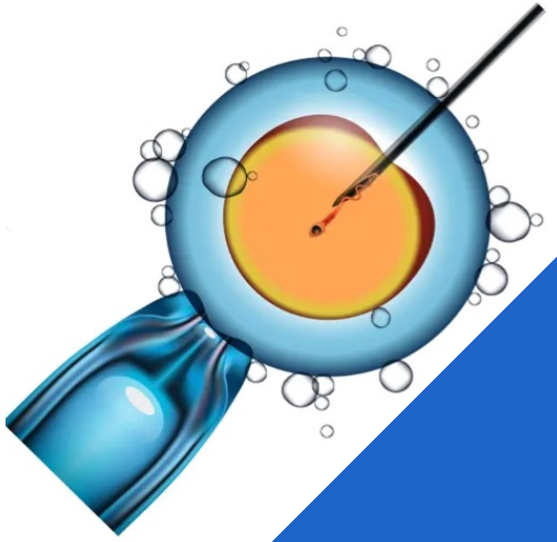

Arantxa Cardona Barberán

Treatment options to overcome impaired fertilization and embryonic development caused by an **oocyte-related deficiency** in the ***Patl2*$^{-/-}$ mouse model**

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What is known? PATL2 function

RNA-binding protein that represses translation of maternal RNAs during oocyte maturation

- Abundant in germinal vesicle (GV), but still detected in metaphase II (MII)
- *Patl2* deficiency causes abnormal expression of maternal RNAs

- *PATL2* variants cause mainly GV arrest, but some patients produce MII oocytes
- *PATL2* protein degradation or accumulation disrupts translational repression

Nakamura *et al.,* 2010 [Dev Biol]; Christou-Kent *et al.,* 2018 [EMBO Mol Med]; Chen *et al.,* 2017 [Am J Hum Genet]

What is known? Patients with *PATL2* variants

Gene	*PATL2* variants	Detection rate (N affected pat/N pat screened)	Phenotype	Population	Study
PATL2 Autosomal recessive inheritance	**37**				
	8	2.8% (5/180)	OMA, FF, EDA	Chinese	Chen *et al.,* 2017
	2	2/2	OMA (GV arrest)	Arabic	Maddirevula *et al.,* 2017
	1	26% (6/23)	OMA (GV arrest)	Tunisian	Christou-Kent et al., 2018
	6	44.4% (4/9)	OMA (GV arrest)	Chinese	Huang et al., 2018
	6	3.2% (7/216)	OMA, FF, EDA	Chinese	Wu et al., 2019
	2	7.5% (3/40)	OMA	Chinese	Liu et al., 2020
	7	6/6	OMA, FF	Chinese	Cao et al., 2021
	2	22,2% (2/9)	OMA	Chinese	Huo et al., 2022
	1	1/1	OMA (GV arrest)	Chinese	Sun et al., 2022
	2	16,7% (2/12)	OMA, EDA	Chinese	Huang et al., 2022

OMA: oocyte maturation arrest, FF: fertilization failure, EDA: embryo developmental arrest

Oocyte donation referral

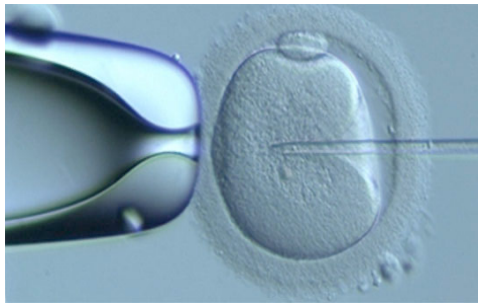
What is known? Treatment options

PATL2 variants

1. OMA → **IVM protocols** Not effective

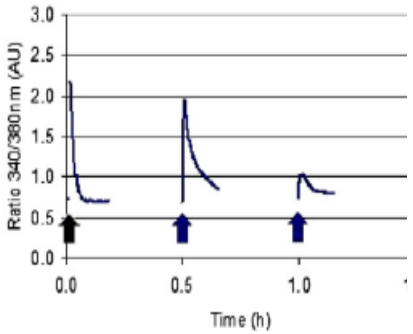
2. FF/EDA

Assisted oocyte activation (AOA)?



