TRANSLATOR

Funded by NIH's National Center for Advancing Translational Sciences

CDC get_creative() 'ARA'
Translator SEP2022 Relay Meeting
Ongoing Work

What drugs may treat Disease X?

Disease X = Rare Pulmonary Diseases

- primary ciliary dyskinesia (MONDO:0016575)
- cystic fibrosis (MONDO:0009061)
- idiopathic bronchiectasis (MONDO:0018956)
- lymphangioleiomyomatosis (MONDO:0011705)
- idiopathic pulmonary fibrosis (MONDO:0008345)

**MVP query list*

GitHub Repository

SMEs

- Dr. Michael Knowles, UNC Chapel Hill
- Dr. Margaret Leigh, UNC Chapel Hill

Cystic Fibrosis (CF) - Initial Use Case

Problem Statement

- CF is caused by genetic variants in *CFTR*
- CFTR modulators, which are relatively new, act to either correct CFTR trafficking to the plasma membrane (Class II genetic variants) or potentiate CFTR channel conductance (Class III and V genetic variants); these drugs have demonstrated remarkable improvement in lung function and quality of life among patients with CF and are estimated to be used in ~80% of patients with CF
- However, ~10% of patients with CF express Class I and IV genetic variants, for which CFTR modulators are ineffective
- In addition, a subset of patients expressing variants that are responsive to CFTR modulators either cannot tolerate them or are not responsive for other reasons such as irreversible lung damage

Translator Challenge Question

- Can Translator identify drugs for repurposing or targets for new drug development that may treat disease in those patients for whom CFTR modulators are ineffective or not tolerated?

Initial Results

Known drugs

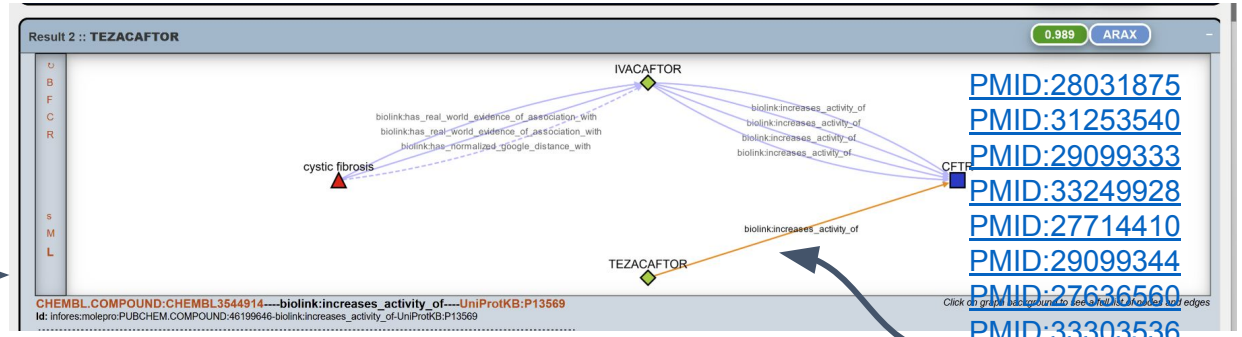
- Tezacaftor (CFTR potentiator)
- Rifaximin (antibacterial, SIBO in CF)
- Betamethasone (topical nasal steroid, nasal polyps in CF)

Possibly relevant drugs in clinical trials

- Letermovir (antiviral, trial on human cytomegalovirus in certain immunocompromised patients, but possibly relevant to CF)

Potentially interesting drugs

- 10-Substituted artemisinin analogue, (derived from the sweet wormwood plant *Artemisia annua*, which is used in traditional Chinese medicine)



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PMID:25083129
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PMID:32546431

Cytomegalovirus – an unrecognised potential contributor to cystic fibrosis disease progression?

Michael D. Parkins, Kathleen J. Ramos, Christopher H. Goss, Ranjani Somayaji
European Respiratory Journal 2019; **DOI:** 10.1183/13993003.01727-2018

Neural Regen Res. 2019 Sep; 14(9): 1494–1498.
doi: 10.4103/1673-5374.255960

PMCID: PMC6557089
PMID: 31089038

More than anti-malarial agents: therapeutic potential of artemisinins in neurodegeneration

Bing-Wen Lu,[1,2] Larry Baum,[3,4,5] Kwok-Fai So,[2,3,4,6] Kin Chiu, PhD,[2,3*] and Li-Ke Xie, MD[1,*]

