ICH Considerations on Viral/Vector Shedding; and Overview of Gene Therapy Activity in Canada

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Open Workshop on Gene Therapy
Yokohama, June 12, 2009

Regulatory Authority for Gene Therapy

- meets F&D Act definition of drug
- satisfies Schedule D to the Act as:

"Drugs obtained by rDNA procedures"

"Drugs, other than antibiotics, prepared from micro-organisms"

"Immunizing agents"

(there are no specific regulations)
(there are no gaps in regulation)

Regulatory Responsibility

Government of Canada

- Health Canada
- Health Products and Food Branch
- Biologics and Genetic Therapies Directorate
- Biologics and Radiopharmaceuticals Evaluation Centre
- Biotherapeutics Division & Clinical Evaluation Division

Scientific Issues I

- Route of administration; intralesional, systemic, intra-vascular (organ-targeted)
- Replication competence of virus vectors; pathogenicity
- Vector integration into host genome
- Vector dose
- Expressed product dose

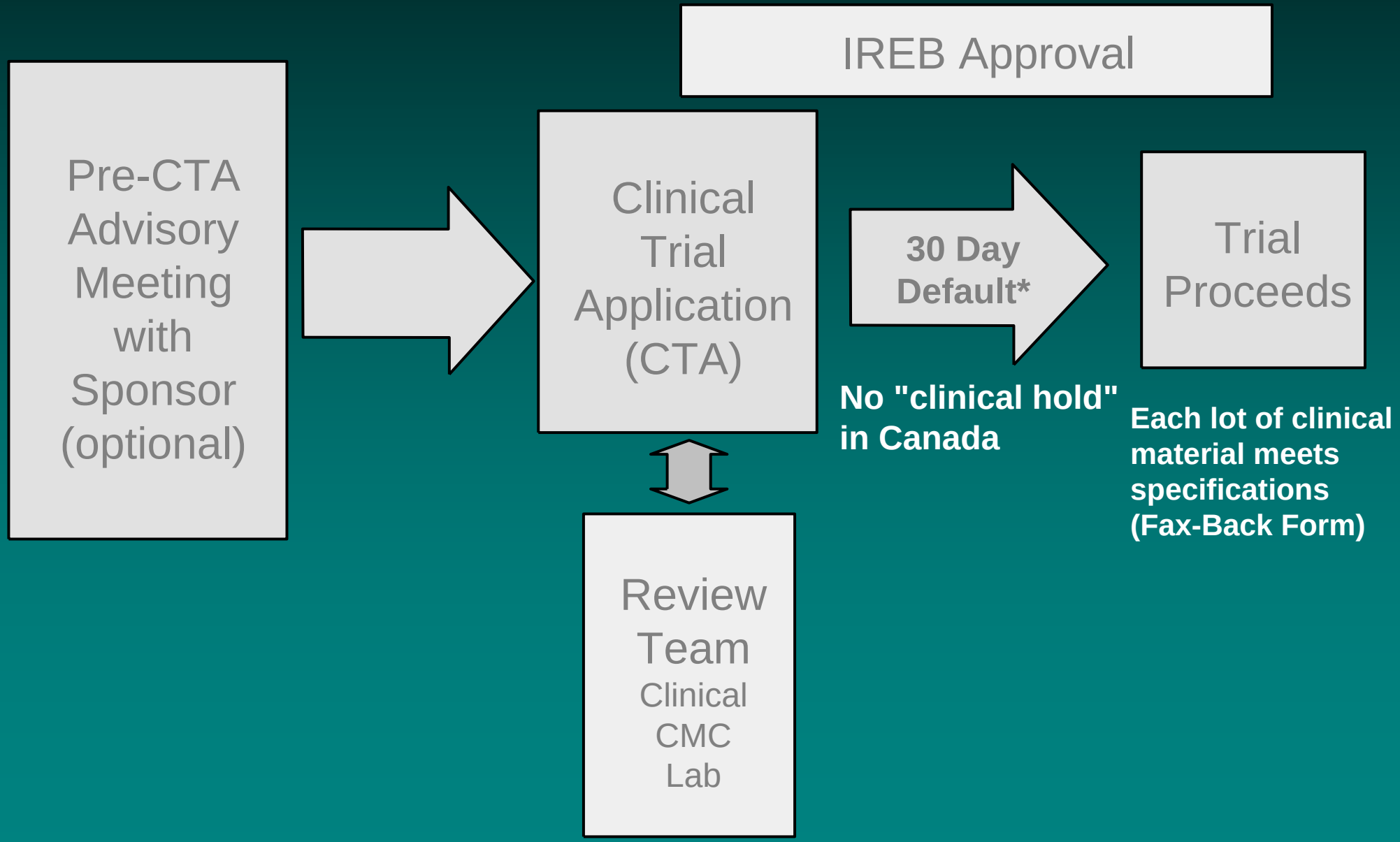
Scientific Issues II

- Frequent lack of appropriate animal models
- Choice of toxicologic investigations; (revealing unanticipated toxicities ?)
- Targeting specificity
- Regulation of gene expression
- Immunogenicity
- Contamination of drug product

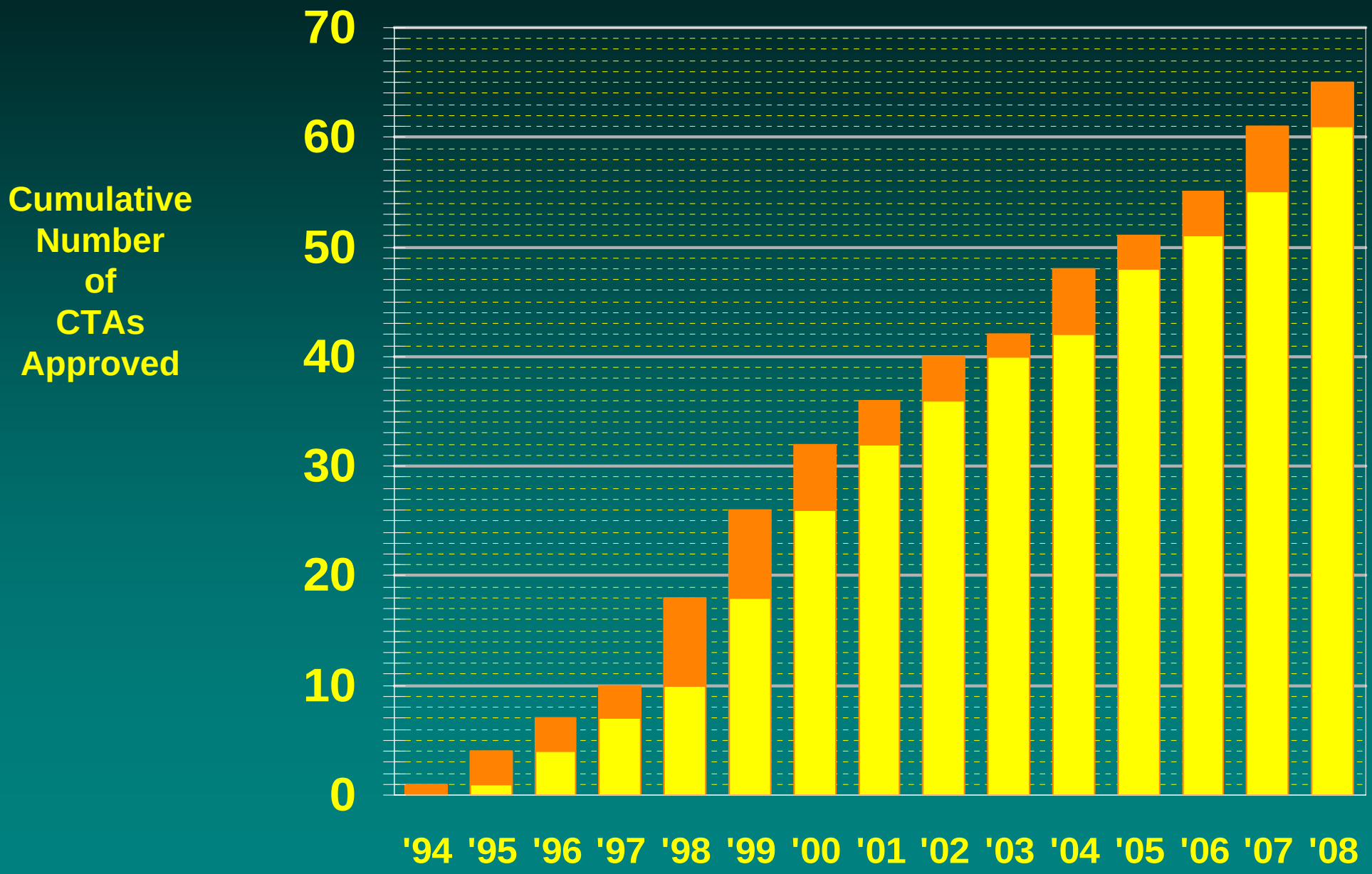
Safety & Ethics Considerations

- Informed Consent
  - full disclosure of risk
- Institutional Review is critical
  - protocols and consent forms
- Alteration of host genome
  - 'contamination' of non-target tissues, especially germ cells
- Vector “shedding” and inadvertent generation of RC virus
  - pathogenicity and exposure of patient and contacts

