ErbB signaling – an academic use case

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Open PHACTS Community Workshop

The 'Researchathon'

- 18 scientists from 8 academic institutions and 2 EFPIA companies
- Aims:
    - Identification of use-cases
    - Evaluation of data set and API call requirements

- Use-cases:
    - Comparison of existing public and proprietary pharmacology data for DRD2
    - Compounds active against targets in the ErbB signalling pathway and their disease relevance
    - Broadening the therapeutic opportunities from the Vitamin D pathway

- Paper submitted

Compounds active against targets in the ErbB signalling pathway and their disease relevance

- ❖ Epidermal growth factor receptors (ErbB):
  ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4
- ❖ Different dimers activate different downstream signalling pathways
- ❖ Insufficient ErbB signalling: associated with the development of neurodegenerative diseases (e.g. multiple sclerosis and Alzheimer's disease)
- ❖ Excessive ErbB signalling: associated with cancer

- ❖ Aims:
  - – Visualisation of pharmacology data available for targets in the pathway
  - – Comparison of activity profiles for compounds with known activity against cancer or neurodegenerative diseases
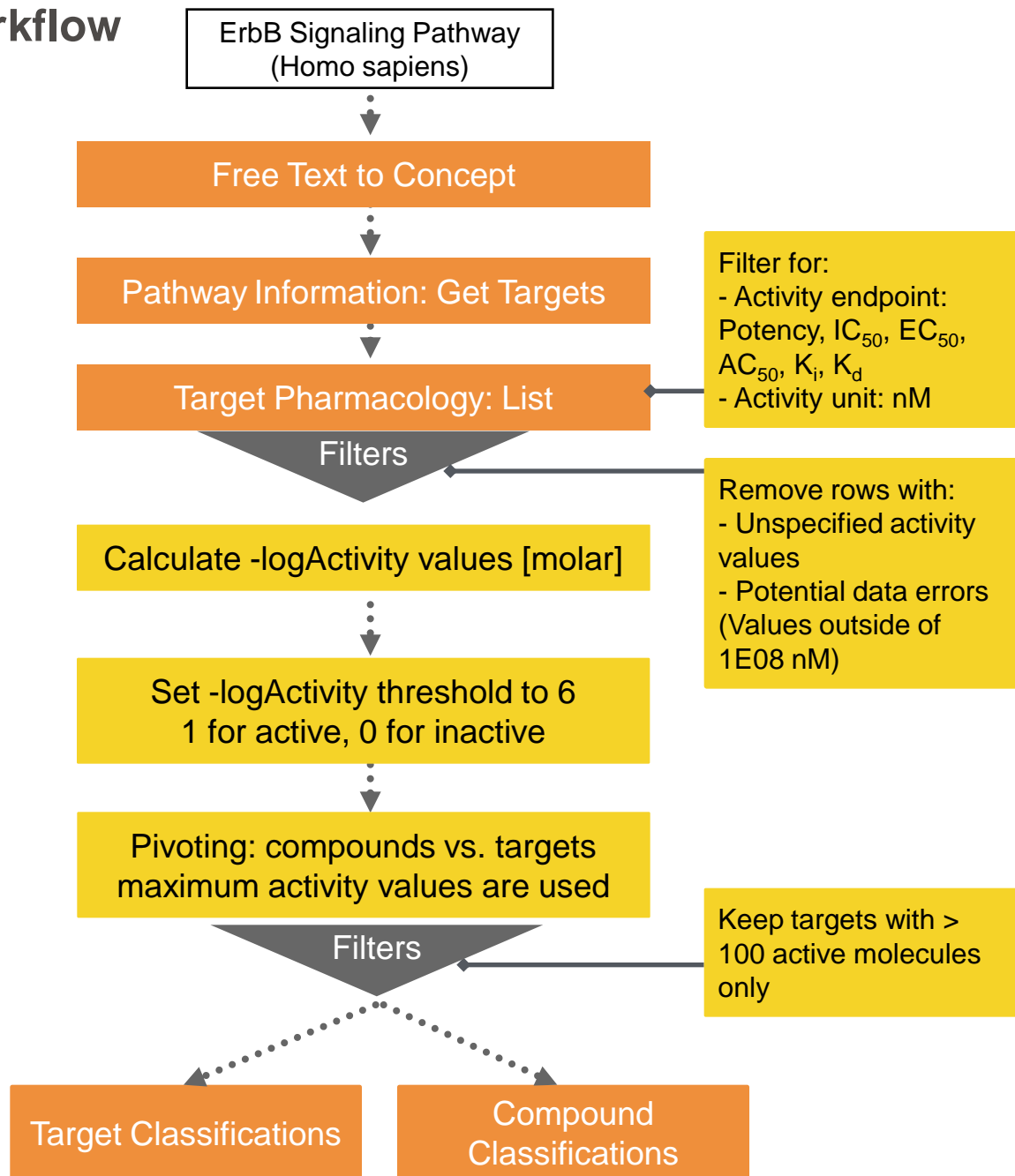
The Erbb signaling pathway
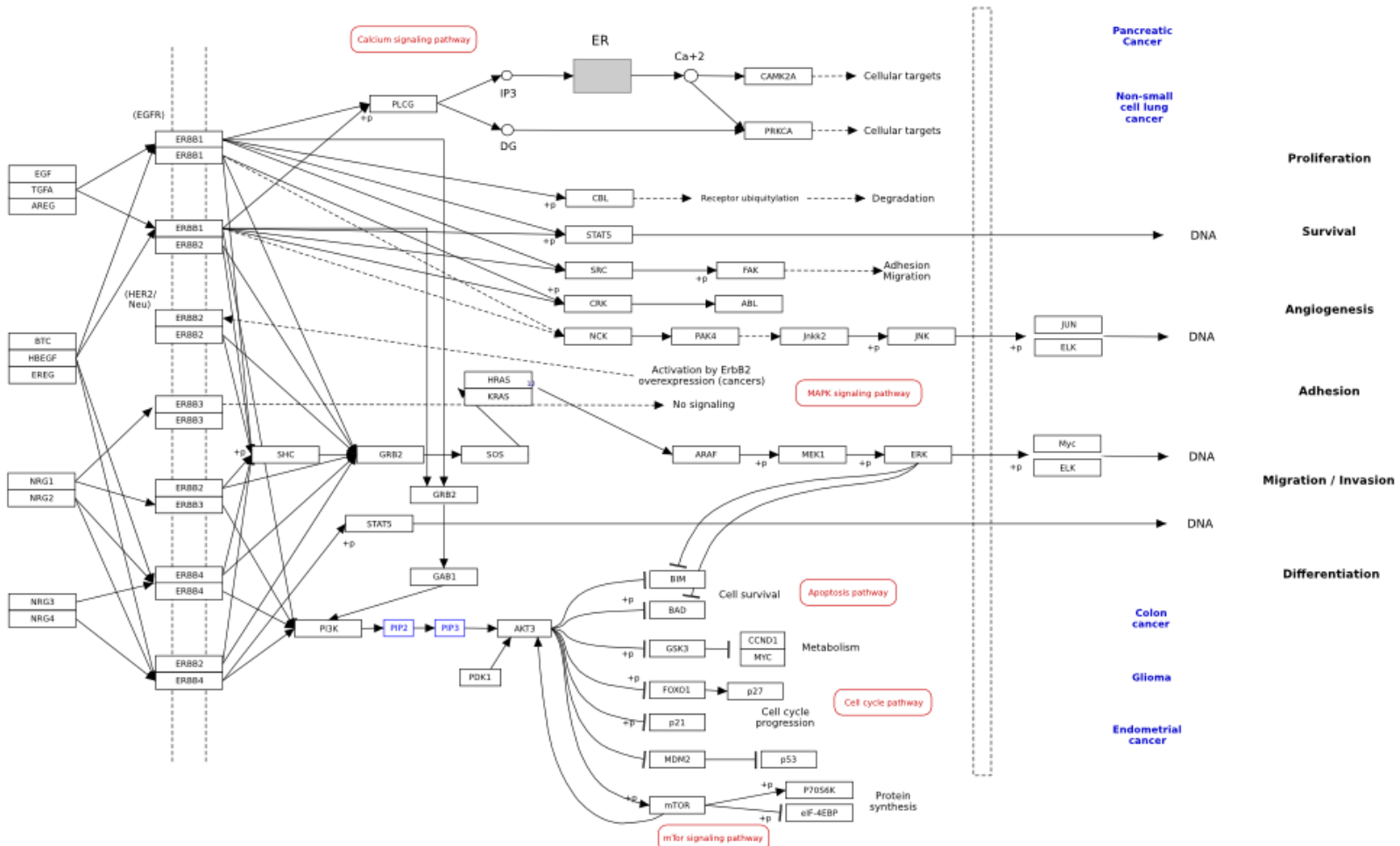
Methods

