

SME-Academia Nuclear Receptor Knowledge Transfer

SME RECEPTOR brings top scientists from industry and academia together to develop new methodology for drug design targeting metabolic diseases.

Marie Curie Fellows

Partner Organisations

From Lab to Market

Marie Curie

(IAPP) Industry – Academia
Partnerships & Pathways

PIAP-GA-2008-217877

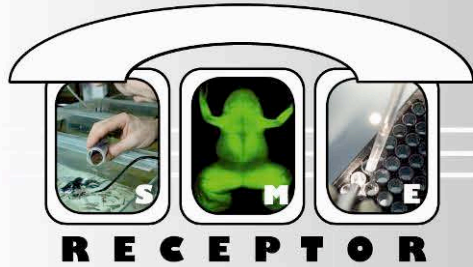


Studying nuclear receptor (NR) mechanisms,

Circadian regulation of NRs and its influence
on drug delivery and efficacy

Use of zebrafish and *Xenopus* embryos as
small model organisms for basic and applied
research in cardiovascular physiology and
molecular endocrinology

Building Academia-Industry Partnerships

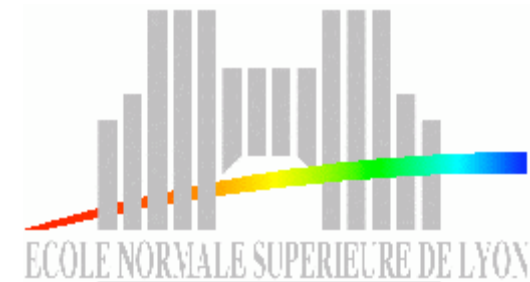


SME-Academia Nuclear Receptor Knowledge Transfer

Partner Organisations



Karolinska
Institutet

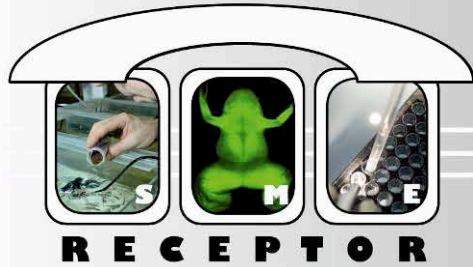


Marie Curie

(IAPP) Industry – Academia
Partnerships & Pathways

PIAP-GA-2008-217877





SME-Academia Nuclear Receptor Knowledge Transfer

Marie Curie Fellows

Industry

- Axcentua AB
- AliX S.A.
- Watch Frog S.A.S.

Academia

- KI, Sweden
- ENSL, France
- CNRS, France



Seconded Fellows
Specialist

Experienced Researcher



Recruited Fellows

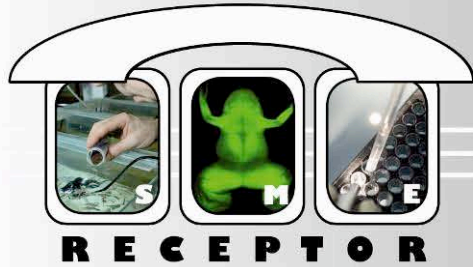


Marie Curie

(IAPP) Industry – Academia
Partnerships & Pathways

PIAP-GA-2008-217877





SME-Academia Nuclear Receptor Knowledge Transfer

**An example of collaboration in SME RECEPTOR :
The use of Small Model Organisms (SMOs) for endocrine disruptors research**

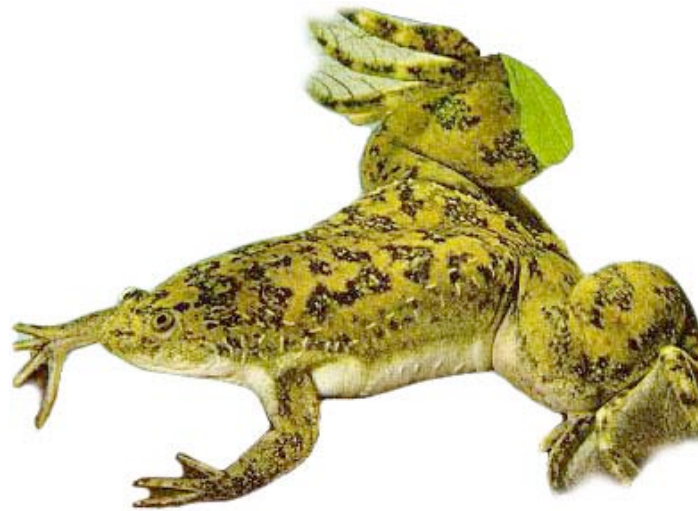
Zebrafish: Effect and mode of action of Bisphenol A

