Explaining natural product-drug interactions with biomedical knowledge graphs

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Natural Products Promoted for Complementary Health

Green Tea

Complementary Health Approaches – herbal/dietary supplements

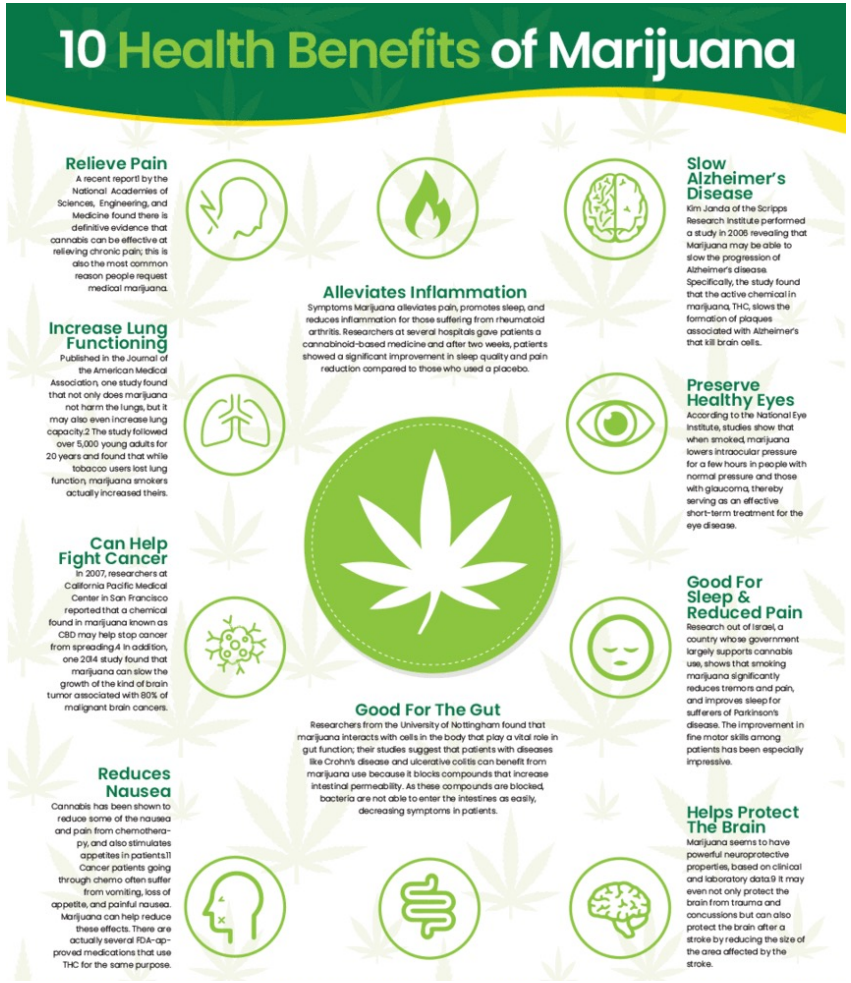
Acai berry

Source: Healthyhubb.com, https://vipcodon.net/what-are-benefits-of-acai-berry/

Natural Products Promoted for Complementary Health

Complementary Health Approaches – Pain Relief

Kratom – promoted for analgesic/pain relief



Cannabis/cannabidiol (CBD)–
promoted for all kinds of health benefits

Source: https://www.chicagoreader.com/chicago/six-best-kratom-vendors-top-places-to-buy-quality-kratom-online-in-2021/Content?oid=86891725, https://cannabisbusinesssummit.com/0201/10/23/marijuana-health-benefits-infographic/

Natural Product (NP) Safety Concerns

St. John's wort

+ cyclosporin → Transplant or graft rejection

- NPs are not nearly as regulated as drugs by the FDA
- Large number of NPs now available
  - 76,000 in dietary supplements database
- Increasing consumer market for NPs
  - Up to 18% adults in US

Source: https://www.nccih.nih.gov/health/st-johns-wort-and-depression-in-depth

References: Gurley BJ, Fifer EK, Gardner Z. Pharmacokinetic herb-drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta medica. 2012 Sep;78(13):1490-514.

NP Safety Concerns

Adverse events due to intake of NP

- Concomitant intake of drugs and NPs by older adults
  - Up to 80% adults in US
- Generally, natural products not reported to physicians or in EHR
- Effects range from mild, severe to deadly depending on the interaction
- Occurs when substance/constituent interacts with a drug or inhibits it
  - Makes drug ineffective and/or toxic to body

NP Safety Concerns

FDA Adverse Event Reporting System (FAERS)

- Platform for consumers, physicians, legal agencies to report drug interactions and adverse effects
- Able to find natural products in reports

New Examples – natural products with > 20 reports in FAERS since 2004

Natural Product	Reported Adverse Events
Kratom	Vomiting, pulmonary congestion, death
Horse Chestnut	Somnolence, gastroesophageal reflux disease, coma
Cannabis	Cardiac arrest, respiratory issues
Green Tea	Rash, burning skin sensation, itchy skin, erythema
Cinnamon	Increased blood glucose, abdominal pain
Saw Palmetto	Death

NP Safety Concerns Related to Interaction with Drugs

Examples

Widely studied and known

Grapefruit juice

One whole grapefruit or small glass of juice – common food item

Interacts with →

Antiarrhythmic agents, antihistamines, statins, benzodiazepines, cough suppressant etc.

St. John's wort

Treat mild to moderate depression, menopause symptoms

Interacts with →

HIV protease inhibitors, cyclosporin, hormonal contraceptives, antineoplastic agents, Xanax, antidepressants, barbiturates, immunosuppressive drugs, cough suppressant etc.

References: https://medlineplus.gov/druginfo/natural/946.html, https://en.wikipedia.org/wiki/Grapefruit%E2%80%93drug_interactions

NP Safety Concerns Related to Interaction with Drugs

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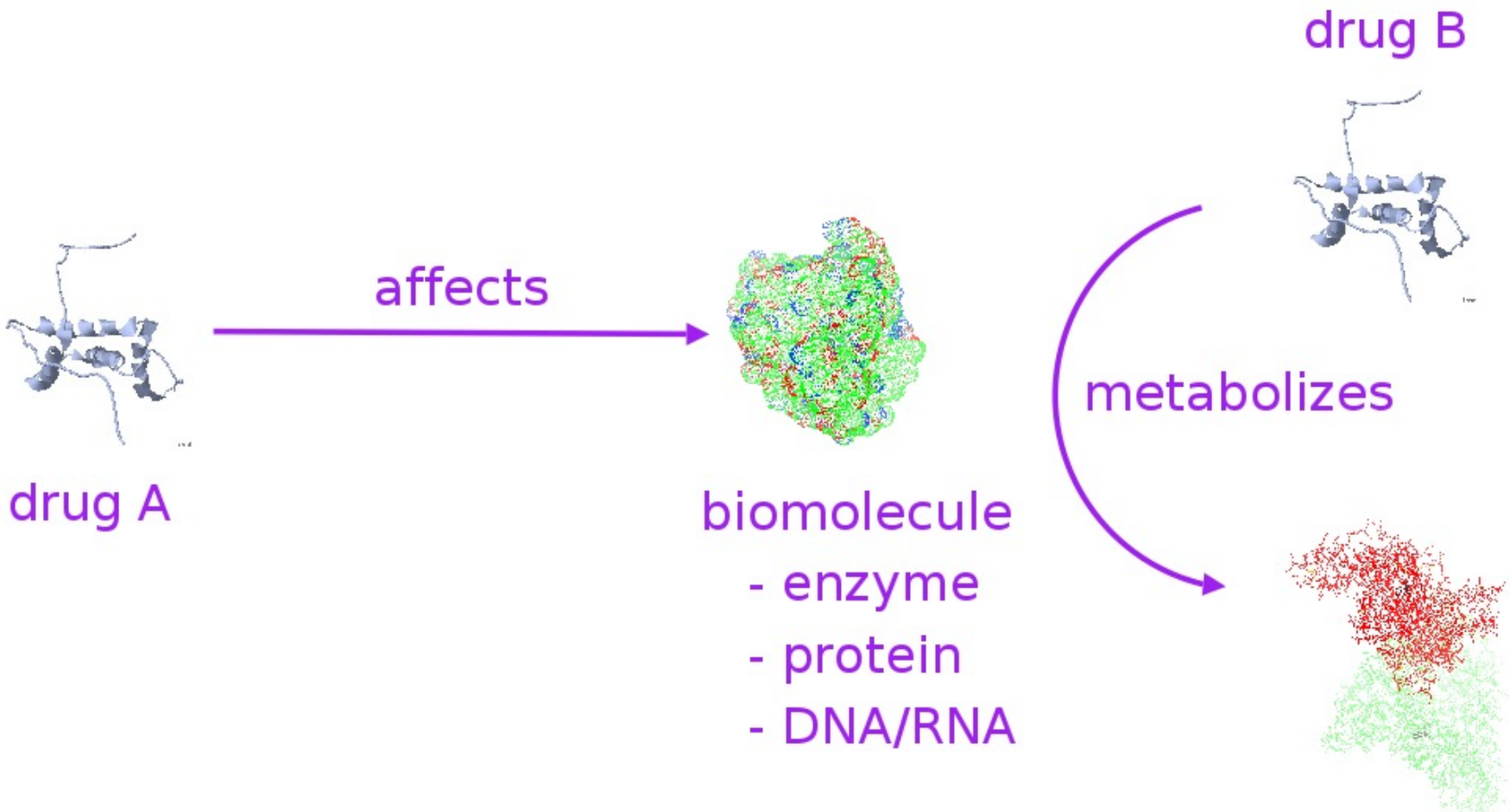
Antiarrhythmic agents, antihistamines, statins, benzodiazepines, cough suppressant etc.

