Outline

• Childhood cancer incidence, survival, and mortality
• NCI research programs for children with cancer
• TARGET update
• How to move forward and identify more effective treatments?
Mortality for All Malignant Cancers (Age < 20 years): 1975 to 2010

Mortality for All Leukemia/Lymphoma versus Other Cancers (Age < 20 years): 1975 to 2010

Childhood Cancer Incidence (< 20 years, SEER 9 registries from 1975 – 2010)

- **All Sites Combined, APC=0.59***
- **All Sites Other than Lymphoid Leukemia and CNS, APC=0.47***
- **Lymphoid Leukemia, APC=0.75***
- **Central Nervous System, APC1=-0.62, APC2=9.56, APC3=0.14**

Five-year Relative Survival for Bone Sarcomas

**Osteosarcoma**

<table>
<thead>
<tr>
<th>Years</th>
<th>&lt;15 years</th>
<th>15-19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975-78</td>
<td>59%</td>
<td>20%</td>
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<tr>
<td>1979-82</td>
<td>45%</td>
<td>38%</td>
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<tr>
<td>1983-86</td>
<td>56%</td>
<td>51%</td>
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<tr>
<td>1987-90</td>
<td>47%</td>
<td>55%</td>
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<tr>
<td>1991-94</td>
<td>74%</td>
<td>74%</td>
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<tr>
<td>1995-98</td>
<td>73%</td>
<td>73%</td>
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<tr>
<td>1999-02</td>
<td>60%</td>
<td>76%</td>
</tr>
<tr>
<td>2003-07</td>
<td>78%</td>
<td>80%</td>
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</tbody>
</table>

**Ewing's sarcoma**

<table>
<thead>
<tr>
<th>Years</th>
<th>&lt;15 years</th>
<th>15-19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975-78</td>
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<td>45%</td>
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</tr>
<tr>
<td>1987-90</td>
<td>68%</td>
<td>55%</td>
</tr>
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<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>1995-98</td>
<td>70%</td>
<td>73%</td>
</tr>
<tr>
<td>1999-02</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>2003-07</td>
<td>76%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Five-year Relative Survival for CNS Cancers

CNS tumors other than medulloblastomas

- 1975-78: 52%, 65%, 60%
- 1979-82: 56%, 60%, 63%
- 1983-86: 63%, 63%, 74%
- 1987-90: 64%, 68%, 75%
- 1991-94: 67%, 73%, 77%
- 1995-98: 79%, 77%, 78%
- 1999-02: 77%, 75%, 82%
- 2003-07: 79%, 77%, 77%

Medulloblastoma

- 1975-78: 49%, 45%, 45%
- 1979-82: 45%, 57%, 79%
- 1983-86: 49%, 62%, 77%
- 1987-90: 37%, 71%, 75%
- 1991-94: 44%, 67%, 71%
- 1995-98: 49%, 81%, 85%
- 1999-02: 57%, 79%, 79%
- 2003-07: 57%, 73%, 58%

Mortality for All Malignant Cancers (Age < 20 years): 1975 to 2010

> 45,000 deaths averted since 1975

Overall survival mask cancers for which outcome remains highly unfavorable

- For some brain cancers (e.g., DIPG & supratentorial high-grade gliomas), outcome has not improved over the past 3 decades.
  - Note: the poorer outcome in the more recent period is the result of more precise diagnosis of DIPG and exclusion of brainstem low-grade gliomas.
Causes of Childhood Cancer Mortality

~ 2000 children and adolescents die of cancer each year in the US

1. **<15 Year Mortality 2007-2010**
   - CNS, 31%
   - ALL, 13%
   - AML, 9%
   - Oth Leuk, 7%
   - Bone, 5%
   - Soft Tissue, 6%
   - Neuroblastoma, 11%
   - Hodgkin, 0.2%
   - NHL, 3%
   - Gonads, 0.2%
   - Liver, 3%
   - Other, 7%

2. **15-19 Year Mortality 2007-2010**
   - CNS, 16%
   - AML, 10%
   - Oth Leuk, 7%
   - Bone, 16%
   - Neuroblastoma, 2%
   - Soft Tissue, 10%
   - NHL, 7%
   - Hodgkin, 2%
   - Gonads, 2%
   - Liver, 2%
   - Other, 14%

