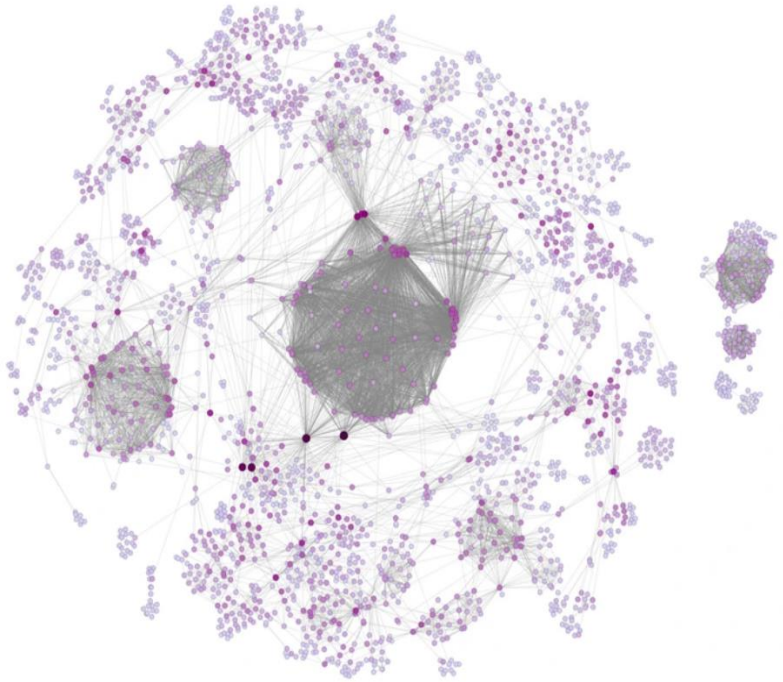
Prediction of the function of the protein interactions using machine learning

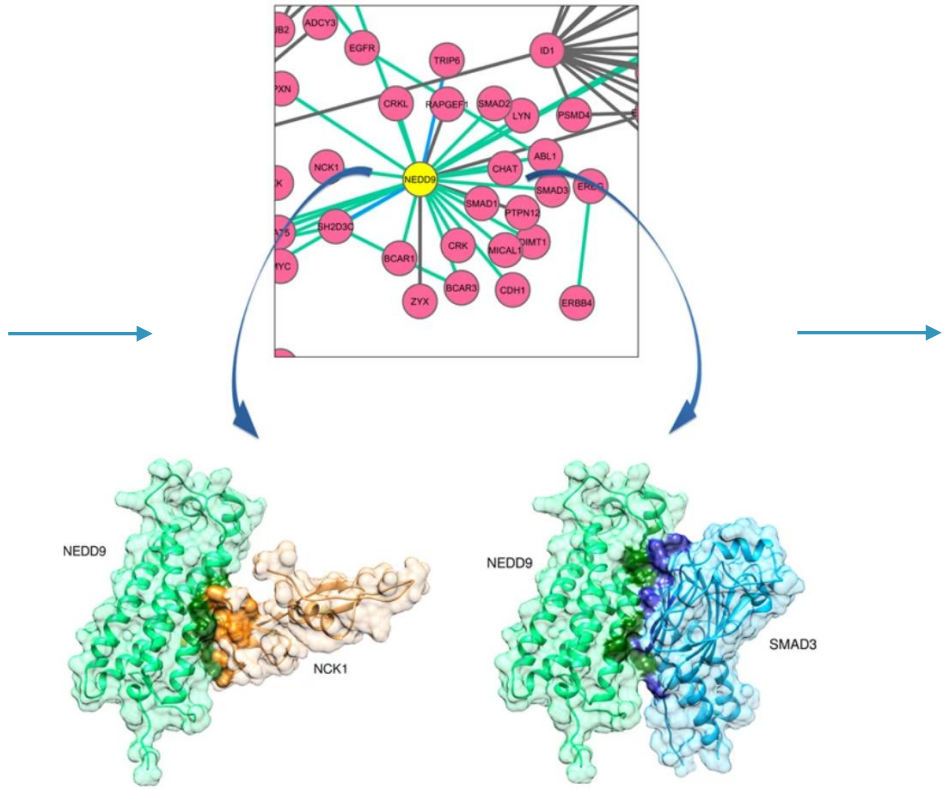
Aimilia Christina Vagiona
Supervisor: Miguel Andrade

