

Translating laboratory anti-aging biotechnology into applied clinical practice: Problems and obstacles

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Abstract

Although the use of biomedical technologies against ageing (rejuvenation biotechnologies) is considered by many as an effective way of controlling all age-related degeneration, in reality this belief cannot be justified. The human body is notoriously resistant to external perturbations and can respond in unpredictable or undesirable ways. Basic concepts of science, evolution and disease must also be considered. In this paper, I discuss some relevant problems associated with the application of any putative rejuvenation biotechnologies

such as stem cell therapies, genetic engineering, tissue manipulation, as well as pharmacological approaches. I conclude that these and other biotechnologies will not be applicable to humans in the community. This is due to a wide spectrum of problems and obstacles, such as unpredictable therapeutic results, unrealistic expectations, lack of infrastructure, cellular network disruption, and many more. Even if some such technologies are developed, the totality of the problems, issues and side effects will prove an insurmountable final hurdle, rendering the development of such therapies, essentially and practically useless.

Key words: Rejuvenation; Biotechnologies; Translational medicine; Ageing; Clinical medicine

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Core tip: Those who rely on biomedical technologies in order to achieve rejuvenation (global reduction of age-related degeneration) are bound to be disappointed. Such a reductionist approach will not have an impact on reducing mortality as a function of age. This is due to problems and obstacles associated with human nature, which are much more complicated than hitherto recognised. The use of biomedical rejuvenation technologies in radically reducing the impact of ageing is conceptually naive, scientifically reductionist, technologically unfeasible, and medically undeliverable.

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INTRODUCTION

Research into ways of treating age-related disease is

progressing in leaps and bounds. Proposed treatments based not only on pharmaceuticals but also on biotechnology give hope to millions of people who have degenerative diseases such as Alzheimer's dementia^[1] osteoarthritis^[2] or cardiovascular disease^[3]. Some researchers and academics^[4] also hope that these disruptive biotechnologies may enable us to repair age-related damage before this becomes clinically relevant, and thus reduce or eliminate the impact of aging on humans, with a consequent dramatic extension of healthy lifespan. However, it is surprising how few people (both the public and academics) actually consider the translational and clinical issues relating to such treatments^[5]. For instance, a PubMed online search of "rejuvenation biotechnologies in aging" reveals 53 papers discussing theoretical or laboratory aspects of rejuvenation biotechnologies, but a search of "clinical applications rejuvenation biotechnologies in aging", reveals just one relevant paper, analysing the clinical application of these technologies.

Laboratory research may appear promising, but when it comes to applying the results of this research onto real patients in the community, then a host of new problems become evident^[6]. The difficulties in developing new pharmaceutical treatments for age-related conditions are well known. Clinicians have already begun to also apply biotechnological therapies in clinical situations, for example treatment of stroke with neural stem cells^[7], Parkinson's disease with stem cells^[8] arthritis with tissue engineering^[9], and diabetes with new drugs^[10] with variable success.

DISCUSSION

It is very plausible that laboratory and clinical research will progress in tandem, mutually providing feedback and adjustments, but only insofar as the treatment is aimed at carefully selected patients suffering from one clinically manifest age-related condition. The issue becomes much more complex if we consider a large number of patients with multiple, clinically-relevant degenerative illnesses, or patients who are disease-free but are subjected to as yet sub-clinical chronic degeneration processes that need to be treated by these technologies^[11]. The rationale of many of these regenerative biotechnologies is based on the assumption that, even if developed, they can easily be applied and used by the public. However, a host of problems, obstacles and ill-defined thinking impedes this application. In a recent paper^[12] we highlighted two principal issues which pose dramatic problems with the practical application of disruptive rejuvenating biotechnologies. These issues are the interference with the complex organic and dynamic properties of the human body, and the actual impracticality of use of these treatments by the general public. We have argued that biomedical technologies applied on humans at large have effects which cannot be predicted and may result in situations where adverse effects and practical

problems become uncontrollable.

