Drug Discovery

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Does Chemistry Have a Future in Therapeutic Innovations?**

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biopharmaceuticals · drug development · medicinal chemistry · therapeutic innovation

Dedicated to Robert Corriu

With the intensive development of biopharmaceuticals during the last two decades, policy makers have tended to consider that drugs based on small molecules made by chemists will disappear by 2030. This is a misleading idea for several reasons, which are discussed in the present Essay.

In fact, the key question is the appraisal of the real position of chemical-based drugs in the panel of drugs that will be used in the future for treating different diseases ranging from viral, bacterial, and parasitic infections, to cancers, central nervous systems disorders, neurodegenerative diseases, immunological disorders, and diseases induced by aging. It is important to assess the role and future position of medicinal chemistry in the design of new therapeutic agents, in order to reach a reasonable balance between small molecules and biopharmaceuticals. The equilibrium between these two types of drugs will in fact depend on several factors, including the necessity of having highly efficient drugs for the treatment of diseases and health disorders at a minimal cost. The challenge is to cure the largest possible number of patients at a cost that is compatible with the foreseen limits of national health budgets in 2030.

As a start, we can consider the historical evolution of the use of chemicals as therapeutic tools. With the early development of analytical chemistry and extraction methods during the first half of the 19th century, chemists and pharmacists were able to extract the active substances from plants that were used in traditional medicine. Quinine was extracted and identified by Pelletier and Caventou in 1820 and can be considered the first milestone of alkaloid pharmacology. The development of organic synthesis in the middle of the same century made it tempting to prepare alkaloids by total synthesis. The attempt of Perkin to prepare quinine from aniline was a "successful failure": he obtained mauveine, the famous dye that would be known as Perkin's mauve.[1] At the beginning of the 20th century extractive and synthetic chemistry, in association with the emerging field of biochemistry, formed the origin of modern pharmacology with the lock-and-key concept introduced by H. E. Fischer in 1894[2] and the notion of receptors formulated by P. Ehrlich in 1906. The chemistry–biochemistry tandem was the scientific base of the "business model" of all pharmaceutical companies for nearly a century. We all have in mind the names of the giants in Europe and in the USA that dominated the drug industry with a strong connection between chemistry and pharmacology. In Europe, Bayer, ICI, and Rhône–Poulenc were classical examples of these pharmaceutical companies based on chemicals. In the 1980s, this industrial paradigm changed under the pressure of the evolution of scientific domains and economic parameters. In a non-exhaustive fashion, some of these parameters will be considered in the following sections.

The "Merging Period" in the Pharmaceutical Industry

In the 1950s, the pharmaceutical industry consisted of a large number of different companies, each with a small share of the world drug market. Few companies had more that 2 or 3% of the world's drug market and the development of these companies was driven by new discoveries that had a long period of patent protection while the period "from patent to market" was rather short, usually between five and seven years. In response to drug-induced tragedies related to poor toxicological studies (Thalidomide, a sedative drug with high teratogenicity, is one example that comes to mind), the level of safety regulations was significantly increased in the 1960s. After several conferences under the auspices of the World Health Organization (WHO), the International Conference on Harmonisation of Technical Requirements for Pharmaceutical Use (known as ICH) was created in 1990. The ICH rules were quickly applied in the USA, Europe, and Japan. The increasing cost of safety studies at the preclinical stage was one of the driving forces for merging operations. Sanofi, initially formed from the fusion of more than 40 small companies, merged with Synthélabo, and then with Aventis, the latter being the result of the merger of Roussel-Uclaf with Marrion-Merrell-Dow and Hoechst-Pharma. The second driving force for merging companies was the natural tendency to strive to be the biggest pharmaceutical company in the world, the "Big Pharma" syndrome! As the pharmaceutical companies grew in size, the management was also strongly modified. Gradually, people with scientific expertise or medical background were excluded from decision-making and relegated to so-called technical positions. The new

