Synergy and complementarity of rules: the importance of public organizations in anticancer development

Florence Blandinieres [1]

[1] *F.SchillerUniversity, Jena*

Abstract

In this paper, we look at the emergence of a new practice in terms of delivering medications and how the different sources of knowledge have affected its technological developments. To do so, we develop an original approach by looking at the inventor level to take into account the culture of academic entrepreunership in the US. We depict the technological developments in terms of type of applications by looking at the patent abstracts and extend them with a historical perspective thanks to scientific review. Based on this technological evolution, we look at how these technological developments have influenced the current search routine in anticancer drug development through the lens of the Sarewitz-Nelson rules and evaluate how rules from different search routines interact with each other. We show the emergence of a new regime, as a sort of hybrid result between the two search routines.

1 Introduction

Recently, most of Western countries face an increasing life expectancy that creates new social issues linked to a more numerous ageing population. In the USA, the average life expectancy has gone from 45 years old to 77 years old over one century ([40]). However, living older does not necessarily mean living better. Health and disease preventions are the main challenges that the "Silver economy" seeks to take up. Actually, health expenditures put in doubt the sustainability of health care system, especially in recession period.

The increasing amount of ageing population is attracting attention on several disease areas linked to this age group such as diabetes, neuro-degenerative diseases or cancer. Cancer represented the second leading cause of death for adult population is the USA in 2011 ([36]). Unfortunately, the disease remains misunderstood and uncured.The recent progress in fundamental cancer biology rejected the previous scientific paradigm about defining cancer as an' 'infectious" disease or a threat gangrening her host ([26]), to get a new definition. Previously, cancerous "sick" cells were assumed to be different from the normal ones as a result of "a fundamental derangement" ([26]) and needed to be eradicated before overwhelming the host. This vision depicts the "cell-kill" paradigm and justifying the use of chemotherapy as the main solution and cytotoxic drugs as the cornerstone of cancer treatment (Faguet, 2005). This new scientific knowledge increased the number of competing theories about the source(s) of carcinogenesis to form a limited and fragmented understanding about the transformation of cancerous cells ([26]; [26]), depriving the emergence of a scientific heuristic to guide the technological search. Despite the absence of a new scientific paradigm, cancer has been the testing ground for new therapies,

While previous studies have underlined the uneven nature of medical innovation (see [18, 55]), our investiagtion aims at understanding the current technological expansion in the cancer field and what drove this accumulation of know-how(s). Taking drug delivery systems as field of enquiry, we look at what makes some search routines more innovative than others and how drug delivery systems affected existing search routines in anticancer drug development. To do so, we will analyze search routines by disentangling them through the Sarewitz-Nelson rules and by linking them to the organization of search. The paper is organized as follow, we will first present the main characteristics of medical innovation and the main components of the Sarewitz-Nelson rules. Citation network analysis has been used to get a historical vision of the different problem-solvings that face the field to analyze them through the Sarewitz-Nelson lens. Based on previous works ([56,64]) and historial data ([22,26]), we described the previous search routines in the same way and compare the interactions of rules between routines in the discussion part.

2 Theoretical framework

2.1 Characteristics of medical innovation

Medical innovation studies have underlined the lack of relevancy of "scientific-push " or "demand-pull " approaches to explain the innovation process and rather point out its non linearity ([29]) by being rather the result of three co-evolving pathways: a better understanding of the disease, technological capabilities linked to new modalities of medical diagnosis or treatment and its clinical implementation involving learning mechanisms ([15, 55]) . Previous studies have evidenced that clinical practice is probably the most important channel to develop new medical innovations, starting and ending the journey of medical progress ([16]). These three pathways interact strongly to create a paradigm in a Kuhnian fashion, defining what is appropriate in practice to deal with a disease, connected and in line with the body of understanding, and a set of problem-solving strategies and methods that can be used when the standard solution is not working ([55]). Medical innovation is thus the result of a creative synthesis coming from elements belonging to different contexts and combined in an unique way ([30]) and for these reasons, medical innovation can be defined as an evolutionary and learning process ([18, 31]): a medical innovation can change the perception of a problem, leading to a path-dependent exploration of an emergent design space ([18, 49]). Therefore, knowledge is accumulated in a sequential way: by challenging the previous set of understanding, innovation generates new knowledge which, in turns, implies the refinements and improvements of the new procedures, extending the scope of their applications ([18]). Previous studies have underlined the cumulative and the historical time dimensions of medical knowledge which is accumulated along trajectories ([16,49,50]). More so than any other sectors, knowledge appears as the driving force of medical innovation. This exacerbated role of knowledge and learning is explained

by the “penumbra” of uncertainty associated to the medical arena which is the result of several dimensions (see [6]): first, the complexity of human body and heterogeneity of human population limit the capacity of prediction of a new treatment or practice ([6, 30]), secondly, the limitations linked to the clinical testing procedures associated to clinical trials which mainly focus on narrow criteria to determine the safety and effectiveness ratio in order to get a market approval ([31]).

Innovation and diffusion are not defined in a Schumpeterian way ([18]) in the sense that, after the diffusion process on the market and implementation in clinical practice, a substantial phase of learning occurs to create a “post-innovation” process ([30]). Clinicians will define the degree of relevancy of the solutions according to their needs and influence the design of new artefacts ([62]) also due to specific abilities by solving specific problems that can be used by manufacturers (see [10, 62, 67]). After a certain time, clinical practice can also detect additional uses in terms of shortocomings or uses (off-label drugs for example, see [21]) or new areas of applications (see

2.2 Sarewitz- Nelson rules: ensuring technological progress

Looking at the unenven progress of human know-how, Sarewitz and Nelson (2008) define 3 main rules to delineate which problem can be technologically solved in an efficient way. The three rules depicts an ideal situation where online experimentation and replication are easy and enlightening, creating technical progress and inducing scientific advances. This increasing body of understanding sheds light on the way(s) to improve the current practice, implying a virtuous innovative circle. Actually, the first rule refers to the establishment of the cause-effect mechanism to solve the problem at hand. In this case, the technology relies on a “strong body of knowledge" ([56]) defining what and how the technology should do to solve this problem. Scientific evidences and understanding play thus a key role in the establishment of the first rule and enable to hold the cause-effect mechanism in any context. The second rule refer to the capacity of the technology to be applied in a wide range of conditions by relying on routinized core rule. This standardized core rule lies into a standard procedure, device, prototype, or substance that gives the possibility to search in one direction. Therefore, stronger is the body of understanding around the core, better and more numerous are the technological improvements. The last rule is associated to the definition of an “enlightening" testability rule that helps to distinguish between technological alternatives and guides the search towards the best one. The testability rule refers to an ambiguous, clear and stable criteria that prescribe how to improve and to be efficient in answering to the given problem, closed to the idea developed in [54]). The testability rules allows to apply the technology in different contexts and conditions and to compare the related outcome. Rather than providing a framework to ensure technological progress, Sarewitz and Nelson suggest a method to detect anomalies or disfunctions within the technological search responsible for hindering progress. In

this regard, we will pay a specific attention towards the degree of synergy within search routine and of complementarity between routines to explain the influence of liposome search routine in existing anticancer search routines.

