INTERVIEW

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Brain cancer translational research from an academic perspective

Dr Gregory Riggins* speaks to Simi Thankaraj, Assistant Commissioning Editor:

Gregory J Riggins is the recipient of the Irving J Sherman MD Research Professorship in Neurosurgery and the Director of the Division of Neurosurgery Research. He received his MD and PhD degrees from Emory University (GA, USA) where he graduated from the Medical Scientist Training Program. After graduation, he then trained as a postdoctoral fellow with Bert Vogelstein and Ken Kinzler at the Johns Hopkins University (MD, USA) in the Department of Oncology. Now a Professor of Neurosurgery and Oncology, and

Genetic Medicine at Johns Hopkins, the main goal of his research is to develop and evaluate new brain tumor therapies. A major component of this research is identifying new small molecules.

Q What led to your interest in the field of oncology?

I had a strong interest in medical research even from a young age. As a medical student I had the unfortunate experience of also being a cancer patient for 3 years. During my recovery, I spent time doing research and afterwards I entered a medical scientist training program. I felt I was lucky that my cancer was cured but it was obvious we needed better therapies. After medical school I gained a large amount of cancer research training experience as a postdoc working in the Vogelstein Kindzler laboratory at Johns Hopkins University (MD, USA). Then at a new faculty I focused on positioning our laboratory so it could develop better therapies for cancer, in particular for brain cancer.

Q What is your research focusing on at the moment?

Our laboratory is trying to bring more effective cancer therapies to the clinic. We've launched the first clinical trial from our research, an investigator-initiated trial, at Johns Hopkins Hospital and we

are working on developing more trials. We're trying to bring as many promising therapies to trial as possible! Our most recent paper pertains to targeting tumors that have a mutated *IDH* gene and using demethylating drugs to induce terminal differentiation in these tumors [1]. This has been quite promising and we are vigorously pursuing this therapeutic strategy.

The second of the four main research areas we have going on in the laboratory is the use of a small molecule procaspase activator to activate apoptosis in glioblastomas. This is currently very successful and we are trying to take this preclinical work to Phase I trials with our collaborators at the University of Illinois (IL, USA).

A third line of research I would like to highlight, is already in clinical trials and is the closest to reaching patients. We are repurposing a tubulin-targeting small molecule that prevents tubulin polymerization. It is an old antiparasitic drug called mebendazole, which is now being used in a Phase I dose escalation trial for newly diagnosed glioblastomas. We have

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improved the formulation of mebendazole and are working on other means of further improving the efficacy of the drug. It is surprisingly nontoxic and appears to be very effective in the laboratory.

The fourth area is small molecule combinations in collaboration with the National Center for Advancing Translational Sciences that is part of the National Cancer Institute. This has been proven to be even more difficult than expected but it is work that we are pursuing to determine whether we can better predict better drug combinations to use for chemotherapy.

Q What do you feel is the most promising novel treatment for brain tumors?

That's a good question. To slow or stop brain tumor growth, I think the use of demethylases for the subset of brain tumors that have a *IDH1* mutation, which is a very high fraction of the grade 2 and grade 3 gliomas. The strategy of inducing differentiation looks quite promising and there are now questions about drug delivery, dosing and timing to optimize differentiation, but we are working this out. I do think this is quite promising.

Another area I think is promising is research into activating apoptosis. I think that this is a very promising avenue to slow and stop tumor growth. However, I think all of the small molecule approaches are limited by drug resistance. It is very hard to design a combination chemotherapy that will completely eradicate an advanced cancer.

Something that is of higher risk and higher yield that we think has a curative effect involves the immune system: using live bacteria to create a bacterial infection in the tumor, a controlled and safe bacterial infection as people are very worried about that. For example, using the *Clostridium novii*-based therapy developed by Bert Vogelstein's group [2]. It is something that we have been investigating for the previous 5 years using re-engineered anaerobic bacteria to make this therapy safe and useable for CNS cancers. It is already in canine trials for tumors outside the brain [3]. Using it inside the brain presents extra level of challenges that I think we can now address.