Xenopus: Detection of endocrine disruptors targeting thyroid hormone signalling

Marie Curie

(IAPP) Industry – Academia
Partnerships & Pathways

PIAP-GA-2008-217877





NF 52

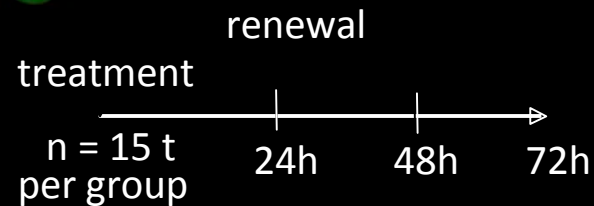
(3 weeks)



NF 45

(one week)

Use of young tadpole: proof of principle



T_3 $10^{-8}M$

Automatized and
imaging for quantification
of fluorescence



TH/bZIP

GFP



TH/bZIP

GFP

GFP induction under the TH/bZIP promoter

Possible at both stages 42 et 45

Stage 42 not reproducible

Stade 45 reproducible

Automatised quantification and images quantification
= comparable results (Fini et al., 2007)

Automatised lecture used for validation tests

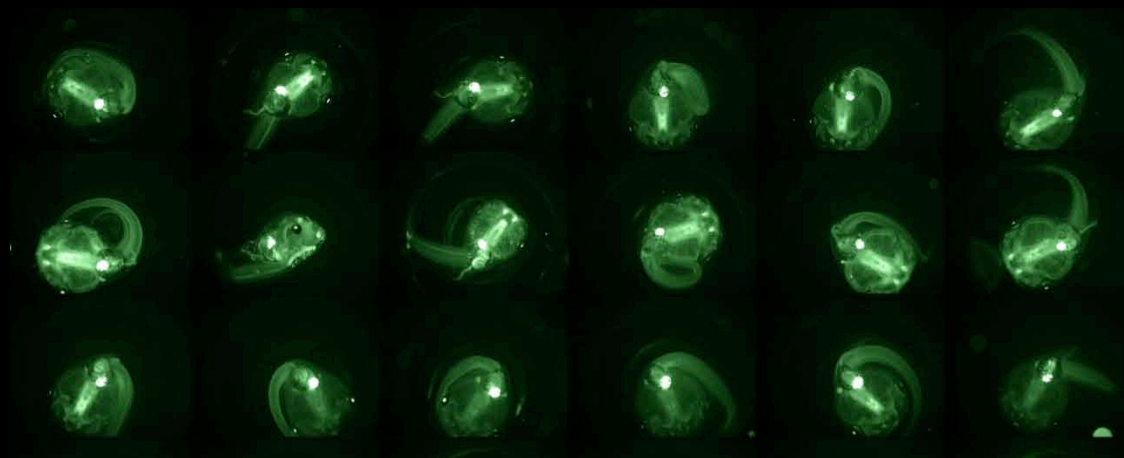


Automatisation of fluorescence reading

One week old tadpole

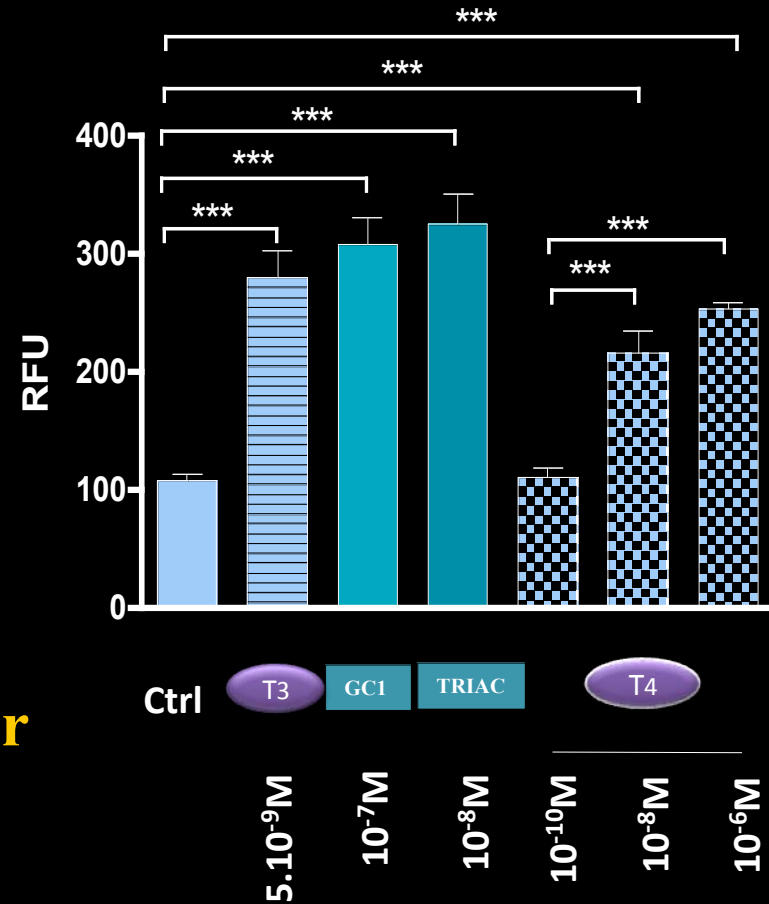
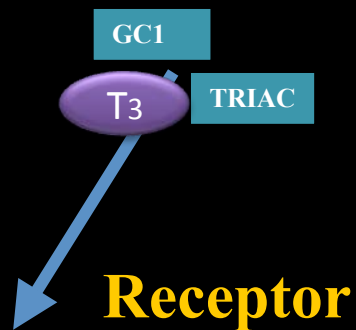
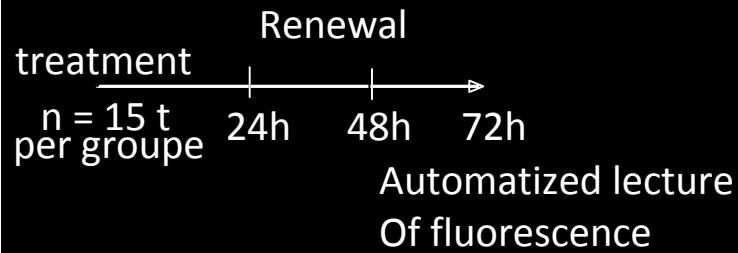
Three days treatment
with daily renewal

1 tadpole per well
In 96 well plates





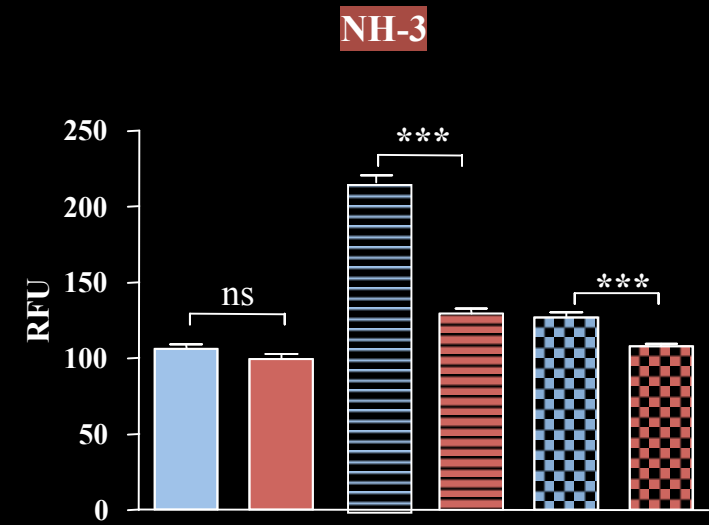
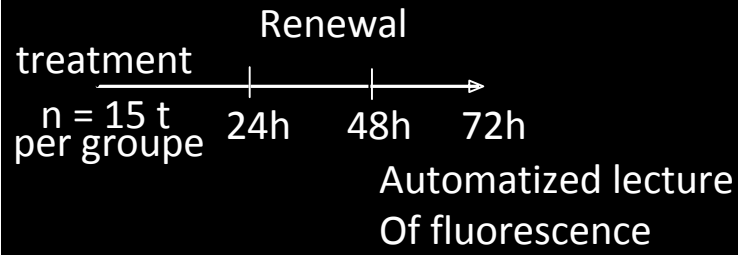
Validation I: Thyroid hormones and TRs agonists