Mainz, December 2022

Why we study protein-protein interactions



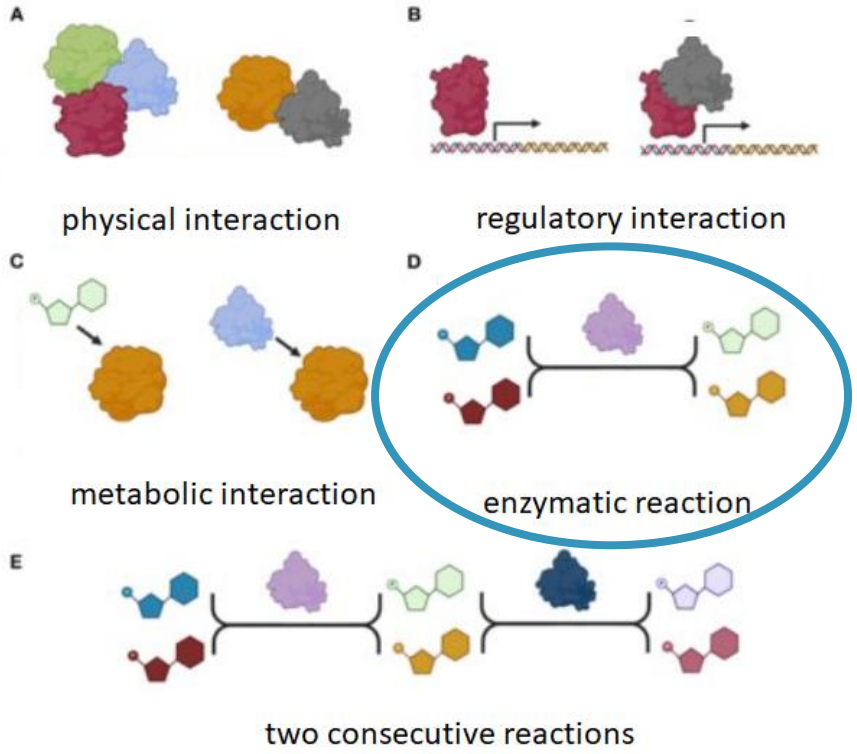
Balogh et.al, 2022

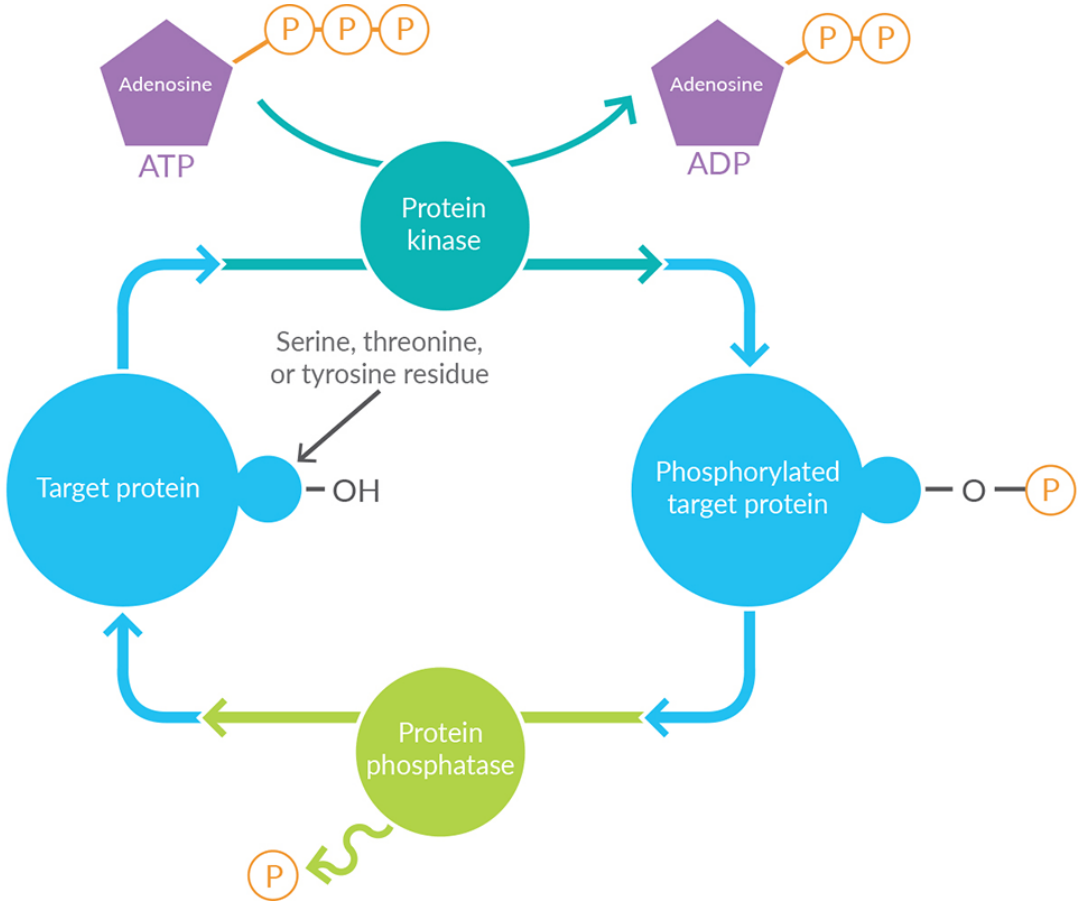


Halakou et.al, 2017

- signal transduction
- growth
- differentiation
- apoptosis
- metabolic reactions
- aberrant PPIs are associated with diseases

