

EvoYon: Computational Discovery of Cystic Fibrosis Mutation Specific Drugs



Ori Inbar, PhD

Technological Product Manager, Evogene
Father of a 12 years old boy with CF
Chairperson, the CF Foundation of Israel



Agenda

- **Introduction: Evogene + Yonatan = EvoYon**
- EvoYon approach
- Initial results
- Summary

Introduction to Evogene



► We are...

A leading biotechnology company for the improvement of crop productivity and performance, addressing the world's increasing demand for food, feed and fuel

Technology platform

Analysis platforms

Proprietary algorithms and modules to prioritize the best product candidates

ATHLETE™
Gene discovery

PointHit™
Chemical discovery

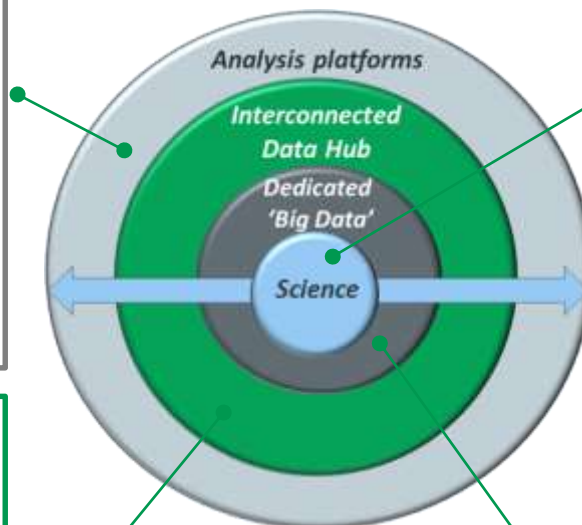
PlaNet_{NG}
Stack discovery

Gene2Product™
Gene optimization

PoinTar™
Target discovery

BiomeMiner™
Toxin discovery

Driving Ag Innovation
via predictive biology



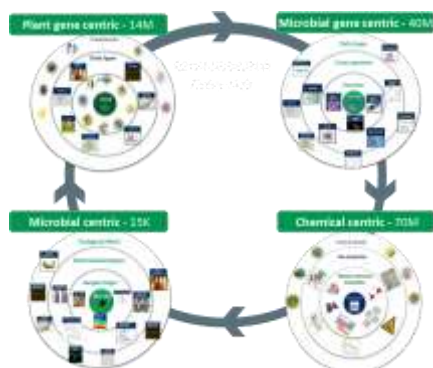
Science

Multidisciplinary scientific approach driving our R&D



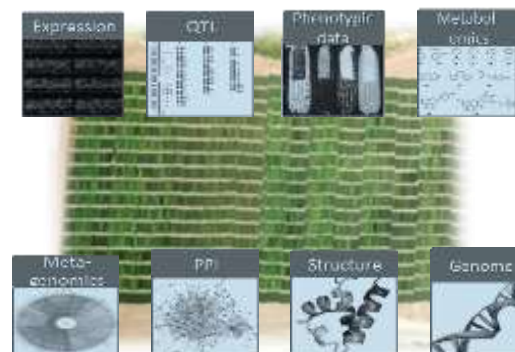
Interconnected Data Hub

Computational integration of 'Big Data' - currently four interconnected databases

