Caroline Symmes Foundation Updates and Future Plans

7 November 2019

Riley Hospital for Children
Indiana University Health

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Critical Importance of Pediatric Cancer Data

Even our most effective treatments don't work for all patients

Improve understanding of why some cancers develop resistance or don't respond to treatment

Virtually no progress for some cancer types

Generate new ideas for interventions

Short- and long-term adverse effects of cancer and its treatment

Identify less toxic treatments and strategies for management

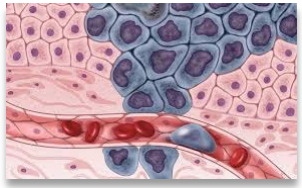
Our Mission…

To develop effective, higher-quality healthcare and to provide insights that will accelerate the development of better treatments for improving outcomes for children with aggressive cancers. Our ultimate goal is to optimize efficacy and minimize toxicity of life-saving treatments for childhood cancer.

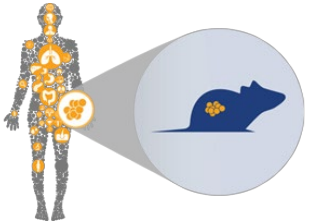
What Is Precision Oncology?

Child with high risk, refractory or relapsed cancer

Blood sample



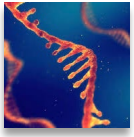
Tumor Biopsy



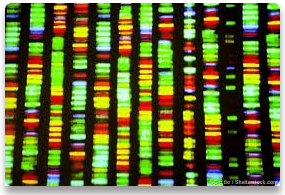
PDX model

Normal DNA

Tumor DNA

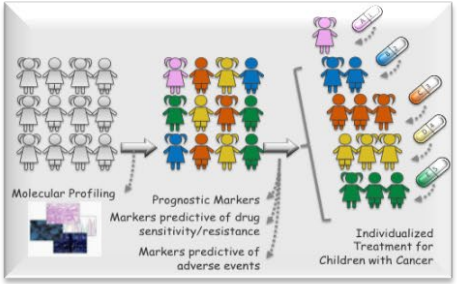


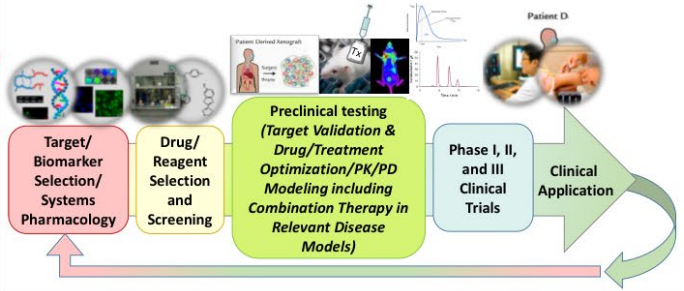
Tumor RNA



- Somatic (tumor) mutations
- Germline (hereditary) cancer gene variants
- Cancer gene expression

Optimization of therapeutic approaches for children with aggressive solid tumors using precision medicine





Aim 1: Clinical Therapeutic Tailoring (

Aim 2: Preclinical Assessment of Potential Predictive Biomarkers

OUR GOALS

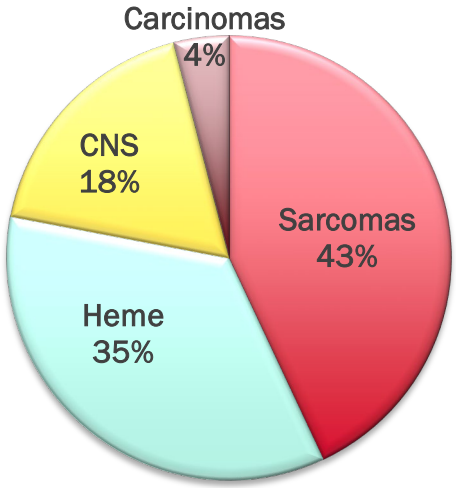
- ***Provide*** additional or ***new options*** for children without a standard option
- Translate genomic & pharmacogenomic medicine into pediatric oncology
- Consider both efficacy & toxicity for best drug selection
- Follow patient responses for evidence of success & failure

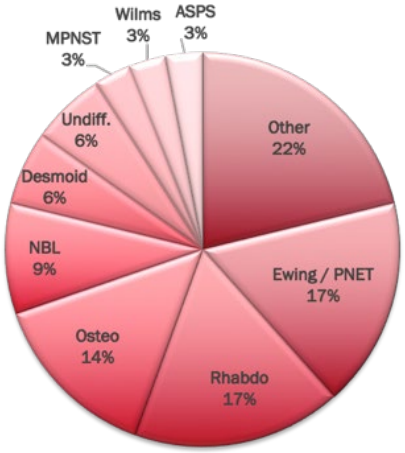
Aim 3: Bioinformatics-Systems Pharmacology: Novel Pediatric Cancer Targets

