EPTRI
European Paediatric Translational Research Infrastructure

THE CHILDREN'S MEMORIAL HEALTH INSTITUTE

EPTRI General Assembly and Scientific Meeting
Warsaw, 28-29 July, 2026

AI-Based Digital Platforms for Early Drug Repurposing Studies in Paediatric Diseases

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UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

EPTRI Scientific Meeting | 28–29 July 2026 | Warsaw, Poland

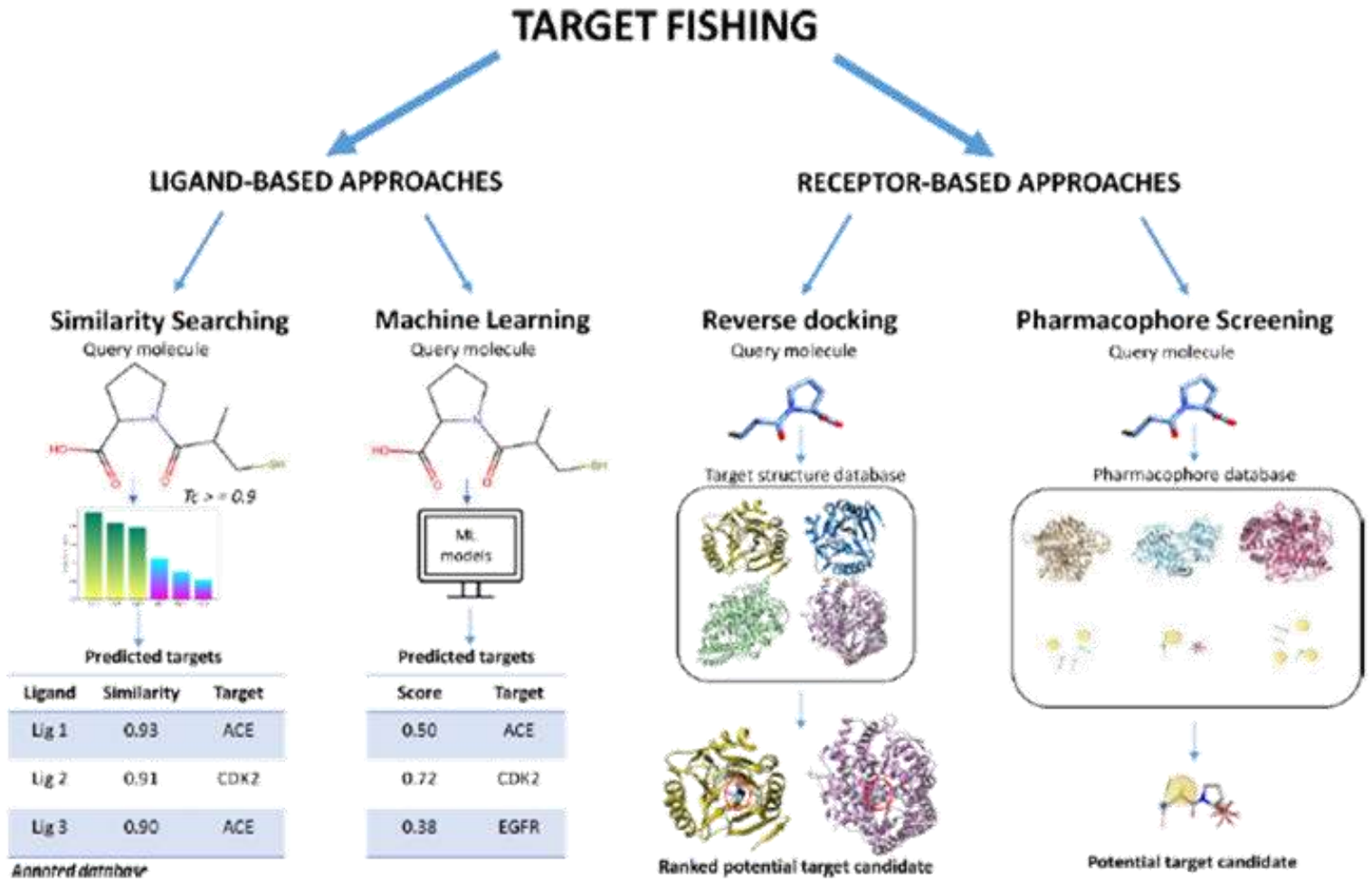


Figure 1. Overview of the main target fishing approaches.

In silico target fishing, aiming at identifying possible protein targets for a query molecule, has a wide variety of applications in Drug Discovery.

Prometheus Lab

PLATO

POLYPHARMACOLOGY PLATFORM PREDICTION

SCAN ME

TIRESIA

TOXICOLOGY INTELLIGENCE AND REGULATORY EVALUATIONS FOR SCIENTIFIC AND INDUSTRY APPLICATIONS

SCAN ME

CIRCE

CANNABINOID ITERATIVE REVALUATION FOR CLASSIFICATION AND EXPLAINABILITY

SCAN ME

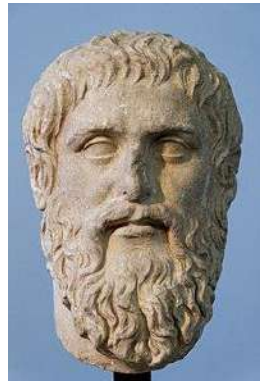
TISBE

TIRESIA IMPROVED BY STRUCTURE-BASED EXPLAINABILITY

<< JUST SUBMITTED>>

PLATO (Polypharmacology pLATform predictiOn)

Free and user-friendly web platform for target fishing and bioactivity prediction



SCAN ME

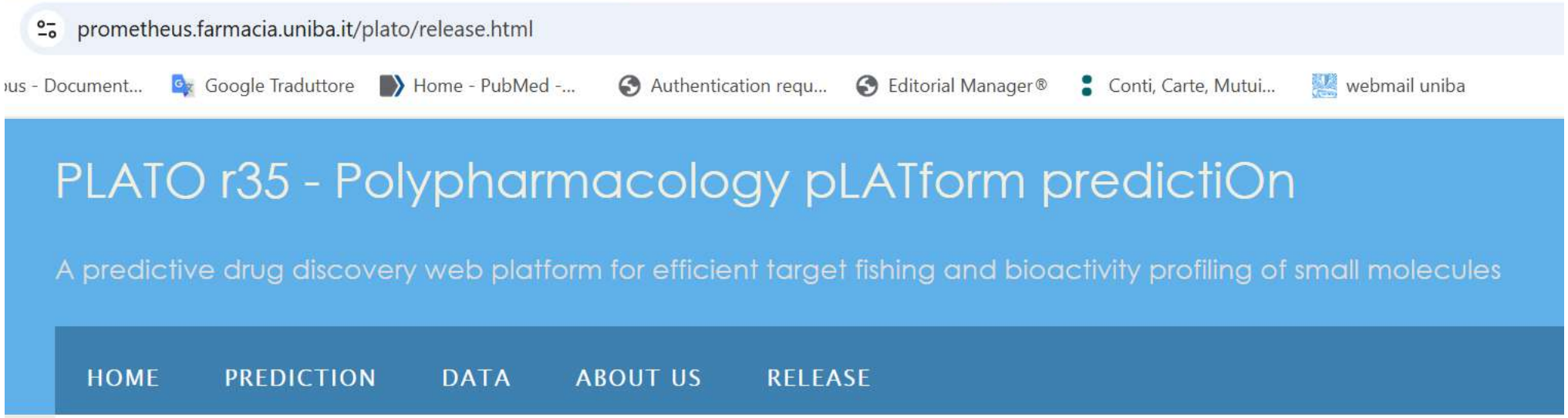
Open Access | Communication

PLATO: A Predictive Drug Discovery Web Platform for Efficient Target Fishing and Bioactivity Profiling of Small Molecules

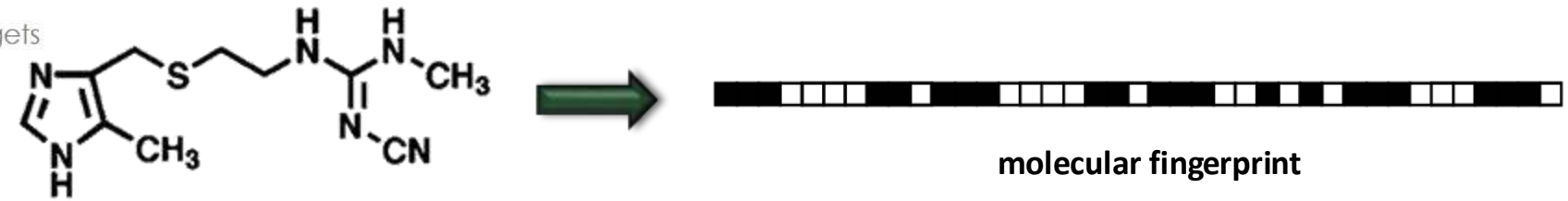
by Fulvio Ciriaco, Nicola Gambacorta, Daniela Trisciuzzi and Orazio Nicolotti