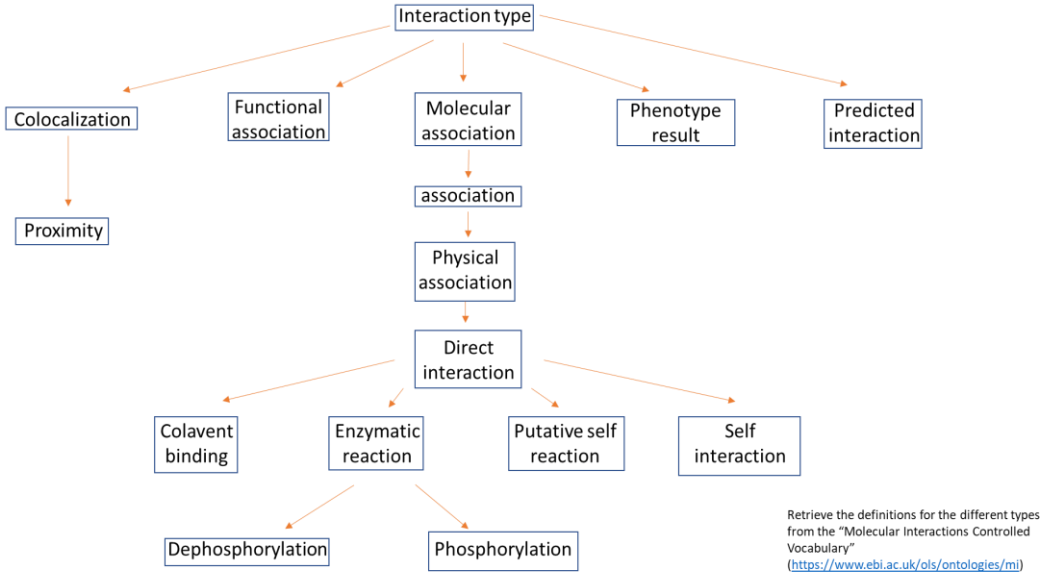
Function of PPIs - Enzymatic

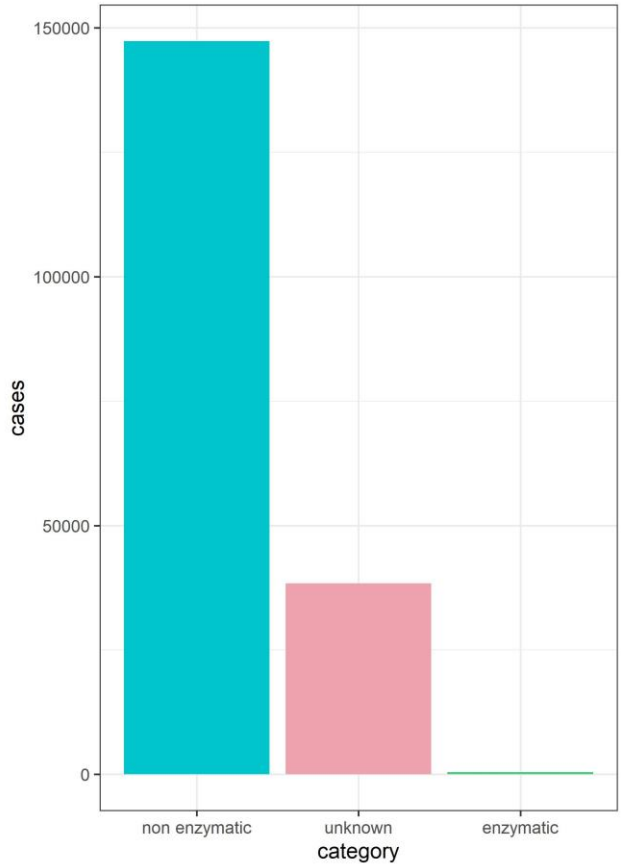




Gómez-Romero et.al, 2020

However…



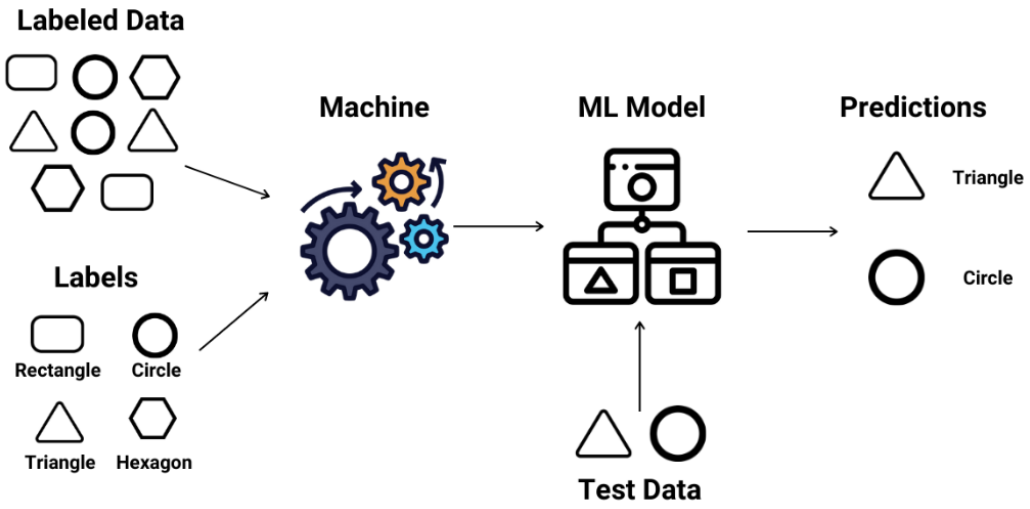


Goal

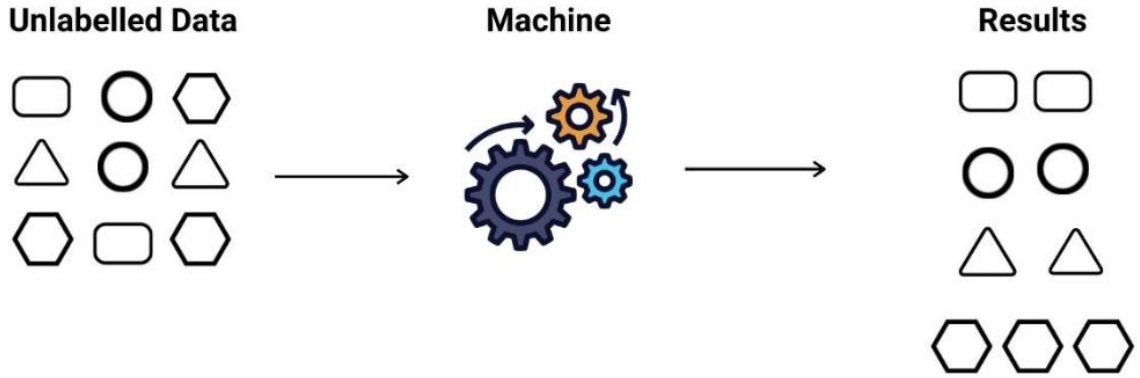
- predict the function of the protein interactions
- classification as enzymatic and non enzymatic
- information about the direction of the interaction (effector and target)

What is machine learning?

Supervised Learning



Unsupervised Learning



Example of supervised machine learning

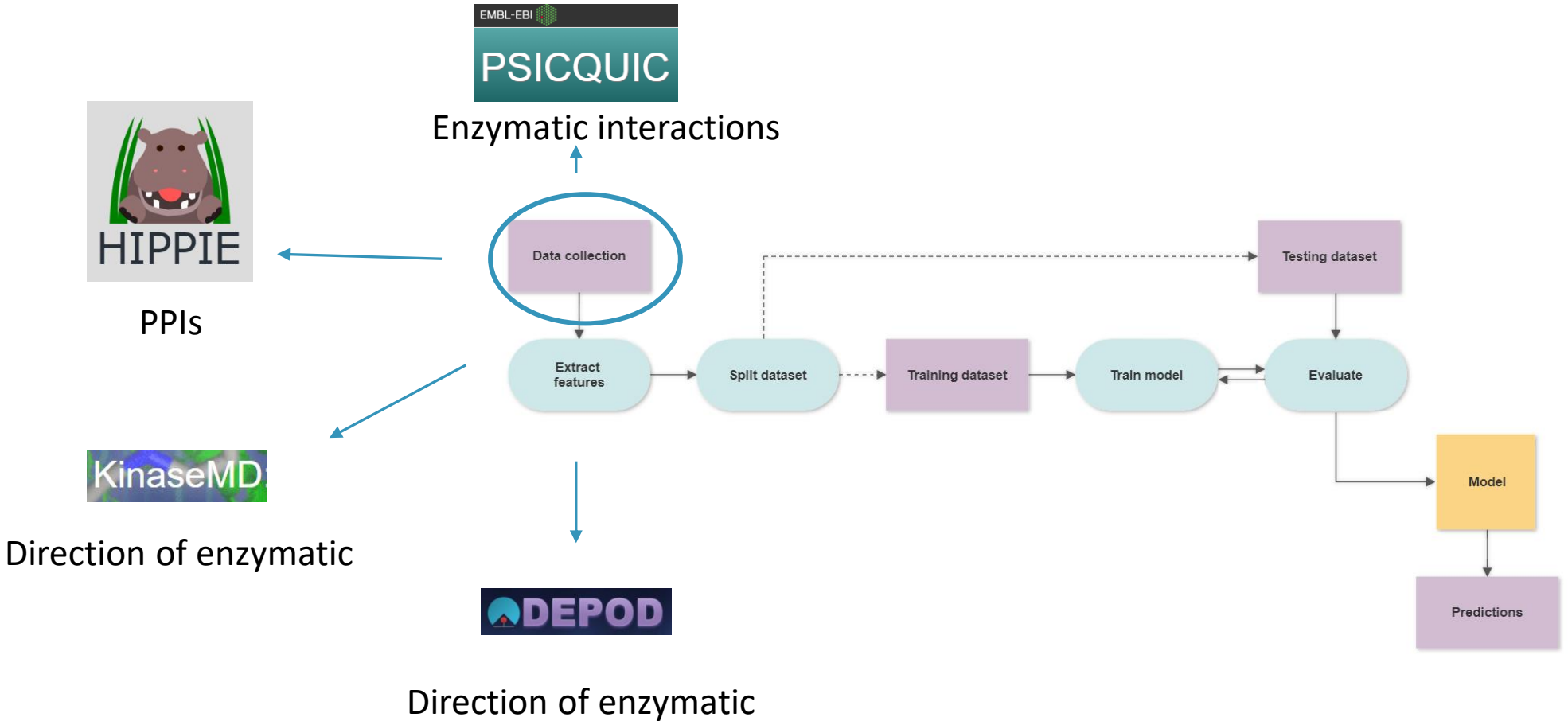
Height (feature)	Weight (feature)	Gender (label)
1.87	80	Male
1.65	50	Female
1.99	99	Male
1.45	70	Female
1.80	87	Male
1.78	65	Female
1.87	60	Male

Training set

Height (feature)	Weight (feature)	Predictions	Gender (label) (real data)
1.82	82	Male	Male
1.67	53	Male	Female
1.92	99	Male	Male
1.50	70	Female	Female

