REPORTER MICE

FOR A THERAPY PHYSIOLOGY-DRIVEN

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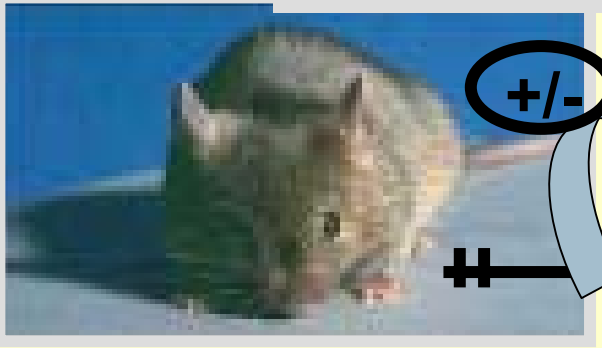
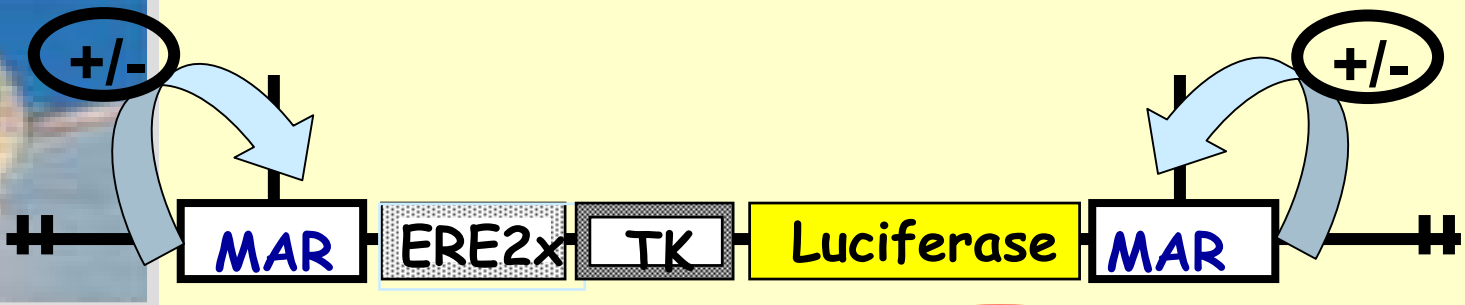
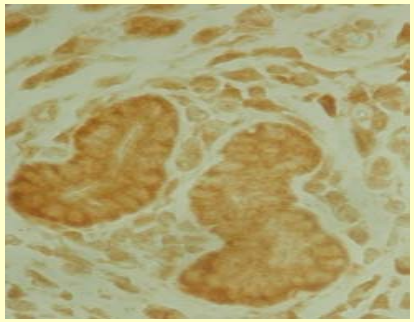
REPORTER MICE
FOR IN VIVO STUDY OF RECEPTOR ACTIVITIES



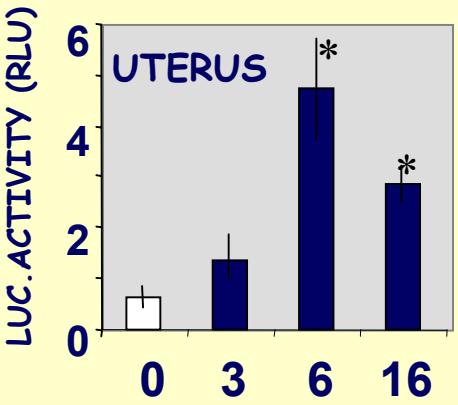


RAPID TURNOVER!

