



NIR & Children's Health

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ELF Animal Studies, Mechanisms of Action

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OUTLINE

- **ELF EMF and development**
- **ELF EMF and cancer**
- **Mechanisms of action**



Development



- **Review by Juutilainen, 2005**

- “The only finding that shows some consistency is an increase in minor skeleton alterations in several studies”
- “Taken as a whole, the results **do not show robust adverse effects** of ELF fields on development”

- **EMF-NET project, 2008**

Skeleton anomalies: not confirmed

Other developmental effects in mammals: weak evidence

Cancer

Cancer related to children

- **Brain tumours**
 - gliomas
 - medulloblastomas
- **Hematopoietic tumours**
 - lymphomas
 - leukaemias



Cancer

IARC monographs

International Agency for Research on Cancer



VOLUME 80 NON-IONIZING RADIATION, PART 1: STATIC AND EXTREMELY LOW-FREQUENCY (ELF) ELECTRIC AND MAGNETIC FIELDS, 2002

- Possibly carcinogenic to humans
- ***Childhood leukaemia***
- Based on an association in epidemiology and lack of experimental support (biology and mechanism)

Cancer: hematopoietic tumours

- Brain et al (2003) Environ Health Perspect.
– Review in animals
- Sommer and Lerchl (2004) Radiat. Res.
- Sommer and Lerchl (2006) Radiat. Res.
- Bernard et al (2008) J. Radiat. Res.

Cancer: hematopoietic tumours (1)

Brain et al (2003)

- 5 studies, 1 – 5000 μT

Species	Group size	Exposure	Percent incidence of hematopoietic neoplasia		Reference
Rats (F344)	100/both sexes/ exposure group	Sham control	Leukemia: male	Leukemia: female	Boorman et al. (1999)
		10 G (continuous)	50	20	
		10 G (intermittent; 1 hr on/off)	50	25	
		2 G (continuous)	36*	22	
		0.02 G (continuous)	47	24	
		60 Hz, 18.5 hr/day	44	18	
Rats (F344)	48/both sexes/ exposure group	Sham control	Leukemia: male	Leukemia: female	Yasui et al. (1997)
		50 G	10	16	
		5 G	8	14	
		5 G	8	12	
		Sham control	Lymphoma: male	Lymphoma: female	
		50 G	0	0	
5 G	0	2			
50 Hz, 22.6 hr/day	0	2			
Rats (F344)	50 female/ exposure group	Sham control	Leukemia		Mandeville et al. (1997)
		20 G	10		
		2 G	10		
		0.2 G	6		
		0.02 G	18		
		60 Hz, 20 hr/day	8		
Mice (B6C3F1)	100/both sexes/ exposure group	Sham control	Lymphoma: male	Lymphoma: female	McCormick et al. (1999)
		10 G (continuous)	8	32	
		10 G (intermittent)	7	26	
		2 G (continuous)	6	20*	
		0.02 G (continuous)	4	22	
		60 Hz, 18.5 hr/day	7	31	
Mice (C57BL/6)	190 or 380 female/ exposure group	Sham control	Total hematopoietic neoplasms		Babbitt et al. (2000)
		14 G (circularly polarized)	56		
		14 G (circularly polarized)	59		
		Sham control	Lymphoma		
		14 G (circularly polarized)	35		
		60 Hz, 18 hrs/day	37		

* $p < 0.05$ versus sham control.

Cancer: hematopoietic tumours

Brain et al (2003)

- 3 studies, 1 – 1000 μ T
- *Pim-1*, TSG-*p53* mouse models

Species	Group size	Exposure	Percent incidence of lymphoma		Reference
			Male	Female	
Mice (<i>pim-1</i>)	30/both sexes/ exposure group	Sham control	49	47	McCormick et al. (1998)
		10 G (continuous)	23*	47	
		10 G (intermittent)	57	53	
		2 G (continuous)	43	45	
		0.02 G (continuous)	47	45	
		60 Hz, 18.5 hr/day, for 26 weeks			
Mice (<i>pim-1</i>)	100 female/ exposure group	Sham control	T-cell 5	B-cell 23	Harris et al. (1998)
		10 G (continuous)	8	22	
		10 G (intermittent)	7	28	
		1 G (continuous)	8	18	
		0.01 G (continuous)	4	25	
		50 Hz, 20 hr/day, up to 18 months			
Mice (TSG- <i>p53</i>)	30/both sexes/ exposure group	Sham control	Male 3	Female 3	McCormick et al. (1998)
		10 G (continuous)	0	7	
		60 Hz, 18.5 hr/day, for 26 weeks			

* $p < 0.05$ versus sham control.

