UNC ESHELMAN SCHOOL OF PHARMACY

MML UNC.EDU

Biomedical Knowledge Graphs: Development and Application to Drug Discovery and Repurposing.

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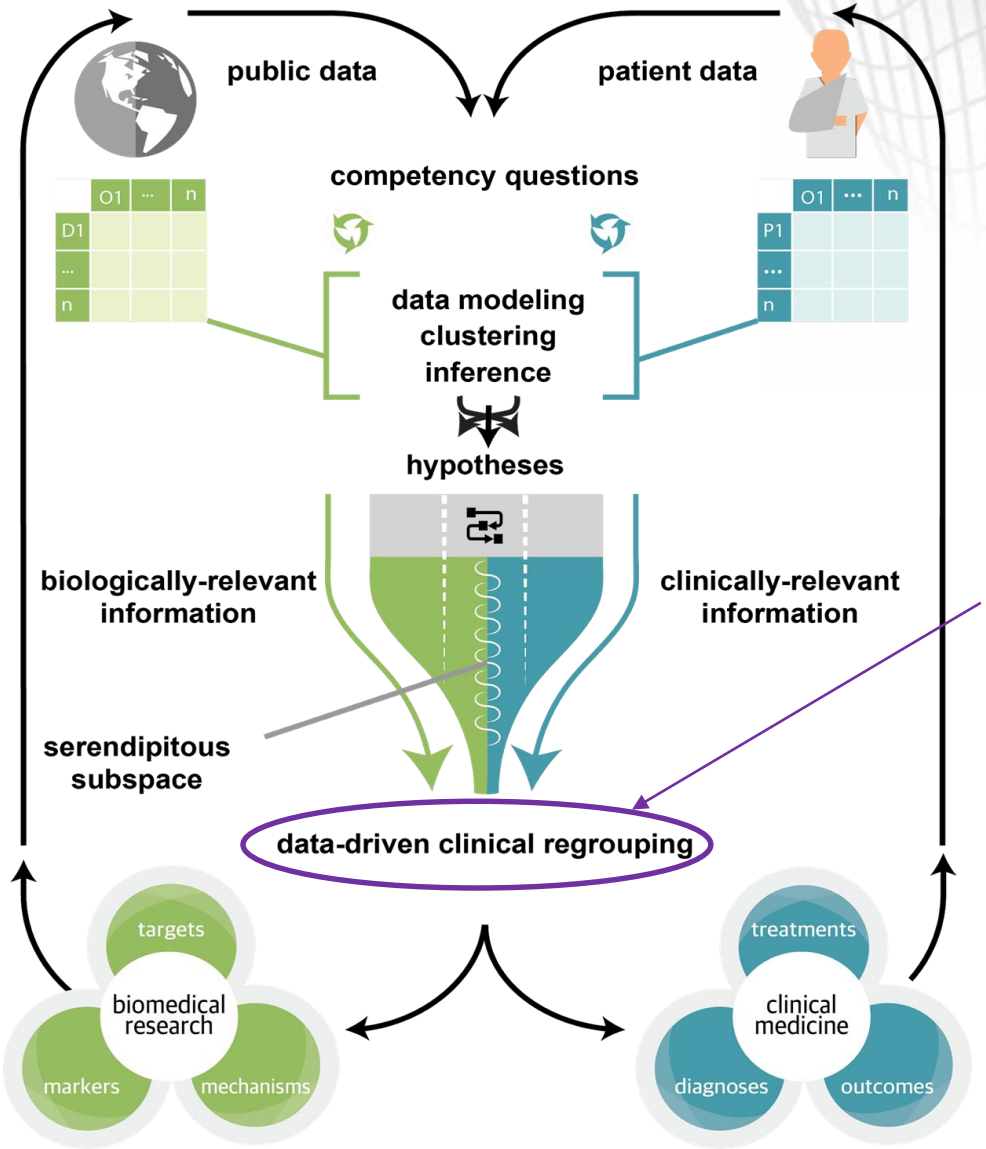
Biomedical Data Translator

"Two hundred years ago, chemists created a comprehensive enumeration of the elements and systematic relationships among them. We envision the Translator doing the same for translational science."

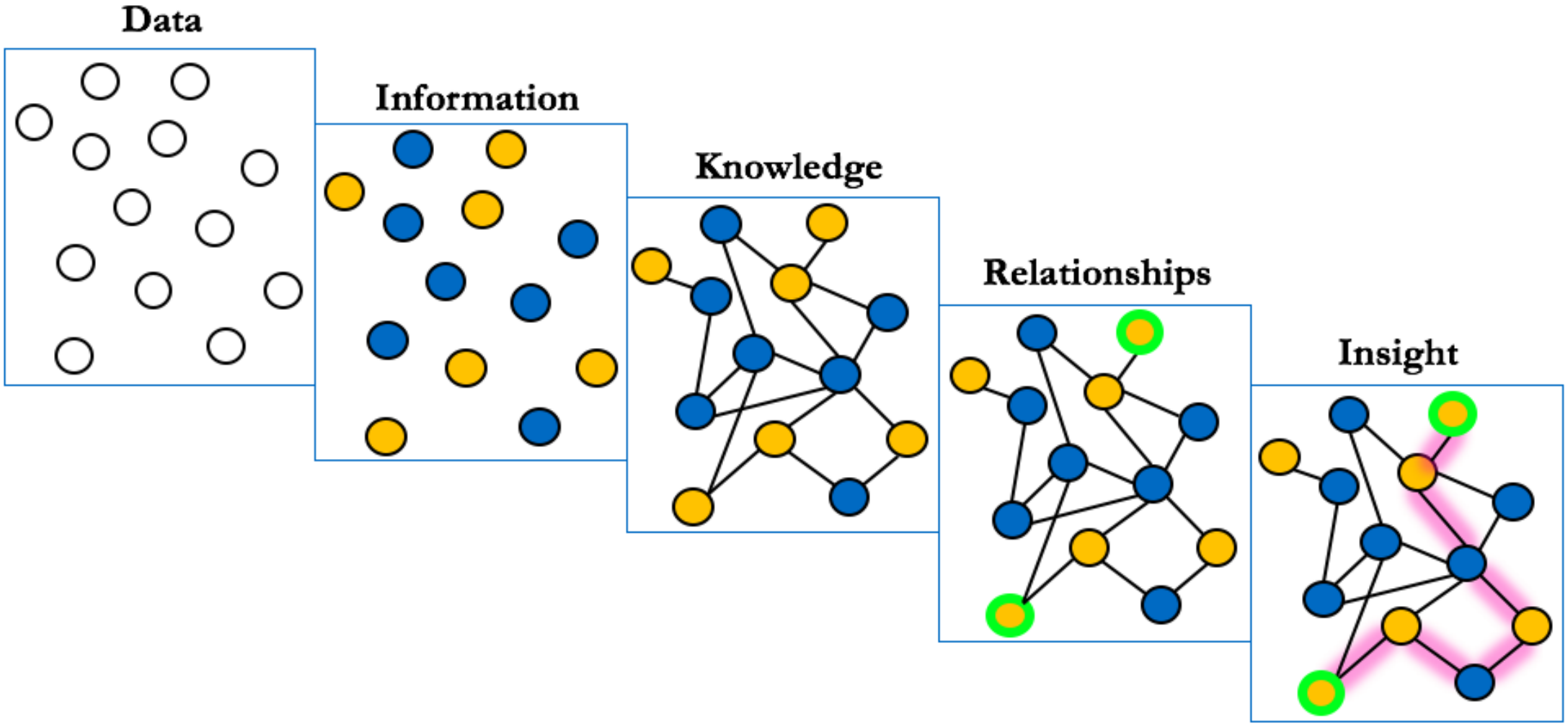
— Christopher P. Austin, MD, director of NCATS, with Christine M. Colvis, PhD, Noel T. Southall, PhD



