SELECTED OPPORTUNITIES IN NEUROSCIENCE

Anti Notch3 antibody for CADASIL treatment (BIO11607)

ANTI NOTCH3 ANTIBODY FOR CADASIL TREATMENT (BIO11607)

Product factsheet

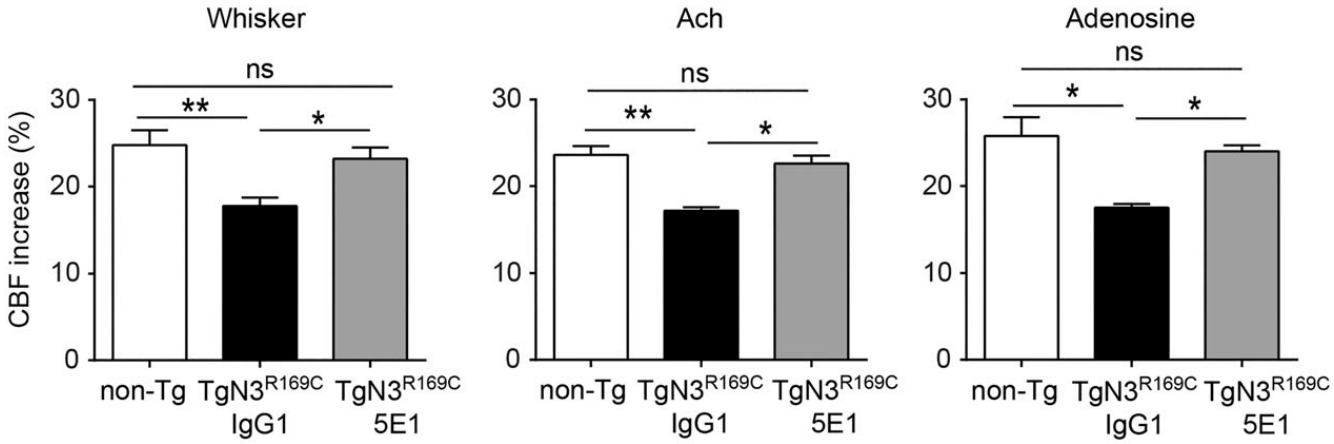
- **Product: Monoclonal Antibody**
- **Mechanism :**
  - CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is the most common hereditary cerebral small vessel disease.
  - CADASIL is caused by dominant mutations that alter the number of cysteine residues in the extracellular domain of Notch3 (Notch3ECD), a heterodimeric receptor predominantly expressed in blood vessels
  - These mutations lead to extracellular deposition of Notch3 ectodomain (Notch3ECD) around smooth muscle cells or pericytes in small vessels
  - There is no disease modifying treatment
- **Phase of development: POC in vitro and in vivo**
  - Several weeks of passive immunization targeting Notch3ECD in a CADASIL mouse model protects against cerebrovascular dysfunction
- **Potential applications:** CADASIL
- **Patents:** Immunological treatment of CADASIL. WO2016046053A1. Priority: 2014/09/25
- **Publications :**
  - Ghezali L., et al., 2018. Notch3ECD immunotherapy improves cerebrovascular responses in CADASIL mice. **Ann Neurol.** 2018.
  - Monet-Leprêtre et al., 2013. Abnormal recruitment of extracellular matrix proteins by excess Notch3 ECD: a new pathomechanism in CADASIL.

ANTI NOTCH3 ANTIBODY FOR CADASIL TREATMENT (BIO11607)

Proof of Concept

Chronic administration of 5E1 protects against cerebrovascular dysfunction in a CADASIL mouse model

- TgNotch3R169C mice and wildtype (WT) littermates were treated 4 months with weekly injections of 5E1 monoclonal antibody or control IgG1 antibody (10 mg/kg).
- Cerebral blood flow (CBF) increases evoked by whisker stimulation, the endothelium-dependent vasodilator acetylcholine (Ach), or the smooth muscle-dependent vasodilator adenosine were analyzed at study completion



- CBF responses were strongly attenuated in IgG1-treated TgNotch3R169C mice compared to WT but were rescued in 5E1-treated mice.