✦ Queries from the Open PHACTS API (v 1.3):

   – Free Text to Concept

   – Pathway Information: Get Targets

   – Target Pharmacology: List

   – Target Classifications

   – Compound Classifications

✦ KNIME:

   – connection of API calls

   – additional processing of the data

Outline of the workflow

ErbB Signaling Pathway
(Homo sapiens)

Free Text to Concept

Pathway Information: Get Targets

Target Pharmacology: List

Filter for:
- Activity endpoint: Potency, IC_{50}, EC_{50}, AC_{50}, K_i, K_d
- Activity unit: nM

Filters

Remove rows with:
- Unspecified activity values
- Potential data errors (Values outside of 1E08 nM)

Calculate -logActivity values [molar]

Set -logActivity threshold to 6
1 for active, 0 for inactive

Pivoting: compounds vs. targets
maximum activity values are used

Filters

Keep targets with > 100 active molecules only

Target Classifications

Compound Classifications

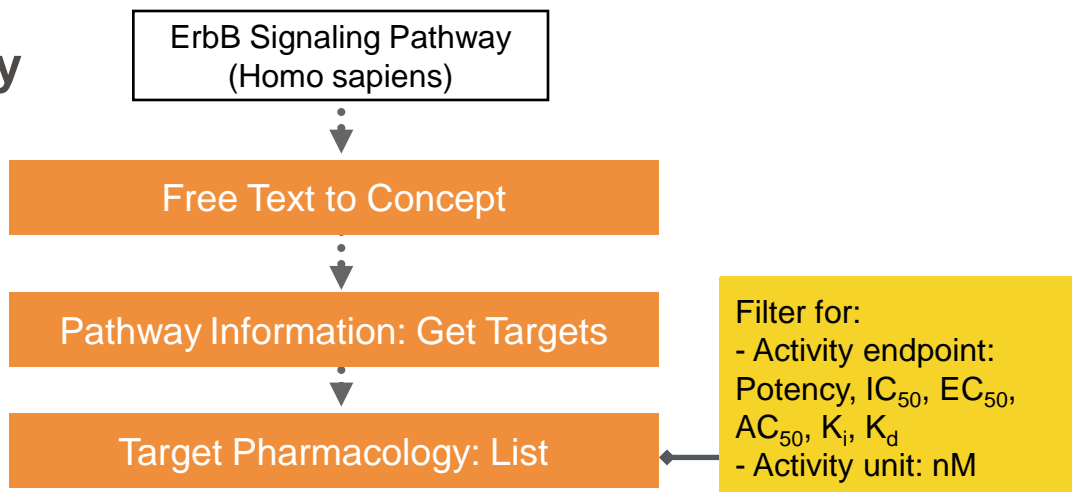![Open PHACTS - Open Pharmacological Space]

From pathway to pharmacology

- ✤ Free Text to Concept
  - – Input: ErbB Signaling Pathway (Homo sapiens)
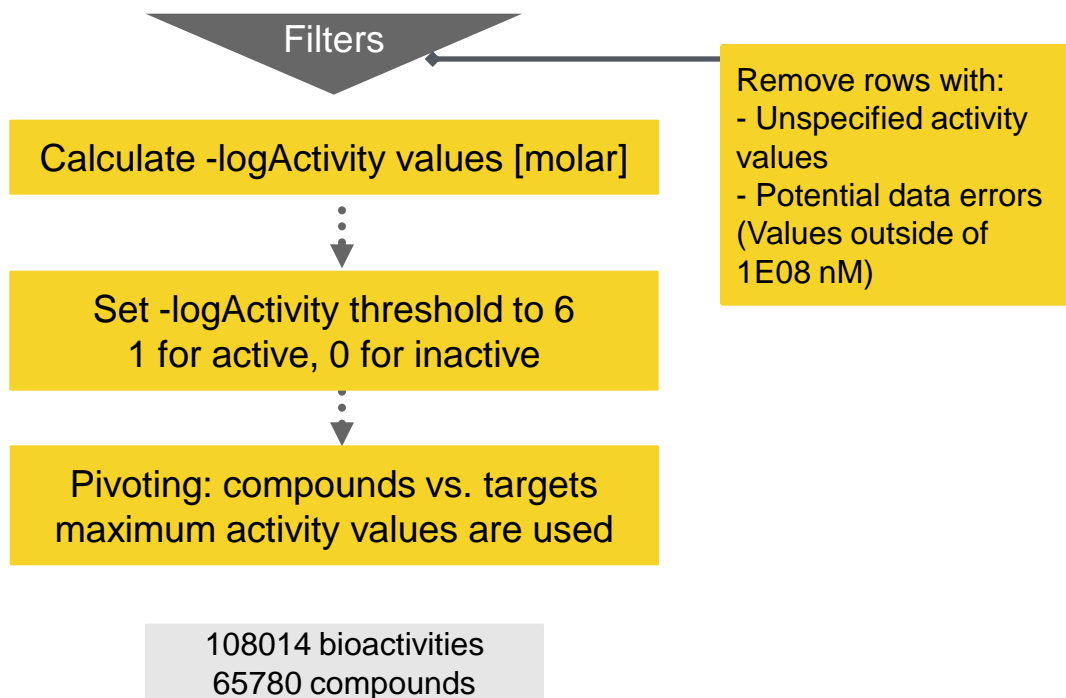 - – Output: 1 Pathway URI

