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How science responds to technology push from new research tools. Translational medical research as a case of â€œnew scienceâ€•

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Abstract

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As a case of RT-driven science, we study translational medical research in a specific oncological field. Using bibliometric data, we assess the impact of translational studies benchmarked against simultaneous standard clinical research in the exact same field. Whereas reductionism sets its mark within both approaches, we find that a number differentiating traits appearing for RT-driven research: impact of translational articles depends on how broadly it sources its intellectual

inputs, how well it accommodates multi-disciplinarity in its own problem solving, the diversity of subsequent research serving as its recipients. Knowledge integration, not reductionism, emerges as the predominant principle in RT-driven research.

Jelcodes:O31,O33

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Translational medical research as a case of "new science"

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Keywords: science dynamics; knowledge accumulation; new sciences; translational research; bibliometrics.

Introduction

The increasing interest in relationships between science and technology has principally been concerned with the translation of scientific results into technological innovation, as exemplified e.g. by the long lived discussion regarding the linearity of that translation (Balconi et al. 2010;Kline and Rosenberg 1986). Less attention has been spent on the effects of this relationship on the internal dynamics of science, although the discussion on Mode-II science (Gibbons et al. 1994), or on shifts into "Pasteur's Quadrant" (Stokes 1997) exemplify exceptions. Yet, even these exceptions stop short of asking how intensified relationships to technology may affect the internal dynamics of science, its patterns of knowledge accumulation in particular.

The internal dynamics of science are affected by technology through both push and pull mechanisms. Pull mechanisms typically gain significance when important social issues direct the agenda of the scientific community towards new technological solutions, often giving rise to new fields of interdisciplinarity (defence programs, the war on cancer, the climate challenge are cases in point). Science studies have examined the adjustment made by the scientific community in response to this pull for scientific answers to new problems (Eyre et al. 2004;Graham 2004;Hansson 1999;Karlqvist 1999;Stevens et al. 2007).

Less attention has been given in science studies to the *push* mechanisms by which research technologies (RTs) shape the internal dynamics of science (Rosenberg 1992;Shinn and Joerges 2002). RTs often emerge from significant advances in theoretical understanding of more fundamental levels (Joerges and Shinn

2001) and extend the space for observation, manipulation, exploration of the basic units of matter. RTs have played a critical role in the revolutions in life- and material sciences over recent decades enabling explorations at molecular and atomic level (Jones 2004;Judson 1979;Morange 1998). At the same time new RTs expand empirical observation beyond what may be explained by reduction to underlying theory, giving rise to what could be referred to as "epistemic disproportionality". This disproportionality between data generation and reductionist capacity has been highlighted as one of the defining traits of so-called the "new sciences", which include bio-, materials, and computer sciences (Bonaccorsi 2008;Bonaccorsi and Vargas 2010).

Reductionism implies the importance of "theoretical coordination" (Whitley 1984) in the accumulation of scientific knowledge. Therefore those research contributions become more salient which extend and improve the power of reductionist reasoning, as reflected in the pattern that basic research results attract more citations from applied studies than vice versa (Bordons et al. 1996;Boyack 2006;Narin and Hamilton 1996;Seglen 2009). Therefore, if in the new sciences reductionist understanding fails to keep up with the expansion of data and "local" conceptualisations, it becomes important to understand if other - non-reductionist - principles emerge in the accumulation of scientific knowledge. That is the issue addressed in the present paper. In an empirical study of epistemic disproportionality in one of "the new sciences", we examine its knowledge accumulation, focusing on changes in the prominence of reductionism and on emergence of alternative, non-reductionist principles of coordination.

The paper takes as its case a research approach defined by its explicit objective of intensifying the exploitation in applied research of more basic RTs. Towards the end of 1990s dissatisfaction was increasingly articulated with the ability of medical research to translate the advances obtained in the basic life sciences over the previous decades into new drugs, diagnostics, and devices (Contopoulos-Ioannidis et al. 2003;Moran 2007). *Translational Research* emerged as an effort to step up the application of basic discoveries and to allow clinical insights to migrate "upstream" to the laboratories so as to guide research aimed at new therapies, more directly addressing patients' problems (Ioannidis 2004;Marincola 2003;NIH 2008;O'Connell and Roblin 2006). The research program of translational research leverages on the application to clinical research of the technologies made available by the advances in more fundamental fields such as molecular biology, genetics and bioinformatics. This strategy puts into light that a reductionist approach falls short in providing exhaustive interpretation of complex medical phenomena, inviting for alternative, non-reductionist explanations (Marincola 2007). In this sense translational medicine clearly exemplifies a state of "epistemic disproportionality".

We study knowledge accumulation in Breast Cancer Research (BCR), where translational research has been particularly pronounced. However, even in this field most research still follows a more traditional paradigm of clinical studies, and in a companion paper we observe a low level of intellectual exchange between the standard and translational communities. For these reasons BCR has developed into a field allowing the translational approach to be rigorously compared with the standard approach within the exact same disease, and our study is designed to capitalize on this methodological opportunity. We shall refer to the translational approach as "RT-driven research", and in its benchmarking against traditional clinical research we shall refer to the latter as the "standard" approach.

Our main findings indicate reduced role of reductionism - the key driver of scientific advance in established sciences. In RT-driven settings, reductionist reasoning no longer offers adequate explanations of complex phenomena. Complementary principles of coordination of scientific inquiries are needed. We identify

cognitive integration as one of these principles. Three dimensions of integration - the targeting of issues spanning disciplinary boundaries, the combination of heterogeneous cognitive inputs, and the exploitation of heterogeneous inputs to develop versatile outcomes - are specific to RT-driven research. We also find that the novelty generated by integration is balanced by the costs associated to the cognitive distance among the disciplines. Because of those opposite effects, the scientific impact of a contribution is an inverted-U shaped function of its level of cognitive integration.

This article aims at contributing to the literature on science dynamics offering one of the first applications of the theory on the New Sciences to interpret the patterns of development in applied research. Searching for a conceptualization of the cognitive economies complementing reductionist reasoning, the article operates an extension of the theory of modularization from technology- to science-dynamics. Finally, the articulation of the mechanism of cognitive integration introduces the dimension of versatility to subsequent research, a facet generally poorly conceptualized in the literature on interdisciplinarity.

The article begins presenting the theoretical framework that allows the comparison of reductionism and integration as drivers of scientific accumulation. From the theoretical propositions we derive a set of hypothesis that are tested in the empirical study. After presenting the methodology, we present the results of the empirical study. The final section is devoted to the discussion of the findings and to the concluding remarks.

Theory

Directions of scientific knowledge accumulation

We draw on the notion offered by Evolutionary Epistemology that knowledge accumulation, like natural selection, is a two-step process (Bradie 1986;Campbell 1974). At first, competing explanations of a research problem are generated; next they are selected based on their fitness to the solution of the problem. In this sense, scientific communities develop selection criteria that filter the relevance of theories, approaches, and contributions and control the direction of development. These criteria are signalled through the reputational system of science (Barnes 2007;Dasgupta and David 1994;Merton 1957). In this system citations are the key informational device, since their signals combine the priority for single discoveries with their impact[1] on subsequent research. From an evolutionary perspective, citations indicate the extent to which a given idea "fits" the criteria of selection set by a community (Gittelman and Kogut 2003). For those reasons, from the attributes of high impact contributions we learn about those dimensions which shape the accumulation of scientific knowledge, even if they have not (yet) been articulated into an a "philosophy of science" of the type that has been rationalized in the case of reductionism. That is what we attempt in this paper, focusing on patterns in differentially cited results in the field of BCR, to see if they reflect new principles, replacing the reduced role of reductionism.

