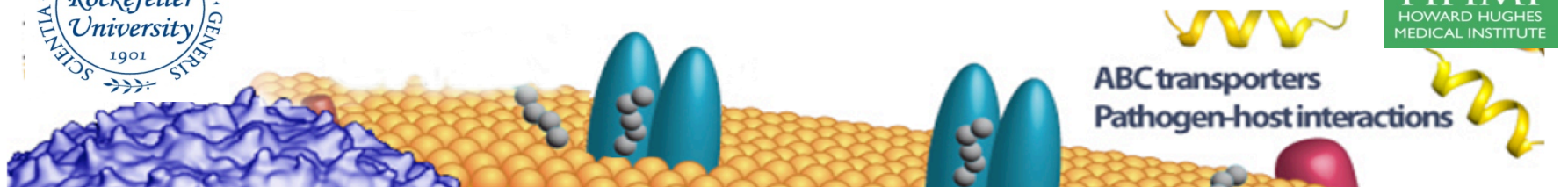# CFTR, the odd ABC transporter responsible for cystic fibrosis
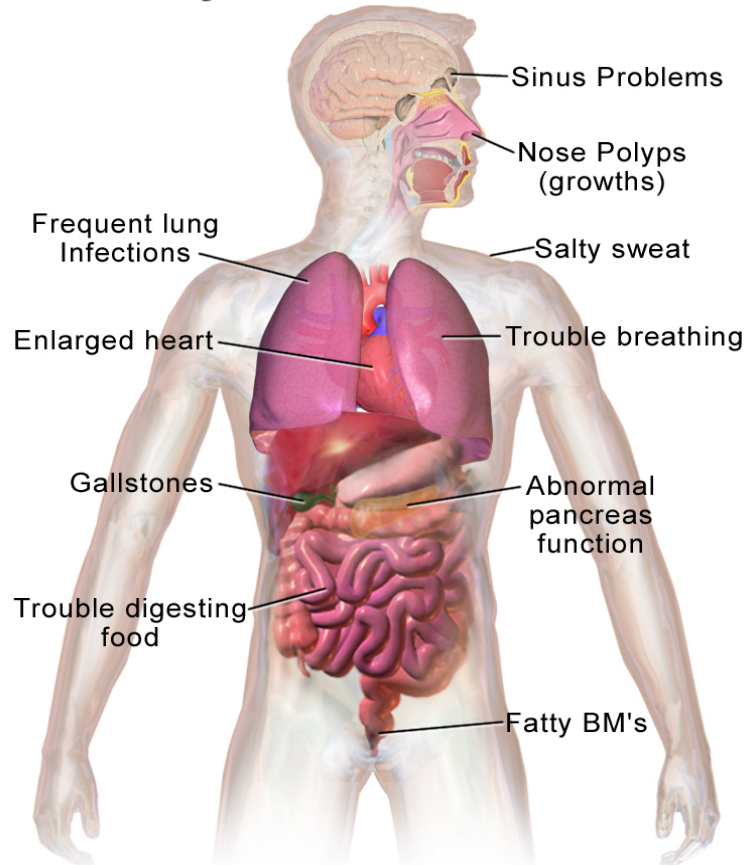
Jue Chen

Laboratory of Membrane Biology and Biophysics
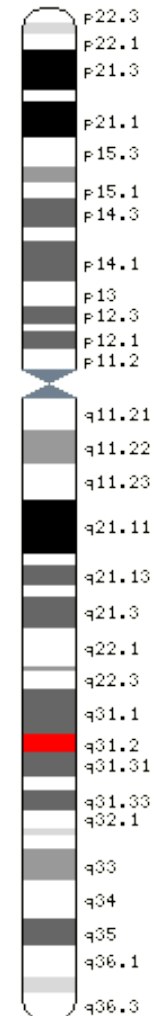
Cystic Fibrosis is a genetic disease
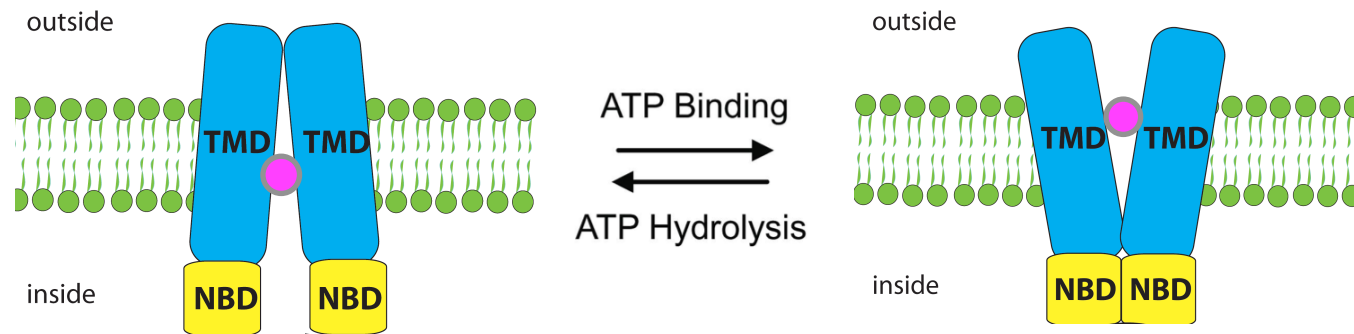

Health Problems with Cystic Fibrosis

- Sinus Problems
- Nose Polyps (growths)
- Frequent lung Infections
- Salty sweat
- Enlarged heart
- Trouble breathing
- Gallstones
- Abnormal pancreas function
- Trouble digesting food
- Fatty BM's

Picture credit: Bruce Blaus
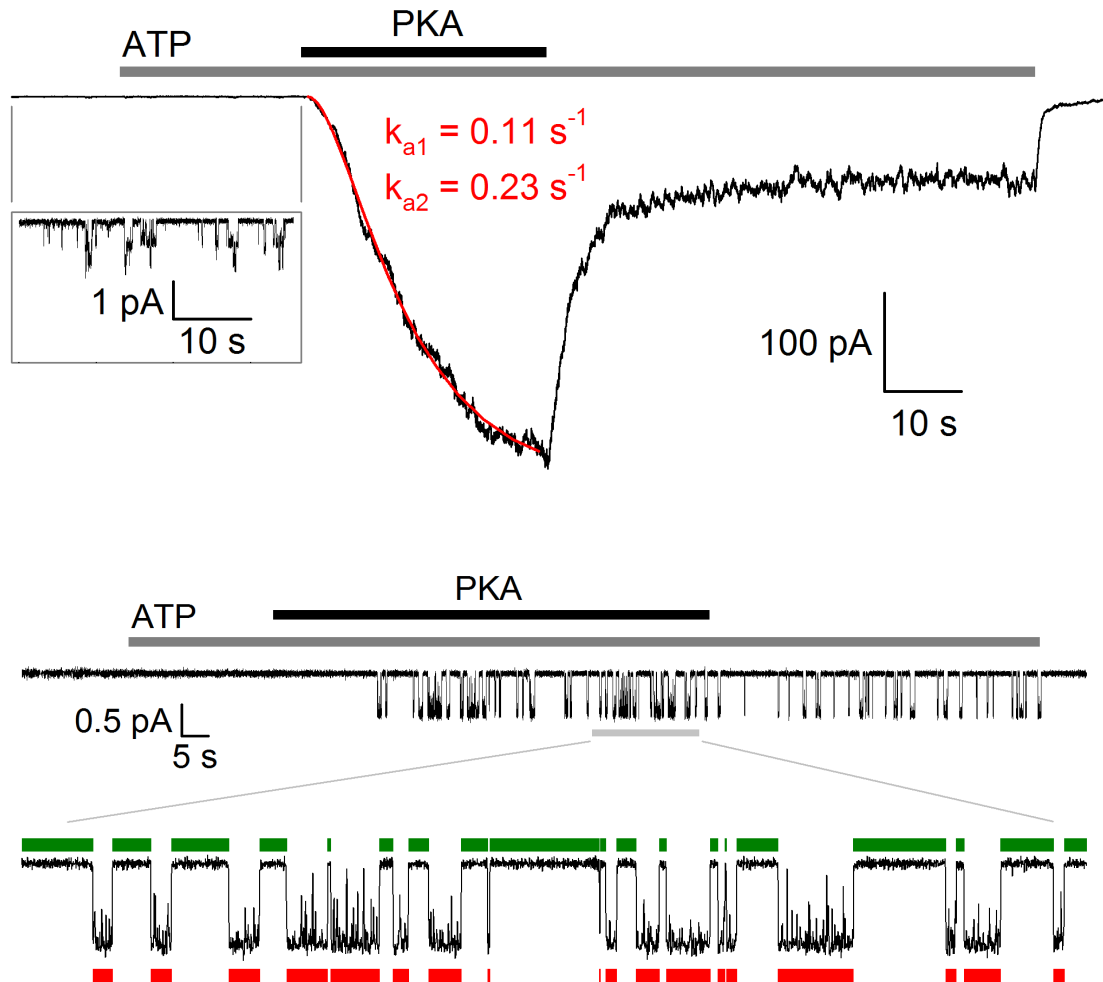
Chromosome 7

cftr

CFTR, an odd ABC transporter

Typical ABC transporters: ATP-powered pumps

Phosphorylation gates the CFTR channel

ATP

PKA

$k_{a1} = 0.11$ s^{-1}

$k_{a2} = 0.23$ s^{-1}

1 pA

10 s

100 pA
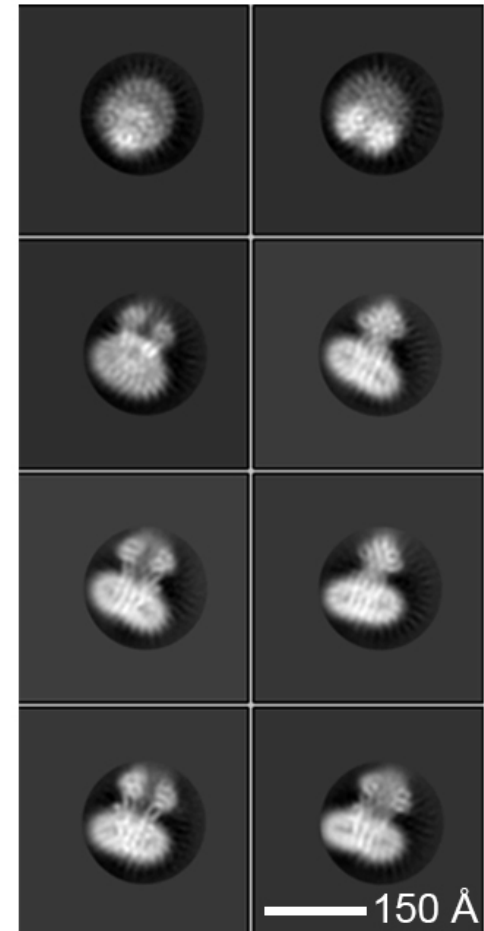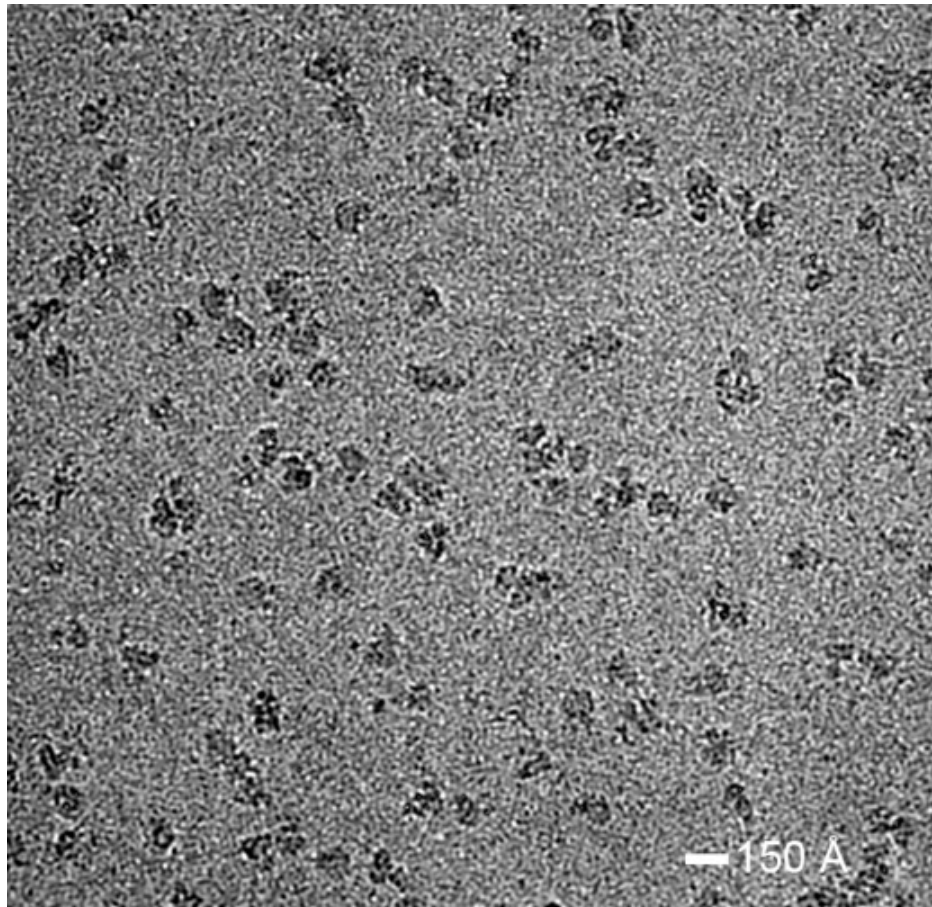
10 s

ATP

PKA

0.5 pA

5 s

László Csanády

Phosphorylation also regulates ATPase activity
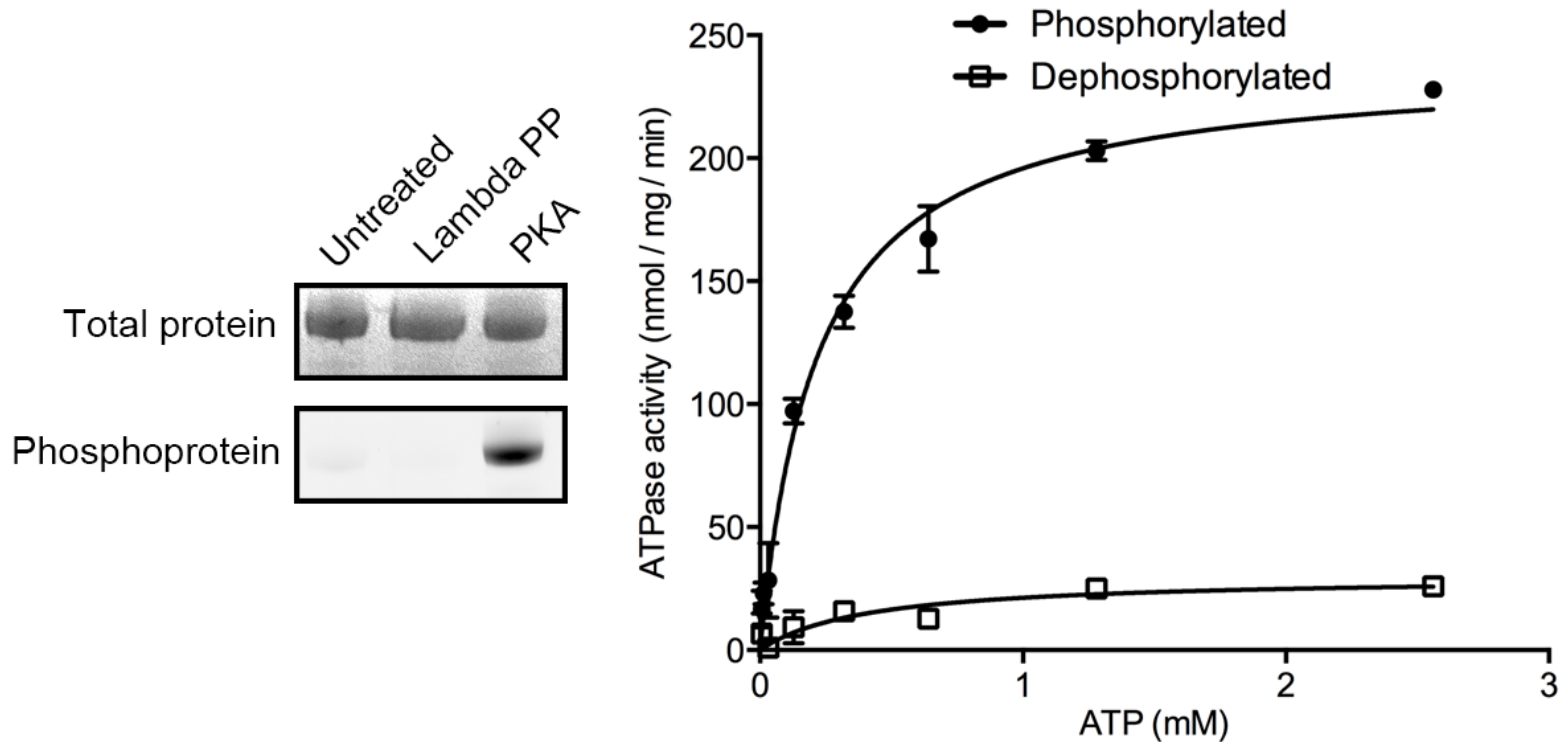
Zhe Zhang

