

Chapter

Introduction: gene transfer lost in translation

Introduction

French and British researchers have treated X-linked severe combined immune deficiency syndrome (X-SCID), otherwise known as “bubble boy” disease. Italian and UK researchers have also treated a related disease, ADA-SCID. Though only three patients were enrolled in the study, Swiss and German researchers have treated yet another severe immune disorder, chronic granulomatous disease. And some commentators believe American researchers are on the cusp of a durable treatment for hemophilia B. In these instances, it would appear that gene transfer – briefly, the administration of genetic materials to human beings – has finally earned the title of *gene therapy*.

But the field’s development has been, and continues to be, a long, strange trip. As I write, the most visible name associated with gene transfer, W. French Anderson, is serving a fourteen-year prison sentence on child molestation charges.¹ Another leading figure, James Wilson, has nearly finished a five-year, FDA-imposed ban on leading clinical studies.² Other sanctions in the field’s thirty-year history include one of the earliest ever violations of rules for human research issued by the US Department of Health and Human Services (Martin Cline, for initiating a study without proper IRB review³), and a widely publicized rebuke of two other leading figures (Ronald Crystal and Jeffrey Isner) for not reporting trial deaths to the NIH.⁴ In 1995, a high-level panel at the NIH faulted the field for rushing into clinical trials.⁵ In 2000, two prominent researchers editorialized in the pages of *Science* magazine “gene therapy has many of the worst examples of clinical research that exist.”⁶

Doubts surround even gene transfer’s triumphs. Five children cured in the X-SCID studies, for example, developed a rare leukemia linked to the gene transfer; one subsequently died. In the chronic granulomatous disease study mentioned above, genetically modified tissues expanded in a manner such that some researchers worry that it might signal the start of a cancer.⁷ Some enthusiasts in the field like to cite the fact that regulatory authorities in China have licensed Gendicine®, the first ever gene transfer treatment to be commercialized anywhere. Skeptics, however, question the quality of evidence supporting licensure, inconsistencies between Chinese- and English-language published reports, and conflicts of interest in the regulatory process.^{8,9}

Clearly, the process of translating the idea of gene transfer into clinical application has proven far more difficult than anticipated. Some of the difficulties are the product of untoward vectors (which shuttle genetic materials into cells) and immune systems (which seem bent on attacking vectors and the cells that receive them). Other difficulties include the untoward conduct of clinical researchers and investors. What I would like to advance in this book is the proposition that some of gene transfer’s difficulties have arisen from a failure to translate ethical concepts for medical research, which were developed largely for controlled clinical trials (where compounds are relatively simple, and uncertainties bounded), to the context

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of small-scale, scientifically intensive translational trials (where uncertainty is unbounded). What I mean to suggest is not that gene-transfer researchers have been delinquent in their adherence to clinical research ethics, though there certainly have been instances of this. Rather, all parties to the research – investigators, ethicists, IRB members, policy makers, patients, and research advocates – have appeared lost in trying to apply ethical concepts that are not well matched to early-phase tests of novel interventions.

In 1997, Leroy Walters and Julie Gage Palmer echoed a sentiment expressed as early as 1983 in a US Presidential Commission report:¹⁰ that somatic gene transfer (that is, genetic modification of tissues that will not be passed on to future generations) could be considered, from an ethical standpoint at least, a “natural and logical extension of the current techniques for treating disease.”¹¹ This position has gone largely unchallenged. Yet in emphasizing the continuity of gene transfer with conventional medicine, I believe the “gene transfer as natural extension” position obscures the distinctive – if not quite unique – ethical and social challenges associated with translating gene transfer into clinical application.

Hemophilia and gene transfer: some challenges

Recent gene transfer trials for hemophilia B illustrate my argument. In several respects, clotting disorders like hemophilia represent the perfect systems for validating basic principles of gene transfer. Whereas many genetic diseases require delivering genes to specific parts of the body, coagulant factors (proteins involved in triggering clotting) are secreted and can thus be expressed from easily accessed tissues like muscle. Second, hemophilia therapies have a wide therapeutic window. That is, coagulant factor levels as low as 5 percent of normal amounts are sufficient for converting severe hemophilia into a mild form; investigators need only to achieve a modest elevation in factor levels in order to achieve clinical correction.

