Integrating research and development: the emergence of rational drug design in the pharmaceutical industry

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Abstract

Rational drug design is a method for developing new pharmaceuticals that typically involves the elucidation of fundamental physiological mechanisms. It thus combines the quest for a scientific understanding of natural phenomena with the design of useful technology and hence integrates epistemic and practical aims of research and development. Case studies of the rational design of the cardiovascular drugs propranolol, captopril and losartan provide insights into characteristics and conditions of this integration. Rational drug design became possible in the 1950s when theoretical knowledge of drug-target interaction and experimental drug testing could interlock in cycles of mutual advancement. The integration does not, however, diminish the importance of basic research for pharmaceutical development. Rather, it can be shown that still in the 1990s, linear processes of innovation and the close combination of practical and epistemic work were interdependent.

1. Introduction

Pharmacologists typically distinguish two approaches to the development of pharmaceuticals, one termed ‘empirical’, the other ‘rational’, ‘deductive’ or ‘a priori’. The opposition is not, however, about experience or reason being the ultimate source of knowledge, as the terminology could be taken to suggest. Pharmacology, following either of the two methods, is a discipline thoroughly based on experimentation and empirical data. Instead, the distinction is about the role of theoretical understanding in pharmaceutical development. The empirical approach proceeds by testing large numbers of random substances for certain desirable effects in biological test systems or model organisms. Typically, drugs can emerge from this method without their target (receptor, enzyme etc.), their mode of action or the mechanism of disease being understood. In contrast to this, the rational method usually involves a theoretical

understanding of which protein is targeted by the drug, how the drug acts on it, and which mechanisms lead to the desired therapeutic effects.

The rational method, often called 'rational drug design', has gradually become more popular in drug development since its first instances in the 1950s. Triggered by a number of impressive successes such as the development of the cholesterol-lowering drug lovastatin or the antihypertensive drug captopril (discussed below) in the 1970s, rational drug design has acquired status as professed methodological ideal in the 1980s (cp. Gambardella, 1995, ch. 2). This is also evidenced by the awarding of the Nobel prize for medicine or physiology of 1988 to the pharmacologists Sir James Black, Gertrude B. Elion and George H. Hitchings, three pioneers of rational drug design (Nobel Assembly 1988).[1]

In this paper, three case studies of the rational design of cardiovascular drugs – propranolol, captopril, and losartan – will be presented. Their development histories range from the beginnings of rational drug design in the late 1950s to the mid 1990s. Each of these drugs has been developed in the pharmaceutical industry and has introduced a new pharmacological principle into medicine. Up to the present, they (or their direct descendants) are important therapeutics for various cardiovascular conditions. They are, for instance, the prototype drugs for three of the five classes of therapeutics that are most commonly used in the treatment of hypertension (Brown, Quirk & Kirkpatrick 2003). Beyond this impact on clinical practice, the development of the drugs also included research that contributed considerably to the scientific understanding of drug action and of physiological and pathological mechanisms. The studied cases thus closely combined two aims of research and development: on the one hand, the practical aim of developing techniques and tools for the practically useful control of and intervention into a system; and on the other hand the epistemic aim of gaining a theoretical understanding of fundamental features of the natural (or artefactual) world. An analysis of the three cases can therefore test a claim that has been put forward by many authors: that integrated practical and epistemic projects are of growing importance for the overall relationship of science and technology.[2]

In order to make more precise what is meant by 'practical' in this claim, epistemic and non-epistemic domains of practice have to be kept distinct. On the one hand, scientific research of course includes a practice (as opposed to theory) in that, for example, experiments

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[1] Since then, empirical methods have regained ground to a certain extent, in particular due to the rise of combinatorial chemistry and high-throughput screening. However, these methods are often not used as alternatives to rational approaches, but in combination with rational methods such as structure determination by nuclear magnetic resonance and in silicio design. See, e.g., Good, Krystek & Mason (2000).

[2] Previous studies of rational drug design have mainly explored the changes in the management and organization of corporate pharmaceutical research. Important findings include that the methodological reorientation led to a scientification of corporate research, with corporate researchers being given more freedom to participate in the scientific debate and incentives to publish in peer-reviewed journals being set. Conversely, the influence of industrial needs on academic research has increased, and the research is found to be organized more and more often in complex networks that involve large and small companies and public research institutions (Gambardella 1995, Cockburn, Henderson & Stern 1999, Walsh 1998).

are conducted or research technologies developed. However, this practice can be directed entirely or largely at epistemic aims. As such, it can well be (and regularly is) part of basic research, which I roughly understand as research that is directly and primarily targeted at the fundamental scientific understanding of some area.[3] On the other hand, technological practices are often concerned with non-epistemic problems, and the development of novel technologies then aims at devices or procedures that are useful for the solution of these problems. The main field of practical application of pharmacological research in this second sense is of course medicine. The main non-epistemic aims of pharmacological research are therefore the alleviation and the cure of diseases (or the economic profits to be drawn from therapeutic usefulness). The claim about the increasing integration of epistemic and practical work refers to practical utility in this second sense that stands in contrast to epistemic purposes.

With respect to pharmacological research and development, a number of options for the relationship of practical and epistemic projects offer themselves. To start with, there are two basic ways how to conceive of the practical and epistemic aims as being pursued separately rather than in an integrated manner. Firstly, as in the theoretically uninformed pharmacological empiricism, development can aim at the empirical establishment of useful causal connections between possible drugs and desirable effects without addressing the precise mechanisms that account for the causal dependency. Even though the development of new drugs can disclose phenomena which are also epistemically important, the elucidation of the underlying mechanisms would be left to subsequent research. Secondly, pharmacology could instantiate the familiar linear model of innovation. In this case, there would be a successive or top-down relationship between epistemic and practical work. Research in physiology, biochemistry, pharmacology or pathology would come first and provide fundamental knowledge of physiological and pathological mechanisms. Only subsequently, this knowledge is applied and guides the design of drugs. Even though the practical and the epistemic project can be *linked* according to both models, they are not *combined* in one enterprise, but succeed one another both temporally and logically.

The linear model of innovation has found many critics. They have in general objected that many projects in science and technology have *both* epistemic and practical aims or implications.[4] Donald E. Stokes has argued that a type of research that he terms “use-inspired basic research” has been prominent at least since the end of the 19th century. He finds in Pasteur a paradigmatic researcher of this type. Such researchers choose their subjects in direct response to practical needs that they aim to solve. However, they also strive for a fundamental understanding of the phenomena (Stokes 1997). Other authors make out more recent

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[3] See section 5.2 for a detailed discussion of this notion of basic research.

[4] See, e.g., Rosenberg 1991, Etzkowitz & Leydesdorff 1998 and Kitcher 2001. For claims of an increasing integration particularly of *pharmacological* research and development see Maxwell 1984 and (with special attention to the role of clinical practice) Vos 1991 and Keating & Cambrosio 2003.

transformations in the combination of epistemic and practical projects. Philippe Larédo and Philippe Mustar, for instance, stress organizational characteristics of what they call "basic technological research". They observe the formation of "techno-economic networks" that include academic and industrial researchers, but also public and financial institutions, and which are engaged both in the development of new products and the gain of scientific knowledge (Larédo & Mustar 1996; cp. Walsh 1998). Michael Gibbons and co-authors capture further novel features of research in the context of the development of specific applications under the heading of "mode 2 knowledge production". According to them, such integrated activities often take place in a framework that includes the resources from various disciplines and combines them to a new capability for problem solving. In addition, they see a transformation in the procedures for validating scientific knowledge, since the users of this knowledge (in politics, economy, or society) get included in its establishment (Gibbons, Limoges, Nowotny et al. 1994).

