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A methology to assess the unlinear medical innovation process. The example of Liposomes

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Abstract

Medical innovation studies bring to the fore the emergence of atheoretical framework (« Health Innovation System ») that underlines the distributed and dynamic characters of the innovation process. These two dimensions are associated to the radical uncertainty in which medical innovation takes place, a condition that implies continuous learning along the innovation process and across different sources (science, technology and clinical feedbacks). Clinical implementation represents a crucialway to evaluate the relevancy and side-effects of a medical technology, creating the need of new technological refinement or scientific investigations to understand the results achieved in the clinical arena. The impotance of feedback loops have already been underlined theoretically whereas most of empirical analysis focused on one specific source of medical innovation. This study aims at filling this gap by proposing a methodology to delineate each component of medical innovation and to map these feedbacks loops. We select a medical technology to test the methodology due to its connection with all components by being mature enough to benefit from clinical feedbacks and its relevancy in terms of using publications and patents to evaluate the importance of science and technology. Our results suggest that technology initiated the search process that has been mainly driven by scientificknowledge, combining feedbacks from practice and technology.In doing so, we highlight the organizational and institutional

dimensions underlying the innovation process ; we shed lights on public actors in producing knowledge but more importantly, by integrating distant and situated bodies of knowledge.

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1 Introduction

Medicine is of interest to innovation scholars by virtue of the multiple forms of uncertainty that characterize both its pursuit and its implementation in practice. Health problems generally emerge in the context of the clinics, or "on-line", while the search for solutions often occurs in controlled environments, or "off-line" (Arora and Gambardella, 1994; Gavetti and Levinthal, 2000; Nelson, 2003). This is cause of mismatches between what is known in theory and what can be done in practice, for not all health problems have solutions within the prevailing state of knowledge and, conversely, workable solutions do not always rely on a clear understanding of the basic bio-chemical processes involved. Yet another key source of uncertainty in medicine is that known diagnostic and therapeutic strategies often prove to be of very differing efficacy across domains of expertise. This is due to various reasons, sometimes technical other times institutional or even ethical, which undermine the likelihood that successful know-how can be easily transferred from one disease area to others (Nelson et al., 2011). The established wisdom in health economics or health policy emphasizes the role of scientific research for understanding the nature of disease. This is a legacy of the policy discourse of the 1950s when technology creation and diffusion were conceived of as a linear process stemming from basic research and unfolding through to adoption and use (Bush, 1945). Recent research emphasizes that medical innovation often relies on multiple pathways (Nelson et al., 2011). One is the traditional mechanism whereby research elucidates the key mechanisms behind disease. The second is associated with advances in technology originating from contexts that were not necessarily related to medicine. This is the case of electronics, computing or new materials which ended up playing a pivotal role in the development of new drugs and devices. Interestingly, some technologies gained relevance independently of basic science thanks to the proactive role of skilled practitioners who envisioned specific routines for the translation to the bedside, such as insulin, penicillin or the diffusion of artificial disc replacement surgery. A third, often unappreciated, pathway is that stemming from learning in the context of the clinics. Whether a technique or artifact works as predicted can be judged only in circumstances that can reveal its actual strengths and weaknesses. At the same time effective use of new devices often requires the development of dedicated procedures and organizational routines through a process of trial-and-error that straddles competences and institutional boundaries. The bottom line is that behind the emergence of successful medical innovations there are significant interactions and feedback loops across the boundaries of three independent yet interrelated domains: science, technology and practice. To date, this connection has only been appreciated theoretically (e.g. Gelijns and Rosenberg, 1994; Consoli and Mina, 2009; Nelson et al., 2011) and existing empirical studies have only focused on these pathways individually but

somewhat neglected their mutual interactions (Mina et al., 2007; Consoli and Ramlogan, 2007; Barberá-Tomás and Consoli, 2012; Yaqub and Nightingale, 2012). The present paper seeks to fill this gap and elaborate an empirical analysis of the emergence and co-evolution of innovation trajectories in scientific knowledge, technological invention and clinical practice of Liposomes. This is an interesting field of analysis for a number of reasons. Liposomes are primarily an artifact, in the sense that they are used as the basis for drugs and as carriers for diagnostic agents. Their diffusion speaks to the connection between two domains, namely technology development and clinical practice. But Liposomes have also played an important role in science, even before being considered a promising medical technology, in particular in the context of laboratory testing to study the composition and the structure of cell membranes. The stock of experimental knowledge associated to the membrane model in this context of use played a significant role in subsequent technological developments, and represents a clear connection between the domains of science and of technology occurred mainly in the realm of academia. At the same time liposomes represent a mature artifact of its category (**??**) as market approvals and ongoing clinical tests demonstrate. This calls attention to yet another important interaction, since liposomes developments are supposed to be also shaped by clinical feedbacks. The goal of the present paper is to detect and map the feedback loops underpinning the discovery processes that facilitated the diffusion of Liposomes in different, yet interrelated, contexts: science, technology and the clinic. In so doing we also aim at emphasizing the organizational and institutional changes that enabled these processes.

2 Methodology

In this section, we will define the sources of data and strategies we developed to define each component of the innovation system and the actors responsible for the accumulation of knowledge as well. We start by assessing the dynamic of knowledge at the meso-level and take a closer look at it and its implications at the micro-level. Actually, biological research is highly "contextual" in the sense that results are dependent on the conditions in which experiments are performed (instruments, protocols etc...) that limit their generalization (West and Nightingale, 2009). The capacity of replicating the experiment is thus crucial to accumulate knowledge about a give phenomenon and to distinguish the underlying causal mechanism from the conditions or how they modify this last one (Nelson, 2008; Yaqub and Nightingale, 2012).
Taking into account the tacitness of knowledge generated in the lab in "off-line" conditions and "on-line" conditions, we can assume that scientists and clinicians can embody a certain amount of this stock of knowledge thanks to

their everyday-life practice. Indeed, the feedback loops coming from practice are not necessarily reported: on the one hand, by lack of time due to many other requirements (pointed it out by Van Eck et al. 2013) and on the other hand, because the cost of opportunities represented by the codification of this knowledge limits the full codification of it. As Agrawal (2006) notices, only a limited part of the knowledge generated is considered as being associated to a reward: only the last and most refined stage of an experiment is published to deliver the most valuable part of it. Therefore, codified knowledge concentrates successes rather than failures while the most crucial part would be about how individuals ensured the performance of the experiments and under which conditions the results hold. Let us notice that despite tremendous efforts and a different system of reward regarding codification, it is not necessarily possible to fully codify an experiment and multiple sources of bias can remain (see Zander and Kogut, 1995). Therefore, a "latent" experimental stock of knowledge is not published and remains embedded into scientists and clinicians. From a different perspective, Mogoutov et al. (2008) also choose the inventor's level to gather the research efforts performed within the Triple-Helix Model in the field of micro-assays. Focusing at the individual level in the field of medical innovation is fundamental to understand the dynamic of knowledge associated to an economic activity where practice matters so much.

2.1 Strategy to delineate the boundaries of each component

2.1.1 Technological component

Liposomes refer to chemical entities that are parts of pharmaceutical formulation. For this reason, patents appear as the main mean of appropriation should be an appropriate proxy to measure technological efforts. We selected patent families that belong to the Cooperative Patent Classification A61K9/127 as a criterion to evaluate the technological capabilities. This class refers explicitly to the physical definition of a liposome as a lipid bilayer. We selected and considered relevant all patents which refer to this class as a primary or secondary class, disregarding whether their field of application that may be medical or not. Earlier studies, such as Rosenberg (1992) or Gelijns and Rosenberg (1995b), showed that an important factor leading to medical innovation was the migration of technological capabilities coming from other fields to the medical arena.

Considering the importance of the national system of innovation on the development of medical innovation, we also bounded the study to US applications to limit additional noise within the analysis. The USA represent the biggest market for pharmaceuticals and the largest scientific driving force worldwide in cancer research (Faguet, 2005). In addition to this, the US pharmaceutical industry has been widely studied over time and allow us to

benefit from institutional and organizational insights. We also decided to bound the time-window to 2012 to fit the decline observed in publications linked to a certain lag within Web of Science updates over the most recent period.
our sample is composed of 1970 patent families over the period 1978-2012, representing 3167 patents among which 2786 have been granted. Actually, only granted patents were used to assess their interactions at the meso-level with science and clinical practice because their publication is associated to non-patent references.

2.1.2 Scientific component

The knowledge base related to medical innovation encompasses a wide range of fields, from fundamental physics to biomedical sciences (Gelijns and Rosenberg, 1995a). In order to catch this diversity, we crossed two databases, namely Web Of Science and PubMed.

We built a lexical query related to the main observed scientific phenomenon characterizing liposomes within tumors ("enhanced permeability and retention") that is not indexed within the Medical Subject Headings (MeSH). An additional set of keywords has been added to delineate the field of cancer and liposomal research based on the most common concepts found within patents and the Handbook of Medical Applications of Liposomes.

The lexical query refers to the following:
("Liposomes"[MeSH] OR "Liposomes"[Pharmacological Action] OR "Phospholipids"[Mesh] OR "SPI-77,liposomal"[Supplementary Concept]
OR "enhanced permeability and retention" [all fields])
AND ("Antineoplastic Agents"[Pharmacological Action] OR "Antineoplastic Protocols"[MeSH] OR "genes, Tumor Suppressor"[MeSH] OR "early detection of cancer"[MeSH] OR "cancer vaccines"[MeSH] OR "chemotherapy, cancer, regional perfusion"[MeSH] OR "neoplasms"[MeSH])

Regarding the requests run on PubMed, we relied on the MeSH classification to select all publications related to liposomal developments involved in the field of cancer. Their related PMID have been extracted in order to be run simultaneously with the lexical query on Web of Science. Publications have been downloaded on both sources: on PubMed, in order to get its related publication type and MeSH indexes; on Web Of Science to define the authors affiliations and the respective cited references. Among this scientific publications, a careful attention has been given to disentangle

a specific flow of knowledge associated to the liposomal "testing regime" (Yaqub and Nightingale, 2012) that deals with learning by doing and using in our case. Actually, as mentioned above, liposomes were first used in the lab as membrane models to test and to infer cell membrane properties. Therefore, technological developments have benefit from knowledge accumulated in a set of controlled and simplified conditions before being used in the clinical environment. Following (Yaqub and Nightingale, 2012), we will make a distinction between the type of intermediate conditions in which are performed the experiments to accumulate knowledge. More precisely, we will distinguish in vitro conditions from in vivo conditions characterized by a higher degree of complexity.
To determine the set of publications that used initially liposomes as membrane models in different experimental settings, we relied on the indexed MeSH and respective definitions. Concerning in vitro conditions, a set of 6 keywords have been selected (Membranes, Artificial; Membrane Lipids; Cell Membrane; Membranes; Phospholipids; Lipid Bilayers). Concerning in vivo testing regime, we selected MesH keywords that were explicitly refering to animal models (mice, rats, dogs, primates). in the case of overlap between MeSH, we chose to create a hierarchy between in vivo over in vitro considering the importance of animal testing in anticancer developments. To keep the maximum of information in our sample, we consider relevant only scientific publications that were both found on Web Of Science and PubMed. 28268 publications were found on Web Of Science and 38031 on PubMed, whereas 25102 were overlapping both databases. As we want to keep an institutional dimension and considering the importance of national institutions in medical innovations, we kept only publications which refer to, at least, one US affiliations. The final sample consists of 22 725 publications.

2.1.3 Clinical practice component

Practice is defined among our scientific publications thanks to the PublicationType defined on PubMed, the following classes have been selected as relevant: Guideline, Practice Guideline, Clinical Conference, Consensus Development Conference, Validation Studies, Cases Report, Evaluation Studies, Multicenter Study, Observational Study, Clinical Trial, Clinical Trial Phase I, II, III, Controlled Clinical Trial and Randomized Clinical Trials. The related definitions can be read online on the NIH website: http://www.nlm.nih.gov/mesh/pubtypes.html. This set of publication types is not exhaustive and refers to the ones encountered in our sample, someone might find additional relevant publication types to add regarding their technology and take this list as a starting point. Practice is also defined by a set of institutions (formal or informal) that aim at prescribing the most appropriate way of doing things (i.e. producing medical technologies and its appropriate use). In this regards, communities of practice through physi-