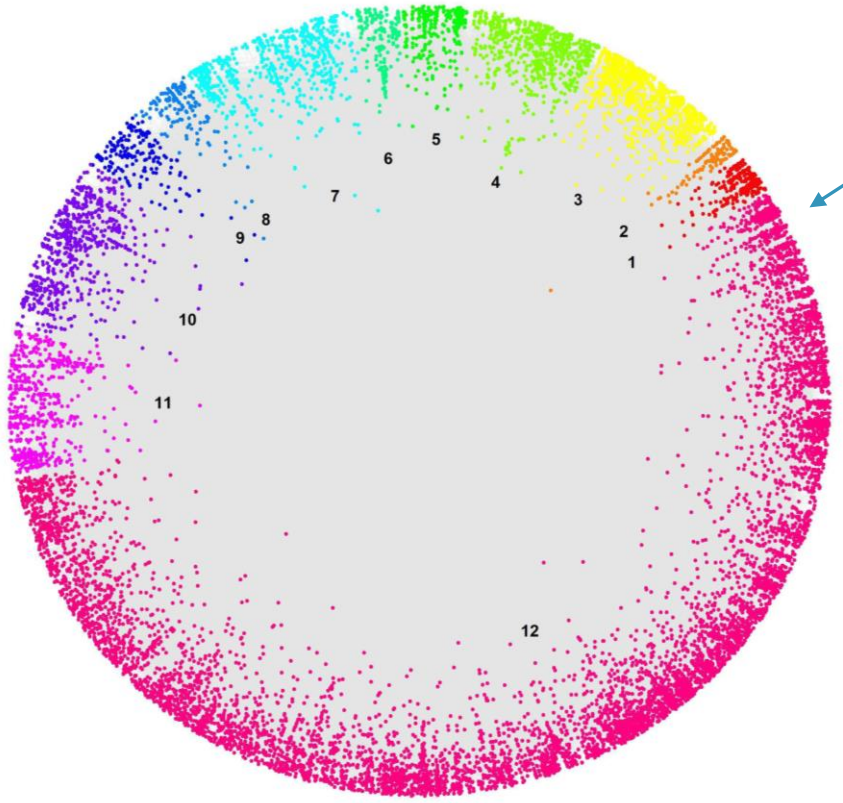
Test set

Workflow

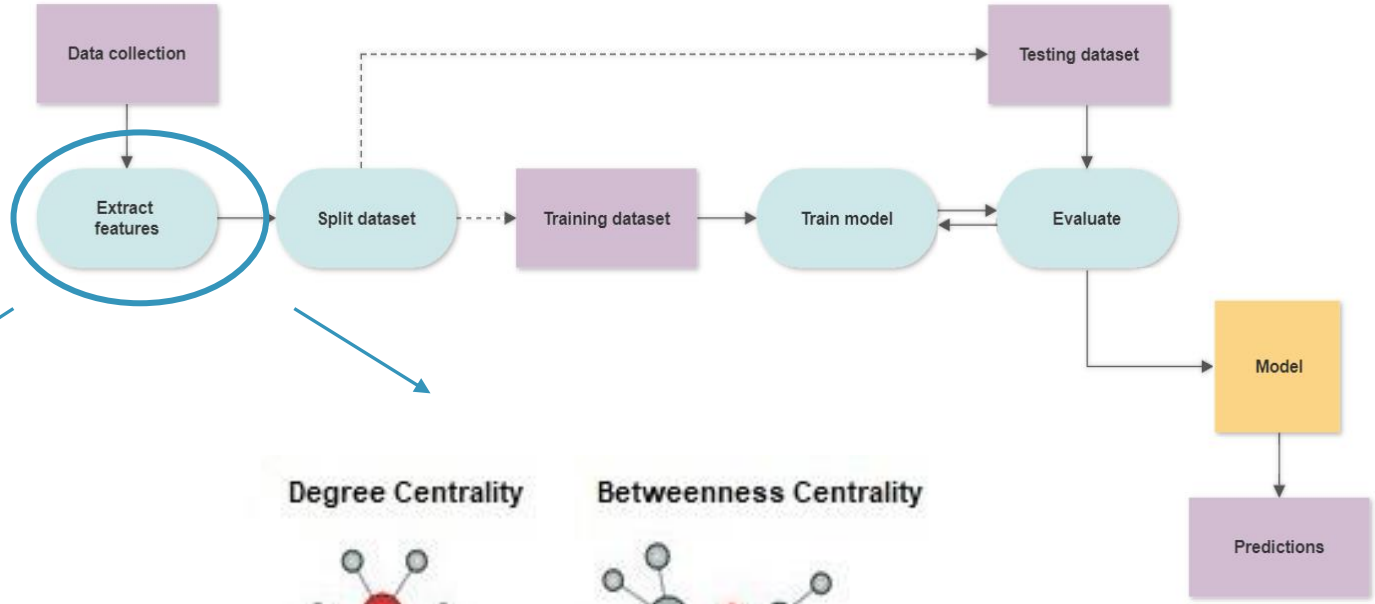

EMBL-EBI
PSICQUIC
Enzymatic interactions
HIPPIE
PPIs
Data collection
Testing dataset
Extract features
Split dataset
Training dataset
Train model
Evaluate
Model
Predictions
KinaseMD
Direction of enzymatic
DEPOD
Direction of enzymatic

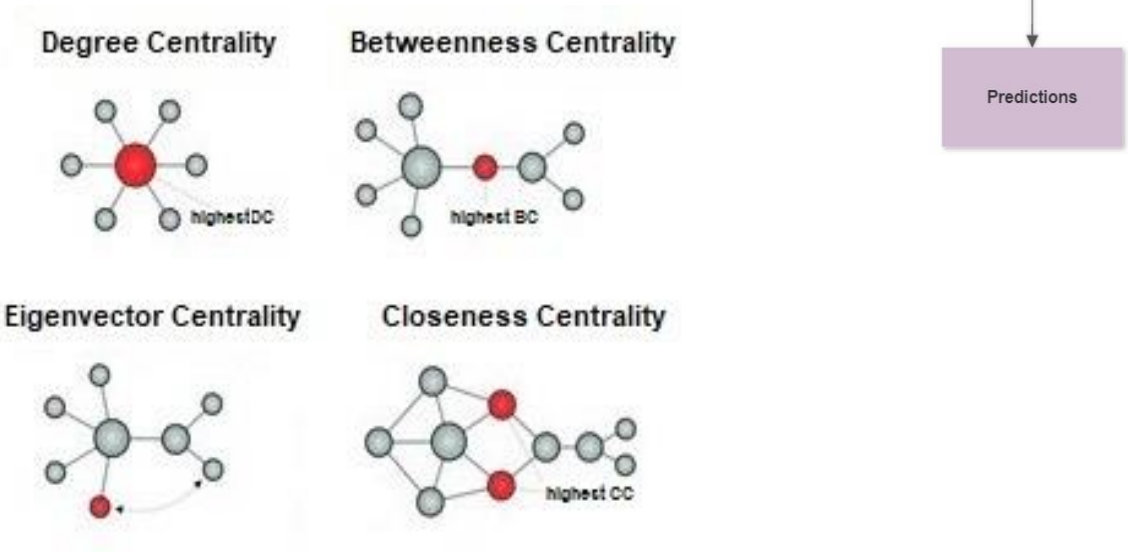
Hyperbolic Topological properties

(r and theta coordinates)

