



Gene Therapy Workshop

ICH Activities - Regional Topics

Yokohama, June 2009

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Representing

EFTA



Overview

- **ICH GTDG - Role of EFTA**
- **Retroviral Vectors**
 - 1) Overall Experience
 - 2) SCID
 - 3) GCD
 - 4) Thalassemia
- **Regulation of Gene Therapy in Switzerland (representing EFTA)**



ICH – EFTA

- European Free Trade Association (EFTA) was founded in 1960
- 4 Countries: Iceland, Liechtenstein, Norwegian, Switzerland
- ICH: EFTA has a role as observer together with Canada and WHO
- Swissmedic represents EFTA (according to the ICH Procedures)





ICH GTDG

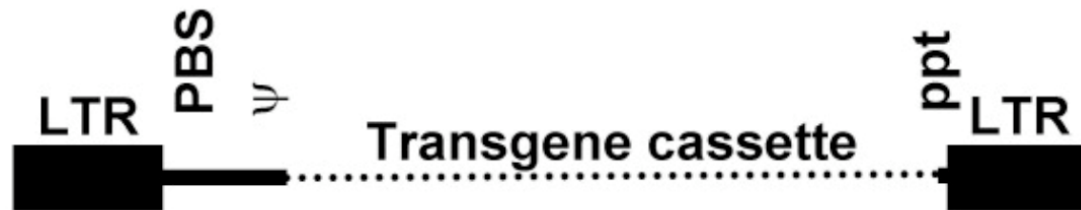
- **First meeting in Tokyo 2001**
- **Subjects under discussion:**
 - RCA, reference material
 - Inadvertent germline integration
 - Oncolytic viruses
 - Viral/Vector shedding
 - Insertional mutagenesis

ICH GTDG

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 - **Insertional mutagenesis**



Retroviral Vectors (RV)

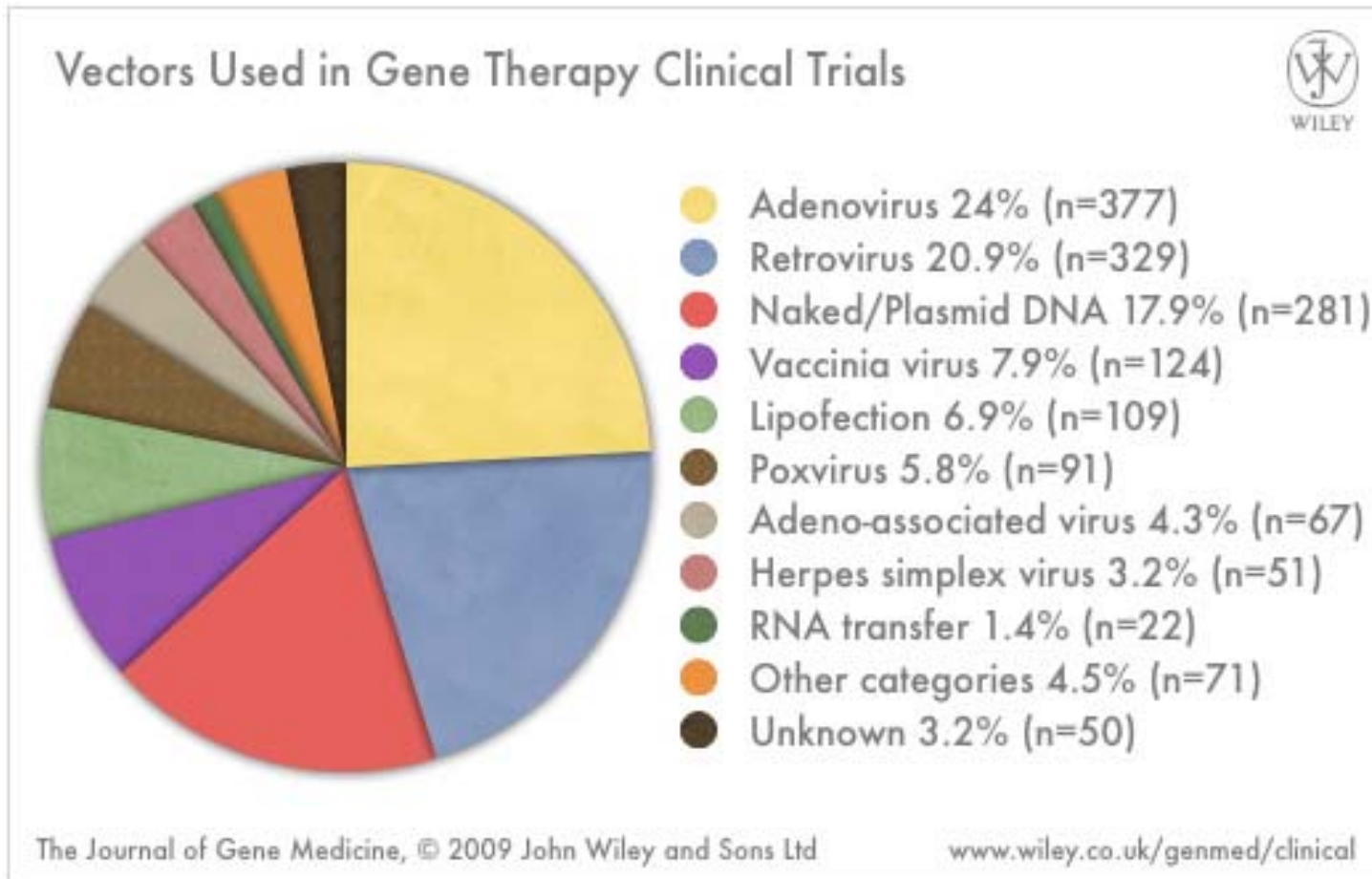


Genome integration may lead to:

- Gene disruption
- Distal gene activation
- Read-through transcription

Eventually resulting in:

- Dysregulated gene expression
- Tumorigenesis

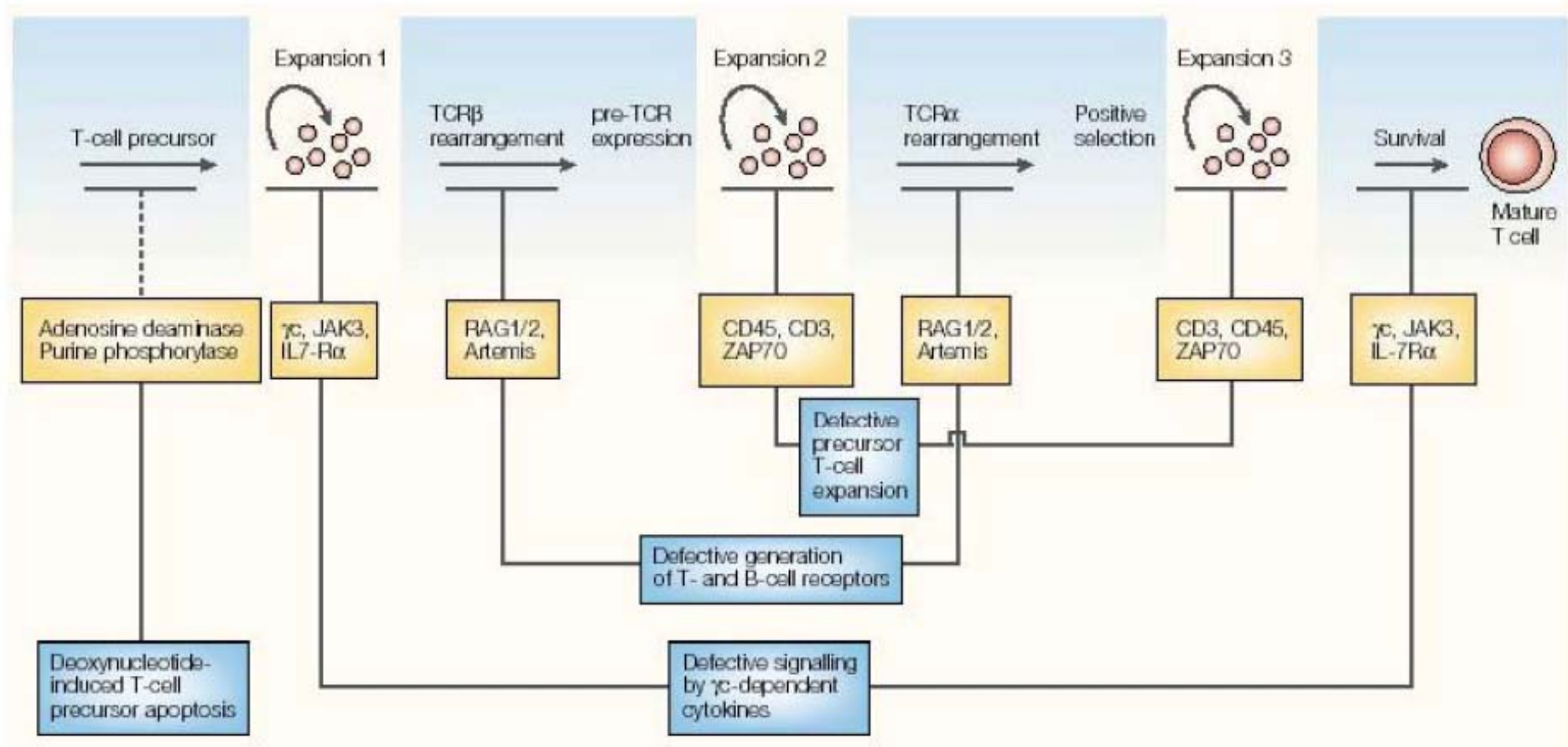


Retroviral vectors: 21% of all clinical studies

SCID

Disease	Cells affected	Defective gene and/or protein	Chromosomal location
X-linked SCID	T, B(?), NK	γ c	Xq13.1
Autosomal recessive SCID	T, B, NK(?)	ADA	20q12–13.11
	T, B, NK(?)	PNP	14q11.2
	T(?)	CD3 ϵ /CD3 γ	11q23
	T	ZAP 70	2q12
	T, NK	JAK-3	?
MHC class II deficiency	T, B	RAG1/RAG2	11p13
	T, B	RFX5	?
	T, B	RFXAP	?
MHC class I deficiency	T, B	CIITA	?
	T, B	TAP2	6p21.3

