



# 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  $\mu\text{T}$

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  $\mu$ 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  $\mu\text{T}$
- Initiators : X rays, dimethylbenz[a]anthracene

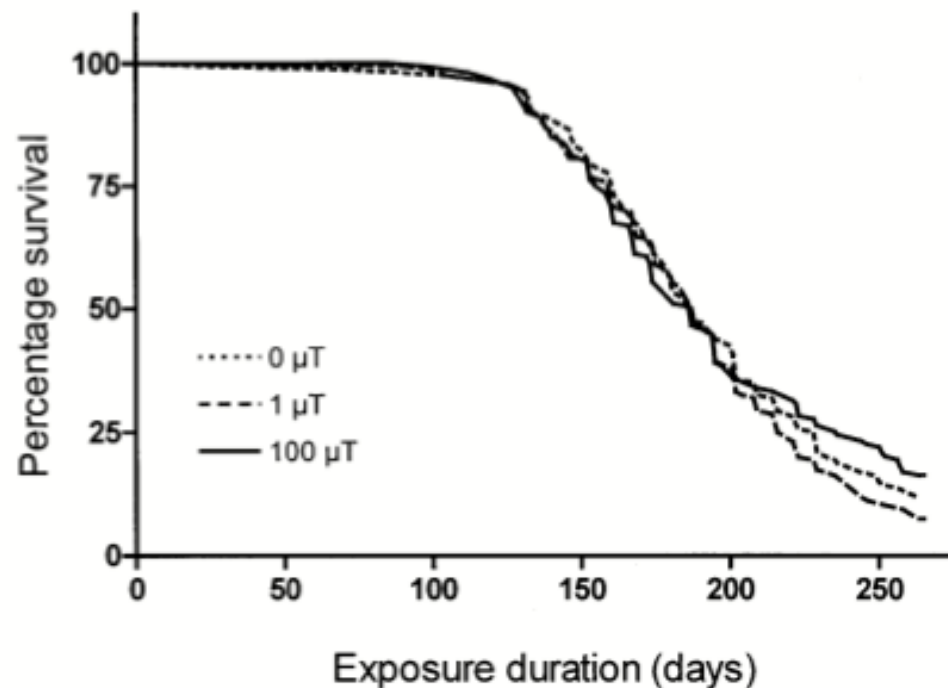
Species	Group size	Exposure	Percent incidence of lymphoma			Reference
Mice (C57BL/6)	380 female/ exposure group	X-ray:	3.0 Gy	4.0 Gy	5.1 Gy	Babbitt et al. (2000)
		Sham control	41	38	53	
		14 G (circular) 60 Hz, 18 hr/day, lifetime	34	41	47	
Mice (Swiss Webster)	155–165/ exposure group	Dimethylbenz[a]anthracene:				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  $\mu\text{T}$
- 24 h/d or night-time, 7 d/w, 32-38 weeks

