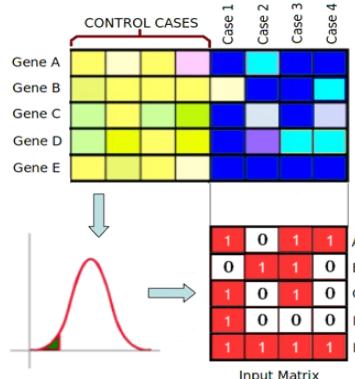
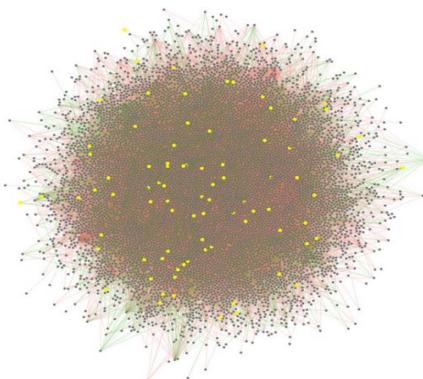


Network Medicine GPT

- Drug repurposing -

5 years ago vs. today





Jan Baumbach



Jan Baumbach

Director of Computational Systems Biology

University of Hamburg

CEO of Albatross.ai

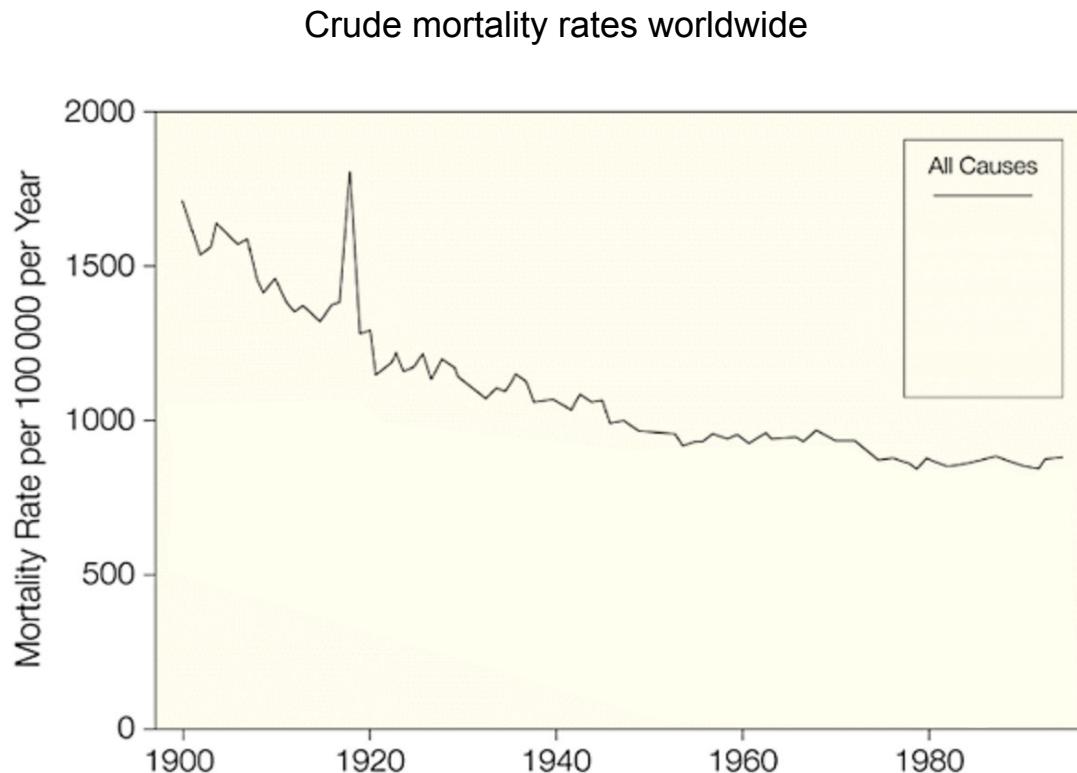
CSO of Dehaze and Omiya.ai

Germany

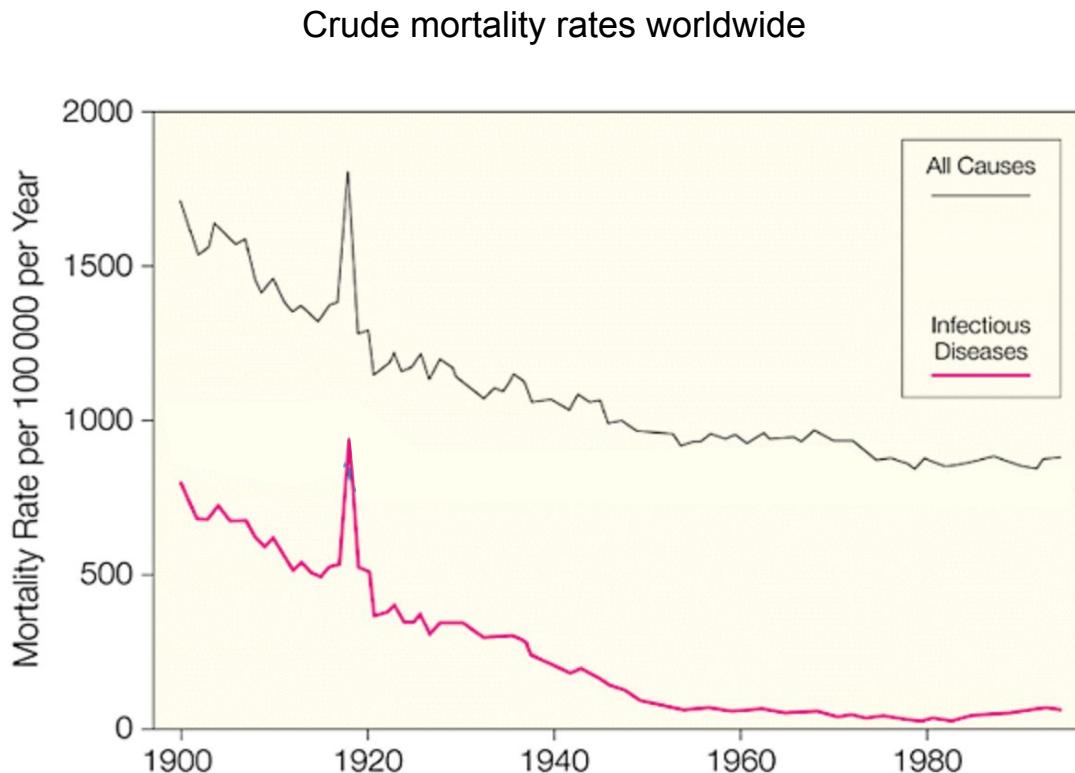


Network Medicine

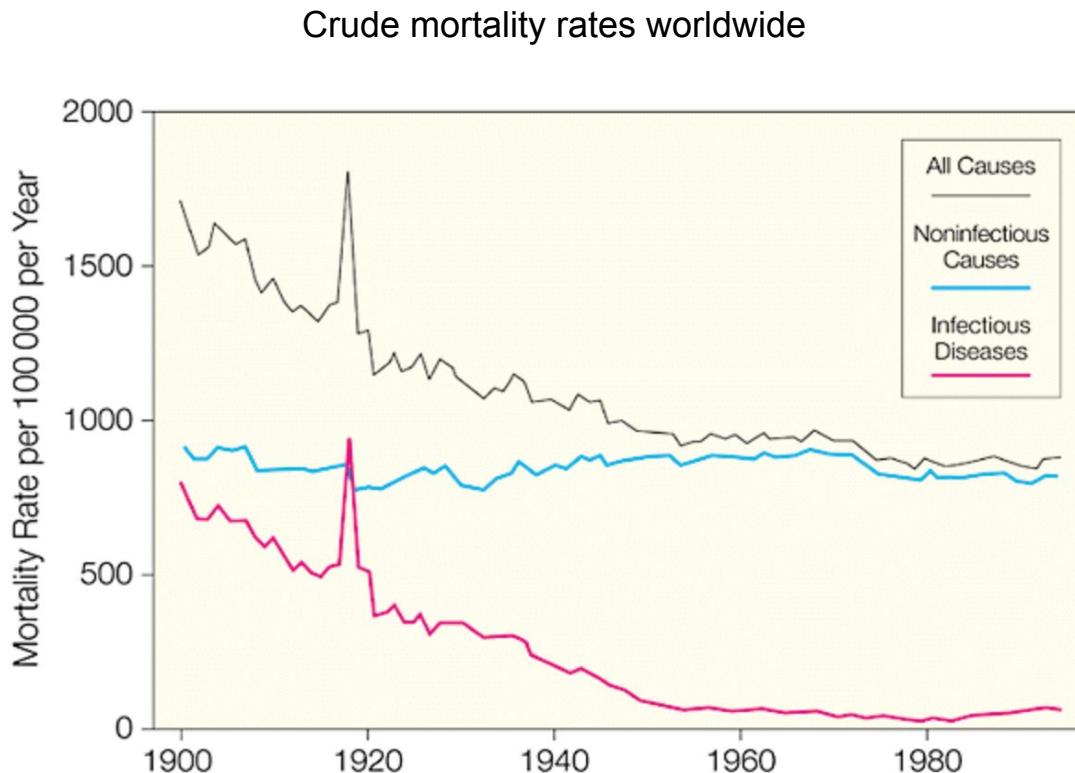
My motivation: Symptom-based disease definitions



My motivation: Symptom-based disease definitions

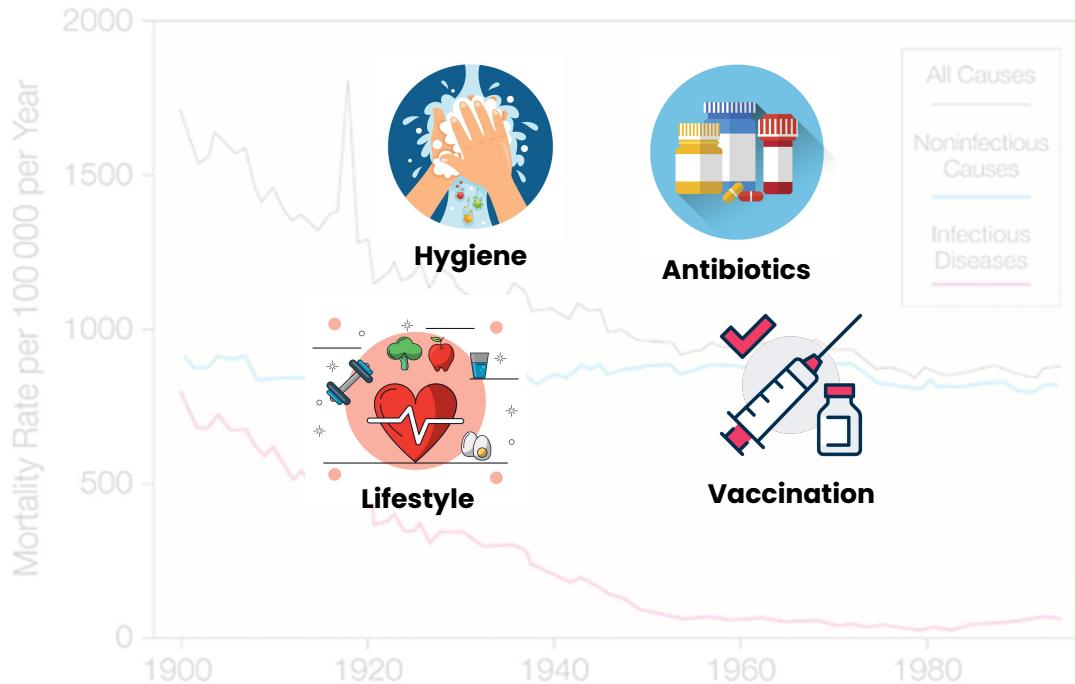


My motivation: Symptom-based disease definitions



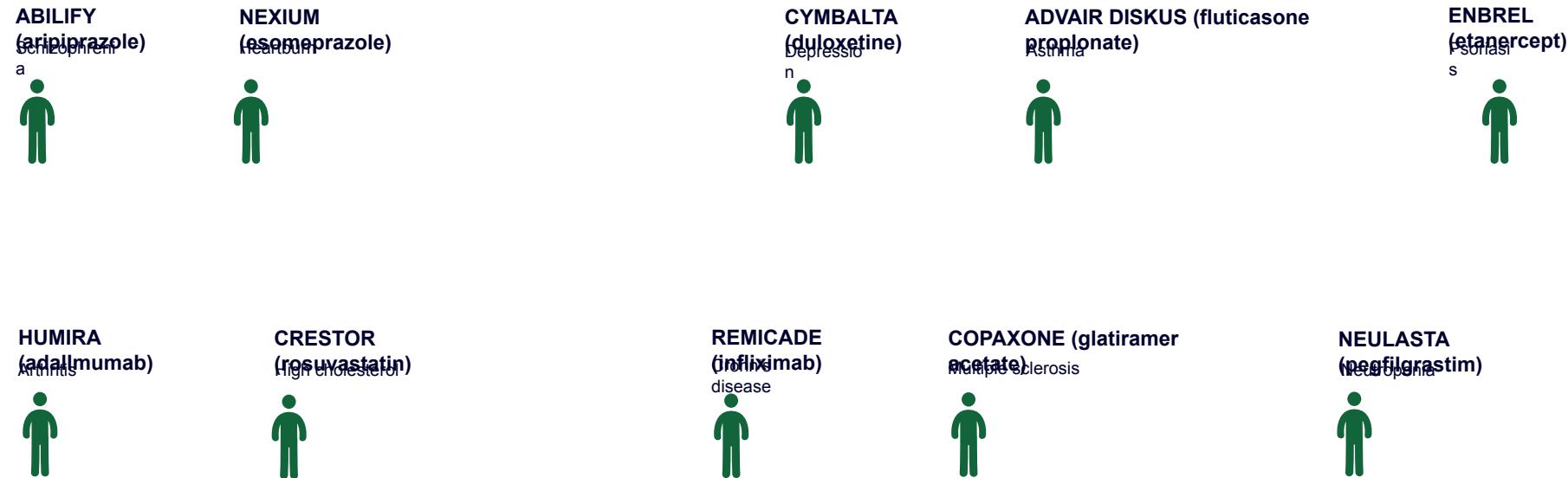
My motivation: Symptom-based disease definitions

Lifespan as KPI? □ What had most impact?



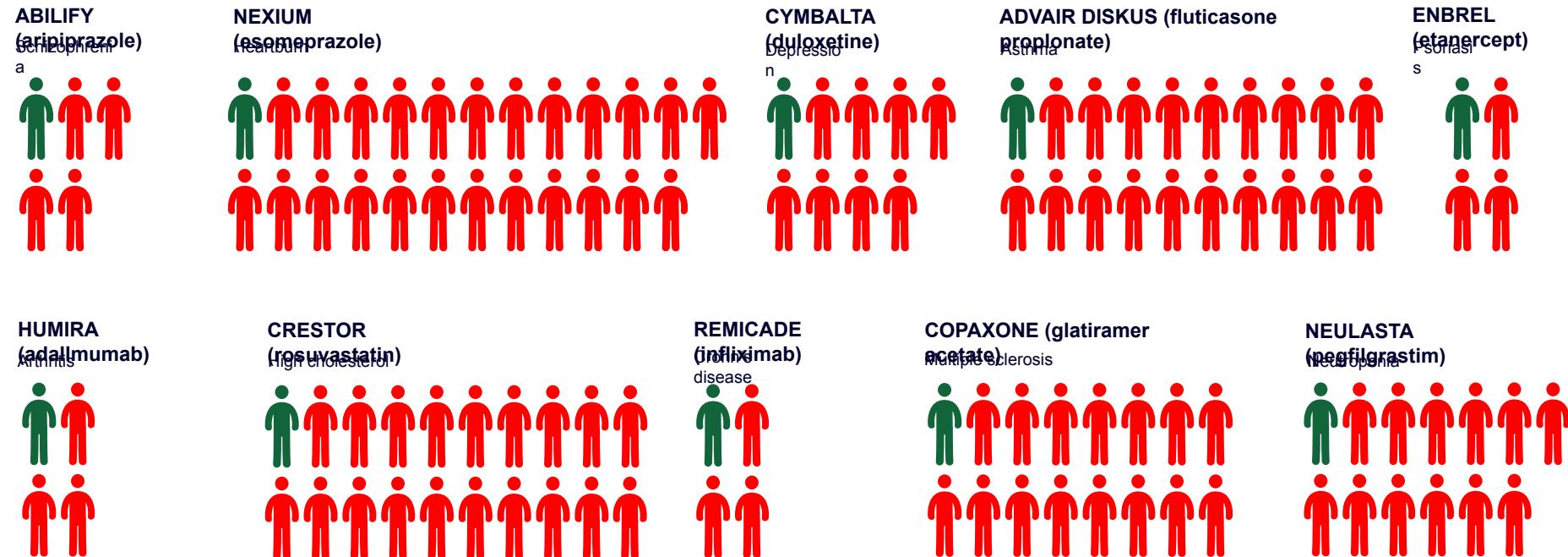
My motivation: Symptom-based disease definitions

Existing drugs lack precision **High Numbers Needed to Treat (NNT)**



My motivation: Symptom-based disease definitions

Existing drugs lack precision High Numbers Needed to Treat (NNT)



My motivation: Symptom-based disease definitions

19th/20th Century disease definitions and structure of medicine

By organ

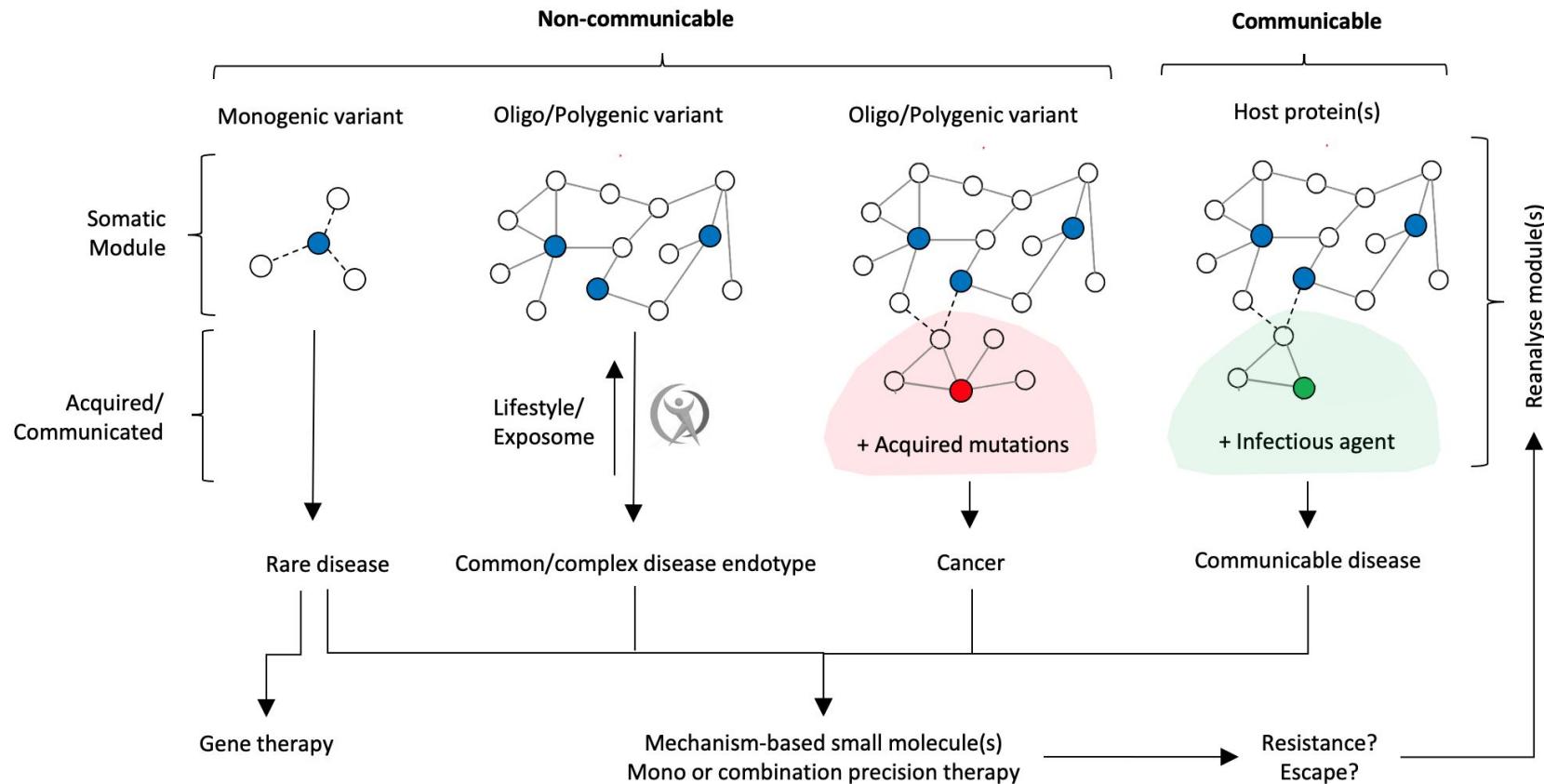


By the name of a
doctor



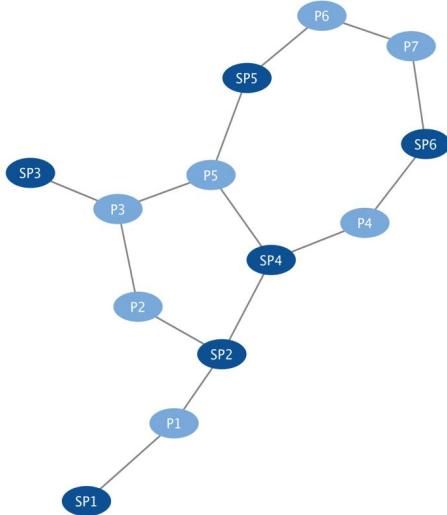
By symptom

Network & Systems Medicine: The idea



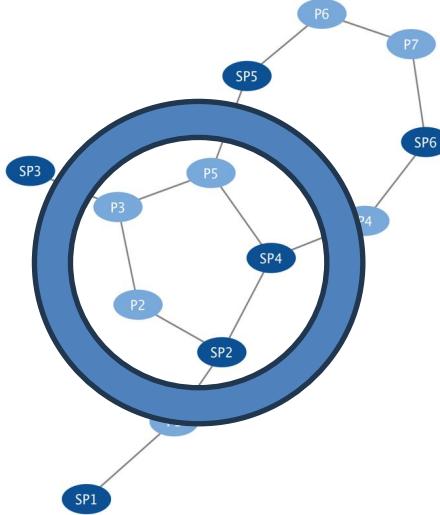
Network Medicine: Druggable targets

Imagine a small network.



