GENETICS OF CHILDHOOD ACUTE LEUKEMIA

THE PONTENTIAL CONTRIBUITION OF BRAZILIAN STUDIES

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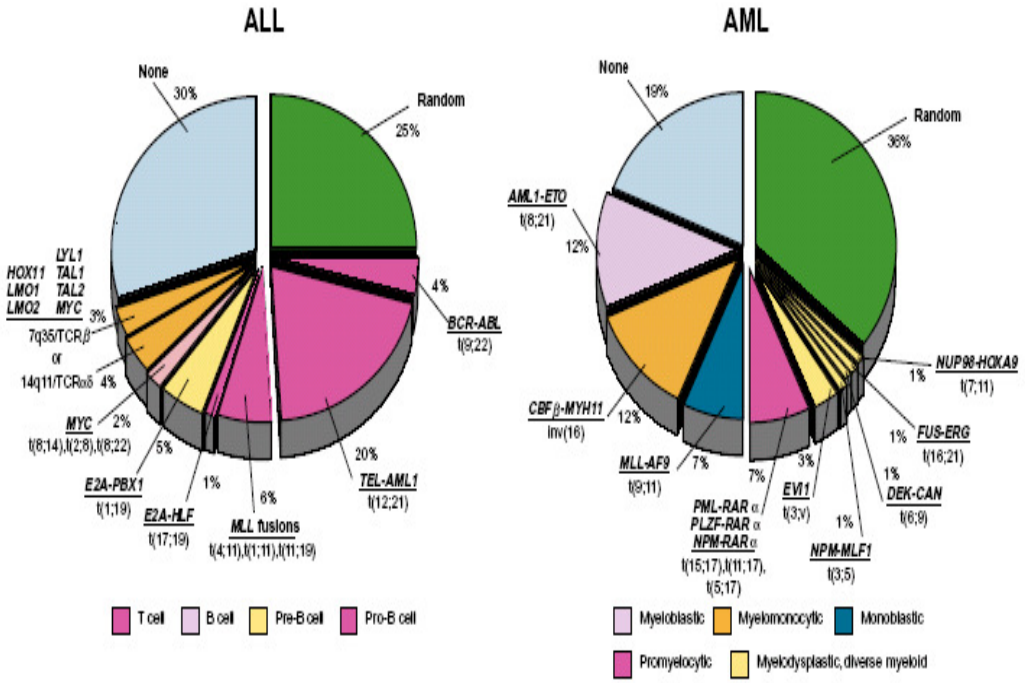
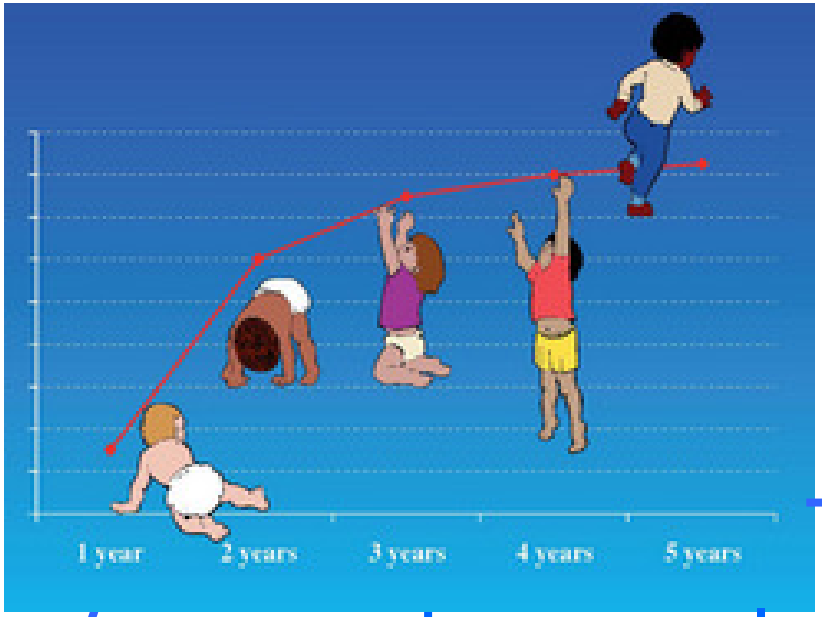
GENETICS OF CHILDHOOD ACUTE LEUKEMIA