Regulatory Process for Clinical Trials



Growth of Gene Therapy in Canada



Immune Therapy
Rationale

- recruit immune system into renewed response

- address immune avoidance by cancer
  - reduced antigenicity
  - outgrowth of antigenic variants
  - defective T-cell function
  - other deficiencies (immunosuppressive factors?)

Immune Therapy
Approaches

Ex vivo

- tumour antigen into autologous dendritic cells

- T-cell co-stimulatory molecules into autologous tumour cells
  - cytokine gene often included
  - cells irradiated

In vivo

- intratumoral delivery of genes
  - may involve direct cell killing

Induction of Apoptosis

- Re-introduction and expression of tumour suppressor genes (e.g. p53 gene)
  - intratumoral delivery
  - only transduced cells affected

Direct Cell Killing

- induced cell suicide using pro-drug
  e.g. HSV-tk gene & ganciclovir

- wt viruses that replicate preferentially in cancer cells
  - reovirus
  - Newcastle disease virus
  - vesicular stomatitis virus

- viruses genetically modified to limit lytic infection to cancer cells

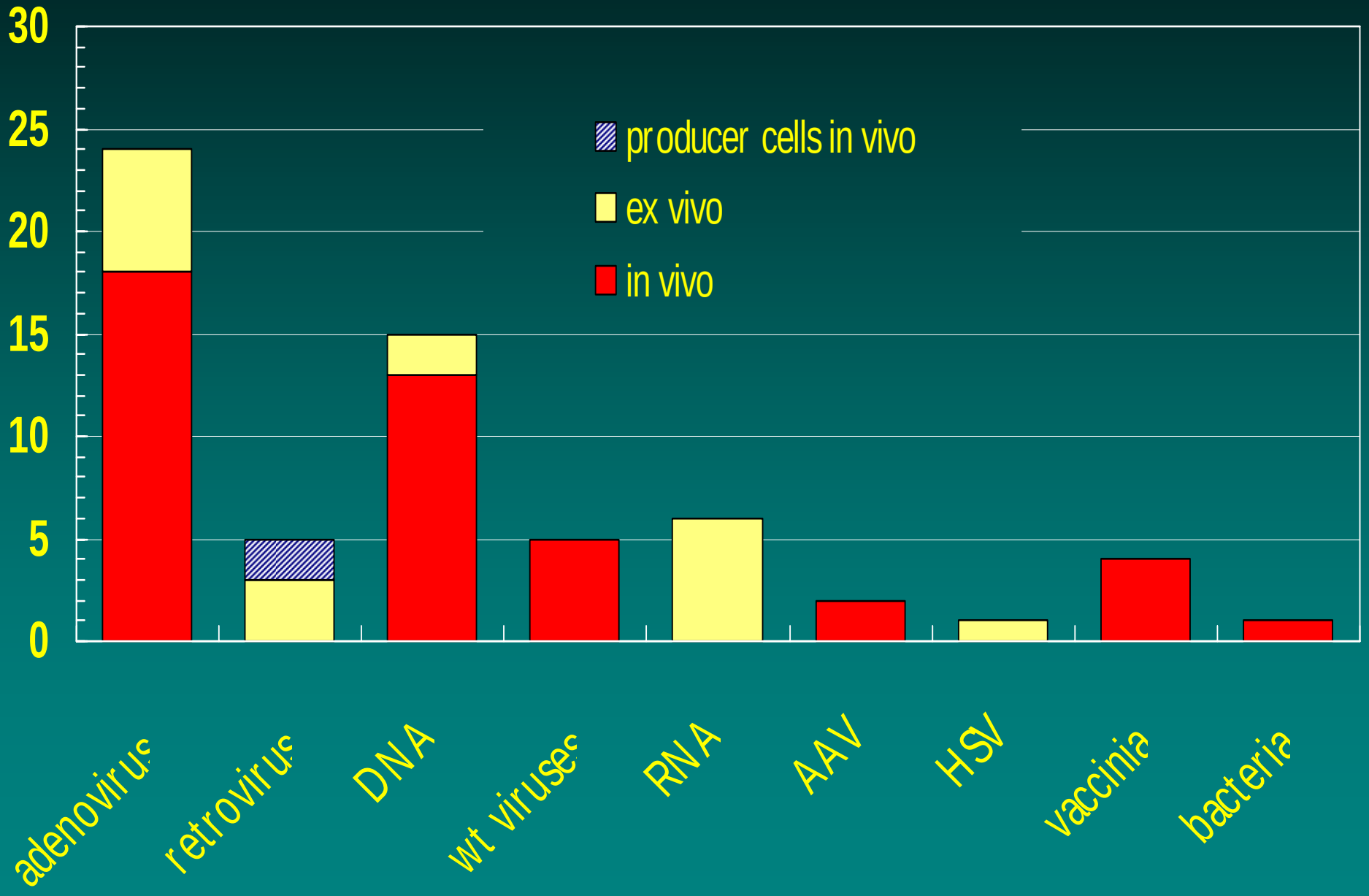
Chemoprotection

- enhance delivery of high-dose chemotherapy by limiting immune toxicity
- introduce MDR gene to hematopoietic stem cells prior to BMT/PSCT

