Scientific and Logistical Considerations in applying "The List"

Lia Gore, MD
University of Colorado School of Medicine
Children's Hospital Colorado

Outline

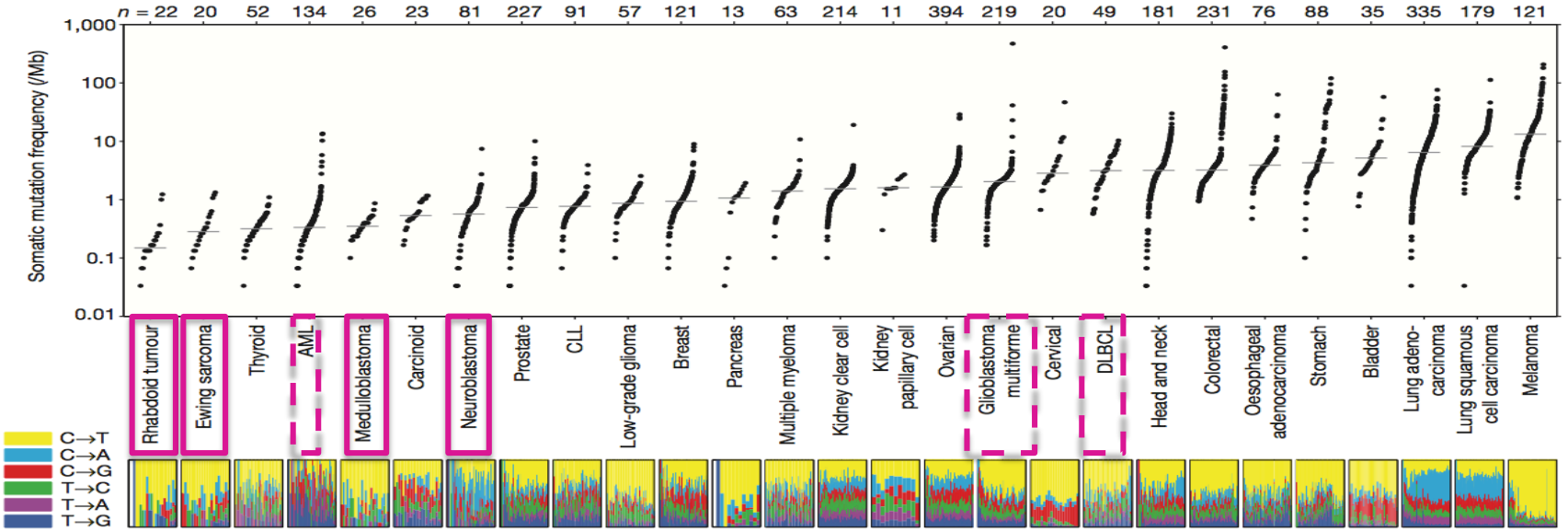
- Scientific Challenges
  - Tumor Biology
  - Technology
- Logistical Challenges
  - Practical
  - Operational
  - Societal / Ethical
- Select Target Examples
- Reasons to be Optimistic

Scientific Challenges: Tumor Biology

- Targets differ by disease from the adult cancer types for which treatments are often developed
- The vast majority of pediatric cancers are aberrations in developmentally important pathways or genes, and non-randomly occurring cytogenetic fusions
  - Very few mutations per pediatric tumor
  - Fusion proteins are (usually) harder to target
- The more “adult” cancers have higher mutational burden and lower frequency of gene fusions
  - Easier or better targets for certain approaches

Identifying Targetable Mutations

- Increasing capacity to define molecular aberrations in malignant cells and activating pathways
- Still a lag in knowledge between the molecular definitions of disease in pediatric vs. adult cancers
  - "Cleaner" and more homogeneous diseases in children
  - Fewer copy number abnormalities and "lesions" per pediatric tumor



Lawrence MS, et al. Nature 2013;499:214–8.

