

In cancer science, many "discoveries" don't hold up



By Sharon Begley
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(Reuters) - A former researcher at [Amgen Inc](#) has found that many basic studies on cancer -- a high proportion of them from university labs -- are unreliable, with grim consequences for producing new medicines in the future.

During a decade as head of global cancer research at Amgen, C. Glenn Begley identified 53 "landmark" publications -- papers in top journals, from reputable labs -- for his team to reproduce. Begley sought to double-check the findings before trying to build on them for drug development.

Result: 47 of the 53 could not be replicated. He described his findings in a commentary piece published on Wednesday in the journal *Nature*.

"It was shocking," said Begley, now senior vice president of privately held [biotechnology](#) company TetraLogic, which develops cancer drugs. "These are the studies the pharmaceutical industry relies on to identify new targets for drug development. But if you're going to place a \$1 million or \$2 million or \$5 million bet on an observation, you need to be sure it's true. As we tried to reproduce these papers we became convinced you can't take anything at face value."

The failure to win "the war on cancer" has been blamed on many factors, from the use of mouse models that are irrelevant to human cancers to risk-averse funding agencies. But recently a new culprit has emerged: too many basic scientific discoveries, done in animals or cells growing in lab dishes and meant to show the way to a new drug, are wrong.

Begley's experience echoes a report from scientists at Bayer AG last year. Neither group of researchers alleges fraud, nor would they identify the research they had tried to replicate.

But they and others fear the phenomenon is the product of a skewed system of incentives that has academics cutting corners to further their careers.

George Robertson of Dalhousie University in Nova Scotia previously worked at Merck on neurodegenerative diseases such as Parkinson's. While at Merck, he also found many academic studies that did not hold up.

"It drives people in industry crazy. Why are we seeing a collapse of the pharma and biotech industries? One possibility is that academia is not providing accurate findings," he said.

BELIEVE IT OR NOT

Over the last two decades, the most promising route to new cancer drugs has been one pioneered by the discoverers of Gleevec, the [Novartis](#) drug that targets a form of leukemia, and Herceptin, Genentech's breast-cancer drug. In each case, scientists discovered a genetic change that turned a normal cell into a malignant one. Those findings allowed them to develop a molecule that blocks the cancer-producing process.

This approach led to an explosion of claims of other potential "druggable" targets. Amgen tried to replicate the new papers before launching its own drug-discovery projects.

Scientists at Bayer did not have much more success. In a 2011 paper titled, "Believe it or not," they analyzed in-house projects that built on "exciting published data" from basic science studies. "Often, key data could not be reproduced," wrote Khusru Asadullah, vice president and head of target discovery at Bayer HealthCare in Berlin, and colleagues.

Of 47 cancer projects at Bayer during 2011, less than one-quarter could reproduce previously reported findings, despite the efforts of three or four scientists working full time for up to a year. Bayer dropped the projects.

Bayer and Amgen found that the prestige of a journal was no guarantee a paper would be solid. "The scientific community assumes that the claims in a preclinical study can be taken at face value," Begley and Lee Ellis of MD Anderson Cancer Center wrote in *Nature*. It assumes, too, that "the main message of the paper can be relied on ... Unfortunately, this is not always the case."

When the Amgen replication team of about 100 scientists could not confirm reported results, they contacted the authors. Those who cooperated discussed what might account for the inability of Amgen to confirm the results. Some let Amgen borrow antibodies and other materials used in the original study or even repeat experiments under the original authors' direction.

Some authors required the Amgen scientists sign a confidentiality agreement barring them from disclosing data at odds with the original findings. "The world will never know" which 47 studies -- many of them highly cited -- are apparently wrong, Begley said.

The most common response by the challenged scientists was: "you didn't do it right." Indeed, cancer biology is fiendishly complex, noted Phil Sharp, a cancer biologist and Nobel laureate at the Massachusetts Institute of Technology.

Even in the most rigorous studies, the results might be reproducible only in very specific conditions, Sharp explained: "A cancer cell might respond one way in one set of conditions and another way in different conditions. I think a lot of the variability can come from that."

THE BEST STORY

Other scientists worry that something less innocuous explains the lack of reproducibility.

