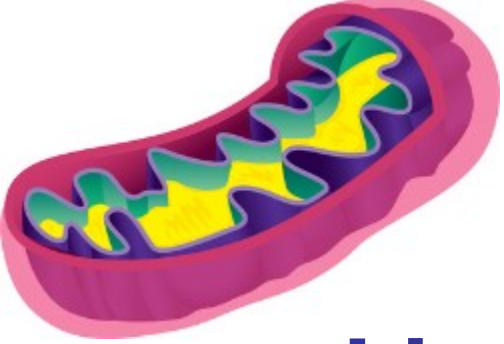


# L’aventure d’un projet de recherche sur l’embryon humain


## J. STEFFANN

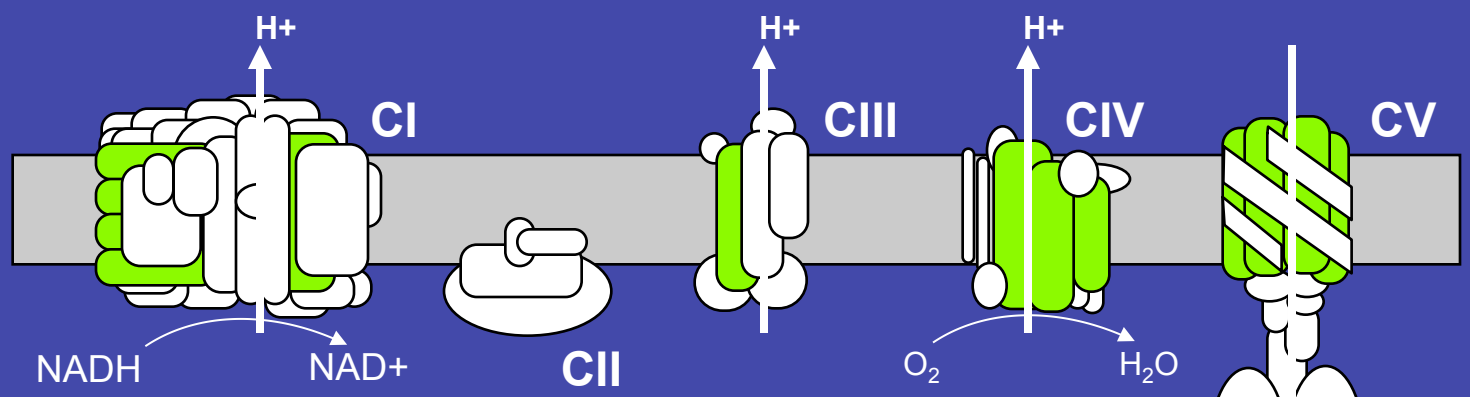
**Equipe “Génétique des maladies mitochondriales”**
**Institut Imagine-hopital Necker**

