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Functional properties of the lysosomal amino acid transporter PQLC2

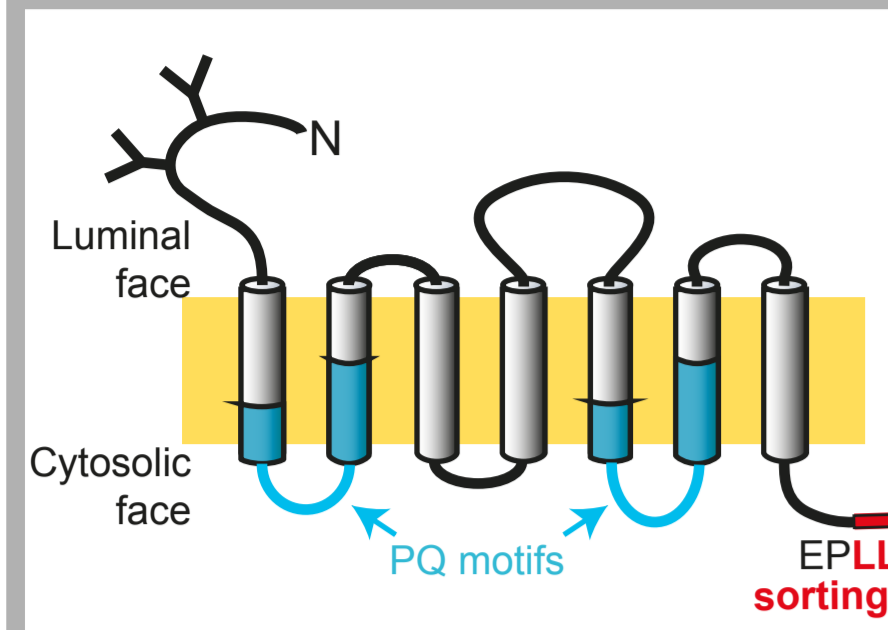


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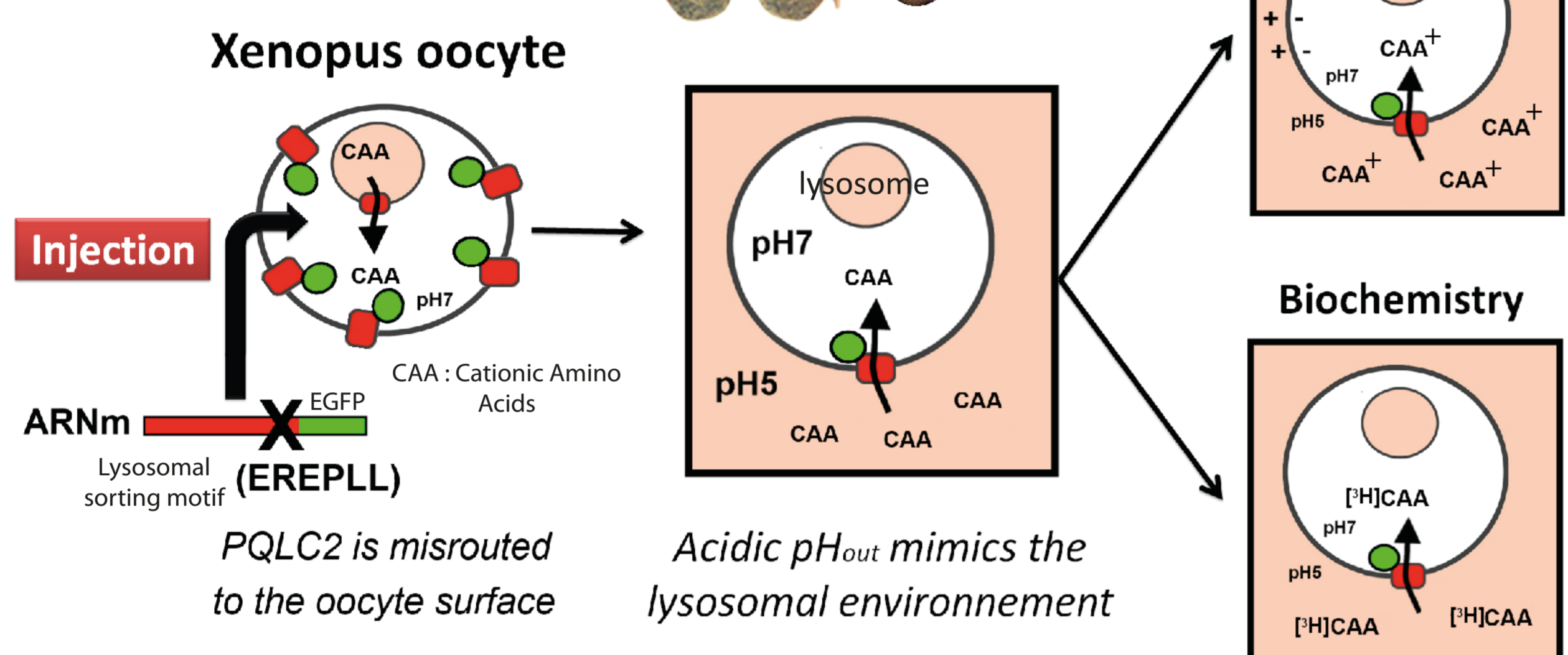
* Xavier Leray is a fellow of the Cystinosis Research Foundation



