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editorial

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Drug discovery: a research sector stricken in France that can sometimes pay off

In France, drug discovery is a research sector in crisis. Projects initiated by medicinal chemists from the public sector could be a way to counter this weakness. The present paper reports the case of a French drug design company: Trophos, founded by academic researchers and purchased by Roche Pharmaceuticals for €400 million in 2015. Following this success story, some Trophos founders persevered in starting two new 'drug design' companies. Since the creation of Trophos in 2000, the costs of completing the preclinical phase have dramatically increased. This is why government research organizations should facilitate biotech creation by academic and public researchers – to make French drug discovery business competitive again. Some ideas are suggested here: for example, a non-profit foundation that can de-risk investments and encourage innovation toward important unmet medical needs.

Drug discovery and therapeutic innovation today

The numbers of FDA-approved drugs coming from France have dropped significantly in recent years: 9 in 10 years, 2 in 3 years and none at all in 2018 [1]. Nevertheless, drug sales are expected to increase by 4.8% in 2018 [2]. There were 59 drugs approved by the FDA in 2018 [3]. The majority of these drugs emerged from US pharma. The number of FDA-approved drugs originating from SANOFI, the only French big pharma company, has dropped significantly in recent years. Only one FDA-approved drug came from the French company Servier in 2018 [4]. In fact, the situation of drug discovery and drug making across the world is more complicated for several reasons: new drugs can include therapeutic proteins as well as antibodies, a factor that is not taken into account very often. Given that multinational firms market the majority of medicines, figuring out where each one of their drugs originated requires investigation of some extensive data vaults. Looking at the Sanofi case, with its US acquisitions (Boston-based Genzyme or MA-based Alnylam Pharmaceuticals), much of the company R&D work is done in the USA. Because Sanofi is located in Paris, can we consider that Sanofi US drugs originate from France? Contrast this with Roche Pharmaceuticals, based in Switzerland, one of the biggest blockbuster producers, where the majority of drugs are made in the USA at Genentech San Francisco, making Switzerland the largest European country for innovative pharmaceutical drug production. Today, probability of a drug making it all the way to full approval is just under 14%. Up until 5 years ago, the probability of success was nearer 10% [5].

Conditions for small biotech ventures are more encouraging, particularly those targeting niche diseases and unmet needs. Their costs are generally lower. They do not have the infrastructure, management or compliance expenses of bigger groups. However, early-stage drug developers burn through investor cash, the attrition rate in startup ventures remains high and the costs of failure for investors are enormous [6].

The challenge is even greater for biotech startups, which need to raise significantly more money and make sure it lasts long enough. Investors, who have a long-term profit outlook, are key in the early stages of a startup, but gaining their trust takes time, meaning a company should start conversations with investors before it is even established. It is never too early to start preparing for the next

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round, founders should keep networking at all stages of development to meet potential partners to either invest in the company or strike a licensing deal in the future.

Let us attempt to appraise the French public research potential in drug discovery and therapeutic innovation. France has 67 universities and four national public research organizations: Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Institut National de la Recherche Agronomique (INRA) and Commissariat à l'énergie atomique et aux énergies alternatives (CEA), as well as a few other smaller research agencies. Among the 40 CNRS scientific sections, seven belong to the CNRS Chemistry Institute, which are often linked to University Chemistry Laboratories. Altogether, public and academic French chemistry research represents between 150 and 200 research teams. Around one-third of these teams develop research projects related to organic chemistry, bioorganic chemistry and/or medicinal chemistry, including biomolecular chemistry, marine chemistry, natural products, fine chemistry, therapeutic chemistry, carbohydrates, amino acids and proteins, among others. One of the biggest French success stories in drug discovery is the anticancer drug Taxotere (docetaxel) discovered by a team from CNRS-Paris France [7], the licensing sale of which provided between €300 million and €350 million between 1999 and 2008 to CNRS. Imagine, the Gilead shareholders' happiness when they announced that the first hepatitis C drug: sofosbuvir, would be sold at US$1000 per pill (or US$84 000 for a 3-month course of treatment).

Such drug discovery success stories should encourage 'hard working and optimistic' medicinal chemists to step up efforts to create and develop potent new drugs for the good of mankind. Unfortunately, many reasons discourage dealing with such challenges. Prophets of doom discourage medicinal chemist research saying that it is better to stop looking for innovative families of therapeutic molecules and, instead, shift toward immunotherapy, which is more promising, less random and less expensive. It could be argued to these naysayers that it is possible to create >26 million molecules containing no more than 11 atoms of C, N, O, and F possible under consideration of simple valency, using conventional methods of synthesis and that only 63 850 (0.24%) have been synthesized [8]. Moreover, 49% of approved drugs between 1982 and 2002 were natural product derivatives. No doubt, drug therapeutic discovery can look forward to a bright future.

