

DISPUTATIO OF BARCELONA 2013

Producing progress? Issues to consider*

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Summary. There is a growing gap in productivity in the biopharmaceutical industry. The money spent on developing new drugs has increased substantially, but the hoped-for dramatic increase in new therapies based on recent revolutions in molecular biology and genetics has yet to materialize. Long approval times, high-failures rates, and high-competition account in part for this situation. Some argue that entrepreneurs are not promoting fundamental, new discoveries and instead are simply profiting from the knowledge generated by academia. In fact, publicly funded research is driving progress in a completely new field and the development of a completely new landscape of medicine. The knowledge thereby acquired has dramatically changed the approach to targeting disease. In response, a new model is needed, one that addresses how investment in innovation is driven, but also how innovation is done.

Pharmaceutical innovation

Human progress has two interlinked components: innovation, i.e., creation, invention, and discovery, and diffusion, i.e., the dissemination and uptake of knowledge. In the realm of human healthcare and drug discovery, innovative products can be defined as those that cure or prevent a disease or condition, decrease mortality or morbidity, decrease the cost of care, improve the quality of life, are safer or easier to use, or improve patient compliance and persistence.

In recent years, there has been a decrease in the number of molecular entities or biological license applications that have

been approved. In the USA, 2012 was a surprisingly “productive” year compared to the past two decades, with 33 new molecular entities (NMEs) and 6 biologic license applications (BLAs) approved by the US Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER). The annual average is 30 FDA approvals, but there are years with as few as 18 [8].

Nonetheless, during those same years investment in the search of new drugs increased. Nowadays, the cost of developing new drugs has risen to the point that Francis Collins, the director of the National Institutes of Health, described it as a horrendous failure: “One point your numbers tell you is how horrendous the failure rate is and how that causes the cost of success

*Based on the lecture given by the author at the *Saló de Cent* of the Barcelona City Council, on November 28, 2013, for the *Disputatio of Barcelona 2013*, on “Social and State-of-the-Art Medicine”, and the inauguration of the Barcelona Knowledge Hub of the *Academia Europaea*.

Keywords: innovation · pharmaceutical industry · genomic medicine · epigenetics · healthcare system

to be so much higher” [5]. In fact, if we compare the number of new drugs approved per dollar spent, the decrease in the former is indeed alarming. There is a growing gap in productivity in the biopharmaceutical industry: money spent on developing new drugs has increased substantially, but the hoped-for rapid proliferation of new therapies based on recent revolutions in molecular biology and genetics has yet to materialize.

Why is this? In the USA, one important reason is that the FDA’s approval process, driven by extreme caution, is extremely long. The amount of time from the ‘eureka’ moment of discovering a drug candidate to its final approval by the FDA can take 10 to 15 years, with an average cost of US\$ 1.32 billion per drug [9]. Assuming that a new effective drug could save approximately 10,000 lives, a 10-year wait for its approval means that 100,000 people will die in the meantime.

Huge investments without success also point to another problem. In addition to high failure rates, the failures normally come at the very end of the process: 40 % in phase III of clinical trials, with two-thirds of the failures due to lack of efficacy [15]. For some drugs, for example those targeting components of the central nervous system, this is extremely important because failures at the late phase of a clinical trial greatly increase the cost of an ultimately successful drug. In addition, once this drug is approved, the market abounds with companies competing to sell it, analogous to “too many cooks spoiling the broth.” This results in a very high expenditure on promotion and related activities. In the USA—the only country for which data on expenditures on all major marketing and sales activities are available—total real spending on pharmaceutical promotions rose from US\$ 11.4 billion in 1996 to US\$ 29.9 billion in 2005 [11]. Another study suggests that the true figure (including meetings and e-promotions) is closer to US\$ 57.5 billion [12]. Also in the USA, the number of sales representatives is three times the number of clinicians. This means that physicians receive three to four visits per week.

The January 2013 issue of *The Economist* contained an article with the title ‘Has the ideas machine broke down?’ The argument was that entrepreneurs are not leading new, fundamental discoveries but are simply profiting from knowledge coming from academia, from publicly funded research: “Almost no entrepreneurs discover things fundamentally new, at least while working on their own nickel. Rather, in the words of Isaac Newton, they stood on the shoulders of giants. In this case, the giants were those scientists and engineers funded by society, through tax payer largess, that created the building blocks that led to many of the technological breakthroughs we have today.”

The new science of personalized medicine and the genomic era

Publicly funded research has powered a completely new field of medicine, with a completely new landscape. This knowledge has radically changed the strategies for targeting diseases. Some examples of this new landscape are genomic medicine, the ENCODE project, synthetic biology, and robotics.

