Alexis Brice – Director, Brain & Spine Institute (ICM), France



Mixing public and private research was the idea behind the creation of ICM

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Prof. Alexis Brice, director of the French Brain & Spine Institute (Institut du Cerveau et de la Moelle épinière (ICM)), reveals the recipe behind the success of the center since its foundation eight years ago and discusses the future of research on neurodegenerative diseases.

Could you please introduce your exceptional career to our international audience and tell us what led you to get involved in the field of neurosciences?

I was trained as a neurologist and I always wanted to understand more about the brain and its functions. Throughout my career, I got more and more interested in molecular biology – a developing field – and its applications in understanding brain diseases. This led to my research activity in neurogenetics, since 40 percent of genetic disorders actually affect the nervous system. This approach led us to identify many of the genes responsible for these conditions. From there, my team moved on to more physio-pathological approaches, where models are developed to understand precise dysfunctions and identify new therapeutic approaches. This genetic approach did not concern only rare diseases, but also very common ones, like Parkinson's, which includes a subset of purely monogenic forms. All in all, I had a team; I was a hospital practitioner and a university professor, and I had the opportunity to assemble a department here, at the Pitié-Salpêtrière Hospital, aimed at creating a multidisciplinary approach to genetic disorders. I got

involved in structuring the biomedical research at a national level through the creation of AVIESAN (the French National Alliance for Life Sciences and Health), a useful experience to get a complete picture of the research quality in France and have an impact in structuring neurosciences. Lastly, six years ago, I became the director of the newly created ICM institute.

Today, the ICM is recognized as a center of excellence in neurosciences, ranked third in Europe and first in France. How was it possible to achieve this status in only eight years?

It is the combination of excellent choices. First, the institute was created on the site of the Pitié-Salpêtrière Hospital, where clinical neurosciences were extremely strong, with a very long tradition and a large number of experts. The environment not only provided clinicians but also a large patient pool: one hundred thousand patients per year are treated in the neurology section. The second winning choice was to team up with Inserm, the CNRS and Sorbonne University to create an institute with a new spirit and a unique ecosystem including patients, clinicians, researchers and entrepreneurs. The idea was not only to do excellent research or to provide excellent care, but also to be able to develop new tools and applications for patients.

Have you seen progress in the reconciliation between the historically opposed private and public research sectors in France?

Mixing public and private research was the idea behind the creation of ICM. It was a bet that worked very well thanks to the strength of the research already in place and the attraction of international young scientists as team leaders. We managed to rejuvenate the institute and bring new ideas, new practices, and new technologies. The presence of startups changed our mentality, creating a very well-integrated community that is producing reciprocal benefits. Indeed, CEOs save a considerable amount of time, as any question can be answered by our experts, while the research teams can engage in collaborations. This led to the creation of two LabComs, joint ventures between startups and ICM.

Fostering public-private partnerships was also one of the key points made by Prime Minister Edouard Philippe at the CSIS of July 2018…

Fortunately, we did not wait for that! It was an initiative that was ongoing, but the same spirit of the CSIS guided us. I think it is very important to underline that the difference between public and private is not that huge, because research done in the private sector at high levels is excellent. This was not the case 20 years ago, when everything that was private was considered unethical. At ICM, we operate in a world of relative freedom for the researchers. We have teams addressing very fundamental questions who have no natural links with the startup companies, while other teams have fostered strong relationships with our private partners. There is a whole spectrum of teams ranging from very basic research to research linked to diseases. However, we do not see the institute as a competition of individual teams, but rather a collaboration of scientists with exquisite expertise.

What do you consider the key successes of the center and its priorities for the near future?

There are many success stories. At this stage, our success is our capability to attract the best talents, even if we cannot offer the same packages given in the US. Also, despite not being a huge institute, we have 10 ERC (European Research Council) grants, which is a very high proportion and we are expecting a few more. It shows that the quality of the research is great; according to a bibliometric analysis by Inserm, we rank second among 35 international institutes in neurology. We are also proud to be awarded the IHU (University Hospital Institutes) program, which accelerates our research and has allowed us to invest in unique technological platforms, facilitating the sharing of information among teams, in accordance with the institute spirit.

We have also developed industrial partnerships, and this is another success: the revenues from public-private partnerships have been multiplied by a factor of ten since the creation of the institute. We are members of the Carnot network, a public label for various kind of research that includes 20 to 30 institutes and offer support to professionalize our offer. On top of this, our incubator has hosted 35 companies, with more than EUR 150 million (USD 174 million) of raised capital and 300 jobs created. The incubator is in the building and we have a branch at Station F (a Paris-based business incubator for startups) with around 100 seats. There are many candidates and we have to be very selective, and, due to the lack of space, we cannot keep the startups in our environment for long enough to benefit from their development. Hence, we are planning to expand.

