Capture en vie réelle de l'activité des canaux ioniques responsables de l'excitation neuronale

Une prospective scientifique pour l'ATS grenobloise

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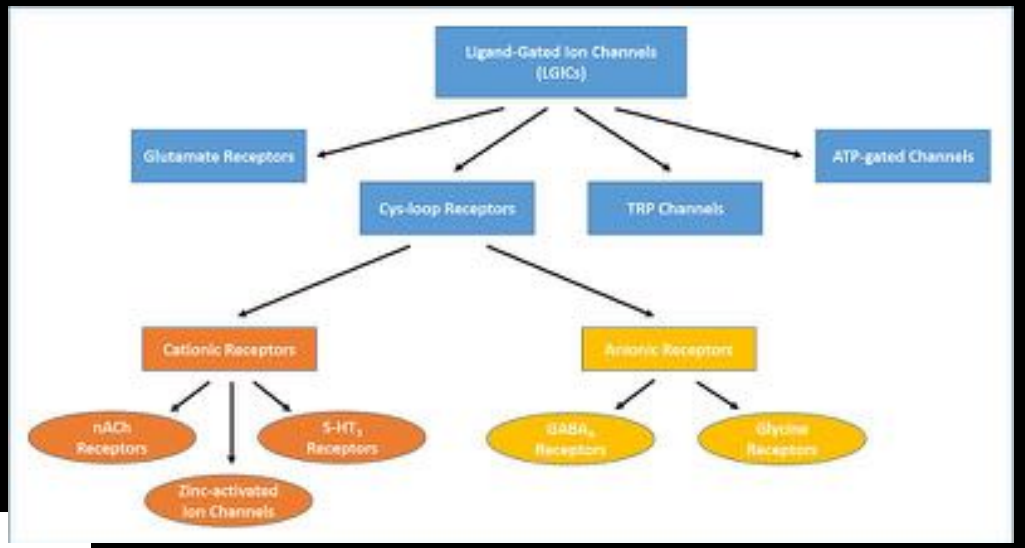
Université Grenoble Alpes

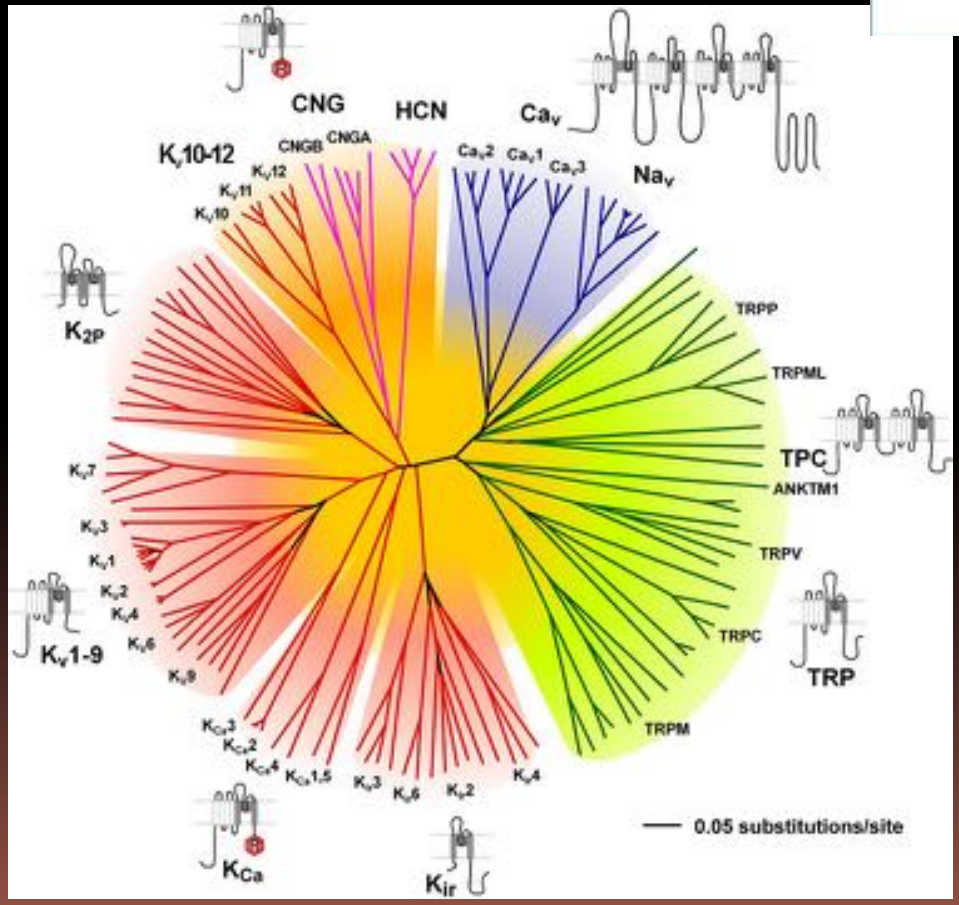
cnrs

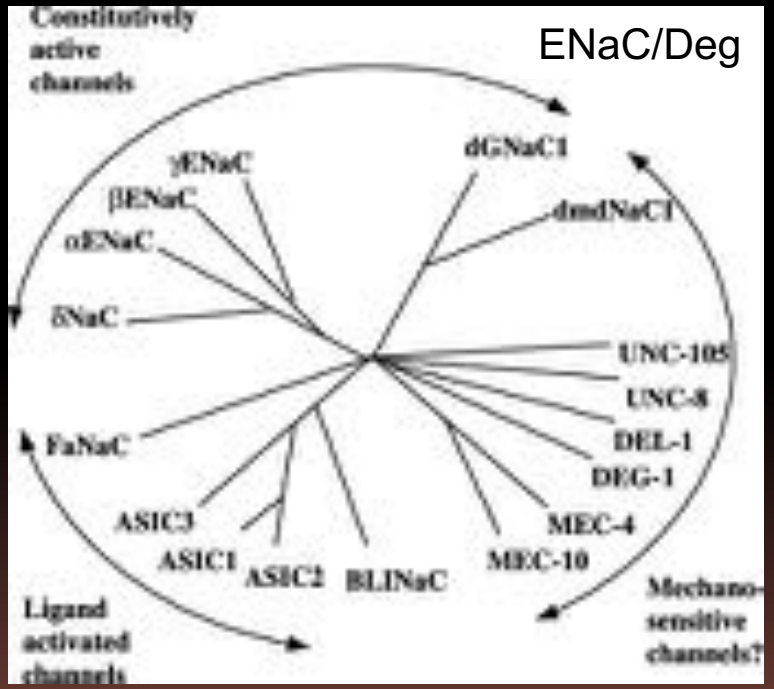
LabEx ICST
Ion Channel Science and Therapeutics

