

The Philadelphia Inquirer

THURSDAY, DECEMBER 17, 2009

National

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Cancer-treatment gamble starts to pay off

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Every day last summer, researchers John Maris and Yael Mosse waited eagerly for e-mail from a 24-year-old woman named Anna O'Connor—or her father, who was closely involved in her fight against a rare cancer.

Since her diagnosis at 17, Anna had kept going by trying every treatment she could. One had left her so radioactive that she had to spend two weeks in isolation in a hospital room covered in plastic. Her cancer continued to spread.

Now she was the first person who stood to gain from an enormous gamble that Maris started taking 20 years ago at Children's Hospital of Philadelphia, betting that genes would offer hope for this disease, called neuroblastoma.

It was a gamble that led nowhere until recently. There were years of no leads and false leads. Although Maris saved some children with chemotherapy and radiation, he lost others, including the plucky Lower Merion girl Alex Scott, who founded the famous Alex's Lemonade Stand, a funder of the work at Children's.

Several strokes of luck had led the Children's team members not just to a genetic finding but to a new drug they are already testing for safety.

As Anna started taking the pills, she felt a total cure was beyond reach. But maybe this treatment would at last stop the cancer's spread.

The researchers had decades of work on the line. Even a small gain would be notable. Above all, they wondered: Would it help young children, the usual victims of neuroblastoma?

Teamwork

Maris, 48, is a muscular, intense man with close-cropped gray hair. He's a firm believer in teamwork, not just to share brainpower but to help absorb the pain in treating toddlers and other children who too often die anyway.

About half the 650 to 700 cases diagnosed each year in the United States get a "high risk" form that's deadly in most cases. The other half get a milder form that's curable with chemotherapy but can still cause lifelong health problems.

It's a brutal business, treating little children with cancer and seeing so many die. That's why the Children's Hospital neuroblastoma team relies on a social worker to help everyone cope—including the doctors.

Back in the 1980s, nobody knew what caused the disease. Some thought it was a carcinogen, others said it was genetic. In the mid-1990s, Maris became convinced it was caused by a combination of inherited predisposition and some unlucky genetic mistakes that turned a few cells malignant.

In rare cases, neuroblastoma did run in families, apparently passed through the generations by some as-yet-unknown cancer gene. Maris thought those families held a clue.

"Rare occurrences in nature can be particularly informative when teaching us about things that are more common," he said. He had seen the same approach lead to insight into other cancers.

So Maris started to collect data on neuroblastoma families, digging through records at Children's and asking other doctors to alert him to possible family connections.

Once, he drove to a reunion of such a family, near the Poconos, where he sat at the kitchen table collecting blood.

Only one of the two children was diagnosed with the disease, but all three of the mother's siblings had died of neuroblastoma in childhood. The grandmother never had any symptoms, but a chest X-ray showed she had a tumor near her spine, suggesting she had a benign form of the disease - mild enough that she could act as a carrier.

With just two extended families, he started trying to locate a gene that was passing cancer through the generations. As a first step, he started looking for suspicious "markers," common genetic variants that showed up more often in the family members who got cancer.

In 2002, he found something on Chromosome 16. He and his colleagues published the apparent breakthrough in the journal *Cancer Research*.

That narrowed their search down to dozens of possible genes. Finding the exact one fell to Mosse, an energetic, petite woman who was born in Israel and grew up in France. Now 37, she is widely seen as an up-and-comer.

For the next few years, she combed Chromosome 16 for cancer genes but found nothing. The breakthrough had been a statistical fluke.

Protruding rib

2002 was also the year that Anna O'Connor first noticed that one of her ribs was jutting out a bit. It was early in the



DANIELLE GARDNER/For the Inquirer

Anna O'Connor, 24, at her home in Wheaton, Ill., learned in 2002, at age 17, that she had cancer. After other treatments failed, she got a new drug in May and her tumors started to regress.

summer before her senior year in high school.

It didn't hurt, and she felt fine. And there were many more exciting things to think about, including the church trip to the Dominican Republic, where she would help build a school.

When she returned, the foreign food and hard work had left her five pounds lighter, making the protruding rib more obvious. She asked her grandfather, a doctor, to take a look. Four days later, she learned she had a rare children's cancer that is even rarer in older teens. "It really came out of nowhere," she said.

The situation got even more surreal for her after surgery revealed the tumor was the size of a cantaloupe, and that it had spread.

