Regulated toxicity-testing: Spinning out a company in a rapidly changing market

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ABSTRACT

Today, various chemicals and materials are introduced into our daily life. To guarantee their safety, number of tests have to be applied, ranging from simple testing on cell cultures (*in vitro*) to costly animal tests (*in vivo*). In case chemicals are planned to be delivered to a human body, many clinical tests are also required to be performed on humans. Logically, earlier stages of testing are used in selection, for example, of drug candidates or vaccines, or in early decision, for example, to remove dangerous materials from R&D pipelines as soon as possible. Unfortunately, the very expensive intermediate step – *in vivo* animal-based testing often provides wrong answers. Alternatives are being searched for and entire market is about to change with political decisions overtaking scientific and technological developments.

This article covers a relatively new field of how to deal with a situation arising from the fact that an associated novel IP is generated in public research institutions. It depicts how it becomes challenging for the institution and steps to be taken to spin the technology out into a company to a particular turbulent sector.

The article also touches upon the main dilemma on how to keep the novel technology solutions hidden if they need to be adopted by the regulators first. Related to this is also the question, how can one convince the committees at the research institutions as well as the investors that the technology in question actually do hold (enormous) business potential.

Keywords

Biotechnology, spin out, IP transfer, disease prediction, animal alternatives.

POVZETEK

Danes se v naše vsakdanje življenje uvaja različne kemikalije in materiale. Da bi zagotovili njihovo varnost, je treba uporabiti številne teste, od preprostih preskusov na celičnih kulturah (*in vitro*) do dragih testov na živalih (*in vivo*). Če je predvideno, da se kemikalije vnašajo v človeško telo, je treba na ljudeh opraviti tudi veliko kliničnih testov. Logično je, da se prejšnje faze testiranja uporabljajo pri izbiri, na primer pri ožanju nabora kandidatov za zdravila ali cepiv, ali pri zgodnji odločitvi, na primer za čimprejšnjo odstranitev potencialno nevarnih snovi iz razvojnih aktivnosti. Žal zelo drag vmesni korak - testiranje na živalih in vivo pogosto daje napačne odgovore. Zato se iščejo alternative, ki bodo spremenile celotni trg, kar sicer nakazujejo že politične odločitve, ki prehitevajo znanstveni in tehnološki razvoj.

Ta članek zajema sorazmerno novo področje, kako se spoprijeti s situacijo, ki izhaja iz dejstva, da se v javnih raziskovalnih ustanovah ustvari povezan novi IP. Prikazuje, kako postaja omenjeni IP izziv za institucijo, in korake, ki jih je treba sprejeti, da se tehnologija pretvori v podjetje v nek turbulenten sektor.

Članek se loti tudi glavne dileme, kako naj nove tehnološke rešitve ostanejo skrite, če jih morajo regulatorji najprej sprejeti. S tem je povezano tudi vprašanje, kako lahko prepričamo odbore na raziskovalnih institucijah in tudi vlagatelje, da zadevna tehnologija dejansko ima (ogromen) poslovni potencial.

Ključne besede

Biotehnologija, spinout podjetje, prenos intelektualne lastnine, napovedovanje bolezni, nadomestki za živalska testiranja.

1. INTRODUCTION

1.1 The prior art of the technology

Currently, drug, vaccine and material development workflows heavily rely on expensive animal testing, used to reduce selection of possible candidates later on entering the preclinical and clinical testing phases that need to prove these candidates do not harm human health. Unfortunately, molecular driven disease mechanisms are very much different between test animals and humans [1], leading to almost catastrophic 95% probability of failure of, for example, drug candidates at the end of drug developments cycle [2].

This makes the later extremely cost inefficient with costs of 300 - 2000 MIO $ per drug development [3]. Other sectors, such as material safety testing, somewhat ignore this fact and stoically wait for the solution that more exposed and rich pharma sector can bring out.

To boost the launch of numerous new material and chemicals in a safe, hazard-free way, the material-related health adverse effects should be more reliably predicted [4,5]. Currently, the most promising alternatives involve test assays [6] and QSAR [7,8] models, but neither *in vitro* nor *in silico* tools can reliably predict *in vivo* adverse outcomes [9,10]. Particularly, the models unsuccessfully predict the systemic and chronic adverse effects [11].

