Citations in Life Science Patents to Publicly Funded Research at Academic Medical Centers

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Abstract

Background: The contributions of Academic Medical Centers (AMCs) to biomedical innovation have been difficult to measure because of the challenges involved in tracing knowledge flows from their origin to their uses.

Methods: The authors examined patent citation linkages between AMC research funded by the National Institutes of Health (NIH) and patents. In prospective analyses, they examine the extent to which articles resulting from NIH grants to AMCs awarded between 1990 and 1995 were cited in drug and medical patents. The authors then examine the extent to which these patents are associated with marketed drugs. In retrospective analyses, they examine the share of drugs approved between 2000 and 2009 that have citation links to NIH-funded AMC research.

Results: The prospective analyses show over a third of AMC grants resulted in publications that were cited in patents. Most the patents are drug and biotechnology patents, and are assigned to private firms. Patents citing NIH-funded AMC publications were associated with 106 new FDA approved drugs, half of which are new molecular entities and a quarter of which are priority NMEs. The retrospective analyses showed that about half of the new molecular entities approved over the 2000–2009 period had citations links to NIH-funded AMC research.

Conclusions: There are strong links between articles from NIH-funded AMC research and private sector medical patenting, including drugs. More research is needed to better understand the types of links the citations represent and their implications for public policy.
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Introduction

Academic Medical Centers (AMCs) are thought to play critical roles in public health and health care, the teaching of health professionals and biomedical research and discovery (the "triple mission"). Significant public funding for Academic Medical Centers is aimed (in part) at spurring the development of new medical technologies. Accordingly, evaluating the effects of publicly funded AMC research on innovation is important.

Tracing the effects of academic knowledge on innovation is difficult. Previous research has examined the effects of public sector institutions on the development of new drugs, showing that approximately one-in-ten new drugs and one-in-five important drugs emanates from public sector biomedical research institutions, including AMCs.[1] These analyses highlight the role of AMCs and other academic institutions in discovering molecules and proteins that are licensed to private firms that develop and market them.

AMCs also affect innovation in other ways beyond developing therapies. Previous research suggests that academic institutions provide scientific knowledge and technical information that provides a map for research and problem solving, which helps firms focus their research on more promising avenues.[2,3] AMCs have also been active in developing research tools that facilitate industrial research.[4] Qualitative and quantitative studies[3,5,6] emphasize this "enabling" role of academic research is a more frequent form of university-industry knowledge transfer than the development of molecules that are patented and licensed.

These indirect effects of AMC research are not captured by measures of their own patenting activity. While some research has used citation to academic patents to measure such effects[7] this is limited for AMCs since publication not patenting is the main way in which AMC researchers disseminate their results.[8,9] Moreover, recent research suggests patent-to-patent citations are commonly inserted by patent examiners, calling into question whether they are useful signals of knowledge flows.[10]

By contrast, citations in patents to publications are less likely to be from examiners.[11] There is recent evidence that patent–publication citations perform better at measuring the effects of public sector institutions that patent–patent citations.[12] Patent–publication citations have been used to assess the academic–industry links across industries, countries, and over time, to assess the effects of NIH funding in drug development, and to examine the geography of knowledge flows in medicine.[6,13,14]

In this paper, we extend this methodology to specifically examine linkages between AMC research supported by public funds and private sector patenting in the drugs/medical and chemical arena. We start with a prospective analysis, determining which NIH grants to AMCs resulted in publications that were cited by patents, and which of these patents are on marketed drugs. The prospective analysis provides information on the share of grants linked to patents and drugs. However, it does not tell us about the share of innovation that can be linked to AMCs. Accordingly, we also conducted retrospective analyses, where we start with a sample of drugs recently approved for marketing, and ask what share of these drugs can be linked back to AMC research. *Figure 1* shows an example and provides more detail.

