



Electrophysiologie moléculaire - troubles du rythme et de la conduction cardiaques



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Equipe Canaux ioniques et arythmies
cardiaques

L'unité de recherche de l'institut du thorax

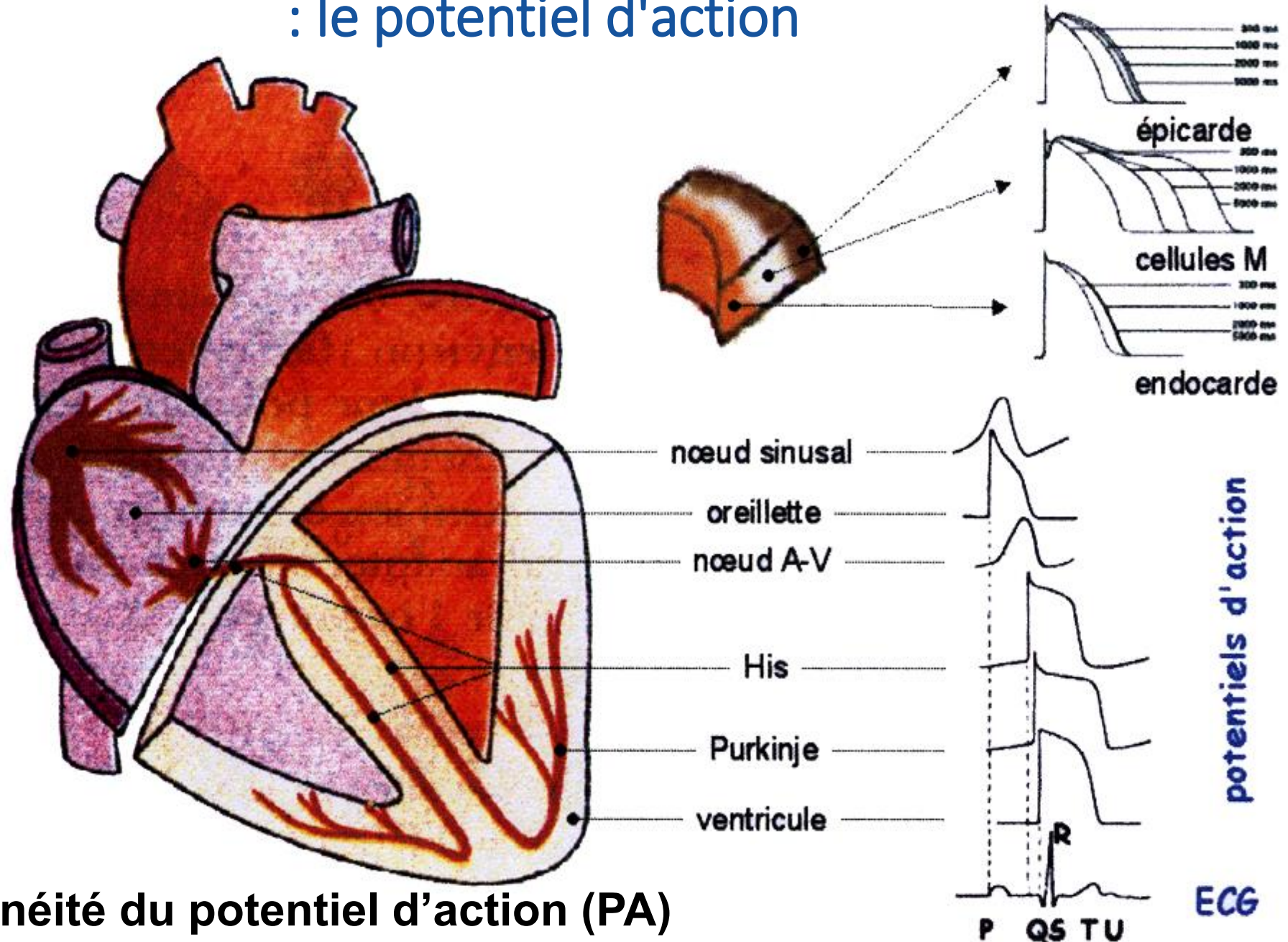
Inserm UMR 1087 / CNRS UMR 6291

Nantes, France

MASTER 1 Biologie et Santé - Thorax

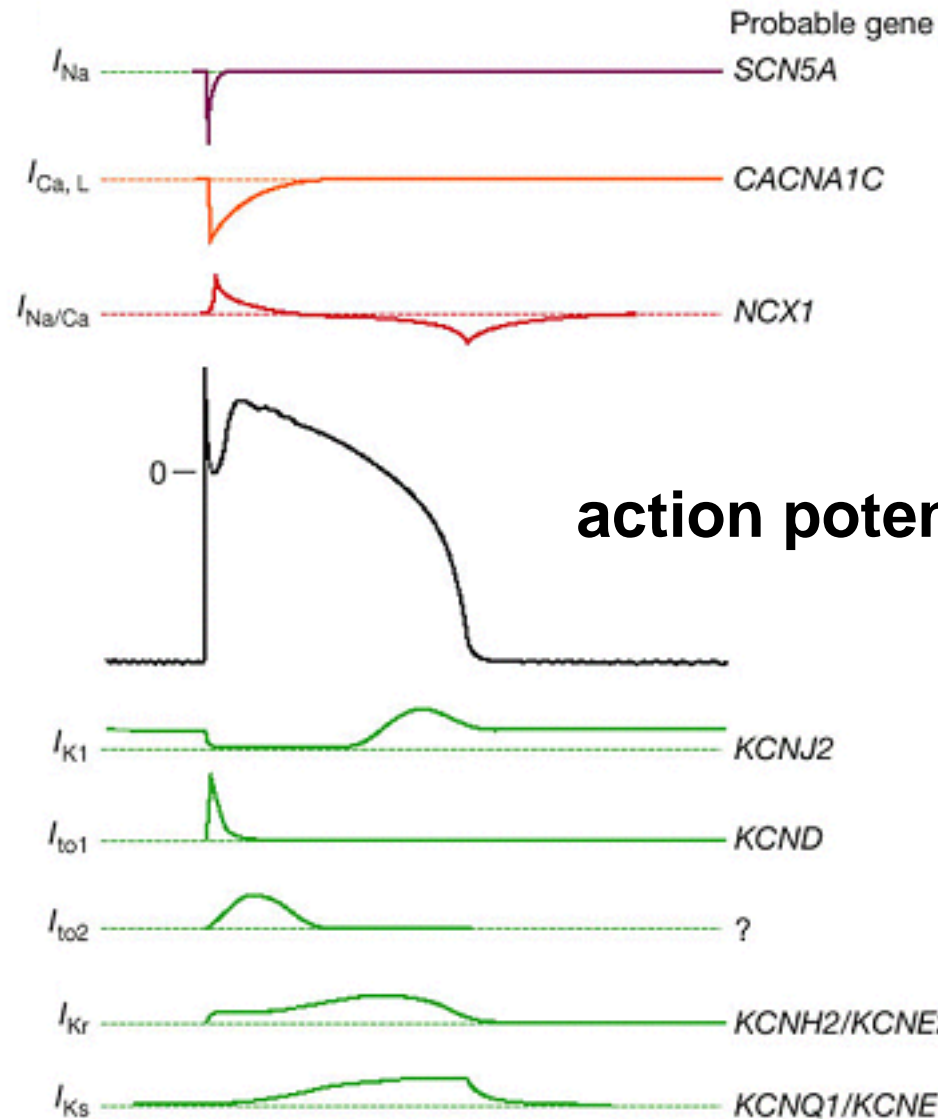
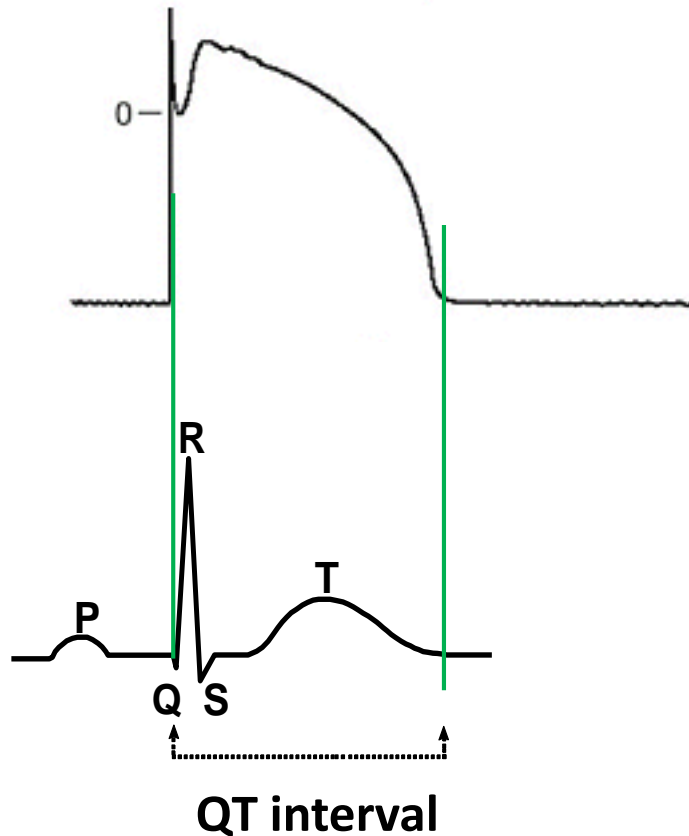
2023-2024

Activité électrique du cardiomyocyte : le potentiel d'action



hétérogénéité du potentiel d'action (PA)

Activité électrique du cardiomyocyte ventriculaire : le potentiel d'action



early depolarization

plateau

diastolic potential

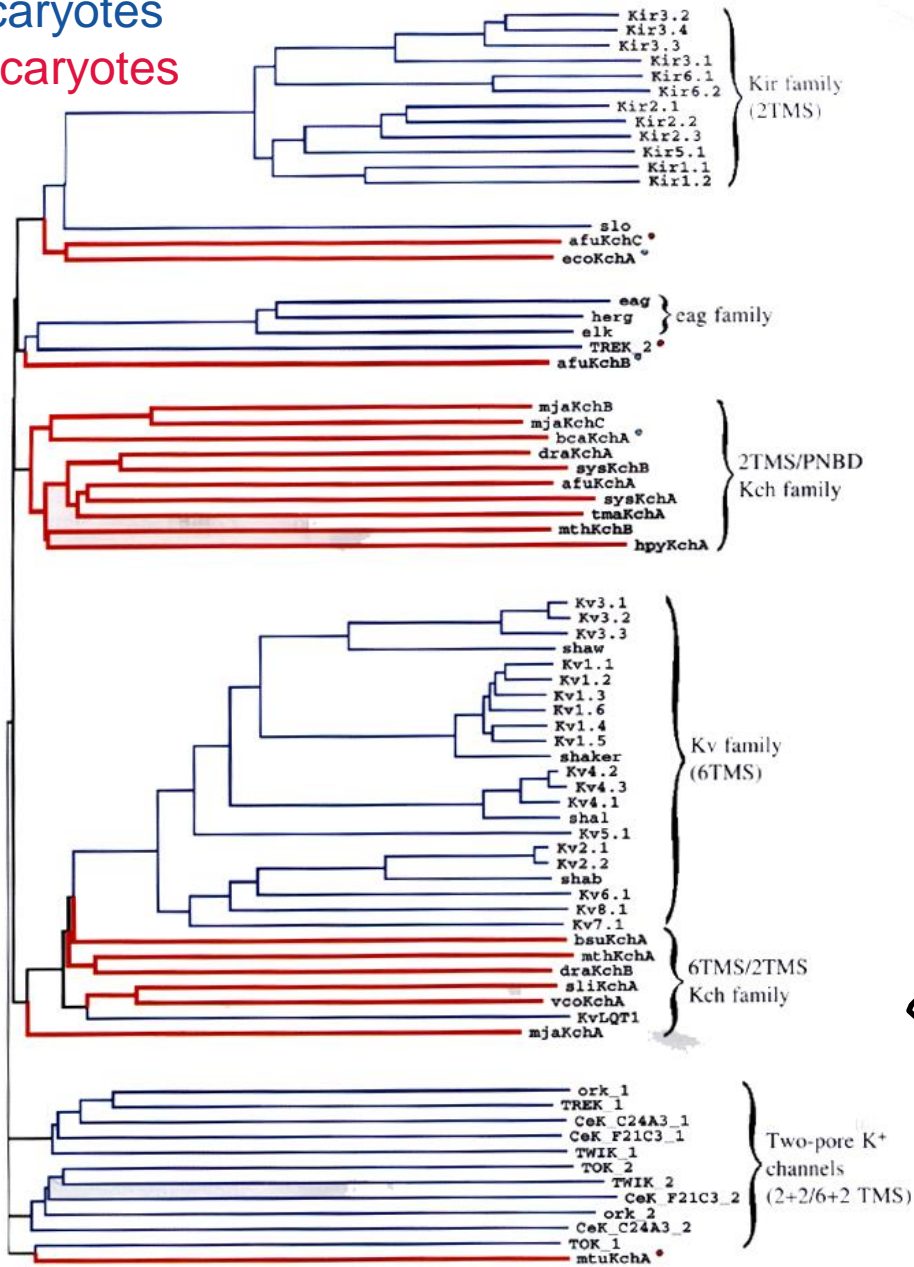
early repolarization

late repolarization

dendrogramme

Canaux potassiques

eucaryotes
procaryotes

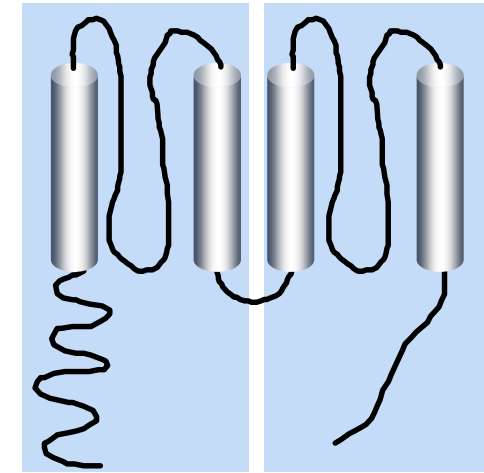
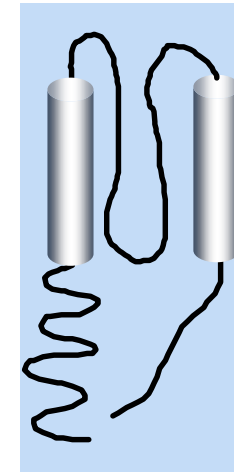
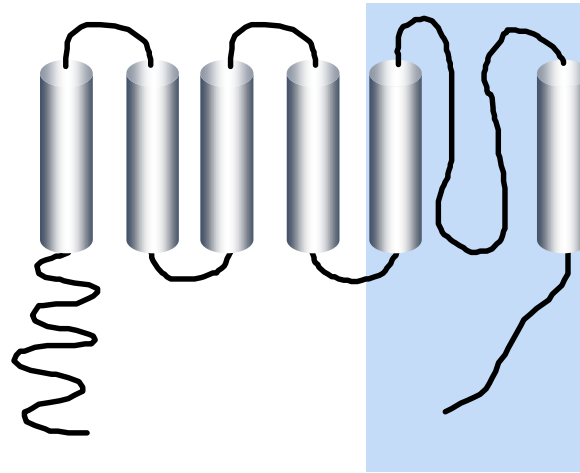


→ 3 classes

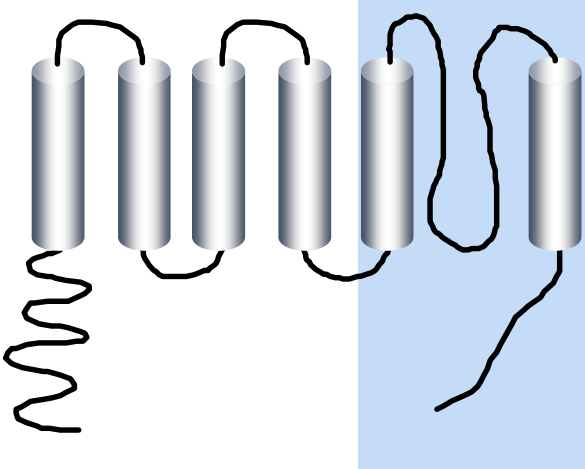
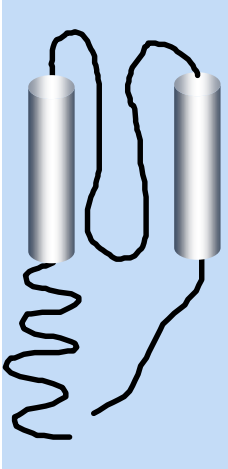
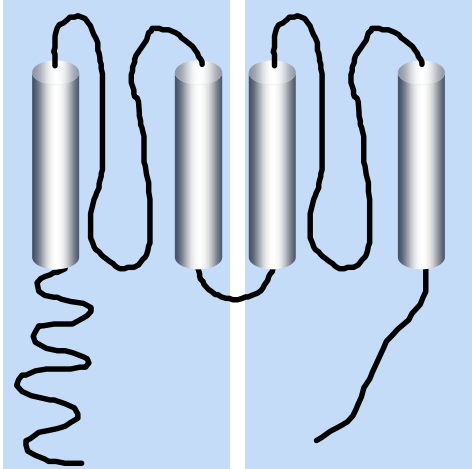
6 segments
transmembranaires
(TMS)
et 1 boucle du pore

2 TMS
et 1 boucle du
pore

4 TMS
et 2 boucles du
pore

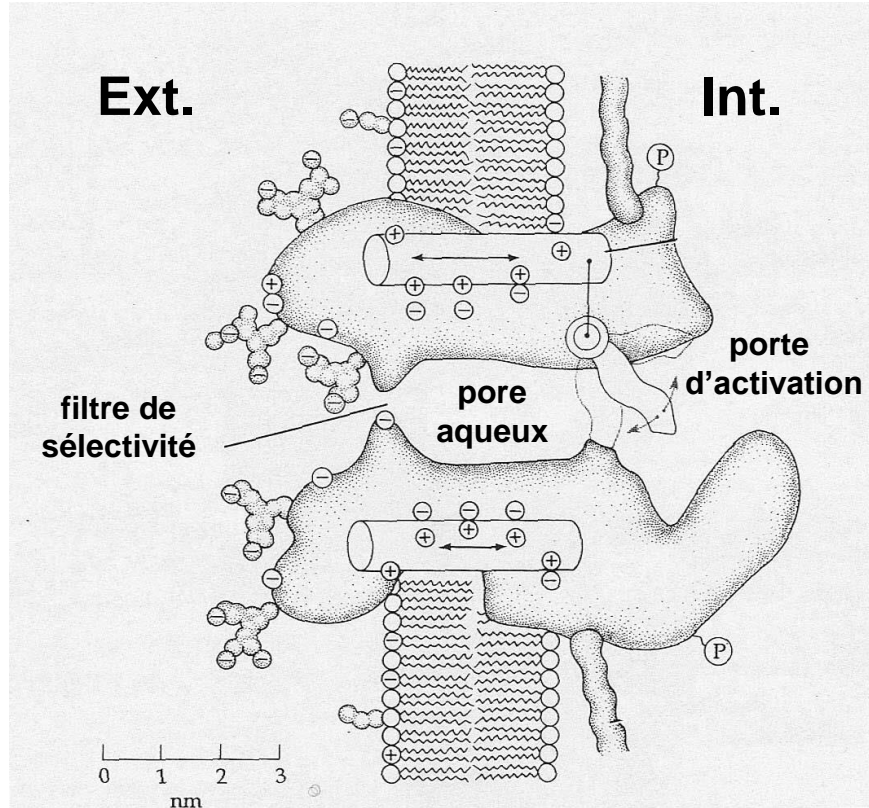


3 classes de canaux K⁺

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

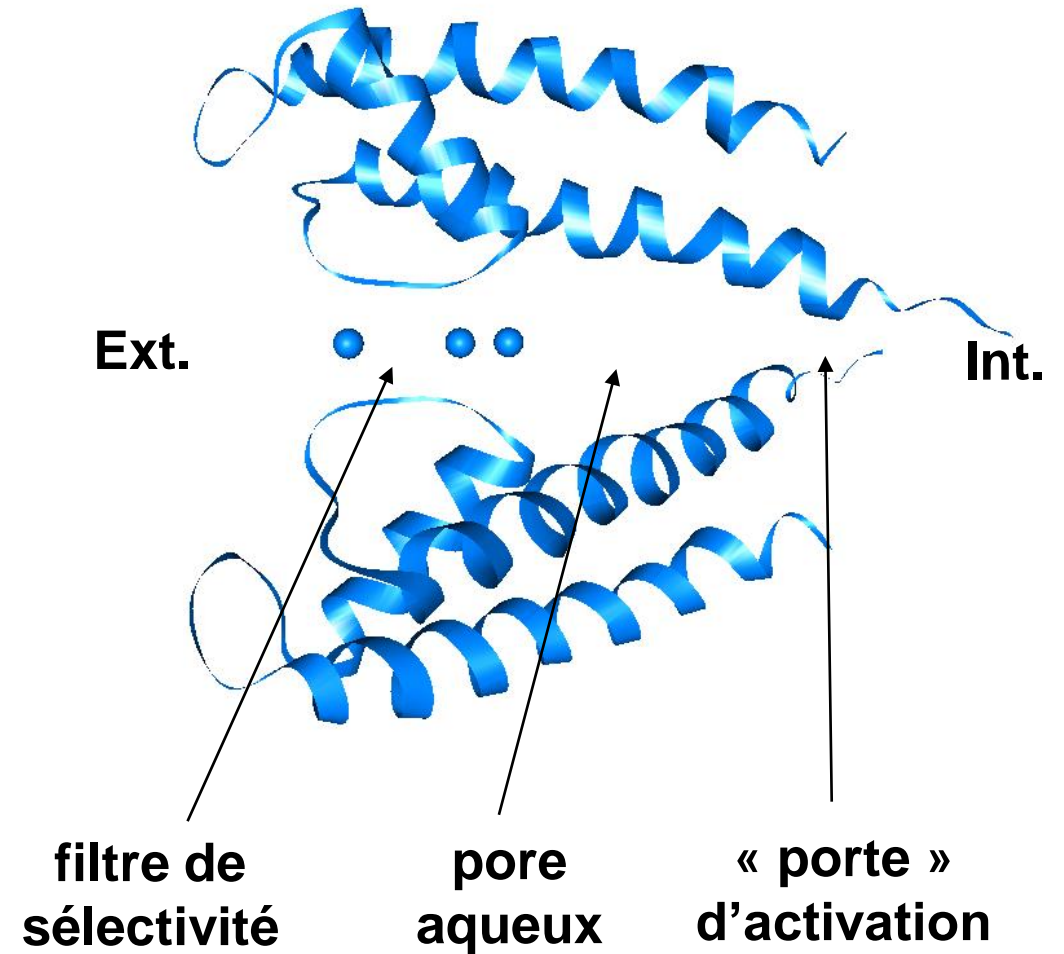
Structure cristallographique d'un canal K⁺ à 2 TMS et 1 pore

Hypothèse de travail (1992)



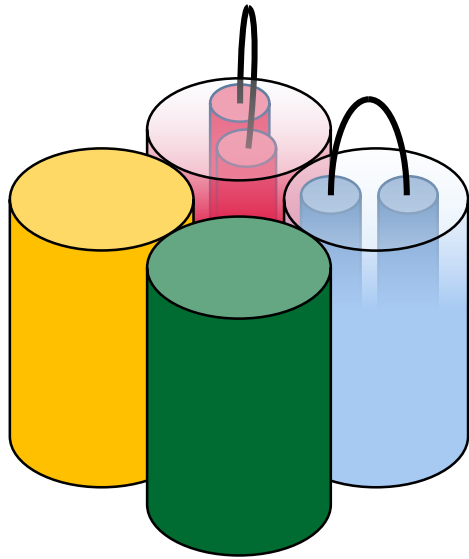
from Hille B *in* Ionic Channels of Excitable Membranes (2nd edition). 1992; Sinauer Associated, MA 01375, U.S.A.

Structure de KcsA (1998)



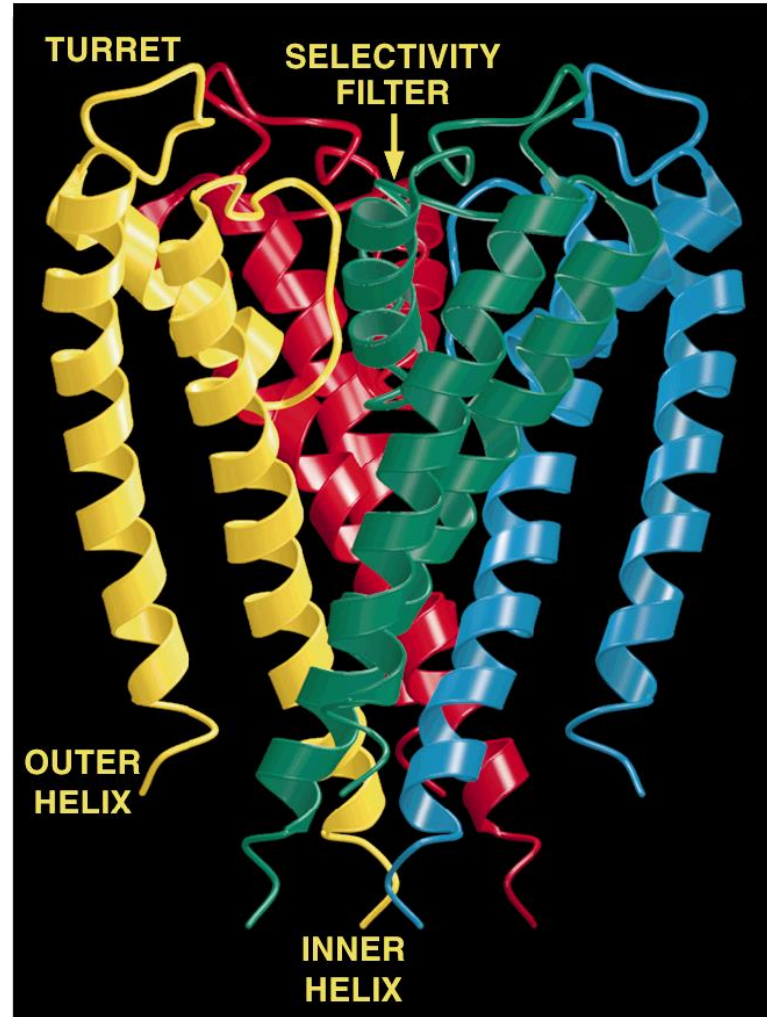
from Doyle DA *et al.* Science. 1998 Apr 3;280(5360):69-77