Enhance (but not replace) human reasoning, move beyond symptom-based definitions of disease toward a more mechanistic understanding

Austin CP, Colvis CM, Southall NT. Deconstructing the translational tower of babel. *Clin Transl Sci* 2019;12(2):85. doi:10.1111/cts.12595;
Fecho K, et al. The Biomedical Data Translator Consortium. Toward a universal biomedical data translator. Clin Transl Sci 2019;12(2):91–94. doi:10.1111/cts.12591.

From Data to Serendipity

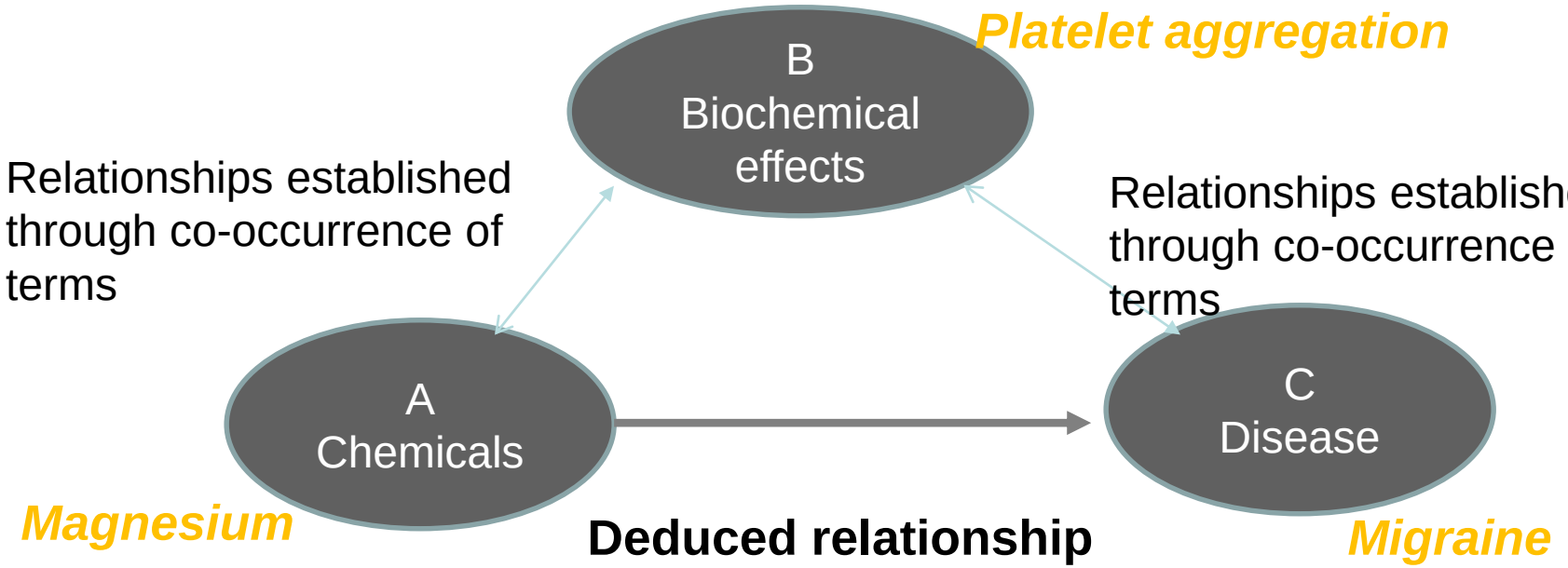


Scientific literature as a source of data: Swanson's ABC approach to drug discovery via text mining*

Don R. Swanson

American information scientist

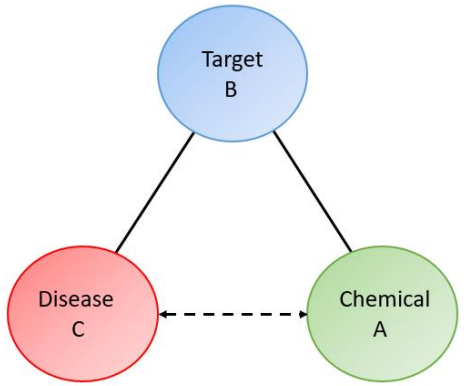
Vasodilation
Spreading cortical depression
Platelet aggregation



*Swanson DR. Medical literature as a potential source of new knowledge. Bull Med Libr Assoc 1990;78(1):29–37

Chemotext (chemotext.mml.unc.edu)

- A publicly-available Web server that mines the entire PubMed using Medline Subject Heading (MeSH) terms
  - » Data retrieved from the MEDLINE/PubMed Baseline Repository (MBR)
  - » Chemotext database contains ca. 30M articles and 100K connections (vertices) between terms
  - » Connections are made based on MeSH terms
    - » Chemical terms = A
    - » Protein/Pathway terms = B
    - » Disease terms = C



- Mining PubMed affords rapid identification of connections between vertices and enabling new inferences of such connections