The transporter PQLC2 exports cationic amino acids (CAA) derived from lysosomal proteolysis to the cytosol. It is also required for drug therapy of cystinosis (Jézégou et al., PNAS 2012; Liu et al., Science 2012). We previously showed that PQLC2 is electrogenic and sensitive to pH. In this new set of experiments, we investigate the transport mechanism of PQLC2 by the use of the two-electrode voltage clamp technique (TEVC) with a construct that misroutes the protein to the plasma membrane of *Xenopus* oocytes.

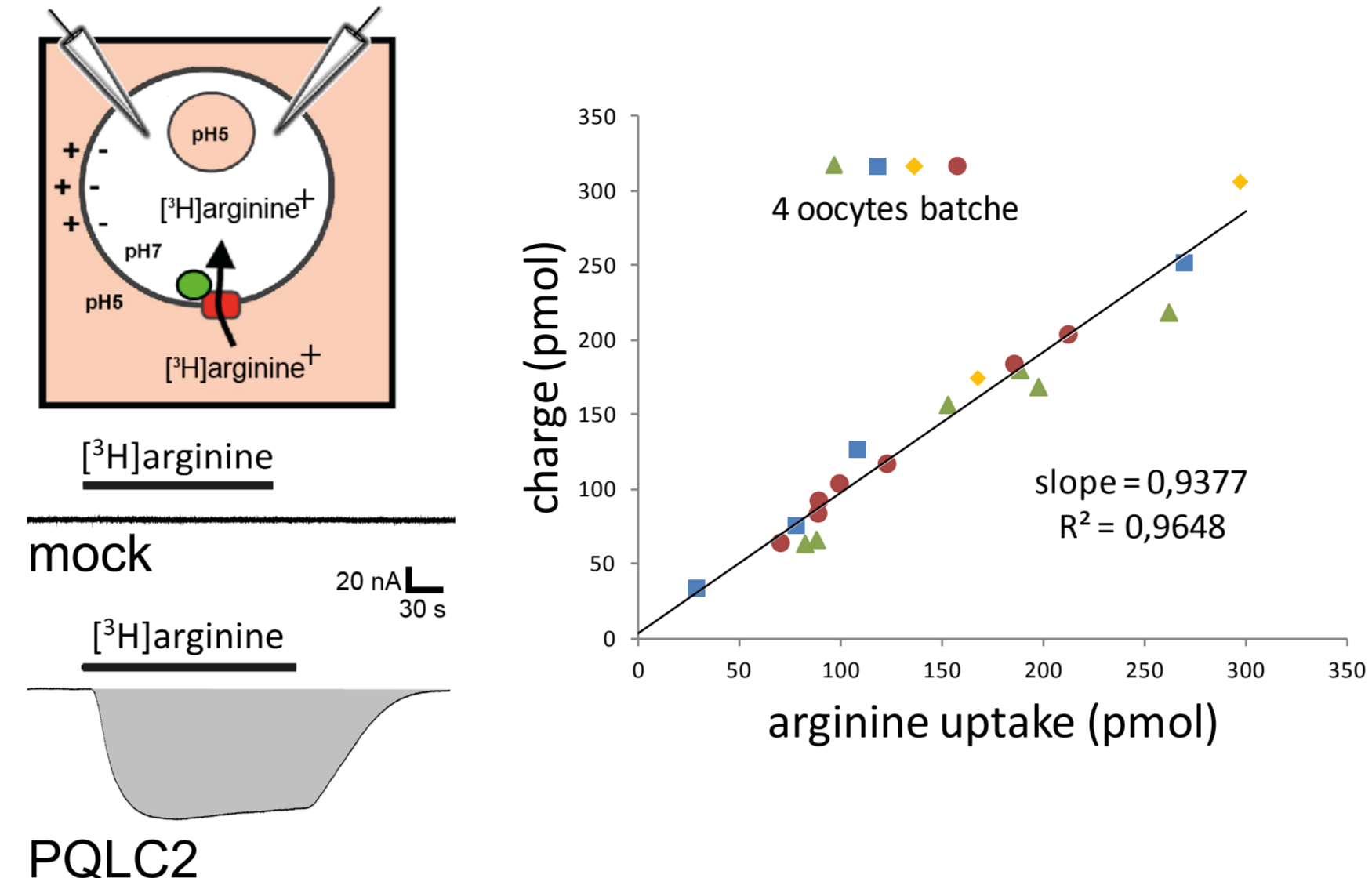
We first show that PQLC2 transports one charge per arginine molecule and is not coupled to protons. It is thus most probably a **uniporter**. In agreement with this mechanism, PQLC2 is very **sensitive to membrane potential**. Finally and surprisingly, PQLC2 appears to **exchange selectively lysosomal arginine for cytosolic cationic amino acids in an electroneutral transport mechanism**. This last property supports a selective role of PQLC2 in mobilizing Arg from lysosomes or in regulating lysosomal Arg level.

