



The value of networks in driving phase I trials: the Peter MacCallum Cancer Centre experience

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Abstract: The Peter MacCallum Cancer Centre is strongly focused on the conduct of translational research in driving towards better outcomes for patients. Central to this is our clinical trials program, with a strategic focus on early phase trials. Our efforts in developing a world-class program focused on early phase trials have been critically dependent on the creation and collaboration with key networks: local, regional and global. In this paper, we will articulate how the early drug development landscape has evolved in Australia, and how and why collaboration has been such a critical enabler for us in driving success.

Keywords: Networks; early drug development; Australia

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Background

The Peter MacCallum Cancer Centre is a leading cancer research, education and treatment centre and is Australia's only public hospital solely dedicated to caring for people affected by cancer. At the heart of our institute's overall research strategy is translational research, with a significant effort placed on driving individual programs, and developing enablers to conduct bench-to-bedside and bedside-to-bench research. Underpinning this is our strategy around clinical trials and the drug development process, with a large clinical trials program that is deliberately focused on the conduct of Early Drug Development trials (phase I trials). Our Early Drug Development program supports the critical steps in drug development, starting from protocol design and selection of a starting dose, to conducting the 'first-in-human' dose-finding study and clinical translation of scientific proof-of-concepts.

Our efforts in developing a world-class EDD program are critically dependent on the creation and collaboration with key networks: local, regional and global. Firstly, our Local networks, namely within the cancer centre and our immediate surrounds, provide the building blocks of a

successful program, providing the resources (intellectual, infrastructure) that enable the execution of complex early phase trials, and have the ability to adapt quickly to rapidly changing requirements in this space. Regional networks (both around Melbourne, and more recently around Australia) have been critical to our growth over the last 2 decades. Focusing our collaborative efforts on these partnerships have helped to develop critical mass regionally, beyond what would be achievable through our centre if we were to function in isolation, and have ultimately helped bring more EDD trials to Australia. Finally, Global networks have helped bring us onto the world-stage, providing a seat at the table when key decisions are made regarding how and where a given drug will be developed by pharmaceutical and biotech companies, and have thus enabled us to enhance our relationships with industry as well as other academic centres.

Local trials program and network: building a successful program

Having a well-structured and highly functioning trials unit

is obviously essential to the performance of any individual trial, particularly for complex early-phase trials. In 2016, the Peter MacCallum Cancer Centre (PeterMac) moved to its new home in the biomedical precinct of Melbourne known as Parkville. This area encompasses the main campus of the University of Melbourne, several tertiary hospitals (including the Royal Melbourne Hospital (RMH), the Royal Women's Hospital (RWH) and the Royal Children's Hospitals (RCH); and also research institutes that focus on cancer research (including the Water and Eliza Hall Institute (WEHI) and the Doherty Institute). This major re-development of cancer and research infrastructure has enabled a more coordinated and harmonized manner of delivering cancer care and expanding cancer research. This is further enhanced by bringing together geographically, a multidisciplinary team of clinicians and research investigators with diverse research interests and expertise. Prior to the move, both the PeterMac and RMH had the largest EDD programs in Australia. Following the move, the newly formed joint trials unit is providing a great opportunity to redevelop a program that would best suit the changing landscape of cancer drug/trial development. The new unit is known as the Parkville Cancer Clinical Trials Unit (PCCTU), referred to as the "PeterMac's EDD program" in this article, and ultimately reflects the strategy and function of the combined PCCTU program (1).