Childhood Cancer Survivor Study (CCSS)

- Retrospectively ascertained cohort of survivors of pediatric cancer diagnosed between 1970-1986:
  - Cohort initiated with first CCSS award in 1994
  - 14,370 long-term (five-year or more) survivors of childhood cancer diagnosed between 1970 and 1986
  - 3,737 sibling controls recruited for comparison purposes

- Data collected:
  - Clinical data on malignancy and treatment abstracted from medical records
  - Self-reported data on risk factors (e.g., family history), and health and psychosocial outcomes data collected via baseline and follow-up questionnaires

- Biospecimens; second cohort (1987-1999); intervention studies, public use dataset
NCI’s Investment in Pediatric Cancer Research

- The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative
- The Pediatric Preclinical Testing Program (PPTP)
- COG Phase 1 / Pilot Consortium
- Pediatric Brain Tumor Consortium
- NCI intramural program
- Children’s Oncology Group (COG)
- Childhood Cancer Survivorship Study (CCSS)
- Investigator-initiated research projects
- Other research
## Comprehensive Characterization

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patient Data</th>
<th>Case # (Relapse)</th>
<th>Chip-based</th>
<th>Sequencing</th>
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<tbody>
<tr>
<td>Acute Lymphoblastic Leukemia (P-I)</td>
<td>Y</td>
<td>189 (0)</td>
<td>Y Y</td>
<td>&lt;Y</td>
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<tr>
<td>Acute Lymphoblastic Leukemia (P-II) (ALL)</td>
<td>Y</td>
<td>184 (84)</td>
<td>Y Y</td>
<td>&lt;Y</td>
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<tr>
<td>Acute Myeloid Leukemia</td>
<td>Y</td>
<td>200 (100)</td>
<td>Y Y Y Y</td>
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<td>Induction Refractory Acute Myeloid Leukemia</td>
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<td>30 (25)</td>
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<tr>
<td>Neuroblastoma (NBL)</td>
<td>Y</td>
<td>180 (9)</td>
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<td>&lt;Y</td>
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<td>Osteosarcoma</td>
<td>Y</td>
<td>92 (0)</td>
<td>Y Y Y Y</td>
<td>&lt;Y</td>
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<tr>
<td>Wilms Tumor</td>
<td>Y</td>
<td>113 (5)</td>
<td>Y Y Y Y</td>
<td>&lt;Y</td>
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<tr>
<td>Clear Cell Carcinoma of the Kidney</td>
<td>Y</td>
<td>13 (0)</td>
<td>Y Y &lt;Y</td>
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<td>Rhabdoid Tumor (kidney)</td>
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<td>40 (0)</td>
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<td>Pediatric Preclinical Testing Program</td>
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<td>ALL Xenografts</td>
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<td>33 [244]</td>
<td>Y Y</td>
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<td>NBL Models</td>
<td>L</td>
<td>7 [27]</td>
<td>Y Y</td>
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</table>

L=Limited [# of samples]
Validation in New Cohorts, in progress

~400 genes to 500X coverage

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
<th>Patient Data</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>800</td>
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<td>1597</td>
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<tr>
<td>Neuroblastoma</td>
<td>500</td>
<td>Y</td>
<td>1000</td>
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<tr>
<td>Wilms Tumor</td>
<td>570</td>
<td>Y</td>
<td>670</td>
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Planned

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Acute Lymphoblastic Leukemia</td>
<td>750</td>
<td>Y</td>
<td>1500</td>
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<tr>
<td>Osteosarcoma</td>
<td>200</td>
<td>Y</td>
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</table>
TARGET Initiative:

**Tissue Specimens COG & BPC**

- **Transcriptomic Profiling**
- **Disease Expertise**
- **Sequencing**
- **Genomic Characterization**

All data types except raw sequence files are stored the DCC.
Selected Vignettes
Favorable Histology Wilms Tumors: Mutations in miRNA Processing Genes