Is drug design and therapeutic innovation doomed to failure forever in France? Should France still promote creation of new drug discovery startups?

The Trophos case: a success story

A significant example of a French drug discovery success story is Trophos, a startup initiated by three researchers, two neurobiologists from CNRS and one university medicinal chemist professor, which was founded with the help of two experienced biotech development managers. The main objective of Trophos was the discovery of new drugs active on rare motor neuron diseases. After 14 years, following the discovery and the development of the drug olesoxime, dedicated to curing proximal spinal muscular atrophy linked to the SMN1 gene, Trophos was acquired in 2015 by Roche Pharmaceuticals (Switzerland) for €470 million [9]. This was no stroke of luck; the company's success is based on five main strategies:

- All Trophos founding members purchased a stake in the company's shares capital, showing investors their confidence in the project.
- Trophos had a good management team, and the set of skills needed to operate in a dynamic biotech startup were met.
- Before committing to the project of the discovery of new SMN drugs, Trophos's team ensured that there was a market need and the approach was innovative and superior to that of competitors. Trophos's project was innovative because it faced a huge unmet need related to the treatment of the rare disease spinal muscular atrophy (SMA).
- Because development of pharmaceutical drugs takes considerable time, Trophos has made swift decisions at the right time, which must have been crucial for its success.
- Knowing that a majority of successful companies had to go through one or more major change before landing on the right product or technology, Trophos had the flexibility and the guts to dramatically change direction: admit your mistakes and do the right thing – not an easy thing to achieve.

The success of the Marseille-based biotech company has sparked debate from French prophets of doom and raised many questions. What was possible 15 years ago is no longer possible today because of economic constraints in France, because of the reluctance of investors to invest in biotech projects led by young startups and/or because of the belief that the innovative drug creation business should only be undertaken by the largest pharmaceutical companies.

Not all young startups in drug discovery end in tremendous success stories

A few years later, encouraged by the Trophos success story, one former Marseille Trophos academic founder embarked with other academic colleagues on the adventure that saw the creation of a new drug discovery startup company: Biopharmed, with the aim of developing new anticancer drugs in the field of glioblastoma therapy. A promising hit analog JLK1486 was discovered and patented. Unfortunately, after 4 years of intensive *in vitro* and *in vivo* studies on animal models, when it came time for the preclinical phase including regulatory toxicity studies, the founders could not raise the necessary funds to proceed and Biopharmed had to cease its activity. The moral of this biotech adventure is very simple: not all the young startups in drug discovery end in tremendous success. Business failure does not mean renunciation. Biopharmed founders' willingness to innovate in the field of drug discovery remained intact. With academic collaboration, two new drug discovery companies were started: Biosqual, which aims to develop antibacterial compounds; and Planktovie, which aims to discover new highly active phytotoxins from dinoflagelates plancton biomass.

What are the prerequisites for Biosqual and Planktovie success? New financial support and facilities from different national or regional agencies that did not exist at the time of Trophos are now available: Public Bank for Innovation (PBI), Regional Loan to Creation-Innovation, International Collaborative Research Project (PRCI), Société d'Acélération de Transfert de Technologie (SATT) – Programme investissement d'Avenir (PIA3) and PACA Regional Emergence. Such agencies enable financing of the maturating phases of a project. Unfortunately, it is sometimes difficult to navigate the complexities of these agencies but at least they exist and are helpful for the

company-launch phase. It should also be underlined that facilities offered by new business incubators, which host new startups, allow the setting up of perennial companies.

Let us say that Biosqual and Plankovie have good management teams, and develop innovative approaches superior to the competitors, in a field where there is a huge market need. After the maturation phase, the next step is to find funding to move to the higher level: the clinical phase for Biosqual and its antibacterial hit; or higher phytotoxin production scales for Planktovie. The funding for this onerous phase of toxicological preclinical tests based on several different animal species is mandatory to check whether Phase I clinical trials can be launched. It is only once this financing challenge is addressed that the company will be able to further develop. To progress swiftly from a startup venture to an established medium-sized pharmaceutical company, the funding bottleneck between preclinical and clinical phases should be lifted as a priority.