1. Strategy to study PQLC2

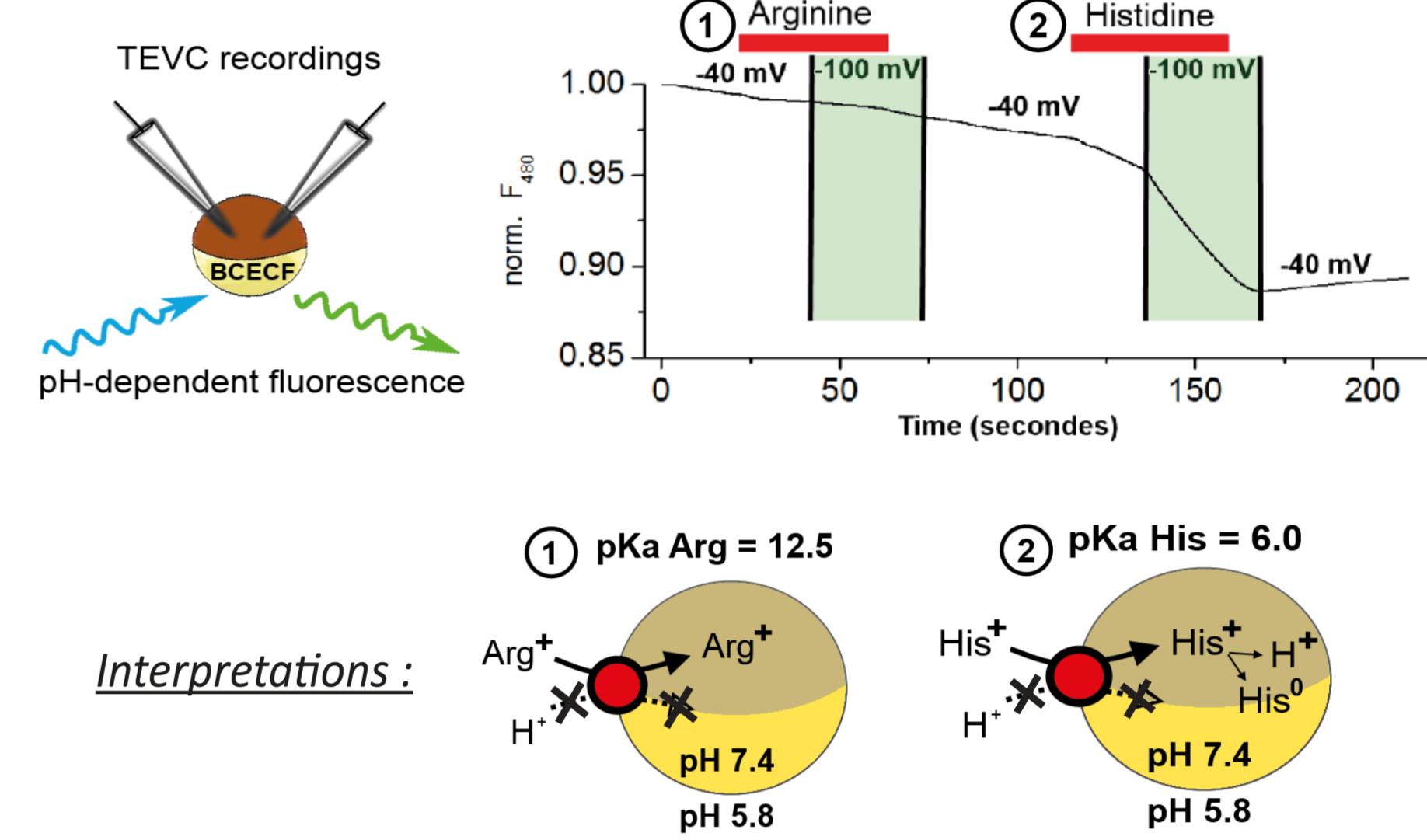


2. PQLC2 is most probably a uniporter

A. PQLC2 transports one charge per arginine



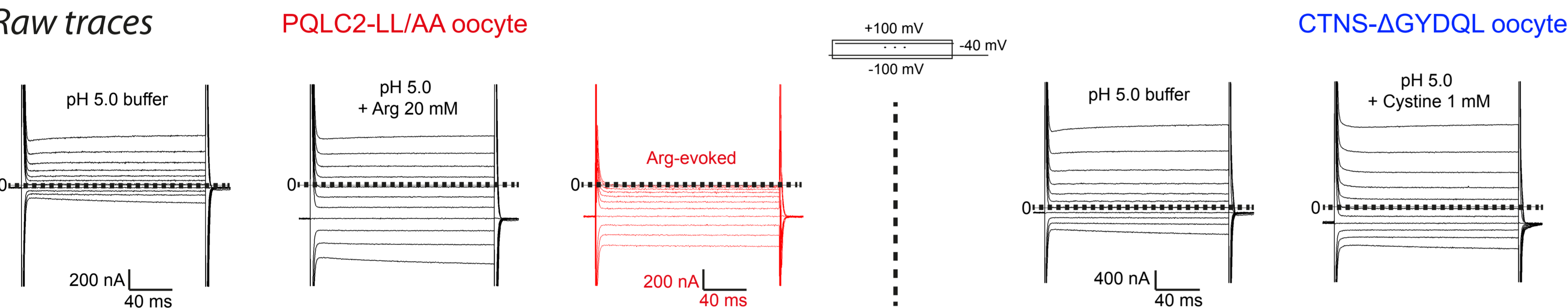
B. PQLC2 does not cotransport protons