Int. J. Mol. Sci. **2022**, *23*(9), 5245; **https://doi.org/10.3390/ijms23095245** - 08 May 2022

https://prometheus.farmacia.uniba.it/plato/

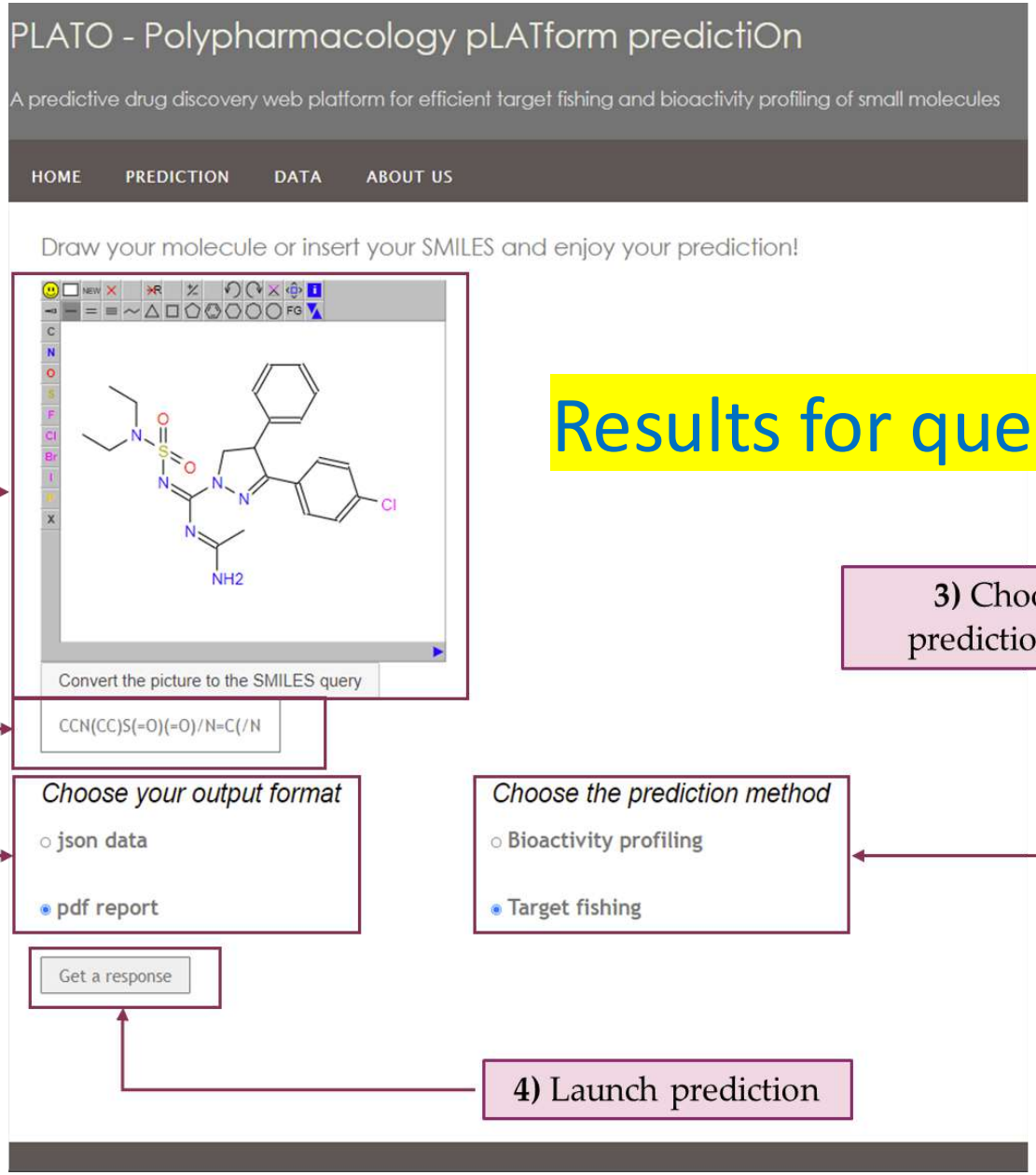


A ligand-based screening of a large collection of bioactive chemicals (small molecules) on **protein targets** implementing two optimized **multifingerprint similarity-based algorithms**.



cimetidine

bit string or feature set representations of molecular structure and properties



1a) Draw your molecule using sketch and convert in SMILES format

1b) Input query molecule as SMILES

2) Choose your output format

3) Choose your prediction method

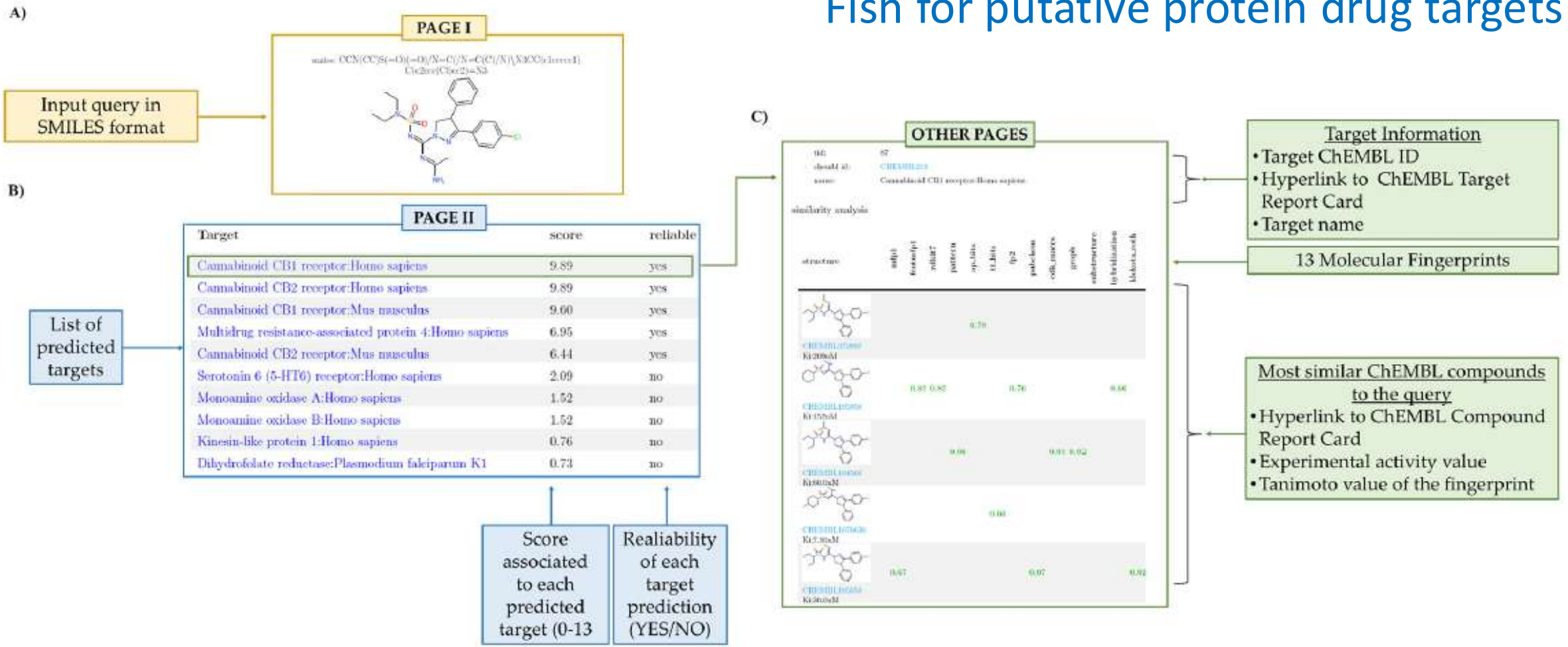
4) Launch prediction

Results for query in less than 20 s

Workflow

Outputs

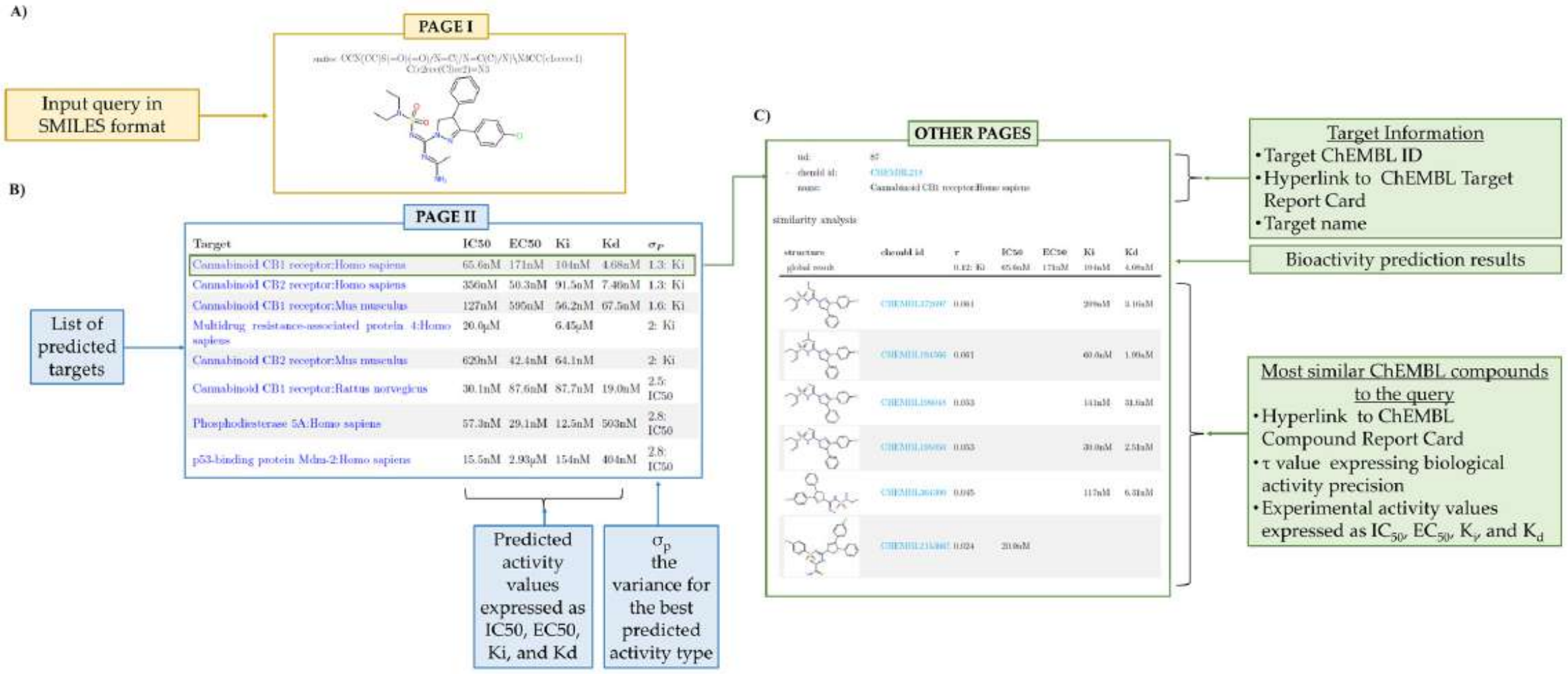
Fish for putative protein drug targets



Target	score	reliable
Cannabinoid CB1 receptor:Homo sapiens	9.89	yes
Cannabinoid CB2 receptor:Homo sapiens	9.89	yes
Cannabinoid CB1 receptor:Mus musculus	9.60	yes
Multidrug resistance-associated protein 4:Homo sapiens	6.95	yes
Cannabinoid CB2 receptor:Mus musculus	6.44	yes
Serotonin 6 (5-HT6) receptor:Homo sapiens	2.09	no
Monoamine oxidase A:Homo sapiens	1.52	no
Monoamine oxidase B:Homo sapiens	1.52	no
Kinesin-like protein 1:Homo sapiens	0.76	no
Dihydrofolate reductase:Plasmodium falciparum K1	0.73	no