Several Big Pharma players have encountered failures in terms of drug trials in dementia. Last year, Pfizer announced it intends to pull out of the field, while Lilly and Merck also faced setbacks. R&D costs in neurosciences are enormous and the failure rate is high. What do you think will be the effect of this and what is your approach to industrial partnerships?

We have considerably increased our partnerships, not only with the pharma industry but also in other areas, like connected health. Our objective for the future is to accelerate clinical research, as our ecosystem offers a great potential. We have developed some tools for that. The first is Neurotrials, offered to private partnerships with the pharma industry. It is a contract research organization (CRO) that provides all of the services of a typical CRO and offering, in addition, the unique interaction with our experts who are dedicated to improving the trial design and to developing new biomarkers and readouts. Neurotrials have the potential to attract many proof-of-concept trials to France, as it is a tool that specifically addresses early-phase trials, allowing the companies to have a go or no-go in a quick and extremely organized way. Our clinical investigation center (CIC) will work very closely with Neurotrials. Second, we aim to generate more proof-of-concept studies for the institute (not only from the private industry) and we have created a program to which teams can apply for support for conducting a clinical trial.

Neurodegenerative diseases are a real emergency. Dementia is bankrupting our civilization as Professor John Hardy from UCL pointed out, and there is no cure. What could be the role of ICM and France in this field, and how important are international collaborations for ICM?

ICM is very well linked internationally. We participate and lead consortia on various disorders and work a lot at the international level. It is time to understand why so many trials for neurogenerative diseases are failing. It could be a question of irreversible lesions or it could be that the drugs tested are not aimed at the appropriate target. Our teams are tackling exactly these issues. From a clinical point of view, we know that many neurodegenerative disorders start much earlier than the appearance of symptoms. The follow-up on patients that are not demented but have a high risk of dementia is of great importance in detecting the first dysfunctions identifying very early biomarkers. The objective is to treat before we reach some irreversible damage. In this sense, ICM is very well placed, because we have set up interesting cohorts of patients who are clinically normal but relatively aged; within this cohort there is a proportion of patients that already have amyloid load in the brain, suggesting that they will develop Alzheimer’s disease. Studying this

cohort offers a lot of information between the steps of the accumulation of amyloids and the development of the disease many years later. We have this type of approach with several other neurogenerative diseases, particularly genetic forms, and this is leading to the possibility of pre-symptomatic treatments for preventing future manifestations. The second aspect is finding new targets. Everything is based on the amyloid hypothesis, which is certainly a component of the disease but it has not been proven efficient so far. It is necessary to bring new knowledge on possible disease mechanisms and to think out-of-the-box of the amyloid hypothesis.

A few words that you would like to send to our international audience to conclude?

In addition to clinical research, there are other processes that we are trying to develop. One is our role in education and training: we have created a summer school to train the future neuro-entrepreneurs and an international master on neurogenerative diseases in collaboration with the Universities of Louvain (KUL), Munich (TUM) and Vienna. It is a great initiative. Also, we would like to take advantage of our knowledge in cognitive neuroscience to apply some of these discoveries to society, at large. We have teams working on motivation, fatigue and other common problems within our society. Last by not least, we want to be leaders in neuroinformatics. Another project that we want to have a role in (and hopefully take leadership in) involves big data analytics. Here we have cohorts with deep phenotyping, longitudinal data for several disorders and we have access to the AP-HP (Hospitals of Paris) data warehouse. In-house, we have the talent necessary among our data scientists, bioinformaticians, mathematicians, and physicians, all of whom are working together on this new challenge in our Center of Neuroinformatics.

All in all, ICM was a gamble initially, but it has proven to be a great success. Now, we have the perfect environment for research: soon, we should see important discoveries both in basic science and clinical research. I am quite optimistic about the future as long as the IHU grant is renewed. Even if we have developed our own resources through partnerships and fundraising (constituting 25 percent of our total budget), we still need some public support in the long term. The first period of IHU is ending, and the renewal has been announced on a competitive basis and with the expectation that recipients will be completely self-sustaining at the end of the five-year grant. It is risky to think that we will be self-sustaining in just five years. The leading role that we have in the area cannot be maintained in the long term without short-term support. We have done well so far: in the first period the multiplicator factor of the public funding was 2.7, in the next period is forecasted to be about five. This is a sound investment for the government, and we hope that they see it as such.

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