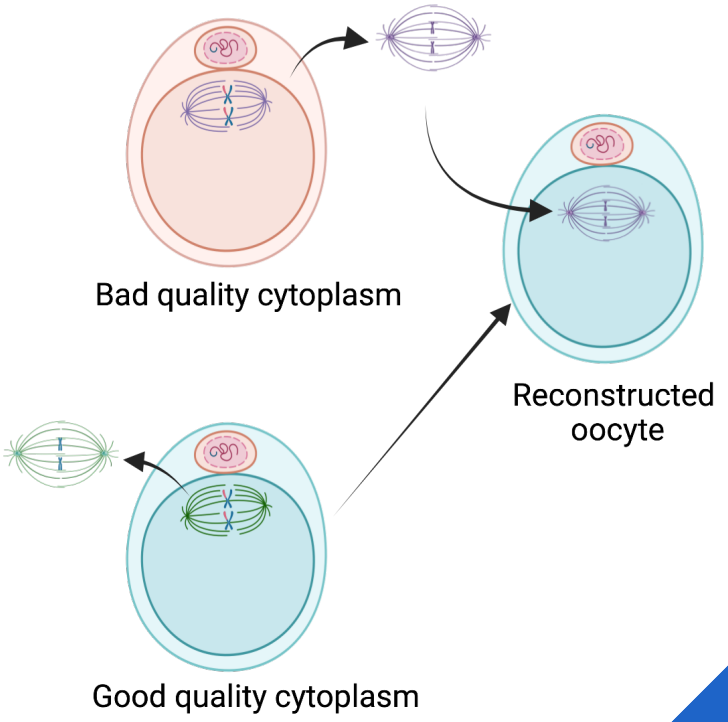
ICSI

+



Ca^{2+} ionophore exposure

Spindle Transfer (ST)?

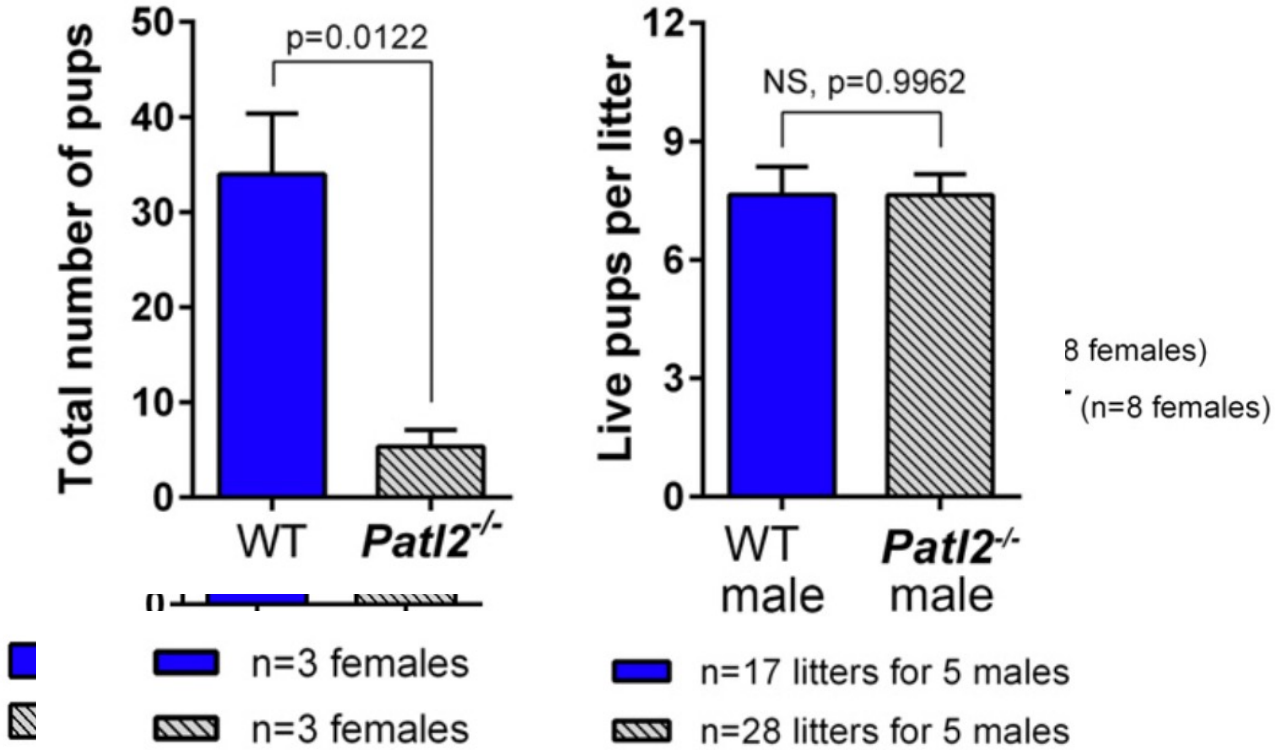


Cao *et al.,* 2021 [Front Cell Dev Biol]; Bonte *et al.,* 2019 [Fertil Steril]; Craven *et al.,* 2017 [Hum Reprod Update]

What is known? *Patl2*$^{-/-}$ mouse model

***Patl2*$^{-/-}$**

- ♀ subfertile ♂ fertile
- ↓ oocyte maturation rates ↓ diameter
- ↓ 2-cell ↓ blastocyst formation after IVF