SME Feedback on Initial Results

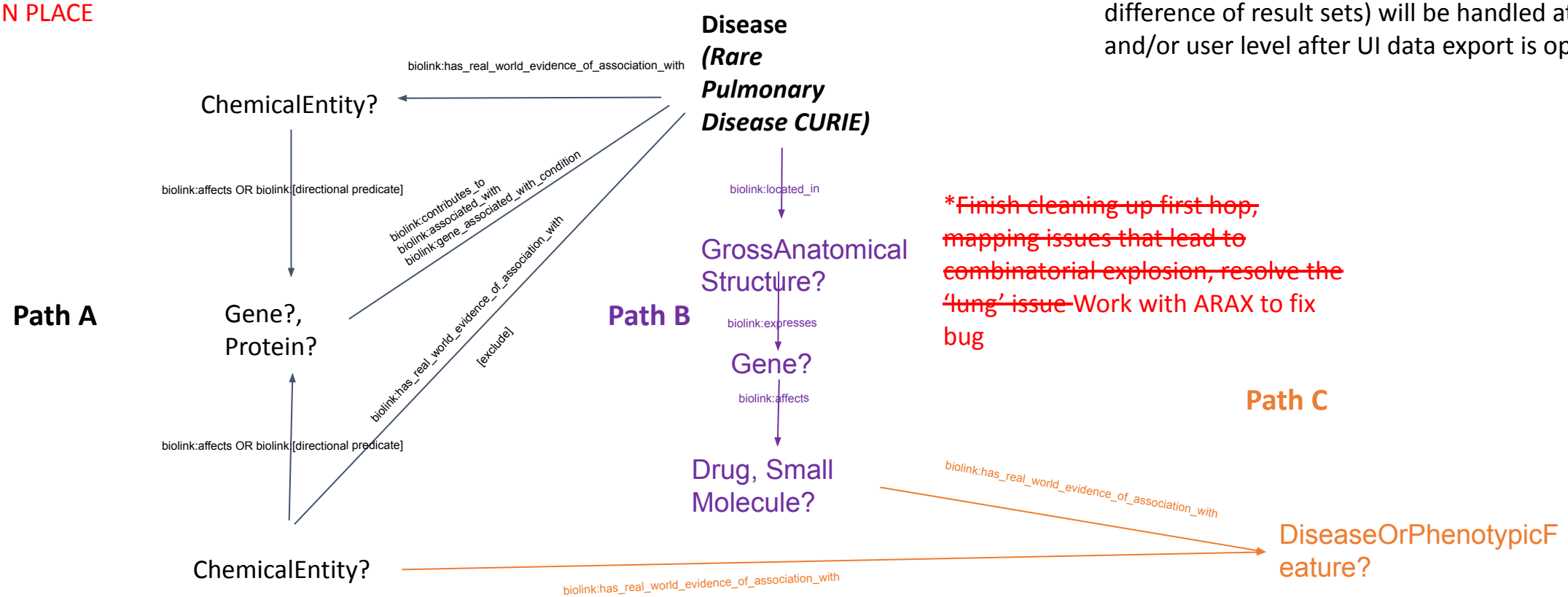
- Tezacaftor (CFTR potentiator) and betamethasone (topical nasal steroid, nasal polyps in CF) are highly used in patients with CF ✓ ✓ ✓
- Rifaximin (antibacterial, SIBO in CF) is occasionally used in patient with CF for treating SIBO ✓ ✓ ✓
- Letermovir might be used in patients with CF who occasionally have significant infection with CMV, although highly effective anti-viral agents are already available ✓
- 10-Substituted artemisinin analogue might be used in any disease process that has an inflammatory component, and CF has a significant inflammatory component in the lung, although CFTR modulators should decrease the need for anti-inflammatory treatments such as artemisinin analogues ✓

TCDC Curated ARA (CARA): Current Workflow

- *What drugs may treat rare pulmonary disease?*

*Add exclude edge for first hop (biolink:EnvironmentalExposure) to remove ICEES KG chemical exposures such as acetaldehyde, benzene, etc. - ~~ticket posted to ICEES KG repo, fix underway~~ ICEES FIX IN PLACE

*Exclude/compare functionality moved from O&W to TRAPI; lightweight operations (union, intersection, difference of result sets) will be handled at the UI level and/or user level after UI data export is operational.



*~~Finish cleaning up first hop, mapping issues that lead to combinatorial explosion, resolve the 'lung' issue~~ Work with ARAX to fix bug

[Path A validation test of [exclude] edge + RWE for ChemicalEntity not in first hop of Path A]

*~~Update and test TRAPI query for Path C after refinements are made to Paths A and B~~ - Hold off on Path C until CARA up and running

Clinical Evidence to Support O&O

Task: Create a list of concrete, immediately actionable approaches for incorporating clinical evidence into O&O

