CAC2 2016
PEDIATRIC CANCER RESEARCH CONFERENCE

From Bench To Bedside And Beyond

Uniting the childhood cancer community in a **collaborative forum** to advance research for **childhood cancers**

Cold Spring Harbor Laboratory

2016 Conference Proceedings

Cold Spring Harbor Laboratory (CSHL) is a private, not-for-profit research and education institution at the forefront of efforts in molecular biology and genetics to generate knowledge that will yield better diagnostics and treatments for cancer, neurological diseases, and other major causes of human suffering.

cshl.edu

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Conference Overview

Advocates | Funders | Researchers | Clinicians | Federal Regulators | Industry Representatives

2 Days
of mixing and mingling with advocates, funders, scientists, industry, and government representatives.

18 Speakers
from the front lines of emerging technologies and patients' bedsides.

150 Participants
engaging in a collaborative forum with the full range of stakeholders for childhood cancer.

Together with our co-host, Cold Spring Harbor Laboratory, we united members of the childhood cancer community in an unprecedented collaborative forum to help advance the cause for childhood cancer research. We gathered at the historic Cold Spring Harbor Laboratory campus for an inspiring multi-day exchange of knowledge and networking. Looking back at the relationships forged, the connections made, and the information shared among attendees, it was a truly engaging and exciting meeting. Connecting and collaborating are key to finding the cures!

Please visit the conference website to read full speakers bios, see the complete event photo gallery, and find specific contact information for CAC2, CSHL, and the Conference Planning Team.

Conference Team

Thank you to the following individuals who gave so generously of their time and talents to ensure the success of this conference:

Scientific Advisors

Chris Vakoc, MD, PhD, Cold Spring Harbor Laboratory
David Tuveson, MD, PhD, Cold Spring Harbor Laboratory
Peter Adamson, MD, Children's Oncology Group

CAC2 Conference Planning Team

Phil Renna - Christina Renna Foundation
Donna Ludwinski - Solving Kids' Cancer
Julie Sutherland - Make Some Noise: Cure Kids Cancer Foundation

CAC2 Conference Team Leaders

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Finance
Steve Pessagno - CAC2 individual member

Marketing & Publications
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Registration/Invitations
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Trish Kriger - Jeff Gordon Children's Foundation

CAC2 Host
Vickie Buenger - CAC2 individual member

Conference Proceedings
Amy Weinstein - A Kids' Brain Tumor Cure Foundation
Laurie Orloski - CAC2 individual member

Website
Julie Sutherland - Make Some Noise: Cure Kids Cancer Foundaion

Cold Spring Harbor Laboratory

A world-class facility on the picturesque North Shore of Long Island, Cold Spring Harbor Laboratory has long been at the forefront of cancer research. From genetics research in the early 1900s to the development of molecular and cell genetics in the 1940s to its historic involvement in the revelation of DNA's structure, the initiation of the Human Genome Project and the U.S. government's War on Cancer, CSHL and its NCI-designated Cancer Center is linked inextricably with our rapidly advancing knowledge of cancer biology and our efforts to develop new and more effective treatments.

CAC2 is very grateful to our friends at Cold Spring Harbor Laboratory for their generosity and support in hosting this conference.

For 125 years, Cold Spring Harbor Laboratory has shaped contemporary biomedical research and education with programs in cancer, neuroscience, plant biology and quantitative biology.

Home to eight Nobel Prize winners, the private, not-for-profit Laboratory employs 1,100 people including 600 scientists, students and technicians. The Meetings & Courses Program hosts more than 12,000 scientists from around the world each year on its campuses in Long Island and in Suzhou, China.

The Laboratory's education arm also includes an academic publishing house, a graduate school and programs for middle and high school students and teachers.

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CSH Cold Spring Harbor Laboratory

CAC2
COALITION AGAINST
CHILDHOOD CANCER

CAC2 is a membership organization with over 90 member organizations and more than 50 individual and student members who care greatly about, and invest themselves in, making an impact on childhood cancer. We are organized around four basic pillars of interest that our members share: Research and Treatment, Family Support, Advocacy, and Awareness, and we work to share information with and among our members and to provide numerous opportunities for education within each pillar. We also promote coordinated action, broad-based collaboration, and shared projects among our members.

History
The founders of CAC2 first convened in 2011 to explore ways in which the community could work together to raise awareness and collaborate, without duplicating the efforts of existing organizations. This grassroots movement brought together representatives of small, medium, and large organizations, along with committed individuals, to fight childhood cancer and provide support to the children and families affected by cancer. They hoped that by working together they could bridge some of the natural fragmentation that arises from having a diverse community of passionate advocates. Much of the strength of the community comes from the many different groups and individuals who have joined the fight. The CAC2 founders recognized that by encouraging greater cooperation, more coordinated action, and higher levels of collaboration among its members, they could make more progress, faster and with greater impact.

Vision
CAC2 exists to ensure that the childhood cancer community benefits from greater levels of coordinated action and collaboration that: (1) leverage the unique strengths of its members, (2) minimize waste of precious resources and expertise, and (3) drive better outcomes for patients and their families. The primary values underlying CAC2 are to put the children and their families first in all initiatives and to support organizations active in the fight against childhood cancer. CAC2 supports member organizations and the childhood cancer community through action-oriented, member-directed projects and a variety of educational outreach initiatives.

In December 2015, the CAC2 Board began an extensive strategic planning and goal-setting process geared towards ensuring healthy organizational growth and sustainable member engagement. The iterative and participatory process helped the Board align on three overarching goals to help advance CAC2's mission and improve pillar activity: (1) improve support and involvement of members; (2) build organizationally sustainable processes, and (3) improve external communications and public engagement. The desired outcomes from these goals include:

- Bridging, connecting, and engaging our diverse community
- Establishing sustainability in a manner that is complementary to, and non-competitive with, our members
- Providing value and meaningful experiences to members
- Ensuring CAC2 is viewed as a resource to members and non-members alike

CAC2 Members hail from 34 states and 5 countries. They include childhood cancer organizations, individual members, advocates, and survivors that support children with cancer and their families. They join CAC2 for myriad reasons. Many have experienced childhood cancer first- or second-hand. Almost all have found tremendous frustration in the outrageous scarcity of and lack of priority in funding for research into innovative treatments for pediatric cancers. They often express appreciation that CAC2 effectively advances a variety of childhood cancer causes by unifying the childhood cancer community and minimizing duplication of effort through broad-based coordinated action and collaboration that leverages the strengths and expertise of our individual members. To learn more about CAC2, become a member, and/or support the organization, please visit cac2.org.

CHILDHOOD CANCER ORGANIZATIONS

3/32 Foundation
A Kids' Brain Tumor Cure Foundation
Addison Bryan Foundation
Aiden's Army
Alex's Lemonade Stand Foundation
Along Comes Hope
Andrew McDonough B+ Foundation
aPODD Foundation
Arms Wide Open Childhood Cancer Foundation
Arya's Kids Foundation
Bear Necessities Pediatric Cancer Foundation
BeatNb
Braden's Hope for Childhood Cancer
Caleb's Crusade Against Childhood Cancer
CancerFree Kids
Candlelighters NYC
Canines-n-Kids Foundation
cc:Thrive
Chase After a Cure
Childhood Cancer Awareness Group of Coffee County
Childhood Cancer Guides
Children's Cause for Cancer Advocacy
Children's Neuroblastoma Cancer Foundation
Children's Oncology Camping Association, International (COCA-I)
Children's Specialty Center of Nevada
Christina Renna Foundation
CJ's Journey
Cure Childhood Cancer
Cure4Cam Childhood Cancer Foundation
CureSearch for Children's Cancer
Curing Kids' Cancer
Dragon Master Foundation
Emily Whitehead Foundation for Childhood Cancer Research
DC Candlelighters Childhood Cancer Foundation
Evan's Victory Against Neuroblastoma Foundation
Fishin' for the Cure
Flashes of Hope
Francesco Loccisano Memorial Foundation / Frankie's Mission
Go Gold Fund
Gold in September Charitable Trust
Gold Rush Cure Foundation
Have Faith Be Strong
Hope & Heroes Children's Cancer Fund
Hugs for Brady Foundation
I Care I Cure Childhood Cancer Foundation
Jack's Angels Foundation
Jeff Gordon Children's Foundation
Jeremy Cares
Journey4ACure
Kids' Cancer Research Foundation
Kids v Cancer
Luck2Tuck Foundation

CHILDHOOD CANCER ORGANIZATIONS

Make Some Noise: Cure Kids Cancer
Martin Truex Jr Foundation
Mattie Miracle Cancer Foundation
Max Cure Foundation
MIB, (Make It Better) Agents
Morgan Adams Foundation
Mystic Force Foundation
Nathan's Hope
National Pediatric Cancer Foundation
Noah's Light Foundation
Northwest Indiana Cancer Kids Foundation
Open Hands Overflowing Hearts
Pediatric Brain Tumor Foundation
Pediatric Cancer Foundation
People Against Childhood Cancer
Precious Jules Childhood Cancer Foundation
Princesses on a Mission
Richi Childhood Cancer Foundation
Ryan's Case for Smiles
Sammy's Superheroes
Solving Kids' Cancer
Sophia's Fund
Steven G AYA Cancer Research Fund
Swifty Foundation
tay-bandz
Team Daniella's Foundation
Team G Foundation
TeamConnor Childhood Cancer Foundation
Tennessee Cancer Consortium / Childhood Committee
The Grayson Saves Foundation
The Naya Foundation
The Nicholas Conor Institute
The Scarlett Fund
The Truth 365
The Truth 365 - Australia
This Star Won't Go Out
West Virginia Kids Cancer Crusaders
Zoe4Life

STUDENT MEMBERS

Amber Bannon
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Brendan Krimsky
Lindsay Petrey
MacKenzie Cruse
Maddie Curtis
Malkiel Cohen
Melinda Marchiano
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S. Biddle
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INDIVIDUAL MEMBERS

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Bobbi Burke
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Robert Michael Madonna
Robert Weker
Sheri Sallee
Stephen Crowley
Steven L. Pessagno
Susannah Koontz
Tom Pilko
Tom Stypulkoski
Vickie Buenger
Wendy Carvotta
William Burns
William Murray

SUPPORTING ORGANIZATIONS

Faith and Grief Ministries
National Brain Tumor Society
Novartis Oncology
Rare Cancer Research Foundation

CAC2 2016 PEDIATRIC CANCER RESEARCH CONFERENCE
Cold Spring Harbor Laboratory | Oct. 31 - Nov. 1

Sunday, October 30		
Time		Location
1:00 pm - 5:00 pm	Registration	Grace Auditorium
3:00 pm - 5:00 pm	Guided Tours of Cold Spring Harbor Laboratory Campus	CSHL Campus
3:45 pm - 5:00 pm	Working Session for Conference Team	
5:30 pm - 6:30 pm	Dinner	Blackford Dining Center
6:00 pm - 7:00 pm	Late Registration Open	Grace Auditorium
7:00 pm - 11:00 pm	Bar is open	The Eagle

Monday, October 31 - Emerging Technologies			
Time	Session	Speaker	Location
7:30 am - 8:00 am	Registration		Grace Auditorium
8:00 am - 9:00 am	Breakfast		Blackford Dining
9:00 am - 9:40 am	Keynote: The Landscape of Cancer Research	Bruce Stillman	Grace Auditorium
9:40 am - 10:20 am	CRISPR Precision Targets	Chris Vakoc	Grace Auditorium
10:20 am - 10:35 am	Break		Grace Lobby
	Chair: Chris Vakoc		
10:35 am - 11:15 am	Cancer Genomics	Javed Khan	Grace Auditorium
11:15 am - 11:45 am	Resistance to Targeted Therapies	Sara Buhrlage	Grace Auditorium
12:00 pm - 12:45 pm	Lunch		Blackford Dining Center
	Chair: Chris Vakoc		
1:00 pm - 1:40 pm	Cancer Immunotherapy	Paul Sondel	Grace Auditorium
1:40 pm - 2:20 pm	Nanoparticle Drug Delivery	Garrett Brodeur	Grace Auditorium
2:20 pm - 2:35 pm	Break		Grace Lobby
	Chair: Chris Vakoc		
2:35 pm - 3:15 pm	Computational Biology	Gurinder Atwal	Grace Auditorium
3:15 am - 3:55 pm	Commercialization of Technologies	James Olson	Grace Auditorium
4:00 pm - 5:00 pm	Panel: Bringing Better Therapies to Children with Cancer - Challenges & Opportunities With: Javed Khan, Paul Sondel, Jim Olson, Martha Donoghue, Hubert Caron, Vickie Buenger	Moderated by: Lee Helman	Grace Auditorium
5:00 pm - 6:30 pm	Wine & Cheese Social		Nicholls Biondi Hall
5:00 pm - 6:30 pm	Poster Session: Emerging Technologies and Clinical Pipeline		Nicholls Biondi Hall
6:30 pm - 7:30 pm	Dinner		Blackford Dining Center
7:30 pm - 11:00 pm	Bar is open		The Eagle

Tuesday, November 1 - Clinical Pipeline			
Time	Session	Speaker	Location
8:00 am - 9:00 am	Registration		Grace Auditorium
8:00 am - 9:00 am	Breakfast		Blackford Dining
	Chair: Chris Vakoc		
9:00 am - 9:40 am	Keynote: Childhood Cancer Drug Development: Closing the Gaps	Peter Adamson	Grace Auditorium
9:40 am - 10:20 am	Pediatric Oncologist's "View from the Frontlines"	Lia Gore	Grace Auditorium
10:20 am - 10:40am	Break		Grace Lobby
	Chair: Peter Adamson		
10:40 am - 11:20 am	Industry Perspective: Getting New Agents into Trials	Hubert Caron	Grace Auditorium
11:20 am - 12:00 pm	Pediatric Solid Tumors: The Challenge of Dose Intensity	Paul Meyers	Grace Auditorium
12:00 pm - 12:45 pm	Lunch		Blackford Dining
	Chair: Chris Vakoc		
1:00 pm - 1:40 pm	FDA Perspective on Regulatory Issues	Martha Donoghue	Grace Auditorium
1:40 pm - 2:20 pm	Clinical Trials: Challenges in Pediatrics	Victor Santana	Grace Auditorium
2:20 pm - 2:40 pm	Break		Grace Lobby
	Chair: Victor Santana		
2:40 pm - 3:20 pm	Pediatric Hematologic Cancers: Where Are We Now?	Stephen Hunger	Grace Auditorium
3:20 pm - 4:00 pm	Pediatric Brain Tumors : Where Are We Now?	Roger Packer	Grace Auditorium
4:00 pm - 4:40 pm	Pediatric Solid Tumors: Where Are We Now?	Kimberly Stegmaier	Grace Auditorium
4:40 pm - 5:00 pm	An Individualized Approach Requires Collaborative Efforts	Vickie Buenger	Grace Auditorium
5:00 pm - 6:30 pm	Wine & Cheese Social		Grace Lobby
6:30 pm - 7:30 pm	Banquet		Blackford Dining
8:00 pm - 11:00 pm	Bar is open		The Eagle

Wednesday, November 2		
Time		Location
8:00 am - 9:00 am	Check-Out & Departure	Grace Auditorium
8:00 am - 9:00 am	Breakfast	Blackford Dining Center

Thank you to all our speakers, chairs, and panelists

Your commitment to childhood cancer and your willingness to share your valuable time and expertise at this meeting is truly inspiring.

