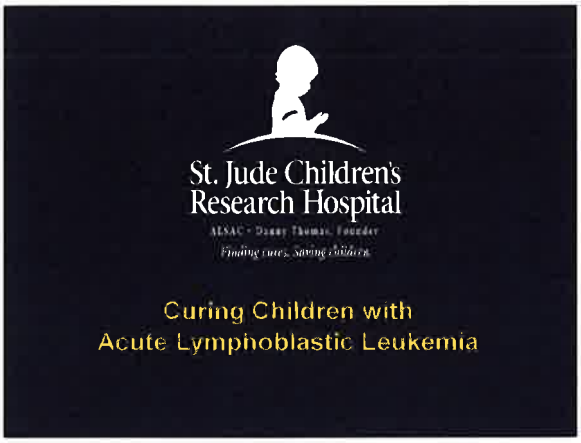
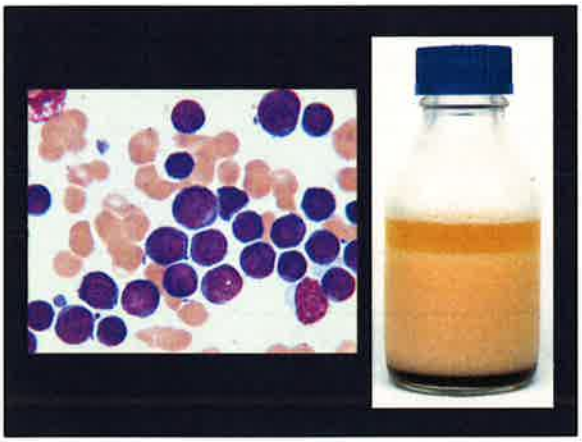
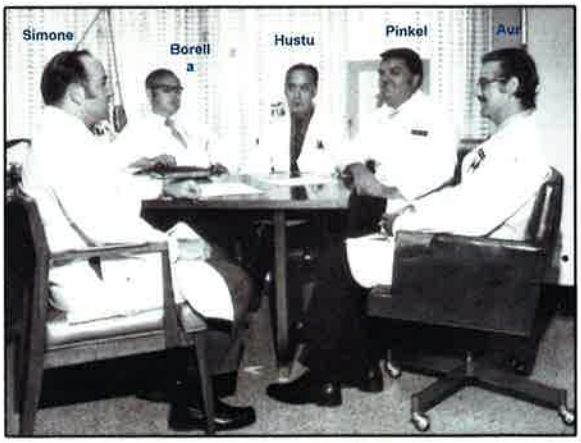

St. Jude Children's
Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.
Curing Children with
Acute Lymphoblastic Leukemia



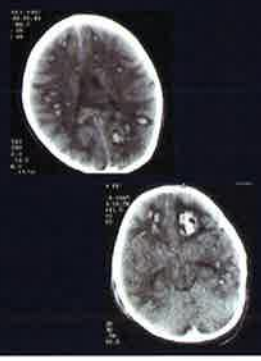

Hyperleukocytosis


Simone
Borell
a
Hustu
Pinkel
Aur

Total Therapy Studies I-IV 1962-1967

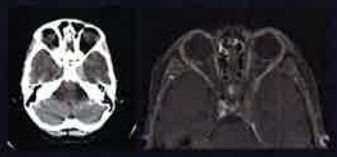
- Introduce combination chemotherapy with prednisone, vincristine, cyclophosphamide, daunorubicin, cytarabine, mercaptopurine, methotrexate
- Began Total Therapy with remission induction; intensification; central-nervous-system (CNS)-directed therapy; continuation (maintenance) therapy
- Began cranial irradiation to prevent and treat CNS leukemia

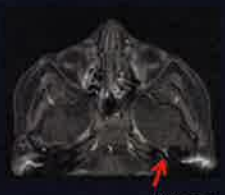
Central Nervous System Leukemia

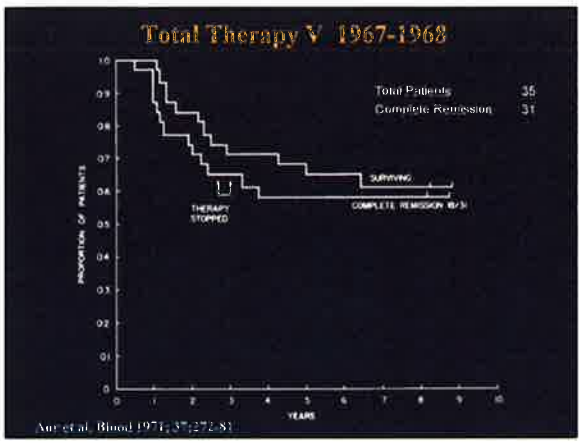


- Symptoms include: headache, mental status changes, vision changes, seizures, coma, death
- Intracranial hemorrhage

