Cell Stem Cell
Synthesis

Commercialization and Collaboration: Competing Policies in Publicly Funded Stem Cell Research?

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DOI 10.1016/j.stem.2010.06.010

Advances in bibliometrics present new methods for analyzing emerging collaborative innovation models. These methods are illustrated by the Canadian Stem Cell Network, which fosters high-profile multidisciplinary, collaborative, international research. However, patenting negatively impacts collaboration patterns in published research. Policies directed at collaboration and commercialization may be in conflict, depending on the degree to which one activity is emphasized over the other.

Commercialization has become a dominant theme in the innovation strategies of industrialized countries, particularly in the context of stem cell (SC) research in which economic benefit resulting from commercialization is used to justify funding and political support (Winickoff et al., 2009). The priority placed on commercialization exists against a background of funding programs designed to encourage research networks and collaborations. Such programs bring researchers in multiple fields together, with the expectation of promoting basic and applied research and the translation of that research into products and therapies (Lee and Bozeman, 2005; Munos, 2009). However, an increasing body of evidence suggests that commercial activities of academic scientists undermine academic collaborations, resulting in secrecy and withholding of materials and data (Walsh et al., 2005; Hong and Walsh, 2009). Such negative impacts on multidisciplinary academic collaborations are particularly concerning for SC research, which Giebel (2005) argues, "needs to be incubated in academia much longer before it is ready to graduate into a business that can commercialize the technology and deliver real products."

Advances in the field of bibliometrics allow for new objective analyses of research networks and the impact of policies on such networks (Strandbourg et al., 2006; Moed, 2005). Our case study of a Canadian Network of Centers of Excellence (NCE), the Stem Cell Network (SCN), illustrates both the utility of a bibliometric approach and addresses how key variables, including commercialization activity, impact on academic research collaborations. Commercialization activity in the form of patenting has been shown to have a negative impact on scientific knowledge in the public domain (Huang and Murray, 2009). For example, the number of citations of key academic articles on human genes decreases after the gene identified in the article is claimed in a published patent application. The publication of the patent application, 18 months after it was filed, is when the patent application becomes public knowledge. Here, we question whether there is also a negative impact of patenting and other commercialization activities on academic collaborations measured through coauthorship.

The NCE program was established in 1989 and marked a change in science funding models in Canada. Instead of being directed toward individual or small groups of investigators, it was designed to create networks of primarily academic researchers in specific fields, such as SC research (Atkinson-Grosjean, 2005). Most importantly, however, the NCE brought in a new philosophy for inclusion of individuals within partnerships, requiring network researchers to seek cofunding from the private sector and to focus development on commercializable outputs. This requirement constituted a significant policy shift imposed from the top down to change research culture to focus more on application rather than investigator-driven inquiry (Atkinson-Grosjean, 2005).

Funded since 2000 and till 2011, the SCN is directed at translating SC research into clinical applications, commercial products, and public policy (http://www.stemcellnetwork.ca/). It is a nonprofit corporation comprising academic researchers, clinicians, and bioengineers, as well as ethicists, lawyers, and social scientists, the latter three fields collectively known as ELSI. Its program is assessed by external peer review for research excellence and its ability to bring together most of Canada's SC community to facilitate networking, research excellence, and commercialization of network funded research.

However, although the SCN at the time of data collection had contributed funding to two projects that moved into phase I and IIb clinical trials, the majority of SCN-funded research prior to 2008 used animal models and cell-based research. This was so despite the creation, and now dissolution, of Aggregate Therapeutics, Inc. (ATI), a company created to pool and manage the intellectual property and know-how of 37 SCN researchers (Herder and Brian, 2008) who voluntarily agreed to participate. ATI failed to attract private sector investment, probably because of issues commonly identified as barriers to the commercialization of cell-based therapies, including: (1) the early stage of much of the research; (2) questions about the development of

exploitable intellectual property, definable products, and profitable business models, and (3) a host of regulatory and ethical challenges (Giebel, 2005; Little, et al. 2006; Plagnol et al., 2009).