# Evaluating the safety of the procedures to prevent mtDNA mutation disorders

# LA CHAINE RESPIRATOIRE

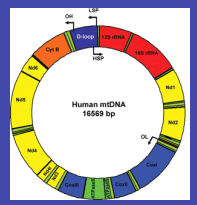
ADN nucléaire

70 polypeptides



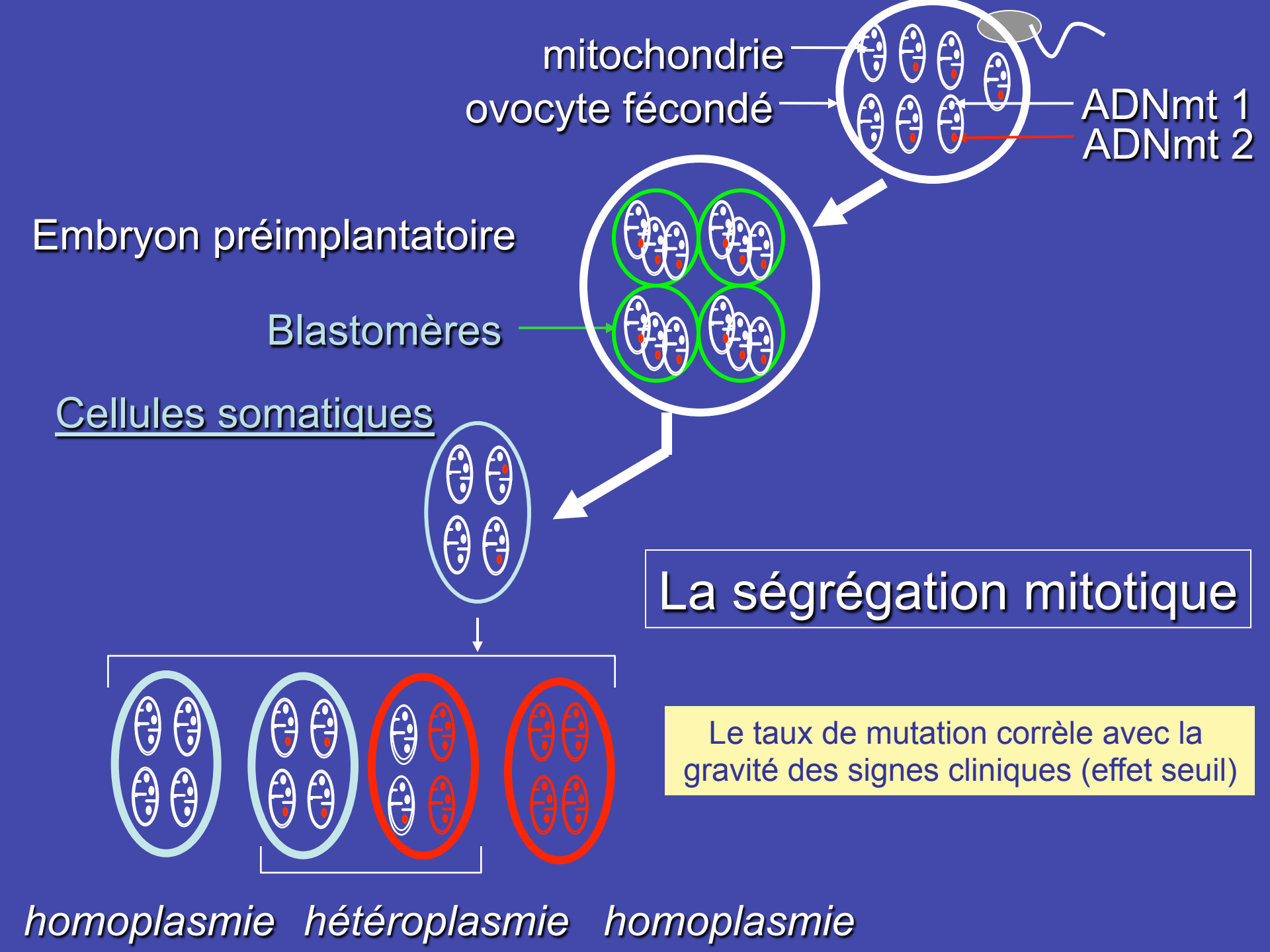

13 polypeptides

ADN mt




22 tRNA et 2 rRNA

ADP H+ ATP




# La ségrégation mitotique

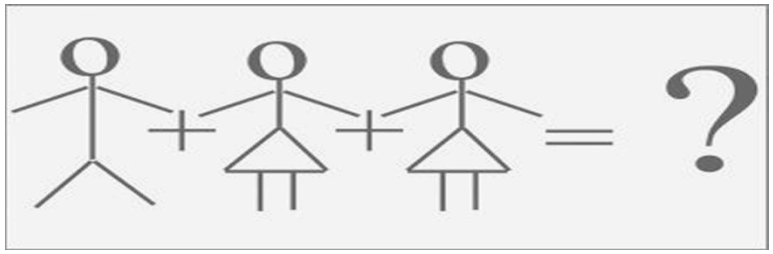
Le taux de mutation corrèle avec la gravité des signes cliniques (effet seuil)