From a scientific perspective, hemophilia is appealing because factor protein circulates in the bloodstream, which means that investigators can monitor gene expression with a simple blood test (other diseases require complicated imaging or invasive biopsies). Additionally, factor production can be quantified objectively and reproducibly by assaying plasma factor concentration. Finally, hemophilia offers various ethical and safety advantages over other disease models. Few areas of translational research have animal models as effective and faithful as those used in hemophilia. Subjects, because they have access to recombinant factor replacement therapy, are less likely to be impelled to trial participation by medical desperation. And having survived blood contamination scandals, the hemophilia community is politically energized, scientifically sophisticated, and more likely to view invitations to participate in clinical research with an appropriate level of caution.

As with any clinical research protocol, a proposal to conduct a human gene transfer study in hemophilia patients would be evaluated on the basis of its adherence to a set of widely agreed-upon ethical principles: respect for persons, beneficence, and justice.¹² As to how to implement these principles, ethicists and policy makers have evolved a set of frameworks and practices. Many of these map awkwardly, if at all, to the types of small-scale, scientifically intense studies that characterize gene-transfer trials.¹³ Consider the following:

- *When is the appropriate time to initiate clinical testing?* Discussions around various hemophilia trials show this to be a major point of contention. The standard, controlled clinical trial answer would draw on the concept of clinical equipoise – that is, uncertainty among the expert clinical community as to the relative advantage of either arm in a comparative trial. The concept of clinical equipoise was originally intended to guide investigators conducting controlled clinical trials. Translational studies, however,

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are usually uncontrolled (that is, they do not involve other study arms that enable comparison with another intervention). There is, as yet, no ethical “indicator” of a translational trial’s ripeness.

- *How should the validity and value of a translational trial be judged?* Standard accounts would suggest the ability to perturb clinical equipoise for randomized, controlled trials or, in the case of phase 1 studies, the ability to provide sufficient information for phase 2 testing. In fact, very few gene-transfer trials lead directly to phase 2 testing. For example, five phase 1 studies have been conducted for hemophilia gene transfer to date; none have produced a phase 2 trial. Does this mean that the studies are valueless, or does it mean that the way many investigators, subjects, and ethicists conceive the value for translational studies is somehow flawed?
- *What is fair subject selection?* One little-noticed phenomenon in gene-transfer research is the recruitment of subjects from low- and middle-income countries. One of the most significant hemophilia gene-transfer trials conducted to date, for example, recruited subjects from Brazil (successfully) and India (unsuccessfully). Standard accounts of justice would require providing a plan for post-trial access to medications developed in a study, and an assessment of a study’s responsiveness to health needs in the host community. Both have clear implications for large, late-stage trials involving prevalent disorders that are exported to low-income countries. How do the ethics change when studies are *importing* subjects to participate in studies of rare diseases?
- *What is the appropriate population in which to test a study drug?* In later-phase research, this question is settled by an assessment of a study’s risks and direct medical benefits. Toxic oncology drugs, thus, are tested in cancer patients who have a chance of benefiting from the study drug (or, at least, less to lose should the drug prove toxic). In translational research, however, diseases that present the best opportunity for gathering knowledge often offer a less favorable balance of risks and direct benefits. Persons with hemophilia, for example, are medically stable – at least with respect to their clotting deficiency – because validated therapies are already available. When hemophilia patients enter early-phase trials of novel agents, they place their stable health status at risk. When, and under what conditions, is it ethically defensible to recruit medically stable subjects into a study testing a novel intervention with indeterminate risks?
- *How should study risks be evaluated, and how should they affect study design?* Unlike later-stage studies, first-in-human trials often have little or no human experience on which to draw in performing a risk–benefit analysis. Risk assessment, as such, involves much intuition, and surprises occur with unsurprising frequency. In various hemophilia gene-transfer trials, these have included stronger than anticipated immune responses to vectors, higher than expected expression of the corrective gene, and vector contamination of subjects’ semen. How should we define a “good guess” of study safety? And how might protocols be designed to minimize or manage the unusually high levels of indeterminacy?
- *How should risks to study volunteers be appraised?* Research ethics has evolved a well-developed framework for ethically evaluating risk in human studies. Under this framework, known as component analysis, research risks are divided into those deriving from procedures that have a therapeutic warrant (e.g. study drugs) and risks deriving from those that do not (e.g. extra medical tests). The demarcation of therapeutic and non-therapeutic procedures is generally straightforward for randomized controlled trials. But for first-in-human phase 1 studies, the demarcation is far from obvious. Should

