Electrophysiologie moléculaire
- troubles du rythme et de la conduction cardiaques

Isabelle BARÓ, PhD

Equipe Canaux ioniques et arythmies cardiaques

L'unité de recherche de l'institut du thorax

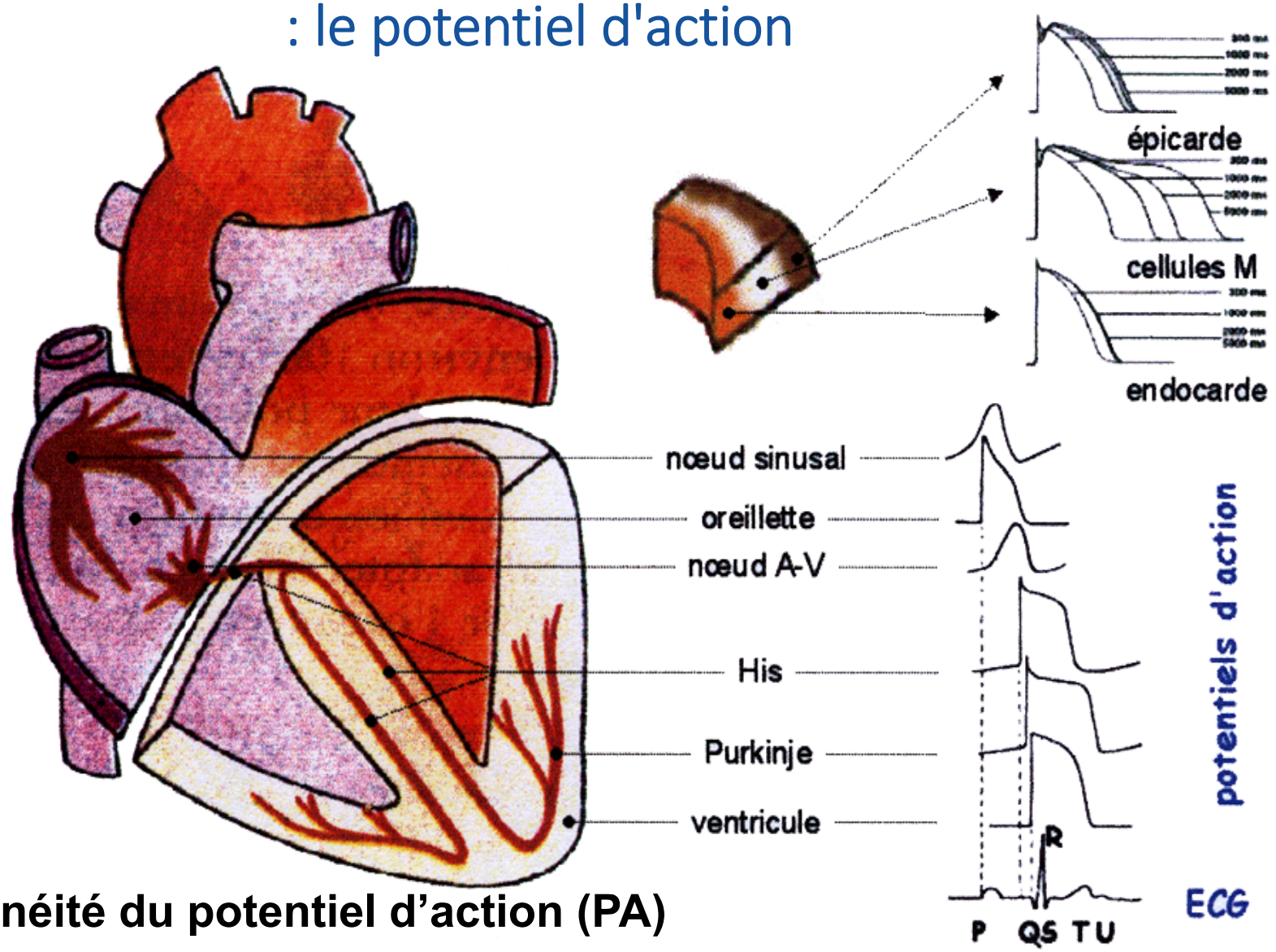
Inserm UMR 1087 / CNRS UMR 6291

Nantes, France

MASTER 1 Biologie et Santé - Thorax

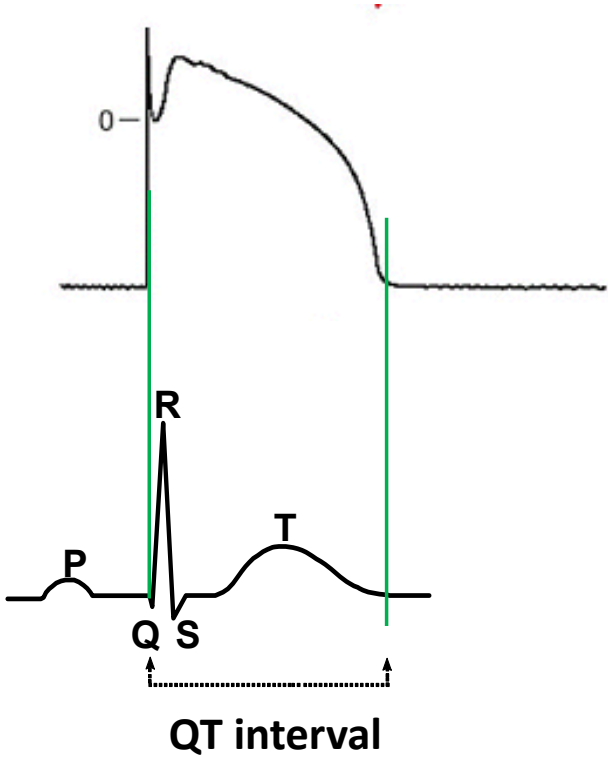
2024-2025

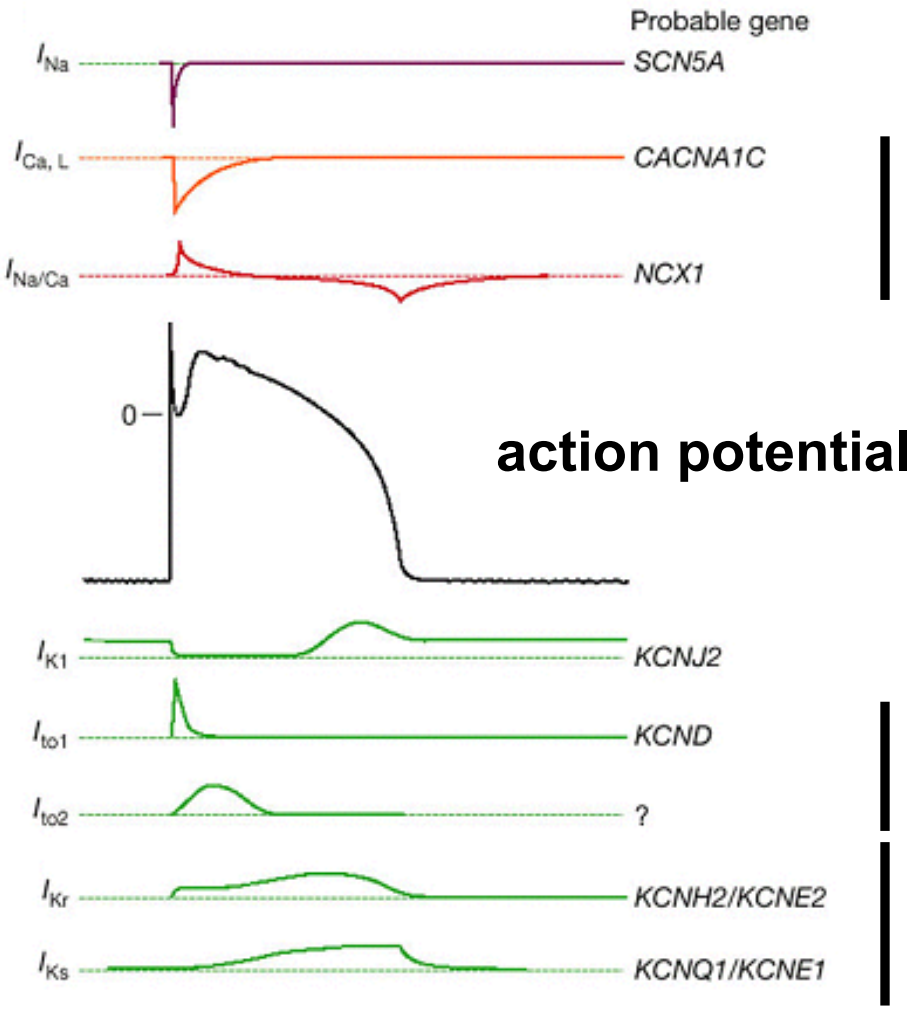
Activité électrique du cardiomyocyte : le potentiel d'action



hétérogénéité du potentiel d'action (PA)

Activité électrique du cardiomyocyte ventriculaire : le potentiel d'action





action potential

early depolarization

plateau

diastolic potential

early repolarization

late repolarization

from Marbán E. Nature. 2002 Jan 10;415(6868):213-8 ← https://pubmed.ncbi.nlm.nih.gov/

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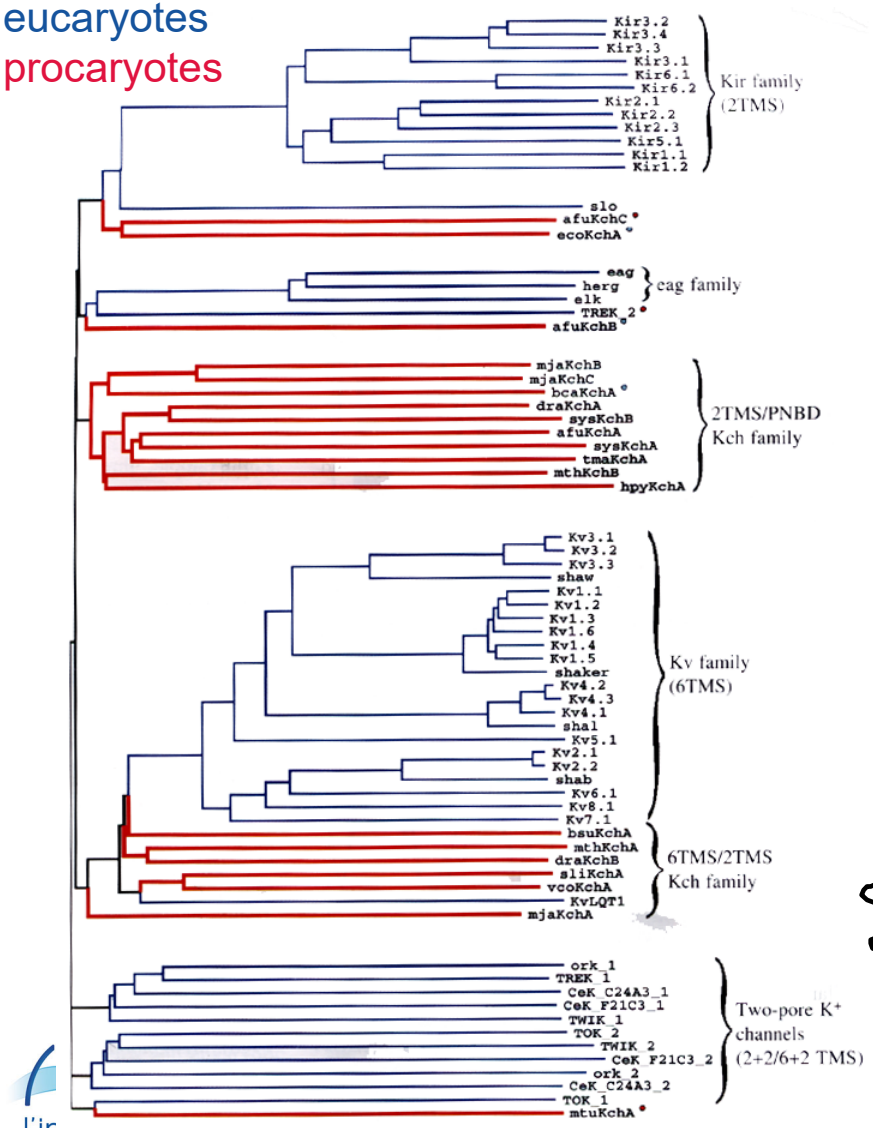
Canaux potassiques

dendrogramme

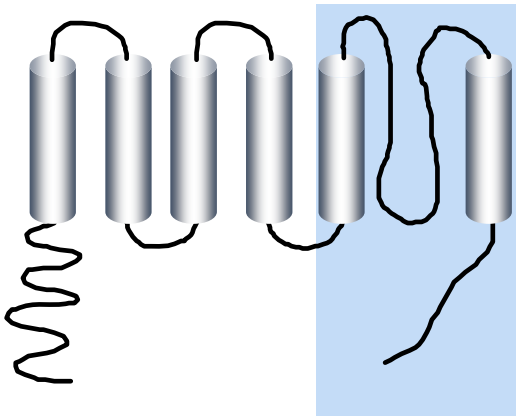
eucaryotes
procaryotes



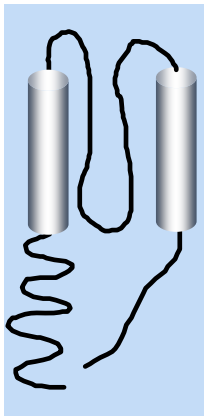
from Derst C, Karschin A. J Exp Biol. 1998 Oct;201(Pt 20):2791-9

→ **3 classes**

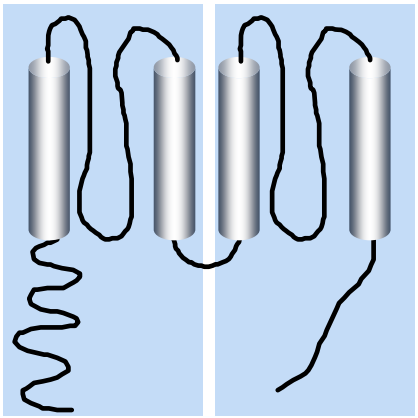
6 segments transmembranaires (TMS) et 1 boucle du pore



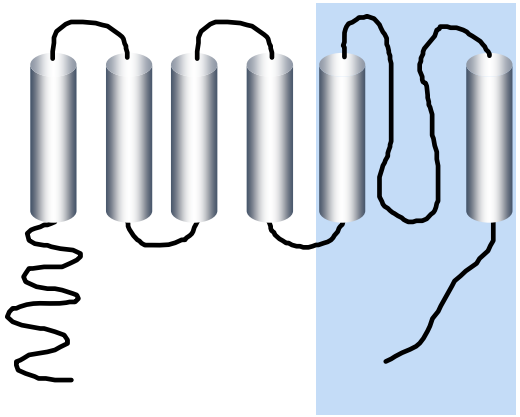
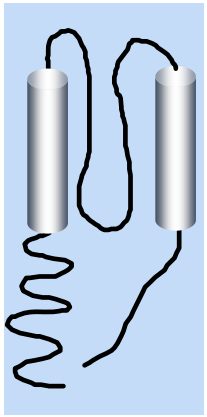
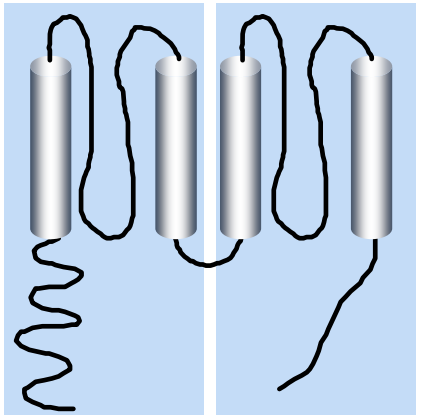
2 TMS et 1 boucle du pore



4 TMS et 2 boucles du pore



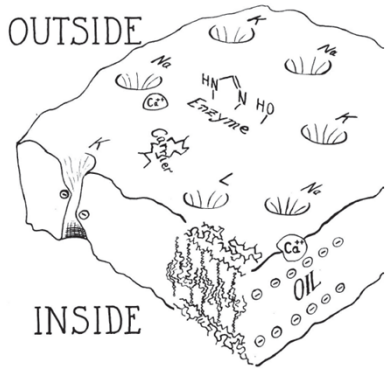
3 classes de canaux K^+

	6 segments transmembranaires (TMS) et 1 boucle du pore	2 TMS et 1 boucle du pore	4 TMS et 2 boucles du pore
Trace hydropathie			
Structure	tétramère	tétramère	dimère
Régulateurs	principalement $V_{membrane}$	principalement ligand: ATP, Prot G	stimuli physiques chimiques
Cibles	$V_{membrane}$; [ion]		

De l'hypothèse à la structure cristallographique d'un canal

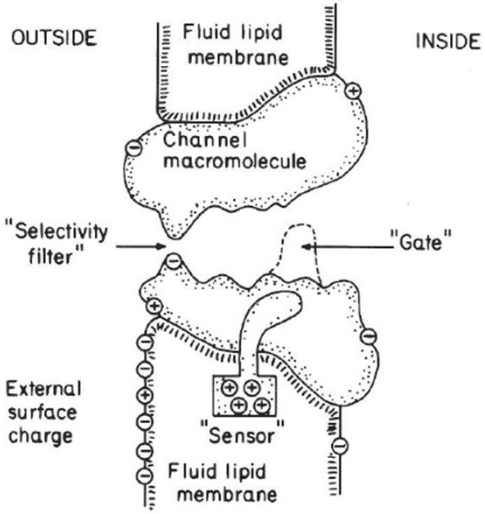
Hypothèse de travail (1967)

Hille B. 1967. A pharmacological analysis of the ionic channels of nerve. PhD thesis, Rockefeller Univ., New York



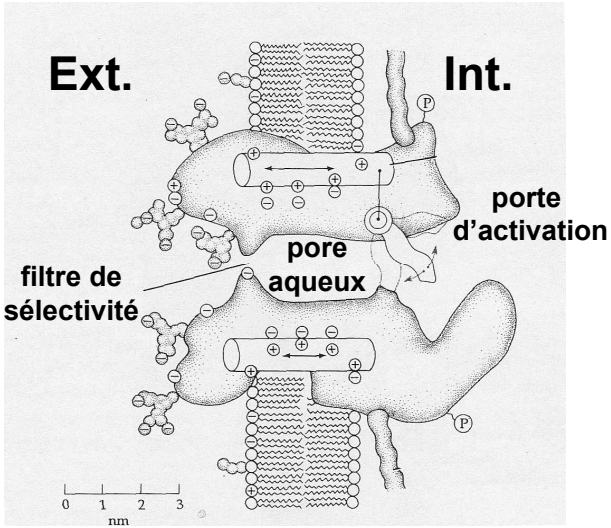
Hypothèse de travail (1977)

Hille B. 1977 J. Gen. Physiol. 69:497–515



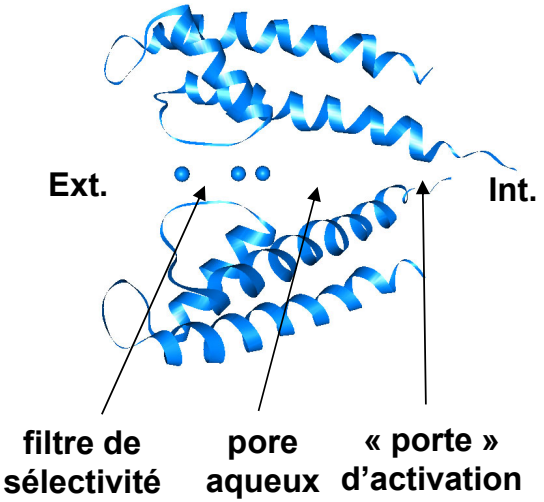
Hypothèse de travail (1992)

Hille B *in* Ionic Channels of Excitable Membranes (2nd edition). 1992; Sinauer Associated, MA 01375, U.S.A.



Structure de KcsA (1998)

from Doyle DA *et al*. Science. 1998 Apr 3;280(5360):69-77



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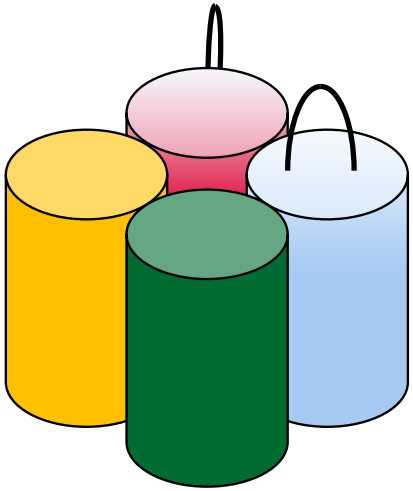
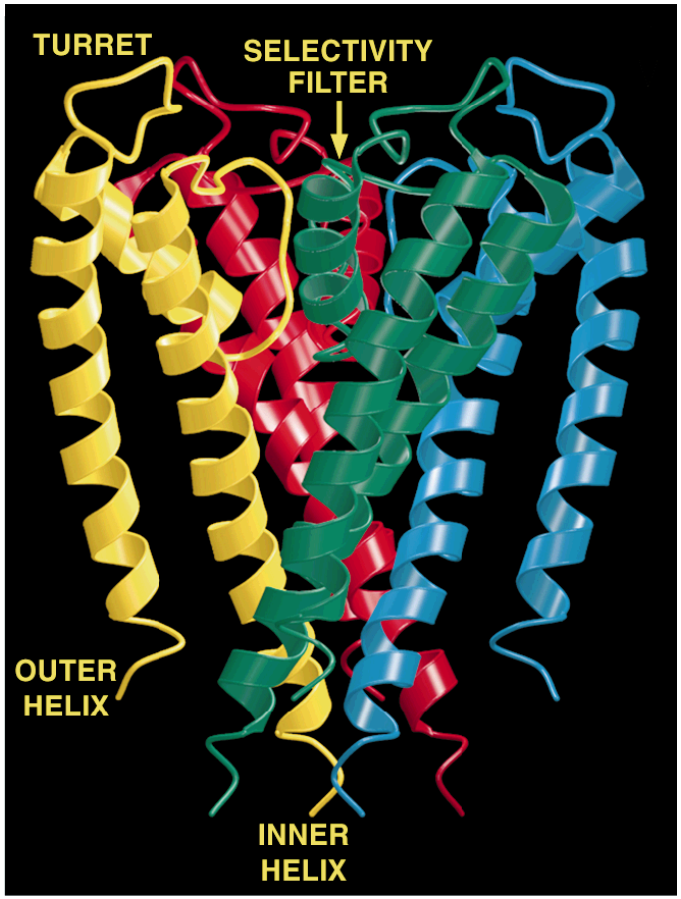
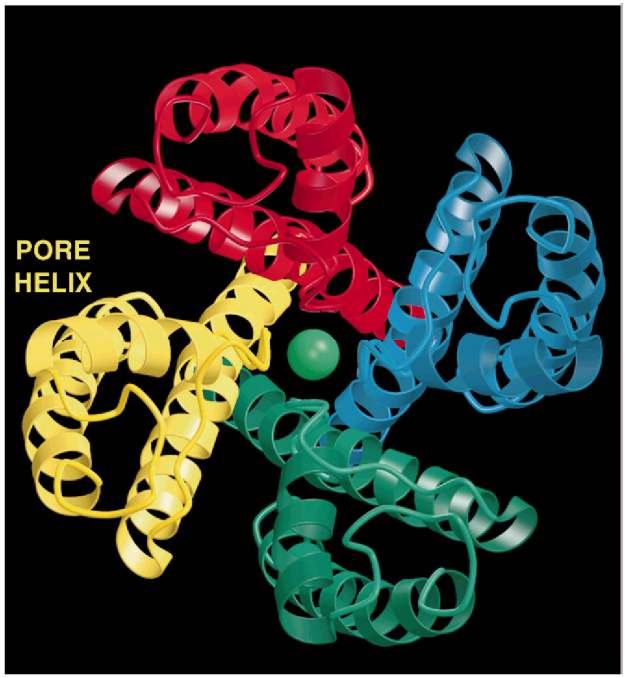
Structure cristallographique d'un canal K^+ à 2 TMS et 1 pore



Tétramères



KcSA



Prix Nobel de Chimie 2003 : Roderick Mac Kinnon

(resolution: 3.2 Å)

