

Expanded Access and Insights from the Pioneering Work of Dr. Thomas E. Starzl

Christopher M Snyder cms339@pitt.edu
University of Pittsburgh

Collaborators: Zachary Brodt, Jason Rampelt, Nicholas Zautra

Summary //

Expanded Access is a program designed to connect patients with experimental therapeutics when no other FDA-approved options are available for their given disease. In the 1980s, Dr. Thomas E Starzl, the father of modern organ transplantation, pursued the development and approval of multiple experimental immunosuppression compounds to prevent acute organ rejection in transplant patients. We will examine a historical case study of Dr. Starzl's work with OKT-3 (muromonab) which will provide context for a discussion regarding the degree of autonomy we should grant physicians to make ethical decisions in critical Expanded Access cases, as well as the amount of oversight necessary to protect these vulnerable patients. Although this case is historical, we may gain insight into the modern problem of Expanded Access which parallels Dr. Starzl's compassionate use requests for experimental therapies nearly three decades ago.

Introduction //

Due to the rapid pace of medical research and the ever-growing landscape of potential treatment options for patients, Expanded Access (EA), also known as Compassionate Use (CU), and Right to Try laws (RTT) give Physicians the ability to request experimental therapies that from drug companies when no alternative therapies are available. To qualify for EA, the patient must have an immediate, threatening illness for which the benefits of treatment with an experimental therapeutic (ET) outweigh the potential risks. In particular, scientific advances in the area of cancer immunotherapy have led to accelerated innovation in drug discovery and

development, accompanied by an increase in the availability of targeted therapeutics with fewer adverse side effects than traditional chemotherapy. Improvements, variations, and countless treatment combinations provide unique EA opportunities for patients who have exhausted all available, approved treatments. Currently, oncologists view EA programs as necessary tools in their repertoire, with a majority asserting that they are able to look over the data of ETs and make informed decisions in the best interest of their patients (1).

The EA process involves three major steps: obtaining the investigational new drug (IND) application from a pharmaceutical company, receiving institutional review board (IRB) approval, and clearing the request with the US Food and Drug Administration (FDA) (2). This multi-step process may take a considerable amount of time for physicians to gain all of the necessary permissions and approvals which is not practical for critical, time-sensitive situations. Recently the FDA has streamlined the process for emergency cases down to a day, and the IRB can be notified up to 5 days after treatment (3). Additionally, the ethical oversight involved in these cases can be complex, but the gravity of these situations warrants expediency; it is difficult for the FDA to review the patient history and the ET research thoroughly within an appropriate time frame. The complexity of this process, along with the time-sensitive nature has caused some physicians to question whether the current required level of oversight is redundant or truly beneficial to these critically ill patients. As a result, the vast majority of states have passed RTT laws, which remove the FDA and IRBs from their oversight roles, simply requiring physicians to gain approval from drug companies to use their ETs and to obtain informed consent from their patients before proceeding with treatment (4).

However, RTT laws have received criticism for promoting a “wild west” culture of drug experimentation, with critics maintaining that the current EA program is superior as it protects patients with the benefit of additional oversight. Yet there are still many problems associated with the process of EA as it stands. The history of medicine can offer much-needed perspective to the modern problem of EA requests for critical patients. One historical example, which parallels the modern case of EA in oncology, was the once-burgeoning field of organ transplantation in the 1980s. Specifically, we will analyze how the father of modern transplantation, Dr. Thomas E. Starzl, navigated the complexity of EA (at the time called CU) to treat acute organ rejection patients with experimental anti-rejection drugs. Dr. Starzl’s work in the 1980s represents a unique intersection between the old guard of physician-scientists

accustomed to making ethical decisions autonomously and new policies necessitating IRB oversight. This is distinct from the regulations today which require approval from an institution's respective IRB for the vast majority of research/treatment involving experimental treatment of human subjects. Since the balance of autonomy and oversight requires constant negotiation, this case study of the innovative ideas and work of Dr. Starzl provides insight into the level of oversight appropriate for cases involving the present-day compassionate use of a therapeutic. We will examine how Dr. Starzl's knowledge of the literature and emphasis on ethical responsibility represents an archetypical physician utilizing EA as an ethical agent; additionally, we will discuss EA for critical patients in the context of Dr. Starzl's work, observing how he navigated this ethically challenging landscape.

