Francis Tally and the Discovery and Development of Tigecycline: A Personal Reminiscence

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For Francis Tally, both medicine and science were highly personal undertakings. Tally thought that emotional engagement was important in one’s work and one’s life, which were inseparable in his case. Indeed, Tally materially participated in no fewer than 4 programs that resulted in the approval and commercialization of novel antibiotics. These included piperacillin-tazobactam (which is currently the injectable antibiotic with the largest volume of sales worldwide) and daptomycin. This article focuses on the discovery and development of tigecycline.

Francis Tally was known for his feisty nature, a characteristic that one would expect from an undersized high school football lineman. Indeed, I also have been known for my feisty nature, and I like to think that Dr. Tally and I communicated in some very fundamental (although politically incorrect) ways. Soon after Tally arrived at Lederle Laboratories (Pearl River, NY) from Tufts to head the reformed Infectious Diseases Department at American Cyanamid Medical Research Division, he initiated a program to discover novel antibiotics with clinical efficacy against multidrug-resistant bacteria, especially methicillin-resistant Staphylococcus aureus. One of the key projects in that effort was to focus on studies of tetracyclines that occurred at Lederle (where that family of antibiotics was originally discovered) over the previous decades [1]. Tally reasoned that the current knowledge about the molecular basis of tetracycline resistance, as well as the large amount of chemical and natural product equity in the field of tetracycline microbiology and biochemistry, well positioned the scientists in Lederle to discover novel forms of tetracycline that would be active against resistant strains. Indeed, Stuart Levy, a colleague of Tally’s at Tufts, discovered the first tetracycline resistance gene, tet; Levy found that this gene encoded a dedicated tetracycline efflux pump. One of the hallmarks of Tally’s work was his insistence on understanding the underlying biology as the cornerstone for any drug discovery effort, and in the case of tetracycline resistance, our knowledge had improved to the point that researchers of drug resistance understood the basis of resistance in most (if not all) clinically drug-resistant bacteria. Therefore, it was possible to establish a relatively straightforward microbiological screen to test the tetracycline compounds in the Lederle compound library. Early in the process, it was realized that substituents at the 9 position of the tetracycline scaffold led to compounds with better activity toward strains carrying efflux pump–encoding strains. A key breakthrough was an innovation of an American Cyanamid chemist and chemistry team leader for the then referred to as glycylcyclines project, Phaik-Eng Sum, who developed a novel method to modify the tetracycline scaffold at the 9 position. Three years of medicinal chemistry and microbiological screening resulted in a series of novel compounds with activity not only against strains expressing efflux pumps but also against strains with the other major form of tetracycline resistance through the mechanism of ribosomal protection encoded by tet.

It was against that backdrop in 1993 that I was recruited from my academic position at the Public Health Research Institute to American Cyanamid (which became Wyeth after its acquisition by American Home Products in 1994). Indeed, not only was I an expert in