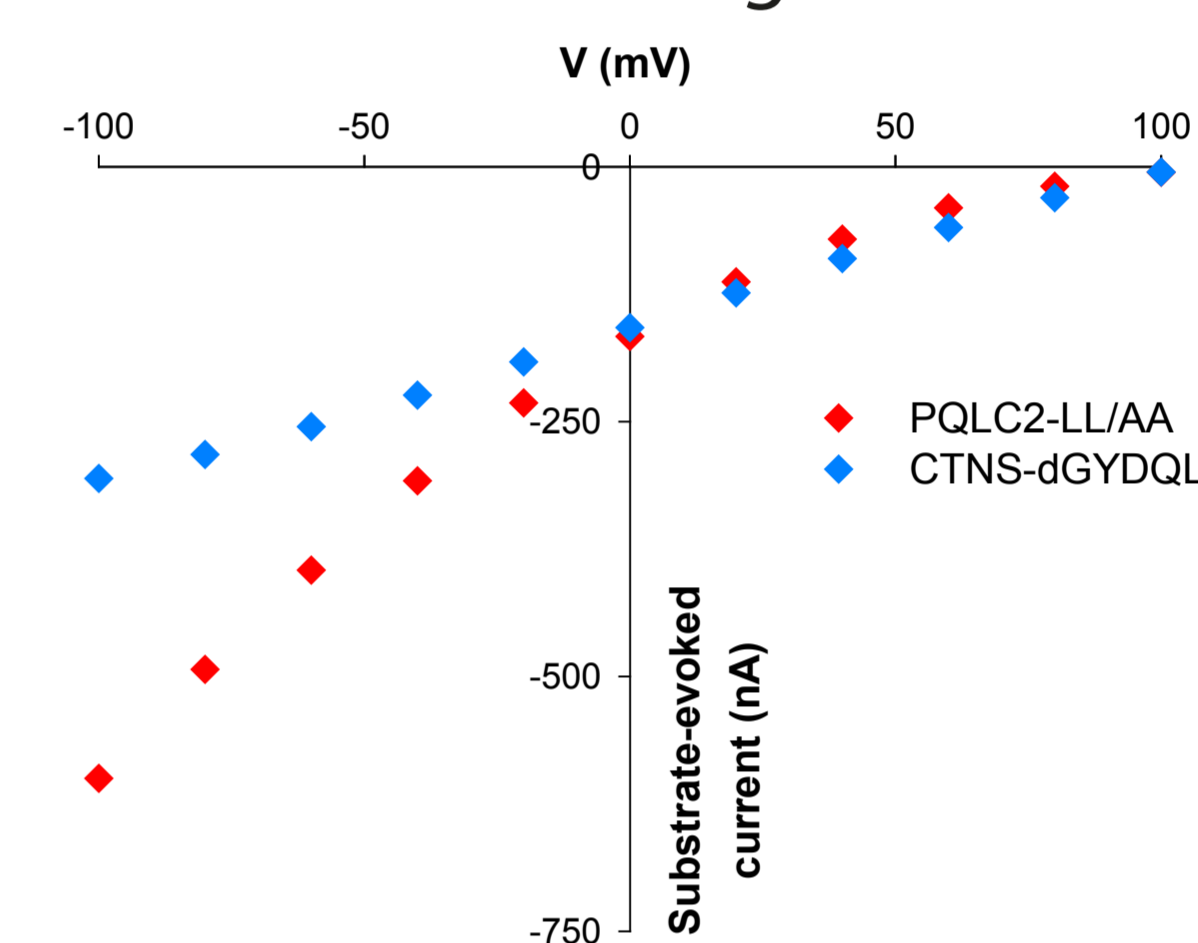
3. PQLC2 transport activity is strongly modulated by the membrane potential

Comparison of current-voltage relationships of CTNS, a lysosomal H⁺-cystine symporter, and PQLC2