Three Year History of Precision Genomics at Riley Hospital for Children

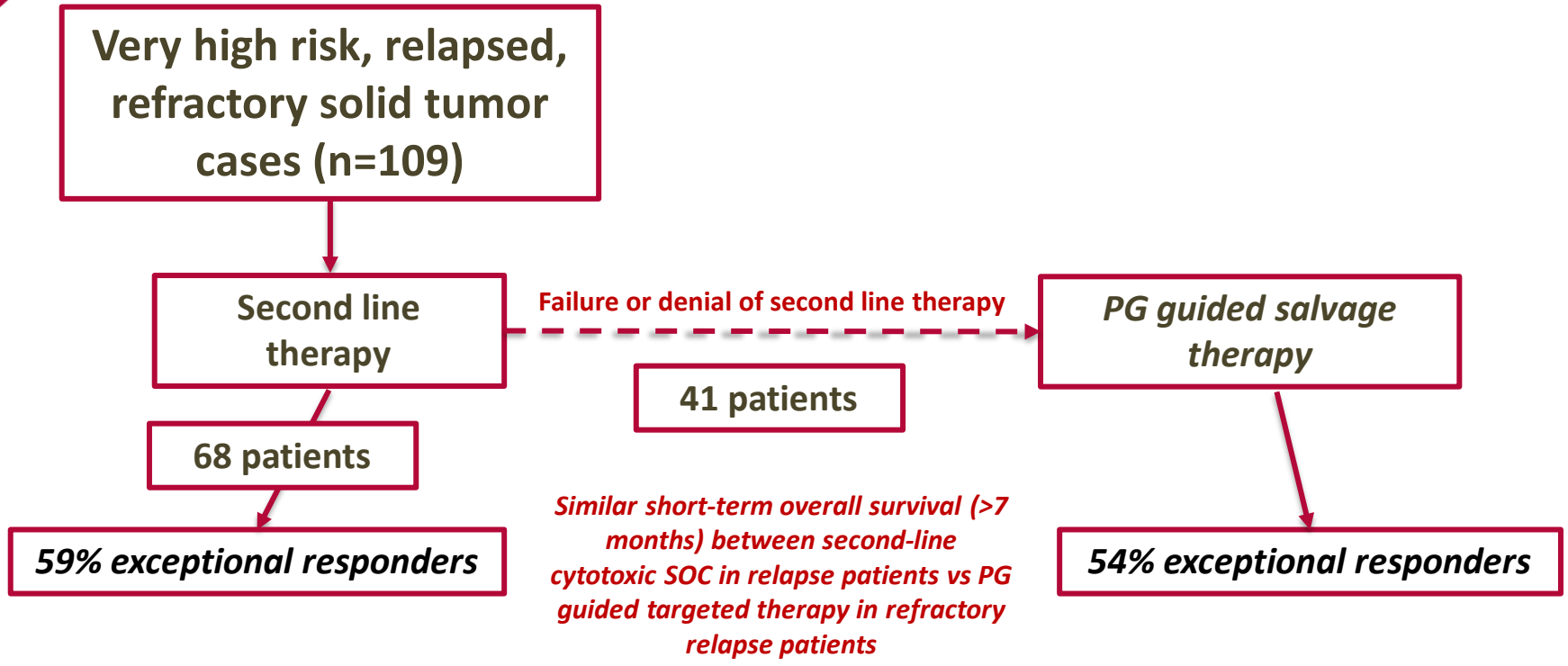
296 VHR, relapsed, refractory cases referred → 225 cases sent for analysis → 172 cases successfully analyzed → 136 (46%) cases receive treatment recommendations

- 50% cases do not receive PG guided therapy
- **50% cases receive PG guided therapy**



