Statement on the Nomination of Dr. Thomas E. Starzl, MD, PhD

Dr. Starzl's accomplishments and contributions qualify him for consideration for the designation of Distinguished University Professor. Most notably, his contributions transcend numerous fields including transplantation, immunology, and liver development and pathobiology. Furthermore, his contributions to these fields have placed him at the forefront of many of the most pressing ethical questions in medicine over the past century. Below is a summary of Dr. Starzl's research as well as his contributions and stature within the University as a whole. Not detailed, however of equal importance, is his role in training an entire generation of surgeons and physicians, as well as ethicists and public health practitioners, during the course of his remarkable career.

Dr. Starzl's Research

It would be exceedingly difficult to overstate the impact of Dr. Thomas Earl Starzl on the practice of Medicine in the 20th and early 21st centuries. Many of his achievements endure in the lives of his patients and in the work of those who were influenced, directly or indirectly, by his professional ethos. Such endpoints currently lie beyond our ability to measure. Fortunately, there also exists an extensive first-hand account of these efforts in his medical writings (www.starzl.pitt.edu). The website presents this historical but in many ways still current literature as a series of interrelated themes. This approach imposes a sense of orderliness on a large volume of work but this is to a large extent artificial, as many of these themes were concurrent, or were temporarily set aside until they could be readdressed after seemingly intractable barricades had been overcome. Additionally, a thematic summary may in some ways dilute appreciation of the scope of Starzl's contributions, since many themes contain multiple subcategories, any one of which would independently suffice for a successful medical career. A high level view of these separate areas of investigation is shown in Table 1.

Some selected highlights of this collection are abstracted here, and expanded within individual sections that focus upon specific themes of investigation.

Liver transplantation

The name of Thomas E. Starzl is first and foremost synonymous with liver transplantation. Starzl not only single-handedly developed the surgical techniques necessary for both donor and recipient operations at a time when organ transplantation was considered unachievable, but he also provided the conceptual breakthroughs necessary to allow a foreign organ to exist for an extended time within the body of an unrelated person.

It is difficult for the modern reader, knowing the outcomes, to reproduce the vacuum of hopelessness that existed in that era regarding organ transplantation. It is even less likely that one would stake a career on the prospect of venturing deeply enough into an area of obvious science fiction in an effort to save those standing at the brink of nonexistence. This <u>www.starzl.pitt.edu</u> website stands as a post hoc testament to the man who actually did that.

The years 1945-1992 encompass the theoretical beginnings of organ transplantation and include the year in which liver transplantation was recognized as a valid clinical service. Figure 1 illustrates the top 20 individuals who were cited as primary (first) authors on medical articles of liver transplantation during this period. All of these individuals have made unique contributions and are deserving of

recognition in their own right. However, the overarching predominance of Starzl's achievements is uncontestable and is clearly highlighted in this figure.

If we look at this period from the perspective of the most cited publications in liver transplantation, we reach the same conclusion. Figure 2 shows the top 25 most highly cited publications in the area of "liver transplantation" during this time. Starzl is the first author on 13 of these 25 (53%) papers, including the top three, and is first or coauthor on a total of 17 (68%) of these publications. In total, his publications dealing specifically with liver transplantation have been cited over 21,000 times to date.

Kidney Transplantation

Kidney transplantation was a surgically less demanding operation than implantation of the liver, but in the 1950s the barriers to long-term kidney allograft survival remained insurmountable. Dr. Starzl realized that the road to liver transplantation must of necessity travel through the kidney, and he devoted himself to dissecting this riddle. In 1963 he overthrew the established wisdom regarding the irreversibility of organ rejection by showing that immune rejection of the kidney could be successfully reversed by the timely addition of corticosteroid medication. Again, as we look back from a perspective of over 331,000 patients whose lives have been extended by kidney transplants, it is difficult to imagine that a single individual could precipitate such a massive mid-course correction in medical practice. But the record is clear and the results are unequivocal. The current success in kidney transplantation links directly back to Starzl's dog experiments and subsequent human kidney transplant series that leapfrogged the work of other equally adept investigators who were constrained by the prevailing concepts of the time.

