

# Genomic research delivering on promises: From rejuvenation to vaccines and pharmacogenetics

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## Abstract

**What is known and Objective:** There has been astounding progress made in the treatment of disease over recent years. This progress is particularly marked in cell therapy and in the personalization of therapy based on genetic insight, an approach known as genomic medicine. Our objective is to comment on the progress made in cell and genomic medicine against an historical backcloth of the search for rejuvenation.

**Comment:** In 1741, close to seven decades after Antoine van Leeuwenhoek first saw his microscopic animalcules, Abraham Trembley, a tutor in Leiden, reported on an organism that could regenerate itself. The strange organism was thought to hold the secret of life. If it does, we have yet to prise the secret out. However, the ensuing study of cell programming and induced stem cells has shed considerable light on cellular development and provided new insights on the rejuvenative capacity of organisms. Inventive scientists have provided a deeper understanding of cell replication and, from this, developed new medicines for an increasing range of diseases. Targeted therapies, oligonucleotide therapy, therapeutic monoclonal antibodies and pharmacogenetics are all new therapeutic areas originating from the improved insights. More will surely follow.

**What is new and conclusion:** Immortality is for the gods, but man's search for its elusive secrets, perhaps as old as man himself, will continue. Huge leaps have been made, and effective medicines have been developed from our improved insights into the mechanism of life. However, only the foolish will predict how far this new knowledge will lead us, and more particularly, at what speed new therapies will follow.

## KEYWORDS

cell therapy, gene editing, immortality, pharmacogenetics, pharmacogenomics, pluripotent stem cells, regenerative medicine, targeted therapy

## 1 | WHAT IS KNOWN AND OBJECTIVE

The search for rejuvenation and immortality is an old one with records dating back to 1800 BC<sup>1</sup> There has been astounding progress made in the treatment of disease since then and, more particularly, since the rise of synthetic chemistry at the end of the nineteenth century.<sup>2</sup> Over more recent years, new insights into the molecular basis of life have led to major progress in cell therapy and in the personalization of therapy

based on genetic insight, an approach known as genomic medicine. Our objective is to comment on the progress made in cell and genomic medicine against an historical backcloth of the search for rejuvenation.

## 2 | COMMENT

On 16 February 1741, Abraham Trembley, an unknown children's tutor, based in Leiden, but originally from Geneva, wrote to René-Antoine Réaumur, a leading French entomologist, about a discovery

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that was so unbelievable that he thought it needed independent validation. Trembley had discovered an aquatic organism, later named *Chlorhydra viridissima*, that could regenerate itself. Carl Linnaeus would describe this genus of polyps as *Hydra*.

'On 25 November 1740', Trembley had cut a polyp into two. After ten days, the two halves had regenerated into polyps that were indistinguishable from those 'that had never been cut... They extended, contracted and walked'.<sup>3</sup>

Trembley was not one to rush to publication. He was way ahead of those now calling for independent validation of experiments.<sup>4</sup> Excited, he sent 40 specimens to Réaumur, urging him to repeat his studies to see for himself. He wanted Réaumur's imprimatur. The specimens arrived dead but, as a true researcher, Trembley persisted, and live specimens were delivered, not only to Réaumur but also to other leading lights of the scientific world, including Martin Folkes, the President of the Royal Society, who wanted to study their amazing rejuvenating capacity. With easy validation using Trembley's specimens, the scientific world, including 'metaphysicians, moralists and physicists', was persuaded, believing that the hydra held the secret to rejuvenation, and perhaps even to an understanding of 'life and soul'.<sup>5</sup> The eighteenth-century moralists find echo in today's ethicists commenting on the wisdom of aspects of genetic medicine such as gene editing of human embryos.

A frenzy of research followed Trembley's discovery. It seemed as if the polyp was the only subject worthy of scientific study. Both Réaumur and Folkes were in their fifties, and ageing was no doubt focussing their minds. They might also have thought that they would perhaps be able to offer kings and emperors the path to rejuvenation they so longed for, and make themselves some ducats along the way.

