A Proposal to Accelerate Progress Towards Human Rejuvenation

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Executive Summary

1. Aging is by far the greatest cause of human morbidity and mortality.

2. Rejuvenation therapies that will greatly reduce unnecessary late life suffering and death are under development, but slowly, and with limited funding.

3. Accelerating the development of rejuvenation therapies is an important goal that, if achieved, will improve quality of life and save many lives in the years ahead.

4. At present there is only limited public support for the goal of human rejuvenation.

5. Faster progress towards rejuvenation therapies will follow greater public and institutional support for rejuvenation therapies. It will mean more funding, more research programs, more biotech companies.

6. A few low-cost rejuvenation therapies exist today, already approved by US regulators for other uses. They can in principle be prescribed off-label in the US, but are not yet widely used.

7. Broad public and institutional support to accelerate the development of rejuvenation therapies will emerge following the widespread use of at least a few rejuvenation therapies.

8. Widespread use of the first rejuvenation therapies requires physician adoption of those therapies, as patients largely follow the options presented by physicians.

9. Physician adoption of an off-label rejuvenation therapy requires a convincing presentation of safety and efficacy in the treatment of common age-related conditions. This can be provided by favorable results from low-cost, few-hundred-patient clinical trials conducted by a reputable organization, and then marketed to physicians and physician organizations.

10. The cost of clinical trials to produce robust, trustworthy data for an existing therapy, already approved by regulators, can be a fraction of that required for clinical trials aimed at regulatory approval of a new treatment.

11. Given this funding, a number of existing organizations are well placed to conduct these trials and publicize the results. All that is needed is the will to act.

Aging is the Greatest Cause of Human Morbidity and Mortality

Age-related disease is by far the greatest cause of human morbidity and mortality. The many different ultimately fatal degenerative conditions of old age result from a much smaller number of underlying mechanisms of aging. These include the accumulation of senescent cells and forms of metabolic waste such as cross-links and amyloids, DNA damage, and more. [1][2]

The First Rejuvenation Therapies Exist ...

Historically, treatments for age-related disease have focused on the symptoms rather than the causes, and thus comparatively little headway has been made towards prevention and reversal – towards actual rejuvenation. Even though this remains true today, it is nonetheless the case that the first rejuvenation therapies exist, each capable of reversing to some degree a single contribution to degenerative aging.

For example, the senolytic combination of dasatinib and quercetin has been shown in human clinical trials to significantly reduce the burden of senescent cells in aged tissues following a single course of treatment. [3] Senescent cells grow in number with age, and their inflammatory secretions are disruptive of tissue structure and function, contributing to many of the common fatal age-related diseases. [4] Dasatinib is an FDA-approved drug that can be prescribed off-label at low cost, while quercetin is a supplement, readily available to all at an even lower cost.

As a second example, fecal microbiota transplant (FMT) from young to old individuals has been demonstrated in animal studies to produce a lasting reset of the aged gut microbiome and improved health. [5][6] Restoring the balance of microbial populations in the intestine to a youthful state reduces the harmful effects of an aged gut microbiome on long-term health, including raised inflammation, increased generation of toxic metabolites, and reduced generation of beneficial metabolites. One implementation of this treatment was recently approved by the FDA for treatment of C. difficile infection. [7] This makes it available off-label, in principle at least, and gives support to the community of practitioners that has for years been conducting FMT procedures on an ad hoc basis to treat various forms of dysbiosis.

… But are Not Widely Adopted

Despite the existence of these rejuvenation therapies, and evidence for their benefits in the context of aging, the two treatments noted above are neither widely used nor widely known. The broader public still sees aging as largely set in stone, and treatment of aging as the domain of frauds and snake oil salesmen. The public does not realize that a small number of low-cost medical therapies can, with a single program of treatment, produce a lasting improvement to late life health by addressing one of the contributing causes of aging. Comparatively few physicians are both aware of these therapies and comfortable prescribing them. Comparatively few research groups are working on human clinical trials that would produce further supporting evidence.

If must be noted that clearance of senescent cells and adjustment of the gut microbiome, while supported by evidence to show them to be individually beneficial, are not on their own sufficient for comprehensive rejuvenation of the old. Other contributing causes of aging must also be addressed, such as protein aggregates, cross-linking, stem cell decline, mitochondrial dysfunction, and so forth. [1] A faction within the biotech industry is working on new classes of rejuvenation therapy, and the funding for this effort has risen to a few billion dollars, spread unevenly across a few score companies. [8] This

sounds like a lot, but it is an insignificant fraction of the funding devoted to more mainstream medical development; the end to end cost of developing a single therapy was reportedly more than $2 billion in 2013. [9]

If we wish to see rapid progress towards the effective treatment of aging within our lifetimes, a dramatic reduction of age-related disease, an end to frailty and dementia, then initiatives aimed at the production of rejuvenation therapies must greatly expand in size and number, and do so sooner rather than later. At the large scale, public support and understanding is necessary for the biggest, most conservative institutions to choose to put their shoulders to the wheel and advance the field of rejuvenation research. That support and understanding is missing at present, in large part because the first rejuvenation therapies are not widely used, and therefore remain largely unknown and unappreciated.