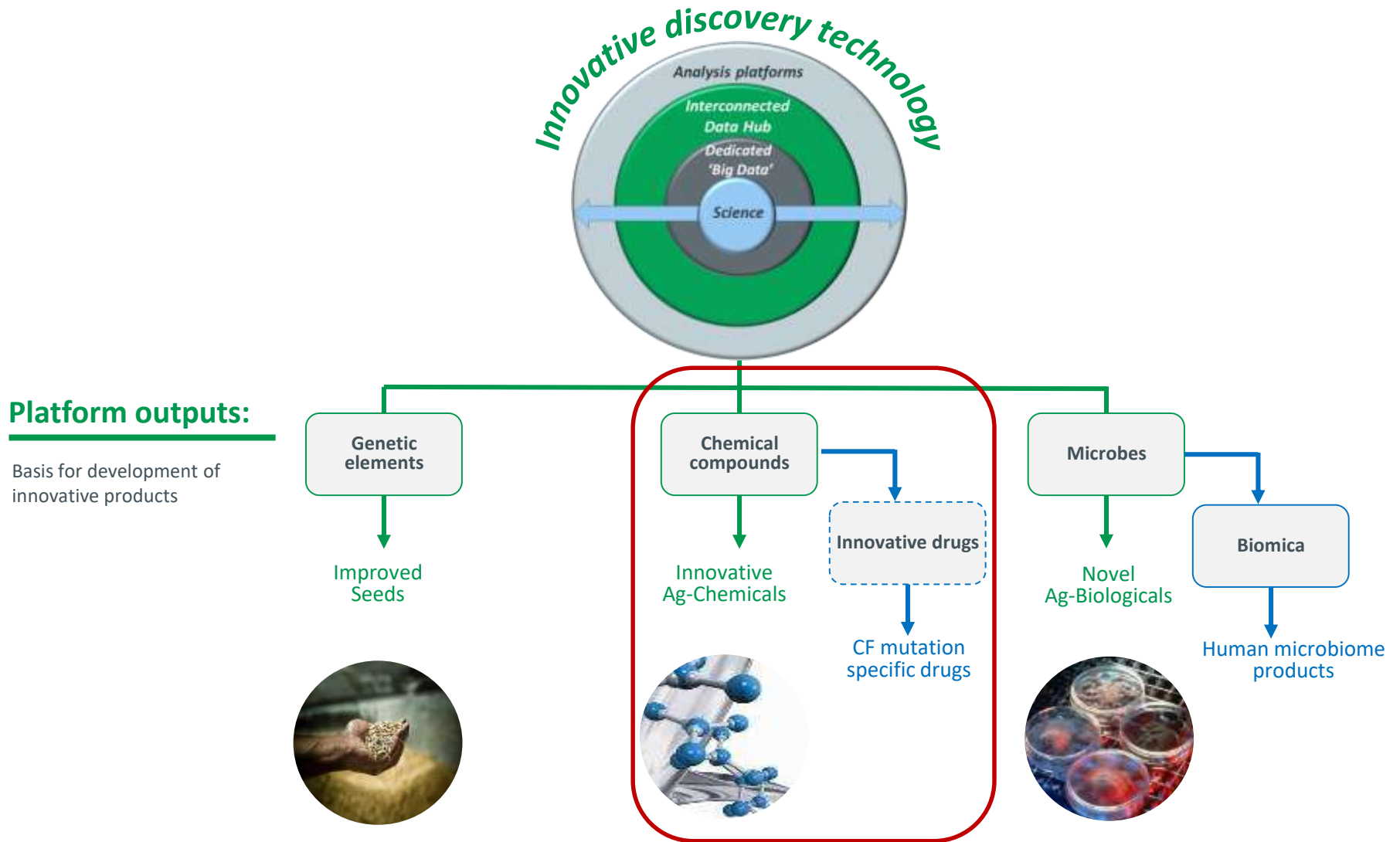


Dedicated 'Big Data'

On-going accumulation - public resources and problem-tailored experiments



Application pathways



Market Information – Drug Market Size

Treatment is divided into:

Tier 1

Symptomatic drugs
for all CF patients

- Average annual cost per patient is ~\$50,000*
- Market size **\$3.7 billion**



Tier 2

Mutation specific drug
to restore gene function

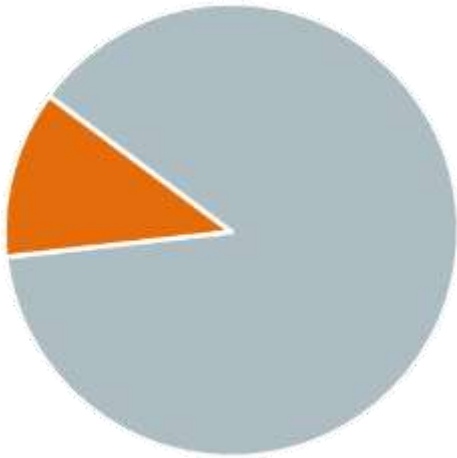
- Emerging market:
 - only 2 available treatments, consisting of a market of ~ **\$ 2.1B in 2017**
 - Most mutations do not have a solution
- Average annual cost per patient is ~\$275,000

* Heimeshoff et al, 2012

Tier 2 Market

Kalydeco

Potential populations:
5,000 patients



Lunched: **2012**

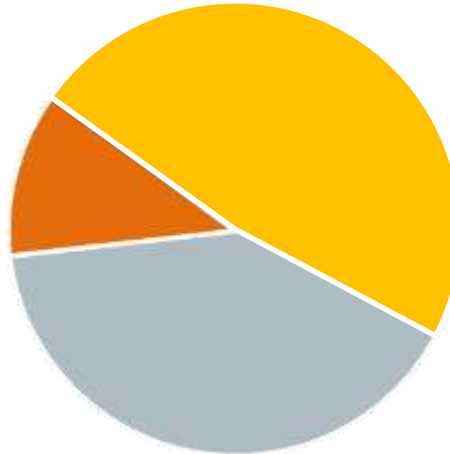
Annual cost per patient: **\$310,000**

2017 revenue : **\$800M**

Market penetration: **~50%**

Orkambi

Potential populations:
25,000 patients



Lunched: **2015**

Annual cost per patient: **\$265,000**

2017 revenue : **\$1.3B**

Market penetration: **~20%**

Next Generation (phase II)

Potential populations:
65,000 patients



**~5,000 CF patients with other mutations
do not have a solution in the CFF pipeline**

Non-conventional motivation: Yonatan, 12 years old with N1303K and a splicing mutation



Bronze Medal, Israeli National Judo
Championship, up to 30 Kg,
3 years in a row
(Malnutrition has its benefits)

Agenda

- Introduction: Evogene + Yonatan = EvoYon
- **EvoYon approach**
- Initial results
- Summary

EvoYon's Approach

Discover and screen small molecules for treatment of specific mutations, utilizing Evogene's computational tools & experts:

- Proprietary algorithms and pipelines- PoinTar™ and PointHit™
- Big data infrastructure
- “Chemunity”: virtual database of 156 million compounds

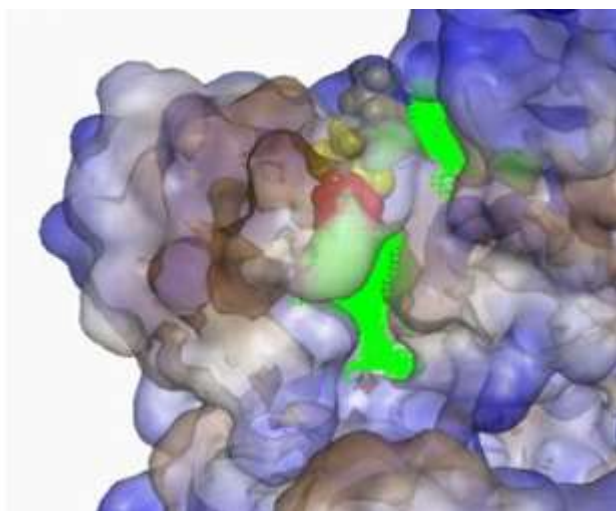
Test molecules in high throughput *in vitro* screen (using Ussing chambers) to be advanced to clinical trials



