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Venom peptides: emerging biological tools for lung cancer imaging

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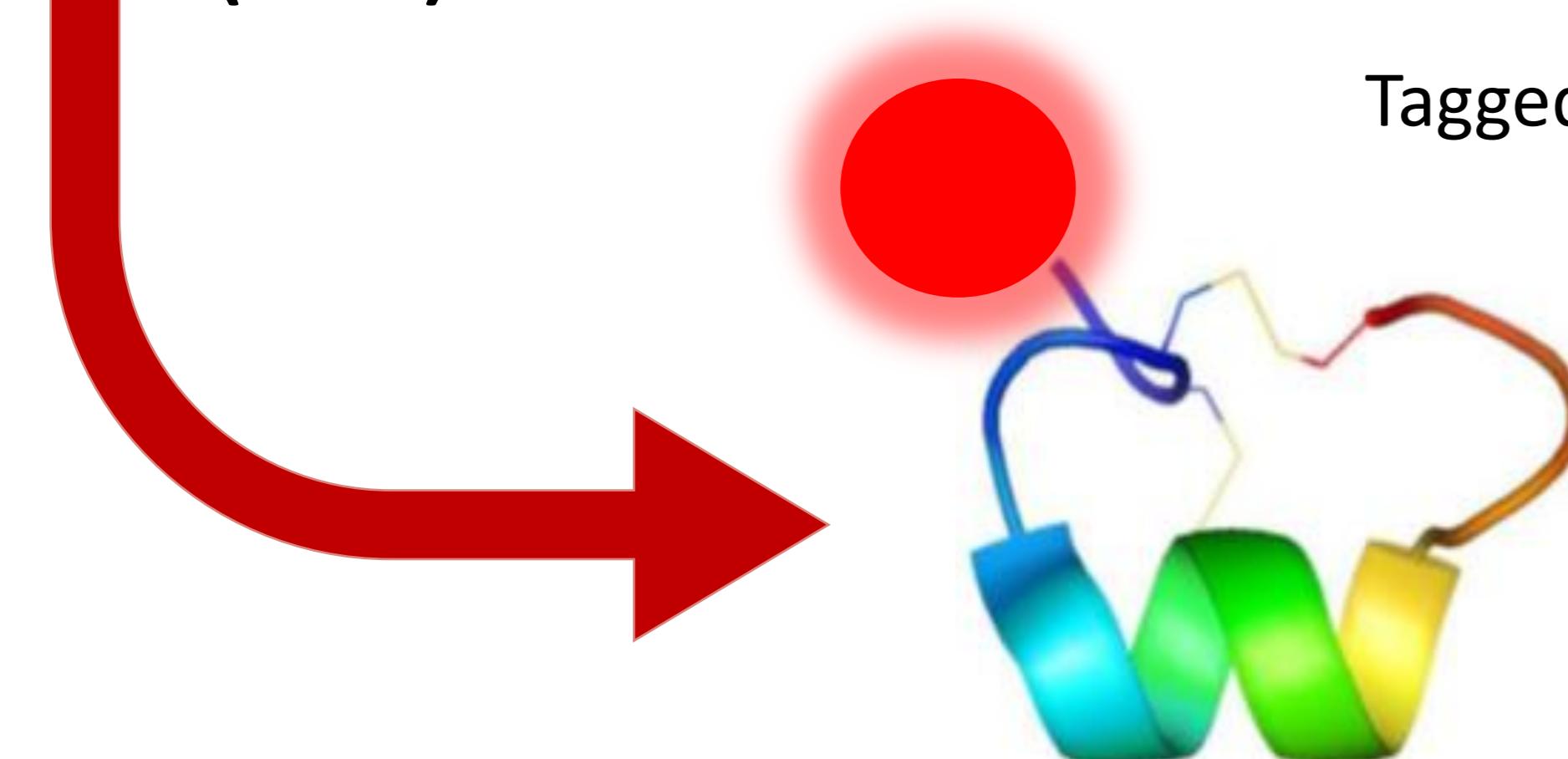


Many cancers, and the non-small cell lung cancer (NSCLC) in particular, are associated with significant overexpression of various ion channels such as certain subtypes of sodium, calcium and potassium channels, pH-sensitive channels (ASICs for acid sensing ion channels) or nicotinic acetylcholine receptors. Activation of these ion channels plays an important role in cancer cell aggressiveness 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 of their limitations require the development of new imaging probes more specific of overexpressed molecular targets in lung adenocarcinomas. Peptide toxins, which have 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 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 ₅₀ (nM)
Huwentoxin-IV (HwTx-IV)	<i>Cyriopagopus schmidti</i>	c c c c c c 35 AA		hNa _v 1.7	9
Charybdotoxin (ChTx)	<i>Leiurus quinquestriatus</i>	c c c c c c 37 AA		hK _{Ca} 3.1	5
Mambalgin-1	<i>Dendroaspis polylepis</i>	c c c c c c 56 AA		hASIC1b hASIC1a+1b	192 72
α-IM1	<i>Conus imperialis</i>	c c c c 11 AA		hnAChR α7	200
α-Bungarotoxin	<i>Bungarus multicinctus</i>	c c c c c c c c 74 AA		hnAChR α7 α9/α10	0.8 32

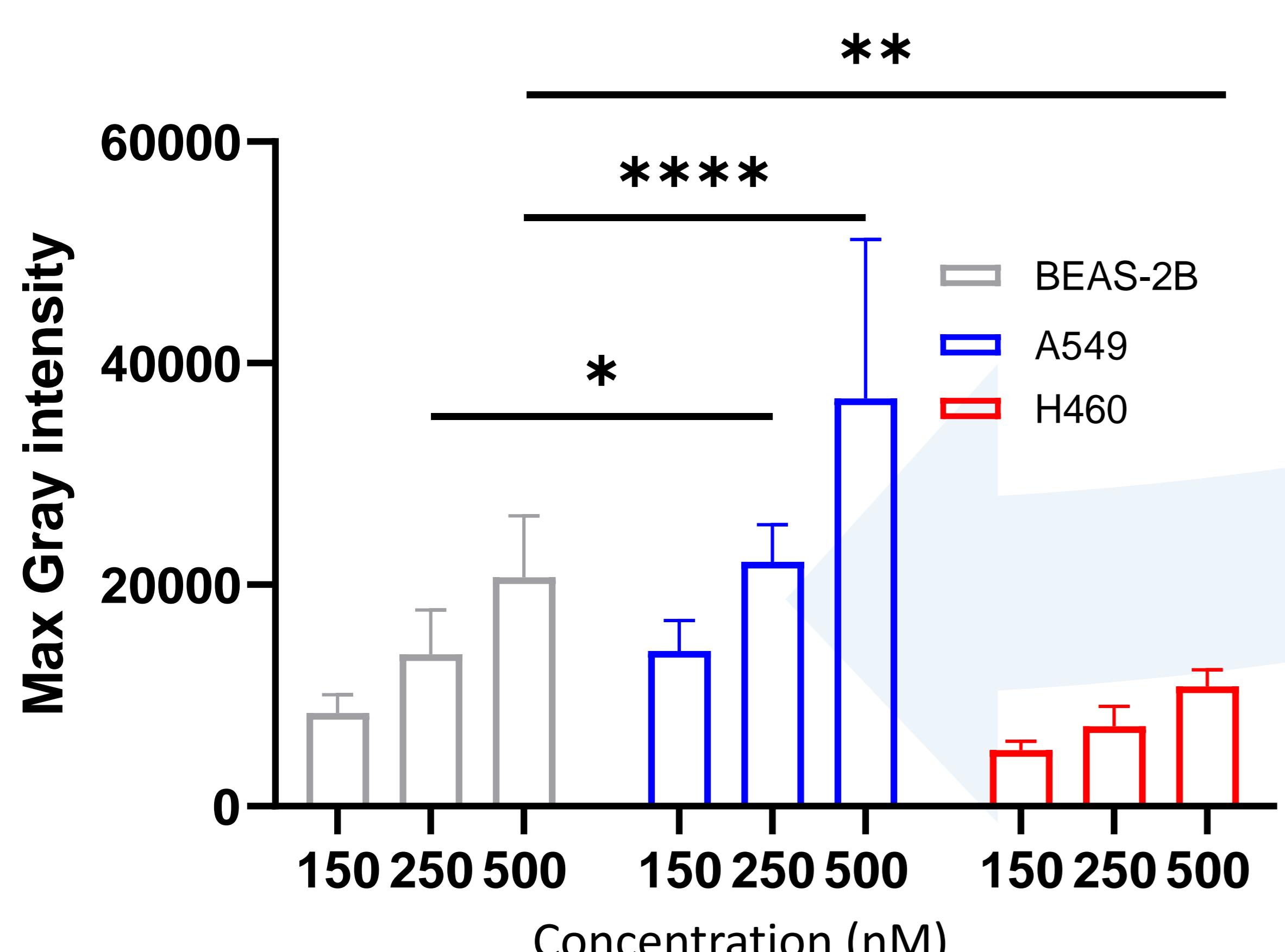
Solid-Phase Peptide Synthesis (SPPS)