A. Raw traces



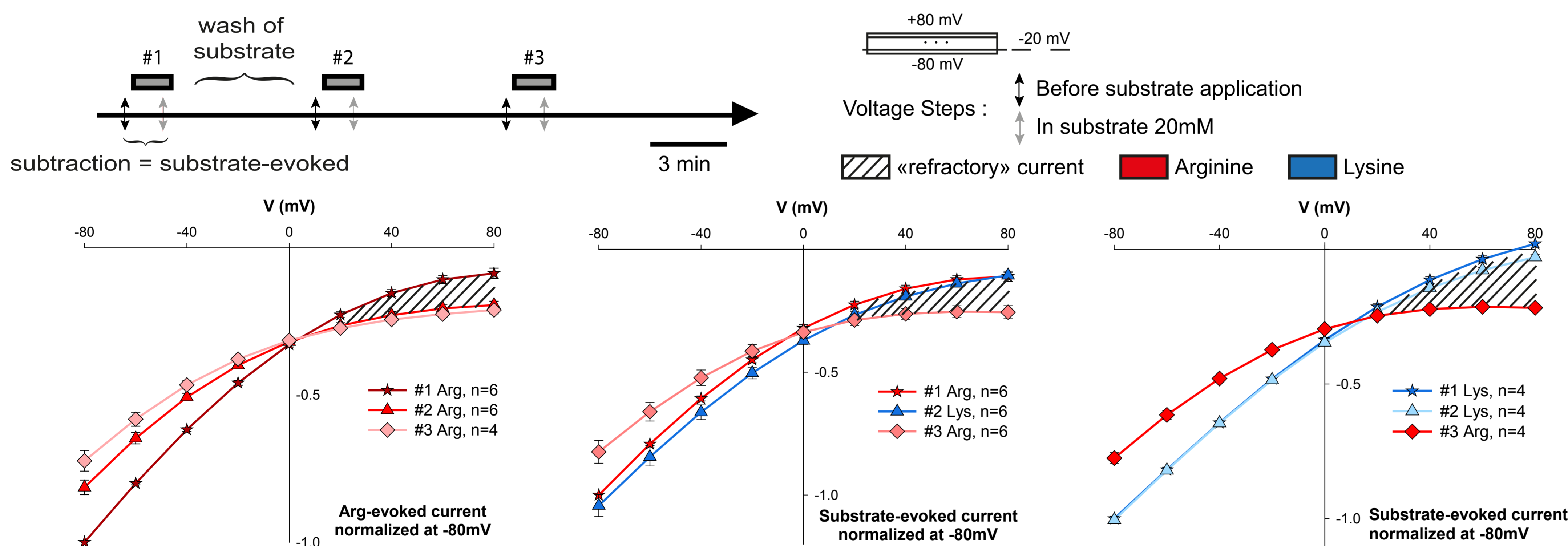
B. Current-voltage curves



4. In the presence of intracellular CAA, PQLC2 can shift from an efflux mode to an electroneutral exchange mode

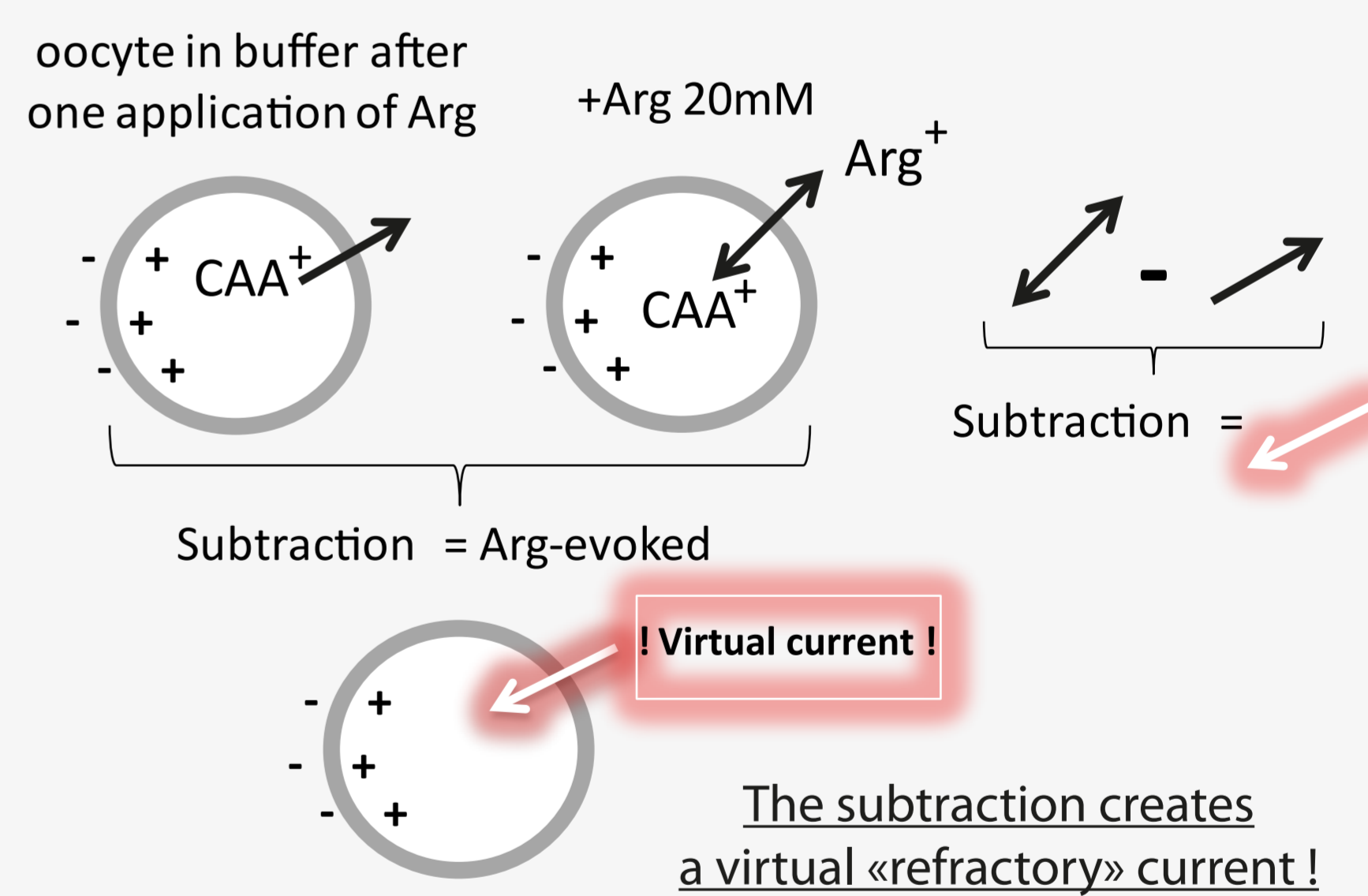
A. Prior CAA loading (#1) induces a «refractory» current at positive potentials (shaded area) upon subsequent application of Arg, but not Lys