Inserm
La science pour la santé
From science to health

Ion channels superfamilies in mammals

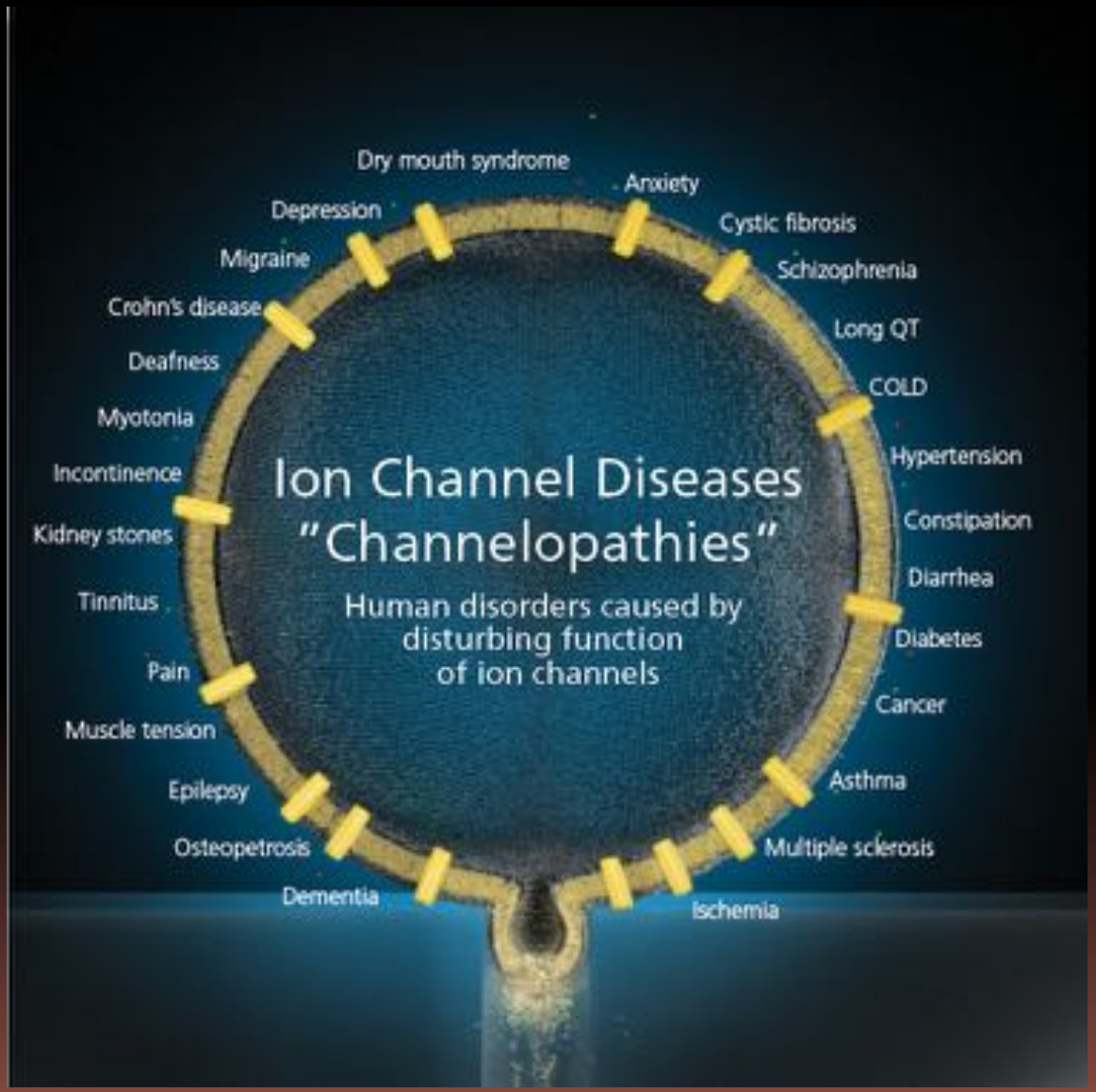






Ion channels in internal membranes
RyR/IP3, mitochondrial,…

Ion channels: diseases and therapeutics

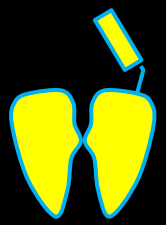


Drugs modulating ion channels activity generate more than 10 billion € in worlwide sales per year :

anaesthetics,
analgesics,
anxiolytics,
anti-epileptics,
anti-arrhythmics,
anti-diabetics,
etc.