D'après Doyle DA *et al*. Science. 1998 Apr 3;280(5360):69-77

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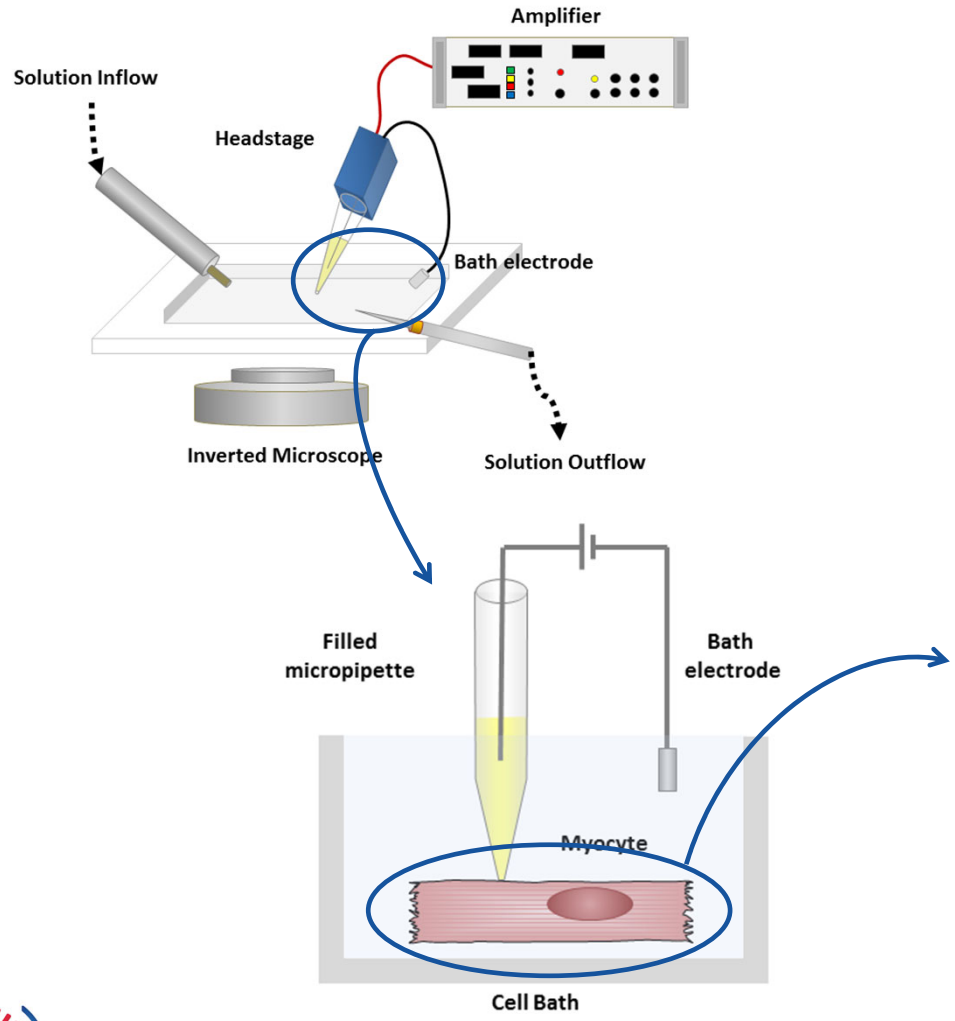
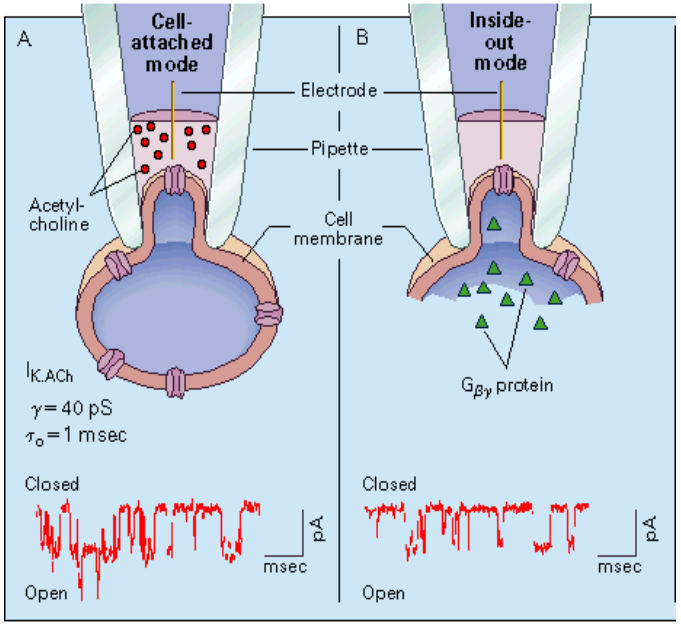
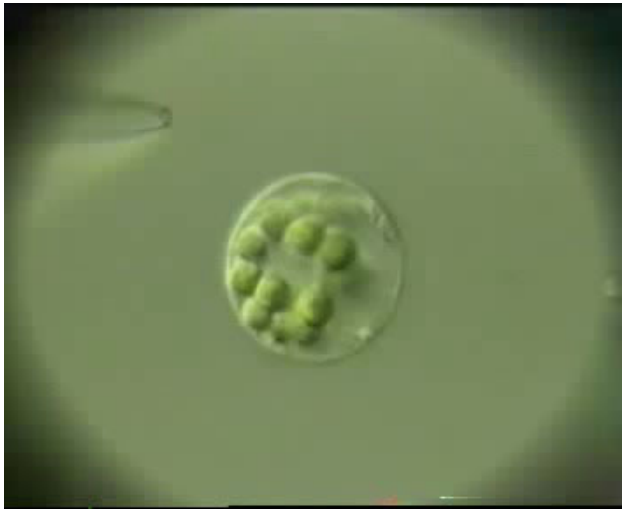
Enregistrement d'un courant unitaire : le patch-clamp





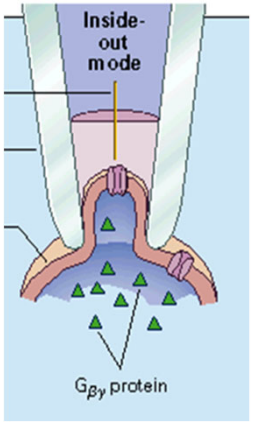


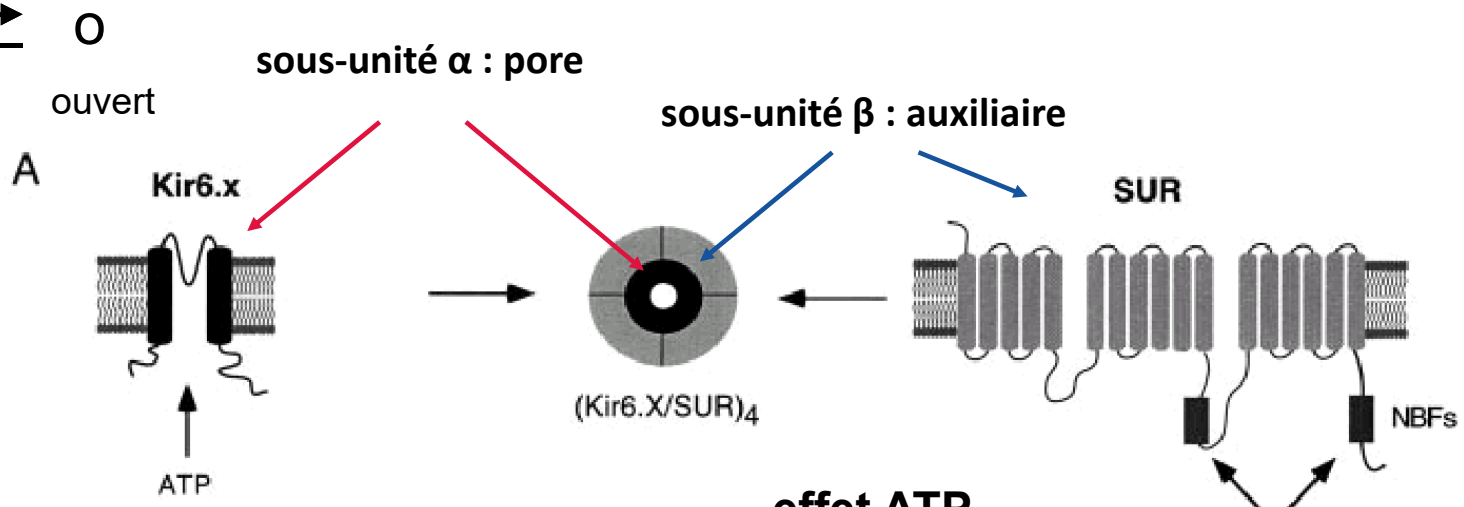
Prix Nobel de Physiologie 1991 : Erwin Neher & Bert Sakmann

canaux K_{ATP} du pancréas (cellules ß des ilôts de Langerhans)

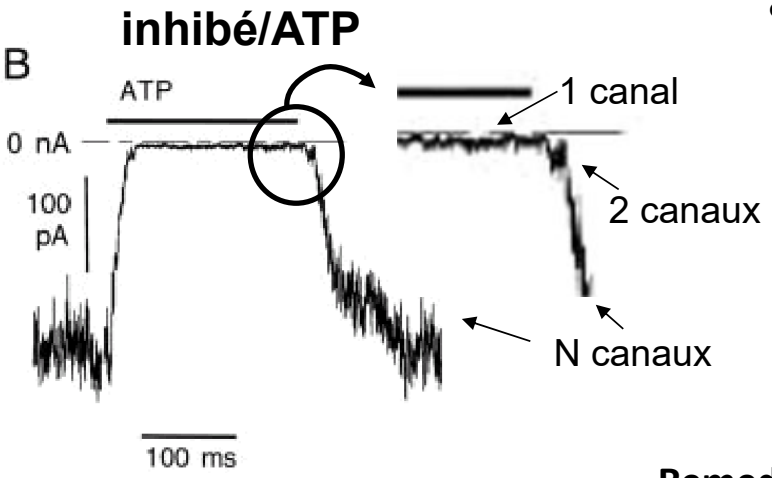
C ⇄ O

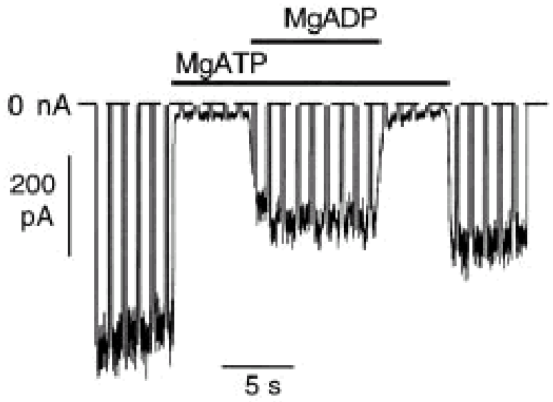
fermé ouvert





effet ATP antagonisé/ADP





Remedi MS, Koster JC. Pflugers Arch. 2010 Jul;460(2):307-20.

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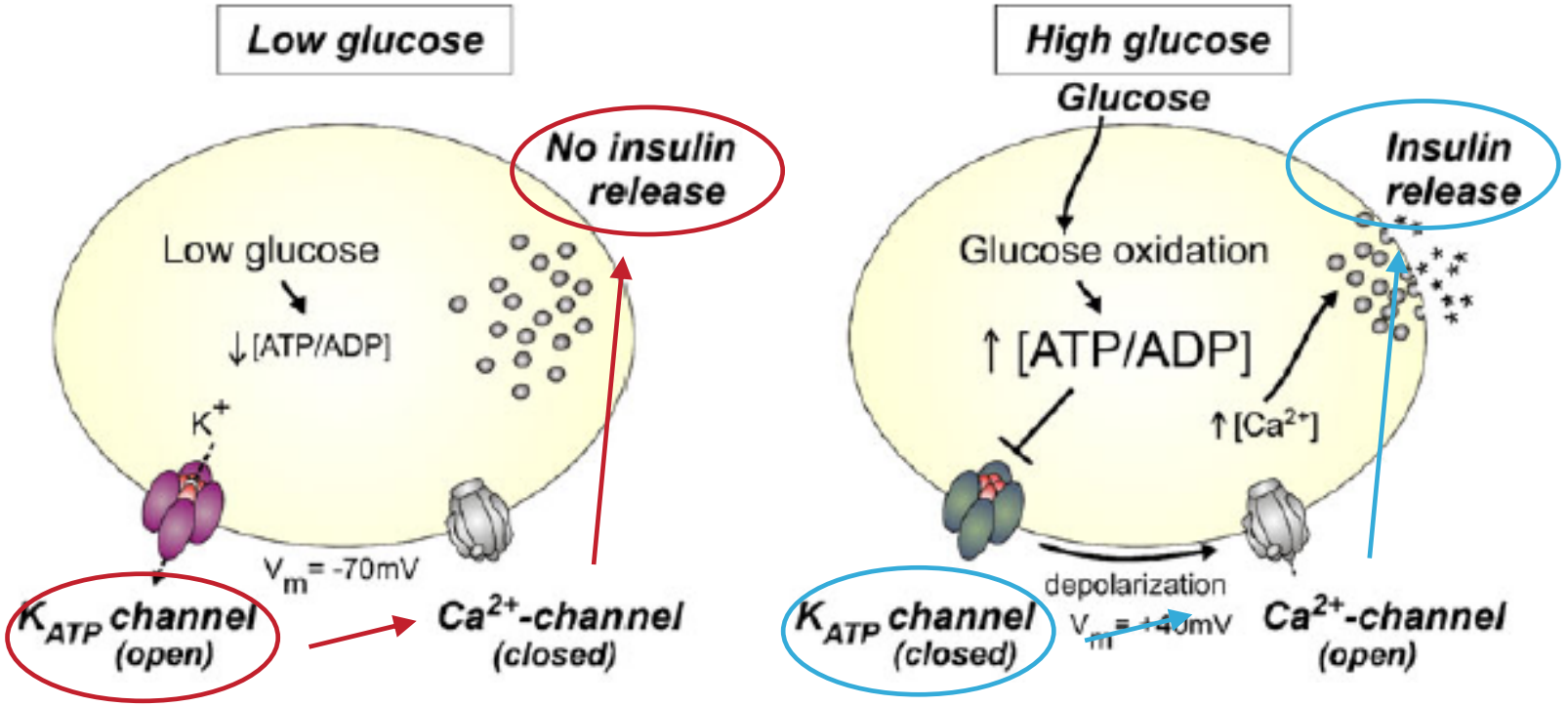
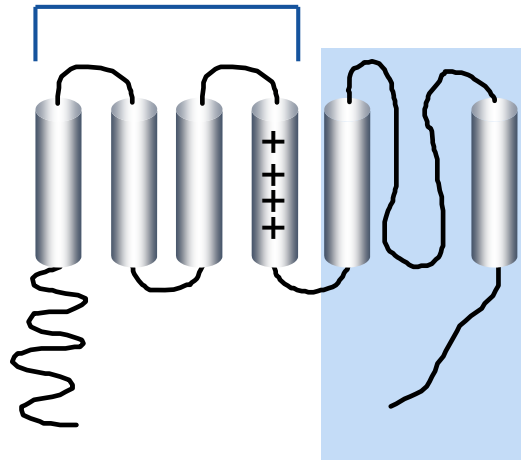
canaux K_{ATP} du pancréas (cellules ß) rôle dans la sécrétion d'insuline

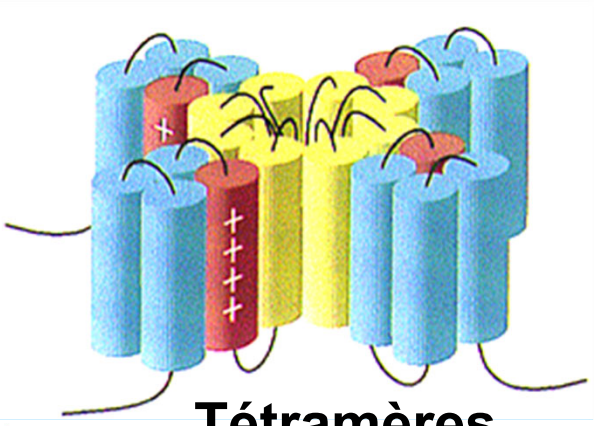


Remedi MS, Koster JC. Pflugers Arch. 2010 Jul;460(2):307-20.

Structure d'un canal K^+ 6 TMS et 1 pore

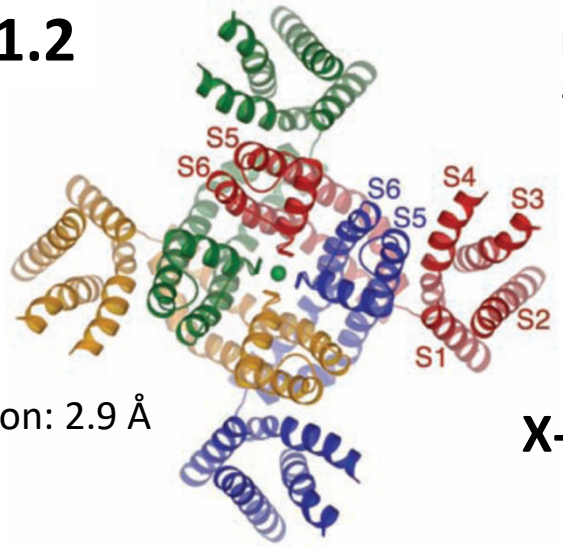
voltage sensor





Tétramères

Kv1.2



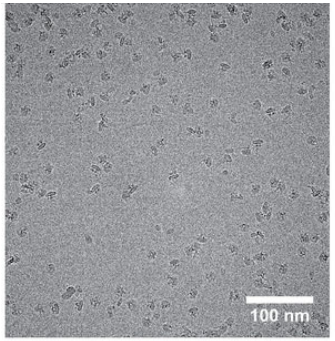
Long SB *et al.* Science. 2005 Aug 5;309(5736):897-903.

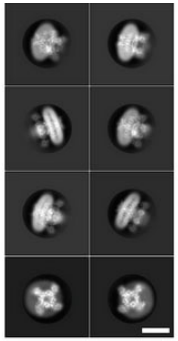
resolution: 2.9 Å

X-ray crystallography

hERG

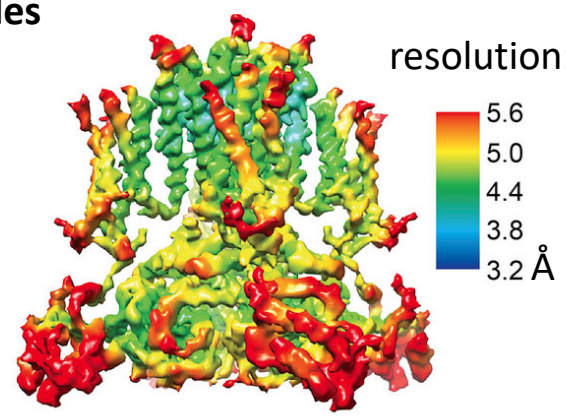
~144,000 particles





10 nm

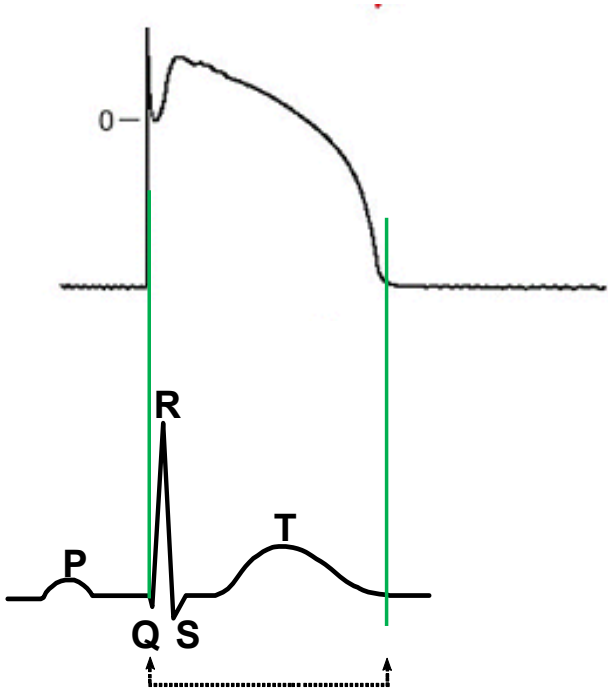
resolution:

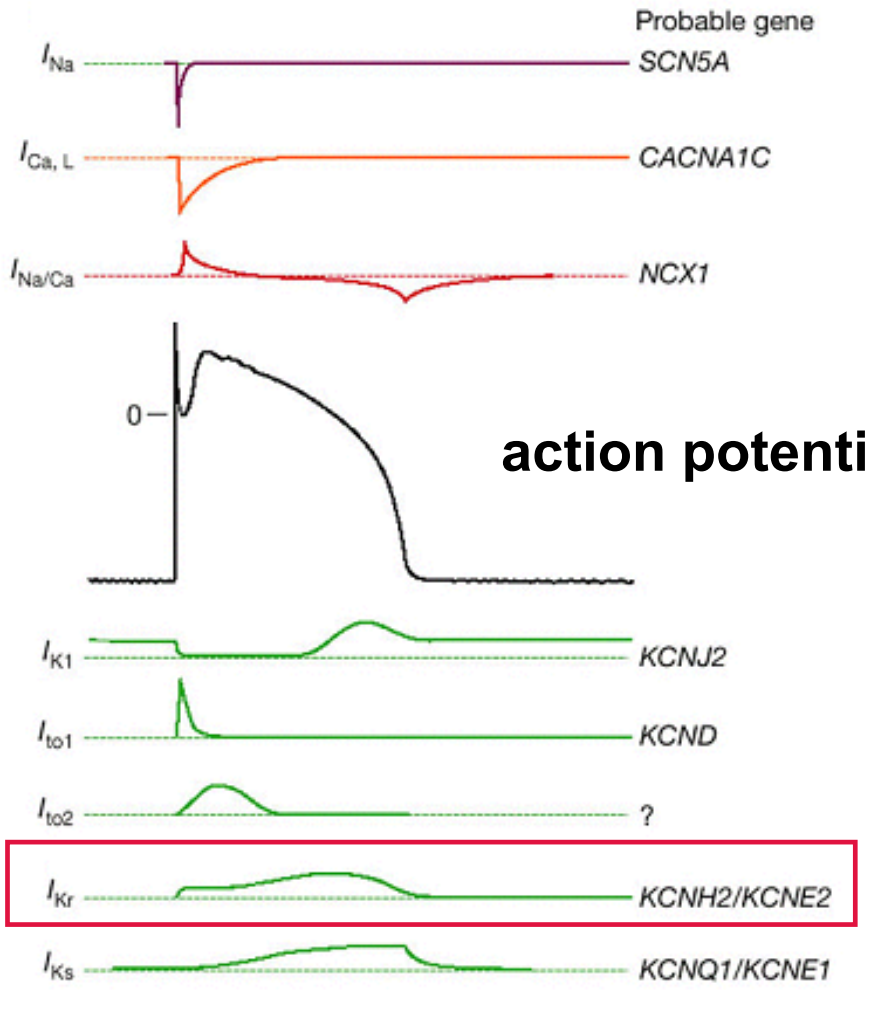


Cryo-electron microscopy

Wang W *et al.* Cell. 2017 Apr 20;169(3):422-430.e10.

Activité électrique du cardiomyocyte ventriculaire : le potentiel d'action





early depolarization

plateau

action potential (AP)

diastolic potential

early repolarization

late repolarization

from Marbán E. Nature. 2002 Jan 10;415(6868):213-8

Etude d'une mutation de hERG associée au Syndrome du QT long

- **Syndrome du QT long (ECG : intervalle QTc > 450-470 ms), fibrillation ventriculaire (torsades de pointes), mort subite**

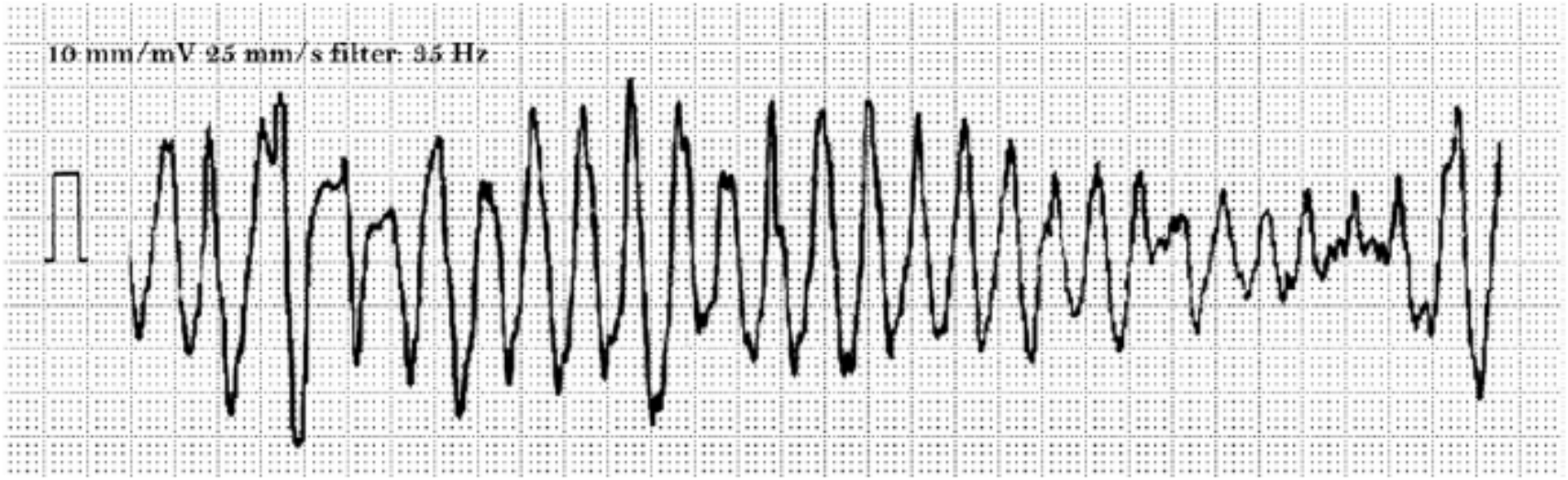


Fig. 1. ECG recording showing an ongoing episode of Torsade de pointes. This polymorphic ventricular arrhythmia is characterized by the progressive rotation of the electrical axis (180 ° in about 10–12 cycles) which shows on the surface ECG as the sinusoidal undulation of the electrical signal.

Saenen JB, Vrints CJ. J Mol Cell Cardiol. 2008 Apr;44(4):633-46.

