# Stanislas Lyonnet – Director, Imagine Institute, France

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*Prof. Stanislas Lyonnet, director of the Imagine Institute in Paris, France, explains his organization's unique ecosystem that brings together researchers, physicians, patients and private actors to find the cure to genetic diseases.*

**Could you please introduce yourself and tell us why you decided to take the helm of the Imagine Institute in July 2016?**

I am both a physician and a scientist. Currently, I am a professor at Paris Descartes University, the co-head with Prof. Jeanne Amiel of the Laboratory of Embryology and *Genetics* of *Human Malformation* and also a physician in the department of genetics at Necker Enfants Malades Hospital. On top of those more traditional roles, I am trying to spearhead the Imagine Institute towards the future.

The core purpose of the Imagine Institute is to combine the talents of scientists and physicians and bring their shared expertise to the families and children affected by genetic disorders. Our motto is "integration of basic sciences with clinical forces." We add our expertise in the field of genetics to cure the patients of the Necker Hospital: of its 400,000 annual cases, ten percent comes to us. In a nutshell, we identify genetic diseases and gene mutations, discover whether they are hereditary, consult previous research, and refer parents to support groups. Our institute, much like other University Hospital Institutes (IHUs), is the clinical link to *understanding to cure.* We created an ecosystem that allows the interaction of families, children, basic science, and physicians.

**How does the peculiar mix of private and public players in the Institute's governance lend to its innovative stance?**

This is a very important point. Because the Future Investment Plan promoted the idea of regulating institutes like ours through private law and not recognizing us as public entities, we have a Board of Trustees. The Foundation of Scientific Cooperation (*Fondation de Coopération Scientifique*, or FCS), promoted in 2005 by Minister Goulard, is the basis of private-public foundations like Imagine. In our board of directors, we have the Paris Hospital (the *Assistance Publique Hospital of Paris,* or AP-HP), the National Institute for Health and Research (*Institut national de la santé et de la recherche médicale,* known as Inserm), Université Paris Descartes, as the institutional investors. However, they are not alone, as we have non-institutional founders: the city of Paris, the AFM-Telethon and the *Hôpital de Paris–Hôpital de France* (HP-HF) *Foundation*.

We have a mix of motives and expertise; this mix does not contradict the ambitions of our public founders, though. Rather, the mix complements them.

This structure allows the institute to undertake projects without necessarily going through public actors like Inserm, Paris Descartes University, Hospital of Paris and the Necker Hospital. We know very well the usual pattern: the bureaucracy loses time, money and efficacy! At Imagine we accelerate the system, without short-circuiting the founders' philosophy thanks their controls at the Board of trustees.

**Is this the reason why Imagine is a unique institution?**

Absolutely. It makes us more dynamic. This new 20,000 sqm building serves as an example. The goodwill of the Necker Hospital, a significant contribution by Inserm of EUR three million and the University contributed just 10 percent of the financing, while the remaining 90 percent was covered by other actors, such as the Foundation, the greater region of Paris, and the Ministry of Health. Also, we are allowed to fundraise, and we have brought this to a professional level, involving high level corporate executives. Every year we host a charity gala named Heroes. This year, the event raised EUR 7 million (USD 8.2 million) in a single evening. EUR 2.4 million was raised by a shared announcement by the MSD Avenir Foundation, while the remaining was generated through the charity dinner, an art auction and another auction for what we call 'exceptional moments', experiences that do not have a price, such as meetings with the CEO of Kering François Pinault or with Antoine Arnault and Natalia Vodianova, CEO of Berluti and chairman of Loro Piana, and founder of the Naked heart foundation.

**In France it seems as though private and public research operate in two different worlds. Do you think that this is changing?**

I do think so, and my fundraising story serves as an example. We raised zero Euros in 2012 by fundraising, while this year, we raised several million. We are also becoming an ecosystem for private companies. We have built three startups – it is not a lot, relative to other groups, but it is a start. For instance, in August 2014 Alexion wanted to establish an R&D lab in France and consulted several biotech incubators for a space of 400 sqm. We barely offered them 200 $m^2$ but they chose us regardless, as we had the expertise, an ecosystem, a database and more than 100,000 patient cases with DNA profiles. The contract was meant to last two years, but they have been here for four years now. Thanks to this proximity with a pharma company, we now have three collaborative projects for retinitis pigmentosa, kidney disorders and the application of AI in rare diseases. The idea behind the latter is very interesting: as rare diseases are fragmented in many disorders and mutations, we are trying to regroup patients not by mutations or syndrome names but rather by mechanisms addressed by drugs. Ultimately, we realized that the DNA of Alexion research is not so different than that of Imagine!

**France has historically played a pioneering role in rare disease research as it was the first country in Europe to unroll a national rare diseases plan. Minister of Higher Education, Research & Innovation Frédérique Vidal and Minister of Solidarities & Health Agnès Buzyn are launching the third plan for 2018-22. What are your thoughts on it?**

Very positive. It has been constructed with very broad and solid bases with expert physicians, family groups, scientists, industry and laboratories. The intent of promoting the diagnostic cause is very good. Currently, families lose time, money, and hope in identifying the disease. *The Plan Maladies Rare 3* (the Third Plan for Rare Diseases) connects very well with the *France Medecine Génomique 2025* (the France Medicine Genomic Plan), because it is based on the idea that we have to change the paradigm of using genetic testing in the diagnostic setting and not only in research, given that there is a control of good practices in prescription, information to patients and quality of the interpretation of data.

**What is the role of local University Hospital Institutes (IHUs) compared with public research organizations such Inserm (National Institute for Health and Research)?**

At some point it has been said that the IHUs were in contradiction with Inserm. It is not true. Inserm tries to promote plans at a national level, whereas it is not its role to fully control the intents of an IHU at the local level. It is about the position of the research organizations that have been invented in the post-war period, like Inserm, or pre-war times, like CNRS (the French National Center for Scientific Research). The landscape has changed in the past 15 years, as evinced by the Goulard law, the establishment of the FCS, the creation of the ANR (National Agency for Research) to finance projects, the external evaluation of the Hcéres (High Committee for the Evaluation of Science, Research and Higher Education), the Investments of the Future program, and last but not least the law of autonomy for universities (2007).

However, the roadmap of the nationwide research organizations has not changed. All is a question of ‘philosophy of science’. At Imagine, we try to show that local-regional initiatives do not aspire to take supremacy on the national stage. We just want to be open to the ecosystem, to work with partners, philanthropists, industry, startups, and so forth. These initiatives should be welcomed positively by the organization and not hindered – quite the opposite, they should be given more autonomy. National organizations could use them as a tool while enacting national plans. These big research organizations were quite successful in fulfilling the need for research in France, but now we have to shift a little more to Public-Private Partnerships and regional university initiatives.

This partial autonomy goes with a price. The first implication of this autonomy is that there should be a high-level international evaluation with no PT: if you fail, you are closed or reduced. The second is that organizations need to show and demonstrate that the local IHUs are able to produce a return on investment and are not merely cost centers. Finally, we need to show we are able to raise the money we were given one decade ago. Imagine is an investment, not a cost!

**There are around 7,000 forms of rare diseases. How do you narrow your focus and how does Imagine want to stand internationally, compared to other institutes?**

First of all, we focus on the patient cohorts in Necker Enfants Malades, which are children. Second, we operate according to what we call Integrated Care and Research Programs (ICaRP). ICaRPs are not administrative departments, but rather the links between research and the clinic. An ICaRP is formed when there is one or more experts of the Rare Disease Plan, one or more clinical platforms or laboratories of the hospital, or one or more basic science laboratories. The largest ICaRP we have is on immunology, infectiology and hematology, comprising a third of the institute. We also have one on neurosciences, cardiology, development and morphogenesis, gastroenterology and nephrology. The idea is condensing complete support in a domain where basic science is connected with translational research. It can evolve with the need and according to competencies too. We have for example closed weak ICaRps and opened new, innovative ones.

Lastly, you never walk alone on the rare diseases’ road, even though cases are unique. You might have a child with a single gene mutation we know nothing about and no other reference case. The international gene or genotype matcher database helps us in finding other cases and in coordinating the effort with other institutes. This reference network is actually an idea of France’s first Plan for Rare Diseases, and it was later on done at a European level, through the European Research Network (ERN).

**Is Brexit a window of opportunity for France?**

As a trader, maybe, but as a scientist, I would say it is absolutely not. Our British colleagues are probably the best in Europe in the field of genetics. In France, we often care about regulations prior to walking, while the Brits walk and invent, and then adoptthe administrative frame. The collaboration with the UK might be seriously impaired by Brexit. For instance, we have a joint scientific program to attract new talents. Through this program we found a professor of genetics from Manchester, Prof. Yanick Crow. Yanick came to France in 2014, he has been incredibly successful with his research here and he just got a European Research Council (ERC) grant, the most prominent grant for outstanding scientists in Europe. He intended to duplicate his lab in Edinburgh, but in case of a hard Brexit the ERC will be cut. This shows that the impact of Brexit could be disastrous and concrete.

**What are your priorities for Imagine for the years to come?**

First of all, we have to maintain the excellence of science. Second, we need more financial autonomy, as our physicians and scientists deserve upgraded research opportunities. Third, I want to create a social awareness about science and genetics. Fourth, it is imperative to create more opportunities for the young French scientists that, although extremely well trained, are forced on going abroad too often. Finally, it is important to maintain the link with the clinical aspect: our purpose is not to become an ivory tower of basic science. We want to be open to hospitals, possibly more than one. Martin Hirsch, CEO of AP-HP wants to connect all the hospitals of the greater Paris area with the Paris Descartes University (APHP.5 initiative). Imagine would be honored to be the IHU of at least all the surrounding hospitals, for the genetic questions of course.

Imagine is not a usual laboratory, it is not a usual clinic: it is a mix between the two. Come and visit us! Also, the French people should be a bit more informed in order to be open to science, in particular to genetics.

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