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## Justice, ethnicity, and stem-cell banks

Stem-cell research has been plagued by controversy about the ethics of using human blastocysts for research and therapy. Although this issue is important, it is by no means the only ethical issue facing stem-cell research. When stem-cell researchers begin to develop therapies for human disease, their work will raise important questions of justice. Some of these questions are not unique to stem cells. Like many newly developed treatments, stem-cell therapies are likely to be expensive; at least initially, they will probably benefit only the wealthy. But stem-cell therapies present a further problem, because even without economic barriers to their use the biological properties of stem cells might make these therapies less accessible to some than to others. We have discussed this problem,<sup>1</sup> which we refer to as the problem of biological access to stem-cell therapies, as it might arise in the USA. Here we develop our arguments and extend them to European nations.

We assume that in the immediate future, stem-cell therapies will involve the transplantation of donor stem cells rather than the development of autologous stem-cell lines. One of the biggest threats to the success of both conventional and cell-based transplants is immune rejection. At present, the only reliable defence against this rejection is close matching of HLA types between the donor and recipient coupled with immunosuppressive therapy, and we assume that for the foreseeable future this combination will remain the best means of preventing rejection.

The necessity of HLA matching for successful transplantation raises serious questions of public policy and justice. For example, in the USA, African-American transplant recipients are much less likely to find a good match than members of other ancestral or ethnic groups. Public-policy responses to this situation have been limited to attempts to increase overall

donation rates coupled with specific efforts to increase donations in the African-American community. Fortunately, however, the characteristics of cell-based therapies allow for a more proactive approach to the problems presented by HLA matching. Whereas we are not currently able to produce solid organs or tissues for transplantation, we can create stem-cell lines for research and therapy. And whereas donated organs can be used only once, stem-cell lines can provide cells for transplantation into many patients. This means that unlike their counterparts in organ banks and distribution systems, the designers of stem-cell banks will have the ability to decide which lines to include, and thus to consider which should be included if the bank is to satisfy considerations of justice.

The ideal stem-cell bank would include a sufficient variety of HLA types to allow every potential recipient to receive a good match. However, a bank structured in this way would require the creation and maintenance of an enormous number of stem-cell lines. Unfortunately, creating a bank with such a large number of lines is impractical for various reasons, including the huge financial cost. Because we cannot design a bank so that all can benefit, we must ask which principles justice requires that we follow in deciding which stem-cell lines to include and which to omit.

### Coverage-maximising strategy

The most obvious strategy is to include in the bank those stem-cell lines that would allow the greatest percentage of the population to find a match in the bank. Because some haplotypes are more common than others, including lines with common haplotypes would allow more people to benefit from stem-cell therapies. The advantage of the coverage-maximising strategy is that it provides for the largest number of potential

beneficiaries of HLA-matched stem-cell-based treatments. In public policy, maximising benefit is a compelling moral consideration. Public resources are always scarce, and their prudent deployment is a moral imperative. Considerable public funds will have been invested in the development of stem-cell-based therapies, and it is reasonable for the public to expect these investments to result in as much benefit as possible.

However, this strategy has one important drawback. The frequency with which particular haplotypes occur varies considerably from one ancestral/ethnic group to another. Although some of the haplotypes most common in whites are also common in other ancestral/ethnic groups, most are not. In the USA and Europe, those haplotypes that would allow the greatest number of people to find a match are likely to be haplotypes common in whites, simply because in those countries whites are the most populous group. Moreover, the inclusion of a haplotype found in even a small percentage of whites could extend coverage to a larger number of people than the inclusion of even the most common haplotype of a different ancestral/ethnic group. Therefore, if a bank included stem-cell lines with the 50 most common haplotypes in, for example, the UK, the likely result would be a bank composed mainly of lines whose haplotypes are common to those members of the UK population who are white. Residents of African descent, who as a group continue to experience systematic disadvantage and have poorer health status than whites, would be unlikely to find matches in the bank and thus are unlikely to gain from whatever health benefit stem-cell science is likely to bestow.