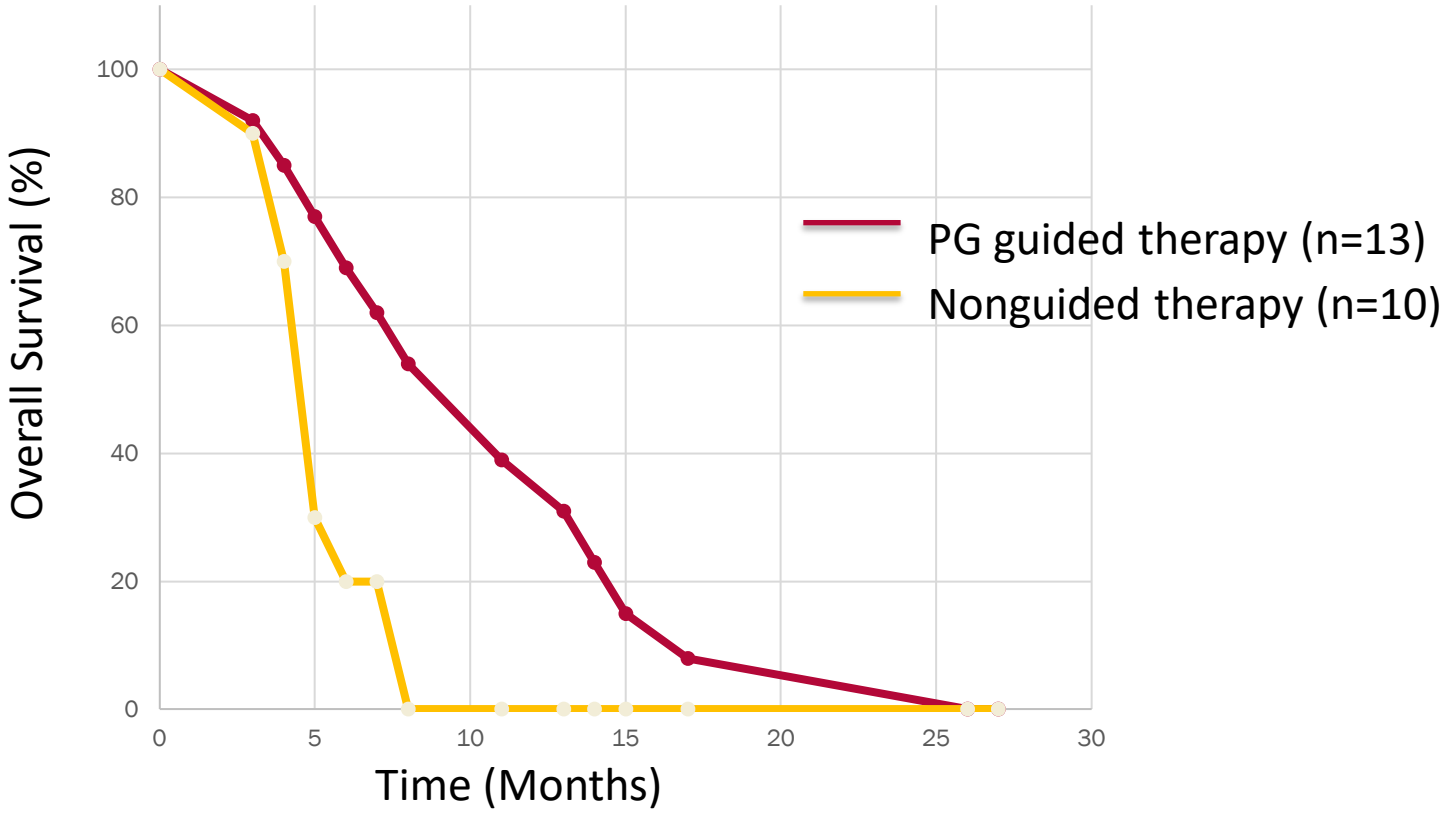


Identification of Exceptional Solid Tumor Responders in Riley Precision Genomics Program



Exceptional responders here defined as >9 month event free survival.

Solid Tumor Patient Survival During Participation in Precision Genomics Program – An Very Early Look



Internal and Collaborative Pediatric Cancer Genomics Database Sharing Efforts

- Internal to Indiana University – The Precision Health Cloud. A repository for clinical and genomic data acquired for adult and pediatric cancer patients within the IU Health system
  - Clinical and genomics viewers for individual patients
  - Patient cohort building capability
  - Clinical trial searching
  - Data analysis through dedicate tools and cBioPortal

- External to Indiana University - The Oncology Research Information Exchange Network (ORIEN)
  - Research partnership among top cancer centers
  - Large scale data sharing of both adult and pediatric cancer patient data. 20,700+ AYA patients consented to date.
  - DNA and RNA sequencing provided by TGen. Sequencing completed for 1000+ AYAs

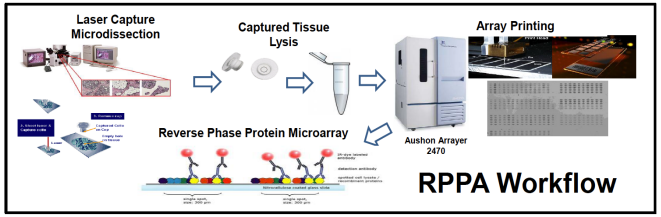
New Research Projects Launching as a Results of Your Support

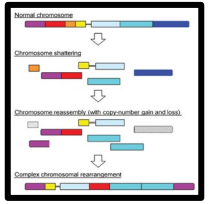
- Clinical trials
  - Molecular-guided maintenance therapy for metastatic sarcoma
  - Palbociclib combined with chemotherapy In pediatric patients with recurrent/refractory solid tumors

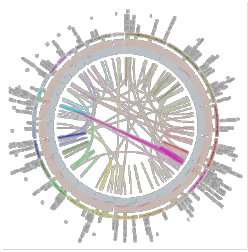
- Collaboration with George Mason University to develop CLIA/CAP proteomic analysis to support mRNA biomarker findings in patients (Emanuel Petricoin).

- Understanding mechanisms driving the origin of pediatric sarcomas: Chromoanagenesis (Bryan Helm, IUSM)

- Complex germline mechanisms of sarcoma predisposition (Bryan Helm and Francesco Vetrini, IUSM)







Autosomal dominant cancer-predisposition genes (60) + Autosomal recessive cancer-predisposition genes (29) + Tyrosine kinase genes (23) + Tumor-suppressor genes (58) + Other cancer genes (395) = **Total (565)**

Cancer Predisposition									RASopathy	
ALK	*CDC73*	*DICER1*	*MLH1*	*PAX5*	*RB1*	*SDHC*	*SUFU*	*WT1*	*BRAF*	*NRAS*
APC	*CDH1*	*EPCAM*	*MSH2*	*PHOX2B*	*RET*	*SDHD*	*TMEM127*		*CBL*	*PTPN11*
BAP1	*CDK4*	*FH*	*MSH6*	*PMS2*	*RUNX1*	*SMAD4*	*TP53*		*HRAS*	*RAF1*
BMPR1A	*CDKN1C*	*GATA2*	*NF1*	*PRKAR1A*	*SDHA*	*SMARCA4*	*TSC1*		*KRAS*	*SHOC2*
BRCA1	*CDKN2A*	*MAX*	*NF2*	*PTCH1*	*SDHAF2*	*SMARCB1*	*TSC2*		*MAP2K1*	*SOS1*
BRCA2	*CEBPA*	*MEN1*	*PALB2*	*PTEN*	*SDHB*	*STK11*	*VHL*		*MAP2K2*	

Linking Patient-specific molecular profiles and clinical treatment history with patient-derived tumor models

