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# Venom peptides: promising tools for lung cancer imaging

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Many cancers, and the **non-small cell lung cancer (NSCLC)** in particular, are associated with significant **overexpression of various ion channels** such as certain subtypes of sodium, calcium and potassium channels, pH-sensitive channels (ASICs for acid sensing ion channels) or nicotinic acetylcholine receptors. Activation of these ion channels plays an important role in the aggressiveness of cancer cell and tumor invasion, their overexpression seeming to be correlated with the appearance of metastases. Although **imaging approaches** (radiography, CT-scan for computed tomography scanning, PET-scan for positron emission tomography) are commonly used in the anatomical characterization of lung cancer, some **limitations** of these approaches require the development of **new imaging probes** more specific of overexpressed molecular targets in lung adenocarcinomas. **Peptide toxins**, which possess unique pharmacological properties, are well known to act selectively and with high affinity on certain overexpressed ion channels in cancer cells. Therefore, a promising solution towards the development of new imaging agents of lung cancer biomarkers appears to be the **chemical synthesis** of these toxins allowing them to be **labelled by "click" chemistry** using various fluorescent or radioactive probes.

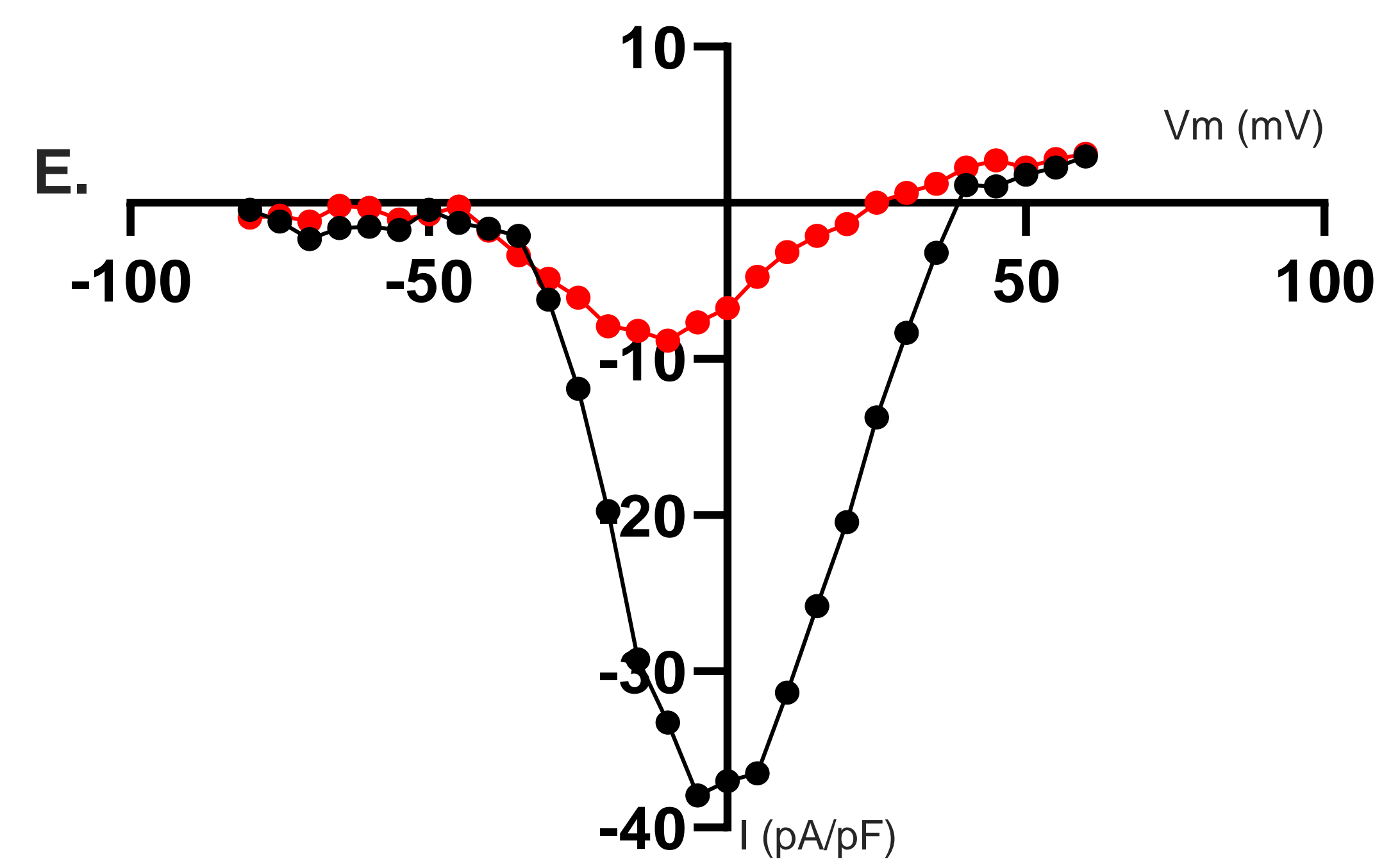
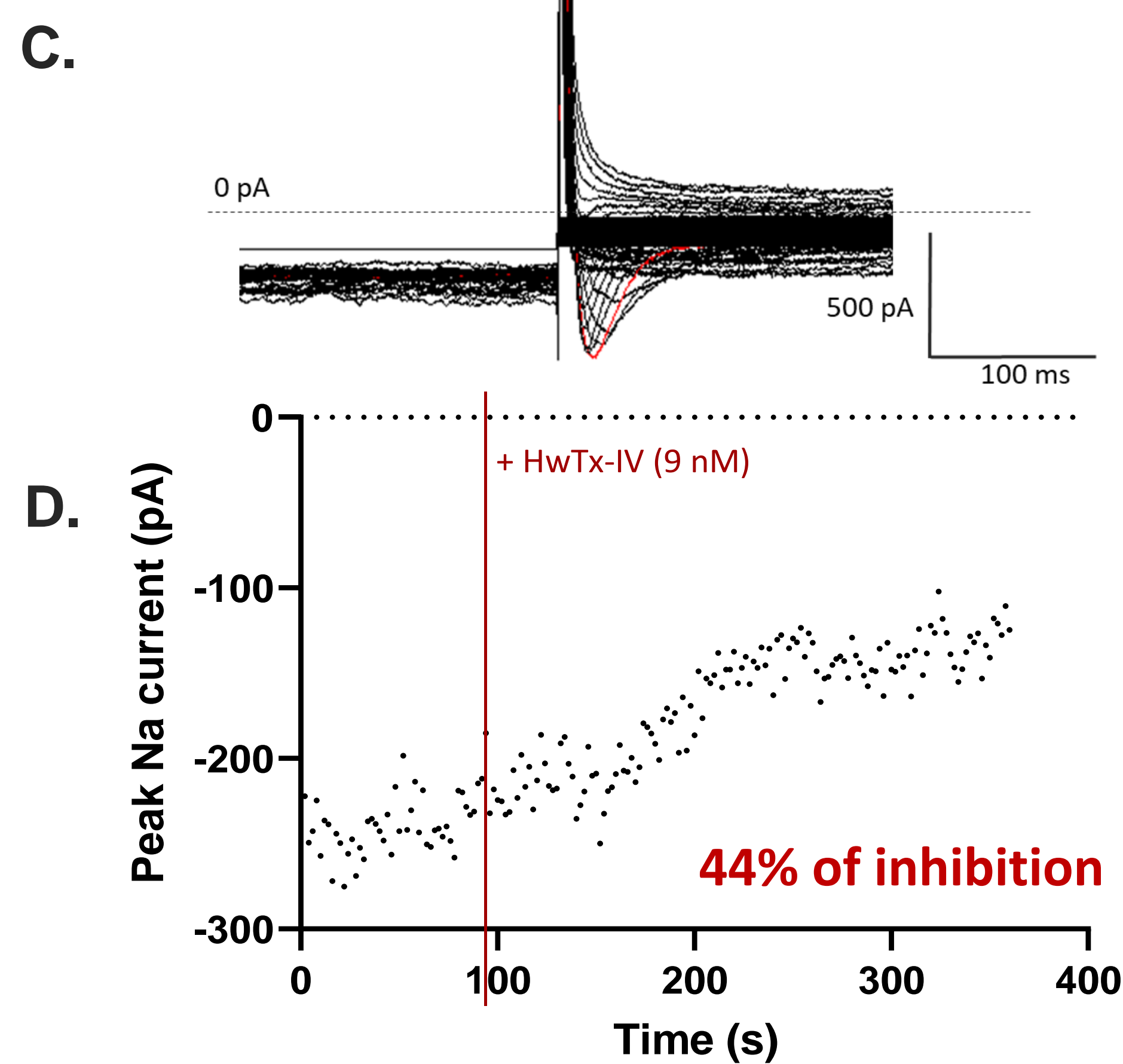
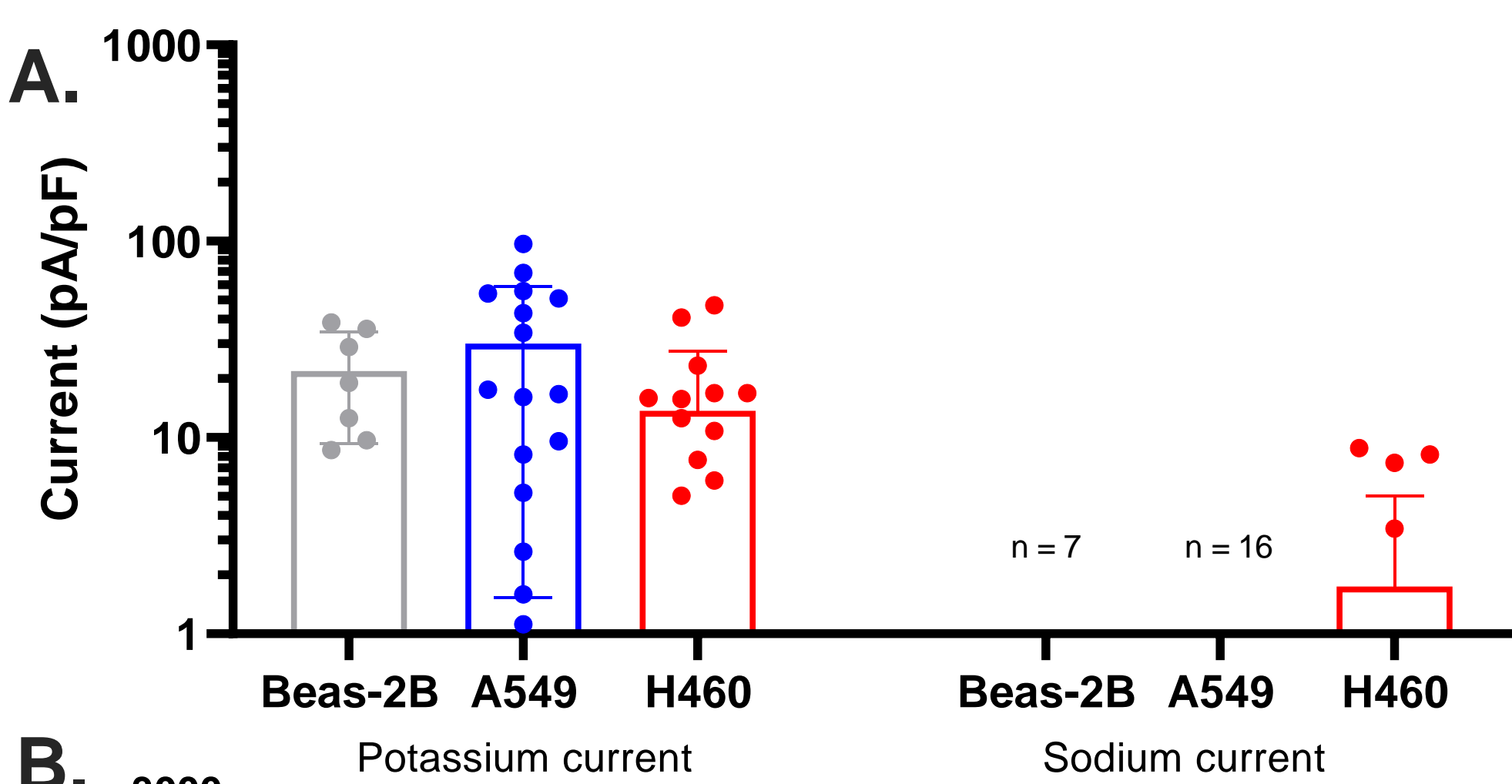
## 1. Peptide synthesis

