About OMICS Group

OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS Group Conferences

OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Clinical & Experimental Cardiology

OMICS Group Conferences April 15-17, 2013 Hilton Chicago/Northbrook, USA

A novel mechanism of an *SCN5A* mutation causing mixed arrhythmias associated with dilated cardiomyopathy

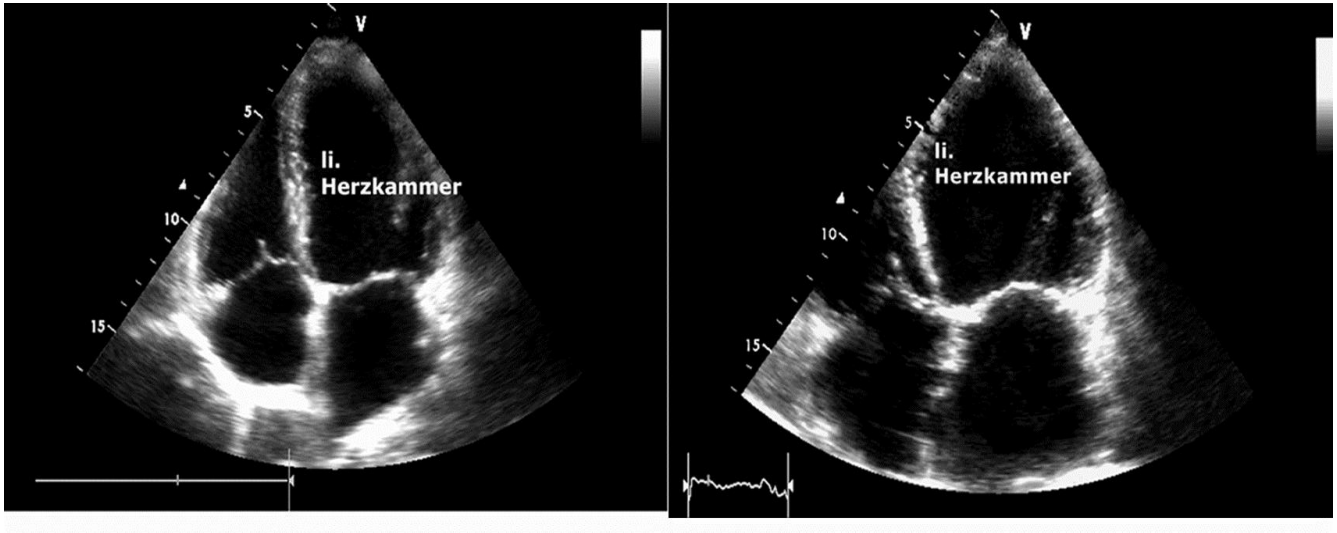
Mohamed Chahine Ph.D.
professeur titulaire

UNIVERSITÉ LAVAL
Faculté de médecine
Département de médecine

Dilated Cardiomyopathy (DCM)

Definition: Dilatation of cardiac cavities,
Impaired contractility and systolic function

Aetiology: Idiopathic, secondary, familial in at least 20-30%



SCN5A gene: Chronology

1992: Cloning and characterization of *SCN5A* *(Gellens et al)*

1995: Mapping *SCN5A* to chrom 3p21 *(George et al)*

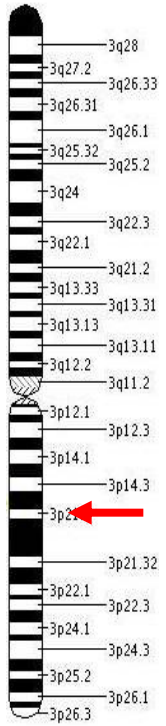
SCN5A: candidate gene for Long QT Syndrome type 3

1998: *SCN5A* mutations in Brugada Syndrome *(Chen et al)*

1999: *SCN5A* mutations in Progressive Cardiac Conduction Defect *(Schott et al)*

2003: *SCN5A* mutations in Congenital Sick Sinus Syndrome *(Benson et al)*

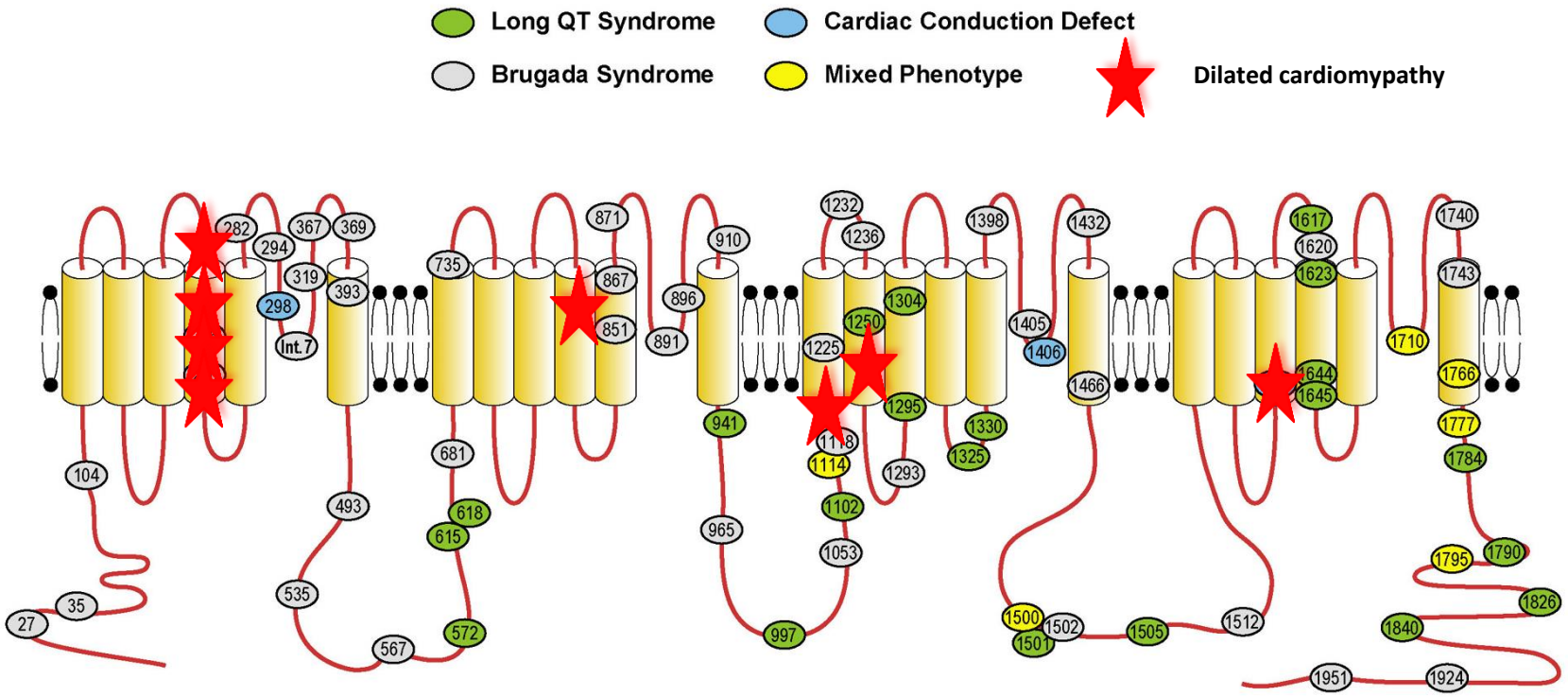
2004: *SCN5A* mutation in dilated cardiomyopathy *(McNair et al)*



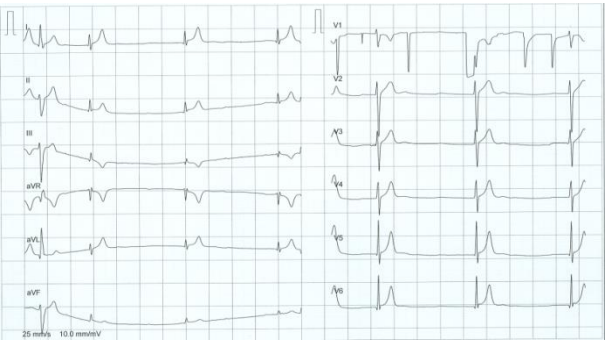
SCN5A gene is ranked as the sixth most common cause of familial DCM

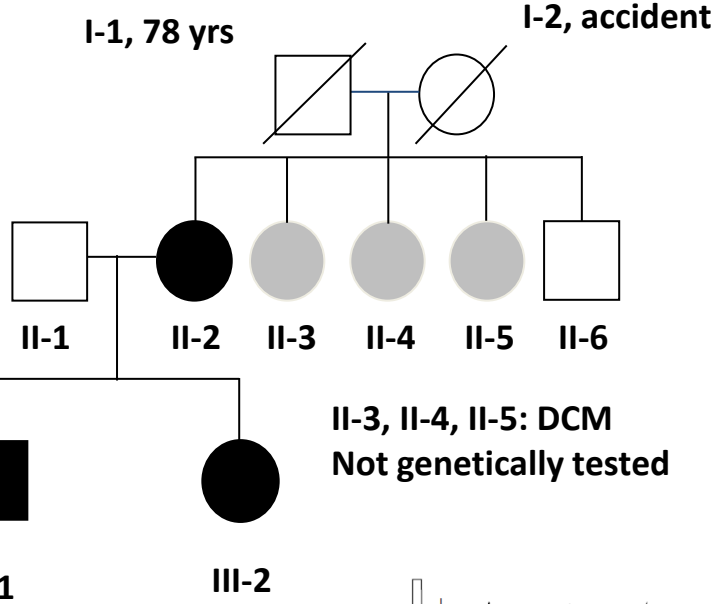
Gene†	Protein	Function	OMIM	Estimated Fraction of DCM†
LMNA	Lamin A/C	Structure/stability of inner nuclear membrane; gene expression	150330	0.06
MYH6	Alpha-myosin heavy chain	Sarcomeric protein; muscle contraction	160710	0.043
MYH7	Beta-myosin heavy chain	Sarcomeric protein; muscle contraction	160760	0.042
MYPN	Myopalladin	Sarcomeric protein; Z-disc	608517	0.035
TNNT2	Cardiac troponin T	Sarcomeric protein; muscle contraction	191045	0.029
SCN5A	Sodium channel	Controls sodium ion flux	600163	0.026
MYBPC3	Myosin-binding protein C	Sarcomeric protein; muscle contraction	600958	0.02
RBM20	RNA-binding protein 20	RNA-binding protein of spliceosome		0.019
TMPO	Thymopoietin	Also LAP2, a lamin-associated nuclear protein	188380	0.011
LAMA4	Laminin alpha 4	Extracellular matrix protein	600133	0.011
VCL	Metavinculin	Sarcomere structure; intercalated discs	193065	0.01
LDB3	LIM domain-binding 3; cypher; Z-band alternatively spliced PDZ motif-containing protein	Cytoskeletal assembly; clustering of membrane proteins	605906	0.01
TCAP	Titin-cap; telethonin	Z-disc protein that associates with titin; sarcomere assembly	604488	0.01
PSEN1/2	Presenilin 1/2	Transmembrane proteins; gamma secretase activity	104311/600759	0.01
ACTN2	Alpha-actinin 2	Sarcomere structure; anchor for myofibrillar actin	102573	0.009
CRYAB	Alpha B crystallin	Cytoskeletal protein	123590	0.007
TPM1	Alpha-tropomyosin	Sarcomeric protein; muscle contraction	191010	0.006
ABCC9	Sulfonylurea receptor 2A	Kir6.2 regulatory subunit; inwardly rectifying cardiac potassium ATP channel	601439	0.006
ACTC	Cardiac actin	Sarcomeric protein; muscle contraction	102540	0.005
PDLIM3	PDZ LIM domain protein 3	Cytoskeletal protein	605889	0.005
ILK	Integrin-linked kinase	Intracellular serine-threonine kinase; interacts with integrins	602366	0.005
TNNC1	Cardiac troponin C	Sarcomeric protein; muscle contraction	191040	0.004
TNNI3	Cardiac troponin I	Sarcomeric protein, muscle contraction; also seen as recessive	191044	0.004
PLN	Phospholamban	Sarcoplasmic reticulum calcium regulator; inhibits sarco/endoplasmic reticulum calcium-ATPase pump	172405	0.004
DES	Desmin	DAGC; transduces contractile forces	125660	0.003
SGCD	Delta-sarcoglycan	DAGC; transduces contractile forces	601411	0.003
CSRP3	Cysteine- and glycine-rich protein 3; muscle LIM protein	Sarcomere stretch sensor/Z-discs	600824	0.003
TTN	Titin	Sarcomere structure/extensible scaffold for other proteins	188840	N/A
EYA4	Eyes absent 4	Transcriptional coactivator	603550	N/A
ANKRD1	Ankyrin repeat domain-containing protein 1	Cardiac ankyrin repeat protein; localized to myopalladin/titin complex	609599	N/A
DMD‡	Dystrophin	DAGC; transduces contractile force	300377	N/A
TAZ/G4.5‡	Tafazzin	Unknown	300394	N/A