Computational Discovery

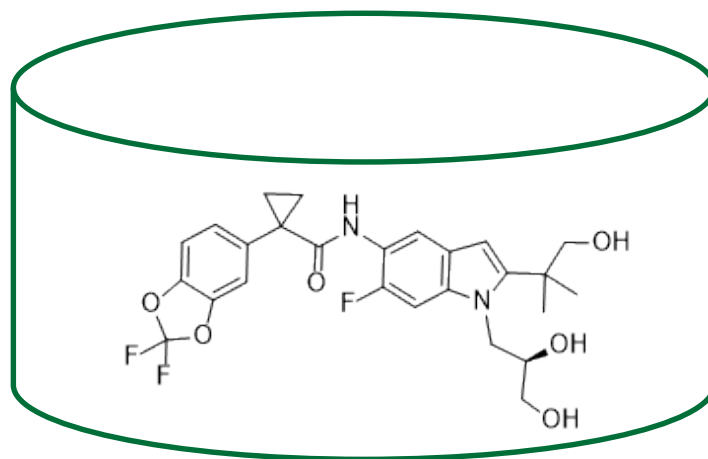
Target Protein Structure

Strategy for restoring mutant protein functionality



Chemical Database

156 M small molecule virtual database: **Chemunity™**



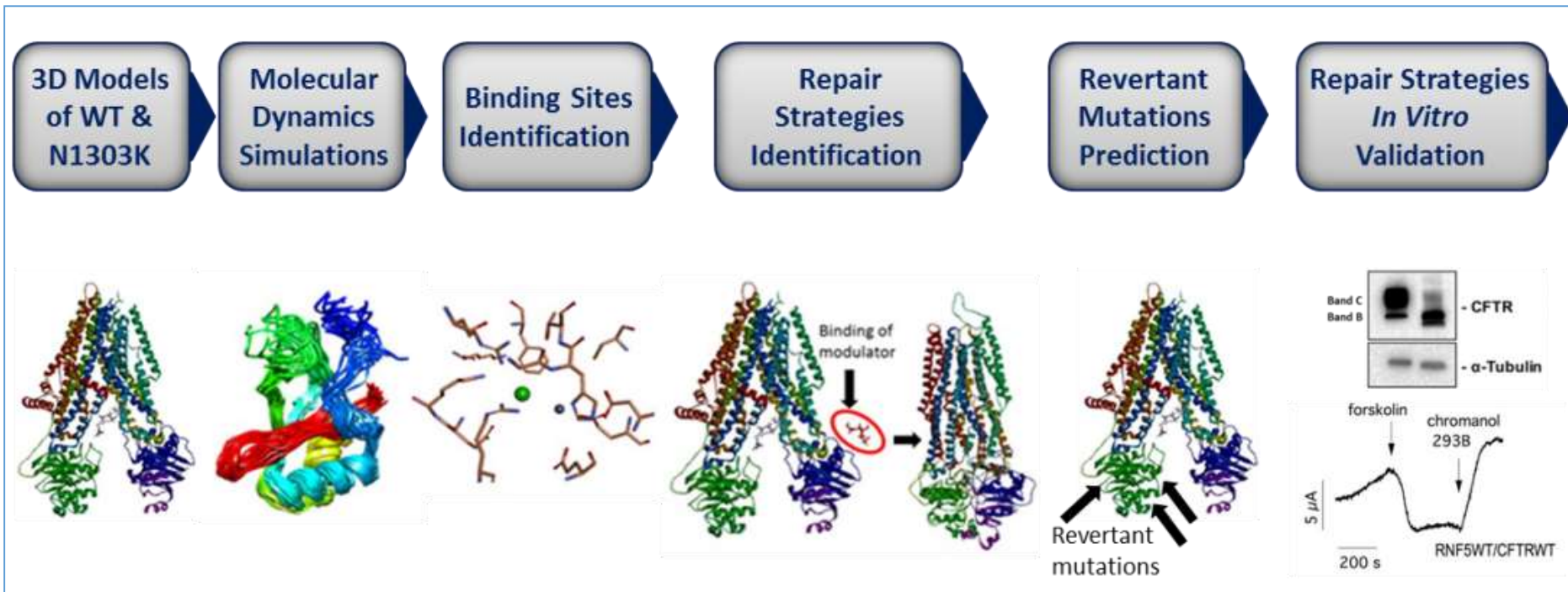
PointHit™

High throughput virtual screening pipeline
To provide a library of prioritized molecules

Computational Discovery

Target Protein Structure

Strategy for restoring mutant protein functionality:



Computational Discovery

Chemical Database

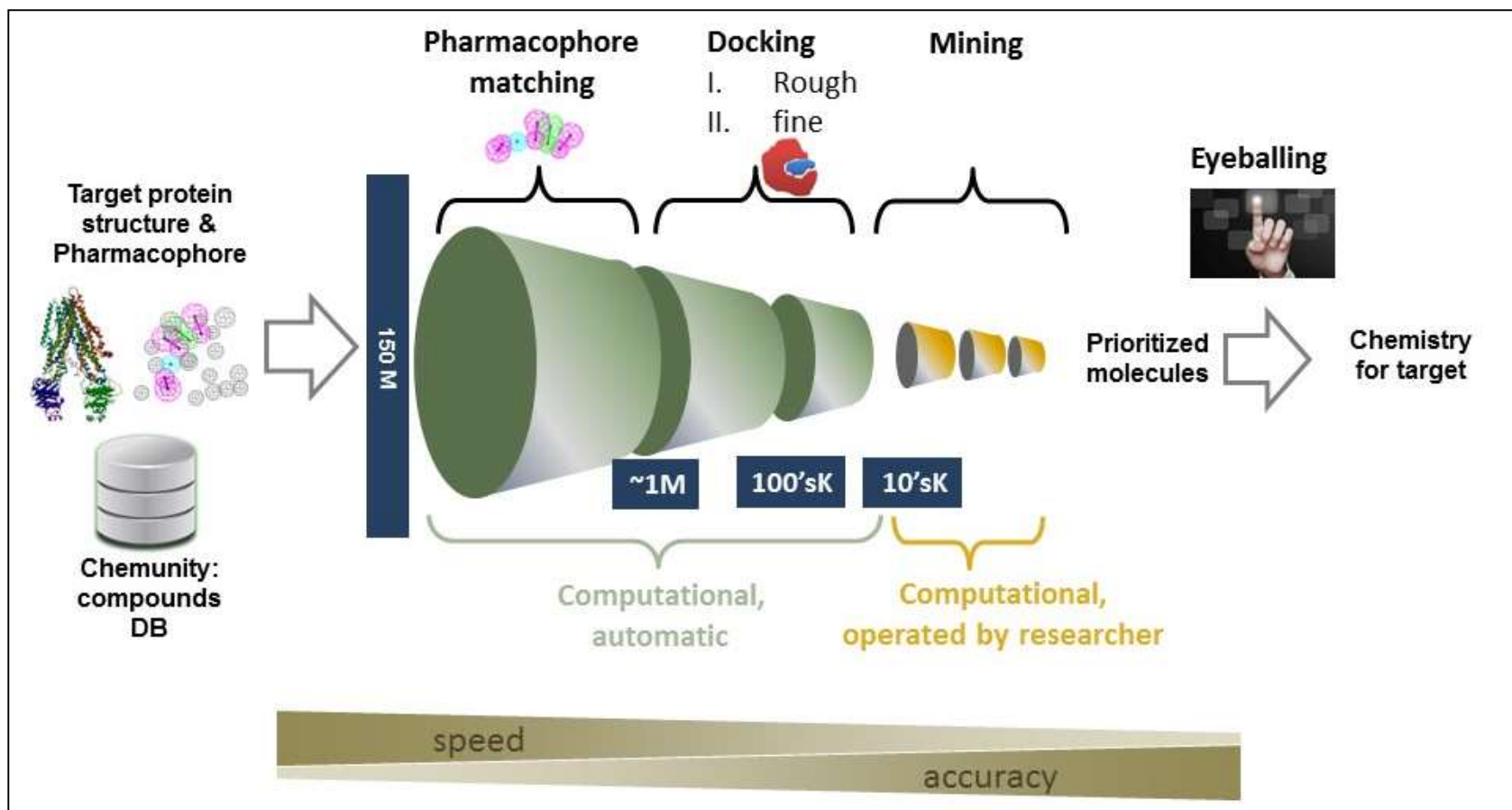
156 M small molecule virtual database (Chemunity™):



Computational Discovery

PointHit™

- PointHit performance is 156M, greater by 100x than existing pharmaceutical standard
- Very short processing time: 5 days
- Increased molecule diversity lead to greater potential of finding best candidate for a drug