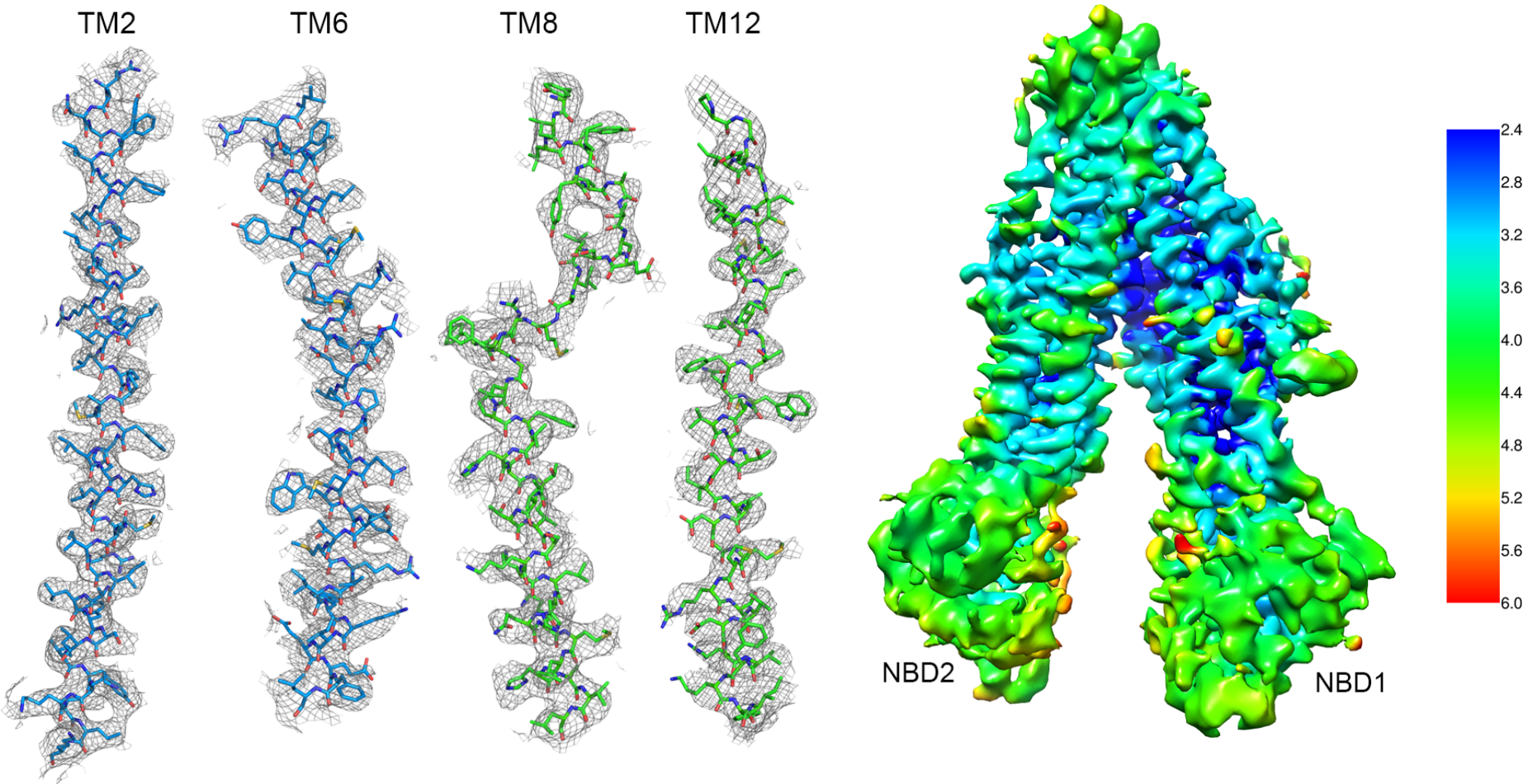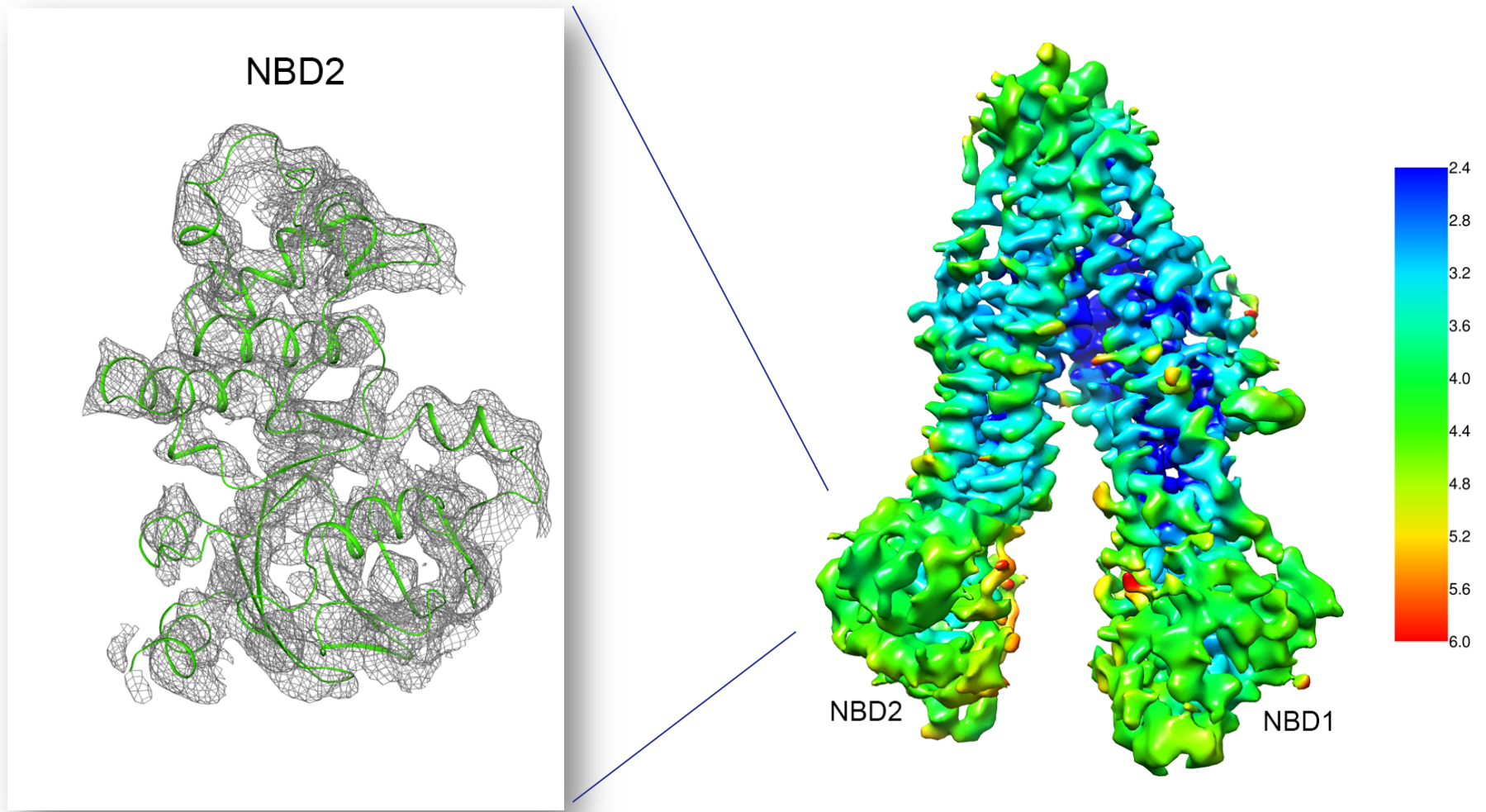# Cryo-EM analysis of CFTR

Zhe Zhang

Cryo-EM analysis of CFTR

- Movie alignment and exposure filter
    -- **Unblur**: Grant & Grigorieff, eLIFE, 2015

- Particle alignment
    -- **alignparts_lmbfgs**: Rubinstein & Brubaker, J Struct Biol. 2014

- Estimate defocus parameters
    -- **CTFFND4**: Rohou & Grigorieff, J Struct Biol. (2015)

- Particle picking and subsequent processing
    -- **Relion**: Scheres, J Struct Biol. 2015

- Final runs of 3D refinement
    -- **Frealign**: Lyumkis & Grigorieff, J Struct Biol. 2013

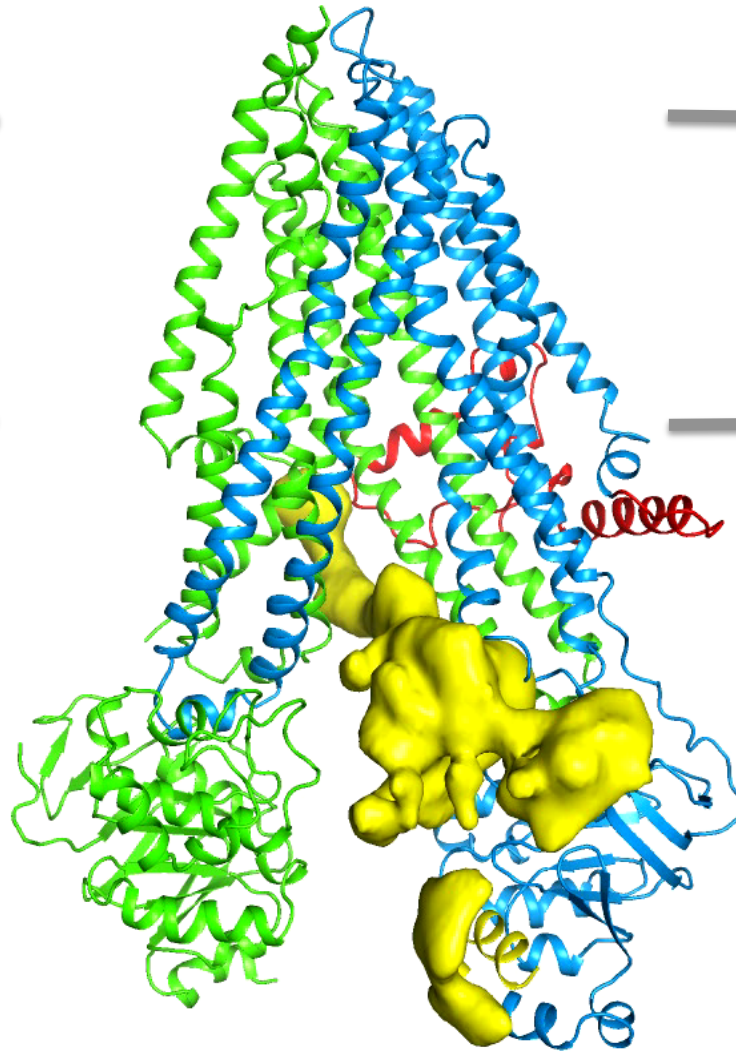# Cryo-EM analysis of zebrafish CFTR
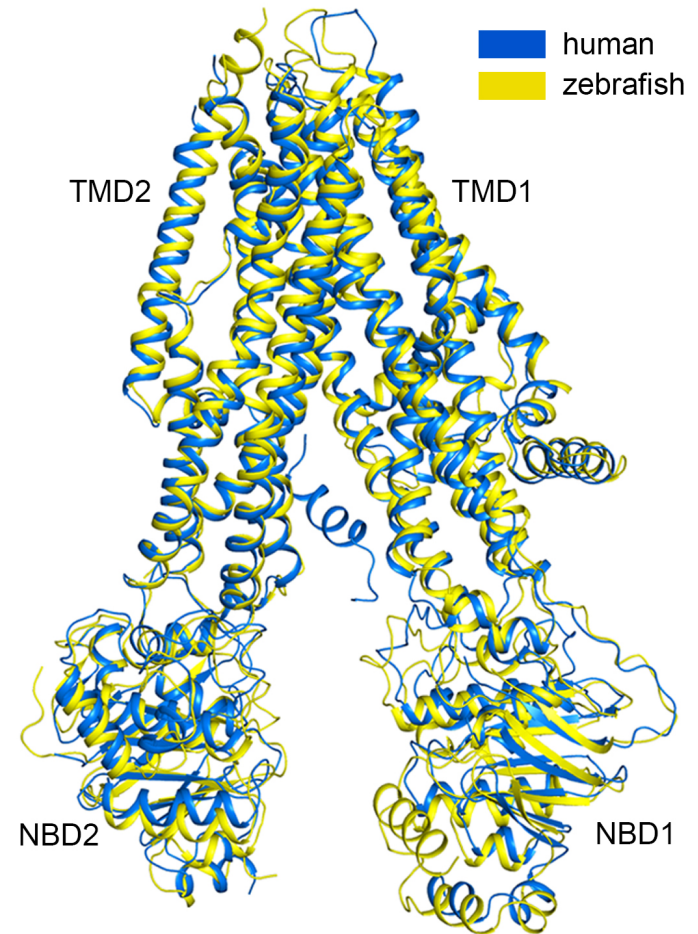
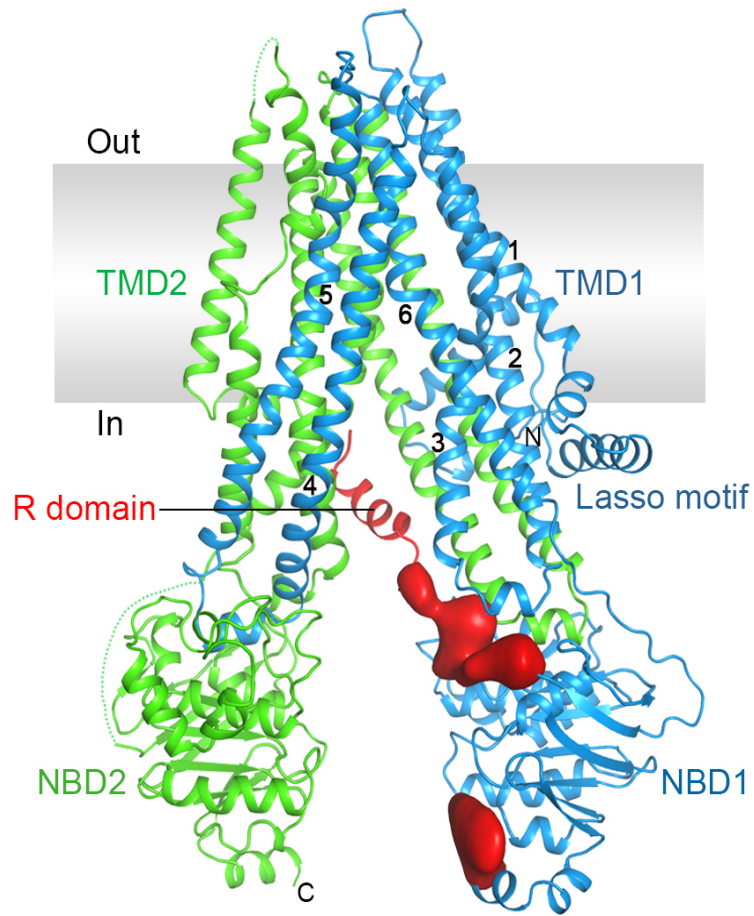# Cryo-EM analysis of zebrafish CFTR