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



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



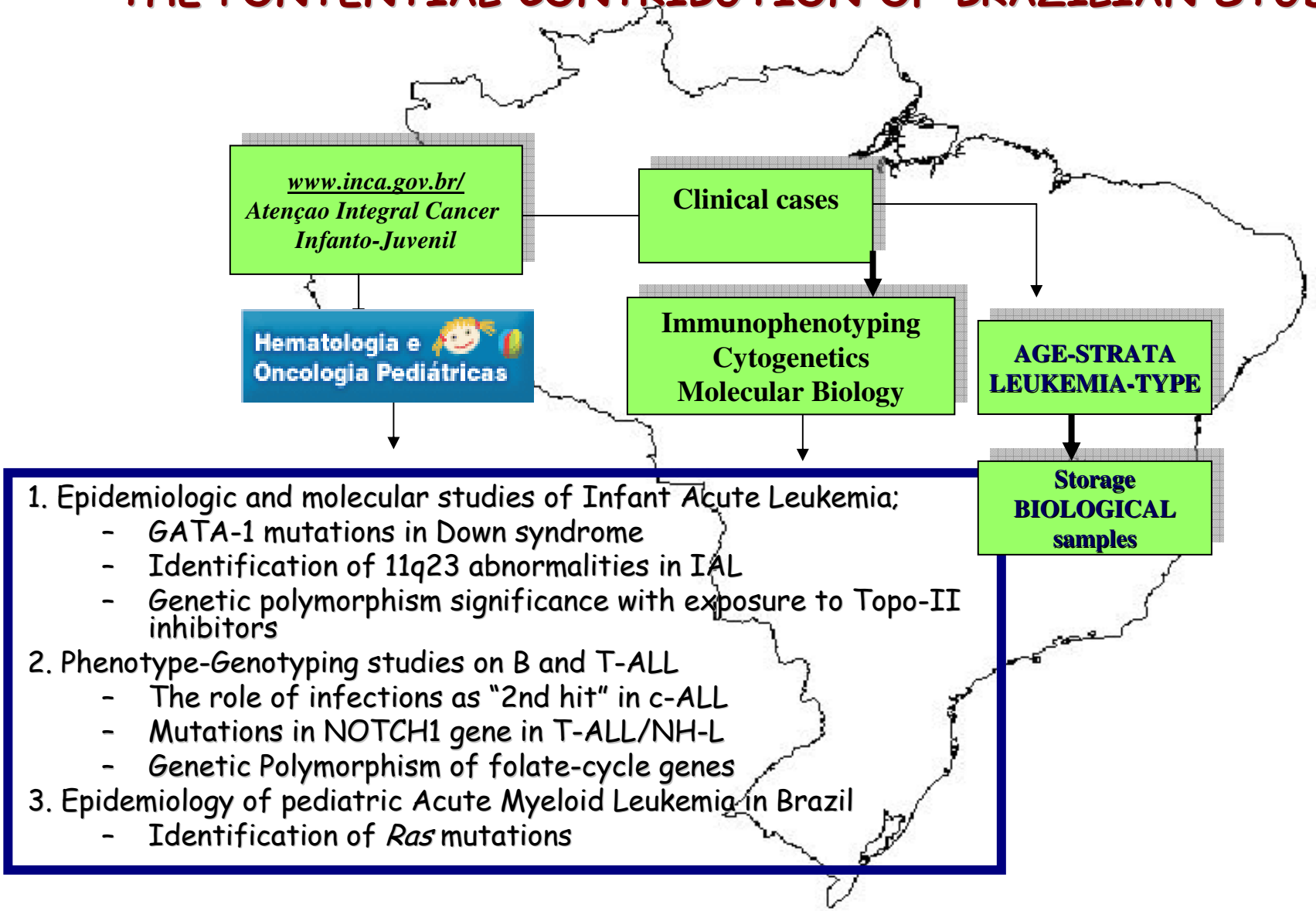
>9 ys

pro-B ALL, AML ***MLL/AF4, ENL, AF9,AF6, ELL; GATA-1 mut*** *Hox11L2*	***ALL-CD10+*** ***TEL/AML1+*** *E2A/PBX1, Hyperdiplod FLT3* Mut.	T-ALL,AML *SIL/TAL1, NOTCH1, HOX11l2, BCR/ABL, AML1/ETO*