Facial Palsy in ALL





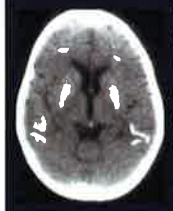


Legacy of Donald Pinkel

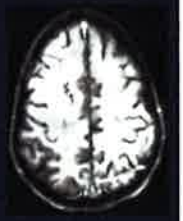
Nothing changed the fate of children with ALL (and St Jude Hospital) like Danny Thomas's appearance on tonight show with Johnny Carson on June 26, 1972

Quote of Yaddanapudi Ravindranath

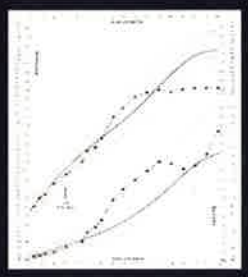
Neuroimaging Abnormalities After Cranial Irradiation



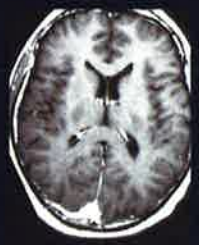
- Brain atrophy
- Encephalomalacia
- Cerebral lacunes
- Dystrophic calcification
- Leukoencephalopathy
- Necrosis/gliosis



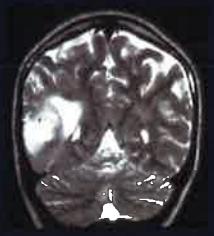
Endocrinopathy After Cranial Irradiation



Brain tumors after cranial irradiation

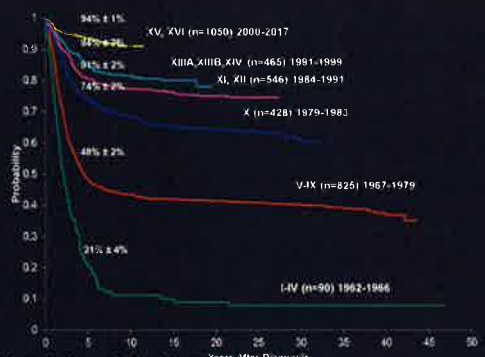


Meningioma
median onset: 20 years



Malignant astrocytoma
median onset: 8 years

Overall Survival of Childhood ALL by Treatment Era at St. Jude

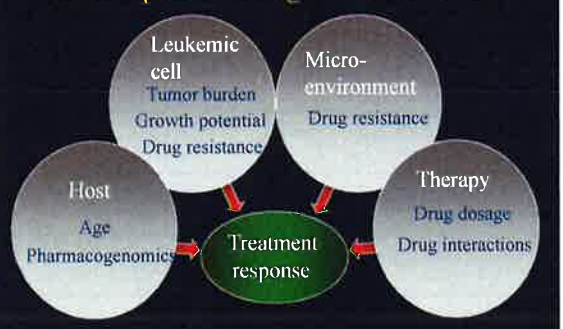


Pui et al. Unpublished Data

Total Therapy XV (2000-2007): Principle of Therapy

- Adopt effective treatment components of successful clinical trials
  - Reinduction therapy
  - Intensive asparaginase
  - Early intensive triple intrathecal therapy
- Personalized therapy (Precision medicine)
  - -Risk assessment based on minimal residual disease
  - -Individualized dosage of methotrexate and mercaptopurine based on pharmacokinetics and pharmacodynamics
- Elimination of cranial irradiation in all patients
  - Early intensification of intrathecal therapy

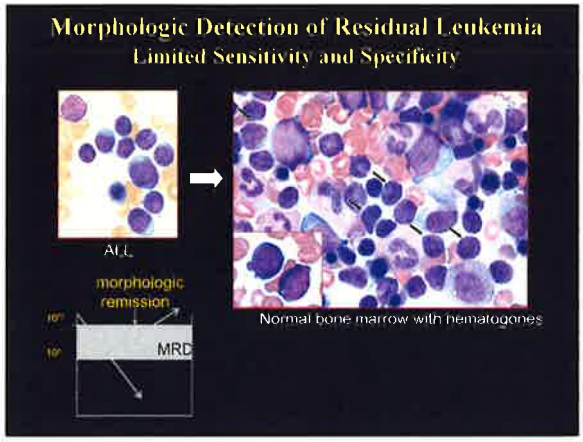
Treatment Response: Most Important Prognostic Indicator