The aim of this paper is to contribute in two major respects to the understanding of the integrated model of innovation. Firstly, it intends to elucidate epistemic characteristics and conditions of combined practical and epistemic projects. The investigation of the three consecutive cases shows that the emergence of the integrated method of rational drug design is closely connected to specific progress both in theory and experimental techniques. The theoretical modeling of the chemical interactions between drugs and targets together with a mechanistic interpretation of experimental test systems enabled the close combination of theory and practice in cycles of mutual advancement.

Secondly, the paper aims to improve the broader understanding of the relation between research and development by elucidating the role of basic research in rational drug design. It will turn out that the integrated epistemic and practical work presupposes input from basic research, while basic results gain practical importance only through additional investigations within the contexts of development. Contrary to the initial impression, the linear and the integrated modes of innovation do therefore not exclude each other. Instead, rational drug design shows how the operation of each can be dependent on the other.

2. Theories of drug action for pharmaceutical development: propranolol (1958-1964)

2.1 The rational design of propranolol

Propranolol, the first beta-blocker, was developed by a group around James Black at the U.K. firm Imperial Chemical Industries between 1958 an 1964. The rationale behind the drug development and the main steps leading to propranolol seem straightforward. Propranolol was designed to inhibit the action of adrenaline (also called epinephrine) on the β-adrenoreceptor. Activation of the β-receptor leads, among other things, to an increased pulse rate, which in turn increases the oxygen consumption of the heart. Since angina pectoris and myocardial infarction can be caused by a lack of oxygen of the myocardial muscle, their incidence can be

lowered by a substance that blocks the action of adrenaline on the β-receptor, i.e. by a β-receptor antagonist.

Propranolol was derived from adrenaline in a number of steps. The chemical structure and various cardiovascular effects of adrenaline had been known and studied since the early 20th century. When Black started his project on β-receptor antagonists, it was known that a close analogue to adrenaline, isoprenaline, selectively stimulated the β-receptor, but not the other known adrenaline receptor, the α-receptor. The structural change from adrenaline to isoprenaline – see fig. 1 – could therefore be taken to bring about selectivity. The task remained to find a modification of this molecule that turned the activation of the receptor into its inhibition, i.e. agonism into antagonism.

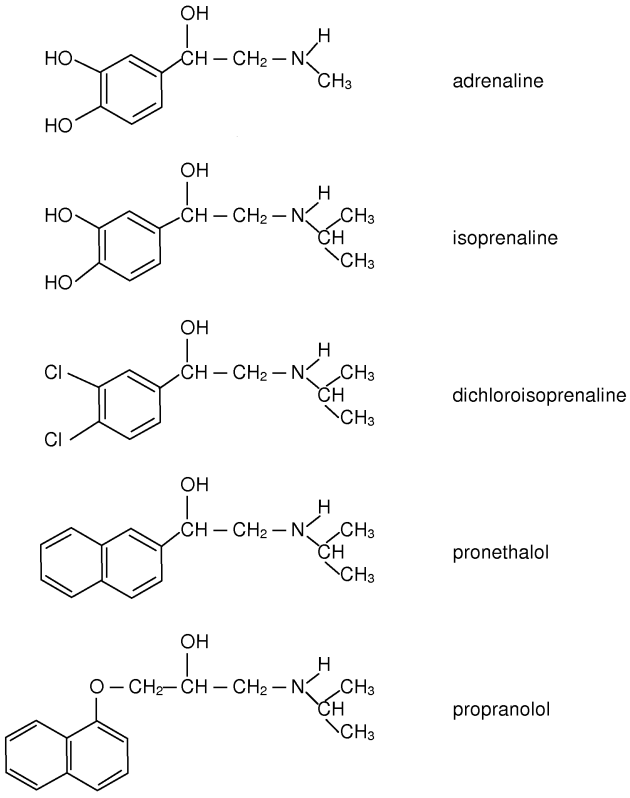

Fig. 1: Chemical structures of adrenaline and derived substances (after Black 1989 and Maxwell & Eckhardt, 1990, p. 8).

After modifying isoprenaline without success, Black's group read a report by C. E. Powell and I. H. Slater from the U.S. company Eli Lilly about another analogue, dichloroisoprenaline (DCI) (Powell & Slater 1958). DCI was classified by Neil C. Moran and Marjorie E. Perkins (Emory University, Atlanta) as a β-receptor antagonist (Moran & Perkins 1958, Shanks 1984). Black's group found, however, that DCI blocked the stimulative action of isoprenaline only in some tissues, while it showed agonist action in others. DCI thus turned out to be a weak or partial agonist. In the light of this classification, the modification from isoprenaline to DCI accounted for a weakening of the agonist activity. Since an antagonist should show no agonist activity at all, it seemed natural to extrapolate the modification. In chemical terms, the

substitution of the hydroxy-groups of isoprenaline by chlorine atoms meant that the size of the side-groups increased, while now being conformationally fixed due to π-bonding. The medicinal chemist of the group, John S. Stephenson, therefore proposed to "make the naphtyl-analogue of isoprenaline" (Black, 1989, p. 488), i.e. to substitute the chlorine by a fused benzene ring. This would further increase the size while preserving the conformational stability. In addition, it would substitute a polar by an unpolar group. The result was pronethalol.

This step from DCI to pronethalol did not follow the same method of trial and error as the previous variations on the known substances. Instead, specific hypotheses about the chemical properties responsible for the drug-target interaction stood behind its synthesis and nourished the researchers' expectations that the extrapolation in size and structure would further weaken the substance. Pronethalol fulfilled these expectations and proved to be a β-receptor antagonist without any agonist activity. It reduced the pulse rate in animal models and in healthy humans and allowed a patient suffering from angina of effort to do more work before pain started (Black, 1989, p. 488).

Still, pronethalol was not yet propranolol. Even though pronethalol entered into clinical trials in late 1961, it was withdrawn later. Pronethalol had side effects on the central nervous system (such as nausea) and displayed local anesthetic action. In addition, it was found to cause thymic tumors in mice. A much enlarged chemical group under the direction of A. F. Crowther was set up to find a safer and more active derivative of pronethalol. Propranolol is the result of this optimization and was first marketed in the U.K. in July 1965. It soon proved to be effective not only in patients with angina pectoris and myocardial infarction, but also with hypertension and irregularities of heart beat (Weatherall, 1990, p. 241; Vos, 1991, pp. 85ff).

