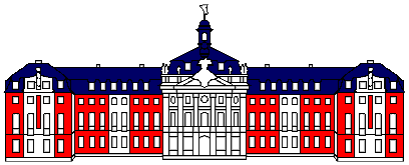


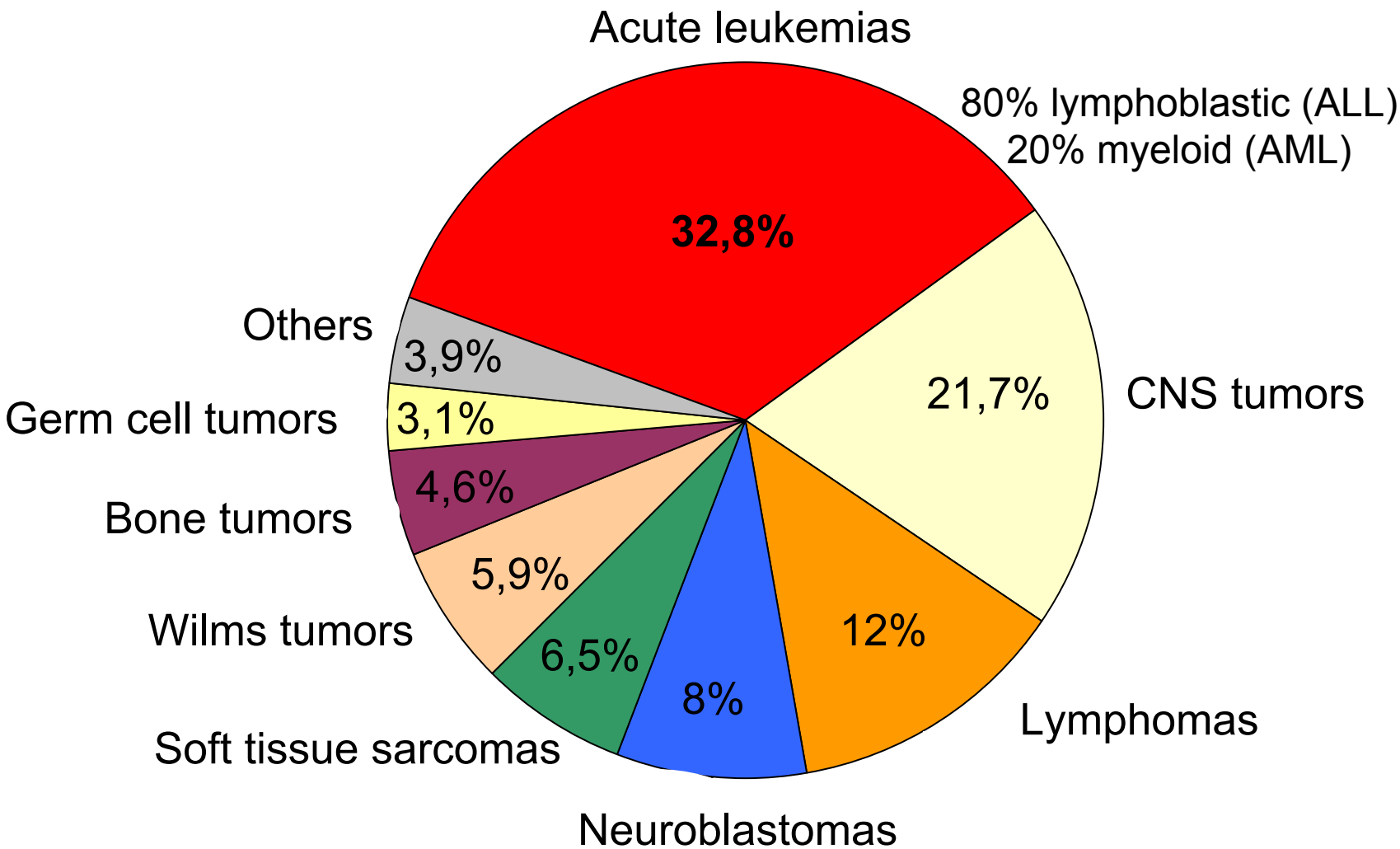
Etiology of Acute Childhood Leukemias

PD Dr. med. Claudia Rössig

Universitätsklinikum Münster
Klinik und Poliklinik für Kinderheilkunde
- Pädiatrische Hämatologie und Onkologie -
Direktor: Univ.-Prof. Dr. med. H. Jürgens

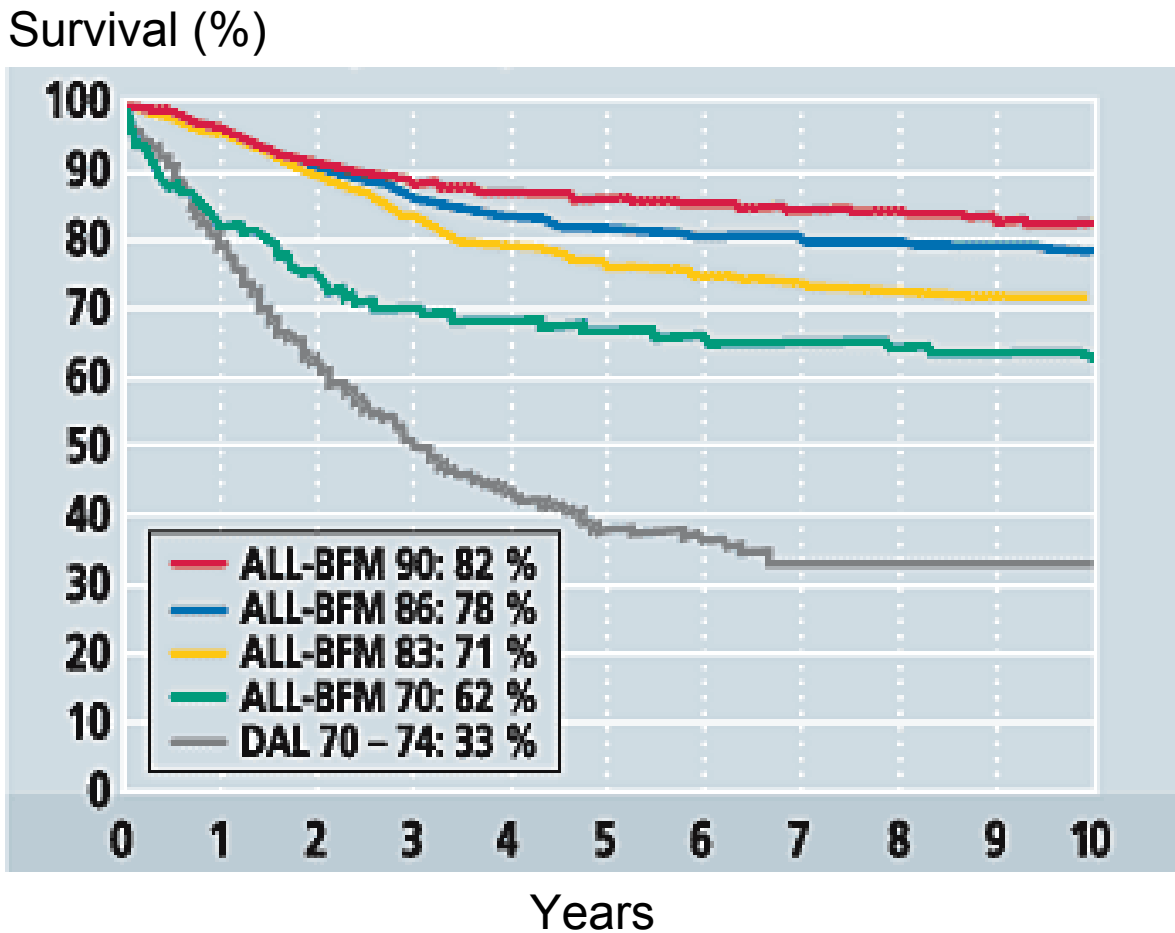
May 2008

Cancer in Childhood (<15y)



GCCR Mainz, Germany

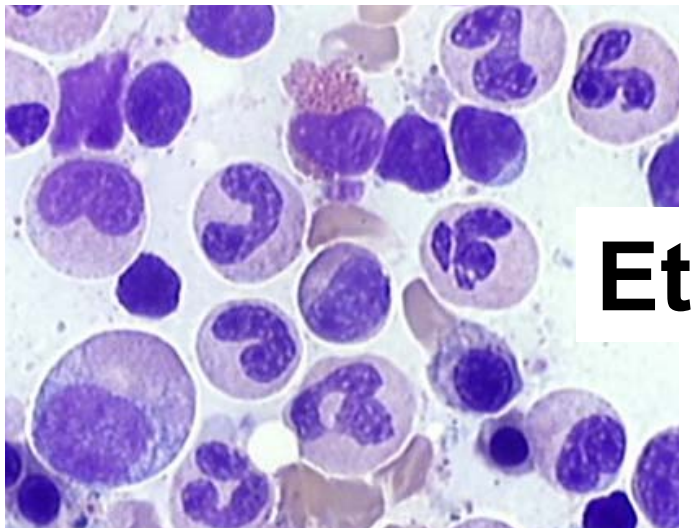
Survival of Children with Acute Lymphoblastic Leukemia (ALL)



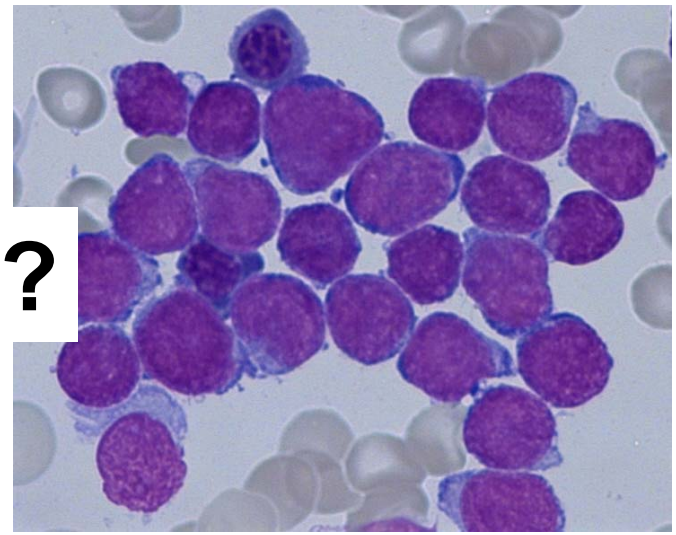
Creutzig et al., Deutsches Ärzteblatt 2003

Leukemogenesis

Normal bone marrow

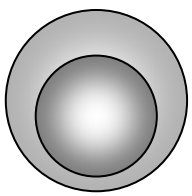


Acute leukemia



Etiology?

Stem cell

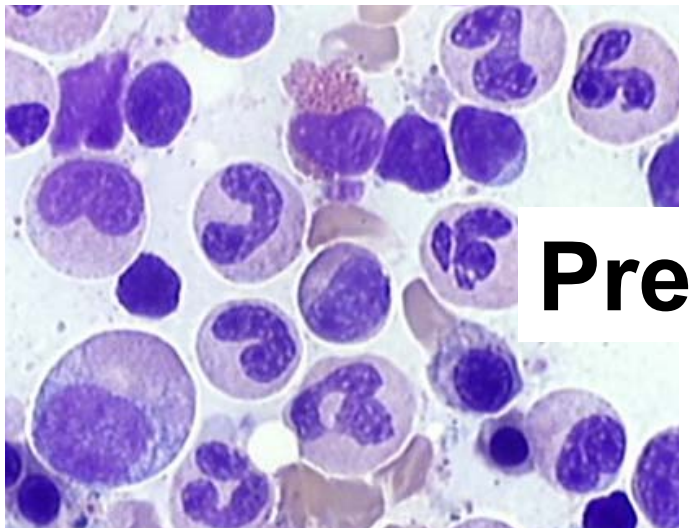


Molecular events

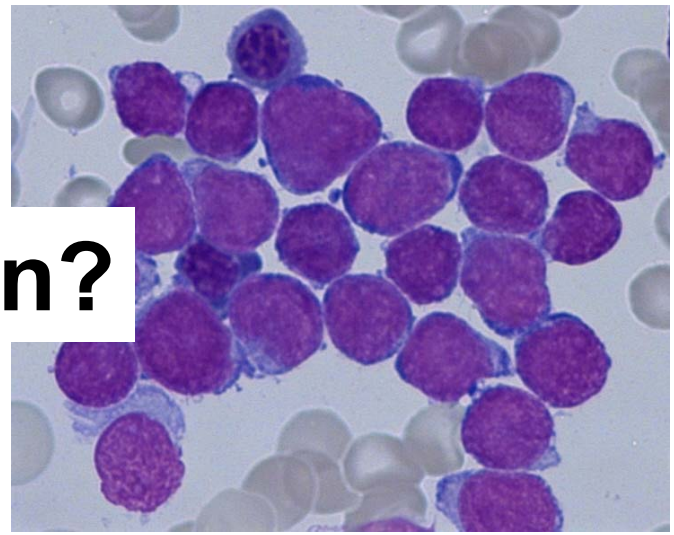
Disruption of process of differentiation, survival, self-renewal

Leukemogenesis

Normal bone marrow

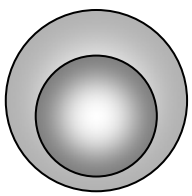


Acute leukemia



Prevention?