Cancer: hematopoietic tumours

Brain et al (2003)

- 2 studies, 1000 and 1400 μT
- Initiators : X rays, dimethylbenz[a]anthracene

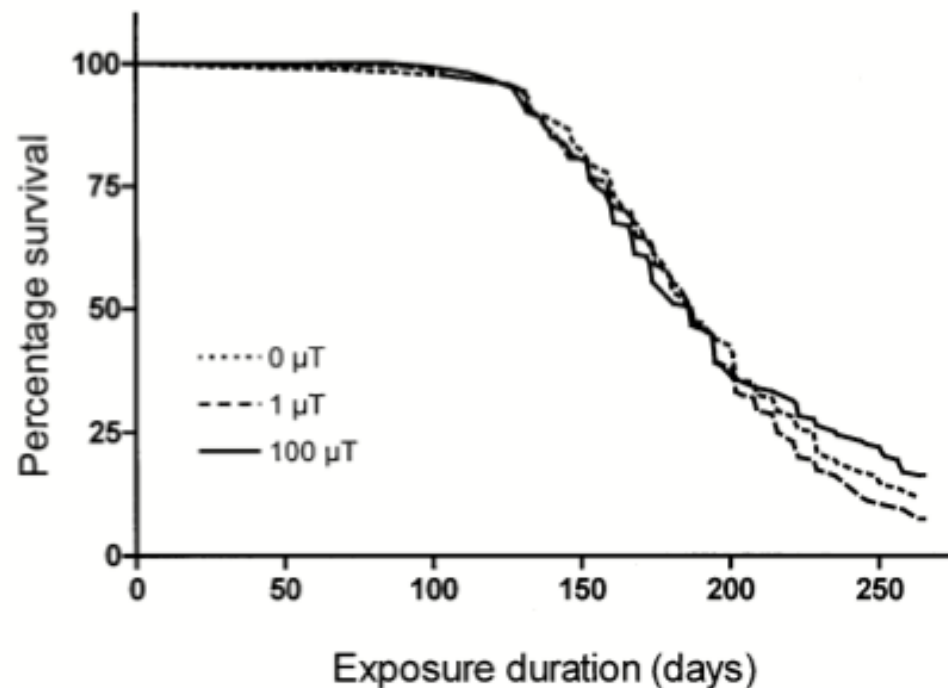
Species	Group size	Exposure	Percent incidence of lymphoma			Reference
			3.0 Gy	4.0 Gy	5.1 Gy	
Mice (C57BL/6)	380 female/ exposure group	X-ray:				Babbitt et al. (2000)
		Sham control	41	38	53	
		14 G (circular) 60 Hz, 18 hr/day, lifetime	34	41	47	
Mice (Swiss Webster)	155–165/ exposure group	Dimethylbenz[a]anthracene:				Shen et al. (1997)
		Sham control		24		
		10 G 50 Hz, 3 hr/day, 5 days/week, for 16 weeks		22		

No evidence of effect

Cancer: hematopoietic tumours (2)

Sommer and Lerchl (2004), (2006)

- AKR/J mouse model of lymphoma
- 1, 100, and 1000 μT
- 24 h/d or night-time, 7 d/w, 32-38 weeks

