

### L'ASSEMBLAGE DES RÉCEPTEURS NICOTINIQUES ET SES CONSÉQUENCES SUR LEUR ÉTUDE

Marie Prevost

Unité Récepteurs-canaux

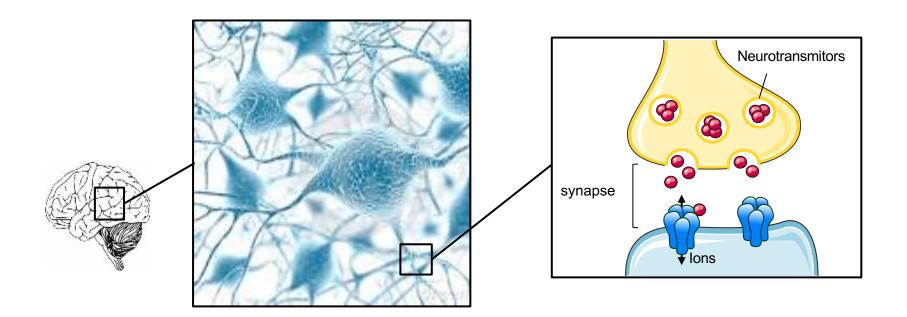
Institut Pasteur





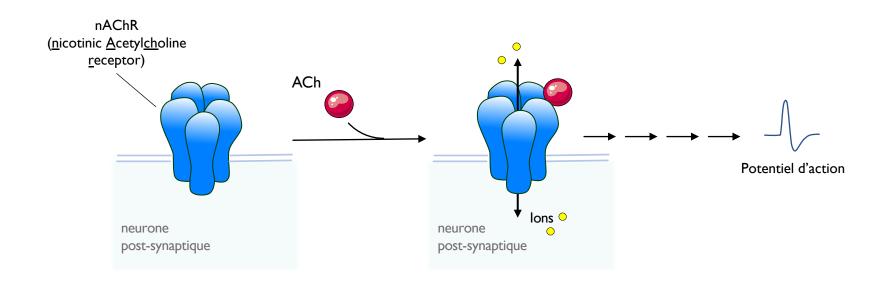


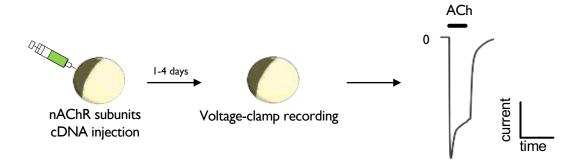
### Les récepteurs à la nicotine sont avant tout des récepteurs au neurotransmetteur Acetylcholine (ACh)





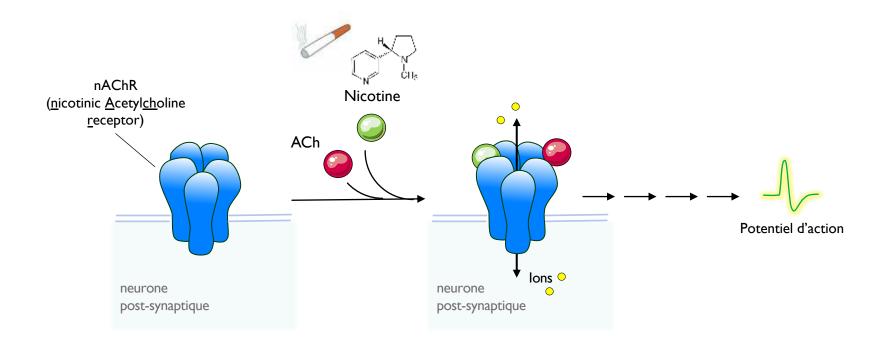
### En absence de nicotine, les nAChRs sont activés par l'ACh et transmettent un signal excitateur de neurones en neurones







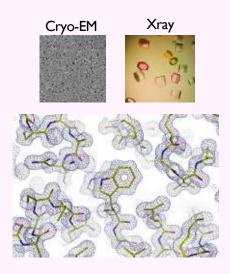
### Chez le fumeur, la nicotine interfère avec la liaison d'ACh et modifie le signal