Etude d'une mutation de hERG associée au Syndrome du QT long

Table 1 Classification of genes responsible for cardiac channelopathies. Adapted from Schwartz et al. [2]

LQTS type	Gene	Mutation frequency among LQTS population (%)	Locus	Protein (functional effect)
Romano–Ward (RWS) **mut/WT**				
LQT1	KCNQ1	40–55	11p15.5	K_V7.1 (↓)
LQT2	KCNH2	30–45	7q35–36	K_V11.1 (↓)
LQT3	SCN5A	5–10	3p21–24	Na_V1.5 (↑)
LQT4	ANKB	< 1	4q25–27	Ankyrin B (↓)
LQT5	KCNE1	< 1	21q22.1	MinK (↓)
LQT6	KCNE2	< 1	21q22.1	MiRP1 (↓)
LQT7	KCNJ2	< 1	17q23	Kir2.1 (↓)
LQT8	CACNA1C	< 1	12p13.3	L-type calcium channel (↑)
LQT9	CAV3	< 1	3p25	Caveolin 3 (↓)
LQT10	SCN4B	< 1	11q23.3	Sodium channel-β4 (↓)
LQT11	AKAP9	< 1	7q21–22	Yotiao (↓)
LQT12	SNTA1	< 1	20q11.2	Syntrophin α1 (↓)
LQT13	KCNJ5	< 1	11q24	Kir3.4 (↓)
LQT14	CALM1	< 1	14q32.11	Calmodulin 1 (dysfunctional Ca^{2+} signaling)
LQT15	CALM2	< 1	2p21	Calmodulin 2 (dysfunctional Ca^{2+} signaling)
Jervell and Lange-Nielsen syndrome (JLNS) **mut/mut**				
JLN1	KCNQ1	< 1	11p15.5	K_V7.1 (↓)
JLN2	KCNE1	< 1	21q22.1–22.2	MinK (↓)

Arrows up (↑) or down (↓) showing gain or loss of protein function, respectively

LQT long QT, *RWS* Romano–Ward syndrome, *JLNS* Jervell and Lange-Nielsen syndrome

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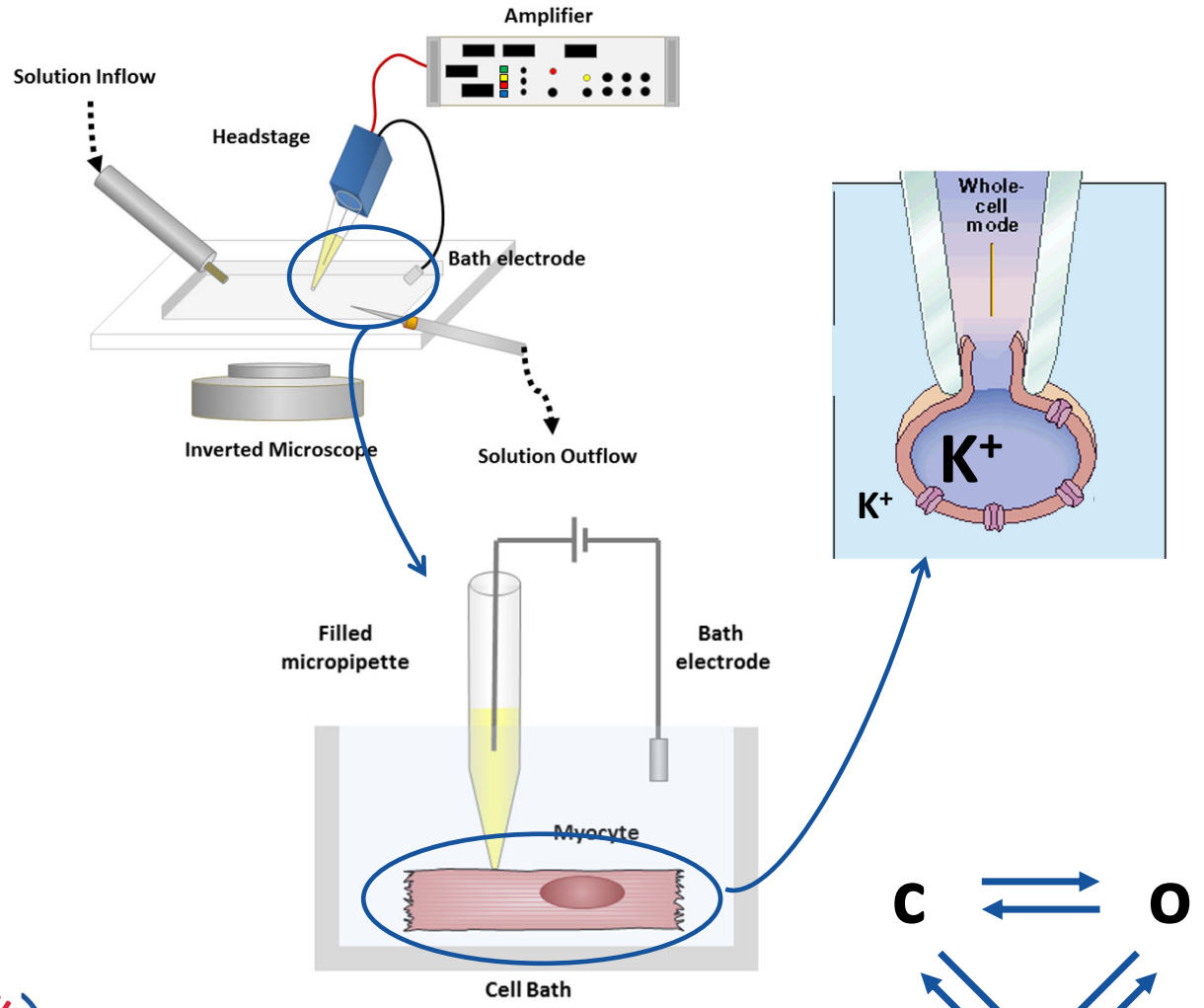
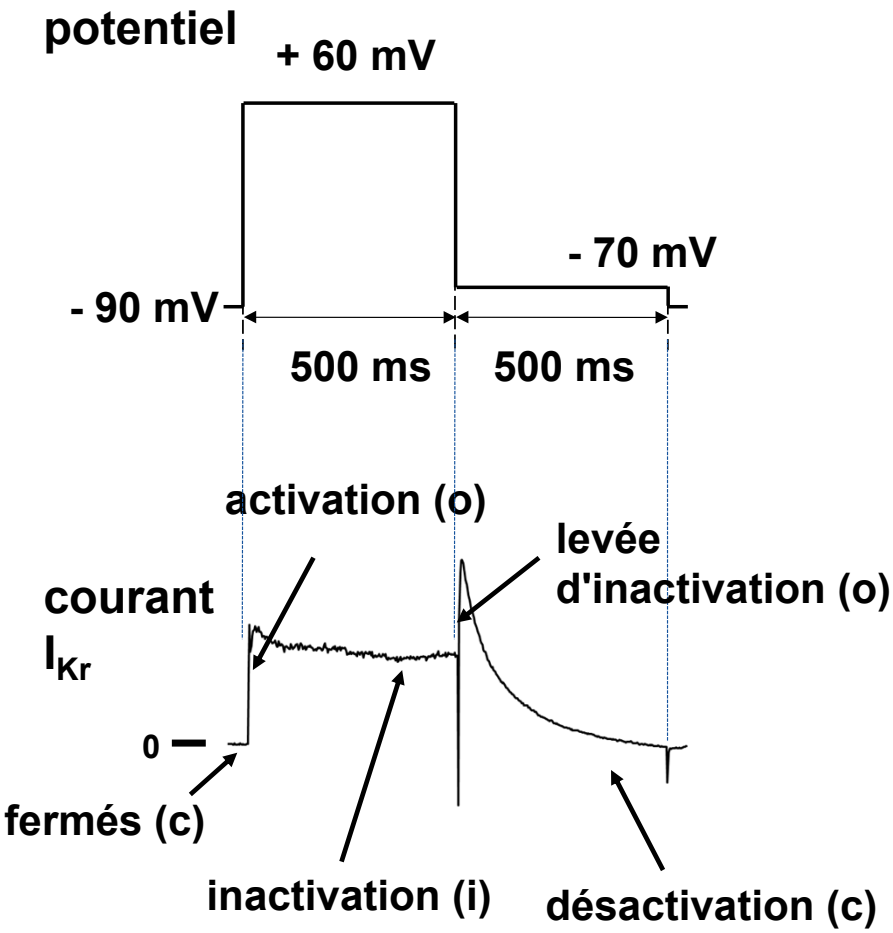
Wallace E *et al*. Pediatr Cardiol. 2019 Oct;40(7):1419-1430.

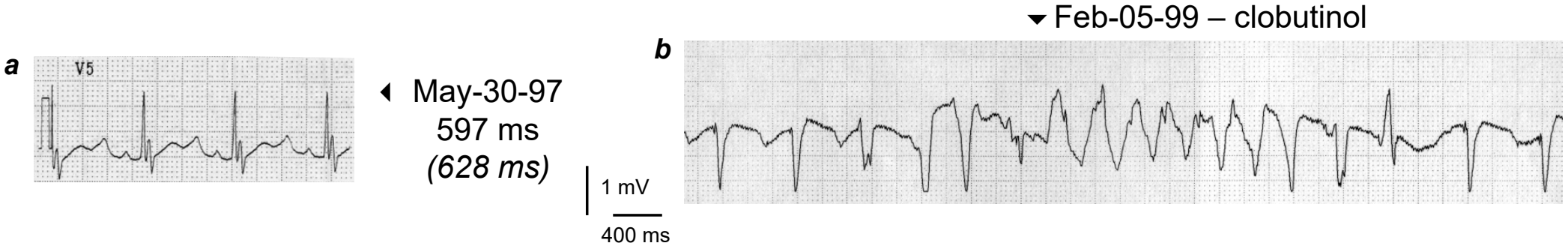
Enregistrement d'un courant trans-membranaire : le patch-clamp



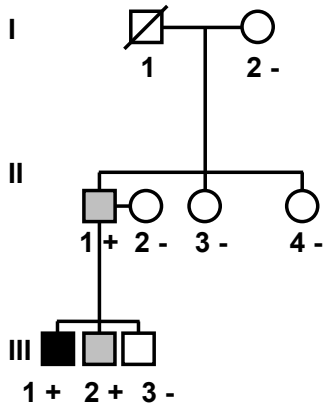


Etude d'une mutation de hERG associée au Syndrome du QT long

Propositus : fibrillation ventriculaire (torsades de pointes)



Génotypage



+ : hERG A561P ← **causal ?**

- : hERG WT

porteur hétérozygote :

Modèles cellulaires

- **Lignées cellulaires modifiées - canalopathies monogéniques**

expression hétérologue de protéines WT et mutées

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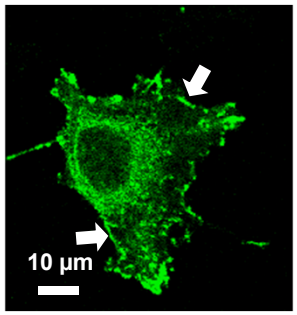
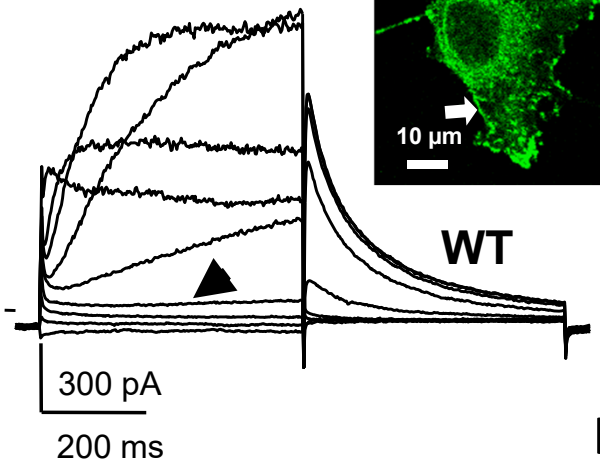
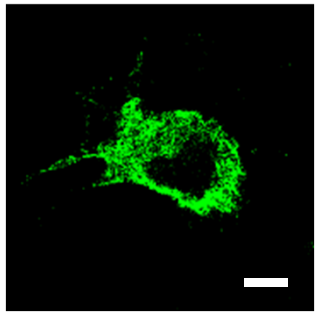
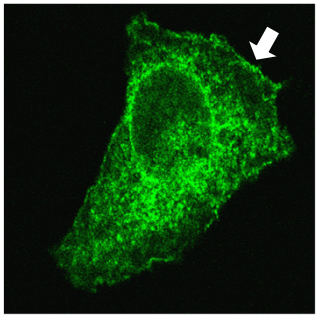
Bellocq C *et al*. Mol Pharmacol. 2004 Nov;66(5):1093-102

injected COS-7





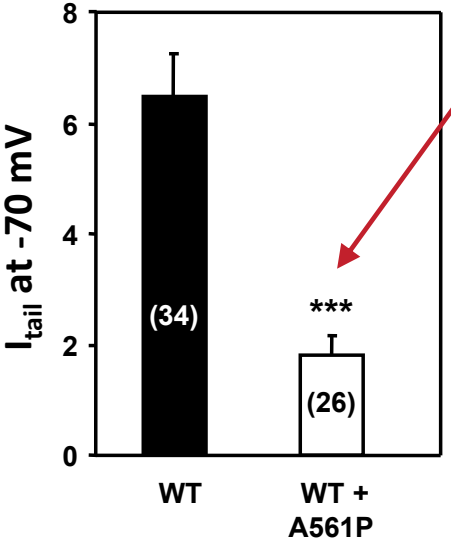


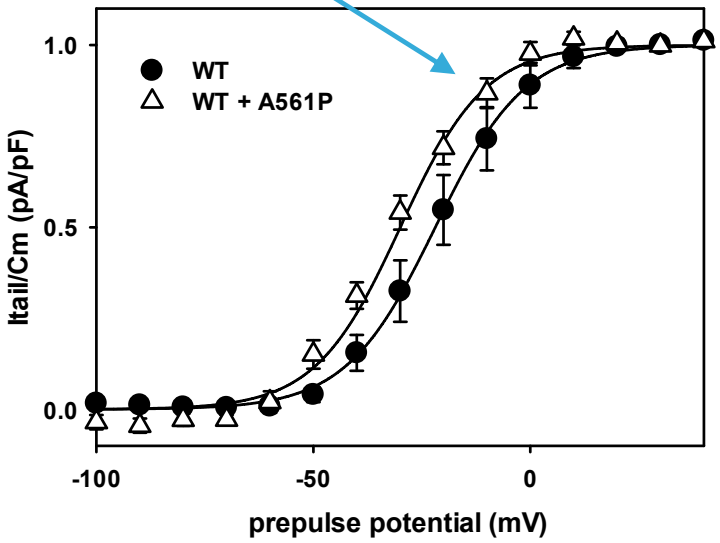


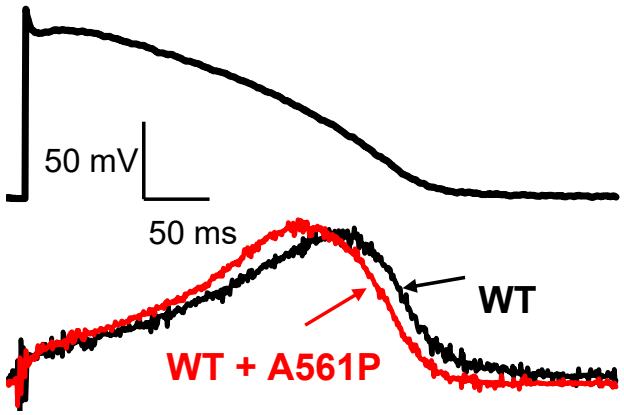
WT + A561P

perte/gain de function ?

WT + A561P







Bellocq C *et al*. Mol Pharmacol. 2004 Nov;66(5):1093-102

Modèles *in silico*

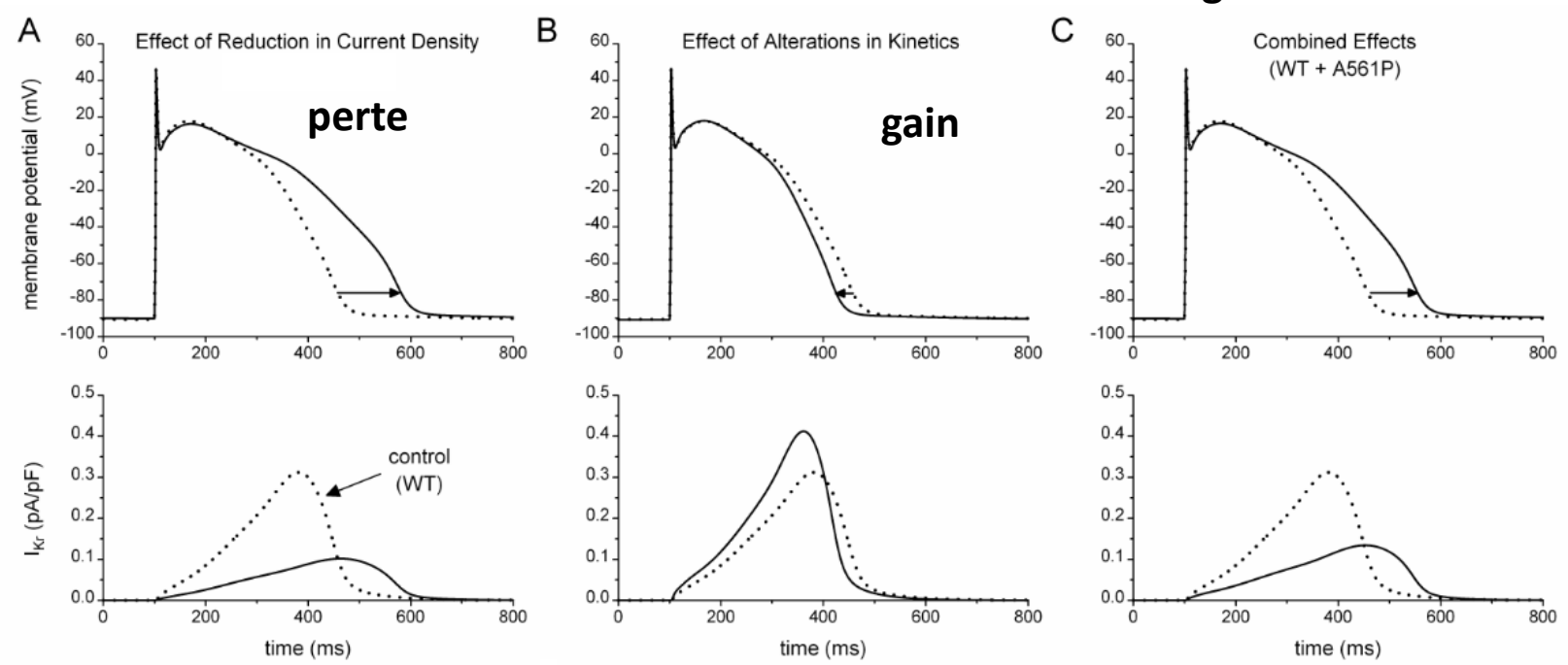
- **Modèle de potentiel d'action ventriculaire humain Priebe and Beuckelmann (1998) - modèle d'Hodgkin et Huxley (Prix Nobel de Physiologie 1963)**

perte/gain de function : allongement ➔ causal

$$I_K = n^4 \bar{g}_K (V - E_K)$$

$$1-n \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$



Rapidly Activating Current: I_{Kr}

$I_{Kr} = g_{Kr,max} \cdot Xr \cdot rik \cdot (V - E_K)$

$E_K = (RT/F) \cdot \ln([K^+]_o/[K^+]_i)$

$g_{Kr,max} = 0.015$ mS/μF

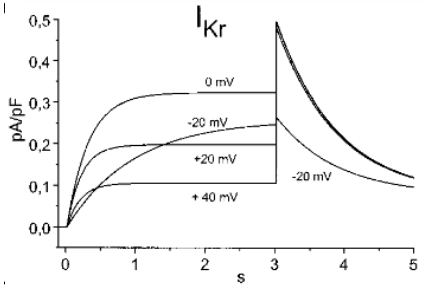
$\alpha_{Xr} = \{0.005 \cdot \exp[5.266 \cdot 10^{-4} \cdot (V+4.067)]\}/\{1+\exp[-0.1262 \cdot (V+4.067)]\}$

$\beta_{Xr} = \{0.016 \cdot \exp[1.6 \cdot 10^{-3} \cdot (V+65.66)]\}/\{1+\exp[0.0783 \cdot (V+65.66)]\}$

$rik = 1/\{1+\exp[(V+26)/23]\}$

$$\frac{dXr}{dt} = \alpha_{Xr}(1-Xr) - \beta_{Xr}Xr = \frac{Xr_\infty - Xr}{\tau_{Xr}}$$

where $g_{Kr,max}$ is g_{max} for I_{Kr}, Xr is the activation gate of I_{Kr}, rik is the inward-rectification factor of I_{Kr}, and E_K is the equilibrium potential for I_K.

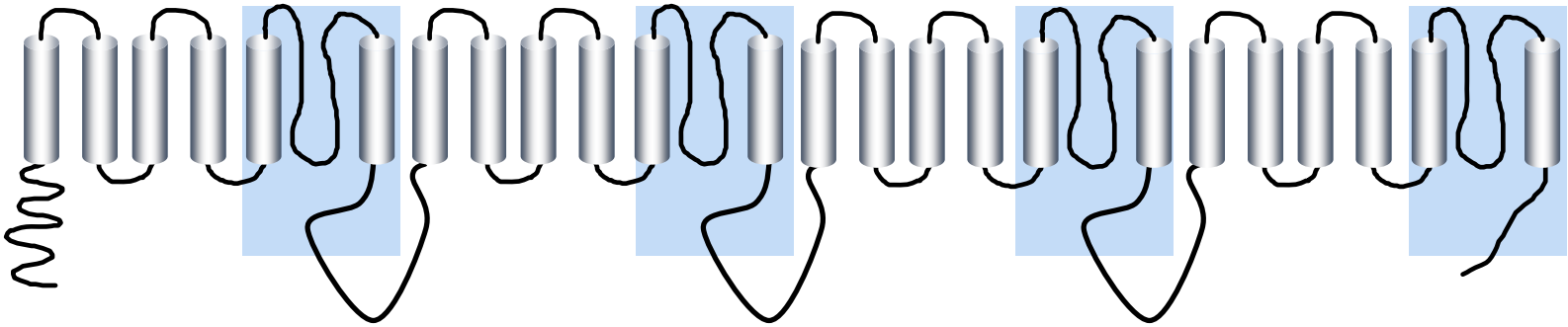


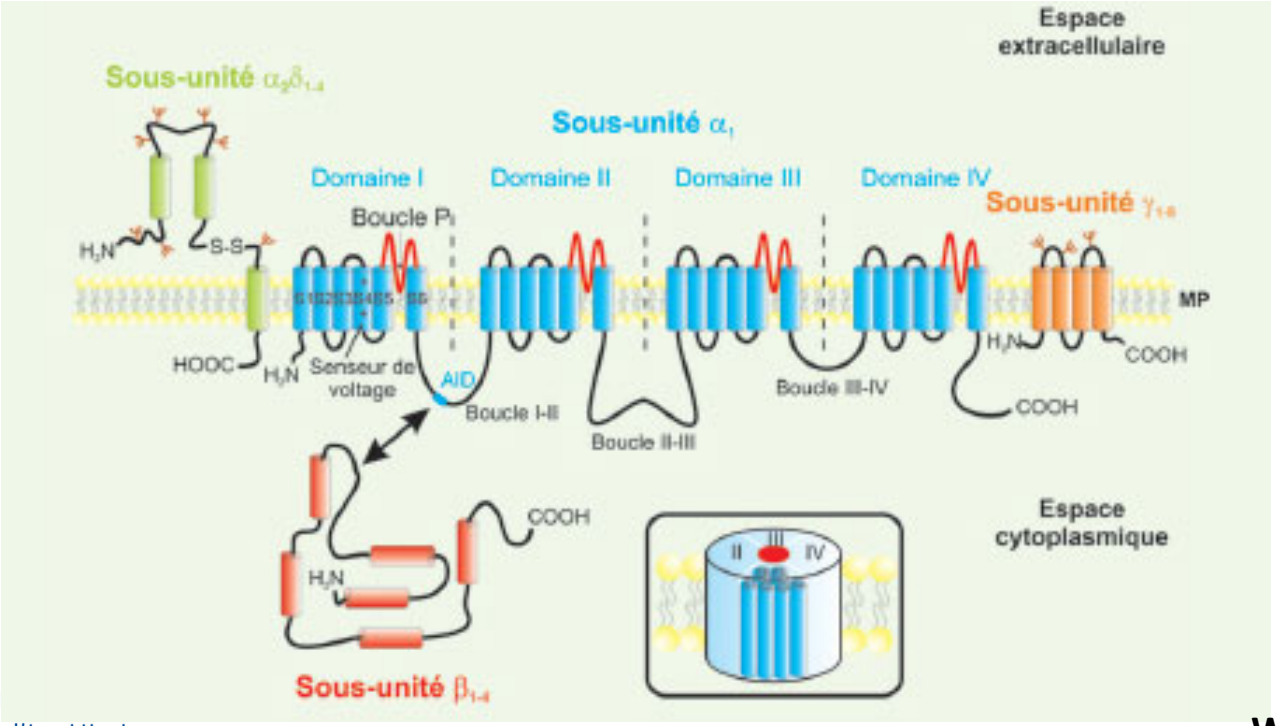
Hodgkin AL, Huxley AF. J Physiol. 1952 Aug;117(4):500-44.