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



Tétramères

KcSA



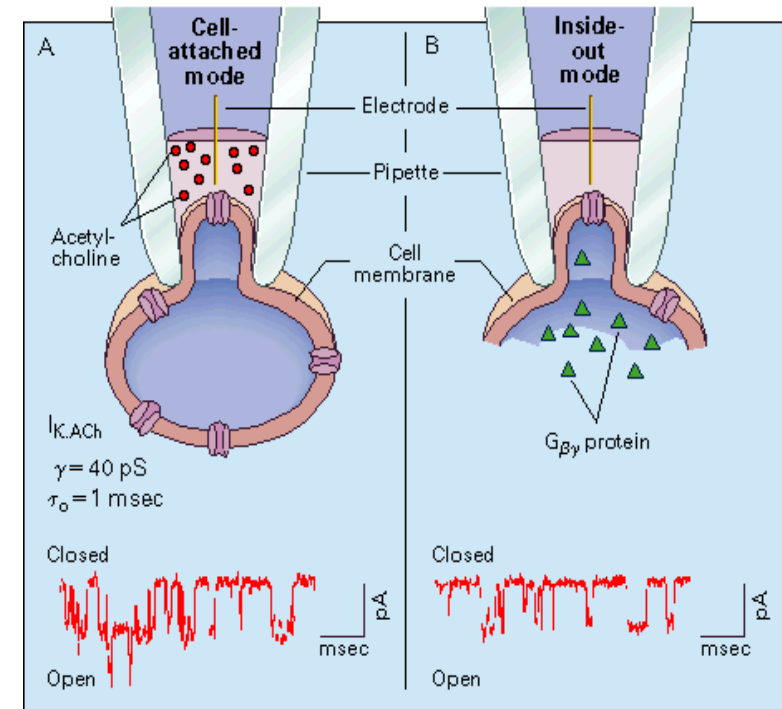
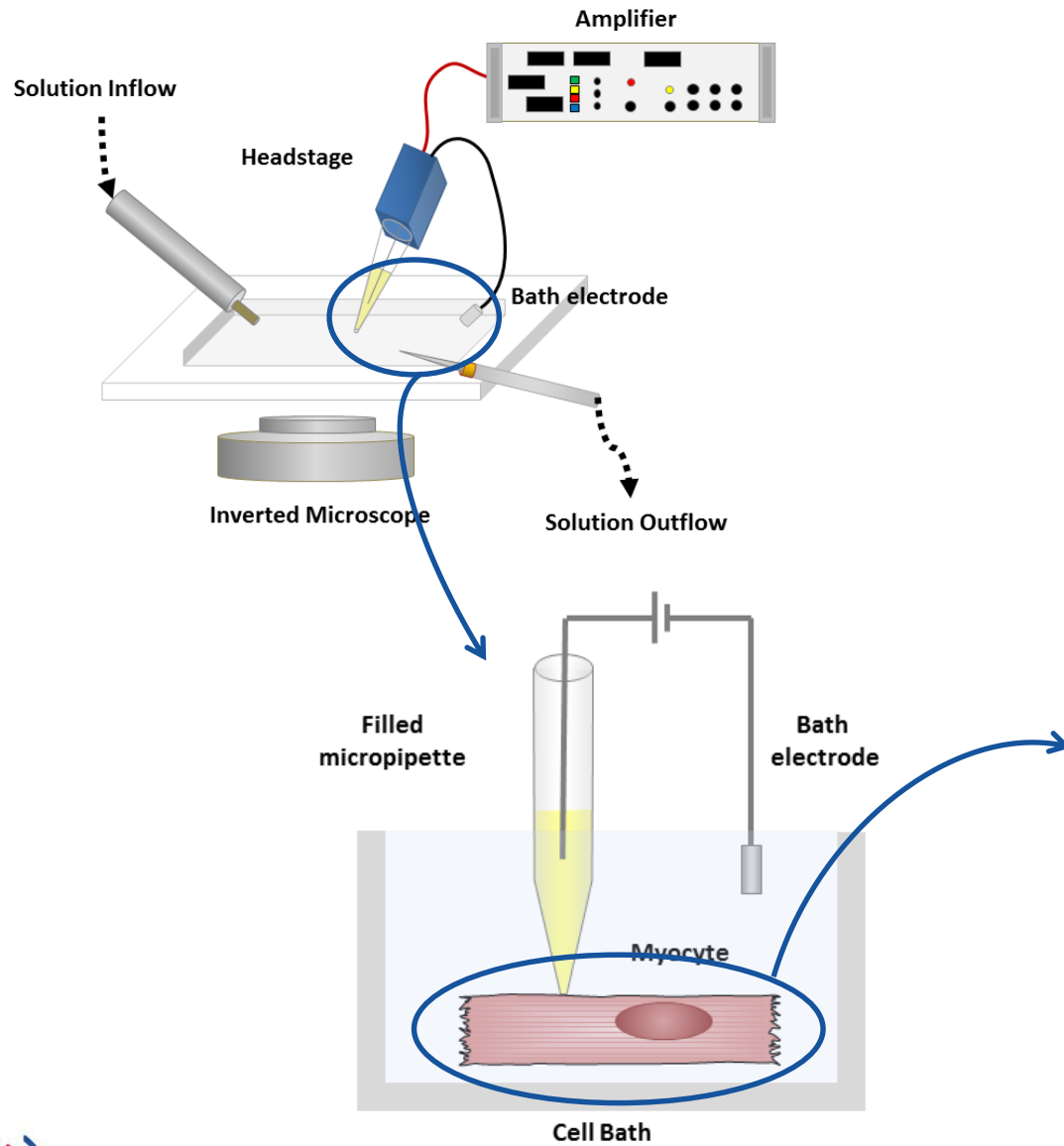
(resolution: 3.2 Å)



Prix Nobel de Chimie 2003 :
Roderick Mac Kinnon

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

Enregistrement d'un courant unitaire : le patch-clamp



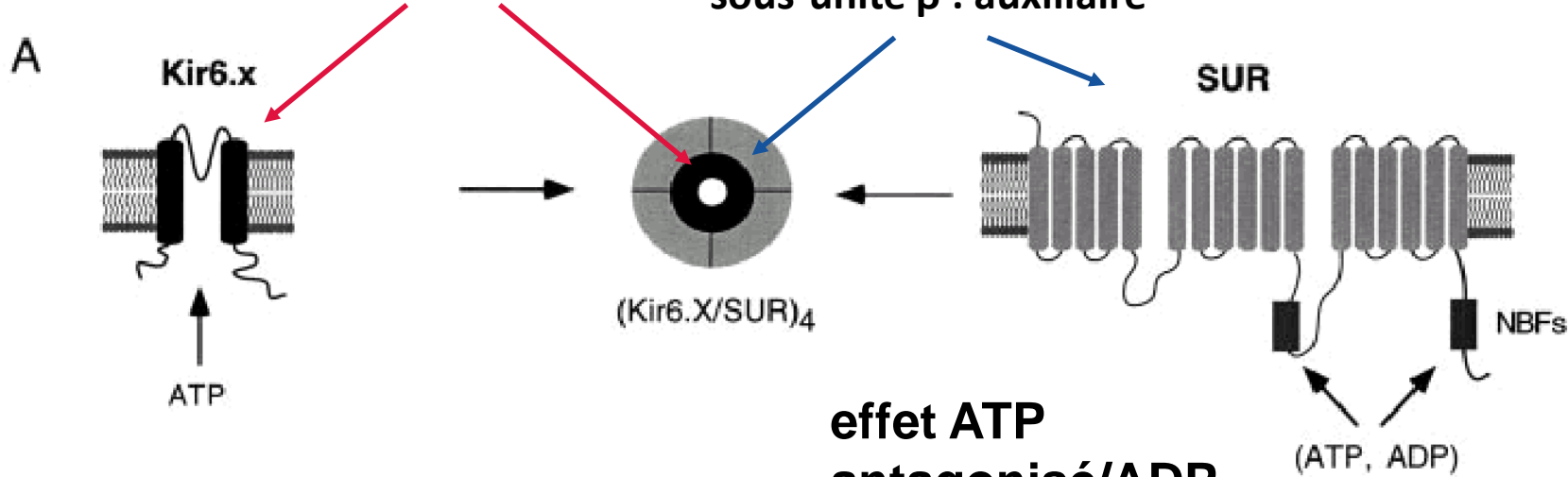
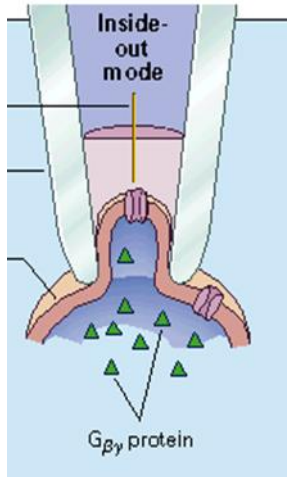
Prix Nobel de Physiologie 1991 : Erwin Neher & Bert Sakmann

canaux K_{ATP} du pancréas (cellules β des îlots de Langerhans)

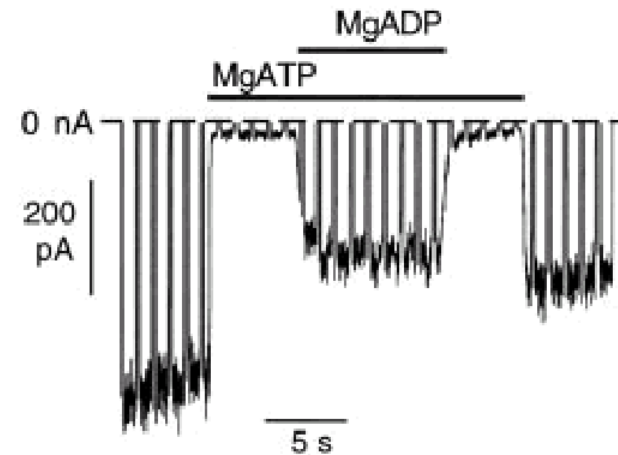
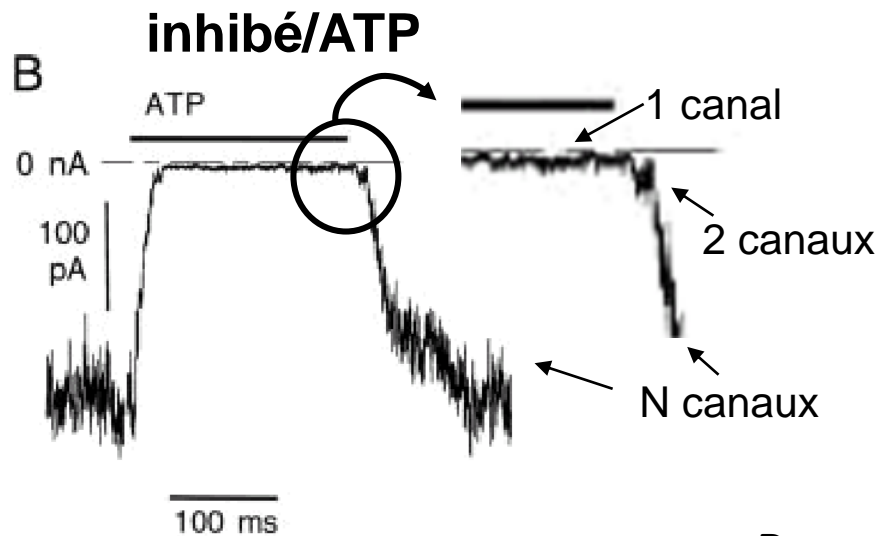
C \rightleftharpoons O
 fermé ouvert

sous-unité α : pore

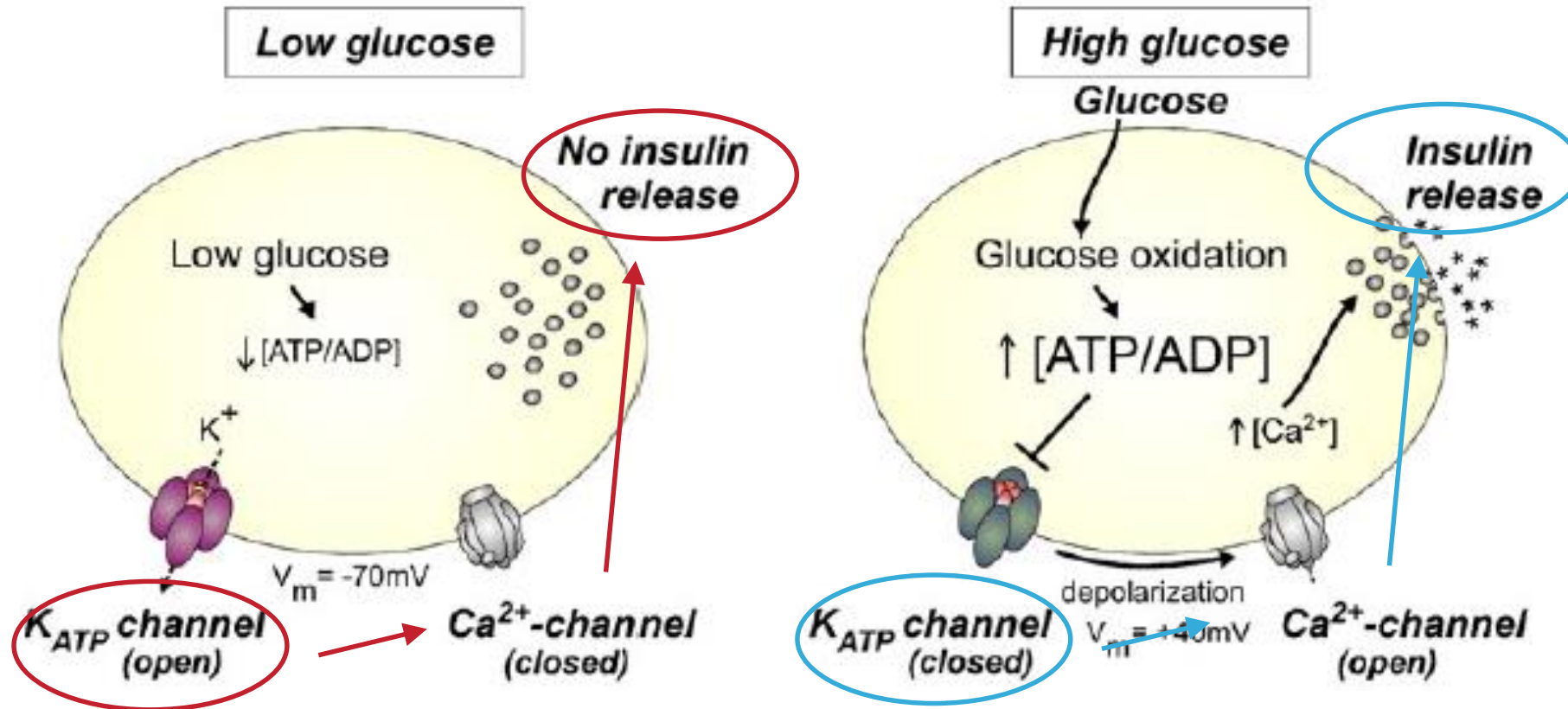
sous-unité β : auxiliaire



effet ATP
 antagonisé/ADP

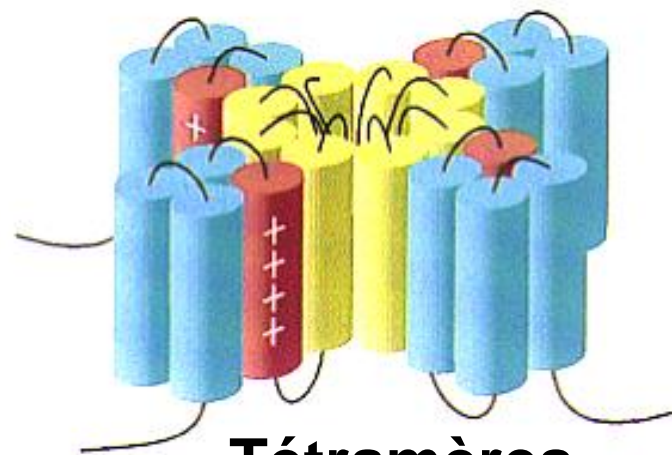
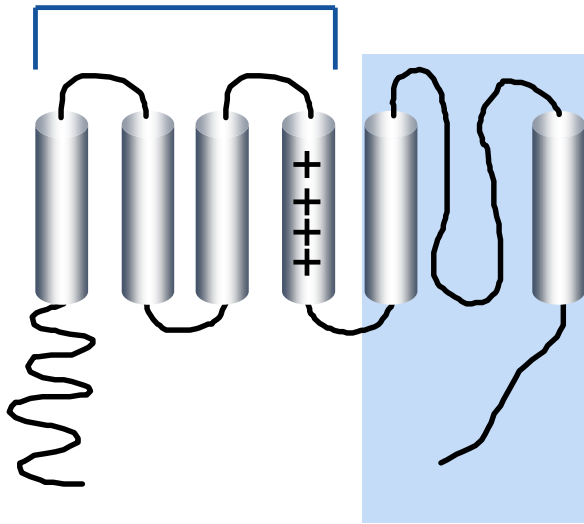


canaux K_{ATP} du pancréas (cellules β) rôle dans la sécrétion d'insuline

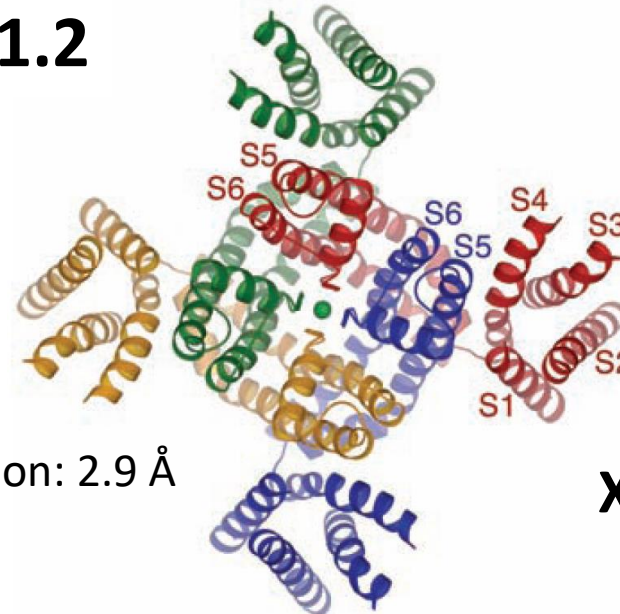


Structure d'un canal K⁺ 6 TMS et 1 pore

voltage sensor



Kv1.2

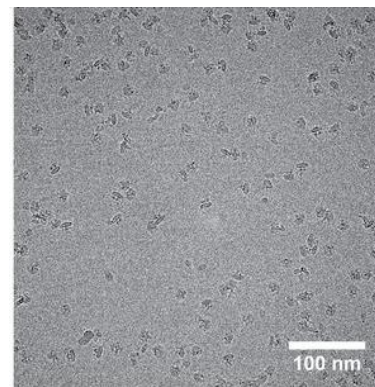


resolution: 2.9 Å

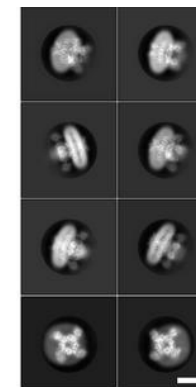
Long SB *et al.* Science. 2005 Aug 5;309(5736):897-903.

X-ray crystallography

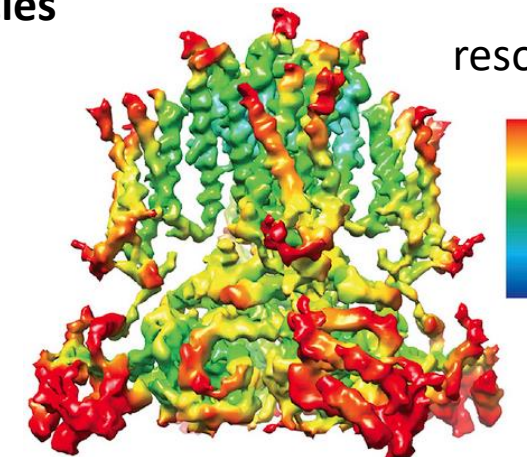
hERG



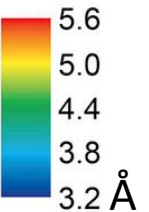
~144,000 particles



10 nm



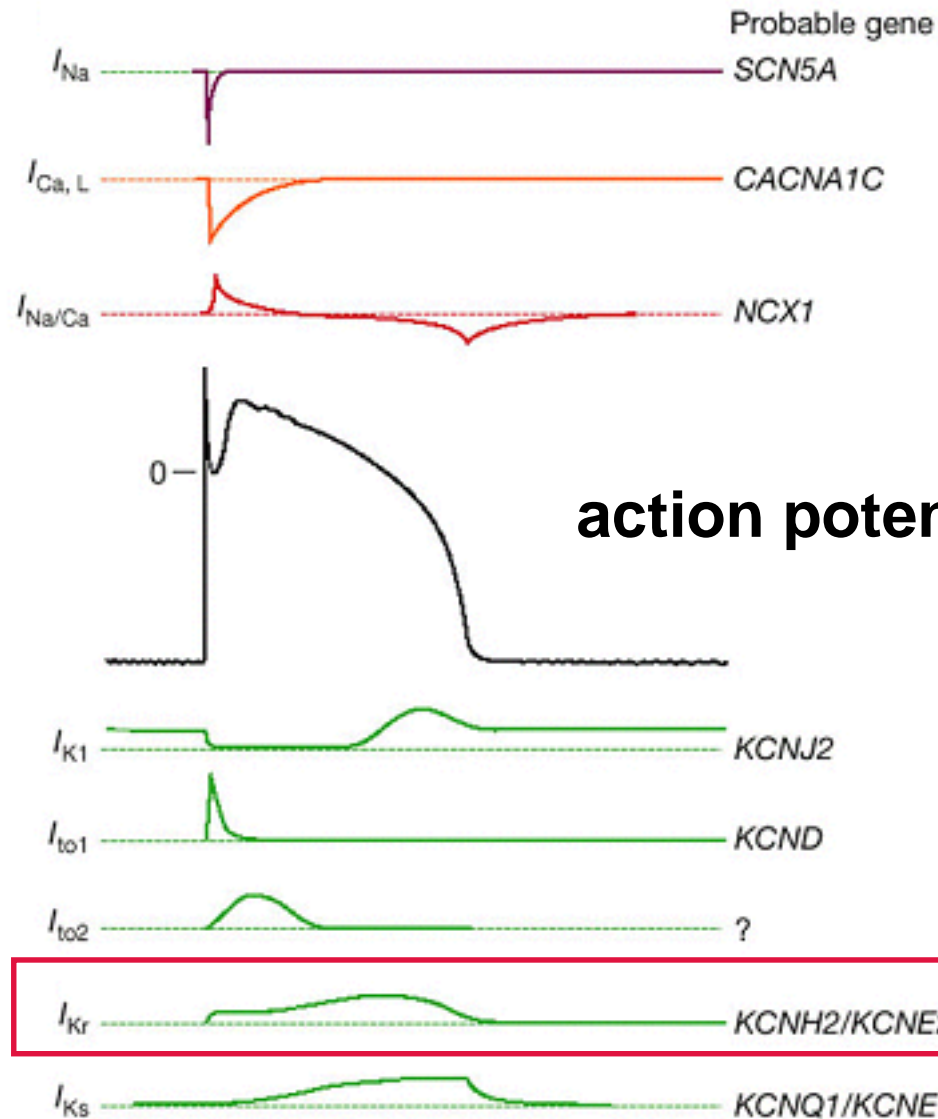
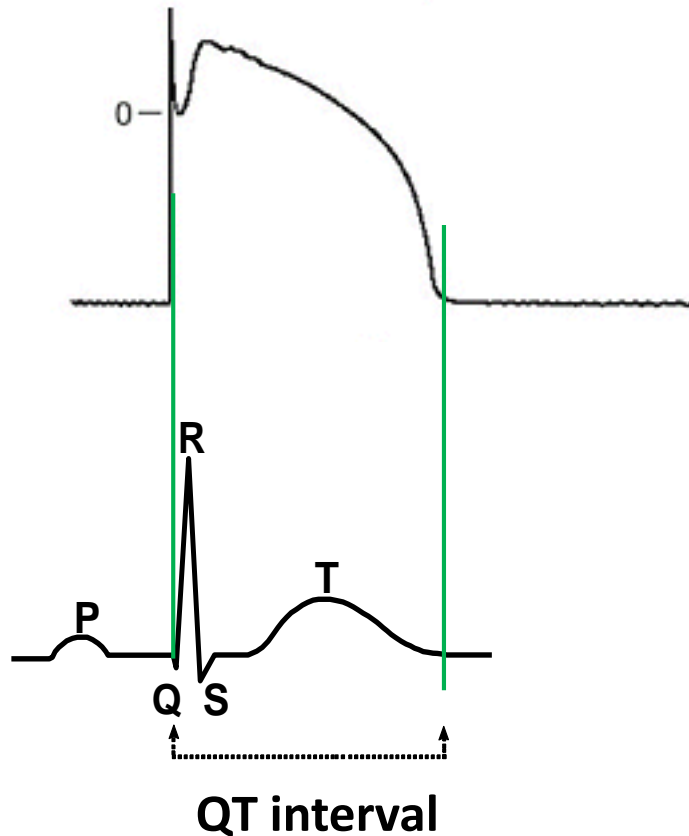
resolution:



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

diastolic potential

early repolarization

late repolarization

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**

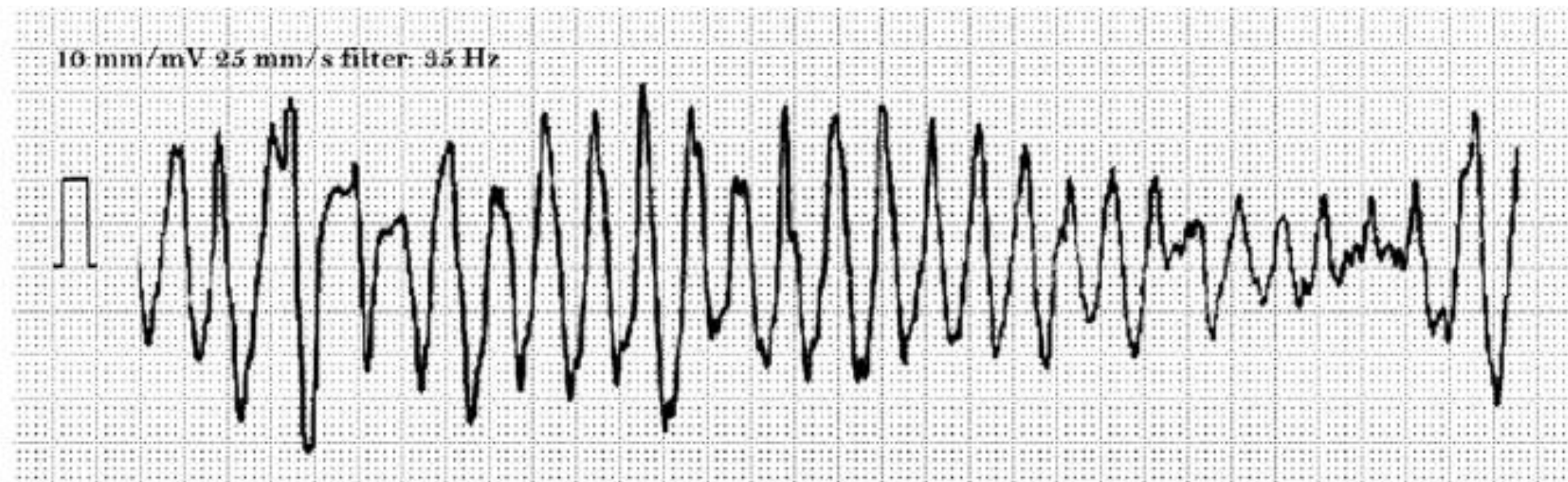


Fig. 1. ECG recording showing an ongoing episode of Torsade de pointes. This polymorphic ventricular arrhythmia is characterized by the progressive rotation of the electrical axis (180 ° in about 10–12 cycles) which shows on the surface ECG as the sinusoidal undulation of the electrical signal.