Capturing ion channels activity in real life

Ion channel state



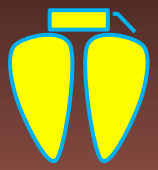
closed

open

ionic current

Membrane potential (V_m) change

Ion concentration change (ionic current)



inactivated

Technologies

- **Electrode techniques:** *patch clamp, MEAs, ISEs, …*
- **Optical techniques:** *imaging, optogenetics, photostimulation,…*
- **Other techniques:** molecular biology, biochemistry, artificial membranes, pharmacology, biosensors, computational…

Ion channels in Grenoble: meetings in 2017, 2018, 2019

Organizer: Alexandre Bouron

Jacques Thelu
Jean-Pierre Alcaraz
Donald Martin
Eric Esteve

Mohamed Benharouga
Alexandre Bouron

Marco Canepari

Alain Buisson
Fabien Lanté
Mireille Albrieux
Isabelle Marty
Julien Faure
Lauriane Travard

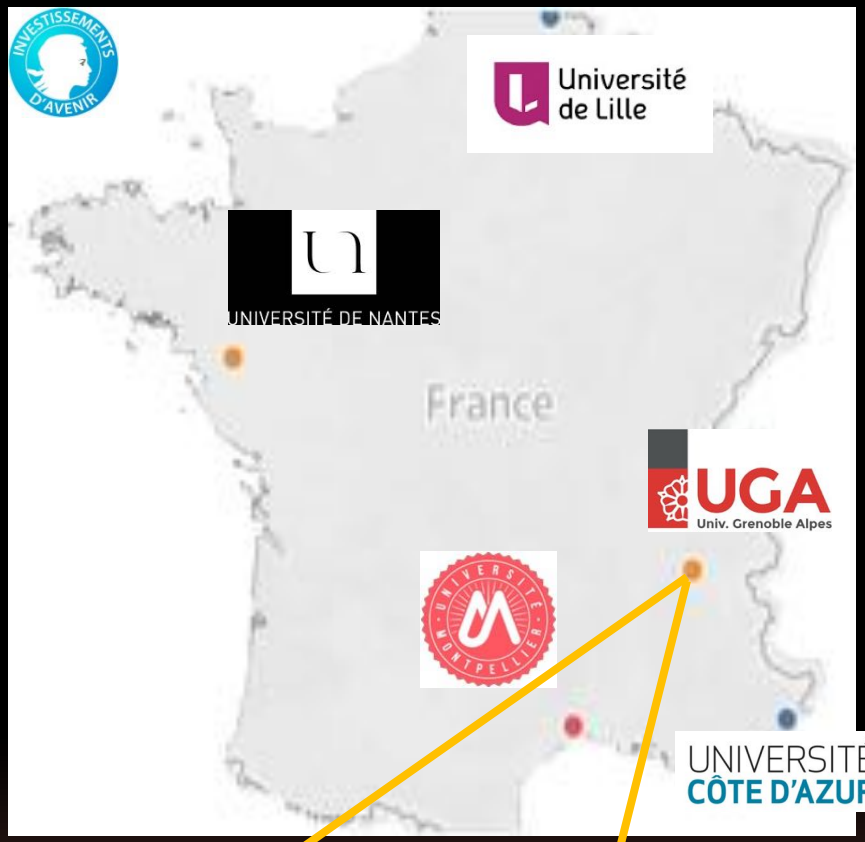
Christophe Moreau
Michel Vivadou
Jacques Neyton
Hugues Nury
Beatrice Schaak

