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SUCCESS OF DRUG DEVELOPMENT IN CANCER DISEASE: RADICALNESS AND SOCIAL CAPITAL[1]

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Abstract

Cancer is the most dangerous noncommunicable disease. It causes nine million people deaths per year, and patients need effective drugs to cure it, so how to improve its success rate becomes a major issue. We explore whether an organization that develops radical or incremental drugs has more opportunities to succeed. We also try to ascertain whether social capital embedded in health networks is an important channel to foster the impact of radicalness on the success of drug development. To this end, this paper provides a new method to link indicators of radicalness and success of drug development. We collect data about cancer clinical trials and classify drugs into molecular entities and therapeutic biological products. The results show that in molecular entities development, the organizations with radical drug development are more likely to get success. However, this relationship is not significant in therapeutic biological product development. Social capital is a favorable source to increase the success possibility of drug development, but it does not foster the impact of radicalness of drug development on success. This research gives some theoretical contributions on the benefits of drug development for organizations and provides some suggestions to organizations and policymakers on how to improve drug development in the field of cancer disease.

Keywords: radicalness of drug development, success of drug development, social capital

1. Introduction

In the pharmaceutical industry, the efficiency of new drug development has been declining for decades (Scannell et al., 2012). The organizations adopt different methods to stimulate the efficiency of new drug development in different sectors (Inauen & Schenker-Wicki, 2012, Robbins & O'Gorman, 2015). The development of a new drug follows a standardized chain of events, which starts with basic research and ends with the market launch of a new drug. In general, it takes more or less eight years to develop a new cancer drug before commercialization (e.g. Kaitin, 2010, Kaitin & DiMasi, 2011, Puthumana et al., 2017). Since the 1990s, research on genetic alterations in

human cancers has led to a better understanding of molecular drivers of cancer diseases. Although in the cancer field this knowledge could provide more useful drugs, the effectiveness of drug development is remarkably low (Hutchinson & Kirk, 2011). Compared with other therapeutic areas, drug development has the highest failure rate in cancer disease (Begley & Ellis, 2012). For these reasons, it is necessary to increase the success rate of cancer drug development.

According to Hay et al. (2014), there are two types of success of drug development: "Phase success" and "success of approval". "Phase success" means that the drug enters into one development phase of a clinical trial, gets a good result and starts the next phase[1]. "Success of approval" means that the drug is approved by a national authority (notably, the U.S. Food and Drug Administration, FDA). In this research, we mainly focus on the final success of drug development, "success of approval". Drug development is time-consuming, costly, risky and complicated, which hinders the productivity of the pharmaceutical industry and the success rate of drug development (Hay et al., 2014). The high unmet need of patients and huge market size cause that many suboptimal preclinical drugs enter into clinical trials in cancer disease. The success rate of cancer drug development increases by raising standards of preclinical cancer research and accumulating more basic knowledge (Begley & Ellis, 2012). Building a diverse drug development cooperating network, including companies, hospitals, universities, public or private research centers, and patient groups, is also a method to share risks and to improve the approval success rate of drug development (Kaitin & DiMasi, 2011). The general objective of this research is to refine understanding how to promote successful drug development in cancer disease. More specifically, we will investigate the role of two mechanisms, radicalness of drug development and strength of social capital, whose importance we will justify now.

Although cancer drugs continue to dominate the drug approval list in the therapeutic area (Mullard, 2018), the mortality rate of cancer disease is still higher than in other non-communicable diseases (World Health Organization, 2017). Most of the cancer patients without effective drug medication need radical drugs to cure their disease. By radicalness of drug development, we mean the drug development with new molecular entities or new therapeutic biological products which will subvert existing drugs to cure disease[2]. In the history of drug development, the

[1] Clinical trials are divided into different phases. The phases of clinical research are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment.

[2] Our definition is based on the classification of drugs by the USFDA (2015) and the definition of radical innovation: according to the theory of Christensen (1997), radical innovation is a new paradigm that transforms or replaces existing products with high income. The characteristics of radical innovation are revolutionary or discontinuous. The other definitions of radical innovation are contrasted with incremental innovation. Radical innovation changes existing technologies or marketing structures, whereas incremental innovation uses existing technologies to improve process or product for existing markets (Garcia & Calantone, 2002).

success of radical drug development not only substantially reduces costs and improves efficiency but also decreases patients suffering, promotes the health of human beings and brings social value, from small molecules to biological products. However, in general, the success rate of radical drug development is less than 10% (Lo, 2017) with a cost of US$ 802 million per new drug (DiMasi et al., 2003). Our first concrete objective is to analyze the effects of radicalness on the success of drug development in cancer disease.

Because drug development obtains the knowledge from academic or technology areas (Vertès, 2011, Clark et al., 2012), it seems that the diversity of a collaboration team could increase the success rate of drug development (Aagaard & Gertsen, 2011). In the cooperation network, social capital is regarded as an essential value creation mechanism by better group communication and knowledge sharing (Burt, 2000; Tsai et al., 2014), enhanced use of intellectual capital (Leana & Van Buren, 1999), and reduction of operations cost (Carey et al., 2011). Creating and maintaining scientific social capital attract more interaction between university and industry and improve translational output. Social capital improves biotechnology start-ups' performance (Maurer & Ebers, 2006) and the success of pharmaceutical companies (Arechavala-Vargas et al., 2012). Our second concrete objective is to study the role of social capital in the success of drug development in cancer disease.

