Arcadi Navarro â?? Director, Pasqual Maragall Foundation

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*The Pasqual Maragall Foundation is a Spanish non-profit research organization dedicated to the research of Alzheimerâ??s disease. Its director, Arcadi Navarro, takes from his decades-long scientific career in genomics to explain the main theories and discoveries shaping the push to find a next-generation treatment, or even possible cure, for Alzheimerâ??s. Navarro comments on Biogenâ??s aducanumab, the challenges it has faced in Europe after its controversial approval in the United States and explains why such novel therapeutic strategy could result in breakthroughs down the line. Finally, the Catalan professor shares important considerations to take when looking at Alzheimerâ??s statistics and how the Pasqual Maragall Foundationâ??s ambitious Alfa Study is helping advance research in the field.**

Arcadi, you became director of the Pasqual Maragall Foundation at the beginning of 2020 and have been involved with genomics research for over two decades. Can you state your credentials and how you became involved with Alzheimerâ??s research?

I am a researcher and genetics university professor. My experience in research goes back 25 years, working mostly on genomics, comparative genomics and so on. I have ventured out of academia a couple of times, first working in the pharmaceutical industry for a CRO (contract research organization) during my PhD, and the second with the government of Catalonia where I served as secretary for universities and research.

I came back to academia to continue doing research and teach at the university while at the same time working as director of the Pasqual Maragall Foundationâ??s research center. After a while, I was named director of the foundation, trying to contribute to the fight against Alzheimerâ??s disease. At the Universitat Pompeu Fabra, I teach masterâ??s-level courses on a couple of subjects related to genome analysis, looking at the most recent developments in how to associate genetic variation to phenotypic variation, mostly focusing on disease or pharmacogenomics.

According to recent interviews with your colleagues in Spain, the scientific community has pinpointed three main causes of Alzheimerâ??s disease: aging, environmental factors and genetic factors. As an experienced researcher on the latter, how should we think about the commonly used statement that genetic factors account for only 1 percent of all cases?

How much time do we have? To clarify that 1 percent statement since it can be misleading. Alzheimerâ??s disease takes two main forms: early onset which follows a highly inheritable monogenic (or Mendelian) pattern with mutations that run within families and that affect a few genes, such presenilins, amyloid precursor proteins (APP), and so on. This very early onset form accounts for about 1 percent of all Alzheimerâ??s cases. In those cases, if your parents had that form of the disease, which usually manifest at 40-50 years of age, and you inherit the mutation, you do have a high risk of that form of the disease.

Now, there is another form of the disease, which is the late onset, more complex, non-Mendelian one that usually has an age of onset beyond 65 years. That for is very clearly associated with age and, while it also has a genetic component, it does not run in families. The vast majority of Alzheimerâ??s cases, up to 99 percent, correspond to this form of the disease.

In a sense, it could have been clearer if from the start we would have spoken about two different diseases because the genetic etiologies [branch of medicine that studies the cause of diseases] of the two forms are completely different. This is the case with many other diseases: because the phenotypes are very similar, we end up referring to the same disease even when the genetic causes are different. Nowadays, after learning more about genetics, it is obvious that you can have the same diagnosis, perhaps even the same prognosis and treatment, but a very different genetic profile.

Frequently cited data has identified age as the determinant factor when it comes to Alzheimerâ??s risk, showing that 50 percent of people over the age of 90 suffer from the disease, a number that drops to 15 percent for people 85 years old, 2-5 percent for people in their 70s and only 2 percent of 60 years old. How do you interpret those statistics?

Those numbers are correct. As we discussed, all of them have a degree of genetic components, but only the early onset form runs in families. On top of genetics, there are a series of environmental factors and non-environmental such as age.

Age is precisely the main risk factor due to decades-long exposure to environmental factors that have an impact on the brain; we all become fragile and suffer deterioration of organs. And yes, if people lived longer than 100 years, if what we know holds, at least 50 percent would develop Alzheimerâ??s. Among environmental factors we have pollution, lack of exercise and other lifestyle-related issues.

Generally speaking, what is bad for the body is bad for the brain. I like to explain these factors the other way around, instead of calling them risk factors I call them protective factors because addressing them will decrease the risk of developing the disease; if you exercise, donâ??t smoke or drink too much, donâ??t have high-blood pressure, live in place with little pollution and enjoy a rich social life, your risk of drastically decreases.

Today, it is possible to predict the risk of Alzheimerâ??s with high precision very early, perhaps even 15-20 years before the first clinical symptoms appear, through blood-based biomarkers. This opens a large window of time in which patients can intervene either with pharmacological treatments, when they become available, or with lifestyle interventions or intellectual activity, although the latter has been proven to be less significant than previously thought; perhaps physical activity and a good diet are more important.

What is the life expectancy in Spain for diagnosed Alzheimerâ??s patients and how relevant is that number?