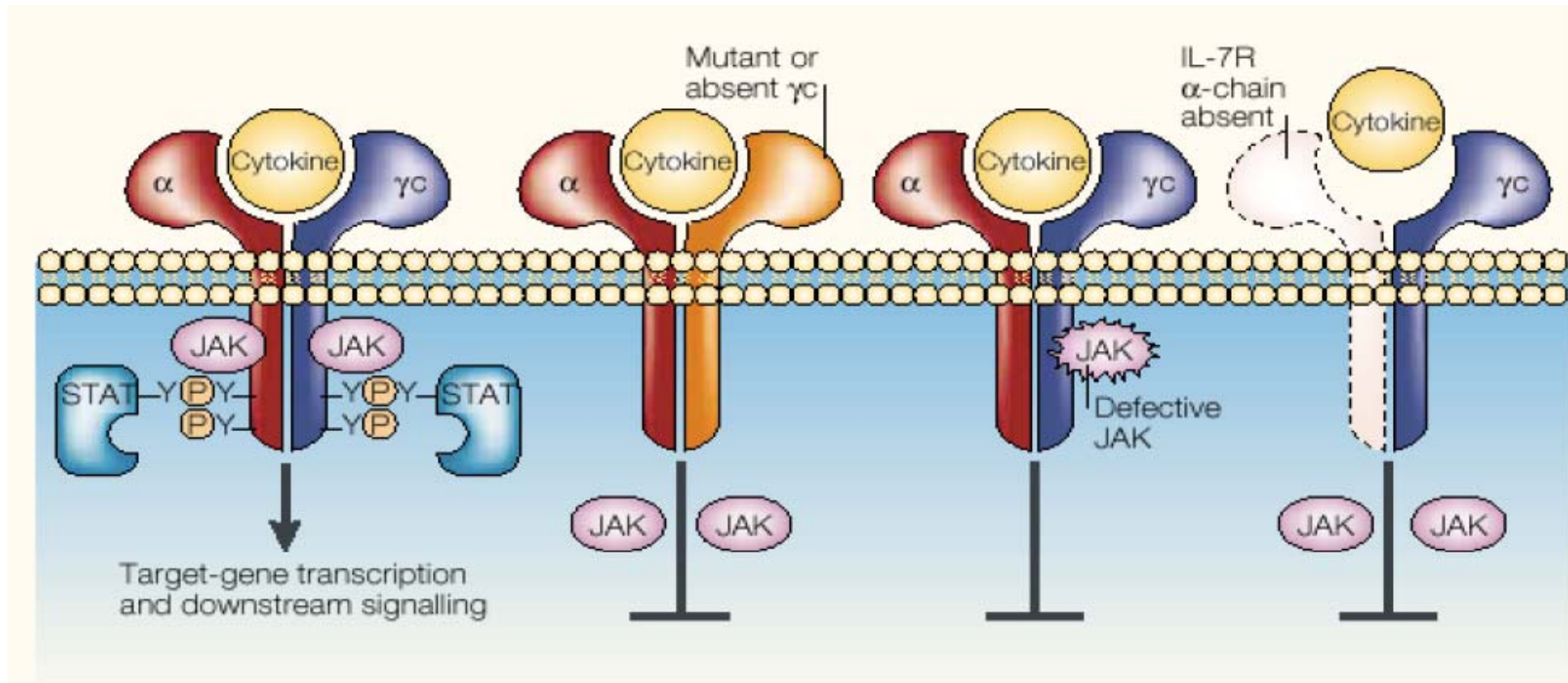
SWISSmedic
SCID



Fischer et al. 2002

GT Workshop, Yokohama, June 09

SWISSmedic
SCID



Cavazzano-Calvo et al. 2005

GT Workshop, Yokohama, June 09

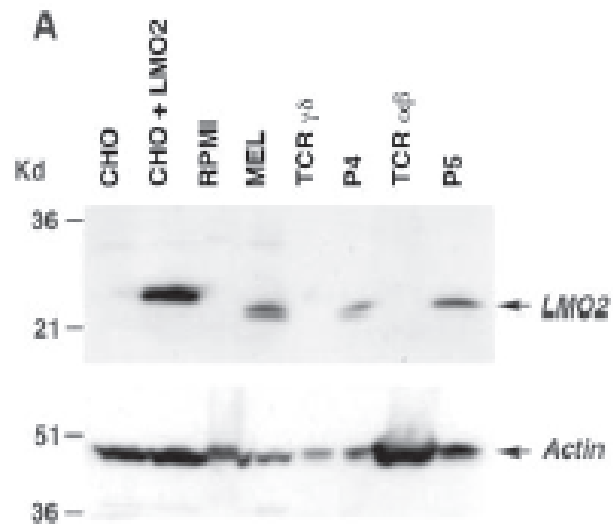
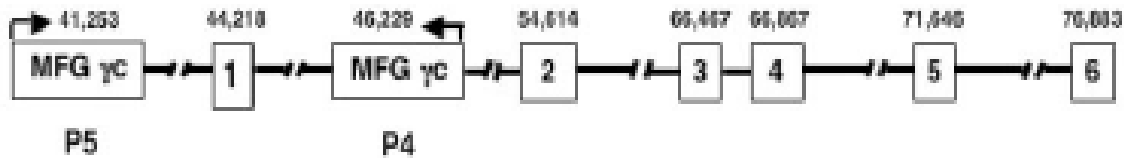
X-SCID (γ_c)

Fischer Trial (1999)

- PIs: Fischer, Cavazzana-Calvo, et al.;
Hôpital Necker-Enfants Malades, Paris
- Enrollment: 11 subjects (note: an additional subject received the same vector product in Australia), primarily infants/toddlers
- Vector: MFG
- Transgene: γ_c
- Transduction efficiency: 20-40% (in most subjects 35%)

X-SCID (γ_c) French Trial

Clonal T-cell proliferation – insertional mutagenesis



Upregulation of LMO-2

Comparison of Patients with Leukemias

Characteristic	P4*	P5*	P10#
Age at time of treatment	1 month (m)	3m	9m
Dose γc^+ , CD34 ⁺ cells/kg	18 x 10 ⁶	20 x 10 ⁶	11 x 10 ⁶
Time, Type T cell proliferation	30m (2002) $\gamma\delta^+$ TCR	34m (2002) $\alpha\beta^+$ TCR	33m (2005) V β 5 TCR
Retroviral Vector Integration	In 1 st Intron, LMO-2	In 5' UTR, LMO-2	3 vector integrants Sites TBD

*Hacein-Bey-Abina, S., et al, 2003, Science 302:415

#J.-H. Trouvin, Afssaps, and A. Fischer

X-SCID (γ_c)

Thrasher Trial

- PIs: Thrasher, Gaspar and Veys;
Great Ormond Street Hospital for Children, London
- Enrollment: 3 infants
- Vector: MFG (GALV pseudotyped)
- Transgene: γ_c
- Transduction efficiency: greater than 50%

X-SCID (γ_c) - French / English Trials

- Selective advantage of corrected cells
- About 20 patients
- Demonstrated benefit
- 5 SAEs
- 1 patient died
- No overexpression of γ_c
- No constitutive activation of JAK3
- Contribution of LMO-2 and γ_c ?

