



# GENETICS OF CHILDHOOD ACUTE LEUKEMIA

## THE PONTENTIAL CONTRIBUTION OF BRAZILIAN STUDIES

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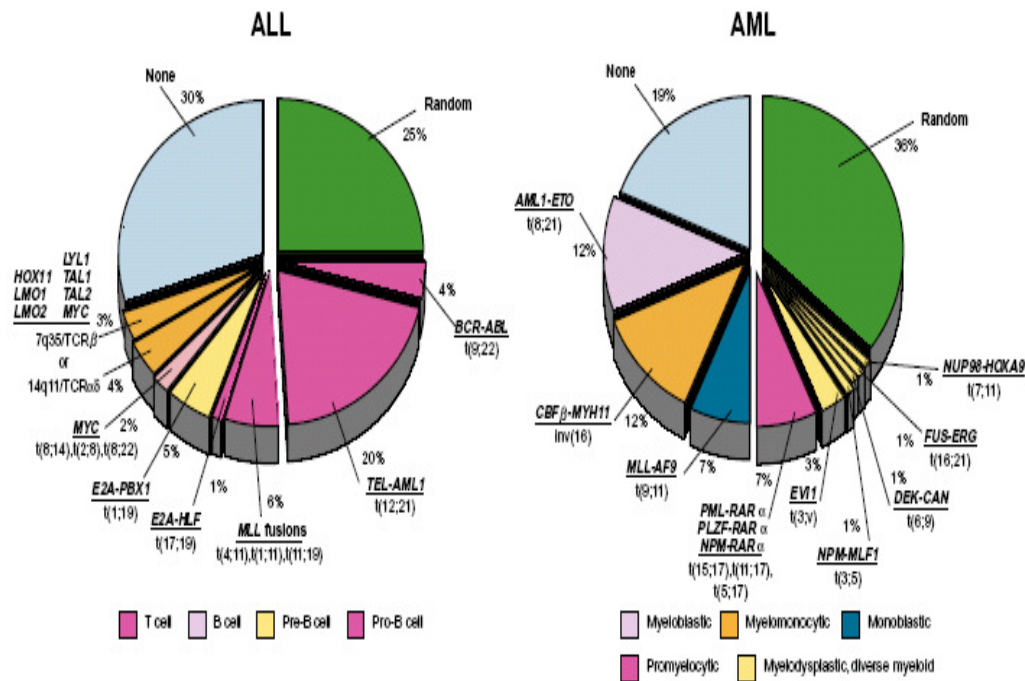
Ministério  
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# GENETICS OF CHILDHOOD ACUTE LEUKEMIA

I- SOMATIC OR ACQUIRED pathogenetic events leading to acute leukemia (85%)

II- CONSTITUTIVE inherited predisposing genetic synd. (5%)



• Trisomy 21 (Down synd)

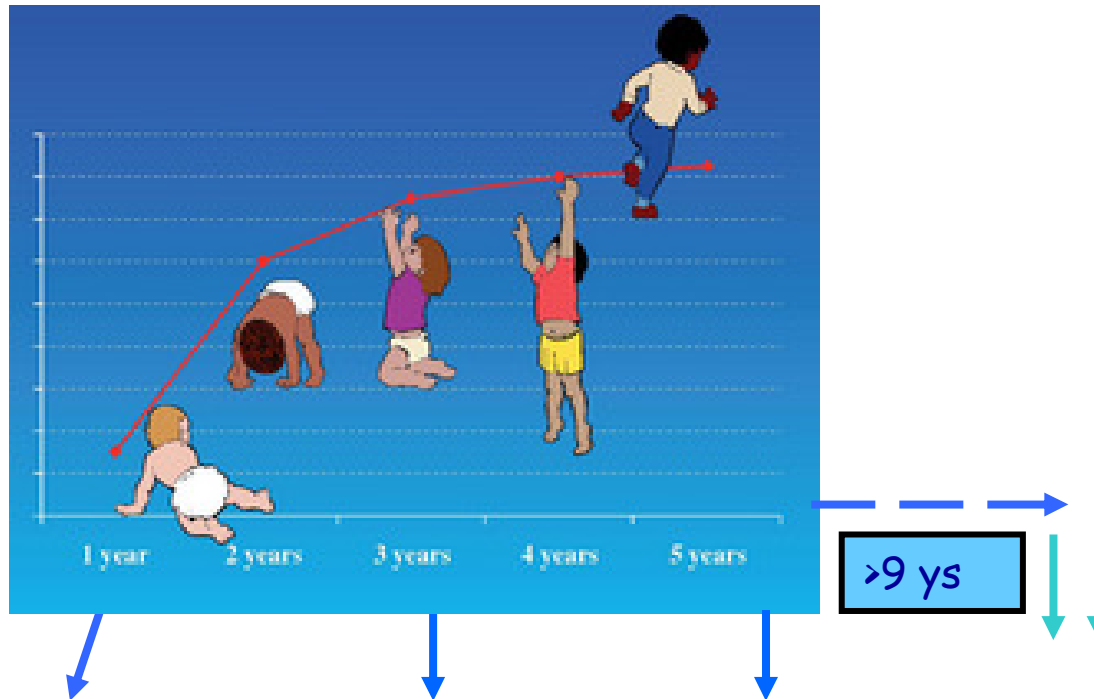
• *BLM* mut 15q26.1 (Bloom Synd)