Previous research has not addressed the relationship between radicalness, social capital, and success in the drug development stage. With our two concrete objectives, we aim at filling this gap. A possible reason why it has not been tackled before may be the lack of a method to link indicators on radicalness and success. Other works have separately measured radicalness (Omta et al., 1994; Jong & Slavova, 2014; Coccia, 2017) or success (Hay et al., 2014), and we try to go a step further by proposing a method to overcome the difficulty of their joint analysis.

2. Literature review and hypotheses

In this section, we analyze the relationship among the organizational radicalness of drug development, the success of drug development and social capital. Figure 1 shows our research framework and hypotheses.

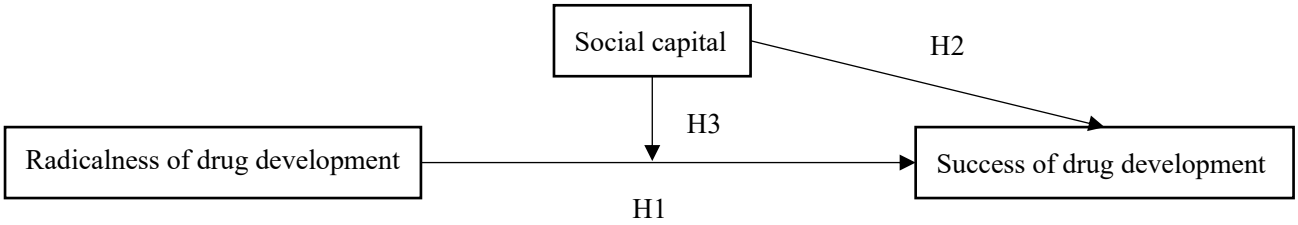

Figure 1 Research framework and hypotheses

2.1. Radicalness and success of drug development

There are two types of drug development: radical and incremental. Radical drug development represents a genuinely new product and provides a new chance to cure cancer disease. Incremental drug development represents an enhancement or modification of an existing product (Jong & Slavova, 2014). The capabilities and resources are different and often opposed to developing radical and incremental drugs successfully (e.g. Cardinal, 2001). Radical drug development relies on the combination of knowledge from internal R&D groups as well as external communities (Jong, 2011, Phene et al., 2006). Radical drug development also destroys traditional drug development way of products based on new knowledge and resources. The status is broken by radical drug development, and some new, novel and unconventional ideas are generated, like nanocarrier and immunotherapy. Radical drug development leads to new trends and technologies to cure diseases with high risk, many costs and a long time. If radical drug development gets success, existing drugs or methods will be obsoleted and even be eliminated. These situations simulate organizations to develop radical drugs.

In contrast, incremental drug development is less dependent on external sources of knowledge. Actually, the previous clinical expertise is much more beneficial to incremental drug development (e.g., Aiken et al., 1980). The organization with incremental drug development always utilizes existing knowledge, resources, and products to expand its market niche. The organization operates under a safety framework with incremental drug development, and tends to refuse novel ideas instead of existing knowledge, resources, or products. The incremental drug development on already existing drugs expands classes of drugs to provide more treatment tools to a diversity of patients, and increases the quality of health care. At the same time, with incremental drug development, expanding drug classes increases the possibility of lower drug prices as competition between manufacturers is enhanced (Wertheimer & Santella, 2004).

However, compared with the risk of safety and efficacy in radical drug development, incremental drug development has to take care of patent disputes. The manufacturers of radical drug development often work to delay the approval of incremental versions of their products by patenting peripheral aspects of a drug or modified formulations that do not add clinical value, paying generic manufacturers to settle lawsuits challenging the validity of patents on brand-name drugs (“reverse payment” settlements), denying generic manufacturers access to drug samples necessary for bioequivalence testing, misusing risk evaluation and mitigation strategies, and filing citizen petitions with the US Food and Drug Administration (FDA) (Vokinger et al., 2017), which decrease the success rate of

incremental drug development. For these reasons we formulate:

Hypothesis 1. Radicalness of drug development will increase the chances of succeeding in drug development.

2.2. Social capital and success of drug development

Social capital is the resources embedded in an interactive and networked social structure that benefits the actors and other members of her group (Portes, 1998; Lin, 2002). The embedded resources include information, social credentials, influence, and reinforcement that could be used by actors to enhance their outcomes (Lin, 2017). The more relationships an organization maintains with others, the higher the chance to access relevant useful information, which is helpful to develop a safer and more effective clinical trial. Compared with other industries, the pharmaceutical industry incurs in huge amounts of costs due to the drug development process (DiMasi et al., 2003). In a cooperation network, social-ties also provide some opportunities to access financial support for drug development from alliances. At the same time, organizations not only focus on getting valuable resources from other cooperators, but they also have an interest in protecting their valuable resources (Das & Teng, 2000). The powerful organization has the ability to influence the evaluation criteria of clinical trial results and even the development of clinical trial standards. Social capital also reinforces identity and recognition of an organization, which could be used to confirm the reliability of clinical trial results and drugs. It is critical for peer recognition of drugs and subsequent drug marketing.