(Fini et al., 2007)



Validation II: Thyroid signalling inhibitors



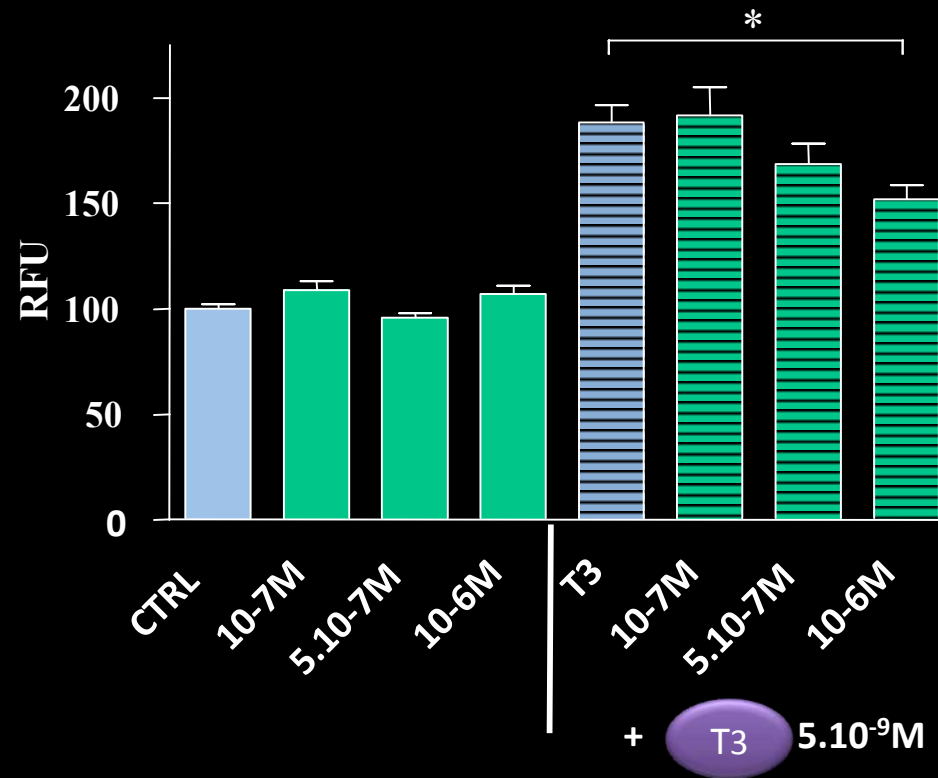
NH-3

Receptor

NH3 2.10 ⁻⁶ M	-	+	-	+	-	+
T ₃ 5.10 ⁻⁹ M	-	-	+	+	-	-
T ₄ 10 ⁻⁸ M	-	-	-	-	+	+



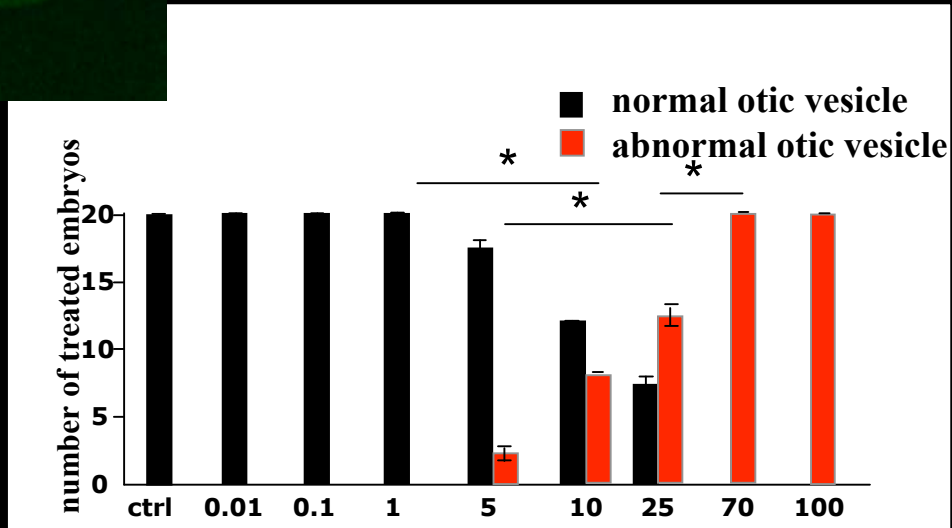
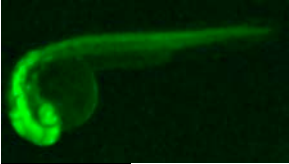
TBBPA anti thyroidian effects Confirmed by our transcriptional test



(Fini et al., 2007)

Effects observed at larval stages but also during embryogenesis (unpublished)

How TBBPA exerts its anti thyroidian effect?



BPA treatment induces abnormalities of the zebrafish otic vesicle.

Treatment at 5hpf, observation at 50hpf

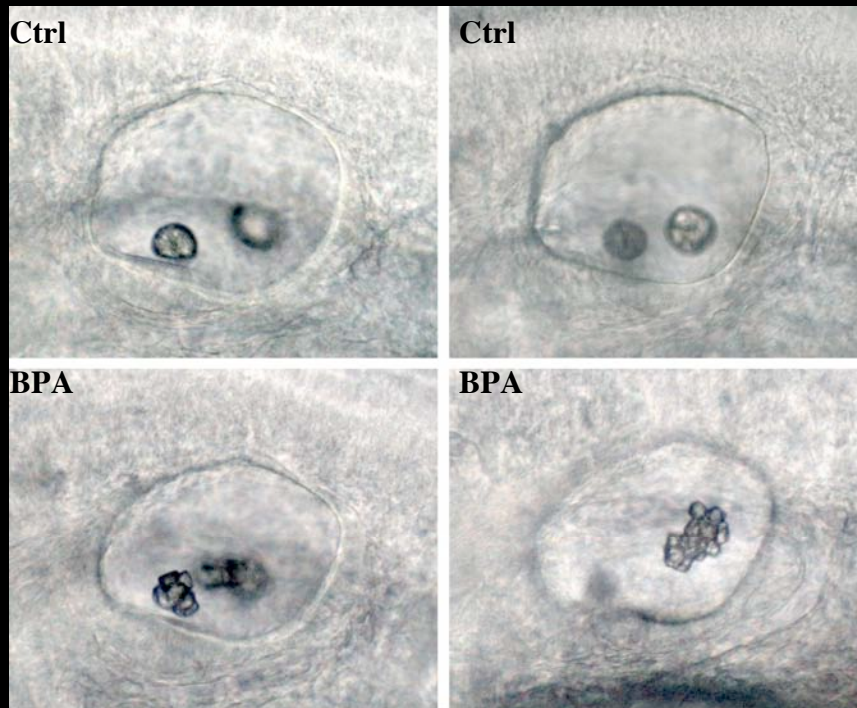
Bilateral aggregation of both the anterior and posterior otoliths

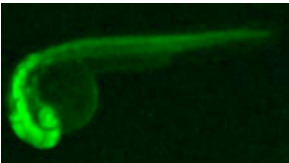
In some cases, alterations of semi-circular canals development

<5% of embryos with abnormalities at 5 μM.

More than 50% of affected embryos at 25 μM.