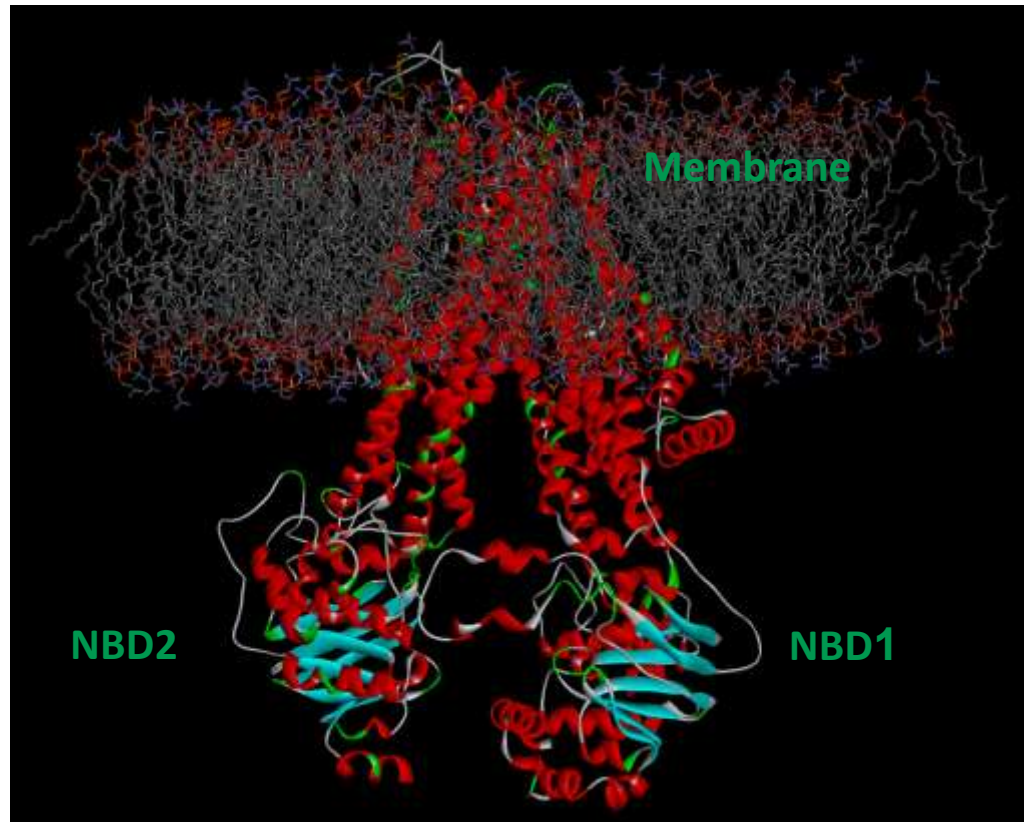


Agenda

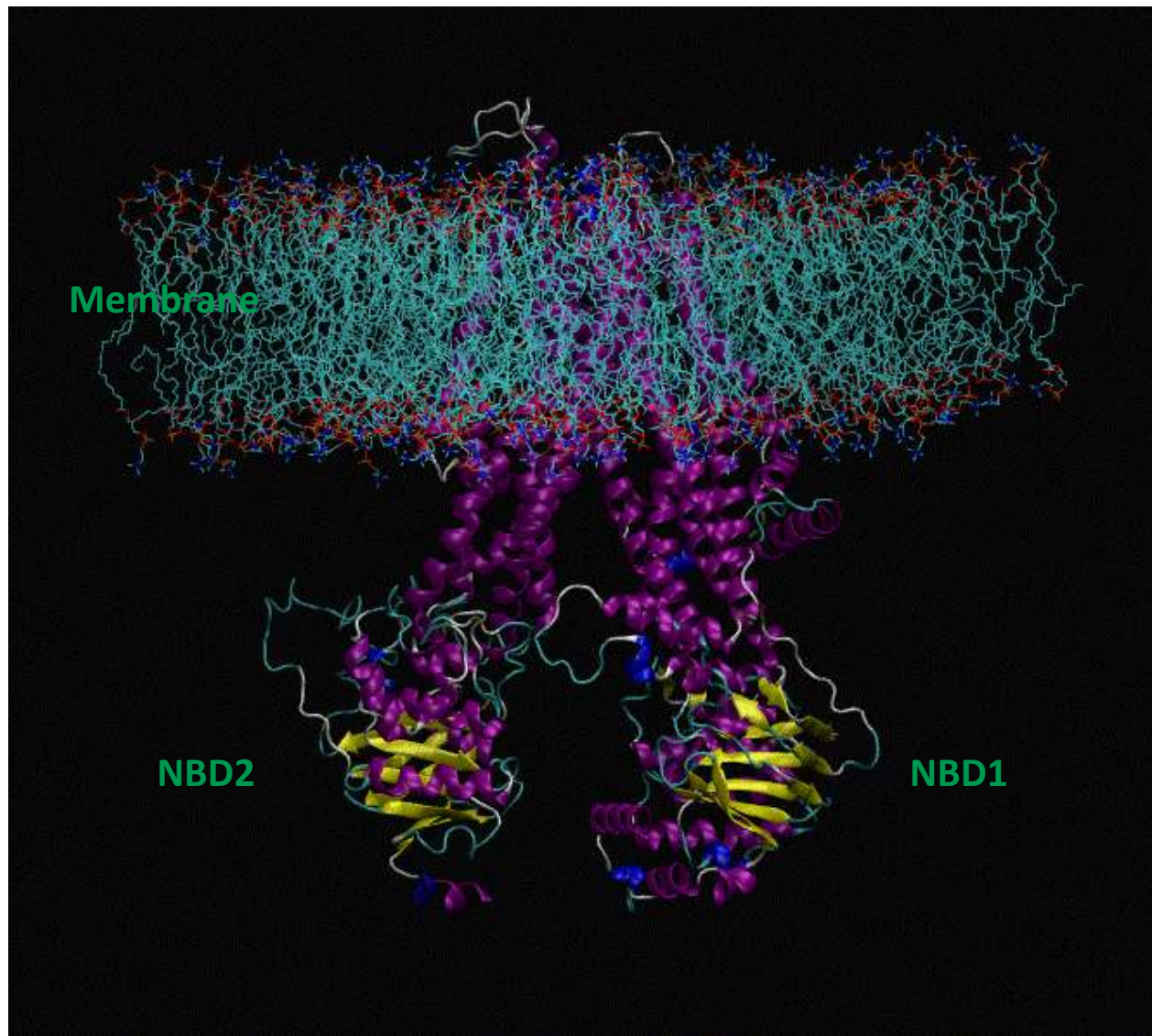
- Introduction: Evogene + Yonatan = EvoYon
- EvoYon approach
- **Initial results**
- Summary

EvoYon CFTR WT model

- Based on human PDB code: 5uak (Liu F. et al., Cell 2017)
- Missing loops were modeled using public CFTR models (Mornon and Dalton)
- The R domain (segment 671-843) was not modeled
- Overall: ~180,000 atoms in the system composed of: CFTR, membrane, *explicit water* and counterions

