Partnering with the US National Cancer Institute

Research underway to treat rare brain cancers

The dawn of the millennium brought with it a new era of computer programming as well as a novel cancer medicine. Temodar (temozolomide), a chemotherapy agent, was approved by the US Food and Drug Administration to treat adult patients with highly lethal, late-stage brain cancer as the year 2000 approached. In 2005, the same medicine was authorised for concurrent use with radiotherapy for adults with newly diagnosed glioblastoma multiforme (GBM) and as maintenance therapy after radiotherapy[1].

Fifteen years later, Temodar remains the last drug approved to treat late-stage brain cancers. Consequently, adults and children with this highly lethal type of cancer have not benefited from recent research advances – in contrast to other, previously poorly treated cancers. GBM – the most common brain tumour in adults and most common solid tumour in children – remains a harbinger of a poor prognosis with average survival under 15 months[2]. The reality facing the development of new treatments is the unacceptable 5.6% overall likelihood of approval for solid tumour treatments in Phase 1 trials – remaining at an unacceptable 40% even if the treatment progresses to Phase 3. The average oncology drug development time is more than nine years. Clearly, novel therapeutic development paradigms are needed; new drugs alone will not suffice.

Drug development's long and costly route has created a risk-averse culture in the pharmaceutical industry – especially for orphan indications such as GBM that may not have the market size to attract innovation and the commitment of resources. The hurdles include difficulties in obtaining sufficient biospecimens to carry out timely patient recruitment during clinical studies. Researchers historically have had limited resources to study the disease and develop new therapies. Progress could be partially addressed with a drug development paradigm leveraging more predictive and accurate preclinical models. This would offer opportunities to mitigate some of the risks associated with drug development. Such an alternative strategy is being substantively enabled by comparative tumour oncology, pathology, and genomics – and developed through various public-private partnerships.

Brain cancer poses unique challenges

The modest attention devoted to brain cancer – compared with more prevalent cancer types such as breast and lung – has implications for patients and researchers. All primary adult central nervous system (CNS) tumours are rare. Thus they pose unique challenges to patients and researchers, from insufficient preclinical models to obtaining sufficient biospecimens and patient recruitment during clinical studies. Patients struggle to find expert care and treatments, and researchers historically have had limited resources to study the disease and develop new therapies. They must deal with the fact that few places offer truly innovative clinical trials.

Patients may not be located near a clinical centre conducting a single-site trial; the time and physical exertion of repetitive treatments and follow-up is challenging. A cancer type impacting the central nervous system (CNS) generates a myriad of symptoms – headaches, dizziness, and loss of motor function. It can be challenging to adequately demonstrate that such quality-of-life impacts are due to disease progression rather than the experimental treatment itself. Nonetheless, clinical investigators are usually required by regulatory agencies to document side effects and theorise as to their cause. Cutting-edge treatments usually lack the necessary body of historical data so that more informed connections can be made regarding whether physical and mental decline is likely due to treatment or to disease progression. Thus, there is a large unmet need to improve the care and treatment of patients with primary CNS tumours.

Brain cancers overall have other, unique treatment hurdles because of where they develop in the body. The confined space of the skull can certainly complicate matters. However, there are additional, major factors as well – such as the blood-brain barrier (BBB). The BBB is a protective system of blood vessels and tissue that shields the brain from damaging materials. However, this network may also block access to the brain when anticancer drugs are given through traditional routes such as by mouth, skin, muscle, or bloodstream. Brain cancer researchers consider the BBB as one of the most important factors impacting progress. But there are others. Each patient's tumour is genetically unique, often resulting in a wide disparity in treatment benefit. A population of treatment-resistant cells may survive and expand, eventually leading to recurrence.

Consortia as a model

So, how to overcome these numerous challenges? Not surprisingly the answer is to bring together a team of experts who represent the wide range of expertise needed to give hope to those suffering from GBM and their loved ones. At the National Cancer Institute (NCI), teams are formed with outside experts through consortia as well as one-on-one partnerships.

The NCI's Centre for Cancer Research (CCR), Neuro-Oncology Branch (NOB) is addressing this need through leading two consortia – the Brain Tumor Trials Collaborative (BTTC) and NCI-CONNECT (Comprehensive Oncology Network Evaluating Rare CNS Tumors)[3]. NCI-CONNECT aims to advance the understanding of rare adult CNS cancers by establishing and fostering patient-advocacy-provider partnerships and networks to improve approaches to care and treatment. NCI-CONNECT uses the BTTC consortium infrastructure to conduct clinical studies.