Moreover, the differences in biological access to stem-cell therapies for different ancestral/ethnic groups are likely to be large. We calculate that a stem-cell bank containing homozygous lines with the 25 most common haplotypes in the USA would provide matches for about 40% of white Americans, but only 7.8% of African-Americans and 3.6% of Asian-Americans.<sup>1</sup> These differences would probably be even greater in European countries, since they have proportionally smaller non-white populations.

### Ancestral/ethnic representation strategy

This problem could be avoided if the designers of a stem-cell bank included enough of the most common haplotypes from each of the major ancestral/ethnic groups in the country for which the bank is being designed to allow an equal proportion of members of each group to find a match. This ethnic-representation strategy would be less efficient than the coverage-maximising strategy because it would take more cell lines to match the same number of patients overall. There are two reasons for this decrease in efficiency. First, the point of the ethnic-representation strategy is to extend coverage to the same proportion of each ancestral/ethnic group, even though a given percentage of a smaller group includes fewer total people than the same percentage of a larger group. Second, because of varying HLA diversity between ancestral/ethnic groups, different numbers of cell lines would be needed to cover the same percentage of different groups.

Thus the designers of stem-cell banks must choose between different strategies. Of the two we have mentioned, the

coverage-maximising strategy makes stem-cell therapies biologically accessible to the greatest number of people, but in North America and Europe those people would be overwhelmingly white. The ethnic-representation strategy would provide coverage for the same proportion of people from each ancestral/ethnic group, but it would cover fewer people overall. We do not take lightly the idea of designing a bank in such a way that fewer patients can benefit from it. Nonetheless, we believe that the ethnic-representation strategy should be adopted in societies that have a history of subjecting others to substantial indignities and reduced opportunities and rights merely because they are members of stigmatised groups, and where such a strategy is needed to ensure that the interests of members of these groups are protected.

### Arguments for the ethnic-representation strategy

There are two main arguments for this view, one of which can be met by proponents of the coverage-maximising strategy whereas the other cannot. First, the comparative welfare of groups that have been systematically disadvantaged matters morally, especially when members of those disadvantaged groups are less well off than others. When such disparities occur in health, expressed either in life expectancy or burden of disease, they are rightly priorities for public-health policy.<sup>2</sup> If health disparities between disadvantaged groups and others in society are understood as present injustices, public policy should not be formulated in ways that make them worse. It is important to note that increases in health disparities are not necessarily unjust. If, for example, increasing health disparities were the necessary consequence of improving the condition of the disadvantaged groups, such increases would arguably be consistent with principles of justice. The presumption against widening the gap is thus a defeasible one. However, we do not see any considerations that would defeat this presumption in the case at hand. If, in addition to being present injustices, health disparities are the result of past injustices, as members of the society that perpetrated those injustices we have a positive obligation to take steps to ameliorate their effects. For these reasons, we should not adopt policies that worsen the effects of group oppression, even if the factors that lead our policy to have this effect—eg, greater HLA diversity in one population group compared with another—are themselves unrelated to any historical or current social injustices, and even if the policy that widens the disparity does not reflect an intentional effort to deny access to stem-cell therapies to any group.

Supporters of the coverage-maximising policy might accept this argument, but deny that it rules out the strategy they prefer. The problem with the coverage-maximising strategy is that it exacerbates health disparities between ancestral/ethnic groups in the country for which a stem-cell bank is being designed. But there are many ways of reducing such disparities, and making stem-cell therapies biologically accessible to disadvantaged groups is unlikely to be the most cost-effective. If some other measure would allow us to reduce the disparities between ancestral/ethnic groups more cost effectively, we could construct a bank with as many stem-cell



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Inside the Medical Research Council's UK stem-cell bank

lines as we would have included from the majority group, take more cost-effective steps that would provide as great a reduction in health disparities between groups as the ethnic-representation strategy, and use the resources left over to reduce those disparities even more or to include more stem-cell lines in the bank. In either case, this approach would be preferable to the ethnic-representation strategy, because it would achieve at least as great a reduction in health disparities while providing greater benefits overall.

