



CKJ REVIEW

ERA-EDTA fellowship, a ‘bonne opportunité’: the scientific and human experience of a fellow

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ABSTRACT

As a fellow of the ERA-EDTA long-term fellowship programme, I spent two fantastic years as a post-doc in Prof. D. Eladari’s laboratory at Inserm U970, Paris-Cardiovascular Research Centre. It was a highly formative and productive scientific experience. On a personal level, immersion into the French society and the international environment of the laboratory were added bonuses that enriched my experience. I am honoured to report my experience here from the ERA-EDTA fellowship programme. I hope this will inspire young fellows to apply for such a programme and pursue their career in science. Good mentorship, a passion for scientific investigation and determination are required.

Keywords: fellowship, mentoring, nephrology training, scientific career, translational nephrology

APPLICATION TO THE ERA-EDTA LONG-TERM FELLOWSHIP PROGRAMME

I applied for the ERA-EDTA long-term fellowship programme in February 2013. At that time, I had just obtained my PhD from Aarhus University in Denmark a few months before. I was very determined to pursue a scientific career, and I could count on the support of my mentor Prof. G. Capasso and my former supervisors at Aarhus University Prof. S. Nielsen and Prof. B. Christensen.

So even though, as a nephrologist, I was in charge of an ambulatory haemodialysis clinic, I decided to apply for the fellowship and to move, once again, from clinical practice back to scientific research. In my application, I proposed a project in line with my PhD research. While investigating how the collecting duct recovers from the toxic effect of lithium, we found evidence for cellular inter-conversion between intercalated cells (ICs) and principal cells (PCs) [1]. To further address this concept, once back in Naples, I continued with part-time research in the laboratory of translational nephrology headed by Prof.

Capasso at Biogem, Ariano Irpino. Here, to map the fate of PCs during lithium treatment, we generated a mouse model expressing a fluorescent yellow protein in PCs, which are aquaporin 2 (AQP2)-expressing cells. However, this would have addressed only part of the story and, in particular, whether PCs could convert into ICs, and not the opposite. So to also investigate the role of ICs, I contacted Prof. D. Eladari and his team at Inserm U970, Paris-Cardiovascular Research Centre (PARCC), one of the expert teams on IC physiology.

At that time, Prof. Eladari’s group were providing new evidence on the role of ICs in sodium and chloride reabsorption—a role that has been attributed, in all textbooks, almost exclusively to PCs, still to this day. This was very intriguing for me. For the first time, the two cell types of the collecting duct epithelium seemed not to be completely independent in structure and function. In my young and speculative mind, this was a clear sign that they could also inter-convert with each other. So after prior approval from Prof. Eladari (believe me, it was not easy to convince him), I applied and finally was awarded the fellowship (Figure 1).

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THE POST-DOC IN PARIS: THE HUMAN AND SCIENTIFIC EXPERIENCE

Thanks to the ERA-EDTA fellowship programme, I had the opportunity to spend 2 years in Prof. Eladari's laboratory. It was my first time in Paris. When, in the middle of a hot July, I arrived to show my post-doc project to the laboratory, I was hosted in a fantastic apartment facing both the Eiffel Tower and the Montparnasse Tower, and this helped a lot to erase doubts about me moving away again from my country, my family and my Neapolitan sunshine. I will never regret this choice, which I found fantastic on the scientific, as well as on the human, side. The boss was very demanding, but this was easy to cope with, thanks to the colleagues and friends I found in the PARCC. Young and highly motivated fellows were around me, working in the different facilities of the institute in the morning and ready to party at night. Having the administrative director who has a great passion for disco music helped a lot with the social life of the institute. Unfortunately, during my stay, a tragic event hit our laboratory and the entire PARCC. One of the young post-docs Yosuke Kumai died tragically during his summer vacation on the Isle of Skye in Scotland. It was a terrible loss for us and, I guess, for the entire renal physiology field. Yosuke was a brilliant guy with already considerable experience and curriculum despite his young age. Being with his mother as she entered his empty room is one of the memories that Dominique and I will never forget.

On the scientific front, this Paris experience was very productive. I was author of eight manuscripts published in prestigious scientific journals, and my research activity was mainly focused on the function of ICs.

