Finanziato dall'Unione europea NextGenerationEU

Ministero dell'Università e della Ricerca

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PIANO NAZIONALE DI RIPRESA E RESILIENZA

HEAL ITALIA ROADSHOW
TECNOLOGIE E INNOVAZIONE
INNOVATION ON THE ROAD

PRIMO CONVEGNO NAZIONALE DEL CENTRO DI MEDICINA DI PRECISIONE – HEAL ITALIA PER LE MALATTIE RARE

www.ancona.centridimedicinadiprecisione.it

Responsabile scientifico
Prof. **Gianluca Moroncini**

UnivPM – Ancona
Aula Montessori
Facoltà di Medicina
e Chirurgia

venerdì 28 febbraio
14:30 → 18:30
sabato 1 marzo
09:00 → 13:00

Progetto "Health Extended ALliance for Innovative Therapies, Advanced Lab-research, and Integrated Approaches of Precision Medicine (HEAL ITALIA) Codice PE00000019, CUP I33C22006900006 – finanziato dal PNRR M4C2 I1.3 – DD MUR 341 del 15/03/2022

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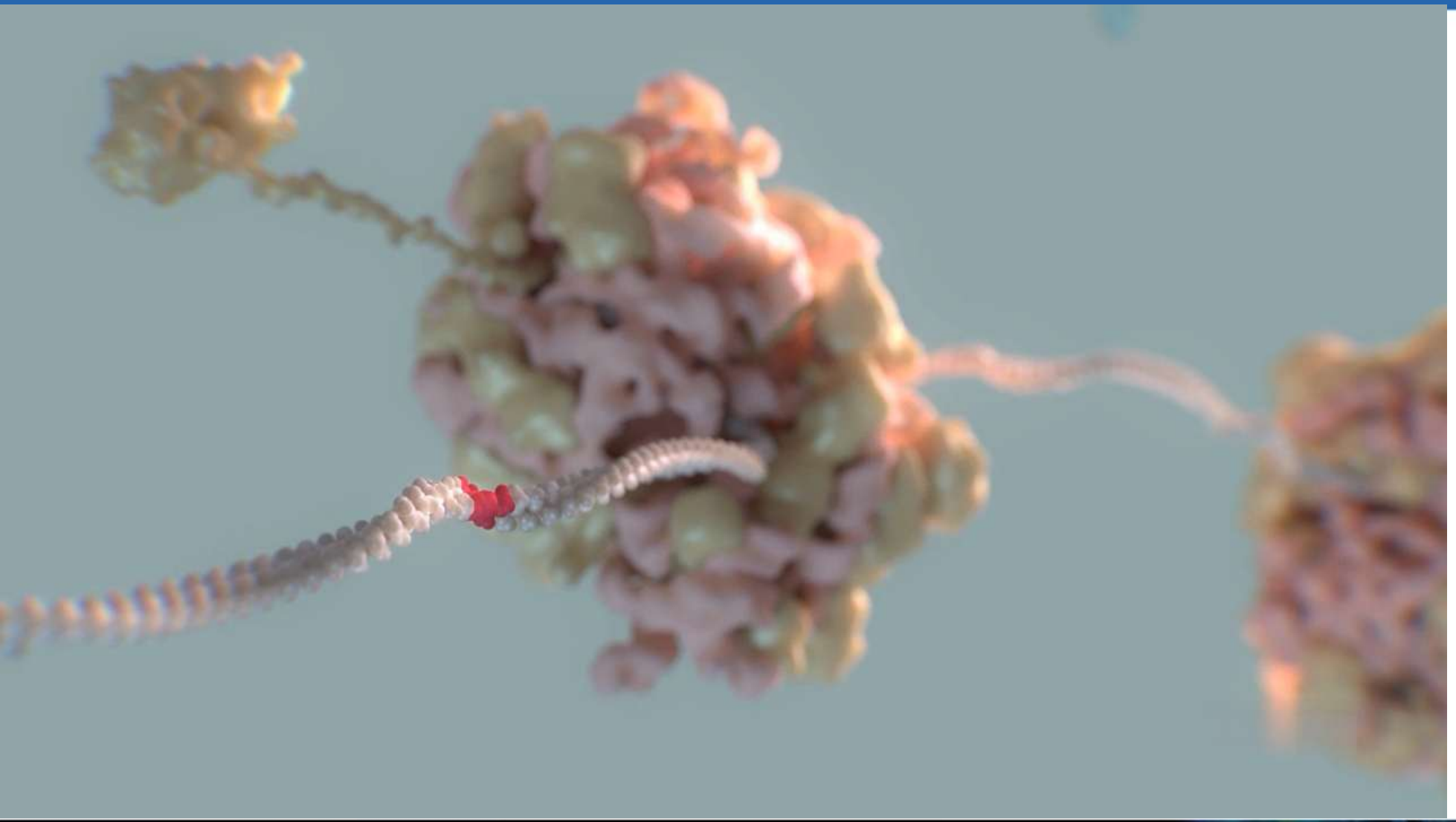
Medicina di Precisione per le Malattie Rare: Strategie Mirate per le Mutazioni Nonsense

Ivana Pibiri e Laura Lentini

Professore Associato di Chimica Organica,
Università degli Studi di Palermo
Collaboratore Spoke "Next Gen Therapeutics"
Progetto HEAL ITALIA



