Study Finds Rare Mutation Driving GBM, Potential Therapy

A poorly understood mutation in the brain cancer glioblastoma (GBM) is now being implicated for the first time as the driver of rare but deadlier cases of the disease, a team of researchers from the Perelman School of Medicine at the University of Pennsylvania and the Ludwig Institute for Cancer Research reported last week in Cancer Cell. While the study links the mutation to worse survival rates than what’s typically seen in GBM, it offers fresh hope for the small group of patients who harbor it: complementary preclinical work performed at Ludwig suggests targeting the mutation with an investigational drug or other targeted therapies may reduce the tumor’s size and extend lives.

Analyzing the genetic, clinical and imaging data from 260 GBM cases housed at Penn Medicine, the researchers discovered that patients with an epidermal growth factor receptor (EGFR) mutation, known as A289D/T/V, had increased tumor invasion compared to the rest of the cohort and an overall survival rate of six months. The median overall survival for GBM patients is 15 months.

EGFR is amplified in nearly 60 percent of cases, and EGFR mutations occur frequently in the disease. The most common, EGFRvIII, is found in 30 percent of patients. About six percent of patients, the researchers found, have the A289D/T/V mutation. With over 400 GBM patients, Penn has one of the largest data sets, second only to the National Institutes of Health’s Cancer Genome Atlas. Without it, researchers likely wouldn’t have been able to recognize the significance of the mutation.

“Having such a large number of cases helped paint a clearer picture about this rarer EGFR mutation, that these patients die sooner and have invasive and proliferative tumors,” said first author Zev A. Binder, MD, PhD, a senior research investigator in Neurosurgery. “But we also needed to drill down deeper to the cellular level to confirm and better understand what we were seeing in patients with this mutation, the so-called ‘gas pedal’ driving tumor growth, and how to potentially stop it.”

The Penn team, including lead investigator and senior author, Donald M. O’Rourke, MD, the John Templeton, Jr. MD associate professor of Neurosurgery and a member of Penn’s Abramson Cancer Center’s Tumor Biology Program, collaborated with Frank Furnari, PhD and his team at Ludwig to conduct a series of preclinical investigations to corroborate Penn’s findings.

In cell line models, researchers showed that the A289V mutation lead to EGFR activation and tumor growth, and that mice harboring the A289V mutation had significantly worse survival rates – 65 percent – compared to those with wildtype (non-mutated) EGFR-expressing tumors. The study also revealed a striking increase in invasive tumors in the mice.

Next, the researchers administered a monoclonal antibody drug, mAb806, which has shown promise in phase I and II clinical trials for GBM patients, to mutated mice. The drug specifically recognizes EGFRvIII and wildtype EGFR, but it also has a high degree of specificity for the A289V mutation, hypothesized based on structural data from Laura Orellana, one of the co-authors. The therapy significantly reduced tumor growth and enhanced animal survival in mice expressing the A289V mutation, as well as mice with the EGFRvIII mutation. It only had a mild effect on the wildtype EGFR mice, the team reported.

“Glioblastoma is a heterogeneous enough of a disease that I don’t think we will find that one single target that will stop all the cancer cells from growing,” Binder said. “But showing that we can increase survival in mice by targeting this specific mutation means that we are hitting a significant number of tumor cells and blocking what is really driving their growth. That tells me that if we directly target the mutation in these patients, it may make a significant impact.”

Penn researchers will continue to focus on targeted therapeutic possibilities to treat patients with this mutation, as well as others. What’s more, because the mutation is tumor specific and extracellular, it’s an attractive target for immunotherapy approaches, the researchers said.
Therapy for Glioblastoma Multiforme

(Continued from page 1)

Currently, GBM, which is diagnosed in about 22,000 Americans a year, has four U.S. Food and Drug Administration-approved therapies. But tumors often become resistant to these therapies, and in general only 50 percent of people with the cancer live longer than 15 months, underscoring the need for improved approaches to treat the disease.

Meanwhile, Ludwig researchers will continue to explore unanswered questions about the basic mechanisms underlying this invasive type of GBM to push the work further.

“This multi-institutional collaboration has allowed us to take the clinical data and combine it with basic-science aspects to present a well-rounded story of translational research into GBM,” O’Rourke said. “These results show us that mAb806 is a viable therapeutic option for tumors expressing EGFR mutations, other than EGFRvIII, that should be investigated further. And that we should not ignore these less-frequent GBM mutations, as they provide valuable insight for not only patient stratification, but also the other mutations common in this population. There is the potential for broader applicability beyond just a single target.”