[1] I.e. as distinct from other, less clearly defined notions of "scientific quality". As it is the case with core signals of most institutions, citations have come to express a number of additional dimensions, requiring cautiousness when using them as bibliometric indicators even to capture the single dimension of impact (Leydesdorff 2008).

On the inadequacy of reductionism

The standard model by which we conceptualize scientific progress – reductionism – emerged to characterize the development of the core disciplines of natural science. Reductionism operates at three levels: at the *ontological* level, it proposes that a full understanding of complex phenomena can be derived from the knowledge of its constituent entities. At the *epistemological* level, it defines a hierarchy of fields, with the most fundamental generalizing and providing explanation at a smaller scale for large-scale phenomena (Silberstein 2002). According to this model, investigations in fundamental disciplines increase our understanding of the basic building-blocks of reality from which a deeper understanding of higher level phenomena can be drawn. At discipline-level, basic research - i.e. the development of scientific knowledge, analytical skills, and technicalities that are not specific to the particular empirical contexts (Zellner 2003) - guides scientists in the recognition, formulation and interpretation of a variety of empirical phenomena (Stokes 1997;Ziman 1984;Ziman 2000). Without necessarily embracing an ontological or an epistemological position, *methodological* reductionism assumes that the most efficient strategy of research to understand a phenomenon is the isolation and investigation of its constituent elements and underlying processes.

The program of Translational Research - aimed at establishing two-way relationships between clinical outcomes and underlying genetic and biological causes - is undoubtedly guided by a methodological reductionist approach, rather than the theoretical adhesion to a reductionist view of diseases. The absorption in the medical research practice of the scientific instrumentation based on molecular biology - e.g. recombinant-DNA, monoclonal antibodies, sequencing, PCR, high throughput screening, combinatorial chemistry, computer simulation, three dimensional visualization (Galambos and Sturchio 1998;McElheny 2010) - as well as the rise of hybrid technologies in the field of bioinformatics paved the way to research strategies seeking to reveal the associations between clinical phenomena and underlying genetic determinants. Translational Research mines large bodies of biodata with the goal of interpreting pathological outcomes with the lenses of more fundamental disciplines. Rather than leading to a general theory on disease mechanisms (Denny et al. 2010;Feero 2010) those inquires have put into light the epistemic disproportionality existing between complex medical phenomena and their underlying causes, i.e. the growth of new data exceeds the power of reductionist interpretative schemes, preventing the reduction of the former to the latter. Nonetheless, the reductionist approach to these phenomena has contributed with partial and local explanations to our understanding of the causal patterns of pathological processes. This pattern is consistent with the characteristics of the New Sciences proposed by (Bonaccorsi 2008) and (Bonaccorsi & Vargas 2010). Hence the conjecture of

Hypothesis-1: *Both in standard and in RT-driven research reductionism is a driver of knowledge accumulation.*

Other sources of cognitive economies

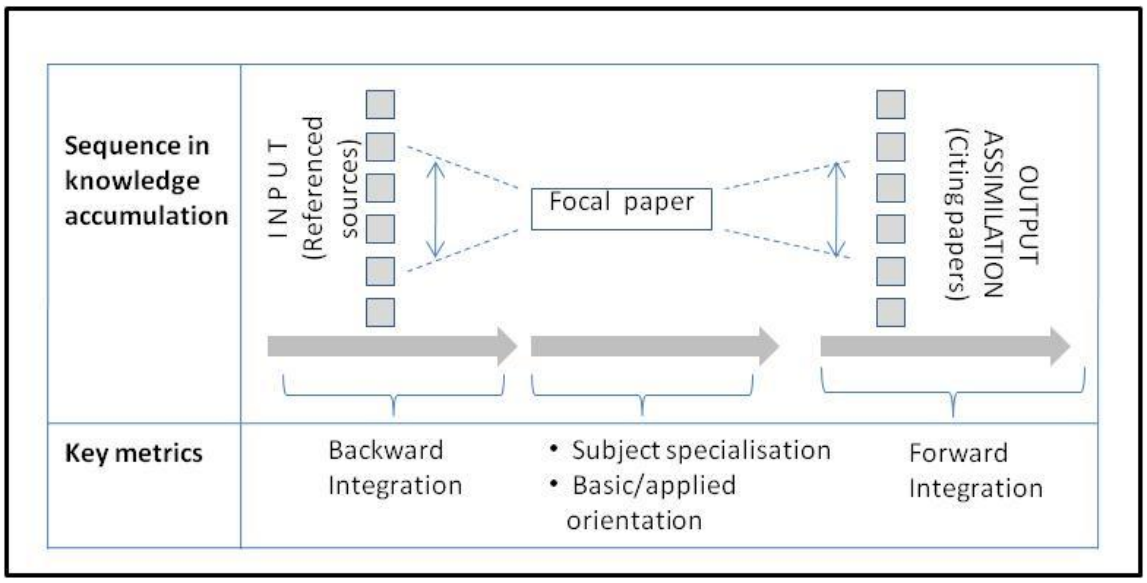
Reductionism draws its prominence in the advancement of science from the contribution of basic theories to *cognitive economies* (Rescher 1989). Basic theories offer not only a parsimonious interpretation of a large variety of empirical phenomena, but also economies of search in the exploration of new phenomena (David et al. 1994). Reductionism has worked as the principal approach to interpret the simpler phenomena addressed by the old sciences; when the growth of new data on systemic phenomena cannot be handled with reductionists reasoning, interpretative schemes fall back on different logics which still offer cognitive economies, although not as powerful as that offered by recourse to fundamental theories.

These interpretative schemes come in various types of pattern recognition whereby relationships that have been validated in one area are invoked to aid the understanding of new findings in other areas. This

transfer across areas takes the form e.g. of identification of isomorphic patterns, or analogies between cause-effect linkages. These non-reductionist transfers share the common characteristic of establishing novel connections between entities previously perceived as unrelated. We suggest that the establishment of such new linkages contribute to knowledge accumulation by offering cognitive economies similar to those offered to technological development by modularisation. In technological design, modularisation refers to advantages obtained from improved understanding of the interface between components, facilitating their combination into different product variations. Modularisation often requires that new and deeper knowledge is developed about interfaces between components (Sanchez 2001). Therefore learning in this respects enhances the flexibility and the complexity of architectures that can be achieved both by single actors and by their production networks (Brusoni et al. 2007;Langlois and Robertson 1992). In scientific knowledge accumulation, we suggest, the discovery of isomorphic or analogous relationship between phenomena A and B similarly adds to our understanding of their interface. Although that knowledge may still be highly imperfect it may be enough to allow the configuration of knowledge referring to A+B to serve as a building block in subsequent knowledge accumulation.