Olivier Destang
Christophe Arnoult

Cécile Delacour

LABEX ICST
ION CHANNEL SCIENCE AND THERAPEUTICS

Coordinator: Florian Lesage



Michel Vivadou

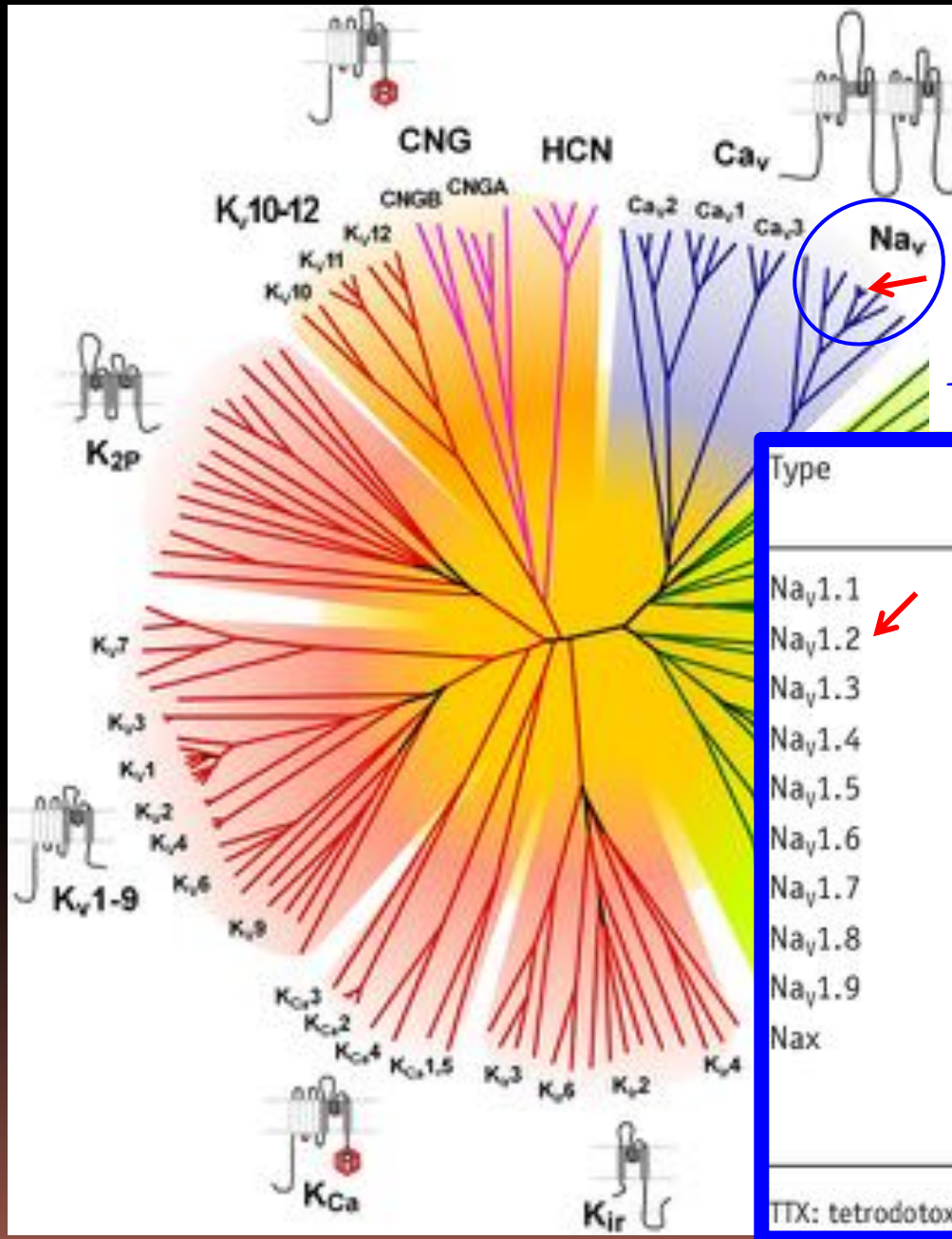
ibs Institut de Biologie Structurale

Marco Canepari

LiPhy

- Major scientific achievements (2012-2020)
  - ➢ identification of novel targets of therapeutic interest, ion channel and their modulators
  - ➢ validation of targets, at the molecular, cellular, organ and animal levels
  - ➢ development of new approaches for the study of ion channels
  - ➢ emergence of young group leaders in the ion channel field
- > 500 publications (30% of them related to a disease, a therapeutic effect or a pathological state), 13 patents
- 32 PhDs
- Program in progress (2021-2025)
  - ➢ exploring the role of chloride channels
  - ➢ oncochannelopathies, sodium-calcium interplay in cancer cell metastatic potential
  - ➢ protection against epilepsy, stroke and myocardial infarction
  - ➢ excitability disorders in epilepsy, autism and pain
  - ➢ zebrafish ion channel models
  - ➢ high-throughput drug screening with automated patch clamp system
