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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.

Keywords: Pharmacology; Biomedicine; Corporate research; Interaction model; Experiment; Sir James Black

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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, and so on), 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 (cf. 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

[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, for example, Good, Krystek, & Mason (2000).