Critical to the development of the PCCTU's EDD program was collaboration by all 3 partners (PeterMac, RMH and RWH) to developing a world-class cancer trials program, for that program to receive institutional support and for all revenue to be re-invested to enable sustainable growth and a degree of autonomy, and for EDD to remain a high priority. Essentially, without institutional (local network) support for phase 1 trials/EDD, our ability to build a world-class program, would not have been possible. PeterMac (and the other institutions) place a very high strategic value on early-phase translational trials, and many of the key metrics used to assess the success of our research programs, are ones that are intrinsically critical to the success of EDD. These include efforts placed on rapid start-up of clinical trials through expediting the regulatory approval process, the training of dedicated protocol submission coordinators; strong engagement by the study investigators such as the mandatory service at the institutional ethics committee by all the Principal Investigators (PI) of clinical trials (especially phase I). By directly investing in this (both financially and intellectually), we have managed to improve the efficiency and quality of

the ethics review process, and are now considered a "rapid-activating centre" when compared to other dedicated Phase I programs globally. Focusing on a metric such as this (rapid activation) has allowed us to benchmark ourselves against key institutions globally in an objective manner, and this alone has facilitated focused investment and support from key enablers within the network to improve our efficiencies. As discussed below, this has also translated into developing regional initiatives (such as the rapid first time in human/FTIH program as explained below) to improve our efficiencies, given we function in a public health care environment which receives significant funding, and therefore oversight, from state and federal governments.

Conducting phase I oncology trials is often complex logistically, and this requires significant expertise and a culture that is supportive of taking on these often highly labor-intensive trials. This includes both long and short-term strategic initiatives and specific investment. Perhaps the most important long-term investment relates to developing a focused and highly skilled workforce. Passionate, well-trained, high-quality investigators are obviously critical to the success of any trials program, but arguably this is even more critical in the context of EDD trials given the requirements for hands-on PI involvement, not just in the conduct of the trial. This extends beyond simply managing patients on trials, but also requires close engagement with other study-PIs and the study sponsors through regular teleconferences and face-face meetings. The responsibility of PIs in the EDD space is perhaps greater than during any other stage of drug development, as individual events and the decision-making around this may have an enormous impact (in both a negative and positive way) on the development of a particular oncology drug. The "PI-time" requirements are much greater than for later phase trials, and this needs to be understood to ensure they are well supported from within their institutions. Investment in experienced research nurses and study coordinators is increasingly important in EDD trials, given the need to not just care for patients, but to also deal with complex protocols and increasingly onerous protocol requirements. Nurses and coordinators need to be highly skilled in being able to juggle a medley of often competing study requirements such as multiple pharmacokinetic (PK) blood sampling time-points, serial pharmacodynamic tests including biopsies and complex imaging, specific safety monitoring such as cardiac /telemetry with prolonged (including overnight) hospital stays. Our teams also need to be comfortable with understanding complex science-driven

protocols, so they can themselves remain heavily invested in the trial, and understand the value of performing these complex assessments. Within our unit, an enormous amount of time is spent on continually educating the study team so they understand the value of conducting translational, proof-of-concept trials, not just those with simpler clinical endpoints. This extends well beyond broader education in areas such as good clinical practice or new cancer developments in general (e.g., latest research updates from academic conferences); to specific emphases on the trials we are currently conducting by providing real-time updates on teleconference discussions, how and why decisions are made following dose-escalation meetings, and interpretation of key data on PK, biomarkers, drug toxicity and activity. Team engagement is enhanced considerably with this approach, and we are continually refining how we approach the area of “workforce education”. There is a clear sense of excitement with observing things for the first time, given that we are often working with new agents/classes of agents, and sharing this with all of the team members is a strong motivator in continually striving for excellence. Simply put, embedding this culture of inclusion and teamwork is critical to the value that we all get from working with EDD trials.

A number of short-term investments in other programs have been made by our trial units that have particularly benefitted EDD trials. A prime example of this is molecular pathology, which has for the last decade been a critical requirement for the conduct of molecularly-targeted trials. PCCTU investigators have been involved in multiple such drug-development trials from first-in-man dose-finding trials to Phase III registration trials, including agents targeting pathways such as anaplastic lymphoma kinase (ALK) in non-small cell lung cancer (NSCLC), and BRAF mutations in melanoma and colorectal cancer (2-5). Molecular testing has of course been an absolute requirement for such participation, but with limited external resources available for testing, pragmatism was required. This has included the trials unit directly investing in that department to develop its capabilities. Our experience has shown that successful cross-disciplinary collaborations in translational research is strongly dependent on a number of factors such as joint applications for competitive government-sponsored grants, solicitation for charitable or philanthropic support, as well as strategic and advisory support in clinical research. Our Molecular Pathology leadership has in-turn been heavily engaged in assisting us with specific molecular testing (such as the development of a molecular co-diagnostic such as FISH/IHC for ALK) to the development of broader panels using “next-

