www.elsevier.com/locate/hlpt

PROBLEM-DRIVEN INNOVATIONS IN DRUG DISCOVERY: CO-EVOLUTION OF THE PATTERNS OF RADICAL INNOVATION WITH THE EVOLUTION OF PROBLEMS

Mario Coccia

PII: S2211-8837(16)00011-3
DOI: http://dx.doi.org/10.1016/j.hlpt.2016.02.003
Reference: HLPT172

To appear in: *Health Policy and Technology*

Received date: 28 April 2015
Revised date: 20 October 2015
Accepted date: 8 February 2016

Cite this article as: Mario Coccia, PROBLEM-DRIVEN INNOVATIONS IN DRUG DISCOVERY: CO-EVOLUTION OF THE PATTERNS OF RADICAL INNOVATION WITH THE EVOLUTION OF PROBLEMS, *Health Polic and Technology,* http://dx.doi.org/10.1016/j.hlpt.2016.02.003

PROBLEM-DRIVEN INNOVATIONS IN DRUG DISCOVERY: CO-EVOLUTION OF THE PATTERNS OF RADICAL INNOVATION WITH THE EVOLUTION OF PROBLEMS

Mario Coccia[1]
CNR -- NATIONAL RESEARCH COUNCIL OF ITALY & ARIZONA STATE UNIVERSITY
Current Address: IRCRES-CNR -VIA REAL COLLEGIO, 30 - 10024 MONCALIERI (TO)-ITALY
E-mail: mario.coccia@cnr.it; mario.coccia@ircres.cnr.it

Abstract.

A fundamental problem in the field of the product innovation management in biopharmaceutical industry is how to explain the *general* source of drug discovery and radical innovations that sustain the competitive advantage of firms and technological progress in medicine. The current study confronts this problem by developing a conceptual framework of problem-driven innovation. The inductive study, based on ground-breaking drugs for lung cancer treatment, shows *de facto* that the perception and solution of problem is an invariant force that supports source of radical innovation and evolution of new technology. This evolution of radical innovations, driven by the evolution of problems, generates a major technological change in medicine. This finding, in a Schumpeterian world of innovation-based competition, is due to the organizational behaviour of leading firms that have a strong incentive to find innovative solutions to unsolved problems in order to achieve the prospect of a (temporary) profit monopoly. The vital linkages between observed facts support a theoretical framework of the source and evolution of path-breaking innovations in medicine, which can be generalized to explain the long-term technological change in society. The finding here is also important to design data-sharing health policy in order to promote innovation for better therapies and an efficient "healthcare ecosystem".

Keywords: Product Innovation Management, Cancer, Technological Paradigm, Target Therapy, Radical Innovation, Commons, Problem Solving, Data Sharing, Drug Discovery, Ecosystem, Health Policy.

[1] This research began in 2014 at the UNU-MERIT (The Netherlands) and was further developed in 2015 at Arizona State University (Phoenix, USA) while I was a visiting scholar funded by National Research Council of Italy. This paper benefited from helpful comments and suggestions by Christopher S. Hayter (ASU, Phoenix, USA), R. Filippini (Università di Padova, Italy), A. Messeni Petruzzelli (Politecnico di Bari, Italy), participants at XXVI conference of RSA AiIG 2015 (Vicenza, Italy, 15-16 October) and two anonymous referees of the journal *Health Policy and Technology*. The author declares that he has no relevant or material financial interests that relate to the research discussed in this paper.

PROBLEM-DRIVEN INNOVATIONS IN DRUG DISCOVERY:
CO-EVOLUTION OF THE PATTERNS OF RADICAL INNOVATION WITH THE EVOLUTION OF PROBLEMS

Authors[2]
Affiliations

Abstract.

A fundamental problem in the field of the product innovation management in biopharmaceutical industry is how to explain the *general* source of drug discovery and radical innovations that sustain the competitive advantage of firms and technological progress in medicine. The current study confronts this problem by developing a conceptual framework of problem-driven innovation. The inductive study, based on ground-breaking drugs for lung cancer treatment, shows *de facto* that the perception and solution of problem is an invariant force that supports source of radical innovation and evolution of new technology. This evolution of radical innovations, driven by the evolution of problems, generates a major technological change in medicine. This finding, in a Schumpeterian world of innovation-based competition, is due to the organizational behaviour of leading firms that have a strong incentive to find innovative solutions to unsolved problems in order to achieve the prospect of a (temporary) profit monopoly. The vital linkages between observed facts support a theoretical framework of the source and evolution of path-breaking innovations in medicine, which can be generalized to explain the long-term technological change in society. The finding here is also important to design data-sharing health policy in order to promote innovation for better therapies and an efficient "healthcare ecosystem".

Keywords: Product Innovation Management, Cancer, Technological Paradigm, Target Therapy, Radical Innovation, Commons, Problem Solving, Data Sharing, Drug Discovery, Ecosystem, Health Policy.

Contents

[2] This research began …..The author declares that he has no relevant or material financial interests that relate to the research discussed in this paper.

Overview of the problem in the process of technological innovation

A technological paradigm and radical innovation are the main components of technological change in support of new products and services in markets; this technological change in turn induces social and economic change (Coccia, 2005; 2005a; 2012)[3].

In the field of the management of technology, it is important to explain the source and evolution of path-breaking innovations and *how* economic subjects (*e.g.* biopharmaceutical firms) achieve and sustain competitive advantage with new technology (Sahal, 1981; Dosi, 1988; Colombo *et al.*, 2014)[4]. In general, radical innovation is driven by several concomitant forces that may coexist in specific circumstances, and some scholars have described different approaches to explain the source of technological innovation (*e.g.* Ruttan, 1997; *cf.* Dixon, 1997; Hall and Rosenberg, 2010). However, the *general* driving force of the evolution of technology is a complex problem, which is hardly known.

The current study confronts this scientific issue by developing the conceptual framework of *problem-driven innovation*, which endeavours to explain the source and evolution of new technology in biopharmaceutical industry.

Theoretical background

Dosi (1982, p. 152, original emphasis) states that a technological paradigm is a: " 'model' and 'pattern' of solution of *selected* technological problems, based on *selected* principles derived from the natural science and on *selected* material technologies*"*. Technological paradigms play a vital role in society since they tend to support corporate, industrial and economic change (Coccia 2009a; 2012b; 2014c). The theoretical structure and dynamics of technological paradigms can be described by Teece (2008, p. 509, original emphasis): "Technological paradigms impose behavioural structures

[3] This study interchangeably uses the terms technological paradigm and radical innovation to indicate path-breaking innovations in society (Coccia, 2005; 2005a).

associated with 'normal' problem-solving activity. Paradigms imply the use of established problem-solving routines; they indicate where to focus resources and help identify blind alleys to avoid . . . . In short, technological paradigms fill a theoretical void by connecting the market to (at least some) technological possibilities".

In particular, the origin of new technological paradigms is underpinned in basic sciences such as physics, chemistry, and biology (Nelson, 2008). These scientific fields support technological advances that "break-out" current technological trajectories (Dolfsma and Leydesdorff, 2009, *passim*). As a matter of fact, scientific research activity can spur a faster progress of some technological paradigms, although "relationships between the ability to advance practical know-how and the strength of scientific knowledge underlying that know-how are complex" (Nelson, 2008, p. 487). Scholars argue that the evolution of science and technology is supported by a process of accumulation based on the ability to identify, control and replicate practices with "a certain amount of the 'routine' " (Nelson, 2008, p. 488). This process of (technical) knowledge accumulation is "vital for the growth of effective 'know-how' " (as quoted by v. Tunzelmann *et al.* 2008, p. 479). Sahal (1985, p. 70, original emphasis) claims that: "the origin of *revolutionary innovations* lies in certain *metaevolutionary* processes involving a combination of two or more *symbiotic* technologies whereby the structure of the integrated system is drastically simplified".

In general, the evolution of technological paradigms is driven by demand factors and technological opportunities associated with fruitful learning processes (Dosi, 1982; Dosi, 1988; Coccia, 2014c). According to Nelson (2008, p. 486 *passim*) a major role in the source and evolution of technological paradigm is played by the "conscious direction of efforts to advance practice, and recognition that efforts . . . are strongly oriented by the body of human know-how to advance practice". As a matter of fact, patterns of technological innovation are supported by investments in economic and human

[4] *Cf. also* Coccia, 1999; 2005; 2005a; 2005b; 2005c; 2005d; 2007; 2009; 2009a; ; 2009c; 2010; 2010a; 2010b; 2012b;2012c; 2012d; 2014; 2014a; 2014b, 2014c; 2014e; 2015a; Cariola and Coccia, 2002.

resources within R&D labs, and to a lesser degree by "effective demand" of markets (Nelson, 2008, p. 487)[5].

Usher (1954) proposed a theory to explain the evolution of innovations, using the theoretical framework of the Gestalt psychology (*cf.* Ruttan, 1959). Usher's theory of cumulative synthesis is based on four concepts (*see* Basalla, 1988, p. 23):

1. Perception of the problem: an incomplete pattern in need of resolution is recognized.
2. Setting stage: assimilation of data related to the problem.
3. Act of insight: a mental act finds a solution to the problem.
4. Critical revision: overall exploration and revision of the problem and improvements by means of new acts of insight.

This theory focuses on acts of insight that are basic to solve the problem. When the stage *two* is set and solution of the problem revised, economic intervention to the process of invention can be effective. The main implications of Usher's theory are the psychological aspects of invention and the evolution of new technology with a vital cumulative change (Basalla, 1988, p. 24).

In short, the evolution of new technology (*e.g.* technological paradigm) depends on several elements such as needs of society, economic resource, inventor's act of insight, effective demand, institutional interest, democratization, demographic change, major conflicts, etc. (*cf.* Coccia, 2010; 2014; 2014d; 2015a; Coccia *et al.,* 2012). A holistic view of the innovation process, based on interrelatedness and interactiveness of social, cultural economic and political factors, is important to understand the "ecology of innovation" that supports the technological change (Marcus, 1981, p. 446). The role of these factors in the impetus of technological paradigms changes according to the specificity of industries and geo-economic environment.