Hypothesis 2. Social capital increases the probability of successful drug development.

2.3. Social capital and the relationship between radicalness of drug development and the success of drug development

Social capital is the channel for the organizations to collect diverse knowledge from external alliances. Radical drug development involves the integration of distant and diverse knowledge (e.g., Cassiman et al., 2005; Kaplan and Vakili, 2015). Radical drug development faces more uncertain outcomes than incremental drug development, like overdose, toxic and side reactions; social capital provides plenty of external knowledge to react and solve these perils. The primary risk of radical drug development is the potential side effects, which hinders the entry of most radical drugs into the clinical trial stage. Social capital also decreases these risks by evaluation and selection of

industry, academia, and regulating authorities (Baba & Walsh, 2010). This is why we posit:

Hypothesis 3. Social capital plays a positive moderating role on the relationship between radicalness and success of drug development.

3. Model, data and methodology

Our aim is to estimate the following model:

$$P\left(Success\ of\ Drug\ Development_{i,j}\right) = f(Radical\ Drug\ Development_{i,j}, Social\ Capital_{i,j}, Social\ Capital_{i,j}^2,$$
$$Radical\ Drug\ Development_{i,j} * Social\ Capital_{i,t},$$
$$Drug - Organization\ level\ Control\ variables_{ij},$$
$$Organization\ level\ Control\ variables_j, \varepsilon_{i,j})$$

Where *i* represents a drug and *j* represents an organization.

3.1 Data sources

We built variables referred to the process of drug development through information on clinical trials[3] and FDA approved drug products in cancer disease. We chose the US Clinical Trials Registry because its larger number of records vis-à-vis other administrations (331,536 until 2019, compared for instance with 36,638 clinical trials records in the EU Registry, 29,688 in the Chinese Registry and 44,051 in the Japanese Registry). We collected data from several sources:

- **NLM Drug Information Portal**, which provides a gateway to gather drug information from the U.S. National Library of Medicine and other key U.S. Government agencies. The reason to collect data from the NLM Drug Information Portal instead of ClinicalTrials.gov directly is that the clinical trials should be searched by "Condition or disease" in ClinicalTrials.gov, which ignores the clinical trials of cancer drugs to treat other diseases (e.g. Hepatitis, Uveitis, Scleroderma and so on) and leads to some radical drugs missing and underestimating the success rate of drug development. In addition, the drug names should be collected from "Interventions" in ClinicalTrials.gov, but the "Interventions" also include other processes

[3] According to the FDA's drug development process, clinical trials are only used on human beings. Pre-clinical trials are used on animals.

and actions in the clinical study, like medical devices, procedures and even noninvasive approaches, which is difficult to clean.

- **ClinicalTrials.gov**, a database maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH), that publishes studies of the US Clinical Trials Registry in all 50 States in the U.S. and in 210 countries, to collect clinical trials data
- **Drugs@FDA**, a database with information about most of the drug products approved since 1939, to get data of FDA approved drug products
- **Dietary Supplement Label Database**, a database that includes all label information on dietary supplement products in the US
- **ChemID*plus***, a dictionary database of over 400,000 chemicals, to classify molecular entities and therapeutic biological products.

NLM Drug Information Portal classifies drugs by therapeutic class, so we got the list of cancer drugs using the "antineoplastic agents" category. In the "antineoplastic agents" list, there were 978 antineoplastic agents. We identified 27 dietary supplements[4] through Dietary Supplement Label Database that were not intended to diagnose, treat, cure or prevent any disease, so we deleted them. Our final database contains 518 antineoplastic drugs developed in 42,653 clinical trials.

To improve the matching rate of data between ClinicalTrials.gov and Drugs@FDA, we normalized organization names. The details of normalization are in section 3.2. The ChemID*plus* helped us to classify subsamples, which is described in section 3.3. We used Python 3.7 to scrape clinical trial data, FDA approved drug products, information of dietary supplement and MeSH information based on the gateway of the NLM Drug Information Portal to ClinicalTrials.gov, Drugs@FDA, Dietary Supplement Label Database and ChemID*plus* respectively.

3.2 Normalization of organization names

We extracted organization names from ClinicalTrials.gov's field "Sponsor/Collaborators". In the original database, there were 10,601 different organization names. Considering that the field could contain individuals (not

[4] The 27 dietary supplements are Genistein, Curcumin, Resveratrol, Epigallocatechin gallate, Lycopene, Ursolic acid, Cinnamaldehyde [NF], Fucoidan Sulforaphane, Cryptoxanthin, Hypericin, Vitamin A palmitate, Betulinic acid, Indole-3-carbinol, Biochanin A, Carvone [ISO], Acteoside, Formestane [INN:BAN], Timonacic [INN], 3,3'-Diindolylmethane, Methylselenocysteine, Alliin, Ascorbyl palmitate [NF], Perillyl alcohol, Perilla seed oil, Isobutyramide and Grifolan.

organizations) and that one organization could wrongly appear with more than one name, or one name could be wrongly attributed to different organizations, we used the following three steps to normalize organization names, based on Jonnalagadda & Topham (2010).