#### Les récepteurs-canaux à l'échelle moléculaire

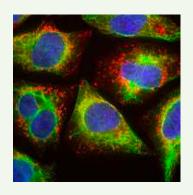
#### Biologie structurale



Récepteurs à l'ACh Récepteurs à la sérotonine Récepteurs à la Glycine Récepteurs au GABA

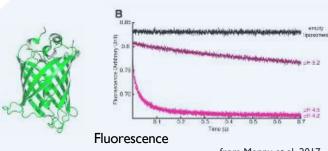


#### Biologie cellulaire Electrophysiologie

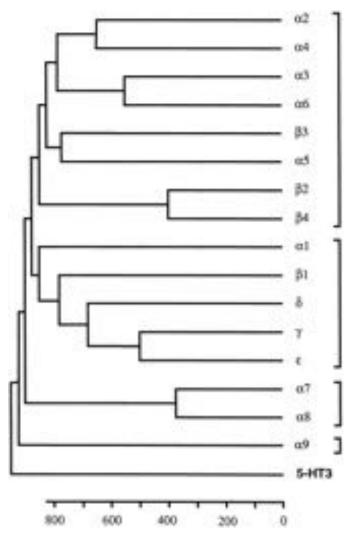




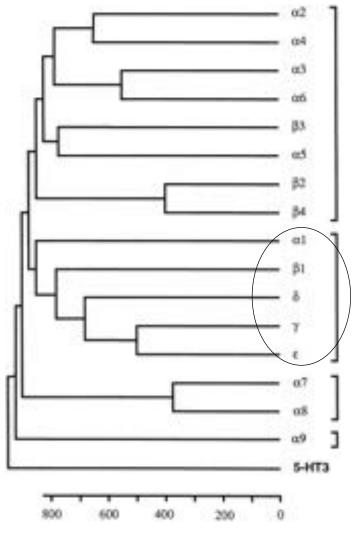
#### Biophysique





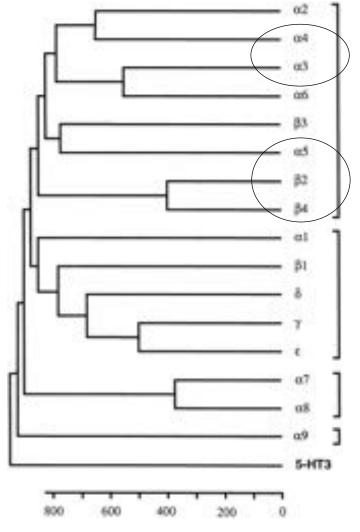






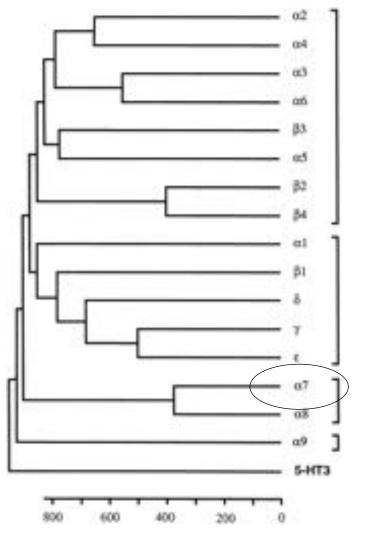
Présents à la jonction neuro-musculaire