Stem cell



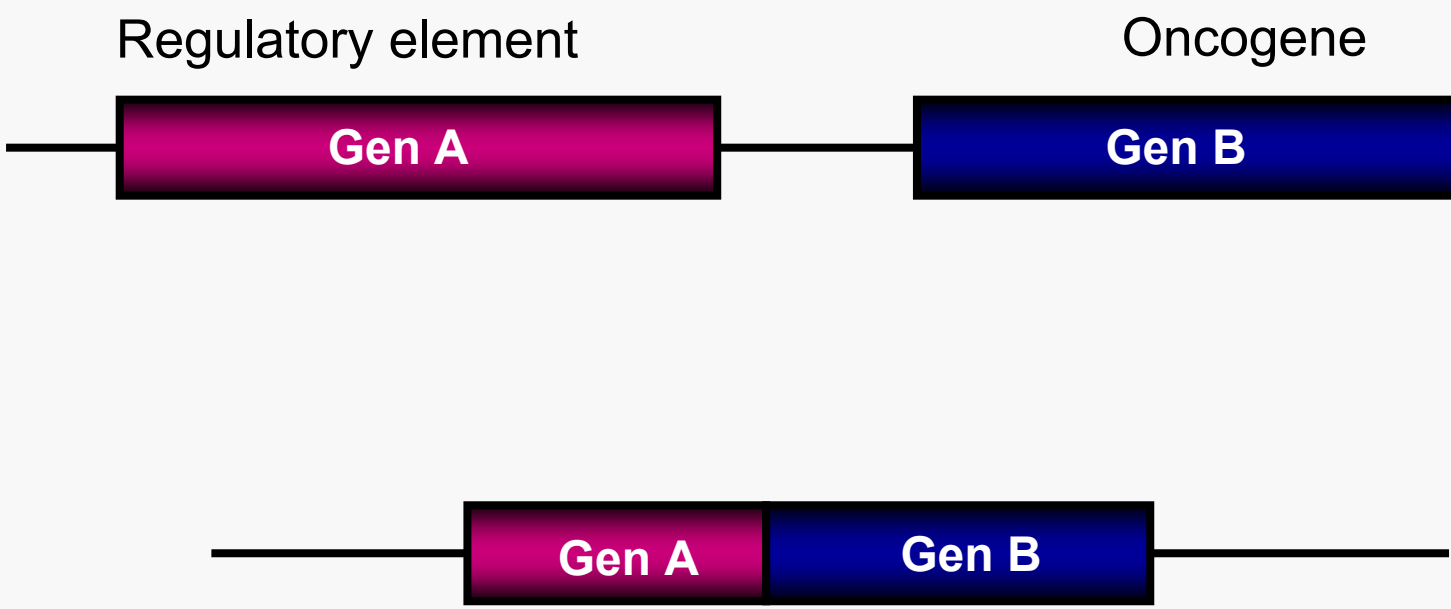
Molecular events

Disruption of process of differentiation, survival, self-renewal

- Natural History of the Disease
- Role of Genetic Factors
- Role of Environmental Factors

- Natural History of the Disease
- Role of Genetic Factors
- Role of Environmental Factors

Childhood Leukemia: Gene Dysregulation by Chromosomal Translocation



⇒ **Genetic dysregulation**

B-Cell Precursor ALL: Translocation t(12;21)

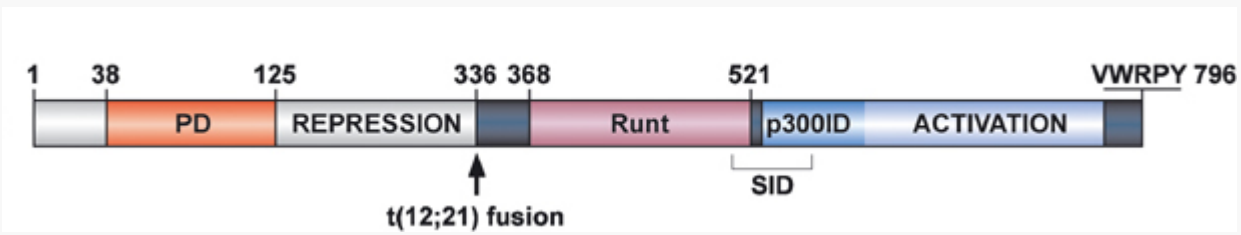
TEL

Chromosome 12

AML1

Chromosome 21

TEL-AML1 (t12;21)



⇒ **Genetic dysregulation**

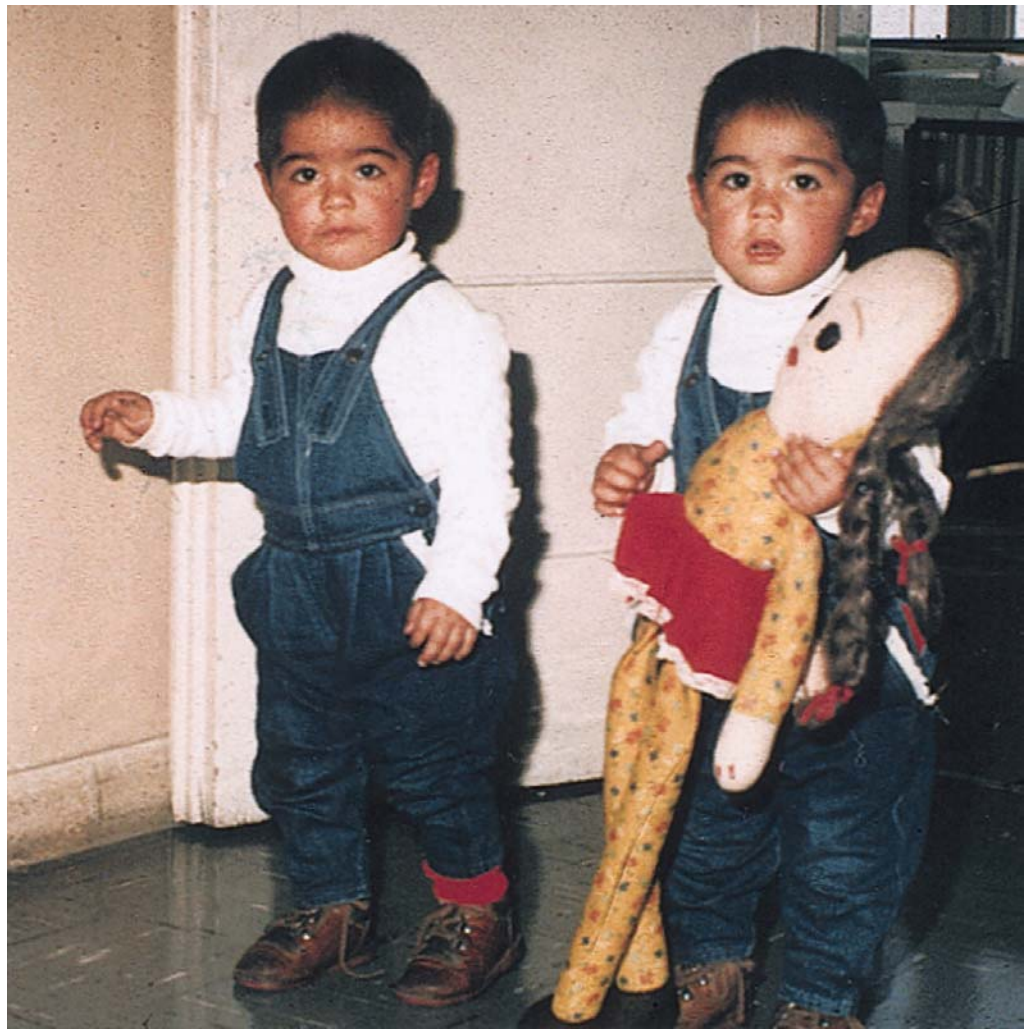
Leukemia in Twins

Monozygotic twins have concordance rate of ~5%

Genetic predisposition?

Simultaneous exposure to a common leukemogenic event?

Placental crossing of leukemic cells?

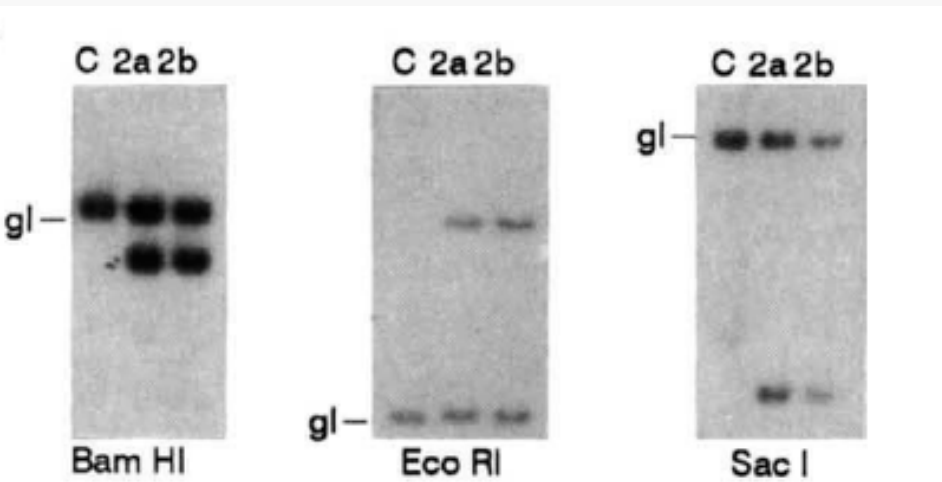


From: Greaves, M. F. et al., Blood 2003

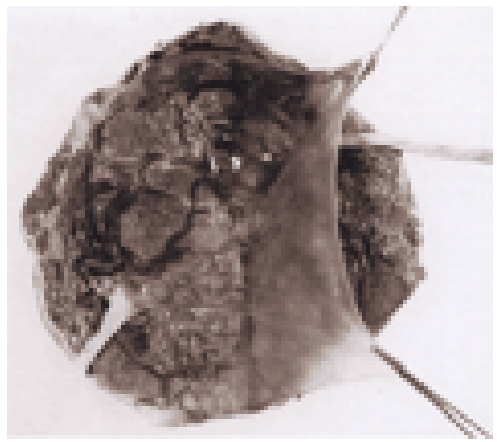
Leukemia in Twins

***In utero* rearrangements in the trithorax-related oncogene in infant leukaemias** NATURE · VOL 363 · 27 MAY 1993

Anthony M. Ford*, Susan A. Ridge*, Maria E. Cabrera†, Hazem Mahmoud‡, C. Michael Steel§, Li C. Chan|| & Mel Greaves*