Genomic medicine. Genomic medicine has provided an abundance of information about the genetic basis of disease, thus providing insight into the physiopathology of disease and identifying new therapeutic targets.

This knowledge is driving a major change in how medicine is perceived; a revolution is underway, based on personalized genomics and direct-to-consumer genomic services. Services such as 23andMe, a private DNA testing company, will analyze your saliva sample and, a few hours later, will send your genotype to your mobile phone, where you can share it with your friends on Facebook, perhaps garnering a “like.” Although, following ethical concerns, 23andMe no longer offers health-related services, initially it provided information on the risk of developing certain diseases. Additionally, you can buy access to your ancestry to find out whether you are more similar to your mother or your father, and where your ancestors came from.

Genomic medicine is driving a new approach to therapy, based on a new medical model, personalized medicine. This model proposes customizing healthcare via decisions and practices tailored to the individual patient, by exploiting genetic and other relevant information. Consider that, for a single patient group with the same diagnosis and treated with the same medication, there will be responders, non-responders, and those who exhibit signs of increased drug toxicity. Personalized medicine, by tailoring medications based on genetic information, will greatly contribute to optimizing treatment.

The ENCODE project. The Encyclopedia of DNA elements (ENCODE) project is a public research consortium that was launched in September 2003 by the US National Human Genome Research Institute (NHGRI) to identify all functional elements in the human genome [3]. An achievement of ENCODE has been the recognition that most of the non-coding DNA is involved in the regulation of the expressions of coding DNA, with important effects on health.

Synthetic biology. Another major discovery that is driving and will drive a change in productivity is the capability of

creating new life from inert chemicals. In 2010, Craig Venter and his team at the J. Craig Venter Institute reported the creation of a bacterial chromosome which they used to successfully replace the DNA of a bacterium [4]. Similar new entities will probably be capable of replicating and of evolving into new forms. Craig Venter said: “This is an important step both scientifically and philosophically.” We must think about the potential uses of future new living organisms. They could be used, for example, for producing new drugs.

Robotics. Brain-computer and body-computer interfaces that help people with disabilities to be more independent are already available. Computer science has contributed to improving not only the health, but also the social inclusion of the disabled, decreasing the cost of dependency.

Genetics, the environment, and medicine

One of the most important discoveries of recent years is that we can shape ourselves, both our brains and our bodies, and that these changes can be passed on to the next generation. This discovery is based on the recognition that there are changes in gene activity and expression that are not dependent on gene sequence; moreover, they are heritable—but not necessarily. The study of those changes in single genes or sets of genes is called epigenetics, and the global analysis of epigenetic changes across the entire genome, epigenomics. Epigenomics is one of the fastest emerging scientific fields, promising a huge growth potential by revolutionizing the therapeutics and diagnostics industries in healthcare. The US NIH Roadmap Epigenomics Mapping Consortium was launched as a public resource of human epigenetic data to facilitate disease-oriented research [<http://www.roadmapepigenomics.org/>].

Experiments have shown that a puppy that is raised by an anxious, low-nurturing mother becomes an anxious adult, whereas a puppy that is raised by a relaxed, high-nurturing mother becomes a relaxed adult. The genome of this puppy actually changes, and this change will be transmitted to its progeny. More importantly, we can also change the impact of the environment pharmacologically. The study of heritable changes in genome function and gene expression has opened a new gateway in biology, allowing us to understand the basis of diseases, and presents incredible opportunities for disease diagnosis and drug discovery. The epigenomic therapeutic market is expected to explode in the coming years.

The problem, however, is that this basic research is lost in translation when it comes to converting findings into real therapeutic advances. The substantial increase in investment in pharmaceutical research has yielded only slight progress, since the new compounds are only marginally better, but much more expensive, than existing ones. Moreover, it has increased the gap between treatment available to the rich vs. the poor. In a survey of physicians, from 2000 to 2010, out of approximately 1000 new drugs, only 2 % earned one of their top two ratings, corresponding to a real therapeutic advance [7]. This is because most of the new drugs are simply the result of drug repositioning—the application of known drugs and compounds to new indications. Drug repositioning has grown in importance over the past few years because it is less expensive, and the risk versus reward trade-off of the available strategies is much better. But it also means that innovation does not reach the market.

