REVIEW

Drug Discovery: A Historical Perspective

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Driven by chemistry but increasingly guided by pharmacology and the clinical sciences, drug research has contributed more to the progress of medicine during the past century than any other scientific factor. The advent of molecular biology and, in particular, of genomic sciences is having a deep impact on drug discovery. Recombinant proteins and monoclonal antibodies have greatly enriched our therapeutic armamentarium. Genome sciences, combined with bioinformatic tools, allow us to dissect the genetic basis of multifactorial diseases and to determine the most suitable points of attack for future medicines, thereby increasing the number of treatment options. The dramatic increase in the complexity of drug research is enforcing changes in the institutional basis of this interdisciplinary endeavor. The biotech industry is establishing itself as the discovery arm of the pharmaceutical industry. In bridging the gap between academia and large pharmaceutical companies, the biotech firms have been effective instruments of technology transfer.

The Evolution of Drug Discovery

As an interdisciplinary endeavor with an industrial base, drug research is not much older than a century. Drug research, as we know it today, began its career when chemistry had reached a degree of maturity that allowed its principles and methods to be applied to problems outside of chemistry itself and when pharmacology had become a well-defined scientific discipline in its own right (*1*). By 1870, some of the essential foundations of chemical theory had been laid. Avogadro's atomic hypothesis had been confirmed and a periodic table of elements established. Chemistry had developed a theory that allowed it to organize the elements according to their atomic weight and valence. There was also a theory of acids and bases. In 1865, August Kekulé formulated his pioneering theory on the structure of aromatic organic molecules (*2, 3*).

This benzene theory gave a decisive impulse to research on coal-tar derivatives, particularly dyes. In turn, the evolution of dye chemistry had a profound influence on medicine. The selective affinity of dyes for biological tissues led Paul Ehrlich (Fig. 1), a medical student in the laboratory of the anatomist Wilhelm Waldeyer (between 1872 and 1874) at the University of Strasbourg, to postulate the existence of "chemoreceptors." Ehrlich later argued that certain chemoreceptors on parasites, microorganisms, and cancer cells would be different from analogous structures in host tissues, and that these differences could be exploited therapeutically. It was the birth of chemotherapy, a particular type of drug therapy, that in the course of the 20th century led to unprecedented therapeutic triumphs (*4*).

Analytical chemistry, in particular the isolation and purification of the active ingredients of medicinal plants, also demonstrated its value for medicine in the 19th century. In 1815, F. W. Sertürner isolated morphine from opium extract (*5*). Papaverin was isolated in 1848, but its antispasmodic properties were not discovered until 1917 (*6*). As active ingredients from plants became available, many pharmacies addressed the problem of providing standardized preparations of these often still impure drugs.

Coal-tar, an abundant by-product of the industrialization, contained many of the aromatic or aliphatic building blocks that became the toolkit of medicinal chemistry from its beginnings to the present (*7*). Finally, pharmacology, which had its roots in the physiological experiments of François Magendie and Claude Bernard, claimed its place among the medical disciplines. Under the leadership of Oswald Schmiedeberg, the institute of pharmacology at the University of Strasbourg laid many of the intellectual and experimental foundations of pharmacology between 1871 and 1918 (*8*). However, none of the institutions that had supported these seminal efforts—pharmacies, university laboratories, or the chemical companies producing dyes—represented suitable platforms for the newly emerging drug research that was driven by chemistry but increasingly controlled by pharmacology and by clinical sciences. New institutions to support interdisciplinary drug research and development had to be created. They either grew out of pharmacies or were founded as pharmaceutical divisions in chemical or dye companies. A new way of finding, characterizing, and developing medicines led to the formation of a new industry (*9*).

The Impact of New Technology on Drug Discovery

During the first half of the 20th century drug research was shaped and enriched by several new technologies, all of which left their imprint on drug discovery and on therapy. In 1938, E. Chain, Howard Florey, and their collaborators selected penicillin, a metabolite from a penicillium mold that could lyse staphylococci, for further study (*10*). Penicillin had been discovered in 1929 by Alexander Fleming (*11*), and a large number of antibiotic substances had been described in the scientific literature between 1877 and 1939. Chain and Florey's choice turned out to be very fortunate. Because of its efficacy and lack of toxicity, penicillin made the most compelling case for antibiotics in general. It opened the door to a new era in the treatment of bacterial infections. After the discovery of penicillin and subsequently of other antibiotics, many drug companies established departments of microbiology and fermentation units, which added to their technological scope. There were only a few large companies that did not participate in the search for new antibiotics. Some companies, for example Merck, Sandoz, and Takeda, used their microbiological capabilities to find drugs that exerted other pharmacological or chemotherapeutic properties: Ivermectin, a superior drug against tropical filariosis; lovastatin, a HMGA-Co reductase inhibitor; and the immuno-

