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Genetic modification of somatic stem cells

The progress, problems and prospects of a new therapeutic technology

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Some of the illnesses that plague mankind are directly related to our genes. Severe genetic disorders with no current therapeutic options—immunodeficiencies, haemophilia, thalassaemia, muscular dystrophies and cystic fibrosis, for example—could potentially be treated with gene therapy, which uses genetic information to correct a mutation or to provide new functions for human cells. The aim of gene therapy for the past two decades has been to fix the genetic defects in diseased cells of the body, or in the stem cells that can regenerate a diseased tissue or organ.

A precise correction of a genetic defect, or the replacement of one or more genes in the human genome, will not be technically possible for years to come

The spectacular development of genetic technologies—such as gene targeting and homologous recombination—now allows scientists to routinely generate transgenic animals with defined genetic modifications. The clinical application of this technology, however, is still in its infancy. A precise correction of a genetic defect, or the replacement of one or more genes in the human genome, will not be technically possible for some years to come. Currently, the only therapeutic option is gene replacement or the transfer and expression of therapeutic genes through virus-derived vectors. Clinical studies carried out in the past 10 years have proven that gene transfer into the organs of a patient—*in vivo* gene therapy—or the transplantation of genetically modified somatic cells—*ex vivo* gene therapy—is feasible and might cure severe diseases or notably improve existing therapies. Other studies, however, have been less successful, and have shown limited efficacy and serious safety problems associated with the use of viral vectors, both *in vivo* and *ex vivo*.

The main reason why *in vivo* gene therapies have failed is the human immune system, which rejects the therapeutic vector or the genetically corrected cells (Manno *et al*, 2006), or causes acute toxic reactions that have been fatal in at least one case (Raper *et al*, 2003). For *ex vivo* gene therapy, the trouble has come from the uncontrolled insertion of the vector into the human genome, which has resulted in perturbed normal cell functions and has, in the worst cases, caused tumours (Hacein-Bey-Abina *et al*, 2003).

These successes and failures have resulted in a rollercoaster ride of enthusiasm and disappointment during the past five years. Unfortunately, the bad news seems to have attracted more attention from the general media and scientific journals than the good news. Gene therapy has often been described as an inefficient and dangerous technology that has never delivered on its promises and expectations. The credibility of gene therapy has been negatively affected by a history of ill-conceived or rushed clinical trials, and by too much hype from scientists and biotechnology companies, as much as from the press. Much of this negative perception, however, is unfounded. It is unrealistic—and unfair—to expect from genetic medicine what no other medical intervention has ever provided: a perfect and safe cure without any side effects. In reality, gene therapy has made steady progress towards clinical efficacy, and researchers are learning how to make it safer and more efficient. Just like many others in the field, we have little doubt that gene therapy will finally deliver on its promises. The story of using gene therapy to correct genetic disorders of the blood and skin helps us to understand the technical challenges and ethical dilemmas.

Severe combined immunodeficiency (SCID) was the first genetic disease to be treated by gene therapy. This rare disorder is characterized by profound defects in all immune functions—T cells, B cells and natural killer cells—and recurrent infections that are often fatal in the first years of life (Fischer, 2001). Adenosine deaminase-deficient SCID (ADA^- SCID) is caused by the lack of an essential enzyme in DNA synthesis, which causes the accumulation of toxic metabolites that are deleterious for T lymphocytes and B lymphocytes. X-chromosome-linked SCID (X-SCID) is caused by mutations in the gene encoding a shared component of several receptors for T-cell and B-cell growth factors: the common γ-chain.