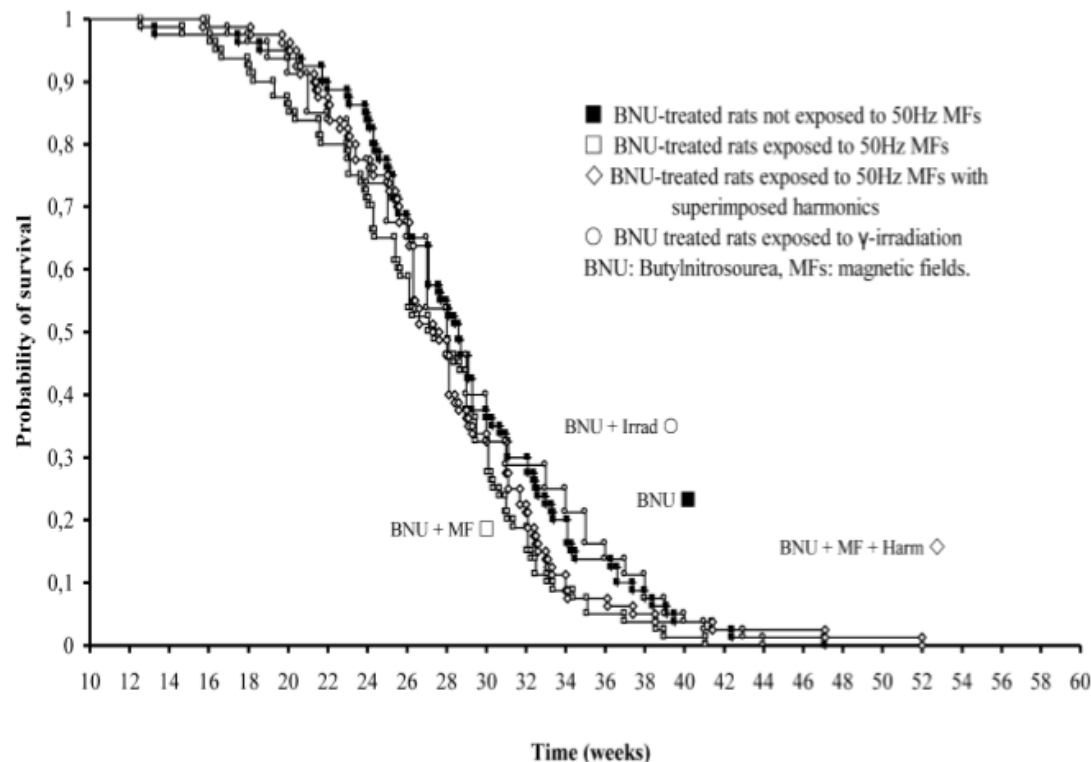


**No evidence  
of effect**

# 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  $\mu\text{T}$ ), 250 Hz (6  $\mu\text{T}$ ), 350 Hz (5  $\mu\text{T}$ )
- 18 h/d, 7 d/w, 13 months