The need of urgent development of more reliable prediction have been expressed by all the important policy- and decision-makers around the world (OECD, US EPA, NIH, EC, ECHA, etc.), which have highlighted the necessity of exploring the molecular mechanisms behind and identification of the key events in toxicity pathways associated.

During the last 5 years, 12 partners, joined within the SmartNanoTox European project, have worked pushed the mechanistic-prediction of toxicity-related diseases beyond the scientific frontiers. Within this consortium, our group of biophysicists at Jožef Stefan Institute in Ljubljana has led one

of the most distinguished breakthroughs in the field in the last decade – the first mechanistic explanation of the transition from acute to chronic inflammation. This discovery enabled us to predict a spectrum of inflammatory outcomes without animal tests for the first time [12].

1.2 The story behind the market and the opportunity

The only way to solve the lack of predictive testing that doesn't rely on animal tests is to develop living organ models (for testing purposes) that develop physiologically relevant responses to various drugs and other toxicants [13,6]. Several research groups and companies (Figure 1) are struggling to make such animal replacement models in a form of miniature and reliable organ copies.

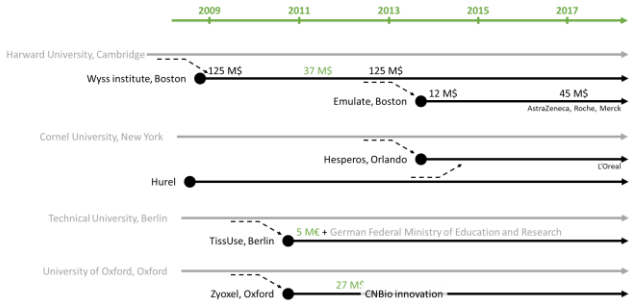

Figure 1: Small R&D institutes (black arrows), spun out from large universities (grey arrows), led the fields of *in vitro* model development. Some initial investments are shown with respect to the source – private (black) and public (green).

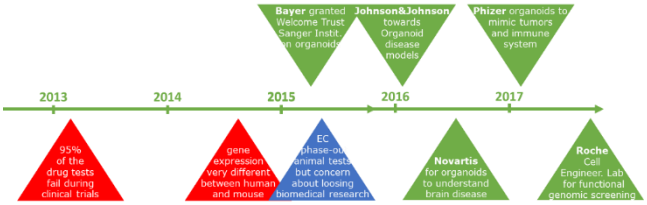

Figure 2: The important moments and decisions that boosted transition from animal-based testing into *in vitro* - or organoid – based testing and forced big pharmaceutical companies to get more involved into the *in vitro* model development

But, as expected this become a tedious, far from straightforward task full of trial-and-error steps. This makes the current developments look like being stuck and represent big challenge for regulatory bodies, which actually don't have clear plans on how to implement political decisions [14] (Figure 2) and public pressure (to eliminate animals from testing).

In terms of market size, toxicology testing market (Figure 3) currently values at around 20.000 MIO EUR per year [15]. Around of 10% of this market is driven by REACH EU legislation [16], which implies testing procedures for about thousands of substances that are produced annually with amounts greater than 1 ton per year. 2% of this REACH-associated segment includes acute & short-term repetitive dose exposure testing with 10,000 animal tests required per year. Value of this market is around 400 MIO EUR per year. Taking into account that most of the market need to be changed, this clearly represent a big opportunity for biotech companies that can bring new alternative solutions to the testing market. Currently, the testing market exhibit 12% annual growth. But is soon to reach its limits in terms of testing capacity, that originate in limited number of animal tests that can be performed in the EU and other players around the world.

On the other hand, there is new material development sector with a fast growth of 20% per year that also requires extensive toxicology testing [17]. With 10.000 patents filed every year to protect various nanomaterials and their applications in addition to around 50,000 publications on the same subject, this sector will soon require much larger testing capacities. The only possible boost can thus come from new technologies and new players to guarantee material safety throughout new smart prediction approaches [12].

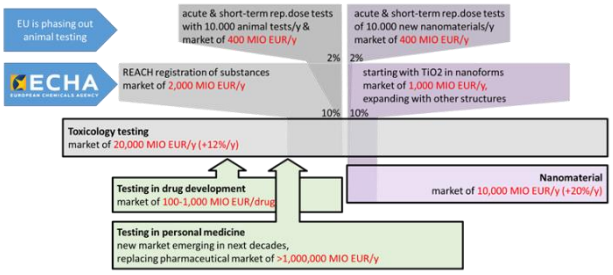

Figure 3: Target markets of acute & short-term repetitive dose toxicology testing in safety assessment of various substances and nanomaterials presented in the context of regulatory framework and political decisions.