Bibliometrics as a Tool for Innovation Policy Analysis

At present, new innovation models are emerging in the life sciences in which the emphasis is placed on collaboration and partnerships (Gold, et al. 2008; Edwards, et al., 2009). There is a recognition that no one entity can itself do most of the research and development given increasing technological complexities and enhanced understanding of the complexity of living systems. Indeed, even pharmaceutical companies that traditionally have relied on a vertical integration of research through product development and marketing activities now recognize that new drugs will only be developed through innovative partnerships with public research institutions and biotechnology companies (Munos, 2009).

Bibliometrics enables an exploration of these complex collaborative systems. Bibliometric analyses are based on the wealth of data available on the Internet or from other digital records in, for example, publications, patents, citation, sequence, and chemical databases. The main difference between these analyses and traditional metrics for innovation is that instead of merely counting indicators of success along a linear innovation pathway, such as number of publications, patents, or funding, bibliometric analyses can measure networking activities such as researchers who publish, patent, or seek funding together. Further, when combined with statistical modeling, they can assess the significance of factors such as geography, institutional affiliation, and personal or group attributes.

Other bibliometric tools illustrate the structure of a field of research (cocitation analysis) or how the field changes over time (citation trail analysis). Citation trail analysis tracks citations through generations of publications in a field and may be used to track or identify seminal research publications, technologies, or patents. Further, bibliometrics can also be used to explore the influence or the activities of specific groups of researchers in a global research environment. For example, tracking key publications both over time and geography allows for visualization of uptake and diffusion of new technologies, methods, or knowledge. Geographic information software (GIS) such as Google Earth (http://earth.google.com) can help track the movement of researchers and their students around the world. Collectively, these tools allow for a more nuanced understanding of the benefits flowing from innovation networks.

In this Synthesis article, we overlay the attributes of individual researchers on a network of researchers who coauthor academic articles (coauthorship network) in the field of SC research. This approach enables us to explore, when combined with statistical modeling, whether individuals who engage in commercialization activities, such as patenting and company formation or participation, collaborate in the academic realm as much as individuals who do not. We ask this question while controlling for other attributes of individual authors such as institutional affiliation, geography, seniority, impact of research, and research field, among others. We show that, while there are limitations in the available data and analytical tools, network visualization combined with statistical modeling of attributes of individuals within the network may be a powerful tool for policy analysis.

Collaboration networks, in general, may be used for visualizing patterns of linkages between individuals or research groups, including coauthorship of scientific or other publications, copatenting, patentee-assignee relationships, licensing and cofunding relationships, materials exchange, and training. Network Statistics can indicate how central or important an actor is within the network. Here, we only visualized a coauthorship network for SCN Principal Investigators (PIs).

A second bibliometric analysis tool we used was author cocitation analysis. Author cocitation analysis uses information on how authors are cited together in the literature to define fields of interest (i.e., whether two authors have been cited together in a third, fourth, and multiple articles is an indication that they are in the same field). Taken together over a large number of publications, author cocitation analysis can be used for visualizing the subfields within a field of research such as stem cell research (Figure S1 available online). We used cocitation analysis to identify subfields and to objectively assign SCN PIs to those subfields (e.g., hematopoietic SC), which then became an attribute used in the statistical model.

Our approach involves six steps, which are fully described in the Supplemental Information: (1) data collection (publications, patents, and attributes of individual SCN PIs), (2) data cleaning (for example, ensuring that individual authors could be indentified from multiple versions of their names such as John Smith, J Smith, JA Smith, John A Smith or that "J Smith" was in fact two individuals), (3) constructing and visualizing the coauthorship network (where each individual author appears as a node and the lines connecting the nodes are based on the number of times two individuals have coauthored a paper), (4) analyzing the coauthorship network (deriving two network statistics from the full network based on the number of coauthors for each SCN PI), (5) performing the cocitation analysis so that each SCN-PI could be assigned to a subfield of research, and (6) developing a series of generalized linear models (GLMs), a type of regression analysis, to explore, for each of the two network variables (from step 4), if commercialization activity had an effect on coauthorship after taking into account the other attributes of individual SCN PIs.

Data Collection

The initial data were provided by the SCN, including: a list of 83 science PIs, publications funded by the SCN, the names of PIs involved in independent start-up companies, and the names of PIs involved in the SCN commercialization company ATI. In our statistical model, we excluded four honorary PIs and all ELSI PIs because of different publication and citation patterns in the social sciences (Moed, 2005) and because these researchers were minimally linked through coauthorship with science PIs (Figure 1). All statistics are calculated with data on the 79 active science PIs.

