JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.83702
J Inonu Liver Transpl Inst 2024;2(2):47–51

Editorial

The Story of FK 506 Begins with Thomas E. Starzl

Sezai Yılmaz

Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Keywords: FK506, Liver transplantation, Thomas Starzl

Please cite this article as "Yilmaz S. The Story of FK 506 Begins with Thomas E. Starzl. J Inonu Liver Transpl Inst 2024;2(2):47–51".

Tsukaba University was founded in Tsukaba village, located at the foot of Tsukaba Mountain, 45 miles from Tokyo. As can be understood, the university and the village took their name from this mountain. Tsukaba Mountain is one of the most famous mountains in Japan. Since the surface color of the mountain turns purple in the morning and evening sun, the mountain was considered a sacred mountain and was called purple mountain. It is especially known for its twin peaks and is a place of spiritual worship. The two peaks are said to represent male and female deities. They are worshiped as husband and wife and couples visit here to pray for marriage and happiness.[1] Along with Mount Fuji, Mount Tsukaba is one of the famous mountains of Japan. According to folk legend, a god named Mioyano-Mikoto once asked these two mountains for a place to spend the night. Due to its size and grandeur, the proud Mount Fuji rejected this request. However, when the god approached the Tsukaba mountain, he was welcomed with warm hospitality. Since then, Mount Tsukaba has been blessed with rich vegetation, while Mount Fuji has remained a cold and arid mountain.[2]

While Tsukaba University was only in its second decade, it contained 10-15% of all scientists in Japan. Because in addition to more than 40 government institutes, about 100 private institutes were located on this university campus and were working with major corporations. Starzl mentions that Tsukaba village was a large farmland during his visit in 1977, but during his visit a decade later, he says that he saw that it was one of the fastest growing cities in Japan and even an intellectual hotbed.[3]

The chairman of the Department of Surgery at Tsukaba Medical Faculty in 1975 was Yoji Iwasaki, the founder of this department. While Iwasaki was a transplant fellow at the University of Colorado, he worked on anti-lymphocyte globulin, an important discovery in the field of transplantation, in 1964 and 1965.[4] In 1986, in addition to being chair of surgery, Iwasaki was appointed chair of the Institute of Clinical Medicine. Yoji was responsible for training in all clinical medical fields.

In the spring of 1986, there was news of a drug called FK900506 cod, discovered by scientists at an institute established by Fujisawa Pharmaceutical Corporation on the Tsukaba University campus. The aim of these scientists was to investigate natural substances in soil for their anticancer and antirejection features. The research was related to a fungus, which is a type of microorganism. It was found in the soil at the foot of Tsukaba Mountain, near Iwasaki's office. The substance produced from the fungus prevented

Address for correspondence: Sezai Yılmaz, MD. Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye
Phone: +90 532 120 23 76 **E-mail:** sezai.yilmaz@inonu.edu.tr

Submitted Date: 05.09.2024 **Revised Date:** 05.09.2024 **Accepted Date:** 18.09.2024 **Available Online Date:** 09.10.2024

immune reactions in their test system. The substance has not yet been described in the scientific literature and has not been examined outside of Fujisawa Laboratories. Studies on this substance had not attracted much attention until Starzl went to a meeting of the biannual Transplantation Society in Helsinki in August 1986. In one of the small sessions, which was attended by 40-50 people at most, a Japanese surgeon named Takenori Ochiai from Chiba University would present a study with the mysterious code number FK900506 in its title. In a nearby amphitheater, which was filled with congress participants, cyclosporine treatment in kidney transplantation were being discussed. At this major meeting, the wonderful qualities of cyclosporine were praised, but the limitations associated with immunosuppression were noted. The most serious side effect, well known since 1980, was that while cyclosporine protected the kidney from rejection after kidney transplantation, it also damaged the kidney. The same kidney damage was also reported in liver and heart graft recipients. Additionally, high doses of cyclosporine caused high blood pressure, hirsutism, gingival hyperplasia and tremor. When the cyclosporine dose was reduced, the side effects disappeared, but the risk of rejection increased.