• *ATM* mut 11q22-23(A-T synd)

• *NBS1* mut and/or inv. Transl 7q13, 7q35, 14q11, 14q32 (A-T variant or Nijmegen breakage synd)



**AGE vs ACUTE LEUKEMIA= may reflect correlation with environmental risk factors**

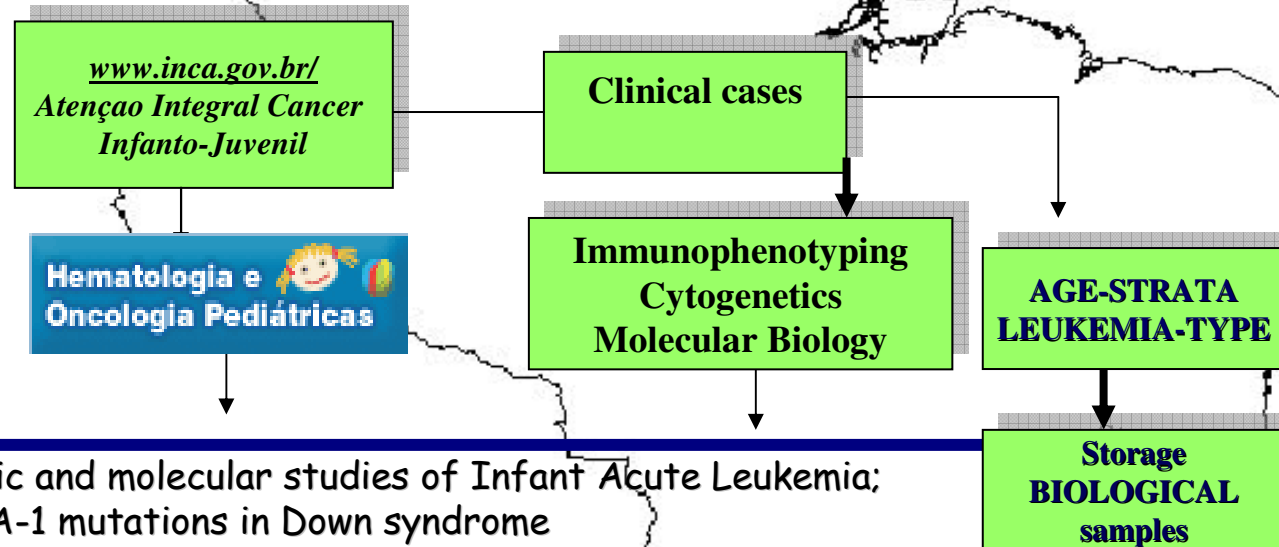


pro-B ALL, AML  <i>MLL/AF4, ENL, AF9, AF6, ELL; GATA-1 mut Hox11L2</i>	ALL-CD10+  <i>TEL/AML1+ E2A/PBX1, Hyperdiplod FLT3 Mut.</i>	T-ALL,AML  <i>SIL/TAL1, NOTCH1, HOX11L2, BCR/ABL, AML1/ETO</i>
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B- and T-NHL/AL  
*BLM, ATM, NBS1*



