

Drug Discovery over the Past Thirty Years: Why Aren't There More New Drugs?

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The rate of drug discovery has not kept pace with the exponential increase in biomedical knowledge. For the past 30 years, the number of new molecular entities approved by the United States Food and Drug Administration has averaged 20 to 30 drugs per year, except for a peak in the mid-1990s that briefly doubled this rate. This modest productivity cannot be explained by lack of funding, as the research budgets of government- and industry-funded programs have increased threefold to fivefold over the past three decades. Various arguments have been proposed to account for the relative lack of innovative new drugs, but little consideration has been given to the focus on hypothesis-driven trans-

lational research. In theory, the emphasis on translational research should have led to an increase in the number of new drugs. However, in considering the historical perspective of drug discovery and the role of serendipity, it can be argued that the emphasis on translational research diverts scientists from pursuing basic-science studies that give rise to fundamental discoveries. In many cases, retro-translational research (from clinic to basic science) is necessary before the disease process can be understood well enough for scientists to develop therapeutics. Ultimately, a balance of disease-oriented and basic-science research on fundamental processes is optimal.

The pace of drug discovery paralleled the pace of science in general for most of the 1900s. As more was learned about the basic principles of biology and the molecular basis of disease, it became easier to develop rational medicines to treat diseases. At least in theory. In practice, most drug discoveries were based on random chance, or to use a nicer-sounding word, serendipity. A classic example is that of penicillin—a paradigm-shifting drug discovered by a chance observation of lysed bacteria on a culture dish by Alexander Fleming (although technically the discovery of penicillin was made decades earlier by Ernest Duchesne, a medical student who never published his discovery except in his thesis). There are many other examples of drugs discovered by chance, and these far outnumber the drugs that were developed by rational design.

The general strategy for rationally designing a drug involves identifying a target and developing a molecule that binds to the target and affects its properties in the desired way. Then the molecule is optimized for drug like properties (nontoxic; good absorption and distribution). A classic example is that of angiotensin converting enzyme (ACE) inhibitors, rationally designed to block ACE activity and reduce hypertension. There are other examples of drugs that were rationally designed, but in most cases the story had a bit of a twist. For example, sildenafil was rationally developed as an inhibitor of cGMP-specific phosphodiesterase-5, with the idea that it would be useful for treating hypertension and angina pectoris. During clinical trials men given the drug reported a pleasurable side effect, and Pfizer ended up marketing the drug for erectile dysfunction rather than for the originally intended application.

Another classic example of rational drug design is sumatrip-

tan, an antimigraine drug approved by the Food and Drug Administration (FDA) in 1991. This drug was developed as an agonist of serotonin 5HT-1b and 1d receptors; activation of these receptors was known to lead to vasoconstriction, which was thought to be beneficial for treating migraine headaches. The drug worked well in clinical trials and has been a major advance in the treatment of migraines. But while the mechanism of the drug is still thought to involve serotonin receptors, the original idea has been questioned. The current hypothesis is that sumatriptan and related drugs prevent the secretion of inflammatory peptides such as calcitonin gene-related peptide. Therefore, the original concept that led to the drug's development may have been wrong, but useful drugs were ultimately developed.

FUNDING FOR BIOMEDICAL RESEARCH AND DRUG DISCOVERY

During the 1970s and early 1980s, there were only modest increases each year in the amount of money spent by drug companies for research and development (Figure 1). Similarly, when adjusted for inflation the total budget of the National Institutes of Health (NIH) showed small yearly increases or decreases during this period. Since 1982, both the NIH budget and pharmaceutical company research expenditures rapidly rose from \$8 billion to between \$30 billion and \$50 billion (all numbers are inflation-adjusted to 2012); this represents a three- to fivefold increase. If drug development were proceeding on par with scientific discoveries, we would be adding significantly more and more drugs each year. But except for a surge of new drugs in the mid-1990s, the average rate of FDA approval of new molecular entities is only 20 to 30 per year (Figure 1). Counting only new molecular entities means each drug is counted only once, when it is approved for the first time; this excludes older drugs that were reformulated, which