This approach obviously requires that both the construction of a stem-cell bank and the additional measures to reduce health disparities actually be undertaken. In some contexts, advocates of reducing such disparities might worry that if this approach were adopted, a stem-cell bank would be constructed according to the coverage-maximising strategy, but the further measures to reduce health disparities would fall by the wayside. But such an outcome would imply not that the coverage-maximising strategy is not preferable in principle, but only that the best alternative—constructing a bank in accordance with the coverage-maximising strategy while taking more efficient steps to reduce health disparities between groups—is not politically feasible.

The second argument for the ethnic-representation strategy is that it would prevent the expressive harm that would result from unequal representation. The justification for adopting the coverage-maximising strategy is that it would provide medical benefits to the greatest number of people, without regard for the implications for different ancestral/ethnic groups. That adopting the coverage-maximising strategy would make the benefits of stem-cell research available almost exclusively to whites is an unfortunate consequence of this strategy, not part of its justification. However, since in practice it would prevent most members of non-white ancestral/ethnic groups from finding matches within the stem-cell bank, members of those groups might wonder whether their interests had been taken seriously by those who decided how to structure the bank. In view of the history of colonialism and race relations in the USA and Europe, this concern cannot be dismissed as unreasonable. We should not act in ways that give some members of our

societies reason to doubt that they are regarded as full and equal citizens whose interests are taken seriously, especially when those doubts have often been well founded.

That this concern is reasonable is important to our argument. We cannot require that stem-cell banks be designed in such a way that no-one could possibly believe that their interests had not been taken seriously, since there is no policy so obviously noble that no-one could conceivably misinterpret the motives behind its adoption. However, the creation of a stem-cell bank that covers a much greater proportion of whites than of other ancestral/ethnic groups is not just a policy that someone might misinterpret as reflecting a failure to take non-white citizens' interests seriously; it is a policy that plainly invites that interpretation. This is not simply because such a bank would overwhelmingly favour members of one population over another. If, for example, the coverage-maximising strategy were to result in disproportionate coverage of people who are left-handed, that fact alone would not make it reasonable for right-handed people to conclude that their interests had not been taken into account. Since North American and European countries have no history of discrimination against the right-handed, there would be no reason for right-handed people to think that the disproportionate coverage of left-handed people reflected a failure to take seriously the interests of the right-handed.

By contrast, members of non-white ancestral/ethnic groups share two features. First, they would be significantly under-represented in a bank designed according to the coverage-maximising strategy. That these groups would be significantly under-represented is important. If the coverage-maximising strategy would result in a bank that covered 51% of whites and 49% of members of other groups, it would arguably not be reasonable to conclude that only the interests of whites had been taken into account. What degree of discrepancy in coverage would make that conclusion reasonable is an interesting question. But because the results of adopting the coverage-maximising strategy in any North American or European country would clearly exceed it, we will not consider it further. The second feature is that non-white ethnic groups have endured a history of discrimination in the USA and Europe. It is only because non-white ethnic groups would be significantly under-represented and because they have endured a discriminatory history that members of those groups might reasonably conclude that their interests had not been taken into account if a stem-cell bank were designed according to the coverage-maximising strategy.

Adopting the coverage-maximising strategy would give members of minority ancestral/ethnic groups reason to wonder whether those who decided how to structure the bank had taken their interests into account at all. We believe that this outcome is not just a political problem. When citizens in a democracy come to believe that their government does not take their interests into consideration when formulating public policy, they question whether they are regarded as full and equal citizens of the country in which they live. This belief harms members of minority ethnic groups directly; it harms all citizens indirectly, insofar as it affects participation by members

of minority groups in politics; it affects the quality of our political decision-making; and it damages our relations with one another and the fabric of the democracies in which we live.