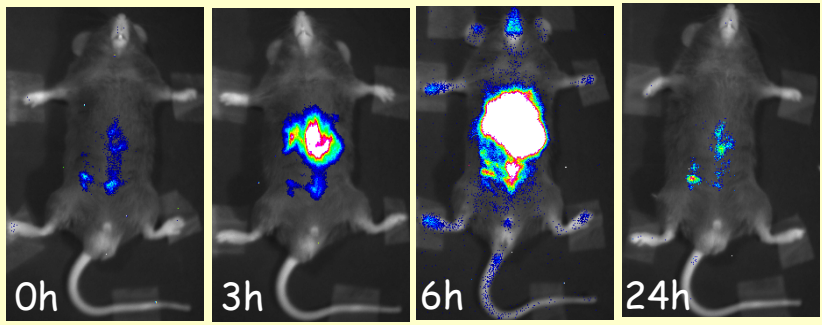
immunohistochemistry



quantitative
enzymatic assay



'in vivo' imaging

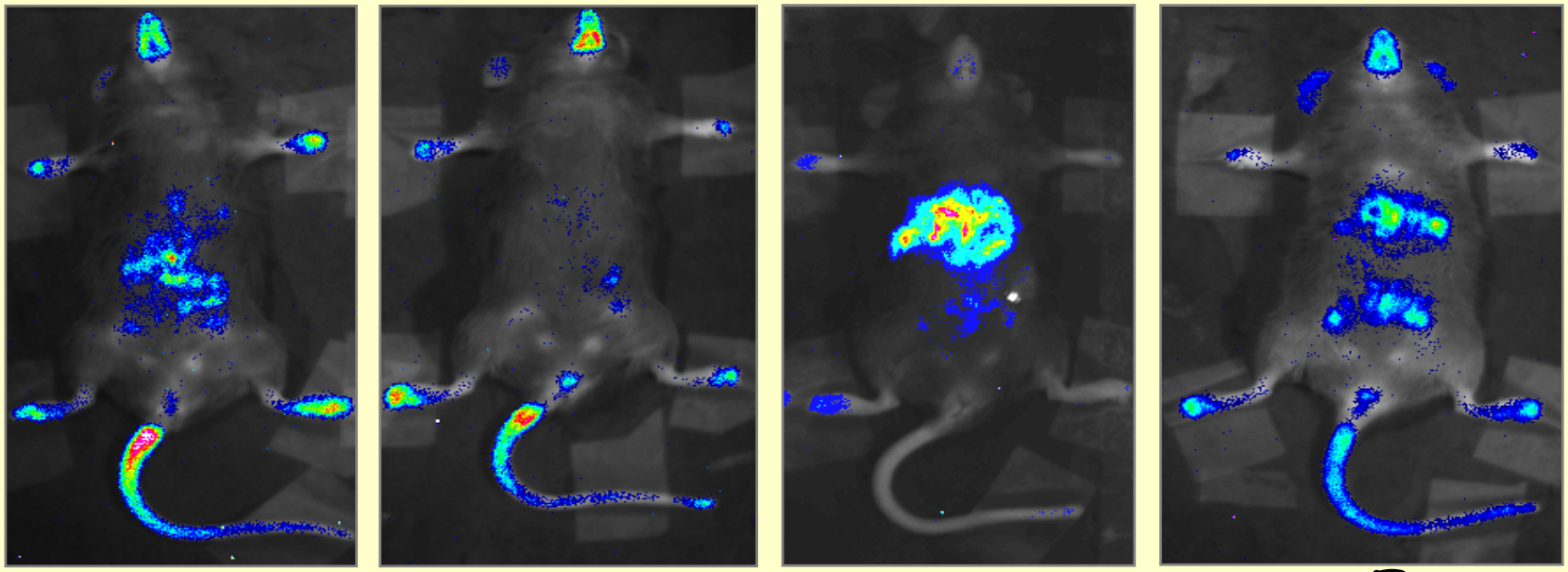


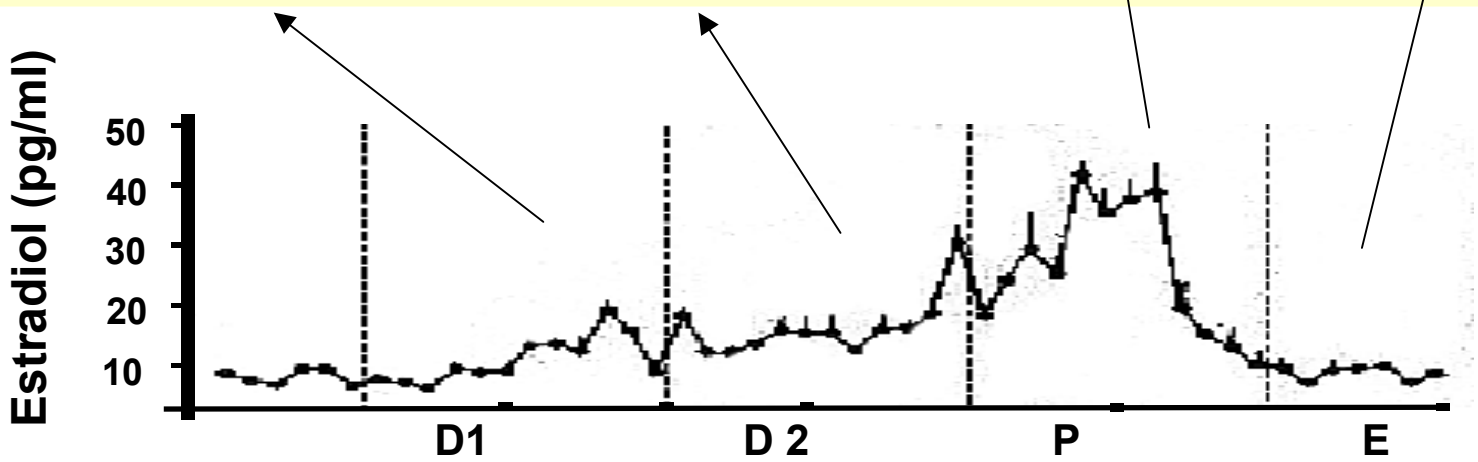
IS THE ERE-LUC MOUSE A FAITHFULL REPORTER OF THE ACTIVITY OF ESTROGEN RECEPTORS?

- ANALYSIS OF RESPONSIVE TISSUES
- CO-LOCALIZATION OF ERs AND LUCIFERASE BY IMMUNOCYTOCHEMISTRY STUDIES
- TIME-COURSE, DOSE-RESPONSE AFTER ADMINISTRATION OF ESTRADIOL
- PARALLEL MEASUREMENT OF ENDOGENOUS ESTROGEN-RESPONSIVE GENES (PROGESTERONE RECEPTOR)
- ANALYSIS OF LUCIFERASE ACTIVITY AFTER TREATMENT WITH ICI 182,780 TO MEASURE THE CONTRIBUTION OF ERRs