- Relapsed Osteosarcoma
- Metastatic Wilms Tumor

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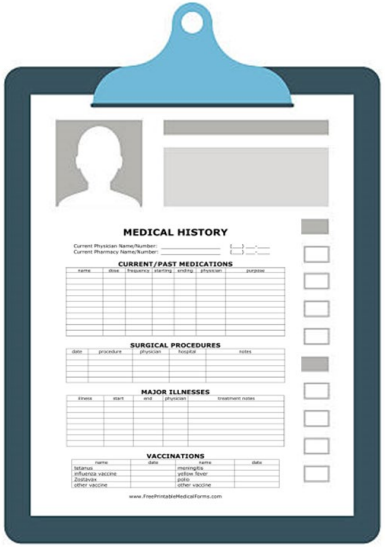
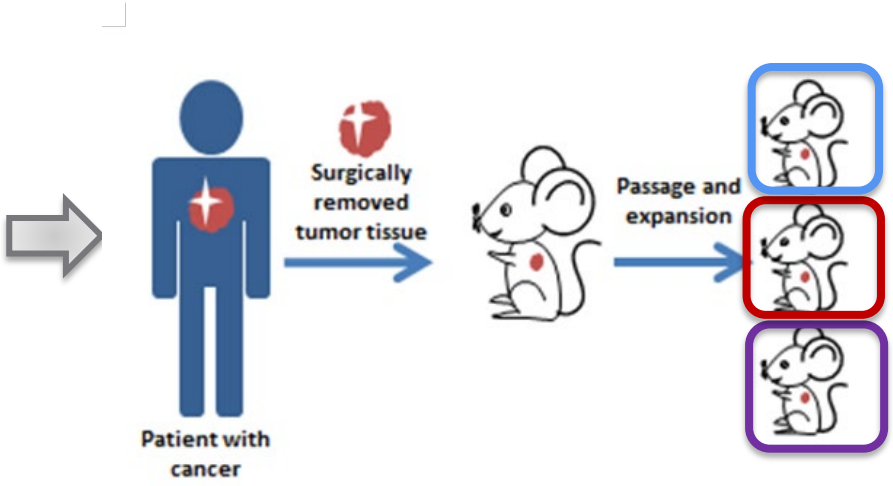
Precision Genomics Program at Riley: Pipeline for Studying Pediatric Cancers Going From The Clinic to Research Lab

Patient Clinical History



Development of Osteosarcoma Models



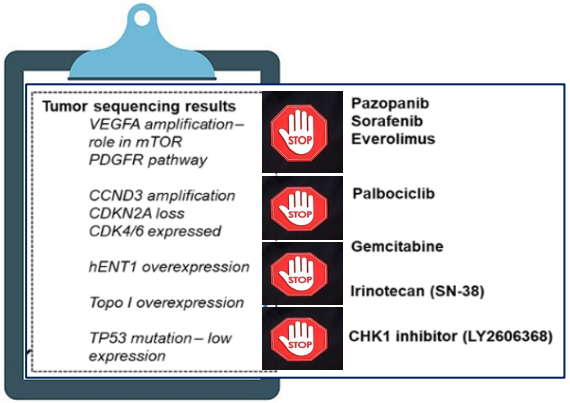
Screening of Osteosarcoma Model

Tumor Profiling for Mutations

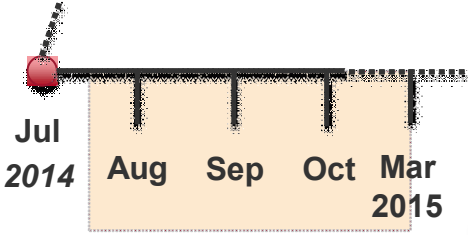
Osteosarcoma Example: Riley Precision Genomics Pipeline
Designing new treatments for Pediatric Cancers
Integration of clinical data with the research lab

Relapse & Biopsy
Patient Referred
to PG

PG directed
therapy I



Osteosarcoma
Diagnosis

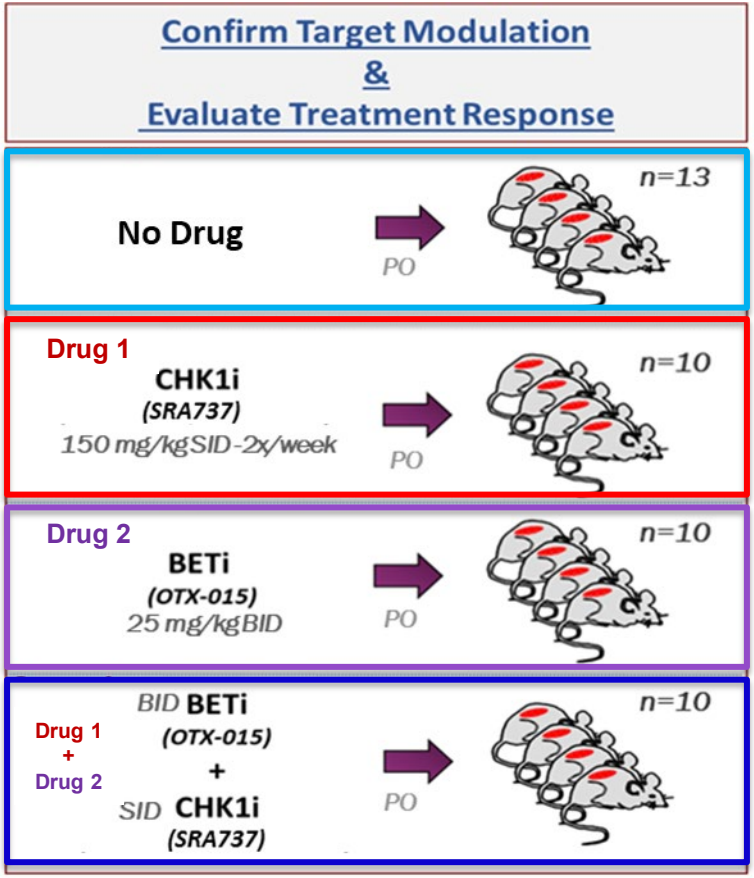


First -Line Therapy
Standard-Care of Agents
(Chemotherapy, Surgery)

