Found in Translation:

Tracking & Tagging Translational Research

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# Structured Abstract

## Objective:

The NIH Roadmap includes an initiative to encourage the translation of basic science into clinical applications[[1]](#footnote-1). Billions of dollars are being spent on this effort to improve healthcare, and the question of how long it takes for NIH research to lead to new therapies needs to be answered. This project looks at identifying and tracking translational research papers at the NIH with the goal of eventually shortening the time it takes for science to move from bench to bedside.

## Methods:

A list of 6,800 term combinations (of 2 or 3 components, e.g. “potential therapeutic target”) was created using vocabulary from known translational articles and a thesaurus. These term combinations were used to search PubMed using E-Utilities, limited by date of publication (before 12/31/2008) and NIH affiliation. The term combination, PubMed ID (PMID), PubMed Central ID (PMC ID, if available), and year of publication were collected for each retrieved citation.

Citations from the full retrieved set were chosen at random, and after removing false positives and reviews, 25 basic science citations remained. These 25 citations were searched in Web of Science and Scopus, large citation and abstracts databases that also track where an article is cited. The articles that cite the 25 were coded by type (clinical trial, research, reviews, etc.) and broken up into 5-year “generations” to track if, how and when NIH basic research was translated into clinical applications.

Additionally, a Medical Subject Heading (MeSH) suggestion was submitted to the NLM’s MeSH Unit to determine the feasibility of establishing an indexing term to “tag” future translational research (TR).

## Results:

The chosen term combinations returned TR citations with only a few false positives identified. Of the 6,800 queries, 127 returned PMIDs for a total of 955 unique citations (136 are also in PMC). The data indicate that the number of TR article citations in both PubMed and PMC are steadily growing since the first retrieved citation published in 1988. Results include finding that the 25 sample articles have been cited 1546 times in the two databases and that the percentage of clinical applications stemming from those original articles is very small compared with other basic research.

In addition, the MeSH suggestion has resulted in the inclusion of the term “Translational Research” for 2010’s vocabulary (going live November 1, 2009), to be assigned to articles that describe the field of TR and/or its progress.

## Discussion and Conclusions:

The retrieved PubMed citations indicate that TR articles can be positively identified with the terms combinations developed. These identified citations show that the number of TR articles is steadily rising, possibly corresponding with the recent attention from NIH. The growth trend also underscores the importance of determining whether NIH research leads to clinical applications. Presently, the 1546 citations of the sample set show that NIH research is being translated into additional work of some type.

The citation analysis demonstrated that clinical applications are not occurring often from basic research; increasing translation is therefore an appropriate goal for NIH. Finally, the MeSH term will not routinely describe specific studies containing translatable research, but it will aid in the discovery of articles on the field, supporting its progress and leading to new solutions.

# Introduction

The National Institutes of Health are well known in the United States and around the world as a premier research center influencing and improving health care. Through work in basic science from biology to physics, new breakthroughs funded by NIH occur on a regular basis. However, moving these breakthroughs from the lab to the population is not an easy task. The NIH Roadmap includes an initiative to encourage the translation of basic science into clinical applications. Billions of dollars are being spent on this effort to improve healthcare, and the question of how long it takes for NIH research to lead to new therapies needs to be answered.

By specifically looking at NIH intramural research and how long it takes for this research to turn into clinical work, this project is a first step in identifying and tracking translational research papers with the goal of eventually shortening the time it takes for science to move from bench to bedside.

# Methods

Before work began on the project, some background reading was on work similar to this project’s:

1: Crowley WF Jr. Translation of basic research into useful treatments: how often does it occur? Am J Med. 2003 Apr 15;114(6):503-5. PubMed PMID: 12727585.

2: Contopoulos-Ioannidis DG, Ntzani E, Ioannidis JP. Translation of highly promising basic science research into clinical applications. Am J Med. 2003 Apr 15;114(6):477-84. PubMed PMID: 12731504.

In addition, an on-campus research workshop was attended related to translational research in order to get a feel for current issues: the National Center for Research Resources – Decision Making in T1 Translational Research Workshop, held February 10-11, 2009.

Data collection for the project was broken into two main parts: identifying articles of “translatable research,” and a citation analysis of a random set of articles from the whole “translatable research” set. In order to identify translatable research, a list of 6,800 term combinations (of 2 or 3 components, e.g. “potential therapeutic target”) was created using vocabulary from known translational articles and a thesaurus. This set includes 4860 combinations developed through the prior work of Kevin Cravedi, Fang Liu, and project leader Paul Fontelo. These term combinations were used to search PubMed using E-Utilities, limited by date of publication (before 12/31/2008) and NIH affiliation.

