MEDICINE

# A History Lesson for Stem Cells

Factors that led to the decline of gene therapy at the turn of the century should be considered by the stem cell community to avoid a similar outcome.

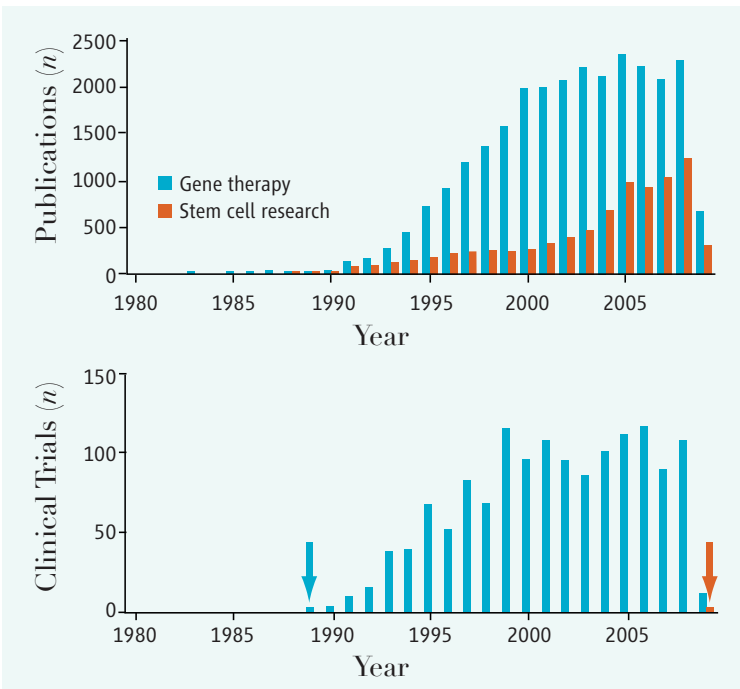
**James M. Wilson**

When President Barack Obama signed an Executive Order on 9 March 2009 rolling back the previous administration's restrictions on federal funding of human embryonic stem cell (hESC) research, he took pains to temper Americans' hopes for quick fixes. "At this moment, the full promise of stem cell research remains unknown and it should not be overstated," the president said. "I cannot guarantee that we will find the treatments and cures we seek" (*1*). Unfortunately, some stakeholders in hESC research have failed to exhibit the same restraint, effectively promising cures for Parkinson's disease, Alzheimer's disease, spinal cord injuries, diabetes, cancer, heart disease, multiple sclerosis, muscular dystrophy, macular degeneration, and hearing loss, to name a few.

Studies of hESCs and their non–embryo-derived counterparts, induced pluripotent stem (iPS) cells, will likely deepen our understanding of cell differentiation, human development, and birth defects. Hopefully they will also lead to novel therapeutics for some diseases, and I applaud President Obama for giving scientists longer leashes as they explore this exciting field. But in today's clamor of stem cell enthusiasm it is possible to detect haunting echoes of the early and ultimately troubled days of gene therapy.

The field of gene therapy began with laboratory studies in the mid- to late-1980s and grew linearly during the 1990s (see figure, right). Very early in this evolution, clinical trials were initiated, and their number and overall patient recruitment figures grew in step with the science. During that period, gene therapy was touted as a potential cure for a huge array of ailments. By 2000, researchers had launched more than 400 clinical trials, testing the approach against a wide spectrum of illnesses. Yet the Food and Drug Administration concluded in a September 2000 review, "the hyperbole has exceeded the results" and "little has worked" (*2*). Although the field has improved since then, with notable successes against inherited blindness (*3*–*5*) and immune deficiency (*6*), those successes are shadowed by several tragic adverse events, including treatment-induced cancers in some volunteers (*7*) and, in 1999, the death of an 18-year-old, Jesse Gelsinger, in a gene therapy clinical trial that I led (*8*). Gelsinger's death initiated a chain of events that seriously derailed the field.

It would be unfortunate if the field of hESC research missed this lesson from history and took a similar trajectory. Yet many of the social and economic forces that drove gene therapy's burst of clinical activity also exist today in the stem cell arena. Without passing judgment on the scientific merits of any individual clinical study or plan, I am concerned that expectations for the timeline and scope of clinical utility of hESCs have outpaced the field's actual state of development and threaten to undermine its success.




**Publications and clinical trials (1980–2009) related to gene therapy and hESCs.** (Top) Publication data were retrieved from ISI Web of Knowledge (www.isiknowledge.com). Gene therapy publications include English language articles or reviews retrieved by using the search terms "gene therapy." ESC publications include English language articles or reviews found by using the search terms "embryonic stem cell," "ES cells," or "ESC." (Bottom) Gene therapy clinical trial data was extracted from Gene Therapy Clinical Trials Worldwide (*15*). ESC clinical trial projected start date taken from (*16*). Data for 2009 are incomplete. Arrows indicate the point when clinical trials started for gene therapy and are projected to begin for hESC.

The hyperaccelerated translation to the clinic that occurred in the field of gene therapy in the 1990s was driven by multiple factors, including: (i) a straightforward, if ultimately simplistic, theoretical model indicating that the approach "ought to" work; (ii) a large population of patients with disabling or lethal diseases and their affiliated foundations harboring fervent hopes that this novel therapy could help them; (iii) unbridled enthusiasm of some scientists in the field, fueled by uncritical media coverage; and (iv) commercial development by the biotechnology industry during an era in which value and liquidity could be achieved almost entirely on promise, irrespective of actual results.

