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Turning back the clock

At the end of this month, the US Senate is expected to hold hearings and vote on legislation that would outlaw all forms of human cloning. If approved, the legislation would go beyond banning federal funds for research: it would make human nuclear transplantation a criminal offense punishable by a $1 million fine and up to ten years in prison. It would also prohibit the import and use of any treatments developed through this technique in countries, such as the United Kingdom, where therapeutic cloning is now legal. The bill is an unprecedented step backward because it makes basic scientific research not just unlawful, but criminal.

The central argument behind the legislation goes something like this: nuclear transplantation research is bad *per se* because it requires the creation and destruction of embryos. Embryonic stem (ES) cell research is slightly less bad (but still unpalatable) because it also involves embryo destruction (though not creation). And adult stem cell research is not bad at all because it circumvents troublesome embryos altogether. Essentially, scientists cannot be trusted to work with cloned human embryos (those that do must be punished); and they cannot be trusted to derive new ES cell lines (they must work only with the scant supply of pre-existing ones). Instead, they can perform miracles with adult stem cells, transforming preliminary research into life-saving treatments for debilitating diseases and spinal injuries.

US president George W. Bush has also been indulging in stem cell rhetoric (p. 421). In a speech at the White House in April, he made his strongest condemnation of human cloning to date, announcing his intention to "prevent human cloning by stopping it before it starts." In supporting the legislative ban, he warned that the research would inevitably lead to "embryo farms," "the exploitation of women's bodies," and "a society in which human beings are grown for spare body parts and children engineered to custom specifications." Simplistically, the same speech singled out adult stem cells as a medical treatment of particular promise.

The Brownback–Landrieu bill sets a dangerous precedent that threatens an entire branch of the biotechnology enterprise worldwide, not just in the United States. If there is no market for ES cell or cloning products in the United States, there is, in essence, no market anywhere. No venture capital group would invest in a technology robbed of its major market by legislation when there are so many other permitted technical avenues to back. For many reasons, the bill does not stand up at the level of international trade and it does not stand up scientifically.

First, it would clearly contravene the US's World Trade Organization commitments, commitments that are precisely equivalent to those that the US is keen to see other economic powers respect. European legislators, for instance, might offer arguments of moral repugnance in defense of their indefensible stand on GM crops. Under WTO rules, the US could argue against products derived from nuclear transplantation or ES cells if they were a threat to human or environmental health. But this is hardly tenable.

The bill is also suspect in that it relies on the flimsiest and most preliminary of evidence that adult stem cells might provide alternative solutions to the problems for which embryo technology is needed. Research does suggest that, under the right conditions, certain adult cells can be programmed to clonally expand into cells of another type. However, the full potential plasticity of adult stem cells remains largely undetermined. There is certainly no proof that they can reconstitute all the 220 specialized cell types that make up an adult human body. And though multipotent adult progenitor cells have purportedly been isolated from human skin, muscle, and bone marrow, most of these reports remain unconfirmed.

The difficulties of working on the elusive stem cells that lurk in adult tissues have not helped. In February, for example, one group retracted its previous claim that muscle stem cells could give rise to blood cells and another failed to reproduce earlier work that turned neural stem cells into blood cells. Perhaps most serious of all, the finding that ES cells can fuse with adult stem cells in coculture throws into question whether previous observations of transdifferentiation were due to reversion of adult stem cells or expansion of abnormal hybrids (e.g., see pp. 425 and 426).

Stem cell technology is currently a work in progress. It is thus completely premature to frame adult stem cells as a viable alternative to cloned ES cells. Now is not the time to stop research in its tracks. What is needed is a systematic characterization of the signals and mechanisms that trigger the reprogramming of an adult nucleus. We need to understand the growth factors and genes that control plasticity in ES cells because this will facilitate understanding of plasticity in adult cells.

To do that we must first focus on the cytoplasm of human eggs. Currently, nuclear transplantation into the cytoplasm of an egg is by far the most effective means of resetting the genome of an adult donor nucleus. It would be very interesting to discover the factors in egg cytoplasm that confer the unique capacity to reprogram nuclei. The cytoplasm of different ES cells might also be a good place to look, although there are likely to be differences among species. Technologies such as the *in vitro* reprogramming system described on p. 460 may also be used to complement ES cell work.

Ultimately, such research should make it possible to identify sets of proteins involved in chromatin remodeling, imprinting, silencing, and DNA methylation and packaging that can be used for dedifferentiation and reprogramming. Such proteins could then be produced by recombinant means and used to transdifferentiate adult stem cells into more primitive forms capable of forming cell types suitable for medical applications. These medical needs could be served without "embryo farming"—but some experimentation on eggs or ES cells is needed now so that we can start to understand what is going on.

Instead of pursuing a law to ban cloning technology, the US government should be funding it. In doing so, it could set up stringent guidelines, tighten regulatory oversight, and beef up internal review boards to ensure that researchers use the technology appropriately. If this flawed bill passes the Senate, it will stop cloning research in its tracks in the United States, and it will halt investment in the applications of cloning worldwide. But the real losers will be those patients in need of cloning-derived therapies who die or suffer unnecessarily before US legislators see sense.