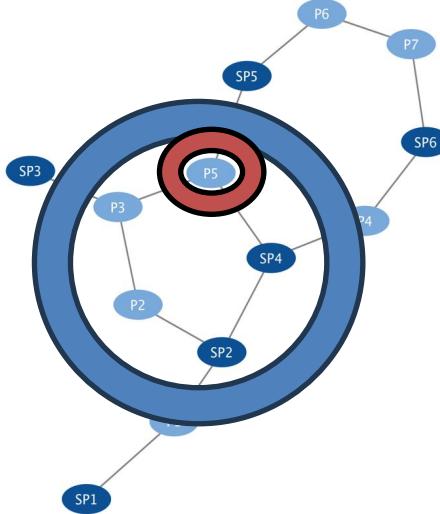
Network Medicine: Druggable targets

With a **protein complex** being the **disease driver**, i.e. a small subnetwork.



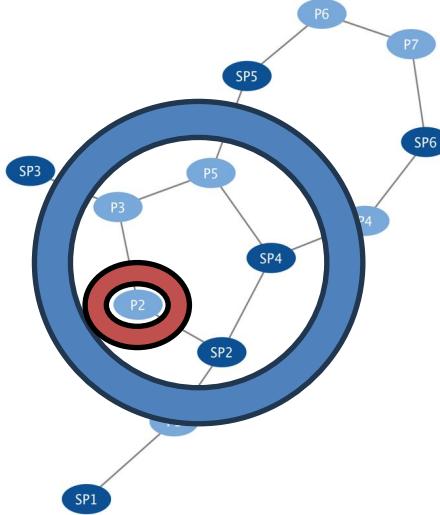
Network Medicine: Druggable targets

- If **P5** is “misbehaving” the complex “misbehaves”, and **drives the disease**.



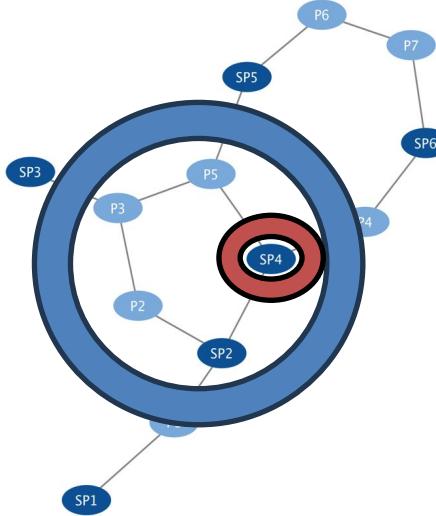
Network Medicine: Druggable targets

- If **P2** is “misbehaving” the complex “misbehaves”, and **drives the disease**.



Network Medicine: Druggable targets

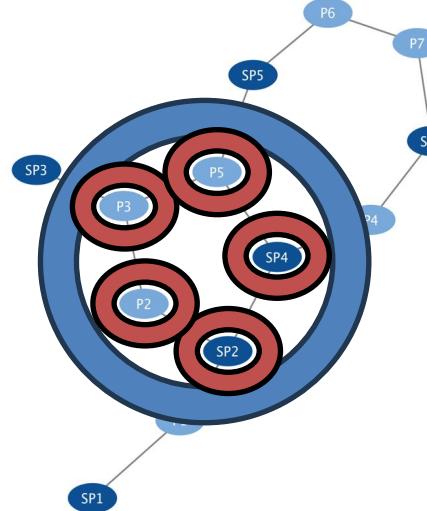
- If **SP4** is “misbehaving” the complex “misbehaves”, and **drives the disease**.



Network Medicine: Druggable targets

Given **omics** data, **each gene** would have only **a 20% chance to be “hit”**.

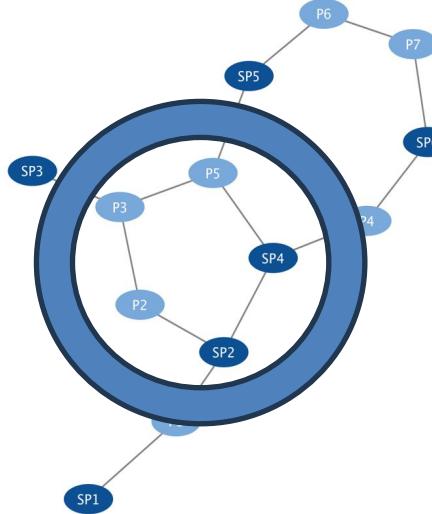
	P2	P3	P5	SP2	SP4
P1	X	-	-	-	-
P2	-	X	-	-	-
P3	X	-	-	-	-
P4	-	X	X	-	-
P5	-	-	-	X	-
P6	-	-	-	X	-
P7	-	-	-	-	X
P8	-	-	X	-	-



Network Medicine: Druggable targets

None would be identified as statistically **significant**.

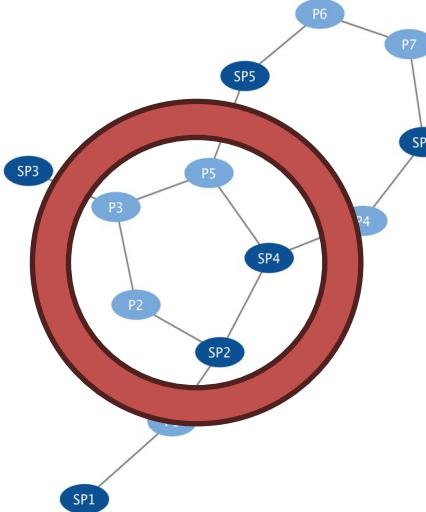
	P2	P3	P5	SP2	SP4	Sig?
P1	X	-	-	-	-	no
P2	-	X	-	-	-	no
P3	X	-	-	-	-	no
P4	-	X	X	-	-	no
P5	-	-	-	X	-	no
P6	-	-	-	X	-	no
P7	-	-	-	-	-	X
P8	-	-	X	-	-	no
Sig?	no	no	no	no	no	no



Network Medicine: Druggable targets

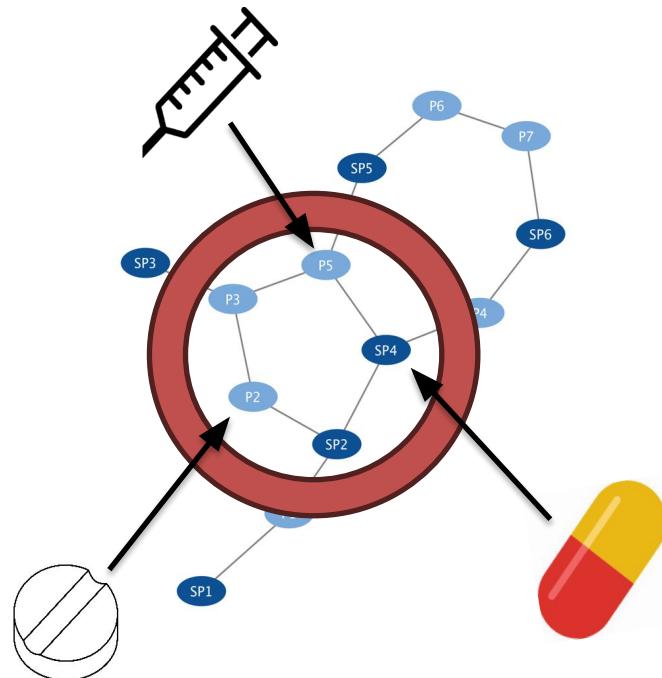
But all **together**, as a **module**, they would be **significant**.

	P2	P3	P5	SP2	SP4
P1	X	-	-	-	-
P2	-	X	-	-	-
P3	X	-	-	-	-
P4	-	X	X	-	-
P5	-	-	-	X	-
P6	-	-	-	X	-
P7	-	-	-	-	X
P8	-	-	X	-	-
Sig?	yes				



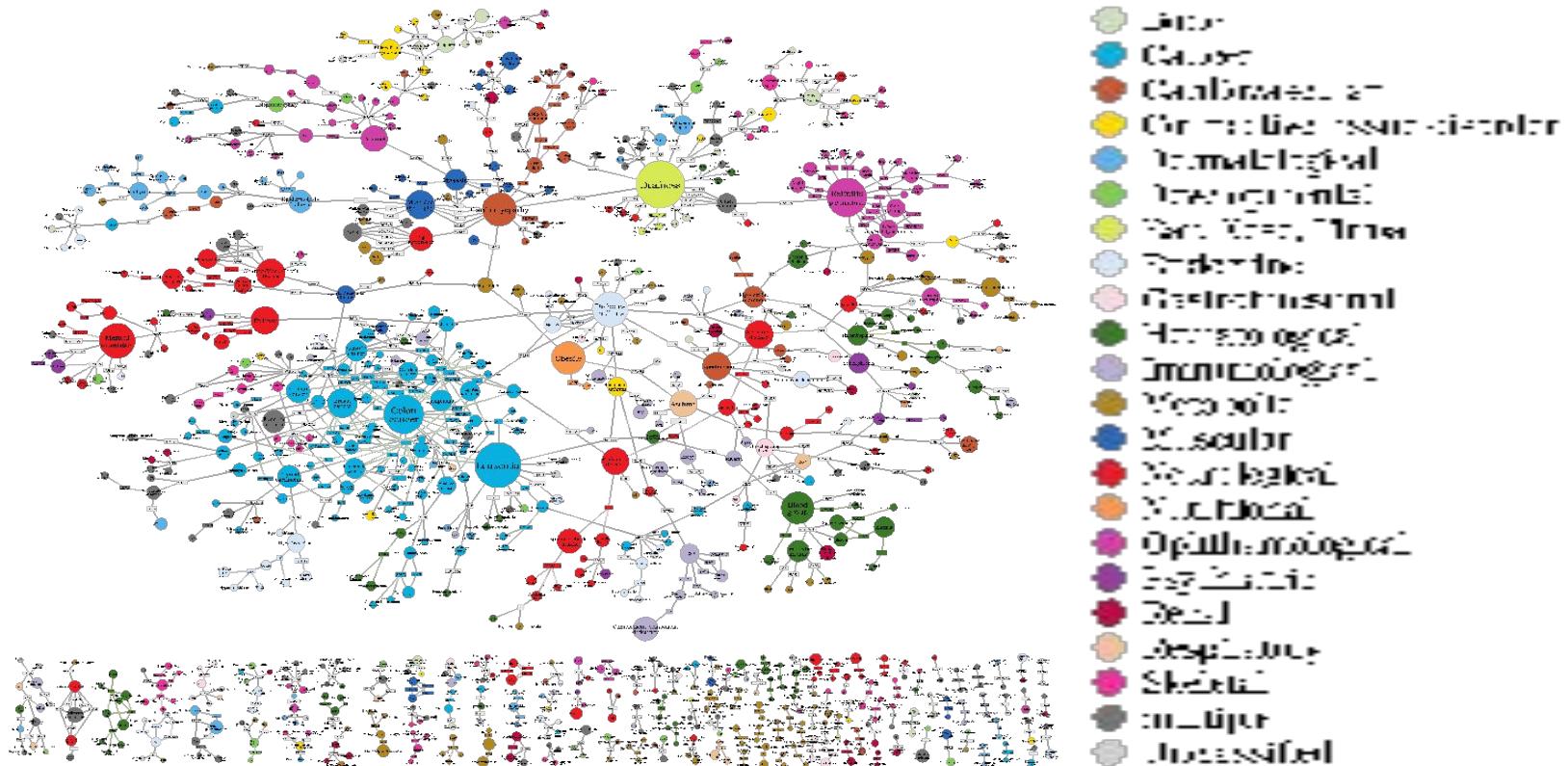
Network Medicine: Drug repurposing

Now we can look for **drugs targeting the driver mechanism**,
i.e. the cause, not the symptom.



The metabolic hypertension / stroke mechanism(s)

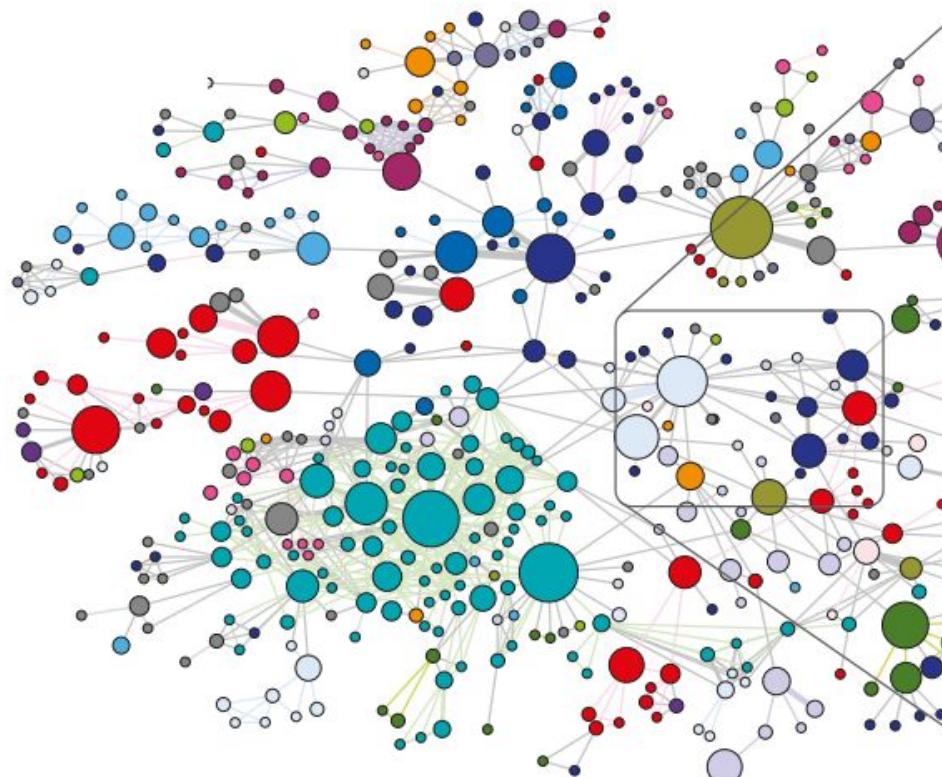
Network Medicine: The diseasesome



Network Medicine: The cGMP-related disease cluster

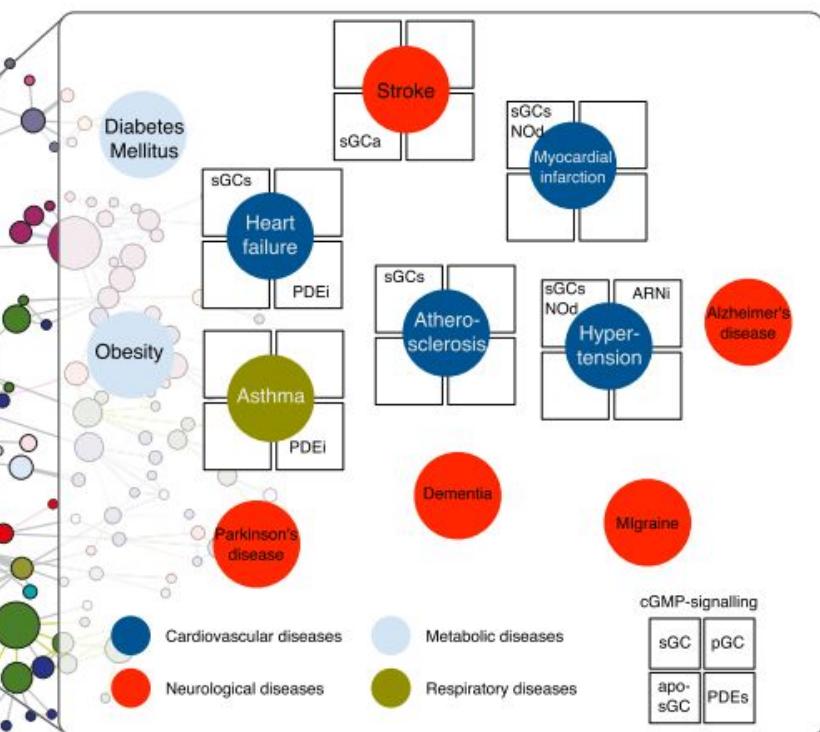
A

Human Disease Network



B

cGMP related cluster



Network Medicine: The ROCG disease cluster

Cyclic GMP signalling pathway

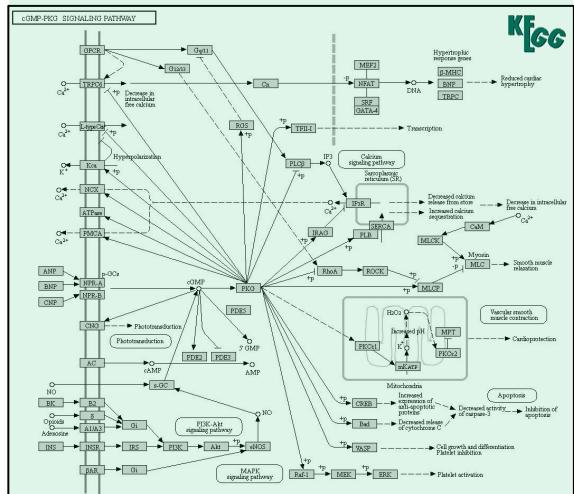
ANP [NPPA]
BNP [NPPB]
Furin [PCSK3]
eNOS [NOS3]
NPR1 [NPR1]
PDE5A [PDE5A]
sGCa1 [GUCY1A3]
sGCa1 [GUCY1A3]
CCTg [CCT7]
sGCh1 [GUCY1B3]

Reactive Oxygen metabolism (“Oxidative Stress”)

eNOS [NOS3]
MPO [MPO]
NOX1 [NOX1]
CY24B
NOX3 [NOX3]
NOX4 [NOX4]
NOX5 [NOX5]
XDH
LDM1A [AOFA, KDM1A]
LDM1B [AOFB, KDM1A]
PPARGC1 ESRR induced regulator, muscle 1 [PERM1]

Network Medicine: The ROCG disease cluster

Cyclic GMP signalling pathway

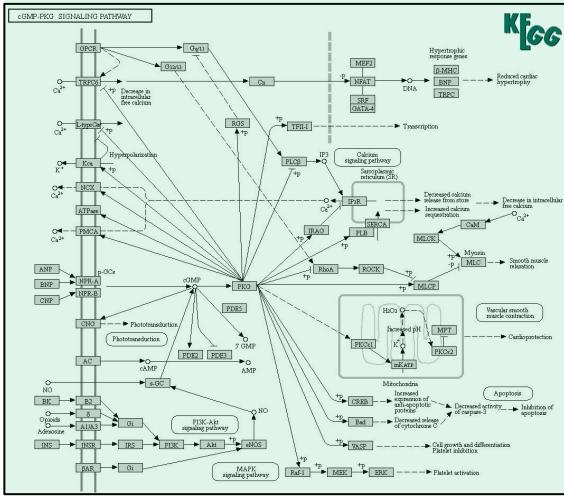


Reactive Oxygen metabolism (“Oxidative Stress”)

