FEATURE SPOTLIGHT

Gateway Champion – Christine Brown, PhD

Heritage Provider Network Professor of Immunotherapy
Deputy Director, T cell Therapeutics Research Laboratory
City of Hope

Malignant glioblastoma is one of the most vexing cancers to oncologists. Close to 24,000 new cases are diagnosed each year in the US; with a 5.5 percent survival rate, most patients will not survive beyond two years.

With funding support from Gateway for Cancer Research, Christine Brown, PhD, and her colleagues at City of Hope aim to reverse the statistics using chimeric antigen receptor (CAR) T cell therapy. At the forefront of CAR T cell research, their work to date shows significant promise.

Entering the therapeutic pipeline in the early 1990s, CAR T cell approaches earned FDA approval in 2017 for treatment of pediatric acute lymphoblastic leukemia and adult non-Hodgkin’s lymphoma. Brown believes the next frontier for CAR T cell therapy is in solid tumors, namely glioblastoma.

Building on earlier research and continued Gateway funding, today Brown is leading a Phase I clinical trial of IL13Rα2-targeted CAR T cell therapy in combination with immune checkpoint inhibitors to treat recurrent and refractory malignant glioblastoma.

IL13Rα2 is over-expressed in most hi-grade gliomas, making it a good target for immunotherapy. An earlier Gateway-funded Phase I trial led by Brown and City of Hope’s Chief of Neurosurgery Benham Badie, MD, showed that an IL13Rα2-targeted CAR T cell therapy was safe, well-tolerated and showed promising anti-tumor response.

In a case study published in the New England Journal of Medicine, the pair reported one patient had tumor regression sustained for more than seven months, enabling him to return to work and daily activities (NEJM 2016 375(26): 2561-9).

“The most exciting thing about our study is that it proves a better treatment may be attainable,” Brown said at the time. “We can take a patient who has actively growing, advanced, metastatic multifocal glioblastoma, and we can see regression of all legions, including in the spine. To date, that’s unheard of.”

With the knowledge that PD-L1 is expressed in about a third of glioblastomas, Brown’s team moved on to explore adding checkpoint inhibitors. Preclinical trials found that IL13Ra2-targeted CAR T cell plus PD-L1 checkpoint blockade showed antitumor activity in glioma mice.

Currently, with continued Gateway funding, Brown and colleagues are testing whether IL13Ra2-targeted CAR T cells with or without nivolumab and ipilimumab can decrease immunosuppression from PD-1 signaling and enhance CAR T cell response in the fight against glioblastoma. The team has treated two patients thus far and three more are enrolled.
Since its inception in 1991, Gateway for Cancer Research has invested over $90 million in more than 180 cancer clinical trials, making a meaningful difference in the lives of 6,000 cancer patients. In 2019 alone, we awarded $1.6 million in new grants, increasing our active trials to 57 globally. Together, Gateway-funded investigators have advanced cancer research in the fields of immunotherapy, epigenetics, targeted therapies, integrative oncology and more, helping to end cancer as we know it.

Compared to more traditional research funding sources, Gateway has a remarkably short grant funding timeline. To accelerate the pace at which we make measurable impacts on the lives of cancer patients, we have developed a streamlined grant application process for investigators.

“This extraordinarily short timeline allows investigators to launch their trials quickly and begin enrolling patients,” says Delora Senft, Director of Strategic Partnerships. “Our goal is to reduce the grant application and administrative burden so clinician-investigators can spend their valuable time at the bedside caring for patients.”

Here is how the grant application process works:

First, review Gateway’s funding guidelines to determine if your study meets our intended impact and funding requirements. Gateway supports Phase I and Phase II clinical trials for new drug discovery and novel uses for existing drugs, and to pilot integrative therapies. Proposals should meet our focus on patient-centered, immunotherapy, targeted therapies and integrative oncology to prolong survival and improve patients’ quality of life.

Next, submit a Letter of Intent (LOI) through the online portal. The LOI should provide a concise summary of the research proposal, including objectives, methodology and estimated budget. Gateway typically funds studies with a budget in the range of $200,000 to $1,000,000 with grant terms from one to three years.

Gateway accepts LOIs submitted through the portal on a continuous basis. LOIs are aggregated four times a year for review by our Peer Review Committee.

Submitted LOIs are independently peer reviewed by a subset of Gateway’s Research and Grants Committee for mission fit and scientific merit. Applicants who are approved will be invited to submit a full grant application which includes the entire detailed clinical protocol, budget and other information.

Full grant applications are peer reviewed and scored to indicate funding priority by the full Research and Grants Committee. Grant applications that fall within the fundable scoring range are sent to Gateway’s Board of Directors for final review.