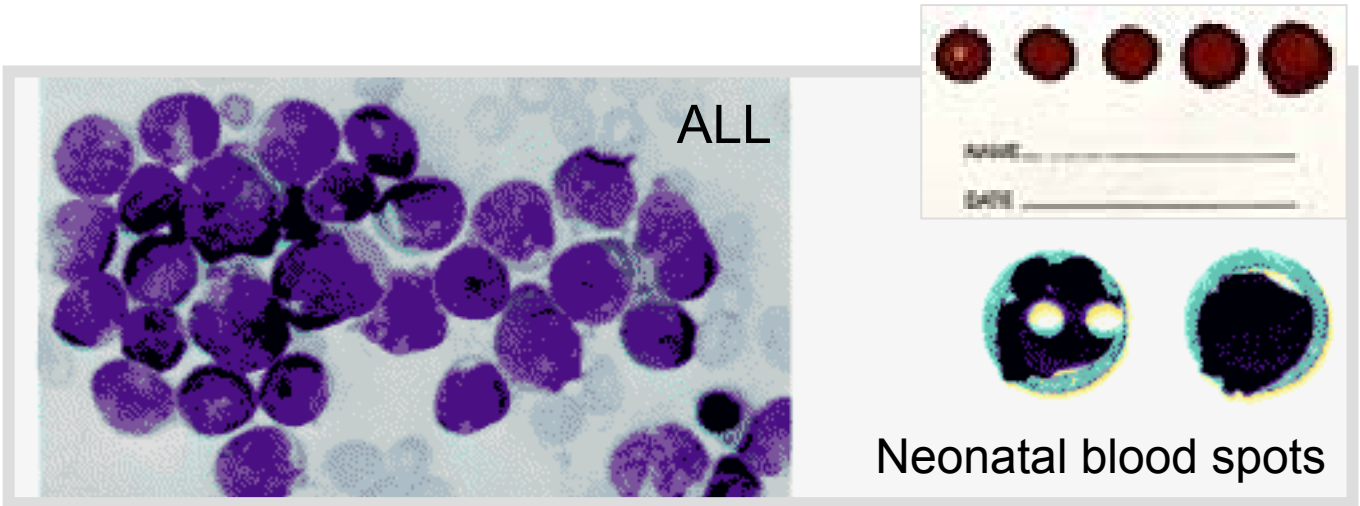
chromosome 11q23



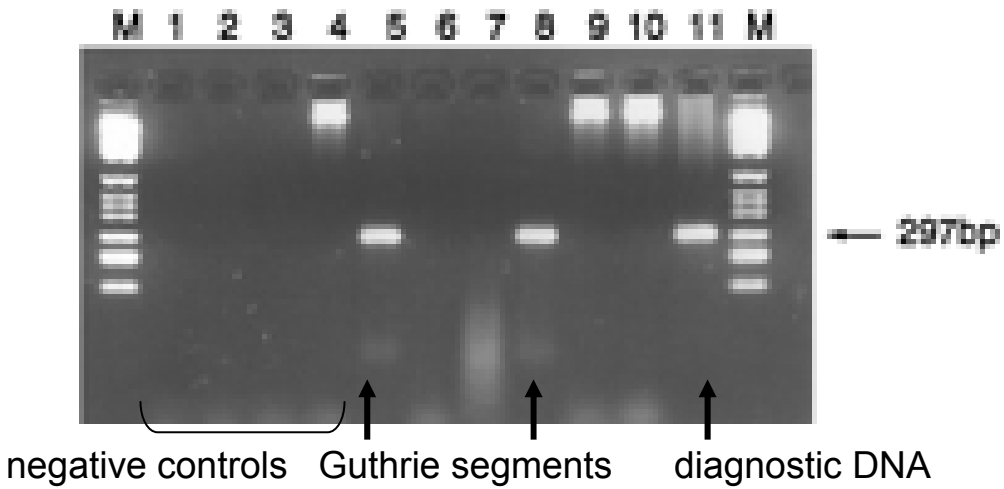
From:
Greaves et al., Blood 2003

Prenatal Origin of Childhood ALL

Gale, …Greaves, PNAS 1997



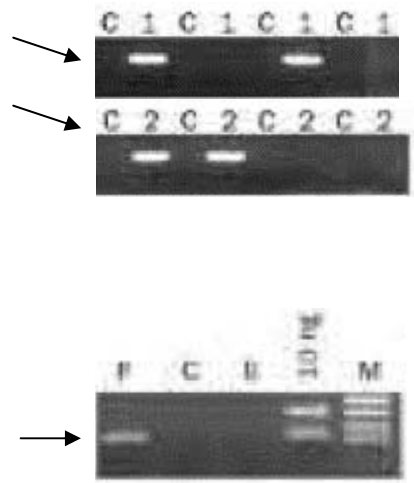
3 patients
5, 6 and 24 mo old
t(4;11), MLL/AF4+



Prenatal Origin of Childhood ALL

Wiemels, …Greaves, Lancet 1999

Patient	Patient's age at diagnosis	Guthrie segments tested	Guthrie segments positive for *TEL-AML1*
K Twin A	3 years 11 months	4	2
K Twin B	4 years	4	2
1	2 years 1 month	3	3
2*	2 years 10 months	4	1
3	3 years 3 months	12	1
4	3 years 4 months	14	0
5	3 years 5 months	12	0
6*	3 years 6 months	4	1
7	3 years 11 months	14	0
8	4 years 3 months	20	6
9*	5 years 1 month	2	2

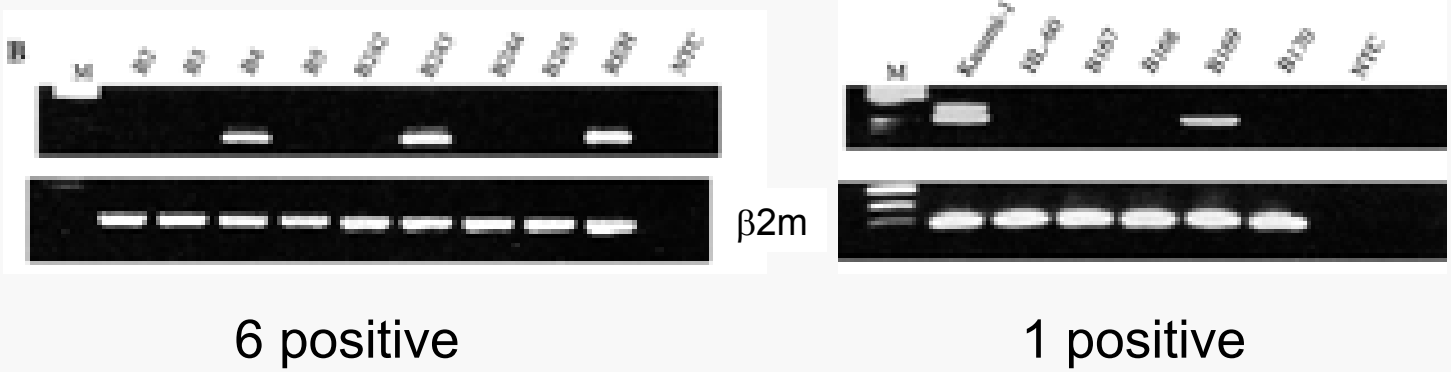


*Patients from Italian centre. Other patients are from UK.

Prenatal Origin of Childhood ALL

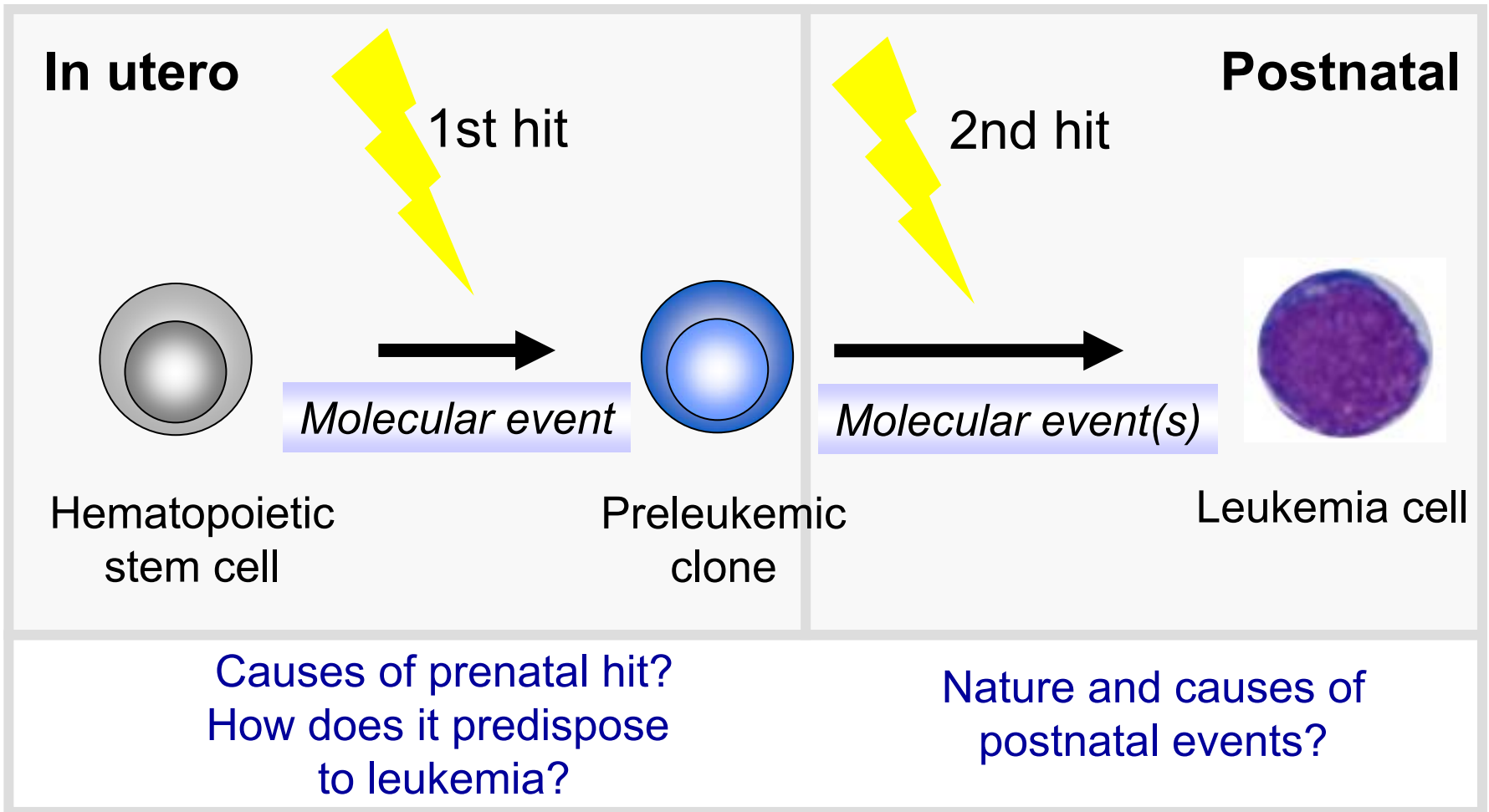
Mori,…, Greaves, PNAS 2002

PCR screening of 496 cord blood samples
for the presence of preleukemic fusion transcripts



⇒ Estimated frequency of fusion gene-positive cord bloods: ~1/100
Frequency of overt childhood leukemia: ~ 4-5/100.000

Model for Leukemogenesis in Children

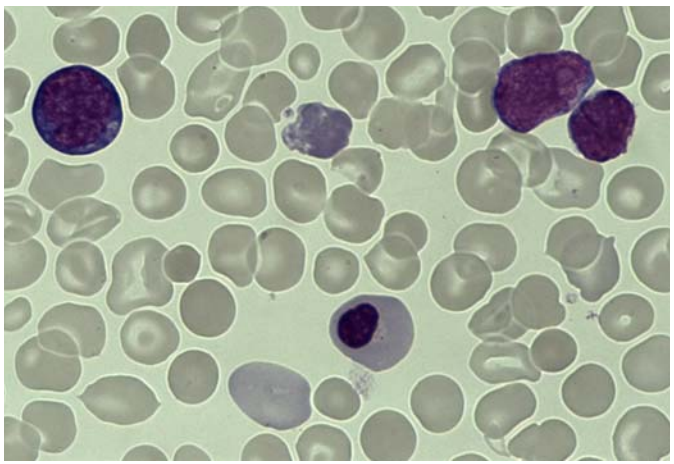


- Natural History of the Disease
- Role of Genetic Factors
- Role of Environmental Factors