# PREVENTING TRANSMISSION OF MITOCHONDRIAL DNA MUTATIONS
## the limitations

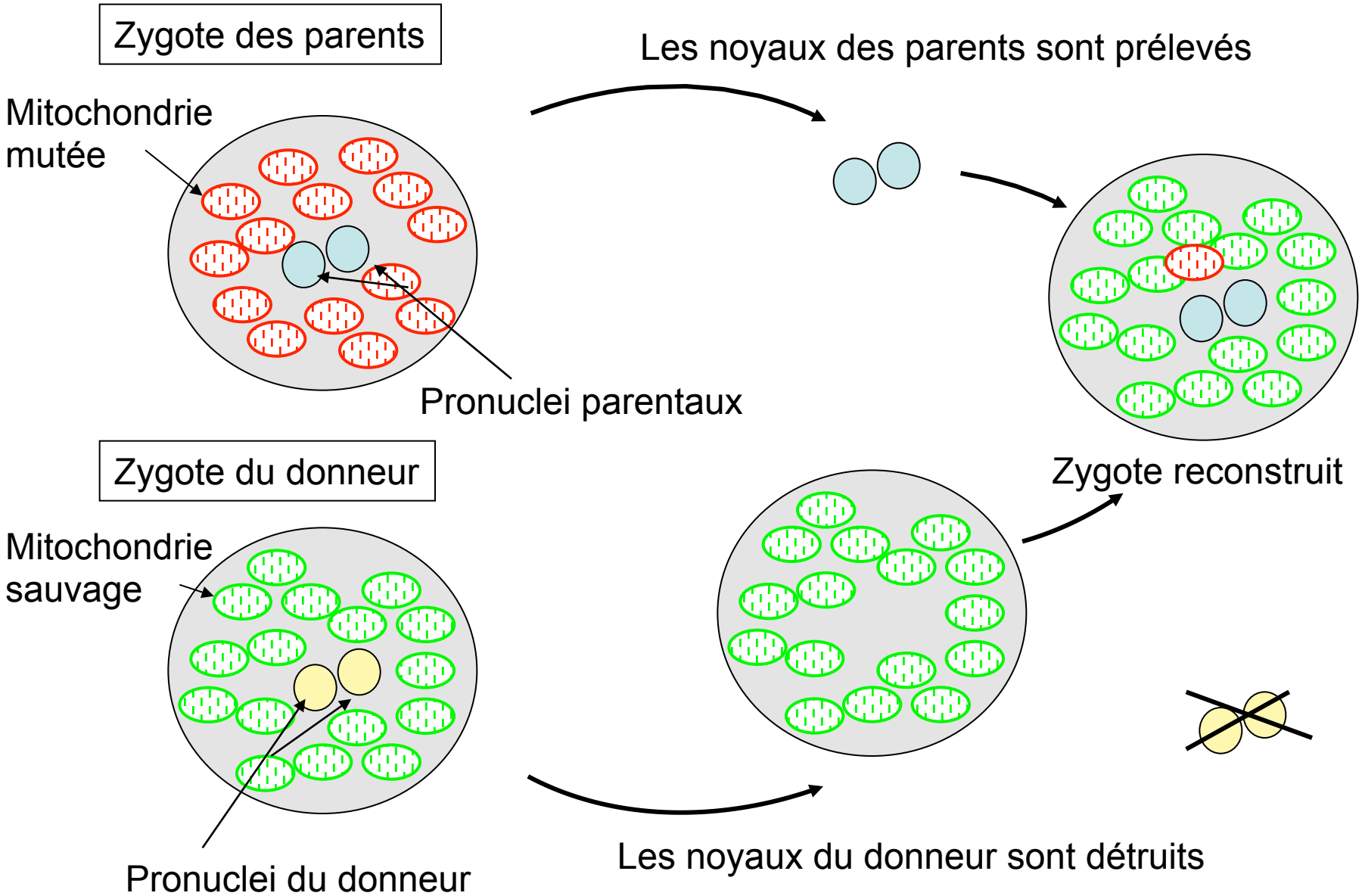
- Prenatal diagnosis / Preimplantation Genetic Diagnosis
  - High risk of pregnancy termination (PND)
  - High risk to have no healthy embryos to transfer (PGD)
  - Residual risk to develop symptoms in case of heteroplasmic embryo/fetus
  - No option for homoplasmic mutated patients

➢ Oocyte donation

➢ Nuclear transfer ?