Récepteurs neuronaux Principaux responsables de l'addiction à la nicotine

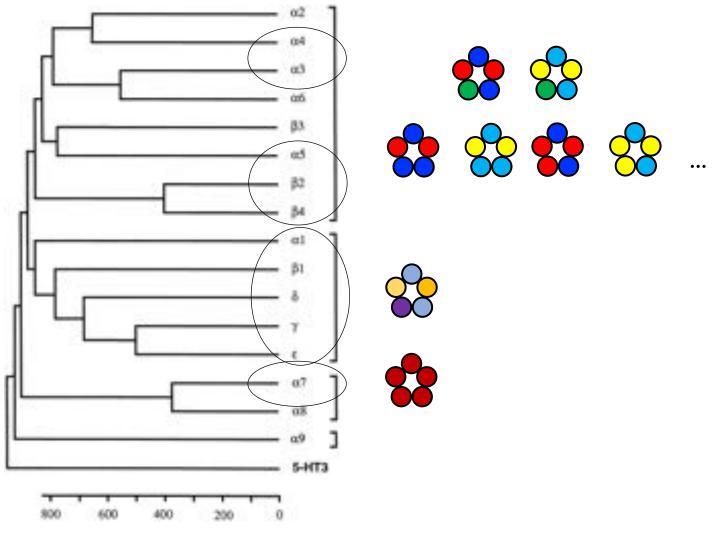




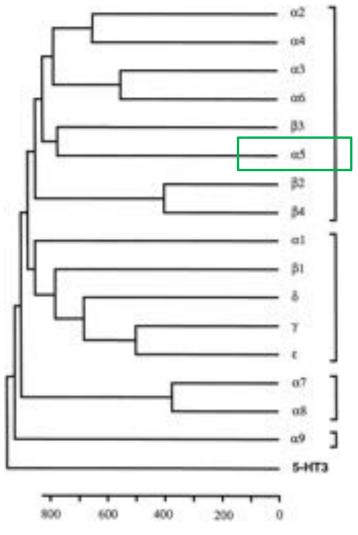
Récepteurs neuronaux Impliqués dans la schizophrénie/AD



### Assemblage des sous-unités

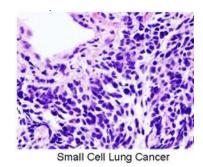






Changeux et al. 1998

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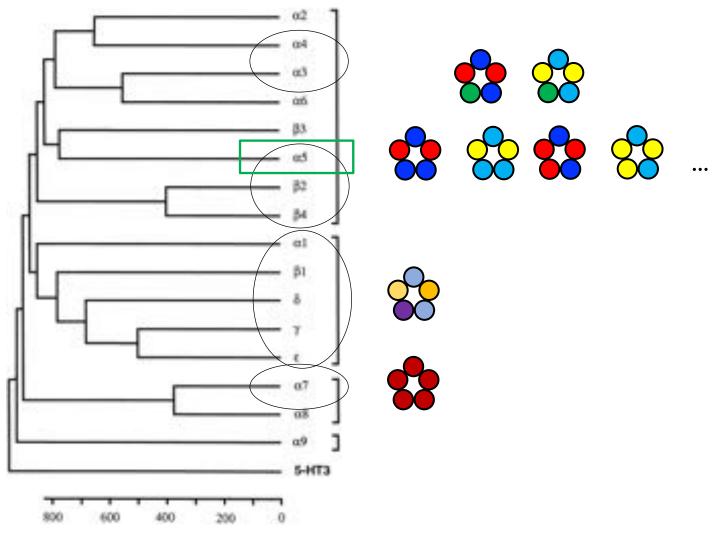
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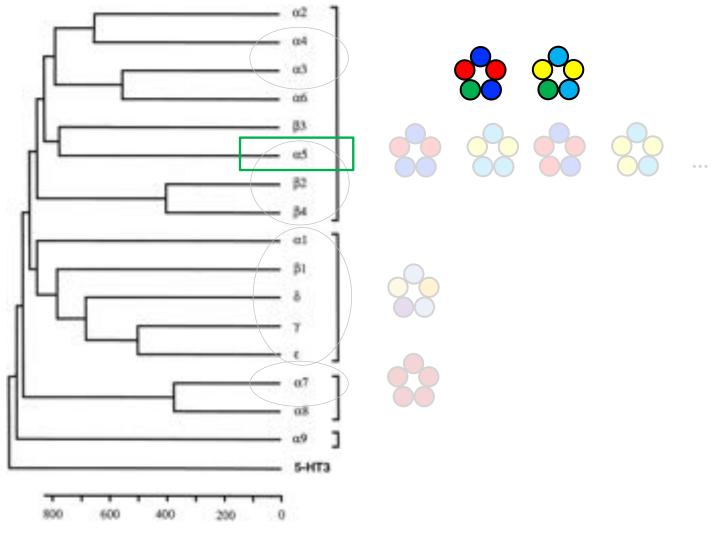


