


Molecular mechanisms of ABC transporters and beyond

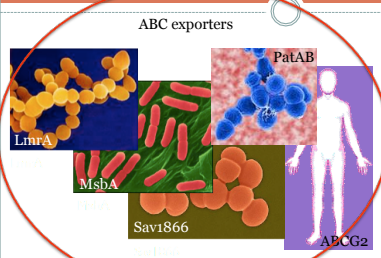


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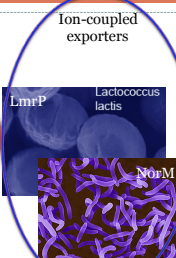
Brussels 2012

Our studies on molecular mechanisms of multidrug transporters


ABC exporters



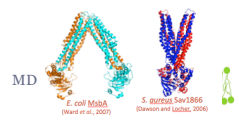
Ion-coupled exporters



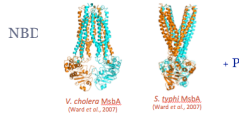
Initial studies on mechanisms of multidrug transporters



MD



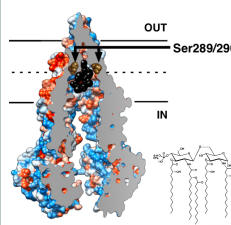
NBE



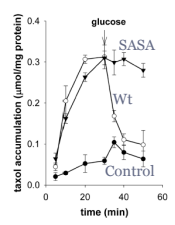
+ Pi

Van Veen *et al.* PNAS 93 (1996); Nature 391 (1998)

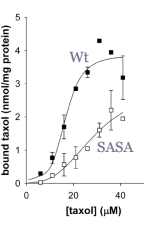
Conservation of function



taxol accumulation (μmol/mg protein)




bound taxol (fmol/mg protein)

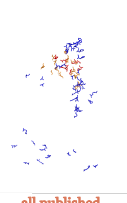


Reuter *et al.* J Biol Chem 278 (2003); Woebking *et al.* Biochemistry 47 (2008)


Location of drug binding in ABCB1?




ABCB1



all published mutations



change-in-specificity mutations

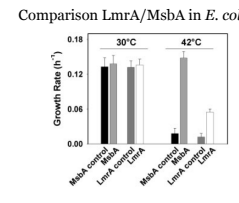


cysteine residues reactive with MTS-drug

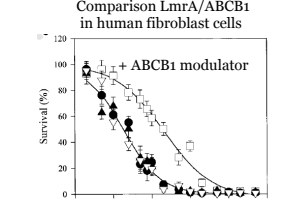
Loo and Clarke, various JBC papers ; Shilling *et al.* TIPS 27: 195-203 (2006)

Conservation of function between LmrA, MsbA, and human ABCB1

Comparison LmrA/MsbA in *E. coli*

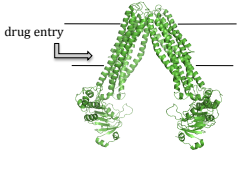


Comparison LmrA/ABCB1 in human fibroblast cells




Reuter *et al.* JBC 278: 35139 (2003); Van Veen *et al.* Nature 391: 291-5 (1998)

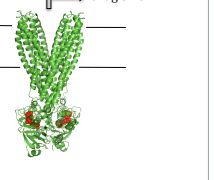
Model for alternating access



Nucleotide-free "inward-facing"

Mg-ATP

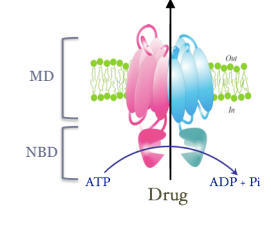


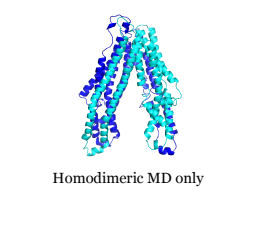


ATP-bound "outward-facing"

Martin *et al.* Biochemistry 39: 11901 (2000); van Veen *et al.* EMBO J 19: 2503 (2000)