- 15 / 79 cases somatic
- 5 / 79 cases germline

DGCR8
- p.E518K (4)
- p.P61T
- p.R414
- WW Domain
- dsRNA-bd
- dsRNA-bd
- 774

DROSHA
- p.Q46
- Arg-Rich
- Pro-Rich
- RNase IIIA
- RNase IIIB
- 1975

XPO5
- p.R159
- p.R440
- p.V632I
- p.M1082fs
- Expertin-1
- 1250

DICER1
- p.I85M
- Dicer Dimer
- p.R1368C
- p.Y1874
- DEAD/DEAH
- Helicase C
- PAZ
- RNase IIIA
- RNase IIIB
- 1923

E. Perlman & WT PT, unpublished

Black = Somatic Mutation
Red = Germline Mutation
Osteosarcoma Genomes Are Mostly Rearranged
Integrated Genomics of Osteosarcoma

Mutations in 92 tumors

AT LEAST 1 OF THESE 8 GENES: 96%

C. Lau, P. Meltzer & OS PT, unpublished
Gene Mutations are Different in Children vs. Adults with Acute Myeloid Leukemia

S. Meshinchi, R. Arceci and AML PT
83% of Acute Myeloid Leukemia Cases Have Mutations in 11 Functional Categories

Tyrosine Kinases    Transcription Factors    Tumor Suppressors    RAS family    Protein Phosphatases    Epigenetic Modifiers    Nuclear Transport    Spliceosome    ETS    Cohesin    Oncogenes

0.38    0.33    0.23    0.19    0.17    0.12    0.09    0.04    0.03    0.02    0.02

S. Meshinchi, R. Arceci & AML PT, unpublished
Publications from the ALL Team

- Ph-like ALL, IKZF1 deletions and mutations (Mullighan, NEJM 2009)
- JAK mutations in HR-ALL (Mullighan, PNAS 2009)
- CRLF2 genomic alterations in HR and Down syndrome ALL (Mullighan, Nature Genetics 2009; Harvey, Blood 2010; Chen Blood 2012)
- Expression profiles-supervised (Kang, Blood 2010)
- Expression profiles-unsupervised (R8 group) (Harvey, Blood 2010)
- Recurrent mutations in 4 key pathways in HR ALL (Zhang, Blood 2011)
- Kinase activating lesions (Roberts, Cancer Cell 2012) but no point mutations (Loh, Blood 2013) in Ph-like ALL
- GATA3 SNPs and risk of Ph-like ALL (Perez Andreu Nature Genetics 2013)
- Comprehensive genomics of Ph-like ALL (Roberts, submitted)
Gene Fusions Discovered in BCR-ABL1-like Acute Lymphoblastic Leukemia

- Unsupervised analysis of gene expression data identified a Ph+ like “signature” without BCR-ABL1 fusion transcript
- Sequence analysis of kinase genes found mutations in RAS (~30%), JAK2, but nothing which would explain the expression profile
- mRNA-seq identified at least one chimeric transcript in most of these cases

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Known fusions</th>
<th>New fusions</th>
</tr>
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<tbody>
<tr>
<td>PAKHZT</td>
<td>IGH@-CRLF2</td>
<td></td>
</tr>
<tr>
<td>PAKKCA</td>
<td></td>
<td>EBF1-PDGFRB</td>
</tr>
<tr>
<td>PAKKXB</td>
<td>IGH@-CRLF2</td>
<td></td>
</tr>
<tr>
<td>PAKTAL</td>
<td></td>
<td>STRN3-JAK2</td>
</tr>
<tr>
<td>PAKVKK</td>
<td></td>
<td>NUP214-ABL1</td>
</tr>
<tr>
<td>PAKYEP</td>
<td></td>
<td>BCR-JAK2</td>
</tr>
<tr>
<td>PALETF</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>PALIBN</td>
<td></td>
<td>IGH@-EPOR</td>
</tr>
<tr>
<td>PALJDL</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>PAMDRM</td>
<td>IGH@-CRLF2</td>
<td></td>
</tr>
<tr>
<td>PANNGL</td>
<td></td>
<td>PAX5-JAK2</td>
</tr>
<tr>
<td>PANSFD</td>
<td></td>
<td>ETV6-ABL1</td>
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<td>PANHEF</td>
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<td>RCSD1-ABL1</td>
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<td>SJ BALL085</td>
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<td>NUP214-ABL1</td>
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<tr>
<td>SJ BALL010</td>
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<td>RANBP2-ABL1</td>
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</table>

