

As a major global public health actor focused on patients' needs and recognizing that older people want to continue living full and active lives in spite of medical challenges, SANOFI has created a research & development group, called TSU Aging, dedicated to better management of chronic diseases affecting older individuals and patients. The innovation in our approach to aging is a paradigm shift from the study of one disease in isolation, to the study of certain major diseases and disease processes of aging in parallel, as well the integrated health needs of the elderly, with the aim of maximizing their overall capacity for independent living.

SANOFI's research teams are looking for innovative, inter-connected ways to increase the timeframe of healthy ageing through strategies centered both on prevention and improved management of multi morbidities. We are attempting this through a multidisciplinary, multi-team approach based on an in-depth analysis of the older populations' unmet needs.

Our R&D strategy in aging targets both age-related chronic neurodegenerative diseases such as Alzheimer's, Parkinson's, recovery after stroke, and osteoarthritis; as well as, age-related syndromes such as chronic disabling pain, age-related muscle loss (sarcopenia), and physical frailty.

The vision in establishing TSU Aging was to organize the team in a manner that would allow it to address the principle scientific challenges facing biomedical research generally, and the pharmaceutical industry in particular, in developing innovative medicines to tackle the major age-related disease of aging.

Historically, the industry has been most successful in discovering and developing medicines for either acute illness, such as bacterial and viral infections, and cancer; or major chronic illness that strikes otherwise healthy younger middle-aged individuals, such as heart disease, autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis) and diabetes. In such contexts, because there are high levels of physiologic distinction between health and disease, science has been able to develop models defining that distinction and uncover biologic pathways whose modulation specifically addresses the disease state. In contrast, with perhaps the exception of chronic cardiovascular disease, the industry and biomedical research generally has been less successful in developing appropriate models and new medicines for most of the chronic diseases of aging. In many of the conditions, while symptomatic therapies have been developed, medicines that address the underlying cause of such diseases and conditions remain elusive. As a result, patients continue to develop increasing disability and morbidity, while incurring ever more health care costs.

The major scientific challenge posed by chronic diseases of aging and the geriatric syndromes is that the distinction between what would be considered "normal" aging and disease are less clear because more complex, than with acute illnesses of younger populations; often subtle dysfunctions accumulate in each of multiple organ systems leading to decreased autonomy and lack of well-being on the part of an individual patient. This is particularly true of geriatric syndromes such as Frailty, where various combinations of

disease and aging processes come together to lead to an overall decline in function. Indeed the treatment and management of geriatric syndromes is a challenge for medicine overall as no one abnormality drives the physical complaint, and as a result no one treatment is able to address the medical problem; instead, often frail individuals are treated with multiple medications that treat each of the individually identified laboratory abnormalities, but the underlying conditions of aging and physical frailty remains unaddressed. For pharmaceutical R&D the challenge that is posed by these subtle changes and the overlap between normal aging and disease is that it is scientifically difficult to define and model the specific biologic mechanism that is aberrant and therefore to find a medicine that specifically addresses the mechanisms causing the medical condition.

Additional challenges in addressing age-related chronic disease is that as we grow older our inherent capacities for repair and recovery after injury diminished, and we become more sensitive to environment stress. As a result, disease interventions should ideally be considered early in the disease process, at a point when the body still has the capacity to repair and recover. In addition, therapeutic interventions must take into account environmental factors, such as nutrition, degree of physical activity, etc., as well as the internal biology to optimally address these conditions; and doing so may require combining pharmaceutical interventions with non-pharmaceutical interventions, technologies or services designed to address environmental stressors.

To address these challenges, Sanofi and many others active in the aging field believe that what is required are fundamental shifts in the scientific approach to discovering and developing innovative medicines for age-related diseases. In accordance, the three pillars of the TSU Aging's scientific strategy are as follows:

- In order to cross fertilize ideas and concepts, as well as developing therapies that address common age-related biologic mechanisms, integrating the scientists working on the major age-related disease and syndromes under one Aging R&D organization.
- Place greater emphasis on intervening earlier in disease process, rather than treatments at late stages of disease, when there may already be irreversible loss of function.
- Whenever possible, consider multi-pronged strategies in integrated healthcare solutions that not only provide pharmaceutical products, but also address healthcare needs in integrated solutions that may encompass novel technologies and services.

From an operating model standpoint, SANOFI R&D globally has recognized that our internal efforts for such complex disease situations will not be sufficient and has adopted over the last several years an Open Innovation model, whereby we work in a networked manner with academia and other players in the biotech and pharmaceutical industry; both in direct one-on-one private partnerships as well in larger public-private consortia.

More broadly, for this concept of R&D that is specifically focused on Aging and Age-related diseases/syndromes to succeed, policy change within and outside government will also likely be required to move away from the traditional structures and perspectives. For example, the regulatory process and framework for novel drug development, as well as the treatment paradigm in clinical medicine, is very much based on assumptions of frank disease with a clearly definable disease process and cause that can then be addressed with a specific medicine. And again, geriatric syndromes such as Frailty do not follow such direct rules and principles, and as a result is generally not recognized as a distinct entity in either clinical practice or by regulatory guidance. Establishment of Frailty as distinct clinical entity would allow for research to be conducted to understand underlying disease mechanisms, potentially paving the path for developing specific medicines directed towards the syndrome.

Moving earlier in the disease process also poses challenges that may need to be addressed by policy change. While moving earlier in disease, particularly to preventing disease, improves the probability of success from the scientific standpoint, proving the effect of an intervention with traditional clinical endpoints of irreversible morbidity or mortality may take 5, 10 or more years of clinical studies. As a result, for the industry to succeed in developing medicines for many of the chronic diseases/syndromes of aging will require the identification of surrogate endpoints that then will need to be adopted by regulatory agencies. In addition, for reimbursement and business success, systems will likely need to be put in place to capture the long-term health benefits and cost reductions from intervening earlier in the disease process.

Finally, of the three pillars, the one that may be the most difficult for the industry to realize is the development of effective integrated health care solutions because it may require significant business model innovation as it moves far beyond our traditional product commercialization strategy and will involve stakeholders with whom we traditionally do not work (e.g. telecommunications companies for remote monitoring). Sanofi and others in the industry today are working on establishing pilots generally through public-private partnerships to explore how one could best propose such solutions, but the field remains in its infancy.

By developing novel innovative medicines and integrated healthcare solutions for the aging population, notably through partnerships involving public and private stakeholders, SANOFI is dedicated to finding solutions to the 21st century worldwide challenge of increased demand in healthcare for an aging population. Our goal is to become a leader in this field, making a real difference for older adults and their caregivers.