For instance, technological paradigms in drug discovery are generated by complex interactions of demand- and supply-side determinants (Afshar, 2003; Perpich, 2004). Coccia (2012, p. 271*ff*) argues that scientific research in medicine -to solve vital problems- generates radical innovations (*e.g.*

[5] Teece, 2008; *cf. also* Dosi, 1982, p. 148; Dosi, 1988 *passim.*

new drugs/therapies) that are associated, *a posteriori*, with moderate and/or severe side effects. Some studies have shown that the introduction of a path-breaking innovation in medicine is "probably never the optimal version" and problems (*e.g.* adverse effects) can be detected only *ex-post* in clinical practice (Gelijns and Rosenberg, 1994, p. 31). The problems of new drugs spur feedback mechanisms, which support a co-evolution of innovation in parallel pathways: *1*) incremental innovations in the presence of side effects; *2*) emergence of new radical innovations induced from severe side effects and/or major problems.

Overall, several works have provided many valuable insights into the theory of technological paradigm. However, the complex driving force of the source and evolution of path-breaking innovations is unknown (v. Tunzelmann et al. 2008, pp. 481-482; Teece, 2008, p. 510-511; Nelson, 2008, p. 496; Dixon, 1997). Ruttan (1997, p. 1524) argues that "each of the three approaches to understanding the source of technical change - induced technical change, evolutionary theory, and path dependence - is approaching a dead end. Attempts to construct bridges linking the separate approaches are now necessary to advance our understanding of the source of technical change".

It is clear that current approaches to the economics of technical change have trouble explaining the driving forces concerning the evolution of new technology. In particular, current literature does not explain the *evolution of technological paradigms, the core of technological change*. In fact, a more comprehensive framework about the *general* source of radical technology does not exist yet (*cf.* Ruttan, 1997).

Hence, the current study has the purpose to show one contributing factor the evolution of new technology in biopharmaceutical industry.

Conceptual framework and study design

The hypothetical approach of this study is based on the following working hypothesis ($HP\theta$), which the research design intends to instantiate:

HPθ: The source and evolution of new technology are driven by relevant and consequential *problems/needs* emerging during the general patterns of technological innovation, *ceteris paribus*.

This *HPθ, called problem-driven innovation,* is the core of the causal model in Figure 1.

In effect, this study hypothesizes that a relevant problem in society supports the origin of a new technological paradigm, uncertain and consequential problems induce the evolution of new technology by different trajectories, *ceteris paribus*.

- A basic assumption of the study is: The existence of a relevant problem/need in society.
- A relevant problem is a problem that induces high mortality in society.

The study design focuses on established and emerging radical innovations in oncology that are generating a revolution in the practice of medicine by new biopharmaceuticals and small-molecules.

- A radical innovation, generated from drug-discovery process, solves a specific problem, such as reduction of the mortality, reduction of side effects, increase of the life expectancy and wellbeing in society, etc.

Through an inductive study[6], based on new drugs for lung cancer, this paper endeavours to substantiate the *HPθ* explaining the evolution of technology in biopharmaceutical industry.

[6] For building theories from case study research, *see:* Eisenhardt (1989), Eisenhardt and Graebner (2007).

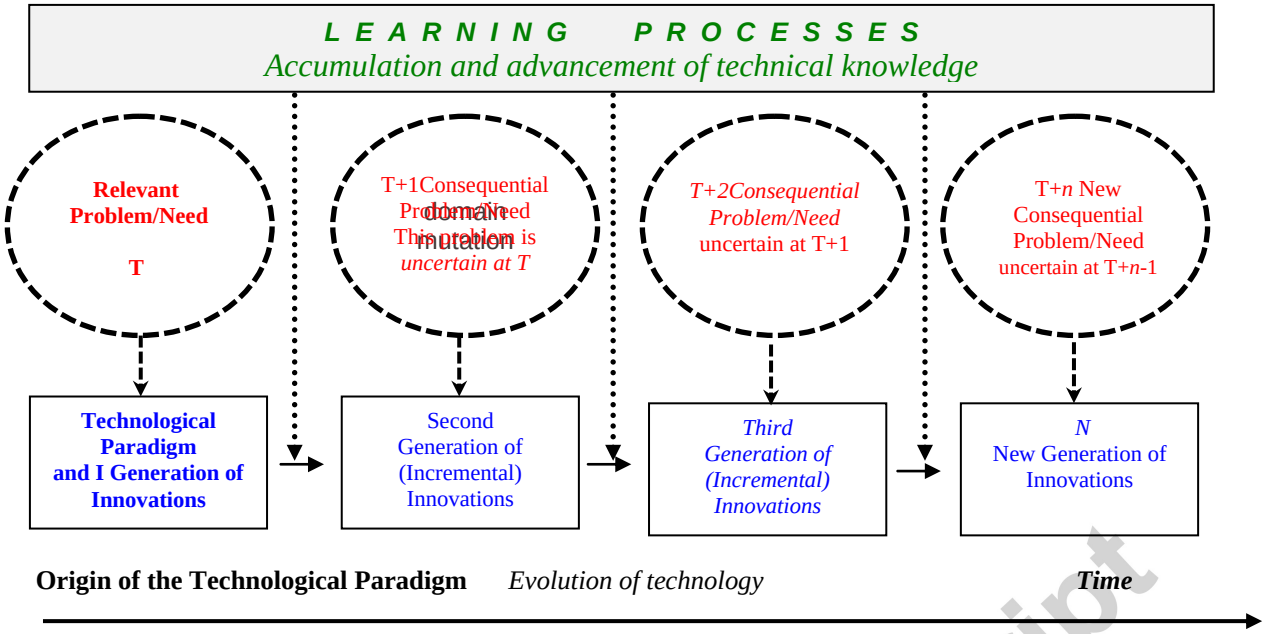

Figure 1: Conceptual framework of problem-driven innovation supporting the evolution of new technology

Lung cancer has one of the highest worldwide mortality rates of any disease—for both sexes (*cf.* Ferlay *et al.*, 2013). This study assumes that lung cancer is a relevant problem in society, and in a Schumpeterian world of innovation-based competition, leading firms in the drug-research industry have a primary incentive to find innovative solutions to unsolved problems in order to achieve the prospect of a (temporary) profit monopoly. This problem-solving activity of purposive firms generates a main impetus for the source and evolution of path-breaking anticancer drugs.

Overall, this new conceptual framework seeks to explain a vital determinant of the origin and evolution of radical innovations in medicine. It has also the potential to explain one main contributing factor of the long-term technological change in society.

Evidence

The evidence here instantiates the hypothesis HPθ by an inductive study based on new path-breaking drugs (innovations) for lung cancer.

- *A relevant problem in society: the lung cancer*

First of all, industrialization and population growth in modern societies induce more consumption and some damaging effects on ecosystem and society by resource depletion, pollution and also

diffusion of carcinogens (Rivers, 2003, p. 409; Belpomme *et al.*, 2007; Constant *et al.*, 2014; Coccia, 2013; 2015). Irigaray *et al.* (2007) argue that the growing incidence of a variety of cancer in advanced countries, after World War II, is due to several factors such as ageing of the population, progress in health technology, expansion of diagnostic and screening programs, and in particular, diffusion of environmental carcinogens driven by increasing industrialization of advanced countries (*cf.* Obe *et al.*, 2011; Hsu and Stedeford, 2010; Lewis and Maslin, 2015). In fact, cancer incidence (the number of new cases occurring annually) increased by 85% from 1950 to 2001 (Zeliger, 2011, p. 434). AstraZeneca (2015), a leading biopharmaceutical company, states that cancer is the world's biggest healthcare challenge because the deaths estimated are expected to reach more than 12 million by 2030.

Table 1 lists the four main types of cancer that have the highest worldwide incidence and mortality (*cf.* Vineis and Wild, 2014).

Table 1. Incidence and Mortality of main cancer across worldwide population (both sexes)

	Incidence			Mortality		
Cancer	Number	(%)	ASR (W)	Number	(%)	ASR (W)
Breast	1,671,149	11.9	43.1	521,907	6.4	12.9
Prostate	1,094,916	7.8	30.7	307,481	3.7	7.8
Lung	**1,824,701**	**13**	**23.1**	**1,589,925**	**19.4**	**19.7**
Colorectum	1,360,602	9.7	17.2	693,933	8.5	8.4

Note: Incidence data for all ages. ASR (W) and proportions per 100,000. Age-standardized rate (W): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer

Source: GLOBOCAN 2012 (IARC) *Section of Cancer Surveillance,* http://globocan.iarc.fr/Pages/fact_sheets_population.aspx *(16/1/2015)*

Among these cancers, lung cancer is a relevant problem in society because it has the highest worldwide mortality rate of all types of cancer (*see* Table 1, last column). Lung cancer can be either small cell lung cancer or non-small cell lung cancer (NSCLC), with the latter representing about 80% of cases. Risk factors include smoking (Buonanno and Ronzani, 2013), passive smoking (Payne, 2001), air pollution (*cf.* Molina *et al.*, 2008, *passim*), etc. Wang and Zhao (2011) claim that concentrations of industrial air pollutants and fine atmospheric particulates in some areas can be the carrier of toxic and carcinogenic agents (*e.g.* heavy metals, SO_2, etc.), which are the main causes of

cancers such as lung cancer[7]. Raaschou-Nielsen *et al.* (2013) show that each 5 μg/m^3 increase in $PM_{2.5}$ concentration[8], due to industrialization, can induce an 18% increase in lung cancer incidence. In short, the high mortality rate of lung cancer is a major unsolved problem in society. The following inductive study focuses on this issue as the impetus for the origin and evolution of new radical innovations in biopharmaceutical industry to solve it (as theoretically hypothesized by HPθ).

- *Evidence to substantiate HPθ and sequential linkages of the causal model in figure 1.*
  - ☐ *The relevant problem of high mortality rate of lung cancer and ineffectiveness of current chemotherapy-based treatments: the insurgence of radical innovation for lung cancer treatments as reversible inhibitor (Origin of a new technological paradigm).* Because it has the highest mortality rate of all cancers, lung cancer is a *vital problem* to solve in modern society. The current therapeutic treatments (technology) for advanced non-small cell lung cancer (NSCLC) are again mainly based on traditional chemotherapy agents (such as cisplatin and gemcitabine; carboplatin and paclitaxel, and so on). However, this traditional technology of anticancer drugs has low efficacy, which is confirmed by the current high mortality rate (19.7% ASR-W)[9] in comparison to breast and other cancers (*see* Tab.1). In order to solve this and other problems concerning the lung cancer, higher R&D investments by advanced countries and leading biopharmaceutical companies have generated critical scientific advances in genetics, genomics and proteomics[10]; these breakthroughs in molecular biology have laid the foundation for a major technological paradigm shift in therapeutic treatments for cancer, given by targeted cancer therapies, which "are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression" (as defined by National Cancer Institute, 2015).