Step 1. Removing individuals' names: Some of the clinical trials do not show organizations but individuals (e.g. principal investigators) in the field "Sponsor/Collaborators". To delete records with person names, we searched the co-occurrence of names and personal titles: prof.*, M.D.*, MD*, M D *, PhD*, and Dr.*. We also used the Name Corpus (http://www.cs.cmu.edu/Groups/AI/util/areas/nlp/corpora/names/), a package that contains a list of 13,484 surnames and 58,257 names (Kantrowitz & Ross, 1994). After these processes, we manually removed 548 individuals' names.

Step 2. Cleaning strings with geographic information: Some records with incomplete geographic information in the field "Sponsor/Collaborators" had to be deleted. We identified the Geopolitical Entity (GPE) through the GeoWorldMap database (https://geobytes.com/freeservices/), which includes 275 country names and 39,484 city names. We retrieved 2,198 organization names with GPE. However, there were two types of strings with geographic information.

- The first one linked the organization with one geographic information only. We manually cleaned the location information of these organizations. For example, the only GPE of "Copenhagen University Hospital, Denmark" is Denmark. We removed "Denmark", and only kept "Copenhagen University Hospital".
- The second type linked one organization to more than one GPE. In this case, we kept the place and organization names together. For example, "Ministry of Health" could be attributed to more than ten GPEs (e.g. China, Spain, France, Czech Republic, Japan, Republic of Korea and so on). We kept the location of these organizations, like Ministry of Health, China or Ministry of Health, France.

Step 3. Resolving synonymy: One major challenge in normalizing organization names is to identify and replace Non Standard Words (NSWs). NSWs can be broadly classified as abbreviations, misspellings and miscellaneous (Sproat et al., 2001). The category 'miscellaneous' includes the unconventional word and phrase boundaries, intentional informal spelling, URL and formatting abnormalities. There are two types of miscellaneous NSWs in our database – those with trademark logos like ©, ™, ®, and types of companies like LLC., Ltd., and GmbH. and those with special alphabets from other languages like ó, ç, ñ and so on. We removed the trademark logos and types of

companies, and used similar English alphabets instead of special alphabets. Abbreviations are replaced by their full forms. For example, NIH needed to be replaced by the National Institutes of Health. To solve the misspellings, we used OpenRefine, a powerful tool for working with messy data, to compare string similarity and normalize the different strings as the same organizations if they had less than two different letters as in the example in Table 1. The other important reason for misspellings was some non-English organizations that might appear with English translations or original names. To disambiguate these synonyms, we translated each non-English organization name to English using Google Translate as in the example in Table 2.

After we normalized the organizations, there were 8,738 organizations engaged in clinical trial development on antineoplastic agents.

Table 1 Normalized organization name by OpenRefine

Input	Output
National Centre for Parasitology	National Center for Parasitology
National Center for Parasitology	National Center for Parasitology

Table 2 Normalize non-English organization name by Google Translate

Input	Output
Hanusk Krankenhaus Wien	Hanusch Hospital Vienna
Havenziekenhuis	Port Hospital

3.3 Building the sample and subsamples

Since 2005, clinical trials are required to be registered in ClinicalTrials.gov by the International Committee of Medical Journal Editors before the results are published. We only considered the clinical trials from 2005 to 2018. There were 491 antineoplastic agents, 7,655 organizations and 39,886 clinical trials. To build the indicators, we converted our data from the drug-clinical trial level (Table 3a) into the drug-organization level (Table 3b). There are 59,239 observations in our database.

Table 3 Sample level examples

a: Drug-clinical trial level

Drug Name	NCT Number	Sponsor/Collaborators
(-)-Epicatechin-3-O-gallate	NCT00611416	University of Copenhagen|Unilever R&D
(-)-Epicatechin-3-O-gallate	NCT00692731	Provident Clinical Research|Kao Corporation
10-Hydroxycamptothecin	NCT00003735	Children's Oncology Group|National Cancer Institute (NCI)
2-Chloro-3'-deoxyadenosine	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute (NCI)

b: Drug-organization level

Drug Name	Organization name	Number of clinical trials
(-)-Epicatechin-3-O-gallate	University of Copenhagen	2
(-)-Epicatechin-3-O-gallate	Kao Corporation	1
10-Hydroxycamptothecin	Arno Therapeutics	4
2-Chloro-3'-deoxyadenosine	National Cancer Institute	17

We will also test the robustness of our results by distinguishing molecular entities (ME) and therapeutic biological products (TBP) subsamples. ME drugs do not contain active moiety and have well-defined structures, whereas TBP drugs are generally derived from living material with complex structure, and thus are usually not fully characterized (U.S. FDA, 2015). Because ME drugs have well-defined structures, organizations could make sure they use the same ME drugs in the different stages of clinical trials by analyzing the structure of the product. By contrast, TBPs are sensitive to every minor change in the manufacturing process. Organizations that produce TBPs must tightly control the source and nature of starting materials, and the manufacturing process to make sure TBPs have the same consistency, quality, and purity in different stages of the clinical trials. Furthermore, TBP approval requires a special biologics license.

The classification by drug type is based on Medical Subject Headings (MeSH). This is a controlled and hierarchically-organized vocabulary produced by the U.S. National Library of Medicine, used for indexing, cataloging, and searching of biomedical and health-related information. There are 326 MEs and 165 TBPs in our database.