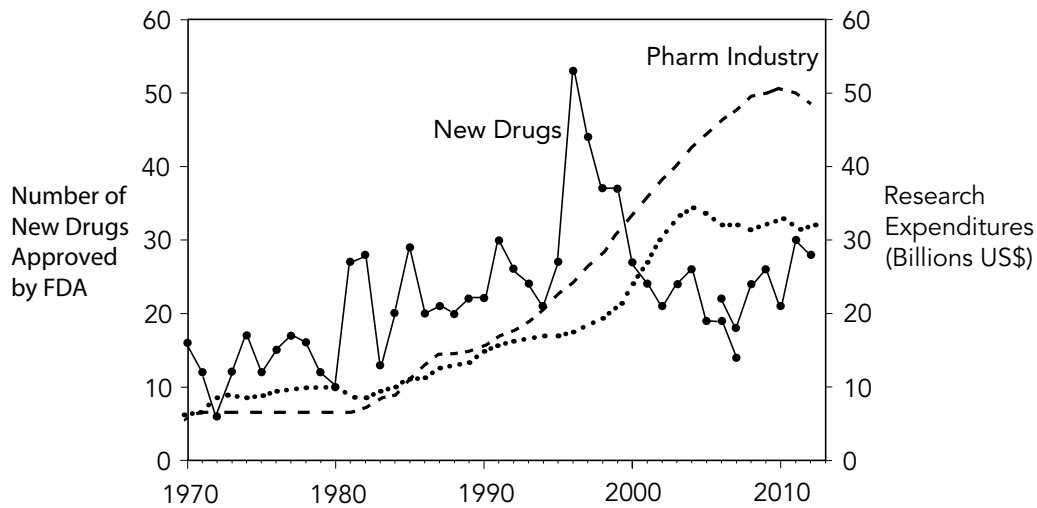


Figure 1 | Drug development and research expenditures from 1970 to 2012. Circles and left axis show the number of new molecular entities approved by the FDA each year; these include compounds from new drug applications as well as biologicals from biologics license applications to the FDA. The 1970–2007 data are from *Goodman and Gilman's The Pharmacological Basis of Therapeutics* and the 2006–2012 data are from the FDA website (www.fda.gov); the two sources give slightly different numbers for the two years of overlap. Squares and right axis show research and development costs of the U.S.-based pharmaceutical industry; the 1970–2007 data are from *Goodman and Gilman's The Pharmacological Basis of Therapeutics* and the 2007–2012 data are from the Pharmaceutical Research and Manufacturers of America website (www.phrma.org). Diamonds and right axis show the total NIH budget, of which the majority represents the extramural and intramural research programs. Increased money for the NIH from the American Recovery & Reinvestment Act of 2009 is not included. Both pharmaceutical industry expenditures and the NIH budget are in billions of U.S. dollars and are adjusted for inflation to 2012 using the U.S. Bureau of Labor Statistics consumer price index adjustment website (<http://www.bls.gov/cpi/>).

requires FDA approval, as well as older drugs for which new uses were discovered and approved.

From 1970 through 1996 (Figure 1), the rate of new-drug discovery generally parallels the amount of research money, even though there is a time lag between basic research and the approval of a drug by the FDA. Extrapolating from the plot of drug approvals per year from this time period, one would have predicted that in 2012 there would be 50 to 100 new drugs approved. However, the period from 1996 through 2006 shows the opposite trend: a falling rate of drug approval while research expenditures dramatically rise. Extrapolating from this time period, one would predict that fewer than five new drugs would have been approved in 2012. When the number of new drugs approved over the past five years is included in the analysis, it appears that there has been a steady state of 20 to 30 drug approvals per year for the past 30 years, except for a brief increase in the mid-1990s. Clearly, the number of new drug approvals hasn't risen to more than 50 or shrunk to fewer than five. But shouldn't there be many more new drugs when one considers the three- to fivefold increase in research funding?

IS THE PROBLEM WITH THE APPROVAL PROCESS?

One possibility to consider is that the problem has been the approval process, not the actual development of drugs. It is conceivable that many new drugs were developed in recent years but didn't make it through the FDA approval process.