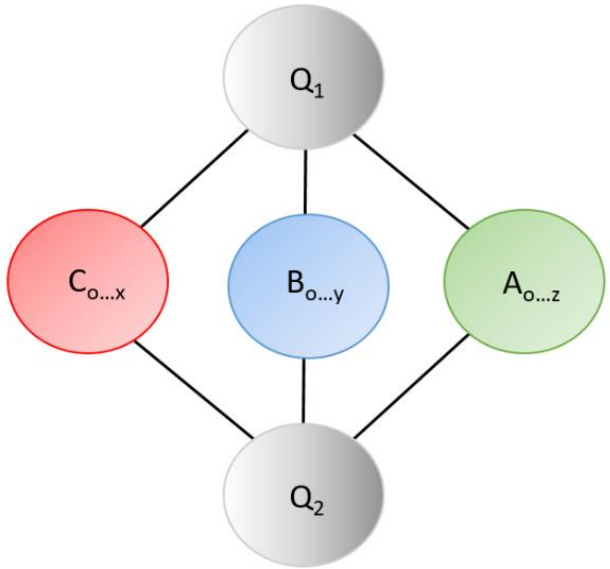
MeSH terms

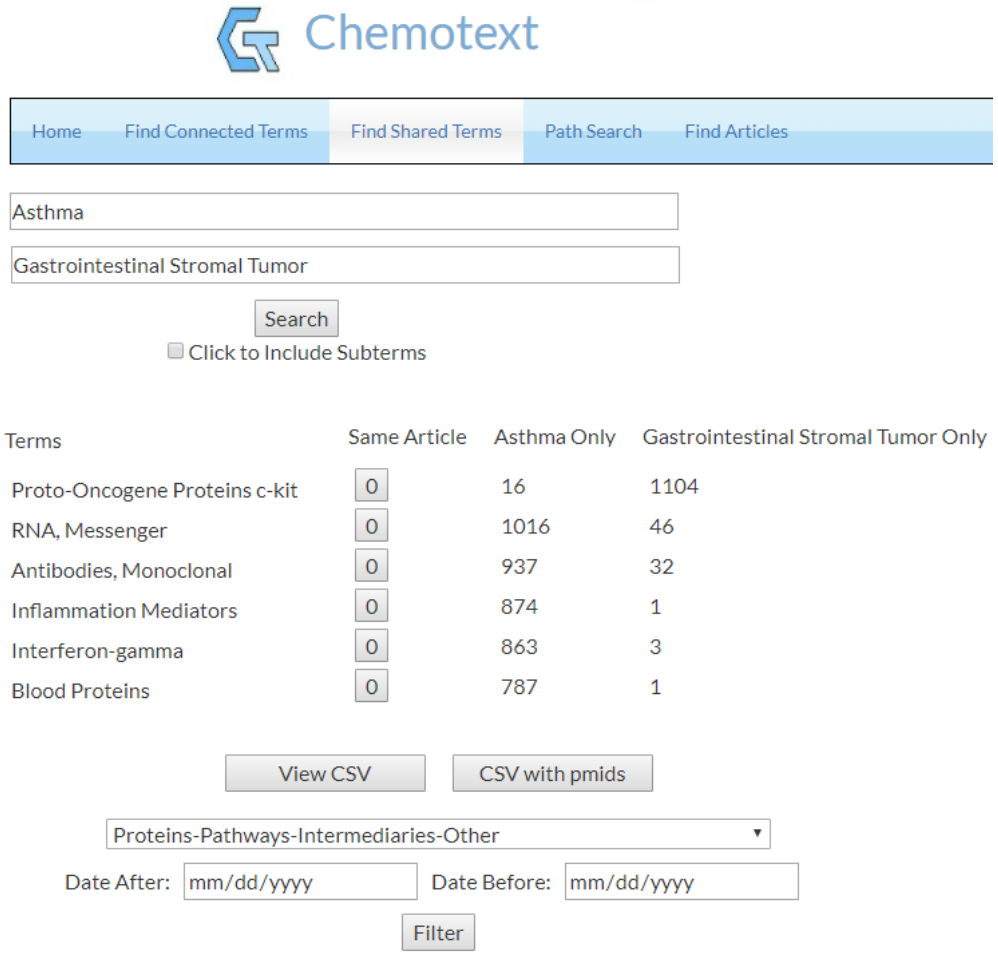
Airway Remodeling/physiology*
Animals
Asthma/chemically induced
Asthma/metabolism
Asthma/physiopathology*
Benzamides/pharmacology
Bronchi/drug effects
Bronchi/metabolism
Bronchi/pathology
Bronchial Hyperreactivity/chemically induced
Bronchial Hyperreactivity/metabolism
Bronchial Hyperreactivity/physiopathology*
Cells, Cultured
Chemokine CCL2/metabolism
Disease Models, Animal
Female
Humans
Imatinib Mesylate
In Vitro Techniques
Interleukin-13/metabolism
Male
Mice
Mice, Inbred C57BL
Mice, Knockout
Myocytes, Smooth Muscle/pathology
Myocytes, Smooth Muscle/physiology*
Ovalbumin/adverse effects
Piperazines/pharmacology
Proliferating Cell Nuclear Antigen/metabolism
Protein Kinase Inhibitors/pharmacology
Proto-Oncogene Proteins c-abl/deficiency
Proto-Oncogene Proteins c-abl/genetics
Proto-Oncogene Proteins c-abl/physiology*
Pyrimidines/pharmacology

Capuzzi SJ, et al., Chemotext: A Publicly Available Web Server for Mining Drug-Target-Disease Relationships in PubMed. J Chem Inf Model. 2018 58(2):212-218

Shared Terms Module

- Two query terms are input, and co-occurring terms that are shared between the queries are returned.