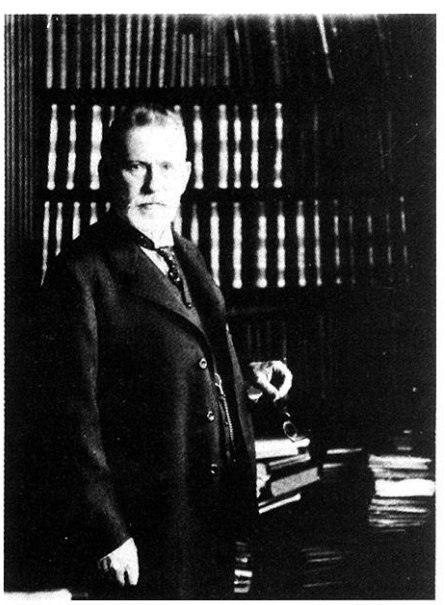

Fig. 1. Paul Ehrlich, who was the first to argue that differences in chemoreceptors between species may be exploited therapeutically. [Image: National Library of Medicine]

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suppressants Cyclosporin A and FK 506 are examples (*12–15*). Cyclosporin A was discovered as early as 1972 in a screening program for antimicrobial compounds (*14*).

Biochemistry influenced drug research in many ways. The dominant concepts introduced by biochemistry were those of enzymes and receptors, which were empirically found to be good drug targets. The description and characterization of carboanhydrase in 1933 (*16*) was fortuitously followed by the discovery that sulfanilamide, the active metabolite of the sulfonamide (sulfa drug) Prontosil, inhibited this enzyme and that this effect led to an increase in natriuresis and the excretion of water (*17*). Sulfanilamide gave rise to better carboanhydrase inhibitors such as acetazolamide and later led to more effective diuretics such as hydrochlorothiazide and furosemide (*18*). There are structural genealogies that link sulfanilamide with more advanced sulfonamides like sulfathiazole, with sulfonylureas like tolbutamide, used in the treatment of type II diabetes mellitus, and with diuretics that are being used to treat edema, glaucoma, or essential hypertension (Fig. 2).

Structural pathways such as the one shown in Fig. 2 illustrate the fact that the sequential development of different therapeutic areas could well be interpreted as chemical diversification that at first occurred spontaneously. After serendipitous biological findings had been made, certain prototypic structures were further derivatized in order to obtain compounds with improved or altogether novel effects.

The idea of a receptor as a selective binding site for chemotherapeutic agents, first proposed by Paul Ehrlich, has already been mentioned. A more functional concept in which the receptor serves as a "switch" that receives and generates specific signals and can be either blocked by antagonists or turned on by agonists was introduced into pharmacology by J. N. Langley in 1905 (*19*). A crucial further step in this direction was taken by R. P. Ahlquist in his seminal paper on adrenotropic receptors, in which he proposes the existence of two types of adrenergic receptors (*20*). The pharmacological characterization of receptors in almost all organs, including the brain, provided the basis for a large number of very diverse drugs: β-blockers (*21*); β-agonists (*22*); benzodiazepines, which enhance the effects of γ-aminobutyric acid and chloride flux by way of the benzodiazepine receptor (*23*); and monoclonal antibodies, which block receptors of growth or differentiation factors on tumor cells (*24*).

A comprehensive analysis of the drug targets underlying current drug therapy undertaken in 1996 showed that present-day therapy addresses only about 500 molecular targets. According to the analysis, cell membrane receptors, largely heterotrimeric GTP-binding protein (G protein)–coupled receptors, constitute the largest subgroup with 45% of all targets, and enzymes account for 28% of all current drug targets (Fig. 3) (*25, 26*).