[7] *cf.* also Bray *et al.*, 2013; Obe *et al.*,2011; Hsu and Stedeford, 2010; Pope *et al.*, 2002.

[8] µg=10^{-6} grams; PM=Particle pollution, also called particulate matter, is a mixture of solids and liquid droplets floating in the air. Fine particles ($PM_{2.5}$) are 2.5 micrometers in diameter or smaller, and are produced from all types of combustion, including motor vehicles, power plants, residential wood burning, and some industrial processes.

[9] Age-standardized rate (W): A rate is the number of new cases or deaths per 100 000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure. Standardization is neces-

In particular, molecular biology has shown that cancer cells display self-sufficiency of growth signals through the accumulation of genetic and epigenetic changes[11] (*e.g.* Epidermal Growth Factor: EGF). The EGF acts by binding with high affinity to the Epidermal Growth Factor Receptor (EGFR) on the cell surface and by stimulating the intrinsic protein-tyrosine kinase activity of the receptor, which ultimately leads to cancer cell proliferation. The presence on lung cancer cells of the EGFR (in the exon[12] 19 or 21), identified by biomarkers[13], is important to understand patient differences and a precondition for applying effective target therapies of personalized medicine, which blocks this cancer-specific target: EGFR (*cf.* Singer and Marsh, 2012; Van Dyck *et al.*, 2012). The *first generation of target therapy for non-small cells lung cancer(NSCLC)*—a new technological paradigm in lung cancer treatments—is based on the discovery of the EGFR blocking agents Gefitinib and Erlotinib to treat patients who have EGFR mutations in exon 19 or 21 (Fig. 2). Two main radical innovations apply these blocking agents to solve the relevant problem of high mortality for lung cancer: Iressa® (based on the blocking agent Gefitinib) by AstraZeneca Company (UK-Sweden) and Tarceva® (based on the blocking agent Erlotinib) commercialized by the Roche Group (Switzerland)[14]. These path-breaking anticancer drugs are generating a revolution in therapeutic treatments of NSCLC with EGFR because they block specific enzymes and growth factor receptors involved in cancer cell proliferation (Mitsudomi, 2005; Laack *et al.*, 2010; Boehringer-Ingelheim, 2015). These target therapies, called EGFR tyrosine kinase inhibitors (TKIs), represent ground-breaking anticancer drugs that are easily administered as

sary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer GLOBOCAN (2012, http://globocan.iarc.fr/ -accessed February 2015).

10 *Cf.* Afshar, 2003; Fraser and Pai, 2014.

11 Epigenetics is the study, in the field of genetics, of cellular and physiological phenotypic trait variations that are caused by external or environmental factors that switch genes on and off and affect how cells read genes instead of being caused by changes in the DNA sequence.

12 An exon is the portion of a gene that codes for amino acids.

13 A biomarker is a measurable indicator of the severity or presence of some disease state: " ' A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention' " (National Institute of Health, as quoted by Amir-Aslani and Mangematin, 2010, p. 204).

14 The literature is vast and not fully cited here, but a good list of references is found in Dempke *et al.* (2010, pp. 262-263 and pp. 271-274) and Coccia (2012a; 2014a).

one pill per day (taken also at home), unlike the standard platinum-based chemotherapy for lung cancer, which is administered intravenously at the hospital for treatment of solid malignancies (such as Cisplatin associated with gemcitabine for adenocarcinoma of the lung; Coccia, 2012; 2012a; 2014a). Patients with metastatic non-small cell lung cancer treated with the *first generation of target therapy for lung cancer* (Gefitinib and/or Erlotinib) have significantly longer progression-free survival in comparison with patients who received a combination of carboplatin plus paclitaxel (standard chemotherapy agents). In addition, Erlotinib in some cases decreases the mortality risk by 19% with an increase in median overall survival of patients, associated with lower toxicity and side effects (*cf.* Brugger *et al.*, 2009).

- *Consequential problem: Cancer can also grow by angiogenesis and other ways; these new problems have induced the evolution of this technology with the second generation of lung cancer target therapies based on irreversible inhibitors*. The progression-free survival of patients treated with path-breaking anticancer drugs of the first generation is increased but lung cancer mortality within a five-year period is always high (*i.e.* 5-year prevalence is low)[15]. Main studies of the biology of diseases show that cancer cells continue to grow by also attracting new blood vessels to receive nutrients and oxygen (Reck and Crinò, 2009).

  In order to solve this consequential problem for lung and other cancers by blocking the growth of blood vessels to tumors (angiogenesis) and, as a consequence, tumor growth, R&D investment of biopharmaceutical firms has led to the second generation of targeted therapy for (lung and other) cancer (commercialized from 2014). This second generation of targeted therapies (radical innovations) can block the growth of blood vessels feeding tumors (angiogenesis). In particular, new anticancer drugs target the vascular endothelial cell growth factor (VEGF), which plays a critical role in cancer angiogenesis of NSCLC and

[15] "cancer prevalence refers to the number of people who have previously received a diagnosis of cancer and who are still alive at a presented time point ... Therefore prevalence reflects both the incidence of cancer and its associated survival pattern" (Cancer Research UK, 2015).

other varieties of cancer[16] (Reck and Crinò, 2009, p. 2). These further scientific breakthroughs to treat NSCLC support the evolution of the initial technological paradigm, which is developing multi-inhibitor blocking agents targeting EGFR, human epidermal growth receptor 2 (HER2), and VEGFR signaling pathways (Figure 2). Promising target therapies for NSCLC are BIBF 1120- nintedanib (triple angiokinase inhibitor) and BIBW-2992 MA2- afatinib dimaleate (Dual irreversible EGFR and HER-2 inhibitor), both produced by the Boehringer-Ingelheim company (Germany). In July 2013, afatinib dimaleate (BIBW-2992, commercial name Gilotrif®) was approved by the U.S. Food and Drug Administration (FDA). Gilotrif is a new generation of target therapy indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) in exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test (Coccia, 2012a; 2014a). Minkovsky and Berezov (2008) show that Gilotrif® is active against lung cancers resistant to the first generation of EGFR inhibitors (*i.e.* Gefitinib and Erlotinib). Nintedanib, commercial name Vargate, is also a second-generation target therapy launched in 2015 for the treatment of NSCLC as a triple angiokinase inhibitor that inhibits vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR) tyrosine kinases, which may result in the induction of endothelial cell apoptosis. Crizotinib is another new drug used to treat advanced non-small cell lung cancer that has a mutated (changed) form of a gene called anaplastic lymphoma kinase (ALK). Crizotinib blocks the protein made by the mutated ALK gene and may stop the growth and spread of cancer cells. Crizotinib may also prevent the growth of new blood vessels that tumors need to grow. This second generation of target therapy is a type of tyrosine kinase inhibitor and a type of anti-angiogenesis agent (National Cancer Institute, 2015a).

[16] The evolution of technological paradigms in medicine is also based on developing new technological trajectories by "inventive analogical transfer" from experience and solutions in one knowledge area—source domain *e.g.* a type of

Overall, second generation of ground-breaking anticancer drugs is based on irreversible inhibitors and multi-targeted tyrosine kinase inhibitors with fruitful activity against EGFR and other ERBB family members[17] that further reduce lung cancer mortality, increasing the survival of patients.

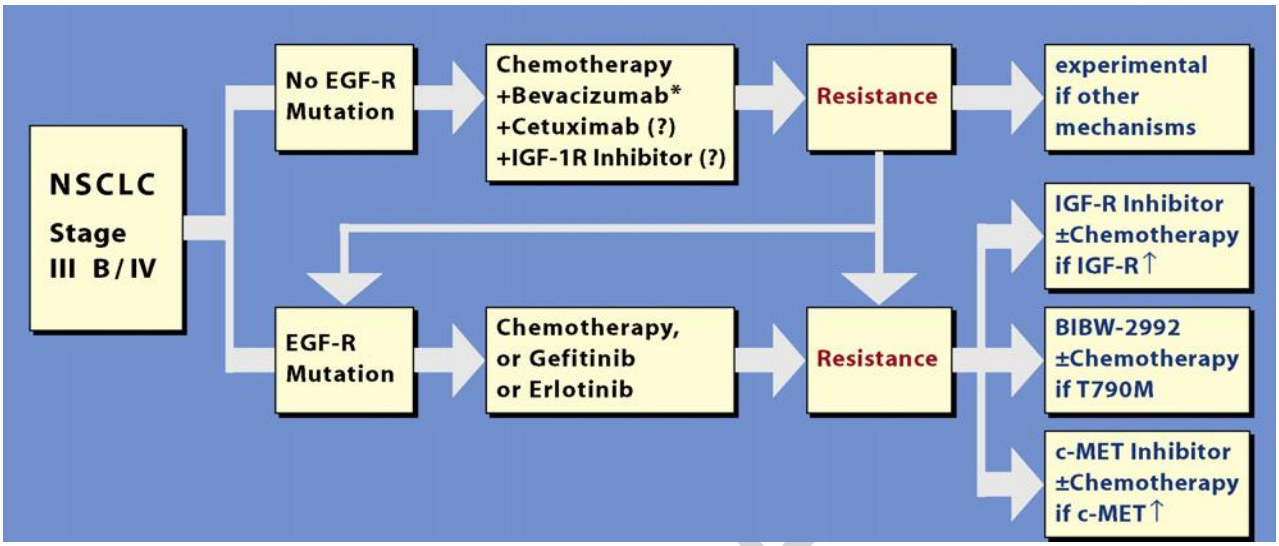

Figure 2: Treatment algorithms for EGFR blocking agents in lung cancer and evolution of technology to confront drug resistance.
Source: Dempke et al. (2010) Targeted therapies for non-small cell lung cancer, *Lung Cancer*, vol. 67, p. 265.