Roy Calne from Cambridge, along with Starzl, was one of those waiting for Ochiai's presentation. A Japanese surgeon named Satoru Todo was sitting next to Starzl. Starzl states that he met Todo in October 1980 in Fukuoka, a city on Kyushu Island at the southern tip of Japan. Kyushu was It was Todo's hometown and the city where the university where he received his surgical training was located. Todo was a 33-year-old surgeon who was extremely open to improvement and desired it. He was determined to get a master's degree in liver transplantation, an operation he only knew about from books and journals. This operation had not been performed in Japan until then. Brain death was not accepted in Japan and would not be accepted for many years, so cadaver liver donors were out of the question. He decided to come to Colorado to pursue his dreams, but he was unaware that the program would be moving to Pittsburgh. There was no position available for him in Pittsburgh, but he eventually landed a job in Pittsburgh in January 1984 and was willing to work without a salary for the first 12 months. He was ready to learn and perfect liver transplantation in dogs and rats, which allowed efficient testing of new drugs every day for 2.5 years. He also assisted more experienced transplant surgeons in the operating room almost every night. Ochiai began his speech with a summary of the properties and mechanisms of action of FR900506. He also reported results on heart transplantation in a small number of rats. Rejection was prevented, with remarkable reliability and safety. [5] Later during the discussion, Calne said he had tested the drug supplied to him by Fison Corporation, a British pharmaceutical company that obtained the drug through a trade agreement with Fujisawa. Calne was concerned about the drug's toxicity and the severe vomiting it caused, especially in dogs.[6] Over the following months, Calne became more convinced of the drug's shortcomings. However, according to Starzl, FR900506 was 100 times more potent than cyclosporin and seemed too promising not to abandon this drug. This was the beginning of a debate that would last for more than 3 years.

A trade agreement between Fujisawa and Fison prevented Starzl from supplying FR900506 for testing through normal channels. Thereupon, Starzl and Todo went from Pittsburgh to Japan and met with Fujisawa executives in Nagoya and discussed their laboratory research plans. In response to this meeting, FR900506 development executive director Hiroshi Imanaka flew to London for a meeting with Fison officials. During this trip to Japan, a celebration called Kanreki was held to mark Starzl's 60th birthday. Reaching age 60 is ignored in most American Institutes, but reaching this age is a major traditional event in Japan. A belated Kanreki ceremony was held, organized by approximately 100 former Japanese students, Shun Iwatsuki and Hiro Takagi (Head of the Department of Surgery at Nagoya University). In Japan, it is traditionally believed that after the age of 60, people's burden decreases and a new life begins. The timing of this ceremony was apt for Starzl, as the physical and emotional toll of the past decade had taken its toll on him. Fatigue always accompanied him. Maybe it would be better for him not to get the medicine and start a new discussion. Starzl and Todo waited in Japan for the outcome of the Fujisawa negotiations in London. During this time, they traveled from Nagoya to Tokyo and then south to Fukuoka, where Todo's house was located. A week later Dr. Imanaka returned from England and reported the outcome of the talks with Fison executives in the lobby of a hotel in Fukuoka. Translation was extremely slow, Todo was translating. In the end, Starzl was given a very small amount of FR900506, enough to fill the bottom of a small thimble. Adriana Zeevi and other cellular immunologists in Pittsburgh were able to test this extremely small amount of the drug. Within 1 month, more drugs arrived for testing. Thousands of transplantation experiments have been done on rats, dogs, monkeys and baboons. A research conference was held every Monday night. Initially, 8-10 people attended these meetings. At the end of 1986, the conference hall was not large enough for the crowd exceeding 100 people. Everyone was waiting with great curiosity for the weekly reports on tissue culture experiments. A pediatric surgeon named Nariko Murase was the subject of these meetings, where liver transplants on rats or the results of dog experiments

performed by Todo were the subject of these meetings. The excitement was increasing with each new information. FR900506 was more potent than cyclosporine and did not appear to be very toxic.

The findings in Calne's experiments in the British laboratory that FR900506 was intolerably toxic not only in dogs but also in mice and baboons reduced optimism for this drug. Reports describing these experiments were presented to the congress organizing committee for the ESOT June 1987 meeting to be held in Gothenburg, Sweden. Fearing that the presented abstracts would kill promising developments regarding this drug, Starzl arranged, through transplant surgeons Carl Groth (Stockholm), Hans Brynger (Gothenburg) and Walter Land (Munich), an afternoon symposium the day before the official congress, where all available information on FR900506 could be exchanged. No article about the drug has been published yet. Essentially all research took place in 4 centers: Fujisawa laboratories (Tsukaba and Osaka), Chiba University (Tokyo), University of Cambridge (England) and University of Pittsburgh. The Gothenburg symposium was published in a separate volume in Transplantation Procedings.[7] Anyone reading the papers, especially someone in the audience at the Gothenburg conference, might have wondered whether different researchers were discussing the same drug. Reports from Cambridge were bleak. Those from Pittsburg were optimistic, and those from Chiba were abstaining. The funeral ceremonies of controversial drugs are well known. If this was the fate of this drug, it would be easy to read its tombstone because the name of FR900506 was shortened to FK506.