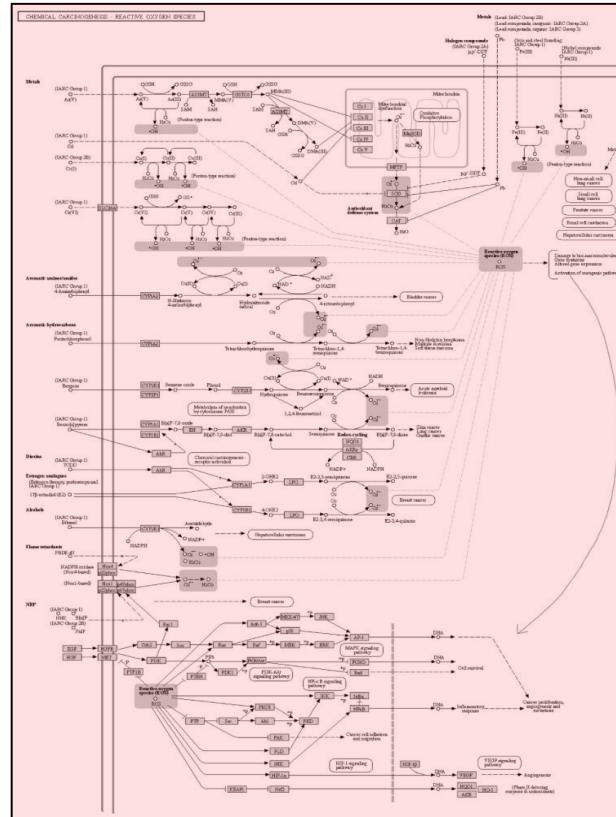
eNOS [NOS3]
MPO [MPO]
NOX1 [NOX1]
CY24B
NOX3 [NOX3]
NOX4 [NOX4]
NOX5 [NOX5]
XDH
LDM1A [AOFA, KDM1A]
LDM1B [AOFB, KDM1A]
PPARGC1 ESRR induced regulator, muscle 1 [PERM1]

Network Medicine: The ROCG disease cluster

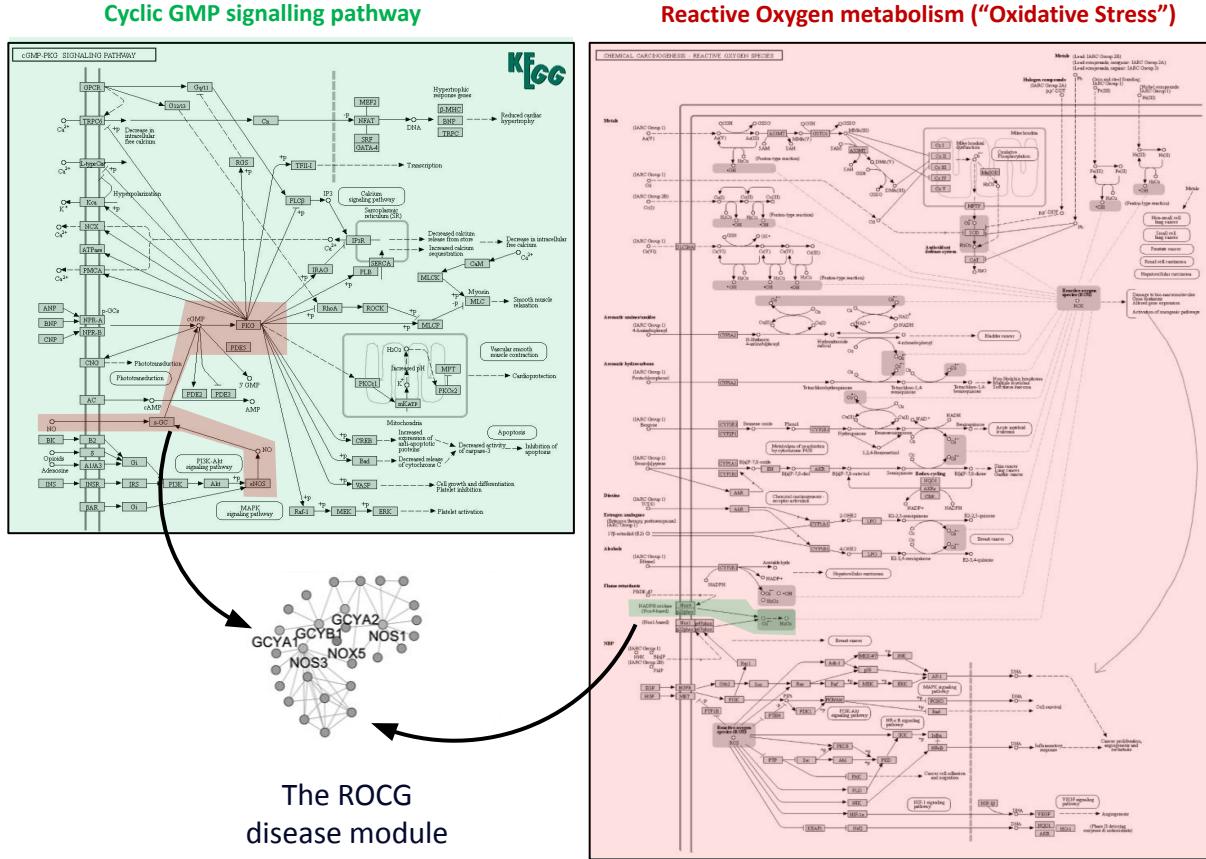
Cyclic GMP signalling pathway



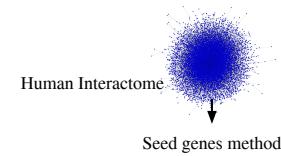
Reactive Oxygen metabolism (“Oxidative Stress”)



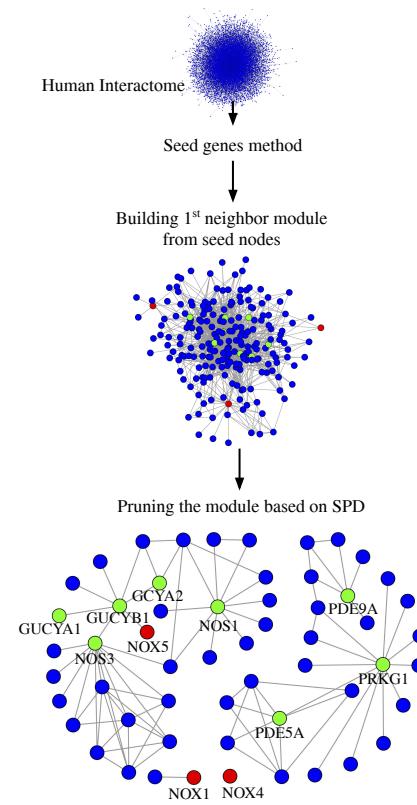
Network Medicine: The ROCG mechanism



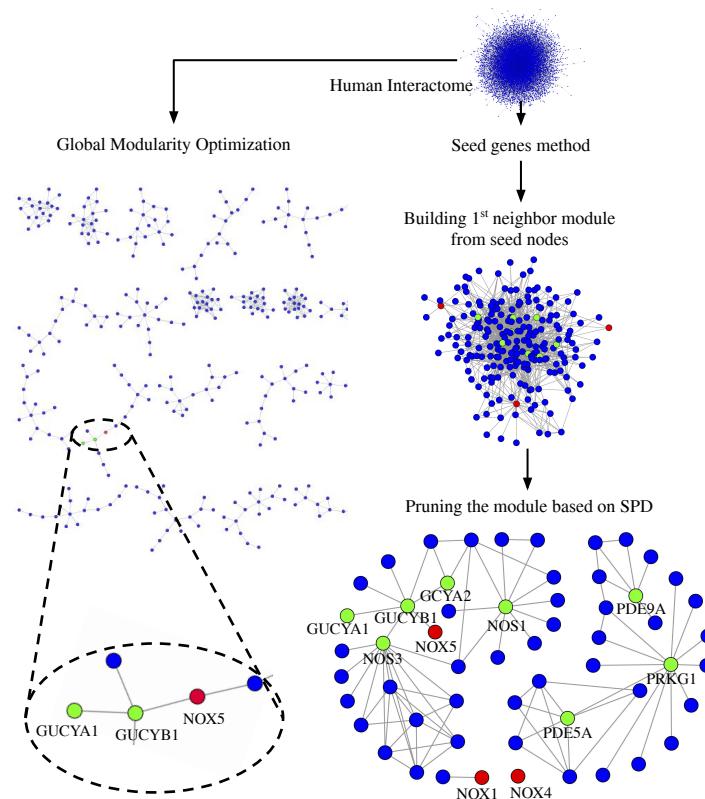
Network Medicine: Unbiased *de novo* reconstruction of ROCG mechanism



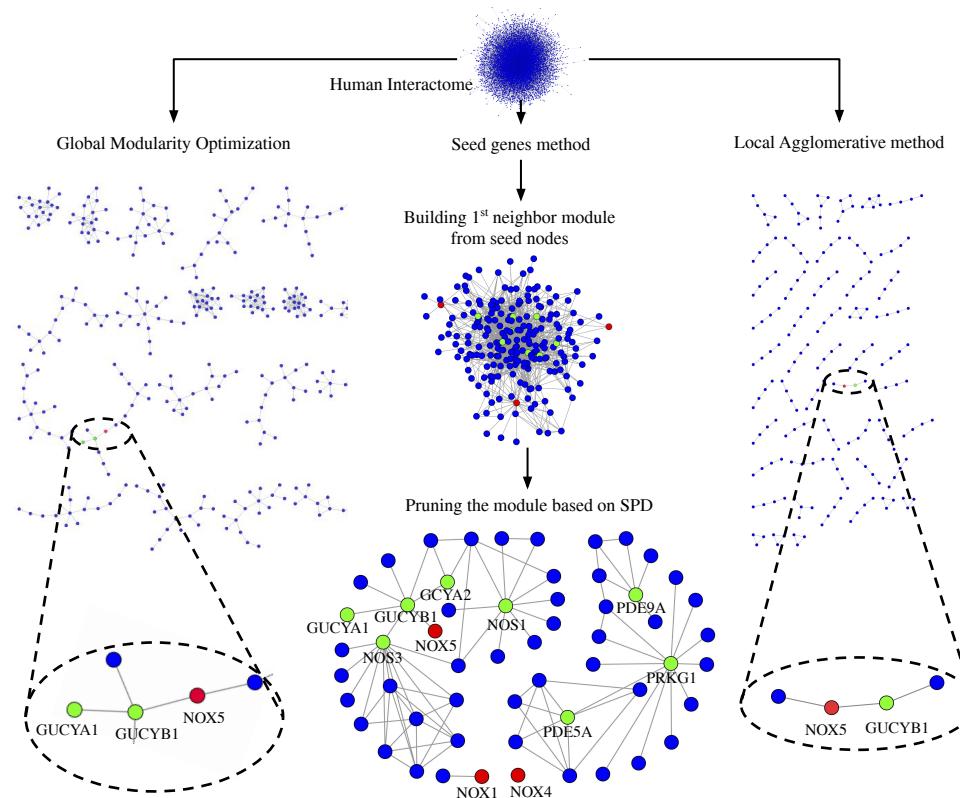
Network Medicine: Unbiased *de novo* reconstruction of ROCG mechanism



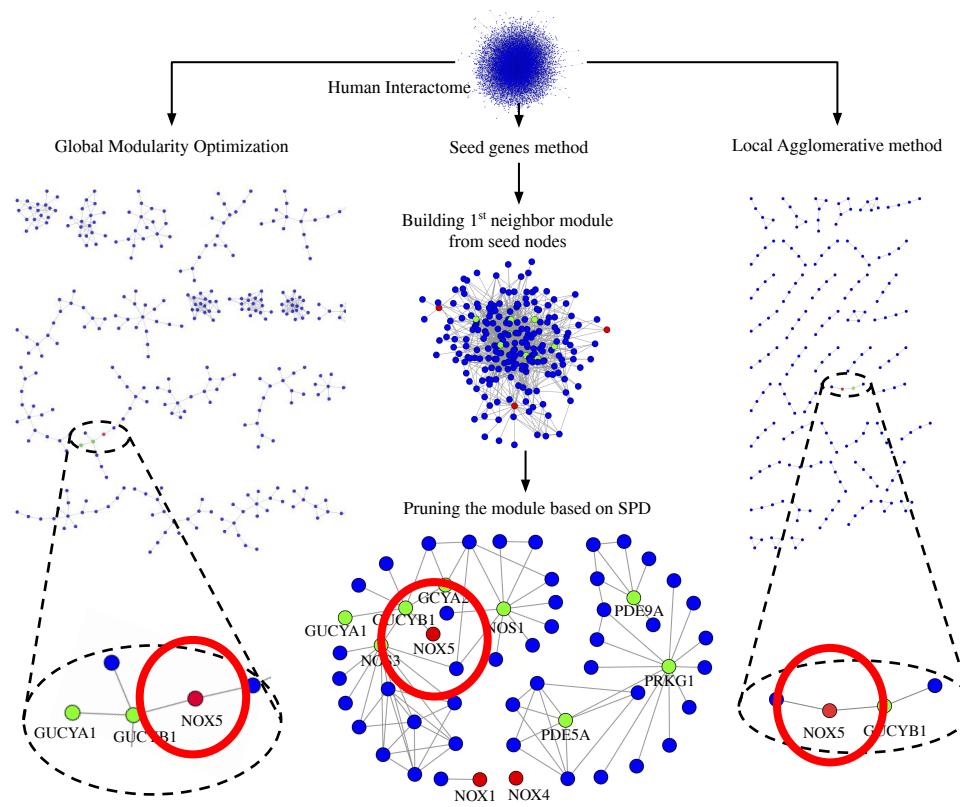
Network Medicine: Unbiased *de novo* reconstruction of ROCG mechanism



Network Medicine: Unbiased *de novo* reconstruction of ROCG mechanism



Network Medicine: Key player NOX5 of the ROCG mechanism



ROCG mechanism: The hypertension hypothesis

1. Old hypothesis: **Oxidative stress is a mechanism of hypertension.**

ROCG mechanism: The hypertension hypothesis

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2. **Reactive oxygen species (ROS)** interfere with vasodilation (**widening of blood vessels**) by the endothelium-derived relaxing factor **nitric oxide (NO)**.

ROCG mechanism: The hypertension hypothesis

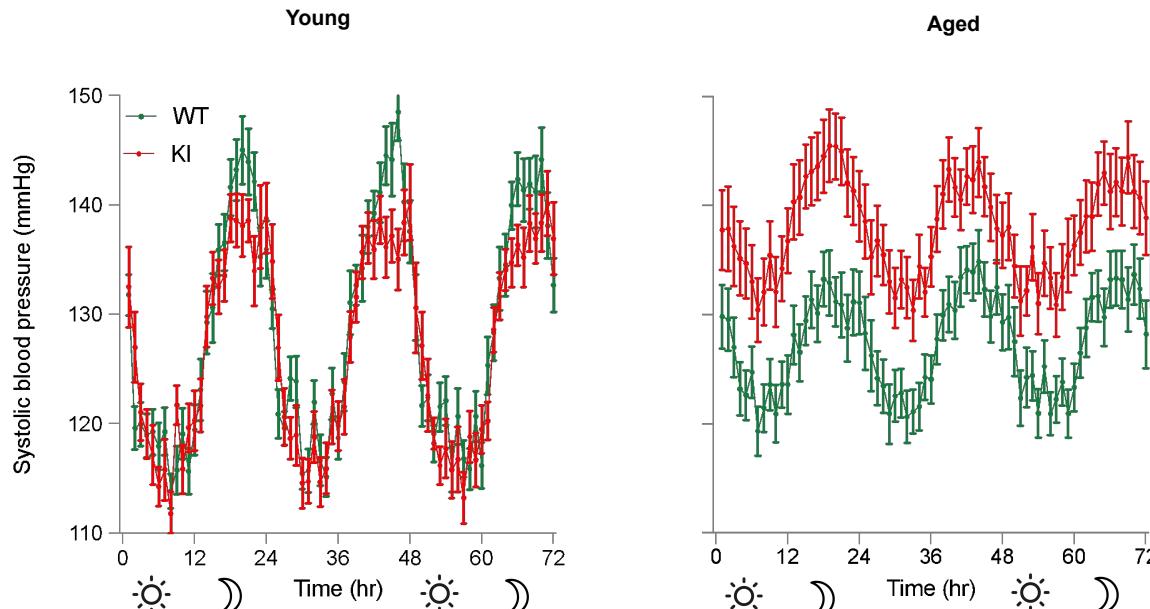
1. Old hypothesis: **Oxidative stress is a mechanism of hypertension.**
2. Reactive oxygen species (**ROS**) interfere with vasodilation (**widening of blood vessels**) by the endothelium-derived relaxing factor **nitric oxide (NO)**.
3. Yet, no hypertension-relevant cellular source of ROS has been identified.

ROCG mechanism: The hypertension hypothesis

1. Old hypothesis: **Oxidative stress is a mechanism of hypertension.**
2. Reactive oxygen species (**ROS**) interfere with vasodilation (**widening of blood vessels**) by the endothelium-derived relaxing factor **nitric oxide (NO)**.
3. Yet, **no hypertension-relevant cellular source of ROS has been identified.**
4. **No mechanism-based curative clinical therapy.**

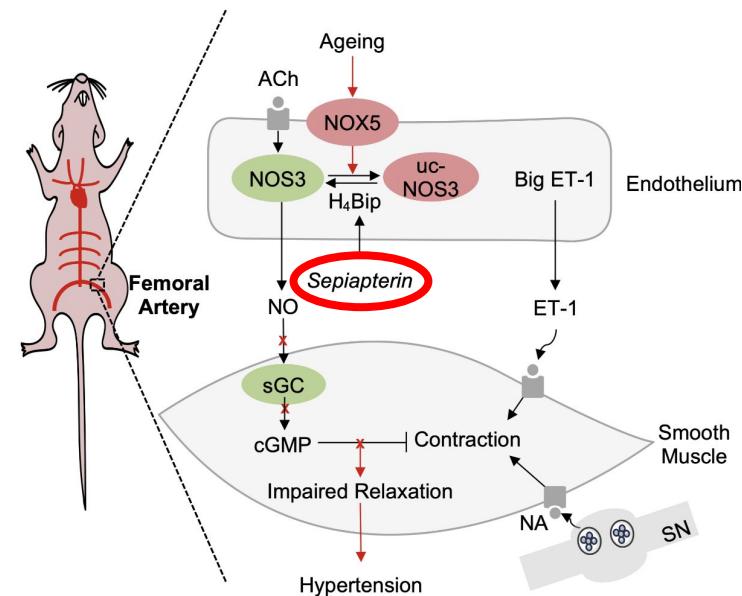
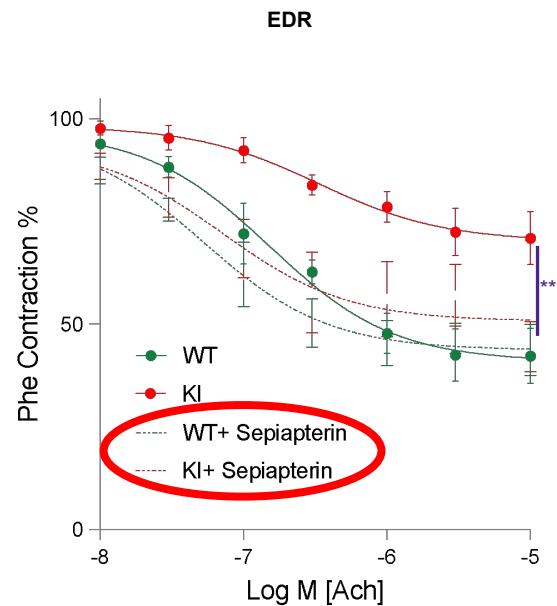
ROCG mechanism validation: NOX5 knock-in induces hypertension in mice

In ageing, endothelial NOX5 is activated and interferes with normal NO-cGMP signaling, which results in impaired vascular smooth muscle relaxations and raised blood pressure.

