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DO MYTHIC HEROES PERVERT THE BEAUTY OF BASIC RESEARCH?

by Roald Hoffmann

The Sunday *New York Times Magazine* (30 September 1990) headline reads "The Drug That Works in Pittsburgh." Barry Werth's article begins:

> Dressed in a red turtleneck with two pens stuck in the collar, Dr. Thomas Starzl strides through the mobbed liver transplant clinic at the University of Pittsburgh Medical Center. Graying, six feet tall, and thin on the verge of being gaunt, Starzl, predominantly a surgeon, is best known as perhaps the world's leading transplant pioneer, and the man who has built Pittsburgh into the largest, busiest, most successful organ transplant center in the world.
>
> Now 64 years old, Starzl is spearheading the use of an extraordinary new drug, FK-506, a highly specific immunosuppressant that prevents patients from rejecting transplanted tissue.

The article goes on to paint a picture of the driven surgeon, establishing the new immunosuppressant's remarkable effectiveness, fighting to demonstrate on an exclusive basis its utility in reducing rejection, balking at double-blind tests of FK-506 versus an older drug, cyclosporin A, in contention with his own hospital's Institutional Review Board. The author is careful to let Starzl's adversaries speak, and the rough edges of the surgeon emerge. But on balance this is a tale of heroic proportions—a portrait of a man with faults, but a man justly impelled by a search for the better, who overcomes all obstacles put in his way by, least of all, nature, most of all, by other less visionary men and women. Dr. Starzl is the man responsible for a new miracle drug.

But who really "discovered" FK-506? It was a group of Japanese chemists first of all, who isolated it in 1982 from a fungus, *Streptomyces tsukubaensis*, growing in a soil sample. Could it be that because their names were Toru Kino, Toshio Goto, M. Iwami, N. Inamura, Akio Kuroda, T. Ochiai, Hiroshi Hatanaka, Hasanobu Kohsaka, Hatsuo Aoki, Hiroshi Imanaka, they didn't deserve mention in the *New York Times* article? What Werth says is: "FK-506 is manufactured by its discoverer, Fujisawa Pharmaceutical Company of Japan. But in an unusual set of circumstances, Starzl and his team of researchers and surgeons have had the drug almost exclusively through four years of preclinical and clinical testing. Without them, the drug would undoubtedly have been shelved."

I doubt that "undoubtedly." FK-506's potent im-

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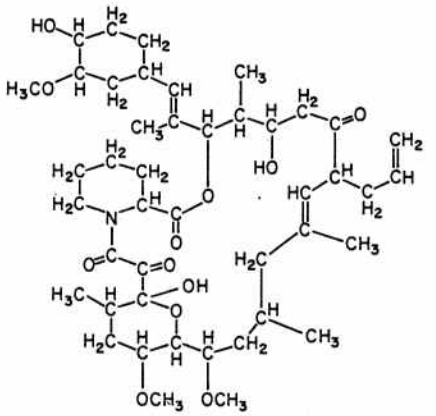
munosuppressant activity was made clear by the true discoverers of the drug. In collaboration with other Japanese scientists, they determined the structure of the molecule and reported it publicly in 1987. The molecule is called a macrolide lactone, the "macro" prefix referring to a whopping 21-membered ring.



As soon as the molecule's structure was reported, many groups raced to synthesize it. Why? To make available more of the naturally occurring molecule is but one reason; to provide access to related molecules (perhaps more active, perhaps less toxic) is another. I suspect that the motive of the Merck Sharp & Dohme team that first succeeded (Todd K. Jones, Sander G. Mills, Robert A. Raemer, D. Askin, Richard Desmond, R. P. Volante and I. Shinkai) was probably simply competitive—Jujisawa refused to supply a rival drug company with more than a minuscule amount (10 milligrams) of the drug. The Merck collective made FK-506 beautifully, in 1989.

A dozen further syntheses followed. An example of how the simple (in this case not so simple, a sequence of 52 transformations) making of a molecule may be transfigured by the use to which it is put is to be found in the beautiful work of Stuart L. Schreiber and his coworkers. The Harvard group (and one at Merck, Sharp & Dohme) found the protein (FKBP, for FK-506 Binding Protein) that binds FK-506 and activates the immune system's workhorse T-cell. They did the molecular biology required to produce substantial quantities of that protein. And in a spectacular feat of tough synthesis made to appear simple, the Schreiber group used its knowledge of ways to stitch together FK-506 to assemble carefully modified variants of FK-506 that carried little probes that could map out the chemical topography of the protein binding the drug. Knowing the landscape of the biological receptor will guide the design of better pharmaceuticals.

Japanese, American names, a multitude of them, blend in the marvelous competitive yet openly communicating panoply of human intellectual and physical effort that is the FK-506 story. A story in which Thomas Starzl's surgical, therapeutic, and managerial quest is but one segment. The *New York Times* article hardly hints at the rest; in my opinion it perverts the process of discovery by focusing on the Pittsburgh surgeon's role.

Who is responsible for such skewing of a beautiful story? I was going to blame the author, Barry Werth. And Dr. Starzl, who obviously thrives on publicity, and whose team supplied Werth with choice quotations that could have pointed to the contributions of others but opted not to do so.

But it's not so simple. The main villains here are we, ourselves. We mythologize. We want to read and believe the myth of the hero-scientist, singlehandedly overcoming obstacles. We desire hagiography; in a corrective fit of seeming realism, catering to jealousy as well as hero-worship, we even want our heroes and heroines to have rough edges. But the archetypical myth is what we crave, oh so strongly.

Not only does Mr. Werth know this, but the publicity offices of our universities and medical schools know it, dishing out stories in the proper mold, of course stressing the local. So do the editors of the *New York Times*. Catering to the myth, a slow, unpremeditated chain of ever-so-slight distortions sets in to pervert a beautiful story of science crafted by a hundred people, some with names we have trouble pronouncing, to twist it into a fable with one slightly fallible but conquering hero. □