The ethnic-representation strategy does not make stem-cell therapies available to the greatest possible number of people. However, the strategy does make those therapies available to the greatest number that is consistent with an expression of respect for the fundamental equality of members of minority ancestral/ethnic groups. Given the history of oppression of minority groups in the USA and Europe, and the continued fragility of race relations, a policy that made the benefits of stem-cell research available almost exclusively to whites would signal a failure to acknowledge the equal worth of people of

all ethnic groups. Because the coverage-maximising strategy would have this effect, we believe that the ethnic-representation strategy should be adopted.

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## Searching for reputability: first randomised study on bone-marrow transplantation in the heart

Blood stem cells gained attention as early as 35 years ago. 1968 saw the report of their clinical use for restoring the blood and the immune system in children with congenital immunodeficiencies.<sup>1</sup> Haemopoietic stem cells are now used routinely in clinics, mainly for treating disorders of the haemopoietic and immune system. However, in the past few years, it has been found that this type of adult stem cell has higher plasticity than anticipated—ie, it can “transdifferentiate” into other tissue types. Orlic et al<sup>2</sup> reported massive transdifferentiation of bone-marrow-derived haemopoietic stem cells into cardiomyocytes after cardiac injury in mice. Such transdifferentiation was an exciting discovery in the search for cell-replacement therapy in patients with cardiac infarction, heart failure, or both. Human clinical trials began immediately. Left ventricular function could be improved somewhat,<sup>3</sup> regardless of whether the cells were injected into the affected coronary artery,<sup>4,5</sup> directly into heart muscle surrounding the injured area,<sup>6</sup> or transendocardially via laser.<sup>7,8</sup> However, the increase in ejection fraction was only 5–8%. This moderate improvement, combined with reports that the prominent transdifferentiation of haemopoietic stem cells into heart-muscle cells cannot be reproduced in mice,<sup>9–11</sup> raised serious doubts about the concept of differentiation across tissue lineage-boundaries.<sup>12,13</sup> Furthermore, existing clinical studies were limited by lack of randomisation and double-blinding.<sup>3–7</sup>

Therefore the randomised trial in today’s *Lancet* by Kai Wollert and colleagues is an important first. These investigators randomly assigned patients after myocardial infarction to be controls or to receive bone-marrow-derived cells injected into the artery supplying the infarct-affected area (30 per group). Left ventricular ejection fraction improved by 6.7% in the bone-marrow group, but only by 0.7% in the controls.

Clinicians and basic scientists will now wonder about how to move forward. Because of the studies in mice<sup>9–11</sup> and the clinical variables in the human studies indicating the lack of prominent transdifferentiation, it is essential to understand the mechanism(s) underlying the clinical amelioration. The mechanism might involve improved angiogenesis or vasculogenesis, better

survival of hibernating myocardium, paracrine effects of injected cells, or modulation of the wound tissue. Human clinical studies are unlikely to be helpful in discovering the mechanism, and laboratory and animal studies will be needed. Such research is even more important now, because another clinical trial that is using treatment with granulocyte-colony stimulating factor and intracoronary infusion of collected peripheral-blood stem cells was halted because of a higher incidence of intrastent restenosis.<sup>14</sup> Furthermore, intracoronary injection of bone-marrow-derived mesenchymal stromal cells, which are also present in the fraction of cells administered to patients in most studies, induced acute myocardial ischaemia and subacute myocardial microinfarctions in dogs.<sup>15</sup> We still do not know the degree of engraftment of the administered bone-marrow-derived cells, their long-term fate, and the potential pitfalls of this pragmatic therapeutic approach. The clinical studies have

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**Bone-marrow collection**

Donor’s marrow is collected via large-bore needle inserted through iliac crest.