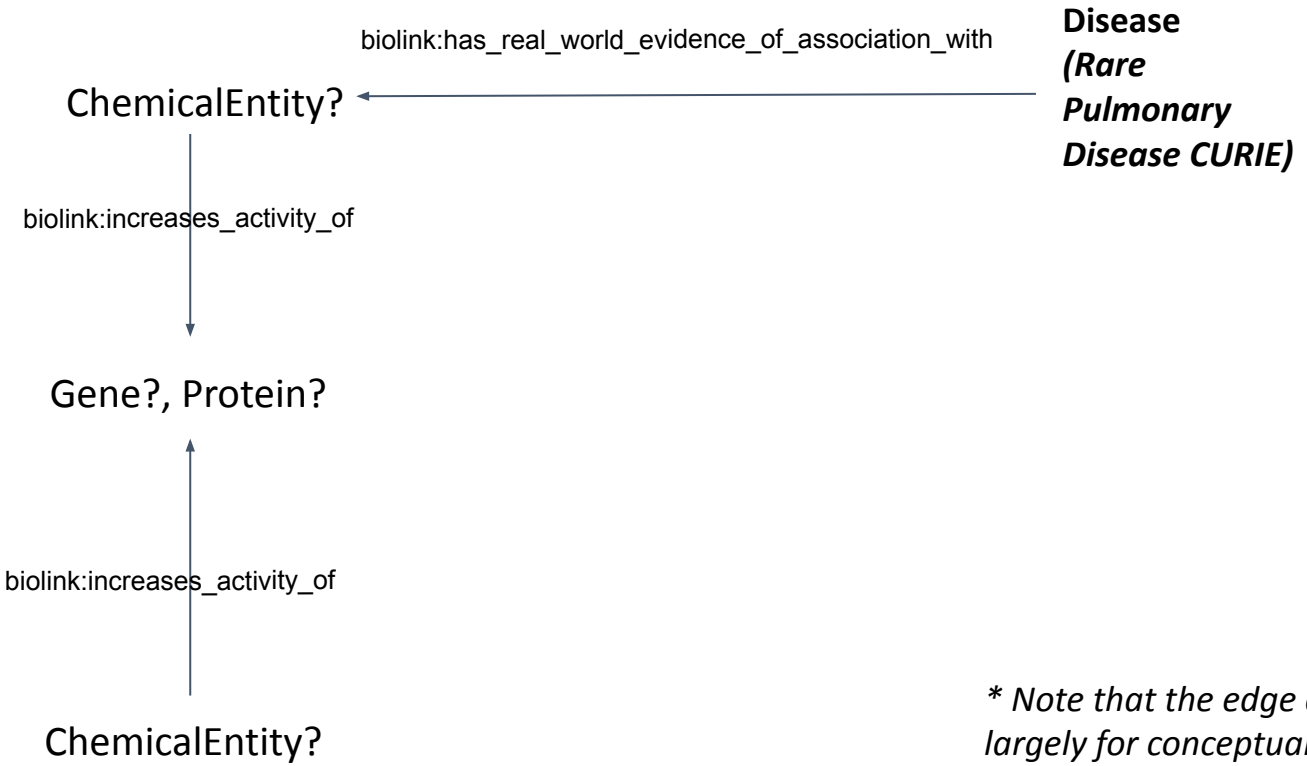
- One-hop clinical support for relative safety of candidate drugs
    - Use clinical edge attributes to determine if a candidate drug is actually administered to patients in the real world, regardless of indication
        - Example: if a clinical edge exists to support an identified relationship between disease X and drug Y, then there is evidence that at least one healthcare provider believed the drug was safe enough to be prescribed for a patient(s), regardless of the indication; if multiple clinical edges exist, especially in data derived from multiple healthcare systems, then that increases the evidence in support of the safety of a drug
- One-hop clinical support for inferred answers: threshold for the “known” and “unknown”
    - Use clinical edge attributes to filter out both “known” and “novel” answers
        - Example: high co-occurrence counts could be used to set a threshold and filter results for “known” answers; likewise, low co-occurrence counts could be used to set a threshold for potentially “novel” answers
- One-hop clinical support for weighting literature-based scores: weighting clinical evidence vs research literature evidence
    - Use clinical edge attributes to weight research literature evidence
        - Example: *P* values (or specified α) could be factored into PubMed-based scores
- Clinical support for grouping answers: RWE
    - Use clinical predicate(s) to group answers
        - Example: add the RWE clinical predicate (and any others) as a ‘decoration’ to the meta-KG so ARAs can select clinical KPs for grouping answers

Extra Slides

Translator get_creative() mode

What drugs may treat Disease X?