The Influence of Molecular Biology on Drug Discovery

Chemistry, pharmacology, microbiology, and biochemistry helped shape the course of drug discovery and bring it to a level where new drugs are no longer generated solely by the imagination of chemists but result from a dialogue between biologists and chemists. This dialogue, centered on biochemical mechanisms of action, stems from the understanding of biological structure and function and gives rise to the creation of novel chemical structures. Molecular biology has exerted a profound influence on drug discovery, allowing the concept of genetic information to be dealt with in very concrete biochemical and chemical terms. At first, however, the influence of molecular biology appeared to be restricted to cloning and expressing genes that encode therapeutically useful proteins.

The total number of protein drugs, largely recombinant proteins and monoclonal antibodies that are often referred to as "biotech" drugs, currently amounts to 59 (*27*). Recombinant proteins have become important additions to the therapeutic armamentarium. After some delay, monoclonal antibodies, a specialized form of recombinant protein, arrived on the scene (*28*). In 1998, biotech products, most of them recombinant proteins and monoclonal antibodies, accounted for 15 out of 57 drugs introduced worldwide (26.3%). Among the 50 leading research-based companies, the corresponding figures were 7 out of 40 (17.5%) (*29*). The human genome contains 12,000 to 14,000 genes encoding secreted proteins. Even if only 1 or 2% of these proteins were to qualify as drugs, there would be between 120 and 280 novel therapeutic proteins, most of which still remain to be discovered and developed. This figure

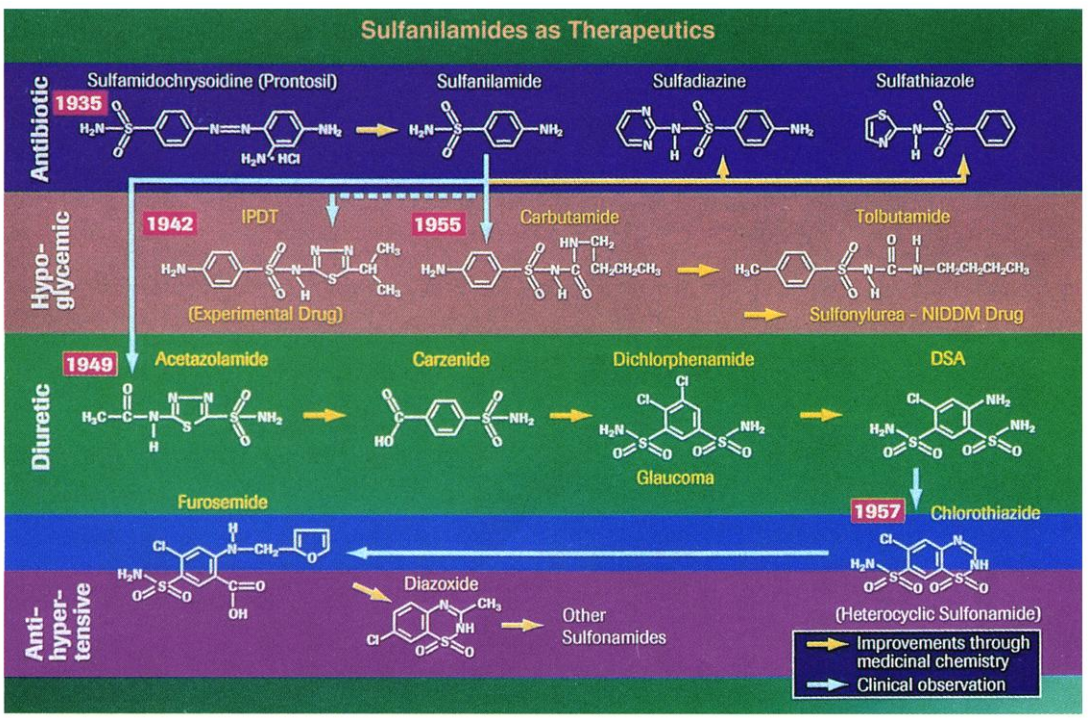

Fig. 2. Sons of sulfanilamide. A schematic representation of drugs that originated from sulfanilamide. A single chemical motif gave rise to antibiotics, hypoglycemic agents, diuretics, and antihypertensive drugs.

does not, of course, include monoclonal antibodies, which today are produced in three different ways. They can be generated as mouse antibodies that are subsequently "humanized" by recombination with human antibody genes (*30–32*). Alternatively, and perhaps preferably, human antibodies can be directly raised in nude mice grafted with human immune cells (*33*). Finally, antibodies can also be made by phage display techniques. Huge libraries of human antibody genes in phages allow the production and subsequent optimization of a wide array of antibodies (*34–36*). In fact, antibodies may be more attractive from a therapeutic point of view than recombinant cytokines or chemokines because they can be targeted to very specific structures with almost "surgical" precision, whereas many cytokines have evolved as proteins with redundant, or pleiotropic, actions. Given the therapeutic success of the interferons, tissue plasminogen activator, erythropoietin, granulocyte-macrophage colony-stimulating factor, Herceptin, Rituximab, and many others, protein drugs are likely to make many additional therapeutic contributions.