Table 4 lists the top 20 organizations in clinical trial development of cancer drugs. The US National Cancer Institute ranks first, with around 350 drugs. Every organization got success in cancer drug development at least once, except Dana-Farber Cancer Institute and Southwest Oncology Group.

Table 4 Top 20 organizations in clinical trials development from 2005 to 2018

Rank	Organization's name	Number of drugs developed	Number of successful drugs developed
1	National Cancer Institute	346	18
2	MD Anderson Cancer Center	227	4
3	National Institutes of Health Clinical Center	192	6
4	Memorial Sloan Kettering Cancer Center	191	2
5	University of California	186	19
6	Dana-Farber Cancer Institute	181	0
7	Merck	175	33
8	Novartis	169	49
9	Pfizer	163	51
10	Massachusetts General Hospital	161	10
11	Roche	159	47
12	University of Washington	154	9
13	Mayo Clinic	148	9
14	Bristol-Myers Squibb	147	22
15	Washington University School of Medicine	142	6
16	Southwest Oncology Group	141	0
17	Duke University	141	1
18	Stanford University	140	11
19	Genentech	134	9
20	H. Lee Moffitt Cancer Center and Research Institute	132	8

3.4 Variables

Table 5 shows the definitions and descriptive statistics of the variables. The dependent variable is *Success of Drug Development*. For a given drug and organization, it takes value 1 if that organization gets success in this drug development, 0 otherwise. We consider that an organization gets success in drug development if the FDA approves the corresponding clinical trial, in the case of firms, or it enters into Phase 4 (indicating that the drug is in the market), in the case of other organizations (Willmann et al., 2008). The average value of *Success of Drug Development* is 0.1, which means the success rate of cancer drug development is very low.

Our first independent variable is *Radicalness of drug development*. A radical drug is a drug with a new ME or a new TBP (US Food and Drug Administration, 2015). For a given drug of an organization, *radicalness* takes value 1 if this organization is the first organization to develop this drug based on the start year of clinical trials. The average value of *Radicalness of drug development* is remarkably low (0.01). It is not only due to the risk of radical drug development, but also because of the special design of the clinical trials in cancer disease. Due to ethical issues, for

most of the control groups of patients, radically new drugs must be compared with previous drugs, whereas in non-cancer research it is enough to compare with placebos. Comparison with previous drugs requires more technical capabilities than with placebos, so cancer research organizations have relatively fewer incentives to develop radical drugs than other organizations.

The second independent variable is *Social Capital,* which we measure as the Efficiency of an organization's cooperation network. We retrieved the cooperation data from the field "Sponsor/Collaborators". If two organizations appear in the field "Sponsor/Collaborators" of one clinical trial, there is a cooperation relationship between these two organizations. There are 13,0164 cooperation relationships in our database. Efficiency is used to calculate the nonredundant information of the organization. The higher this Efficiency is, the more nonredundant information the organization holds, and the more she benefits from the structural holes between other organizations in the network, which reinforces its social capital (Burt, 2000). The calculation of the Efficiency of structural holes is as follows:

$$Efficiency_j = \frac{\sum_z [1 - \sum_q p_{jq} m_{zq}]}{N}, q \neq i, j$$

Where p_{iq} is the organization *j*'s number of ties with organization q divided by *j*'s total number of ties in the cooperation network, and m_{zq} is the organization z's number of ties with organization q divided by z's higher number of ties with anyone. N is the organization *j*'s total number of ties in the cooperation network.

In our model, we also control for the effects of some characteristics: *Patients* (a proxy of firm size in terms of drug development), *Gender, Age* and *Sources of Funding*, at the drug-organization level, and *Organization Type,* at the organization level. The gender of patients reflects the type of cancer disease to which the tested drugs applied. Most organizations test drugs to cure the diseases in both males and females (mean *Both genders* is 0.84), and there are more organizations developing drugs for female cancer disease (mean 0.12) than for male cancer disease (mean 0.05). The age of patients reflects the suitability of the tested drug to patients of different ages. Most organizations develop drugs to cure cancer disease of adults and older adults (0.76), since both are more susceptible to cancer disease than children (Balducci & Ershler, 2005). Regarding funding sources, because there are a lot of non-profit organizations sponsoring clinical trials, e.g. topic-oriented foundations and disease-specific societies, especially orphan drugs clinical trials (Davies et al., 2017), most drug development gets funding from Other Sources (70%). A quarter of the funding comes from industry, and only a few from NIH and the U.S. Federal Government. The drugs are mainly developed by companies and hospitals (26% and 29% of all drugs, respectively).