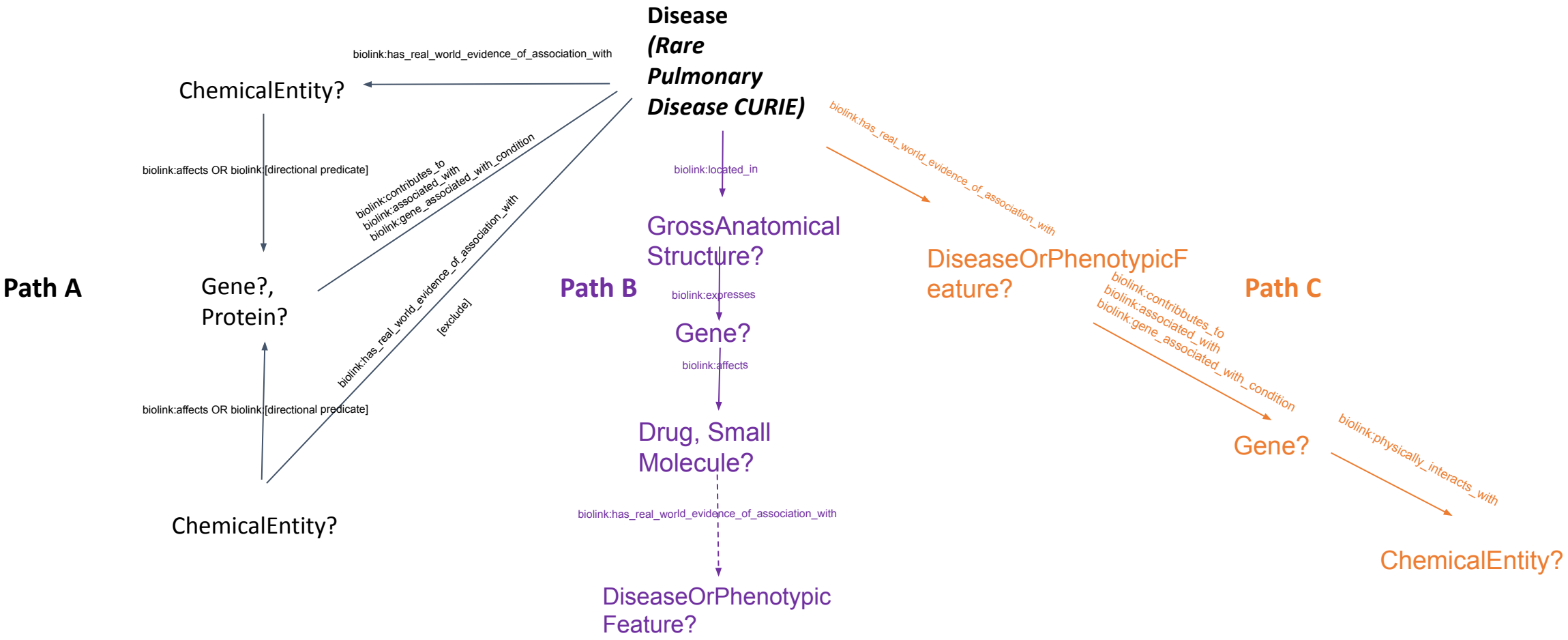
CDC get_creative() ‘ARA’ - Initial Workflow



** Note that the edge directionality/arrows are largely for conceptual purposes*

CDC get_creative() ‘ARA’: Current Workflow

- Specialized to run curated, SME-informed workflows
- Potential to serve as a general model for committees/WGs/teams to stand up their own get_creative() ‘ARA’



