

# Characterizing the chloride translocation pathway in the CFTR channel

Tamás Hegedűs

tamas@hegelab.org

MTA-SE Molecular Biophysics Research Group  
Dept. Biophysics and Radiation Biology, Semmelweis University

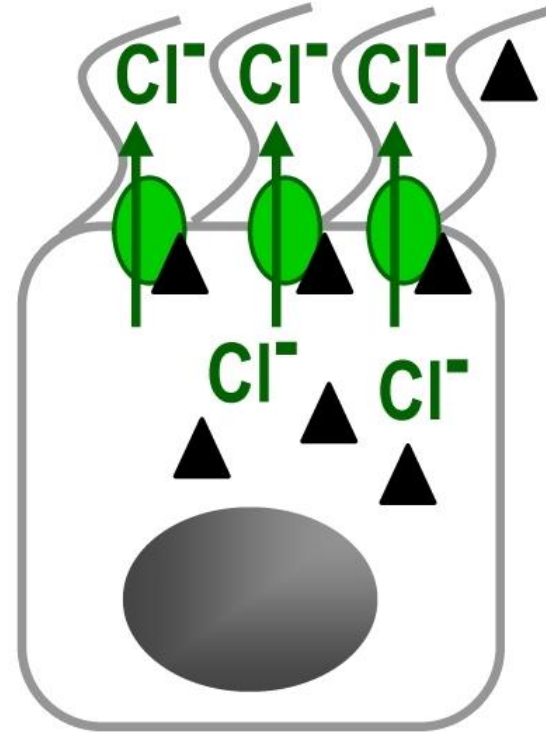
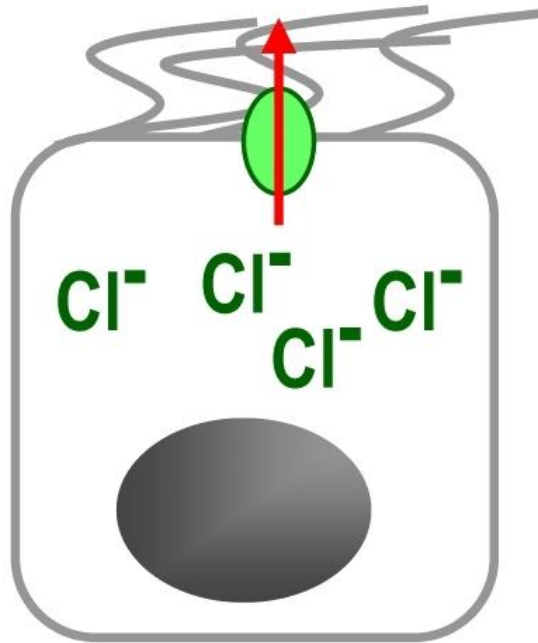


# Cystic Fibrosis (CF)

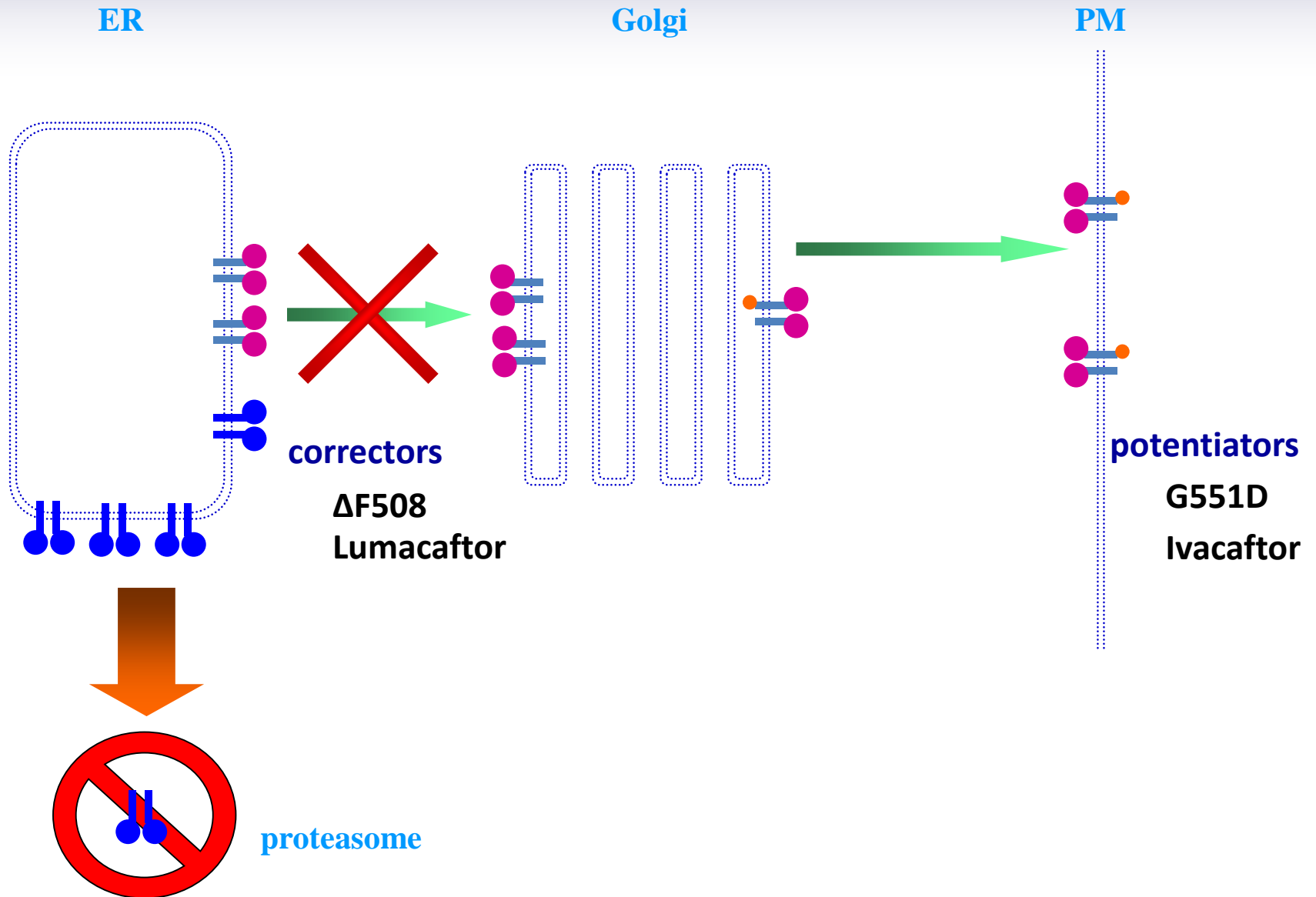
- **monogenic disease** (~1:2,500)
- **high mortality and morbidity**
- **affected water and salt homeostasis**
- **over 2,000 mutations are known**
- **ΔF508 is present in over 80% of patients**

