Pediatric Oncology Update

June 24, 2014
• 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

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**

- 1975-78: 40%, 56%
- 1979-82: 57%, 45%
- 1983-86: 56%, 50%
- 1987-90: 68%, 61%
- 1991-94: 68%, 68%
- 1995-98: 70%, 62%
- 1999-02: 67%, 65%
- 2003-07: 76%, 66%

**Ewing's sarcoma**

- 1975-78: 59%, 20%
- 1979-82: 38%, 45%
- 1983-86: 51%, 55%
- 1987-90: 47%, 54%
- 1991-94: 74%, 52%
- 1995-98: 73%, 60%
- 1999-02: 76%, 51%
- 2003-07: 78%, 69%

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

> 45,000 deaths averted since 1975

Children’s Oncology Group
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.
~ 2000 children and adolescents die of cancer each year in the US

Causes of Childhood Cancer Mortality

<15 Year Mortality 2007-2010

- CNS, 31%
- AML, 9%
- ALL, 13%
- Oth Leuk, 7%
- Neuroblastoma, 11%
- Bone, 5%
- Soft Tissue, 6%
- NHL, 3%
- Gonads, 0.2%
- Hodgkin, 0.2%
- Liver, 3%
- Kidney, 3%
- Other, 7%

15-19 Year Mortality 2007-2010

- CNS, 16%
- AML, 10%
- Oth Leuk, 7%
- Neuroblastoma, 2%
- Bone, 16%
- Soft Tissue, 10%
- NHL, 7%
- Hodgkin, 2%
- Gonads, 2%
- Liver, 2%
- Kidney, 1%
- 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
Brief Update

target.cancer.gov

BSA/NCAB
Bethesda MD
June 24, 2014
## 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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<td>Expression</td>
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<tr>
<td>Acute Lymphoblastic Leukemia (P-I)</td>
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<td>189 (0)</td>
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<td>Acute Lymphoblastic Leukemia (P-II) (ALL)</td>
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<td>184 (84)</td>
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<td>Acute Myeloid Leukemia</td>
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<td>200 (100)</td>
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<td>Induction Refractory Acute Myeloid Leukemia</td>
<td>Y</td>
<td>30 (25)</td>
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<td>Neuroblastoma (NBL)</td>
<td>Y</td>
<td>180 (9)</td>
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<td>Osteosarcoma</td>
<td>Y</td>
<td>92 (0)</td>
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<td>Wilms Tumor</td>
<td>Y</td>
<td>113 (5)</td>
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<td>Clear Cell Carcinoma of the Kidney</td>
<td>Y</td>
<td>13 (0)</td>
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<td>Rhabdoid Tumor (kidney)</td>
<td>Y</td>
<td>40 (0)</td>
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<td>Pediatric Preclinical Testing Program</td>
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<td>131</td>
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<td>Y</td>
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<td>ALL Xenografts</td>
<td>Y</td>
<td>33 [244]</td>
<td>Y</td>
<td>Y</td>
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<td>NBL Models</td>
<td>L</td>
<td>7 [27]</td>
<td>Y</td>
<td>Y</td>
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L=Limited [# of samples]
## Validation in New Cohorts, in progress

~400 genes to 500X coverage

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<tr>
<th>Disease</th>
<th>Cases</th>
<th>Patient Data</th>
<th>Samples</th>
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<td>Acute Myeloid Leukemia</td>
<td>800</td>
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<td>Neuroblastoma</td>
<td>500</td>
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<td>Wilms Tumor</td>
<td>570</td>
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### Planned

<table>
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<tr>
<td>Acute Lymphoblastic Leukemia</td>
<td>750</td>
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<td>1500</td>
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<tr>
<td>Osteosarcoma</td>
<td>200</td>
<td>Y</td>
<td>TBD</td>
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TARGET Initiative:

Tissue Specimens COG & BPC

Disease Expertise

Transcriptomic Profiling

Sequencing

Genomic Characterization

All data types except raw sequence files are stored the DCC

OCG Data Portal

Computation Stack
Favorable Histology Wilms Tumors: Mutations in miRNA Processing Genes

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

**DGCR8**

- Black = Somatic Mutation
- Red = Germline Mutation

**DROSHA**

**XPO5**

**DICER1**

E. Perlman & WT PT, unpublished
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

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<tr>
<th>Functional Category</th>
<th>Percentage</th>
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<td>Tyrosine Kinases</td>
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<tr>
<td>Transcription Factors</td>
<td>0.33</td>
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<tr>
<td>Tumor Suppressors</td>
<td>0.23</td>
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<tr>
<td>RAS family</td>
<td>0.19</td>
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<tr>
<td>Protein Phosphatases</td>
<td>0.17</td>
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<tr>
<td>Epigenetic Modifiers</td>
<td>0.12</td>
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<tr>
<td>Nuclear Transport</td>
<td>0.09</td>
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<tr>
<td>Spliceosome</td>
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<tr>
<td>ETS</td>
<td>0.03</td>
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<tr>
<td>Cohesin</td>
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<tr>
<td>Oncogenes</td>
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</table>