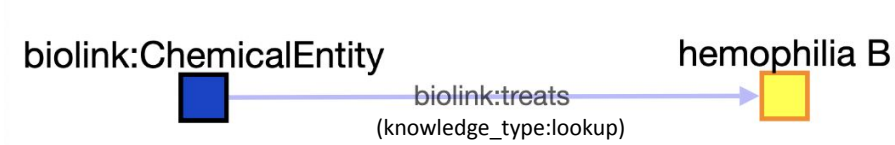
CDC get_creative() ‘ARA’: Next Steps

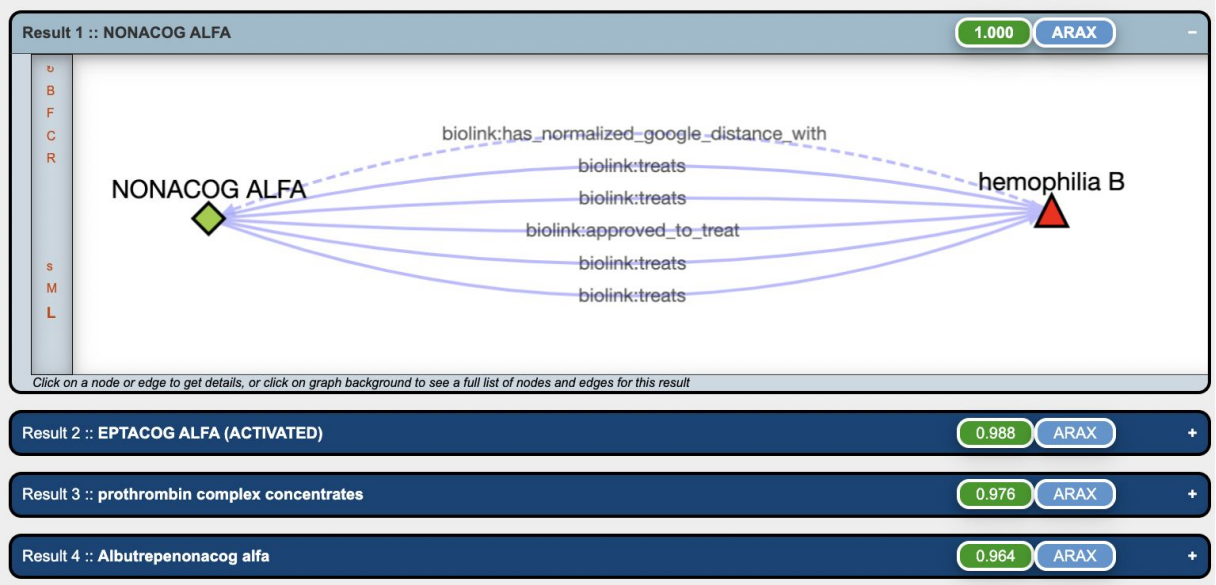
- TBD
- Standup call?
- November QotM?

https://github.com/NCATSTranslator/OperationsAndWorkflows/tree/main/docs

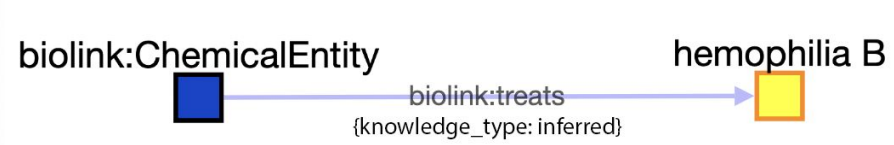
get_creative() vs lookup

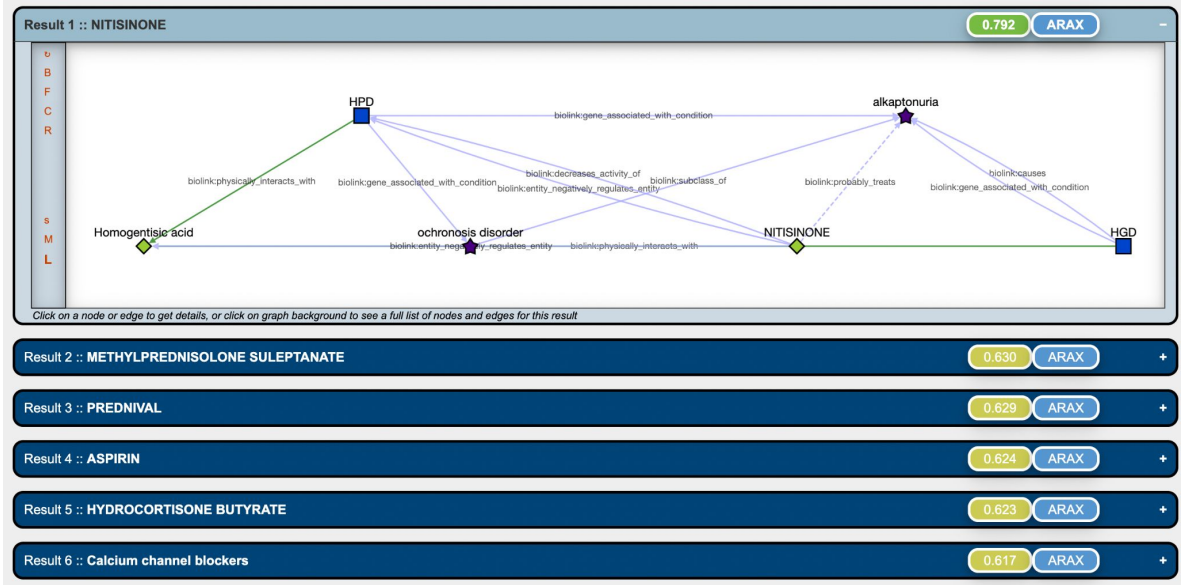
TRAPI lookups:





TRAPI creative:





Slides 7-8 adapted from slides provided by David K.

get_creative() vs operations/workflow

Operations and Workflow (O/W): Extension to TRAPI to expose ARA ***prescribed*** functionality beyond lookups