# Cystic fibrosis

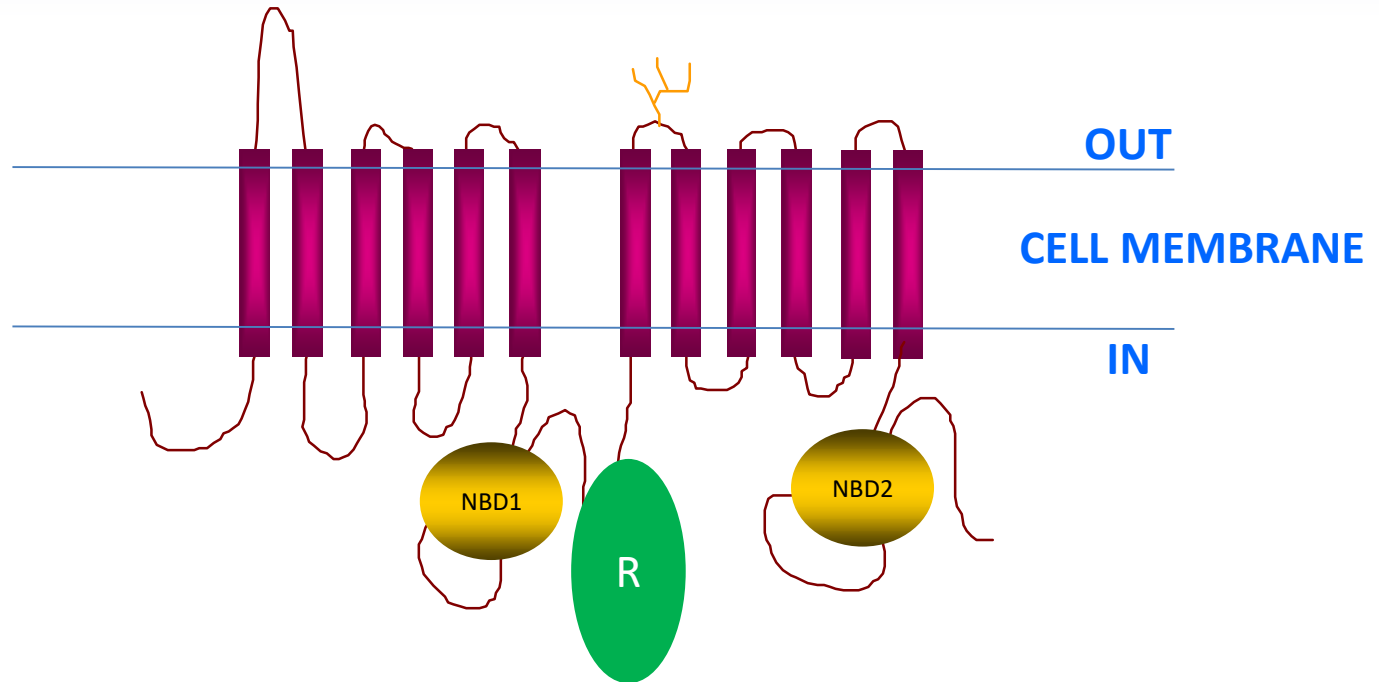
CFTR (cystic fibrosis transmembrane conductance regulator)