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study drugs be considered to have therapeutic warrant even for diseases like hemophilia, where an effective standard of care is well established? Even if, for safety reasons, initial volunteers are to receive doses below which investigators expect to observe a therapeutic response? Or should vector risks be classified as research risks, despite the fact that animal evidence suggests that volunteers might benefit medically from participation?

- *How should risks to others be evaluated?* Most drug trials involve only minor burdens for persons other than the trial subject. Gene-transfer studies, however, occasionally pose ethically important risks to non-subjects. In one of the most successful hemophilia trials to date, gene transfer vector sequences were detected in the semen of six out of seven subjects, raising concerns about the possibility of transmission to sexual partners or offspring. In this case, it turned out that the vector sequences only transiently contaminated semen, and appeared not to have actually modified subjects' sperm. Nevertheless, the episode raises important questions about incorporating inter-generational risks in the ethical appraisal of some trials.

Gene transfer as a model for translational research

Over the past several years, medical centers have announced major gifts directed toward translational research.^{14,15} Universities have broken ground on new translational clinical research facilities,¹⁶ and the NIH recently announced 12 grants of unprecedented size to create infrastructure for translational trials.¹⁷ The grants are part of the NIH's "Roadmap", a program to accelerate the application of basic biomedical discoveries.¹⁸ The United Kingdom has a counterpart: a network of eight centers for early-phase oncology studies.¹⁹ Perceiving an inordinate lag between discovery and drug development, the Food and Drug Administration recently issued new guidelines to stimulate first-in-human studies.²⁰ The European Organization for Research and Treatment of Cancer announced new efforts to coordinate translational research efforts and strengthen their scientific basis.²¹

If these and other initiatives are to succeed – and avoid some of the challenges that have befallen gene transfer – it seems critical that an ethical framework particular to translational research be elaborated. This book offers a series of proposals in the hopes first of improving current practice, and second, stimulating further ethical analysis.

Gene transfer offers a particularly promising "model organism" in which to observe the emergence of ethical problems in translational research. First, the past two decades have witnessed extraordinary investment in genetic and genomic research. Gene transfer represents perhaps the culmination of these investments, and will likely play a significant role in enabling the application of other treatment strategies like cell and immunological therapies. Second, perhaps because of its medical promise – and its associated controversies – gene transfer has received an unusual degree of public scrutiny. News reports of advances and setbacks are therefore abundant. Third, gene-transfer research is more transparent than other areas of translational research. The operations of the NIH's Office of Biotechnology and its Recombinant DNA Advisory Committee afford the ethicist a rich record of ethical deliberation and practices. Finally, the pattern and organization of gene transfer research are characterized by an unusual degree of cohesiveness and collaboration. For example, professional societies like the American Society of Gene Therapy and the European Society of Gene Therapy have sprung up, as have medical journals. As will be discussed in the next chapter, gene transfer exemplifies a trend toward large, dispersed, collaborative, transdisciplinary networks of basic researchers, clinicians, and investors in translational research.

In portraying gene transfer as the translational research ethicist's *Drosophila*, I do not want to deny important discontinuities with other translational research realms. For example, gene-transfer agents are far more complex than targeted, small-molecule drugs or monoclonal antibodies. As well, the field has historically centered on low-incidence genetic diseases (though the majority of gene transfer protocols involve non-hereditary cancers and cardiovascular diseases). These don't significantly undermine my thesis, however. Human beings don't have wings, bristles, and compound eyes; model systems always have their limits.

