Drug Design and Discovery: Translational Biomedical Science Varies Among Countries

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Abstract

Drug design and discovery is an innovation process that translates the outcomes of fundamental biomedical research into therapeutics that are ultimately made available to people with medical disorders in many countries throughout the world. To identify which nations succeed, exceed, or fail at the drug design/discovery endeavor—more specifically, which countries, within the context of their national size and wealth, are "pulling their weight" when it comes to developing medications targeting the myriad of diseases that afflict humankind—we compiled and analyzed a comprehensive survey of all new drugs (small molecular entities and biologics) approved annually throughout the world over the 20-year period from 1991 to 2010. Based upon this analysis, we have devised prediction algorithms to ascertain which countries are successful (or not) in contributing to the worldwide need for effective new therapeutics. Clin Trans Sci 2013; Volume 6: 409–413

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Introduction

As the Global Burden of Disease Study for the time-period 1990–2010 has recently shown, healthy life expectancy differs substantially among countries, with marked regional variation for many diseases including diabetes, cirrhosis, hepatic cancer, melanoma, trypanosomiasis, and multiple other disorders.[1,2] Since human sickness and wellness exhibit marked inter-regional variability, is there also inter-regional variability with regards to translational science efforts focussed on devising therapeutic cures via drug design and discovery? Drug design and discovery is the innovation process that translates the outcomes of fundamental biomedical research into therapeutics that are ultimately made available to people with medical disorders in many countries throughout the world. It may be instructive to identify which nations succeed, exceed, or fail at the drug design/discovery endeavor; more specifically, which countries, within the context of their national size and wealth, are "pulling their weight" when it comes to developing medications targeting the myriad of diseases that afflict humankind?[3] To address this question, we have compiled and analyzed a comprehensive survey of all new drugs (small molecular entities and biologics) approved annually throughout the world over the 20-year period from 1991 to 2010.[4] Based upon this analysis, we have devised prediction algorithms to ascertain which countries are successful (or not) in contributing to the worldwide need for effective new therapeutics.

Worldwide Drug Discoveries: 1991–2010

Tabulating data from the *Annual Reports in Medicinal Chemistry* from 1991 to 2010 provides the total number of drugs originated in every country worldwide (*Table 1*).[4] The results are separated into two decades (1991–2000, 2001–2010) so that chronological changes in a country's contributions can be quantified.[5] Although one nation is typically credited with each drug discovery, such assignments may not be completely accurate; for instance, researchers may move from country to country for reasons of academic/industrial position, or some drugs may be acquired during their development process by companies located in a different country. Consequently, we have endeavored to count the country in which the scientific discovery was first reported, as arguably this may be a better indication of national capacity for drug innovation.

Drug Discovering Countries Compared by Economic Comparators

There is no flawless algorithm with which to assess a country's success as a drug innovator, but using a few relevant comparators can provide initial insights. A commonly employed method is to correlate a country's Gross Domestic Product (GDP; the market value of all officially recognized final goods and services produced within a country in a given period) with the statistic of interest. Considering that several studies have assessed the average cost of developing a new drug and bringing it to market at an estimated US $1.3–1.8 billion[5,6] (although others have disputed this value),[7,8] GDP should be a good initial descriptor; obviously, only wealthy nations can invest heavily in the advanced stages of drug research.

Tabulating data from the World Bank Group (WBG) and the International Monetary Fund (IMF),[9,10] a correlation between the GDP of a country and the number of drugs discovered within that country is noted (*Table 2*). For both decades, five of the six top countries in the world in terms of drug discovery were also in the top six in terms of GDP. Nevertheless, there are some obvious problems with only using GDP as a comparator. There are multiple countries, such as China, Brazil, and Mexico, which have relatively high GDPs,[9,10] but which have no significant drug discoveries to their credit. The reason that these countries have high GDPs is because they are so populous, but they do not necessarily have as high a GDP per capita as the countries that do discover drugs. It may then be considered that GDP per capita is a better measurement, but this also has associated problems. Countries such as Liechtenstein, Luxembourg and Monaco all have a high GDP per capita,[9,10] but they have too few people to support a viable drug discovery industry.