3 Methodology

Drug delivery systems are considered as devices and pharmaceuticals, and patents appear as the main mean of appropriation (

3.1 Data sources

The selection of the sample has been made by considering relevant all granted patents which include the technological class 424/450 as the primary or one of the additional technological classes claimed in the patent. Contrary to other technological classes, this one refers explictly to the physical definition of the liposomes, disregarding their function. We extract patent data and their relevant citations from the Patent Network Dataverse available online on the Harvard Business School website. 2397 patents were extracted, covering the period 1975 to 2006; the number of patents increases slowly over time until knowing a first peak in 1995 (first liposomal approval) and an acceleration in 1998. The knowledge base encompasses chemistry, microbiology, in vivo and in vitro diagnostic technological classes mainly. However, two main technological classes are dominating the composition our sample (around 21% of the patents refer to the class 514 and more than 73% refer to the class 424, both dealing with "drug, bio-affecting and body treatment composition"). The schock occuring in 1995 in terms of patent growth and citations can be probably explained by the first liposomal drug approval (Doxil) at the FDA.

The sample has been bounded to 2006 in order to get precise information at the assignee level thanks to the NBER database. In order to define patents belonging to community of practice in hospitals, we rely on the inventor's level rather than the assignee information and crossed different sources of information to get the most precise picture. Previous studies have evaluated the importance of public research in drug development with surveys or cases studies and a recent investigation has been done with patent data by relying on the assignee's information (see [57]). However, the application of the Bayh-Dole Act and the attitude toward patenting activity differs across public organizations. Some hospitals can decide to let the inventor free to patent her invention on her own or to support her. Additional institutional specificities can also underestimate the importance of hospitals and medical schools due to the presence of a patent office inside universities. Actually, in some cases, medical schools and hospitals can be integrated into universities and therefore, benefit from the university patent office to fill applications under the university's name. The growth of academic start-ups have been widely studied and revealed the importance of "star scientists" as a way to signal the feasibility and profitability of innova-

tive projects (see [35]). This synergy between governmental incentives and new sources of funding has certainly pushed medical researchers to patent based on academic reputations let us extend existing works by relying on inventor's names. Other studies have focused on individual inventor as a proxy for community of practice (see [43]) while several reasons can explain the use of an individual assignee. As [17] evidence it for the tennis industry, an inventor can patent as an individual assignee can also patent under a firm's assignee too.In a different context, [60] focus only on academic start-ups founders rather than inventors by crossing several sources of knowledge. [14] rely on the American Medical Association file to define the physicians' involvement into the medical devices industry.
Relying on firm's assignee, we first selected firms created after the Bayh-Dole Act. Then, we checked for each assignee, information related to their founders' background with firm' website, following [60] approach. We excluded academic spin-off coming from basic science, firm' spin-offs and kept the ones referring to founders' clinical experience or medical school position. The remaining set of US corporations and independent inventors have been investigated at the inventor' level thanks to the US Patent Inventor database available on the Harvard Business School website with disambiguated names of USPTO inventors. We propose a broader picture by relying on inventor's name thanks to the [44]'s work and [59] to get the disambiguated names of US inventors who are also PubMed authors in order to check their institutional affiliation. We consider relevant affiliations the one referring to medical schools, clinics or hospitals from the beginning of the publishing activity of the inventor until two years before the year of patent grant. The sample is mainly the result of US firms', their patenting activity representing 48.57% of the sample, 21.41% is attribued to basic science (universities and institutes) and 22.83% is coming from teams with at least one inventor with a clinical experience, the remaining 7.19% is associated to governmental agencies (US and foreign ones).

3.2 Citation network analysis

As mentioned above, we used citation network analysis in order to simplify the technological evolution of our field. We selected the Main Path algorithm based on the Search Path Count weight, available on Pajek, to establish the main sequence of problem-solvings. The Search Path Count method assumes that the network is acyclic (meaning the network does not contain cycles: there is at least one vertex with an indegree 0 and one vertex with an outdegree 0). Each vertex (or arc between a pair of vertices) receives a value based on the input and output paths going through it divided by the total number of the entry and exit paths (normalization of the SPC) (Batagelj et al., 2008). With the associated citations, the investigated network is composed by 10 808 nodes, 31 825 arcs and an average density closed to 5,89.

3.2.1 Tracking the main trajectory

Based on the transversal counts calculated by the SPC method on citation, the Main Path (MP) analysis identifies the highest weights on arcs of the network over time: when the largest weights is identified, the algorithm selects the arc with the highest weights in its forward neighborhood. The implicit assumption is the following: a patent which contains knowledge from several previous patents and which is widely cited by following patents represents a crucial piece of knowledge in the network. The MP is supposed to reflect the important junction of knowledge assuming that knowledge flows through citations. Therefore, as [19] point out "a citation that is needed in paths between many articles is more crucial than a citation that is hardly needed for linking articles" ([19]). However, despite its popularity in Science & Technology studies ([7, 11, 24, 25, 47, 50, 66]), this approach has some drawbacks.

As [46] pointed it out, the MP analysis is not per se the main trend of a field especially because "all citations are treated equally, cited-citing pair is always assumed to be the same, although obviously this is not true" (p.540). Even though the MP analysis simplifies the knowledge developments, it offers only a very narrow focused point of view. Actually, important patents can be absent from the MP for many reasons (competing technologies, strategic patenting, different propensity to cite across different scientific communities, secrecy). Moreover, this approach tends to focus on the most incremental part of technological developments by relying only on the arcs weights. We develop an alternative by relaxing the constraint of the Main Path and extending these last one with lower line values (main subnetwork or self-organized map). We realized a line-cut at 0.003 and removed the single vertices to get a map with 237 nodes. As illustrated on the picture, different trajectories can be identified and their different widths represent the importance of the taken paths.