Plan for the book

Gene transfer is complex, and many of the ethical issues encountered in this book articulate with complicated scientific questions. Chapter 2 introduces the science, sociology, history, and ethics of gene transfer, and highlights some of the features about gene transfer that make it distinctive from ethical, social, and policy standpoints.

In Chapters 3 and 4 I examine gene transfer's most conspicuous ethical challenge: risk. I use the death of a volunteer in a 1999 experiment, and the lymphoproliferative disorders observed in five volunteers participating in an X-SCID study, as springboards for addressing what makes gene-transfer research risky, how risks might be evaluated, and how uncertainty should be managed in novel research arenas.

Chapter 5 turns to the question of medical benefits for study volunteers. Is a translational trial a form of therapy, or is it a vehicle for delivering care to desperate patients? This chapter looks askance at claims that early-phase trials of novel interventions have therapeutic value. But it also questions the drawing of too sharp a distinction between care and therapy.

Another point of contestation that has received very little attention is the purpose of a phase 1 trial. Arrayed around this question are clinicians and sponsors, who view the first-in-human studies as a pivotal step in designing phase 2 trials, and bench scientists who take a longer view in seeing phase 1 studies as a way of pursuing scientific questions. Chapter 6 offers an analysis of value and validity as they pertain to translational research trials, and explores the implications of this analysis for study design, assessment of risk, and informed consent.

Chapter 7 turns to the question of when to initiate human trials. Astonishingly, research ethics has yet to provide a sustained analysis of the ethical basis for launching first-in-human studies. This chapter presents a framework – the principle of modest translational distance – that might provide some ethical guidance for deciding trial initiation. It also suggests factors that investigators, IRBs, policy makers, ethicists, and others should consider in deciding whether a research program has sufficient maturity to move into human subjects.

Chapter 8 examines questions of justice and fairness in translational research. As is true for later-stage research, many early-phase gene-transfer trials recruit volunteers from low and middle-income countries. However, the prevailing ethical framework for deciding whether such studies fulfill fair subject selection has limited applicability to early-phase gene-transfer studies. This chapter explores various promising avenues that researchers might explore in order to comply with international consensus on transnational research.

Many commentators have castigated the field of gene transfer for “overselling” the technology's promise and “spinning” trial results. In Chapter 9 I reframe ethical concerns underlying these criticisms as problems of expectation management, and explore how various investigators and leadership figures have attempted to shape the public reception of both favorable and unfavorable developments. This chapter offers a more epistemologically informed ethical analysis of how translational research teams might interact with various publics.

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Chapter 10 pulls together various themes presented in this book, anchoring the narrative around the ethical difficulties presented by uncertainty. I then advance a series of research agendas extending from my analysis.

The issues explored in this book are largely situated at the juncture between the laboratory and the clinic. One consequence of this focus is that I will not explore with great depth a number of ethical and social questions traditionally associated with gene transfer. These include the deliberate inheritable genetic modification, the application of gene transfer to embryos and fetuses, and the use of gene transfer for cosmetic or enhancement interventions. I have elsewhere argued that the ethical questions raised by all three are no longer abstract or speculative: in vitro fertilization (IVF) clinics outside the USA *are* practicing a blunt form of inheritable gene transfer through ooplasmic transfer; clinical researchers *are* running trials investigating “life-style” conditions like erectile dysfunction.²² Still, these phenomena lead us away from the primary focus of this book, which can be distilled to the question of how to best protect human subjects and the public where medical knowledge is at its most uncertain.

Obviously, a premise underwriting this book is that indeterminacy alters the ethical calculus surrounding human experiments. If so, a necessary first step for ensuring ethical research conduct would be for scientists and ethicists to recognize the profound uncertainty they confront when testing novel interventions in human beings for the first time. Most researchers probably need no reminder of this point. Nevertheless, I have witnessed numerous occasions of high-profile researchers offering blustery pronouncements that were demonstrably refuted by scientific developments a year or two later. In a letter to King Frederick William of Prussia in 1767, Voltaire wrote that “Le doute n’est pas une condition agréable, mais la certitude est absurde” (Doubt is unpleasant, but to be certain is absurd). The admonishment applies equally well to ethics. The issues discussed in the book abound with moral uncertainty, and the analysis offered here is intended not as the final word, but as an invitation for more sustained social and ethical analysis.