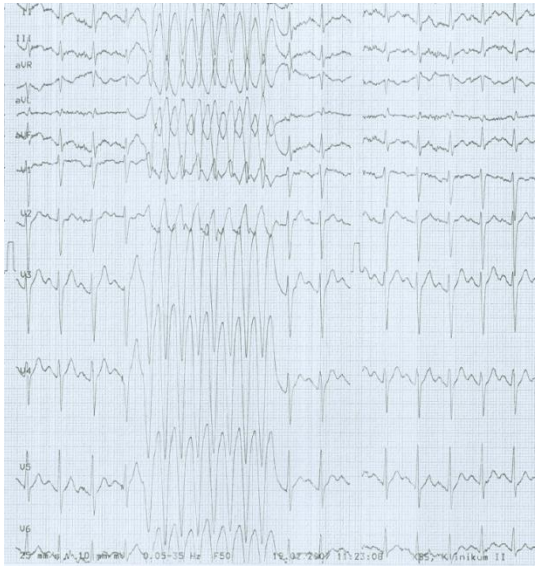
DCM and $Na_v1.5$

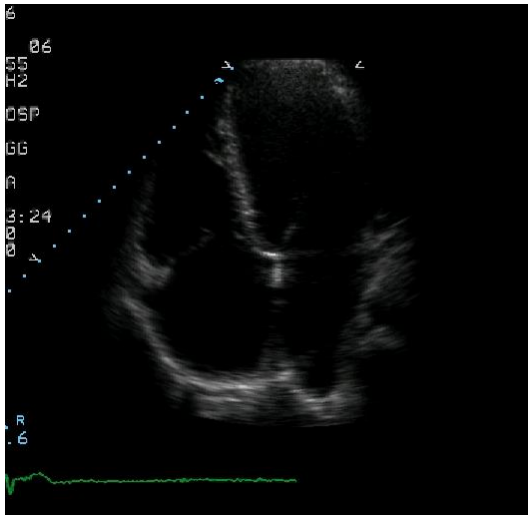


Patient with conductance disturbances, AFib, Ventricular fibrillation and DCM





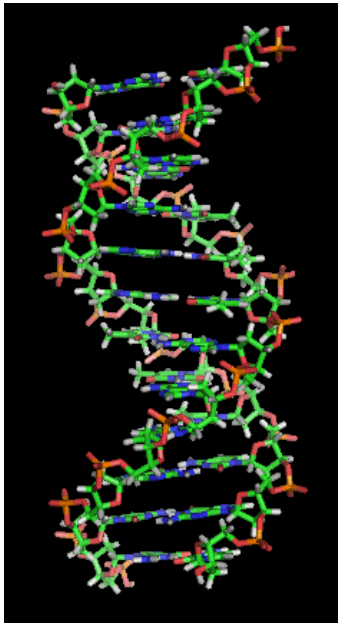




Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

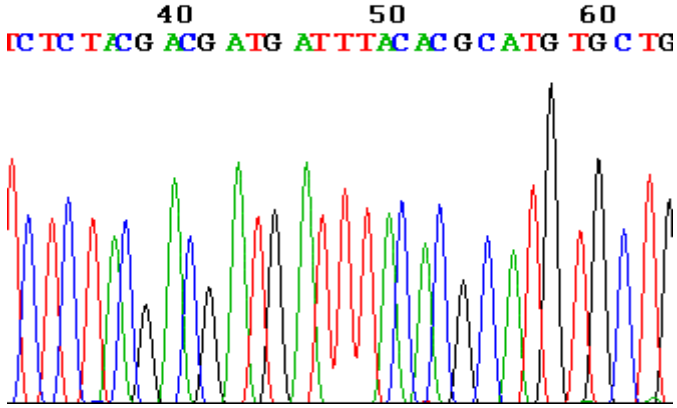
Genotyping

Collecte de sang



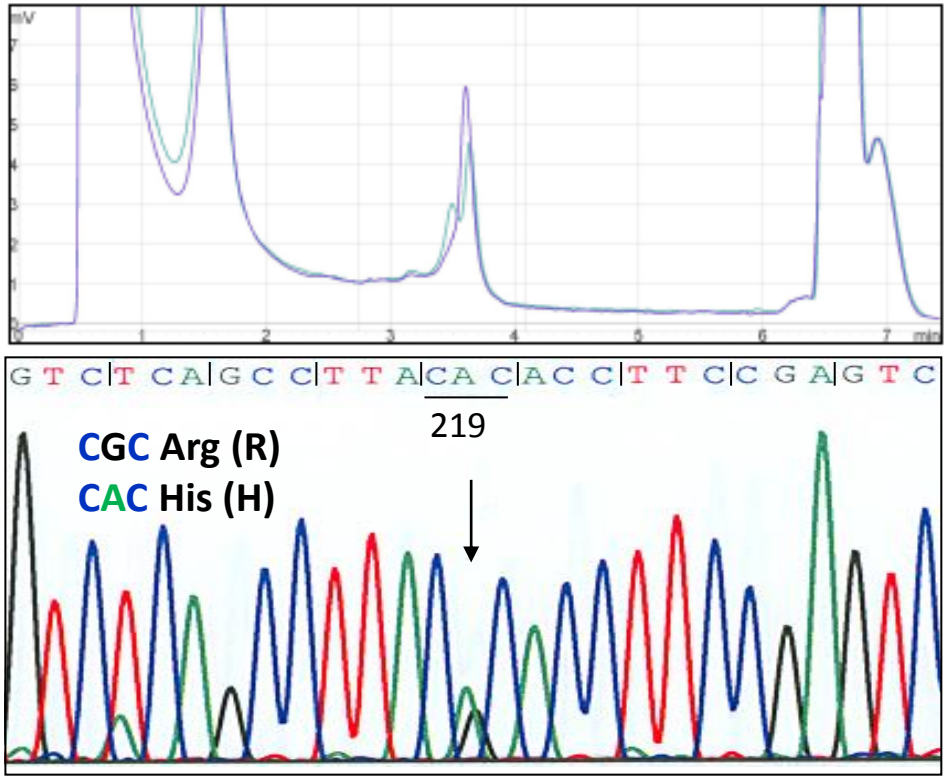
Extraction de l'DNA

PCR et dHPLC



Séquençage

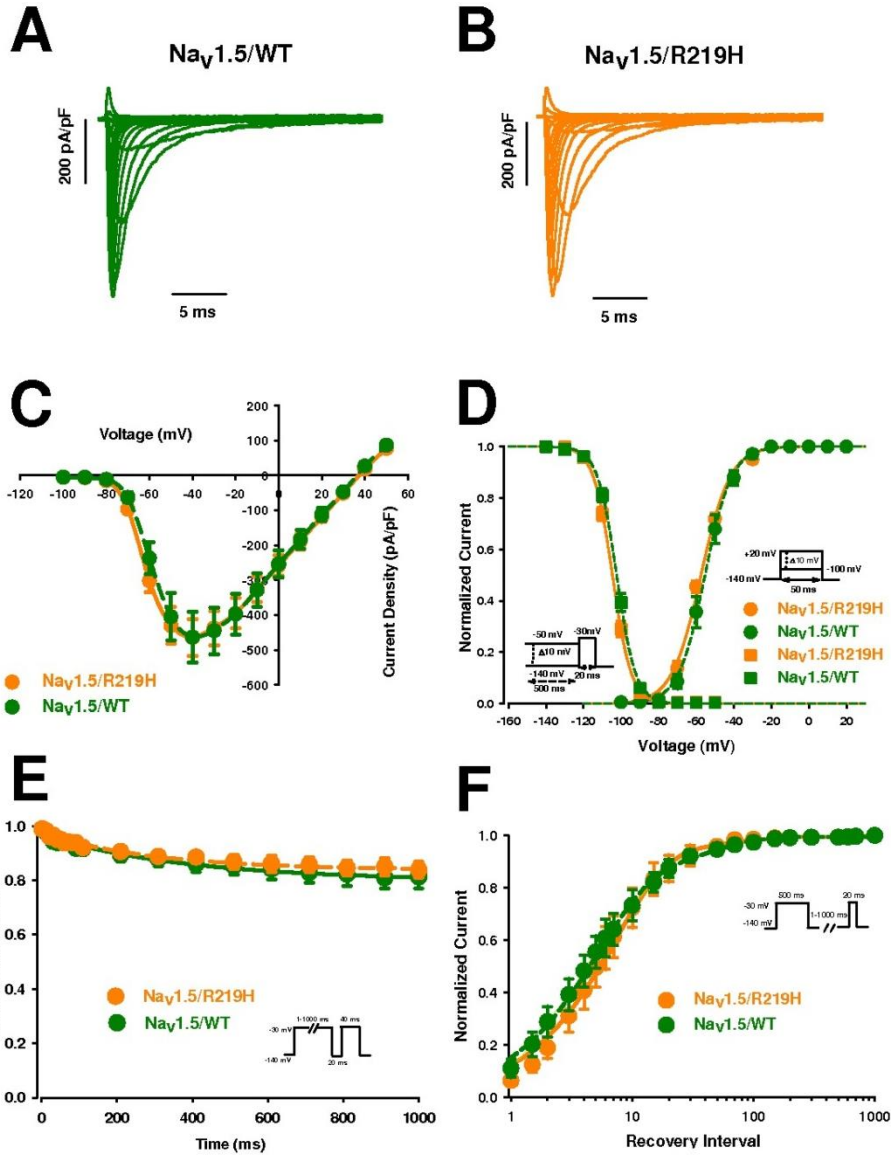
Identification of a novel SCN5A mutation

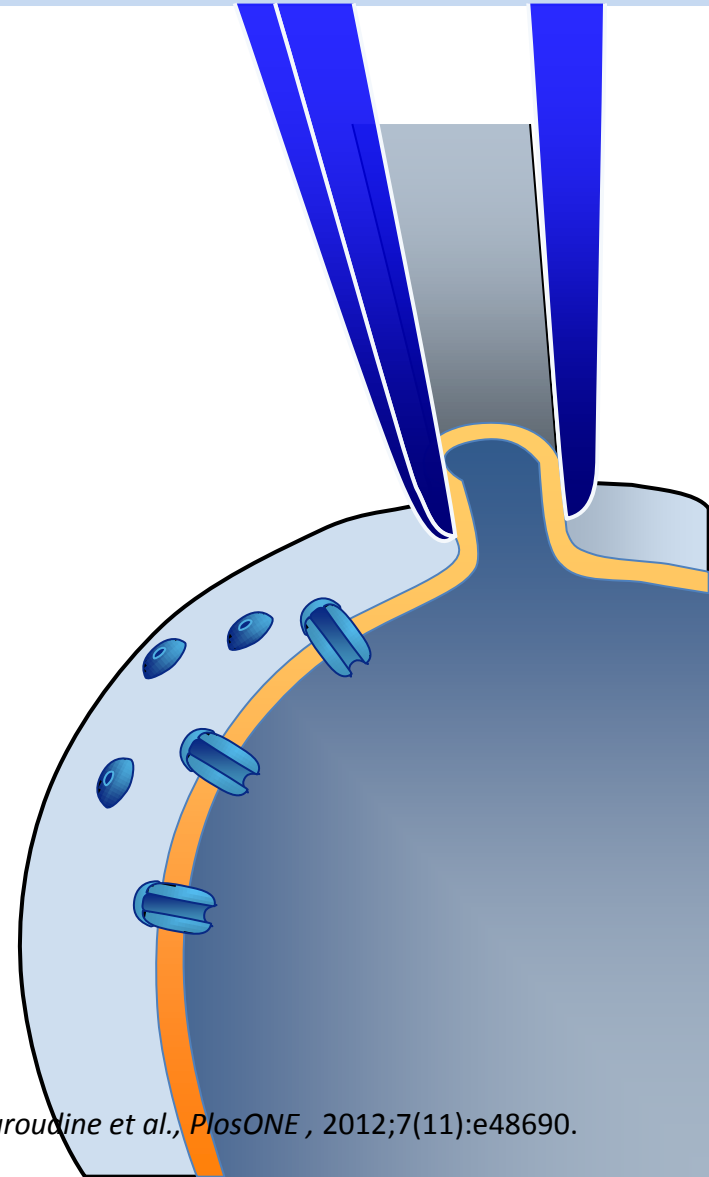


Shaker B	261	ILRVIRLVRVFRIF
Squid, DI	143	GLRTFRVLRALRTL
$Na_v1.4$, DI	217	ALRYFRVLRALKTI
$Na_v1.5$, DI	217	ALRYFRVLRALKTI
$Na_v1.5$, DI(DCM Patient)	217	ALHYFRVLRALKTI

Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

Biophysical properties of SCN5A/R219H mutation





Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

The omega current: Chronology

A proton pore in a potassium channel voltage sensor reveals a focused electric field

Dorine M. Starace & Francisco Bezanilla

Department of Physiology and Department of Anesthesiology, David Geffen Scho of Medicine at UCLA, Los Angeles, California 90095, USA

Published in final edited form as:
Neuron. 2005 February 3; 45(3): 379–388.

Voltage-Sensing Arginines in a Potassium Channel Permeate and Occlude Cation-Selective Pores

Francesco Tombola[1], **Medha M. Pathak**[2], and **Ehud Y. Isacoff**[1,2,*]
1*Department of Molecular and Cell Biology University of California, Berkeley Berkeley, California 94720*

2*Biophysics Graduate Group University of California, Berkeley Berkeley, California 94720*

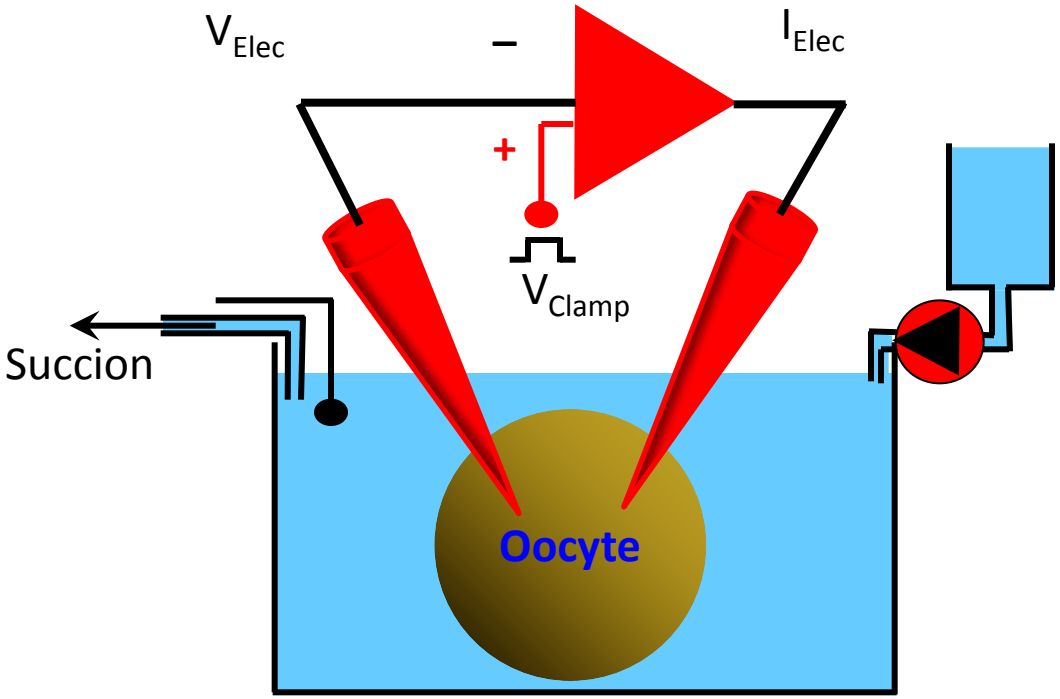
nature Vol 446|1 March 2007|**doi:10.1038/nature05598**

LETTERS

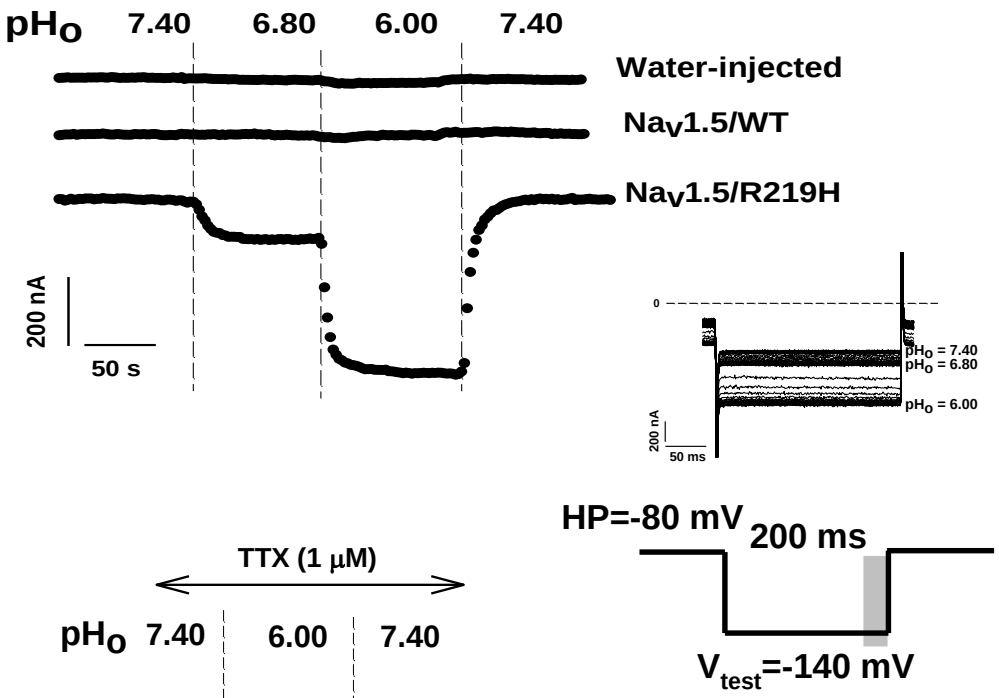
Gating pore current in an inherited ion channelopathy