Adverse Events

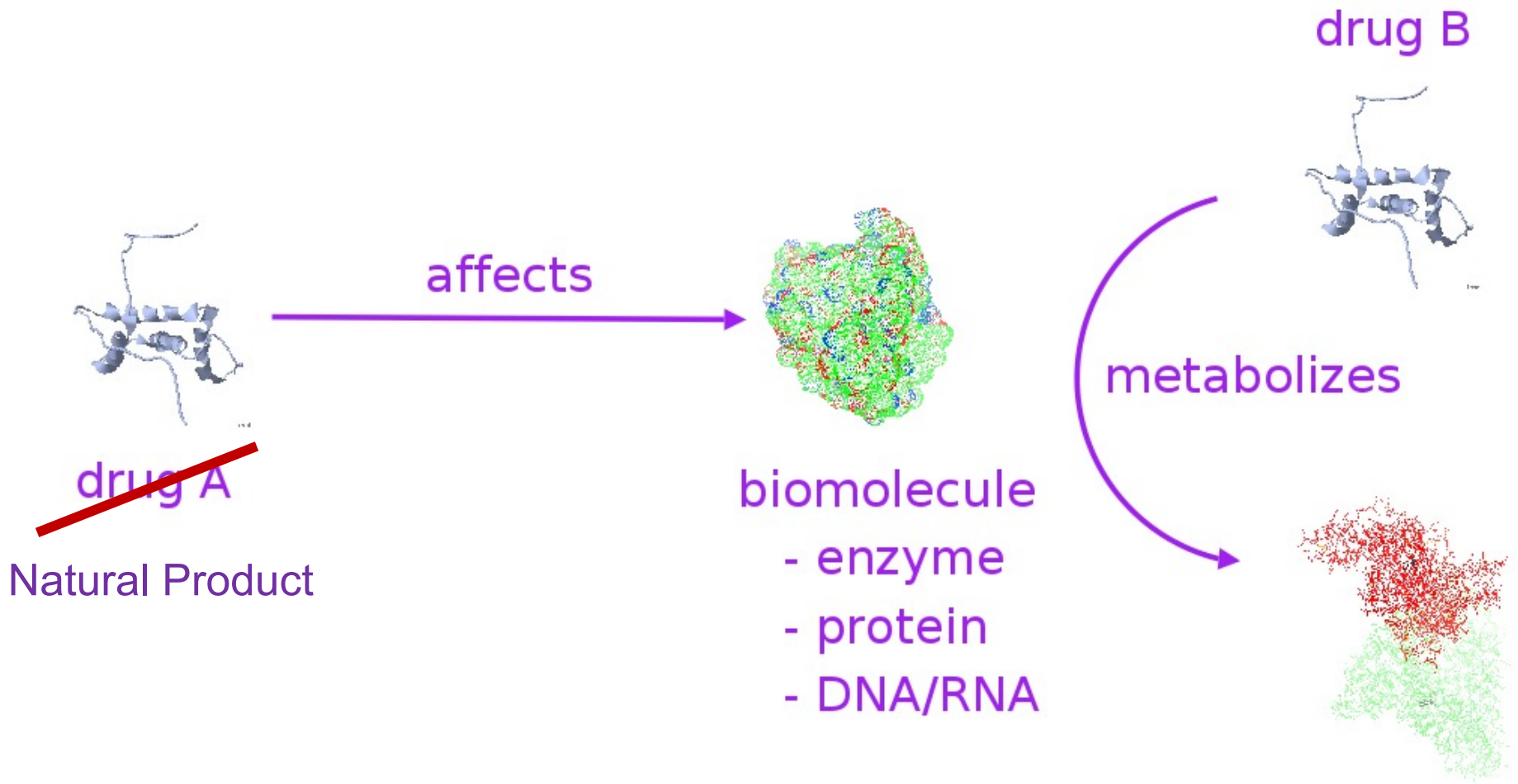
- Rhabdomyolysis
- Torsade de pointes
- Respiratory depression
- Nephrotoxicity
- Gastrointestinal bleeding
- Bone marrow suppression

References: https://medlineplus.gov/druginfo/natural/946.html, https://en.wikipedia.org/wiki/Grapefruit%E2%80%93drug_interactions

Pharmacokinetic Drug Interactions

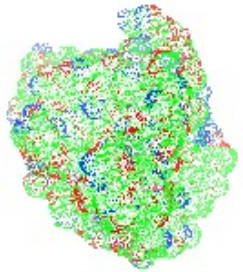


Pharmacokinetic NP-Drug Interactions



Pharmacokinetic NP-Drug Interactions

affects



Grapefruit juice

One whole grapefruit or small glass of juice – common food item

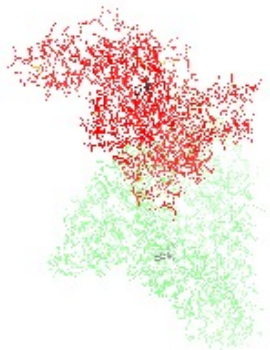
CYP3A4

Major metabolizing enzyme

drug B

E.g. Simvastatin

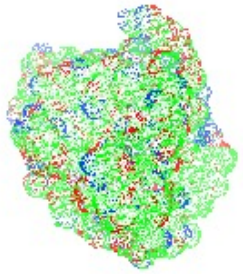
metabolizes



Pharmacokinetic NP-Drug Interactions

St. John's wort

affects

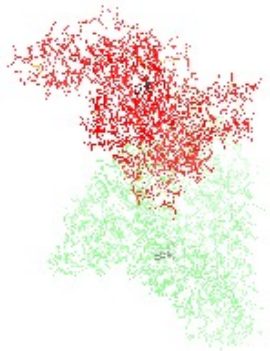


CYP3A4, P-glycoprotein

drug B

E.g. hormonal contraceptive

metabolizes

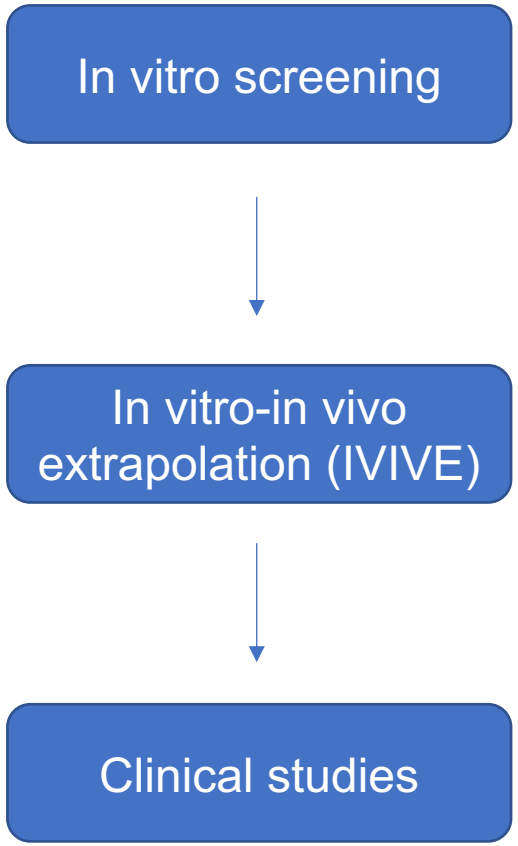


Treat mild to moderate depression, menopause symptoms

Major metabolizing enzyme, drug transporter

Discovering Pharmacokinetic NP-Drug Interactions

Understanding the mechanism is key to preventing major adverse events due to pharmacokinetic interactions.



Discovering Pharmacokinetic NP-Drug Interactions

In vitro screening

In vitro-in vivo extrapolation (IVIVE)

Clinical studies

Kratom

Green tea

Goldenseal

Licorice

Cinnamon (in progress)

NaPDI Center of Excellence for Natural Product-Drug Interaction Research

2015-2021, 2021-ongoing

References: https://napdicenter.org/

Discovering Pharmacokinetic NP-Drug Interactions

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NaPDI Center of Excellence for Natural Product-Drug Interaction Research

2015-2021, 2021-ongoing

Expanding investigation to over 600 known unique natural products

References: https://napdicenter.org/

Pharmacokinetic NP-Drug Interactions Signal Detection

New Examples – natural products with > 20 reports in FAERS since 2004

Natural Product	Reported Adverse Event
Kratom	Vomiting, pulmonary congestion, death
Horse Chestnut	Somnolence, gastroesophageal reflux disease, coma
Cannabis	Cardiac arrest, respiratory issues
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Saw Palmetto	Death

Others include adverse effects from grapefruit juice and St. John's wort.

Objectives of My Research

Develop an automated hypothesis generation tool that can explain

- mechanistic information about pharmacokinetic interactions
- pathways that lead to adverse events.

Overall goal:

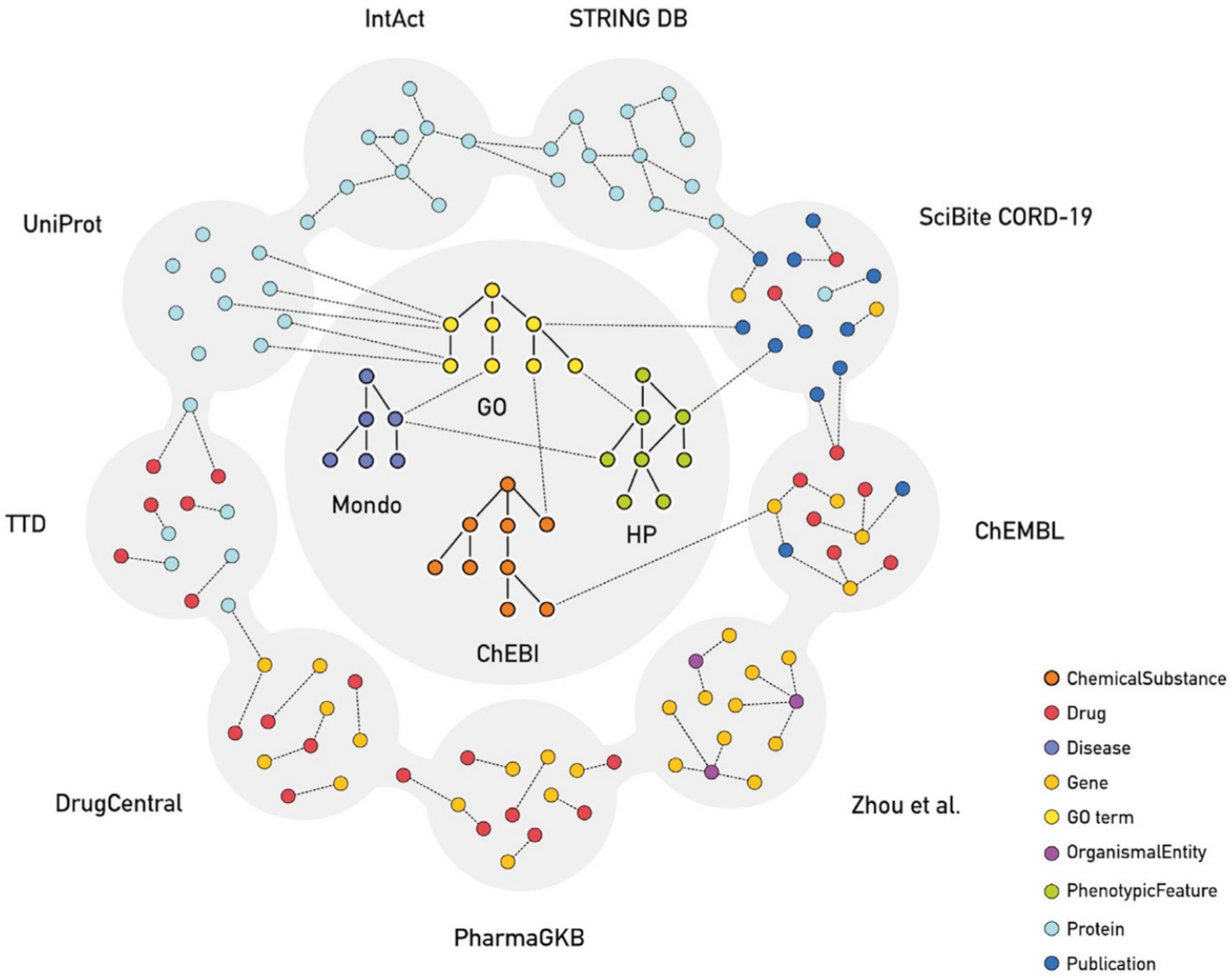
Using signals generated from FAERS and poison center reports, identify natural products with risks, generate hypotheses to explain the pharmacokinetic natural product-drug interaction and mechanism, and validate with in vitro and clinical studies.