Outputs

Compute bioactivity values for small molecules

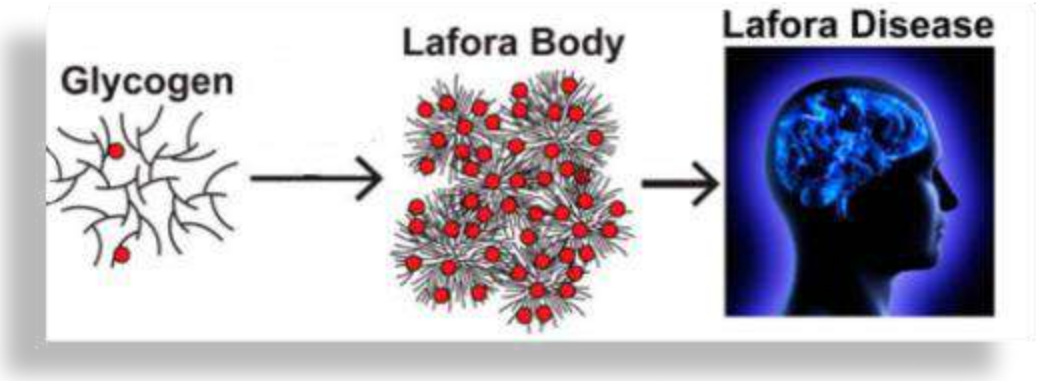


Lafora disease (LD)

Fatal and ultra-rare **autosomal recessive progressive myoclonus epilepsy, characterized by a rapid psychomotor deterioration**

Symptoms typically begin during **late childhood or adolescence**: typically, 8-19 years (peak onset 14–16 years)

The hallmark of the disease is the presence of **insoluble forms of glycogen named Lafora bodies** in the brain and peripheral tissues



LD is caused by **loss-of-function (mutations)** of:

- *EPM2A* encoding for **laforin** (glycan phosphatase)
- *EPM2B* encoding for **malin** (E3 ubiquitin ligase)

In the absence of a functional laforin-malin complex, structurally abnormal glycogen becomes insoluble and accumulates as **Lafora bodies** which drive disease progression in the brain

Clinical progression of Lafora disease

Teenage onset with myoclonic and generalized convulsive seizures

Diminishing response to anti-seizure medication

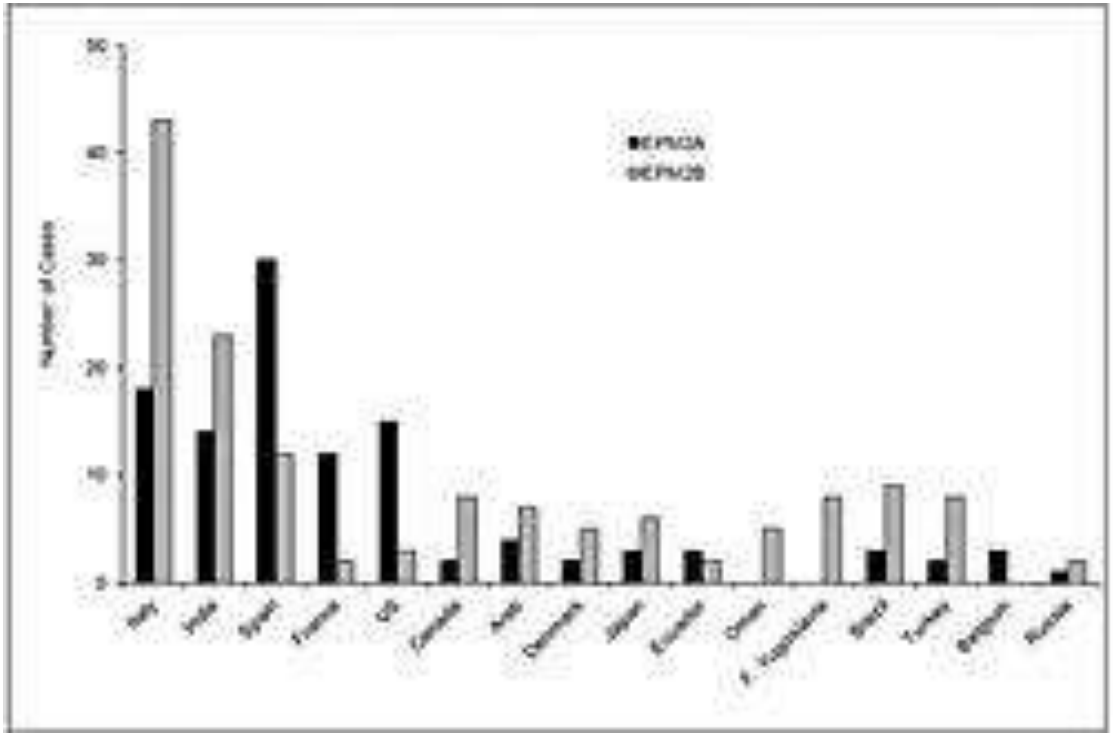
Intractable seizures, near-constant myoclonus, epileptic hallucinations and absence attacks

Dementia and a vegetative state in constant myoclonus

Death within 10 years of symptom onset in status epilepticus

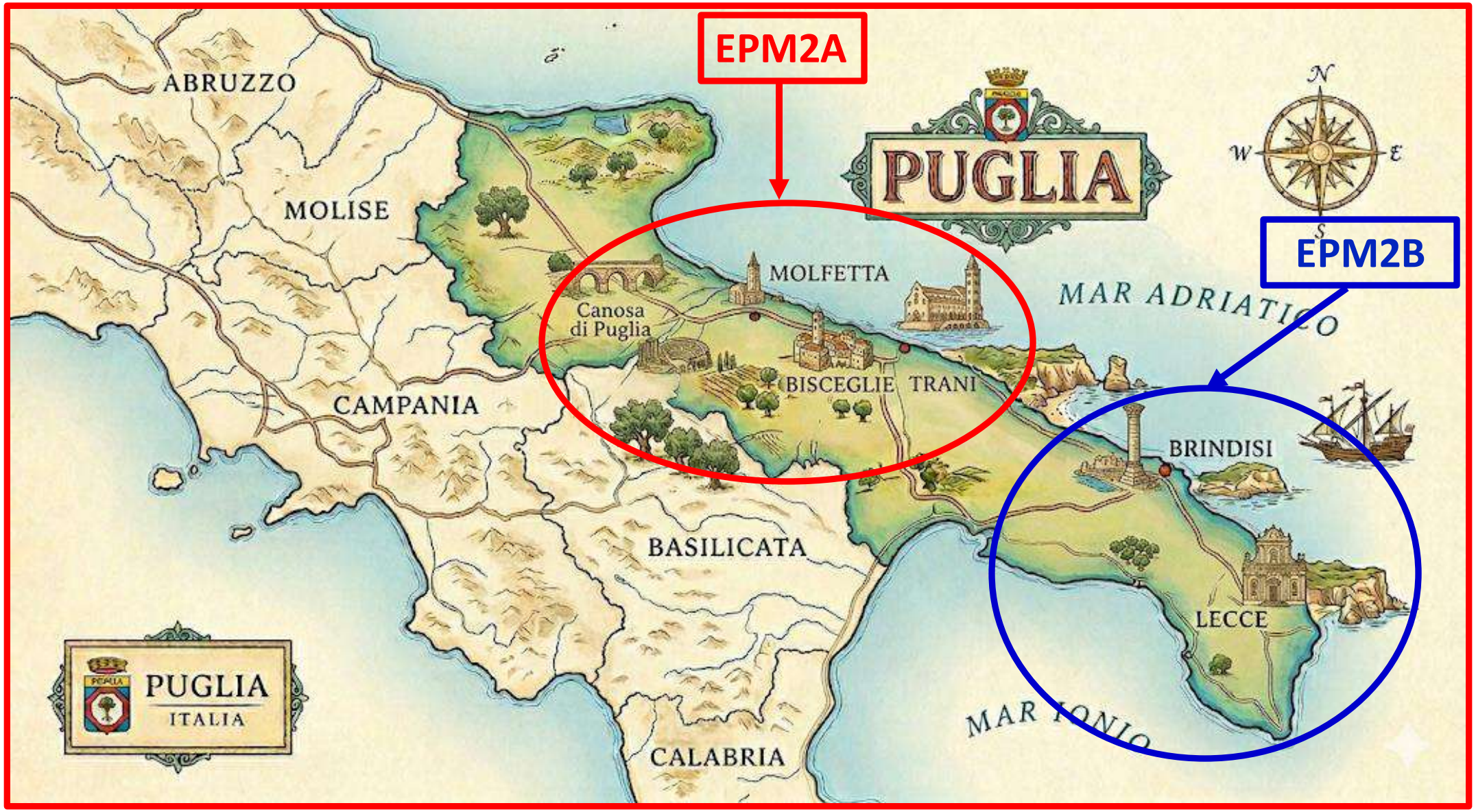
Estimated global prevalence of **fewer than 1 cases per million individuals**

Geographic prevalence: Mediterranean countries (including **Southern Italy/Apulia**), North Africa, the Middle East, and parts of Southern India