In Spain the average life expectancy for diagnosed patients is rarely beyond 15 years but the statistic is not very meaningful due to a huge variation in social components. People with middle class backgrounds usually have the opportunity of receiving help from family members but people with underprivileged backgrounds have a harder time accessing care. Around 87 percent of the socio-economic cost of Alzheimerâ??s in Spain, which is estimated at 22,000 euros per patient per year, is covered by family members, meaning that patients need someone looking out for them 24 hours a day. Also, it is important to mention that caregivers are usually women, which adds a further layer of inequality.

This last element is quite interesting because it means that, on top of caring for other patients, women are affected more dramatically since they have a higher prevalence than men.

Regarding the Pasqual Maragall Foundation, it was founded by Barcelonaâ??s former mayor, who at the time was governor of Catalonia, soon after he was diagnosed with Alzheimerâ??s disease. Can you comment on the origins of the organization and the work you do to research and tackle the disease?

Pasqual Maragall, former mayor of Barcelona and president of Catalonia, was diagnosed with the disease back in 2007. He has a very advanced Alzheimerâ??s and is taken care of by his family, particularly his three children since his wife, who used to be the main caregiver, passed away a couple of years ago.

Mr Maragall was a very peculiar politician that always thought about the long term which is why he invested in major projects that shaped our society. After being diagnosed, he realized that, since the causes of the disease were not known and its socio-economic implications were huge, the only solution that humanity could provide to Alzheimerâ??s was science; he wanted society to â??science this outâ?•.

The first thing he did had immense implications, he went public to announce his diagnosis and explain to society that the only solution was to use science. That was extraordinary because dementia has historically carried stigma. 30 years ago, people did not talk openly about cancer, they would speak about â??a long diseaseâ?•, but today they in fact do mention cancer because it has been proven that there is nothing about it that is their fault. However, the stigma remains in

Alzheimerâ??s patients.

Throughout history, the best solution that humans have come up with when facing key challenges has been science, whether it is transport, hygiene, vaccines, climate change or energy or: it is a question of doing research.

That is the leitmotif of the Pasqual Maragall Foundation, to foster science and change societyâ??s perspective on Alzheimerâ??s disease. We use the support given by society in the form of 50,000+ members and large-scale philanthropic donations to carry out research. I was not here at the time, but a very revealing thing occurred just after the foundationâ??s creation. The foundation was started with a long-term project, a cohort of about 3,000 people that were totally healthy at the time, cognitively unimpaired, and in the risk population. That approach was heavily criticized by some because the foundation was investing in research on volunteers that did not have the disease. However, the organization was committed to a long-term approach, believing that following them throughout their lives would give unique insights. The study, called Alfa Study (for Alzheimerâ??s and families), was started in 2013 and follows biomarkers and cognitive tests to describe in great detail how Alzheimerâ??s develops, thus enabling accurate predictions years in advance.

We were initially targeting a cohort of 400 people but, with the help of Mr. Maragall, we obtained more than 10,000 volunteers and ended up recruiting many of them. The patients voluntarily give us their time, blood and spinal fluid; we follow them more or less once every three years but that is changing because, as they age, we must follow up more closely. We are about to start a third round of visits that will provide valuable data. Other organizations have followed that model but at the time was heavily scrutinized.

Are you able to share specific learnings acquired from the Alfa Study, or is it too early to say?

It took a while to get them, but once we got started, results are being amazing. For instance, researchers in the foundation have developed AI algorithms that use information from neuroimaging done by magnetic resonance, not PET scans, that allow for good assessments of the level proteins accumulation in peopleâ??s brains, a very valuable filtering criterion for clinical trials.

Last year, a young researcher from our institution showed that the level of of Phospho-Tau proteins can be estimated simply using biomarkers in the blood, a non-invasive and very precise method. In addition, we have been conducting research on how lifestyle factors such as sleep, or dietary patterns affect someoneâ??s risk of Alzheimerâ??s. We have been able to prove, for instance, that that blue fish helps reduce the risk of the disease.

According to the foundationâ??s website, your research activities are done by the BarcelonaÎ²eta Brain Research Center. Can you explain how both entities interact?

It is more of an operational question because Spanish law makes it difficult to have a non-profit organization that at the same time operates as a research center. The BarcelonaÎ²eta Brain Research Center (BBRC) also supported La Caixa Foundation as well as by the Pasqual Maragall Foundation does research and the foundation takes care of social awareness and fundraising. Up to now, the BBRC has been in charge of all the science and research fostered by the foundation. Both institutions apply together for competitive money, grants from Europe, America, the Bill Gates Foundation, the European Research Council. Moreover, we collaborate with industry players to do clinical trials by helping recruit patients.

The organizationâ??s main research subject, Alzheimerâ??s disease, has attracted many headlines in recent months due to the US FDAâ??s contested approval of Biogenâ??s aducanumab, a drug that claims to clean deposits of a specific protein in the brain believed to be linked with the disease. Can you walk us through the latest scientific discoveries and approaches around treatments for Alzheimerâ??s?

The basic fact is that research on Alzheimerâ??s has been terribly underfunded compared to cancer or cardiovascular diseases.