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

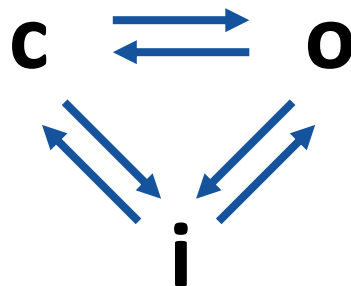
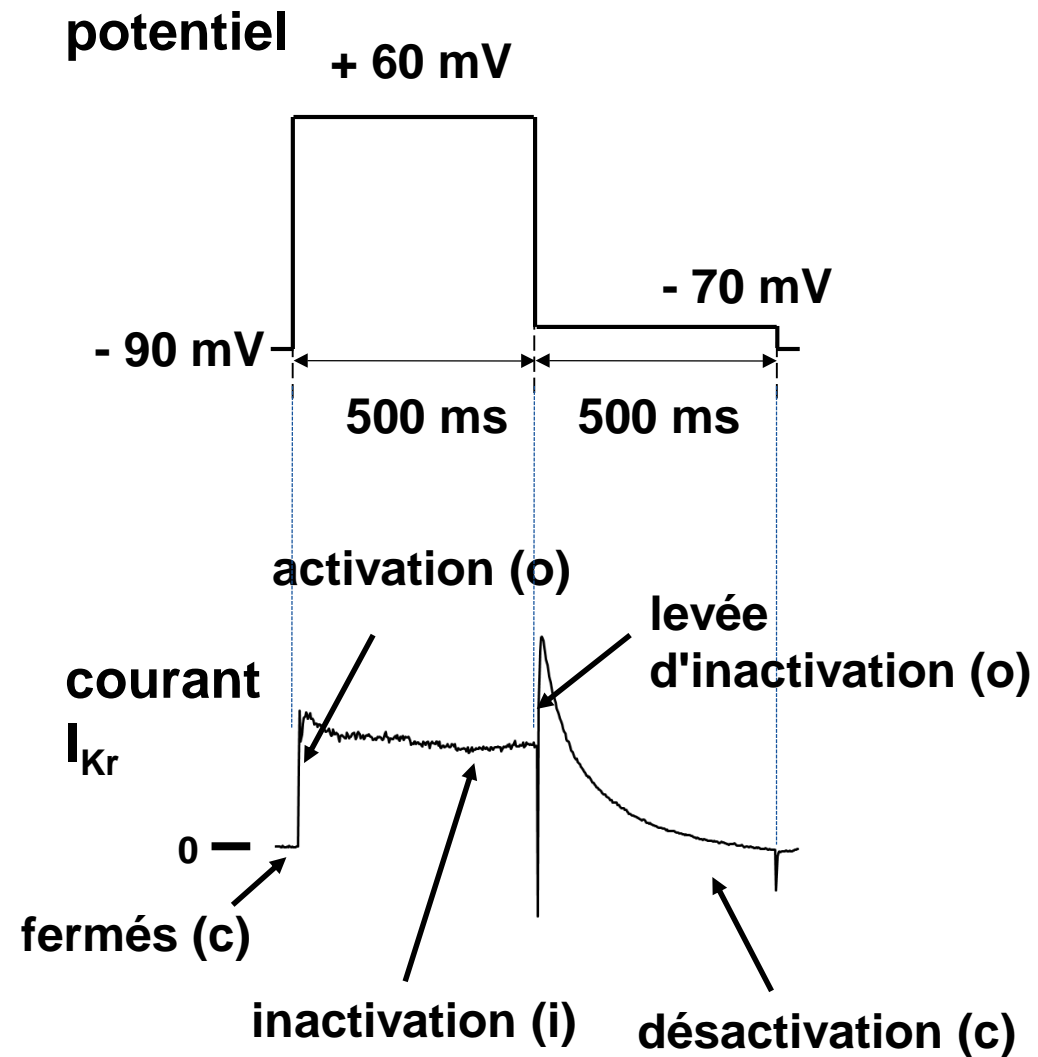
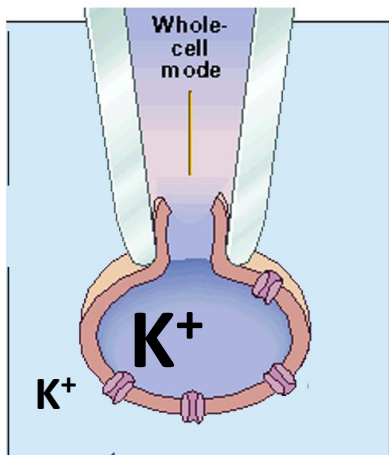
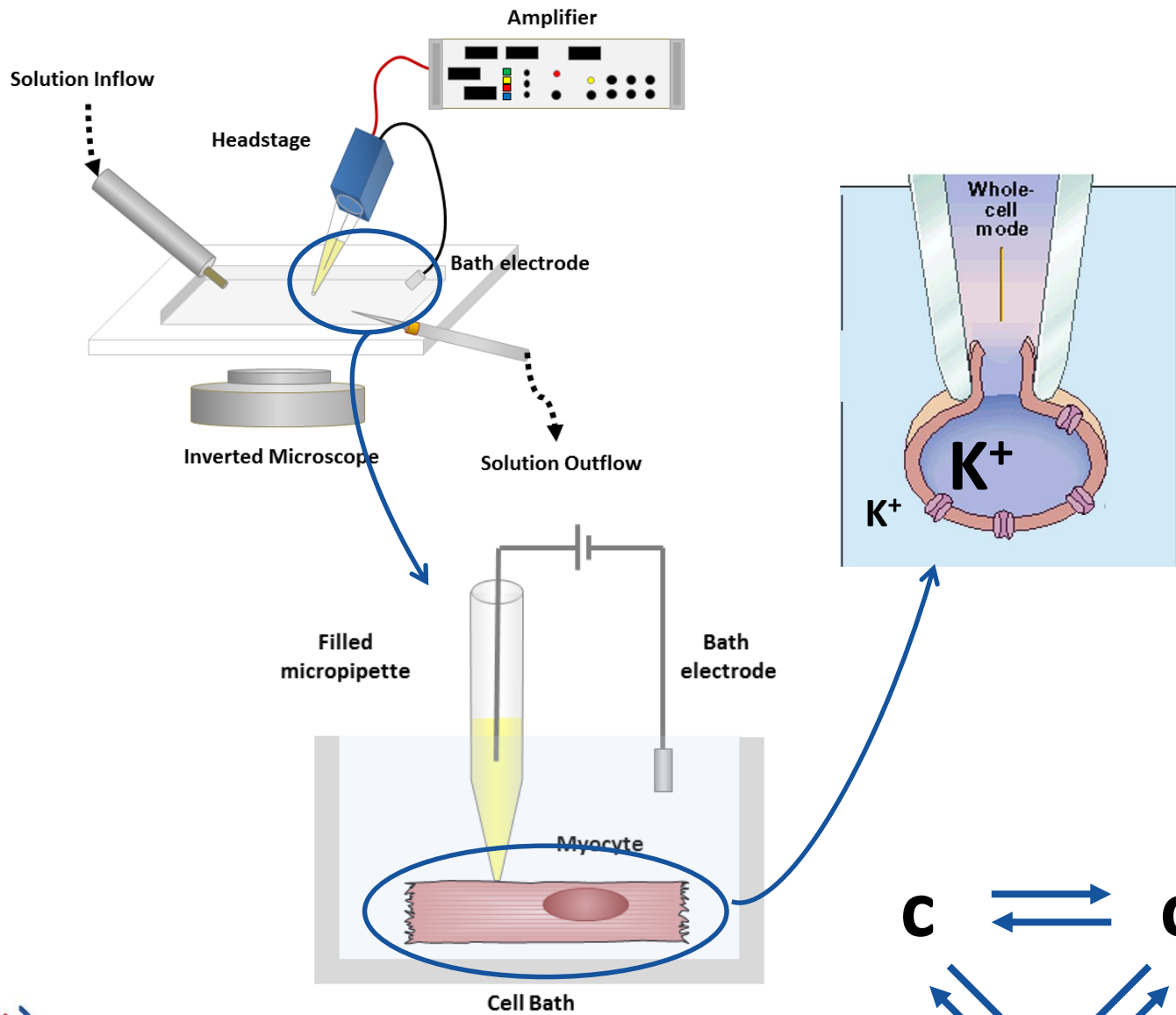
Table 1 Classification of genes responsible for cardiac channelopathies. Adapted from Schwartz et al. [2]

LQTS type	Gene	Mutation frequency among LQTS population (%)	Locus	Protein (functional effect)
Romano–Ward (RWS) <i>mut</i>/<i>WT</i>				
LQT1	KCNQ1	40–55	11p15.5	K _v 7.1 (↓)
LQT2	KCNH2	30–45	7q35–36	K _v 11.1 (↓)
LQT3	SCN5A	5–10	3p21–24	Na _v 1.5 (↑)
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) <i>mut</i>/<i>mut</i>				
JLN1	KCNQ1	< 1	11p15.5	K _v 7.1 (↓)
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

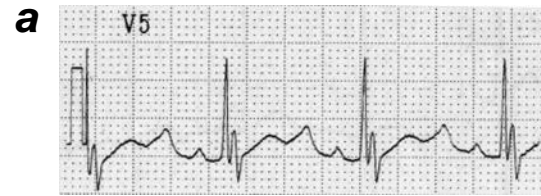
Enregistrement d'un courant trans-membranaire : le patch-clamp



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

Propositus : fibrillation ventriculaire (torsades de pointes)

▼ Feb-05-99 – clobutinol

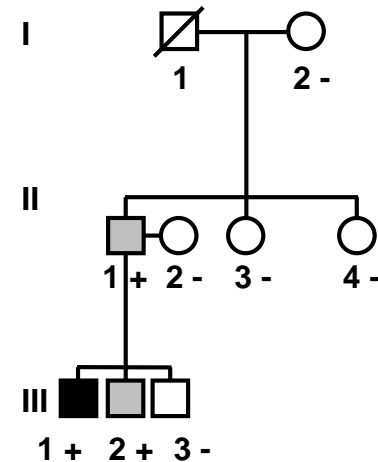


◀ May-30-97
597 ms
(628 ms)

1 mV
400 ms



Génotypage



+ : hERG **A561P** ← causal ?
- : hERG WT

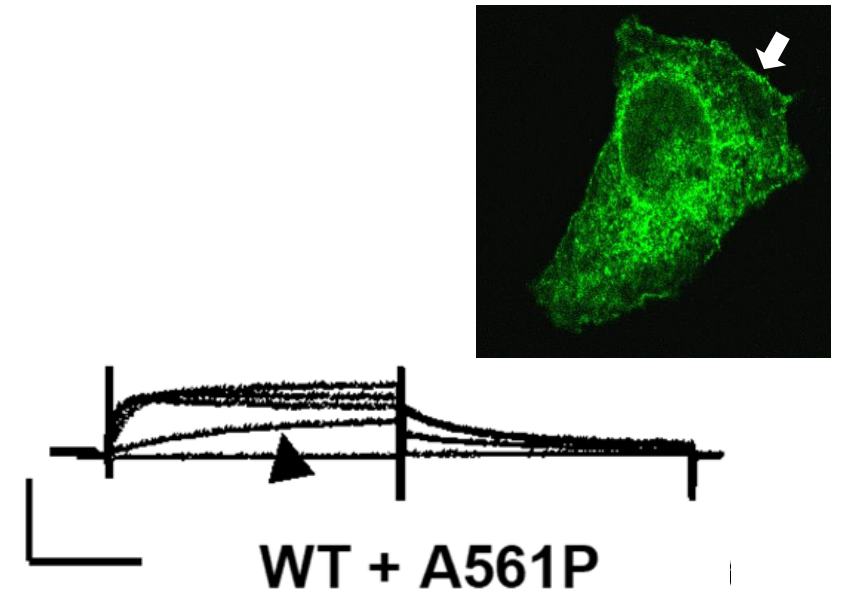
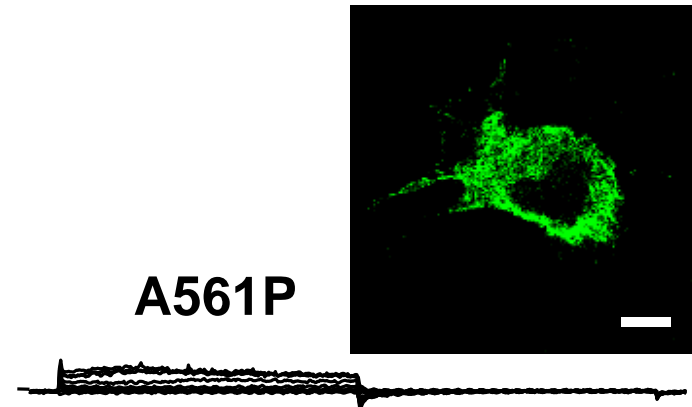
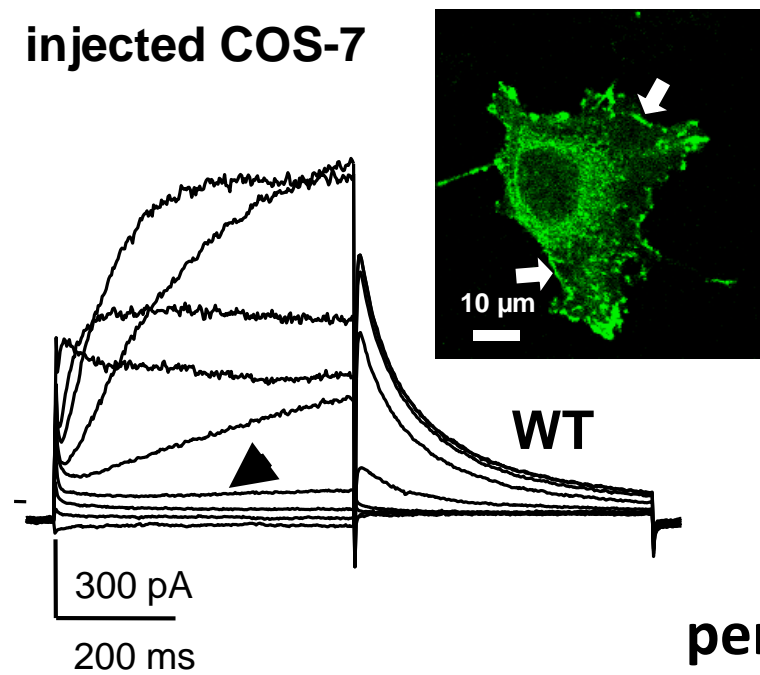
porteur hétérozygote :

Modèles cellulaires

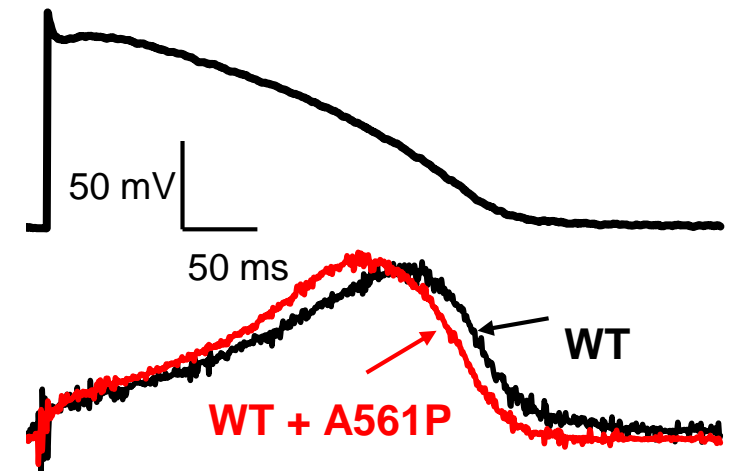
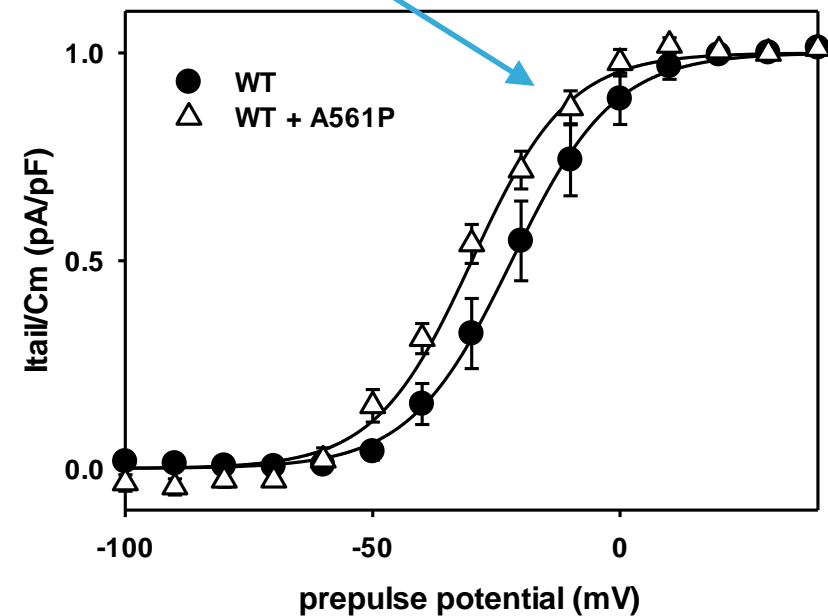
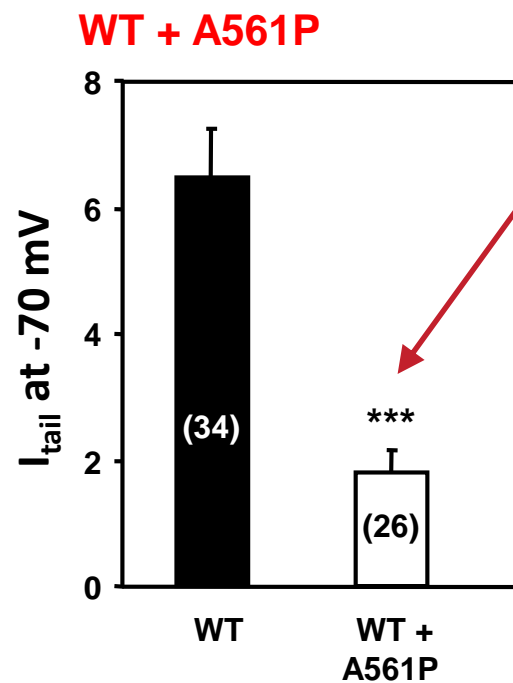
- Lignées cellulaires modifiées - canalopathies monogéniques

expression hétérologue de protéines WT et mutées

injected COS-7



perte/gain de fonction ?

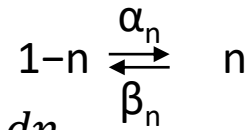


Modèles *in silico*

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

perte/gain de fonction :
allongement → causal

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



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

Rapidly Activating Current: I_{Kr}

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

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

$$g_{Kr,max} = 0.015 \text{ mS}/\mu\text{F}$$

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

$$\{1 + \exp[-0.1262 \cdot (V+4.067)]\}$$

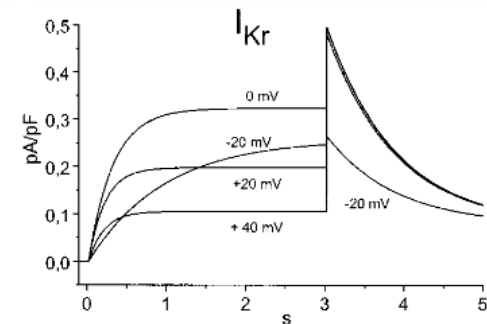
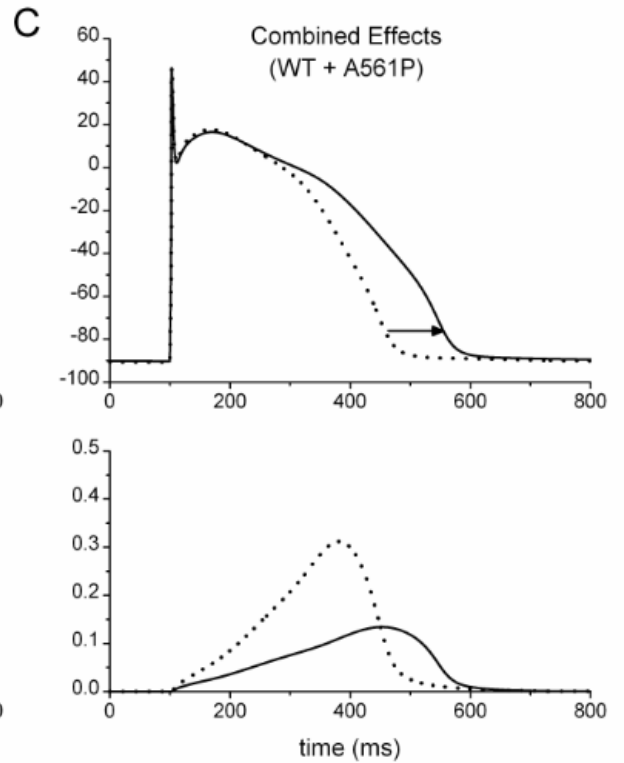
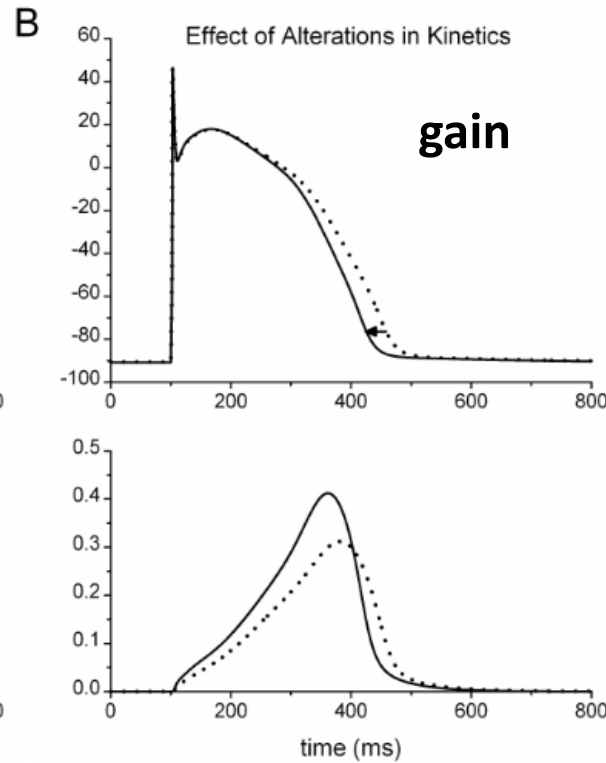
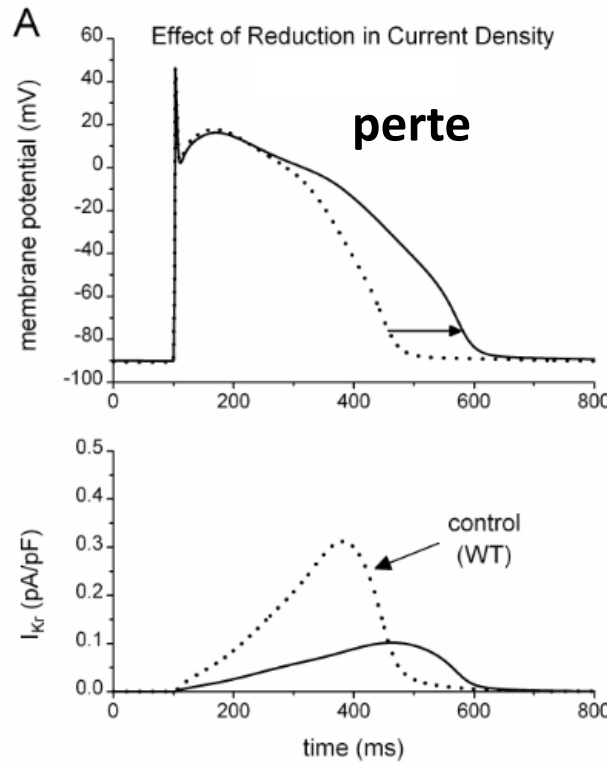
$$\beta_{X_r} = \{0.016 \cdot \exp[1.6 \cdot 10^{-3} \cdot (V+65.66)]\} /$$

$$\{1 + \exp[0.0783 \cdot (V+65.66)]\}$$

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

$$\frac{dX_r}{dt} = \alpha_{X_r}(1 - X_r) - \beta_{X_r} X_r = \frac{X_{r\infty} - X_r}{\tau_{X_r}}$$

where $g_{Kr,max}$ is g_{max} for I_{Kr} , X_r 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 .

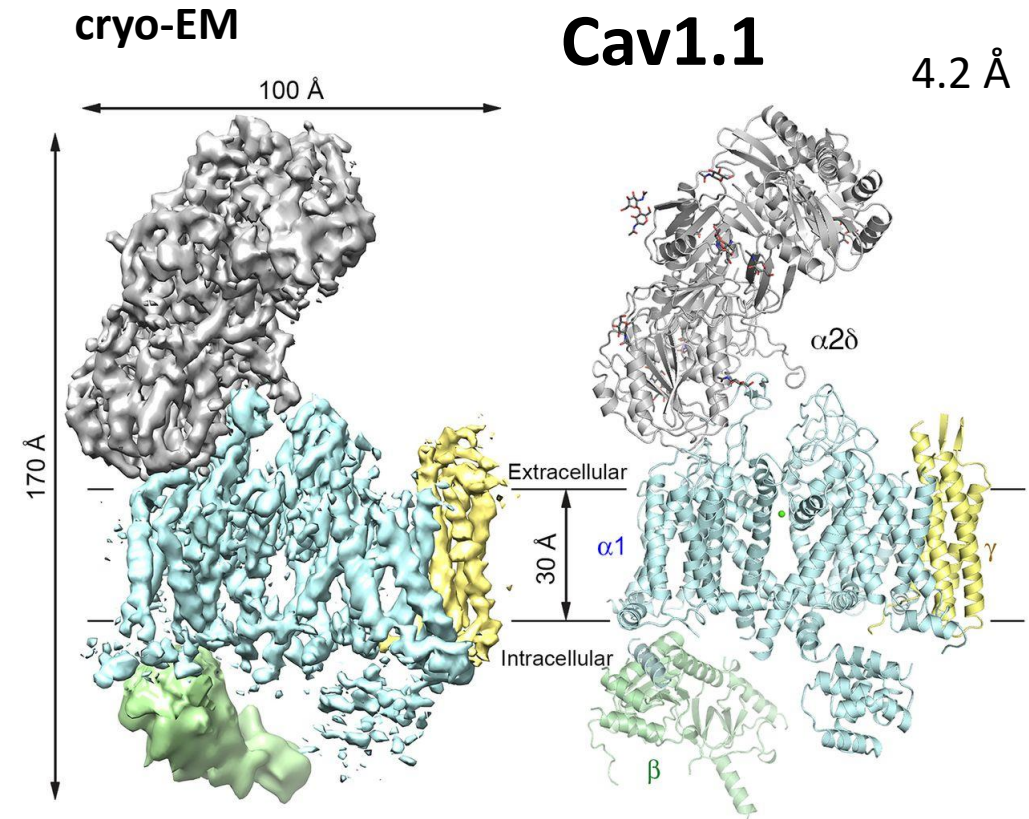
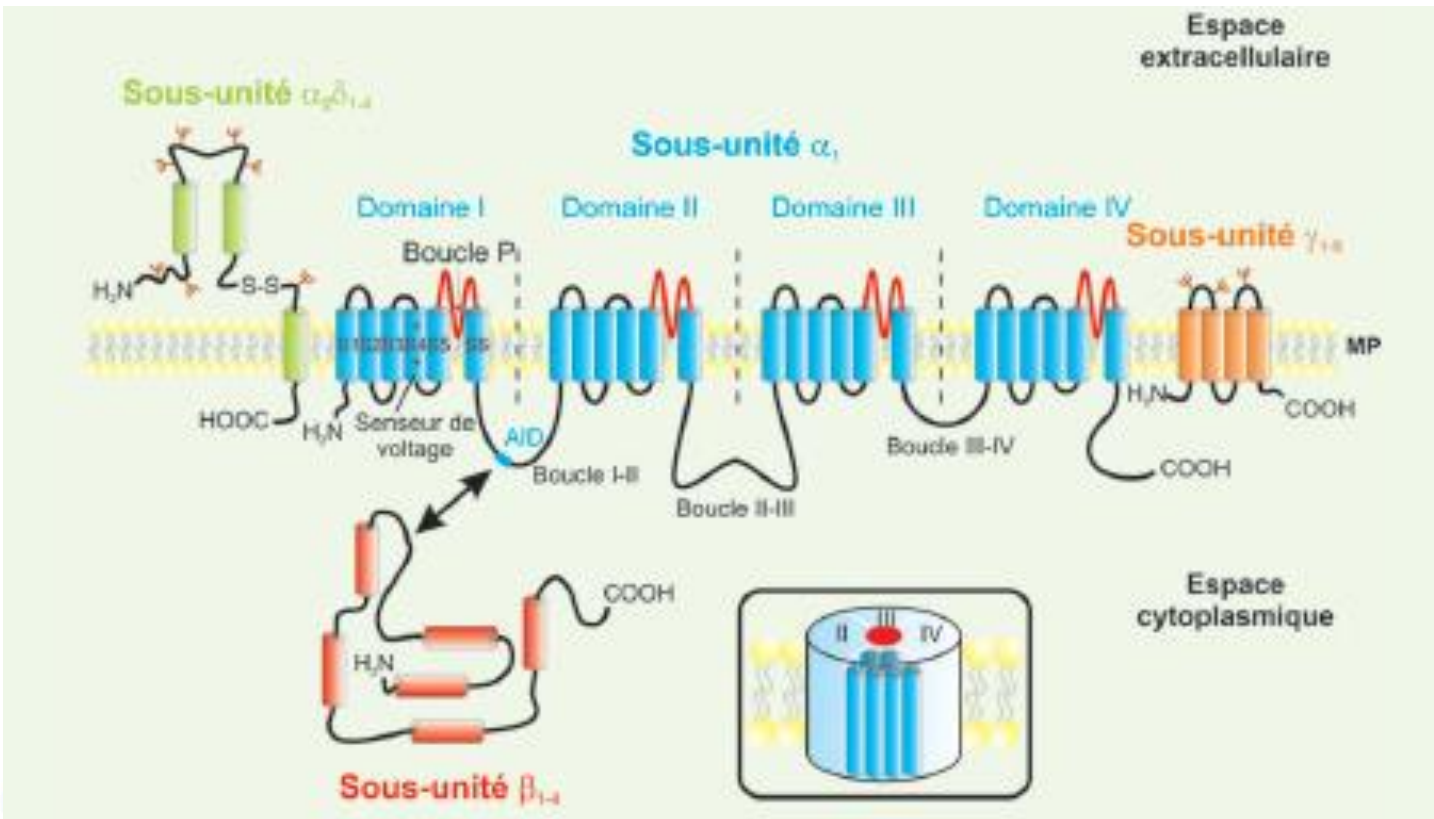
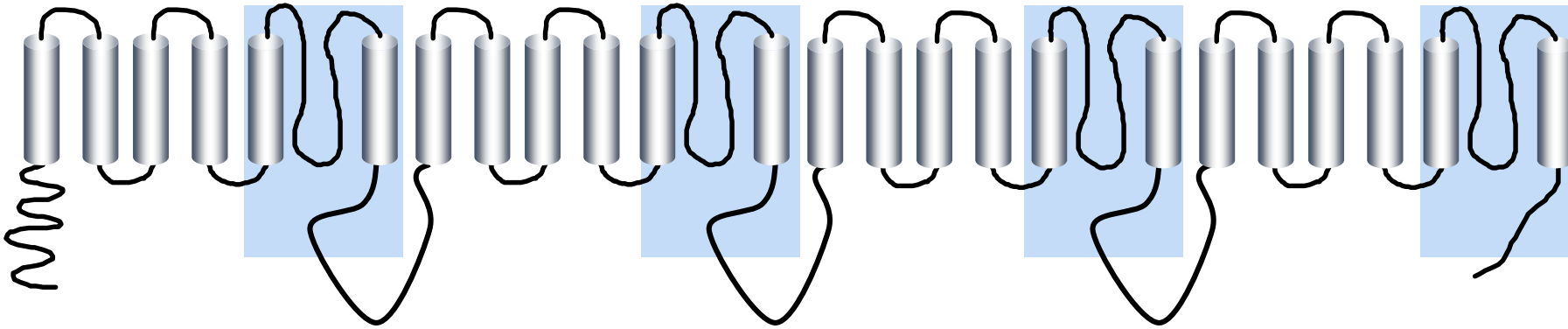


Hodgkin AL, Huxley AF. J Physiol. 1952 Aug;117(4):500-44.