ICH GTDG Discussion on X-SCID

Japan

- Integration site analysis required (LAM-PCR)
- Monitoring for clonality

USA / EU

- Transient hold of retroviral SCID trials
- Sponsor must be able to monitor for clonality
- EU requires archival of samples, LAM-PCR not required (not validated)
- Integrations can be repeated in animal systems
- Restrict copy number in cells to integrated 1 copy on average

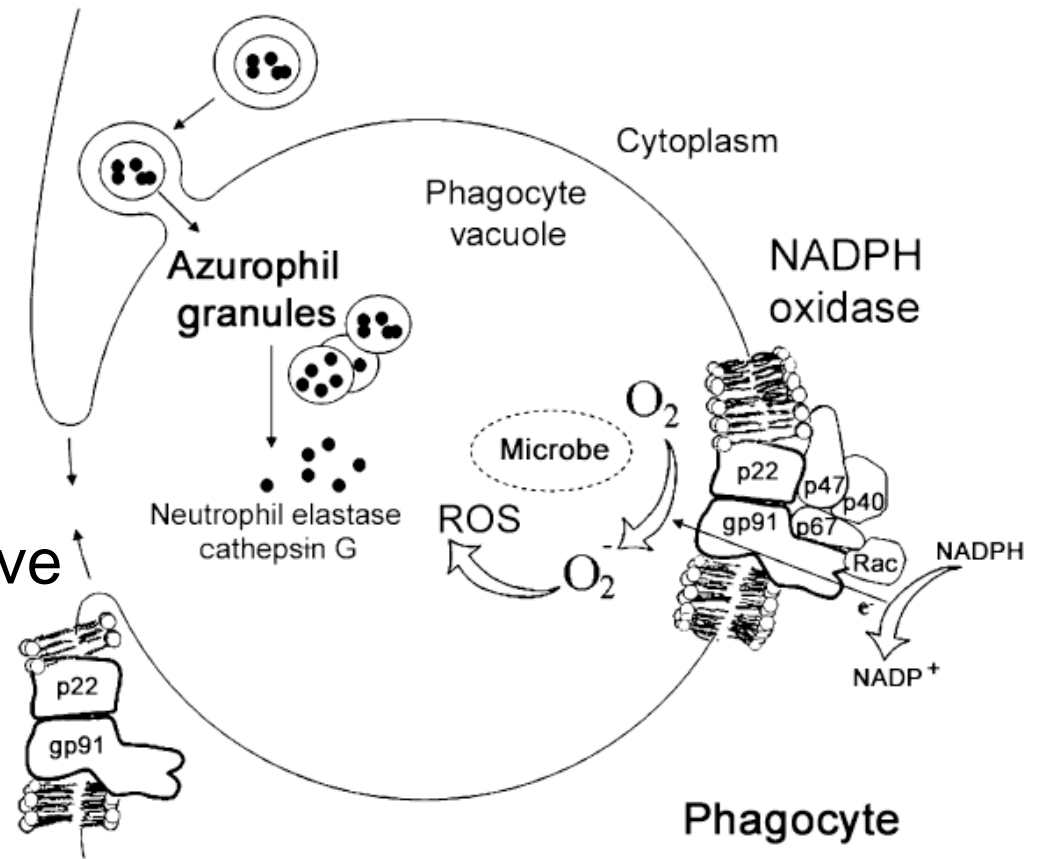
ICH GTDG Discussion on X-SCID

USA

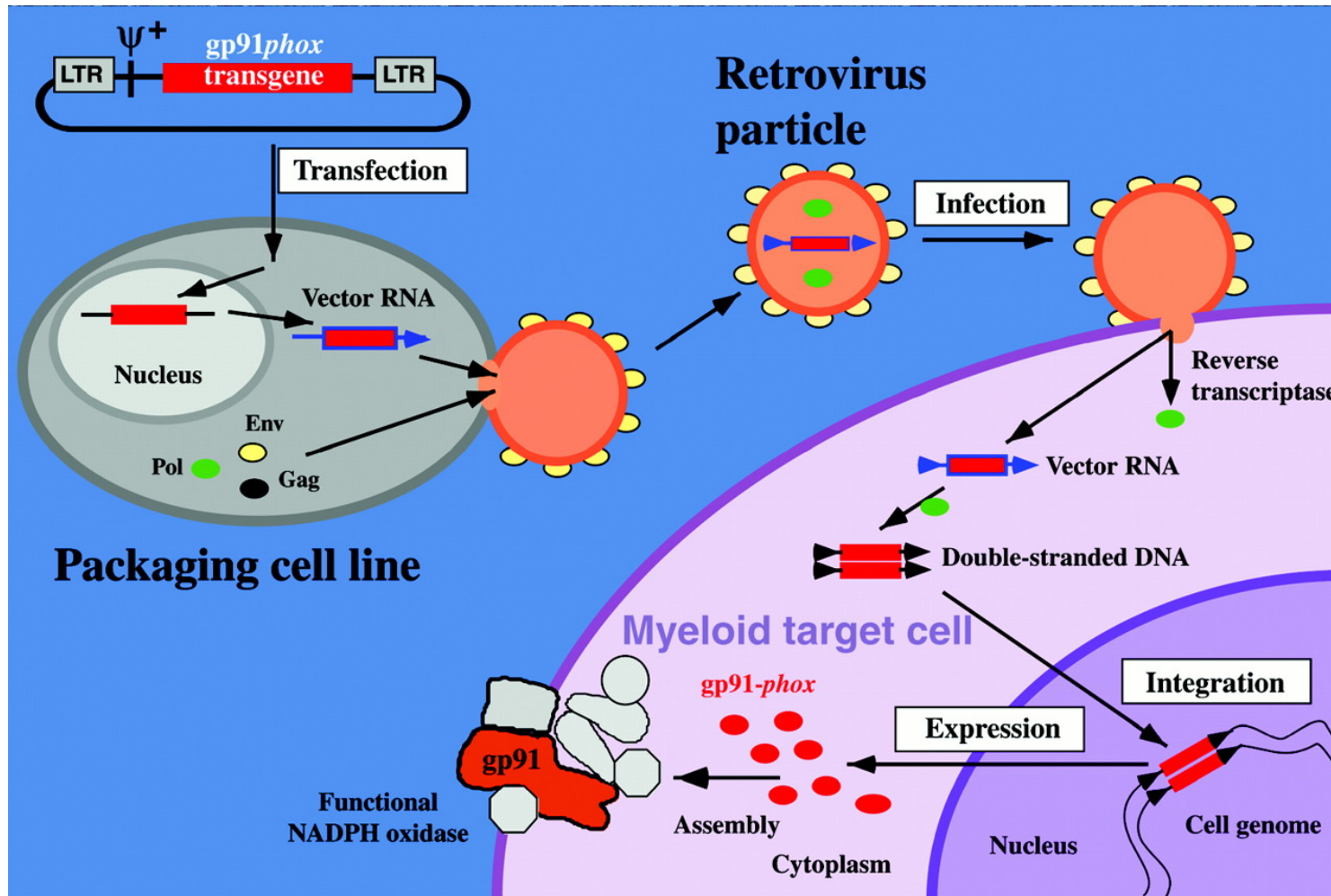
- Until data accumulate to change the risk benefit assessment in a more favorable manner, retroviral