References

- Okean MR. Anderson gets 14 years for child molestation. *Pasadena Star News* 2007 February 3.
- FitzGerald S, Smith VA. Penn to pay \$517,000 in gene therapy death. *Philadelphia Inquirer* 2005 February 10.
- Beutler E. The Cline affair. *Mol Ther* 2001; 4(5): 396–7.
- Weiss R. NIH not told of deaths. *Washington Post* 1999 November 3.
- Orkin SH, Motulsky AG. *Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy*. National Institutes of Health, 1995.
- Friend T. It’s in the genes: Scientists confront money issues. *USA Today* 2000 February 22.
- Naldini L. Inserting optimism into gene therapy. *Nat Med* 2006; 12(4): 386–8.
- Xin H. Chinese gene therapy. Gendicine’s efficacy: hard to translate. *Science* 2006; 314(5803): 1233.
- Guo J, Xin H. Chinese gene therapy. Splicing out the West? *Science* 2006; 314(5803): 1232–5.
- President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Splicing Life: A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings*. US Government Printing Office, 1982; 126.
- Walters L, Palmer JG. *The Ethics of Human Gene Therapy*. New York, Oxford University Press, 1997; 36.
- The National Commission for the Protection of Human Subjects of Biomedical, and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. US Department of Health, Education, and Welfare, 1979.
- Jayson G, Harris J. How participants in cancer trials are chosen: ethics and conflicting interests. *Nat Rev Cancer* 2006; 6(4): 330–6.

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14. Richter R. \$25 million gift to support bench-to-bedside research at Stanford. *Business Wire* 2006 September 14.
15. \$13 million grant creates Wallace H. Coulter Center for Translational Research at University of Miami Miller School of Medicine. *University of Miami News* 2005 December 16.
16. The Translational Research Facility: Where collaboration leads to improved human health. *UMN News* 2004 Winter.
17. Kaiser J. Biomedicine. NIH funds a dozen 'homes' for translational research. *Science* 2006; **314**(5797): 237.
18. Zerhouni EA. Translational and clinical science – time for a new vision. *N Engl J Med* 2005; **353**(15): 1621–3.
19. Rowett L. U.K. Initiative to boost translational research. *J Natl Cancer Inst* 2002; **94**(10): 715–16.
20. Wadman M. Drive for drugs leads to baby clinical trials. *Nature* 2006; **440**(7083): 406–7.
21. Lehmann F, Lacombe D, Therasse P, Eggermont AM. Integration of translational research in the European Organization for Research and Treatment of Cancer Research (EORTC) clinical trial cooperative group mechanisms. *J Transl Med* 2003; **1**(1): 2.
22. Kimmelman J. The ethics of human gene transfer. *Nat Rev Genet* 2008; **9**(3): 239–44.

Chapter

2

What is gene transfer?

Introduction

Gene transfer researchers and others with historical inclinations like to describe an experiment performed by virologist Stanfield Rogers in the early 1970s as the first attempted gene transfer in human subjects.^{1–4} The Oak Ridge National Laboratories scientist had observed that Shope papilloma virus infections, which normally cause warts, also depress blood serum levels of the amino acid arginine in rabbits. Studies also showed that workers handling the virus also had lower serum arginine.⁵ Rogers then postulated that the virus contains a gene that codes for the enzyme arginase, which breaks down arginine.

Around the same time the German physician H. G. Terheggen in Cologne encountered a series of patients with various neurological impairments due to a deficiency in the enzyme arginase.^{6,7} On learning of the report, Rogers contacted Terheggen and proposed administering the virus to patients with the enzyme deficiency. The study, notwithstanding its bold vision, proved unsuccessful in either improving disease symptoms or in producing biological insights. In fact, the virus used in the experiment “degenerat[ed]... in storage,”⁸ and much later studies revealed that in fact the virus did not encode arginase after all.

