Vascular effects of ERα membrane initiated signaling

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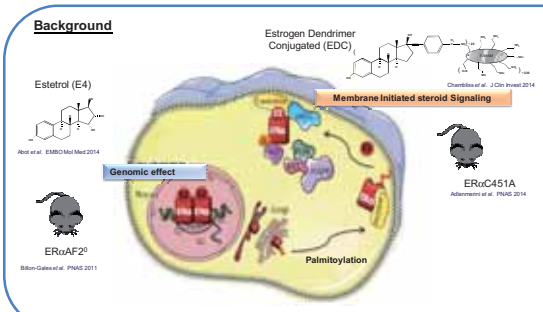
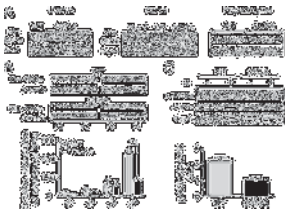
Background

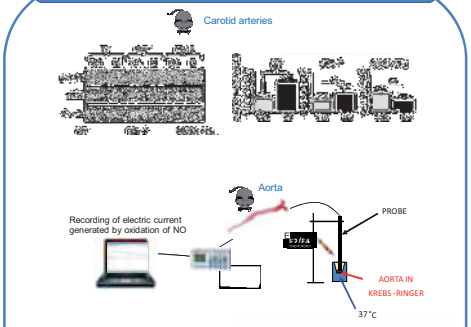


Validation of the C451A-ERα mouse model

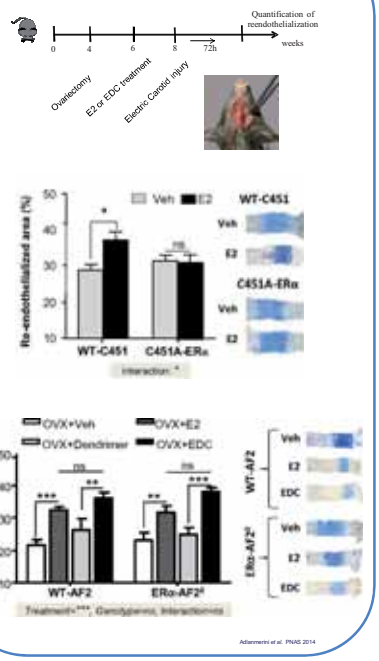


Adlanmerini et al. PNAS 2014

ERαMISS is necessary to increase NO production in response to E2

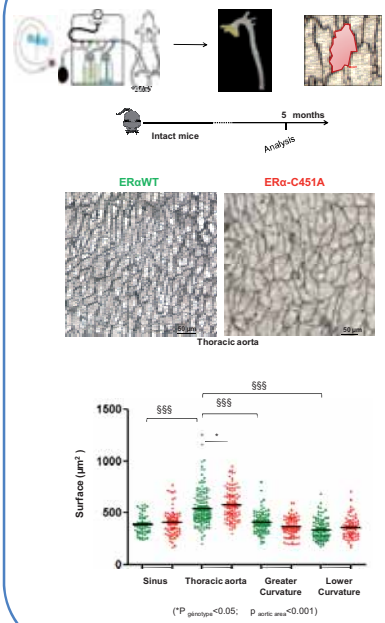


ERαMISS is necessary and sufficient to induce endothelial healing

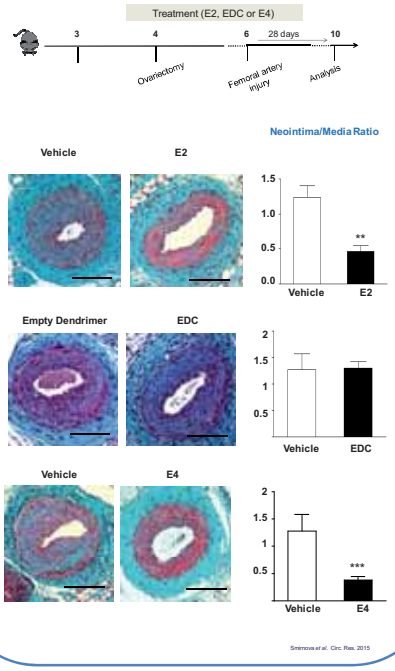


Adlanmerini et al. PNAS 2014

Endothelial cell morphology is altered in ERαC451A mice

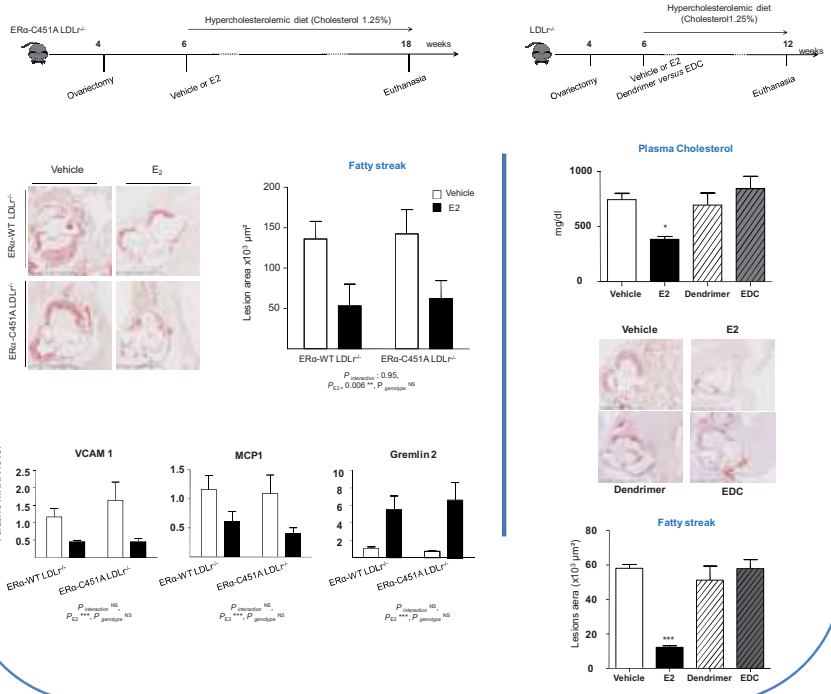


Activation of nuclear, but not membrane, ERα is sufficient for the suppression of neointimal hyperplasia



Smirnova et al. Circ. Res. 2015

ERαMISS is dispensable for the prevention of early atheroma at the aortic sinus in the mouse



CONCLUSION

	Genetically modified mouse model = Loss-of function		Pharmacological approaches =Gain of function		