☐ *A new consequential problem: Cancer can become drug resistant to previous target therapies and grow due to a new mutation, called T790M. The evolution of technology with the ongoing third generation of lung cancer target therapies.*

The current generation of target therapy is effective for patients with non–small cell lung cancer (NSCLC) harboring activating mutations in the epidermal growth factor receptor (*EGFR*) kinase domain. These patients tend to respond well to these tyrosine kinase inhibitors (*i.e.:* Gefitinib, Erlotinib, Gilotrif, etc.). However, key studies show that lung cancer can become resistant in the short run to previous new drugs (*see* Lovly *et al.*, 2015, 2015a; 2015b). In particular, approximately 60 percent of patients with NSCLC typically relapse

cancer—to solve new problems in another field -target domain *e.g.* another type of cancer (*cf.* Kalogerakis *et al.*, 2010, p. 418).

[17] The ERBB protein family consists of 4 members: ErbB-1, also named epidermal growth factor receptor (EGFR); ErbB-2, also named HER2 (human epidermal growth receptor); ErbB-3, also named HER3; ErbB-4, also named HER4.

within 1–3 years of treatment due to drug resistance of the 1st and 2nd generation of target therapy. The drug resistance is caused by an acquired secondary *EGFR* kinase domain mutation, called *T790M* within exon 20[18]. The drug resistance to EGFR-directed therapy, due to the emergence of the T790M secondary mutation, generates a progression of lung cancer with several metastases and, as a consequence, mortality within five years. Currently, no targeted therapies are approved for treatment of this mutation, but this new consequential problem is supporting *new inhibitors of mutant EGFR lung cancer and other types of cancer* (Clovis Oncology, 2015). The 1st and 2nd generation of target therapy is originally designed to target wild type EGFR, whereas third generation of target therapy in lung cancer is mutant-selective designed to target mutant EGFR better than wild type EGFR. These new drugs for lung cancer are in clinical development in some biopharmaceutical firms (*e.g.* Clovis Oncology, AstraZeneca, etc.). Figure 3 shows new anticancer drugs developed by Clovis Oncology firm: Rociletinib (CO-1686), which is in Phase II development for the treatment of non-small cell lung cancer and Lucitanib, which is commencing Phase II clinical trials for the treatment of breast and lung cancers. In particular, Rociletinib (CO-1686) is a novel, oral, targeted covalent (irreversible) inhibitor of the cancer-causing mutant forms of epidermal growth factor receptor (EGFR) currently being studied for the treatment of non-small cell lung cancer (NSCLC). Rociletinib was designed to selectively target both the initial activating EGFR mutations and the T790M resistance mutation, while sparing normal EGFR at anticipated therapeutic doses, with an improved toxicity profile. Accordingly, it has the potential to be a first-line treatment in NSCLC patients with activating EGFR mutations and a second or later-line treatment in NSCLC patients who become resistant to EGFR-directed therapy due to the emergence of the T790M secondary mutation. In short, new anticancer

[18] T790M mutation results in an amino acid substitution at position 790 in EGFR, from a threonine –T- to a methionine –M. There is also L858R mutation within exon 21, which encodes part of the kinase domain, and occurs with a frequency of approximately 43% in EGFR-mutated lung tumors; The L861Q mutation occurs within exon 21, which occurs with a frequency of approximately 2% in EGFR-mutated lung tumors. The new anticancer drugs for these mutations are in progress (*cf.* Lovly *et al.*, 2015, 2015a; 2015b).

drug, Rociletinib, is designed to potently inhibit the mutant forms of EGFR (Clovis Oncology, 2015; 2014; 2014a).

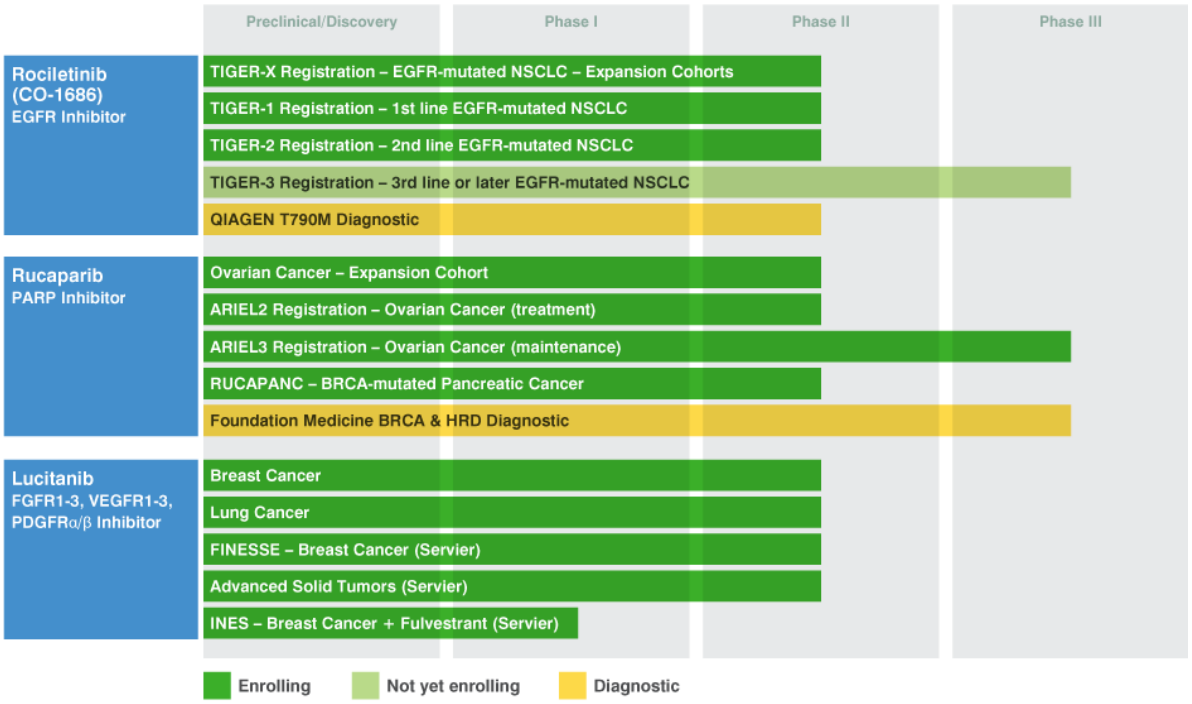

Figure 3: Third generation of path-breaking anticancer drugs in development pipeline by Clovis Oncology (2015) in pursuit of meaningful improvement in cancer treatments.

The biopharmaceutical company AstraZeneca is generating a similar potent, selective, irreversible inhibitor of both EGFR sensitising and T790M resistance mutations with less activity towards wild-type EGFR: this new compound is called AZD9291 (AstraZeneca, 2015a).

- *Evolution of innovative therapies in lung-cancer treatments.* The next generation of target therapies is for EGFR-mutant lung cancer. However, Thress *et al.* (2015, p. 560) in a recent study, which tests the new anti-cancer therapy AZD9291 for EGFR-mutant lung cancer (a subtype of non–small cell lung cancer), show new problems that will affect the evolution of technology of these target therapies, such as the: "diversity of mechanisms through which tumors acquire resistance to AZD9291 and highlight the need for therapies that are able to overcome resistance mediated by the EGFR C797S mutation".

Overall, then, this inductive study seems to substantiate the *HP0*: the origin of new technological paradigms and evolution of technology are driven by relevant and consequential problems emerging during their evolutionary pathways, *ceteris paribus.*

In fact, leading firms, within a Schumpeterian world of innovation-based competition—as in the drug-discovery industry—have the chief incentive to find innovative solutions/products for unsolved problems in order to achieve the prospective goal of a (temporary) monopoly of profits. Figure 4 shows the evolution of technology of new target therapies for lung cancer as hypothesized in the conceptual framework here.

The hypothesis of problem-driven innovation can explain the origin of new technological paradigms and evolution of technology in medicine by improved generations of path-breaking radical innovations to solve consequential problems, unknown at initial phases of development. In addition, this conceptual framework has also the potential to explain the *general* source and evolution of technology that support the long-term technological change for human development and progress in society.

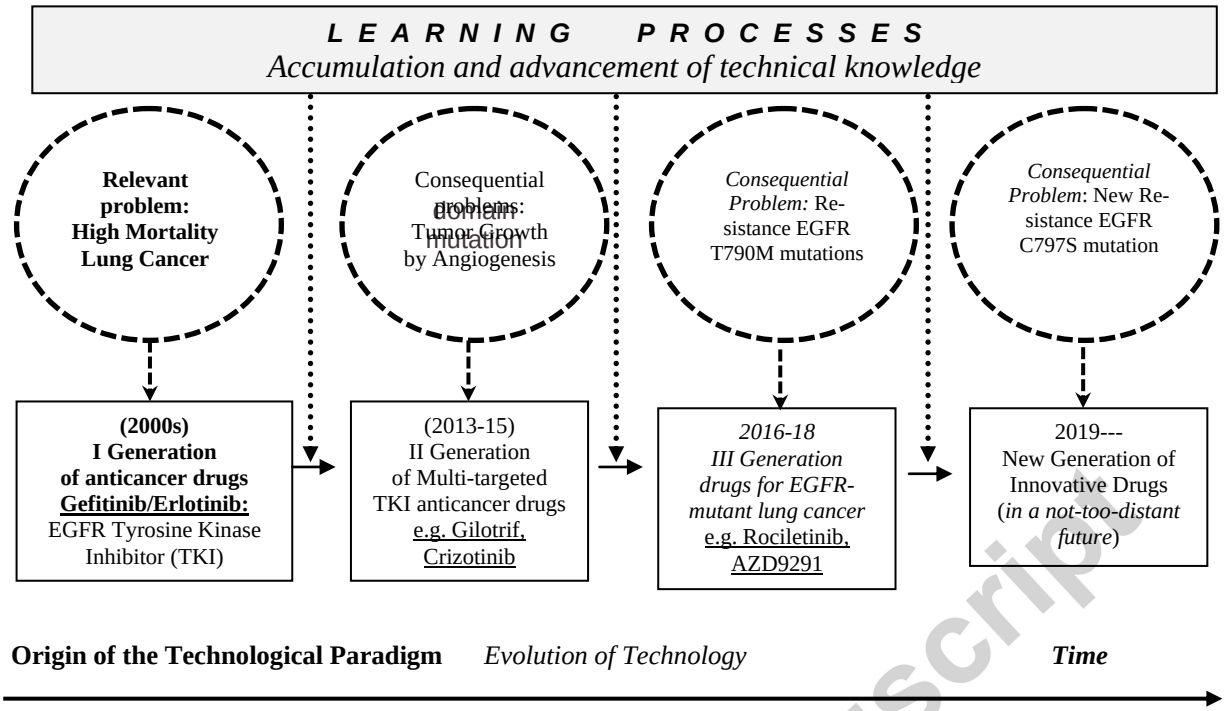

Figure 4: Model of co-evolution of the technological paradigm of target therapy in lung cancer with the evolution of consequential problems: problem-driven innovation hypothesis
Note: Names of new drugs are underlined; in parentheses are the year/period of approval by health authorities in the US/Europe.