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

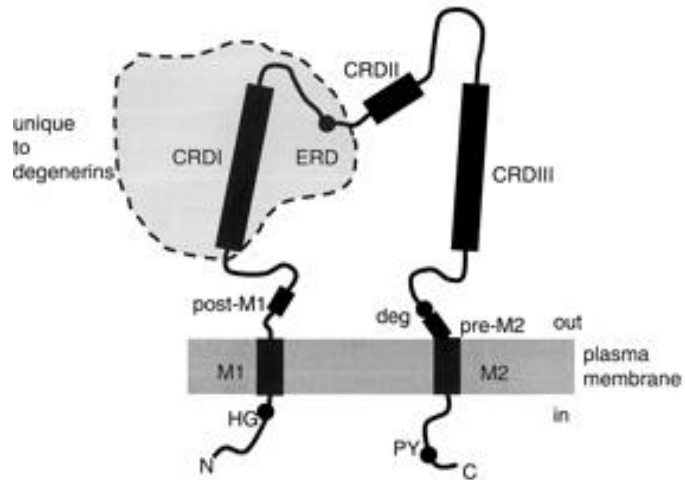
Belloq C *et al.* Mol Pharmacol. 2004 Nov;66(5):1093-102.

Canaux Ca^{2+} : 4 domaines homologues

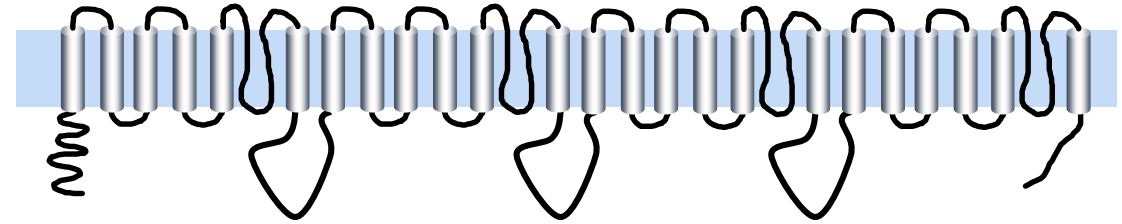


Wu J *et al.* Science. 2015 Dec 18;350(6267):aad239519

Canaux Na⁺ : 2 classes

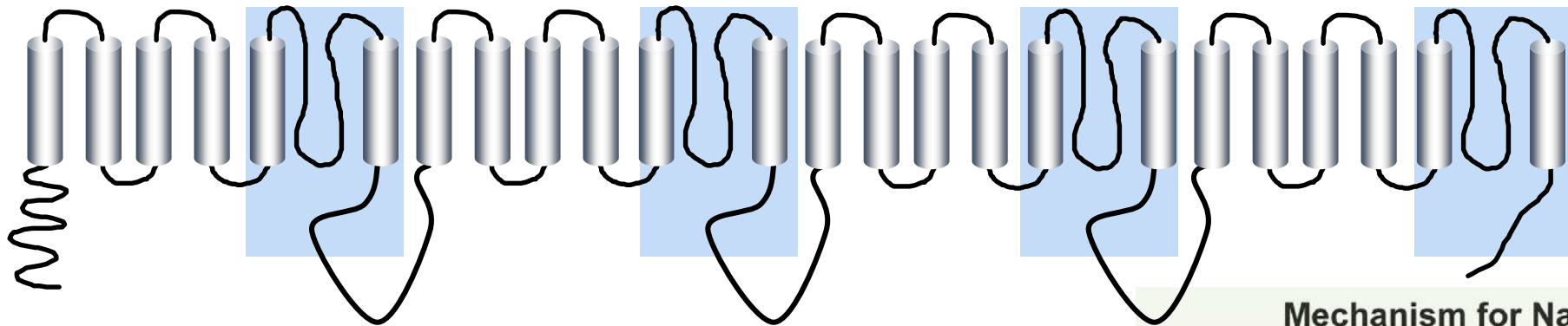


- ENaC (epith. Na⁺ channel)

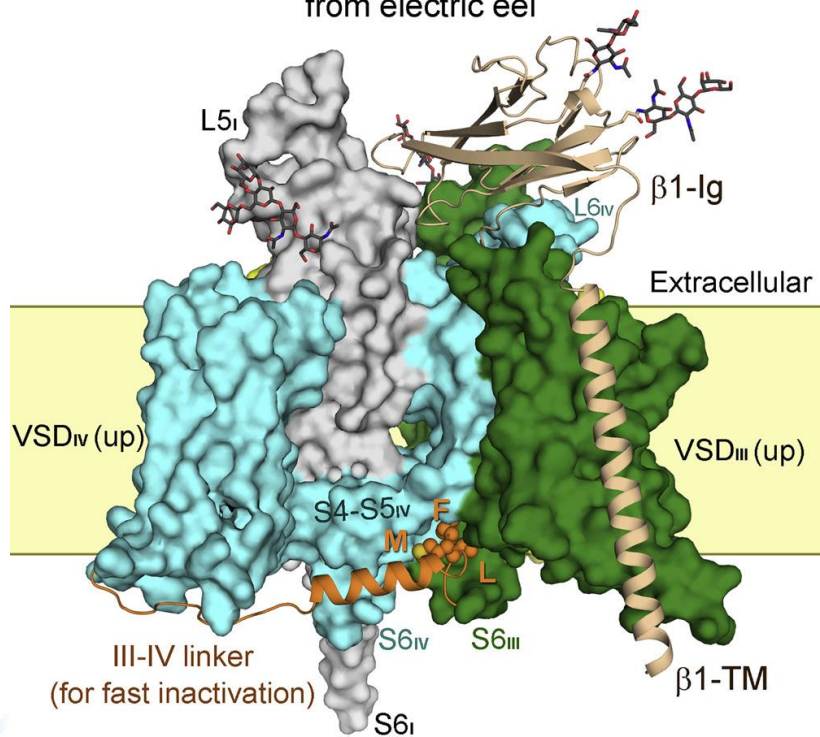


- Nav: voltage-gated
- canal Na⁺ cardiaque : Nav1.5 + Navβ1 (*SCN5A* et *SCN1B*)

Canaux Nav : structure

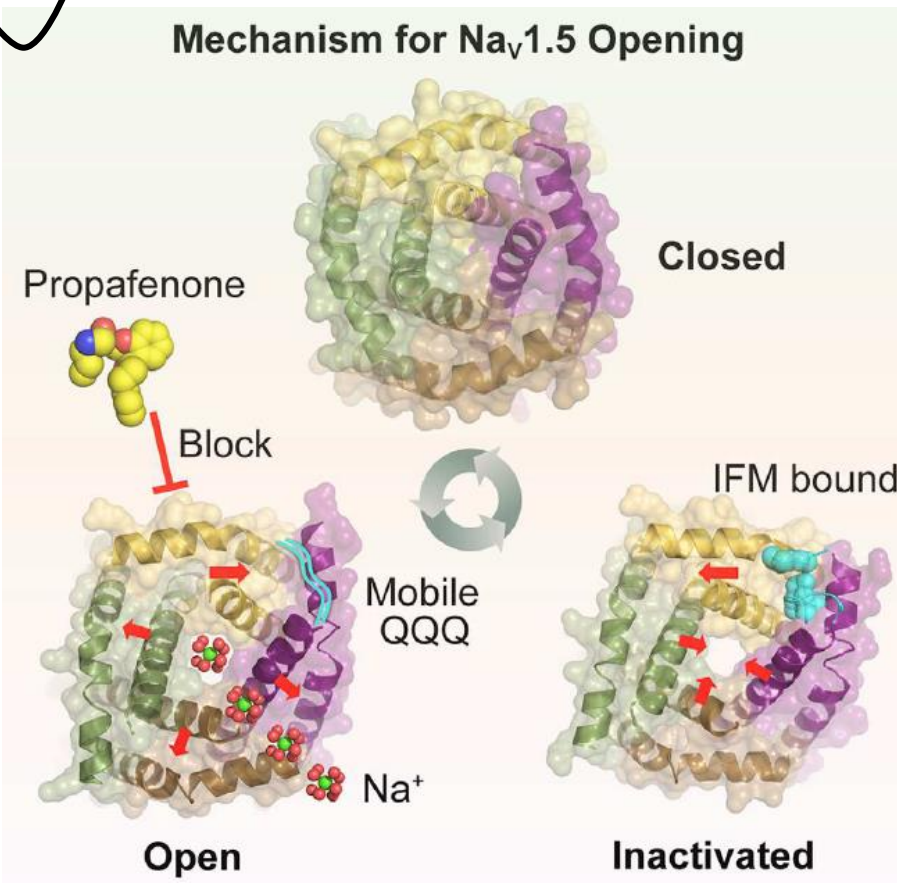


Cryo-EM structure of the Nav1.4-β1 complex from electric eel



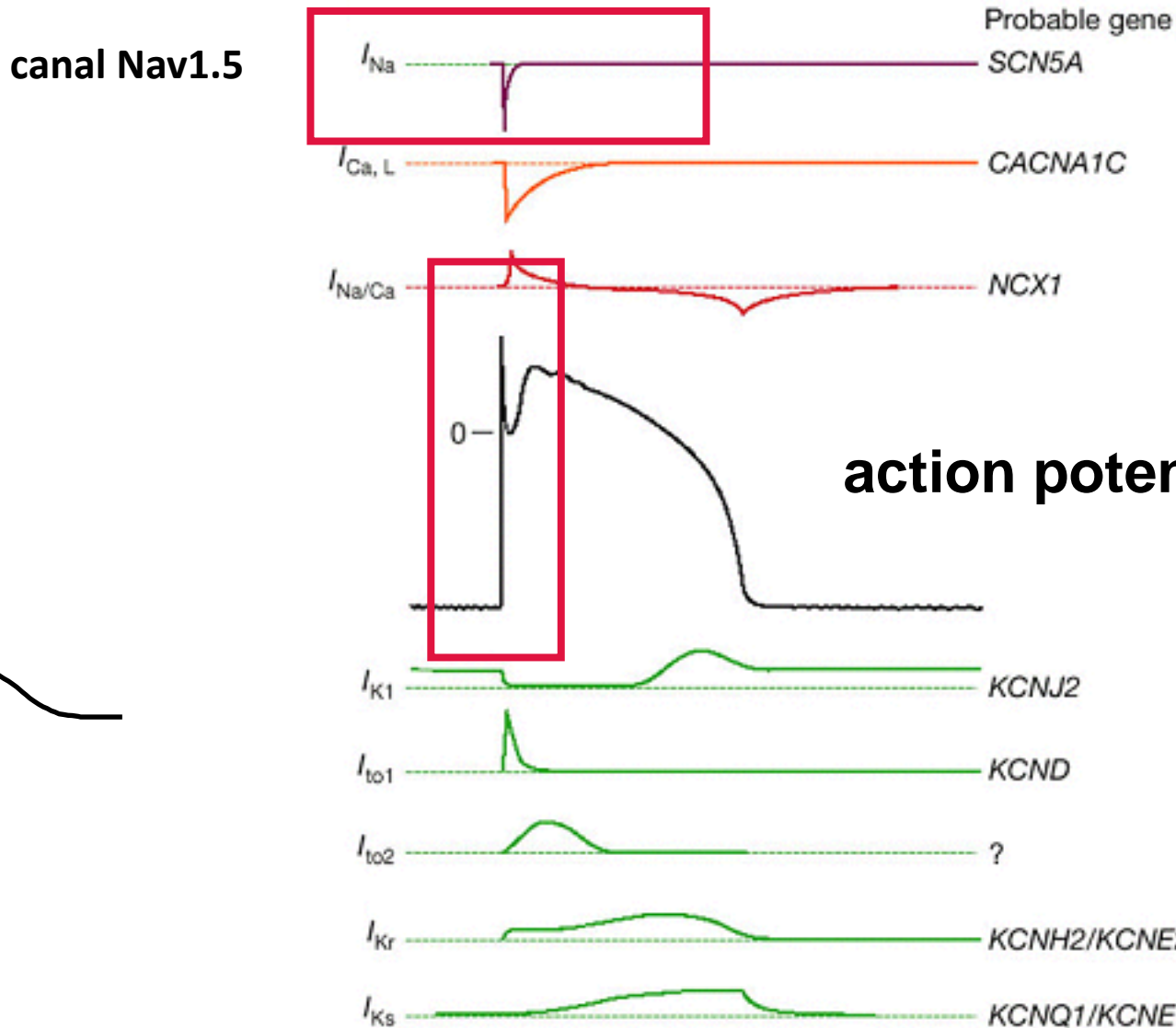
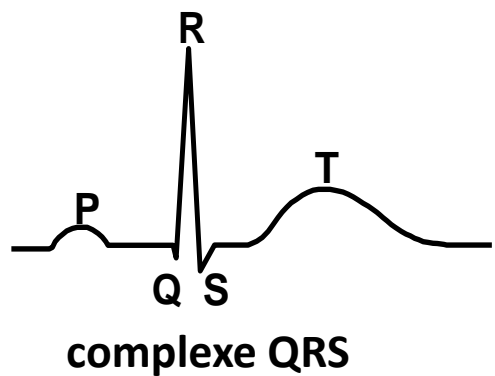
Yan *et al.* Cell. 2017 Jul 27;170(3):470-482.e11.

Mechanism for Nav_v1.5 Opening



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

Activité électrique du cardiomyocyte ventriculaire : le potentiel d'action



early depolarization

plateau

diastolic potential

early repolarization

late repolarization

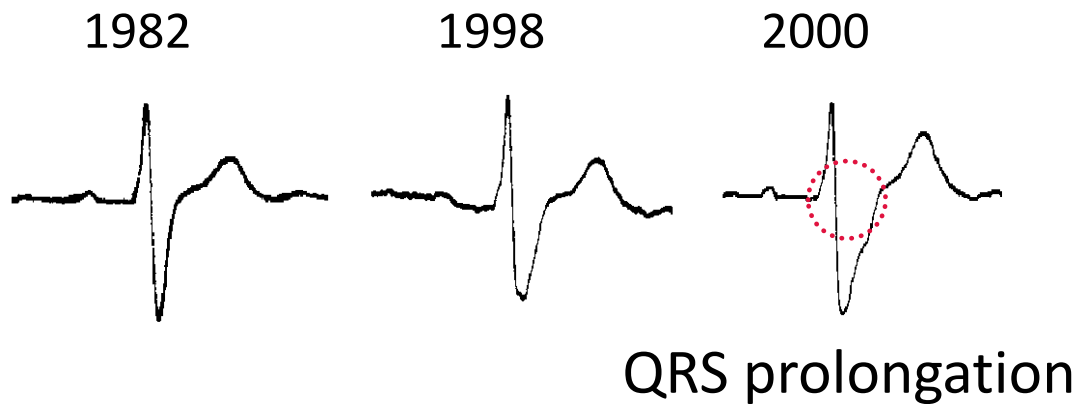
Du modèle cellulaire au modèle murin du syndrome de Lenège

- Syndrome de Lenège : ralentissement de la conduction cardiaque héréditaire

→ bloc de conduction

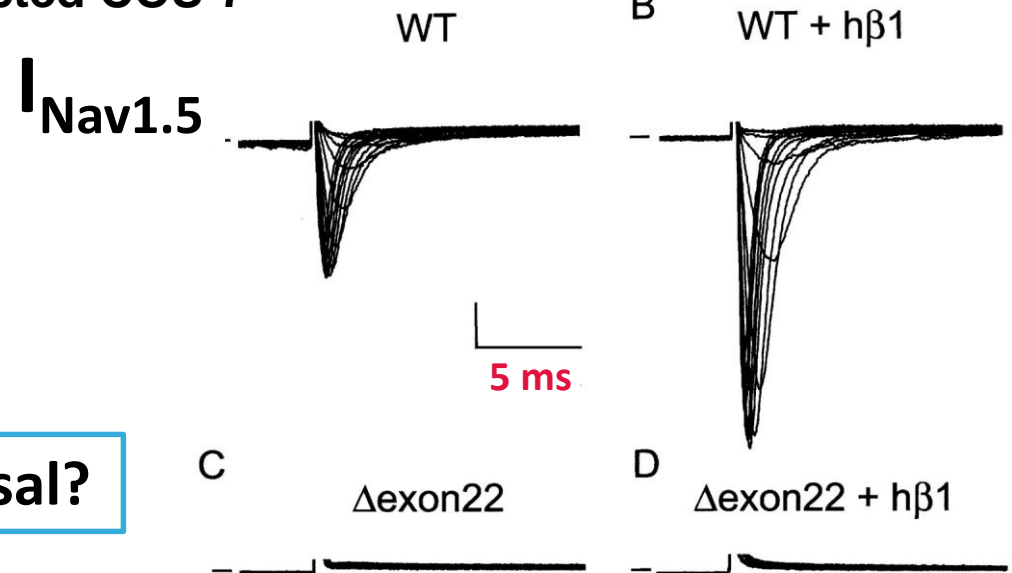
- Modèles cellulaires: lignées cellulaires modifiées - canalopathies monogéniques

Expression hétérologue de protéines Nav1.5
WT et mutées



Mutation *SCN5A* : canal Nav1.5 Δ exon22 ← causal?

transfected COS-7



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 Lenège

1982

1998

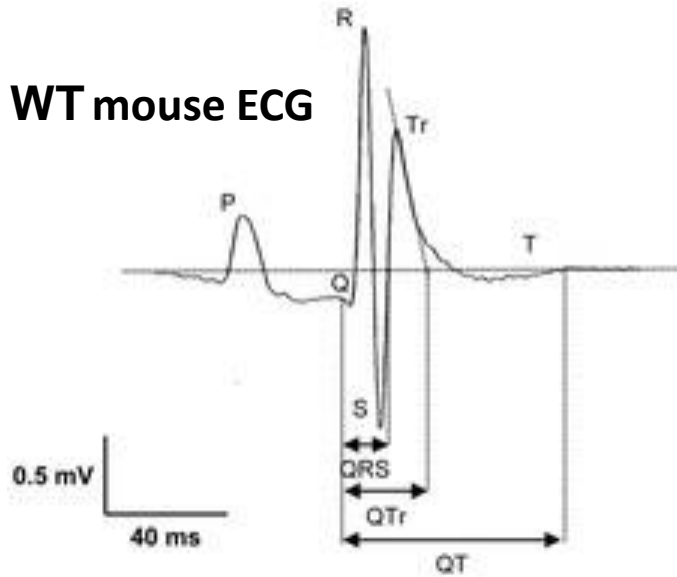
2000

QRS prolongation



SCN5A mut : exon 22 absent

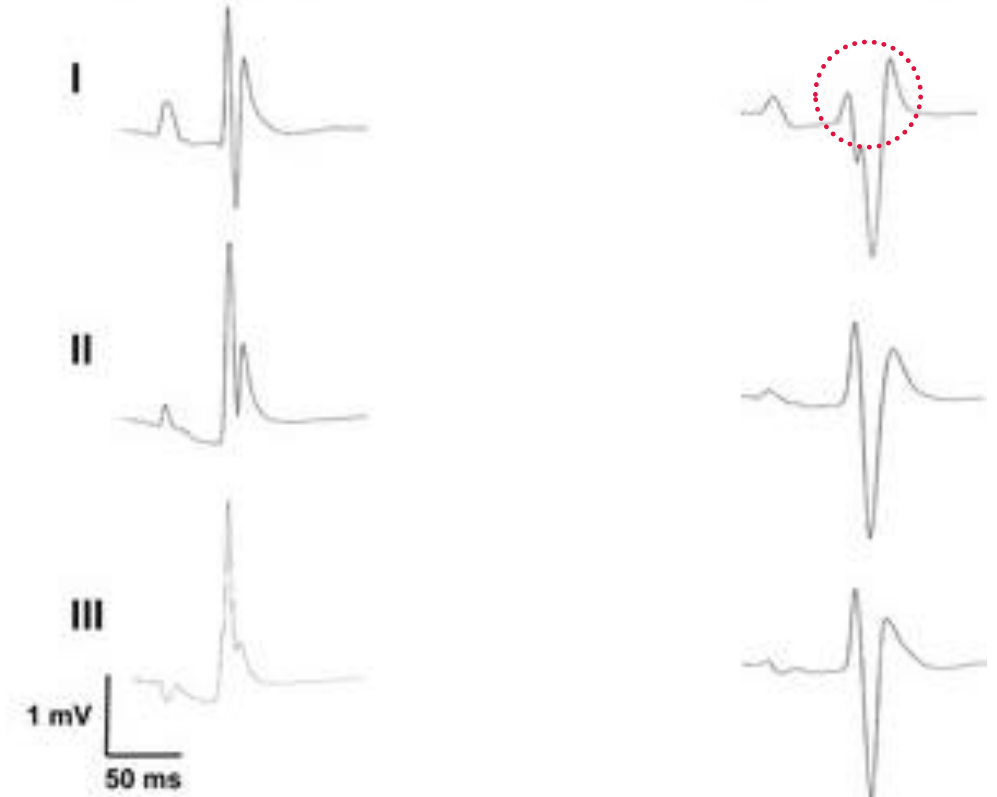
WT mouse ECG



Scn5a^{+/-} mouse

**Z502
(wild-type)**

**Y95
(Scn5a^{+/-})**



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

Haplo-insuffisance de SCN5A → causal

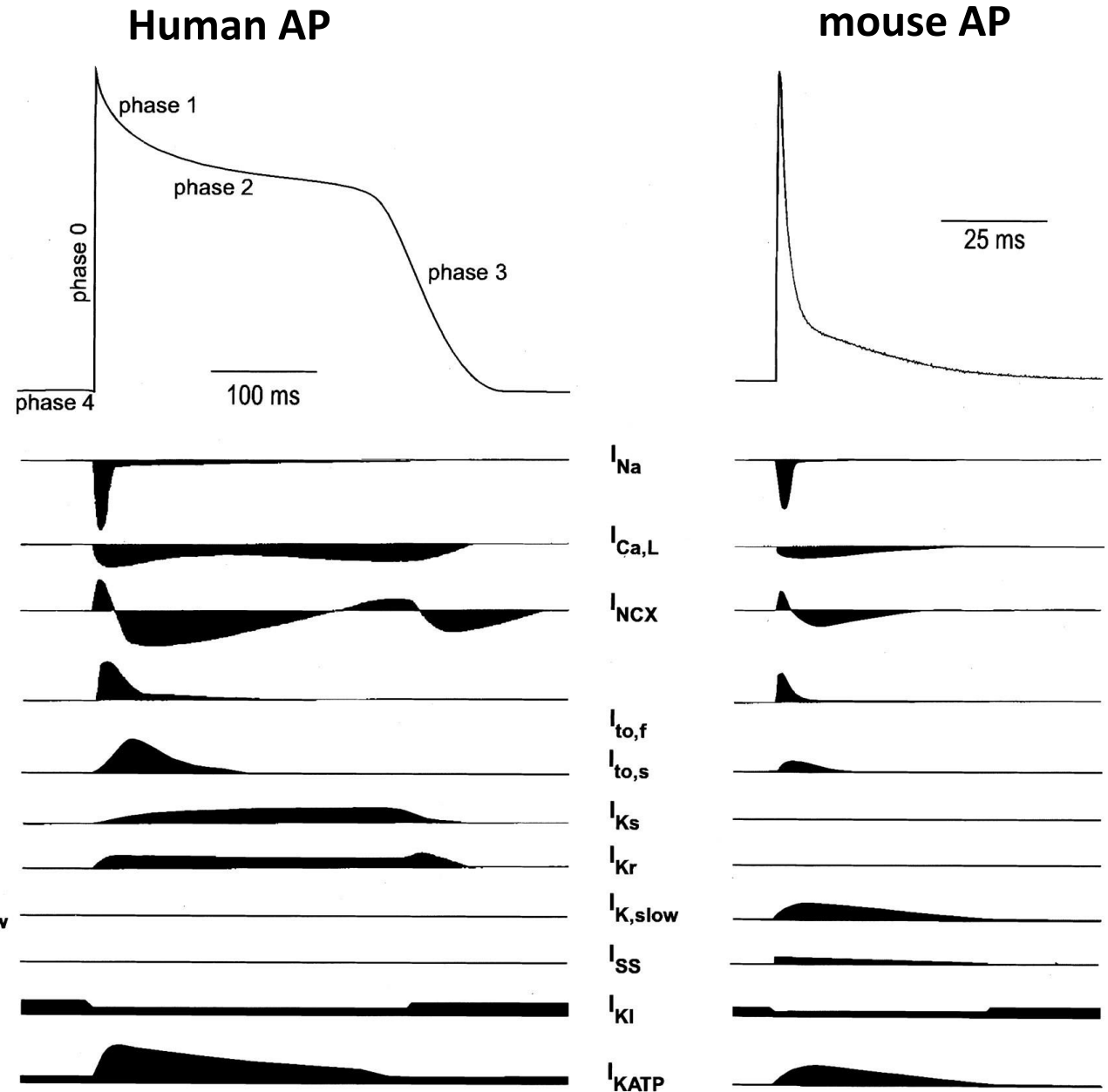
Limites

Modèles unicellulaires

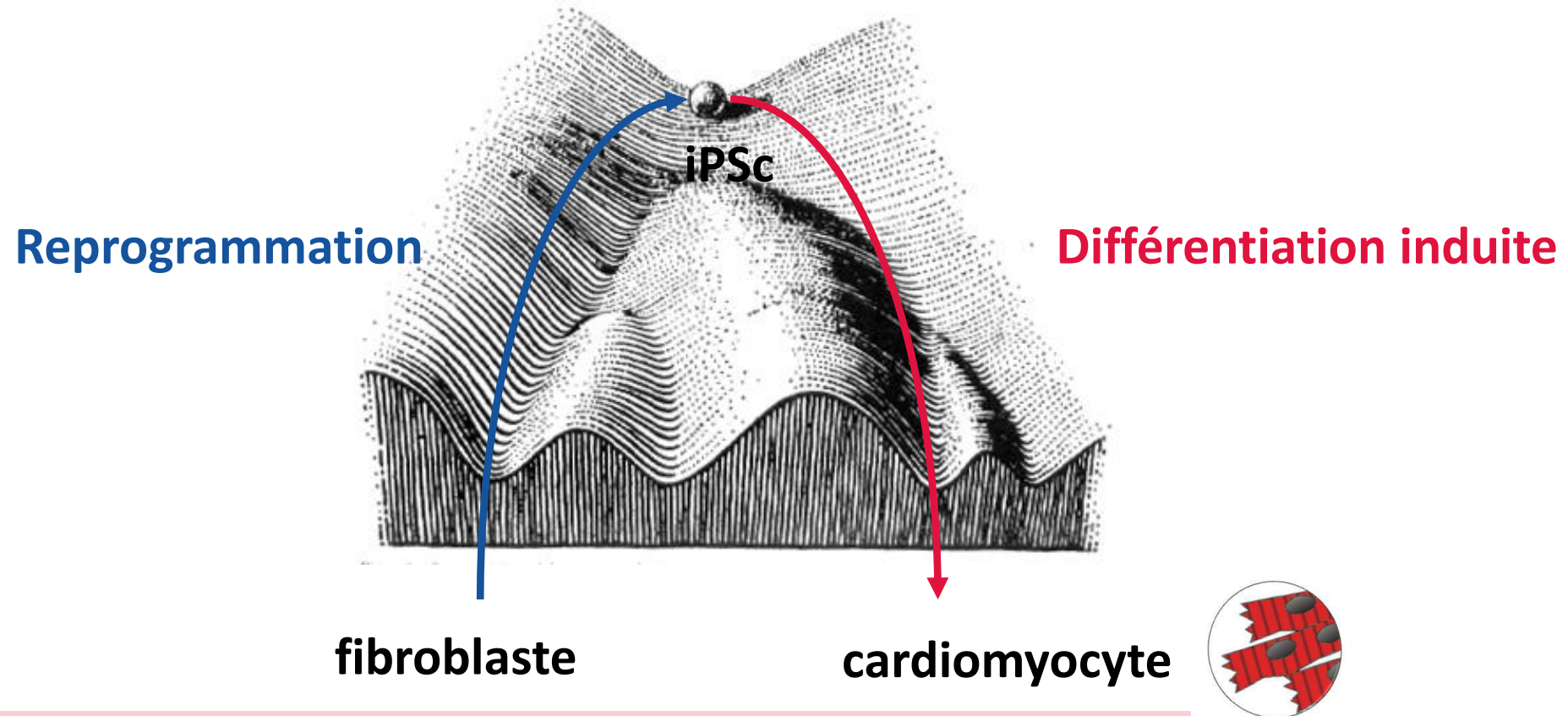
- lignées cellulaires : environnement protéique ? (complexe canalaire)
- modèles animaux : expression espèce-spécifique?