PROTEIN SYNTHESIS

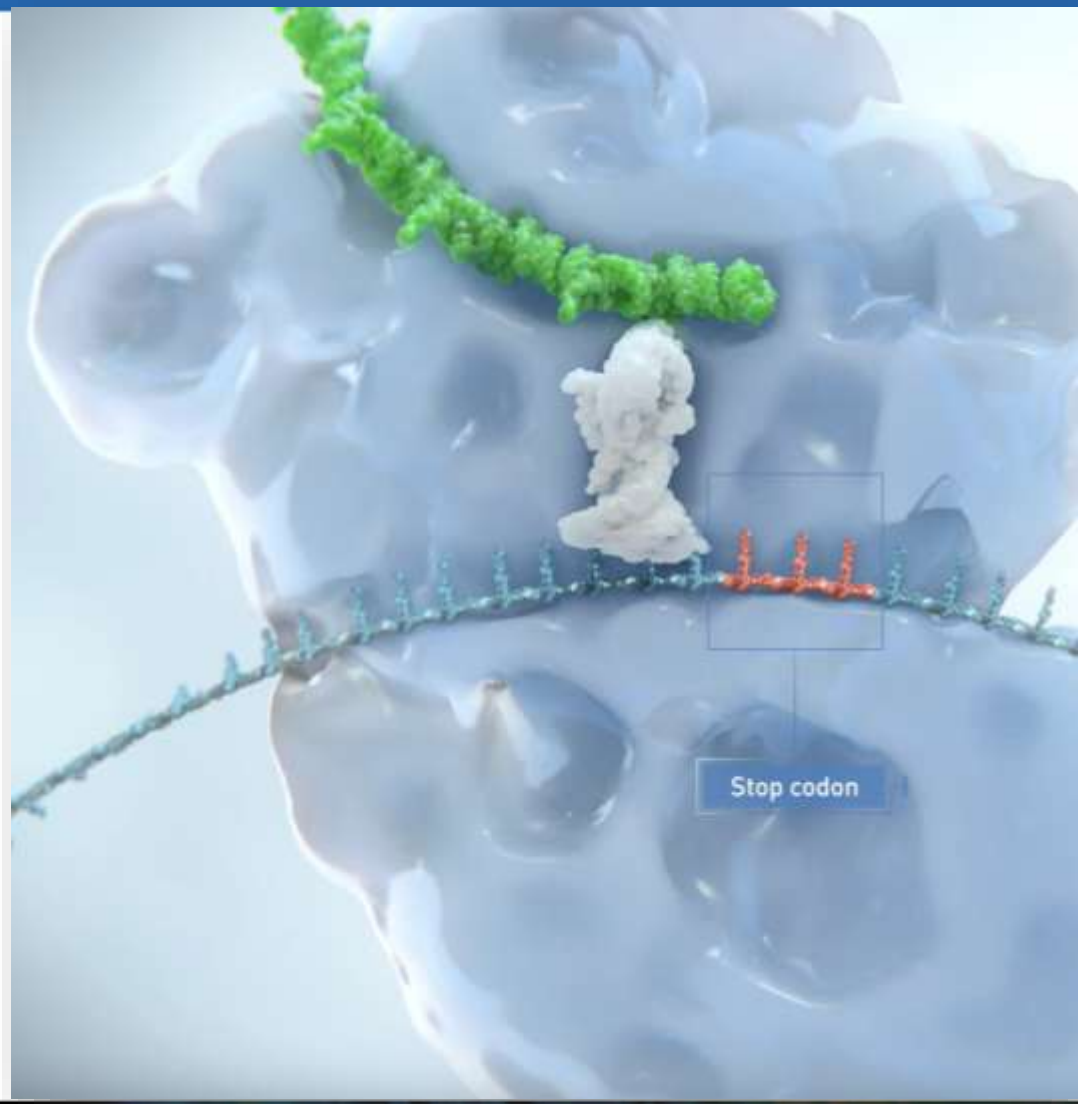
Nonsense mutations

generate premature stop codons causing a premature termination of the protein synthesis and the production of truncated polypeptide

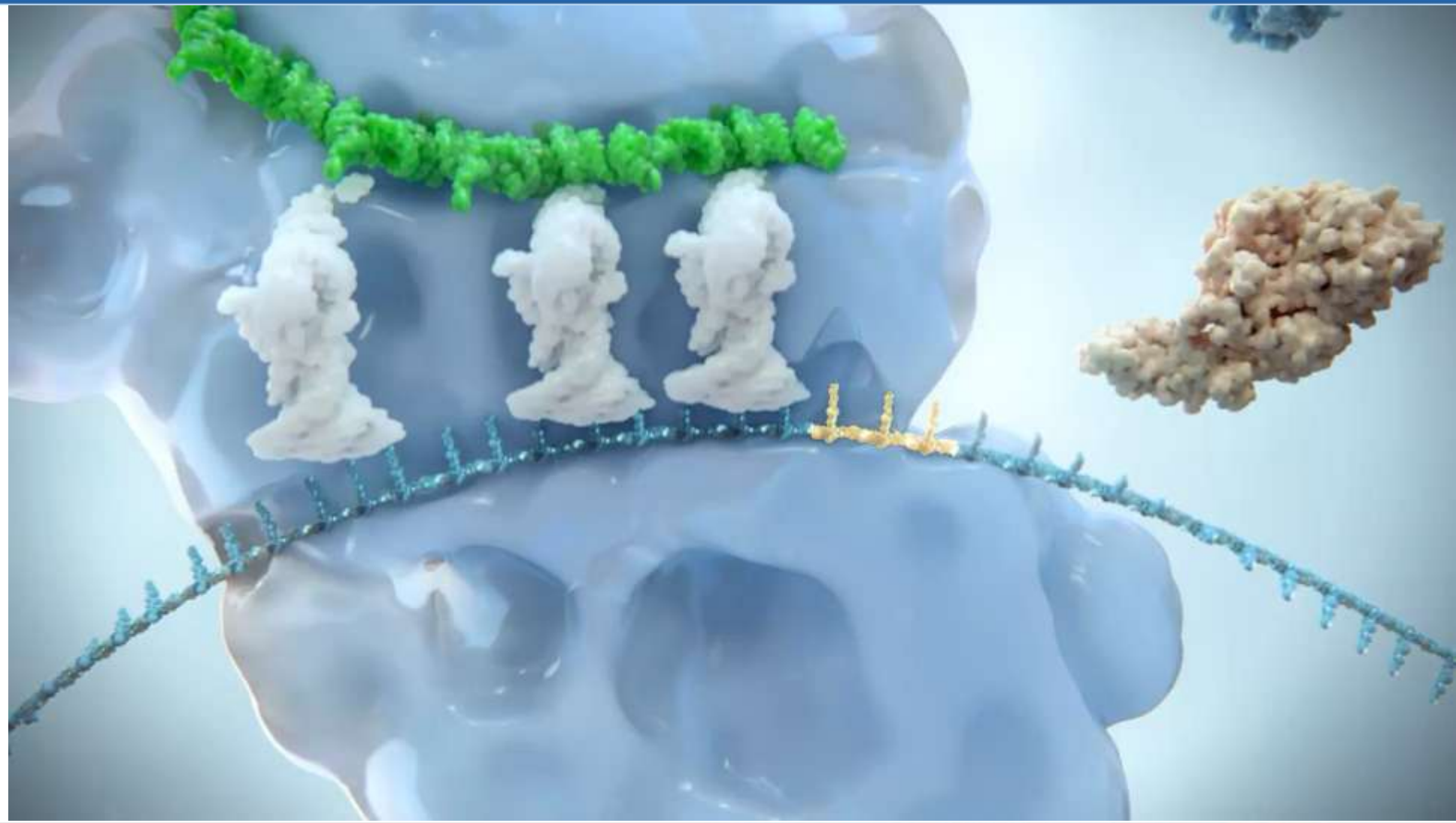
Rare genetic disease

nonsense mutations are the cause of about 11% of all genetic disorders, among these :

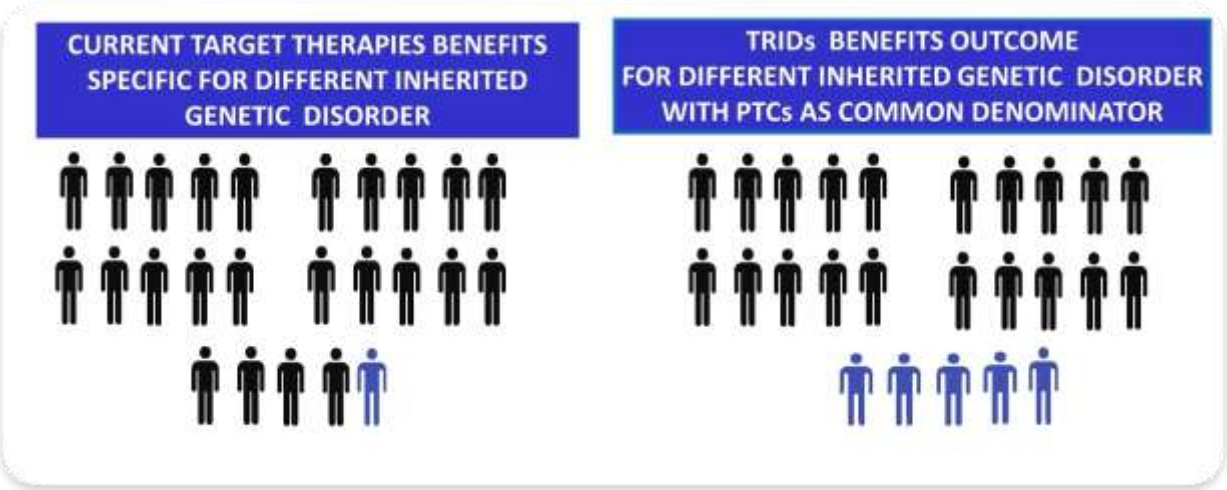
Affected gene	Disease
DMD	Duchenne Muscular Dystrophy
CFTR	Cystic Fibrosis
CHM	Choroideremia
GLA	Fabry disease
LRBA	Primary Immune Deficiency (LRBA deficiency)