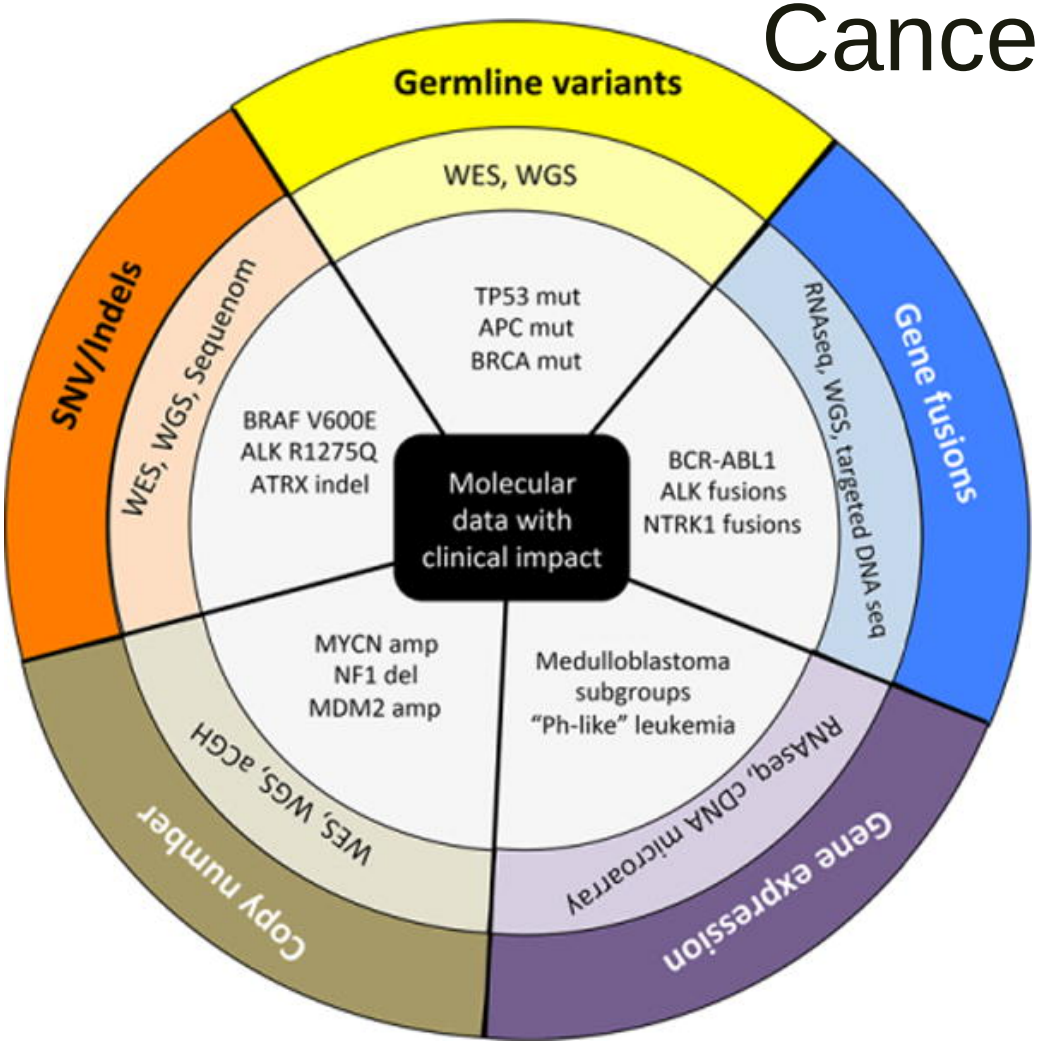
Topical Genomic Subgroups that don't do so well...

- **pTEN, IL7R, JAK, RAS, NF1/TP53, Akt** mutations in pediatric ALL have worse outcomes to date
- **MDM2**: still confusion around efficacy of inhibition in p53 wild type versus p53 mutant clones
- **Severe hypodiploidy** in pediatric ALL
  - ~80% of hypodiploid patients have TP53 mutations
- **IL7R signaling** mutations drive steroid resistance and depend on R3C1 transactivation
  - Ruxolitinib can sensitize steroid-resistant cells but not in T-ALL samples
- **Akt activation/phosphorylation** in ~85% of T-ALL
  - To date, targeting efforts have been indirect/upstream

Scientific Challenges in Applying the Technology

- Ever-advancing technology makes available data on molecular targets rise exponentially
  - increasing number of platforms = lower cost
  - increasing number of platforms ≠ clearer answers
  - not all targets are (currently) identified by NextGen sequencing
- Current technologies are dependent on bioinformatic interpretation of the explosion of data
  - Bioinformaticians are human beings – different people "read" data differently
- Current turn-around times are improving but still require time between testing and application to patient utilization

Sample Strategies for NGS in Pediatric Cancer



Mody RJ, et al. Pediatr Blood Cancer 2017;64.