Biomedical Knowledge Graphs

- Graph structure with nodes and edges
  - Nodes -> entities
  - Edges -> relationships

- Heterogeneous data sources
  - Ontologies (Gene Ontology, Pathway Ontology, MONDO Disease Ontology)
  - Drug databases (Drug Bank, Drug Central)
  - Literature

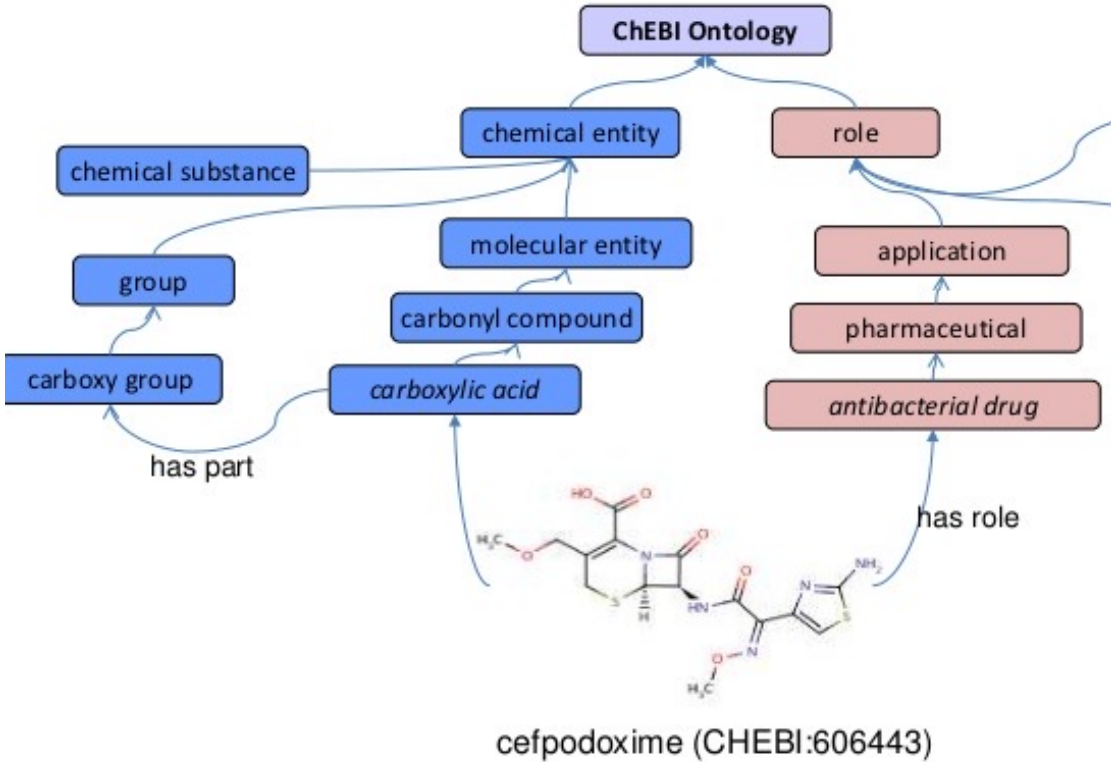
- Can be existing curated knowledge or new information



References: https://github.com/Knowledge-Graph-Hub/kg-covid-19

Biomedical Knowledge Graphs: Ontology

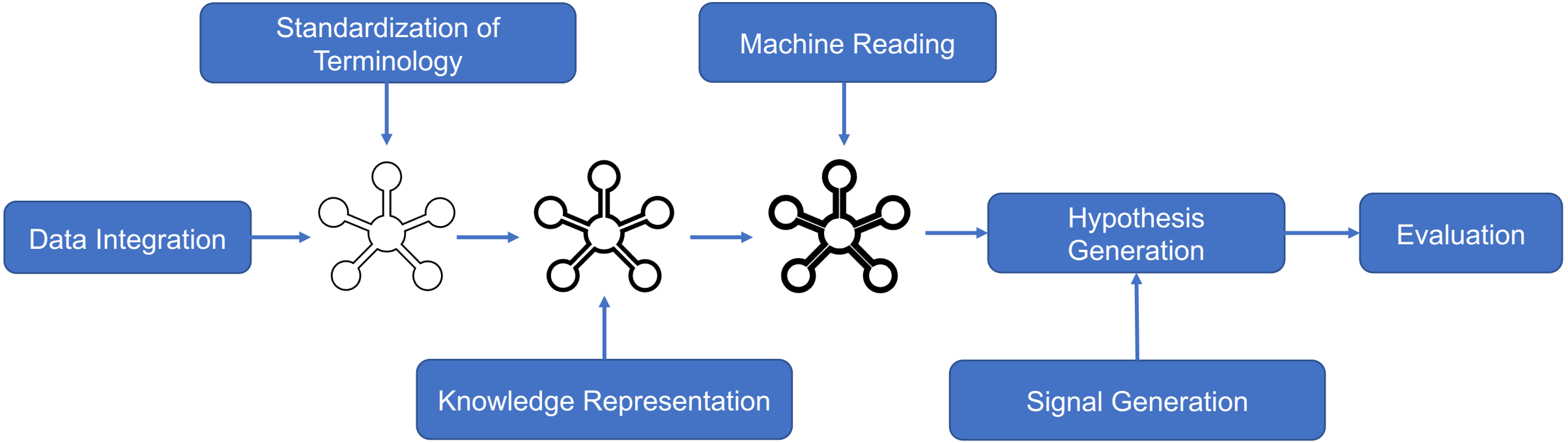
- Hierarchical representation of entities in a domain with formal relations defined between the entities.
- Examples:
  - Gene ontology
  - Disease ontology
  - Chemical Entities of Biological Interest (ChEBI) ontology



References: https://www.slideshare.net/jannahastings/from-chemicals-to-minds-integrated-ontologies-in-the-search-for-scientific-understanding

Methods

Goal: Use search algorithms and heuristics to find mechanistic pathways and hypotheses that explain pharmacokinetic natural product-drug interactions and adverse events.



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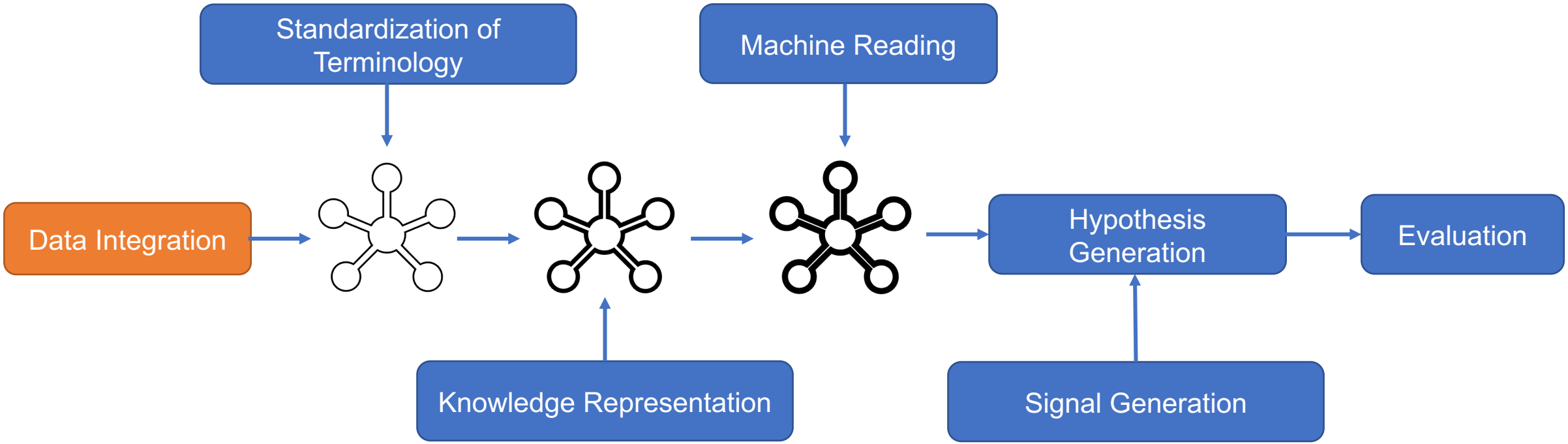
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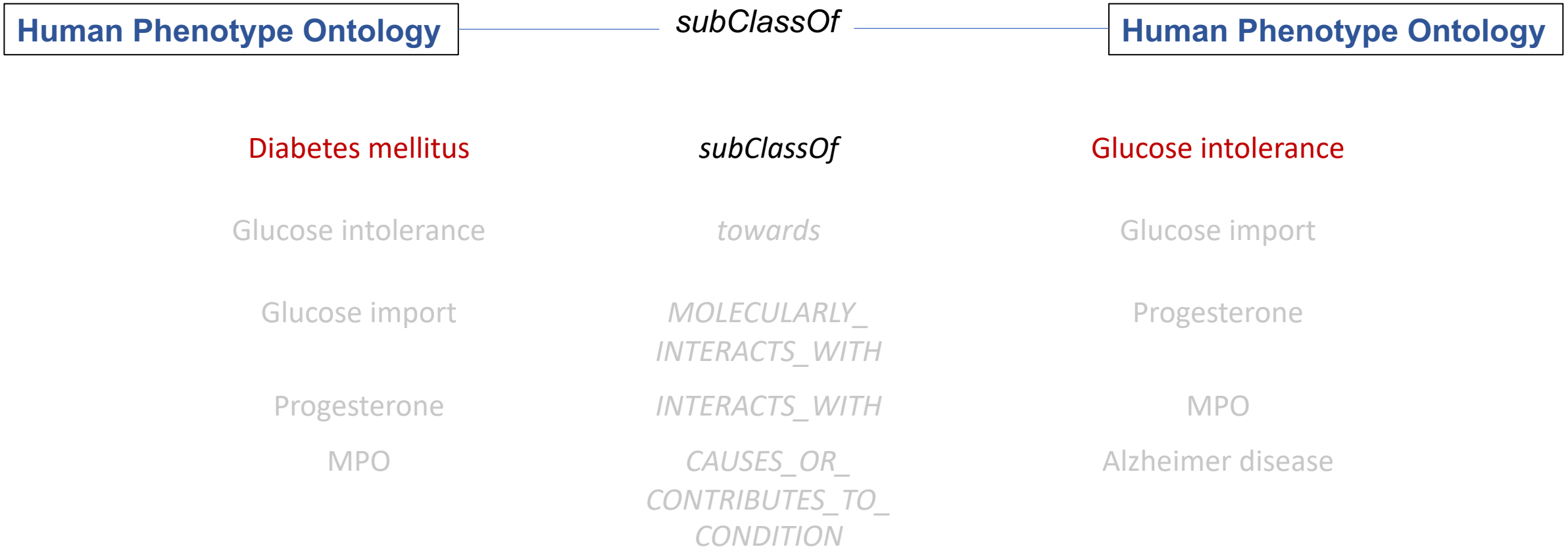
Semantic Integration of Data