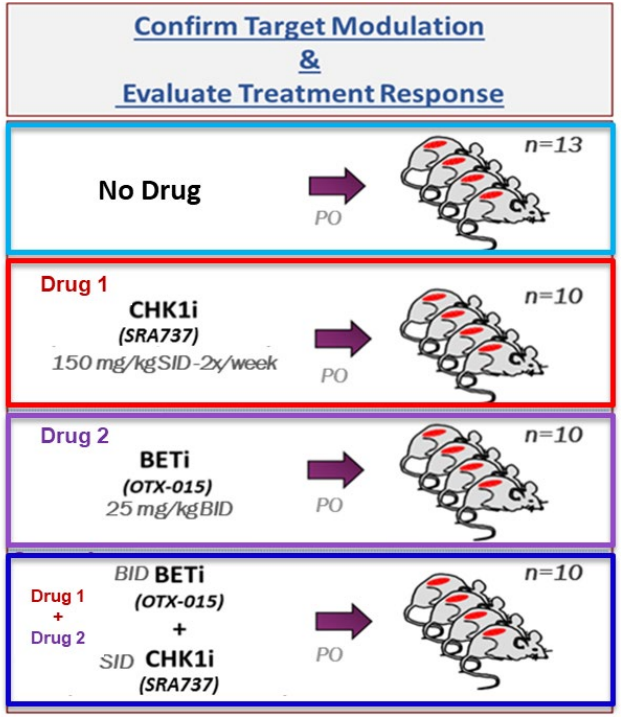
Tumor Resection
Sample Collected (TT1)

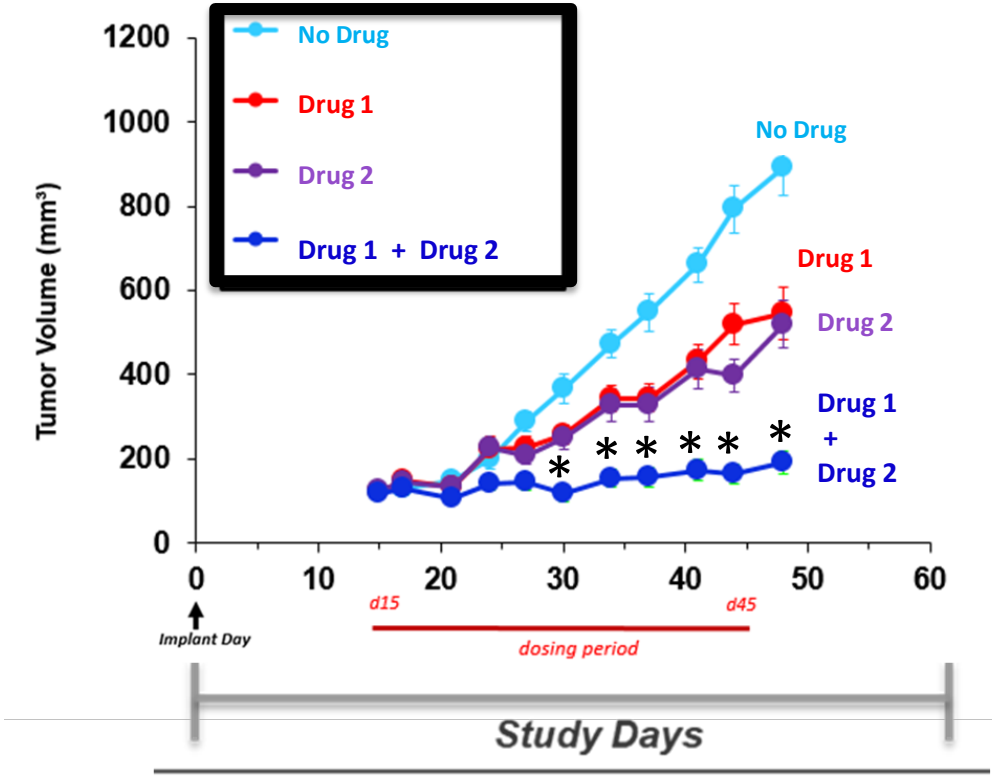
Tumor Resection
Sample Collected (TT2)

