AACR Conference Spotlights Innovative Brain Cancer Research

BY PEGGY EASTMAN

WASHINGTON—The growing trend in science toward team-research collaborations that cut across disciplines was on display in studies presented here at the American Association for Cancer Research "Advances in Brain Cancer Research" conference.

Primary brain tumors are relatively rare; estimates are that even the most common, glioblastoma, is diagnosed in fewer than 15,000 Americans a year. Progress in developing effective chemotherapy regimens for brain cancers has been slow.

AACR CEO Margaret Foti, PhD, said the conference was specifically designed to discuss novel approaches to brain cancer research and treatment, especially the role of mathematics and computational modeling in analyzing data.

Added conference co-chair **Eric C. Holland, MD, PhD**, Senior Vice President and Director of the Human Biology Division and Director of Solid Tumor Translational Research at Fred Hutchinson Cancer Research Center: "We have a lot of brain tumor meetings where people present their work," but the presentations have tended to be incremental updates specific to the researchers' own scientific silos.

ERIC C. HOLLAND, MD, PHD

But this conference was planned instead, he said, to be more expansive, providing a "rich interface" of cross-disciplinary research reflecting contributions from multiple fields. Thus one goal of the conference was to spotlight novel studies "using different computational strategies to detect brain tumors or to identify better ways of treating them," added Holland, who is also Director of the Nancy and Buster Alvord Brain Tumor Center, holder of the Chap and Eve Alvord and Elias Alvord Chair in Neuro-Oncology, and Professor of Neurological Surgery at the University of Washington.

Molecular Profiling

Many of the studies presented focused on molecular profiling and on using genomic data more precisely and in innovative ways—such as with systems biology methodology—to classify brain tumors in order to target patients' treatments more effectively.

"The current paradigm in precision cancer medicine is predicated on the identification of actionable genetic alterations that can be targeted with high-affinity inhibitors," said **Andrea Califano, PhD**, the Clyde and Helen Wu Professor of Chemical Systems Biology, Biochemistry & Molecular

ANDREA CALIFANO, PHD

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often strikes those who are no longer directly in touch with customers and 'ordinary' employees, and restrict themselves to bureaucratic matters, thus losing contact with reality, with concrete people."

Rivalry and Vainglory

"When appearances, our perks, and our titles become the primary object in life, we forget our fundamental duty as leaders—'to do nothing from selfishness or conceit but in humility count others better than ourselves.' As leaders we must look to the interests of others."

This is probably the simplest and most important disease; what is a leader for but to lead and help those under his/her leadership?

Gossiping, Grumbling, and Back-biting

"This is a grave illness which begins simply, perhaps even in small talk, and takes over a person, making him a 'sower of weeds' and in many cases, a cold-blooded killer of the good name of colleagues. It is a disease of cowardly persons who lack the courage to speak out directly. Let us be on guard against the terrorism of gossip."

Idolizing Superiors

"This is a disease of those who court their superiors in the hope of gaining favor. They are victims of careerism and opportunism. They honor persons rather than the larger mission of the organization. This disease can affect superiors themselves when they try to obtain the submission, loyalty, and psychological dependency of their subordinates, but the end result is unhealthy complicity."

I would add that overdependence on superiors can be equally damaging and can lead to a career catastrophe.

I shall simply list the remaining diseases since some overlap with the above and I will record only a brief comment by the Pope or me, if any:

Indifference to Others

This is ably covered above and speaks for itself.

Closed Circles

This is also covered above, particularly in "gossiping" and "idolizing," although the closed circles of cliques that exclude many colleagues is a very specific and destructive disease.

Extravagance and Self-exhibition; and Hoarding

These two are covered tangentially in "closed circles" and "indifference to others." But Francis makes explicit points about the turning of one's service role into a vehicle for storing power. As a Catholic, I see it as a rebuke of cardinals and bishops who focus on rising up the hierarchical ladder, and do it with extravagance in their own lives. However, academia has no shortage of this disease. It is no coincidence that Francis chose not to reside in the Vatican with its upscale and elaborate quarters, but rather in a simple apartment nearby; and he has chosen to wear simple vestments when he travels. He is a leader by example.

The Disease of a Downcast Face

"You see this disease in those glum and dour persons who think that to be serious you have to put on a face of melancholy and severity, and treat others—especially those they believe are their inferiors—with rigor, brusqueness, and arrogance. In fact, a show of severity and sterile pessimism are frequently symptoms of fear and insecurity."