Diabetes mellitus	*subClassOf*	Glucose intolerance
Glucose intolerance	*towards*	Glucose import
Glucose import	*MOLECULARLY_ INTERACTS_WITH*	Progesterone
Progesterone	*INTERACTS_WITH*	MPO
MPO	*CAUSES_OR_ CONTRIBUTES_TO_ CONDITION*	Alzheimer disease

Semantic Integration of Data



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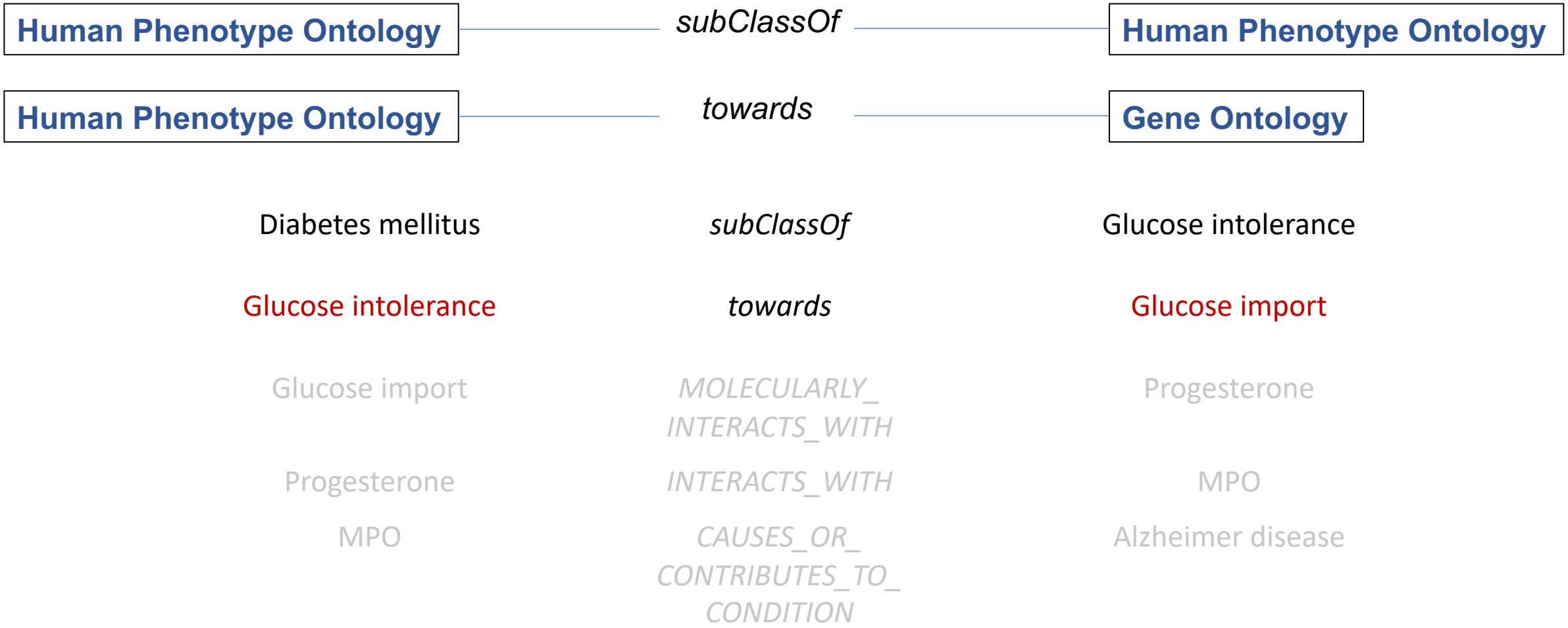

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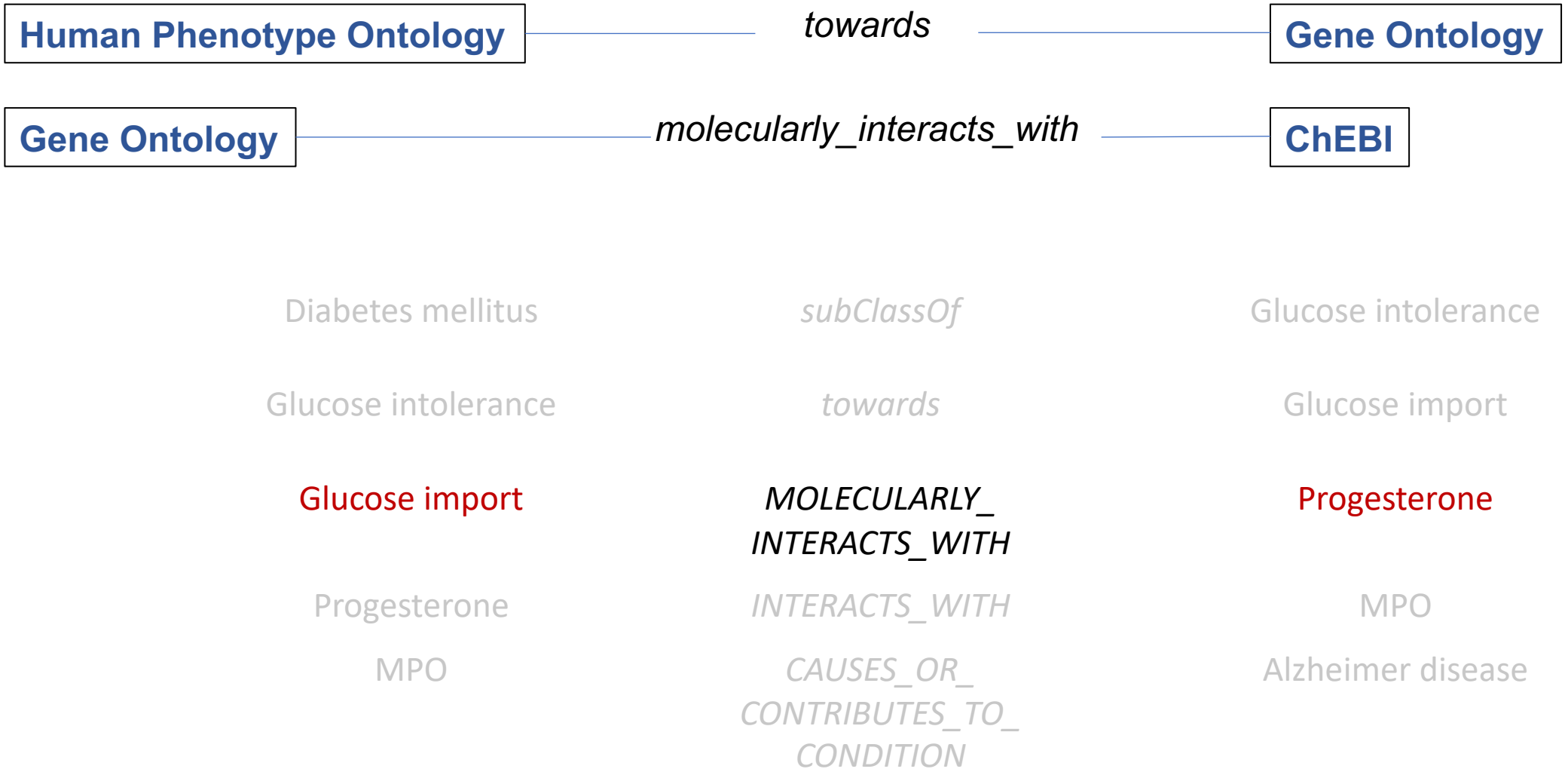

