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DISCUSSION PAPER

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Anatomy of the Medical Innovation Process – What are the Consequences of Replicability Issues on Innovation?

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Anatomy of the Medical Innovation Process - What are the Consequences of Replicability Issues on Innovation?

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Abstract

This paper is concerned with exploring the implications of replicability issues over the medical innovation process. Each research setting is characterized by a specific level of replicability, variability increasing with the complexity of the testing settings. The study introduces new measures to quantify the research efforts across different medical experimental settings. Doing so allows to map the dynamics of knowledge along the medical R&D spectrum and over time. The lack of replicability of experiments was overcome by recombining technological knowledge coming from distinct uses (laboratory tool and other medical applications) with clinical insights. The citation analysis suggests that science, technology, and clinical learning interact strongly and have an uneven importance over time. The study stresses the importance of economics of scope between experimenting and technology developments. In this process, a new type of chemotherapy emerged without a centralized institution governing the testing efforts. Research and innovation policy implications are discussed.

Keywords Medical innovation - knowledge translation - replication - instrumentation
JEL Codes: I12 - O31 - D83 - D85

- Replication issues affect the scope of the medical knowledge base
- Replication issues are overcome by the other innovation pathways
- Uneven role played by the innovation pathways over time
- "Testing regimes" can develop without related institution

1 Introduction

Science moves forward by corrobation: scientists' aim at challenging the scope of existing results, or theories. The capacity to replicate research findings [1] is thereby the cornerstone of scientific research. Put in other words, only if observations present a similar pattern, hypothesis and theories can be developed in order to explain the laws of nature. Only in this specific case, science can guide our understanding of a given studied phenomenon."Despite being a defining feature of science, reproducibility is more an assumption than a practice in the present scientific ecosystem" (see Errington *et al.*, 2014, :1). To illustrate this quote, Prinz *et al.* (2011) report that only 25% of pre-clinical studies in cancer could be replicated. In 2012, researchers from Amgen delve further into question by publishing a study describing their failure to replicate 47 of 53 cancer landmark papers (Begley & Ioannidis, 2015). Even more worrying, the authors of published studies face also difficulties in reproducing their own studies (Baker, 2016). The relative validity of published results has become an increasing concern for the scientific community, especially in the biomedical area. Some authors even talk about a "crisis of replicability" (see Ioannidis, 2005). In this context, science can hardly be expected to guide innovative efforts through a conscious process of planning and designing (Gelijns *et al.*, 2001).

The debate has focused on the links between replicability and the "publish or perish" culture (i.e. incentives to publish rather innovative results over replications, inaccurate reporting of methodologies, and scientific misconducts through the lack of transparency regarding methods, or falsification of results) (Alberts *et al.*, 2014). However, few studies have investigated the impact of the lack of replicability on innovation. Replicability has been mainly indirectly investigated in the context of building experimental conditions to make research results *predictable* (Nightingale, 1998, 2004). Building "appropriate" experimental conditions (e.g. complex enough to reflect reality but in the same time, simple and controllable enough to learn about a given phenomenon) generates predictable results, which are used in turn as "operational principles" to innovate (Vincenti, 1997). The capacity to learn through experiments would be one of the reasons explaining the uneven character of innovation across sectors, or diseases (Nightingale, 2004; Nelson, 2008; Yaqub & Nightingale, 2012; Yaqub, 2017a,b). Hence, the limitations (or absence) of experimental conditions to learn about a given technology does not affect only the rate of innovation but also the direction of innovative efforts (see Nightingale, 2004; Nelson, 2008; Yaqub & Nightingale, 2012). The characteristics of the experimental conditions shape also the features of specific technological designs (Yaqub, 2017a,b). This study contributes to this stream of medical innovation literature by documenting how the characteristics of the experimental conditions affect the dynamic of the medical innovation process over time. The uncertainty coming from the numerous and competing assumptions about the behaviour the technology is overcome by combining insights from unrelated technological areas and clinical insights. Consequently, the lack of guidance from science is responsible for expanding the scope of the knowledge base to unrelated technological fields (e.g. polymers), to unrelated medical applications (e.g. technological properties accumulated for non-medical purposes), and other medical complementary technologies. Regarding the limited fundamental understanding of the problem to solve, the issues related replicability are overcome by clinical learning. As suggested in Yaqub (2017a), clinical trials are more than a tool to select design but question the relevancy of the current bodies of understanding accumulated in laboratory settings. Combining insights from experiments conducted in different contexts of use was the key to overcome

[1] Performing an existing study in order to confirm its results by independently testing the significance of a given set of results

the replicability issues. While the importance of experimental learning and the integration of distant technological knowledge was mainly investigated in the context of devices and vaccines respectively (for an overview see Gelijns & Rosenberg, 1995; Consoli *et al.*, 2016), this study shows that the latter hold in the case of drugs as well. Contrary to the general belief that science guides the translation of research findings to the clinic, this study echoes Nightingale (2000) who show that testing technologies more than science influence the rate and direction of innovative efforts in pharmaceuticals. To do so, the study aims at contributing to the medical innovation literature: i) by introducing new measures to quantify experimental learning conducted across different contexts (i.e. pre-clinical, clinical settings), ii) by providing an illustration of the dynamics of feedback mechanisms coming from the different medical innovation pathways (i.e. science, technology, clinical learning) over time.

The study traces the evolution of a technology - liposomes - which started their career as a research tool and ended as a new type of chemotherapy. Liposomal research, like cancer research, benefited from a limited guidance from science due to numerous sources of variations in the lab. In both cases, the replication of findings was very difficult and did not lead to identify specific mechanisms to let science guiding technological progress. This case suggests that recombining knowledge accumulated across different experimental contexts of use was crucial to cope with the radical uncertainty linked to the disease and the technology. The complex feedback mechanisms between science, technology, and clinical practice led to a "synthesis of knowledge" which heavily relies on knowledge accumulated during the initial career of the technology. Despite the absence of an institution governing the coordination and organization of testing activities (see Yaqub & Nightingale, 2012; Yaqub, 2017b,a), the insights coming from different experimental contexts have been channelled through an *instrumental community* (Mody, 2011) which benefited from a certain degree of standardization coming from the rules of anticancer drug developments. This study shows also that *testing regimes* can develop in a more decentralized fashion than what was described in the literature (see Yaqub & Nightingale, 2012), and adopt the existing rules governing other testing regimes to be standardized. The latter comes at the price of being less efficient by generating a lot of variations coming from the adoption of testing rules which are not necessarily fitting the same issues. The paper is structured as follows: section 1 introduces the specificities of the medical innovation process and the background of the case, section 2 details the data sources and methodology, section 3 presents the main results, section 4 discusses the institutional determinants explaining how the knowledge produced across different experimental contexts were coordinated, and section 5 summarizes the main findings and limitations of the study.

2 Medical Innovation Framework

Medical technologies, like other technologies, can achieve different functions which can evolve over time. Technologies fit "artificial purposes" that are imposed to them, meaning that, they are designed to reach a preconceived end (see Nightingale, 1998, 2004). The functions of technologies are the results of two main dimensions: on the one hand, the *intrinsic* properties of the technology which determine objectively how the technology should behave, and on the other hand, the non-intrinsic *function* which is socially constructed, and subjectively specifies how the technology should behave (Nightingale, 1998). While the *intrinsic* part is time-invariant, the *function* of a technology can be adapted across contexts of uses, or evolves over time. A same technology can thus perform several functions across different contexts of uses, or users. Nightingale (2004) takes various examples of

sectors (i.e. pharmaceuticals, combinatorial chemistry, aerospace, software, chemical engineering) in which innovation lies in adaptating technologies to a given function. To do so, substantial experimental learning is needed to achieve the desired technological purpose by accumulating knowledge about its intrinsic properties in different experimental conditions.

2.1 The concept of Testing Regime: learning by experimenting

In the medical context, the experimental demonstration that a technology can achieve a certain purpose establishes its use in medical practice. This process is achieved through an intensive period of testing activities which is heavily regulated in pre-clinical and clinical conditions. Recent contributions highlight the *difficulties* in learning from experiments in preclinical (Yaqub & Nightingale, 2012), and/or in clinical settings (Yaqub, 2017b,a). Learning in experimental settings requires the capacity to isolate, to control, and to replicate a given phenomenon (Nelson, 2008). To do so, building an appropriate *infrastructure* is needed to observe patterns and to *create predictability* (see Pavitt, 1998; Nightingale, 1998, 2004). Yaqub & Nightingale (2012) introduce the concept of *"testing regime"* to describe the environment (i.e. the institutional and physical settings - techniques, skills, and context of experimentation - characterizing a given experiment) in which knowledge is accumulated. Without appropriate experimental conditions, the capacity to accumulate knowledge about the properties of a given technology is severely hampered (Yaqub & Nightingale, 2012; Yaqub, 2017a,b). When experiments become stable environments, researchers can study technologies with the aim of providing scientific answers about their underpinning mechanisms. To stabilize or routinize the research environment, the use of specific *instrumentalities*[2] is thereby needed to test different assumptions about the behaviour of a given technology (Nelson, 2008). By becoming predictable contexts, scientific explanations are "true", in the sense that scientific knowledge is used to "match" the function of a given technology with a desired purpose (Nightingale, 1998, 2004). The fundamental understanding of the behaviour of a technology can only be investigated when it becomes predictable. In this sense, technology can emerge and precede scientific understanding (Nightingale, 2004).