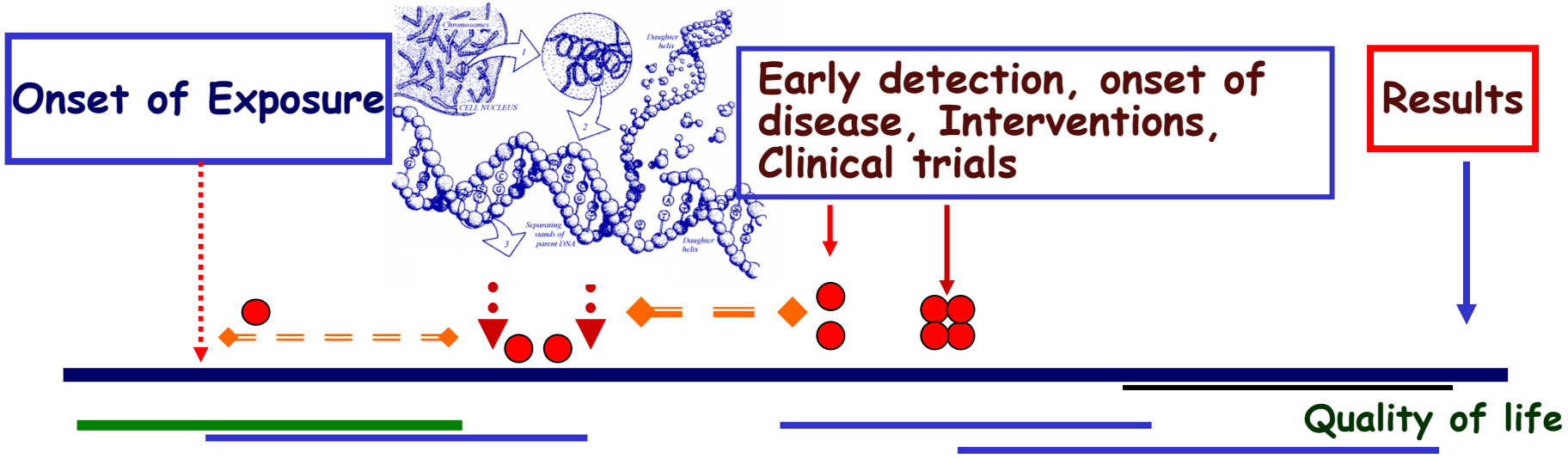
B- and T-NHL/AL

BLM, ATM, NBS1

THE PONTENTIAL CONTRIBUTION OF BRAZILIAN STUDIES



Why to study Infant Leukemia?



Observational, Ecological; Genetic-environmental interactions; Earlier detection; able to anticipate the clinical onset of the disease, Prognostic factors