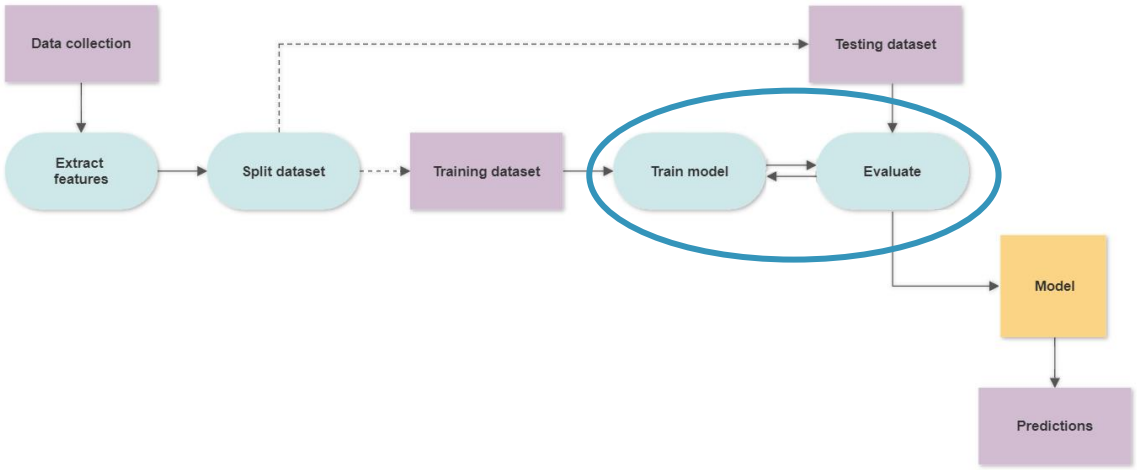


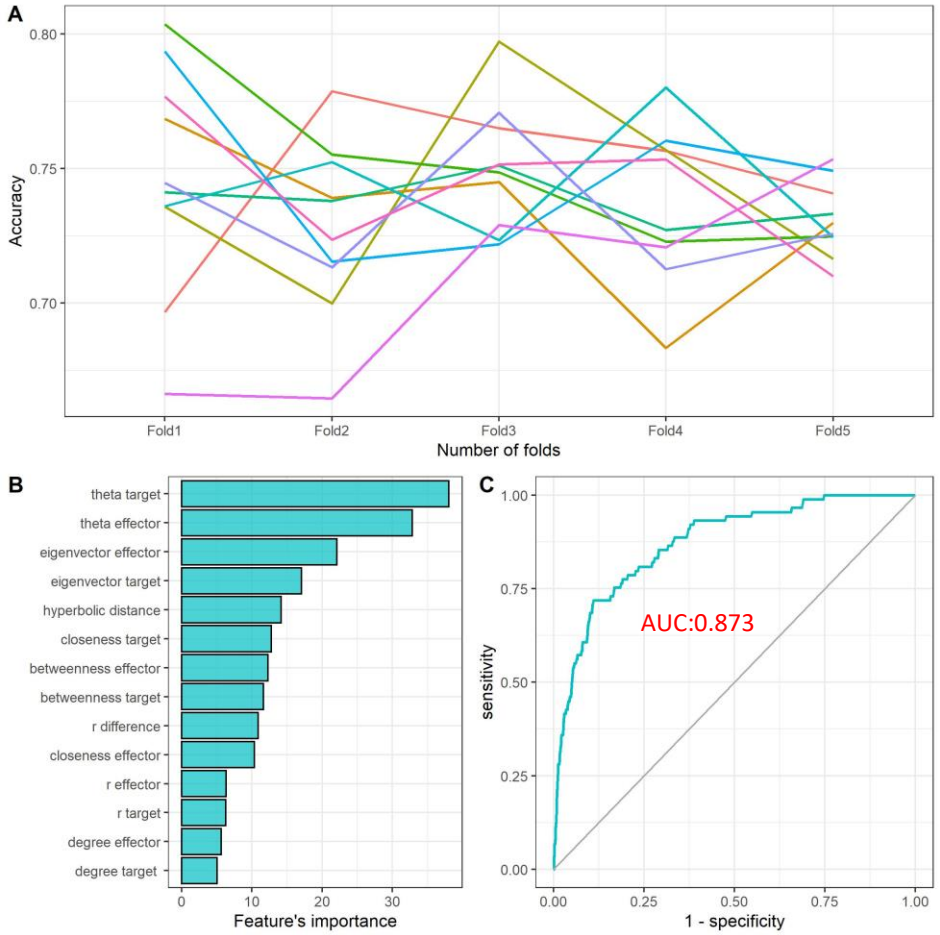
Vagiona et.al, 2022



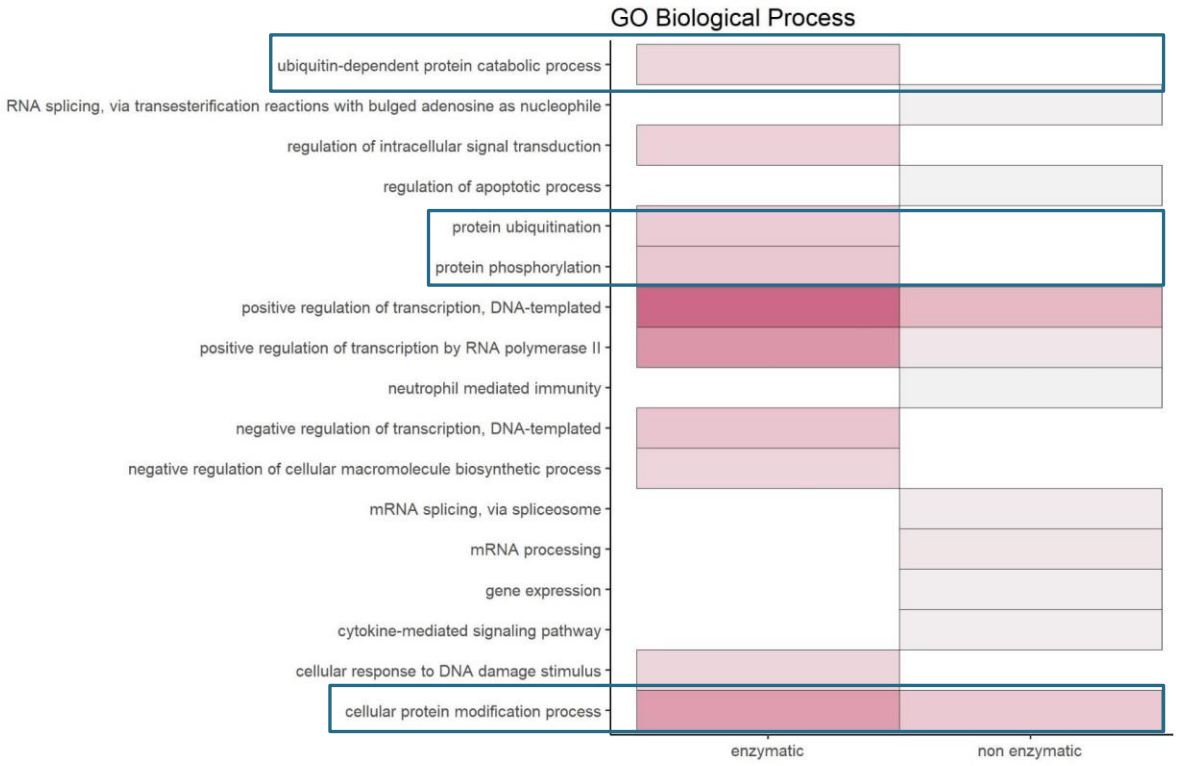


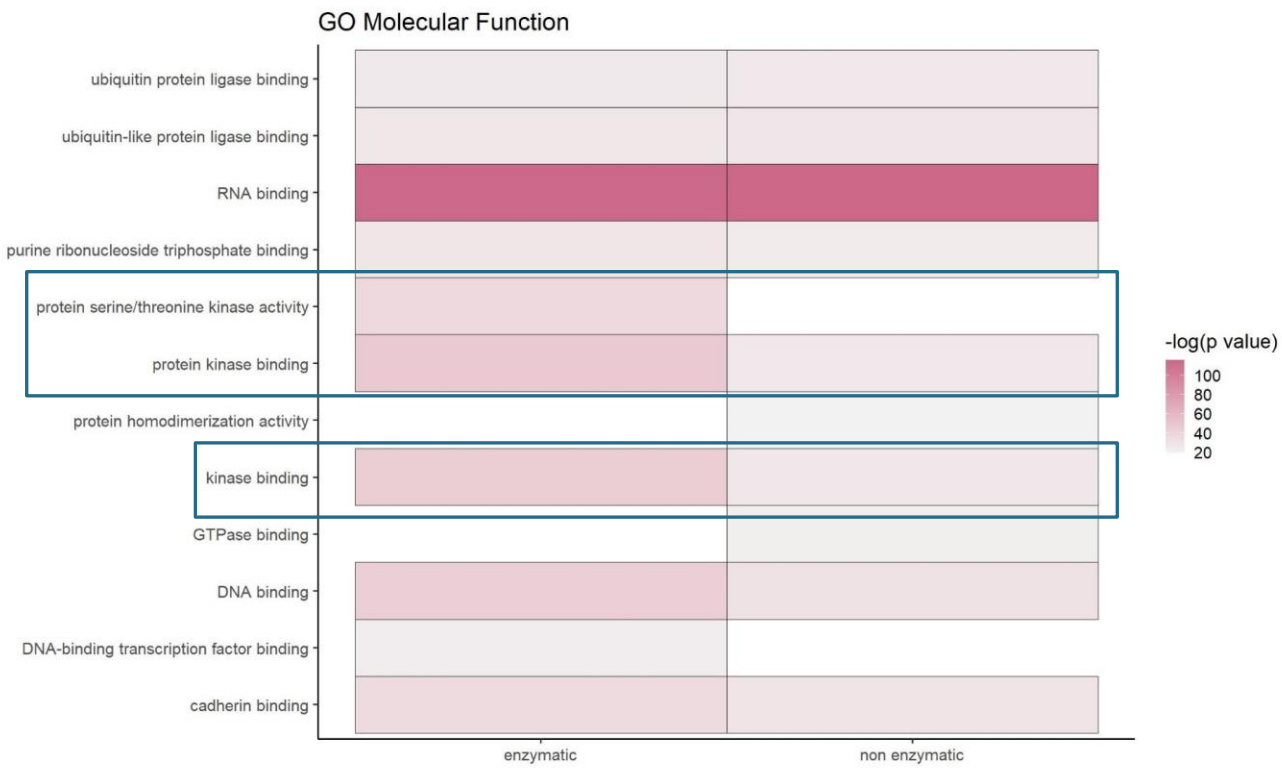
Model evaluation





Enrichment analysis





Why is it important to study effectors of enzymatic reactions?

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Post-translational modifications: Regulators of neurodegenerative proteinopathies

Rohan Gupta [1], Mehar Sahu [1], Devesh Srivastava [1], Swati Tiwari [1], Rashmi K. Ambasta, Pravir Kumar *

Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110042, India

frontiers in Cellular Neuroscience