To resume, the market is driving into a dramatic change:

- animal tests are considered as golden standard, but are phasing out;
- alternatives are lacking, imposing huge pressure on the regulatory bodies.

This opens new exciting opportunity for new knowledge-based companies, but at the same time impose great risk due to unpredictable development of regulatory framework.

The main contributions of the new companies in this field would cover exactly the market's greatest pains: the animal-free testing of drugs for human use and the prediction of the drug effects on the molecular level.

Not surprisingly, based on our new technology, which is registered as a secret know-how of the Jožef Stefan Institute, we decided to address this market need and participate in the product development and service provision in the new animal-free drug testing as explained above.

2. INITIAL STEPS TOWARD THE SPINOUT COMPANY

The initial steps we took were connected to shaping the idea into a market plan and creating a team to enable the creation of the market plan, sorting out the IP issues with possible other institutions and settling the IP relations within the research organization.

Interestingly, in the need for a business plan, expressed by any of our first investing contacts, we faced a lack of the expertise to create this business plan. Writing a business plan thus lead to complementing the existing team members. In our case, we have identified the need for getting involved someone with more economic background. This was a strenuous task for a group of scientists that have rarely think about nonscientific issues. But, when solved, another perspective enlightened the problem of

value creation leading us to much better vision of what the company can do and where it can be after 10 years. Recursively, the business plan have become much more solid while increasing the core team and focusing to its strengths.

While constructing financial projections for our business plan, we have "accidentally" discovered where the business models of the current service providers fail and where our scientific discoveries can really make a difference on a market (and in our budget). As said before, the toxicity testing, as we know today, requires many *in vitro* and *in vivo* tests. Even without clinical tests, all these tests cost lot of resources, making the business very resource-limited and, if you want to pay experts with a reasonably good salary, struggling with either low added value or being uncompetitive on the market. The problem is that it is required to run them all, but the results are not really being used in a smart ways or assembled in bigger picture. They are just there to be reported.

As discussed earlier, in the mean time, our scientific discoveries brought us several steps further, identifying how to use simple but well defined *in vitro* tests to predict disease development, that was till now possible only with much more expensive animal tests. This in turn release the business model from its limitations to human resources and make it more knowledge dependent (with higher added value). This will be beneficial for our company and the market, because the company business will be more competitive and the market prices will decrease at the same time.

Conceptualizing a new company in our case was a challenging task, yet alone in a field that is about to change dramatically and where the constraints are blurring rapidly with time.

The way that a company can be prepared to deal with such a challenge is stricktly by assembling together one big brain with out-of-the-box thinking ability. Inspired by many extraordinary business cases from the human history, we learnt the following lessons, while trying to set up our own company, Infinite-biotech:

- The core team need to dream about it, feel it by heart, and be ready to invest more than it can predict in the worst thought scenarios;
- Although there is always one that lead them all, the brainstorming is the real weapon of the team; the main leader needs others to challenge each other while searching for solutions that really makes the core idea;
- The core team members must complement each other in terms of expertise and at the same time be ready to listen to each other and adjust their ideas; nevertheless, they build entire story from scratch; so they must function as one big organism;
- Finding market opportunity is hard, but even harder is creating business out of it; the team have to search for their strengths enabling them to create high added value and be recognizable by the market;

To conclude, although everyone expects that you have the core team ready and you have already clarified all the business points ahead of writing the business plan itself, its actual the act of assembling the business plan that enables you to clarify of the details. It helps you to search for the missing expertise and complement the team members as well as to clarify many in particular business/finance related points of the very same business plan.

3. SPINNING OUT AND THE IP TRANSFER

Generally, a complex knowledge, required to elucidate basic mechanisms and further develop mechanisms-based testing or even disease prediction, as alternative toxicity testing concepts, logically arise from large publically financed projects that mostly run in well-equipped research laboratories in public research institutions.