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generation of top-level managers was hired from financial and business areas. One of the consequences was that spontaneous creativity was stifled as a result of excessive "reporting methods". Researchers were spending more and more time writing reports and notes. At the same time, improvements in personal computers and word-processing have led to a dramatic increase in the volume of these reports while lowering their usefulness ("the more you get, the less you read"). The distance between scientific observations and the strategic decisions made by managers has increased year by year. All in all, many different factors have contributed to reducing the creativity of Big Pharma companies and increasing the time and the cost of the "from patent to market" period. Nowadays, the cost for having a drug approved often exceeds one billion U.S. dollars and the time from the drug patent to market approval can be more than 12 to 14 years. Fortunately, the decline of creativity in large pharmaceutical companies is mainly compensated by the emergence of new small companies focused on drug discovery.

The Key Role of Small Companies in Drug Discovery

In a well-documented study concerning the number of NMEs (new molecular entities) that have been declared to the FDA (Food and Drug Administration of the USA), Munos has clearly noted the reduction of the number of NMEs registered by large companies compared to the number claimed by small companies.[3] In 1950, 80% of the NMEs were declared by large companies; in the early 1980s this dominance declined, and in 2002 the smaller companies reached parity and have since have taken over the lead (see Figure 1).

Small is beautiful and creativity is saved! With this new trend, Big Pharma companies have to feed their drug pipelines with the discoveries of small companies. This business model implies that the pharmaceutical industry will mainly survive in countries or economic zones that can create an ecosystem favoring the generation of startup companies. The discussion of the different parameters of such an ecosystem is far beyond the scope of this Essay, and all of us have personal opinions on this point. Despite official claims of the European Council in Lisbon in March 2000 to shape Europe as "the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more jobs" by 2010, currently, many people feel that the EU is better at creating regulations than conditions for the development of industrial jobs. In addition, the "precautionary principle" is now integrated within the constitutional law in some European countries, and the benefit/risk ratio of drugs can be examined with risk as the unique parameter, leaving unrealized potential health benefits.

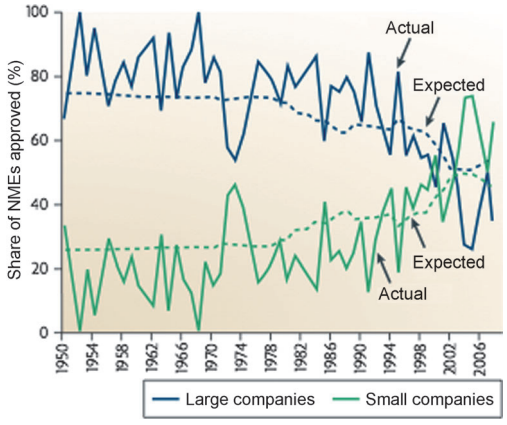

Figure 1. Evolution of the percentage of FDA-declared NMEs claimed by large companies and small companies from 1950 to 2007. Reproduced with permission from Ref. [3].

The New Look of the Pharmaceutical Industries since 2000

Medicinal chemistry has been largely modified since 1980 by the fast development of sophisticated techniques (e.g. NMR spectroscopy, mass spectrometry, crystallography) and computing facilities (e.g. virtual screening methods) that speed up the production and the characterization of molecules up to a level that would impress medicinal chemists trained in the 1960s.[4] The exploration of "chemical space" is only at its beginning. Fink and Reymond calculated that more than 26 million molecules could be prepared with up to 11 atoms of carbon, nitrogen, oxygen, and fluorine by using established synthetic methods.[5] Within this nearly unlimited chemical space, only 63850 molecular entities are already registered in public databases, that is, only 0.24% of the theoretical possibilities.[5] Chemists have an open space to create new NMEs and they should not pay too much attention to people claiming that we already have enough molecules for biological evaluation! Chemical libraries will be diversified in the future by the development of efficient multicomponent reactions[6] and there will be continued improvements to improve high-throughput screening (HTS) methods. After an euphoric period followed by disappointment owing to the rather low yield of druggable molecular entities, one should consider HTS as one tool among others and not as a magic wand to "fix" the decline of productivity in the pharmaceutical industry.[7] There is no fast track "from gene to drug". This fact has been illustrated by the difficulties to find new antibacterial drugs with genomic studies. For example, GlaxoSmithKline spent seven years (1995–2001) evaluating more than 300 gene products as potential targets for novel antibacterial agents and 70 HTS campaigns were run using large libraries of synthetic chemicals (260000–530000 compounds).[8] The capacity of HTS to deliver high-quality hits is highly dependent on the size and the structural diversity of the chemical libraries associated with this robot-driven screening method. We can also trust the chemists' brains to generate chemical diversity by rational design. HTS will not replace highly qualified medicinal chemists with their "rational" approach to drug design. One of the limits of HTS is that it cannot be used for cellular or phenotypic screening on animal models.