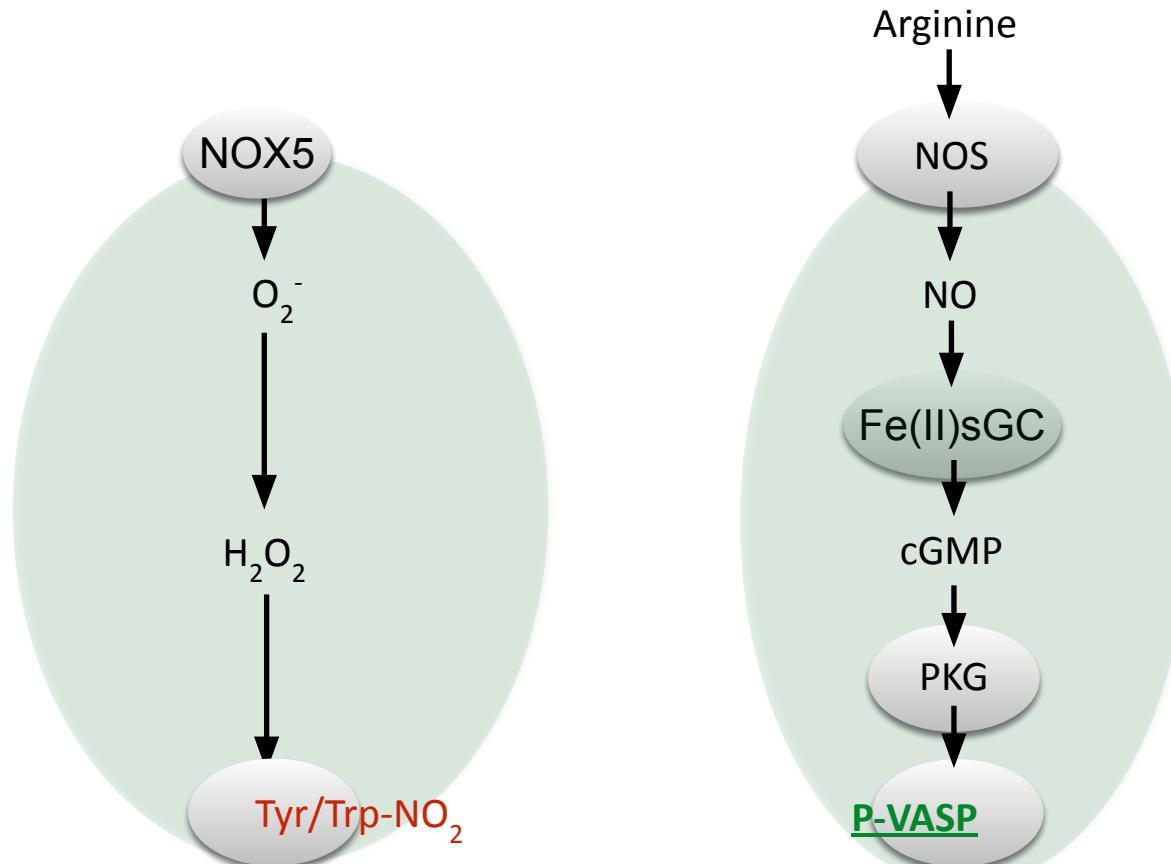


ROCG mechanism validation: NOX5 knock-in induces hypertension in mice

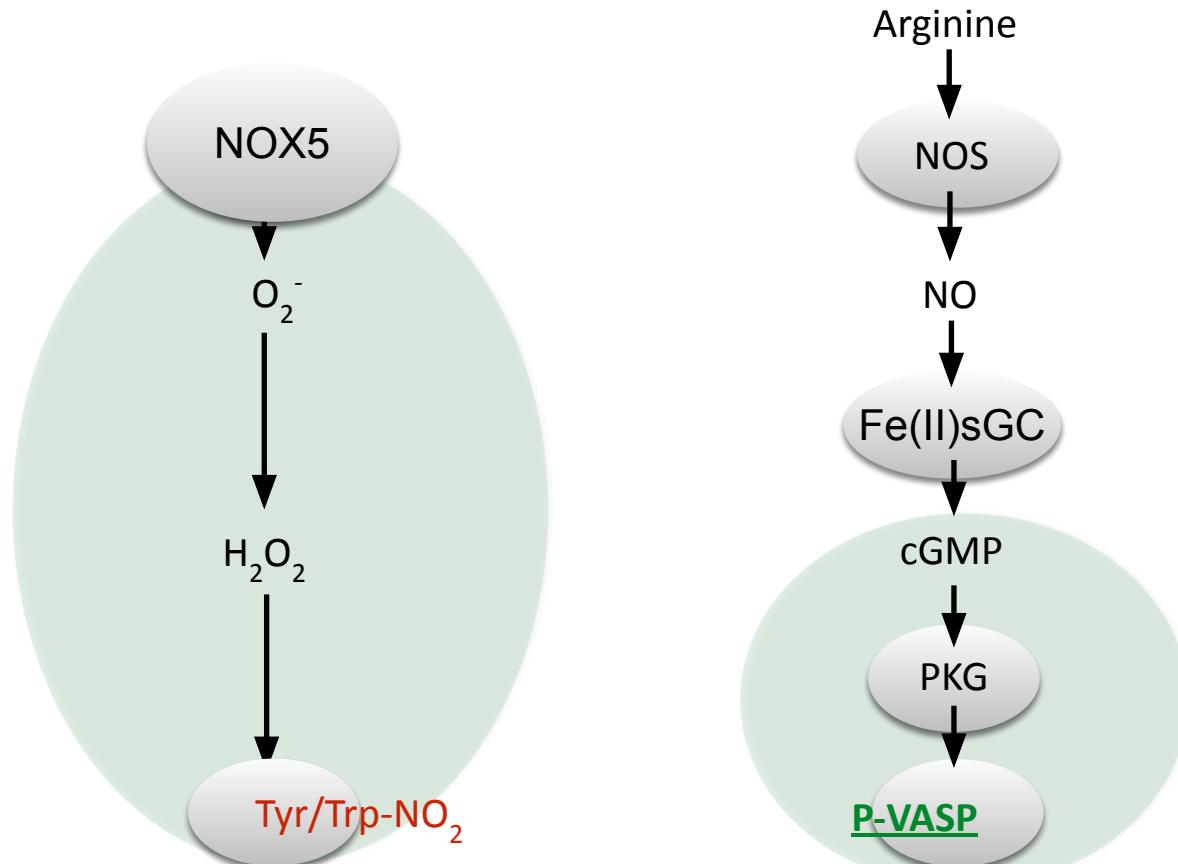
An intervention may include the (H_4 Bpi precursor and) NOS recoupling agent **Sepiapterin** or (once clinically available) a NOX5 inhibitor.



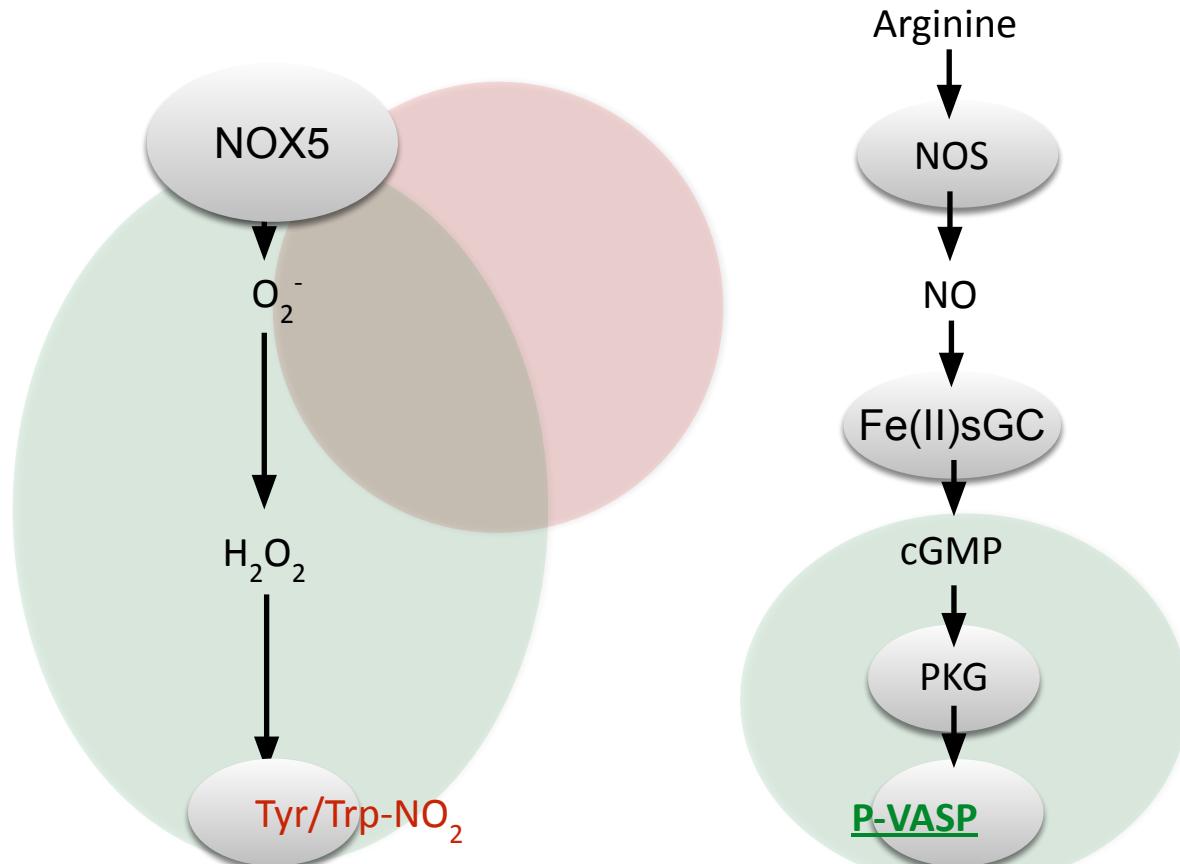
Synergistic pharmacology: REPO-HYPER IIa, REPO-HFpEF II



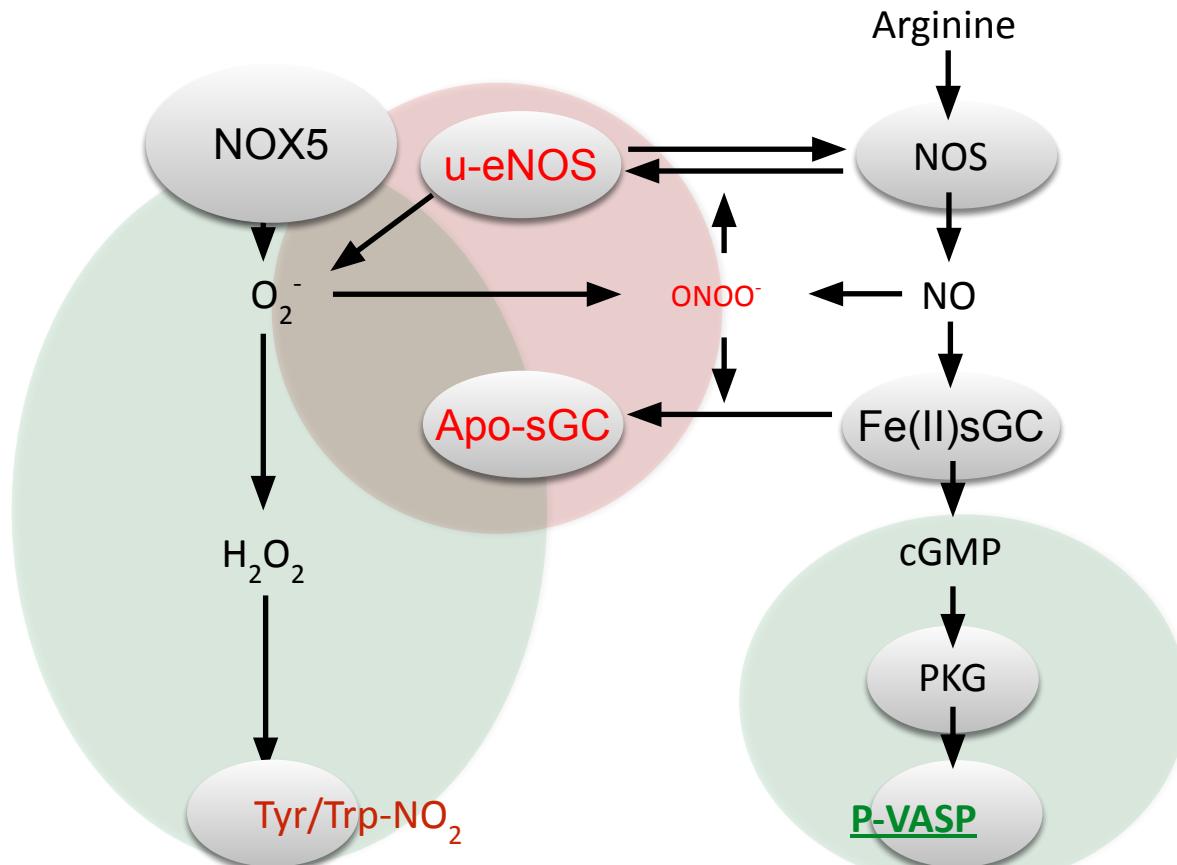
Synergistic pharmacology: REPO-HYPER IIa, REPO-HFpEF II



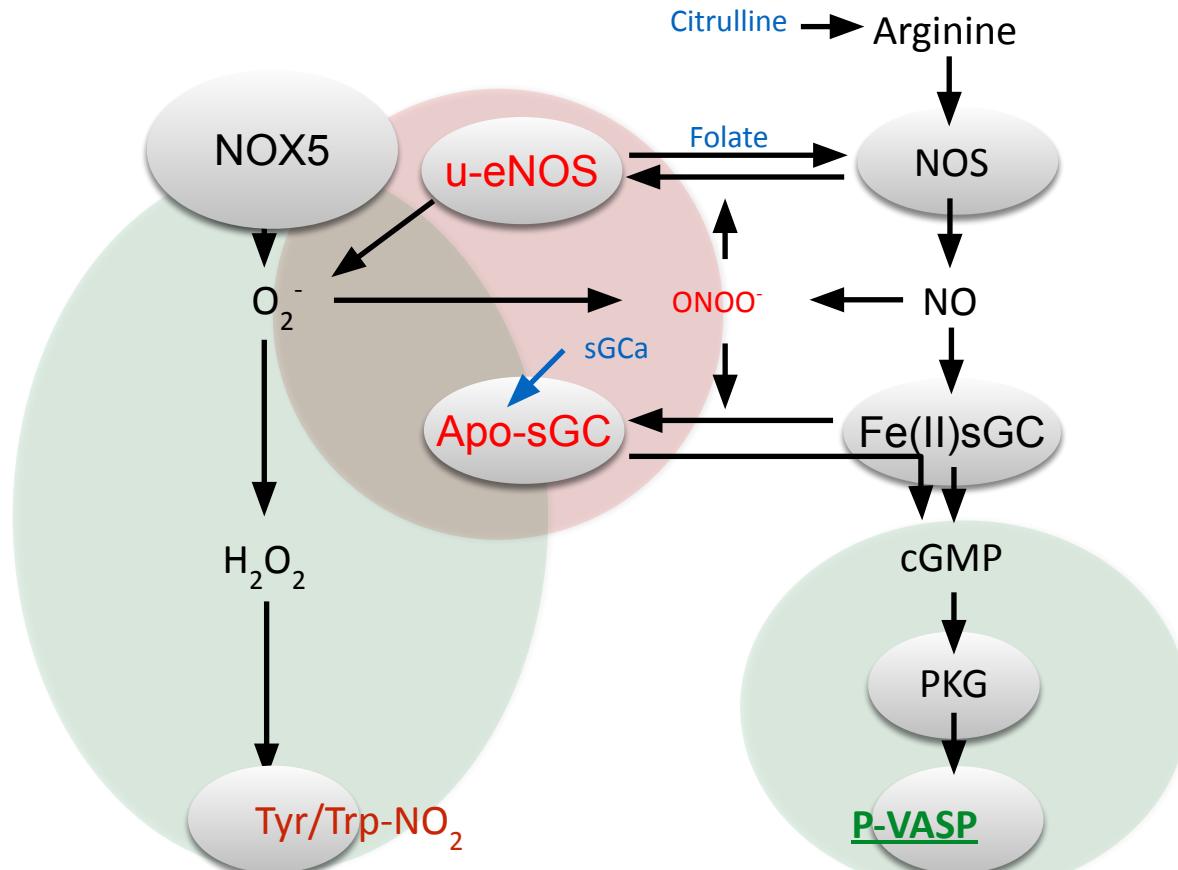
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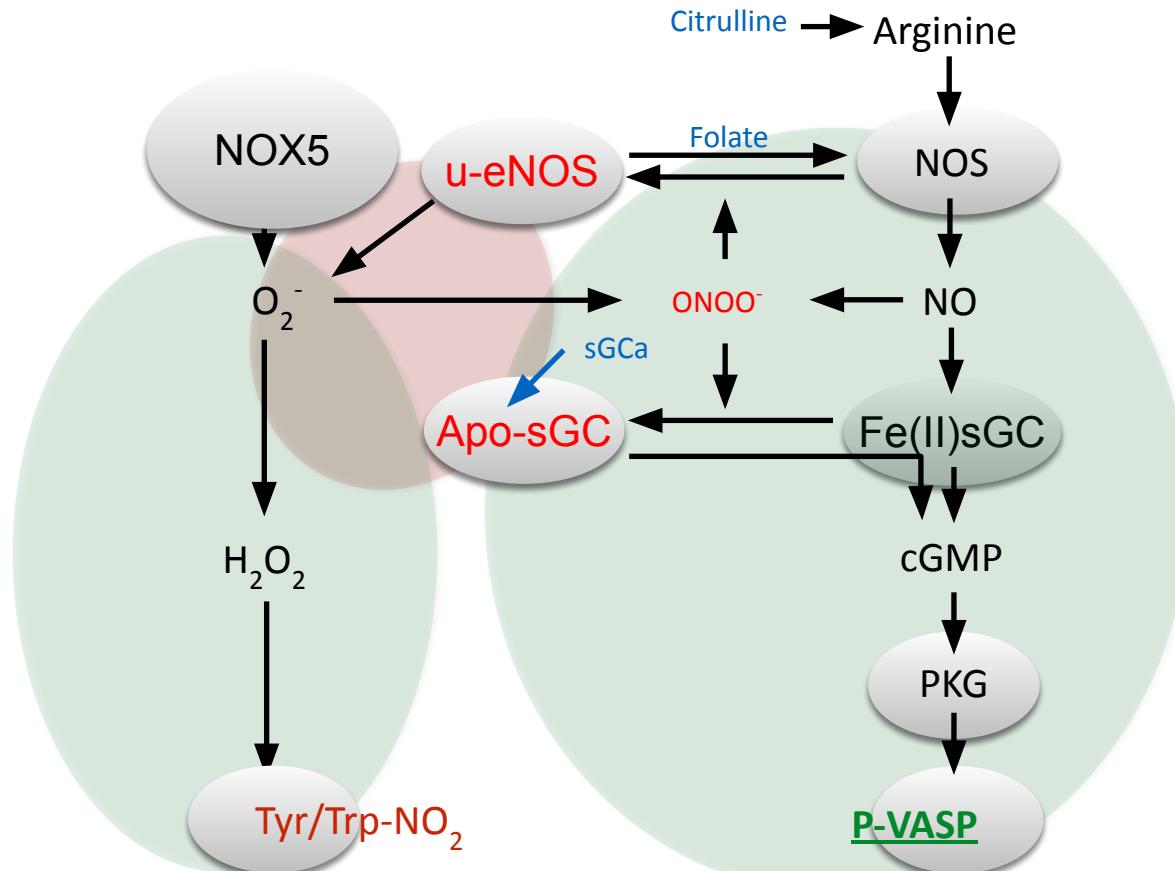
Synergistic pharmacology: REPO-HYPER IIa, REPO-HFpEF II



Synergistic pharmacology: REPO-HYPER IIa, REPO-HFpEF II

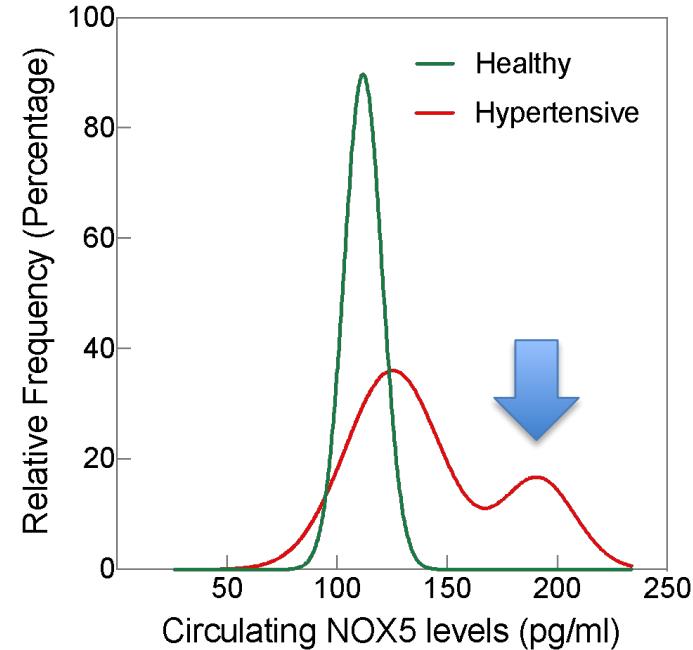
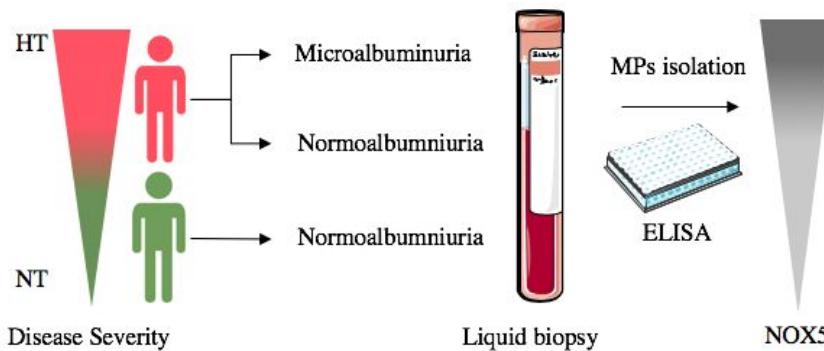