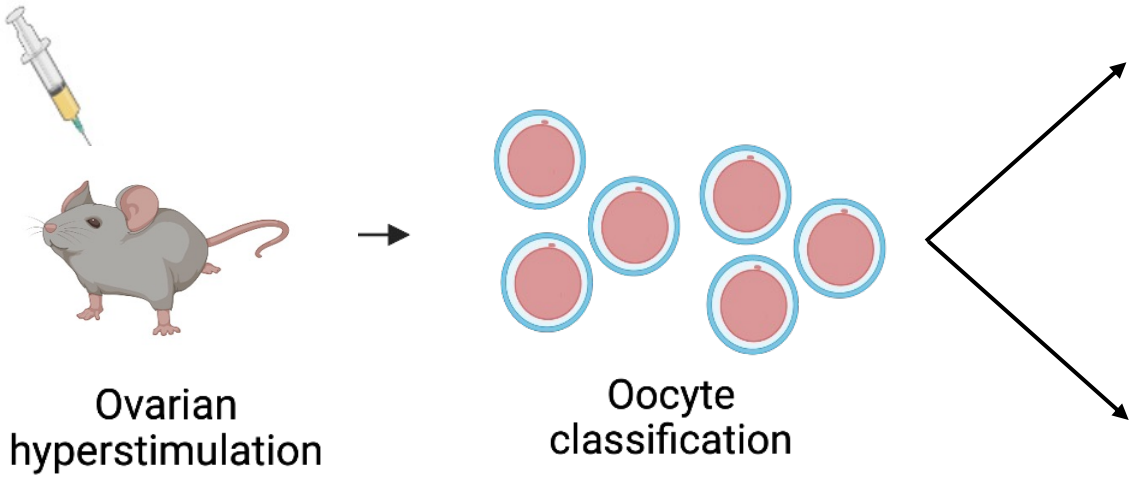
Christou-Kent *et al.,* 2018 [EMBO Mol Med]

Objectives

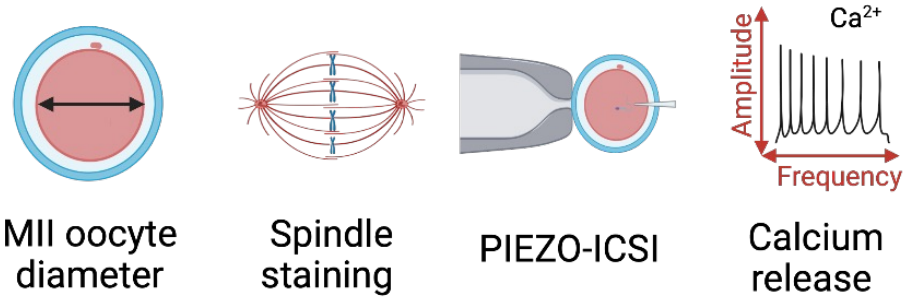
1. **Characterization of subfertility** observed in the ***Patl2*$^{-/-}$ mouse model** by assessing different **oocyte quality markers.**

2. Comparison of efficacy of **assisted oocyte activation** (AOA) and **spindle transfer** (ST) treatments **to overcome *PATL2*-related infertility**.