Results: Poor outcome of Ph-like ALL

- Childhood high risk ALL
  - COG P9906
  - Event-free survival probability
  - Not Ph-like (n = 159)
  - Ph-like (n = 41)
  - \( P < 0.0001 \)

- Adolescent
  - COG AALL0232
  - Event-free survival probability
  - Not Ph-like (n = 491)
  - Ph-like (n = 81)
  - \( P < 0.0001 \)

- Young adult

Roberts & TARGET PT, ASH Annual Meeting
Acknowledgements

❖ **CTEP**
Malcolm A. Smith MD. Ph.D. – Associate Branch Chief

❖ **OCG**
Jaime M. Guidry Auvil, Ph.D. – Scientific Program Manager
Martin Ferguson, Ph.D. – Consultant
Shannon Behrman, Ph.D. – Science Communications Manager
Jessica Mazerik, Ph.D. – Health Communications Fellow

❖ **OCG Data Coordinating Center**
Tanja M. Davidsen, Ph.D. – Bioinformatics Program Manager
Patee Gesuwan – Senior Bioinformatics Engineer
Leandro C. Hermida – Bioinformatics Scientist / Software Engineer

❖ **Leidos (SAIC) Support**
Jeanne Lewis – Senior Contract Specialist
Ellen Miller -- COTR

❖ **TARGET Project Team Members**
Precision Medicine:
Following the Adult Paradigm
Precision Medicine: Following the Adult Paradigm

- Ph$^+$ acute lymphoblastic leukemia (ALL)
- ALK$^+$ anaplastic large cell lymphoma (ALCL)
- BRAF mutations in pilocytic astrocytoma and high-grade gliomas
- Ph-like ALL
Impact of Imatinib added to standard chemotherapy for Ph+ ALL (AALL0031)

- Adding imatinib to standard chemotherapy more than tripled EFS for Ph+ ALL in COG AALL0031
- 7-yr EFS of 71.7% vs. 21.4%

Schultz K. R., Leukemia 2014
Anaplastic Large Cell Lymphoma
Anaplastic Large Cell Lymphoma in Children

• Approximately 15% of childhood NHL cases.
• NPM-ALK is oncogenic driver.
• CD30 is uniformly expressed at high levels.

Heavy chain

Auristatin derivative: average of 4 molecules per antibody

Light chain

CD30 antigen binding site

Drug binds tubulin

ADC (Brentuximab Vedotin (SGN-35)) traffics to lysosome

Endocytosis

Drug released from ADC

G2/M cell cycle arrest & apoptosis

Target

Drug binds target
Crizotinib (MET and ALK inhibitor)

- >95% of pediatric ALCL are ALK+
- ALK translocations in ALCL include:
  - t(2;5) – NPM/ALK – 85%
  - t(1;2) – TPM3/ALK – 3%
  - Inv (2) – ATIC/ALK
  - t(2;3) – TFG/ALK
  - t(2;17) – CLTC/ALK
  - t(2;X) – MSN/ALK
  - t(2;19) – TPM4/ALK
  - t(2;22) – MYH9/ALK
  - t(2;17) – ALO17/ALK
ANHL12P1: Comparison of standard chemotherapy + either brentuximab vedotin or crizotinib

- Target is 64 eligible patients per arm.
- Compare each arm to historical control: 70% EFS
Ph-Like Acute Lymphoblastic Leukemia (ALL)
Ph-like (BCR-ABL1-like) B-ALL

- Cases with a gene expression profile similar to that of Ph+ ALL (but without BCR-ABL1 fusion) (Mullighan NEJM 2009; Den Boer Lancet Onc 2009; Harvey Blood 2010; Roberts Cancer Cell 2012)

- Genomics of Ph-like ALL (as defined by COG)
  - 50% have CRLF2 alterations ± JAK mutations
  - Remainder have variety of gene fusions targeting ABL1, ABL2, CSF1R, PDGFRB, JAK2 and other kinase genes

Prognosis for Children with Ph-Like ALL

- Ph-like ALL patients have greatly increased risk of treatment failure and death

