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Theranostics in Australia: The Importance of Vision and Training, and the Power of Collaboration

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Nuclear medicine began as a therapeutic oncological specialty over 75 years ago principally on the back of the discovery, and then widespread adoption, of Iodine-131 as an effective and safe treatment for differentiated thyroid cancer [1]. With a half-life of just over 8 days, this physical attribute meant that Iodine-131 could be centrally produced by neutron bombardment of tellerium in a reactor and then distributed widely to patients. Thus, dissemination of this therapy occurred over the ensuing years throughout the world, including into Australia.

In Australia, the first nuclear reactor was constructed, in the late 1950s, at Lucas Heights in the outskirts of Sydney [2], and following its commissioning, began producing not only Iodine-131 for therapeutic nuclear medicine, but also other neutron-rich radioisotopes such as technetium-99m for diagnostic nuclear medicine. In the 1960s through to the 1980s, nuclear medicine in Australia transitioned into a predominantly diagnostic specialty heavily focused on technetium-99m, and to a lesser degree, the imported cyclotron produced radioisotopes gallium-67 and thallium-201. Almost 50 years after the initial reactor, a replacement nuclear (OPAL—Open Pool Australian Lightwater) reactor was commissioned at Lucas Heights in 2007.

The first national medical cyclotron was established in Camperdown, Sydney, in the early 1990s [2]. This cyclotron was situated across the road from one of the first PET scanners in Australia at the Royal Prince Alfred Hospital in Sydney. Smaller cyclotrons were subsequently set up in the 1990s at the Austin Hospital and then at the Peter MacCallum Cancer Institute in Melbourne. With the introduction of this technology came the early foray into positron emission tomography utilising cyclotron-produced radioisotopes, predominantly Fluorine-18. These developments expanded the diagnostic capability of nuclear medicine. By the end of the 1990s, there were over 160 nuclear medicine sites with over 300 gamma cameras in public institutions, private hospitals and suburban practices in Australia. Only three PET cameras were in operation at the end of the 1990s. By 2020, however, PET had grown to over 80 centres across Australia with cyclotrons now present in every state and territory apart from Tasmania and the Australian Capital Territory.

With the development of nuclear medicine practice, the Australian and New Zealand Association of Nuclear Medicine (ANZSNM) was founded in 1969, and around the same time, the Australian and New Zealand Association of Physicians in Nuclear Medicine (ANZAPNM),

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more recently known as the Australasian Association of Nuclear Medicine Specialists, also came into existence. Over the 1970s and 1980s, training in nuclear medicine for medical graduates developed into structured programmes under the direction and supervision of the Royal Colleges of both radiology and medicine (Royal Australian and New Zealand College of Radiologists—RANZCR; Royal Australasian College of Physicians—RACP). The structure evolved such that training could be obtained either as part of a 4 + 2 year programme within the postgraduate radiology training programme or part of the 6 year postgraduate physician (internal medicine) training programme. As part of the 6-year radiology training programme, nuclear medicine comprised the last 2 years of training after completing 4 core years in radiology training. This allowed such trained practitioners to be dual qualified in both general radiology and in nuclear medicine. Positron Emission Tomography (PET) accreditation was incorporated into core nuclear medicine training in Australia in the early 2000s. Advanced training in nuclear medicine is supervised by a joint committee made up from representatives from the RANZCR and the RACP. There are now over 40 accredited training sites for nuclear medicine and PET sites around Australia in both public and private practice settings.

Within the physician stream, advanced training in nuclear medicine comprised of a minimum of 2 core years of nuclear medicine +1 elective year. Advanced training in nuclear medicine commenced after completing a minimum of 3 years of basic physician training post-intern year and passing the rigorous basic physician written and clinical exams. It is possible also in the physician training stream to specialise in two subspecialities of internal medicine by completing a minimum of 2 core years of nuclear medicine training and then an additional 2 core training years in a separate medical specialty (e.g. medical oncology, respiratory medicine, cardiology, endocrinology). This pathway allows physicians to become dual qualified in two subspecialties, a pathway very relevant to current and future theranostic practice.