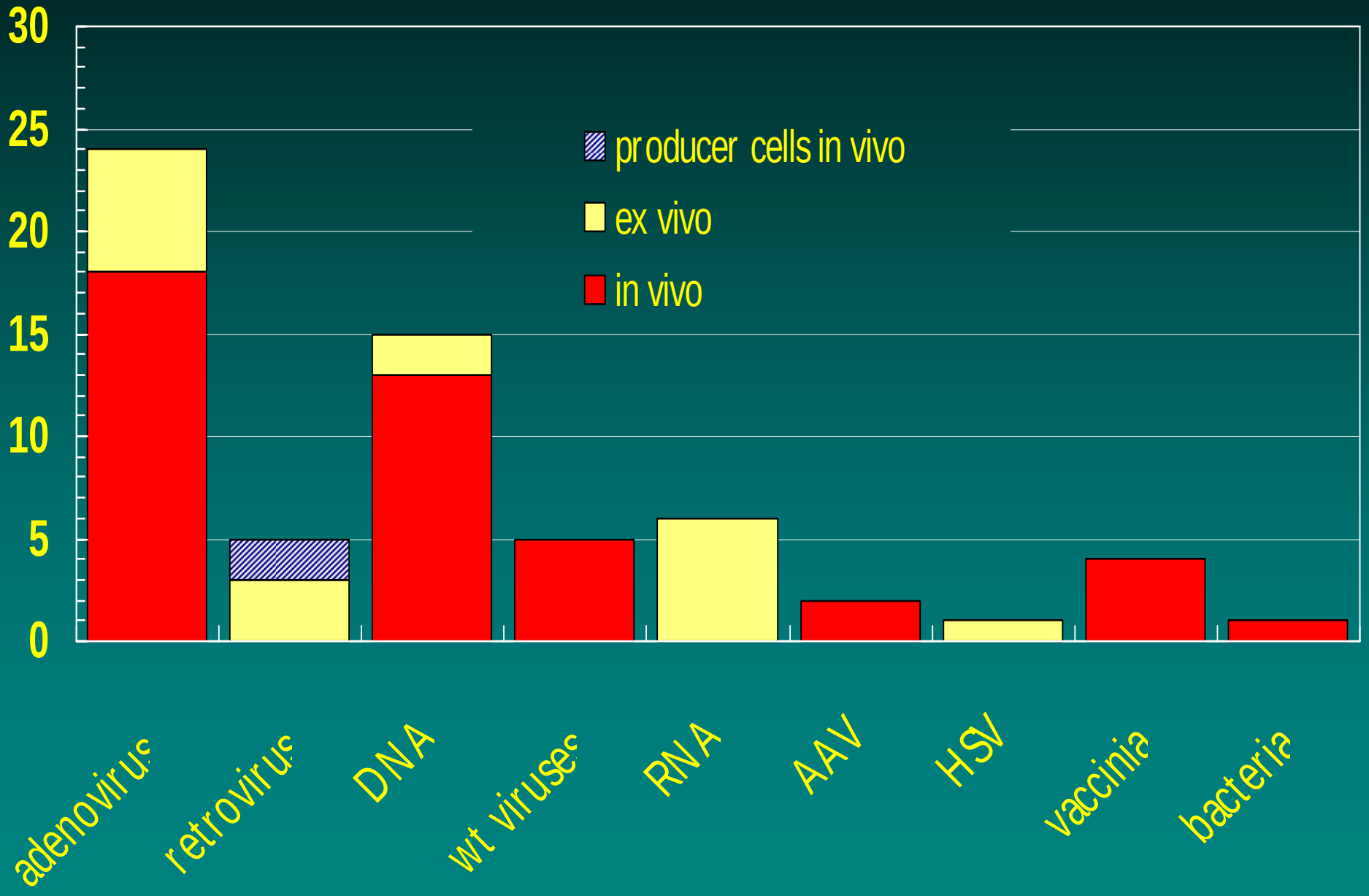
Gene Marker Studies

- allow information gathering upon which a true therapy may be based
- expression of the marker gene can be used to:
  - follow migration, expansion and persistence of cells modified *ex vivo* (after stem cell transfer)
  - assess *in vivo* gene delivery system for cell targeting and for regulation of the encompassed gene

Gene Therapy Trials in Canada I



Gene Therapy Trials in Canada I



Gene Therapy Trials in Canada II

	number and type of vectors used								
	16 adenovirus	3 retrovirus	7 DNA	2 wt viruses	RNA	2 AAV	1 HSV	1 vaccinia	1 bacteria
indications	carcinomas: breast liver prostate ovary bladder NSCLC SCCHN metastatic melanoma malignant myeloma AML **CAD** **prophylactic HIV vaccine**	glioma carcinoma of breast metastatic melanoma multiple myeloma ***BMT (mdr)***	metastatic solid tumours metastatic melanoma **PVD** **CAD** **multiple sclerosis** **pulmonary arterial hypertension** **BMT** ***(neo)***	metastatic solid tumours carcinoma of prostate colorectal cancer	renal cell carcinoma **HIV infection** chronic lymphocytic leukemia	**rheumatoid arthritis** **monogenic lipoprotein lipase deficiency**	metastatic melanoma	malignant melanoma primary hepato-cellular carcinoma solid tumours	**ulcerative colitis**