4 Results

Technological developments can be distinguished through three main periods (see 1): a first period of exploration focusing on immunological applications (mainly vaccines), a second period devoted to liposomes basic science and related applications (processes, and preparation), and finally a new period of exploration in which new therapeutics appear (theranostics, gene therapy, or improved formulations of existing treatments with new routes of administration among several disease areas). As developed below, the first period could rely on a limited burst of knowledge about fundamental properties of liposomes, technological development were mainly coming from empirical observations and chemistry. This explains why firms (chemical and cosmetic firms) were present at the beginning of the period to define new liposomes preparations. However, the main important "basic" building blocks came from univerisites and

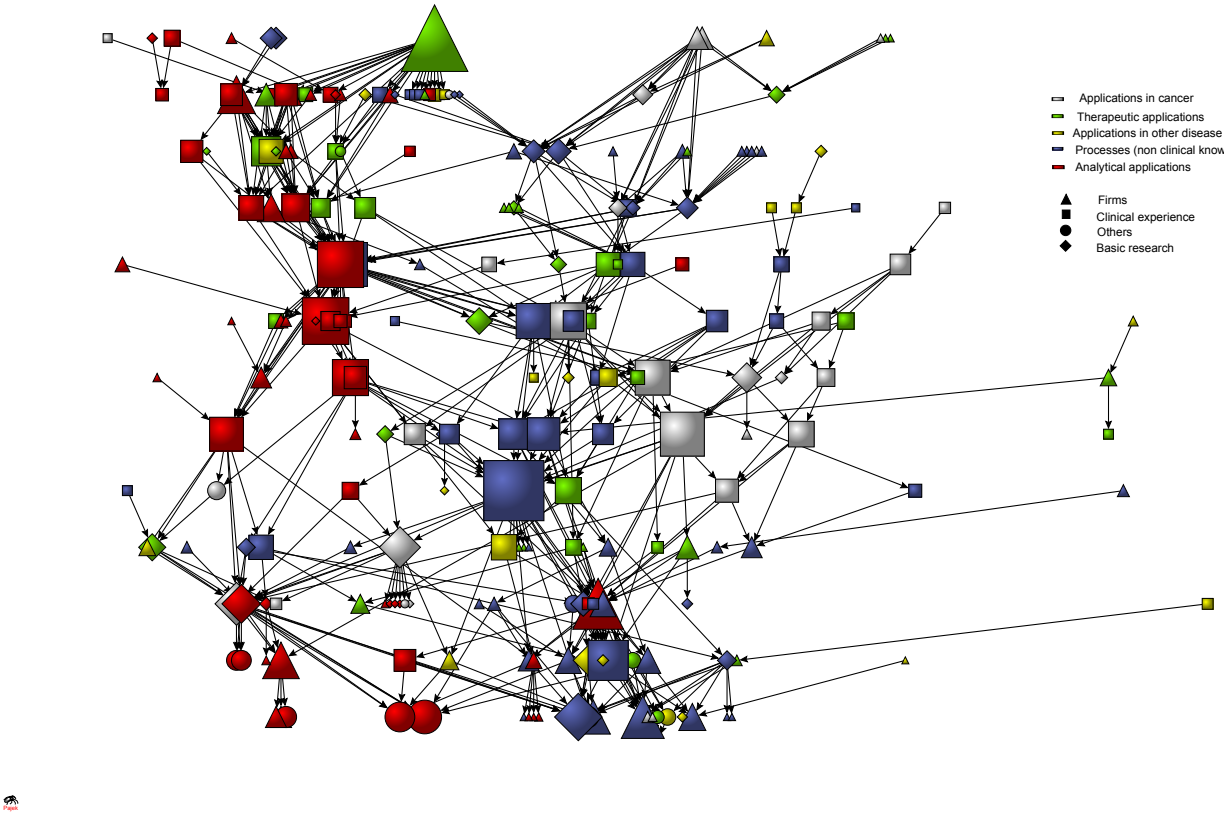

Figure 1: Main technological trajectories (1957-2006)

governmental agencies as pointed out by the patents making authority. The lack of pharmaceutical firms in the liposomal research effort is explained by a misalignment of skills concerning drug delivery system. Drug development in pharmaceutical firms is initiated by medical chemists, with a limited training in pharmacokinetics properties but rather in modifying chemical structure ([13,61]). On the contrary, drug delivery systems are defined as a "symphony of sciences" ([13]) and require an interdisciplinary approach. Liposomes have been first defined as the "baby" of academia by starting their life as model membrane since 1965 ([8]).

On the contrary, the second period is marked by inventors with an experience in clinical activity (mainly biochemists and radiologists) while the last period is led by pharmaceutical firms. This changing trend probably revealed the consequences of mergers and acquisitions between incumbents and new-business formations and diminishing venture capital fundings as well rather than a technological catching-up process. Liposomes modularity in terms of quantity of loaded substances and surface treatment explains the tremendous fad for this artefact. Moreover, its low toxicity and immunogenecity properties have seduced clinicians to adopt them as part of their therapeutic armoury.

4.1 Intertwined technological trajectories

Two main trajectories are distinct among the results before entering in the most radical innovative period: on the one hand, a trend focusing on analytical purposes, and on the other hand, one trend focusing on therapeutic formulations and the problems raised by their preparation via process innovations. Liposomes preparation have faced 5 main issues: stability, scale-up and loading methods, control release of its contents, and increasing targeting. The first analytical applications are related to in vivo ones because the technological requirements for a controlled environment were less demanding. They also represent a sort of weak path-dependency related to immunological period by dealing with the detection of specific antigens in vitro (immunoassays) or biosensors (detection of agents, bacteria). Liposomes are here as analytical tools rather than carriers thanks to their property of signal enhancement ([37]). These applications have improved the one of the first steps of selection of candidates by providing better technics for assay developments ([69]).
This trend is then replaced by in vivo tools thanks to the emergence of more stable liposomes, ready to face in vivo conditions ([65]). Liposomes are here used as carriers of radioisotopes and different labeled markers for diagnostics purposes. More elaborated diagnostic tools emerged, with applications with ultrasound echography, Magnetic Resonance Imaging, Computer Tomography in which liposomal solutions are used as contrast agents. This trend has been marked by the willingness to avoid side-effects coming X-rays diagnostic technics and to provide new tools for non-invasive diagnostics. Cancer is once again the most important field of applications of diagnostics due to the need of monitoring response treatment. These liposomal applications are designed to improve

prognodiagnostics and monitoring treatment response in clinical trials to improve their results in drug development ([69]). Some early patents dealing with cancer biomarkers bridge this testing trend with the main trajectory, reflecting research efforts linking lipids and fundamental cancer biology.
As mentioned above, the emergence of new stable carriers thanks to different coating methods are responsible for the technological opportunity maturity. A new type of innovation emerged as at the crossroads between the diagnostic tools and therapeutics. This technological hybridization is the result of by three technological opportunities described below dealing with, carriers stability, controlled release and active targeting. The creation of new generation of liposomes have enables clinicians to develop tailored-made approach by getting carriers able to go at the site-specific and act directly through different modalities. In the case of cancer, different approaches are described, both enabling to develop tailored-made approach in clinics: warming the area to treat to burn tumourous cells (hyperthermia), or the controlled delivery of drugs following liposomes migration thanks to diagnostic substances or specific enzymes present at the tumor-level.