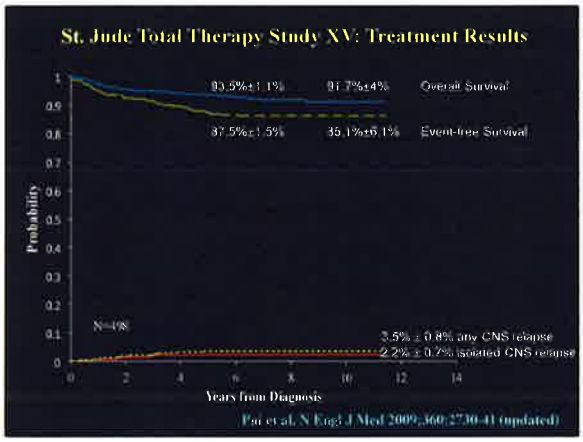


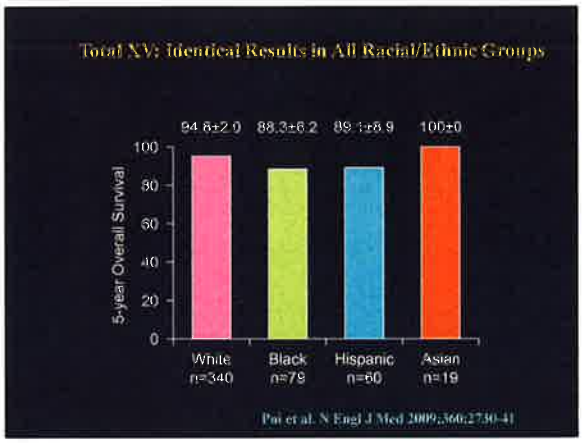
Risk Stratification by Minimal Residual Disease Level

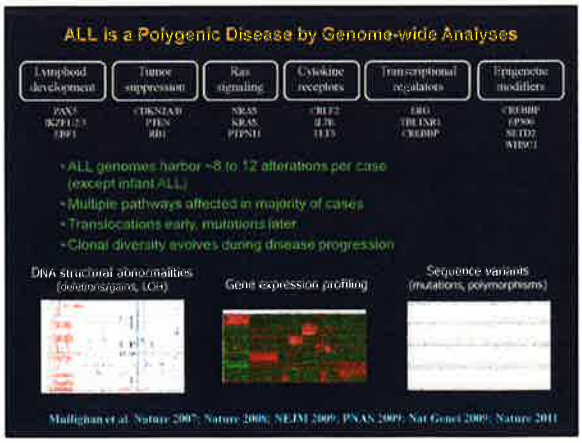
- During induction (day 19)
  - MRD ≥1% → intensified remission induction
- End of induction (day 46)
  - MRD ≥ 0.01% → intensive continuation therapy
  - MRD ≥1% → allogeneic transplantation
- Continuation treatment (week 7)
  - MRD ≥ 0.1% → allogeneic transplantation

491/492 (99.8%) patients monitored by flow and/or PCR of Ig/TCR genes; the remaining one patient with *MLL-AF9* was studied with RT-PCR; hence 100% had successful studies

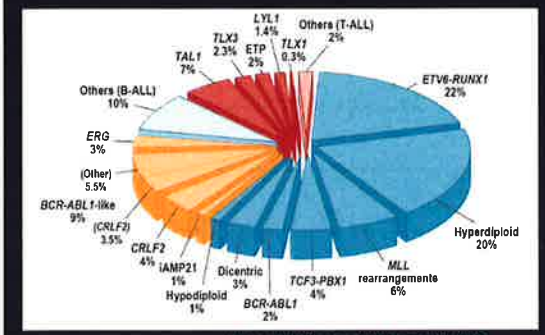

Morphologic Detection of Residual Leukemia
Limited Sensitivity and Specificity
ALL
morphologic remission
MRD
Normal bone marrow with hematogones


St. Jude Total Therapy Study XV: Treatment Results
93.5%±1.1%
91.7%±4%
Overall Survival
87.5%±1.5%
85.1%±6.1%
Event-free Survival
Probability
N=98
3.5% ± 0.8% any CNS relapse
2.2% ± 0.7% isolated CNS relapse
Years from Diagnosis
Pui et al. N Engl J Med 2009;360:2730-41 (updated)


Total XV: Identical Results in All Racial/Ethnic Groups
94.8±2.0
88.3±6.2
89.1±8.9
100±0
5-year Overall Survival
100
80
60
40
20
0
White n=340
Black n=78
Hispanic n=60
Asian n=19
Pui et al. N Engl J Med 2009;360:2730-41

