Imperial College London

Basic and Applied Renal and Gastrointestinal Physiology and Pathophysiology

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Basic and Applied Renal and Gastrointestinal Physiology and Pathophysiology

Personal statement in support of my submission and application for consideration of the award of DSc

Robert J. Unwin (2020)

In my statement below, the number and scope of the publications chosen are intended to represent the different elements of my research work and studies over the years; they are highlighted in yellow by Curriculum Vitae (CV) order number in the following text that outlines the main topics of investigation and tries to summarise my published work and place it in a wider context.

To lend further support to my scientific contributions and publication record, I have also referred, to and referenced, other relevant publications as additional examples, and as they are listed by order number in my accompanying CV (as CV# in parentheses) for cross-reference.

The papers cited and included in the listed (at the end and included in my submission in pdf format) and representative 27 publications are all conjoint work to which I have made a significant contribution in deciding the topic for study, in the experimental planning and execution, in writing up the findings for publication, and in providing financial support.

I have never insisted on any specific author order for myself, considering it a team effort, and I have always given due recognition to the lead author, a research student, post-doctoral fellow or senior collaborator, without whom the work could not have been completed.

My scientific contributions have been in basic renal physiology and pathophysiology, more specifically, in the mechanisms controlling renal and gut epithelial transport, clinical renal tubular disorders, and renal stone disease. They have been relatively broad and integrative, with an emphasis on applying advances in renal and gastrointestinal physiology to clinical practice and teaching, especially in nephrology.

Most of my published work has, by necessity, been highly collaborative, because of the nature of the various research projects I have undertaken (basic and clinical); although I have been largely responsible for, or taken an equal part in, their original planning and inception, and/or conduct and writing[1].

1. *Gut-renal interactions*

I began my early research in renal physiology with the concept of 'gut sensing' – an entero-renal axis – in response to changes in dietary composition, particularly sodium (Na), and latterly phosphate (Pi), and I published a series of early papers (1983-95) on the adaptive renal electrolyte and hormonal changes seen in patients with ileostomies, studied as an exaggerated human model of the renal responses to acute dietary Na deprivation (CV#**11,20,21**), and on the effects of various known and (at the time) novel gastrointestinal peptide hormones on renal function, initially in a conscious rabbit animal model, and later in humans, to study whole kidney function, including the antinatriuretic effect of insulin; and

[1] '*Art is I; science is we'* – a quotation attributed to the early experimentalist Claude Bernard (1813-78).

demonstrating that the initial renal conservation of Na did not coincide with increases in the circulating hormone aldosterone (CV#**1-5,7,11,15-18,20,36**).

Some of these papers, and the idea of gut-derived neuropeptides controlling renal function, stemmed from my original PhD thesis work and were brought together later in an early invited editorial (CV#**191**) in *Kidney International* and cited in two subsequently invited textbook chapters (CV#**224**), including the notion of an 'intracrine' system of renal regulation (CV#**258**), and a later invited review (CV#**259**) in *Annual Review of Physiology*. The concept of gut-renal cross-talk has since remerged in studies on the control of Pi balance, which I have also worked on and reviewed (CV#**273,295**), and potassium (K) balance, respectively; as well as a local intrinsic system of factors controlling renal function (see later for ATP and renal purinergic signalling)[2].

2. *Single nephron studies - renal tubule micropuncture and microperfusion <u>in vivo</u>*

I went on to master for myself the renal micropuncture/microperfusion technique *in vivo* in rodents to study single nephron ion and fluid transport in the intact kidney, and I investigated K, Na and acid-base transport along (mainly) the distal nephron. I studied the loop of Henle in some detail and published a series of papers (1991-98: CV#**22,30,31,33-35,39,51**) characterizing the main transport processes involved in bicarbonate reabsorption in this nephron segment, including the influence of adrenal steroids, the effect of changes in

[2] In a later study we were unable to confirm findings reported by others that short-term postprandial increases in Pi excretion depended on release of an unidentified gut-derived phosphaturic factor (CV#**165**), although we did show that a known phosphaturic factor (a phosphatonin), MEPE, could inhibit both renal and intestinal Pi transport (CV#**110,116**). Our own preliminary unpublished studies of MEPE mRNA expression had detected its presence in the normal rat small intestine (CV#**273,295**) and brush border membrane of the kidney; however, a very recent publication in *Pflügers Archiv* (Aniteli et al, 470:623-632, 2018) has now confirmed the presence of MEPE at the protein level, mainly in the duodenum, and that MEPE levels are increased in response to a high Pi diet in a renal failure model, which may be part of an adaptive response to limit Pi retention and hyperphosphataemia in chronic kidney disease (CKD).