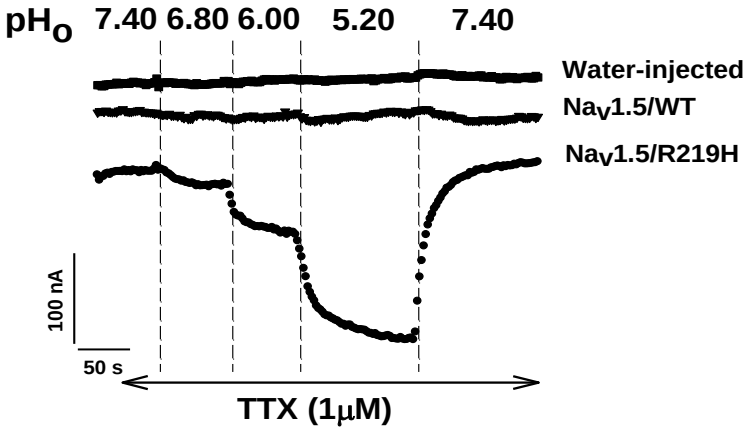
Stanislav Sokolov[1], Todd Scheuer[1] & William A. Catterall[1]

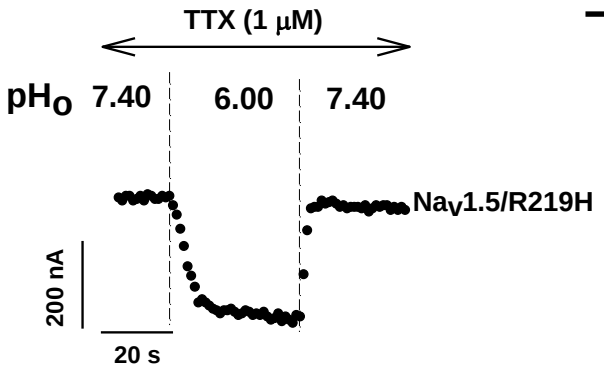
The two microelectrode technique

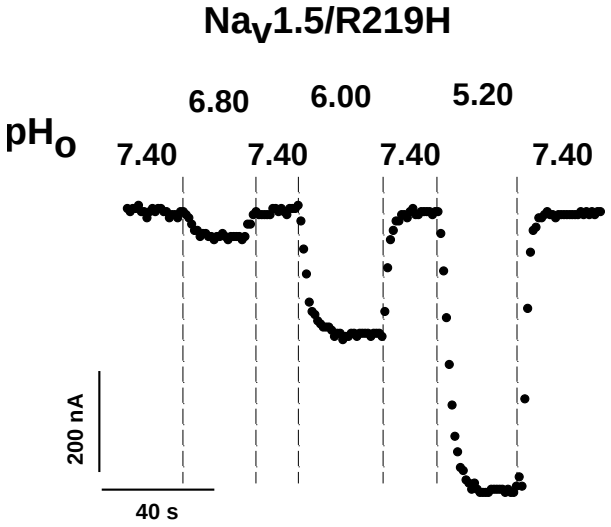


SCN5A/R219H revealed an inward current



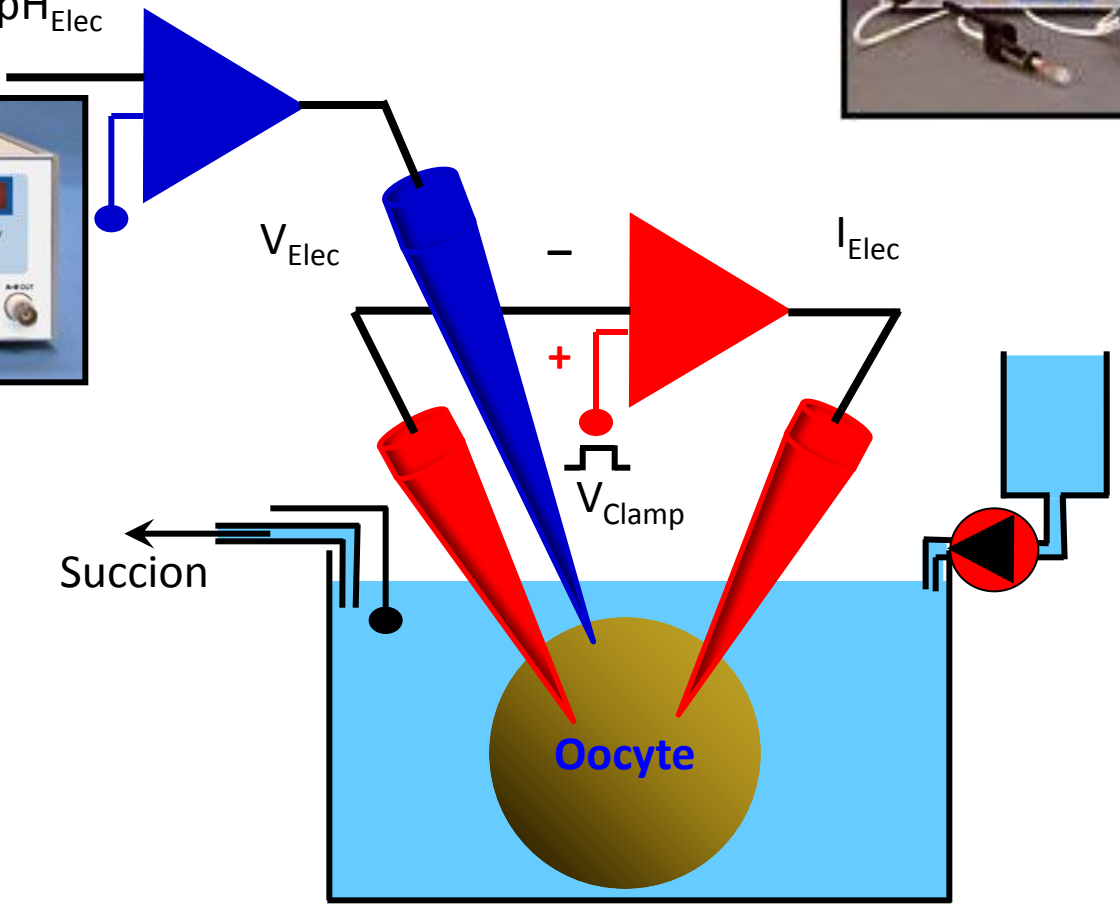




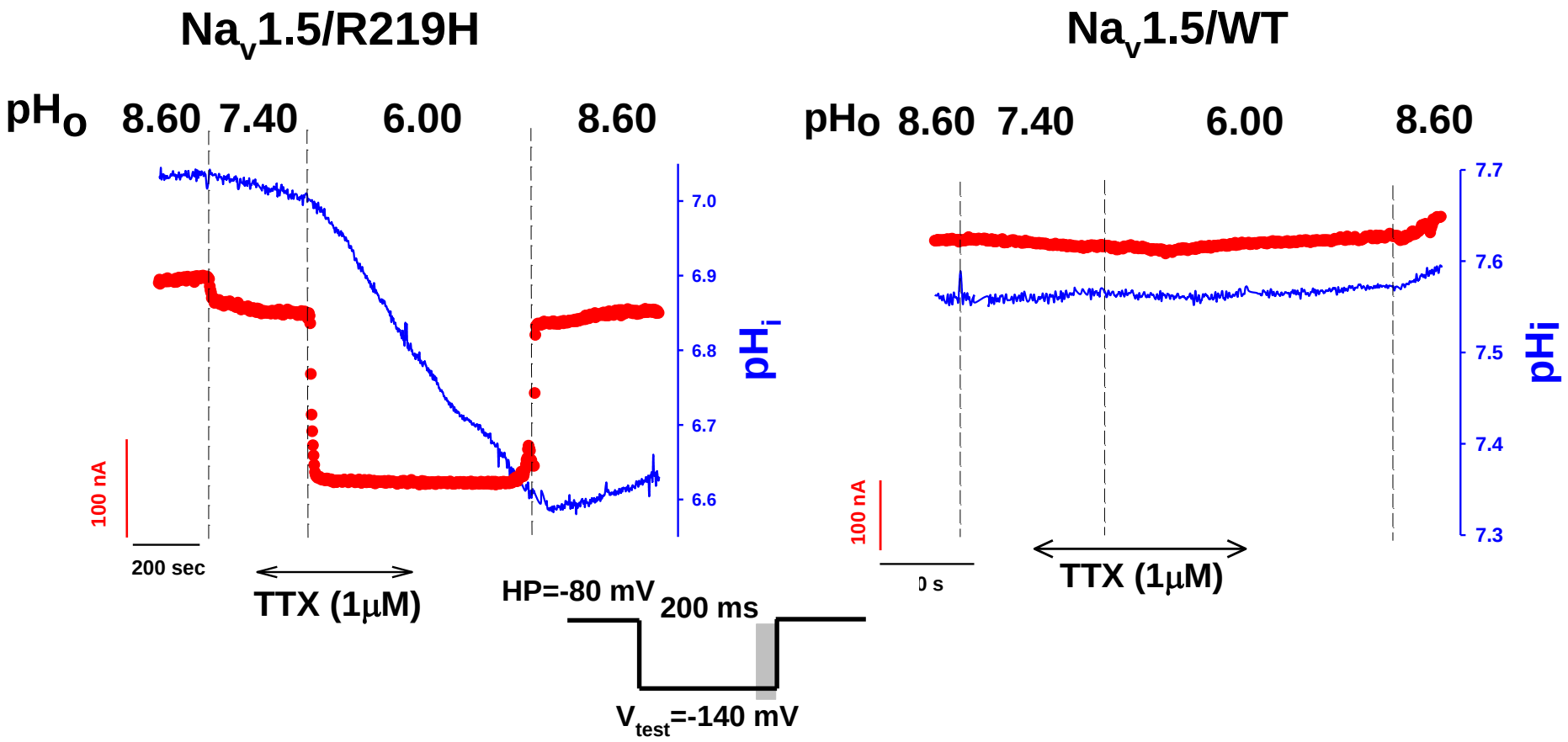


Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

Intracellular pH measurments

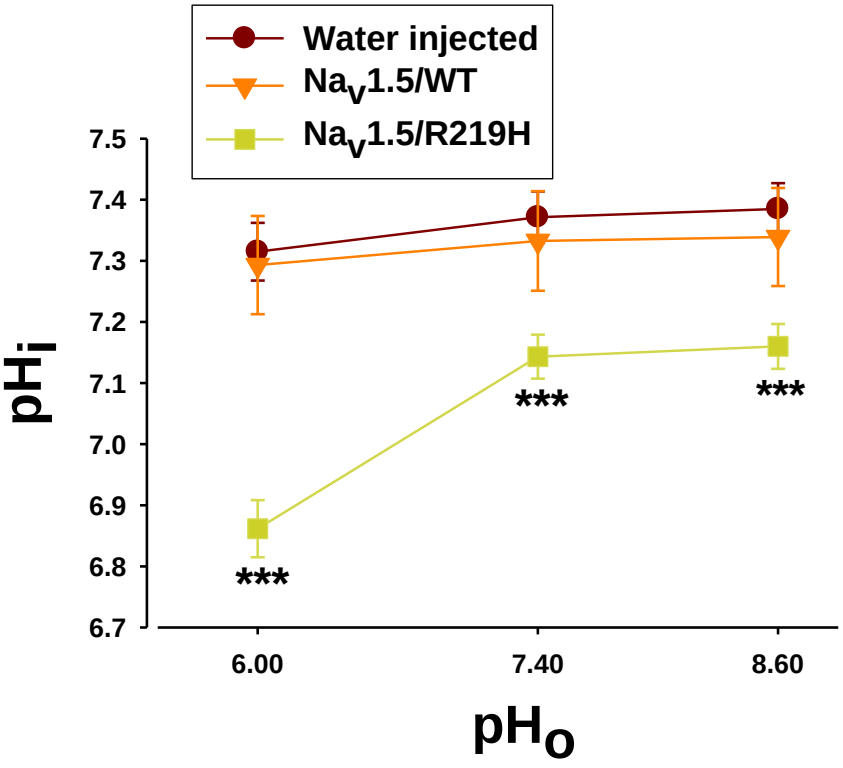


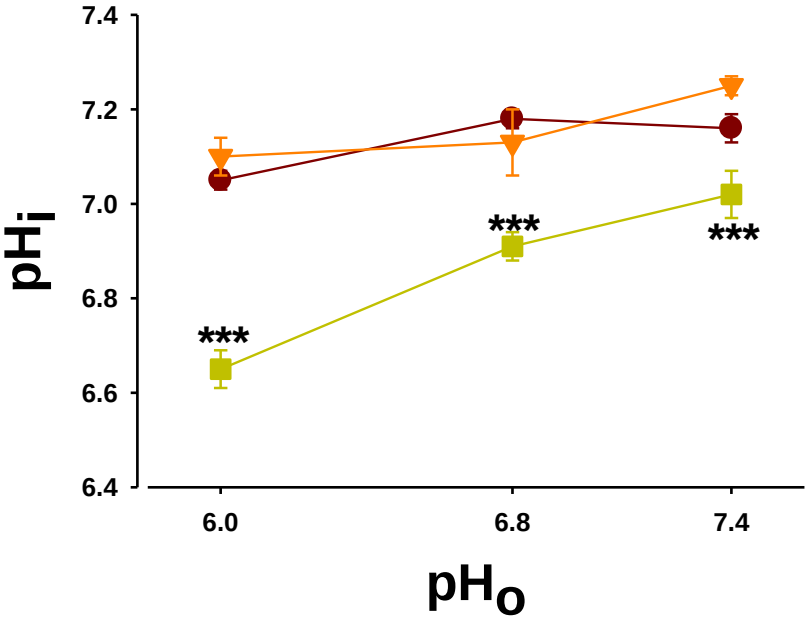
SCN5A/R219H induce a proton current



Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

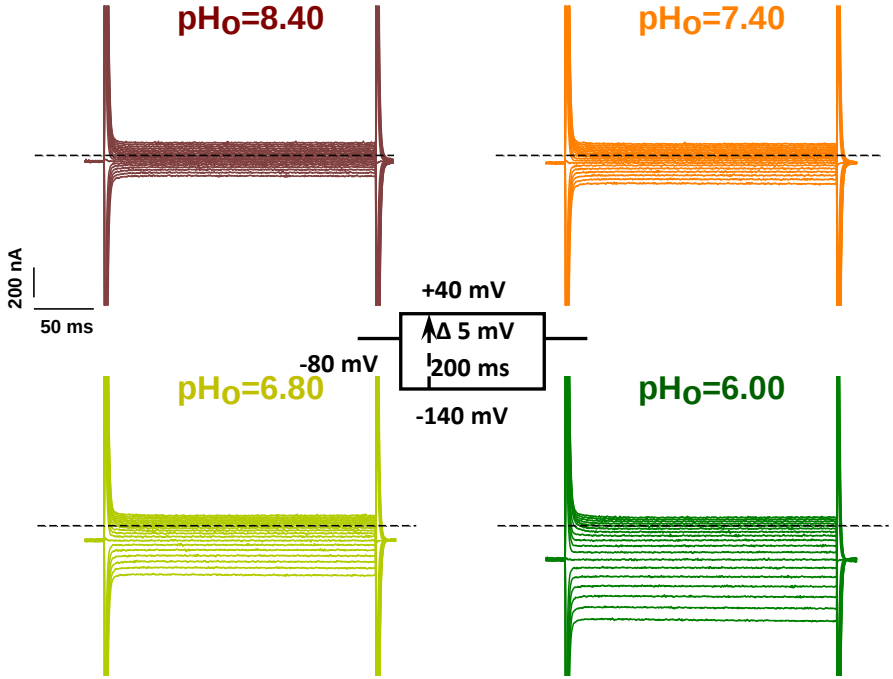
SCN5A/R219H induce an intracellular acidification