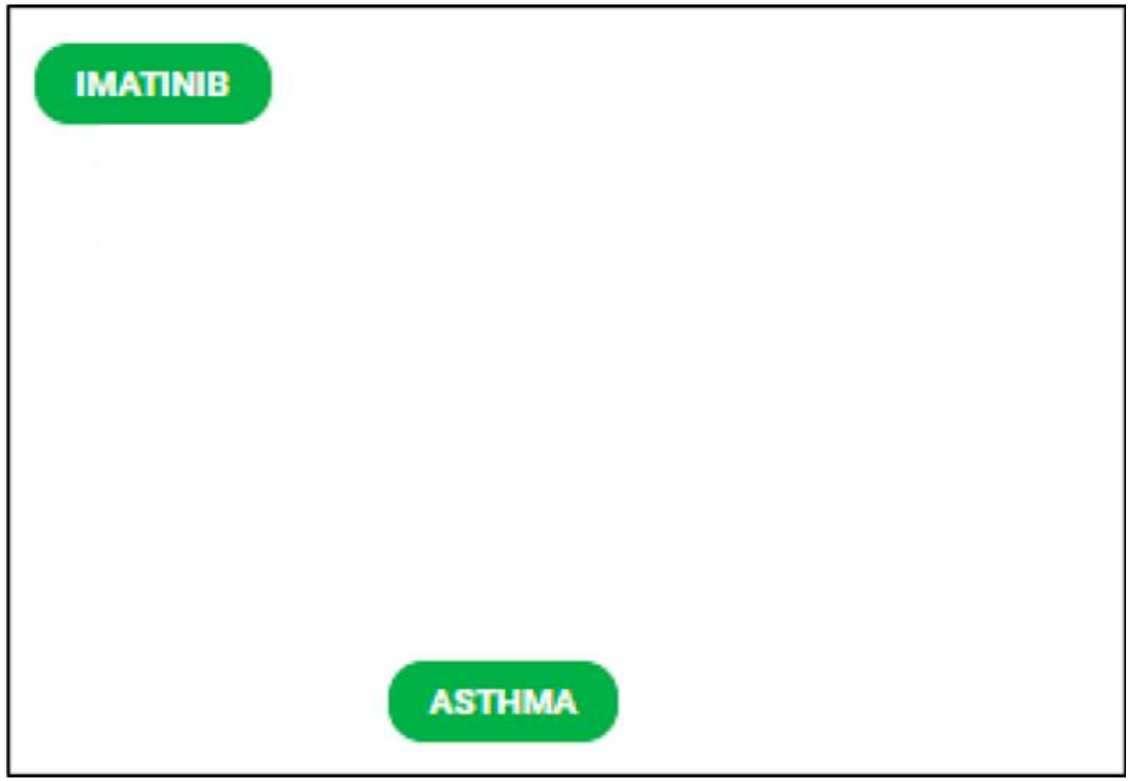




Chemotext (chemotext.mml.unc.edu)

Establishing Clinical Outcomes Pathways (COPs) of drug action

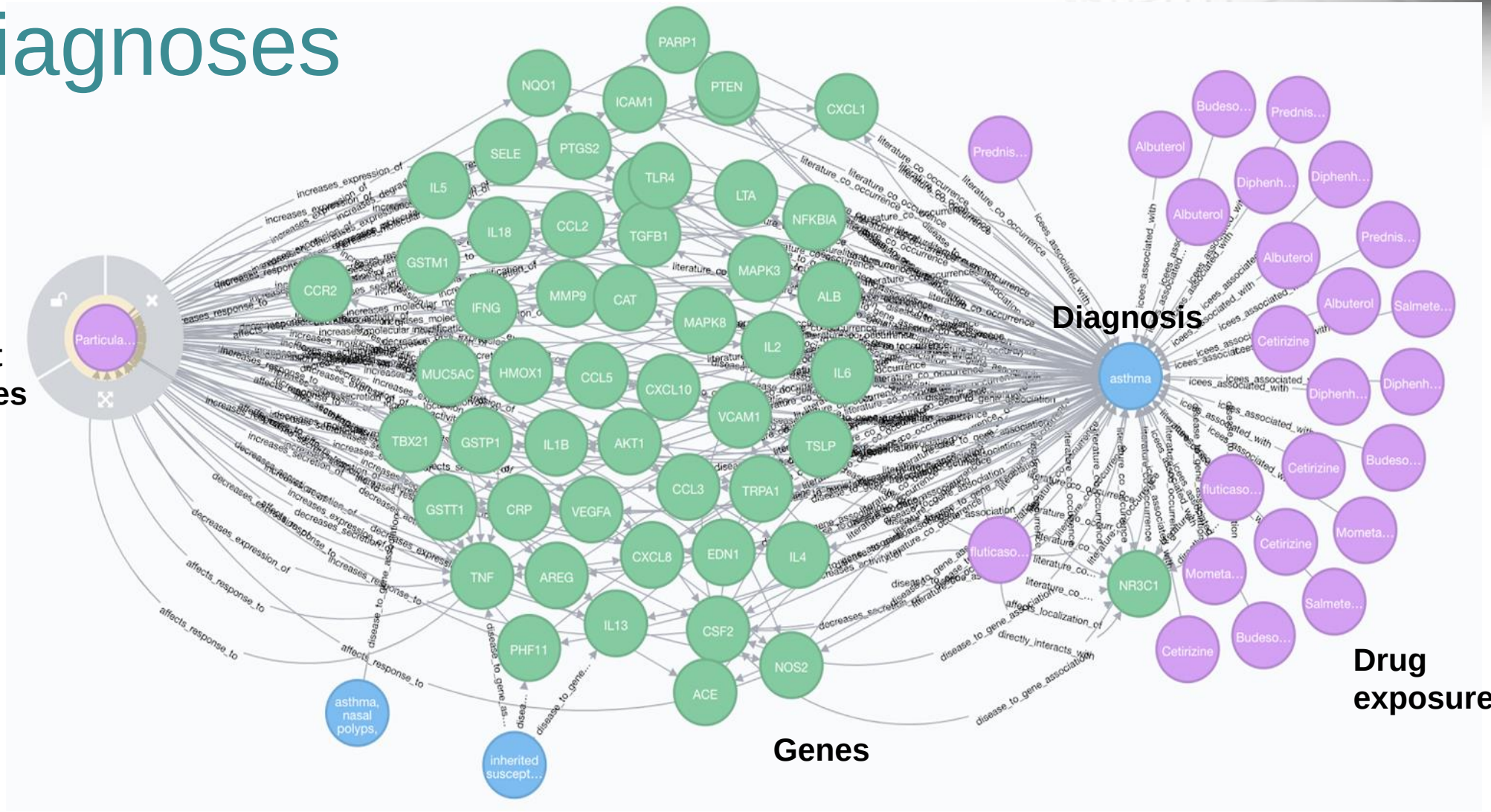
- COPs explain how a drug elicits its effect on a disease
- Chemotext can be used to elucidate COPs



Translator System Architecture

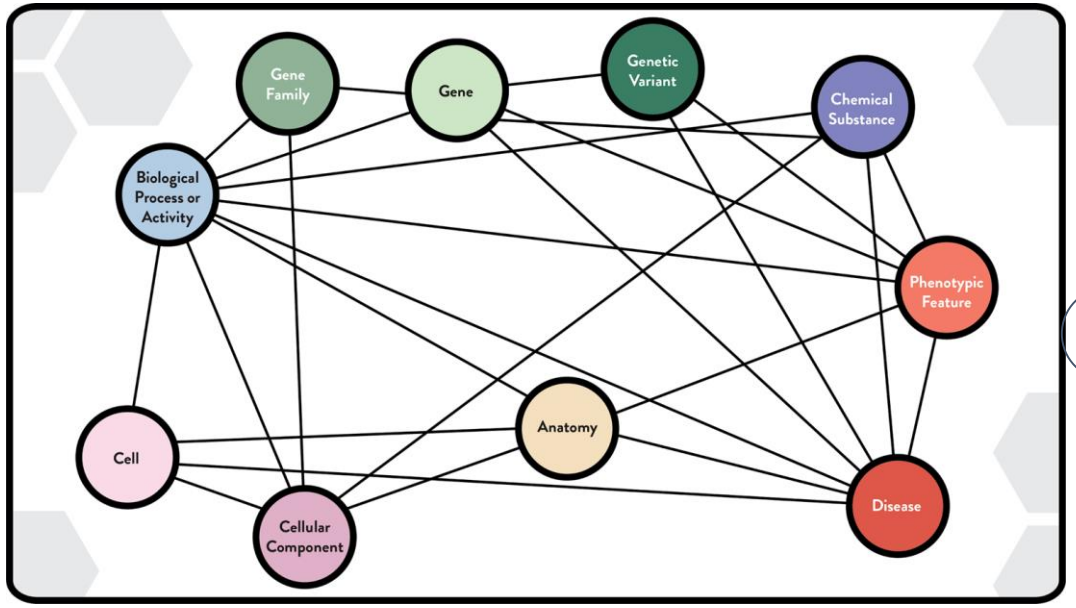
Fecho K, et al. Clin Transl Sci 2019;12(2):91–94. doi:10.1111/cts.12591.