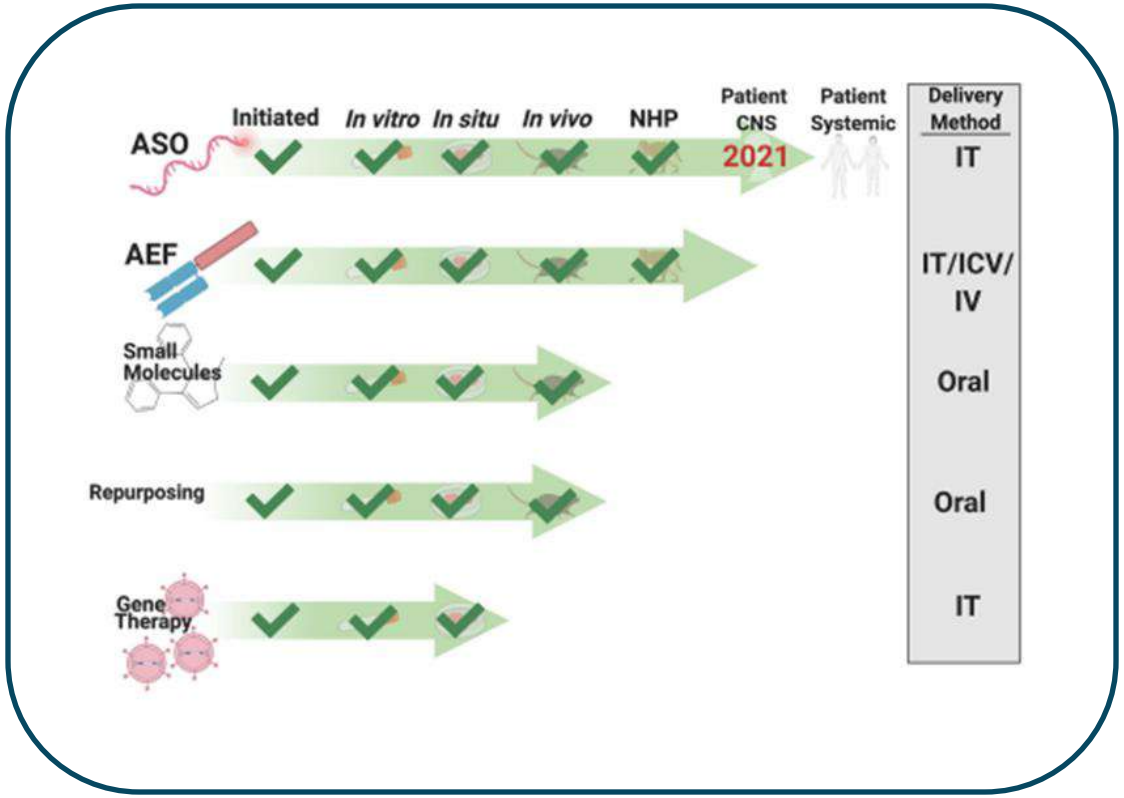
Distribution (2021)

LD in Puglia


EPM2A
EPM2B
PUGLIA
ABRUZZO
MOLISE
CAMPANIA
BASILICATA
CALABRIA
MAR ADRIATICO
MAR IONIO
MOLFETTA
Canosa di Puglia
BISCEGLIE
TRANI
BRINDISI
LECCE
N
W
E
S
PUGLIA
ITALIA

There is no effective therapy

Patients are initially treated with anti-seizure medications, to which, after some time, they develop resistance



Metformin, orphan drug since 2016

Drug repurposing in Lafora disease

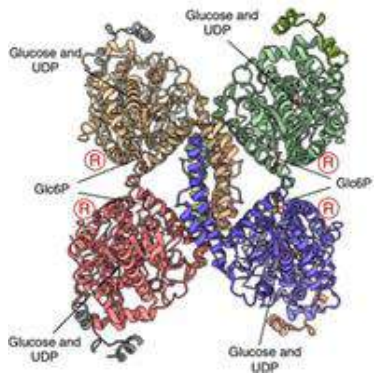
To identify new drug candidates for LD by using ***in silico*** **tools (reverse docking, similarity search)** and ***in vitro*** **assays to speed-up (new) therapies**

✓ Working hypothesis

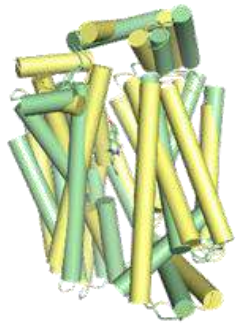
Modulating **glucose access** into neurons and astrocytes or **inhibiting glycogen synthesis**, could we **reduce glycogen accumulation** and **Lafora bodies formation?**

✓ Drug targets selection

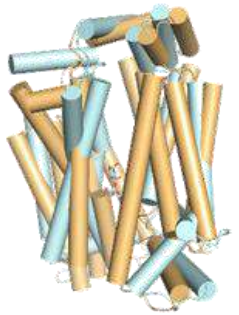
Glycogen synthase (hGYS-1)



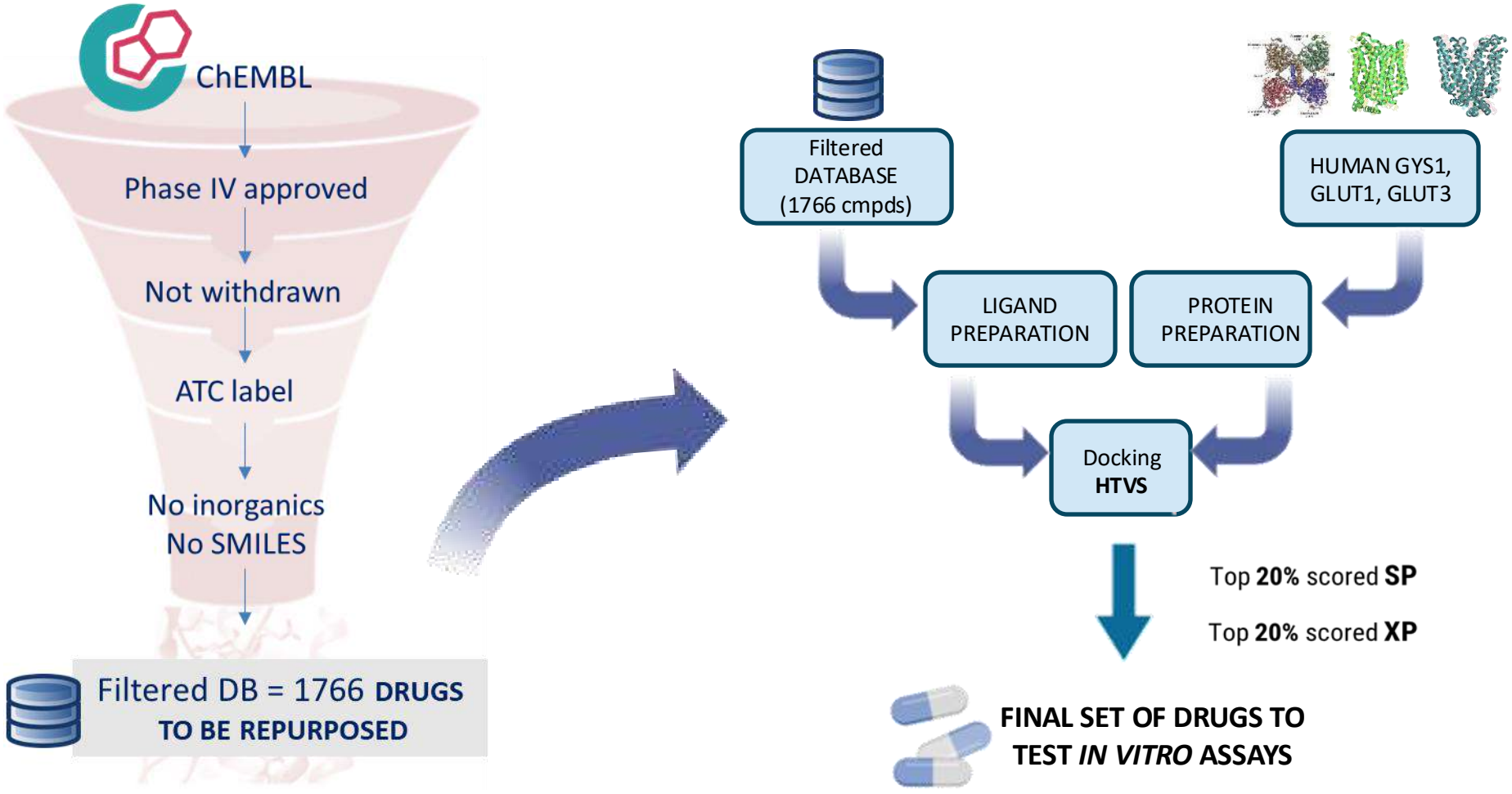
hGLUT1 (astrocytes, BBB)



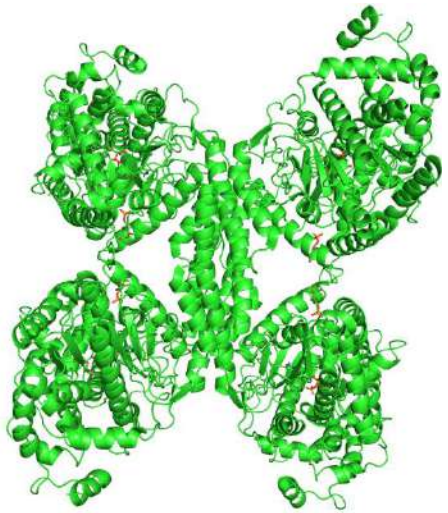
hGLUT3 (neurons)

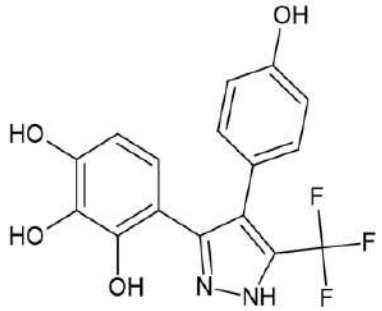


Docking-based virtual screening of commercial drugs from a filtered ChEMBL database towards hGYS-1 and hGLUT1-3