A related possibility is that the drug companies were more rigorous in their screening, and prevented unsafe drugs from being put into the pipeline and marketed. However, both of these possibilities are unlikely to account for the lack of correlation between drug approval and research expenditures. The ratio of drugs approved by the FDA to all submissions for new drug applications has remained relatively constant. The FDA has blocked the approval of some drugs. For example, rimonabant is a CB1 cannabinoid receptor antagonist that produces modest weight loss. The drug was approved in 2006 in Europe but not approved by the FDA because of safety concerns. Rimonabant was withdrawn from the European market in 2009 due to adverse events. Before it was withdrawn, some people argued that the FDA was too restrictive, preventing a useful drug from being marketed. After the side effects emerged, the FDA was lauded for protecting the population. Some people claim that the FDA is erring on the side of approving too many drugs, in part because of a 1992 law that charges drug companies money to offset the cost of the approval process. The purpose of this law, the Prescription Drug User Fee Act, was to shorten the time it takes for the FDA to evaluate drugs and reduce its large backlog by allowing the hiring of more personnel. This law may have contributed to the increase in approved drugs in the mid-1990s, although it has been argued that this was not a contributing factor (Graham, 2005). Regardless of what caused the spike in approvals in the mid-1990s, the fraction of requests approved by the FDA has not changed dramatically over

the past few decades, suggesting that other factors are the major contributors to the limited number of new drugs.

The other related possibility—that drug companies are doing a better job of avoiding potentially unsafe drugs—may be partially correct, as there are improved methods of predicting toxicities of drugs and their metabolites. However, it is unlikely that this is a major contributor to the dearth of new drugs, for two reasons. First, the number of drugs withdrawn from the market due to toxicities is rather small; only 3% of the drugs approved over the period from 1975 to 2000 were later withdrawn (Lasser et al., 2002). A larger fraction (8%) of the drugs approved during this period required new black-box warnings after marketing, indicating additional toxicities that were not known at the time of approval, but these drugs have remained on the market. Although higher than one would hope, the 3% rate for drug withdrawal is so small that if companies had somehow figured out how to avoid marketing such drugs, the number of new drugs would decrease by only one drug per year (at the current rate of approximately 30 new drugs per year). Second, companies do not seem to have figured out how to avoid marketing toxic drugs. In the past decade, a number of approved drugs have been withdrawn from the market—rofecoxib (Vioxx), tegaserod (Zelnorm), and sibutramine (Meridia), just to name a few. It would be hard to argue that drug companies are holding back drugs because of toxicities; they seem to withdraw drugs only when faced with overwhelming evidence of adverse reactions.

DRUGS NOT DEVELOPED

Because the drug-approval process does not appear to be the major reason for the small number of new drugs relative to the amount of money spent, it appears that fewer drugs were developed per dollar spent (even when adjusted for inflation). This may be for one of two reasons: money was spent on the right things, but it takes more money now to develop drugs, or money was not spent on the right things. The popular answer among scientists I have consulted is the first: that research in general is much more expensive than it was in the past, even when costs are adjusted for inflation. While this may be true for clinical research, the cost of most basic research is higher only because we can accomplish so much more with current techniques. For example, DNA sequencing used to be done manually in the early 1980s, and a single person working full time could sequence several kilobases in a year. With the current generation of DNA-sequencing instruments, a single person can accomplish this much in a fraction of a second. In the past decade the cost of sequencing a million bases of DNA has dropped from thousands of dollars to under 10 cents (<http://www.genome.gov/sequencingcosts/>). And it's not just DNA sequencing that has gotten cheaper; advances in many other techniques have also lowered the cost of science by allowing much more to be accomplished in the same amount of time. When looking at the cost per experiment, yes—the costs have gone up for most things. But when considering the cost relative to the amount and

quality of data, there has definitely been a cost reduction in nearly all fields of basic research. Large amounts of information are available for free on the Internet, further reducing the overall cost of science.