Synergistic pharmacology: REPO-HYPER IIa, REPO-HFpEF II

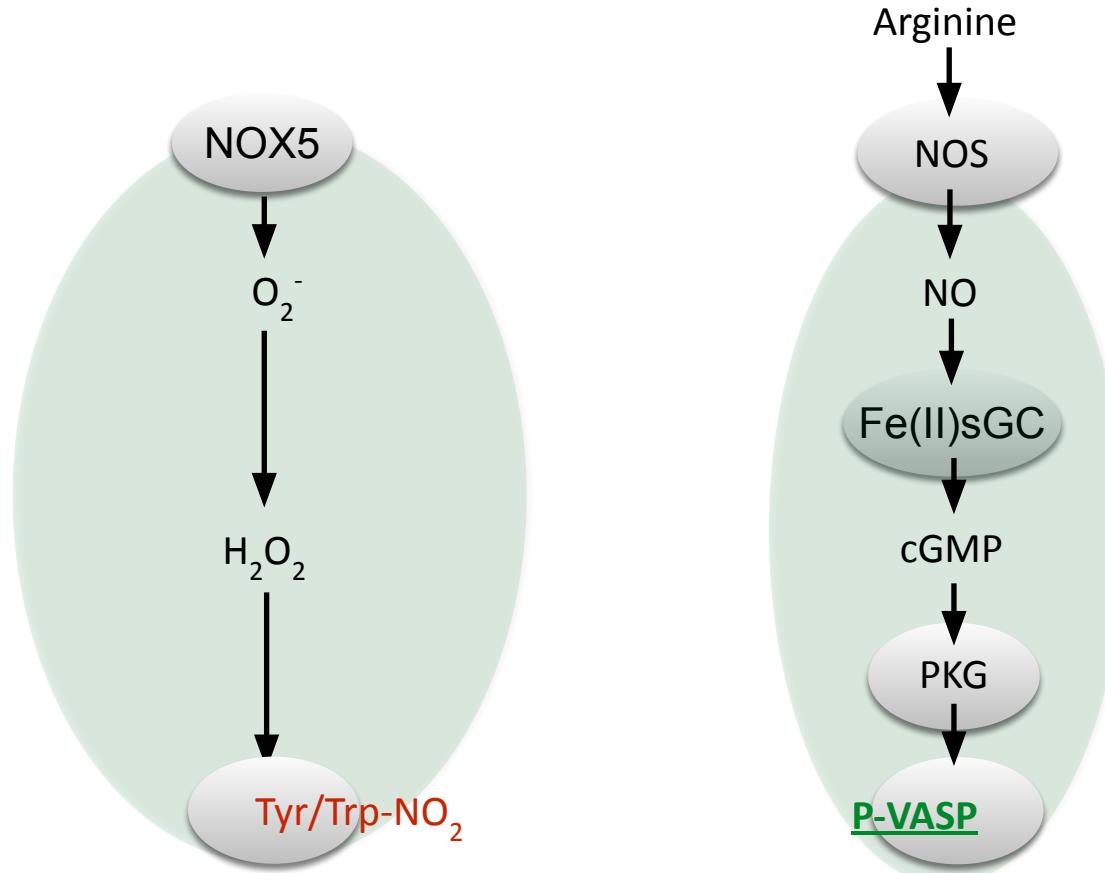


ROCG subtype detection: REPO-HYPER IIa, REPO-HFpEF II

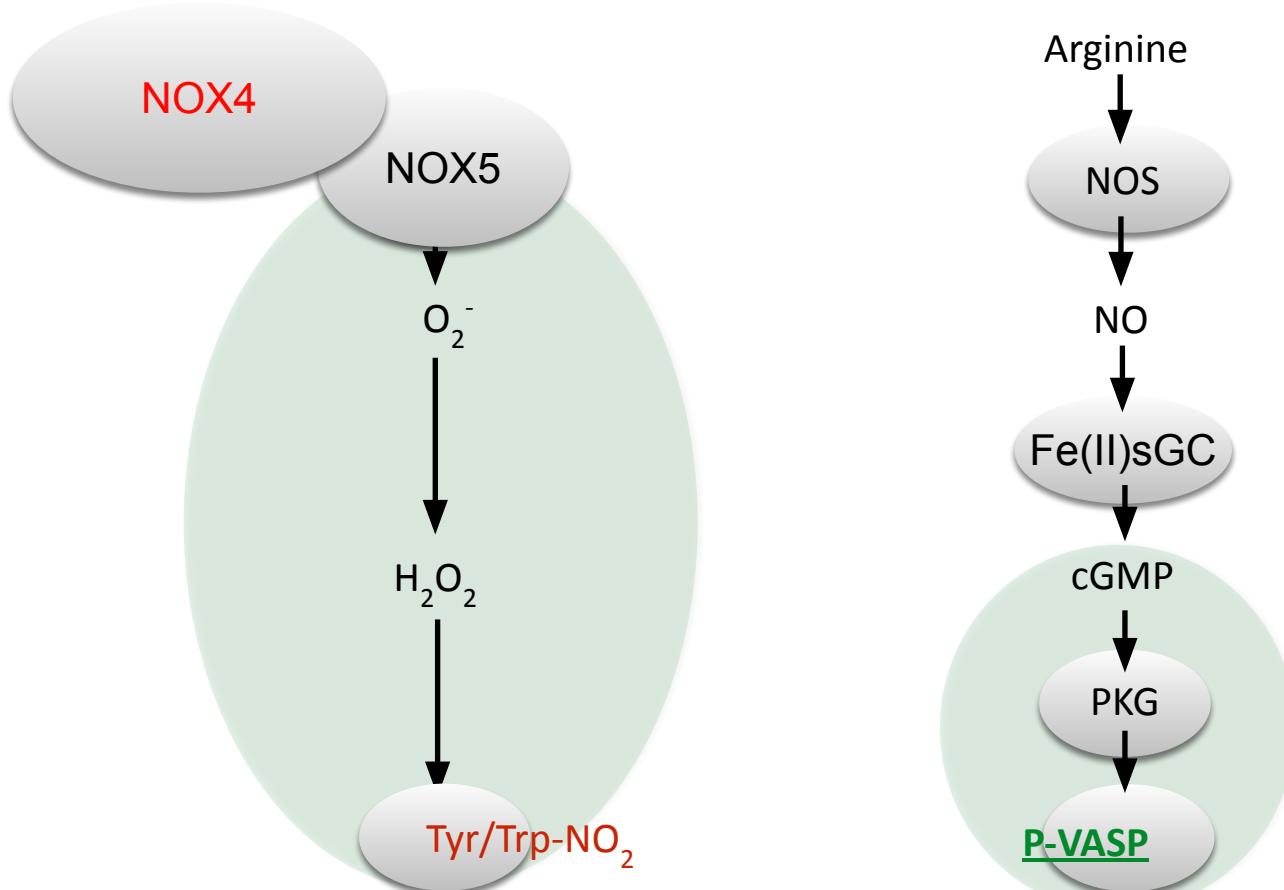
Approximately **1/4** of the hypertensive patients would fall into a **high-NOX5 mechanotype**, which causes **NO-cGMP signaling dysfunction**.



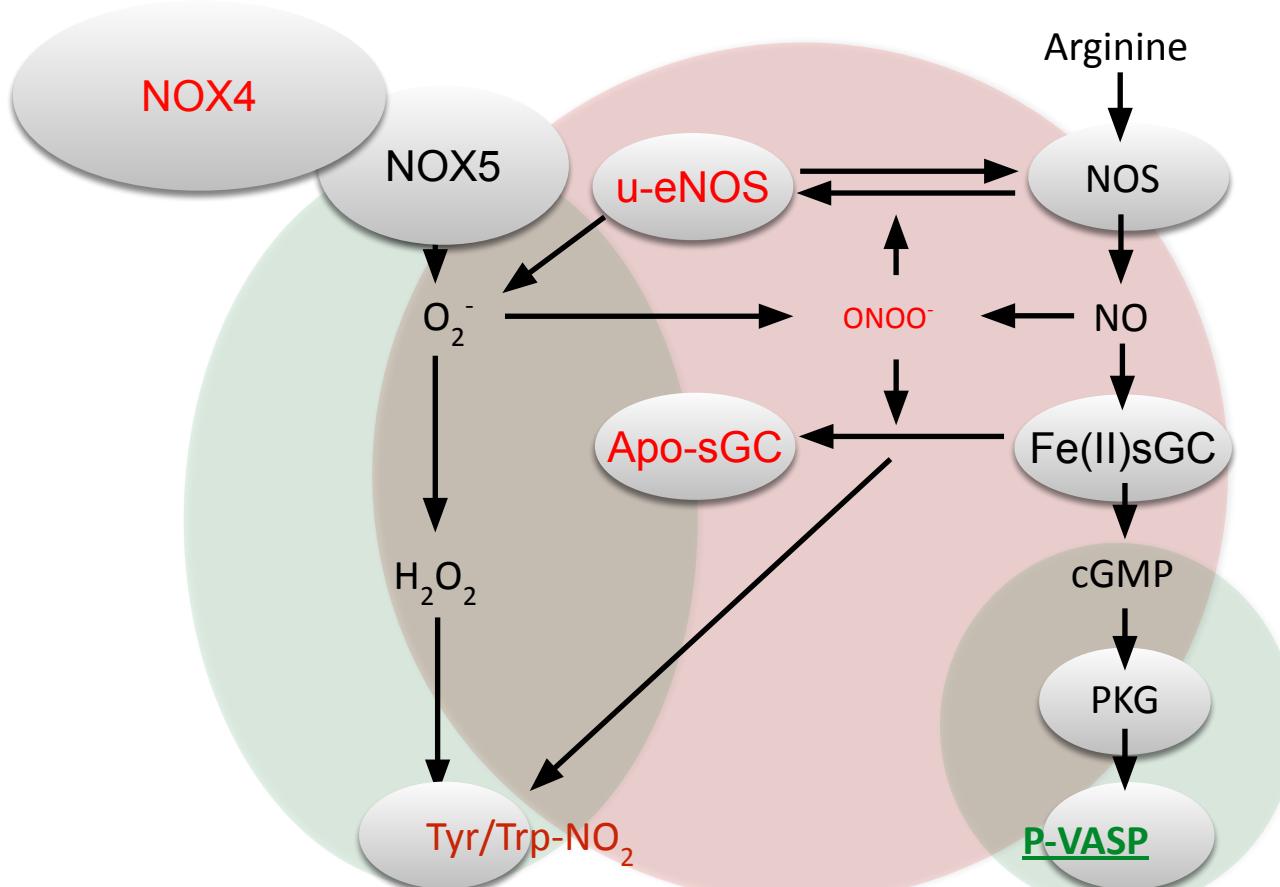
Synergistic pharmacology: REPO-STROKE IIa



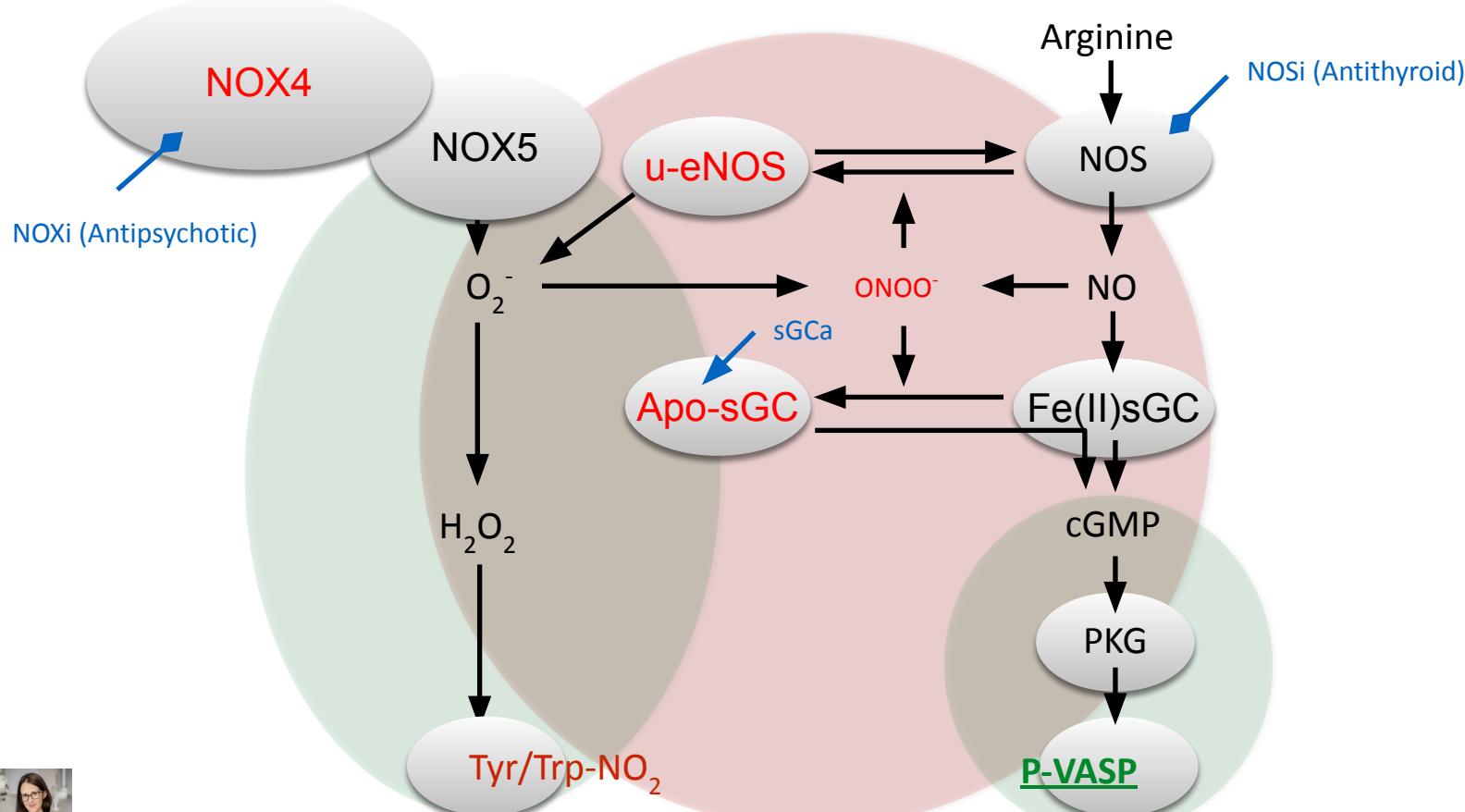
Synergistic pharmacology: REPO-STROKE IIa



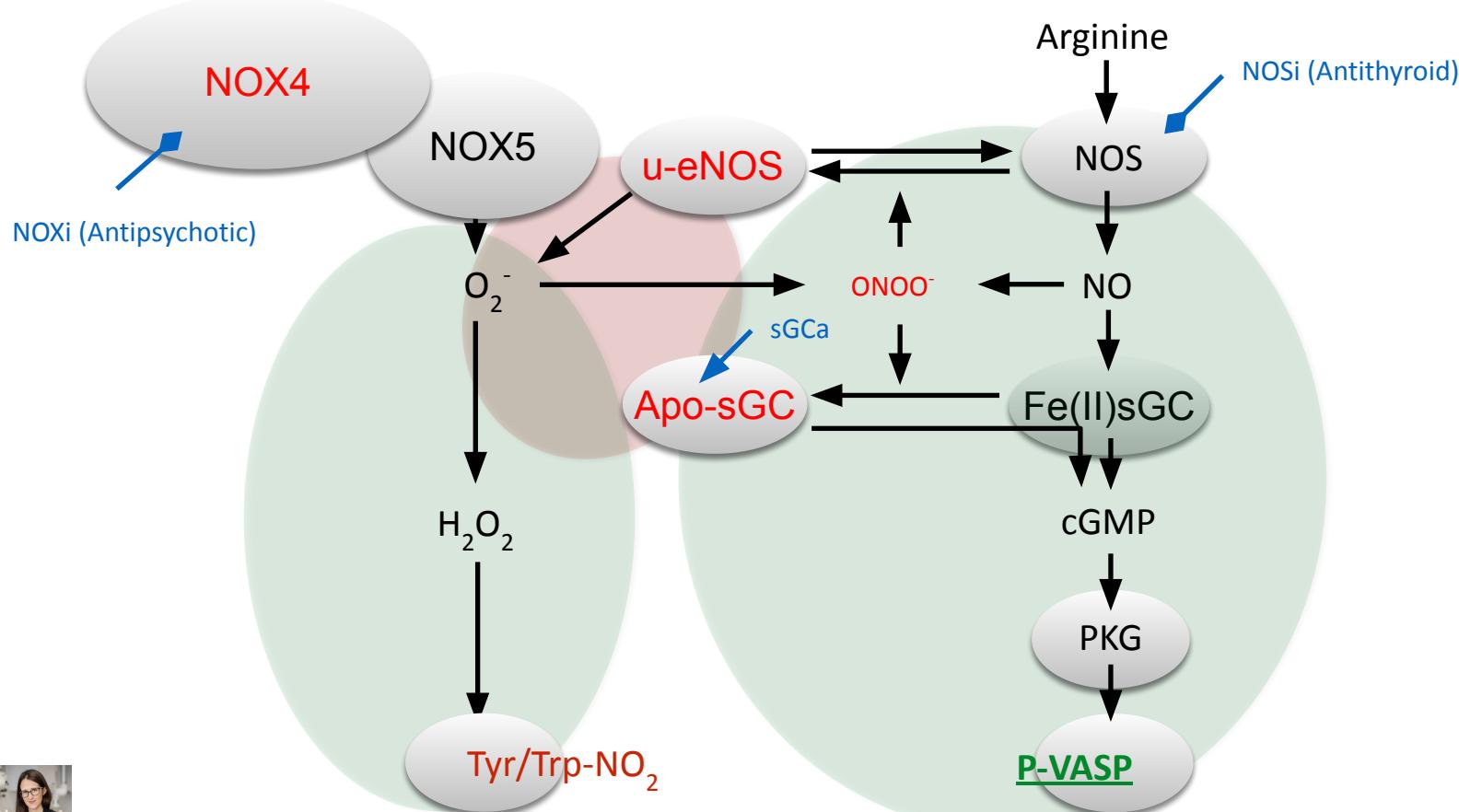
Synergistic pharmacology: REPO-STROKE IIa



Synergistic pharmacology: REPO-STROKE IIa

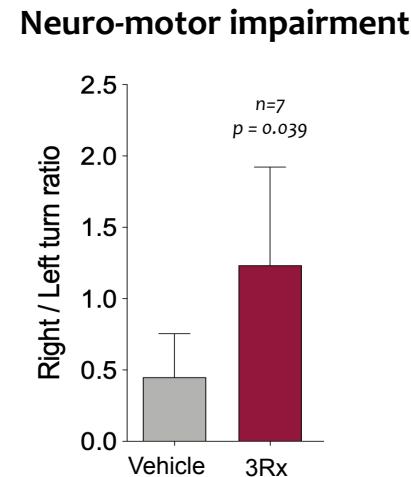
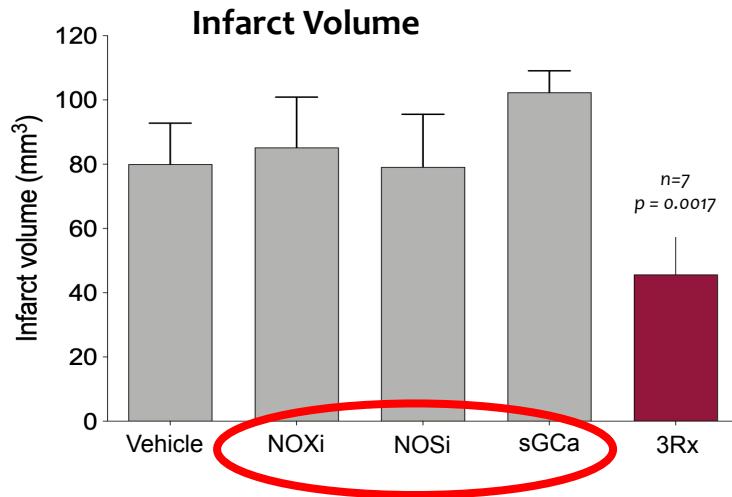


Synergistic pharmacology: REPO-STROKE IIa



Synergistic pharmacology: REPO-STROKE IIa

Low dosage of each individual drug has no effect, while synergistic triple low-dosage treatment has high efficacy.