Since the 1990s, there has been a resurgence in interest in therapeutic nuclear oncology and the development of significant expertise in this area in Australia. This has occurred for several reasons. Australia still has a relatively large number of nuclear physicians trained via the physician route under the clinical internal medicine model. These nuclear physicians have traditionally gravitated more to academic institutions and academic endeavours rather than the dual-trained radiologist/nuclear physicians who, due to their breadth of diagnostic capabilities and expertise, are highly sought after for private radiology practice. The length and rigour of training, the emphasis on research and evidence-based medicine in an academic teaching hospital environment and the hands-on clinical nature of internal medicine physician training subsequently led to a number of Australian nuclear physicians developing further subspecialty interest in therapeutic nuclear oncology. Dual-trained radiologists/nuclear physicians by and large were more comfortable and interested in the imaging aspects of nuclear medicine practice, rather the clinical, hands-on-patient, therapeutic practice.

The well-equipped and well-funded public Australian teaching hospitals working closely with excellent partnering tertiary universities allowed new techniques and radioisotope-based therapies to be developed such as Yttrium-90 SIR (Selective Internal Radiation) spheres at Royal Perth Hospital (Prof Bruce Gray, University of Western Australia) [3–6] and Iodine-131 rituximab at Fremantle Hospital (Prof Harvey Turner, University of Western Australia) [7–10]. The Australian Therapeutic Goods Administration Special Access Scheme allowed (and continues to allow) for compassionate use of in-hospital radiopharmacy-produced agents thus facilitating early use and adoption of both diagnostic and therapeutic agents long before formal regulatory approval occurred (e.g. Gallium-68 DOTATATE and Lutetium-177 DOTATATE for imaging and treating neuroendocrine tumours) [11–16]. Through this mechanism, a number of investigator-initiated single and multiple site studies could be and were performed. This coupled with the vision, drive and passion of a number of key individuals such as Prof Rod Hicks, Prof Andrew Scott and Prof Paul Donnelly meant that over the last 25 years institutions, such as the

Peter MacCallum Cancer Institute and the University of Melbourne, have driven discovery of new agents and have evolved to become world-class centres of translational research and clinical excellence in the fields of diagnostic and therapeutic nuclear oncology.

In the early 2000s, the introduction of PET in Australia necessitated, for the first time, the development of a collaborative multi-site, interstate approach towards data capture and data management in Australian nuclear medicine practice. This programme, called the Australian prospective multicentre PET data collection project, was mandated by the Australian federal government as they pursued objective data for justification for the introduction and reimbursement of PET into the national medical system. This programme utilised a change of management measure (developed by Prof Rod Hicks at the Peter MacCallum) [16] to determine the clinical impact of the new diagnostic modality of PET. The Australian PET data collection project [17] collected a large amount of high-quality data on multiple cancer types which confirmed the clinical utility of PET. The project led to multiple publications [18–22] and eventually the widespread reimbursement of PET by the Australian Federal government from 2004. This programme, I believe, was the nidus for what we are now seeing with the collaborative networks that have started in the last few years in both the public and private sectors. The Australian PET data collection project brought different institutions together for a common aim, and despite some initial difficulties and some latter controversy [23], overall, the programme proved the power of the collective, collaborative network.

Apart from physician resources, university-trained nuclear medicine technologist, physicist, radiochemist and radiopharmacy services have been available at all teaching hospital nuclear medicine departments since the 1980s. This has been critical to foster high-quality clinical and research work. Interest in peptide, chelation and metal chemistry at a number of universities, but in particular the University of Melbourne, has been critical for the development of novel theranostic agents such as sartate [24, 25] now licenced to Clarity Pharmaceuticals (Sydney, Australia). The government-funded Australian Nuclear Science and Technology Organisation (ANSTO) has also supported therapeutic nuclear oncology, most notably in recent years with the licencing of technology from Germany allowing for local production of Lutetium-177 in the replacement OPAL reactor. The premier government-backed scientific research organisation within Australia (CSIRO) has also committed, in the last 5 years, to research endeavours in this area developing a theranostics division within the organisation. The Australian Government itself has recognized the importance in supporting and developing the field of theranostics and through Australian Research Council and the Modern Manufacturing Initiative has committed tens of millions of dollars in the last 2–3 years to develop collaborative inititatives between public and private institutions in Australia in the areas of alpha particle therapy and novel radiometal PET pharmaceuticals.