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The treatment of choice for both diseases is the transplantation of bone marrow from a related and fully compatible donor, but this possibility is only available for less than 30% of SCID patients. Transplantation from unrelated or mismatched donors carries a high risk of early mortality or severe immunological complications (Antoine *et al*, 2003). The first attempts to treat ADA^- SCID with gene therapy were made in the early 1990s when peripheral blood lymphocytes, bone marrow or umbilical cord blood cells—in which an

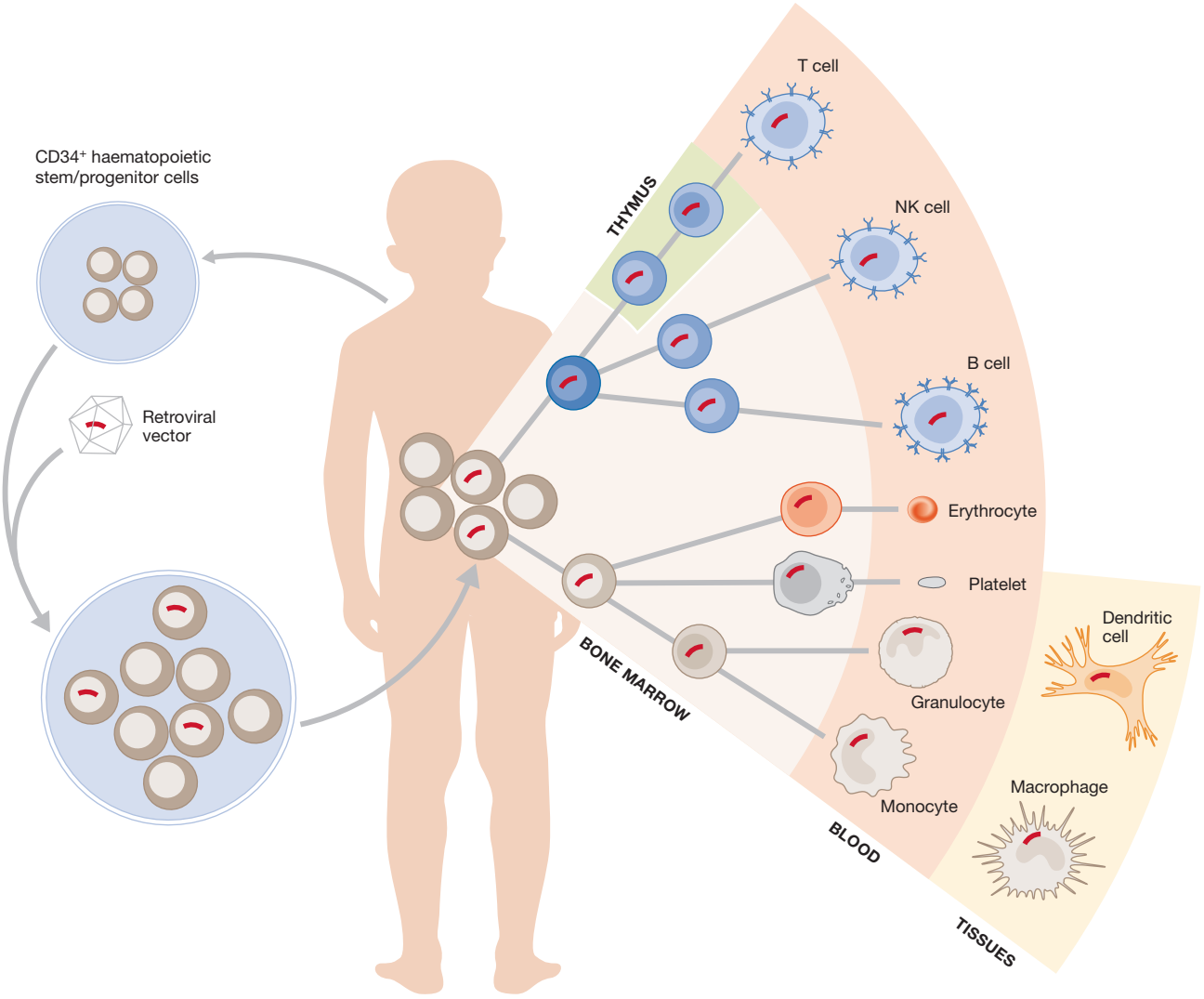

Fig 1 | Treatment of genetic blood disorders by the transplantation of genetically corrected stem cells. Blood stem/progenitor cells are harvested from the bone marrow or from the peripheral blood of patients who are affected by a blood-related genetic defect. These are purified using antibodies against the surface marker CD34 and exposed in culture to a retroviral vector carrying the therapeutic gene (red bar). The cells are then transplanted back into the patient where they colonize the haematopoietic organs (thymus and bone marrow) and eventually give rise to various types of blood cell. If stem cells are genetically corrected in sufficient numbers, their progeny will carry the therapeutic gene and cure the disease. NK cell, natural killer cell.