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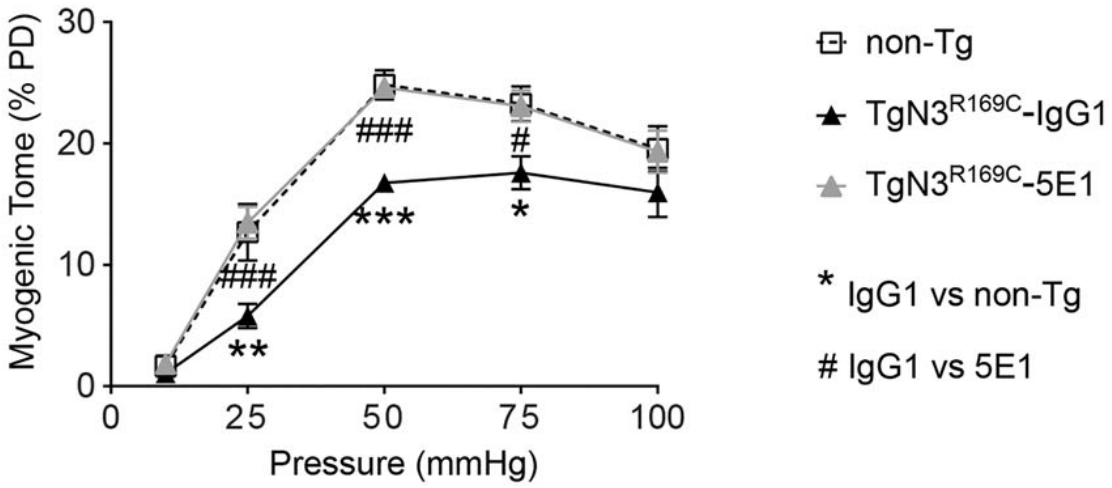
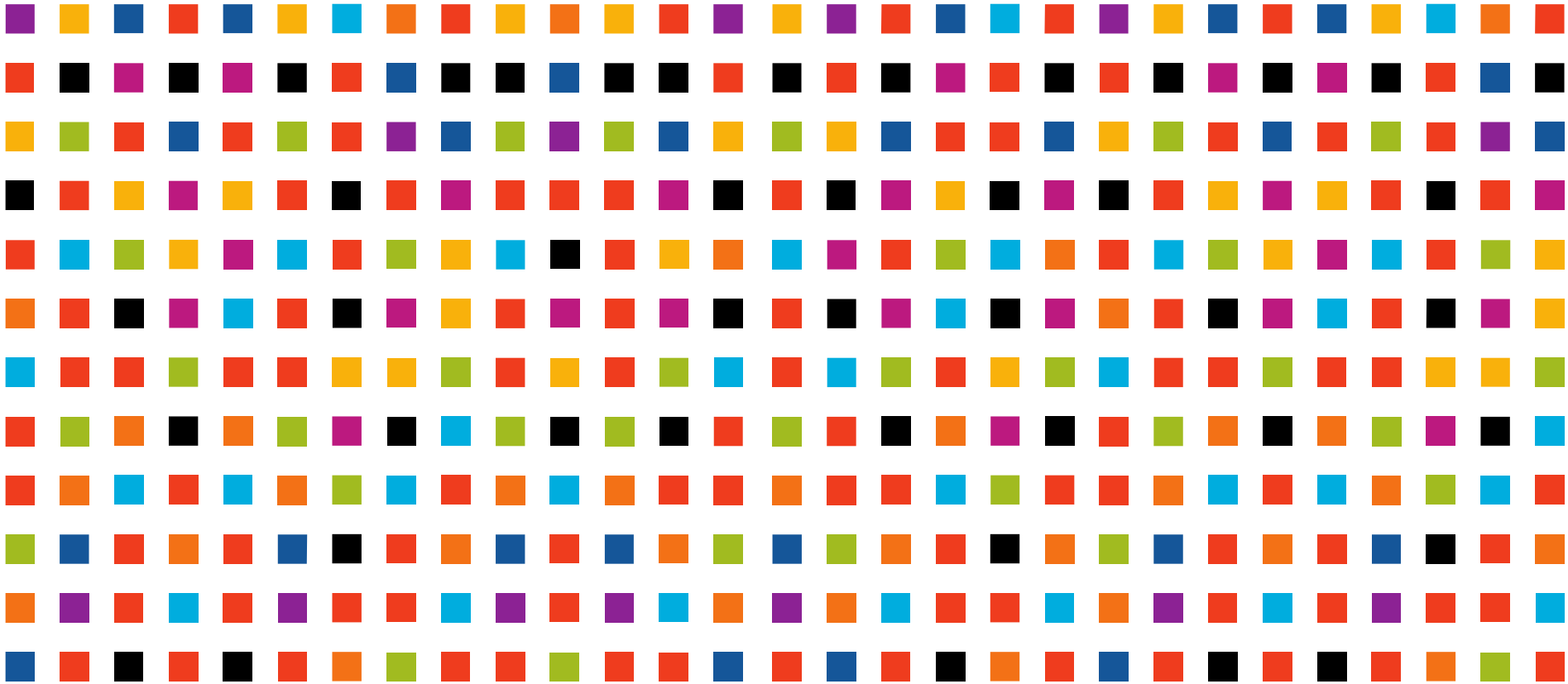
Proof of Concept

Chronic administration of 5E1 protects against cerebrovascular dysfunction in a CADASIL mouse model

- TgNotch3R169C mice and wildtype (WT) littermates were treated 4 months with weekly injections of 5E1 monoclonal antibody or control IgG1 antibody (10 mg/kg).
- Myogenic responses of brain arteries were analyzed at study completion



- Myogenic responses were strongly reduced in IgG1-treated TgNotch3R169C mice but were rescued in 5E1-treated mice.



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