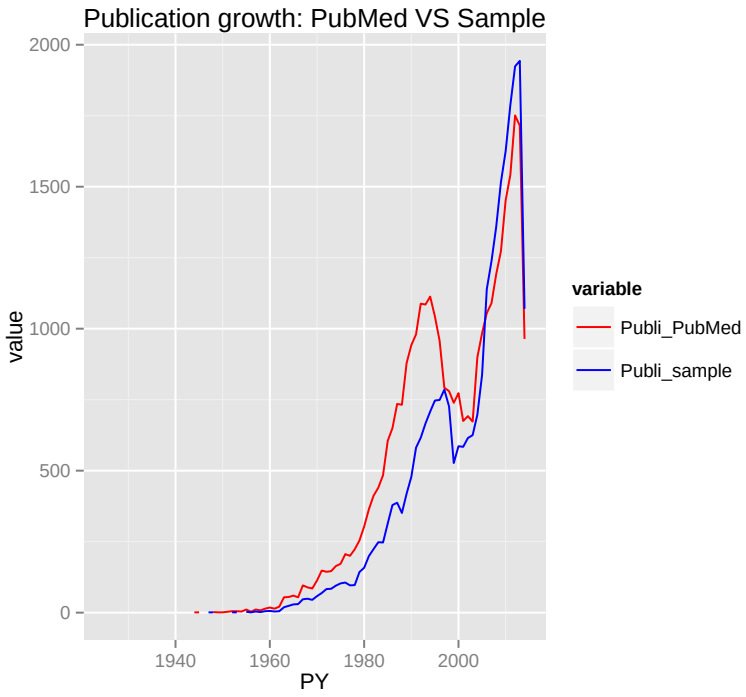


Figure 1: Growth of publications over time: overlap WoS-PubMed vs PubMed

cian's associations and public organizations play a leading role in setting standards and norms that constrain the technological evolution. Therefore, a particular attention has been devoted to track references associated to them. This set of references has been defined as belonging to the practice components with lexical queries, mainly dealing with new legislation (in terms of toxicity, safety, standards) and governance practice (laboratory and clinical guidelines, recommandations coming from medical professional associations). The main institutions concerned are WHO, FDA, NIH and the NCI.

2.2 Linking components

As mentioned above, the process of medical innovation requires the integration of insights coming from different contexts that might be tracked thanks to references and related sources. Other examples in the field of bibliometrics mainly related to the concept of translational research (Cambrosio et al., 2006; Jones et al., 2011) rely on inter-citations between what they define as basic and clinical journals. However, important disparities in terms of citations exist between type of journals (see for example van Eck et al., 2013) for a bias related to h-index in clinical journals between different medical specialties) but also within type of journals, considering the heterogeneity of citations across disciplines (see for example Leydesdorff and Opthof, 2010; Opthof and Leydesdorff, 2010). In order to take into account this heterogeneity across fields and journal types, we decided to measure the intensity of "use of specific knowledge" as the percentage of references of a given component devoted to itself or another one, normalizes by the percentage of outputs represented by this specific component over the period. In other words, our measure is associated to the relative importance of citations towards a specific body of knowledge divided by its relative importance over the period. We will describe more precisely how we proceed at the micro-level at the end of the section.

2.2.1 Extraction and taxonomy of non-patent references (NPR)

Linking Science and Technology by relying on non-patents references has a long tradition in the field of innovation studies (see for example Price, 1963; Narin and Noma, 1985; Narin et al., 1997; Schmoch, 1997; Meyer, 2000; Verbeek et al., 2002; Breschi and Catalini, 2010). Concerning health technologies, Hicks et al. (2001) conclude their comparative studies by stating that these technologies tend to get an increasing propensity to cite scientific publications than all other technologies, denoting a more linear process of innovation. However, this conclusion is undeniably linked to the heterogeneity of non-patent references and NPR should not be seen as indicating a direct and linear link between Science and Technology (Meyer, 2000). Looy et al.

(2007) suggest to interpret NPR as an indicator of the distance between scientific findings and technological developments, highlighting the role of the distance between both contexts. As already mentionned in **?** and Callaert et al. (2011, 2013) non-patent references can refer to scientific articles, manuals, books, firm's catalogue, databases... Therefore, NPR require a careful treatment to distinguish their different components that are not necessarily scientific.

Until now, the existing efforts were devoted to search for scientific articles in Web Of Science in order to build a taxnomy of NPR in terms of types of publications (see Hicks et al., 2001; Verbeek et al., 2002; Callaert et al., 2011) but also about their nature measured by disciplines (Schmoch, 1997; Verbeek et al., 2002; Callaert et al., 2011). Based on previous works (see Callaert et al., 2011, 2013), we built an original strategy to improve the existing methodology in the field of medical innovation. After parsing the NPR, we obtained 38722 references associated to US patents. Among them, we selected the most comprehensive ones defined by five fields: author, title, journal, published year and begin page. First, we checked the presence of this group of NPR among our existing stock of scientific publications that we already downloaded. If they did not belong to our publications, we queried PubMed via Entrez service thanks to a PHP script that was using two criteria, namely author's name and published year, and a set of keywords defined as the less commong words among our NPR. Considering the heterogeneity of NPR, we used lexical queries to define 3 categories (scientific material, technology-instrument and practice) that do not refer to scientific publications. Scientific material refer to chemical abstracts, database, books and handbooks mainly. Technology and instruments refer to manual of specific instruments, software, and existing products (drugs). Finally, practice refer to reports or guidelines associated to practice coming from public institutions or association of practitioners. 2048 have been treated by hand due to the incompletness of the NPR. In total, we identified 36326 references that were scientific publications, 4189 were belonging to the different components without being scientific publications and only 336 remained unfound among any category.

2.2.2 Using cited references

The sources of the relevant knowledge involved into the medical process are also analyzed from an organizational and cognitive point of view. First, we checked whether the cited references among our initial sample of publications were part of it. If not, we relied on the associated DOI (if available) by checking its relevancy online thanks to dx.doi.org. If the DOI made it possible, we downloaded the related publications on PubMed and Web Of

Science. If not, we re-structured the cited references and checked if the content of each field was the relevant one. We used PubMed website in a similar way as described above for NPR in order to extract PMID to use them on Web Of Science to cross both data sources: 1217597 PMID were found and 221 380 publications were inconclusive. Science and Technology relationship cannot be only described in a linear way in which scientific knowledge influences technological development but rather co-interact in different ways (Price, 1963).To explore this reverse relationship between Science and Technology, we developed lexical queries to determine the importance of patents and instrumentations on scientific advances. In our case, beyond technological advances, we also wanted to evaluate the role of practice in shaping scientific progress. We developed additional lexical queries to take into account the importance of guidelines (mainly coming from the FDA and NIH), clinical trials thanks to their numbers. Relying on the cited reference PMID, we check in our database if its Publication Type was related to practice.