vector-mediated gene transfer should only be used in children with X-SCID under the following conditions:
 - Failed previous hematopoietic stem cell/bone marrow transplantation
 - Have no reasonable alternative therapies
 - e.g., patients precluded from transplantation because of unacceptably high risk from previous infections.

CGD

- Rare inherited immunodeficiency
- Life threatening bacterial and fungal infections
- >50% of mutations in the gp91phox gene
- HLA-matched BMT curative



Seger 2008



Hossle et al 2002

CGD – German Trial

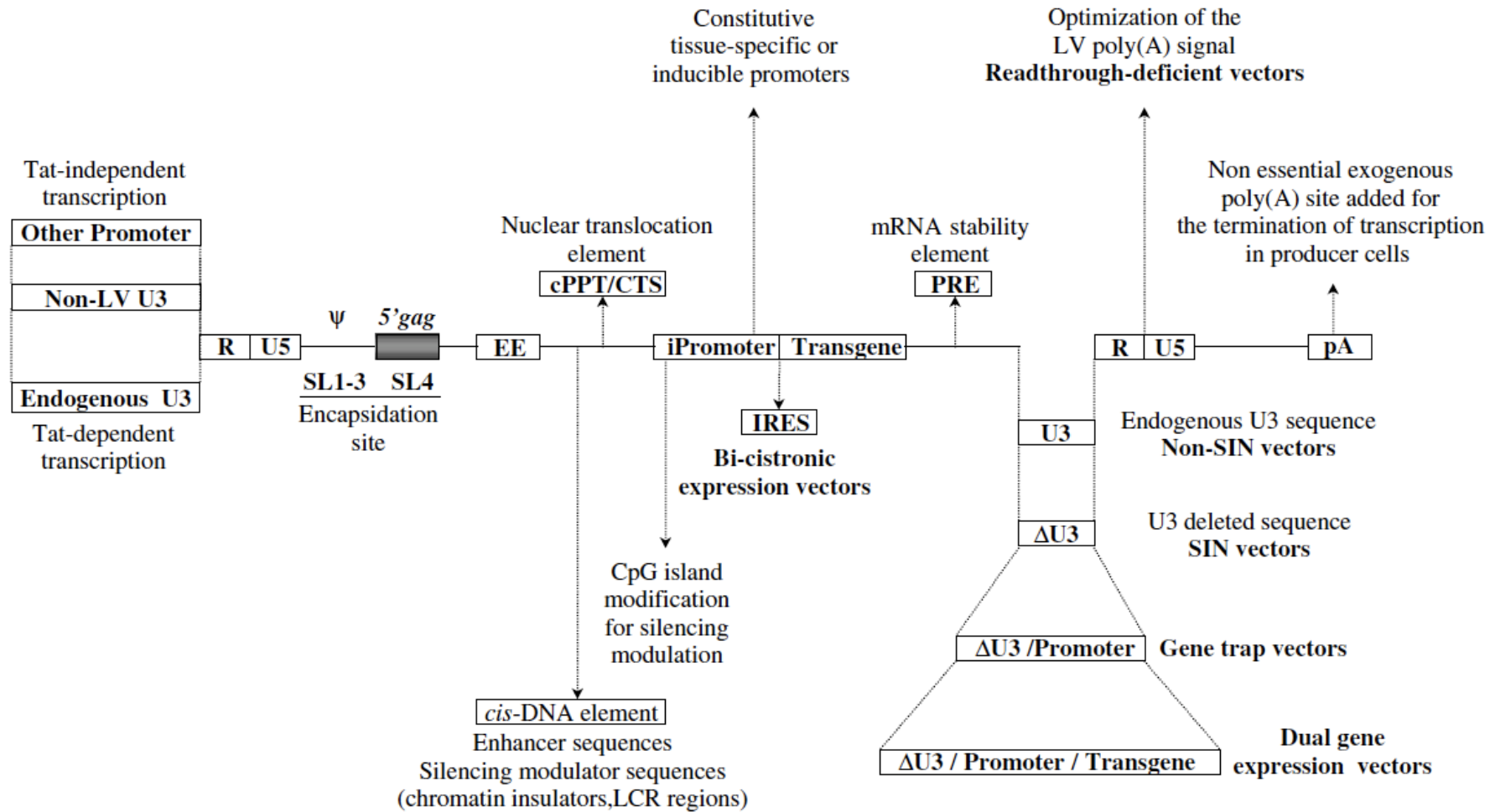
Grez Trial (2001)