Translational Readthrough Inducing Drugs TRIDs

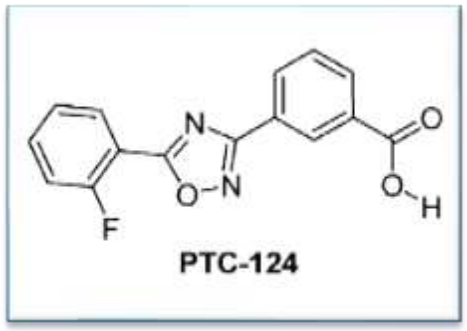


Nonsense Strike

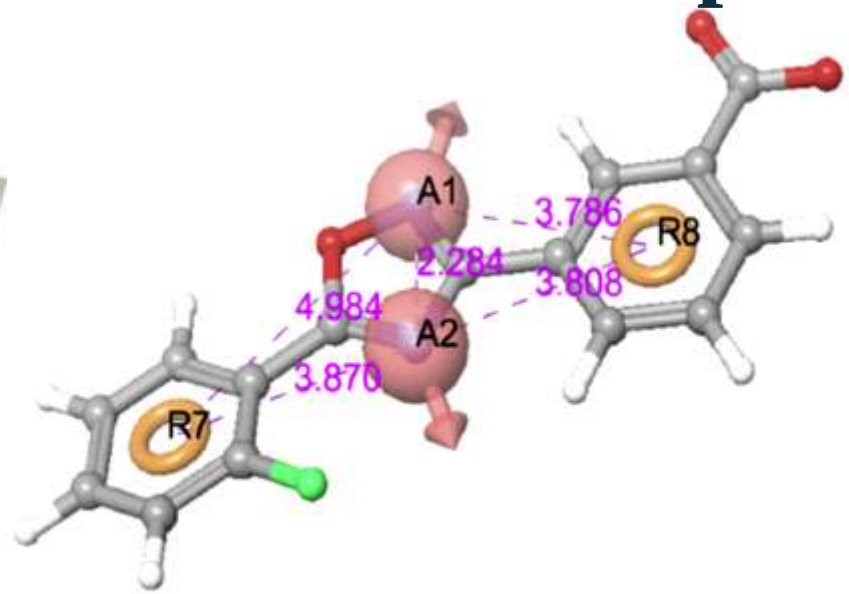


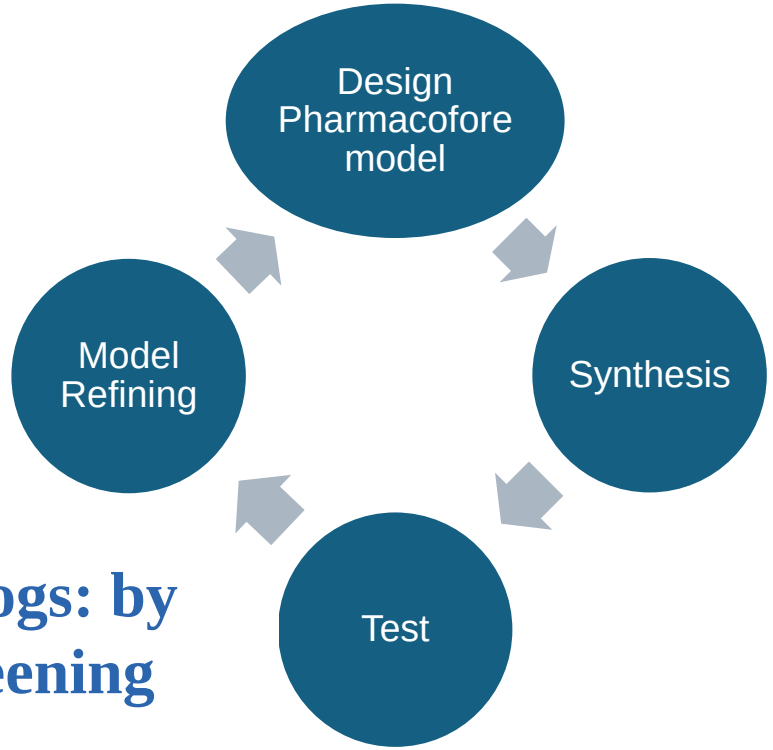
Precision Medicine Impact

New TRIDs are a Therapeutic Need

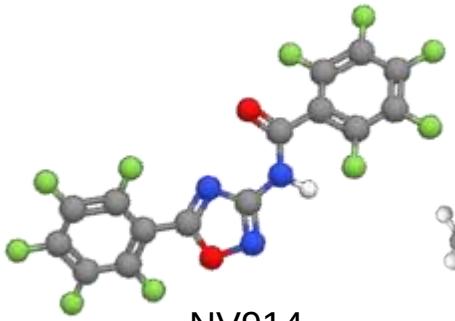


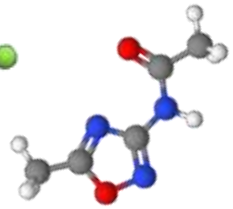
E.M. Welch et al. Nature 2007

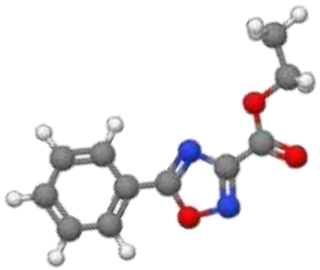




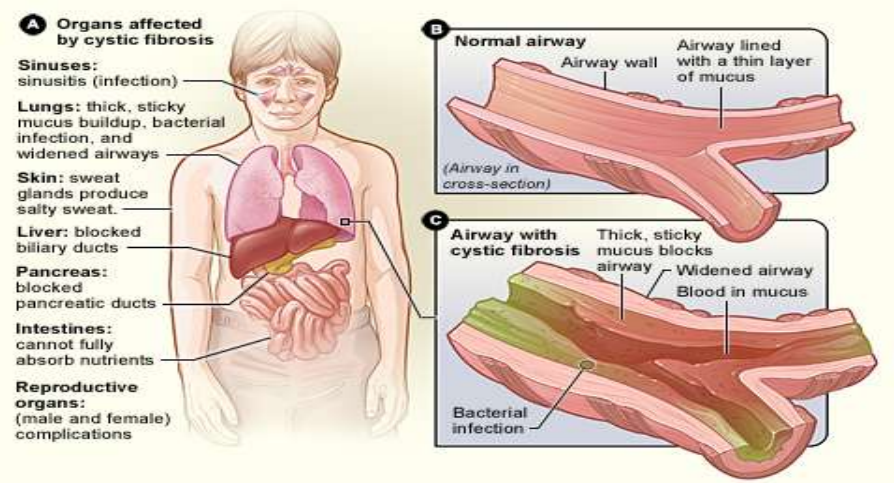
Design of Ataluren analogs: by ligand based virtual screening