- ✤ Pathway Information: Get Targets
  - – Input: Pathway URI
  - – Output: 54 NCBI Gene URIs

- ✤ Target Pharmacology: List
  - – Input: NCBI Gene URIs, applied filters
  - – Output: Pharmacology data for 55 ChEMBL targets from > 65k compounds (~108k bioactivity datapoints).
  - – Targets: 35 single proteins, 12 protein families, 5 protein complexes, 2 protein-protein interactions and 1 chimeric protein.
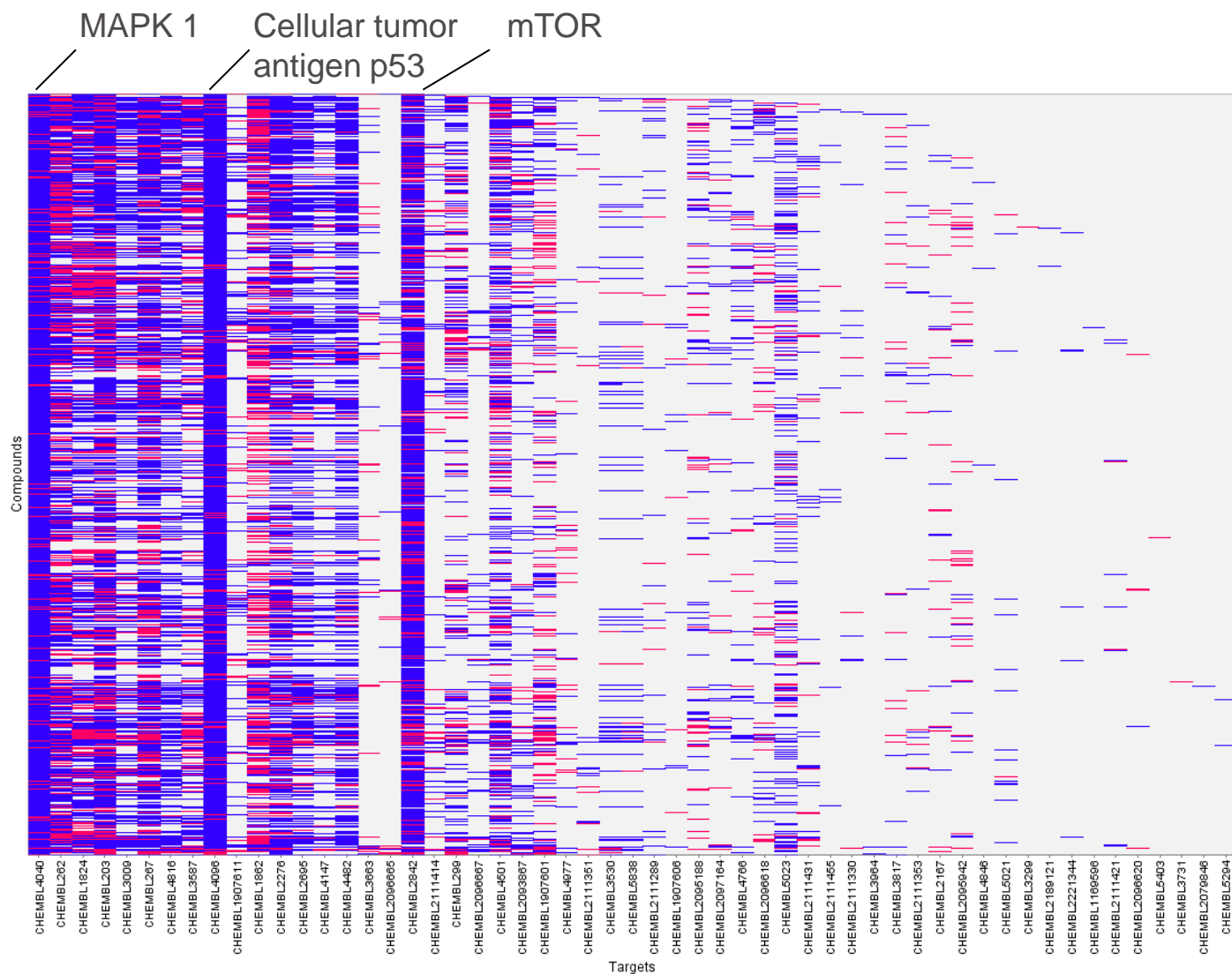
ErbB Signaling Pathway (Homo sapiens)