- ARS invokes workflow runner

Creative lookup: indicates inference is desired in an ***unprescribed*** fashion

- ARAs implement

TRAPI operations/workflow:

```
{"message": {
      "query_graph": {
         "nodes": {
            "n1": { "ids": [ "MONDO:12345" ]},
            "n0": { "categories":[ "biolink:ChemicalEntity" ] }
         },
         "edges": {
            "e0": { "subject": "n0",  "object": "n1", “predicates”:[“biolink:treats”] }
         }
      }
   },
“Workflow”:[
   “id”:”lookup,
   “id”:”overlay_compute_ngd”, “parameters”:{“qnode_keys”:[“n0”, “n1”], “virtual_relation_label”:”NGD1”},
   “Id”:”filter_results_top_n”, “parameters”:{“max_results”: 10}]
}
```

TRAPI get_creative():

```
{"message": {
      "query_graph": {
         "nodes": {
            "n1": { "ids": [ "MONDO:12345" ]},
            "n0": { "categories":[ "biolink:ChemicalEntity" ] }
         },
         "edges": {
            "e0": { "subject": "n0",  "object": "n1", “predicates”:[“biolink:treats”],
“knowledge_type”:”inferred”}
         }
      }
   }
}
```

Post-relay Plan and Action Items, updated 06.22.2022

Continue developing get_creative() workflow; this includes: (1) implementing and testing new workflow operations; (2) invoking clinical KPs; (3) invoking new services (e.g., CHP's gene-tissue index); (4) evaluating approaches for grouping/binning answers; and (5) evaluating the quality of answers and ranking, guided by SME input

Homework assignments:

1. Use David's example query as training example of how to write TRAPI queries with workflows/operations [Andy, Kara, Bill, others]
2. Develop new Multi-omics EHR Risk Provider predictions for target rare pulmonary diseases [Basazin]
3. Add additional evidence, ranking/grouping support from Text Mining Provider [Bill]
4. Refine existing queries, evaluate answers, follow-up with SMEs [Kara]
5. Explore queries that leverage CHP's tissue-gene index [Greg]
6. Refine CF queries - target modulator-resistant CFTR variants, link CF to irreversible lung damage - consider in context of (4) and (5) [Kara, Greg, others]
7. Test queries for other rare pulmonary diseases - continue focus on CF for now
8. Apart from get_creative() in the context of *"what drugs may treat disease X?"*, identify additional opportunities for the CDC to partner with other Translator efforts [All]

*See UI Team's list of diseases for MVP (Kara requested clarification on comment box suggestion on 06.23.2022)

