SELECTED OPPORTUNITIES IN NEUROSCIENCE

Apelin analogs for the treatment of dysfunction associated with aging (BIO11315)

APELIN ANALOGS FOR THE TREATMENT OF DYSFUNCTION ASSOCIATED WITH AGING (BIO11315)

Product factsheet

- **Product:** Apelin (APJ) receptor agonist or apelinomimetic

- **Mechanism:**
  - Sarcopenia is a deficit of muscle strength and mass in elderly population ;
  - Sarcopenia contributes to the progressive loss of autonomy and is tightly correlated with the development of other age-associated pathologies (osteoporosis, heart failure or cognitive diseases) ;
  - Chronic loss of mature myofiber metabolic capacities, and particularly mitochondrial alterations, promotes muscle wasting by different molecular pathways such as lack of energy supply, decrease of protein turn-over or oxygen species production ;
  - Sarcopenia can also be explained by a deficiency in muscle renewal observed during acute phases such as physical exercise or injury. In that case, it is now known that proliferation as well as differentiation potential of muscle stem cells is altered.

- **Potential applications:** Age-related dysfunctions (sarcopenia)

- **Patents:** WO2013079487, Priority 28/11/2011
- **Publication:** ongoing

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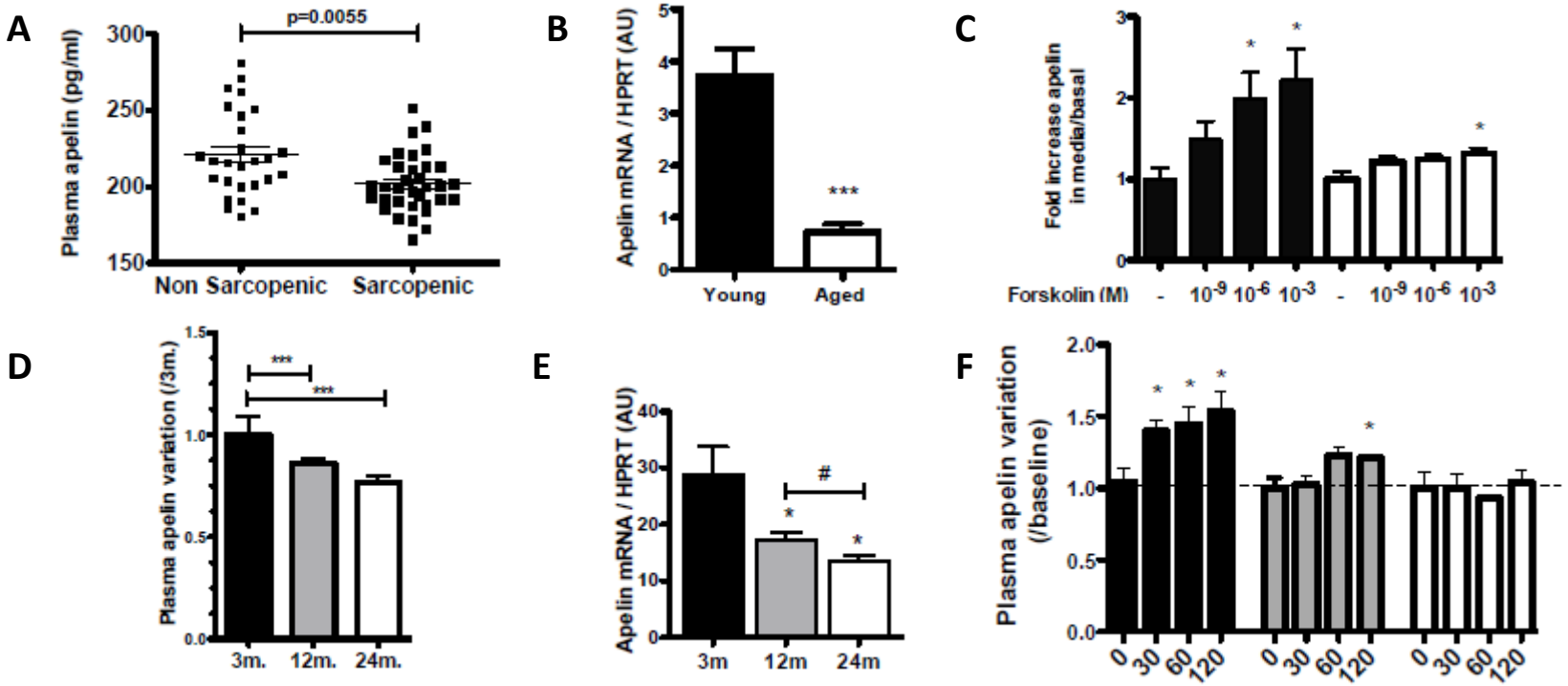
Cohort & animal studies



Activity-induced muscle apelin production is blunted during aging in human and mice.