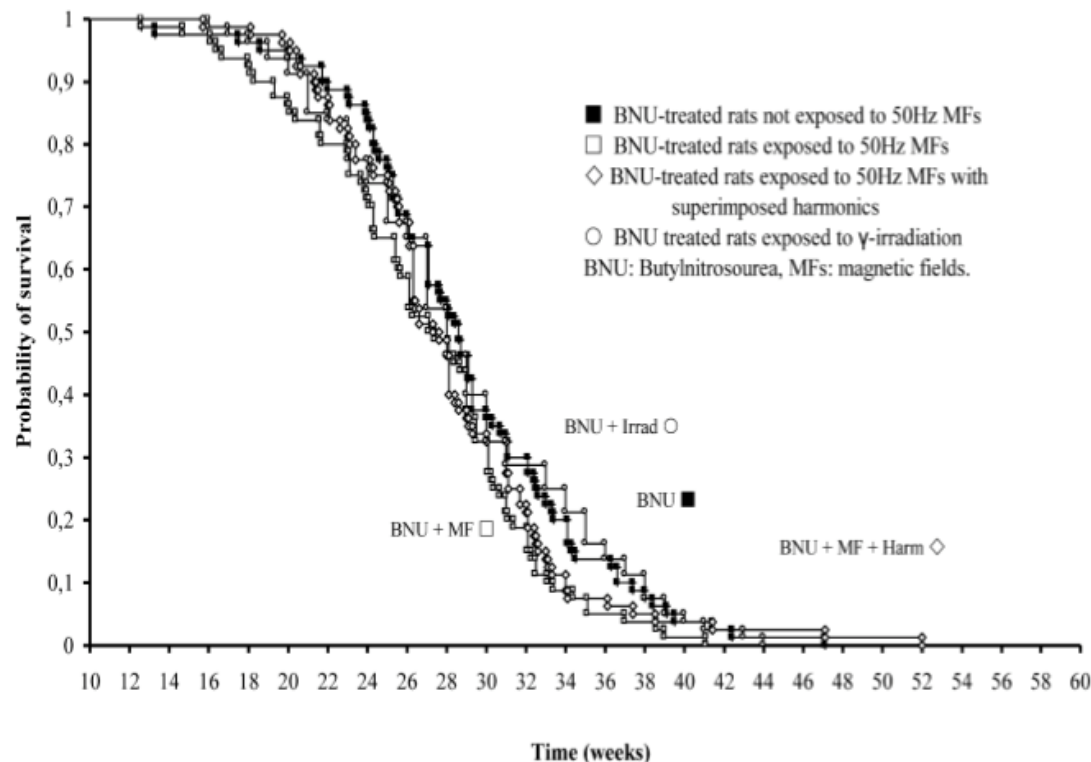


**No evidence
of effect**

Cancer: hematopoietic tumours (3)

Bernard et al (2008)

- WKAH/Hkm rat model of leukemia (B-ALL)
- 100 $\mu\text{T} \pm$ harmonics:
150 Hz (5 μT), 250 Hz (6 μT), 350 Hz (5 μT)
- 18 h/d, 7 d/w, 13 months



**No evidence
of effect**

Cancer :

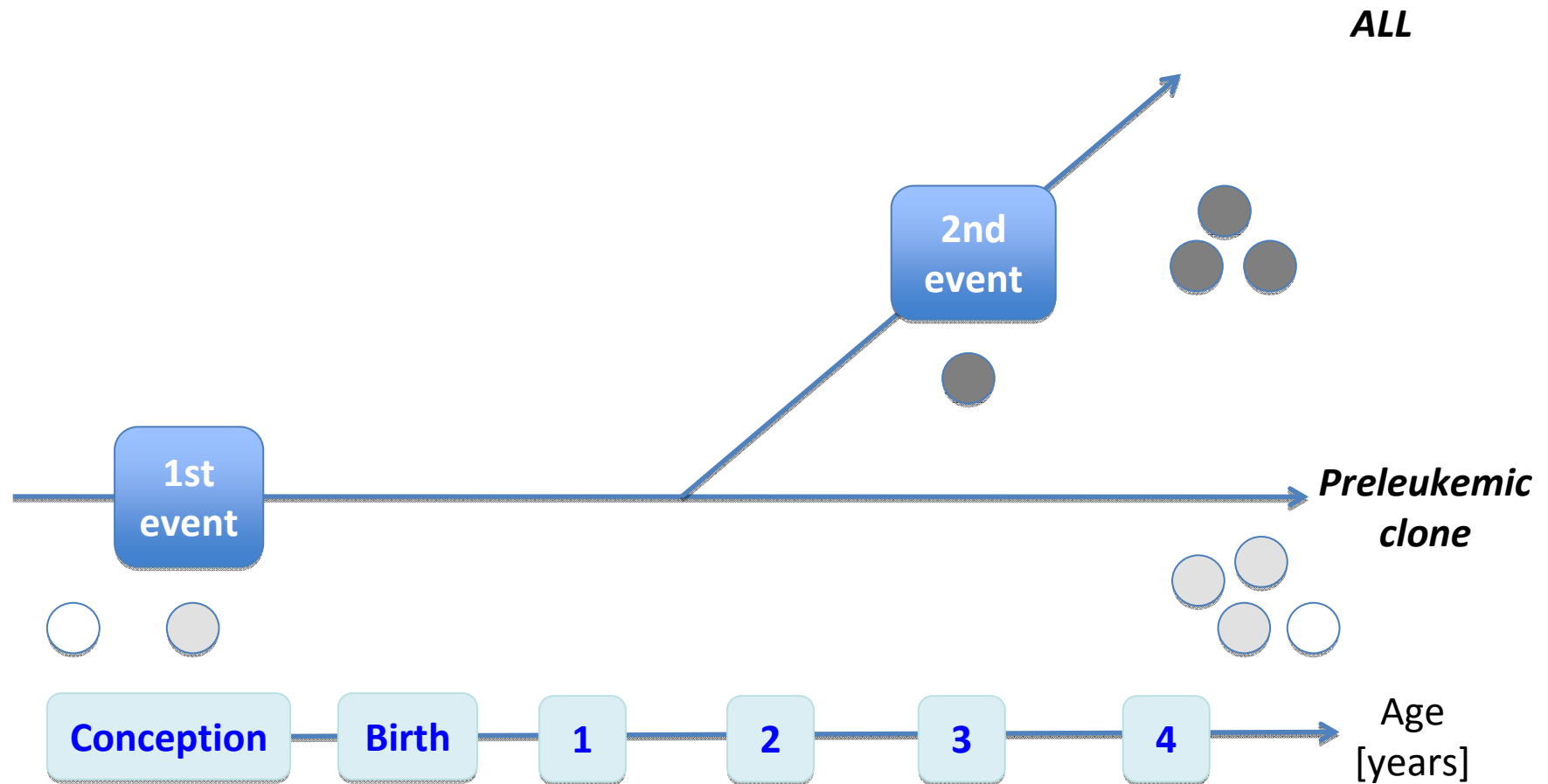
Conclusions on hematopoietic tumours

- 13 studies investigated hematopoietic tumours
 - 1 to 5000 μT
 - 16 weeks to lifetime
 - 3 to 22.6 h/d
- 4 /13 investigated leukaemia
- 1 /13 investigated B-ALL

Globally, no evidence of effect

... only one study relevant to children leukaemia

ELF EMF and childhood leukaemia



Any track to go further?

To go further: track 1

- **Ziegelberger et al, Blood Cancer Journal (2011)**

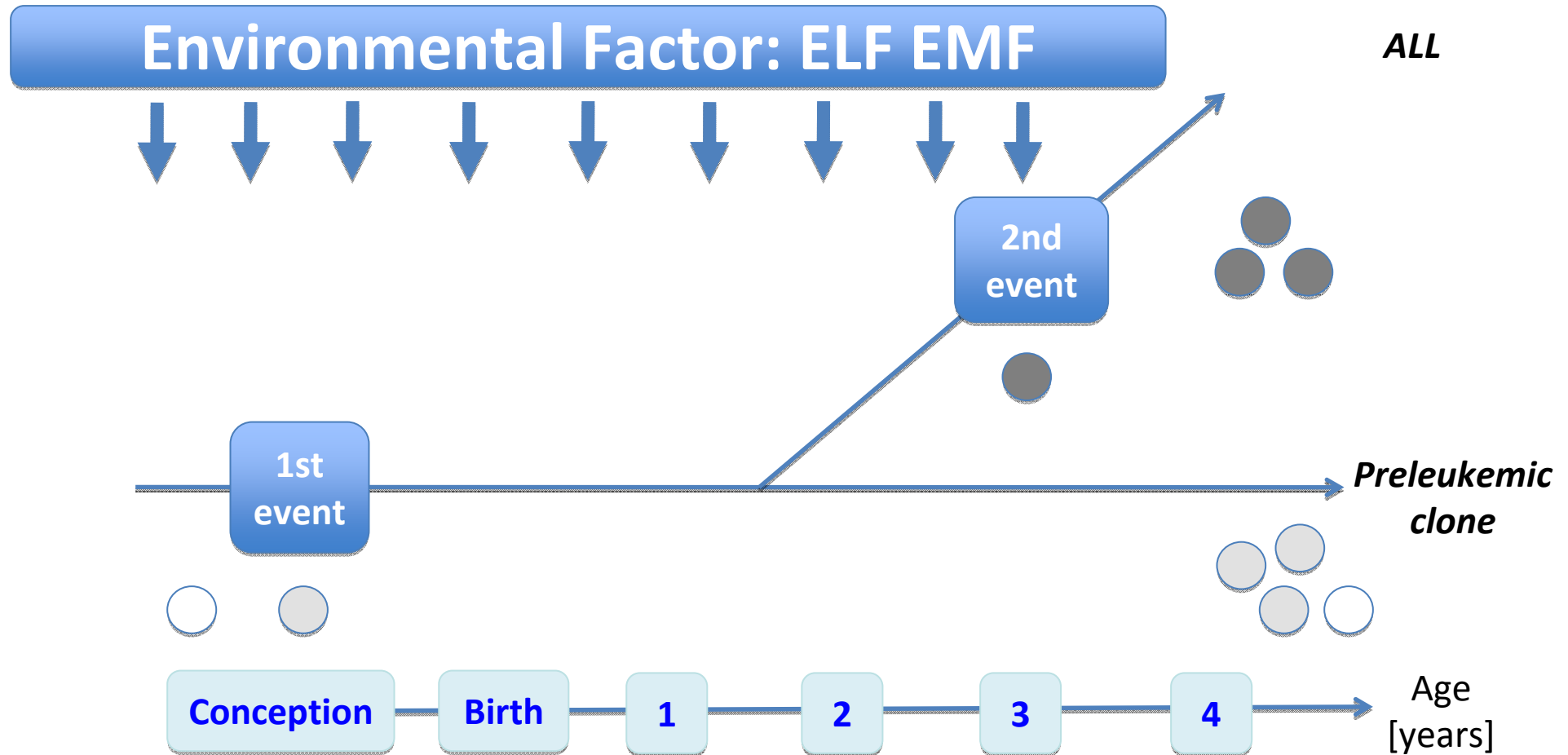
- MLL-AF9 mouse model (Stubbs et al, 2008)
- TEL-AML1 mouse model (Ford et al, 2009; Schindler et al, 2009)
- Double- p19Arf/Rag1 knockout mouse model (Hauer et al)
- WKAH/Hkm rat model: not included

- **Escribano et al, IJRB (1997)**

1 Gy X-rays during gestation affects the developing murine hemotopoiesis.

**Track 1: Use available B-ALL animal models
as a starting point**

To go further: track 2



Track 2: Expose animals starting *in utero* and/or genitors

To go further: track 3

bjh review

Gene silencing by DNA methylation in haematological malignancies

2007

Jacqueline Boulton and James S. Wainscoat

PNAS

MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia

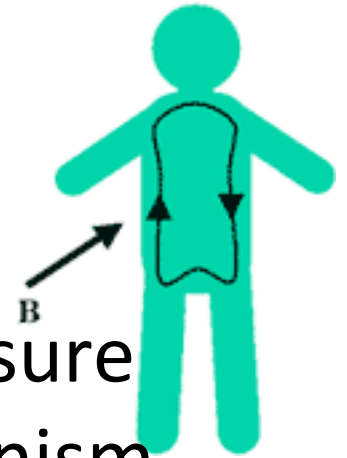
2007

Shuangli Mi[†], Jun Lu^{‡§}, Miao Sun[†], Zejuan Li[†], Hao Zhang[†], Mary Beth Neilly[†], Yungui Wang[¶], Zhijian Qian[†], Jie Jin[¶], Yanming Zhang[†], Stefan K. Bohlander[¶], Michelle M. Le Beau[†], Richard A. Larson[†], Todd R. Golub^{‡§††††}, Janet D. Rowley^{†††}, and Jianjun Chen^{†††}

Track 3: Test the capability of ELF EMF to induce epigenetic changes

Mechanisms:

Internal electric fields



- **Induction of E fields and currents** by exposure to ELF EMF is the currently accepted mechanism
 - Target: Excitable tissues (muscle and nerve)
 - Exposure limits to prevent such phenomenon
 - Exposure limit recommendation for public: 200 μT
- **Cannot explain the epi data**

Mechanisms:

The radical pair mechanism (RPM)

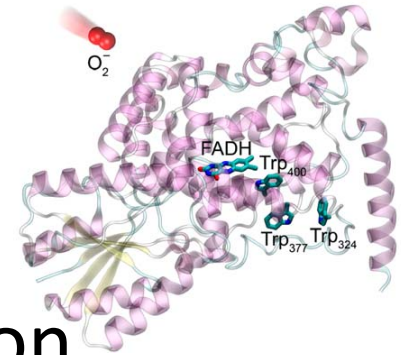
- Magnetic fields have an effect on radical pairs and thus on biochemistry *in vivo*
- Best evidence comes from bird navigation
- Could this have an effect on the leukemic cells and/or their microenvironment?



Mechanisms:

The radical pair mechanism (RPM)

- **Example: cryptochrome (CRY)**
- Plausible candidate for bird navigation
- The radical pair is formed following blue light absorption by CRY
- CRY involved in circadian rhythms in the whole organism and all cells



Conclusion



- **Since the 2002 IARC classification**
 - B-ALL mouse models available
 - Better knowledge gained on childhood leukaemia
 - RPM testable due to the ubiquitous presence of CRY
- **FP7 project: ELF magnetic fields and childhood leukaemia**
 - To begin soon
 - Will close the debate ?

Thank you