Modèles informatiques

- environnement fonctionnel ?



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."

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

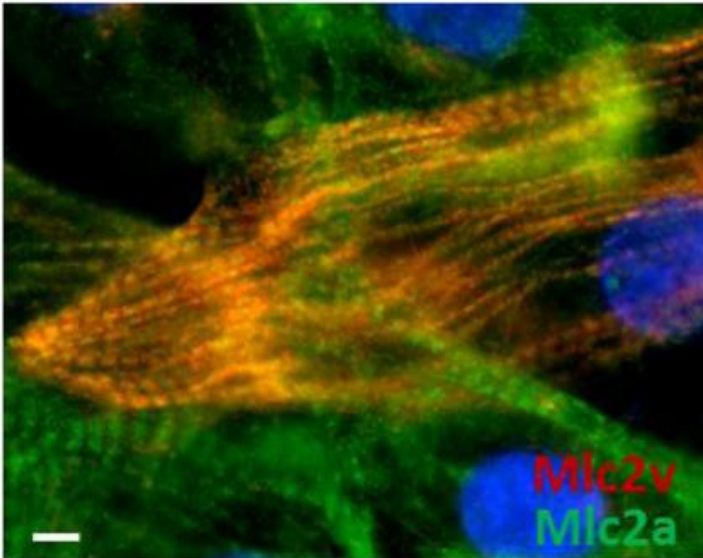
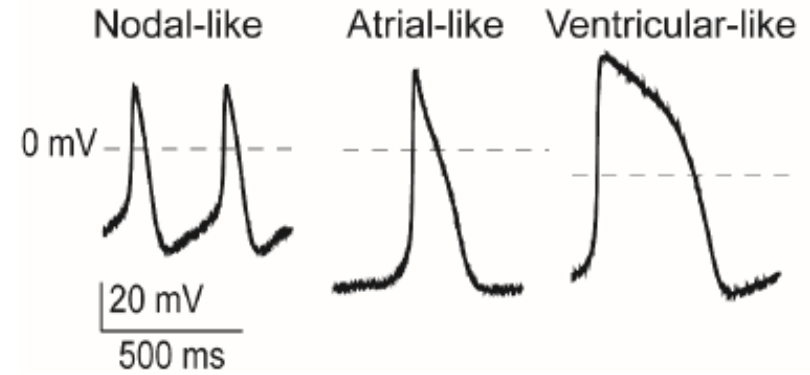
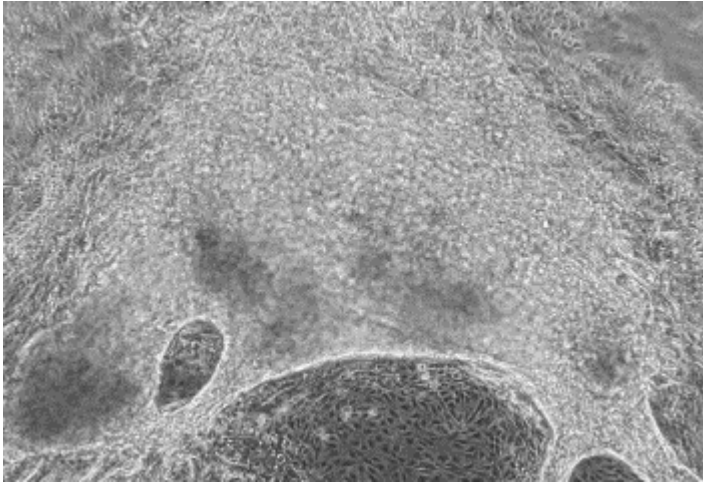
Cellules d'origine :

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

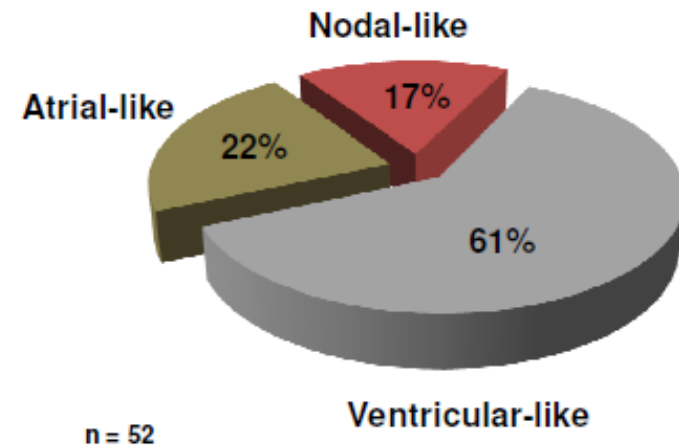
Cardiomyocytes issus d'iPSc

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

hiPS-cardiomyocytes



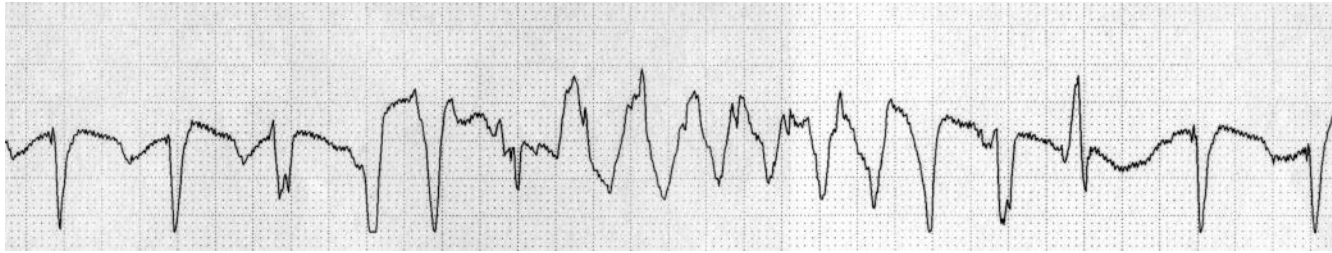
Hétérogénéité phénotypique



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

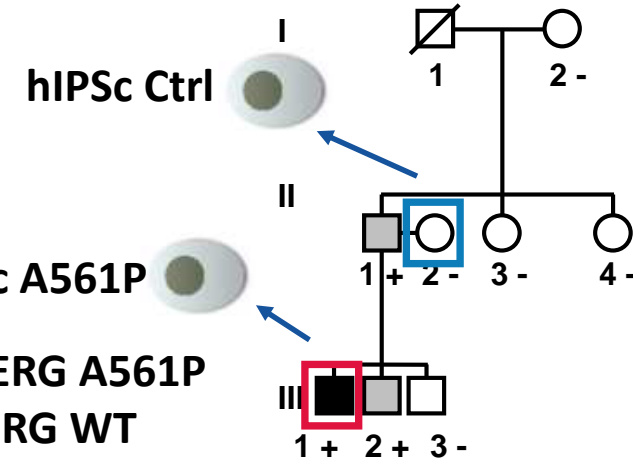
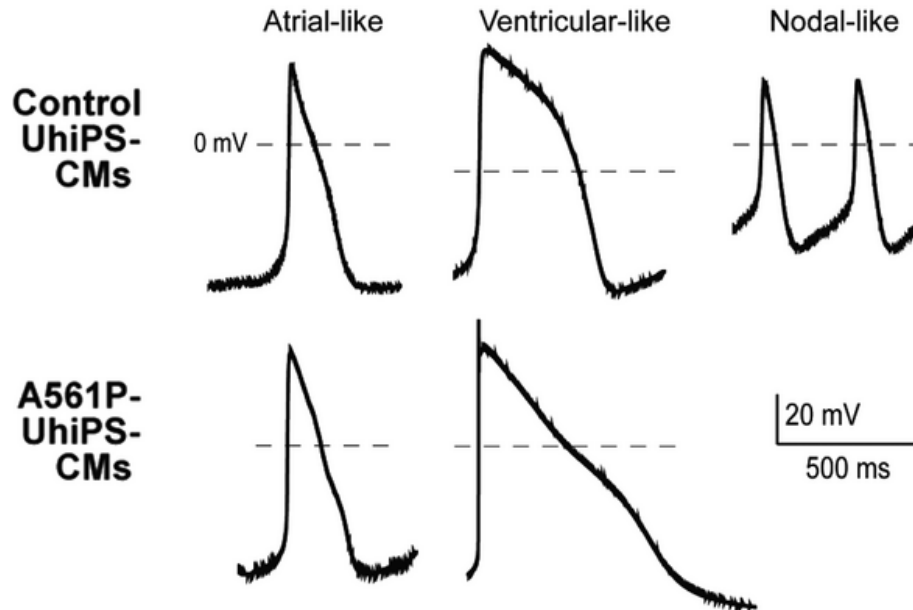
urinary cells

hiPSc

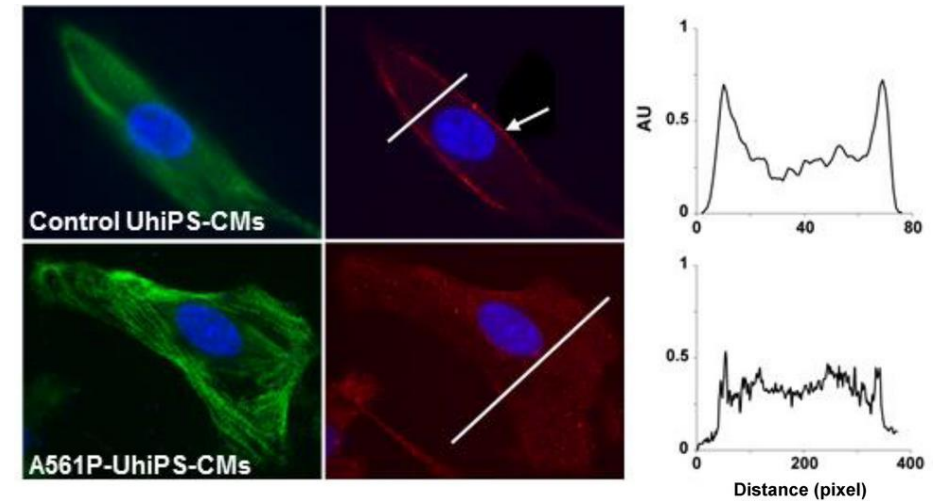
hiPS-CM



• current-clamp



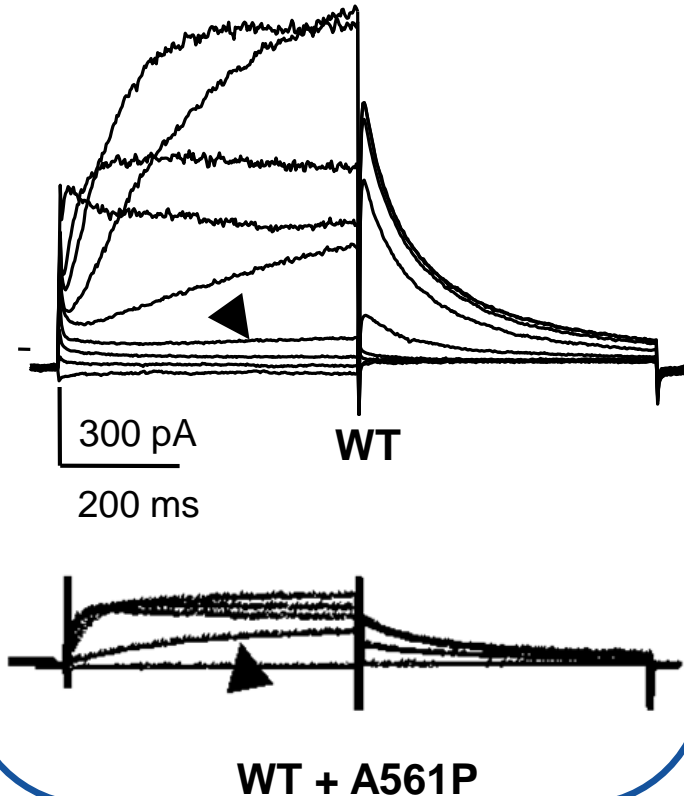
• immuno-cytofluorimétrie



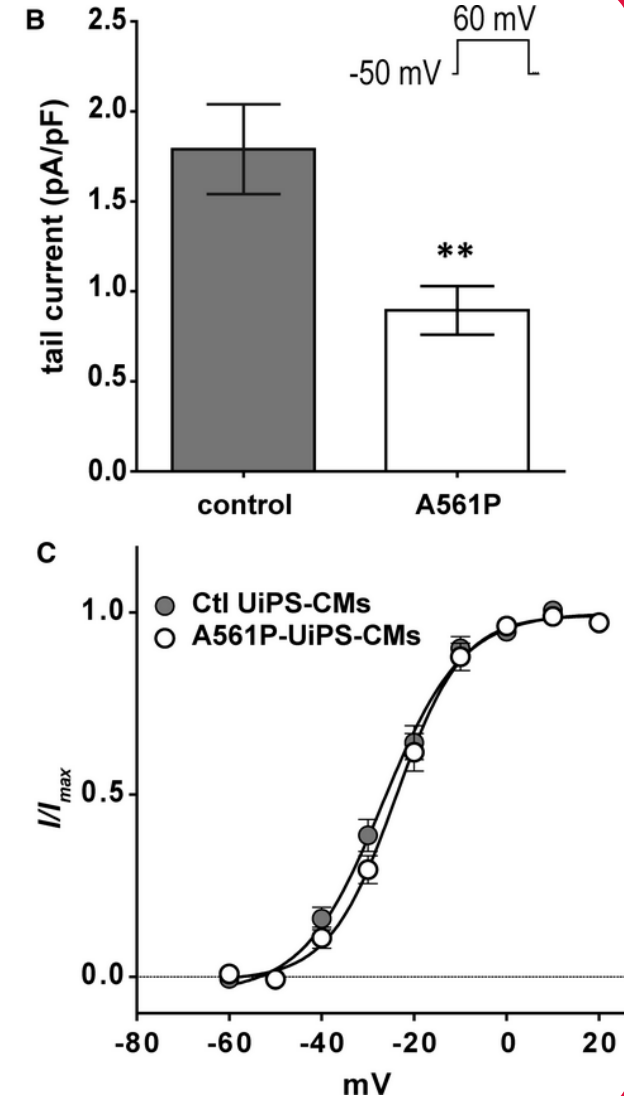
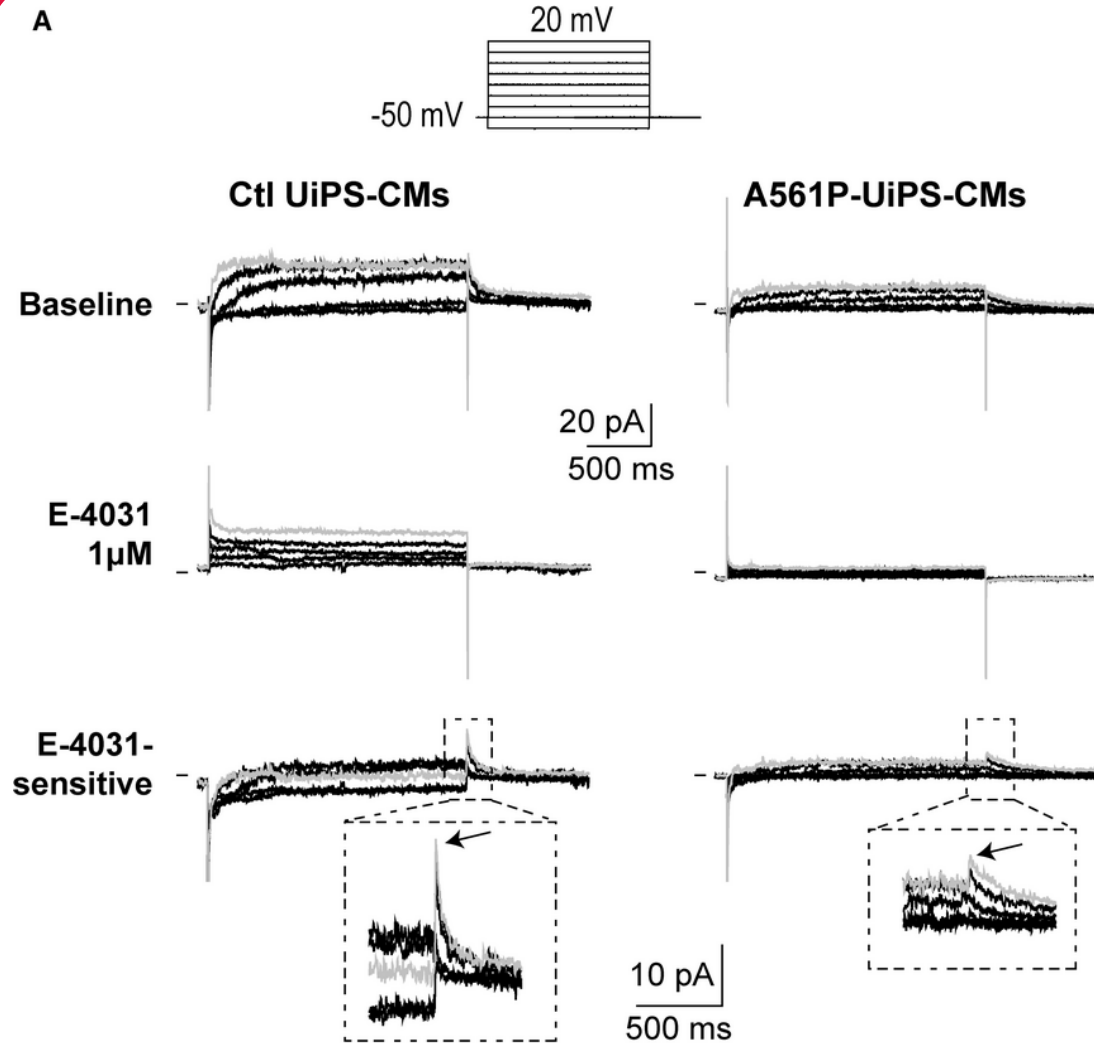
Transfected cells vs hiPS-cardiomyocytes

- voltage-clamp

transfected COS-7 cells

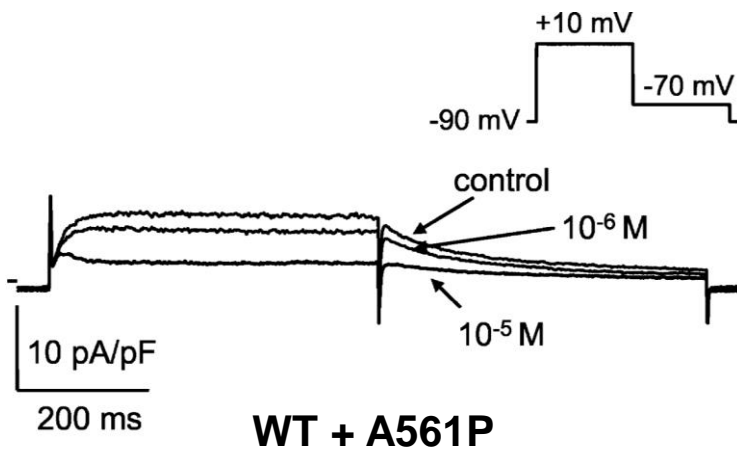
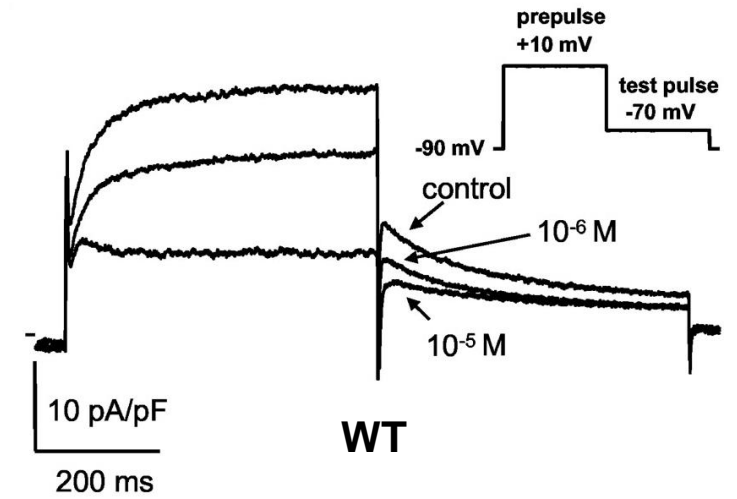


Bellocq C *et al.* Mol Pharmacol.
2004 Nov;66(5):1093-102



Transfected cells vs hiPS-cardiomyocytes

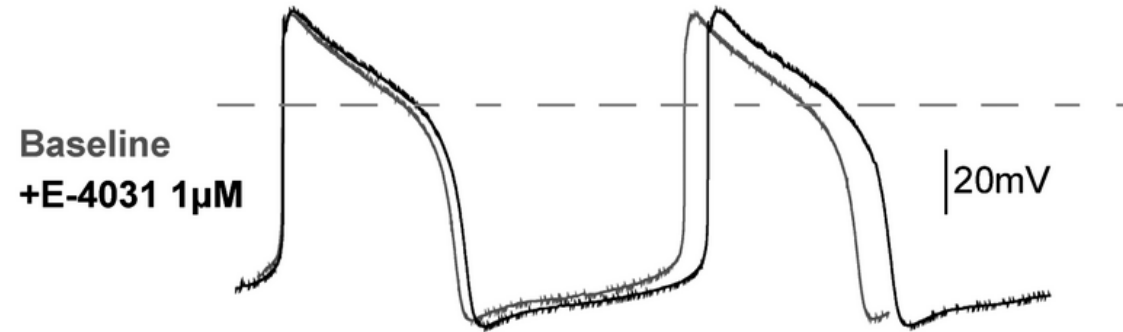
+ clobutinol (I_{Kr} inhib.)



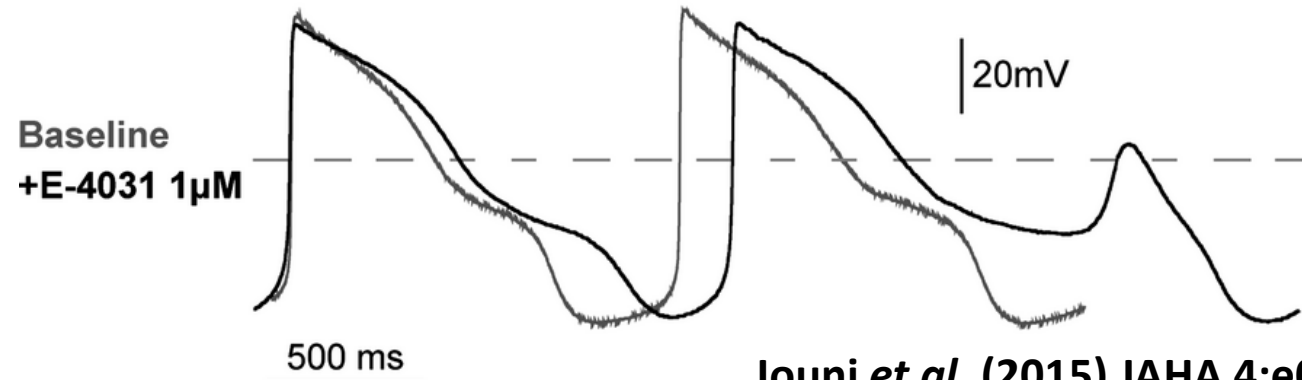
Belloq C *et al.* Mol Pharmacol. 2004 Nov;66(5):1093-102

+ E4031 (I_{Kr} inhib.)