However, the main promise of molecular biology for drug discovery lies in the potential to understand disease processes at the molecular (genetic) level and to determine the optimal molecular targets for drug intervention. As mentioned, current drug therapy is based on less than 500 molecular targets. Early work by the British geneticist Sewall Wright indicated that the number of genes contributing to multifactorial traits may not be very high (*37*). Current estimates based on Wright's work and more recent studies on hypertension and diabetes mellitus in inbred strains of rats suggest this number to be between 5 and 10 (*38, 39*). If we count the nosological entities that can be classified as multifactorial diseases and include only those that pose a major medical problem in the industrial world, on account of their prevalence and severity, we arrive at a figure between 100 and 150. [In fact, the repertoire of diseases targeted by large pharmaceutical companies at the end of the 20th century is considerably smaller (*40*).] If one accepts the larger figure of 10 as representing the correct average of the number of the genes that contribute to a multifactorial disease, then the total number of "disease" genes relevant from an industrial point of view may be 1000. Not every "disease gene" may in itself be a feasible target. However, its function will likely be linked to that of other proteins in physiological or pathophysiological circuits. Assuming that the number of such "linked" proteins that constitute suitable targets for drug intervention is between 5 and 10 per disease gene, we concluded that the number of potential drug targets may lie between 5,000 and 10,000 (*25*). In other words, there are at least 10 times as many molecular targets that can be exploited for future drug therapy than are being used today.

Target Identification and Validation

The advent of genomic sciences, rapid DNA sequencing, combinatorial chemistry, cell-based assays, and automated high-throughput screening (HTS) has led to a "new" concept of drug discovery. In this new concept, the critical discourse between chemists and biologists and the quality of scientific reasoning are sometimes replaced by the magic of large numbers. Large numbers of hypothetical targets are incorporated into in vitro or cell-based assays and exposed to large numbers of compounds representing numerous variations on a few chemical themes or, more recently, fewer variations on a greater number of themes in high-throughput configurations. It was hoped that this experimental design would be suitable to identify many substances, which can modify the targets in question. Many such "hits"—compounds that elicit a positive response in a particular assay—would then give rise to more leads, i.e., compounds that continue to show the initial positive response in more complex models (cells, animals) in a dose-dependent manner. Eventually, the number of compounds also would increase. Based on my experience at Hoffmann–La Roche and information provided from other sources (*41*), the number of data points generated by large screening programs at a pharmaceutical company amounted to roughly 200,000 at the beginning of the 1990s. Data points are screening results describing the effect of one compound at one concentration in a particular test. This figure rose to 5 to 6 million at the middle of the decade and is presently approaching or even passing the 50-million mark. So far, this several hundredfold increase in the number of raw data has not yet resulted in a commensurate increase in research productivity. As measured by the number of new compounds entering the market place, the top 50 companies of the pharmaceutical industry collectively have not improved their productivity during the 1990s (*42, 43*). There is of course the possibility that the average number of compounds committed to development has increased in the last few years. In this case, we would see a greater number of original new chemical entities entering the world markets within the next decade.

It is difficult to judge the "success" of the new paradigm of drug discovery on the basis of published data. Some pharmaceutical companies have acknowledged that HTS has resulted in a large number of "hits" (*44*)—an impression that is corroborated by a number of recent publications (Fig. 4) (*45–47*). However, some industry leaders have expressed disappointment that very few leads and development compounds, if any, can be credited to the new drug discovery paradigm (*44*). On the one hand, the meager results may be due to the relatively short period during which the new drug discovery paradigm has been seriously implemented. On the other hand, the lack of meaningful results may indicate that the system has not yet been optimized. What might have gone wrong during this initial phase?

