Interview with Prof. Bruno Vellas, Founding President of IHU HealthAge

The IHU HealthAge, the only IHU in France dedicated solely to aging, was officially launched on April 2, 2024. What are its goals, missions, resources, and international collaborations?

The creation of IHU HealthAge, focusing on prevention, geroscience, and healthy aging, has been a long journey. We began over 12 years ago with the first call for projects on IHUs, where we proposed a project centred around frailty. At the time, frailty was not widely discussed. We were not selected, but we created the first Day Hospital for Frailty, developed frailty in clinical practice, and were later recognised by the WHO as a Collaborating Centre on frailty and dependence prevention. A few years later, we re-applied, were pre-selected, but ultimately, only one IHU was chosen, the one in Paris focused on vision. Carole Delga, President of the Region, who had joined us for the oral presentation, called me a few days later saying, "Your project seems very important," and she provided significant funding from the Region, as well as European FEDER funds, which enabled us to establish the IHU cohorts, including the INSPIRE-T cohort, which consists of 1,000 people aged 20 to 100 years whom we will follow for 12 years to study biological aging. Additionally, there is the INSPIRE mouse cohort, with 1,500 mice followed for 24 months to collect samples and tissues for a better understanding of the biological mechanisms of aging, and finally, the Killifish colonies, which live around six months but have a genetic heritage similar to humans, making them an excellent model for aging. We applied again for the last call and were ultimately funded. In the meantime, we brought Prof. Felipe Sierra, who led aging biology research at the U.S. National Institute on Aging, to Toulouse, and he guided us towards the field of geroscience.

The objectives of IHU are to enable healthy aging. We will now spend an average of 30% of our lives after the age of 60. Our societies have never faced this phenomenon, which could be an opportunity if aging is active, productive, supportive, and helpful, and this is possible, or it could become a disaster if it continues to lead to dependence, which is both a human tragedy and a significant cost to our society, especially when we lack the human resources to care for it.

The missions of IHU include developing the WHO's ICOPE program, which was established to maintain essential functions for healthy aging. According to the WHO, aging healthily means preserving our functions to continue doing what is important to us. The WHO has identified six essential functions to maintain: vision, hearing, memory, mental well-being, mobility, and nutrition. Maintaining these functions must not be done in isolation but integrated (the I in ICOPE stands for Integrated Care for Older Adults), as these functions interact with one another. We have developed the ICOPE program and digitalised it with the ICOPE Monitor, thanks to support from ARS Occitanie and the Ministry. We are currently monitoring over 64,000 individuals in the ICOPE Monitor Digital program, with 200 new participants daily, mostly from Occitanie but also from across France. I would like to thank all the teams working on this innovation. **Another mission of IHU is to better understand why these intrinsic abilities decline**, which is why we have set up the cohorts I mentioned earlier to gather all the necessary resources for studying these mechanisms and biological age. The resources include

these cohorts, as well as the human resources from the Toulouse Gerontopole, recognised by the Ministry of Health, and all the INSERM teams from major research institutes associated with the programme, including CERPOP on aging epidemiology, of which we are an integral part, as well as RESTORE, an INSERM research institute focused on aging biology, I2MC, INFINITY, and, of course, the University of Toulouse, Paul Sabatier.

International collaborations are numerous. We are a WHO Collaborating Centre, so we must develop WHO actions worldwide. We work closely with the Buck Institute in San Francisco, as well as with Prof. Mike Weiner's team, which established the large ADNI study in the U.S., a model for our INSPIRE study. This study validated several biomarkers for Alzheimer's disease, and we plan to do the same for aging. We also collaborate with Paul Aisen of the Alzheimer's Therapeutic Research Institute in San Diego, the University of New Mexico, where we are implementing ICOPE within the framework of MEDICAID, as well as with other collaborations in many countries, including the University of Science and Technology of China.

What is geroscience, and how does it open up new perspectives for the prevention of chronic diseases?