There is, of course, a sense in which the conceit behind contemporary gene transfer can find precedent in this episode. But Rogers’s experiment predated recombinant DNA technologies, which emerged in the mid 1970s and enabled manipulation of genetic sequences. It also predated the development of a biotechnology industry, or the knowledge economy, or the emergence of the “triple helix” configuration of universities, the private sector, and the government.⁹ And in their wholesale abandonment of the strategy, Rogers’s experiment stands in stark contrast to the perseverant and programmatic orientation of gene transfer research today. In this sense, Rogers’s “first gene-transfer experiment” bears as much relation to contemporary gene transfer as semaphore does to modern telecommunications.*

So what is gene transfer? Scholar Sheila Jasanoff distinguishes between three different ways that biotechnologies have been framed in policy: as products, processes, and programs.^{10,11} The first is the most familiar, and most accounts of the ethics of gene transfer begin with a description of the hardware. This book will not depart from that tradition. But a comprehensive account of gene transfer policy and ethics should also consider the processes by which these technologies are developed and applied, as well as how gene transfer fits within broader economic and social agendas. To that end, this chapter approaches the question “what is gene transfer?” from three different standpoints.

* At any rate, numerous earlier “gene-transfer” precursors can be identified. They include the use of oncolytic viruses in cancer treatment (traceable to the turn of the 20th century); earliest use of blood transfusion to treat hemophilia (1840s); and the development of organ and bone marrow transplantation throughout the 1950s and 1960s.

The product

I define human gene transfer as follows: *the use of genetic materials, genetic-based strategies, or genetically modified organisms to study or modify human biology*. This is more generic than conventional definitions, which tend to use the term “gene therapy” to mean “the use of normal genes or genetic material to replace or cancel out the ‘bad’ or defective genes in a person’s body that are responsible for a disease or medical problem.”^{12†}

There are many reasons why the conventional terminology and definition are unsatisfactory. One is that that, for years, many in the research community have called these techniques “gene therapy” despite a lack of evidence of efficacy. Because this optimistic characterization of the technology can cloud risk assessment, public communications, and informed consent, this book will use more the neutral terminology of “gene transfer.” In addition, the conventional definition lacks comprehensiveness. For example, some of the most informative “gene therapy” studies in the first five years of clinical testing involved “gene marking,” in which cells were tagged with genetic sequences in order to determine whether certain cells proliferated in the human body, or where they traveled. Lastly, one of the most controversial extensions of “gene therapy” is genetic enhancement (that is, the use of gene transfer technologies towards cosmetic ends such as increased muscle mass for athletes, or higher intelligence in children). Such applications fit very uncomfortably under the category of “therapy.” According to Sheldon Krimsky, the term “gene therapy” originated as a kind of lexical foil to 1980s controversies surrounding human genetic engineering.¹⁸ Regardless of whether this account is historically accurate, I think it is safe to say that “gene therapy” obscures many of the central ethical issues surrounding the techniques and practices it embodies (the same goes for “cell therapy,” which I prefer to call “cell transplantation,” and for “therapeutic cloning,” which I prefer to call “somatic cell nuclear transfer.”)

Another reason to question conventional definitions is that there is much they leave out. This will be apparent upon the most casual browsing of gene transfer journals like *Molecular Therapy*. For example, researchers are currently developing genetically modified viruses aimed at stimulating powerful immune responses to infectious disease agents like HIV. Others are attempting to genetically modify intestinal bacteria to secrete growth factors in order to treat conditions like Crohn’s disease.^{19,20} Another promising technique is modifying viruses so that they selectively infect and kill tumor tissues. Such strategies do not involve modifying genes in a person’s body, unless one counts unwelcome viruses, or gut flora, as part