The problem we face is circular in nature. Little use of existing rejuvenation therapies means little knowledge of those therapies. Little knowledge in turn ensures little use. Presently sparse research and development means a slow pace of transmission of knowledge from the scientific community to thought leaders and the public at large. That lack of broad knowledge ensures that there is comparatively little support for greater funding and an expanded range of initiatives.

A slow process of bootstrapping is the usual way forward when faced with such self-reinforcing roadblocks, years of slow and incremental growth to open up a new field. There are other, faster ways paths ahead, however, enabled by the cost-effective deployment of philanthropic funding.

To Ensure Adoption, Persuade Physicians to Prescribe

The best way to break the cycle described above is to focus on physician adoption, to ensure that physicians and clinicians become comfortable prescribing and providing the few presently available rejuvenation therapies. Most patients only become familiar with the medical technologies presented by their physicians. Ensuring widespread off-label use by the medical community of the few existing, easily implemented, low-cost rejuvenation therapies would lead to a sizable improvement in public knowledge and attitudes regarding human rejuvenation.

A world in which most physicians routinely prescribe beneficial rejuvenation therapies to older patients is a world in which both the public and larger, conservative institutions will come to support further development of this form of medicine, aimed at ever more effective control of aging and age-related disease. Just as importantly, expanding the use of beneficial rejuvenation therapies is a great good in and of itself, a way to alleviate suffering and mortality in the older population.

Clinical Trial Data Persuades Physicians

The best way to convince physicians that a given FDA-approved treatment can be used off-label to treat many diseases of aging, or aging itself, is for reputable organizations to publish favorable results from multiple human clinical trials that employ the treatment. Such trials do not have to be anywhere near as expensive as the formal clinical trials conducted to persuade the FDA to approve a new therapy, as they do not need to be encumbered by the full set of regulatory concerns. They only need to be well run, such that the data produced is of high quality, and run by organizations with a good reputation, to ensure that the message is heard.

Trials of the few existing rejuvenation therapies are taking place, but only to a limited degree, and very slowly. The Mayo Clinic was one of the first groups to run clinical trials using dasastinib and quercetin in kidney disease [10], pulmonary fibrosis [11], and Alzheimer's disease [12], for example. But only for these few age-related conditions, with a limited budget, and at a sedate pace over years. Data has been published for only two of these trials over the last five years. Much more than the work of this single organization is needed to move the needle when it comes to persuading physicians.

It is possible to run a well-managed clinical trial of a low-cost, FDA-approved therapy in as many as two hundred patents for under $1 million, provided that the primary goal is to produce robust data rather than to satisfy regulators. Consider the PEARL trial for rapamycin [13], for example, which was crowdfunded with under $200,000 in charitable donations [14]. Trials for dasatinib and quercetin treatment or fecal microbiota transplantation need not be that much more expensive.

Existing Organizations Can Administer Clinical Trials

Given philanthropic funding for such trials, a number of reputable organizations are well positioned to undertake the task of trial administration. In practice this requires connections to potential principal investigators and clinics capable of performing the work, project management as the work progresses, and analysis and presentation of the results. Again, this is far less onerous for the type of clinical trial envisaged here than is the case for formal clinical trials conducted for regulatory approval of new therapies.

The non-profit Lifespan.io runs crowdfunding campaigns to support research goals, and has collaborated with AgelessRx [15] to fund and organize the PEARL clinical trial for rapamycin. The non-profit Forever Healthy Foundation [16] performs research analysis and holds conferences, is connected to the Kizoo Technology Ventures fund that invests in biotech companies, and could make the transition to organizing small trials. The LongevityTech investment fund [17] is constructing a network of clinics in a number of different locations for the express purpose of running first-in-human clinical trials for new therapies relevant to aging.

Each of these organizations has an existing reputation that can be built upon and expanded by taking on the task of running clinical trials aimed at persuading physicians to make use of the first rejuvenation therapies worthy of the name.

Outreach to Physicians

Given favorable data and reputable trial-running organizations, outreach to physicians is more or less a solved problem. It only requires funding and effort. Organizations that market therapies to physicians and clinical practices exist, while established physician networks and conferences can act as channels for broader discussion and outreach.

In Summary

The first rejuvenation therapies worthy of the name already exist, but are barely used. Ensuring a reasonable proof of efficacy and more widespread use of the first few of these will not just improve late life health, but also change the public perception of the treatment of aging. Physician adoption of these therapies is the key to widespread use, and can be achieved by running multiple, rapid, low-cost clinical trials for the first rejuvenation therapies, followed by marketing favorable results to physicians and physician organizations. Widespread physician-led adoption of the first rejuvenation therapies will

produce far greater public and institutional support for progress towards a comprehensive set of rejuvenation therapies, technologies that, together, are capable of producing a dramatic reduction in late life suffering and mortality.

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