The BTTC is a network that includes more than 30 institutions with expertise in brain cancer. It investigates new treatments for primary adult CNS tumours, allowing patients across a broad geographic range to participate in cutting-edge clinical trials and helping medical professionals more rapidly determine the benefits of various therapies. NCI's CCR serves as the lead institution – providing

Terms used in this article

NCI: National Cancer Institute

NIH: National Institutes of Health

CCR: Center for Cancer Research

NOB: Neuro Oncology Branch

BTTC: Brain Tumor Trials Collaborative

NCI-CONNECT: Comprehensive Oncology Network Evaluating Rare CNS Tumors

TTC: Technology Transfer Center

CRADA: Cooperative Research and Development Agreement

administrative infrastructure, clinical databases and oversight for both consortia. The mission of the BTTC is developing and conducting state-of-the-art clinical trials in a collaborative and collegial environment to advance treatments for patients with rare CNS tumours. Trials are conducted in a manner that merges good scientific methods with concern for patient well-being and outcome. The voice of the patient is important during trial design and execution, providing perspective to help researchers and clinicians understand how the drug impacts the patient's quality of life.

Since 2003, the BTTC and NCI-CONNECT have continued to design and conduct studies for adult patients with rare CNS cancers. Some are treatment clinical trials, while others are primarily designed to help researchers better understand the disease to improve patient outcomes and develop new therapies. For example, one clinical trial currently recruiting at 14 BTTC sites is: "Radiation Therapy Plus Temozolomide and Pembrolizumab With and Without HSPPC-96 in Newly Diagnosed Glioblastoma (GBM)." This trial will help determine whether adding a PD-1 inhibitor and a personalised heat shock protein-peptide complex-96 vaccine (HSPPC-96) improves the standard treatment for GBM.

NCI's Technology Transfer Centre

NCI's Technology Transfer Centre (TTC) is responsible for crafting, negotiating, and executing the numerous agreements required for BTTC and NCI-CONNECT. NCI has developed consortia agreements which institutions can sign if they want to participate in BTTC or NCI-CONNECT as a member site. TTC has also designed a customised Cooperative Research and Development Agreement (CRADA) template for BTTC and NCI-CONNECT studies. NCI establishes these CRADAs with industry collaborators for new clinical studies. Further, TTC develops customised BTTC and NCI-CONNECT agreement templates for clinical and biospecimen research studies. NCI establishes these agreements with the participating member sites.

One major challenge that NCI overcame was crafting consortia agreements acceptable to over 30 different institutions. Another major challenge was finding a mechanism to fund the participating member sites. A recent landmark agreement with Medical Science & Computing provides unprecedented opportunity for intramural and extramural collaboration on state-of-the-art clinical trials.

These two consortia are extremely beneficial for all the parties involved. Patients with rare CNS tumours who participate in BTTC and NCI-CONNECT studies have access to new treatments; medical professionals are able to more rapidly evaluate new treatments in state-of-the-art clinical trials; and NCI's industry partners are able to accelerate the clinical development of their agents.

Company partnerships with the NCI

The NCI's neuro-oncology branch (NOB) also meets the challenge of developing treatments and diagnostics by forming industry partnerships for first-in-human studies for these rare CNS cancers. Such studies are conducted at the National Institutes of Health's (NIH) Clinical Centre – the world's largest clinical investigation centre. NOB-industry collaborations test innovations that have developed to the stage of assessing safety and efficacy. Each side shares the harmonised mission to meaningfully improve the clinical care and outcomes of people with brain and spine tumours. Such studies are multidisciplinary, connecting basic science to patient outcomes research and scientifically based clinical trials with the aim of establishing better therapies and standard of care. In both models – multi-centre consortia and first-in-human studies – NCI's TTC is responsible for crafting, negotiating, and executing the numerous agreements required. Patients participating in clinical trials at the NOB can go to sites closer to their home (consortia model) or travel to the NIH (single-site, first-in-human model) at no cost. Higher enrolment means more rapid completion of trials that determine the benefit of the treatment being investigated

For decades, NCI has worked alongside global industry partners. These opportunities, as a starting point, need to fit our mission and generate interest within our research or clinical faculty. Company location can potentially be anywhere in the world. Companies do not need to have the US or other developed-world geographies as the focus of their go-to-market strategy. NCI collaborations have resulted in six FDA approvals since 2017[4]. The commercial partner in-licenses the technology and brings it to market. NCI-industry partnerships are a well-established, successful approach that leverages the unique capabilities of pharmas, biotechs, and the world's largest clinical investigation centre. (At any one time, the NIH Clinical Centre is conducting more than 1,000 trials).

One constant is the assistance of NCI's TTC – which supports the National Institutes of Health's goal to improve global health. NCI is one of the 27 institutes and centres that comprise the world's largest basic biomedical research facility. Technology transfer, at its most basic, is the concept that the NIH cannot commercialise the technologies it creates. Thus, there needs to be a path to get important medical solutions to the patients who desperately need them. To accomplish this, the NIH *technologies are transferred* to outside entities – primarily pharmaceutical and biotechnology companies – via various legal agreements. NIH researchers and clinicians' inventions worthy of patent protection and prosecution are offered to suitable development and commercialisation partners and licensees. Potential licensees and collaborators with corresponding

strategic interests and pipelines learn what is available via the NIH website, the Federal Register, conferences, and other means of notification. Discussions between the interested, external entity and the NIH technology transfer specialist may progress to agreement negotiations. Both sides seek to execute a licence or other collaboration agreement to continue developing the invention until it becomes a commercialised medical product[5].

Technology transfer is essential. NIH is not permitted to bring inventions to market. It does not have the translational – let alone go-to-market expertise – required to create a commercially viable medical product. There are no incubators or accelerators associated with the facility, nor an internal environment of entrepreneurship. As a result, NIH technologies are limited in their development progression, until entities step up to advance them along the product development continuum, obtain regulatory approval to market, and make them available to the public[6]. Pharma and biotech, entrepreneurs and investors, are needed to advance early-stage technologies to the patient and market. NIH technology transfer offices are ready and waiting to connect technologies with potential partners[6]. When it comes to negotiations, NIH policy recognises the inherent risk in technology commercialisation and has policies that align with this reality. Companies and similar entities in the ecosystem can negotiate appropriate IP rights for certain indications and geographies. The NIH has a business model somewhat different from other research institutions and academic centres. Unlike most technology transfer offices, we do no seek to maximise the amount of money brought in – be it through direct partnership funding, milestone payments, or royalties. This holds across the spectrum of collaborative and licensing agreements[6].

As with any academic research centre or institute, there are payments and fees associated with any agreement. The agreement could be a straightforward licence of an asset conceived by a faculty member or something jointly created. Either way, both sides negotiate fees, milestone payments, and percentage royalty payments that supplement funding from the US taxpayer. Monies taken in are passed along to our 27 institutes and centres. In this way, we are analogous to a venture capital firm's evergreen fund – in that monies taken in go right back out to support more investment in basic science and medical research. Unlike other academic institutions and research centres, our business model is not to maximise how much money is taken in on every agreement. Instead, we seek fair value that tends to offer more reasonable financial terms to the buy-side community. This spurs company growth and overall economic development of the region or country.

Economic development is a result

Economic development is the natural result of partnerships and licences. It may be surprising to learn that economic development is part of the NIH mission. And the NIH has an established track record of stimulus activity in the life sciences sector. NIH basic and clinical financial support of a particular sector spurs the growth of private investment focused on that sector[7]. Each dollar of NIH funding of public basic research more than doubles the corresponding amount of industry R&D expenditures after three years; increasing to more than eight times after eight years[8]. Basic research supported by NIH fuels the entrance of impactful medical solutions into the marketplace and results in a positive return on the public investment of more than 40%[9].

In summary, NIH-industry partnerships to advance scientific innovation and medical solutions have been proven successful whether the consortia or one-on-one model is used. The consortia approach – such as the BTTC and NCI-CONNECT – and one-on-one projects are models to develop innovative therapies, incorporating pioneering clinical trial designs to expedite early-stage or clinical trial completion. Both can reduce technology development time requirements or lessen the number of patients needed to reach conclusions about treatment benefit. Each incorporates measures to assess the impact on the individual by data sharing (and when relevant, the inclusion of patient reported outcomes). Both models offer ways for companies to meaningfully de-risk treatments of rare cancers (e.g. GBM) in order to become more attractive for commercial development. Interested parties should reach out to NCI's TTC to begin the process. Technology transfer experts stand ready to help begin creating the next success story.

References:

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(2) https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga/studied-cancers/glioblastoma

(3) BTTC Annual Meeting *(July 2019)* – The NCI-CONNECT (Comprehensive Oncology Network Evaluating Rare CNS Tumors) and Brain Tumor Trials Collaborative (BTTC) Annual Meetings were held on April 29-30, 2019 at the National Institutes of Health (NIH).

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