REVIEW
published: 19 September 2018
doi: 10.3389/fncel.2018.00290

Roles of Post-translational Modifications in Spinocerebellar Ataxias

Linlin Wan[†], Keqin Xu[†], Zhao Chen[†], Beisha Tang[†] and Hong Jiang[*]

brain sciences

MDPI

Review

Do Post-Translational Modifications Influence Protein Aggregation in Neurodegenerative Diseases: A Systematic Review

Larissa-Nele Schaffert and Wayne G. Carter *

School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Uttoxeter Road, Derby DE22 3DT, UK; larissaschaffert@yahoo.de

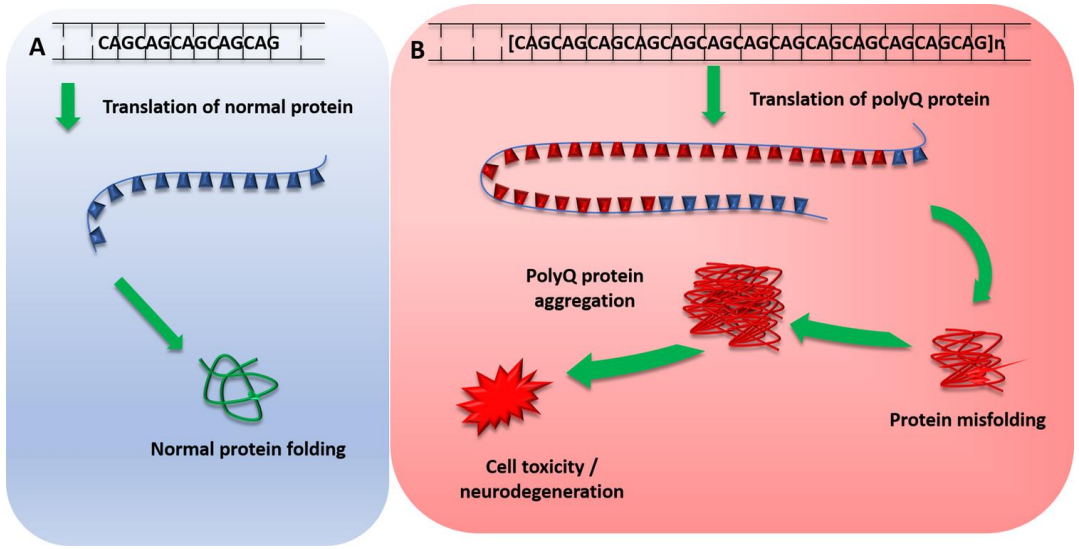
* Correspondence: Wayne.Carter@nottingham.ac.uk; Tel.: +44-(0)1332-724738