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Country	1991–2000 Drug discoveries	Rank	2001–2010 Drug discoveries	Rank	1991–2010 Total	Rank
Australia	1	19	0	-	1	20
Austria	2	15	0	-	2	17
Belgium	1	19	0.5	15	1.5	19
Canada	3	13	3	8	6	11
Cuba	0	-	1	12	1	20
Czech Republic	0	-	0.5	15	0.5	23
Denmark	6	9	2	11	8	10
Finland	3	13	0	-	3	15
France	15	6	8	6	23	6
Germany	32	4	12	5	44	4
India	4	12	0	-	4	14
Israel	2	15	1	12	3	15
Italy	13	7	1	12	14	7
Japan	93	2	45	2	138	2
Kazakhstan	1	19	0	-	1	20
Netherlands	6	9	3	8	9	9
Norway	2	15	0	-	2	17
South Korea	2	15	3	8	5	12
Spain	7	8	5	7	12	8
Sweden	4.5	11	0	-	4.5	13
Switzerland	23	5	13	4	36	5
United Kingdom	38.5	3	16	3	54.5	3
United States	108	1	137	1	245	1
Total number of countries		**21**		**16**		**23**
Total number of drugs	**367**		**251**		**618**	

Table 1. Drug discoveries by country and decade (1991–2010).

To incorporate these diverse variables, we combined the aforementioned considerations to ultimately identify GDP²/Population as a useful quantitation descriptor. Again using data from the WBG and IMF (*Table 2*),[9,10] a strong relationship is demonstrated between GDP²/Population and the number of drugs that a country discovered. These data demonstrate that from 1991 to 2000 the top 18 countries in the world in terms of GDP²/Population all discovered drugs (in total, only 21 countries invented new drugs during this time frame); these 18 countries accounted for over 98% of the new drugs produced. Furthermore, no country in the top five in terms of GDP²/Population had a rank worse than sixth in terms of drug discovery. The exact same statistic is true for 2001–2010. Also from 2001 to 2010, 13 of the top 16 countries in terms of GDP²/Population discovered a new drug (only 16 countries discovered new drugs during this time frame) accounting for over 99% of the new drugs produced.

Drug Discovering Nations: A Quantitative Algorithm

To quantitatively determine the number of drugs that any given nation should discover as a function of its size and wealth, we performed a regression analysis on data for 187 countries from 1991 to 2000, yielding the following relationship between GDP²/Population and drug discovery within a given country:

$$\text{New Drugs Discovered} = 0.542(\text{GDP}^2/\text{ Population}) + 0.162 \qquad R^2 = 0.95 \tag{E.1}$$

Similarly, linear regression analysis on data from 2001 to 2010 yields the following relationship:

$$\text{New Drugs Discovered} = 0.246(\text{GDP}^2/\text{ Population}) - 0.469 \qquad R^2 = 0.97 \tag{E.2}$$

Using equations E.1 and E.2 with Canadian data (from *Table 2*) provides a predicted value of seven new drugs for 1991–2000 and a predicted value of nine new drugs for 2001–2010.

From 1991 to 2010, six new drugs actually originated from Canada, whereas 16 were predicted to have been discovered—a "predicted drug ratio" of 6/16 [PDR = 0.38], and a "drug discovery deficit" of 10 drugs over 20 years [DDD = 0.5 yr^{-1}]. This drug discovery deficit value relegates Canada to the bottom three countries in the world, with only France (12 fewer drugs than predicted; DDD = 0.6 yr^{-1}) and Italy (10 fewer drugs than predicted; DDD = 0.5 yr^{-1}) doing as poorly. However, Australia and Germany should also possibly be considered within this

1991–2000		
Country, *(Drug Discovery Rank)*	GDP (10^9), *(Worldwide Rank)*	GDP² / Population (10^{15}), *(Worldwide Rank)*
United States, *(1)*	7777.1, *(1)*	220.74, *(1)*
Japan, *(2)*	4409.8, *(2)*	150.56, *(2)*
United Kingdom, *(3)*	1237.9, *(5)*	26.26, *(5)*
Germany, *(4)*	2137.5, *(3)*	55.85, *(3)*
Switzerland, *(5)*	268.2, *(16)*	10.24, *(8)*
France, *(6)*	1410.6, *(4)*	33.38, *(4)*
Italy, *(7)*	1172.1, *(6)*	24.02, *(6)*
Spain, *(8)*	580.1, *(10)*	8.49, *(10)*
Denmark, *(9)*	162.6, *(25)*	5.03, *(15)*
Netherlands, *(9)*	374.7, *(13)*	9.02, *(9)*
Sweden, *(11)*	248.4, *(19)*	7.05, *(12)*
India, *(12)*	369.8, *(15)*	0.13, *(53)*
Canada, *(13)*	615.1, *(9)*	12.80, *(7)*
Finland, *(13)*	119.0, *(32)*	2.76, *(18)*
Austria, *(15)*	205.7, *(23)*	5.32, *(14)*
Israel, *(15)*	93.4, *(36)*	1.49, *(24)*
Norway, *(15)*	143.6, *(27)*	4.71, *(16)*
South Korea, *(15)*	445.1, *(12)*	4.15, *(17)*
Australia, *(19)*	372.7, *(14)*	7.59, *(11)*
Belgium, *(19)*	246.0, *(20)*	5.95, *(13)*
Kazakhstan, *(19)*	13.6, *(70)*	0.03, *(79)*

2001–2010		
Country, *(Drug Discovery Rank)*	GDP (10^9), *(Worldwide Rank)*	GDP² / Population (10^{15}), *(Worldwide Rank)*
United States, *(1)*	12671.0, *(1)*	538.13, *(1)*
Japan, *(2)*	4575.7, *(2)*	163.20, *(2)*
United Kingdom, *(3)*	2179.7, *(5)*	78.41, *(4)*
Switzerland, *(4)*	394.3, *(18)*	20.66, *(11)*
Germany, *(5)*	2829.4, *(4)*	97.50, *(3)*
France, *(6)*	2167.2, *(6)*	76.35, *(5)*
Spain, *(7)*	1149.9, *(9)*	30.22, *(8)*
Canada, *(8)*	1156.2, *(8)*	40.94, *(7)*
Netherlands, *(8)*	654.4, *(16)*	26.18, *(10)*
South Korea, *(8)*	807.2, *(14)*	13.49, *(15)*
Denmark, *(11)*	260.2, *(27)*	12.41, *(16)*
Cuba, *(12)*	47.6, *(62)*	0.51, *(53)*
Israel, *(12)*	154.2, *(40)*	3.47, *(30)*
Italy, *(12)*	1789.9, *(7)*	54.30, *(6)*
Belgium, *(15)*	385.3, *(19)*	13.94, *(14)*
Czech Republic, *(15)*	143.0, *(42)*	1.91, *(37)*

Table 2. Economic data for drug discovering nations. Each economic factor is an average over the course of the corresponding decade. GDP is measured in current US$.

group, having produced nine and eight fewer drugs than predicted, respectively. Australia's under-performance is noteworthy: 44 new drugs originated in Germany, while the prediction was 52 (PDR = 0.85); one new drug originated in Australia, whilst the prediction was 10 (PDR = 0.10). Excluding countries that produced no drugs (the most drugs any of these countries was predicted to have discovered was three), Australia exhibits the lowest ratio of drugs discovered to drugs predicted by a considerable margin. Using the same predictive algorithms, multiple countries produced more drugs than were predicted (i.e., PDR>1, DDD<0): Switzerland (26), the United Kingdom (23), Japan (18), and the United States (11).

The R^2 coefficient of determination for E.1 and E.2 is 0.95 or better using GDP²/ Population as the only comparator. Clearly, GDP is an all-encompassing complex variable within this comparator and is strongly correlated with a wealth of other constituent variables (including direct and indirect government support for research, total private research activity, workforce education level, measures of interdisciplinary and translational research collaboration, and well-developed legal/regulatory environments), any of which could provide insights about the success or failings of an individual country with regards to drug innovation. The GDP²/ Population comparator does not adequately account for countries such as Switzerland which based upon historical location decisions possess an extremely strong pharmaceutical industrial sector that nurtures a national strength in drug innovation. Nonetheless, the GDP²/ Population comparator has general utility in identifying which countries are attaining passing or failing grades in terms of drug innovation as a function of national size and wealth.

Conclusions and Future Prospects

From the perspective of national productivity and population, some countries are succeeding in drug innovation, others are not. The reasons underlying successes or failures are many and varied, but in general countries with vibrant basic research (reflected by the number of scientific publications), strong translational research (as indicated by number of patent filings), robust R&D expenditures (both governmental and private) and a well-educated workforce (typified by number of science PhD graduates per year) tend to have more successful track-records in drug innovation (see *Table 3*).[11]

Nevertheless, since disease does not recognize national boundaries, the drug-discovery war against disease-mediated human suffering needs to be waged by more than just a few countries. Arguably, if there is money for bombs and missiles, there should also be money for beakers and microscopes. Because drugs take 10–15 years of research and development time to reach people with medical problems,[5] government imposed decreases in research funding are current events that will profoundly affect the future success of drug discovery in that country. Potential funding cuts to basic and translational biomedical research across North America, Europe and other countries could foreshadow a possible drug innovation crisis, possibly even in countries which heretofore have been stalwarts of drug discovery.[12-14] Regrettably, the magnitude of this impending drug discovery shortfall, and the worldwide impact that it shall inflict, is worsened by the evolving realization that the Big Pharma model for drug innovation is failing—the pipelines of major pharmaceutical companies are shockingly depleted, with the result that, from 2000 to 2009, 45% fewer new

	Drugs discovered (1991–2010)	Scientific research papers (2010)	Patents issued (2010)	Education (PhDs graduated in science—2009)	Expenditure (on R&D in 2009)
1.	United States	United States	United States	United States	United States
2.	Japan	Germany	Japan	Germany	China
3.	United Kingdom	China	Korea	United Kingdom	Japan
4.	Germany	Japan	Germany	Japan	Germany
5.	Switzerland	United Kingdom	Taiwan	France	France
6.	France	France	Canada	Italy	United Kingdom
7.	Italy	Canada	France	Brazil	Russia
8.	Spain	South Korea	United Kingdom	Canada	Italy
9.	Netherlands	Italy	China	Spain	Canada
10.	Denmark	Spain	Italy	Australia	Spain
11.	Canada	Switzerland	Australia	Sweden	Australia
12.	South Korea	Australia	Israel	Switzerland	Sweden
13.	Sweden	Netherlands	Netherlands	Poland	Netherlands
14.	India	India	Switzerland	Netherlands	Switzerland
15.	Finland	Taiwan	Sweden	Turkey	Austria
16.	Israel	Israel	India	Portugal	Turkey
17.	Austria	Singapore	Finland	Czech Republic	Israel
18.	Norway	Sweden	Belgium	Austria	Belgium
19.	Belgium	Belgium	Austria	Belgium	Finland
20.	Australia	Denmark	Denmark	Mexico	Denmark

Table 3. Scientific productivity of "top twenty" drug discovering nations.[9]

molecular entities became drugs via the Big Pharma route, than from 1991 to 2000.[8,15,16] Although there has been considerable speculation about the source of the decline (including harder discovery targets, preoccupation with less-innovative "me-too" drugs, industry consolidation, change in regulatory stance, introduction of structure-based design/combichem methods, metric-driven research approaches, etc.), the bottom line is that whatever the reasons this is still a problem in evolution.[15,17] But crises produce opportunities, and the opportunity arising from this crisis may be the emerging and growing phenomenon of "micropharma."[18,19]

Micropharma are academia-originated, biotech start-up companies that are efficient, flexible, innovative, product-focused, and small (having less than 25, and frequently less than 10, employees)—arising from universities, hospitals, or research institutes *in any country*. They are created by two or three academic researchers who join forces to design, discover, and develop new therapeutics (or diagnostics) for human health.[18] Although micropharma are lower tier organizations within the hierarchy of the pharmaceutical ecosystem, and although Big Pharma will ultimately be required for definitive large scale Phase III clinical trials, the rise of micropharma may level the playing field, enabling universities and hospitals in smaller or developing countries to play key roles in the future of drug innovation. Hopefully, 20 years from now, the GDP²/ Population comparator developed in this study will be completely inadequate for describing the likelihood of success or failure in drug discovery.

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