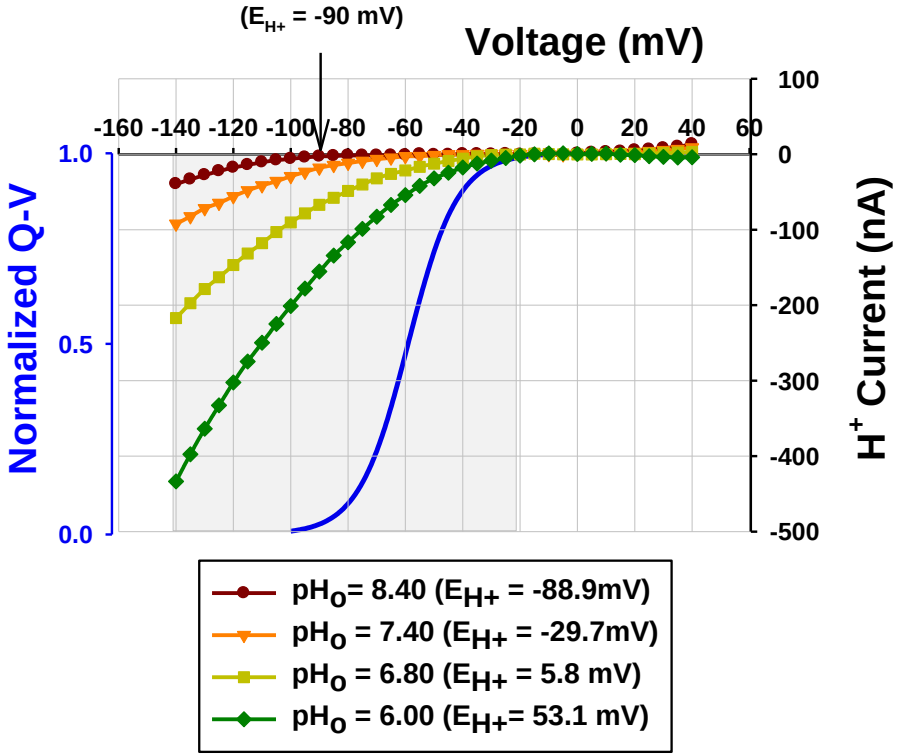




Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

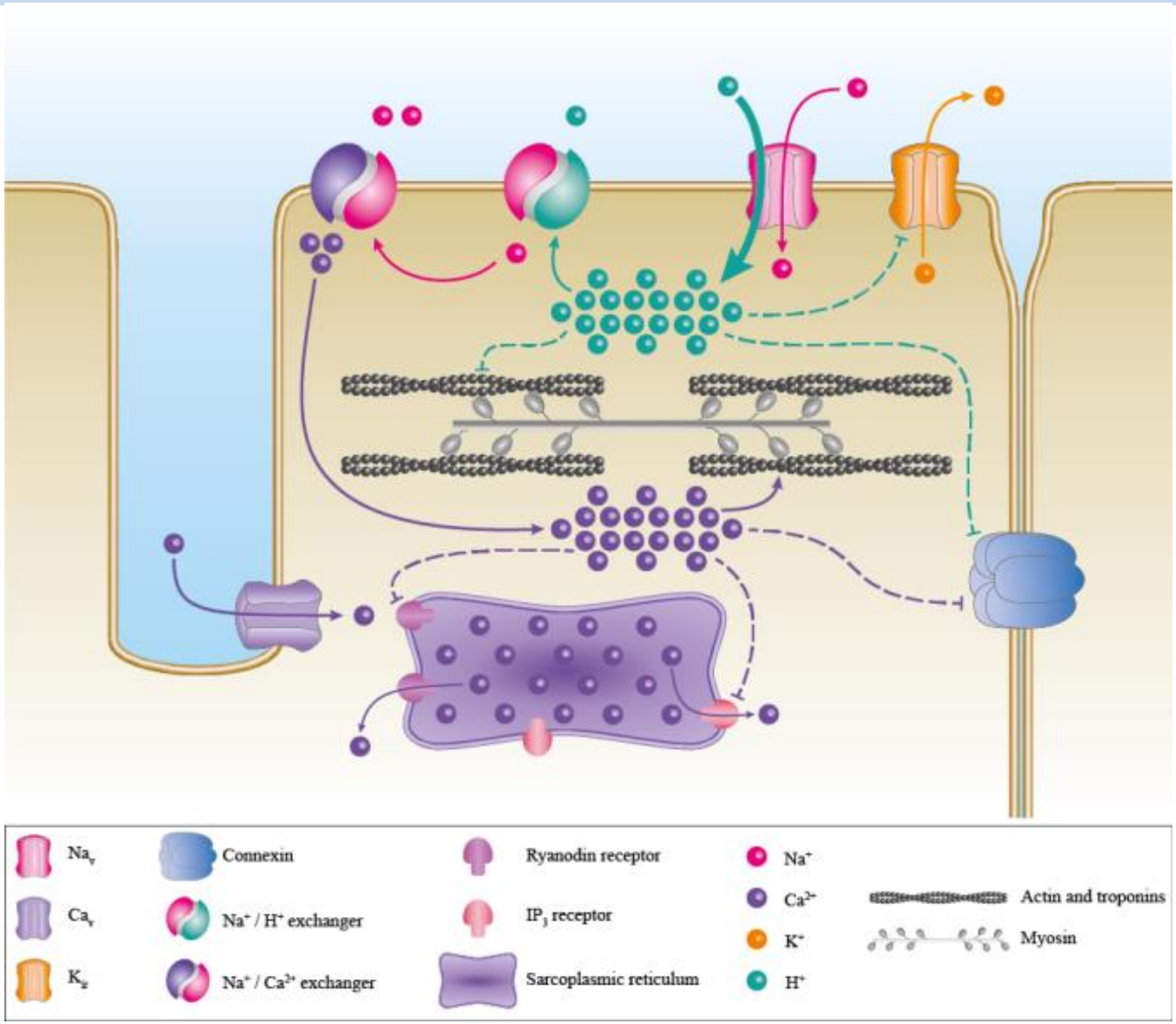
Biophysical caracterization of the proton current



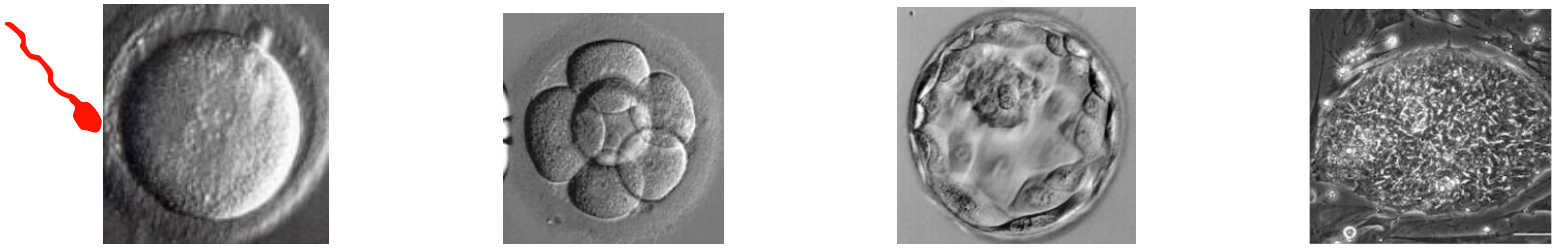


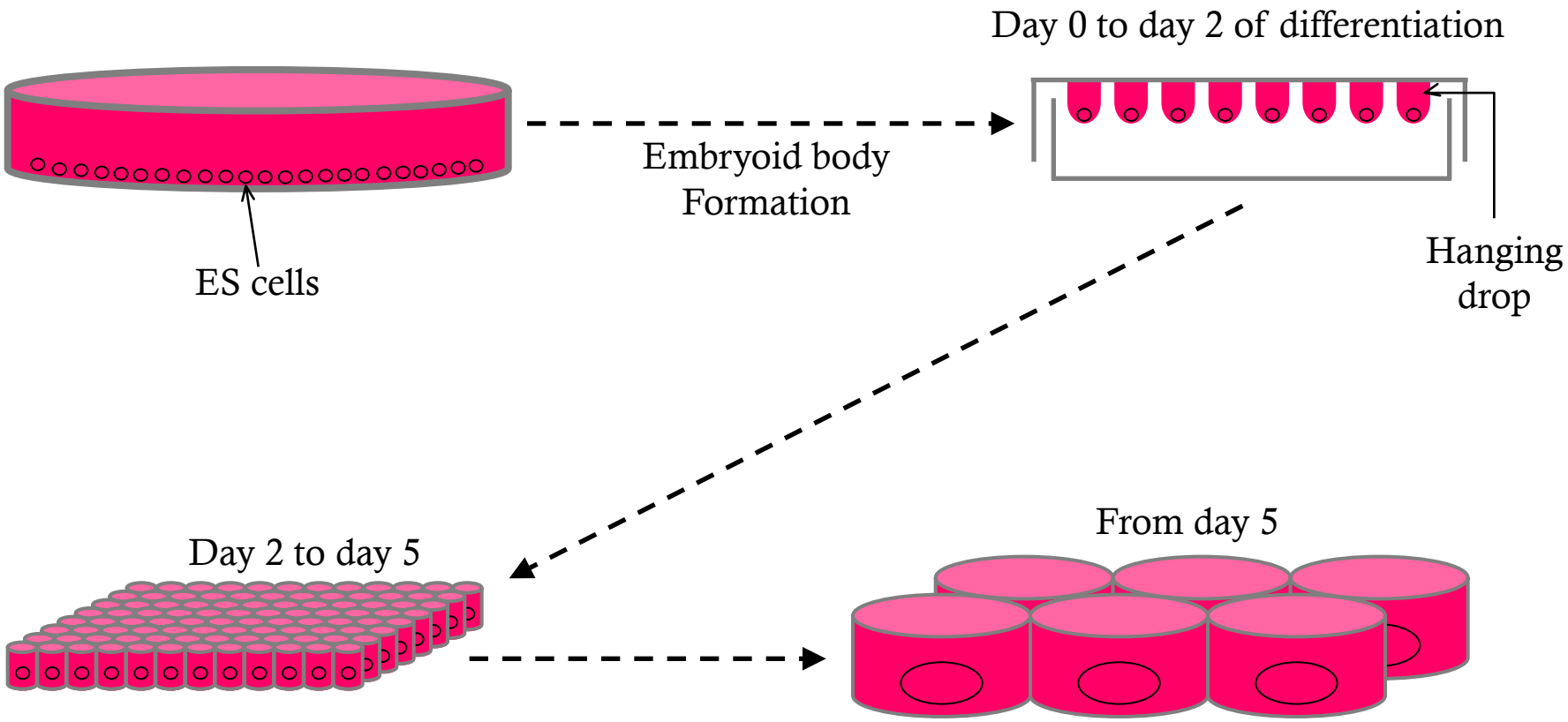
Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

Intracellular mechanisms

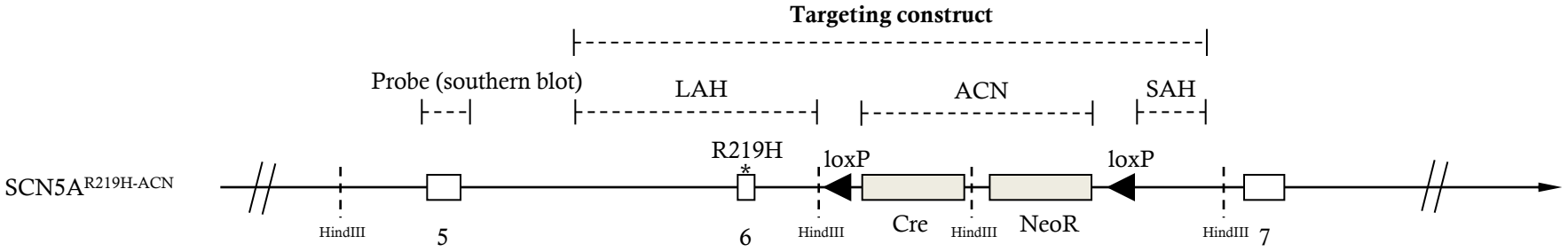


Mouse ES cells differentited into cardiac myocytes

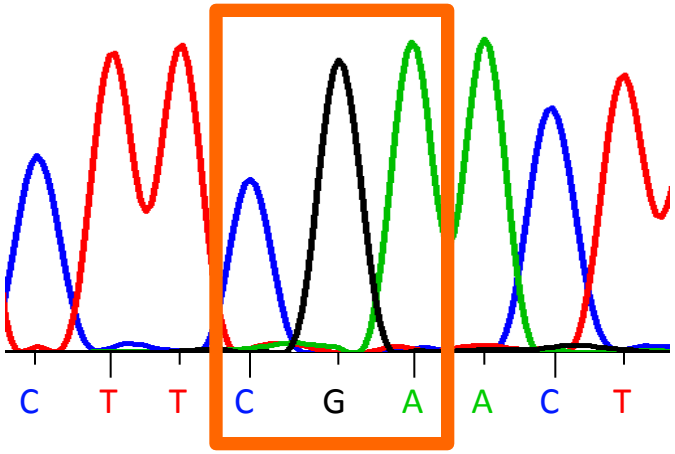




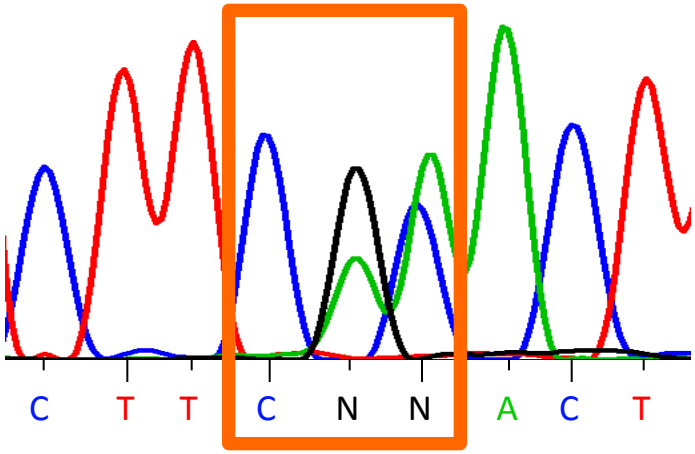
Homologous recombination: CGA to CAC to obtain the heterozygous R219H mutation