C Control UhiPS-CM



A561P-UhiPS-CM



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

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

Perte de fonction et allongement confirmés ➔ causal

Analyse d'article



Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

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



Original Article

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



Zeineb Es-Salah-Lamoureux ^{a,1}, Mariam Jouni ^{a,1}, Olfat A. Malak ^a, Nadjat 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*

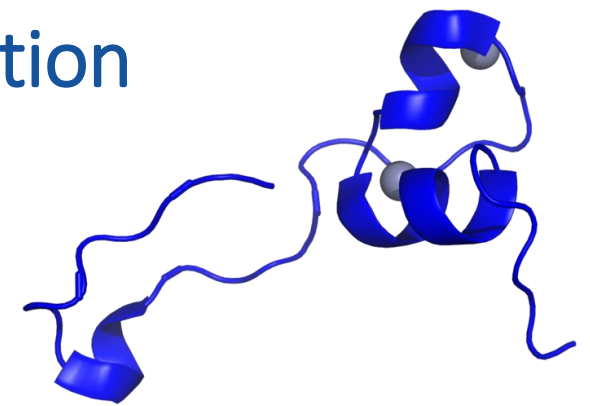
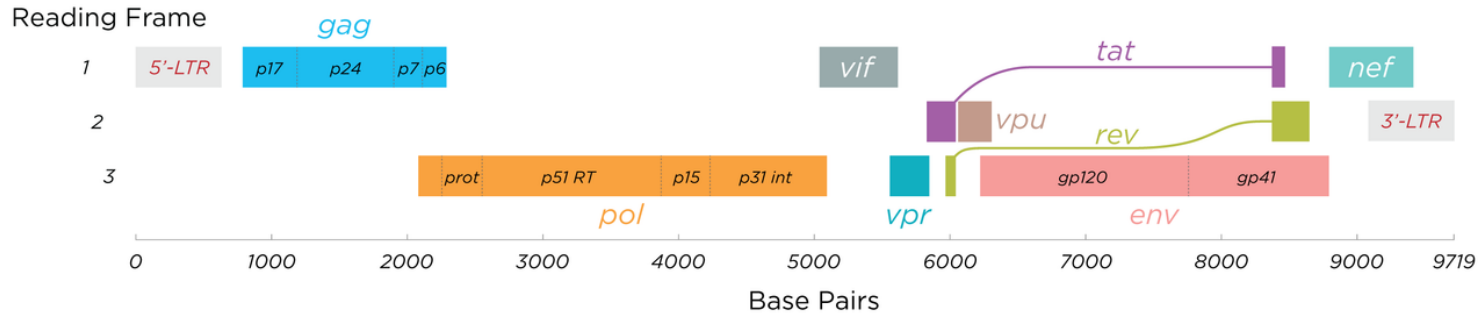
^b *l'institut du thorax, Inserm, CNRS, Université de Nantes, CHU Nantes, Nantes, France*

^c *ERO45, 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*

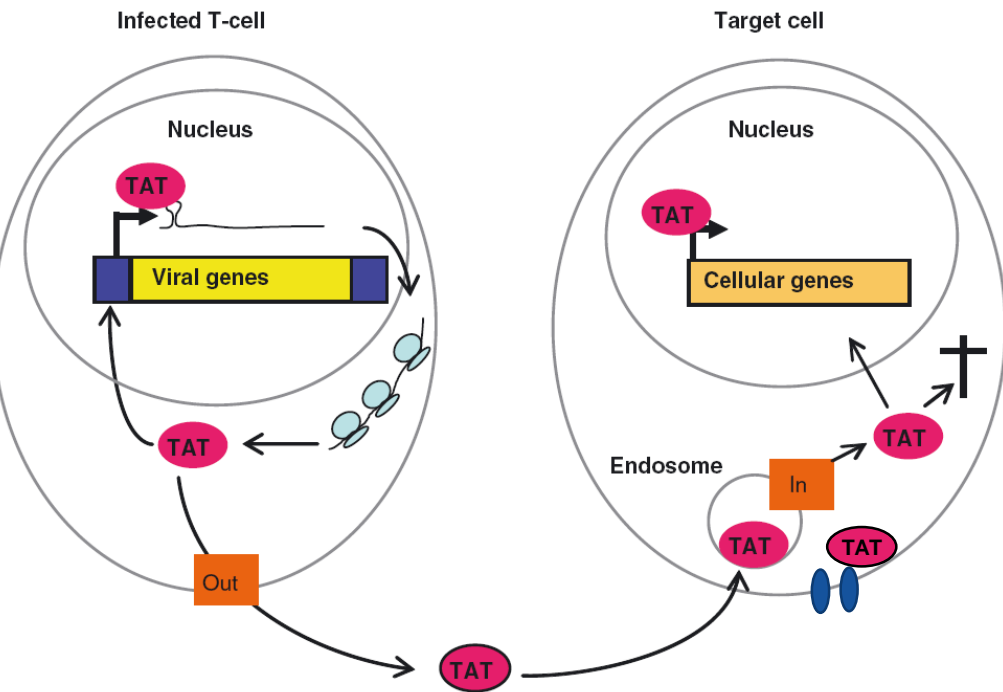
- **Les patients HIV+ présentent un intervalle QT allongé et un risque de mort subite élevé par rapport à la population générale. Origine ?**
- **Des études précédentes suggèrent un effet direct du virus (plus que des anti-viraux)**

Tat = Trans-Activator of Transcription



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

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



- Protéine Tat du HIV-1 : présente dans le sérum des patients, peut pénétrer les cellules et interagir avec le PIP₂ (phosphoinositide).
 - KCNQ1 et hERG, canaux repolarisants, nécessitent du PIP₂ 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}

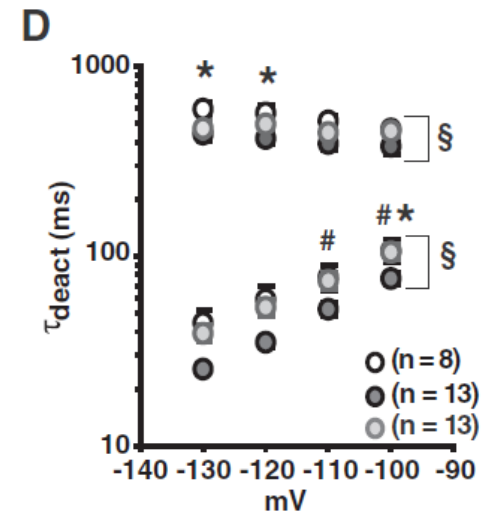
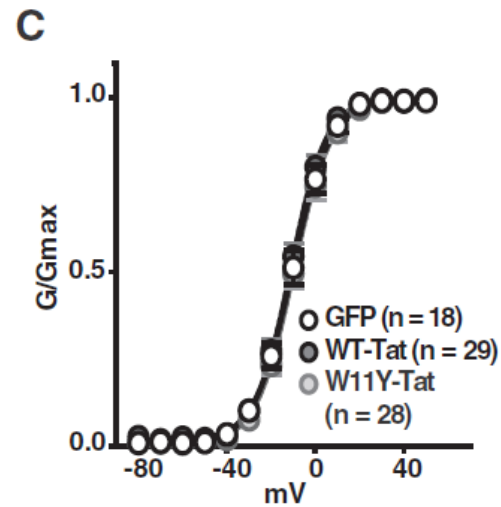
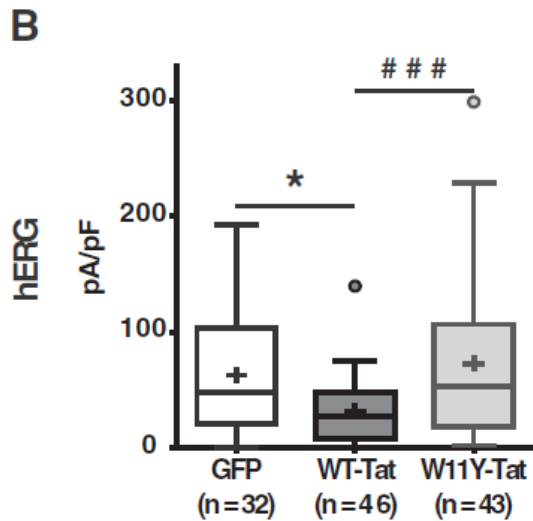
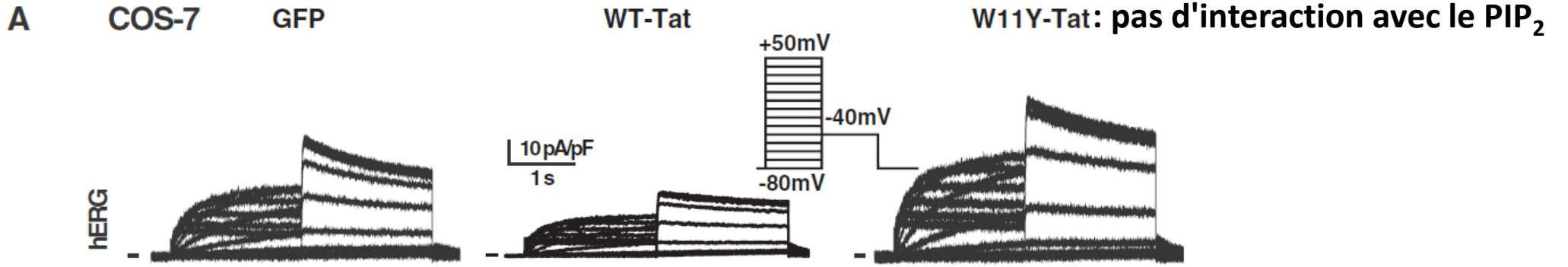


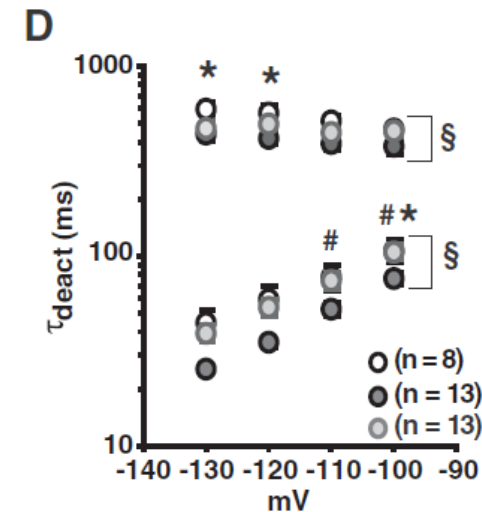
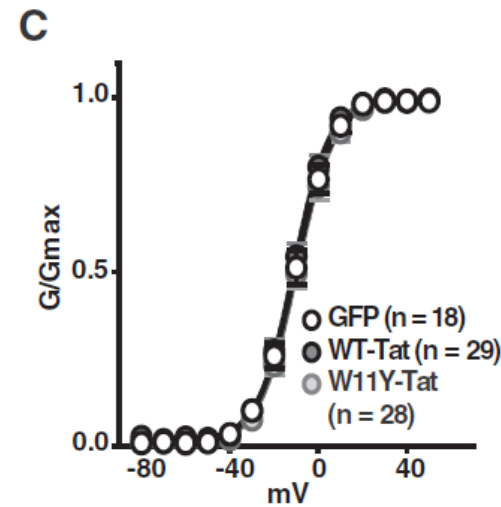
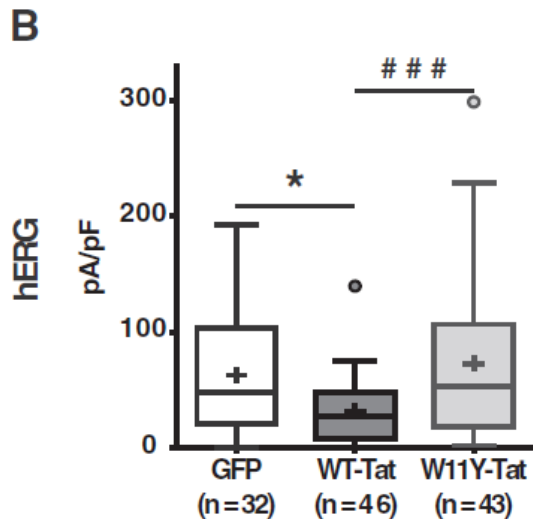
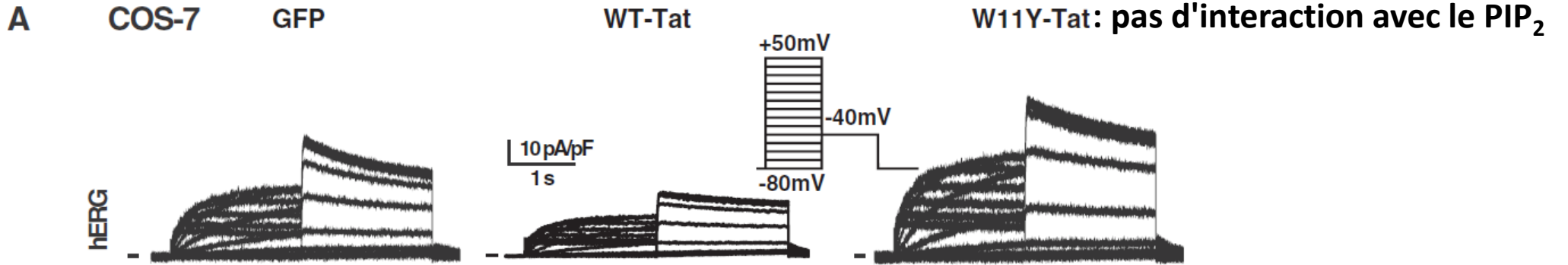
Figure 1



cellules
COS-7

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

- Courant I_{hERG}



- 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 PIP₂ : pas d'effet

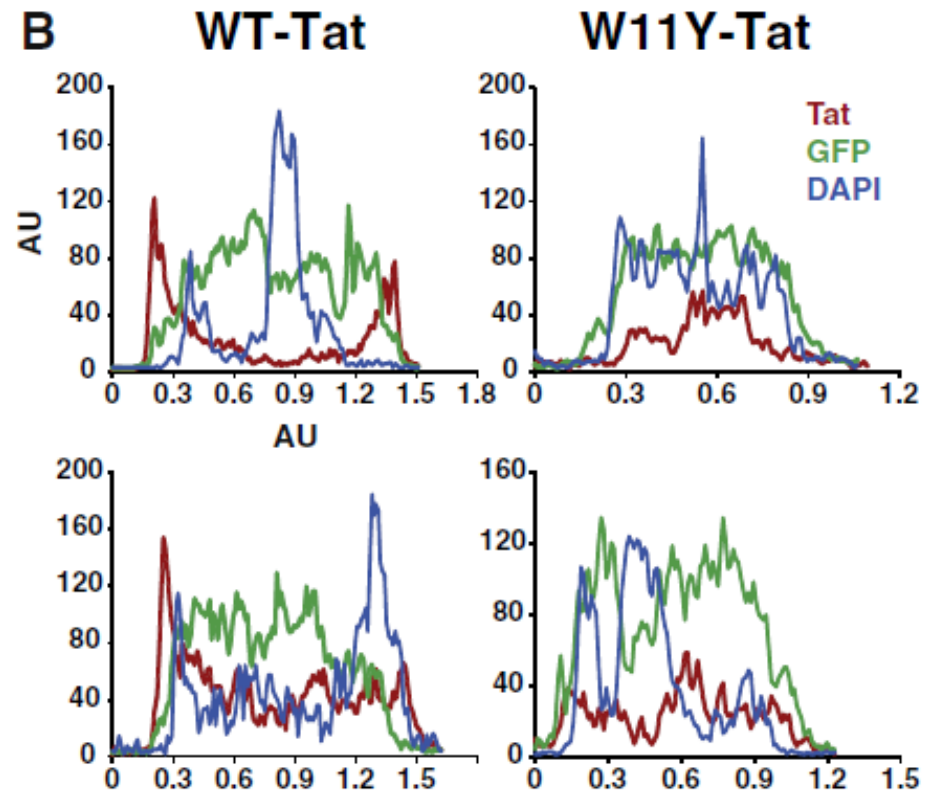
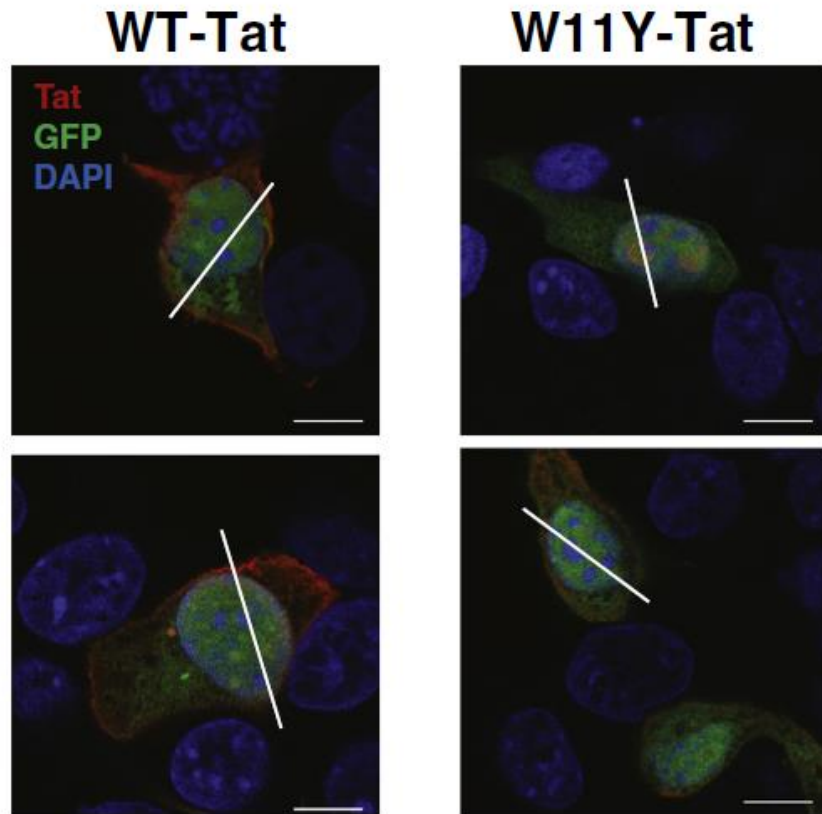


cellules
COS-7

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 A



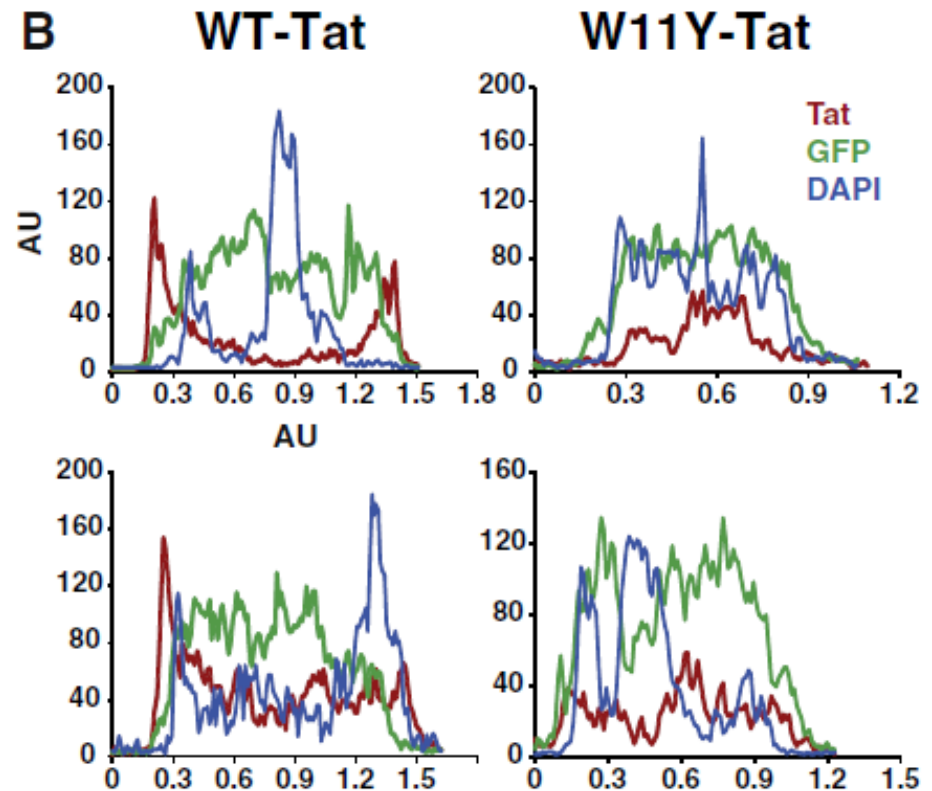
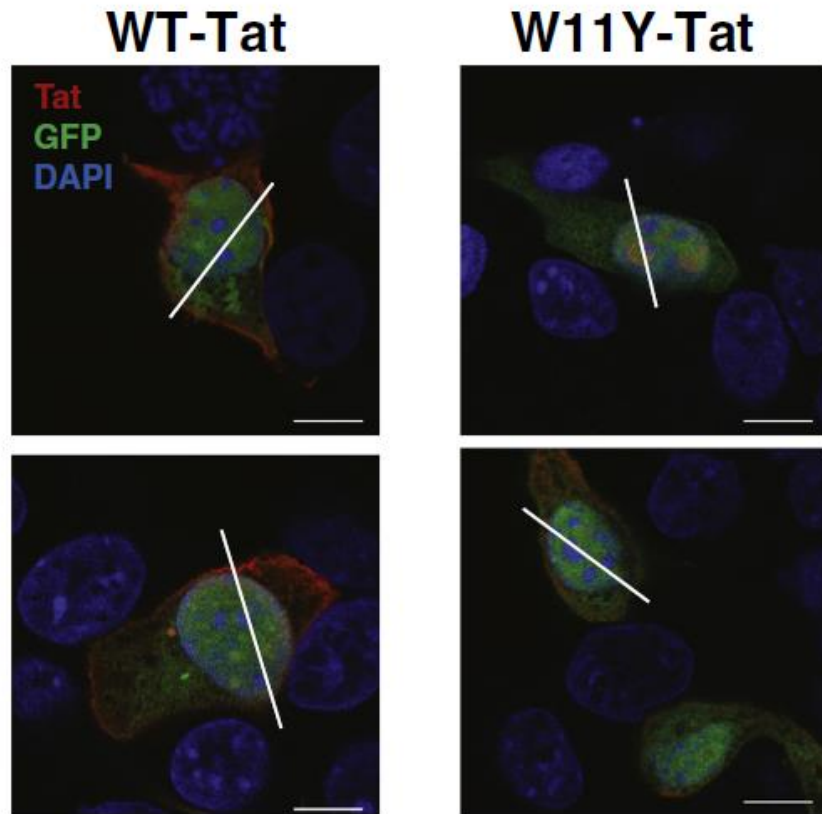


cellules
COS-7

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 A



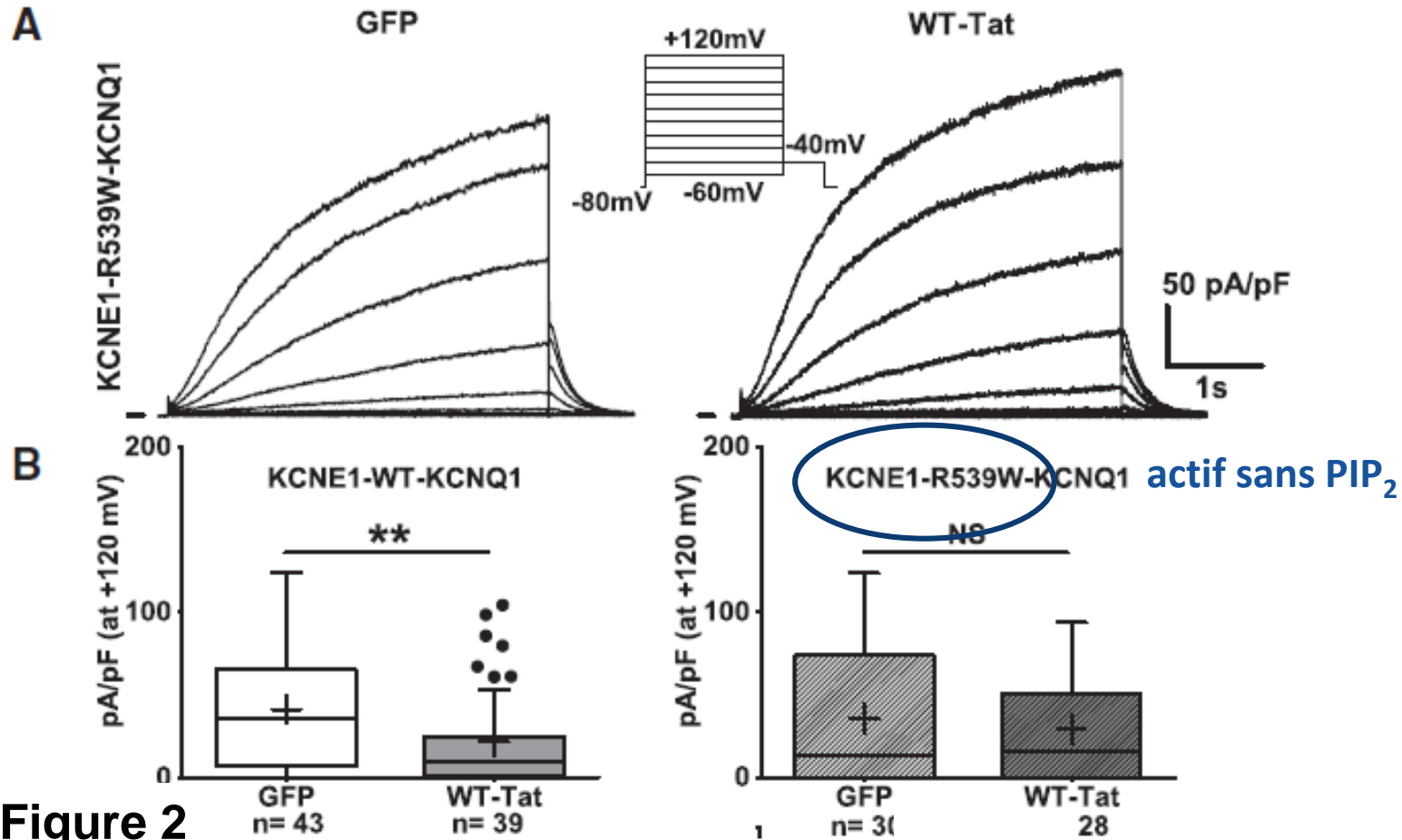
- WT-Tat : membranaire, comme le canal
- W11Y-Tat : non membranaire, car elle n'interagit pas avec le PIP₂



cellules
COS-7

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

- Courant $I_{\text{KCNE1-KCNQ1}}$

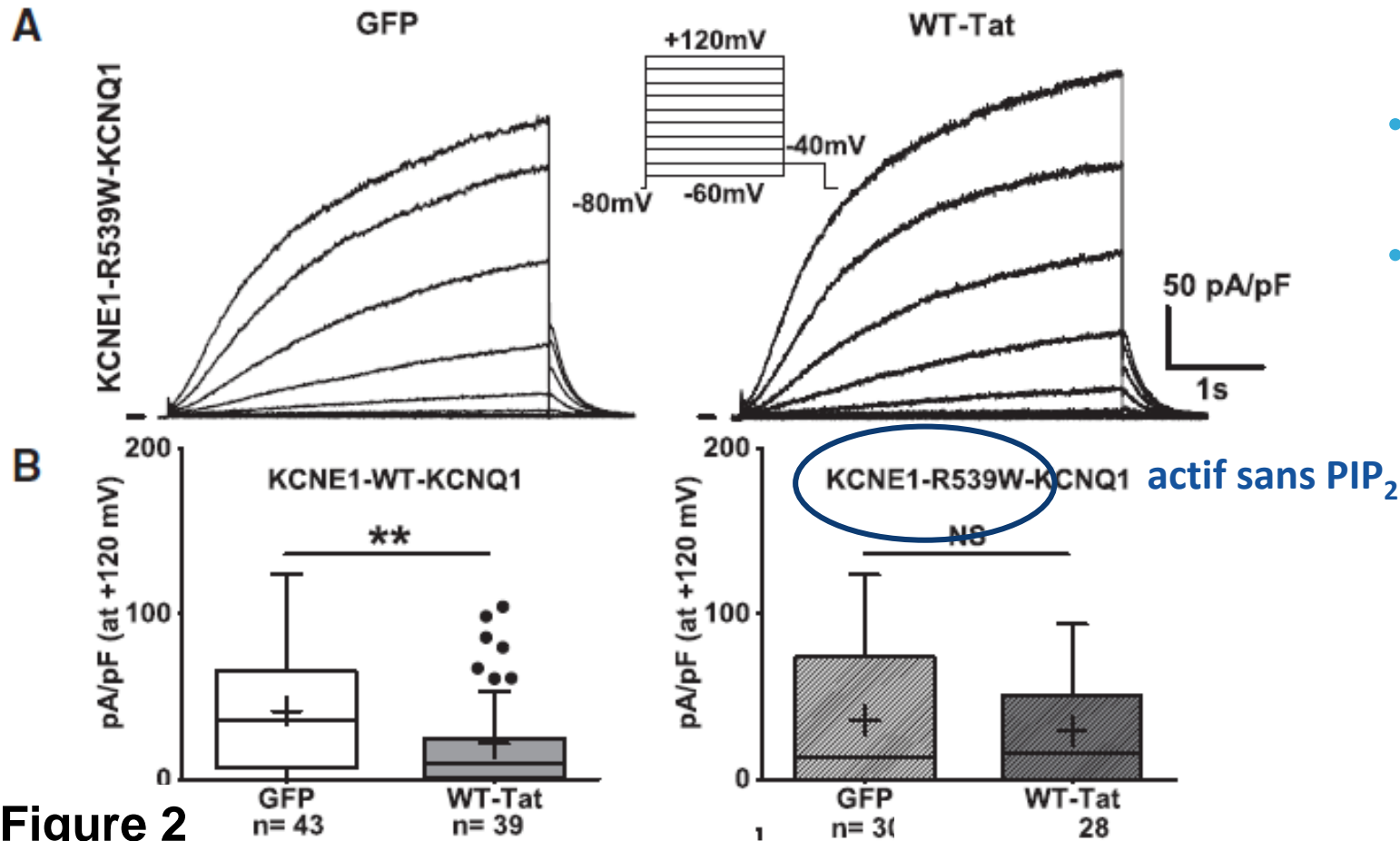




cellules
COS-7

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

- Courant $I_{\text{KCNE1-KCNQ1}}$



- 3B: canal WT sensible au PIP₂ : sensible à la Tat
- 3A & B canal insensible au PIP₂ : insensible à la Tat