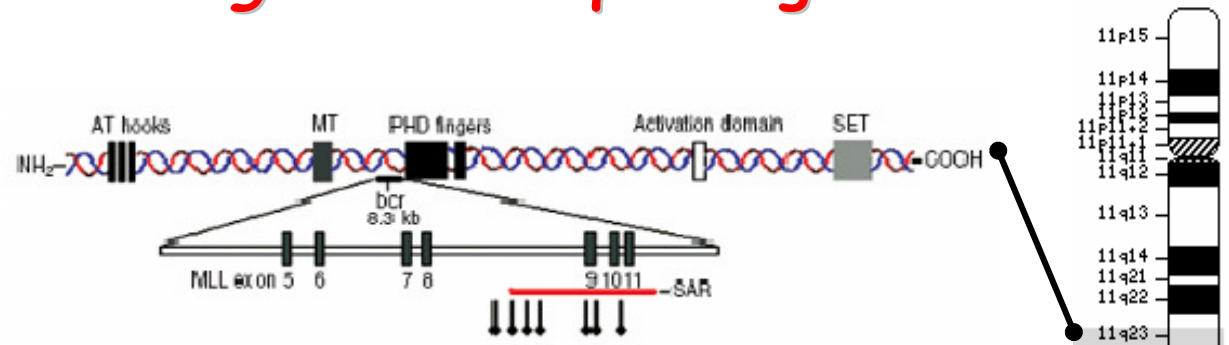
IN UTERO EVENT

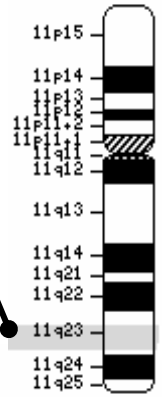
... MOLECULAR EVIDENCE

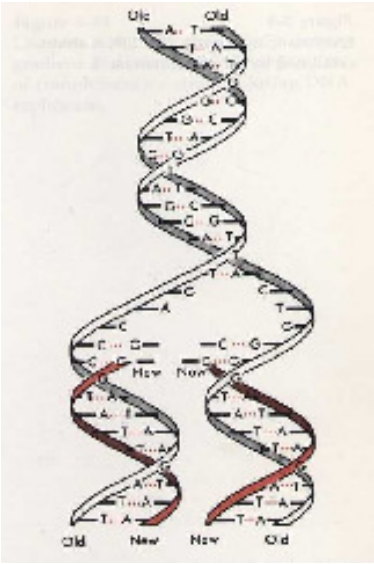
1. Direct evidence:
   - sets of infants twins with concordant leukemia (Ford,1993);
   - Backtracking MLL abnormalities in Gathrie cards of IAL (Gale, 1997);

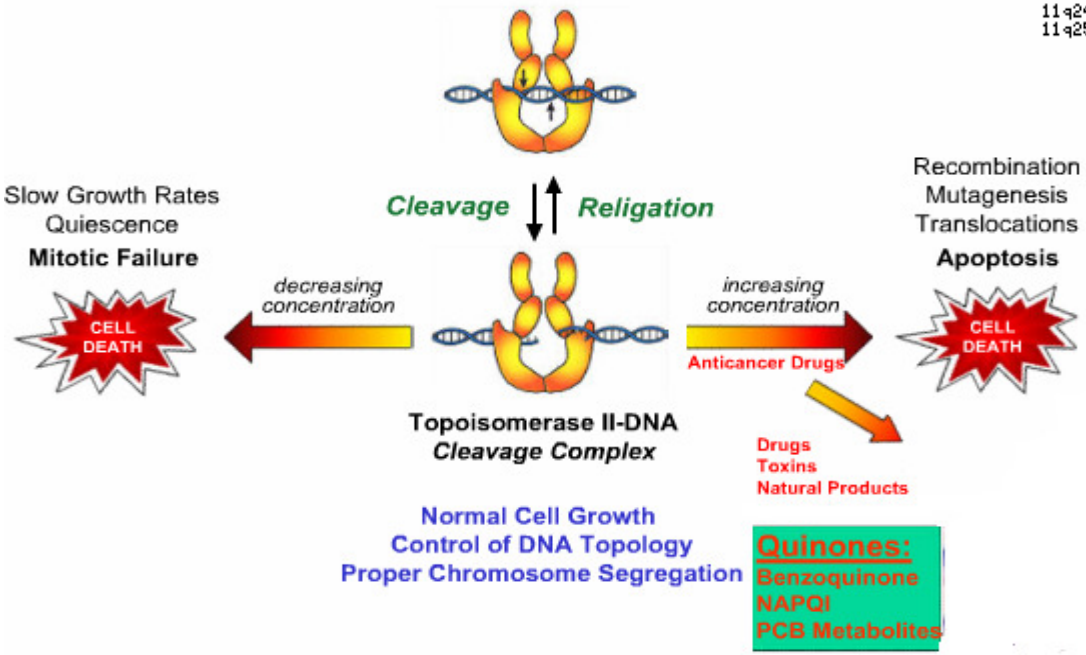
2. Experimental (indirect) evidence:
   - Modeling the initiation and progression of human acute leukemia in mice
     (Barabe, 2006)