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Q What impact do you think further research into activated kinase proteins will bring to the field?

I think it will have an incremental impact because the kinase proteins face the problems of pre-existing resistance mutations. A resistance mutation in the DNA will invariably yield a single kinase drug ineffective before the tumor can be eliminated. On the positive side, a combination treatment could be an effective means to extend survival. I think it will be challenging for brain tumors, as there are a lot of pre-existing mutations, and so activated pathways that have parallel signaling make targeting one protein kinase at a time ineffective. There is the added challenge of intracranial delivery: some of the kinases that could work don't reach effective concentrations in the brain. This has really limited the efficiency of this therapy for the use of protein kinases for brain tumors.

Q What do you feel is the most difficult aspect of deciphering the genes responsible for brain cancers?

Determining the genes responsible for brain tumors is one of the most successful areas of the field. It has largely been accomplished by determining the most frequently mutated driver genes for the major brain tumors. A very challenging aspect of brain tumors is that there are many different rare types that haven't yet been sequenced or studied, therefore, assembling a quality set of samples for the sequencing study is very hard. There are over 120 different types of brain tumors that have been classified by the WHO. We've sequenced the major ones but a lot of the less known ones haven't yet been completed.

Q You were part of the research team responsible for establishing the first primary chordoma xenograft, which can be used as a preclinical model for this disease & as a platform for therapeutic development. What challenges did you face when developing this model & how did you overcome them?

I was part of that team but it was led by Gary Gallia who's my neurosurgeon collaborator – he is also the principal investigator for our laboratory's clinical trials. Growing

xenograft models from rare tumors can be a very long process and requires a lot of patience, and it's a process that's not really supported by large grants. Although some small foundations have the foresight to support this work, it generally takes years of work to establish these models. Another issue is that it is quite difficult to maintain these models, as they require passage from mouse to mouse.

Q What is the biggest advancement you have seen while working in the field of CNS oncology?

We now have a better understanding of the genetic basis of cancers and the dynamics of how the tumor evolves. We also have a better understanding of what we're up against, in terms of the complexity of driver mutations, as well as the heterogeneity of the mutations and the existence of pre-existing resistance mutations. I think that this understanding has led us to better alter our strategies for therapy – and also why previous strategies have not had a high success rate.

Q What are you most excited to work on in the future? How do you foresee the field progressing in the next 5 years? What major challenges need to be faced?

The most exciting prospect, for me personally and for our group, is to take our discoveries to the clinical trial stage, to see if we can get something to work in patients. Producing a therapy that has a survival benefit is the big goal. It's a long process but we are very hopeful that we can find something useful for this group of patients do not have enough hope of long-term survival. I am optimistic it is within our reach.

My prediction is that there will be major advances in brain tumors from better uses of drug combinations, live biologics and advances in immunotherapy.

There are, however, still a lot of challenges to be faced. A significant challenge is the aversion to risk in the system, it is inherent, it may not be an individual scientist, but the way that the research, preclinical investigations, funding mechanisms and clinical trials systems work. They push the research into incremental steps and are biased against high-risk high-yield projects that are necessary for fundamental changes and advances – especially for new therapies.

Q What are you most proud of in terms of career achievements?

Overall I think it is taking research discoveries to clinical trials, and when we've found things that are good enough to convince the necessary people in order to take it to trial. We've done this with a small group and a modest amount of resources, and have shown that it can be done using a very efficient system in a nimble and effective way.

Disclaimer

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Financial & competing interests disclosure

G Riggins is a member of the scientific advisory board and receives compensation from Vanquish Oncology, which is developing PAC-1, a procaspase activator. He also receives proceeds from intellectual property related to the IDH1 mutation licenced by various for-profit companies. Both of these financial arrangements are managed by Johns Hopkins University in accordance with their conflict of interest policies. G Riggins has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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