We identified institutional affiliations of PIs by using Google and/or PubMed searches and created PI citation reports with the ISI Web of Knowledge. The main attributes of PIs, namely the number of publications, number of citations, average number of citations per publication, H-index, and years since first publication, are shown in Table 1. The H-index is

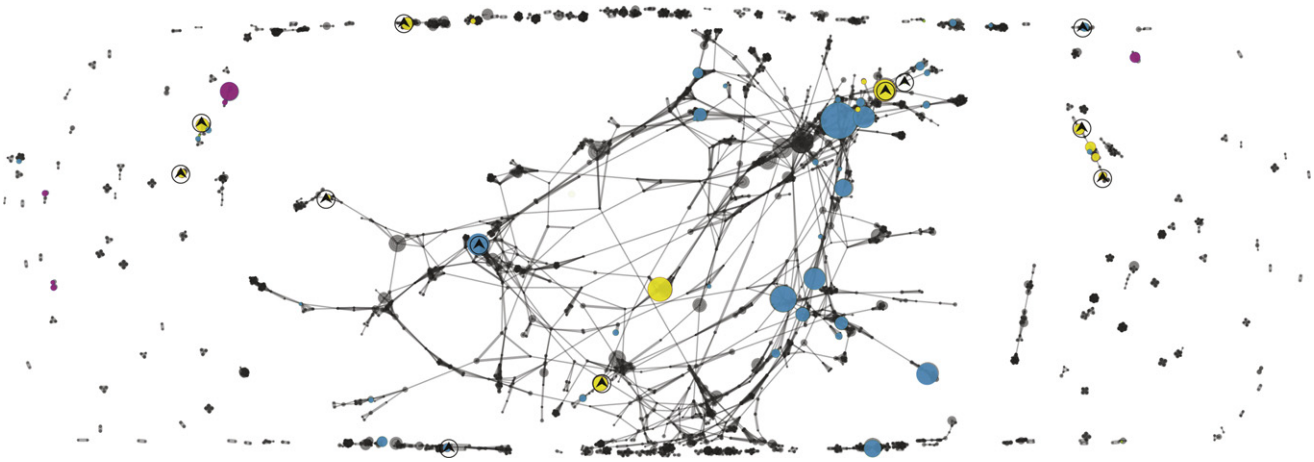

Figure 1. Coauthorship Network for SCN PIs Showing Effect of Patenting and Involvement in Start-Up Companies
Coauthorship network is visualized with CiteSpace (http://cluster.cis.drexel.edu/~cchen/citespace), based on a subset of the full data set, namely (1) publications by SCN PIs (n = 507), (2) publications cited by and (3) citing those publications, and (4) all publications cited in the citing publications. Sustained coauthorship on at least three publications is required in order to appear as a linked author. SCN PIs appear as colored circles, with the size of the circle representing the relative number of publications. Approximately one-quarter of SCN PIs have never coauthored three times or more with the same coauthor. Yellow denotes the top 20 PIs in terms of their patent/publication ratio, blue denotes other science PIs, and fuchsia denotes social science and humanities (ELSI) PIs. Triangular symbols denote those PIs who have been involved with an independent start-up company. PIs with high patent/publication ratios and who have been involved in start-ups are generally less well connected to the central network and are more peripheral compared to those with low patent/publication ratios. This effect is statistically significant.

a measure of research impact based on publications and citations. We used PubMed, ISI Web of Knowledge, and Scopus citation databases to collect four types of publications: (1) the unique Medline indexed scientific publications funded by the SCN (n = 507), (2) publications cited by and (3) citing those publications, and (4) all publications cited in the citing publications. We collected the PIs' international filed and granted patents by using the Canadian Intellectual Property Office database and Delphion (Table 1). Three measures of commercialization used were: (1) patents (applications and granted), (2) involvement in ATI, and (3) involvement in other start-up companies (Figure 1).