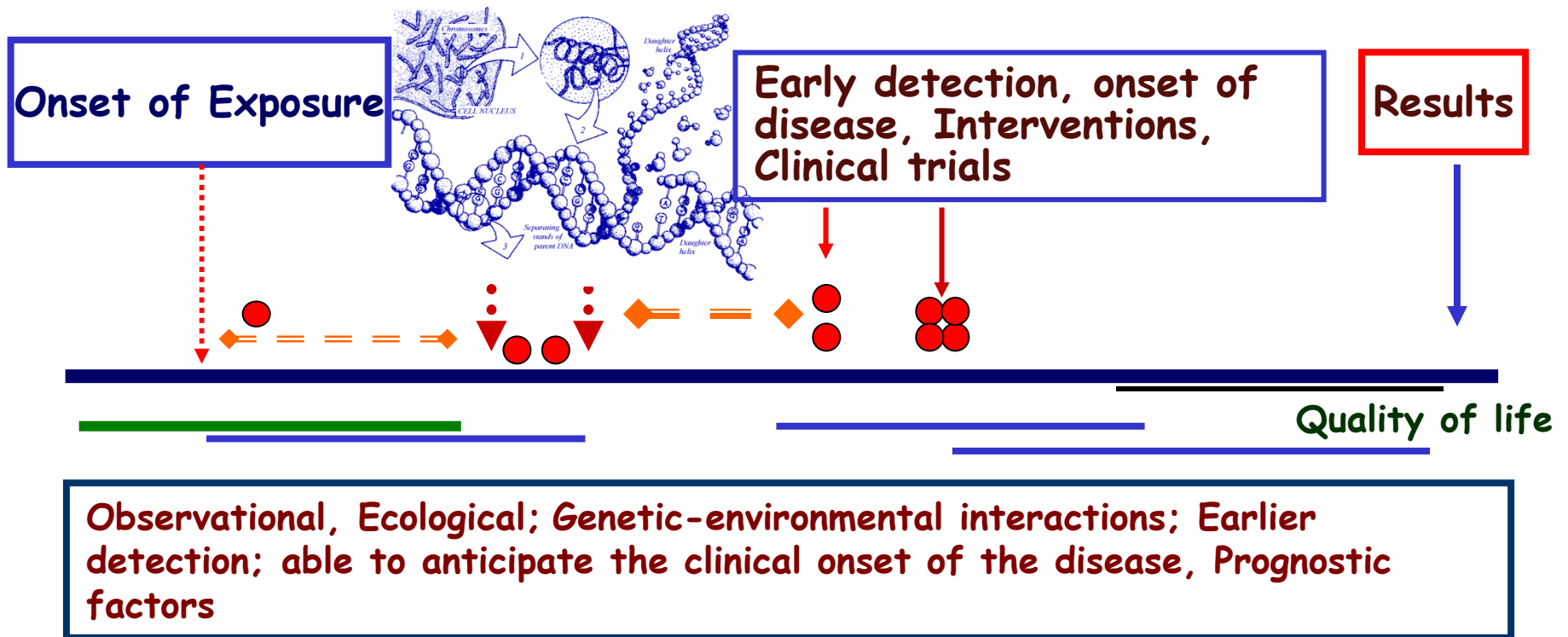
# THE PONTENTIAL CONTRIBUTION OF BRAZILIAN STUDIES



1. Epidemiologic and molecular studies of Infant Acute Leukemia;
  - *GATA-1* mutations in Down syndrome
  - Identification of 11q23 abnormalities in IAL
  - Genetic polymorphism significance with exposure to Topo-II inhibitors
2. Phenotype-Genotyping studies on B and T-ALL
  - The role of infections as "2nd hit" in c-ALL
  - Mutations in *NOTCH1* gene in T-ALL/NH-L
  - Genetic Polymorphism of folate-cycle genes
3. Epidemiology of pediatric Acute Myeloid Leukemia in Brazil
  - Identification of *Ras* mutations