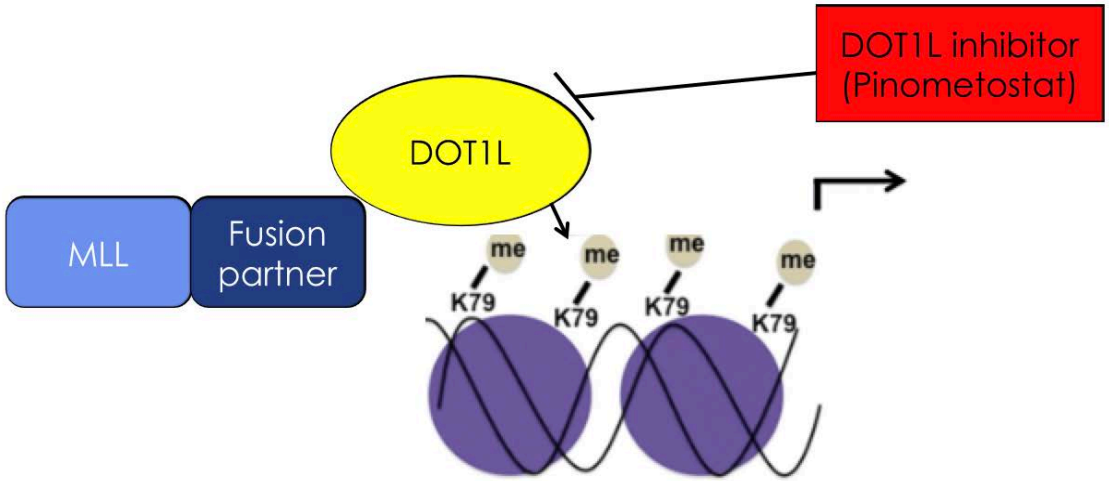
- FoundationOne: gene panel by targeted capture
  - >300 genes
  - TAT: ~2 weeks
- GAIN (iCat2): gene panel (OncoPanel)
  - 305 genes
  - +/- array CGH, FISH, IHC
  - TAT: 2–4 weeks
- LEAP Leukemia: gene panel (RapidHeme)
  - 95 genes
  - +/- fusion testing, drug screen assay
  - TAT: <5 days + 1-2 weeks
- MATCH: gene panel by amplicon (OncoMine)
  - 143 genes
  - TAT: 2–3 weeks

9 Candidate targets identified for CureSearch Summit - February 2017

PI3K	Adult studies not as promising; future unclear
b-Raf	✓
Mek	✓
PDL / PDL-1	✓ -- ? too many
CDK 4/6	✓
Bcl-2	✓
MDM2	study planned
Myc – N, C	the Holy Grail….
EZH2	✓ – challenging recent weeks

Prioritized as single agents vs combinations and then EWS-FLI1, MLL, PARP added

An Example Scientific Challenge



- *KMT2A* fusion proteins recruit the histone methyltransferase DOT1L, causing hyper-methylation at H3K79 of target genes that enhances expression of critical pro-leukemogenic genes (i.e. *HOXA9* and *MEIS1)*
  - DOT1L is necessary for the development and maintenance of *KMT2A*-r leukemia
  - Pinometostat (EPZ-5676) is a potent & selective small molecule inhibitor of DOT1L
  - Early trials of single agent in children with *KMT2A*-r leukemia did not yield not stellar responses --- what to do next ?