We conceptualise the role in knowledge accumulation of a focal body of research (represented by a research article) by means of a simple three-stage sequence (Figure 1). The first stage refers to that research which is available prior to the focal contribution and used as inputs by the latter, as brought out in the references the focal paper. The integration of inputs drawn from heterogeneous disciplinary areas indicates the establishment of novel interfaces and combinations among previously disconnected entities. We shall refer to this input diversity as the level of *Backward Integration* generated by the focal contribution. To enter a scientific debate, a contribution must conform to the theoretical and methodological principles recognized as valid by the scientific community. The second stage refers to the positioning of the contribution with respect to its core audiences along the dimensions of its *subject specialization* and its *orientation* towards more basic or applied issues. The third stage refers to the subsequent research which uses and assimilates the output produced by the focal contribution. The diversity of this assimilating research will be referred to as the *Forward Integration* obtained by the focal contribution.

Figure 1 Sequence in knowledge accumulation



While in tightly coordinated fields adherence to the disciplinary conventions and the adoption of a reductionist approach is rewarded, in non-reductionist settings our application of the theory on modularisation to knowledge accumulation suggests increasing impact for contributions the more they establish connections between different fields of specialised knowledge.
This higher connectivity could be reflected both in the subject matter of the focal contribution and in its Backward Integration. As for the subject matter of the focal contribution we conjecture:

Hypothesis-2: *In RT-driven research, the spanning of multiple subject fields on part of the focal contribution increases it impact where in standard research it detracts from impact.*

For a similar argument, we suggest that in RT-driven research the establishment of conceptual bridges among poorly connected components of previous research is regarded as a driver of intellectual innovation establishing fertile cognitive complementarities. Multiple studies of combinatorial knowledge formation suggest that the advance emerging from original combinations of inputs drawn from different bodies of knowledge will increase (up to a point) with their ex-ante cognitive distance (Adams et al. 2005;Alkærsig 2009;Fleming 2006;Llerena and Meyer-Krahmer 2003;Nooteboom et al. 2007;Schoenmakers and Duysters 2010). In fact, cognitive costs associated with the integration of heterogeneous knowledge detract from the potential generation of novelty. Hence we conjecture:

Hypothesis-3: *In RT-driven research, but not in standard research, the impact of a focal contribution to subsequent research is an inverted-U shaped function of its Backward Integration.*

We suggest that the variety of the communities that absorb the outcomes of a given focal contribution is a function of its *versatility*. Discoveries affecting our understanding of the interface between phenomena are likely to be absorbed by disparate research agendas, and thus to receive citations from heterogeneous fields, hence expanding their Forward Integration. The possibility of offering insights to solve multiple problems is likely to come at the expense of the *focalization* necessary to contribute effectively to the debate in a given discipline. Because of this trade-off, we expect that also the impact of a focal contribution is an inverted-U shaped function of its Forward Integration. Both reductionist and non-reductionist setting may generate discoveries that contribute to subsequent research by virtue of their versatility, although we expect this tendency to be stronger in the latter.
Based on modularization theory we expect increasing scope of Forward Integration on part of the focal contribution to be associated with increasing Backward Integration, since improved modularisation of components enable their assimilation into heterogeneous contexts. We expect this combined effect of Backward and Forward Integration to be found in non-reductionist settings only, since this is where Backward Integration is assumed to be a driver of scientific advance. From this argument we derive:

Hypothesis 4: *In RT-driven research, the impact of a focal contribution increases with the combined increase of Backward and Forward Integration.*

Research design

The empirical study builds on a bibliometric dataset that allows the comparison of the drivers of scientific impact between the two epistemic communities emerged in the latest stage of evolution of BCR. The lack

of simple bibliometric markers offering reliable isolation of work based on the translational approach (Luwel 2008) required the combination of multiple criteria to identify a set of Laboratory Leaders (LLs) specialized in BCR that can be considered as representative of the two communities. Senior scientists can be regarded as LLs when they establish a stable team of collaborators endowed with technological and financial resources and lend the group a shared vision and a coherent strategy, unifying the contributions of specialists.

To identify one set of articles unambiguously based on a translational approach and one control group of articles coming out of "standard" clinical research, we applied the procedure described in Annex-I to WoK-recorded articles published in 2003-2007. Then, we excluded articles that received no citations and those that gathered no references from WoK-recorded publications, since Backward and Forward Integration measures cannot be calculated for those articles. Thus, we obtained 356 articles - 177 based on the translational and 179 on the clinical approach. Low numbers reflect the shortage of cases allowing unambiguous classification. We considered only European cases to avoid influence from the notable differences between Europe and the USA regarding the organization and funding of medical research (Owen-Smith et al. 2002).

Our analytical strategy first addresses the hypothesis dealing with the role of reductionism in translational and standard research. We articulate the reductionist approach into two orthogonal dimensions: the orientation towards more analytical vs. empirical issues and the contribution to a fundamental vs. applied discipline. Then, we turn to the analysis of cognitive integration analysing at first the separate effects of BI and FI, and then that rising from their combination.

We express the impact of an article by the number of citations received from original research articles and review articles until December 2010. Citations from the first kind of documents signify that the focal article served to develop further research; citations from reviews suggest that it submitted a major discovery or that it outstandingly represents some broader trends of the field. We depurated the performance measure from self-citations, since they are not meaningful of impact (Aksnes and Rip 2009). We adopted a variable citation window in order to capture citations received in the longest time possible after publication. Although the Life Sciences are recognized as a fast developing field - which means that citations to a paper peak early after publication - discoveries "ahead of their time" can be effectively used only when complementary research has been produced (van Raan 2004). The window spans 3 to 7 years. We adjusted the regression models with the "exposure" option to take into account the time that a paper is available for citation and we included some time-related controls.

To assess the impact of a reductionist approach, we used the dummy ORIENTATION coding the focal article 1 if its CHI-Level is 3 or 4, and 0 otherwise. The CHI classification is widely adopted in the bibliometric literature (Brusoni and Geuna 2003;Grant et al. 2000;Van Looy et al. 2006). Taking its point of departure in a main distinction between empirical, "clinical" medicine and fundamental research, the classification makes a further differentiation within these two main categories, distinguishing among 1) *clinical observation*, 2) *clinical mix*, 3) *clinical investigation*, and 4) *basic research*. Journals are referred to one of the four levels based on expert assessment and on inter-level citation patterns (Narin et al. 1976). Most of the publications in our data are categorised at Levels 2 and 3, distinguished primarily, according e.g. to the editorial criteria of the lead "Journal of Clinical investigation", by orientation of the latter towards "*mechanistic*" or "*major biological insights*", "*illuminating novel principles*" (http://www.jci.org/kiosk/publish/policies). While clearly different from the fundamental, abstract insights stressed at Level-4, Level-3 criteria do emphasise conceptual and causal orientation offering stepping

stones by which empirical work can be connected to fundamental principles. For lack of a better single term we refer to CHI-3 and 4 as representing a *causal orientation* since they imply an effort of interpretation of the phenomena studied with eventually theory-building purposes; CHI-1 and 2 are referred to as an *observational orientation*, since they consist in a mere description of the phenomena, informed to theory but without explicit theory-building purposes.