Constitutional Chromosomal Abnormalities in Childhood Leukemia

Constitutional Chromosomal Abnormalities in Childhood Leukemia

Peripheral blood at birth

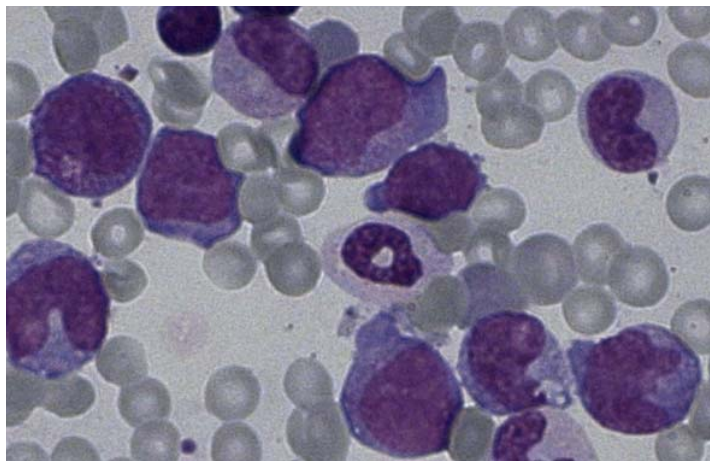


„Transient leukemia“

⇩

Spontaneous resolution within 3 months

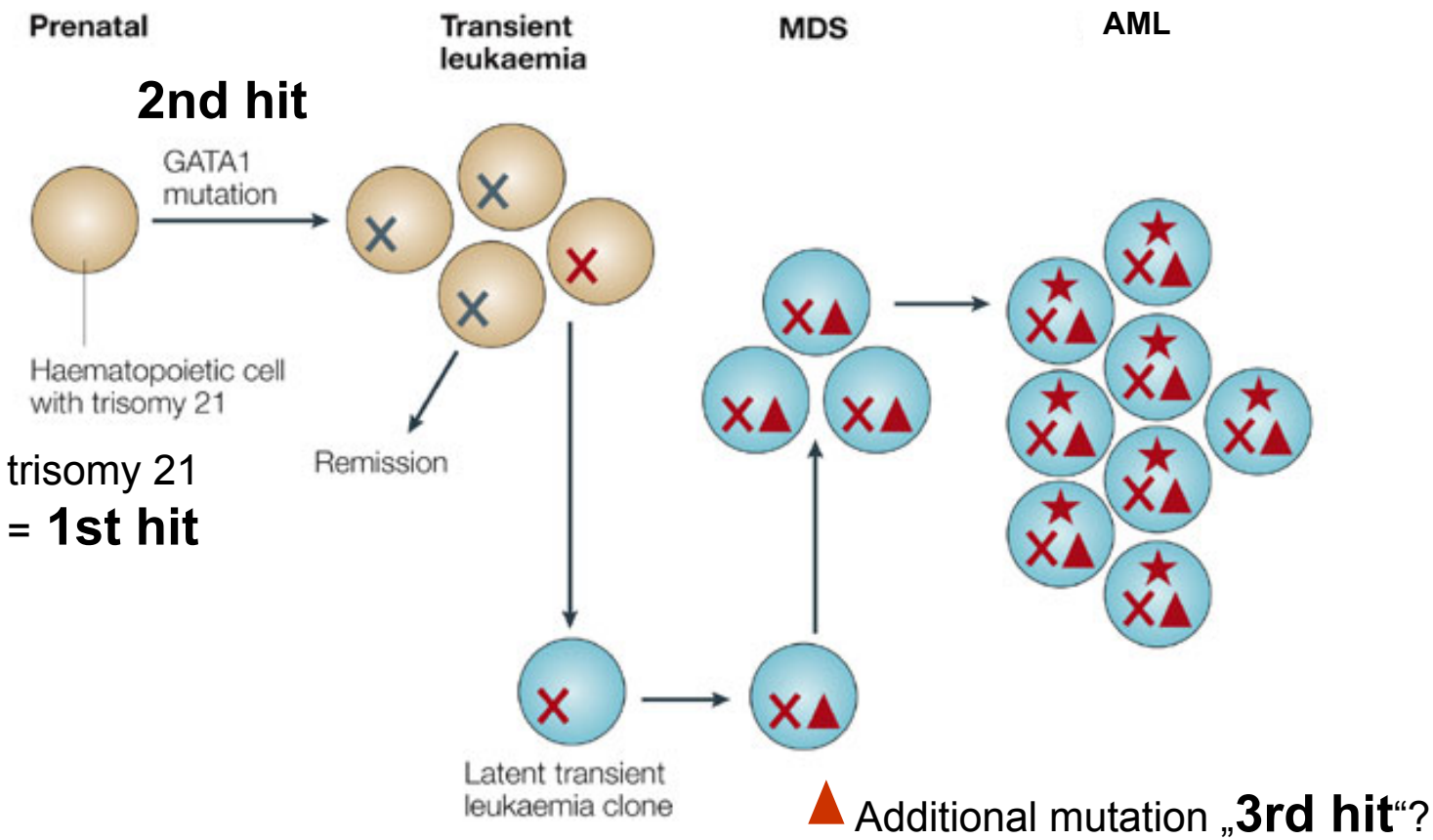
Bone marrow at 2 yrs of age



AML FAB M7

Incidence 500x increased in Down´s syndrome!

Pathogenesis of Down AML



Nature Reviews | Cancer

Hitzler/Zipursky 2005

Constitutional Chromosomal Abnormalities in Childhood Leukemia

	% of childhood leukemias *(Narod, BJC 1991)*
• Down´s syndrome	2.3
• Germline BRCA2 mutations	0.3
• Beckwith-Wiedemann syndrome	
• Neurofibromatosis type I	
• Fanconi´s anemia	
• Shwachman Diamond syndrome	
• Ataxia teleangiectatica	

Inherited susceptibility through normal allelic variation, involved in gene-environment interactions?

- Natural History of the Disease
- Role of Genetic Factors
- Role of Environmental Factors

Prenatal Exposures

Birthweight and Leukemia

Recent population-based case control study, USA:

	Controls (N = 4980) %	ALL cases (N = 376) %	ALL cases (N = 376) OR[a] [95% CI]	AML cases (N = 85) %	AML cases (N = 85) OR[a] [95% CI]
Infant characteristics					
Birthweight (g)[b]					
<2500	5.1	5.5	1.2 [0.8, 1.8]	10.0	2.2 [1.1, 4.4]
2500–3999	81.0	74.4	1.0 Reference	74.4	1.0 Reference
4000+	13.9	20.1	1.6 [1.2, 2.0]	15.6	1.2 [0.7, 2.1]

Podvin, Paediatr and Perinatal Epidem 2006

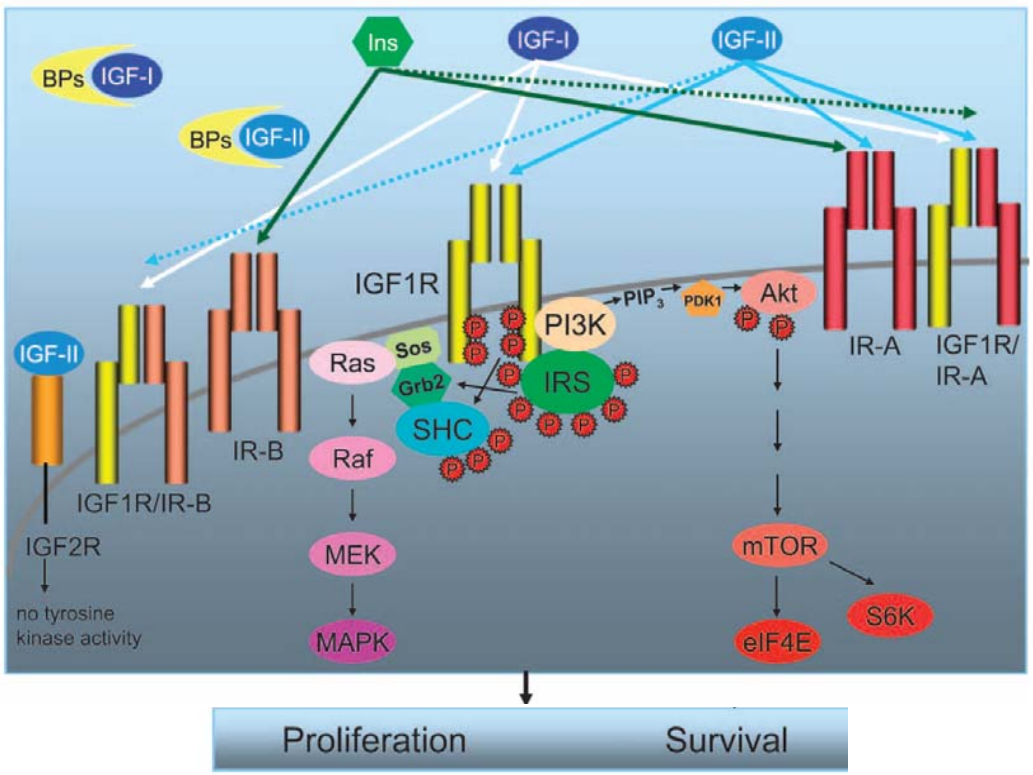
⇒ Association of high birthweight with ALL;
consistent with most but not all studies

Birthweight and Leukemia

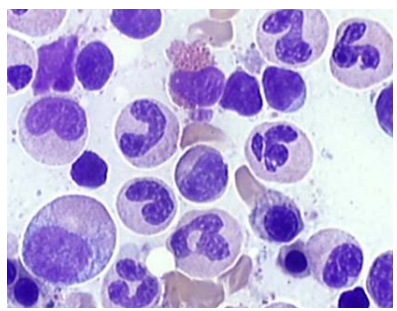
HYPOTHESIS:

Increased fetal exposure to growth hormones?

Big baby



Proliferative stress on hematopoiesis



Maternal Age and Leukemia

Many (but not all) studies report association of advanced maternal age >35 yrs with childhood leukemia

- Chromosomal mutations in germ cells?
- Environmental exposures to carcinogens?
- Confounding socioeconomic variables?
- General increase of both maternal age and incidence of leukemia in many populations!

Maternal Diet during Pregnancy

Naturally occurring **topoisomerase inhibitors**:
Risk factors for infant leukemia?

Soy beans
Fruits, vegetables
Cocoa, tea, wine
Coffee

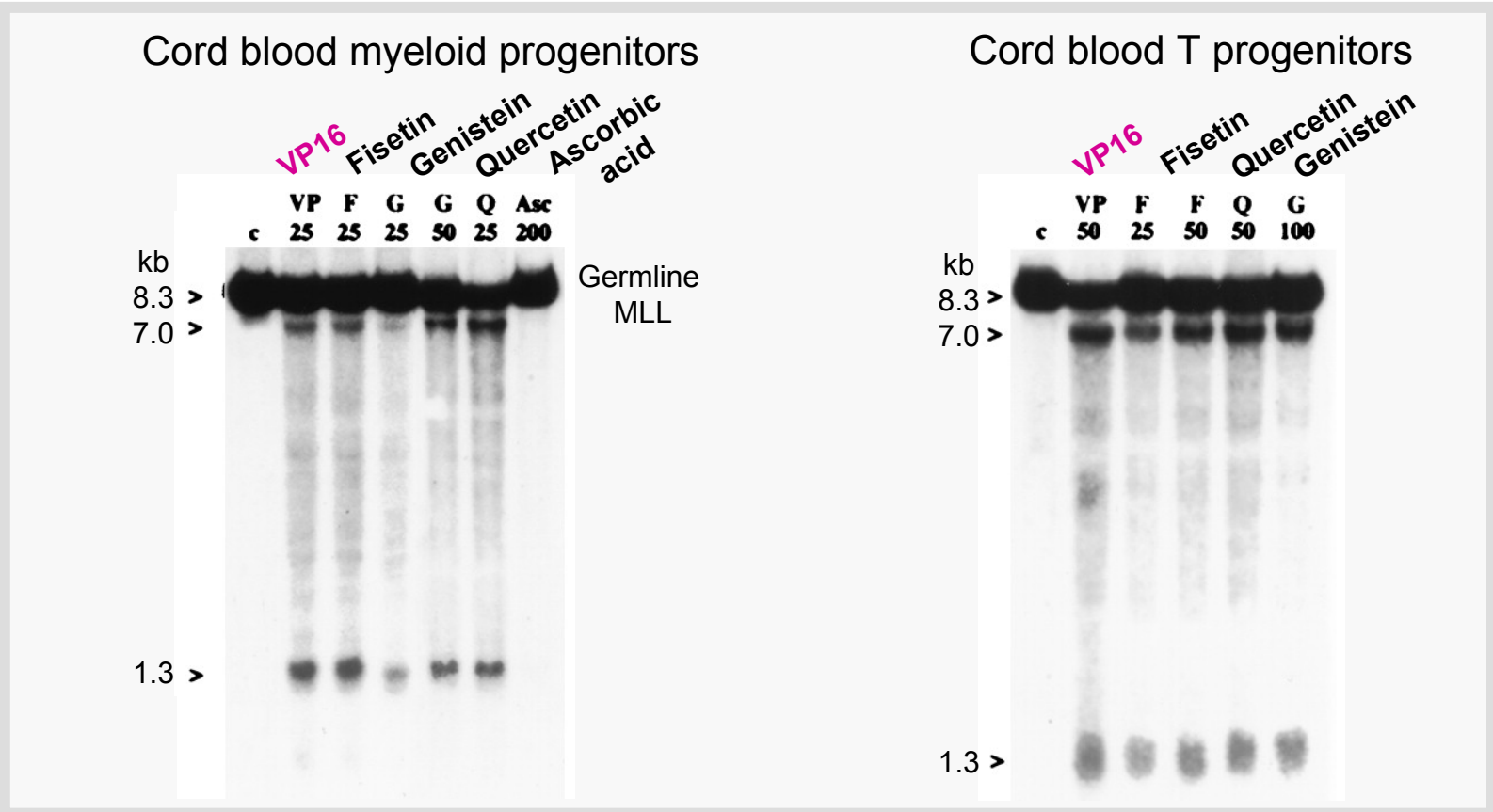
Combined exposure variable ⇩

	n = 84 matched sets			n= 54 matched sets			n = 30 matched sets		
Category of exposure[b]	Overall dataset			infant ALL only			infant AML only[c]		
	OR[d]	(CI)[e]	Cases	OR[d]	(CI)[e]	Cases	OR[d]	(CI)[e]	Cases
Low	1.0	—	21	1.0	—	17	1.0	—	4
Medium	2.1	(0.9-5.0)	38	1.3	(0.4-4.2)	26	9.8	(1.1-84.8)	12
High	1.1	(0.5-2.3)	23	0.5	(0.2-1.4)	10	10.2	(1.1-96.4)	13