The IP created has passed a well-defined procedure that, in our case at Jožef Stefan Institute, involves IP recognition by an expert panel followed by IP transfer to newly registered spin out company. IP must remain confidential during the processes and at the same time ambitious enough. This becomes challenging due to several reasons:

- procedures usually involve many different experts and some of them might have competing interests, but are involved in accordance with their elected position in the panels;
- protection of IP in a form of patents might be problematic because the patent application is disclosed to public sooner than the company might start making revenue to defend its IP, making it more vulnerable; The strategy of filing a patent and then preventing the disclosure by withdrawing the patent it in 18 months (and filing it again, in the same or in a modified form) has been disregarded. Patents might later on be filed, at this point in time the invention is protected as a secret know how;
- hiding IP in a form of secret knowhow might leave the impression that the inventions are not novel enough; many experts evaluating the proposal for IP recognition and company-associated business plans might therefore doubt about the potential of the idea;
- the use of university-internal panels to evaluate invention disclosures and IP can be considered of limited usefulness and it remains to be proven that the panel adds value in the eyes of the VC's.

The role of IP-transfer-dedicated department is thus even more important. In our case, both the Center for Technology Transfer and Innovation at the Jožef Stefan Institute and the Scientific Council of the Jožef Stefan Institute, were flexible and ambitious enough to recognize the dilemma above and support us in all possible (right) ways: the IP has been registered by the institute in a timely manner, the Scientific council confirmed the creation of the spinout company and the Center for technology transfer and innovation made way and glued together all the necessary pieces for the procedures to come together and obtain the general official support.

Last but not least, as mentioned before, the IP is often created within larger publically financed projects, likely to involve several partners. This inevitably exposed entire process of setting up a spin out company to a problem of shared IP, which can delay entire process substantially. While some universities almost hysterically claim their shares even when it is hard for them to prove their participation yet alone their contribution, this fortunately did not happen in our case.

Partners of the H2020 project SmartNanoTox easily realized that the core idea has originated from the work of our laboratory. However, in relation to multi-partner research projects and shared IP, it is important to distinguish between inventorship and the commercial rights. Inventorship is well-defined and one can contain inventorship even in larger projects. On the other hand the commercial rights can be shared, but the consortium

agreement should clearly state, that the partners will not block commercialization. However, in our particular case no partner claimed his share – despite the fact that the general trends were clearly defined already in the afore-mentioned H2020 project.

4. SEARCHING FOR THE FIRST INVESTMENT

As expected, the fact that our idea and technology is disruptive to the established market, adds to the complexity that we have experienced in their search for investors.

While transferring the IP might be enough to start making service-based revenue, it is actually far from sufficient to make revenue from products that allow a company to run into more stable and less human-work-dependent business model. Keep in mind that the research labs often focus on the basic mechanisms thus developing solutions up to a relatively low technological readiness level (TRL). Rarely, the TRL exceeds that of a proof-of-concept or a demonstrator yet alone that of validation of technology in a lab or real environment. Up to a prototype, which is really the one of the most important milestones of the company to enter the market, there is long way to go.

To speed up the required development cycle, a spin out company urgently needs an investment, which usually exceeds several MIO EUR. And despite the numerous venture capital funds (VC) and national agencies that all create an impression of straightforward access to financial sources, the investment into a business, whose potential is yet to be truly developed, is very difficult to find.

On a first sight, incubators might look the best option for spin out company. Nevertheless, they are expected to support startup at regional or national level. However, it turned out they are completely inappropriate choice for spin out companies arising from public-funded basic research due to extremely limited financial support that fails to meet the need for large investment after IP transfer. As stated previously, the TRL of the knowledge in a given situation rarely exceed the proof-of-concept making it far less attractive for direct financial investments.

During establishing our spin out company, we have learnt the two very important factors that influence the decision of an investor to invest into such story are:

- a proof that the entire business endeavor does not belong to a “green field” category;
- a proof that a company can start making revenue associated with the core technologies.

In business, a “green field” means an idea that can be written on a piece of paper with a dubious value that might hide lots of possible pitfalls and obstacles, far from being developed to a TRL high enough to start running even a small revenue. Despite its more or less clear message, we have noticed a very important difference in feedback of the scouts and VCs related to the IP origin. At the beginning, we approached them as a team with potentially powerful idea of the business and they rejects us almost instantaneously. Later on, when we approached them already as a legal entity with IP transfer in progress, their response has changed. Although they were aware of the origin of the IP – in both cases it originates from a large/renowned research institution, their attitude change simply because of the fact that there was an expert panel, which has already identified value of this IP before them. Passing this milestone has clearly brought us closer to reach the final investment.