Aging is the main risk factor for age-related diseases. Everyone agrees that the older we get, the more likely we are to develop diseases, whether cancer, cardiovascular conditions, or neurodegenerative diseases. Until now, we've considered aging as an unmodifiable factor, but this may be where we were wrong. What is unmodifiable is our chronological age, but our chronological age only tells us how many years we've lived, not the true biological aging process. However, this biological aging process does exist. It is what underlies aging-related diseases, and when we can better measure it, we can assess biological age and better understand its role in the development of diseases. This could be a major revolution in medicine. Once we understand the biological aging process, we can better understand the causes of aging-related diseases and develop therapeutic solutions. For example, as we age, we accumulate senescent cells. Depending on our lifestyle, these senescent cells may accumulate in specific organs. Currently, the U.S. government is running a major programme to study where these senescent cells are located, how to measure them, map them, and then investigate therapies to either destroy them or prevent the secretion of these cells, which gradually spread to other cells and make them senescent. This opens up extremely important therapeutic perspectives for diseases such as Alzheimer's, heart failure, osteoarthritis, and immune system deterioration.

How is the ICOPE program being deployed in France and internationally? Have you already observed any initial results regarding cost-effectiveness?

The ICOPE program follows WHO guidelines, meaning it has passed all the WHO's rigorous standards, backed by sufficient medical and scientific evidence to be recommended. It consists of five steps: the first is screening to detect various functions (easy to perform and low-cost, and can also be self-assessed by downloading the free ICOPE Monitor app). If the screening is positive and the anomaly is new or not already addressed, we move to step two. Then, we proceed to step three, where patients generally enter the traditional healthcare system. Next, we move to monitoring, as we continue to age and need to keep track of our functions. The fifth step involves ensuring a supportive ecosystem. STEP 1 includes simple questions, such as: can the person stand up from a chair five times without using their arms in under 14

seconds? If someone can do this, they have a low risk of losing mobility; if not, they have a significant risk, and at that point, we assess how we can intervene.

We are conducting a large randomised controlled trial called RCT ICOPE France, studying 1,000 patients, half of whom will be monitored through ICOPE and the other half will follow their usual medical care. The aim is to assess both economic effectiveness and the maintenance of functional abilities, as well as to explore biological aging markers. This study will take several years to complete, but in the meantime, it is crucial to expand the ICOPE program, **as it ensures that the right patient is seen at the right time by their doctor**. Some patients who come to our consultations have made appointments but don't show up, others come for unclear reasons, some have chronic conditions, and others come at the right time. With ICOPE, we can identify older individuals who are losing weight or appetite and need to be seen before it's too late, those who feel depressed and have lost interest in activities they once enjoyed, those with mobility issues, or those with troubling memory concerns. This helps us identify the right patients at the right time, and through this approach, we have been able to identify thousands of patients with these issues and guide them back into the healthcare system. The RCT ICOPE France will demonstrate the relevance of ICOPE not only for healthy aging but also in terms of healthcare savings and biological aging markers.

How does the INSPIRE translational research platform work?

The INSPIRE translational research platform includes our mirror cohorts in mice, humans, and fish, which help answer various scientific questions to better understand the determinants of intrinsic capacity loss, search for therapeutic targets, and ultimately enable better aging. These cohorts are the subject of an increasing number of scientific publications in leading journals, and our data is available to the scientific community.

What do you see as the short, medium, and long-term challenges for preserving healthy longevity in an aging society? What role will IHU HealthAge play in these challenges?

The challenges are numerous. First, we must stop doing things that are harmful. We conducted a study at the CHU in Toulouse, the fourth-largest hospital in France, where we looked at patients over the age of 70 and their baseline autonomy levels at admission and discharge. These findings, published in a study, show that about 60% of patients leave as they were, 20% improve, likely due to treatment for conditions that were beneficial, and 20% deteriorate. Among those who deteriorated, half have no clear medical explanation—this is likely due to hospital-acquired dependency. We need to address hospital-acquired dependency in the same way we tackled hospital-acquired infections. This likely affects tens of thousands of cases annually. If we stop doing what's ineffective and adapt our healthcare system to better care for and monitor individuals, we could have an aging society that becomes a great asset, with older individuals often being more available to help their loved ones.

It is in this context that we are working with the National Academy of Medicine on a report on **the Clinique de la longévité en santé, i.e. what is reasonable and necessary to age well? What is the annual assessment?** This involves 1. maintaining our functions with ICOPE and having an optimal vaccination status, which is becoming increasingly complex today; 2.

identifying aging-related diseases at an early stage to repair the organs before it's too late; and 3. benefiting from future advances in geroscience.

The role of IHU HealthAge is to develop translational research to discover new biomarkers, therapeutic solutions, and the most appropriate healthcare system, as well as to contribute to training.