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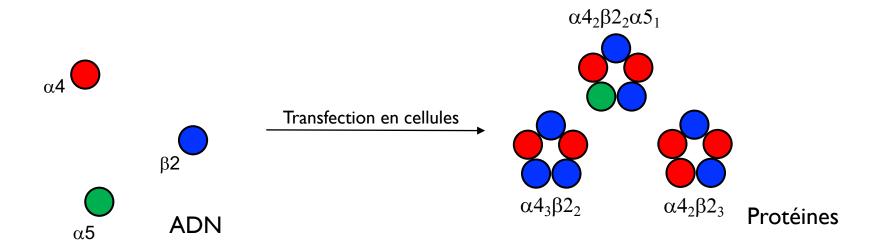




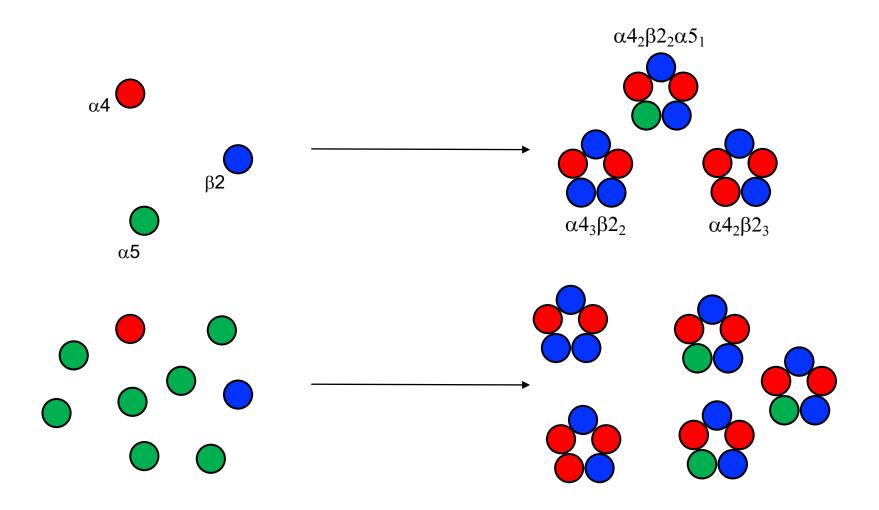
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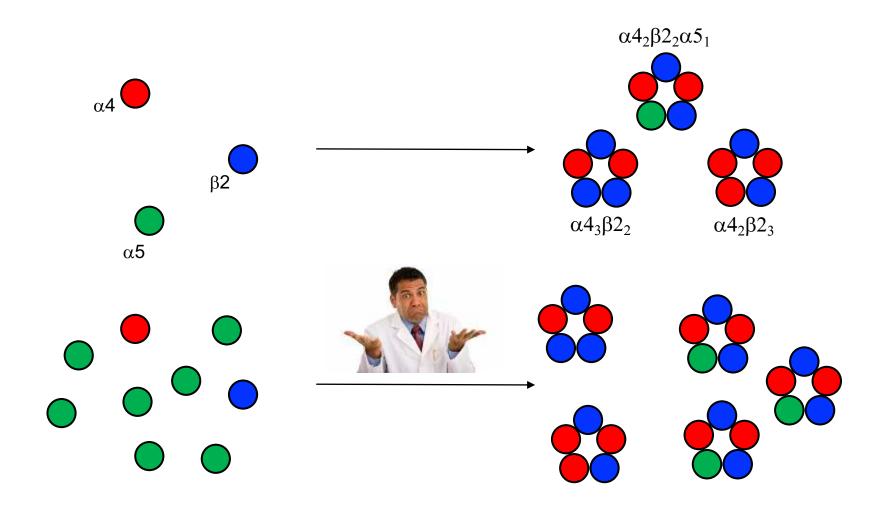














### La littérature est assez partagée sur les conséquences fonctionnelles de D398N

Acetylcholine Receptor (AChR) α5 Subunit Variant Associated with Risk for Nicotine Dependence and Lung Cancer Reduces  $(\alpha 4\beta 2)_2 \alpha 5$  AChR Function