Doses higher than 100 μM BPA induces mortality

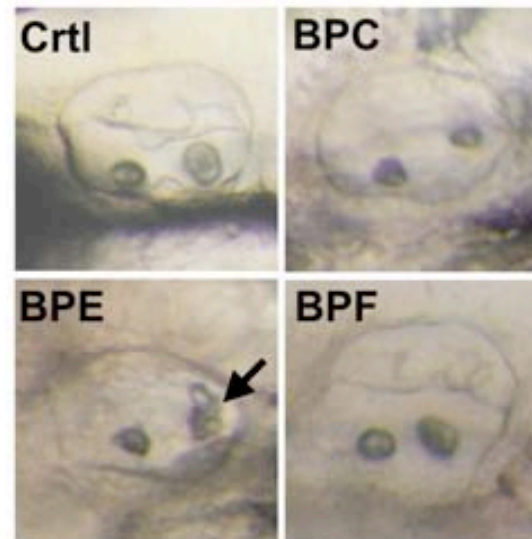




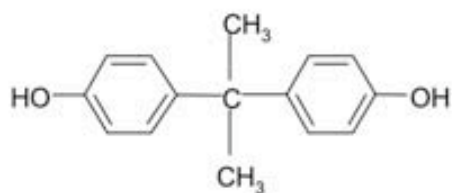
Bisphenol effects are time and compound specific

Specific time window: 5-20 hpf

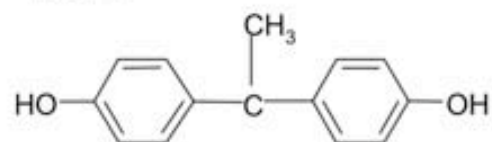
	Effect on otoliths	Effect on pigmentation
WT	-	-
BPA	+++	+/-
BPC	+/-	+/-
BPE	+++	+++
BPF	+/-	+++