In my career, this last sentence rings very true, and I could name a dozen who fit the description; they are unhappy people who make those around them unhappy.

"A leader must make an effort to be courteous, serene, enthusiastic and joyful, a person who transmits joy everywhere he goes. A happy heart radiates an infectious joy: it is immediately evident! So a leader should never lose that joyful, humorous, and even self-deprecating spirit which makes people amiable even in difficult situations."

I must say that this is my favorite of all the diseases, especially the curative prescription offered by Francis.

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Biophysics and Biomedical Informatics at Columbia University.

That paradigm is fine as far as it goes, but "less than 25 percent of aggressive malignancies present with actionable alterations, and not all of these respond to targeted therapy."

In addition to tumors with a lack of response, many brain tumors with actionable genetic alterations may initially respond to targeted treatment but eventually relapse to drug-resistant disease, which is ultimately lethal," said Califano, who is also founding Chair of the Department of Systems Biology, Director of the JP Sulzberger Columbia Genome Center, and Associate Director of the Herbert Irving Comprehensive Cancer Center.

"There is therefore a critical and impending need to complement the actionable mutation paradigm with approaches targeting critical and more universal tumor dependencies that are not necessarily represented by genes harboring activating mutations." These tumor dependencies, Califano said, are non-oncogene master regulators, which include individual genes and synergistic gene combinations.

Once identified, these master regulators can be targeted with rationally based drug treatments tested in preclinical screens, including an apoptotic screen done in mouse model xenografts. "We just ask, is this drug hitting these vulnerabilities?" he said.

> The growing trend in science toward team-research collaborations that cut across disciplines was on display in the studies presented at the meeting.

Califano described how his laboratory uses a combination of computational and experimental methodologies to reconstruct the regulatory logic of human cells in a genome-wide manner; then, analysis of this regulatory logic can be used to identify the master regulator proteins responsible for cancer. He and his colleagues then develop methods and compound combinations based on the analysis that can pharmacologically inactivate the culprit master regulator proteins on an individual patient basis (N of one). He has used this approach for human glioblastoma.

Califano is now about to launch a new precision medicine clinical trial which seeks to enroll 260 patients across six distinct rare or incurable tumors, including glioblastoma and anaplastic meningioma. The goal, he said, is to identify the best individualized drug or drug combination for treatment based on matching patient-specific tumor master regulator proteins with a specific drug's mechanism of action—as elucidated from computational data.

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Asked by a conference participant if he is using FDA-approved compounds in this clinical trial, Califano said yes, that he is concentrating on FDA-approved drugs and not investigational agents, because he wants the results of his studies to have an impact on the clinical care of brain cancer patients.

Mathematical Computation

Other speakers described how they are also using mathematical computation to better characterize brain tumors in hopes of treating them more precisely and

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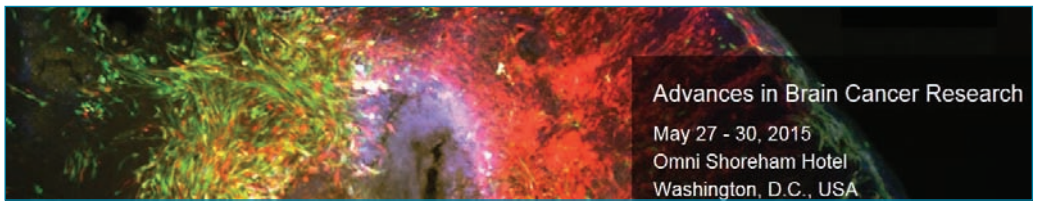
effectively. To understand the relationships between glioblastoma subgroups, conference Co-Chair **Franziska Michor, PhD**, Professor of Computational Biology in the Department of Biostatistics and Computational Biology at Dana-Farber Cancer Institute, uses mathematical modeling to predict the time sequence of driver events during tumorigenesis. She and her colleagues found that the most common order of evolutionary changes is chromosome 7 gain and chromosome 10 loss, followed by CDKN2A loss and/or TP53 mutation, and then alterations specific to their subtypes.

FRANZISKA MICHOR, PHD



Michor and her colleagues then developed a computational methodology to identify drivers of broad copy number changes, identifying PDGFA (chromosome 7) and PTEN (chromosome 10) as driving initial nondisjunction events. The evolutionary predictions were validated in mouse models.