Table 1. Impact of Patenting and Publications on Coauthorship Patterns

Variable (n = 79 PIs)	Average ± SE (Range)	Model One[a]: Coauthors Beta Coefficient ± SE (Pr (>|z|))	Model Two[a]: Neighborhood Size Beta Coefficient ± SE (Pr (>|z|))
Dependent Network Variables			
Number of coauthors[b]	114 ± 134 (11–828)		
Neighborhood size[c]	3779 ± 546 (75–23,151)		
Independent or Predictor Variables			
Number of patents	11 ± 1.8 (0–99)	−0.189 ± 0.082 (0.021)	−0.308 ± 0.102 (0.003)
Total number of publications	128 ± 14.4 (16–591)	1.051 ± 0.202 (0.001)	1.178 ± 0.255 (0.001)
Total number of citations	5590.4 ± 699.3 (153–29935)	2.406 ± 0.741 (0.001)	3.161 ± 0.918 (0.001)
Average number of citations per publication	40.9 ± 3.5 (9–149)	–[d]	–
H-index	29 ± 1.9 (7–81)	–	–
Years since first publication	21.5 ± 0.9 (9–43)	–	–

Attributes of SCN science PIs used as dependent and independent variables in generalized linear models to assess which independent or predictor variables explained variance in the two dependent variables. The statistical significance of three independent variables used in the top model for each dependent network variable is shown. Other variables included in the top model for each of the two dependent network variables were type of PI, field of research, year the researcher became a PI in the SCN, and institutional affiliation. Statistical details (regression coefficients with standard errors and significance values) on all variables included in the top models are shown in Table S2. The beta coefficients can be used to calculate the effect size because they indicate the proportional increase (+) or decrease (–) in the dependent variable for every one unit increase in the independent network variable.

[a] Calculated on log-transformed data for patents, publications, and citations so that these variables better approximated a normal distribution.

[b] Number of distinct coauthors of a PI in the coauthorship network.

[c] Number of authors who collaborated either with the PI or with one of the PI's collaborators.

[d] These independent variables were not included because they were highly correlated with other variables included in the top model (Table S1).

Network Characteristics

After data cleaning to eliminate duplicate publications and to correctly identify authors and the links between them (Supplemental Information), we built a computational model of the full coauthorship network on the basis of individual author nodes and the number of coauthored papers (links) between them. The full coauthorship network was based on 162,555 unique PubMed publications with close to a million author name occurrences and 361,064 individual author nodes. There were 2.77 million links between coauthors, weighted by the number of times the two linked individuals appear as coauthors of a publication. For comparison, up to December 2007, there were 157,122 PubMed records with "stem cell" as a MeSH Term, indicating that our search strategy, despite using the interdisciplinary SCN publications as a starting point, captured a significant percentage of research publications in this field.

Network PIs exhibited a wide range of collaborative behaviors, patenting activity, and other characteristics (Table 1). The PIs belonged to 22 Canadian universities and other publicly funded research institutions in 12 cities across the country. All PIs were linked in some way to the overall international coauthorship network of SC researchers, and many had large numbers of international coauthors, ranging from 11 to 828 (Table 1). The SCN classified the 79 active science researchers as basic (54), clinical (14), and bioengineering (11).

To assign SCN PIs to research areas, we performed an all-author cocitation analysis (see Supplemental Information; Figure S1) of the most highly cited researchers in the dataset along with the SCN PIs; 17% of SCN PIs were included in this category of most highly cited researchers. This result indicates the profile of SCN researchers with 14 PIs among the one hundred most highly cited researchers in this field.

All-author cocitation analysis identified seven subfields—hematopoietic SCs; SCs and the nervous system; SC growth and cancer; SCs and early development; SCs and muscles (including cardiac); genetic vectors; and ELSI. We then categorized SCN PIs accordingly by identifying the research areas most closely related to their research publications (Figure S1). This label became another attribute of the SCN PIs to use as a categorical variable for the statistical analysis.

Coauthorship Patterns

Our approach goes beyond a descriptive analysis of a visualized network by combining the coauthorship network with further statistical analyses. We used GLMs to examine the influence of a series of independent variables on two measures of a PI's collaboration intensity (network variables). Note that additional attribute data were collected only for the SCN PIs who were embedded within the complete coauthorship network. GLMs allowed us to determine, for each network variable, whether commercialization activity had an effect after correcting for other statistically significant variables in the model.