  - ➢ control of ion channels by light
- 16 PhDs

Ion channels and neuronal excitability



Na^+ *channels*

Type	Gene	Expression pattern	TTX sensitive
$Na_v1.1$	SCN1A	CNS and PNS	+
$Na_v1.2$	SCN2A	CNS	+
$Na_v1.3$	SCN3A	CNS and PNS	+
$Na_v1.4$	SCN4A	Skeletal muscle	+
$Na_v1.5$	SCN5A	Heart	–
$Na_v1.6$	SCN8A	Nodes of Ranvier	+
$Na_v1.7$	SCN9A	PNS and CNS	+
$Na_v1.8$	SCN10A	Sensory Neurons	–
$Na_v1.9$	SCN11A	PNS and CNS	–
Nax	Neuronal and non-neuronal tissues	SCN7A	

TTX: tetrodotoxin; CNS: central nervous system; PNS: peripheral nervous system.

Voltage-gated Na^+ channels mediate the action potential

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN and A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

Summary of equations and parameters

We may first collect the equations which give the total membrane current I as a function of time and voltage. These are:

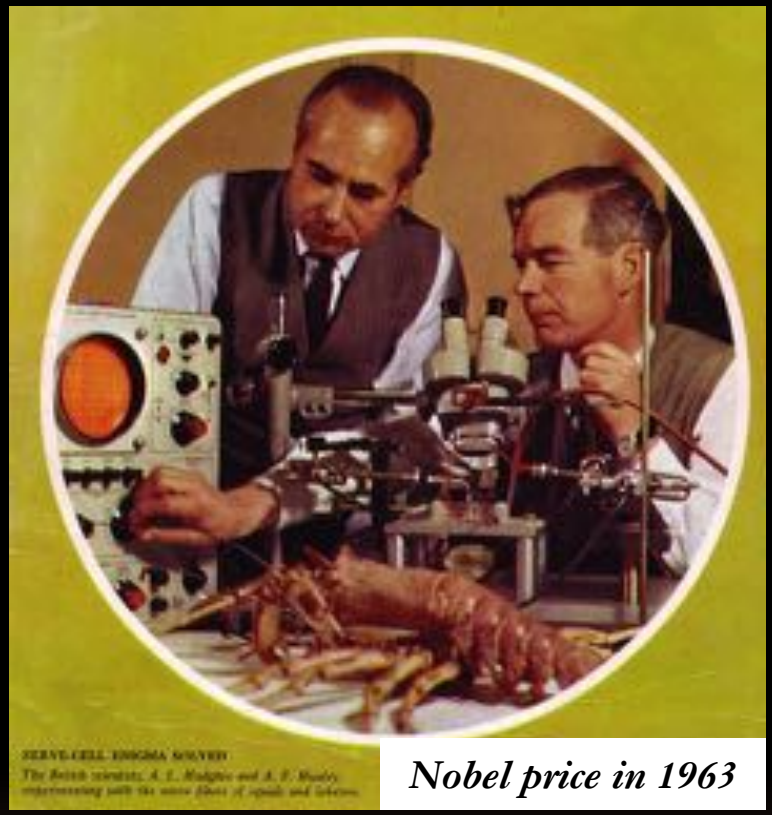
$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l), \quad (26)$$

where

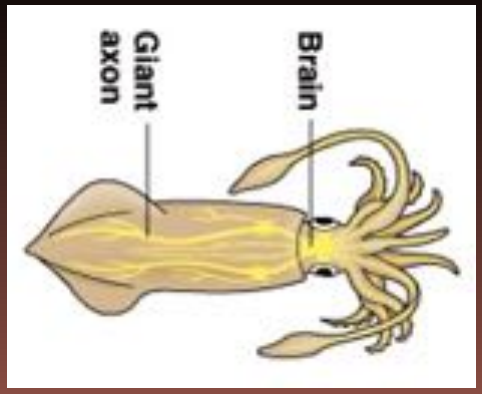
$$dn/dt = \alpha_n (1 - n) - \beta_n n, \quad (7)$$