The Genomic Landscape of Ph-Like ALL
Ph-Like ALL Team

- NCH
  - Julie Gastier Foster
  - Shalini Reshmi
  - Eileen Stonerock
- SJCRH
  - Charles Mullighan
  - Kathryn Roberts
  - Jinghui Zhang
- UCSF
  - Mignon Loh
- U Colorado
  - Stephen Hunger
- UF
  - Mini Devidas
- UNM
  - Cheryl Willman
  - Rick Harvey
  - Iming Chen
Identification & Treatment of Ph-Like ALL

**Identify Ph-like ALL by LDA Card**

**Candidate testing**
- Fusions: RT-PCR
- CRLF2 alterations: FISH/PCR
- JAK/IL7RA/SH2B3 mutation

**RNA-seq**
- If candidate screens negative

**WGS**
- If above negative

**Retrospective phase (Year 1)**
- Assay all cases enrolled on: AALL1131: 1420 pts
  - Ph-like: N=230
  - ABL1/PDGFRB/ABL2/CSF1R fusions: N=58
- No changes in therapy

**Prospective phase (Years 2-4)**
- AALL1131: 2821 pts
  - Ph-like: N=456
  - ABL1/PDGFRB/ABL2/CSF1R fusions: N=114
- Change therapy based on results

**ABL1/ABL2/PDGRFB/CSF1R fusion positive:**
Add dasatinib in prospective phase and compare outcome to that of pts from retrospective phase
Grants to Support Ph-Like Clinical Translation

- SBF Consortium grant (Hunger et al); 7/1/13-6/30/16
- LLS SCOR (Carroll) Project 1 (Hunger/Mullighan); 10/1/13-9/30/18
- SPECS II (Willman/Hunger); 4/1/11-3/31/16
- Children’s Oncology Group Operations and Statistical awards (Adamson, Devidas)
Precision Medicine: Following the Adult Paradigm
~ 2000 children and adolescents die of cancer each year in the US

Children Are not Just Little Adults

• And childhood cancers aren’t just early-developing adult cancers
Childhood Cancers Show Lower Mutation Rates Compared to Adult Cancers

- Somatic mutation frequencies observed in exomes from 3,083 tumor–normal pairs

The Genomic Landscape of High-Risk Neuroblastoma

- 240 matched tumor and normal pairs (age > 18 mos and Stage 4 disease) by WES (221 cases), WGS (18 cases), or both (1 case)

Analyses of ependymoma tumors revealed a gene rearrangement in 1 subtype, but no recurring DNA mutations in 2 others:

Chromatin Remodeling Defects in Pediatric and Young Adult Glioblastoma

- K27M-H3.3 or H3.1 (yellow stars) occur mainly in brainstem HGA and K27M-H3.3 mainly thalamic HGA (70%-80% of all GBM in these locations).

Genomic Landscapes of Other Childhood Cancers

• Osteosarcoma

• Ewing sarcoma

• Rhabdomyosarcoma

• Rhabdoid tumor
A Strategy for Pediatric Precision Medicine

- Focusing on liabilities created by the primary genomic lesion or liabilities associated with the cell of origin, for example:
  - Rhabdoid tumors: SMARCB1 mutation/deletion
  - MLL leukemias: MLL gene rearrangement
  - Ewing sarcoma: EWS-FLI1
  - Alveolar rhabdomyosarcoma: PAX-FKHR
  - DIPG: Histone 3.3 K27M mutation
Rhabdoid tumors and EZH2 inhibition

- Knockout of EZH2 completely blocked the growth of SMARCB1 mutant cancers but had no effect on osteosarcomas driven by p53/Rb loss.

• MLL-rearranged leukemia is dependent on aberrant H3K79 methylation by Dot1L
• Effect of EPZ-5676 administration on MV4-11 xenograft tumors implanted SC in immunocompromised rats
Ewing Sarcoma and PARP Inhibition

- Reports of sensitivity of EWS-FLI1 expressing tumors to PARP inhibition.
- PPTP identified dramatic synergy for the PARP inhibitor BMN 673 and low-dose temozolomide
- COG Phase 1 trial ongoing: NCT02116777