Before the Gothenburg symposium, the work done in Pittsburgh laboratories was presented by six members of the team to a smaller, more critical group, scientists from the FDA's Oncology and Pulmonary Disease Section in Rockville, Maryland. The preliminary meeting in Rockville, Maryland, was held at Starzl's initiative to alert the FDA to a possible negative atmosphere towards FR900506 at the upcoming conference in Sweden in May 1987. Positive reports from Pittsburgh and negative reports from Cambridge were summarized. Starzl specifically clarified at this meeting that he had no financial connection with Fujisawa Corporation. The goal was to early apply with the FDA, get scientific advice from FDA scientists, and make sure what was being done complied with FDA regulations. In the end, they completed the deficiencies in the research, mostly related to toxicology, in accordance with the FDA's suggestions. It was soon announced that one of the FDA team members, physician oncologist Gregory Burke, had been appointed to lead the FK 506 project and would be the contact person for further questions and discussions. Burke was friendly and hardworking, and was promoted to FDA director for the evaluation of FK 506. His suggestions for FK 506 were always creative, and the last one, almost 2 years later, prevented a tragedy that might have occurred when it was first introduced to humans as a drug. The studies of these medically carefully studied healthy young men and women provide preliminary information about how the drug affects the body when the human body encounters new drugs. Likewise, all over the world, these people are selected from people who do not have alcohol or substance addiction. Such volunteers may have abnormal liver or other organ function tests during and after test doses of new drugs. These people are paid generously and given informed consent. This first step in drug development can be neglected in dangerous drugs used for cancer chemotherapy. When Burke gave the Pittsburgh team a new drug registration for the FK 506 study, steps had not been taken. How to proceed is left to the Institutional Review Board of the University of Pittsburgh (IRB). Then, examples from cyclosporine trials 8 years ago were shown. Richard Cohen, professor of pediatric psychiatry, was chairman of the IRB throughout the development of FK 506. His energy, grasp of complex issues in transplantation, and despite disagreements with him inspired the trust of IRB members and investigators. His initial decision regarding FK 506 was so shrewd that no further escape was possible. The therapeutic superiority of FK 506 was demonstrated almost from the beginning. Since preliminary testing of FK 506 was not done in healthy volunteers, Cohen wanted to give FK 506 for the first time to patients who lost their organs, even though transplanted liver patients were given the most powerful anti-rejection drug (cyclosporine). In other words, FK 506 was given to this patient group for the first time, not to volunteers. These patients were facing death and retransplantation and had nothing to lose. Burke was willing to follow this strategy. However, when the first patient was selected for rescue treatment, Burke immediately called the team to tell them that the initial IV dose was too high. He came to such a conclusion based on what we learned from the laboratory experiences. According to his recommendation, the dose was reduced. If Burke's recommendation had not been followed, the first patient could have died from overdosage. The person whose life was spared with Burke's recommendations was a 28-year-old woman named Robin Ford, who slowly rejected her third liver graft 8 months after her liver transplant. Rescue treatment with FK 506 started on February 28, 1989. Robin recovered. The next patient, a 38-year-old man who had received five liver grafts over the previous 4 years, was a more difficult test for FK 506. Just 3 months after the last transplant, he was rejecting his fifth liver graft. As with Robin, rejection was controlled. Many more patients were treated this way.

From February to July, 1989, in the first 10 liver recipients switched from cyclosporine to FK 506, 7 of the grafts were saved and the livers were functioning well over 2 years of follow-up.[8]

The surgeon who would lead these investigations had to have skills, ideas, and techniques that would allow the flowers to direct or force light through the cracks in the concrete. John Fung was a halfway surgeon but a full-fledged immunologist when he arrived in Pittsburgh in June 1984, a few months after Todo's arrival. In addition to his medical doctor degree, he earned a doctorate from the University of Chicago and took a 2-year leave of absence for laboratory work while in the middle of his general surgery residency at the University of Rochester. Fung helped Adriana Zeevi and Rene Duquesnoy develop tissue culture systems called "mini-transplant" models that in the past required months or years but now allow learning much about the efficacy and mechanisms of action of FK 506 in a matter of days.[9] Not yet 32 years old, he joined the program as a fully trained surgeon and professional researcher equipped with unique knowledge and skills.

