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Through the lens of COVID-19: The challenges to overcome age-related disease

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Over the last few years the field of longevity and health span research has exploded and our understanding of the processes underpinning ageing and age-related disease has expanded greatly. In spite of this there are several challenges facing researchers, drug developers and society in general that must be overcome before we start seeing broader treatments that can fundamentally change the underlying pathology of ageing.

In the age of COVID-19 the need for progress has never been more urgent. The disparity in mortality rates we are seeing during the ongoing crisis is a stark reminder that age greatly impacts health. According to statistics shared by the CDC, age is a strong determinant of mortality in patients with COVID-19. There's little doubt that people fall into a high-risk category for death from infection with this virus once they reach middle age.

A similarly notable finding was reported recently in The Journal of Infection that age-related comorbid conditions also represent a major risk factor for severe morbidity and death from COVID-19, including type 2 diabetes (OR 3.68), hypertension (OR 2.72), and underlying respiratory disease (OR 5.15). Whether directly associated with co-morbid conditions of aging or biological aging itself, it is clear that age and age-related diseases are in the spotlight as accelerants for serious complications of COVID-19.

The excess morbidity and mortality associated with aging, apart from COVID-19, comes with staggering implications for healthcare costs. This is driven in part from the fact that over 80% of people 65 years and older suffer from multiple comorbid conditions, and that over 70% of healthcare spending is allocated to the ~32 percent of people with more than one chronic condition.

Age-related diseases like atherosclerosis, diabetes, congestive heart failure, arthritis, chronic kidney disease, some cancers, and dementia tend to cluster – not surprisingly – because they are age-related and people who are older develop multiple conditions as they experience decline in stem cell function, and increased cellular senescence, inflammation, and fibrosis. It's not just wear and tear. Underlying progressive pathologies drive multiple diseases. It has become increasingly clear among doctors practicing geriatric medicine that chronological age seems less important than 'biological age' for many conditions. A 'frailty score' or 'viability score' might become more relevant than age defined by years lived.

Historically we have treated these individual conditions separately, prescribing blood pressure medication for hypertension – anti-inflammatory drugs for osteoarthritis – statins, stents, and other surgical interventions for atherosclerosis – chemotherapy and immunotherapy for cancer. This has been due to the lack of understanding of root cause biological changes that provide the foundation for these disparate diseases.

With our increased scientific understanding of the underlying drivers of cellular senescence, control of protein synthesis and degradation (proteostasis), cellular renewal (autophagy, mitophagy, ribophagy), and fibrosis, it is more likely that the underlying pathophysiological processes of aging will become treatable, preventable, and potentially reversible.

Progress in the science of aging presents some particularly interesting challenges from a drug development and regulatory perspective.

If we are able to reduce these underlying age-related disease mechanisms - this could lead to novel therapies potentially impacting the root causes of pathology. But what's the best path to assess therapeutic efficacy, gain regulatory approval and determine reimbursement for new therapies?

One relatively simple path forward based on where we are today is to focus development of novel aging pathology-targeted therapies on individual indications that represent a 'good enough' fit for the drug. Examples might include idiopathic pulmonary fibrosis or osteoarthritis for a senolytic agent or diabetic kidney disease for an mTORC1 inhibitor.

Both indications represent significant unmet medical need, high value creation opportunities, and are rational in that the underlying pathology is soundly linked to the disease – and accordingly represent solid contemporary approaches to drug evaluation and potentially commercialization. On the other hand, by focusing on only one indication, meaningful time and value are lost in the opportunity cost of NOT evaluating the compounds more broadly, and by focusing only on those patients with IPF or diabetic kidney disease, in these examples.

Current challenges

Societal beliefs

Today "ageing" is not an indication in and of itself. Socially, it is not viewed as a disease but simply the natural course of life, and there are misconceptions about the intention of improving healthspan (to reduce the time of life spent suffering from debilitating disease). Trying to stop or ameliorate ageing sounds impossible to many as well, and the field needs to deal with hype – there are many sources of products and promotions that are not based on rigorous scientific grounds or supported by randomized controlled clinical trials.

Evolving the regulatory toolkit

From the regulatory standpoint we hear that when it comes to ageing or longevity, industry and academia have not yet defined the condition, developed endpoints or described meaningful outcomes. A partnership needs to be developed between academic researchers, advocacy groups, regulators, and government health agencies to establish a path (if possible) that facilitates advancement of therapeutics belonging to this new category. A better understanding of the pathophysiology of aging could uncover the druggable targets that might initiate this process.

Additionally, regulatory agencies are currently organized to assess medicines in different therapeutic areas and for different indications.

Their construction and organization are based on the underpinning structure of how diseases are defined. The way these bodies are organized continues to change in light of technological and scientific advances, so it follows to posit; how would regulators have to adapt the way they are organized and assess drugs in the face of new diagnosis, new targets and new disease definitions?

Biomarker scarcity

Today there are not enough validated biomarkers for age related diseases, especially in the neurodegenerative space. It will take a coordinated effort among industry, science and academic communities coming together across therapeutic areas to collect and validate biomarkers for these areas to support advancement of novel therapeutics.

Given that the costs of biomarker validation can sometimes approach those of developing a new therapy, the lack of overall incentives for these activities would need to be addressed as well.

Reimbursement

Presently, we lack clarity on the true economic benefit that would surface from the effective treatment of ageing. We need to understand the drivers of healthcare costs, and understand the ways in which innovation in this space could drive value for society. Alzheimer's Disease is estimated to cost payers and governments about $1 trillion by 2050.

To bring new thinking and processes that will support the advancement of therapies addressing the underlying biology of aging we need to pose questions such as:

- What if we could develop a drug that would reduce the severity of multiple age-related conditions in one shot? Does emerging gene therapies for childhood conditions that are disrupting the traditional pricing and reimbursement system give us a sense of their economic impact?
- What if these conditions spanned multiple therapeutic areas? How would key regulatory agencies need to organize to assess these products appropriately? Would a shift from therapeutic divisions be necessary?
- How do we bridge from the approach today to a regulatory path that approves therapies that drive to an endpoint of improved and increased health span/lifespan?

As a community of researchers addressing aging, we need to work together to answer these questions to identify a path forward that includes key stakeholders. A number of organizations including the NIH-NIA, NIHR, the Alliance for Aging Research, and Longevity Leaders are supporting innovation in this area and can provide a valuable service in supporting dialog.

With the wakeup call from COVID-19 that age is a risk factor for more than just chronic diseases, perhaps it is time to put our heads together. We have new and unprecedented insights into the mechanisms driving our 'biological age,' and we have an array of new therapeutic strategies emerging to address them. It's time to build a tool kit, identify strategies for regulatory approval, and build the health economics case for new interventions. Watch the leaders in this space who are tackling this interesting challenge – or better yet, join the effort.

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As CEO of the NDA Group since 2013 Johan has worked to expand the NDA's capabilities across the continents working with a team of exceptional skill and expertise. Johan has a background as serial entrepreneur in the IT and technology industry, serving the life science industry for over 20 years. His main focus remains on developing NDA's unique ability to provide world leading advice and a client experience second to none.