The first successful kidney transplant on identical twins (without the possibility of rejection) by Dr. Joseph Murray at the Peter Bent Brigham Hospital on December 23, 1954 was a technical tour de force and ushered in the era of modern kidney transplantation. Murray was appropriately awarded the Nobel Prize in 1990 for his achievements. However, if one examines the contemporary kidney transplant literature (Figure 3), arbitrarily selecting the encompassing period of 1945-1979, it is again clear that Dr. Starzl's contributions are at the forefront. His over 1600 citations dwarfed those of the luminaries of kidney transplantation. Many years later, a number of Dr. Starzl's long-surviving kidney transplant patients would reprise their role as pioneers of transplantation by confirming that significant fragments of the donor immune system persisted in the recipient pari passu with organ allograft acceptance, or, in common parlance, "tolerance". This first-hand experience of long-term transplant organ survival would again force Starzl into the position of an iconoclast against prevailing medical opinion with his conclusion that not only were organ and bone marrow transplantation intimately related, but somehow a peaceful coexistence between donor and recipient immune active cells was a necessary precondition to long term survival of transplanted organs or cells.

<u>Chimerism</u>

Work in the 1940s and 1950s replicated naturally occurring chimeras (i.e., animals with in utero exposure to foreign blood cells) to study immune interactions underlying the permanent acceptance of the foreign blood cells by these animals. Experimental weakening of the host immune system by, for example, irradiation with subsequent blood cell delivery could lead to "radiation chimeras" with one set

of genes in the body organs and another in the blood cells. This formed the basis of bone marrow transplantation. In contrast, organ transplantation was thought to consist of the implantation of an antigenic but otherwise immunologically inert organ (i.e. kidney) into a recipient with an immune system that would need to be chronically weakened to prevent rejection.

In 1962 Starzl pointed out that an animal with blood cell chimerism was more likely to accept subsequent tissue grafts from the same donor without the need for chronic immunosuppression, if a certain critical time threshold could be successfully crossed. The tools to study this so-called mutual adaptation in any detail had yet to be developed. However, the concept of aiming for tolerance, as opposed to chronic immunosuppression, as the desired endpoint in organ transplantation suffused Starzl's approach to drug therapy. The early dog kidney transplant experiments served not only as the basis for successful clinical transplantation, but also provided evidence of long-term tolerance when using Starzl's prototypic drug regimen incorporating pre-transplant induction therapy and a steroid-sparing approach.

Thirty years later, the ability to genetically identify chimeric cells in extremely small numbers enabled Dr. Starzl and colleagues to discover that such donor cells persisted in the bodies of long-term kidney transplant recipients who were clinically tolerant of their grafts. This finding has been extended to patients who have received other types of organ transplants, and even to bone marrow transplant patients who were previously thought not to retain any vestige of their own blood cells. Dr. Starzl realized this finding as conceptually unifying bone marrow and solid organ transplantation. He interpreted this as evidence that "mutual accommodation" is an underlying principle in graft cell or organ tolerance, and that the small population of chimeric immune active cells, i.e., microchimerism, was active in, and represented evidence of, this process. This discovery has been subsequently confirmed in many other laboratories and the implications of this finding are presently the subject of intense investigation.

When the time period incorporating the discovery of microchimerism and subsequent widespread confirmation of its existence is examined (arbitrarily 1991-2005), the papers authored by Dr. Starzl are again seen to comprise the most heavily cited publications in this area of the medical literature (Figure 4).

Literature Impact: Publications, Citations and Medical Journals

In addition to the documented impact that Dr. Starzl's work has had in multiple areas of Medicine, the sheer volume of the publications appears unlikely to be soon surpassed. The Web of Science (WoS) records 2281 publications in a total of 248 journals. In one remarkably productive period spanning 15 years (1985-1999 inclusive), from ages 59-73, Starzl published over 50 papers annually. Within this time frame, that number surpassed 100 per annum for a consecutive period of 8 years (1988-1995 inclusive) with a peak output of 197 publications in 1991. Assuming a 365 day work year- which seems appropriate- this averages to one publication every 3.5 days for 15 consecutive years with a peak of 1.8 days per publication in 1991. (Figure 5)