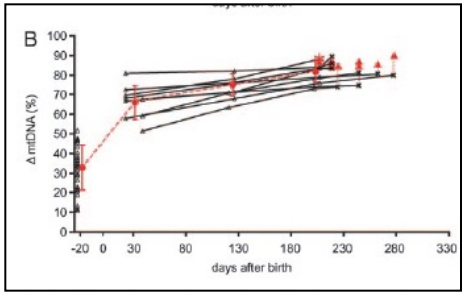
# PREVENTING TRANSMISSION OF MITOCHONDRIAL DNA MUTATIONS
## the nuclear transfer

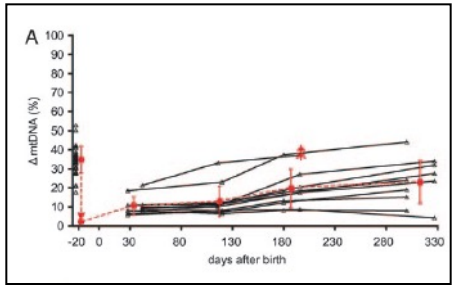


# NUCLEAR TRANSFER : is it safe?

Animal models

- **Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation.** Sato A et al., *PNAS* 2005

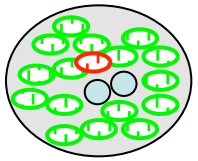


- **Mitochondrial gene replacement in primate offspring and embryonic stem cells.** Tachibana M et al. *Nature,* 2009

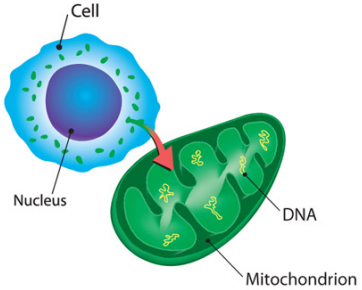
Heteroplasmy state

- **Heteroplasmy of mouse mtDNA is genetically unstable and results in altered behavior and cognition.** Sharpley et al. *Cell*, 2012



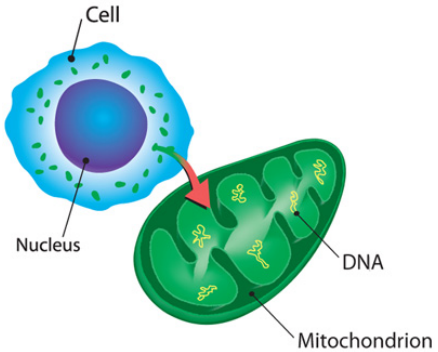
Mitochondrial-nuclear cross talk disruption

- **Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing.** Latorre-Pellicer et al. Nature, 2016
- **Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice.** Roubertoux et al. *Nature*, 2003