We proceeded in a similar fashion with publications that were established as belonging to medical practice thanks to their publication type. In total, 1217596 citations have been identified and only 130965 were not found. 6.98% of the total of references are associated to practice, 2.05% of references belong to the testing regime, 0.25% references deal with patents, drugs or instrumentation and the wide majority of the references belong to science (89.53%). Within Science, 0.28% refer to books, databases or other scientific materials and 89.25% is composed by scientific publications. The rest of the sample is related to other types of journals (such as weekly journals) and unfound scientific references.

Patents have been extracted and standardized among the scientific references. The way of citing patents among scientific references appears very heterogeneous, sometimes refering to its publication number or application number. To maximize the overlap between science and technology, we used the patent number and checked its presence within the patent families extracted from Derwent. In the meantime, we focused on the references made explictly to US patents to ease the process. In total, only 257 patents cited in scientific publications were found in our patent dataset. Patents with a complete US patent number were extracted from Derwent Innovation database to complete the analysis. 185 patents were added into the data. Similarly, references refering to new norms or laws have been identified with lexical queries based on the institutions publishing them (WHO, FDA, NIH, Committee Toxic Criterion, Center of Disease Control and Prevention, National Committee for Clinical Laboratory Standards, NCI, American Cancer So-

ciety among others). We also identified 25 clinical trials thanks to their numbers registered on the US clinical governmental website.

2.3 Organizations: patents and publications

To identify the sources of knowledge, we relied on the acronyms defined on Derwent Innovation to standardize the patent assignees in order to distinguish between public vs private science and practice. The advantage of using this source of knowledge regarding the assignee types was the standardization of firm's names that takes into account the mergers and acquisitions done over the investigated period. Actually, the USA over the eighties and nineties were characterized by a specific set of institutions (Bayh-Dole Act, Venture Capital) that gave birth to academic entrepreunership and ensured US leadership in biotechnologies industry (Henderson et al., 1999; Mowery and Nelson, 1999). This specific context has generated several studies about the increasing verticalization of research in biotechnologies where small-business formations were perceived as the "middlemen" to achieve knowledge transfer from the academic research to the industry (see Henderson et al., 1999; Arora and Gambardella, 1994). However, the increasing amount of commercial failures and deceptions about the ineffective biotechnology revolution (Hopkins et al., 2007). Therefore, in the 2000s the decreasing amount of Venture Capital (or more complicated obtained than providing a drug target, McCammon et al. (2014) and the pressure exerted by IPR on "big pharmas" exacerbated ongoing trends of mergers and acquisitions (Danzon et al., 2007).
Regarding publications, we standardized the different organizations involved thanks to the authors'affiliations available on Web Of Science and keywords analysis. Among 68920 affiliations, only 1284 remained unknown and we could disentangle them between private vs public science and practice.
In both cases, we considered universities, departments from schools or universities and public institutions as relevant organizations belonging to public science. In a similar fashion, university hopsitals and medical centers refer to public practice. On the contrary,firms and their related laboratories, were considered as private science. Private institutions, societies, clinics and hospitals are defined as private practice. Institutions remained unclear between public and private organizations, and constituting a mix between science and practice as well.Considering this heterogeneity, institutions were added at the Other category. We proceeded in the same way to define the organizations cited among scientific publications.

2.3.1 Science and Clinical practice impact on Technology: micro-level

As explained above, the feedback loops generated in scientific or clinical practice are not necessarily codified and published. In the case of liposomes, this effect has been probably all the stronger due to their specificities in terms of variability of designs and production processes (Weinstein, 1987). Therefore, the improvements of liposomal formulations has been hampered by a limited stock of available knowledge to ensure replication of published experiments (in vivo or in vitro). Actually, research efforts have been mainly impeded by the lack of details about the conditions of performing it in terms of preparations: the sequence of actions performed and components used over the production process defining the liposomes properties (Weinstein, 1987; Immordino et al., 2006). Therefore, even in a simplified framework in vitro, this source of variations reduces the chances to distinguish between conditions of experiments and investigated causal phenomenon to understand liposomes properties. We share the idea that failures in experiments, via learning by doing and by using, constituted an important stock of knowledge and sources of intuition about new applications. Although patents constitute a mean of appropriation of the invention due to its chemical nature (Pavitt, 1984), the related appropriation of knowledge remains incomplete. The importance of contextual embeddedness linked to practice in experimental and clinical settings has probably limited the "absorption" of knowledge by firms that could only rely on the limited amount of knowledge published which could not "spill-over" from public organizations as it is widely assumed. This idea has been underlined by Agrawal (2006), showing how inventor's support matters to ensure commercialization of patented knowledge.

For these reasons, we decided to get a closer look at the inventors involved in scientific and clinical activities but also distinguishing the public and private efforts based on an inventor's level. Considering the importance of practice performed in a lab or clinical settings, public organizations seem appropriate loci of innovation by concentrating such kind of activities. In this regards, teaching-hospitals appear as "hubs of knowledge"(Djellal and Gallouj, 2005-08; Consoli and Mina, 2009) by being at the interface between scientific and clinical practice.

To do so, we use the standardized inventors' names provided by Derwent Innovation and PubMed authors' names to evaluate the amount of inventors who benefited from returns coming from scientific and clinical activities. Then, we used our classification of public organizations to select only authors who kept a public affiliation over the period and of whom were patenting with a firm or individual assignee, meaning they were privatizing public research. Considering the importance of academic mobility in patenting activity (see Balconi et al., 2004; Crespi et al., 2006; Breschi and Lissoni,

2009), we decided to define a time-window between the application year of the patent and its related publication output 2 years before or after it. To compare the impact of scientific or clinical activities coming from public vs priavte organizations in patenting, we used new indexes inspired from citation analysis network methods that represent an alternative to using a raw count of forward citations (Martinelli and Nomaler, 2014). The analysis was performed on patents applied before 2010 to allow for 5-years of lag to let them acquire the maximum burst of citations (Lanjouw and Schankerman, 1999).

3 Results

3.1 Public vs private developments: division of labor?

Not surprisingly, organizations belonging to private science (private institutions, firms, individuals) drives the patenting activity and seems to represent the most important source of knowledge about technological developments. Public science (academics, medical/pharmacy schools) comprises the second group of patentees but with a much more modest role. Organizations involved in clinical practice activities (teaching-hospitals, medical centers, clinics, hospitals) seem to play a more marginal role in developing technological solutions.

