while high costs and uncertain returns are discouraging industrial investment and therefore technological development.

Governments, funding agencies and other stakeholders should develop a new model to facilitate clinical development of cell and gene therapy, while maintaining high scientific, ethical and safety standards. There are many ways of reaching such goals, from redesigning the regulatory framework, to building centralized manufacturing facilities and/or providing public funding to those in the biotechnology industry that are willing to accept the challenge and see returns on their investment that could not materialize otherwise. The vaccine industry is a precedent that should be taken into serious consideration.

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EMBO reports (2010) **11**, 75.
doi:10.1038/embor.2009.284