PPQ-102 is the most potent inhibitor of the CFTR chloride channel in the rectal gland of the shark, *Squalus acanthias*

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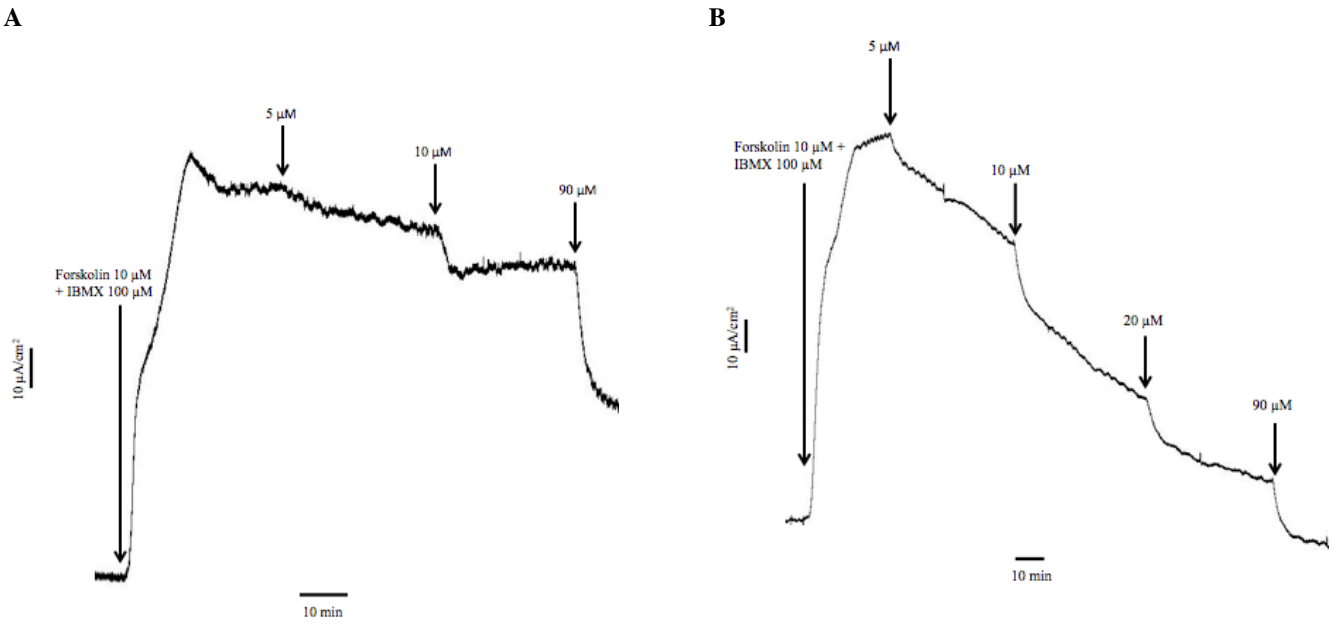
Inhibitors of the Cystic Fibrosis Transmembrane Regulator (CFTR) chloride channel have potential clinical applications. Three inhibitors of CFTR, GlyH-101, PPQ-102 and PPQ-27, were compared in experiments measuring short-circuit current (I_{sc}) in primary cultured monolayers of shark rectal gland tubular cells. All inhibited shark rectal gland epithelial chloride secretion through CFTR. PPQ-102 was the most potent inhibitor at low doses and appears to be the best universal inhibitor of CFTR identified to date.

The rectal gland of the spiny dogfish shark (*Squalus acanthias*) is an ideal model for studying epithelial chloride secretion as its membranes contain record amounts of CFTR[1]. This gland serves osmoregulation in the shark by secreting a chloride-containing fluid hypertonic to the shark's plasma. Primary cultured monolayers of shark rectal gland tubules were used to measure transepithelial chloride transport through CFTR as short-circuit current (I_{sc})[4].

CFTR inhibitors have several potential clinical indications including reducing fluid loss in secretory diarrhea and slowing renal cyst expansion in polycystic kidney disease[2]. In 2009, Verkman et al[2] studied several mammalian tissues, Fischer Rat Thyroid cells (FRT), T84 cells and human bronchial epithelial cells and provided data that indicated PPQ-102, a pyrimido-pyrrolo-quinoxalinedione derivative, is the most potent CFTR inhibitor identified to date. This PPQ compound has the advantage that at physiological pH it is uncharged and thus not subject to membrane potential effects including block efficiency or cellular partitioning. In 2012, Stahl et al[3] showed that GlyH-101 is the most potent inhibitor of shark rectal gland CFTR of the inhibitors studied (GlyH-101, $CFTR_{inh}172$ and glibenclamide). To compare the effect of CFTR inhibitors GlyH-101, PPQ-102 and PPQ-27 on chloride secretion by shark rectal gland CFTR, 15 I_{sc} experiments were performed in monolayers of shark rectal gland cells. All inhibitors were added to the apical solution.



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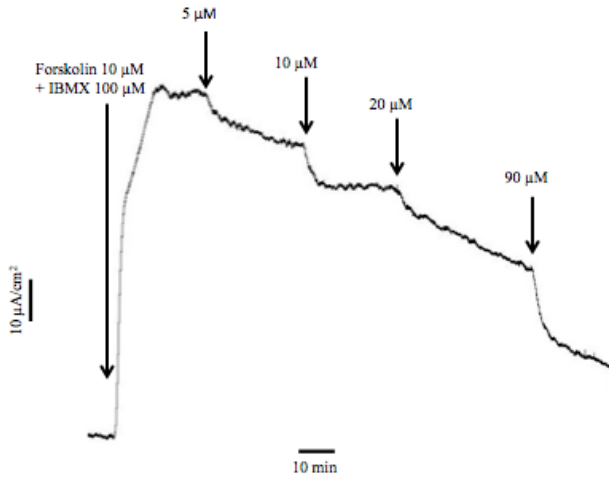

Figure 1. Representative experiments of transepithelial chloride transport as I_{SC} in shark rectal gland primary cultured monolayers. Panel A: CFTR inhibition by GlyH-101 (n=6). Mean % inhibition: 10.6 ± 3.6 at 5 μM, 27.6 ± 5.8 at 10 μM, and 87.3 ± 9.6 at 90 μM. Panel B: CFTR inhibition by PPQ-102 (n=5). Mean % inhibition: 20.6 ± 2.6 at 5 μM, 44.9 ± 3.8 at 10 μM, 68.6 ± 3.6 at 20 μM and 81.5 ± 6.8 at 90 μM. Panel C: CFTR inhibition by PPQ-27 (n=4). Mean % inhibition: 13.1 ± 2.9 at 5 μM, 57.0 ± 17.2 at 10 μM, 60.7 ± 5.5 at 20 μM and 78.3 ± 8.6 at 90 μM.

PPQ-102 is the most potent inhibitor of shark CFTR and is more potent than GlyH-101 at low doses (5 and 10 μM) ($p < 0.05$ by *t*-test). All other differences were not statistically significant. PPQ-102 appears to be the best universal inhibitor of CFTR from multiple species identified to date.

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