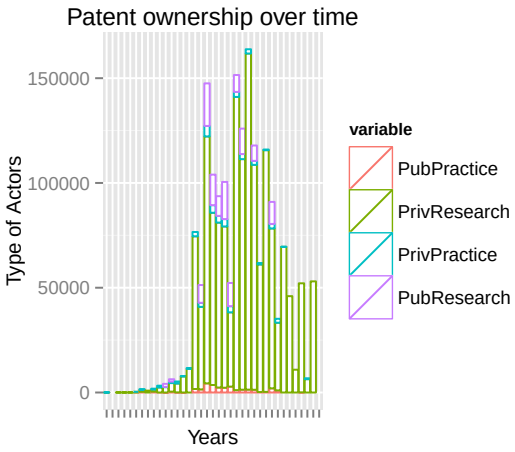


Figure 2: Granted patents by type of organizations over time

More specifically, firms represent the leading force in terms of technological developments. Individuals play also an important role in developing liposomal formulations and are more numerous than firms in absolute terms. Rather than illustrating hobbists' or garage inventors, this result is in line with the US "entrepreneurial culture", pushing researchers or physicians to patent their discoveries.

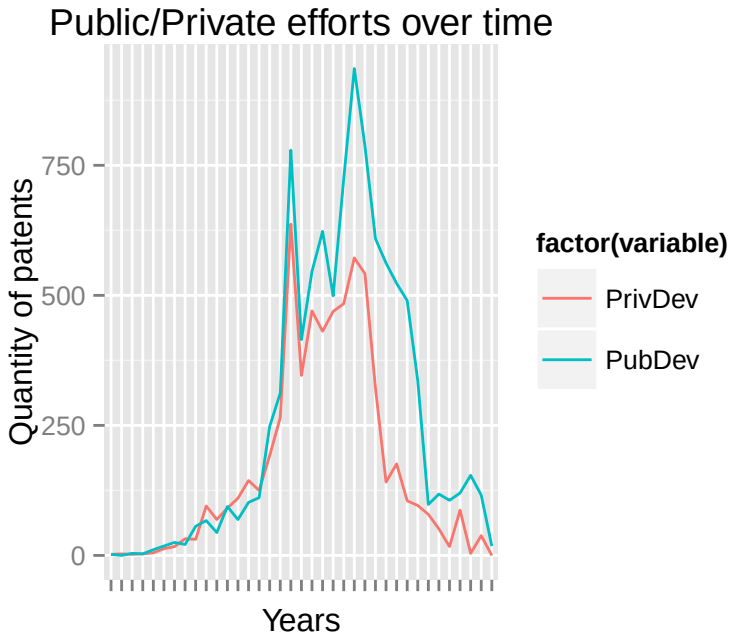


Figure 3: Public efforts with academic inventors vs private efforts in patenting over time

As already well understood in the literature, small groups of individuals correspond to very prolific inventors, this "research front" could benefit from their status of "star scientists" to get better conditions in terms of fundings in order to patent or to start their own start-ups (Zucker et al., 1998; Higgins et al., 2011). Opening the firm's black box and looking at the inventor's level provides another picture in terms of the sources of knowledge behind patenting activity. The following graph represents the amount of public efforts in patenting by considering also the firm and individual assignees patents in which at least one of the inventors was publishing in public organizations over the period. Far from initiating the technological efforts, patenting coming from public research remains high and faced a lower decline at the end of the period.

Non-patent references allow us also to compare different behaviours in terms of citations according to the patent origin and check whether we can assess different knowledge bases between public and private actors. Far from representing the influence of scientific knowledge within technological search, NPR seem to suggest that to some extend, all components play a role in technological development for all assignees. Contrary to what we could expect, firms and not universities, tend to cite more scientific publications in non-patent literature. The technological component (testing regime,software, instrumentation, existing products) plays the most crucial role in the case of individual assignees but remain important for each type of assignee. Practice appears as playing a more modest role in technological developments, even for clinical assignees. However, the use of knowledge coming from clinical practice is more used within academic patents.This is in line with the previous idea according to which, public science plays a crucial role within the innovative process by connecting the contribution coming from the different components.

Using publications allow us to get another picture in which public is the leading force in knowledge generation, defining the whole trend of publications. In this case, private science and organizations involved in clinical activities tend to play a similar role in terms of publications. As mentioned above, certain fields of clinical practice are maybe more valuable than others in terms of publications (van Eck et al., 2013) and represent different opportunities costs beside the clinical care missions.

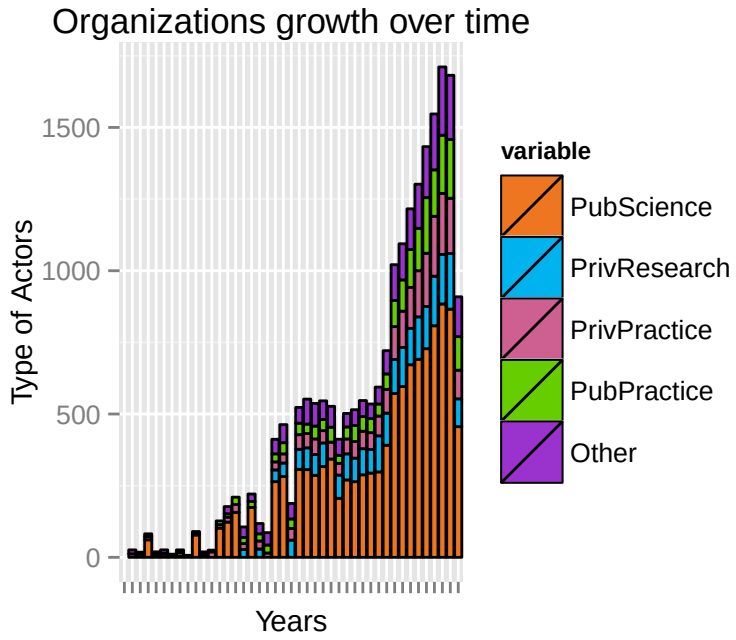


Figure 4: Quantity of organizations over time

Moreover, the national boundaries appear more porous considering the scientific knowledge base rather than only looking at foreign institutes patenting in the USA. Even if US organizations produce the most important part of publications, numerous foreign public organizations are also connected to these ones. The importance of public organizations in patenting and publishing is also explained by the increasing number public actors involved in the research efforts. The next table illustrates the importance of public science in the generation of knowledge, considering all types of knowledge involved (scientific, practice and testing regime). Scientific feedbacks from practice seems also to be broadcast through university channels rather than coming from hospitals nor medical centers. Firms publish slightly more than organizations involved in practice and tend to focus on scientific knowledge rather than the two other components. However, university-hospitals and medical centers constitute also an important source of knowledge, more oriented towards science and practice. The role of public science is also underlined by the quantity of citations they receive. However, considering the amount of publications, firms and laboratories seem to make also significant contributions. This point is going in the direction of the importance of individuals coming from universities, schools mentioned above. Concerning organizations involved in practice,they apparently make less significant contributions or are too contextual to be used in the scientific or technological

arenas.