2.2 Experimental learning: its consequences on the medical innovation process

The limited fundamental understanding about the interaction(s) of a technology within the human body explains that uncertainty remains even after its commercialization. The nature of health problems (see section 3.1) combined with the limitations of the experimental condititons in which knowledge is accumulated reduce the scope of the results predicted in the lab. Therefore, a market approval does not constitute the end of the journey of a given technology but rather initiates an extensive learning period in clinical settings (see the *post-implementation* in Gelijns *et al.* (1998)). A technology can reach the market and then, be modified to refine an existing medical purpose (see the case of contraceptive pills in Gelijns *et al.* (1998)) or, to achieve new medical purposes (see for example off-label drugs in DeMonaco *et al.* (2006)). In this context, innovation is not linear, initiated in the lab with scientific knowledge guiding research efforts in clinical trials. Instead, medical innovation comes from an "original synthesis of knowledge" (Nelson *et al.*, 2011). Relevant knowledge can come from different institutional contexts (i.e. hospitals, academia, industry), experimental contexts (i.e. laboratory, pre-clinical, and clinical settings), or non-medical sectors (see Gelijns & Rosenberg, 1995, for a discussion of the medical innovation knowledge base). Nelson *et al.* (2011) determine three main

[2]Beyond physical devices, instrumentalities refer to all models, statistical methods, or protocols used in experiments, (see deSolla Price, 1984, for more details)

sources of insights coming from the contexts previous described: science, technological capabilities, clinical learning. These three innovation pathways interact through "continuous feedback" over the innovation process (Gelijns & Rosenberg, 1995). The medical innovation process is thereby defined as being non-linear, highly complex, and dynamic (Gelijns & Rosenberg, 1994, 1995; Gelijns *et al.*, 1998). The dynamic and non-linear nature of the medical innovation process is responsible for putting the locus of medical innovation at crossroads between institutions and disciplines (Gelijns & Rosenberg, 1995; Consoli *et al.*, 2016).

2.3 Testing to adapt functions: From research technologies to new medical devices

The uncertainty previously described is more pronounced in some disease areas (see section 3.1). Consequently, one way to innovate was to adapt the function of existing technologies to reduce uncertainty coming from the limited understanding of the disease, symptoms, or pathologies. Deepening the understanding of a pathology by adapting the use of a technology to a medical diagnostic purpose was also an important driver in this process (see von Hippel & Finkelstein (1979) for chemical analyzers, Spetz (1995) for laser applications, Blume (1995) for cochlear implants, Blume (2002) and Rosenberg (1992) for MRI). The adaptation of technological functions has been described as a long process of trial and errors in which scientists at crossroads between institutions and/or disciplines played a leading role. More specifically, these studies put to the front the role of individuals with a dual background who are able to: first, align the needs of different actors who do not necessarily share the same perspective on the design or purpose of a given technology, second, articulate knowledge from unrelated medical areas (von Hippel & Finkelstein, 1979; Spetz, 1995; Blume, 1995). Another shared characteristic between these technologies is that they all were developed for research purposes (measurements in the case of laser and chemical analyzers, modelling internal ear for the cochlear implants, and spectral scanning in physics for MRI). Due to the nature of research purposes, academic researchers played a leading role in this process, not only by diffusing the use of instruments to industry (Rosenberg, 1992) but also creating new medical uses with the help of medical practitioners (Rosenberg, 2009). While initially used as laboratory apparatus, a long process of experimenting was used to adapt these technologies to a medical function to end their "career" as a medical technology (Blume, 2002). Blume (2002) defines the "career of a medical technology" as organized around four main steps: *exploration, development, diffusion-assessment, and the feedback* stages. After finding *how* and *why* a specific medical function can be achieved, the medical and industrial communities focus their efforts in demonstrating the feasibility of the new function to achieve. The *diffusion-assessment* phase is more oriented towards medical communities, who specify and legitimize the use of a given technology in medical publications. Finally, over the last stage, improvements of the first design are determined after an extensive of use of the technology in clinical settings. The medical and industrial communities work hand in hand to refine the first technology design. In each step, the technology is shaped and reshaped while the locus of R&D efforts gradually shifts between academia, industry, and hospitals (Blume, 2002). This process of refinement takes place within an *interorganizational structure* (Blume, 2002) which coordinates efforts to avoid their fragmentation. The results will follow a similar structure as the "career" steps described in Blume (2002) and section 6 will discuss the enabling factors responsible for creating an interorganizational structure.

3 Contextual background

3.1 Cancer: the limited power of science

Human body is a complex system consisting of billions of cells, molecules, and biochemical processes. Likewise, deepening the fundamental mechanisms related to a given disease requires unravelling the complexity of human body. This implies being able to identify the role(s) and the various interactions between multiple pathways (i.e. gene, proteins, and cells) (Dougherty & Dunne, 2012). Cancer is not an exception to this rule. The disease is known and has been described since the Ancient Greece. Its name comes from the word *karkinos* which refers to the crab-liked pattern that characterizes cancerous cells development. Cancer is defined as "an abnormal cells divide without control and that can invade nearby tissues" (National Cancer Institute website[3]). While initially put under the same umbrella, scientific progress suggested that different types of cancerous diseases exist and emerge as a result of genetical and/or various environmental factors. Despite significant progress in genetics (Fujimura, 1988; Faguet, 2008), cancer remains a disease area where the emergence of solutions is still limited. The nature of the mechanisms, like most of health problems, is thereby defined by a high degree of complexity, dynamism, non-linearity, and interdependencies (West & Nightingale, 2009). Reducing the complexity of cancer-related problems by breaking them into a set of independent sub-problems, like in engineering, is still limited.

The difficulties related to studying health problems in the lab are also the result of clinical variability (Gelijns *et al.*, 1998; Ali & Gittelman, 2016): a given cancerous form affects people differently. Put in other words, the predictions from the lab are relevant at best for a sub-sample of the patients. For example, progress in genetics initiated the development of targeted therapies. The latter, based on predictions made by algorithms about gene expressions, does not necessarily take into account their variations across patients. While having enthusiastic results in the lab, clinical trials failed for having underestimated ethnic variations (Duconge *et al.*, 2015). This example illustrates the *"weak-predictability"* argument developed by Pavitt (1998) and Nightingale (2004). Considering this radical uncertainty about the mechanisms underpinning cancerous processes, science has a limited guidance on technological progress. As developed below, technological progress in this disease area tends to precede scientific understanding and its rate increases with improvements coming from testing activities.

3.2 Radical uncertainty and consequences on innovation

Chemotherapy emerged as the paramount solution against cancer. Even if different clinical options can be used (i.e. radiotherapy, surgery, immunotherapy and target therapies in some cases), chemotherapy is usually used in combination with other modalities. Cancer chemotherapy emerged in the 1960s as a result of a substantial testing campaign ran in the 1950s. However, the fundamental understanding of the chemical compounds effects on the DNA of cancerous cells was suggested only in the 1970s (DeVita & Chu, 2008). The idea of using chemical compounds to treat patient came from experimental observations linked to the use of Mustard gaz during WWI and WWII. Over WWI, military doctors observed the destructive power of mustard gas on cells from the bone marrow (Faguet, 2008). These preliminary observations were extended by the consequences of the bombing attacks in the harbour of Bari (Italy). The illegal possession of Mustard gaz among US navy boats spread massive amounts of

[3] `https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cancer`

chemicals around the region of Bari in Italy[4]. The first observations from WWI were hence confirmed by this second episode which reinforced the idea of using chemical compounds to treat cancer. This idea paved the ground to the so-called "cell-kill" paradigm (Faguet, 2008).

In absence of scientific understanding, technology was offering an avenue: destroying the cancerous cells before letting them overwhelming the patient. However, defining the appropriate compounds and dosage in order to develop a medical solution required tremendous testing efforts. This unique testing campaign benefited from the support of a dedicated institution, the National Cancer Institute, established in 1971 when the Nixon's administration launched the War on Cancer (for more details about the testing campaign Faguet, 2008; DeVita & Chu, 2008). This testing campaign created the need to develop evaluation standards in testing activities: it gave birth to statistical procedures to assess the risks and benefits of the chemical compounds in clinical trials (Keating & Cambrosio, 2007). Over time, new guidelines and rules were developed and refined in pre-clinical and clinical settings as well (see section 6 for more details). However, without a fundamental scientific understanding of the effect of chemical compounds on cancerous cells, tumor-shrinkage remains the standard to evaluate the treatment success (Faguet, 2008). Advances in screening technologies led to economics of scale and scope in testing (see for an illustration Thomke *et al.*, 1998; Nightingale, 2000) which helped detecting molecules but without guaranteeing their efficacy after leaving the lab (see the "hit and miss approach" described in Faguet (2008)). The serious side-effects related to the use of chemotherapy represented a barrier to adopt the latter among practitioners[5]. In absence of therapeutic alternative, chemotherapy entered the oncologist armatorium but the idea of using "a magic bullet" (Himmelweit *et al.*, 1960) remained in the head of the medical community in order to foster the therapeutic benefits and to decrease the side-effects.

3.3 Liposomes: from the lab to the clinic

Liposomes refer to a nano-structure which is similar to a little bubble. Their discovery comes from the observations of horse blood cells by two hemaetologists at the Bangham Institute in 1961. By testing the electronic microscope recently acquired within their laboratory, Bangham and Horne could better observe the structure surrounding the blood cells. The pictures coming from the electronic microscope put an end to a long debate in the field of biology in which the structure of the cell membrane was still heavily discussed. The importance of this finding has been compared to the impact of the DNA double helix structure in the field of life sciences (Deamer, 2010). Consequently, this finding attracted the attention of scientists from numerous fields beyond cell biology (i.e. physiology, biophysics, physical chemistry, molecular biology)[6].

3.3.1 Liposomes as a research technology

Bangham and Horne, in collaboration with other biophysicists, established the chemical and physical properties of such structure and coined the term of "liposomes". In 1965, Bangham developed a method to produce artificially liposomes. Considering their proximity with cell membranes, liposomes

[4]Considering the Geneva treaty, the use of chemicals was forbbiden. For more details about this event, see (Faguet, 2008)

[5]As described in DeVita & Chu (2008), the first medical practitioners who used chemotherapy against cancer were called "butchers" by their peers

[6]Mody (2011) underlines the proximity and porosity of these fields in the 1960s and the use of similar apparatus (microscopy techniques) eased the dialogues between these fields

were hence initially used in the field of membrane modelling to test various properties (e.g. how does the cell membrane reacts with changing pH, temperature). Liposomes started their career as a research technology, or "instrumentality" (deSolla Price, 1984). Therefore, by being at the core of experiments to test scientific assumptions about cell behaviour, numerous knowledge about the technological properties of liposomes was accumulated in biophysics, physical chemistry, and even biomolecular engineering. However, building a strong body of science was hampered by numerous variations in experimental settings. First, liposomes can be synthesized by using various chemical formulations, creating a lot of variations in designs. Second, besides the inputs, the sequence of production steps also influences their properties (Wagner & Vorauer-Uhl, 2011). Put in other words, the chemical inputs used, the methods, protocols, and bodies of practice involved in their production were responsible for changing their technological features. Consequently, the accumulation of knowledge about their technological properties was bounded to the specificities of their designs and production methods, giving a limited scope to the results generated in the lab.