□ Evaluation of the theory

The problem-driven innovation theory presented here can be assessed considering three main concepts of the philosophy of science: *consilience, simplicity and analogy* (Thagard, 1988, Chp. 5).

- The conceptual framework here (based on $HP\theta$) seems to be *consilient* (Thagard, 1988), since it explains a greater number of facts than other approaches. This conceptual framework seeks to explain one of the general driving forces of technological innovation in drug discovery. In fact, existent and emerging problems are an invariant feature of the origin and evolution of new technology. The $HP\theta$ has also the potential to be a general framework to explain source and evolution of technology in other research fields.
- The approach of problem-driven innovation is *simple* with few ad hoc and/or auxiliary assumptions, such as the existence of relevant and/or consequential problems. Moreover, the simple elements of the conceptual framework here are well known in the economic literature and man-

agement of technology. The idea that a problem is associated with a technological paradigm and radical innovation is not new in economics of technical change. It has already been used to explain this concept in economics of innovation (Usher, 1954; Dosi, 1982; Teece, 2008) and product innovation management (*cf.* Restuccia *et al.*, 2015; Atuahene-Gima and Wei, 2011). However, the concept of future consequential problems, unknown at initial stages, has not been used to explain the evolution of innovations in new, uncertain and different technological directions (Fig. 1).

- The characteristic of the *analogy* of this theory to explain different innovations is well established in the biopharmaceutical industry[19]. The problem-driven innovation $HP\theta$ is a theoretical framework that can be generalized because also in other industries the consequential problems play a vital role to induce innovation and new product development (*cf.* Calabrese *et al.*, 2005). Ruiz *et al.* (2012, p. 385ff) argue that innovation product management depends on accurately identifying problems across consumers. For instance, the "problem solving cycle" is a key activity of prototype-driven problem solving in heating products by using information of users (Bogers and Horst, 2014, p. 744). Restuccia *et al.* (2015) analyze the industrial equipment and supply sectors and show that the concept of product-related problems is vital for new product development; in particular, the role of distributors can support the innovation during the product life-cycle management. Critical problem-solving activity is also present in the semiconductor industry and it is associated with the main variable of speed because in this specific industry, with short product market life cycles, expeditious problem solving is an important goal to support continuous technological innovations in fast-changing and turbulent markets (Appleyard *et al.*, 2006). Macher and Mowery (2003), in semiconductor manufacturing, also find that allocating engineering resources to problem-solving activities, associated with information technology and schedule production, influence new process technologies and better manufacturing performance. In general, problem-solving competence is an important factor to develop and sustain

[19] *Cf.* Rosenberg *et al.*, 1995; Arora and Gambardella, 1995; Coccia, 2012.

competitive advantage of firms. In addition, Savino *et al.* (2015) show that innovations, in several industries, are due to a process of searching and recombining existing knowledge elements. Hence, problem-solving activity is basic for new product development since it translates environmental and organizational inputs into valuable new products and technology (*cf.* Atuahene-Gima and Wei, 2011, pp. 81-82; Coccia, 2001; Coccia and Rolfo, 2007; 2009; 2013, Coccia and Cadario, 2014)[20]. Overall, these similarities across several industries show that the problem-driven innovation hypothesis seems to be a comprehensive framework with the potential of explaining the general source and evolution of technology in different industries in the ecosystem.

Discussion and health policy implications

Analysing the underlying determinants of technological innovation in drug discovery is a complex task but it is very important to explain some general driving forces of technological change in society and support appropriate health policy (Gelijns and Rosenberg, 1994, p. 30*ff*; Rosenberg *et al.*, 1995). Laubach (1995, p. 212) argues that breakthroughs in biomedical sciences are based on continuous small scientific advances driven by the interaction between clinical research and clinical practice[21]. As a matter of fact, initial radical innovations in medicine have often several shortcomings[22] and feedback mechanisms with users and medical staff play a key role in the R&D process to detect problems and spur new drugs with higher efficacy and/or lower adverse effects (Gelijns and Rosenberg, 1994, p. 32*ff*; Coccia, 2012). In general, medical innovation, after introduction to the market, has a lot of uncertainty due to a variety of environmental circumstances (Gelijns and Rosenberg, 1994, p. 31-32; Coccia, 2012). Clinicians and patients provide the majority of information on shortcomings and consequential problems of new drugs to further support the *Development* phase by means of (incremental) innovations (Gelijns and Rosenberg, 1995a, p.91*ff*). A main factor of these patterns of technological innovation is a learning process, to solve specific problems, that supports the accumulation and advancement of technical knowledge (*cf.* Gelijns and Rosenberg,

[20] *See* Coccia (2009b) for some organizational issues that reduce technological performances.

21 An interesting example of fruitful technological development is the endoscope described by Gelijns and Rosenberg (1994; 1995; 1995a).

1995, p. 4*ff*). In fact, the Development phase, based on a bidirectional information flow between clinical research and clinical practice, supports the improvement of new drugs (Gelijns and Rosenberg, 1995a, p. 67). In particular, in the biopharmaceutical industry, the *Development* process of innovations continues after the drug is introduced to the market, driven by solution of consequential problems with breakthroughs and learning processes (Galway *et al.*, 2013; Gelijns and Rosenberg, 1994, p. 31). Hence, the *Development* phase deserves a particular attention by modern health policy to support drug-discovery process and overall "healthcare ecosystem" (Schulthess, 2013, p. 178; *cf.* also Gelijns and Rosenberg, 1994, p. 31).

The inductive study here has focused on a major health problem in society, the high mortality of lung cancer, which has laid the foundation for a vital technological paradigm of new anticancer targeted therapies. The evidence seems to substantiate the $HP\theta$: the origin of a new technological paradigm and the evolution of technology are driven by relevant and consequential problems emerging during their evolutionary pathways, *ceteris paribus* (*cf. also* Coccia, 2014b).

This evidence can be reinforced with the results showed by Coccia (2014a) in a quantitative analysis based on publications and patents. These findings are also confirmed by other studies, such as Coccia and Wang (2015, p. 155*ff*) show that: "the sharp increase of several technological trajectories of anticancer drugs applied by nanotechnology seems to be driven by high rates of mortality of some types of cancers (e.g. pancreatic and brain) in order to find more effective anticancer therapies that increase the progression-free survival of patients". The "technological trajectories mortality driven" are also problem-driven, because of high mortality in pancreatic and brain cancer. In short, relevant and consequential problems tend to be a main and general driving force (invariant) for orienting new directions of the evolution of technology.

The problem-driven innovation management is reinforced by continuous advances in molecular biology that investigate the root causes of problems concerning diseases within translational

22 *Cf.* Coccia (2009) for negative effects of other typologies of technological innovations in medicine.

medicine[23]. Future problems are in a *terra incognita* at the insurgence of a radical innovation, but the solution plays a vital role for the evolution of technology. This process supports new path-breaking drugs for a "personalized healthcare strategy" (Singer and Marsh, 2012). Moreover, the evolution of technology in medicine is also due to "inventive analogical transfer": from experience and solutions of consequential problems in one knowledge area—source domain *e.g.* a type of cancer—to solve new consequential problems in another field—target domain *e.g.* another type of cancer (Kalogerakis *et al.*, 2010, p. 418). In short, the co-evolution of a technological paradigm progresses with the interaction between new consequential problems and learning processes, such as in drug discovery with the continuous interaction of biomedical sciences, clinical research advances and clinical practice (cf. Gershon, 1998; Hirsh, 1997; Lenfant, 2003; Morlacchi and Nelson, 2011). In particular, the problem-driven innovation in biopharmaceutical industry is strictly associated with " 'learning via diffusion' …. The increased adoption of a technology paves the way for improvement in its characteristics" (Sahal, 1981, p. 114).

Overall, the conceptual framework here explains the co-evolution of new technology with the evolution of consequential problems, which is an invariant factor in the patterns of technological innovation.

- *Health policy of commodification of data concerning specific problems of new drugs*

The genomics Era plays a vital role to explore how human genes influence several diseases, and how the knowledge gained can contribute to better health through new therapies. International collaboration is important to study specific cancers and gather several data about problems of new anticancer drugs in order to improve the innovation processes in medicine (Kosseim et al., 2014). The integration of these data in health ecosystem is a main goal for science. A fruitful health policy is to induce a commodification of health information (concerning the emergence of problems-genetic mutations- with the use of new target therapies). A similar data-sharing health policy has:

[23] Translational medicine is: "the interplay between basic laboratory science and exploratory clinical research. It encompasses preclinical investigations of the biological effects of therapeutics as well as clinical investigations aimed at enhanced understanding of disease biology" (as defined by Roche, 2012).

"varying implications for how disease susceptibility and drug-response research will be pursued by the scientific community, and for who will benefit from resulting medical discoveries" (Foster and Sharp, 2007, p. 633). The data-sharing of genetic mutations induced by new drugs, as commons[24], is a basic resource in research labs to further support drug-discovery processes (Lucchi, 2013,). An appropriate health policy should promote a culture of collaborative data-sharing of results of these therapies, by means of international consortia and public research agreements, in order to support new patterns of technological innovation (Kaye *et al.*, 2009).

Figure 5: Health policy of data sharing to support drug discovery and new technology in biopharmaceutical industry.