ADA gene was inserted by means of a viral vector—were administered to patients. These attempts were only partly successful, owing to insufficient gene transfer into long-lasting stem cells (Blaese *et al*, 1995; Bordignon *et al*, 1995; Kohn *et al*, 1995).

However, by the end of the 1990s, technological improvements finally allowed the successful treatment of both forms of SCID with the transplantation of genetically corrected stem cells (Aiuti *et al*, 2002; Cavazzana-Calvo *et al*, 2000). A crucial factor in the success was the selective advantage provided by the therapeutic genes in genetically corrected cells either in lymphopoietic organs or in peripheral blood. So far, 18 X-SCID patients and 13 ADA$^-$ SCID patients have been treated by gene therapy in Paris, Milan and London. Most of the patients have been infants, and all but two of them have achieved effective and life-saving immune reconstitution lasting for up to 10 years after treatment. These trials have shown for the first time that the transplantation of genetically corrected stem cells is an efficacious treatment for a severe genetic disorder (Fig 1).

The optimism generated by these initial successes turned into disappointment at the end of 2002 when two patients in the French X-SCID trial developed a leukaemia-like lymphoproliferative disorder (Hacein-Bey-Abina *et al*, 2003). Genetic analysis of the malignant cells showed that in both cases—and in two more cases subsequently observed in 2006 and 2007 in Paris and London, respectively—the therapeutic vector had been inserted into, and had activated, a proto-oncogene called LIM domain-only 2 (*LMO2*). In all cases, the

regulation of *LMO2* expression was apparently overrun by regulatory elements from the viral vector (McCormack & Rabbitts, 2004). A fifth X-SCID patient developed a similar disorder caused by viral insertion into a different gene.

Knowing the risks of a therapeutic approach—and understanding the causes of its failures or side effects—is the only way to improve the technology

LMO2 has an important role in the differentiation of blood progenitor cells and is known to be involved in chromosomal translocations associated with childhood acute T-cell leukaemia. However, the long latency of more than 30 months, and the finding that vectors were inserted into the *LMO2* gene in non-malignant cells, indicated that additional events had contributed to the development of leukaemia (Hacein-Bey-Abina *et al*, 2003). Expression of common γ-chain, the product of the therapeutic gene, was itself thought to be a concurrent risk factor (Dave *et al*, 2004)—indeed, none of the ADA$^-$ SCID patients who had a different therapeutic gene inserted has ever developed blood abnormalities, despite the evidence of vector integration into *LMO2* in their T cells (Aiuti *et al*, 2007).

These serious complications came as a surprise: extensive studies in animal models of human immunodeficiencies had provided no evidence that gene therapy could cause cancer; the problem obviously arose from the viral vector. The genetic modification of stem cells requires the stable integration of the therapeutic gene into the genome to ensure its maintenance in the stem cells and their progeny. The vectors used were derived from murine oncoretroviruses (typically Moloney murine leukaemia virus or MLV; Coffin *et al*, 1997), which integrate at high efficiency into mammalian genomes. Despite the known oncogenic potential of the original viruses, retroviral vectors were considered relatively safe in a human context and have been used in hundreds of gene therapy trials since 1991.

Fortuitous activation of oncogenes has always been considered to be a possible consequence of the random insertion of foreign genes into the genome; however, on statistical grounds, the probability of such an event was originally estimated to be less than 1 in 10 million. As it turns out, these calculations were based on a wrong assumption; in fact, retroviral integration into the human genome is anything but random. After the first cases of leukaemia in X-SCID patients, several studies showed that retroviral vectors integrate preferentially into active regions of the genome, and particularly around gene promoters and other regulatory elements (Bushman *et al*, 2005). This 'preference' markedly increases the probability of hitting genes that are involved in crucial cell functions, such as proliferation and differentiation, including oncogenes. In addition, the viral regulatory elements influence the expression of genes that are located far away from the insertion points and at high frequency (Recchia *et al*, 2006). Tumour viruses have probably evolved these characteristics in order to maximize their ability to transform cells, thereby increasing their chances of being propagated. Retrospectively, the high frequency of leukaemic transformation observed in X-SCID patients can be explained by the biology of retroviruses, which was unknown when retroviral vectors were developed for medical applications.