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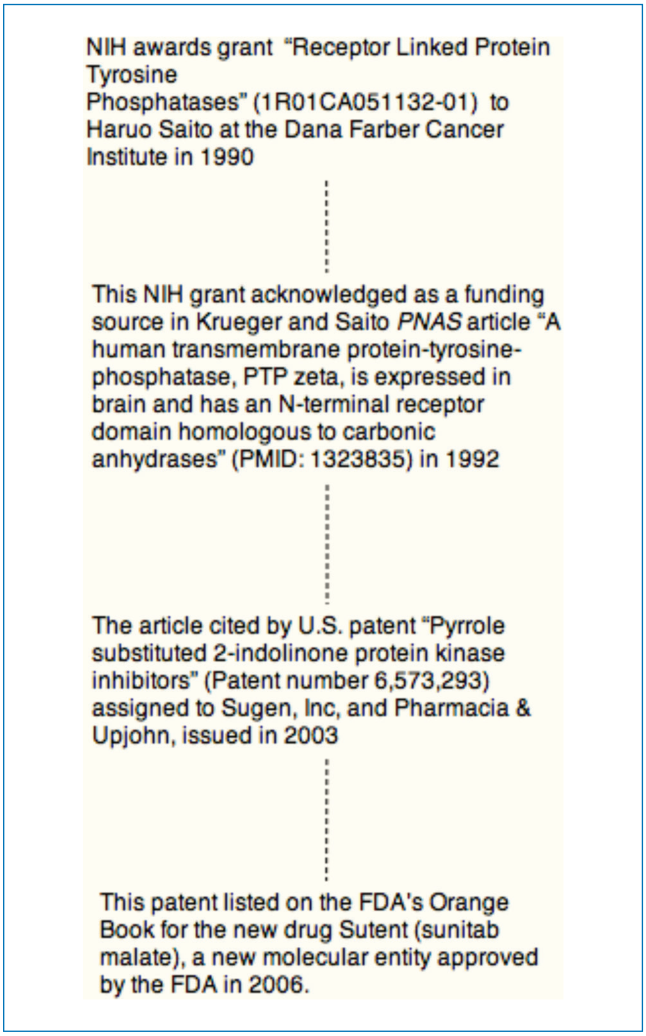

Figure 1. Grants to AMCs and FDA drugs.

Methods

AMC grants

For the prospective analyses, we constructed the pool of relevant AMC research by examining NIH grants to AMCs. We collected information from the NIH RePORTER (Research Portfolio Online Reporting Tool) database on all new grants awarded between 1990 and 1995.[15] We focused on this time period since research takes time to translate into outcomes: more recently awarded grants would be more susceptible to right-censoring, that is, we would be less likely to observe all outcomes. Over this period, RePORTER lists 54,440 new grants. Of these, about half, that is 27,393, were to Academic Medical Centers (Appendix A).

Publications

Next, we collected information on all publications acknowledging these grants, from RePORTER and PubMed. As the RePORTER database documentation notes, "Publications are associated with projects, but cannot be identified with any particular year of the project or fiscal year of funding. This is due to the continuous and cumulative nature of knowledge generation across the life of a project and the sometimes long and variable publishing timeline."[15] Accordingly, we collected all publications that emanated from a new grant and all continuations of that grant. Overall, the 27,393 grants were acknowledged in 308,267 publications (sometimes, a publication cites multiple grants. There are 208,700 unique publications associated with the grants.)

Patents citing these publications

Next, using an algorithm described elsewhere[6,14] we determined which of the PubMed articles resulting from AMC grants were cited among the 5.8 million publication citations in the 717,873 biomedical and chemical patents issued between 1990 and 2010.[16] We used USPTO data[16] on the application years of citing patents to determine lags between AMC research and patent applications citing this research. We used a concordance between patent classes and technology categories[17] to determine the technological categories of these citing patents. We identified the institutions that own the patent using the USPTO assignments file.[16] We also determined which of the citing assignees were private sector firms using data from the USPTO and National Bureau of Economic Research.[16,17]

Drugs

We collected information on all marketed drugs associated with the cited patents using data from the U.S. Food and Drug Administration (FDA) database, Approved Drugs and Therapeutic Equivalents, commonly known as the Orange Book.[18] Using the Orange Book, we collected new drug application numbers, drug names, and FDA approval years for the resulting drugs. We focused on drugs approved until 2009, and used information from another FDA database, Drugs@FDA, to determine whether these new drugs are new molecular entities, and whether they received priority approval.[19] NMEs that earn priority approval are sometimes characterized as the most innovative new drugs.[20]

Retrospective analyses

We used Drugs@FDA to examine the extent to which drugs approved between 2000 and 2009 link (through their patents, and the publications cited in these patents) to NIH grants to AMCs (defined as above) funded between 1985 and 2009. For these drugs, we determined drug information (names, approval year whether they received priority review), patent information (from the Orange Book), and whether they cite to publicly funded AMC research (using the algorithm described above).

We used these data to determine the share of drugs linking to AMC research, overall and by priority review status. This retrospective approach provides a conservative estimate of citation linkages to AMCs, since information on AMC grants and resulting publications is available only beginning in 1985.