generation sequencing (NGS) platforms to enhance EDD recruitment (6). These newer panels have been critical to the growth of our precision oncology program, which heavily leverages investment in both a broadening trials program in parallel with molecular testing. Staff members within the pathology department are co-funded by the PCCTU, to both help take direct control of trial-specific requirements (e.g., tissue processing for patents being biopsied) as well as facilitating inter-disciplinary engagement. Our model of co-investment with other clinical trial stakeholders has also improved the efficiency and quality of service delivery from our strategic partners such as the department of radiological imaging—which provides an important service in reporting subjective drug response. Although such a co-investment model may require an initial financial start-up and commitment, these short-term strategies pay off in the long-run because they could quickly resolve an operational bottle-neck, as well as fostering a long-term collaborative culture in the institution. This culture highlights the importance of oncology clinical trials (including complex EDD trials) as being part of the continuum of care for cancer patients, and not simply a niche interest of small group of researchers.

As drug development has evolved with the use of immunotherapy, it is increasingly apparent that a more seamless approach (from the sponsor’s perspective) from first-in-human cohorts to large phase Ib expansions and often directly into phase III, is becoming the norm. As a consequence, a strong EDD program is even more valuable in providing an internal pipeline for the unit to take these trials forward into phase II/III trials, and for those investigators to continue to play a leading role. From an operational perspective, studies now stay open for long periods of time, and evolve, requiring flexibility and adaptive approaches. Tumour agnostic phase I studies are increasingly evolving into Seamless phase 1 studies with multiple large-sized expansion cohorts (“SUMO” trials) (7). Within the PCCTU, working as a team allows us to be agile and adapt to evolving phase I trial design, and their requirements. We have deliberately embedded our Phase I/EDD trials with other tumour-stream trials, to ensure that we do not function in a siloed manner. Essentially, a first-in-human trial can start in EDD, and then transition into one of the tumour-specific streams as it evolves, particularly if large tumour-specific cohorts open or the agent moves into phase II/III. This allows the EDD team to focus resources on opening new complex phase I studies, and to ensure that tumour-specific expertise can be incorporated as early

as possible. The EDD team has its own team of research nurses and coordinators with the necessary expertise. But from an investigator perspective, there is a high degree of cross-over between EDD and tumour teams. This “balanced” approach allows us to still focus on EDD trials, but this is not the exclusive domain of the EDD team alone. The team environment we have tried to create also allows sharing of intellectual resources. For instance, investigators and research nurses (or study coordinators) could support each other in developing expertise with complex new drugs such as bi-specific antibodies and chimeric antigen receptor T Cells (CAR-T) directed therapies. Finally, our EDD approach needs to support and drive investigator-initiated research, thus mobilising and sharing the intellectual resources shared within our unit. This applies to both the scientific and clinical leadership which are needed to develop a translationally-focused bench-bedside clinical trial, as well as nurture the operational skills that are needed to execute such trials. The most impactful of these has been the development of B-cell lymphoma 2 (BCL2) inhibitors, an extraordinary story which began at the WEHI where researchers focused on understanding the role of cellular apoptosis in cancer, which subsequently led to the discovery of a novel chemical compound at the WEHI’s biochemistry program that target key proteins in the bcl-pathway. This was followed by the first-in-man phase I clinical trial of venetoclax and eventual multi-centre registrational phase III trials led by investigators at the RMH and at PeterMac (8,9). Using a similar approach, and decades of collaboratively developed intellectual infrastructure, we have recently manufactured a tumour-vaccine at PeterMac based on years of translational science, and brought it into the clinic in a first-in-man investigator-initiated trial; a challenging but rewarding experience (NCT03287427).