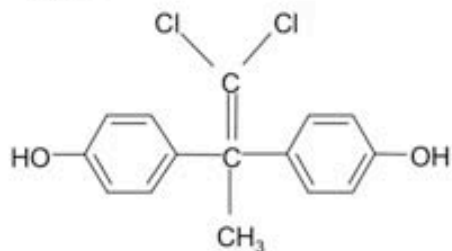
BPA



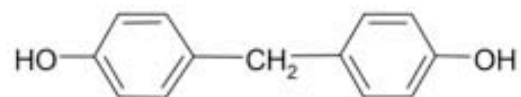
BPE

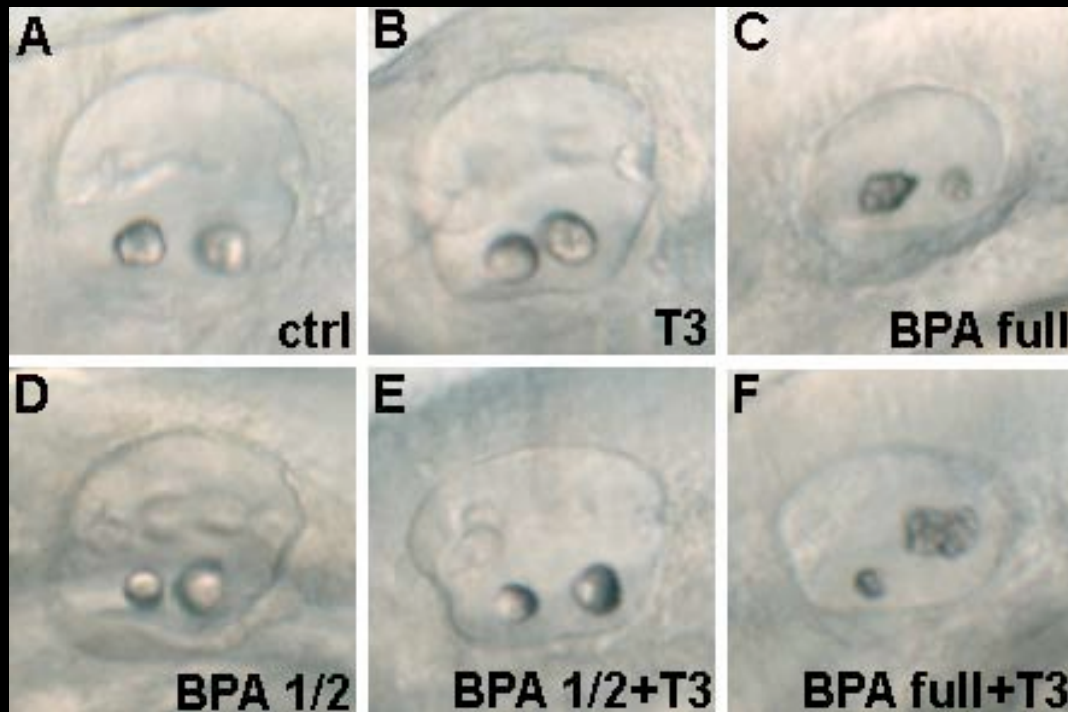


BPC



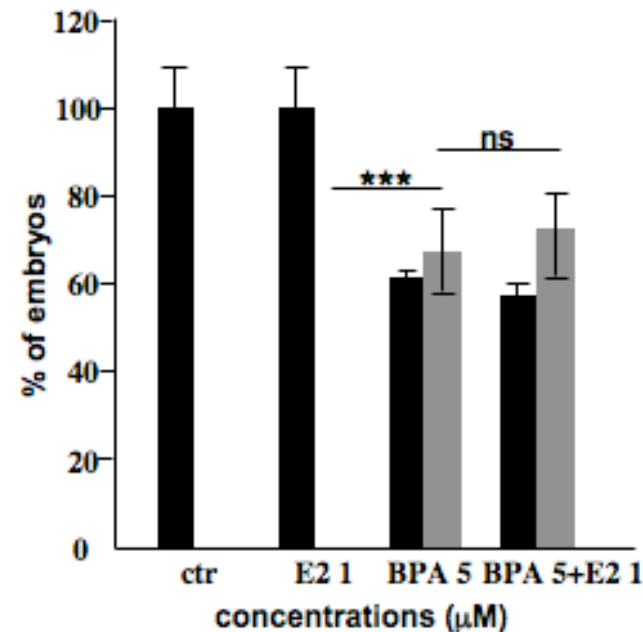
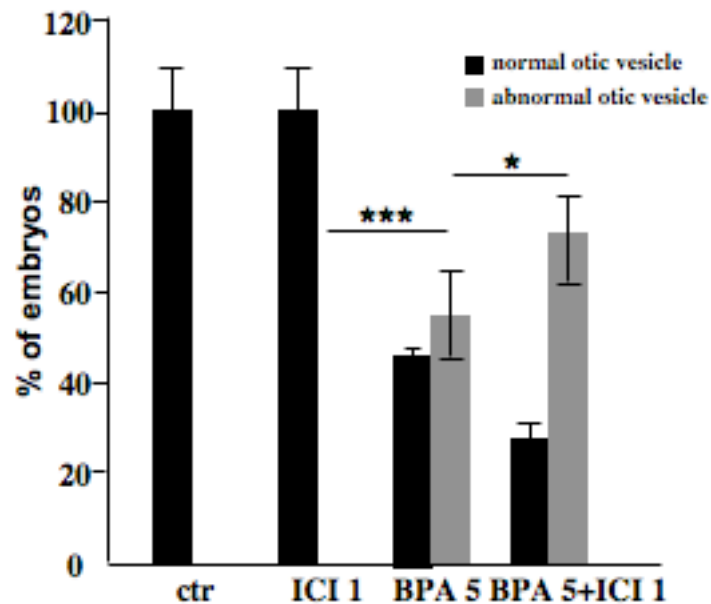
BPF