The health policy should promote the link and network of genetic banks that will enable researchers to access to these research resources. This health policy of commodification of genetic data and other information of new drugs, through international collaboration of different public and private subjects, can accelerate discovery processes and translate research findings into clinical practice (Fig. 5). Moreover, the evolution of technology in oncology can be supported by an appropriate regulatory framework in "healthcare ecosystem" that improves the communication between developmental phase of new drugs in biopharmaceutical firms and clinical practice (cf. Schulthess, 2013; Troshani *et al.*, 2012). In fact, a modern health policy should support digital governance mechanisms to spur flows of data across subjects involved in drug discovery processes (Kaye, 2011). However, similar health policies of data sharing, *E*-governance and appropriate regulatory framework may have several impediments due to a complex interplay of stakeholders and their interests in biopharmaceutical industry.

[24] In economics, the commons is the cultural and natural resources accessible to all members of a society, not owned

Concluding Observations

The high mortality rate of lung cancer is a major unsolved problem in society and as theoretically hypothesized by $HP\theta$ has induced the origin of a new technological paradigm and evolution of technology of new anticancer drugs. The origin and development of path-breaking innovations in medicine tend to be driven by relevant and consequential problems; this nexus is confirmed by current R&D process of leading biopharmaceutical firms. For instance, Roche (2015) argues that the research process in medicine has to find: "innovative solutions for serious, currently unsolved medical problems". In fact, leading firms, within the Schumpeterian world of innovation-based competition, as in the biopharmaceutical industry, have a main incentive to find innovative solutions/products for unsolved problems in order to achieve the prospective goal of a (temporary) profit monopoly (Etro, 2004; Calvano 2006). The hypothesis of problem-driven innovation can explain the driving force of several innovations in medicine and has also the potential to explain the *general* source and evolution of technological paradigms that support the long-term development of technological change in several industries. Overall, the conceptual framework here is able to improve current approaches that explain the source of technology change (Dixon, 1997; Ruttan, 1997; von Tunzelmann *et al.*, 2008).

In particular,

(1) The conceptual framework assigns a central role to relevant problems to explain the origin of path-breaking innovations that sustain and safeguard the competitive advantage of firms and industries;

(2) The conceptual framework here is able to explain the evolution of new technology by consequential problems that induce learning processes and, as a consequence, innovative solutions;

---

privately (*cf.* Ostrom, 1990).

(3) The conceptual framework here is able to explain the *general* dynamics of the long-term development of new technological paradigms for sustaining corporate, industrial and economic change.

(4) Finally, the findings support a data-sharing policy and commodification of genetic resources and information of consequential problems detected in several cancers (such as, adverse effects, drug resistance, etc.) to construct biobank globally (as a commons) in order to induce drug discovery and better target therapies (innovations).

Hence, the conceptual framework here, substantiated in the field of drug discovery, has several components of generalization that could easily be extended to explain the source and evolution of new technology across several industries. In addition, this theoretical framework can support a new health policy that should be data-sharing oriented to accelerate the drug discovery, new therapies, and an efficient "healthcare ecosystem" (Schulthess, 2013, p. 178).

To explore the general implications of a comprehensive theoretical framework of the source of radical innovations in socio-economic systems, future research should (1) analyze the origin and evolution of additional forms of path-breaking innovations in different industries; (2) examine the general interaction between the problem-driven innovation approach and corporate, industrial, economic and social change; and (3) design a regulatory framework of *E*-governance of data sharing (as commons) to spur innovations in biomedical sciences.

Overall, then, this theory instantiated with an inductive study in drug discovery seems to show one main driving force of the evolution of new technology: problem-driven innovation, which is an invariant factor in product innovation management. However, the nexus from perception and solution of problems to technological innovation is a complex and problematic matter, since we know that other things are often not equal in current turbulent markets and technological change; in fact, Wright (1997, p. 1562) properly claims: "In the world of technological change, bounded rationality is the rule".

References

Afshar M. (2003) "From genes to products: innovations in drug discovery", *Drug Discovery Today*, vol. 8, n. 9, pp. 392-394.

Amir-Aslani A., Mangematin V. (2010) "The future of drug discovery and development: shifting emphasis towards personalized medicine", *Technology Forecasting & Social Change*, vol. 77, n. 2, pp. 203-217.

Appleyard M. M., Brown C., Sattler L. (2006) "An International Investigation of Problem-Solving Performance in the Semiconductor Industry", *Journal of Product Innovation Management*, vol. 23, n. 2, pp. 147–167.

Arora A., Gambardella A. (1995) "The division of innovative labor in biotechnology" in Rosenberg N., Gelijns A. C., Dawkins H. (Eds.), *Sources of Medical Technology: Universities and Industry*, Ch. 8

Astra Zeneca (2015) http://www.astrazeneca.com/Research/areas-of-interest (accessed April 2015)

AstraZeneca (2015a) "openinnovation", http://openinnovation.astrazeneca.com/what-we-offer/compound/azd9291/ (accessed October, 1st);

Atuahene-Gima K., Wei Y. (2011) "The Vital Role of Problem-Solving Competence in New Product Success", *Journal of Product Innovation Management*, vol. 28, n. 1, pp. 81–98.

Basalla G. (1988) *The History of Technology*, Cambridge University Press, Cambridge.

Belpomme D., Irigaray P., Hardell L., Clapp R., Montagnier L., Epstein S., Sasco A.J. (2007) "The multitude and diversity of environmental carcinogens", *Environmental Research*, vol. 105, n. 3, pp. 414-429.

Boehringer-Ingelheim (2015) https://www.boehringer-ingelheim.com/research_development/drug_discovery/drug_discovery_process.html (accessed April 2015).

Bogers M., Horst W. (2014) "Collaborative Prototyping: Cross-Fertilization of Knowledge in Prototype-Driven Problem Solving", *Journal of Product Innovation Management*, vol. 31, n. 4, pp. 744–764.

Bray F., Ren J.-S., Masuyer E., Ferlay J. (2013) "Global estimates of cancer prevalence for 27 sites in the adult population in 2008", *International Journal of Cancer*, vol. 132, n. 5, pp. 1133–1145.

Brugger W., Kim J.H., Hansen O., Triller N. (2009) "Molecular markers and clinical outcome with erlotinib: results from the phase III placebo-controlled SATURN study of maintenance therapy for advanced NSCLC", WCLC 2009: B9.1.

Buonanno P., Ranzani M. (2013) "Thank you for not smoking: Evidence from the Italian smoking ban", *Health Policy*, vol. 109, n. 2, pp. 192-199.

Calabrese G., Coccia M., Rolfo S. (2005) "Strategy and market management of new product development: evidence from Italian SMEs", *International Journal of Product Development*, vol. 2, n. 1-2, pp. 170-189.

Calvano E. (2006) "Destructive Creation", *Working Paper Series in Economics and Finance* no. 653, December, Stockholm School of Economics.

Cancer Research UK (2015) http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/prevalence/prevalence-uk (accessed April 2015).

Cariola M., Coccia M. (2002) "Analisi di un sistema innovativo regionale e implicazioni di policy nel processo di trasferimento tecnologico", *Working Paper Ceris del Consiglio Nazionale delle Ricerche*, Anno IV, n. 6, Torino (Italy).

Cavallo, E., Ferrari E., Bollani, L., Coccia M. (2014) "Attitudes and behaviour of adopters of technological innovations in agricultural tractors: A case study in Italian agricultural system", *Agricultural Systems*, Vol. 130, pp. 44-54.

Cavallo, E., Ferrari E., Bollani, L., Coccia M. (2014a) "Strategic management implications for the adoption of technological innovations in agricultural tractor: the role of scale factors and environmental attitude", *Technology Analysis & Strategic Management*, Vol. 26, n. 7, August, pp. 765-779.

Clovis Oncology (2014) CO-1686-Presented at the IASLC 14th Annual Targeted Therapies of the Treatment of Lung Cancer Meeting February 2014.

Clovis Oncology (2014a) Phase 1 evaluation of CO-1686, an irreversible, mutant-selective inhibitor of EGFR mutations (activating and T790M) — *Presented at the 4th European Lung Cancer Conference March 2014*

Clovis Oncology (2015) http://www.clovisoncology.com/products-companion-diagnostics/rociletinib/, accessed February 2015

Coccia M. (1999) "Trasferimento tecnologico ed autofinanziamento", in *Working Paper Ceris del Consiglio Nazionale delle Ricerche*, Anno I, n. 2, Torino (Italy).

Coccia M. (2001) "Satisfaction, work involvement and R&D performance", *International Journal of Human Resources Development and Management*, vol. 1, no. 2/3/4, pp. 268-282.

Coccia M. (2005) "Technometrics: Origins, historical evolution and new direction", *Technological Forecasting & Social Change*, vol. 72, n. 8, pp. 944-979.

Coccia M. (2005a) "Measuring Intensity of technological change: The seismic approach", *Technological Forecasting and Social Change*, vol. 72, n. 2, pp. 117-144.

Coccia M. (2005b) "Countrymetrics: valutazione della performance economica e tecnologica dei paesi e posizionamento dell'Italia", *Rivista Internazionale di Scienze Sociali*, vol. CXIII, n. 3/2005, pp. 377-412.

Coccia M. (2005c) "A taxonomy of public research bodies: a systemic approach" in *Prometheus*, vol. 23, n. 1, pp. 63-82.

Coccia M. (2005d) "Metrics to measure the technology transfer absorption: analysis of the relationship between institutes and adopters in northern Italy" in *International Journal of Technology Transfer and Commercialization*, vol. 4, n. 4, pp. 462-486

Coccia M. (2007) "A new taxonomy of country performance and risk based on economic and technological indicators", *Journal of Applied Economics*, vol. 10, n. 1, pp. 29-42.

Coccia M. (2009) "Measuring the impact of sustainable technological innovation", *International Journal of Technology Intelligence and Planning*, vol. 5, n. 3, pp. 276-288.

Coccia M. (2009a) "What is the optimal rate of R&D investment to maximize productivity growth?", *Technological Forecasting & Social Change*, vol. 76, n. 3, pp. 433-446.

Coccia M. (2009b) "Bureaucratization in public research institutions", *Minerva, A Review of Science, Learning and Policy* - vol.47, n. 1, pp. 31-50.