Scientific study of rejuvenation predates the coining of the word 'scientist' in 1833. The promise of the regenerating polyp has yet to metamorphose into clinically useful interventions in routine patient care. However, a recent study showed that its allure still holds firm in the public's imagination as populations age throughout the industrial world. Direct-to-consumer stem cell rejuvenative therapy is big business despite being still largely at the level of snake-oil therapy.<sup>6</sup> Those wanting new skin for old still have to rely on palliative botox, while they experiment with the hyped 'miracle' stem cells.

## 2.1 | Cell therapy re-engineered

Cell therapy though has made enormous progress in the forms of haematopoietic stem cell replacement, the only form of curative therapy for some forms of leukaemias,<sup>7</sup> molecularly engineered T-cell therapy, often curing patients who would have otherwise died prematurely,<sup>8</sup> and induced pluripotent stem cells.<sup>9,10</sup>

## 2.2 | Monoclonal antibodies

On 2 April 1953, James Watson and Francis Crick reported on the structure of DNA. According to Watson, a few days earlier, on

'February 28, 1953 ... during lunch at the Eagle, the pub adjacent to the Cavendish Lab, Crick, ever the talker, could not help to tell everyone we had just found the "secret of life"'. Soon after, commenting on the implications of their discovery, the pair stated that.

*'Despite these uncertainties we feel that our proposed structure for deoxyribonucleic acid may help to solve one of the fundamental biological problems - the molecular basis of the template needed for genetic replication'.*

Watson and Crick did not discover the secret of life, but their discovery, with a little help from a bevy of other Nobel Prize winners and a few not so lucky, has transformed the management of several diseases. If cancer is not yet tamed, great progress has been made. For example, no woman with breast cancer, and access to leading oncology centres, would now be treated without tumour DNA profiling. Genetic work-up is now common not only for an increasing range of cancers but also for other diseases including muscular dystrophies and cystic fibrosis.<sup>11,12</sup>

Insight is particularly useful if it can be translated into useful interventions. One of the greatest therapeutic successes in this was underpinned by groundwork laid by Kohler and Milstein (Nobel Prize 1984). Their demonstration of how exquisitely specific monoclonal antibodies (mAbs) could be made has transformed the physician's formulary. Well over a hundred mAbs are in therapeutic use, and many more are used in diagnostics. The trend continues. In 2019, the US Food and Drug Administration (FDA) licensed seven mAbs for therapeutic use. However, this pathway of drug development is starting to feel like the molecular roulette of the previous therapeutic revolution during which more and more small organic molecules were developed through combinatorial chemistry, each new but each much of a muchness. It was the age of 'me-too' benzodiazepines, beta-blockers and ACE inhibitors, all new but with only marginal improvements if any. However, molecular roulette optimization is still needed even for protein therapeutic agents to maximize efficacy and minimize adverse effects.

## 2.3 | Oligonucleotide therapies

The discovery of the DNA template and base pairing, and the association of specific diseases with specific DNA and RNA variations led to another dream—that of directly interfering with pathogenic nucleic acid sequences such as those of invading microorganisms or those translated to neurotoxic proteins associated with some of the most devastating genetic diseases. This therapeutic approach of specific targeting with short-chain nucleic acid molecules is known as oligonucleotide therapy. Although fomivirsen, the first such therapy, was introduced for the treatment of cytomegalovirus retinitis in 1998, it was not commercially successful, being soon superseded by highly active small-molecule antiretroviral drugs. However, recent developments suggest that there is now a clearer path to success.<sup>13</sup> The high degree of personalization of therapy using this approach is illustrated in a recent report of the management of a rare genetic

neurodegenerative disease, from diagnosis to synthesis and evaluation of a new oligonucleotide therapy in a single-patient (N of 1) trial.<sup>14</sup>

Several new oligonucleotide therapies have been licensed over recent years for similar highly specific therapeutic targeting. These include mipomersen for homozygous familial hypercholesterolaemia in 2013, eteplirsen for Duchenne muscular dystrophy and nusinersen for spinal muscular dystrophy, both in 2016, and golodirsen in 2019 for the same condition. As their approvals were based on short-term trials with a limited number of patients, the true worth of those agents is still unclear. However, pharmaceutical companies continue to be optimistic enough to invest heavily in their search for oligonucleotide therapies and mAbs that might help the management of difficult-to-treat diseases such as Alzheimer's despite early disappointments.<sup>15</sup>

