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Biology of tumour changes when childhood brain cancer recurs, Canadian study finds

TORONTO/VANCOUVER – New research co-led by The Hospital for Sick Children (SickKids) and the BC Cancer Agency offers a simple explanation as to why new and experimental treatments fail for children with recurrent medulloblastoma, the most common cancerous brain tumour in children. The study, part of the Medulloblastoma Advanced Genomics International Consortium (MAGIC) project, is published in the January 13 online edition of *Nature*.

Using samples of children's and mouse models' medullobastoma tumours, the research team found the biology of tumours at the time of diagnosis had significantly transformed in recurrent medulloblastoma tumours. Their findings suggest that targeted therapies tested on, and found to successfully treat initial untreated tumours in the lab, are ineffective in treating recurrent tumours because the identified targets in the initial tumour are absent in the recurrent tumour. The biology is completely different.

Clinical trials testing new drugs for children with brain cancer have generated very few success stories over the past few decades. New, biologically based treatments for childhood brain cancers – the most common type of solid cancer in children – are rare. Medulloblastoma is known to be difficult to successfully treat, and side-effects from current therapies, including chemotherapy, radiation and surgery, can have a devastating impact on a child's developing central nervous system. Nearly 30 per cent of cases result in a recurrence of the tumour, which is nearly universally fatal.

Dr. Michael Taylor, co-principal investigator of the study and Neurosurgeon and Senior Scientist at SickKids, explains, "Almost all of the research done to understand the biology of childhood brain cancer, and to identify new drugs that might work, is done using tumour tissue removed at the time of the first surgery, before the children have received any radiotherapy or chemotherapy. Conversely, almost all of the experimental drugs that are identified are then tested in clinical trials that enrol children who have received extensive therapy of their cancer. This work flow is based on the assumption that the biology of the tumour when it is first diagnosed is very similar to the biology of the tumour after it has been treated."

Taking a step back from this assumption, Taylor, co-principal investigator Dr. Marco Marra from the BC Cancer Agency, and their Canadian-led research team decided to test its validity. The scientists used whole genome sequencing to test matched pairs of tumour samples from 33 children with medulloblastoma. Each pair included tissue removed at diagnosis (before the child began any form of therapy), and at the time of cancer recurrence (after undergoing therapy). They found a substantial genetic change in the recurrent tumours. They also treated genomic 'humanized' mouse models with surgical and radiation therapies, finding a poor overlap (under 5 per cent) between recurrent tumours and untreated diagnostic samples. In both mice and humans, the dominant genetic target at recurrence was different from the one identified at diagnosis.

"To everyone's surprise, the biology of the recurrent tumour was vastly different than the pre-treatment tumour, with only about one in 10 mutations found initially still there at recurrence. This massive change in biology offers a simple reason for why new drugs discovered to work in the laboratory on pre-treatment samples do not work when they are tested in children with recurrent tumours – it's like trying to make orange juice out of apples. This simple explanation could change the way we test drugs in children," says Taylor, who is also Principal Investigator at the Arthur and Sonia Labatt Brain Tumour Research Centre at SickKids and Associate Professor in the Departments of Surgery and Laboratory Medicine and Pathobiology.

Dr. Marco Marra, Distinguished Scientist at the BC Cancer Agency and Director of Canada's Michael Smith Genome Sciences Centre, adds that recurrent and treatment-resistant tumours should be studied further to identify treatments that may be effective in treating them. "Genomic profiling of treatment-resistant cancers has much to contribute to informing treatment decision-making in medulloblastoma and other cancer types," says Marra, who is also Professor and Head of the Department of Medical Genetics at the University of British Columbia.

The study was supported by Genome Canada, Genome British Columbia, Ontario Institute for Cancer Research, Terry Fox Research Institute, Canadian Cancer Society Research Institute, Stand Up to Cancer St. Baldrick's Dream Team Translational Cancer Research Grant, Pediatric Brain Tumor Foundation, the National Institutes of Health and SickKids Foundation, as well as a number of other generous funders.

This study is an example of how SickKids is contributing to making Ontario Healthier, Wealthier and Smarter. www.healthierwealthiersmarter.ca.

About The Hospital for Sick Children

The Hospital for Sick Children (SickKids) is recognized as one of the world's foremost paediatric health-care institutions and is Canada's leading centre dedicated to advancing children's health through the integration of patient care, research and education. Founded in 1875 and affiliated with the University of Toronto, SickKids is one of Canada's most research-intensive hospitals and has generated discoveries that have helped children globally. Its mission is to provide the best in complex and specialized family-centred care; pioneer scientific and clinical advancements; share expertise; foster an academic environment that nurtures health-care professionals; and champion an accessible, comprehensive and sustainable child health system. SickKids is proud of its vision for *Healthier Children. A Better World*. For more information, please visit www.sickkids.ca.

About the BC Cancer Agency
The BC Cancer Agency, an agency of the Provincial Health Services Authority, is committed to reducing the incidence of cancer, reducing the mortality from cancer, and improving the quality of life of those living with cancer. It provides a comprehensive cancer control program for the people of British Columbia by working with community partners to deliver a range of oncology services, including prevention, early detection, diagnosis and treatment, research, education, supportive care, rehabilitation and palliative care. For more information, visit www.bccancer.bc.ca.

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