The Old Guard// The Physician as an Ethical Agent

Physicians prescribing ETs should be well-versed in the literature surrounding these novel therapies in keeping with the knowledge available at the time. Dr. Starzl's list of credentials is lengthy: he is one of the most published medical scientists of the 20th century, pioneering protocols for some of the first successful kidney transplants in the 1960s and the first-ever successful liver transplant in 1967 (5). These feats, among many others, have resulted in his recognition as one of history's greatest surgeons. After an early string of successful kidney transplants in 1963 at the University of Colorado and the establishment of the efficacy of Imuran/Prednisone immunosuppression, Starzl's ultimate goal, liver transplantation, became possible (6). However, his goal was not without risk.

Dr. Starzl was accustomed to making clinical decisions based on experimental data. Often, he would have to make ethically challenging decisions such as whether to move from an animal model to its clinical implementation in patients for transplantation procedures on the basis of animal research data. During the advent of kidney and liver transplants, there were no formal oversight committees or IRBs, leaving all decisions regarding the technical details and use of these procedures up to the surgeon (7). Dr. Starzl performed over 200 liver transplants in dogs, refining the protocol over time (6). Liver transplants are intricate and technically-intensive procedures, requiring dissection and anastomoses of many vital blood vessels. Additionally, factors released by the liver can prevent blood clotting, requiring a delicate balance of blood

coagulation factors while preventing embolisms from forming (8). Starzl began to treat children with biliary atresia cases. These patients lacked other treatment options and early mortality was certain. The transplants seemed successful initially, but after about 20 days, a complication of the surgery revealed itself. The administered clotting factors necessary to prevent excessive blood loss resulted in pulmonary embolisms that were not seen in the canine model. Starzl and his team self-imposed a 3-year moratorium on liver transplants, in which he continued to research this problem, until the first, true success in 1967 (6).

Dr. Starzl thought deeply about medical ethics, believing that the ethical choice was to continue researching the liver transplant procedure in animal models before trying again in humans. Later in his career, he reflected back on this moratorium; “In such efforts, surgeons bear a deep moral responsibility to distinguish between what is best studied in laboratory animals and what is a reasonable clinical experiment” (9). The number of variables in experimental surgery made it exceedingly difficult to transition from testing a novel procedure in an animal model to treating a human patient. Making this morally intensive decision required careful assessment of the available research and weighing its potential benefits versus risks; this is akin to the decision regarding whether to prescribe an ET treatment for a patient – physicians must decide whether there is sufficient evidence of ET efficacy based on the available data prior proposing the ET as a last-ditch treatment option for the patient.

Eventually, the decision to move forward with experimental therapies was no longer solely in the hands of the physician-scientist. Public demands for oversight of human research prompted the National Research Act in 1974, which established that federally sponsored studies involving human subjects would need IRB approval (7). Subsequently, IRBs began popping up in university medical centers across the country. To Starzl, IRBs posed somewhat of a hindrance to his research, and he was often at odds with the nascent IRBs over the design of his experiments; Starzl was a surgeon who cared deeply about his patients and spent much of his life reflecting on medical ethics. In one correspondence with his colleague Dr. Henry Bahnson, chair of surgery at the University of Pittsburgh, Starzl explained that physicians need to actively negotiate the ethical design of human experimentation. He said,

“It would be a pity, for example, if the transplantation team continued its dependence on the [IRB] for the design of investigations, of which some may (and in my opinion, will

be) later viewed as unjust. A great University like Pittsburgh cannot afford to slavishly mimic the imperfections (or advances) which are reported from elsewhere”(9).

The so-called “imperfections” Starzl discusses are illustrated by Starzl’s correspondence with the University of Pittsburgh’s IRB over his proposed design of a pilot study for “A Trial of Liver Transplantation under Immunosuppression with [Tacrolimus]” in 1989. His correspondence with Dr. Richard Cohen, head of the IRB at the time, reveals that the IRB wanted the study to be randomized and blinded. Randomized clinical trials were coined the ‘gold standard’ of evidence-based medicine in the 1980s. Surgeons in general could appreciate the utility of RCTs, yet some viewed RCT design as approaching somewhat of a dogma in research and presented a particular challenge for surgical experimentation.

