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Cellular Signaling in PKD: Foreword

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This monograph is dedicated to the memory of Dr. Jared James Grantham (1936-2016), a wonderful man, a compassionate physician, a passionate researcher, and an exceptional scientist. Without his vision, achievements and impact on countless collaborators and disciples, the field of Polycystic Kidney Disease would not be where it is today. His intellect, tenacity, modesty and kindness continue to be an inspiration to all.

Dr Grantham was born in 1936 in Dodge City and grew up in Pratt and Johnson City, Kansas. Very young, he learned to overcome adversity when he was affected by poliomyelitis and was left with residual right shoulder weakness. The family physician who diagnosed him became his mentor and spurred his interest in science and medicine. After high school, he attended college at Baker University in Baldwin City, Kansas, with a full scholarship. There he met Carol Elaine Gabbert who became his wife after the senior year. He was accepted to Medical School at the University of Kansas Medical School. Between his freshman and sophomore year, his interest in science led him to work with Dr. Paul R. Schloerb, a surgeon interested in the treatment of kidney failure, and to his first publication on “Acute Magnesium Depletion and Excess Induced by Hemodialysis” in the American Journal of Physiology in 1960 (1).

Having savored the joy of medical research and decided that this was how he wanted to spend his life, “From Fish to Philosopher” by Homer W. Smith became his Bible. After a residency in Internal Medicine at the University of Kansas (1962-1964), he was accepted for a two-year research fellowship in the National Heart Institute's Laboratory of Kidney and Electrolyte Metabolism under the mentorship of Robert W. Berliner, Jack Orloff and Maurice B. Burg. During these two years, he perfected the microdissection of renal tubules without enzymatic digestion, developed a pipette to collect urine from microperfused tubules, discovered that the collecting duct was the site for the action of vasopressin to concentrate the urine, and that this effect was mediated by cyclic AMP (2-3). He stayed as a staff investigator at the National Institutes of Health for three additional years during which he showed with Charles E. Ganote how water flows through the cellular layer of collecting ducts (4-5) and demonstrated with Maurice B. Burg that the collecting

duct was the site of the sodium-potassium exchange process critical to maintain potassium balance (6).

In 1969, he moved to the University of Kansas and established his renal research laboratory. He became Director of Nephrology in 1970, a position he held for 25 years. In 1972, he made the startling discovery that mammalian proximal tubules could secrete as well as reabsorb fluid (7-8). Fluid secretion was a tubule function believed to function only in lower, aquatic animals lacking glomerular filters. Inspired by the memory of Ronnie Wilkerson, a friend from childhood with polycystic kidney disease, and working in a clinical environment, he associated the discovery of tubule fluid secretion with the mechanism by which cysts derived from renal tubules might fill with fluid.

After 1972, understanding the pathogenesis of Polycystic Kidney Disease and eventually finding a cure became Dr. Grantham's passion. The initial research highlighting the ultrastructure of human renal cysts led him to conclude that cysts are unusual benign neoplasms whose mass was due primarily to fluid rather than cells (9). He found that most cysts are disconnected from the parent tubule, meaning that fluid secretion is the only mechanism by which fluid can enter the cysts (10). Next, he discovered that cyclic AMP and hormones stimulating the production of this second messenger are powerful agonists of fluid secretion by Madin-Darby canine kidney (MDCK) cells as well as by cells cultured from human cysts (11-12). In a landmark study, he showed fluid secretion into intact cysts dissected from human polycystic kidneys in a way that was dependent on the sodium pump and was stimulated by cyclic AMP (13). He subsequently demonstrated that fluid secretion by mural epithelial cells of human cysts was also dependent on the transport of chloride into the cysts through the cystic fibrosis transmembrane conductance regulator (CFTR) channel activated by cyclic AMP (14).

Collaborations with James P. Calvet and colleagues at the Kansas University discovered that renal cysts expressed increased levels of proto-oncogenes, in keeping with their putative neoplastic nature (15-18). In the light of its new-found role in promoting fluid secretion, they investigated the effect of cyclic AMP and

cyclic AMP agonists on the proliferation of normal renal epithelial- and cyst-derived cells (19-21). They were surprised to learn that cyclic AMP agonists inhibited cell proliferation in cells from normal kidneys, but stimulated proliferation in mural cells from human polycystic kidney cysts by activating the ERK signaling pathway. Later they showed that the treatment of wild-type collecting duct cells with calcium channel blockers replicated the abnormal proliferative response of the ADPKD cells to cyclic AMP, while treatment of ADPKD cells with calcium ionophores or calcium channel activators corrected the proliferative phenotype of the cystic epithelium. These observations suggested a direct link between the putative role of the polycystin complex as a calcium channel and the abnormal proliferative response to cyclic AMP of the cystic epithelium.

