# The search for child cancer drugs grows up

"Off the top of my head, I really can't think of a single cancer drug that was developed specifically for pediatric use," says Peter Houghton, director of the Center for Childhood Cancer at Nationwide Children's Hospital in Columbus, Ohio. "All have had their origin in adult clinical trials…wait, I lie: there is an antibody that was developed specifically for kids with neuroblastoma." Houghton is referring to ch14.18, an experimental drug in the process of seeking approval by the US Food and Drug Administration (FDA).

Houghton's remarks highlight a systemic problem with how cancer drugs are developed for children. Of the approximately 120 approved cancer therapies, roughly 30 are used in children, and only half of those have pediatric information included on their labels. Moreover, new cancer therapies are usually considered for use in children only several years after the results of successful adult clinical cancer trials have been published. "This means there's a delay of two to seven years before we know if children could benefit from a new drug," Houghton explains. "That's too long."

As recently as last month, an international collection of scientists penned an opinion article deploring the lack of attention and coordination in child cancer research (*ecancermedicalscience* **5**, 210, 2011). In their review of the scientific literature, the authors found that pediatric oncology papers had lower citation rates than those expected for the journals in which they appeared.

Pediatric cancers differ substantially from those found in adults. For example, about one third of children with cancer have a form of leukemia, which is comparatively rare in adults. The most common types of solid tumors found in children are brain tumors, whereas adults tend to suffer from lung, breast and prostate cancers. And children's cancers often differ with respect to drug sensitivity and prevalence of biomarkers.

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Part of the problem with finding cures for child cancers has to do with identifying enough participants for clinical trials. Only 1% of people diagnosed with cancer each year are under the age of 21.

To remedy the situation, in 2001 Houghton, together with Malcolm Smith, associate branch chief for pediatric oncology at the US National Cancer Institute (NCI) in Bethesda, Maryland, and Peter Adamson from the Children's Hospital of Philadelphia orchestrated a meeting to bring together twenty leading experts in the field from twelve institutions. The two-day brainstorming session produced the idea of establishing a Pediatric Preclinical Testing Program (PPTP) for new anticancer agents.

Three years later, the NCI launched the PPTP, which is now partway through its second five-year funding term. The funding, currently set at $3 million per year, is split across six main testing sites: five in the US and one in Australia. The PPTP's primary goal is to help determine which of the myriad new cancer therapeutics in development should be clinically evaluated in children, given that it is not logistically possible to test them all.

Paul Sondel, a pediatric oncologist at the University of Wisconsin–Madison, who has helped develop ch14.18 but is not involved with the PPTP, says the program fills an important gap. "The pharmaceutical industry is less eager to invest in the development of agents with perceived limited applicability due to the small market for rare diseases," which include many child cancers.

### Zeroing in on xenografts

Houghton says that testing involving human tumor tissue transplanted into immune-deficient mice—known as mouse xenografts—is the PPTP effort's mainstay, because the xenografts have proved capable of accurately predicting clinical activity of anticancer drugs. "Xenograft models have been maligned over the years, but ours have several significant differences. They are created by directly grafting patient biopsies into the mice, rather than using cell culture to propagate and expand the cancer cells," he says.

Across the PPTP there are currently 45 xenograft mouse models of solid tumors and leukemias that represent most of the common types of childhood cancers. The leukemia-testing component of the PPTP is carried by an Australian team led by Richard Lock at the Children's Cancer Institute Australia near Sydney. Over the last six years, they have tested almost 50 investigational agents supplied by more than 30 pharmaceutical companies on their xenograft panels of eight different leukemia samples from humans.

James Gommel

**Antibody and soul:** Five-year old Kaylee Gommel, who suffers from neuroblastoma, received a 20-hour infusion of ch14.18 at the Cleveland Clinic in September 2010.

The agents tested by the PPTP include nine that are FDA-approved for use against one or more adult cancers but lack a defined role in children. Not all of these have produced good results in the xenograft tests. "For the leukemias, where the cure rate is already 80%, we aren't interested in any compound that doesn't elicit at least a 50% response rate, and more than 75% of the agents we've tested have not met that criterion," says Lock.

Despite this surprising finding, Lock and the other PPTP scientists are particularly excited about a new compound manufactured by the Cambridge, Massachusetts–based Millennium Pharmaceuticals named MLN8237, which entered NCI-sponsored pediatric clinical trials in 2008, just ten months after presentation of PPTP-supported data showing its strong activity against neuroblastoma and refractory acute lymphoblastic leukemia in mice. The small-molecule drug, which blocks an enzyme called Aurora A kinase, is currently in phase 2 trials. The overall success of the PPTP will be evaluated in 2014 when the current five-year funding term ends.

"In terms of cost effectiveness and life years saved, investing in therapy for pediatric cancers is very economic," Houghton says in support of the effort. "The way I look at it, if you cure an adult with a carcinoma, we extend their median lifespan by three years, whereas if we cure a six-year-old kid with leukemia, we give them another 70-plus years."

***Branwen Morgan***