

The **Children's Cancer Research Unit (or CCRU)** is the research-dedicated arm of the Cancer Centre for Children at The Children's Hospital at Westmead, and combines the expertise of leaders in basic research, translational research and data science to increase our understanding of childhood tumours and other cancers. Researchers within the CCRU investigate a number of cancer types, with a focus on the solid tumours in children and adolescents that have a poor patient prognosis, such as neuroblastoma, brain tumours and sarcomas.

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The impact of health research funding models on the availability of funding for research into cancers with low survival rates, with particular reference to:

- a. **the current National Health and Medical Research Council funding model, which favours funding for types of cancer that attract more non-government funding, and the need to ensure the funding model enables the provision of funding research into brain cancers and other low survival rate cancers;**

(i) Competition is essential in medical research, in order to drive and reward performance and thereby ensure that government and other funding is provided to high quality research. However, it is also recognised that excessive levels of research competition have both unintended and undesirable consequences (1, 2). In terms of the NHMRC funding model, success rates for NHMRC project grant applications have dropped from historical levels of 20-25% to less than 15% since 2015. This low success rate is creating a hypercompetitive environment, and may lead to research proposals targeting low survival rate cancers being increasingly disadvantaged.

NHMRC project grant applications are scored based upon their perceived "scientific quality", "significance and innovation", and "team quality & capability relevant to the application", and these combined scores determine whether an application is funded. In order to obtain NHMRC project grant funding, grant applications need to be scored as "outstanding by international standards" (category 7, the highest score) or as "excellent" (category 6). Only a minority of the grant applications rated "very good" (category 5) are funded since success rates have fallen below 15%. In order to be rated as category 6 or 7, applications must have "objectives that are well-defined, highly coherent and strongly developed (and be either)

well designed (or have) a near flawless design”. In order to score a category 6 or 7 for “significance and innovation”, the planned research will “result in a (highly) significant advance ... which addresses an issue of great importance to human health, ... (that will) translate into fundamental outcomes” and/or be considered “highly innovative and (using) (very) advanced approaches...”

We believe that characteristics of low survival rate cancers can make it more difficult for associated research grant proposals to be considered “well designed (or to have) a near flawless design”. The fact that a particular cancer is characterised by poor survival rates can reflect a more limited research base, leading to less scientific knowledge. This can mean a greater need for more open-ended research grant applications seeking to (for example) identify treatment targets, or biomarkers of response. However, these more open-ended proposals can be viewed by grant review committees and reviewers as “fishing expeditions” that may be less likely to be considered to have “objectives that are well-defined, highly coherent and strongly developed (and be either) well designed (or have) a near flawless design”. Similarly, low survival rate cancers may have fewer experimental models (cell lines, mouse and other animal models) available for study. It can also be challenging to access statistically informative and representative sample cohorts, or patient cohorts for clinical trials. Reduced resources for research could therefore also lead to reduced “scientific quality” and “significance and innovation” scores for NHMRC project grant applications, as well as negatively impacting the team’s “track record”. One of the most problematic issues is how the determination of “an issue of great importance to human health” is made, as this judgement can clearly be made according to various criteria. The association between lower cancer incidence and reduced patient survival can mean that research into some cancers with poor outcomes could be viewed as less “important”.

In light of these issues, we suggest that **the wording of the scoring matrix for NHMRC grants be revised** to ensure that in the current hyper-competitive environment, applications proposing to focus upon low survival rate cancers are not disadvantaged. We note that track record is scored “relative to opportunity”, which is intended to reduce the disadvantage to researchers who have experienced career interruptions. A similar concept could be applied to the scoring of “scientific quality” and “significance and innovation”, to ensure that these are also scored “relative to opportunity”. This would mean that applications are scored according to the current capacity to study that particular cancer, as opposed to standards that may more broadly apply in more established and/or better resourced fields. If a particular application is proposing approaches that are clearly the state of the art for that field, the application should be scored accordingly, even if these approaches may not be as comprehensive as those that could be undertaken in the study of more common cancers.

(ii) In a similar vein, sustainable funding is also required for the **infrastructure** that enables research on low survival rate cancers, notably the **specialised technical staffing support** that is required to establish and then maintain use of “capacity”, such as (i) biorepositories to allow the sustained and uninterrupted collection of rare cancers over time, and (ii) representative cell line and animal models of low-survival cancers.