Coccia M. (2009c) "A new approach for measuring and analyzing patterns of regional economic growth: empirical analysis in Italy" in *Italian Journal of Regional Science- Scienze Regionali*, Vol. 8, n. 2, pp. 71-95.

Coccia M. (2010) "Democratization is the driving force for technological and economic change", *Technological Forecasting & Social Change,* vol. 77, n. 2, pp. 248-264.

Coccia M. (2010a) "Energy metrics for driving competitiveness of countries: Energy weakness magnitude, GDP per barrel and barrels per capita", *Energy Policy,* vol. 38, n. 3, pp. 1330-1339.

Coccia M. (2010b) "Public and private R&D investments as complementary inputs for productivity growth" *in International Journal of Technology, Policy and Management,* vol. 10, n. 1/2, pp. 73-91.

Coccia M. (2012) "Driving forces of technological change in medicine: Radical innovations induced by side effects and their impact on society and healthcare", *Technology in Society,* vol. 34, n.4, pp. 271-283.

Coccia M. (2012a) "Evolutionary growth of knowledge in path-breaking targeted therapies for lung cancer: radical innovations and structure of the new technological paradigm", *International Journal of Behavioural and Healthcare Research,* vol. 3, ns. 3-4, pp. 273-290.

Coccia M. (2012b) "Political economy of R&D to support the modern competitiveness of nations and determinants of economic optimization and inertia", *Technovation,* vol. 32, n. 6, pp. 370–379.

Coccia M. (2012c) "Cartilage tissue engineering with chondrogenic cells versus artificial joint replacement: the insurgence of new technological paradigms" in *Health and Technology,* vol. 2, n. 4, pp. 235-247.

Coccia M. (2012d) "Converging genetics, genomics and nanotechnologies for groundbreaking pathways in biomedicine and nanomedicine", *Int. J. Healthcare Technology and Management,* Vol. 13, No. 4, pp. 184-197.

Coccia M. (2013) "The effect of country wealth on incidence of breast cancer", *Breast Cancer Research and Treatment,* vol. 141, n. 2, pp. 225-229.

Coccia M. (2014) "Driving forces of technological change: The relation between population growth and technological innovation-Analysis of the optimal interaction across countries", *Technological Forecasting & Social Change,* vol. 82, n. 2, pp. 52-65.

Coccia M. (2014a) "Path-breaking target therapies for lung cancer and a far-sighted health policy to support clinical and cost effectiveness", *Health Policy and Technology,* vol. 1, n. 3, pp. 74-82.

Coccia M. (2014b) "Emerging technological trajectories of tissue engineering and the critical directions in cartilage regenerative medicine", *Int. J. Healthcare Technology and Management,* vol. 14, n. 3, pp. 194-208.

Coccia M. (2014c) "Converging scientific fields and new technological paradigms as main drivers of the division of scientific labour in drug discovery process: the effects on strategic management of the R&D corporate change", *Technology Analysis & Strategic Management,* Vol. 26, n. 7, pp. 733-749.

Coccia M. (2014d) "Socio-cultural origins of the patterns of technological innovation: What is the likely interaction among religious culture, religious plurality and innovation? Towards a theory of socio-cultural drivers of the patterns of technological innovation", *Technology in Society,* vol. 36, n. 1, pp. 13-25.

Coccia M. (2014e) "Emerging technological trajectories of tissue engineering and the critical directions in cartilage regenerative medicine", *Int. J. Healthcare Technology and Management,* vol. 14, n. 3, pp. 194-208.

Coccia M. (2015) "The Nexus between technological performances of countries and incidence of cancers in society", *Technology in Society*, vol. 42, August, pp. 61-70.

Coccia M. (2015a) "General sources of general purpose technologies in complex societies: Theory of global leadership-driven innovation, warfare and human development", *Technology in Society*, vol. 42, August, pp. 199-226.

Coccia M., Cadario E. (2014) "Organisational (*un*)learning of public research labs in turbulent context", *International Journal of Innovation and Learning*, vol. 15, n. 2, pp.115-129.

Coccia M., Rolfo S. (2007) "How research policy changes can affect the organization and productivity of public research institutes", *Journal of Comparative Policy Analysis, Research and Practice*, vol. 9, n. 3, pp. 215-233.

Coccia M., Rolfo S. (2009) "Project management in public research organization: strategic change in complex scenarios" in *International Journal of Project Organisation and Management*, vol. 1, no. 3, pp. 235-252.

Coccia M., Rolfo S. (2013) "Human Resource Management and Organizational Behavior of Public Research Institutions", *International Journal of Public Administration*, vol. 36, n. 4, pp. 256-268.

Coccia M., U. Finardi, D. Margon (2012) "Current trends in nanotechnology research across worldwide geo-economic players", *The Journal of Technology Transfer*, vol. 37, n. 5, pp. 777-787.

Coccia M., Wang L. (2015) "Path-breaking directions of nanotechnology-based chemotherapy and molecular cancer therapy", *Technological Forecasting and Social Change*, Vol. 94, May, pp. 155–169.

Colombo M. G., Franzoni C., Veugelers R. (2014) "Going radical: producing and transfering disruptive innovation", *The Journal of Technology Transfer*, vol. 40, n. 4, pp. 663-669.

Constant K., Nourry C., Seegmuller T. (2014) "Population growth in polluting industrialization", *Resource and Energy Economics*, vol. 36, n. 1, pp. 229-247.

Dempke, W.C.M., Sutob, T. and Reck, M. (2010) "Targeted therapies for non-small cell lung cancer", *Lung Cancer*, vol. 67, n. 3, pp. 257–274.

Dixon H. (1997) "Controversy: The Source and Measurement of Technical Change- Editorial Note", *The Economic Journal*, vol. 107 (September), pp. 1518-1519.

Dolfsma W., Leydesdorff L. (2009) "Lock-in and break-out from technological trajectories: Modeling and policy implications", *Technological Forecasting and Social Change*, vol. 76, n. 7, pp. 932-941.

Dosi G. (1982) "Technological paradigms and technological trajectories. A suggested interpretation of the determinants and directions of technical change", *Research Policy*, vol. 2, n.3, pp. 147-162.

Dosi G. (1988) "Sources procedures and microeconomic effects of innovation", *Journal of Economic Literature*, vol. 26, n. 3, pp. 1120-1171.

Eisenhardt K.M. (1989) "Building theories from case study research", *The Academy of Management Review*, vol. 14, n. 4, pp. 532-550.

Eisenhardt K.M., Graebner M. E. (2007) "Theory Building from cases: opportunities and challenges", *The Academy of Management Review*, vol. 50, n. 1, pp. 25-32.

Etro F. (2004) "Innovation by leaders", *The Economic Journal*, vol. 114, April, pp. 281-303.

Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., Rebelo M., Parkin D.M., Forman D., Bray, F. (2013) *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]*. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 19/06/2014.

Foster M. W., Sharp R. R. (2007) "Share and share alike: deciding how to distribute the scientific and social benefits of genomic data", *Nature Reviews - Genetics*, vol. 8, August, pp. 633-639.

Fraser H., Pai A. (2014) "The role of genomic medicine in transforming healthcare", *Health Policy and Technology*, vol. 3, n. 4, pp. 223–225.

Galway L., O'Neill S., Donnelly M., Nugent C., McClean S., Scotney B. (2013) "Stakeholder involvement guidelines to improve the design process of assistive technology: lesson from the development of the MPVS system", *Health and Technology*, vol. 3, n. 2, pp. 119-127.

Gelijns A. C., Rosenberg N. (1994) "The dynamics of technological change in medicine", *Health Affairs*, vol. 13, n. 3, pp. 28-46.

Gelijns A. C., Rosenberg N. (1995) "The changing nature of medical technology development", in Rosenberg N., Gelijns A. C., Dawkins H. (1995) Eds. *Sources of Medical Technology: Universities and Industry*; Ch. 1.

Gelijns A. C., Rosenberg N. (1995a) "From the scalpel to the scope: endoscopic innovations in gastroenterology, gynecology, and surgery" in Rosenberg N., Gelijns A. C., Dawkins H. (1995) Eds. *Sources of Medical Technology: Universities and Industry*; Ch. 4.

Gershon, E.S. (1998) "Making progress: Does clinical research lead to breakthroughs in basic biomedical sciences?" *Perspectives in Biology and Medicine*, vol. 42, n. 1, pp. 95–102.

GLOBOCAN (2012) IARC-*Section of Cancer Information*, Available from http://globocan.iarc.fr/ (accessed 16 January 2015).

Hall B. H., Rosenberg N. (eds.) (2010) *Handbook of the Economics of Innovation*, vol. 1 and 2, Elsevier.

Hirsh J. (1997) "The role of clinical investigation in medicine: historical perspective from the Rockefeller University", *Perspectives in Biology and Medicine*, vol. 41, n. 1, pp. 108-117.

Hsu C. H., Stedeford T. (2010) *Cancer Risk Assessment: Chemical Carcinogenesis, Hazard Evaluation, and Risk Quantification*, Wiley.

Irigaray P., Newby J. A., Clapp R., Hardell L., Howard V., Montagnier L., Epstein S., Belpomme D. (2007) "Dossier Cancer: Influence of environment Lifestyle-related factors and environmental agents causing cancer: An overview", *Biomedicine & Pharmacotherapy*, vol. 61, n. 10, pp. 640-658.

Kalogerakis K., Lüthje C., Herstatt C. (2010) "Developing Innovations Based on Analogies: Experience from Design and Engineering Consultants", *Journal of Product Innovation Management*, vol. 27, n. 3, pp. 418–436.

Kaye J. (2011) "From single biobanks to international networks: developing-governance", *Hum Genet*, 130, pp. 377–382.

Kaye J., Heeney C., Hawkins N., de Vries J., Boddington P. (2009) "Data sharing in genomics - reshaping scientific practice", *Nat Rev Genet*, 10, pp. 331–335.

Kim, L., Nelson, R.R. (2000) *Technology, Learning and Innovation*, Cambridge University Press, Cambridge, UK.

Kosseim P., Dove E. S, Baggaley C., Meslin E. M., Cate F. H., Kaye J., Harris J. R. and Knoppers B. M. (2014) "Building a data sharing model for global genomic research", *Genome Biology*, 15:430, pp. 1-7.