dietary K, changes in respiratory acid-base status (CV#**43**), and the transport of lithium (Li). The latter had important implications for the use of Li clearance in humans as a then popular (and still used) non-invasive measure of proximal tubular Na reabsorption [CV#**30,39**]. I also helped to lead a series of published papers defining the renal functional role of the enzyme 11β-hydroxysteroid dehydrogenase type 2 *in vivo*, at the time a newly identified regulator of glucocorticoid activity conferring mineralocorticoid specificity at the tissue level where the enzyme is expressed, on distal nephron Na reabsorption (CV#**49,57**,65,67). An aspect of renal physiology covered in an invited textbook chapter on aldosterone and the kidney (CV#**204**).

3. *Potassium transport and diuretic actions*

I was a leading participant in one of the first micropuncture studies to demonstrate active K reabsorption in the distal tubule and collecting duct, which had only been speculated on at the time, since this nephron segment was considered to be a main and exclusive site of K secretion, rather than reabsorption. However, earlier discovery of the gastric H^+/K^+-ATPase exchanger, the target of 'proton pump' inhibitors used clinically to suppress gastric acid secretion, had led to identification of a similar enzyme in the kidney. Using a pharmacological inhibitor (a precursor to omeprazole), this transporter was shown to be able to mediate K reabsorption under conditions of dietary K restriction (CV#**24**).

I also explored the renal effects of diuretics and the responses affected by dietary changes in K and Na (CV#**28,40,61**), as well as the basis of diuretic resistance ('diuretic breaking') following chronic diuretic administration, and provided a rationale for combined use of loop and thiazide diuretics (CV#**19**). This paper formed the basis of other studies demonstrating

the benefit of combining a loop diuretic with a thiazide diuretic to overcome diuretic resistance - a combination used commonly in clinical practice to treat both advanced heart failure and renal failure with refractory oedema - and its ultrastructural origins shown by others for diuretic compensation due to adaptive hypertrophy of downstream (of the thick ascending limb, the site of loop diuretic action) distal tubular cells. A further study on diuretic resistance in rodents showed that hypokalaemia itself, a common consequence of chronic loop diuretic treatment, also reduced the diuretic and natriuretic response to furosemide (CV#**28**), and another on localising diuretic effects along the loop of Henle and effects on K secretion *in vivo* using micropuncture (CV#**61**); and the effect of K ion channel blockade in this segment, proposed as a mechanism for diuretic action and one that is still being explored as a novel diuretic class (CV#**68**). These diuretic studies resulted in invitations to contribute textbook chapters and reviews on diuretic action and their clinical uses (CV#**195,196,197,201,203,205,212,215,332**).

Again, using micropuncture I examined further the consequences of chronic K depletion by studying its effects on transepithelial electrochemical gradients in the proximal tubule (CV#**52**) and on increased acid secretion (a factor contributing to the phenomenon of 'hypokalaemic alkalosis') by favouring and stimulating electrogenic H^+-ATPase (proton secretion) activity in the distal nephron (CV#**50,53**).

4. Renal purinergic signalling

From 1998, I began to explore and characterise the renal purinergic (P2 purinoceptor) system, a new field at the time, defining the extent and mix of purinergic receptor subtypes present in the kidney and their role in salt and water transport, as well as in some

inflammatory and non-inflammatory renal diseases (CV#**44,58,63,73,76,77,81,84,86,87,89,92,93,97,98,99,101,103,104,111,118,122,126,135,141,146,149,151,157,168,173,177**).

I provided support for intraluminal control of renal tubular transport (referred to earlier) by demonstrating the presence of secreted (luminal) ATP (CV#**101**) and its effect on Na and water reabsorption (CV#**97,98,122**], an originally contested, but now widely accepted finding. This has resulted in an ever-expanding literature on renal purinergic signalling in health and disease, and for which my published work is still widely cited. I have written several invited contributions on renal P2 receptors (CV#**216,221,235,236,246,280,286,292,299,300,304,315**) (and which has continued), including for a leading reference work of renal physiology and pathophysiology (Seldin & Giebisch: *The Kidney: Physiology and Pathophysiology*) (CV#**257,291**), and a recent major collaborative review article in *Physiological Reviews* (CV#**325**), and a short recently invited commentary, based on my published work on the pro-inflammatory P2X7 receptor (CV#**321**)[3].