Toxin	Organism	Sequence	3D-Structure	Target	IC <sub>50</sub> (nM)
Huwentoxin-IV (HwTx-IV)	<i>Cyriopagopus schmidti</i>	35 AA		hNa <sub>v</sub> 1.7	9
Charybdotoxin (ChTx)	<i>Leiurus quinquestriatus</i>	37 AA		hK <sub>Ca</sub> 3.1	5
Mambalgin-1	<i>Dendroaspis polylepis</i>	56 AA		hASIC1b hASIC1a+1b	192 72
α-IM1	<i>Comus imperialis</i>	11 AA		hαAChR α7	200
α-Bungarotoxin	<i>Bungarus multicinctus</i>	74 AA		hαAChR α7 α9/α10	0.8 32

All peptides are synthesised by Solid-Phase Peptide Synthesis (SPPS)

## 3. Functional characterization

Exemplified by HwTx-IV effect on HEK-293 cell line stably overexpressing hNa<sub>v</sub>1.7



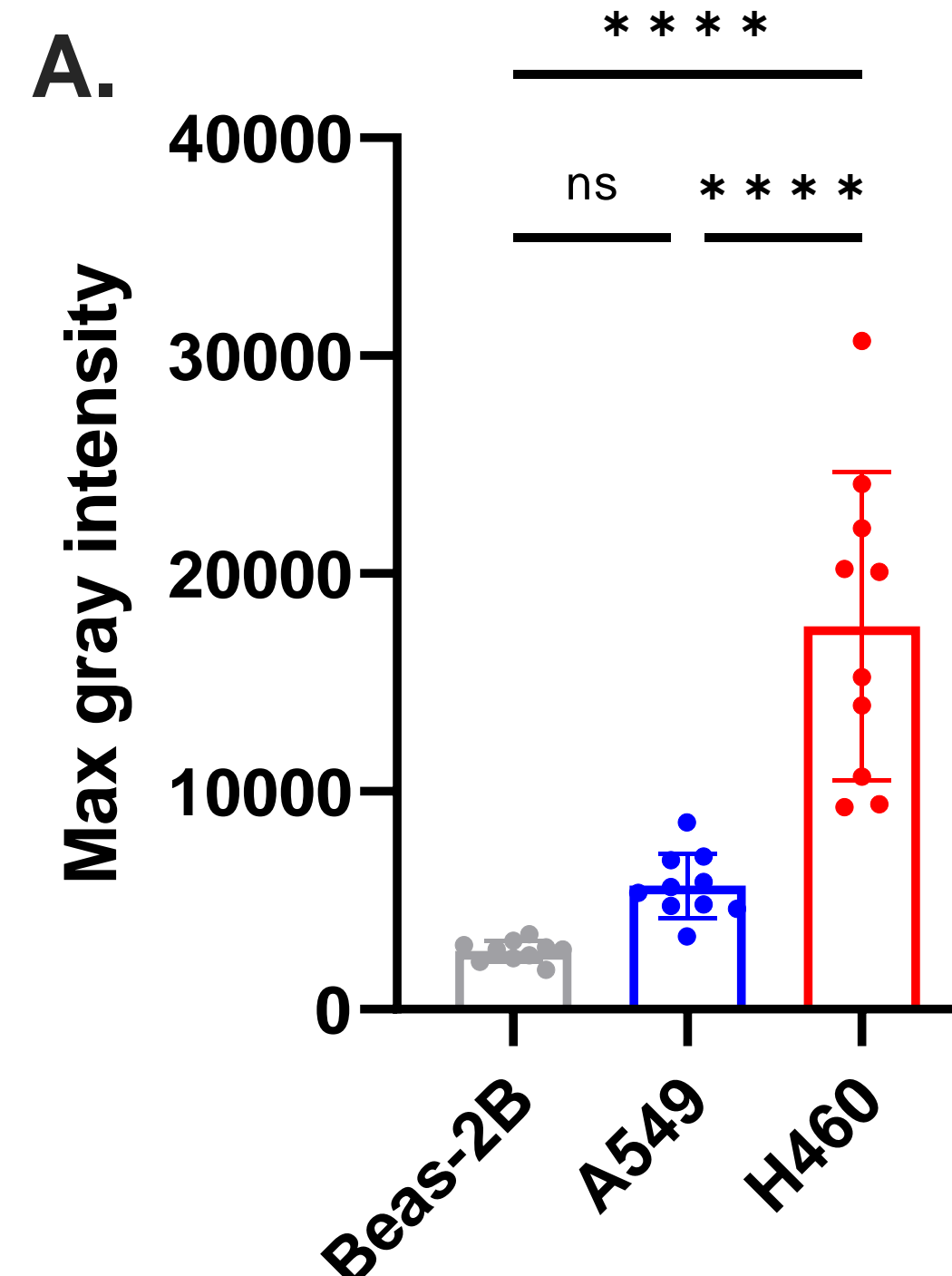
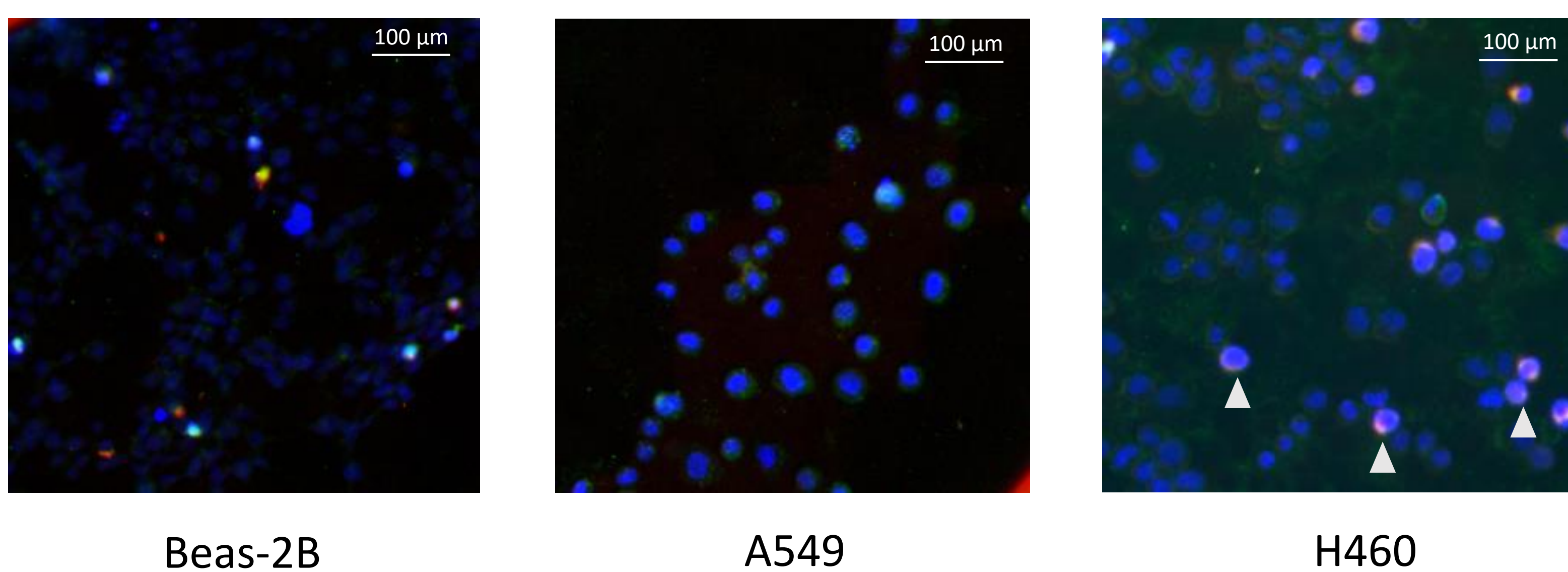
- No detectable sodium current in Beas-2B and A549 cells
- Weak sodium current in H460 (unexploitable for HwTx-IV studies)
- ➔ Use of HEK-293 cell line stably overexpressing hNa<sub>v</sub>1.7
- ➔ Experiments with HwTx-IV-Cyanine 5 to be done