WoS also provides a high ranking to these publications on the basis of citation analysis. At the time the website <u>www.starzl.pitt.edu</u> was launched in 2012, the entire output of 1582 publications for the 1985-1999 period had received an average of 35.2 citations per paper, with an h-score of 117 (i.e., 117 publications were cited 117 times or more). Individual articles on diverse topics during this period that

already had been highly cited by 2012 were of special interest. By the end of 2015 (4 years after the website launch), all of the citations had expanded. The subjects of these articles included, but were not limited to, liver surgery for cancer (473 citations), review and update of liver transplantation (545 citations), oncologic complications of immunosuppression (484 citations), first-ever demonstration of immunologic surveillance of a human malignancy (1091 citations), introduction of FK506 (Tacrolimus) (837 citations) and the primary papers describing transplant-associated microchimerism (2 publications with 837 and 610 citations).

The year 1985 also marked the first time that Starzl's papers were cited over 1000 times per annum in the literature. This pattern has continued uninterrupted to date (31 years) with 1356 citations for 2015. The annual citation frequency exceeded 2000 per year for the period 1989-2009, with a peak of 4114 citations in the year 1996 (i.e., 1 citation every 30 minutes). When viewed from the overall perspective of his (to date) 65 year career (1950-2015 inclusive), publications by Starzl have been cited 90,316 times, averaging 1348 citations per year (Figure 6). When looked at from the perspective of individual publications, Dr. Starzl has had 233 different papers each cited between 100-1100 times. A breakdown of citation frequency on a per paper basis is given in Table 2.

Dr. Starzl's Contributions to the University of Pittsburgh

Dr. Starzl is currently a Distinguished Service Professor (a title bestowed in 1986) and Professor of Surgery at the University of Pittsburgh, a position he has held since 1981. Dr. Starzl was Founding President of the American Society of Transplant Surgeons (ASTS), has served as President of the international Transplantation Society, and Society of Transplant Surgery and is the recipient of numerous honorary degrees and awards. Among the most notable recognitions during his 35 years at Pittsburgh include the following:

- Recipient of the Chancellor's Medal from the University of Pittsburgh (2004)
- Recipient of the Lasker Award (Lasker/DeBakey Clinical Medical Research Award, 2012)
- Recipient of the Presidential National Medal of Science (2006)
- Recipient of the Gustav Lienhard Prize (highest distinction) of the Institute of Medicine of the National Academy of Sciences (2009)
- Election into the National Academy of Science (2014)
- Election into the Institute of Medicine of the National Academy of Sciences (1999); now National Academy of Medicine

Dr. Starzl's contributions have brought great prestige to the University of Pittsburgh and he has and continues to have a dramatic impact on academic life at the University. In fact, an entire University/UPMC building, the Thomas E. Starzl Biomedical Research Tower was named in his honor. He is the founding director of a University-wide institute, which has become the leading institute of transplant surgery in the world, the Thomas E. Starzl Transplantation Institute. This has included a significant development effort that includes raising an endowment now valued at over 35 million dollars. The financial success of the clinical programs under his leadership contributed significantly to

the advancement of the University as well as the creation of UPMC. It should be recognized that Dr. Starzl has always maintained the highest personal ethical standards and has never sought to benefit personally financially from his contributions to the clinical successes. Dr. Starzl's contribution to the Pittsburgh community was recognized twice with his naming as "Pittsburgh Man of the Year" by Pittsburgh Magazine. He has been a profoundly effective ambassador for the University and its mission. Through his efforts many major figures within the School of Medicine have been recruited to the University of Pittsburgh. Importantly, he remains an active contributor to University life, to the success of the School of Medicine, and to the ongoing success of the Thomas E. Starzl Transplant Institute and the Department of Surgery. Appendix

