Office of Technology Licensing
Intellectual property newsletter
St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
2005 Issue 1

The Office of Technology Licensing (OTL) will begin publishing a newsletter twice a year to provide information relating to St. Jude intellectual property. The TPMT technology, which is currently benefiting St. Jude and other patients, is highlighted in this first edition. Figures showing the number of agreements overseen by the OTL in the last three years are presented along with information on licensing income received and inventor allocations distributed since 2000. We also show information relating to patent activities and US patents granted to St. Jude in 2004. Other technologies and agreements with industry will be highlighted in future editions.

TPMT: An Unlikely Technology Licensing Success Story?

Ten years ago, in 1995, Drs. William Evans and Eugene Krynetski made an important discovery for St. Jude acute lymphoblastic leukemia (ALL) patients. They discovered why some pediatric ALL patients do not react well to 6-mercaptopurine, one of the drugs included in their standard therapeutic regimen. The cause turned out to be three specific single nucleotide polymorphisms (SNPs) occurring in the thiopurine S-methyltransferase (TPMT) gene, designated TPMT*2, TPMT*3A and TPMT*3C. These SNPs adversely affect the function of the TPMT protein encoded by this gene, which is the enzyme responsible for metabolizing 6-mercaptopurine. Drs. Evans and Krynetski discovered that these SNPs were responsible for 80–95 percent of decreased or deficient TPMT enzyme activity observed among ALL patients treated at St. Jude.

Leukemia patients with diminished TPMT activity caused by these SNPs experience severe toxicity when standard dosages of 6-mercaptopurine are administered. The toxicity can be fatal for the one in 300 patients who are completely TPMT deficient and lack all ability to metabolize the drug by this pathway. Additional research conducted by Dr. Evans established that patients with decreased and deficient TPMT activity can receive substantially the same benefit from reduced dosages of thiopurines without experiencing the side effects associated with toxicity to the drug. This meant that adverse reactions to 6-mercaptopurine could be avoided and all ALL patients could still receive benefit from this drug simply by screening for these SNPs prior to treatment.

All of this was great news for our leukemia patients, but could the TPMT test become a commercially successful product? The odds were definitely against it. The affected population of leukemia patients was too small to interest most companies. On top of that the SNPs are rare, affecting a small portion of the already small patient population. Further decreasing the chances for this assay was the fact that it represented a whole new and unproven type of diagnostic based on the relatively new field of pharmacogenomics (i.e., the study of how an individual's genetic identity affects the body's response to drugs).

Despite these odds, the St. Jude Office of Technology Licensing took a chance and invested its resources and time into patenting and licensing the TPMT assay. A patent application was filed in August of 1995 and 3½ years later U.S. Patent No. 5,856,095 covering the TPMT technology was granted on January 5, 1999. After an initial lack of commercial interest this technology was licensed in 1997. Then, through a series of subsequent mergers, acquisitions and licensing deals, the TPMT patent rights wound up in the hands of Prometheus Laboratories. Prometheus successfully developed a commercial TPMT diagnostic assay and expanded the market to patients treated with other drugs metabolized by the TPMT enzyme. Prometheus even acquired one of these drugs, azathioprine, and placed a recommendation for the TPMT test on its label. This is believed to be the first time that a recommendation for a pharmacogenomic test has appeared on a drug label. Anyone interested in learning

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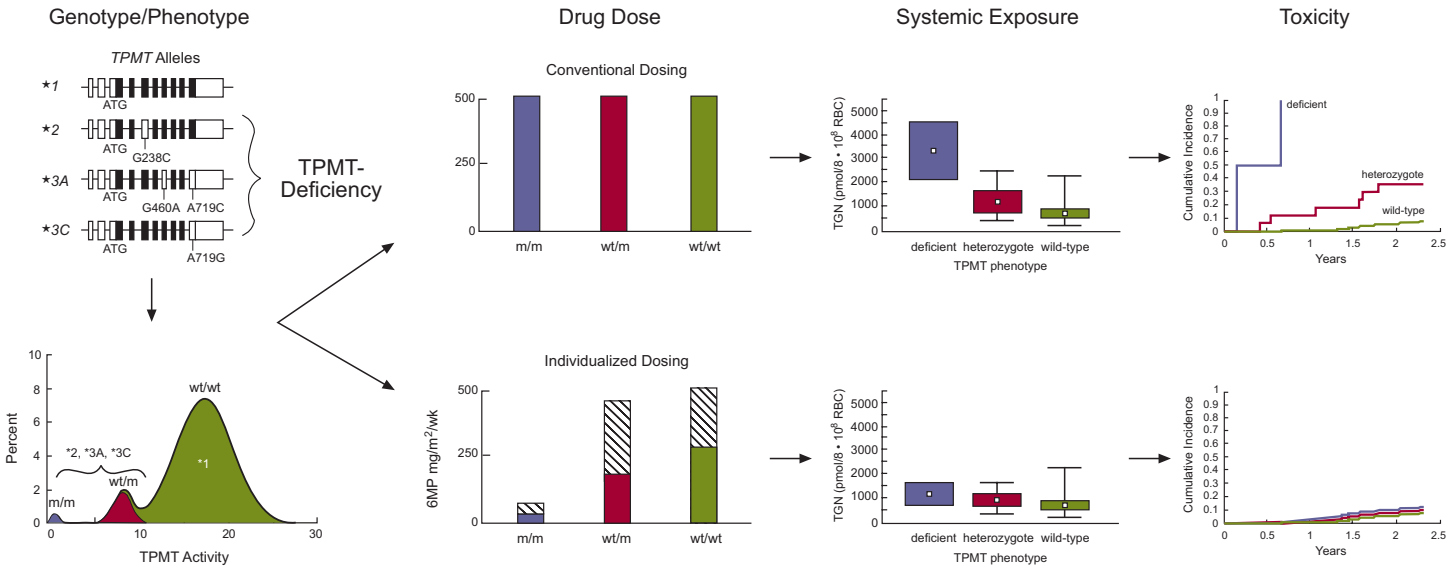
TPMT cont from p. 1