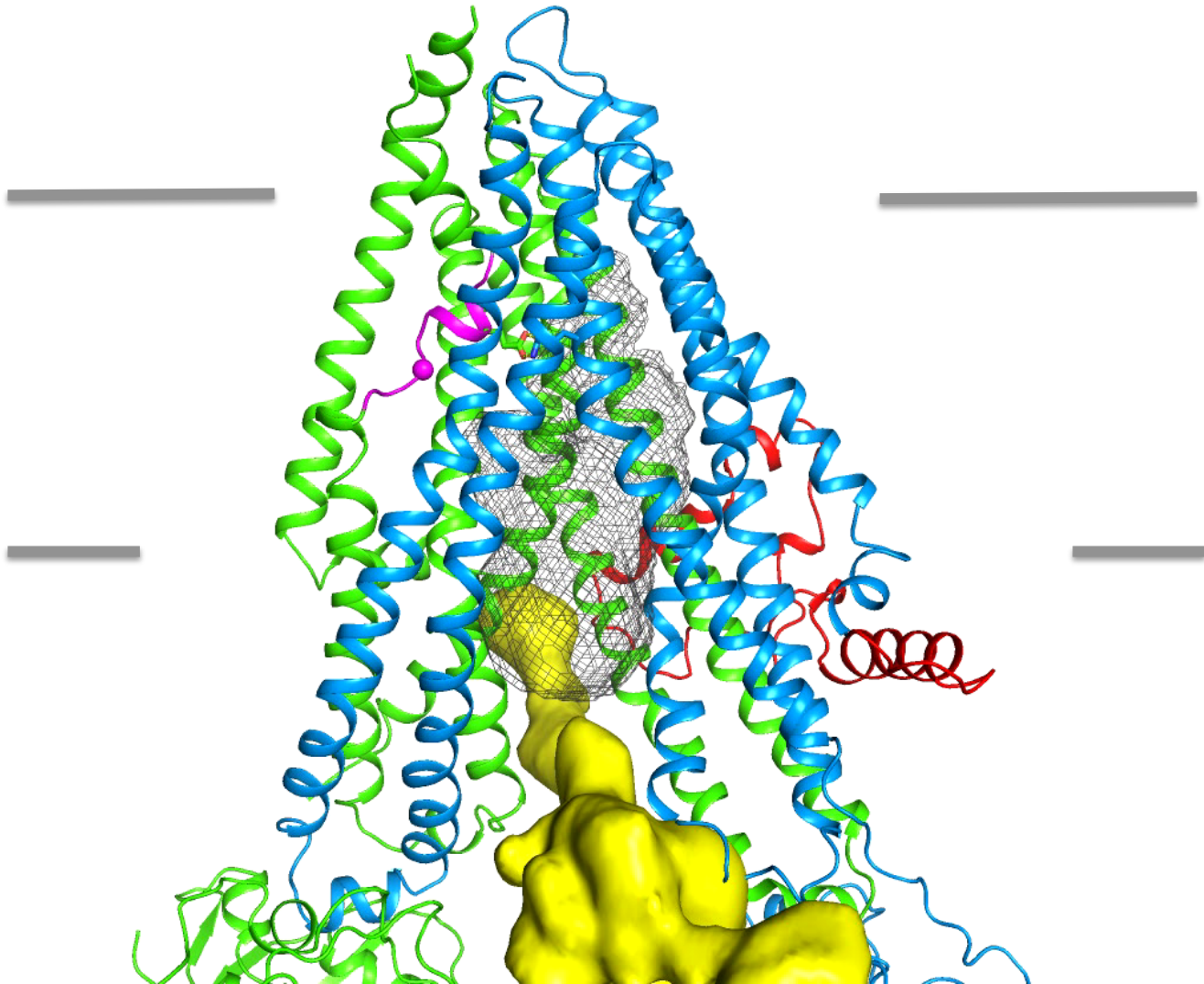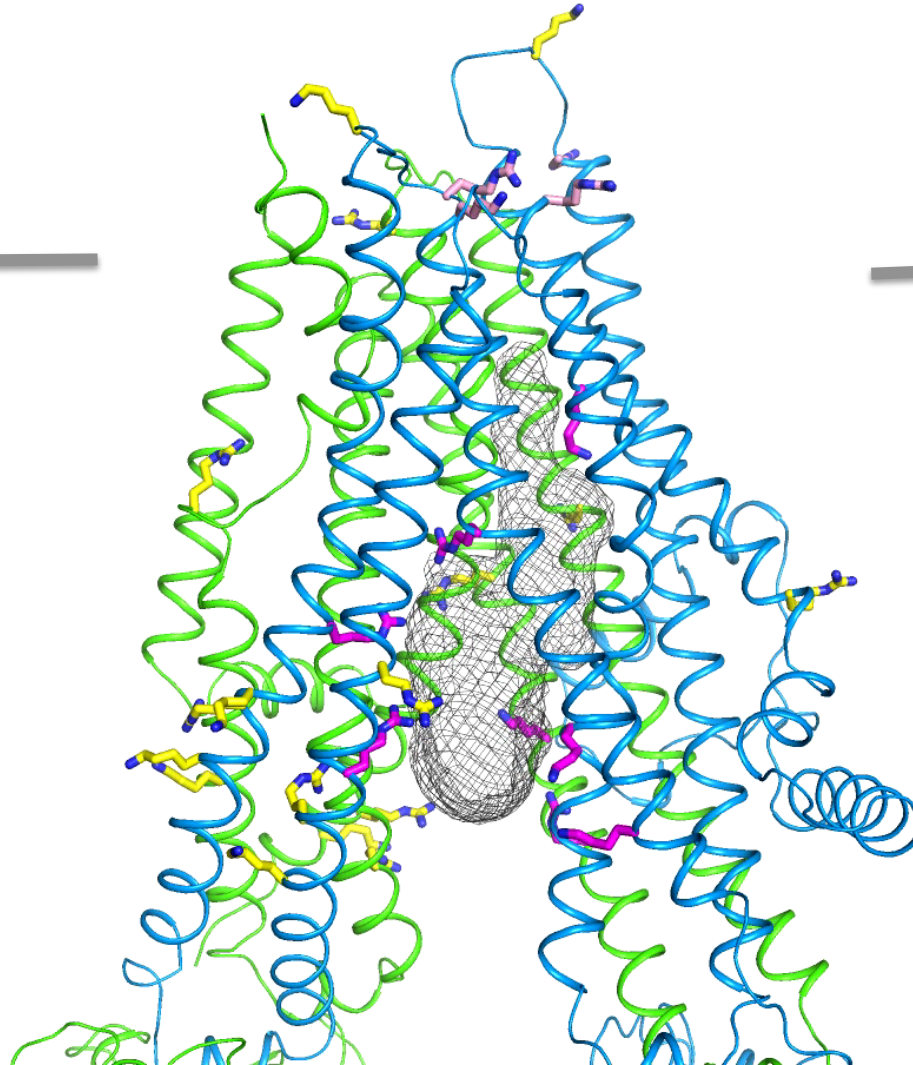# Cryo-EM analysis of zebrafish CFTR
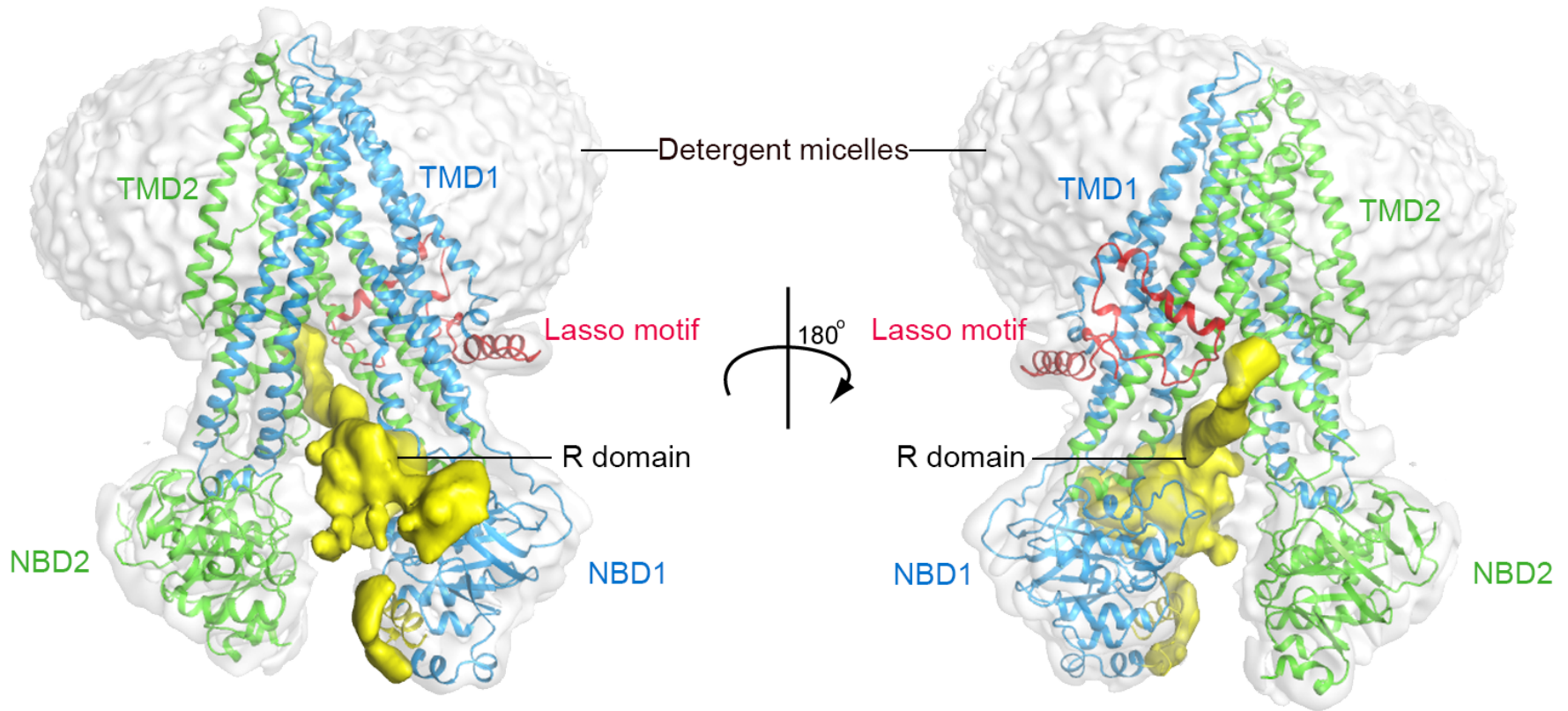
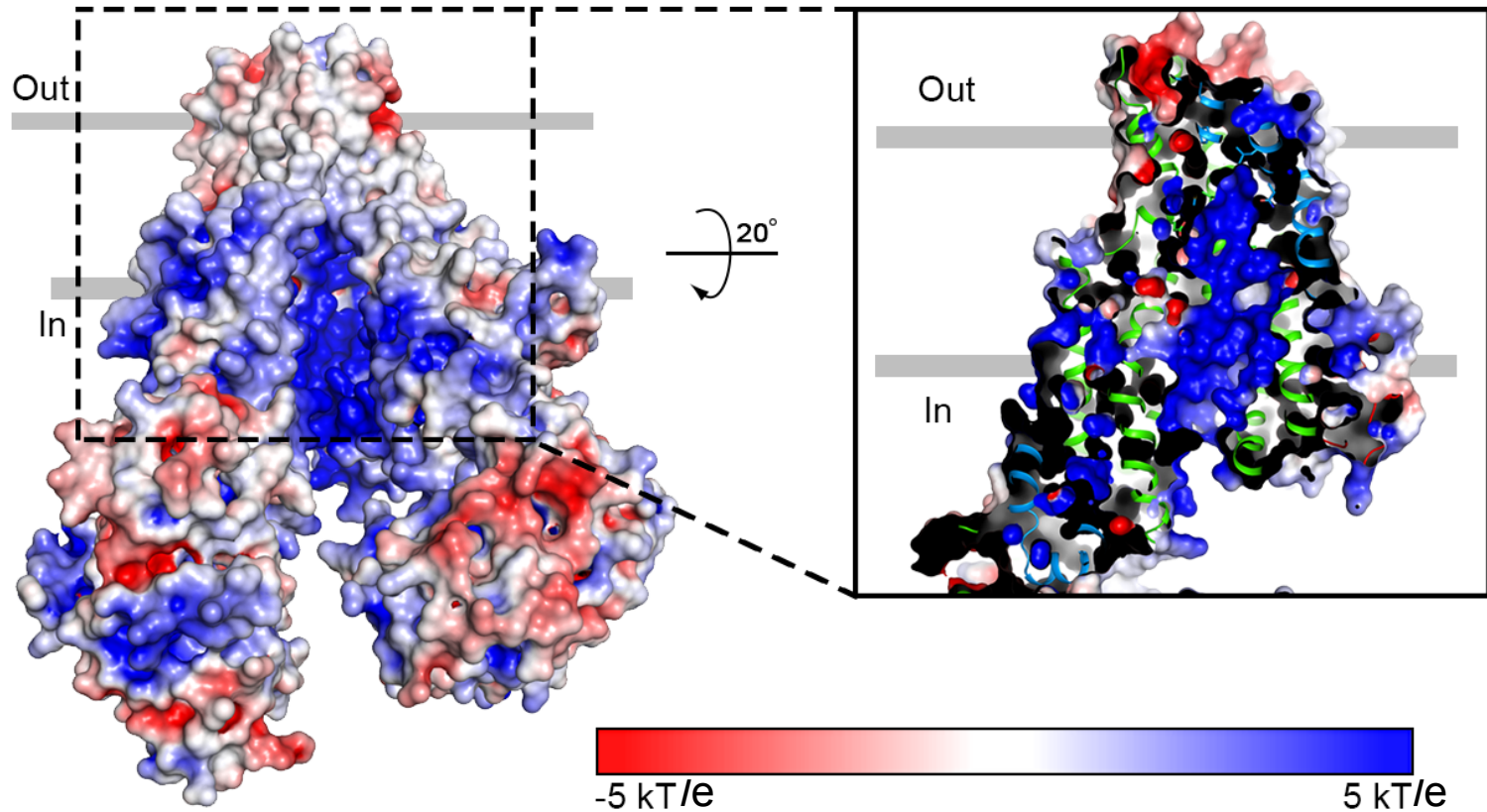# Zebrafish CFTR