(“#TERMCOMBO#”) AND (NIH[Affiliation] OR National Institutes of Health[Affiliation]) AND ("1900/1/1"[PDAT] : "2008/12/31"[PDAT])

**Sample PubMed Search**

The term combination, the count of articles for each term combination, the PubMed ID (PMID), the year of publication, and, if available, the PubMed Central ID (PMC ID) were collected for each retrieved citation in an Excel spreadsheet (Figure 1).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Term1** | **Term2** | **Term3** | **count** | **PMID** | **Year** | **PMC ID** |
| Potential | Application |  | 37 | 2496918 | 1989 |  |
| Potential | Use |  | 108 | 2221866 | 1990 | 171873 |
| Potential | Therapeutic | Target | 15 | 12629211 | 2003 | 152312 |
| Potential | Clinical | Treatment | 1 | 12633748 | 2003 |  |
| Potential | Clinical | Benefit | 2 | 11592835 | 2001 |  |
| Potential | Cure |  | 5 | 1985751 | 1991 |  |

Figure – example of data collection method

In order to carry out the citation analysis, forty-two citations from the full retrieved set of were chosen at random. Four false positives were subsequently removed. A decision was then made for the sake of time to look only at original research articles, and so 13 reviews were also removed from the set. At final count, 25 original research citations remained (Appendix I). During the month of April, these 25 citations were found in Web of Science and Scopus, large citation and abstract databases that also track how many times and where a given article is cited. The two databases were used to retrieve a broader set of related citations than would be possible with either database on its own. For each original citation, Scopus was searched using the citation’s PMID, Web of Science was searched using the article title and author, and the combined set was sent to EndnoteWeb and placed in a reference group the corresponded with the original citation’s author. The number of citations imported into EndnoteWeb was confirmed against the number of citations found in each database to ensure that nothing was lost in the transition. Then each group within EndnoteWeb was manually examined for duplicates. If an article was found in both Web of Science and Scopus, the Scopus entry was removed (the choice was made to remove the Scopus entry because Scopus did not work as well with EndnoteWeb and abstract information was often lost in those citations).

Once the 25 groups of articles citing the originals were finalized, each groups’ citations were printed out with all available information including the abstract. The abstracts were all individually read, coded by type and broken up into 5-year “generations” to track if, how and when NIH basic research was translated into clinical applications. If an article’s abstract was not in EndNoteWeb (for example, because it was lost in the transfer with Scopus), some time was spent finding the abstract by searching PubMed, Locator Plus (NLM’s online catalog) and/or going back into the appropriate database. If no abstract was found, the article was coded as “Miscellaneous.” Every article was assigned one of the following codes, based on its abstract:

| **Articles** | Abstract |
| --- | --- |
| **Systematic Reviews** | “According to the Cochrane Library, a systematic review identifies an intervention for a specific disease or other problem in health care, and determines whether or not this intervention works. To do this authors locate, appraise and synthesize evidence from as many relevant scientific studies as possible. They summarize conclusions about effectiveness, and provide a unique collation of the known evidence on a given topic, so that others can easily review the primary studies for any intervention.” –Becker, <http://becker.wustl.edu/impact/assessment/knowl/systematic.html> |
| **Meta-analysis** | “Works consisting of studies using a quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc. It is often an overview of clinical trials. It is usually called a meta-analysis by the author or sponsoring body and should be differentiated from reviews of literature.” – MeSH (Becker uses NLM def.), <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Meta-Analysis> |
| **Reviews** | – “A review is defined by [EMBASE](http://www.embase.com/) as a publication of a significant review of original research, usually with an extensive bibliography. Reviews serve as evidence of knowledge transfer in that they add to the body of knowledge about a given disease, disorder, or condition. Reviews can also be very helpful in determining whether a finding from a research study has resulted in clinical applications. Reviews are not the same as a meta-analysis or a systematic review.” – Becker, http://becker.wustl.edu/impact/assessment/knowl/reviews.html  “An article or book published after examination of published material on a subject. It may be comprehensive to various degrees and the time range of material scrutinized may be broad or narrow, but the reviews most often desired are reviews of the current literature. The textual material examined may be equally broad and can encompass, in medicine specifically, clinical material as well as experimental research or case reports. State-of-the-art reviews tend to address more current matters.” – MeSH, <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Review> |
| **Clinical trials** | “Work that is the report of a pre-planned clinical study of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects. While most clinical trials concern humans, this publication type may be used for clinical veterinary articles meeting the requisites for humans.” – MeSH, <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Clinical+Trial> |