Within Alzheimerâ??s there are several hypotheses including the beta-amyloid hypothesis and the Tau protein hypothesis. Even though the causes of Alzheimerâ??s are not known, there are some clear candidates that are very reasonable to study. The accumulation of some misfolded or miscut proteins in the brain clearly go together with the disease but correlation does not necessarily imply causation because, first, there are people with accumulation of those proteins that do not appear to present clinical manifestations, and there are different clinical manifestations with a varying range of protein accumulation.

My impression, which is only a personal intuition, is that too much attention has been paid over the last few decades to the amyloid hypothesis while the research of many other possible causes has been severely underfunded. The fact that it is too early to make absolute conclusions.

Nevertheless, the fact that perhaps too much attention is being put on the beta-amyloid and Tau theories â?? which, again, is a debatable statement â?? does not mean that having monoclonal antibodies attacking those proteins, such as aducanumab, is a bad idea. Perhaps, over time, some of these new treatments will work; there are over 110 trials being run as we speak that use similar therapeutic strategies as aducanumab. In short: we do not know if those proteins trigger the disease or are its ultimate cause, but cleaning them up from our brains particularly if we do it early on, may be a good therapeutic strategy.

You said that it is not a bad idea to have or research drugs that, while not representing a cure, can clean the beta-amyloid or Tau protein deposits in the brain. Can you elaborate on that and how they compare to treatments currently available in the market?

There is no question that aducanumab helps clean and reduce the load of beta-amyloid protein in the brain. However, it is not so obvious that it does so at a price we can afford; the drug has important secondary effects, which was one of the main concerns during the FDA discussions. Also, it is not obvious that it significantly decelerates the clinical manifestations of the disease, which is why the EMA has not approved the treatment yet.

Having said that, it has become evident that after more than 300 failed Alzheimerâ??s drugs we have a huge dilemma. Many efforts to find a solution have been abandoned by the pharma industry because they were coming up with drugs for patients who already had clinical manifestations; that is, when neurodegeneration was already quite advanced.

The strategy that Biogen and other companies are proposing is to attack the disease before the clinical manifestations are obvious. If such molecule succeeds, we will have in our hands the first drug against Alzheimerâ??s that actually changes the course of the disease, that modifies it rather than just delaying its progression. As of today, there are 3-4 approved symptomatic drugs that have an effect for a while but fail to stop the process of neurodegeneration, patients are able to stop neurotransmitters from degenerating, but patients produce less and less of them.

Even though aducanumab has struggled with patients, we know that their strategy gives hope to the community, which in turn could develop solutions with less secondary effects and more efficiency. Who knows? Biogen obtained a problematic approval from the FDA â?? I very much prefer the cautious EMAâ??s positionâ?? but the paradigm proposed by the drug justifies more research.

Having established age as the main risk factor for Alzheimerâ??s, how advantageous is it for the foundation to be in one of the countries with the highest life expectancy in the world? Also, what factors do you believe contribute the most to Spainâ??s high life expectancy rate (around 82.4 years)?

Spain has a combination of traditional lifestyle choices â?? tightly woven families and a Mediterranean diet, plus a successful healthcare system set up decades ago. The combination of these elements has resulted in a high life expectancy.

In addition, the country has a fairly successful research environment. However, it is clear that our aging population has not been leveraged enough to lead on aging research. We have great researchers working on the age question such as Pura MuÃ±oz who focuses on sarcopenia [age-associated muscle decline and wasting] or Maria Blasco on telomere length and used to have great people working inside the country like Manolo Serrano. These people have done beautiful research on aging, but it is more on the molecular nature of ageing than on its epidemiology.

We hope that eventually the aging population will be leveraged but it has not been done so far.

As a last question, given your deep research expertise in genomics, in your opinion, which technologies being developed today are will have the biggest impact on the future of healthcare or biotechnology research?

Iâ??m afraid I donâ??t have a good answer for that. The reason is that we are living a technological golden age in several aspects. First, we have enjoyed more than a decade of high-throughput data in genomics, which is moving quickly to the world of phenomics, the phenotypes, and epigenomics, proteomics, wearables that measure very subtle things all day long and so on. They are fundamental technological developments.

At the foundation, we recently opened a new machine in our lab that allows us to measure the presence or absence of proteins in any fluid in an automatic way.

I am not able to choose one single technology that I am the most excited about. Perhaps it is a personal bias related to my years-long work with genomics, but anything related to it has been an extremely useful success. Game changers not only because of the technology itself, but also because it has opened the door to the right conceptualization of high throughput data.

Second, we have unprecedented computer power in our hands by which I do not only mean machine learning or artificial intelligence, (omething with lots of hype around it), but also the possibility to use that computer power on top of high-throughput technology.

Third, on top of that we have an international scientific community willing to do open science; there is no science without collaboration. For example, I am co-responsible of the European Genome-Phenome Archive at the Center for Genomic Regulation which, together with the European Bioinformatics Institute, has worked for more than 10 years to make sure that we can have FAIR (findable, accessible, interoperable, and reusable) genomic data.

These three things â?? high-throughput data, computer power and the push for data sharing â?? taken together could form the single game changing ecosystem that is advancing the science the most.

** This is a transcription of PharmaBoardroomâ??s recent conversation with Arcadi Navarro, lightly edited for clarity*

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