Gene Therapy

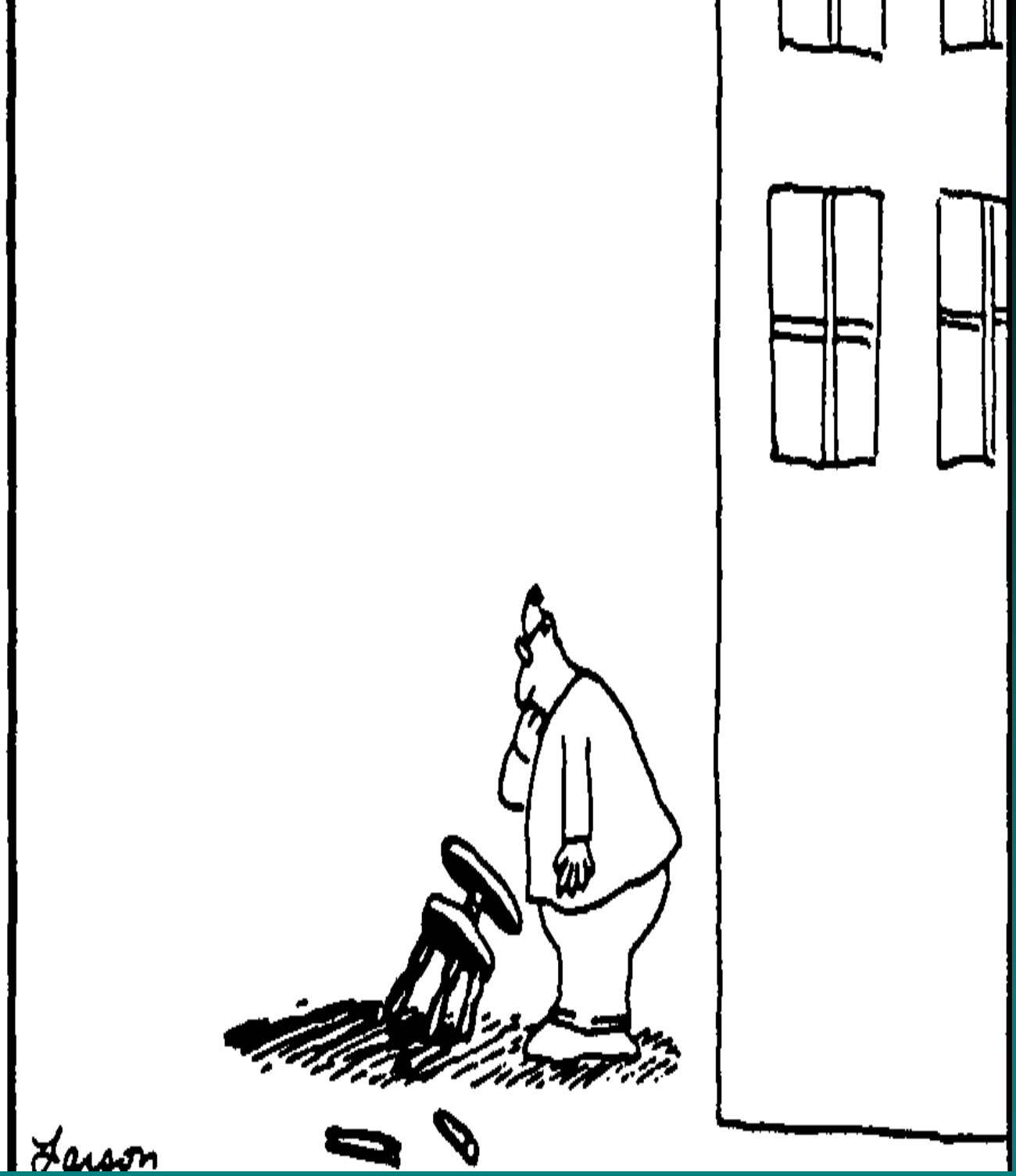
Regulatory Comments I

- Canada is consistent with the international community in the regulation of gene therapy
- Canada has experienced significant growth in gene therapy clinical trials
- Regulatory and ethical challenges have been few due to the serious and often terminal nature of the diseases treated

Gene Therapy

Regulatory Comments II

- Careful attention is paid to minimizing the chance of third party exposure to virus
- Germ-line gene transfer is prohibited by law in Canada
- We fully endorse international exchange of information and ideas perhaps leading to harmonised understanding or approach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Scope

Regarding what is shed

- Gene therapy vectors
  - Viral vectors
  - Plasmid vectors
  - Bacterial vectors
  - Excluding gene-modified cells (except when harbouring a virus)
- Oncolytic viruses (including non-recombinant wt)
- Bacteria

Scope

Routes of shedding

- Focus is on excreta and secreta (e.g., urine, faeces, saliva, and secretions sampled using buccal swabs, nasal swabs, bronchial lavage)
- Some consideration of potential for transmission from vector escaping the body via leaking injection site or blood from open wound

Scope

Outcomes of shedding

- Focus is on the potential for human-to-human transmission and associated cocnerns
- Does not address release to environment
  - Not under ICH umbrella