Human CFTR

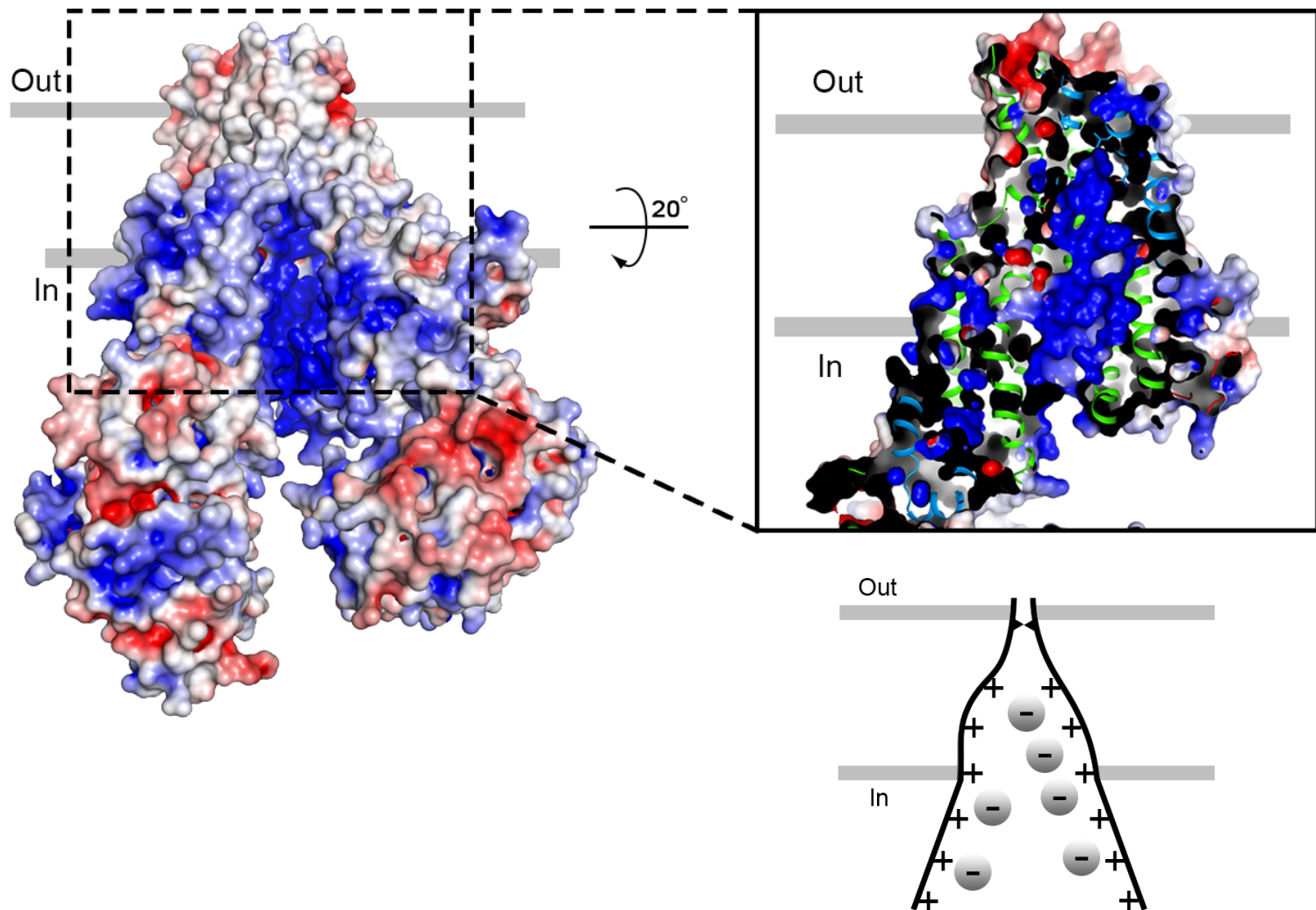Fangyu Liu and Zhe Zhang

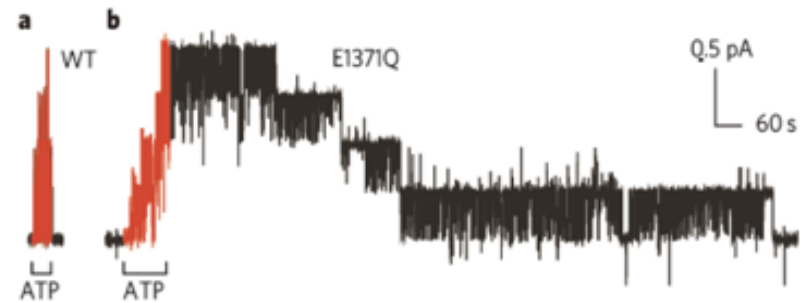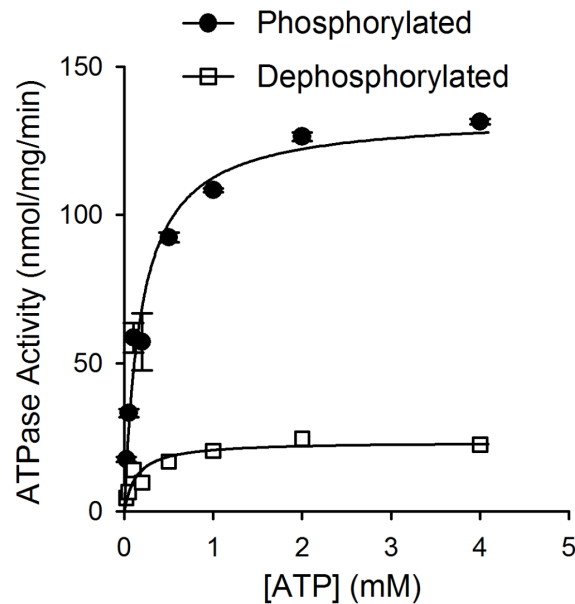# The ion conduction pathway

Positively charged residues

Reviewed in Linsdell, 2017

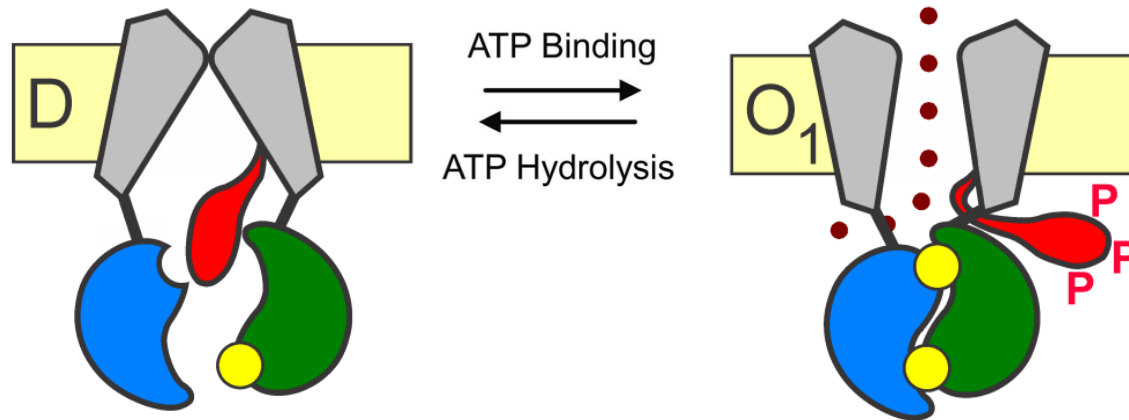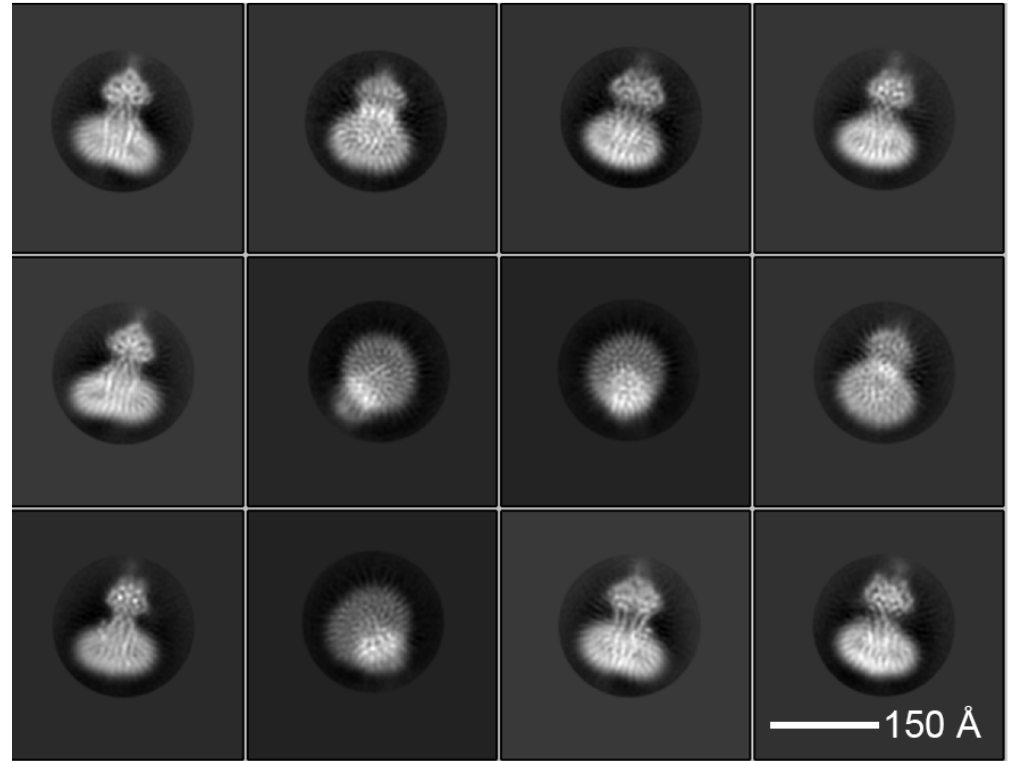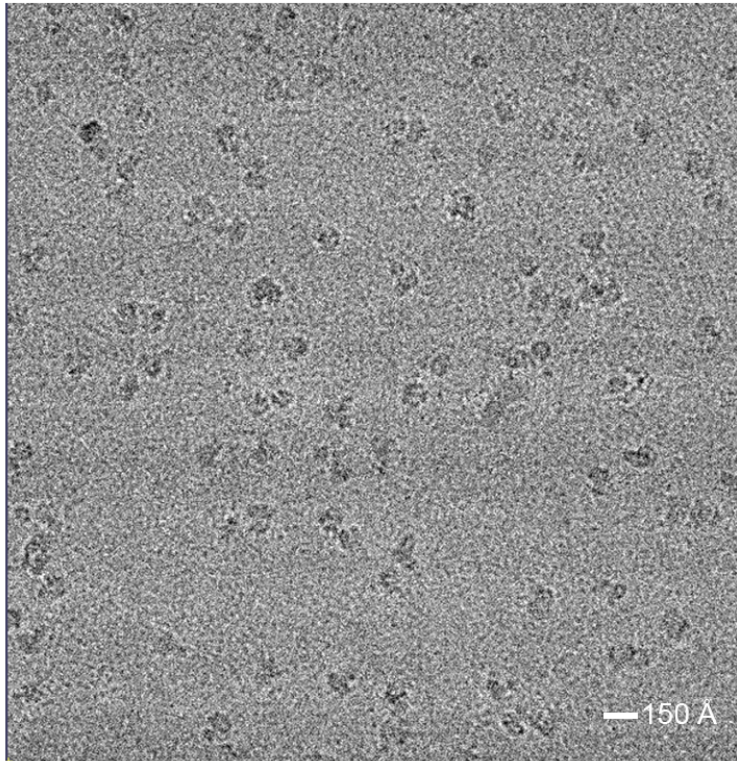# Anion selectivity
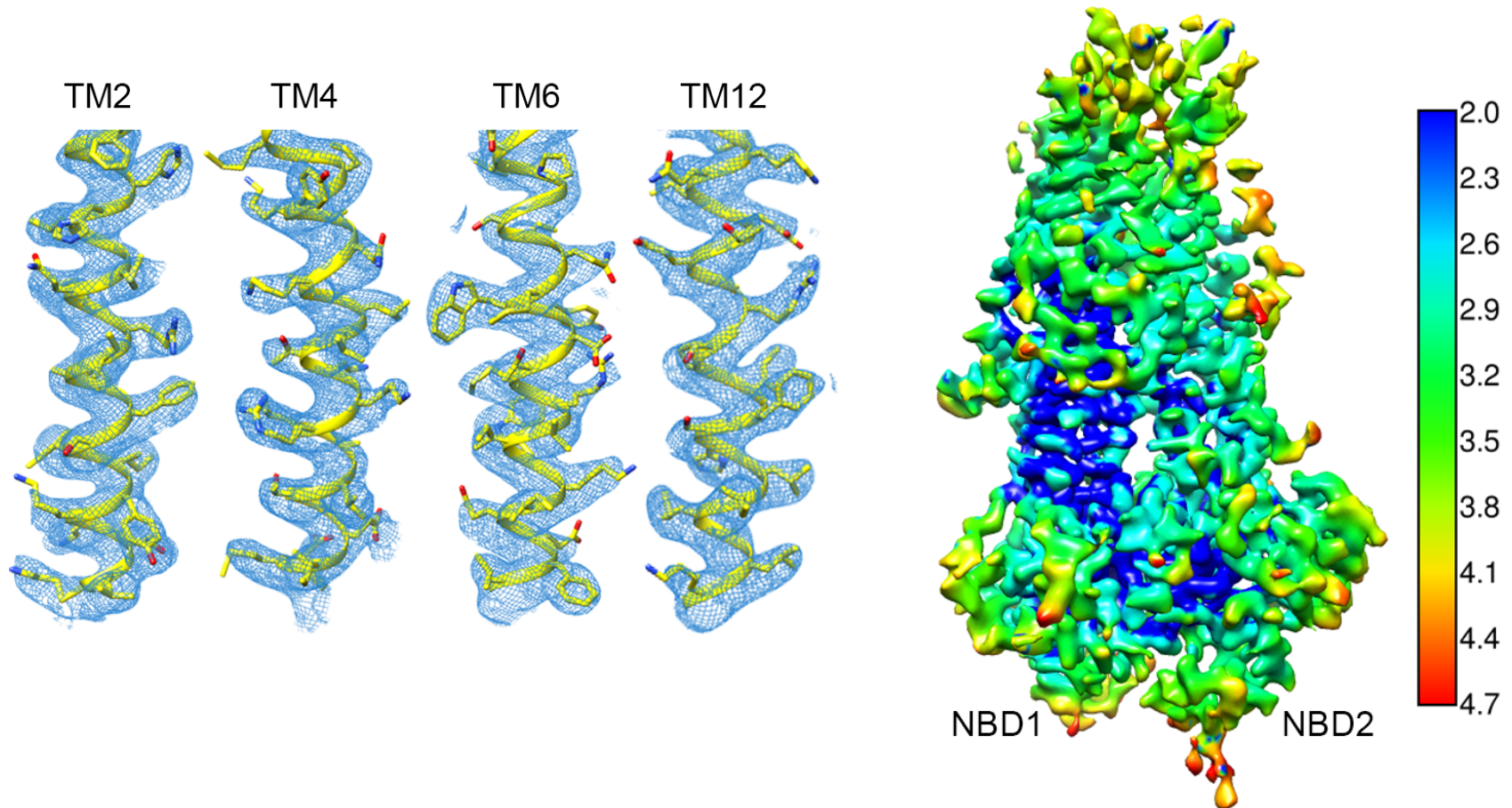
Selectivity

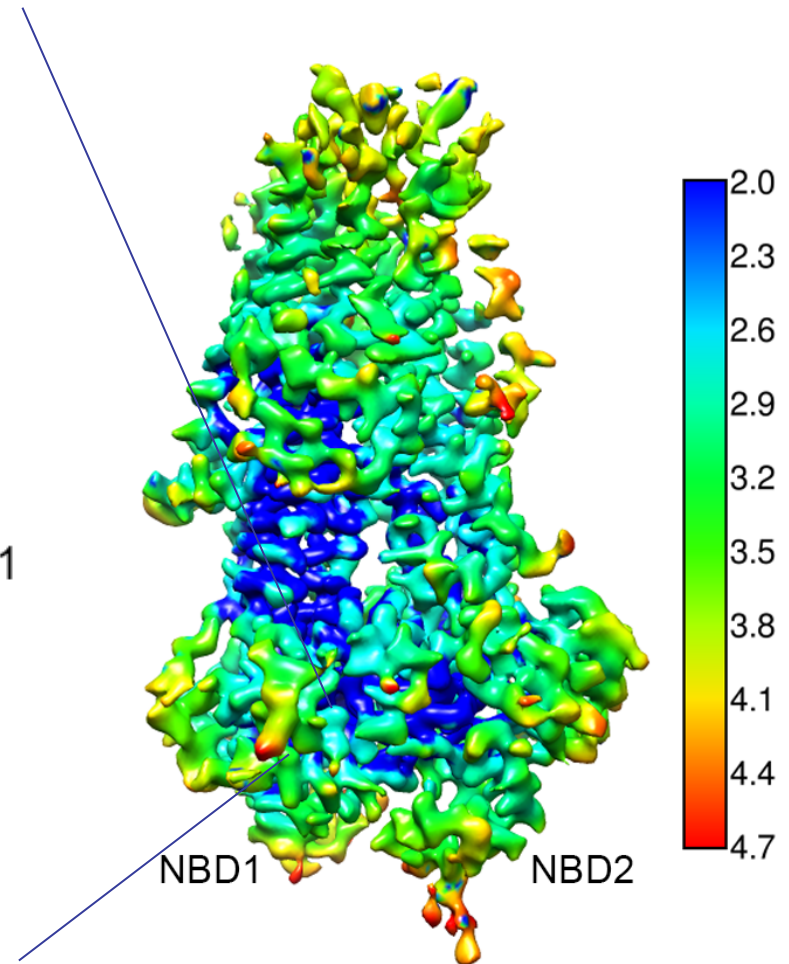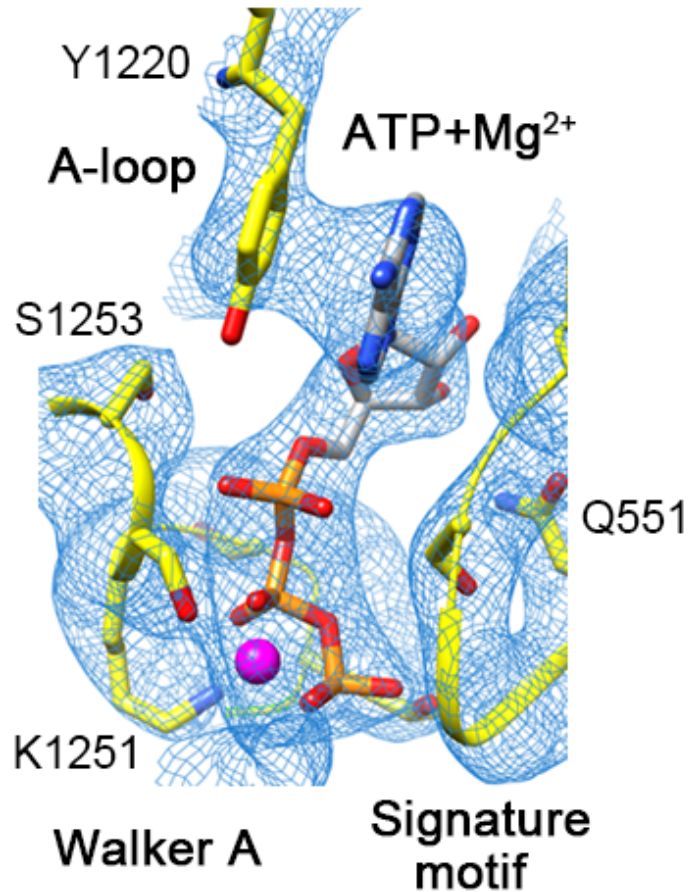# Towards an open channel conformation