## 2.4 | Recombinant nucleic acids

When the technology became available to produce recombinant DNA, and thereby open the possibility of producing therapeutic proteins in abundance, some raised justifiable concerns about its safety. 'No one should be able to do [such] ... messy experiments in secret and present us with a reprehensible and/or dangerous *fait accompli* at a press conference', said Pollack, one of the major investigators.<sup>16</sup> Over time and after sober thought,<sup>17,18</sup> procedures for safe work were possible and today we have available an array of proteins produced by recombinant technology—hormones, replacement enzymes, diagnostic molecules and vaccines.<sup>19</sup>

## 2.5 | Coronavirus vaccines

Perhaps one of the most dramatic examples of the power of genomic research is the current live demonstration of its application in the management of the emerging infective COVID-19 coronavirus. Within days of the identification of the new infection, Chinese investigators had isolated the RNA virus and, in a feat that Trembley would have cheered, made its genomic sequence available to the world so that vaccine development could begin.<sup>20,21</sup> In fewer than 4 weeks, laboratories around the world were already inserting gene sequences into cellular cassettes to produce proteins for investigation as potential vaccines. However, as the recent failure of an HIV vaccine shows, viruses are elusive, mutating frequently. How quickly a vaccine can be developed is difficult to predict.<sup>22</sup> Yet, the approval of the first Ebola vaccine in December 2019 has transformed despair to optimism.<sup>23</sup>

## 2.6 | Gene editing

In a retrospective of recombinant DNA technology, Berg and Metzler commented—'Emerging from myriad investigations has

been the appreciation that nothing in the man-made world rivals the complexity and diversity of this earth's organisms'. That complexity was again shown with the discovery of gene editing in the microbial defence repertoire.<sup>24</sup> This observation was soon turned into a new technology (CRISPR-Cas) for the precise editing of any genome, including humans. Despite the caution raised by Baltimore and others about human germline editing, and Pollack's disdain of 'secret' experiments, the first human genome edited was announced to the world as a *fait accompli*.<sup>25</sup> Although the investigator was condemned as reckless and imprisoned,<sup>26</sup> history tells us that in the ethics of human affairs, red lines are moveable.

## 2.7 | Pharmacogenetics

One of the less ethically fluid and more promising applications of genomic medicine arose from recognition that a generally safe drug could cause serious adverse effects in some patients.<sup>27</sup> The study of DNA profiling for predicting response to drugs by individuals is known variously as pharmacogenetics, pharmacogenomics, and personalized and precision medicine. Early success in explaining why Black soldiers were more prone to haemolysis than White soldiers when given the antimalarial pamaquine, and later primaquine, led to increased interest in the genetics of drug response even before the structure of DNA variation had been worked out.<sup>28,29</sup> Deficiency in glucose-6-phosphate dehydrogenase (G6PD) due to genetic variation explained this adverse effect, and soon after, a number of other adverse drug effects were ascribed to this deficiency.<sup>30</sup> This led an enthusiastic editorialist at the British Medical Journal to suggest that 'To prevent attacks persons deficient in G6PD must avoid all potentially harmful drugs and foods. There is a case to be made for the use of routine screening tests, such as the spot-test, on all males of Mediterranean, Asian, or African extraction before treatment with sulphonamides, aspirin, phenacetin, and other drugs<sup>31</sup>'. With more sober appraisal, this suggestion was not taken up, being neither practical nor economically or scientifically justifiable.