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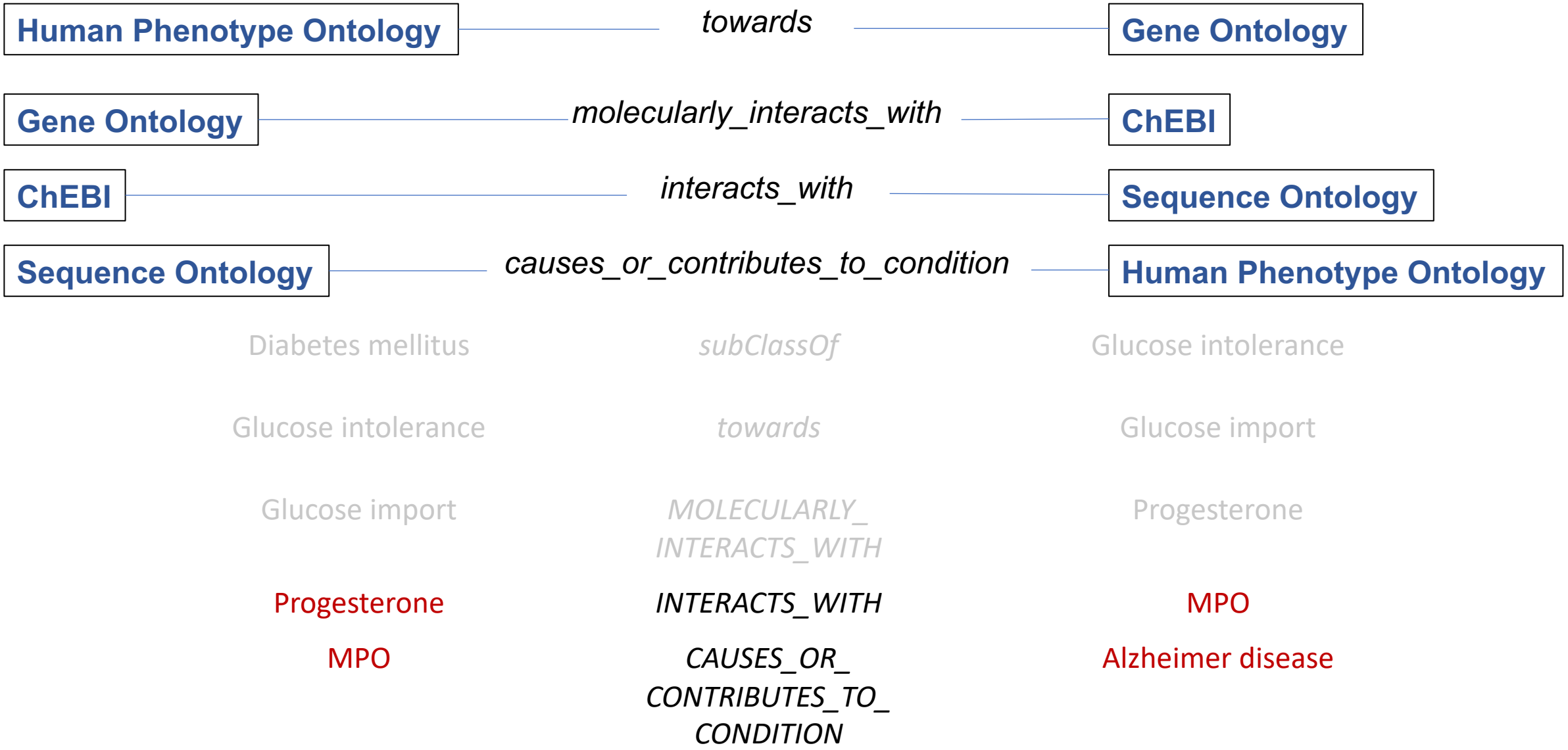
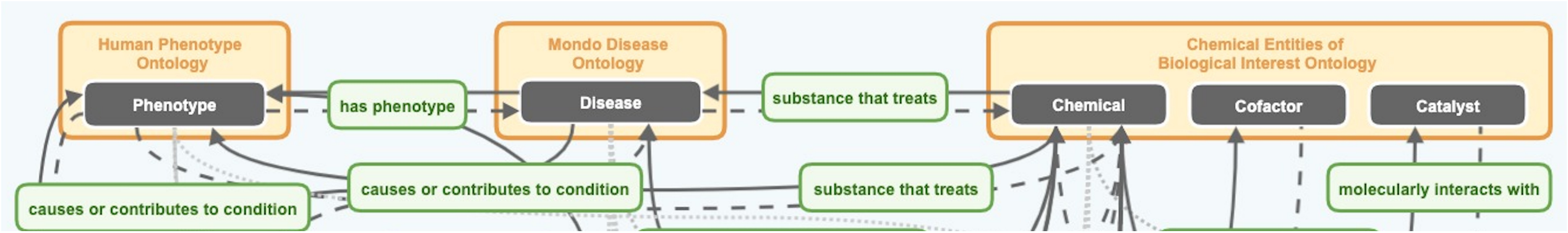


Semantic Integration of Data: PheKnowLator



References: https://github.com/callahantiff/PheKnowLator/wiki/v2.0.0

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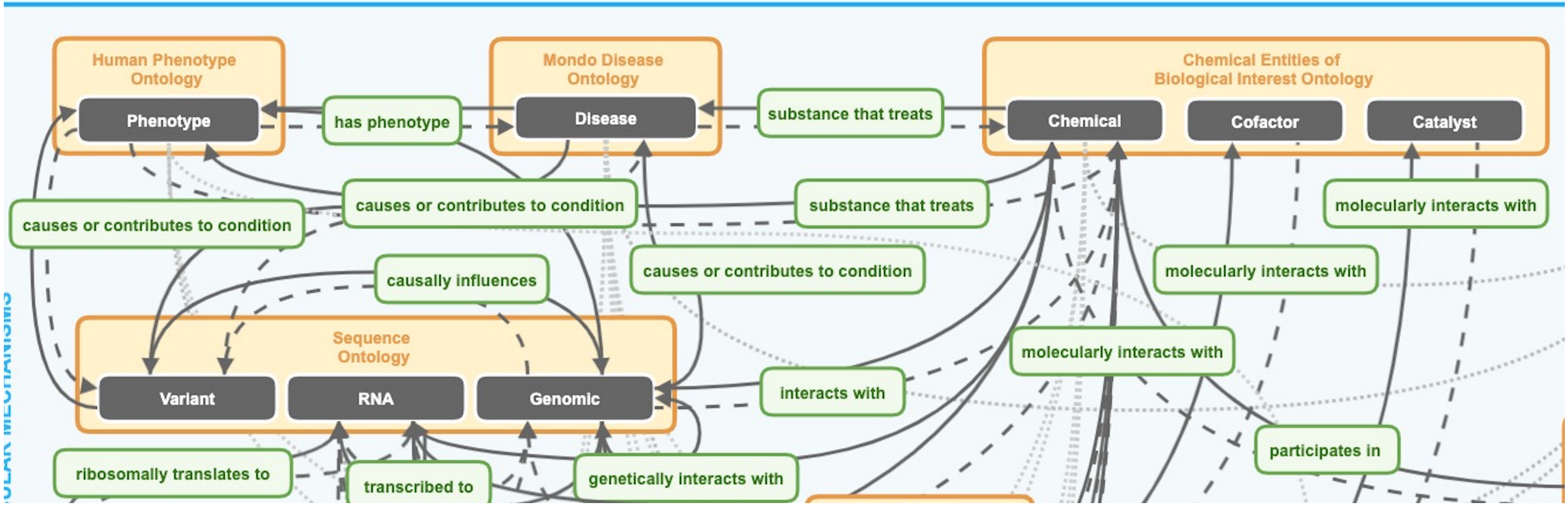

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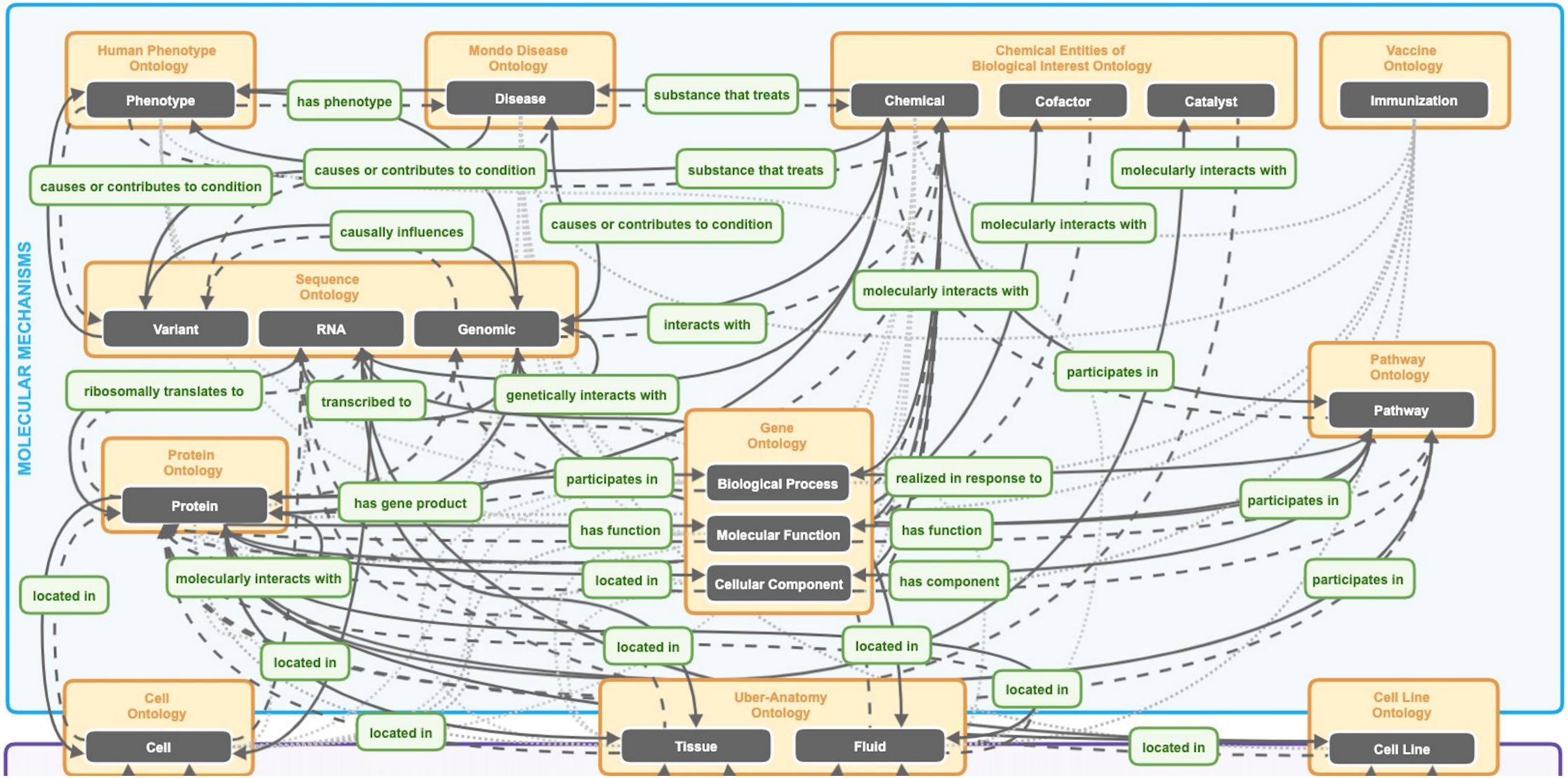