| **Articles** | Abstract |
| --- | --- |
| **Research studies (new/ancillary)** | *Ancillary:* “There are instances where the knowledge gained as a result of a research study allows for additional research studies that expand on the research findings in related or ancillary areas.” – Becker, <http://becker.wustl.edu/impact/assessment/knowl/ancillary.html>  *New: “*Just as there are instances where knowledge gained from a research study results in future research studies that expand on the original research findings, there are studies that focus on previously unexplored areas that were identified as a result of the original research study.” Becker, <http://becker.wustl.edu/impact/assessment/knowl/new.html> |
| **In Vitro** | “Studies using excised tissues.” MeSH, <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=In+Vitro> (specific type of new/ancillary research?) |
| **Case reports** | “Clinical presentations that may be followed by evaluative studies that eventually lead to a diagnosis.” – MeSH, <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Case+Reports> |
| **Comparative studies** | “Comparison of outcomes, results, responses, etc for different techniques, therapeutic approaches or other inputs.” – MeSH, <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Comparative+Study> |
| **Misc.** | (comments, errata, retractions, no abstracts, historical, interviews, non-review lectures, news, foreign language, etc.) |
| **Treatment Outcome** | “Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety, practicability, etc., of these interventions in individual cases or series.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Treatment+Outcome> |
| **Epidemiologic Studies** | “Studies designed to examine associations, commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of analytic study are CASE-CONTROL STUDIES; COHORT STUDIES; and CROSS-SECTIONAL STUDIES.” – MeSH (seroepidemiologic studies were also included in this category)  <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Epidemiologic+Studies> |
| **Evaluation Studies** | “Works consisting of studies determining the effectiveness or utility of processes, personnel, and equipment.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Evaluation+Studies> |
| **Validation Studies** | “Works consisting of research using processes by which the reliability and relevance of a procedure for a specific purpose are established.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Validation+Studies> |
| **Patient Selection** | “Criteria and standards used for the determination of the appropriateness of the inclusion of patients with specific conditions in proposed treatment plans and the criteria used for the inclusion of subjects in various clinical trials and other research protocols.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Patient+Selection> |
| **Practice Guideline** | “Work consisting of a set of directions or principles to assist the health care practitioner with patient care decisions about appropriate diagnostic, therapeutic, or other clinical procedures for specific clinical circumstances. Practice guidelines may be developed by government agencies at any level, institutions, organizations such as professional societies or governing boards, or by the convening of expert panels. They can provide a foundation for assessing and evaluating the quality and effectiveness of health care in terms of measuring improved health, reduction of variation in services or procedures performed, and reduction of variation in outcomes of health care delivered.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=PRACTICE+GUIDELINE> |
| **Disease Outbreak** | “Sudden increase in the incidence of a disease. The concept includes epidemics and pandemics.” – MeSH  <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Disease+Outbreaks> |
| **Population Surveillance** | “Ongoing scrutiny of a population (general population, study population, target population, etc.), generally using methods distinguished by their practicability, uniformity, and frequently their rapidity, rather than by complete accuracy.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Population+Surveillance> |
| **Clinical Protocol** | “Precise and detailed plans for the study of a medical or biomedical problem and/or plans for a regimen of therapy.” – MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Clinical+Protocols> |
| **Twin Study** | “Work consisting of reporting using a method of detecting genetic causes in human traits and genetic factors in behavior using sets of twins.” –MeSH <http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term=Twin+Study> |

These codes were chosen after exploring the Becker Medical Library’s website “Assessing the Impact of Research.”[[2]](#footnote-2) The impact indicators from the Becker site provided a good starting point for considering the types of items to code for, but they did not have all the specificity desired for this project. Codes for articles related to the translation from bench to beside (specifically, clinical trials) were needed, and the decision was made to also look at appropriate MeSH terminology. As a standardized and accepted vocabulary, MeSH provides a solid foundation of well-defined codes in the correct subject area. In addition, as a number of articles were in journals indexed in PubMed, they had already been assigned MeSH terms that could be used for cross-referencing. However, although occasionally PubMed was used to determine the code for an ambiguous article (which also occasionally led to the addition of a new code, such as “clinical protocol”), the MeSH terms already assigned to these articles were not automatically used as the codes for this project as different indexers assign the terms to different articles. By having one person go through the entire set, applying the codes by the definitions listed above (and taking both the MeSH and the Becker into consideration), the hope was that the collected data would be more consistent.