Figure 2

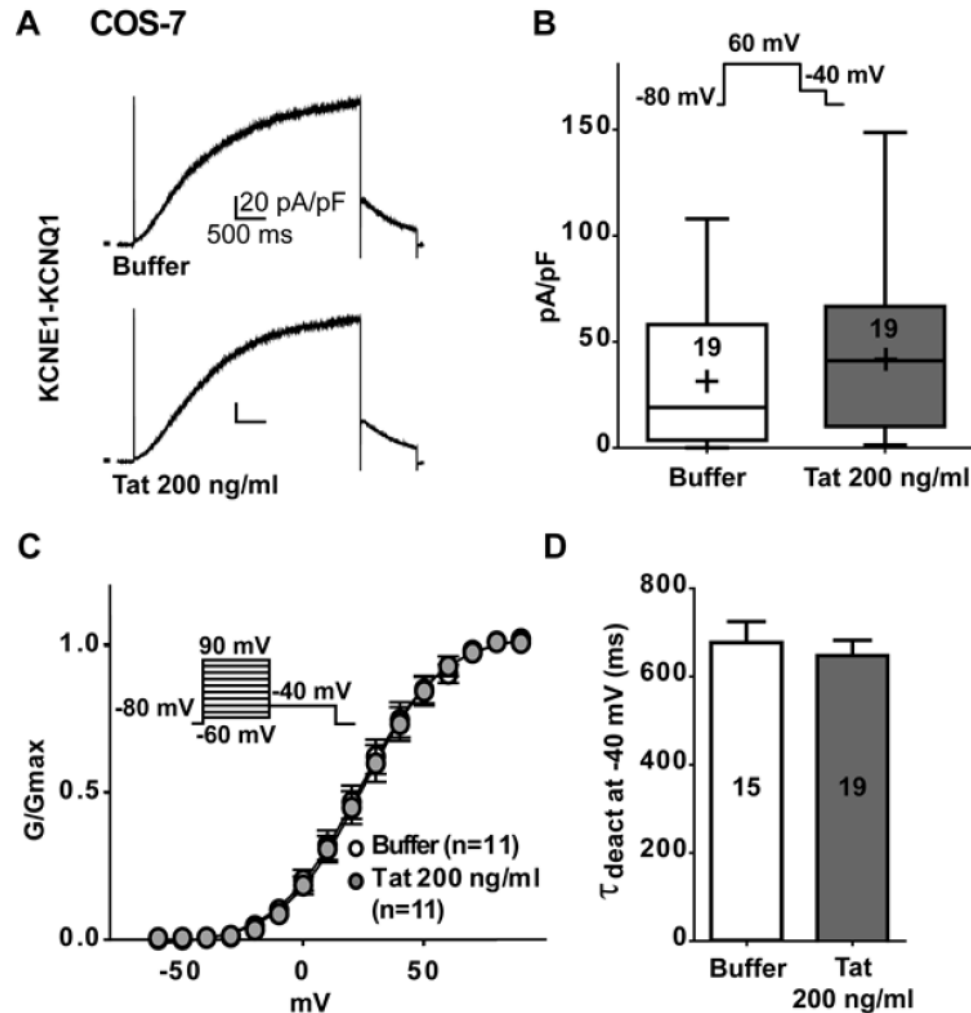


cellules
COS-7

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

- Courant $I_{\text{KCNE1-KCNQ1}}$

Suppl. Figure 4



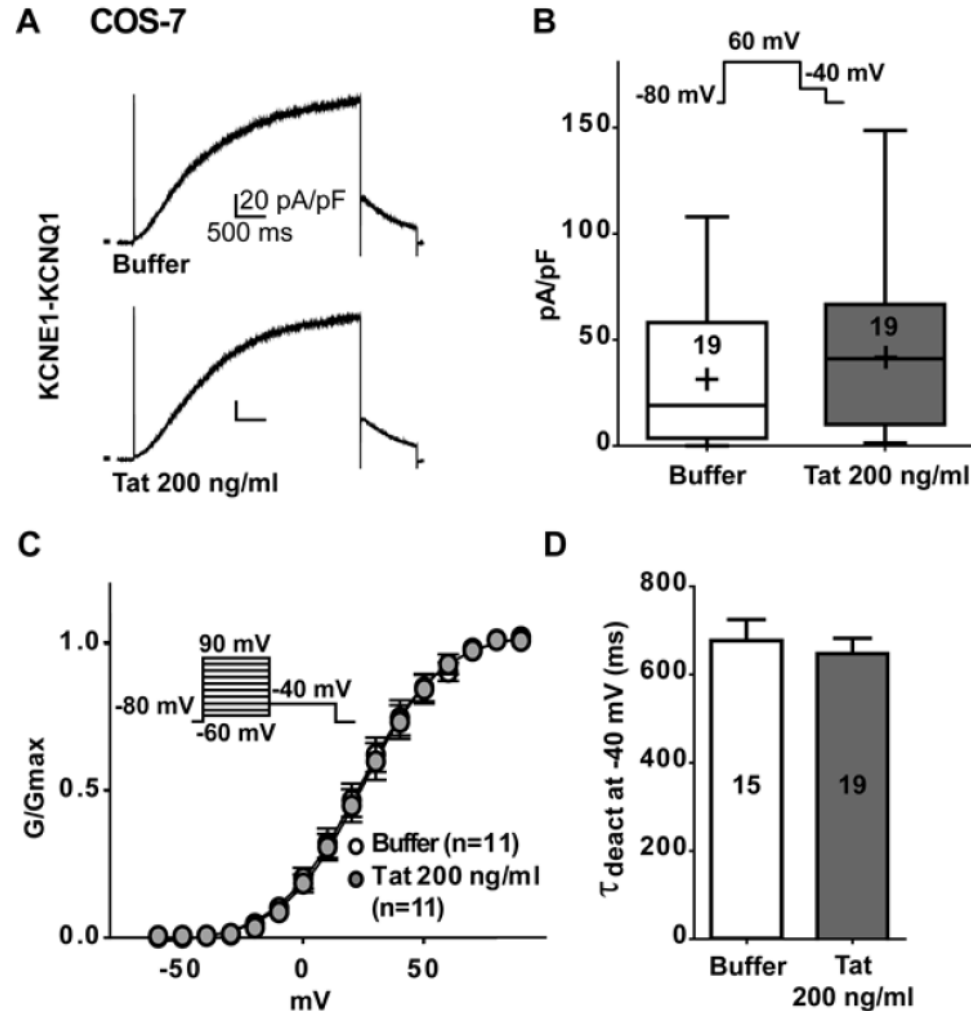


cellules
COS-7

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

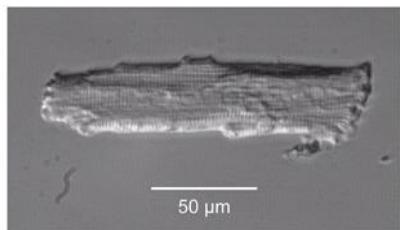
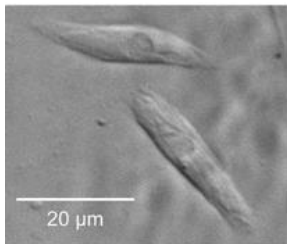
- Courant $I_{\text{KCNE1-KCNQ1}}$

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)

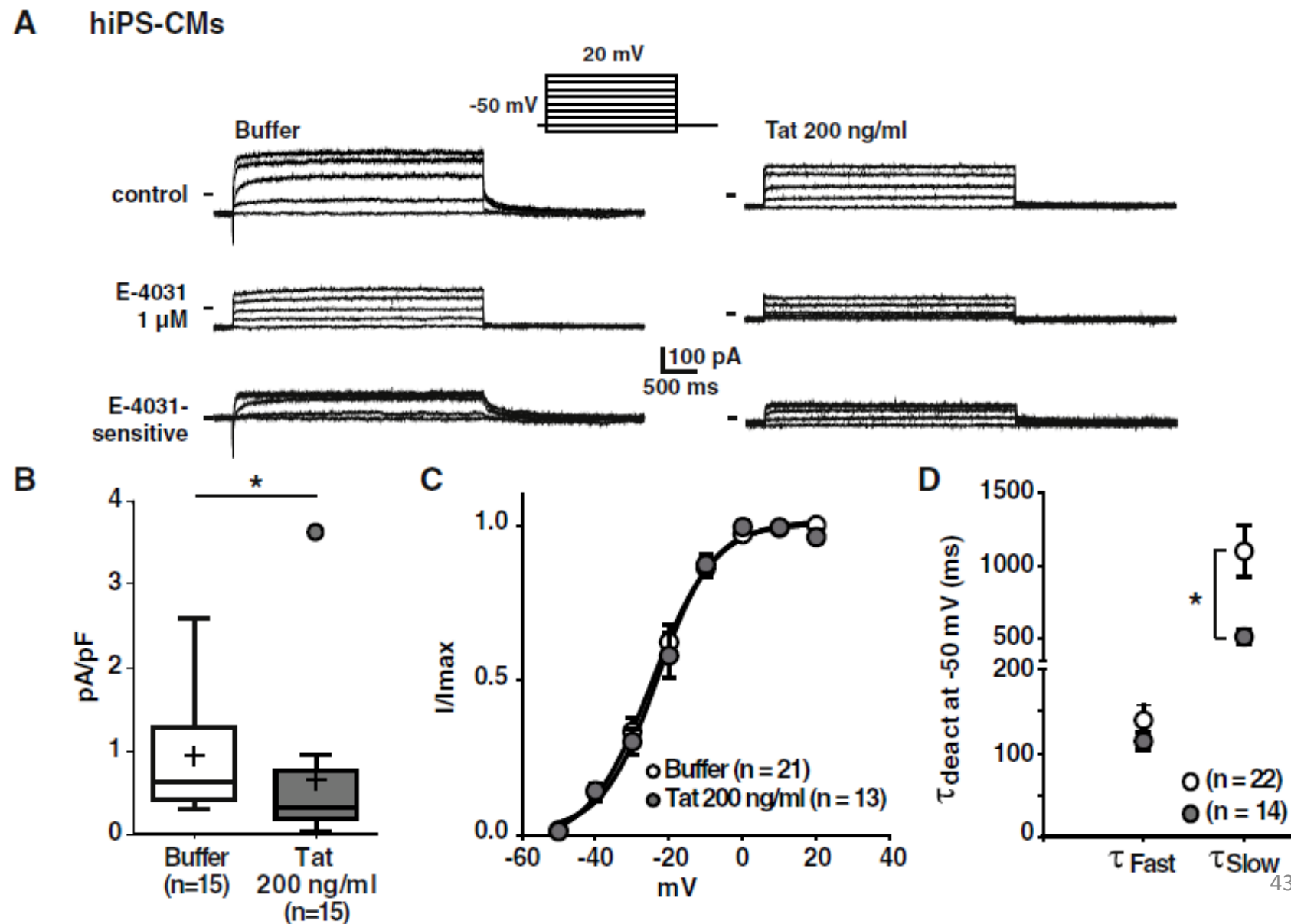
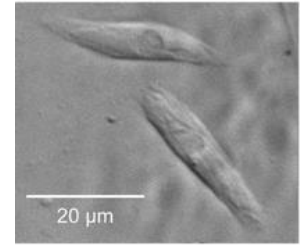
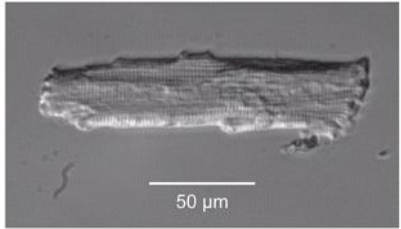


Figure 4



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)

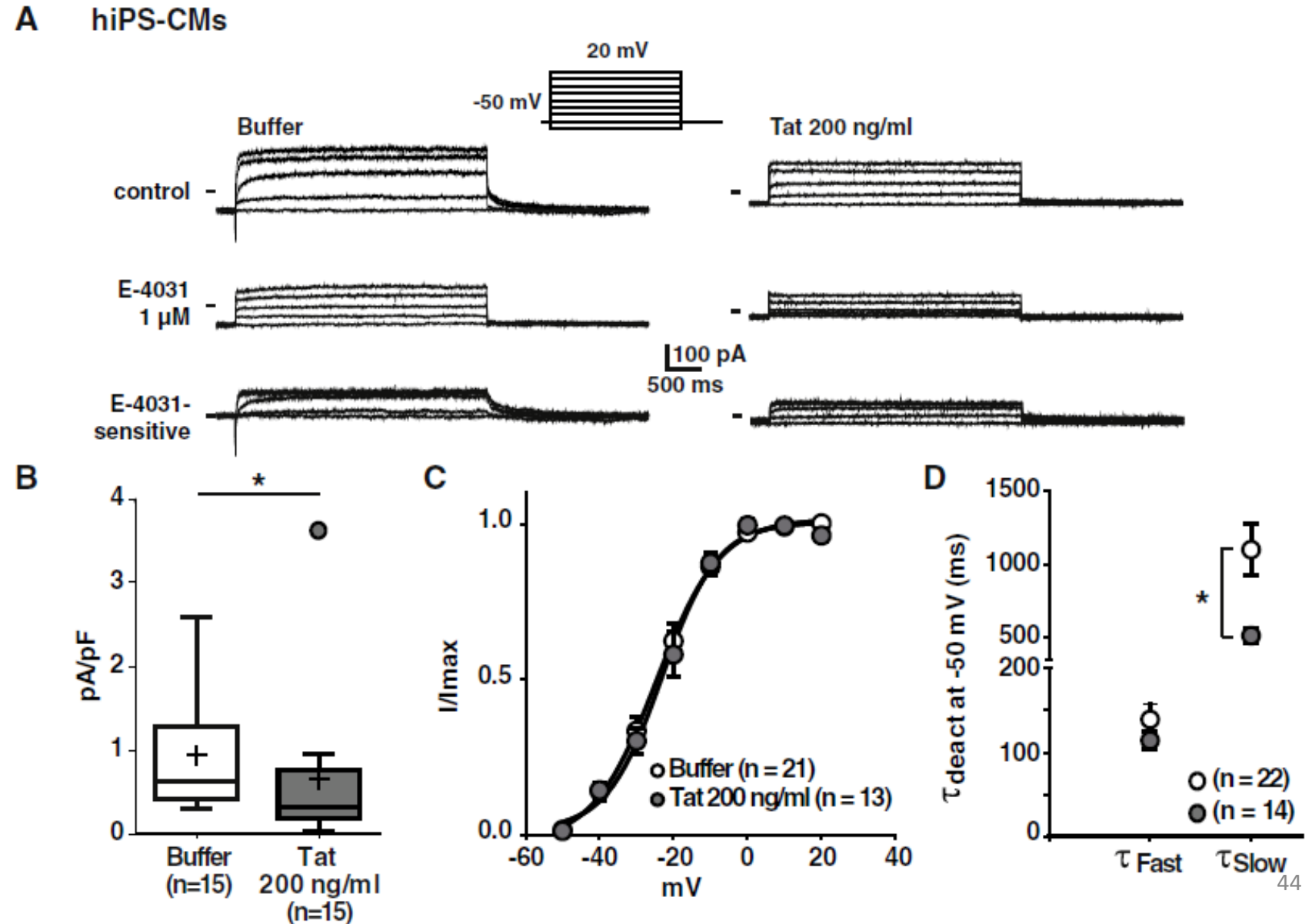
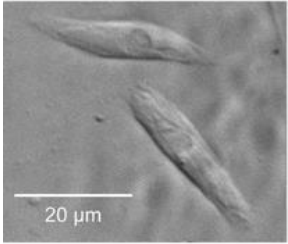


Figure 4



cardiomyocytes
issus de cellules hiPS

Condition : **application extracellulaire de la protéine Tat**

- expression de hERG ARNm et protéine

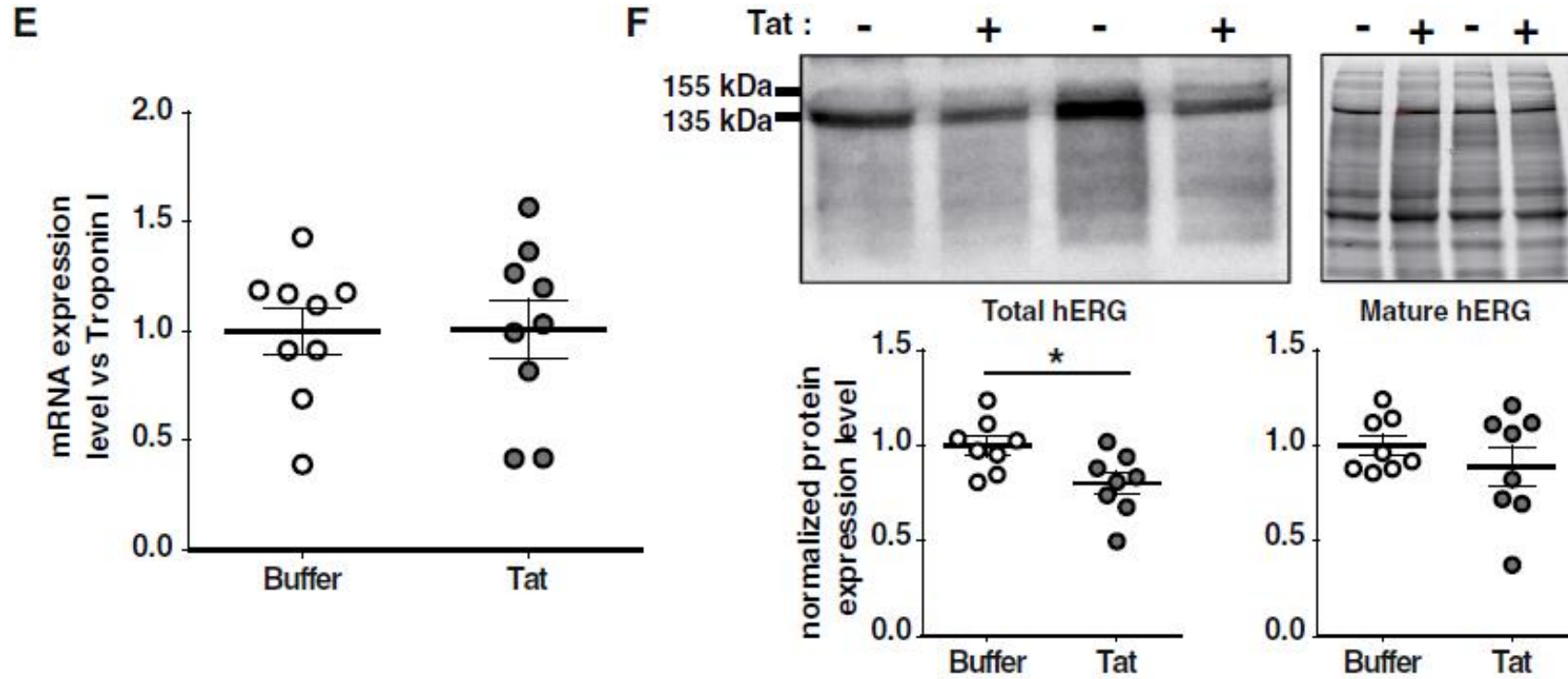
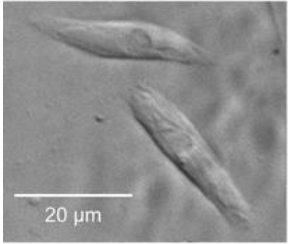


Figure 4



cardiomyocytes
issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- expression de hERG ARNm et protéine

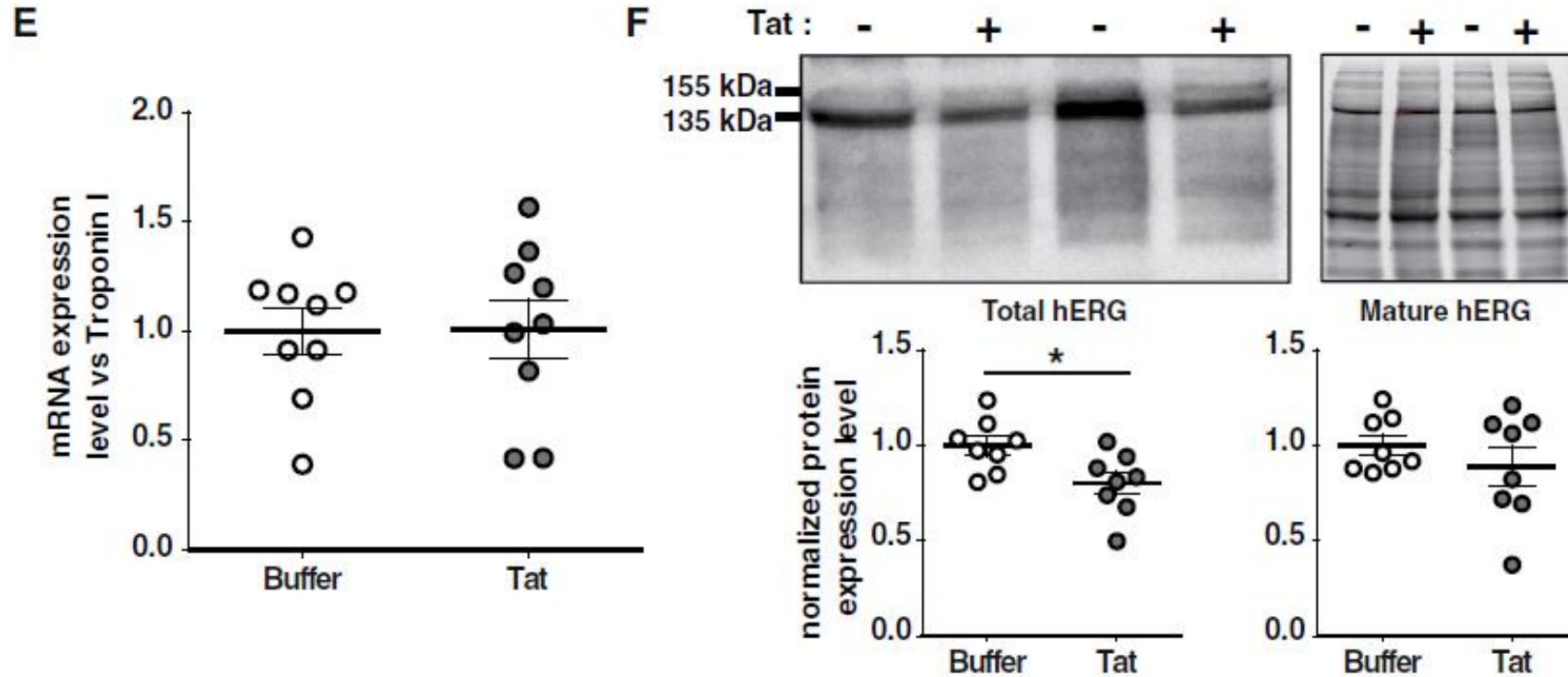


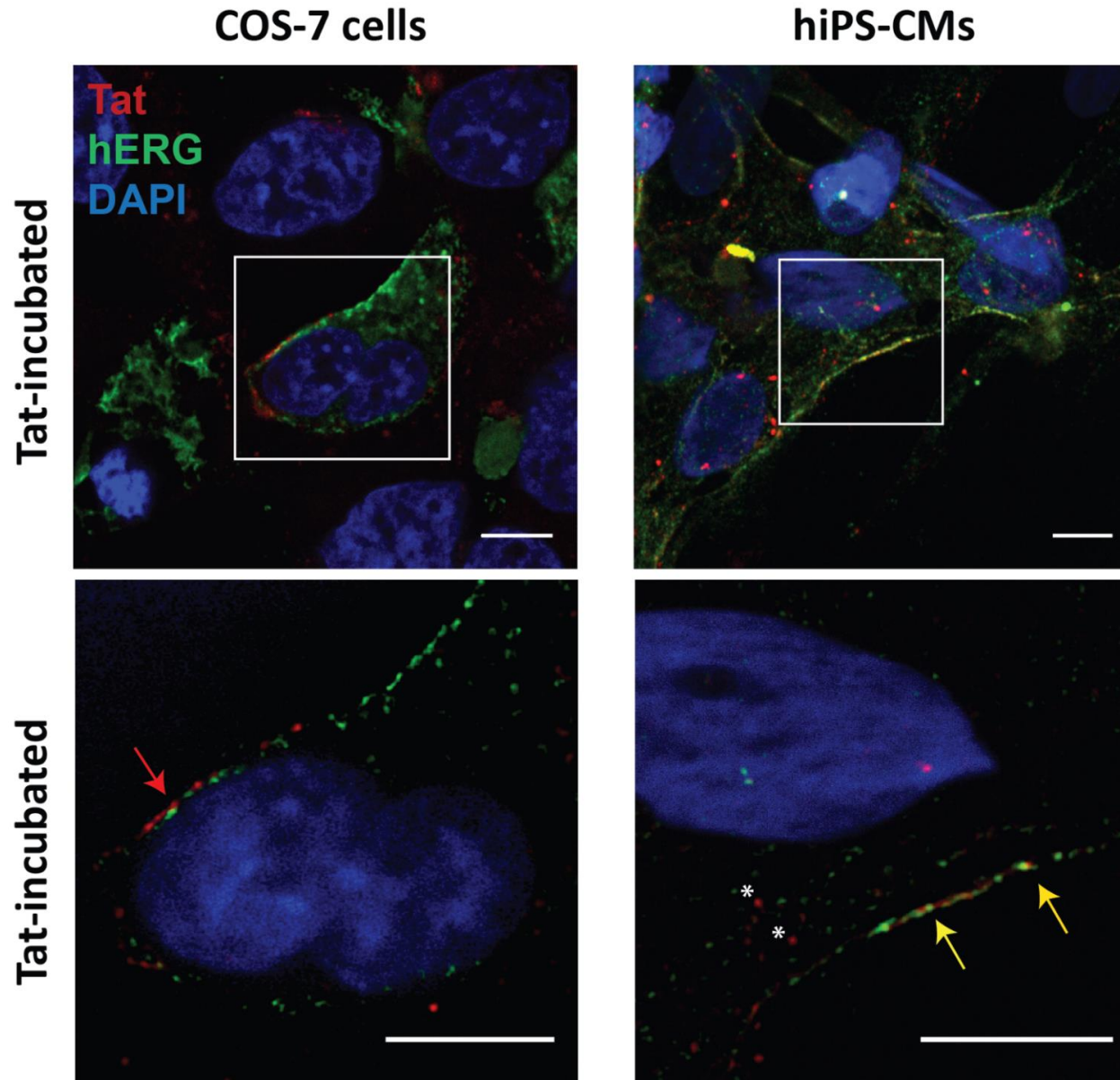
Figure 4

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

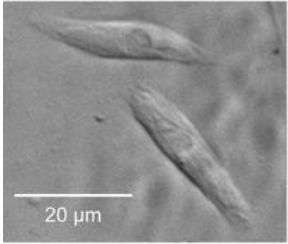
Condition : application extracellulaire de la protéine Tat

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

Figure 5



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



cardiomyocytes
issus de cellules hiPS

Condition : application extracellulaire de la protéine Tat

- potentiel d'action

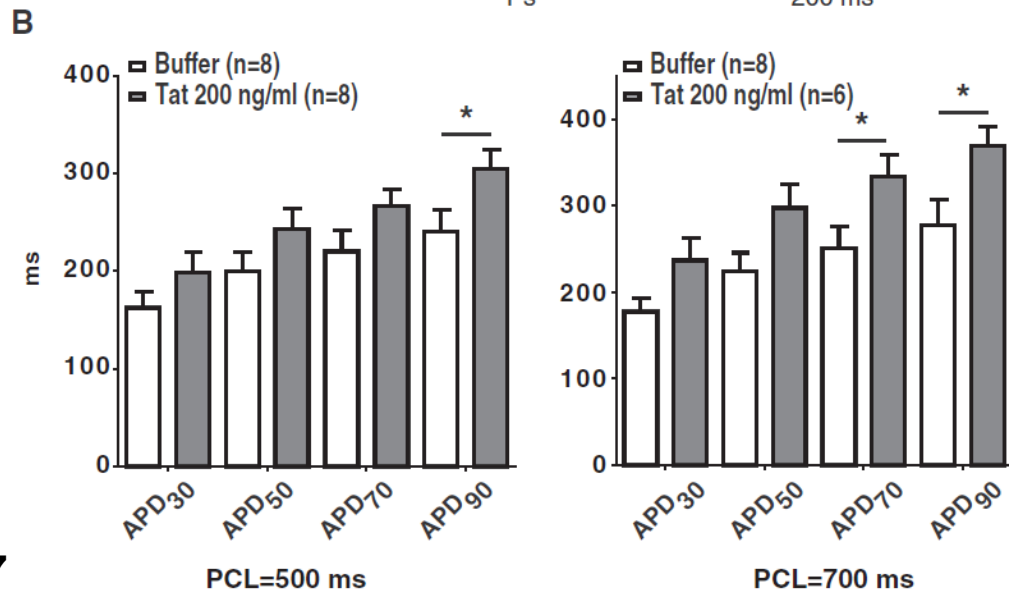
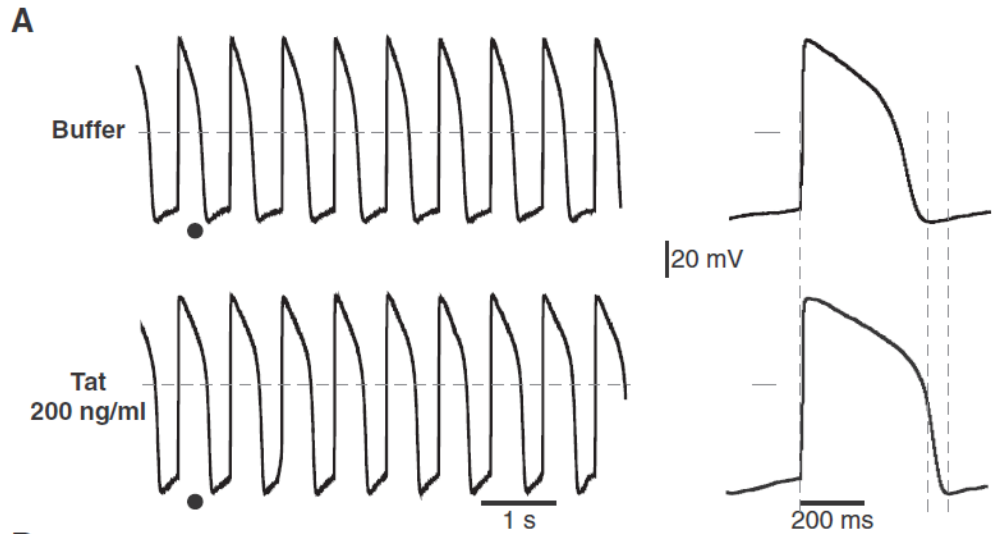
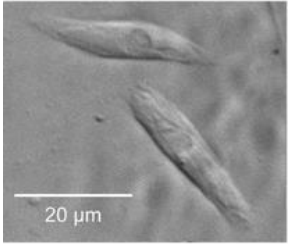