The impressive development of molecular genetics in the 1980s had a direct impact on the evolution of the pharmaceutical industry. With restriction enzymes and ligases it

became possible to manipulate genomes, first of bacteria and plants, and then of mammal species. Shortly after, genomes were routinely analyzed for many living systems. The combination of these discoveries led to the production of genetically modified organisms, including knockout mice that are routinely used to validate a mechanism of action of a drug by the inactivation of an existing gene coding for a receptor or a particular protein. Transgenic drosophila, zebrafish, and mice are used to screen of drug-candidate molecules for different diseases, including diabetes and Alzheimer's disease.[9] However, the application of transgenic animals to drug screening is limited because many diseases are driven by a sophisticated collection of gene modifications, which cannot be reproduced easily with two or three gene modifications on these animal models. The cost of genomic analyses has quickly decreased and nowadays there are companies that offer to sequence your own personal genome for less than 10000 U.S. dollars; they provide the data on a regular USB mass-storage device that can be given to your doctor. The facile access to human genome data has opened the area of so-called personalized medicine. Drug treatments could be adapted to each individual depending on different factors that are accessible from DNA analyses (e.g. metabolic profiles, drug responses). The current era is now marked by "-omics sciences": genomics, proteomics, pharmacogenomics, metabolomics. These new fields of molecular biology are enrolling more and more researchers with a cash consumption that is far from being satisfied by taxpayers' money only, but is currently supported by an increasing number of powerful private foundations. The impact of U.S. foundations on the rapid development of biotechnology companies through financial support provided directly to young creative researchers, with the help of business angels, was mainly at the origin of the booming period of startup companies in the United States in the 1980s. The huge financial risks assumed by U.S. private investors allowed the creation of thousands of biotech firms with the emergence of some big companies (e.g. Genentech, Chiron, Genzyme). Europe has been unable to facilitate the development of big biotech companies and still has a deficit of world-class firms; consequently European pharmaceutical companies look to purchase biotechs mainly based on either coast of the USA. Considering that Europe missed out on the development of powerful biotech companies with their biopharmaceuticals and that chemistry and small molecules are too often considered out-of-fashion, one may wonder what the state of the pharmaceutical industry in Europe will be in twenty years. With this in mind, it is urgent to explain to decision makers that the decline of chemistry in the drug industry is not inexorable for scientific and economic reasons and that Europe, with its long tradition of medicinal chemistry, must keep as intact as possible its know-how in this field. The chemical industry is one of the main employers in Europe.

Is There a Future for Drugs Based on Small Molecules?