In addition to the data collection, a desired outcome for this project was to develop a way to identify translational research on a regular basis. The method for this component of the project was to submit a MeSH suggestion to the NLM’s MeSH Unit through their online form[[3]](#footnote-3) and to follow up as the term went through the consideration process. In essence, this method was used to determine the feasibility of establishing an indexing term to “tag” future translational research.

# Results

Of the 6,800 queries, 127 returned PMIDs for a total of 955 unique citations (136 of which are also in PMC). When the number of PubMed and PMC IDs are graphed over time by publication year, they demonstrate that the number of TR article citations in both PubMed and PMC have been steadily growing since the first retrieved citation published in 1988 (Figure 2).

Figure

Looking at the abstracts of the entire randomly chosen set of 42, it was determined that the chosen term combinations returned the translatable research citations desired with only a few false positives identified. These false positives were hits on the term combinations that had no explicit or implied clinical relevance, e.g. a numerical algorithm related to biologic molecule sedimentation or short comments on someone else’s work.

The 25 sample articles used in the second part of the project were found to have been cited 1546 times in the two databases. The individual counts of each code for each article abstract are included in Appendix II. Due to low counts for several of the codes used, two combination groups were created to get a more general picture of the results: “Clinical” (containing the counts for systematic reviews, practice guidelines, clinical protocols, patient selection, and treatment outcome) and “Other” (somewhat more related to the general research group and consisting of evaluation studies, validation studies, in vitro, disease outbreaks, population surveillance, twin studies, and meta analysis). The results for the sample set as seen in 0-4 years, 5-9 years, and 10+ years after publication can be seen in the graphs that follow:

In addition, the number of times the first author of the original citation was found as an author (not necessarily first) in the citing articles was tallied:

The final result of this project was that the MeSH suggestion has resulted in the inclusion of the term “Translational Research” in the 2010 vocabulary (going live November 1, 2009). It will be assigned to articles that describe the field of TR and/or its progress (see Appendix III for the MeSH Active Descriptor Record).

# Discussion

Underlying these results are several assumptions that should be addressed. Although attempts were made at all times during this project to be as objective as possible, in the end the decisions regarding what words identify translatable research, which articles are translational research, and which abstracts should be assigned a clinically-relevant code or not may all be seen differently by different people. To try to balance this, a broad definition of translational research was used at all times in order to reduce exclusion and consistency was an emphasis throughout the work. In addition, there were challenges with coding the sample set. First of all, the sheer number of citations made it fairly easy to forget to assign a code when going through the long lists. Although the numbers were all cross checked and were correct in the end, this made the project much longer, perhaps making it more difficult to always maintain consistency as the weeks turned into months. The coding was also done by a non-scientist with no medical training, and it was often difficult to determine exactly which code should be assigned. This problem was alleviated by cross-checking with the MeSH terms assigned in PubMed when an abstract was found in MEDLINE, but this was not always possible. However, even with these caveats, the results of this project can be seen to yield interesting discussion.

First of all, it is evident that the amount of research that could be “potential therapy” is growing. This could indicate increased awareness of the goals of the NIH Roadmap or perhaps even a shift in the mentality from producing good, publishable basic science as an end goal to truly improving the world’s health. That may be a big jump, especially since 955 articles represents a tiny percentage of all the NIH-affiliated research published between 1988 and 2008 (a quick PubMed search yields 60,489 citations), but it may help convince some that this is a growing field that deserves some study. In fact, the growth chart was used as part of the justification for the creation of the MeSH term suggested for this project. The growth may also be notable within the context of the NIH Public Access Policy[[4]](#footnote-4). As the public now has access through PubMed Central (where there was also demonstrated growth in translational research) to NIH-funded research because of this mandatory deposit policy, there is now perhaps more pressure to undertake the type of science that will improve the health of the taxpayers who fund it. It may also be easier for clinical scientists and their translational teams to access older findings and uncover “lost” translatable research for new work.