Two reasons come to mind, one relating to biology, the other to chemistry. The fact that "targets" can be hypothetically associated with certain diseases—e.g., leptin or the leptin receptor with obesity (*48*), the low density lipoprotein receptor with atherosclerosis (*49*), complement receptors with inflammation (*50*), or interleukin-4 (IL-4) with allergic diseases (*51*)—does not mean that they represent suitable intervention levels for new drugs. They need validation, a stepwise process in which the role of a hypothetical target in relation to a disease phenotype is understood. There are several levels of target validation: The "credibility" of a target depends on the complexity and disease relevance of the model in which the target is tested. Reproducible and dose-dependent

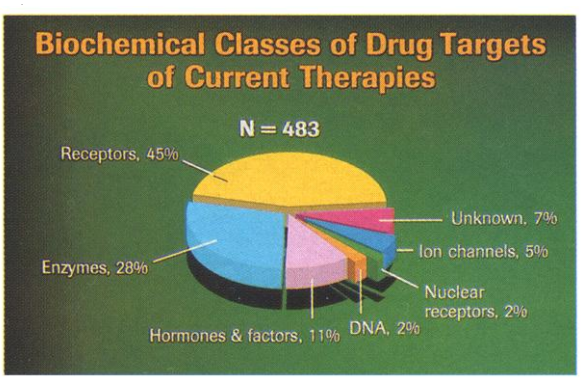

Fig. 3. Molecular targets of drug therapy. Classification according to biochemical criteria. Based on a modern standard work of pharmacology, the molecular targets of all known drugs that have been characterized as safe and effective have been collected and listed according to their biochemical nature (*62*).

phenotypic changes in isolated cells elicited by a compound that modifies the target constitute the lowest level of validation. If phenotypic changes can reproducibly be induced in an animal model that represents at least some disease-relevant mechanisms, the degree of validation is higher. The credibility of a target grows with the number of relevant animal models in which target modifications lead to the desired phenotypic changes. Of course, the highest degree of validation lies in demonstrating that the modification of a target, e.g., the blocking of a receptor or the inhibition of an enzyme, leads to the reversal of disease symptoms in a clinical situation. Screening tests are questions directed at a compound: What is the efficacy, potency, or toxicity of a substance in a given situation? Inappropriate questions will lead to meaningless answers, and this is what usually happens in screening programs that are based on nonvalidated or poorly validated targets.

The genetic definition and functional analysis of several thousand drug targets will inevitably include the description of the various alleles of a given target found in different human populations. These isogenes are the most likely cause of variations in drug responses. There are a few striking examples in which polymorphisms in target genes (the β_2 adrenoceptor for albuterol or the CETP protein for pravastatin) influence drug responses (*52, 53*). Therefore, the selection of drug targets will also have to rely on epidemiological data. Obviously, economic factors will compel the use of such data not only as keys to "individualized therapy" but—perhaps more importantly—to identify those targets that allow for the broadest coverage in the treatment of a particular disease.

Combinatorial Chemistry and High-Throughput Screening

Most recent attempts toward the design of combinatorial libraries have been driven by the intent to generate a high degree of structural diversity within a library. It is, however, by no means certain to what extent molecular diversity as viewed by chemists and as calculated by structural descriptors resembles diversity as "seen" by a biological target molecule. Dixon and Villar (*54*) have shown that a protein can bind a set of structurally diverse molecules with very similar affinities in the nanomolar range, whereas a number of analogs closely related to one of the good binders display only weak affinities (>2.5 mM). The design and sampling of compound libraries should, therefore, be guided not only by structural descriptors, but also by descriptors of biological activity. This can be achieved by screening all compounds in a library against a panel of functionally dissimilar proteins and determining the binding affinity of each compound for each protein. The set of binding affinities for a given compound is termed its affinity fingerprint. The similarity of affinity fingerprints has been shown to correlate with the biological activities of druglike substances (*55*).

Improvements in structural biology, more specifically in nuclear magnetic resonance spectroscopy, robotic crystallization, cryogenic crystal handling, x-ray crystallography, and high-speed computing have greatly facilitated protein structure determination (*56, 57*). Indeed, technological advances have propelled structural biology to a position where the elucidation of the three-dimensional structure of medically relevant proteins on a large scale appears possible. The feasibility of this concept of "structural genomics" is supported by the fact that the universe of compact globular protein folds is quite limited. It may not exceed 5000 distinct spatial arrangements of peptide chains (*58*).