Visualizing the drug target landscape: ranking/grouping/binning results

A: High risk repurposing opportunities

B: Some druggable opportunities, high false-positive rates expected

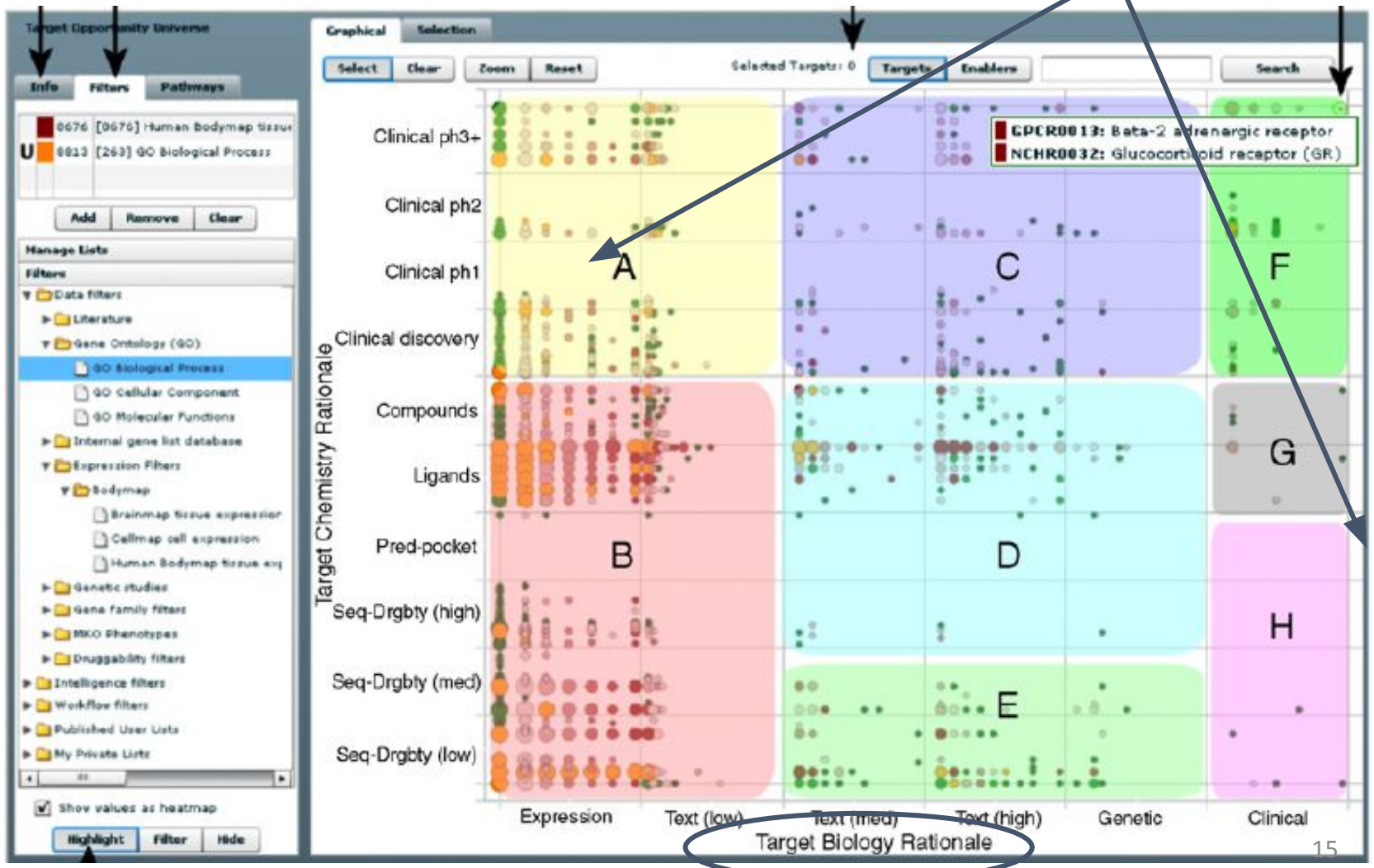
C: Compound repurposing opportunities

D: Novel chemical applications

E: Opportunities for biotherapeutics

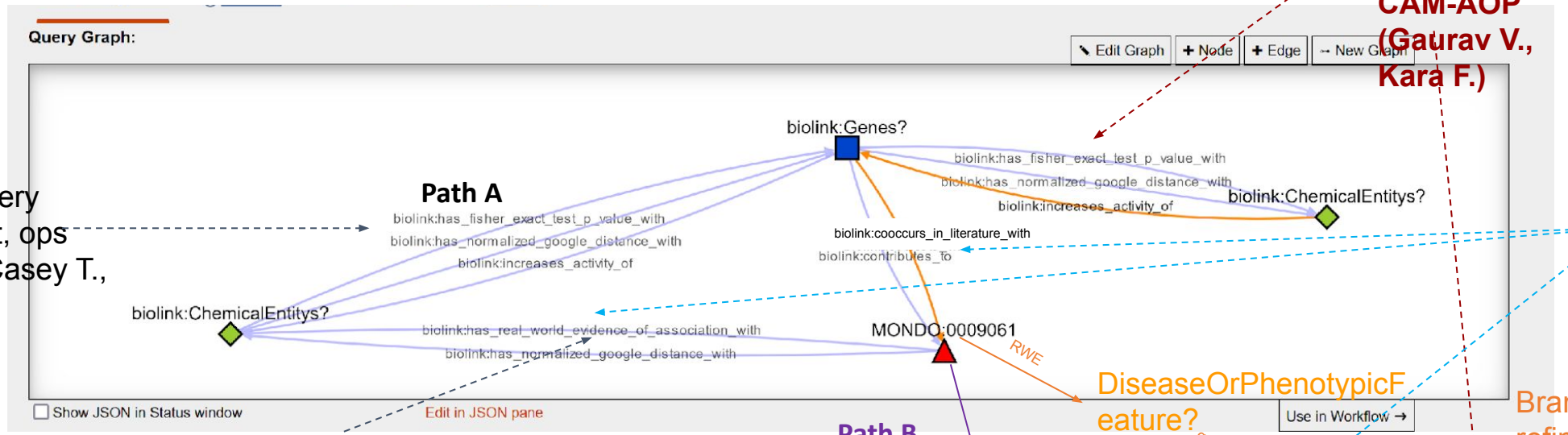
F: Competitor activity, pre-indicated drugs

G, H: Competitor activity, likely in the pipeline of some pharmaceutical manufacturer



Summary of Progress to Date

ARAX get_creative() query structure: What drugs may treat rare pulmonary disease?



Branch query refinement, ops (Kara F., Casey T., David K.)

COHD, ICEES-PCD (Kara F., Casey T.), Multiomics EHR Risk Provider to be added (Basa B.)

Edge support from CAM-AOP (Gaurav V., Kara F.)

Edge support from Text Miner (Bill B.)

Path B

Tissue?

Branch CHP query refinement, ops (Greg H.)

Gene?

Edge support from CAM-AOP (Gaurav V., Kara F.)

Drug, Small Molecule?

biolink:has_real_world_evidence_of_association_with

DiseaseOrPhenotypic Feature?