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Semantic Integration of Data

Data Sources

Cell Ontology

Cell Line Ontology

Chemical Entities of Biological Interest (ChEBI) Ontology

Gene Ontology (GO)

Human Phenotype Ontology (HPO)

Mondo Disease Ontology

Pathway Ontology

Protein Ontology

Relations Ontology (RO)

Sequence Ontology

Uber-Anatomy Ontology

Drug Bank

Drug Central

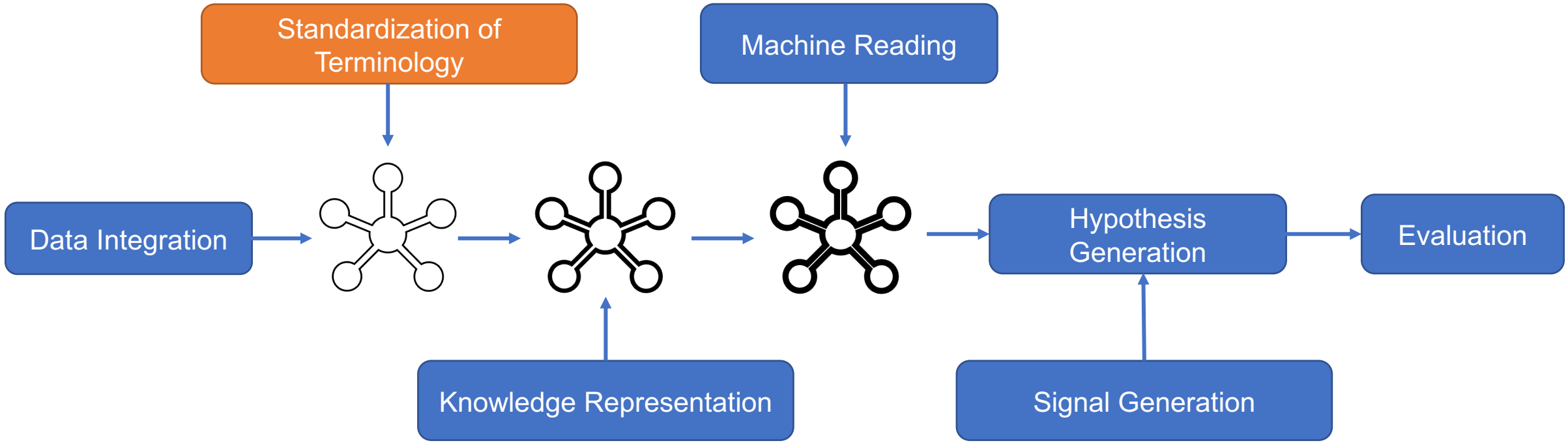
Ontology of Adverse Events (OAE)

Drug-Drug Interaction Evidence Ontology (DIDEO)

Current knowledge graph version

78,317,102 triples

Methods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Standardization of Terminology

Why standardization?

- Standard identifiers
- Interoperability
- Access to domain relevant information (genus, species, constituents, chemical characteristics)
- Comprehensive coverage of natural products
- Non-ambiguous names

Potential standardization data sources:

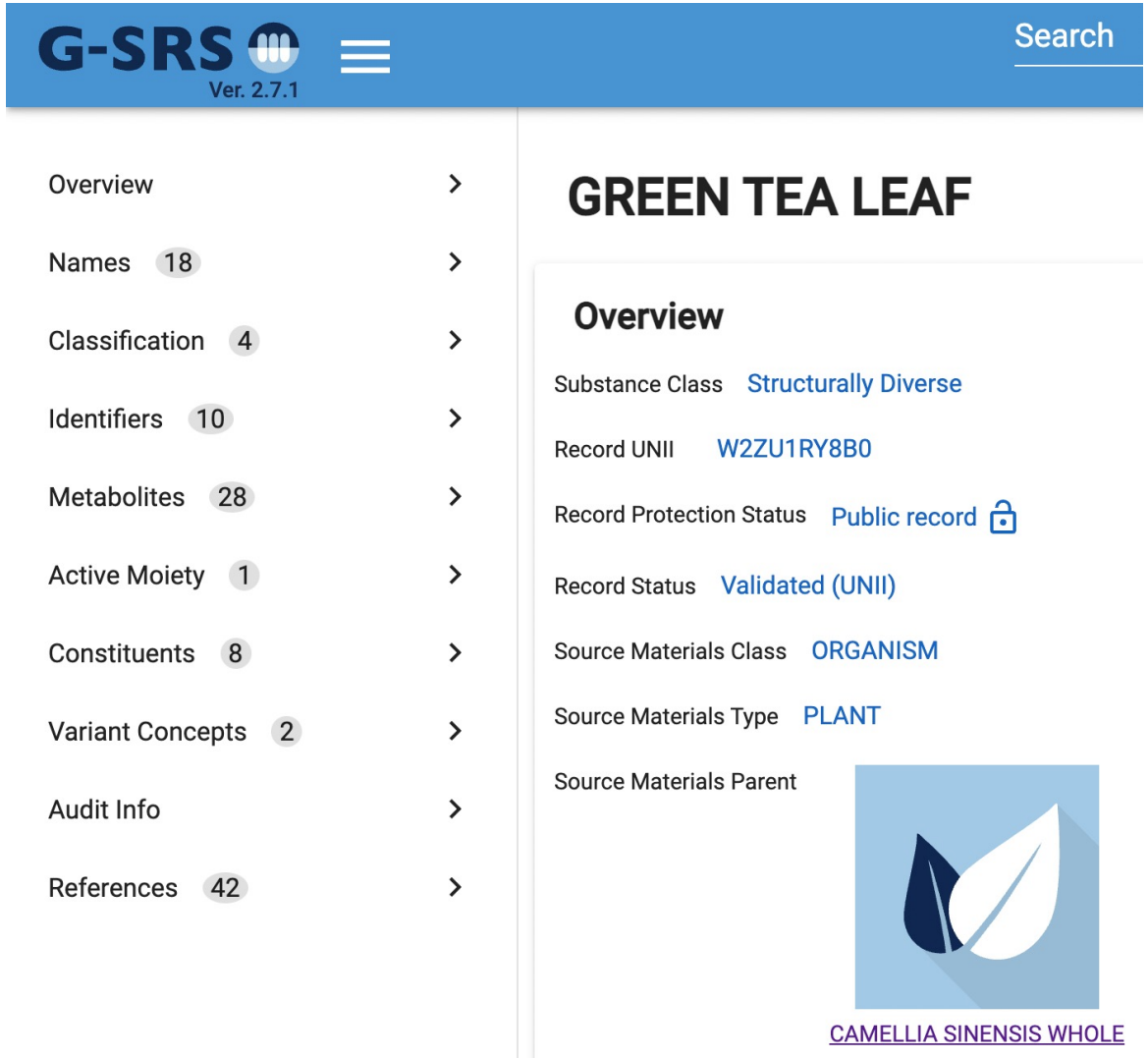
- **FDA Global Substance Registration System (G-SRS)**
- Dietary Supplement Label Database (DSLD)
- Licensed Natural Health Products Database (Canada)
- Unified Medical Language System (UMLS)
- Others (NDF-RT, RxNorm, Natural Medicines Database, RxNorm, MESH, SNOMED-CT)

Standardization of Terminology

Global Substance Registration System (G-SRS)

Goals of standardization with G-SRS:

- Create vocabulary of natural products to map “drugs” (user input strings) in FAERS to standard terminology
- Import natural products (and characteristics) into knowledge graph



Standardization of Terminology: G-SRS

Natural products with > 20 reports in FAERS since 2004

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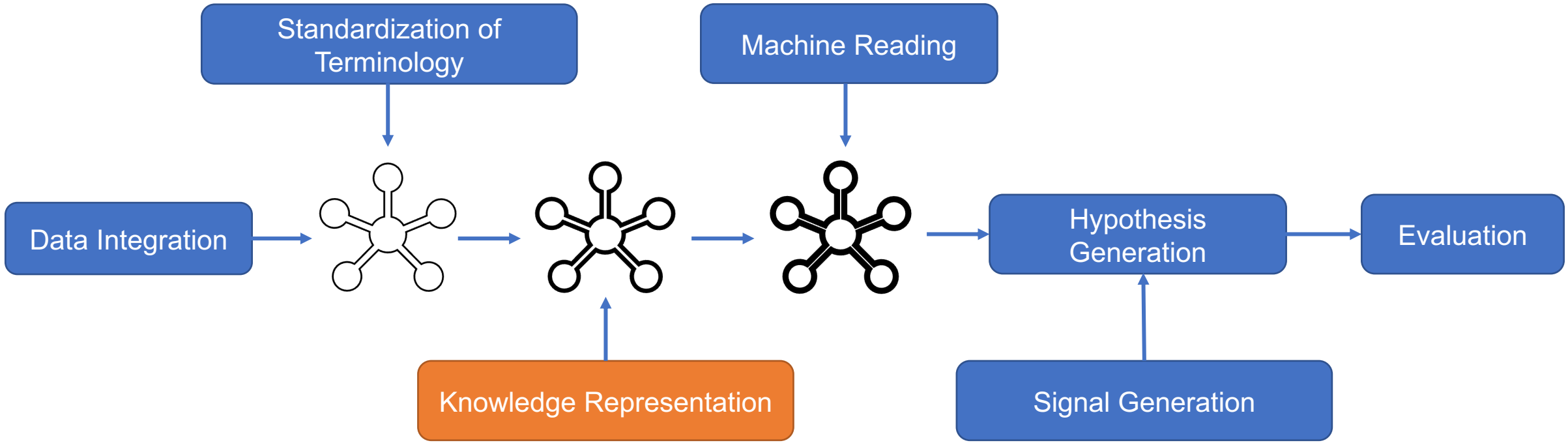
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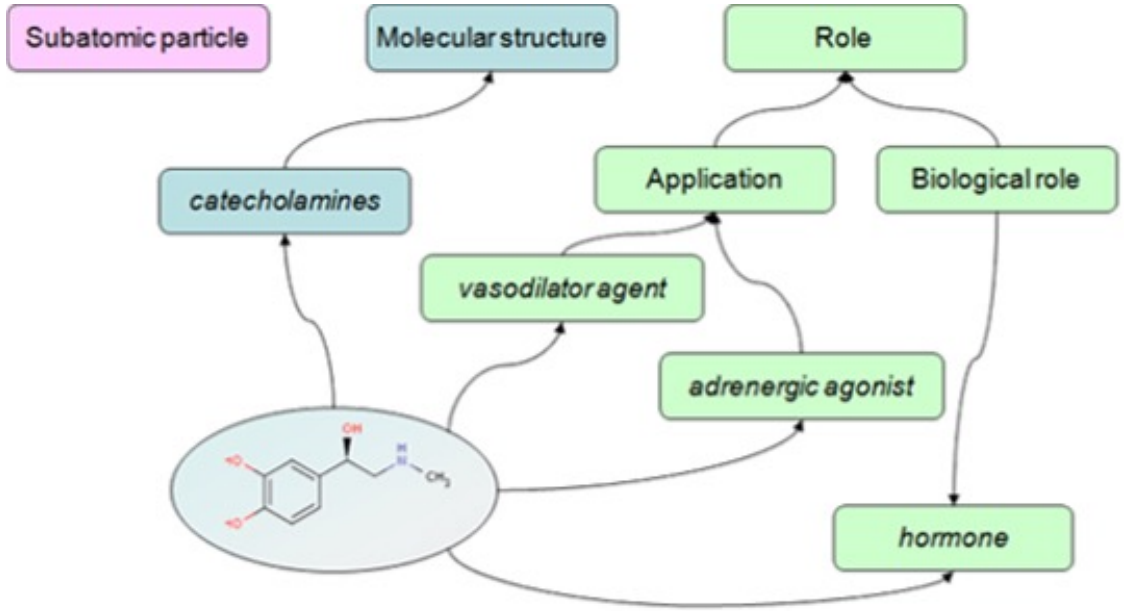
Knowledge Representation