Day 1 Emerging Technologies: Presentations & Speakers

Keynote

The Landscape of Cancer Research

Bruce Stillman, PhD, Cold Spring Harbor Laboratory

Dr. Stillman kicked off the conference by reviewing the hallmarks of cancer—the series of events necessary to develop a full-blown metastatic cancer—and how the understanding of the process led to ideas for the development of therapeutic approaches. He noted the original concept initially focused on the cancer cell itself, and now has expanded to include immune cells and other cells known to play a role in the pathogenesis of cancer. He presented 2014 data on pediatric cancers, including incidence and survival data. Dr. Stillman noted that many regard cancer as a disease of aging, due to the larger number of older patients with cancer and the observation that cell duplication over a long life will tend to generate more anomalies. Our bone marrow alone produces 500 million cells every minute of our lifetime. Inherited genetic mutations and environmental effects, some well known and others not yet discovered, contribute to the burden of cancer. He explained how very young patients tend to achieve high rates of survivorship, but often without a clear understanding of causal factors. Young patients may have a better-primed immune system or superior tissue tolerance. Other hypotheses relate to the spasticity of cells. At the same time, some cancers remain incurable. Furthermore, given the prolonged and heavy burden of side effects childhood cancer survivors experience, we must continue our quest for better treatments and better ways to deliver therapy.

One area of unmet need in pediatric cancer relates to the lack of markers that allow for early detection of cancer, and research is ongoing to identify genetic and other surrogate biomarkers. Dr. Stillman went on to address the question of why cancers are so resilient, explaining the remarkable heterogeneity that occurs within a single tumor and how tumors evolve over time. This heterogeneity contributes to the ability of cells to develop treatment resistance; thus, researchers have focused on this area of study. Thanks to the efforts of The Cancer Genome Atlas (TCGA), we have gained an understanding of the complex genetic abnormalities of cancer and have since entered a new era of genomic analysis. From that analysis, we have learned that targeting the cancer cell alone is simply not enough.

Another aspect of cancer that needs research attention is the immune system abnormalities that allow cancer to evade immune destruction. Better and safer ways of using cytotoxic chemotherapy also hold potential for improved outcomes in cancer. We know now that targeting tumor cells will require combination approaches, such as using nanotechnology to carry toxic particles and those that induce immune reactions. Dr. Stillman noted that precision targets are great when they work, but that the nature and diversity of cancer will make it difficult to identify precision medicines for all cancers. Targeting the metabolism and signaling of cancer cells may hold promise as alternative approaches to treating cancer. Dr. Stillman concluded his keynote address by highlighting the various topics that would be covered during the conference.

Emerging Technologies

CRISPR Precision Targets

Chris Vakoc, MD, PhD, Cold Spring Harbor Laboratory

Dr. Vakoc reviewed the history of CRISPR technology and focused on its application to cancer research. CRISPR is a technology analogous to "molecular scissors" that enables a genetic engineering technique to "cut and replace" DNA alterations. In the context of biologic research, investigators can use CRISPR to develop new genetic models of disease as well as new cancer drugs. It is also applicable in non-biologic areas, such as in agriculture. Dr. Vakoc explained how CRISPR occurs naturally as a mechanism developed by bacteria. CRISPR refers to a system of molecules that bacteria have evolved to protect itself from viruses. A few different components comprise the system, including a "hard drive" of viral DNA that is subsequently converted to RNA. The Cas9 protein, discovered in 2013, is present in bacterial but not human cells and has a unique function that uses RNA as a zip code to identify the precise location of the chromosome where double-strand DNA should be cut. This allows for cells to be fooled into repairing the DNA in a customizable fashion.

The discovery of CRISPR dates back to the 1980s, not in the context of biomedical applications, but to understand how bacteria are protected against viruses. Three major applications of CRISPR technology apply to cancer research: as an approach to generate of human cancer models more rapidly, as a means of anti-cancer therapy, and to aid cancer drug development. In the case of cancer models, which typically take five to seven years to create, CRISPR can complete a model from start to finish in under a year. In one example, a new animal model, based on a demonstration first observed in 2013, was published in 2014.

Dr. Vakoc showed that CRISPR not only can knock out genes efficiently, but is also amenable to engineering oncogenic chromosomal rearrangements, such as those observed in sarcomas. CAR T-cell therapy represents an example of direct use of CRISPR as a cancer therapy. In the area of cancer drug development, CRISPR is capable of identifying vulnerabilities in cancer cells and can be applied in a high-throughput manner to discover genes required for cancer cell growth.

Emerging Technologies

Cancer Genomics

Javed Khan, MD, National Cancer Institute

Dr. Khan opened by noting the complexity of cancer—how it is a genetic disease, a rapidly evolving heterogeneous disease, and an epigenetic disease—as well as the potential to immunologically target pediatric cancer. He showed an example of an early genomic discovery of how fibroblast growth factor receptor 4 (FGFR4) acts as an oncogenic driver in rhabdomyosarcoma (RMS), with mutations implicated in roughly 7.5% of all cases of RMS. This discovery has fueled the search for other driver mutations in this disease, leading to the National Cancer Institute-Children's Oncology group (NCI-COG)-Broad RMS Genomes Project which showed that paired box (PAX) 3/7 fusion-positive and negative RMS have distinct genetic profiles, and that many of the identified somatic changes or pathways are druggable. Based on whole transcriptome sequencing, an alteration of FGFR/RAS signaling was subsequently implicated in PAX fusion-negative tumors.

Dr. Khan transitioned to opportunities for pediatric cancer in the post-genomics era, reviewing how pediatric tumors have a low number of somatic and actionable mutations at initial diagnosis. He presented a pilot study conducted using comprehensive genomic analysis to identify clinically actionable mutations in pediatric and young adult patients with metastatic, refractory, or relapsed solid tumors. The patient population included 59 patients, age 7 months to 25 years, across twenty diagnostic categories. This study found that somatic mutational burden at relapse doubles or triples that observed at initial diagnosis and that approximately 50% of patients had actionable mutations at relapse. He highlighted the importance of conducting parallel germline sequencing (with approximately 10% of pediatric cancers thought to carry actionable germline mutations) and that the increased tumor burden in relapsed tumors has implications for immunotherapy. COG-NCI has planned single-agent pediatric MATCH-like trials, and the NCI's Center for Cancer Research is launching the ClinOmics program to enable precision genomics trials for cancer.

Challenges ahead include the development of resistance in cases of single-agent therapy use to target actionable mutations, yet the higher mutational burden at relapse provides an opportunity for immunotherapy. Dr. Khan concluded his talk by reviewing the aims of the Stand Up To Cancer (SU2C)-St. Baldrick's Immunogenomics Dream Team.

Specific Aims

SU2C-St Baldrick's Immunogenomics Dream Team

- Specific Aim 1: Discover and validate cell surface targets for immunotherapy of high-risk pediatric cancers.
- Specific Aim 2: Generate and develop therapeutic proteins targeting prioritized cell surface molecules.
- Specific Aim 3: Conduct pivotal multi-institutional pediatric cancer immunotherapy trials.

Emerging Technologies

Resistance to Targeted Therapies

Sara Buhrlage, MD, Dana-Farber Cancer Institute

Dr. Buhrlage covered the topic of resistance to targeted therapies by discussing two projects at Dana-Farber Cancer Institute (DFCI). She first provided a background on pediatric low-grade astrocytomas (PLGAs), noting that while prognosis is good for surgically resectable tumors, many cases occur in surgically inaccessible regions of the brain. These tumors tend to respond to radiation and chemotherapy; however, relapse commonly occurs, and the evolution to a relapsing/remitting disease ultimately leads to poor quality of life. In this setting, patients truly need targeted therapies. A target has presented itself, with more than 3 of 4 PLGAs having activating BRAF mutations. Unfortunately, a majority do not respond well to approved RAF inhibitors, which affect BRAF monomers but not the dimers found in PLGA.

A research project at DFCI found that a pair of investigational kinase inhibitors have the ability to bind to the site of interest while acting through on-target effects. Investigators subsequently demonstrated brain penetration and preclinical activity for one of these agents (MLN2480). A clinical trial will open soon.

The second research project discussed by Dr. Buhrlage focused on the potential to degrade oncogenic proteins through deubiquitinating (DUB) enzyme inhibition. Investigators have developed an annotated library of DUB inhibitors for use in identifying genes of interest for targeting certain mutations in AML—including FLT3 mutant AML (17% to 24% of pediatric AML cases). One DUB inhibitor (HBX19813) demonstrated activity in suppressing cell growth of mutant FLT3 AML cell lines, with additional evidence that it can overcome FLT3 inhibitor resistance and that combining DUB and FLT3 inhibitors may lead to synergistic activity. Growth-suppressing effects have also been demonstrated in AML primagrafts. According to Dr. Buhrlage, DUB enzymes represent an exciting new class of undruggable resistance targets in selected patients with pediatric AML.

Emerging Technologies

Cancer Immunotherapy

Paul Sondel, MD, PhD, University of Wisconsin – Madison

Dr. Sondel provided an historical overview of cancer immunotherapy, beginning in 1968 with the first bone marrow transplant which led to the recognition that donor cells have anti-leukemia effects. Subsequently, investigators became interested in the possibility of using the patient's own immune cells to stimulate antitumor effects. Fifty years of mouse models ensued. However, only in the last twenty-five years have researchers scaled up for clinical development, and only in the last decade have we realized an impact on patient care. In 2013, cancer immunotherapy was named the breakthrough of the year, and in 2016 the toolbox includes approaches related to antibody immunity, innate immunity, T-cell recognition, adoptive cellular therapy, and the countering of tumor-induced immunosuppression (checkpoint blockade). Monoclonal antibodies (mAbs) are available to target tumor markers as well as molecules on immune cells.

Dr. Sondel's team has developed tumor-reactive mAbs for use as off-the-shelf therapy, including those to be given with cytokines in patients with minimal residual disease. He showed examples using anti-GD2 antibodies and noted that clinical translation in GD2-positive tumors is ongoing in adults with melanoma and in children with neuroblastoma. The first ever transatlantic clinical trial for neuroblastoma is planned, representing the first clinical testing of the combination of radiation, anti-GD2 immunotherapy, and checkpoint blockade. It will open at four sites, in the United Kingdom, Germany, and the United States. This work (anti-GD2 mAb) may translate to tumor-reactive mAbs in other cancers.

Dr. Sondel concluded by reiterating the vision for childhood cancer: the development of more effective, less toxic treatments. He also noted that immunotherapy carries potential, including the incorporation into up-front and salvage therapy for most childhood cancers. As data allows, gradual incorporation of immunotherapy in place of some chemotherapy and radiation regimens may open the door to reducing long-term toxicity, genotoxic damage, and the risk of secondary malignancies.

Emerging Technologies

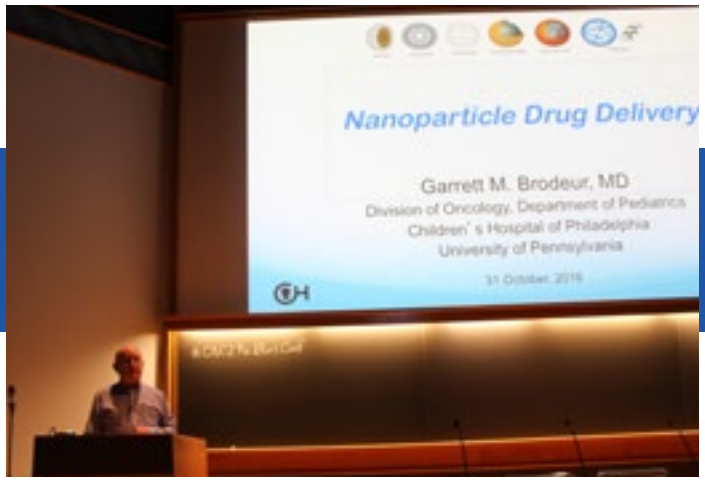
Nanoparticle Drug Delivery

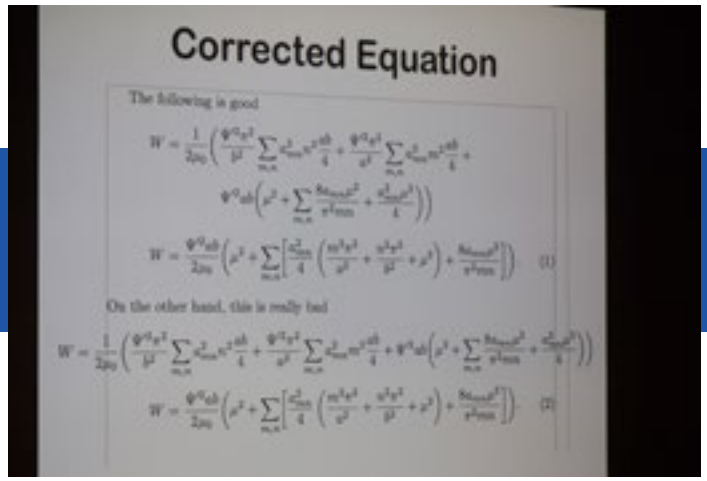
Garrett Brodeur, MD, Children's Hospital of Philadelphia

Dr. Brodeur explained that nanoparticle (NP) delivery is based on the premise that tumor blood vessels are more disorganized and leaky relative to normal blood vessels. With most conventional agents delivered at maximum tolerated doses, only about 0.1% of the drug reaches the tumor. NP encapsulation avoids the problems of solubility, protein binding, and off-target effects, while delivering around ten times more drug to the tumor. Not only can NP drug delivery make conventional and biological agents more effective and less toxic, it can reduce the total amount of the drug needed and can extend circulation within the body for hours or days.

Dr. Brodeur discussed using NPs in a neuroblastoma model. SN38, the active metabolite of irinotecan, is very toxic and not very soluble. A co-drug of SN38-tocopherol succinate (SN38-TS) has greater NP retention and the potential to improve drug delivery, possibly overcoming irinotecan resistance. Other co-drugs are in development: according to Dr. Brodeur, NP therapy has possible application in sarcomas and brain tumors, and other research groups have begun clinical trials testing nanoformulations in other settings. Affinity targeting, sometimes called "active targeting," may improve NP effectiveness against circulating tumor cells or marrow involvement.