Priebe L, Beuckelmann DJ. Circ Res. 1998 Jun 15;82(11):1206-23.

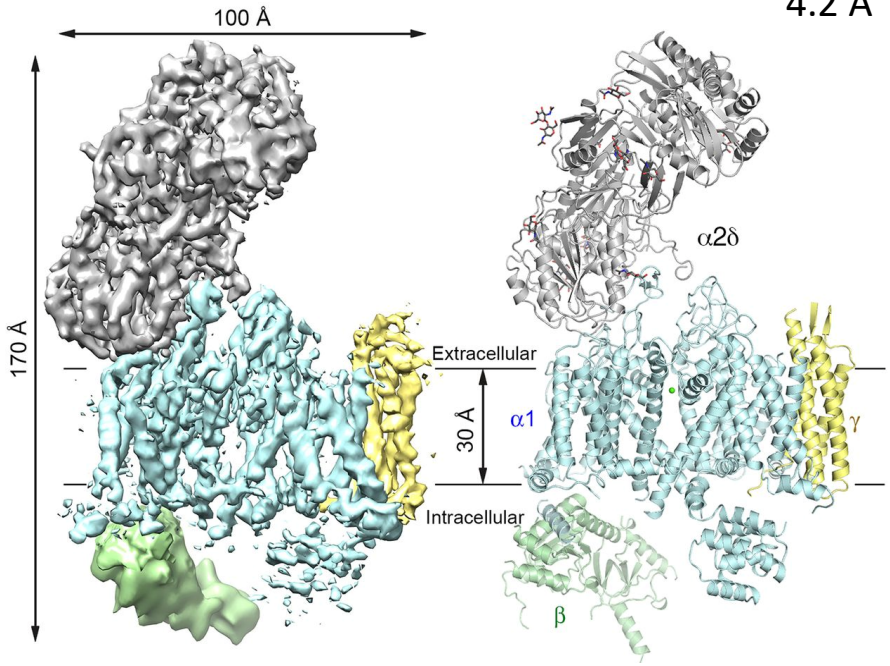
Bellocq C *et al.* Mol Pharmacol. 2004 Nov;66(5):1093-102.

Canaux Ca^{2+} : 4 domaines homologues





cryo-EM **Cav1.1** 4.2 Å



Wu J *et al*. Science. 2015 Dec 18;350(6267):aad2395

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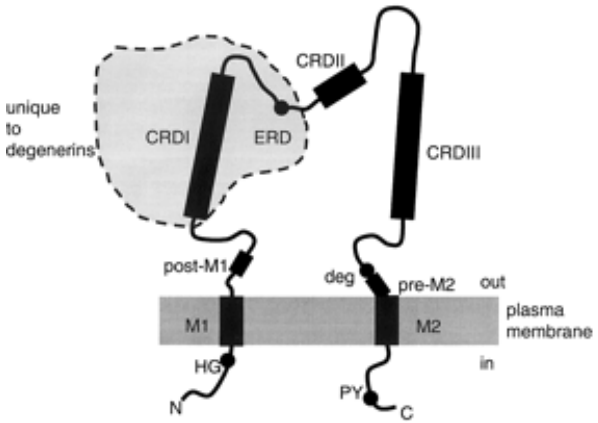
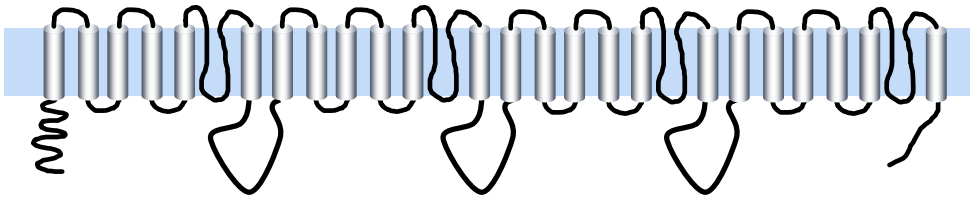
Canaux Na^+ : 2 classes

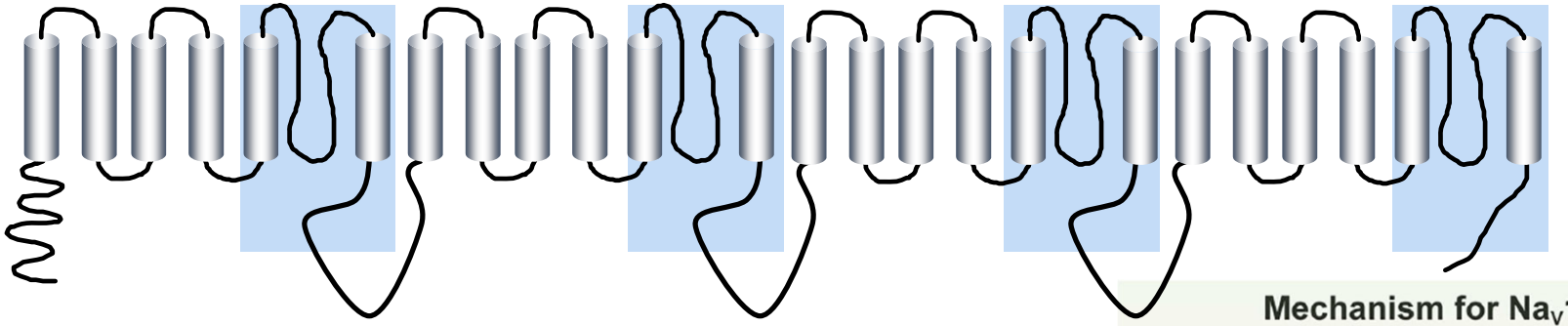


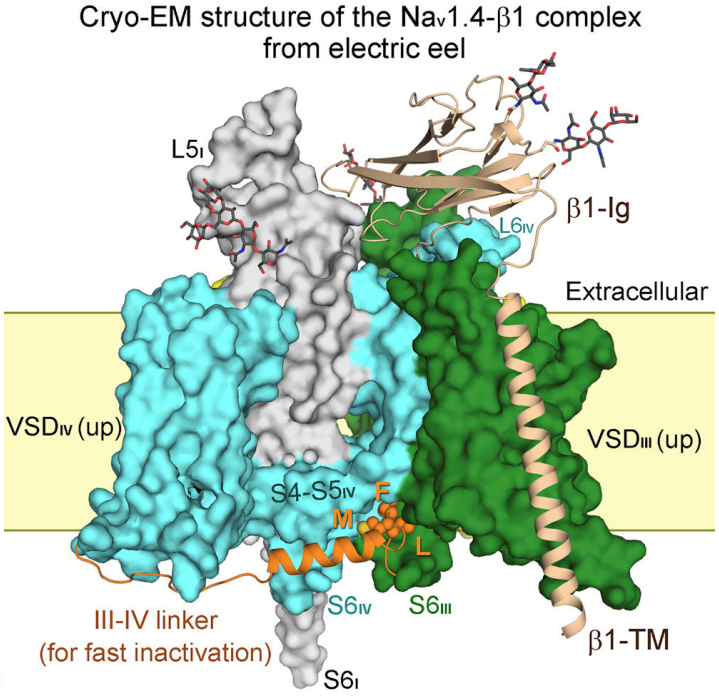
- **ENaC (epith. Na^+ channel)**



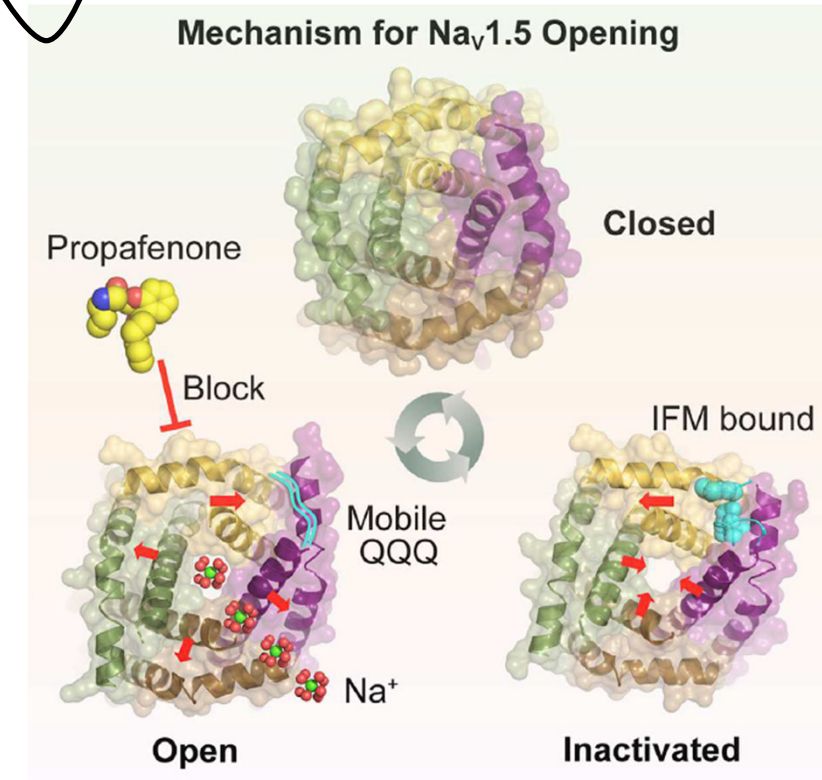
- **Nav: voltage-gated**
- **canal Na^+ cardiaque : Nav1.5 + Navß1 (*SCN5A* et *SCN1B*)**

Canaux Nav : structure





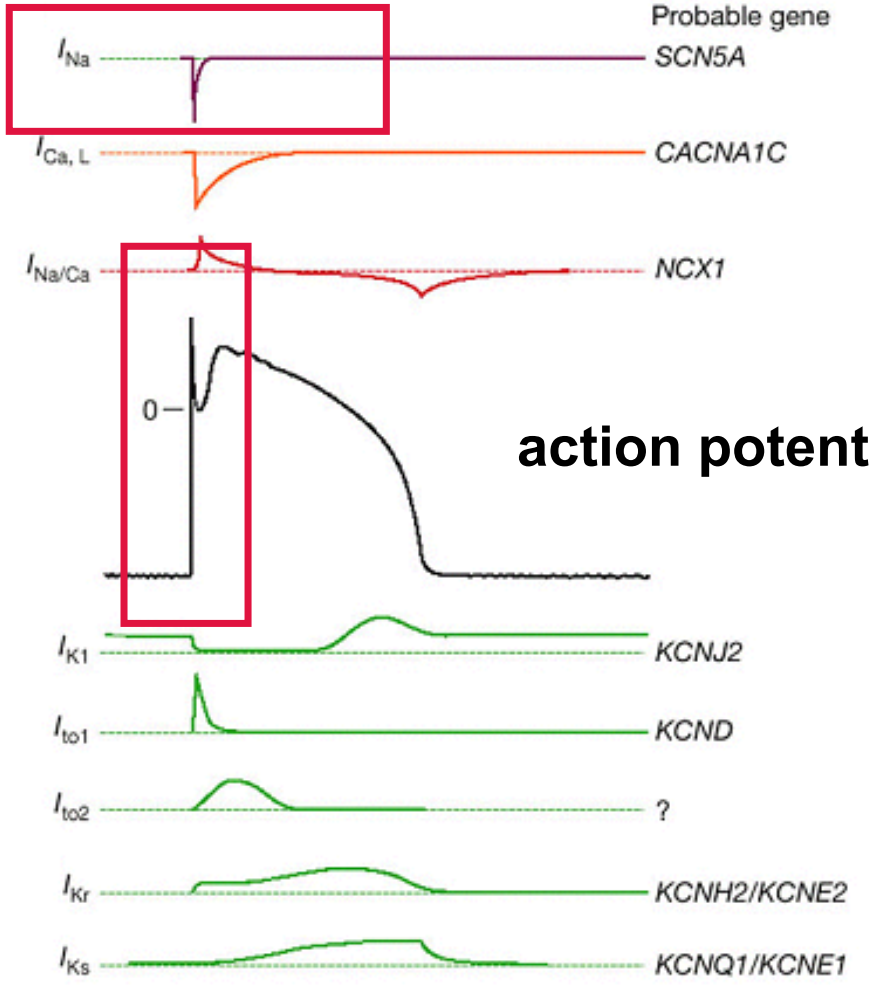
Yan *et* al. Cell. 2017 Jul 27;170(3):470-482.e11.



Jiang D *et al*. Cell. 2021 Sep 30;184(20):5151-5162.e11

Activité électrique du cardiomyocyte ventriculaire : le potentiel d'action

canal Nav1.5



early depolarization

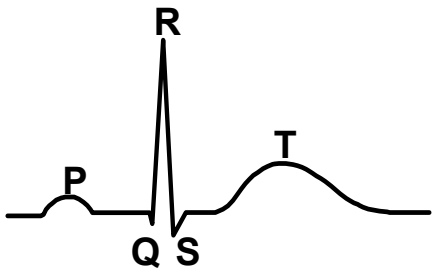
plateau

action potential (AP)

diastolic potential

early repolarization

late repolarization



complexe QRS

from Marbán E. Nature. 2002 Jan 10;415(6868):213-8

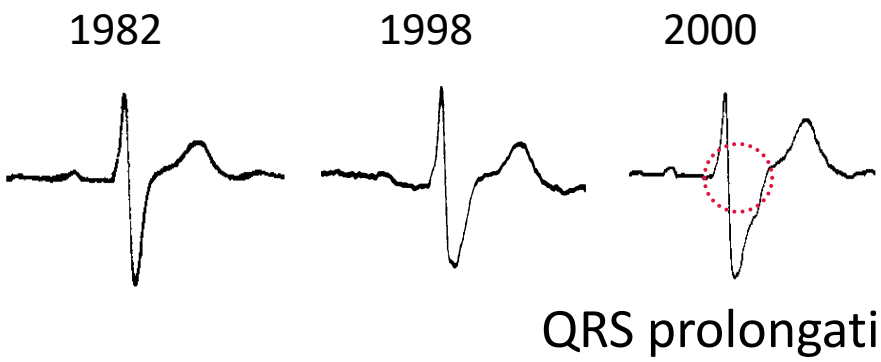
Du modèle cellulaire au modèle murin du syndrome de Lenègre

- **Syndrome de Lenègre : ralentissement de la conduction cardiaque héréditaire**

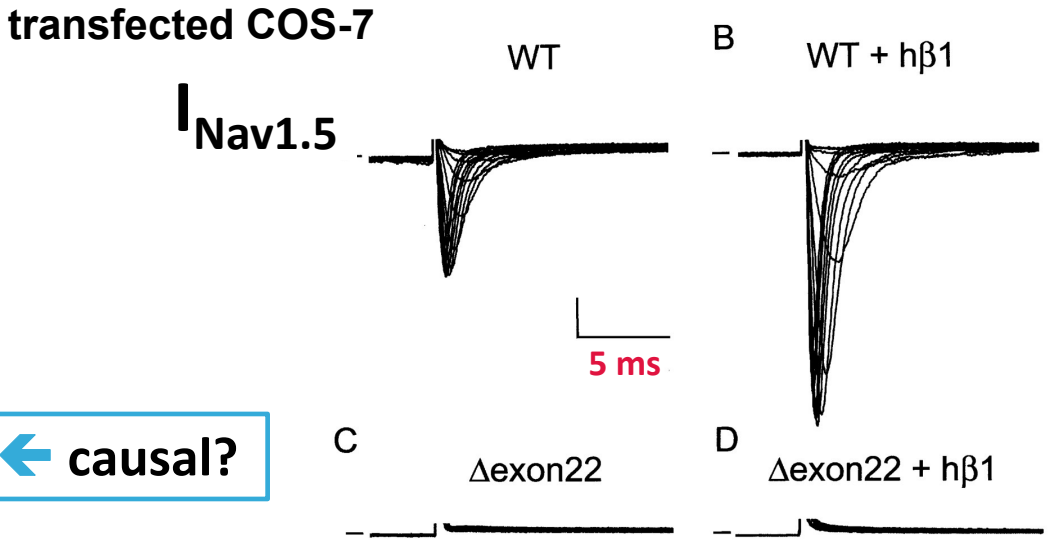
➔bloc de conduction

- **Modèles cellulaires: lignées cellulaires modifiées - canalopathies monogéniques**

Expression hétérologue de protéines Nav1.5 WT et mutées



QRS prolongation

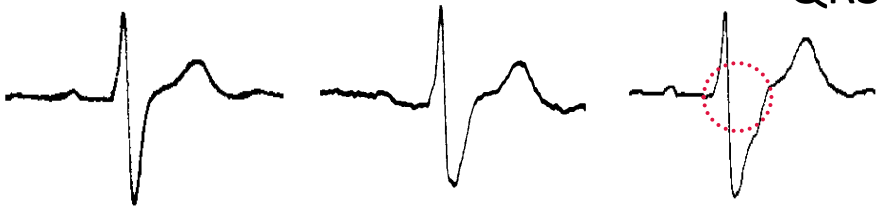


Mutation *SCN5A* : canal Nav1.5 Δexon22 ← causal?

Schott JJ *et al.* Nat Genet . 1999 Sep;23(1):20-1.
Probst V *et al*. J Am Coll Cardiol. 2003 Feb 19;41(4):643-52.

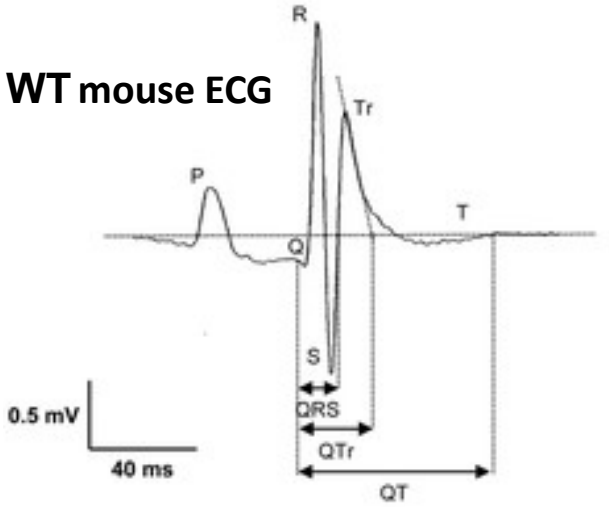
Du modèle cellulaire au modèle murin du syndrome de Lenègre

1982 1998 2000 QRS prolongation

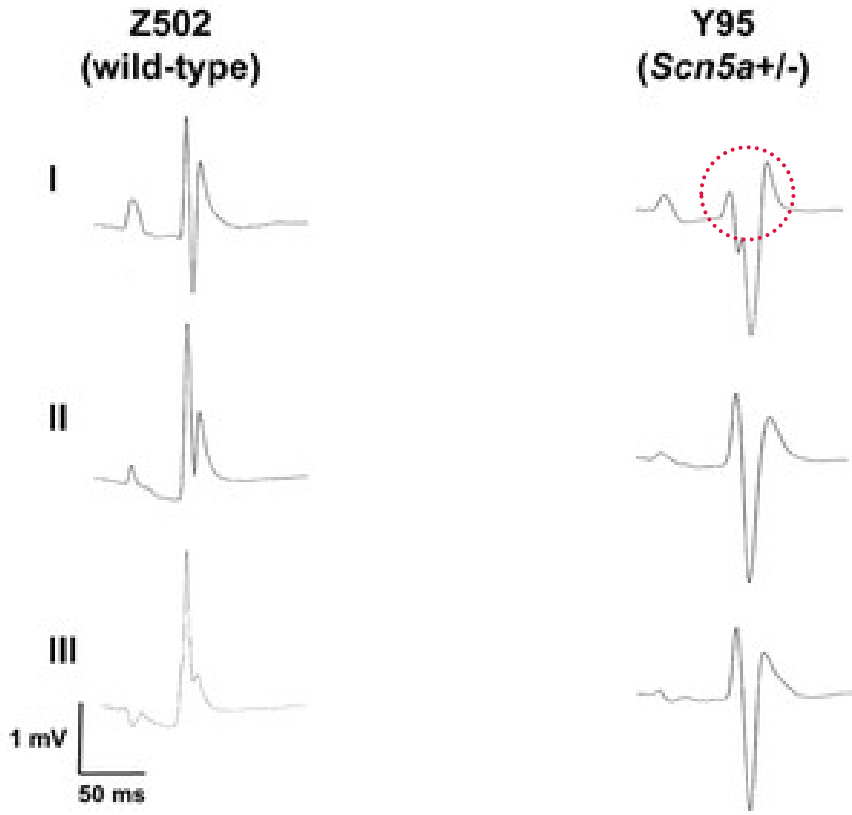


***SCN5A* mut : exon 22 absent**

WT mouse ECG



***Scn5a*$^{+/-}$ mouse**



Haplo-insuffisance de *SCN5A* ➔ causal

Schott JJ *et al.* Nat Genet . 1999 Sep;23(1):20-1.
Probst V *et al*. J Am Coll Cardiol. 2003 Feb 19;41(4):643-52.
Royer *et al.* Circulation. 2005 Apr 12;111(14):1738-46

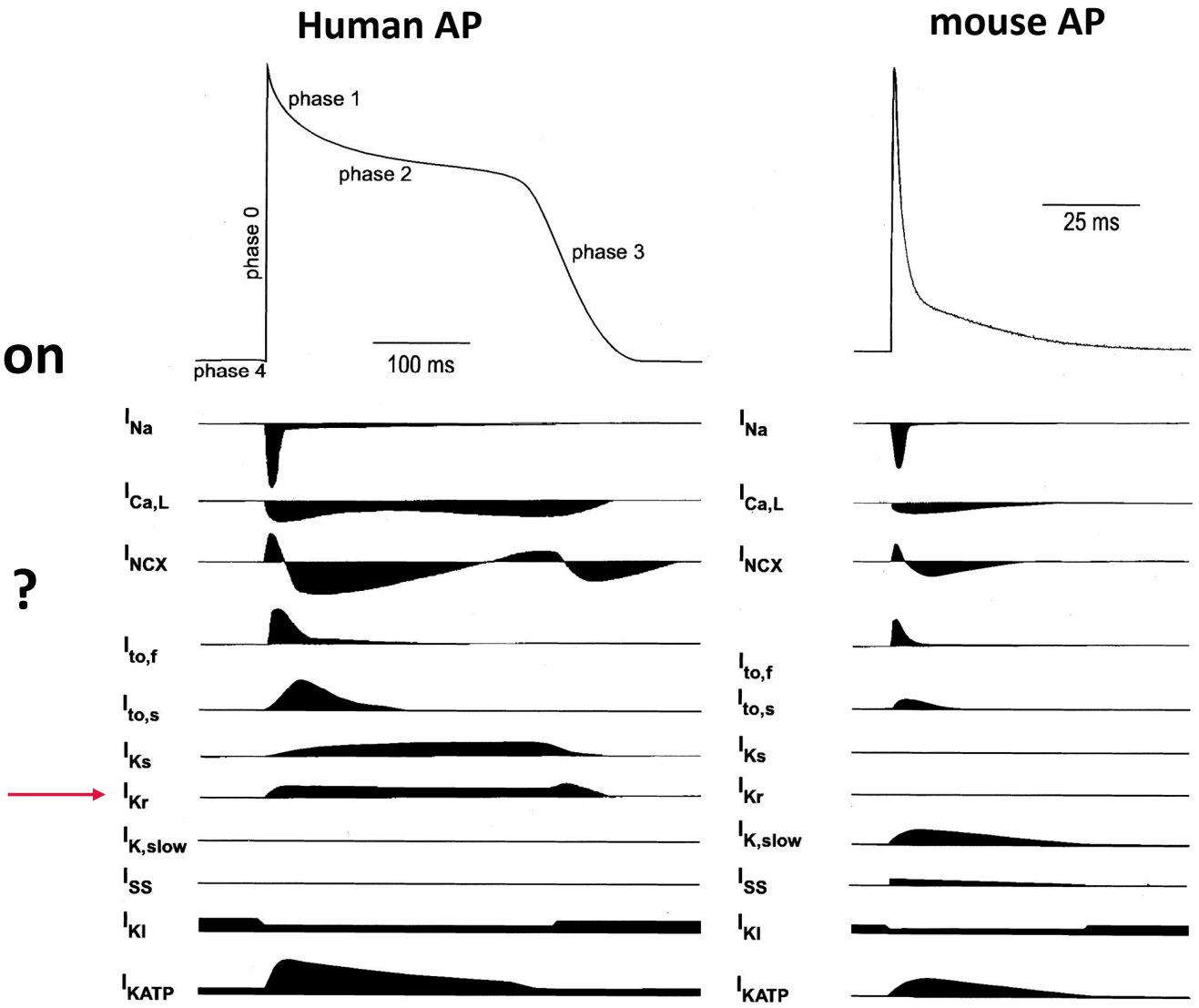
Limites

Modèles unicellulaires

- **lignées cellulaires : environnement protéique ? (complexe canalaire)**
- **modèles animaux : expression espèce-spécifique?**

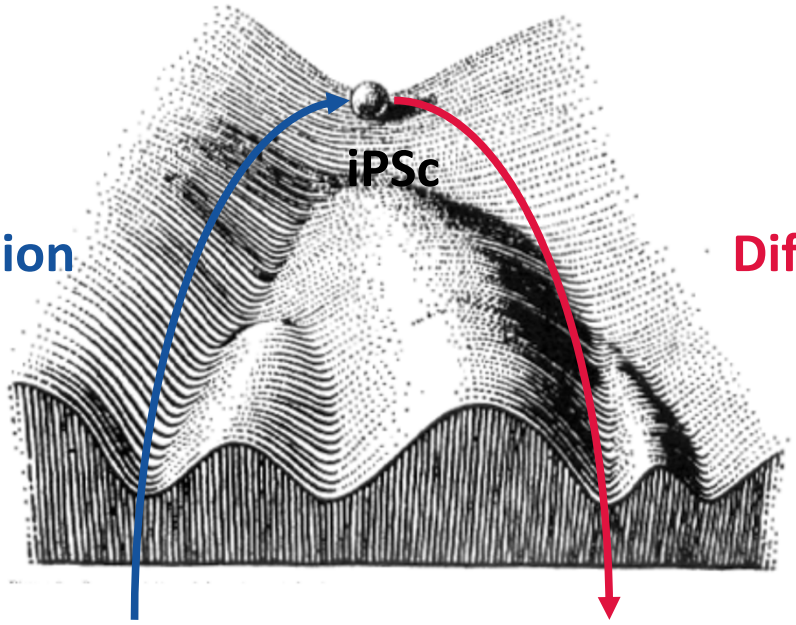
Modèles informatiques

- **environnement fonctionnel ?**



Nerbonne JM *et al*. Circ Res. 2001 Nov 23;89(11):944

Cardiomyocytes issus de cellules souches pluripotentes induites humaines (hiPS-CM)



Yamanaka S, Gurdon J: Prix Nobel de médecine 2012
"...for the discovery that mature cells can be reprogrammed to become pluripotent."