Table 1: Importance of Private and Public efforts(publications, citations,patent count)

	Public Science	Private Science	Public practice	Private Practice	Others	total
Publications	18411	4516	4207	2845	793	22725
Received citations	643550	191614	145733	123135	32224	817394
Shared or full ownership of Patents	706	2669	115	128		3115

3.2 The Relationship between components: meso-level

The next figure represents the quantity of scientific publications related to Science and Practice respectively and Technology is proxied by the quantity of patents and publications associated to the testing regime. As we could expect, the quantity of scientific publications grows almost continuously over time. However, the technological and practice trends do not follow the same paths. Contrary to what is usually thought, science does not represent the starting point of the innovative process. Technology, via the liposomal testing regime, initiates the path to liposomal search efforts. Despite insights from membrane models that we catch at the beginning of the period, the in vivo regime has also provided the basis to establish the rational use of liposomes in cancer (Weinstein, 1987). Exploiting liposomes as carriers for diagnostics, Matsumura and Maeda (1986) underlined the retention of liposomes as the tumor site, called "enhanced permeability retention" that became the "golden standard" in anticancer (Azzopardi et al., 2013).
Practice follows another trend, more dynamic at the end of the period. Let us note that the first market approval for liposomal formulation was in 1995 that could explain why feedbacks required more time to appear. Interestingly, the first market approval year marks the beginning of a decreasing trend for Technology and Science until the 2000s. We can also notice a shift from in vitro to in vivo testing regimes that seem to increase as clinical practice articles increase. The following pictures describes the evolution over time of the interactions, between and within components. The reported scores are associated to the proportion of citations towards on given components and its relative probability based on the quantity outputs that is observed over the period. We define 3 main period over liposomal research to represent the successive dominant designs that have been the

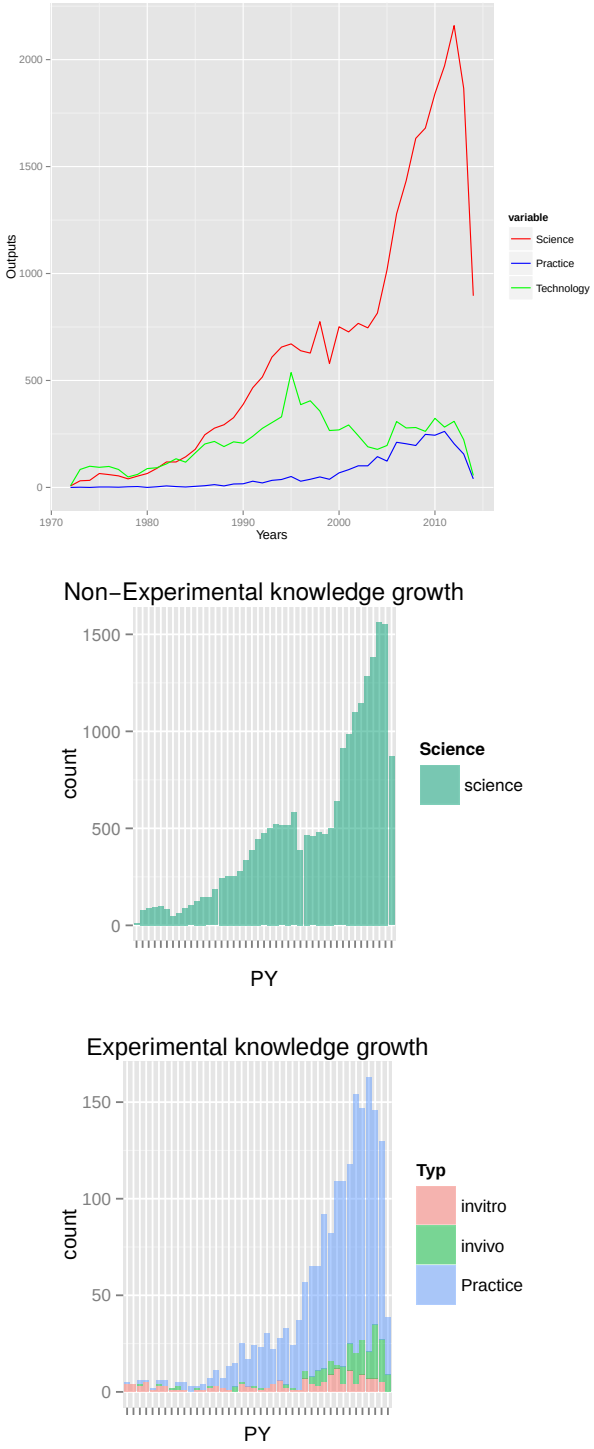


Figure 5: Evolution publications types over time

results of insights from science, experimental knowledge and clinical practice. The first period refers to the "dark ages" of liposomal research that faced technological constraints to be able to propose a formulation to be considered as a serious clinical option. The second period is marked by the clinical trials of the 1st dominant design of liposomes that failed in clinical practice despite numerous experimental testings in vitro and in vivo. Finally, the last period that slowly relaxes the pressure exerted by the path-dependency associated to membrane model (Weinstein, 1987) to take into account new insights coming from polymers and give birth to the second dominant design (PEGylated liposomes). The last period is characterized by the emergence of new types of derivated-liposomes technologies applied in clinics: new designs (immunoliposomes), new modalities (combining hyperhtermia and chemotherapy, gene delivery, prodrugs), but also new derivated forms of liposomes (niosomes, polymersomes, archaeosomes... (Mozafari and Khosravi-Darani, 2007).

The first period is characterized by a concentration of the research efforts within components and science seems to get an influence on technological and clinical knowledge. Regarding the scientific component, it is disconnect from clinical practice seems to get feedbacks from the experimental knowledge and technologies. Technological knowledge, mainly through the testing regimes, ensure the articulation between science and clinical practice. This aspect is in line with the beginning of clinical trials performed in the eighties and the emergence of the 1st design of liposomes as a result insights coming from the testing regime in vitro and in vivo.
The second period indicates a higher amount of citations between and within components, the use of scientific citations within scientific publications is all the stronger. This period initiates also the beginning of clinical feedbacks in science but a relative decline of their importance in technology. This phenomenon illustrates the end of the 1st dominant design of liposomes to let emerge the second generation of liposomes (PEG) due to unforecast toxicity effects in clinical settings (Immordino et al., 2006). Clinical practice seems to be slightly more connected to science and keeps a similar link with technological insights. Technological and experimental knowledge seem to start to be more concentrated and to substitute insights from science and clinical practice.
The last period depicts another dynamic by showing a reduced amount of feedbacks within and between components except for technology: science and clinical practice tend to rely on more technological and experimental knowledge than before. Technological and experimental knowledge tend to be more isolated from potential insights coming from clinical practice and science. Another reason that might be responsible for a reduced amount of

citations in clinical and scientific journals is the introduction of new rules, limiting the amount of citations that pushed researchers to substitutes specific investigations to reviews (personal comunication with EMBO Press managers).