  - Different Regional laws and approaches

Intended value

To help understand the potential for transmission to others or to environment

- **Provide recommendations r.e. design of non-clinical and clinical shedding studies**
  - **Analytical assays for detection**
  - **Sampling profiles and schedules**
  - **Interpretation of non-clinical shedding data (and use in designing clinical studies)**
- **Interpretation of clinical shedding data (and potential need for transmission studies)**

2.0 Biological properties of the virus/vector (and other factors)

- Biological properties of the virus / vector
  - Replication competence
  - Genetic modification to affect cell / tissue tropism
  - Route of transmission of parental virus
- Duration of dosing
- Potential for immune response
  - Attributes of parental virus
  - Pre-existing immunity
- Immune status of the patient population

3.0 Analytical assays considerations

Molecular detection vs infectivity

- Need suitable qualified analytical assays
  - Specific, sensitive & reproducible
  - Quantitative preferred
  - qPCR and infectivity assays typically used

4.0 Non-clinical Considerations

- 4.1 Animal species
- 4.2 Dose and route of administration
- 4.3 Duration of the study
- 4.4 Samples to be taken
- 4.5 Sampling frequency
- 4.6 Interpretation of non-clinical data and transmission studies

5.0 Clinical Considerations

- 5.1 Samples
- 5.2 Sampling frequency and duration
- 5.3 Assessment