Challenges ahead include the substantial accumulation of NPs in the liver and spleen, observations that NP studies in humans have been less encouraging than those in mice, poorer penetration of NPs in large tumors, and a lack of leaky blood supply in some tumors. The future of NP includes incorporating imaging agents, selective activation (enzymatic or pH changes), targeted activation (magnetic fields, ultrasound, infrared or other body-penetrating technologies), and selective vascular and cytoreductive priming.





Emerging Technologies

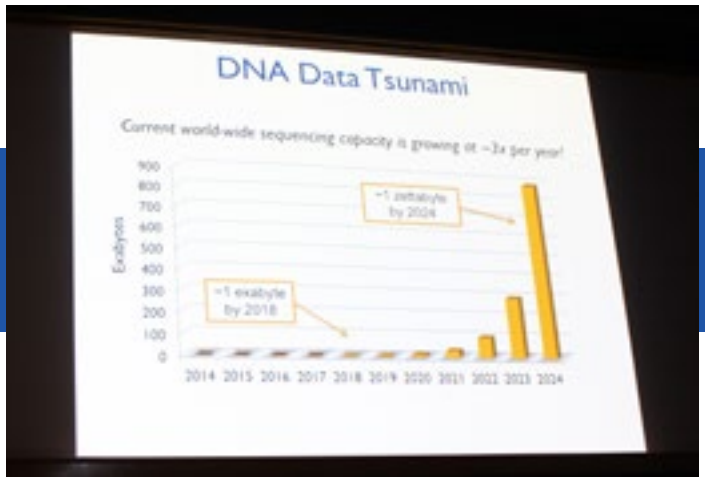
Computational Biology

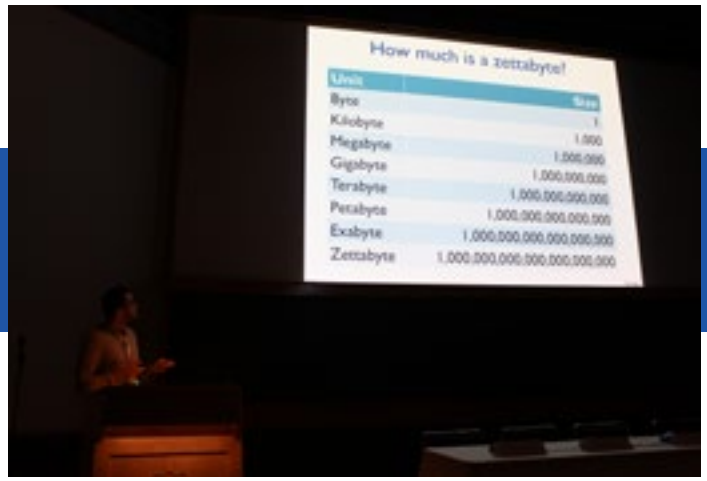
Gurinder Atwal, PhD, Cold Spring Harbor Laboratory

Dr. Atwal covered the need for and use of computational biology—an intersection of genomics, machine learning, and cancer biology—in cancer research. He explained that sequencing a single genome generates about 300 gigabytes of data and that a "DNA tsunami" is under way, with current worldwide sequencing capacity tripling each year; about one exabyte expected by 2018 and one zettabyte by 2024. This capability explosion will stimulate interest in incorporating other types of data, such as imaging, exposure, other 'omic, phenotypic, and clinical data. The Cancer Genome Atlas (TCGA) is the world's largest public genome dataset, with about two petabytes of data; however, these data are primarily derived from adult cancers.

The Cancer Genomics Cloud Pilot could help overcome challenges related to the storage and transfer of such large amounts of data. After this introduction, Dr. Atwal transitioned to the challenge of tumor heterogeneity and how bulk analysis of tumor samples misses much of this detail. Conducting single cell sequencing overcomes some of these issues, but generates "noisy" results. Nonetheless, single cell sequencing is so important that it was named method of the year in 2013 by ***Nature Methods*** and is poised to transform many areas of biology and medicine. Dr. Atwal went on to enumerate a number of outstanding questions, including whether it is better to understand a single cell exceptionally well or many cells to a lesser degree.

He then touched on the area of computational immunotherapy research. He explained that while somatic mutations occur less commonly in pediatric cancer patients than adult patients, deletions, amplifications, and translocations occur more frequently in children than adults. To take advantage of this observation, Dr. Atwal's group has built computational predictive models of novel germline tumor antigens, showing that pediatric tumors are enriched for germline antigens—opening up opportunities for vaccine or CAR T-cell-type therapy. Possibilities also exist to use computational prediction as a tool to predict which patients will benefit from immunotherapy.





Emerging Technologies

Commercialization of Technologies

James Olson, MD, PhD, Fred Hutchinson Cancer Research Center

Dr. Olson provided an overview of drug development costs to begin his presentation. He noted that a single drug might cost in the range of $4-11 billion, with a rock-bottom minimum of $100 million. For investors with a need to recoup their investment and achieve positive net profit, small patient populations pose a real problem and serving those makets will require new approaches either to reduce the cost of development or to provide investment incentives (eg, orphan drug designation, pediatric priority review vouchers). Another way to reframe the problem is to find pediatric tumor targets whose solutions apply to other diseases. Dr. Olson also reviewed the development of a new imaging technique referred to as "tumor paint," which illuminates malignant areas in an organ during surgery to guide resection and reduce the occurrence of residual disease. To make tumor paint, investigators attach a mini protein derived from scorpion toxin to a cyanine dye and circulate it through the entire body. The modified protein binds to and is internalized by cancer cells for several days. Laser technology then highlights the areas of malignancy, giving surgeons better visibility of cancerous tissue.

Dr. Olson showed early preclinical data that demonstrated its permeability through the blood-brain barrier and potential in brain cancers. He also demonstrated applications in other tumors such as prostate cancer, leading to the creation of a company to commercialize this technology (BLZ-100 fluorescence, Blaze Bioscience). This technique has moved from mouse models through a successful canine study. A phase 1, open-label dose-escalation/expansion study has begun in patients with brain cancer, with early results confirming that BLZ-100 correlates with the anticipated site of the main tumor mass. He noted that the pediatric protocol allows for the laser to be turned on at the completion of surgery, providing for the removal of residual disease. To date, over 70 patients have enrolled in clinical trials of BLZ-100, with no dose-limiting toxicity and effective illumination of over 80% of tumors. He showed the proposed design of a registration trial in patients with pediatric brain cancer undergoing surgery. Given the early philanthropic support from parents of children with brain tumors, the mind-set is to continue to keep "kids first," while also evaluating potential in other tumors (eg, breast cancer). Dr. Olson's laboratory is developing next-generation therapeutics with tumor paint, including peptide-drug conjugates and exploring knottin peptides as a platform for new drug development. Dr. Olson closed with a list of the many steps necessary before taking a drug into clinical trials and subsequently to the FDA—illustrating the complexity of the commercialization process.

Emerging Technologies

Panel Discussion
Bringing Better Therapies to Children with Cancer - Challenges & Opportunities

Moderated by: Lee Helman
With: Javed Khan, Paul Sondel, Jim Olson, Martha Donoghue, Hubert Caron, Vickie Buenger

This panel discussion brought together experts representing basic and clinical science with representatives from regulatory bodies, industry sponsors, and advocacy in a productive and enlightening discussion around concrete actions we can all take to break down barriers to progress and speed the development process for children with cancer. The panel members addressed questions posed by Moderator Lee Helman as well as those raised by the audience.

Day 2 Clinical Pipeline Presentations & Speakers

Keynote

Childhood Cancer Drug Development: Closing the Gaps

Peter Adamson, MD, Children's Hospital of Philadelphia and the Children's Oncology Group

Dr. Adamson kicked off day two of the conference by providing a high-level overview of the drug development process in childhood cancer, highlighting some of the challenges and what he sees as the promising signs. He reviewed the traditional, linear approach to drug development that starts with target identification and ends in clinical trials, but noted that the process has become less linear as new technologies and opportunities have emerged. He then spoke about the National Cancer Institute's (NCI) TARGET Initiative– a program focused on five major areas. This deep genomic dive resulted in some interesting findings, including the identification of a subgroup of acute lymphoblastic leukemia (ALL) patients with poor outcomes that shared a translocation of the BCR-ABL1 (Philadelphia) chromosome. With a potentially druggable targets, these patients are now being screened to identify candidates for treatment with targeted tyrosine kinase inhibitors.

Dr. Adamson then shifted his focus to the topic of funding discovery research and noted the insufficiency of NCI's $60-70 million allocation per year to model systems, biology, and the etiology of childhood cancer. However, the Cancer Moonshot has presented some promising opportunities. The Moonshot Blue Ribbon Panel advises NCI of potential opportunities poised for research acceleration, and pediatric cancer has its own working group within the panel. Of thirteen recommendations provided across all the working groups, three apply to childhood cancer: (1) fusion oncoproteins in childhood cancer, (2) immunogenomics-immunotargets for childhood cancer (distinct from ongoing efforts in adult cancers), and (3) new therapeutic targets to overcome cancer resistance. The last of these was a joint recommendation from the Pediatric and Tumor Evolution Working Groups, poised to address the major challenge of relapse despite high rates of response to initial therapy in children with cancer. Dr. Adamson presented a classic example of a fusion oncoprotein in childhood cancer; over two decades have passed since its discovery, and still no drugs have been developed to target it. This observation led to a discussion of the "Valley of Death" of clinical drug development in oncology, focusing on how the Institute of Medicine (IOM) recommendations that call for a new public-private partnership are capable of addressing the challenges inherent in pediatric cancer drug discovery and development.

These recommendations, made ten years ago, are still pending as 'unacted upon' ideas and remain valid today. Dr. Adamson also noted that the existing clinical trial infrastructure of the Children's Oncology Group (COG) provides an advantage for clinical development of new treatments for childhood cancer. About 90% of children with cancer in the US are treated at COG sites, and many of these trials extend across borders because of international collaboration efforts. Building on COG's positive track record for accruing patients into clinical trials, this infrastructure will facilitate the administration of the Pediatric MATCH trial, which will be using genetic sequencing to identify actionable mutations. After discussing the discovery and ongoing efforts surrounding the ALK gene in anaplastic large cell lymphoma and how the gains in pediatric leukemia demonstrate the ability of research to improve outcomes, Dr. Adamson returned to the Cancer Moonshot and closed with optimism, a call for investment and appropriations to fund the recommendations, and a desire to restore a sense of urgency to the burden of childhood cancer.

Clinical Pipeline

Pediatric Oncologist's "View from the Frontlines"

Lia Gore, MD, Children's Hospital Colorado

Dr. Gore opened by discussing the success story of pediatric acute lymphoblastic leukemia (ALL)—how success in generations of clinical trials have led to progressive advancements in prognosis for most patients, with some distinct subsets having a 99% chance of long-term survival. She attributed these successes to ongoing collaboration, as the treatment regimens have been refined yet have not changed dramatically. The question she posed: how can we do even better? Across childhood cancers, outcomes range from excellent to dismal. In many tumor types, we have reached the limits of dose intensification, and toxicity remains a real problem. Using novel agents may help, but legal and regulatory barriers pose challenges to up-front testing. Dr. Gore noted how cancer "is evolving toward a polyglot collection of many small populations," making clinical trial designs more complex. To gain up-front experiences with new agents, investigators must overcome a variety of cultural, financial, scientific, logistical, and regulatory barriers/challenges. Studying smaller molecular subsets may require international studies and necessitate increasing harmonization of regulations across borders.

Dr. Gore reviewed the various categories of considerations in drug development, including disease characteristics, trial design, agent of consideration, and environment in which the drug is being evaluated. She suggested the need to revisit traditional trial designs to overcome the disadvantages faced by small populations, given the limited feasibility of conducting randomized controlled trials. Dr. Gore also explained the legal context of existing US regulations and how the exclusion of pediatric patients from most clinical trials of cancer drugs results in high rates of off-label use, which leads to a high level of dissatisfaction among all parties. From a regulatory standpoint, it is necessary to demonstrate not only efficacy but also higher efficacy than standard of care, and the lack of an international regulatory agency further complicates matters. Dr. Gore outlined a list of characteristics that may make children suited for earlier use of new drugs, such as those for whom there is a strong biologic rationale, a lack of curative options, or a need for more tolerable therapy. We need very carefully designed clinical trials, including the addition of interim analyses and stopping rules. Dr. Gore closed with a proposed model for moving new agents into earlier lines of treatment in the pediatric ALL population that could hold promise for reducing cardiotoxicity and other side effects.

Clinical Pipeline

Industry Perspective: Getting New Agents into Trials

Hubert Caron, MD, PhD, Roche

Dr. Caron emphasized that the pediatric cancer research community urgently needed paradigm shifts in drug development and began by highlighting the various challenges and opportunities. One of the key opportunities is the increasing emphasis on mechanism of action (MOA)-based development by health authorities. Academia and industry have complementary strengths, necessary for the shared goal of curing cancer. Dr. Caron reviewed the vision, missions, and actions of the voluntary, pediatric-centric, MOA-based collaborative approach at Roche for children with cancer. The missions include early access to drugs for children with high unmet needs, improved patient care through pediatric product labeling, and the fulfillment of pediatric regulatory obligations to timely registrations in adults. As part of its development of a pediatric oncology portfolio, Roche has implemented iMATRIX—an innovative oncology clinical trial platform to investigate several drugs across multiple tumor types, from the preclinical assessment for pediatric use to the conduct of pivotal trials. Dr. Caron highlighted his ultimate goal: to allow for molecule and disease prioritization within the regulatory framework. He also emphasized the non-exclusive nature and intent of Roche's iMATRIX platform. Roche has initiated single-agent studies of two compounds. Its Master trial protocol is currently under review at the Food and Drug Administration and the European Medicines Agency, and it has begun outreach efforts to implement future multi-sponsor collaborations that will allow industry to fulfill its mission of addressing unmet needs for children with cancer and provide rare tumor patients with the most promising therapy.

Dr. Caron presented the Roche oncology portfolio, noting where pediatric development is ongoing or under assessment. Given the large number of compounds, prioritization becomes crucial. Dr. Caron transitioned to providing more details about the Roche approach to matching molecule MOA with pediatric tumor biology, which is based on systematic literature reviews and 'in silico' analyses (such as those based on the NCI's TARGET database). Roche hopes to make this analysis available to pediatric academic researchers. He closed with a discussion of Europe's Innovative Medicine Initiative 2 (IMI2) Innovative Therapy for Children with Cancer Consortium (ITCC) Pediatric Preclinical Proof-of-Concept (POC) Platform, designed to enable clinical molecule development for children with cancer by spurring preclinical drug development. It is structured to include pre-competitive pharma and an academic consortium, with partners that include Roche and Eli Lilly (co-leads), Bayer, Pfizer, PharmaMar, and the ITCC academic consortium. Although designed as a five-year program, the goal is to continue beyond that time frame.