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Received May 14, 2010; accepted September 29, 2010

SCIENTIFIC REPORTS

Increased nicotine response in iPSC-derived human neurons carrying the CHRNA5 N398 allele

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Mid Pharmocol WC-818-RDT, 2011

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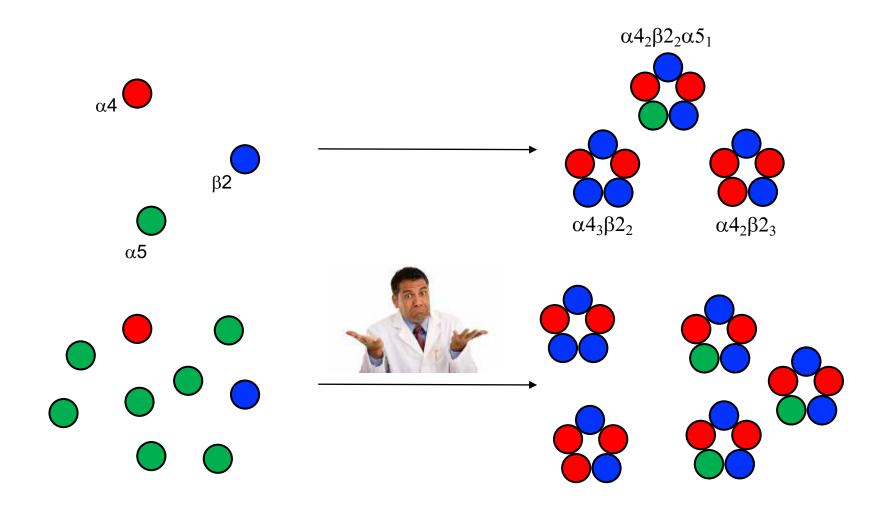
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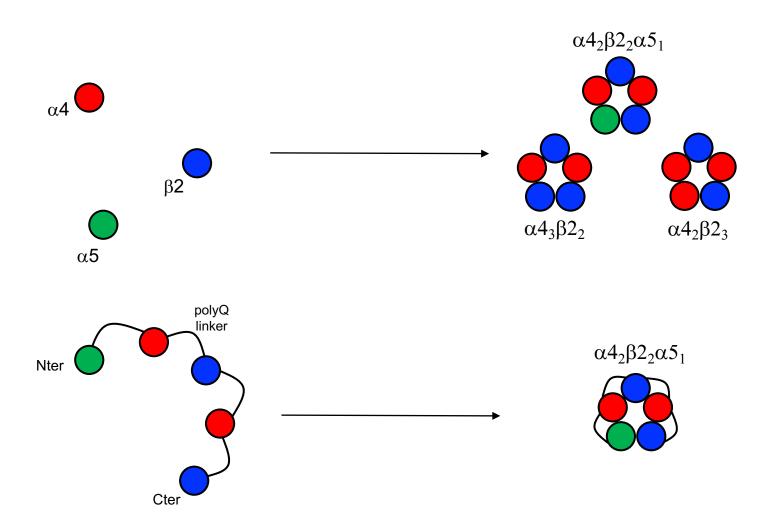
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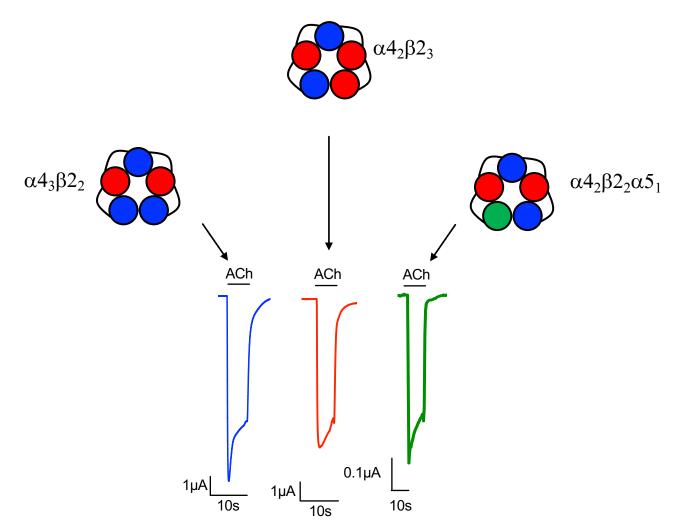


