Introduction: The Drug With No Name

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THE FIRST two major conferences on FK 506 were at satellite meetings of the European Society of Organ Transplantation (ESOT), which met in Gothenburg (June 1987) and Barcelona (October 1989). In both of these European conferences, the highly focused objective was to assess the potential role of the drug with no name (as FK 506 came to be called) in improving the results after whole organ transplantation. Improvement was construed in terms of patient and graft survival, but also as quality of life. A prime purpose of this meeting was to examine these same clinical issues from the cumulative but still preliminary experience acquired in more than 30 centers in the United States, Europe, and Japan. Clinical reports were concentrated on Friday (August 23, 1991), and included transplantation of previously forbidden organs such as the intestine.

The first descriptions of FK 506 were published in 1987 in Japan. The drug was introduced clinically in early 1989 as a therapeutic last resort in patients who were rejecting their liver grafts in spite of maximum therapy with drug cocktails based on cyclosporine (CyA) and steroids. Because allograft rejection is an analogue of autoimmune disease, the ability to rescue a significant number of these liver recipients as well as recipients of hearts and kidneys from rejection, excited immediate interest in using FK 506 for a wide variety of autoimmune diseases. The results in patients with the skin disease, psoriasis, and nearly a dozen other autoimmune disorders were discussed on Saturday (August 24, 1991).

However, the clinical reports of FK 506 are only the tip of the iceberg with this drug. Research on FK 506, CyA, as well as a third agent called rapamycin (RPM) has created a fruitful new field for sophisticated inquiry about signal transduction in cells. These three drugs (FK 506, CyA, and RPM) bind to small molecular weight proteins in the cell cytoplasm (called immunophilins) and act by altering the way that messages from the environment are conveyed to the interior of the cell and ultimately enscribed on the nucleus. Because the drugs *alter* signal transduction, they can be used as *probes* of signal transduction as described at the meeting.

As discussed, the physiology that is changed by the drugs is not limited to that of cells of the immune system. The most extensively studied nonimmunologic function is that of growth control, and specifically growth control of liver cells. However, the nephrotoxicity, neurotoxicity, and diabetogenecity of these drugs may also reflect altered signal transduction via the immunophilin network.

Now that the meeting is over I hope that we have a better idea of the potential clinical value and proper use of FK 506, as well as a new insight into some previously obscure secrets of cell function.

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