We consider the DISCIPLINARY SPECIALIZATION of the focal article with the twofold intention of appreciating the impact of research referring to *disciplines* characterized by different positioning along the fundamental-applied continuum, and of comparing research that contributes to a *single* disciplinary area to research that span *multiple* domains. For this purpose, we aggregate the Subject-Categories in four Disciplinary-Specializations: ONCOLOGY, consisting only of the homonymous Subject-Category, the core discipline in BCR; PRACTICE-GROUP that includes medical specialties defined by their main operational principle (e.g. surgery, pathology, general medicine, pharmacology etc); DISEASE-FIELDS that includes medical specialties defined by disease type or organ(-system) (e.g. endocrinology & metabolism; obstetrics and gynaecology; immunology); RT-FIELDS, that refers to the disciplines from which the RTs applied in medical research originate, e.g. biochemistry molecular biology, cell biology, genetics and heredity. We introduce a set of dummies taking value 1 if the focal article is attributed only to one of the Disciplinary-Specializations; we use a fifth dummy, taking value 1 if the focal article is associated with multiple Disciplinary-Specializations. In this way, we are able to compare multidisciplinary research (MULTIPLE) to mono-disciplinary research specialized in more fundamental issues (RT-FIELDS), applied medical research (ONCOLOGY, DISEASE-FIELDS), and downstream medical practices and techniques (PRACTICE-GROUP).

We consider two variables indicating cognitive integration. BI indicates the level of Backward Integration of a focal contribution, i.e. the disciplinary diversity of the inputs that enter a given research project; FI expresses the Forward Integration of a focal contribution, i.e. the scope of disciplinary areas it contributes to. We construct both measures using the methodology developed by (Porter et al. 2007) to measure the diversity of a set of papers. The metric takes value 0 for papers with all references falling in a single SC. It increases to a maximum of 1 with i) the number of disciplines referenced, ii) their reciprocal cognitive distance, and iii) the heterogeneity of the distribution of references across SCs. The latter measure is derived by a Matrix of Science expressed by the frequency of co-citation between SC[2]. We extend this metric, originally developed to assess the diversity of the knowledge base an article draws on, to the diversity of forward citations. We apply a normalization on the mean and standard deviation before entering the variables in the regression models.

We define six CONFIGURATIONS coming out from the intersection of BI and FI to appreciate their combined impact. We consider three modalities of BI - *low*, *moderate*, and *high* - defined using as cut-off points the 33rd and 67th percentile of the distribution, and two modalities of FI - *low* and *high* - defined on the median. Table 1 presents the configurations generated by the two variables.

Table 1 Configurations of BI and FI

Level of FI	High	**Configuration-2**	**Configuration-4**	**Configuration-6**
	Low	**Configuration-1**	**Configuration-3**	**Configuration-5**
		Low	Moderate	High
		Level of BI		

[2] We are grateful to Prof. A. L. Porter for providing us with the Matrix of Science.

To separate the effect of key explanatory variables in the two approaches, we use an interaction with the dummy APPROACH, taking value 1 for translational research and 0 otherwise.

We apply six controls.

The first one considers the disciplinary field of the journal in which the focal article was published - to account for the different average citation-level of disciplines (Althouse et al. 2009;Moed et al. 2004) - and, at the same time, for the number of years the article had the chance to get citations. The Expected Citations (EXPCIT) of a focal article published in year *x* and classified in field *y* is the average number of citations received until the end of 2010 by articles published in that combination of year and Subject-Category. Fields are defined by combinations of Subject-Categories - i.e. the value for a given year is different for *Oncology*, *Surgery*, and *Oncology & Surgery*.

Within a research program, complementarities among distinct projects may exist. A later paper may build on earlier investigations in related areas, thus exploiting synergies and cumulativeness among projects; on the other hand, subsequent papers might lack originality if compared to prior knowledge. In order to account for the effect of complementarities, we considered the dummy COMPLEMENTARITY that takes the value 1 when a focal article cites other LL's production in the period considered.

We control for the novelty of the base of knowledge on which the focal paper builds on. We avoid the distortive effect of references to "classical" contributions, considering the age of the most recent quartile of the references. We used a dummy (AGE) taking value 1 for an age higher than three years, i.e. the average of the most recent quartile of references in the sample.

Collaborative research is known to have greater impact than individual research (Adams, Black, Clemmons, & Stephan 2005), so we control for the size of the team. We used a dummy (AU) taking value 1 if the article has more than 10 co-authors, being 10 the median of the distribution.

The factors characterizing each LL - e.g. individual talent, organization of the team of inner collaborators, age of the team - are captured by a set of dummies.

Finally, we add a control for the publication year (PY) of the focal article.

We used negative binomial regression models since our dependent variable - the number of citations received by each article - is a nonnegative count with an over-dispersed distribution. For ease of interpretation, we display Incidence Rate Ratios (IRR). An IRR greater than 1 should be interpreted as a positive contribution to citations, while an IRR between 0 and 1 indicates a negative contribution. We checked for heteroscedasticity with graphical and numerical techniques. To account for the correlation of observations, we cluster robust standard errors based upon 40 LL-publication year combinations. We can exclude that the results of the models are substantially biased by multi-collinearity since the maximum Variance Inflation Factor (VIF) is under the cut-off point of 10 in all models except one, in which the maximum VIF takes the value of 12.70.

Significance at 0.10, 0.05 and 0.01 levels is signalled by *, **, and *** respectively.

Results

Descriptive statistics

The descriptive statistics presented in Table 2 indicate that translational and standard clinical research constitute distinct patterns of specialization. Rather than lying in the impact of research - slightly superior in Translational Research (row a.) - the approaches differ in the disciplinary interest and in the levels of cognitive integration. In both the approaches more than half of the production is represented by mono-disciplinary studies in Oncology (row g.). Differences emerge outside the main disciplinary domain, with translational LLs more frequently operating in the areas of RT- and Disease-Fields (rows h., j.) while the control group specialises in the Practice-Group (row i.). The share of articles covering multiple disciplinary areas (row. k) is similar, indicating that also the standard approach regularly embraces interdisciplinary studies. As for cognitive integration, the levels of BI and FI are respectively 30% and 25% higher in translational than in standard research. Considering both dimensions simultaneously we notice that standard research concentrates a substantial share of its production (36%) in the configuration characterized by low levels of both BI and FI (row t.), while the 32% of translational articles pursue at the same time high BI and FI (row y.). It emerges a substantial attitude of Translational Research towards both forms of cognitive integration.