Ross, Cancer Causes Control 1996

Maternal Diet during Pregnancy

Dietary bioflavonoids cause *MLL* gene cleavage in human hematopoietic progenitor cells by inhibition of topoisomerase II



Strick,..., Rowley. PNAS 2000

Radiation

Marie Curie

The Nobel Prize in Physics 1903
The Nobel Prize in Chemistry 1911

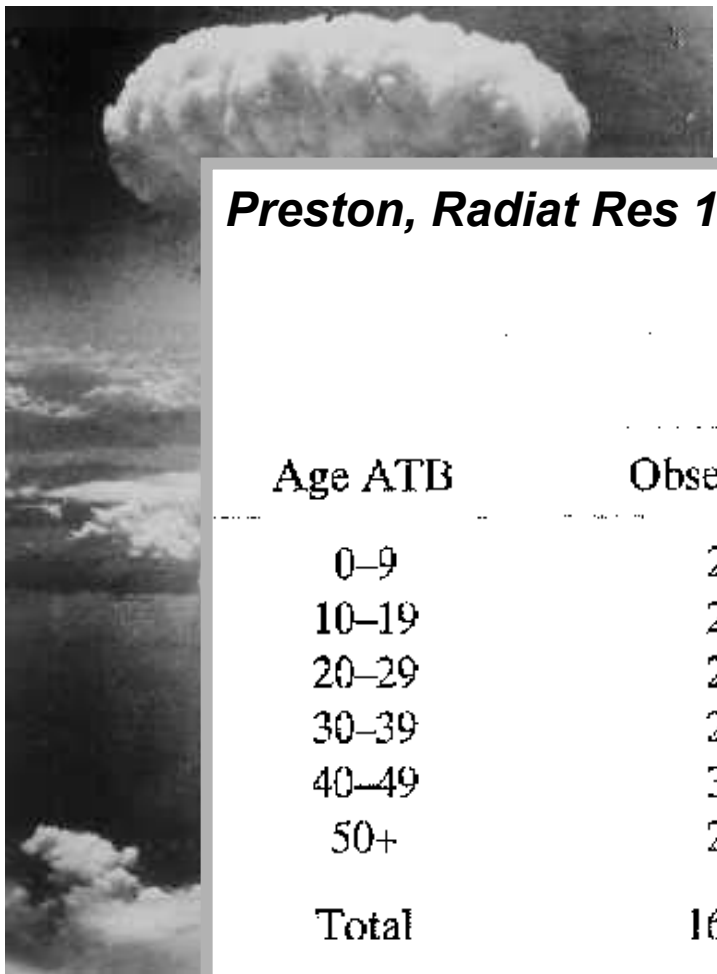
Died from leukemia
aged 66

Irène Joliot-Curie

The Nobel Prize in Chemistry 1935

Died from leukemia
aged 58

Radiation-induced Leukemia: Atomic Bomb



Hiroshima, August 6, 1945

Preston, Radiat Res 1994

Leukemia Deaths by Age at Exposure
among 93,696 survivors

	1950–1975		1976–1985	
Age ATB	Observed	Excess	Observed	Excess
0–9	29	20	3	–3
10–19	29	18	7	–2
20–29	21	12	8	1
30–39	21	6	22	12
40–49	37	15	15	4
50+	23	–1	6	2
Total	160	70	61	14

In Utero Radiation Exposure

- *Stewart, Lancet 1956 (UK):*
  ↑ leukemia after in utero exposure to **diagnostic x-rays** (10 mSv)

- Supported by large medical-record based epidemiological studies (*Mac Mahon, Nat Acad Sci USA 1980*):

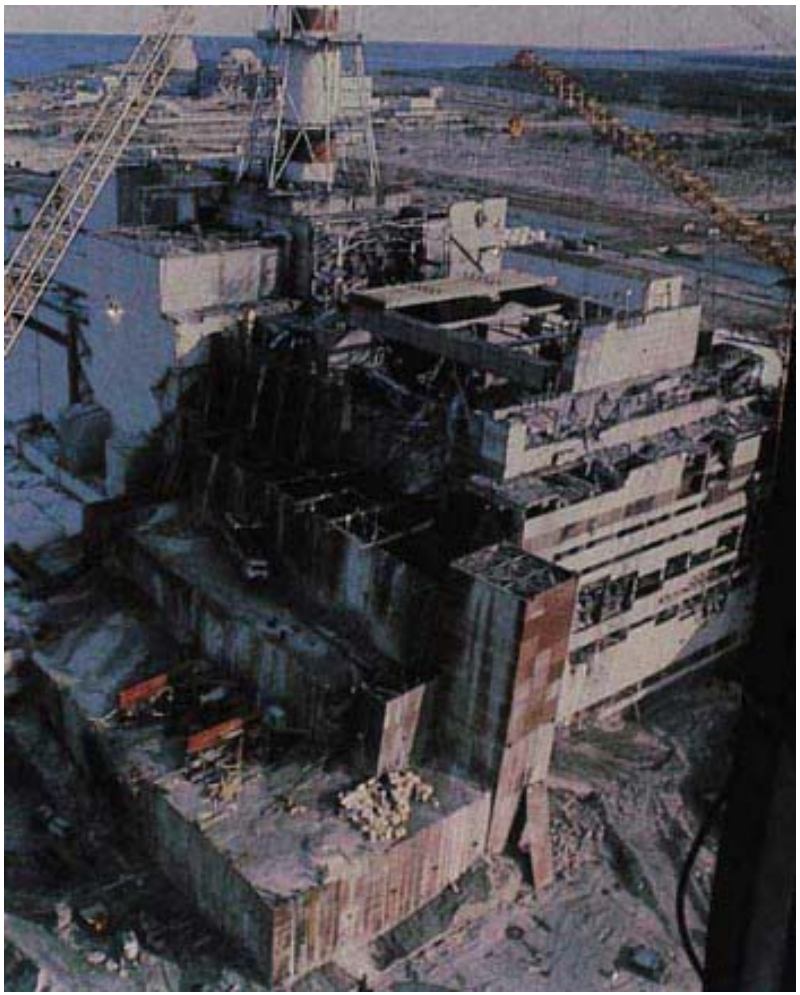
  5x ↑ risk after diagnostic x-rays in 1st trimester

BUT:

- *Yoshimoto, Lancet 1988* (Japan):
  Among **atomic bomb** survivors, no ↑ leukemia in children exposed in utero (up to 200 mSv).

  1263 children → 2 cases of childhood cancer, no leukemia

Nuclear Accidents and Leukemia



Chernobyl, April 26, 1986

Reports from

• Soviet Union	Ivanov Nature 1993 Davis Int J Epid 2006
• Sweden	Hjalmars BMJ 1994
• Finland	Auvinen BMJ 1994
• England	Cartwright Lancet 1998
• Scotland	Gibson Lancet 1988
• Germany	Michaelis Nature 1997
• Greece	Petridou Nature 1996

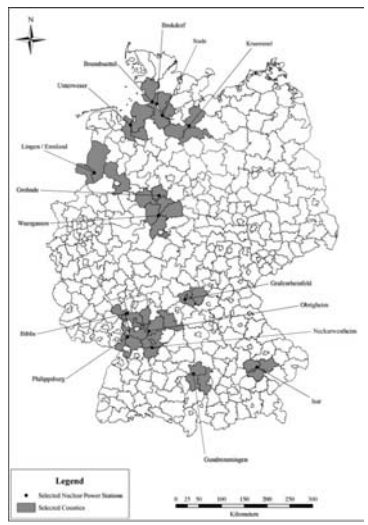
No strong evidence for increased risk of childhood AL

Residence near Nuclear Power Plants

KiKK study, Germany *(Spix et al., EJC 2008)*

Null hypothesis: No association between proximity of housing to a nuclear power plant and the risk of cancer ≤5 yrs of age

Preselected areas around 16 nuclear power plants
1592 cases: All cancers ≤5 yrs in 1980-2003
4735 matched controls



⇒ Null hypothesis rejected

⇒ Statistically significant effect for ALL

⇒ Population-attributable risk of 0.3% for housing within 5 km

Electromagnetic Field Exposure

- Initial report in 1979 (Wertheimer and Leeper)
- No association in large studies from U.S.A, U.K., Canada (Linet NEJM 1997; Cheng Lancet 1999; McBride Am J Epidem 1999)
- Metaanalysis (Ahlbom BJC 2000)

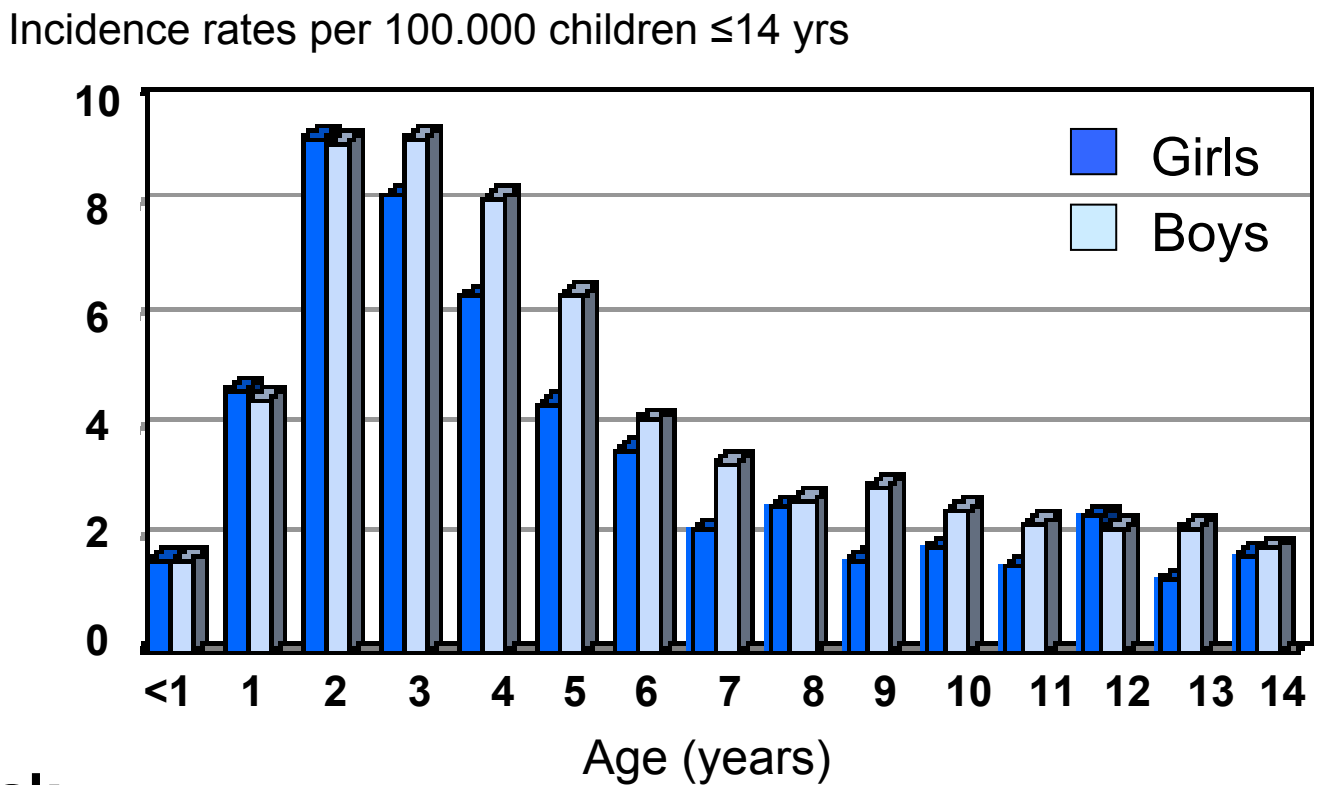
Relative risks (95% CI)