"We further performed integrated genomic and epigenetic profiling of patient-derived cell lines to identify additional genes driving subtype transformation as well as alterations in the three-dimensional architecture of the glioblastoma genome during subtype changes," she said, noting that while these methods were applied in this case to glioblastoma, the techniques can also be applied to for other cancers as well.

> "There is a critical need to complement the actionable-mutation paradigm with approaches targeting more universal tumor dependencies that are not necessarily represented by genes harboring activating mutations."

HITS-CLIP Method of Precision Mapping

To improve the prognosis for glioblastoma patients, the New York Genome Center has launched a multi-institutional, multi-disciplinary study called the Glioblastoma Outcomes Trial, said **Robert B. Darnell, MD, PhD**, President and Scientific Director of the New York Genome Center, Professor of Cancer Biology at Rockefeller University, and a Howard Hughes Medical Institute investigator.

ROBERT B. DARNELL, MD, PHD

Darnell said the new study will seek to characterize individual patient tumors through deep sequencing, with a goal of developing clinically actionable applications (treatable targets) that can be offered to current glioblastoma patients.

Darnell said that by studying a rare group of autoimmune brain diseases associated with cancer, his laboratory discovered unique systems for regulating RNA metabolism which can be co-opted by tumor cells. This work led to his invention of the HITS-CLIP (high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation) method to precisely map RNA-protein interaction in living brain or tumor tissues.

"HITS-CLIP is a general method, and we will leverage it here to study non-coding tumor variants on a transcriptome-wide scale," said Darnell, noting that genomic and epigenomic mapping, together with computational tools, can then be used to establish insights into variants that relate to cancer biology and targeted therapy.

Describing a 76-year-old male glioblastoma trial participant who presented with gait difficulty, Darnell cited revealing results of the "deep-dive" genomic profiling of this patient, which showed structural variants including one related to the MET gene. "We're quite encouraged by the in-depth look at this single patient," he said, noting that today whole genome sequencing and RNA sequencing can be done rapidly—an important factor for physicians in practice. "We don't want this to be onerous for clinicians," Darnell emphasized.

Additional Research Highlights

Additional research highlights reported at the AACR conference included the following:

- An imaging-guided approach to biopsy allows the tumor genomic and transcriptome evolutionary process to be focused on malignant transformation, said Joseph F. Costello, PhD, Professor in Residence in the Department of Neurological Surgery and holder of the Karen Osney Brownstein Endowed Chair in Molecular Neuro-Oncology at the University of California, San Francisco.

"The clonal evolution of tumor cell populations can be reconstructed from patterns of genetic alterations," said Costello, who is also a member of the Helen Diller Family Comprehensive Cancer Center. In contrast, tumor epigenetic states are reversible and sensitive to the tumor microenvironment.

Costello described how he used mutation patterns to learn how low-grade brain tumors evolve over time, and how he discovered that treatment of low-grade glioma with the oral alkylating drug temozolomide—commonly prescribed for aggressive glioblastoma—can actually induce hypermutation and progression to glioblastoma.

- Tumor stem cell heterogeneity can be modeled through studying the growth and expansion of human glioblastoma organoids (miniature organs in vitro) in a three-dimensional culture system, said Christopher Hubert, PhD, a postdoctoral fellow in the Lerner Research Institute of Cleveland Clinic.

"This is the first culture system to allow simultaneous culture of functionally and phenotypically diverse stem and non-stem glioblastoma cell populations amidst microenvironmental gradients," he said, adding that the model shows that proliferative capacity largely arises from cells in high-oxygen, high-nutrient environments.

- The GA-bindng protein (GABP) transcription factor, which integrates intracellular signaling, selectively binds and activates the mutant telomerase reverse transcriptase (TERT) promoter across multiple cancer types, thus enabling cancer cells to overcome the replicative senescence of normal cells and escape apoptosis, according to a study from the University of California, San Francisco, and the University of Illinois, Urbana-Champaign, on which Costello was a coauthor. The enzyme telomerase governs telomeres; and as part of the aging process in normal cells, when telomeres become too short, the chromosome can no longer replicate and the cell dies. Up to 83 percent of glioblastomas harbor highly recurrent mutations in the TERT promoter specific to two nucleotide positions, according to this study.

These mutations allow glioblastoma cells to proliferate and flourish. "Because GABP directly links TERT promoter mutations to aberrant expression, this protein may provide a novel therapeutic target for multiple cancers," the authors concluded.

> For now, less than 25 percent of aggressive malignancies present with actionable alterations, and not all of these respond to targeted therapy.