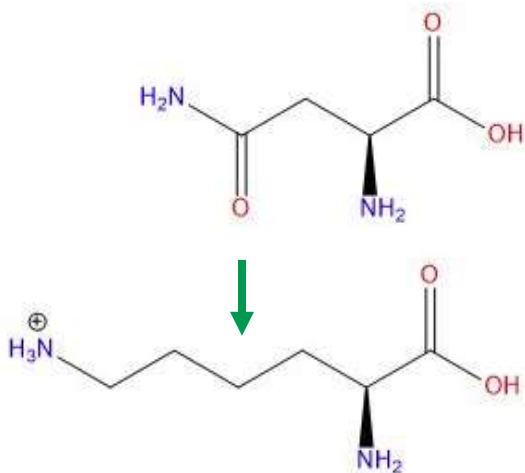


EvoYon CFTR WT model – 100ns Molecular Dynamics (MD) simulation

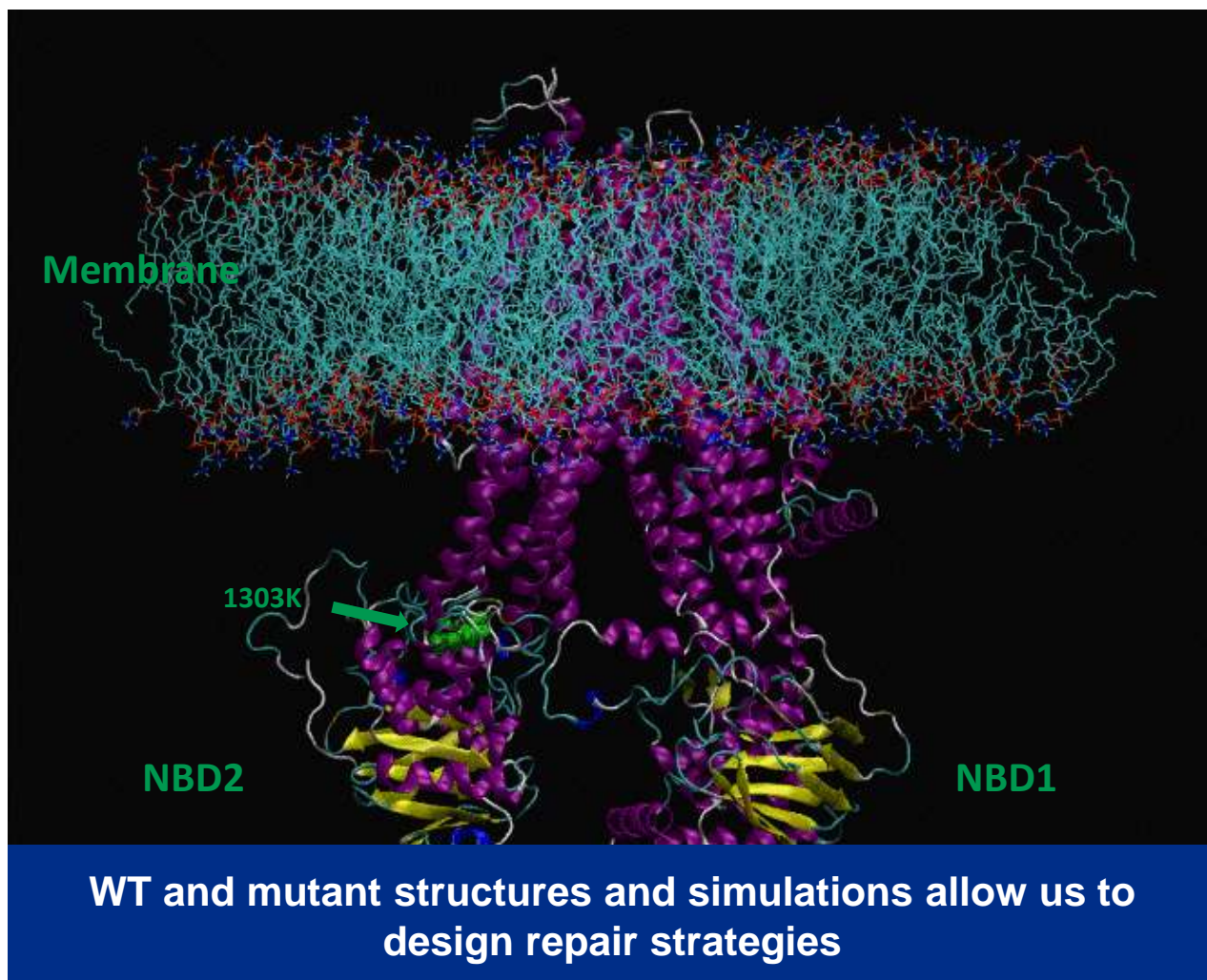


The N1303K mutation

- N1303K is a class II mutation
- Asparagine (short, polar amino-acid) is changed to Lysine (long, positively charged)
- Lysine1303 is repulsed by adjacent Lysine at 1302
- The overall folding of N1303K is similar to the folding of the WT – except for the NBD2 domain (Partial support: Meacham et al., 1999 and further support from our molecular dynamics stability analysis)



EvoYon CFTR N1303K model – 100ns MD Simulation



N1303K Repair Strategy

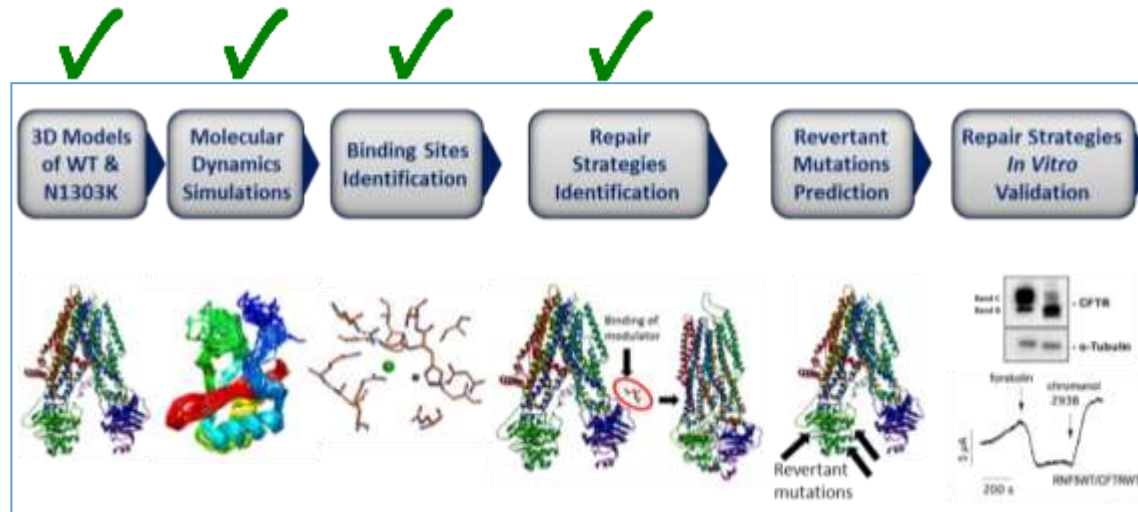
Primary assumptions

- N1303K is a class II mutation – undergoing degradation in the ER, not reaching the apical cell membrane
- N1303K is actively degraded by one of the cellular degradation systems (Inhibition of proteasomes or aggresomes rescues N1303K, Rapino et al, 2015)
- If N1303K avoids degradation and reaches the cell membrane, it is functional (treatment with cysteamine & EGCG, Tosco et al, 2016)