- PIs: Grez, Ott, Seger, et al;
University Hospital, Frankfurt
- Enrollment: 2 subjects, age 25 (P1) and 26 (P2)
- Vector: MoMLV, SFFV-LTR
- Transgene: gp91^{phox}
- Dose: 5×10^6 CD34⁺/kg (P1), 3.6×10^6 CD34⁺/kg (P2)
- No selective advantage
- Busulfan 4 mg/kg
- Transduction efficiency: 45% (P1), 39.5% (P2)
- Level of correction: granulocytes up to 50-60%

CGD – German Trial

- Initial benefit after treatment
- Limited expansion in a number of clones
- Development of myelodysplasia
- Integrations sites characterized by LAM-PCR:
 - **MDS-EVI1**
 - **PRDM16**
 - **SETBP1**
- Silencing of TG expression
- One patient died due to underlying disease

New Lentiviral Vectors



β -Thalassemia - French Trial

- Clinical Phase I/II trial sponsored by Genetix France
- Safety, tolerance and efficacy of a lentiviral vector encoding β -globin
- Several safety features have been introduced in this self-inactivating vector
- 19-year old patient suffering from a severe form of β -thalassemia, dependent on transfusions since the age of 3, splenectomized at the age of 6, did not have an HLA geno-identical sibling donor
- Stable haemoglobin levels above 9.5 g/dL

β -Thalassemia - French Trial

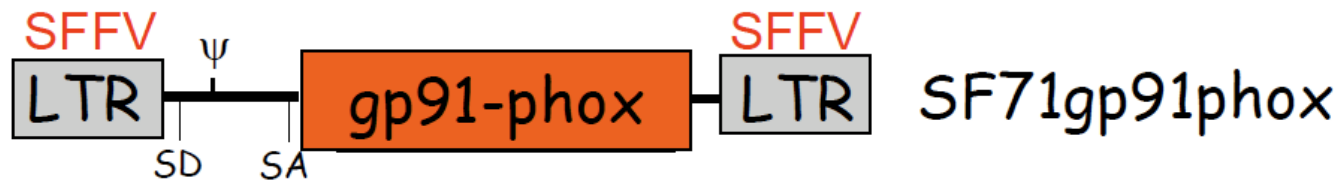
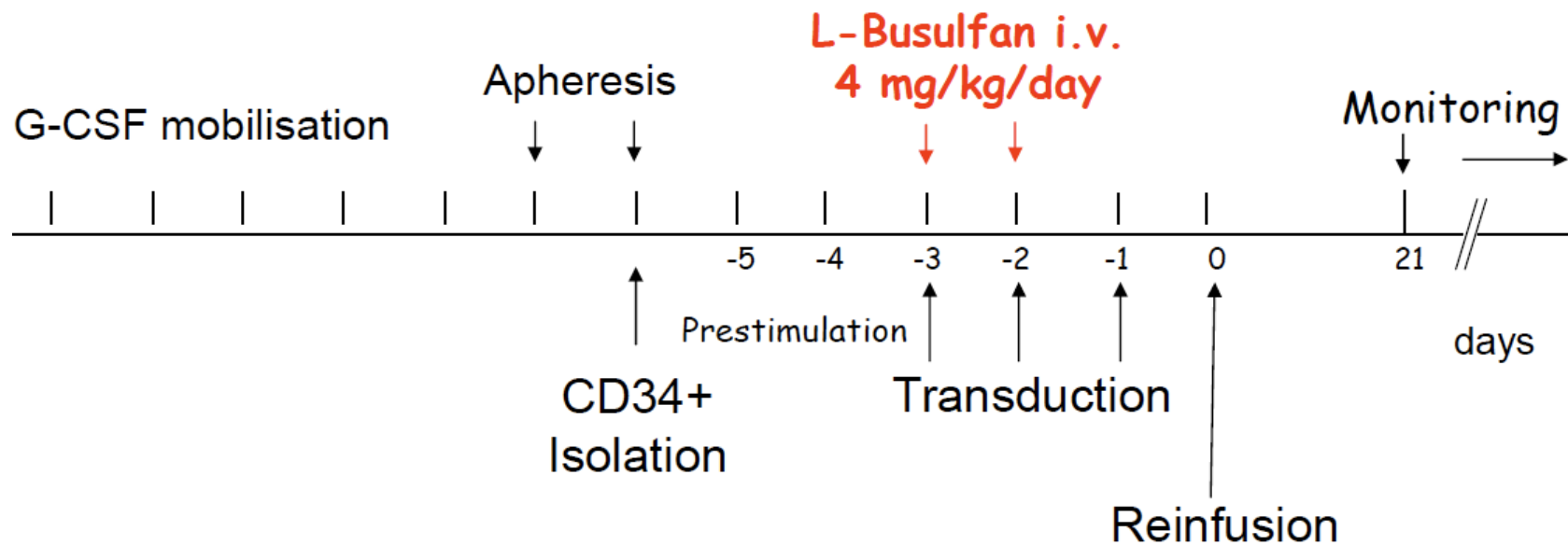
- Relative dominance of a haematopoietic clone
- Vector insertion within the HMGA2 gene
- 12% of circulating granulocytes
- 2% of circulating erythroblasts
- Truncated HMGA2 RNA highly expressed in erythroblasts
- HMGA2 overexpression associated with either benign or malignant tumours
- Dominant clone stable for the last 5 months