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Cardiomyocytes issus de cellules souches pluripotentes induites (iPS-CM)

Cellules d'origine :

- **peau, sang, urine**
- **porte le patrimoine génétique du patient (mutations, variants, SNP...)**

Cardiomyocytes issus d'iPSc

- **générés au laboratoire dans des conditions acceptables (éthique, temps et budget)**
- **environnement génétique humain**

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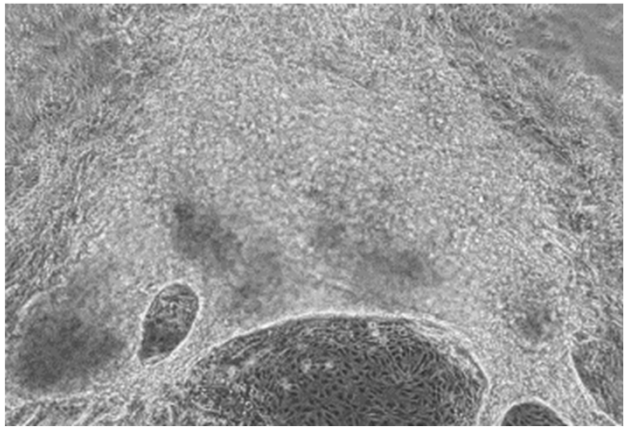
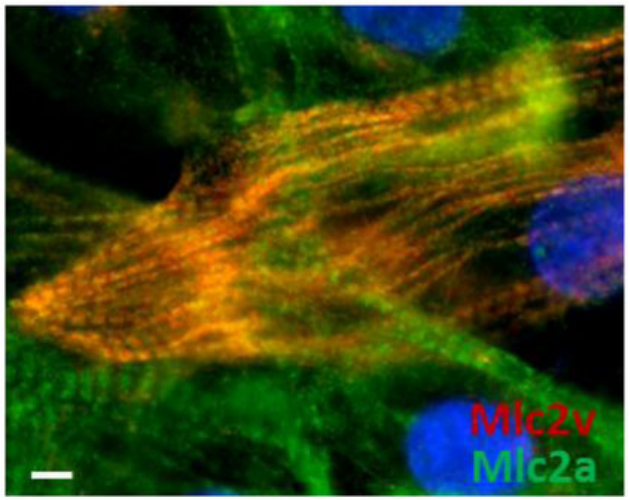
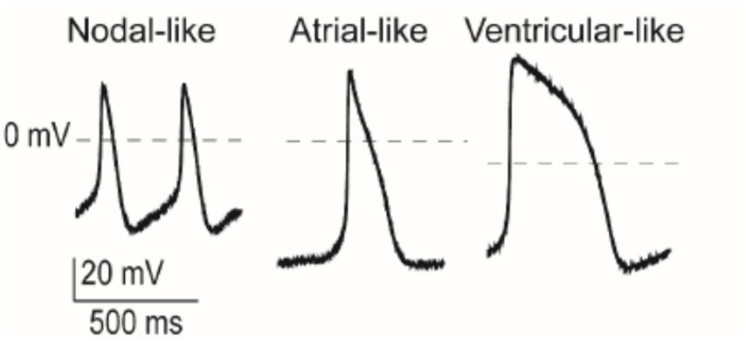
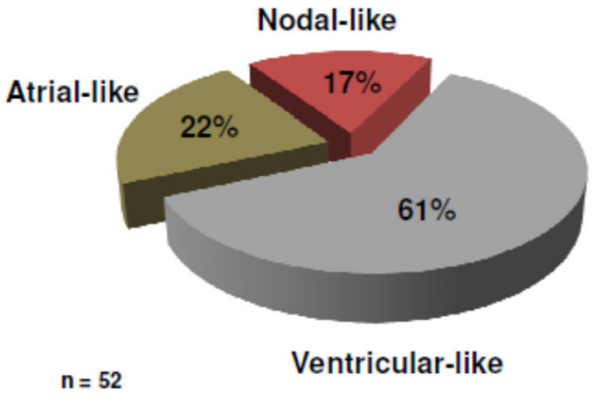
hiPS-cardiomyocytes







Hétérogénéité phénotypique

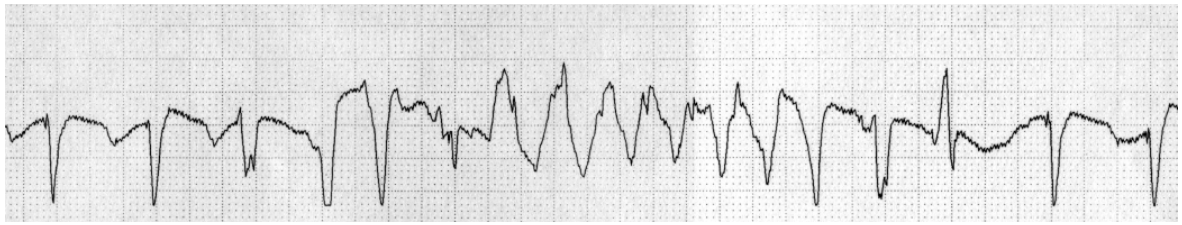


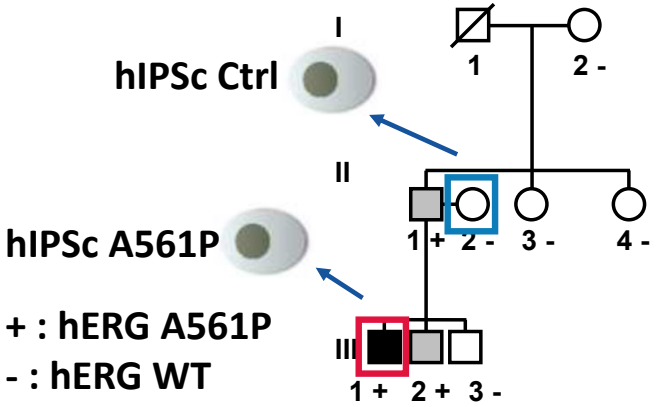
Jouni M *et al.* J Am Heart Assoc. 2015 Sep 1;4(9):e002159.

Modélisation du syndrome du QT long: A561P HERG

➔ **hERG A561P modifie-t-il le potentiel d'action des cardiomyocytes du malade ?**

Feb-05-99 – clobutinol





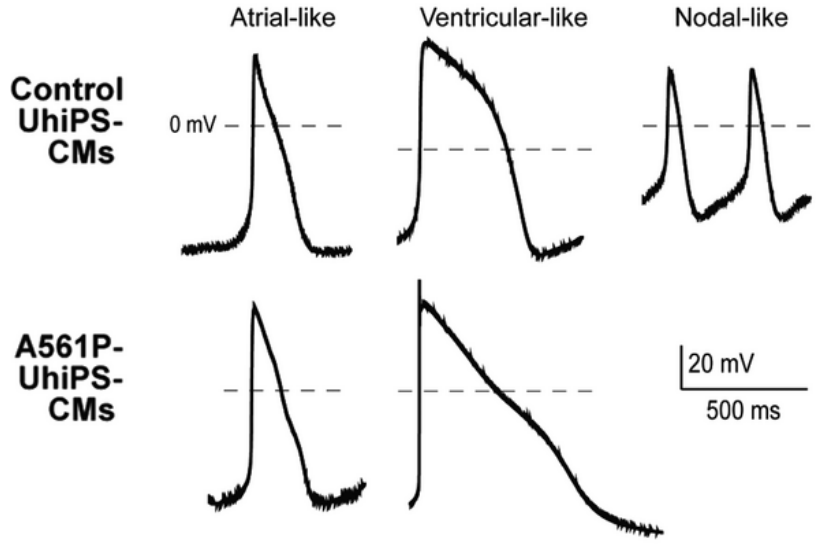
- **re-programmation**

urinary cells

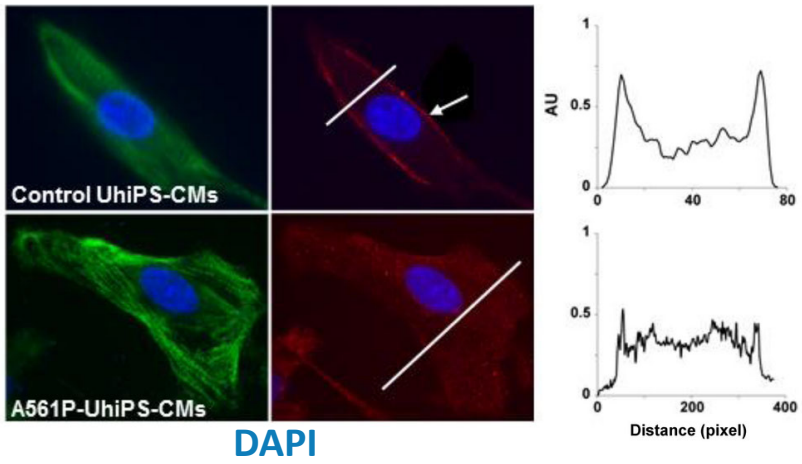
hiPSc

hiPS-CM

- **current-clamp**



- **immuno-cytofluorimétrie**



Jouni M *et al.* J Am Heart Assoc. 2015 Sep 1;4(9):e002159.

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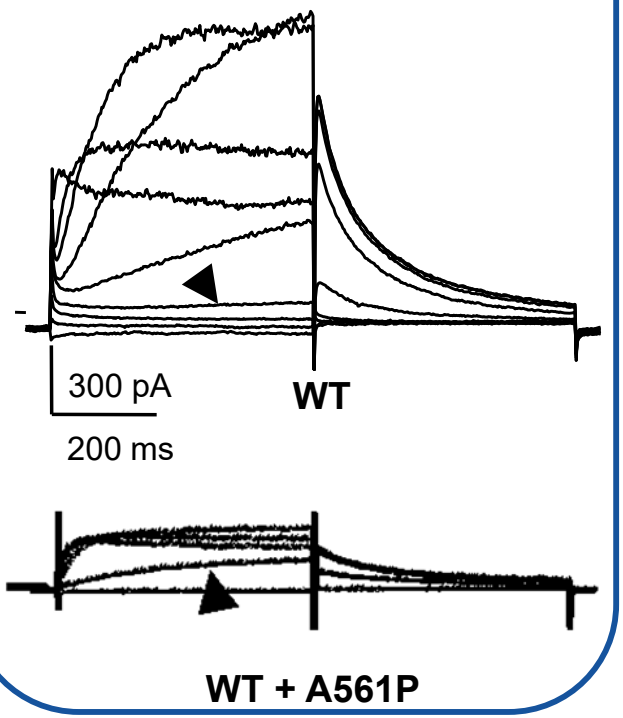
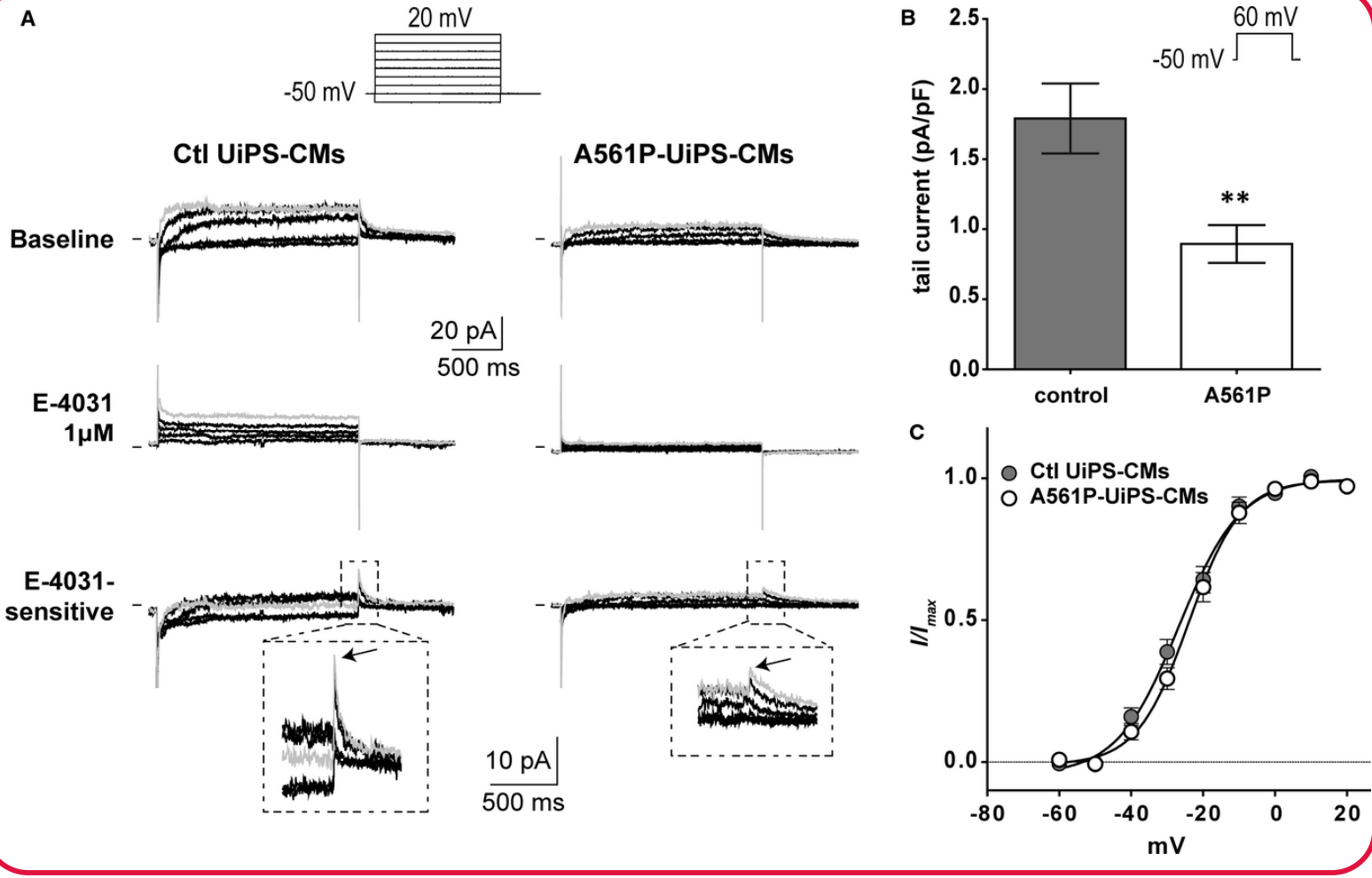
Transfected cells *vs* hiPS-cardiomyocytes

- **voltage-clamp**

transfected COS-7 cells



Bellocq C *et al*. Mol Pharmacol. 2004 Nov;66(5):1093-102



Jouni M *et al.* J Am Heart Assoc. 2015 Sep 1;4(9):e002159.

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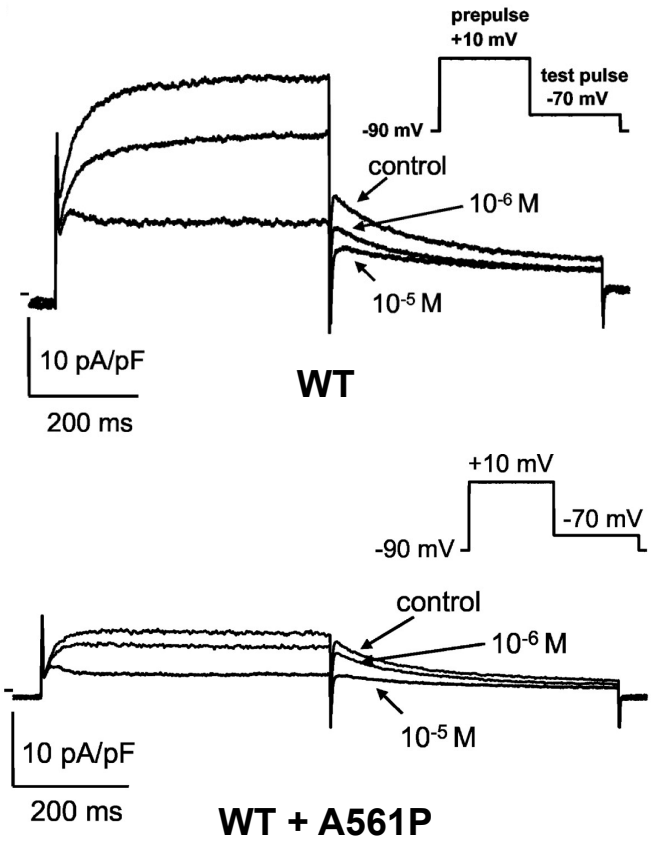
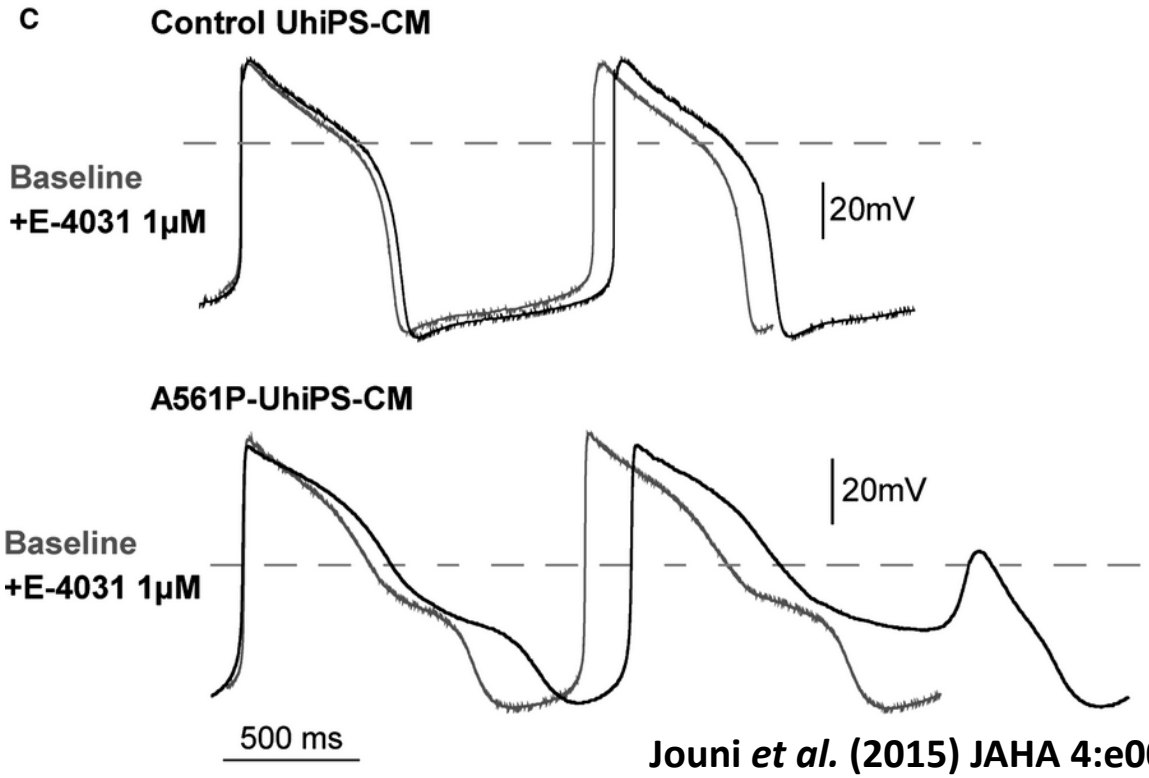
Transfected cells *vs* hiPS-cardiomyocytes

+ clobutinol (I_{Kr} inhib.)



Bellocq C *et al*. Mol Pharmacol. 2004 Nov;66(5):1093-102

+ E4031 (I_{Kr} inhib.)



Jouni *et al.* (2015) JAHA 4:e002159

- ✓ Défaut de transport
- ✓ Réduction d'I_{Kr}
- ➢ Prolongation durée du PA
- ➢ Evènements arythmiques

Perte de function et allongement confirmés ➔ causal

Analyse d'article

Journal of Molecular and Cellular Cardiology 99 (2016) 1–13

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journal homepage: www.elsevier.com/locate/yjmcc

Original Article

HIV-Tat induces a decrease in I_{Kr} and I_{Ks} *via* reduction in phosphatidylinositol-(4,5)-bisphosphate availability

Zeineb Es-Salah-Lamoureux [a,1], Mariam Jouni [a,1], Olfat A. Malak [a], Nadjet Belbachir [a], Zeina Reda Al Sayed [a], Marine Gandon-Renard [a], Guillaume Lamirault [b], Chantal Gauthier [a], Isabelle Baró [a], Flavien Charpentier [b], Kazem Zibara [c], Patricia Lemarchand [b], Bruno Beaumelle [d], Nathalie Gaborit [a,*,1], Gildas Loussouarn [a,1]

[a] l'institut du thorax, Inserm, CNRS, Université de Nantes, Nantes, France
[b] l'institut du thorax, Inserm, CNRS, Université de Nantes, CHU Nantes, Nantes, France
[c] ER045, PRASE, Laboratory of stem cells, Lebanese university, Beirut, Lebanon
[d] Centre d'études d'agents Pathogènes et Biotechnologies pour la Santé, CNRS, Université de Montpellier, Montpellier, France

- **Les patients HIV+ présentent un intervalle QT allongé et un risque de mort subite élevé par rapport à la population générale. Origine ?**
- **Des études précédentes suggèrent un effet direct du virus (plus que des anti-viraux)**

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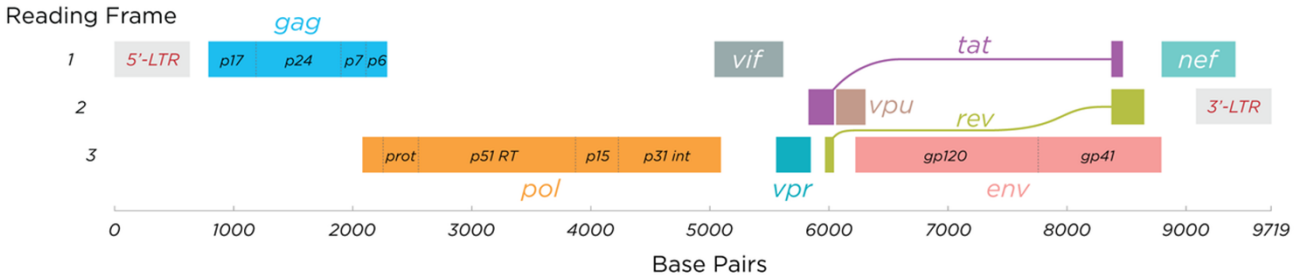
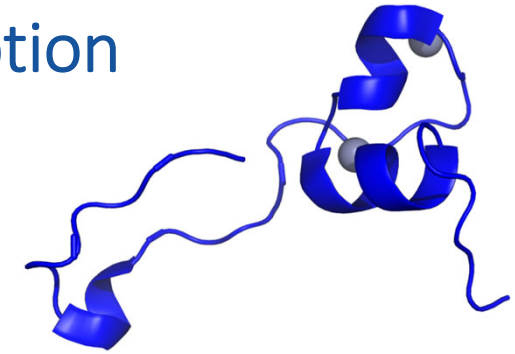
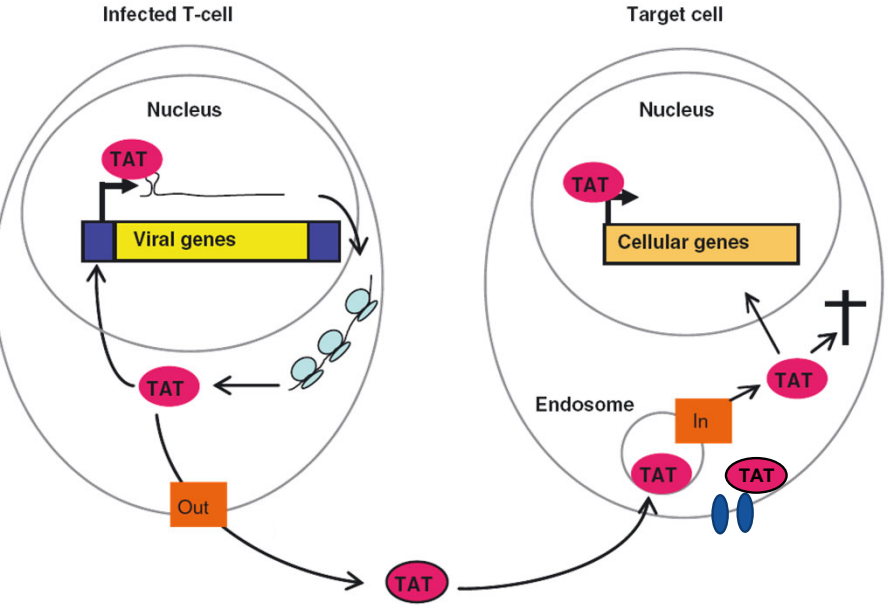
Tat = Trans-Activator of Transcription



https://commons.wikimedia.org/w/index.php?curid=33943759



https://commons.wikimedia.org/w/index.php?curid=79119847



d'après Debaisieux *et al.* Traffic. 2012 Mar;13(3):355-63.