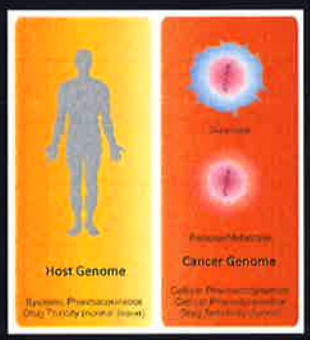

ALL is a Polygenic Disease by Genome-wide Analyses
Lymphoid development
Tumor suppression
Ras signaling
Cytokine receptors
Transcriptional regulators
Epigenetic modifiers
PAX5
IKZF1
EBF1
CDKN2A/B
PTEN
RB1
NRAS
KRAS
PTPN11
CRLF2
IL7R
JAK2
ERG
TBL1XR1
CREBBP
CREBBP
EP300
SETD2
WHSC1
• ALL genomes harbor ~8 to 12 alterations per case (except infant ALL)
• Multiple pathways affected in majority of cases
• Translocations early, mutations later
• Clonal diversity evolves during disease progression
DNA structural abnormalities (deletions/gains, LOH)
Gene expression profiling
Sequence variants (mutations, polymorphisms)
Mullighan et al. Nature 2007; Nature 2008; NEJM 2009; PNAS 2009; Nat Genet 2009; Nature 2011

Recent Genetic Classification of ALL



Pui et al. J Clin Oncol 2015;33:2938-2948

Two Genomes Influence Every Cancer Patient



Evans & Relling

US FDA: Pharmacogenetics in Drug Label

- Oncology
  - 6MP: *TPMT*
  - Irinotecan: *UGT1A1*
  - Erlotinib/gefinitib: *EGFR*
  - Imatinib: *BCR-ABL*
  - Tamoxifen: *CYP2D6*
- Hematology
  - Warfarin: *CYP2C9* and *VKORC1*
- Cardiovascular
  - Clopidogrel: *CYP2C19*
- Antiviral
  - Abacavir: *HLA-B*
- Analgesics
  - Codeine: *CYP2D6*
- Neurology
  - Carbamazepine: *HLA-B*

- 164 drugs with pharmacogenomic biomarkers labeling
- 18 therapeutic areas: oncology, hematology, antiviral, cardiovascular, analgesics, etc.

Priority list of pharmacogenetic tests to move from research to clinical care

- TPMT---thiopurines
- CYP2D6 --- codeine, amitriptyline, ondansetron
- G6PD---rasburicase, Septra
- CYP2C9, VKORC1---warfarin
- CYP2C19---clopidogrel, voriconazole
- DPYD---5FU
- HLA-B*5701 --- abacavir
- HLA-B*1502 ---carbamazepine (Asians ancestry)
- HLA-B*1502 --- phenytoin
- HLA-B*5801---allopurinol
- UGT1A1---irinotecan

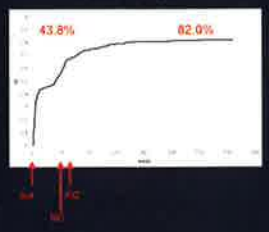
Interactions affecting drug metabolism

- CYP450 substrates: anthracyclines, epipodophyllotoxins, vinca alkaloids, and cyclophosphamide
- CYP450 enzyme inducer
  - Anticonvulsant (e.g., phenytoin, phenobarbital, carbamazepine)
  - Increase the clearance of agents metabolized by CYP450
- CYP450 enzyme inhibitor
  - Valproic acid, azole antifungals (e.g., fluconazole, voriconazole, and posaconazole), macrolide antibiotics (clarithromycin, erythromycin, and azithromycin)
  - Increase plasma drug concentration and cause greater toxicity

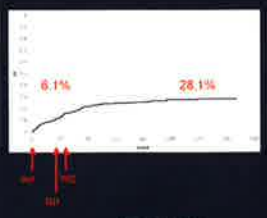
Peripheral Neuropathy in Total XVI

Peripheral neuropathy (sensory and motor) and neuropathic pain

Grade 2 or above

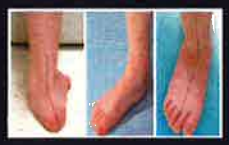


Grade 3 or above



Dr. Sima Jeha

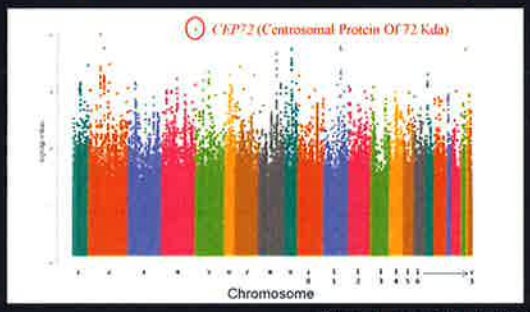
Vincristine Neuropathy



Hind foot valgus - collapsed longitudinal arch

Kristin Scobey and Kiri Ness

A SNP in the promoter region of *CEP72* (encoding a centrosomal protein involved in microtubule assembly) is associated with vincristine-induced neuropathy



