CURRENT NEEDS FOR NEW THERAPEUTIC AGENTS AND DISCOVERY STRATEGIES—A SYSTEMS PHARMACOLOGY APPROACH

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1 INTRODUCTION: A BRIEF HISTORY OF DRUG DISCOVERY

The use of remedies to treat or alleviate symptoms of a medical condition can be traced as far back as ancient Egypt. The Ebers papyrus, dating from 1555 BC, was found to contain 876 concoctions to treat a wide variety of disorders [1]. Early medicinal efforts were also used by the Greeks, most notably Hippocrates, and by several Asian cultures including the Chinese [2]. However, the identification of active ingredients and the development of the interdisciplinary science of pharmacology that bridged organic chemistry, zoology, and pharmacology did not emerge until the late 1800's. These advances were made possible by progress in chemistry, including theories on acids and bases and on the structure of aromatic molecules such as dyes [3]. In the 1870's, Paul Ehrlich proposed the existence of "chemoreceptors", which differed between microorganisms and the host tissue, based on his studies of dyes in biological tissues [3]. He suggested these could be used therapeutically, which eventually gave rise to the development of a class of drug treatments known as chemotherapy.

At the beginning of the twentieth century, pharmacology progressed quickly. In 1905, J. N. Langley introduced the concept of a "receptive substance", the modern basis for the study of receptor agonists and antagonists [4, 5]. In 1933, Meldrum and Roughton identified the enzyme carbonic anhydrase while studying the effects of sulfanilamide, the active metabolite of the antibiotic sulfamidochrysoidine [6]. This discovery led to the concept of enzymes as a good target for drug discovery and gave further importance to the biochemical characterization of cellular functions. Following Alexander Fleming's discovery of penicillin as a product from the *Penicilium* mold that killed *Staphylococcus* bacteria [7], many drug companies invested in microbiology, resulting in the discovery of more antibiotic and other therapeutic agents [3].

Over the next decades, drug discovery progressed along with our understanding of the basic sciences that underlie the discipline of pharmacology. What is currently referred to as interdisciplinary and translational basic science became known as pharmacology and experimental therapeutics. The large explosion of chemical libraries in the 1980's by the large scale implementation of combinatorial chemistry required the simultaneous development of high-throughput screening (HTS) methodologies. With these new technologies, many hundreds of thousands of compounds could be synthesized and then screened against a target of interest. However, this approach was often largely detached from a physiologically relevant screening signal. Another major breakthrough that changed the way society as

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