Clinical Pipeline

Pediatric Solid Tumors: The Challenges of Dose Intensity

Paul Meyers, MD, Memorial Sloan Kettering Cancer Center

Dr. Meyers provided an overview of the role of Memorial Sloan Kettering Cancer Center in introducing the concept of high-dose therapy, showing the design and results of its initial protocol for high-dose alkylating agents in Ewing sarcoma (ES). Given the substantial improvement in outcomes in this trial, the investigators initiated a randomized clinical trial of dose-intensified vs. standard therapy for ES/PNET of the bone and soft tissue. Dr. Meyers explained the dosing in this trial and how it may have contributed to the results, which showed no difference in efficacy between the arms. At the same time, other groups studied alternative dose intensification strategies, including a reduction in the dosing interval (from every three weeks to every two weeks), allowing for dose intensification of all agents. Both approaches demonstrated improved event-free and overall survival, resulting in interest in even further dose intensification.

Dr. Meyers then showed a series of findings that collectively demonstrated the high toxicity and unimpressive efficacy of such efforts and concluded that there were few benefits and perhaps even an overall detrimental effect. He then went on to discuss autologous stem cell reconstitution. Most studies in high-risk sarcoma have been small, with a variety of study design-related issues, including the exclusion of many patients (such as those not proceeding to the transplant for various reasons) from the analysis. Trials that have attempted to address some of these shortcomings have failed to establish autologous stem cell therapy as an ideal approach to treating ES. Dr. Meyers also showed examples of the futility of dose intensification in rhabdomyosarcoma, reinforcing his conclusion that too little or too high of a dose leads to inferior outcomes. The final part of Dr. Meyers' presentation shifted to the targeting of fusion proteins in ES and the design of an ongoing phase 1 trial of the small molecule TK216 (given as a continuous infusion for one of three weeks) in patients age ≥12 years with ES, representing the first-in-human trial of this agent. As a prior study in dogs had demonstrated evidence of a risk of hepatotoxicity, the Food and Drug Administration required that dosing be initiated at 1/20th of the maximum-tolerated dose in dogs, raising concerns about creating delays to reaching a clinically meaningful dose of this agent. While data from this study are not yet available, Dr. Meyers expressed optimism that this area of targeting fusion proteins in ES will continue to intensify.

Clinical Pipeline

FDA Perspective on Regulatory Issues

Martha Donoghue, MD, Food and Drug Administration

Dr. Donoghue gave a brief overview of the challenges and opportunities in pediatric oncology, noting that leveraging discoveries in adults presents both opportunities and challenges. She outlined how Food and Drug Administration (FDA) initiatives are under way to increase the role of the agency in promoting a collaborative approach to timely pediatric cancer drug development, leverage existing regulatory incentives, proactively identify promising new treatments while engaging with industry, academia, and advocacy groups, and harness the regulatory science to meet drug development challenges. Dr. Donoghue reviewed criteria for conducting pediatric studies from a regulatory standpoint, including evidence of biological activity, the prospect of clinical benefit, reasonable expectations of safety, and information to guide the appropriate study dose. The FDA may consider first-in-human trials in children when there is limited or no application in adults, and Dr. Donoghue further suggested that studies in pediatric patients with unmet needs should be initiated as soon as possible after completion of adult phase I trials. According to the FDA Advisory Committee Consensus, pediatric oncology drug development should generally be coordinated with development in adults, as part of the overall plan. Dr. Donoghue noted that the FDA is working to provide consistent recommendations to sponsors regarding the inclusion of adolescent patients who meet the eligibility for "adult trials" and to increase timely access to treatments early in adult development.

Dr. Donoghue also discussed regulatory mechanisms to incentivize pediatric drug development, including the Pediatric Research Equality Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). The FDA conducts quarterly meetings with the academic community as part of the BPCA, has been engaging in outreach in the pediatric cancer advocacy community, is developing a pediatric oncology guidance document, and conducts pediatric mini-symposia with invited advocates and researchers. Dr. Donoghue emphasized that one of the most important tools is the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), which holds non-decisional public meetings for interactive discussion. She went on to point out that a harmonized global approach is imperative to pediatric oncology drug development. She further noted that the complexity of clinical trial design in the precision medicine era has spurred interest in a master protocol approach, along with FDA support of early pediatric clinical trials (including first-in-pediatric trials when appropriate), seamless study designs (including embedding pediatric expansion cohorts into some adult phase 1 & 2 trials), and the use and sharing of "big data." Dr. Donoghue closed by noting that while the FDA is a gatekeeper, the agency should also be thought of as a resource and partner.

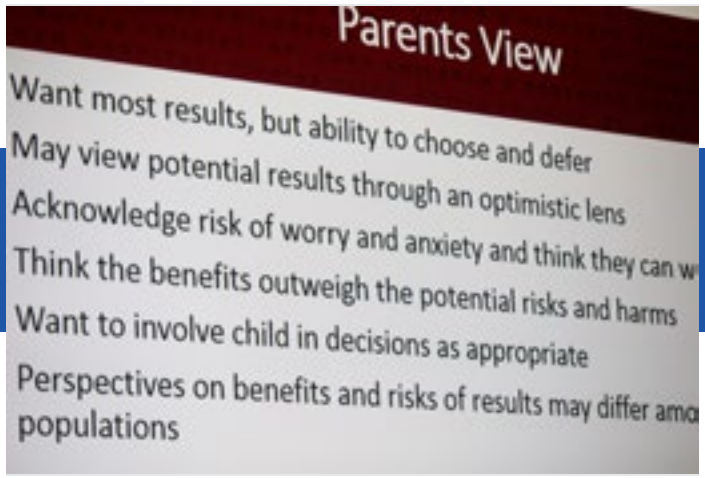
Clinical Pipeline

Clinical Trials: Challenges in Pediatrics

Victor Santana, MD, St. Jude Comprehensive Cancer Center

Dr. Santana reviewed the complexity of clinical trials, offering some highlights from his own perspective. "Clinical trial" is often used interchangeably with "research protocol." Dr. Santana reviewed the goals of clinical trials along with the components of a written protocol, which not only guides the research but also informs what was done so that the study can be evaluated, reproduced, and modified. Conducting clinical trials is an iterative process that includes review committees, the development of contracts, electronic orders, and case report forms and other mechanisms that guide the process, such as pharmacy operations. Dr. Santana emphasized that protocols are living documents, prone to modifications and require oversight as a matter of public trust. Various levels of accountability guide the process, including federal, global, state, institutional, contractual, and practice standard components. Dr. Santana then went on to review recent developments in the area of multi-site logistics. National Cancer Institute (NCI) guidance now allows for a single review by the Scientific Review Committee at the lead site, with other participating sites responsible only for a prioritization-focused review looking at competing studies and site feasibility. Institutional Review Boards (IRBs) have also evolved, with the creation of a number of central IRBs in the last decade.

The National Institutes of Health (NIH) recently came forth with a policy requiring all NIH-funded clinical trials to rely on a central IRB. The NCI has four central IRBs, one of which focuses on pediatrics. Dr. Santana reviewed the pros and cons of central IRBs and drew the conclusion that this area was still very much a work in progress. Next, Dr. Santana moved to informed consent in the context of genetic discoveries that may be unveiled as part of a research study. He explored the question of whether the duty to warn outweighs the right to know. The American Academy of Pediatrics (AAP) guidelines for pediatric predictive genetic testing encourage decisions to be made in the "best interest of the child" and the deferral of predictive testing for adult-onset conditions, unless an intervention exists that if initiated in childhood would reduce morbidity and mortality. Evidence indicates that most parents want results, yet also desire choices and the option to defer certain results Dr. Santana moved on to a discussion of the issue of rebiopsy for research purposes and concluded by presenting a framework for analyzing the risks and potential benefits of pediatric rebiopsy.

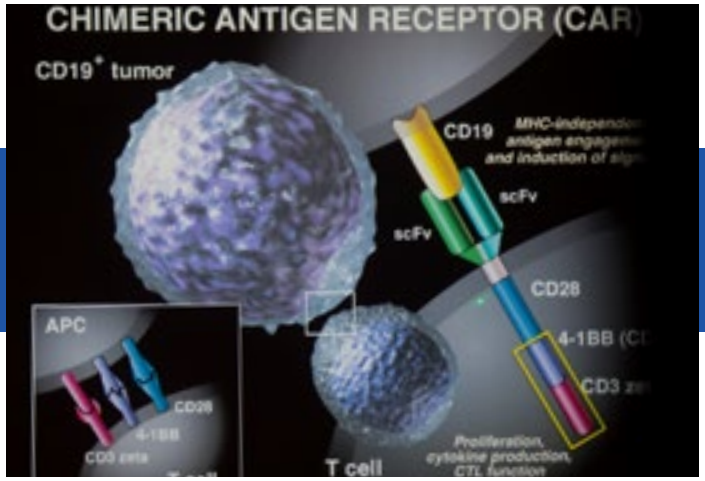


Clinical Pipeline

Pediatric Hematologic Cancers: Where Are We Now?

Stephen Hunger, MD, Children's Hospital of Philadelphia

Dr. Hunger provided an update on the current landscape for pediatric hematologic malignancies, including both leukemias and lymphomas (accounting for 40-45% of all childhood cancers). He reviewed the changes that occur in leukemias across age groups, noting that acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) outcomes vary greatly by age. Despite those differences, he highlighted dramatic improvement in outcomes over time. Dr. Hunger then drew attention to one of the major outstanding questions around pediatric hematologic malignancies: how to further improve cure rates using precision medicine and cellular immunotherapy. Philadelphia chromosome (Ph)-positive ALL, which was once associated with the poorest outcomes, is regarded as the poster child for precision medicine in pediatric oncology. The gains achieved in this subgroup demonstrate the possibility for dramatic gains: an effective inhibitor (imatinib) safely combined with chemotherapy to target a leukemia-dependent driver lesion. Explaining this success allowed Dr. Hunger to pivot to the ALL component of the TARGET initiative and other research efforts by the Children's Oncology Group (COG), which identified exploitable vulnerabilities in patients with Ph-like ALL. In light of the finding that perhaps as many as two-thirds of patients with Ph-like ALL have a targetable lesion, two clinical trials using targeted approaches are under way. Dr. Hunger then switched to the topic of cellular immunotherapy, including the science and clinical experiences with CAR T-cell therapy in relapsed and refractory ALL. Investigators have observed a very high and durable response rate with CAR T-cell therapy, which has fueled urgency for its use earlier in the treatment course. Dr. Hunger moved on to discuss other major types of pediatric hematologic malignancies, highlighting the importance of identifying appropriate candidates for and optimal timing of targeted therapies in AML, determining the long-term risk of tyrosine kinase inhibitors in chronic myeloid leukemia, and addressing the urgent need for effective therapies for juvenile myelomonocytic leukemia (JML). A subset of JML where stem cell transplant is the only curative therapy looks particularly promising for cellular immunotherapy advances because of expanded genomic understanding. Dr. Hunger concluded by covering new therapeutic targets and opportunities for novel therapies emerging for pediatric lymphomas, including both Hodgkin's lymphoma (eg, CD30, immune checkpoints) and non-Hodgkin's lymphoma (eg, CD30, ALK).

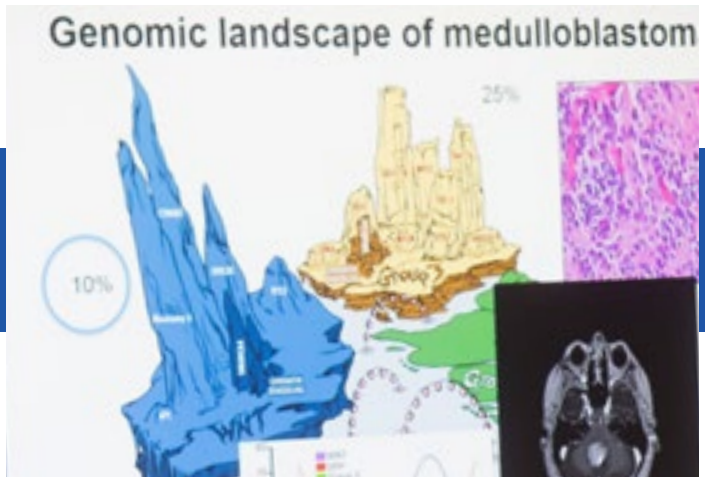


Clinical Pipeline

Pediatric Brain Tumors: Where Are We Now?

Roger Packer, MD, Children's National

Dr. Packer began by highlighting the clinical dilemma of pediatric brain tumors, which are the leading cause of childhood cancer-related morbidity and mortality. Furthermore, in the pre-molecular era progress was slow and limited. His talk focused on three types of pediatric brain tumors: embryonal (including medulloblastoma), low-grade glioma (LGG), and high-grade glioma (HGG)/diffuse intrinsic pontine glioma (DIPG). Dr. Packer reviewed clinical trial data in medulloblastoma that support high event-free survival with chemotherapy and radiation; however, these gains have been met by secondary malignancies and substantial reduction in IQ scores. When a large randomized trial of reduced- vs. standard-dose craniospinal radiation was conducted, an unacceptable reduction in EFS was observed in the former group. Investigators have begun to establish molecular subtypes in the hopes of identifying new molecular targets that pairs with ongoing efforts to explore therapy reduction in patients with a favorable prognosis. Dr. Packer explained that determining germline mutations in patients with genetic conditions associated with brain tumors might have therapeutic implications in the future; additionally, the 2017 World Health Organization classification has replaced the primitive neuroectodermal tumor (PNET) classification with many small subgroups, for which therapeutic implications are unclear. For LGG, the 2017 classification is already outdated and does not capture some of the nuances of pediatric tumors. Dr. Packer emphasized the high importance of maintaining quality of life in patients with LGG. New biologics have demonstrated the ability to improve visual acuity and functional outcomes in this population, and the discovery of BRAF gene abnormalities has opened the door to new therapeutic approaches. Currently, the lack of insight into the long-term effects of BRAF-targeted therapies and resistance mechanisms pose challenges in the LGG population. At the same time, molecular understanding of HGG/DIPGs is exploding yet no progress has been made in four decades. Despite the present clinical situation, renewed hope has grown from new molecular techniques, dedicated scientists, safer biopsies, and insights from human tissue. In fact, more advances in the molecular understanding of DIPG have occurred in the past five years than in the previous fifty. Investigators have identified discernible mutations in >80% of DIPGs and other midline HGG, providing possible targets for both drug and vaccine approaches. Dr. Packer also highlighted emerging data sharing collaborations and close cooperative relationships involving industry and national/international consortiums. In concluding, Dr. Packer noted that molecular insights have altered the understanding, classification, and management of pediatric brain tumors; the question remains whether such efforts will alter the prognosis/outcomes of patients.



Clinical Pipeline

Pediatric Solid Tumors: Where Are We Now?