Table 5 Variable definitions and descriptive statistics (n=59,239)

Role of variable	Variable name	Description	Mean	Std. Dev.	Min	Max
Dependent variable	*Success of Drug Development*	1 if the organization got success in this drug development, 0 otherwise.	0.10	0.30	0.00	1.00
Independent variables	*Radicalness of drug development*	1 if the organization was the first organization to develop this drug, 0 otherwise, centralized	0.01	0.09	0.00	1.00
	Social Capital	Effective size of structural holes in the cooperation network, i.e. the amount of nonredundant information an organization has in the network, centralized	0.75	0.25	0.00	1.00
Control variables	***Drug-Organization level***					
	Patients	The average number of patients participating in clinical trials of this drug in each organization (ln)	4.48	1.41	-0.69	14.08
	Both Genders	The percentage of clinical trials which have both male and female patients in this drug development of each organization	0.84	0.35	0.00	1.00
	Only Male	The percentage of clinical trials which only have male patients in this drug development of each organization	0.05	0.20	0.00	1.00
	Only Female	The percentage of clinical trials which only have female patients in this drug development of each organization	0.12	0.30	0.00	1.00
	All Ages	The percentage of clinical trials which have all age patients in this drug development of each organization	0.08	0.24	0.00	1.00
	Only Child	The percentage of clinical trials which have only child patients in this drug development of each organization	0.03	0.15	0.00	1.00
	Child and Adult	The percentage of clinical trials which have child and adult patients in this drug development of each organization	0.08	0.26	0.00	1.00
	Only Adult	The percentage of clinical trials which only have adult patients in this drug development of each organization	0.06	0.22	0.00	1.00

Role of variable	Variable name	Description	Mean	Std. Dev.	Min	Max
	Adult and Older Adult	The percentage of clinical trials which have adult and older adult patients in this drug development of each organization	0.76	0.40	0.00	1.00
	NIH	The percentage of clinical trials which was fund by U.S. National Institutes of Health in this drug development of each organization	0.05	0.15	0.00	1.00
	Other U.S. Fed	The percentage of clinical trials which was fund by Other U.S. Fed (including Food and Drug Administration, Centers for Disease Control and Prevention, or U.S. Department of Veterans Affairs) in this drug development of each organization	0.01	0.05	0.00	1.00
	Industry	The percentage of clinical trials which was fund by pharmaceutical and device companies in this drug development of each organization	0.25	0.33	0.00	1.00
	Other Funding	The percentage of clinical trials which was fund by Other Sources (including individuals, universities and community-based organizations) in this drug development of each organization	0.70	0.18	0.00	1.00
	Organization level					
	Company	1 if the organization is company, 0 otherwise	0.26	0.44	0.00	1.00
	Hospital	1 if the organization is hospital, 0 otherwise	0.29	0.45	0.00	1.00
	Higher Education	1 if the organization is higher educational institution (include university, college and so on), 0 otherwise	0.19	0.39	0.00	1.00
	Public Research Organization	1 if the organization is public research organization, 0 otherwise	0.18	0.39	0.00	1.00
	Other Organization	1 if the organization is other organization, 0 otherwise	0.08	0.27	0.00	1.00

As aforementioned, our sample contains ME and TBPs. Because their development follows different dynamics, we will distinguish both to perform a robustness check. Table 6 breaks down the descriptive statistics of the variables for the ME and TBP subsamples. We classify a drug-organization observation into ME/TBP based on MeSH. Our sample contains 82% of ME and 18% of TBP drug-organizations. The *Success of Drug Development* in ME (0.1) is a little bit higher than that in TBP (0.09). However, they differ considerably in that TBP organizations develop more radical drugs and have more social capital than ME ones. The appearance of new biotech provides some novel paths to develop drugs, thus the pharmaceutical companies with more capabilities to develop radical drugs and social capital reconvert to develop biotech and product TBP-drugs. ME-active organizations rely more on *Other U.S. Fed* and *Other Funding* (other than *Industry*) than TBP-active organizations. The distributions are fairly similar in terms of *Patient, Gender, Age, Funding Sources* and *Organization Type.*

Table 6 Descriptive statistics of variables: ME and TBP subsamples

	ME (n=48,612)				TBP (n=10,627)			
Variables	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
Success of Drug Development	0.10	0.30	0.00	1.00	0.09	0.28	0.00	1.00
Radicalness of drug development	0.01	0.08	0.00	1.00	0.02	0.12	0.00	1.00
Social Capital	0.75	0.25	0.00	1.00	0.76	0.25	0.00	1.00
Patient	4.52	1.41	-0.69	14.08	4.29	1.38	-0.69	10.63
Both Genders	0.82	0.36	0.00	1.00	0.91	0.27	0.00	1.00
Only Male	0.05	0.21	0.00	1.00	0.02	0.11	0.00	1.00
Only Female	0.12	0.31	0.00	1.00	0.08	0.25	0.00	1.00
All Ages	0.08	0.24	0.00	1.00	0.06	0.22	0.00	1.00
Only Child	0.03	0.15	0.00	1.00	0.02	0.13	0.00	1.00
Child and Adult	0.09	0.26	0.00	1.00	0.06	0.23	0.00	1.00
Only Adult	0.06	0.21	0.00	1.00	0.07	0.24	0.00	1.00
Adult and Older Adult	0.75	0.41	0.00	1.00	0.79	0.39	0.00	1.00
NIH	0.05	0.15	0.00	1.00	0.05	0.16	0.00	1.00
Other U.S. Fed	0.01	0.05	0.00	1.00	0.00	0.04	0.00	1.00
Industry	0.24	0.32	0.00	1.00	0.28	0.34	0.00	1.00
Other Funding	0.71	0.33	0.00	1.00	0.66	0.34	0.00	1.00
Company	0.25	0.43	0.00	1.00	0.28	0.45	0.00	1.00
Hospital	0.29	0.46	0.00	1.00	0.25	0.44	0.00	1.00
Higher Education	0.19	0.39	0.00	1.00	0.20	0.40	0.00	1.00
Public Research Organization	0.18	0.39	0.00	1.00	0.18	0.39	0.00	1.00
Other Organization	0.08	0.27	0.00	1.00	0.08	0.28	0.00	1.00

4. Results

Since *Success of drug development*, our dependent variable, is a dummy variable, we employ Probit regression for the estimations. In Table 7, Column 1, we include the control variables only. In Column 2, we test the impacts of *Radicalness of drug development* and *Social Capital*. In Column 3 we test the moderating role of *Social Capital*.