ICH GTDG Discussion – Retroviral / Lentiviral Vectors

- Lack of convincing pre-clinical studies in animal models that demonstrate new vector designs significantly reduce the risk of insertional mutagenesis
- Current data from French β -thalassemia suggest continued risk with newer vector designs
- Unclear how to change inclusion/exclusion criteria

Regional Topics EFTA

CGD clinical study in Switzerland



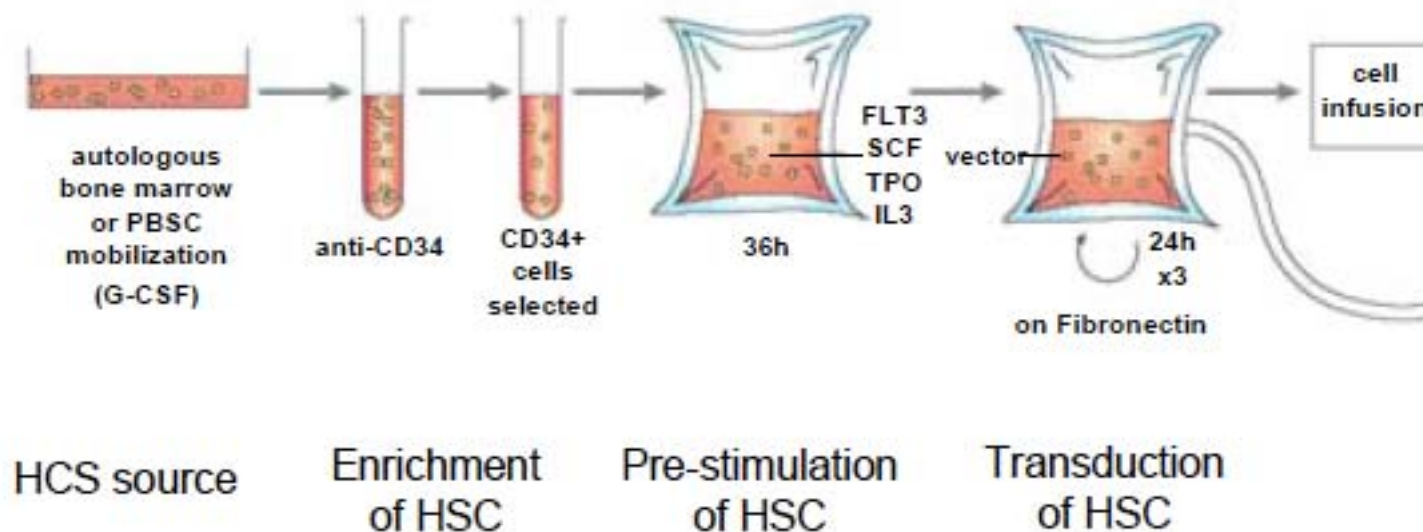
SFFV-LTR more active in myeloid cells



R. Seger

Regional Topics EFTA

CGD clinical study in Switzerland

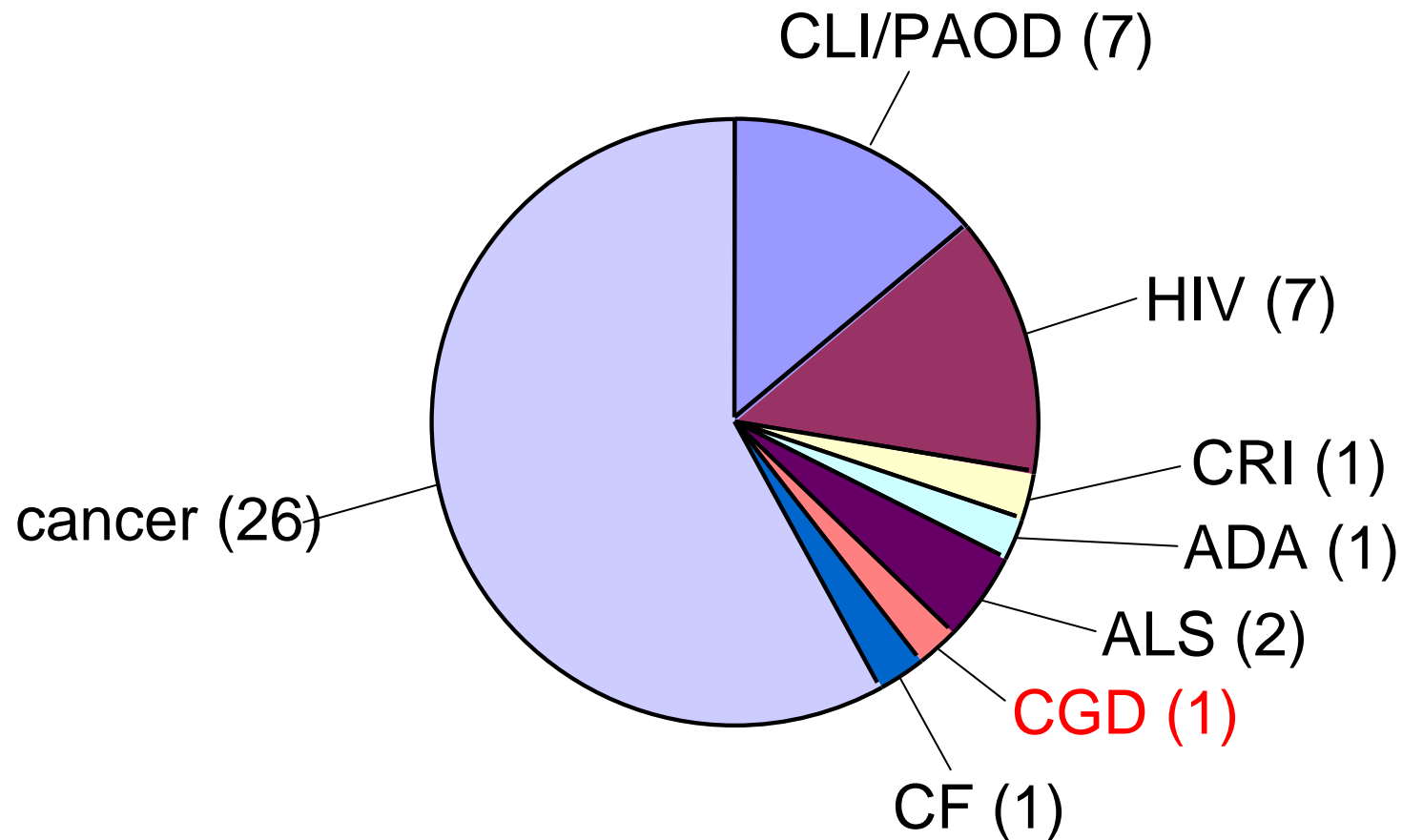


Regional Topics EFTA

CGD clinical study in Switzerland

- Treatment of one child (10y) in the year 2005
- Had severe aspergillosis
- BMT not possible (lack of donor)