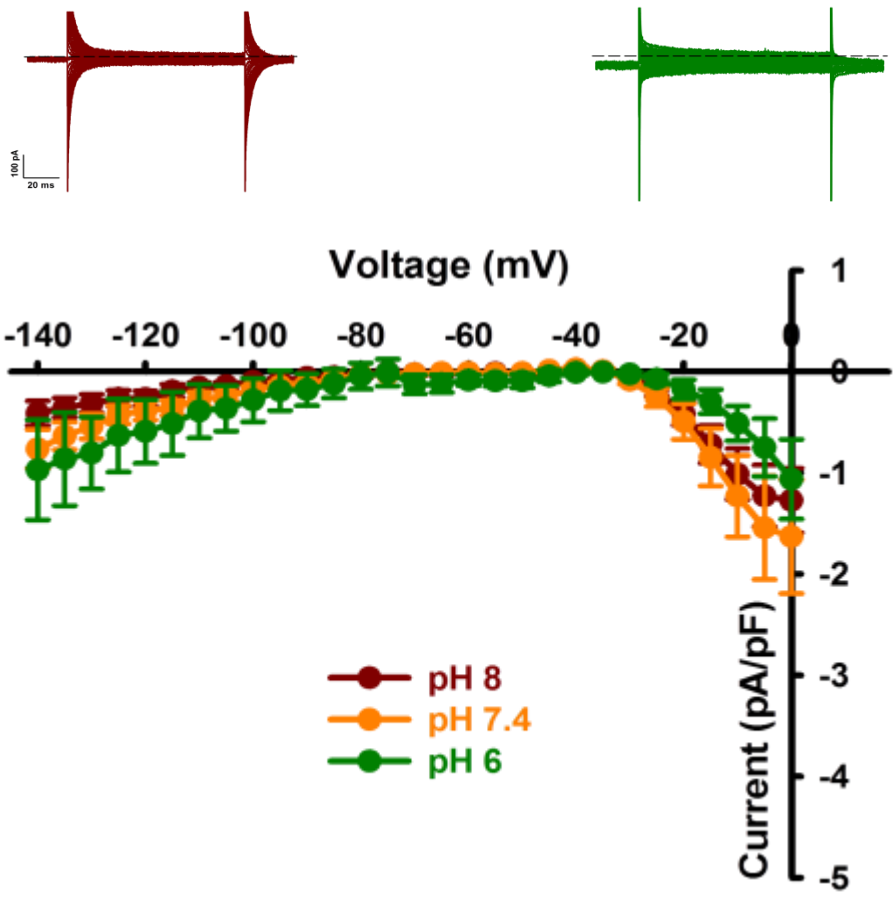
$Na_v1.5$ / WT



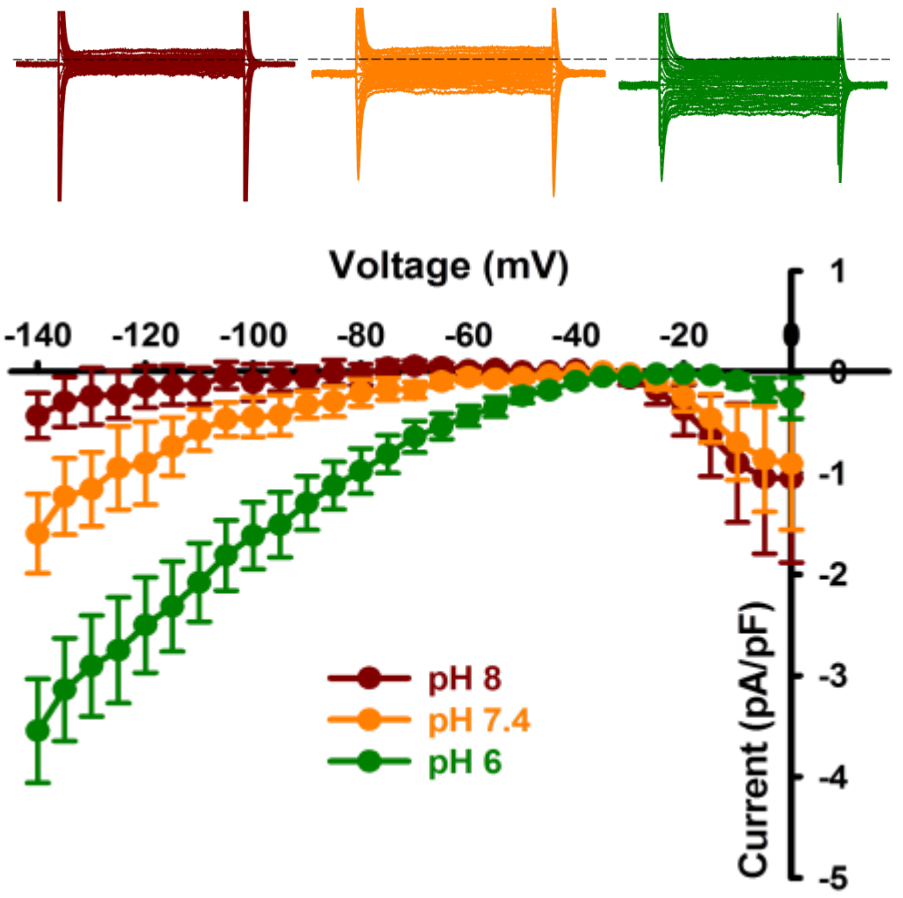
$Na_v1.5$ / R219H



$Na_v1.5$ / WT

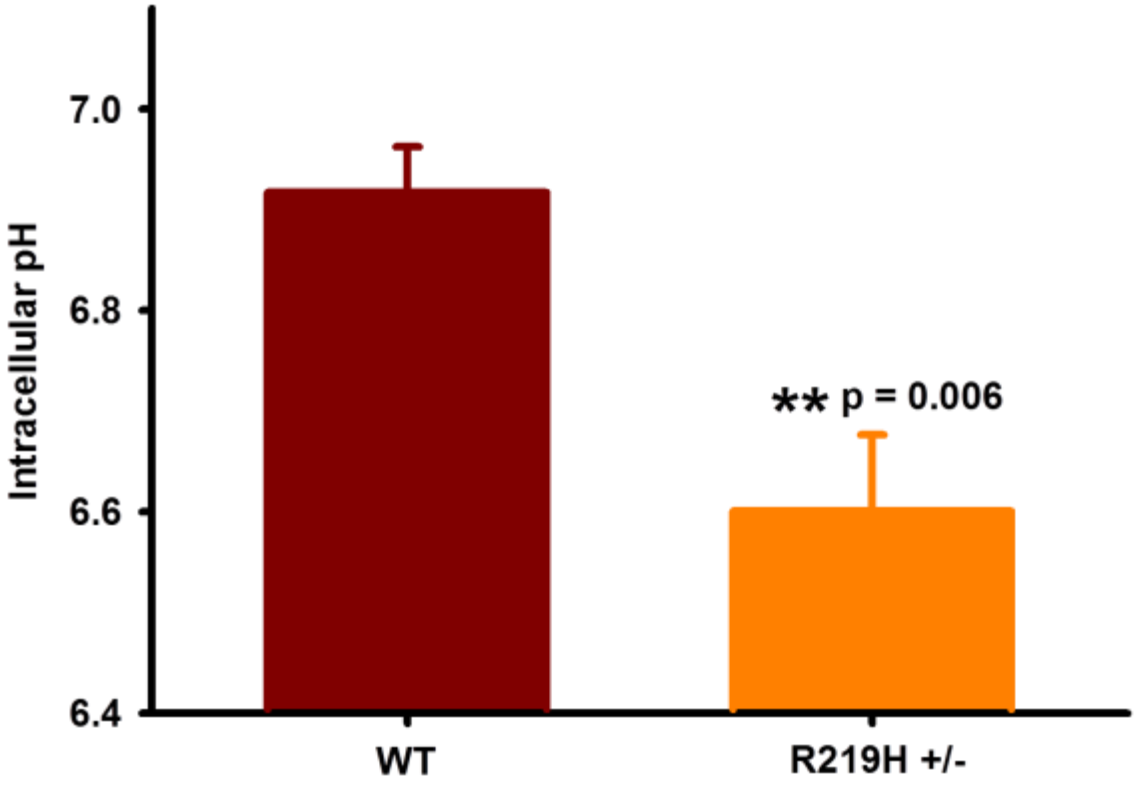


$Na_v1.5$ / R219H



$$R = \frac{\left(F_{\lambda=490}\right) - \left(Background_{\lambda=490}\right)}{\left(F_{\lambda=440}\right) - \left(Background_{\lambda=440}\right)}$$

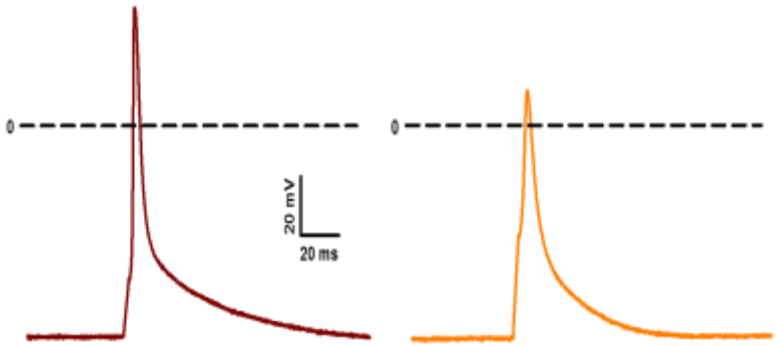
$$pH = pK_a - \log \frac{\left(R - R_{pH5}\right)}{\left(R_{pH8} - R\right)} \cdot \frac{F_{pH5(\lambda=440)}}{F_{pH8(\lambda=440)}}$$

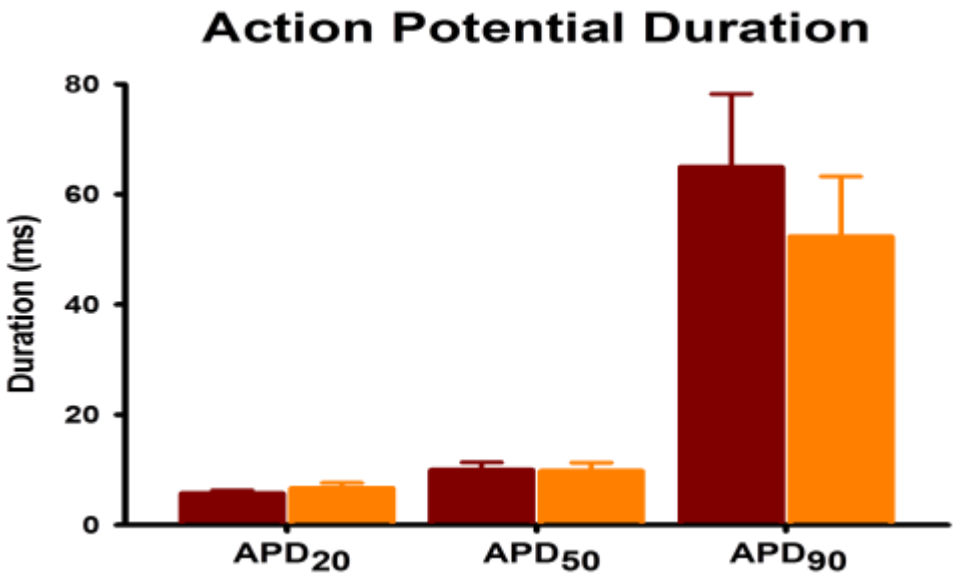


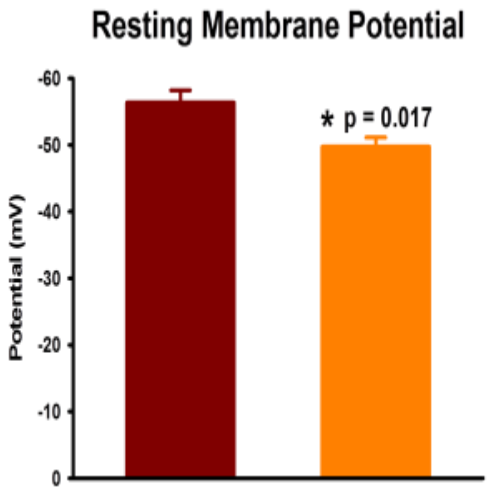
The BCECF ratiometric dye allow to measure the cellular acidification caused by the specific proton leak.

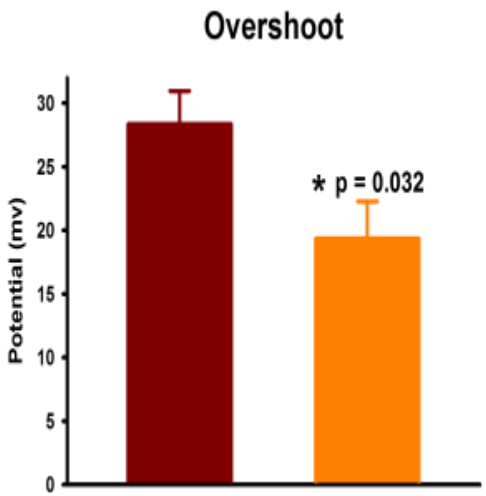
Cardiomyocytes expressing $Na_v1.5$ / WT

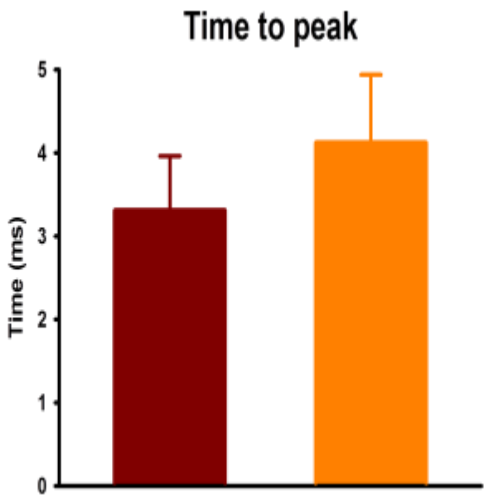
Cardiomyocytes expressing $Na_v1.5$ / R219H

