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Full title :
Drug discovery, a research sector stricken in France, which sometimes can pay off in a good way.

Short Title
Drug discovery, start-ups creation, academic and public research.

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Teaser
Should **french** government promote drug design discovery in helping academic and public researchers to create start-ups based on their own research projects ? Proposal: creation of a non profit public foundation.

''Drug discovery'', a research sector stricken in **France**, which sometimes can pay off in a good way.

Abstract

Drug discovery is a research sector stricken in France. Projects initiated by medicinal chemists from public sector could be a way to countervail this weakness. The present paper reports the case of a french drug design company, Trophos, founded by academic researchers, purchased by Roche Pharmaceuticals for 400 millionseuros in 2015. Following this success story, some Trophos founders have persevered in starting two new *''drug design companies*''. Since Trophos creation in year 2000, the costs to fulfill the preclinical phase have dramatically increased. It is why goverment research organizations should facilitate biotech creation by academic and public researchers, to make french drug discovery business competitive again. Some ideas are suggested in this paper: a non-profit foundation which can de-risk investments and encourage innovation toward important unmet medical needs.

1- *Drug Discovery and therapeutic innovation to-day: foreword*

FDA approved drugs has dropped significantly in recent years: 9 out of 10 years, 2 in 3 years, 0 in 2018 [**1**]. Nevertheless drug sales are expected to increase by 4.8% in 2018 [**2**]. There are 59 drugs approved by the FDA, in 2018 [**3**].The majority of these drugs emerged from US big pharma. The number of FDA approved drugs originated from SANOFI, the only french big pharma has dropped significantly in recent years. Only 1 FDA approved drug comes from the french company Servier in 2018 [**4**]. In fact the situation of drug discovery and drug making in the world is more complicated for several reasons ;- New drugs may include therapeutic proteins as well as antibodies, which is not very often taken into account - Given that multi-national firms market the majority of medicines, figuring out where each one of their drugs originated, requires digging through some extensive data vaults. Let's take 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 US. Since Sanofi is located in Paris, can we consider that Sanofi US drugs are originated from France? Same example with Roche Pharmaceuticals based in Switzerland, one of the biggest blockbusters producer, but which majority are born in USA at Genentech San Francisco, making Switzerland the first largest european country for innovative pharmaceutical drugs. To-day probability of a drug making it all the way to full approval, is just under 14 per cent. Up until five years ago, the probability of success was nearer 10 per cent (**5**).

Conditions for small biotech ventures are more encouraging, particularly those targeting niche diseases and unmet needs. Their costs are generally lower. They don't have the infrastructure, management or compliance expenses of bigger groups. However, early-stage

drug developers burn through investors'cash, the attrition rate in start-up 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 which have 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's even established. It's never too early to start preparing for the next 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's try to appraise the ''*french public research potential*'' in drug discovery and therapeutic innovation. France, is strong of 67 universities and four national public research organisations : 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), Commissariat à l'énergie atomique et aux énergies alternatives (CEA) and few others smaller research agencies.
Among the 40 CNRS scientific sections, 7 belongs to the CNRS Chemistry Institute, which very often are associated to University Chemistry Laboratories. Together public and academic french chemistry research represent between 150 and 200 research teams.
Around 1/3 of these teams develop research projects related to organic chemistry, bio-organic or medicinal chemistry, including biomolecular chemistry, marine chemistry, natural products, fine chemistry, therapeutic chemistry, carbohydrates, amino acids, proteins etc.
One of the biggest french success in drug discovery is the anticancer drug taxotere (docetaxel) discovered by a team from CNRS-Paris France **[7]** which licencing sale provided between 300 and 350 millions euros between 1999 and 2008 to CNRS. Imagine, US Gilead shareholders hapiness when they have been announced that the first hepatitis C drug, ''sofosbuvir'' was sold at $1,000 per pill or $84,000 for a three-month course of treatment !!!!.
Such drug discovery success stories should encouraged ''hard working and optimist medicinal chemists'', to step up efforts in order to create and develop new potent drugs for the good of mankind. Unfortunately many reasons discourage to deal with such challenges. Prophets of doom discourage medicinal chemists researchers saying, it is better to stop looking for innovative families of therapeutics molecules, and shift towards immunotherapy which is more promising, less random and less expensive. It could be argued to these naysayers that it is possible to create more than 26 million molecules containing no more than 11 carbon atoms, nitrogen, oxygen or fluorine, using conventional methods of synthesis and that only 63850 (0.24%) have been synthesized **[8**]. Moreover 49% of approved drugs between 1982 and 2002 were natural products derivatives. No doubt, drug therapeutic discovery can look forward to a bright future.

2-Is drug design and therapeutic innovation doomed to failure for ever in **France**? Should **France** still promote creation of new drug discovery start-ups ? the ''Trophos case'' a success story.

A significant example of French drug discovery success story, was the case of Trophos, a start-up initiated by three researchers, two neurobiologists from CNRS and one university medicinal chemist professor, and founded with the help of two experienced biotech developers

managers.The main objective of Trophos company was the discovery of new dugs active on rare motoneuron diseases. After 14 years, following the discovery and the development of the drug ''Olesoxime'', dedicated to cure proximal spinal muscular atrophy linked to SMN1 gene, Trophos was acquired in 2015 by Roche Pharmaceuticals (Switzerland) for 470 millions euros **[9].** Don't think that this success story was made possible because the oracles of God have been favorable to Trophos or because luck has smiled on Trophos. Trophos success is based on four main reasons:

- The whole Trophos founding members, purchased a stake in the company's shares capital, showing to investors their confidence in the project.