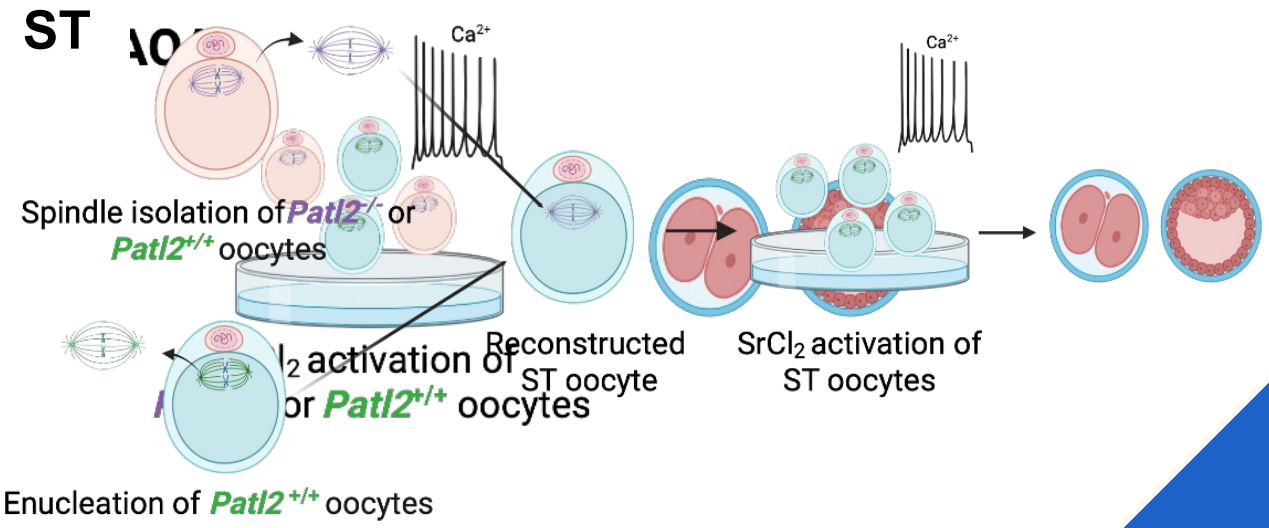
Study design and methods



1. Study of oocyte quality markers: *Patl2*$^{-/-}$ vs *Patl2*$^{+/+}$



2. Treatment efficacy comparison: *Patl2*$^{-/-}$ vs *Patl2*$^{+/+}$



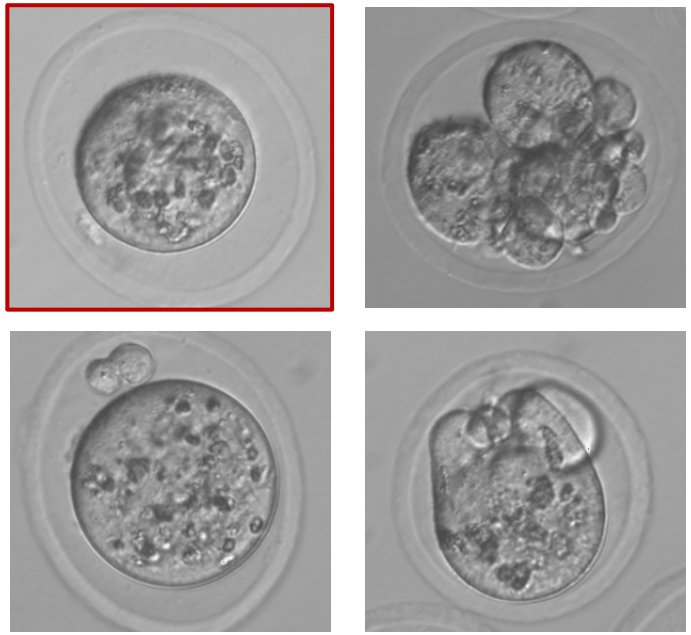
C57BL/6NTac-Patl2tm1a → ***Patl2***$^{-/-}$

C57BL/6NTac → ***Patl2***$^{+/+}$

Results 1 - Oocyte maturation and growth in *Patl2*$^{-/-}$ females

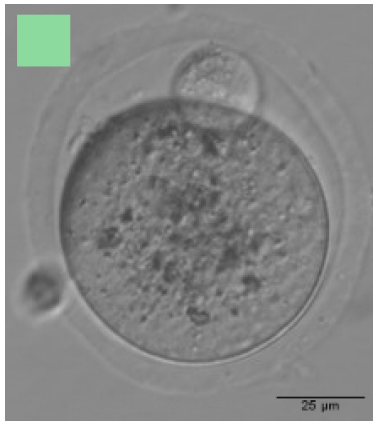
	Patl2$^{+/+}$	*Patl2*$^{-/-}$	*p-value*
N females	7	5	
Total COCs	179	162	
COCs/mouse	25,57	32,40	
Total MII	160	129	
MII rate (%)	**89,39%**	**79,63%**	0,015
MII/mouse	22,86	25,80	
Abnormal oocytes	19	33	
Abnormal oocyte rate (%)	**10,61%**	**20,37%**	
Abnormal oocytes/mouse	2,71	6,60	

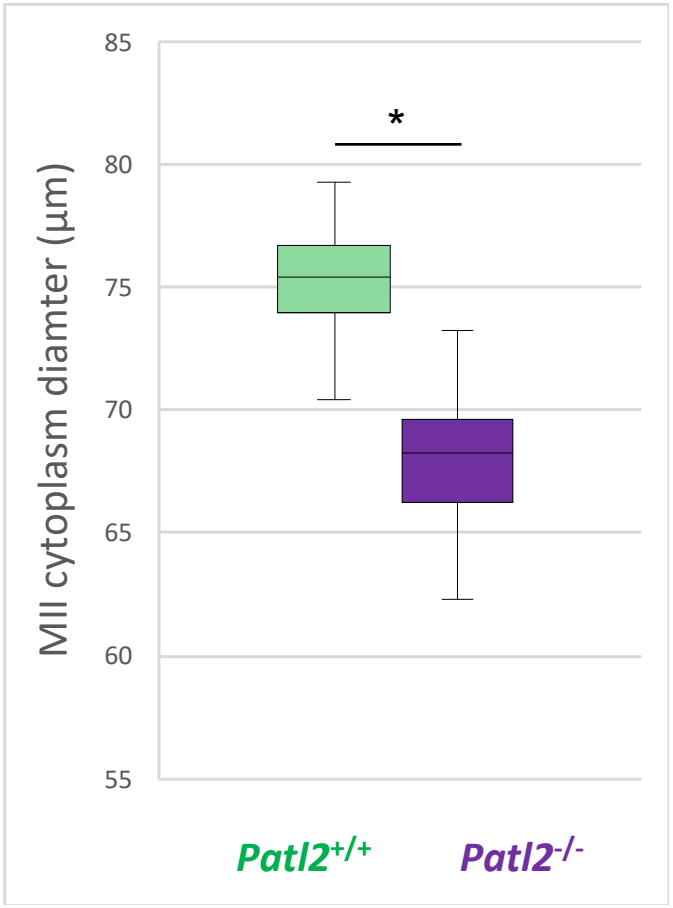
4 experimental replicates, Fisher's exact test