Table 2 Descriptive statistics

	Variable	Total		Clinical		Transl.		Test
a.	**Total n. of articles**	356		179		177		
		Mean (Std. Dev.)	**Median**	**Mean (Std. Dev.)**	**Median**	**Mean (Std. Dev.)**	**Median**	[1]
b.	**N. of Citations**	26.736 (55.489)	11	26.084 (56.650)	11	27.395 (54.443)	12	-1.659*
c.	**BI**	.449 (.151)	.471	.391 (.164)	.413	.508 (.110)	.500	-6.798***
d.	**FI**	.432 (.172)	.446	.384 (.176)	.411	.480 (.154)	.495	-5.612***
e.	**EXPCIT**	19.483 (8.798)	18.938	18.648 (8.396)	18.938	20.327 (9.134)	18.938	-1.470
		n.	**%**	**n.**	**%**	**n.**	**%**	[2]
f.	**ORIENTATION**	111	31.18	21	11.73	90	50.85	p=.000
	Disciplinary Specialization							
g.	**ONCOLOGY**	198	55.62	104	58.10	94	53.11	p=.393
h.	**DISEASE-FIELDS**	17	4.78	5	2.79	12	6.78	p=.087
i.	**PRACTICE-GROUP**	45	12.64	32	17.88	13	7.34	p=.004
j.	**RT-FIELDS**	18	5.06	1	0.56	17	9.60	p=.000
k.	**MULTIPLE**	78	21.91	37	20.67	41	23.16	p=.609
l.	**COMPLEMENTARITY**	196	55.06	79	44.13	117	66.10	p=.328
m.	**AU**	160	44.94	84	46.93	76	42.94	p=.871
n.	**AGE**	123	34.55	58	32.40	65	36.72	p=.496
	PY							p=.839
o.	**2003**	80	22.47	42	23.46	38	21.47	
p.	**2004**	60	16.85	29	16.20	31	17.51	
q.	**2005**	70	19.66	35	19.55	35	19.77	
r.	**2006**	64	17.98	33	18.44	31	17.51	
s.	**2007**	82	23.03	40	22.35	42	23.73	
	Configurations							[3] 49.622***
t.	**CONFIGURATION-1**	84	23.60	65	36.31	19	10.61	
u.	**CONFIGURATION-2**	33	9.27	21	11.73	12	6.70	
v.	**CONFIGURATION-3**	62	17.42	34	18.99	28	15.64	
w.	**CONFIGURATION-4**	60	16.85	18	10.06	42	23.46	
x.	**CONFIGURATION-5**	32	8.99	14	7.82	18	10.06	
y.	**CONFIGURATION-6**	85	23.88	27	15.08	58	32.40	

[1]Wilcoxon-Mann-Whitney test; [2]Fisher-test; [3]Pearson Chi-Squared.

As one could expect from the procedure followed to build the sample, translational research shows a clear orientation towards more basic issues (row f.). As for the controls, no significant differences exist between the approaches.

Drivers of scientific impact

The models presented in Tables 3, 6, 8 investigate the drivers of scientific impact. After considering a model with controls only (Model-1), in Models-2 and 3 we address the issue of the role of reductionism in the new and old sciences looking at the effects of positioning along the causal-observational continuum and of the disciplinary specialization. We take as benchmarks the observational orientation and mono-disciplinary articles in ONCOLOGY: the estimates in the models refer to the effect of causal-oriented articles, and of articles addressing other disciplinary areas compared to the benchmark. From Model-4 we tackle the non-reductionist drivers, appreciating at first the impact of research spanning disciplinary boundaries, and then

that of BI and FI in Models-5 and 6. Since we assume that the effect of these variables is inverted-U shaped, we interact the approach dummy with both linear and squared terms in the regressions. Finally, Model-7 considers the six configurations defined by BI and FI. In the models including interactions, the non-interacted terms refers to the standard approach while the interaction refers to the difference between the approaches. In Tables 4, 7, 9 we provide the results of a Wald-test estimating the effect of the variable in translational research.

Table 3 Drivers of scientific impact - Models 1-4

		Model-1	Model-2	Model-3	Model-4
		IRR (Std. Err.)	IRR (Std. Err.)	IRR (Std. Err.)	IRR (Std. Err.)
a.	**APPROACH**		.871 (.176)	.901 (.188)	.744 (.163)
b.	**ORIENTATION**		1.356** (.169)	1.493* (.352)	1.348** (.165)
c.	**APPROACH*ORIENTATION**			.870 (.222)	
d.	**DISEASE-FIELDS**		.815 (.155)	.822 (.157)	.853 (.161)
e.	**RT-FIELDS**		.592*** (.109)	.599*** (.112)	.626** (.115)
f.	**PRACTICE-GROUP**		3.024*** (.653)	3.055*** (.658)	2.887*** (.631)
g.	**MULTIPLE**		1.093 (.172)	1.098 (.174)	.716* (.143)
h.	**APPROACH*MULTIPLE**				2.135*** (.450)
i.	**COMPLEMENTARITY**	1.147 (.169)	1.237 (.164)	1.245* (.161)	1.206 (.156)
j.	**EXPCIT**	1.041*** (.007)	1.056*** (.009)	1.056*** (.009)	1.057*** (.009)
k.	**AU**	2.002*** (.315)	1.752*** (.253)	1.754*** (.252)	1.741*** (.248)
l.	**AGE**	.910 (.135)	.852 (.100)	.851 (.010)	.864 (.105)
m.	**PY**	YES	YES	YES	YES
n.	**LL**	YES	YES	YES	YES
	VIF	1.70 (2.45)	2.24 (6.76)	2.65 (7.90)	2.32 (7.08)

Table 4 Effect of interacted terms in translational-research.

		Formula	IRR
o.	**ORIENTATION**	h.*i.	1.299**
p.	**MULTIPLE**	m.*n.	1.528**

Model-1 including only the controls shows that EXPCIT (row j.) and AU (row k.) have a positive and strongly significant impact effect on citations. This effect is confirmed by all the subsequent models. As for the other controls, AGE is always neutral (row l.), while some models recognize an advantage for articles building on previous work by the same LL (row i.).

Model-2 introduces ORIENTATION and the dummies relative to the disciplinary specialization. The former indicates that, after controlling for the differences among disciplinary fields, causal-oriented articles have 35.6% (row b.) more chances to receive an additional citation than observational ones. In Model-3 we assess whether differences exist between the approaches. We find that this is *not* the case: moving from the *observational* to the *causal* pole, standard research increases its impact by 49.3% (row b.) and translational research by 29.9% (row o.), the difference between the approaches being not significant (row c.). Consistently with the reductionist method, the adoption of a causal orientation turns out to represent a driver of scientific progress both in the standard approach and in the translational.

We deepen the analysis addressing the effect disciplinary specialization. To better appreciate this dimension, at first we provide the average and the median EXPCIT for each specialization in Table 5. These data should be considered with particular care since they are not fully representative of the broad trends of BCR. In fact, the variable was constructed considering the Subject-Categories in which the LLs published in a given year: they thus exclude all the Subject-Categories not addressed in a given year by any LL. Nonetheless, the data turn particularly useful to benchmark the effect of disciplinary specialization for the LLs in our sample.

Table 5 Expected citations of the disciplinary specializations.

	Disciplinary Specialization	Average (Median) EXPCIT
a.	**ONCOLOGY**	22.89 (24.65)
b.	**DISEASE-FIELDS**	20.40 (24.28)
c.	**RT-FIELDS**	25.36 (25.53)
d.	**PRACTICE-GROUP**	12.97 (10.01)
e.	**MULTIPLE**	12.99 (10.94)

The results shown in Table 5 suggest that research in more fundamental disciplinary areas such as RT-Fields (row c.) offer the expectation of slightly higher citations than studies in applied domains such as Oncology and Disease-Fields (rows a., b.), and notably higher than more practice oriented research (row d.). It also indicates a poorer performance of boundary crossing studies (row e.).

Model-2 indicates that contributions addressing one of the upstream RT-Fields suffer a 40.8% penalty as compared to the benchmark Oncology (row e.). Since translational studies account for almost the entire number of articles in that specialization, we attribute the effect of this variable to this approach. By contrast, there is strong reward (more than three times than a mono-disciplinary Oncology article, row f.) for focussing on the more specific applied issues of the Practice-Group. In models not presented here, the approach-dummy revealed that the effect is similar in both the approaches.