David C. Gadsby
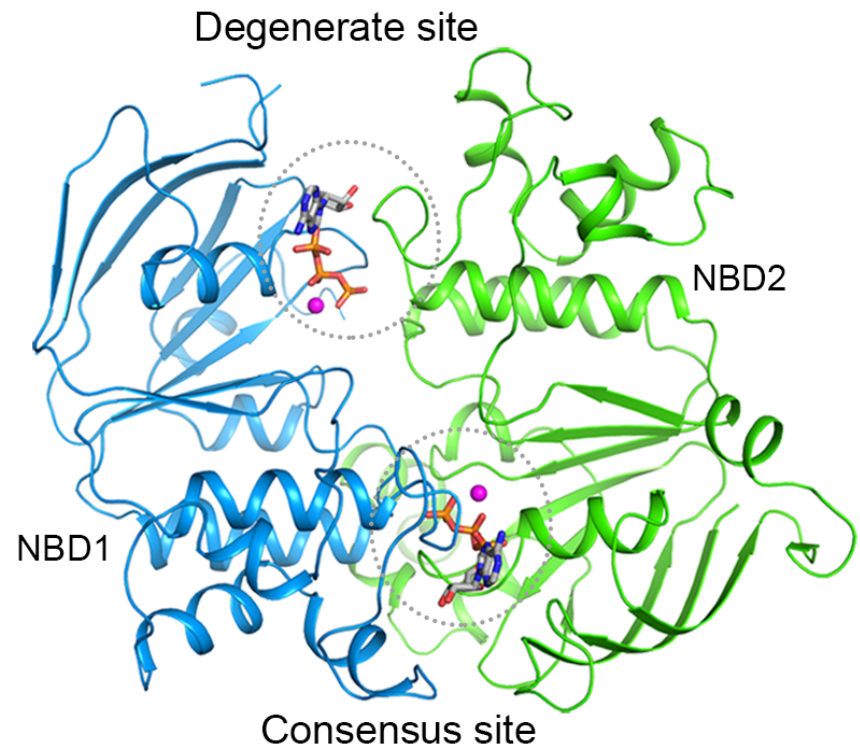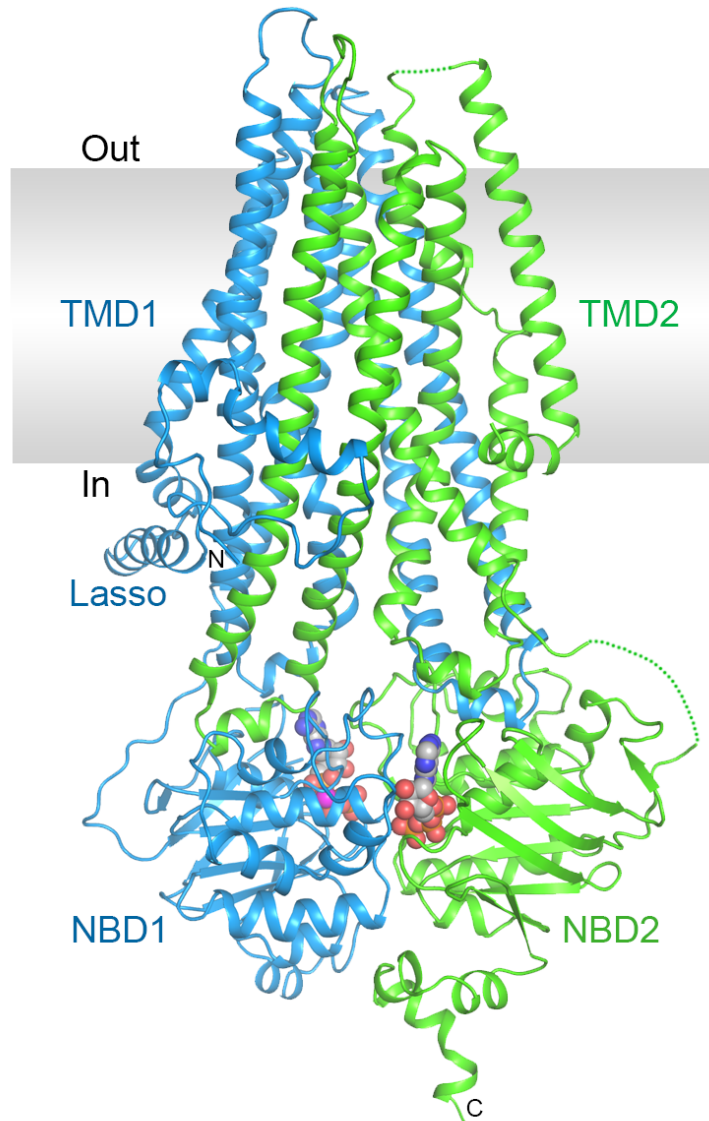
Cryo-EM analysis of phosphorylated CFTR

Cryo-EM analysis of phosphorylated CFTR
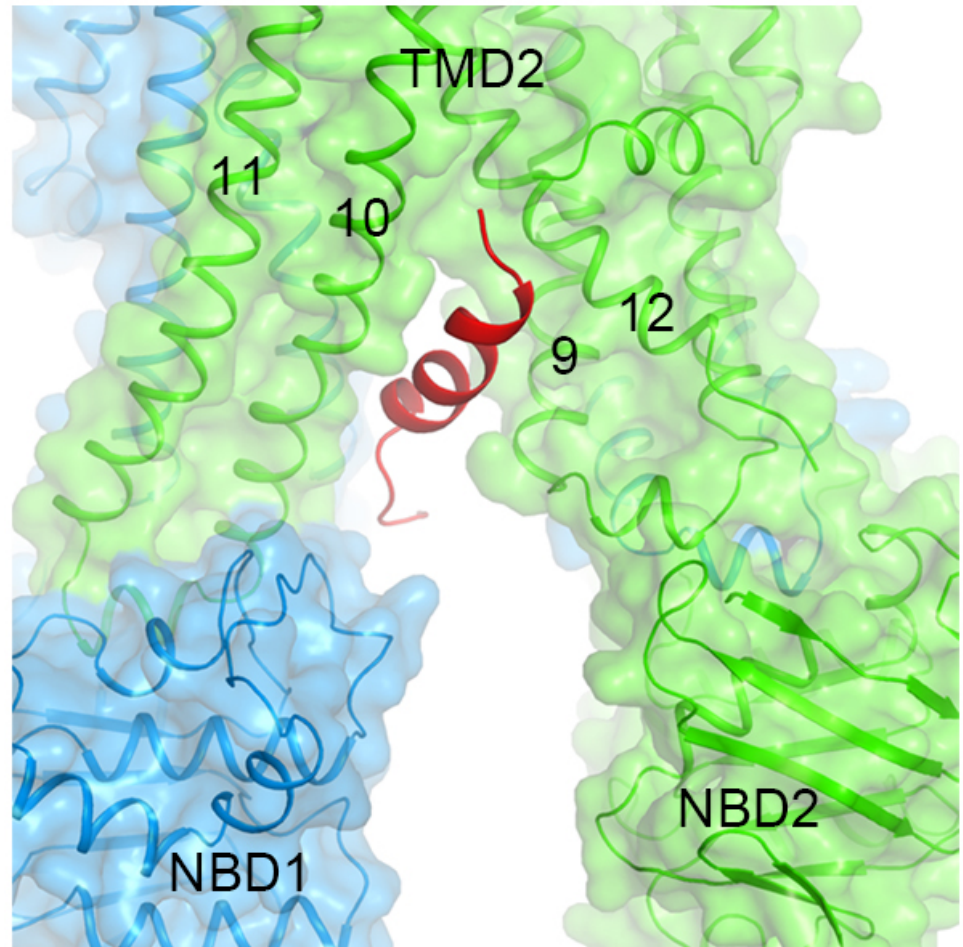
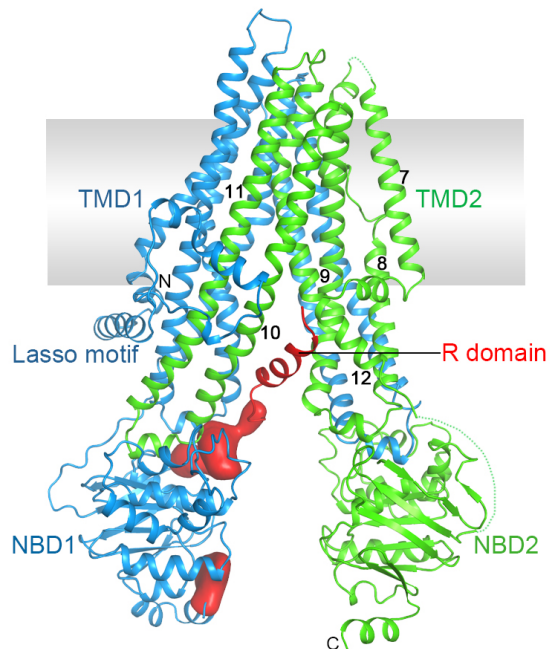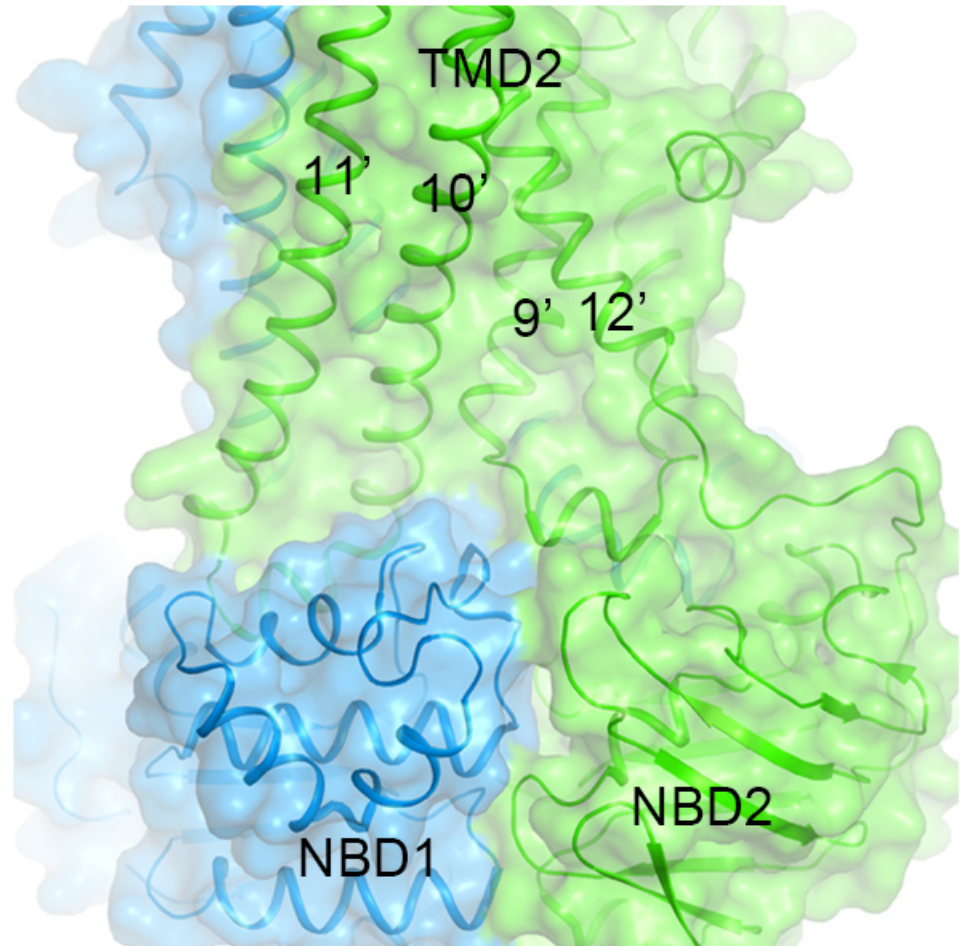# Cryo-EM analysis of phosphorylated CFTR
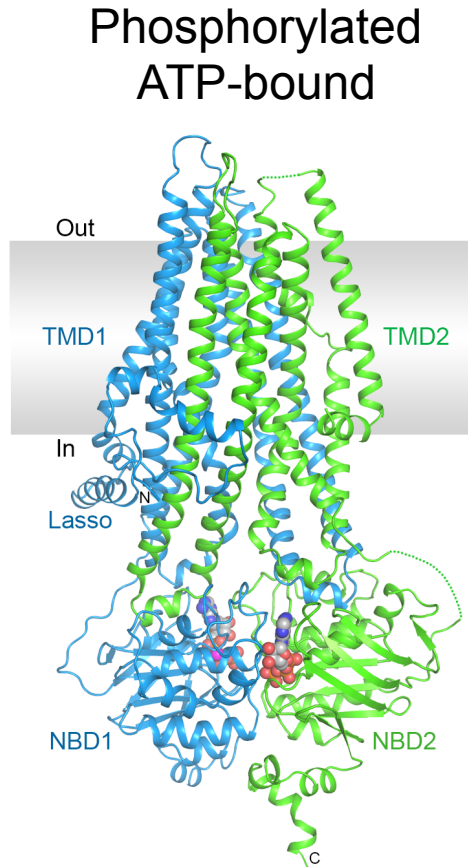
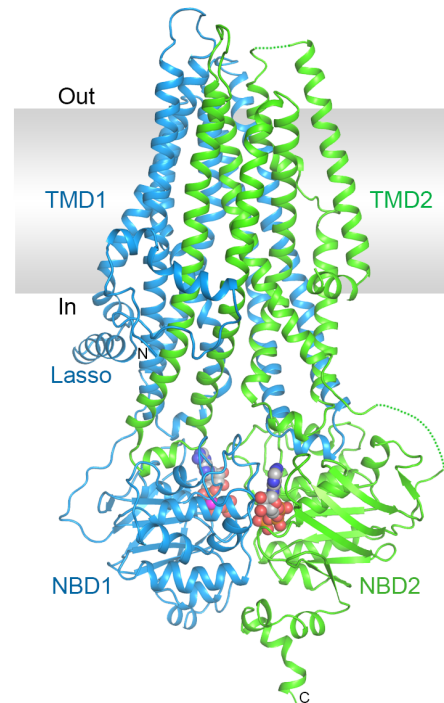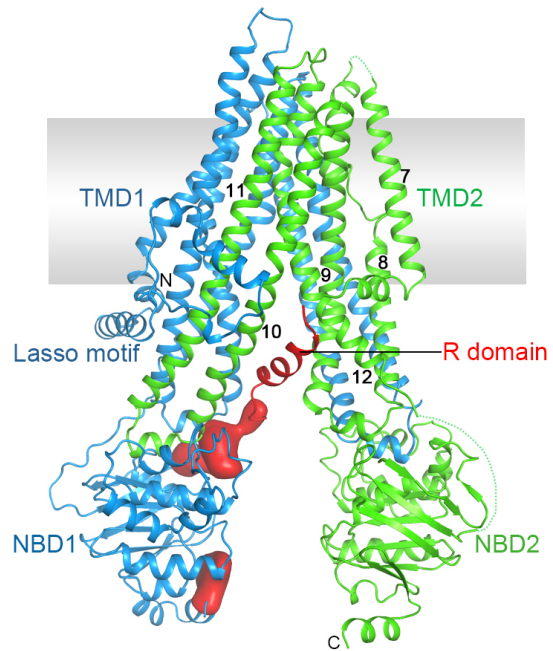# Cryo-EM analysis of phosphorylated CFTR

R domain prevents NBD dimerization

Dephosphorylated ATP-free

R domain prevents NBD dimerization
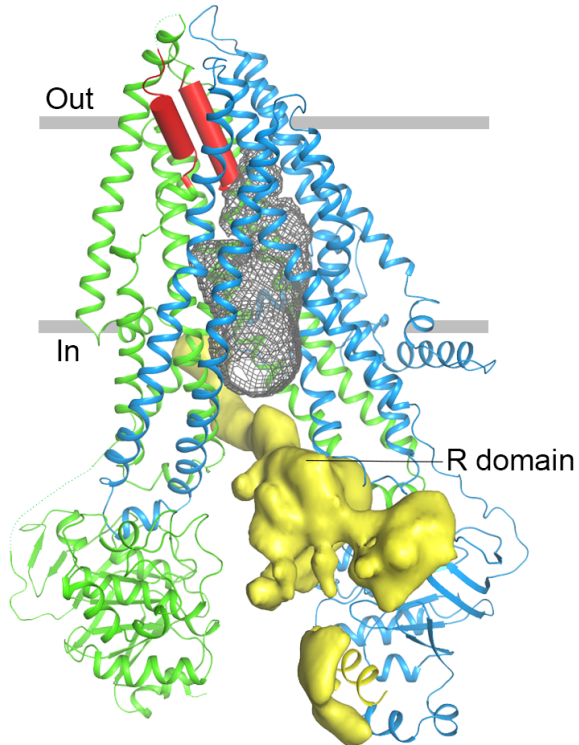

Phosphorylated
ATP-bound

Conformational changes
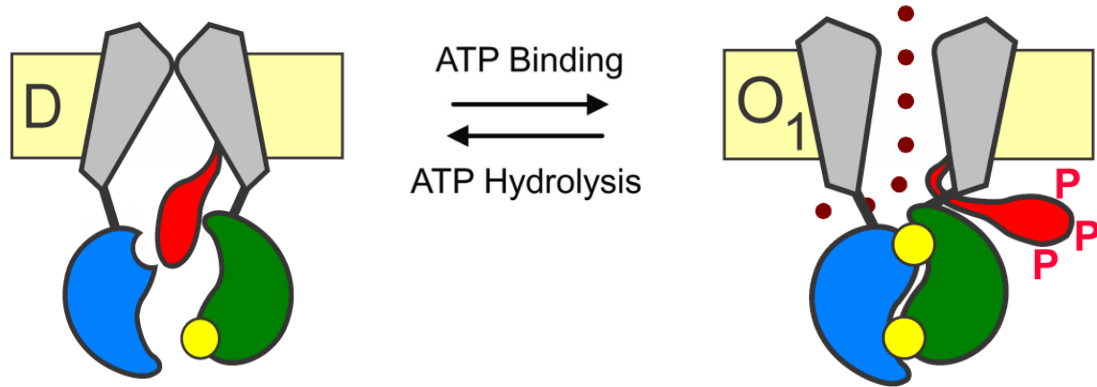
Conformational changes
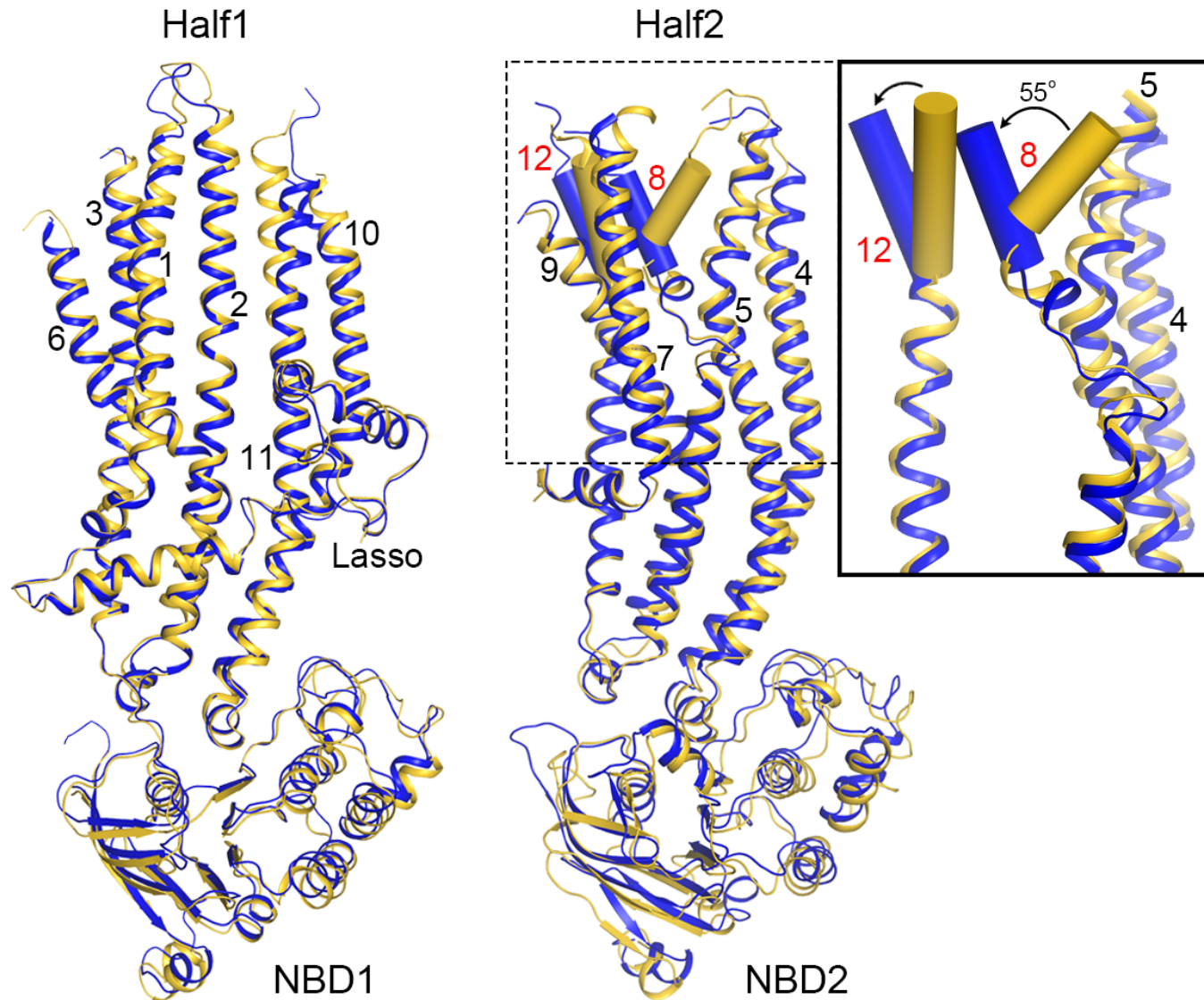
Local conformations control ion access
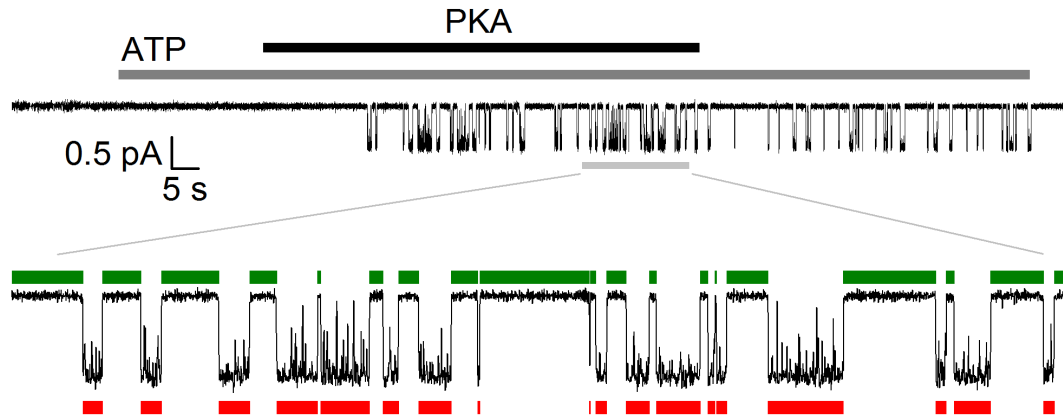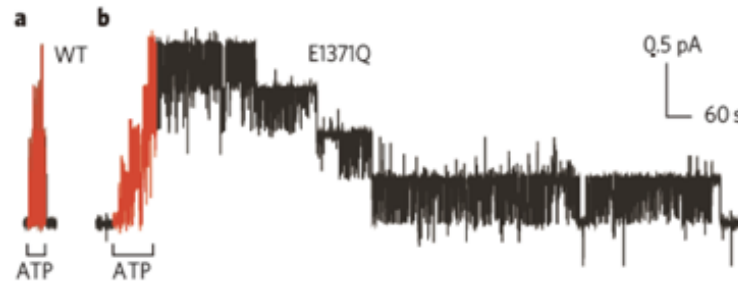

Dephosphorylated, ATP-free

Out

In

R domain

A modeled "Open" state
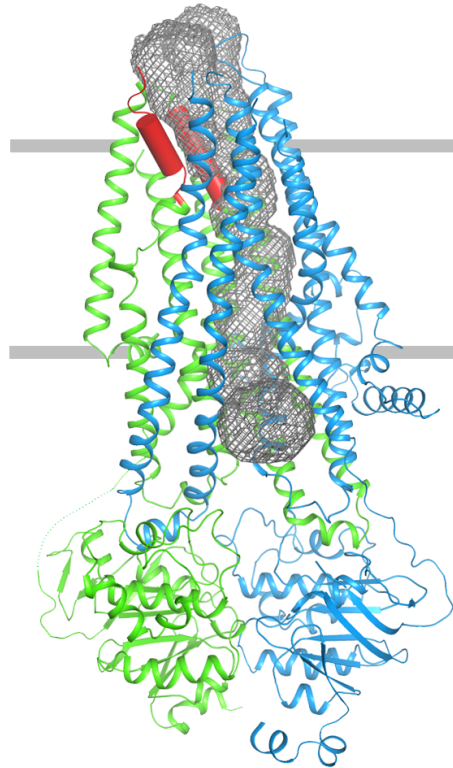
Phosphorylated, ATP-bound