No GV or MI oocytes!

Results 1 - Oocyte maturation and growth in *Palt2*$^{-/-}$ females

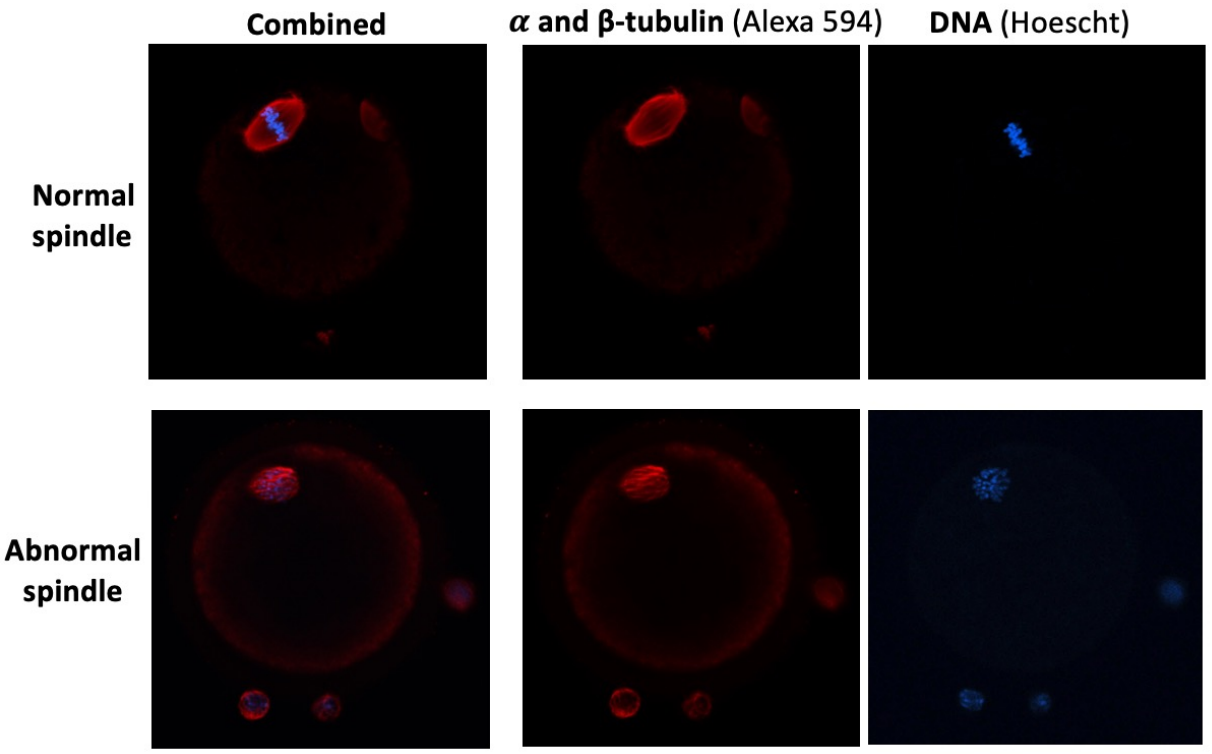




	N	MII cytoplasm ⌀	*p-value*
***Patl2*$^{+/+}$**	76	75,29 ± 1,93	<0,001
***Patl2*$^{-/-}$**	79	68,11 ± 2,25	