Simple application: A Knowledge Graph of Exposures, Genes, Drugs, and Diagnoses



ROBOKOP (Reasoning Over Biological Objects in Knowledge Oriented Pathways): High-level Concepts Connected by Knowledge Sources

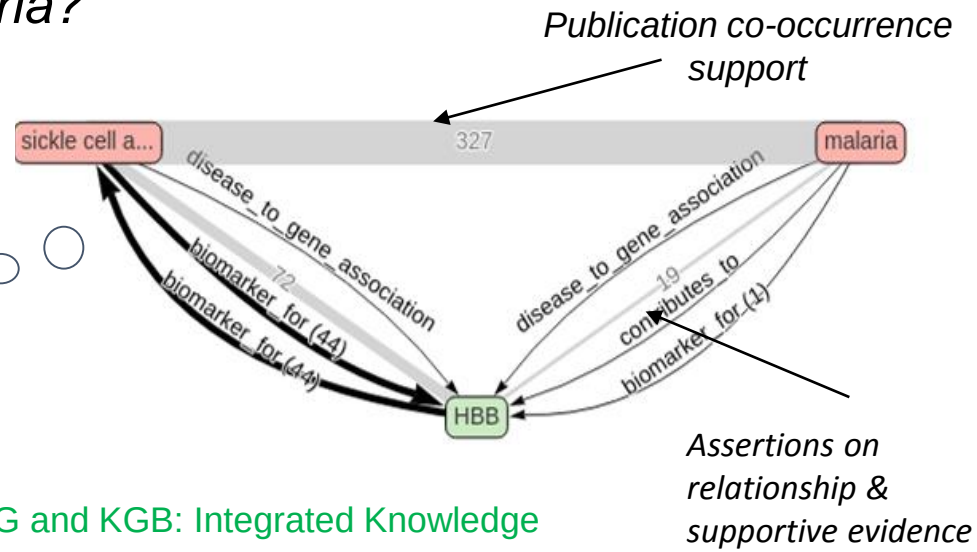
Robokop.renci.org



"Why does imatinib help people with asthma?"

"Why does clonadine interact with propranolol?"

"Why is sickle cell disease protective against malaria?"



- Current KG incldues ca. 600K nodes and 12+M edges.

Bizon C, Cox S, Balhoff J, Kebede Y, Wang P, Morton K, Fecho K, Tropsha A. ROBOKOP KG and KGB: Integrated Knowledge Graphs from Federated Sources. J Chem Inf Model. 2019, 59(12):4968-4973

Morton K, Wang P, Bizon C, Cox S, Balhoff J, Kebede Y, Fecho K, Tropsha A. ROBOKOP: An Abstraction Layer and User Interface for Knowledge Graphs to Support Question Answering. Bioinformatics. 2019 35(24):5382-5384

Case study: query ROBOKOP for carbon monoxide – multiple sclerosis association.

A.

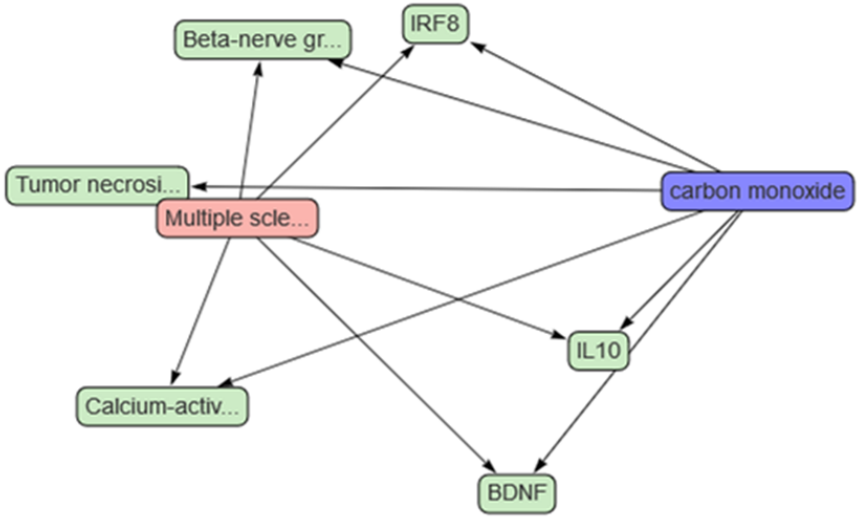
Natural Language Question

What genes might mediate the association between workplace exposure to carbon monoxide and multiple sclerosis?

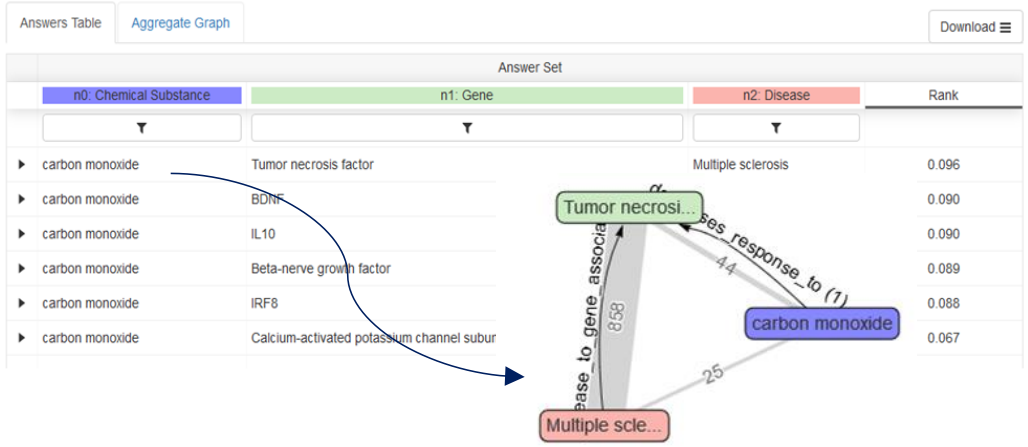
B.