The work of the Polycystic Research Program initiated by Dr. Grantham provided a strong rationale for the therapeutic targeting of cyclic AMP signaling. An initial observation by Vincent Gattone with the vasopressin V2 receptor antagonist mozavaptan in the cpk mouse, later confirmed in orthologous rodent models of ADPKD, led to clinical trials and finally the approval of Tolvaptan to treat rapidly progressive autosomal Dominant Polycystic Kidney Disease in multiple countries including the USA in April 2018. It also provided the rationale for the utilization of long-acting somatostatin analogs for severe polycystic liver disease.

Because the decline of renal function occurs late in the clinical course of ADPKD, glomerular filtration rate is not an optimal endpoint for clinical trials. This is particularly true at early stages of the disease when effective treatments are likely to be most beneficial. To evaluate the effect of cyst ameliorating drugs it was necessary to find an earlier biomarker of disease progression. Early in the path towards the development of effective treatments for ADPKD, Dr. Grantham was the first to propose, in an article published in 1981, that the progression of ADPKD could be quantified by changes in kidney volume at early stages of the disease when measurements of glomerular filtration rate are not informative (22). Afterwards, he was the strongest advocate of kidney volume not only as a prognostic biomarker but also as a surrogate endpoint in clinical trials for this disease. Thanks to his vision and leadership, the NIH sponsored the Consortium of Radiologic Imaging Studies of PKD (CRISP), a twenty-year, large observational study of ADPKD which has become

the best source of accurate information on the natural history of ADPKD, and the PKD Foundation sponsored the PKD Outcomes Consortium (PKDOC) (23). These studies led to the qualification of total kidney volume as a prognostic biomarker in ADPKD by the Food and Drug Administration and the European Medicines Agency. The importance of TKV as a prognostic biomarker and as an endpoint has been shown in the two largest clinical trials for ADPKD, in both of which Dr. Grantham has been a leading investigator (24-25).

Although ADPKD is the leading monogenic cause of end-stage kidney disease (ESKD) accounting for 5-10% of ESKD cases, public awareness and interest of scientists and the NIH in this disease, when Dr. Grantham initiated the Polycystic Kidney Disease Program at the University of Kansas, were very low. He often referred to Polycystic Kidney Disease as the Rodney Dangerfield disease because it got no respect. Therefore, in 1982, with the help of Joseph Bruening, a Kansas business man, he created in Kansas City, the Polycystic Kidney Research Foundation (later renamed Polycystic Kidney Disease Foundation). The Foundation has greatly accelerated the pace of research on Polycystic Kidney Disease by increasing public awareness, attracting scientists to this field of research, and stimulating grant portfolios dedicated to this disease by various funding agencies in the USA and world-wide.

Beyond Polycystic Kidney Disease, Dr. Grantham made many other contributions to Nephrology, was the founding Editor of the Journal of the American Society of Nephrology, served as Secretary-Treasurer of the Society, and was the founding Director of the Kidney Institute of the University of Kansas. He has been the recipient of numerous awards and recognitions. From the American Society of Nephrology, he received the Homer Smith Award in 1992 and the John P. Peters Award in 2011. He was the recipient of the Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease from the International Society of Nephrology and the PKD Foundation; the Jean Hamburger Award from the International Society of Nephrology; the David Hume Award from the National Kidney Foundation; and the Scientific Council's Distinguished Achievement Award and the Award of Merit from the American Heart Association.

Dr. Grantham was designated a University of Kansas Distinguished Professor and the Harry Statland Professor of Nephrology.

In addition to his devotion to his wife Carol, children and grand-children and his love for nephrology, Jared had diverse interests and talents, including singing and writing children's books and poetry. He had a full and exciting life which he delightfully captured in the inspirational, entertaining and humorous autobiography "Why I Think About Urine".

On behalf of all the contributors to this special issue on 'Cellular signaling in PKD', we are honored to dedicate these articles to Jared's memory in recognition of his many contributions but especially his seminal role as the 'Father of PKD research'.

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(Guest editors)