Regional networks (both around Melbourne, and more recently around Australia) have been critical to our growth over the last two decades. Focusing our collaborative efforts on these partnerships have helped develop critical mass regionally, beyond what would be achievable through our centre if we were to function in isolation, and have ultimately helped bring more EDD trials to Australia.

Regional networks: enhancing collaboration

The development of local/regional collaborative networks of cancer trials programs in Australia, which first began over 25 years ago, has played an enormous role in driving success in the EDD space. The key network for us has been Cancer

Trials Australia (CTA), which began as a collaboration amongst three phase I cancer trials units (PeterMac, RMH and the Austin Hospital) and the two research institutes—the WEHI and Ludwig institutes. Historically, researchers from these research institutes were responsible for developing granulocyte colony stimulating factor (G-CSF) in 1993. Originally known as the Centre for Developmental Cancer Therapeutics, CDCT, the organisation has grown over the decades and has become incorporated in 2005. During this time, its function evolved to extend beyond facilitating academic collaboration and education for its investigators, to developing an office serving a central administrative function and being an interface between sites and sponsors; and thereby managing trial start-up activities with hospital’s ethics, budgets, contracts and ongoing financial management of trials. The CTA network has since expanded to now include over 25 member sites across Australia (10).

The network and “CTA office function” has proven invaluable in a number of ways. Firstly, at its most simple level, the economies of scale with a larger operation and focus on developing sophisticated tools and expertise in trial management as articulated above has meant that, at a clinical trial site level, investigators can consolidate our research efforts internally, rather than each of us trying to replicate the same functions with minimal resources and expertise. Having a consistent approach across a number of key clinical trial sites has many advantages in practice, such as in dealing with sponsors and clinical research organizations (CROs) regarding trial budget, contracts and financial management, or liaison with hospital ethics committees and government or regulators regarding approval and governance processes. As a consequence, we have been able to develop a number of initiatives that have driven our ability to conduct EDD trials and compete globally. One of the key early initiatives was developed in 2006, and known as the First Time in Human, FTIH protocol, in which the CTA worked with our ethics committees, government and regulatory agencies (both locally and federally) to establish an expert, rapid review process for FTIH trials. Unlike a typical government regulatory approval, which may take from many weeks to many months, this process takes only 10 business days in our network.

Although CTA’s responsibilities are much broader than just managing EDD, EDD remains a key focus of CTA’s mantle. In addition to providing operational support, the CTA works hard on nurturing a strong focus on academic engagement, sharing and mentorship amongst investigators,

particularly in the EDD space. We have a dedicated phase I group, which includes both medical oncologists and haematologists, and have regular meetings in which we discuss our trials portfolios, develop specific projects and key strategic initiatives. Some of these joint projects have included the development of shared precision medicine and genomic testing protocol with common consent approaches across the network. At a simple level, the network helps facilitate cross-site referrals for early phase (and other) oncology trials, especially in trials with niche patient populations. Some recent examples have included clinical trials targeting NTRK gene fusions and ALK, where a conscious decision was made to open these trials at one enrolment site, so that all the clinical referrals from other centres will be directly siphoned to that single site. This approach has the advantages of improving the efficiency of trial initiation and speed of enrolment. The network collaboration has also been valuable in improving access to unique technologies and resources that may only be available at a limited number of sites, such as sophisticated functional imaging (positron emission tomography, PET with novel tracers). PET has been a research focus of our network since the early 2000's, and the development and resourcing of this has been leveraged through cross-referrals from other sites for patients, thereby adding both efficiencies of scale as well as the ability for multiple sites to participate in trials they otherwise would not have been able to do. More recently, a fully integrated EDD program encompassing cross-disciplinary collaboration between haematologists and medical oncologists has also placed Peter Mac at the forefront of accelerated advances in CAR-T cell therapy in Australia by allowing the rapid translation of existing clinical and laboratory expertise in this field from haematology to the treatment of solid tumours.