**A.** Global potassium and sodium voltage-dependent currents recorded in lung cell lines. **B.** Representative current traces of sodium current recorded from HEK overexpressing hNa<sub>v</sub>1.7 without (black) and with (red) HwTx-IV (9 nM). **C.** Representative current traces of sodium current recorded from HEK overexpressing hNa<sub>v</sub>1.7 as a function of membrane potential. **D.** Kinetics of HwTx-IV effects on the peak sodium current. **E.** Sodium current-voltage curve without (black) and with (red) HwTx-IV (9 nM).

## 4. Fluorescence imaging

Exemplified by HwTx-IV-Cyanine 5 effect on lung cell lines

50 nM HwTx – Cyanine 5  
Concanavaline A (Membrane)  
Hoechst (Nucleus)



**A.** Maximum gray intensity at the membrane of ten cells for each cell line, representing the intensity of HwTx-IV-Cyanine 5 fixed on Na<sub>v</sub>1.7

HwTx-IV-Cyanine 5 interacts with Na<sub>v</sub>1.7 channels. Noted that the fluorescence intensity is significantly higher in H460 cells as compared to A549 and Beas-2B cells

Certain ionic channels are overexpressed in lung cancer cell lines. These channels can be targeted with high affinity and selectivity by some venom toxins that are easily tagged with fluorescent or radioactive group. The results show that the Na<sub>v</sub>1.7 and HwTx-IV-Cyanine 5 couple is promising to detect tumors, especially invasive ones. To complete these results, TEP imaging will be done on xenografted mice.

**This study will participate to the development of new lung cancer biomarkers**

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