References

1. **Grantham JJ**, Tu WH, Schloerb PR. Acute magnesium depletion and excess induced by hemodialysis. Am J Physiol 198:1211-6, 1960. PMID: 13828983.
2. **Grantham JJ**, Burg MB. Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. Am J Physiol 211:255-9, 1966. PMID: 5911047.
3. **Grantham JJ**, Orloff J. Effect of prostaglandin E1 on the permeability response of the isolated collecting tubule to vasopressin, adenosine 3',5'-monophosphate, and theophylline. J Clin Invest. 47:1154-61, 1968. PMID: 4296382
4. **Grantham JJ**, Ganote CE, Burg MB, Orloff J. Paths of transtubular water flow in isolated renal collecting tubules. J Cell Biol 41:562-76, 1969. PMID: 5783874.
5. **Grantham JJ**. Vasopressin: effect on deformability of urinary surface of collecting duct cells. Science 168:1093-5, 1970. PMID: 4315087
6. **Grantham JJ**, Burg MB, Obloff J. The nature of transtubular Na and K transport in isolated rabbit renal collecting tubules. J Clin Invest 49:1815-26, 1970. PMID: 5456795.
7. **Grantham JJ**, Irwin RL, Qualizza PB, Tucker DR, Whittier FC. Fluid secretion in isolated proximal straight renal tubules. Effect of human uremic serum. J Clin Invest 52:2441-50, 1973. PMID: 4738063.
8. **Grantham JJ**, Qualizza PB, Irwin RL. Net fluid secretion in proximal straight renal tubules in vitro: role of PAH. Am J Physiol 226:191-7, 1974. PMID: 4809880.
9. Cuppage FE, Huseman RA, Chapman A, **Grantham JJ**. Ultrastructure and function of cysts from human adult polycystic kidneys. Kidney Int 17:372-81, 1980. PMID: 7401457.
10. **Grantham JJ**, Geiser JL, Evan AP. Cyst formation and growth in autosomal dominant polycystic kidney disease. Kidney Int 31:1145-52, 1987. PMID: 3599654.
11. **Grantham JJ**, Mangoo-Karim R, Uchic ME, Grant M, Shumate WA, Park CH, Calvet JP. Net fluid secretion by mammalian renal epithelial cells: stimulation by cAMP in polarized cultures derived from established renal cells and from

normal and polycystic kidneys. Trans Assoc Am Physicians. 102:158-62, 1989. PMID: 2561639.

12. Grant ME, Neufeld TK, Cragoe EJ Jr, Welling LW, **Grantham JJ**. Arginine vasopressin stimulates net fluid secretion in a polarized subculture of cyst-forming MDCK cells. J Am Soc Nephrol 2:219-27, 1991 PMID: 1659462.
13. Ye M, **Grantham JJ**. The secretion of fluid by renal cysts from patients with autosomal dominant polycystic kidney disease. N Engl J Med 329:310-3, 1993. PMID: 8321258.
14. Davidow CJ, Maser RL, Rome LA, Calvet JP, **Grantham JJ**. The cystic fibrosis transmembrane conductance regulator mediates transepithelial fluid secretion by human autosomal dominant polycystic kidney disease epithelium in vitro. Kidney Int 1996 50:208-18, 1996. PMID: 8807590.
15. **Grantham JJ**. Polycystic kidney disease: neoplasia in disguise. Am J Kidney Dis 15:110-6, 1990. PMID: 2405652.
16. Cowley BD Jr, Chadwick LJ, **Grantham JJ**, Calvet JP. Elevated proto-oncogene expression in polycystic kidneys of the C57BL/6J (cpk) mouse. J Am Soc Nephrol 1:1048-53, 1991. PMID: 1912403.
17. Rankin CA, Grantham JJ, Calvet JP. C-fos expression is hypersensitive to serum-stimulation in cultured cystic kidney cells from the C57BL/6J-cpk mouse. J Cell Physiol 152:578-86, 1992. PMID: 1506416.
18. Harding MA, Gattone VH 2nd, **Grantham JJ**, Calvet JP. Localization of overexpressed c-myc mRNA in polycystic kidneys of the cpk mouse. Kidney Int. 41:317-25, 1992. PMID: 1552705.
19. Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, Rome LA, Sullivan LP, **Grantham JJ**. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. Kidney Int 57 :1460-71, 2000. PMID: 10760082.
20. Yamaguchi T, Nagao S, Wallace DP, Belibi FA, Cowley BD, Pelling JC, **Grantham JJ**. Cyclic AMP activates B-Raf and ERK in cyst epithelial cells from autosomal-dominant polycystic kidneys. Kidney Int 63:1983-94, 2003. PMID: 12753285.
21. Yamaguchi T, Wallace DP, Magenheimer BS, Hempson SJ, **Grantham JJ**, Calvet JP. Calcium restriction allows cAMP activation of the B-Raf/ERK

pathway, switching cells to a cAMP-dependent growth-stimulated phenotype. J Biol Chem. 279:40419-30, 2004. PMID: 15263001.

22. Levine E, **Grantham JJ**. The role of computed tomography in the evaluation of adult polycystic kidney disease. Am J Kidney Dis 1:99-105, 1981. PMID: 7332005.
23. **Grantham JJ**, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, Wetzel LH, Baumgarten DA, Kenney PJ, Harris PC, Klahr S, Bennett WM, Hirschman GN, Meyers CM, Zhang X, Zhu F, Miller JP; CRISP Investigators. Volume progression in polycystic kidney disease. N Engl J Med 354(2:2122-30, 2006. PMID: 16707749.
24. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, **Grantham JJ**, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 367:2407-18, 2012. PMID: 23121377.
25. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, **Grantham JJ**, Harris PC, Flessner MF, Bae KT, Moore CG, Chapman AB; HALT-PKD Trial Investigators. Blood pressure in early autosomal dominant polycystic kidney disease. N Engl J Med 371:2255-66, 2014. PMID: 25399733.