Within the public and academic sector, ARTNET (Australasian Radiopharmaceutical Trials Network) was developed in 2014 as a joint initiative of the AANMS and the ANZSNM to address the need for a formal research network in Australia for collaborative multicentre clinical trials using radiopharmaceuticals for imaging and therapy. ARTNET provides advice on appropriate facilities for clinical trials, helps with protocol design if required, provides equipment and site validation and facilitates large-scale data collection. ARTNET has an executive committee which is responsible for overall governance, strategic planning and financial management of ARTNET and a scientific committee with wide representation from around Australia that oversees the scientific research activities of the network and reports to the committee. A similar network has recently been developed by the initially Australian, but now multinational, company GenesisCare. GenesisCare is one of the largest private oncology service provider in the world with over 150 cancer clinics throughout Australia, the UK and Spain. The GenesisCare network has a number of sites that provide imaging and therapy infrastructure for clinical trials as well as routine care of patients. This network differs from ARTNET in that GenesisCare also

incorporates trial sites outside of Australia, has its own site research management within each jurisdiction (state or country) and has an overarching global contract research organisation liaising with pharma to facilitate efficient execution of mainly pharma-sponsored trials both within and outside of the GenesisCare trial network, thus linking both private and public institutions to achieve the aim of providing responsive high-quality research output. The network also works with external contract research organisations bringing pharma sponsored trials to the network. Due to the cost effectiveness of performing trial work in Australia, the high quality of research performed and the research and development tax incentives for overseas sponsors provided by the Australian government, there has been much interest from pharmaceutical companies to use this network as well as other Australian institutions, to perform, in particular, first-in-human, phase I and phase II theranostic trials in Australia.

Ultimately the aims of these networks, both in the public and private domains, are to obtain high-quality clinical trial evidence as quickly as possible to make the case for, or against, new theranostic agents. An additional benefit of a clinical network of sites utilising standardised protocols across the network is the ability to obtain high-quality real-world registry data as well as become an effective means to pursue post-marketing (phase IV) drug surveillance when the new theranostic agents are eventually approved and come into more widespread clinical use. This network registry approach has already yielded clinically significant findings for compassionate Lutetium-177 PSMA use in the Australian setting [26–29].

The success of this network approach is demonstrated in the speed of recruitment to trials, the high-quality, robust data collected, and the impact of the publications stemming from the data. The Pro-PSMA Study [30] and Thera-P study [31] looking at Gallium-68 PSMA and Lutetium-177 PSMA-617, respectively, are testament to this approach. This has had the consequence of further trial funding being successfully obtained for the newly initiated, Novartis-sponsored, ENZA-P and Upfront trials. An added benefit of the network is by providing exposure in a controlled setting; this allows for the development of familiarity, experience and expertise across the whole nuclear medicine department, not only in running clinical trials but more importantly, in learning how to safely manage oncology patients. Thus, expertise in clinical decision-making and symptom management is developed on the back of the clinical trial. This will place the physicians and the departments involved in a position of knowledge and heightened clinical expertise for when these agents eventually become reimbursed and more freely available. Ultimately, this bodes well for the profession as it ensures patient safety and solidifies trust in the nuclear oncologist and the nuclear medicine department treating the patient.

In this chapter, I have hoped to guide you through the multiple reasons why Australia, like Germany, is currently one of the leaders in provision of cutting-edge techniques and new research in the areas of diagnostic and therapeutic nuclear medicine. A well-trained, academically focused work force, well-equipped facilities, attractive regulatory framework, supportive government nuclear and research science organisations and a strong commitment by practitioners in the field to develop well-organised collaborative networks with the aim of obtaining high-quality and robust data in a timely fashion are the combination of factors that have led to Australian nuclear medicine's current position in the world of theranostics and therapeutic nuclear oncology.

Potential Conflicts of Interest Dr. Lenzo is an employee and minority shareholder of GenesisCare. Dr Lenzo is also the founder and major shareholder in Cyclowest.

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