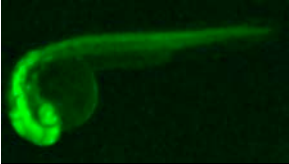




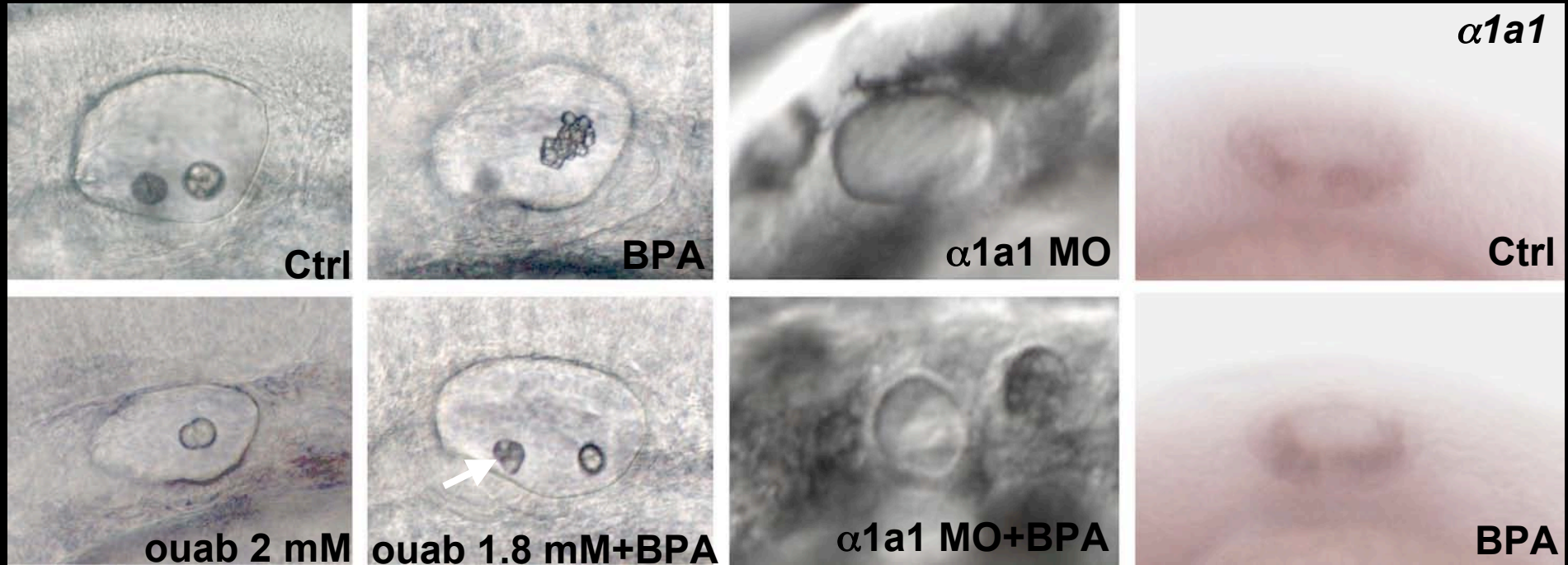
The BPA-induced otic vesicle phenotype is ER- and TR-independant

Pharmacological approach
Genetic approach



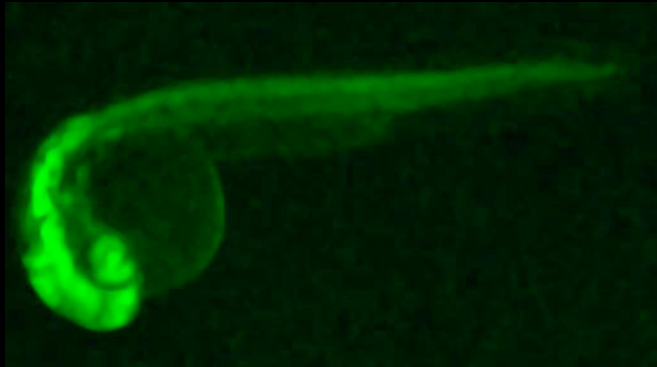


BPA effect on otic vesicle formation is NaK ATPase-dependant.





Jean-Baptiste Fini
Sébastien Le Mevel
Karima Palmier
Gregory Lemkine
Barbara Demeneix



Yann Gibert
Sana Sassi
Jean-Paul Renaud
Vincent Laudet

Vincent.Laudet@ens-lyon.fr



Ingemar.Pongratz@ki.se

Ingemar Pongratz
Manuela Hase
Lisbeth Sjödin