Although the growth in translatable research is arguably a good thing, the results of the sample set coding indicate that there are certainly still barriers to making the leap from bench to bedside. Basically, there seems to be a general lack of clinical trials. The data set used for this work shows no large differences in the number of clinical trials between the 0-4, 5-9, and 10+ year sets; the real problem demonstrated in these results is simply increasing the number of clinical trials rather than decreasing the time it takes for them to appear. However, there is a major limitation in that more than half the randomly chosen set were published in 2002 or later (the result of the growth trend that shows a much higher percentage of the original 955 articles were published in these years and the reason why the 10+ n is much smaller), and it is possible these more recent articles will lead to more clinical trials farther out. So the goal of decreasing the amount of time between research and trial may still be valid. It is also impossible to tell from the methods used in this project whether looking at a chain of linked research (a simplified example: original research -> animal model -> clinical trial without the clinical trial citing the original research) would yield better results in terms of more clinical applications. However, it still possible to see that original research is not being directly translated into clinical trials. The picture is not much better if the case reports (which do show some growth farther out from original publication) and the clinical group are included. More basic research and reviews are the vast majority of work produced after any period of time from original publication. Although some (and potentially a large amount) of the related research may itself be translatable, this data supports the NIH emphasis on (and funding for) making translational research a priority.

These results also raised the question as to what the progression from original research to clinical trial to public health standard actually is. Animal models, in vivo studies, genome comparisons, and epidemiological studies are all part of the picture, but there is no exact order. The type of disease or condition considered appeared to have a large impact; looking at the number 23 citation of psychiatric work by Swedo on pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), there was a very large number of case controls and other epidemiological studies as opposed to number 4 Chen’s restraint of proinflammatory cytokine biosynthesis which yielded almost all additional basic research articles. The codes used for this study were general and served the intended purpose, but the sample set itself demonstrated that generalizing to create a big picture of the translation process may not work.

The third part of this project, suggesting a MeSH term, was ultimately successful to a certain level. The term created will not be used as an indicator of research that is translatable, but rather to describe articles on translational research as a field or the progress of such research within a given area of study. Although the original intention was to create a means for scientists to easily identify research to translate, this alternative is still extremely helpful. Articles in PubMed describing the translational progress on Parkinson’s Disease (or lack thereof) can now be indicated as such and will help push the field forward. It also legitimizes the idea of translational research as field in and of itself; the MeSH term “Translational Research” falls under “Biomedical Research” along with “Genetic Research.”

# Recommendations

The work done for this project is only the first step. It has demonstrated that NIH intramural research is generally not moving towards clinical applications as much (let alone as soon) as is desired. In order to take the next steps and continue to improve the process and ultimately improve health, several recommendations have been identified.

* Additional work done using citation analysis (including potentially re-examining the citations used for this project), planning for and completing statistical analyses will help create more concrete conclusions.
* Further study on translational trends within different fields of science and medicine, as indicated by the differences in the sample set results, should be undertaken to yield better models for different disciplines.
* This project focused on looking at original research. Thirteen review articles were also randomly chosen but were not analyzed for the sake of time. Doing a similar citation analysis of a review article sample set may lead to an interesting comparison.
* Look into the translation of extramural research (expanding beyond the NIH-affiliation to institutions publishing research using NIH funding). The findings of this report may not generalize to science done outside of NIH.
* Work is being done currently by project leader Paul Fontelo along with Fang Liu on a searchable database to collect translational articles identified by the 6400 term combinations. This project has shown that this database will be important, as the number of translational articles is growing but is still a very small number of the total articles available in PubMed. In addition, there will be no MeSH term to identify them within PubMed itself. However, the MeSH term will be able to identify articles within a specific field, and articles related to associated disease(s) could then be found using the tool that Paul and Fang are creating. Although work is also needed in actually identifying the barriers in translation, accessing relevant work is likely one of them, and the availability of a translational research database may be able to have an impact which could be shown in a project similar to this one in the appropriate time.

# Appendix I: Citation Set

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# Appendix II: Article Code Counts

# Appendix III: MeSH Active Descriptor Record

1. NIH roadmap for medical research [Internet]. Bethesda (MD): National Institutes of Health [reviewed 2009 Jul 16]. Translational Research; [reviewed 2009 May 6, cited 2009 Jul 16]; Available from: http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp [↑](#footnote-ref-1)
2. <http://becker.wustl.edu/impact/assessment/knowl/index.html> (accessed 8/18/2009) [↑](#footnote-ref-2)
3. <http://www.nlm.nih.gov/mesh/meshsugg.html> (accessed 8/18/2009) [↑](#footnote-ref-3)
4. http://publicaccess.nih.gov/ [↑](#footnote-ref-4)