# Why to study Infant Leukemia?





# ***IN UTERO EVENT***

## **... MOLECULAR EVIDENCE**

### **1. Direct evidence:**

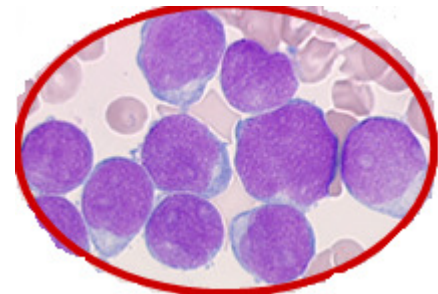
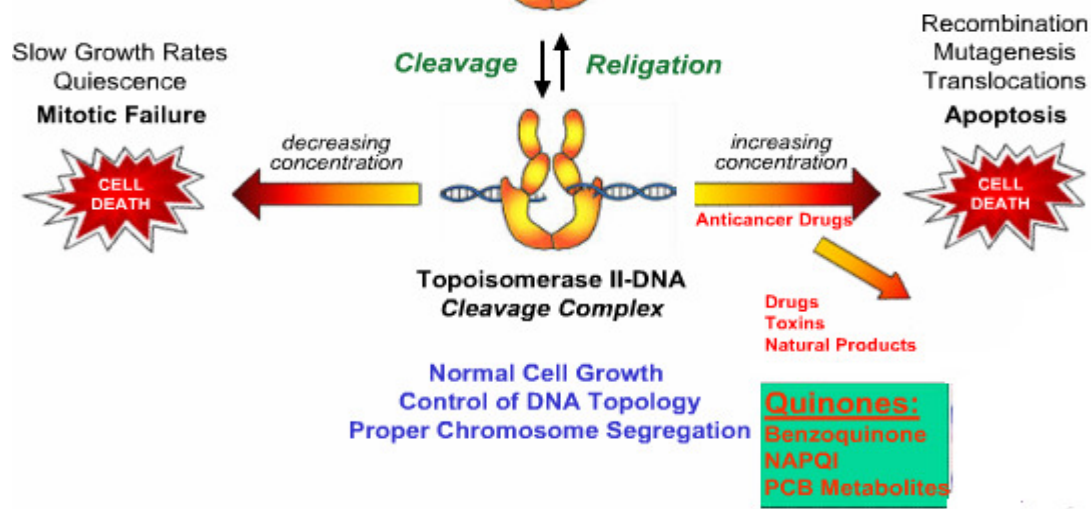
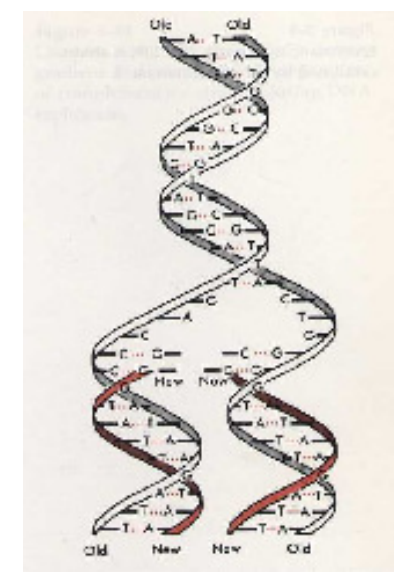
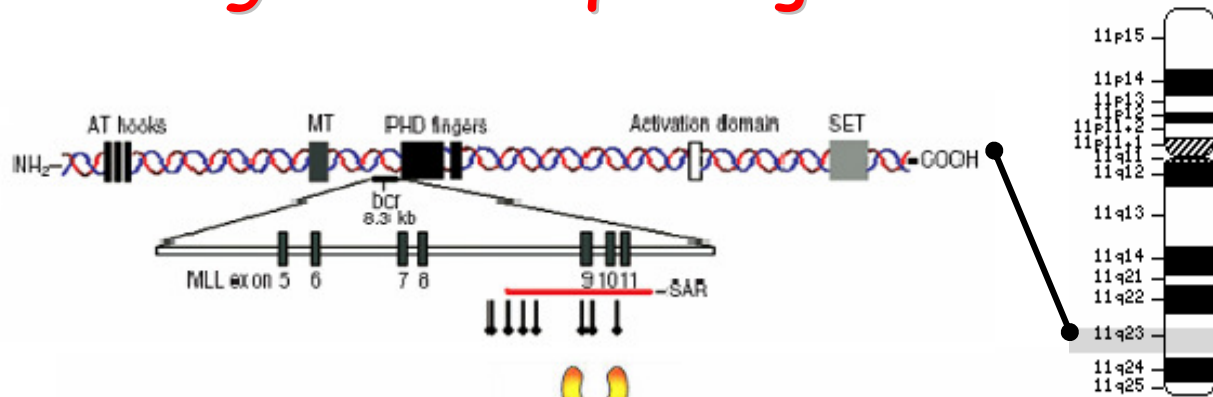
- sets of infants twins with concordant leukemia (Ford, 1993);
- Backtracking MLL abnormalities in Guthrie cards of IAL (Gale, 1997);

### **2. Experimental (indirect) evidence:**

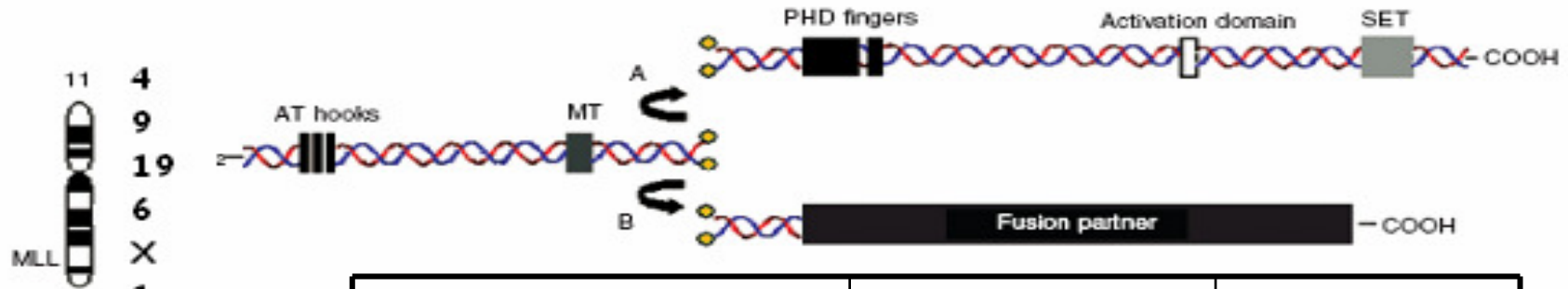
- Modeling the initiation and progression of human acute leukemia in mice (Barabe, 2006)



# MLL gene at 11q23 region



# DIFFERENCES OF FUSION PARTNERS



	IAL	s-AML
<i>AF4</i>	42%	3%
<i>AF9</i>	23%	3%
<i>ENL</i>	5%	-
<i>ELL</i>	5%	34%
<i>AF10</i>	5%	10%
<i>AF6</i>	5%	-
<i>VARIADOS</i>	15%	50%