Machine Question or Meta-Graph

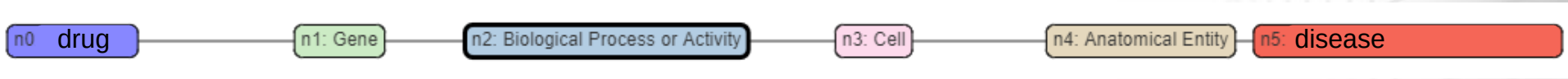
C.



D. **Answer Table**

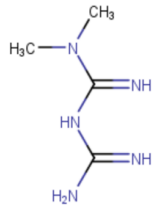
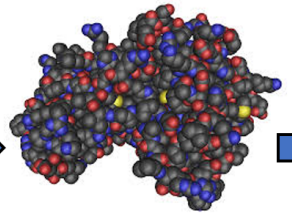
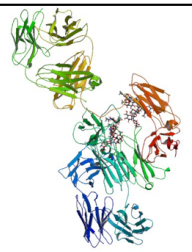
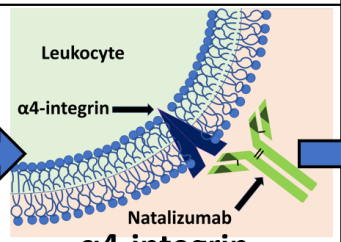
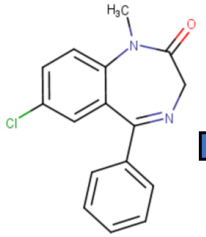
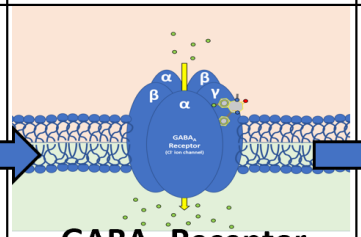


COPs built using knowledge graphs



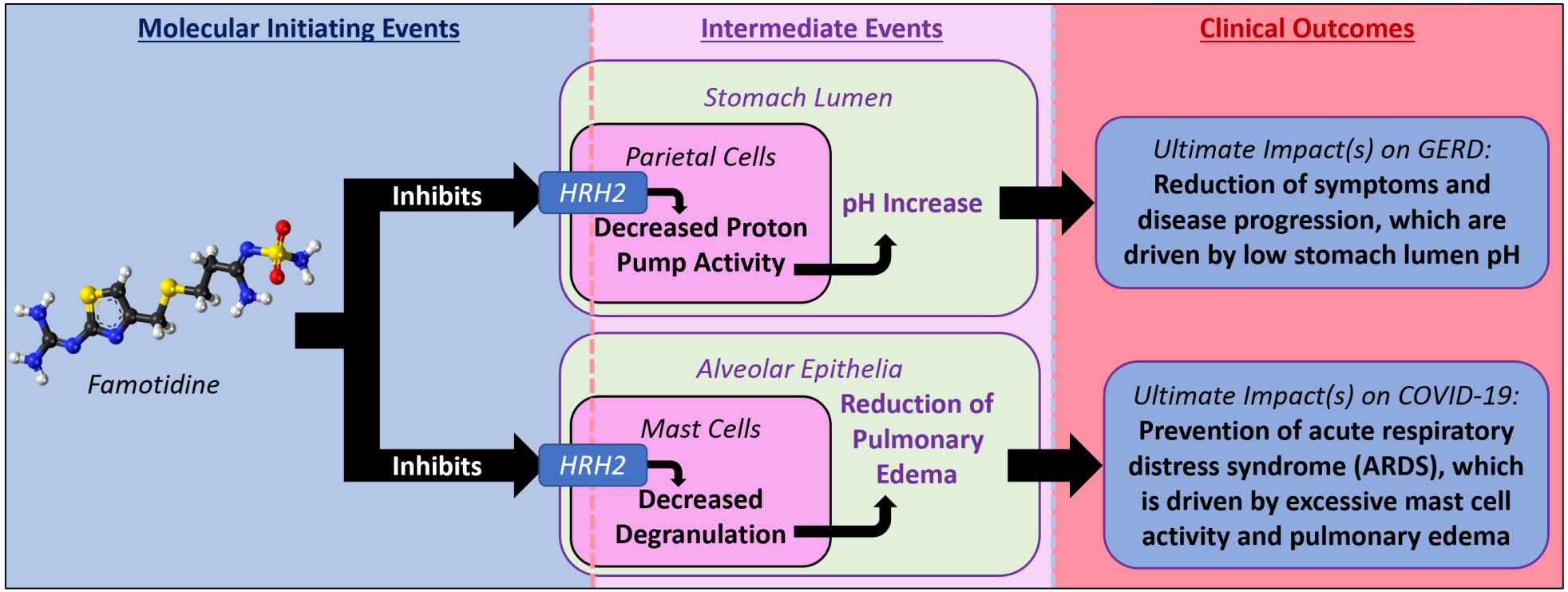
Ketamine	N-Methyl-D-Aspartate	Neurotrans-mission	Neurons	Central Nervous System	Depressive Disorder
Glipizidine	Potassium ATP channel	Potassium ion transport	Beta cells	Liver	Diabetes Mellitus, Type2
Maraviroc	C-C chemokine receptor type 5	Cell-cell signaling	Leukocytes	Immune System	Acquired Immunodeficiency Syndrome
Mizolastine	Histamine H1 receptor	Cellular response to histamine	Mast Cells	Immune System	Rhinitis, Allergic, Seasonal
Dipyridamole	Equilibrative nucleoside transporter	Nucleoside transport	Blood Platelets	Circulatory System	Thrombosis

Clinical Outcome Pathways for known drugs and their indications

FDA Approved Drugs	Molecular Initiating Events	Intermediate Events	Clinical Outcomes
 Metformin	 AMPK Activation	1. Inhibition of glucagon-induced increase in cAMP concentration 2. Decreased gluconeogenesis in the liver	Decreased insulin tolerance, and better control of blood glucose levels in patients with type II diabetes mellitus
 Natalizumab	 α4-integrin Inhibition	1. Inhibition of α-4-integrin binding to VCAM receptors on epithelial cells of blood-brain barrier 2. Decreased migration of lymphocytes into CNS	Decreased adaptive neuroimmune response, which decreases symptoms and disease progression in patients with multiple sclerosis
 Diazepam	 $GABA_A$ Receptor Modulation	1. Increased response to GABAergic signaling in CNS 2. Enhanced hyperpolarization of CNS neurons leading to neuronal depression	Symptom reduction in patients with generalized anxiety disorder and/or panic disorder

Clinical Outcome Pathways for known drugs and proposed indications (*i.e.*, repurposing)