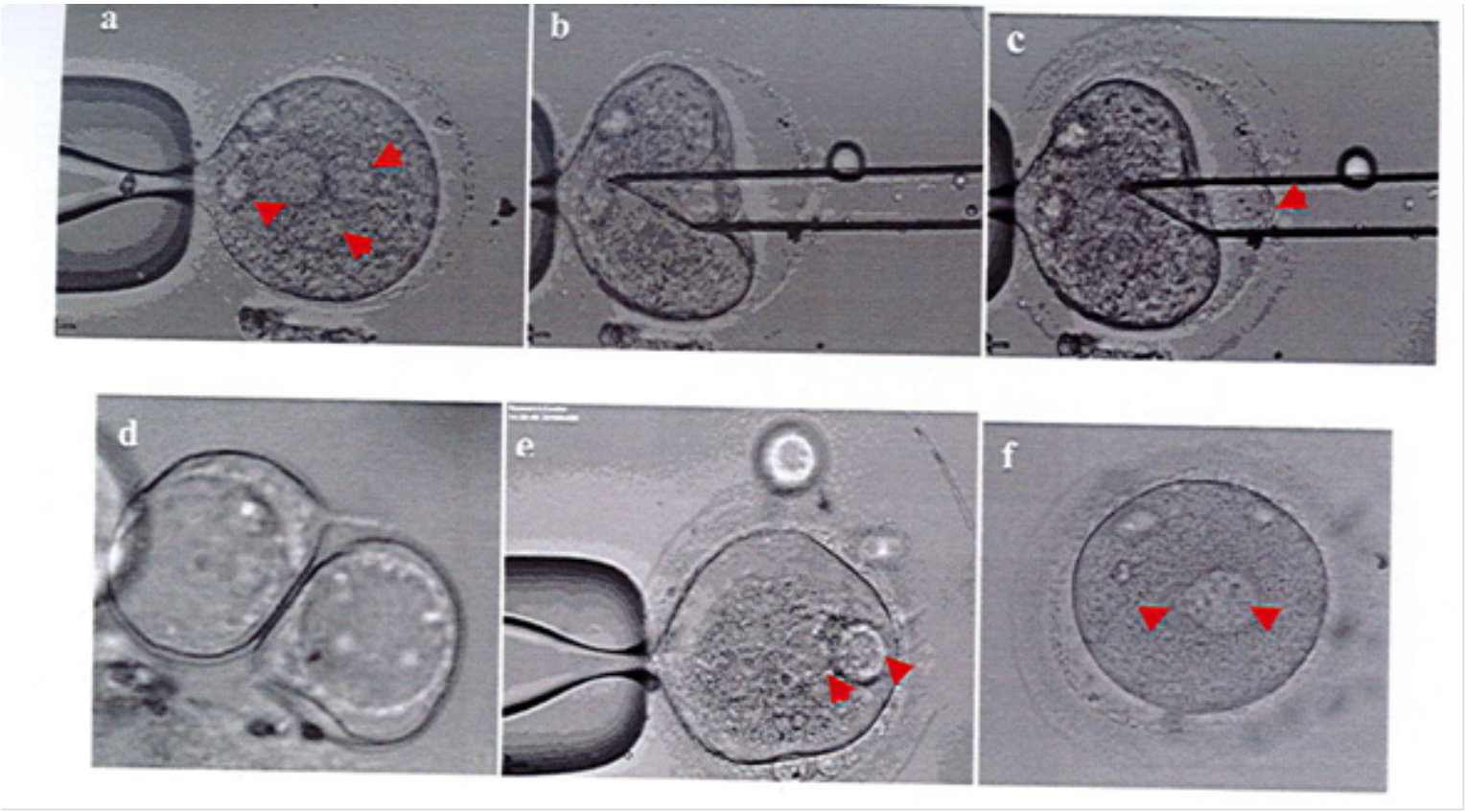
# Notre projet:

**Does nuclear transfer alter mitochondrial-nuclear cross-talk in the human preimplantation embryo?**



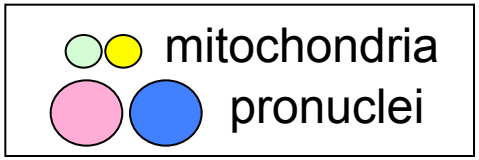
**Does nuclear transfer alter mitochondrial-nuclear cross-talk in the human preimplantation embryo?**

**Studying the expression levels of nuclear and mitochondrial genomes in embryos submitted to nuclear transfer vs unmodified embryos.**