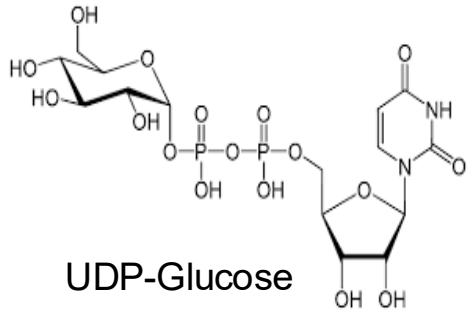
Docking-based virtual screening of filtered ChEMBL database towards hGYS-1





Reference compound

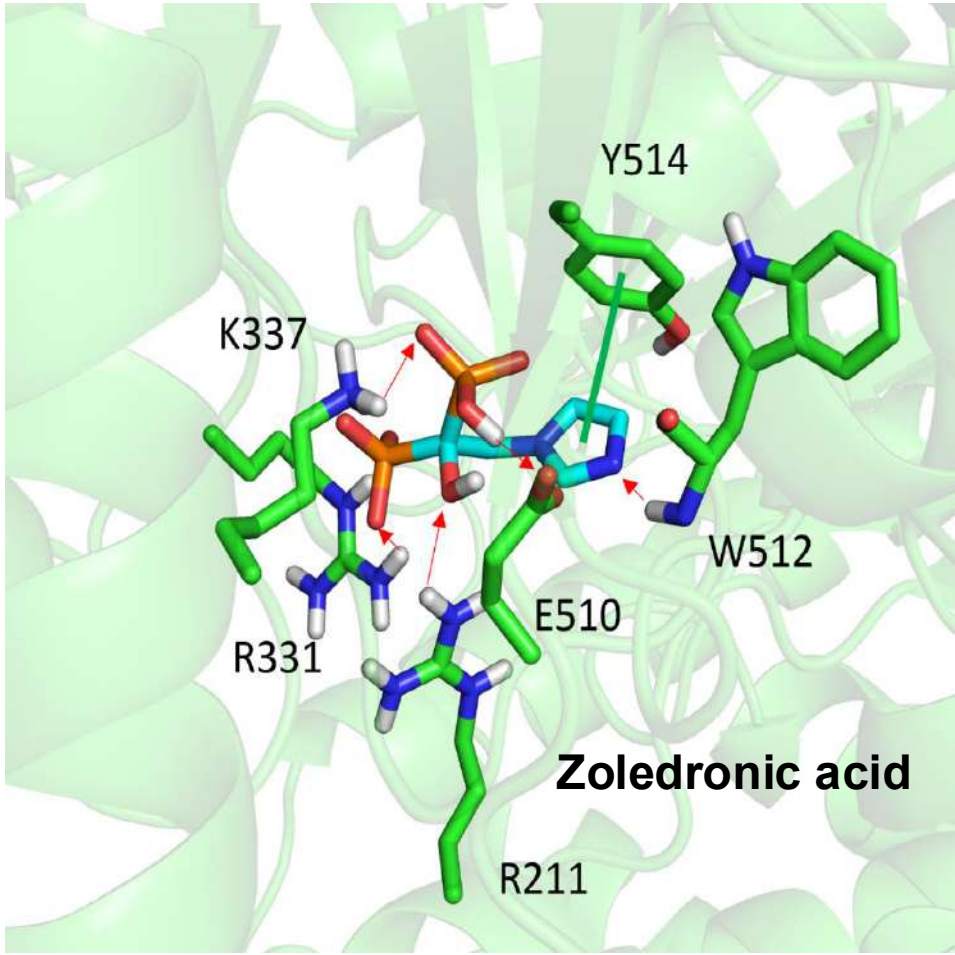
IC_{50} ~ 2.75 μM



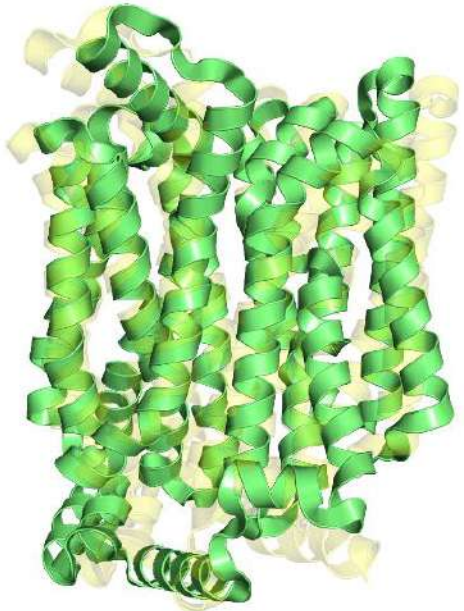
UDP-Glucose

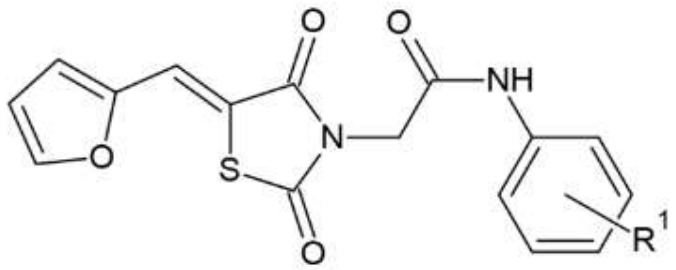
Docking score [UDP-glucose] = -10.118 kcal/mol

Compound	docking score (kcal/mol)	ligand efficiency
ZOLEDRONIC ACID	-10,178	-0,636
RISEDRONIC ACID	-9,636	-0,567
ZOLEDRONIC ACID	-9,583	-0,599
RISEDRONIC ACID	-9,255	-0,544
DICUMAROL	-7,012	-0,28



Docking-based virtual screening of filtered ChEMBL database towards hGLUT1



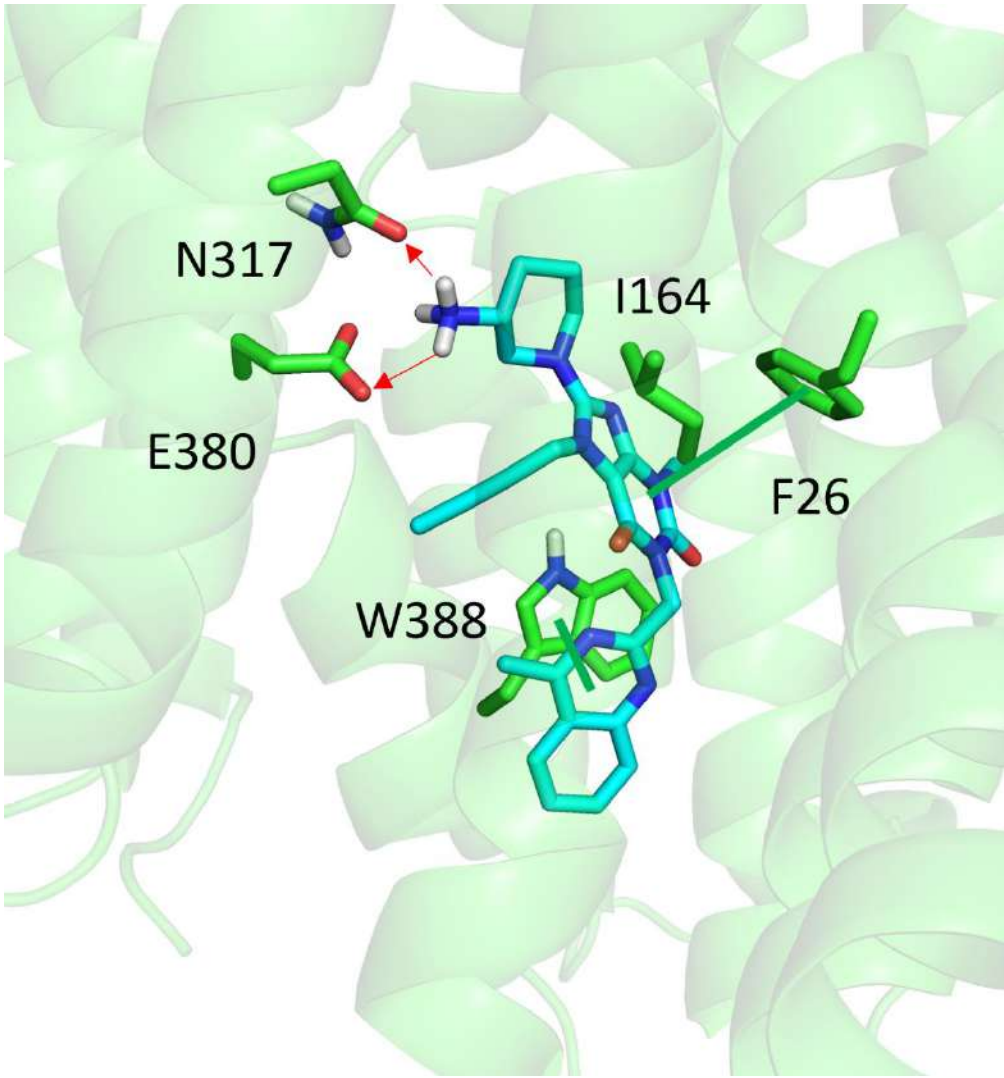


Reference compound

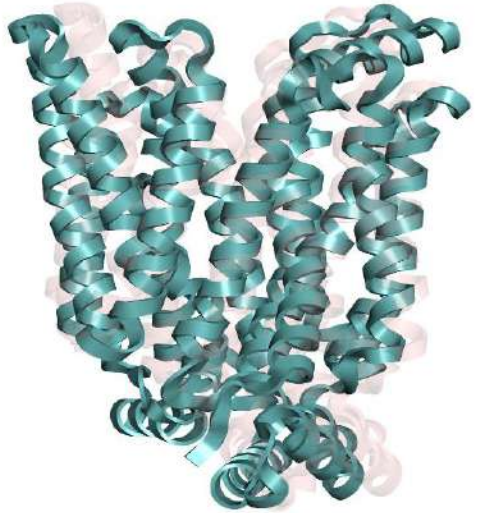
IC_{50} ~ 11.4 μM

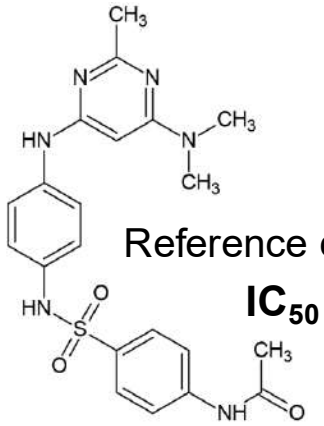
Docking score [Reference compound]= -8.613 kcal/mol

