WOMEN IN CANCER PROFILE

From bedside to bench and back: my journey in thyroid disease

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I am the oldest of three girls in a Belgian family. I was born in the USA in 1970, whilst my parents were studying at the University of Wisconsin. Upon completion of their postgraduate studies, my parents returned to their native country Belgium when I was aged one. From a young age I was fascinated by medicine and in secondary school, human biology was my favourite subject. Whilst neither of my parents is medically trained, they always encouraged me and my sisters to have an inquisitive spirit and fuelled a thirst for knowledge and discovery. Following completion of my secondary school studies in 1988, I entered medical school at the Catholic University in Leuven, Belgium, to fulfil my aspiration of becoming a doctor.

The medical course in Belgium in those days encompassed 3 years of pre-clinical and 4 years of clinical studies. Although I was thrilled to study subjects such as physiology, anatomy and biochemistry during the preclinical years, it was the study of pathology and diseases as well as the patient interaction during the clinical years of study, which affirmed my feeling that I had made the right career choice. In 1993, during my 6th year of study, I was given the unique opportunity of participating in an Erasmus exchange programme, which allowed me to complete a period of elective placements in Dublin, Ireland and in Kirkcaldy, Scotland, studying Obstetrics and Gynaecology and Paediatrics respectively. During my placement on the neonatal unit in Kirkcaldy, I befriended Bhaskar, a junior trainee in Paediatrics and fell in love. As I still had to complete about 18 months of training following my elective in Scotland, I returned to Belgium, maintaining a long-distance relationship through sporadic phone calls, occasional visits and regular letter writing. When I qualified as MD (Summa cum Laude) in 1995, I took up a house officer job in Medicine in Wolverhampton, UK, where Bhaskar was working at the time. We were married in 1996 and have remained around the West Midlands where we now live with our two children Nathan (aged 17) and Indu (aged 15).

During my training as a junior doctor at the Royal Wolverhampton NHS Trust, I developed a fondness for Endocrinology and Diabetes, fascinated by the complex, yet logical, control mechanisms involved in the regulation and secretion of hormones. I obtained Membership of Royal College of Physicians (MRCP) in 1998, whilst heavily pregnant with my son Nathan. During my maternity leave, I approached Professor Jayne Franklyn at the University of Birmingham to explore the possibility of participating in a research project to broaden my horizon in the field of Endocrinology. This was the start of my career in Academic Endocrinology and Jayne has remained my trusted mentor and friend over the last 16 years.

I was fortunate enough to obtain a Wellcome Trust Entry level fellowship in 2000, allowing me to conduct a 12-month research project to study the role of the pituitary tumour transforming gene (PTTG), a newly diagnosed proto-oncogene, in pituitary adenomas. I was introduced to my other mentor, Prof Chris McCabe, and under his and Jayne's guidance, we established

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DOI: 10.1530/ERC-16-0396

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that PTTG and its binding factor PBF are overexpressed in pituitary tumours and that this is associated with overexpression of growth factors including fibroblast-growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF) (McCabe *et al*. 2002, 2003, Tannahill *et al*. 2002, Rabbitt *et al*. 2003). It soon became apparent that PTTG and PBF are involved in other endocrine tumours, and I identified that overexpression of PTTG and PBF are markers of prognosis in thyroid cancer, independent of patients' age and gender and of tumour type and size (Boelaert *et al*. 2003*a*, Stratford *et al*. 2005). Subsequent studies in our group have confirmed overexpression in other endocrine-related neoplasia including colon (Read *et al*. 2016) and breast cancers (Boelaert & Franklyn 2003, Watkins *et al*. 2010). Further functional investigations have unravelled some of the mechanisms through which these genes signal indicating roles in the initiation (Kim *et al*. 2005) as well as the promotion of tumourigenesis through the upregulation of pro-mitogenic and pro-angiogenic growth factors (Kim *et al*. 2006*a*,*b*). I helped to identify the functional motifs within PTTG and PBF (Boelaert *et al*. 2004) and the role played by phosphorylation in the interaction of these proteins with others thereby governing a number of cellular processes (Smith *et al*. 2013).

After my entry-level fellowship and the birth of my daughter Indu in 2001, I successfully obtained a Wellcome Trust Clinical Training Fellowship to further investigate the pathogenesis of thyroid tumours. Detailed investigations determined that both PTTG and PBF repress the expression, localisation and function of the sodium iodide symporter (NIS), thereby crucially affecting treatment of thyroid tumours with radioiodine (Boelaert *et al*. 2007, Smith *et al*. 2009). PTTG was also identified as human securin, an important protein in normal mitosis, and additional investigations performed during my PhD studies elucidated a potential role for PTTG in human foetal brain development (Boelaert *et al*. 2003*b*, Pemberton *et al*. 2007). Overall, the findings obtained during my PhD studies have laid the foundations for a large collaborative programme of laboratory research investigating the pathogenesis of endocrine neoplasia and more recently the exploration of novel approaches into the re-engineering of radio-iodine for refractory thyroid cancer.

Having obtained my PhD in 2005, I went back into a period of clinical training as a Lecturer in Endocrinology at the University of Birmingham. This allowed me to establish a portfolio of translational research through the exploration of large, detailed and unique clinical databases. Notable findings include the identification of the concentration of serum TSH at diagnosis as an independent predictor of malignancy in patients with thyroid nodules, findings which were subsequently confirmed by various different researchers (Boelaert *et al*. 2006, Boelaert 2009). Moreover, I have conducted a number of clinical studies evaluating the diagnosis and management of patients with thyroid dysfunction (Boelaert & Franklyn 2005, Manji *et al*. 2006*a*,*b*, Franklyn & Boelaert 2012, Boelaert 2013, Chortis *et al*. 2014, Edmunds *et al*. 2015). Important studies have confirmed the lack of symptoms in elderly patients presenting with hyperthyroidism (Boelaert *et al*. 2010*b*, Boelaert 2013, Jones & Boelaert 2015), the associations between autoimmune thyroid disease and other autoimmune conditions (Boelaert *et al*. 2010*a*) and the demonstration of radioactive iodine as a safe and effective treatment in patients with hyperthyroidism (Boelaert *et al*. 2009, 2013).