In response to growing concerns that the field was getting ahead of itself, Harold Varmus, then director of the National Institutes of Health (NIH), convened a panel in 1995 chaired by Stuart Orkin and Arno Motulsky to "assess the NIH investment in research on gene therapy" (*9*). Prime among the committee's conclusions was that scientists' basic understandings of gene-transfer vectors and host-vector interactions were inadequate to support successful clinical development of the field and that stakeholders had oversold their results. Indeed, the panel concluded that "only a minority" of clinical studies had been designed in ways likely to yield "useful basic information." The report recommended that researchers get back to basics and develop a

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more robust understanding of gene transfer in animals.

The researchers continued to pursue clinical trials aggressively. And the hype continued until the turn of the century when a confluence of events—the tragic and widely publicized death of Jesse Gelsinger, questions regarding regulatory oversight of gene therapy, bursting of the overall biotech bubble, and stakeholder impatience due to unmet expectations—led to a precipitous decline in financial and public support.

The central concern of the Orkin-Motulsky panel, a lack of scientific understanding about vectors and vector-host interactions, proved to be on the mark. Virtually every major unexpected toxicity encountered in gene therapy clinical trials can be attributed to complex interactions between vector and host that were not predicted by, or understood at the time of, preclinical studies. Learning from these travails, the gene therapy community eventually adopted a more sober approach to clinical trials and bolstered its commitment to basic vector biology and disease pathogenesis.

Many of the factors that fueled gene therapy's premature expansion are major drivers of the hESC and iPS research agenda today. A large and vocal population of patients suffering from a wide variety of ailments is pressing for stem cell–based therapies. Disease-specific stem cell research groups are more politically sophisticated than ever, in some cases employing congressional lobbyists. Unrealistic expectations have been fueled by relentless media coverage, driven in part by a factor not present in the gene therapy roll-out: a debate over the ethics of research on human embryos and embryo cells, which has served as a "news hook" that brings media attention to even the most incremental of advances.

It is difficult to avoid getting caught up in the unabashed enthusiasm that attends the emergence of a novel, but untested, therapeutic technology platform, as I myself experienced. Still, January's media coverage of the first U.S. Food and Drug Administration (FDA) approval of a hESC-related clinical trial—an experiment sponsored by Geron Corporation of Menlo Park, California, aimed at spinal cord injuries—was surprising for its lack of restraint. News reports characterized Geron's mere gaining of federal permission to test the cells in patients as a "breakthrough" (*10*). And in a highly questionable move, *Good Morning America* accompanied its news report with faux video footage depicting the paralyzed actor Christopher Reeve getting out of his wheel chair and walking again (*10*).

Proponents of clinical trials can argue that by some measures, at least, the stem cell field is further along than gene therapy was when clinical studies began in 1990. More papers have been published on the basic biology of hESCs than were published on gene therapy before that field's first clinical trials (see figure on page 727). Furthermore, we have witnessed during the last 2 years a multitude of discoveries in the basic cell biology of stem cells.

Despite advances, our understanding of the biology of hESCs and iPS cells remains thin with regard to clinical safety and utility. Controlled incorporation of transplanted stem cells into host tissues and organs remains a major challenge. Questions about engraftment, rejection, and toxicity abound. Steps involved in transformation of hESCs, iPS cells, or their derivatives into tumor cells (and strategies to ablate any tumors that might arise) need further investigation. In February, researchers in Israel reported that a 13-year-old boy with ataxia telangiectasia who had received injections of human fetal neural stem cells into his brain as part of an experimental treatment performed in a Russian clinic developed brain tumors apparently derived from the injected stem cells (*11*).

The purpose of raising these issues is not to undermine policy changes now under way at the National Institutes of Health that aim to increase support for basic stem cell studies. Such basic studies are exactly the kind that must be done if embryonic or iPS cells are to move responsibly into the clinical arena. The key question is how can stem cell therapeutics avoid the pitfalls encountered in clinical gene therapy research?

Excellent preclinical regulatory review is key, of course, and, for example, Geron's cells are different from those used in the Russian study and have withstood rigorous FDA analysis. Professional societies, such as the recently established International Society for Stem Cell Research (ISSCR), can also play an important role in steering this young discipline in the right direction. Leadership of the society must steadfastly discourage overselling the clinical reality of stem cell therapeutics (*12*) and must effectively communicate how long it takes to go from laboratory bench to bedside. To get ahead of the impending avalanche of clinical trial proposals using hESC- and iPS-derived cells, the society has promulgated thoughtful and comprehensive guidelines for clinical translation (*13*). However, adherence to these guidelines is voluntary because the society does not have regulatory authority.

A high degree of transparency is also necessary to secure the public's trust and support. This was accomplished in gene therapy through the Recombinant DNA Advisory Committee (RAC) of the NIH, to which adverse events had to be reported and whose deliberations, though nonbinding, were open to the public. After the reports of Jesse Gelsinger's death, gene therapy's public image suffered further when news stories revealed that a number of researchers had failed to report adverse events to the RAC as required. The NIH should consider the potential value of a RAC-like board for the early generations of stem cell–related clinical trials (*14*)—not to add an extra layer of pre-clinical review to that already done by FDA, but to oversee a public registry of clinical trials and to serve as an open forum for addressing novel trial-related issues. The board should also consider whether some of the ISSCR's recommendations on clinical trials should be codified in NIH guidelines.

It is gratifying that through its current crafting of new funding guidelines and the launching of new initiatives (*17*), the NIH is making basic stem cell research a high priority. But, I encourage hESC and iPS researchers to remember the Orkin-Motulsky report's central theme: that no one is served by bypassing the hard work of basic research and experiments in animal models.

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