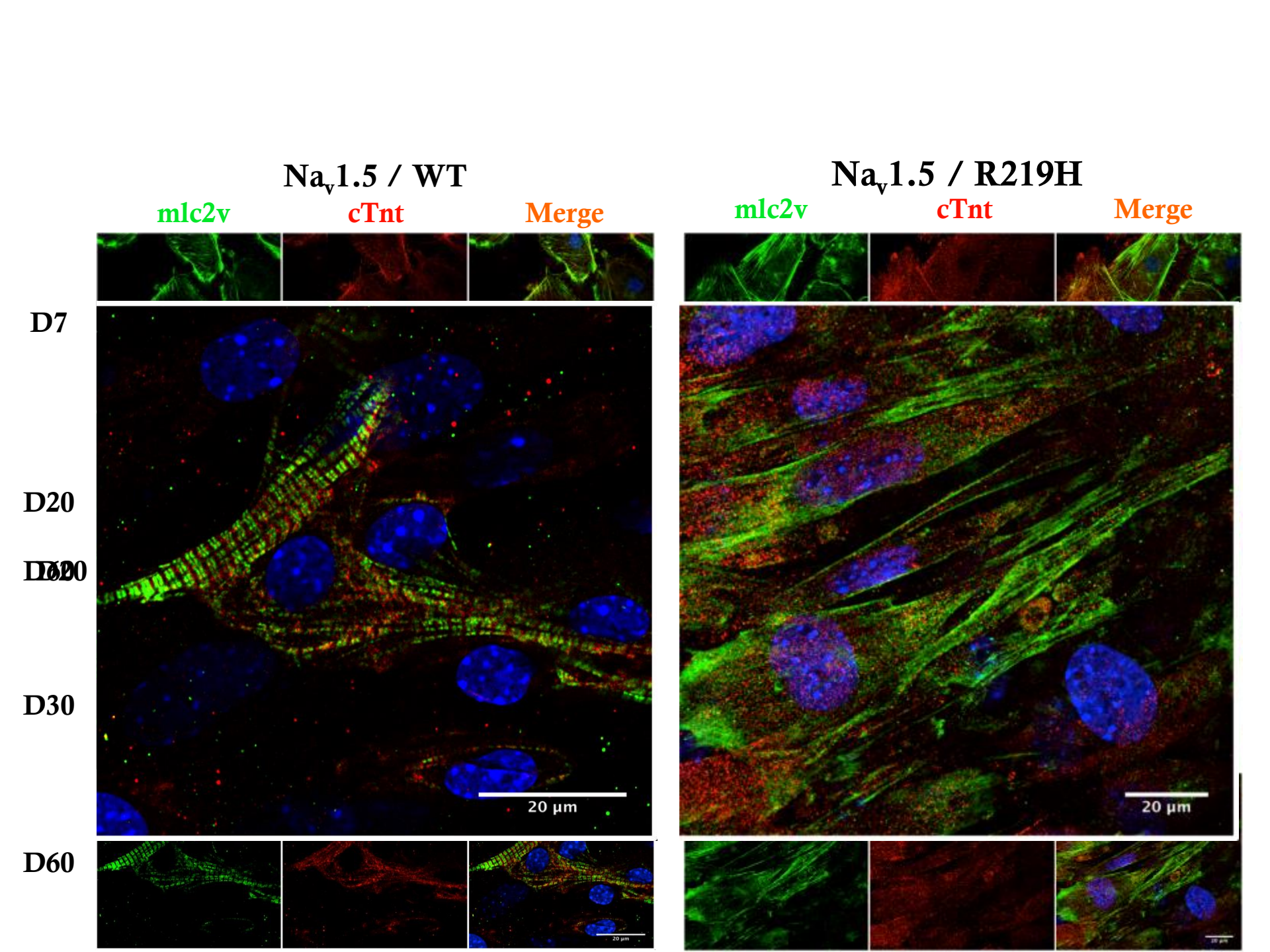











Na$_v$1.5 / WT
mlc2v
cTnt
Merge
Na$_v$1.5 / R219H
mlc2v
cTnt
Merge
D7
D20
D30
D60
20 µm
20 µm

CONCLUSION

✓ **The R219H mutation found at the heterozygous state:**

- **Generate a proton leak**
- **Unbalance the ionic homeostatsis**

✓ **The DCM is not an adaptative phenomena**

✓ **Cardiac myocytes derived from ES cells are good model to study SCN5A mutations linked to DCM**

THANKS…

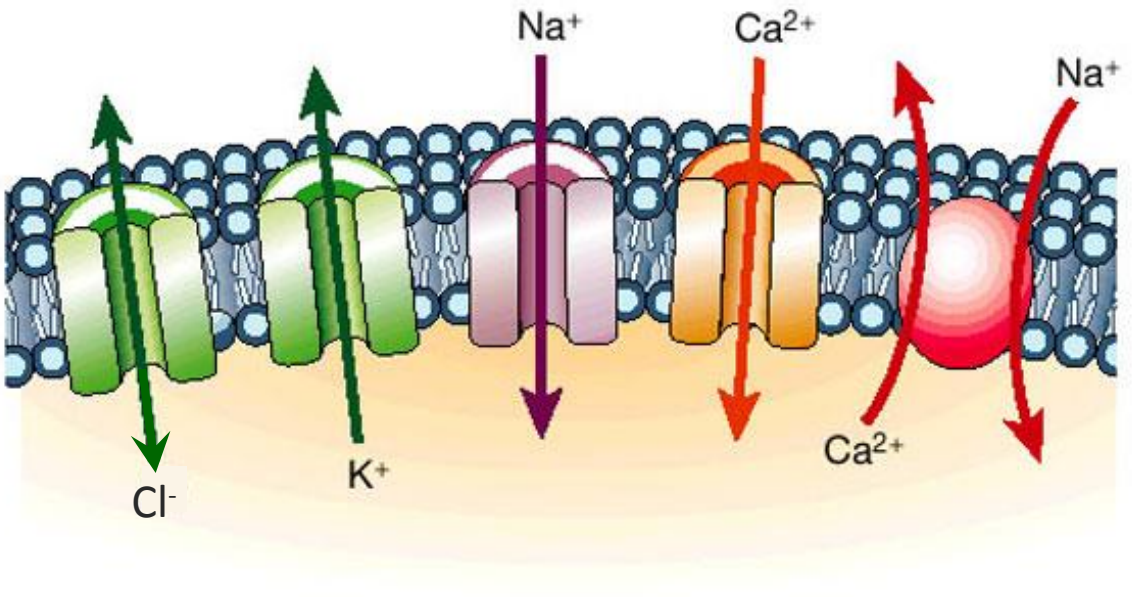
Zurich

Dagmar I. Keller M.D.
University Hospital Zurich, Zurich, Switzerland

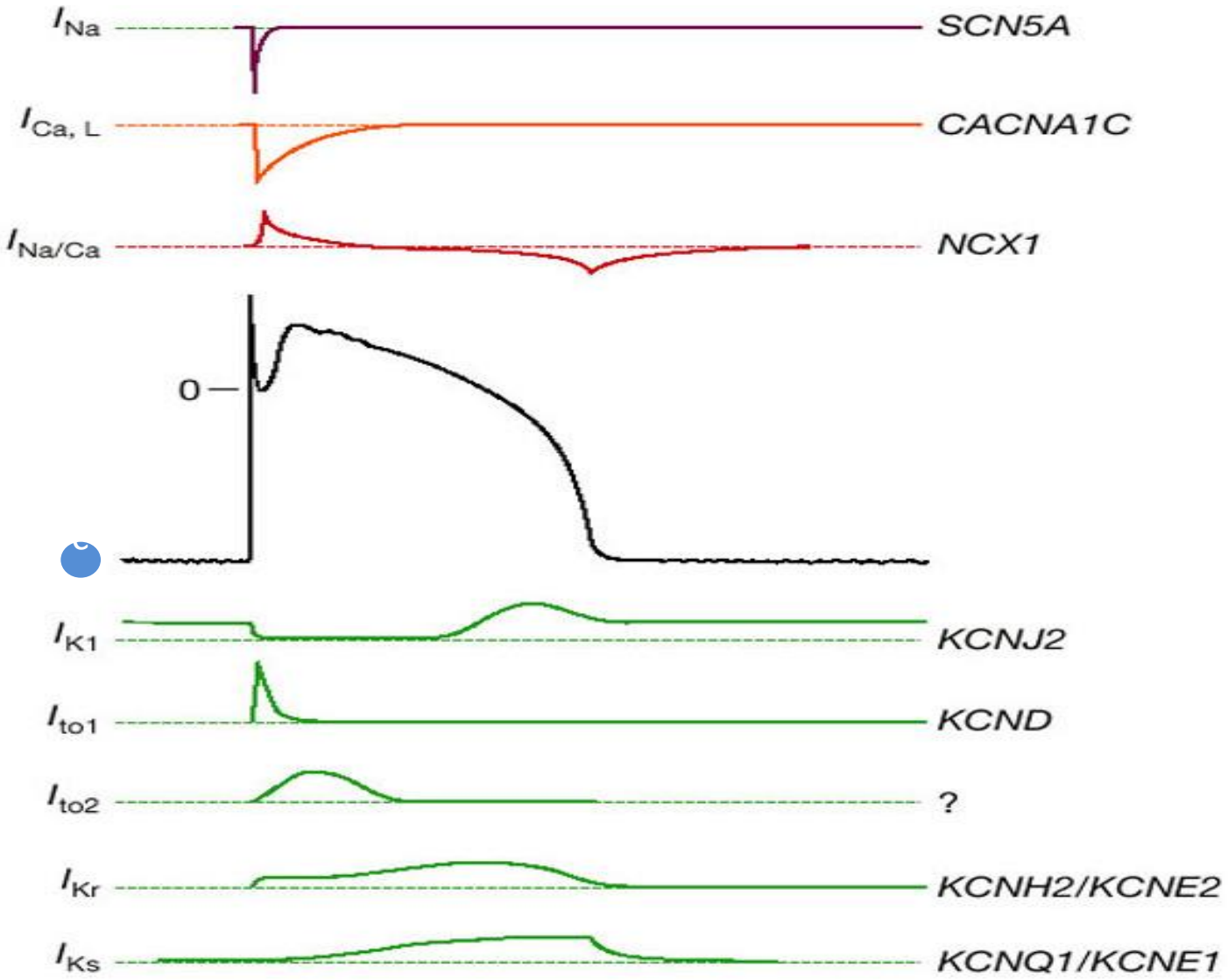
Québec

Pascal Gosselin-Badaroudine
Adrien Moreau
Hugo Poulin
Valérie Pouliot

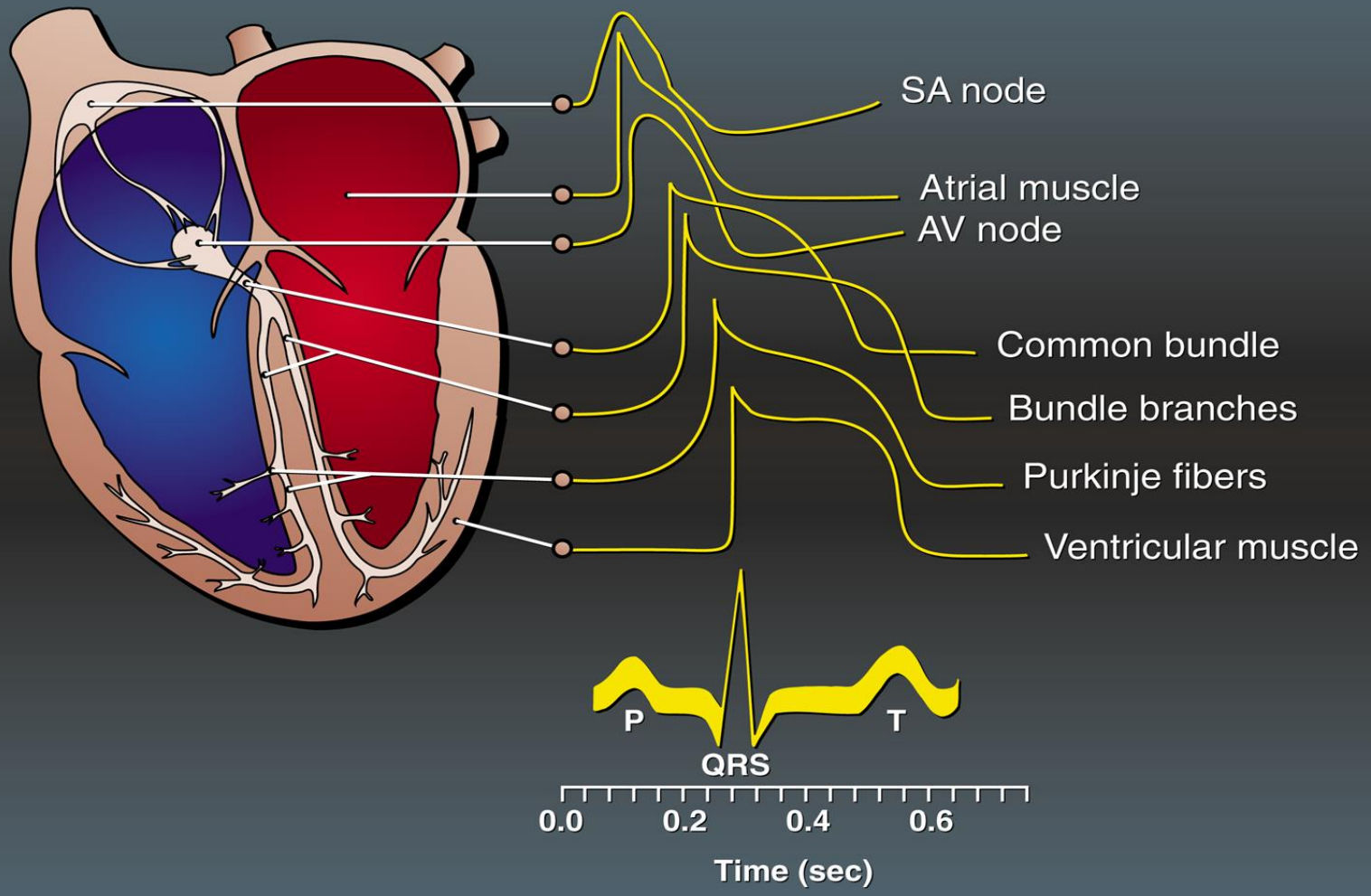
LES CANAUX IONIQUES



COURANTS IONIQUE ET POTENTIEL D'ACTION



POTENTIELS D'ACTION ET ECG



Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 554–558, January 1992
Medical Sciences

Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel

(complementary DNA/heart muscle/electrophysiology/antiarrhythmic)

MARY E. GELLENS*, ALFRED L. GEORGE, JR.*†, LIQIONG CHEN†, MOHAMED CHAHINE‡, RICHARD HORN‡, ROBERT L. BARCHI†§¶, AND ROLAND G. KALLEN†§‖

Departments of *Medicine, †Biochemistry and Biophysics, ¶Neurology, and the §David Mahoney Institute of Neurological Sciences, University of Pennsylvania, Philadelphia, PA 19104; and ‡Department of Neurosciences, Roche Institute of Molecular Biology, Nutley, NJ 07110

Communicated by Eliot Stellar, September 23, 1991

J Mol Cell Cardiol **24**, 1231–1236 (1992)

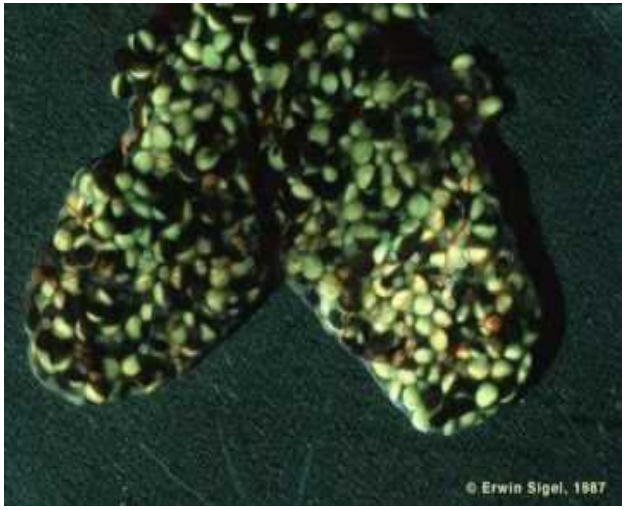
Lidocaine Block of Human Heart Sodium Channels Expressed in *Xenopus* Oocytes