2.2 Rationality, experiments and hypotheses

The steps that led to propranolol could give the impression that the development was largely a matter of deriving the structure of the most effective substance from existing physiological and chemical knowledge. In this sense, it has been claimed that the development of propranolol formed an important step in the introduction of the rational method of drug discovery, which is based on the understanding of physiological and biochemical processes (Nobel Assembly 1988). This certainly captures an important aspect of the development process, if not the whole of it. While the use of physiological and chemical knowledge in drug development as such is nothing which is new to the 1950s, they witness a new quality of interaction between scientific knowledge and drug development. This is illustrated by contrasting propranolol with the development of the sulfonamides in the 1930s.

The first sulfonamide that was widely used against streptococcal infection, sulfachrysoidin, was found by Gerhard Domagk, Fritz Mietzsch and Joseph Klarer at Bayer in Germany in 1932. A rich array of biological and chemical considerations formed the background of its

development, in particular on the classification of bacteria, on the causes of their pathogenicity and about the modes of systemic action. In addition, a wealth of experience with the antimicrobial action of dyes and their derivatives was used in the development (Lesch 1993). Still, the physiological and chemical knowledge was not specific enough to give direct rational guidance on which chemical structures would act against streptococci. Instead, random variations of known substances were empirically tested in vitro and in infected mice, while the range of chemical variation was successively narrowed down as activity was found. The mode of action of sulfachrysoidin was elucidated only in follow-up research. Jacques Tréfouel and colleagues at the Institut Pasteur of Paris showed in 1937 that sulfachrysoidin acts through its simpler metabolite, sulfanilamide, while Donald Woods at the Middlesex Hospital in London found in 1940 that sulfanilamide is a metabolic antagonist to the chemically related substance p-aminobenzoic acid that is essential for bacterial growth (Lesch 1993; Weatherall, 1990, pp. 150ff).

The comparison of this case with propranolol exhibits the crucial difference between empirical and rational drug development. For rational design, one has to be able to attribute expected physiological effects to drug candidates on the basis of their chemical structure. For such a prediction, specific knowledge of the pathologically relevant physiological mechanism and the mode of pharmacological intervention into this mechanism is required. With propranolol, not only the pathological mechanism (from adrenaline over its receptors to oxygen consumption and angina pectoris), but also the pharmacological modes of intervention for a number of substances were already known. This made the extrapolation to pronethalol possible. Comparable mechanistic knowledge on the action and the underlying mechanism emerged for the sulfonamides only after the drugs had been identified.

However, it would be wrong to assume that with its ‘rationalization’, drug discovery became a matter of simply applying existing chemical and biological knowledge. For one, experimental methods for testing the pharmacological activity of the substances played a crucial role in the development. When early in 1959 Black’s group first read of Moran and Perkin’s classification of DCI as a β-receptor antagonist, the substance was immediately tested with the bioassay the group had started with, the classical Langendorff preparation. It consisted of an isolated, spontaneously beating guinea pig heart. The amplitudes of the contractions were measured, which, because of the inertia of the mechanical transducer, were in fact a combination both of the rate and the force of the contractions. However, DCI was as stimulative as isoprenaline in this preparation, and did not show any antagonist activity at all. The assessment of DCI was only reversed late in 1959, after a different preparation had been developed by the group, made of guinea pig papillary muscle. With this preparation, the contraction could be measured independently from the heart beating rate, and in this bioassay, DCI antagonized the stimulative action of isoprenaline. This led to the classification as a weak or partial agonist, crucial for the idea that an antagonist could be obtained by

extrapolating the modification that led to the weakening (Black, 1967, p. 112; Black, 1996, p. 2; Black, 1989, p. 487).

In addition, the theories and hypotheses assumed for the development were far from being established scientific knowledge. Rather, many of them were highly hypothetical or were contrary to dominant opinions. The standard theory of the action of adrenaline (and of the closely related noradrenaline) was not the two-receptor theory put forward by Raymond P. Ahlquist in 1948, but the sympathin-theory of Walter B. Cannon and Arturo Rosenblueth. According to them, adrenergic substances A combine with either of two postulated molecules E or I to form the complexes AE or AI. While AE causes all the excitatory reactions associated with adrenaline – in particular the increases in blood pressure and pulse rate –, AI brings about the inhibitory actions (Cannon & Rosenblueth 1937). Ahlquist, in contrast, postulated two receptors α and β. In comparison to Cannon and Rosenblueth, Ahlquist associated the receptors not with excitatory and inhibitory effects, but with different respective subsets of the known adrenergic effects. While the stimulation of the α-receptor among other things constricts the blood vessels and increases blood pressure, the β-receptor modulates the pulse rate. Ahlquist argued for this by comparing the potency of adrenaline and close analogues to bring about these effects. He showed that if the effects are divided into these two subgroups, consistent orderings of the substances according to their potency for all effects in the subgroups can be found (Ahlquist 1948). Ahlquist's theory can explain this finding if one assumes that the activities of the substances depend on the receptor types that mediate the respective effects. Nevertheless, the sympathin theory was widely accepted until in 1958, Moran and Perkins used Ahlquist's theory to explain why DCI specifically reversed increased pulse rate.[5] At that time, Black had already started with his search for a β-receptor antagonist (Moran & Perkins 1958, p. 235; cp. Black, 1976, p. 12).

Black's development program not only relied on a dissentient theory of adrenaline action, it also presupposed an at the time very recent and important deviation from the established general receptor theory. According to the dominant opinion, the agonist activity of a drug depends only on the proportion of the receptors that it occupies (Clark 1970 [1937]). Contesting this view, R. P. Stephenson proposed in 1956 that agonists act by virtue of two separable properties, namely affinity and efficacy.[6] The affinity determines the proportion of receptors that are occupied in any given concentration. The efficacy expresses the propensity of the drug to cause, if combined with the receptor, the receptor response. The overall activity of a substance is then a function of both its affinity and efficacy, and not only of its affinity,

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5 Black makes out the influence of the eminent British pharmacologist Henry H. Dale as one of the factors because of which Ahlquist's theory faced so cool a reception. Dale had discussed but rejected the idea that neurotransmission in the sympathetic nerve by adrenergic substances should be explained in terms of the interaction of neurotransmitters and receptors. According to Black's assessment, "Dale's attitude seems to have had a powerful effect in delaying the introduction of the idea of receptors into pharmacological teaching and his impact was still dominant when Ahlquist's paper appeared in 1948" (Black, 1976, p. 12).

6 A similar proposal had been made by E. J. Ariens (Ariens 1954).

as Clark had it. This modification allowed Stephenson to introduce the notion of a partial agonist. Such a substance can be active to some degree due to a certain low efficacy, but at the same time block the action of more effective agonists by its high affinity (Stephenson 1956). As seen above, the classification of DCI as a partial agonist is crucial for the hypothesis that a further weakening of the agonist action leads to an antagonist. In fact, without affinity and effectivity being separate properties, a chemical road from an agonist to a competitive antagonist would not be conceivable, since then, lowering the activity of the agonist would appear to necessarily bring along a decreased affinity, which would undermine the potency of the substance to block the receptors. Only if the two properties are distinct can there be *some* chemical modifications that lead to more selective affinity while *different* modifications lower the effectivity. This opens the path for a stepwise transformation of a natural receptor agonist into a selective antagonist, as the one from adrenaline to pronethalol.[7]

The therapeutic hypothesis, finally – that angina pectoris can be treated by lowering the oxygen consumption of the heart – was perhaps the most original contribution to the underlying theoretical assumptions. The idea seems to have arisen during studies in the Department of Physiology at the Veterinary School of Glasgow, which Black had joined in 1950. It was found that when animals were exposed to hyperbaric oxygen, thus improving the oxygen supply to the heart, cardial complications were improved. However, while most other pharmacological groups tried to increase the oxygen supply to the heart – in particular with substances that dilate the blood vessels –, Black instead looked for a substance that lowered the cardial oxygen consumption. This strategy coincided with the proposal of Wilhelm Raab that the release of adrenergic substances leads to an oxygen consumption of the heart that is much higher than required by the cardiac work alone (Raab 1953). Again, until the first administration of pronethalol to a patient, this therapeutic hypothesis, even though based on a number of observations, was very much that: a hypothesis (Black 1989, Stapleton 1997, Vos, 1991, p. 82).