**No evidence  
of effect**

# Cancer :

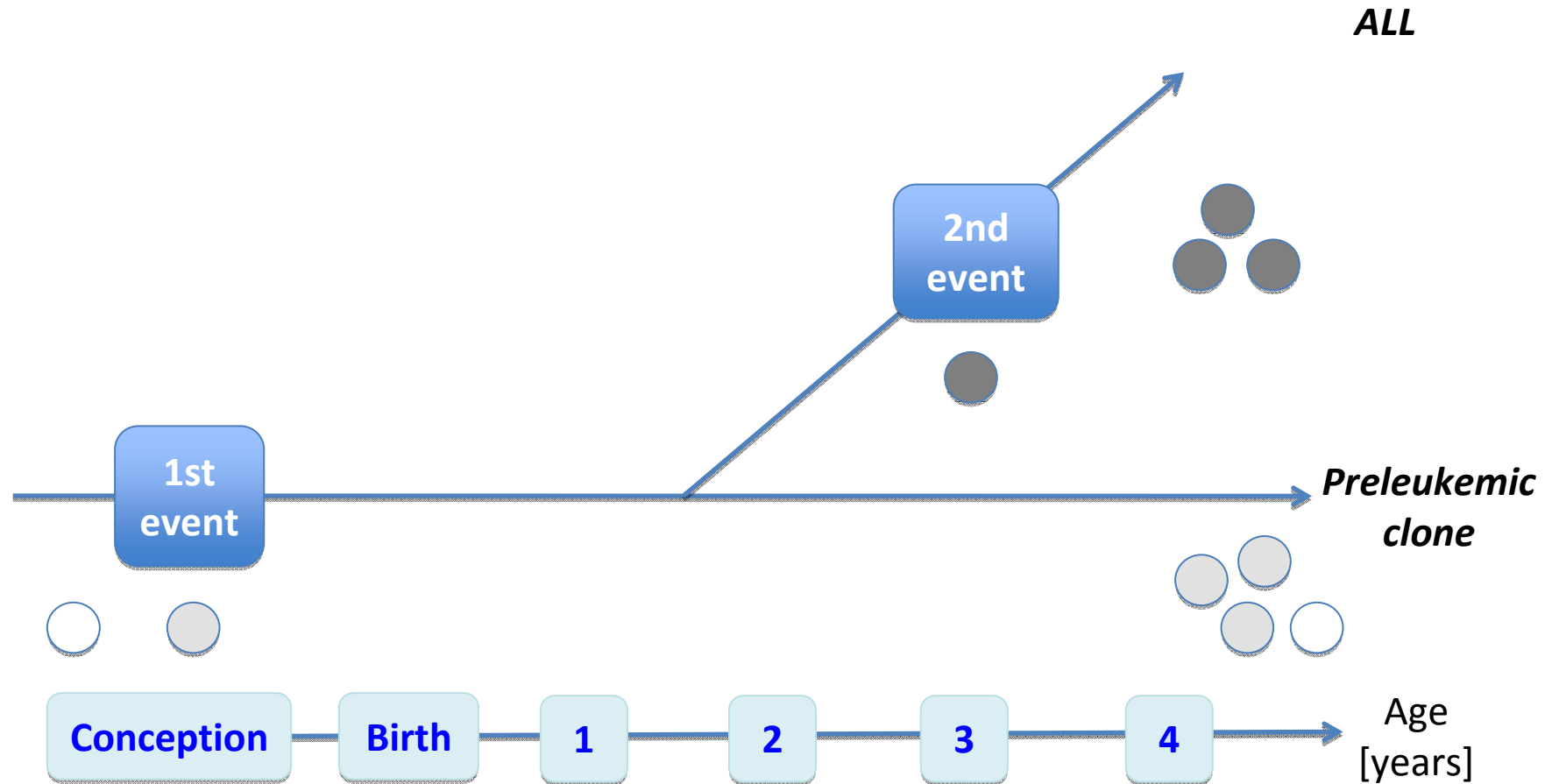
## Conclusions on hematopoietic tumours

- 13 studies investigated hematopoietic tumours
  - 1 to 5000  $\mu\text{T}$
  - 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)**