more about the Prometheus TPMT assay may do so by visiting the Prometheus website at *www.prometheuslabs.com*.

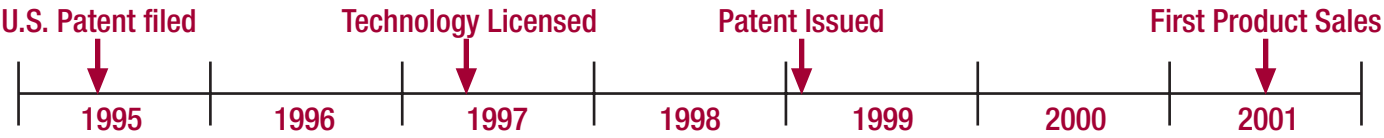
Through the combined efforts of St. Jude and Prometheus, the TPMT assay has achieved commercial success. After investing over $50,000 in patenting the TPMT assay, St. Jude began to reap the rewards of its investment in 2002 as the initial skepticism among clinicians toward this new type of test gave way to an appreciation of its utility. In 2004, over 11,000 TPMT assays were performed in a wide spectrum of specialties including pediatric and adult oncology, gastroenterology, rheumatology and internal medicine. License income from the TPMT assay has now exceeded a half million dollars and is expected to continue to generate substantial income until St. Jude's patent rights expire in 2015. In addition to Prometheus providing its certified test to clinicians, St. Jude continues to freely provide its protocols and reagents to academic investigators studying the TPMT polymorphisms.

While the success of the TPMT assay was unpredictable, the TPMT story is not unusual. All across the U.S., universities and private institutions like St. Jude are patenting early stage technologies with the hope of eventually licensing them for development into a product that will benefit the public and generate revenue. Even though this practice does not always lead to a viable commercial product, the number and magnitude of the successes have been sufficient to validate this approach as useful for encouraging the development of academic research discoveries into products.



Genetic polymorphism of TPMT, and its role in determining the response to thiopurine medications. The left panels depict the predominant TPMT mutant alleles causing autosomal codominant inheritance of TPMT deficiency. As depicted in the subsequent top three panels, when uniform (conventional) dosages of thiopurine medications are administered to all patients, TPMT-deficient patients accumulate markedly higher (10-fold) cellular concentrations of the active thioguanine nucleotides (TGN) and heterozygous patients accumulated about twofold higher TGN concentrations, translating into a significantly higher frequency of hematopoietic toxicity (far right panels). As depicted in the bottom three panels, when genotype-specific dosing of thiopurines is administered, comparable cellular TGN concentrations are achieved, and all the three TPMT phenotypes can be treated without acute toxicity. Reproduced with permission from Evans (Pharmacogenetics, 12, 1-3, 2002)

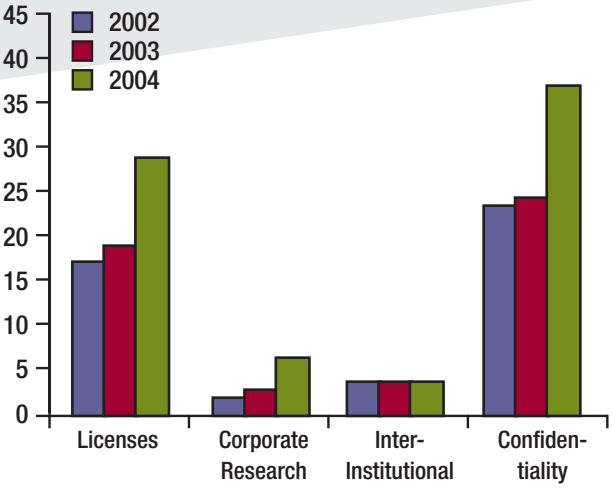
TPMT diagnostic assay timeline: initial discovery to product development