Screening of TT2 Relapsed Osteosarcoma Model: Targeting the Identified Mutations



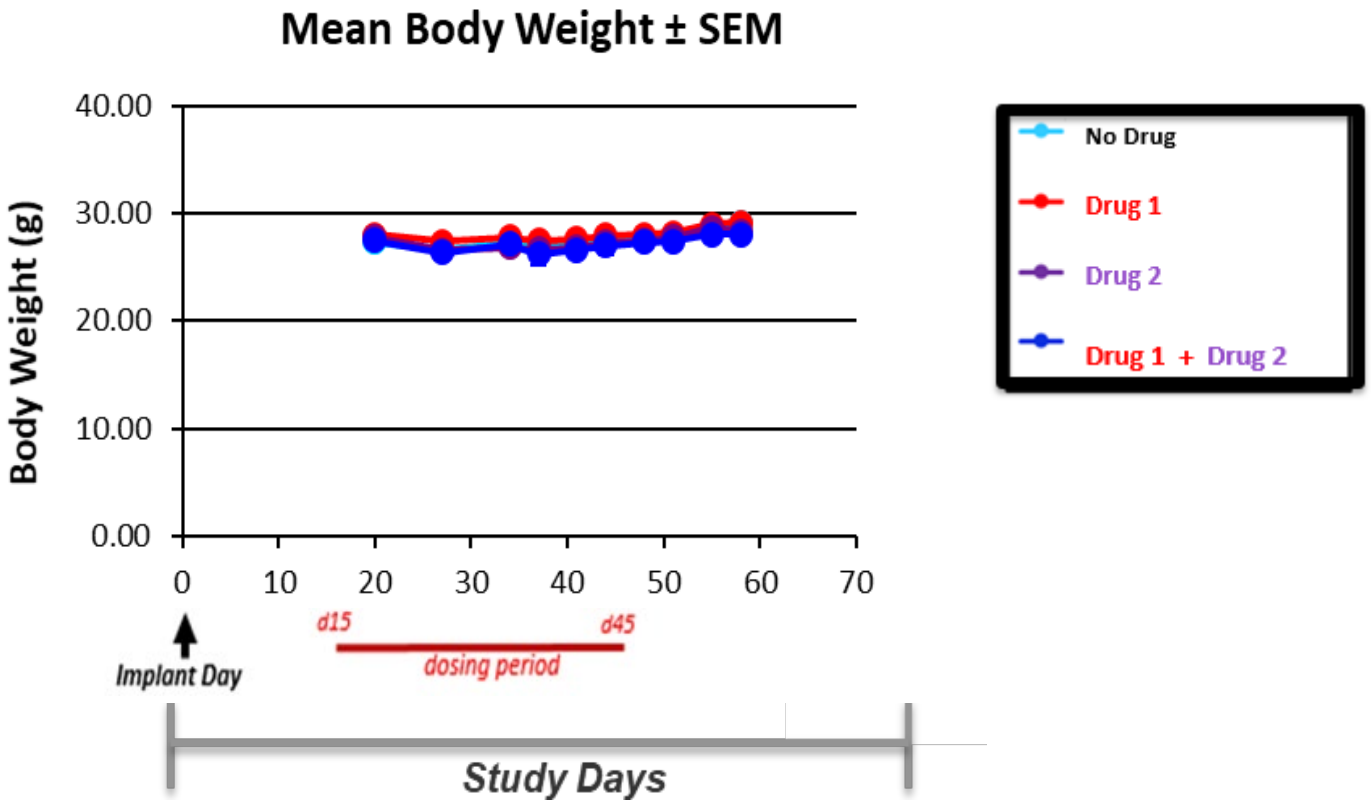
Drug Combination Blocks Tumor Growth The Best





Tumor growth over time

Drug Combination Therapy Is Well-Tolerated (Not Toxic) and Efficacious



Body weights over time

“Targeting the in-vivo adaptive response induced by inhibition of RAS/PI3K hyperactivation in Wilms tumor xenografts “

Principal Investigator: M. Reza Saadatzadeh

Co-investigators: Karen E. Pollok, Khadijeh Bijangi-Vishehsaraei, Pankita Pandya and Jamie Renbarger

Funded research project through the Wells Center for Pediatric Research

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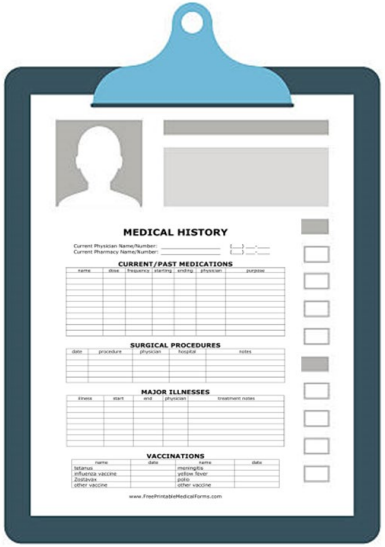
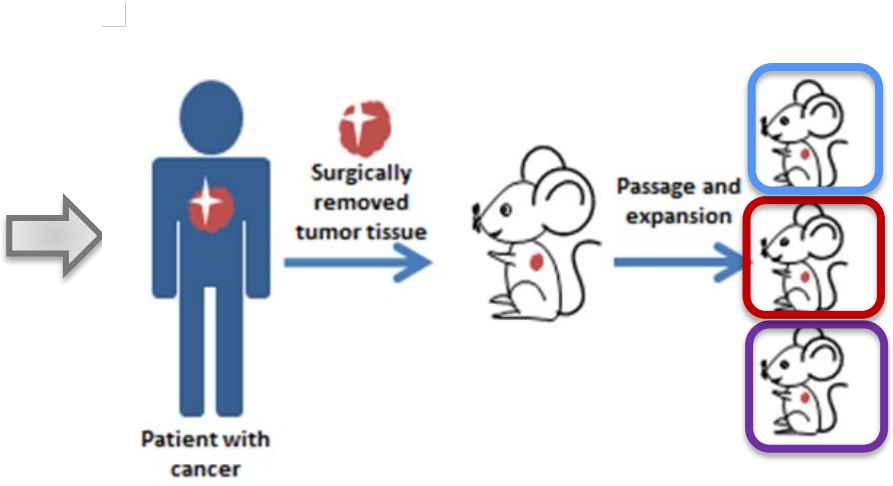
Patient Clinical History