4.1.1 Bridging immunology and chemotherapy

Historically, the first application using liposomes as drug delivery system has been made in the context of an orphan liver child disease. In 1969, Ryman developed a liposomal enzyme delivery after the discovery of hepatic galactose receptor which laid the ground to establish the concept of a targeting vesicle. This idea has been fully settled after an increasing understanding of the receptor mediated endocytosis from a biophysical point of view and shed light on antibodies to mediate this phenomenon ([32]). The results of the study also evidenced an enhancing immune response, creating the idea of using liposome as adjuvant property in vaccine ([2,39], see for example US 4053585).Despite a limited understanding about this immune-push, liposomes have laid the ground for several vaccine applications after the demonstration by [63, 70] to encapsulate poliovirus and picornaviruses, respectively. This trend in immunology has demonstrated the capacity of liposomes to deliver intracellularly contents, and adds a new type of liposomal applications in gene therapy. Very early, demonstration of using liposomes as genetical carriers were effective in vitro ([28]). However, several steps is basic liposome science were needed to be achieved before using the solution in vivo to optimize liposomes characteristics.

This first successful application in liver highlighted another immunological phenomenon known as mononuclear phagocyte system or Reticuloendothelial System. This immune phenomenon refers to the clearance of liposomes from blood system by macrophages, implying their storage in liver, lymph nodes and spleen. This “natural" property has been first exploited to treat pathologies localized at these different sites. Empirically, a link has been made between the size of liposomes and the mitigation of this effect ([38]). A first temporary solution was set up in empirically by using small liposomes, explaining a focus on this

type of liposome in medical applications at the beginning of our results while large and medium vesicles were developed in the context of cosmetics. Mentionned as a drawback of liposomal formulations for others, important efforts have been made to overcome this clearance effect. An increasing understanding of the RES at the biomolecular level and advances in polymers have created the conditions to create a new type of liposomes ("stealth"), becoming "invisible" to macrophages attacks. The end of the self-organized map and the specialization trends show that coated liposomes with polymers opened an open airway for a new exploration phase with new applications in different diseases areas and routes of administration. As mentionned above, an increasing knowledge stock about antibodies and ligands have pushed researchers to design active targeting liposomes: limited in a first time by the polymer coated surface treatment ("mask effect"), a new design has emerged to add both dimensions by plugging the ligand at the end of the polymer chain thanks to new proteins coupling methods (see for example US 5527528, US 5399331). The active targeting has tuned the design of new liposomal solutions as therapeutics but also influenced the design of better diagnostic tools.

Parallel technological explorations have created distinct medical applications trends. The first idea of using liposomal formulation to reduced toxic side-effects and to increase therapeutic efficiency has been made in the context of leishmaniasis. The publication of the first in vivo results with antimonial compounds loaded in liposomes has popularized the idea liposomal chemotherapy ([3], US4186183). The application of liposomal chemotherapy has become increasingly evident due to the observation of another property between liposome and tumors. In 1985, [51] evidenced the accumulation of liposomes in sites of infection and inflammation in humans, followed by [48], who demonstrated the same phenomenon at the tumor level in animal model and coined the term "Enhanced Permeability Retention". This trend has been extremly important in cancer applications (diagnostics and therapeutics), liposomes appearing as a tool for passive targeting of cytotoxic agents ("local chemotherapy") and represents the most mature field in our results. This approach has become a gold standard in anti-cancer drug design ([5]). However, the enthusiam associated to passive targeting has been quickly removed due to the RES phenomenon mentionned above, and a first practical rule of thumb as been made to mitigate these limitations by injecting first empty liposomes ([1]) before the availability of "stealth" liposomes.

4.1.2 Liposomes: from membrane models to life science

The technological progress in lipid bilayers has been hindered by basic scientific knowledge about their properties and behaviour in the body: the first period of exploration being punctuated by a long trend of patents focusing on processes and physico-chemical properties (see the self-organized map). First used as model membranes, the accumulated fundamental knowledge about liposomes were dealing with their physico-chemical properties ([33, 34]). This body of

knowledge has been first exploited by a limited community of physical chemists and physicists due to a misalignment of skills with life scientists ([52]) and explains why the first technological solutions rely on lipid chemistry. The stability issue of liposomes before being solved by polymers, has first been solved by substituting phospholipids to cholesterol (see US4544545) and sphingomyelin (US 5429823). Another chemical solution was used to compensate the liposome leakage by loading a hydrophobic drugs, as it mostly the case among anti-cancer drugs, to maintain the liposome stability ([42]). This approach explains also why cancer has been an early field of investigation.

The problems encountered in the medical arena created the need for a better understanding of liposomes properties by an increasing community of researchers. The need to know and to understand the physical chemistry of lipid membranes in biology have pushed life scientists to adopt new approaches and methods, replicating to some extent what was done previously in the field of physical chemistry ([52]). The increasing degree of quantification in molecular data and the boom of tools coming from physical chemistry and biophysics have accelerated this trend ([45, 52]). This expanding community focused on lipids from different perspectives has given birth to a new discipline, lipdomics, gaining gradually its independance from metabolics ([45,52]). The importance of physical chemistry is particularly evident regarding the technological efforts related to the question of controlled release, and illustrates the focus on lipid in biology described above. After creating stable carriers, another desirable property was related to the idea of controlling the drug delivery, especially in the case of gene therapy in which the liposome needs to fuse with cell. Therefore, tremendous efforts have been done to accumulate knowledge about the properties of liposomes and use them to design controlled system, such as pH, temperature sensitive liposomes, or charged surface liposome. Fundamental cancer biology has also focused on determining the “lipid fingerprint" of tumor and highlighted a exploitable mechanism due to the higher presence of an enzyme in tumor ([52]). Loading methods have also benefited from a better understanding of physico-chemical properties to increasing substance loading (see US 5192549, US 6083530 for example).