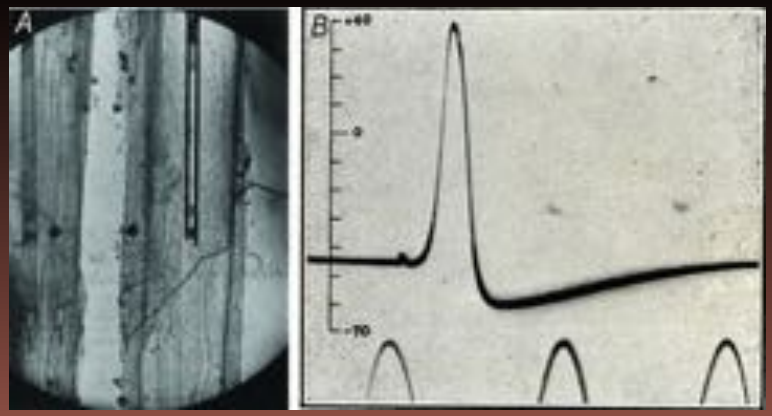
$$dm/dt = \alpha_m (1 - m) - \beta_m m, \quad (15)$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h, \quad (16)$$



Nobel price in 1963





Donations can be mailed to: FamilieSCN2A Foundation, PO Box 82, E. Longmeadow, MA 01028 DONATE NEWSLETTER STORE BLOG

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ABOUT US & OUR MISSION

Home About Us

We are an organization created by parents of children diagnosed with rare forms of Epilepsy and Autism as a result of a change in the SCN2A gene.

Our **vision** is to find effective treatments and a cure for SCN2A related disorders.

Our **mission** is to improve the lives of those affected by SCN2A related disorders through research, public awareness, family support and patient advocacy.

We are a registered 501(c)(3) organization.

To accomplish our vision and mission, we will:

- Coordinate and collaborate with the global scientific community to understand the function of the SCN2A gene in order to develop effective treatments and a cure for SCN2A disorders
- Increase medical community and public awareness of the complexity and potential severity of SCN2A disorders
- Provide educational and emotional support for those affected by SCN2A disorders


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We are an organizatio
result of a change in t
Our vision is to find ef
Our mission is to imp
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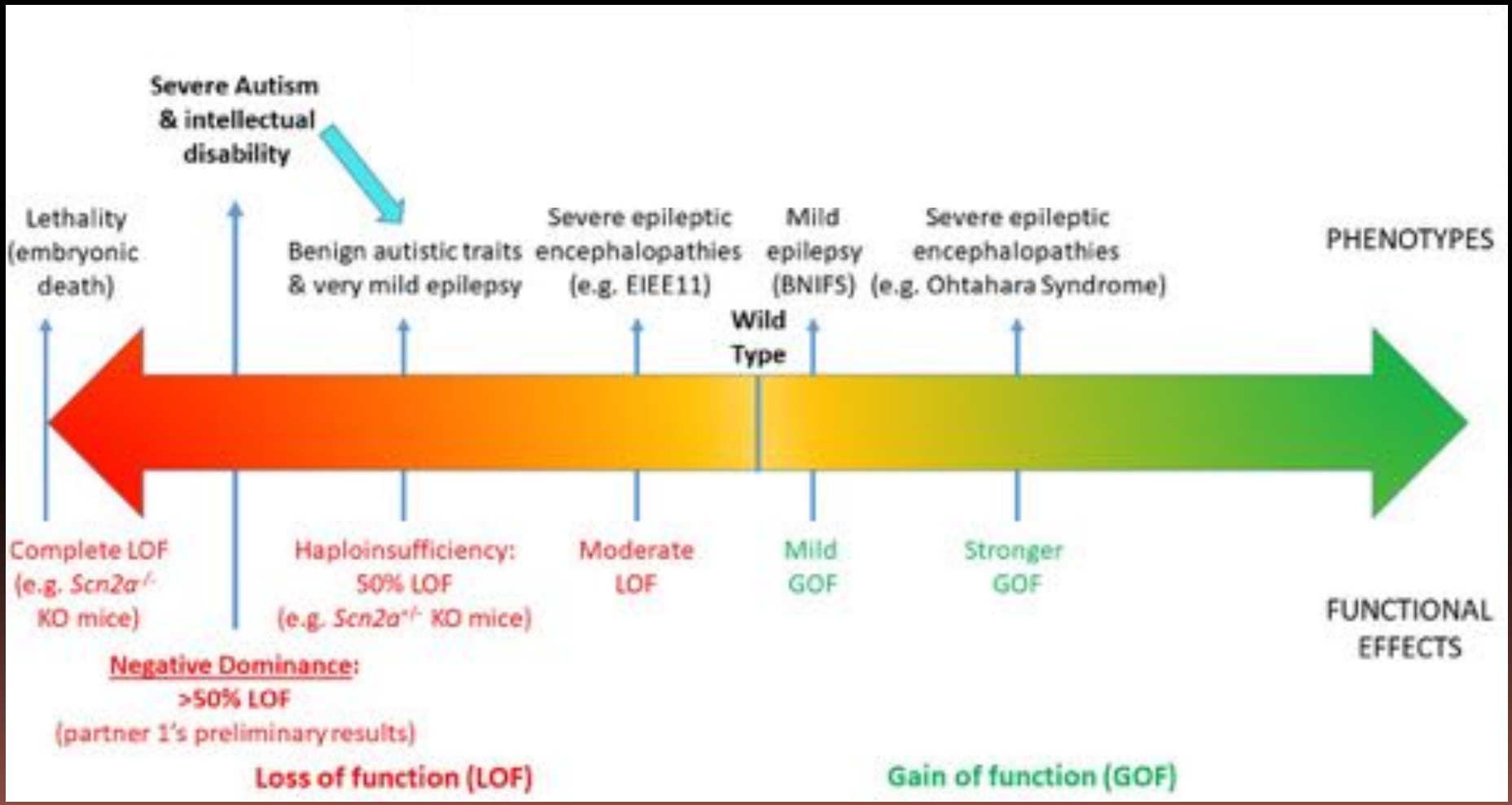
We are a registered 50
To accomplish
Coordinate and collaborate with the global scientific community to understand the function of the SCN2A gene in order to develop effective treatments and a cure for SCN2A disorders
Increase medical community and public awareness of the complexity and potential severity of SCN2A disorders
Provide educational and emotional support for those affected by SCN2A disorders
SCN2A is one of the genes most commonly associated with early-onset epilepsy, and has recently been linked to autism spectrum disorder and developmental delay. SCN2A encodes a neuronal voltage gated sodium channel, NaV1.2 that is primarily found in excitatory neurons throughout the brain. Different mutations in SCN2A contribute to the different forms of epilepsy, including benign infantile seizure and epileptic encephalopathy, and how these mutations contrast with those that contribute to autism. The distribution of NaV1.2 within neurons develops over the first few years of life and these changes affect neuronal function. This development has important implications for understanding these disorders and in designing potential therapies in the future.