5. *Renal intracrine signalling*

As part of my continuing interest in renal intracrine signalling, I used a particular technique in tubule micropuncture, direct microinjection, which I had used earlier to investigate the effect of intraluminal ATP on collecting duct Na reabsorption referred to above (CV#**97**). This approach involves the injection of radioactive ^{22}Na directly into a late, surface-

[3] I have just been asked to contribute a paper entitled 'Purines in kidney pathophysiology' to *Biochemical Pharmacology* as a tribute to Professor Geoffrey Burnstock who died earlier this year.

accessible, distal tubule segment feeding a collecting duct, and measuring what is excreted in the final urine of the delivered dose, and determining by subtraction what has been reabsorbed. In this particular instance, the question being addressed was the concept that in glomerular diseases associated with the nephrotic syndrome (with sodium and water retention causing oedema), filtered proteases contribute to the underlying pathophysiology by stimulating Na reabsorption via direct activation of the epithelial Na channel (ENaC). This had been shown to occur *in vitro* in the isolated collecting duct, although not *in vivo*, which we were able to confirm does occur (CV#**147**).

6. *Renal acid-base transport and homeostasis*

My longstanding interest in renal acid-base transport led me clinically to initiate the early collaborative work leading to identification of SLC4A1 (AE1), the red cell and kidney chloride/bicarbonate anion exchanger, as the cause of autosomal dominant distal renal tubular acidosis (RTA) (CV#**211**,**42**], an important advance in renal acid-base physiology (CV#**42,45,46,62,72,105,114,142,211,229**). I became a recognised authority on clinical RTA and continuing my collaborative studies I developed a modified renal acidification test for patients with a suspected diagnosis of RTA that (although with acknowledged limitations) has become a more convenient screening tool in clinical practice (CV#**106,160**); I have been invited to contribute educational book chapters and reviews (CV#**226,228,231,244,250,266,290,300**), and to lecture on the subject of RTA at national and international meetings.

7. Potassium, sodium and hypertension

I participated in the original work that identified the role of WNK kinases in Gordon's syndrome (hypertension, hyperkalaemia and acidosis) (CV#**69**), as well as other genes leading to the growing field of WNK-related renal biology in hypertension and Na and K balance (CV#**140**), and also showed that this pathway is the basis of the well-known (following transplant immunosuppression) calcineurin inhibitor-induced hypertension, hyperkalaemia and acidosis, a similar phenotype to Gordon's syndrome (CV#**137**,**284,338**). WNK biology has become an important and new area of renal physiology in understanding the dichotomous control of renal K and Na excretion, and has also touched again recently on the earlier concept of gut-renal crosstalk and the response to changes in dietary K, and signalling to the kidney through changes in serum or plasma K concentration, and the basis of the well-known phenomenon of natriuresis (and a lowered blood pressure) following a K load and on a high K diet.

8. Renal and intestinal glucose and phosphate transport

Maintaining my interest in the links and parallels between renal and gastrointestinal transport physiology, I began collaborative studies of glucose and phosphate (Pi) handling by the gut and kidney, again seeking parallels in shared transport mechanisms and the potential for cross-talk, beginning with an invited review on renal glucose transport in diabetes mellitus (#CV**209**). We went on to show the importance of an increase in GLUT2-mediated transport and its shuttling to the proximal tubular cell apical membrane (as originally observed in the small intestine) in both insulin deficient and insulin resistant rat

models of diabetes, and closely related to the increase in blood glucose concentration (CV#**85,109,162**). However, the role of renal GLUT2 in this setting is still unclear (CV#**337**), although in the gut it has been proposed as a therapeutic target to control glucose absorption and limit post-prandial hyperglycaemia, but it has since been eclipsed by current interest in SGLT2 in the kidney, and SGLT1 in the gut[4]. Although other SLC5 family members have been implicated in gut sensing once again, which I have also reviewed (CV#**318**).

For gut phosphate handling, we identified an important difference between axial patterns of gastrointestinal Pi reabsorption in the rat and mouse; the former having a pattern much closer to human and therefore a potentially better experimental model (CV#**100,155**), though limited by the greater difficulty in its genetic manipulation; moreover the rat gastrointestinal tract, unlike the kidney, does not show adaptation (downregulation) in Pi reabsorption when kidney function is reduced (in a model of renal failure) (CV#**107**), part of the explanation for why controlling hyperphosphataemia is so difficult clinically and requires gut targeting in some form, currently still relying on the use of often unpalatable oral Pi 'binders'. However, our work helped to sustain an interest and to increase awareness of Pi transport in the gut and ongoing studies of how this might be controlled more directly[5].

[4] However, we did hypothesise a role for the proximal tubule in the pathogenesis of diabetic kidney disease (CV#**319**) and a potential link to abnormal intracellular glycogen accumulation (a noted finding in renal tissue of diabetic animal models and in humans [Sullivan & Forbes, *eBioMedicine*, 47:590-97, 2019]) as a cause of proximal tubular cell injury in diabetic kidney disease, drawing on findings in the Fanconi-Bickel syndrome in which GLUT2 loss-of-function mutations cause glycogen accumulation in liver and kidney, resulting in a renal Fanconi syndrome and diabetic-like glomerulopathy; and our own as yet unpublished finding that SGLT2 inhibition may reduce intracellular glycogen and in this way improve both liver and kidney function.

[5] I have just been asked to contribute a paper on the 'Physiological regulation of phosphate' for the next volume of *Vitamins & Hormones*.

9. Confocal and multiphoton imaging and mitochondria

I pioneered the application of confocal (initially single laser) live kidney imaging in two papers demonstrating the principle, and an application to image in 'real-time' the renal tubular response to diuretics (CV#**48,88**), which in its multiphoton configuration has become widely applied.

Following on from, and building on, this work, and as part of a new interest in mitochondrial biology and function in renal disease (CV#**251,260**), I was able, in a further collaboration, to apply multiphoton imaging to kidney slices and to show differences in mitochondrial energetics between the proximal and distal tubules (CV#**117**); and subsequently in the intact isolated kidney, and changes in response to ischaemia-reperfusion injury (CV#**134**). This work has spawned a growing literature on the application of multiphoton imaging to the kidney *in vivo* and continues with a recent collaborative publication describing the much higher glycolytic capacity of the renal collecting duct (CV#**182**), and wider interest in the importance of mitochondria in normal renal function (CV#**125**) and in kidney injury and disease (CV#**172,251,260**).

10. Experimental application of spectroscopic methods

I have also carried out early work on the application of urinary proteomics (CV#**239,253,261**) Nuclear Magnetic Resonance (NMR; metabolomics/metabonomics) (CV#**143,148**), and, more recently, ATR-FTIR (infra-red) spectroscopy to studies of renal tubular function and in the nature of renal stone disease in patients (CV#**158,163**); all relatively novel at the time. This has been part of my ongoing aim of introducing new analytical techniques and methods to studies of renal physiology and clinical nephrology.

The use of urinary and renal tissue proteomics, and metabonomics, was initially applied to studies of patients with isolated defects in proximal tubular function (the renal Fanconi syndrome with 'tubular' low molecular weight proteinuria) to better understand the changes in filtered protein and small peptide handling (CV#**80,90,91,108,150,152**) in the proximal tubule, and to analyse the composition of isolated proximal tubular brush border membrane vesicles isolated from the rat renal cortex (CV#**94**). This was done to establish feasibility and utility, and resulted in several invited reviews on the subject (CV#**239,240,248,252,253,261**). Allied clinical studies on filtered protein handling in the renal Fanconi syndrome with a long-time collaborator sought to determine human *in vivo* glomerular permeability coefficients and further characterise the defect in post-glomerular small protein and peptide uptake (CV#**56,71,113,283**), including the importance of megalin that is key to tubular endocytosis (CV#**74**), and the clinical basis of the use of the proximal tubular function biomarker urinary retinol-binding protein (uRBP4) (CV#**299,323**).

The above is an outline of the research work I have undertaken since the 1980s in renal and gastrointestinal physiology. My approach has been, and continues to be, broad, descriptive and holistic, and intended to apply physiological knowledge and principles by linking experimental observations to their clinical correlates; and to improve disease understanding, recognition and management, especially in clinical situations of disturbed electrolyte and acid-base balance.

List of publications attached in pdf format for consideration and in order of citation in the supporting statement above:

1. CV# **191**

UNWIN, R.J., GANZ, M.B. & STERZEL, R.B. (1990). Brain-gut peptides, renal function and cell growth. Kidney Int. 37:1031-1047.