Logistical Challenges: Practical, Operational

- Limited number of Phase I institutions – difficult for patients to access therapies closer to home
- Historic regulatory endpoints are DFS and OS
  - Randomized trials favored when possible
  - Evolution toward ORR, valid historical controls
- Current therapies are less often traditional cytotoxics, and therefore CR may be less likely
- New endpoints to consider / being considered more commonly
  - Progression-free survival
  - Non-inferiority with or without QOL advantage

Logistical Challenges: Financial

- Investment in pediatrics trials has lagged behind those for adults
  - The vast majority of drugs developed will only go forward if there is a potential adult indication → Lack of a "market" for drugs developed only for pediatric diseases
- Difficulty recouping R&D costs in the market
- Majority of R&D costs for most drugs is still borne by private industry
- Pediatric-friendly formulations are costly to develop and require additional safety and pharmacology testing
  - Limits implementation in peds – relative or absolute

Access to and Operations for Relevant Agents

- Annually, 900+ compounds in development for cancer targets
- Relatively small number available for pediatric trials at any given time
  - Success of pediatric cancer treatment overall means relatively smaller numbers of patients available for early phase trials
- Pediatric patients enrolled in early phase trials are typically very heavily pre-treated, multiply relapsed or refractory
  - ? fair toxicity evaluations
  - ? shortened life expectancy/disease-free interval limits long-term follow up, which is increasingly important for biologic inhibitors
- Requires substantial expertise and support for complex trials at each center

Logistical Challenges: Societal/Ethical

- Traditionally, drug development in children has lagged substantially behind that for patients over age 18
  - Concern for exposing vulnerable subjects to unknown risks
  - Studies which rely on biomarkers for eligibility and/or response have traditionally required biopsies and serial biopsies
    - Circulating belief that children cannot be subject to serial biopsies or potentially painful procedures
- Fear of what would happen if a child had a bad event on a new drug

Reasons to be Optimistic

- What if cancer became a chronic disease – like diabetes ? Or hypertension ? What if cancer becomes more a disease that one lives WITH ?

- Newer legislation hopes to improve incentives to conduct pediatric studies but expectations should be realistic

- Newer approvals and newer applications
  - Example: approvals that are (nearly) age agnostic
  - Example: pembrolizumab approval is tumor-type agnostic

Summary of TAP Review of Target-Drug Pairs

Rank by Average TAP Score	Agent Class	Average TAP Score (range)	Example Response of Biomarkers	Example Resistance Biomarkers	Final Priority for Pediatric MATCH Trial
1	MTOR inhibitor	1.5 (1–2)	*TSC1/2 LOF* mutations, *MTOR* mutations, *PIK3CA* p.H1047R and *p.E545K, PTEN* deletion	• *KRAS* mutation	Included
2	MEK inhibitor	1.5 (1–2)	*NF1 LOF* mutation *H/K/NRAS/BRAF*-activating mutations	• *MAPK1, MAPK2,* and *MEK2* mutations reported to cause resistance	Included
3	PI3K inhibitor	2 (1–3)	Same as mTOR inhibitors	• *KRAS* mutations	Included
4	PDGFRA inhibitor	2 (1–3)	*PDGFRA* amplification, *PDGFRA* activating mutation	• Unknown	Included
5	BRAF inhibitor	2 (1–3)	*BRAF* p.V600E mutation and other documented activating mutations, *BRAF* fusions, amplification *WT BRAF*	• Reported resistance mutations: *NRAS Q61,* amplification mutant *BRAF, MAP2K1* mutations	Included
6	Extended ALK inhibitor	2 (1–3)	*ROS1* translocations; *ALK*-activating mutations, *ALK* translocations	• For crizotinib: *ALK, C1156Y, L1196M, G1123S, L1152R, G1202R*, • for 2nd/3rd generation: *ALK I1171T, V1180L, F1174c, F1245C, R1275Q*	Included
7	TRK inhibitor	2.5 (1–4)	Translocations involving *NTRK1/2/3*	• Unknown	Included
8	BET bromodomain inhibitor	2.5 (1–4)	*MYC,* or *MYCN* amplification, *MYC* translocation, *BRD4* translocation	• *TP53* mutation (early preclinical data suggests possible association w/resistance)	Not included
9	CDK4/6 inhibitor	2.5 (1–4)	*CDK 4/6* amplification, *CCND2* amplification, *SNF5* del	• Loss of *RB1* expression (no standard assay)	Not included
10	FGFR inhibitor	2.5 (1–4)	*FGFR*-activating mutations, *FGFR* amplification, *FGFR* fusions	• Depends on agent selected (range of *FGFR* selectivity)	Included
11	2nd–generation ALK inhibitor	2.66 (1–5)	*ALK*-activating mutations, *ALK* translocations	• For crizotinib: *ALK, C1156Y, L1196M, G1123S, L1152R, G1202R* • For 2nd/3rd generation: *ALK I1171T, V1180L*	Not included
12	AKT inhibitor	3 (1–5)	Same as *mTOR/PI3K* inhibitors	• Unknown	Not included
13	EGFR inhibitor	3 (1–5)	*EGFR*-activating mutations, *EGFR* amplification	• Unknown	Not included
14	IDH 1/2 inhibitors	3 (2–4)	*IDH 1/2* mutations	• Unknown	Not included
15	SMO inhibitor	3 (1–5)	*PTCH1* mutations	• *GLI2* amplification, *SUFU* mutations, *NMYC* amplification	Not included
16	PARP inhibitor	3 (2–4)	*BRCA1/2* mutation, *ATM* mutation, *EWSR1-FLI1* translocation	• Unknown	Not included
17	ERK inhibitor	3.5 (3–4)	Activating *MAPK* pathway mutations	• Unknown	Not included