Part way through his project to reproduce promising studies, Begley met for breakfast at a cancer conference with the lead scientist of one of the problematic studies.

"We went through the paper line by line, figure by figure," said Begley. "I explained that we re-did their experiment 50 times and never got their result. He said they'd done it six times and got this result once, but put it in the paper because it made the best story. It's very disillusioning."

Such selective publication is just one reason the scientific literature is peppered with incorrect results.

For one thing, basic science studies are rarely "blinded" the way clinical trials are. That is, researchers know which cell line or mouse got a treatment or had cancer. That can be a problem when data are subject to interpretation, as a researcher who is intellectually invested in a theory is more likely to interpret ambiguous evidence in its favor.

The problem goes beyond cancer.

On Tuesday, a committee of the National Academy of Sciences heard testimony that the number of scientific papers that had to be retracted increased more than tenfold over the last decade; the number of journal articles published rose only 44 percent.

Ferric Fang of the University of Washington, speaking to the panel, said he blamed a hypercompetitive academic environment that fosters poor science and even fraud, as too many researchers compete for diminishing funding.

"The surest ticket to getting a grant or job is getting published in a high-profile journal," said Fang. "This is an unhealthy belief that can lead a scientist to engage in sensationalism and sometimes even dishonest behavior."

The academic reward system discourages efforts to ensure a finding was not a fluke. Nor is there an incentive to verify someone else's discovery. As recently as the late 1990s, most potential cancer-drug targets were backed by 100 to 200 publications. Now each may have fewer than half a dozen.

"If you can write it up and get it published you're not even thinking of reproducibility," said Ken Kaitin, director of the Tufts Center for the Study of Drug Development. "You make an observation and move on. There is no incentive to find out it was wrong."

(Note: Amgen researcher C. Glenn Begley is not related to the author of this story, Sharon Begley)

(Reporting By Sharon Begley; Editing by Michele Gershberg and Maureen Bavdek)

Could 89% of Landmark Cancer Research Be Untruthful?

Posted on: Friday, April 12th 2013 at 5:00 am

Written By: Eleni Roumeliotou

The last years several different studies investigating the objectivity of scientific research have shown that this quality of science may be seriously compromised by industrial funding. In fact, it looks like the scientific literature is contaminated with a growing number of tainted studies, which may reach 89%, the results of which are not reproducible by any means. This means that to an extent, we have based our healthcare and clinical guidelines on fake studies that reported untruthful results in order to accommodate the interests of industrial corporations.

Cancer is a major killer in US. The American Cancer Society reports that in 2012, more than half a million Americans died from cancer, while more than 1.6 million new cases were diagnosed. Given the seriousness of these statistics and the necessity of evidence-based medicine, it would make sense to trust that honest, objective research is tirelessly trying to find the best cancer therapies out there. In March 2012, *Nature*, the famous high-impact factor scientific journal, published a shocking study. Glenn Begley and Lee Ellis double checked the results of 53 landmark studies in cancer research, but they were only able to reproduce the published results in 11% of them.

There are two very worrying points here. First of all, the cross-checked studies were published in high-impact factor journals and secondly, they have served as the basis for the "state of the art" cancer therapies that millions of people are receiving this very moment. Unfortunately, the authors were not able to disclose these fake studies, because when they contacted the original authors and asked for details of the experiments, they had to sign an agreement that they would not disclose their findings or sources. This shows that the scientists, who published the tainted research, were all along, fully aware of the discrepancies of their articles and criminally conscious of the fact that they were misleading the medical and public opinion.

The connection and support that many scientists enjoy from big pharmaceutical companies seems to be the core of this problem. Exposing such connections should be enough to either limit this situation or at least put the credibility of the study in question. However, most people involved in such interactions try to hide them as much as possible. While all authors are gently encouraged to sign the conflict of interest and funding statements prior to publication of their work, data show that only a small percentage of scientists publishing research on anticancer targeted therapies disclose potential sources of bias. A study from the University of Michigan has found that only 29% of cancer studies report conflict of interest.

This situation is certainly not limited to the area of cancer research. In fact, clinical guidelines may be severely biased as well. While very few authors of clinical practice guidelines declare conflict of interest, a big percentage of those who do, have financial relationships with the pharmaceutical industry that may range from consultancy, equity/stock ownership to old-fashioned research support. These reports

paint a disturbing picture indeed and suggest that there is good chance that the greatest part of the clinical healthcare and medical system has slowly been established on corrupted foundations.