# HYPOTHESIS

- Growing foetus is more sensitive to effects of potential DNA damage insults
- Junction + Inhibition of *TOPO II* during the embryogenesis
- MLL rearrangements and Hybrid protein
- Additional gene aberration

Self-  
renovation

SCF  
(c-kit)

Flk1

Flt1



Cellular growth

Kit-ligand

GM-CSF, G-CSF, CSF-1

IL-3, 6

FLT3-ligand

Differentiation

*GATA-1 e 2*

*SCL/TAL-1*

*PU-1*

*Ikaros*

*HOX gene*

Apoptose

BCL2

MYC

P53

BAX



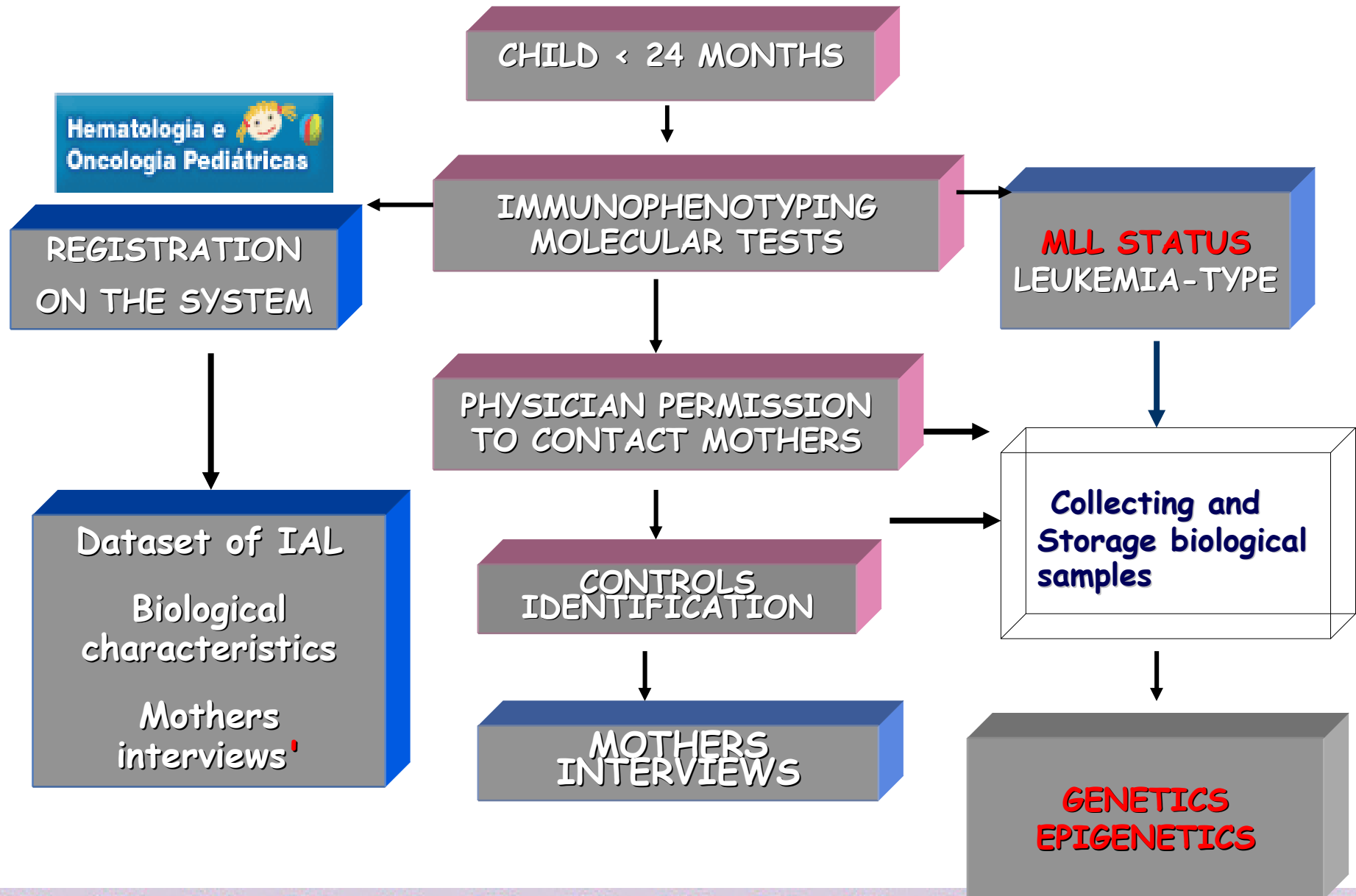
# EPIDEMIOLOGY OF ACUTE LEUKEMIA

In utero Radiation:	During pregnancy is generally accepted as risk factor. Nowadays the low frequency of use is diminishing the magnitude of risk
Alcohol use during pregnancy:	Maternal use is associated with 2-fold increased risk of AML (children <3yrs of age). So far, not demonstrated in IAL
Maternal Reproductive History:	Consensus an increased risk of IAL
High Birth weight*:	The majority of epidemiological studies showed an increased risk (ALL) in IAL who weight > 4,000gm.