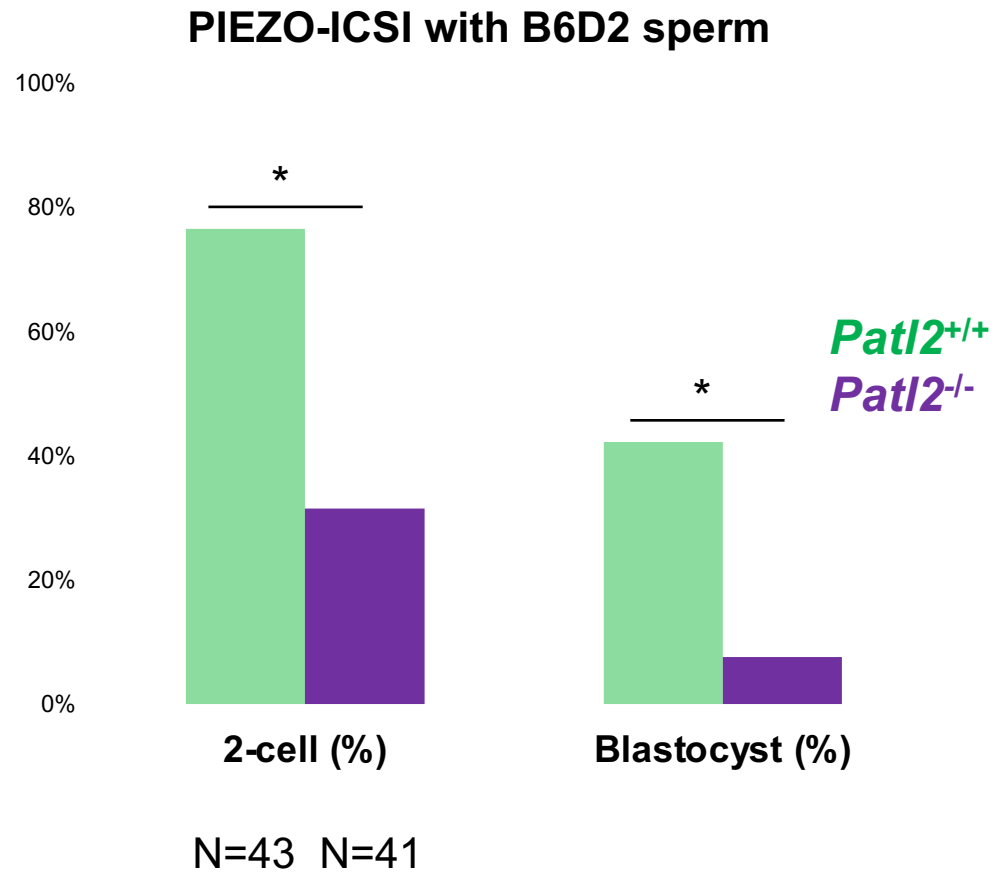
3 experimental replicates, t-test

Results 2 - Nuclear and cytoplasmic maturity in *Patl2*$^{-/-}$ MII oocytes

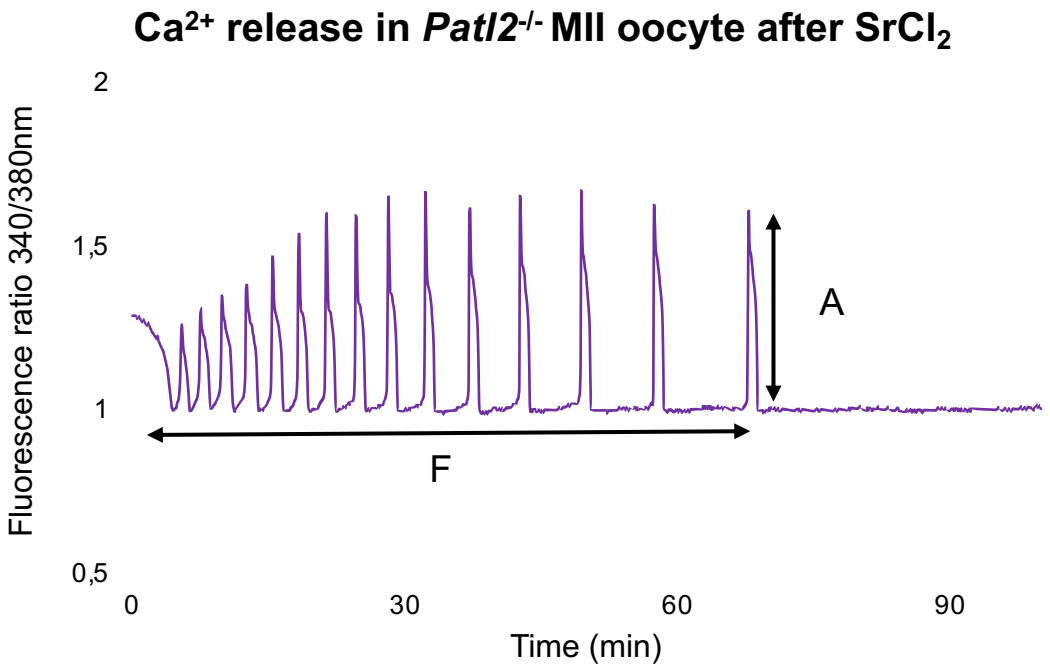


	Patl2$^{+/+}$	*Patl2*$^{-/-}$	*p-value*
N	48	42	
% Normal spindle	42 (87,5%)	31 (73,8%)	0,113
% Abnormal microtubule structure	3 (6,25%)	4 (9,52%)	0,700
% Misaligned chromosomes	5 (10,42%)	10 (23,81%)	0,099