Classens et al<sup>32</sup> recently studied the pharmacogenetics of clopidogrel, an antiplatelet agent known to be associated with marked genetic variability in response, in the prevention of thrombotic events in patients undergoing percutaneous coronary interventions. Clopidogrel is a prodrug, that is a drug that requires activation by metabolic enzymes including the cytochrome P450 enzyme CYP2C19. In their randomized, but open, trial, they compared CYP2C19 genotype-guided clopidogrel therapy versus standard treatment with ticagrelor or prasugrel, two newer agents known to be effective without genetic guidance. They showed that their genotype-guided therapy was not inferior to the control drugs and resulted in a lower incidence of bleeding. This led Roden, an editorialist, to suggest that one should not wait any further before implementing genotype-guided clopidogrel therapy.<sup>33</sup>

Some of the main reasons for lack of enthusiasm for wider implementation of pharmacogenetics in most areas of therapeutics is suggested in Roden's editorial: the variability in frequency of different

genetic variants in different populations and recruitment of subjects with primarily European ancestry. In fact, in some populations, different variants of the same gene are often found. Clopidogrel has a complicated metabolic pathway, and although CYP2C19 is important, it is not clear to what extent pathway substitution occurs.<sup>34,35</sup> Drug metabolism is often as complex as roadways into large cities but biologically more malleable. Block one pathway and another takes over. For conventional drugs, regulators usually require three robust controlled randomized controlled trials to replicate beneficial results and test their generalizability. Trembley would have applauded such caution.

The history of genotype-guided warfarin therapy provides cause for caution. Important reasons for such caution are highlighted by Shah in his well-argued contribution in this issue of the Journal.<sup>36</sup> Notable is the fact that inventive drug designers invariably come forth with drugs that need less individualization, such as the direct-acting anticoagulants to improve on warfarin, and new antiplatelet drugs such as prasugrel and ticagrelor to improve on clopidogrel although they too have their own shortcomings.

## 2.8 | Meta-analysis: to pool or not to pool

The development of meta-analysis has advanced the interpretation of results from multiple trials. However, meta-analytic point estimates of effect provide little clinical guidance when the populations studied are heterogeneous. Identifying what factors contribute to any observed heterogeneity would be of greater value. For example, in one meta-analysis of studies of the value of self-monitoring and self-determination of anticoagulation the dominant trial contributed close to half of all randomized patients. 20% of the patients were not competent in the use of self-monitoring equipment, and the superiority of self-testing was not shown. Yet, the conclusion of the meta-analysis of highly heterogeneous studies was that self-monitoring improved outcome.<sup>37</sup> The unanswered question is who is most likely to benefit.<sup>38</sup> Shah observed that even the four major randomized controlled trials designed to test the value of genotype-guided warfarin therapy were so heterogeneous that greater insight is to be had by scrutiny of the individual trials than by the reported pooled point estimate of effect.<sup>36</sup>

## 2.9 | Renewed optimism

When Desmaizeaux reported on the research undertaken by British 'savans' in 1743 in the wake of Trembley's discovery, he observed that Cromwell Mortimer, the editor of the *Philosophical Transactions of the Royal Society*, seemed to have given the entirety of issue 467 over to the study of the 'marvellous properties of the new [Trembley's] polyp'. Readers of recent issues of the *New England Journal of Medicine* can be forgiven for having the same thoughts about genomic medicine. In one of the recent issues, for

example, four of the five main articles had molecular genetics at their core,<sup>14,32,39,40</sup> and two accompanying editorials commented on their implications, raising the thorny issues of regulatory approval, cost-effectiveness and timely clinical adoption.<sup>33,41</sup> A further article discussed the modelling of the placenta with stem cells,<sup>42</sup> the new marvellous hydra.

## 3 | WHAT IS NEW AND CONCLUSION

Overenthusiastic scientists chasing the next funding or the next glitter, and marketeers the next sale, sometimes overpromise, sometimes overstep the red lines and sometimes mislead. That has always been the case since the dawn of medicine. For this reason, although genomic medicine, which now encompasses cell therapy, is delivering on its promise at an accelerating pace in the form of effective therapies and interventions, the hawkish eyes of critical appraisers are still needed.

Immortality is for the gods, but man's search for its elusive secrets, perhaps as old as man himself, will continue. Huge leaps have been made, and effective medicines have been developed from our improved insights into life. Only the foolish will predict how far this new knowledge will lead us, and more particularly, at what speed new therapies will follow.

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