Path C

gene_associated_with_condition

Gene?

physically_interacts_with

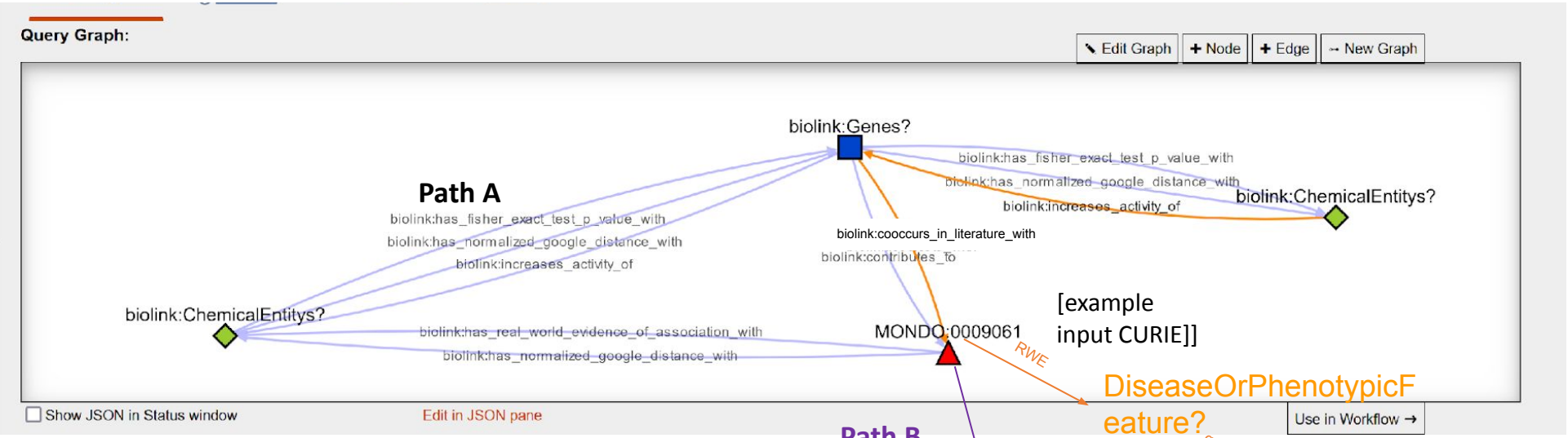
ChemicalEntity?

Branch query refinement, ops (Kara F., Casey T., David K.)

https://github.com/NCATSTranslator/Clinical-Data-Committee-Tracking-Voting/tree/main/GetCreative()_DrugDiscoveryRepurposing_RarePulmonaryDisease/June2022Relay

CDC get_creative() workflow

ARAX get_creative() query structure: What drugs may treat rare pulmonary disease?



Path B

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biolink:has_real_world_evidence_of_association_with

DiseaseOrPhenotypic Feature?

Path C

gene_associated_with_condition

Gene?

physically_interacts_with

ChemicalEntity?

***Note that the finalized TRAPI queries for each path may include slightly different nodes and/or predicates than those listed here**

Three-hop from Casey: https://arax.ncats.io/?r=54352

First five answers:

Ruxolitinib is **used to treat intermediate or high-risk myelofibrosis**, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Sorafenib (rINN), marketed as Nexavar by Bayer, is a drug approved for the treatment of advanced renal cell carcinoma (primary kidney cancer). It has also received "Fast Track" designation by the FDA for the treatment of advanced hepatocellular carcinoma (primary liver cancer), and has since performed well in Phase III trials.

Tofacitinib, sold under the brand Xeljanz among others, is a medication used to treat rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.

Neratinib, sold under the brand name Nerlynx, is a tyrosine kinase inhibitor anti-cancer medication used for the treatment of breast cancer.

A quinazoline derivative and ANTINEOPLASTIC AGENT that functions as a PROTEIN KINASE INHIBITOR for EGFR associated tyrosine kinase. It is used in the treatment of NON-SMALL CELL LUNG CANCER.

Last five answers:

Carboplatin belongs to the group of medicines known as alkylating agents. It is **used to treat cancer of the ovaries**.

Estramustine phosphate sodium (estramustine phosphate), a unique antitumour agent, is selectively taken up by prostate cells and exerts antineoplastic effects by interfering with microtubule of dynamics and by reducing plasma levels of testosterone.

Teniposide is a semisynthetic derivative of podophyllotoxin with antineoplastic activity.

A seasonally-specific component of the influenza vaccine.

Peginterferon beta-1a', sold under the brand name Plegridy, is medication used to treat multiple sclerosis.

Considerations:

1. Remove NGD?
2. Increase # answers (or is 100 real?)
3. Restrict to Gene (not Gene, Protein)?