(iii) In the current funding environment, NHMRC project grant applications require substantial amounts of preliminary data in order to be successful. Low survival rate cancers receiving proportionally less funding (including cancers of the pancreas, brain, oesophagus, kidney, stomach and bladder, myeloma and cancer of unknown primary) may have a smaller associated workforce (3). This can create a potentially vicious cycle, where fewer results can be generated to drive successful grant applications, leading to fewer funded applications, and so forth.

We believe that dedicated funding is required to **build the workforce** studying low survival rate cancers. Research leaders are increasingly reliant upon non-grant funded research staff, such as research students, to obtain preliminary results for grant applications. In the absence of grant funding, entire projects may be completed by PhD students during their candidature. However, there are few PhD scholarship opportunities to actively encourage students to study low survival rate cancers. The **NHMRC co-funded scholarship scheme** could be substantially expanded to provide dedicated opportunities for students examining low survival cancers.

References

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- b. **the obstacles to running clinical trials for brain cancers and other cancers with relatively lower rates of incidence, with regard to:**
 - i. **funding models that could better support much-needed clinical trials**

To address this point, we can describe a gene therapy clinical trial undertaken by the Children's Cancer Research Unit. This phase I trial examined the feasibility of employing gene therapy to permit chemotherapy dose escalation for pediatric brain tumour patients that either have no curative therapy available, or have exhausted all treatment options. Because of the complexity and novelty of the proposed trial, a total of 12 years were required to prepare reagents for the trial, and to obtain regulatory approval. This trial was supported by The Kids' Cancer Project, which allowed its opening in 2012 (Australian New Zealand Clinical Trials Registry reference ACTRN12612000535875). Clearly the timeframe and resources required to prepare for and undertake this trial, even in an academic setting, were (and indeed remain) beyond the scope of any current government funding model. However, the benefits of this trial extend to other gene therapy approaches to other diseases, and resulted in direct experience in the conduct of gene therapy trials that can be applied to other rare diseases. The availability of these resources substantially reduces the cost of performing clinical trials within an academic setting, and needs to be recognised when considering requested budgets for clinical trial support.

Funding models for clinical trials for rare cancers therefore need to supply sustained funding, due to the time required for patient accrual. These funding models also need to recognise the **substantial in-kind support** that is provided by institutions towards conducting clinical trials, such as the support of clinical staff, operations, governance and administrative staff, as well as the provision of specialised in-house facilities that in turn require dedicated support. Our success in undertaking a technically complex clinical trial, recruiting from patients with low survival cancer patients, relied upon input from specially trained technical support staff throughout the period of development and conduct of the trial. Funding for these staff is very difficult to sustain throughout the research cycle spanning pre-clinical development to clinical trial in the absence of an academic or clinical appointment.

ii. **funding support for campaigns designed to raise awareness of the need for further research, including clinical trials;**

Awareness campaigns need to underscore the past and ongoing importance of evidence-based medicine that is based upon research. Cancer patients with poor predicted outcomes and few/ no curative options, as well as their families and their carers can all be susceptible to the false hope offered by alternative poorly- or untested therapies, frequently obtained from non-peer reviewed internet sites and/or social media. Patients pursuing these treatments may lose the opportunity to receive evidence-supported therapies, or to participate in clinical trials. The current post-truth environment characterised by a growing distrust in authority, and in the opinions of experts, may add to the need for **active awareness campaigns promoting the past and ongoing contributions of science and medicine.**

c. **the low survival rate for brain cancers, lack of significant improvement in survival rates, and strategies that could be implemented to improve survival rates**

(i) We note the need to recognise the different sub-types of brain tumours occurring in adults and children. In the pediatric setting, while the overall survival of some children with brain tumours has improved, the groups of children with poor outcomes are becoming smaller, and therefore increasingly challenging to study.

(ii) Improvements in survival for rare brain cancer sub-types with a comparatively limited underpinning knowledge base will depend upon investments in basic or discovery research. The history of science has indicated that major breakthroughs often come from researchers who have had the capacity to explore difficult problems over long periods of time with comparatively few distractions (4, 5). This type of research is increasingly difficult to sustain in the current hyper-competitive NHMRC funding environment. Funding bodies aiming to improve the survival rates of brain and other cancers should consider making dedicated funding available to **innovative projects with limited preliminary data available**, that should be **accessible to small research teams and/or early career researchers.**

(iii) We support **maintaining and strengthening the standards of evidence required for clinical trials of new cancer therapies.** Patients of low survival cancers are required for clinical trials and research, and yet there are simply not enough patients for all the clinical trials that could be designed, particular for combined therapies (6). It is important to better understand the predictors of clinical trial success, and to apply this information to design more informative clinical trials that will best serve the needs of patients.

References

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