# Maturation of the CFTR protein



# CFTR ABCC7 (ATP Binding Cassette)



# *In silico* study of NBD1 destabilization

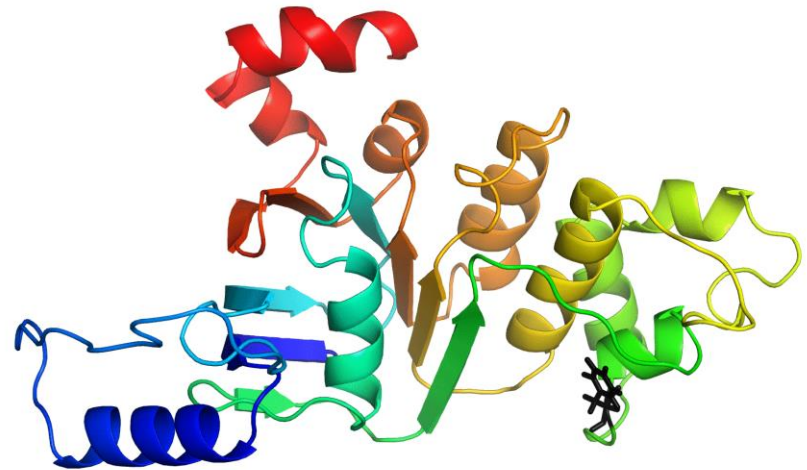
*Experiments: Gergely Lukács, McGill, Montreal*

## Molecular dynamics (MD) simulations

- WT and mutants
- 100-100 ns
- *all-atom force field*

## Analysis of motions in NBD1

- correlations in motions (pairwise)
- building a graph
- analysis of the graph



# Distance Correlation Coefficient

G. J. Szekely *et al.* (2007), *Annals of Statistics*, 35 (6): 2769–2794.

## Nodes:

amino acids

## Edges:

if correlation exists

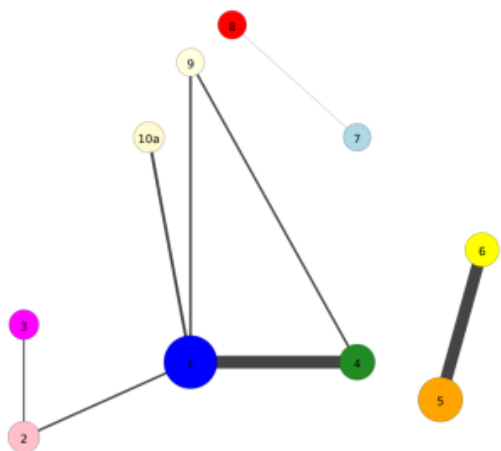
## Nodes2:

communities

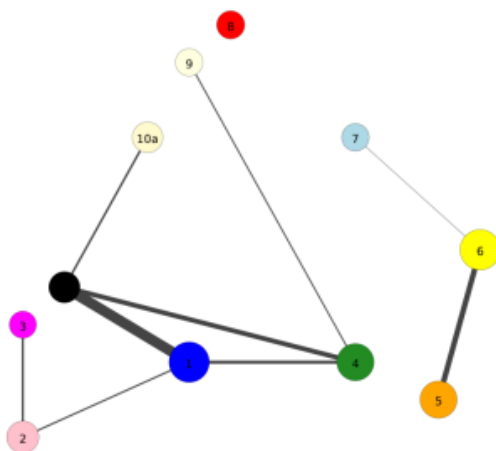
## Edges2:

sum of edges between residues if DiCC>0.7

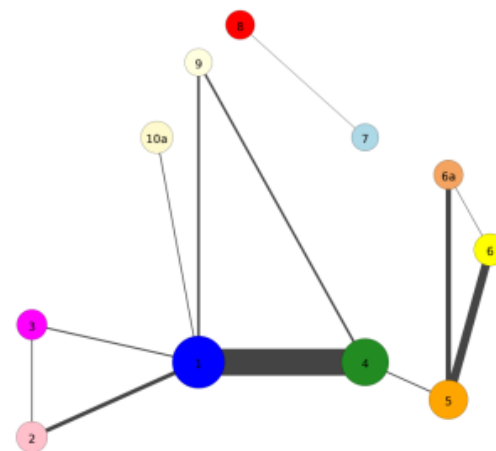
WT 1S



$\Delta$ F508 1S

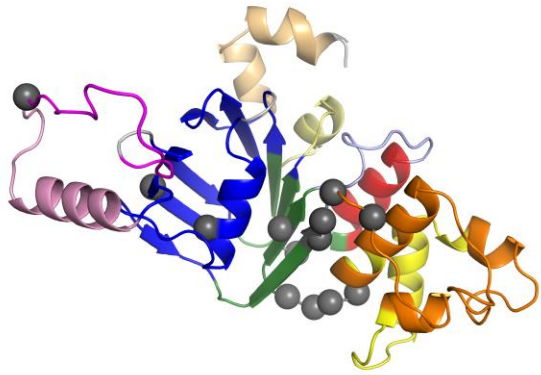


$\Delta$ F508 3S

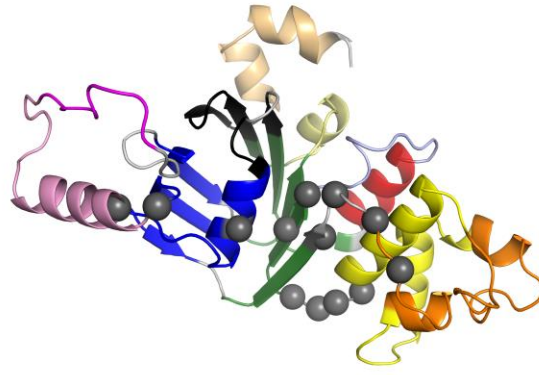


# Rescue by effecting dynamic coupling

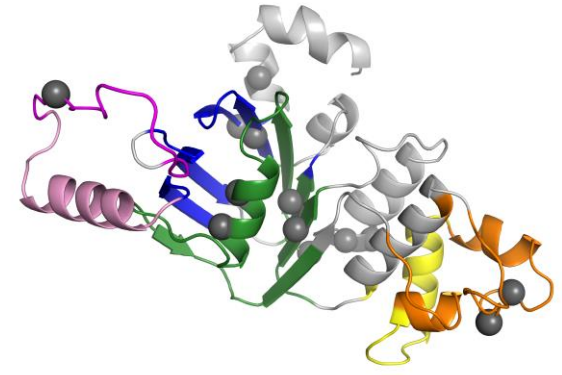
WT 1S



$\Delta$ F508 1S



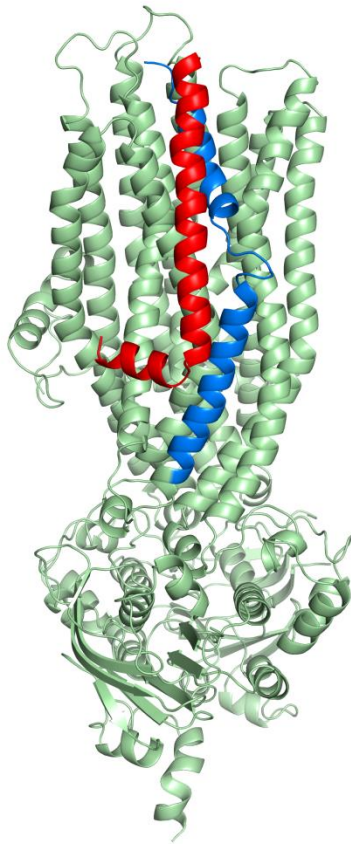
$\Delta$ F508 3S