If we compare the results from Model-2 with the descriptive statistics in Table 5, we find that the pattern of rewards for the scientists in our sample is opposite from that one could expect from the average pay-off offered by the fields. To interpret these results we keep in mind that our scientists are specialized in Oncology, a discipline that, in the hierarchy of fields suggested by reductionist thinking, is positioned between RT-Fields and the Practice-Group. Accordingly with the hierarchy argument, the application of theories and methodologies developed in a more upstream field (Oncology) to a more technical (Practice-Group) assures supra-normal rewards, and, in parallel, they turn inadequate to contribute to the debate in more fundamental fields (RT-Fields).

From the analysis of the effects of orientation and disciplinary specialization we find support for Hypothesis-1 that both in standard and in translational research reductionism is a driver of knowledge accumulation.

It is important to notice that the standard approach concentrates a considerable share of their production (18%) in the Practice-Group, thus exploiting this advantage; instead, RT-Field articles amount to about 10% of translational production, being the third most important specialization. Model-4 deepens the analysis of non-reductionist drivers of impact, tackling the effect of addressing issues that span multiple disciplinary domains. The Model reveals that the irrelevance of MULTIPLE indicated by Models-2 and 3 is the consequence of a spurious effect, having the effects in opposite directions in the two approaches. When

spanning multiple fields the standard approach is penalized by 28.4% (row g.) in comparison to a mono-disciplinary article in Oncology. The opposite effect characterizes translational research that instead enjoys a reward of 52.8% for this kind of studies (row p.). Such reward comes *in contrast* to the poorer payoff for multi-disciplinary studies indicated by Table 5. Hence Hypothesis-2, that in RT-driven research the spanning of multiple subject fields on part of the focal contribution increases it impact where in standard research it detracts from impact, finds support.

Model-5 addresses the impact of research based on increasing levels of BI. The model shows that BI is a driver of scientific impact only for Translational Research: the estimates for the standard approach (rows g., h.) are not significant, while the significance of both the linear and squared term for the translational one (rows. u., v.) indicate that the effect is inverted-U shaped. Calculations on the coefficients derived from IRR, indicate that the pay-off is maximum for Translational Research for a value of BI equal to .547: more than one third of translational articles (61 out of 177) exceed the optimum level of BI. Hypothesis-3 finds support regarding both the specificity of Backward Integration as a driver of cognitive advance for translational but not for standard research, and its inverted-U shaped effect on citations.

Table 6 Drivers of scientific impact - Models 5-6

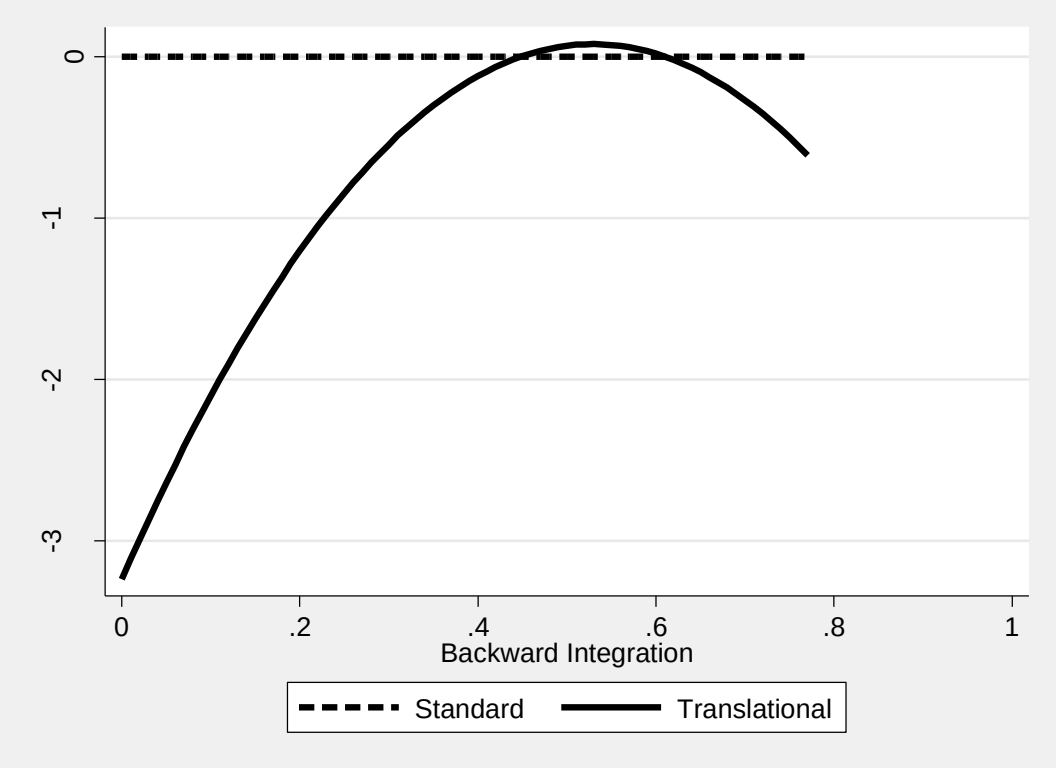
		Model 5	**Model 6**
		IRR (Std. Err.)	IRR (Std. Err.)
a.	**ORIENTATION**	1.326** (.173)	1.314** (.158)
b.	**DISEASE-FIELDS**	.856 (.164)	.826 (.146)
c.	**RT-FIELDS**	.603*** (.111)	.633*** (.105)
d.	**PRACTICE-GROUP**	2.996*** (.660)	3.247*** (.719)
e.	**MULTIPLE**	1.098 (.171)	1.156 (.158)
f.	**APPROACH**	.495*** (.136)	.438*** (.110)
g.	**BI**	.923 (.086)	
h.	**BI-squared**	.990 (.059)	
i.	**APPROACH*BI**	1.350** (.164)	
j.	**APPROACH*BI-squared**	.852 (.087)	
k.	**FI**		1.330*** (.127)
l.	**FI-squared**		.789*** (.051)
m.	**APPROACH*FI**		1.169 (.169)
n.	**APPROACH*FI-squared**		1.010 (.093)
o.	**COMPLEMENTARITY**	1.259* (.167)	1.221* (.144)
p.	**EXPCIT**	1.055*** (.009)	1.051*** (.008)
q.	**AU**	1.787*** (.282)	1.604*** (.216)
r.	**AGE**	.851 (.100)	.812* (.094)
s.	**PY**	YES	YES
t.	**LL**	YES	YES
	VIF	2.53 (8.52)	2.50 (8.34)

Table 7 Effect of interacted terms in translational-research

		Formula	IRR
u.	**BI**	m.*o.	1.246***
v.	**BI-squared**	n.*p.	.843**
w.	**FI**	q.*s.	1.555***
x.	**FI-squared**	r.*t.	.799***

From the estimates of the coefficients derived from IRR, we obtain the equations expressing the effect of Backward Integration on citations (Figure 2).