In contrast with the uniporter model, membrane depolarisation does not fully suppress the Arg-evoked current. Instead, a «refractory» current persisted at positive potential and was strongly increased by prior CAA application. Surprisingly, this effect was selectively observed with extracellular (lysosomal) Arg.

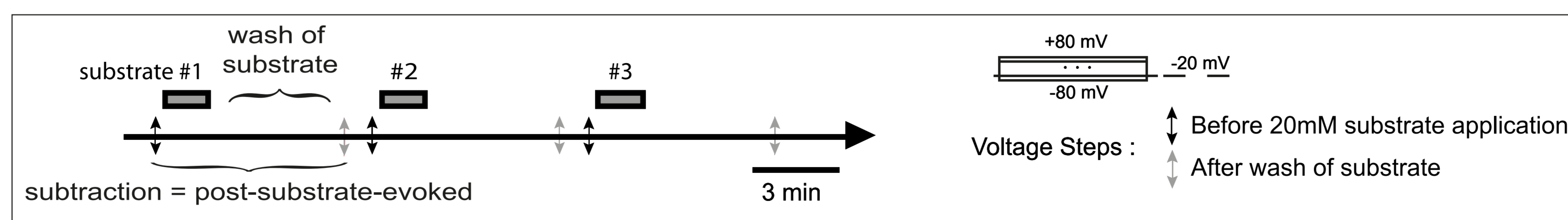


Model proposed to explain the «refractory» current

After prior CAA loading of PQLC2 oocytes, at positive potential, the efflux of intracellular Arg is transformed into an electroneutral exchange.