Source: Penn Medicine Communications

Why Randomized Trials for Proton Therapy Are Difficult to Complete ...

Randomized clinical trials are the gold standard of cancer research and can shed light on whether innovative, new therapies with great potential actually have clear benefits over usual care for patients. However, the seven randomized trials funded by the National Cancer Institute (NCI) and the Patient Centered Outcomes Research Institute (PCORI) to test proton therapy are enrolling more slowly than expected. Commercial insurance medical policies that do not cover treatment with proton therapy can make it difficult for patients to participate in randomized clinical trials funded by the NCI, part of the National Institutes of Health, that are evaluating the therapy. That’s the message from an expert at the Perelman School of Medicine at the University of Pennsylvania and colleagues at the NCI who are calling attention to what the authors say is a major barrier these trials face. The authors published their commentary, and proposed solutions, earlier this month in the Journal of Clinical Oncology.

“Most commercial insurers and state Medicaid plans do not cover proton therapy for the cancers under study,” said lead author Justin E. Bekelman, MD, an associate professor of Radiation Oncology and Medical Ethics and Health Policy and senior fellow in the Leonard Davis Institute for Health Economics at the University of Pennsylvania’s Perelman School of Medicine, and member of the Abramson Cancer Center’s Cancer Control Program. Bekelman is also the principal investigator of one of these trials, the RadComp trial for breast cancer, which is funded by PCORI and the NCI. “While coverage denial is used to reduce inappropriate use of medical technologies, a downside when applied to proton therapy is that patients cannot participate in randomized clinical trials designed to answer crucial questions about its benefits and harms.”

Co-authors include Andrea Denicoff, MS, RN, head of Clinical Trials Operations for the NCI’s National Clinical Trials Network, and senior author Jeffrey Buchsbaum, MD, PhD, AM, medical officer and program director in the Radiation Research Branch at the NCI.

“Some research has shown the benefits of proton therapy, but other studies have demonstrated expected and sometimes unexpected toxicities in certain cancers,” said Buchsbaum. “That’s why these randomized trials are so important. We need the evidence from these trials to determine whether proton therapy is better than usual care at reducing side effects or extending survival.”

There are currently six randomized trials comparing proton therapy to photon (x-ray) therapy funded by the NCI and one by PCORI. All of these trials have faced enrollment challenges. For example, in the RadComp trial for breast cancer, nearly two-thirds of patients have insurance coverage policies that do not cover proton therapy for breast cancer; thus, the majority of patients eligible for RadComp cannot actually enroll and participate in the clinical study. In contrast, Medicare typically does cover proton therapy through local coverage determinations, thus allowing patients to participate in trials. However, inclu-

(Continued on page 3)
...and What We Can Do About It

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sion of only Medicare eligible patients over 65 significantly limits the number of patients who can participate in the trials and may reduce the generalizability of the results.

“NCI’s randomized trial program for proton and photon therapy is designed to provide evidence comparing these two therapeutic options,” said Denicoff. “Future patients will benefit directly from the knowledge gained. If we can complete the trials in a timely fashion, the results will enable patients to make more informed treatment decisions.”

All stakeholders are aware of the dilemma and are attempting to find solutions. Some commercial insurers and some proton centers have made arrangements to cover proton therapy for selected cancers under study. For example, some insurers cover proton therapy for selected cancers under study or have established coverage with study participation policies. The researchers are proposing an approach that leverages lessons learned from these successful experiences – bringing together public and private insurers, proton therapy centers, hospitals, radiation therapy equipment vendors and patient advocates to establish a program of coverage that includes trial participation in one of the seven trials. The NCI is hosting a meeting with insurers later this month to consider opportunities and challenges to establish such a program. Other barriers will be addressed, including physician and patient engagement in the clinical trials.

“The seven trials that are currently enrolling patients will definitively compare cancer control and side effects between proton and photon therapy across prevalent cancers,” Bekelman said. “To complete these trials, we need a coalition of patients, clinicians, payers, vendors, hospitals, and funders. If we are successful, our efforts could serve as a model to evaluate new advanced technologies in the future.”


