SELECTED OPPORTUNITIES IN NEUROSCIENCE

VDAC1 inhibition for the treatment of peripheral demyelination (BIO15042)

VDAC1 INHIBITION FOR THE TREATMENT OF PERIPHERAL DEMYELINATION (BIO15042)

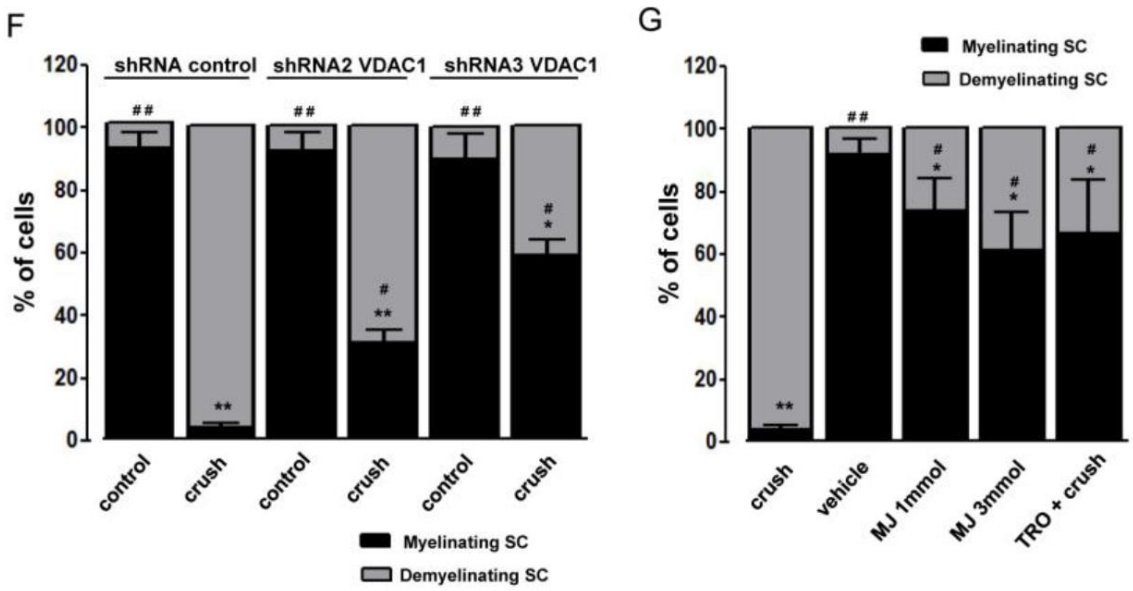
Product factsheet

- **Product: VDAC inhibitor such as Olesoxime (TRO19622)**
- **Mechanism:** The release of calcium by mitochondria through VDAC1 is the earliest step recorded after nerve injury and this step is necessary and sufficient for triggering Schwann Cells demyelination program
- **Phase of development: in vivo POC**
  - **VDAC1 shRNA or a VDAC1 inhibitor (TRO19622) reduces** mitochondrial calcium release and thus the following molecular signs of **demyelination**
    - Increase in mitochondrial matrix pH
    - decrease of mitochondrial motility
    - Schwann cells dedifferenciation
  - **In vivo blockade of VDAC in diabetic or CMT animal models reduces demyelination** and mitochondrial abnormalities
  - Ongoing product development
- **Potential applications: Demyelinating neuropathies** (CMT, ALS, Diabetic neuropathy,Tangier disease, Metachromatic leukodystrophy, Fabry's disease, hypothyroïd neuropathies, …)
- **Patents: PCT application** Priority 18/05/2015

VDAC1 INHIBITION FOR THE TREATMENT OF PERIPHERAL DEMYELINATION (BIO15042)

Proof of Concept

The release of calcium by mitochondria through VDAC1 is the earliest step recorded after nerve injury and this step is necessary and sufficient for triggering Schwann Cells demyelination program



Quantification of myelinating and demyelinating SC frequency after VDAC1 silencing (F), and MJ and TRO19622 treatment (G). methyl jasmonate (MJ) is a drug that increases VDAC permeability

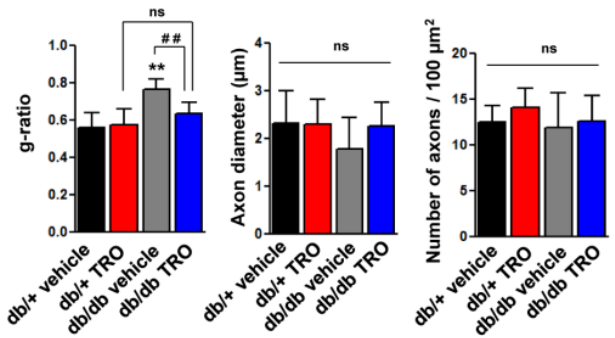
Data are expressed as the mean ± SEM. Error bars indicate SEM. n = 3 to 5 mice for each group. Asterisks and hashes mark statistical differences over non-crushed and crushed nerves respectively. Two-tailed Student's *t* test: * and #p < 0.05, ** and ##p < 0.01, *** and ### p< 0.001.