To facilitate start-up, Gateway provides its grantees with 20 percent of the grant award as seed funding at the start of the trial, then uses a “pay-per-patient” method for grant payments based upon patient enrollment. Researchers are required to submit semi-annual progress reports to trigger subsequent payments. Final payments are released upon receipt of the final impact report. Gateway will follow up with grantees each year after the grant closes to receive critical post-trial patient data. Gateway also requests that grantees share patient success stories to be used in future fundraising efforts. Patient stories support fundraising by clearly demonstrating to donors the real-world impact of their gifts, and thus enable Gateway to sustain a robust grantmaking program.

For more information or to apply for a Gateway research grant, please contact Delora Senft at (847) 342-6976 and Delora.Senft@GatewayCR.org.
Gateway’s Research and Grants Committee is responsible for the peer review of research grant funding applications submitted to the organization. The committee convenes quarterly to advance the most promising proposals to Gateway’s Board of Directors for final funding decisions.

At its most recent meeting, the committee reviewed and scored eight grant proposals in integrative oncology and targeted therapies, including:

- Exploring whether the use of CBD product can reduce aromatase inhibitor-associated musculoskeletal pain in women with HR+ breast cancer.
- Developing strategies to predict early disease stage of pneumonitis, which non-small cell lung cancer patients are at increased risk for developing, and tailoring cancer therapies to minimize toxicities.
- Determining whether depleting copper levels can prevent metastases in triple negative breast cancer patients.
- Using reverse phase protein array to identify biomarkers for a targeted list of drugs for patients with advanced breast cancer.

Also on the agenda was a discussion centered on the COVID-19 pandemic and its impact on research and clinical operations. Colleagues reported that many health systems are shifting resources away from research initiatives as they prepare to meet anticipated peaks of the pandemic. As a result, many Gateway-funded clinical trials have faced challenges.

It’s a very stressful time for cancer patients who may be apprehensive about traveling to the hospital for treatment despite knowing the importance of adhering to their protocols, one committee member said. Another reported working with patients on integrative strategies, such as using dietary supplements to enhance their immune health. This has been hard to implement as the general public is over-buying supplements in response to the pandemic.

If there is a silver lining to the pandemic it is the exciting convergence of research resources to develop vaccines and therapies against COVID-19, says Research and Grants Committee member Sameek Roychowdhury, MD, PhD, The James – The Ohio State University Comprehensive Cancer Center. This has accelerated drug development timelines, which will ultimately benefit patients, and also has underscored the importance of funding biomedical research.

With summer around the corner and May designated as Skin Cancer Prevention Month by the American Academy of Dermatology, we are highlighting two Gateway-funded clinical trials focused on innovative treatments for melanoma. While researchers have made significant progress in melanoma research, new treatment approaches are urgently needed for this fifth most-common cancer type affecting men and the sixth most-common in women.

**Molecularly Targeted Therapy for Patients with BRAF wild-type Metastatic Melanoma**

Patricia LoRusso, DO  
Professor of Medicine, Yale School of Medicine  
Associate Cancer Center Director of Experimental Therapeutics, Yale Cancer Center

For about half of patients with metastatic melanoma, targeting the BRAF gene mutation with kinase inhibitors such as MEK162 has shown progress in slowing cancer growth. However, there has been no meaningful clinical response in patients with the BRAF wild type gene. In this Phase II trial, LoRusso and colleagues explored a personalized medicine approach, characterizing BRAFwt metastatic melanoma tumors and using 20 novel agents and genome profiling to treat this specific type of cancer. The trial closed in 2019 and preliminary results are pending.

**Intratumoral CAVATAK (CVA21) and Pembrolizumab in Patients with Advanced Melanoma**

Janice Mehnert, MD  
Associate Professor of Medicine, Rutgers University Robert Wood Johnson School of Medicine  
Director of Phase I/Developmental Therapeutics, Rutgers Cancer Institute of New Jersey

Based on their earlier findings that the common cold virus (CVA21) stimulates an immune response in melanoma patients and promotes PD-L1 expression in the tumor microenvironment, Mehnert and colleagues conducted a Phase 1b trial combining the oncolytic biologic CAVATAK (CVA21) with pembrolizumab in patients with advanced melanoma for whom the immunotherapeutic agent would be considered standard of care. They hypothesized that the oncolysis of melanoma cells by CVA21 would amplify the T-cell potentiating effects of pembrolizumab. The trial is closing, and preliminary results are expected soon.
UPCOMING MEETINGS AND EVENTS

May 2020

23-24
European Society for Medical Oncology Breast Cancer Meeting 2020
Virtual

29-31
ASCO Annual Meeting 2020
Virtual
The inaugural recipient of the $1.5 million Gateway Discovery Grant and the recipient of the 2020 Young Investigator Award will be announced.

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– Yale Cancer Center, May 14, 2020

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– Memorial Sloan Kettering Cancer Center