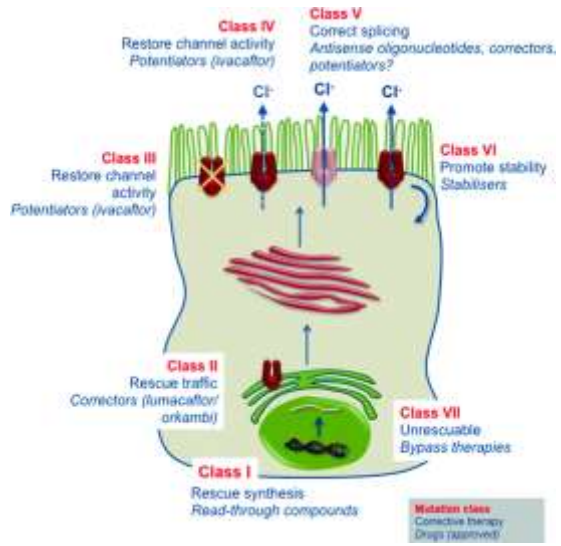

NV914


NV848

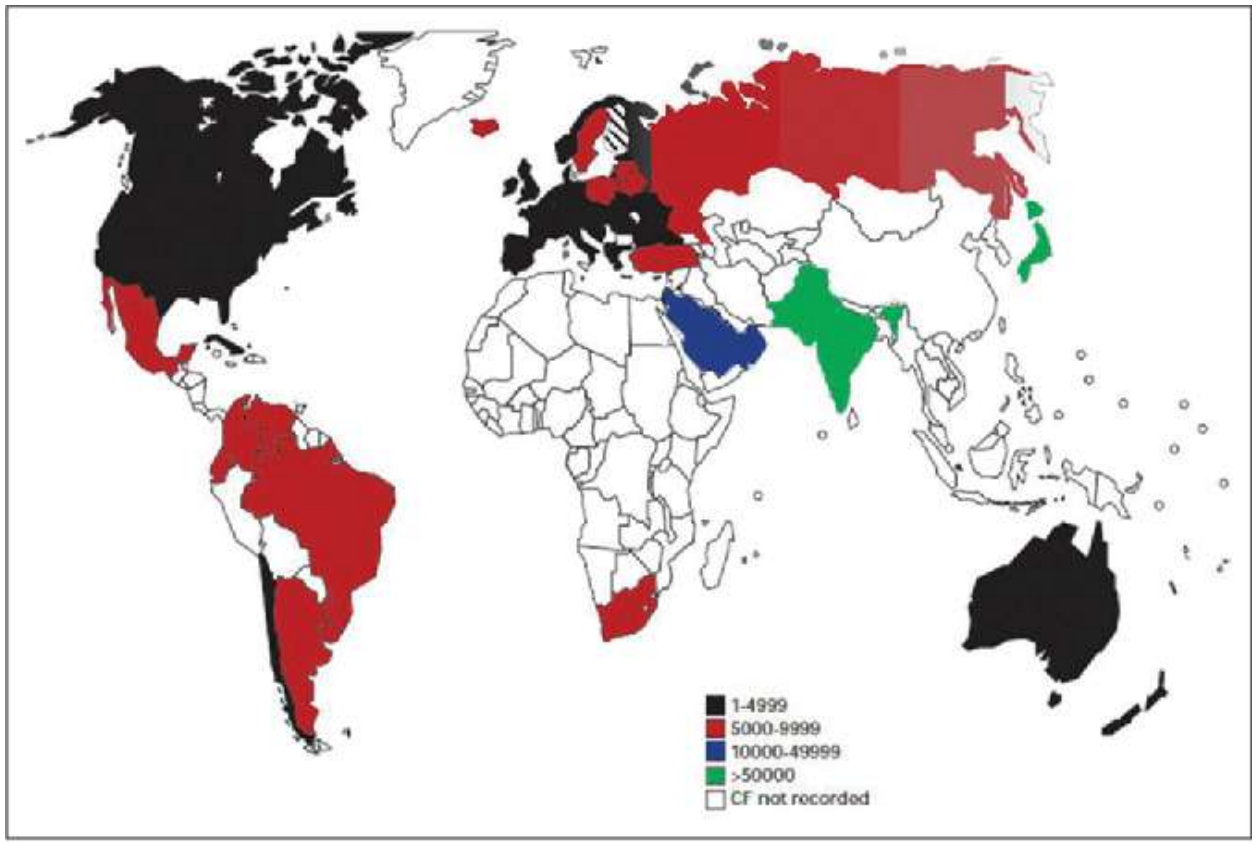

NV930

A disease model : Cystic Fibrosis



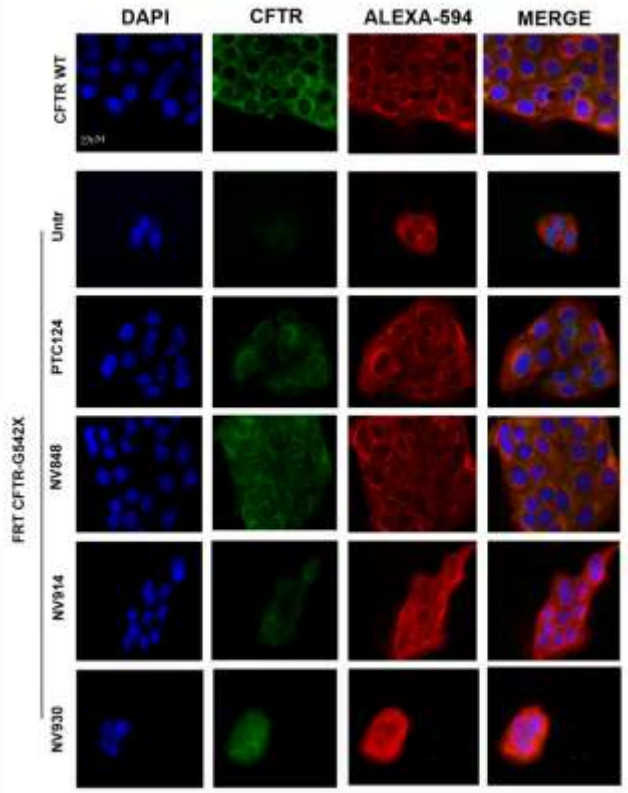


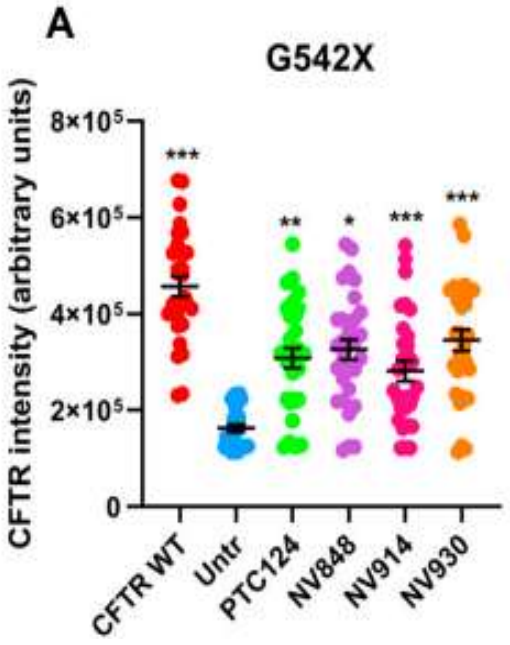
CFTR

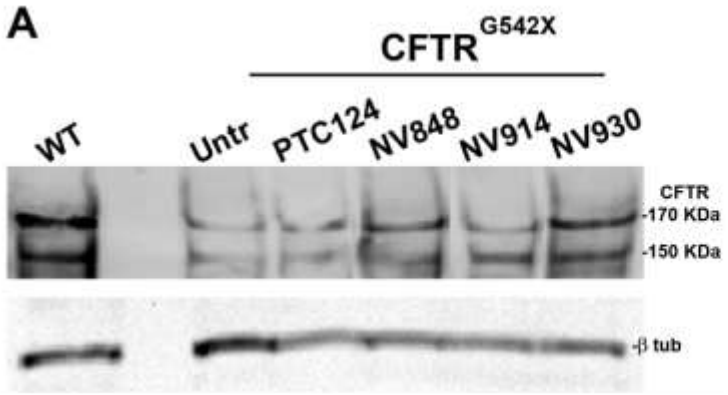


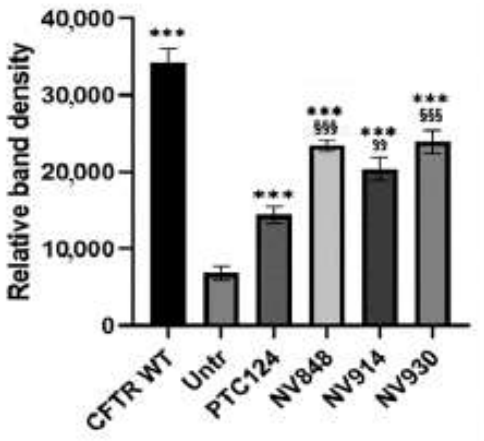
Validation of three new Leads on ndCF

MODEL FOR CYSTIC FIBROSIS: The treatment with the three molecules NV848, NV914, NV930 induced CFTR expression in Fisher rat thyroid cells expressing a stop CFTR mRNA after 24h