Results

Figure 2 summarizes results from the prospective analysis. About 37% of the grants (10,140) generated publications that were cited in one or more patents. Overall, these were cited in 44,149 distinct patents issued by 2010. Based on information on the first assignee of each patent, the majority (66%) are assigned to private sector firms (or individuals). However, public sector patentees also commonly cited AMC research. Thus of the citing patents nearly

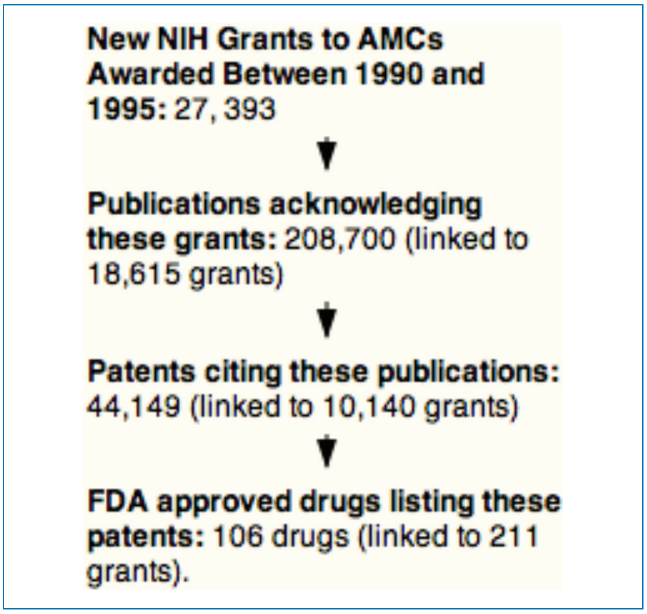

Figure 2. Prospective analysis.

a quarter belonged to universities (22%), and the remainder to hospitals, research institutes, and government agencies.

Table 1 shows the distribution of the 44,149 patents across technology categories. Since we started by examining citations in biomedical and chemical patents, it is no surprise that all the patents are in these categories. The table indicates that the majority of the citing patents relate to pharmaceuticals and biotechnology, though about a quarter fall in chemical or surgery (including device and instrument) related classes.

How long did it take a grant to be cited? To examine this, for each grant cited by a private sector patent we determined the number of years between the grant and when first cited by a private sector patent. The average lag from grant to first private patent application was 6.2 years (SD = 3.3 years); the median lag was 6 years. What about the lag between a grant and any patents that cite to its research outputs (not just the first)? On average, this lag was 9.3 years (standard deviation = 3.5); the median lag was 9 years. Note, however these figures are conditional on a grant resulting in an article cited by 2010. This right censoring leads to exclusion of citations that take a long time to occur (for 1990 grants, only 20 years of citations are seen; for 1995 grants 15 years), and thus underestimates the true mean and median.

Category	Count	Share
Medical: drugs	17,645	40%
Medical: biotechnology	14,943	34%
Chemical: resins	3,738	8%
Chemical: organic compounds	3,589	8%
Medical: surgery and med inst.	2,334	5%
Chemical: miscellaneous	1,443	3%
Medical: miscellaneous	294	1%
Chemical: coating	145	0%
Chemical: agriculture, food, textiles	18	0%
Total	44,149	

Table 1. Distribution of medical and chemical patents citing AMC articles, by technology category. AMC articles are those based on new NIH grants to AMCs between 1990 and 1995.

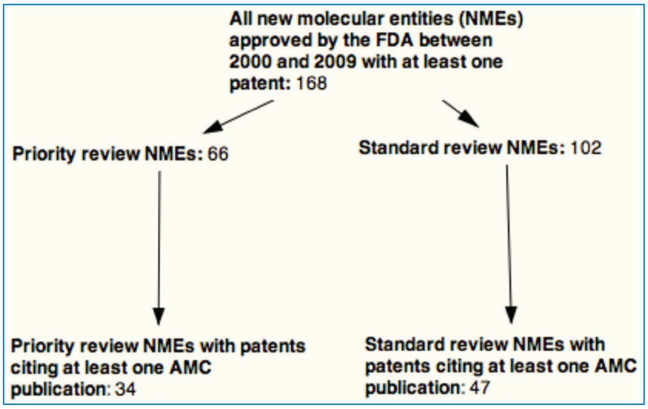

Figure 3. Retrospective analysis.

Of the 44,149 patents, only 146 (citing research funded by 211 grants) were listed on the Orange Book as pertinent to marketed drugs. This is not surprising, since many of the citing patents are not on compounds or proteins. The pharmaceutical and biotechnology categories include not only therapeutic compounds and proteins, but also a range of processes, intermediates, and research tools. And nearly a quarter of the citing patents are outside of these categories. Moreover, even among the patents that are on therapeutic compounds and proteins, many were never tested in clinical trials, and there is a high failure rate even among those that do.