This last stage suggests that the observed boom of scientific papers reflects scientific externalities coming from liposomal research in cancer and gave birth to new types of technologies that do not necessarily interact with liposome patenting (Weinstein, 1987). We try to illustrate this by the dynamic of disciplines involved into our sample of publications considered proxies for science. The initial insights from molecular biology and biophysics disappeared whereas new field emerged at the end of the period (acoustic, radiology, nanosciences). Moreover, the reduced amount of patents at the end of the period can artificially increases the score of technology. Finally, as suggested in Webb et al. (2007) early patents in the field of liposomes research were probably pretty "upstream" in terms of knowledge and made more costly some scientific inquiries by raising the cost of study. As suggested elsewhere (Dosi et al., 2014; Stiglitz, 2014), patenting might also impede other types of learning that closed additional pathways for scientific understanding and clinical solutions. By being off at the end of the period, the additional costs to study them in different settings was reduced.

Table 2: Variation of interactions between/within components: changes in percentages

Table 3: Variation 1st-2nd periods

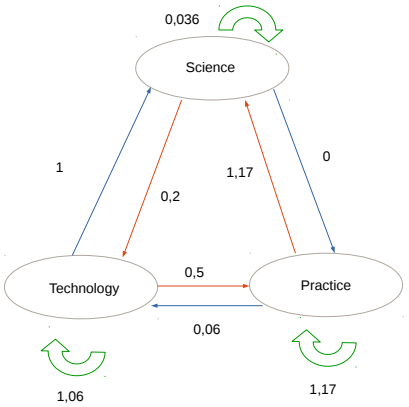
Citing-Cited	S	T	CP
S	35,94	-0,65	+
T	-0,02	0,17	-0,34
CP	0,04	-0,20	0,42

Table 4: Variation 2nd-3rd periods

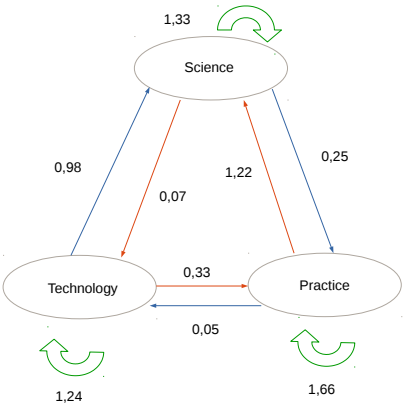
Citing-Cited	S	T	CP
S	-0,18	6,14	0,00
T	-0,14	4,04	-0,62
CP	-0,14	4,00	-0,90

3.3 Implications of scientific and clinical feedbacks on technology: micro-level

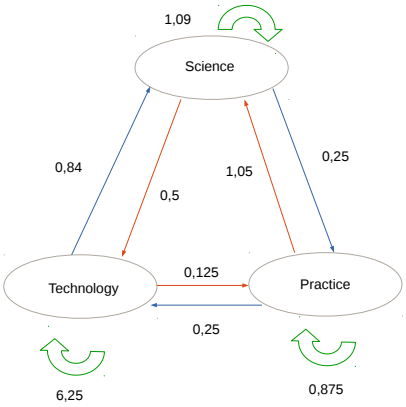
Author-inventors represent 1602 individuals over the 4716 distinct inventors. Among them, only 847 of them could have been identified as part of public, hybrid or private organizations. More precisely, 689 individuals publish in public organizations, 284 with private affiliations and 132 in hybrid organizations between public and private status. The patenting activity is mainly associated to scientific publications and follows the global trends obtained at the meso-level, with a relative increased importance of clinical practice and in vivo testing regime. The number of related publications over time suggests closer links between both components. The decline after 1998 is probably linked to phenomenon of mergers & acquisitions and reduced the



(a) Period (1972-1992)



(b) Period (1993-2005)



(c) Period (2006-2012)

Figure 6: Evolution of the Interaction between Science, Technology and Clinical practice

access to Venture Capital reduced the amount of academic start-ups and limited the academic individual patenting. For example, Sequus pharmaceuticals which represented a very prolific patentee with several insights from numerous authors was acquired by Alza in 1999 (Bloomsberg website).

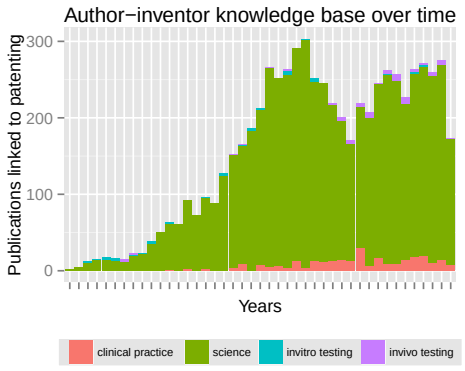


Figure 8: Publications related to patenting of author-inventors over time

Public and private inventors with publishing activities follow similar trend despite the absence of invivo testing insights among private inventors. Clinical insights are also more limited in hybrid or private inventor patenting and more pronunced in public organizations. The sudden jump at the end of the period is related to the introduction of the singular author-affiliation on web of science. An important point to note is the constant patenting activity of public inventors and does not disappear over time as it is assumed in a division of labor framework. Both indexes are associated to citation network analysis that aims at compensating the methodological drawbacks linked to using absolute number of forward citations. Actually, one important patent can be put in the shadow of an intermediate patent that take benefit from its technological insights. This methodology aims at filling this gap by taking into account the pivotal role of intermediate patents among citation networks. The genetical scores refers to the capacity of patents to provide a meaningful contribution to the other generations of patents, considering the whole period of technological developments. The persistence index evaluates the direct descendants of patents looking at how much knowledge from a given patent is retained into the following developments as a measure of associated technological pedigree (for the detailled explanation, see Martinelli and Nomaler (2014)). As the indexes are defined between 0 and 1 and their distribution is extremly skewed, we decided to represent the results with a log-scale.