Compound	docking score (kcal/mol)	ligand efficiency
SALMETEROL	-11,134	-0,371
NEBIVOLOL	-10,449	-0,36
LINAGLIPTIN	-8,581	-0,245
THEOPHYLLINE	-8,043	-0,619
ZOLEDRONIC ACID	-6,254	-0,391



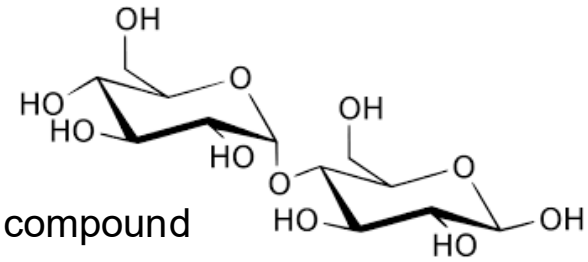
Docking-based virtual screening of filtered ChEMBL database towards hGLUT3





Reference compound

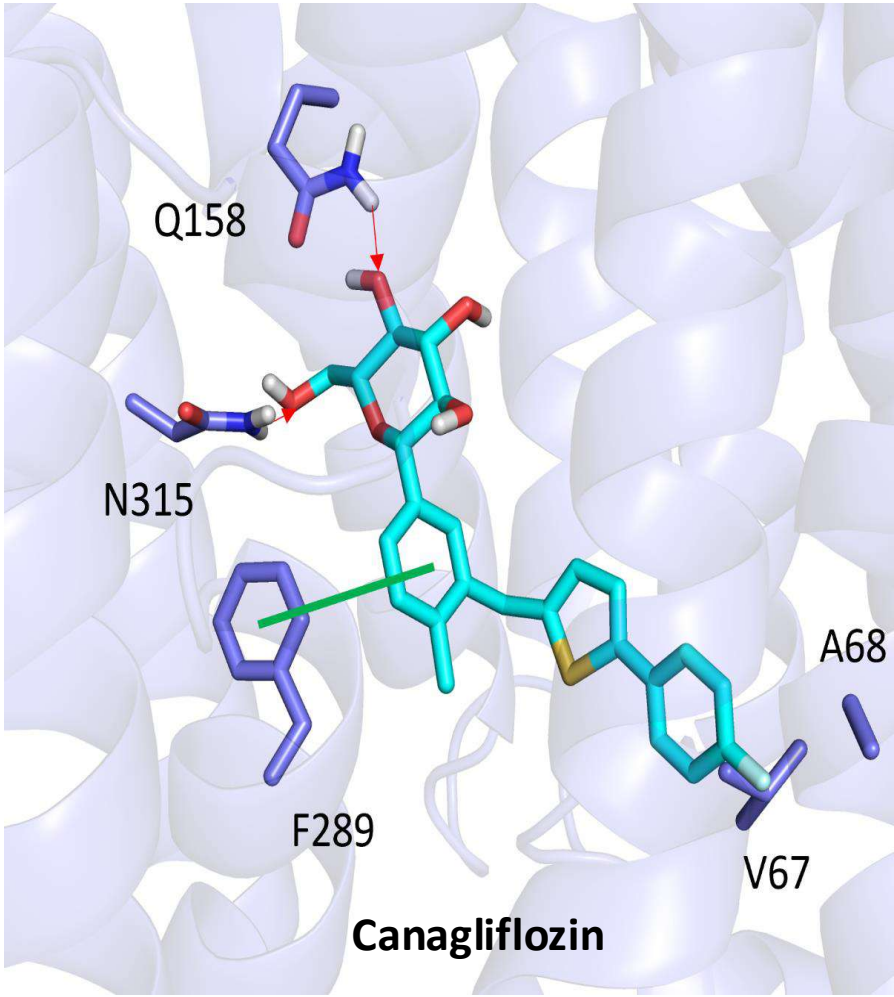
IC_{50} ~ 7.01 μM



alpha-maltose

Docking score [alpha-maltose]= -7.573 kcal/mol

Compound	docking score (kcal/mol)	ligand efficiency
CANAGLIFLOZIN	-12,130	-0,391
GEFITINIB	-10,685	-0,345
CARVEDILOL	-10,050	-0,335
LINAGLIPTIN	-9,400	-0,269
SITAGLIPTIN	-9,040	-0,323



List of approved drugs identified from docking studies

1. TUDCA (Item No. 20277Il TUDCA, Cayman)
2. Dapagliflozin (CAS: 004CA11574-50, Cayman)
3. Canagliflozin (CAS: 004CA11575-50, Cayman)
4. Empagliflozin (CAS: 004CA17375-100, Cayman)
5. **Cannabidiol**
6. **Acetazolamide**
7. Gefitinib
8. Nebivolol
9. Sitagliptin
10. Bicalutamide
11. **Carbamazepine**
12. **Levetiracetam**
13. **Stiripentol**
14. **Piracetam**
15. **Etosuccimide**
16. Dicumarol (DMSO-9mM)
17. Zoledronic Acid (stock in water, 1mM)

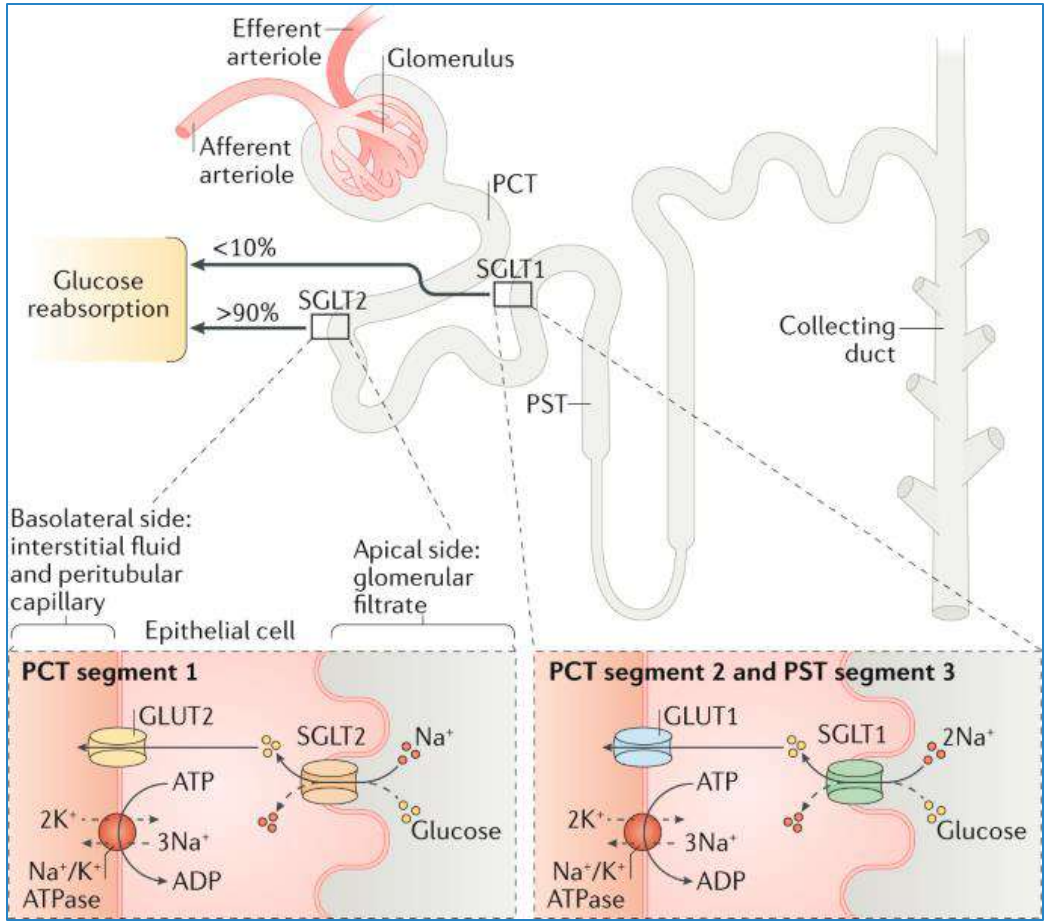
→ Starting point for *preclinical* studies

Sodium glucose co-transporters 2 (SGLT2) inhibitors (gliflozins)

In EU, SGLT2i currently authorized to treat DM-2:

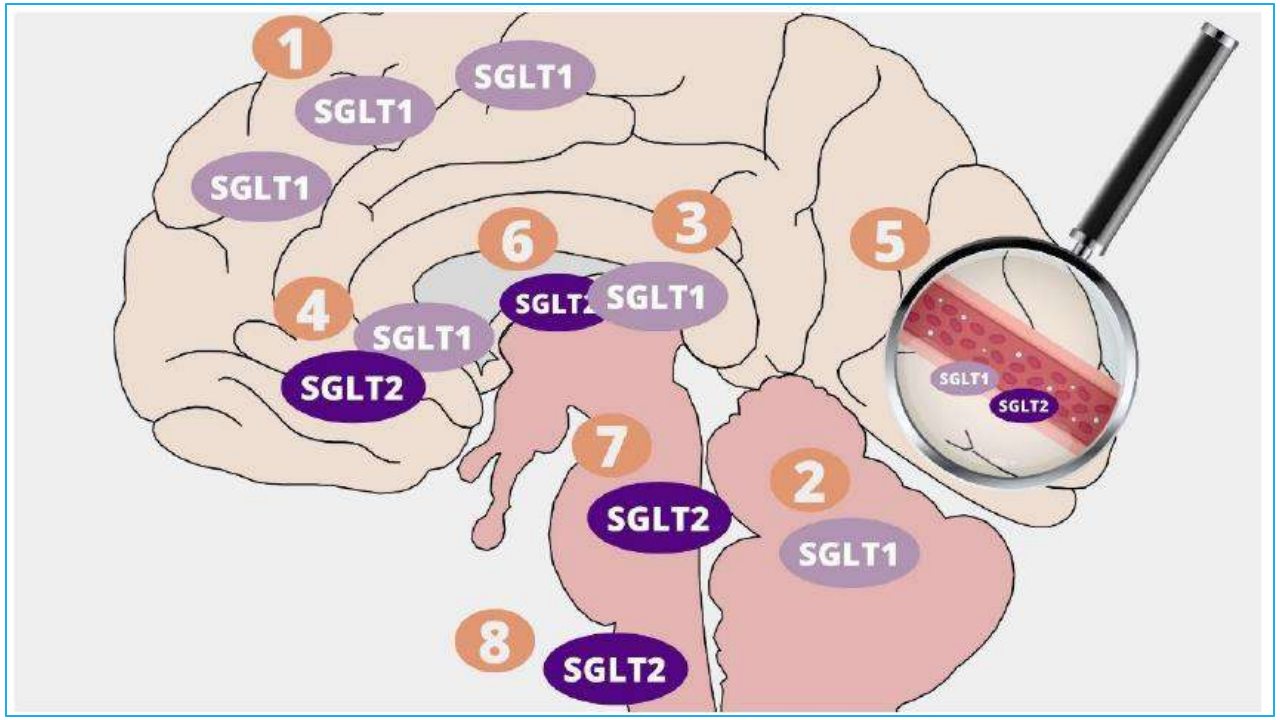
- **dapagliflozin** (*Forxiga* , Xigduo)
- **empagliflozin** (*Jardiance*, *Synjardy*, *Glyxambi*)
- **canagliflozin** (*Invokana, Vokanamet*)
- **ertugliflozin** (*Steglatro, Segluromet*)
- **sotagliflozin** *(Zynquista)*

Mechanism of action: antihyperglycemic drugs, favour glucose excretion from the kidney targeting SGLT2



Hypotheses and evidences supporting the use of gliflozins in LD

Localization of SGLT1/2 in the brain



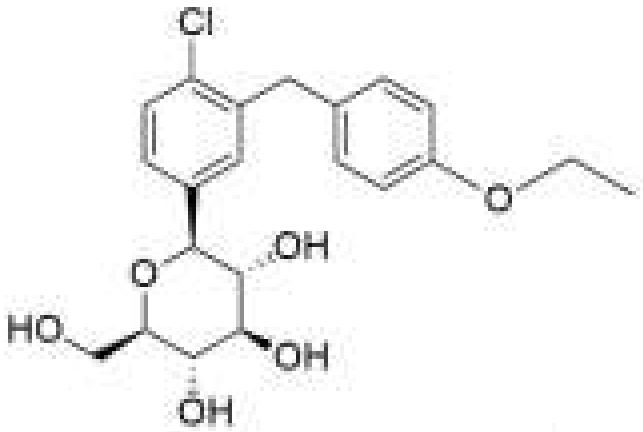
SGLT1 receptor is expressed in brain areas such as hippocampus (CA1, CA3 and the dentate gyrus), cortical and cerebellar neurons, BBB endothelial cells while significant expression of **SGLT2** has been identified in the cerebellum and at BBB endothelial cells.

Pawlos et al., 2021

PLATO (Polypharmacology pLATform predictiOn)

Target fishing

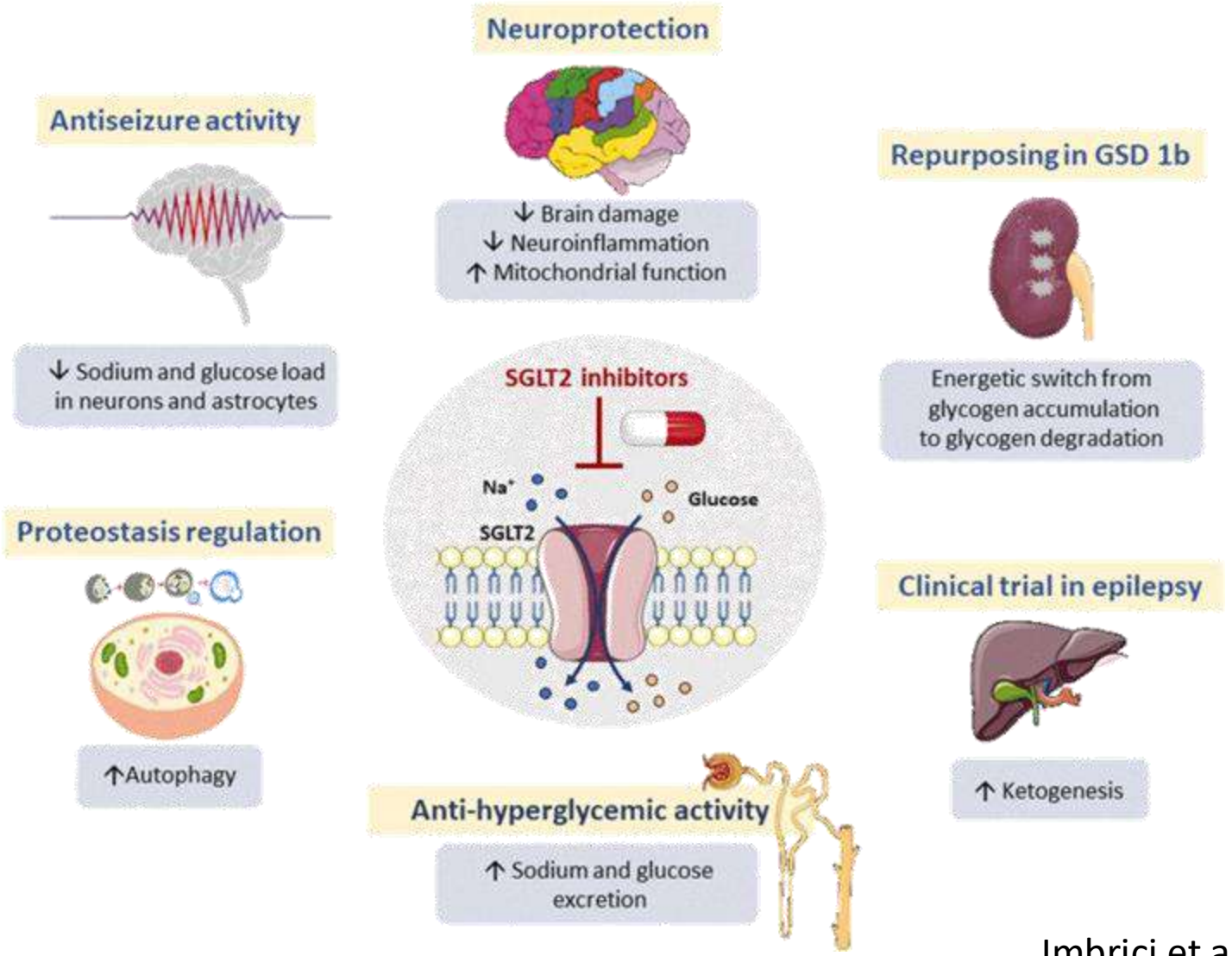
smiles: CCOc3ccc(Cc2cc([C@@H]1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1O)ccc2Cl)cc3



Dapaglifozin

Target	score	reliable
Sodium/glucose cotransporter 2:Rattus norvegicus	13.00	yes
Low affinity sodium-glucose cotransporter:Homo sapiens	13.00	yes
Sodium/glucose cotransporter 2:Homo sapiens	13.00	yes
Sodium/myo-inositol cotransporter 2:Homo sapiens	13.00	yes
Sodium/glucose cotransporter 1:Homo sapiens	13.00	yes
Sodium/glucose cotransporter 2:Mus musculus	10.69	yes
SGLT1 protein:Mus musculus	7.64	yes
Glycogen phosphorylase, muscle form:Oryctolagus cuniculus	5.19	no
Adhesin protein fimH:Escherichia coli K-12	3.70	no
Aldose reductase:Rattus norvegicus	3.65	no
Carbonic anhydrase XII:Homo sapiens	2.88	no
P-selectin:Homo sapiens	2.83	no
Carbonic anhydrase IX:Homo sapiens	2.82	no
Carbonic anhydrase I:Homo sapiens	2.82	no
Leukocyte adhesion molecule-1:Homo sapiens	2.81	no
Tyrosinase:Homo sapiens	2.79	no
Tyrosinase:Agaricus bisporus	2.78	no
Aldose reductase:Homo sapiens	2.76	no
Epoxide hydratase:Homo sapiens	2.44	no
Monoamine oxidase B:Rattus norvegicus	2.34	no
Cytochrome P450 3A4:Homo sapiens	2.30	no
Acetylcholinesterase:Electrophorus electricus	2.28	no
Peroxisome proliferator-activated receptor delta:Homo sapiens	2.27	no
Cyclooxygenase-2:Homo sapiens	2.19	no
Glucose-6-phosphate 1-dehydrogenase:Homo sapiens	2.15	no
Dipeptidyl peptidase IV:Homo sapiens	2.13	no