The network variables were: (1) the number of distinct coauthors of a PI in the collaboration network ("coauthors") and (2) the number of authors who collaborated either with the PI or with one of the PI's collaborators ("neighborhood") (Table 1). The independent variables were those hypothesized to have a significant statistical influence on collaboration: (1) commercialization activity (patents); (2) research quantity (number of publications); (3) research quality (total number of citations, average number of citations received per publication, and H-index); (4) seniority (years since first ISI-indexed publication) (Table 1). In addition, we included (5) type of PI (basic researcher, bioengineer, or clinician); (6) field of research; (7) the year in which a PI joined the SCN to distinguish SCN founders from more recent arrivals; and (8) institutional affiliation (Table S2).

Other attributes collected, but not included in the final models, were city and patent to publication ratio. These were not included because statistical variables were separated into sets of mutually highly correlated variables (Pearson's $|r| > 0.7$; Table S1), and only one variable from each set was used for any given GLM to avoid multicollinearity of variables. For example, no statistical model included both city and institution because these are highly correlated. The H-index was highly correlated with both number of publications and number of years since the first publication. A PI's patents/publications ratio was almost perfectly correlated with the natural logarithm of his/her number of patents. The analysis was run multiple times with different combinations of independent variables. The selection of the top model followed an "information-theoretic approach" that balanced the model fit against minimizing the number of variables within the model. Table 1 and Table S2 provide the beta coefficients, standard errors, and significance levels for the top models. The beta coefficients can be used to calculate the effect size because they indicate the proportional increase (+) or decrease (−) in the dependent variable for every one unit increase in the independent network variable.

We used natural logarithms of publication, citation and patent numbers so that these variables better approximated a normal distribution. Categorical variables (e.g., city, institution) were automatically converted into a set of "dummy variables," such that for each combination of a category (e.g., city) and a possible value of that category (e.g., Toronto or Edmonton), one dummy variable is introduced into the statistical model, with value 1 if that value applies to a PI in this category. This is a standard method for using categorical variables in regression analysis.

For the first dependent network variable, "coauthors," the top model (R^2 = 0.852, indicating a very strong fit for the model) showed that institutional affiliation affected coauthorship much more strongly than geographical location (in this case, city) —possibly an indication that institutional culture or policy influences researchers more than mere proximity. We are able to make this distinction because each run of the analysis includes only one of the highly correlated variables at a time (e.g., institution or city). In this case, the top model containing institution was a better fit with the data than another run of the model containing city. The three most collaborative institutions were the Lawson Health Research Institute, BC Cancer Agency, and the Samuel Lunenfeld Research Institute, Toronto (Figure S2). Not surprisingly, more senior PIs tended to coauthor with more individuals, and more productive researchers also tended to exhibit higher levels of coauthorship. Both research quantity (number of publications) and quality (number of citations) predicted coauthorship (Table 1). In addition, bioengineers had

fewer coauthors than basic and clinical researchers (ANOVA: $F_{2,76} = 3.52$, $p = 0.034$), but this was not significant in the model. Tukey posthoc tests indicated bioengineers had fewer coauthors than basic researchers but clinicians did not differ from either group.

In terms of commercialization activity, the 15 PIs known to be involved in independent start-ups had, on average, five times as many patents as those not involved (Figure S3), and the 15 individuals involved in start-ups had an average 90 ± 18 coauthors compared to an average of 120 ± 14 for those not involved, a nonsignificant difference. Thus increased patenting captures researchers actively engaged in commercialization as opposed to incidental patenters, for whom patents are a metric increasingly valued by institutions and funders. Indeed, the pressure to patent may be inferred from the fact that 76% of science PIs had at least one patent. There was no difference in patents or coauthors for PIs involved in ATI. This is not surprising because approximately half of PIs agreed to participate, whether they in fact commercialized research or not. Therefore, there was no statistical reason to include either start-up or ATI in the model, especially since patenting captured involvement in start-ups.

Patenting had a statistically significant negative impact on coauthors even after taking into account the other variables that are highly predictive of collaborative behavior (Table 1). The effect size (Supplemental Information) was a 17% decrease in the number of coauthors from a one unit change in the number of patents (log transformed). Figure 1 illustrates these effects: the top 20 patenters and those involved in start-up companies are less well connected to the central coauthorship network, and many are peripheral.