Table 1

Area of investigation	First Publication (Year)	Last Publication (Year)	Time Span (Years)	Number of Publications	Total Citations
Neuroscience	1951	1953	3	5	1019
Cardiac physiology	1955	1985	31	8	400
Dog liver models	1959	2002	44	12	1763
Hepatotrophicphysiology	1959	2008	50	97	4799
Miscellaneous innovations and observations	1959	1999	41	30	471
Liver transplantation	1962	2010	49	495	21117
Muitivisceral and intestinal transplantation	1962	2006	45	100	3678
Partial liver resection	1962	2009	48	30	3017
Kidney transplantation	1963	2008	46	159	9404
Microchimerismdiscovery	1963	2008	46	29	3976
Organ procurement and preservation	1963	2000	38	49	2310
Transplant paradigm generalization	1963	2007	45	12	3136
Transplant paradigm therapy implications	1963	2008	46	46	4001
Drug immunosuppression	1964	2009	46	264	13542
Transplant infections	1964	2008	45	74	3895
Xenografts	1964	2008	45	62	2133
Tissue matching	1965	2008	44	71	3049
Cancer immunology	1969	2008	40	37	5159
Thoracic organ transplantation	1982	2008	27	19	1165
Pancreas transplantation	1984	2008	25	16	1171
Autoimmunity	1989	2008	20	22	640
Pancreatic islet transplantation	1990	2008	19	43	1375
A new transplant immunology paradigm	1992	2008	17	61	4077

Citation Frequency of 1923 Journal Articles of Thomas E. Starzl, M.D., Ph.D.

Times Cited (range)

Number of Articles

>400-1100	21
200-399	64
100-199	149
50-99	278
25-49	334
10-24	449
3-9	421
0-2	207

TABLE 2 (January 29, 2016)

Figure 1

Top Authors in Liver Transplantation Literature 1945-1992



Top 20 Most Cited Publications in the Early Liver Transplantation Literature



STARZL TE, 1982, HEPATOLOGY, V2, P614 STARZL TE, 1969, EXPERIENCE HEPATIC TRANSPL STARZL TE, 1963, SURG GYNECOL OBSTET, V117, SHAW BW, 1984, ANN SURG, V200, P524 DEMETRIS AJ, 1985, AM J PATHOL, V118, P151 SNOVER DC, 1984, HEPATOLOGY, V4, P1212 KAMADA N, 1979, TRANSPLANTATION, V28, P47 STARZL TE, 1960, SURG GYNECOL OBSTET, V111, STARZL TE, 1979, GASTROENTEROLOGY, V77, P3 STARZL TE, 1965, SOUTHERN MED J, V58, P131 STARZL TE, 1981, NEW ENGL J MED, V305, P266 STARZL TE, 1976, SURG GYNECOL OBSTET, V142, BISMUTH H, 1984, SURGERY, V95, P367 STARZL TE, 1989, NEW ENGL J MED, V321, P1014 STARZL TE, 1968, ANN SURG, V168, P392 STARZL TE, 1985, SEMIN LIVER DIS, V5, P349 SHAW BW, 1985, TRANSPLANT P, V17, P264 MOORE FD, 1960, ANN SURG, V152, P374 SNOVER DC, 1987, AM J SURG PATHOL, V11, P1 STARZL TE, 1985, TRANSPLANT P, V17, P250 BISMUTH H, 1987, LANCET, V2, P674 STARZL TE, 1984, SURG GYNECOL OBSTET, V158, IWATSUKI S, 1985, ANN SURG, V202, P401 KALAYOGLU M, 1988, LANCET, V1, P617 KAMADA N, 1983, SURGERY, V93, P64

Top-Cited Authors in the Early Kidney Transplant Literature 1200 1400 1600 1800 0 200 400 600 800 1000 STARZL, TE HUME, DM PORTER, KA MURRAY, JE OPELZ, G DEMPSTER, WJ SIMMONS, RL HAMBURGER, J **RIFKIND, D** WILLIAMS, GM **BELZER, FO** TERASAKI, PI KOUNTZ, SL PATEL, R **GUTTMANN, RD** Sum Times Cited of All Authored Publications STUART, FP Sum Times Cited of Publications as 1st Author **KISSMEYERNIELSEN, F** MERRILL, JP FINE, RN CALNE, RY

Figure 3

Figure 4

Top Cited Authors in Chimerism & Transplantation Literature





Figure 5 (January 29, 2016)

Annual Publications



Figure 6 (January 29, 2016)

Annual Citations