A: Plasma apelin levels in age-matched sarcopenic (n=27) or non-sarcopenic (n=34) patients from MAPT cohort. **B**: Apelin expression in aged and young donors differentiated myotubes. Data represent mean ± s.e.m (n=4 independent experiments). **C**: Apelin accumulation in media of human myotubes (young, black bars ; aged, white bars) after forskolin treatment (20 min). Data represent mean ± s.e.m (n=4 independent experiments). **D**: Plasma apelin variation in middle-aged (grey bar) and aged (white bar) mice compared to young animals (black bar). Data represent mean ± s.e.m (n=6 animals/group). **E**: Apelin expression (mRNAin plantaris-isolated fibers in mice. Data represent mean ± s.e.m (n=6 animals/group). **F**: Plasma apelin variation after a 30, 60 or 120 minutes treadmill-induced physical exercise in young, middle-aged and aged mice. Data represent mean ± s.e.m (n=4-6 animals/group).

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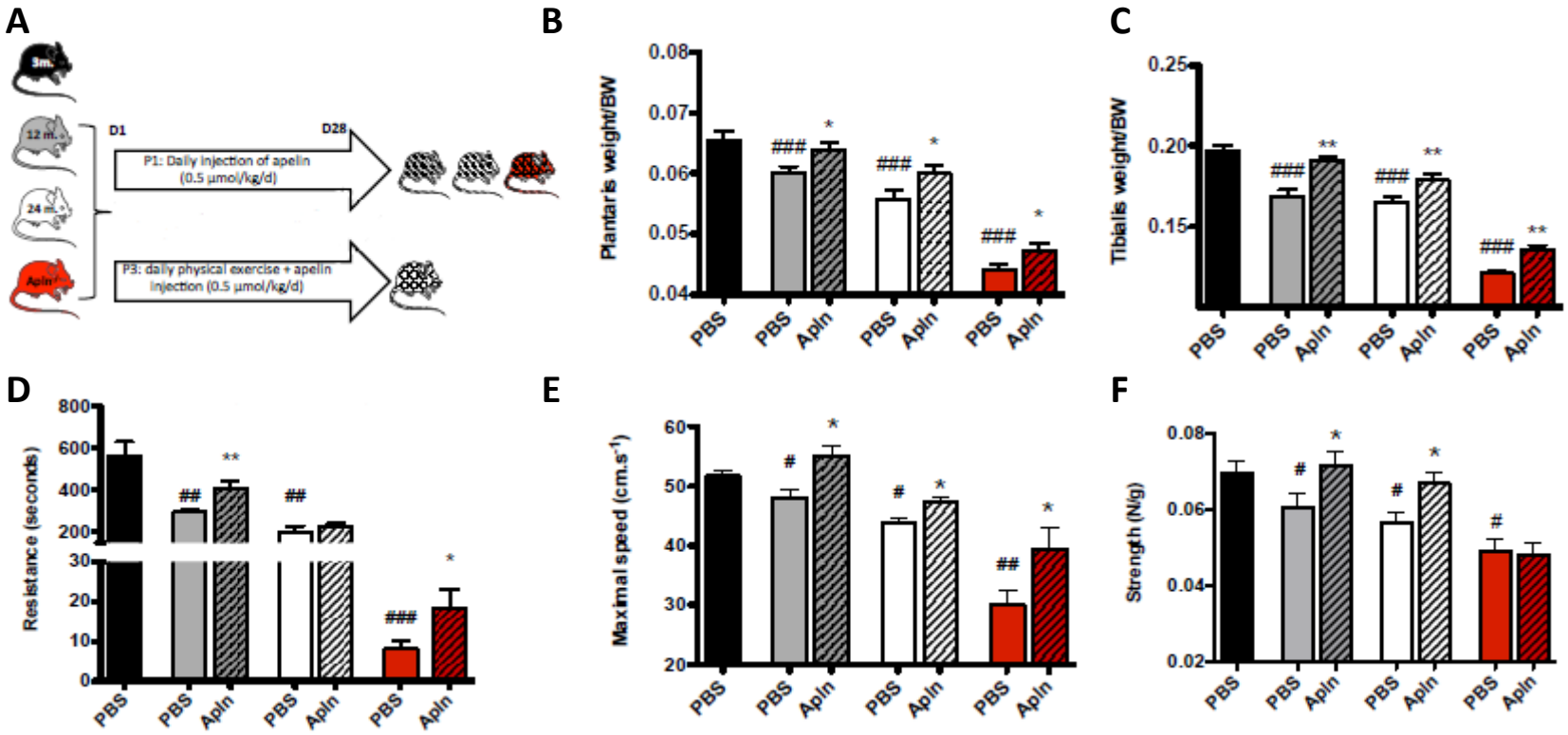
Animal studies



Chronic apelin supplementation reverses age-associated muscle weakness.