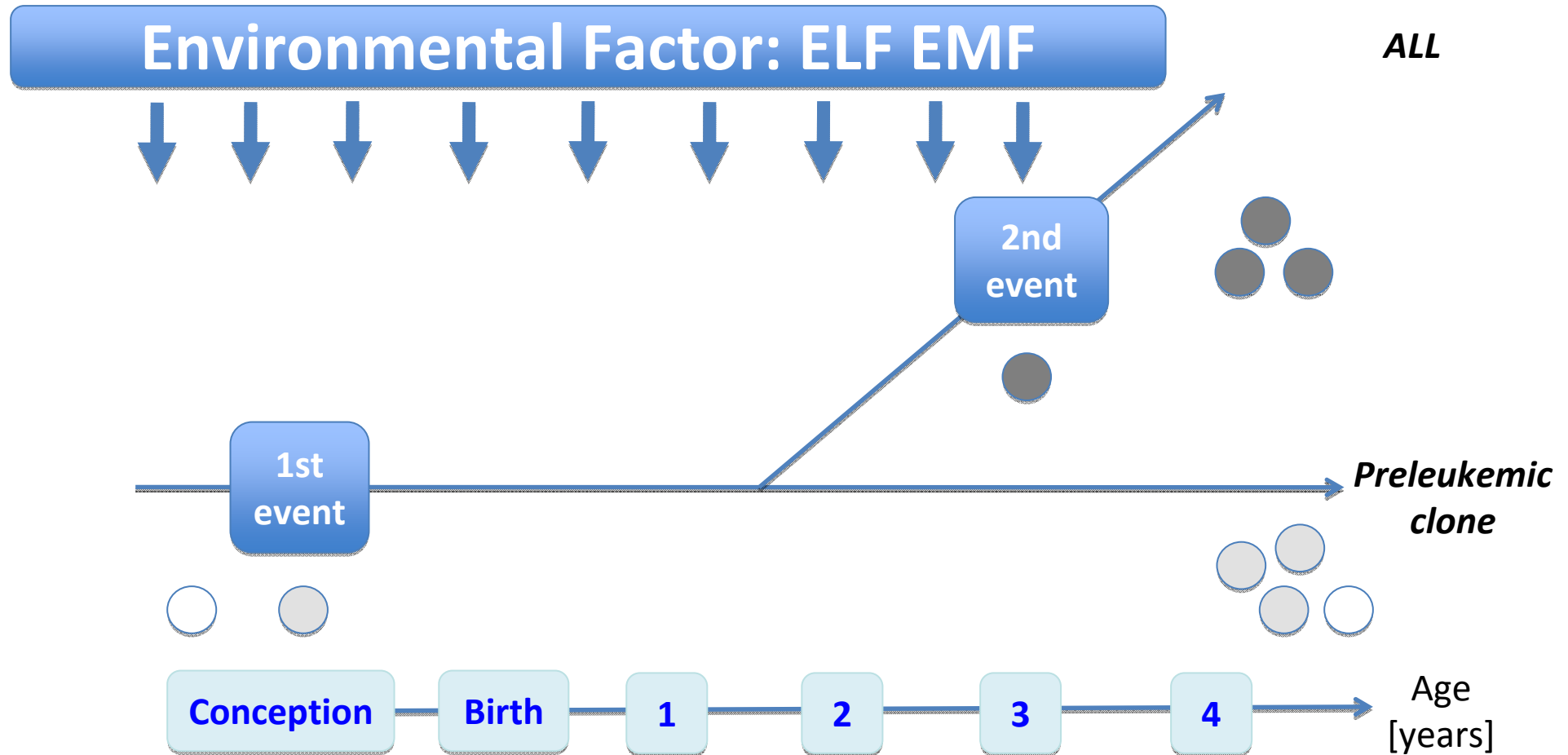
- MLL-AF9 mouse model (Stubbs et al, 2008)
- TEL-AML1 mouse model (Ford et al, 2009; Schindler et al, 2009)
- Double- p19Arf/Rag1 knockout mouse model (Hauer et al)
- WKAH/Hkm rat model: not included

- **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**

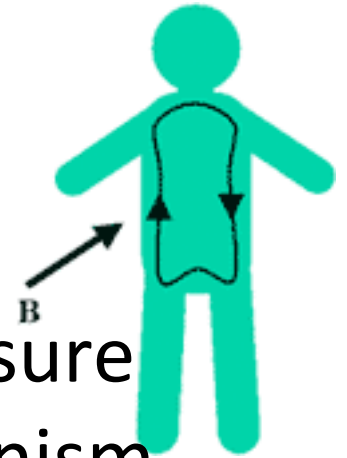
2007

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

**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  $\mu\text{T}$
- **Cannot explain the epi data**

# Mechanisms:

## The radical pair mechanism (RPM)

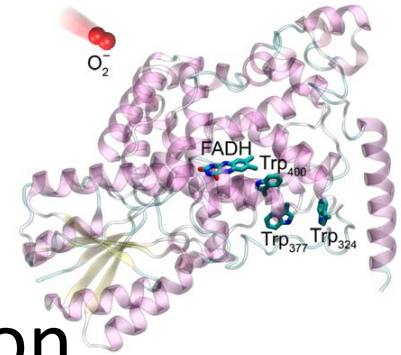
- Magnetic fields have an effect on radical pairs and thus on biochemistry *in vivo*
- Best evidence comes from bird navigation
- Could this have an effect on the leukemic cells and/or their microenvironment?



# 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