Network pharmacology: Acknowledgements



Harald Schmidt, Maastricht University

Coordinator of REPO-TRIAL, REPO4EU



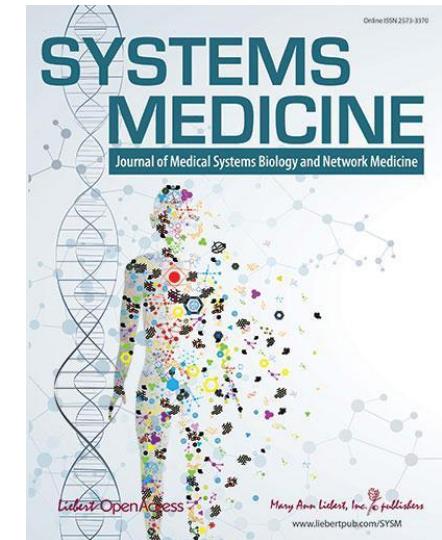
Ana Casas, University Hospital Essen

REPO-STROKE lead



Joseph M. Loscalzo, Harvard

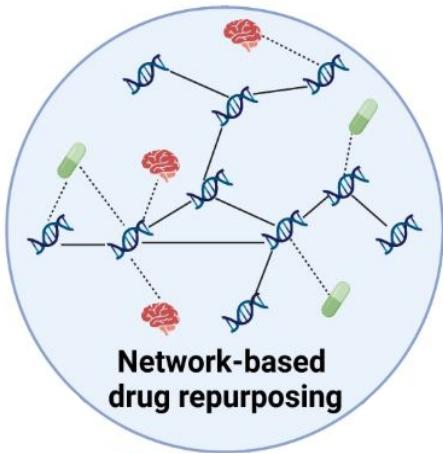
Chair of Intl. Network Medicine Alliance



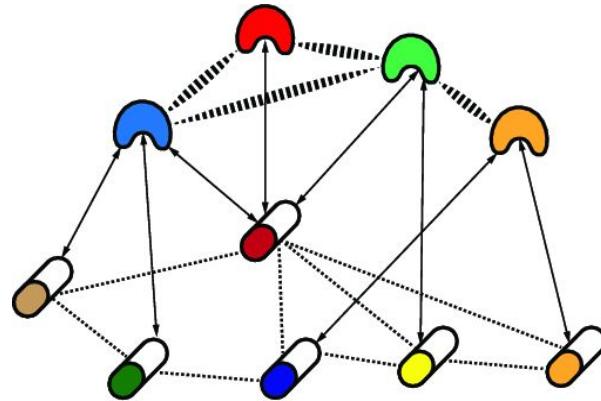
Network Medicine in a Nutshell Foundation Model

NetMedGPT: Knowledge Graphs

Drug Repurposing



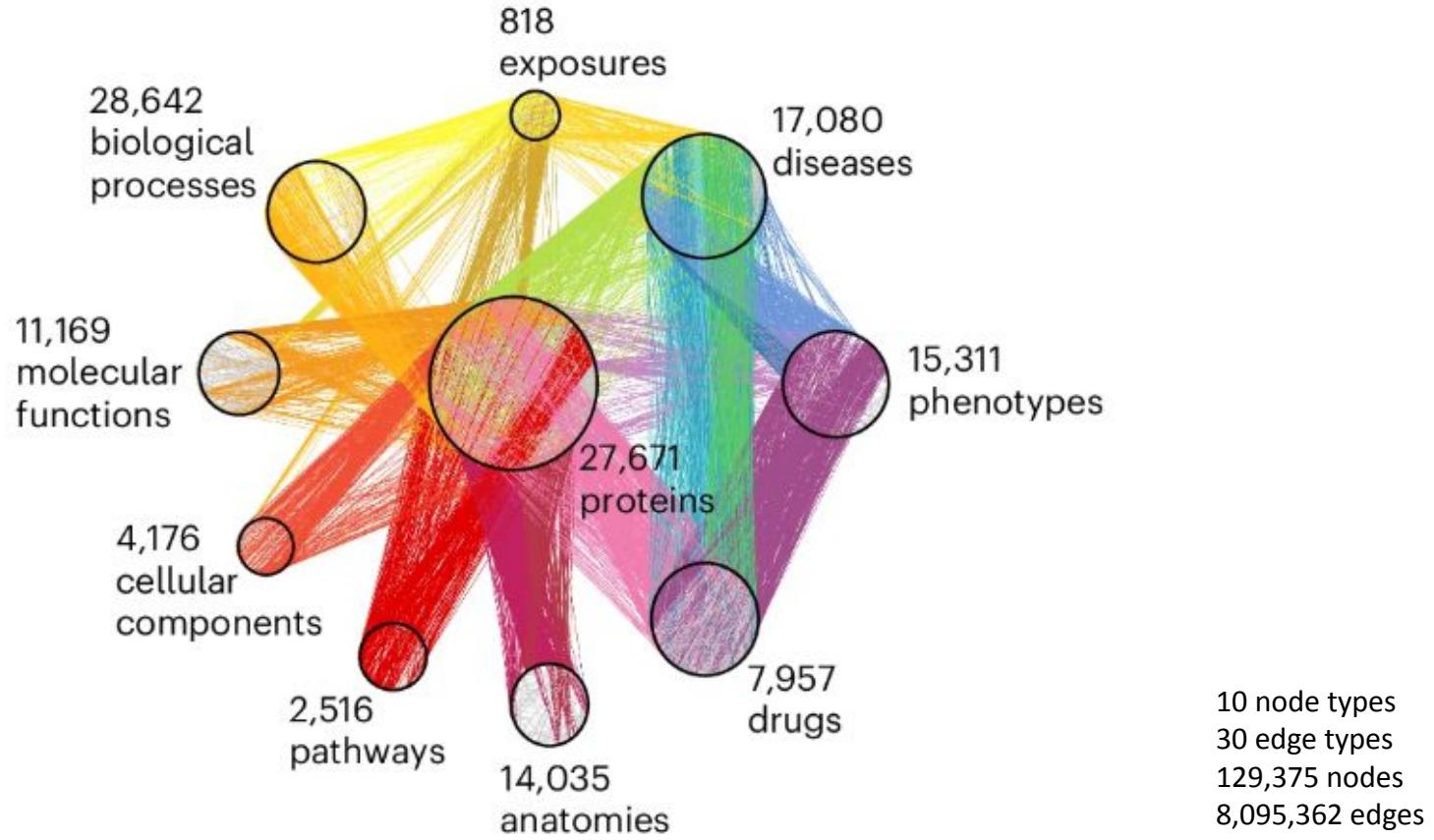
Drug target prediction



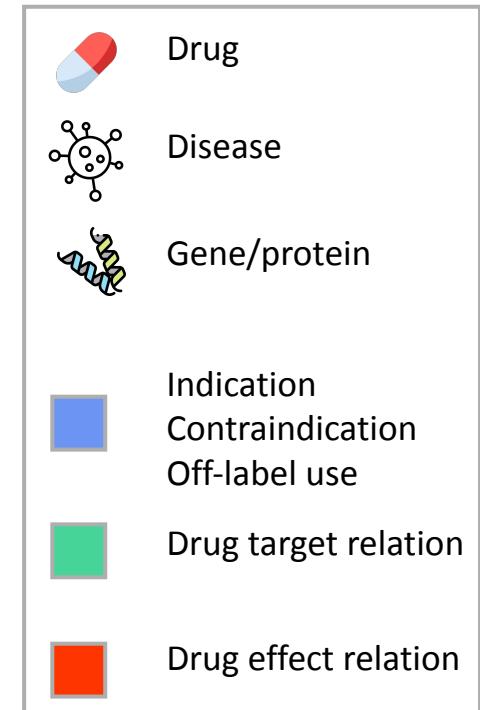
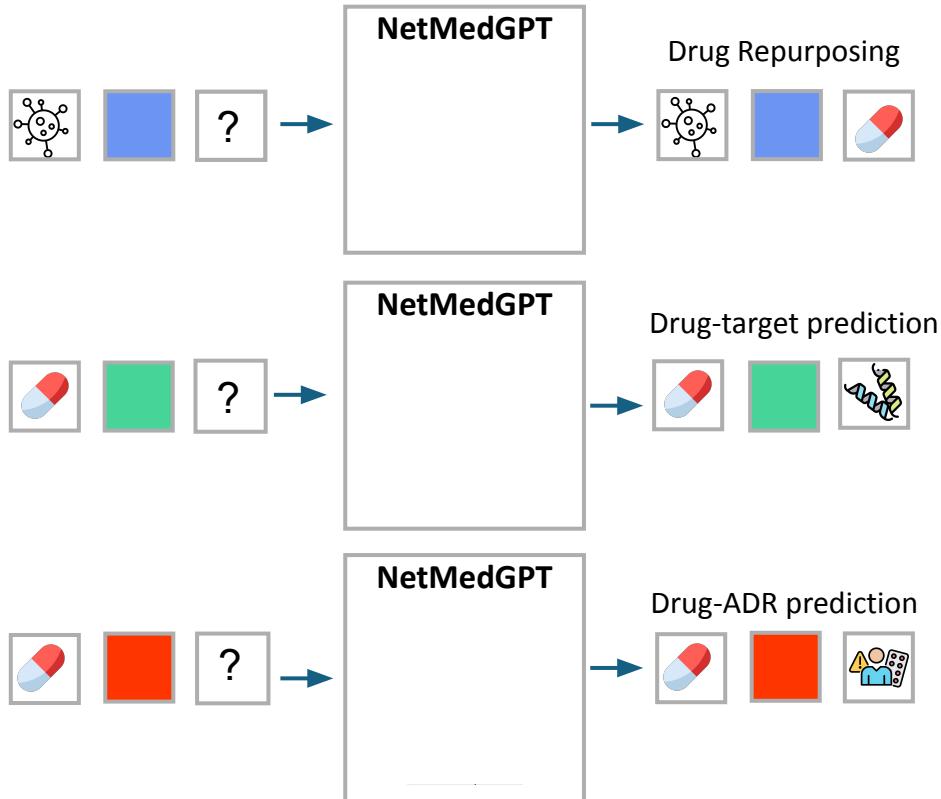
Drug ADR prediction



NetMedGPT: Knowledge Graphs

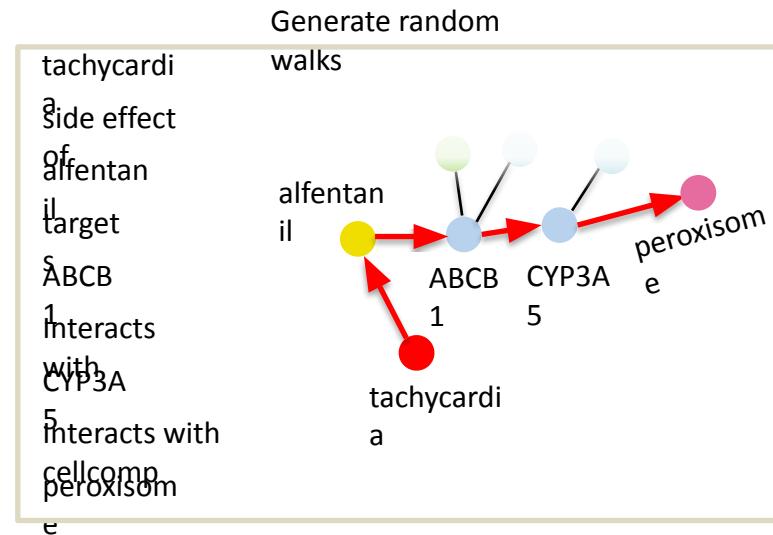
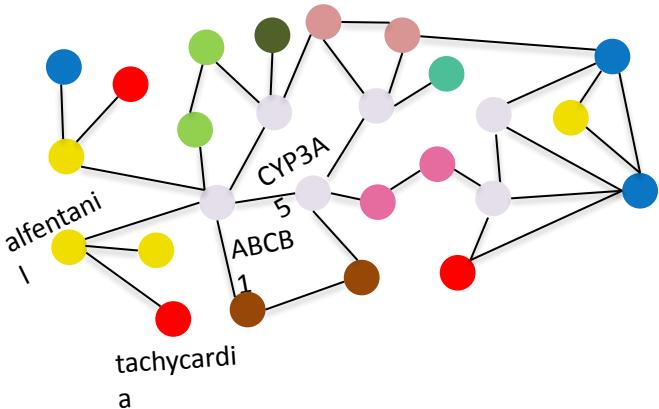


NetMedGPT: The idea



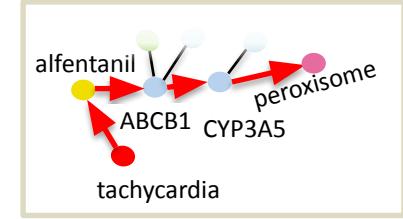
NetMedGPT: Use KGs to generate pseudo sentences

- Dru
- g
- Diseas
- e
- Phenotyp
- e
- Anatom
- y
- Protei
- n
- Pathwa
- y
- Exposur
- e
- Cellular
- component
- Molecular
- function
- Biological
- process



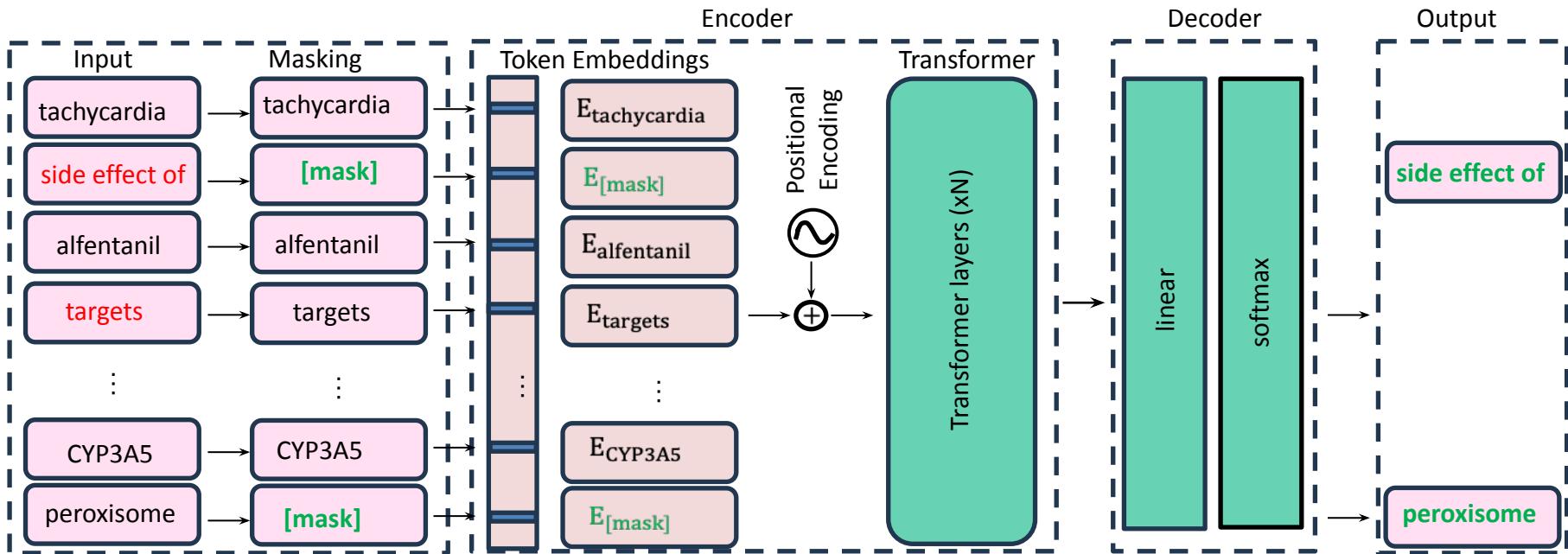
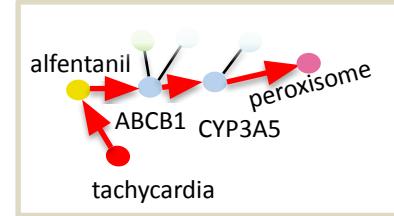
NetMedGPT: Train the Transformer using word/node/edge masking

Tachycardia / side effect of / alfentanil / targets / ABCB1 /
interacts with / CYP3A5 / interacts with cellcomp / peroxisome



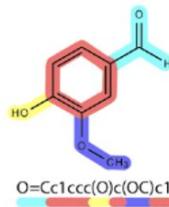
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NetMedGPT: Node embeddings

- Drug features: Description and SMILES* of the compound from DrugBank
- ADR feature: Textual names
- Disease features: Description
- Phenotype features: Description
- Protein features: Description and amino acid sequence obtained from Uniprot



Examples:
CC[C@H](C)[C@H](NC(=O)[C@H](CCC(=O)O)O)O
meddra.10019269 : heart block sinoatrial
A decreased magnitude of the sensory perception of sound.
Dermatophytosis involving the stratum corneum of the skin of the scalp and beard.
ABL1 (uniprot.Q86Y36): ENKTNFFSQFSLPFSFFCSPLSLPEALQRP

* SMILES: A textual representation of a molecule that encodes structure of a compound using short ASCII strings

NetMedGPT: Node embeddings

- **Protein features:** Description and amino acid sequence obtained from Uniprot

ABL1 (uniprot.Q86Y36):
ENKTNFFSQFSLPFSFFCSPLSLPEALQRP

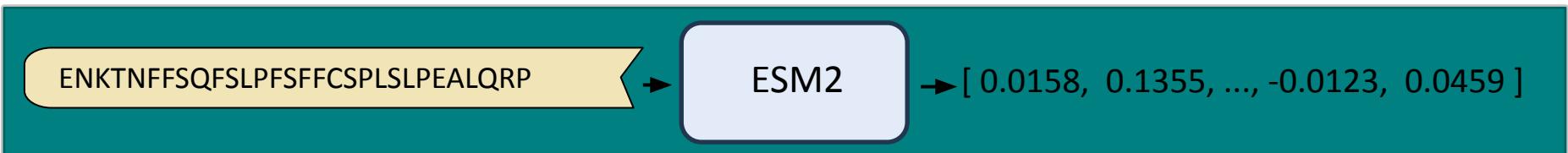
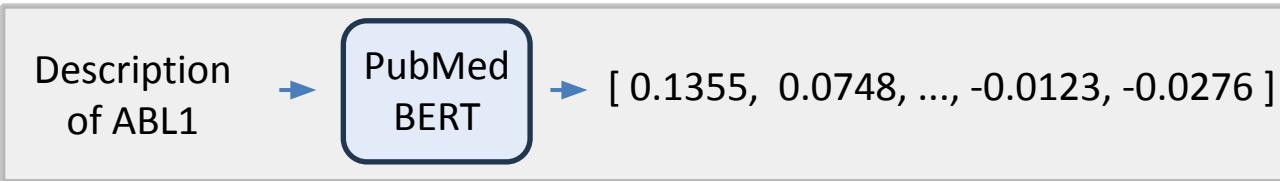
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ABL1 (uniprot.Q86Y36):
ENKTNFFSQFSLPFSFFCSPLSLPEALQRP