3.3.2 Liposomes as drug delivery systems

The career of liposomes took a different direction very early due to the involvement of young researchers in clinical research. After the liposomes discovery, Gregory Gregoriadis who was finishing his PhD in biochemistry decided to visit Bangham's laboratory. Trained in animal work and testing, his background helped to connect the founding fathers of the liposomal field with the medical community (Gregoriadis, 2018). Bangham and his colleagues, like Gregoriadis, were convinced that liposomes could encapsulate drugs. The first step towards medical applications of lipsomes as delivery systems was made when Gregoriadis joined the Royal Free Hospital in 1971. He collaborated with Brenda Ryman on the first medical application of liposomes[7]. After this demonstration that liposomes could be used as a carrier, a dedicated research group involved in clinical settings was established at the Charing Cross Hospital School of Medicine (Gregoriadis, 2018). This group was responsible for demonstrating that liposomes could be used as drug delivery in patients by using liposomes as immunological adjuvant (Allison & Gregoriadis, 1974). The latter established the career of liposomes as drug delivery systems. A following successful therapeutic application against Gaucher's disease reinforced the vision related to this new function (Gregoriadis, 2018).

These clinical successes "crystallized" the expectations related to liposomes across a wider range of researchers. Consequently, the demonstration of their potential as drug delivery systems attracted an increasing amount of researchers, from a larger set of scientific and medical disciplines (Gregoriadis, 2018). However, the development of medical applications of liposomes was plagued by the limited capacity to accumulate technological knowledge. By becoming a medical technology, liposomes entered more complex conditions (e.g. pre-clinical and clinical settings) than the settings characterizing their use as a research technology. The issues linked to the replication of experiments were exacerbated by the sources of variations coming from the type of loaded chemical compounds and the variations in the models used (e.g. type of cells involved in in vitro testing, animal models, anticancer compounds). The loaded chemical affecting the properties of a given liposome formulation, it was difficult to identify the causes explaining the variations observed across experiments (i.e. the loaded substances, the formulations and related production methods, or the experimental conditions). Despite all these difficulties characterizing the R&D efforts, the first US market approval in cancer chemotherapy was

[7]Liposomes were first used as a way to deliver glycogen into the liver to fight against a child disease

made in 1995. The next sections investigate how the liposomal community overcame these replication issues to adapt the function of liposomes.

4 Methodology

Citation network analysis has been the reference method to understand the dynamic of medical innovation knowledge (Mina *et al.*, 2007; Consoli & Ramlogan, 2008; Barberá-Tomás *et al.*, 2011). In this regard, the Main Path algorithm has been identified as an appropriate way to observe the main sequence of medical problem-solving (Mina *et al.*, 2007; Consoli & Ramlogan, 2008; Barberá-Tomás *et al.*, 2011). This trajectory depicts an emergent knowledge space, in which knowledge is accumulated in a path-dependent fashion. The trajectory reflects the set of relevant problems to solve and the solutions that prevail (Metcalfe *et al.*, 2005). The analysis of the patent and publication maps is cross validated by several historical reviews (mainly Weinstein, 1987; Gregoriadis, 1989; Barenholz, 2012; Allen & Cullis, 2013). Two experts in the field, Prof. Theresa Allen[8] and Prof. David Deamer[9], who were both involved in patenting and publishing over the investigation period has checked the main sequence of problem-solving. The next subsection explains in details the assumptions made on the citations and how they are used to delineate the most important developments. This study aims at going a step further than previous medical studies (see Consoli *et al.*, 2016, for a recent overview) by representing the knowledge flows across science, technology, and clinical learning (see subsection 4.2).

4.1 Assumptions about the key trajectories

The Main Path analysis constructs a knowledge space which can be organized in layers. Like in genealogy, each layer represents a generation of knowledge reflecting the scientific, or technological, state of art related to a given period. The time dimension is considered in a historical manner rather than in a continuous span fashion (Metcalfe *et al.*, 2005): the introduction of new techniques, or new observations, modifies structurally the accumulation of knowledge and is reflected within the dynamics of citations. Thereby, the identification of each generation of research efforts is based on their structure. The analysis is performed in two steps: first, the network is structured in layers thanks to the Search Path Count method, then, the algorithm identifies the most important knowledge pieces based on the previous step. In this context, a node refers to a piece of knowledge (patent or publication) and a citation represents an arc linking two nodes.

4.1.1 The Search Path Count: defining the structural properties of the network

The Search Path Count method has been developed by Batagelj (1991) and is available on Pajek software [10]. This procedure relies on a previous approach elaborated by Hummon & Dereian (1989). Hummon and Dereian develop and compare different methods to assess the importance of a node within a given network. The Search Path Count seems to be the most efficient method, and is the

[8]Theresa Allen is one of the pioneers of lipid-based drug delivery and made ground breaking contributions to the development of liposomal anti-cancer drugs. In this regard, she participated in the development of the approved liposomal anti-cancer drug, Doxil®.

[9]David Deamer is a biophysicist who built his career on the field of lipids after a sabbatical in Bangham's laboratory in 1975 after the liposome discovery. The latter applied his knowledge about lipids in a more basic fashion by investigating the role of the cell membrane in the origin of life.

[10]http://mrvar.fdv.uni-lj.si/pajek/

least dependent approach regarding the network size (Batagelj, 2003). First, the Search Path Count detects all vertices that are "sources" (nodes which only cite) and "sinks" (nodes which only receive citations) according to the structure of citations. The algorithm computes the total number of paths between all sources and vertices based on their respective citations. Then, the algorithm assigns a value to the different paths by measuring the number of times a given path is followed. The frequency of passing through a given path is determined by the structure of the citations within the network. This step defines the transversal counts of the arcs between the different nodes. The latter are then used in the identification of the Main Path.

4.1.2 Identifying the main trajectory of interest

The main path (MP hereafter) analysis simplifies the sequence of problem-solving that faces the medical actors over time. The related algorithm is available on Pajek. The MP algorithm identifies the highest weights among the different paths described in the previous section to detect the most important pieces of knowledge. When the largest transversal is found, the algorithm selects the arc with the highest weights in its neighbourhood. The algorithm processes backward, starting from the latest period, until reaching the earliest period. The implicit assumption is the following: "a citation that is needed in paths between many articles [patents] is more crucial than a citation that is hardly needed for linking articles [patents]" (Nooy *et al.*, 2011, p.282). The MP is supposed to reflect the most important junctions of knowledge, assuming that knowledge flows through citations.

4.1.3 The Main Path algorithm: limitations and extensions

Despite its popularity in innovation studies (Mina *et al.*, 2007; Leydesdorff & Schank, 2008; Fontana *et al.*, 2009; Barberá-Tomás *et al.*, 2011; Martinelli, 2012; Epicoco, 2013), the MP approach represents an oversimplification of the main developments and provides a very narrow-focused perspective about the main developments of a given field (Liu & Lu, 2012). This extreme simplification can be overcome by relaxing the maximization approach: the extended version of the MP (main subnetwork or self-organized map) contains important pieces of knowledge which are ignored by the maximization approach. This extended version underlines the different paths explored to solve a given problem, such as dead-ends or variations of solutions, which are on average less cited. In this study, a threshold of 0.02 for publications and 0.003 for patents have been used. The key publications and the list of patents used for the interpretation of the results are available in appendix.

4.2 Data: crossing patents and publications

Publications and patents are jointly crossed to analyze how the issues of replicability influenced the fundamental understanding of the new function of liposomes and the related technological problem-solvings. The analysis differentiates the characteristics of the testing conditions in which a cited piece of knowledge was generated. On the one hand, the sources of variability increase along the spectrum of R&D, multiplying the chances to lead to unreplicable results. On the other hand, the degree of relevancy characterizing the testing settings more downstream increases and aim at capturing the complexity of the human body, relaxing the simplifying assumptions made initially in the lab. This degree of sophistication characterizing the context of experiments comes at the expense of increasing sources of variability (see Figure 1).

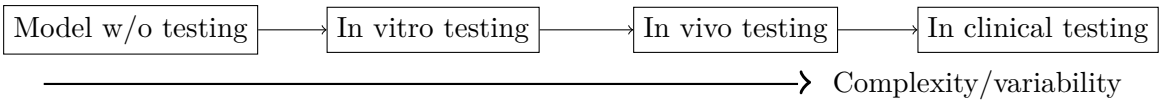


Figure 1: Delineating the context of experiments

This methodology assumes that the prior art reflects the accurate sources of knowledge involved in solving/answering a problem/scientific question. Doing so captures and maps the dynamic of feedback mechanisms coming from different experimental contexts over time. The delineation is based on publication information and is computed at the publication level. Regarding patents, the analysis crosses author-inventors' names in order to measure to which extent problem-solving relies on insights from experiments. As mentioned in section 3.3.2, liposomes were initially used as research technologies and numerous properties about their behaviour were accumulated. This knowledge represents thereby interesting depositories of knowledge to adapt the function of liposomes. Moreover, clinical learning might have been as well necessary to overcome the radical uncertainty coming from misleading results in the lab. Distinguishing the relevant sources of knowledge helps to see how replicability enlarged the scope of the knowledge base and influenced the type of knowledge recombination over time.

The sample is bounded to the USA, e.g. US granted patents, and publications with at least one author affiliated to the USA. The choice to focus on one country is mainly justified by the importance of national institutions within the health sector (Consoli *et al.*, 2009). The USA represents the largest market for medical innovation and the biggest player worldwide of cancer R&D efforts[11]. Finally, focusing on granted patents only help focusing on the most significant technological milestones over time.