Tagged α-IM1 conotoxin

3. Fluo/TEP imaging

Exemplified by ChTx-TAMRA effect on cancerous cell lines

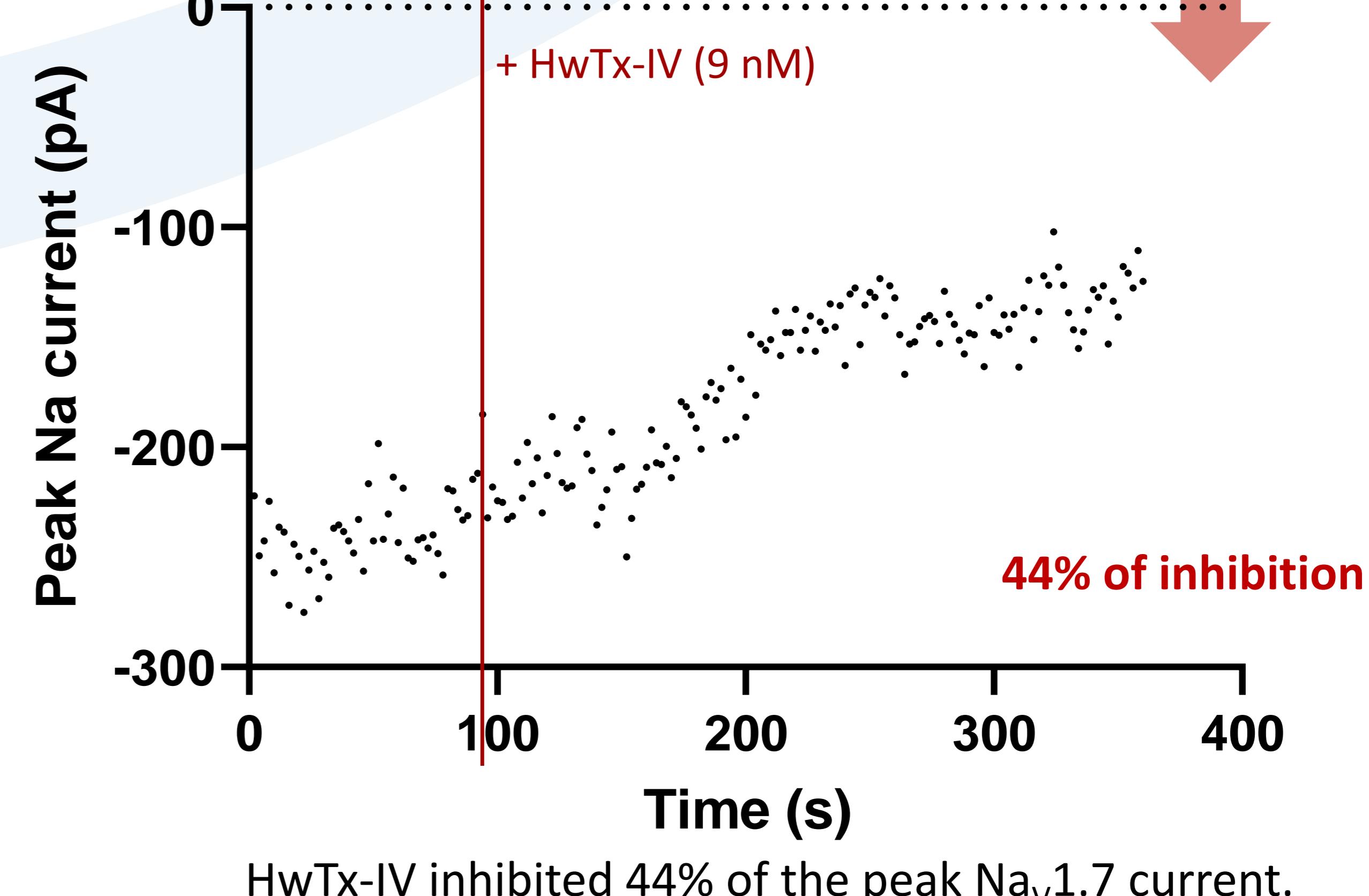
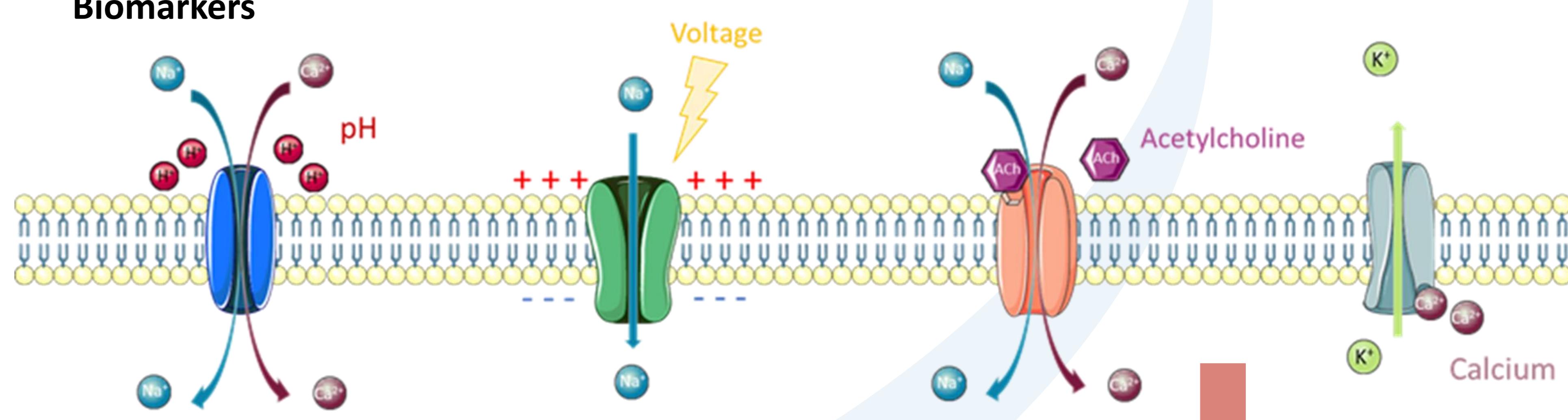


ChTx-TAMRA interacts with K_{Ca}3.1 channels. Noted that the fluorescence intensity is significantly higher in A549 cells and lower in H460 cells, compared to BEAS-2B cells.

2. Functional characterization

Exemplified by HwTx-IV effect on HEK-293 cell line stably overexpressing hNa_v1.7

Biomarkers



HwTx-IV inhibited 44% of the peak Na_v1.7 current.

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.

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