After a period of specialist training in endocrinology in Birmingham, I successfully applied for an MRC Clinician Scientist Fellowship, which was awarded in 2007. This allowed a further dedicated period of laboratory research and also laid the foundations for me to start establishing my own independent research group. The studies performed during my post-doctoral work have generated and developed mouse models of thyroid tumourigenesis further detailing the molecular pathways activated in thyroid neoplasia by PTTG and PBF. Their crucial interactions with the sodium iodide symporter have identified potential new therapeutic targets in the treatment of thyroid cancer with radioiodine (Read *et al*. 2011, Smith *et al*. 2012, Lewy *et al*. 2013). We have set up a large programme of research to identify the maximal therapeutic strategy to enhance radioiodine therapy in pre-clinical models of thyroid cancer. We are aiming to acquire new scientific insights into the fundamental mechanisms of action of NIS *in vivo*, as pre-requisites to clinical trials, which are required to enhance radioiodine treatment for all patients with thyroid cancer and to address the poor 5-year survival of those patients who currently do not respond to 131-I treatment.

I have maintained a keen interest in collaborative clinical research including the evaluation of the efficacy of fine needle aspirations in patients with medullary thyroid cancer (Essig *et al*. 2013), contributions to a meta-analysis exploring recurrence and mortality in papillary thyroid micro-carcinomas (Mehanna *et al*. 2014) as well as the evaluation of metyrapone as an effective treatment in the management of Cushing's syndrome (Daniel *et al*. 2015). I have been fortunate to have the opportunity to establish

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a team of clinical and scientifically trained researchers in continued collaboration with Chris McCabe. Working with these talented pre- and postdoctoral fellows and students has allowed me to adopt a true bench to bedside research approach into various aspects of thyroidology.

In addition to the laboratory and clinical research avenues described previously, my most recent endeavours extend further into translational patient-centred care. I am involved in a number of multi-centre clinical trials including the ELATION trial, which is exploring the efficacy of elastography in the diagnosis of malignancy in patients presenting with thyroid nodules. Moreover, I have developed a keen clinical interest in the management of endocrine disorders during pregnancy (Chan & Boelaert 2014, Brabant *et al*. 2015) and am taking part in the TABLET trial, which is exploring the efficacy of levothyroxine replacement in TPO antibody-positive euthyroid women during pregnancy. I have helped to determine the prevalence and economic consequences of mild-to-moderate iodine deficiency in the UK (Vanderpump *et al*. 2011, Monahan *et al*. 2015, Zimmermann & Boelaert 2015). Additionally, I work closely with a number of patient organisations and some of our studies have investigated the application of novel software to assess the readability of patient information leaflets for patients with thyroid disorders (Edmunds *et al*. 2014). These findings have been crucial in the editing of Revised UK Thyroid Cancer Guidelines, which I have co-authored (Perros *et al*. 2014).

Future research avenues which I hope to pursue include the continued exploration of novel ways to overcome radio-iodine-resistant thyroid cancer, the optimisation of management of thyroid dysfunction during pregnancy and the exploration of novel diagnostic and therapeutic approaches for patients with thyroid nodules. My aim is to deliver a varied portfolio of innovative research by adopting a true translational bench-to-bedside approach, by leading an impressive team of talented researchers and by working highly collaboratively within a network of national and international leaders in the field.

Through dedicated and committed guidance by my mentors, I have learned to appreciate the importance of training the next generation of researchers and clinicians. I continue to supervise a number of PhD students and have taken on leadership roles in nurturing the careers of budding clinical academics, locally, regionally and internationally. I take part in the setting of standards for clinical trainees both nationally and internationally through contributions to the National Diabetes and Endocrinology Specialist Certification Examination and the American Endocrine Society Self-Assessment Committee (SAC). I also lead the national training scheme for radioiodine administration in patients with goitre and thyrotoxicosis, directly impacting on the management of patients with thyroid neoplasia.

Looking back on my career so far, I feel incredibly lucky to have met a number of people who have helped to shape my academic path. I am forever indebted to Jayne Franklyn and Chris McCabe for providing me with their unconditional support and guidance. I have been very fortunate to be in a position to forge collaborations with high-flying researchers locally, nationally and internationally as well as to encounter a large number of very talented clinical and scientifically trained students and fellows who form part of my research group. I feel that often I have been in the right place at the right time but also that my overriding spirit of trying to grasp opportunities when they present themselves has allowed me to develop a varied and fulfilling professional life. Finally, and most importantly, I could not have undertaken this journey without the unconditional support of my husband Bhaskar and my children Nathan and Indu who continue to put up with me during the bad times as well as the good.

I started off at the bedside aiming to provide patients with the best possible care, then learned the power of science in advancing medicine to newer heights at the bench and hope to continue the translation of carefully conducted cutting-edge research back to the bedside.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this profile.

Funding

My work has been supported by Research Funding from the Wellcome Trust (066569/Z/01/Z), MRC (MR/J001414/1, G070064, G060181), NIHR-HTA (110399), NIHR-EME (09/100/10), The British Thyroid Foundation and The Get-a-Head Charity.

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Received in final form 13 September 2016
Accepted 15 September 2016
Accepted Preprint published online 15 September 2016

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