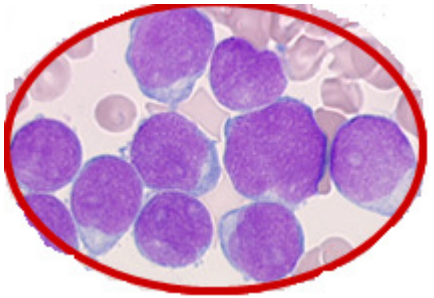
MLL gene at 11q23 region



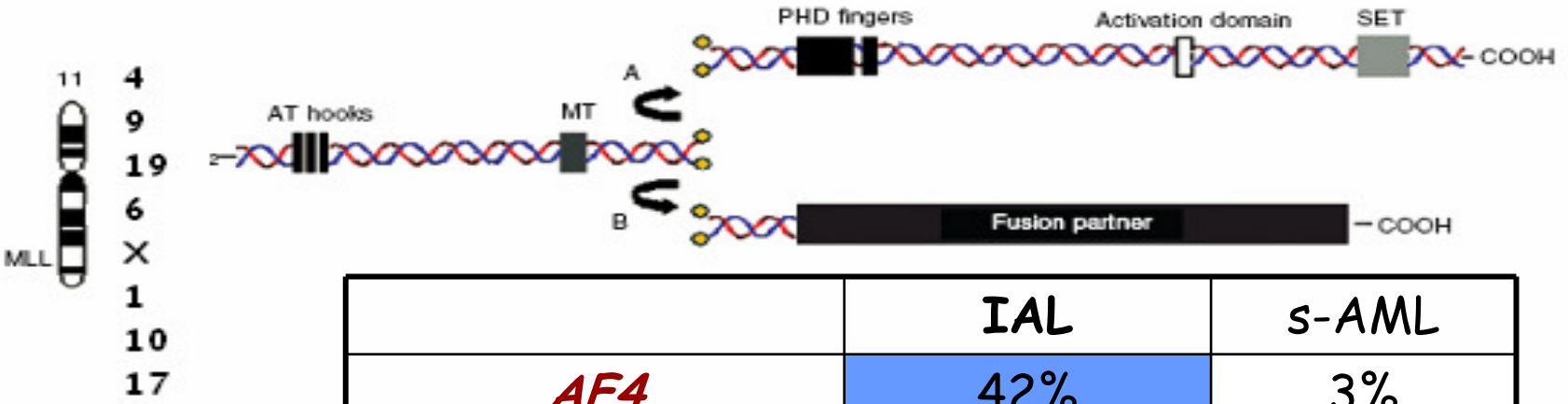








DIFFERENCES OF FUSION PARTNERS



	IAL	s-AML
AF4	42%	3%
AF9	23%	3%
ENL	5%	-
ELL	5%	34%
AF10	5%	10%
AF6	5%	-
VARIADOS	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

Cellular growth

Kit-ligand

GM-CSF, G-CSF, CSF-1

IL-3, 6

FLT3-ligand

Self-renovation

SCF (c-kit)