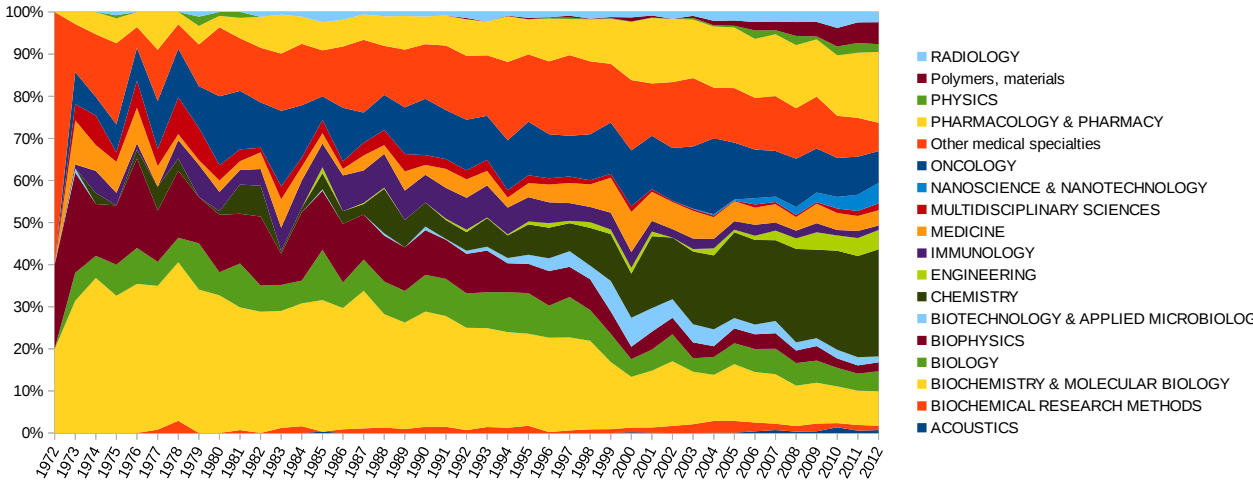
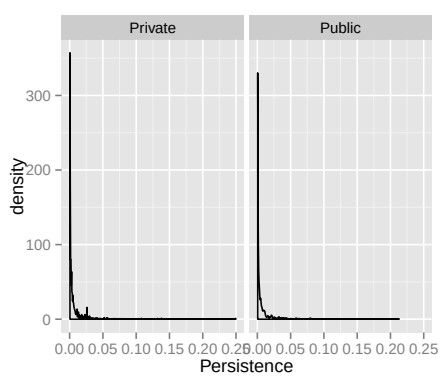
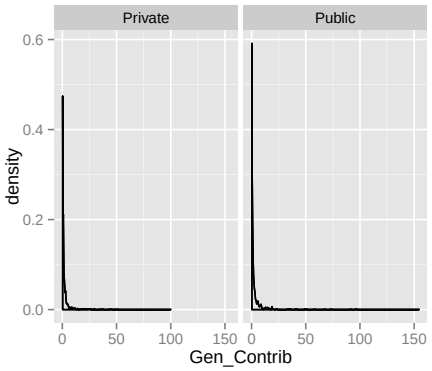


Figure 7: Evolution of disciplines over time



(a) Persistence index: public vs private patents



(b) Genetical contribution of patents: public vs private

The graphs suggest that the technological contribution of patents coming from public activities appear more meaningful and useful for future technological developments while the capacity to transmit their technological characteristics among a higher amount of patent with private efforts. This last one may be the result of a higher amount of patents vis-à-vis the amount of public ones.

4 Conclusion and limitations

This study sheds light on the role played by science, technology and clinical practices within the medical innovation process. Their interaction and feedback loops have been measured with a novel empirical approach, crossing patents and scientific publications with their respective citations. The interaction of such components has been put in perspective with their organizational context to understand the capacity of public and private organizations to absorb and master these different sources of knowledge.
Following the theoretical model of medical innovation, we show that continous feedbacks interlink all components even if the first period highlight that scientific knowledge did not benefit from clinical pratice insights. This suggests that scientific investigations were probably facing issues "off-line" to determine which formulations to select as an appropriate design due to the nature of the artefact, limiting the replicability of experiments. Thus, already in the most simplified conditions, learning was restricted and could not ease the selection process in more complex conditions (invivo and clinical settings). These scientific insights have first influenced the technological developments and first concentrated the citations within each innovative component. Reaching clinical practice, the feedbacks from "online" experiments influenced the body of scientific knowledge to recombine and in turn, influenced the type of technology to consider. This phenomenon describes

the higher intensity in terms of knowledge use, between and within components over the second period. The third period seems to depict a new stage in which technological and experimental knowledge plays a leading role, substituting insights from science and clinical practice. One explanation is linked to the boom of derivated-liposomes technologies that relied on a substantial amount of externalities linked to the liposomal problem-solvings and achieve additional technological improvements according to their intended purposes. The other explanation lies in the effects associated to upstream patenting over the first period that might have limited additional empirical studies in vivo until being off over the last period. Therefore, our results depict a dynamic in which science, clinical practice play a leading role sequentially. Technology and experimental knowledge seem to bridge both contexts thanks to the invivo testing regime.

Our results suggest that science, through public organizations, aims at connecting, articulating, and codifying independent and distant bodies of knowledge. This aspect is linked to the mission of public organizations that are in charge of several activities along the innovation process, from fundamental scientific research to clinical observations. In this regards, teaching-hospitals play a crucial role in generating knowledge. At the micro-level, the evaluation of academic inventors over time underline also the importance of integrating feedbacks from experiments (invivo and in clinical settings). The role of absorbing these feedbacks from distant bodies of knowledge is also reflected in the impact indexes between public and private organizations: public organizations appear as giving more important technological contributions than private ones. By singling out feedback loops between the components, we can assess whether the division of labor among different public and private organizations is not really effective. Despite the role of connector played by public science and several degrees of firms' "absorptive capacities", the tacit dimension of liposomal research implied direct insights from scientific and practical practices.
Despite empirical limitations, the crucial feedbacks dynamic between the lab and the clinical arena and the limited codifications of it put in doubt the complementarity assessed theoretically the public and priavte activities. We share the idea that more contextual insights are required to understand the heterogeneity of disease areas and biotechnologies to assess whether big pharmas are able to integrate this knowledge and justify the public/private division of labor. Many authors alarmed about the cost for society related to pharmaceutical innovations by subsidizing firms' research, we argue that in addition to this, the properties of medical innovations do not necessarily fit with this division of labor which impedes the accumulation of knowledge and in turn, the capacity of innovation.

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