(\* ) Hypothesis that high levels of insuline-like groth factor-1 in association with high birth weight may contribute to leukemogenesis pathway

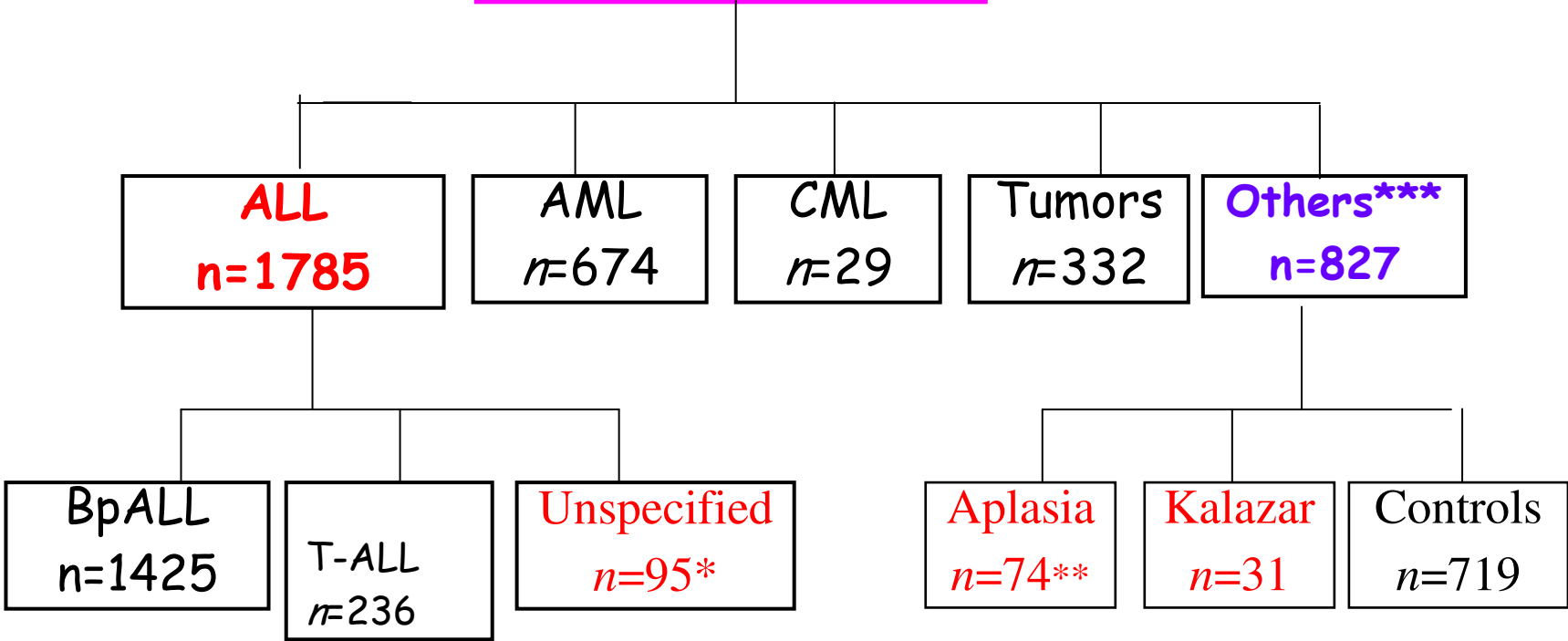


# IAL: CASE-CONTROL STUDIES





[1999-2008];n=4088



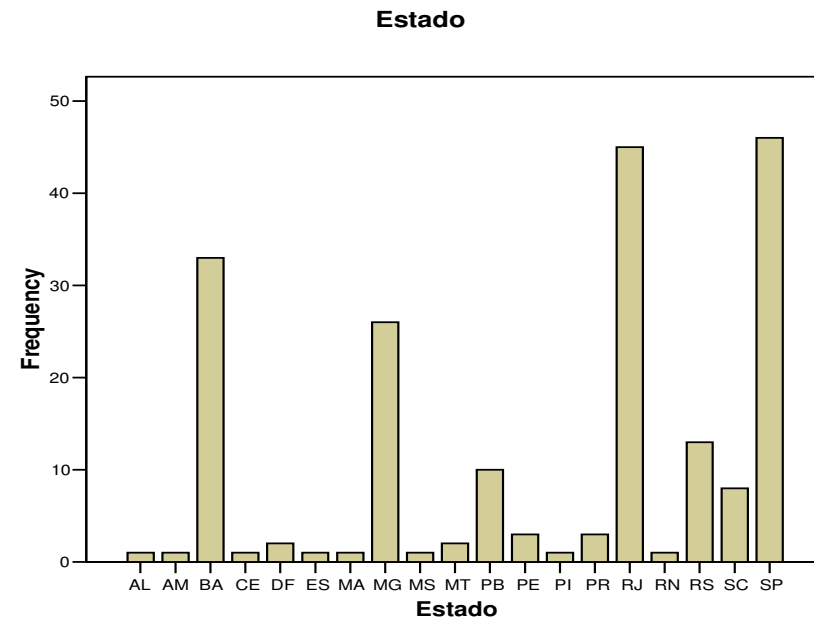
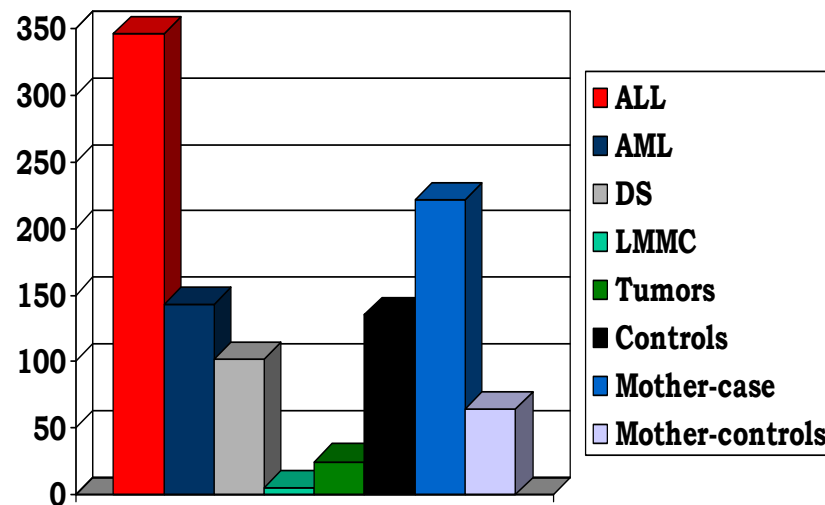
(\*) Previous use of glycocorticoides, Abnormal phenotypes

(\*\*) Outcome unknown; (\*\*\*) Samples from mothers (Case/Control= 286)





# 1) Ascertainment and samples from cases and controls in the IAL study 1999-2008 (n=904)\*



(\*) Preliminary analysis 1999-2005: 202 cases/440 controls  
2006-2008: 119 cases/138 controls





# GENETIC MOLECULAR MARKERS IN IAL

## ...Unusual data

TABLE III. Summary of Chromosome Translocations According to Age

Fusion gene	0–12 months	12–23 months	P
	n <sup>+ve</sup> /n <sup>total</sup> (%)	n <sup>+ve</sup> /n <sup>total</sup> (%)	
<i>MLL</i>	50/86 (58%)	31/78 (40%)	0.011
<i>TEL/AML1</i>	4/29 (14%)	5/32 (16%)	1.000
<i>E2A/PBX1</i>	1/10 (10%)	3/13 (23%)	0.604
<i>AML1/ETO</i>	1/6 (17%)	2/5 (40%)	0.545

***SIL/TAL1*            3/19 (20.7%)**

***PML/RARA*            4/5 (80%)**

***CBFb-MYH11*        4/5 (80%)**

***MLL DUPL*            2/10 (20%)**

- SNP array analysis of

- **TEL/AML1+ IL patients (\*)**

- *del 9p (4 cases)*

- *del TEL (7 cases)*

- *Dissomy uniparental (q12.2-q21)- (2 cases)*

- *del1 (p22.2) (1 case)*

- *Loss of heterozygose (1 case)*

(\*) Emerenciano M, et al. 2006. *Etv6/Runx1* Fusion Gene And Additional Genetic Changes In Infant Leukemia