4.2.1 Delineating the context of experimental knowledge

Scientific publications constitute the main channel of communication for scientists and physicians to share their respective experience and advances. PubMed and Web Of Science are combined to maximize the amount of information between both data sources. Publications that only deal with liposomes research efforts in cancer were considered. To do so, publications were selected from PubMed based on Medical Subject Headings (MeSH) which bound the sample to the use of liposomes in the field of cancer (see appendix)[12]. The related set of PubMed-Indexed for MEDLINE (PMID) was used to collect the citations and full affiliations information from the Web of Science[13]. Cited references were extracted based on their DOI information and used to extract their related PMID on PubMed and Web of Science. Doing so allows to differentiate the context of knowledge production and citation over time[14].

To delineate the different empirical settings, the main MeSH terms and the publication types available on PubMed have been used. The publication types are used to define the more downstream conditions

[11]The National Cancer Institute represents the largest funder worldwide, see `https://www.cancer.gov/research/nci-role`

[12]Only one keyword ("Enhanced Permeability Retention") was not available within the MeSH classification and was added considering its importance within the developments of liposomal chemotherapy (Weinstein, 1987).

[13]The data was collected in November 2014

[14]Due to data limitations linked to the availability DOI/PMID in the 1970s, Figures 4 and 5 start in 1973 and not 1972

(in vivo preclinical testing and clinical settings) (see Table 4 in appendix). The more upstream settings (laboratory settings vs experiments in vitro) are distinguished based on the main MeSH. In this case, the publication type could not differentiate between the old and the new function of the technology. Therefore, a specific set of MeSH terms related to their initial purpose in cell modelling was used (see Table 4 in appendix for more details). Publications that did not fit any criteria are defined as part of upstream science, or non-experimental knowledge. This assumption implies that research efforts which are less oriented towards testing specific liposomes properties do not belong to any "testing regimes" (Yaqub & Nightingale, 2012).

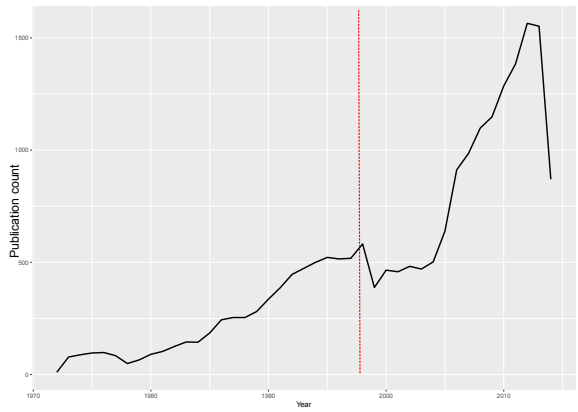


Figure 2: Quantity of publications over time (non-experimental knowledge)

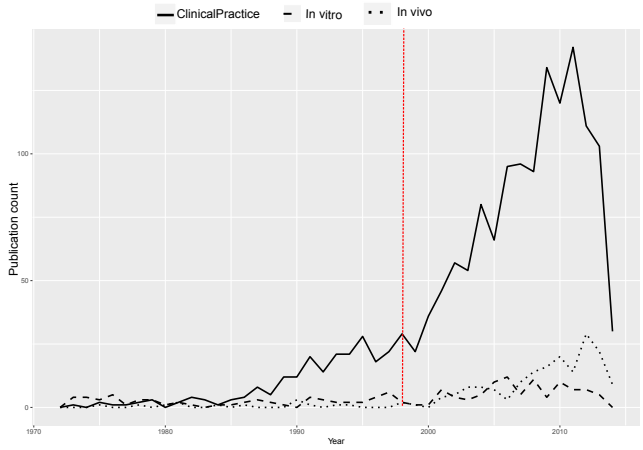


Figure 3: Quantity of publications over time (experimental knowledge)

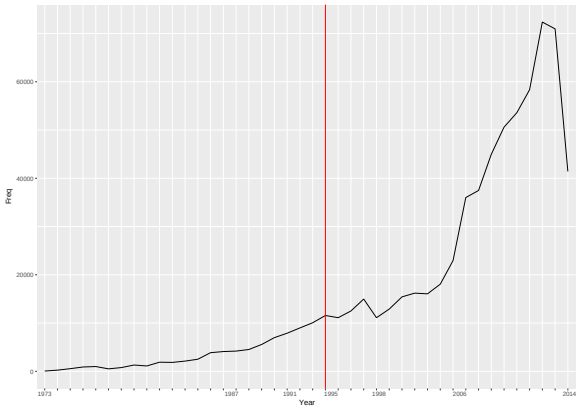


Figure 4: Number of citations over time (non-experimental knowledge)

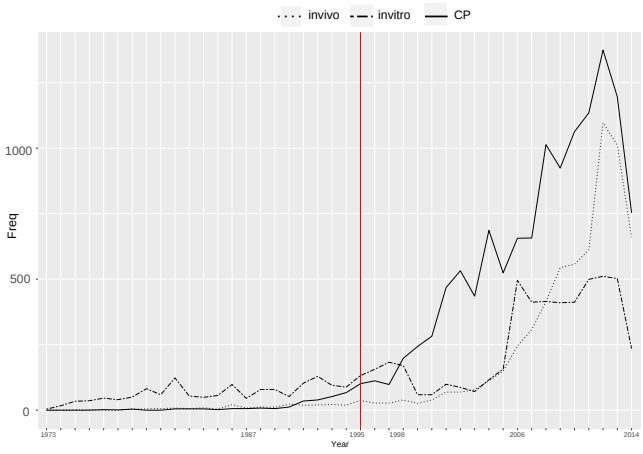


Figure 5: Number of citations over time (experimental knowledge)

The sample is composed of 22683 publications which covers the period from 1972 to 2014. With their respective references, the network is formed by 500864 nodes and 1030630 arcs connecting them. Figures 2 and 3 display the growth of publications according to the context in which knowledge has been generated (in vitro, in vivo, clinical or laboratory settings without specific experimental orientation). Figures 4 and 5 describe the number of citations belonging to different experimental settings (laboratory settings without applied purposes vs experimental testing). References to publications without specific and applied liposomes purposes dominates the citation dynamics over time, limiting the use of share of citations to characterize the citation patterns. The first period, from 1972 until

the 1980s, is marked by producing and using knowledge mainly generated upstream or in vitro. This fits with the initial purpose of liposomes as membrane models. The second period (1980s until 1997) shows that the production of knowledge increases across all settings but the use of knowledge seems to be concentrated rather upstream (non-experimental and simplified testing contexts, in vitro and in vivo). A break emerges around 1997: the production and use of non-experimental knowledge decreases substantially before increasing again in 1998. Moreover, the use of experimental knowledge seems to play a role right after the market approval in 1995. This changing dynamics illustrates the concept of the *post-implementation* period (Gelijns *et al.*, 1998): the extended use of the technology in clinical settings stimulates the need for new scientific explanations about unexpected phenomenon and additional improvements of the existing technology. In this study, the observation in 1998 that liposomes did not cluster around cancerous cells after the first accelerated market approval in 1995 required new scientific understanding, explanations, and new improvements about this phenomenon (see the next section for more details). The different trends suggest that citation counts might be misleading to understand the impact of replicability on innovation efforts and that more qualitative insights are needed.

4.2.2 Delineating the sources of technological developments

Liposomes are defined by their chemical formulation which makes patents a relevant mean of knowledge appropriation (Pavitt, 1984), and an useful measure to understand the evolution of problem-solving over time. Patents have been extracted if their main, or one of their secondary, technological class(es) refers to 424/450[15]. This technological class refers to the physical definition of liposomes (lipid bilayers) related to pharmaceutical preparations. The use of patents coming from secondary classes is necessary to take into account the migration of technological capabilities within the medical arena (see Rosenberg, 1992; Spetz, 1995; Rosenberg & Gelijns, 1995). Two different sources of patent data are crossed to increase the amount of information: the NBER database[16] was used to obtain the patent assignees and the Harvard Dataverse database[17] (Lai *et al.*, 2015) is used to retrieve the patent sample, the respective patent prior art, and the standardized inventors' names. 2397 patents form the sample, covering the period 1975 to 2006. The patent network is composed of the set of selected patents and their respective references (10440 nodes in total) and is connected by 30798 arcs. The quantity of patents increases slowly over time until it shows a peak in 1998; 3 years after the first accelerated market approval in the USA. The decline of granted patents that occurred in the 2000s is linked to a boom of spin-off technologies (Mozafari & Khosravi-Darani, 2007). The latter changed the definition of liposomes as lipid bilayers and their belonging to the 424/450 class. 1063 patents belong to the primary class defining liposomes as carriers of pharmaceutical preparations while 1334 patents refer to the latter as one of the secondary classes. Table 1 summarizes the distribution of the primary technological class for the patents which refer to liposomes as a secondary class. Overall, these patents cover 42 primary classes at the 1-digit level[18]. As expected, the majority of the applications that involve liposomes is on average about health care. However, the scope of the technological classes underlines the generic aspect of the technology.

[15]Only granted patents are considered to focus on relevant patterns of citations. Some noise could emerge from the analysis if some "weak" patents were cited for other reasons (e.g. increasing the value of a firm's portfolio)

[16]available online `https://sites.google.com/site/patentdataproject/Home/downloads`

[17]available online `https://dataverse.harvard.edu/dataset.xhtml?persistentId=hdl:1902.1/15705`

[18]The table reports only the classes which represents more than 1% in the sample.

Table 1: Distribution of the primary classes for patents using 424/450 as a secondary class

Definition	Class	Share
Drug, bio-affecting and body treating compositions	424	53.09%
Material or article handing	414	21.51%
Chemistry: molecular biology and microbiology	435	7.22%
Plastic and nonmetallic article shaping or treating: processes	264	4.74%
Chemistry natural resins or derivatives; peptides or proteins; lignins or reaction products thereof	530	2.84%
Stock material or miscellaneous articles	428	2.04%
Organic compounds	536	1.02%

The multi-purpose aspect of liposomes to carry various substances has been exploited across a wide range of applications beyond medical ones (i.e. cosmetics, analysis, dietetics). Table 2 indicates the share of patent ownership within the sample[19]. It provides some insights about the leading role played by firms and US research institutes within the technological efforts. Besides, the importance of foreign firms is explained by the presence of many multi-national firms (Schering, Novartis, Fugi Photo, Bayer, L'Oreal) among patent assignees who exploited the multi-purpose aspect of liposomes[20]. US universities and institutes represent important patentees, in line with the initial purpose of liposomes applications. However, US hospitals and medical institutions represent a small patentee. To see whether pre-clinical and clinical learning played a role in solving technological problems, the next section goes at the author-inventor's level and applies the same publication delineation previously described. Doing so disentangles between two sources of economics of scope in solving technological problems: learning by experimenting (as research tools or medical technologies) and scientific investigations more upstream where testing their properties was not at the core of the investigation.