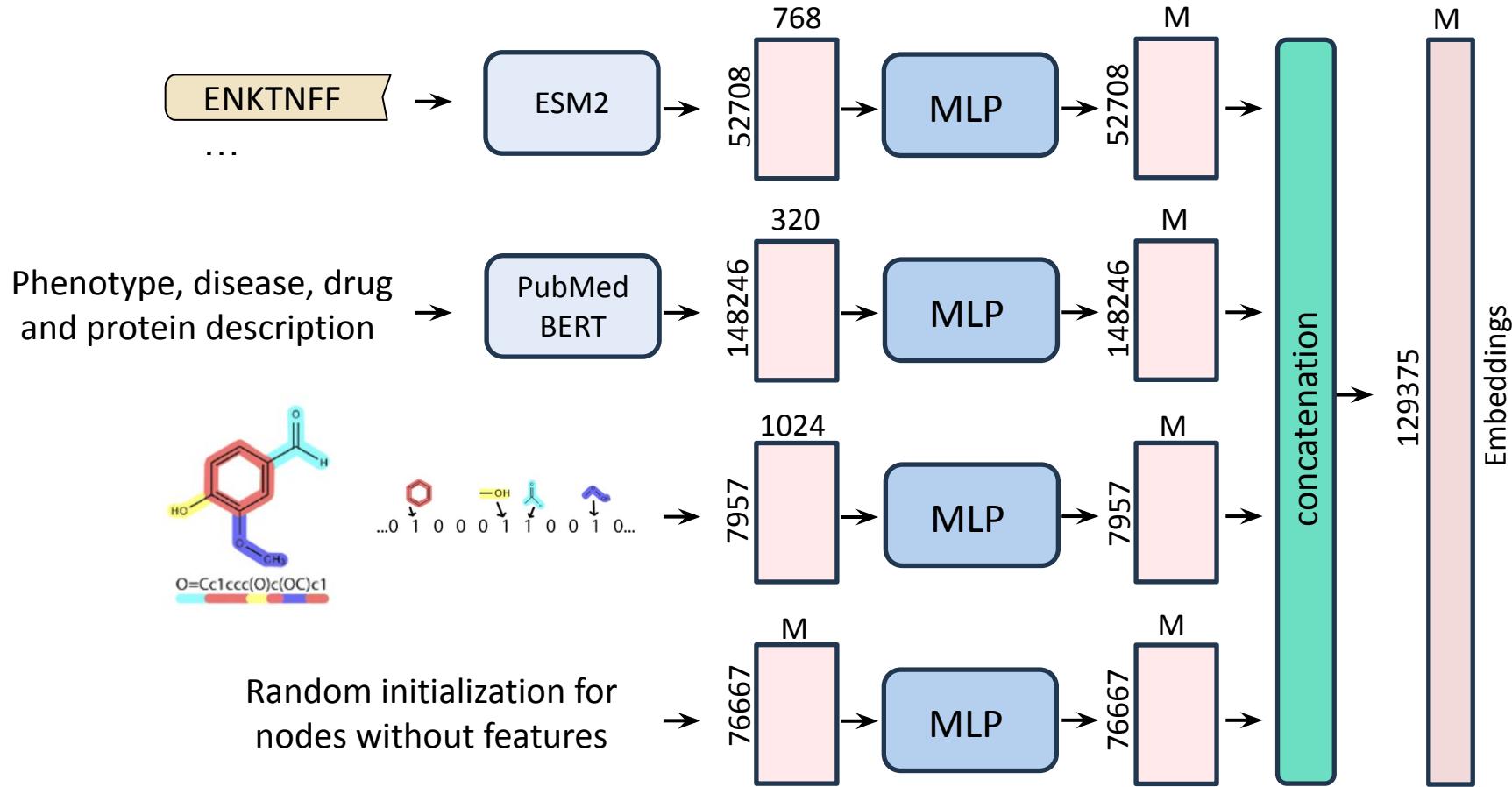
NetMedGPT: Node embeddings



- Protein features: Description and amino acid sequence obtained from Uniprot

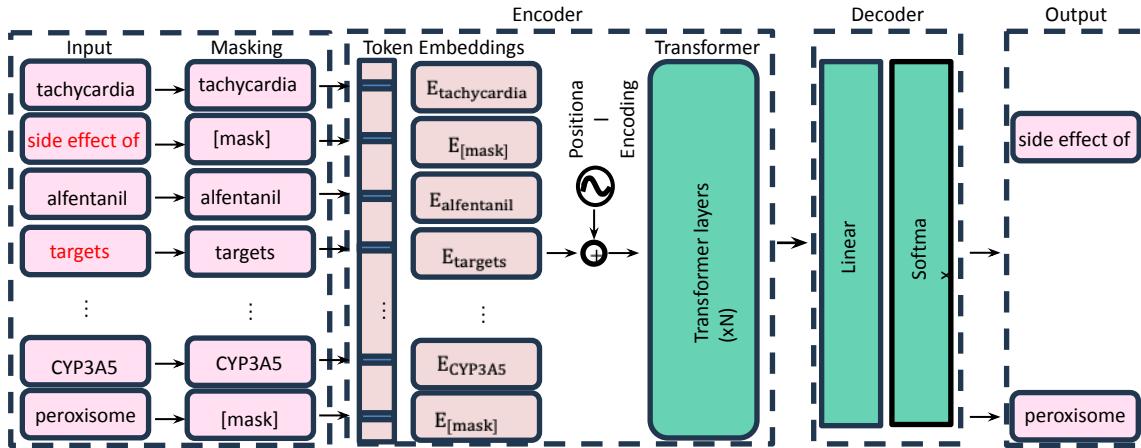
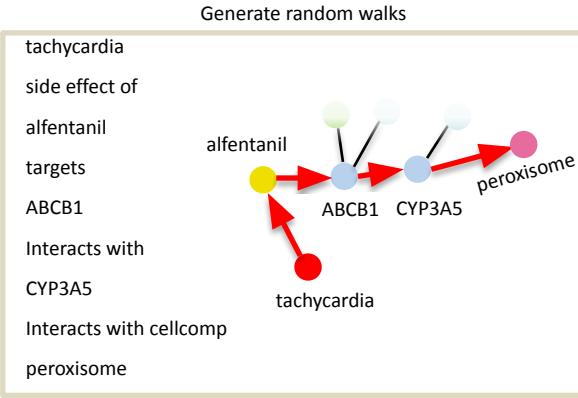
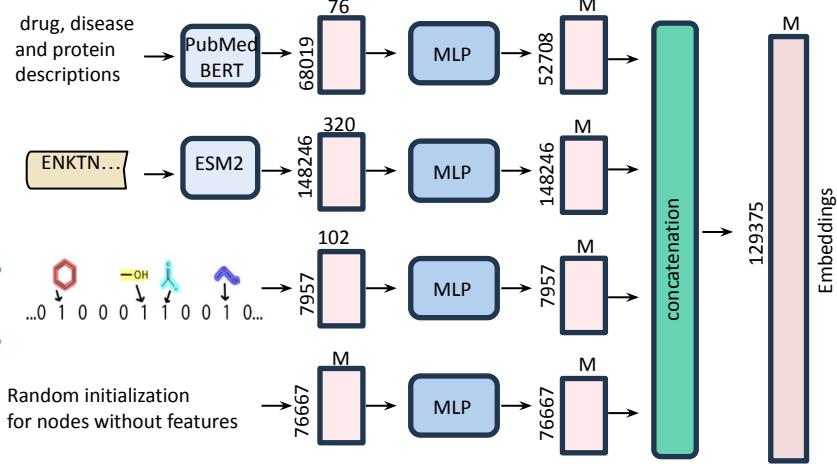
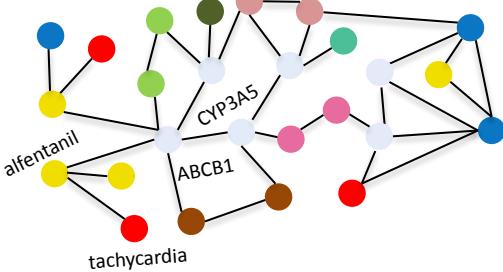
ABL1 (uniprot.Q86Y36):
ENKTNFFSQFSLPFSFFCSPLSLPEALQRP

NetMedGPT: Combine the embeddings



NetMedGPT: Overall architecture

- Drug
- Disease
- Phenotype
- Anatomy
- Protein
- Pathway
- Exposure
- Cellular component
- Molecular function
- Biological process



A foundation model for clinician-centered drug repurposing

Received: 23 September 2023

Kexin Huang   ^{1,9,10}, Payal Chandak   ^{2,10}, Qianwen Wang¹, Shreyas Havaldar³, Akhil Vaid  ^{3,4}, Jure Leskovec  ⁵, Girish N. Nadkarni  ⁴, Benjamin S. Glicksberg^{3,4}, Nils Gehlenborg¹ & Marinka Zitnik   ^{1,6,7,8} 

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Check for updates

Drug repurposing—identifying new therapeutic uses for approved drugs—is often a serendipitous and opportunistic endeavour to expand the use of drugs for new diseases. The clinical utility of drug-repurposing artificial intelligence (AI) models remains limited because these models focus narrowly on diseases for which some drugs already exist. Here we introduce TxGNN, a graph foundation model for zero-shot drug repurposing,

NetMedGPT: Evaluation – Random split

Random split:
randomly splitting
links of a specific
type into train and
test sets



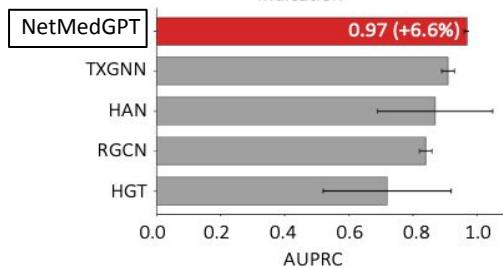
Training set



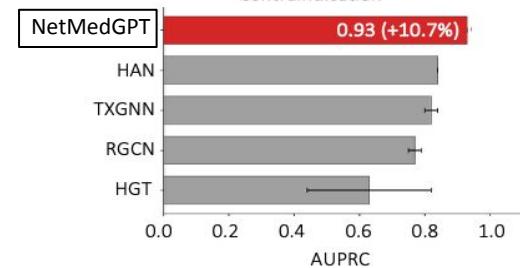
Test set



Indication



contraindication



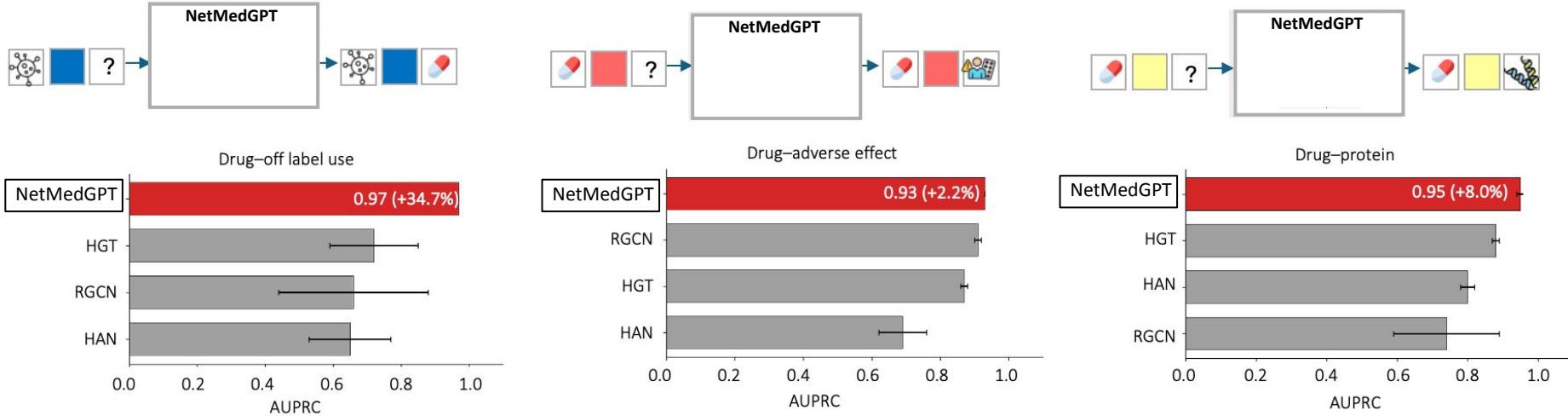
Edge types:

indication contraindication

Remove some edges of one type from
training.

Try to retrieve the removed edges.

NetMedGPT: Evaluation – Random split



Edge types:

off-label use drug–adverse effect drug–target

Remove some edges of one type from training.

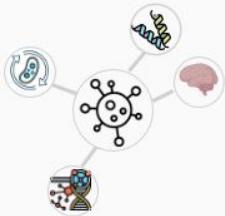
Try to retrieve the removed edges.

NetMedGPT: Evaluation – Zero shot

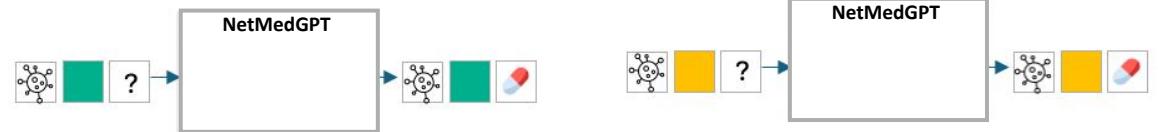
Zero-shot split:
All drug-disease edges associated with a subset of diseases were held out during training



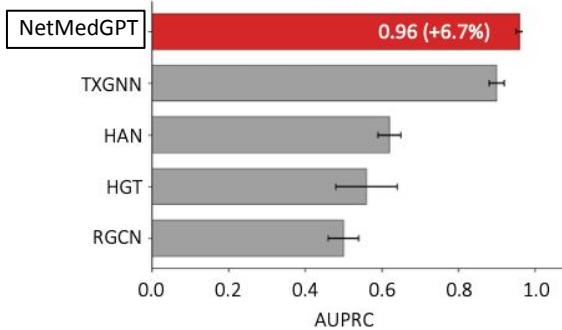
Training set



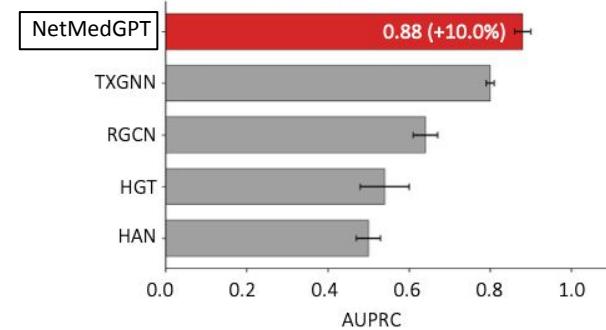
Test set



indication



contraindication



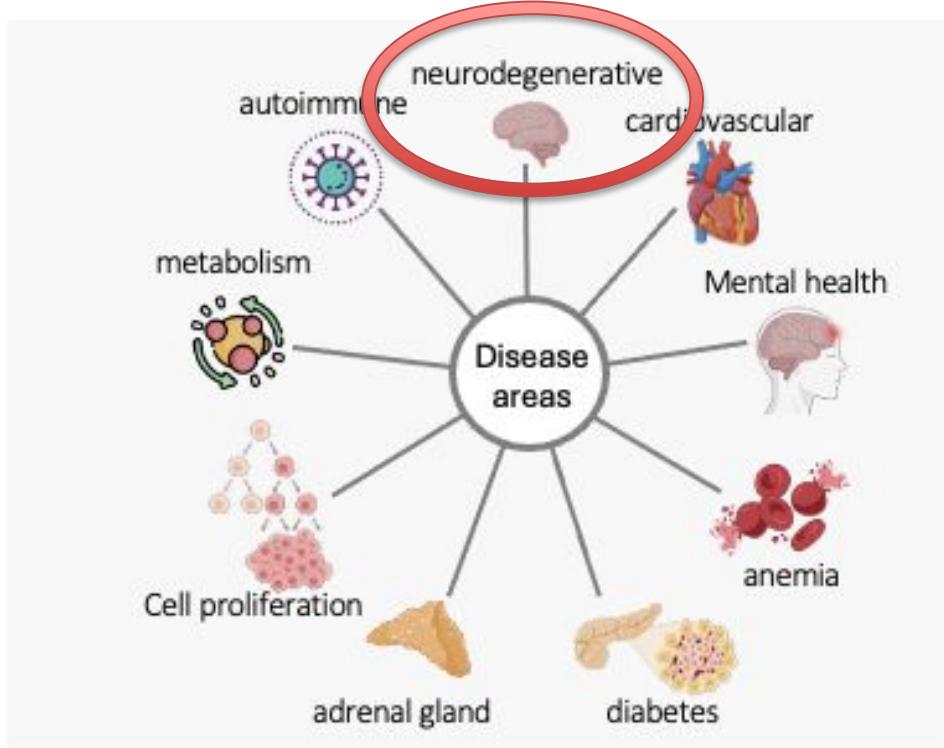
Edge types:

indication contraindication

Pick a set of diseases, and remove all edges of a type from training.

☐ Try to retrieve the removed edges.

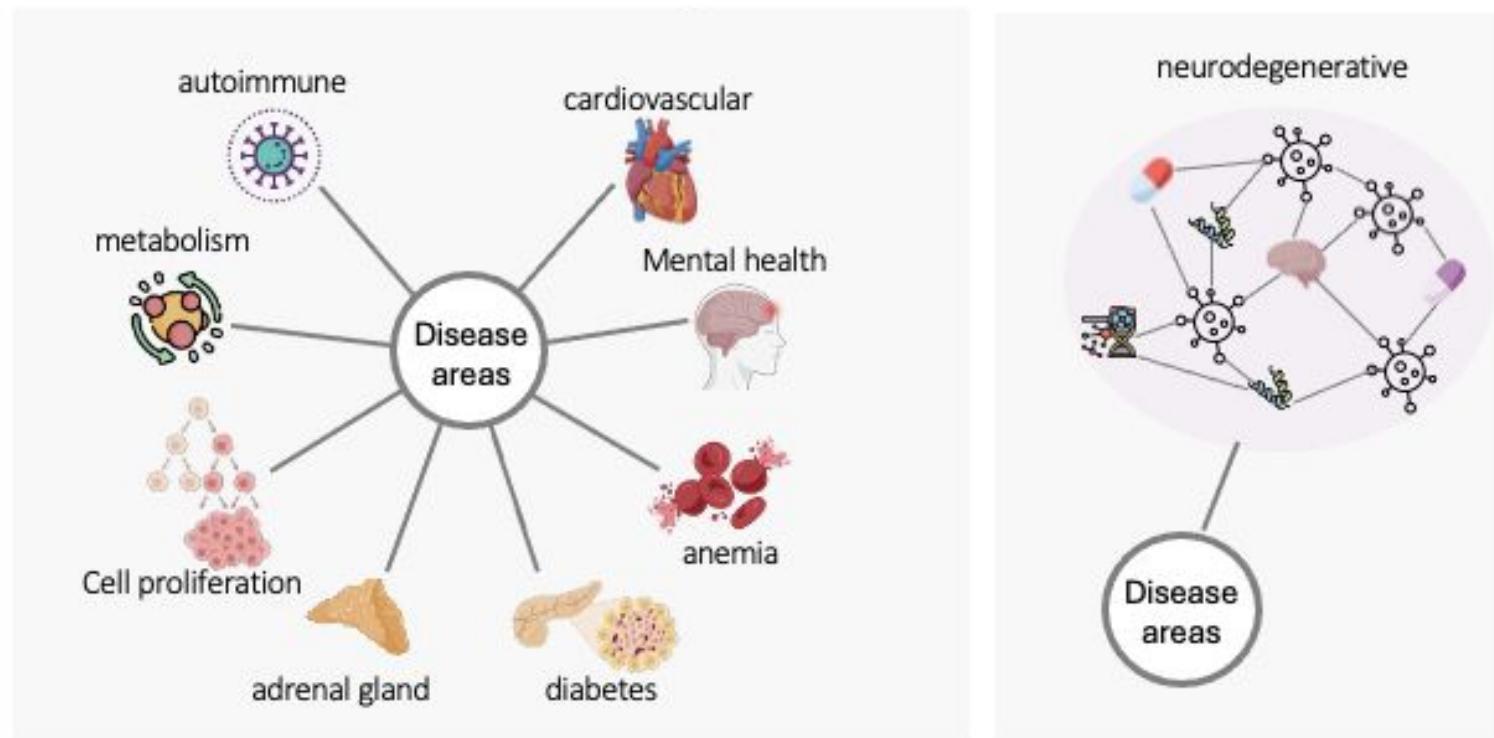
NetMedGPT: Evaluation – Disease-area split



Pick a **disease area**, and remove all their diseases' edges of a type from training.