A Strategy for Pediatric Precision Medicine

• Focusing on liabilities created by the primary genomic lesion or liabilities associated with the cell of origin, including:
  – Rhabdoid tumors: SMARCB1 mutation/deletion
  – MLL leukemias: MLL gene rearrangement
  – Ewing sarcoma: EWS-FLI1
  – Alveolar rhabdomyosarcoma: PAX-FKHR
  – DIPG: Histone 3.3 K27M mutation
Other Priority Clinical Research Areas

- CAR T-cell therapy (e.g., targeting CD19+ ALL)
- Bispecific T-cell engaging antibodies (e.g., blinatumomab targeting CD19+ ALL)
- Immune checkpoint inhibitors
- GD2-targeted therapies for neuroblastoma
Children Are not Just Little Adults

• And childhood cancers aren’t just early-developing adult cancers
• A pediatric-specific approach to precision medicine is needed
• Crucial to identify susceptibilities created by childhood cancer oncogenic drivers
• National and international clinical trials will be essential given the small sizes of genomically defined subgroups
• NCI has a critical role to play
Back-up Slides
Chimeric 14.18 (ch14.18) for High-Risk Neuroblastoma

Illustrating a public-private partnership strategy for pediatric drug development.
GD2: Disialoganglioside

- Over 99% of neuroblastoma expresses GD2
- Reactivities of anti-GD2 to normal tissues is confined mostly to tissues of neuroectodermal origin, e.g., skin and brain tissue
- GD2 is also expressed by selected other tumors, including melanoma and osteosarcoma
ch14.18 characteristics

- Initially developed as a murine IgG3 mAb, 14.18, that bound GD2.
- ch14.18 produced by combining cDNA sequences encoding the variable portions of 14.18 with the constant regions of the human heavy chain IgG1 and light chain κ.
- ch14.18 has potent ADCC and CDC activity
The Development of ANBL0032: phase 3 evaluation of ch14.18

- **1990’s**: Phase I and II clinical trials of ch14.18
  - ch14.18, pilot study of ch14.18+GM-CSF:Yu
  - Phase II study of ch14.18+ GM-CSF (POG9347):Yu
  - Pilot study of ch14.18 +GM-CSF/IL2 in MRD (CCG0935)
- **1998**: Agreement to conduct “intergroup” phase 3 trial by CCG + POG. NCI agrees to manufacture agent for the trial.
- **1998**: Concept Proposal submitted by COG for CTEP review
- **2000**: Protocol submitted by COG for CTEP review
- **2001**: ANBL0032 activated
- **2009**: Positive results for ANBL0032 identified
- **2009**: ANBL0032 continues as single arm study with all patients receiving ch14.18 plus cytokines
- **2009**: ANBL0931 activated
- **2010**: United Therapeutics announced as NCI CRADA partner
COG High-Risk Neuroblastoma Studies 2001 - 2014

Induction

Dx

ASCT + XRT

Randomize post-Consolidation

Consolidation

ANBL00B1

A: Isotretinoin 6 cycles

B: Immunotherapy + Isotretinoin 6 cycles

ANBL0032

ANBL02P1

ANBL0532

ANBL09P1

ANBL12P1

ANBL00P1

ANBL00B1

ANBL00P1

ANBL02P1

ANBL0532

ANBL09P1

ANBL12P1

ANBL0032
Regimen A: standard therapy
Isotretinoin (cis-RA) x 2 weeks q 4 weeks X 6 courses

Regimen B: immunotherapy
Schema for administration of ch14.18 + cytokines + cis-RA

<table>
<thead>
<tr>
<th>Course 1</th>
<th>Course 2</th>
<th>Course 3</th>
<th>Course 4</th>
<th>Course 5</th>
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<td>Cis-RA</td>
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</tr>
</tbody>
</table>
Ch14.18 + Cytokines Improves Event-free Survival for High Risk Neuroblastoma (2009)

COG-ANBL0032, - EFS randomized patients treatment 1 (n=113) & treatment 2 (n=113)

Yu, et al. NEJM 2010
Ch14.18 + Cytokines Improves Overall Survival for High Risk Neuroblastoma (2012)

COG-ANBL0032, OS patients treatment 1 (n=112) & treatment 2 (n=113)

- RA only, trt 1
- RA + anti-GD2, trt 2

p=0.0137

 риск (n)
trt 1 112 98 80 68 52 35 22 13 9 6 0
trt 2 113 102 92 88 66 49 34 18 9 5 0

time (years)

Probability
• Public funds promote basic research for target identification

• Public funds support initial clinical work through existing clinical trials infrastructure

• Public funds support manufacturing of agent for proof-of-principle clinical trials.