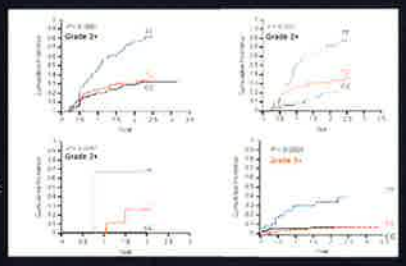
Diouf et al. JAMA 2015;303:815-23

Risk and Severity of VCR-induced Neuropathy Related to *CEP72* Genotype

(Risk allele T associated with low expression of CEP72 mRNA)

COG 0334

SJCRH 1136



Combined Cohort (SJ, COG)

Grade 3+ Only

Diouf et al. JAMA 2015;303:815-23

International Collaboration

- 1988: Teaching, consultation, and collaboration with Taiwan Pediatric Oncology Group
- 1991: Outreach to China: Beijing Children's Hospital and Shanghai Children's Medical Center
- 1995: Founded International ALL working group joined by 15 major national study groups or institutions around the world -- international collaborative research
- 2006: Initiated St. Jude Viva Forum in Singapore -- teaching, networking, and research in Asia
- 2014: Formed First China National ALL Study Group

Childhood Cancer in Mainland China

- 50,000 new cases per year
- 20,000 new ALL cases per year
- Before 2010, < 10% of patients with ALL were treated (increasing to ~ 30% in 2011 and >90% presently)

Estimated 5-year Survival of Children (aged 0-14 years) with Acute Lymphoblastic Leukemia in China

- 1995-99: 10.9% (95% CI, 1.5-20.2)
- 2000-04: 50.0% (95% CI, 39.7-60.2)
- 2005-09: 61.1% (95% CI, 51.3-70.8)

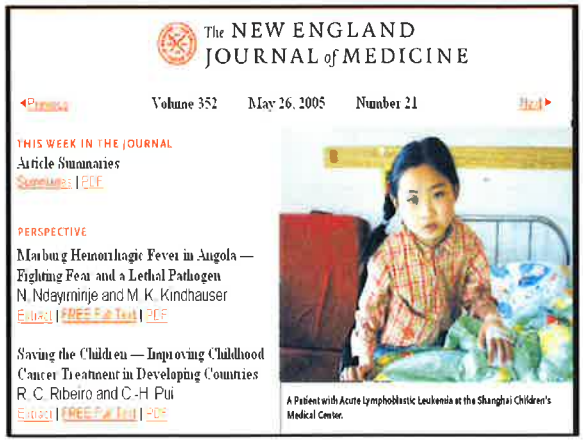
Data from Beijing, Changle, Cixian, Daleng, Dalian, Dongbei, Feicheng, Ganyu, Guanyun, Haimen, Haitang, Jianhu, Jiashan, Jiutan, Qianyungang, Lanzhou, Qidong, Situn, Taixing, Yangzhong, Zhongshan

Allemani et al. Lancet 2015;385:977-1010

China ALL Pilot Protocol

- Developed in December 2004 at St. Jude by the hematologists/oncologists from BCH and SCMC
- The first joint low- and intermediate-risk ALL protocol in China applied at the two leading pediatric centers
- Approved by St. Jude and supported by Partner in Hope foundation Limited (founded by a St. Jude board member)
- Underprivileged patients without any means to pay
- $14,400 - $16,000 per low risk patient

  $22,000 - $24,000 per intermediate patient


The NEW ENGLAND JOURNAL of MEDICINE

Volume 352 May 26, 2005 Number 21

THIS WEEK IN THE JOURNAL

Article Summaries

PERSPECTIVE

Marburg Hemorrhagic Fever in Angola — Fighting Fear and a Lethal Pathogen

N. Ndayimirije and M. K. Kindhauser

Saving the Children — Improving Childhood Cancer Treatment in Developing Countries

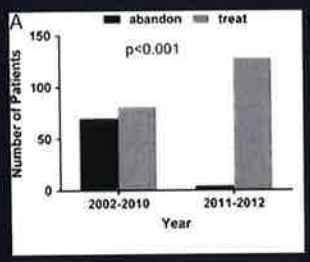
R. C. Ribeiro and C.-H. Pui

A Patient with Acute Lymphoblastic Leukemia at the Shanghai Children's Medical Center.