-Trophos had a good management team, since the set of skills needed to operate in a dynamic biotech startup, were met.

-Before committing the project, Trophos's team ensures that there was a market need and the approach was innovative and superior to that of competitors. Trophos's project was novative, since it's faced a huge unmet need related to the treatment of the rare disease SMA.

-Since development of pharmaceutical drugs takes considerable time, Trophos has made swift decisions at the right time, which could have been critical 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 have had the flexibility and the guts to dramatically change the direction. *''Admit your mistakes and do the right thing, is not an easy thing.*

The success of the Marseille-based pharmaceutical company has sparked debates from french prophets of the doom and raised many questions. What was possible 15 years ago is no longer possible to day, because economic constraints in France, because of the reluctance of investors to invest in biotech projects led by young start-ups, or because of the beliefs that innovative drugs creation business should be only undertaken by largest pharmaceutical companies.

3-Not all new young start-ups in drug discovery, end in tremendous success stories.

Few years later encouraged by Trophos success story, (2000-2014), one former Marseille Trophos academic founder, embarked with other academic colleagues on the adventure of the creation of a new drug discovery start-up company, named *Biopharmed*, which aim was to develop new anticancer drugs in the field of glioblastoma therapy. A promising hit analogue JLK1486 was discovered and patented, unfortunately, after 4 years of intensive in vitro and in vivo studies on animal models,when came the time for preclinical phase including regulatory toxicity studies, the founders could not raise the necessary funds to proceed to this preclinical phase, Biopharmed had to stop its activity.

The moral of this biotech adventure is very simple:*''not all the young start-ups in drug discovery end in tremendous success stories* ''. Business failure does not mean renunciation.

Biopharmed founders willingness to innovate in the field of drug discovery remained intact.

With academic colleagues two new drug discovery companies were started. One named *Biosqual*, which aim is to develop anti–bacterial compounds and second named *Planktovie*, which aim is the discovery of new highly active phytotoxins from dinoflagelates plancton biomass.

What are the prerequisites for ''*Biosqual*'' and ''*Planktovie*'' success? New financial supports and facilities from different national or regional agencies which do not exist by 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)- PACA Regional Emergence.*

Their amounts allow to finance the maturating phase of the project. Unfortunately, it is sometimes difficult to navigate the complexities of these agencies, but at least they exist and are helpful for the company launching phase. Il should be also underlined that facilities offered by new business incubator, which hosts new start-ups, allow the setting up of perennial companies.

Let's say that both Biosqual and Plankovie, have good management teams, and develop innovative approaches superior to the competitors, in a field where there a huge market need. After the maturation phase, the next step is to find funding to move to the higher next step, clinical phase for Biosqual for its anti-bacterial hit, or higher phytotoxine production scales for Planktovie. The funding for this onerous phase of toxicological preclinical tests based on a number of different animal species is mandatory to check whether Phase I can be launched. It is only once this financing challenge adressed to the company founders is overcome, that the company will be enable to further develop. To progress swiftly from a start-up venture to an established medium size pharmaceutical company, the funding bottle neck between preclinical and clinical phase should be lifted in priority.

Our universities aimed at developing high potential, and talented medicinal chemists. Unfortunately, only few are interested to highlight their know-how and expertise through the creation of drug discovery start-up. Different reasons justify their reluctance:

-Most of scientific PhD academic programs, did not include any business-administration and management courses. Consequently, few scientists have both scientific and businness background.

-Culturally, scientists from Academic, CNRS, and Inserm institutions fullfill their selfless research mission as a priesthood, far from any commercial or financial opportunity. They are not committed to become businessmen.

4-How could french goverment help drug discovery start-ups 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 difficult to hold the ''*french ministry of education and research* '' to account for the development of drug discovery start-ups, during the crucial transition from preclinical studies to clinical phase 1, which represents the bottle neck for the development of the company. One solution would be that the goverment helps drug discovery companies to raise money.

An attempt of proposal could be to set-up : a *non profit private foundation* regognized by public utility ? This foundation would ensure the development of several projects presented by young start-ups that have already done the basic innovation work : pharmacodynamics , pharmacokinetics, toxicity studies, preclinical efficacy. This foundation should have financial resources in order of 1 to 2 billion euros. Such foundation exists in Great Britain, 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 come such foundation could worked in France? It can be can proposed to taxpayers imposed on ISF∗ (net wealth tax), to make donations capped at 2 or 3 million euros, tax-free at 75 or 80%. It will be a way to keep within the country rich people wishing to promote the development of medicinal drugs including biodrugs for the health and the well being for all. In respect of policicy cohesion, donations should be extend to any citizen whatever his financial asset.
One can argue that probably french people prefer giving their money to charities fighting against poverty, starvation, handicap, cancer or rare diseases, than to a foundation susceptible to make money by favouring drug development. But we must not lose hope in french high-income payers. Some of them, instead to invest in foreign countries, would prefer to invest in a french non-profit foundation, fighting against health diseases since these donations are tax-free by at least 75%. Such a fondation could be a way to overcome the fear of french people to invest in drug development and biotech business, and cherry on the cake to possibly attract some foreign investors.
It must be borne in mind that invest in such foundation does not mean to lose money inexorably in financing risky projects. When buying a project after positive clinical phase II, high value is added. The created added value would be divided between the foundation and the innovative start-up, and in the event of the failure in phase II, losses would be supported by the foundation. The foundation being non-profit, it will have the ability to take risks.
In conclusion, the creation of a such non-profit foundation dedicated to help new drug discovery companies, could be an additional initiative to the other public and philanthropic initiatives to encourage innovation towards important medical needs

∗ISF : Impôt Sur la Fortune.

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