But, what are scientists truly worrying about? The pharmaceutical industry cannot be the ultimate answer. In fact, the effects of the environment must be taken into account. The environment is a strong determinant of how we develop and function. Genetic susceptibility factors are responsive to environmental ones. Genetically-susceptible individuals, when subjected to an adverse environment, are much more vulnerable and will go on to exhibit, in the case of childhood abuse, for example, antisocial behavior [1]. This finding has political implications. We are aware that we need to improve education, ensure a healthy environment, and change our way of interacting with this environment, but such steps must be initiated by policy-makers. To quote Leonard Schlain, “[T]here is no gene-controlled inheritable trait that cannot be altered by the environment [...] Humans enter the world as a work-in-progress [...] Nature/nurture is not an either/or duality but, rather, represents a both/and type of complementarity.” [4] Gene-environment interactions make people different, and the consequences of these interactions are in many cases decisive.

Given the complexity of how phenotype is determined, how powerful or useful will the delineation of an individual’s genome be in predicting disease and in choosing therapy? Our understanding is far from complete; we need more basic science research, and we need more knowledge. Investment in science at the moment is below what it should be, and we must work to improve this situation. We are fortunate to live in a region of the world where science is important. But regarding research in medicine, there are other problems. Consider the aims of EU Horizon 2020—the eighth phase of the Framework Programs of Research and Technological Deve-

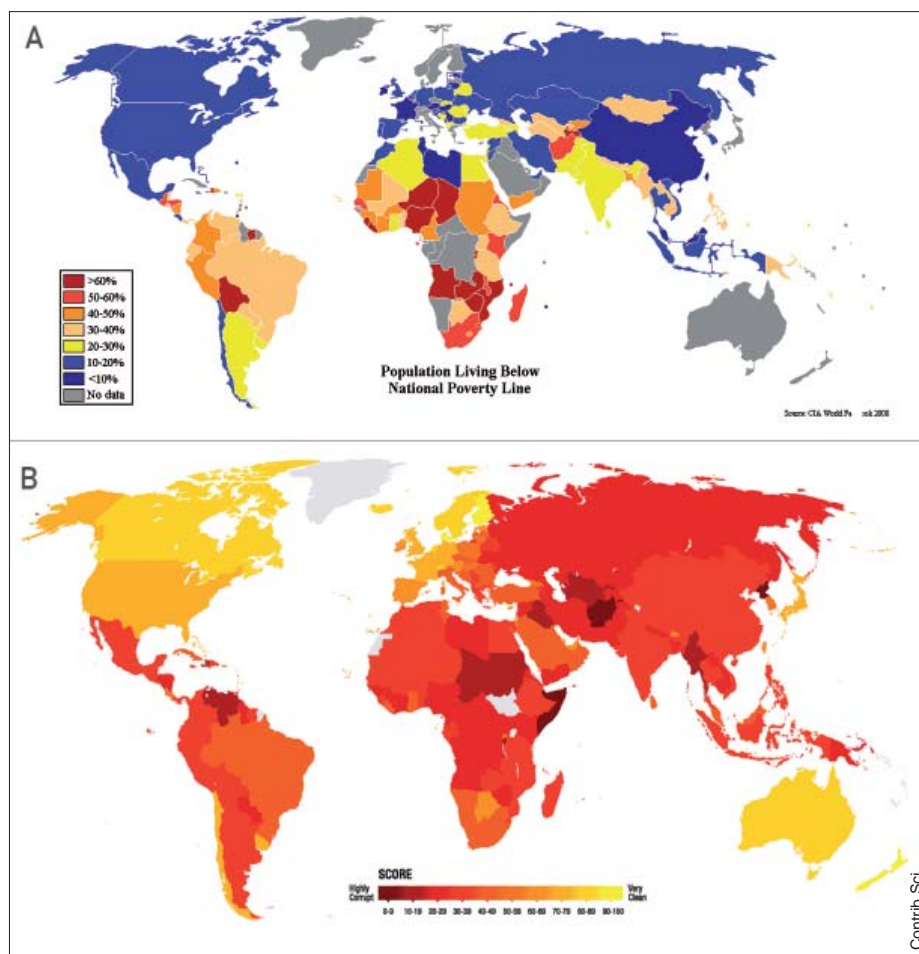


Fig. 1. (A) Estimate of world poverty (2013). CIA Poverty Stats. Source: Wikimedia Commons. (B) World map index of the perception of corruption (2012). The Corruption Perception Index ranks countries and territories based on how corrupt their public sector is perceived to be, using a scale of 0–100, where 0 means that a country is perceived as being highly corrupt and 100 that it is perceived as being very clean. Source: Transparency International.

lopment, the main targets of which are aging and obesity. In other words, funding from public agencies is mostly devoted to the diseases of developed countries.