Table 2: Share of patent ownership (fractional count)

Assignee type	Share
US corporation	36.15%
Foreign corp. incl. state-owned	30.36%
US institute and university	17.24%
Individuals (US and foreign)	7.34%
Foreign institute and university	4.87%
US and US state government	1.80%
Foreign government	1.44%
US hospital/med inst	0.80%

4.2.3 Defining the relevant sources of learning to solve technological issues

Focusing on patent assignees, or technological classification, limits the capacity to explain which type(s) of knowledge were needed to solve technological problems. Inventors' names are therefore used to track related publications in the field of liposomal chemotherapy. The full set of information between Pubmed and the Harvard Dataverse was joined by crossing the first name, middle initial, and author-inventors' surname (see Azoulay *et al.*, 2009, for a similar approach). A time-window of

[19] 432 patents had a dedicated pdpass but did not refer to a specific assignee code within the NBER database. Crossing inventors and assignees' names, this set of patents turns out to be held by inventors is coded as individuals in Table 2

[20] Numerous Israelian start-ups played a leading role in providing technological capabilities to the first market approval related to liposomal cancer chemotherapy, see his review Barenholz (2012) about Doxil®

two years maximum before, or after, for a given pair of patent application(s) and publication(s) is used to take into account inventor mobility[21]. Three types of inventors are defined: inventors without related publications, author-inventors who published without specific experimental purposes linked to liposomes, author-inventors who published studies related to the use of liposomes as research technologies and/or medical technologies. 1022 distinct author-inventors patented from 1070 to 2005 and are related to 1405 different patents. The results being aggregrated at the patent level, 2954 publications could be linked to the patenting activities of author-inventors. Figure 6 shows that author-inventors' contributions follow a similar trend as the ones depicted by inventors without publications until the market approval: the intensity of inventive efforts from inventors without publications increases and decreases faster than their peers publishing. The match between Web of Science and PubMed does not allow to determine the complete set of affiliations for all author-inventors but suggests that author-inventors are rather belonging to public research institutes, who reacted less strongly to the market incentives created by the approval of Doxil. Even if the propensity to patent is similar, the growth of inventors follows the same dynamic as the one characterizing the patent applications. It also suggests that the author-inventors represented a small share of the inventors' population over time but contributed to almost 50% of the overall patenting efforts. Figure 7 reflects a similar trend among the two types of inventors who both faced a peak of inventing activity when the first accelerated market approval was launched.

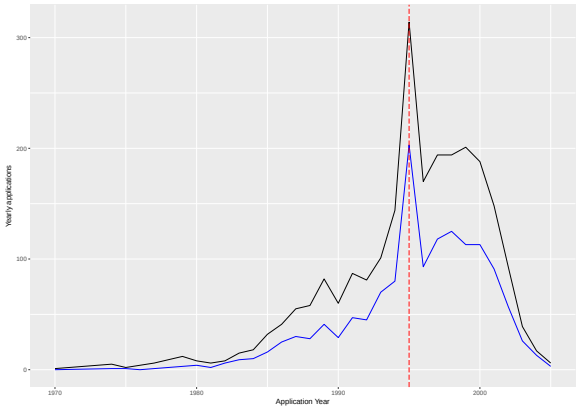


Figure 6: Patenting activity over time: overall sample vs author-inventors

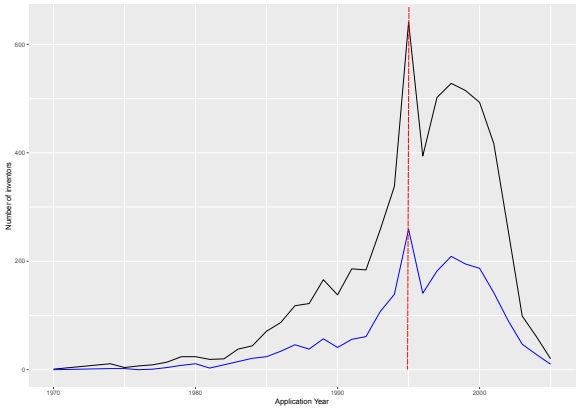


Figure 7: Inventors population over time: overall sample vs author-inventors

To ease the interpretation of the citation network and to take into account the unbalance between publications very upstream and more downstream (e.g. learning by experimenting), only these two categories have been considered. If multiple publications were found for a given team of inventors, the publication with the most complex setting - experimental ones - has been considered. By considering a hierarchy between learning by experimenting and scientific knowledge, the number of publications was reduced to 1790: 996 patents were linked to a scientific publication, 24 patents linked to a publication linked to learning by experimenting only, and 385 patents having a combination of both and were categorized as benefiting from learning by experimenting. After conducting the main subnetwork analysis, merging the list of the patents from the subnet network led to the following partition: 139 patents were not related to publications, 65 patents were associated to publications related without experimental purposes, and 22 patents could be linked to publications with experimental purposes.

[21]Having a time-window before or after the patent application allows to take into account different strategies to diffusing research results which might differ across actors and sectors

5 Results

The respective trajectories are composed of 249[22] patents and 173 publications. Figure 8b maps the main technological trajectories over time whereas Figure 8a displays the evolution of the fundamental understanding related to the use of liposomes as a medical technology. The key publications and patents composing the Main Path analysis are available in appendix. Both maps are organized in generations of research efforts: the first stream of research efforts lies at the bottom of the map whereas the latest developments are located at the top of the maps, the arrows pointing in the direction of the citation. The size of the nodes is defined according to their relative importance within the network [23].

5.1 Difficulties of R&D and recombination of knowledge

Figures 8a and b depict similar problem-solving based on the abstracts of patents and publications (see Table 3). Their overlap illustrates the economics of scope that existed between experimental learning (in laboratory, or clinical settings) and technological developments. The importance of economics of scope between technology and learning through experiment across different contexts of use is also underlined by the importance of author-inventors over time. Figure 8a depicts a sequence occurring within the sources of feedbacks mechanisms (i.e. pre-clinical, clinical, and laboratory settings). Figure 8b reflects a similar dynamic but seems less neat than Figure 8. On the one hand, clinical learning plays an important role in solving problems where other complementary medical technologies are involved (see subsection 5.2.2), and on the other hand, the role of experimental learning is probably underestimated at the beginning of the period due to data limitations[24]. The evolution of technological knowledge relies on two distinct trends: on the one hand, pharmaceutical developments which take their root in chemical related knowledge, and on the other hand, medical applications unrelated to chemotherapy (i.e. vaccines, immunoassays, and diagnostic tools). The links with non-pharmaceutical applications eased to solve different numerous technological bottlenecks (resistant formulation, improved encapsulation methods) in the context of anticancer chemotherapy. The integration of technological knowledge coming from other medical applications helped to accumulate knowledge about liposomes behaviour in more complex settings (i.e. animal models and human body).

[22] 12 patents have been removed from the map because they formed dyads of patents disconnected from the main trajectories, limiting their interpretations in the network

[23] The algorithm sums the different line values linking a given node to the rest of the network but does not reflect the number of citations received by a patent

[24] Some data limitations can explain these differences at the beginning of the analysis NBER and Dataverse start in 1975 and their respective citations go back to the 1950s. Without having standardized inventors' names, the probability of finding them within the publication sample was even more reduced. The latter are responsible for underestimating the role of science and experimental learning on solving technological problems at the beginning of the period.

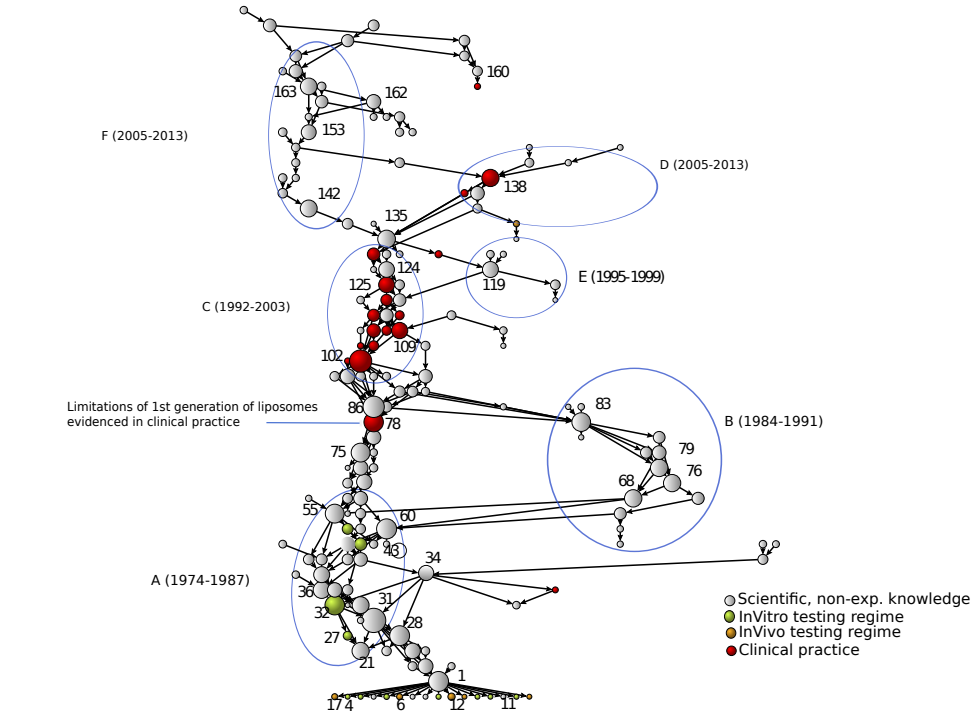
Table 3: Main sequence of problem-solving

Cluster	Description
A	Accumulation of knowledge in vitro and in vivo
B	Polymer
C	Clinical trials (design 2)
D	New uses of design 2
E	Immunoliposomes (active targeting)
F	New designs, therapeutics and/or diagnostics