Repair strategy

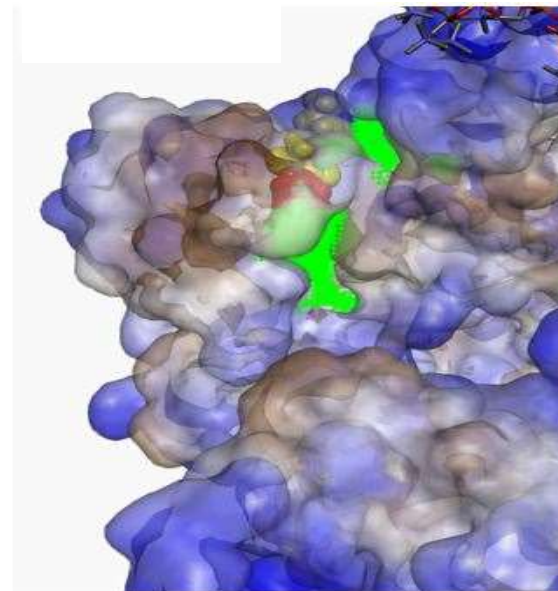
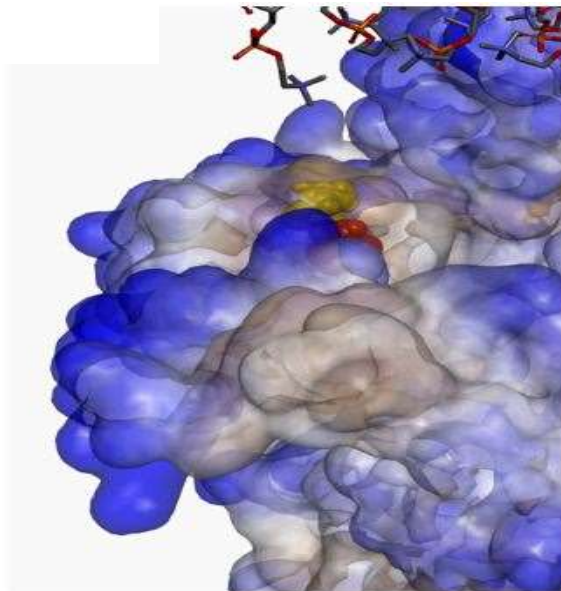
- Identification of WT vs. N1303K structural differences may point out the recognition site of the degradation system(s).
- Blocking these mutation specific recognition site(s) using small molecules may prevent N1303K degradation