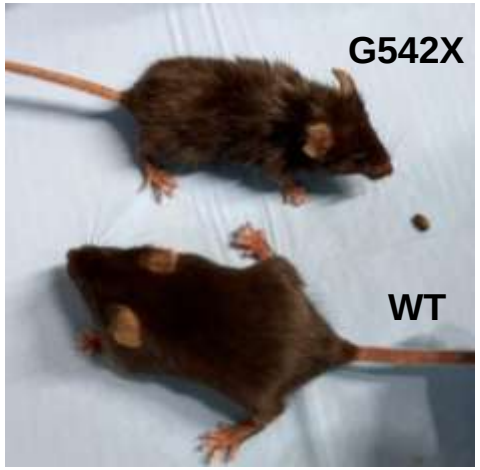


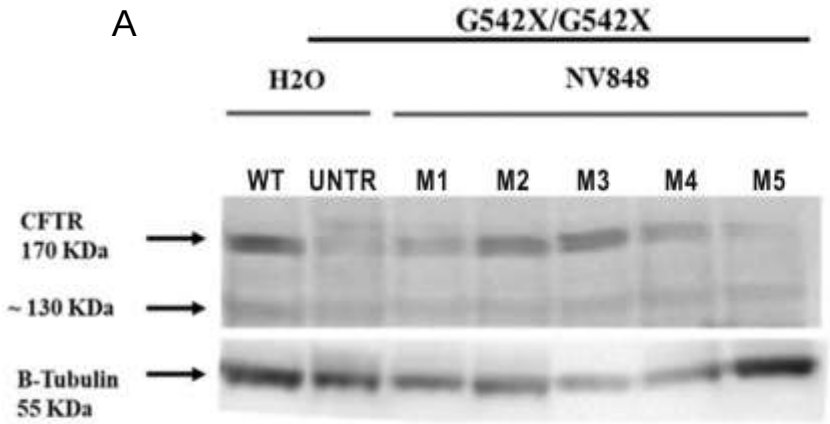


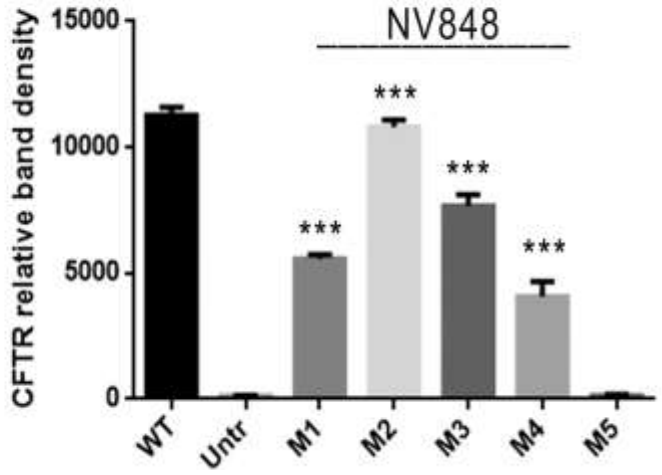


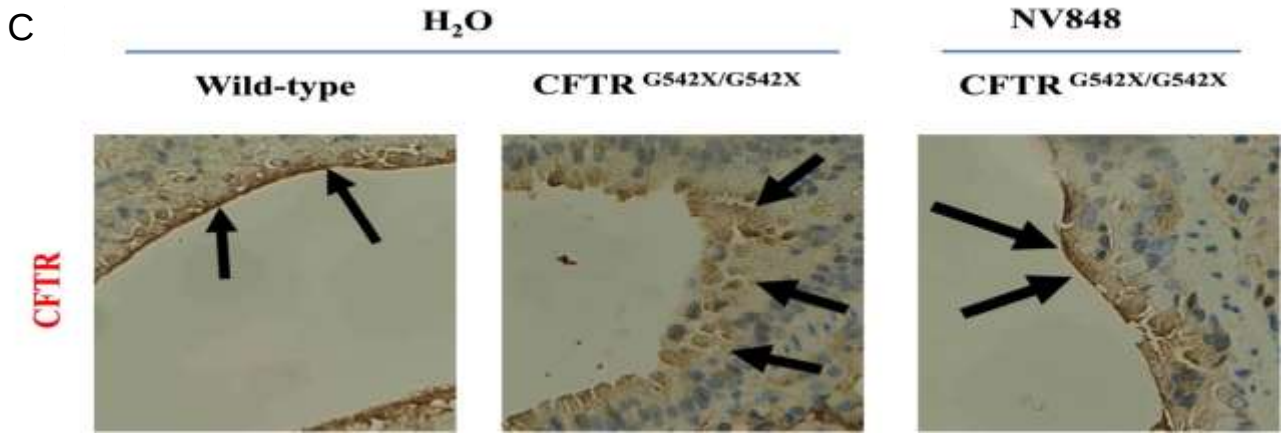
- Pibiri et al. PCT Int. Appl. (2019), WO 2019/101709 A1 20190531
- Pibiri et al. Int. J. Mol. Science 2020

In vivo test: NV848 mg/Kg chronic treatment in CFTR $^{G542X/G542X}$ mice









CFTR expression in the lungs after NV treatment in homozygous CFTR^{G542X} mice

A/B Western Blot analysis

C Immunohistochemical analysis

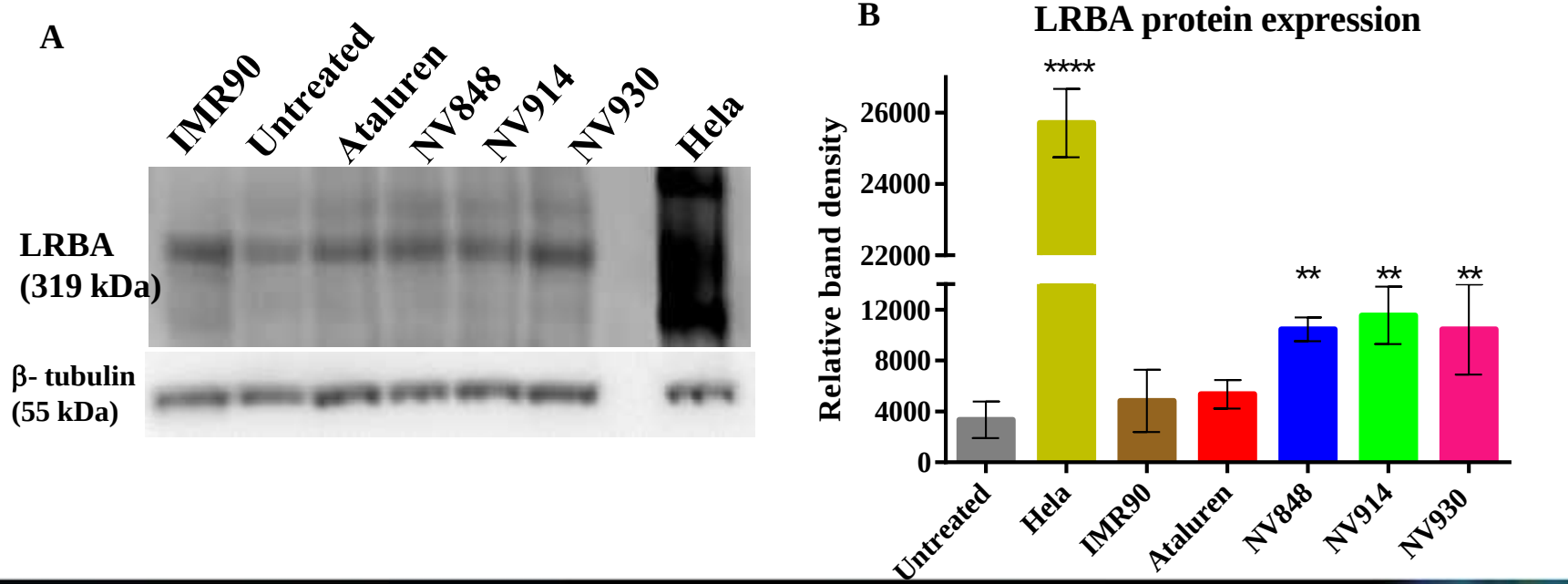
- Fiduccia et al. Mol. Ther. 2024

Primary Immunodeficiency Diseases (PIDs)

Rare genetic diseases characterized by complex clinical phenotype including autoimmune bicytopenia, granulomatous lymphocytic interstitial lung disease, non-cirrhotic portal hypertension, severe chronic diarrhea,
susceptibility to infections, increased risk of autoimmunity, hypogammaglobulinemia and lymphoproliferative syndromes