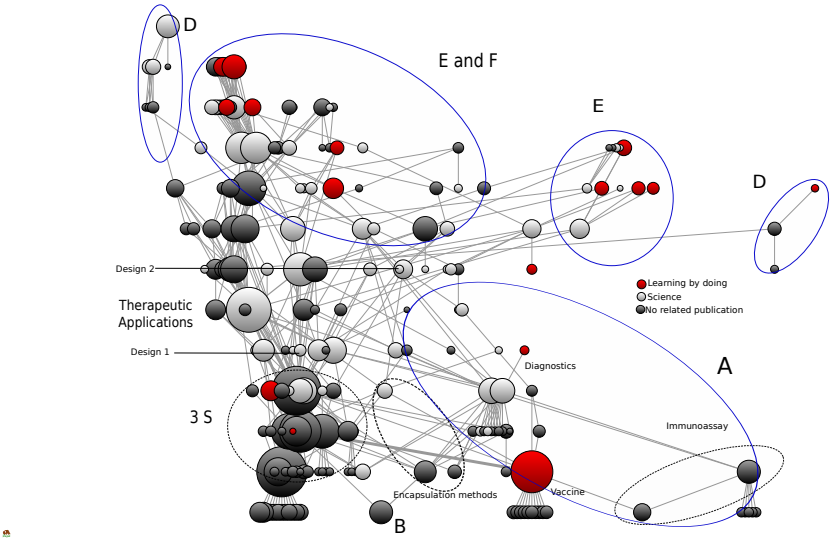
5.1.1 Exploration phase: establishing the feasibility of the solution

Liposomes were first used as a tool and did not require a strong stability to achieve this type of purposes. Their initial function was to mimick cell membrane and played the role of scientific models (see node 4 and 6 on Figure 8a). Establishing liposomes as cell membranes led to numerous empirical investigations across disciplines (biology, physics, and chemistry). The role of liposomes as a research tool was extended by a second type of scientific applications, e.g. carriers to detect substances (see the immunoassays cluster on Figure 8b). The latter was not impeded by issues related to stability and benefited from the knowledge linked to loading methods accumulated during the first medical application of liposomes (represented by the application in vaccine on Figure 8b and described in section 3.3.2). By remaining a research tool, liposomes stayed at the core of experiments to detect the presence of various chemical and biological compounds (see for a review Gómez-Hens & Manuel Fernández-Romero, 2005). This increasing burst of applications linked to the detection of substances in laboratory settings laid the foundations for applications as diagnostic tools. By being introduced as diagnostic tools, knowledge about liposomal behaviour coming from in vivo and clinical conditions was also accumulated and new properties could be checked in more complex settings. In this context, the use of liposomes as protein carriers laid the groundwork for the concept of cancer "passive targeting" (Matsumura & Maeda, 1986). The in vivo observations that liposomes were clustering around the tumour cells rationalized the use of liposomes for cancer chemotherapy and stepped up the research efforts (Weinstein, 1987; Allen & Cullis, 2013). Matsumura & Maeda (1986) coined the term of "Enhanced Permeability Retention" to describe the agglomeration of liposomes at the tumour site.

Even if the potential of liposomes was established, the lack of replication represented a huge burden for the liposome community by limiting the explanatory power of experiments as if it was "impossible to make definitive experiments" (Weinstein, 1987, p.290). Differences in animal models represented another source of variation responsible for making the experiments linked to the design of liposomal chemotherapy as "to some extent heterogeneous and irreproducible" (Weinstein, 1987, p.290). The limited capacity to replicate experiments impeded the identification of the underpinning scientific phenomena explaining why some formulations succeeded, or failed. The variability of results was also exacerbated by the numerous communities involved in solving technological bottlenecks, who used distinct approaches and apparatus. Science could not guide innovation efforts but the bodies of practice learnt in experiments represented a source of insights to solve technological bottlenecks. The issue of replication is also represented in the cluster 3S on Figure 8b in which numerous competing formulations developed by author-inventors in upstream settings co-evolve. This trajectory required insights from more complex settings and benefited from a better understanding of liposomes behaviour from the areas of diagnostics (see the cluster of encapsulation methods on Figure 8b). The development



(a) Evolution of the liposomes' behaviour in chemotherapeutic applications



(b) Main technological trajectories liposomal chemotherapy

Figure 8: Knowledge dynamics over the innovation process

of improved encapsulation methods in the field of diagnostics allowed to incorporate drugs in liposomal formulations which showed being resistant enough to be used in vivo. However, the commercial potential needed to be demonstrated in order to achieve a market approval.

5.1.2 Development phase: Recombining knowledge from the liposomes initial career

Despite the in vivo demonstration that liposomes could become a chemotherapeutic tool, commercial objectives also needed to be fulfilled especially regarding the reduction of the production costs. The search process has been concentrated around 3 main problems: stability, sterility, and scaling-up methods (see the related cluster on Figure 8). First, a formulation known as "conventional liposomes" emerged which was the result of combining knowledge from in vivo experiments with early insights from in vitro research, suggesting that cholesterol was fostering liposomes resistance (see Design 1 on Figure 8b and cluster A on Figure 8a). The first design adapted to chemotherapy relied on using of cholesterol, like an "operational principle" coming from the first career of liposomes (Vincenti, 1997). This explains why author-inventors more upstream in research settings played a leading role in adapting this principle observed in pre-clinical experiments. Adapting observations from experiments accumulated during the first career of liposomes but also bodies of practice constituted ways to solve technological issues to cope with the replication issues. By considering liposomes as "subjects of experimentation", underpinning properties related to their behaviour in simplified conditions led to accumulate bodies of practice (Nelson, 2008). A small "latent stock of knowledge" remained embodied into the individuals who performed the experiment (Agrawal, 2006). More precisely, the experimental design, protocols, and methodologies involved in liposomes experiments constituted a source of inspiration for potential solutions. For example, some methods used to split liposomes in microbiology to break cells with a French Press were then adapted to solve industrial problems (Wagner & Vorauer-Uhl, 2011). After solving the main technological bottlenecks(see the 3S cluster on Figure 8b), the efforts related to therapeutic purposes intensified and led to different trajectories.

In parallel to this new trend in building pharmaceutical formulations, the diagnostics trajectory led to numerous applications in order to use liposomes to target specific cell markers. As mentioned above, the lively interest across distinct scientific communities related to liposomes as a research tool generated basic knowledge across a wide scope of scientific areas: pH gradients, immunology, and cell behaviour (Weinstein, 1987). In this context, the idea of binding liposomes to target specific cell markers emerged from their use as diagnostic tools. Doing so, new methods of production and designs were developed by inventors acting rather upstream in the lab who benefited from scientific insights linked to the use of liposomes as research tools. The next section shows the importance of clinical learning in redirecting the efforts in more promising scientific and technological areas.

5.2 The regulator-user interface

In the context of vaccines, Yaqub (2017b,a) underline the importance of learning in clinical settings to determine which technological features work in "real" conditions, eliminating the noise coming from the simplification made in the laboratory settings. Clinical learning plays hence a crucial role in re-directing scientific and technological searches. The next sections extend what is suggested in Yaqub (2017a) by illustrating that clinical trials constitute an opportunity to accumulate knowledge beyond the selection of technological designs. The *difficulties* characterizing the R&D efforts in the lab previously mentioned were responsible for creating a *weak design*, like in the case of vaccines

(see Yaqub, 2017b). However, observations from clinical trials helped to overcome this weakness by providing a scientific explanation to this failure. The technological answer to cope with the latter came from the basic knowledge generated when liposomes were used as a research technology. As suggested in Yaqub (2017b), the characteristics of the testing activities and their related *difficulties* influence the type of design developed. The results show that *difficulties* characterizing R&D activities tend to expand the scope of the knowledge base to non-medical areas but also rely on inisghts from existing complementary medical technologies to innovate.

5.2.1 Assessment stage in clinical trials and expansion of the knowledge base

After positive results in preclinical testing, conventional liposomes entered in clinical trials in 1987 to provide a new type of chemotherapy against cancer. Reaching clinical settings, conventional liposomes exhibited a limited therapeutic efficiency in terms of stability and targeting power. As a consequence, research efforts shifted in a competing direction and created the need for scientific explanations about this unexpected failure (Barenholz, 2012). Considering the uncertainty about the behaviour of liposomes in human bodies, the medical researchers involved in clinical trials decided to observe in real-settings which design was the most appropriate by injecting a competing formulation used as a control group: the Stealth liposomes. Stealth liposomes were the result of new advances in the field of new polymers (PEG) in the late 1980s and were combining interesting properties for drug delivery (see clusters B on Figure 8). The lack of consensus in the community due to contrasting results observed in animal models could not lead the selection of an appropriate design. Clinical learning removed this uncertainty by providing insights about the potential factors responsible for the lack of conventional liposomes stability.

Figure 8a illustrates the re-orientation of search in a new direction thanks to a better understanding of the clearance mechanism associated to the conventional design coming from clinical learning (see node 81 on Figure 8a). This finding was then checked in the lab: covering the liposome surface with PEG makes them "invisible" in the blood circulation, avoiding their clearance (see node 83 on Figure 8a). The hybridization of knowledge from the field polymers with the ongoing liposome knowledge base (see the distinct trajectory linked to polymers on Figure 8b and cluster B on Figure 8a) marked a turning point in adapting liposomes to chemotherapy. This new formulation known as Stealth liposomes pushed the efforts in a new direction and led to the first market approval.