Received: 18 March 2020; Accepted: 7 April 2020; Published: 11 April 2020

check for updates

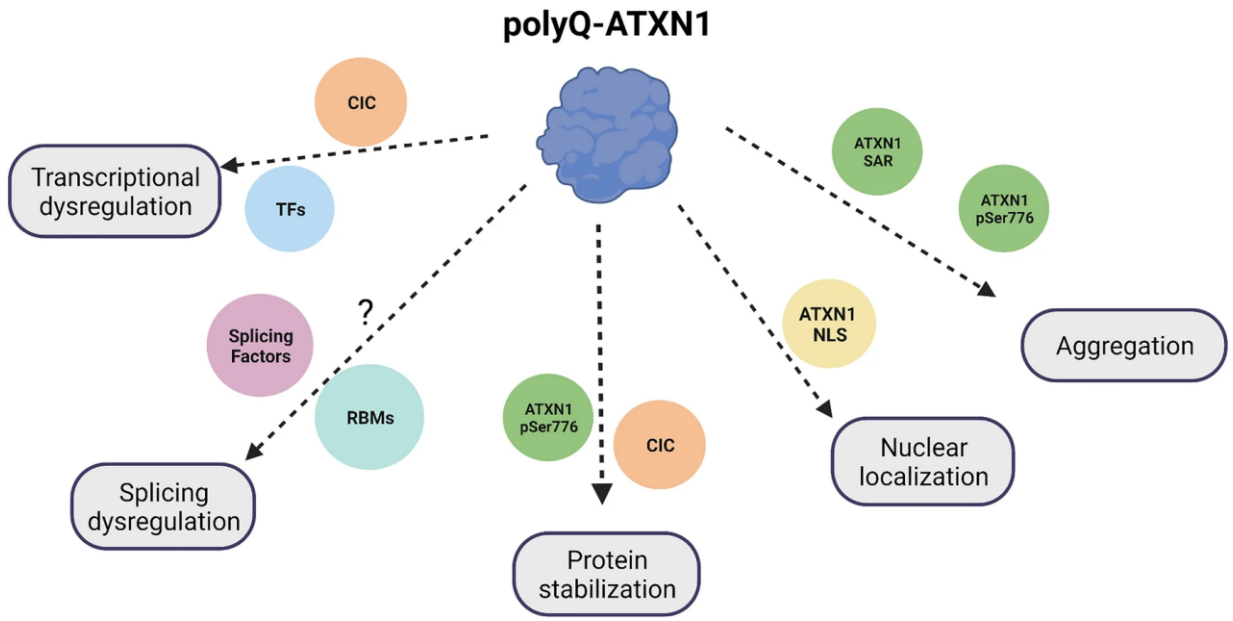
Dysregulated PTMs may influence the propensity for protein aggregation in NDD-proteinopathies (Schaffert et al., 2020)

Case study: Spinocerebellar ataxia 1 (SCA1)



Sullivan et.al, 2019

Molecular mechanisms of SCA1 pathogenesis



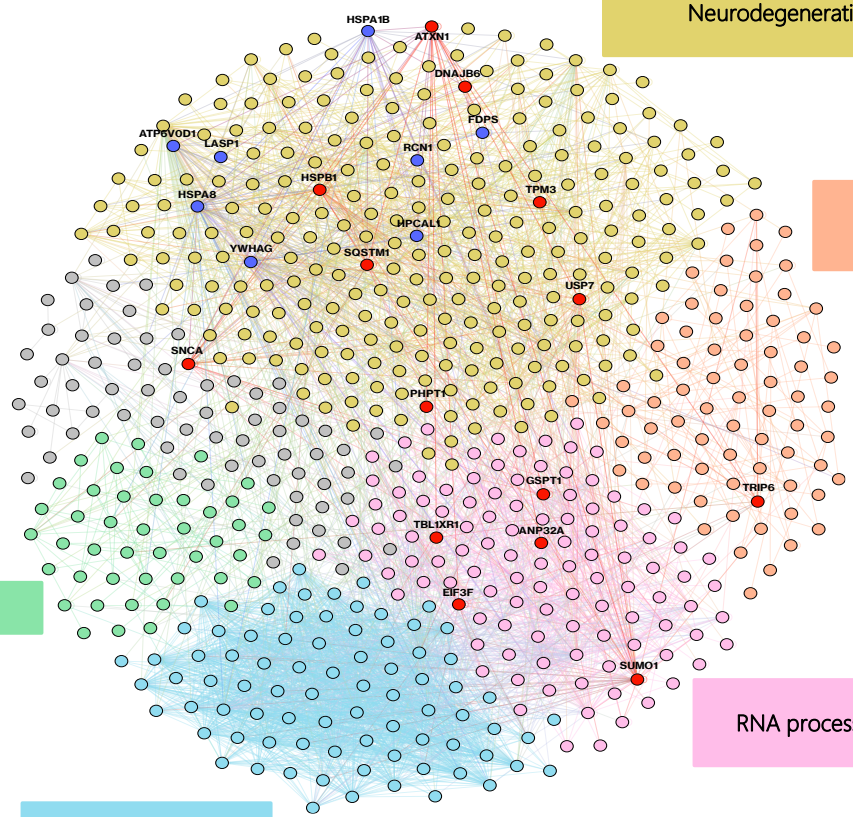
Olmos et.al, 2022

Quantitative proteomics: PPI of 804 dysregulated proteins in SCA1 cell model

ATXN-1 interactors:

Enzymatic (n=13)

Non-enzymatic (n=8)