Literature data supporting the use of gliflozins in LD

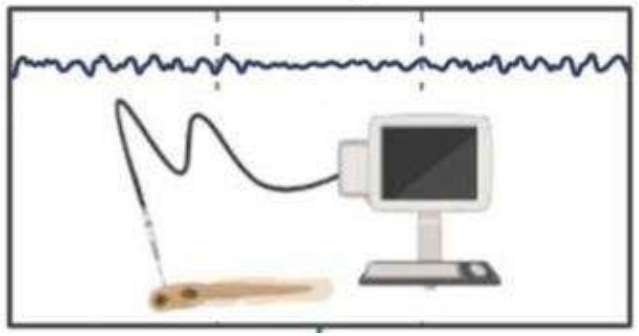


Imbrici et al., *Pharmacol Res* 2024

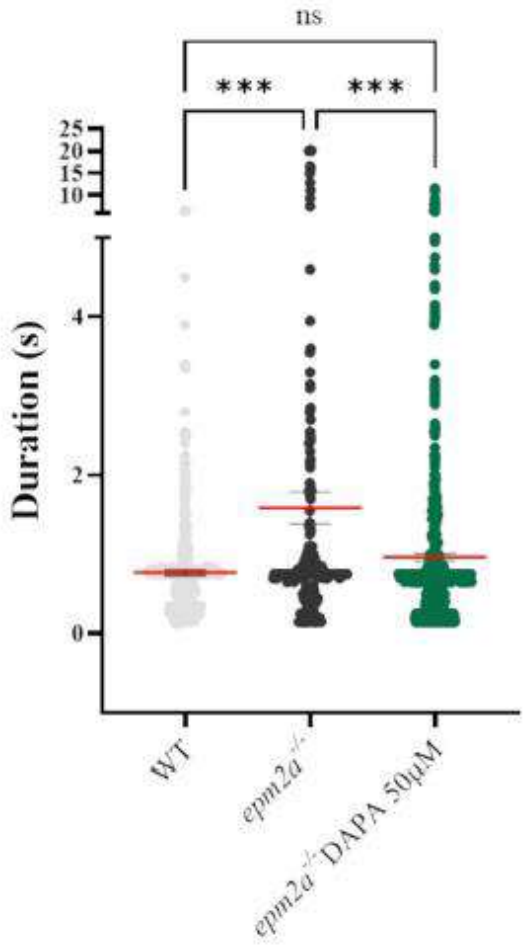
Dapagliflozin attenuated epileptic phenotype in LD zebrafish model

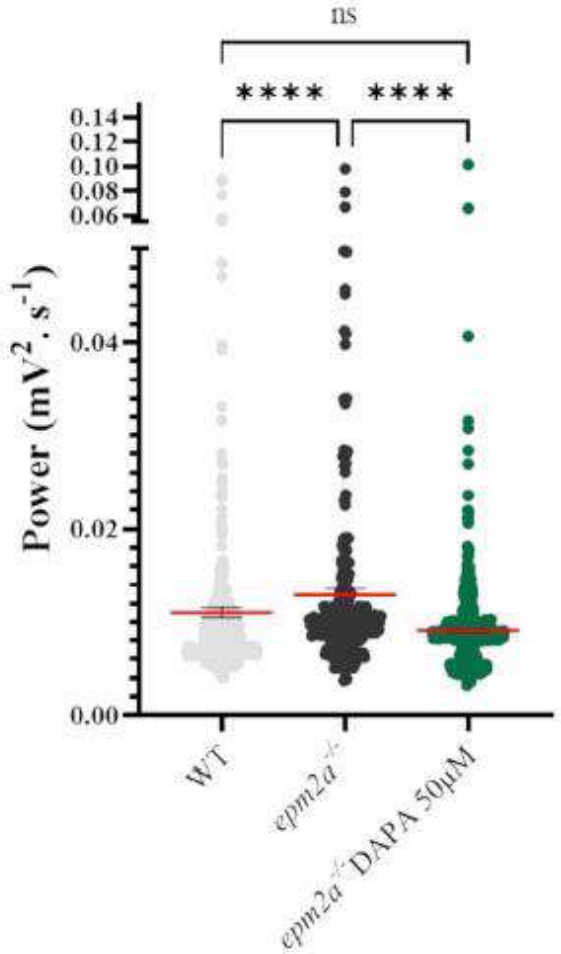
epm2a $^{-/-}$ larvae, 5dpf

Local field potential



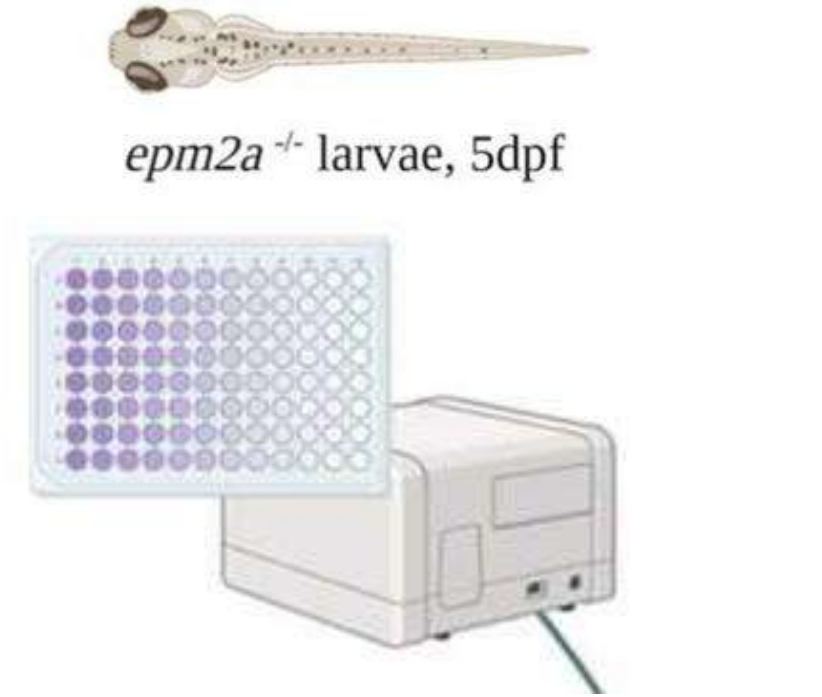
Treatment with DAPA (50 µM) was able to significantly reduce the **duration and power of seizure-like events**



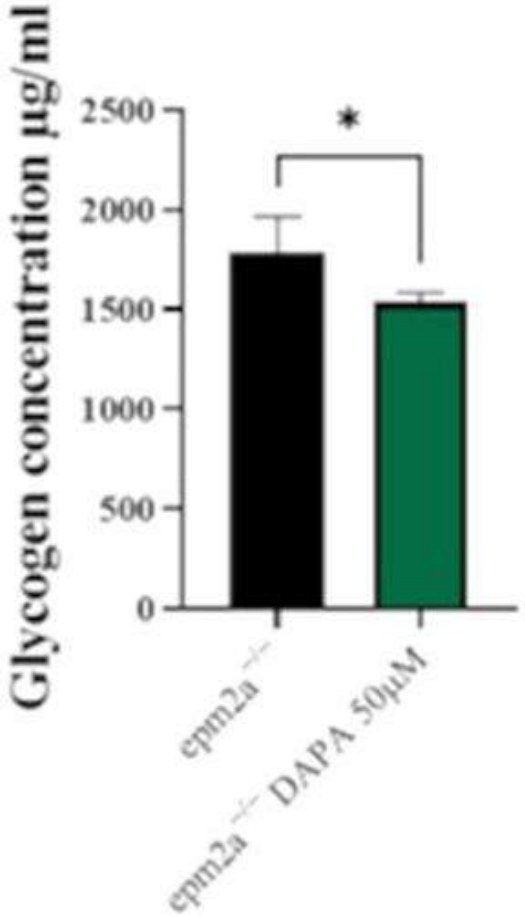


Della Vecchia et al., *Biomed & Pharmacother* 2025

Dapagliflozin slightly reduced glycogen content in LD zebrafish model



Glycogen was quantified in whole LD zebrafish model



Della Vecchia et al., *Biomed & Pharmacother* 2025

ASSESSING THE POTENTIAL OF REPURPOSING EMPAGLIFLOZIN IN LAFORA DISEASE TREATMENT: A STUDY IN PROGRESS

Giuseppe d'Orsi[1], Paola Imbrici[2], Daniela Trisciuzzi[2], Nicola Gambacorta[2,3], Maria Teresa Di Claudio[1], Cosimo D. Altomare[2], Antonella Liantonio[2], Francesca Bisulli[4], Massimo Carella[3] and DEFEAT-LD study group

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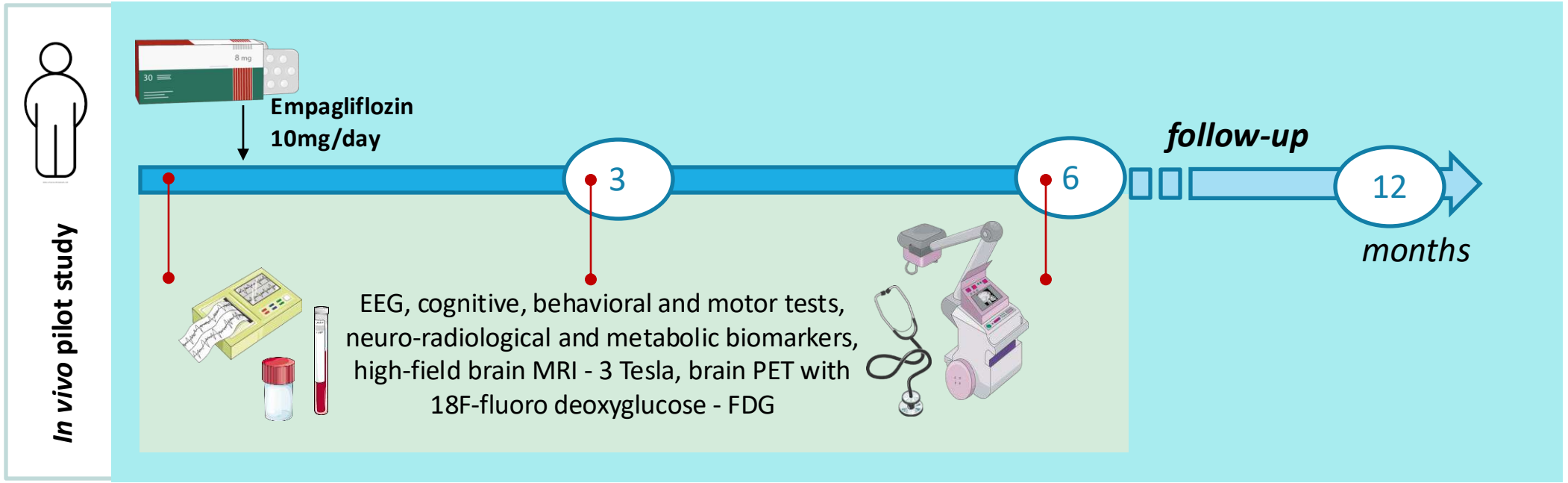

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