The coefficients of *Radicalness of drug development* are positive and significant in models 2-3. It means that radical drug development is more likely to succeed, which supports ***Hypothesis 1***. The coefficients of *Social Capital* are all positive and significant, so social capital helps organizations getting the success of drug development, and hence the evidence supports ***Hypothesis 2***. The coefficient of *Radicalness of drug development * Social Capital* is positive but not significant, which means the moderating role of social capital is not significant in the relationship between the radicalness of drug development and the success of drug development. This result does not support our ***Hypothesis 3***. A possible reason for this result is that social capital is beneficial to generate innovative ideas. However, in the clinical trials stage, radical ideas are already developed. The aim of clinical trials is to ensure the safety and efficacy of new drugs. The role of social capital is more significant in the generation of radical ideas than in the process of radical drug development.

Regarding the control variables, the higher the number of *Patients* participating in clinical trials, the higher the success rate of drug development in an organization. More patients participating in clinical trials means the drug will be tested in more ethnicities and nationalities in different areas, which provides more clinical experiences to improve the success rate of drug development. The coefficients of *Only Male* and *Only Female* are not significant, which means the differences in success rate are not significant between genders. The coefficients of *Child and Adult* and *Adult and Older Adult* are negative and significant, but the coefficients of *Only Child and Only Adult* are not significant, which implies that, although most of the clinical trials are developed for adults and older adults, the success rate is low. Among types of organizations, the ones with positive coefficients are *Hospital* and *Higher Education*, whereas the coefficients of *Public Research Organization* are negative and significant. This is perhaps because most drug developments are sponsored by companies (Angell, 2008), which tend to outsource the task to contract research organizations (Vogel, 2007), including hospitals, universities and public research organizations. Hospitals have more clinical practice, and it is a necessary place to conduct clinical trials, so drug development relays on the support of the hospital. Although both higher education and public research organizations provide knowledge to develop drugs, higher education organizations have more connections with hospitals, so they could

also provide some clinical experience on side effects. On the contrary, the knowledge of the public organization is more basic, like pharmacological action, pharmacokinetics and toxicology, which is useful to select preclinical candidate compounds but not so much to solve side effects in clinical trials.

We also break down the sample to compare the results of ME and TBP drug development in Table 8. *Radicalness* plays a positive and significant role in the success in ME drug development, but not in TBP. The reason may be because the U.S. offers 5 years of exclusivity period to radical ME drugs, whereas for TBP drugs it lasts 12 years. Hence, TBP organizations have a longer period of profit monopoly and more competitive advantage in pharmaceutical markets, which simulates more organizations participate in radical TBP drug development (Coccia, 2017). However, some characteristics of TBP drugs are unstable and sensitive to the environment, like temperature, pH, oxygen and so on (Wang & Singh, 2003), which increases the complexity of drug production in factories and hinders the success rates of radical TBP drugs.

The effect of *Social Capital* on *Success of Drug Development* is positive and significant in both ME and TBP drug development. The coefficients of *Only Male and Only Female* are negative and significant in TBP drug development, which means the success rate is lower in TBP drug development to cure special male/female cancer diseases. The size, sign, and significance of other coefficients are similar to the full sample, and between subsamples.

Table 7 Probit estimation of successful drug development

	(1)	(2)	(3)
Drug-Organization level			
Radicalness of drug development (H1)		0.24***	0.23**
		(0.08)	(0.09)
Social Capital (H2)		0.14***	0.14***
		(0.03)	(0.03)
*Radicalness of drug development*Social Capital (H3)*			0.17
			(0.44)
Patients	0.15***	0.15***	0.15***
	(0.01)	(0.01)	(0.01)
Only Male	0.02	0.01	0.01
	(0.04)	(0.04)	(0.04)
Only Female	-0.02	-0.02	-0.02
	(0.02)	(0.02)	(0.02)
Only Child	-0.01	0.01	0.01
	(0.05)	(0.05)	(0.05)
Child and Adult	-0.46***	-0.46***	-0.46***
	(0.04)	(0.04)	(0.04)
Only Adult	0.06	0.07*	0.07*
	(0.04)	(0.04)	(0.04)
Adult and Older Adult	-0.24***	-0.24***	-0.24***
	(0.03)	(0.03)	(0.03)
NIH	-1.04***	-1.07***	-1.07***
	(0.07)	(0.07)	(0.07)
Other U.S. Fed	0.49***	0.50***	0.50***
	(0.12)	(0.12)	(0.12)
Industry	-0.20***	-0.22***	-0.22***
	(0.03)	(0.03)	(0.03)
Organization level			
Company	0.05	0.06*	0.06*
	(0.03)	(0.03)	(0.03)
Hospital	0.19***	0.20***	0.20***
	(0.03)	(0.03)	(0.03)
Higher Education	0.30***	0.30***	0.30***
	(0.03)	(0.03)	(0.03)
Public Research Organization	-0.20***	-0.19***	-0.19***
	(0.03)	(0.03)	(0.03)
Constant	-1.79***	-1.80***	-1.80***
	(0.05)	(0.05)	(0.05)
Log likelihood	-18012.28	-17995.84	-17995.76
χ^2	1978.77	2011.65	2011.81
P-value	0.00	0.00	0.00
N	59239	59239	59239

Note: Standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$.