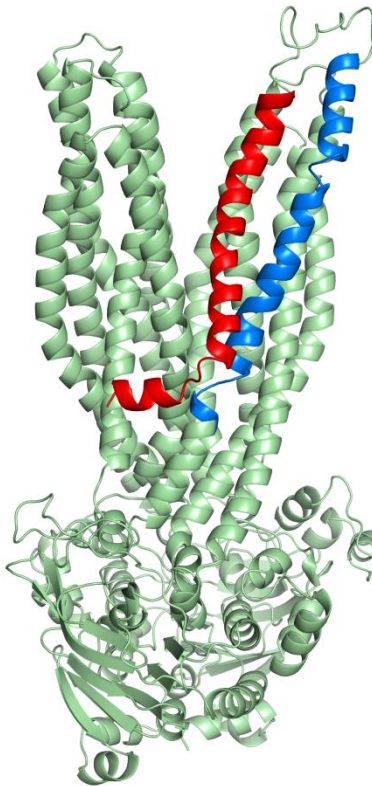


# Full-length CFTR structures

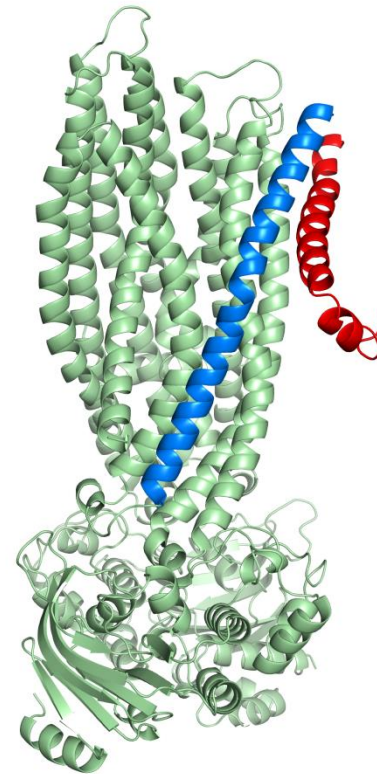
## Cryo-EM revolution



Zhang et al. (2017) Cell 170: 483-491.e8  
PDBID:5W81



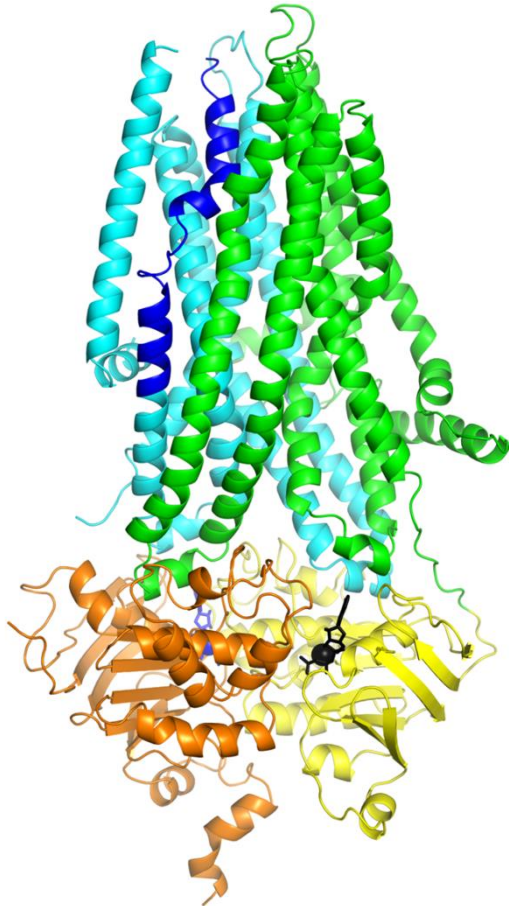
Bob Ford  
University of Manchester, UK



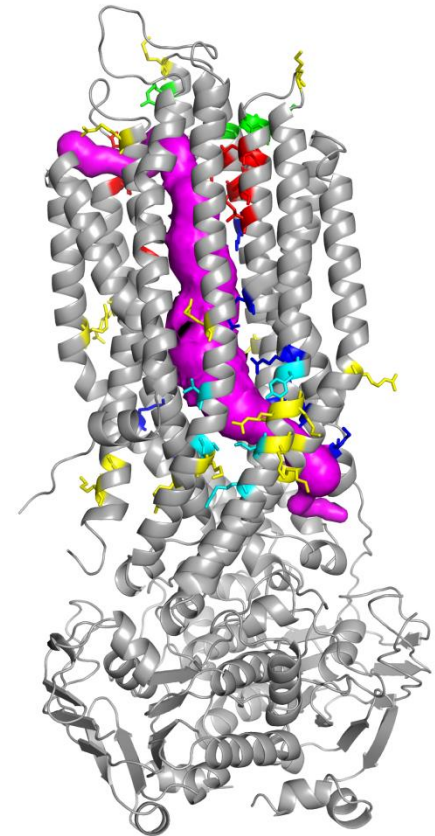
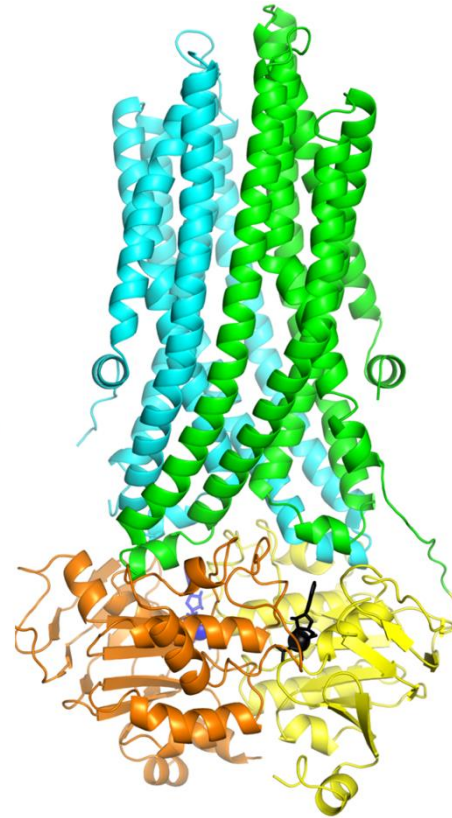
J. Fay, Jack Riordan  
UNC, Chapel Hill, USA