We investigated the pathogenesis of the most common dominant mutation causing distal renal tubular acidosis (dRTA)—R589H SLC4A1. In the mouse model of the disease, we showed that expressing the mutant AE1 protein of the solute carrier family 4 member 1 (SLC4A1) impairs both apical vacuolar H⁺-ATPase (vH⁺-ATPase) sorting and lysosomal activity, leading to a defect in autophagy flux and so reducing the number of type A ICs (A-ICs) [2].

Almost in parallel, we characterized the renal function of a newly identified vH⁺-ATPase subunit, namely the Atp6ap2 subunit, also known as the prorenin receptor (PRR). This study was published in a highly cited manuscript, because it provided a large body of robust evidence on the role of the PRR as a crucial subunit of vH⁺-ATPase, both at the apical membrane of A-ICs and in the lysosomes of medullary thick ascending limb (TAL) and collecting duct cells. Ablation of the PRR resulted in mice with a severe form of dRTA and defective urine-concentrating ability due to resistance to both antidiuretic hormone (collecting duct dysfunction) and a salt-losing component (TAL dysfunction). Our model did not show alteration in blood pressure under normal and angiotensin II infusion conditions. This study suggested a key point to clinicians in their approach to dRTA associated with a salt-losing phenotype. Indeed, these forms should not be considered exclusively secondary to A-IC dysfunction, as commonly believed for dRTA, but also secondary to other renal cell types with impaired lysosomal vH⁺-ATPase. Finally, another message from this study was that compensatory alteration in the expression of other sodium transporters could easily occur in such a setting, but this should be considered in the overall general phenotype of the mice, and not necessarily as a PRR-specific effect [3].

Concerning type B ICs (B-ICs), we investigated their role in sodium reabsorption. By acute genetic ablation of pendrin, we

confirmed its role in blood pressure control. Continuous blood pressure monitoring by telemetry showed a decrease in blood pressure, simultaneous with inducible acute genetic ablation of pendrin. This setting was necessary to avoid compensatory salt-retaining mechanisms shown previously in non-inducible pendrin knockout mice [4]. In line with the role of B-ICs in the maintenance of sodium homeostasis, we investigated *in vivo* the role of the sodium-dependent bicarbonate chloride exchanger (NDBCE). The NDBCE/pendrin system represents a rescue salt reabsorption mechanism, playing a substantial role in salt restriction conditions [5]. By avoiding the compensatory mechanism secondary to the sodium chloride cotransporter (NCC) activity, we simultaneously ablated the NCC and NDBCE in mice. By comparing them with NCC cKO mice, we disclosed *in vivo* that the NDBCE is crucial for maintaining circulating blood volume and potassium homeostasis [6]. At the same time, we showed that the contribution of pendrin is crucial to the development of the clinical features of Gordon syndrome, as shown in a mouse model carrying a WNK4 missense mutation (Q562E) previously identified in patients. Indeed, in this model, pendrin hyperactivity was found to be causative of metabolic acidosis, suggesting, for the first time, that distal nephron bicarbonate secretion can be an additional mechanism of renal tubular acidosis. Finally, an interesting finding from this study was that hyperkalaemia associated with high blood pressure and metabolic acidosis could be reversed by suppression of pendrin, suggesting a direct role of pendrin activity in modulating the function of potassium channels [7].

Coming back to the original project on the plasticity of the collecting duct epithelium, the lesson we learned from the mouse model constitutively expressing a fluorescent probe in AQP2-positive cells was that the origin of the fully differentiated epithelial cells along the distal nephron is complex. Indeed, the A-ICs and B-ICs derive from a cellular precursor expressing AQP2, while, moreover, B-ICs also derive from a cellular precursor expressing the NCC [8]. This latter event seems in line with evidence of vH⁺-ATPase expression in distal convoluted tubule



FIGURE 1: Dominique Eladari (left) and Francesco Trepiccione (right) walking on the Etna volcano.

cells of humans and rodents [9]. Investigation on the cellular plasticity of the collecting duct is still ongoing with Prof. Eladari's team, signifying that our collaboration did not cease with the end of the fellowship.

CONCLUSION

I am honoured to report here my human and scientific experience made possible by the ERA-EDTA fellowship programme. I hope this report proves inspiring for those young fellows in pursuit of a career in science—in particular, for MD fellows who are attracted, on one hand, to clinical practise that is charming and ego-feeding and, on the other hand, by the enthusiasm and adrenaline given by basic research and physiology. I chose both, and I am firmly convinced that a translational research partner is beneficial to any multidisciplinary research team. I do not yet have the recipe for success, but good mentorship, a passion for scientific investigation and determination are essential.

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