Neurodegeneration

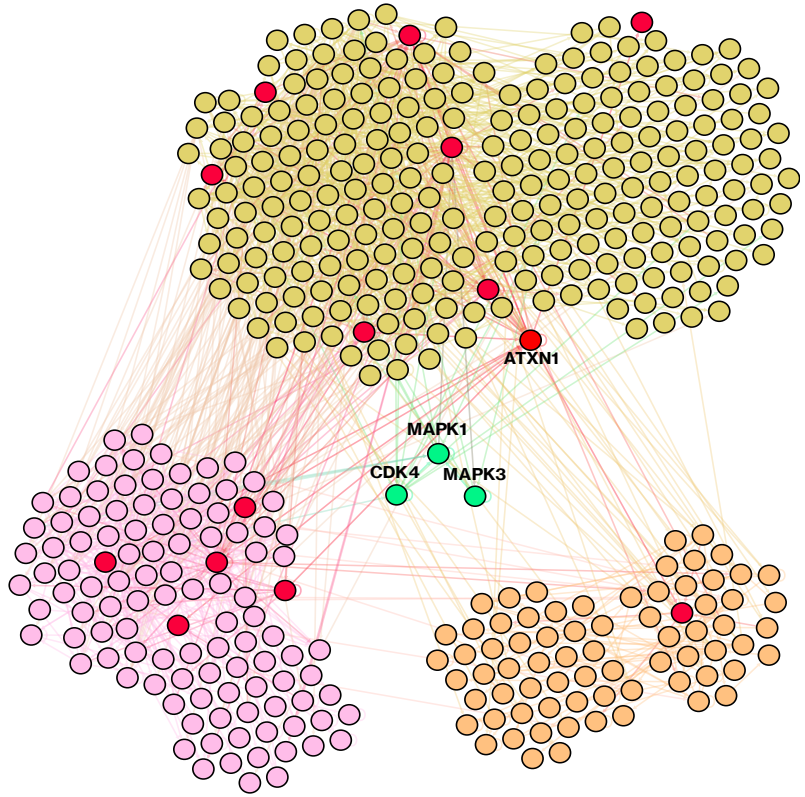
Lysosome activation

Not enriched

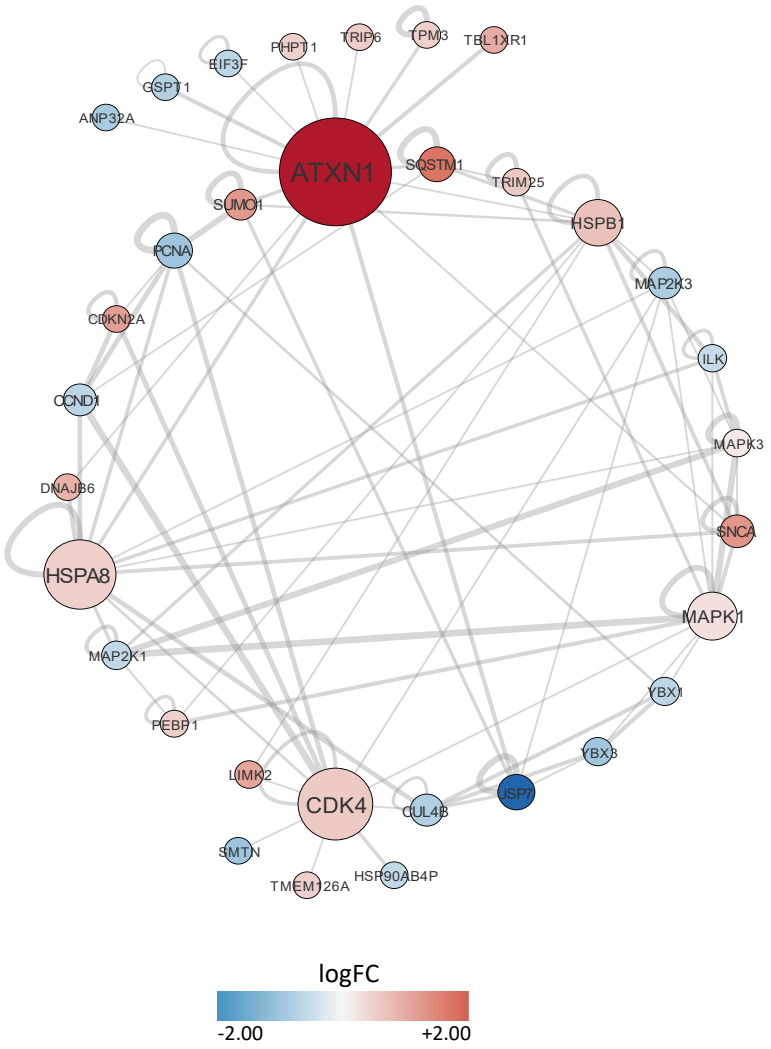
Metabolism

RNA processes

Ribosome assembly



Common dysregulated kinases of the three clusters that predicted enzymes targeting ATX1 are participating



L1000FWD

drug	similarity score	p-value	q-value	Z-score	combined score
linifanib	-0.2069	1.07e-05	3.39e-02	1.71	-8.51
BRD-K76938712	-0.2069	2.08e-05	4.95e-02	1.68	-7.85
artesunate	-0.1724	1.23e-04	6.91e-02	1.82	-7.12
HLI-373	-0.1724	1.30e-04	6.91e-02	1.82	-7.07
BRD-K05402890	-0.1724	1.44e-04	6.91e-02	1.80	-6.92
BRD-K73261812	-0.1724	1.52e-04	6.91e-02	1.81	-6.91
betamethasone	-0.1724	1.69e-04	6.91e-02	1.83	-6.89
proscillaridin	-0.1724	1.60e-04	6.91e-02	1.81	-6.89
BRD-K56024573	-0.1724	1.44e-04	6.91e-02	1.78	-6.83
testosterone	-0.1724	1.92e-04	7.04e-02	1.83	-6.81

Study Overview

ClinicalTrials.gov

Brief Summary:
This dose-escalation study is aimed at investigating a novel application for artesunate in the treatment of Friedreich **ataxia**. It will evaluate this novel application of oral artesunate using a surrogate biological marker as primary endpoint in a phase I-II open trial

OFFICIAL TITLE

Evaluation of the Effect of **Artesunate** in Friedreich **Ataxia** (FA) Phase I-II Efficacy-Toxicity of **Artesunate** in Friedreich **Ataxia**

CONDITIONS	STUDY TYPE	ENROLLMENT (ESTIMATED)
Friedreich **Ataxia**	Interventional	20
INTERVENTION / TREATMENT	**PHASE**	**OTHER STUDY ID NUMBERS**
Drug: Artesunate Oral Product	Phase 1 Phase 2	C20-54
STUDY START (ESTIMATED)	**PRIMARY COMPLETION (ESTIMATED)**	**STUDY COMPLETION (ESTIMATED)**
July 1, 2021	June 30, 2022	June 30, 2022

Neurology®
The most widely read and highly cited peer-reviewed neurology journal

Subscribe My Alerts Log in

Home Latest Articles Current Issue Past Issues Neurology Video Journal Club Residents & Fellows

April 08, 2014; 82 (10 Supplement) APRIL 28, 2014

Sodium-Potassium ATPase Inhibitors as Inhibitors of ATXN2 Expression (P1.046)

Daniel Scoles, Lance Pflieger, Thomas Dexheimer, David Maloney, Anton Simeonov, Ajit Jadhav, Stefan Pulst
First published April 9, 2014,

J Biol Chem. 2022 Aug; 298(8): 102228.
Published online 2022 Jul 2. doi: 10.1016/j.jbc.2022.102228

PMCID: PMC9356275
PMID: 35787375

A quantitative high-throughput screen identifies compounds that lower expression of the SCA2-and ALS-associated gene *ATXN2*

Daniel R. Scoles,[1,*] Mandi Gandelman,[1] Sharan Paul,[1] Thomas Dexheimer,[2] Warunee Dansithong,[1] Karla P. Figueroa,[1] Lance T. Pflieger,[3] Scott Redlin,[1] Stephen C. Kales,[2] Hongmao Sun,[2] David Maloney,[2] Robert Damoiseaux,[4] Mark J. Henderson,[2] Anton Simeonov,[2] Ajit Jadhav,[2] and Stefan M. Pulst[1,*]

Conclusions

- Computational: Generate a model to predict enzymatic reactions (0.74 accuracy) predicting also the enzymes of these interactions

- Biological validation: compare the overlap between predicted enzymes targeting Ataxin 1 and dysregulated proteins of SCA1 cell line model

- Drug discovery for the nodes of a critical network based on “potential” regulators of the pathogenesis of the disease

Thank you very much

Any questions?