Protein-protein interactions, e.g., the binding of immunoglobulin E, vascular endothelial growth factor, or IL-2 or IL-5 to their respective receptors, may represent very attractive drug targets in the case of allergies, cancer, autoimmune diseases, or asthma. Traditional small-molecule drug discovery has largely failed with these targets. However, protein-protein interfaces have "hot spots," small regions that are critical to binding and that have the same size as small molecules. The targeting of these hot spots by small molecules may turn out to be capable of disrupting undesirable protein-protein interactions (*59–61*).

Eventually, the structure of well-validated old and new targets should be able to guide the chemical effort directed at new drugs. The novel approaches mentioned above all aim at this objective.

The Institutional Basis of Drug Research Will Change

History does not repeat itself—at least not in a simple and linear way. Nevertheless, there are parallels between the drug research in 1900 and in the year 2000. One hundred years ago, an alliance between chemistry and pharmacology was created that needed much time to develop but turned out to be highly successful. The pharmaceutical industry provided a home for this alliance. Today, many additional forces are at work. As with chemistry and pharmacology during much of the 20th century, genomics, bioinformatics, and structural genomics will generate unprecedented results in the new century. Drug discovery has become so complex that it cannot be contained within the confines of the pharmaceutical industry. Discovery and, for that matter, drug development need a diversified and flexible industrial base. The emergence of the biotech industry as a "discovery" industry as well as the establishment of many contract research organizations show that free markets will be capable of generating the technical and institutional instruments that are needed to apply scientific advances to the solution of societal problems.

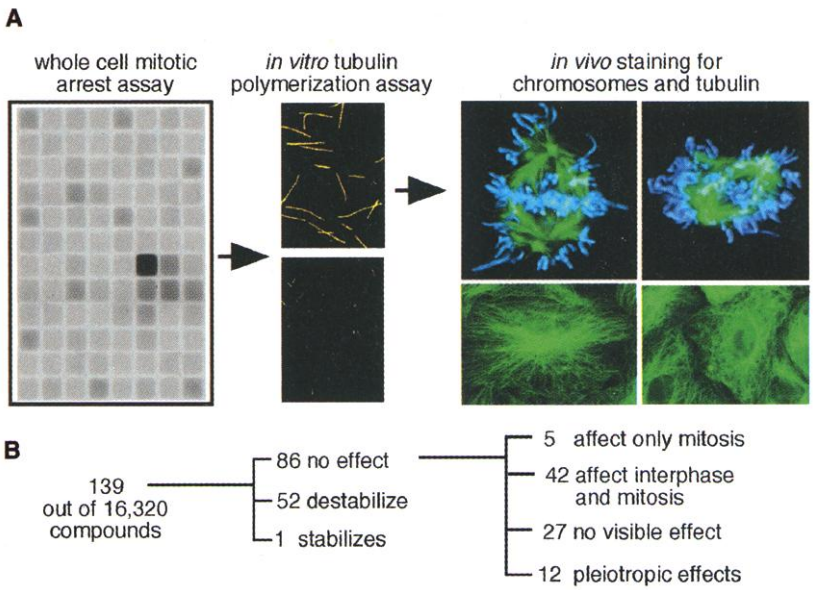

Fig. 4. Example for the identification of "hits" in a high-throughput screening assay that identified five small molecules affecting mitosis. **(A)** From a whole-cell immunodetection assay, 139 cell-permeable compounds were selected that caused increases in phosphonucleolin staining in A549 cells. After eliminating molecules that target pure tubulin, the effect of the antimitotic compounds on microtubules (green), actin (not shown), and chromatin (blue) distribution was imaged. Examples of the effects of two different small molecules on BS-C-1 cells in mitosis (upper) and in interphase (lower) are shown. **(B)** Summary of the screening results. Twelve antimitotic compounds tested on cells had pleiotropic effects and were not evaluated further. [From (*45*)]