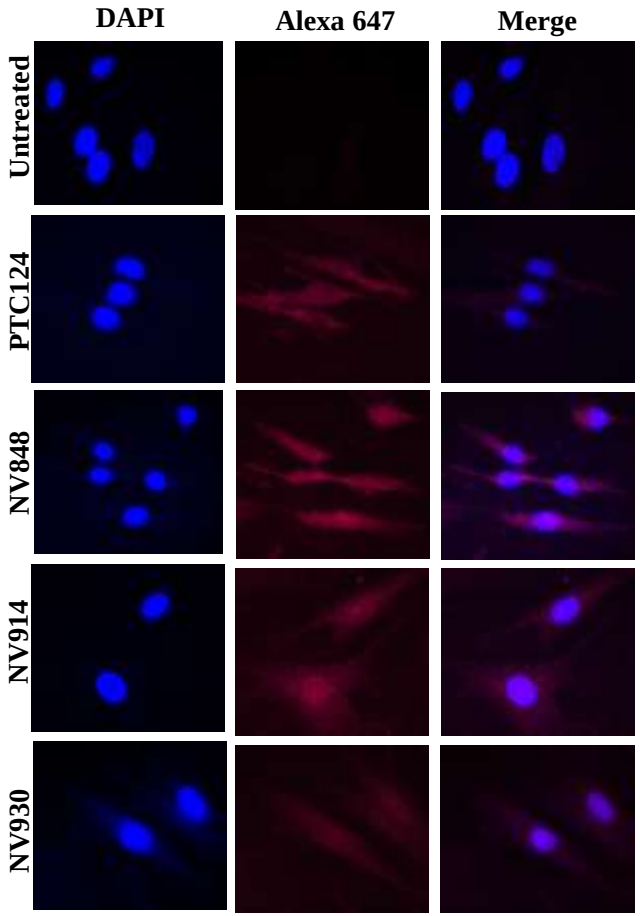
Validation of three new Leads on ndPID

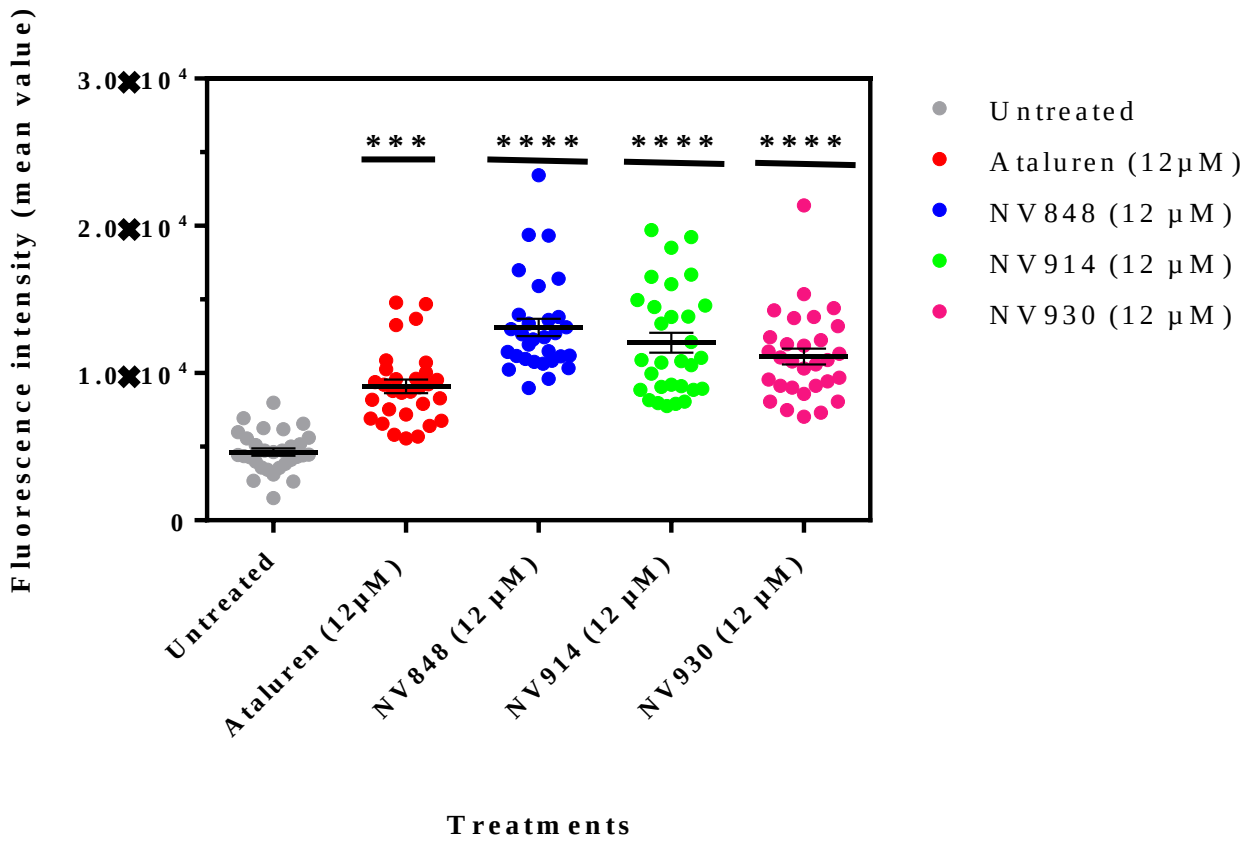
NV molecules outperform Ataluren in the readthrough



A) Western blot analysis showing LRBA protein expression after the indicated treatments in human LRBA R1683X fibroblasts. b-tubulin was used as loading control. Images were analysed by ImageJ software and the band density reported in graph B). p value <0.0001 was calculated by one-way ANOVA test statistical analysis.

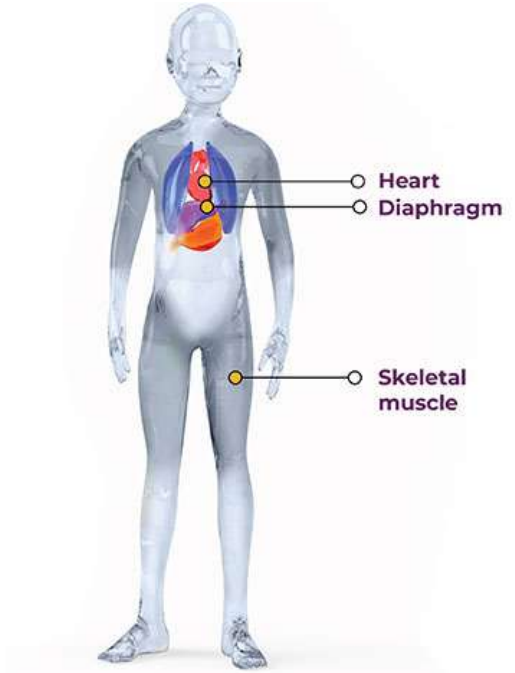
Immunofluorescence assay for evaluation of LRBA protein expression and correct localization