Measurement studies	0.1–<0.2 μT	0.2–<0.4 μT	≥0.4 μT
Canada	1.33 (0.85–2.07)	1.44 (0.79–2.60)	1.65 (0.68–4.01)
Germany	1.29 (0.58–2.89)	2.19 (0.62–7.71)	2.21 (0.29–16.7)
New Zealand	0.71 (0.21–2.44)	3 cases/0 ctrls	0 cases/0 ctrls
UK	0.89 (0.59–1.34)	0.87 (0.42–1.84)	0.88 (0.23–3.39)
USA	1.11 (0.81–1.53)	1.01 (0.65–1.57)	3.44 (1.24–9.54)
Calculated fields studies			
Denmark	0 cases/2 ctrls	0 cases/8 ctrls	2 cases/0 ctrls
Finland	0 cases/19 ctrls	4.31 (0.50–37.2)	6.79 (0.74–62.6)
Norway	2.25 (0.78–6.55)	1.49 (0.30–7.45)	0 cases/10 ctrls
Sweden	0.88 (0.11–7.19)	0 cases/20 ctrls	3.46 (0.84–14.3)
Summary			
Measurement studies	1.07 (0.87–1.31)	1.15 (0.84–1.56)	1.95 (1.14–3.35)
Calculated fields studies	1.42 (0.58–3.45)	0.84 (0.25–2.81)	2.22 (0.88–5.65)
All studies	1.08 (0.88–1.32)	1.12 (0.84–1.51)	2.08 (1.30–3.33)

Increased risk at highest exposure levels (>0.4 μT)

Socioeconomic Status

Age-specific Incidence of ALL



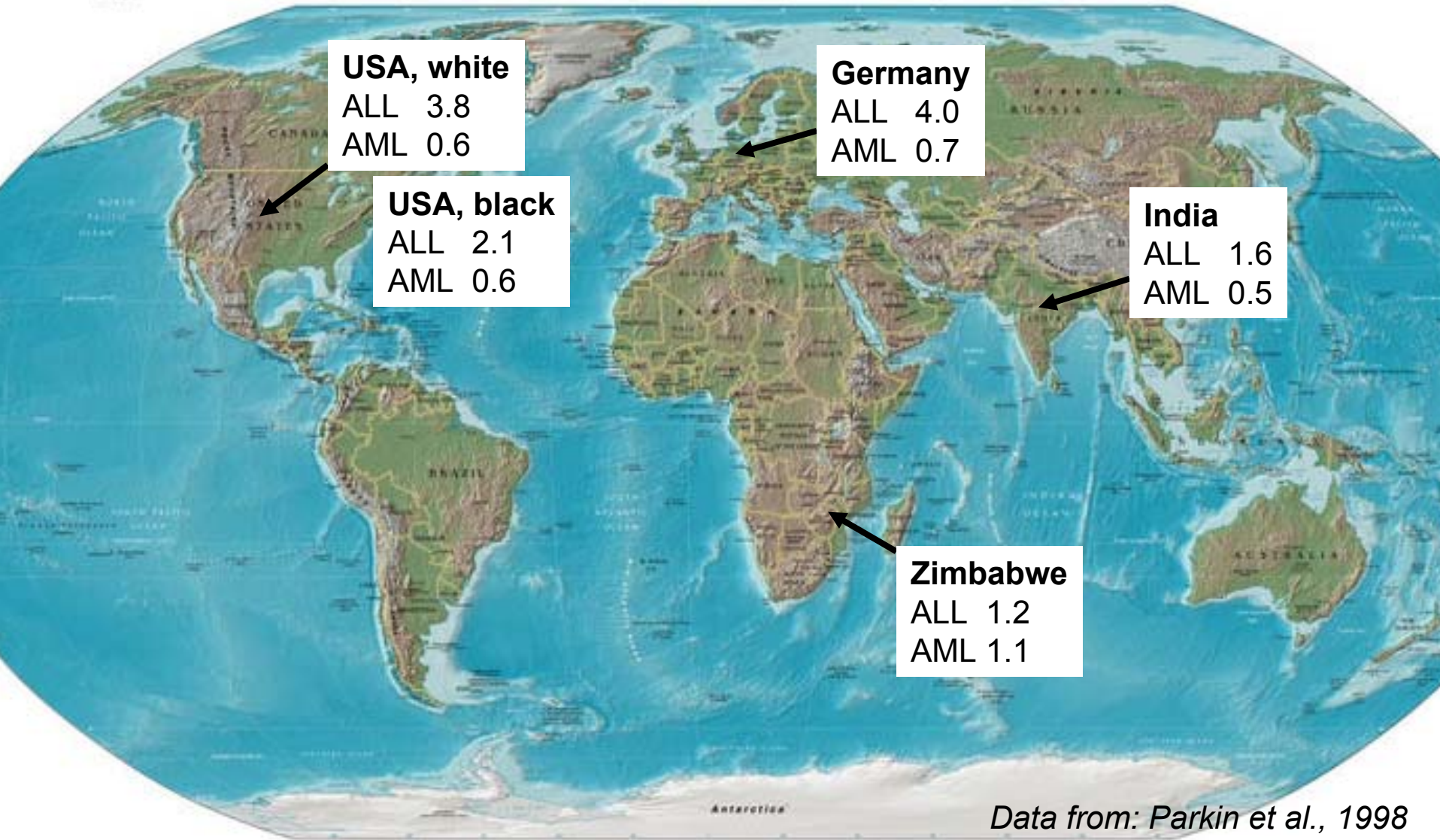
Age peak

- Emerged at beginning of 20th century
- Restricted to B cell precursor ALL
- Lacks in less developed countries

Kinderkrebsregister Mainz
1980-2003

Geographical Pattern

Annual rates per 100 000 in children (≤14 yrs)



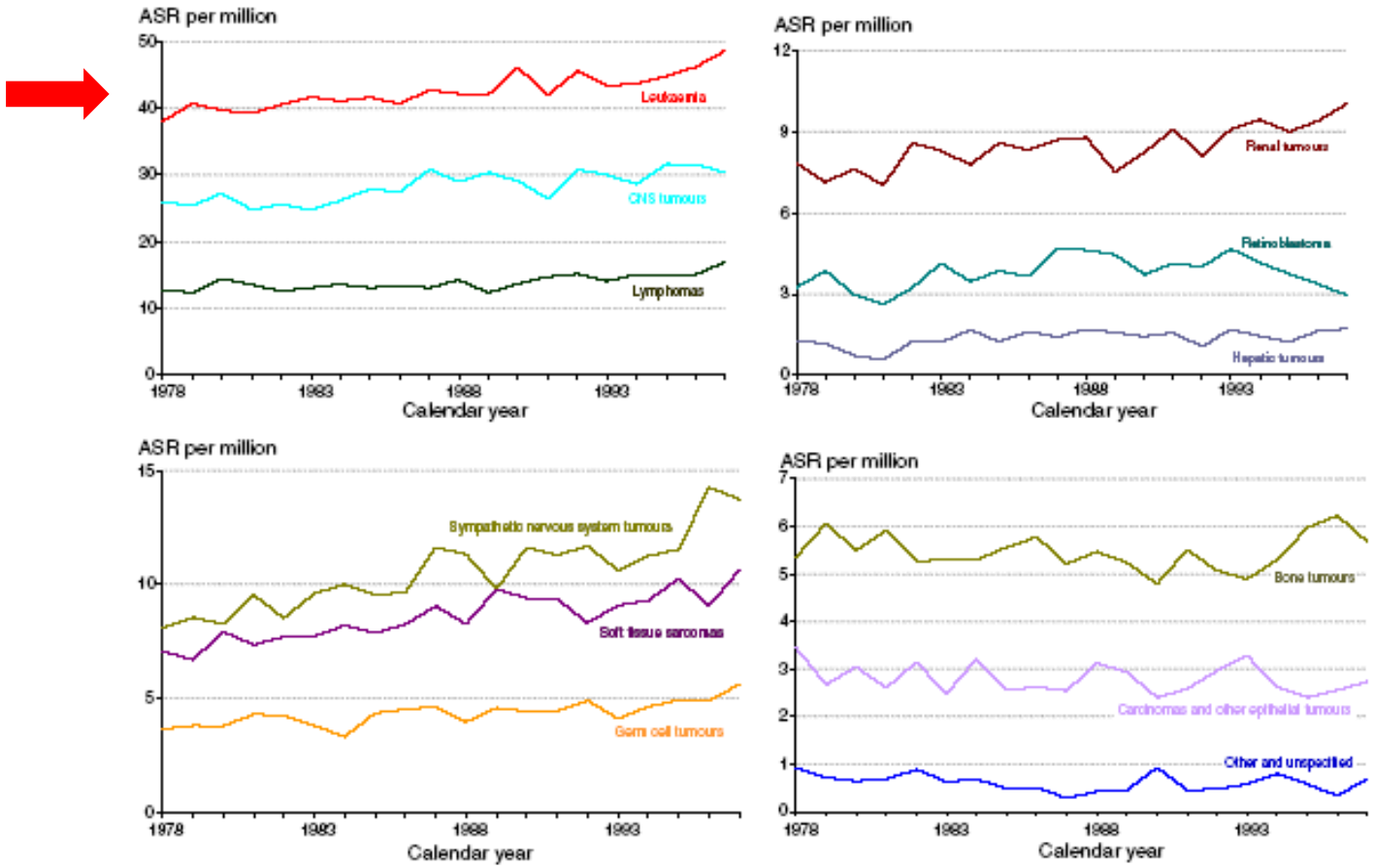
Data from: Parkin et al., 1998

EUROPEAN JOURNAL OF CANCER 42 (2006) 1961–1971

Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

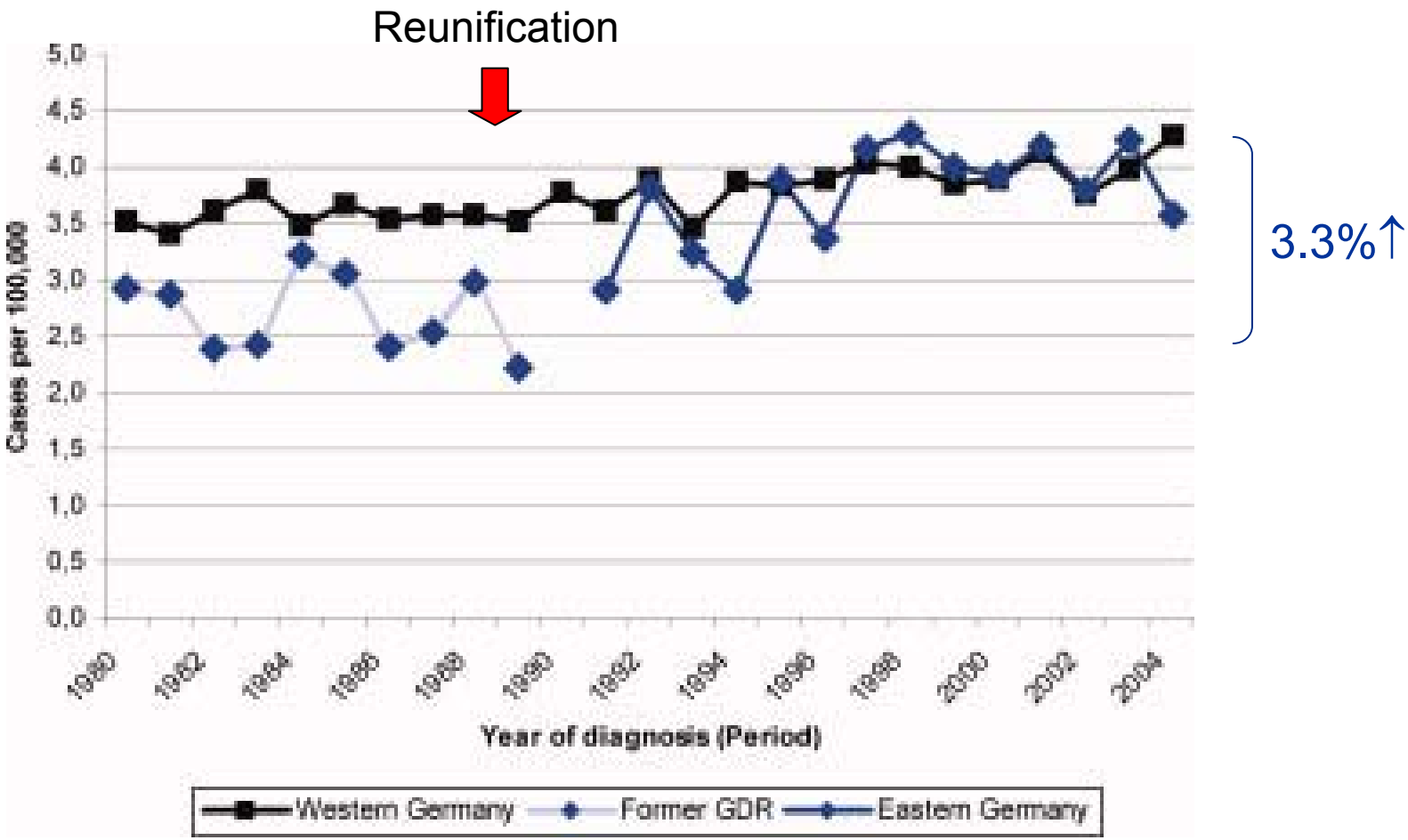
Peter Kaatsch[a,*], Eva Steliarova-Foucher[b], Emanuele Crocetti[c], Corrado Magnani[d], Claudia Spix[a], Paola Zambon[e]