In Starzl’s case, he originally designed this tacrolimus pilot study to be historically controlled, evaluating tacrolimus against historical data for the standard of care, cyclosporin A (10). Preliminary data for the use of tacrolimus as rescue therapy for CsA patients showed that tacrolimus was more effective in preventing liver rejection as compared with CsA use alone. All 8 liver-transplant patients treated preliminarily with tacrolimus had no signs of rejection or complications, but Dr. Starzl wanted more data on the dosages before he compared the two drugs directly. He claimed that the study physicians should not be blinded since they needed to adjust the dosage of tacrolimus and stated that the RCT would be unethical as a result (10). The IRB disagreed, maintaining that only a head-to-head RCT would prove tacrolimus to be superior to CsA(11). In this case, the IRB was more focused on this design feature of the RCT to enable an unbiased comparison of the treatments, rather than on the tacrolimus dose adjustment to protect the safety of patients, replying that they did not see RCT as unethical, even in light of his responses. This exchange highlights the necessary role of the physician as an ethical agent in the ever-present negotiation between autonomy and oversight in medicine and experimental design.

Standards of Care // Transplant Rejection in 1984

The case we will discuss examines Dr. Starzl’s use of OKT-3 (muromonab) for 11 patients from August to October of 1984. OKT-3 was the first monoclonal antibody approved for transplants by the FDA in 1986 and is used to inhibit T-cell function through targeting of CD3 protein, but it was still an ET in 1984 (12). What was it about these patients that prompted Dr.

Starzl to use an ET instead of an FDA-approved treatment? Despite being treated with the standard of care (CsA and Prednisone), certain transplant patients still rejected their grafts despite CsA being the strongest approved immunosuppressive agent at the time. With the large volume of transplants performed at the University of Pittsburgh – one of the premier transplant centers in the 1980s – a significant proportion of kidney, liver, and pancreas patients did not tolerate CsA, or they were contraindicated for this treatment. Around this time, CsA was also found to cause kidney damage after sustained use (13), an especially counter-productive effect for kidney transplant patients. Alternatively, Anti-Thymocyte Globulin (14) was approved in 1981 to prevent organ rejection, yet ATGAM was a mixture of polyclonal antibodies which targeted lymphocytes in general (14). This meant a patient’s B-cell and T-cell counts would often fall to dangerously low levels, raising susceptibility to infections. If organ rejection did not kill them, bacteria or viruses likely would.

These standards of care were effective in the majority of cases but had many undesirable side effects. The patients who did not respond well to treatment lacked other viable FDA-approved options. This led Dr. Starzl to search for another experimental immunosuppressive agent. In the early 1980s, the Ortho Company refined the polyclonal ATGAM serum, manufacturing monoclonal antibodies, called OKT-3, to target and inhibit T-cells that infiltrated and attacked the organ grafts (15). After reviewing the literature, Dr. Starzl found OKT-3 to be a “more-potent” immunosuppressive option, without the long list of side effects of the less specific, but FDA-approved, ATGAM (16).

Patient vs Protocol// A Case Study of Starzl’s Use of OKT-3 for Acute Organ Rejection

Patient A received a kidney transplant at the University of Pittsburgh in late July of 1984 (17). After a month, she began to show typical signs of acute organ rejection: sensitivity to pressure and graft infiltration. Despite being given the CsA standard of care, her body’s immune system rejected the graft. Dr. Starzl, reached out to the Ortho Company to request the use of OKT-3. On August 20th the Ortho Company replied with details on the treatment protocol along with a direction to notify the IRB, which he neglected to do (18). The following day, Dr. Starzl began OKT-3 treatment for 14 days, and Patient A had a “spectacular recovery,” going home without further complications (19). Over the following two months, Dr. Starzl requested

individual compassionate use clearances from the IRB for just seven out of eleven patients showing serious signs of acute rejection, and the IRB approved all submitted cases within about 3 days. On October 22nd, the IRB approved the broad CU for OKT-3 as a rescue treatment for previously treated, non-responsive rejection patients (20). On this same date, Starzl replied to Dr. Cohen, of the IRB, and reported that he failed to request permission for four patients with OKT-3 treatment (19). It is curious why he requested approval for seven patients during this time but neglected to notify the IRB about these other four cases until after the broad mandate was approved. The mystery surrounding these four cases will guide the following discussion.