Flk1

Flt1

Apoptose

BCL2

MYC

P53

BAX

Differentiation

GATA-1 e 2

SCL/TAL-1

PU-1

Ikaros

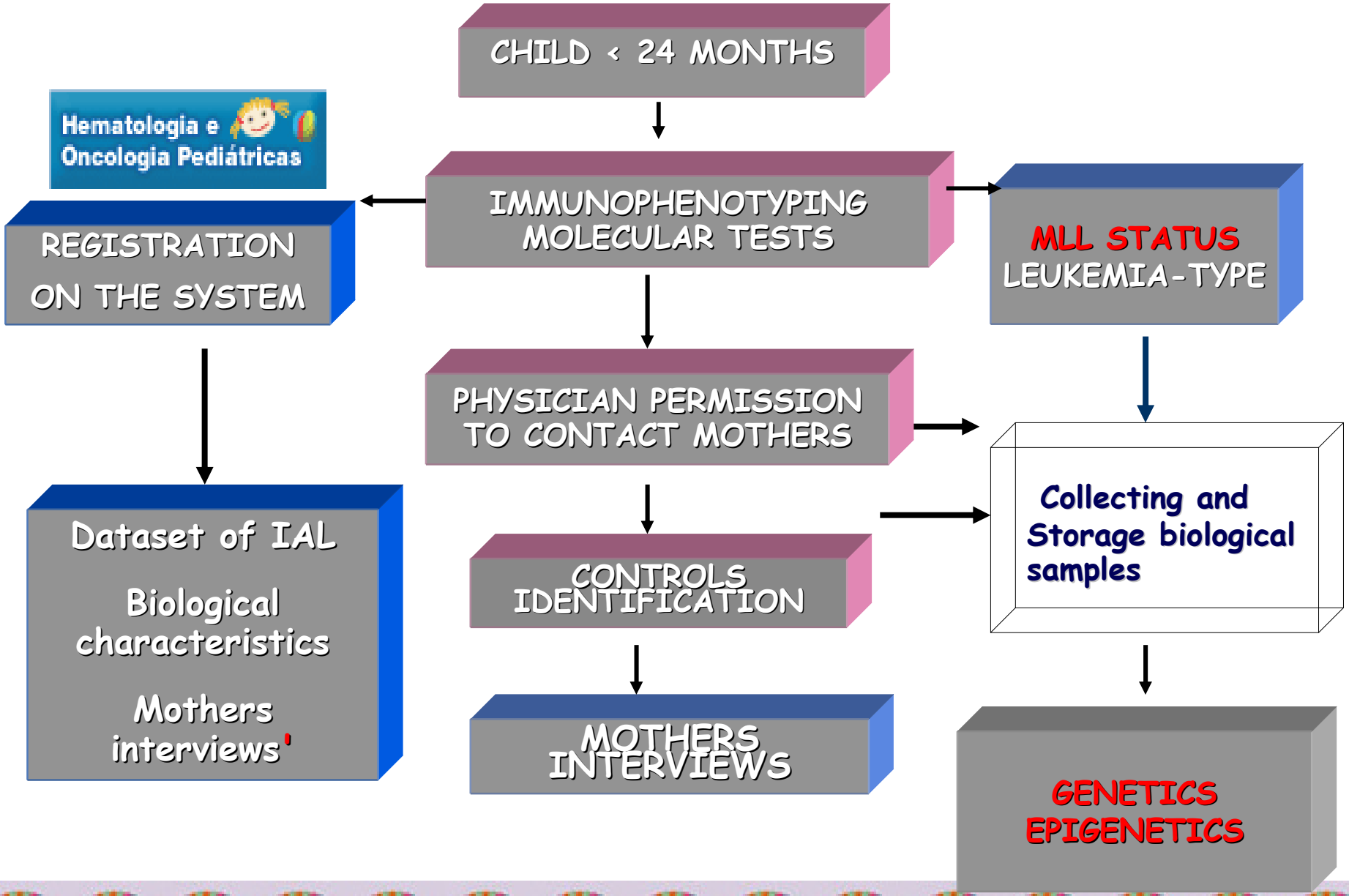
HOX gene

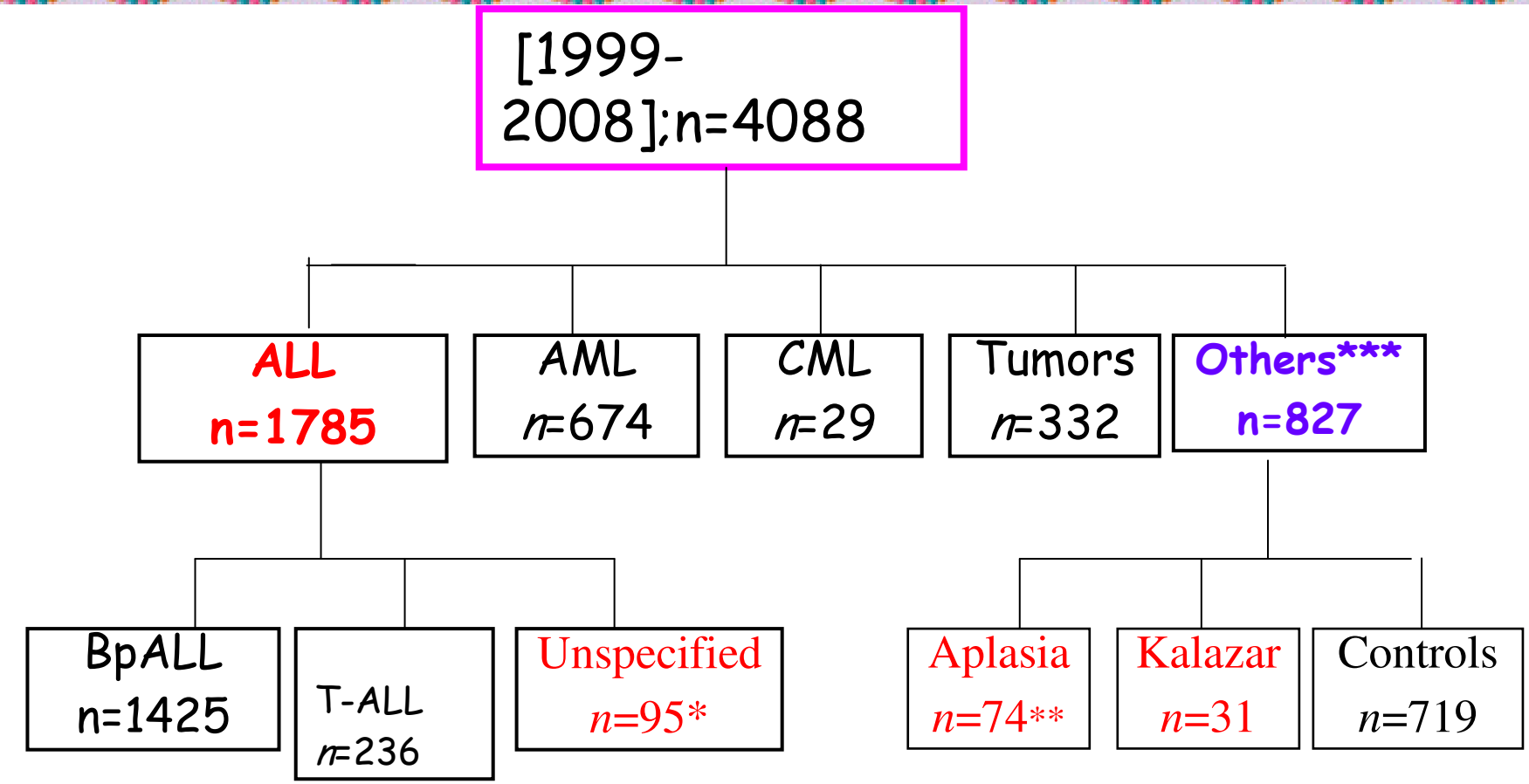
EPIDEMIOLOGY OF ACUTE LEUKEMIA

In utero Radiation:	During pregnacy is generally acepted as risk factor. Nowdays the low frequency of use is diminishing the magnitude of risk
Alcohol use during pregancy:	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