Childhood Cancer in China

- The ALL program was introduced to Chen Zhu (then Director of Shanghai Institute of Hematology) in 2005.
- Chen Zhu became Health Minister of China in 2007
- The success (86% in continuous complete remission and affordable cost) was published in Pediatr Blood Cancer by Shanghai Children's Medical Center (Dr. JY Tang) in 2009 and drew the attention of Chen Zhu
- In 2010, Chen Zhu initiated New Rural Cooperative Medical Care System (新农合医疗保险), starting with childhood ALL.

Abandonment Rates in Remote Areas Before and After NRCMCS* (新农合医疗保险) (1151 patients 2002 – 2012 in Suzhou City)

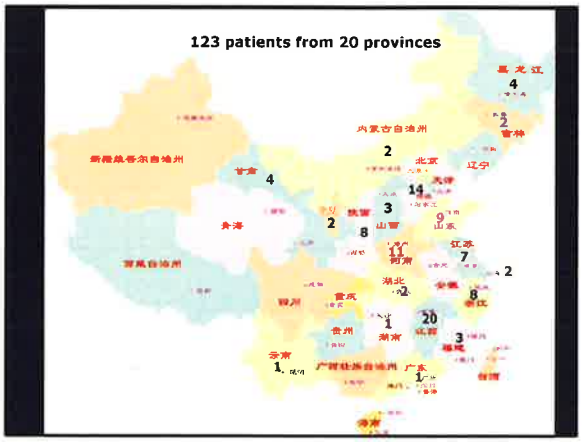


New Rural Cooperative Medical Care System (NRCMC 新农合医疗保险)

Zhou Q, et al. J Ped Hem Onc; 2015; 37:181-184

China National Multi-Center Childhood ALL Study Group

- Established in October 2014 with the full support of Shanghai Children's Medical Center and chaired by Dr. Tang Jingyan
- Included 20 major hospital/medical centers in 16 provinces, 3 direct-controlled municipalities and Hong Kong
- Adapted a uniform risk-stratified treatment protocol on the basis of St. Jude Total Therapy study with some modifications according to the tolerance of Chinese patients
- Targeted to enroll 1,200 – 1,500 cases per year



China National Multi-Center Childhood ALL Study Group

VIVA –China Children's Cancer Foundation

- Established by Jennifer Yeo (Founder of Singapore VIVA Foundation) and registered in Hong Kong in 2014 to support CCCG-ALL Group
- Budgeted RMB 3.6 millions per year with total 5-year budget RMB18 millions to support data management, diagnostic laboratory tests, education/training, etc.

Inaugural Meeting of China National Multi-Center Childhood ALL Study Group

China National Multi-Center Childhood ALL Study Group (CCCG-ALL)

October 2014 – March 2016

Total 1257 patients have been enrolled

- 675 low-risk, 552 intermediate-risk, 30 high-risk
- Age: 4 months – 16 years
- Adverse Events
  - 8 patients had resistant disease
  - 19 (1.5%) relapsed
  - 26 (2.1%) abandoned treatment mainly due to financial reason
  - 23 (1.8%) died of toxicity
  - 3 off protocol due to toxicity

Remaining 1178 (94%) patients are receiving treatment in remission.

Recommendation for Future Direction

Establish a National Child Health Center

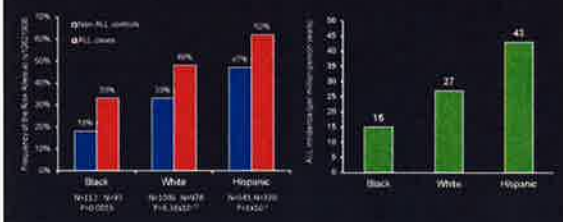
- Education and training
  - Establish bases for continual education and training of healthcare providers
  - Establish healthcare provider qualification examination system to ensure the quality of medical care
- Enhancement of collaboration of multidisciplinary teams
- Research Priorities
  - Develop the necessary infrastructure to support clinical research
  - Apply and develop efficient mechanisms for timely application of effective new treatments
  - Prioritize emerging research initiatives

Inherited Gene Variants Associated with the Development of Childhood ALL*

Gene	Odd Ratio 95% CI	Comment
IKZF1[1,2]	1.69	Associated with B- and T-ALL
ARID5B[3,4]	1.5-1.7	Associated with hyperdiploid ALL. Hispanics>Whites>Blacks
CEBPE[5]	1.2-1.4	Associated with B- and T-ALL
CDKN2A[6]	1.1-1.5	Associated with B- and T-ALL
BMI1-PIP4K2A[6,8]	1.2-1.5	Hispanics>Whites>Blacks
GATA3[9]	1.2-5.4	Associated with Ph-like ALL and risk of relapse
TP63, PTPRJ[8]	0.5-0.8	Associated with *ETV6-RUNX1* ALL