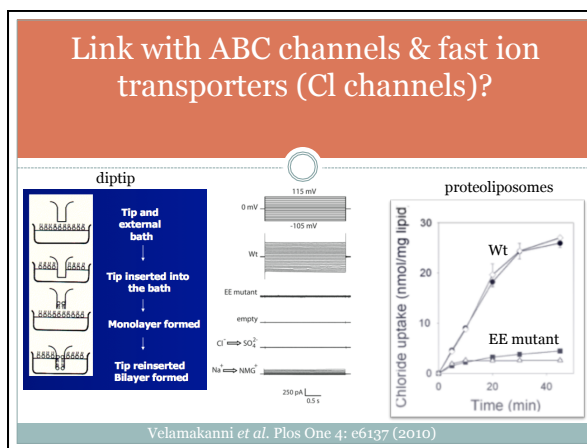
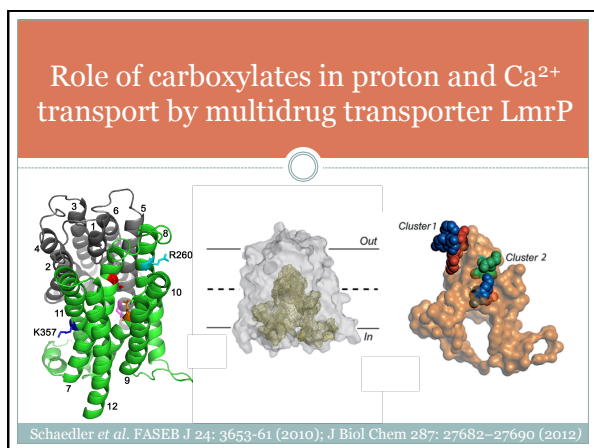
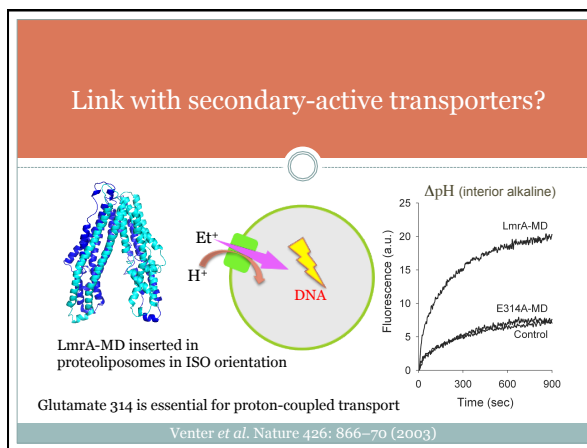
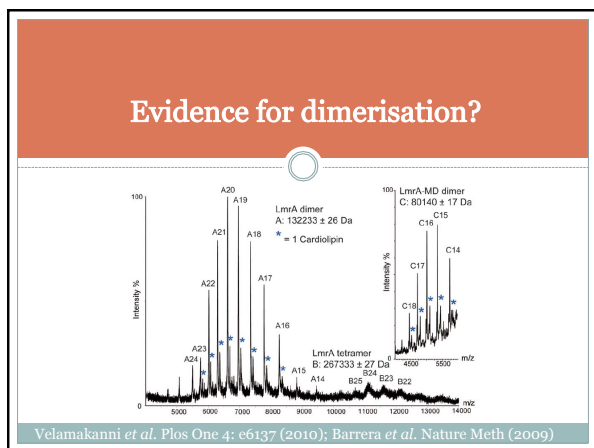
Is this all there is to be discovered about mechanisms?

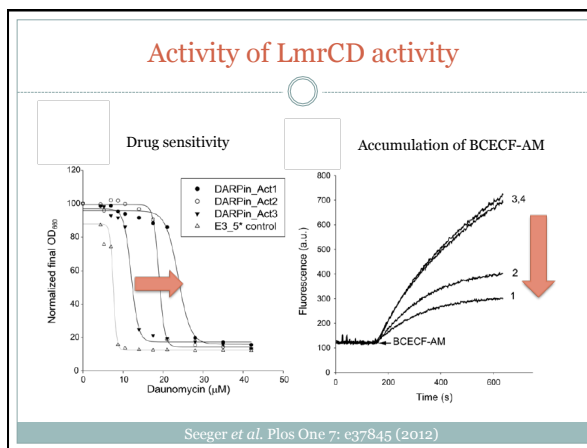
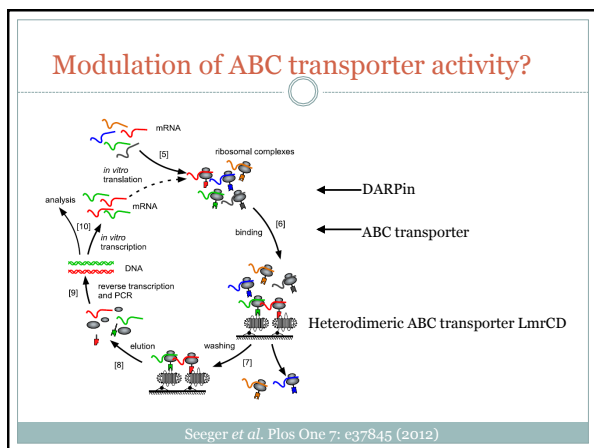




Homodimeric MD only

Venter *et al.* Nature 426: 866-70 (2003)





Acknowledgement

Current & former members of Van Veen lab

| | |
|--------------------|----------------------|
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