In 2003, after chemotherapy, radiation, and an antibody treatment that made her bones ache day after day, she went to Children's Hospital to try experimental radiation. It left her so radioactive that she had to live in isolation for two weeks. Everything in her hospital room was covered in plastic — the bed, the pillow, the remote control.



Researchers John Maris and Yael Mosse. Maris began the work 20 years ago at Children's Hospital of Philadelphia. In September, Children's started testing the drug in children.

That treatment, too, failed. But it caused her to cross paths with John Maris and Yael Mosse.

Tech upgrade

In 2006, with no gene in sight, Mosse spoke with Hakon Hakonarson, an Icelandic native whom Children's had just recruited to start a new genetics center. Hakonarson suggested she and Maris upgrade their gene-hunting technology.

Mosse agreed, but she wanted to go back and examine all 23 chromosomes again - not just Chromosome 16. She wasn't convinced she was looking in the right place.

By then, Maris had found a new family from Italy with five cases spread over three generations. Their genes added much-needed statistical power.

With three big families and several smaller ones in hand, they soon found a much likelier genetic neighborhood on Chromosome 2.

But the right segment still carried 104 genes, and the researchers disagreed which one was the likely culprit. Maris thought it was a gene called MIC, because it gets copied extra times inside tumor cells.

But Mosse thought it was a gene called ALK because it was associated with other cancers, including a rare type called anaplastic lymphoma.

Mosse went back to the DNA she and Maris had collected from the cancer fami-

lies and started looking for misspellings in the ALK gene. By January 2008, she found something. In eight different families, all of the people with the disease had misspellings in the same place: ALK was their gene.

But that didn't tell the researchers whether ALK had anything to do with the vast majority of cases, the ones like Anna O'Connor's that arise spontaneously. Could the tumor cells carry mistakes in ALK, leading them to grow so aggressively?

To find out, they started DNA testing on a collection of 167 tumors cells they had taken from patients over the years and stored in freezers.

They found that the ALK gene was damaged in about 15 percent of their tumors. Those patients would be the most likely to respond to the drug, but the researchers thought others might be helped as well.

When they published this finding in August 2008 in the journal *Nature*, it made waves.

"This is a big deal," said oncologist Gregory Reaman with the National Children's Cancer Center in Washington. It was the first such gene finding linked to neuroblastoma that looked as if it might be "druggable."

But who would make such a drug when it would work only in a couple of rare cancers?

What the researchers didn't know was that a year earlier, Japanese researchers had found ALK mutations in 8 percent of non-small-cell lung cancer. Since this type of lung cancer affects thousands of people, drug giant Pfizer began looking for an "ALK inhibitor," a drug that would block the protein made from the gene's instructions.

Within weeks, Pfizer scientists discovered an ALK-attacking compound and started testing it on lung-cancer patients whose tumors had an ALK mutation.

So far, it has helped beat back lung cancer in 70 percent of the patients with only mild side effects. "That's almost unheard of," Mosse said.

Maris and Mosse began testing the drug on neuroblastoma cells in the lab and then on mice with the disease. The drug shrank the mouse tumors with ALK mutations. And it worked in some tumors without the mutation.

Anna O'Connor and her father had been tracking the ALK work, and when the gene findings were published last year, they wanted her tumors tested for an ALK mutation.

It took a complicated surgery to get a tumor sample from her. It tested positive. Mosse and Maris tried to convince Pfizer to give her the drug under a compassionate-use policy.

Instead, the company agreed to put her in the lung-cancer trial, since it was also open to patients with other types of cancer as long as the tumors had a mutated ALK.

She got her first pills in May. After two months on the drug, her tumors started to regress for the first time since she was diagnosed seven years earlier, Mosse said. A CAT scan showed that it had cleared from her pancreas and that about 8 percent of her total cancer cells were gone.

Since then, her progress has leveled off, but she said she feels much better. For the first time in months, she has been able to stop taking narcotics for her bone pain.

The ALK drug upsets her stomach and makes her tired. She sleeps 12 hours a night — but she has returned to her normal life for now, which means graduate study in psychology, aiming to become an end-of-life counselor.

"Stable is a beautiful thing and anything that hints at decrease is an extraordinary answer to prayer," her father, Robert, wrote in an e-mail.



Anna O'Connor, diagnosed with neuroblastoma at 17, is now 24. She has been taking the drug since May.

On Sept. 21, Children's Hospital started testing the drug in children who had failed to improve with chemotherapy and other standard treatments.

Ten children are getting the drug, and so far they have had only minor side effects.

"I'd be lying if I wasn't hoping we'd see tumor shrinkage," Maris said.

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