# Structural anomalies

zfCFTR

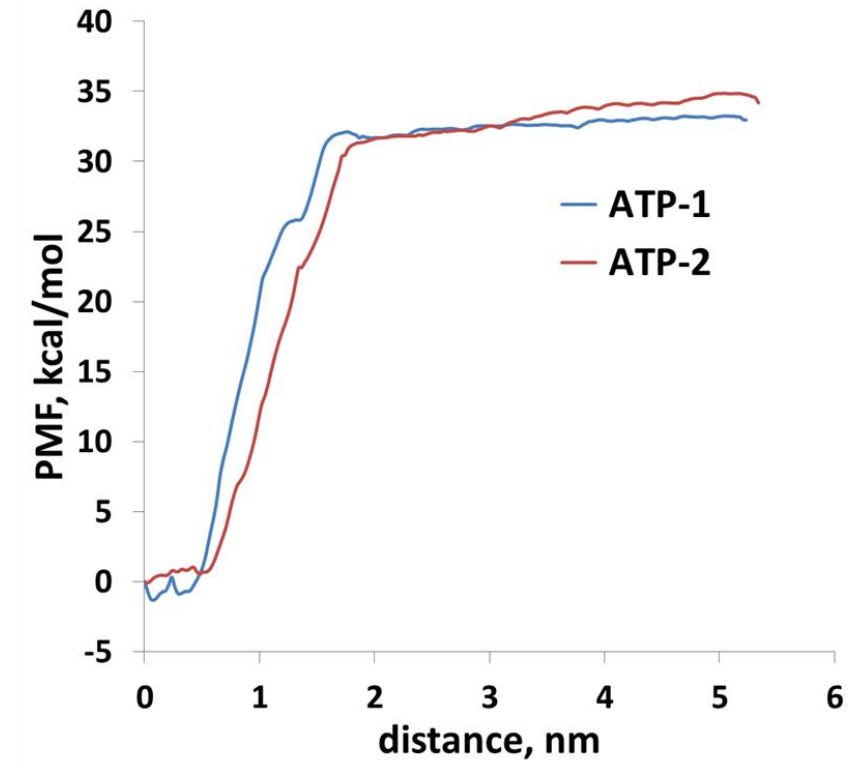
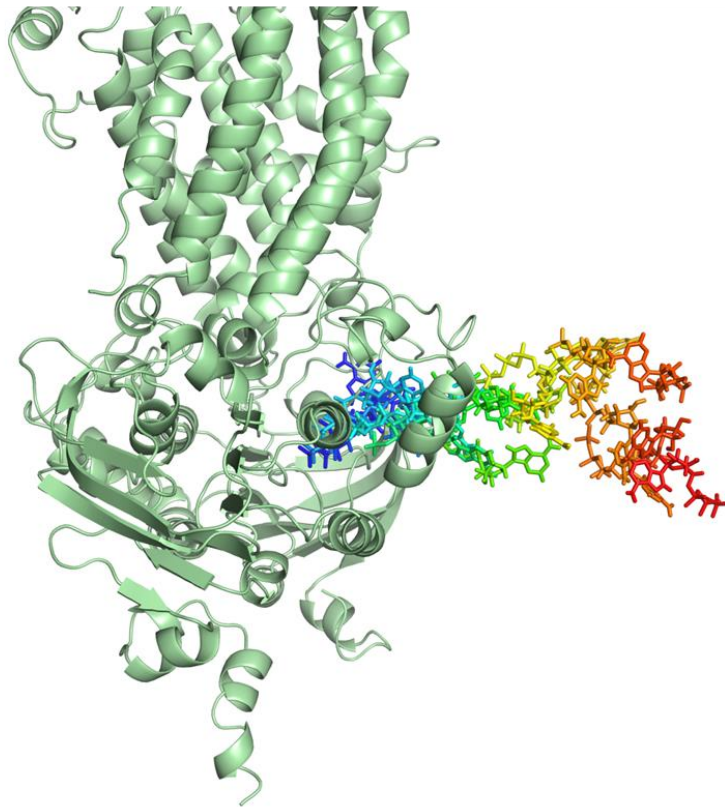