Development of Wilms Tumor Models



Screening of Wilms Tumor Model

Tumor Profiling for Mutations

Treating metastatic Wilms tumor

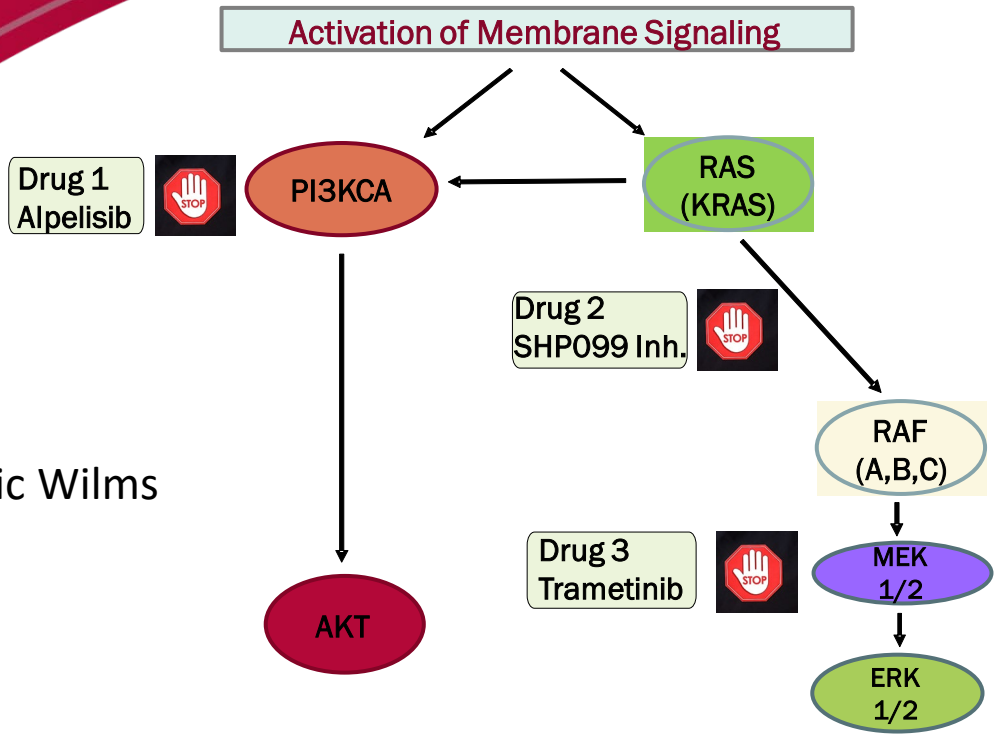


Figure 1. Hyperactivationof RAS/PI3K signaling in metastatic RHT120 PDX.