- **Protéine Tat du HIV-1 : présente dans le sérum des patients, peut pénétrer les cellules et interagir avec le PIP_2 (phosphoinositide).**
- **KCNQ1 et hERG, canaux repolarisants, nécessitent du PIP_2 pour être fonctionnels**

➔ **Les canaux KCNQ1 ou hERG sont-ils impliqués dans les effets cardiaques de l'infection HIV par l'intermédiaire de Tat?**

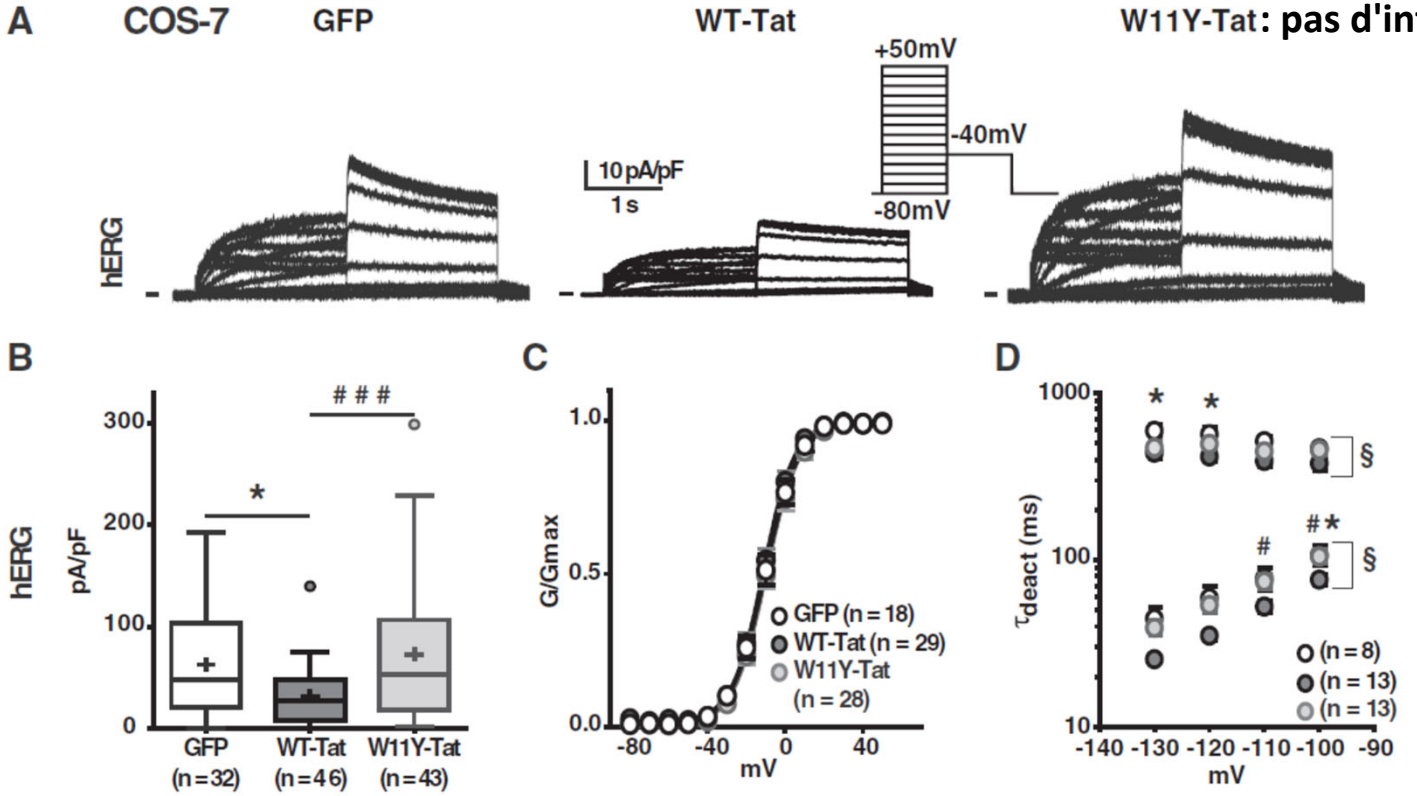
cellules COS-7

Condition : sur-expression du canal hERG et de la protéine Tat (WT et mutée) après transfection (plasmides)

- **Courant I_{hERG}**

W11Y-Tat: pas d'interaction avec le PIP_2

Figure 1

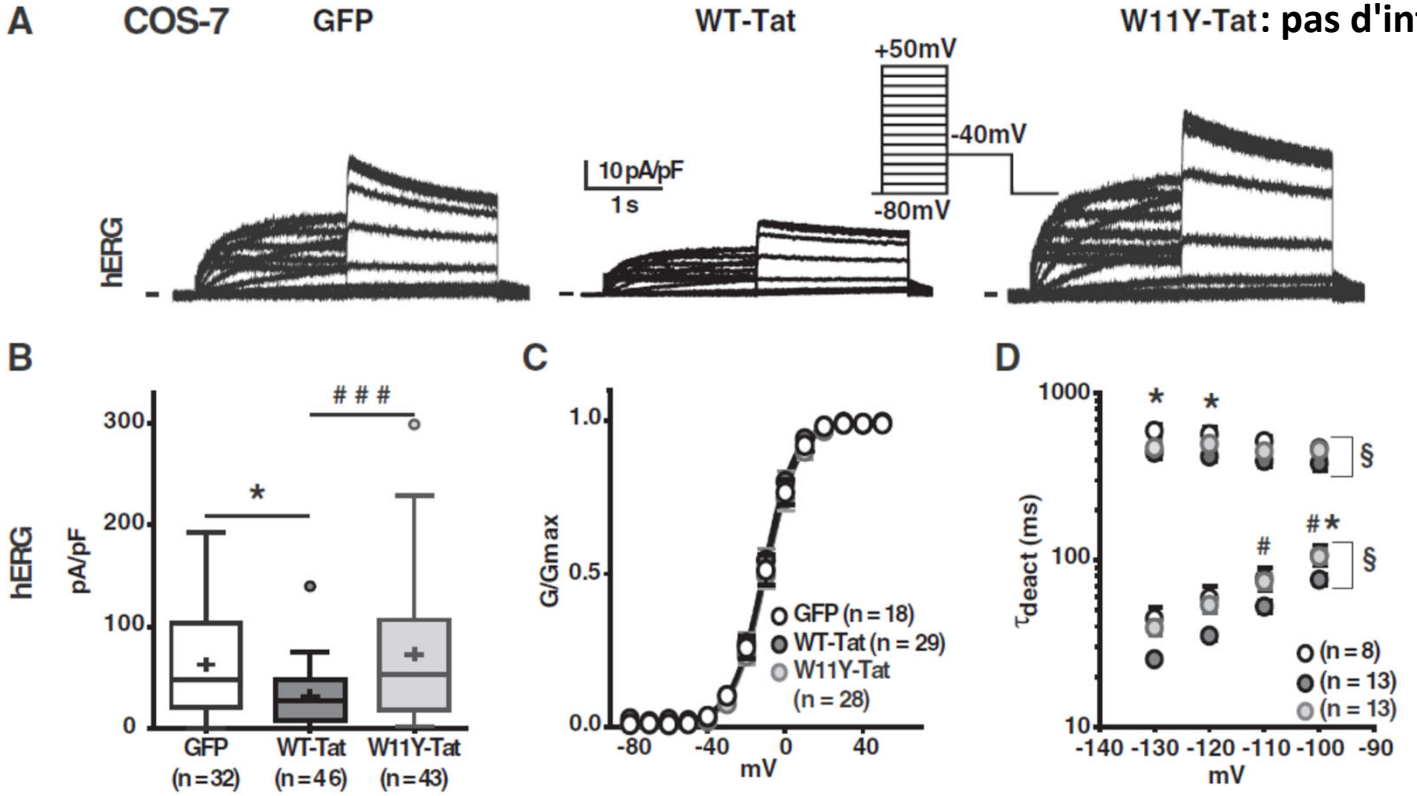


cellules COS-7

Condition : sur-expression du canal hERG et de la protéine Tat (WT et mutée) après transfection (plasmides)

- **Courant I_{hERG}**

Figure 1



- **WT-Tat : 1A & B : diminution du courant hERG (et KCNQ1)**
- **WT-Tat : 1D : accélération de la désactivation du courant hERG (et KCNQ1)**
- **W11Y-Tat, qui n'interagit pas avec le PIP_2 : pas d'effet**

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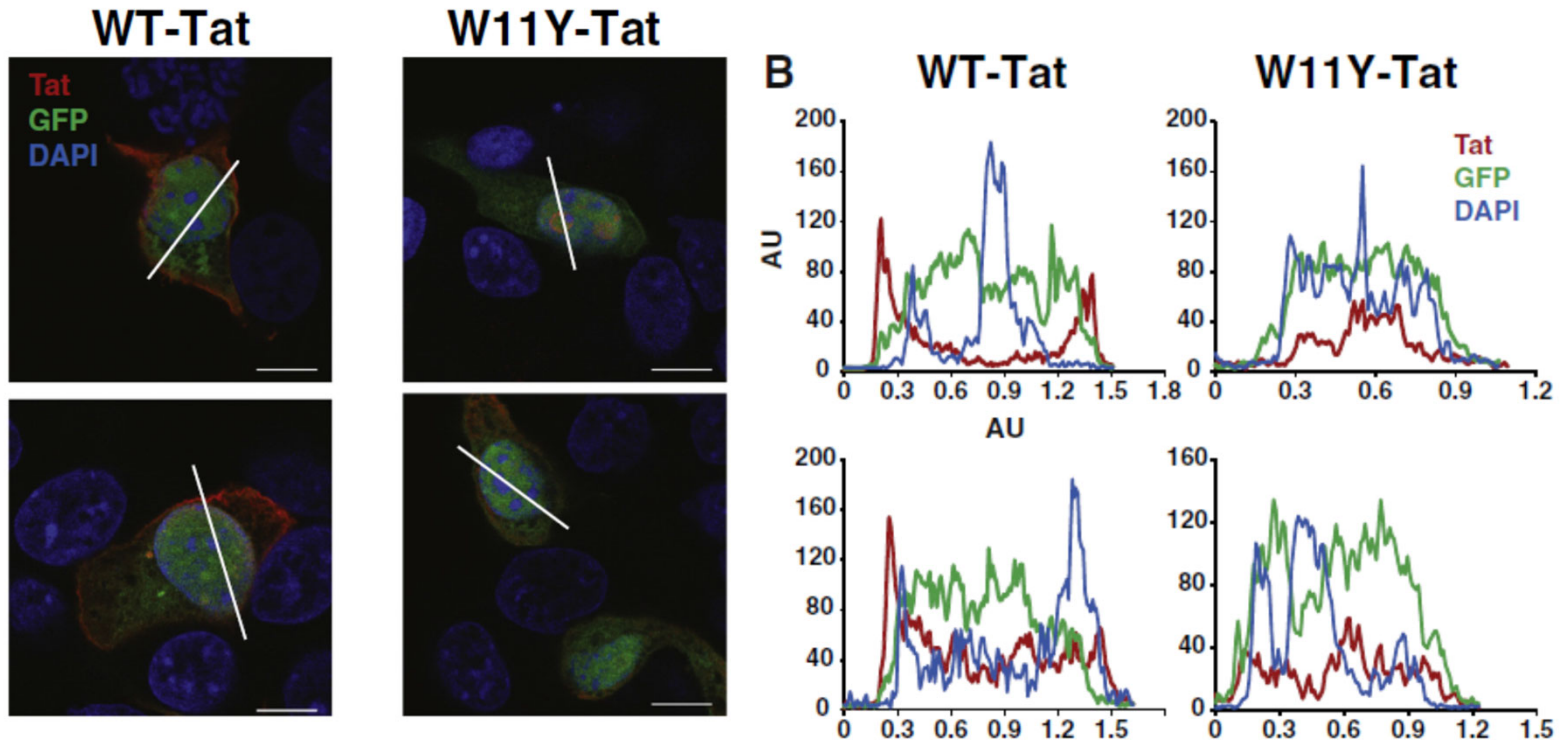
cellules COS-7

Condition : sur-expression du canal hERG et de la protéine Tat (WT et mutée) après transfection (plasmides)

- **Localisation de la protéine Tat (immunomarquage et microscopie confocale)**

Figure 3

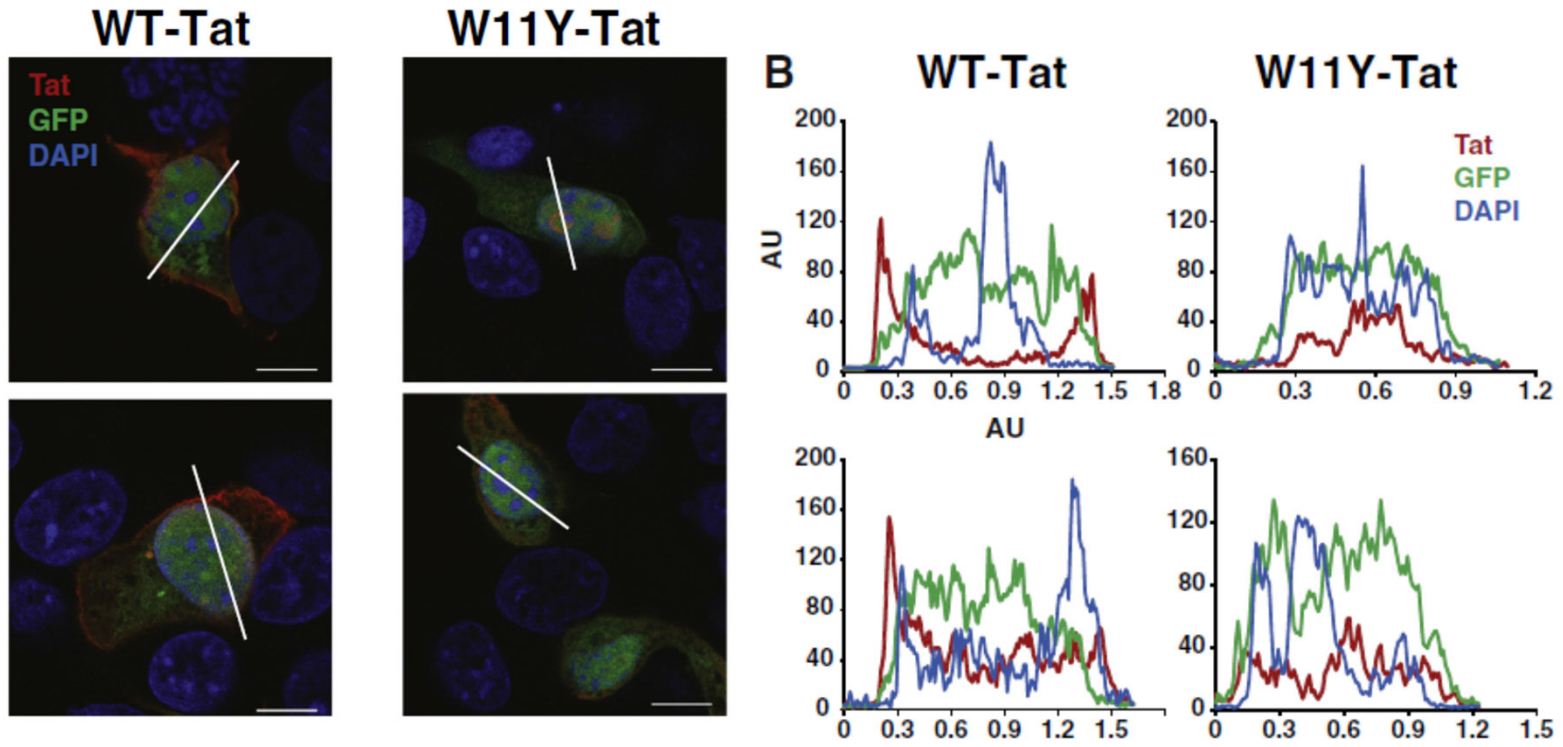


cellules COS-7

Condition : sur-expression du canal hERG et de la protéine Tat (WT et mutée) après transfection (plasmides)

- **Localisation de la protéine Tat (immunomarquage et microscopie confocale)**

Figure 3

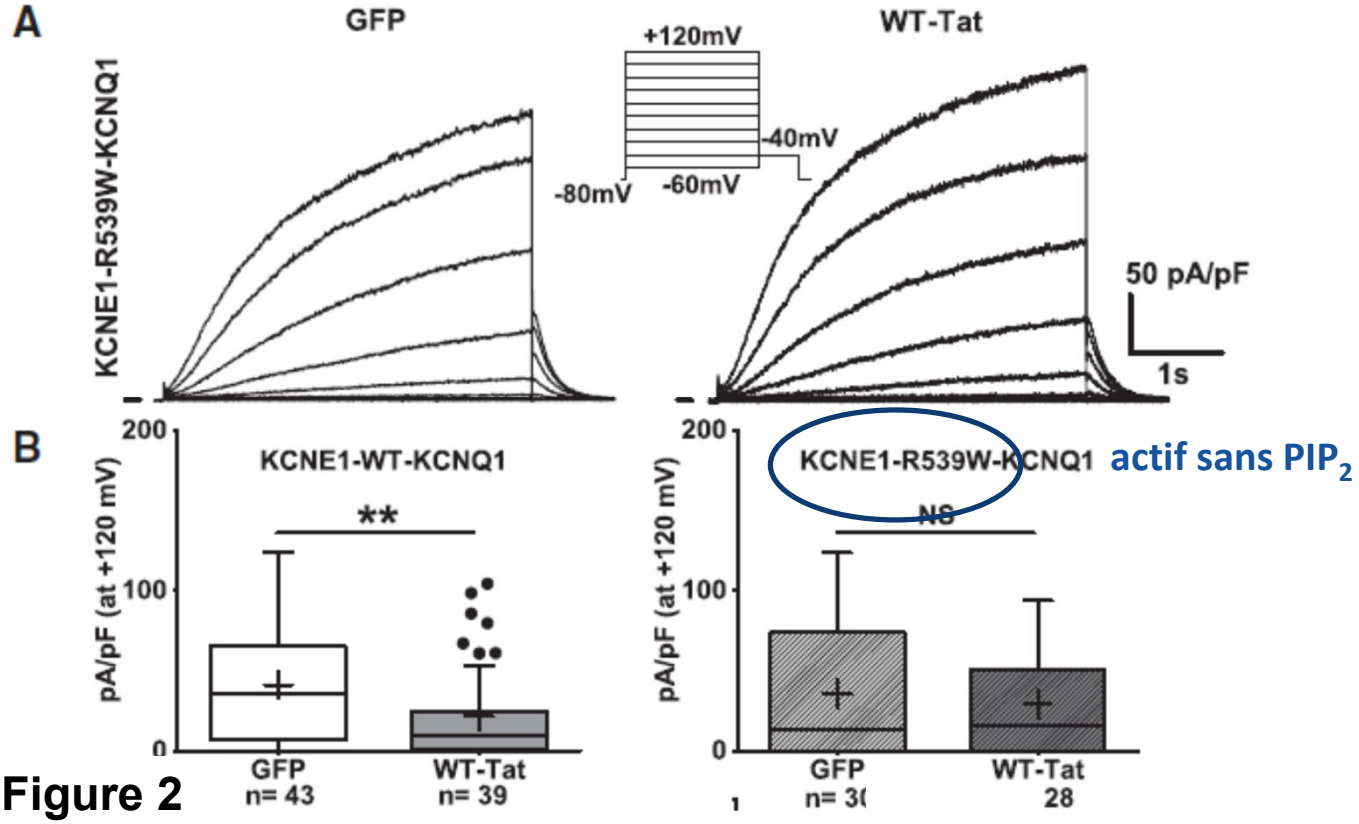


- **WT-Tat : membranaire, comme le canal**
- **W11Y-Tat : non membranaire, car elle n'interagit pas avec le PIP_2**

cellules COS-7

Condition : sur-expression du canal KCNE1-KCNQ1 (WT et muté) et de la protéine WT-Tat après transfection (plasmides)

- **Courant $I_{KCNE1-KCNQ1}$**



actif sans PIP_2

Figure 2

cellules COS-7

Condition : sur-expression du canal KCNE1-KCNQ1 (WT et muté) et de la protéine WT-Tat après transfection (plasmides)

- **Courant $I_{KCNE1-KCNQ1}$**

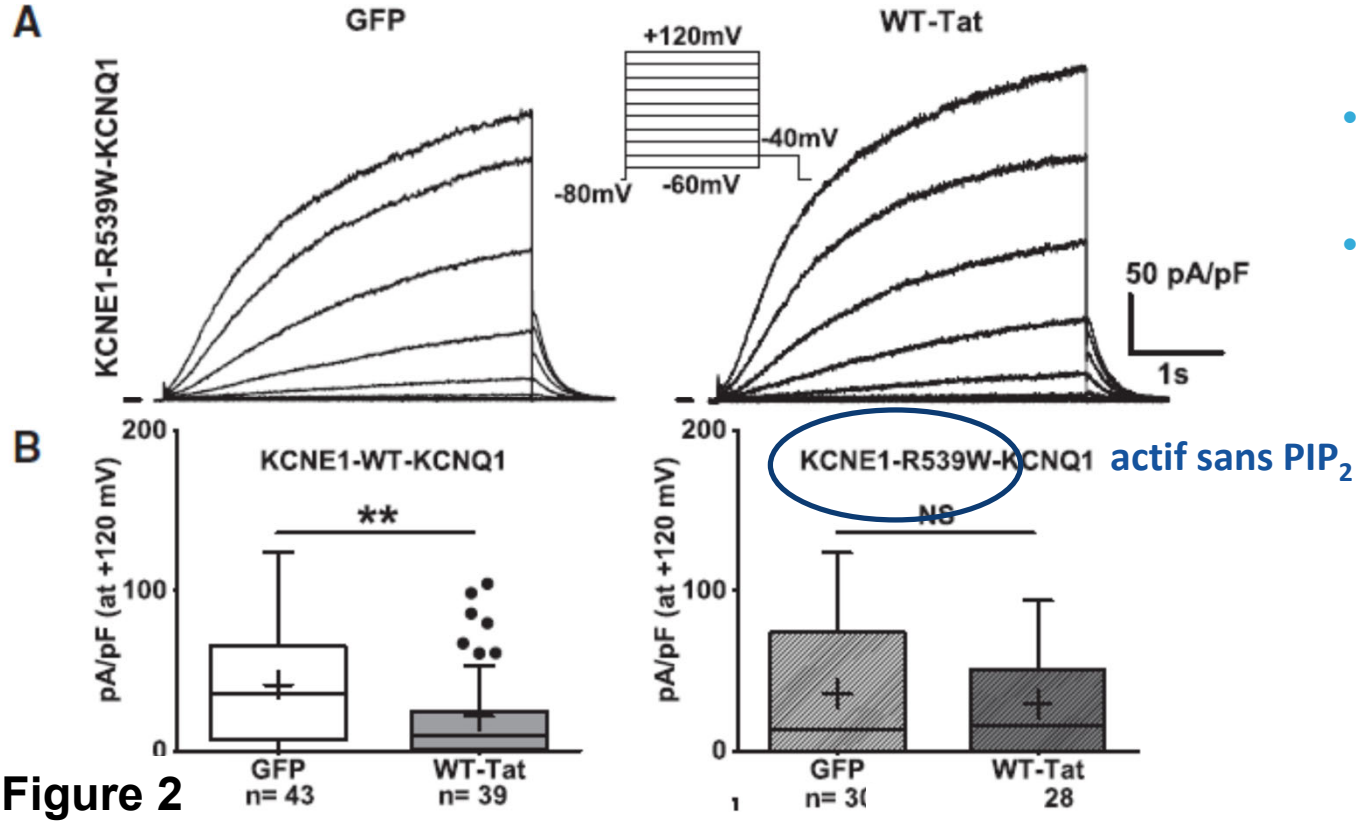


Figure 2

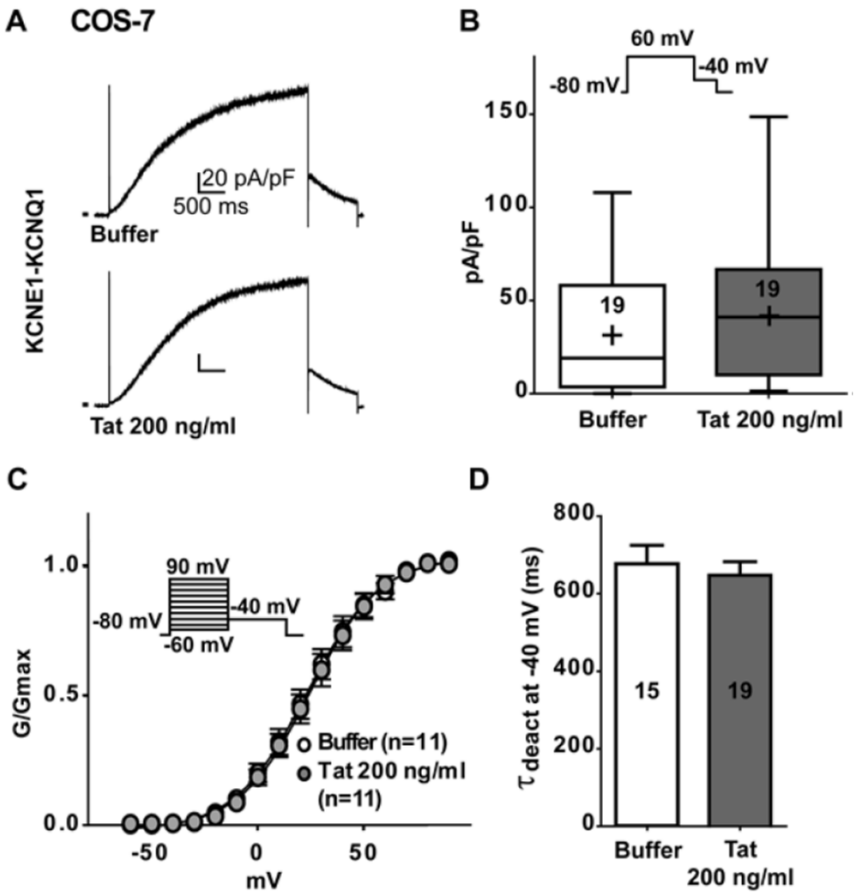
- **3B: canal WT sensible au PIP_2 : sensible à la Tat**
- **3A & B canal insensible au PIP_2 : insensible à la Tat**

cellules COS-7

Condition : sur-expression du canal KCNE1-WT- KCNQ1 après transfection (plasmides), application extracellulaire de la protéine Tat