4 experimental replicates, Fisher's exact test



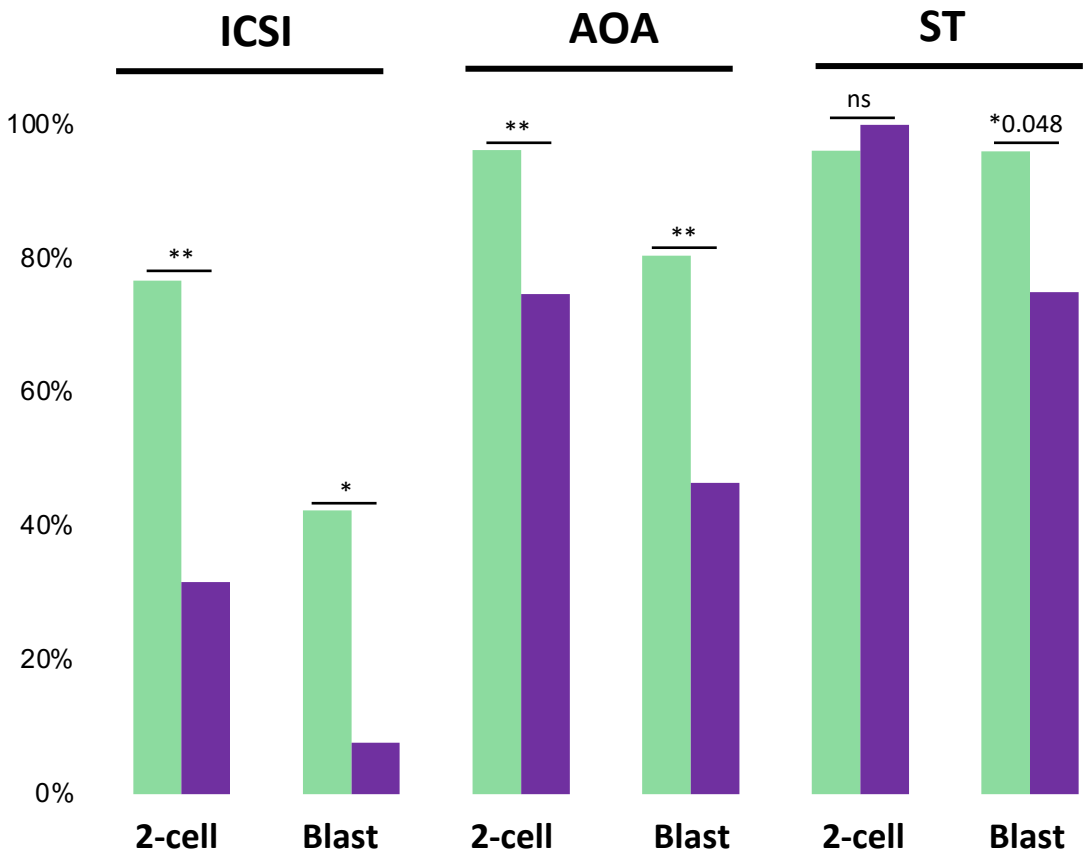
Results 3 - Calcium releasing capacity of *Patl2*$^{-/-}$ MII oocytes



	Patl2$^{+/+}$	*Patl2*$^{-/-}$	*p-value*
N	28	30	
mean A	0,54 ± 0,24	0,45 ± 0,15	<0,001*
mean F	9,39 ± 5,12	15,23 ± 9,89	0,007*
Mean AxF	5,04 ± 2,90	6,88 ± 4,78	0,087