ANR: Nav12RESCUE (AAP 2021: Innovation biomédicale, 2022-2025)

Restauration des fonctions du canal sodique Nav1.2 dans des troubles neurodéveloppementaux graves

- **Coordinator:** **Massimo Mantegazza, IPMC, Nice**
- **Partner 1:** **Michel De Waard, Thorax, Nantes**
- **Partner 2:** **Marco Canepari, LIPhy, Grenoble**

Spectrum of Nav1.2 channelopathies: Courtesy of Massimo Mantegazza



Capturing Na^+ channels activity in real life

J Physiol 599.1 (2021) pp 49–66

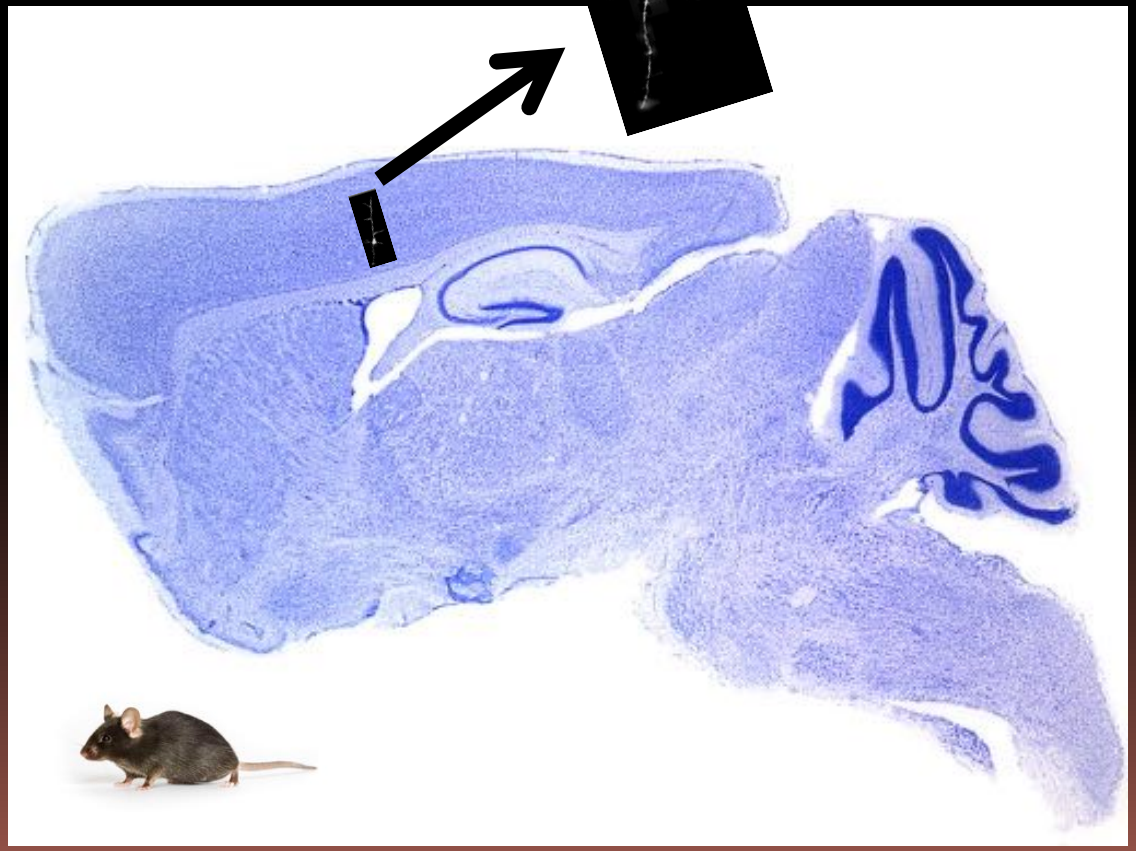
TECHNIQUES FOR PHYSIOLOGY

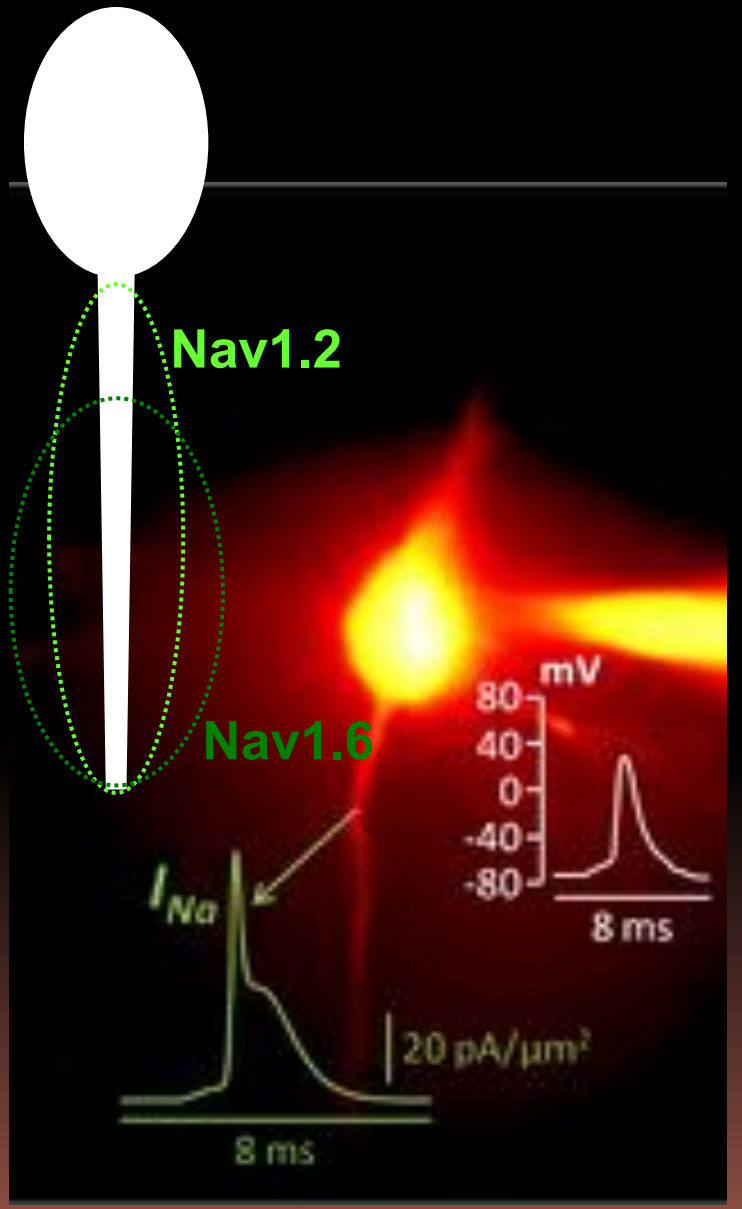
Optical measurement of physiological sodium currents in the axon initial segment

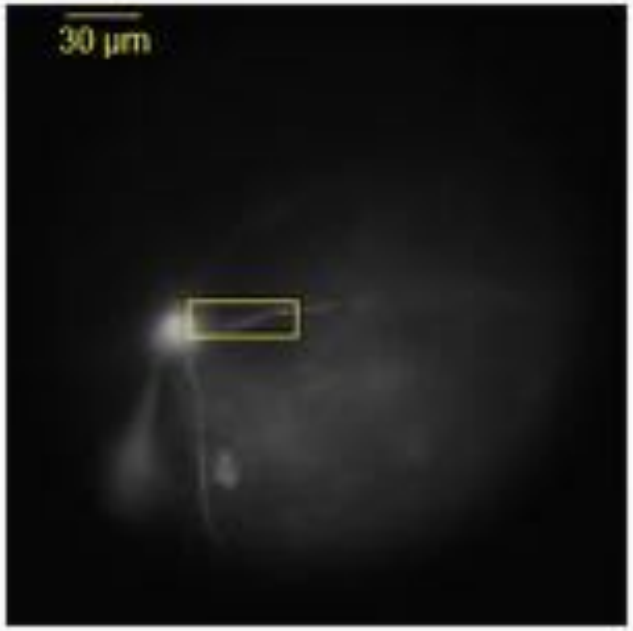
Luiza Filipis[1,2] and Marco Canepari[1,2,3]

[1]*University of Grenoble Alpes, CNRS, LIPhy, Grenoble, F38000, France*
[2]*Laboratories of Excellence, Ion Channel Science and Therapeutics, France*
[3]*Institut National de la Santé et Recherche Médicale, France*

