Breakout Session 1: Track B

UniProt Knowledgebase to Enable AI/ML Readiness and Applications

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UniProt AI Readiness

https://www.uniprot.org/

NIH ODSS AI Supplement Program PI Meeting

NIH FY22 AI-Readiness program (3U24HG007822-09S2)

UniProt - Protein sequence and function embeddings for AI/ML readiness

MPIs: Alex Bateman & Cathy Wu

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Cathy Wu

University of Delaware

Project Goals

1. Organize UniProt data to be AI-ready
   - Enable the community to harness AI/ML using UniProt data
2. Work with the community to advance AI-readiness and applications
   - Focus on useful problems through setting challenges
3. AI-driven innovation for UniProt resource development
   - Identify opportunities and new partners for collaborative development

Lack of well-curated data
is a major barrier for AI Research

AI/ML-Readiness, Engagement & Innovation

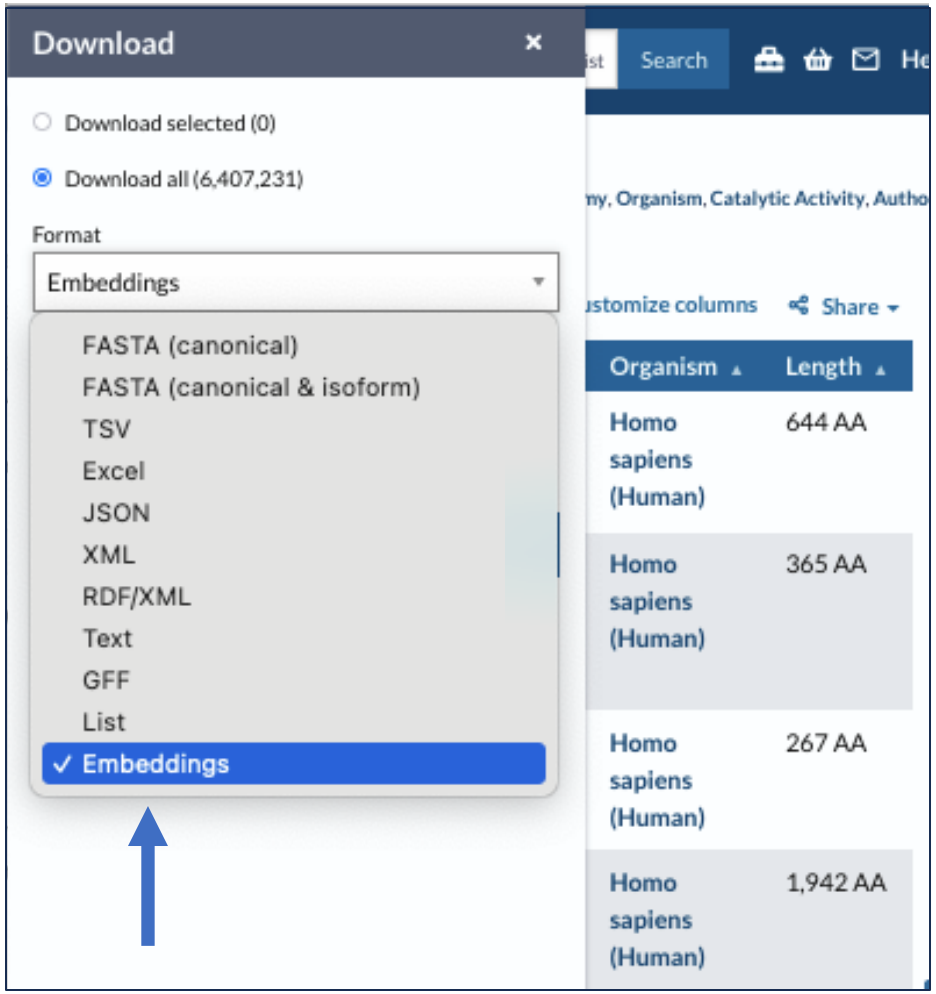
1. Dissemination of AI/ML models/data (collaborator-generated)
   - Alphafold 2.0
   - ProtT5 sequence embeddings
2. AI/ML community engagement
   - Challenge evaluation – CAFA-UniProt metal binding challenge
   - Community workshops to discuss AI/ML readiness and applications
3. Collaborative development with AI communities
   - ProtNLM language model for protein name and function prediction
   - OntoGPT for extracting structured information from text with Large Language Model (LLM)
   - Text mining and LLM for UniProt annotation

AI/ML Dissemination – AlphaFold

- Deep-learning based **AlphaFold 2.0** demonstrates atomic accuracy
- EMBL-EBI collaborated with **DeepMind** to release AlphaFold models and launched the AlphaFold Protein Structure Database in 2021
- UniProt has developed a process for making AlphaFold structures available from UniProt when the structures are released in the AlphaFold database
- Currently over 188 million UniProtKB proteins have AlphaFold 2.0 predictions

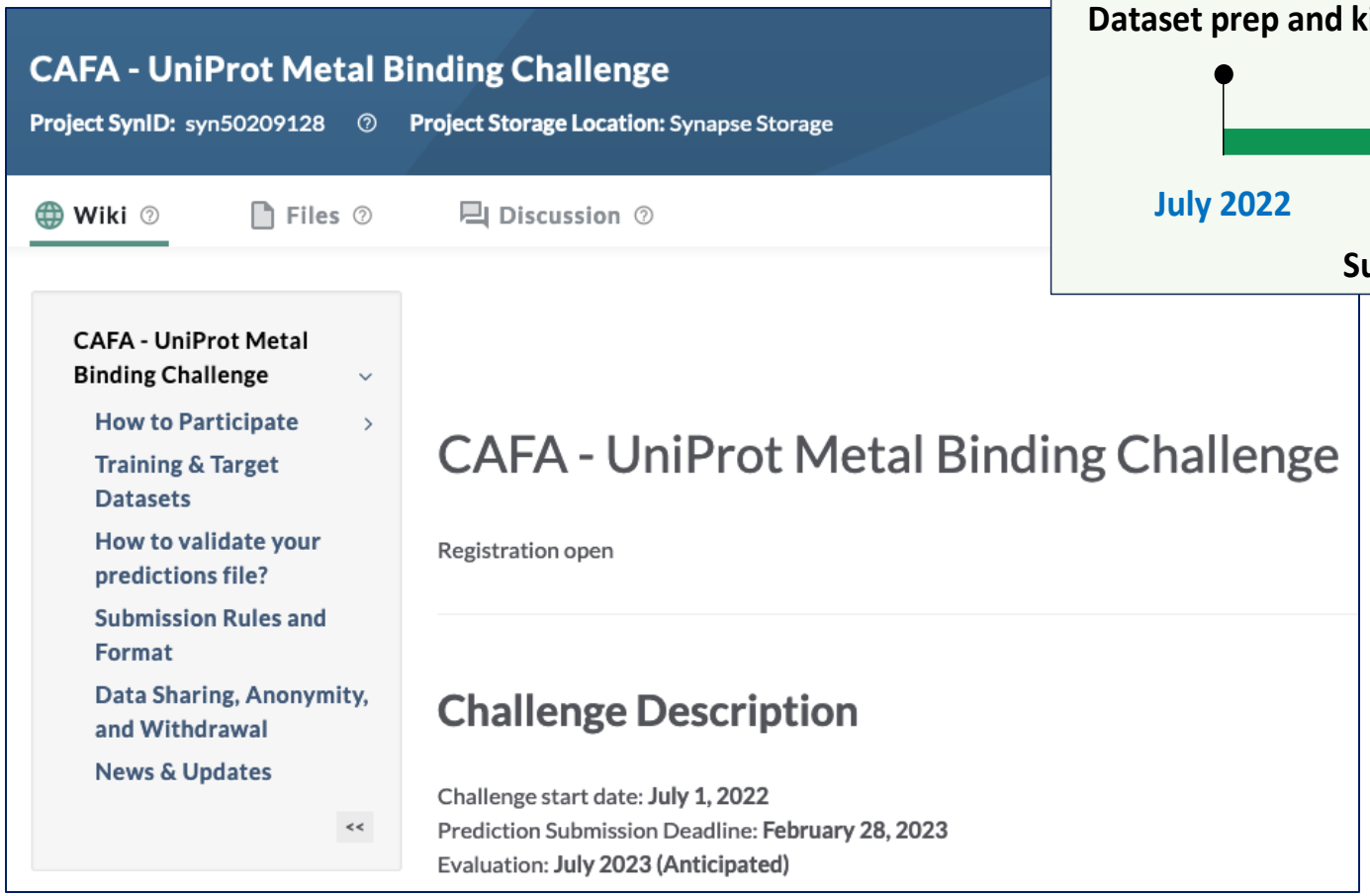
AI/ML Dissemination – Sequence Embedding

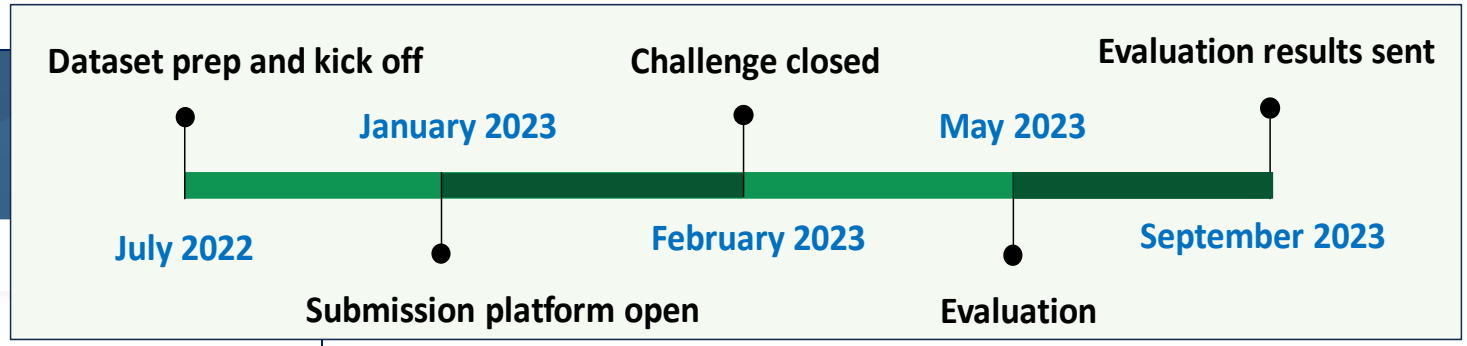
- Protein **sequence embedding**: Encode functional and structural properties of a protein from its sequence in a vector representation
- UniProt **data ready for AI/ML** via sequence embedding: Save community compute and enable the community to harness AI/ML
- Provide a generic framework for a wide range of AI/ML tasks
- Precomputed UniProtKB datasets
- User-tailored datasets through website (e.g., all proteins with structure from PDB, all bacteria)



Model developed by Burkhard Rost lab at Technical University of Munich

Community Engagement – CAFA-UniProt Challenge





Evaluation

- Metal Binding Challenge hosted on **Synapse**
- 17 registered participants
- High false positives in the submissions

Next steps

- Host challenge on **Kaggle** to attract more participants and data scientists
- Leverage CAFA expertise and frameworks

Community Engagement - UniProt AI Workshop

Provider of useful AI-ready datasets and embeddings to the community

UniProt

User of AI methods that improve aspects of its functioning, e.g., functional annotation

Community Engagement Workshop, 2023

- Working with the community to advance **AI-readiness and applications**

- Sharing advances of UniProt AI development
- Learning ongoing AI development to be leveraged in UniProt
- Understanding community needs through solicitation of use cases

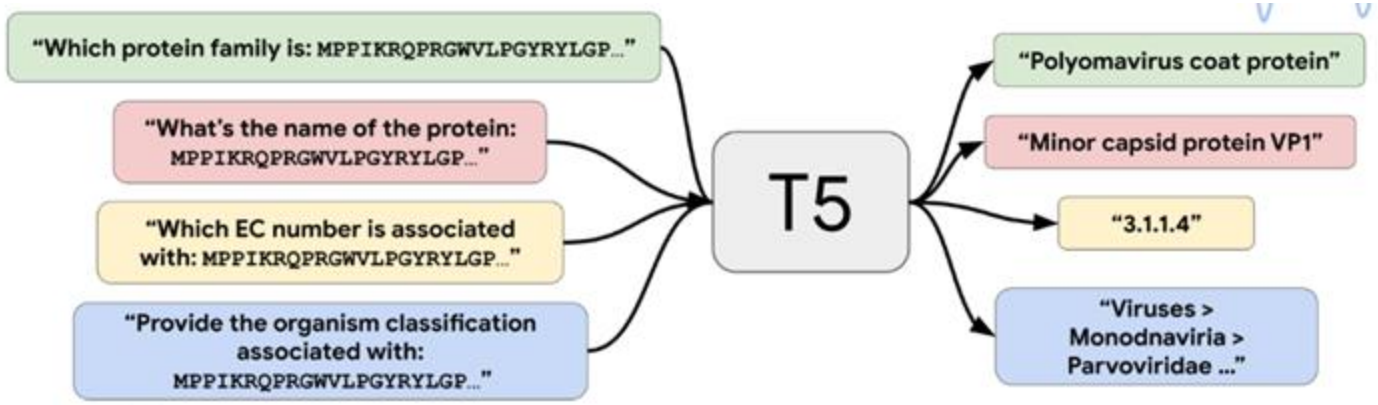
ProtNLM Natural Language Models for Annotation

ProtNLM (Name predictions to uncharacterized proteins)

- Fine-tuned algorithm and improved naming in training data set – better prediction quality
- 28,972,944 uncharacterized proteins have names from ProtNLM in UniProt 2024_01

ProtNLM (full UniProt predictions) - in progress

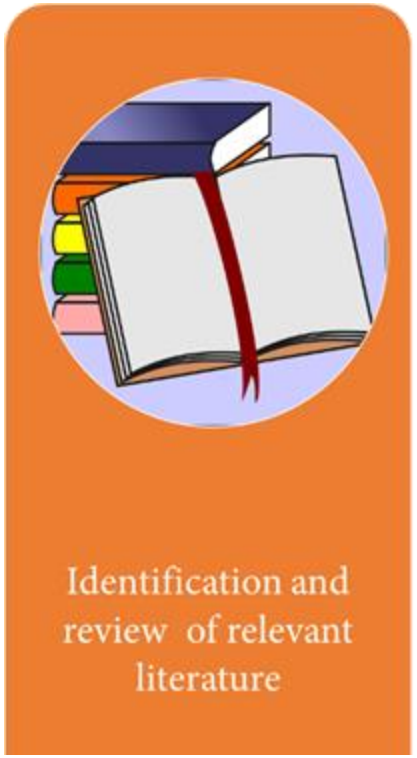
- Selection of prediction types (EC numbers, Function, etc.)
- Preliminary assessment of annotations
- Evidence strategy (e.g., compare with other annotations in entry and pHMMER alignments)



Collaboration with Lucy Colwell and Max Bileschi groups at Google Research (DeepMind)

https://ebrevdo.github.io/publication/gane-2022-az/

Future Work & Pilots: LLM in UniProt



Manual Curation

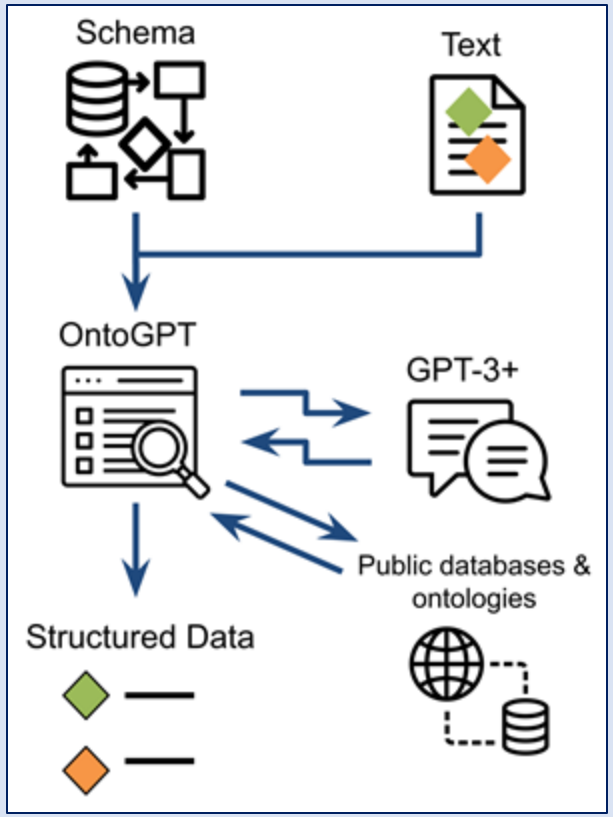
- To scan/summarize published papers with a focus on the gene of **function** interest
- To automatically identified which ones are adding “new information”
- To be used a co-pilot for curators writing scientific summaries (integrating information from multiple papers)

Automatic Annotation

- To summarize literature
- To “extract” relevant information to create annotation types (e.g., GO terms)

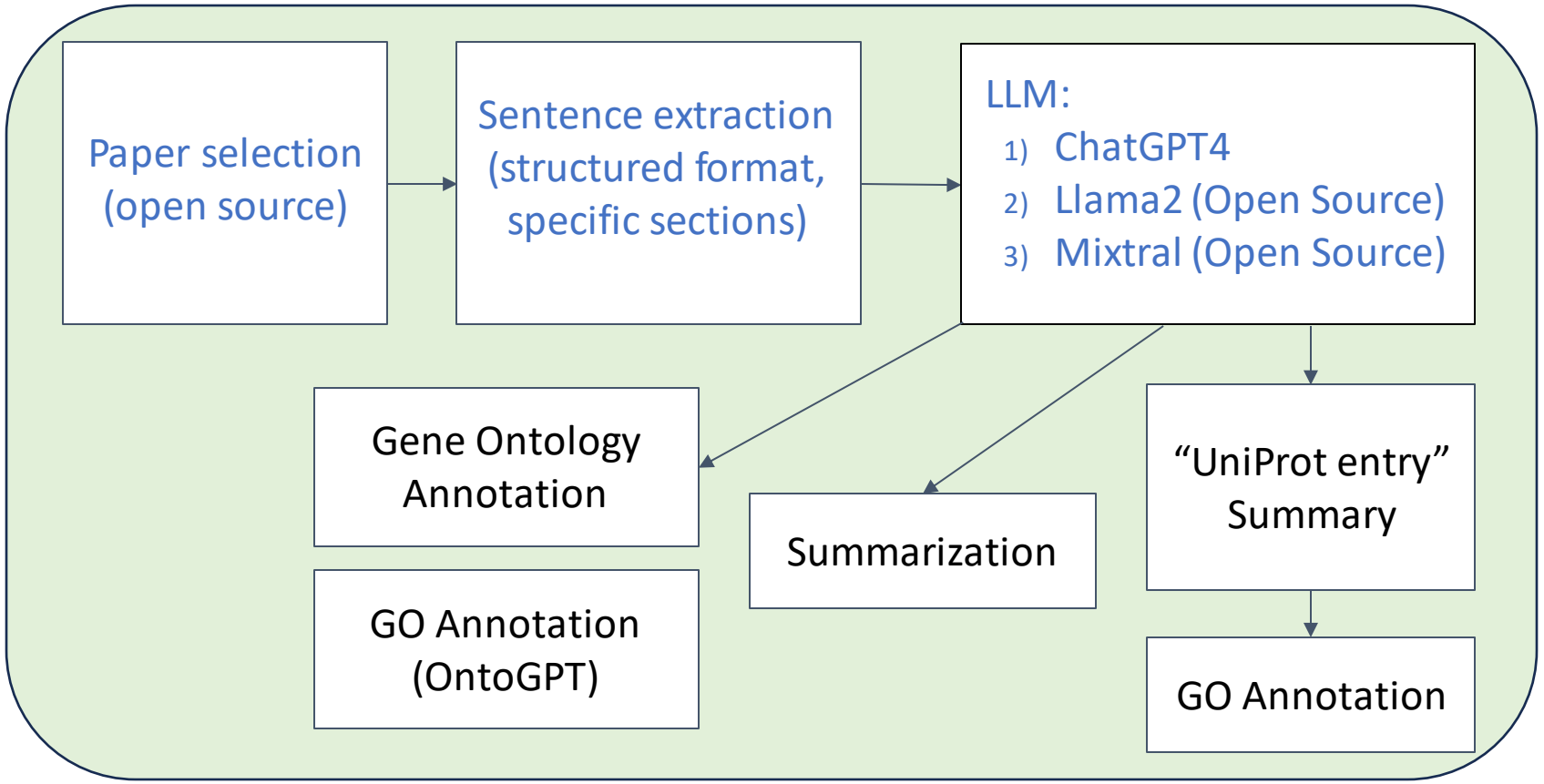
LLM for Summarization and Term Extraction

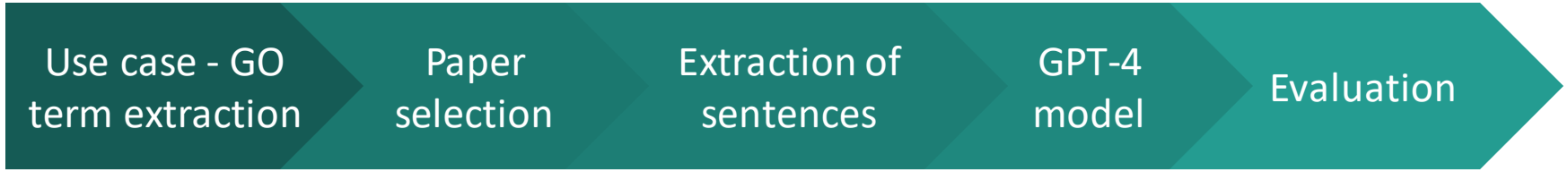
SPIRES – OntoGPT



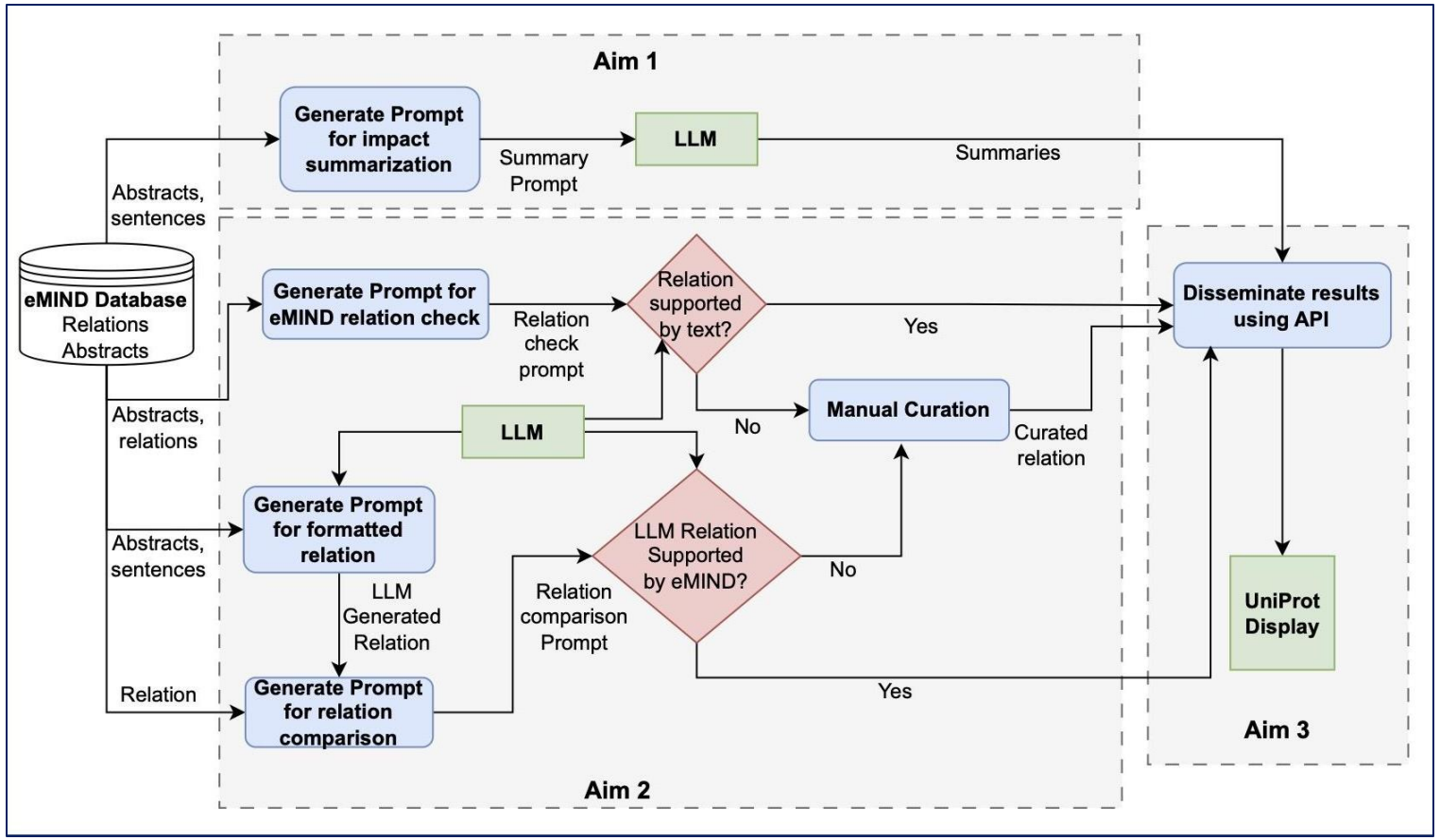
doi: 10.1093/bioinformatics/btae104

Collaboration with Chris Mungall, LBNL





Text Mining & LLMs for UniProt Annotation



- **eMIND text mining** pipeline to process all PubMed abstracts and extracts information on functional consequences of variants in Alzheimer's Disease (AD)
- Combine eMIND output with ChatGTP to **write summaries** and **extract relations** about the impact of AD-associated variants

doi: 10.1101/2023.09.07.556602
Collaboration with Vijay Shanker
University of Delaware

Display of Results – Confidence Scoring

Disease & Variants

Involvement in disease

Alzheimer disease 1 (AD1)

30 Publications

Note The disease is caused by variants affecting the gene represented in this entry

Description A form of Alzheimer disease, a neurodegenerative disorder characterized by progressive dementia, loss of cognitive abilities, and deposition of fibrillar amyloid proteins as intraneuronal neurofibrillary tangles, extracellular amyloid plaques and vascular amyloid deposits. The major constituents of these plaques are neurotoxic amyloid-beta protein 40 and amyloid-beta protein 42, that are produced by the proteolysis of the transmembrane APP protein. The cytotoxic C-terminal fragments (CTFs) and the caspase-cleaved products, such as C31, are also implicated in neuronal death. It can be associated with cerebral amyloid angiopathy. Alzheimer disease can be associated with cerebral amyloid angiopathy.

See also MIM:104300

UniProt Annotations | **AI-powered Summaries**

MUTATION	IMPACT	SOURCE (PMID)
E693G	causes decreased Abeta42 and Abeta40 levels in plasma	11528419
	leads to dementia with clinical features similar to Alzheimer's disease	19329229
	is sufficient to cause amyloid deposition and cognitive dysfunction	19329229
	leads to dementia with clinical features similar to Alzheimer's disease	21880397
	favors proamyloidogenic APP processing by increased beta-secretase cleavage	17448150
	exhibits a purely cognitive phenotype that is typical of Alzheimer's disease	28890319
	decreases cell viability in human neuroblastoma cells and enhances sensitivity to toxic stress	12052536
	facilitates amyloid-β protofibril formation and generates clinical symptoms of Alzheimer's disease	22118948
	displays intracellular amyloid deposits but not plaques and has a relatively mild epilepsy phenotype	26825094
A673T	attenuates APP-BACE-1 interactions	26642089
	not relevant in Asian population	23652020~24126161
	reduces the risk for Alzheimer's disease	28003277
	reduces the incidence rate of Alzheimer's disease	24646423

SUMMARY ✕

LLM summary for the role of E693G mutation in APP

1. The E693G mutation in the APP gene, also known as the Arctic mutation, is associated with Alzheimer's disease and leads to enhanced formation of amyloid-beta (Abeta) protofibrils (11528419, 21880397).
2. Carriers of the Arctic mutation exhibit decreased levels of Abeta42 and Abeta40 in plasma (11528419).
3. The Arctic mutation causes amyloid deposition and cognitive dysfunction, similar to Alzheimer's disease, and can be studied using the TgAPParc mouse model (19329229).
4. The Arctic mutation favors proamyloidogenic APP processing by increased beta-secretase cleavage, resulting in increased levels of Arctic Abeta, particularly at intracellular locations (17448150).
5. Mice with the Arctic mutation display intracellular amyloid deposits but not extracellular amyloid plaques (26825094).
6. The Arctic mutation enhances sensitivity to toxic stress, contributing to the pathogenic pathway leading to Alzheimer's disease (12052536).
7. The Arctic mutation leads to distinct plaques and accumulation of truncated forms of amyloid-beta (22118948).
8. Tracers for amyloid-beta fibrils show reduced binding affinity toward the Arctic mutation compared to the native type (28898051).

In conclusion, the E693G mutation in the APP gene, known as the Arctic mutation, plays a significant role in the pathology and neurodegeneration associated with Alzheimer's disease. It leads to enhanced formation of amyloid-beta protofibrils, amyloid deposition, cognitive dysfunction, and increased sensitivity to toxic stress. The mutation also affects APP processing and the accumulation of truncated forms of amyloid-beta.

AI summary powered by OpenAI

Publications

PMID: 28898051
Effect of Alzheimer Familial Chromosomal Mutations on the Amyloid Fibril Interaction with Different PET Tracers: Insight from Molecular Modeling Studies
Balamurugan K, Murugan NA, Långström B, Nordberg A, Ågren H.ACS Chem Neurosci. 2017 Dec 20 8(12):2655-2666.
doi: 10.1021/acschemneuro.7b00215. Epub 2017 Oct 3.

PMID: 26825094
Increased Epileptiform EEG Activity and Decreased Seizure Threshold in

Assign confidence score to output of text mining tools

Using eMIND as a test tool to:

a. Collect eMIND positive abstracts
b. Ask LLM to answer what impact of mutation is
c. Check with overlap with eMIND output

Scalable framework for other text mining/relation extraction tools

UniProt Vision for AI

- Transformative Impact of AI: Enable the user community to harness AI using UniProt data
- AI approaches are being applied to many aspects of UniProt: Close collaboration with the AI research communities to innovate new approaches and solutions
- Scaling up protein functional annotation: AI-assisted literature information extraction and automated functional annotation
- Organizing and sustaining the growing sequence space: AI-enabled sequence clustering and similarity search

Lack of well-curated data is a major barrier for AI Research

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UniProt well-curated and AI/ML-ready data