Source: Penn Medicine Communications

Brian Capell, MD, PhD, Wins Damon Runyon Clinical Investigator Award

Brian C. Capell, MD, PhD, an assistant professor of Dermatology in the Perelman School of Medicine at the University of Pennsylvania, a core faculty member of the Penn Epigenetics Institute, and a member of the Abramson Cancer Center’s Tumor Biology Program, has been awarded a prestigious Damon Runyon Clinical Investigator Award for 2018. The award comes with a $450,000 unrestricted research grant over three years. Capell will use the funds to continue his research into epigenetic targets in the skin, specifically in hopes of developing effective therapies for squamous cell carcinoma – a common form of cancer that most often develops in the skin. Capell is one of just six researchers in the United States to receive the award this year.

The Damon Runyon Cancer Research Foundation selects the Clinical Investigator Award winners at its spring 2018 Clinical Investigator Award Committee review. The recipients are outstanding early career physician-scientists conducting patient-oriented cancer research at major research centers under the mentorship of the nation’s leading scientists and clinicians.

The Clinical Investigator Award program is specifically intended to help address the shortage of physicians capable of translating scientific discovery into new breakthroughs for cancer patients. Capell’s research examines epigenetic markers in the skin to understand their function and to see how they differ in healthy, sun-damaged, and cancerous skin. The long-term goal is to clearly define the role of these markers and to understand how they change as skin is further damaged, then to ultimately use that knowledge to identify targets for topical skin cancer treatments.

“We are thrilled to continue to fund high-quality, patient-focused research like the work proposed by Dr. Capell,” said Yung S. Lie, PhD, Deputy Director and Chief Scientific Officer at Damon Runyon. “This award will help him continue to develop his cancer research program, which has the potential to make an impact in a cutting edge area of the cancer field.”

The Damon Runyon Cancer Research Foundation has committed nearly $63 million to support the careers of 99 physician-scientists across the United States since 2000, including three researchers at Penn.

Award Info: Damon Runyon Research Foundation

Source: Penn Medicine Communications
Funding Opportunities

Leukemia & Lymphoma Society Specialized Center of Research Program (SCOR)

LOI DEADLINE: August 31, 2018

LLS’s Specialized Center of Research (SCOR) grant program is intended to bring together established investigators from one or several institutions to develop a focused research program, foster new interactions and cooperation, and enhance interdisciplinary research among the participants. As part of LLS’s Pediatric Blood Cancer Research Initiative, one funded SCOR will be focused on pediatric hematological malignancies.

Details here.

Leukemia & Lymphoma Society Translational Research Program (TRP)

LOI DEADLINE: August 31, 2018

APPLICATION DEADLINE: October 31, 2018

The purpose of the LLS Translational Research Program (TRP) is to foster collaboration between basic and clinical scientists with the intent of enhancing the transfer of basic research findings to clinical usefulness. Applications are sought proposing novel approaches to the prevention, diagnosis or treatment of hematological malignancies and related pre-malignant conditions.

In addition to the traditional TRP initiatives, this year LLS is offering two special initiatives: the LLS Pediatric Blood Cancer Initiative, and the LLS-Snowdome Foundation TRP for the Treatment of Pediatric Blood Cancer.

Details here.

Leukemia & Lymphoma Society Career Development Program

ELIGIBILITY DUE DATE: September 1, 20018
ABSTRACT DUE DATE: September 15, 2018

The LLS Career Development Program (CDP) provides support so that you can devote yourself to researching questions of direct relevance to hematological malignancies and/or relevant pre-malignant conditions. LLS offers career development awards to postdoctoral fellows and instructors, as well as early career, independent investigators.

Details here.

Susan G. Komen 2019 Career Catalyst Research (CCR) Grants

LOI DEADLINE: August 1, 2018

APPLICATION DEADLINE: October 18, 2018

Susan G. Komen® is requesting Letters of Intent for the FY19 CCR Grant program that propose outstanding translational research into the understanding, detection, and treatment of metastatic breast cancer which will lead to a reduction in breast cancer deaths by 2026.

Over the past 10 years, Komen’s Career Catalyst Research (CCR) Grants have fostered promising breast cancer researchers who are in the early stages of their faculty careers by providing support for up to three years of “protected time” for research career development under the guidance of a Mentor Committee. It is expected that following the successful completion of a CCR Grant, awardees will launch independent research careers, successfully compete for subsequent research project funding, and emerge as key leaders in the fight against breast cancer.

Details here.


APPLICATION DUE DATE: October 24, 2018

The purpose of these FOAs is to support basic research examining how Electronic Nicotine Delivery Systems (ENDS) aerosols affect normal and disease states relevant to human cells, tissues and organs.