Ciana et al., 2001, 2003

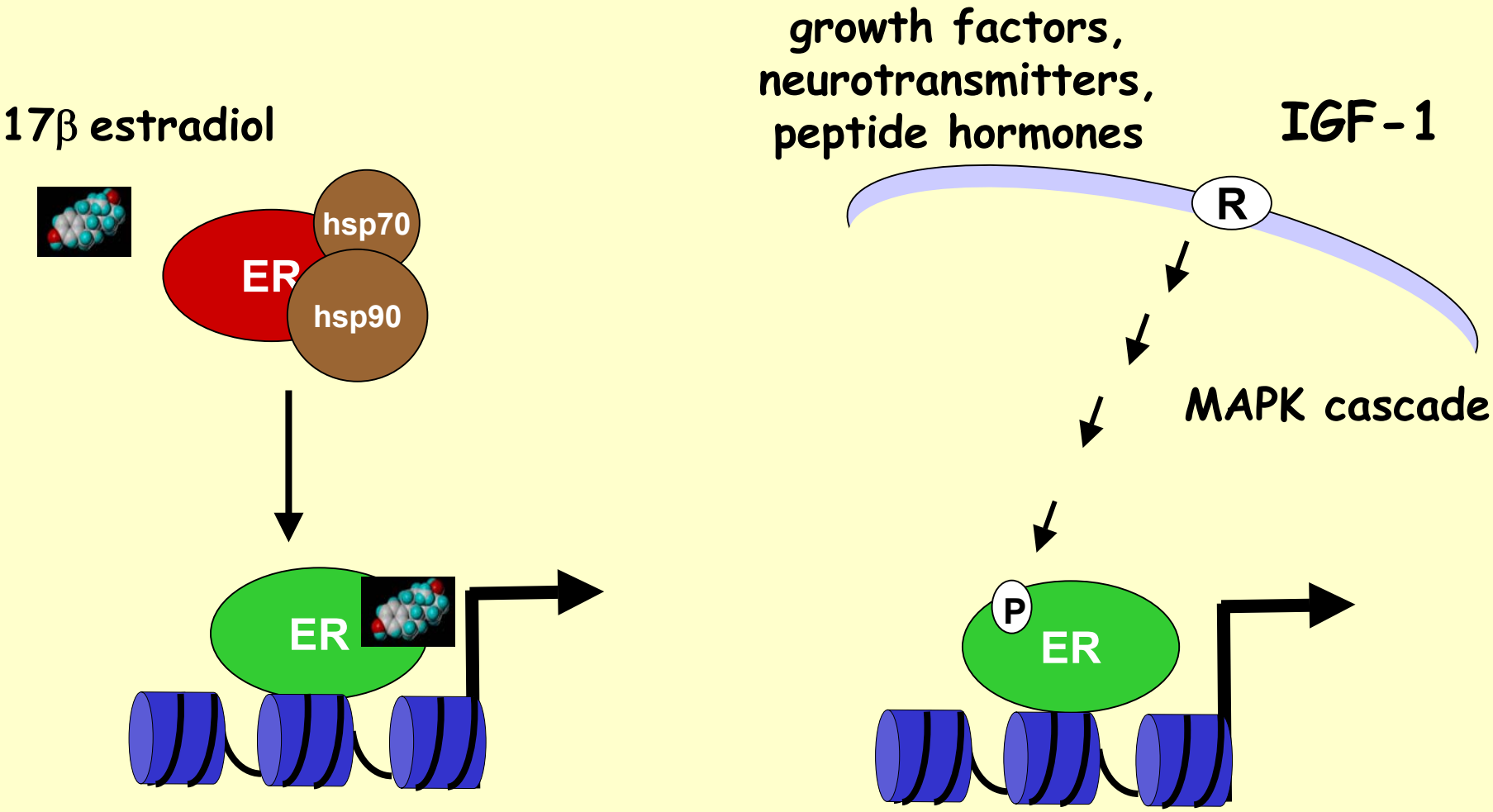
BIOLUMINESCENT REPORTER IMAGING IN CYCLING ERE-luc MICE