Not surprisingly, ability of the company to start making revenue with its core knowhow is very important signal to investors. We noticed that this is particularly important for large VC funds. In addition, any effort of entering the market as soon as possible pays off with better business plan. In particular, it helps a company to identify the group of services and products that have higher added value and larger market potential. Further developments of spin out core technologies might thus be heavily influenced with the experiences gained through the first sales activities.

After exploring different possibilities, the best investor turned out to be a person (“angel”) that is aware of the lack of solution and that can see the market niche your new company is trying to address. In many cases, he/she is the CEO of already another company. He/She is able to clearly see the potential of your knowledge and is willing to invest his/her resources (and/or attract others as well) and wait the minimum amount of time needed for the company to develop its core technologies for the future.

5. CASE SPECIFIC DATA AND THE IMPORTANT MILESTONES

The following details of our case timeline wants to illustrate the above and put all the discussion into a proper perspective:

- Market niche identification: 2017
- First idea of the company: July 2018
- Decision to protect IP as secret knowhow: September 2018
- First round to potential investors / contact type / contact location: December 2018 / scout, mentor / Switzerland
- 1st version of the business plan: February 2019
- First Financial plan and complementing the team: March 2019
- Second round to potential investors / contact type / contact location: June 2019 / intermediary / Germany
- Third round to potential investors / contact type / contact location: June 2019 / venture capital (VC) fund / Slovenia
- Final decision to make the company a spin out of Jožef Stefan Institute: October 2019
- 2nd version of the business plan: October 2019
- Start / End of the process of IP recognition (as secret knowhow): October 2019 / December 2019
- Approval of the scientific council of Jožef Stefan Institute: January 2020
- Fourth round to potential investors / contact type / contact location: November 2019 / angel related to venture capital (VC) fund / Austria
- Major breakthrough done on scientific side relevant for company business: September 2019 – January 2020
- Negotiation for IP transfer conditions and formal cooperation with date of signing the contracts: February 2020 – July 2020
- Fifth round to potential investors / contact(s) type / contact(s) location: March 2020 – June 2020 / venture capital (VC) funds & angels / Austria, Switzerland, Germany
- First demonstrator of the technology planned to use in a product: April 2020
- Sixth round to potential investors / contact type / contact location: April 2020 / angel, CEO, mentor / Slovenia
- First round to offer services: June 2020
- Complete marketing/sales plan for the company’s services: September 2020

As can be noticed, from the market niche identification to a complete marketing/sales plan three years have passed. The main issues we encountered were twofold:

- In the field of registering the technology at the Public research organizations (PRO) the deadlines constantly

moved because we were not sure if the registration is necessary and for what reason; as it turns out, the registration itself is needed to enable the PRO to officially participate in the creation of the company in Slovenia; these clarifications took about a year to settle in with the team and the responsible at the research department;

- In the same field the time lag was also a consequence of a rigid PRO structure in the sense of the time urgency in which a typical spinout company finds itself; however, the procedures were carried out in the end in a timely manner; these procedures were ultimately carried out in less than two months;
- In the field of clarifying internationally on how to create a suitable team and how to attract with confidence a suitable amount of financing necessary to pursue with further technology development; these procedures took about two years; the main issue being that a researcher at a PRO is not in a position to devote a significant amount of time into the development of the market relations;
- With this in mind it needs to be said that an additional issue might be seen in the state of the mind of the researchers who believe that themselves are the only people who can properly present the technology and attract financial support.

In any case, the marketing and sales plan has been completed in September 2020. We plan to continue with the technology development and plan to deliver the services to the market in early 2021.

6. CONCLUSION

Scientific studies have clearly identified the need for a major change in the toxicity testing framework and the politics decides to realize this as fast as possible. This has created an exciting opportunity for business that can be started directly from basic research discoveries.

Because of the huge pressure to bring the future into reality faster than the new tech evolves, several milestones have to be met almost instantaneously: discoveries of the basic concepts, acceptance of the regulatory frameworks and establishment of the alternative testing market (and the trust in the same) that can replace the classical animal testing. Investors became reserved, simply because it is such a big step to the future. Despite the fact that the future is already here and a revolution of the testing market is inevitable.

In June 2019, I have been involved in an interesting discussion on tissue-on-chip technologies and the associated startup companies. The key dilemma associated with these small companies was: why they still get big investments if they can't and don't make big revenues. Yet. The answer given by the CEO of one of the first companies of this kind was marvelous: investors invest into teams that will be capable of reacting to the new market as soon as it will become approved (by the regulators).

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