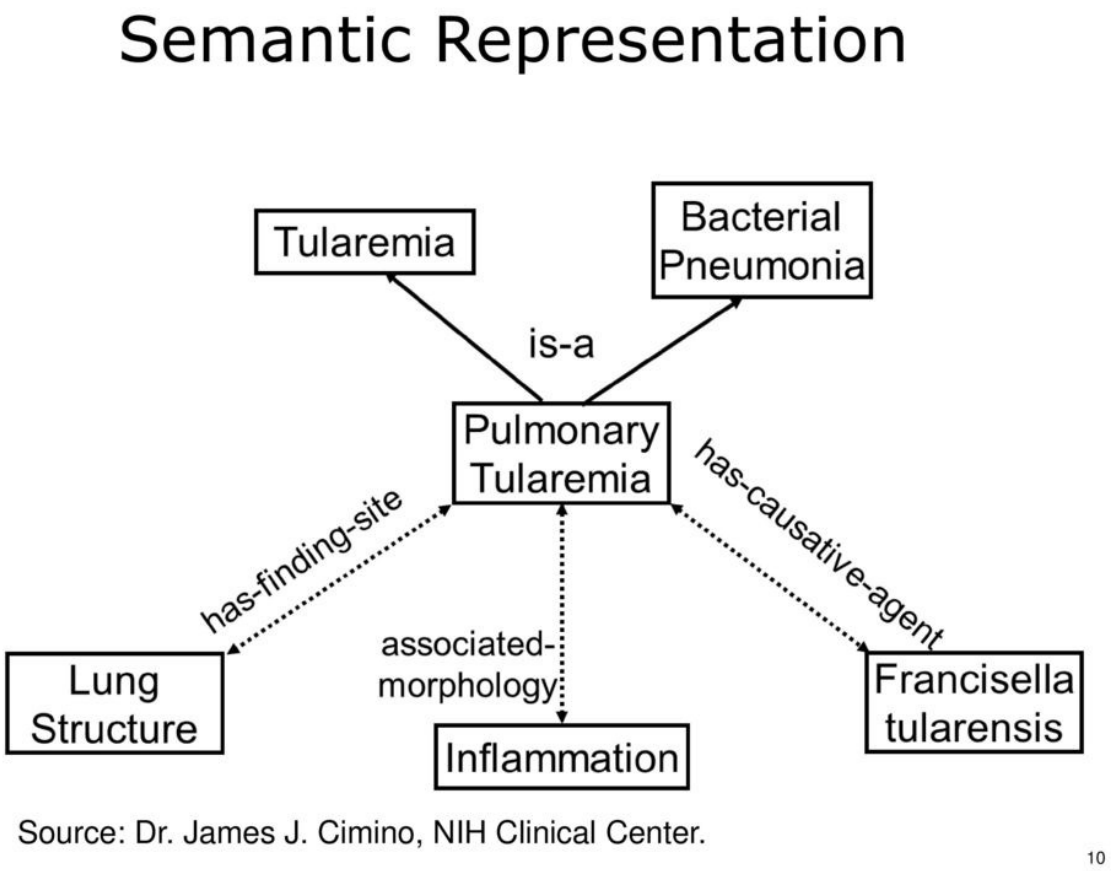
ChEBI: Chemical Entities of Biological Interest

- Dictionary of molecular entities
- Identifiers, names, synonyms, chemical characteristics
- “Relations” between entities – has_functional_parent, has_role, is_enantiomer_of
- Large number of drugs and chemicals
- Only some natural product constituents (mitragynine – kratom, catechin(s)– green tea)



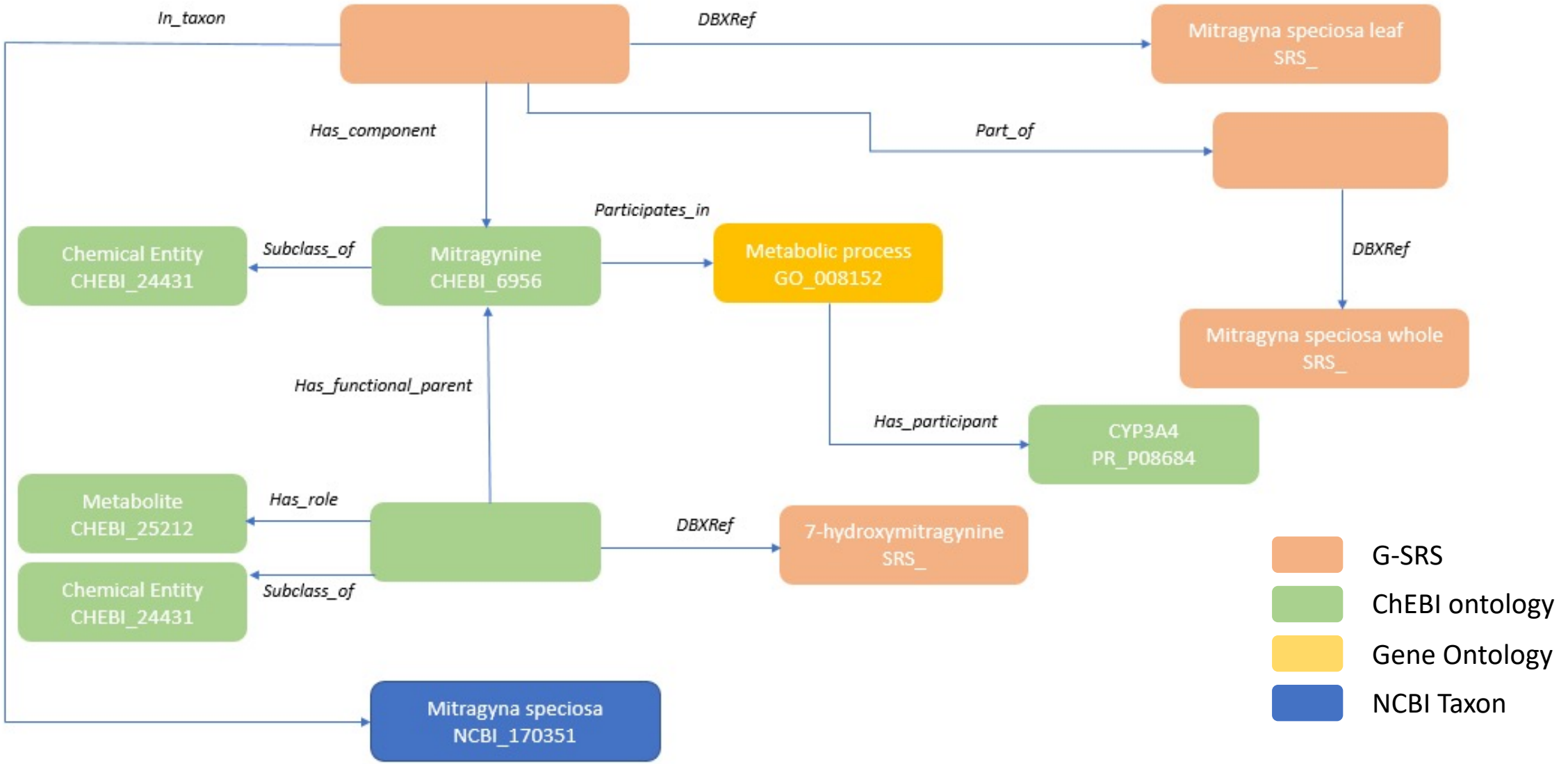
References: https://www.ebi.ac.uk/training/online/courses/chebi-the-online-chemical-dictionary-for-small-molecules/chebi-ontology/

Knowledge Representation



- Knowledge graph made of triples
  (subject-predicate-object)
- Goal: Extend the ChEBI ontology with natural product information from G-SRS and NaPDI Center
- Steps:
  - Build semantic representations
  - Generate ontology/web ontology language files
  - Merge into knowledge graph