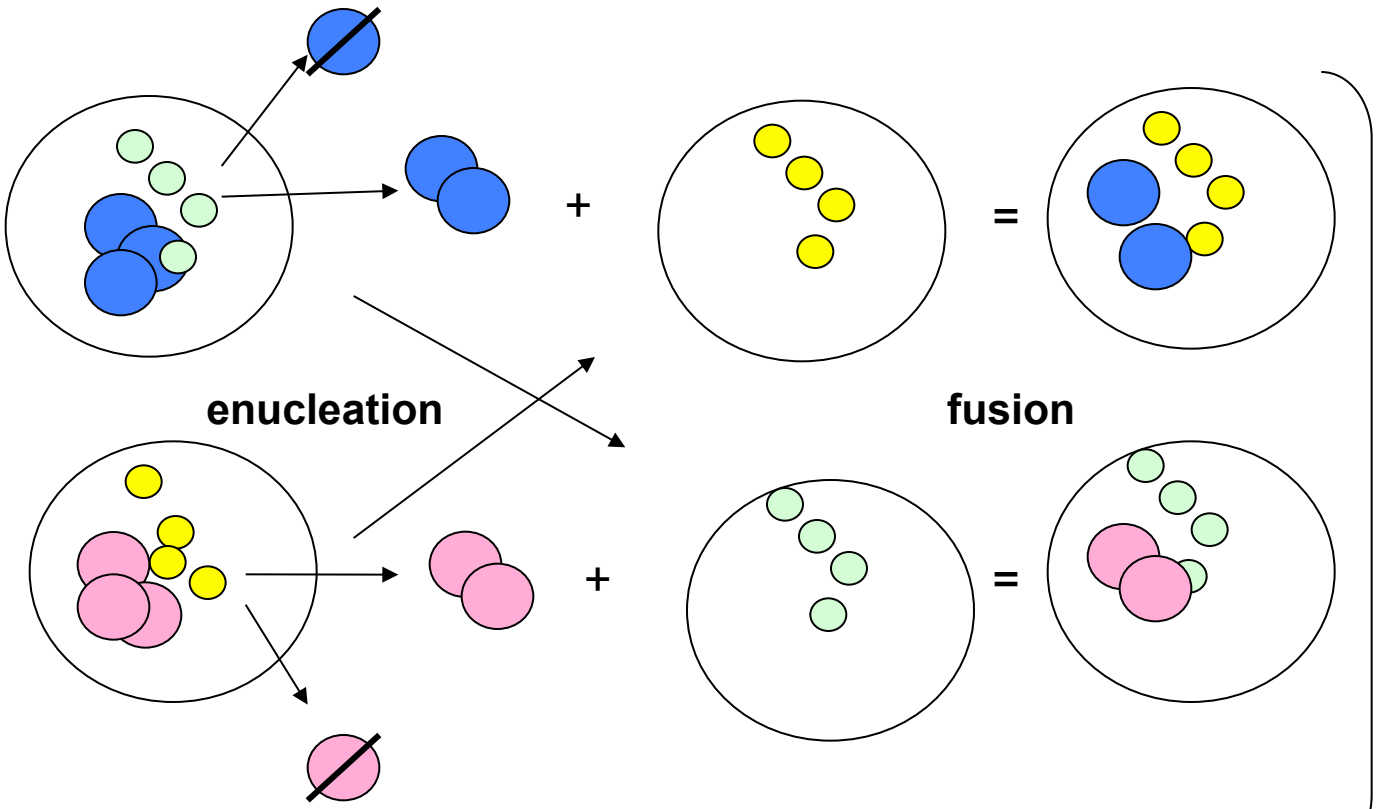



*Images from Laura Irving thesis*
*« IVF Based approaches towards the treatment and prevention of mitochondrial diseases »:*