After the first reports of leukaemia, scientists and regulatory authorities called for a halt to clinical experiments and a return to the drawing board. In most countries, trials were eventually allowed to resume—after a temporary hold—on the well-founded basis that the benefits outweighed the risks. Many argued that there was a need for developing new, safer vectors to avoid the problem of fortuitous gene activation or of integration altogether, and for more pre-clinical studies to assess the risk of insertional oncogenesis. It is difficult to disagree with these positions. Research must go on, particularly into systems that could overcome many of the problems of the current vectors.

Ironically, the most promising current vectors are derived from a dangerous human pathogen—the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS). These vectors minimize the probability of activating oncogenes, in part owing to the fact that HIV is not a tumour virus, and in part owing to more advanced vector design that removes any viral transcriptional enhancers from the vector (Kay *et al*, 2001). HIV-derived or lentiviral vectors are expected to improve the safety of the genetic modification of stem cells substantially, although developing clinical-grade vectors based on this technology, and assessing their full safety and efficacy profile might take years.

In the meantime, we still have a life-saving treatment with proven efficacy that could be given to numerous patients who have no therapeutic alternatives or alternatives that carry even higher risks of morbidity and mortality. In the case of SCID, particularly ADA$^-$ SCID, a patient still has a greater chance of being cured by gene therapy than by receiving bone marrow from a mismatched donor, and has a better chance of surviving treatment, even taking the risk of leukaemia into consideration. Is it therefore ethical to treat patients with a technology that carries such risks?

As for any other medical intervention—with cancer therapy being a perfect example—a correct assessment of the risk–benefit ratio should be the only criterion for deciding whether to use an experimental therapy. When the benefits outweigh the potential risks, the decision not to use a new therapy would prevent the assessment of its full therapeutic potential, postpone its development and ultimately affect the right of patients to have access to an efficacious treatment in due time. Knowing the risks of a therapeutic approach—and understanding the causes of its failures or side effects—is the only way to improve the technology. Unfortunately, there is no real substitute for clinical investigation to provide a comprehensive risk assessment of a new therapy, which comes only at the end of extensive clinical studies. Even the best animal model is far from being predictive of the full range of risks of human intervention. In the case of X-SCID, animal models had certainly failed to predict insertional oncogenesis as a risk factor.

It can be argued that extrapolating safety concerns from one disease to another is a weak rationale for putting a promising treatment on hold

An example of the complexity of determining the risk–benefit ratio is gene therapy of skin-adhesion disorders. These are a group of severe inherited diseases, collectively known as epidermolysis bullosa (EB), which are caused by defects in the proteins that mediate the adhesion of the skin to the underlying dermis. EB is often lethal in the first weeks of life, and the non-lethal

forms are characterized by severe and disfiguring blistering, recurrent infections, visual impairment and a high risk of developing skin cancer (Uitto & Richard, 2005). There is no cure for EB, and current therapeutic approaches are essentially aimed at controlling infections and maintaining an acceptable quality of life.

Recently, a new therapeutic approach became available based on the transplantation of cultured skin derived from genetically corrected epidermal stem cells by using a retroviral vector similar to those used to treat SCIDs. A pilot clinical study that began in 2005 on an adult patient showed that the transplantation of genetically corrected skin was feasible, well tolerated and led to long-term functional correction of the skin-adhesion defect (Mavilio *et al*, 2006). Unfortunately, based on the severe side effects observed in the SCID patients, the regulatory authorities in Italy—where the study was being carried out—issued a directive to limit the use of retroviral vectors to life-threatening disorders and to patients with a life expectancy of a few months. Under this regulation, the study had to be closed. The only basis for limiting the implementation of a gene-therapy treatment for EB was that a similar vector had caused cancer in other patients with a different disease.