The second dependent network variable, "neighborhood," showed a similar pattern ($R^2 = 0.844$, also a very good fit for the model), but research field was also significant. Researchers in the field of SCs and early development collaborated more than those in other fields, probably because it contained the highest number of PIs (24) and a few highly productive individuals. Patenting also had a statistically significant negative impact on neighborhood (Table 1). Again, there was a 26.5% decrease in neighborhood size from a one unit increase in patenting (log transformed).

Thus, our study demonstrates that bibliometric methods, combined with statistical modeling, have great potential for evaluating science funding policies (Moed, 2005). Here, we assessed whether policies directed at commercialization are compatible with policies directed at enhancing academic networking through research collaborations and the functioning of virtual networks, such as the SCN. Our objective analysis of all SCN PIs showed that individuals actively engaged in commercialization activities had fewer coauthors. This finding is in contrast to the subjective evaluation of a third of SCN PIs in responding to a survey on the impact of commercialization pressure on research activities in which the majority found the overall impact to be positive (11 PIs) or neutral (13 PIs), rather than negative (2 PIs) (Caulfield, et al., 2008).

Some Limitations

The main limitation of our analysis was the use of proxy measures for commercialization and collaboration. Coauthorship incompletely captures the full extent of collaborative research activities, which include training and tacit knowledge exchange (Katz and Martin, 1997). However, it is the most commonly used indicator for academic research activity, and especially appropriate for research that contributes knowledge promptly to the public domain. Similarly, patents were an appropriate proxy for commercialization activity because the filing of a patent application is an early and essential step in the commercialization process, and researchers involved in start-up companies had more patents. This study focuses solely on academic collaborations and future research is required to determine whether PIs involved in commercialization activities developed greater industry collaborations, which, in the long term, could lead to the more socially beneficial outcomes of clinical trials and therapies. However, SCN research, although moving toward those objectives, is still largely academic in cases where the major metrics for success are publications and strong research collaborations.

Finally, our case study uses a Canadian SC research network. Nevertheless, given the well-characterized barriers to commercialization of cell-based therapies internationally (Giebel, 2005; Little, et al., 2006; Plagnol et al., 2009), and mid-sized economies with strong, networked, publicly funded stem cell research programs such as the United Kingdom, Australia, and Germany, our results may be applicable in other contexts, with the degree requiring further exploration.

Concluding Thoughts

In conclusion, science researchers in the SCN exhibit a high degree of collaboration both nationally and internationally and many have significant international profiles. Collaboration patterns were best explained by institutional affiliation rather than broader geography; research quality (average number of citations) and quantity (number of publications); research area; and, not surprisingly, seniority. Most importantly, however, commercialization activity, measured by the number of patents, negatively impacted the degree of collaboration that results in published research.

Thus, policies directed at enhancing collaborative networks and policies directed at commercialization are moderately antagonistic. The extent of this effect will depend on the degree to which one activity is emphasized over the other. Our finding has significant implications for the evolving field of SC research in which commercialization pressures and patenting activity are high (Bergman and Graff, 2007), but future clinical application will depend on highly collaborative interdisciplinary research. Our findings speak to the importance of appropriate policies that balance incentives for interdisciplinary collaboration with commercialization and that enable a culture of sharing for data and bioresources in precompetitive research (Winickoff et al., 2009; Schofield et al., 2009).

SUPPLEMENTAL INFORMATION

The Supplemental Information includes three figures, two tables, and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.stem.2010.06.010.

ACKNOWLEDGMENTS

Funding for this project was provided by a Catalyst Grant from the Stem Cell Network to T.B., a Genome Canada Grant to Geoff Hicks, Manitoba Institute of Cell Biology, and Janet Rossant,

Hospital for Sick Children, at which T.B. is a coinvestigator; and a SSHRC INE grant to E. Richard Gold in whose lab T.B. was a coinvestigator. These grants have provided postdoctoral fellow salary support to A.S. Dangzhi Zhao provided great assistance and expertise in all aspects of the bibliometric analyses, and Logan McLeod and Gian Jhangri provided additional assistance with regression models. Helpful comments were provided on earlier drafts of the manuscript by Timothy Caulfield, Richard Gold, David Castle, and David Hik.

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