The limits of the development of the biopharmaceutical arsenal can be illustrated by three different examples taken from gene therapy, monoclonal antibodies, and personalized medicine. Most of the current drugs in clinical use are small molecules that target protein receptors or enzymes, not DNA or RNA. The genome revolution opened the field of gene therapy and the possibility to act directly at the level of pre-mRNA and RNA, and even at the level of double-stranded DNA. Because mRNA encodes for all cellular proteins, oligonucleotides able to block the expression of mRNAs by any possible mechanism have been considered as new therapeutic tools after the initial work of Zamecnik and Stephenson in 1978.[10] Elbashir et al. discovered in 2001 that short double-stranded RNA, named siRNAs for small interfering RNAs, are able to degrade mRNAs in human cells.[11] These two landmark reports have inspired an impressive amount of scientific research and have been at the origin of many startup companies. Billions of U.S. dollars were raised on the financial market despite remarks concerning the very poor cellular uptake of these large polar oligonucleotides, which deviate from Lipinski's Rule of Five (based on empirical considerations on the biodisponibility parameters of oral drugs marketed over a 30 year period).[12] The only antisense oligonucleotide that has been registered up to now is Fomivirsen (registered in 1998), a drug delivered by intraocular injection to treat cytomegalovirus-induced retinitis in immuno-compromised patients with AIDS. This is a very limited market for an antisense oligonucleotide considering the billions of dollars that have been invested by many companies for the development of such drugs. Poor cellular uptake and low stability in plasma, in addition to chemistry-dependent toxicities, are intrinsic drawbacks of this class of biopharmaceutical drugs.[13] RNA therapeutics and aptamers will probably face the same limitations.[13,14] Targeted therapies with monoclonal antibodies have gained ground in oncology practice.[15] Such biopharmaceuticals interact with cancer cells more selectively than small molecules and therefore cause less collateral damage, besides dermatological side effects that are often class-specific like for Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor.[16] However, owing to sophisticated manufacturing and purification processes, monoclonal antibodies are much more expensive than small molecules. The balance of the efficacy versus the cost of antibodies is favorable in cancer therapies with treatments limited in time. The extension of the use of costly monoclonal antibodies for the treatment of chronic diseases or some orphan diseases is questionable and will continue to be questioned, in particular when health care budgets reach a plateau. (In 2010 the total health costs reached 17.9% of the gross domestic product (GDP) in the USA compared to 16% in 2005, In Germany and France, the health costs/GDP ratios for 2010 are 11.6 and 11.9%, respectively).[17,18]A Swedish study has pointed out that the treatment of rheumatoid arthritis with antibodies such as Etanercept, Infliximab, or Adalimumab costs between from 10800 to 14400 Euros per patient per year.[19] Such annual costs can be considered economically difficult to sustain for a chronic disease affecting a large number of patients. The cost parameter concerns also some orphan diseases like the glycogen storage disease type II (also called Pompe disease) induced by an α-1,4-glucosidase deficit. The cost of the

treatment with the enzyme produced by recombinant DNA technology using CHO cells (myozyme) can be as high as 300000 U.S. dollars per patient per year according to Genzyme.[20] In addition, we can be sure that generic antibodies will be produced in the future in China or India at low cost, as has been the case for the production of small molecules in the 1990s. The height of the "technical barrier" for the production of externalized biopharmaceuticals is probably overestimated by U.S. or European decision makers. The key point concerning the return on investments will be the duration of patent protection for either type of drugs, small molecules and/or biopharmaceuticals, and not the fact that biopharmaceuticals are considered at the moment as less "genericable".

Does the Recent Decline Announce a Continuous Decline in Chemical Drugs for the Next 20 Years? No.

A plot of the number of new drugs approved by the FDA in the USA over the period 1993–2011 is shown in Figure 2, making a distinction between small molecules (defined by the FDA as new NMEs) and biologics license applications (BLAs, terminology used by the FDA to refer to biopharmaceuticals).[21] Keeping in mind the fact that the first therapeutic monoclonal antibody was approved by the FDA in the late 1990s for Genentech (Trastuzumab or Herceptin used for breast cancer treatment), we will compare the evolution of the ratio between small molecules and biopharmaceuticals from 1993 to 2011. During the total 19 year period the average number of NMEs and BLAs per year was 25.4 and 4.1, respectively. During the most recent 10 year period (2002–2011), the corresponding average numbers of NMEs and BLAs were 20 and 4.7, respectively. The ratio NMEs/BLAs for the last 10 years is now 4.25 compared to 6.2 for the 19 year period. The observable trend is a decrease in the number of NMEs, compared to the 1995–1999 period, during the past 10 years, along with a slight increase of BLAs over the same period. I feel that the slow decline of the NME approval is induced by the fact that chemical drugs are considered as being out-of-fashion by the public and decision makers, both influenced by media messages (chemistry is not good for you!), leading to the reduction of R&D budget dedicated to medicinal chemistry in pharmaceutical companies. At the moment, "biotech" sounds better than "chemtech" for investors and policy makers! However, owing to budgetary constraints worldwide (such constraints having different origins in Europe or in the USA than in countries faced with poverty), the development of expensive biopharmaceuticals will have to face cost-of-goods barrier, whereas cheap chemical drugs will have a brilliant future. The future drug market in 2030 will display a balanced ratio between chemical drugs and biopharmaceuticals that will probably continue to be close to 4:1. Medicinal chemistry and all disciplines involved in the design and development of chemical drugs are still facing the usual open field of challenging discoveries. Moreover, with with the aging population and the related increase of neurodegenerative diseases in all countries, we should keep in mind that small molecules are appropriate therapeutic tools for the treatment of neurodegenerative diseases, because of their ability to cross the blood–brain barrier to reach the brain targets.

The Future of Chemistry in Drug Design and Development: Brilliant and Creative!

I am strongly confident in the future of chemistry in the pharmaceutical industry (despite some unpleasant remarks made by managers without real scientific background on the alleged? fact that chemistry is a "too old science" to efficiently contribute to drug discovery in the 21th century). We have to keep in mind that one of the key advantages of small molecules over biologics, antibodies, and therapeutic proteins is that they are able to reach intracellular targets that cannot be addressed with large macromolecules. The leading companies in 2025–2030 will be the companies that will be able to keep creative chemists working and developing new ideas and concepts in the "molecular sciences", a field created by merging chemistry (all aspects of chemistry, not only

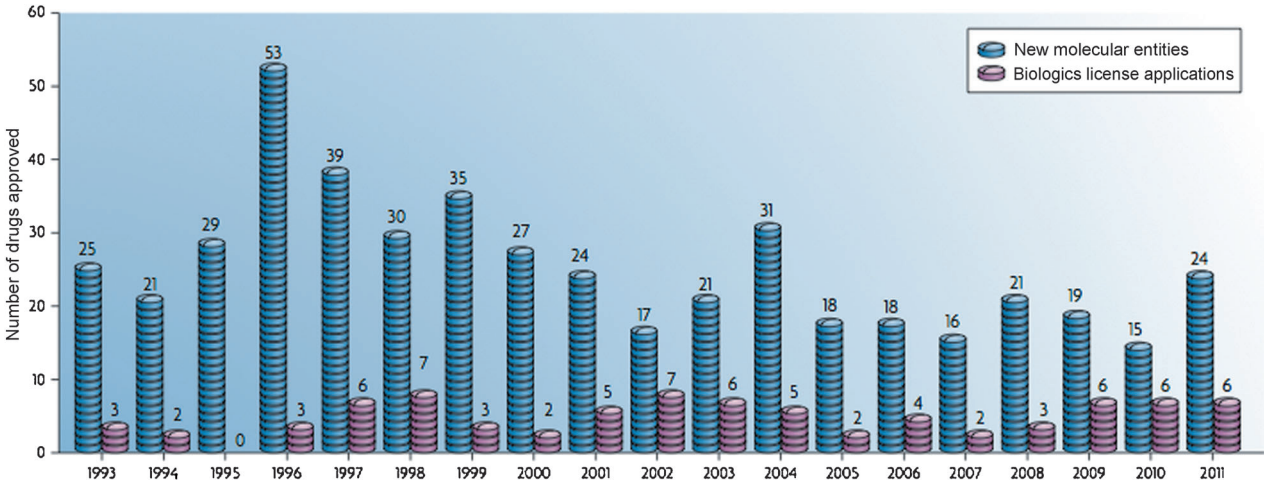

Figure 2. Drugs approved by the FDA since 1993. The term "new molecular entities" stands for small molecules and "biologics license applications" for biopharmaceuticals. Reproduced with permission from Ref. [21].

organic, but also inorganic, analytic, physical, and computational chemistry) with molecular biology. Chemists have made efforts to work with biologists over the last three decades. Biologists should also reach out to chemists to avoid being locked within one of the fast-growing subdisciplines of the vast number of domains in biology. Interdisciplinarity will largely facilitate translational research, from molecules to patient beds and vice versa.

In the future, the production of sophisticated drugs will involve "synthetic biology" and chemical engineering. Fermentation is a classical mode for production of co-enzymes like vitamin B_{12}, but this technology has now been extended to the antitumor drug taxol, by using cells of needles from *Taxus chinensis*.[22] The identification of all key genes coding for the key steps of the biosynthesis of the antimalarial artemisinin by *Artemisia annua* L. has also made possible the production of an artemisinin precursor by using genetically modified plants, in a collaborative work between geneticists and chemists for future mass production.[23] The design of chemical drugs will also be highly modified by predictive calculations based on efficient computational chemistry methods. Within the last decade, examples of predictive chemistry have been documented (see Ref. [24] as an example in enantioselective catalysis). We can be confident in the future of computer-assisted drug design as a source of innovation in the discovery of new drugs.[25-27] Natural products will continue to play a key role in drug discovery. Nearly half (49%) of the small molecules introduced between 1981 and 2002 as new chemical entities (NCEs) were natural products or natural-product-based pharmacophores.[28] These natural products are a source of inspiration for new scaffolds. There is no reason to believe that the time for new drugs based on natural product derivatives or analogues is over.[29] Serendipity, as well as discoveries made by researchers gifted with keen eyes, will also continue to provide new drugs! Serendipity has played and will continue to play an important role in drug discovery.[1] We have to be modest in the domain of drug discovery: for example, the details of the analgesic action of paracetamol, one of the most widely used chemical drugs since the 1950s, have disclosed only recently.[30] The drug metabolite, *N*-acetyl-*p*-benzoquinoneimine, activates the mouse and the human TRPA1 receptor, a unique sensor of noxious stimuli. Most of the investigational new drug (IND) applications to the FDA or to the European agency (EMEA) start the guideline listing with the mechanism of action as item number one, followed by the drug efficacy and the toxicological parameters. It is clear that with such filters, neither paracetamol nor aspirin would ever have passed a current IND examination, since their efficacy was proved in humans decades before their mode of action was understood at the molecular level. Screening of drug candidates with valid and predictive murine models should not be considered as out-of-fashion. In conclusion, medicinal chemists, together with molecular biologists, will obviously continue to contribute to the discovery of new efficient and safe drugs in the future.

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[1] W. Sneader, *Drug Discovery—A History*, Wiley, Chichester, **2005**.
[2] F. W. Lichtenthaler, *Angew. Chem.* **1994**, *106*, 2456–2467; *Angew. Chem. Int. Ed.* **1994**, *33*, 2364–2374.
[3] B. Munos, *Nat. Rev. Drug Discovery* **2009**, *8*, 959–968.
[4] S. Botros, A. W. Lipkowski, D. L. Larson, P. A. Stark, A. E. Takemori, P. S. Portoghese, *J. Med. Chem.* **1989**, *32*, 2068–2071 (Editorial).
[5] T. Fink, J. L. Reymond, *J. Chem. Inf. Comput. Sci.* **2007**, *47*, 342–353.
[6] E. Ruijter, R. Scheffelaar, R. V. Orru, *Angew. Chem.* **2011**, *123*, 6358–6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246.
[7] R. Macarron, M. N. Banks, D. Bojanic, D. J. Burns, D. A. Cirovic, T. Garyantes, D. V. S. Green, R. P. Hertzberg, W. P. Janzen, J. W. Paslay, U. Schopfer, G. S. Sittampalam, *Nat. Rev. Drug Discovery* **2011**, *10*, 188–195.
[8] D. J. Payne, M. N. Gwynn, D. J. Holmes, D. L. Pompliano, *Nat. Rev. Drug Discovery* **2007**, *6*, 29–40.
[9] B. K. Harvey, C. T. Richie, B. J. Hoffer, M. Airavaara, *J. Neural. Transm.* **2011**, *118*, 27–45.
[10] P. C. Zamecnik, M. L. Stephenson, *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 280–284.
[11] S. M. Elbashir, J. Halborth, W. Lendeckel, A. Yalcin, K. Weber, T. Tuschl, *Nature* **2001**, *411*, 494–498.
[12] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26.
[13] R. Kole, A. R. Krainer, S. Altman, *Nat. Rev. Drug Discovery* **2012**, *11*, 125–140.
[14] A. D. Keefe, S. Pai, A. Ellington, *Nat. Rev. Drug Discovery* **2011**, *9*, 537–550.
[15] Q. Zhang, G. Chen, X. Liu, Q. Qian, *Cell Res.* **2007**, *17*, 89–99.
[16] A. L. C. Agero, S. W. Dusza, C. Benventuno-Andrade, K. J. Busam, P. Myskowski, A. C. Halpern, *J. Am. Acad. Dermatol.* **2006**, *55*, 657–670.
[17] http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS.
[18] B. Meunier, *Acc. Chem. Res.* **2008**, *41*, 69–77.
[19] P. Geborek, E. Nitelius, S. Norltorp, H. Petri, L. Jacobsson, L. Larson, T. Saxne, I. Leden, *Ann. Rheum. Dis.* **2005**, *64*, 1805–1807.
[20] http://www.genzyme.com/commitment/patients/costof_treatment.
[21] A. Mullard, *Nat. Rev. Drug Discovery* **2012**, *11*, 91–94.
[22] M. Williams, *Chem. Eng. News* **2010**, *88*, 8.
[23] I. A. Graham, K. Besser, S. Blumer, C. A. Branigan, T. Czechowski, L. Elias, I. Guterman, D. Harvey, P. G. Isaac, A. M. Khan, T. R. Larson, Y. Li, T. Pawson, T. Penfield, A. M. Rae, D. A. Rathbone, S. Reid, J. Ross, M. F. Smallwood, V. Segura, T. Townsend, D. Vyas, T. Winzer, D. Bowles, *Science* **2010**, *327*, 328–331.
[24] A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, A. R. Zhugralin, *Angew. Chem.* **2010**, *122*, 38–49; *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44.
[25] W. J. Jorgensen, *Science* **2004**, *303*, 1813–1818.
[26] T. Geppert, S. Bauer, J. A. Hiss, E. Conrad, M. Reutlinger, P. Schneider, M. Weisel, B. Pfeiffer, K. H. Altmann, Z. Waibler, G. Schneider, *Angew. Chem.* **2012**, *124*, 264–268; *Angew. Chem. Int. Ed.* **2012**, *51*, 258–261.
[27] C. D. Fjell, J. A. Hiss, R. E. W. Hancock, G. Schneider, *Nat. Rev. Drug Discovery* **2012**, *11*, 37–51.
[28] F. E. Koehn, G. T. Carter, *Nat. Rev. Drug Discovery* **2005**, *4*, 206–220.
[29] A. L. Harvey, A. Cree, *Planta Med.* **2010**, *76*, 1080–1086.
[30] D. A. Andersson, C. Gentry, L. Alenmyr, D. Killander, S. E. Lewis, A. Andersson, B. Bucher, J. L. Galzi, O. Stener, S. Bevan, E. D. Högestätt, P. M. Zygmunt, *Nat. Commun.* **2011**, *2*, 551.