Flickering

ATP

PKA

0.5 pA
5 s

László Csanády

55°

5

8

12

4

a   b

WT

E1371Q

0.5 pA

60 s

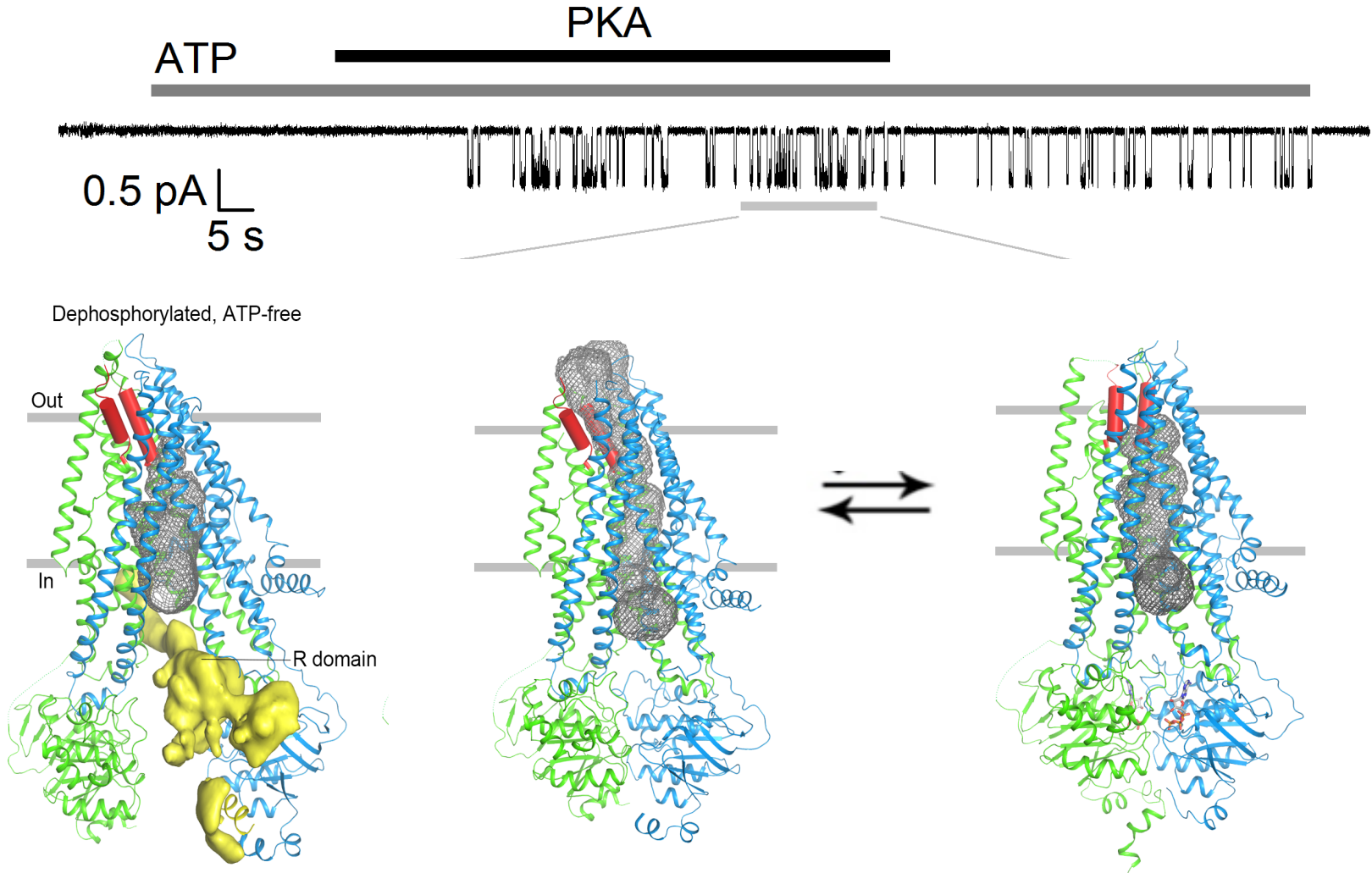ATP   ATP
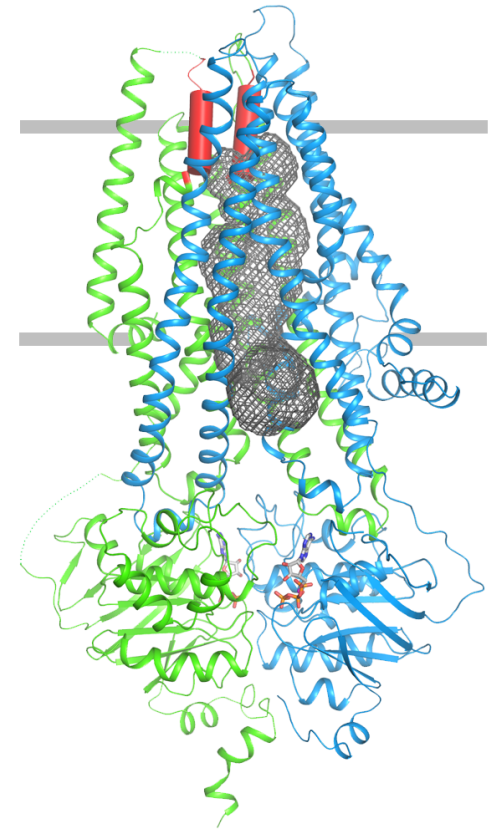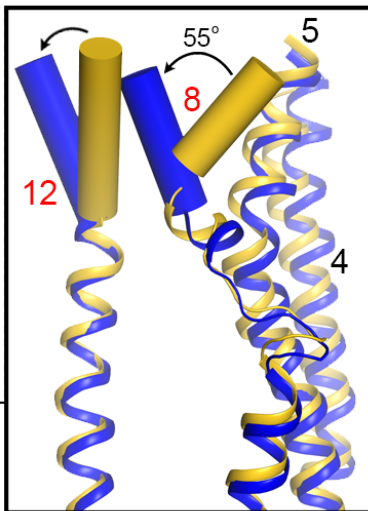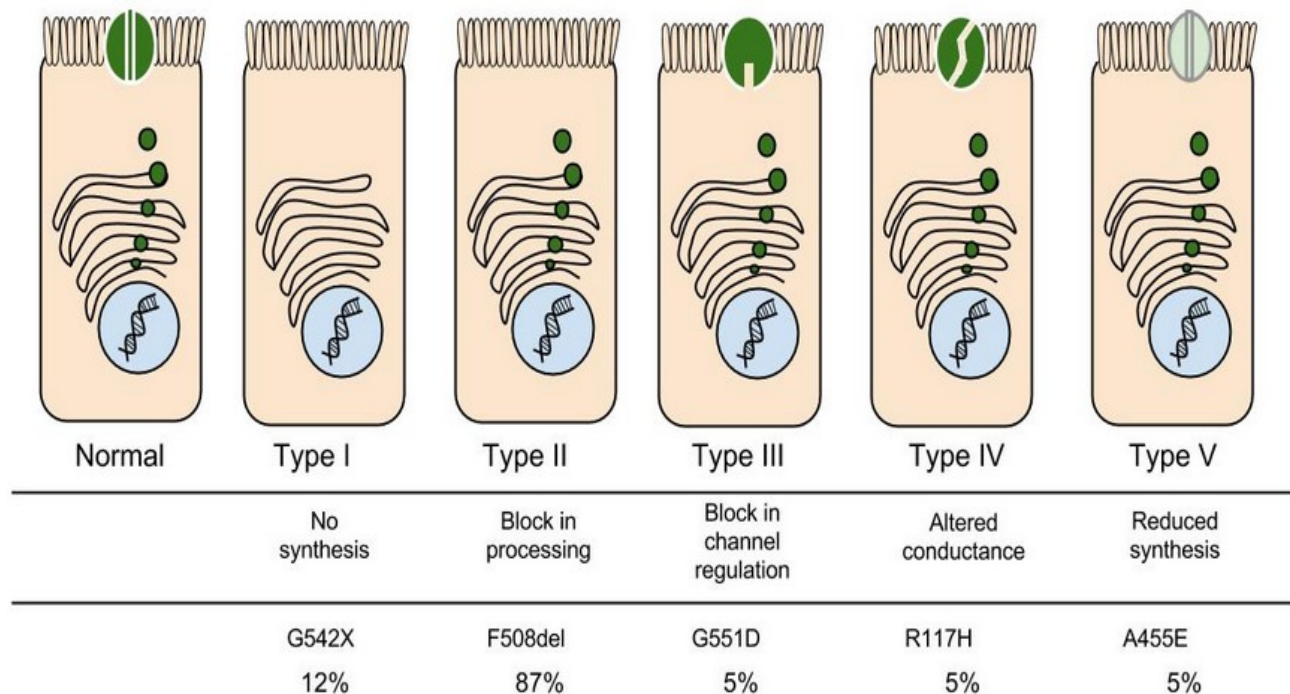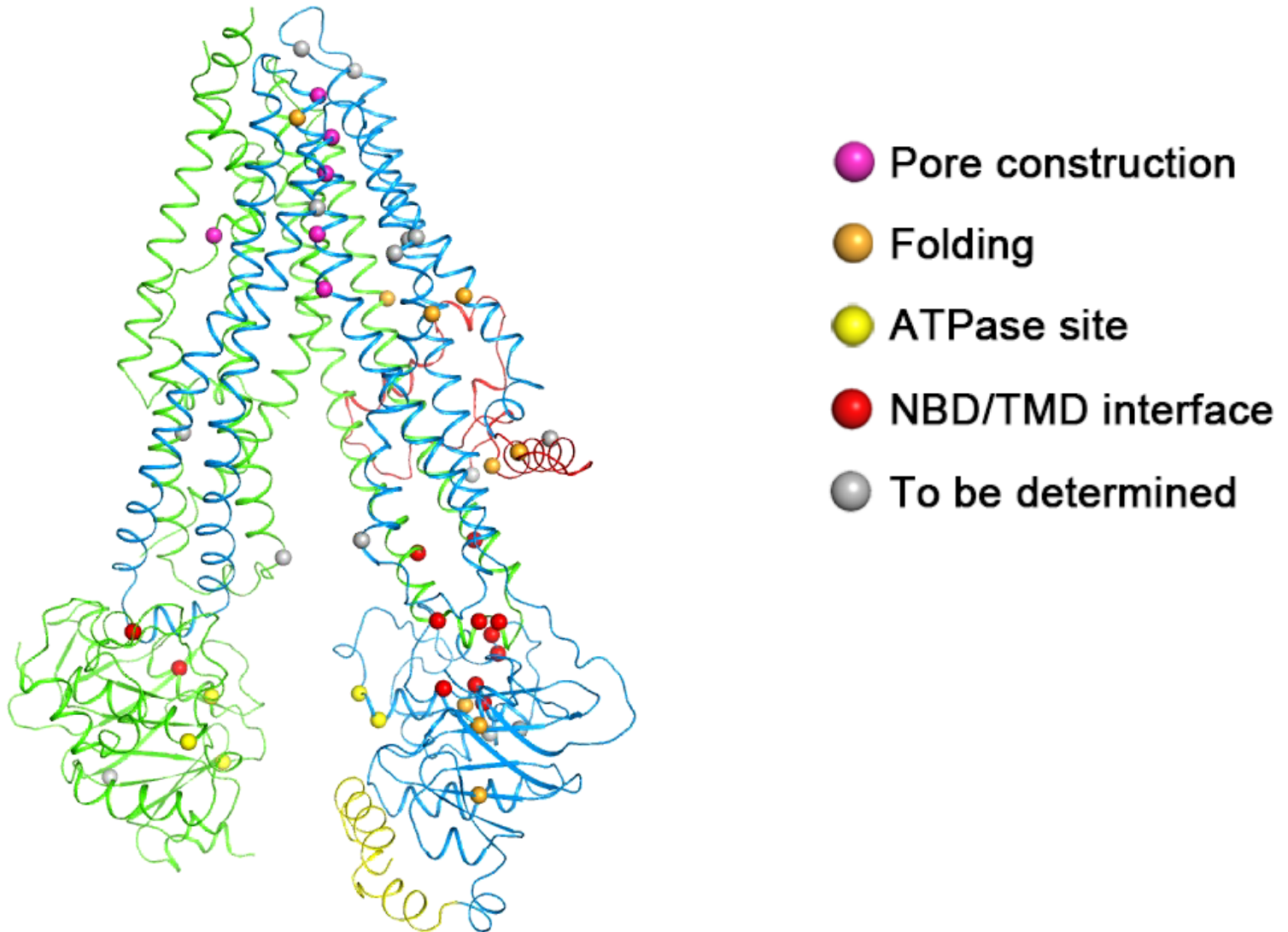
David C. Gadsby

The CFTR gating cycle

The CFTR gating cycle

Cystic Fibrosis-causing mutations

- >1000 mutations in CFTR
- 272 mutations causing CF
- 53 missense mutations at 46 positions

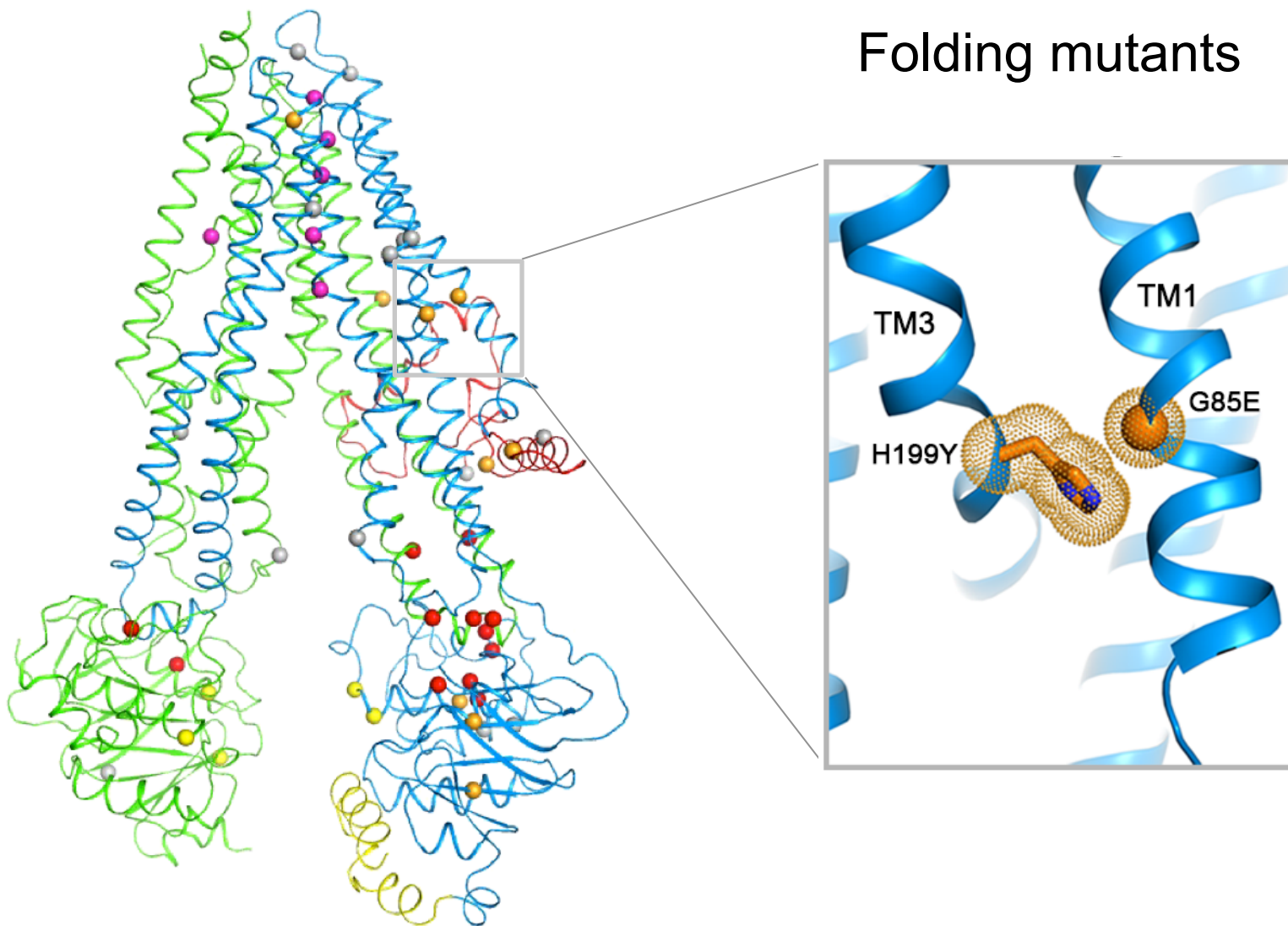| Normal	Type I	Type II	Type III	Type IV	Type V
	No synthesis	Block in processing	Block in channel regulation	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	R117H	A455E
	12%	87%	5%	5%	5%

Cystic Fibrosis-causing mutations

Legend:
- Pore construction (magenta)
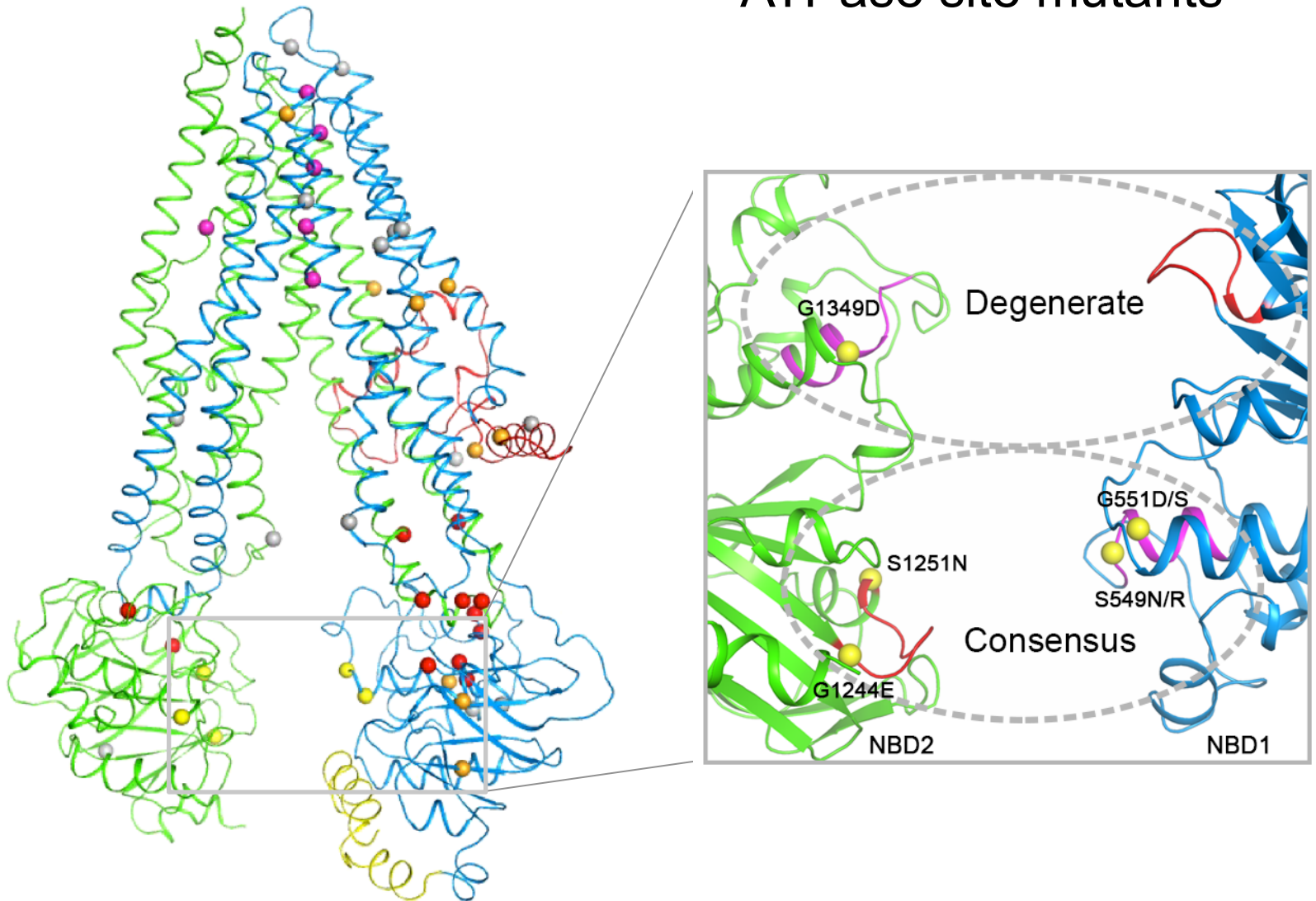- Folding (orange)
- ATPase site (yellow)
- NBD/TMD interface (red)
- To be determined (grey)