5 Discussion

Patent analysis depicts only partially the body of practice involved in anticancer developments. As any medical innovation, protyping is necessary to face uncertainty of the effect and patient risk. Several stages are needed to determine the potential of a given molecule and the selection increases at each step of drug development (based on [53]). A drug candidate journey starts first in pre-clinical studies, in which their anticancer activity is evaluated in vitro with cell cultured models (NCI-60 model that has been introduced in 1990). If the drug candidate is not removed from the process, the drug candidate enters the preclinical efficacy screening ([53, 58]). Following the pre-clinical screening, the pre-clinical

toxicity studies aim at defining the optimal dose of cytotoxic agent to deliver by relying on animal testing. Actually, considering that therapeutic effect and toxicity are attributed to the same effect, the cytotoxic agent is delivered at the Maximum Tolerated Rate. Mice models are used first and a second testing is done in non-rodent species (mainly dogs, monkeys being too expensive).Then, a rule of thumb is applied to determine how much of the compound should be delivered in clinical trials. Underestimation and overestimation are thus the rules due to the metabolic difference accross species and the pharmacokinetic properties of the drug. Cancer drug development gets a specific regulatory feature in compre to others, its evaluation being based on its intended use, mechanism of action and target patient population. Therefore, if the potential benefits are overestimated, higher are the risks taken in terms of toxicity ([20]). Still from a regulatory point of view, preclinical studies are also biased towards cytotoxic agents: on the one hand, the use or combination of cytotoxic compounds that have been already used in humans and got an established safety profile do not require new preclinical toxicology testing ([20]), and on the other hand, cytotoxic agents are administered at short-term phases, disincentiving other types of compounds that require long term administration making their evaluation more complex and expensive. The emergence of durg carriers at the nanoscale, such as liposomes, is responsible for new regulatory requirement to justify their use by comparing the therapeutic impact with and without the carrier (proof-of-concept). Additional studies in terms of stability, biocompatibility of the carrier in human tissues and pharmacokinetic are thus required ([20, 27]). Therefore, liposomes get a comparative advantage in terms of non-carrier formulations in terms of predictability, avoiding the “normal" shortcomings of drug development regarding the pharmacokinetic dimension.

5.1 Search routines in anticancer drug development

Chemotherapy in cancer was established after the WWII, after observing cytotoxic effects on humans exposed to illegal use of chemical warfare in Bari (Italy) in 1946 ([26]). The replication of this “natural experiment" in a laboratory with mice models exposed to mustard gas prescribed, on the one hand, the use of mice models as instrumentalities and on the other hand, tumor shrinkage and increasing animal life span as criteria of evaluation. Toxicity and therapeutic effects being mixed, a huge attention was devoted to the evaluation of harmful effects in drug development, making it more costly and expensive than others ([22]). Without any scientific underlying knowledge about cytotoxic effects, the innovative search has been driven by serendipity defined as “hit and miss" approach([26]). In this context, many drug candidates disgarded because of toxcitiy issues were becoming prime candidates for anticancer drug development. A milestone was made in anticancer drug development in 1955 with the creation of an end-product institution, the Cancer Chemotherapy National Service Center (CCNSC), creating the most extensive review of requirements of drug development ever conducted, creating librairies of thousands screened anticancer compounds. Moreover, beyond screening compounds, “This ensured

a wider collaborative effort and provided standardized techniques and a stable source of funds, heretofore unavailable, for the testing of new approaches to cancer treatment" ([26], p.8646). In addition, "commercial discreet agreement" and specific IPR design were instituted to ensure that firms will keep the benefits from their compounds while the CCNSR was screening and testing private compounds, as well long as the company supplies the market with a product of a highly quality in adequate amount and at a reasonable price [22, 23]). Therefore, a division of labor has been instituted into drug development by letting testings, pharmacology and toxicity studies to the public domain while firms supplied off-the-shelf compounds for screening and making large amounts of a compound for sale and distribution. The tremendous amount of compounds to test pushed the National Cancer Institute to use in vitro models rather than in vivo ones to increase economies of scale. introduced a new primary screen constituted by 60 human tumor cells lines, called the NCI-60 ([53,58,68]). This new rule of selection is actually in line with the new routines made available by instrumentation (

In the eighties, progress in chemotherapy were slow and each small success required large, long term trials which exhibited marginal results on solid tumours ([12]). Moreover, the progress in cell biology let to a new definition of cancer: the disease was not defined as an abnormal cell growth but the result of genetical defect due to mutations. Thedrastic change is rooted in another unrelated program of the NCI called the Special Virus Cancer Program (SVCP), established in 1964 and aiming at defining explanatory mechanisms between viruses and cancer. Although researchers were not able to identify actual viruses, it morphed into a Program of Molecular Biology to study genes involved into cancer, namely oncogenes, suppressor oncogenes, signaling pathways ([22]). This program led to the identification of most of the drug targets and facilitated the sequencing of genome. Mainly, data from genome sequence indicate the role of protein kinase in cancer, paving the way for pharmaceutical companies' efforts towards kinase inhibitors ([22]). A revolution has been in effective in terms of drug development due to the "explosion" of drug targets, starting as a low-budget, government-supported research effort to a high-stakes, multi-billion dollar industry ([12]).Therefore, a new search regime through rational drug design emerged in the field of cancer, driven by progress in instrumentation namely combinatorial chemistry or drug-receptor modelization (

5.2 Synergy and Complementarity of rules

The summary table describing the different search routine in the lens of Sarewitz-Nelson rules and their interactions is described below. A detailed analysis of the problem-solvings in liposomal development is provided in the appendix (**??** Some problems solved within a given standardized core rule could benefit from positive externalities of other standardized core rules, linking more closely two standardized rules. For example, the idea of relying on cancerous cells ligands have shaped the idea of exploiting tumour micro-environment such as specific enzyme, and to exploit this property to design specifc sensitive lipo-

somes. Similarly, the first study about drug distribution which initiated the use of animal models to evaluate liposomal applications reinforced the operational principles related to stealth liposomes and of triggered release liposomes. This synergy among rules within the search routine makes it more robust despite an absence of cause-consequence mechanism. As described below, the testability rules between the two regime seem tobe compatible, the testability rule of the targeted therapies appears as a specific case of the liposome search one. The complementarity between the two search routine is actually indirect. The constitution of the liposome stock of knowledge involved a tremendous research efforts across different communities, ranging from physics to cell biology, and enabled to increase fundamental knowledge about lipids. Liposome research is actually embedded into a bigger regime called lipodomics, encompassing the liposome search and lipodology science ([69]). A real push has been known thanks to the availability of new and better instrumentation, mainly in mass spectrometry, which has eased the quantification and analysis of lipids ([45]). Therefore, besides functional knowledge related to lipids, important work has been done in terms of collecting lipids in sample, especially in cancer field in which several samples are made very often ([9]). Lipid analysis highlighted the importance of metabolism in cancer that has been neglected in targeted therapies search routine which focuses on causal mechanisms with genes and proteins in a linear way, despite a strong scientific stock of knowledge. The understanding of the role of lipids in targeted therapies tends to correct the "anomaly" linked to the cause-effect rule which is more context-dependent due to metabolic reasons. Moreover, liposomes as drug carriers have also played a leading role in paying an increasing attention to pharmacokinetic properties in drug development, to come closer to establish a cause-mechanism of the target, context independent. The importance of practice in building the liposome search routine allowed also a better predictability in drug development, beneficial to predict metabolic effets in targeted therapies development.
The decomposition of the search routine in rules evidences also the importance of public organizations within anticancer drug development. First, the CCNSC was responsible for supplying inputs in the mass screning approach. However, despite a testability rule which has become increasingly ambiguous, the search routine was blind and technology driven. This search routine could not rely on the establishment of a cause-effect rule because cancer disease was considered as an infectious disease, that was to be eradicated before overwhelming the host. The following search routines are still based on public efforts but played a less direct role role within the search routine, learning and innovation being the results of instrumentation in the case of targeted therapies and practice playing a dominant role for liposome search routine.