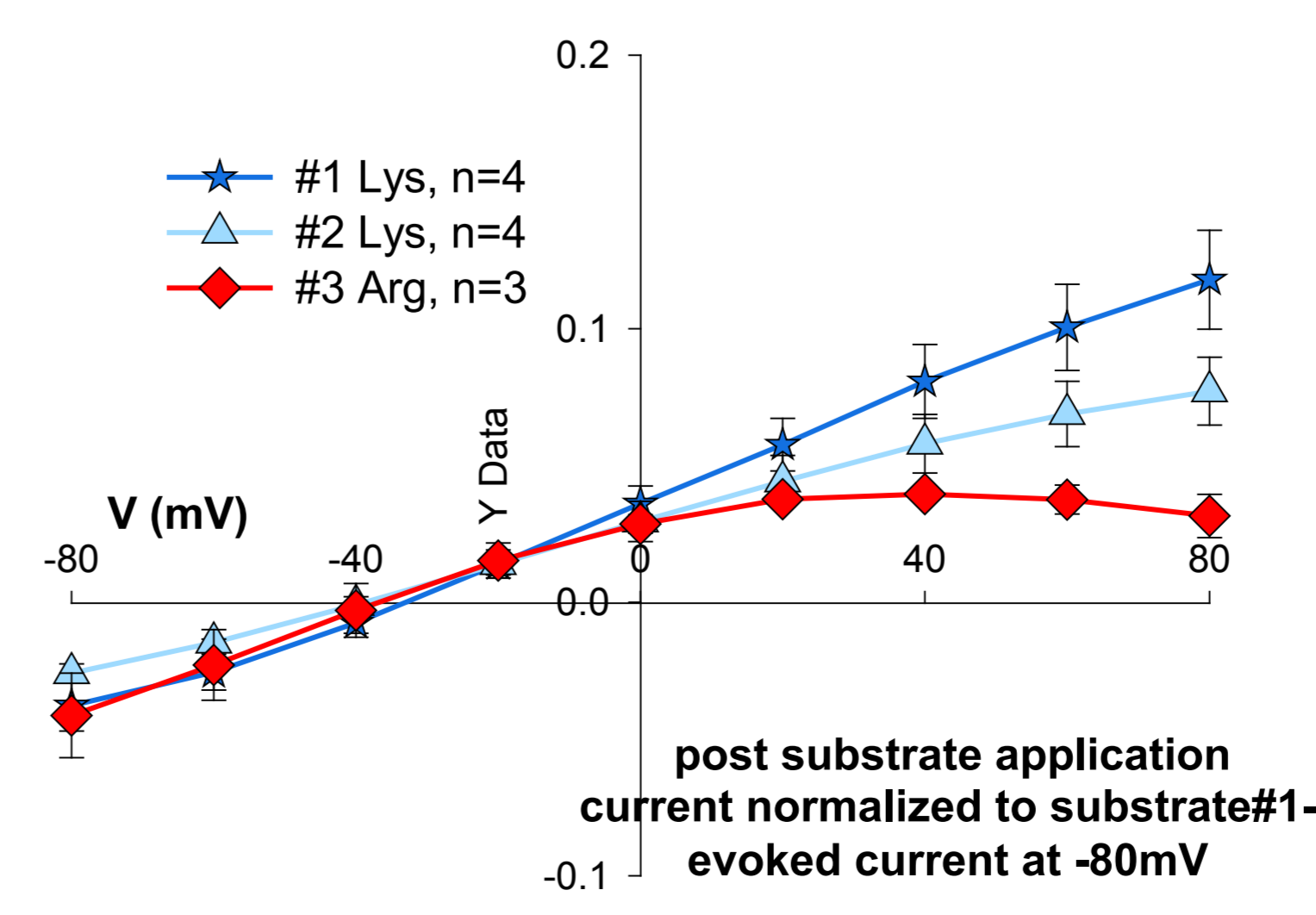
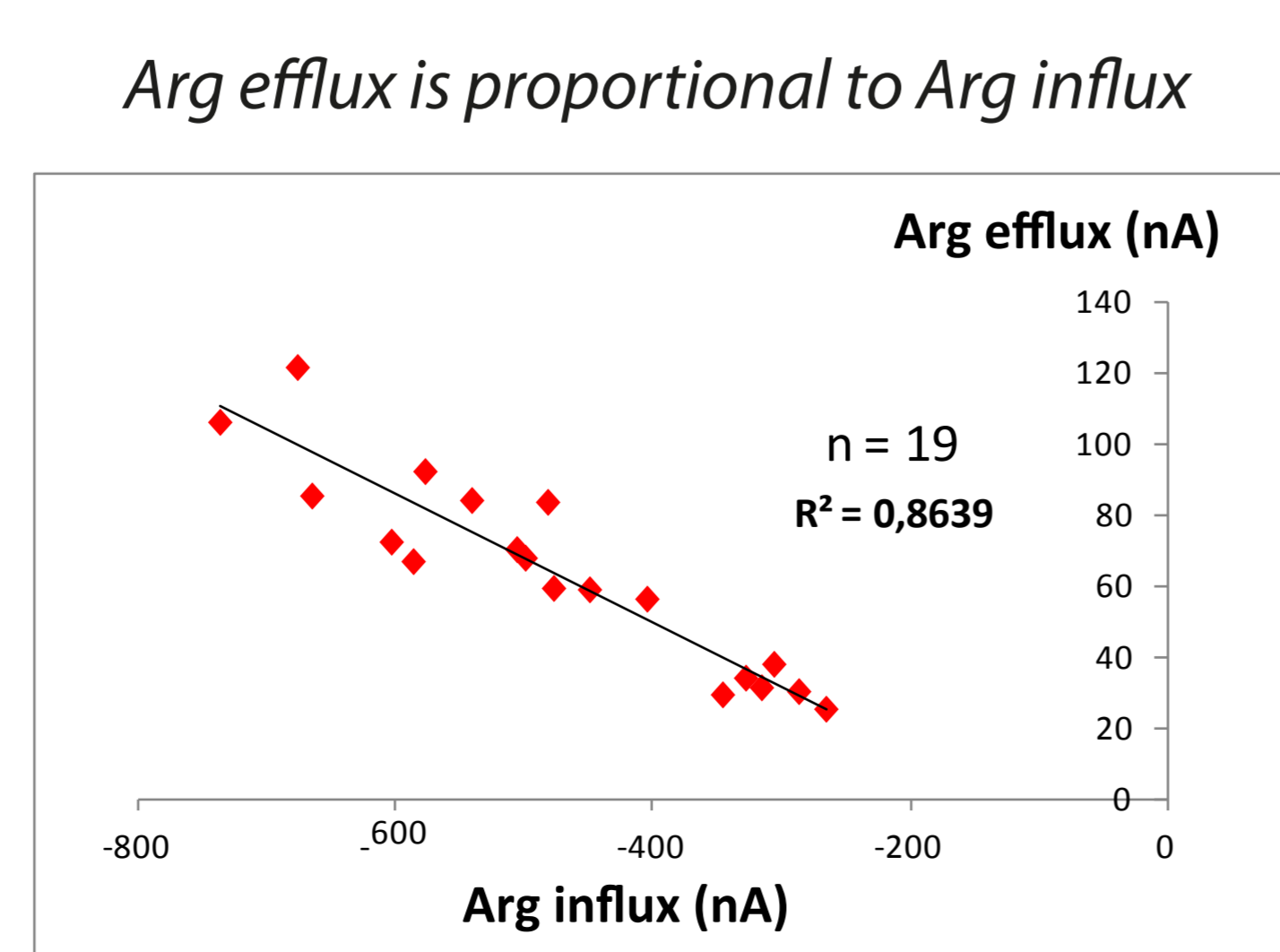
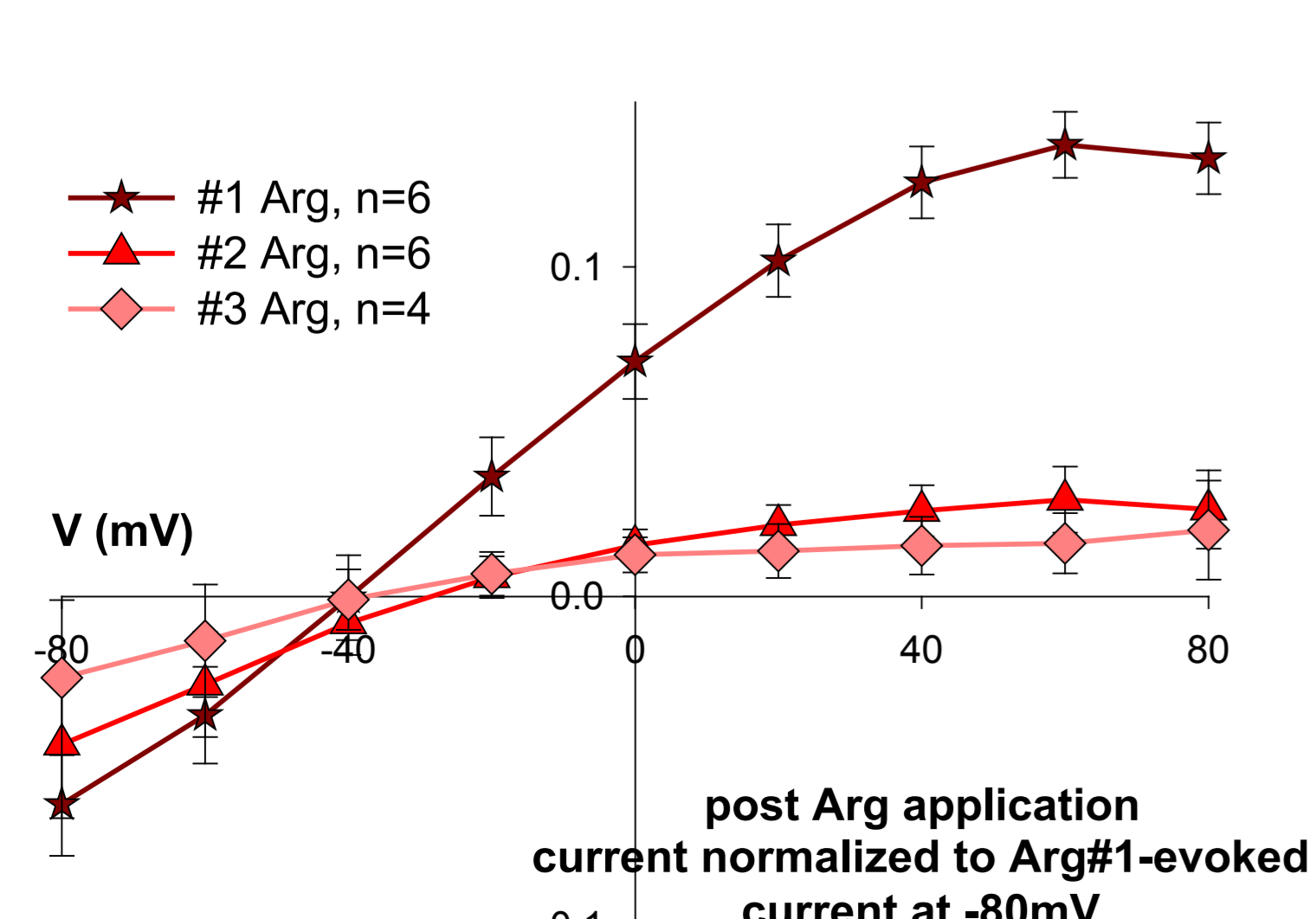


B. Preliminary test of the model: CAA efflux after oocyte loading



Arg-Arg-Arg sequence

Lys-Lys-Arg sequence



Both Arg and Lys are exported... but only Arg is exchanged!