Kimberly Stegmaier, MD, Dana-Farber Cancer Institute

Dr. Stegmaier focused on the connection between new technologies and new targets in childhood cancers. She emphasized the distinction between pediatric cancers and adult cancers and reviewed the current principles of solid tumor treatment, which include local control of the primary site of disease and use of dose-intensive combination cytotoxic therapy. She transitioned to the topic of precision cancer medicine, explaining how several known targets in pediatric cancer are in fact very difficult drug targets (e.g., MYCN, fusion proteins, and loss of tumor suppressors) and that pediatric cancers tend to have very quiet genomes that may influence responses to immunotherapy. Nonetheless, she sees the current era as the most amazing time for cancer research given conceptual advances (epigenetics, immunotherapy), technological advances (omic and single cell sequencing, functional genomics, and liquid biopsies), new models, and novel chemistry.

These various technologies are being directly applied to discovery in pediatric solid tumors such as Ewing sarcoma (ES) and neuroblastoma (NB). Screens are ongoing to identify new EWS/FLI inhibitors that could target a fusion protein identified in patients with ES about 20 years ago, while other investigators search for new targets. While recurrent mutations in ES tend to be few and undruggable, research at Dana-Farber Cancer Institute (DFCI) has uncovered what is believed to be the first genetic biomarker of metastases in ES, known as STAG2. Subsequent research has shown poor prognosis associated with the co-occurance of STAG2 and TP53 mutations, leading to a cooperative investigation with the Children's Oncology Group of these genes and their influence on outcomes in ES. Dr. Stegmaier also showed promising preclinical data for FAK and CDK 4/6 inhibitors in ES.

She then transitioned to NB, focusing on the concept of epigenetics—a complicated area of studying markers that give cells their identity. Based on preclinical data, inhibitors of the EZH2 enzyme and BET bromodomains have emerged as exciting candidates for the treatment of high-risk NB. COG is developing a trial to test BET inhibitors in NB, while Dana-Farber has designed and begun a trial of EZHZ inhibitors. For both of these classes of agents, the next step and highest priority will be to identify synergistic combinations and resistance mechanisms.

Conference Summary

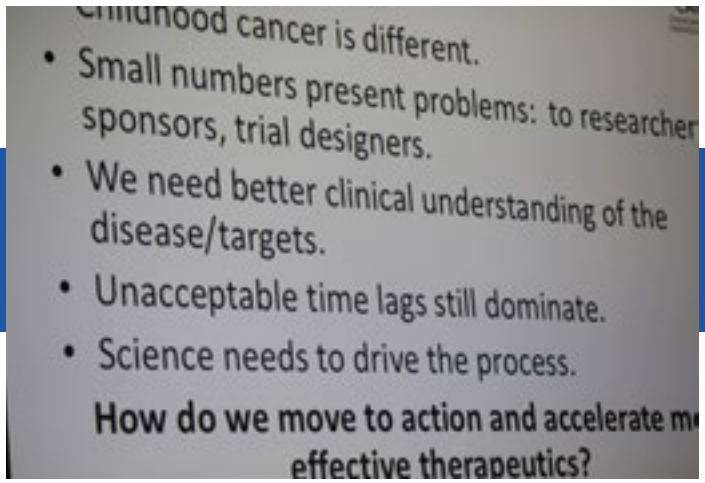
An Individual Approach Requires Collaborative Efforts

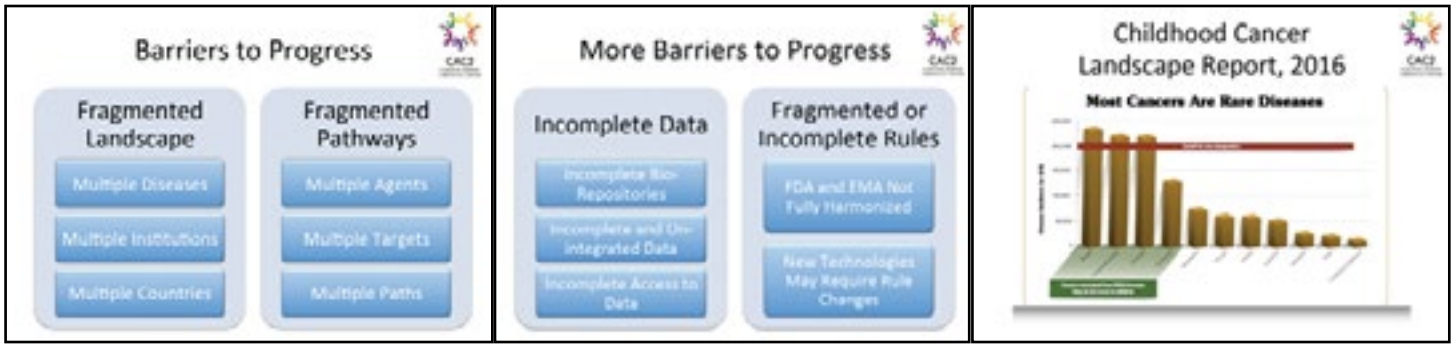
Vickie Buenger, PhD, Texas A&M Universtiy, Coalition Against Childhood Cancer

From Bench to Bedside and Beyond connected childhood cancer advocates, research funders, clinicians, and scientists from academia and industry. A number of common themes emerged from the various investigators' presentations including (1) most childhood cancers are different than adult cancers, (2) the relatively small numbers of pediatric patients presents challenges for researchers designing clinical trials, (3) despite progress in some areas, unacceptable time lags still dominate.

While all conference participants stand ready and energized to move research forward and recognize that scientists will drive the process, there continue to be a number of fundamental barriers to progress. Fragmentation across the landscape abounds. At one time the childhood cancer umbrella categorized twelve different types of cancer. Today, with new information about disease differences the subtypes have increased to well over 100 childhood cancers. In addition to a proliferating identification of childhood cancer tumor types, numerous institutions across the United States and around the world engage in both studying and treating these diseases and hundreds of independent entities power the funding for this work.

Work to solve the problem of multiple diseases, multiple pathways, multiple agents, multiple study teams, and multiple funding equations creates additional information management problems and regulatory issues. The list includes incomplete bio-repositories, incomplete and fragmented data sets, and spotty access to data. Breakthroughs based on newly introduced agents and emerging options (including those discussed at the research conference) may require revisiting regulatory rules and requirements. That agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are not fully harmonized despite informal attempts to coordinate creates additional potential confusion for sponsors tasked with bringing new drugs to market.





Investigators seeking financial support face additional barriers to progress. Within the National Cancer Institute (NCI), there are multiple grant programs, each with their own time lines and requirements. Funding is also available through many, many private foundations and charities. Yet the existence of these potential sources of funding also presents challenges to progress, as grant-seekers have to navigate the funding cycles and proposal requirements of hundreds of individual childhood cancer foundations.

For investigators able to negotiate the fragmented and complex processes in place, the net payoff could be woefully small. In 2016, the NCI pediatric cancer budget combined with foundation support for childhood cancer research slightly exceeds $300 million, while a conservative estimate of spending by Americans on Halloween this year exceeded a staggering $8.2 billion (Fortune, October 31, 2016).

While the challenges are significant, it is abundantly clear that clinicians, researchers, and advocates in the childhood cancer community share a common "**Wish List**" that includes:

- Solve the challenge of small patient numbers
- Collect and analyze more preclinical data
- Encourage greater data collection and sharing
- Secure earlier and more generous access to drugs for children with cancer
- Secure earlier and more generous access to clinical trials for children with cancer
- Make needed adjustments to the clinical trial infrastructure and trial design
- Build pathways to better prioritization for pediatric-specific therapies

Moving to collective action and accelerating the pace of therapy discovery is in order. The criticality of setting up channels of communication cannot be overstated. There will be a shared responsibility among those represented at the CAC2 research conference (Researchers, Clinicians, Sponsors, Regulators, Funders, and Families) to make positive change for children with cancer a reality. The first step in the process will be to use communication and collaboration to "close the gaps"—creating new pathways for the richness, reach, and timeliness of information. The second step, even more challenging than the first, will require bridging the existing gaps in public/private partnerships and may necessitate the formation of a new entity charged with this task and for which potential goals could be along these lines:

- Look for small, evidence-driven wins
- Build templates for cooperation
- Create processes for cooperation
- Improved access to information
- Foster deep and wide communication

Everyone working towards the goal of creating a world without childhood cancer needs to check their egos at the door to foster collaboration among a very diverse group of individuals. We are on the brink of positive change for children with cancer.

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Non-myogenic origin of embryonal rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. Despite aggressive chemotherapy, radiotherapy and surgery, clinical outcomes for RMS have not improved for three decades, emphasizing the need to uncover the molecular underpinnings of the disease. RMS includes two histolopathologic subtypes: alveolar RMS, driven by the fusion protein PAX3/7-FOXO1, and embryonal RMS (ERMS), which is genetically heterogeneous. RMS has been presumed to originate from derailed muscle progenitors based on the histologic appearance and gene expression pattern of the tumors. However, an origin restricted to skeletal muscle does not explain RMS occurring in tissues devoid of skeletal muscle such as the prostate, bladder, biliary tree and the omentum. Previously, we showed that activation of Sonic Hedgehog signaling through expression of a conditional, constitutively active Smoothened allele, SmoM2, under control of an adipocyte-restricted adipose protein 2 (aP2)-Cre recombinase transgene in mice gives rise to aggressive skeletal muscle tumors that display the histologic and molecular characteristics of human ERMS. In this model, tumorigenesis occurs with high penetrance (~80%), is early onset (by 2 months of age), and is restricted to the head and neck. Also, unlike previous RMS models, this model requires no additional background mutations, such as inactivation of p53, and results in only ERMS neoplasia. We illustrated that the gene expression signature of the aP2-Cre;SmoM2 tumors recapitulates both other mouse ERMS models as well as human ERMS.
With the short latency and anatomic restricted tumor location, we sought to leverage this model to explore the cell of origin. Lineage tracing the aP2-Cre in combination with reporter mice illustrated aP2-Cre expression in both brown and white adipose tissue as well as a discrete population of cells lying between skeletal muscle fibers but not beneath the laminin sheath of the muscle fibers. These aP2-lineage cells are distinct from Pax7-positive skeletal muscle stem cells or satellite cells and do not contribute to myofiber formation. When compared to aP2-Cre;R26-Tom mice, the addition of oncogenic SmoM2 (aP2-Cre;R26-Tom;SmoM2) results in embryonic expansion of the aP2-lineage interstitial muscle cells and formation of ERMS. Our findings suggest that non-skeletal muscle progenitors are a potential cell of origin for Sonic Hedgehog-driven ERMS.

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A transposon screen identifies loss of primary cilia as a mechanism of resistance to Smo inhibitors

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Targeted cancer therapies promise high efficacy with limited toxicity. However, acquired resistance to targeted therapies frequently results in tumor recurrence. Mutations of the therapeutic target itself represent one mechanism for resistance, however the broad scope of changes that confer resistance is not known. Aberrant Hedgehog signaling is implicated with many cancers. It is particularly evident in medulloblastoma, the most common malignant brain tumor in children. Preclinical and clinical studies have demonstrated that medulloblastoma exhibit partial or complete responses to Smo inhibitors. However, clinical benefits are limited by de novo or acquired resistance. Identification of resistance mechanisms is essential to overcome resistance and to achieve long-term benefits. Here we carried out a transposon mutagenesis screen in Hedgehog-pathway dependent medulloblastoma cells, and identified mutations in genes essential for primary cilia formation conferring resistance. Analysis of clinical samples indicates loss of primary cilia representing a new class of resistance mutations. This was extremely surprising, as loss of primary cilia is predicted to inhibit growth of Hedgehog pathway-dependent tumors, rather than to confer resistance. We demonstrate that loss of primary cilia confer therapeutic resistance by initiating a persister state, in which slow growing tumor cells maintain a low level of Gli2-dependent transcriptional output in the presence of targeted therapies. Additionally, synergy between cilia loss and heterozygous mutations in tumor suppressor genes can transform slow growing persister cells into rapidly growing tumors. We examined clinical samples and found that loss of cilia is a common feature of resistant tumors. Together these findings reveal novel mechanisms of resistance and identify consistent strategies for treating diverse resistant tumors.

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Genomic landscape of infant acute lymphoblastic leukemia with MLL (KMT2A) rearrangement

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Acute lymphoblastic leukemia in infants <12 months of age is an aggressive cancer with high risk of relapse. Infant ALL with MLL (KMT2A) translocation (MLL-R) has an event-free survival of <50% and the prognosis following relapse is dismal. Other than MLL-R, infant ALL contains remarkably few genomic lesions. We sought to determine if somatic mutations are recurrent among infant ALL cases, if specific mutations may predict resistant disease, and if additional driver mutations emerge at relapse.
Methods: We performed whole genome sequencing (WGS) on blood and bone marrow samples from 25 infants with MLL-R ALL. Cases contained either MLL-AF4 or MLL-ENL. Cohort A included 13 patients with trios of samples from diagnosis, remission, and relapse. Cohort B included 12 non-relapsed patients from diagnosis and remission. WGS was performed using Illumina Hiseq 4000 and 2500, to a minimum of 90Gb. Alignment and variant calling were done using BWA, GATK. Somatic variants were defined as ACMG category 1-3 mutations that were present at diagnosis or relapse, but absent in the remission control, with allelic frequency ≤0.1%, and minimum allelic depth of 7 reads.
Results: In diagnostic samples, we identified 57 non-silent somatic mutations (43 missense, 7 frameshift, 5 nonsense, 1 mitochondrial, and 1 indel) among 48 genes. Recurrent mutations at diagnosis occurred in NRAS (N=5), KRAS (N=3), PIK3R1 (N=2), and PI3KCD (N=2). Mutations in NRAS or KRAS were found in MLL-AF4 cases only. In relapse samples, the number of non-silent mutations increased to 132 (97 missense, 13 frameshift, 9 nonsense, 1 mitochondrial, 3 indel, and 9 spice variants). The mean number of mutations per case increased from 2.2 ± 1.3 at diagnosis to 10 ± 12 at relapse. The median number increased from 2 (range 0-4) at diagnosis to 7 (range 0-44) at relapse. On average, 8.8 mutations were gained (range 0-40), 1.3 were retained (range 0-4) and 0.8 were lost (range 0-3) at relapse. Variant allele frequencies were 0.35 ± 0.17 at diagnosis and 0.38 ± 0.14 at relapse for Cohort A and 0.42 ± 0.12 at diagnosis for Cohort B.
Conclusions: In the largest series of infant ALL trio sequencing to date, we found a paucity of pathogenic mutations at diagnosis or relapse. While NRAS and KRAS mutations were recurrent, they were present in only 21% of cases. Our findings suggest that epigenomic, rather than genomic, factors may drive chemotherapy resistance in MLL-R infant ALL.