33 population-based cancer registries in 15 European countries (77,111 cases)

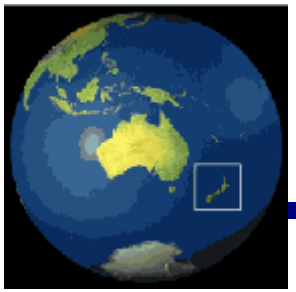


ALL Incidence during Economic Transition: Western and Eastern Germany

Spix et al., Int J Cancer 2008

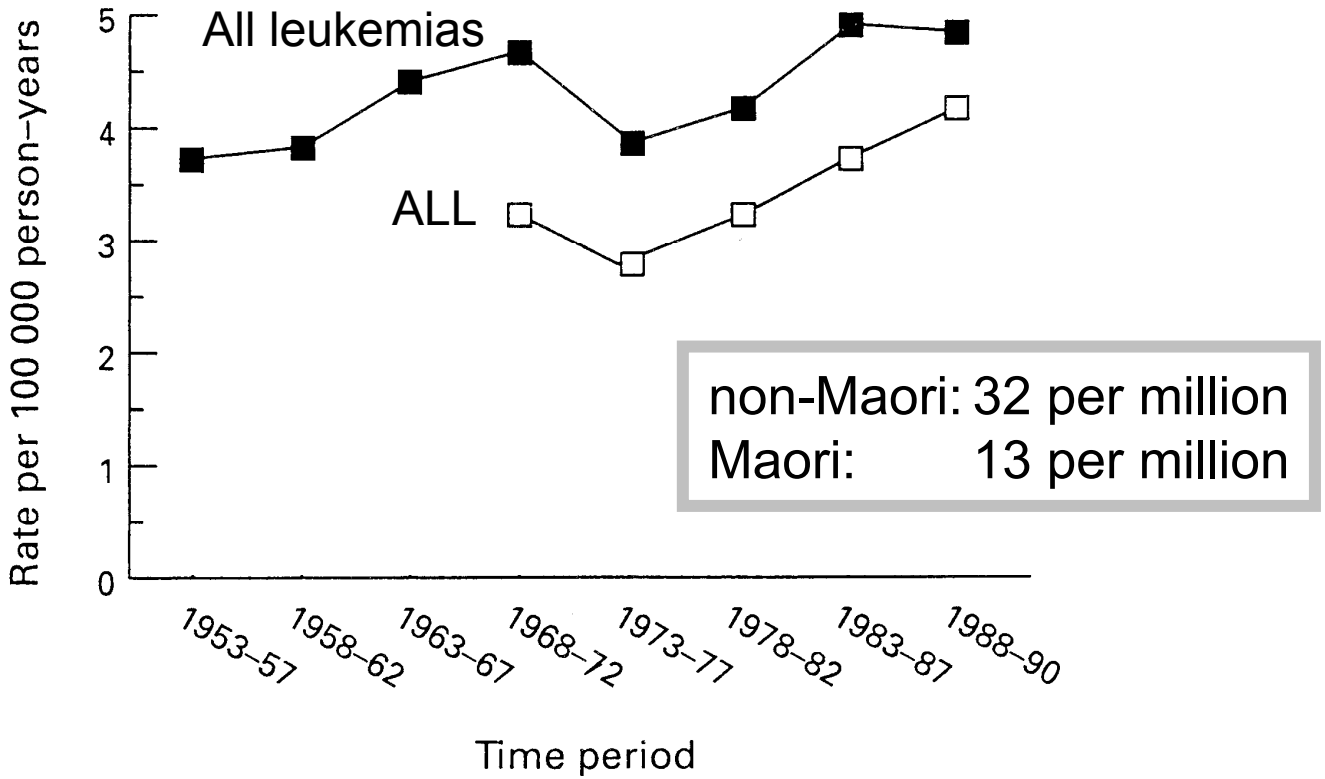


ALL Incidence during Economic Transition: New Zealand



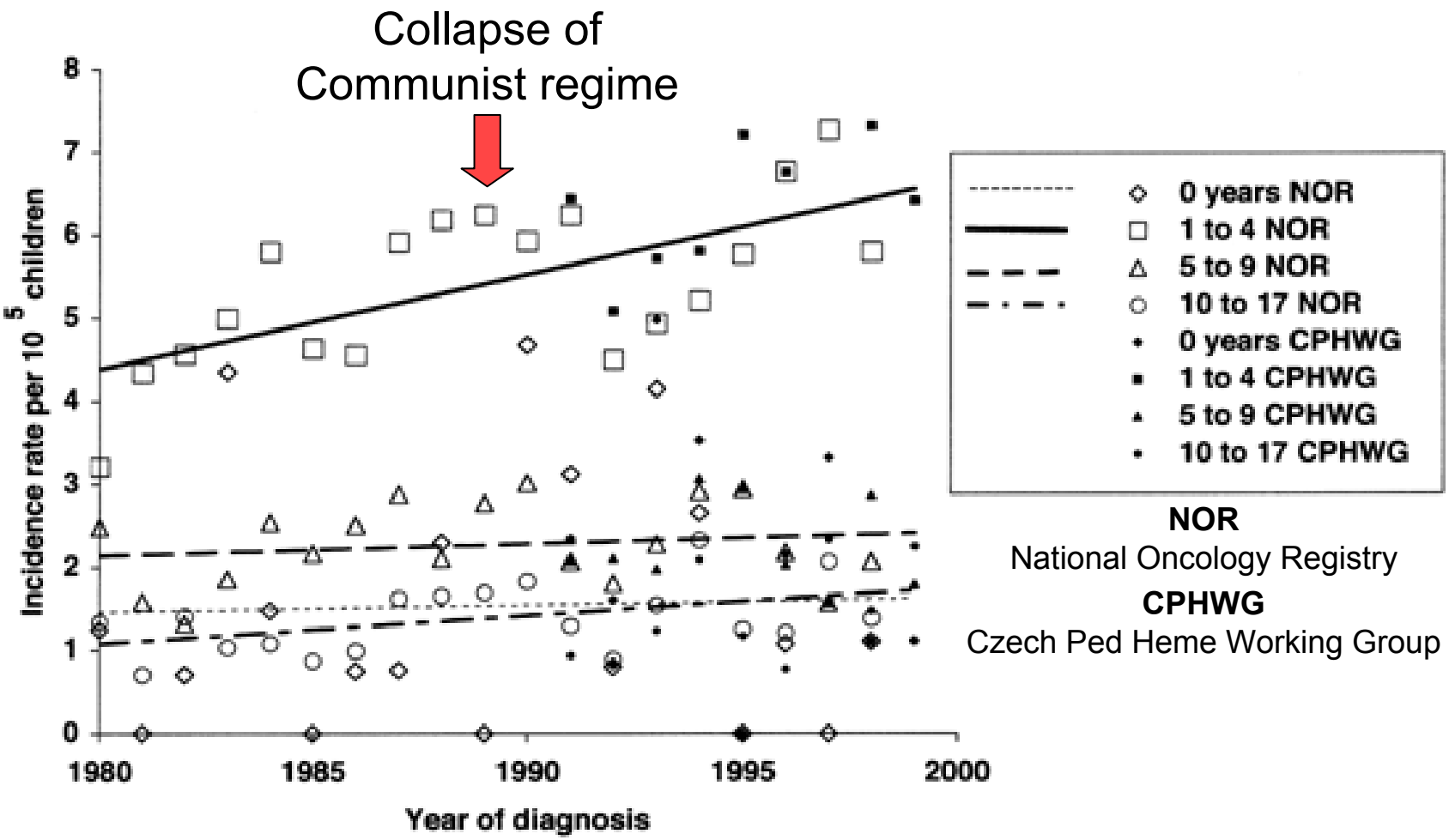
Dockerty/Cockburn, BJC 1996

Childhood leukemias, ages 0-14



non-Maori: 32 per million
Maori: 13 per million

ALL Incidence during Economic Transition: Czech Republic *(Hrusak, Leukemia 2002)*



NOR
National Oncology Registry
CPHWG
Czech Ped Heme Working Group

Childhood ALL and Socioeconomic Status
Population-based studies

Charles Poole et al., Int J Epidem 2006:
Studies on childhood leukemia and individual-level measures of household income

First author	Country	Period	Source	Interview	Association	2-sided *P*
Shu	China	1974-86	Area	Interview	+	>0.05
Rosenbaum	USA	1980-91	Registry	Questionnaire	+	0.90
Infante-Rivard	Canada	1980-93	Registry	Interview	+	0.92
Shu	Canada, USA	1983-88	Phone	Interview	-	0.077
Green	Canada	1985-93	Phone	Interview	-	0.00048
Shu	China	1986-91	Area	Interview	-	0.58
Reynolds	USA	1988-94	Registry	Records	-	0.73
Brondum	Canada, USA	1989-93	Phone	Interview	-	0.00002
Shu	Canada, USA	1989-93	Phone	Interview	-	0.00001
McBride	Canada	1990-95	Registry	Interview	-	0.0088
Ma	USA	1995-00	Registry	Interview	-	0.0013

Factors linked with Affluence and Modernization

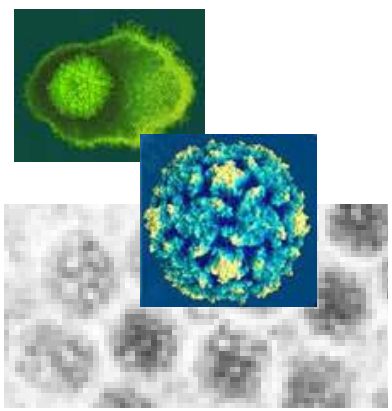
- Maternal age at child-bearing
- Increased exposure to magnetic fields
- Breast-feeding
- Sibship size
- Early child care
- High hygiene level
- Rates of immunization

Infections and immunity?

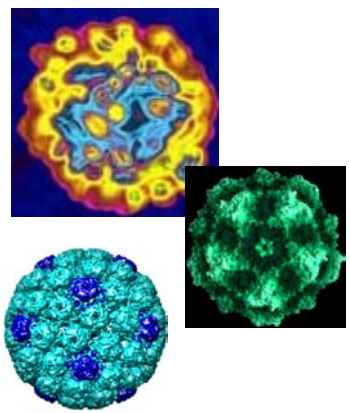
Infectious Etiology?

Search for a **leukemogenic virus** that

- induces mutations
- has limited general oncogenic potential
- has specific effects on B precursor cells



Hepatitis?
EBV, HHV-6?
Parvovirus B19?
JC, BK, SV40?



Infectious Etiology?

The Kinlen Hypothesis *(Lancet 1988)*

Clusters around nuclear reprocessing plants in Sellafield

Due to unusual population mixing due to influx of migrant workers into isolated communities?

⇩

Childhood leukemia due to lack of protective immunity against a common but unidentified infection, transmitted by „population mixing“

Infectious Etiology?