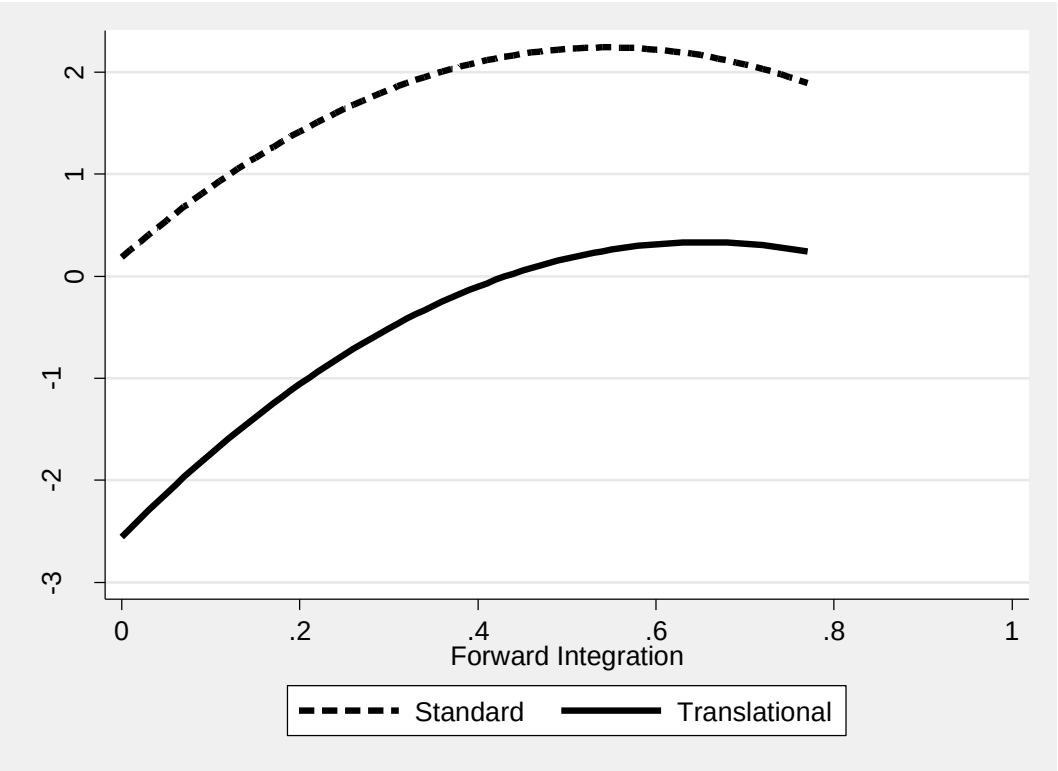
Figure 2 Contribution of BI to impact



The graph offers an important insight about the relative advantage of standard clinical research over the translational approach. We see that the emerging translational approach is generally *penalized* in comparison to the standard one; translational studies have the opportunity to close the gap with the standard approach leveraging on BI. For levels of BI between .449 and .609, the impact of the two approaches is about the same. More than one half of translational production (91 articles out 177, 51.4%) falls in that range.

FI is instead a driver of scientific impact in both the approaches. The coefficients derived from the estimates of Model-6 (rows k., l., w., x.) indicate that the optimum value for Translational Research amounts to .599, while that for the standard approach is slightly lower, .535. In this case, around one fifth of both translational (38) and clinical (34) articles exceeds the respective maximum values. The visualization of the effect of the variable in Figure 3 makes it evident that FI does not allow translational research to close the gap it has with the standard approach.

Figure 3 Contribution of FI to impact



These results reveal that an appropriate selection of the optimal level of BI and partially the disciplinary specialization allow translational studies at overcoming a disadvantage associated to the novelty of the approach, so that the average impact of translational work is slightly superior to that of standard studies (Table 2, row a.).

Model-7 considers jointly BI and FI. The model takes as a benchmark a clinical article with low levels on both dimensions, and estimates the effect on citations in all the other configurations for the two approaches. Rows g.-k., referring to the standard approach, indicate that all the configurations have the same impact as the baseline. In other words, the interaction between BI and FI neutralizes the positive contribution of FI emerged in Model-6: we register the inability of standard research to leverage on the integration of heterogeneous inputs to offer versatile outputs to subsequent studies. As for Translational Research, rows f. and aa.-ae. indicate that the approach has a poorer performance than the clinical one in all the configurations but Configuration-4. This reiterates the previous findings on the structural-disadvantage associated to Translational Research, but it also means that entering an appropriate configuration of cognitive integration (moderate levels of BI and high levels of FI) Translational Research is able to close the gap with standard research.

Table 8 Drivers of scientific impact - Model 7

		Model 7
		IRR (Std. Err.)
a.	**ORIENTATION**	1.249** (.130)
b.	**DISEASE-FIELDS**	.780 (.148)
c.	**RT-FIELDS**	.616** (.130)
d.	**PRACTICE-GROUP**	2.932*** (.630)
e.	**MULTIPLE**	1.104 (.165)
f.	**APPROACH**	.356** (.142)
g.	**CONFIGURATION-2**	1.640 (.502)
h.	**CONFIGURATION-3**	.699 (.191)
i.	**CONFIGURATION-4**	.642 (.179)
j.	**CONFIGURATION-5**	.478 (.217)
k.	**CONFIGURATION-6**	1.132 (.276)
l.	**APPROACH*CONFIGURATION-2**	.766 (.407)
m.	**APPROACH*CONFIGURATION-3**	1.895 (.825)
n.	**APPROACH*CONFIGURATION-4**	3.162*** (1.228)
o.	**APPROACH*CONFIGURATION-5**	1.414 (.802)
p.	**APPROACH*CONFIGURATION-6**	1.354 (.434)
q.	**COMPLEMENTARITY**	1.256* (.155)
r.	**EXPCIT**	1.055*** (.009)
s.	**AU**	1.724*** (.258)
t.	**AGE**	.852 (.098)
u.	**PY**	YES
v.	**LL**	YES
	VIF	2.99 (12.70)

Table 9 Effect of interacted terms in Translational Research.

		Formula	IRR
	Base: Configuration-1 in Clinical		
aa.	**CONFIGURATION-2**	l*m.*r.	.447*
ab.	**CONFIGURATION-3**	l*n.*s.	.471*
ac.	**CONFIGURATION-4**	l*o.*t.	.722
ad.	**CONFIGURATION-5**	l*p.*u.	.241**
ae.	**CONFIGURATION-6**	l*q.*v.	.546*
	Base: Configuration-1 in translational-research		
af.	**CONFIGURATION-2**	m.*r.	1.256
ag.	**CONFIGURATION-3**	n.*s.	1.324
ah.	**CONFIGURATION-4**	o.*t.	2.029***
ai.	**CONFIGURATION-5**	p.*u.	.676
al.	**CONFIGURATION-6**	q.*v.	1.533**

Finally, rows af.-al. take as benchmark Configuration-1 in Translational Research, showing the pay-off of the other five Configurations in that approach. The results indicate that only two Configurations have an impact different from that of Configuration-1, namely Configuration-4 and Configuration-6. The pay-off of the

former is about double than that of the baseline, while that of the latter is 53% higher, consistently with the underlying inverted-U shaped effect of BI. This result indicates that versatile outcomes have a higher impact if they exploit a modularized architecture of their constituent building blocks (corresponding to medium and high, but not to low, levels of BI).