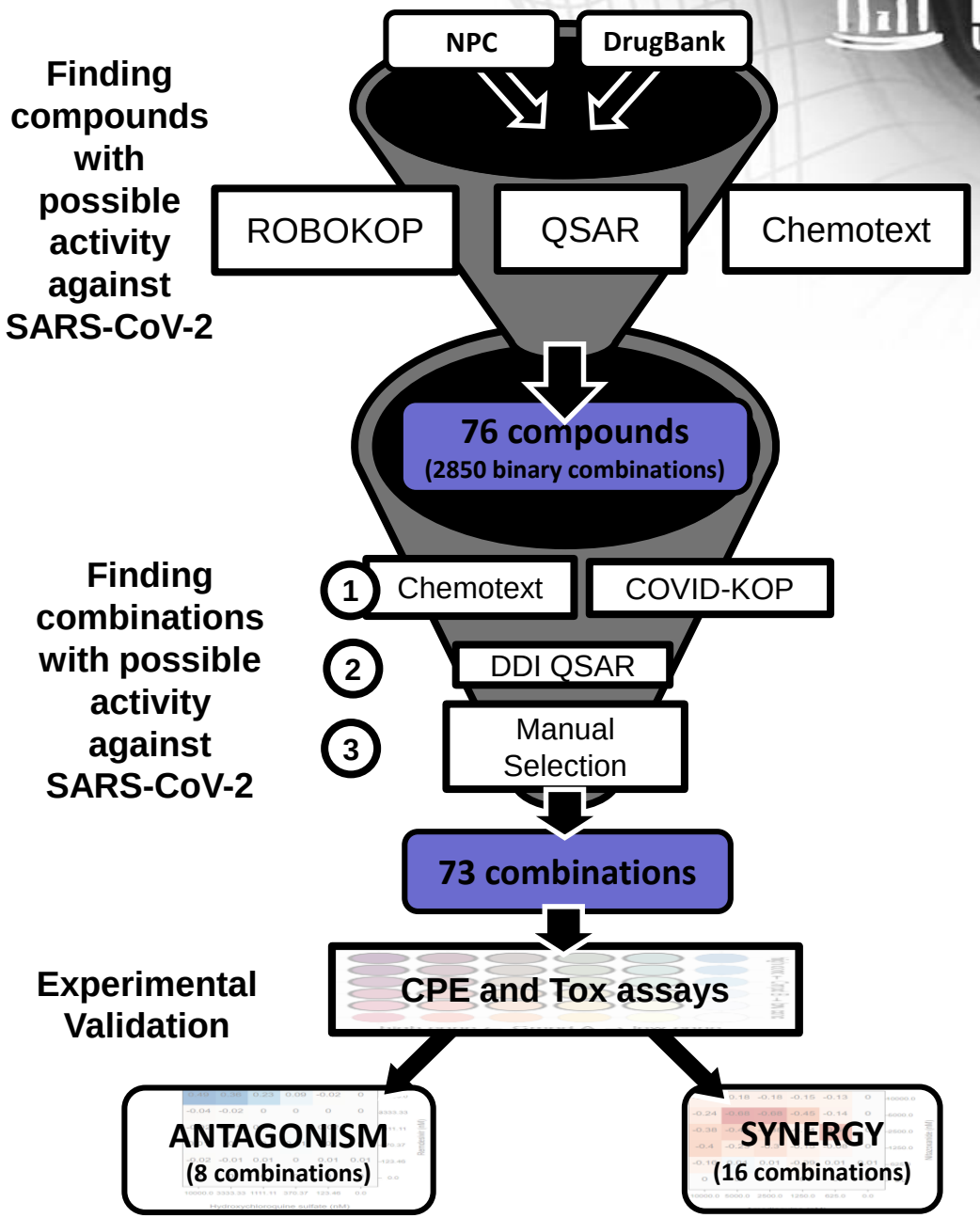
COP for the approved indication for famotidine, gastroesophageal reflux disorder (GERD)



Proposed COP to explain the clinical observation that famotidine reduces COVID-19–related mortality

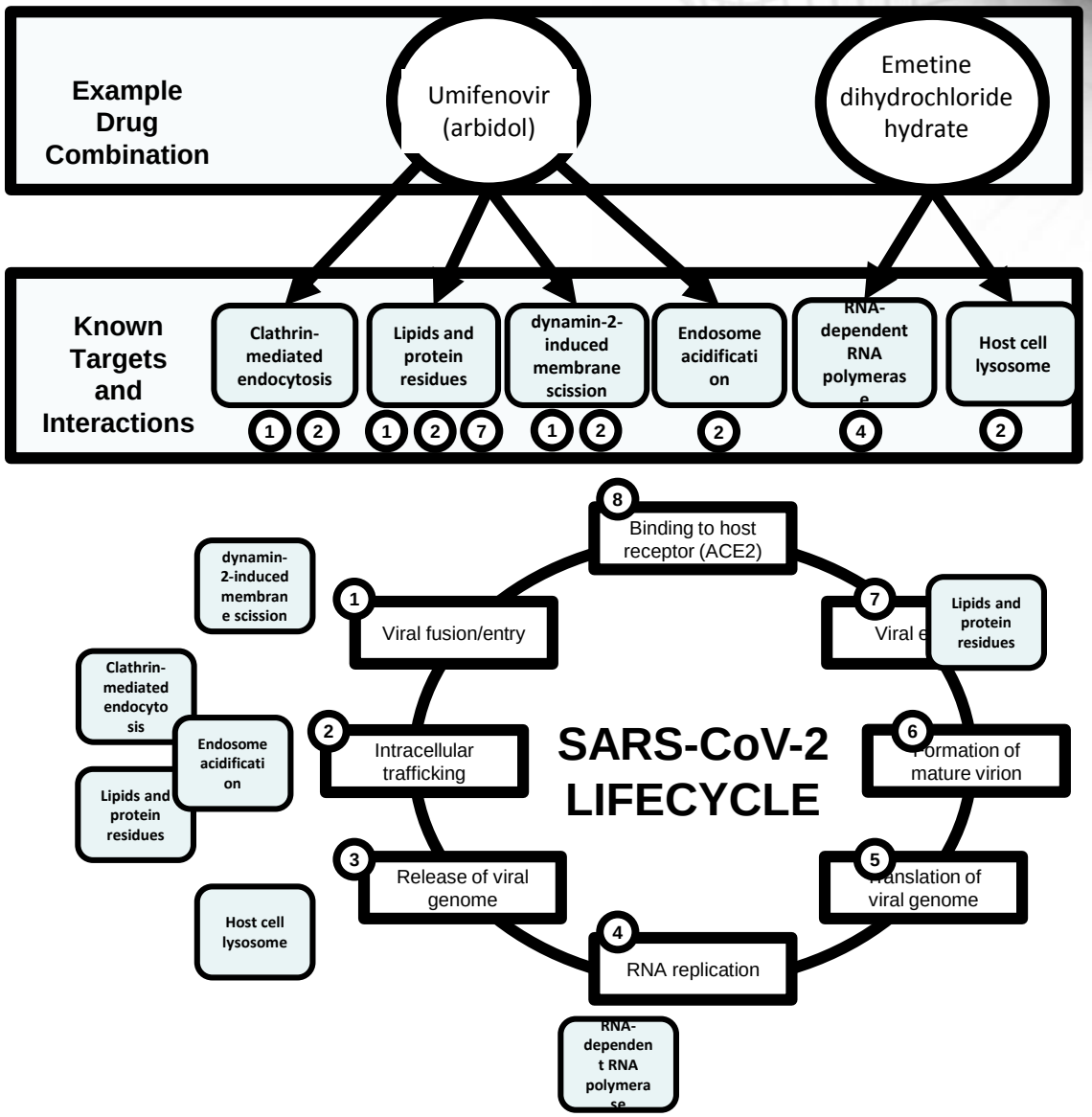
Knowledge mining approaches to find synergistic drug combinations against COVID-19