4 experimental replicates, t-test

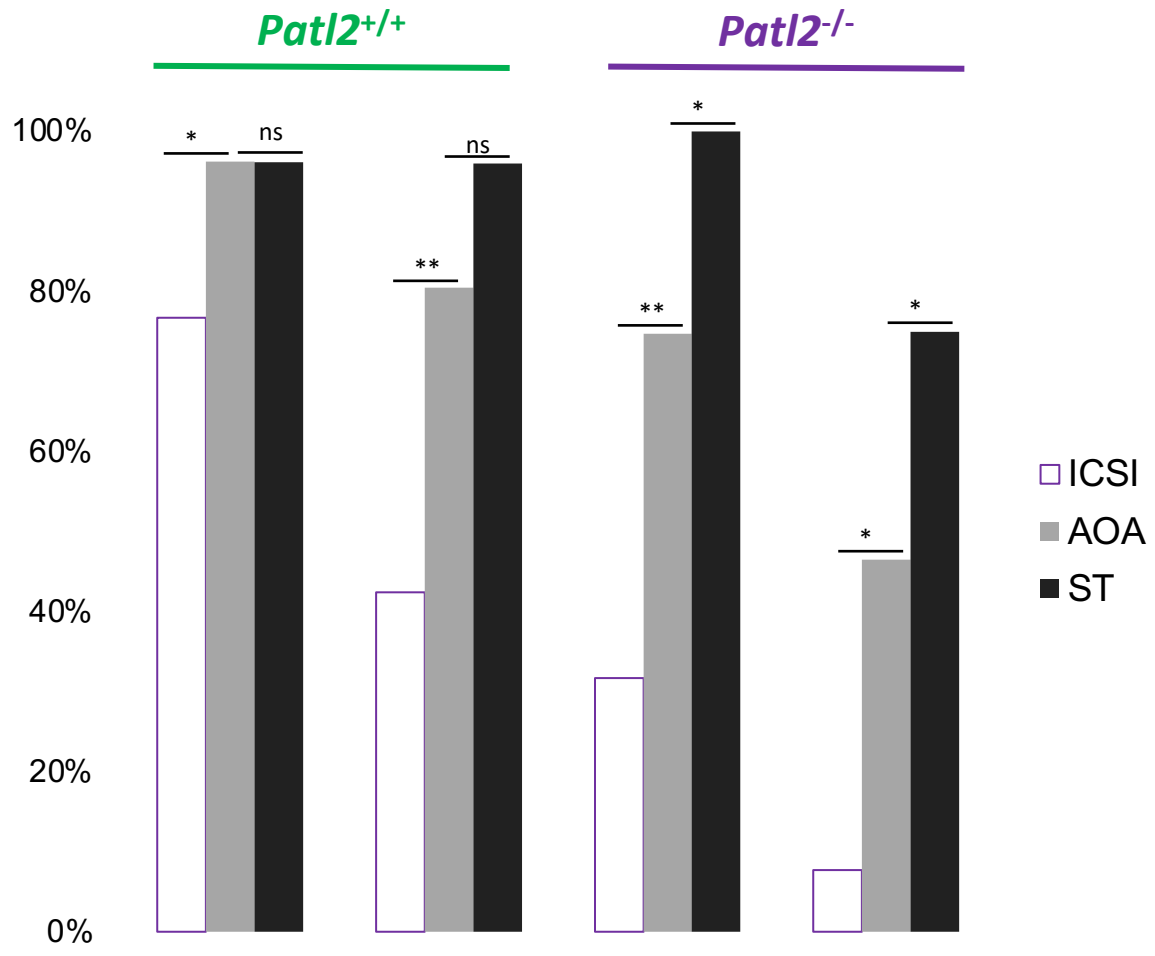
Results 4 - ST vs AOA to restore development in *Patl2*$^{-/-}$ MII oocytes



Treatment	Group	Replicates	N MII	2-cell/MII	Blast/2-cell
PIEZO-ICSI	*Patl2*$^{+/+}$	5	43	76,74% (33)	42,42% (14)
	Patl2$^{-/-}$	3	41	31,71% (13)	7,69% (1)
AOA ($SrCl_2$)	*Patl2*$^{+/+}$	6	133	96,24% (128)	80,47% (103)
	Patl2$^{-/-}$	6	95	74,74% (71)	46,48% (33)
ST - $SrCl_2$	*Patl2*$^{+/+}$	3	26	96,15% (25)	96,0% (24)
	Patl2$^{-/-}$	5	24	100,00% (24)	75,0% (18)

*<0,05; **<0,001; Fisher's exact test

Results 4 - ST vs AOA to restore development in *Patl2*$^{-/-}$ MII oocytes



*<0,05; **<0,001; Fisher's exact test

Conclusions

1. ***Patl2*$^{-/-}$ females produce high rates of MII oocytes**, contrary to patients with *PATL2* variants.

2. **PALT2** does not seem to **influence** nuclear maturity, but **cytoplasmic maturity**.

3. **AOA** would not work for patients with *PATL2* variants, as *Patl2*$^{-/-}$ oocyte-related infertility is **independent from a calcium releasing deficiency**.

4. **ST,** but not AOA**, restores embryo development to control values in *Patl2*$^{-/-}$ oocytes**.

5. **ST** could be use **to treat PATL2-related infertility**, as well as other female infertility caused by poor cytoplasmic quality, linked or not to molecular defects.

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