Our universities are aimed at developing potential and talented medicinal chemists. Unfortunately, only a few are interested in highlighting their knowhow and expertise through the creation of a drug discovery startup. Different reasons justify their reluctance:

- Most scientific PhD academic programs do not include any business-administration and management courses. Consequently, few scientists have the combination of a scientific and business background.
- Culturally, scientists from academic, CNRS and Inserm institutions fulfill their selfless research mission as a priesthood, far from any commercial or financial opportunity. They are not committed to becoming businessmen.

How can the French government help drug discovery startups to raise money? A proposal

Knowing that creativity and discovery processes are the tenants of basic science, the academic institutions should be effective and flexible vehicles for drug discovery and innovation. Unfortunately, the current budgetary constraints make it difficult to hold the French Ministry of Education and Research to account for the development of drug discovery startups, during the crucial transition from preclinical studies to clinical Phase I, which represents the bottleneck for company development. One solution would be that the government helps drug discovery companies to raise money.

A proposal could be to setup a non-profit private foundation recognized by public utility. This foundation would ensure the development of several projects presented by young startups that have already carried out basic innovation work: pharmacodynamics, pharmacokinetics, toxicity studies and preclinical efficacy. This foundation should have financial resources in the order of €1–2 billion. Such a foundation exists in the UK: the Wellcome Trust. The aim of the trust is: to 'achieve extraordinary improvements in health by supporting the brightest minds'; and to support the public understanding of science. How could such a foundation work in France? It could be proposed that taxpayers on ISF (Impôt Sur la Fortune; net wealth tax) make donations capped at €2 million or €3 million, tax-free at 75% or 80%. This could be a way to keep wealth within the country, promoting the development of medicinal drugs including biodrugs for the health and wellbeing for all. In respect to policy cohesion, donations should be extended to any citizen whatever their financial assets.

One can argue that some French people probably prefer giving their money to charities fighting against poverty, starvation, disability, cancer or rare diseases than to a foundation susceptible to making money by favoring drug development. But we must not lose faith in French high-income payers. Some of them, instead of investing in foreign countries, would prefer to invest in a French non-profit foundation fighting against disease, because these donations are tax-free by at least 75%. Such a foundation could be a way to overcome the fear of French people to invest in drug development and biotech business, and the 'cherry on the cake' to possibly attract some foreign investors.

It must be considered that investment in such a foundation does not mean to lose money inexorably in financing risky projects. When buying a project after positive clinical Phase II trials high value is added. The created added value would be divided between the foundation and the innovative startup and, in the event of the failure in Phase II, losses would be supported by the foundation. The foundation being non-profit would have the ability to take risks. In conclusion, the creation of such a non-profit foundation dedicated to helping new drug discovery companies could be an additional initiative to accompany the other public and philanthropic initiatives to encourage innovation toward important medical needs.

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References

1 US Department of health and services. Available at: https://www.fda.gov/drugs:developmentalapprovalprocess/ucm59/.
2 Garthwaite, C. The economics of drug development: pricing and innovation in a changing market. Available at: https://www.nber.org/reporter.
3 Mullard, A. (2017) Synthetic lethality screens point the way to new cancer drug targets. *Nat. Rev. Drug Discov.* 16, 587–591
4 FDA approves longer-acting calaspargase pegol-mknl for ALL from Servier Pharmaceuticals. US Food & Drug Administration. Available at: https://fda.gov/default.htm.
5 Taylor, K. *et al.* (2016) *Balancing the R&D equation: measuring the return from pharmaceutical innovation.* Available at:Deloitte Centre for Health Solutions In: https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-measuring-the-return-pharma-report-2016.pdf
6 Dessain, S. and Fishman, S. (2017) *Preserving the promise. Improving the culture of biotech investment.* Academic Press ISBN: 978-0-12-809216-3
7 Le Roux, M. and Guéritte, F. (2017) La Navelbine et le Taxotère, Histoires de sciences, ISTE Editions, Collection 'chimie moléculaire, verte. *Méd. Pharm.*
8 Fink, T. and Reymond, J.L. (2007) Virtual exploration of the chemical universe up to 11 Atoms of C, N, O, F: Assembly of 26.4 million structures (110.9 million stereoisomers) and analysis for new ring systems, stereochemistry, physicochemical properties, compound classes, and drug discovery. *J. Chem. Inf. Model.* 47, 342–353
9 Copley, C. and Vignal, P. (2015) *Les Echos Investir. Roche achète le français Trophos pour l'olesoxime.* Available at: https://investir.les echos.fr2015

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