• Once sufficient risk removed from agent’s development, then pharmaceutical involvement can successfully occur.
Collaborative Development of ch14.18 for Children with High-Risk Neuroblastoma

- 2001 – ANBL0032 initiated
- 2009 – ANBL0032 randomization stopped
- 2009 – Announcement for CRADA Collaborator
- 2010 – UTC selected, CRADA implemented

**UTC**
- Scale up and make ch14.18 to NCI to COG
- Conduct additional clinical trials as needed
- Submit BLA
Medulloblastoma – Biologically and Clinically Distinctive Subtypes


**Molecular Subgroups of Medulloblastoma**

<table>
<thead>
<tr>
<th>CONSENSUS</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho (2010)</td>
<td>C6</td>
<td>C3</td>
<td>C1/C5</td>
<td>C2/C4</td>
</tr>
<tr>
<td>Northcott (2010)</td>
<td>WNT</td>
<td>SHH</td>
<td>Group C</td>
<td>Group D</td>
</tr>
<tr>
<td>Thompson (2006)</td>
<td>B</td>
<td>C, D</td>
<td>E, A</td>
<td>A, C</td>
</tr>
</tbody>
</table>

**DEMOGRAPHICS**
- **Age Group:** infant, child, adult
- **Gender:** ♀, ♂

**CLINICAL FEATURES**
- **Histology**
- **Metastasis**
- **Prognosis**

**GENETICS**

**GENE EXPRESSION**
- **CTNNB1 mutation**
- **WNT signaling**
- **MYC +**
- **SHH signaling**
- **MYCN +**
- **Photoreceptor/GABAergic**
- **Neuronal/Glutamatergic**
- **MYC +++**
- **CDK6 amplification**
- **MYCN amplification**

**CLINICAL FEATURES**
- **classic, rarely LCA**
- **desmoplastic/nodular, classic, LCA**
- **class, LCA**
- **classic, rarely M+**
- **uncommonly M+**
- **infants good, others intermediate**
- **very frequently M+**
- **poor**
- **frequently M+**
- **intermediate**

**WNT**
- **6-**
- **3q+**
- **9q-**
- **10q-**
- **PTCH1/SMO/SUFU mutation**
- **GLI2 amplification**
- **MYCN amplification**

**SHH**
- **7+**
- **1q+**
- **17q+**
- **18q+**
- **11p-**
- **5q-**
- **8-**
- **i17q**
- **MYC amplification**

**Group 3**
- **C1/C5**
- **Group C**
- **E**
- **A**

**Group 4**
- **C2/C4**
- **Group D**
- **C/D**
- **A, C**
GDC-0449, an inhibitor of Hedgehog pathway signaling, is active against selected medulloblastoma cases. Through the PBTC, NCI supported a phase 2 clinical trial of GDC-0449 in children with recurrent medulloblastoma and a phase 2 trial in adults with recurrent medulloblastoma.

Rudin, et al. NEJM 361:1173-78, 2009
Genome Sequencing of SHH Medulloblastoma Predicts Genotype-Related Response to Smoothened Inhibition

• 10 yr boy with refractory B-ALL – 70% blasts at day 29
• Cytogenetics: 5q33 deletion at PDGFRB
• Molecular testing showed EBF1-PDGFRB translocation
• Imatinib added to standard chemotherapy with immediate clinical improvement
• 1 week: morphologic remission; 2 weeks: MRD 0.017%
• Remains in remission at 2 years after imatinib initiation
BRAF Mutated Pediatric Low-Grade Astrocytomas
• ~80% with BRAF fusion proteins and ~5% with BRAF mutations (primarily V600E)

• Selumetinib: allosteric MEK inhibitor
• Under evaluation for multiple adult cancer indications.

Screening of AZD6244 against Low-Grade Astrocytoma Xenograft (BT-40) with BRAF V600E Mutation

All patients with BRAF genomic alterations showed tumor shrinkage.