Only the actual success of pronethalol and propranolol provided empirical support for the whole sample of presuppositions. Both Ahlquist's two-receptor theory (with the subsequent distinction of further receptor subtypes) and Stephenson's theory and terminology became established pharmacological knowledge (though their final acceptance was based on many additional findings). Black, changing his employer and moving to Smith, Kline & French, used the developmental strategy that the theories suggest – to turn a natural ligand of a receptor into an antagonist – once more successfully in the development of the first histamine H_2 receptor antagonist, cimetidine, a drug used against peptic ulcers (Maxwell & Eckhardt,

[7] The classification of DCI as partial agonist was complicated by the observed tissue dependence of its agonist and antagonist action. Therefore, the rational step from DCI to pronethalol not only presupposed Stephenson's theory but, as Black reports, also taught him about the importance of the notion of partial agonism (Black 1996). This also indicates that the development did not proceed by smooth theoretical derivation, but included much empirical learning.

1990, pp. 365ff; Quirke 2001). Beta-blockade with propranolol and other substances derived from it became firmly established in cardiovascular medicine.

The case thus shows that the emergence of rational drug design went along with an increased epistemic fruitfulness of developmental success. The assumptions on physiological mechanisms and on drug action first established a theoretical link between the chemical structure of drugs and their therapeutic effects. Due to their largely hypothetical character, they at the same time derived important empirical confirmation from the practical success. Altogether, the rational design of propranolol thus combined epistemic and practical work.

The next case, captopril, exemplifies a further important step in the history of rational drug design. It was one of the first development projects which included information on the target from crystallographic structure determination. This information, next to other knowledge, gave rise to a precise chemical model of the target's active site and of the drug-target interactions.

3. Modeling the drug-target interaction: captopril (1967-1981)

3.1 Academic lines of research and their industrial continuation

Captopril is the first antihypertensive drug to inhibit the enzyme ACE ('angiotensin converting enzyme'), which is an important element of the renin-angiotensin system. The renal enzyme renin catalyzes the conversion of the inactive peptide angiotensinogen into angiotensin I, from which ACE cleaves a dipeptide to produce angiotensin II. Through bonding with its receptor, angiotensin II raises the blood pressure, which angiotensin I does not. Hypertension can therefore be treated with substances that reduce the blood level of angiotensin II by inhibiting the enzymatic action of ACE. Even though the basic mechanism from the renal enzymes via the angiotensins to hypertension was known since the early 1960s (Robertson, 1993, p. 1.6; Maxwell & Eckhardt, 1990, pp. 24-25), it is only around 1967 when the U.S. company Squibb took on the task of developing an ACE inhibitor.

Squibb's decision in favor of such a program was based on a combination of scientific and strategic reasons. Since cardiovascular diseases are widespread in the developed world, they are commercially attractive targets for corporate pharmaceutical development. John Vane, pharmacologist at the Royal College of Surgeons of England and consultant to Squibb, convinced the Squibb research staff that ACE inhibition is a promising principle for cardiovascular therapy. He had been working on the role of ACE in hypertension for several years. It was already known that ACE played a role in malignant hypertension, which however only concerned a small proportion of the hypertensive population, and for which medication was available. Instead, Vane presented the concept that ACE was also important for essential hypertension, the condition by which 95% of the hypertensive population is affected. This conception was contrary to what most clinical experts at the time believed. As late as 1975, when with the first clinical success of teprotide a major step towards therapeutic ACE inhibition had already been taken, a review on prospective ways of controlling

hypertension did not even mention ACE inhibition as an option (Maxwell & Eckhardt, 1990, p. 28).[8] However, since Squibb was looking for an opportunity to enter the field of cardiovascular drugs, Vane's therapeutic hypothesis was sufficiently attractive for Squibb to try its luck (Smith & Vane, 2003, p. 788; Cushman & Ondetti, 1991, p. 589).

Two major lines of academic research were taken up by the corporate development. The first strand centered on the venom of the Brazilian viper *Bothrops jararaca*. Sergio Ferreira and Mauricío Rocha e Silva, pharmacologists at the University of Saõ Paulo, had found that an extract from the viper venom potentiated the hypotensive (i.e. blood pressure decreasing) effect of the peptide bradykinin (Ferreira & Rocha e Silva 1965). Ferreira joined John Vane's group at the Royal College of Surgeons of England, which at the time was working on the conversion of angiotensin I into angiotensin II. It was found that the snake venom also inhibits ACE, which was taken to indicate that the same enzyme is responsible both for the conversion of angiotensin and the catabolism of bradykinin (Ng & Vane 1968, Ferreira, Greene, Alabaster et al. 1970, Smith & Vane 2003). Ferreira and his co-workers subsequently isolated a number of peptides from the venom and determined their amino acid composition. For one of the peptides, BPP_{5a}, also the sequence of amino acids was elucidated (Ferreira, Bartelt & Greene 1970).

The Squibb research group, including Miguel A. Ondetti and David W. Cushman among others, continued this line of research. They prepared and isolated the venom peptides Ferreira had been working on and managed to determine the sequence of six longer peptides. In particular, they sequenced a nonapeptide which later came to be named teprotide. Like BPP_{5a}, teprotide inhibited ACE both in vitro and in vivo, but proved to be more stable and therefore longer acting (Ondetti, Williams, Sabo et al. 1971). By studying the natural peptides and synthetic analogues of them, they found that a certain end sequence of amino acids – phenylalanine-alanine-proline (Phe-Ala-Pro) – is optimal for inhibiting ACE. In addition, they formed the hypothesis that ACE is a zinc metalloprotease, i.e. an enzyme of a class which includes a zinc ion as crucial for the enzymatic action of protein cleavage. Teprotide entered into clinical tests, which were however soon stopped despite promising results. Teprotide was of no commercial interest since its production was expensive and it was not active when taken orally, which limited its use in the treatment of chronic conditions. The task therefore remained to develop an ACE inhibitor which is absorbed orally (Cushman, Pluščec, Williams et al. 1973, Cushman & Ondetti 1991).

The whole development program based on the venom peptides came in danger of being discontinued, however, after about 2000 further substances had been tested without major successes. It was saved only by the input from a second, independent line of academic research. As Cushman and Ondetti recall, it was on the 13 March 1974 when they read a paper by Larry D. Byers and Richard Wolfenden (University of North Carolina at Chapel

[8] See section 4.1 for more on the reasons that spoke against a general hypertensive role of angiotensin II.