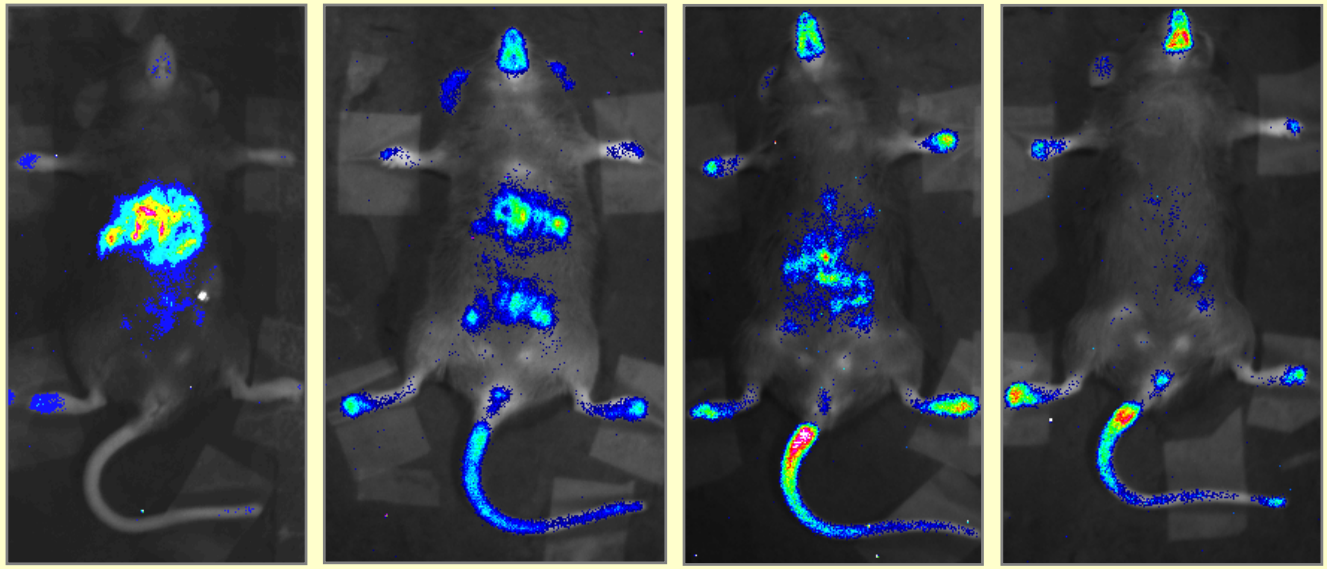
Ciana et al. Nature Med. 2003

ALTERNATE MECHANISMS FOR ACTIVATING ESTROGEN RECEPTORS

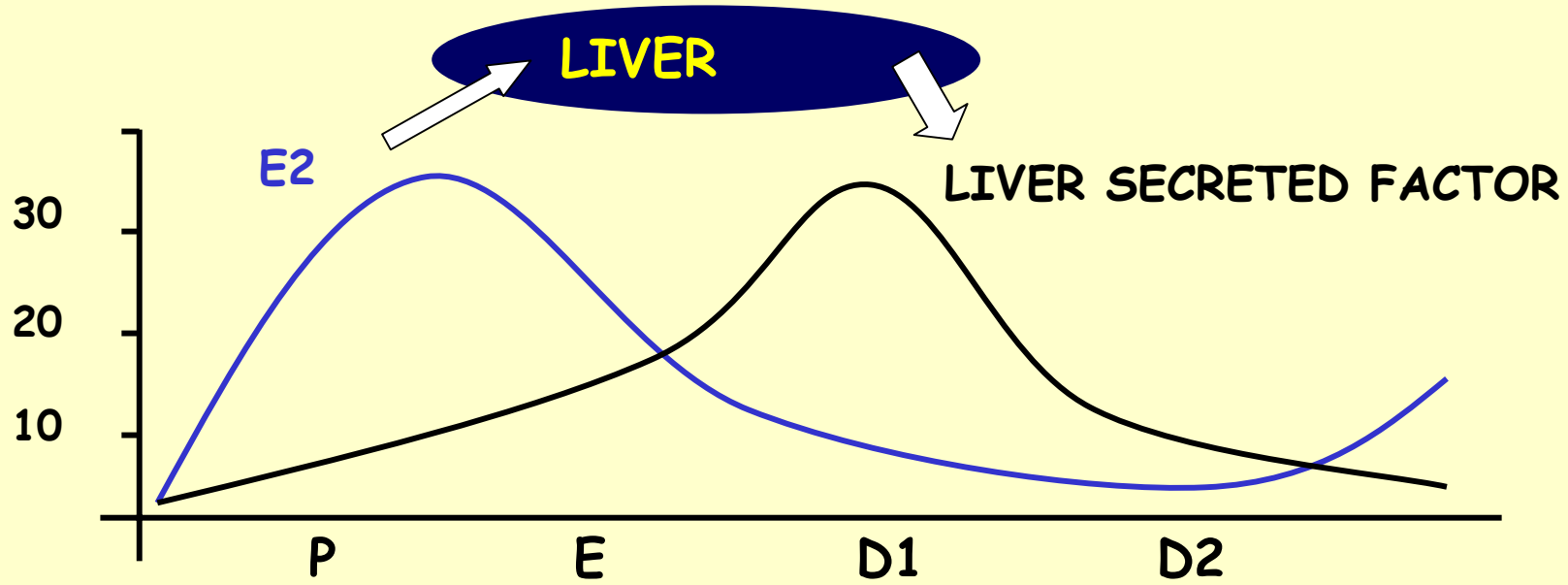


Ma et al 1994, Patrone et al. 1996,1998

THE LIVER AS AN ENDOCRINE ORGAN



P E D1 D2



CONCLUSION

IN FERTILE FEMALES THE MECHANISMS OF ER TRANSCRIPTIONAL ACTIVATION IS:

ESTRADIOL-DEPENDENT in reproductive tissues

ESTRADIOL-INDEPENDENT in non-reproductive tissues

THE USE OF ESTRADIOL IN THE POSTMENOPAUSE

BENEFICIAL EFFECTS

delay in the manifestation of Alzheimer?

prevention of cardiovascular risk?

colon carcinoma prevention

prevention of osteoporosis

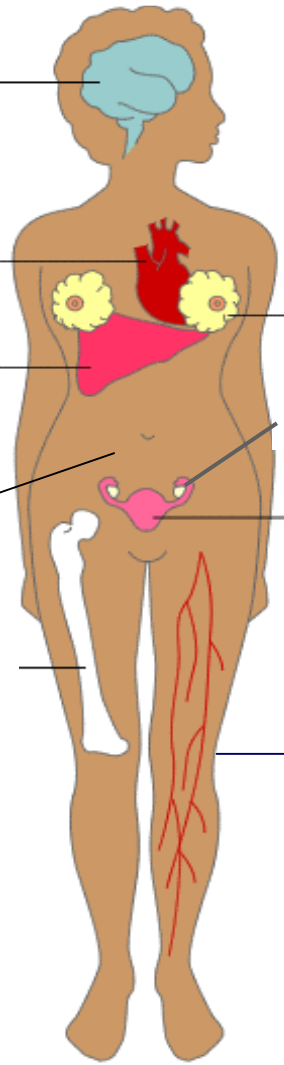
UNDESIRED EFFECTS

breast cancer

ovarian cancer

uterine hyperplasia

Deep vein thrombosis



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1. Exact perception of the organ(s) target
   for the chemical entity to be studied by *in vivo* imaging

2. Evaluation of drug pharmacodynamics after acute or
   repeated administrations in the same animal

3. Drug dosage based on drug pharmacodynamics
   indipendently from blood concentrations

4. Analysis of drug activity in young, mature, aged animals

REPORTER MICE
FOR A THERAPY PHYSIOLOGY-DRIVEN
PRESENT LIMITATIONS

1. Better methodologies to obtain ubiquitous expression of the reporter

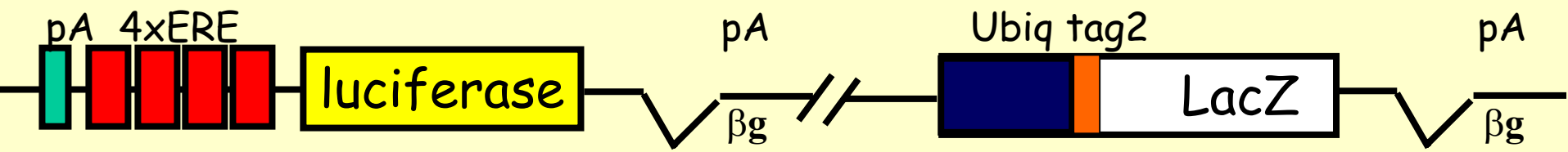
2. Better reporter genes for *in vivo* imaging also in large animals

3. Better vectors for "transient" transgenesis

BETTER METHODOLOGIES TO OBTAIN UBIQUITOUS EXPRESSION OF THE REPORTER

ERE-Luc mice: from 17 lines two positives

PPARE-Luc mice: from 22 lines 1 positive



Inserted in the Hprt *locus*
(EU EDERA Project, S. Rusconi)

BETTER REPORTER GENES FOR *IN VIVO* IMAGING IN LARGE ANIMALS

LUMINESCENCE

FLUORESCENCE

RADIOISOTOPES