5.2.2 Feedback stage: new scientific questions and specialization of designs

Stealth liposomes were used to achieve the first accelerated market approval - Doxil® - which aims at fighting against an orphan form of cancer (see cluster C on Figure 8a). After its market approval, several observations from clinical practice showed that stealth liposomes tend to cluster around the tumour cell without merging with it (see cluster E on Figure 8a). This observation relaunched a fierce debate about the conception of liposomal chemotherapy, opposing the advocates for passive vs active targeting. In absence of scientific knowledge to rationalize the type of design to favor, both approaches co-evolve and are illustrated through different specialized designs. Regarding passive targeting approaches, new formulations of liposomes chemotherapy are developed: either with new compounds in anticancer chemotherapy, or expanding the use of existing formulations to other diseases areas (see clusters D on Figure 8a and 8b). The underpinning problems to solve in this approach rely on different combinations of knowledge, more clinical oriented for new uses beyond chemotherapy while

new anticancer compounds seem to benefit from scientific insights without applied experimental orientation. In terms of active targeting, different designs emerge which aim at concentrating the action of liposomes to tumour cells (see clusters E and E-F). They can be categorized in two main categories through "immunoliposomes"[25] and liposomes with controlled released features. As mentioned in section 5.1.2, basic knowledge generated during the first career of liposomes (here, realm of ligand and antibodies applied in tumourous cells markers (Weinstein, 1987)) provided the building blocks to create active targeting liposomes. The second type of design with controlled release features rely on different strategies (e.g. breaking the liposomes membranes with ultrasounds, or temperature shocks), related to basic knowledge accumulated when liposomes were used as a research technology (i.e. pH, gradients, temperature properties)[26]. In both designs, these bodies of basic knowledge generated when liposomes were still cell models were used as "background knowledge" (Pavitt, 1998) to guide the search via new combinations of these existing bodies of knowledge. This specialization pattern echoes the results found in the case of stents, in which complementary technologies played a leading role in influencing the rate and direction of new specialized medical applications (Mina *et al.*, 2007). Besides new drugs, several diagnostic tools (e.g. Magnetic Resonance Imagining, Computer Tomography) shaped the influence of new uses combining therapeutic and diagnostics properties (see cluster E-F on Figure 8b). The merger of the pharmaceutical and diagnostic trajectories echoes another study (Barberá-Tomás & Consoli, 2012) in which combining technological features was the main answer to cope with radical uncertainty.

6 Discussion

The previous sections show the importance of clinical learning and of the initial bodies of knowledge accumulated during the first career of liposomes as research technologies. The results shows that these distant bodies of knowledge sequentially helped overcoming the issues linked to replication in the lab in order to innovate. In this respect, Blume (2002) underlines the crucial role played by the *interorganizational structure* (e.g. academia, industry, and medical practitioners) in order to ensure the provision of complementary resources and skills to innovate. However, the collaboration within this interorganizational structure can also be hampered by: disagreements about a specific purpose, the divergence, or conflicting needs between this set of heterogenenous actors. Blume (2002) talks about a medical technology having a "non-conformist career", in which the intensity of knowledge flows is reduced due to the divergence among medical actors about the "vision" related to a given medical technology. As a consequence, the feedback mechanisms between science, technology, and clinical learning slow down. This lack of dynamic is responsible for fragmenting knowledge and reducing the chance to innovate. In line with Blume (2002), different studies have illustrated the importance of institutions in standardizing and in coordinating the testing efforts to avoid the fragmentation of knowledge across different actors (Yaqub & Nightingale, 2012; Yaqub, 2017b,a). By creating *research infrastructure* (Nightingale, 1998), specific institutions ease the accumulation of knowledge and the alignment of visions across a wide range of actors. However, in this study, no centralized institution emerged in order to coordinate the efforts across disciplines and organizations. To explain this peculiarity, the next sections shed light on the factors which explain why clinical feedback have been fostered and how federal regulation influenced the standardization of testing activities.

[25] Liposomes coated with ligands or antibodies.

[26] See Barenholz (2012) for more details, or the following patent application for an illustration US5192549A

6.1 Acceptance and demand for an alternative treatment

The changing career of liposomes was also explained by the wide acceptance received from medical practitioners. The delivery of liposomal chemotherapy did not modify the clinical routine used (injection) and the existing standard to evaluate the treatment success (e.g. tumour shrinkage). By following the same clinical routine, the introduction of liposomal chemotherapy did not put in doubt the role of oncologists in treating cancer. Innovation did not legitmize another rival medical specialty in treating cancer which could have been a barrier of adoption (Gelijns & Rosenberg, 1995). By proposing a medical solution with quality-enhancing properties, innovation has thus a "status-enhancing" power within the oncologist community (Geljins & Rosenberg, 1999).

The acceptance of the solution among practitioners helped to foster the feedback coming from the clinical context to the lab. The initial ties with clinical practitioners in the 1970s, combined with the first clinical success participated in sustaining a demand for chemotherapeutic approaches focused on reducing side-effects. The alignment of "visions" from the lab to the benchside influenced the rate and the direction of efforts by creating a demand for invention. Since technological users were also tightly connected with technological producers, aligning visions among a wide range of scientists and medical practitioners created an *interorganizational structure* to foster feedback across different settings. While research efforts in the lab were impossible to perfectly replicate, the efforts more downstream were to some extent standardized due to the specific guidelines that follow anticancer drug development. The variability of the results remains but the rules of anticancer drugs development ease the entry of liposomes in clinical settings.

6.2 Standardizing efforts: testing and proof of concept

Drug development is an expensive process due to the intensive period of testing activity in preclinical and clinical settings. The types of tests involved are heavily regulated by national agencies, such as the Food Drug Administration in the USA. Anticancer drug development is particularly concerned by these proofs of concept due to the nature of the compounds involved. As mentioned earlier, using chemical compounds to kill cancerous cells implies a trade-off between therapeutic benefits (e.g. tumour shrinkage) and the toxicity issues linked to this type of molecule. The risk-benefits balance is measured by specific guidelines and evaluated along a sequence of testing from the most simplified conditions to the more complex ones (i.e. cells, rodents, dogs, and humans). The inputs and protocols to conduct such testing activities are highly regulated and standardized (Narang & Desai, 2009). Despite the absence of an institution to govern and to standardize the testing activities, the regulation framework provided the rules to standardize experiments at a later stage of medical application developments and eased the entry of liposomes in clinical trials. Doing so helped in selecting the most promising technological avenues and participated in deepening the scientific mechanisms explaining the behaviour of some designs.

Liposomal formulations did not lead to additional complex testing guidelines, except the emergence of a test in vitro to demonstrate their therapeutic benefits (Narang & Desai, 2009). Moreover, most of the formulations relied on drugs which were already well-known (cytotoxic compounds) which reduced the development costs by being off-patents and requiring less extensive testing than new compounds (Narang & Desai, 2009). Finally, the decision to conduct clinical trials in the context of orphan disease was also responsible for reducing the cost of development (e.g. lower amount of patients involved in

clinical trials, subsidy from the State to partially cover the cost of development). The latter established the feasibility of the solution as a new way to deliver chemotherapy. Even if clinical knowledge could be accumulated, a dialogue must be established across heterogeneous actors to be able to combine knowledge to innovate. The next section provides some insights about how the feedback mechanisms have been chanelled across disciplines and settings.

6.3 Fostering feedback across settings via an instrumental community

The use of liposomes as a research technology has been a driving force to combine insights from various scientific disciplines. Even if the scientific questions raised across fields differed, the shared use of liposomes as research technologies acted as a *medium* for communicating across fields (Shinn & Lamy, 2006). The research efforts were organized around a technique linked to the use of liposomes and not in a disciplinary fashion. By experimenting with the same research technology, the members of the instrumental community built, developed, and popularized the latter among a wide range of scientific disciplines (Mody, 2011). Breaking down the disciplinary and/or institutional boundaries has been described as the hallmark of medical innovation (Gelijns & Rosenberg, 1995). Rosenberg (1992) and Rosenberg (2009) suggest that scientific instruments can play a leading role in overcoming disciplinary boundaries. Scientific instruments represent carriers to transfer know-hows across scientific fields (deSolla Price, 1984; Rosenberg, 2009): on the one hand, by adopting a new instrument, a given researcher must acquire a new set of practices and skills linked to its use. On the other hand, learning by using in experiments generates reliable knowledge about how does a given instrument, or research technology, work under certain simplified conditions (Nelson, 2008). Instruments are good subjects for experimentation because they are in theory "amenable to control, and replication" (see Nelson, 2008, :495).

Moreover, the involvement of the founding fathers of the field in establishing the career of liposomes as a medical technology helped coping with numerous technological failures (see Blume (2002) for a similar discussion). Since the research community was structured around them, they constituted a sort of "hub of knowledge" at crossroads between numerous scientific fields, experimental, and institutional settings. They became *de facto* an important channel to diffuse the knowledge accumulated across different settings, fields, and communities all united by the use of the same technology. The founding fathers have played a leading role in organizing the research efforts and acted as boundaries spanners. As suggested in Blume (2002), the early orientation of the research efforts towards medical applications kept the research efforts focused in the same direction. The establishment of a dedicated research group in clinical settings in the 1970s has been determinant in initiating a dialogue between the bench and the bedside (Gregoriadis, 2018).

7 Conclusion

The study outlines the impact of the limited guidance from scientific research on the medical innovation process. The lack of replicability in experiments was responsible for creating a long process of trial and errors in different experimental settings to adapt the function of liposomes as a new way to deliver chemotherapy. In absence of guidance from science, the migration of technological capabilities from experimental research in which liposomes were used as a research tool and other medical applications were crucial. The lack of replication was responsible to maintain a strong degree of path-dependency with the bodies of knowledge accumulated for distinct uses. The study shows thereby that the characteristics of experimental research influence not only the design features of technologies (Yaqub, 2017a) but also the scope of the knowledge base. Like for medical devices, the knowledge base of pharmaceuticals can encompass non-medical areas and refinement of the technology be eased with complementary technologies (Mina *et al.*, 2007). The lack of replication was responsible to maintain a strong degree of path-dependency with the bodies of knowledge accumulated for distinct uses. The tacit stock of knowledge which remained embodied in researchers who performed experiments gave them a comparative advantage to adapt the function of liposomes. The knowledge accumulated in different experimental settings was chanelled through an instrumental community. The common purpose of developing liposomal chemotherapy and use of liposomes helped to cross disciplinary barriers. Considering the nature of the problem at hand (e.g. understanding the fundamental behaviour of liposomes in the body to deliver chemotherapy), one can expect that the majority of the patents with author-inventors benefited from academic inventors' expertise. As suggested in Rosenberg (1992, 2009) the role of academic research in diffusing and adapting the use of scientific instrumentation can be seen as a "social rate of return to society". The importance of academia as innovator is currently underestimated in the literature and focuses mainly on complementarity with the private sector Arora & Gambardella (1995).