Study design



Bobrowski et al, Discovery of Synergistic and Antagonistic Drug Combinations against SARS-CoV-2 In Vitro. *Mol Ther*. **2021** Feb 3;29(2):873-885. DOI: 10.1016/j.ymthe.2020.12.016

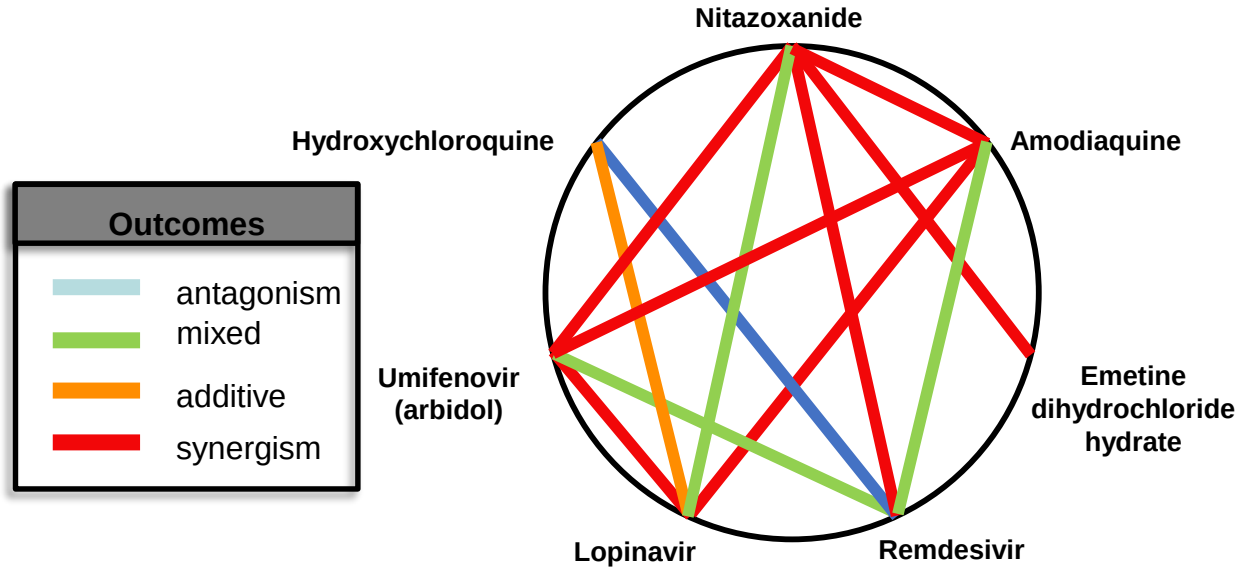
Example of a rationale behind drug mixture selection

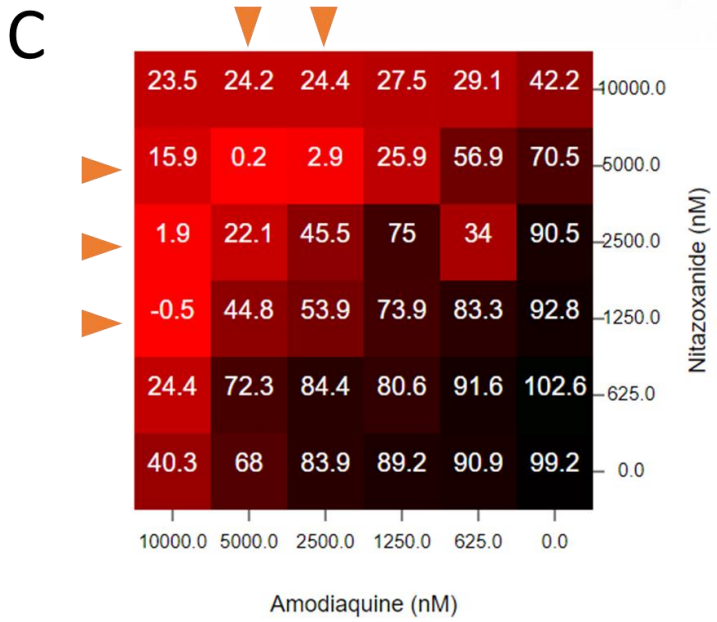


Korn et al., COVID-KOP: Integrating Emerging COVID-19 Data with the ROBOKOP Database. ChemRxiv. 2020 Jun 18. doi:10.26434/chemrxiv.12462623.

Bobrowski et al, Discovery of Synergistic and Antagonistic Drug Combinations against SARS-CoV-2 In Vitro. *Mol Ther*. **2021** Feb 3;29(2):873-885. DOI: 10.1016/j.ymthe.2020.12.016

Experimentally confirmed pairs of synergistic or antagonistic drug combinations (CPE assay, NCATS)





Example: Nitazoxanide/Amodiaquine synergistic combination

Bobrowski et al, Discovery of Synergistic and Antagonistic Drug Combinations against SARS-CoV-2 In Vitro. *Mol Ther*. **2021** Feb 3;29(2):873-885. DOI: 10.1016/j.ymthe.2020.12.016

Summary

- Accumulation of multiple biomedical datasets creates new opportunities for data integration and knowledge mining
- Knowledge graph provide powerful means to mine pathways connecting biomedical entities of interest
- Elucidation of Clinical Outcome Pathways supports novel drug repurposing hypotheses
- Emerging application of machine learning approaches to knowledge graph mining accelerates the discovery of unknown biological pathways such as those linking drugs and diseases

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