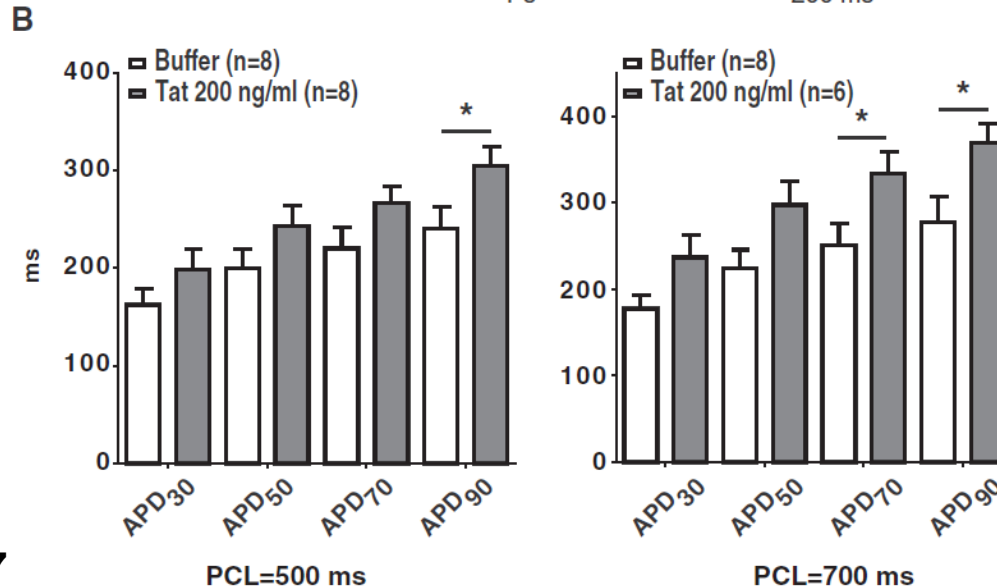
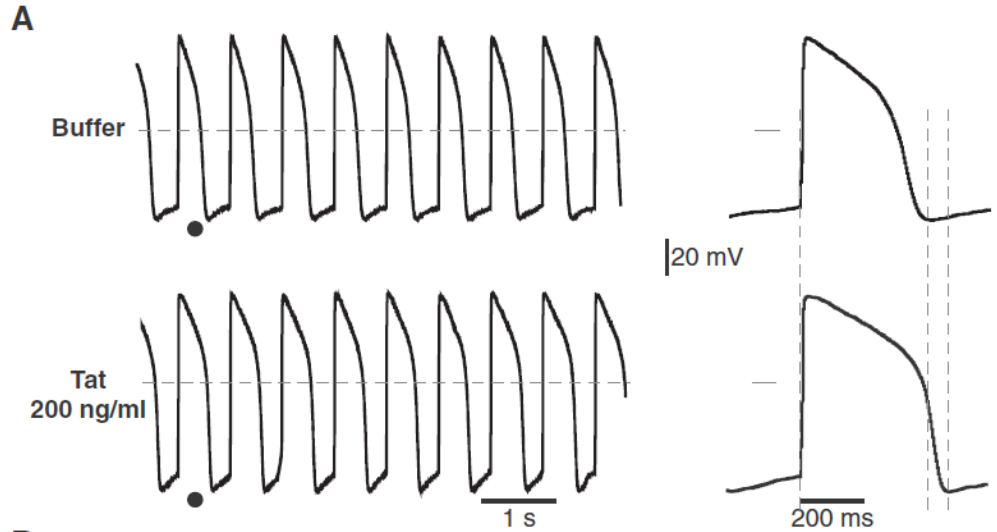
Figure 7



cardiomyocytes
issus de cellules hiPS

Condition : application **extracellulaire de la protéine Tat**

- **potentiel d'action**

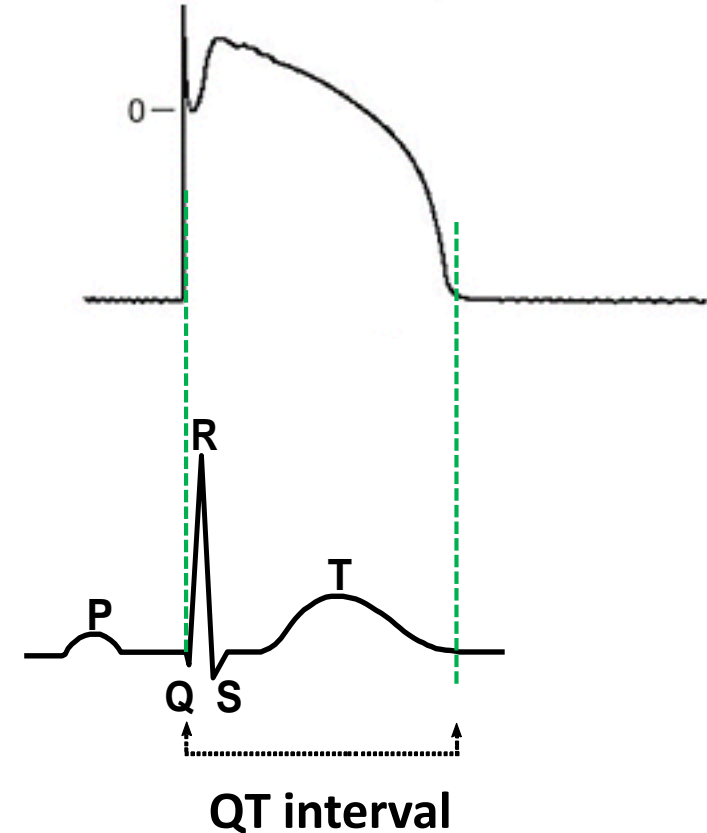
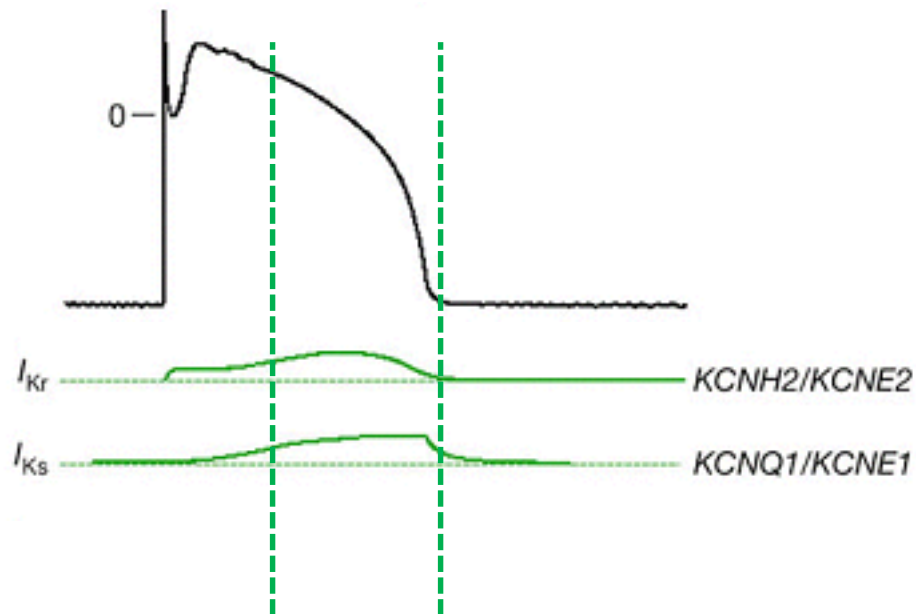


- **allongement de la durée du potentiel d'action induit par la Tat (phases tardives)**

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."

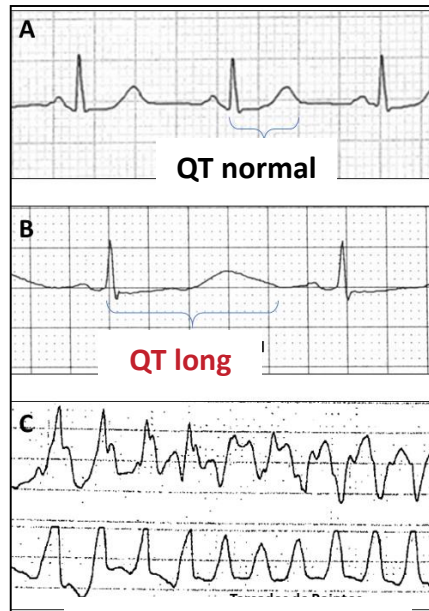


Syndrome du QT long congénital : variants de *KCNH2*

Contexte du projet

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

ECG

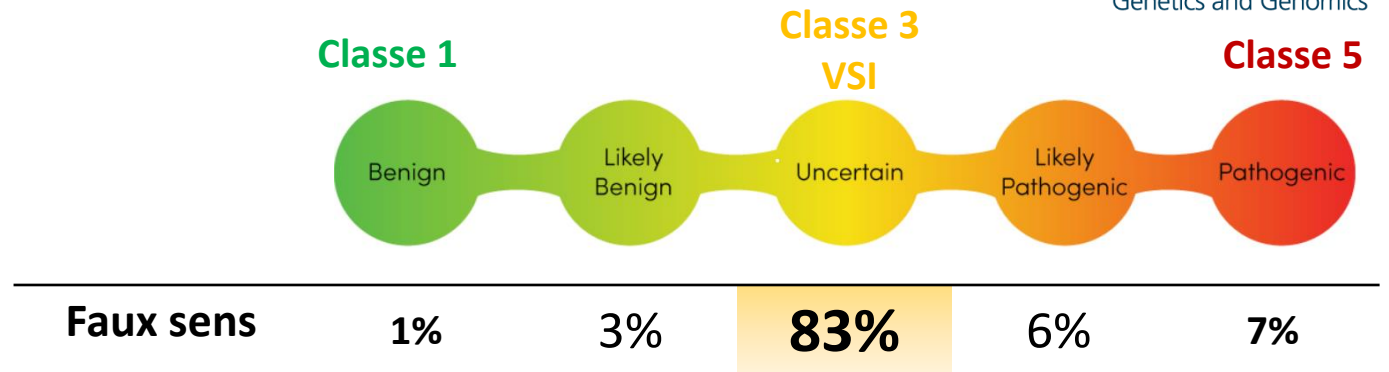


Torsades de pointes

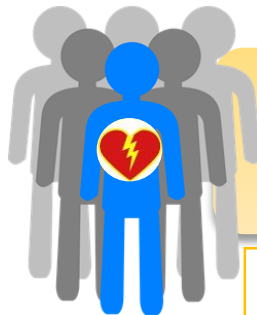
Syncopes et mort subite



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



VSI: Variants de Signification Inconnue




Besoin clinique: caractérisation fonctionnelle à haut débit de variants VSI

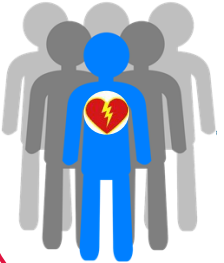
Stratification optimale du risque rythmique des patients

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

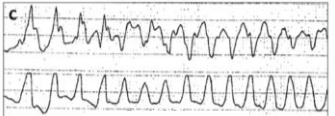
Caractérisation multiparamétrique



349 VSI

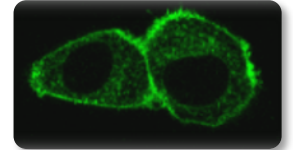


Arythmie

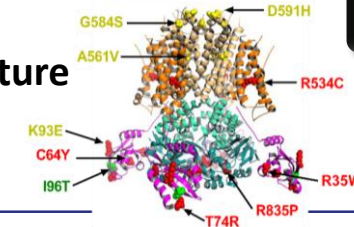


patch-clamp automatisé à haut débit
(384 cellules en simultanément)

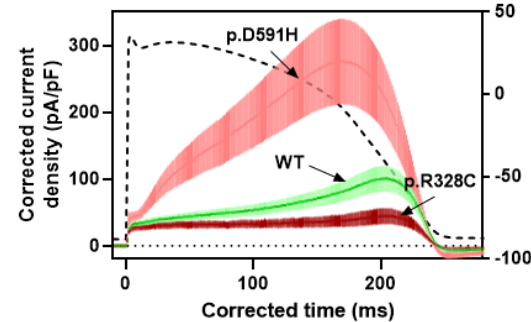
trafic à la membrane



structure



Score de pathogénicité moléculaire



pouvoir de repolarisation



Variantes bénins et pathogènes

Score final de pathogénicité pour le patient

= score moléculaire + score génétique

Informations cliniques

Diagnostic complet

Base de données internationale dynamique



Informations fonctionnelles complètes + génétiques + cliniques

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

Labo. de recherche de
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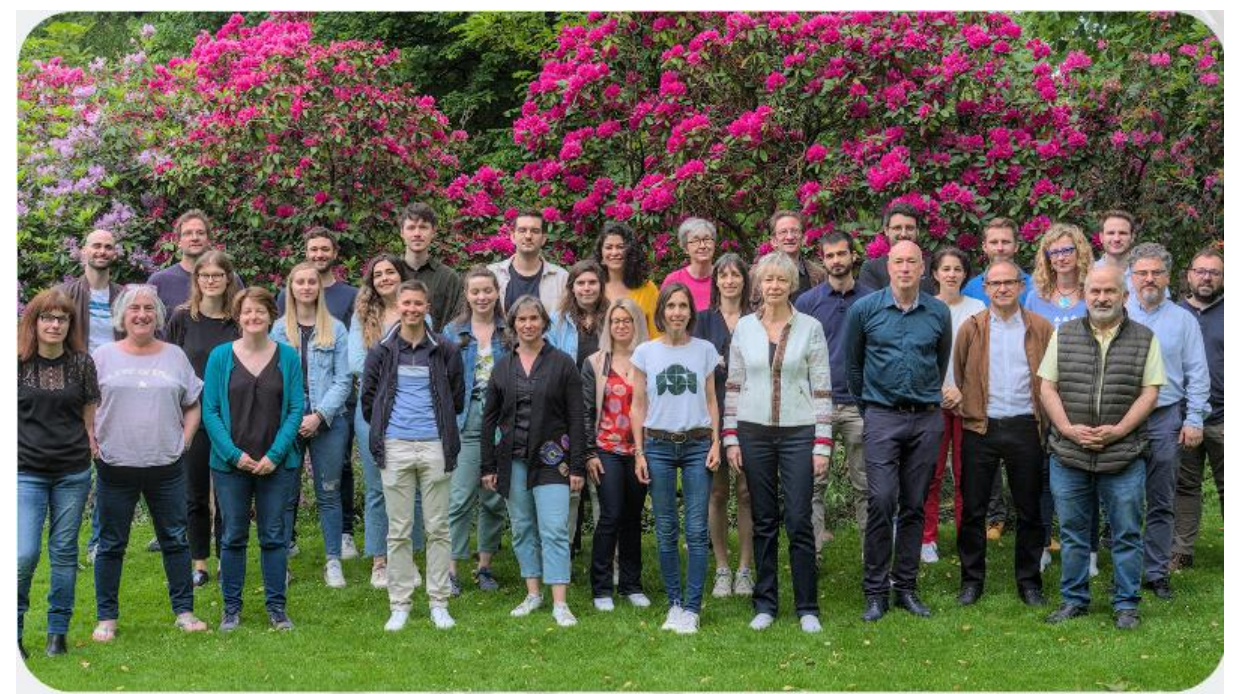


iPSC core facility

Libanese University
Team 045: Stem cells
Kasem Zibara

l'institut du thorax CIC
Vincent Probst
Jean-Baptiste Gourraud

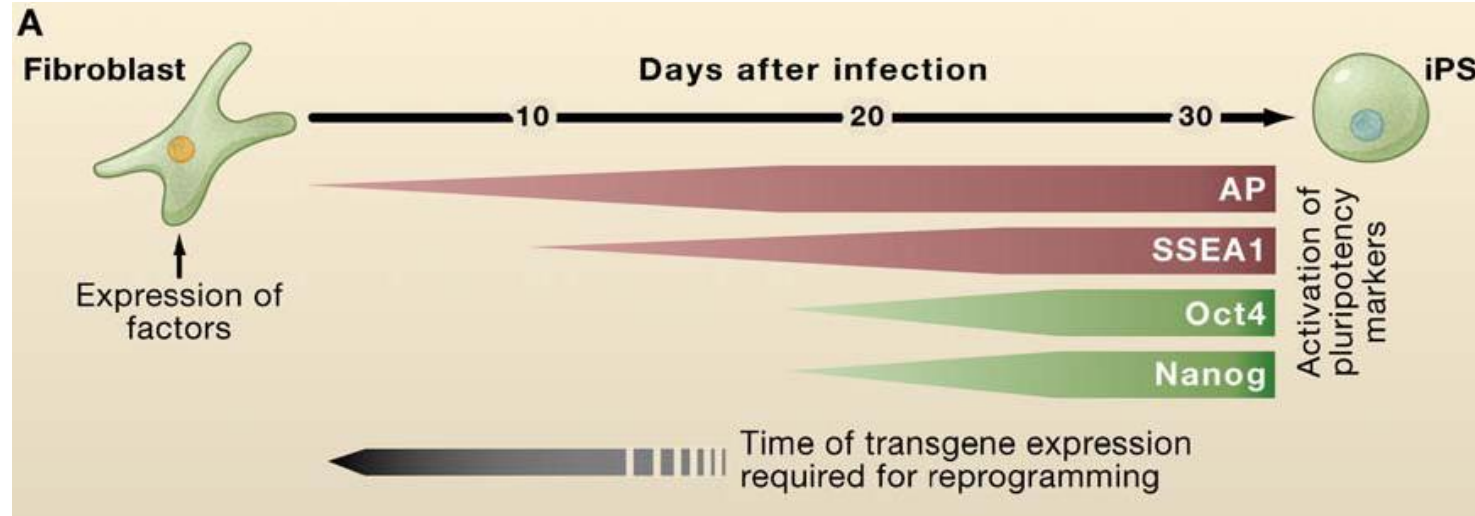
Fundings



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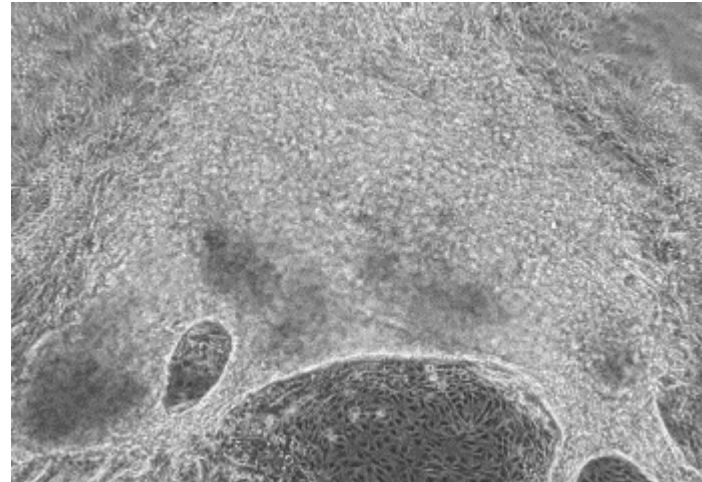


De l'urine au cardiomyocyte

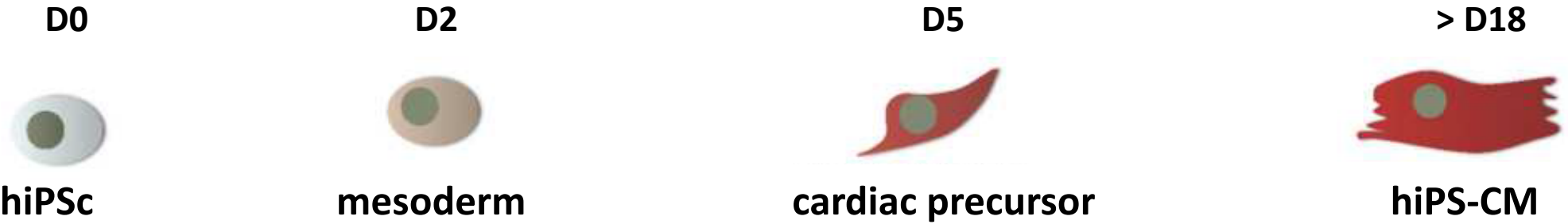


Reprogrammation

Différentiation



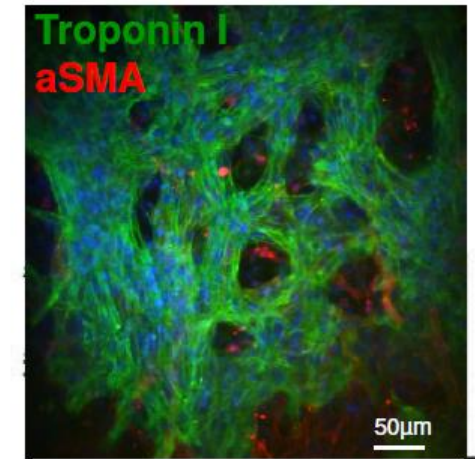
Différenciation cardiomyocytaire: caractérisation



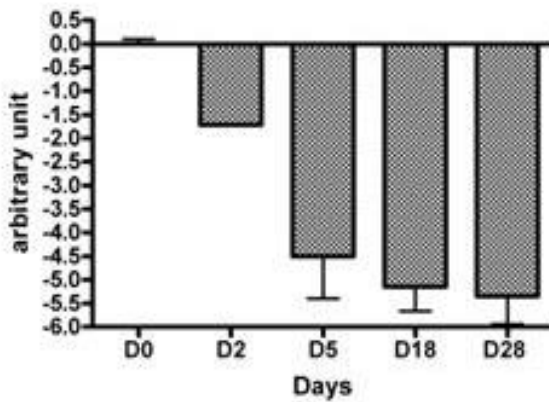
matrigel overlay

+ Activin A
+ FGF2
+ BMP4

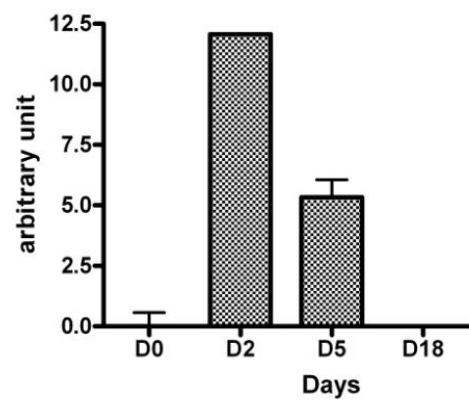
beats



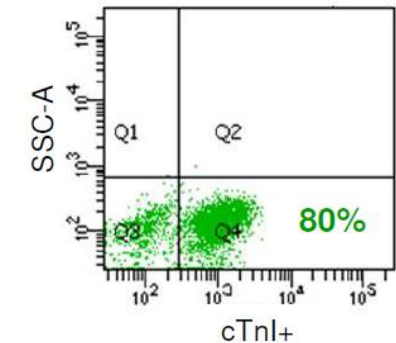
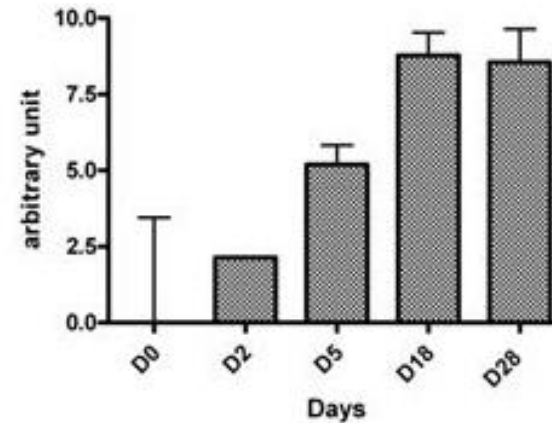
NANOG



BRACHYURY

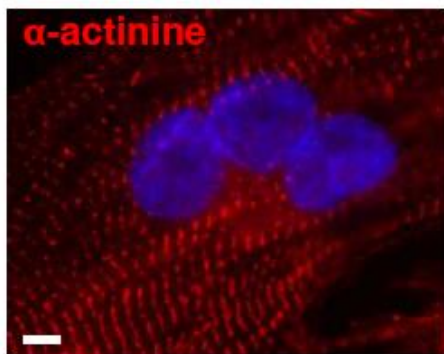
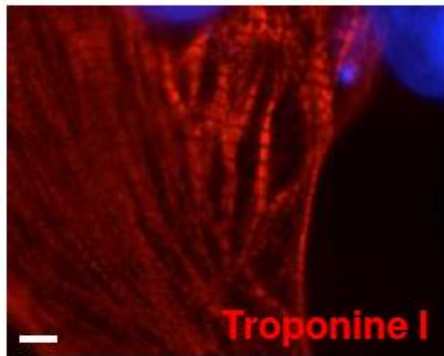
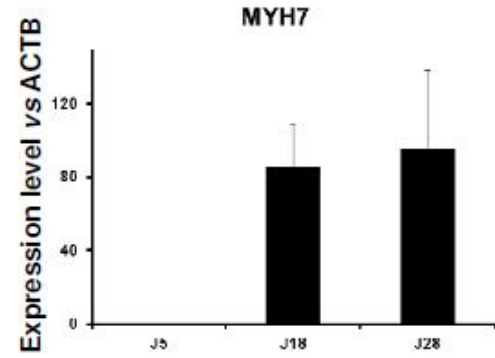


NKX2-5



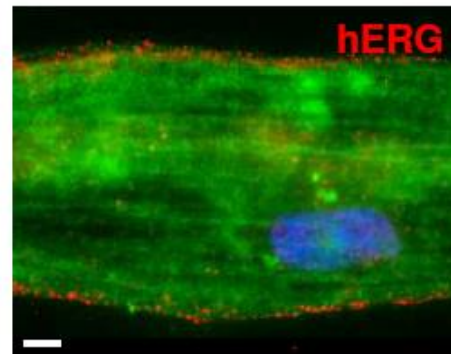
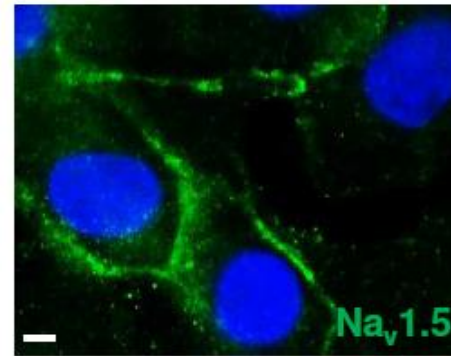
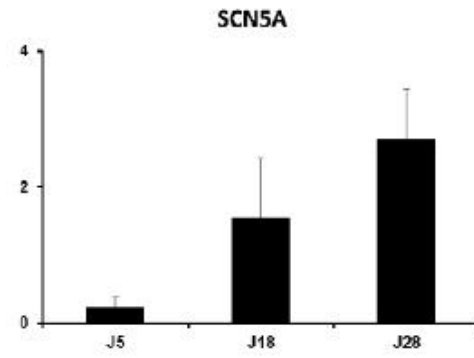
hiPS-cardiomyocytes : caractérisation

sarcomeric organization

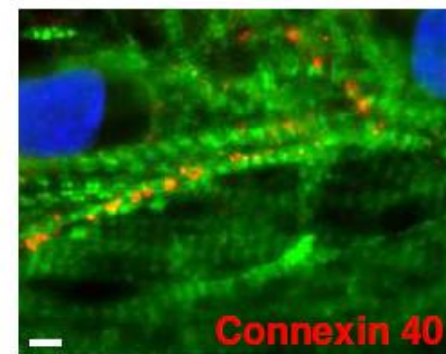
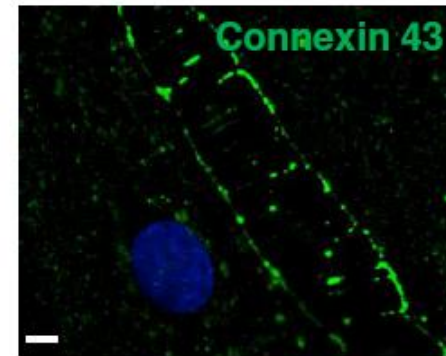
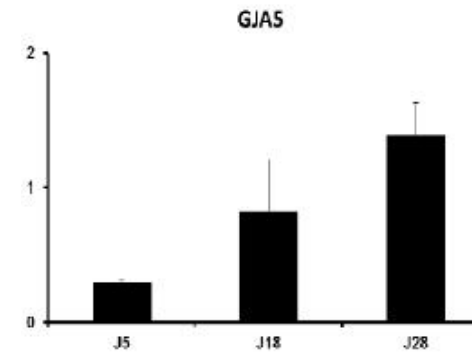


5 μ m

ion channels



gap junctions



Ca²⁺ homeostasis