6 Conclusion

This paper was concerned by understanding how a new method in delivering medication affects existing search routine in anticancer drug development. We

proposed an original approach to investigate the question by disentangling the search routines in rules and to highlight their complementarity, in terms of functions or sources. To do so, we developed an original approach to highlight the importance of clinical practice by relying on the inventor's level. We evidence that an existing search routine is positively influenced by a new search routine if both share a certain degree of complementarity among their rules. The degree of synergy among rules and within search routine seems also to play a role to compensate the lack or the mispecification of other rules. The constitution of the liposome technological opportunity was crucial in guiding the targeted therapies search routine and allowed the emergence of new therapies as well. Liposome technological opportunity relied on the accumulation of fundamental knowledge, on the one hand, biophysical properties and other hand, their behaviour in vivo. It seems that liposomes have played a role of instrumentalities by being used as models and carriers in the same time. Additional investigations would be needed to understand the conditions under which a scientific model of understanding can bridge different scientific communities.Liposomes represent an illustration of social technologies by being physical artefacts that define a new approach to deliver and develop medication, and rely on a division of labor across communities of practice. Public research still plays a leading role in anticancer drug development, even if its implication varied across in terms of type of knowledge and input involved within each search routine.

The previous anticancer drug development search, rational drug design, has been affected by liposomes in different ways:in vitro, thanks to the emergence of new tools in assay development and lead identification stages and thanks to the increasing stock of lipid fundamental knowledge. Liposomes as drug delivery systems and insights from new diagnostic tools have modified the existing search routine at the in vivo level. However, this new search routine known as lipodomics is still at an experimental stage due to the need of standardization in lipid research and regulation in drug development ([9]). The effects on hybridization of rules would require some time to evaluate its effective innovative implications.

References

[1] Theresa M Allen and Pieter R Cullis. Liposomal drug delivery systems: from concept to clinical applications. *Advanced drug delivery reviews*, 65(1):36–48, 2013.

[2] AC Allison and Gregory Gregoriadis. Liposomes as immunological adjuvants. 1974.

[3] Carl R Alving, Edgar A Steck, Willie L Chapman, Virginia B Waits, Larry D Hendricks, Glenn M Swartz, and William L Hanson. Therapy of leishmaniasis: superior efficacies of liposome-encapsulated drugs. *Proceedings of the National Academy of Sciences*, 75(6):2959–2963, 1978.

[4] AmericanCancerSociety. What is targeted therapy? 2013.

[5] Ernest A Azzopardi, Elaine L Ferguson, and David W Thomas. The enhanced permeability retention effect: a new paradigm for drug targeting in infection. *Journal of Antimicrobial Chemotherapy*, 68(2):257–274, 2013.

[6] David Barberá-Tomás and Davide Consoli. Whatever works: Uncertainty and technological hybrids in medical innovation. *Technological Forecasting and Social Change*, 79(5):932–948, 2012.

[7] David Barberá-Tomás, Fernando Jiménez-Sáez, and Itziar Castelló-Molina. Mapping the importance of the real world: The validity of connectivity analysis of patent citations networks. *Research Policy*, 40(3):473–486, 2011.

[8] Yechezkel Barenholz. Chapter 7.1 - design of liposome-based drug carriers: From basic research to application as approved drugs. In D.D. LasicD. Papahadjopoulos, editor, *Medical Applications of Liposomes*, pages 545 – 565. Elsevier Science B.V., Amsterdam, 1998.

[9] Richard D. Beger. A review of applications of metabolomics in cancer. *Metabolites*, 3(3):552–574, 2013.

[10] Stuart Blume. Chapter 2.4- cochlear implantation: Establishing clinical feasibility, 1957-1982. In *Sources of medical technology: universities and industry*. Oxford Univ Press, 1995.

[11] Clara Calero-Medina and Ed Noyons. Combining mapping and citation network analysis for a better understanding of the scientific development: The case of the absorptive capacity field. *Journal of Informetrics*, 2(4):272–279, 2008.

[12] Bruce A Chabner and Thomas G Roberts. Chemotherapy and the war on cancer. *Nature Reviews Cancer*, 5(1):65–72, 2005.

[13] Binghe Wang Chao Han. Chapter 1 - factors that impact the developability of drug candidates: an overview. In *Drug delivery: principles and applications*. John Wiley & Sons, 2005.

[14] Aaron K Chatterji and Kira Fabrizio. How do product users influence corporate invention? *Organization Science*, 23(4):971–987, 2012.

[15] Davide Consoli and Andrea Mina. An evolutionary perspective on health innovation systems. *Journal of Evolutionary Economics*, 19(2):297–319, 2009.

[16] Davide Consoli and Ronnie Ramlogan. Out of sight: problem sequences and epistemic boundaries of medical know-how on glaucoma. *Journal of Evolutionary Economics*, 18(1):31–56, 2008.

[17] Kristina Dahlin, Margaret Taylor, and Mark Fichman. Today's edisons or weekend hobbyists: technical merit and success of inventions by independent inventors. *Research Policy*, 33(8):1167–1183, 2004.

[18] J. Stan Metcalfe Andrea Mina & Ronnie Ramlogan Davide Consoli, Andrew McMeekin. Chapter 2.1 - the process of innovation: incentives, behaviour and organization. In *The Economics of New Health Technologies-Incentives, organization, and financing*. Oxford Univ Press, 2009.

[19] Wouter De Nooy, Andrej Mrvar, and Vladimir Batagelj. *Exploratory social network analysis with Pajek*, volume 27. Cambridge University Press, 2011.

[20] Joseph J DeGeorge, Chang-Ho Ahn, Paul A Andrews, Margaret E Brower, Diana W Giorgio, M Anwar Goheer, Doo Y Lee-Ham, W David McGuinn, Wendelyn Schmidt, C Joseph Sun, et al. Regulatory considerations for preclinical development of anticancer drugs. *Cancer chemotherapy and pharmacology*, 41(3):173–185, 1997.

[21] Harold J DeMonaco, Ayfer Ali, and Eric Hippel. The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 26(3):323–332, 2006.