CFTR<sub>MCJD</sub>



# Binding energies at both ATP sites are the same contradicts with experiments

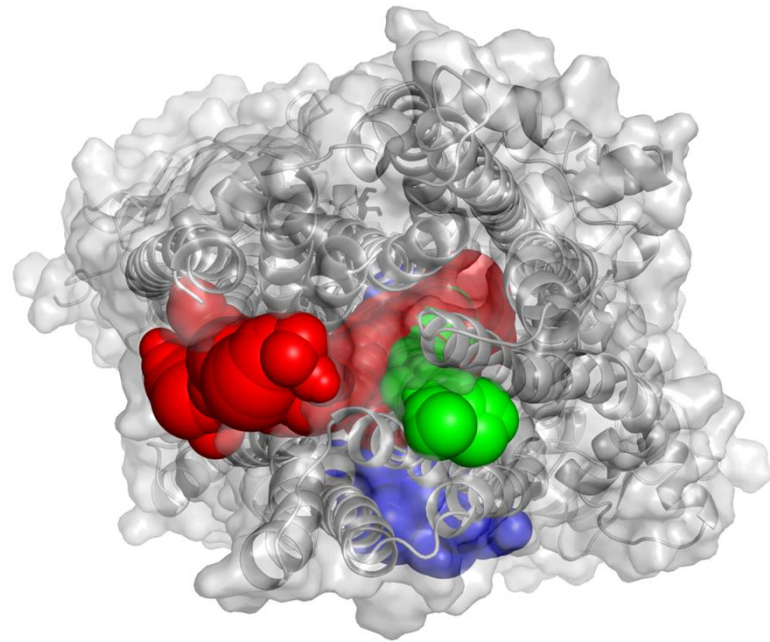
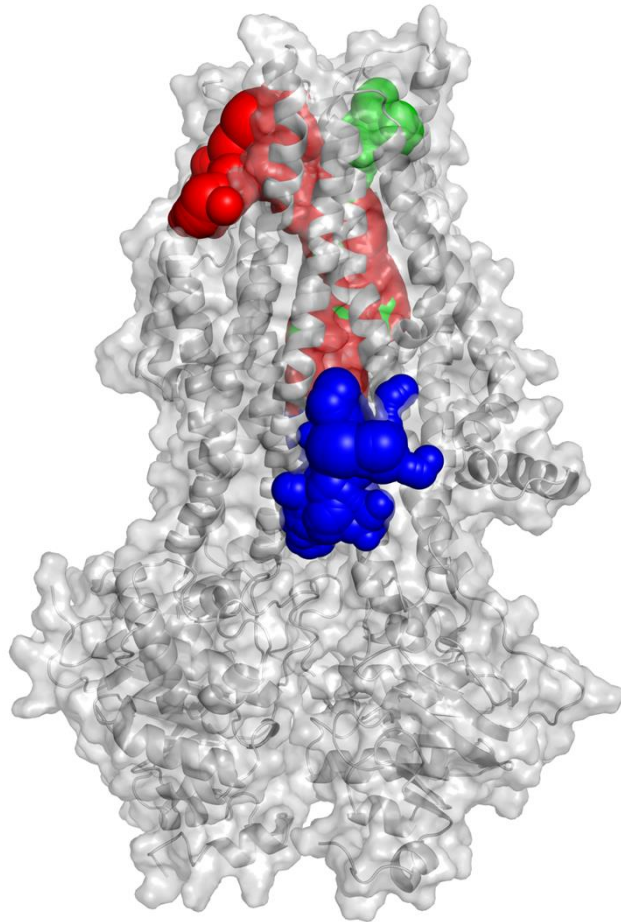
G. Paragi *et al.*, Szeged





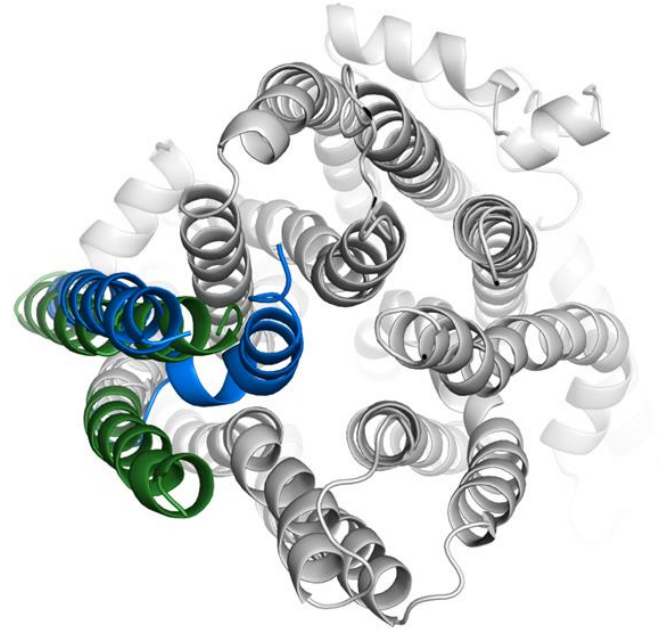
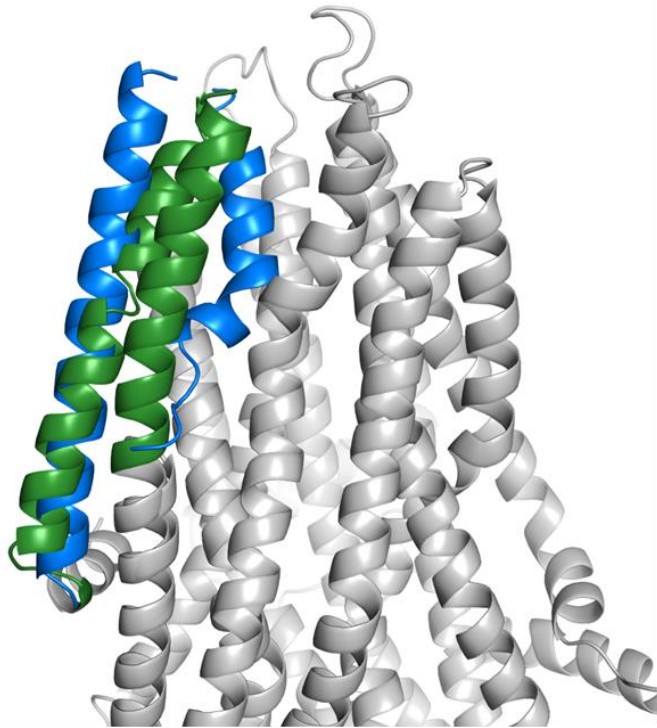
# Where is the chloride channel?