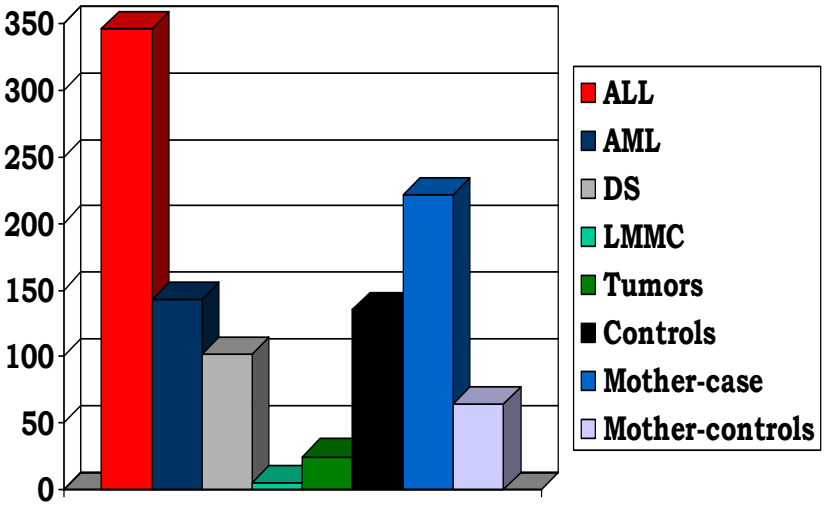


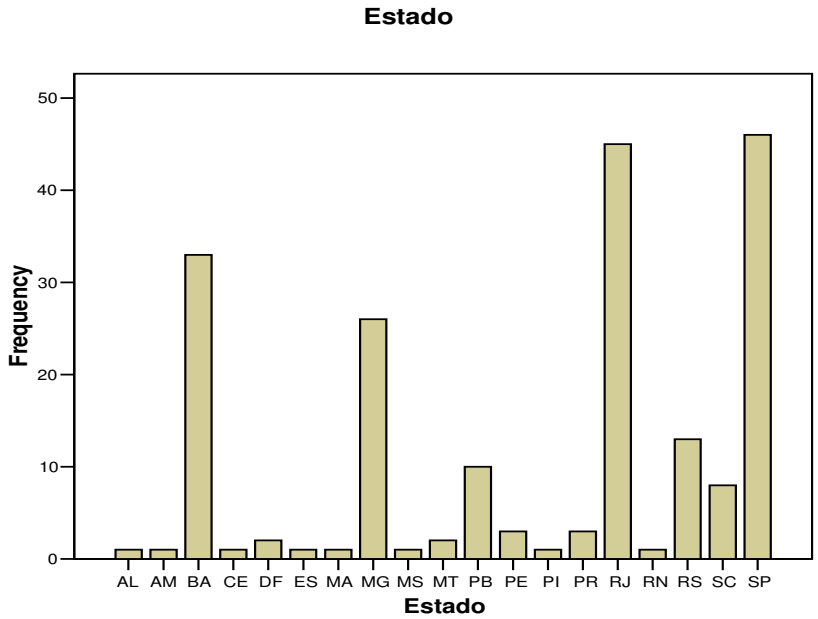


(*) Previous use of glycocorticoides, Abnormal phenotypes

(**) 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

	0–12 months	12–23 months	
Fusion gene	n^{+ve}/n^{total} (%)	n^{+ve}/n^{total} (%)	*P*
MLL	50/86 (58%)	31/78 (40%)	0.011
TEL/AML1	4/29 (14%)	5/32 (16%)	1.000
E2A/PBX1	1/10 (10%)	3/13 (23%)	0.604
AML1/ETO	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	EGIL	MOLECULAR-GENETICS	Status	Interview
1999	A.B. C. S	RJ	20	F	W	86.1	T-I	*MLL-,SIL/TAL1(+)*	D	**Y**
2000	G.S.R	RJ	20	F	W	240.1	T-I	***MLL-*, del (12) (p?), NOTCH1 mut**	D	N
2001	J.O.M.A.S	RJ	20	M	W	380.1	T-II	*MLL-; SIL/TAL1(+);FLT3* mut-ITD	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	*MLL-ENL(+);*	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	*NOTCH1* mut	A	N
2003	MSSA	BA	14	M	W	57.1	T-IV	*MLL-ENL(+); SIL-TAL1(+)*	PFl	**Y**
2004	FGS	PR	17	M	W	180.1	T-I	**del (6) (q23);del (7) (q32)**	A	**Y**
2005	AAA	BA	7	M	W	110.5	T-IV	*MLL-ENL(+);*	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	*MLL-, Notch1 mut*	D	**Y**
2007	MAC	DF	8	M	W	15.4	T-IV	MLL-, 49,XY,+6,+8,+19	A	Y
2008	CMNDL	DF	6	F	W	131.6	T-IV	*MLL-, HOX11L2(+);*	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

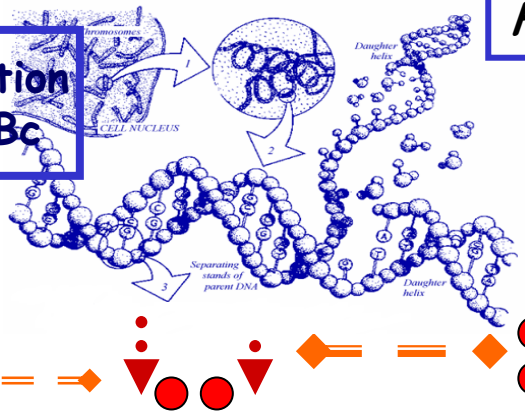
- We looked for *FLT3* gene D835 mutations and internal tandem duplications (ITD) in 159 samples; Overall, 7.5% of patients had *FLT3* mutations
- *FLT3* mutations were found only in ALL {only *MLL*+ samples};
- *FLT3*-ITD was found in 6 cases, being exclusively of AML and only one *MLL*+.
- Our results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

Mariana Emerenciano, Juliane Menezes , Marina Lipkin Vasquez, Ilana Zalcberg, Maria S. Pombo-de-Oliveira*

Infant Leukemia Studies

Acquired genetic alterations:
VDJ illegitimate, *MLL* rear.
***FLT3* AND RAS mutations**

Pre-natal Identification of Fusion genes in CBc



OTHER SOMATIC
HYBRYD GENES
TEL/AML1
E2A/PBX1
SIL/TAL1

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

Prognostic Biomarkers
Therapeutical target

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T-ALL : Marcela Mansur, Liliam Brewer
AMLs : Juliane Menezes, Vitória Gimenez,
Polymorphisms: Crisiane Zanrosso

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Alessandra Faro

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Andrea Biondi, Giovani Casangnila (Italy)
Joseph Wielmels, Patricia Buffler (CLIC,CA)
Ralph Marcheleck, Clauss Meyer (BFM)

SWISS BRIDGE
Support for Cancer Research Worldwide

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