Notable agent classes reviews and prioritized by the TAP committee*

Agent class	Primary reason for exclusion
MDM2 inhibitors	Target (MDM2 amplification) uncommon
ERBB inhibitors	Target uncommon
Met inhibitors	Target (met amplification) uncommon
Src/Syk inhibitors	Target uncommon
C-Kit inhibitor	Target uncommon
Anti-angiogenic(VEGF and Ang/Tie)	Not sufficiently targeted to define biomarker
Pan-tyrosine kinase inhibitors	Not sufficiently targeted to define biomarker
Aurora kinase inhibitors	Target/biomarker not known
Base excision repair inhibitor (TRC102)	Target/biomarker not known
FAK inhibitor	Target/biomarker not known
CK2 inhibitors	Target/biomarker not defined by genomic alteration
IGF1R inhibitors	Target/biomarker not defined by genomic alteration

Target histologies for expansion cohorts

Tumor Type
1. Ependymoma
2. Ewing sarcoma/peripheral PNET
3. Hepatoblastoma
4. Glioma, high grade
5. Glioma, low grade
6. Langerhans cell histiocytosis
7. Malignant germ cell Tumor
8. Medulloblastoma
9. Neuroblastoma
10. Non-Hodgkin lymphoma
11. Non-RMS soft tissue sarcoma
12. Oesteosarcoma
13. Rhabdoid malignancy
14. Rhabdomyosarcoma
15. Wilms tumor
16. Other histology (based on COG/NCI-CTEP approval)

Challenge Points for Consideration

- Improved understanding of the cancer genome has led to increases in
  - molecularly targeted agents in development, and
  - multiple sophisticated genomic sequencing technologies

→ We have entered a new biomarker-driven age of personalized cancer medicine to direct targeted agents to those most likely to respond

Mody RJ, et al, Ped Blood Cancer 2017.

Challenge Points for Consideration

- Important limitations and challenges to employing these advances:
  - Need for potentially multiple tissue collections
  - Disease heterogeneity, complexity, and influence of the epigenome
  - Increasing knowledge = increasingly small disease cohorts / sub-sets
  - Defining pathogenic variants in pediatrics
  - Ethical challenges of germline findings
  - Genomic profiling: cost, turnaround time and lack of standardization
  - Drug availability and formulation

Mody RJ, et al, Ped Blood Cancer 2017.

"Each success and failure of targeted agents in clinical trials has laboriously been declared one histologic subtype at a time…

…it is impractical to efficiently study the landscape of a targeted new agent with this type of approach—a new paradigm is needed."

O'Sullivan Coyne G, et al. Curr Probl Cancer 2017;41:182–93.

acknowledgements

Children's Hospital Colorado

Center for Cancer
and Blood Disorders

COG ALL Committee

Steve Hunger
Mignon Loh
Elizabeth Raetz
Pat Brown

University of Colorado Cancer Center:
Developmental Therapeutics and Heme Malignancies Teams

Collaborators in the iBFM and ITCC

Patients and Families

Countless NPs, PAs, RNs, MDs, CRAs

Funding:

- The Ergen Family Chair