# Nous avons créé un récepteur concatémèrique de façon à revisiter le rôle de $\alpha 5$





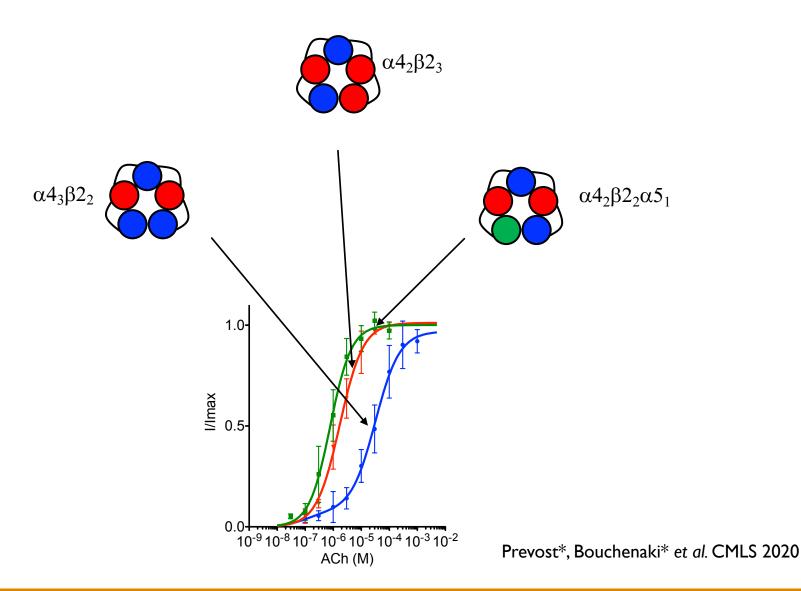
# Les concatémères sont stables et génèrent des courants robustes en ovocyte de Xenope



Prevost\*, Bouchenaki\* et al. CMLS 2020

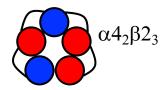


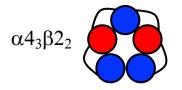
# Avec les paramètres attendus pour ces sous-types de nAChR

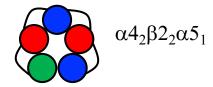




### Les concatémères sont des outils puissants



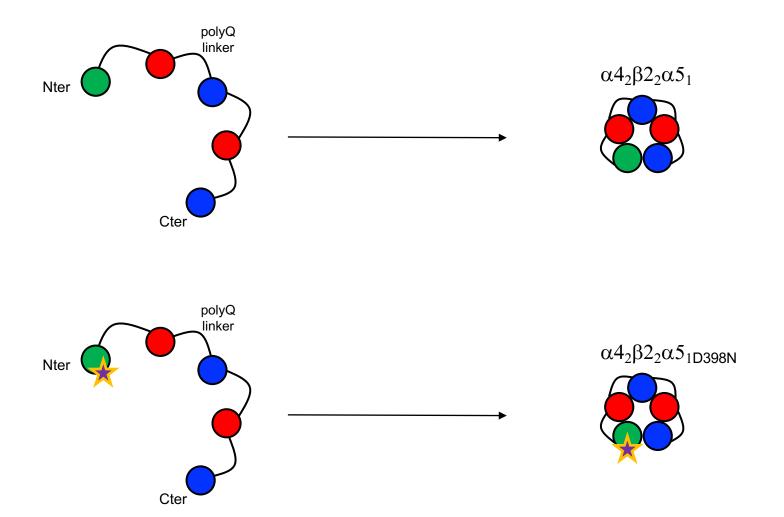




- Propriétés pharmaco-cinétiques
- Spécificité des ligands
- Stabilité
- Mutations ponctuelles
- etc ...