Almost two years later, the FDA sent an investigator, Daniel Mechenbier, to review this controversy. Mechenbier's report after his investigation revealed that Dr. Starzl did not submit a request for FDA approval and did not receive timely IRB approval for 4 patients prior to their treatment with OKT-3 (21). The IRB approved these cases only after the blanket compassionate use protocol. This delay meant that Starzl waited to request permission for these four patients until after he received full sale approval for compassionate use cases in organ transplants. In his response to the FDA, Starzl rebutted that these were rescue cases and time was of the essence: upon the first signs of rejection, the host immune system is already damaging the graft (22). By the time the first round of the standard immunosuppression was shown to be ineffective, the organ would have sustained significant damage, prompting swift rescue measures. In Dr. Starzl's mind, delaying treatment until receiving IRB approval would have been viewed as unethical, especially since the IRB had approved treatments without question for all the requests Dr. Starzl made during these months. The FDA wrote back to Starzl to reiterate the proper CU protocol, but notably, there were not any formal repercussions regarding Dr. Starzl's actions (23).

In one case Dr. Starzl claims he did not receive approval for Patient A prior to treatment with the ET, believing the use of OKT-3 was covered under a different monoclonal antibody which the IRB approved the previous year. The protocol in question was for an antibody known as CBL1, which targets "immunoblasts invading grafts" (24). Could it have been possible that Dr. Starzl did not understand the difference between these two antibodies?

The case for Starzl's confusion between these antibodies is thin. Dr. Starzl and Dr. Paul Terasaki, the pioneering tissue typer at UCLA, were in the midst of a phase I clinical trial of CBL1. The introductory pages of their study begin with a table citing the differences between ATGAM, OKT-3, and CLB1. OKT-3 has an entirely different mechanism of action by targeting

T-cells, rather than immunoblasts (24). Dr. Starzl is the principal investigator of this study, so it is doubtful that he did not understand the differences between these two drugs. Furthermore, he requested IRB approval for seven patients in the following months, so he was aware of the requirement to request access. This points to another reason for failing to request IRB approval for Patient A.

Experimental drugs are often in short supply, or tentatively available depending on FDA rulings. Dr. Terasaki initially reached out to Dr. Starzl about joining his clinical trial for monoclonal CLB1 in November of 1983 and Dr. Starzl accepted the proposal in mid-December after receiving IRB approval (25,26). The two began treating patients with this antibody, similar to what Starzl accomplished later with OKT-3 and the Ortho Company. CLB1 showed “striking reversals of rejections” in patients who had failed other immunosuppression methods prior to treatment (25). However, in February of 1984, the FDA requested volumes of further data for the manufacturing process for Terasaki’s antibodies after minor adverse reactions in patients (27,28). As monoclonal antibodies had not yet been approved at this stage and the FDA was cautious with the new treatment; the result was a halt of the use of this antibody for the foreseeable future. A frustrated Dr. Terasaki wrote to Dr. Starzl and clarified that Dr. Starzl may not use the antibody until further notice (29).

After one short month of using this revolutionary technology, the FDA put a hold on the phase I trial, leaving Dr. Starzl without a supply of antibodies. Once he began working with the Ortho Company in the same year and was granted access to OKT-3 for individual compassionate use cases, there may have been serious doubt over the dependability of the antibody supply. Additionally, there is a concern that with the more dire EA case, there is a greater chance for adverse reactions that may be unrelated to the ET but cause a halt in the ongoing clinical trials. The risk of treating his sicker patients with OKT-3 was that any adverse reactions (whether caused by the drug or not) might negatively affect the approval process for this ET with the FDA or prevent the Ortho Company from continuing to send OKT-3 antibodies for compassionate use cases to help the patients in critical need.

