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Editorial, Journal of Gerontology Biological Science

Organizational innovation for developing new medicines that target aging and age-related conditions

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The imperative to develop pharmacological strategies that increase healthspan, reduce years spent with disability, and prevent and treat age-related diseases and conditions is well recognized (1). The current approach to drug development is to target individual diseases and undertake clinical trials in participants without significant comorbidities or disabilities. Most patients who receive drug therapies in real life tend to be older people with multimorbidity, frailty and polypharmacy and thus are not well served by this drug discovery model. Even in those older people with a single phenotypic disease, the situation is complicated by the fact that their disease will often have a multifactorial pathogenesis underpinned by the biological drivers of aging. The importance of including real life older people in clinical trials of drugs that target single diseases is well recognized, but the need to shift the drug discovery approach towards addressing the unique problems of older people such as multimorbidity, frailty and sarcopenia is less well recognised (2). Moreover, there is a growing appreciation that it may be possible to treat the underlying biological process of aging, thereby influencing the onset of a suite of age-related conditions and diseases with a single intervention (3). The aging process and the complex needs of the older population create both an opportunity and a challenge to develop innovative approaches to drug discovery and clinical trials.

To date, drug development has focussed primarily on single targets linked to single diseases, an approach that has been highly successful in generating a pipeline of new drugs. However, this approach is less likely to be successful in developing drugs that target aging, multifactorial syndromes in older people, or multimorbidity. Such conditions are complex in pathogenesis and involve multiple targets, and clinical trials that have aging as an outcome will be, by necessity, long term (probably many years duration). These attributes increase risks and costs, making aging less attractive to industry. Development of therapeutics in this area is crucial and it may be up to governments and/or public institutions to lead the way. A

highly successful example of this approach is the multi-location based Interventions Testing Program in the USA, which provides preclinical testing of drugs for effects on lifespan in mice and is led by the National Institute of Aging (NIA) (4).

The United Kingdom has also begun to explore new approaches for drug discovery that addresses aging and age-related conditions. In 2018, a multi organisation partnership in the UK announced the formation of the ‘Innovative Therapeutics for Ageing Consortium’ (iTAc), which aspires to accelerate the discovery and development of therapeutics for aging. The consortium spans the expertise and infrastructure required for all phases of drug development from target selection through to phase IIa clinical trials and includes five major centres: The Francis Crick Institute, three universities and the government-funded Medicines Discovery Catapult.

The consortium aims to address the lack of therapeutic interventions for multimorbidity and diseases related to aging processes. Early phase drug discovery activity in iTAc will scout for, explore and exploit targets that are considered to constitute four major cellular mechanisms underpinning aging: inflammation, cellular senescence, DNA damage and repair and metabolic dysfunction (5). The clinical phases of drug development will also focus on generating novel clinical trial approaches that can evaluate therapies that target aging (e.g. multimorbidity, biomarkers of aging, umbrella and basket trial designs) and will leverage national patient cohorts and biomarker platforms. Ultimately, the goal is to produce high quality reagents for novel targets, make these freely available to accelerate new biology, and then produce proprietary industry standard clinical candidates for evaluation in phase IIa clinical studies. It is intended that academics who contribute targets or lead compounds to the

iTAc can remain involved with the entire translational process, publish as part of the drug discovery team, obtain financial support and, along with their institutions, share in any downstream revenue. Initial priming funding has come from a UK government Connecting Capability Fund grant of £5M (US \$7M), with the plan to attract industry funding and matched government funding. The expectation is that the consortium will support 40 target-to-candidate studies, 15 preclinical development programs and 10 First-In-Human to Proof-of-Concept trials.

iTAc is an ambitious attempt to refocus drug development towards combatting core aging processes and thereby meet the complex medical needs of older people. It is likely that future drug development will rely on these types of very large collaborative organizations that can leverage the infrastructure, funding, and expertise that are almost certainly a prerequisite for developing novel therapeutic approaches to aging and age-related conditions.

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