The study contributes to the increasing burst of medical innovation literature which highlights the importance of experimental learning to innovate (see Yaqub & Nightingale, 2012; Consoli *et al.*, 2016; Yaqub, 2017a,b). Despite the absence of dedicated institutions in governing the testing activities, the study illustrates the importance of the federal regulation in easing the access to clinical learning and the role of the founding fathers in coordinating efforts. The study provides new measures to differentiate between the different contexts in which knowledge was accumulated (i.e. upstream in the lab, preclinical, and clinical settings). Doing so, the study suggests that science, technology, and clinical learning played a leading role but in a sequential fashion rather than through continuous feedback (Gelijns & Rosenberg, 1994). It extends what was suggested in the case of vaccines in Yaqub (2017a) by showing that clinical trials are more than a selection tool. Clinical trials represent a source of scientific and technological answers which in this case, expanded the scope of the knowledge base to cope with the lack scientific guidance. Despite its novelty, the methodology suffers from several caveats. The definition of the "in vitro" testing regime is based on the specific definition of liposomes. Additional efforts will be needed to adapt the delineation of publications to other medical technologies. Moreover, the availability of the patent data underestimated the importance of economics of scope between experimentation and technologies in the first years of the analysis. The scope of the results is also by definition limited to the selected case. However, the study suggests some implications regarding the organization of the medical R&D. The study illustrates the importance of a shared "collective

vision" in *crystallizing* expectations (Blume, 1995), but also to mobilize efforts and resources across the large range of actors involved over the medical innovation process. More attention should be dedicated to the training of bio-scientists and physicians to ensure a dialogue between the bench and the bedside. Policy initiatives to align actors' visions and practices should be favoured to increase the chances to innovate (see the NIH support in the case of LVAD development in Morlacchi & Nelson, 2011). Scientific funding needs also to evolve to take into account the validity of the research results and not only the capacity to launch scientific papers. Some steps in this direction have been done in the context of cancer with replication grants and a dedicated initiative (e.g. Reproducibility Project: Cancer Biology). Doing so would shift the debate from funding science due to market failures to building skills in order to tackle complex technological problems (Pavitt, 1991).

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Appendix

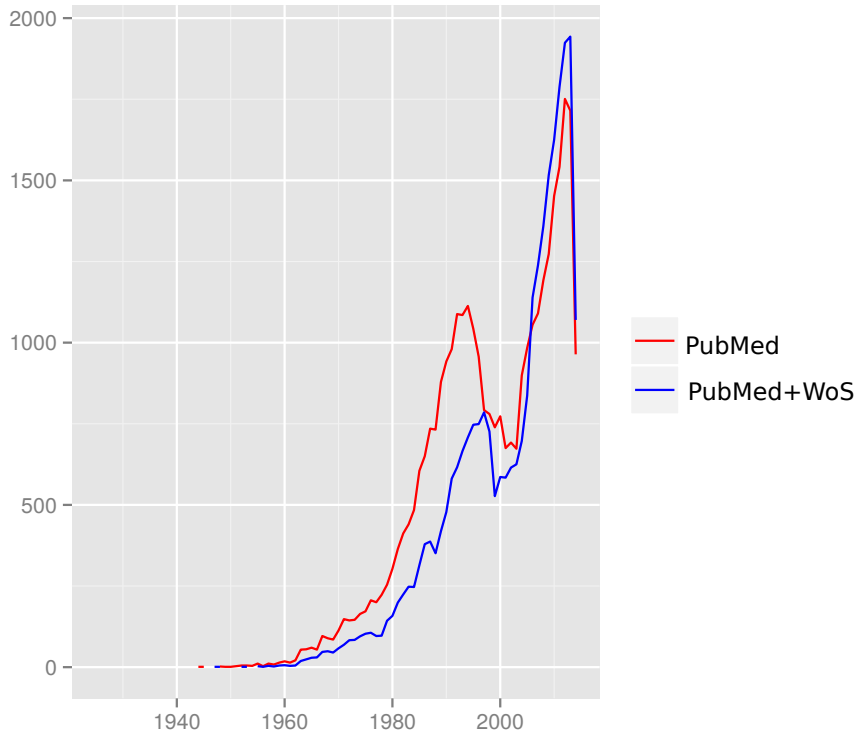
Sampling Publications: combining PubMed and Web of Science

The following keywords has been to used to delineate the set of publications related to investigations linked to the use of liposomes in cancer-related applications:
("Liposomes"[MeSH] OR "Liposomes"[Pharmacological Action] OR
"Phospholipids"[Mesh] OR "SPI-77,liposomal"[Supplementary Concept])

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] OR "enhanced permeability retention" [all fields])
The list of PMID fitting this criteria has been downloaded on PubMed and used in Web of Science to maximize the information related to these publications. However, the journal coverage is not perfect over time which implies some lack of information (e.g. references, affiliations, journal informations) in the 1980s and the 1990s.

Figure 9: Overlap between PubMed and Web of Science over time



Partitioning between scientific knowledge

The different types of knowledge involved have been distinguished based on the type of conditions under which studies were conducted: in vitro, in vivo or clinical settings. The limited number of in vitro studies justified the use of additional Medical Subject Headings (MeSH) linked to the initial use of liposomes as research technologies. Both information is available on PubMed and has been added by NIH librarians specialized in biomedical literature. Contrary to the use of keywords by author, the MeSH and publication types on PubMed represent a more objective measure to characterize the contents of a given study. The publication types and Medical Subject Headings available on PubMed allows to disentangle between them:

Table 4: Delineation between knowledge accumulated in different medical R&D contexts

Testing Regimes	**MeSH, Publication types**
In vitro (green color)	Membranes, Artificial; Membrane Lipids; Cell Membrane; Membranes; Phospholipids; Lipid Bilayers (MeSH)
In vivo (yellow color)	mice, rats, dogs, primates (Publication type)
Clinical (red color)	clinical trials, phase I to randomized clinical trials, validation studies, cases report, evaluation studies, multicenter and observational studies (Publication type)

Publications which did not fit to this taxonomy were assumed to refer to non-experimental knowledge in which liposomes did not play a leading role as research technologies (in grey). In case of overlap between the different criteria, a hierarchy from the most complex to the most abstract papers was used to define the context in which knowledge is produced.

Table 5: List of key publications from the subnetwork

Nodes	Publication
1	Gregoriadis (1973)
4	Bangham (1968)
10	Bosmann (1971)
11	Gregoriadis & Ryman (1971)
12	Gregoriadis & Ryman (1972)
17	Gregoriadis & Buckland (1973)
21	Papahadjopoulos *et al.* (1974)
27	Papahadjopoulos *et al.* (1975)
31	Poste & Papahadjopoulos (1976)
32	Mayhew *et al.* (1976)
34	Gregoriadis *et al.* (1977)
36	Juliano & Stamp (1978)
43	Olson *et al.* (1979)
55	Yatvin (1982)
60	Weinstein & Leserman (1984)
68	Kabalka *et al.* (1987)
75	Gabizon *et al.* (1989)
76	Holmberg *et al.* (1989)
78	Goren *et al.* (1990)
79	Klibanov *et al.* (1990)
81	Gabizon *et al.* (1991)
83	Lasic *et al.* (1991)
86	Vaage *et al.* (1992)
102	Uziely *et al.* (1995)
109	Muggia *et al.* (1997)
119	Drummond *et al.* (1999)
124	Gabizon (2001b)
125	Gabizon (2001a)
135	Gabizon *et al.* (2003)
138	Alberts *et al.* (2004)
142	Torchilin (2005)
153	Drummond *et al.* (2008)
160	Deckers & Moonen (2010)
162	Lindner & Hossann (2010)
163	Hossann *et al.* (2010)

Table 6: List of patents from the subnetwork

Layers of efforts	**US Patent Number**
1	6096336
2	5817334 5827533 5874105 5882679 5935553 5985246 5997898 6001335 6033645 6071495 6117414
3	5628936 5643600 5662957 5705187 5770222 5776429 5804162 5804216 5814599 5830430 5846551 5853752 5874062 5962015 6039960 6040295 6056938 6120751
4	5364633 5376380 5376452 5405615 5415869 5439967 544384 5445813 5474848 5542935 5580575 5585112 5620689 5686102 6004534 6015576 6117449
5	5165994 5190822 5209720 5213804 5219538 5234767 5252263 5260065 5264221 5271928 5316771 5334381 5380519 5422120 5527528 5534241 5552155 5576016 5762904
6	4863739 4917951 4942038 5000960 5013556 5019392 5032457 5059421 5077056 5088499 5104736 5123414 5188837 5192549 5204112
7	4725442 4737323 4753788 4837028 4839111 4853228 4855090 4873088 4877561 4880635 4885172 4898735 4906477 4911928 4921706 4946683 4963363
8	4425334 4429008 4610868 4622219 4673567 4708861 4769250 4938947 5283067
9	4460560 4544545 4603044 4619794 4721612 4731210 4761288 4762720 4776991 4781871 4789633 4880634 4920016 5100662 5160669 5198224 5891465 5910306 5948435 6015575 6017556 6042846 6083513 6120794
10	4310505 4310506 4356167 4394448 4438052 4460577 4485054 4515736 4522803 4529561 4588578 4608211 4744989 4772471 4915951 5019174 5141751 5490985 5605704 5733572 5736157 5855911 5885613 5919466
11	4145410 4148876 4217344 4224179 4229360 4235871 4241046 4247411 4308166 4377567 4532089 5328628 4186183 3993754 3683066 3663685 3522346 3663687 4086330 4115536 3663686
12	4016100 4053585 4089801 4193983 3069370 3607776 3692899 3686701 3041289 2949403 2853423 3630920 3932657 1959930 3361680 3549382 2658020 3060030 3012888 3804776 3937668 3173878
13	3335053 2756178 3590123 3697644 3471624 3533955 3535427 3660566 3835169 3056728 3780195 3579633 3752886 3755557 3492399 3594476 3376199 3608066 3384544 3715432 3887698 3317393 3336155 3849546 3882224 3949065 3996345 4104029

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