Table 1: Timeline of Events

Date	Event
November 10 th , 1983	Terasaki initially reached out to Starzl about joining a phase I clinical trial for CLB1
December 15 th , 1983	Starzl accepted the proposal
February of 1984	FDA requested volumes of further data for CLB1 and halted the study
August 20 th , 1984	Memo from the Ortho company detailing the steps to treat Patient A with OKT3
August 21 st , 1984	Starzl began treatment of Patient A with OKT-3 for 14 days (neglecting to notify FDA and IRB)
September 17, 1984	Starzl to Ortho Company – Patient B’s complications justified as not OKT3
September 28, 1984	Starzl asks for compassionate use for OTK-3 for 2 patients
October 22, 1984	Clinical trial of OKT-3 approved
October 22, 1984	Starzl reaches out to Cohen (IRB) and details how he failed to request permission for compassionate use for Patient A and others
October 31, 1984	IRB approves broad mandate protocol D83-083 for compassionate use of OKT-3 for non-responsive patients
February 2, 1986	FDA sends results of the investigation into Starzl’s lack of notification in 1984
April 24, 1986	FDA’s official response regarding the investigation
August 20 th , 1984	Memo from the Ortho company detailing the steps to treat Patient A with OKT3

Discussion //

The EA process as it currently stands is not efficient enough for critical patients and may not confer the intended benefit of additional oversight. Requesting permission from the drug company and FDA and notification of the IRB requires concerted time and effort on the part of the physician, and this burden may even be multiplied across a number of patients, as in Dr. Starzl’s case. This process became so time-consuming for Dr. Starzl, that he claimed that it was not expedient enough for him to request permission for OKT-3 for one of his patients –

potentially Patient A (30). If additional oversight provided an impactful filter for cases that should not be approved, then it would be worthwhile to wait the time period required for approval; however, the FDA approves over 99 percent of compassionate use requests, which raises questions regarding the utility that additional (FDA) oversight provides for these expedient situations (2). As nearly all EA cases are approved, this process may not provide a meaningful filter to weed out improper or unsafe requests cases and delay timely treatment.

The balance of quality and time-sensitive oversight should be the major concern of the FDA while reviewing critically ill patients. The IRB and FDA are in similar positions in EA cases: they must review vast amounts of patient history and highly specialized literature surrounding the experimental therapy in an expedited amount of time in order to show respect for the dire circumstances. Dr. Cohen noted how Starzl's compassionate use requests made it "necessary for the IRB to have to respond quickly and perhaps without enough information in emergency situations" (31). In Dr. Starzl's case, the experimental therapy OKT-3 was a constant, but there was still enough complexity to warrant Dr. Cohen's concerns: each request involved a special case transplant patient, each with unique comorbidities and vast patient histories that had led them to receive the transplant in the first place. EA requests leave the FDA with one of two difficult choices; either review the extensive research and patient history slowly and carefully (delaying treatment of a sick patient) or rush the approval through as soon as possible without as careful a review.

Additionally, these extra two ethical oversight organizations may be extraneous to the filtering process since the two parties with the most knowledge of the patient and the experimental therapy are the physician and the company which developed it, respectively. In Starzl's case, he may take on the greatest proportion of responsibility for the well-being of the patient. As the patient's attending physician, he is well-versed in their history, past treatments, and the Ortho Company's preliminary OKT-3 research. The Ortho Company was also in a position of immediate responsibility. They would have to review and grant permission to Starzl to use OKT-3 after they decide that the drug use would be appropriate for the specific patient. As the creators of this ET, they were in a strong position of authority and responsibility to approve the use of OKT-3. Furthermore, companies take on the financial responsibility of providing treatment as well as any responsibility for potential adverse reactions of the ET. Progressive diseases weaken patients, potentially making them more susceptible to complications of ETs.

These adverse reactions can adversely affect the outcome for patients and of the clinical trials, as was the case with Dr. Terasaki's CBL1 antibodies, so companies are especially cautious when approving EA permission. After both physician and company approval, further oversight may be unnecessary for expedited and critical cases.