However, the network goes far beyond this, and has been highly effective in serving as a platform for us to share trials amongst members of our network, and on occasion conduct entire phase I dose escalation studies within our network (with 3 to 5 sites leading this, expanding to others in phase Ib) (11,12). The group has, since the CDCT was first formed, worked closely with smaller companies including smaller biotech companies and academic groups that need much support in the drug development process. The collective expertise of a number of experienced investigators has assisted with everything from providing initial preclinical advice, to helping with the development of trial protocols, and to conducting the trials in a highly coordinated manner across our network. From a personal perspective, there is

tremendous value in being able to work with trusted and like-minded colleagues, especially in Phase I trials. Looking beyond this, developing good functional relationships with colleagues, and sharing expertise and supporting (rather than competing with) colleagues ensures that, as a region, we develop a good track record in this space, with both industry and with CROs. As a member of the Asia-Pacific region, Australia still has to compete with North America and Europe, which are the traditional strongholds for attracting early phase clinical trials from large multi-national pharmaceutical companies. Our role is to demonstrate that there is real value for such companies to bring their trials to our region, in terms of saving resources, in start-up costs and monitoring, as well as simplifying communication when dealing with site from multiple time-zones!

A very recent development locally and regionally has been the Victorian Comprehensive Cancer Centre (VCCC) Alliance, which brings 10 sites (five hospitals, four research institutes and the University of Melbourne) together in a collaborative joint venture. The key areas of focus of the VCCC Alliance include oncology clinical trials, translational research, precision medicine, education and workforce development. Many of these initiatives will directly enable improvements in EDD trials as well. The clinical trial program, which takes up the largest proportion of funding, is focused on supporting investigator-initiated clinical trials, developing new tools to assist with clinical trial referrals across distant sites and support a number of translational research programs related to this. These include a precision medicine program (incorporating complex genomic testing and whole genome sequencing, with matched targeted therapy trials), and programmes that are focused on developing pharmacodynamic tools to better understand response and resistance to targeted therapies. Additionally, it has been well recognised that a key bottleneck in expanding our trial programs has been with our workforce, in particular with study coordinators and research nurses. Supporting a culture of mentorship and coaching as a core responsibility at every level of the EDD team is critical to the success of the unit. There are programs developed to help address this, including identifying career pathways and "apprenticeship" programs for individuals coming from non-clinical backgrounds (e.g., science graduates and PhD's) who are interested in clinical trials. A sense of support for those unfamiliar with clinical trials and a clear a path of progression in their careers within the unit and institution at large, ultimately leads to increased efficiency and decreased staff turnover. Finally, a Masters of Cancer Science, developed

from the ground-up, has an important focus on drug development. All of these programs are starting to assist us in the multiple facets needed to run our EDD programs, and will be important in us continuing to improve further.

The PCCTU is now a large and highly functional unit that can in many ways operate completely independently. However, there is little doubt that we continue to derive significant benefit through our collaborative regional networks; thanks to the economies of scale, ability to advocate with key enablers such as government much more effectively, and our collective need to continue to develop a strong clinical trials infrastructure to ensure that sponsors continue to see the value of bring trials to us.

Global networks: providing opportunity

Peter Mac, and the PCCTU partners have had a long history of developing collaborative relationships with other academic centres and with industry. In the drug development space, early engagement with the respective heads in drug development programs within pharmaceutical and/or biotech companies is critical, as decisions regarding which enrolment sites should be selected is often made early. Additionally, first-in-human dose-escalation trials are typically only conducted at a few (three to five) centres, and in this globally competitive space, being selected as one of those sites is difficult. Until recently, direct and deep collaborations have been very limited, with few companies establishing formal relationships. However, this has changed in the last three to four years, with a number of companies investing in establishing global alliances with cancer centres around the world, in an effort to enhance the drug development and translational research process. PeterMac has been fortunate to be a collaborating institution in a number of networks. On an institutional level, we see considerable strategic value in being part of these, with a key point being that each of these collaborations has its own unique value to them, with minimal overlap in terms of how we engage in the translational space. The largest of these networks are with Roche/Genentech, (known as the global cancer immunotherapy Centers of Research Excellence 'imCORE' program) with around 25 global sites, encompassing North America, Europe and Asian partners. Bristol-Myers Squibb has a similar-sized network, with a similar global footprint. The focus of these collaborations is largely, but not exclusively on immunology. A more recently established Network, established by MedImmune/Astra-Zeneca, known as Partners of Choice, has a smaller number of partners, but has deep engagement

across the breadth of their portfolio.