- **Courant $I_{KCNE1-KCNQ1}$**

Suppl. Figure 4

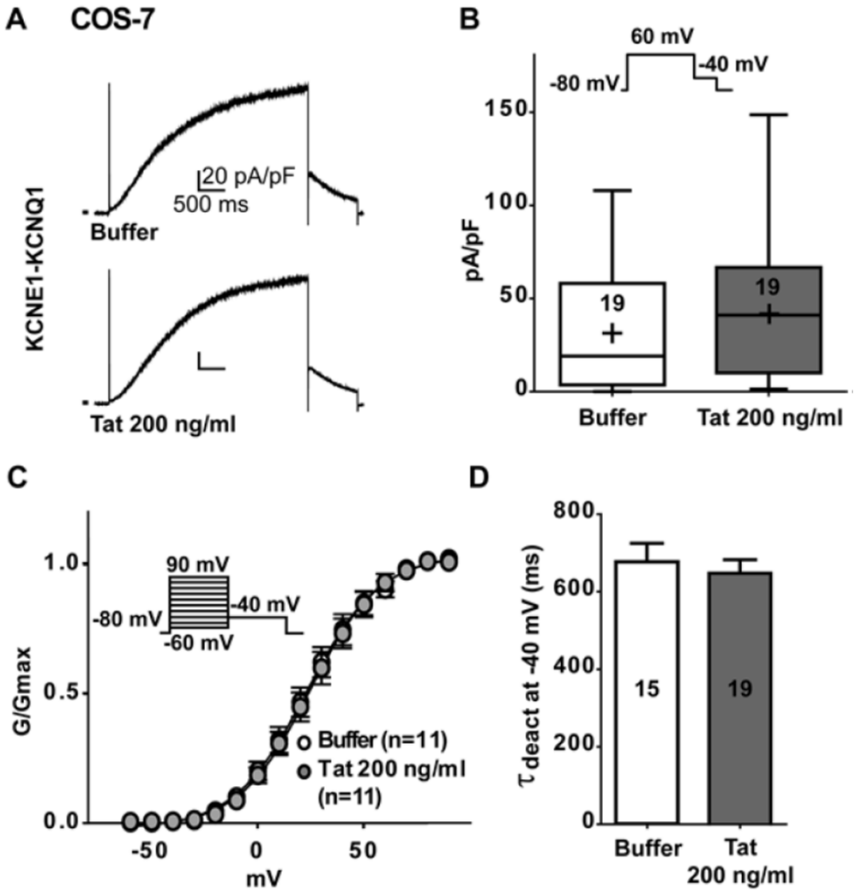


cellules COS-7

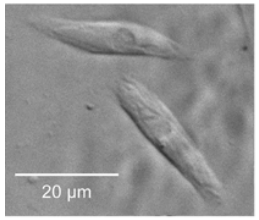
Condition : sur-expression du canal KCNE1-WT- KCNQ1 après transfection (plasmides), application extracellulaire de la protéine Tat

- **Courant $I_{KCNE1-KCNQ1}$**

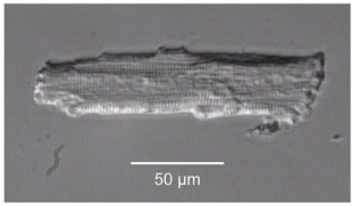
Suppl. Figure 4



- **application de la protéine Tat : pas d'effet**



cardiomyocytes
issus de cellules hiPS



cardiomyocytes humains fraîchement isolés

Condition : application extracellulaire de la protéine Tat

- **Courant I_{Kr} (hERG, inhibé par E-4031)**

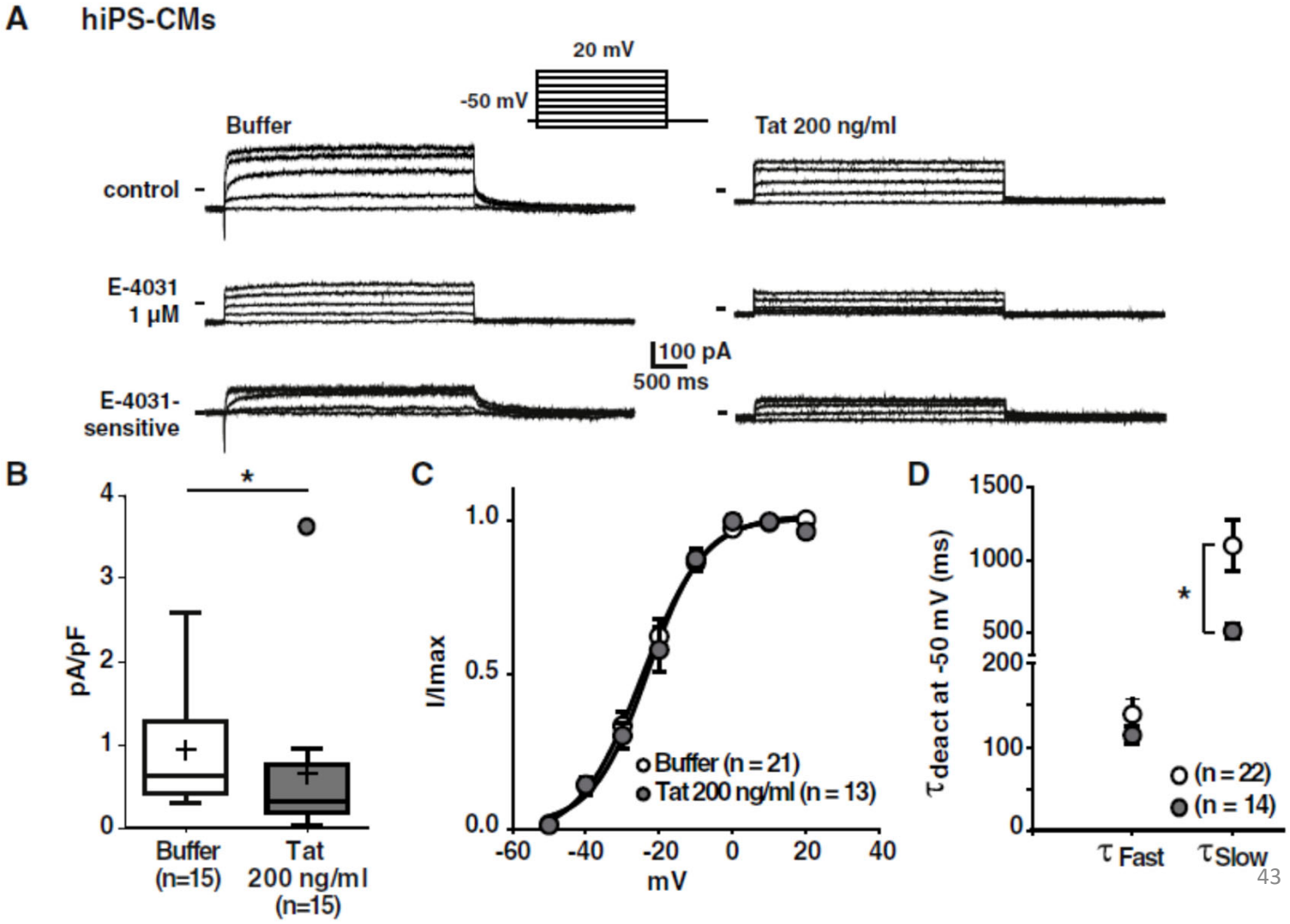
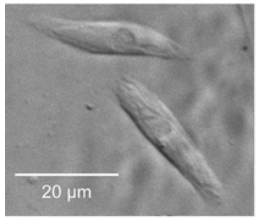
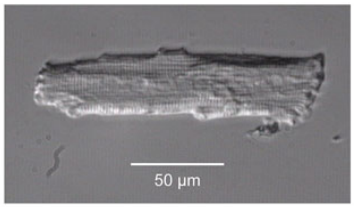


Figure 4



cardiomyocytes
issus de cellules hiPS



cardiomyocytes humains fraichement isolés

- **application de la protéine Tat : effet sur le courant E-4031-sensible, I_{Kr}**

Condition : application extracellulaire de la protéine Tat

- **Courant I_{Kr} (hERG, inhibé par E-4031)**

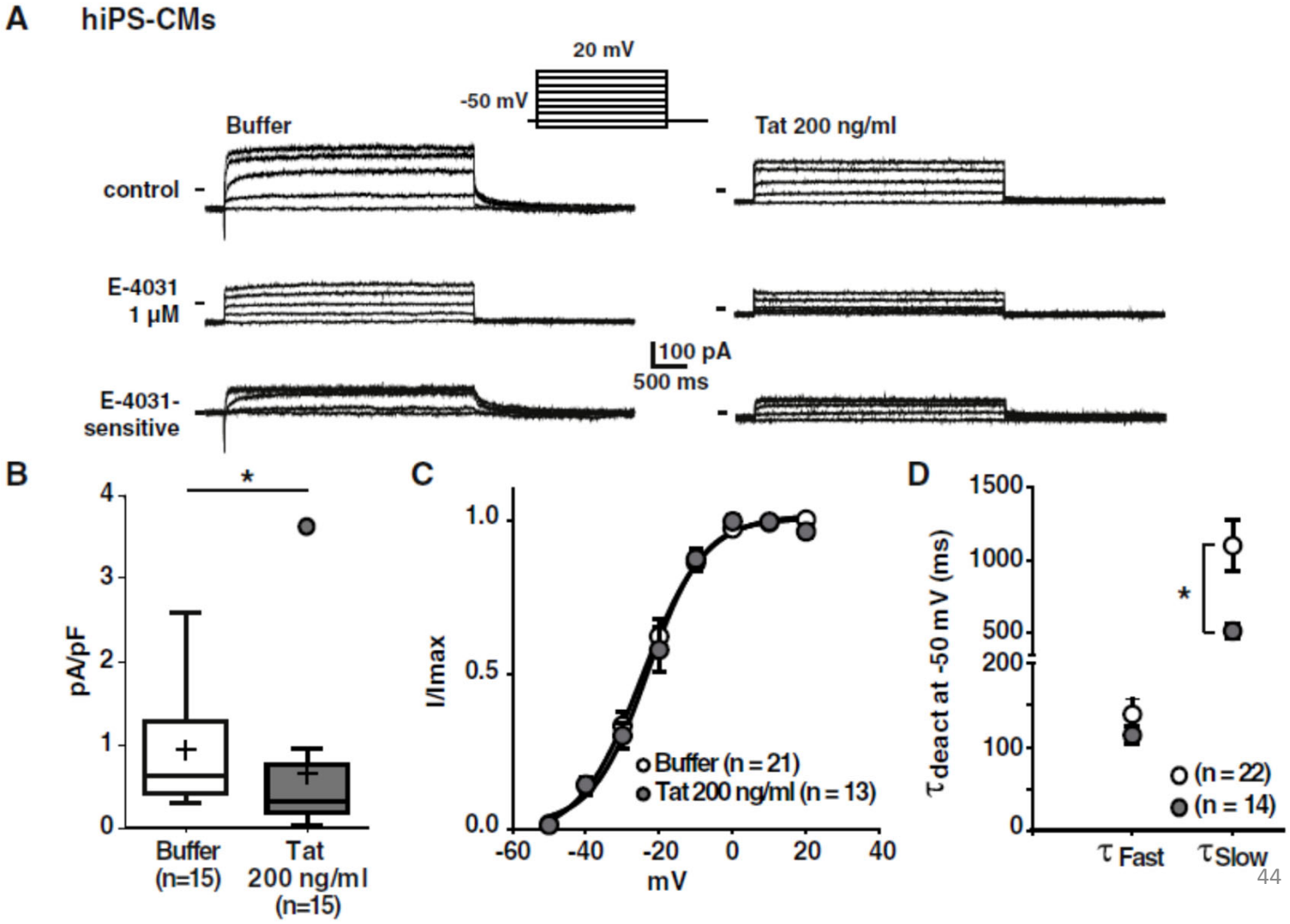
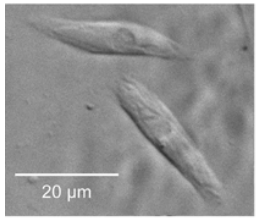


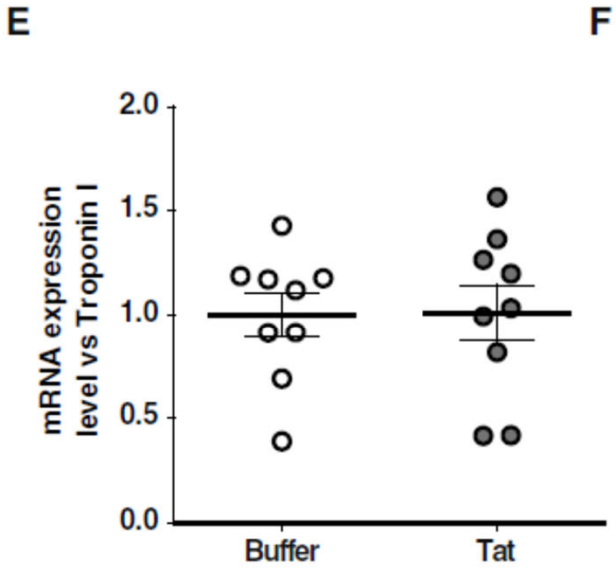
Figure 4



cardiomyocytes issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- **expression de hERG ARNm et protéine**



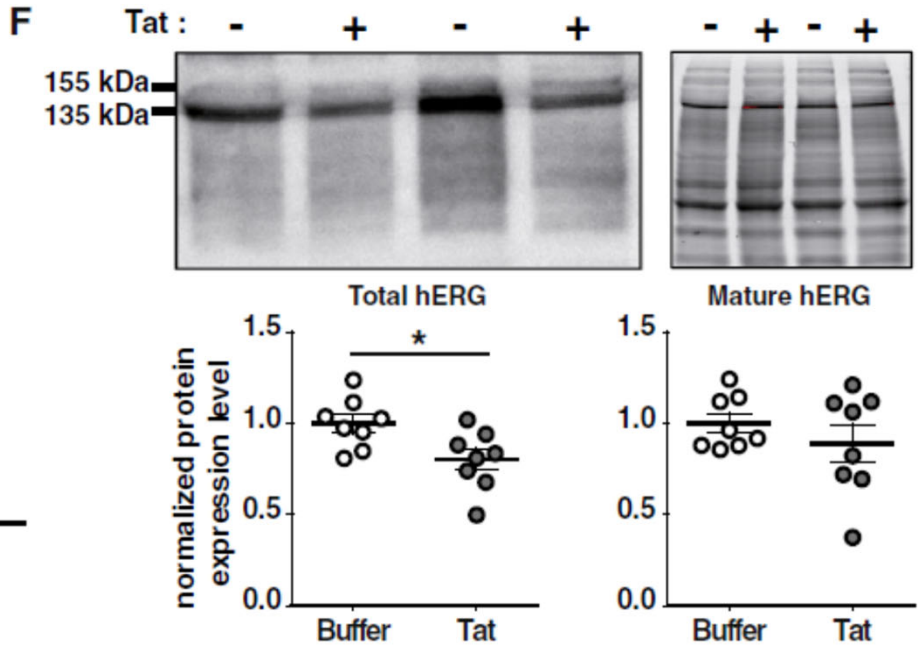
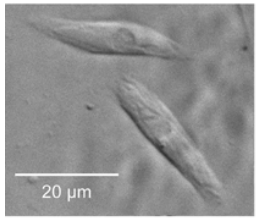


Figure 4

l'institut du thorax



cardiomyocytes issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- **expression de hERG ARNm et protéine**

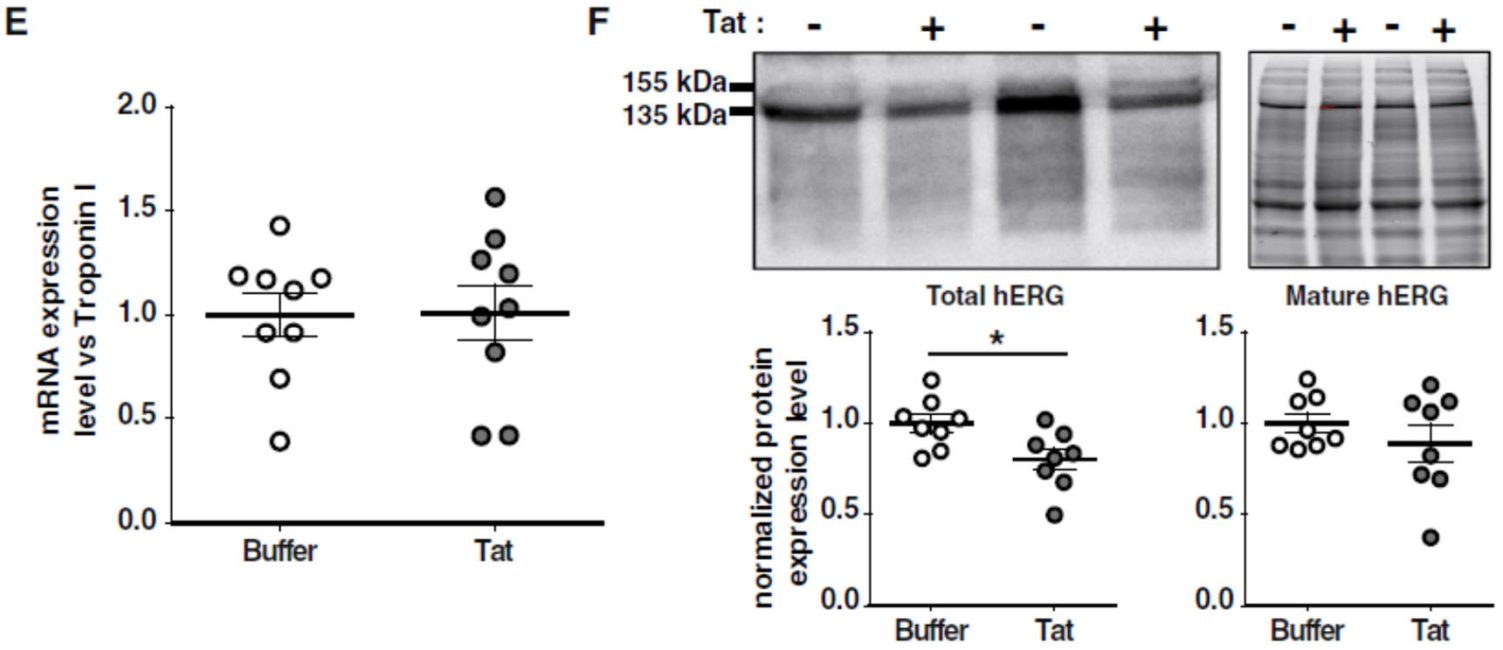


Figure 4

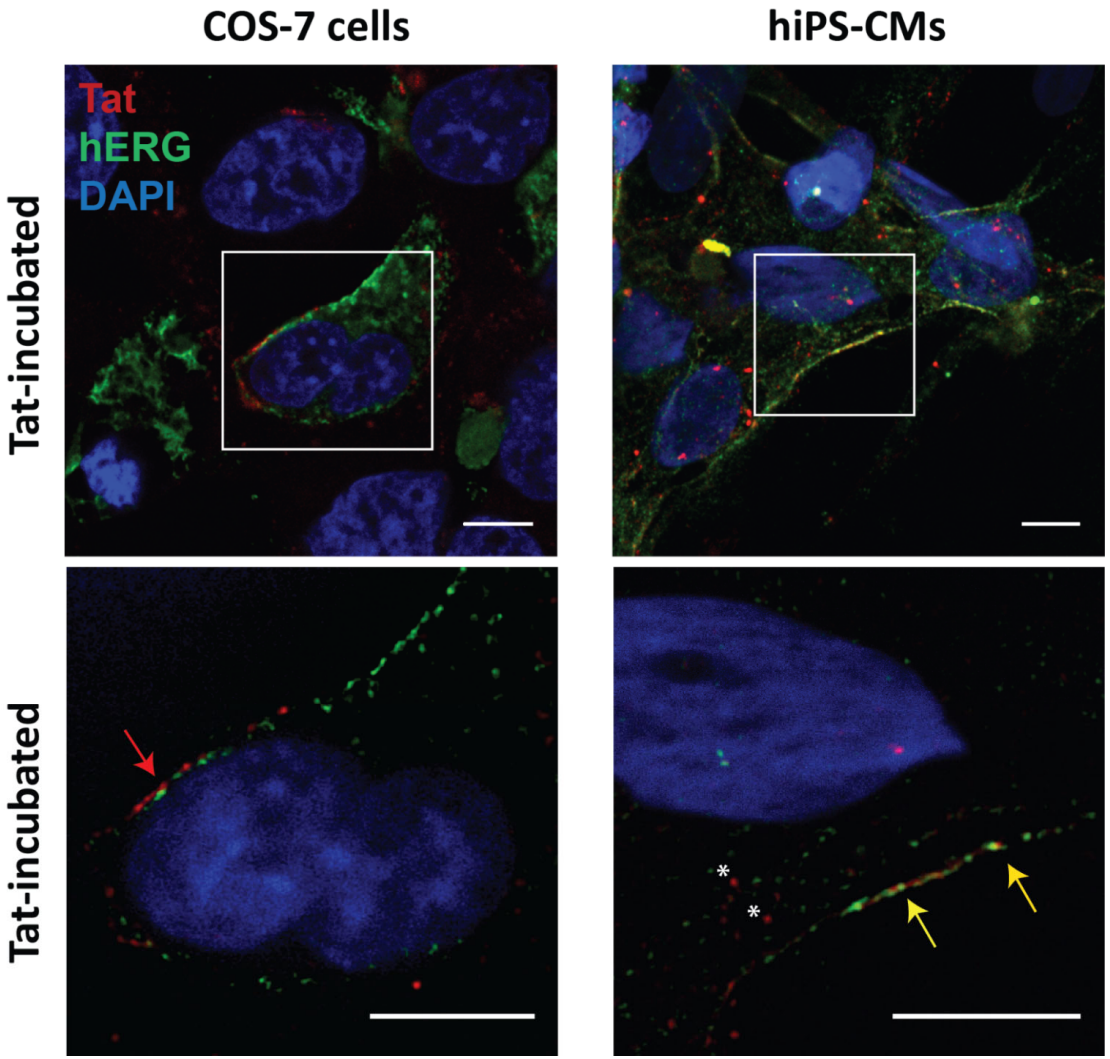
- **protéine Tat : pas d'effet sur la densité de canaux à la membrane plasmique**
- **diminution du courant I_{Kr} par régulation de la fonction**

l'institut du thorax

Condition : application extracellulaire de la protéine Tat

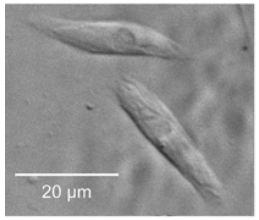
- **Localisation de la protéine Tat (immunomarquage et microscopie confocale)**

Figure 5



- **application de la protéine Tat : endocytose uniquement dans les cardiomyocytes**

l'institut du thorax



cardiomyocytes
issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- **potentiel d'action**