*Papaemmanuil et al. Nat Genet 2009; [1]Trevino et al. Nat Genet 2009; [2]Prasad et al. Blood 2010; [3]Mullighan et al. Nat Genet 2010; [4]Xu et al. J Natl Cancer Inst 2013; [5]Migliorini et al. Blood 2013; [6]Perez-Andreu et al. Nat Genet. 2013; [8]Buitenkamp, Leukemia 2012

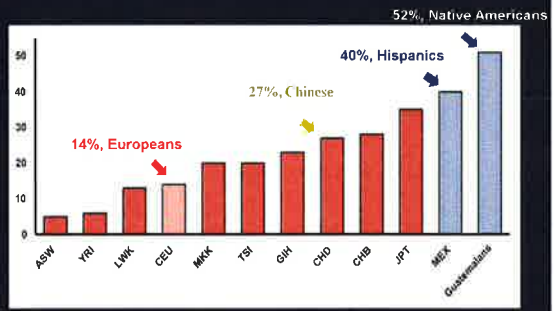
ARID5B Genetic Polymorphisms Contribute to Racial/Ethnic Difference in the Incidence of Childhood ALL



Frequency of the risk allele of *ARID5B* SNP (rs10821936) increases in order for Blacks, Whites and Hispanics, consistent with the racial differences in ALL incidence

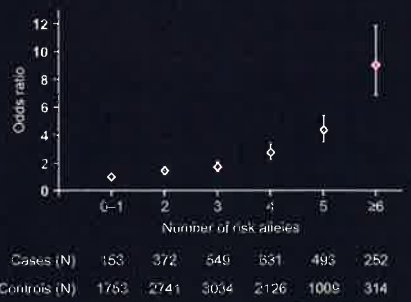
Xu et al., J Clin Oncol 2012;30:751-7

GATA3 Risk Variant Frequency Varied Among Worldwide Populations



Perez-Andreo et al., Nat Genet 2013;45:1494-8

ARID5B, *IKZF1*, *CEBPE*, and *BMI1-PIP4K2A* variants Cumulatively Conferred Predisposition to ALL



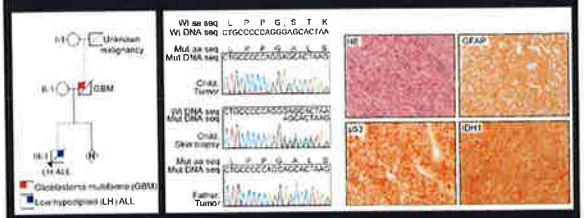
Those with ≥6 risk alleles were at 9-fold higher risk than subjects with 0–1 copies

Xu et al., J Natl Cancer Inst 2013;105:733-42

Germline Mutations and ALL Risk

- *TP53* in low-hypodiploid ALL
- *PAX5* G183S mutations in familial ALL
  - Shah et al. Nat Genet 2013;45:1226-31
- *ETV6* mutations in familial thrombocytopenia and hematopoietic malignancy
  - Zhang et al. Nat Genet 2015;47:180-5
  - Noetzli et al. Nat Genet 2015;47:535-8
  - Topka et al. PLOS Genet 2015;11:e1005262
  - Moriyama et al. Lancet Oncol. 2015;16:1659-66

Inherited TP53 mutation in a low-hypodiploid ALL kindred



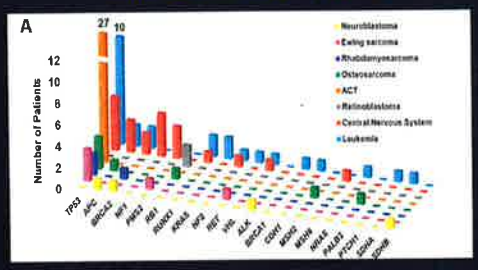
Child: low hypodiploid ALL
Father: glioblastoma multiforme

p.Gly302fs
Homozygous in tumors
Heterozygous skin biopsy

TP53 immunoreactivity in glioblastoma multiforme

Mike Walsh, David Ellison

Germline Mutations in Cancer Predisposition Genes in 1,120 Children with Cancer



98/1,120 patients (8.6%) in PCGP harbored germline mutations within 59 well characterized cancer predisposition genes