[22] Vincent T DeVita and Edward Chu. A history of cancer chemotherapy. *Cancer research*, 68(21):8643–8653, 2008.

[23] KM Endicott. The national cancer chemotherapy program. *Journal of chronic diseases*, 8(1):171–177, 1958.

[24] Marianna Epicoco. Knowledge patterns and sources of leadership: Mapping the semiconductor miniaturization trajectory. *Research Policy*, 42(1):180–195, 2013.

[25] Marianna Epicoco, Vanessa Oltra, and Maïder Saint Jean. Knowledge dynamics and sources of eco-innovation: Mapping the green chemistry community. *Technological Forecasting and Social Change*, 81:388–402, 2014.

[26] Guy B Faguet. *The war on cancer*. Springer, 2005.

[27] FederalDrugAdministration. Guidance for industry - liposome drug products. 2002.

[28] Robert Fraley, Jan Wilschut, Nejat Duzgunes, Craig Smith, and Demetrios Papahadjopoulos. Studies on the mechanism of membrane fusion: role of phosphate in promoting calcium ion induced fusion of phospholipid vesicles. *Biochemistry*, 19(26):6021–6029, 1980.

[29] Annetine Gelijns and Nathan Rosenberg. The dynamics of technological change in medicine. *Health Affairs*, 13(3):28–46, 1994.

[30] Annetine C Gelijns, Nathan Rosenberg, and Alan J Moskowitz. Capturing the unexpected benefits of medical research. *The New England journal of medicine*, 339(10):693–698, 1998.

[31] Annetine C Gelijns, Joshua Graff Zivin, and Richard R Nelson. Uncertainty and technological change in medicine. *Journal of Health Politics, Policy and Law*, 26(5):913–924, 2001.

[32] Joseph L Goldstein, Richard GW Anderson, and Michael S Brown. Coated pits, coated vesicles, and receptor-mediated endocytosis. *Nature*, 279(5715):679–685, 1979.

[33] Gregory Gregoriadis. Chapter 1.2 - liposome research in drug delivery and targeting: Thoughts of an early participant. In D.D. LasicD. Papahadjopoulos, editor, *Medical Applications of Liposomes*, pages 9 – 13. Elsevier Science B.V., Amsterdam, 1998.

[34] Gregory Gregoriadis and Alexander T Florence. Liposomes in drug delivery. *Drugs*, 45(1):15–28, 1993.

[35] Matthew J Higgins, Paula E Stephan, and Jerry G Thursby. Conveying quality and value in emerging industries: Star scientists and the role of signals in biotechnology. *Research Policy*, 40(4):605–617, 2011.

[36] Donna L Hoyert, Jiaquan Xu, et al. Deaths: preliminary data for 2011. *National vital statistics reports*, 61(6):1–51, 2012.

[37] Aldo Jesorka and Owe Orwar. Liposomes: technologies and analytical applications. *Annu. Rev. Anal. Chem.*, 1:801–832, 2008.

[38] RL Juliano and D Stamp. The effect of particle size and charge on the clearance rates of liposomes and liposome encapsulated drugs. *Biochemical and biophysical research communications*, 63(3):651–658, 1975.

[39] Stephen C Kinsky. Antibody-complement interaction with lipid model membranes. *Biochimica et Biophysica Acta (BBA)-Reviews on Biomembranes*, 265(1):1–23, 1972.

[40] Ismail Kola and John Landis. Can the pharmaceutical industry reduce attrition rates? *Nature reviews Drug discovery*, 3(8):711–716, 2004.

[41] John C Kraft, Jennifer P Freeling, Ziyao Wang, and Rodney JY Ho. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *Journal of pharmaceutical sciences*, 103(1):29–52, 2014.

[42] Danilo D. Lasic and Demetrios Papahadjopoulos. Chapter 1.1 - general introduction. In D.D. LasicD. Papahadjopoulos, editor, *Medical Applications of Liposomes*, pages 1 – 7. Elsevier Science B.V., Amsterdam, 1998.

[43] Christopher Lettl, Katja Rost, and Iwan Von Wartburg. Why are some independent inventors heroes and others hobbyists? the moderating role of technological diversity and specialization. *Research Policy*, 38(2):243–254, 2009.

[44] Guan-Cheng Li, Ronald Lai, Alexander DAmour, David M Doolin, Ye Sun, Vetle I Torvik, Amy Z Yu, and Lee Fleming. Disambiguation and coauthorship networks of the us patent inventor database (1975–2010). *Research Policy*, 43(6):941–955, 2014.

[45] Min Li, Li Yang, Yu Bai, and Huwei Liu. Analytical methods in lipidomics and their applications. *Analytical chemistry*, 86(1):161–175, 2013.

[46] John S Liu and Louis YY Lu. An integrated approach for main path analysis: Development of the hirsch index as an example. *Journal of the American Society for Information Science and Technology*, 63(3):528–542, 2012.

[47] Arianna Martinelli. An emerging paradigm or just another trajectory? understanding the nature of technological changes using engineering heuristics in the telecommunications switching industry. *Research Policy*, 41(2):414–429, 2012.

[48] Yasuhiro Matsumura and Hiroshi Maeda. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer research*, 46(12 Part 1):6387–6392, 1986.

[49] John Stanley Metcalfe, Andrew James, and Andrea Mina. Emergent innovation systems and the delivery of clinical services: The case of intra-ocular lenses. *Research Policy*, 34(9):1283–1304, 2005.

[50] Andrea Mina, Ronald Ramlogan, Gindo Tampubolon, and J Stanley Metcalfe. Mapping evolutionary trajectories: Applications to the growth and transformation of medical knowledge. *Research policy*, 36(5):789–806, 2007.

[51] JR Morgan, LA Williams, and CB Howard. Technetium-labelled liposome imaging for deep-seated infection. *The British journal of radiology*, 58(685):35–39, 1985.

[52] Ole G Mouritsen. Lipidology and lipidomics—-quo vadis? a new era for the physical chemistry of lipids. *Physical Chemistry Chemical Physics*, 13(43):19195–19205, 2011.

[53] Ajit S Narang and Divyakant S Desai. Anticancer drug development. In *Pharmaceutical Perspectives of Cancer Therapeutics*, pages 49–92. Springer, 2009.

[54] Richard R Nelson. Factors affecting the power of technological paradigms. *Industrial and Corporate Change*, 17(3):485–497, 2008.

[55] Richard R Nelson, Kristin Buterbaugh, Marcel Perl, and Annetine Gelijns. How medical know-how progresses. *Research Policy*, 40(10):1339–1344, 2011.

[56] Paul Nightingale. Technological capabilities, invisible infrastructure and the un-social construction of predictability: the overlooked fixed costs of useful research. *Research Policy*, 33(9):1259–1284, 2004.