EvoYon's Discovery Initial Results



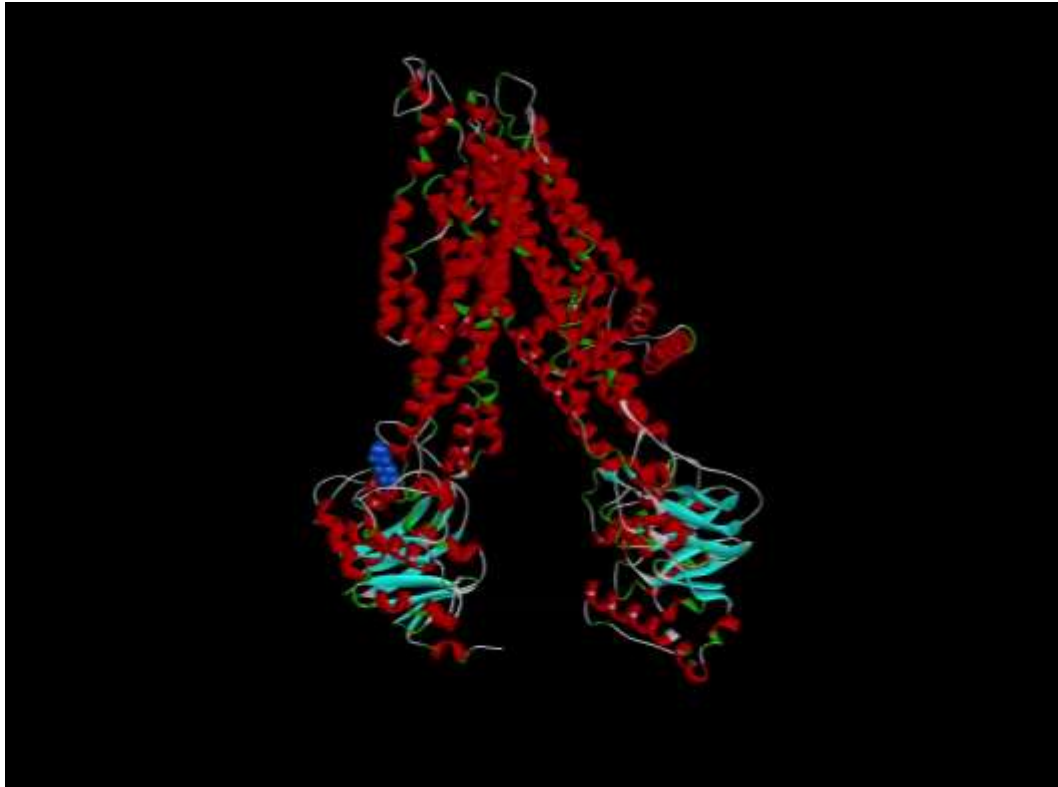
Normal protein

Mutant protein



N1303K Strategy 1: Animation of the new groove

N1303K



Lys1302 – in blue

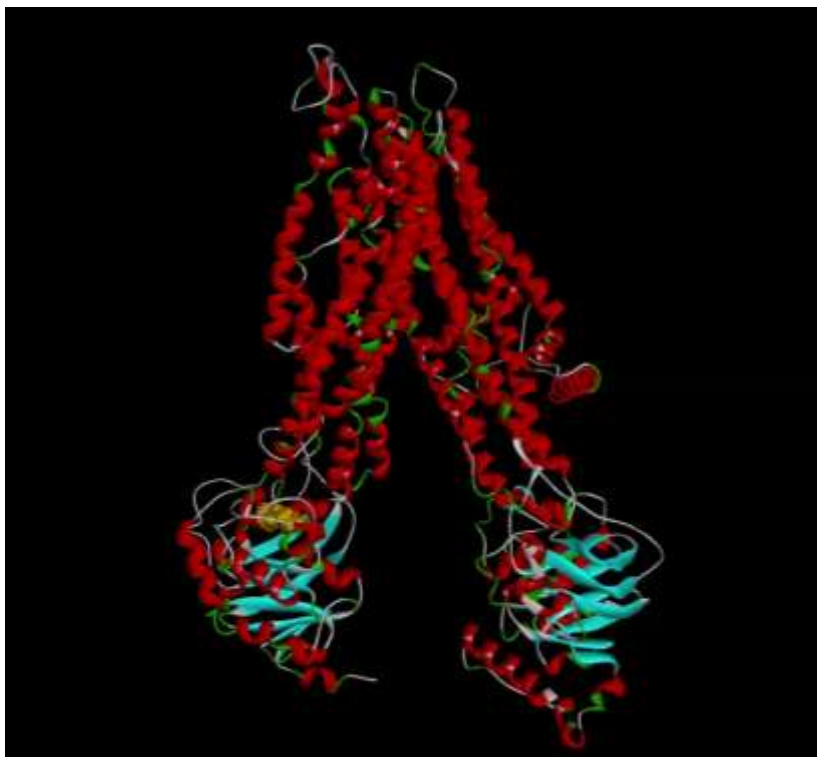
WT



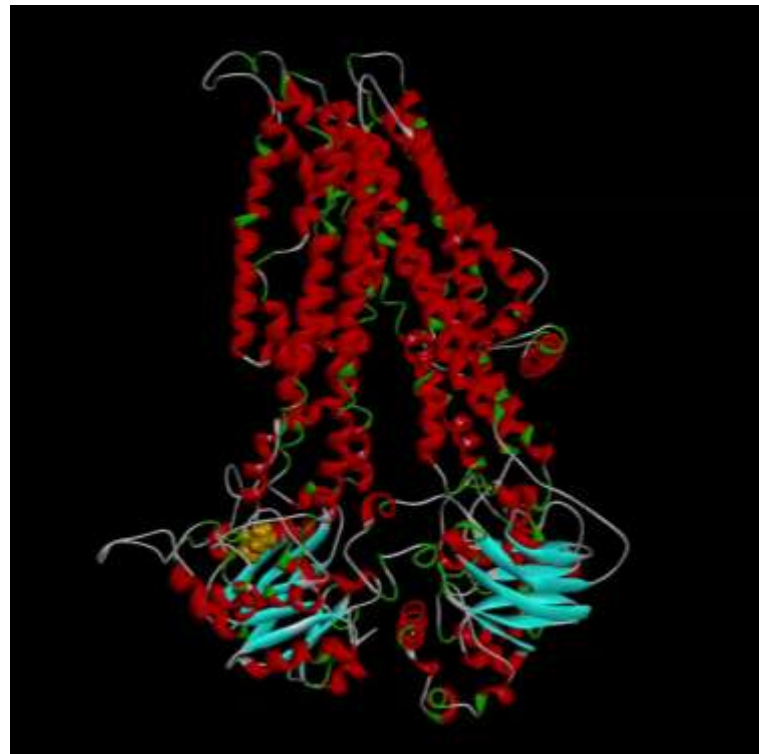
Lys1302 – in blue

N1303K Mutation vs. WT – STRATEGY 2

N1303K



WT



Agenda

- Introduction: Evogene + Yonatan = EvoYon
- EvoYon approach & Initial results
- **Summary**

Summary

- **Evogene is a leader in Ag. Chem., operating innovative high throughput pipelines enable efficient target based small molecule discovery**

- **Significant value of the N1303K mutation:**
 - ~900 patients make a potential drug (on 2025: ~1,500 patients) – commercially viable
 - No competition: this mutation does not have correctors in current pipelines

- **We believe that Evogene's technologies, methodologies, experts and the available new CFTR structures have a good chance to discover innovative mutation specific drugs**
 - Evogene has generated CFTR models for WT and N1303K mutant based on new human structure
 - Innovative strategy for amending class II mutation by obstructing degradation system(s)
 - Development of multiple repair strategies supported by computational resources

EvoYon team

- **Idit** Buch, PhD
- **Ben** Gradus, PhD
- **Gali** Golan, PhD
- **Roberto** Olender, PhD
- **Alex** Tasker
- **Eran** Kosover
- **Hanoch** Senderowitz, PhD, Consultant

EvoYon: Computational Discovery of Cystic Fibrosis Mutation Specific Drugs



Ori Inbar, PhD

Technological Product Manager, Evogene
Father of a 12 years old boy with CF
Chairperson, the CF Foundation of Israel