Zhang et al. N Engl J Med 2015;373:2336-46

Germline Mutations of Cancer Predisposition Genes in Children with leukemia

- Whole-genome or whole-exome sequencing of both of remission bone marrow or blood sample
- 567 genes were selected for in-depth analysis based on their associated inheritance patterns, associated syndromes, penetrance, *de novo* mutation rate, etc
- Germline mutations involved in 26 of 588 leukemia patients (4.4%) vs. 1.1% in 1000 Genome Project and 0.6% in Autism study
- Hypodiploid ALL has the highest rate of germline mutation (*TP53*), 53% among low-hypodiploid cases
- Panel of genes associated with ALL: *ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, SRP72, TERC, TERT, TP53*

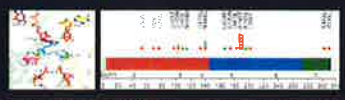
Zhang et al. N Engl J Med 2015;373:2336-46

Genome Sequencing Identified Mutations Associated with Drug Resistance in Relapsed ALL

Activating mutations in *CREBBP*
Glucocorticoid resistance

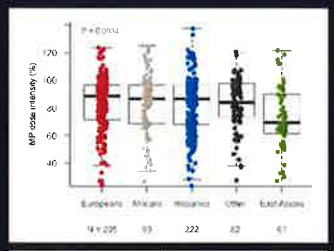
Activating mutations *NT5C2*
Thiopurine resistance

Negative feedback-defective mutations in *PRPS1*
Thiopurine resistance



Mullighan et al. Nature 2011;471:235-9; Meyer et al. Nat Genet 2013;45:290-4; Tzoneva et al. Nat Med 2013;19:368-71; Li et al. Nat Med 2015;21:563-71

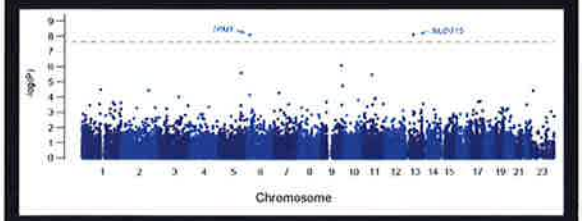
East Asians Have Poorer Mercaptopurine Tolerance



	Regression coefficient estimate	P
East Asian ancestry	-0.14	0.0003

Yang et al. J Clin Oncol 2015;33:2235-42

Second Genome-wide Significant Locus: *NUDT15*

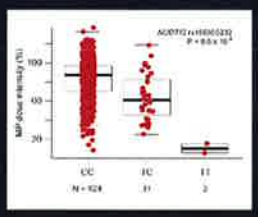


- Each dot is a SNP and color indicates chromosome
- Inverse log-transformed P value on the Y axis
- The taller the peak, the smaller the P value, and the stronger the association

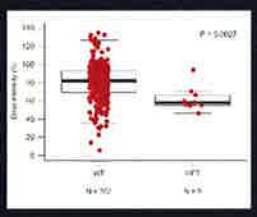
Yang et al., J Clin Oncol 2015;33:1235–42

NUDT15 C415T Variant is Strongly Associated with Mercaptopurine Intolerance

Discovery GWAS (AALL03N1)



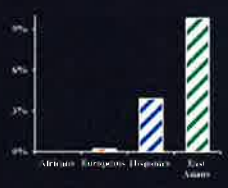
Replication Cohort (St. Jude Total XV)



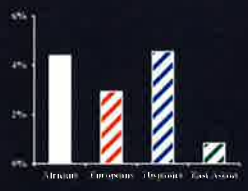
Yang et al., J Clin Oncol 2015;33:1235–42

NUDT15 contributes to Ancestry-related Differences in Mercaptopurine Tolerance

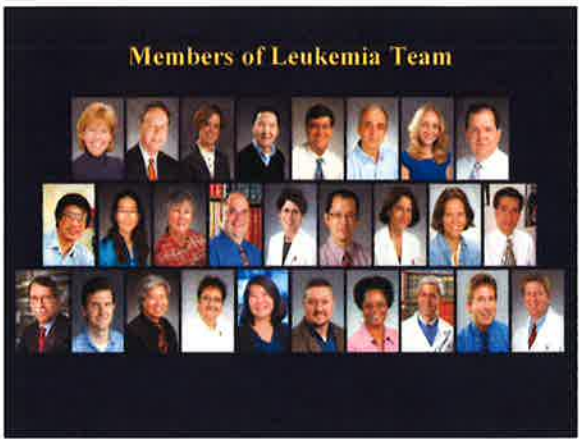
NUDT15 Variant



TPMT Variant



Yang et al., J Clin Oncol 2015;33:1235–42


Members of Leukemia Team