Science Show & Tell: Study uncovers three subgroups of rare children's brain cancer

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Topics: Research

Summary:

> Dr. Annie Huang chats about her SickKids study that uncovered three subgroups of atypical teratoid rhabdoid tumours and identified promising drugs to target each type in the Science Show & Tell series.

Dr. Annie Huang, Senior Neuro-Oncologist in the Paediatric Brain Tumour Program and Senior Scientist in Cell Biology at The Hospital for Sick Children (SickKids), has made a living studying the rare.

Specifically, rare paediatric tumours known as atypical teratoid rhabdoid tumours (ATRTs) that attack the brain, historically considered incurable. While considered a black box to researchers and clinicians, ATRTs are among the most common malignant brain tumours in children less than three years of age. Patients are typically treated with a combination of chemotherapy and radiation, and survival rates are low.

In a massive study published today on the cover of *Cancer Cell*, Huang and her team not only found there are three distinct molecular subtypes of ATRTs but also identified promising new therapeutics for patients.

What did your research find?

Up until now, the medical community has generally considered ATRTs as a single disease as there is one gene that's lost in all the tumours – we typically use a combinations of drugs to treat ATRTs but there is no well proven or established method of treatment.

At SickKids, we have been using high-dose chemotherapy for ATRT treatment for the last decade, and we have seen a significant number of unexpected survivors. Unfortunately some children, regardless of what we give them, do poorly. So that got us thinking that ATRTs are not all the same.
Our study generated cells from different ATRTs and tested them with a variety of drugs, looking at the genomes of the tumours using epigenetic tools.

The results confirmed our clinical observation that ATRTs are not uniform — there are three separate epigenetic subtypes, each associated with different clinical and patient profiles. That is, each of these tumour types comes from different cells that form different parts of the brain. One type in particular — what we called group 2 ATRTs in the study — are particularly resistant to many different therapies, but we discovered that they respond favourably to two well-known cancer drugs, dasatinib and nilotinib.

Why are these findings significant?

When I started in this field 14 years ago, most children died within six months to a year of diagnosis. The survival rate was 10 to15 per cent. Many patients weren't even treated as they are typically very young and such intense treatments can be hard to justify in a futile disease.

This was a first demonstration that different ATRTs indeed have different responses to drugs. It's important because this will allow us to test for these epigenetic groups in future patients and more precisely tailor their treatment to the molecular subtype of ATRT they have.

By breaking down the tumours in this way, we can now refine and improve treatments rather than continue to administer a one-size-fits-all approach. In prior findings , we showed that patients with one subtype of ATRTs did very well even without radiation, but we did not know which types of drugs would be useful for the different tumour types. Together, our studies provide a compelling argument for a more precise clinical trial.

How were you able to study these tumours if they are so rare?

Because ATRTs have been known to be so aggressive and rare, it's been a disease that didn't get much attention. It was our patients' families that raised the initial seed money that sparked our studies of this disease. The seed money helped us launch the Rare Brain Tumor Consortium (RBTC), which enabled us to collect large numbers of these tumours. We were able to translate those early research findings into larger grants so we could have a closer look at the genomes of these rare tumours.

For this study alone, we collaborated with colleagues from close to 40 countries from around the world to amass over 200 of these rare tumours, which we only see two to four times a year at SickKids. For this work, Jonathan Torchia, a PhD student in my lab and the first author on the paper, was recently awarded the prestigious 2016 Schweisguth Prize . Without the help of our patient families and global colleagues, this study would have never have happened.

What hope does this study give to parents with children diagnosed with ATRTs?

It's huge. Studies like ours, and from other groups, are bringing about a change in the way we look at this disease. Just a decade ago, it was considered an incurable disease.

This study uncovered promising drugs that can be incorporated into that treatment of ATRTs, and hopefully replace or reduce doses of harsh conventional drugs. These drugs are not a magic bullet but a new tool in our toolbox that can potentially help lessen treatment side effects, improve survival and make a difference in the lives of patients diagnosed with ATRTs.

What's next in ATRT research?

Because dasantinib and nilotinib have been used widely in leukemia treatment, we know they are generally well tolerated in children, so we're excited to incorporate these drugs into an ATRT trial.

Together with Dr. Cynthia Hawkins at SickKids, we have patented diagnostic tools that can help us identify patients with ATRTs that are most likely to respond to these and other ATRT drugs that we discover in the future. Currently, my lab and that of Dr. Rutka, are working with the drug screening facility at SickKids and the Ontario Institute for Cancer Research (OICR) to test other drugs to see if they can be "re-purposed" for ATRT therapies. Together with the Industry Partnerships & Commercialization team at SickKids, the work is now patented and industry partners have been engaged to further advance the identified therapeutics into clinical evaluation.

We now know it's not an incurable disease — we just have to figure out creative ways to treat it.

Drs. James Rutka of SickKids, Nada Jabado of McGill University and Daniel De Carvalho of the University Hospital Network (UHN) were co-senior investigators on this study .

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This paper is an example of how SickKids and University Health Network are contributing to making Ontario Healthier, Wealthier and Smarter.