The Greaves hypothesis *(Leukemia 1988)*

Correlation between affluence/modernization and peak ALL incidence at 2-5 years

⇩

„Delayed-infection hypothesis“:

Inadequate priming of the immune system, followed by abnormal immune response during late exposure towards common infections

Evidence for Delayed-Infection Hypothesis

Day-care attendance in infancy and risk of childhood ALL

Country	Number of cases	Period	Odds ratio* (confidence interval‡)	References
Greece	136	0–2 years	0.28 (0.09–0.88)	Petridou 1993
New Zealand	121	0–1 year	0.65 (0.36–1.17)§	Dockerty 1999
Quebec	491	0–1 year	0.49 (0.31–0.77)	Infante-Rivard 2000
Hong Kong	98	0–1 year	0.63 (0.38–1.07)§	Chan 2002
France	240	From birth onwards	0.6 (0.4–1.0)	Perrillat 2002
France	408	0–3 months	0.6 (0.4–0.8)	Jourdan-Da Silva 2004
California (a)	140	0–1 year	0.6 (0.45–0.95)	Ma 2002
California (b) ‖	294	0–1 year	0.42 (0.18–0.99)	Ma 2005
United Kingdom**	1286	0–1 year	0.48 (0.37–0.62)¶ 0.69 (0.51–0.93)#	Gilham 2005
United States of America‡‡	1744	0–6 months	0.91 (0.72–1.15)§	Neglia 2000

From: Mel Greaves, Nat Rev Cancer 2006

Type I Diabetes and Childhood Leukemia

„Hygiene hypothesis“
Yazdanbakhsh, Science 2002

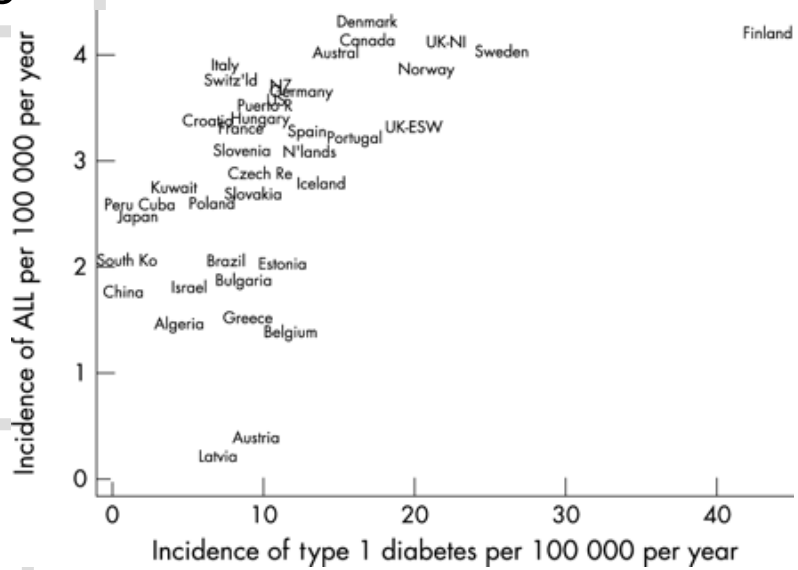
Protection against type I diabetes

Exposure to infections early in life

?

Protection against ALL

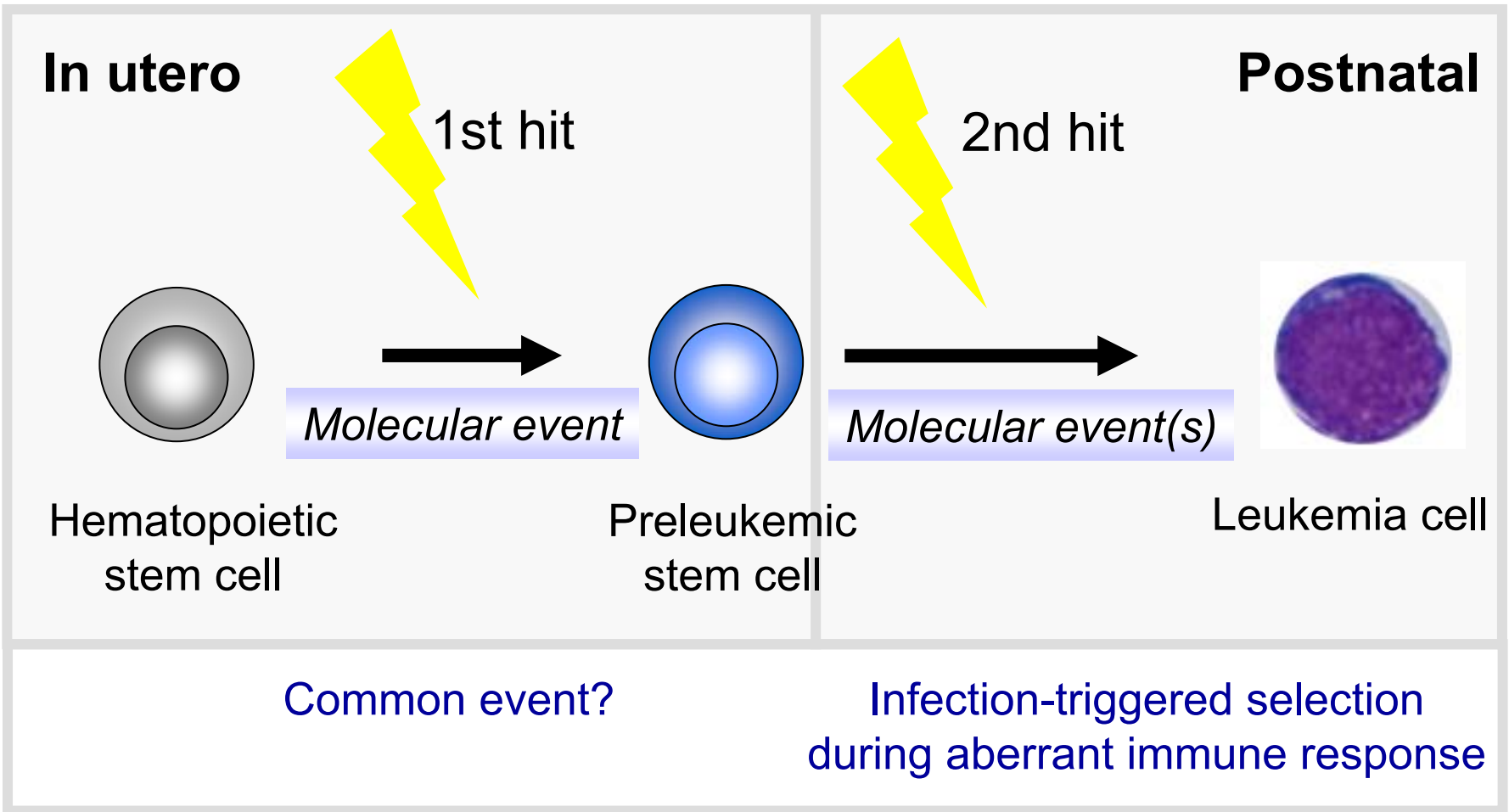
„Delayed-infection hypothesis“
Greaves, Leukemia 1988



Feltbower, ADC 2004

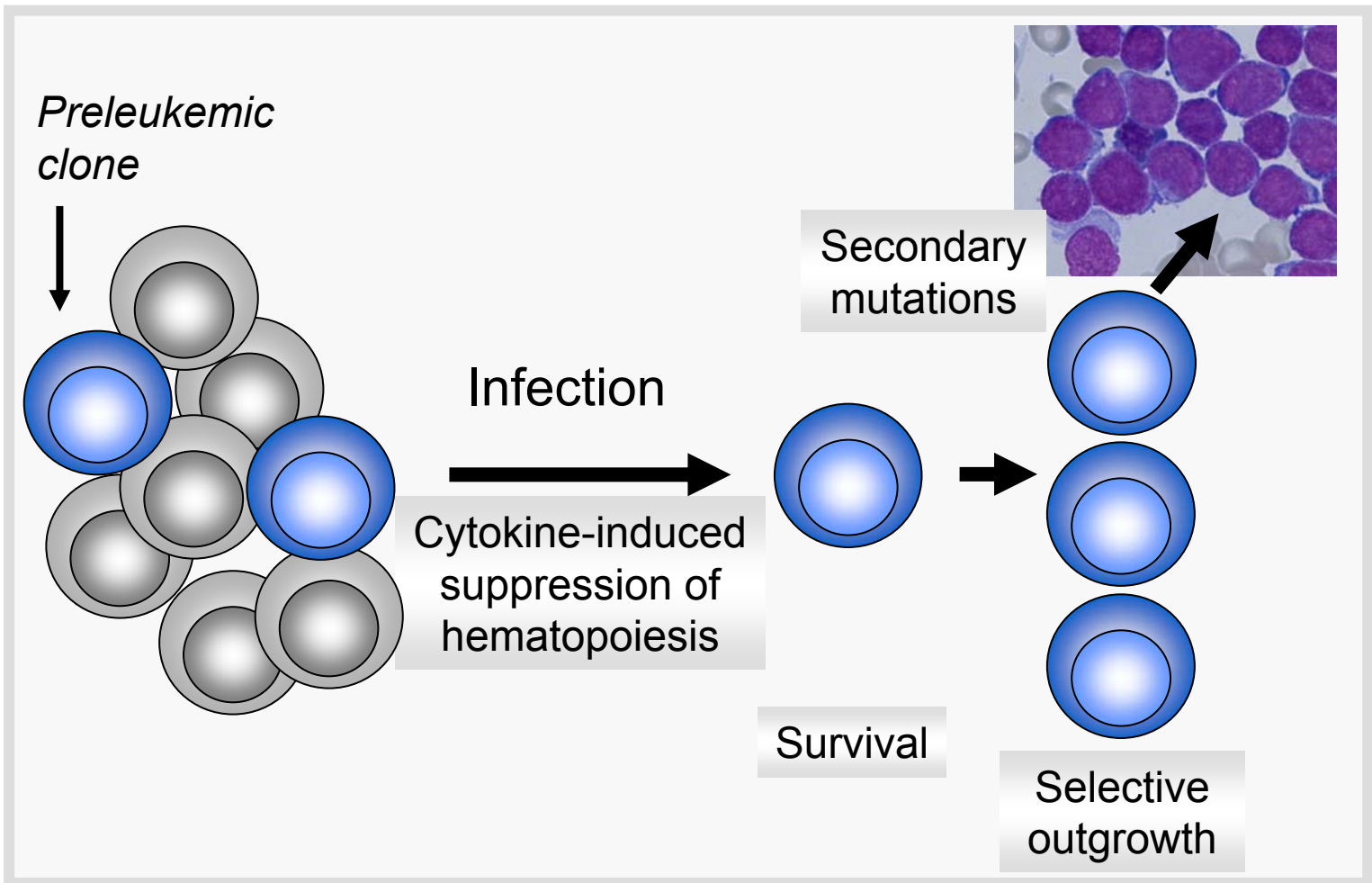

Norman S. Baldwin

Model for Leukemogenesis in Children



Model for Infection-based Selection of Preleukemic Clones

Adapted from Greaves, Nat Rev Cancer 2006



Summary

Causes of childhood leukemia remain unresolved.

Common cause is highly unlikely.

Most cases are not attributable to single specific genetic disorders or environmental exposures.

Abnormal immune response during delayed infections as a plausible etiological mechanism.

Large-scale studies are needed, including biologic specimens, to investigate gene-environment interactions.

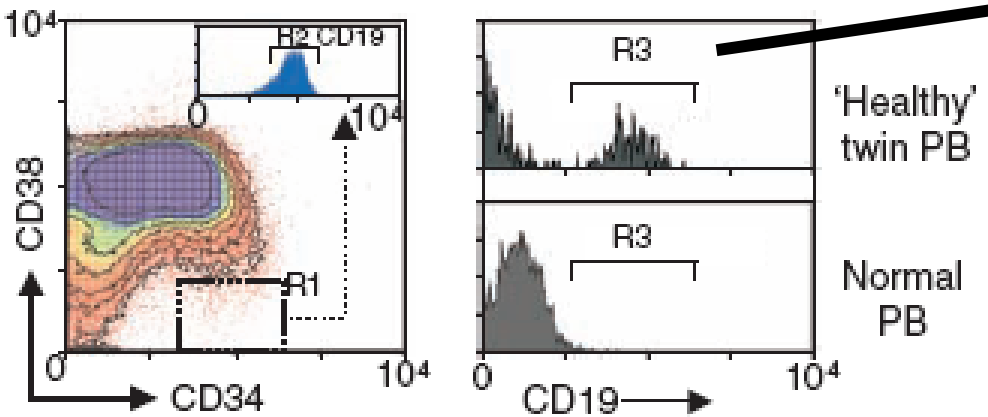

The Future:
A Vaccine against Childhood Leukemia?

The TEL-AML1 leukemia-initiating cell

Hong, …Enver, Science 2008

Initiation and maintenance
of preleukemic state
in vivo?

CD34+ CD38- CD19+
TEL/AML1+
0.002% of blood cells



NOD/scid γ-/- mouse

Engraftment
Self-renewal