[†] The US Department of Energy defines gene therapy as “a technique for correcting defective genes responsible for disease development. Researchers may use one of several approaches for correcting faulty genes.”¹³ The official definition of the American Society of Gene Therapy, the US professional society, is “an approach to treating disease by either modifying the expressions of an individual’s genes or correction of abnormal genes.”¹⁴ Elsewhere, this organization uses a slightly modified definition: “the process of inserting nucleic acids (e.g. usually DNA/genes) into cells or tissues to correct or prevent a pathological process.”¹⁵ The European Society of Gene and Cell Therapy uses the following definition: “a technology by which genes or small DNA or RNA molecules are delivered to human cells, tissues or organs to correct a genetic defect, or to provide new therapeutic functions for the ultimate purpose of preventing or treating diseases.”¹⁶ The OECD definition is: “Gene delivery, the insertion of genes (e.g. via retroviral vectors) into selected cells in the body in order to: Cause those cells to produce specific therapeutic agents; Cause those cells to become (more) susceptible to a conventional therapeutic agent that previously was ineffective against that particular condition/disease; Cause those cells to become less susceptible to a conventional therapeutic agent; Counter the effects of abnormal (damaged) tumour suppressor genes via insertion of normal tumour suppressor genes; Cause expression of ribozymes that cleave oncogenes (cancer-causing genes); Introduce other therapeutics into cells.”¹⁷

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of a person's body. Other strategies do more than simply “replace” or “cancel out” genes in a person's body. For example, one strategy researchers have pursued involves genetically modifying stem cells that give rise to blood tissues in order to enable patients to withstand higher doses of chemotherapy.

Another factor that complicates the definition of gene transfer is the question: what is a gene? Early on, gene transfer experiments used genetic sequences that clearly fit the canonical definition of “gene”: a sequence of nucleotides that encodes a protein product. Quickly thereafter, however, scientists began pursuing oligonucleotide strategies, in which chemically modified DNA sequences are administered to a person to thwart the production of certain gene products. More recently, many researchers have been pursuing RNA interference approaches, in which small genetic sequences are used to produce short RNA molecules that bind to specific RNA sequences in a person's body, thereby “knocking down” expression of genes. These interfering RNAs do, indeed, count as “genes,” but not in the traditional sense.

The target

The techniques and strategies of gene transfer are immensely varied. Nevertheless, they sort into several politically and ethically relevant classes. One key distinction is the entity to which genetic materials are transferred. These divide into three categories: germ cells, somatic cells, and foreign organisms.

Germ cells produce sperm or ova. Genetic modifications of these cells will generally be passed on to the recipient's progeny. Inheritable genetic modification has received considerable attention from ethicists and policy makers. Many jurisdictions, like the European Community,²¹ Canada,²² and India,²³ ban the practice. Officially, the technique is not currently being pursued in human beings (though germ cell modification is being investigated preclinically). “Unofficially,” however, some infertility clinics outside of Europe and North America do offer ooplasmic transfer, which involves transplanting mitochondria from viable ova into those of infertile women.²⁴ Because mitochondria contain their own genome, the technique is arguably an oblique form of germline modification. Readers interested in the ethics of germ cell modification are directed to other sources.^{25, 26}

Somatic cells include any tissues that do not give rise to sperm or ova; they include skin, liver, blood, the nervous system, muscle, tumor cells, etc. The therapeutic benefits or risks of somatic gene transfer stop with the individual recipient of the gene transfer. Somatic cells can, themselves, be divided into two broad categories: those that are highly differentiated and those that are not (stem cells). Differentiated tissues do not develop into different tissue types and, as a rule, do not propagate. If genetically modified, differentiated tissues are often lost to aging or injury. In contrast, stem cells in adults can develop into different tissues and replenish themselves. Gene transfer aimed at adult stem cells (and attendant risks and benefits) is thus more likely to be permanent.

Modified foreign organisms include bacteria, viruses, or fungi. These were briefly mentioned above. Though the target here is the individual patient, one concern these approaches raise is the possibility that modified organisms will spread to members of the public.

Vehicles and vectors

With millions of years of evolutionary pressure, mammalian organisms like human beings have developed numerous ways to safeguard their genomes and repel foreign DNA. One of the central challenges for gene transfer, then, is delivering genetic materials into a person's cells and getting those materials to express themselves.