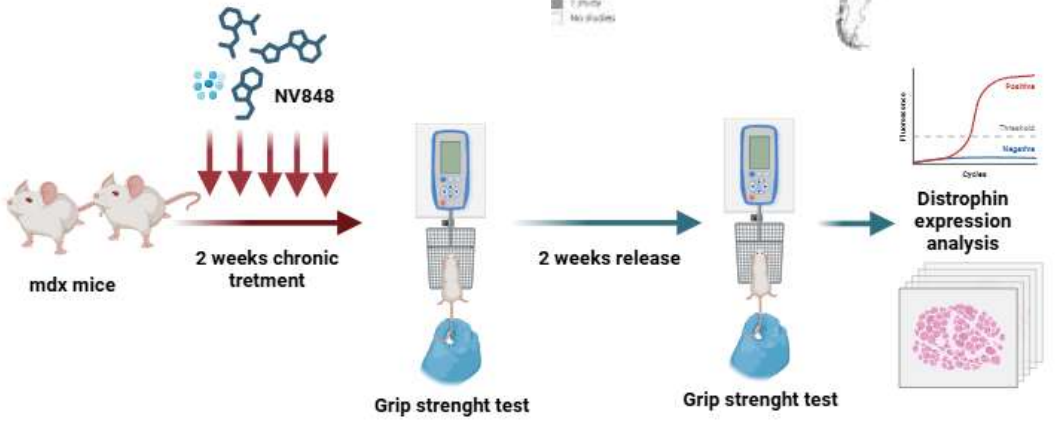




Duchenne Muscular Distrophy

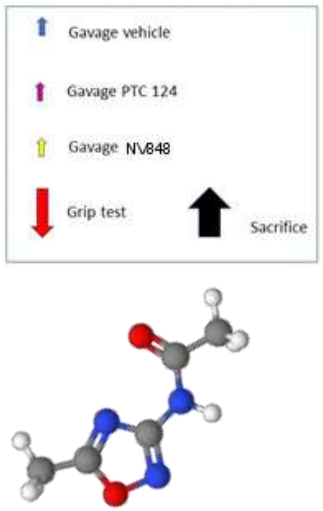
Duchenne muscular dystrophy (DMD) is a severe, progressive, muscle-wasting disease. The earliest symptoms are difficulties with climbing stairs, a waddling gate and frequent falls; patients present with these symptoms around 2–3 years of age