A: Protocols of apelin supplementation. **B,C**: Plantaris and tibialis weight normalized to body weight after 28 days of daily i.p apelin supplementation (hatched bars) (n=20 animals/group pooled from 3 different experiments). **D, E, F**: Apelin treatment enhances muscle function in aged mice. Resistance (D), endurance (E) and strength (F) were evaluated in wild type (3, 12 and 24 m.o, respectively white, grey and black bars) and apln-/- (12 m.o, red bars) mice daily treated by apelin. Data represent mean ± s.e.m (n=8 animals)

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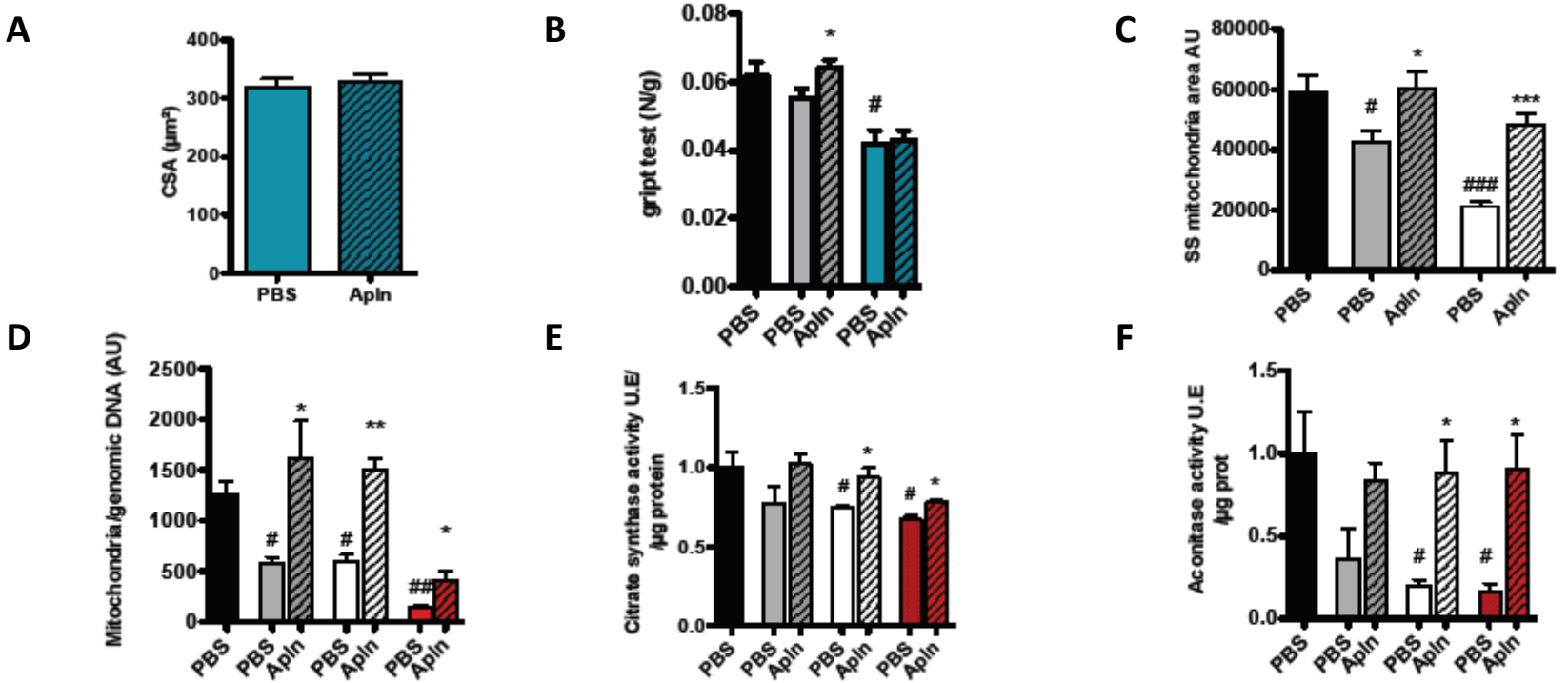
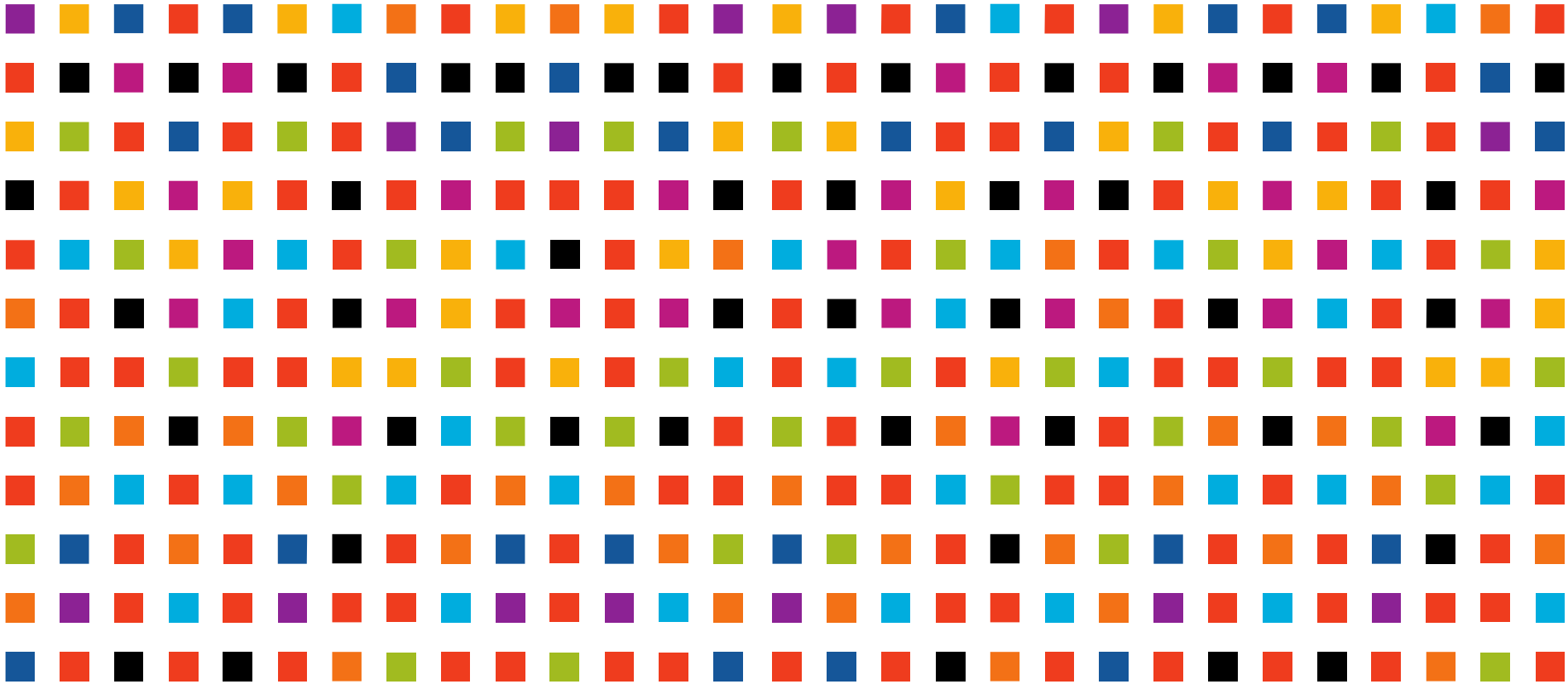


Apelin promotes AMPK-induced mitochondriogenesis in sarcopenic skeletal muscle fibers.

A: Cross sectional area (CSA) of tibialis muscle from wild type or AMPK-DN middle aged (12 m.o) mice daily treated (hatched bar) or not (empty bar) by apelin (0.5 µmol/kg/d) during 28 days. (n=10 animals/group). **B**: Strength measured by grip test in wild type (12 m.o mice, grey bars) and AMPK-DN (12 m.o, blue bars) treated (hatched bars) or not by apelin (0.5 µmol/kg/d) during 28 days. Young mice (3 m.o, black bar) strength is given as a positive control (n=10 animals/group). **C**: Quantification of mitochondrias area in tibialis muscle (n=6 animals/group, 3 images/animal). **D**: Mitochondria DNA content evaluated by the ratio of a mitochondrial encoded gene (cox1) and a nuclear-encoded gene (cyclophilin A) in tibialis muscle. **E, F**: Citrate synthase and aconitase activities in *tibialis* muscle (n=6 animals/group).



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr