Jean-Jacques Garaud – CEO, Inotrem, France



The TREM-1 pathway can be used to develop treatments for different indications besides septic shock, including cardiovascular diseases and chronic inflammatory conditions, which could be interesting to investors or Big Pharma

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Inotrem is a French biotech company developing a novel approach to target inflammatory diseases based on the TREM-1 pathway. Its CEO, Dr Jean-Jacques Garaud explains why he decided to leave Big Pharma for biotech, lays out Inotrem's recent milestones, and outlines his internationalization strategy.

Could you start by introducing yourself to our readers?

I am trained as a critical care physician with a specialization in infectious diseases and tropical medicine. In the 1980s, I decided to jump on the other side of the fence and join the pharmaceutical industry where I had a long international career in drug research and development. I spent 12 years in the US, mainly with Schering-Plough, worked six years at Novartis in the US and Basel and six years at Roche. My last position at Roche was head of research and early development and member of the Roche group extended executive committee.

Before that, I was the CMO of Roche and head of development. I left Roche in 2012 as I felt I could have more impact working for smaller organizations. I moved back to Paris where I worked as a strategic advisor to technology transfer offices, mainly in Paris but also in the UK, to identify and help early-stage projects with the potential to become biotech start-ups. During my time with Inserm Transfert, I was involved with the creation of three companies, two of which I co-founded. One of them was Inotrem which was developing a first-in-class immune-therapy for septic shock. In

2014, we were able to quickly assemble a robust syndicate composed of two French funds, Andera Partners and Sofinnova Partners, the Inserm transfer seed fund and a Swiss fund called BioMedInvest. Together, they invested a total of EUR 18 million in Inotrem. During that time, I was also a member of the board of directors of Circassia in the UK, Polyphor in Switzerland and MedDay in France. The other company I co-founded is called ENYO.

Why did you decide to focus on Inotrem?

As I mentioned, my background is in critical care and infectious diseases, so I was particularly attracted to a new treatment against septic shock which remains a major public health issue worldwide with high mortality and morbidity. I truly believed that the biology behind Inotrem's program was promising and worth looking at carefully. Particularly, it is a program that allows upfront to use a mechanism-based biomarker to treat those patients who are more likely to benefit from the treatment. I wanted to invest my time and effort into an area that could be game-changing and have a greatly positive impact on public health.

What makes Inotrem's drug candidate against septic shock so promising?

Seventy percent of septic shock cases are caused by peritonitis, intra-abdominal sepsis and pneumonia. Septic shock is not necessarily related to the lack of control of the infection but is better characterized as an excessive immune response to an infection. To put it simply, what kills patients is not the infection itself, which can usually be controlled, but the excessive immune response to it. The standard treatment procedure for sepsis includes appropriate antibiotic therapy, surgical control of the source if surgery is needed and possible, and supportive care to failing organs such as vasopressor therapy to maintain viable blood pressure, mechanical ventilation in case of respiratory failure and hemodialysis to support renal function. While the antibiotics target the infection, supportive care only targets the symptoms that are the consequences of the shock itself. However, the excessive immune reaction responsible for the symptoms is not yet addressed. We believe the target we have identified plays a critical role in driving this reaction. Several animal models have demonstrated that acting on this target protects from and can actually reverse the shock, thus reducing excessive mortality. In about half of cases, patients' immune system goes into overdrive. So far, targets that have been identified were not central to this overdrive or were themselves immunosuppressive, putting patients at risk of developing more superinfections. The target we have identified is called TREM-1, hence the name Inotrem. Ino is a reference to the Greek

goddess who helped sailors caught in a storm reach safe havens. If we too can stop the storm like Ino, we can save patients' lives.

What have been the key milestones for the company, and the challenges you have faced along the way?

In the beginning, the main challenge we had was how to run a virtual company without an office as Dr Marc Derive, chief scientific officer and co-founder of Inotrem, and I were working from different locations.

It took us a year and a half to run the pre-clinical development phase, put together the IND and clinical trial documentation, after which we started hiring and surrounded ourselves with advisors and consultants. Looking back, I think we would have done better by bringing people on board earlier instead of trying to do everything by ourselves.

The first milestones we achieved was to enter the clinic and complete Phase I and Phase IIA. We are now entering a large Phase IIb in septic shock patients. In line with our personalized healthcare approach, a major milestone was to sign a partnership with Roche Diagnostics to jointly develop a companion diagnostic tool based on the concentration of soluble TREM-1. The EMA has granted the PRIME status to our lead compound, nangibotide.

In parallel to our septic shock treatment candidate, we have started a monoclonal antibody program also based on the TREM-1 target as we now know its involvement in chronic inflammatory conditions such as rheumatoid arthritis or Crohn's disease. We are close to identifying a drug-candidate.

What have been the key steps during the fund-raising process?

We were initially financed by public funds from the region and the National Research Agency (*Agence Nationale de la Recherche*) as well as loans from the Public Investment Bank (*Banque Publique d'Investissement*). In a second step, we raised money from venture capital firms. The research tax credit (*crédit d'impôt recherche*) was also a big help.

Capital is usually easy to come by at the early stage. However, raising significant funds to scale-up operations is a different ballgame. How have you prepared to manage this transition?

What we have done is propose a plan that goes all the way to registration. We have also positioned Inotrem as a company built around the TREM-1 pathway rather than just a one-time shot at septic shock which could be perceived as risky. The TREM-1 pathway can be used to develop treatments for different indications besides septic shock, including cardiovascular diseases and chronic inflammatory conditions, which could be interesting to investors or Big Pharma. We have already met with representatives of large pharmaceutical companies. Thanks to my previous experience in large pharmaceutical companies, it was relatively easy to connect with them, identify their expectations and build our plan accordingly. We also met with experts from the US FDA and the EMA and I believe our plan is well-suited to their expectations as well.

In the next round of funding, we would like to attract international investors outside of France and Europe.

What are the types of partnerships you would like to establish?

As I mentioned, we have a collaboration agreement with Roche Diagnostics to develop a companion diagnostic tool in parallel to the development of the drug. We own the patent for the soluble TREM-1 biomarker and have an option to license it.

Regarding drug development, quite a few Big Pharma companies are still interested in septic shock. We know the types of data they need to see before taking the risk to invest in a new treatment candidate and we have designed our clinical program accordingly.

The Macron government is seen as pro-business and pro-innovation. In your opinion, has the election of Macron impacted the French biotech scene?

I think things started to change for the better even before, under Nicolas Sarkozy, with the reform of the research tax credit in 2008, the launch of the “investments for the future” (*investissemens d’avenir*) funding program in 2010 and the creation of technological research institutes (Instituts de Recherche Technologique) to foster public-private partnerships, among other things. These reforms have enhanced the attractivity of France on the international stage by creating a more favourable

environment for risk-taking and entrepreneurship.

What would you like to achieve in the next five years?

In five years from now, we should have demonstrated the clinical efficacy of our septic shock treatment and be in the registration trial phase. Our program against chronic inflammatory diseases should be in the clinic with one or two proof of concepts achieved in at least two different conditions.

Regarding our financial and marketing strategy, we are open to every option, either flying solo by going public with a strong IPO, being acquired by a large company or collaborating with Big Pharma. In time, we will choose whatever option brings both the highest return to shareholders and the best chance of bringing our treatments to as many patients as possible in the shortest amount of time.

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