OFFICE OF TECHNOLOGY LICENSING

INTELLECTUAL PROPERTY NEWSLETTER

2020 Issue

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GENE THERAPY FOR X-LINKED SCID WINS SMITHSONIAN MAGAZINE AWARD

The XSCID therapy and inventors featured in last year's newsletter are honored for 'spearheading revolutionary change in society.'

The treatment that successfully generated immune systems in patients born with X-linked severe combined immune deficiency was honored with a Smithsonian magazine American Ingenuity Award for Life Sciences. The therapy uses the bone marrow of the patients and a lentivirus that "installs" a copy of the gene to activate the immune system in the cells. The therapy was developed by Brian Sorrentino, M.D., a faculty member who died in late 2018.

Sorrentino and St. Jude faculty members Ewelina Mamcarz, M.D., and Stephen Gottschalk, M.D., join other American Ingenuity Award 2019 recipients Lil Nas X, Jose Andres, Amy Sherald, Alex Kipman, Sheperd Doeleman and the Event Horizon Telescope Team and Heidi Schreck, being honored across seven wide-ranging categories: Youth, Visual Arts, Social Progress, Technology, Life Sciences, Physical Sciences and Performing Arts. Read more at St. jude.org.

THE BAYH-DOLE ACT, USING THE PATENT SYSTEM, TRANSLATES INNOVATION INTO THERAPEUTIC PRODUCTS AND INCOME; BUT THEN WHAT?

Use of the ALK gene, was patented and licensed as a tool for discovering drugs. Though the original patents expired, ALK continues to be used as a tool to develop a growing new class of drugs.

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths, both worldwide and in the United States. Most patients who have NSCLC present with advanced or incurable disease, and cytotoxic chemotherapy generally results in low response rates and only modest improvements in overall survival. A sub-portion of NSCLC is Anaplastic Lymphoma Kinase positive (ALK+) NSCLC, which is a type of lung cancer associated with younger age, never smoking or light smoking history, and adenocarcinoma histology. Patients who have advanced disease are highly responsive to ALK inhibitors. Current estimates are approximately 3-5% (6,500 to 11,000) of patients with non-small cell lung cancer carry the ALK rearrangement and may be candidates for treatment with ALK Inhibitors.

The anaplastic lymphoma kinase (ALK) gene was discovered (SJ-93-0002) in the 1990s by St. Jude scientists searching for genes affected by a chromosomal change common in the cancer cells of pediatric patients with anaplastic large cell lymphoma (ALCL). This discovery led to issued patent rights that were non-exclusively licensed to companies who would build on the discoveries to find and develop therapeutics for treatment of ALK-driven cancers.

Three companies developed FDA approved ALK inhibitor drugs:

- Pfizer - Xalkori® (crizotinib, approved 8/2011)
- Novartis - Zykadia™ (ceritinib, approved 4/2014)
- Takeda (Ariad) - Alunbrig™ (brigatinib, approved 4/2017)

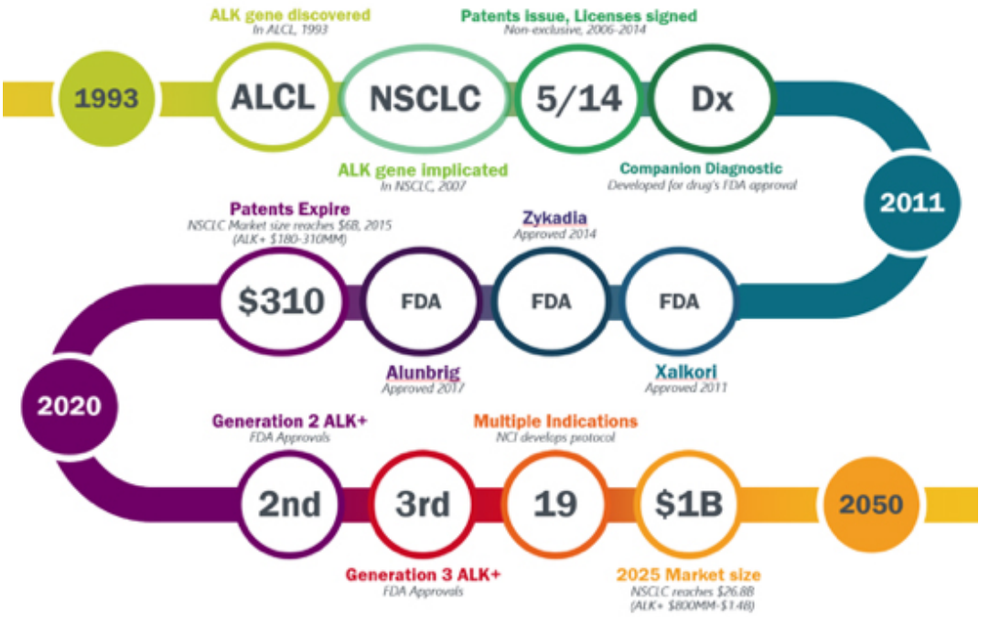
Additional second-generation approved ALK inhibitors include:

- Alectinib (approved 12/2015 (accelerated); 2017 (full))
- Lorlatinib (approved 2018)
- Entrectinib (approved 8/2019)

*The drugs created for **NSCLC** can also be used off label for other ALK+ cancers; in fact, we started using Xalkori here for the pediatric patients with anaplastic large cell lymphoma (ALCL) - the patient population the gene was discovered in.*

These second-generation agents have improved performance; however, the problem with most is that many patients may still develop resistance, particularly central nervous system (CNS) relapse, so third-generation drugs are under development to better penetrate the blood-brain barrier and to retain potency to acquired resistant mutations that developed during therapy with first- and second-generation drugs. Results from a global phase II study of third-generation ALK inhibitors show a high overall response rate and high intracranial response rate for patients with advanced ALK-positive NSCLC, The ASCO Post (2/2019).

The Market



ALK+ Discovery and Drug Development *over 60 years of ALK+ NSCLC market growth.*

The estimated value of the Non-Small Cell Lung Cancer market* was $6.21B in 2015. Just over half of these sales, $3.25B (52%), were generated in the US, with $1.53B (25%) coming from eight European Union Countries, and $981M (16%) and $445M (7%), respectively, for Japan and China. NSCLC sales are expected to rise to $26.8B by 2025. New targeted ALK+ therapies overcome resistance from previous treatments, and/or have superior efficacy in certain subpopulations. The revenue from ALK+ inhibitor portion of the NSCLC drug sub-market should be a similar or slightly higher percentage of the ALK+ patient population (3-5% ($180MM to $310MM, 2015; $800MM to $1.4B, 2025)). Read more about the market size at: *https://drug-dev.com/nsclc-market-global-drug-forecast-market-analysis-to-2025/*

But Wait, What about the Bayh-Dole Act, and Patents?

For the last few years, our newsletter contained a table about our activities (like managing our over 200 licenses, and patient impact) that described the Millions touched our technology through licensed products. This year we explain this in more depth using a specific example: Three ALK+ drugs we licensed impacted about 45,000 people a year, but it grows far beyond those numbers now.

The original ALK+ research was funded by St. Jude Children's Research Hospital along with grant funding from the National Institutes of Health. The Bayh-Dole act was developed as a mechanism for how government-funded research could benefit the public by being transferred to industry using the patent system. This allows industry an accessible and reliable path forward for investment in academic research, to produce and approve a drug or other product; while also stipulating that royalties paid to non-profit institutions must use these funds for more research and to reward their inventors. Some licensees never reached the stage where royalties were paid, but the invention remained alive until drug discovery milestones from Cephalon (now Teva), Ariad, Novartis and Xcovery were achieved and paid, even as the intellectual property ** expired.

In 2015, the US Chamber of Commerce's Global Intellectual Property Center recognized St. Jude Children's Research Hospital with a 2015 IP Champion award for advancing scientific discoveries through the technology transfer process to provide treatments for childhood cancers and adult lung cancer.

During the patent protected portion of this invention's life, it survived intellectual property challenges, and was jointly licensed (w/an ALK monoclonal antibody made by Oxford University) to 5 drug discovery and development companies, 14 diagnostic companies and several reagent companies. In 2011 a law firm was retained to persuade users of the issued patent rights take licenses. This resulted in license income that totaled just under $10MM. After expenses*** of around $3MM were deducted and a portion was allocated to the inventors as required by the Bayh-Dole Act and internal policies, the remainder was used to fund further research at St. Jude. Though the income has stopped; ALK inhibitors continue to be used to treat cancer and ALK continues to be used as a target to discover even better drugs.

** In the 8 major markets; ** This includes the expense the companies paid for patenting in several countries; *** US Patent Nos. 5,529,925; 5,770,421;6,174,674; 6,451,997 and 6,696,548; with Australian Patent No. 679,833; and European Patent No. 731,806 (registered in Germany, France, Great Britain, and Italy)*

ALK Mutation Disease

More than 19 different ALK fusion partners have been discovered in NSCLC.

ALK Rearrangement		ALK Amplification	
Disease	Partner Gene	Disease	Main Point Mutation
Anaplastic large cell lymphoma	NPM1	Inflammatory breast cancer	L1196M
Inflammatory myofibroblastic tumors	TPM3/4	Small cell lung cancer	C1156Y
Diffuse large B-cell lymphoma	TFG	Anaplastic large cell lymphoma	G1269A
Non-small cell lung cancer	EML4	Pulmonary sarcomatoid carcinoma	F1174L
Esophageal squamous cell carcinoma	CLTCL1	Rhabdomyosarcoma	L1152R
Colorectal carcinoma	ATIC	Carcinoma of the esophagus	F1245C
Renal medullary carcinoma	VCL	Adult renal cell carcinoma	G1201E

Also, after years and millions of dollars in industry development, government is reinvesting in the class to optimally sequence mutated ALK genes in inhibitor resistant cancers. The US National Cancer Institute is developing a "Master Protocol" for treatment of patients with advanced NSCLC who have ALK+ tumors, in which the different mutations will direct the given therapy and sequence. It is hoped that such a study concept will lead us to the most optimal treatment strategies by taking molecular biology and new drug development into account.

ESTHER ALLAY MEANS: "MTA, NO DELAY!"

Esther received a Golden Stopwatch Award from Addgene for incoming MTA turnaround times less than two days.

MTAs can be specific to one or several materials, and be with other researchers, institutions, or with industry. Addgene is a global, non-profit repository created to help scientists share plasmids. Addgene has streamlined the process for academic institutions to exchange research materials under terms recognized as standard among academic institutions (e.g., research use only, no redistribution). Addgene has processed over 1,500 requests for materials coming into St. Jude and distributed over 3,700 samples on behalf of the institution since 2007. This partnership helps thousands of researchers access our materials while removing our faculty and staff from having to individually service them. If you are not already doing so, consider depositing materials you often transfer to other academics into the Addgene repository for distribution on your behalf.

Esther Allay *takes care of Material Transfer Agreements (MTAs) in the Office of Technology Licensing. In November, Esther received a Golden Stopwatch Award from Addgene in recognition of outstanding MTA turnaround times – less than two days for incoming material requests and less than one week for outgoing material deposits.*

MTAs can be specific to one or several materials, and be with other researchers, institutions, or with industry. Addgene is a global, non-profit repository created to help scientists share plasmids. Addgene has streamlined the process for academic institutions to exchange research materials under terms recognized as standard among academic institutions (e.g., research use only, no redistribution). Addgene has processed over 1,500 requests for materials coming into St. Jude and distributed over 3,700 samples on behalf of the institution since 2007. This partnership helps thousands of researchers access our materials while removing our faculty and staff from having to individually service them. If you are not already doing so, consider depositing materials you often transfer to other academics into the Addgene repository for distribution on your behalf. **For more information, contact Esther Allay, (901) 595-4700.**

2020 MEMPHIS SCIPRENEUR CHALLENGE (MSC)

The Mid-South Life Science Tennessee (LifeSciTN) Academic Alliance provides networking and the unique MSC program.

The Mid-South LifeSciTN Academic Alliance is made up of graduate students and post-doctoral researchers interested in entrepreneurship, career development and knowledge sharing. Monthly Speakers give advice in clinical, research, policy, and biotechnology business areas, and share personal experiences and perceptions from their various paths that often differ from the academic world, providing members a unique insight into professional growth. Check the Life Science Tennessee website for upcoming monthly Memphis events, or email Chad Riggs. The group is supported by Life Science Tennessee, Memphis Bioworks, LaunchTN; with St. Jude, UTHSC and University of Memphis providing intellectual property for the MSC, a 9-week training and outreach program that showcases intellectual properties (IPs). The participating teams present a business plan and final judged by the Memphis business community.

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PATENTS ISSUED IN 2019

This table below lists the Inventors who received an issued patent in fiscal year 2019. New inventors receiving their first issued patent will receive a special commemorative mug.

FY 2019 Issued Patents		
Disclosure Number	**US Patent Number**	**Inventor**
SJ-03-0015	10,098,945	Richard J. Webby
Genetically engineered swine influenza virus and uses thereof		Robert G. Webster
SJ-11-0018	10,329,584	Allen Portner
Modified Sendai virus vaccine and imaging vector		Toru Takimoto
		Julia L. Hurwitz
		Charles J. Russell
		Karen S. Slobod
SJ-12-0020	10,308,933	Stanislav S. Zakharenko
Methods for diagnosing and treating learning or mental disorders		Laurie Earls
SJ-13-0003	10,124,041	Andrew M. Davidoff
Methods of delivering factor VIII encoding nucleic acid sequences		Amit Nathwani
		Edward Tuddenham
SJ-13-0031	10,144,770	Dario Campana
Chimeric receptors and uses thereof in immune therapy		Kudo Ko
SJ-13-0041	10,266,544	Jason W Rosch
Aryl substituted aminomethyl spectinomycin analogs as antibacterial agents		Jiuyu Liu
		Richard Lee
		Samanthi Waidyarachchi
		Zhong Zheng
		David Bruhn
SJ-14-0011	10,286,000	Wing Leung
Retinoid X receptor-gamma agonists and retinoid X receptor-alpha antagonists for treatment of cancer		Wai-Hang Leung
SJ-15-0007	10,100,090 B2	Jiuyu Liu
Substituted urea depsipeptide analogs as activators of the CLPP endopeptidase		Richard Lee
		Ying Zhao
SJ-14-0019	10,011,589	Philip Cherian
Treatments for gastrointestinal conditions		Julian Hurdle
		Richard Lee
		Xiaoqian Wu

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