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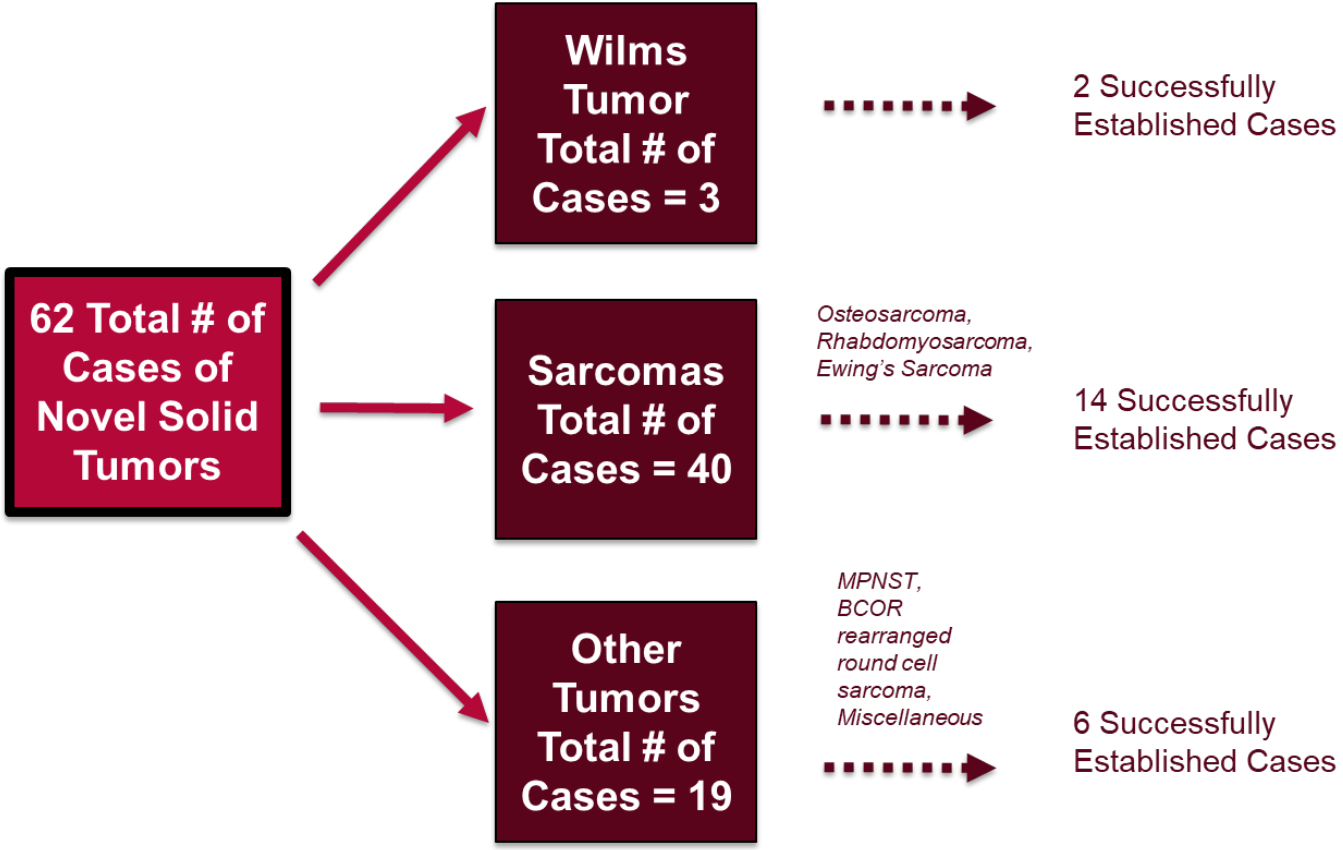
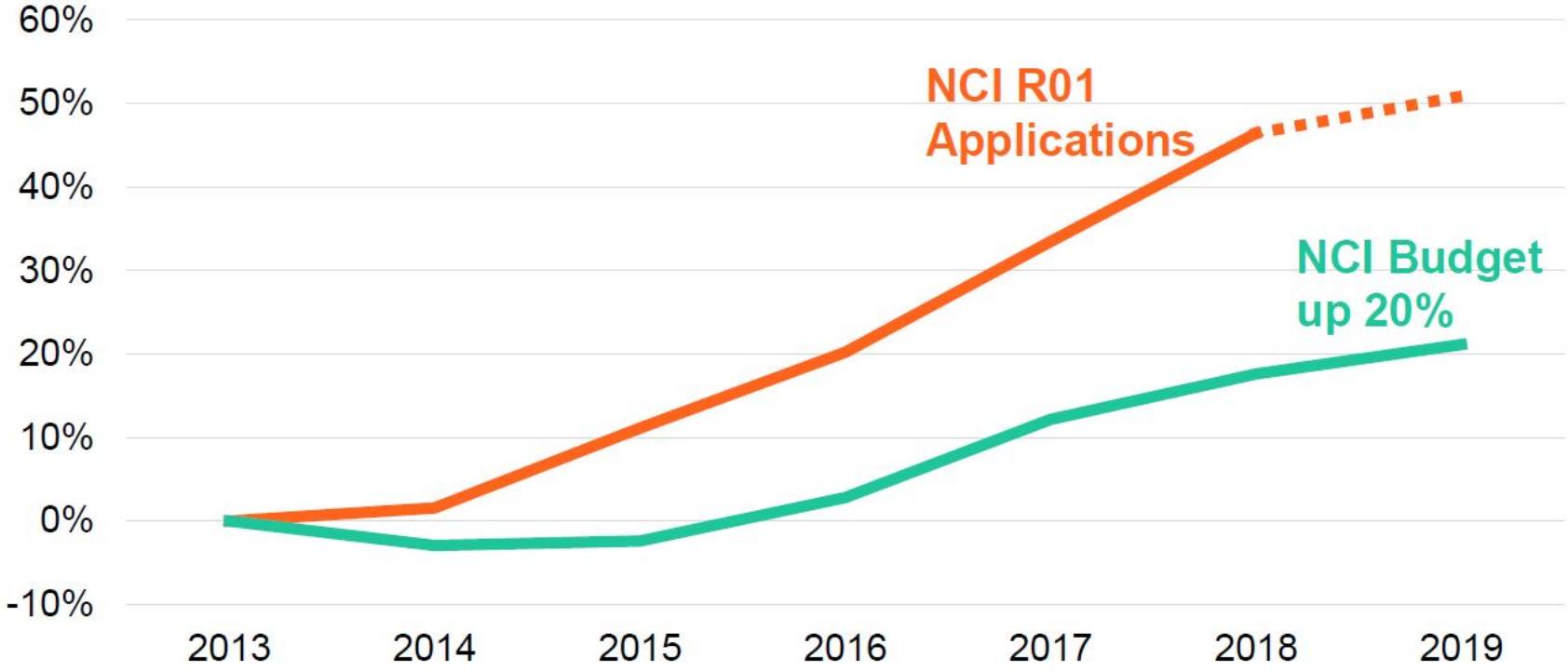
Development of Models to Study Aggressive Pediatric Cancers



Competing R01 applications vs. NCI budget:
Percent change since FY 2013



NIH NATIONAL CANCER INSTITUTE

R01 applications source: NIH RePORTER. 2019 applications estimated.
NCI budget shown here is the base appropriation; does not include Cancer Moonshot.

Despite our success in markedly increasing survival in pediatric cancer patients, there are gaps

You are helping to support:

- Better science to unravel the molecular underpinnings that drive childhood cancer.
- Investigating targeted and combination therapies for better clinical outcomes

Your continued support will help with:

- Designing and executing novel clinical trials aimed at establishing effective strategies to improve outcomes for progressively smaller subsets of drug-resistant cases with specific genetic/molecular alterations.

A Partnership of Intramural and Extramural Resources

Foundations: Supporting pediatric cancer research

NIH/NICHD U54 (2016-2021)

Indiana University Center for Pediatric Pharmacology and Precision Medicine (ICP3M)

(MPIs: Renbarger & Pollok)

Renewal (Due 2021)

IU School of Medicine (PHI, et al): Expand our capabilities to find new options to improve outcomes in children with aggressive disease, including Data and Informatics Sciences.

(MPIs: Renbarger, Pollok, Clapp, Huang)

A big thank you for all your support and dedication!

HOPE HAPPENS HERE

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Supporting Riley Hospital for Children • Camp Riley • Riley Museum Home

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DEPARTMENT OF PEDIATRICS
School of Medicine

Connecting Research with Kids
Herman B Wells Center For Pediatric Research