Knowledge Representation



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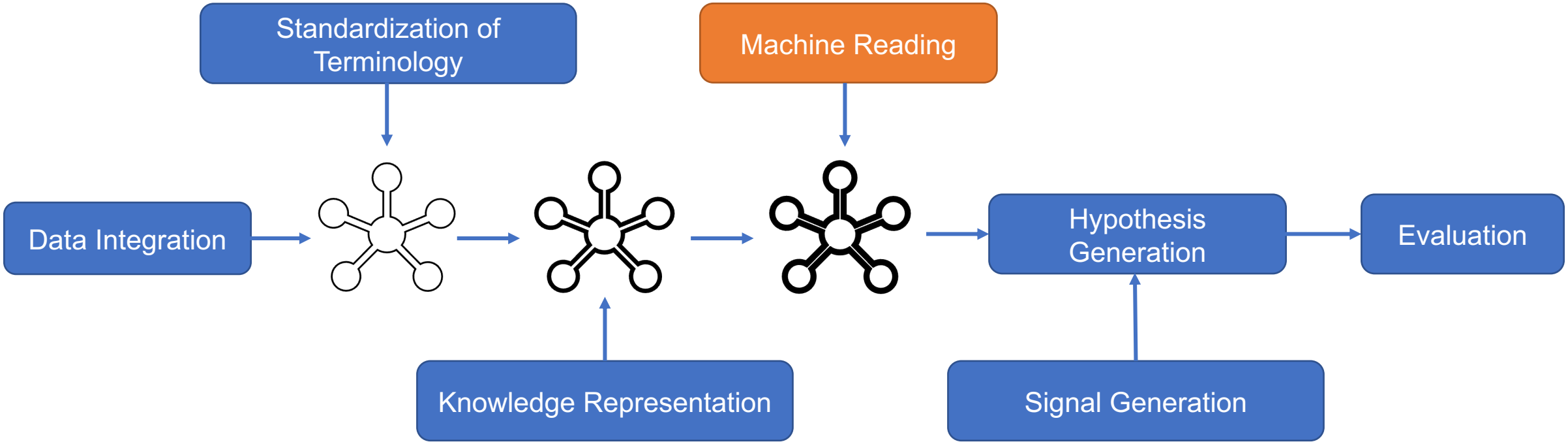
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Machine Reading

Challenge: Incomplete information in existing data sources

- No inhibition/interactions in other data sources (G-SRS, LNHPD, DSLD)
- Drug databases (Drug Bank, Drug Central – drug drug interaction gold standard) do not contain the NP constituents
- Research on natural products since 1900s
  - suggested hypothesis
  - animal models
  - clinical studies
  - observational reports

Thus, we use PubMed and SCOPUS indexed articles with mechanistic information about natural products and their constituents.

- Other sources:
  - Natural Medicines database (manually compiled from literature and systematic reviews)
  - CHEMBL (literature-based)

Machine Reading

- PubMed and SCOPUS indexed articles with mechanistic information about natural products and their constituents

- INDRA: Integrated Network and Dynamical Reasoning Assembler

- REACH: Reading and Assembling Contextual and Holistic Mechanisms from Text

- **Hypothesis: enhancing the KG to include literature related to the natural products will improve our ability to find mechanistic explanations for pharmacokinetic NPDIs and adverse events.**

- Extract INDRA statements as subject-predicate-object triples and merge into knowledge graph
  - Subject and object grounded in OBO ontologies
  - Belief scores (probabilistic)
  - Deduplication
  - Evidence-based

Machine Reading

Kratom results

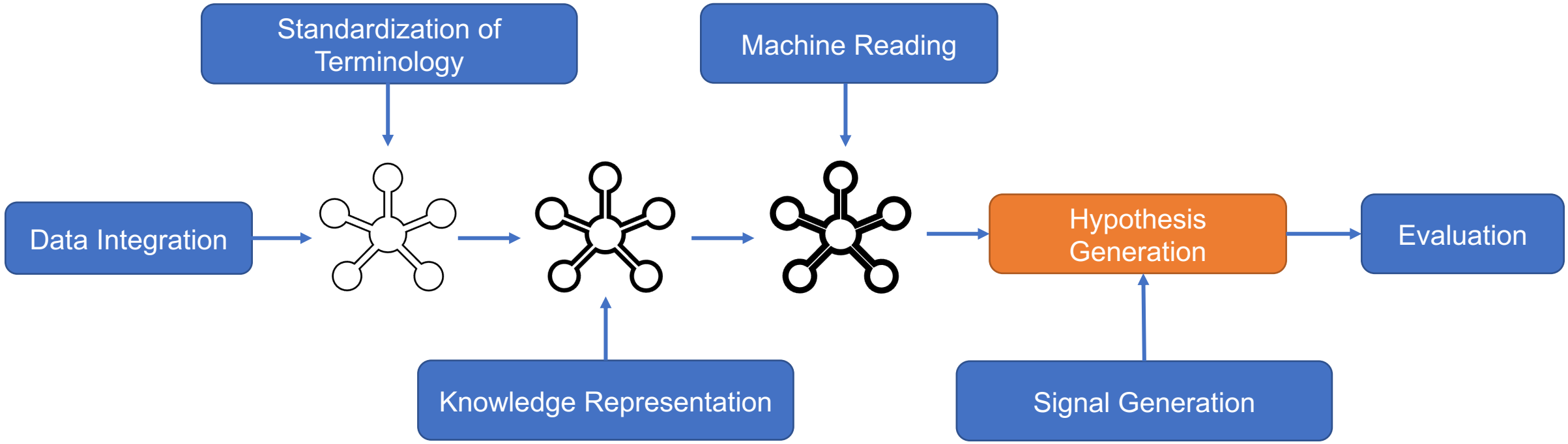
Subject	Predicate	Object	Sentence	Belief
Mitragynine	IncreaseAmount	CYP1A2	Mitragynine was found to induce mRNA and protein expression of CYP1A2.	0.65
Mitragynine	Inhibition	Quinidine	..mitragynine exhibited low permeability across the cell monolayer but inhibited digoxin transport, similar to quinidine.	0.65
Mitragynine	Inhibition	G_protein	In addition, mitragynine was also found to inhibit the hERG1a and GIRK (G protein-coupled inward rectifier potassium) channels in other heterologous expression systems50.	0.65
Mitragynine	Inhibition	STE6 (mapped from P-glycoprotein)	Mitragynine and 7-hydroxymitragynine inhibited P-glycoprotein with EC50 values….	0.65
Mitragynine	Inhibition	Kr (incorrect mapping)	Mitragynine and its analogues at low concentrations (IC50 ranging from 0.91 to 2.47¬μM) potently inhibited IKr in hiPSC-CMs.	0.95

Hypothesis Generation

Goal

Develop an automated hypothesis generation tool using biomedical knowledge graph that can explain

- mechanistic information about pharmacokinetic interactions
- pathways that lead to adverse events.



Hypothesis Generation

- NP signals generated from FAERS
- Identify nodes of interest in graph (natural products, enzymes, adverse events)
- Search algorithms
  - Simple paths between 2 nodes
  - Shortest paths
  - Bidirectional search
  - Embedded search (similarity-based)

Hypothesis Generation

Mitragynine (Kratom)

Seizures

PATH 1A:

Mitragynine *molecularly interacts with* long-chain fatty acid metabolic process
long-chain fatty acid metabolic process *molecularly interacts with* valproic acid
valproic acid *is_conjugate_acid_of* valproate

PATH 1B:

Valproate *is_conjugate_base_of* valproic acid
valproic acid *interacts with* TSC2
TSC2 *causes or contributes to condition* Seizures

Hypothesis Generation

Mitragynine (Kratom)

Pulmonary edema

PATH 2A:

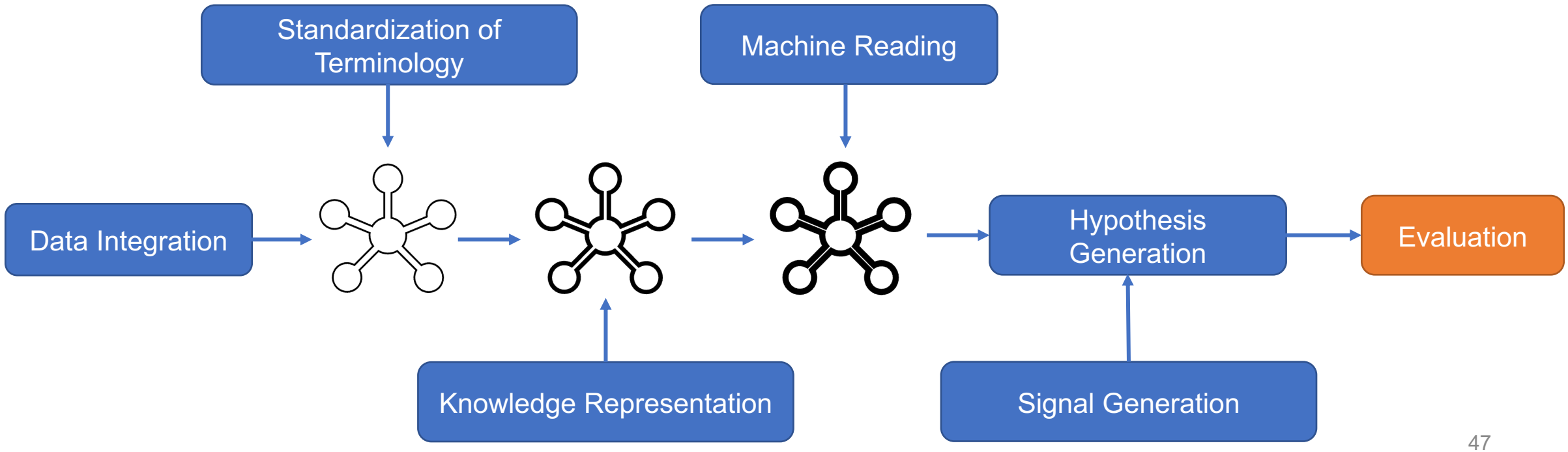
Mitragynine *molecularly interacts with* response to drug
response to drug *molecularly interacts with* diphenhydramine

PATH 2B:

diphenhydramine *molecularly interacts with* positive regulation of biological process
positive regulation of biological process *molecularly interacts with* aflatoxin B1
aflatoxin B1 *interacts with* GHRH
GHRH *causes or contributes to condition* Pulmonary edema

Evaluation

- Gold standard: clinical and in-vitro studies
- Time splicing
- Current NPs for evaluation: kratom, goldenseal, green tea, licorice, cinnamon



Future work and work in progress

- Include information for over 600 natural products of interest
- Signal generation from FAERS database and Pittsburgh poison center reports
- Embeddings for graph completion
- Improve machine reading for better entity recognition, full text extraction pipeline, heuristics to remove noise
- Semantic representation – automated extraction from data sources
- Knowledge graph searches heuristics and closure (transitive)
- Translation to lab/clinical once a strong NPDI is identified with potential mechanism

Thank you!

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Dr. Sandra Kane-Gill, School of Pharmacy

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PI: Dr. Mary Paine (Washington State University)

Discussion