From our perspective, these alliances provide the potential for deep engagement in translational research projects or programs, as well as in the EDD space. Clearly, early and deep engagement and direct involvement in preclinical and translational research has the potential to strengthen a drug's development pathway, and ideally provide partners with more streamlined and earlier pipeline access. Trust and relationship building between collaborators (investigators and sponsors) are an important component in successfully building an EDD program, as many decisions regarding future trials activity are based on this. Other parameters do of course also play a role. Metrics around performance are critical, and these networks are providing us with an opportunity to benchmark ourselves externally against other sites or investigators, and also assist internally in ensuring we remain globally competitive. These metrics include objective measure such as start-up times and accruals, as well as subjective measure based on engagement and contribution in meetings and teleconferences. Access to such data-driven metrics, rather than subjective assumptions regarding performance, need to be used to gain insights into competitive we are in this global space, and allows us to determine what we need to improve upon to be competitive.

An additional benefit of these large collaborative networks is the increased interaction with like-minded international colleagues. In this increasingly connected world, we have progressed from knowing some of our North American and European EDD colleagues by name, to knowing them in person through interactions on teleconferences and meetings as part of early phase trials. However, our participation within these global alliances provides us with a whole new platform for interaction, which facilitates deeper relationships with our colleagues, other EDD investigators from all over the world. Already, this has led to increasing sharing of SOPs and strategic decision making, and exchange of trainees. It can only lead to improved relationships, improved research and improved outcomes for patients from around the world.

These alliances are still reasonably early in their maturity. Ongoing success will likely be measured by how effectively we can collaborate together on shared research projects, and what value-adding can be provided to trials, both investigator-initiated and sponsored early-phase trials. Within Peter Mac, we are using them as a vehicle to help drive internal engagement as well, by bringing together lab and clinical groups in developing translational research projects and investigator-initiated trials. This is not just enhancing our EDD opportunities, but also helping

embed a culture of having a strong EDD program enabling translational research at Peter Mac.

Conclusions

Early drug development is the cornerstone upon which all improvements in cancer treatment are built. Even the most efficacious drugs will fail without the right drug development team, whether that applies to within industry or the selected investigators. Peter Mac has built a strong team within and around it, to ensure that EDD remains a focus and a strength. This has allowed us to provide leadership within our regional networks and guide the role of early drug development in Australia, which in turn has allowed us to become active members and participants in global networks and provide us with the opportunity to shape and guide the future of cancer treatment.

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Footnote

Conflicts of Interest: J Desai—Grants/Research Support: Genentech/Roche, GlaxoSmithKline, Novartis, Bionomics, MedImmune, BeiGene, Lilly, Bristol-Myers Squibb; Advisor/Board Member: Lilly, Bionomics, Eisai, BeiGene, Ignyta, Merck Serono; Honorarium Recipient: Lilly, Bionomics, Eisai. B Tran—Amgen: Speaker, Advisory Role, Travel; Astellas: Speaker, Advisory Role, Travel; Bayer: Advisory Role, Travel; BMS: Speaker, Advisory Role; Janssen-Cilag: Speaker, Advisory Role; MSD: Advisory Role; Novartis: Advisory Role; Sanofi: Advisory Role, Travel; Tolmar: Advisory Role; Ipsen: Advisory Role; Chair-GU Tumour Group-Cancer Trials Australia, Chair-Germ Cell Tumour Subcommittee-ANZUP, Member-Scientific Advisory Committee-ANZUP, Member-Scientific Advisory Committee-Biogrid, Member-Scientific Advisory Committee-Parkville Cancer Clinical Trials Unit, Co-Chair-Molecular Tumour Board-Victorian Comprehensive Cancer Centre. The other author has no conflicts of interest to declare.

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