Hill) about the bovine metalloprotease CPA ('Carboxypeptidase A'), and a particularly strong inhibitor thereof, L-benzylsuccinic acid. Byers and Wolfenden hypothesized that the inhibition was due to the benzylsuccinic acid being a 'by-product analogue'. This means that the inhibitor combines in one molecule the binding properties of both products of the cleavage which the enzyme normally catalyzes (Byers & Wolfenden 1973). This hypothesis of the chemical interaction between enzyme and inhibitor was based, among other things, on previous work by Florante A. Quiocho and William N. Lipscomb from Harvard University. Lipscomb had determined the 3-dimensional structure of CPA by X-ray-crystallography, which was the first determination of the structure of a metalloprotease. Subsequently, they had studied the binding modes of various substrates of CPA (Quiocho & Lipscomb 1971).

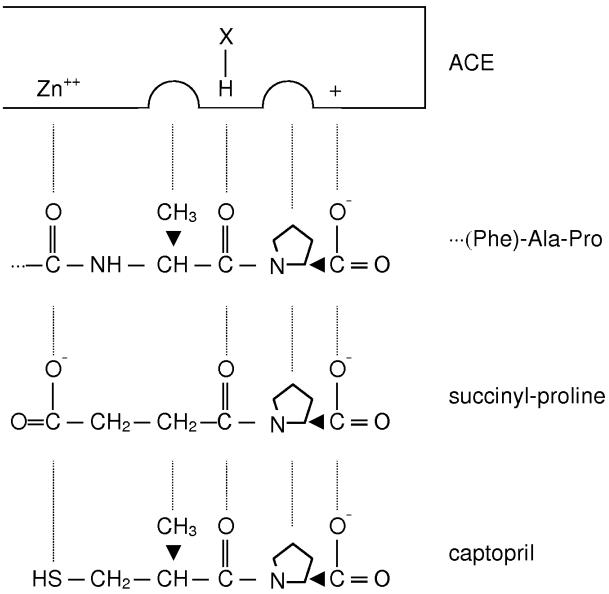

Fig. 2: Interaction model ACE and captopril (after Cushman, Cheung, Sabo et al. 1977 and 1982).

Since the Squibb group had assumed that ACE is a zinc metalloprotease as well, the hypotheses of Byers and Wolfenden immediately suggested to them that ACE could be inhibited by a similar mechanism. An important difference was, however, that ACE splits off a dipeptide from its natural substrate, while CPA liberates only a single amino acid. In addition, Cushman and Ondetti assumed that bonding with the zinc ion plays an important role in the inhibition. These assumptions on the active site of ACE and the mechanism of its enzymatic action together with the previous finding that the Phe-Ala-Pro-sequence binds optimally was the basis for the formulation of a hypothetical model of the interaction between drugs and target. Cushman, Ondetti, Hong Son Cheung and Emily F. Sabo assumed five different chemical interactions between substrate and enzyme, which they captured in an idealized, two-dimensional model (Cushman, Cheung, Sabo et al. 1977, Cushman, Cheung, Sabo et al., 1981, pp. 15-16; Cushman & Ondetti 1991). (See fig. 2.)

This model suggested a specific lead substance, succinyl-L-proline, which was found to be a selective, albeit weak inhibitor of ACE. The ensuing optimization of the lead substance took

one and a half years, involving the screening of about 60 further compounds. However, unlike the previous screening of the about 2000 substances which had not yielded a single specific ACE inhibitor, the interaction model both guided the screening and was confirmed by the activity of its outcome, captopril.

3.2 Reciprocal advancement of research and development

Again, a superficial overview of the development process could give the impression that captopril is to a large extent the result of a rather straightforward application of the fruits of previous research. However, similar to the case of propranolol, the closer inspection shows a more complicated epistemic structure. It is true, of course, that the development could not have started or been successful but for very specific suggestions from previous research particularly on the role of angiotensin and ACE in hypertension, on the action of the venom peptides and on the enzyme CPA. Still, the development process required and yielded a range of original epistemic contributions by the industry researchers.

Again, the development of adequate assays for testing substances was a crucial achievement. The group could work on the venom peptides and eventually disclose the sequence of a number of them only because they had one of the few working in vitro assays for measuring ACE activity, using extracts from rabbit lung and dog lung (Ondetti, Williams, Sabo et al., 1971, p. 4034; Cushman & Ondetti, 1991, p. 589). The major result of the long and frustrating testing of the 2000 random substances was a much improved in vitro assay, developed by Bernard Rubin and colleagues. It was based on guinea pig ileum and provided a simple method for measuring the inhibition of ACE. According to the test, a substance is taken to be an ACE inhibitor if it inhibits the contractile actions of angiotensin I, but not of angiotensin II, and potentiates the contractile action of bradykinin. Such test results allowed for good predictions of antihypertensive activity in vivo (in animals). The first substance to be synthesized according to the CPA-analogous interaction model – succinyl-L-proline – could be identified as a specific ACE inhibitor by this test, even though it was only of weak potency (Cushman & Ondetti, 1991, pp. 590-591).

While the development of the test systems was an important experimental accomplishment of the drug development process, the interpretation of assay results as indicating specific molecular action (namely ACE inhibition) depended on theoretical assumptions. If the mechanism of the renin-angiotensin system had not been known at least in rough outlines, it would not have been possible to define the specific role of ACE and to interpret test results as indicating ACE inhibition. This contrasts with the merely phenomenological understanding of assays in many empirical drug development processes, as e.g. in the development of another class of important cardiovascular drugs, the calcium antagonists. The first substance of this class, verapamil, was found in the early 1960s by researchers of the German firm Knoll. The search here however was not for a substance with a specific molecular action, but with the observable effect of widening the coronary arteries in the test systems, which were an assay

made of isolated rabbit heart and a dog model. These effects were taken as prima facie evidence for usefulness against angina pectoris (Maxwell & Eckhardt, 1990, p. 43). The mechanism of action of verapamil was determined only several years later and after extensive pharmacological debate. Albrecht Fleckenstein from the University of Freiburg showed that verapamil blocks the calcium channels – an at the time new theoretical concept which only retrospectively made clear that verapamil belongs to an entirely novel class of pharmaceuticals (Vos, 1991, pp. 124ff).

Beyond the experimental advances, the development process also made important contributions to the interaction model. The determination of the sequence of the six longer peptides from the snake venom allowed for a comparison of the different structures that showed how affinity depends on sequence, with Phe-Ala-Pro coming out as optimal. Similarly, the model for the enzymatic actions of ACE and its possible inhibition did not merely follow the proposal of Byers and Wolfenden. Their proposal was adapted to ACE and combined with the insights from the peptide studies. In addition, the crucial role of the zinc atom in the inhibition was specified (Cushman & Ondetti 1991).

Very similar to the case of propranolol, the interaction model that guided the design of the lead substance succinyl-L-proline and the subsequent modifications was highly hypothetical. But even if the model was taken at face value, it provided rather rough guidance. The suggested succinyl-L-proline was only a very weak ACE inhibitor. Two modifications of the structure led to captopril and an increase of activity of four orders of magnitude: the addition of a methyl ($-CH_3$) side chain and the substitution of the terminal carboxylate (-COOH) by a mercapto group (-SH). Both modifications were suggested by the interaction model. The methyl group fits into to the pocket that is filled by the alanine methyl group of the optimal amino acid sequence Phe-Ala-Pro. (See fig. 2.) The negatively charged sulfur binds with the positive zinc-ion, replacing the negative oxygen of the carboxylate. Still, the interaction model did not make clear that these particular modifications would raise the activity so enormously and it therefore took another 60 tries before the researchers hit on captopril.

Again, also the therapeutic hypothesis – that the inhibition of ACE is useful in the treatment of essential hypertension – was regarded as doubtful by most clinical experts at that time. It was even difficult to find clinicians to cooperate in clinical tests. From a dozen clinical experts asked, only two expressed interest, among them John Laragh from Columbia University Medical School (Smith & Vane, 2003, p. 788; cp. Maxwell & Eckhardt, 1990, p. 28). Because of the highly hypothetical character of the interaction model itself, of the derivation of specific substances from it and of the underlying therapeutic hypothesis, the whole enterprise was in ample need of empirical support. Such support was provided by the practical success of the suggested substances both in vitro, in vivo, and in the clinic. As Cushman and Ondetti have put it, “our original model of the active site of ACE, a purely theoretical construct, has led to the development of a series of highly optimized enzyme inhibitors that have markedly changed our understanding of the pathophysiological

importance of the renin-angiotensin system and provided excellent therapy for a growing list of cardiovascular disorders" (Cushman & Ondetti, 1991, p. 592).

Rational drug design – as judged by the two prominent examples propranolol and captopril – turns out to be rather semi-rational. The drugs are developed not merely by deriving their structure from existing physiological and biochemical knowledge, but through empirical and theoretical work that itself contributes to the basic understanding of drug action and physiology. Both cases show that knowledge of the chemical interactions between drug and target are of prime importance for the integration of the practical and the epistemic undertaking. While the development is in the beginning guided by an interaction model that is highly hypothetical, practical successes can both confirm and further specify the model, which in turn allows for an improved theoretical guidance of the development. The practical and epistemic ends then combine in such a way that the pursuit of each advances the achievement of the other.

In this fruitful interplay of drugs and theoretical knowledge, also the improvement of biological assays occupies a central position. In both cases, the pharmacological properties of drug candidates could only be identified because of recent improvements of the test systems. At the same time, only the theoretical interpretation of these tests as indicating particular mechanistic actions (beta-blockade or ACE-inhibition) made it possible to identify the specific pharmacological action of the drugs. The comparison with empirical developments of drugs such as verapamil shows that the experimental drug testing provided such rich epistemic gains only because it was imbued with theoretical conceptions of physiological mechanisms and of drug action. These observations on the one hand confirm the importance of experimental practices for scientific advances, emphasized by so many authors since Ian Hacking's *Representing and Intervening* (Hacking 1983). On the other hand, they are striking proof of the productivity of theoretical informedness in experimentation, since the rational method yielded so much more direct mechanistic knowledge than the empirical method in which the experimental practice leads a largely un-theoretical 'life of its own'.

The final case, to which I now turn, will further illustrate how not only the interaction model, but also knowledge about the underlying physiological mechanisms as a whole fruitfully interacts with the development of new drugs. In particular, the selectivity of a drug turns out as central not only to its therapeutic usefulness, but also to its epistemic value as an investigational probe.

4. Beyond drug-target interaction: losartan (1982-1994)

4.1 Establishing a therapeutic concept

Losartan is, like captopril, a drug that targets the renin-angiotensin system. It is the first clinically approved angiotensin II receptor antagonist, i.e. it blocks the binding of angiotensin II to its natural receptor, thus cutting off the renin-angiotensin mechanism one step later than ACE inhibitors. From its start in the early 1980s, the development program that was

eventually successful – conducted by a research group around Pieter Timmermans and Ruth Wexler at DuPont – was directed at a substance with such a pharmacological profile. At the time, it was generally clear that angiotensin II receptor antagonists held good promise to be effective antihypertensive agents. This clarification was due in part to the development of captopril, which has made the therapeutic value of blocking the renal pathway to angiotensin II evident. If lowering the level of angiotensin II is helpful, then blocking its action with a receptor antagonist should be so as well.

In addition, at the same time that ACE inhibitors emerged in the 1970s, there was considerable interest in angiotensin II receptor antagonists themselves. These studies have yielded, by modification of the peptide angiotensin II, peptidic receptor antagonists, most importantly saralasin. Saralasin was not suitable as a drug since it was not orally bioavailable, had short duration of action and showed partial agonist activity. Still, studies with saralasin – among them clinical studies – firmly established the hypertensive role of angiotensin II.

Previous to these studies, assumptions of such a role were based on measurements of the activity of the renin-angiotensin system (plasma renin and angiotensin levels) and of cardiovascular reactions on the infusion of angiotensin II. However, the observations were inconclusive, since severe hypertension sometimes went with low activity of the renin-angiotensin system. This in itself does not, of course, speak against hypertension being caused, in other cases, by high levels of angiotensin II. But in addition, the infusion of angiotensin II did not change the arterial pressure significantly in other patients, for instance those suffering from Addison's disease or from severe cardiac failure. Therefore, only some were convinced that the renin-angiotensin system played an important role in clinical disorders at all (Nicholls, Charles, Crozier et al., 1994, pp. S96-S97).

But then, it was shown that saralasin lowers the blood pressure in those cases in which the donation of angiotensin II did not much alter it. This indicated that in these cases, renin-angiotensin activity was already high, which explains why additional activation did not yield any further effects. Generally speaking, the studies showed that angiotensin II had a stable impact on the blood pressure in very different physiological conditions. While at normal renin-angiotensin activity, infusion of more angiotensin II raises the blood pressure, the blockade of angiotensin II lowers it if the activity is already near to maximum. This general role could only be demonstrated experimentally with a selective inhibitor of the action of the natural substrate (Nicholls, Charles, Crozier et al. 1994).

4.2 Developing losartan: a rational model and a long empirical search

While the great therapeutic value of selective angiotensin II receptor antagonists thus was firmly established by the end of the 1970s, the development of a suitable substance posed considerable difficulties. With saralasin being known, the situation was analogous to the stage when, in the development of captopril, teprotide had been found. Again, the goal was a smaller, non-peptidic substance, yet with similar binding- and inhibitory features. The DuPont

group had already started with the screening of existing substances from chemical libraries and of nonpeptidic mimics of angiotensin II, when in 1982, the publication of two patents of the Japanese company Takeda revealed the discovery of two weak non-peptidic angiotensin II receptor antagonists. This news caused a stir, with many companies starting to investigate the new leads (Timmermans, Duncia, Carini et al. 1995).

After having confirmed that the Takeda substances possessed the desired profile, the DuPont group started a concerted effort to improve the as yet too weak action of the substances. The development was once again guided by a model of the assumed interaction between receptor and drug. It relied on studies of the conformation of angiotensin II by R. R. Smeby and S. Fermandjian. They had investigated the spatial structure of the molecule by nuclear magnetic resonance (Smeby & Fermandjian 1978). The Takeda structures were aligned with the assumed geometry of the natural substrate and the hypothetical chemical bonds were mapped. The chief result of this theoretical effort was the suggestion that the Takeda structures have to be enlarged at a particular position in such a way that they would more closely resemble the much larger peptide angiotensin II. It additionally indicated that an acidic group should be part of the enlargement.

The suggestion provided by the interaction model proved to be helpful, but was at the same time rather vague. It was a laborious undertaking to find losartan. Starting with the Takeda structures, the affinity and bioavailability were markedly improved by four consecutive modifications. Altogether, it took more than 50-person-years of work for chemical modification and biological testing. This gives testimony of the considerable proportion of empirical work within the overall rational methodology. The result was, however, not only the first potent, orally active angiotensin II receptor antagonist. Since the group had checked with more than 11 additional assays that the substance is not active at other receptors, it was also fairly well established that losartan is selective for angiotensin II receptors (Timmermans, Duncia, Carini et al. 1995).

4.3 Characterizing a functional receptor

In fact, it turned out that losartan is even more selective than initially intended. From the range of assays used for the evaluation of receptor antagonism, losartan showed activity only in one type, but not the other. Other reported antagonists that had been found by corporate researchers at Warner-Lambert/Parke-Davis and Ciba-Geigy – labeled PD123177 and CGP42112 – displayed just the opposite activity, antagonizing the second type of assays, but not the first. Saralasin, by contrast, was active in both assays. Andrew Chiu and other members of the DuPont group therefore concluded that two distinct subtypes of angiotensin II receptors exist, subsequently named AT_1 (inhibited by losartan) and AT_2 (inhibited by PD123177 and CGP42112) (Chiu, Herblin, McCall et al. 1989). The research group at Ciba-Geigy independently drew the same conclusions from similar studies with receptor antagonists (Whitebread, Mele, Kamber et al. 1989). While there had been various but

diverging reports about possible angiotensin II receptor subtypes before, it was only these two results obtained with selective antagonists that reliably characterized and firmly established the two subtypes.

The subtype selectivity of losartan and the Warner-Lambert and Ciba-Geigy structures proved to be epistemically most fruitful. Within a few years from the distinction of the two receptor subtypes, the entire mechanisms triggered by the stimulation of the AT_1-receptor in various tissues was elucidated, in part at a molecular level, from G-protein coupling over second messenger and intracellular response to the response of the cell or tissue (e.g. contraction, secretion) and the reaction of the whole organism (as blood pressure). By 1995, AT_1 was therefore fully established as a 'functional receptor' (Timmermans, Duncia, Carini et al. 1995). The studies that provided this elucidation were conducted both at universities (medical, pharmacological and biochemical departments) and companies (in particular DuPont, Warner-Lambert and Ciba-Geigy).[9] They all followed very much the same logic: If the occurrence of some phenomenon is prevented, in vitro or in vivo, by losartan, but not by PD123177 or CPG42112, the AT_1-receptor must be regulating it. Even though with the AT_2-receptor, the same methodology was pursued, the results gained were not consistent, with different effects being proposed by different studies. Therefore, no physiological effects could unambiguously be associated with AT_2, while AT_1 was known to be central for the regulation, among others, of blood pressure, renal function, drinking behavior, growth effects, and endothelial cell proliferation. These effects offered prospects for therapeutic uses in important clinical conditions such as hypertension, heart failure, renal failure, or balloon injury (Timmermans, Duncia, Carini et al. 1995). In retrospect, it turned out that the DuPont researchers had been lucky to hit on an inhibitor of the AT_1 receptor, and not (as the Warner-Lambert and Ciba-Geigy groups) of AT_2.

4.4 Selective substances as 'investigational probes' and as therapeutics

The cases of captopril and losartan show particularly clearly how the development of selective pharmaceuticals and the elucidation of physiological and pathological mechanisms can go hand in hand. As seen, basic knowledge about the renin-angiotensin system allowed for a theoretical interpretation of assays as indicating ACE inhibition, which was crucial for the identification of selective ACE inhibitors. Selective inhibitors of the renin-angiotensin system, in particular captopril and saralasin, firmly established the importance of the renin-angiotensin system for hypertension. The ensuing therapeutic concept guided the development of losartan, the first example of the next generation of renin-angiotensin inhibitors. Losartan, in turn, yielded more details of the system, such as the distinction of the two receptor types. While theoretical preconceptions are necessary for the identification of substances as performing a specific molecular action, their selectivity makes them highly

9 See Timmermans, Duncia, Carini et al. (1995) for a review of these studies.

valuable as "investigational tools" or "probes" in further experiments (Vos, 1991, p. 91; Nicholls, Charles, Crozier et al. 1994).

Also the development of pronethalol and of subsequent beta-blockers exhibits such cycles of mutual advancement between mechanistic knowledge and selective drugs. As seen, the therapeutic success of pronethalol confirmed Ahlquist's two-receptor theory. But soon after the introduction of propranolol, two subtypes of β-receptors, β_1 and β_2, were distinguished with the help of further beta-blockers. While β_1-receptors are dominant at the heart muscle, β_2-receptors are found on the smooth muscles of blood vessels and in the respiratory tract. Since propranolol blocks both subtypes, it can cause side effects such as asthmatic conditions or the aggravation of vascular insufficiency (Maxwell & Eckhardt, 1990, p. 14). This indicates that improved selectivity often also goes with therapeutic progress.[10]

5. Conditions for integrating research and development

5.1 Closing the cycles of epistemic and practical advancement

From an abstract epistemological perspective, the integration of epistemic and practical projects in rational drug design can be understood on the basis of the dual value both of mechanistic knowledge and of tools for intervention. Knowledge of physiological mechanisms allows for causal explanations why certain phenomena occur (cp., e.g., Glennan 2002), but can also point out targets and modes of intervention for practically useful effects. In a similar way, selective substances can be suitable for therapy, but also for targeted experimental intervention into the organism's complex causal web. In general, therefore, the practical usefulness would seem to coincide quite naturally with the epistemic value of pharmacological findings. Given this compatibility, it seems all the more surprising why truly integrated epistemic and practical research and development in pharmacology only emerged in the 1950s.

The case studies have exposed two epistemic advances that were conditional for the integration. Firstly, knowledge of the pathologically relevant physiological mechanisms grew in specificity. In particular, a stage of the mechanism suitable for pharmaceutical intervention became known up to some of the details of the chemical interactions. Secondly, biological test systems were developed that allowed for the identification of substances with theoretically defined modes of action. From the point where both theoretical and experimental capacities achieved a certain advanced state, their further development became closely intertwined and

[10] However, the rejection of non-selective 'dirty drugs' with multiple modes of action is not universal among pharmacologists and clinicians. Such drugs can also offer therapeutic advantages due to a balanced overall influence on the organism. In this sense, also captopril is not perfectly selective, since it has at least two modes of pharmacological action. It not only cuts off the production of angiotensin II, but by inhibiting ACE also blocks the breakdown of bradykinin. It has been suggested that the long-term antihypertensive action of ACE inhibitors is also due this second mode of action (Johnston 1993). However, the elevated levels of bradykinin are also suspected to cause dry cough, one of the most common side effects of ACE inhibitors (Fletcher & Dollery 1993).

gained speed. However, this linkage of theory and experiment not only constitutes epistemic progress. Due to the dual value both of theoretical knowledge and experimental techniques, also the means and the ends of pharmacological intervention for practical purposes got linked. Inferences could now be drawn from chemical structures via the interaction model to effects along the embedding physiological mechanisms. Since organic chemistry enables the synthesis of many of these structures while physiological effects can serve therapeutic purposes, theoretical predictions of the practical utility of feasible technology came into reach of pharmaceutical development. Consequently, epistemic and practical work could combine in the observed cycles of mutual advancement. Physiological knowledge could guide the search for new drugs, while existing or developed drugs turned into valuable experimental tools. Drug development both became more rational and gained in epistemic importance.

5.2 Basic research and the interdependence of linear and integrated innovation

While these observations show in detail how the integrated practical and epistemic pharmacological method of rational drug design arose and operated, the case studies also suggest conclusions that are of relevance for the broader discussion of the relation between research and development (or science and technology). In particular, the cases can help to clarify the role of basic research vis-à-vis work that is immediately directed towards useful applications.

Much of the knowledge on physiological mechanisms and on drug-target interactions that the development projects presupposed was the fruit of basic research. Both Ahlquist's two-receptor theory of adrenaline and R. A. Stephenson's theory of drug action belong to this category, as does the work by Lipscomb, Quiocho, Byers and Wolfenden on CPA and its modes of binding and the studies of Smeby and Fermandjian on the conformation of angiotensin II. These inputs from basic research have been crucial for the developmental successes. This shows that a linear arrangement of research and development can persist also while practical and (further) epistemic work are closely combined. Contrary to initial appearance, the linear and the integrated modes of innovation are not mutually exclusive, but can well be both instantiated in a single episode.

Some authors have expressed reservations on the applicability of the notion of basic research to pharmacology. Jordan Goodman, for instance, has argued that the distinction of basic and applied research is irrelevant since the development of new drugs often has considerable impact on fundamental knowledge (Goodman 1998; cp. Vos, 1991, p. 26). Still, the conception of basic research that I use is of analytic value for the studied cases. Basic research is here roughly conceived of as research that directly and primarily aims at a fundamental scientific understanding of some area. In this sense, it can be distinguished from activities that do not aim at scientific understanding at all, that do not aim at a *fundamental* understanding, or that do not have fundamental understanding as *primary* or *direct* aim. In these senses, basic research is different, among other things, from firstly the mere

development of some technique that does not include any scientific research, secondly research that strives for results that are not fundamental (but might be usefully applied), and thirdly research that yields fundamental insights, but is conducted primarily and directly for non-epistemic, practical purposes (such as research within rational drug design). One consequence of these rough distinctions is that fundamental insights can result from research other than basic if they have not been the primary or direct aim. Another consequence is that basic research can very well aim *also* at practical ends, as long as it does not do so primarily or not directly.[11] Stephenson's theoretical work on drug action, for instance, was basic research in this sense. It was not conducted in view of specific drugs or therapies, but aimed at a general understanding of drug action. Yet, it is clear to him that his distinction of affinity and effectivity can change the terms in which the relation of structural modification and drug action is conceived of in many development projects (Stephenson, 1956, p. 392). Such a primacy of direct epistemic aims can make sense also from a practical perspective. If it is difficult to foresee to which precise practical use some research results can be put, research that aims at fundamental understanding as its proximate end can very well also be most efficient from a practical perspective. Even though one could reasonably expect that the crystallographic study of CPA could be of *some* practical use, it was unforeseeable that its results would be so helpful specifically in the development of ACE inhibitors. Since the precise epistemic demands were uncertain, the best practical prospects were provided by an elucidation of the fundamental molecular structure of CPA, i.e. by basic research.

Still, by far not all of the guiding assumptions came from basic research. Other assumptions arose from previous drug development projects. Pharmacological properties of adrenaline and of derived substances, for instance, were known both from the numerous pharmacological experiments that have been conducted ever since the isolation of adrenaline at the beginning of the 20th century, and from the clinical uses of such compounds. One of these substances that became important for propranolol, DCI, was first synthesized by Powell and Slater from Eli Lilly when screening derivatives of adrenaline. Their aim was to find substances that widen the bronchi just as adrenaline does, but act longer and more specifically than adrenaline. However, DCI displayed an unexpected property. Instead of activities similar to adrenaline, DCI blocked some of the effects of adrenaline without itself eliciting the receptor response (Powell & Slater 1958, Maxwell & Eckhardt 1990). As reported above, this activity was interpreted by Moran and Perkins in terms of Ahlquist's two-receptor theory, which provided a key input to Black's development program. While this input went back to a serendipitous finding in empirical corporate research, other input came from rational drug design itself, as the therapeutic hypothesis for losartan, that was established, among other things, by captopril's clinical effectiveness.

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[11] This is contrary to Vannevar Bush's influential characterization of basic research as "performed without thought of practical ends" (Bush, 1945, ch. 3). Instead, I follow those who have maintained that 'strategic' research can well be a subcategory of basic research. See, e.g., Irvine & Martin, (1989), p. 7.

Altogether, the cases make clear that inputs both from other drug development programs and from basic research were indispensable for the development projects. This suggests, however, that the cycles of mutual advancement of drug design and theoretical knowledge that have been observed within rational drug development are not entirely self-perpetuating. Impulses from basic research have been central for the rational design of the new drugs.

At the same time, the cases indicate that developmental success brings about fundamental insights often because the guidance by basic research is rather vague or rests on presuppositions that are themselves highly hypothetical. The development therefore often requires further specific research on the drug-target interaction and the physiological mechanisms as a whole, while developmental success can provide empirical support of the mechanistic presuppositions. Accordingly, considerably less elucidation often ensues if the development is not in this sense semi-rational, but closely follows lines of development which are already firmly established. The so-called me-too drugs exemplify this type of development, since me-too drugs are typically developed by rival companies by derivation from an already existing innovative drug. Olmesartan, for instance, is the sixth addition to the family of losartan-derived drugs. Having been approved by the U.S. Food and Drug Administration in 2002, the main advantage of olmesartan over losartan is that it needs to be taken only once daily, while losartan often has to be taken twice daily. Chemically, the crucial extensions of the Takeda structures that led to losartan have been preserved, and only minor modifications at other sites were added. No new insights into the pathological mechanisms or the drug-target interaction are known from its development (Mizuno, Sada, Ikeda et al. 1995, Merlos, Rabasseda & Silvestre 1998).

The studied cases thus show that in pharmacology, the linear and the integrated modes of innovation are much more closely interdependent than the basic models suggest. Developmental success can lead directly to theoretical insights because the drug design is guided by knowledge of a fundamental kind, often provided by basic research. At the same time, the fairly hypothetical character of the theoretical guidance accounts for the rich epistemic gains of developmental success. Rational drug design hence combines fundamental research and drug development not *despite* its dependency on basic research, but rather *because* it does not run epistemically on its own.

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