↓

Free Text to Concept

↓

Pathway Information: Get Targets

↓

Target Pharmacology: List

Filter for:
- Activity endpoint: Potency, IC_{50}, EC_{50}, AC_{50}, K_i, K_d
- Activity unit: nM

Data preprocessing

Filters

Remove rows with:
- Unspecified activity values
- Potential data errors (Values outside of 1E08 nM)

Calculate -logActivity values [molar]

Set -logActivity threshold to 6
1 for active, 0 for inactive

Pivoting: compounds vs. targets
maximum activity values are used

108014 bioactivities
65780 compounds

Full heat-map

- red: 'active'
- blue: 'inactive'
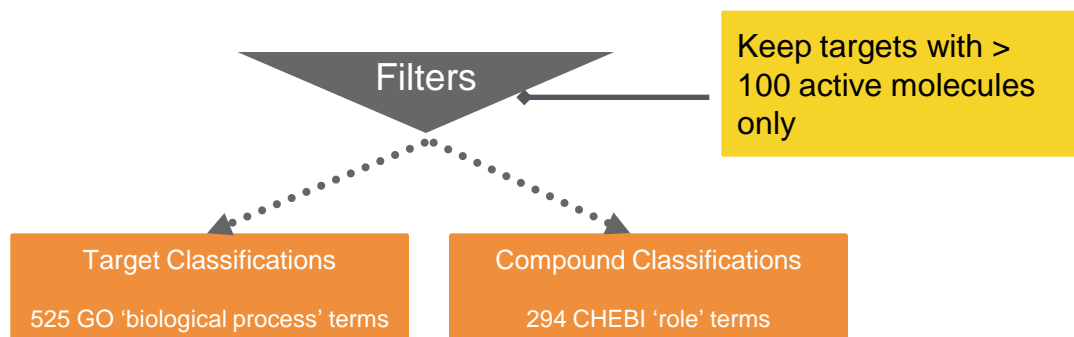
Data analysis

✧ 23 targets with at least 100 active molecules

✧ Target classifications
  – Input: 23 target URIs, used classification: GO
  – Output: 525 'biological process' terms

✧ Compound classifications
  – Input: ~65k compound URIs
  – Output: 294 'role' terms

Filters

Keep targets with > 100 active molecules only

Target Classifications

525 GO 'biological process' terms

Compound Classifications

294 CHEBI 'role' terms

Investigating the compounds: antineoplastic agents

Tyrosine protein kinase ABL

Brc/Abl fusion protein

✧ red: 'active'

✧ blue: 'inactive'

Investigating the compounds: neuroprotective agents

- ✤ 7-Chlorokynurenic acid: active against MAPK1
- ✤ Cilostazol: inactive against MAPK1
- ✤ Memantine: inactive against Serine/threonine-protein kinase mTOR

Current limitations

✦ Directionality of pathways is lost

✦ GO terms often not linked to diseases

✦ limited number of compounds annotated with Chebi terms of interest

Conclusions and Outlook

- ❖ Open PHACTS offers convenient access and visualization of the available data via KNIME.
- ❖ Activity profiles for compound classes (e.g. antineoplastic agents) can be visualized.
- ❖ Final workflow can be reused for other pathways.

- ❖ Next API version will contain disease data for proteins.
- ❖ Investigation of other filtering possibilities to visualize the data.
- ❖ Workflow will be available at myexperiment.org

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