## Infants with T-ALL

Year	IDENT	Proc	Age*	S	R	WBC	EGI L	MOLECULAR-GENETICS	Status	Interview
1999	A.B. C. S	RJ	20	F	W	86.1	T-I	<i>MLL-</i> , <i>SIL/TAL1(+)</i>	D	Y
2000	G.S.R	RJ	20	F	W	240.1	T-I	<i>MLL-</i> , <b>del (12) (p?)</b> , <b>NOTCH1 mut</b>	D	N
2001	J.O.M.A.S	RJ	20	M	W	380.1	T-II	<i>MLL-</i> ; <i>SIL/TAL1(+)</i> ; <i>FLT3 mut-ITD</i>	D	Y
2001	H.C.L.	RJ	21	M	NW	440.1	T-IV	NA*	D	N
2002	MFS	PB	20	F	W	330.5	T-IV	<i>MLL-ENL(+)</i> ;	A	Y
2002	GMSA	PE	12	M	W	80.1	T-IV	NA*	D	Y
2003	JLS	PB	9	M	W	56.2	T-IV	<i>NOTCH1 mut</i>	A	N
2003	MSSA	BA	14	M	W	57.1	T-IV	<i>MLL-ENL(+)</i> ; <i>SIL-TAL1(+)</i>	PFI	Y
2004	FGS	PR	17	M	W	180.1	T-I	<b>del (6) (q23);del (7) (q32)</b>	A	Y
2005	AAA	BA	7	M	W	110.5	T-IV	<i>MLL-ENL(+)</i> ;	A	Y
2005	JCBB	GO	9	M	W	71.1	T-IV	NT	D	N
2007	VSV	SP	9	F	NW	501.9	T-II	<i>MLL-</i> , <i>Notch1 mut</i>	D	Y
2007	MAC	DF	8	M	W	15.4	T-IV	<i>MLL-</i> , <b>49,XY,+6,+8,+19</b>	A	Y
2008	CMNDL	DF	6	F	W	131.6	T-IV	<i>MLL-</i> , <i>HOX11L2(+)</i> ;	A	Y

(\*) Age in months; NA= Notch1 is still under analysis

Mansur M et al. 2008 T-cell acute leukemia and NOTCH1 mutation in infants





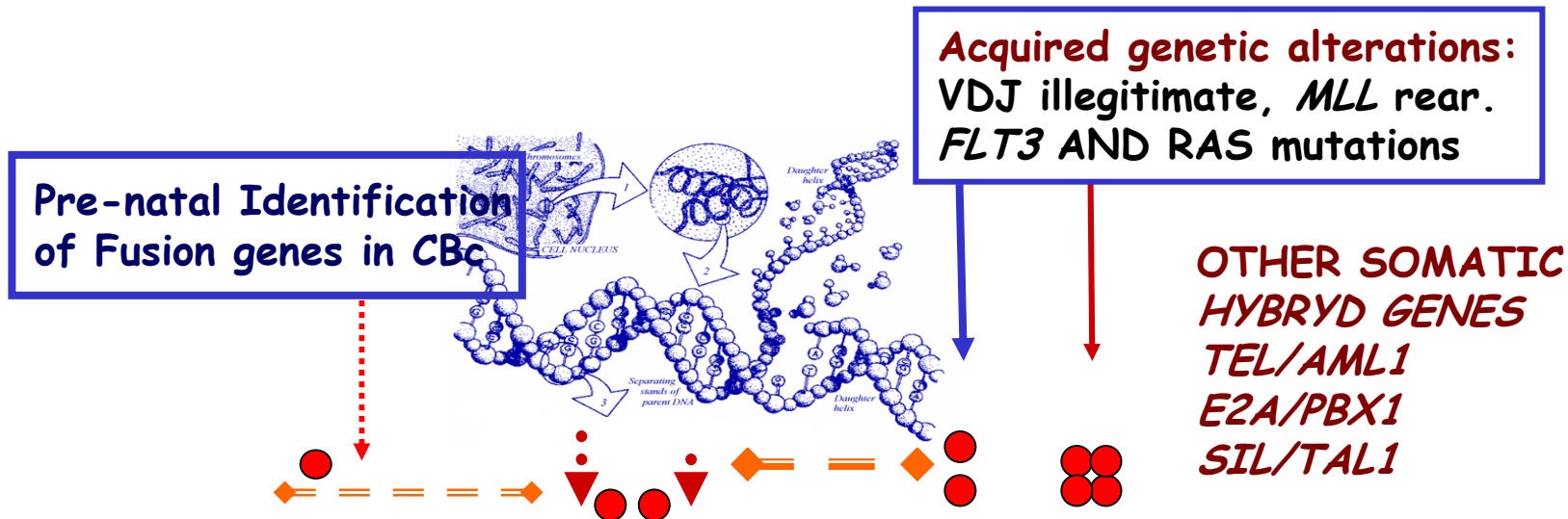
## Mutation analysis of *FLT3* gene in early infancy acute leukemia

- We looked for *FLT3* gene D835 mutations and internal tandem duplications (ITD) in 159 samples; Overall, 7.5% of patients had *FLT3* mutations
- *FLT3* mutations were found only in ALL {only *MLL+* samples};
- *FLT3*-ITD was found in 6 cases, being exclusively of AML and only one *MLL+*.
- Our results show that *FLT3* gene mutations do not constitute a frequent genetic abnormality in *MLL+* ILs

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# Infant Leukemia Studies



**Genetic-environmental interactions;**  
**Exposures and gene polymorphisms:**  
*NAT1/NAT2, MTHFR, IGF1 NQ01, MPO, SULT1, CYP3A4*

**Prognostic Biomarkers**  
**Therapeutical target**



# Acknowledgments



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SWISS BRIDGE

Support for Cancer Research Worldwide