The combination of scientific scepticism, bad press and mixed government reactions has effectively thrown the field into a recession

It can be argued that extrapolating safety concerns from one disease to another is a weak rationale for putting a promising treatment on hold. As none of the patients affected by one form of immunodeficiency (ADA^- SCID) suffered from the side effects observed in the patients with a different form of the same condition (X-SCID), how can the risks be extrapolated to patients suffering from a different disease, who are treated with different stem cells that are transformed with a vector carrying a different gene? Again, gene-transfer vectors can and will be improved; however, in the meantime, patients who have no therapeutic alternatives are prevented from accessing a potentially beneficial treatment without any evidence of the potential risks under their specific circumstances.

It seems unlikely that this odd standard would be applied in a different context—in anti-cancer or anti-AIDS drug therapies, for example. It therefore seems that a different standard is being applied to genetic therapies without any clear medical basis or ethical rationale. Even worse, one could argue that patients suffering from rare disorders are receiving less attention from regulatory agencies than patients with cancer and AIDS, which are diseases with pressure groups that can have an enormous influence on policy and research through the media and public opinion. We wonder whether patients suffering from orphan diseases—so called because they do not represent attractive targets for the pharmaceutical industry—are being unfairly affected by a heated public debate on genetic manipulation and stem cells, which is replacing good medical practice with an ill-defined precautionary principle.

The best example of how gene therapy is evolving—both in terms of technology and planning—is probably that of the thalassaemias. These comprise a heterogeneous group of inherited anaemias and collectively represent the most common monogenic disorders worldwide. β-thalassaemia is characterized by the reduced or ablated production of the β-chain component of haemoglobin. This results in a profound anaemia that, if not treated, leads to death in the first year of life. So far, the only available cure is bone-marrow transplantation from suitable donors, which again is available to less than one-third of the patients. The others are left with a life-long treatment of monthly blood transfusions, side effects owing to excess iron deposition in all soft tissues, impaired growth and a relatively short life expectancy. The situation is considerably worse in less-developed countries, where modern transfusion regimens and drugs are unavailable or unaffordable.

Similar to SCIDs, the transplantation of genetically corrected stem cells is considered to be an attractive therapeutic alternative. The development of lentiviral vectors has provided a great technological advantage and has led to a demonstration of the therapeutic potential of gene therapy in animal models (Sadelain, 2006). The clinical history of thalassaemia—and more than 20 years of experience with bone-marrow transplantation (Lucarelli *et al*, 2002)—allows scientists to predict that even a partial correction of the haemoglobin defect in a fraction of the bone-marrow cells will be sufficient to reduce the anaemia, improve the clinical management of the disease and increase the life expectancy of patients (Gaziev & Lucarelli, 2003; Persons *et al*, 2001). A recent study carried out in an animal model indicated that genetically corrected red-cell precursors are protected from the consequences of impaired haemoglobin synthesis and undergo a positive selection in the bone marrow (Miccio *et al*, 2008).

The pursuit of 'safety first' has created an unprecedented challenge for medical research: some promising technologies might become too difficult to develop and to translate into effective therapies

This selective advantage increases the efficacy of the gene therapy by overcoming the consequences of suboptimal gene-transfer efficiency. This is a crucial point. Bone-marrow transplantation is usually preceded by chemotherapy to 'ablate' the bone marrow of the patient and to make space for the incoming cells. The transplantation of genetically corrected cells would require the same treatment, which is toxic and has serious associated side effects as patients temporarily lose their immune defences against bacterial and viral infections. Much of the mortality associated with bone-marrow transplantation—5–20% in the case of thalassaemia—is caused by pre-transplantation chemotherapy. If genetically corrected cells have a selective advantage when transplanted into thalassaemic bone marrow, the intensity of the treatment, and hence the risk to the patients, could be reduced. Only clinical studies will tell whether scientists are right in predicting that gene therapy could be safer than bone-marrow transplantation for thalassaemic patients, and hopefully just as efficacious.

There are several ethical issues nonetheless. In the Western world, thalassaemia is now a chronic disease, with a treatment that—albeit expensive and demanding on young patients—allows survival well beyond the first three decades of life. A high risk of cancer would be

particularly undesirable for these patients. The issue, therefore, is whether the new lentiviral vectors can overcome the risk of leukaemia that is associated with the use of the old-generation vectors. Studies in cultured cells and animal models predict that this is the case; however, only clinical and long-term follow-up studies will provide a definitive answer.

