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Contact: Suzanne Gold
suzanne.gold@sickkids.ca
416-813-7654 x2059
Wiley-Blackwell

Scientists find new twist on drug screening to treat common childhood cancer

TORONTO – A study led by scientists at The Hospital for Sick Children (SickKids) reveals a new method of identifying drugs to treat children suffering from fatal cancers for which an effective treatment has not been found. Rather than developing a new drug from scratch, which is a complicated and time-consuming process, they tried a different approach: in the lab, they tested existing drugs on cancer stem cells from young patients with neuroblastoma, one of the common cancers of infants and children. Cancer stem cells are the very cells that scientists suspect are responsible for relapses. The study is published in the August 18 advance online edition of *EMBO Molecular Medicine*.

The idea of repurposing existing medications is not new, but testing them on the cells isolated directly from children and that are thought to be responsible for the spread and regrowth of their tumours is novel. According to the study's principal investigator, Dr. David Kaplan, there is an urgent need to develop new treatments for neuroblastoma. Less than 40 per cent of patients over the age of one survive this cancer, and the disease usually relapses, aggressively spreading or metastasizing to other parts of the body.

"We conducted our drug discovery by targeting the cells that we think are responsible for the cancer coming back," says Kaplan, Senior Scientist at SickKids and Professor in the Department of Molecular Genetics at the University of Toronto. "This is a new way of developing drugs for kids, as we are taking the patients' own cancer stem cells and testing them in the lab."

The team, led by Dr. Kristen Smith, postdoctoral fellow in Kaplan's laboratory, had two main goals in this project: to eliminate the cancer cells and to do this without harming healthy cells. Since cancer therapies like chemotherapy kill good cells along with the bad, striking this delicate balance – even in adult cancers – can be challenging. This risk of toxicity is amplified in children, whose growing bodies are particularly vulnerable to the side-effects of powerful treatments, which can result in developmental problems and a higher risk of developing cancers as adults. As a result, some drugs that are proven to effectively treat cancer in adults cannot be used in children, leaving few options for some young patients.

Neuroblastoma, a solid tumour found outside the brain in the nervous system, is the most frequent cause of disease-related death in children.

The research team identified two drugs, DECA-14, a version of an antibiotic that is found in some mouthwashes, and rapamycin, a drug that is used to prevent organ rejection in children who have received transplants. Both medications were found to be effective in treating mice with neuroblastoma and were non-toxic to the normal stem cells from children.

The researchers were able to begin a clinical trial much faster than if a new drug was being developed since one of the therapies, rapamycin, had already been proven to be safe in children, with established protocols that outline the quantity and frequency of treatment. On the basis of this study, a SickKids-led North American Phase I clinical trial is already underway in collaboration with CHU Sainte-Justine in Montreal, as well as two centres in the

US. The trial will evaluate rapamycin in combination with the chemotherapy drug vinblastine, for paediatric solid tumours. This trial is led by Dr. Sylvain Baruchel, Staff Oncologist and Senior Associate Scientist at SickKids and Professor in the Department of Paediatrics at the University of Toronto, who was also a collaborator on this study.

If the clinical trial shows positive results, this could be the beginning of a personalized medicine approach, Kaplan says. "Our dream is that children will come to SickKids, we'll isolate their cancer stem cells, screen them with libraries of drugs and find out whether Patient A will respond to Therapy B.

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