[57] Bhaven N Sampat and Frank R Lichtenberg. What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Affairs*, 30(2):332–339, 2011.

[58] Edward A Sausville. Preclinical models for anticancer drug development. In *Principles of Anticancer Drug Development*, pages 89–114. Springer, 2011.

[59] Neil R Smalheiser and Vetle I Torvik. Author name disambiguation. *Annual review of information science and technology*, 43(1):1–43, 2009.

[60] Sheryl Winston Smith and Sonali K Shah. Do innovative users generate more useful insights? an analysis of corporate venture capital investments in the medical device industry. *Strategic Entrepreneurship Journal*, 7(2):151–167, 2013.

[61] Walter E Sneader. *Drug Discovery (The History)*. Wiley Online Library, 2005.

[62] Joanne Spetz. Chapter 2.3- physicians and physicists: the interdisciplinary introduction of the laser to medicine. In *Sources of medical technology: universities and industry*. Oxford Univ Press, 1995.

[63] Robert Taber, Tazewell Wilson, and Demetrios Papahadjopoulos. The encapsulation of picornaviruses by lipid vesicles: Physical and biological properties*. *Annals of the New York Academy of Sciences*, 308(1):268–274, 1978.

[64] Stefan Thomke, Eric Von Hippel, and Roland Franke. Modes of experimentation: an innovation processand competitivevariable. *Research Policy*, 27(3):315–332, 1998.

[65] Vladimir P. Torchilin. Chapter 6.6 - liposomes as carriers of contrast agents for in vivo diagnostics. In D.D. LasicD. Papahadjopoulos, editor, *Medical Applications of Liposomes*, pages 515 – 543. Elsevier Science B.V., Amsterdam, 1998.

[66] Bart Verspagen. Mapping technological trajectories as patent citation networks: A study on the history of fuel cell research. *Advances in Complex Systems*, 10(01):93–115, 2007.

[67] Eric Von Hippel and Stan N Finkelstein. Analysis of innovation in automated clinical chemistry analyzers. *Science and Public Policy*, 6(1):24–37, 1979.

[68] William R Waud. Murine l1210 and p388 leukemias. In *Tumor Models in Cancer Research*, pages 23–41. Springer, 2011.

[69] Markus R Wenk. The emerging field of lipidomics. *Nature Reviews Drug Discovery*, 4(7):594–610, 2005.

[70] Tazewell Wilson, Demetrios Papahadjopoulos, and Robert Taber. Biological properties of poliovirus encapsulated in lipid vesicles: antibody resistance and infectivity in virus-resistant cells. *Proceedings of the National Academy of Sciences*, 74(8):3471–3475, 1977.

A Appendix

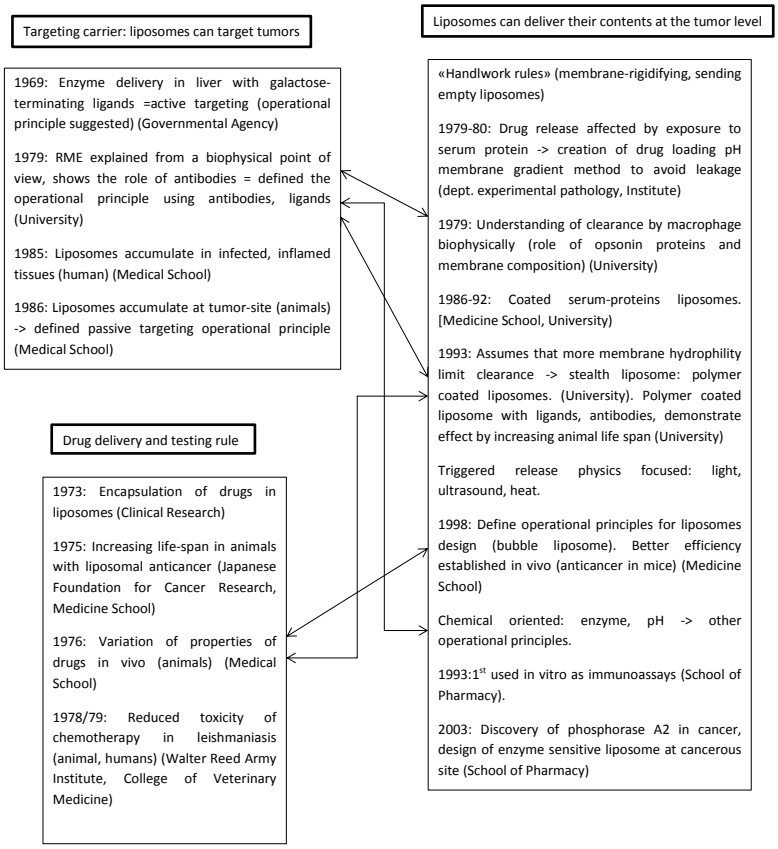

Figure 2: Synergy among rules within the liposome search routine

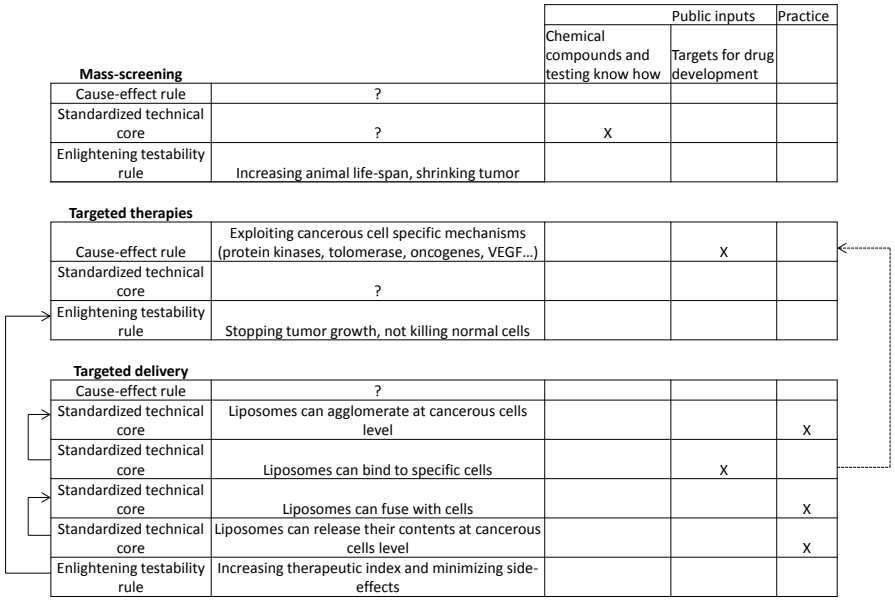

Figure 3: Synergy of rules within liposome search: decomposition of the standardized core rule with problem-solvings