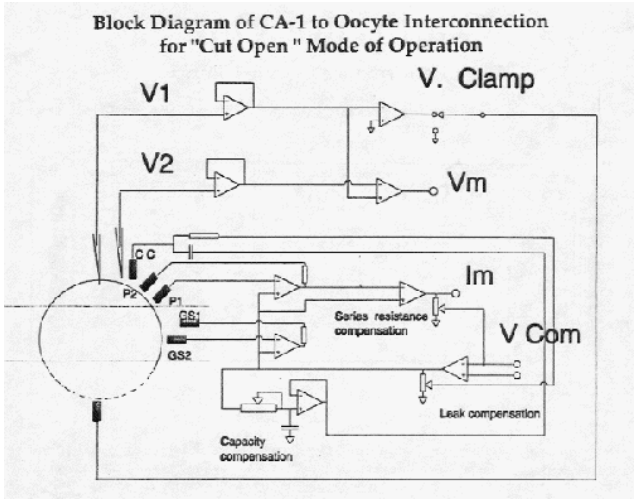
M. Chahine*, L.-Q. Chen†, R. L. Barchi‡§, R. G. Kallen†§ and R. Horn*

**Department of Neurosciences, Roche Institute of Molecular Biology, Nutley, NJ 07110, †Department of Biochemistry and Biophysics, ‡Department of Neurology, and §the David Mahoney Institute of Neurological Sciences, University of Pennsylvania, Philadelphia, PA 19104, USA*

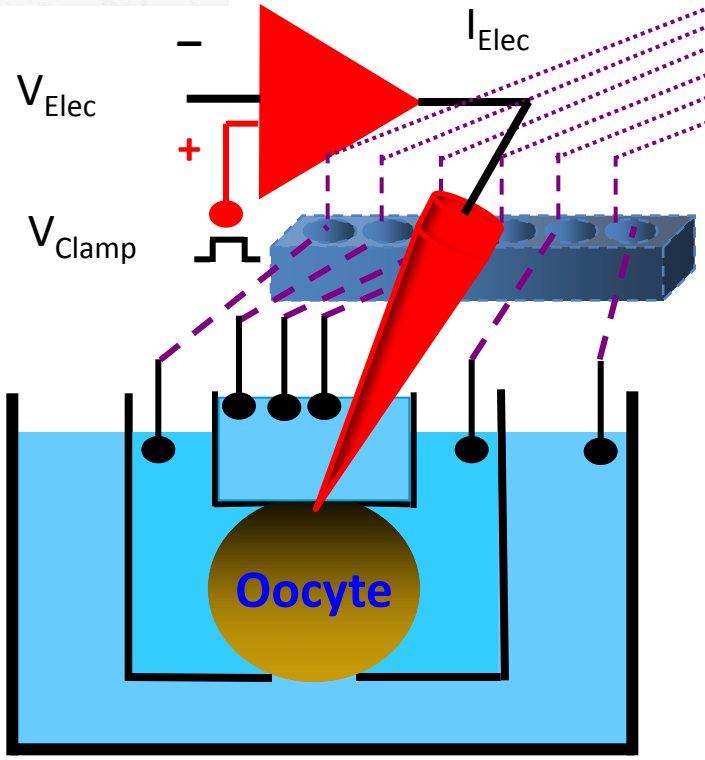
(Received 29 October 1991, accepted in revised form 18 May 1992)

XENOPUS LAEVIS: SYTÈME HÉTÉROLOGUE D'EXPRESSION

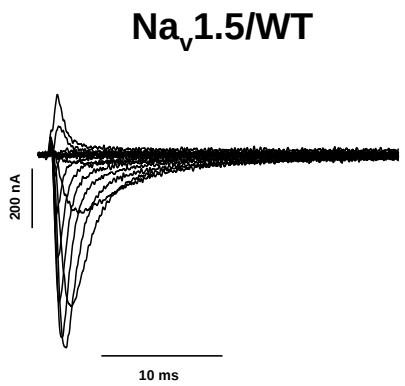


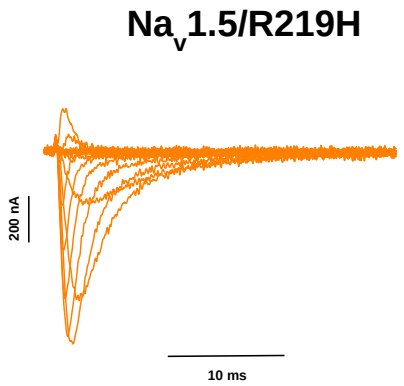

Block Diagram of CA-1 to Oocyte Interconnection
for "Cut Open " Mode of Operation
V1
V. Clamp
V2
Vm
Im
V Com
Series resistance compensation
Leak compensation
Capacity compensation
P2
P1
GS1
GS2

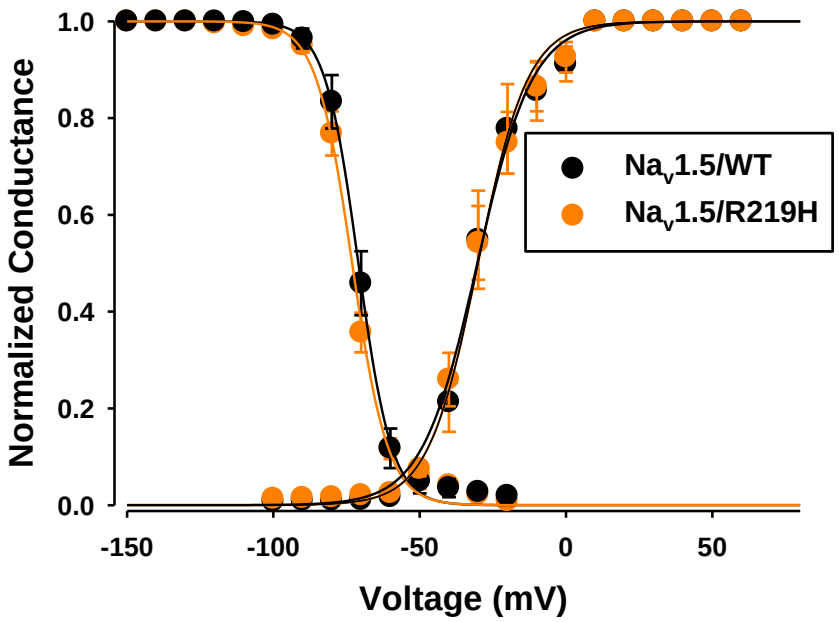

ELECTRODES
500
CLAMP
199
SIGNAL CONDITIONING

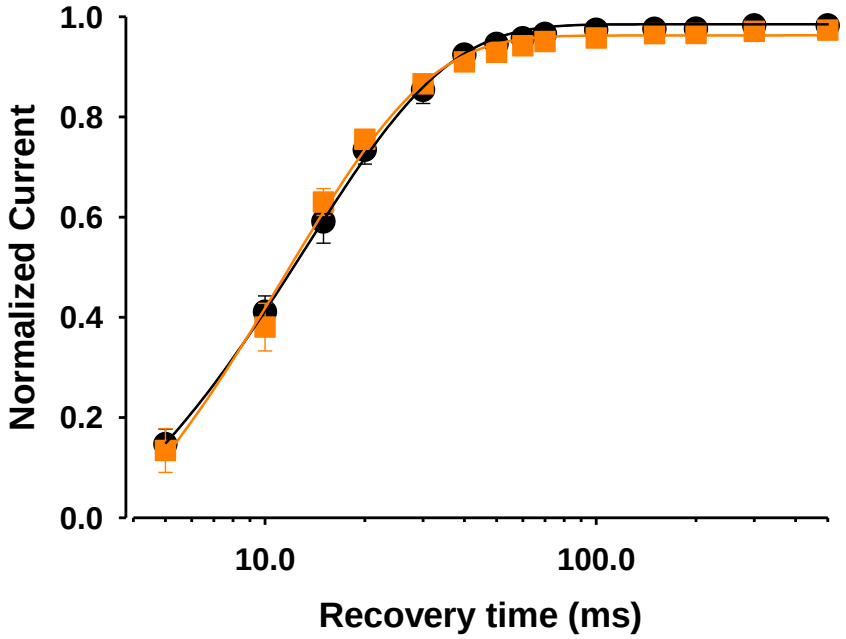

I Elec
V Elec
V Clamp
Oocyte

LE PROPRIÉTÉS BIOPHYSIQUE DE BASES DE SCN5A/R219H SONT INCHANGÉES

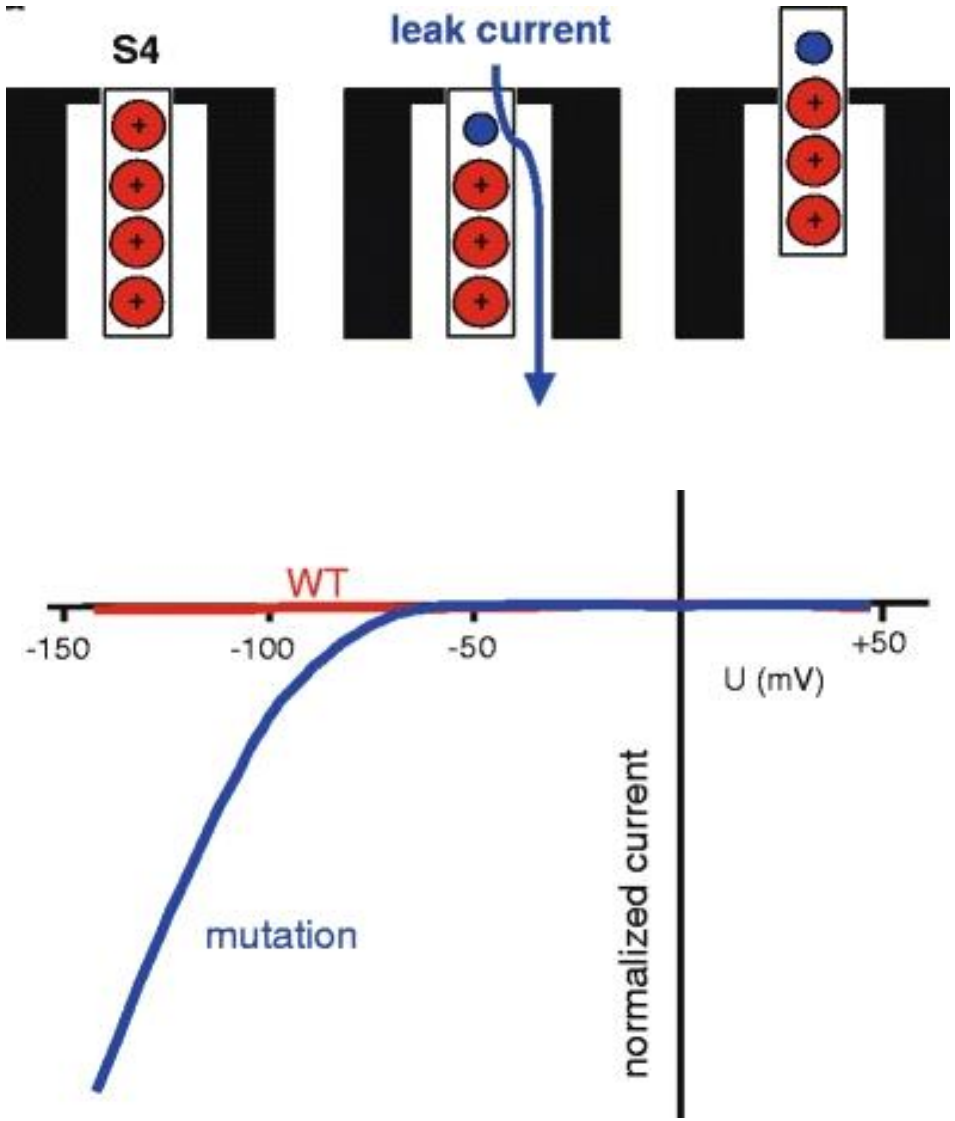


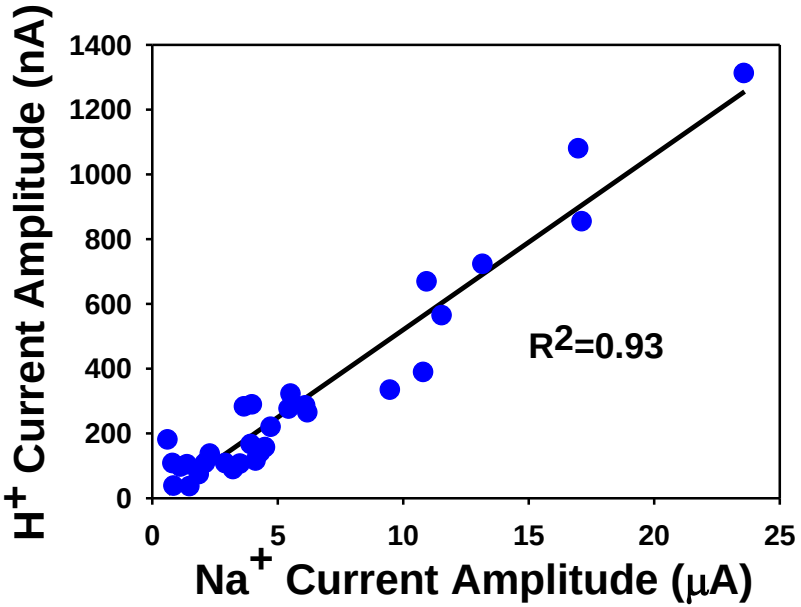


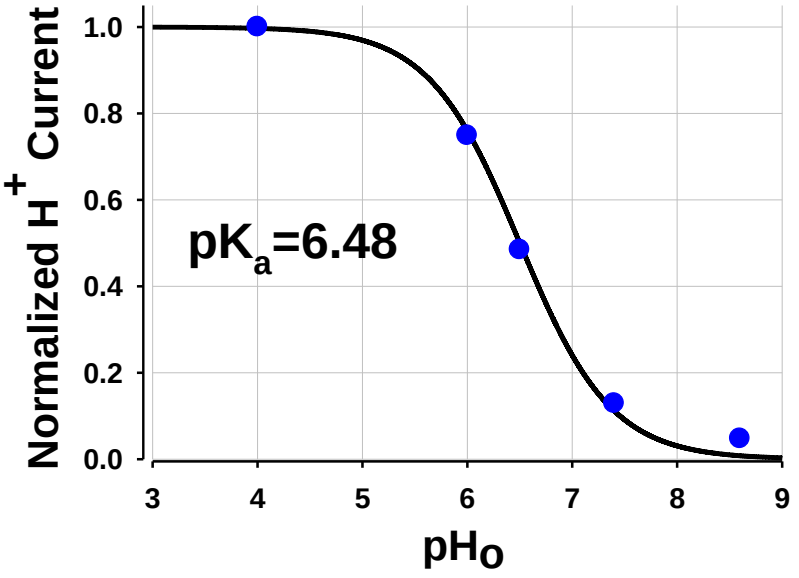




Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.