Innovation-distorting economical inequalities

Focused innovation is distorted by huge economic inequalities, which steer innovators away from seeking treatment of those diseases predominantly affecting the poor. The problem is that the map of some disorders, such as malaria, coincides with the map of poverty, but is in direct opposition with the map of drug and pharmaceutical investment. Moreover, if we compare these maps against the map of corruption, we see that even if the drugs reach these countries, it

cannot be taken for granted that they will reach the people who need them (Fig. 1). In the words of Huguette Labelle, Chair of Transparency International, a non-governmental organization that monitors and publicizes corporate and political corruption, “we must ensure that there are consequences to corruption. ‘No to impunity’ cannot just be a slogan—it must be carried out with all our combined strength and inspire citizens to speak up and no longer tolerate corruption.” [14].


In Spain, there is also a “map of shame.” Government policies of austerity, together with punitive changes to the benefit system, as well as media and ministerial attacks on the claimants, to name just a few [2], are placing an increasing number of people at risk of poverty and social exclusion. While this affects the entire population, the consequences are particularly dire for the young population, the future of

the country. We could appeal to ethical values, to morality. But from neuroscience we know that power (of any kind) equals reduced morality. There are studies showing that higher levels of power, or wealthier economies, drive more unethical attitudes and behaviors [10]. Policy proposals with ethical implications or that aim to achieve the egalitarian distribution of benefits and costs may fail.

You could argue that we live in a democracy, but from neuroscience we also know that there are no rational voters. The political brain is an emotional brain and people are driven by emotions. Politicians use marketing techniques aimed at holding their traditional voters as well as widening their appeal. But in designing their campaigns they should take into account voters' attitudes, by studying how voters' electoral memory, sense of responsibility, and emotional state are associated with their votes. What do citizens think about when they stand in the polling booths? What is the impact of electoral arrangements on voting and voters' perceptions of elections? How do voters evaluate government performance? Answers to these questions would help to generate more coherent systems.

Concluding remarks

The health systems of most countries perform very poorly in terms of cost-effectiveness, which reduces their societal value. Overall efficiency is greatly diminished by lobbying and deal-making, the patent application process, litigation, wasteful marketing, counterfeiting, and deadweight losses. Adverse disturbances of drug development by the scientific or regulatory environment have detrimental effects on social value. Disruptions in the flow of funding from sales to R&D lead to lower social returns. We need to address not only the drivers of investment in innovation, but also how innovation is done. I would like to see more research of these issues and a change in the regulatory environment aimed at raising the social value of innovation.

We need to change the model. The outcome of treatment should be included in an assessment of its value. In other words, payment for pharmaceuticals should be based on performance. We should also improve science funding. And finally, academic knowledge, both theoretical and methodological, should be applied to policymaking. In the words of sustainability expert Gareth Kane, "[t]he true barrier to sustainability is about six inches wide—the space between our ears. Most of the problems and the solutions can be found there" [6]. 

Competing interests. None declared.

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About the author

Mara Dierssen received her degree in medicine (1985) from the University of Cantabria and her PhD (1989) from that university Department of Physiology and Pharmacology. She did her postdoctoral work at the Autonomous University of Barcelona (1990–1993). She was assistant professor at the University of Cantabria (1993–1997), professor of psychophysiology and neurosciences at Ramon Llull University (1997–2006), and senior researcher at the Medical and Molecular Genetics Centre of the Cancer Research Institute (IRO) in Barcelona (1997–2001). Since 2005, she has been the director of the Associated Unit for Behavioral Research (National Biotechnology Centre-CSIC) and, since 2007, investigator of the Centre for Biomedical Research on Rare Diseases (CIBERER). She belongs to several academic societies and is a member of the executive committee of the Federation of European Neuroscience Societies (FENS). Dierssen has received numerous awards, including the National Culture

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Resum. Existeix una creixent llacuna en la productivitat de la indústria biofarmacèutica: els diners gastats en el desenvolupament de nous fàrmacs ha augmentat molt, però el gran augment esperat de noves teràpies basades en les revolucions recents de la biologia molecular i la genètica encara no s'han materialitzat. El llarg temps d'aprovació de nous fàrmacs, l'alt índex de fracassos, i l'alt nivell de competència són algunes de les raons d'aquesta situació. Hi ha qui sosté que els empresaris no estan promovent nous descobriments fonamentals i senzillament es beneficien del coneixement que es genera al món acadèmic. De fet, la investigació finançada amb fons públics està liderant un camp completament nou i el desenvolupament d'un nou escenari per a la medicina. El coneixement adquirit ha canviat enormement la nostra manera d'encarar les malalties. Com a resposta a aquest canvi, cal un nou model que tingui en compte com s'inverteix en innovació, i també com es fa la innovació.

Paraules clau: innovació · indústria farmacèutica · medicina genòmica · epigenètica · sistema sanitari