Another explanation for the high cost of drug discovery is that many of the easy problems have been solved, and the remaining problems are more complex: neurodegeneration, dementia, and obesity, to name a few. But many of the disorders that are often treatable with drugs are also complex: schizophrenia, depression, and epilepsy, for example. How were drugs for treating these disorders found? The short answer is serendipity. The first drug for treating schizophrenia (chlorpromazine) was developed as an antihistamine, and, like many first-generation drugs in this class, was highly sedating. For this reason, it was tested as a sedative to calm highly agitated schizophrenics, and it worked. But what was significant was that, after several weeks of treatment, the underlying symptoms resolved in some of the patients—the voices in their heads were quieted. This drug was clearly doing something that other antihistamines were not, and further research uncovered the dopamine D2 receptor-blocking properties of chlorpromazine, leading to a number of additional antischizophrenic drugs. The discovery of the first antidepressant also involved a large amount of luck. The drug iproniazid was being tested in patients with tuberculosis; it was being compared to the related molecule isoniazid, which had been developed earlier for this disease. The derivative drug also worked for tuberculosis, but in addition seemed to lift the mood of the patients more than what would be expected if the tuberculosis were cured. (Because this disease was often deadly, the curing of the tuberculosis was equivalent to being pardoned from death row, which would certainly improve one's mood.) Because iproniazid was even more effective than isoniazid at making patients happy, the properties of the two drugs were studied, and iproniazid was found to inhibit monoamine oxidase (MAO). This led to many additional MAO inhibitors, some of which are still used today (although they are not frontline therapy).

TRANSLATIONAL VERSUS BASIC RESEARCH

The final possibility to consider is that the relative dearth of new drugs is due to money being spent on the wrong things. But more money than ever has been going into translational research—shouldn't this be leading to more drugs? How could this be the problem?

The term "translational research" was virtually nonexistent prior to the early 1970s (except to refer to the translation of RNA into protein); it has now become commonplace in the literature and funded NIH grants (Figure 2). Although the NIH doesn't break out the dollar amounts for applied and translational research versus basic research, it has been estimated that 41% of the NIH budget was for applied research in 2007, and this increased to 46% in 2010 (<http://www.biocentury.com/promotions/budgetfight/us-budgetfight-over-basic-translational-research-spending-by-nih-a1>).

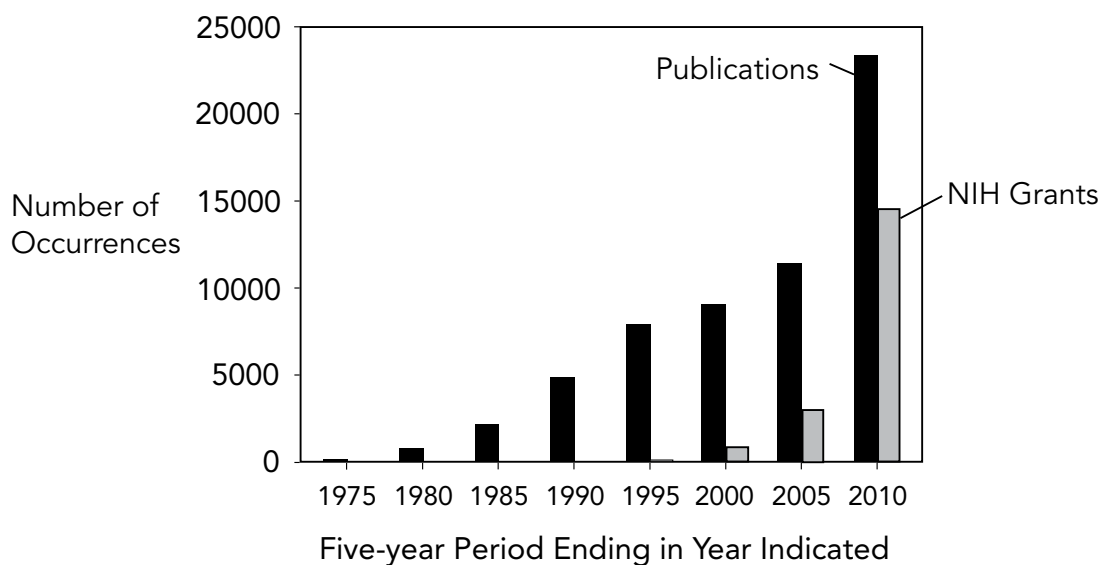


Figure 2 | Appearance of the term “translational research” in publications and research grants from 1971 to 2010. Searches for the term (in quotes) were performed in PubMed (<http://www.ncbi.nlm.nih.gov>) and the NIH Reporter (<http://projectreporter.nih.gov/reporter.cfm>) over the indicated five-year period.

htm). In addition to the large amount of money spent on translational research through existing funding channels, in 2012 the NIH launched a new \$575 million National Center for Advancing Translational Sciences.