On another note, the outcome of the three-pronged framework (FDA, IRB, and drug company) may engender a culture of compliance, rather than responsibility. The responsibility of the decision of whether to treat their patient is outsourced to these two oversight organizations. This is akin to Samuel Bowles's discussion of incentives in *The Moral Economy*: incentives can obscure the intrinsic motivation of operating morally in a market (32,33). By the same token in medicine, the FDA and IRB's current role of ensuring compliance with EA decisions can obscure the motivation of physicians to negotiate this morally pertinent decision. Once the IRB and FDA have signed off on the EA decision, the problem has been effectively answered. For Dr. Starzl, as he developed his moral compass during a time when there was little ethical oversight, he had plenty of practice deliberating ethics in surgery, and this often resulted in back-and-forth discussion of treatment and experimental design with the IRB, rather than simply accepting the suggested revisions to speed up the approval process.

Critics of removing FDA oversight of emergency EA requests may cite that the additional oversight may protect vulnerable patient populations. This criticism may stem from the growing public distrust of both pharmaceutical companies and physicians and conjures the image of rogue physicians conspiring with companies to experiment on patients with ETs. However, the utility of compassionate use data is limited. These cases lack controls and have dozens of potential confounding variables as the patients have been through multiple treatments and have already progressed negatively for a period of time. The only potential value of the CU process which may be discerned from the data may be for patients with rare conditions. Despite this, the ethics of collecting this data is no different from clinical trials, where the patient is given informed consent and agrees to the treatment weighing the risks and the benefits.

A particularly successful example of Physicians and Companies pursuing ethical EA programs was Janssen's 2019 daratumumab for multiple myeloma patients who did not qualify for the phase III clinical trial (34). The program was designed by NYU's medical ethics department, and it aimed to review requests anonymously and quickly facilitate the equitable and transparent distribution of a highly requested drug. All proposals were deliberated on by an

independent committee, with little intervention from Janssen. By modeling this daratumumab compassionate use approval system, drug companies can improve critically ill patients' timely and ethical participation in EA programs across the country.

In summary, the case of Dr. Starzl illustrates the archetypical, morally conscious physician in EA cases. Physicians should model the breadth of knowledge that Starzl had about the available research and deliberate upon the ethics of potential EA cases before recommending an ET to a patient. Additionally, there is potential redundancy in oversight by FDA and IRBs for the EA process in time-sensitive situations. Dr. Starzl's actions follow an early form of Right to Try, whereby the physician and the drug company work together to determine whether patients are eligible for therapy with ETs. The additional oversight may be beneficial in less expedient cases, but in emergency situations, the physician and the drug company provide sufficient ethical oversight for the use of ETs, while respecting the exigent circumstances of critical patients.

References

- 1) Fernandez Lynch H, Salam T, Gould P, Bateman-House A, Kimberly L. Navigating the Expanded Access Pathway to Investigational Drugs as an Academic Oncologist. *JAMA Netw Open*. 2023;6(2):e230060. doi:10.1001/jamanetworkopen.2023.0060
- 2) Jarow JP, Lurie P, Ikenberry SC, Lemery S. Overview of FDA's expanded access program for investigational drugs. *Ther Innov Regul Sci*. 2017;51(2):177-179. doi:10.1177/2168479017694850
- 3) Center for Drug Evaluation and Research. (2020, March 26). Individual patient expanded access applications for emergency use. *U.S. Food and Drug Administration*. <https://www.fda.gov/drugs/investigational-new-drug-ind-application/emergency-ind-timeline>
- 4) Agarwal R, Saltz LB. Understanding the right to try act. *Clinical Cancer Research*. 2020;26(2):340-343. doi: 10.1158/1078-0432.CCR-19-2015
- 5) Eghtesad B, Fung J. Thomas Earl Starzl, MD, PhD (1926–2017): Father of Transplantation. *Int J Organ Transplant Med*. 2017;8(2):e1. Epub 2017 May 1. PMID: PMC5549009.
- 6) Starzl T.E., *The Puzzle People: Memoirs of a Transplant Surgeon*, University of Pittsburgh Press, 1992
- 7) Aulisio MP, Why Did Hospital Ethics Committees Emerge in the US? *AMA Journal of Ethics HISTORY OF MEDICINE*. Vol 18.; 2016. www.amajournalofethics.org546
- 8) Dababneh Y, Mousa OY. Liver Transplantation. 2022 May 29. *StatPearls*. Treasure Island (FL): StatPearls Publishing
- 9) Starzl T.E., Letter to Dr. Henry Bahnson, 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 50, File 1, *University Archives, Archives & Special Collections*, University of Pittsburgh Library System
- 10) Starzl, T.E., A Trial of Liver Transplant Under Immunosuppression with FK506, 15 August 1989, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 316, File 50, *University Archives, Archives & Special Collections*, University of Pittsburgh Library System
- 11) Horton, J.A., A Phase II Historically Controlled Trial of Primary Liver Transplantation Under Immunosuppression FK506, 22 December 1989, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 316, File 50, *University Archives, Archives & Special Collections*, University of Pittsburgh Library System
- 12) Ortho Transplant Center Study Group, Randomized Clinical Trial of OKT3 Monoclonal Antibody For Acute Rejection, 1 June 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-