For example, in our paper we considered the case of bone marrow transplant of stem cells. I quote: World-wide, there are approximately 60000 bone marrow transplants performed each year. If we assume that an arbitrary minimum 1% of all humans could possibly be treated with marrow transplant-dependent rejuvenation biotechnologies each year, then there will be a need to provide 7000000 such transplants a year. Assuming a reasonable, and perhaps generous, yearly 20% increase in our clinical capability to deliver rejuvenation biotechnologies, it will still take us 10 years to reach a mere 1000000 target patients - and at that point, the procedures would need to be repeated, in order to maintain the status quo. In this scenario we would only be able to treat a total maximum of 0.015% of humans, ever.

Any pre-existing illness involving any organ or tissue may cause the treatment to behave sub optimally and result in unpredictable side effects. Some general problems that can be encountered are outlined in Table 1.

Taken in isolation, each of the proposed biomedical treatments is associated with significant translational problems. However, if we also consider that these therapies must be deployed in association with each other so that to achieve a lasting and curative clinical benefit, we are bound to encounter additional emergent problems at least with respect to practical clinical applications.

At this point, it is worth mentioning that many rejuvenation biotechnologies do not take into account newer concepts such as the heterogeneous process of disease evolution, described by Molecular Pathological Epidemiology (MPE)^[21]. Nor do they consider the role of epigenetic regulation in disease^[22]. Ogino *et al*^[23] quote: "MPE is founded on the unique disease principle, that is, each disease process results from unique profiles of exposomes, epigenomes, transcriptomes, proteomes, metabolomes, microbiomes, and interactomes in relation to the macroenvironment and tissue microenvironment. Although epigenome-wide association study attracts increasing attention, currently, it has a fundamental problem in that each cell within one individual has a unique, time-varying epigenome" (emphasis mine).

In other words, unique individual patterns of disease evolution may lead to unpredictable outcomes, and any future treatments designed against age-related disease must address this, by using tools of personalised medicine developed through MPE concepts. Otherwise, these putative treatments may prove ineffective in some individuals, depending on epigenetic factors, *i.e.*, environmentally-dependent changes of their disease phenotype.

We have been criticised for being too pessimistic about the expected problems and that it could be possible that novel developments may diminish the uncertainties and practical difficulties of such a scenario.

Table 1 Problems and obstacles associated with some biomedical technologies

Biomedical technologies	Applied translational and clinical problems
Tissue engineering	Harvesting of autologous material, transplantation surgery, immunosuppression, infrastructure of delivery ^[13]
Stem cell therapies	Clinical harvesting of cells, delivery (such as problems with bone marrow transplants ^[14]), inadequate integration of transplanted cells ^[15] and earlier-than-planned re-treatments
Immune therapies	Side effects, non-compliance, reluctance to accept as a treatment ^[16]
Genetic therapies	Immunity to vector, inadequate integration and assimilation of genes, unknown variables relating to genetic cross-talk ^[17] and over-expression, practical delivery methodologies
Nanomedicine	Unknown and unpredictable side effects (including immune system disruption), unknown end-results, toxicity, inflammation ^[18]
Pharmacological therapies	Ineffective or complex treatments, tolerance, clinical polypharmacy, side effects, interactions and non-compliance ^[19]
Other disruptive interventions (apoptotic modulation, crosslink breakers, chemotherapy, chromosomal interventions)	Unpredictability of the combined effect, adverse effects, cost, compliance, ethical and psychological problems, inadequate clinical capability to deliver the treatments ^[20]

This is a valid point, however the interventions necessary to have an impact on age degeneration will never be completely free of adverse effects or have an easy applicability. Due to the sheer number of interventions needed, these side effects and translational problems will, even if individually mild in themselves, accumulate and multiply, resulting in a situation where emergent problems affect the predictability and applicability of the treatments. Therefore, even if we consider a less pessimistic scenario where technology may be able to deliver individual therapies with a minimal disruption to the patient and with an effective result, the spectrum of age-associated pathologies is so wide that each one of these minimal problems will be magnified and result in a situation where adverse effects become significant, effects which cannot be reduced back to individual isolated problems. This is a typical example of emergence, a process whereby larger entities, patterns, and regularities arise through interactions among smaller or simpler entities that themselves do not exhibit such properties^[24]. As a result, we have a state where a litany of problems continually appear, making the applicability of rejuvenation biotechnologies a truly impossible approach.

The use of biomedical rejuvenation technologies in radically reducing the impact of ageing is conceptually naive, scientifically reductionist, technologically unfeasible, and medically undeliverable.

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