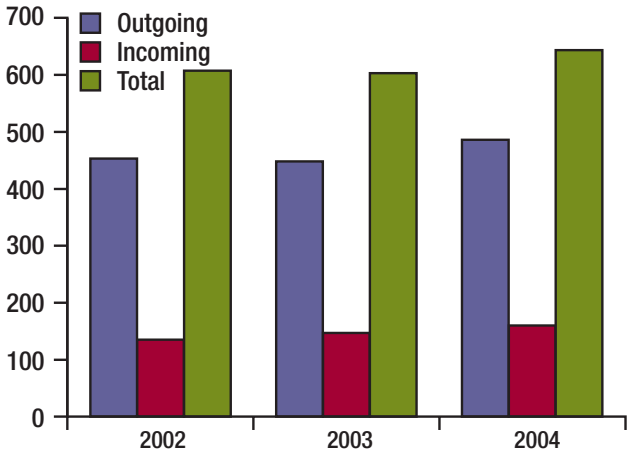
OTL Activities

The OTL is responsible for protecting St. Jude intellectual property and ensuring the appropriate development and dissemination for the public benefit. Many times this is accomplished through patenting and licensing. The OTL works with St. Jude inventors and researchers to identify inventions and then draft and negotiate appropriate agreements with outside entities, both academic and commercial. An overview of some of these activities is provided below.

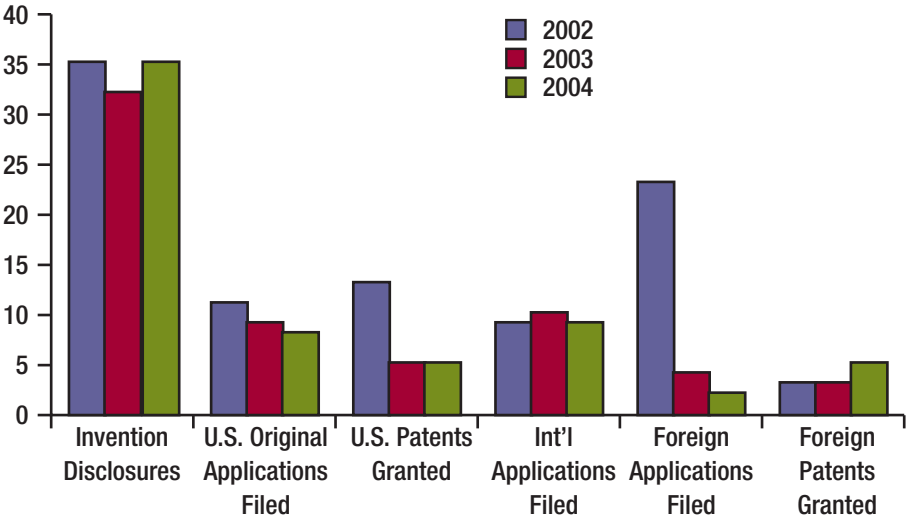
OTL agreements 2002–2004



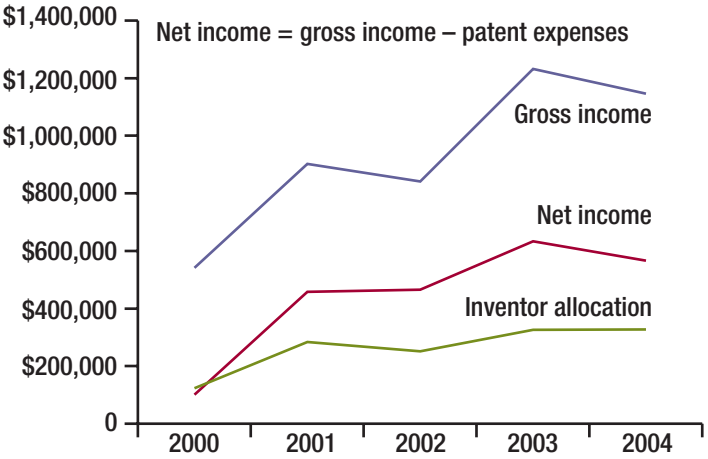
Material transfer agreements 2002–2004



OTL patent activity



Income and allocations 2000–2004



U.S. patents issued to St. Jude during CY 2004

St. Jude #	Inventor	Subject Matter	Issue Date	Patent #
SJ-96-0010E	Sherr, Hirai, Bodner, Inoue	Cyclin D binding factor and uses thereof	1/6/04	6,673,902
SJ-93-0002D	Morris	Novel fusion nucleic acid sequences and fusion proteins present in human t(2:5) lymphoma, methods of detection and uses thereof	2/24/04	6,696,548
SJ-96-0025C	Hurwitz, Owens, Slobod	Preparation and use of viral vectors for mixed envelope protein vaccines against human immunodeficiency iviruses	4/20/04	6,723,558
SJ-98-0013	Schuetz, J., Fridland	Multidrug resistance associated proteins and uses thereof	7/6/04	6,759,238
SJ-98-0001A	Danks, Potter, Houghton, P.	Compositions and Methods for sensitizing and inhibiting growth of human tumor cells	10/5/04	6,800,483

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