2017, UA.90.F68, Box 294, File 2, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System

- 13) Whiting PH, Thomson AW, Blair JT, Simpson JG. Experimental cyclosporin A nephrotoxicity. *Br J Exp Pathol.* 1982 Feb;63(1):88-94. PMID: 7066186; PMCID: PMC2040750.
- 14) Mohty, M. Mechanisms of action of anti-thymocyte globulin: T-cell depletion and beyond. *Leukemia* 21, 1387–1394 (2007). <https://doi.org/10.1038/sj.leu.2404683>
- 15) Ortho Transplant Center Study Group, Randomized Clinical Trial of OKT3 Monoclonal Antibody For Acute Rejection, 1 June 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 294, File 2, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 16) Starzl, T.E., Letter to Herbert Needleman, 25 September 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 2, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 17) Starzl, T.E., Records, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 422, File: Recipients 1973-1996, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 18) Carey, G. Treatment Steps for Patient with OKT3.Pan, 20 August 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314 File 1. *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 19) Starzl, T.E., Letter to Dr. Richard Cohen, 22 October 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314 File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 20) Needleman, H., Letter to Dr. Thomas E. Starzl, 22 October 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 21) Mechenbier, D. Department of Health and Human Services FDA Inspection, 1986, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1. *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 22) Starzl, T.E., Response to FDA Inspection, 24 February 1986, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 23) Kelsey F., FDA Letter to Dr. Thomas Starzl, 24 April 1986, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System

- 24) Starzl T.E., A Phase I Clinical Trial of Monoclonal Antibodies for the Reversal of Intractable Whole Organ Rejection, 23 November 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 294, File 2, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 25) Terasaki, P., Letter to Dr. Thomas E. Starzl, 10 November 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 148, File 51, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 26) Starzl T.E., Letter to Dr. Paul Terasaki, 15 December 1983, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 148, File 51, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 27) FDA, BB-IND 1933 for CBL1, 16 January 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 148, File 51, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 28) FDA, BB-IND 1933 for CBL1, 2 February 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 148, File 51, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 29) Terasaki, P., Letter to Dr. Thomas E. Starzl, 7 February 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 148, File 51, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 30) Starzl, T.E., Letter to Dr. Richard Cohen, 17 September 1984, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 31) Cohen R., Letter to Dr. Thomas E. Starzl, 28 April 1985, Dr. Thomas E. Starzl M.D. Papers, 1908-2017, UA.90.F68, Box 314, File 1, *University Archives*, Archives & Special Collections, University of Pittsburgh Library System
- 32) Bowles, S. (2016). *The moral economy: Why good incentives are no substitute for good citizens.* *Yale University Press.*
- 33) Kranton, Rachel. 2019. "The Devil Is in the Details: Implications of Samuel Bowles's *The Moral Economy* for Economics and Policy Research." *Journal of Economic Literature*, 57 (1): 147-60. DOI: 10.1257/jel.20171463
- 34) Lee SB, Murata AY. The Expanded Access Cure: A Twenty-First Century Framework for Companies. Vol 156.; 2019. <https://www-jstor-org.pitt.idm.oclc.org/stable/45106481?seq=5>