Genotype	ERαAF2⁰ (nuclear)	ERα-C451A (MISS)	WT		
Treatment	Estradiol		Estetrol (nuclear)	Tamoxifen (AF1)	EDC (MISS)
Acceleration of endothelial healing	YES [1]	NO [2]	NO [3]	NO [4]	YES [2]
Increase of NO production	nd	NO [2]	NO [3]	nd	YES [2]
Prevention of neointimal hyperplasia	nd	nd	YES [5]	YES [5]	NO [5]
Prevention of atheroma at aortic sinus	NO [1]	YES	YES [3]	YES [4]	NO

Summarize of the different studies describing the respective role of nuclear ERα and ERαMISS in vasculoprotection using genetically modified mouse models (loss-of-function) and pharmacological tools (gain-of-function).

Nd = not determined

1. Billon-Gales A et al. ***Proc Natl Acad Sci U S A.*** 2011;108:13311-13316
2. Adlanmerini M, et al. ***Proc Natl Acad Sci U S A.*** 2014;111:E283-290
3. Abot A et al. ***EMBO Molecular Medicine*** 2014;6:1328-1346
4. Fontaine C *et al. **Am J Pathol.*** 2013;183:304-312
5. Smirnova NF *et al. **Circulation Research*** 2015

ERαMISS appears to be necessary to support some, but not all, vascular protective actions of estrogen.