These results suggest that Translational Research is rewarded by the scientific community for offering discoveries serving previously disconnected research fields that are enabled by the establishment of new interfaces between existing bodies of knowledge. The results provide support to Hypothesis-4 that in TR-driven the impact of a focal contribution increases with the combined increase of Backward and Forward Integration.

Looking at the distribution of publications (Table 2), we observe that only 23.5% of translational work is characterized by the configuration (n. 4) that assures a pay-off similar to that of the standard approach. About one-third of translational studies (those in Configuration-6) obtains lower rewards because they present an excessive level of Backward Integration. On the whole, about 45% of translational articles fall in configurations different from n. 4 and 6 that assure rewards higher than Configuration-1.

Conclusions

This study investigates the drivers of knowledge accumulation a field of medical research that grounds its investigation strategy in the systematic and intense exploitation of new research technologies, thus falling in the definition of "new sciences" proposed by (Bonaccorsi 2008). The adoption of these technologies enhances the possibilities of exploring complex phenomena with a reductionist approach. Rather than leading to the discovery of more fundamental theories, this research strategy reveals the insufficiency of reductionist reasoning to interpret complex phenomena. This does not mean that science accumulates without patterns: other principles, peculiar to the new sciences, complement reductionism as drivers of scientific progress.

We have identified *cognitive integration* as one of these drivers. Extending the theory on modularization in technological design, we have argued that integration builds on cognitive economies associated to the creation and the explanation of interfaces between previously disconnected cognitive components. These conceptual bridges can be observed both with regard to the heterogeneity of the inputs that enter a research project, and to the scope of application of its outcomes. Although the latter driver is not peculiar to the new sciences, we found that the impact of contribution serving multiple research settings is higher impact if they are grounded on a modularized architecture of their constituent building blocks.

We found that "standard" medical research enjoys an advantage in comparison to translational research, indicating that emerging approaches are penalized until the scientific community adapts the criteria to assess the relevance contributions. However, leveraging on non-reductionist drivers, translational research can already produce outcomes with an impact analogous to the standard approach.

From this picture, it emerges that scientists adopting the translational approach should master both reductionist and non-reductionist methods. Education programs in medicine should favour the development of skills in these areas, in addition to more traditional competencies in the medical specialisations and in the disciplines fuelling the new research technologies.

Finally, our results indicate that the advantages offered by integration are subject to decline with the cognitive distance among the disciplinary fields addressed. For this reason, scientists should position their research at the optimum level of cognitive distance that maximises the potential of novelty generation. In an emerging field like translational research this goal presents considerable difficulties: since the dimensions of relevance have not been fully articulated, scientists lack a map for defining research strategies fitting the selection criteria of the scientific community. Not surprisingly, a considerable portion of translational work pursues sub-optimal levels of cognitive integration.

Annex I: Criteria and procedures for building Dataset-B

From the list of the most prolific European Authors in the sub-field, we considered those who, in 2003-2007, focused on BC in at least 2/3 of the production. We considered LLs specialized in the disease to appreciate the genuine features of an interdisciplinary approach in a bounded area of research, i.e. eliminating the effects of synergies among disease areas. We then identified the Authors who can be regarded as "LL" by excluding those co-authoring a substantial share of their production with a more prolific scientist, or those responsible of larger organizations, such as entire departments. In order to avoid country-specific effects, we did not allow the same country to be represented in the translational and the control group more than once.

We identified translational and clinical LLs on the basis of the predominant CHI-Level of their production. To be considered as adhering to the translational approach at least ¼ of a LL's publications must be categorized at levels 3 or 4. Furthermore the principles and organization of their work must be translational, as per publicly available documents on their research units. Clinical scientists were identified among those presenting less than ¼ of articles in CHI 3 and 4 and indicating no engagement in translational objectives or organization of their work.

The set of translational articles then is a blend of CHI-2 and 3 articles (respectively 45% and 46%) with a marginal presence of *clinical observations* and *basic research* (respectively 2% and 7%). The Clinical control set concentrates the 75% of its articles in CHI-2, and the remaining is evenly split between *clinical observations* and *clinical investigations* while no *basic research* is present. This comparison suggests a more pronounced attitude of translational LLs to span across different Research Levels, and a higher intensity of analytical-oriented studies.

We identified three translational LLs. For the selected LLs we collected complete bibliometric records from 2003 to 2006 from ISI–WoK. Given the lower productivity of clinical scientists meeting the selection criteria, we considered five cases in order to gather a comparable set of publications. The topic of papers and affiliation of authors were checked to remove publications by homonymous scientists; we integrated the dataset with three publications whose authors' name was misspelled in WoK records.

We obtained 384 papers, 184 by translational and 200 by clinical LLs. We excluded articles with more than 50 co-authors because they can hardly be considered as the result of an "actual" collaboration: translational scientists have 4 of such articles and the control group 12. We finally obtained a valid dataset of 369 articles.

Annex II: Attribution of Subject-Categories to Disciplinary-Specializations

Oncology
Oncology

Disease-Fields
Allergy
Anatomy & Morphology
Andrology
Behavioral Sciences
Cardiac & Cardiovascular Systems
Clinical Neurology
Dentistry, Oral Surgery & Medicine
Dermatology
Endocrinology & Metabolism
Gastroenterology & Hepatology
Geriatrics & Gerontology
Gerontology
Hematology
Immunology
Infectious Diseases
Neurosciences
Obstetrics & Gynecology
Ophthalmology
Orthopedics
Otorhinolaryngology
Pediatrics
Peripheral Vascular Disease
Psychiatry
Psychology
Psychology, Applied
Psychology, Biological
Psychology, Clinical
Psychology, Developmental
Psychology, Educational
Psychology, Experimental
Psychology, Mathematical
Psychology, Multidisciplinary
Psychology, Psychoanalysis
Psychology, Social
Public, Environmental & Occupational Health
Respiratory System
Rheumatology
Sport Sciences
Substance Abuse
Urology & Nephrology
Virology

RT-Fields
Biochemical Research Methods
Biochemistry & Molecular Biology
Biology
Biophysics
Biotechnology & Applied Microbiology
Cell Biology
Computer Science, Interdisciplinary Applications
Developmental Biology
Evolutionary Biology
Genetics & Heredity
Mathematical & Computational Biology
Medical Informatics
Medical Laboratory Technology
Microbiology
Nanoscience & Nanotechnology
Reproductive Biology

Practice-Group
Anesthesiology
Critical Care Medicine
Emergency Medicine
Health Care Sciences & Services
Integrative & Complementary Medicine
Medicine, General & Internal
Medicine, Research & Experimental
Nursing
Nutrition & Dietetics
Pathology
Pharmacology & Pharmacy
Physiology
Radiology, Nuclear Medicine & Medical Imaging
Rehabilitation
Surgery
Transplantation
Anesthesiology
Critical Care Medicine
Emergency Medicine
Health Care Sciences & Services
Integrative & Complementary Medicine
Medicine, General & Internal
Medicine, Research & Experimental
Nursing
Nutrition & Dietetics
Pathology
Pharmacology & Pharmacy
Physiology
Radiology, Nuclear Medicine & Medical Imaging
Rehabilitation
Surgery
Transplantation

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