

EDITORIAL

The first, the next, and the cinematographed versions of AZT

Las versiones primera, próxima y cinematográficas de AZT

“Ronald Woodroof died of AIDS in September 12, 1992, seven years after he was diagnosed. A lower dose of AZT became widely used in later drug combinations that saved millions of lives”. These words end the film *Dallas Buyers Club*, a recent, highly awarded movie, that tells the true story of a cowboy diagnosed with AIDS in 1985 and illegally receives the firsthand antiviral AZT but, due to the severe side effects that the drug afflicted, begins to experiment with – and illicitly distribute among the “Club” – non-FDA approved remedies in search of a better treatment for himself and other AIDS patients. Perhaps owing to an artistic strategy, the movie waits until the last couple of lines to do justice to AZT and the impact it had in dealing with AIDS at that day and age.

In real life, at the time the movie begins, in 1985, AZT was still being developed, and it was only made available for patients undergoing clinical trials. Nevertheless, unlawful users such as the members of the “Club” were not exactly uncommon. By 1987, the drug had fast-tracked the FDA approval process, making it to permitted clinical use in a tad over two years. Such speed was justified, at the time, due to the urgency to contain the spread of the disease. Thus, AZT had been proven to slow replication of the virus and to prolong patient’s life. However, toxicity related to the use of the drug had already taken a significant death toll. And it kept on counting while high doses of monotherapy with AZT were the single standard treatment for AIDS patients. It took a while, though, until the mid-90’s, for scientists and doctors to really understand how AZT could work best, and, currently, it may still be employed for controlling HIV/AIDS in combination with other, more recently developed antiretroviral drugs, and compounds with different modes of antiviral action, to make up for the so-called “cocktail”, or more appropriately named HAART (highly active antiretroviral therapy). These combination therapies have been of great clinical success, and promoted AIDS from being a clear death sentence, as it was received by Woodroof, the “Buyers Club” and so many other individuals, to a manageable, although chronic and contagious, infective disease.

Still, the story of AZT starts many decades before, and began, such as life, in the sea.

As of 1951, researchers Werner Bergmann and Robert Feeney published the structure of two new unusual nucleosides isolated from the Caribbean marine sponge *Tectitethya crypta* (formerly and very popularly known as *Cryptotethya crypta*), which were justly named spongothymidine and spongouridine (1). Nucleosides are the building blocks of the nucleic acids RNA and DNA, and are made up of a nitrogenous base (any of adenine, cytosine, guanine, thymine or uracil) and a pentose sugar, either ribose or deoxyribose, respectively. The curious feature of the sponge nucleosides reported in this which is considered by many as the inaugural work of the field of marine natural products, was that they carried an arabinose as their sugar moiety, in place of the usual ribose or deoxyribose.

So, what was so intriguing about the arabinose-containing nucleosides was that, if only ribonucleosides or deoxyribonucleosides have a biological function, as the backbone of either RNA or DNA, what would be the purpose of a sponge having free nucleosides that could not be used for synthesis of neither nucleic acids? Seymour Cohen was one scientist who put some work into answering this question, and speculated that the arabinonucleosides, which, by 1963, had only been found in *T. crypta*, took a role in host defense by threatening pathogens or predators, enabling the sponge to live almost completely buried in the sand (2).

During this period, blending in to the success of antibiotics in remedying infections, pharmaceutical companies were also searching for anticancer drugs and some leads with an anti-metabolic mode of action were already available. The principle of this type of chemotherapy was to mislead a biosynthetic pathway with an unnatural, slightly different substrate from the natural one, inducing the production of a null or a non-functional molecule. Antifolate drugs, such as the antibacterial sulfá drugs, or the

antineoplastics aminopterin and methotexate, which act by deceiving enzymes of the pathway of folate synthesis, were known and used then.

Attempts of altering directly the nucleosides themselves had been made, however, it was thought, then, that maintaining the sugar moiety as either ribose or deoxyribose was essential for the desired effect of the unnatural new compounds. In that context, chemical modifications were initially being made only to the nitrogenous base. The discovery of the sponge nucleosides revolutionized how the rational design of unnatural nucleosides was addressed, as it was shown that the sugar could also be manipulated to achieve the intended therapeutical effects. What followed these findings was an avalanche of new modified nucleosides, substituted with unusual sugars or even acyclic entities, which began to be tested for their anticancer and antiviral potentials. Among those, in 1969, cytosine arabinose or Ara-C, a close analog to the nucleoside deoxycytidine, with a substituted arabinose, began to be marketed as a cancer chemotherapy agent, cytarabine, still used to treat leukemia (3).

Adenine arabinose, or Ara-A, another closely related synthetic arabinose-containing nucleoside, which was later found, along with spongouridine, in a natural source – the Mediterranean gorgonian *Eunicella cavolini* (4) –, followed and, in 1976, became the drug vidarabine, used for the treatment of herpes types virus and other viral infections (5). Lately, most uses of vidarabine have been replaced by acyclovir, which has shown a broader spectrum, high activity and low toxicity. Nevertheless, the design of acyclovir has too benefited from the knowledge gained with the spongonucleosides. This antiviral, which has a chemical name of acycloguanosine, is made up of a guanine base and an acyclic moiety (6).

Zidovudine, better known as AZT (for azidothymidine), was the first drug available for the treatment of AIDS. It is too a synthetic derivative of the sponge nucleosides and a thymidine analog with an azide moiety substitution on the ribose sugar. Interestingly, it had been synthesized in 1964 by Jerome Horwitz, as one of a series of compounds named dideoxythymidines (7), while probing for new anticancer compounds, but was abandoned when proved ineffective in shrinking mice tumors. When the AIDS outbreak came upon, in the mid-80's, a rush for an antiviral that could stop HIV replication – a representative of the retrovirus class, defined as those virus that contain reverse transcriptase, an enzyme that aids in the process of synthesizing new infective complementary DNA from the viral RNA template –, unshelved nearly thousands of compounds, including synthetic nucleosides that were already known for their ability to inhibit elongation of the DNA chain. At that point, AZT showed to be extremely potent against HIV (8), by blocking the viral reverse transcription mechanism, crucial for its replication.

The experimental article included in this number is perhaps a bet that sponges, which are like a gold mine for bioactive molecules, can recur this achievement, and house other relevant antiviral compounds, as side effects and acquired resistance is still a prominent bottleneck of many chemotherapy schemes, rather it is against cancer or infective diseases (9). As for Woodroof, well, he was too performing *his* kind of search for a better AIDS treatment, some 30 years earlier. But, in those days, he had to die trying.

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