Overall, the NIH grants to AMCs between 1990 and 1995 linked to 106 distinct new drugs approved for marketing by 2010. Of the 106, about half (52) of the drugs were new molecular entities. About a third of the drugs (36%) received priority approval, indicating they are significant advances. And a quarter (24%) are priority NMEs.

We also calculated lags between the AMC grants and the first linked drug. On average this lag was 10.8 years (SD = 3.4) and the median lag is 11 years. Lags to any drug (not just the first) were similar, since very few of the AMC grants are linked to multiple approved drugs.

The retrospective analyses, which drugs approved between 2000 and 2009 link back to AMC grants, are summarized in *Figure 3*. Of the 211 NMEs approved over this period, 168 have patents listed on the Orange Book. The other drugs likely relied on non-patent exclusivities, e.g. the Orphan Drug Act.[20] We focused on these 168, since our empirical approach uses information in patents to assess the AMC role.

Of the 168 drugs, 66 were priority review NMEs and 102 standard NMEs. Overall nearly half (81) cited to at least one publication emanating from NIH-funded AMC research. This figure was slightly higher for priority review drugs than others (52% vs. 46%), though this difference was not statistically significant ($p = 0.49$).

Discussion

The prospective analyses show that 37% of AMC grants result in publications that are cited in biomedical patents. Most of the patents are drug and biotechnology patents, and are assigned to private firms. Patents citing AMC publications were associated with 106 new FDA approved drugs, half of which are new molecular entities and a quarter of which are priority NMEs. The prospective analyses also suggest the importance of patience in evaluating returns to AMC research: the average time to patent applications (for grants whose research is cited in a patent application) was 9 years, and (for those linked to drugs) average time to a new drug approval was about 11 years. The retrospective analyses showed that, consistent with results of previous research on NIH-funded research more generally,[6] about half of the new molecular entities approved over the 2000–2009 period had citation links to AMC research.

The results suggest that beyond their role in developing and licensing new molecules, AMCs also have an important indirect role in biomedical innovation. As one indicator of this, though previous research suggests about one-fifth of priority NMEs are based on licensed patents from public sector institutions[1,6] including AMCs and others, the retrospective analyses above suggest that over half cite back to NIH-funded AMC articles. Similarly, while 37% of the grants in the prospective analyses result in publications that are cited by patents, information reported to the NIH suggests that only 5% of the same set of grants directly generate patents.[21] Patenting is a minority activity at medical schools[8] and assessment of the effects of AMCs on innovation needs to account for the full range of channels through which their contributions are realized.

Though our approach facilitates a large-sample examination of the roles of AMCs in the biomedical innovation system, there are several limitations. Most important, even when we do see a citation to an AMC article, we cannot always conclude that the citing patent (or drug with which it is associated) would not exist but for the article. Patents cite publications for many reasons.[22] Appendix B discusses 15 cases where the cited publication was specifically discussed in a citing patent. Our review of these references suggests that these citations reflect different types of relationships between the AMC article and drug patent. In some cases, the cited article provided knowledge directly related to the therapy or its evaluation. In others, the article was about a specific target or class of compounds that guided R&D efforts. In some cases, the article provided general background on the disease or intervention.

Our review of these cases emphasized that assessing the counterfactual is hard: it is possible that the invention embodied in the citing patent would have occurred even absent the cited AMC article, though perhaps later, or at more cost. In almost all cases, the cited AMC articles are typically listed with many other references, suggesting they are part of a broader body of knowledge rather than “magic bullets” that enabled the citing innovation.[22] Finally, even though they are an improvement on patent–patent citations, patent–publication citations are sometimes inserted for legal reasons, as part of firm patent strategies, or discovered only during the patent examination process.[23] Much like citations in scientific articles, citations to publications in articles are noisy indicators of knowledge flows or intellectual influence.

Another set of limitations would underestimate the AMC role on private innovation. In assessing effects on products, we examined drugs with Orange Book listed patents, excluding other therapeutics (biologics, medical devices) without similar product–patent links. AMCs also produce knowledge (e.g., disease risks, epidemiological knowledge) that yields improvements in clinical practice and health behaviors that are not patented, and thus would not be captured in patent citations. We also do not examine references to AMC articles in pivotal trials, though in principle our methodology could be extended to incorporate this.

Our results suggest that a substantial share of AMC research has citation connections with private sector patents, and a substantial share of new drugs have citation links to AMCs. The results are consistent with previous qualitative accounts of AMCs playing an important role in innovation.[24] However, the various limitations to citation based measures discussed above also highlight the need for more research (including case studies) to better understand the types of links between AMC research and life science innovation, and their implications for public policy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix A. Identifying NIH Grants to AMCs.

Appendix B. Patent to Paper Citations.

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