By contrast, in the developing world, the standard of care is lower and thalassaemia is associated with high mortality and a low quality of life. The risk–benefit ratio of gene therapy for patients in Africa or the Middle East would be notably different from that of European or American citizens—even if it did carry a risk of leukaemia. A definitive therapy would bring great benefits to both the individual patients and their societies because other effective treatments are too expensive or simply too difficult to deliver. Apparently, this is a case in which a potentially risky therapy could be more readily justified for patients living in poorer countries based on individual risk–benefit considerations, which are our most trusted ethical standard in determining the eligibility of a patient for an experimental treatment.

So, are we creating double standards essentially based on socio-economic considerations? These are not theoretical dilemmas: thalassaemic patients from North Africa, middle-Eastern and far-Eastern countries are coming to France, Italy and the UK to seek treatment. On the basis of their clinical conditions, they are far more eligible for gene therapy than European patients. But is this an acceptable rationale and an acceptable clinical practice? We believe that it is; however, scientists and ethicists have not yet reached a consensus on such an issue.

The successes and failures of gene therapy have elicited enormous attention from scientists, governments and the general public. Reactions from regulatory authorities in the USA and Europe have ranged from asking researchers to update informed consent and eligibility criteria to imposing a general moratorium on any trial using retroviral vectors. The combination of scientific scepticism, bad press and mixed government reactions has effectively thrown the field into a recession. The 'gene-therapy causes-cancer' mood and uncertainty about the medium-term consequences of tighter regulatory frameworks have discouraged scientists from embarking on new trials, and have scared investors and the biotechnology industry away from the field. Leading industrial players have either closed their operations or have been redirecting their efforts away from gene therapy since 2002. This is a particularly serious consequence because, in the absence of adequate industrial investment, it is unlikely that stem cells and gene therapy will deliver on their promises.

The variegated response from regulatory authorities is a crucial factor of uncertainty because it creates a nightmare patchwork of different rules in various countries, and makes international clinical trials difficult to plan and execute. Harmonization of legislation among European states—and between Europe and the USA—is needed urgently. In Europe, the agency in charge of drug-marketing authorizations, the European Medicines Agency (EMEA, London, UK), has no formal jurisdiction over early clinical studies, and individual European countries resist the idea of giving up national authority on this matter.

To make things worse, the manufacturing of cell and gene therapeutics must now be carried out under the same rules developed for chemical and biological drugs, and only in establishments that are built and operated within industrial standards, and certified by government agencies. These facilities are too expensive for academic centres to operate or for public grant agencies and charities to fund. This is a serious bottleneck that is turning into a vicious circle: industrial interest will only come when clinical studies show the efficacy and safety of gene therapy, but, in the absence of industrial interest, it is difficult to develop and produce the evidence in the first place.

Many scientists argue that cell and gene therapies lie between drug development and organ transplantation and should be regulated by specific rules, particularly in the early phases of clinical development. The pursuit of 'safety first' has created an unprecedented challenge for medical research: some promising technologies might become too difficult to develop and to translate into effective therapies.

In light of this, governments, charities, patient organizations and other stakeholders should develop a new framework to facilitate the early clinical development of these technologies, while at the same time maintaining the high scientific and ethical standards that are necessary for progress. There are many ways of reaching such aims—from building centralized public facilities to providing public funding for the biotechnology industry. The development of the vaccine industry is a precedent that should be taken into serious consideration.

There is a tendency in our media-dominated societies to engage in theoretical debates about what should be done based on pre-formed concepts rather than evidence. The futile debate about the therapeutic potential of 'embryonic' versus 'adult' stem cells is a typical example of an argument that is focused more on establishing principles than finding solutions. The genetic manipulation of stem cells has the vast potential to manage and cure many important diseases. It is therefore in the best interests of all societies—rich or poor—to find a way to translate the creativity of so many scientists into a new generation of therapies that could help many patients live longer and healthier lives.

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