Table 8 Probit estimation of successful drug development in ME and TBP subsamples

	ME			TBP		
	(1)	(2)	(3)	(1)	(2)	(3)
Drug-Organization level						
Radicalness of drug development (H1)		0.32***	0.33***		0.18	0.09
		(0.10)	(0.11)		(0.15)	(0.19)
Social Capital (H2)		0.14***	0.14***		0.16**	0.16**
		(0.03)	(0.03)		(0.08)	(0.08)
*Rad. drug devt.*Social Capital (H3)*			-0.09			0.77
			(0.52)			(1.00)
Patient	0.15***	0.15***	0.15***	0.13***	0.13***	0.13***
	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)	(0.01)
Only Male	0.04	0.04	0.04	-0.50**	-0.51**	-0.51**
	(0.04)	(0.04)	(0.04)	(0.22)	(0.22)	(0.22)
Only Female	-0.00	0.00	0.00	-0.23***	-0.24***	-0.24***
	(0.03)	(0.03)	(0.03)	(0.08)	(0.08)	(0.08)
Only Child	-0.01	0.02	0.02	-0.05	-0.03	-0.04
	(0.05)	(0.05)	(0.05)	(0.14)	(0.14)	(0.14)
Child and Adult	-0.40***	-0.39***	-0.39***	-1.05***	-1.05***	-1.05***
	(0.04)	(0.04)	(0.04)	(0.13)	(0.13)	(0.13)
Only Adult	0.08*	0.08*	0.08*	-0.04	-0.03	-0.04
	(0.04)	(0.04)	(0.04)	(0.10)	(0.10)	(0.10)
Adult and Older Adult	-0.23***	-0.22***	-0.22***	-0.35***	-0.34***	-0.35***
	(0.03)	(0.03)	(0.03)	(0.07)	(0.07)	(0.07)
NIH	-1.14***	-1.18***	-1.18***	-0.67***	-0.68***	-0.68***
	(0.08)	(0.08)	(0.08)	(0.16)	(0.16)	(0.16)
Other U.S. Fed	0.41***	0.42***	0.42***	0.99***	0.99***	0.99***
	(0.13)	(0.13)	(0.13)	(0.33)	(0.33)	(0.33)
Industry	-0.21***	-0.23***	-0.23***	-0.12	-0.14*	-0.14*
	(0.04)	(0.04)	(0.04)	(0.07)	(0.08)	(0.08)
Organization level						
Company	0.06*	0.07*	0.07*	0.00	0.01	0.01
	(0.04)	(0.04)	(0.04)	(0.08)	(0.08)	(0.08)
Hospital	0.19***	0.20***	0.20***	0.18**	0.19***	0.19***
	(0.03)	(0.03)	(0.03)	(0.07)	(0.07)	(0.07)
Higher Education	0.29***	0.29***	0.29***	0.35***	0.35***	0.35***
	(0.03)	(0.03)	(0.03)	(0.07)	(0.07)	(0.07)
Public Research Organization	-0.21***	-0.20***	-0.20***	-0.14*	-0.14*	-0.14*
	(0.04)	(0.04)	(0.04)	(0.08)	(0.08)	(0.08)
Constant	-1.81***	-1.82***	-1.82***	-1.66***	-1.67***	-1.67***
	(0.05)	(0.05)	(0.05)	(0.12)	(0.12)	(0.12)
Log likelihood	-15027.26	-15012.21	-15012.20	-2954.03	-2950.87	-2950.50
χ^2	1673.33	1703.44	1703.47	347.26	353.58	354.31
P-value	0.00	0.00	0.00	0.00	0.00	0.00
N	48612	48612	48612	10627	10627	10627

Note: Standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

5. Potential conclusions and implications

This study improves understanding about which degree of drug development –radical or incremental– leads to success in cancer disease. Methodologically, we offer a new approach that overcomes the huge computational effort to empirically test these links. We find that radical drug development is more likely to be successful, especially for the molecular entities. Furthermore, this research also identifies a key mechanism, social capital, to improve success in cancer disease. Theoretically, we speculate that social capital will have a direct positive impact on success, and an indirect one through the enhancement of the positive effect of radicalness. The results show that the direct impact occurs, but not the indirect one. The reason for this mismatch between our theory and our evidence may be that high levels of social capital go along with knowledge diversity, which is more helpful to generate radical drug ideas than radical drug developed processes. All in all, our research provides organizations and policymakers with the recommendation that both engagement in radical drug development and generation of social capital pay off in terms of success of drug development.

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