Pore construction mutants
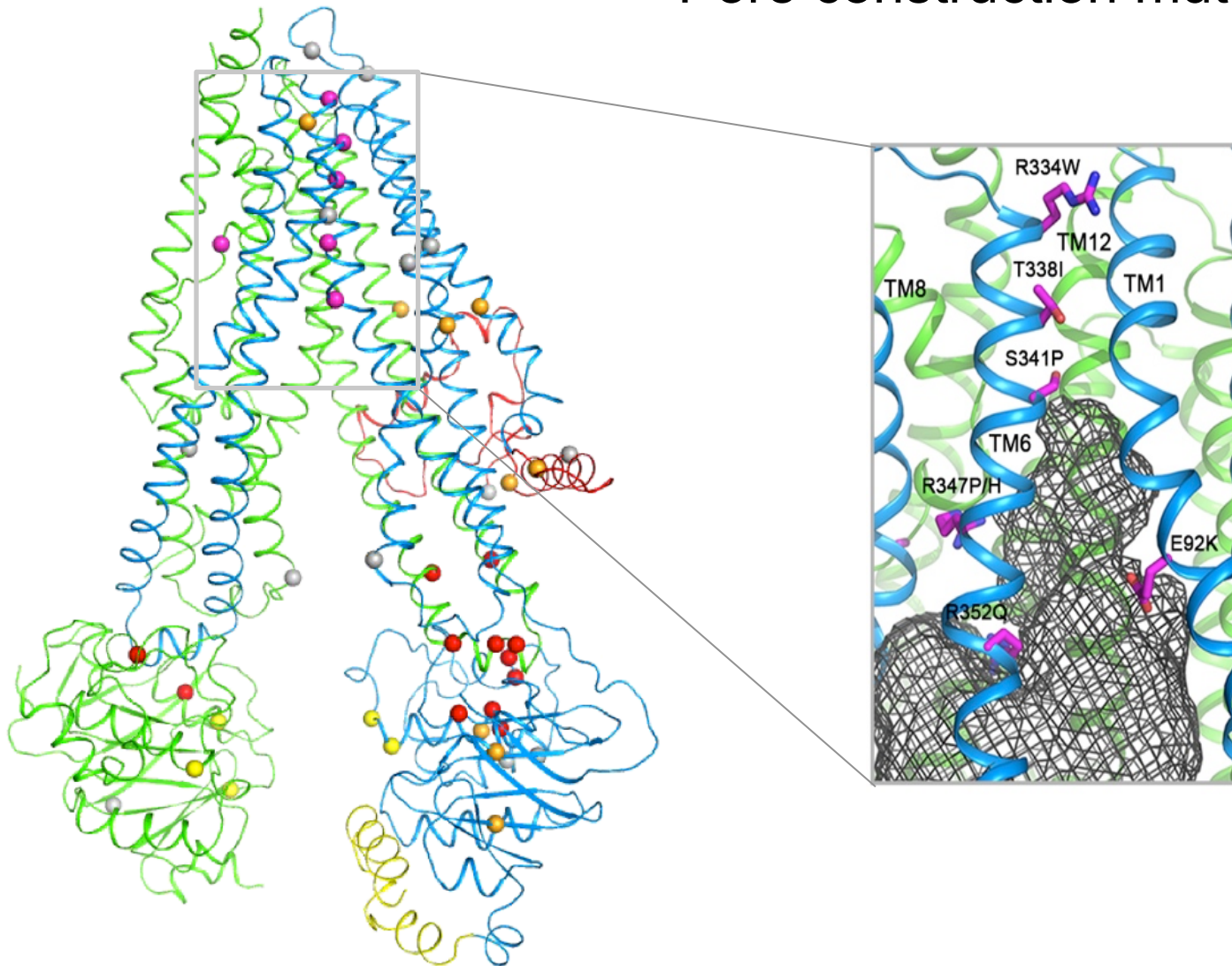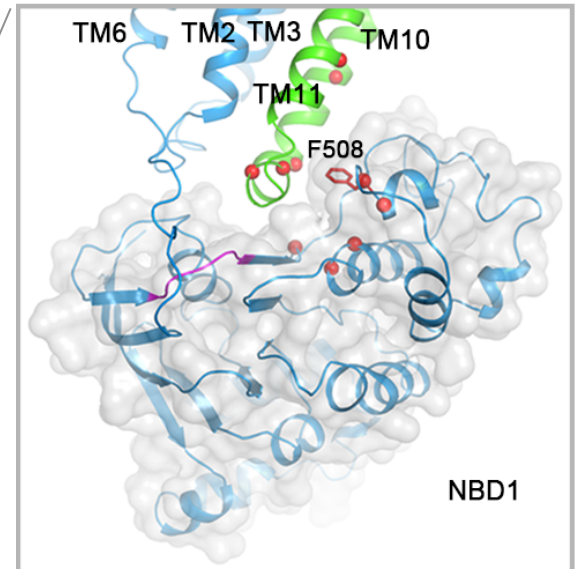
Folding mutants

ATPase site mutants

Degenerate

G1349D

G551D/S

S549N/R

S1251N

Consensus

G1244E

NBD2

NBD1

NBD/TMD interface mutants
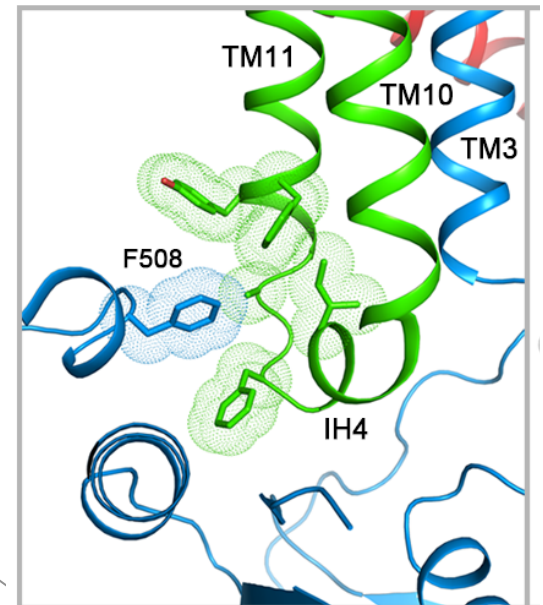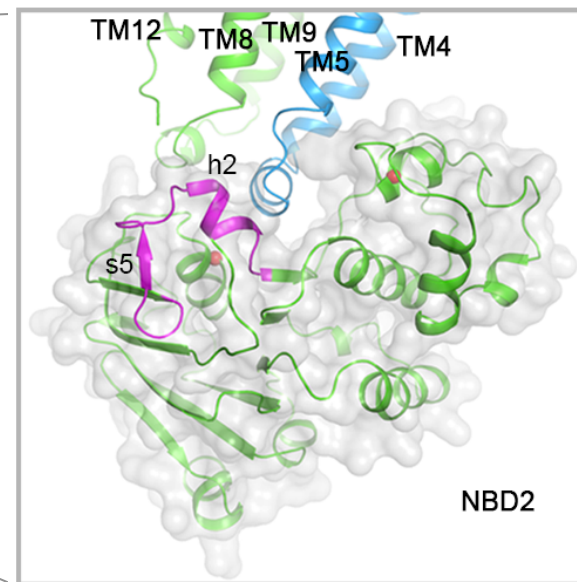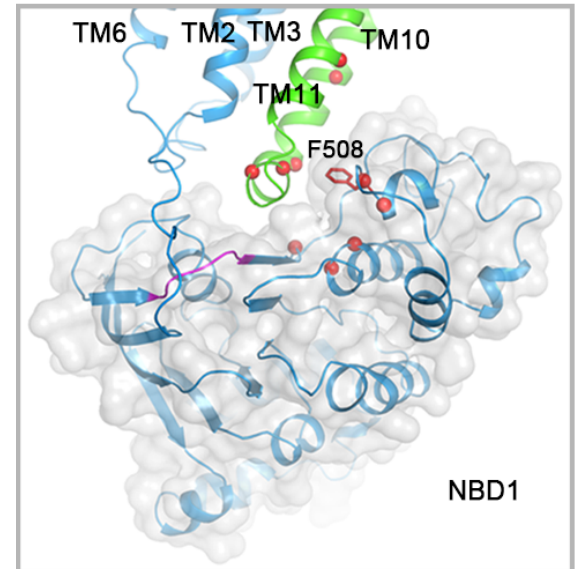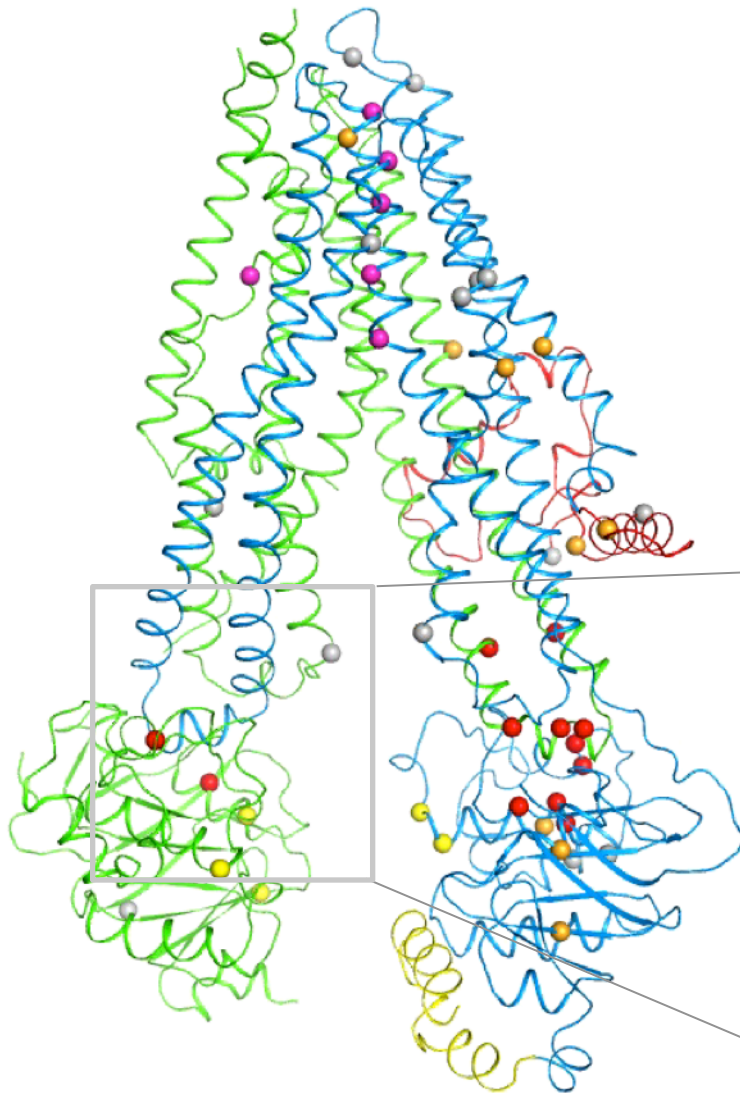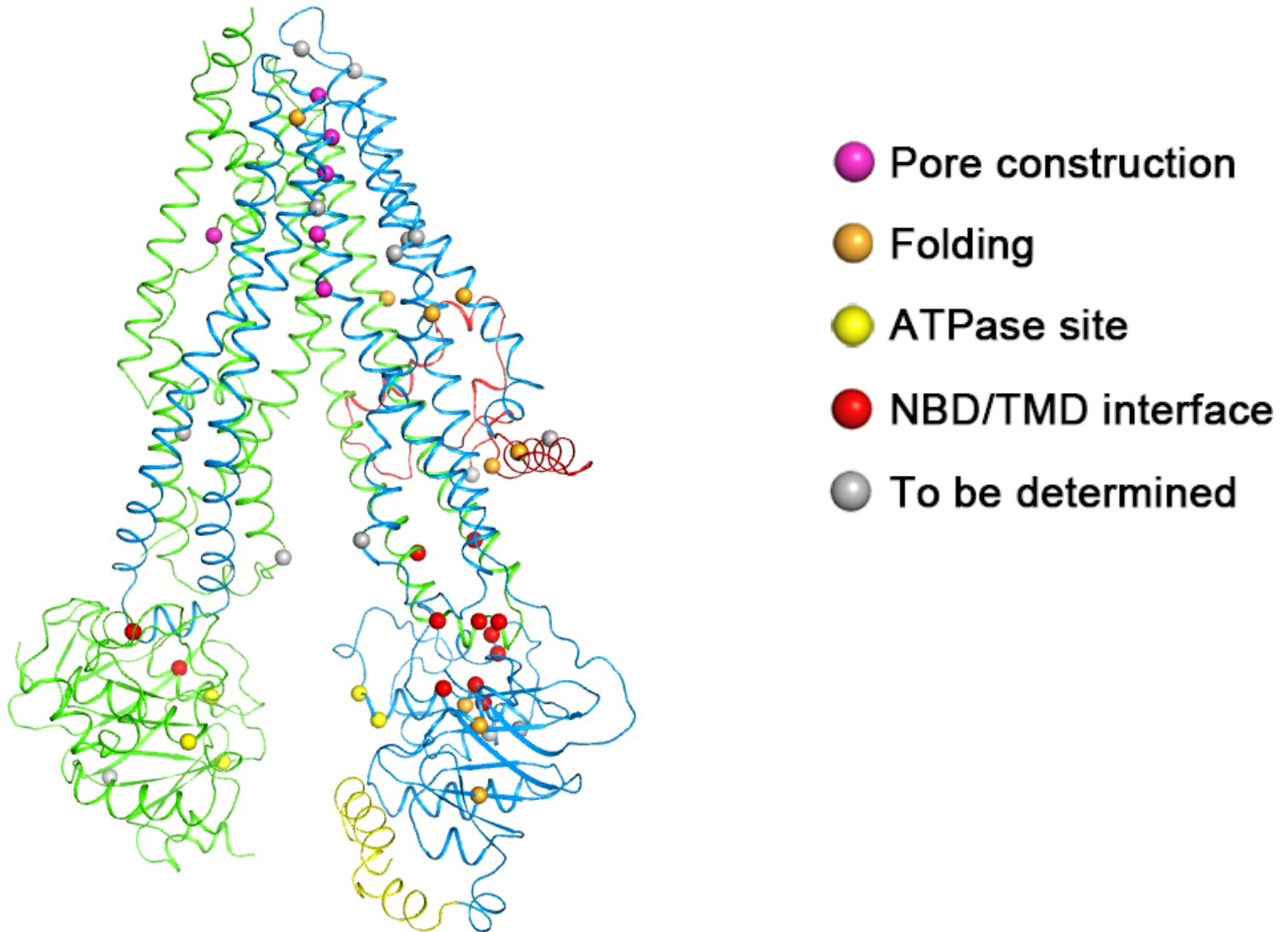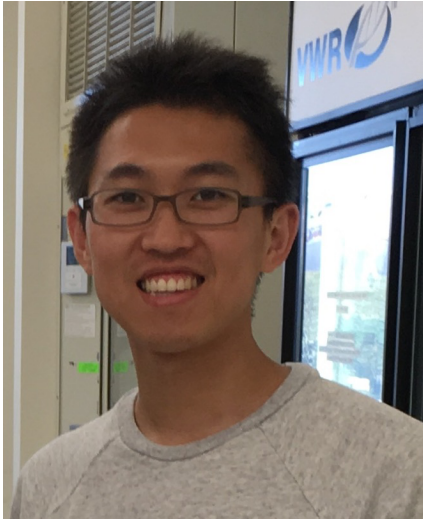
NBD/TMD interface mutants

Cystic Fibrosis-causing mutations
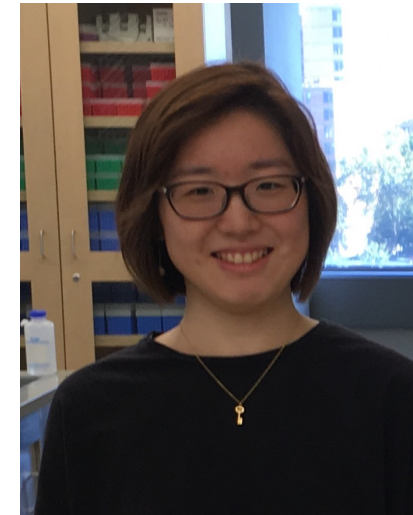
Acknowledgment

CFTR project

Zhe Zhang

Fangyu Liu

David C. Gadsby

László Csanády

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