S. Meshinchi, R. Arceci & AML PT, unpublished
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>
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<tr>
<th>Sample ID</th>
<th>Known fusions</th>
<th>New fusions</th>
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<tr>
<td>PAKHZT</td>
<td>IGH@-CRLF2</td>
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</tr>
<tr>
<td>PAKKCA</td>
<td></td>
<td>EBF1-PDGFRB</td>
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<tr>
<td>PAKKXB</td>
<td>IGH@-CRLF2</td>
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<tr>
<td>PAKTAL</td>
<td></td>
<td>STRN3-JAK2</td>
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<tr>
<td>PAKVKK</td>
<td></td>
<td>NUP214-ABL1</td>
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<tr>
<td>PAKYEP</td>
<td></td>
<td>BCR-JAK2</td>
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<tr>
<td>PALETF</td>
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<td>NONE</td>
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<tr>
<td>PALJ BN</td>
<td></td>
<td>IGH@-EPOR</td>
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<tr>
<td>PALJ DL</td>
<td></td>
<td>NONE</td>
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<tr>
<td>PAMDRM</td>
<td>IGH@-CRLF2</td>
<td></td>
</tr>
<tr>
<td>PANNGL</td>
<td></td>
<td>PAX5-JAK2</td>
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<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)  \( P < 0.0001 \)

Years

COG AALL0232

Event-free survival probability

Not Ph-like (n = 491)  Ph-like (n = 81)  \( P < 0.0001 \)

Years

Adolescent  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.

Brentuximab Vedotin (SGN-35): CD30 Targeted Antibody-Drug Conjugate

Auristatin derivative: average of 4 molecules per antibody

CD30 antigen binding site

Light chain

Heavy chain

Drug binds tubulin

Drug released from ADC

ADC traffics to lysosome

Endocytosis

Target

G2/M cell cycle arrest & apoptosis
>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 Leukemia and DOT1L Inhibition

- 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

Dx

Induction

Consolidation

ASCT + XRT

A: Isotretinoin 6 cycles

B: Immunotherapy + Isotretinoin 6 cycles

Randomize post-Consolidation

ANBL0032

ANBL00B1

A3973

ANBLOOP1

ANBLO2P1

ANBL0532

ANBL09P1

ANBL12P1
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>
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<td>GM-CSF</td>
<td>IL2</td>
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<td>Cis-RA</td>
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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)

p=0.0115

Yu, et al. NEJM 2010
Ch14.18 + Cytokines Improves Overall Survival for High Risk Neuroblastoma (2012)
• 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 → COG
- Conduct additional clinical trials as needed
- Submit BLA
### Molecular Subgroups of Medulloblastoma

<table>
<thead>
<tr>
<th>CONSENSUS</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
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<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>
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</table>

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

### CLINICAL FEATURES
- **Histology:**
  - classic, rarely LCA
  - rarely M+
  - very good
- **Metastasis:**
  - desmoplastic/nodular, classic, LCA
  - uncommonly M+
  - infants good, others intermediate
- **Prognosis:**
  - classic, LCA
  - very frequently M+
  - poor
  - frequently M+
  - intermediate

### GENETICS
- **CTNNB1 mutation:**
  - 6-
- **WDTC1/SMO/SUFI mutation:**
  - 3q+
  - 9q-
  - 10q-
- **GLI2 amplification:**
  - 7q+
  - 17q+
  - 18q+
- **MYCN amplification:**
  - 11p-
  - 5q-
  - 8-
- **MYC amplification:**
  - i17q
- **CDK6 amplification:**
  - 11p-
  - X-
  - 8-

### GENE EXPRESSION
- **WNT signaling:**
  - MYC+
- **SHH signaling:**
  - MYCN+
- **Photoreceptor/GABAergic:**
  - Neuronal/Glutamatergic
  - minimal MYC/MYCN

---

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


<table>
<thead>
<tr>
<th>Gender</th>
<th>infants</th>
<th>children</th>
<th>adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>52%</td>
<td>36%</td>
<td>12%</td>
</tr>
<tr>
<td>9q</td>
<td>42%</td>
<td>45%</td>
<td>12%</td>
</tr>
<tr>
<td>10q</td>
<td>12%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>17p</td>
<td>8%</td>
<td>4%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Potential response

- male
- female
- desmoplastic
- MBEN
- 9q, 13q, or 17p loss
- somatic mutation
- mutation, germline
- SMO response: yes
- SMO response: unknown
- SMO response: no

**B**

Gender

- Male
- Female

Histology

- Classic
- Desmoplastic
- MBEN

9q loss

- Infant-like SHH (PTCH1, SUFU)
- Adult-like SHH (PTCH1, SMO)
- Young adult-like SHH (PTCH1, TP53)

10q loss

- Infant-like SHH (PTCH1, SUFU)
- Adult-like SHH (PTCH1, SMO)
- Young adult-like SHH (PTCH1, TP53)

17p loss

- Infant-like SHH (PTCH1, SUFU)
- Adult-like SHH (PTCH1, SMO)
- Young adult-like SHH (PTCH1, TP53)

SHH pathway mutation

- Infant-like SHH (PTCH1, SUFU)
- Adult-like SHH (PTCH1, SMO)
- Young adult-like SHH (PTCH1, TP53)
• 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
Relevant Dollars by CSO Code for NCI's Childhood Cancer Projects

Graph showing the relevant dollars in millions for different fiscal years (2007-2012) for various categories such as Prevention, Scientific Model Systems, Early Detection, Diagnosis, and Prognosis, Etiology, Cancer Control, Survivorship, and Outcomes Research, Biology, and Treatment.
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.