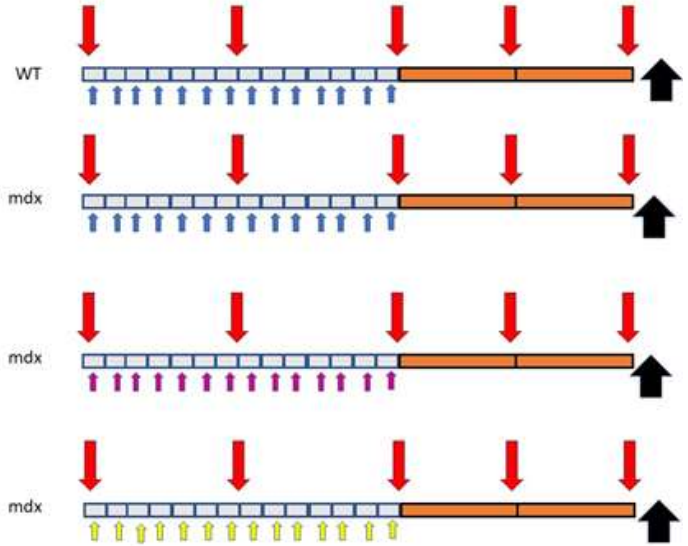


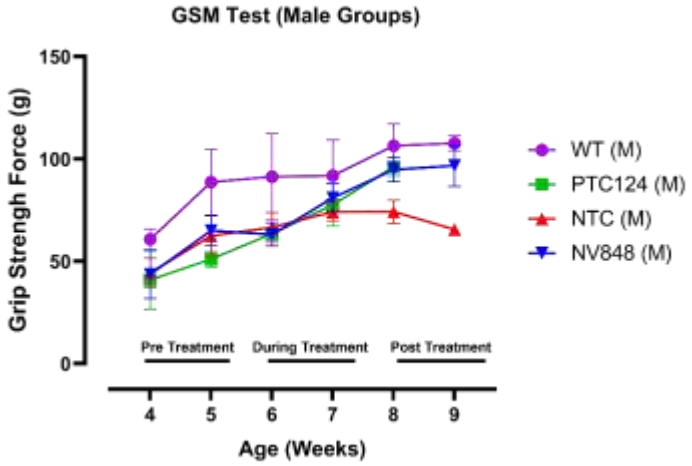


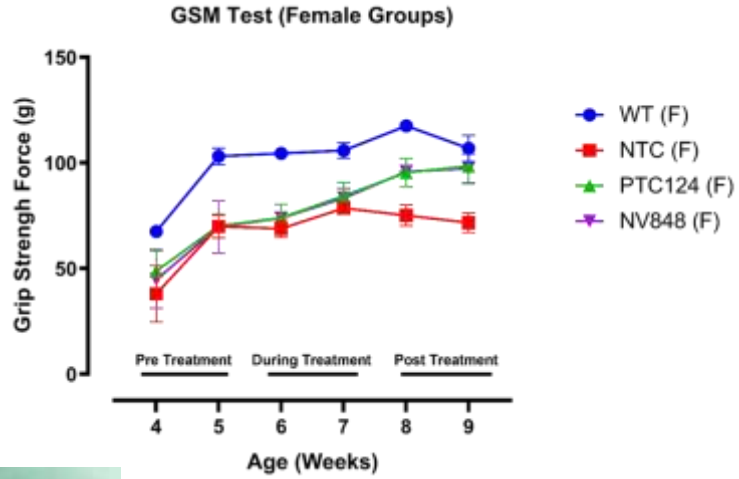
Created in BioRender.com

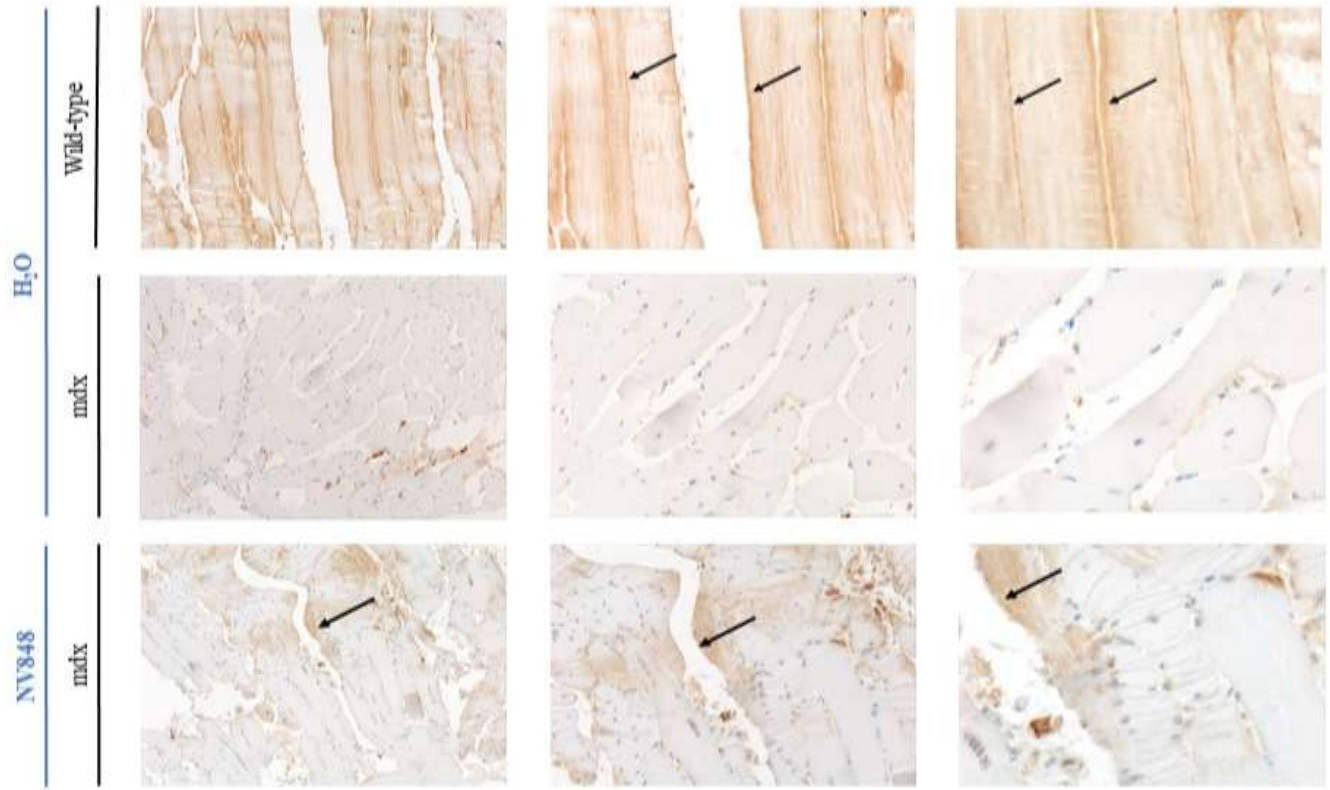
Validation of NV848 on ndDMD





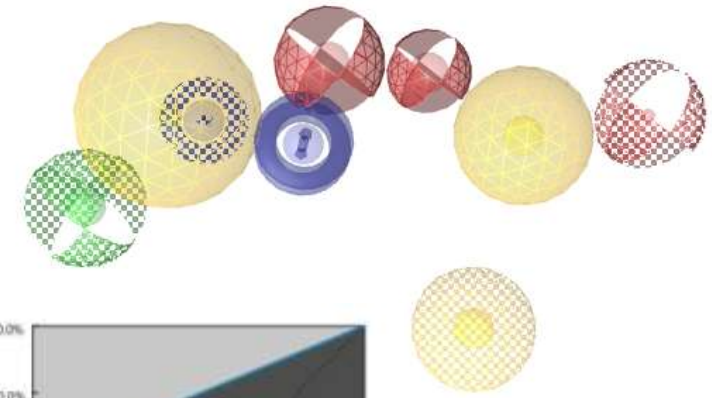


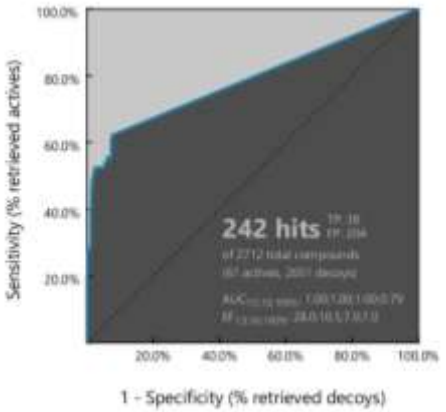




Expression of dystrophin in muscle fibers of the quadriceps femoris of wild-type and mdx mice (untreated or treated with NV848). All images are shown at magnifications of 10X, 20X, and 40X.

Design and Synthesis of new molecules





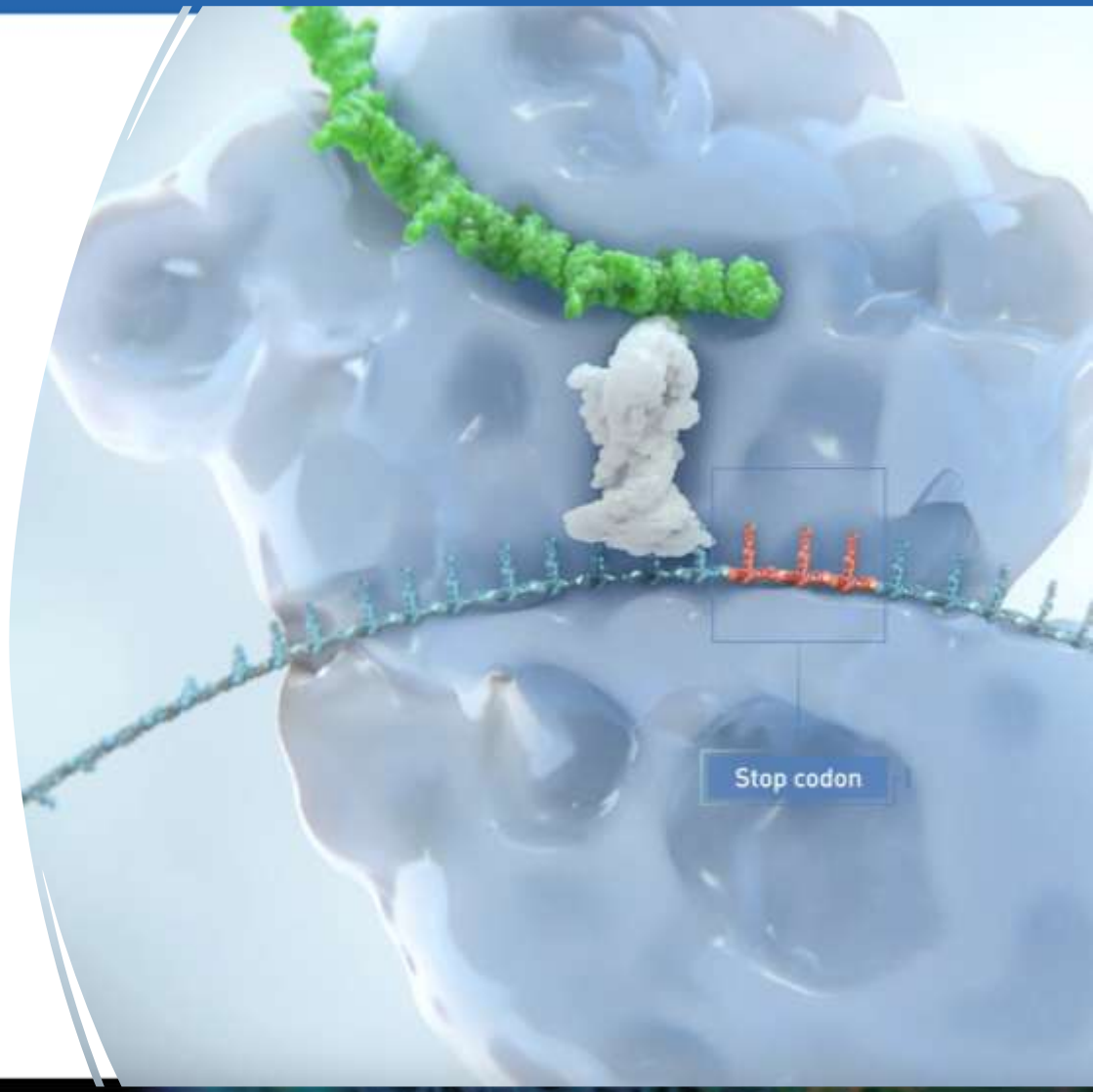
Fluc Reporter model systems to test the activity of the molecules

PHARMACOPHORE MODEL DESIGN

SYNTHESIS AND PRELIMINARY SCREENING

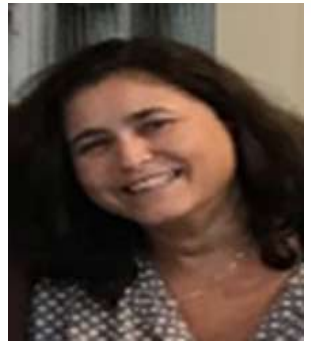
Conclusion

- **TRIDs rescue protein production in different genetic contexts**
- **NV molecules have been validated for the rescue by nonsense of CFTR, Dystrophin, LRBA, P53 proteins**
- **The Impact of the TRIDs paradigma to use ONE DRUG to care SEVERAL NONSENSE DERIVED PATHOLOGIES is great**
- **The possibility to rescue P53 when his lack is due to nonsense open new perspective to boost the care for cancer**



Thanks to:













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Davide Ricci
Emanuele Vitale
Fazal Subhan
Ignazio Fiduccia
Riccardo Perreira
Riccardo Varrica
Michele Menditto

Beatrice Belmonte
Francesco Genovese

Thanks to:

Anabela Ramalho (Leuven, Belgium)

Barry Cooperman (Philadelphia, US)

Hugo Santos (Lisbona, Portugal)

Josè Luis Capelo Martinez (Lisbona, Portugal)

Michel Moutschen (Liegi, Belgium)

Samuel Meier-Menches (Vienna, Austria)






Acknowledgements

The research leading to these results has received funding from

- the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PE_00000019 "HEAL ITALIA" to Pibiri and Lentini (University of Palermo), CUP B73C22001250006
- PRJ -0863 PRIN2022 to Pibiri (University of Palermo) CUP B53D23008390006.