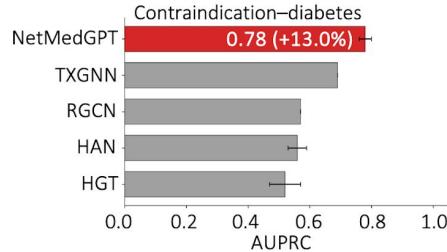
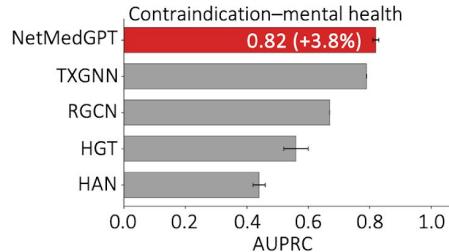
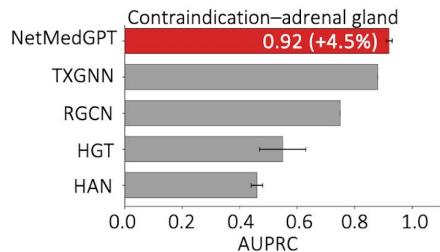
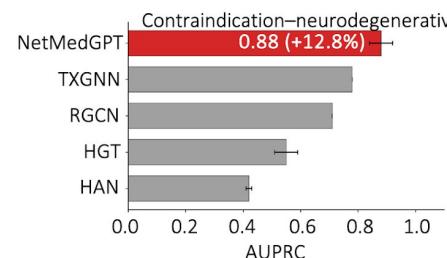
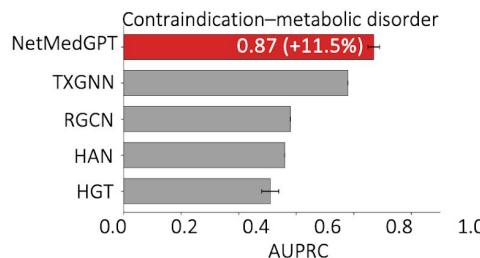
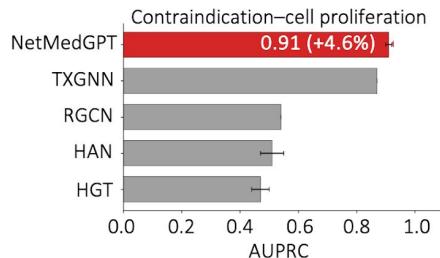
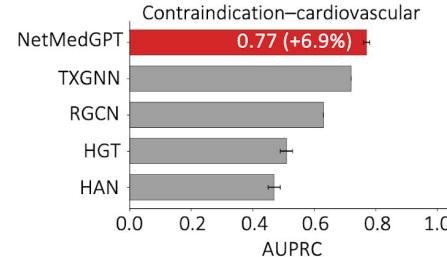
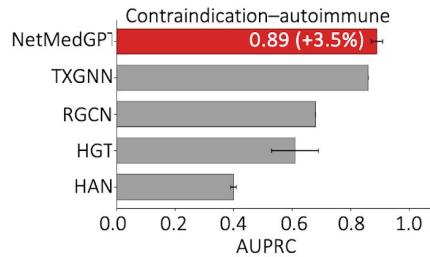
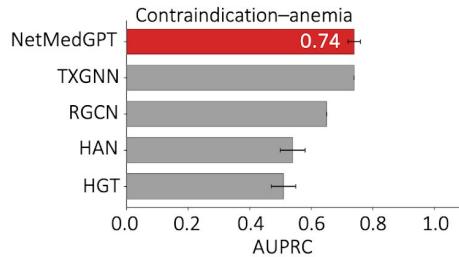
Try to retrieve the removed edges.

NetMedGPT: Evaluation – Disease-area split



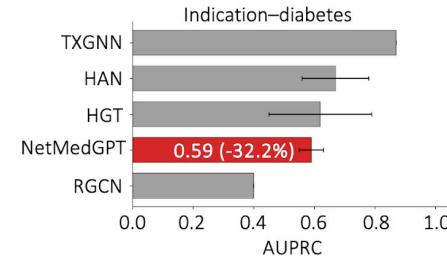
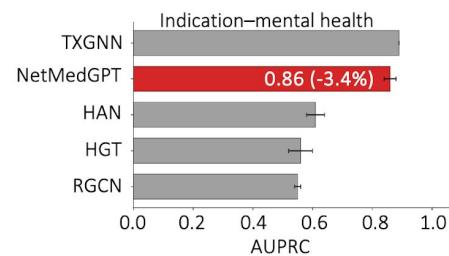
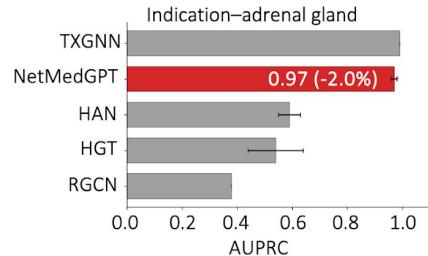
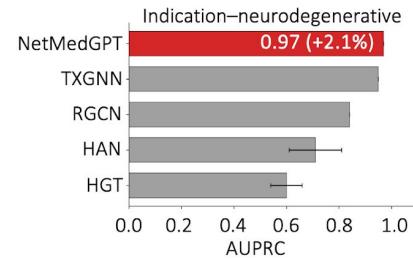
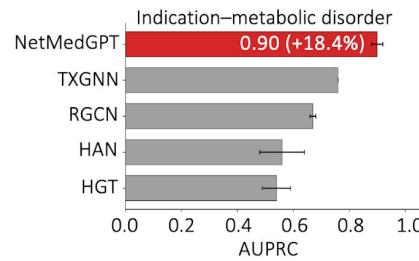
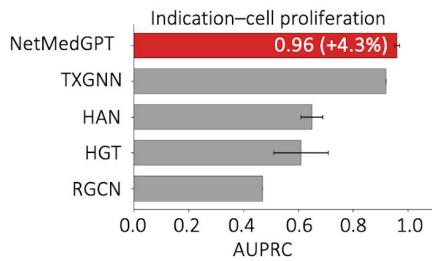
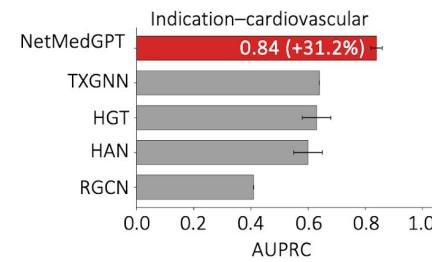
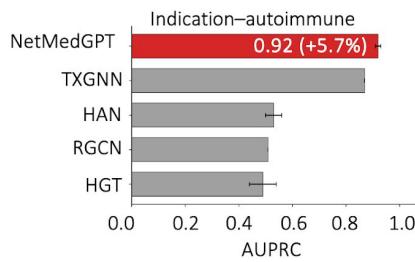
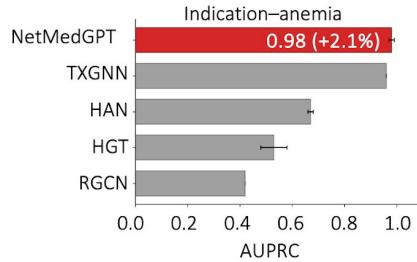
NetMedGPT: Evaluation – Disease-area split

Contraindications



NetMedGPT: Evaluation – Disease-area split

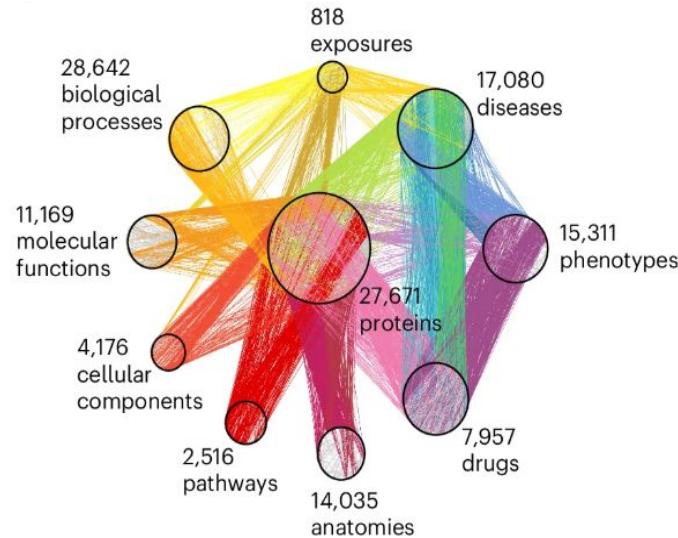
Indications



Having fun with Foundation Models...

NetMedGPT: Clinical trial result prediction?

1. Take the 537,059 studies in [clinicaltrials.gov](#)
2. Map IDs drugs and diseases to mondo-IDs and drugbank-IDs
3. Match drug and disease IDs of trials to knowledge graph
4. Remove overlapping links from clinical trials / KG from training



NetMedGPT: Clinical trial result prediction?

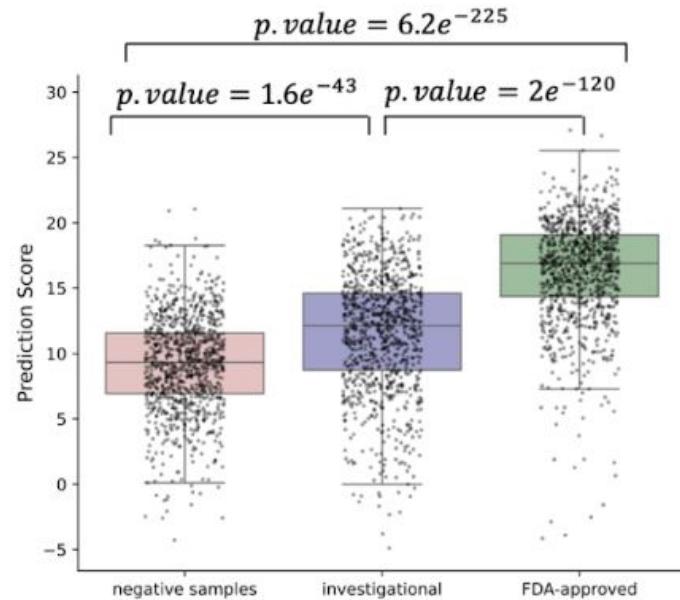
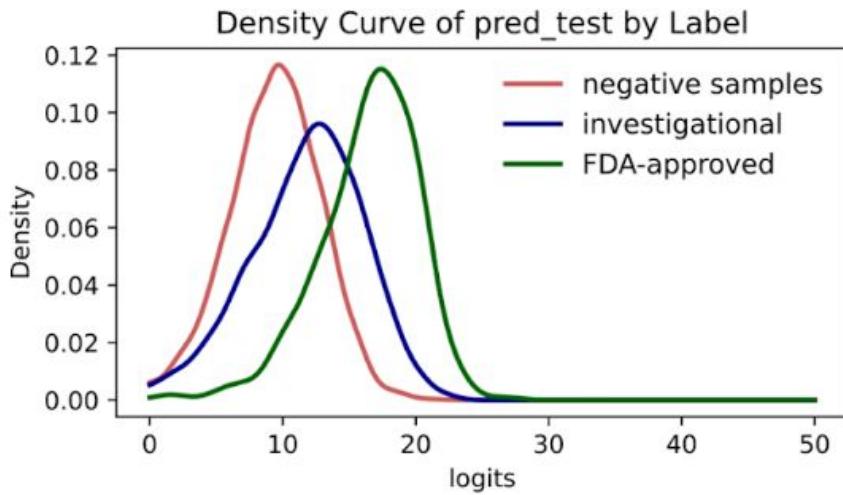
1. Take the 537,059 studies in **clinicaltrials.gov**
2. Map IDs drugs and diseases to mondo-IDs and drugbank-IDs
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4. Remove overlapping links from clinical trials / KG from training

Try to retrieve the removed links.



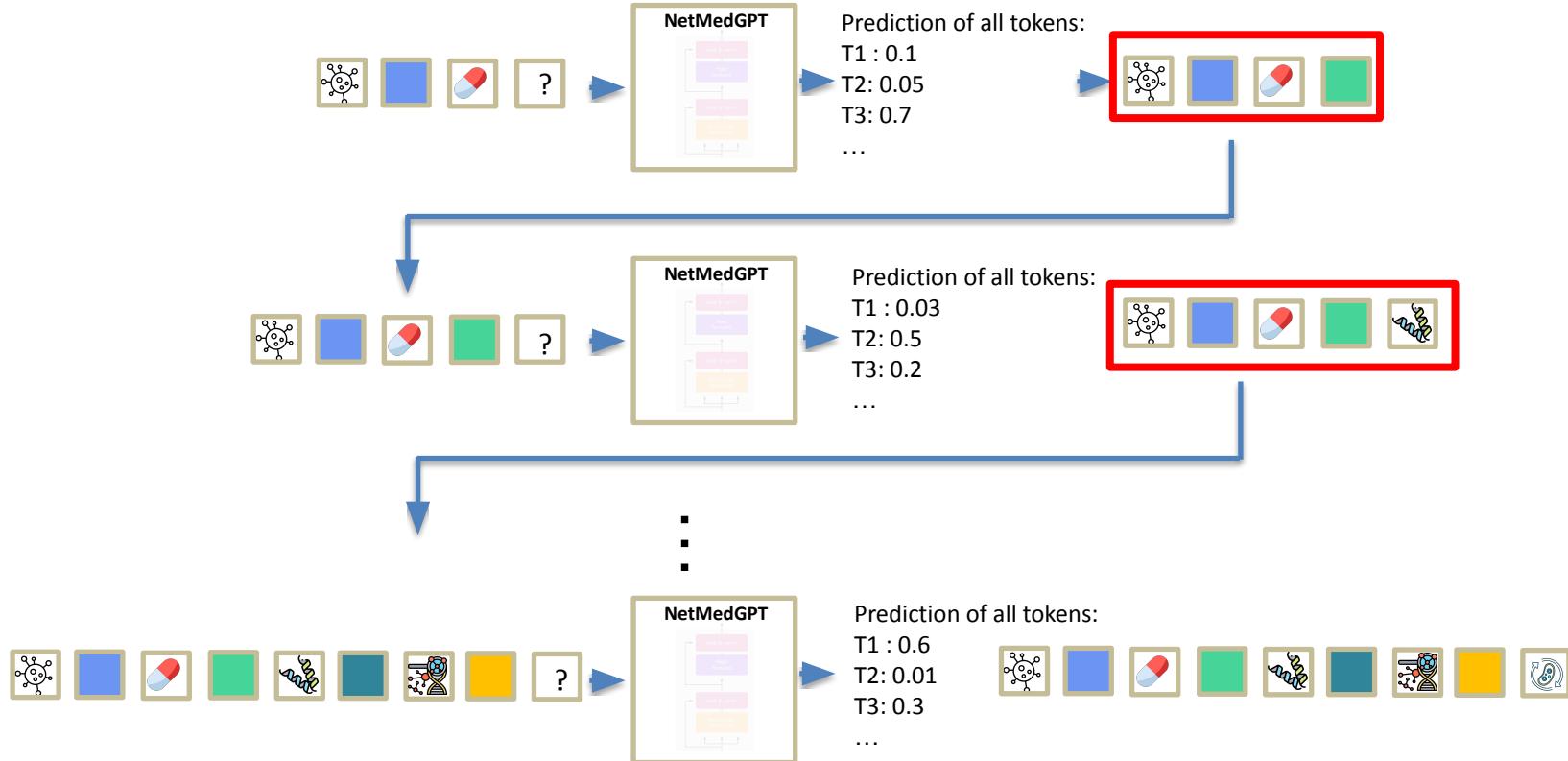
NetMedGPT: Clinical trial result prediction!

Distribution of the predicted link scores



NetMedGPT: Generative AI?

If we can generate pseudo-sentences... we can generate networks.



NetMedGPT: ChatNetMedGPT?



Comparing Mechanisms in DIC disease: Heparin vs. Adomiparin

Question:

In the context of disseminated intravascular coagulation (DIC), considering the mechanisms of action of adomiparin and heparin, which one is more mechanistically linked to PROC?

NetMedGPT: ChatNetMedGPT?



Comparing Mechanisms in DIC disease: Heparin vs. Adomiparin

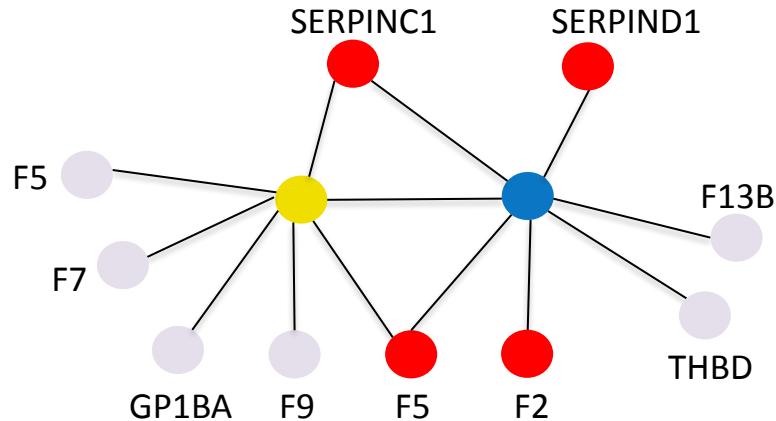
Question:

In the context of **disseminated intravascular coagulation** (DIC), considering the mechanisms of action of **adomiparin** and **heparin**, which one is more mechanistically linked to **PROC**?

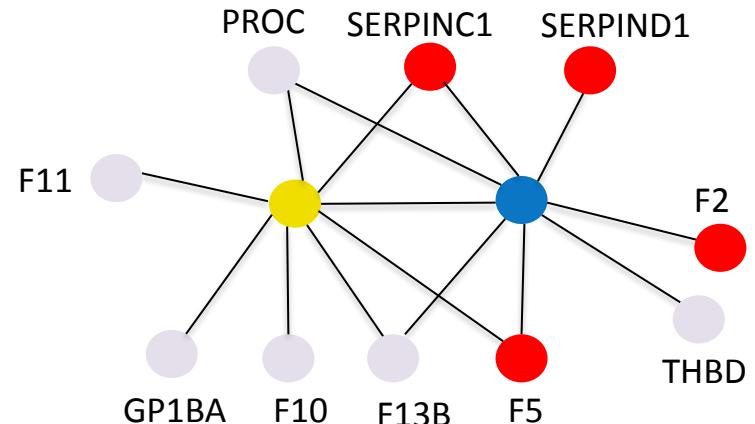
NetMedGPT: ChatNetMedGPT?

Disseminated intravascular coagulation

Drug: adomiparin



Drug: heparin



Disease



Drug



Protein

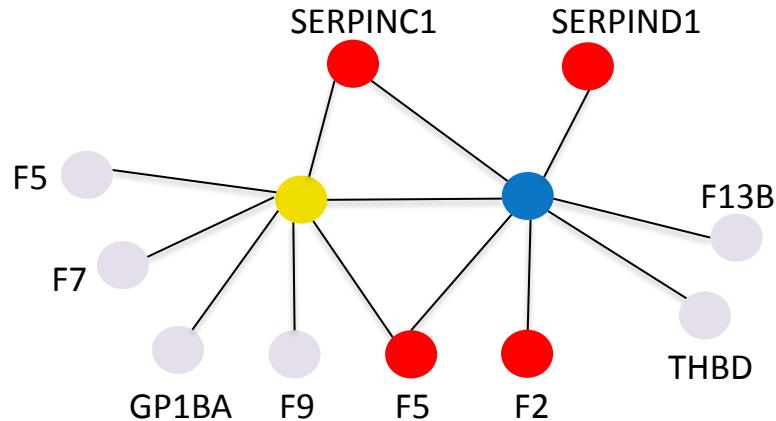


Overlapping proteins

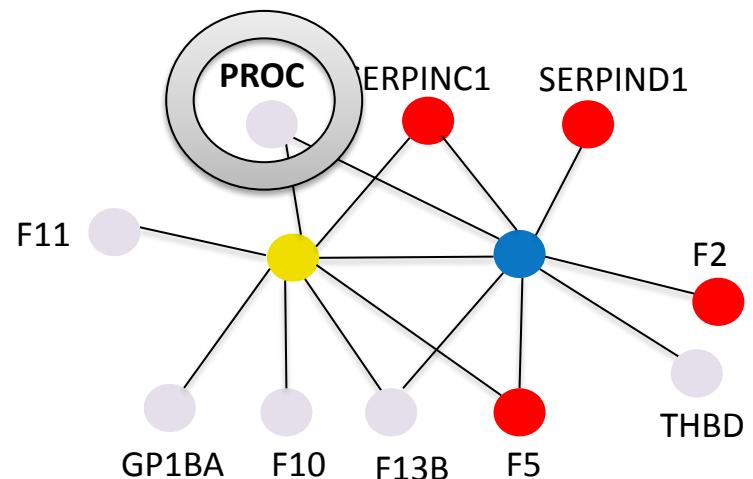
NetMedGPT: ChatNetMedGPT?

Disseminated intravascular coagulation

Drug: adomiparin



Drug: heparin



● Disease ● Drug ● Protein ● Overlapping proteins

NetMedGPT: ChatNetMedGPT?



Comparing Mechanisms in DIC disease: Heparin vs. Adomiparin

Question:

In the context of disseminated intravascular coagulation (DIC), considering the mechanisms of action of adomiparin and heparin, which one is more mechanistically linked to PROC?

Answer:

Protein C (**PROC**) is more mechanistically connected to **heparin** than to **adomiparin**, particularly in **DIC**. Heparin, by reducing thrombin levels and potentially preserving endothelial thrombomodulin function, supports the activation of PROC. In contrast, adomiparin primarily inhibits factor Xa and thrombin without significantly influencing the protein C pathway.

Acknowledgement

Thanks for the funding!



Alexander von
HUMBOLDT
STIFTUNG



Horizon Europe



Deutsche
Forschungsgemeinschaft



Bundesministerium
für Bildung
und Forschung

Thanks to the Cosy.Bio institute!



Alexander von
HUMBOLDT
STIFTUNG



DFG Deutsche
Forschungsgemeinschaft



Bundesministerium
für Bildung
und Forschung

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