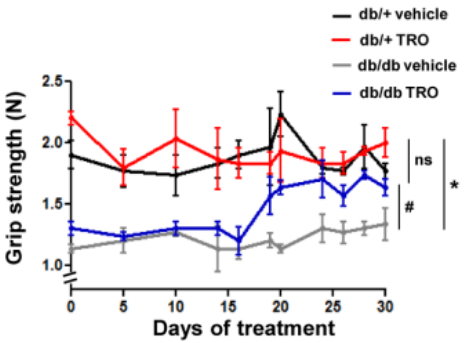
VDAC1 INHIBITION FOR THE TREATMENT OF PERIPHERAL DEMYELINATION (BIO15042)

Proof of Concept

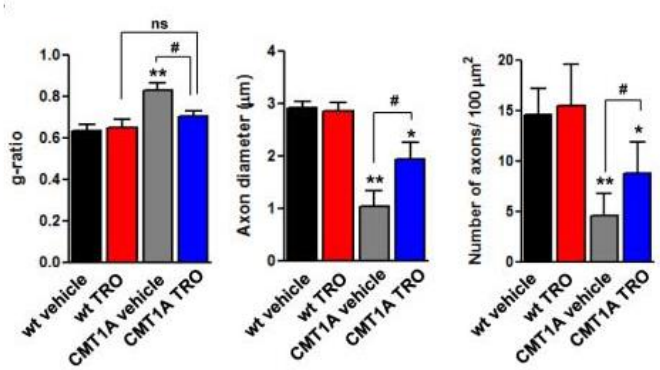
VDAC1 silencing and inhibition prevent SC mitochondrial anomalies and improve the phenotype of:

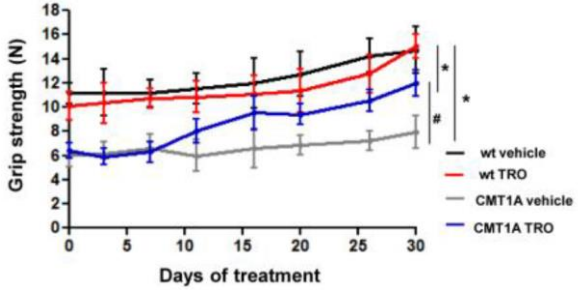
diabetic mice





CMT1A rats





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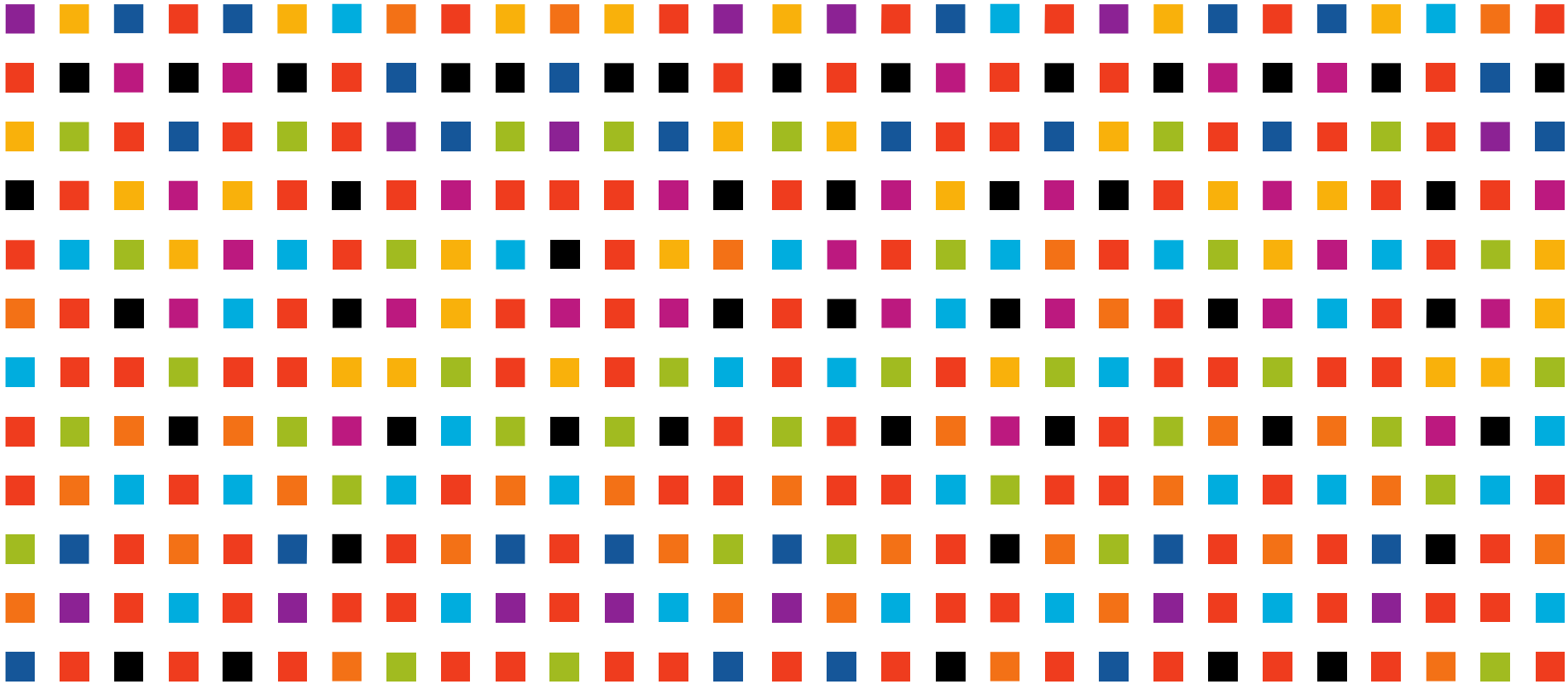

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