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Drug conjugated nanoparticles activated by cancer cell specific mRNA

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We have developed a customizable approach to cancer therapy in which a gold nanoparticle (Au-NP) delivers a drug that is selectively activated within the cancer cell by the presence of an mRNA unique to the cancer cell. Fundamental to this approach is the observation that the amount of drug released from the Au-NP is proportional to both the presence and abundance of the cancer cell specific mRNA in a cell. Concurrent with drug release, the mRNA bound to the Au-NP also undergoes degradation by nucleases targeting DNA/RNA hybrids and, therefore, depletes the cancer cell of a gene required for survival and proliferation. This provides a novel targeting opportunity to dramatically increase the concentration of free drug in cancer cells relative to normal cells and, therefore, maximize efficacy and minimize toxicity while simultaneously depleting the cancer cell of an essential mRNA. This approach is also highly customizable with respect to both the cancer cell specific mRNAs targeted and drugs activated and, thus, has broad applicability across cancer. As proof-of-principle, we have demonstrated both the efficient delivery and selective release of the multi-kinase inhibitor dasatinib from Au-NPs in leukemia cells with resulting efficacy in vitro and in vivo. Furthermore, these dasatinib-conjugated Au-NPs reduced toxicity against hematopoietic stem cells and T-cells. We are now expanding this technology and its therapeutic potential by utilizing SN38, the highly potent metabolite of the topoisomerase I inhibitor irinotecan that is used in the therapy of multiple cancers. SN38 is an ideal drug for this approach as although it is 100-1000 fold more potent than its pro-drug irinotecan, only a small fraction of irinotecan is metabolized to SN38 in patients and it cannot be given clinically due to insolubility. We are currently testing SN38-conjugated Au-NPs with Ewing sarcoma and neuroblastoma cells. This work will provide a strong foundation for both moving this novel cancer therapy approach closer to the clinic and developing more complex Au-NPs that selectively activate two or more synergistic drugs or are functionalized with additional biologic agents to enhance delivery or efficacy.

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5p-derived microRNAs inhibit Wilms tumor growth

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Wilms tumor is the most common kidney tumor of childhood and the third most common pediatric solid tumor overall. One-fifth of Wilms tumors are driven by mutations in the enzymes responsible for microRNA processing, notably DROSHA, DICER1, and DGCR8. microRNAs regulate gene expression post-transcriptionally in a sequence-specific manner, and dysregulation of microRNAs is seen in many cancers. Specifically, mutations in microRNA processing genes are common in a variety of cancers, including pleuropulmonary blastoma, pineoblastoma, and Sertoli-Leydig cell tumor. These mutations act in different ways to block the biogenesis of tumor-suppressing microRNAs, especially those derived from the 5p arms of pre-microRNA hairpins. This implies that 5p-derived microRNAs play an important tumor-suppressive role – a role which may lead to a new therapeutic opportunity, since microRNAs can be pharmacologically re-introduced. For this reason, we sought to test whether re-introduction of specific 5p-derived microRNAs could be a new treatment strategy for Wilms tumors. However, the most important 5p-derived microRNAs to therapeutically replace in this context are unknown. To identify such microRNAs, we analyzed microRNA expression in Wilms tumors bearing mutations in microRNA processing genes. We found that the let-7, miR-16, and miR-34 families are particularly deficient in Wilms tumors with microRNA-impairing mutations. These 5p-derived microRNAs are also key tumor suppressors in other cancers, and liposomes designed to deliver these microRNAs are in development for cancer therapy. To study their impact on cell proliferation in the context of Wilms tumor, we used a lentiviral system for inducible expression of each microRNA at physiologically relevant levels. Specifically, we expressed let-7a, miR-16, and miR 34a in two Wilms tumor cell lines, WiT-49 and WT-CLS1. Expression of each of these microRNAs resulted in repression of target genes and resulting growth suppression. This suppression occurred through both decreased proliferation and increased apoptosis. In both cell lines, miR-16 and miR-34a induction had a larger impact on growth than let-7a. Thus, miR-16 and miR-34a are promising microRNAs for pharmacological re-introduction as a novel therapy for Wilms tumors and other cancers defective for these microRNAs.

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Molecular profiling using targeted next-generation sequencing in pediatric neuro-oncology patients: the UCSF experience

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Background: Molecular profiling is revolutionizing cancer diagnostics beyond morphology and immunohistochemistry and leading to personalized therapeutic approaches. Herein, we describe our institutional experience performing targeted sequencing for 40 pediatric neuro-oncology patients.
Methods: We sequenced approximately 500 cancer-associated genes in DNA extracted from micro-dissected tumor tissue and peripheral blood using a standardized bioinformatics pipeline to identify germline and somatic mutations and copy number changes. Patients were selected from the primary UCSF population or referrals from outside institutions. Cases selected for sequencing were chosen according to diagnostic uncertainty, diagnoses without successful standard of care therapy, or recurrent or treatment-refractory tumors. Results were discussed at a standing multi-disciplinary molecular tumor board to identify clinically relevant alterations and potential therapy options.
Results: Between June 2015 and August 2016, genomic profiling was performed on 41 brain tumors from 40 pediatric patients, including 7 low-grade gliomas, 15 high-grade gliomas, 10 medulloblastomas, 2 high-grade neuroepithelial tumors, 1 CNS neuroblastoma, 1 embryonal tumor with multilayered rosettes, 1 pineoblastoma, 1 uveal ganglioneuroma, 1 chordoma, 1 meningioma, and 1 choroid plexus carcinoma.

One patient had sequencing completed on 2 apparently denovo glioblastomas as based on molecular profiling. In 32 cases (80%), results impacted patient management by 1) clarifying diagnosis, 2) identifying previously unsuspected pathogenic germline mutations, or 3) detecting potentially targetable somatic alterations. Nine pathologic diagnoses were amended based on genomic profiling results, including a high- to low-grade glioma, medulloblastoma to pineoblastoma, and ependymoma to CNS high-grade neuroepithelial tumor with BCOR alteration. Ten patients were identified to have previously 4 unsuspected pathogenic germline mutations including 2 patients with high-grade gliomas harboring novel MUTYH germline mutations and one patient found to have both TP53 and MSH6 germline mutations consistent with concurrent Li-Fraumeni and Lynch syndromes. Potentially targetable mutations were identified in 24 patients (63%) including three patients with hypermutated glioblastomas, recently identified to therapeutically benefit from PD-1 inhibition. Additionally, novel, likely pathogenic alterations were identified in three cases: an in-frame RAF1 fusion in a BRAF wild-type pleomorphic xanthoastrocytoma, an inactivating ASXL1 mutation in a histone H3 wild-type diffuse pontine glioma, and an in-frame deletion within exon 2 of MAP2K1 in a low-grade astrocytic neoplasm.
Conclusions: Our experience demonstrates the significant impact of molecular profiling on diagnosis and treatment of pediatric brain tumors and confirms its feasibility for use at time of initial diagnosis or recurrence.

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Comparative cancer genomic analysis nominates novel therapeutic options for individual pediatric cancer patients

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The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) projects have produced genomic data from thousands of adult and pediatric tumors. However, it is unclear whether these datasets could directly benefit children with cancer today. UC Santa Cruz Treehouse Childhood Cancer Initiative (treehouse.soe.ucsc.edu) enables comparisons of genomic information from children with cancer treated on clinical genomic trials to previously collected cancer genomic datasets. Through this approach, termed "pan-cancer analysis", we aim to identify molecular features that may suggest new therapies for children with cancer.
In our pan-cancer analysis, each tumor's RNA-sequencing profile and/or mutational profile is compared to 10,368 uniformly analyzed tumor profiles from TCGA and TARGET projects (Vivian et al., BiorXiv, 2016). We use Tumor Map, an unsupervised clustering and visualization tool, to identify tumors in the reference cohorts that are most similar to the given tumor. We then perform a gene expression outlier analysis that reveals transcripts, whose expression is significantly enriched or depleted in the given tumor. These data are used to generate hypotheses regarding the molecular pathways that may be driving the disease in each child as well as relevant targeted therapies, providing clinical directions that could be further investigated by the medical teams. We have been evaluating the Treehouse analysis approach as part of California Kids Cancer Comparison, a demonstration project for the California Initiative to Advance Precision Medicine. With the generous funding from St. Baldrick's Foundation, we are expanding our study to include children treated on clinical genomic trials at Stanford University, Pacific Pediatric Neuro-Oncology Consortium, Children's Hospital of Orange County, University of Michigan, Children's Hospital of Philadelphia, and British Columbia Children's Hospital. The analysis of the first 19 patients at Stanford provides evidence of the potential clinical utility of our approach. In 17 of the 19 cases, we found rationale for new therapeutic options, including existing clinical trials, and/or FDA-approved drugs that could be administered off-label at the discretion of the physician. In 2 patients, both of whom had no available treatment options prior to our work, the comparative analysis has contributed to treatment decisions. This study provides a framework for using large, public genomic datasets to help interpret genomic information from prospective pediatric cancer patients. Our study also underscores the importance of releasing cancer genomic datasets to the community immediately following data generation, so that they may be used to benefit new patients.

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OTX2 activity at distal regulatory elements shapes the chromatin landscape of Group 3 medulloblastoma

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Medulloblastoma is the most frequent malignant pediatric brain tumor and is divided into at least four subgroups. Group 3 patients have the lowest 5-year survival and there is a pressing need to identify oncogenic drivers in these tumors in order to develop novel therapies. Here, we characterized gene regulatory mechanisms in Group 3 tumors through the combined analysis of genome-wide chromatin and gene expression profiling in primary tumor samples and established cell lines. Our results show that the majority of active enhancers in this subtype are occupied by the oncogenic transcription factor

OTX2, which is often arranged as clusters of adjacent peaks. Active OTX2 bound enhancers, as opposed to many inactive OTX2 binding sites across the genome, are distinguished by the presence of the transcription factor NEUROD1. These active sites are responsive to OTX2 and NEUROD1 knockdown and could also be generated de novo upon ectopic OTX2 expression in primary cells, showing that OTX2 plays a major role in maintaining and even establishing regulatory elements as a pioneer factor, and that it cooperates with additional factors to shape the regulatory landscape of tumor cells. Among OTX2-regulated target genes we identified the kinase NEK2, whose knockdown and pharmacological inhibition resulted in decreased cell viability. Our studies thus show that OTX2 controls the regulatory landscape of Group 3 medulloblastoma through cooperative activity at enhancer elements and is a major contributor to the expression of critical target genes in this tumor type.

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Functional Multi-omics Identifies Druggable Targets in Renal Medullary Carcinoma

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Renal medullary carcinoma (RMC) is a rare kidney cancer that is primarily seen in adolescent and young adult African American patients with sickle cell trait. Prognosis is poor and treatment options are limited. We have developed one of the first models, CLF-PED-005-M Adherent and Suspension, from a patient who succumbed to this disease in one year's time. We have confirmed by whole exome sequencing that our models have sickle cell trait and loss of heterozygosity of the SMARCB1 loci, both hallmarks of this disease. By RNA-sequencing, we see a lack of SMARCB1 transcription. We have further shown dependency of our models to SMARCB1 re-expression thus suggesting that this cancer is indeed driven by loss of SMARCB1 at a functional level. We performed pooled CRISPR-Cas9 and RNAi loss of function screens and a small molecule screen focused on druggable cancer targets based on our previous work. Integrating these three complementary and orthogonal methods, we identified a number of targets for further validation. These targets, when combined may provide a rational approach to therapeutic targeting for this rare kidney cancer.

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Cavatica: empowering research with a pediatric genomic cloud

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The pediatric cancer genome is severely under-represented in genomic databases as existing data portals have primarily focused on adult cancers. Furthermore, large-scale pediatric datasets like TARGET lack pediatric central nervous system (CNS) data. To address this unmet need, we have developed a new cancer genomic platform named Cavatica. The rationale behind Cavatica is to provide a sustainable application cloud based eco-system that supports many of the aspects associated with basic & translational research. Cavatica is the first of its kind pediatric genomic portal for disease research, and its goal is to serve as a central hub to promote collaborative research between investigators. Cavatica supports the sharing and creation of pipelines, data, algorithms, visualizations, and hypotheses. Currently, one of the biggest barriers and challenges to collaborative research is the transfer and processing of 'big data' such as cancer genomes. By placing data, pipelines, computation, and visualizations on the Cavatica cloud we provide a centralized area for researchers to collaborate on projects and bring their data, algorithms, and expertise.
Currently, Cavatica features the following applications designed to work together: a biorepository and specimen query tool (Harvest, harvest.research.chop.edu), a data visualization application (PedcBioPortal, pedcbioportal.org), data storage in S3 buckets, and data processing via Seven Bridges Genomics. Users can move seamlessly between these applications, and thus can go from points on a graph to physical samples. Cavatica also protects data or pipelines on an individual and group basis so various team members can share a common working space with controlled or a single individual can store experiments in a private space. All current solutions will be constantly evaluated and replaced as technology evolves. Cavatica is set to house data from a number of sources including the Childhood Brain Tumor Tissue Consortium (CBTTC), Pacific Neurooncology Consortium (PNOC), Stand Up to Cancer (SU2C), NCI Therapeutically Applicable Research To Generate Effective Treatments (TARGET), and The Cancer Genome Atlas (TCGA). Cavatica's framework will also allow unique opportunities for data scientists, statisticians, data engineers, programmers, application developers, bioinformaticians, and pre-clinical and clinical researchers to contribute and expand the reach and impact of this application.

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Phase I Study Of LOXO-101, A Selective TRK Inhibitor, In Pediatric Patients With Cancer

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Background/Objectives: Neurotrophin ligands and their receptors TRKA, TRKB, and TRKC (encoded by NTRK1, NTRK2, and NTRK3) are important for growth regulation, differentiation and survival of neurons. Translocations involving the NTRK1/2/3 kinase domain, mutations involving the TRK ligand-binding site, amplifications of NTRK, TRK splice variants, and autocrine/paracrine signaling have been described in diverse tumor types and may contribute to tumorigenesis. A broad range of pediatric malignancies have been found to harbor NTRK fusions, including infantile fibrosarcoma (IFS), congenital mesoblastic nephroma (CMN), secretory breast cancer, pediatric papillary thyroid cancer, gliomas and Ph-like acute lymphoblastic leukemia. Additionally, TRK protein over-expression is common in neuroblastoma. LOXO-101 is the first small-molecule selective inhibitor of TRKA, -B, and -C in clinical development and has demonstrated clinically meaningful responses in patients with TRK fusion cancers in an adult phase 1 trial (5/6 patients with RECIST PRs).
Design/Methods: We have initiated an open-label, multi-center Phase 1 dose escalation/dose expansion study with LOXO-101 in pediatric patients with solid tumors and primary CNS tumors (NCT02637687). Patients with advanced cancer between the ages of 1 and 21 years are eligible, as well as patients as young as 1-month of age with a primary diagnosis of IFS or CMN and a documented NTRK fusion. Twice-daily oral dosing of LOXO-101 capsules is administered on a continuous 28-day schedule. LOXO-101 is available in an oral liquid formulation for patients unable to swallow capsules. Dose escalation utilizes a Rolling 6 design. The objective of the study is to determine the recommended phase 2 dose (RP2D) and initial evidence of the efficacy of LOXO-101 in different tumor types. Eligibility for the dose expansion cohorts will require patient tumor samples to have documented alterations of an NTRK gene or TRK protein. Molecular abnormalities will be characterized through the analysis of archival tissue.
Results: This study is ongoing and open for enrollment. The RP2D has not yet been defined. The initial 16-month old patient with an ETV6-NTRK3 fusion positive infantile fibrosarcoma had a rapid radiographic response (PR by RECIST) which has been maintained through 5 cycles of treatment.
Discussion: Abnormalities of the NTRK gene, including trans locations, have been identified as possible oncogenic drivers in a number of pediatric cancers. LOXO-101 has demonstrated responses adults and children with NTRK fusion positive cancers. Ongoing research will define the dose of LOXO-101 in children and further evaluate NTRK fusions as a therapeutic target in this diverse population.

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Targeting the chromatin regulatory machinery hijacked by EWS/FLI in Ewing Sarcoma

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Ewing sarcoma is an aggressive pediatric tumor characterized by the expression of the oncogenic transcription factor EWS/FLI. EWS/FLI is a fusion protein resulting from a reciprocal chromosomal translocation, involving chromosomes 11 and 22, t(11;22). Apart from this pathognomonic lesion, Ewing sarcoma has one of the lowest mutational rates among all cancers (0.15 mutations/Mb). EWS/FLI is a poor candidate for pharmacological blockade due to its intrinsically disordered nature and convex DNA-binding surface. However, EWS/FLI recruits other chromatin regulatory proteins to alter the epigenetic landscape of Ewing sarcoma cells and maintain malignancy, and these factors represent potentially actionable targets. We have identified one such protein, lysine specific demethylase 1 (LSD1), whose depletion and pharmacological inhibition dramatically impair Ewing sarcoma cell viability. Every Ewing sarcoma cell line in our comprehensive panel (n= 17) displayed sensitivity to benzohydrazide-mediated LSD1 inhibition. LSD1 inhibition with HCI2509 compared to tranylcypromine (TCP) and other TCP derivatives currently in clinical trials demonstrated class-dependent derepression of EWS/FLI-repressed genes. Moreover, mutation of LSD1 in Ewing sarcoma patient tumors was not observed in a meta-analysis of five whole-genome and whole-exome sequencing studies.
The mechanistic details by which LSD1 and EWS/FLI interact remain undefined. In order to test how LSD1-containing complex composition and function are affected by EWS/FLI, we performed co-immunoprecipitation (co-IP) experiments and mass spectrometry to identify how LSD1 protein-protein interactions change in the context of EWS/FLI depletion. Co-IP to mass spec experiments showed several known interactors of LSD1, including CoREST1 and CoREST3, members of the nucleosome remodeling and deacetylase (NuRD) complex, members of the BRAF35 complex, and ZMYM2. Further validation experiments show that EWS/FLI alters the popula

tions of LSD1 protein in the nucleus in "knockdown-rescue" experiments, suggesting an upstream role for EWS/FLI in the regulation of LSD1 in Ewing sarcoma cells. We conclude the LSD1 complexes identified remain relatively stable in Ewing sarcoma with EWS/FLI depletion. However, other facets of LSD1-containing complex biology are regulated by EWS/FLI and the mechanisms by which this occurs remain an area of active study. Understanding these mechanisms and how they relate to the susceptibility of Ewing sarcoma cells to LSD1 inhibition will facilitate rational clinical use of LSD1 inhibitors, not only in Ewing sarcoma, but in other pediatric solid tumors.

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Targeting of WEE1 in Myc-driven medulloblastoma

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Background: Medulloblastoma (MB) is the most common malignant pediatric brain tumor and high-risk patients continue to have poor outcome, with only a 30% survival at 5 years. The Myc oncogene is amplified or overexpressed in about half of this patient population. One potential therapeutic strategy is to exploit Myc oncogene driven replicative stress by inhibiting WEE1, a kinase known to participate in the G2-M cell cycle checkpoint and DNA replication during the S-phase. Recent data from our lab have identified WEE1 as a critical mediator for medulloblastoma cell viability.
Hypothesis: We hypothesize that WEE1 plays a critical role in Myc-driven MB by protecting cells from oncogene-induced replicative stress and promoting DNA damage repair. With this logic, high Myc expressing tumors will be exquisitely sensitive to AZD-1775, a WEE1 small molecule inhibitor. We further hypothesize that combination of AZD-1775 with DNA damaging agents would be a very promising therapeutic strategy.
Methods/Results: Using commonly used MB cell lines, including primary patient derived cell lines, we showed that sensitivity to AZD-1775 correlated with Myc expression levels. Enhanced expression of Myc in retinal pigment epithelial (RPE) cells, made cells exquisitely sensitive to AZD-1775. A high throughput screen of 91 FDA-approved cytotoxic chemotherapy agents identified inhibitors of the replication machinery and nucleotide synthesis to be strongly synergistic with AZD-1775, with gemcitabine having the highest index. Treatment of cells with AZD-1775 and gemcitabine confirmed synergy in killing cells using the Chou-Talalay method. Combination of these two drugs was also synergistic in causing apoptosis, senescence, and an increase in markers of DNA damage. Treatment with these two drugs also caused a markedly abnormal cell cycle distribution and a decrease in DNA replication. In addition, immunohistochemical analysis of patient samples established that elevated WEE1 expression in group 3 high cMYC expressing tumors conveys a worse clinical outcome. A murine orthotopic xenograft model is currently underway to prove the combination of AZD-1775 and gemcitabine in vivo. This project proposes changing the paradigm of MB therapy as it identifies a subgroup of patients that will most likely benefit from new targeted therapy.

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Anti-tumor effect of trastuzumab, GM-CSF and IL-2 combinatorial immunotherapy in preclinical model of high-risk pediatric ependymoma

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A number of studies have demonstrated correlation of host immune factors with outcome in ependymoma (EPN). This supports the development of immunotherapy for EPN, a tumor in which approximately 50% of patients suffer recurrence and for which chemotherapy has not yet shown any benefit. Mechanisms of therapeutic antibody effect in cancer treatment have been shown to include recruitment of host anti-tumor immunity, and may therefore provide an expedient immunotherapeutic approach for EPN. Using a transcriptomic screen of FDA-approved therapeutic antibody targets we identified ERBB2, targetable by therapeutic antibody trastuzumab, as overexpressed in all subgroups of EPN, which was subsequently confirmed by protein analysis. In a series of preclinical studies, we evaluated the combination of therapeutic antibody trastuzumab with immunostimulatory factors GM-CSF and IL2 for the treatment of EPN. Novel EPN 1q+ cell lines 811 and 928 were co-cultured with autologous peripheral blood immune cells to measure immune-cell mediated cytotoxicity using a live cell imaging system (Incucyte). This demonstrated that trastuzumab could effectively target EPN through antibody-dependent cell-mediated cytotoxity (ADCC). Further, this mechanism could be enhanced by combination of GM-CSF with trastuzumab treatment, resulting in increased cytotoxicity. This implicates monocyte/macrophages as effectors of trastuzumab-dependent ADCC in EPN. Addition of IL-2 to trastuzumab and GM-CSF also resulted in further increases in ADCC, suggesting involvement of T-cells. Primary human EPN organotype culture studies demonstrated decreased tumor proliferation and increased immune cell proliferation in response to combined trastuzumab, GM-CSF and IL2. As the first stage in a clinical trial of trastuzumab in recurrent EPN we have recruited patients to a pilot study of GM-CSF delivered prior to surgery. Post-treatment tumor samples demonstrated upregulated antigen processing and presentation genes, a hallmark of GM-CSF activated macrophage/monocyte immunophenotype. These results support the continued testing of GM-CSF in combination with trastuzumab in EPN. Addressing, in part, blood brain barrier penetrance issues, we identified measurable levels of trastuzumab in EPN tumor post-treatment in two clinical cases. Collectively these preclinical and clinical data support continued testing of trastuzumab-based immunotherapy for recurrent EPN.

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Biological response modifiers with metronomic chemotherapy backbones as biomarker-driven add-on treatment strategy in very high risk pediatric solid tumors and NHLs – a single institution pilot study

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Most current anti-cancer therapies are designed with the goal of disease eradication. Although significant progress has been made using this strategy in pediatric ALL, the same cannot be said for histologically and genetically more complex solid tumors. Yet, in cases where chemotherapy with or without radiation does not achieve elimination of all tumor cells, the use of high dose chemotherapy and radiation selectively kills those cells that are chemo-sensitive and leaves highly resistant cancer cell populations free to relapse. Despite the initial reductions in tumor bulk produced by chemotherapy/radiation, the tumors are often quickly re-populated by the resistant cancer population. The purpose of this pilot study was to evaluate toxicity, safety and efficacy of Biomarker-Driven Molecularly-Targeted Metronomic Chemotherapy in n=1 trial setting.
Theranostic approach was tested in real life clinical situation. During 9/2014 – 6/2016 86 children with relapsed, refractory or very high risk solid tumors and NHLs were enrolled. Tumors were assessed using NGS TruSight Tumor panel with 26 most common genes, and where the frozen/fresh tissue was available, whole transcriptome analysis and analysis of RTK and downstream signaling pathways using phosphoprotein arrays were performed. In high-risk neuroblastoma patients, we also analyze expression of selected candidate marker proteins (PBX1, HOXC9, HMGA1, HMGA2 and DDX39A) that may predict resistance or sensitivity to the treatment with retinoids. While using TruSight Tumor, 31 mutations was found in 25 children, with 3 of them as germline. Other germline mutations were proven in 4 other patients in this cohort using candidate gene approach based on mostly phosphoprotein array data. Theranostic approach combining DNA NGS panel, whole transcriptome and phosphoproteomic data are combined with conventional histopathology data and discussed in multidisciplinary molecular oncology tumor board. This data set led to proposal for personalized treatment for 18 children. The treatment consisted from best matched targeted/ biological treatments /e.g. sunitinib, axitinib, nivolumab, or repositioned drugs combined up to 4 such agents with low dose metronomic chemotherapy backbone. The treatment was very well tolerated, however with some severe, despite transitory toxicity. Best therapeutic results were observed in cases, where phosphoproteomic, transcriptomic and genomic data were matching. Surprising and durable responses were observed e.g. in cases of chemorefractory relapsed Burkitt lymphoma, DIPG, GBM, relapsed anaplastic ependymomas and low grade sarcomas with underlying germline abnormities.
Our data are showing feasibility of such approach with promising preliminary data however meticulous follow up of children on new targeted therapies remains necessary.
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Rare but recurrent intrachromosomal 6q22 microdeletions generate targetable ROS1 oncoproteins in glioblastoma and ependymoma

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Brain tumors are the leading cause of cancer-related deaths in children. Among these, glioblastoma multiforme (GBM) poses substantial clinical challenge, contributing to a significant percentageof brain cancer related mortality in children and adults. Perusal of clinically relevant cancer drivers informs novel molecularly-targeted treatment strategies. Chromosomal rearrangements that generate oncogenic kinase-fusion(s) are promising drug targets and selectively inhibiting them has led to unprecedented tumor responses in several malignancies. Rearrangement involving ROS1, an orphan receptor tyrosine kinase gene, was first described in a GBM cell line in the 1990s. More recently, ROS1-fusions were identified in subsets of diverse pediatric and adult malignancies, including infantile fibrosarcoma, spitzoid melanoma, non-small cell lung cancer (NSCLC) and cholangiocarcinoma. We and others have shown dramatic clinical efficacy of ROS1 kinase inhibitors (ROS1i) in ROS1-fusion expressing patients. Positing that similar benefit could be accomplished for primary brain cancer we re-examined the TCGA glioblastoma dataset using

imbalanced 5′/3′ exon expression as metric for further wet-lab interrogation of these tumors. Multiple bioinformatics algorithms previously used to interrogate the TCGA datasets had failed to detect ROS1-fusions in GBM. Here we report the discovery of rare (frequency = 0.5-1%) but recurrent intra-chromosomal 6q22 microdeletions that generate ROS1-fusion proteins in GBM patient samples. Examination of the MSK-IMPACT (MSKCC) and Foundation Medicine genomic sequencing datasets validated the finding that GOPC-ROS1 is a recurrent ROS1-fusion in glioblastoma. We provide the first evidence of GOPC-ROS1 expression in pediatric glioblastoma and ependymoma. Our findings underscore the need for specific clinical tests designed to identify these rare, but important somatic aberrations. To gauge the importance of ROS1-fusions for glioma growth, we performed functional studies assessing their transforming potential using Ba/F3 cells and human astrocytes. Our results demonstrate that ROS1-fusions are dominant oncogenes driving cytokine-independent Ba/F3 cell growth and anchorage-independent colony formation in asgrowth by downregulating critical cell growth and survival pathways mediated by the SHP2/RAS/MAPK and PI3K/AKT signaling axes. Additionally, we demonstrate that oral monotherapy with the brain-permeable ROS1i, lorlatinib, effectively reduces U118MG tumor volume and prolongs survival in an intra-cranially xenografted model of the disease. Taken together, these data strongly suggest that the identification and targeting of ROS1-fusions will permit precision oncology and improve outcome in a subset of adult and pediatric glioblastoma patients.

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Radiosensitization of medulloblastoma by a novel DNA damage checkpoint inhibitor

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Medulloblastoma is a cerebellar tumor and the most common pediatric brain malignancy. Radiation therapy is part of the standard care for this tumor, but its effectiveness is accompanied by significant neurocognitive sequelae due to the deleterious effects of radiation on the developing brain. We have previously shown that the protein kinase MRK/ZAK protects osteosarcoma cells from radiation-induced cell death by regulating cell cycle arrest after ionizing radiation. We now show that siRNA-mediated MRK depletion sensitizes primary medulloblastoma cells to radiation. To translate these findings to the clinic, we set out to develop a small molecule inhibitor of MRK, using as starting point the drug nilotinib, a second generation c-Abl inhibitor that has been shown to be equally effective gainst MRK. Based on a molecular model of nilotinib bound to the MRK active site, we have derivatized nilotinib to covalently bind to a cysteine in the ATP binding pocket of MRK and showed that this drug, M443, inhibits MRK in an irreversible fashion. Furthermore, M443 is highly selective, in that it no longer inhibits c-Abl. We found that M443 strongly radio-sensitizes UW228 medulloblastoma cells as well as IMB226 patient-derived primary cells, but does not radio-sensitize primary human astrocytes or neuronal stem cells. M443 also inhibits radiation-induced activation of both p38 and Chk2, two proteins that act downstream of MRK and are involved in DNA damage-induced cell cycle arrest. Finally, we tested the effect of M443 in an animal model of medulloblastoma that employs orthotopic implantation of IMB226 medulloblastoma cells in nude mice. Intra-tumoral delivery of M443 alone significantly extended animal survival by 5 days compared to vehicle treatment. Combination treatment of M443 with radiation at 2 x 3 Gy, that is not effective on its own (1 day of additional survival over control), achieved a synergistic increase in survival (15 days over the control survival time). Western blotting of tumor lysateswith an activation state-specific antibody demonstrated strong inhibition of MRK activity after M443 administration, thereby validating this antibody as a useful biomarker. A murine model utilizing a paramagnetic gadolinium-based nanoparticle delivery system to bypass the BBB is currently being developed to effectively deliver M443 in vivo.
In conclusion, we have developed a new small molecule inhibitor of MRK/ZAK that selectively radio-sensitizes medulloblastoma cells versus normal cells. We hypothesize that combining radio-therapy with M443 will allow us to lower the radiation dose while maintaining therapeutic efficacy, thereby minimizing radiation-induced side effects.

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Evaluation of the dual mTORC1/2 inhibitor TAK228 and MEK inhibitor Trametinib as possible combined treatment for pediatric low grade glioma

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Introduction: Pediatric low grade glioma (PLGG) is one of the most common childhood tumors. If the tumor is located in a region of the brain that is not accessible for surgical resection or if the tumor recurs after surgery, additional therapies are needed. Recent studies highlighted the important role of mTORC and MEK-activation in LGG. The dual mTORC1/2-inhibitor, TAK-228, and the FDA approved MEK-inhibitor, trametinib, have good brain penetration and promising candidates for targeted therapy for LGG. We hypothesized thatTAK-228 and Trametinib would show synergistic effects both in vitro and in vivo in PLGG models. Methods: We treated the PLGG derived cell lines Res186and Res259with TAK-228 (dual mTORC1/2 inhibitor), Trametinib (Mek-inhibitor), DMSO, or

TAK-228 combined with Trametinib. Cell growth was investigated using MTT-assay over different days and compared to the treatment with the vehicle. DNA replication was measured through bromodeoxyuridine incorporation assay. Cells were analyzed and counted with ImageJ.
Results: TAK-228 and Trametinib inhibited growth of Res186 and Res259 in a dose dependent manner (50% vs control; p = 0.01 as measured by MTT). BrdU incorporation assay revealed a reduction in proliferating cells in 10nM and 100nM Trametinib for Res186 and Res259. Morphological investigation showed an increase in cytoplasm volume with 100nM TAK-228 and Trametinib for both cell lines compared to control groups.
Conclusions and future directions: Our preliminary results show that the PLGG-derived cell lines are sensitive to TAK-228 and Trametinib treatment. All cell lines showed decreased proliferation at various doses of either inhibitor. We will now investigate both drugs in vivoas a next step. Evidence of activity in murine models will be necessary to provide a pre-clinical rationale for combination therapy of these agents in aggressive PLGG.

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Pediatric phase 1/1b dose-finding trial of entrectinib with expansion into patients with primary brain tumors, neuroblastoma, and NTRK, ROS1, or ALK fusions

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The STARTRK-NG ("Studies of Tumor Alterations Responsive to Targeting Receptor Kinases – Next Generation") trial is a Phase 1/1b study of oral entrectinib in pediatric patients with relapsed or refractory solid tumors or primary CNS tumors, with two expansion cohorts for subjects with neuroblastoma and other non-neuroblastoma, extracranial solid tumors that harbor a gene fusion in NTRK1/2/3, ROS1, or ALK. Entrectinib is a potent inhibitor of solid tumors expressing NTRK1, NTRK2, NTRK3, ROS1 or ALK rearrangements. Gene rearrangements in these genes have been observed in a variety of adult solid tumors, including non-small cell lung and colorectal cancers, and in cancers that affect the pediatric population, including salivary gland cancer, papillary thyroid cancer, melanoma, and sarcomas. In addition, overexpression of TrkB (the protein product of NTRK2) and activating ALK point mutations have been observed in neuroblastoma. Thus, a pan-Trk, ROS1, and ALK inhibitor like entrectinib may potentially have broad therapeutic utility in pediatric patients.
Phase 1 studies of entrectinib reported a 79% Objective Response Rate in patients with gene fusions of these targets who had not received a previous kinase inhibitor for these genes, received effective therapeutic dose level, and had extracranial primary disease. In addition, a response was seen in a 22-year-old patient with neuroblastoma with an activating point mutation of ALK, as well as significant tumor regression of CNS metastases in an 18-month-old boy with infantile fibrosarcoma, harboring an ETV6-NTRK3 fusion. As of 7 March 2016, a total of 119 patients had been treated with entrectinib in the phase 1 studies. The most common (>10% incidence) treatment-related adverse events were fatigue/asthenia, dysgeusia, paresthesia, nausea, myalgia, diarrhea, dizziness, arthralgia, vomiting, and constipation; importantly, there was no evidence of cumulative toxicity.
Overall, these gene fusions are rare in the cancer population (< 3%); however, they have been seen in over 40 solid tumor histologies. A survey of two pediatric cancer databases, St Jude pediatric cancer database (PeCan; total n=1,604) and the University of Michigan database (Peds-MiOncoSeq; total n=91) resulted in the identification of gene rearrangements in all three NTRK genes. In addition, according to a literature survey, the following tumor types, largely confined to the pediatric patient population, are also known to harbor gene rearrangements of the NTRK family of genes: congenital or infantile fibrosarcoma, secretory breast cancer, mesoblastic nephroma, and intrinsic pontine gliomas. Thus, targeting Trk receptors with a pan-Trk inhibitor may be of benefit for many cancers in children.

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Germinal mutation of PDGFRalpha in patient with tuberous sclerosis complex

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We are presenting the case report of 9-year-old boy with tuberous sclerosis complex. Within that he has angiomyolipomas of kidneys, bilateral hamartomas of retina, pharmacoresistant epilepsy, hypothyreosis. 11/2014 he was diagnosed with malignant PEComa in the abdominal cavity with the residual disease after the surgery. The mutational analysis from the tumor tissue and then also from the peripheral blood cells proved germinal mutation in PDGFRa – substitution in exon 10. Looking into the literature it remains unclear if this mutation leads to an activation of the protein, but the relationship to the PEComa in this case is suspicious. The analysis of the profile of phosphorylated proteins in the tumor cells revealed highly activated EGFR, InsR, IGF-IR and PDGFRß.
Due to these results we started with personalized treatment encompassing everolimus/sunitinib/metformin orally: The patient is now without measurable disease according to the ultrasound with EFS/OS 16 months. The coincidence of tuberous sclerosis complex with another germinal mutation is rare. This case report shows the possibility to use combination of different targeted therapies, which can help to stabilized/cure malignant tumors in such patients.

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Theranostic approach for relapsed APDS like Burkitt lymphoma

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A 7-year-old previously healthy boy with no family history of cancer was diagnosed with stage III abdominal Burkitt lymphoma in December 2014. He was initially treated standard BFM B-NHL 04 therapy. After 2 cycles, he had a very good partial response reaching < 5% of the initial tumor volume. An episode of the intestinal obstruction in February 2015 led to excision, and the histology confirmed sclerosing mesenteritis, without histological or rtPCR evidence of lymphoma (the original tissue was positive for cMYC translocation).
Unfortunately the child was found to have an isolated radiological progression in the same region in which the intestinal obstruction had occurred two months after completing chemotherapy. The biopsy in June 2015 confirmed relapsed Burkitt lymphoma, this time withmarked areas of sclerosing mesenteritis and mesenteric panniculitis. Mutational analysis of PI3K delta subunit proved germinal mutation/variant C830G at cDNA level and serine 312 cysteine on protein level, which is outside the classical activated PI3K-delta syndrome.
While undergoing the genomic testing, the boy was started on retrieval individualized therapy. It was only when the combination of CyVe cycle with idelalisib and obinutuzumab was used that the disease was stabilized. A new biopsy on 9/2015 showed a CD20 positive tumor, with high degree of proliferation, strong expression of PD-1L and according to the whole transcriptome analysis increased level of PI3K and HR23B, which can be good predictor of response to HDAC inhibitors as valproic acid.
The treatment was changed according to the new findings. He continued with ibrutinib/idelalisib/low dose cyclophosphamide/nivolumab and valproic acid and as of March 2016 the boy is doing very well with Lansky score 100 and OS > 15 months. He has had partial response of the single residual abdominal tumor disease with immune-related adverse His 3rd EFS /7 months/ on personalized therapy is already the longest EFS, compared to 6 months 1st EFS on standard BFM protocol.
The case may illustrate a new variant of Activated PI3K-delta syndrome (APDS). This boy has an atypical germinal mutation in the gene that probably led to the lymphoid hyperplasia, and increases the risk of malignant transformation to B-cell lymphoma. It is our hope that this case illustrates a potential for keeping even children with poor prognosis due to genomically complex cancers at home.

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Pediatric low-grade gliomas with CRAF and BRAF gene fusions respond differentially to targeted therapeutics based on their dimerization profiles

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BACKGROUND: Pediatric low-grade gliomas (PLGGs) are the most commonly diagnosed brain tumors in children. PLGGs have been defined by activating BRAF gene mutations/fusions that dysregulate the mitogen-associated protein kinase (MAPK) pathway, leading to 11 clinical testing of MAPK inhibitors for PLGGs. However, recent largescale sequencing studies have also identified novel CRAF (or RAF1) fusion proteins, QKI-RAF1 and SRGAP3-RAF1, as potential PLGG driver mutations. As CRAF and BRAF are shared targets of MAPK therapeutics, we sought to investigate the mechanistic and /or differential response of CRAF fusions to clinically relevant RAF inhibitors and downstream pathway inhibitors. We focused on comparing the effects and dependency on RAF dimerization for successful targeting.
MATERIALS & METHODS: Heterologous cell model systems with stable expression of CRAF fusions were generated and used for testing downstream signaling pathways via immunoblotting. Soft agar assays and mouse flank xenografts were used to characterize oncogenic properties. We tested responsiveness to first - and second-generation RAF inhibitors, PLX4720 and PLX8394 respectively, novel RAF dimer inhibitors, MEKi, and mTORi as single agents or in combination. Mycand Flag-tagged constructs of CRAF fusions were used in coimmunoprecipitation assays to assess dimerization profiles of CRAF fusions with or without inhibitors.
RESULTS: We found that CRAF fusions respond differentially than BRAF-fusions and do not respond to RAF inhibitors, show partial response to single-agent MEK inhibitors, but robustly respond to combinatorial targeting of both MAPK and PI3K pathways and novel RAF dimer inhibitors. Upon comparing the homo- and heterodimerization profiles of QKI-RAF1and BRAF fusions in the presence of RAF inhibitors, we found that QKI-RAF1 retains robust homo- and hetero-dimerization that, in contrast, are disrupted in BRAF fusions that respond to RAF inhibitors. This suggests that dimerization is essential for MAPK pathway activation and determines responsiveness to RAF inhibitors. Furthermore, we tested the novel RAF dimer

inhibitor, LY3009120, and found that LY3009120 stabilized CRAF fusions in an inactive dimer conformation and suppressed oncogenic potential.
CONCLUSIONS: In summary, our work demonstrates that CRAF fusions are distinct from BRAF fusions in responsiveness to targeted therapies. Our study suggests that molecular classification of PLGGs should inform therapeutic intervention of RAF-altered PLGGs even within RAF-mutant subtypes.

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Translating discovery into cures for children with cancer: Childhood cancer research landscape report

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Purpose: Cancer is the leading cause of death by disease in the United States for children ages 1 to 19, with more than 14,500 children ages 1 to 19 facing a diagnosis this year. While 5-year survival rates have improved significantly, survivors still experience high rates of long-term and late effects. The goal of this report is to examine the process for – and unique challenges of – conducting childhood cancer research and drug development and how the process is both similar and different than for adults.
Methods: Incidence and mortality data were determined using data from the SEER database. Interviews with key opinion leaders were also conducted. Literature searches provided additional information.
Results:
• Childhood cancers are often biologically different than adult cancers, meaning that childhood-specific research is required.
• Side effects from treatment significantly impact children's health because the treatments occur during a time of vital physical and mental development. Longer survival times mean more time for late effects to appear and further impact health.
• The rarity of childhood cancers makes recruiting children to participate in clinical research challenging and also means that the financial incentives to develop and market drugs specifically for these children are too small to entice significant industry research.
Conclusions and Implications: Childhood cancer has distinct research needs from adult cancer that includes addressing different cancers and a greater focus on reducing side effects. These challenges will require a higher level of coordination between research, advocacy, and regulatory communities than exists in adult cancer drug development.
Acknowledgement of Funding.
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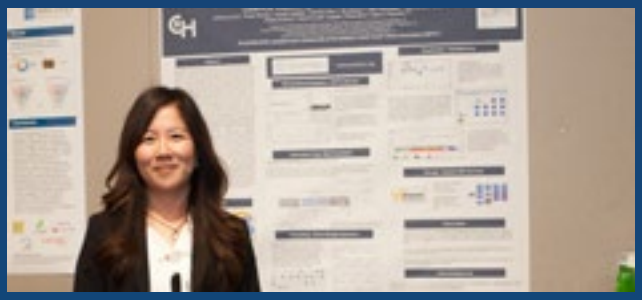


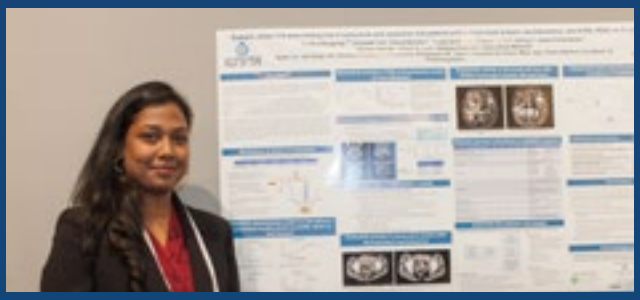
Cavatica: empowering research with a pediatric genomic cloud

Pichai Raman, Alex S Felmeister, Phillip B Storm, Rishi R.Lulla, Angela J Waanders, and Adam C Resnick, on behalf of the complete team membership of the Children's Brain Tumor Tissue Consortium (CBTTC).

Abstract #110

Clinical Pipeline Winner:

Sunitha Rangaraju
Ignyta Pharmaceuticals



Pediatric phase 1/1b dose-finding trial of entrectinib with expansion into patients with primary brain tumors, neuroblastoma, and NTRK, ROS1, or ALK fusions

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Abstract #209

Poster Session attendees selected the Poster Winners by ballot voting. Winners each received a $500 prize awarded by CAC2 Organizational Member, the Steven G. AYA Cancer Research Fund.

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