Laack E., Sauter G., Bokemeyer C. (2010) "Lessons learnt from gefitinib and erlotinib: key insights into small-molecule EGFR-targeted kinase inhibitors in non-small cell lung cancer", *Lung Cancer*, vol. 69, n.3, pp. 259-264.

Laubach G. D. (1995) "Perspectives on industrial R&D management", in Rosenberg N., Gelijns A. C., Dawkins H. (Eds.), *Sources of Medical Technology: Universities and Industry*, Ch. 9.

Lenfant C. (2003) "Clinical research to clinical practice. Lost in translation?" *New England Journal of Medicine*, vol. 349, n. 9, pp.868–874.

Lewis S. L., Maslin M. A. (2015) "Defining the Anthropocene-PERSPECTIVES", *Nature*, vol. 519, pp. 171-180, 1 2 March, doi:10.1038/nature14258.

Lovly C., Horn L., Oxnard G., Pao W. (2015) "EGFR c.2369C>T (T790M) Mutation in Non-Small Cell Lung Cancer", *My Cancer Genome* http://www.mycancergenome.org/content/disease/lung-cancer/egfr/4/(Updated March 5).

Lovly C., Horn L., Pao W. (2015a) "EGFR c.2573T>G (L858R) Mutation in Non-Small Cell Lung Cancer". *My Cancer Genome* http://www.mycancergenome.org/content/disease/lung-cancer/egfr/5/ (Updated March 5).

Lovly C., Horn L., Pao W. (2015b) "EGFR c.2582T>A (L861Q) Mutation in Non-Small Cell Lung Cancer". *My Cancer Genome* http://www.mycancergenome.org/content/disease/lung-cancer/egfr/6/ (Updated March 6).

Lucchi N. (2013) "Understanding genetic information as a commons: from bioprospecting to personalized medicine", *International Journal of the Commons*, Vol. 7, no 2, pp. 313–338.

Macher J. T., Mowery D. C. (2003) "Managing Learning by Doing: An Empirical Study in Semiconductor Manufacturing", *Journal of Product Innovation Management*, vol. 20, n. 5, pp. 391–410.

Marcus A. A. (1981) "Policy uncertainty and technological innovation", *The Academy of Management Review*, vol. 6, n. 3, pp. 443-448.

Minkovsky, N. and Berezov, A. (2008) "BIBW-2992, a dual receptor tyrosine kinase inhibitor for the treatment of solid tumors", *Current Opinion in Investigational Drugs*, vol. 9, n. 12, pp.1336-1346.

Mitsudomi, T., Kosaka, T., Endoh, H., Horio, Y., Hida T., Mori, S., Hatooka, S., Shinoda, M., Takahashi, T. and Yatabe, Y. (2005) "Mutations of the Epidermal Growth Factor Receptor Gene Predict Prolonged Survival after Gefitinib Treatment in Patients With Non–Small-Cell Lung Cancer With Postoperative Recurrence", *Journal of Clinical Oncology*, vol. 23, n. 11, pp. 2513-2520.

Molina J.R., Yang P., Cassivi S.D., Schild S.E., Adjei A.A. (2008) "Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship", *Mayo Clinic Proceedings*, vol. 83, n. 5, pp.584-594.

Morlacchi P., Nelson R. R. (2011) "How medical practice evolves: Learning to treat failing hearts with an implantable device", *Research Policy*, vol. 40, n. 4, pp. 511-525.

National Cancer Institute (2015) http://www.cancer.gov/ (accessed January 2015).

National Cancer Institute (2015a) http://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq#section/_231 (accessed October 2015).

Nelson R. R. (2008) "Factors affecting the power of technological paradigms", *Industrial and Corporate Change,* vol. 17, n. 3, pp. 485-497.

Obe G., Marchant G. E., Jandrig B., Schutz H., Wiedemann P. M. (2011) *Cancer Risk Evaluation: Methods and Trends,* Wiley.

Ostrom, E. 1990. *Governing the Commons: The Evolution of Institutions for Collective Action.* Cambridge: Cambridge University Press.

Page S. E. (2006) "Path Dependence" *Quarterly Journal of Political Science,* vol. 1, n.1, pp. 87–115.

Payne, S. (2001) " 'Smoke like a man, die like a man'?": A review of the relationship between gender, sex and lung cancer', *Social Science & Medicine,* vol. 53, n. 8, pp. 1067-1080.

Perpich, J. G. (2004) "The dawn of genomic and regenerative medicine: new paradigms for medicine, the public's health, and society", *Technology in Society,* vol. 26, n. 2-3, pp. 405-414.

Pope C., Burnett R., Thun M., et al. (2002) "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution", *JAMA,* vol. 287, n. 9, pp. 1132–41.

Raaschou-Nielsen O., Andersen Z.J., Beelen R., et al. (2013) "Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)", *Lancet Oncology,* vol. 14, n. 9, pp. 813–822.

Reck, M. and Crinò, L. (2009) "Advantages in anti-VEGF and anti-EGFR therapy for advanced non-small cell lung cancer", *Lung Cancer,* vol. 63, n. 1, pp. 1-9.

Restuccia M., de Brentani U., Legoux R., Ouellet J. F. (2015) "Product Life-Cycle Management and Distributor Contribution to New Product Development", *Journal of Product Innovation Management,* online : 4 FEB 2015, DOI: 10.1111/jpim.12261

Rivers T. J. (2003) "Technology and the use of nature", *Technology in Society,* vol. 25, n. 3, pp. 403-416

Roche (2012) http://www.rochecanada.com (accessed 15 November 2012).

Roche (2015) http://www.roche.com/research_and_development/who_we_are_how_we_work/ research_process/value_chain.htm (accessed April 2015)

Rosenberg N., Gelijns A. C., Dawkins H. (1995) Eds. *Sources of Medical Technology: Universities and Industry*; Committee on Technological Innovation in Medicine, Institute of Medicine-ISBN: 0-309-58761.

Ruiz D., Jain D., Grayson K. (2012) "Sub-problem Decomposition: An Exploratory Research Method for Effective Incremental New Product Development", *Journal of Product Innovation Management,* vol. 29, n. 3, pp. 385–404.

Ruttan V. W. (1959) "Usher and Schumpeter on invention, innovation and technological change", *Quarterly Journal of Economics,* vol. 73, n. 4, pp. 596-606.

Ruttan V.W. (1997) "Induced innovation, evolutionary theory and path dependence: sources of technical change", *Economic Journal,* vol. 107, pp. 1520–1529.

Sahal D. (1981) *Patterns of Technological Innovation,* Addison-Wesley, Reading, Massachusetts

Sahal, D. (1985) "Technological guideposts and innovation avenues", *Research Policy,* vol. 14, n. 2, pp. 61-82.

Savino T., Messeni Petruzzelli A., Albino V. (2015) "Search and Recombination Process to Innovate: A Review of the Empirical Evidence and a Research Agenda", *International Journal of Management Reviews*, Article first published online: 24 August 2015, DOI: 10.1111/ijmr.12081

Schulthess D. (2013) "Innovation requires a new regulatory framework to improve research and development of new medical therapies", *Health Policy and Technology*, vol. 2, n. 4, pp. 178–180.

Singer D. R.J., Marsh A. (2012) "Challenges and solutions for personalizing medicines", *Health Policy and Technology*, vol. 1, n. 1, pp. 50-57.

Teece D. J. (2008) "Dosi's technological paradigms and trajectories: insights for economics and management", *Industrial and Corporate Change*, vol. 17, n. 3, pp. 507-512.

Thagard P. (1988) *Computational Philosophy of Science*, The MIT Press, Cambridge, MA (USA).

Thress K. S, Paweletz C. P., Felip E., Cho B. C., Stetson D., Dougherty B., Lai Z., Markovets A., Vivancos A., Kuang Y., Ercan D., Matthews S. E., Cantarini M., Barrett J. C., Jänne P. A., Oxnard G. R. (2015) "Acquired *EGFR* C797S mutation mediates resistance to AZD9291 in non–small cell lung cancer harboring *EGFR* T790M", *Nature Medicine*, vol. 21, n. 6, June, pp. 560-564.

Troshani I., Goldberg S., Wickramasinghe N. (2012) "A regulatory framework for pervasive e-health: A case study", *Health Policy and Technology*, vol. 1, n. 4, pp. 199–206.

Usher A. P. (1954) *A history of mechanical inventions*, Harvard University Press, Cambridge.

Van Dyck W., Gassull D., Vértes G., Jain P., Palaniappan M., Schulthess D., Tambuyzer E., Hudson R., and others (2012) "Unlocking the value of personalised healthcare in Europe—breast cancer stratification", *Health Policy and Technology*, vol. 1, n. 2, pp. 63–68.

Vineis P., Wild C. P. (2014) "Global cancer patterns: causes and prevention", *The Lancet*, vol. 383, n. 9916, pp. 549-557.

von Tunzelmann N., Malerba F., Nightingale P., Metcalfe S. (2008) "Technological paradigms: past, present and future", *Industrial and Corporate Change*, vol. 17, n. 3, pp. 467-484.

Wang S., Zhao Y. (2011) "Air Pollution and Lung Cancer Risks", *Reference Module in Earth Systems and Environmental Sciences*, from *Encyclopedia of Environmental Health*, pp. *26-38*, Current as of 10 December 2013.

Wright G. (1997) "Towards A More Historical Approach to Technological Change", *The Economic Journal*, vol. 107, September, pp. 1560-1566.

Zeliger H. (2011) *Human Toxicology of Chemical Mixtures-Toxic Consequences Beyond the Impact of One-Component Product and Environmental Exposures* (Second Edition), Elsevier.

HIGHLIGHTS

PROBLEM-DRIVEN INNOVATIONS IN DRUG DISCOVERY:
CO-EVOLUTION OF THE PATTERNS OF RADICAL INNOVATION WITH THE EVOLUTION OF PROBLEMS

- Molecular biology is supporting the drug discovery
- Specific problems support source and evolution of technology in medicine
- Stakeholders in biopharmaceutical industry have incentives to find innovative solutions for unsolved problems
- Target therapy for lung cancer is generating a revolution in clinical practice
- Data-sharing policies promote R&D process for an efficient healthcare ecosystem