- Beneficial treatment (cure form aspergillosis)
- Clinical hold due AE in German trial
- No SAE
- Plan to treat more children with a new generation of lentiviral vector

Clinical trials in Switzerland



Legal Basis

- Swiss Law on Therapeutic Products
- Swiss Law on Transplantation
- European Pharmacopoeia

Guidelines

- Swiss Guidelines
- International Guidelines (e.g. ICH* Guidelines)

*ICH: International Conference on Harmonisation; www.ich.org

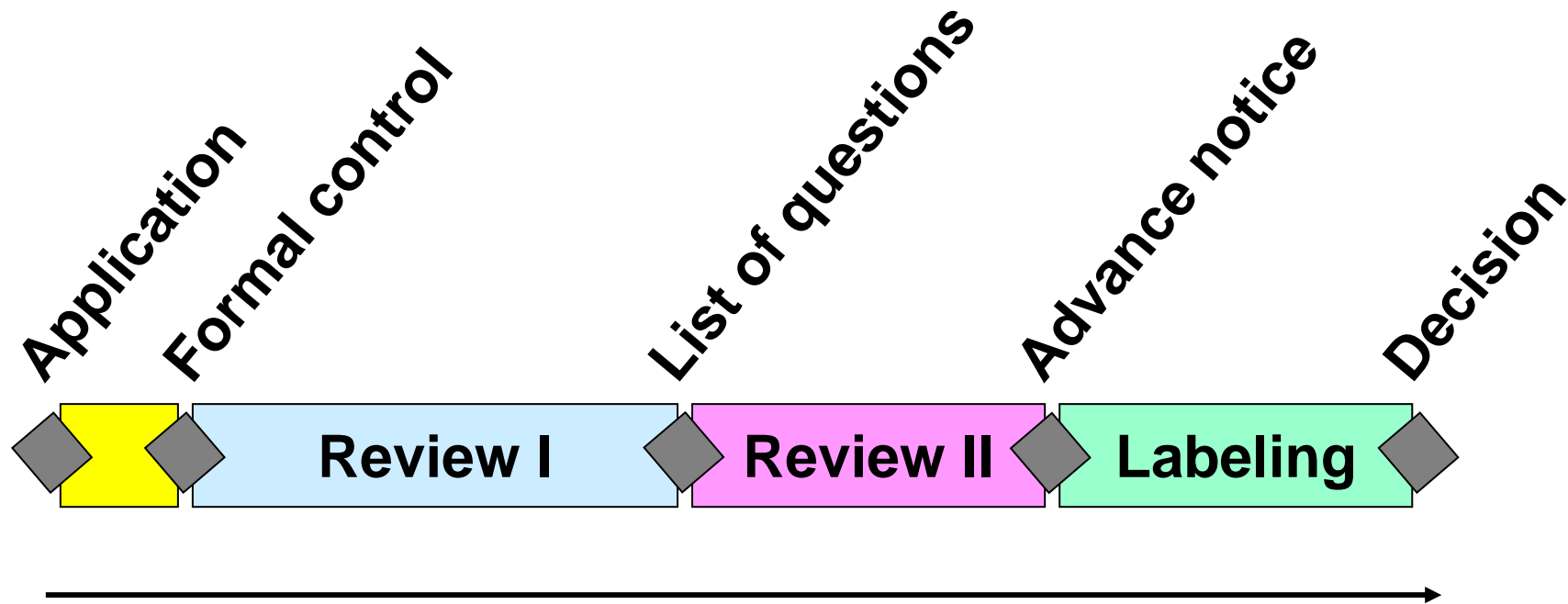
Approval of Clinical Trials (90 days)

(Gene therapy and investigational products containing GMOs)



Marketing Authorization

No gene therapy product authorized in Switzerland



Time to approval 130 – 300 days

(Swissmedic evaluation time)