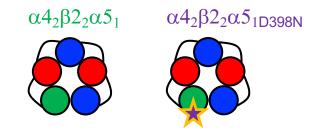


# Nous avons donc un système permettant de regarder précisément l'effet de mutations



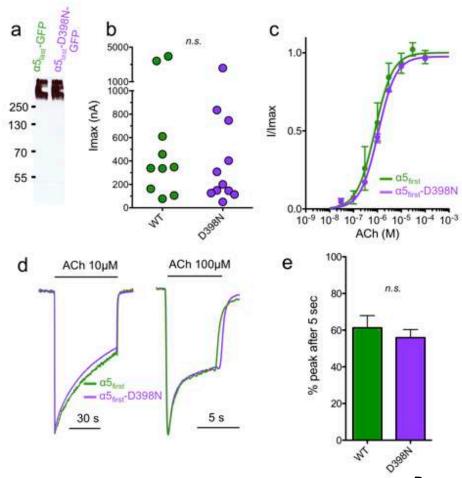


## Nous avons donc introduit la mutation dans notre concatémère





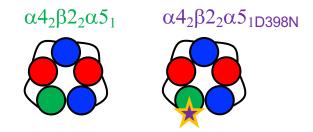
### Nous avons donc introduit la mutation dans notre concatémère Et n'avons pas observé de différence



Prevost\*, Bouchenaki\* et al. CMLS 2020



## Nous avons donc introduit la mutation dans notre concatémère



La mutation ne compromet pas la fonction électrophysiologique



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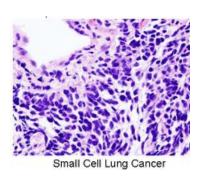
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Mécanismes cellulaires?

- export, assemblage
- partenaires protéiques ?





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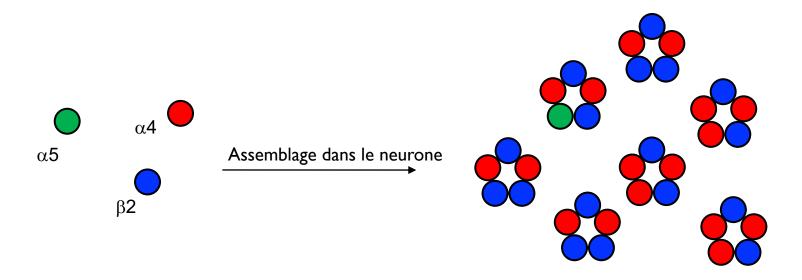
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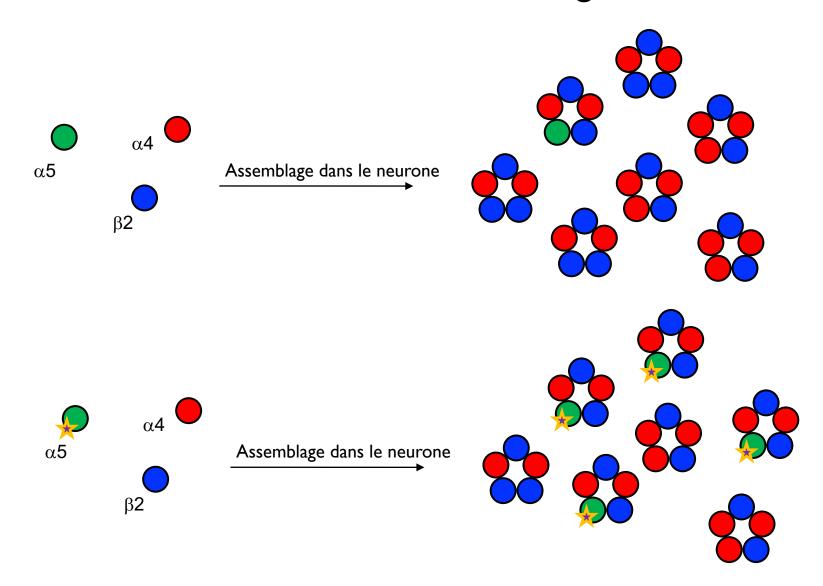


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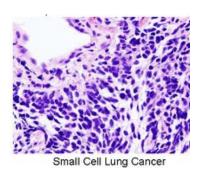
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#### Merci

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Unité RCN