S4
leak current
WT
-150
-100
-50
+50
U (mV)
normalized current
mutation



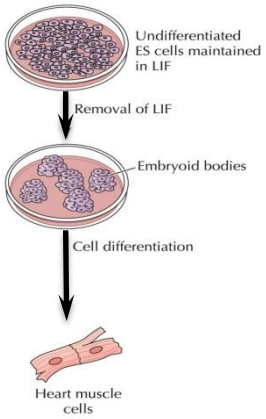


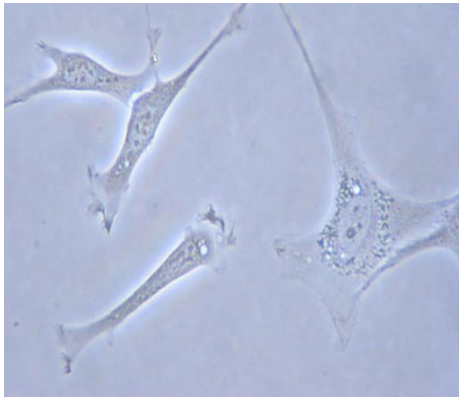
Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

DIRECTIONS FUTURES

✓ **Souris transgénique (Knocking) portant La mutation R219H**

✓**Différencier les cellules ES en myocytes cardiaques**





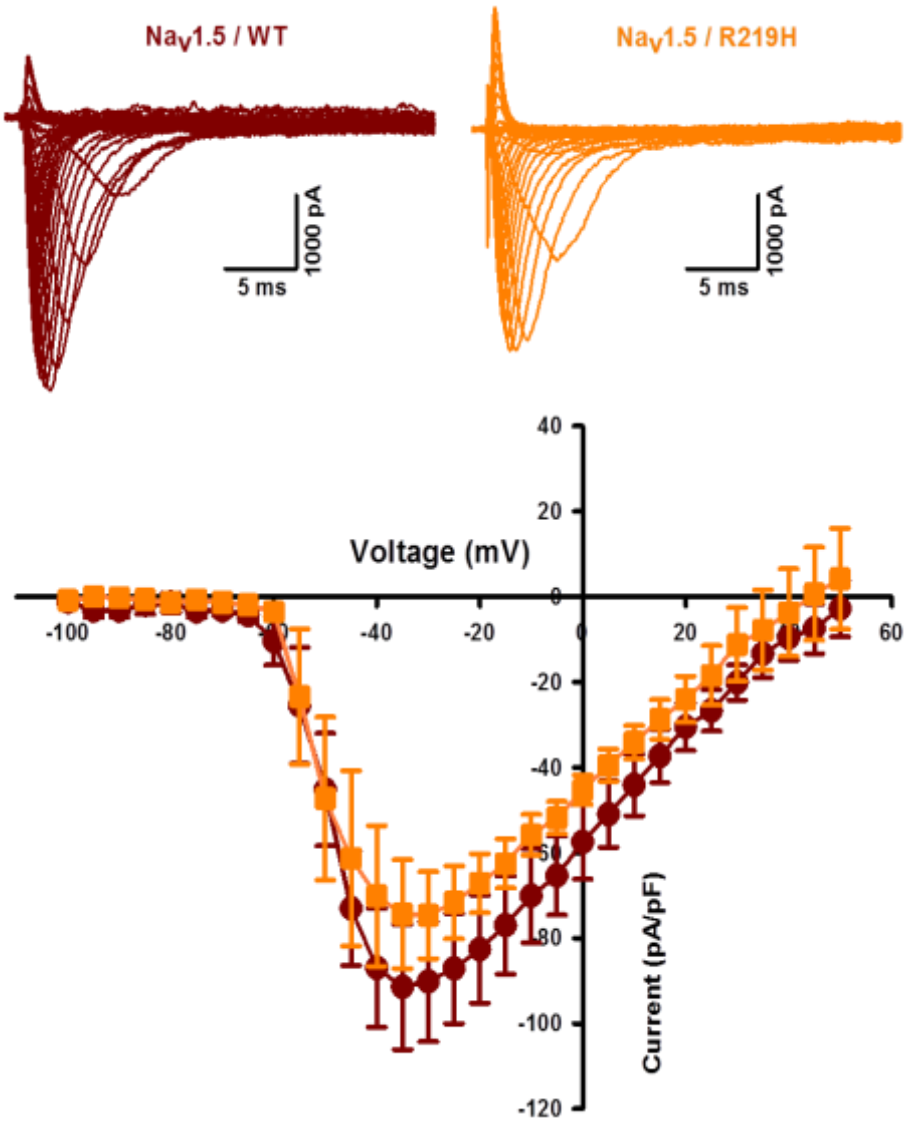
✓ **Reprogrammer les fibroblastes du patient en cellules iPS puis en myocytes**

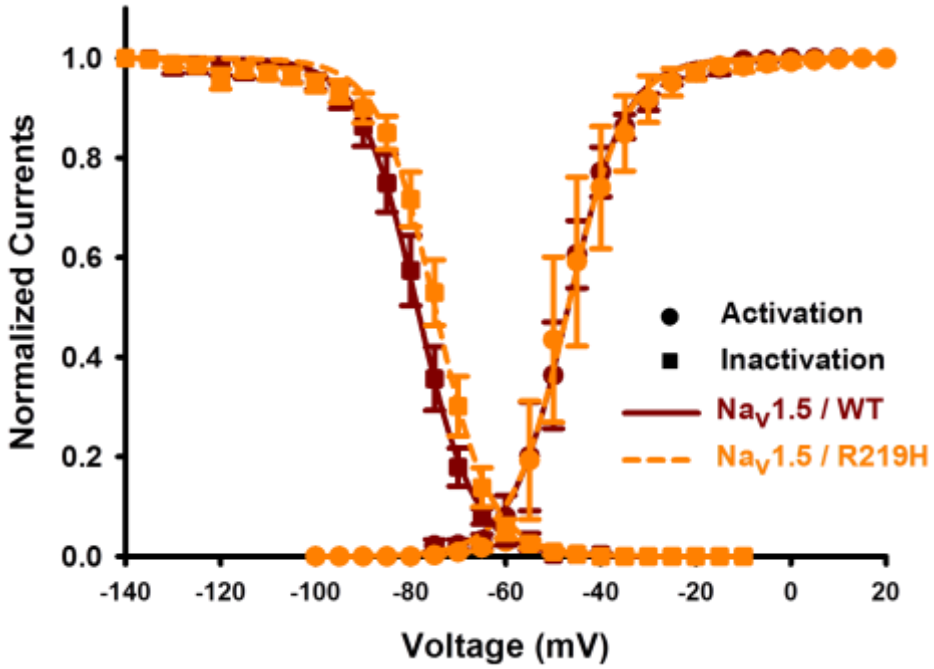
Conclusion

- La mutation n'affecte pas les caractéristiques biophysiques du pore α

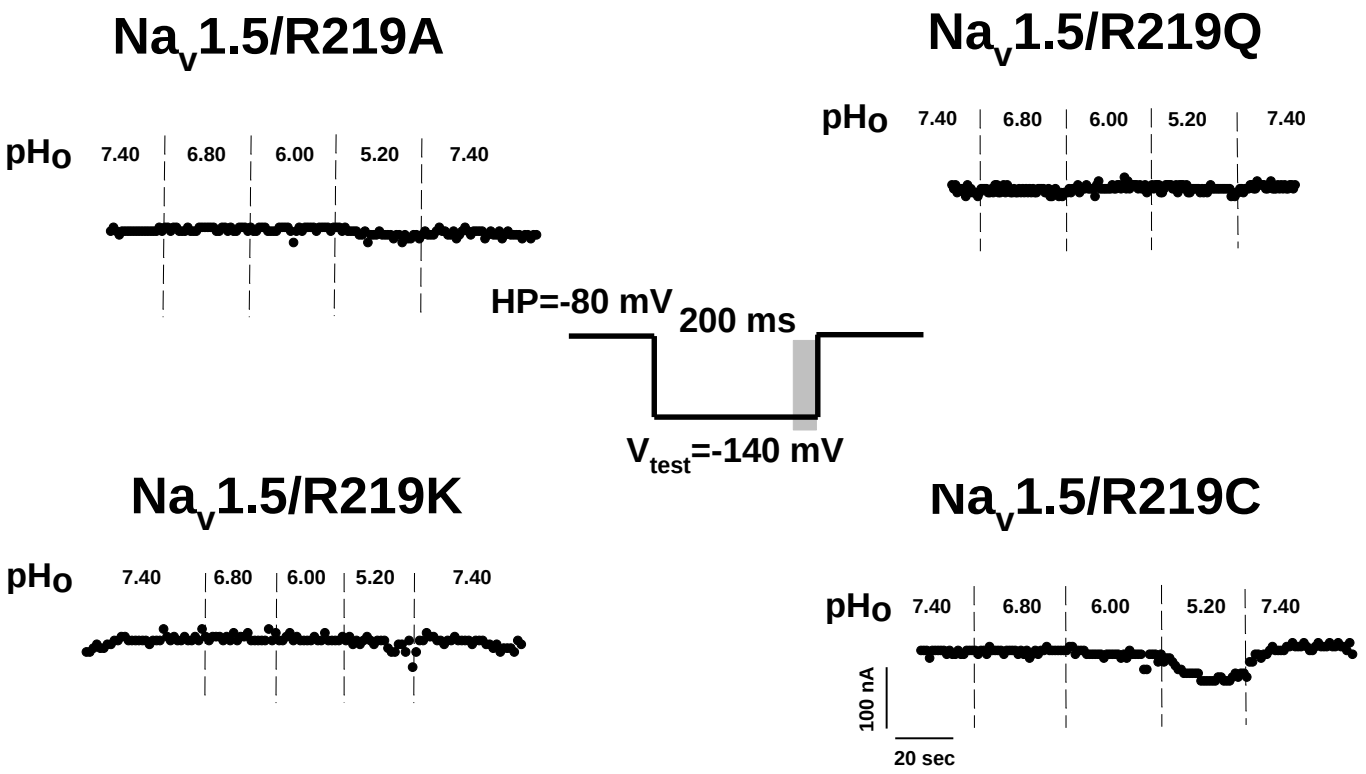
- On observe un courant H^+ passant à travers $Na_v1.5$
  « Proton Wire »

- Ce courant semble être à l'origine du phénotype de cardiomyopathie dilatée de nos patients


Na$_V$1.5 / WT
Na$_V$1.5 / R219H
1000 pA
5 ms
1000 pA
5 ms
Voltage (mV)
Current (pA/pF)
40
20
0
-20
-40
-60
-80
-100
-120
-100
-80
-40
-20
20
60

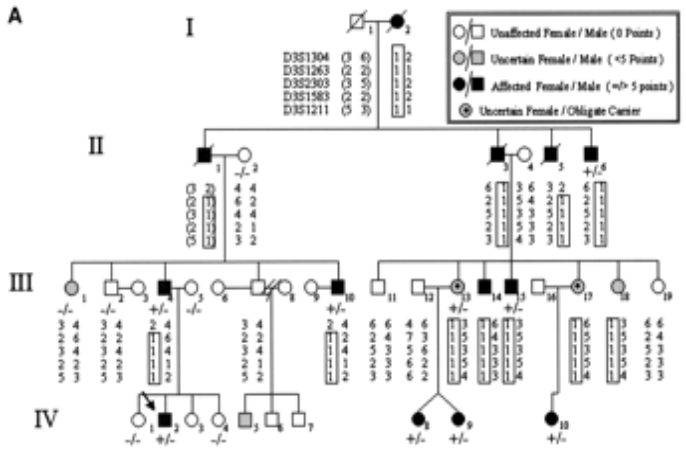

Normalized Currents
1.0
0.8
0.6
0.4
0.2
0.0
-140
-120
-100
-80
-60
-40
-20
0
20
Voltage (mV)
Activation
Inactivation
Na$_V$1.5 / WT
Na$_V$1.5 / R219H

Specificity of R219H substitution



Gosselin-Badaroudine et al., PlosONE , 2012;7(11):e48690.

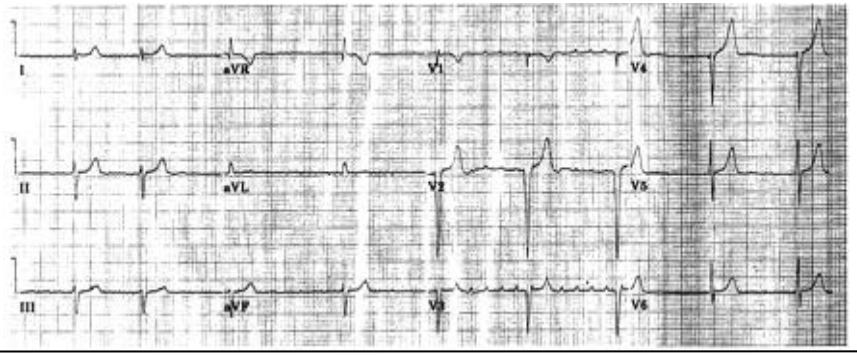
DCM and SCN5A gene

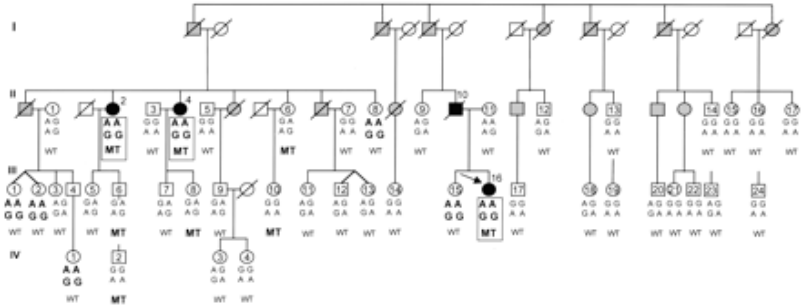


Phenotypes: <u>Conduction disease and DCM</u>

Genotype: D1275N *SCN5A*

McNair et al. Circulation 2004

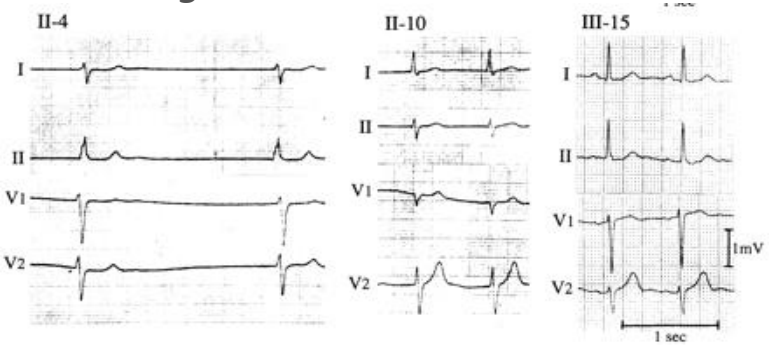




Phenotype: <u>Atrial standstill and DCM</u>

Genotype: D1275N *SCN5A* <u>and</u> Cx40 pol.

Groenewagen et al. Cir Res 2003



Thanks' for your kind attention!!!!!

Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

Please Visit:

www.omicsgroup.com

www.conferenceseries.com

http://cardiology.conferenceseries.com/