Send Orders for Reprints to reprints@benthamscience.ae

168 *Immun., Endoc. & Metab. Agents in Med. Chem.*, 2015, *15*, 168-175

An Engrossing History of Azidothymidine

Vivek K. Sharma[a], Raman K. Sharma[b], Pramod K. Singh[c] and Sunil K. Singh[c,*]

[a]*Department of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK;* [b]*SABIC Innovative Plastics India Pvt. Ltd., Bengaluru – 562125, India;* [c]*Department of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India*

Sunil K. Singh

Abstract: Azidothymidine (AZT) was the first breakthrough drug developed for the treatment of acquired immunodeficiency syndrome (AIDS). It took AZT only 25 months from the first successful laboratory activity against human immunodeficiency virus (HIV) to its approval by the FDA. Similar interesting facts and disputes have persistently been associated with AZT starting from its very first synthesis to the development and approval as drug. This review briefly collates the exciting history of AZT and, as the different stages involved in the discovery and the development of this drug molecule gets recapitulated here, could well serve as a mnemonic for the area of drug discovery and development in general.

Keywords: Azidothymidine, nucleoside reverse-transcriptase inhibitor, antiretroviral drug, human immunodeficiency virus, acquired immunodeficiency syndrome.

INTRODUCTION

Azidothymidine (AZT) or Zidovudine (Fig. **1**), prescribed under the name Retrovir is a nucleoside reverse-transcriptase inhibitor (NRTI), a type of antiretroviral drug used for the treatment of HIV/AIDS [1]. Surprisingly, AZT was initially synthesized in 1964 by Jerome Horwitz, *et al.* [2] to cure cancer, but the search was interrupted due to toxicity of AZT and remained of little interest for application in human virology. Notwithstanding; in February 1985, shortly after the human immunodeficiency virus (HIV) had unambiguously been proved as the cause of AIDS, the first promising results with AZT were seen in the studies conducted at the National Cancer Institute (NCI) [3]. Finally in March 1987, FDA approved the drug for use against HIV, AIDS and AIDS related complex (ARC) [4, 5]. It was approved in the shortest time after a single human trial of only nineteen weeks long. Each stride towards this endeavour had been very confounding, and perpetuated till its patent expired in 2005, making AZT available in the public domain [6]. Before going in to more details of AZT, it would be only appropriate to discuss briefly the overall drug discovery process drug discovery process.

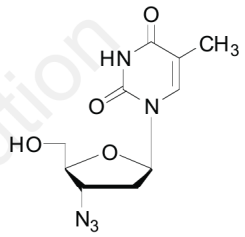

Fig. (1). Structure of azidothymidine (AZT, 3′-azido-3′-deoxythymidine, zidovudine, ZDV).

Recapitulating the Process of Drug Discovery and Development

Drug discovery is a very challenging and expensive process and a new drug molecule synthesized in the lab has to cross multiple stages of challenging hurdles before it can reach a Chemist Shop [7]. A brief summary of the process involved is outlined in (Fig. **2**). Thus the various steps involved in the whole process can be conveniently divided into three separate blocks/parts, namely, medicinal chemistry research, drug development and marketing (Fig. **2**). Thus, the genesis of a new drug starts with the identification of the drug target for which the onus necessarily lies with the biochemists, generally. The subsequent part of the work involves the synthesis of new chemical entities (NCEs) and the onus of this work lies on the chemists who would be required to synthesize a large library (or libraries) of compounds. Out of an estimated 5000-10,000 chemical compounds synthesized by chemists, only about 250 found active by the biochemist/biological chemist reach the preclinical stage. The next step on the way indicated above involves filing application for investigational new drug (IND) to FDA or another equivalent as applicable to the country of origin. If FDA approves the IND, then clinical trials/studies involving screening the drug candidates for safety (Phase I), establishing the efficacy of the drug candidate, usually against a placebo (Phase II) and the final confirmation on its safety and the efficacy (Phase III) issues. On an average it takes an estimated 5-7 years in completing the clinical trials although this time period may be shorter if no drug has been available in the market for the efficacious treatment of the condition for which the particular drug candidate is intended for

*Address correspondence to this author at the Department of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India; Tel: +91-9873106251; Fax: 011-27666579; E-mail: org_sunil@rediffmail.com

187-5/15 $58.00+.00