Given the long history of serendipity in drug discovery, it is somewhat surprising that the current approach to drug development largely ignores it, focusing instead on rational drug design and translational research. It is possible that the intense focus on these areas is exactly the reason for the relative lack of new drugs. Translational research is a one-way street to the clinic. But if one doesn't have a good sense of the basic science, it is impossible to know what is best to translate. An excellent example of this is the discovery that penicillin mold had antibiotic properties, which was made by Ernest Duchesne in 1896. Even though Duchesne had found that penicillin extracts could save the lives of animals infected with toxic amounts of bacteria, it was not considered appropriate for treating humans because the hypothesized mechanism was incorrect—the mold was thought to outcompete the bacteria in a struggle for resources, rather than to secrete an antibiotic substance that could be useful as a drug. When Alexander Fleming rediscovered penicillin several decades later, in 1928, he also misidentified the mechanism and thought it functioned like lysozyme, a bactericidal enzyme he had discovered in 1923. Enzymes do not make good drugs, and partly for this reason (along with the difficulty of mass-producing the penicillin extract), it took more than a decade before the extract was tested in animals and found to be effective.

Fortunately, the role of serendipity in the drug-discovery process has been recognized; the NIH and several major pharmaceutical companies have a pilot project to allow

scientists in academia to test potential drugs for additional uses (“NIH Unveils Plan,” 2012). For the most part, the drugs made available through this program are compounds that were being developed for one purpose, did well in animal studies and phase I human clinical trials, but didn't work so well in the efficacy trials in phase II or III testing. As a result, these haven't been approved by the FDA for marketing, and the companies are eager to find a use (especially one with a lucrative market) for them.

BASIC SCIENCE AND RETRO-TRANSLATIONAL RESEARCH

While the program aimed at finding new uses for compounds already developed is likely to yield some new drugs, there is still a need for more basic research. In times of flat NIH budgets, increased funding for translational research means that there is less funding for basic research. But without a better understanding of the fundamental biology that underlies them, it is not possible to understand disease processes. Little is known about the function of a large fraction of the 20,000 or so human genes, and even well-studied genes and their gene products are far from being understood. For example, tubulin has been known for decades, and a search of PubMed pulls up over 22,000 articles on tubulin. A large number of post-translational modifications of tubulin are known to occur, but the precise molecular forms of tubulin and the functions of each form are not known. Thus, even well-studied genes and gene products are not fully understood, and basic science in these areas may reveal novel targets for drugs. But drug development should not be the main objective of pure basic science aimed at understanding the role of each gene or gene product. Simply learning more about a biological process should be sufficient reason to study something; this

was the common sentiment in the 1970s and 1980s, before the subsequent focus on translational research.

Another area that is likely to enhance drug development is retro-translational research—from clinic (or animal model) toward basic science—to better understand the underlying biology so that the best treatment can be designed. Although the term “retro-translational research” is relatively new, the concept is old. This was the approach used to figure out how chlorpromazine, iproniazid, and many other drugs produced their unexpected results, an approach that ultimately led to breakthroughs in the treatment of schizophrenia, depression, and other disorders. If Duchesne had taken this approach with penicillin, he likely would have realized its amazing potential and been able to interest companies in developing this lifesaving drug decades before Howard Florey, Ernst Chain, and others developed Fleming’s penicillin in the 1930s. Collectively, translational and retro-translational research can be considered disease-oriented research, allowing a two-way street, from basic science to the clinic and back, to be traveled several times before the system is exploited and a drug is developed (if such a drug is possible; not all research is bound to lead to drug development).

CONCLUSION

At some point, the majority of new drugs may be rationally designed based on knowledge of disease processes, underlying biology and biochemistry, and translational research. Up to now, serendipity and retro-translational research have played a much larger role than rational design. The relatively constant number of new drugs approved each year over the past 30 years, despite the great increase in funding, may be due to the emphasis on translational and applied science rather than on basic research.

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Conflict of Interest Disclosure

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No conflicts were noted.

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