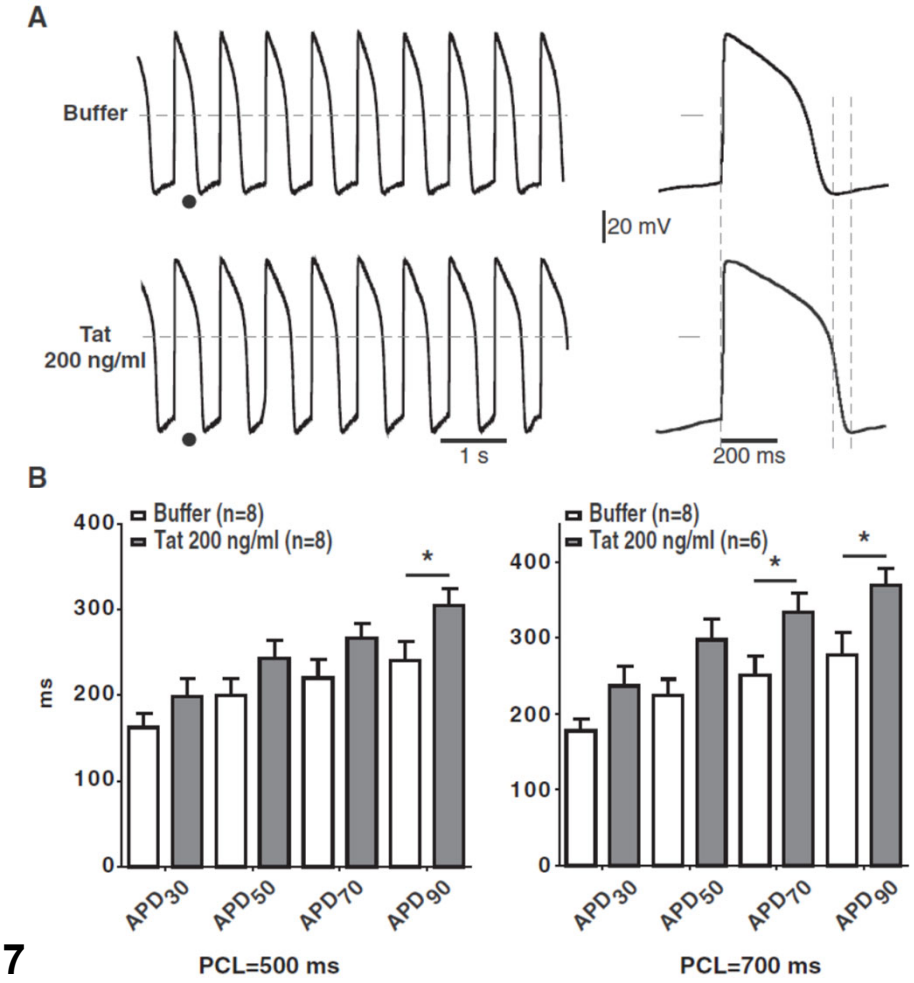
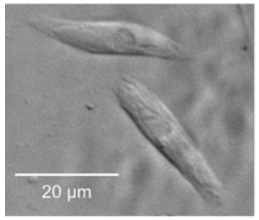


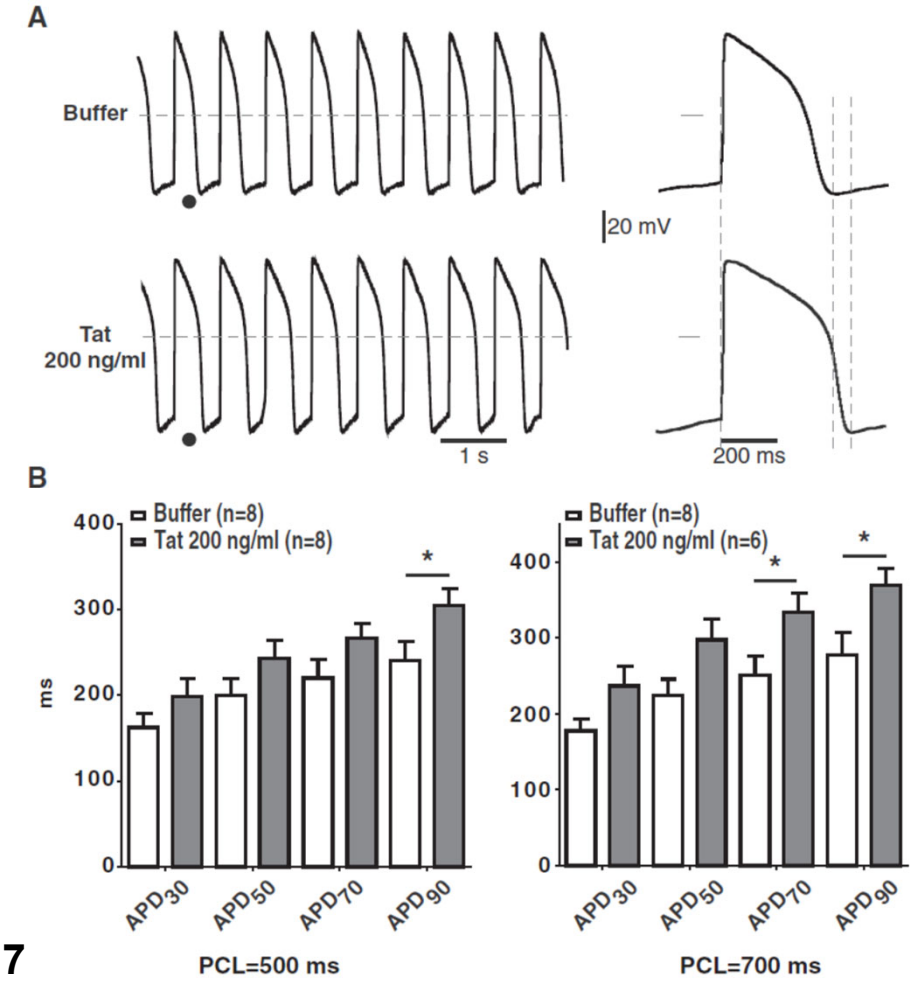
Figure 7



cardiomyocytes issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- **potentiel d'action**

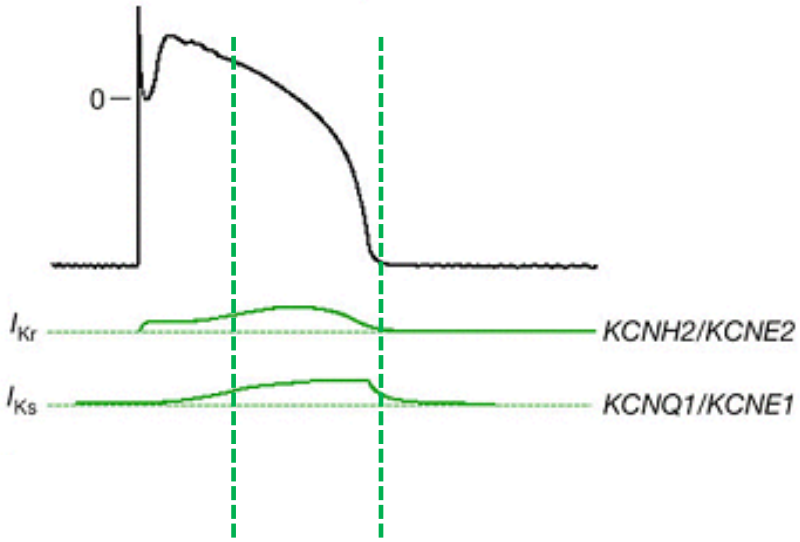


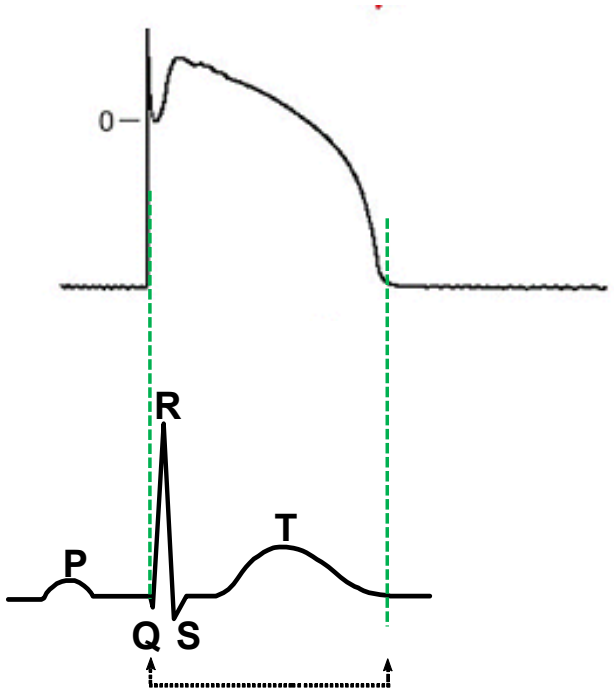
- **allongement de la durée du potentiel d'action induit par la Tat (phases tardives)**

Figure 7

Conclusions

"Altogether, these data obtained on human K^+ channels both in heterologous expression systems and in human cardiomyocytes suggest that Tat sequesters PIP_2, leading to a reduction of I_{Kr} and I_{Ks}, and provide a molecular mechanism for QT prolongation in HIV-infected patients."



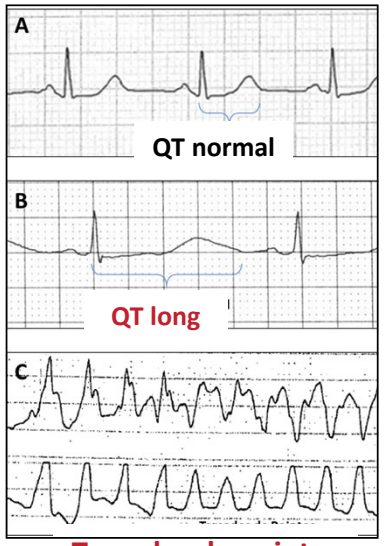


Syndrome du QT long congénital : variants de *KCNH2*

Contexte du projet

Mutations perte de fonction du gène codant le canal hERG (*KCNH2)*

ECG

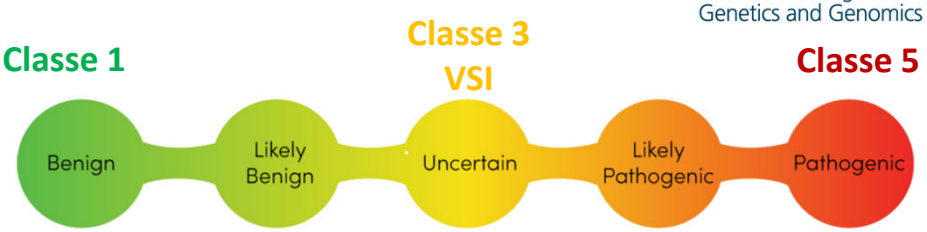


Torsades de pointes

Syncopes et mort subite

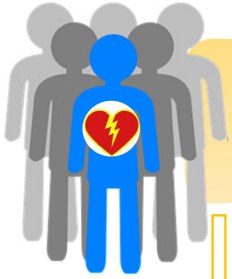
2800 variants de *KCNH2* (1159 a.a.)
dont 2057 faux sens

ACMG
American College of Medical Genetics and Genomics



Faux sens	**1%**	3%	**83%**	6%	**7%**

VSI: Variants de Signification Inconnue



Besoin clinique: caractérisation fonctionnelle à haut débit de variants VSI

Stratification optimale du risque rythmique des patients

Alameh M *et al*. Front Physiol. 2023 Feb 13;14:1132533.

Caractérisation de l'ensemble des variants du gène *KCNH2*

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares

349 **VSI**

Arythmie

Informations cliniques

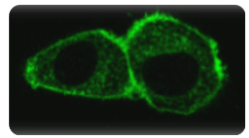
Diagnostic complet

Base de données internationale dynamique

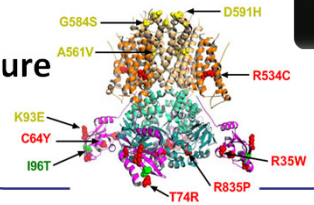
Caractérisation multiparamétrique

patch-clamp automatisé à haut débit (384 cellules en simultané)

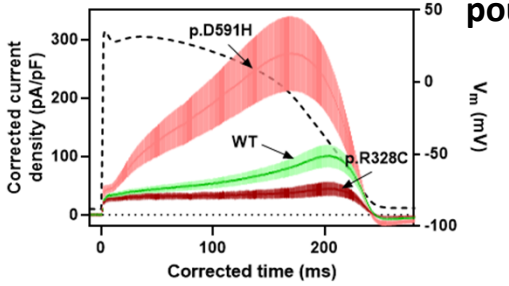
trafic à la membrane



structure



Score de pathogénicité moléculaire



pouvoir de repolarisation

GoF Benign LoF

Variants bénins et pathogènes

Score final de pathogénicité pour le patient

= score moléculaire + score génétique

Informations fonctionnelles complètes + génétiques + cliniques

Oliveira-Mendes BBR *et al.* Clin Transl Med. 2023 May;13(5):e1266.

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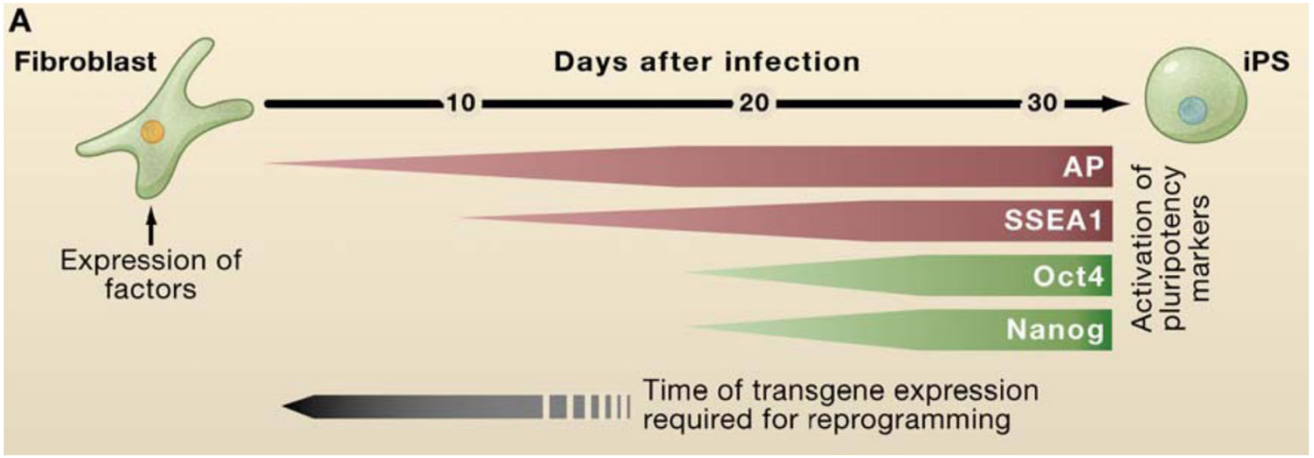
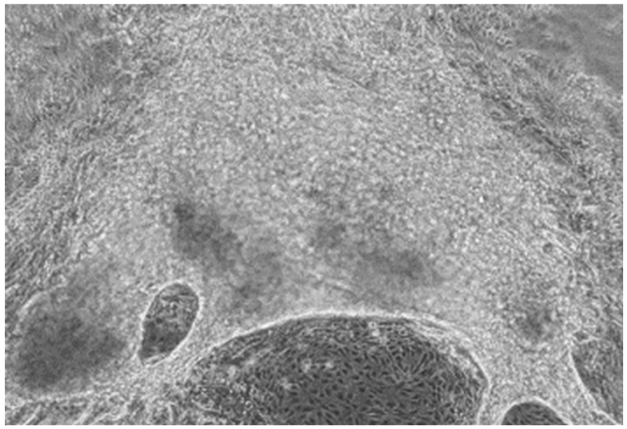
Nantes, France

De l'urine au cardiomyocyte

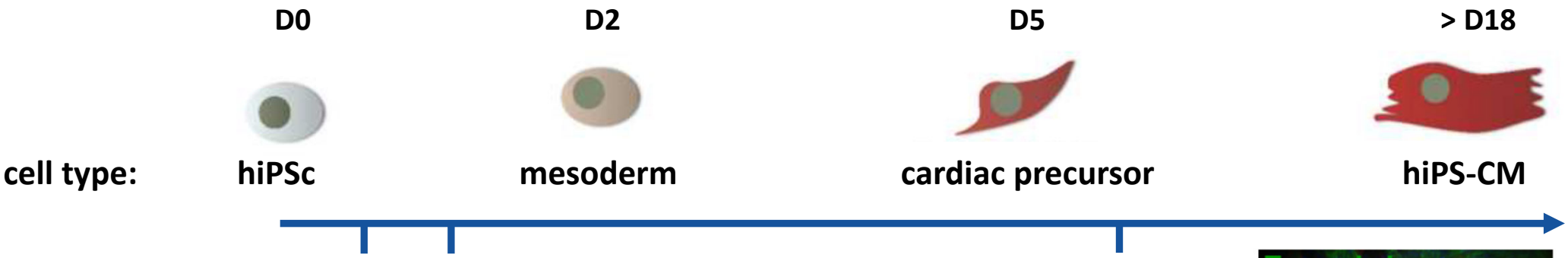


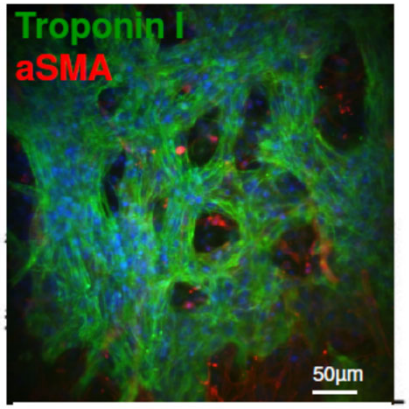
Reprogrammation

Différentiation



Différenciation cardiomyocytaire: caractérisation





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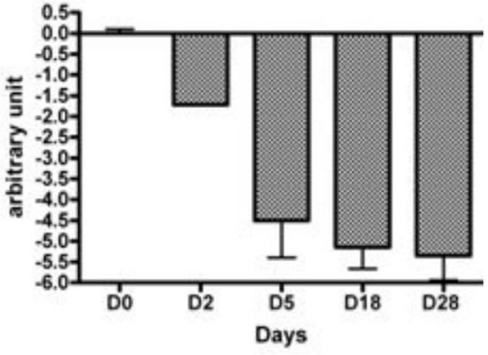

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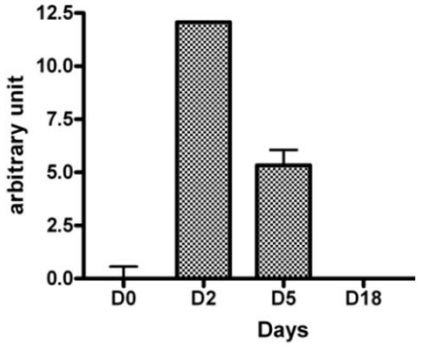
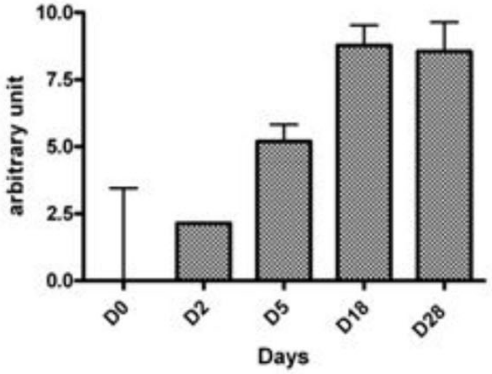
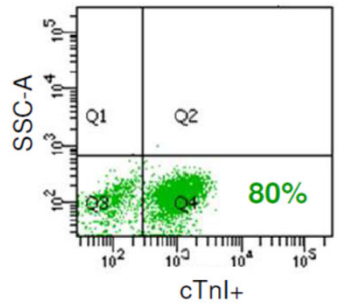


NKX2-5





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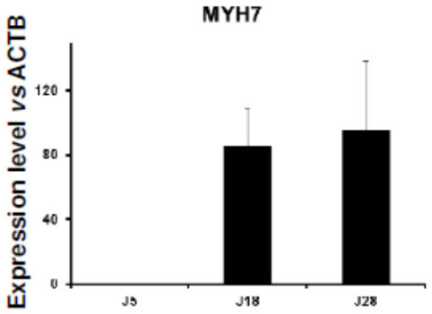
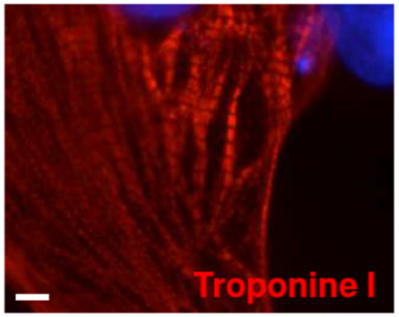
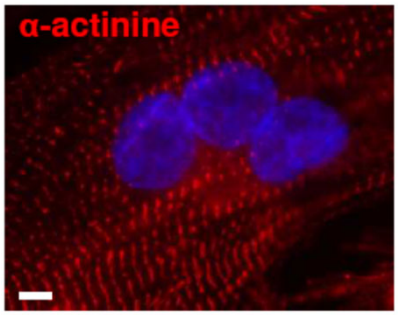
hiPS-cardiomyocytes : caractérisation

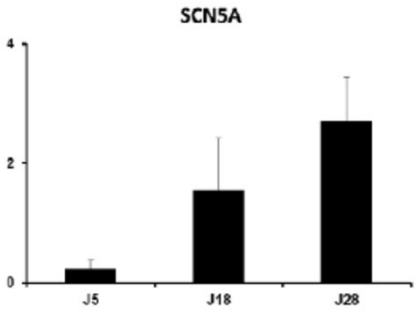
sarcomeric organization

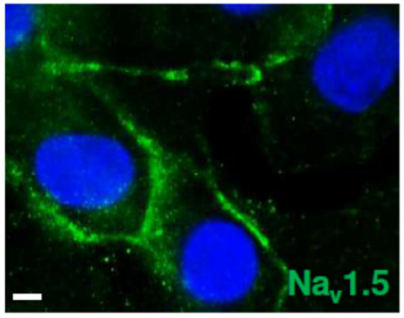


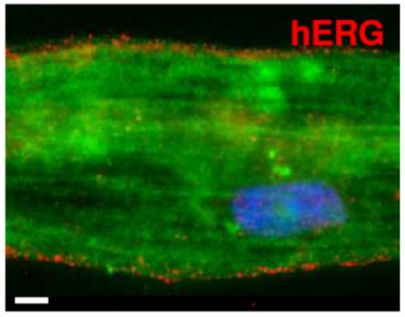




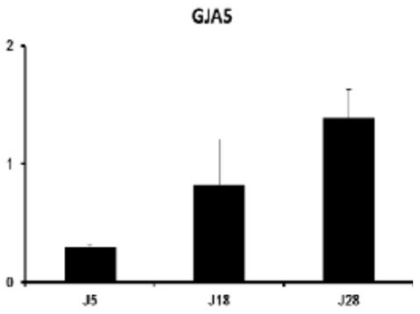
ion channels

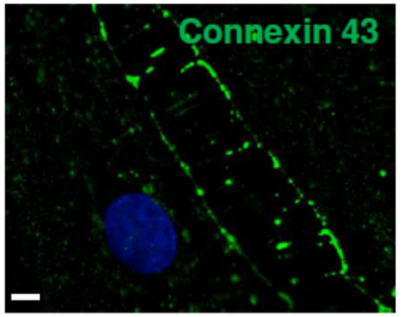


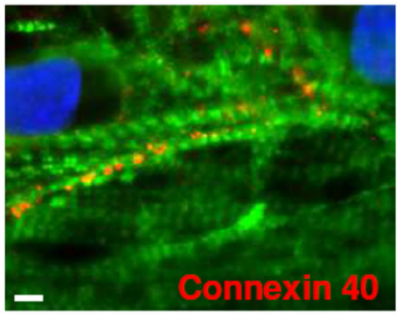




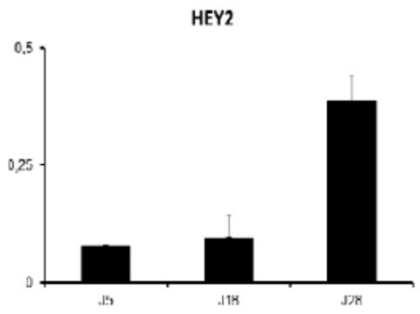
gap junctions

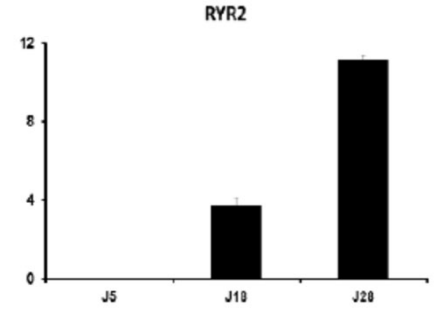


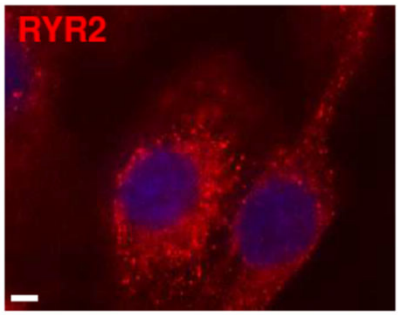




Ca^{2+} homeostasis







5 µm