Edited by: Ian Forsythe & Vincenzo Marra



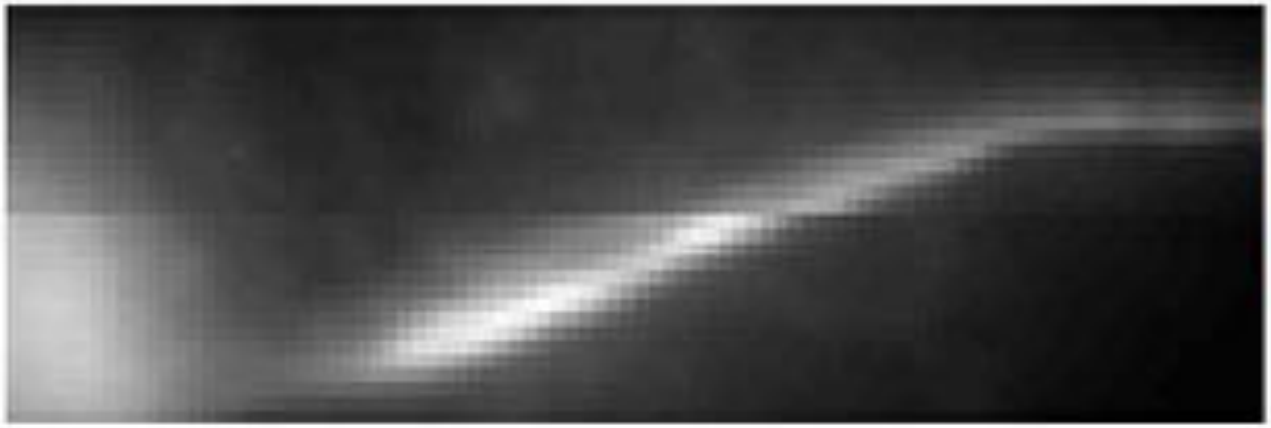




Ultrafast sodium imaging from the axon initial segment

somatic recording

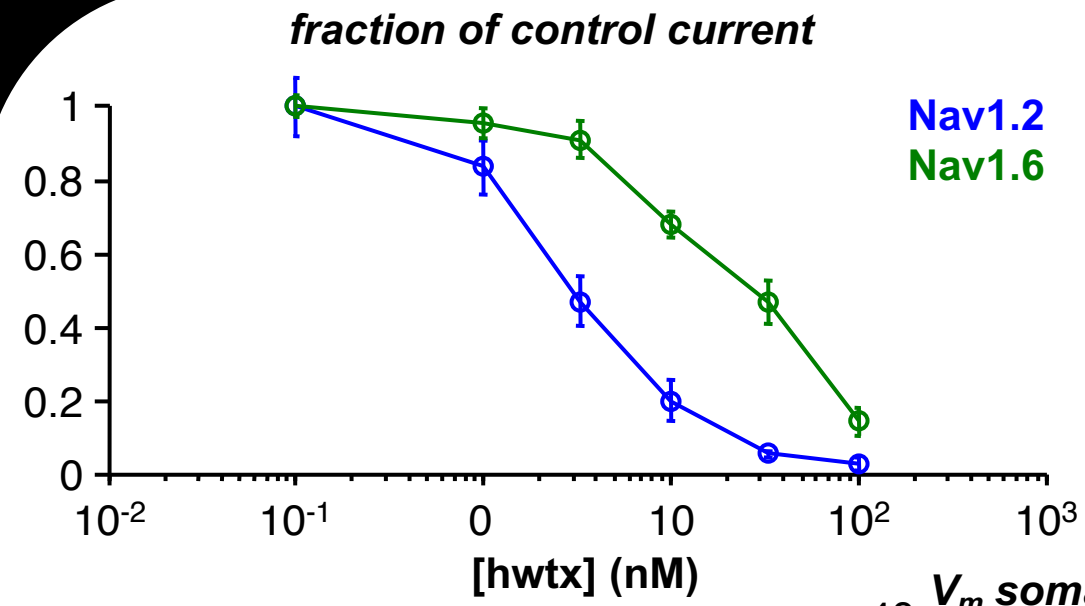
20 mV



Vidéo

0 ms

hwtx: a selective inhibitor of Nav1.2



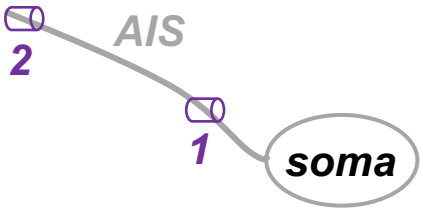
Glu Glu

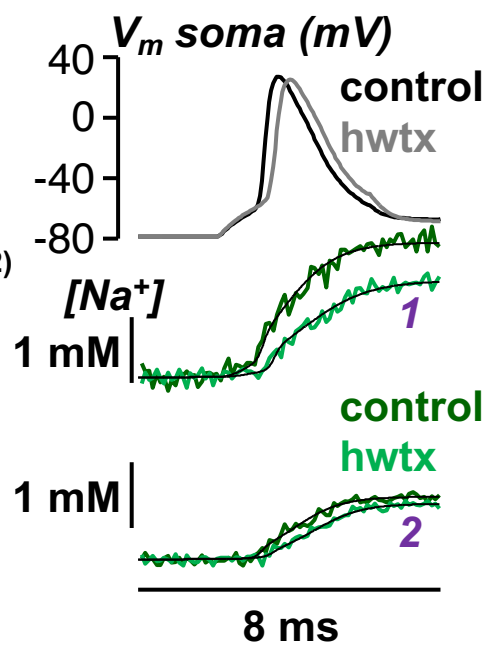
AA sequence: **Gly**-Cys[2]-Leu-**Gly**-Ile-Phe-Lys-Ala-Cys[9]-Asn-Pro-Ser-Asn-Asp-Gln-Cys[16]-Cys[17]-Lys-Ser-Ser-Lys-Leu-Val-Cys[24]-Ser-Arg-Lys-Thr-Arg-Trp-Cys[31]-Lys-Tyr-Gln-Ile-NH_2

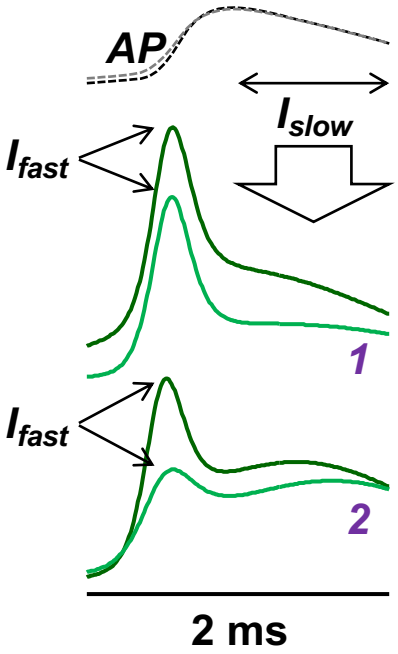
l'institut du thorax

Smartox Biotechnology

ANR: OptChemCom (Technologie pour la santé, 2018-2022)

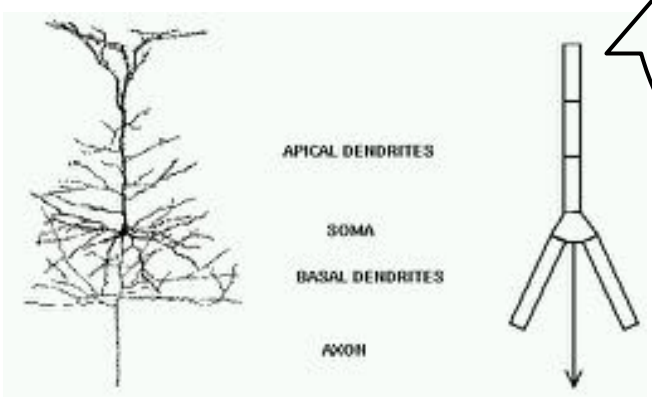






Computational approach

model of WT (healthy) neuron



predicted model of mutated neuron

real model of mutated neuron

Assessment of restoration of neuronal function after rescuing Nav1.2 WT function

Prospective scientifique

Un atelier ATS dédié au canaux ioniques?

Un réseau « canaux ionique » au sein de l'ATS?

- *Pour afficher l'activité grenobloise de technologie pour la santé appliqué aux canaux ioniques*

- *Pour mettre en place des consortia nationaux et internationaux*