References and Notes

1. J. Drews, in *Quest of Tomorrow's Medicines* (Springer-Verlag, New York, 1999), pp. 51–68.
2. F. J. Moore, *A History of Chemistry* (McGraw-Hill, New York, 1918), pp. 212–220.
3. A. M. Roberts, *Serendipity* (Wiley, New York, 1989), pp. 66–74.
4. P. Ehrlich, in *Gesammelte Arbeiten*, F. Himmelweit, Ed. (Springer-Verlag, Berlin, 1957).
5. F. W. Sertürner, *Gilbert's Annalen d. Physik* **25**, 56 (1817).
6. W. Sneader, *Drug Discovery* (Wiley, New York, 1985).
7. E. Farber, *The Evolution of Chemistry; a History of Its Ideas, Methods, and Materials*, L. Fiebiger, Ed. (Ronald Press, New York, 1952), pp. 173–188.
8. J. Koch-Weser and P. J. Schechter, *Life Sci.* **22**, 1361 (1978).
9. H. C. Peyer, *Roche-Geschichte einer Unternehmung, 1896–1996* (Roche, Basel, 1996).
10. E. Chain *et al.*, *Lancet* **i**, 226 (1940).
11. A. Fleming, *Br. J. Exp. Pathol.* **10**, 226 (1940).
12. H. R. Taylor, *Int. Ophthalmol.* **2**, 83 (1987).
13. A. W. Alberts, *Am. J. Cardiol.* **15**, 10J (1988).
14. D. J. G. White, Ed., *Proceedings of an International Conference on Cyclosporin A* (Elsevier, Amsterdam, 1982), pp. 5–19.
15. H. Tanaka *et al.*, *Yakugaku Zasshi* **8**, 542 (1997).
16. N. U. Meldrum and F. J. Roughton, *J. Physiol.* **80**, 113 (1933).
17. W. B. Schwartz, *N. Engl. J. Med.* **240**, 173 (1949).
18. R. A. Maxwell and S. B. Eckhardt, *Drug Discovery: A Casebook and Analysis* (Humana, Clifton, NJ, 1990).
19. J. N. Langley, *J. Physiol. (London)* **33**, 374 (1905)
20. R. P. Ahlquist, *Am. J. Physiol.* **1**, 100 (1948).
21. J. W. Black, in *Drug Responses in Man* (CIBA Foundation Symposium, Basel, Switzerland, 1967), pp. 111–117.
22. Z. Bacq, in *Discoveries in Pharmacology*, M. J. Parham and J. Braunfels, Eds. (Elsevier, Amsterdam, 1983), vol.1, pp. 49–101.
23. W. Hunkeler *et al.*, *Nature* **290**, 514 (1981).
24. C. Buske *et al.*, *Eur. J. Cancer* **4**, 549 (1999).
25. J. Drews, in *Human Disease—from Genetic Causes to Biochemical Effects*, J. Drews and St. Ryser, Eds. (Blackwell, Berlin, 1997), pp. 5–9.
26. J. Drews and St. Ryser, *Classic Drug Targets. Special Pullout [Nature Biotechnol.* **15** (1997)].
27. I. Zipkin and A. Michael, *BioCentury* **7**, 1 (1999).
28. M. S. Cragg *et al.*, *Curr. Opin. Immunol.* **5**, 541 (1999).
29. J. Drews, *Drug Discovery Today* **3**, 491 (1998).
30. G. Köhler and C. Milstein, *Nature* **256**, 495 (1975).
31. G. Winter and W. J. Harris, *Trends Pharmacol. Sci.* **14**, 139 (1993).
32. C. Queen *et al.*, *Proc. Natl. Acad. Sci U.S.A.* **86**, 10029 (1989).
33. M. Bruggemann and M. S. Neuberger, *Immunol. Today* **8**, 391 (1996).
34. W. D. Huse *et al.*, *Science* **246**, 1275 (1989).
35. H. R. Hoogenboom *et al.*, *Immunotechnology* **4**, 1 (1998).
36. D. J. Rodi and L. Makowski, *Curr. Opin. Biotechnol.* **10**, 87 (1999)
37. S. Wright, *Evolution and the Genetics of Populations: Genetic and Biometric Foundations* (Univ. of Chicago Press, Chicago, IL, 1984).
38. P. J. Guillauseau, D. Tielmans, M. Virally-Monod, M. Assayag, *Diabetes Metab.* **23** (Suppl. 2), 14 (1997).
39. R. A. Shimkets and R. P. Lifton, *Curr. Opin. Nephrol. Hypertens.* **2**, 162(1996).
40. J. Drews and St. Ryser, *Drug Discovery Today* **2**, 365 (1997).
41. M. Sills, personal communication.
42. J. Drews and St. Ryser, *Drug Inf. J.* **30**, 97 (1996).
43. J. Drews, *Drug Discovery Today* **3**, 491 (1998).
44. R. Lahana, *Drug Discovery Today* **4**, 447 (1999).
45. T. U. Mayer *et al.*, *Science* **286**, 971 (1999).
46. B. A. Foster *et al.*, *Science* **286**, 2507 (1999).
47. J. Aramburu *et al.*, *Science* **285**, 2129 (1999).
48. S. M. Haffner, L. A. Mykkanen, C. C. Gonzalez, M. P. Stern, *Int. J. Obes. Rel. Metab. Disord.* **7**, 695 (1998).
49. M. M. Hussain, D. K. Strickland, A. Bakillah, *Annu. Rev. Nutr.* **19**, 141 (1999).
50. E. Sakiniene, B. Heyman, A. Tarkowski, *Scand. J. Immunol.* **3**, 250 (1999).
51. L. Chouchane *et al.*, *Int. Arch. Allergy Immunol.* **120**, 50 (1999).
52. St. Ligget, in preparation.
53. J. A. Kuivenhoven *et al.*, *N. Engl. J. Med.* **338**, 86 (1998).
54. St. L. Dixon and H. O. Villar, *J. Chem. Inf. Comp. Sci.* **38**, 1192 (1998).
55. L. M. Kauvar *et al.*, *Chem. Biol.* **2**, 107 (1995).
56. St. K. Burley *et al.*, *Nature Genet.* **23**, 151 (1999).
57. P. F. Lindley, *Acta Crystallogr. D.* **55**, 1654 (1999).
58. S. E. Brenner, C. Chothia, T. Hubbard, *Curr. Opin. Struct. Biol.* **7**, 369 (1997).
59. J. A. Wells *et al.*, *Recent Prog. Hormone Res.* **48**, 253 (1993).
60. K. D. Stigers, M. J. Soth, J. S. Nowick, *Curr. Opin. Chem. Biol.* **6**, 714 (1999).
61. T. Clackson and J. A. Wells, *Science* **267**, 383 (1995).
62. L. S. Goodman *et al.*, Eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (McGraw-Hill, New York, ed. 9, 1996).