using: MD, Caver



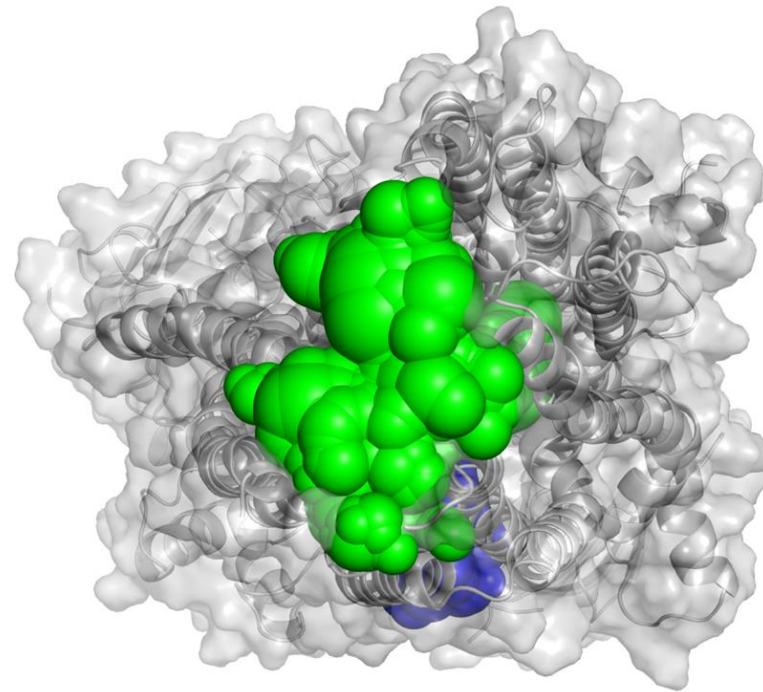
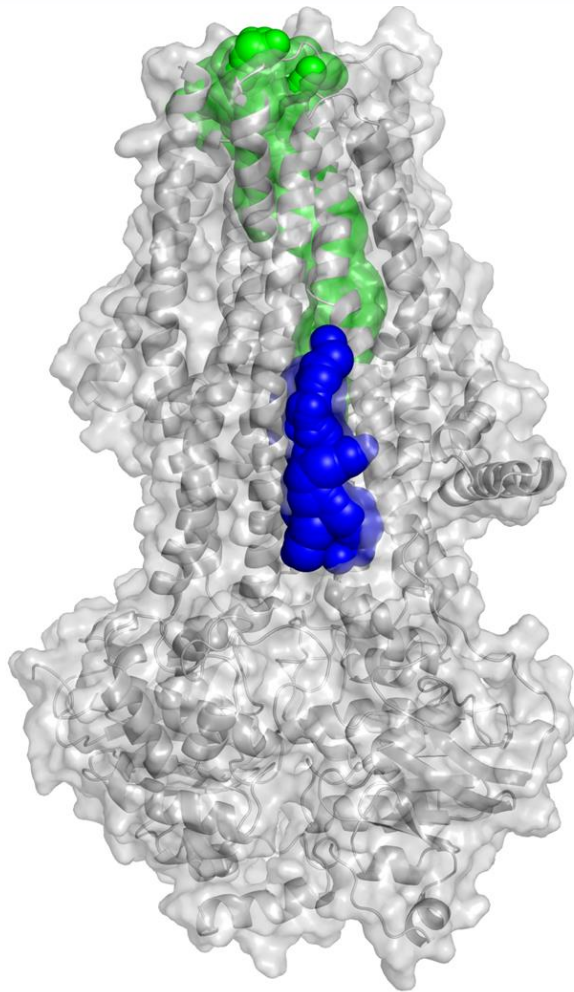
# Remodeling TM8 based on ABCC1/MRP1

PDBID: 6BHU



# Where is the chloride channel?

using: MD, Caver



# Utilization of GPUs – GROMACS 2018

## **GTX 1080Ti vs. Tesla K20, K40 vs. Radeon**

- OpenCL exposes limitations to GROMACS performance

## **CPU/GPU utilization**

- earlier GROMACS versions: only PP on GPU
- GROMACS 2018: both PP and PME on GPU (with some limitations)

# Summary

- **Experiments and simulations revealed the affect of mutations and the mechanism of rescue that lead to rational drug design to correct NBD1**
- **We aim to generate a valid full length structure, describe the chloride passage to facilitate studies of the full length protein**



# Acknowledgement

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[www.hegelab.org](http://www.hegelab.org)

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**Thanks for your attention!**