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29 percent of cancer studies report conflict of interest

U-M researchers suggest increasing public funding of research to decrease potential bias from industry ties



Reshma Jagsi, M.D., D.Phil.

ANN ARBOR, Mich. - Nearly one-third of cancer research published in high-impact journals disclosed a conflict of interest, according to a new study from researchers at the University of Michigan Comprehensive Cancer Center.

The most frequent type of conflict was industry funding of the study, which was seen in 17 percent of papers. Twelve percent of papers had a study author who was an industry employee. Randomized trials with reported conflicts of interest were more likely to have positive findings.

"Given the frequency we observed for conflicts of interest and the fact that conflicts were associated with study outcomes, I would suggest that merely disclosing conflicts is probably not enough. It's becoming increasingly clear that we need to look more at how we can disentangle cancer research from industry ties," says study author Reshma Jagsi, M.D., D.Phil., assistant professor of radiation oncology at the U-M Medical School.

The researchers looked at 1,534 cancer research studies published in prominent journals. Results of this current study appear online in the journal [Cancer](#).

"A serious concern is individuals with conflicts of interest will either consciously or unconsciously be biased in their analyses. As researchers, we have an obligation to treat the data objectively and in an unbiased fashion. There may be some relationships that compromise a researcher's ability to do that," Jagsi says.

For example, she says, researchers might design industry-funded studies in a way that's more likely to produce favorable results. They might also be more likely to publish positive outcomes than negative outcomes.

"In light of these findings, we as a society may wish to rethink how we want our research efforts to be funded and directed. It has been very hard to secure research funding, especially in recent years, so it's been only natural for researchers to turn to industry. If we wish to minimize the potential for bias, we need to increase other sources of support. Medical research is ultimately a common endeavor that benefits all of society, so it seems only appropriate that we should be funding it through general revenues rather than expecting the market to provide," Jagsi says.

Methodology: The researchers looked at all original clinical cancer research published in five top oncology journals and three top general medical journals in 2006. The journals included were the [New England Journal of Medicine](#), the [Journal of the American Medical Association](#), [The Lancet](#), the [Journal of Clinical Oncology](#), the [Journal of the National Cancer Institute](#), [Lancet Oncology](#), [Clinical Cancer Research](#) and [Cancer](#).

Articles were analyzed to determine declared funding sources and conflicts of interest. A conflict of interest was identified if it was explicitly declared by the authors, if an author was an employee of industry at the time of publication, or if the study had industry funding.

Additional authors: Nathan Sheets; Aleksandra Jankovic, M.S.; Amy R. Motomura; Sudha Amarnath; and Peter A. Ubel, M.D.

Reference: [Cancer](#), DOI: 10.1002/cncr.24315; published online May 11, 2009; scheduled for print publication June 15, 2009

Resources:

U-M Cancer AnswerLine, 800-865-1125

Conflict of interest disclosure in off-label oncology clinical trials.

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Source

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Abstract

PURPOSE:

We sought to determine the prevalence, reliability, and predictors of conflict of interest (COI) and funding disclosure statements for studies of anticancer targeted therapies conducted in the off-label prescribing setting.

METHODS:

As a part of a federally funded systematic review, manuscripts were included in the analysis if they were used to support one of 19 indications for cancer targeted therapies that were off-label but reimbursable according to compendia published in 2006 or before. Studies were categorized according to trial design, trial results, average impact factor of journals, and presence of COI and funding disclosure statements.

RESULTS:

Among the 69 included studies, prevalence of COI and funding disclosures was low, at 33% and 58% respectively; time trends showed some improvement between 2002 to 2007, but only 60% of studies had disclosures by 2007. Predictors of COI disclosure were publication in high-impact-factor journals ($P < .001$), large study sample size ($P = .001$), enrollment exclusively in the United States ($P = .04$), and study of the targeted therapy in combination with other agents as opposed to the study drug alone ($P = .03$).

CONCLUSION:

Disclosure of potential sources of bias in COI and funding statements in studies of off-label indications for anticancer targeted therapies was low and did not increase substantially over time.