# ***Treated group***




Zygote tri PN 1



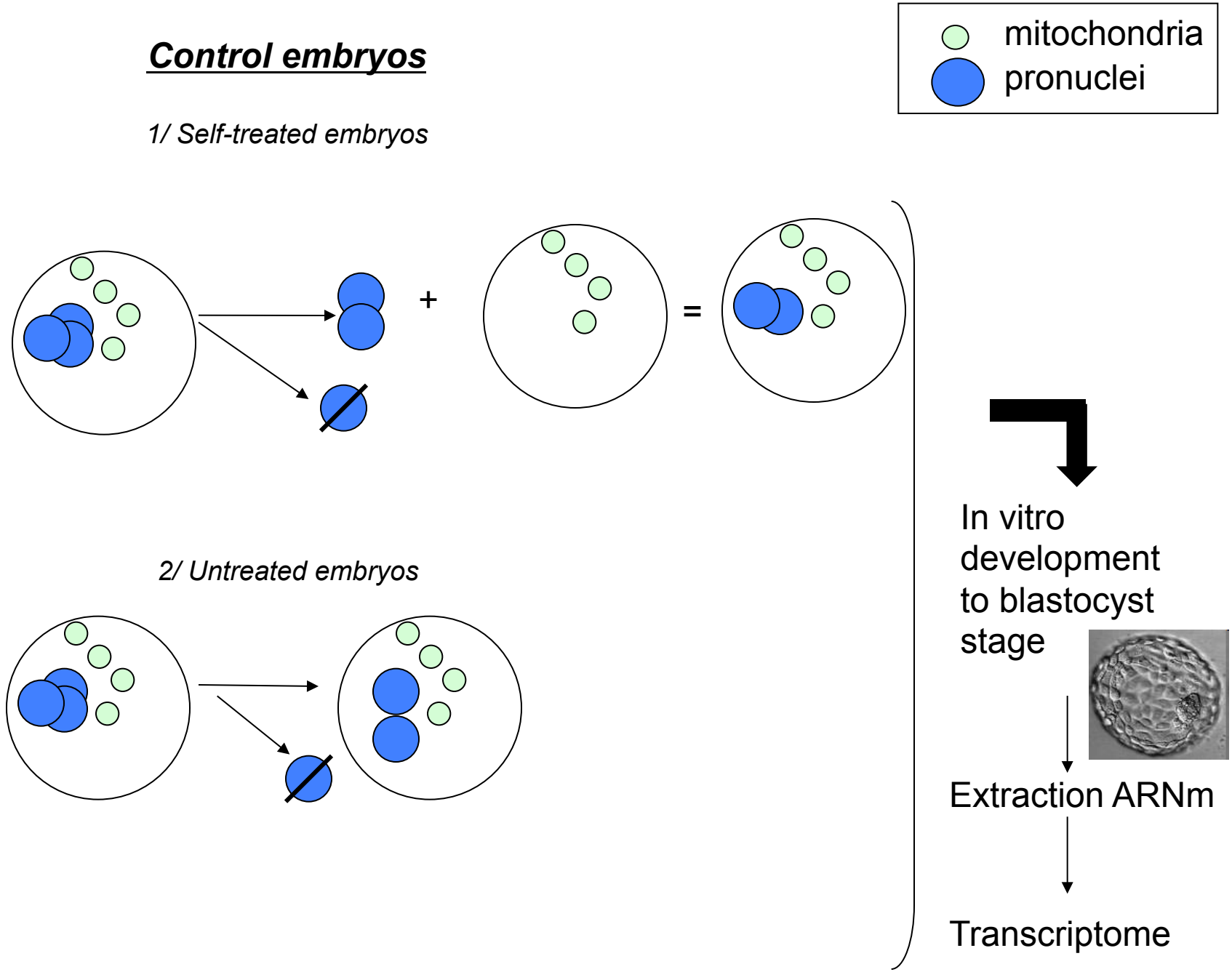

Zygote tri PN 2

In vitro development to blastocyst stage

Extraction ARNm

Transcriptome

## ***Control embryos***



# Les difficultés

- *Administrative* projet déposé en septembre 2015 puis en décembre 2015 (pièces complémentaires) Autorisé en mai 2016 avec publication au JO en septembre 2016
- *Juridique* Recours devant le tribunal administratif par la Fondation Lejeune en décembre 2016
- *Financement* : financement associatif 1 an, recrutement d'un étudiant...

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