The fact that FK 506 could save grafts that had been rejected despite all previously available treatments was known to only a handful of people in the early autumn of 1989. Two of them were Pittsburgh Post-Gazzette science reporter Henry Pierce and deputy editor-in-chief Mark Roth. Both had followed the development of FK 506 closely from the time the drug became interesting and promising. Even though they knew clinical trials had begun, they had promised not to publish the information until it was reported in a medical journal. Larry Altman, a New York Times reporter, arrived in Pittsburgh in late September, a few days after a phone conversation with Starzl about some new and controversial operative procedures involving the transplantation of multiple abdominal organs. There was a wind of criticism against these advanced surgical techniques, the use of which was abandoned some time ago. He was now questioning why operations were restarted and why such an approach was taken. After all attempts to evade telephone cross-examination failed, Starzl reluctantly told Altman that better anti-rejection therapy was available. Altman was an academic physician and the science editor of this newspaper. He realized that FK 506 was the real story, not the operations, and he was intrigued. He spent the next two weeks in Pittsburgh, where he wrote a report on FK 506 that was more expertly written than most and of a scientific quality rivaling that of medical reports. Altman insisted on seeing every patient and examined the records with the meticulousness of a born investigator. He postponed his article to be published in the New York Times, just like the Pittsburgh Post-Gazzette. Both newspapers knew that the first 10 cases were scheduled for publication in The Lancet on October 28, 1989. The voluntary news embargo was important to Starzl because it was feared that premature newspaper reports would jeopardize publication in the Lancet. While the entire team was holding their breath, the embargo lasted only until October 18, 1989, because advance copies of the Lancet article were routinely given to the media. Subsequently, Pierce called Starzl and informed him that the Post-Gazzette would not wait any longer and that the story they had been holding for 6 months would be published in the evening editions. Altman from the New York Times also told Starzl that they would include FK 506 in the morning edition of the Times. News about FK 506 competed with the San Francisco earthquake on the morning of October 19. The article in The Lancet was published as planned.[10]

ESOT's annual meeting was in Barcelona, and 1 week after the article was published, a 10-hour symposium on FK 506 was held in Barcelona. Overnight, FK 506 became the court of appeal (last resort) in the treatment of rejection of liver and other organ recipients that cannot be controlled with conventional treatments. As the news read, patients with failed grafts flocked to Pittsburgh from other centers. Meanwhile, not only rescue but also de novo FK 506 treatments were started in Pittsburgh. By the end of October, much experience and information had been gained regarding de novo immunosuppressive therapy with FK 506 in liver, kidney, heart and lung transplants.[11] Physicians treating all these different organ recipients quickly became convinced that FK 506 was superior to previously available drugs. The incidence of rejection was reduced, the amount of prednisone required was reduced, and the length and cost of hospitalization were reduced. Although side effects, including kidney damage, were similar to those caused by cyclosporine, they were not worse. The new treatment had a better margin of safety than the old one, or so it seemed to the treating physicians.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Holtom DC. A new interpretation japanese mythology and is bearing on the ancestrol theary of shinto. J Relip 1926: 6: 58-77.
2. Yoshida T. The stranger as god: the place of the outsider in Japanese folk religion. Ethnology: An international journal of cultural and social anthropology 1981; 20: 87-100.
3. Starzl TE. The Drug with No Name. In: The Puzzle People. Memories of a Transplant Surgeon. 1st ed. Pittsburgh: University of Pittsburgh Press; 1992: pp288-308.

4. Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 1967 Feb;124(2):301-8. PMID: 4163340; PMCID: PMC2675827.
5. Ochiai T, Nakajima K, Nagata M, Suzuki T, Asano T, Uematsu T, Goto T, Hori S, Kenmochi T, Nakagoori T, et al. Effect of a new immunosuppressive agent, FK 506, on heterotopic cardiac allotransplantation in the rat. Transplant Proc. 1987 Feb;19(1 Pt 2):1284-6. PMID: 2484094.
6. Collier DS, Thiru S, Calne R. Kidney transplantation in the dog receiving FK-506. Transplant Proc. 1987 Oct;19(5 Suppl 6):62. PMID: 2445077.
7. Starzl TE. First International Workshop on FK-506. A potential breakthrough in immunosuppression. Proceedings. Transplant Proc. 1987 Oct;19(5 Suppl 6):1-104. PMID: 2445066; PMCID: PMC3022438.
8. Fung JJ, Todo S, Jain A, McCauley J, Alessiani M, Scotti C, Starzl TE. Conversion from cyclosporine to FK 506 in liver allograft recipients with cyclosporine-related complications. Transplant Proc. 1990 Feb;22(1):6-12. PMID: 1689901; PMCID: PMC2903869.
9. Zeevi A, Yao GZ, Venkataramanan R, Duquesnoy RJ, Todo S, Fung JJ, Starzl TE. Comparative in vitro studies on the immunosuppressive effects of purine and pyrimidine synthesis inhibitors. Transplant Proc. 1993 Feb;25(1 Pt 1):781-3. PMID: 7679843; PMCID: PMC2953385.
10. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramman R, Jain A. FK 506 for liver, kidney, and pancreas transplantation. Lancet. 1989 Oct 28;2(8670):1000-4. doi: 10.1016/s0140-6736(89)91014-3. PMID: 2478846; PMCID: PMC2966318.
11. Todo S, Fung JJ, Demetris AJ, Jain A, Venkataramanan R, Starzl TE. Early trials with FK 506 as primary treatment in liver transplantation. Transplant Proc. 1990 Feb;22(1):13-6. PMID: 1689886; PMCID: PMC2903882.