63. I am indebted to J. Curtis for doing the illustrations.

REVIEW

Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery

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Modern drug discovery often involves screening small molecules for their ability to bind to a preselected protein target. Target-oriented syntheses of these small molecules, individually or as collections (focused libraries), can be planned effectively with retrosynthetic analysis. Drug discovery can also involve screening small molecules for their ability to modulate a biological pathway in cells or organisms, without regard for any particular protein target. This process is likely to benefit in the future from an evolving forward analysis of synthetic pathways, used in diversity-oriented synthesis, that leads to structurally complex and diverse small molecules. One goal of diversity-oriented syntheses is to synthesize efficiently a collection of small molecules capable of perturbing any disease-related biological pathway, leading eventually to the identification of therapeutic protein targets capable of being modulated by small molecules. Several synthetic planning principles for diversity-oriented synthesis and their role in the drug discovery process are presented in this review.

Modern methods for stereoselective organic synthesis have increased the efficiency with which small molecules can be prepared. These compounds include new drugs and drug candidates and reagents used to explore biological processes. However, it is a nearly four-decade-old method for purifying reaction products that is currently having the greatest impact on organic synthesis (*1*). Solid phase organic synthesis (*2–7*), adapted from the original solid phase peptide synthesis (*1*), promises to increase dramatically the diversity and number of small molecules available for medical and biological applications.

The evolution of stereoselective organic synthesis from the solution (*8*) to the solid (*2–7*, *9–11*) phase has created strategic challenges for organic chemists because it has provided the means to synthesize not only single target compounds or collections of related targets but also collections of structurally diverse compounds. Target-oriented syntheses are used in drug discovery efforts involving preselected protein targets, whereas diversity-oriented syntheses are used in efforts to identify simultaneously therapeutic protein targets and their small-molecule regulators. Target-oriented synthesis has benefited from a powerful planning algorithm named retrosynthetic analysis (*8*); a comparable algorithm for diversity-oriented synthesis is only now beginning to be developed. Planning diversity-oriented syntheses will become increasingly important for organic chemists as methods to screen large collections of small molecules become more effective and routine.

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Target-Oriented Synthesis and Retrosynthetic Analysis

Target-oriented synthesis has a long history in organic chemistry. In universities, the targets are often natural products, whereas in pharmaceutical companies, the targets are drugs or libraries of drug candidates. Beginning in the mid-1960s, a systematic method