2. CV# **258**

CAPASSO, G., DEBNAM, E.S., CUTILLAS, R., BRUNSKILL N.G. & UNWIN, R.J. (2007). Classical and novel hormonal influences on renal tubular transport and the emerging concept of 'intracrine' regulation. In: Seldin and Giebisch's The Kidney: Physiology and Pathophysiology (4th edition), eds. Alpern, R.J. & Hebert, S.C. G. Elsevier, San Diego. Chapter 35, pp 979-1004.

3. CV# **259**

DEBNAM, E.S., MICHELL, A.R. & UNWIN, R.J. (2008). Regulation of Renal Function by the Gastrointestinal Tract: Potential role of gut-derived peptides and hormones. Annu. Rev. Physiol. 70:379-403

4. CV# **273**

MARKS, J., DEBNAM E.S. & UNWIN, R.J. (2010). Phosphate handling and the renal-gastrointestinal axis. Am. J. Physiol. Renal. Physiol. 299:F285-296.

5. CV# **43**

UNWIN, R., STIDWELL, R., TAYLOR, S. & CAPASSO, G. (1997). The effects of respiratory alkalosis and acidosis on net bicarbonate flux along the rat loop of Henle in vivo. Am. J. Physiol. Renal. Physiol. 273:F698-F705.

6. CV# **30**

UNWIN, R., WALTER, S., SKINNER, J. & SHIRLEY, D. (1994). Lithium reabsorption in perfused loops of Henle: Effects of perfusion rate and bumetanide. Am. J. Physiol. Renal. Physiol. 266:F806-F812.

7. CV# **49**

SEWELL, K.J., SHIRLEY, D.G., MICHAEL, A.E., THOMPSON, A., NORGATE, D.P. & UNWIN, R.J. (1998). In vivo inhibition of renal 11β-hydroxsteroid dehydrogenase by carbenoxolone in the rat and its relationship to sodium excretion. Clin. Sci. 95:435-443.

8. CV# **24**

OKUSA, M.D., UNWIN, R.J., VELAZQUEZ, H., GIEBISCH, G. & WRIGHT, F.S. (1992). Active potassium absorption by the renal distal tubule. Am. J. Physiol. Renal. Physiol. 262:F488-F493.

9. CV# **40**

SHIRLEY, D.G., WALTER, S.J. & UNWIN, R.J. (1996). Mechanism of the impaired natriuretic response to frusemide during dietary sodium depletion. Clin. Sci. 91:299-305.

10. CV# **19**

LOON, N.R., WILCOX, C.S. & UNWIN, R.J. (1989). Mechanism of impaired natriuretic response to furosemide during prolonged therapy in man. Kidney Int. 36:682-689.

11. CV# **68**

WALTER, S.J., SHIRLEY, D.G., FOLKERD, E.J., & UNWIN, R.J. (2001). Effects of the potassium channel blocker barium on sodium and potassium transport in the rat loop of Henle in vivo. Exp. Physiol. 86:469-474.

12. CV# **53**

BAILEY, M.A., CAPASSO, G., AGULIAN, S. & GIEBISCH G. & UNWIN, R.J. (1999). The relationship between distal tubular proton secretion and dietary potassium depletion: evidence for upregulation of H^+-ATPase. Nephrol. Dial. Transplant. 14:1435-1440.

13. CV#**101**

VEKARIA, R.M., UNWIN, R.J. & SHIRLEY, D.G. (2006). Intraluminal ATP concentrations in rat renal tubules. J. Am. Soc. Nephrol. 17:1841-1847.

14. CV# **97**

SHIRLEY, D.G., BAILEY, M.A. & UNWIN, R.J. (2005). In vivo stimulation of apical P2 receptors in collecting ducts: evidence for inhibition of sodium reabsorption. Am. J. Physiol. Renal. Physiol. 288:F1243-1248.

15. CV# **291**

SHIRLEY, D.G., BAILEY, M.A., WILDMAN, S.S.P., TAM, F.W.K. & UNWIN, R.J. (2013). Extracellular nucleotides and renal function. In: Seldin and Giebisch's The Kidney: Physiology and Pathophysiology (5th edition), eds. Alpern, R.J., Moe, O.W. & Caplan, M. Academic Press (Elsevier), London. Chapter 18, pp 511-537.

16. CV# **325**

VALLON, V., UNWIN, R., INSCHO, E., LEIPZIGER, J. & KISHORE, B. (2020). Extracellular Nucleotides and P2 Receptors in Renal Function. Physiol. Rev. 100:211-269.

17. CV# **147**

JAQUILLET, G., CHICHGER, H., UNWIN, R.J & SHIRLEY, D.G. (2013). Protease stimulation of renal sodium reabsorption in vivo by activation of the collecting duct epithelial sodium channel (ENaC). Nephrol. Dial. Transplant. 28:839-845.

18. CV# **211**

UNWIN, R., WRONG, O., COHEN, E., TANNER, M., THAKKER, R. & FINE, L. (1996). Kidney stones - early unravelling of molecular mechanisms (Grand Round - Meeting of Physicians and Scientists). Lancet 348:1561-1565.

19. CV# **42**

BRUCE, L., COPE, D. JONES, G., SCHOFIELD, A., BURLEY, M-W., POVEY, S., UNWIN, R., WRONG, O. & TANNER, M. (1997). Familial distal renal tubular acidosis (dRTA) is associated with mutations in the red cell anion exchanger (band 3, AE1) gene. J. Clin. Invest. 100:1693-1707.

20. CV# **300**

UNWIN, RJ, WALSH, S.B. & WRONG. OM. (2014). Renal Tubular Acidosis, Stones and Nephrocalcinosis. In: Urinary Stones: Medical and Surgical Management, ed. Goldfarb, D. Wiley-Blackwell, Oxford, Chapter 9, pp 93-105.

21. CV# **69**

WILSON, F., DISSE-NICODEME, S., CHOATE, K., ISHIKAWA, K., NELSON-WILLIANS, C., DESITTER, I., GUNEL, M., MILFORD, D., LIPKIN, G., ACHARD, J-M., FEELY, M., DUSSOL, B., BERLAND, Y., UNWIN, R., SIMON, D., FARFEL, Z., JEUNEMAITRE, X. & LIFTON, R. (2001). Mutations in WNK kinases reveal a novel mechanism of human hypertension. Science 293:1107-1112.

22. CV# **137**

HOORN, W.J., WALSH, S.B., MCCORMICK, J.A., FÜRSTENBERG, A., YANG, C-L., ROESCHEL, T., PALIEGE, A., HOWIE, A.J., CONLEY, J., BACHMANN, S., UNWIN, R.J. & ELLISON, D.H. (2011). The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. Nat. Med. 17:1304-1309.

23. CV# **85**

MARKS, J., DEBNAM, E.S., SURJIT K. SRAI, S.K. & UNWIN, R.J. (2003). Diabetes increases facilitative glucose uptake and GLUT2 expression at the rat proximal tubule brush border membrane. J. Physiol. 553.1:137-145.

24. CV# **107**

MARKS, J. CHURCHILL, L.J. SRAI, S.K., BIBER, J., MURER, H., JAEGER, P., DEBNAM, E.S. & UNWIN, R.J. (2007). Intestinal phosphate absorption in a rat model of chronic renal failure (CRF). Kidney Int. 72:166-173.

25. CV# **117**

HALL, A.M., UNWIN, R.J. PARKER, N. & DUCHEN, M.R. (2009). Multiphoton imaging of intact rat kidney slices reveals differences in mitochondrial function between proximal and distal nephron segments. J. Am. Soc. Nephrol. 20:1293-1302.

26. CV# **108**

VILASI, A., CUTILLAS, P.R., MAHER, A.D., ZIRAH, S.F.M. CAPASSO, G., NORDEN, A.W.G., HOLMES, E., NICHOLSON, J.K. & UNWIN, R.J. (2007). Combined proteomic and metabonomic studies in three genetic forms of the renal Fanconi syndrome. Am. J. Physiol. Renal. Physiol. 293:F456-467.

27. CV# **74**

NORDEN, A.G.W., LAPSLEY, M., IGARASHI, T., KELLEHER, C.L., LEE, P.J., MATSUYAMA, T., SCHEINMAN, S.J., SHIRAGA, H., SUNDIN, D.P., THAKKER, R.V., UNWIN, R.J., VERROUST, P.J. & MOESTRUP, S.K. (2002). Urinary megalin deficiency implicates abnormal tubular endocytic megalin function in Fanconi syndrome. J. Am. Soc. Nephrol. 13:125-133.