Biological Database Mining for LLM-Driven Alzheimer's Disease Drug Repurposing

*Rico Andre Schmitt[1,2], Konstantin Buelau[1,2], Leon Martin[1,2], Christoph Huettl[1,2], Michael Schirner[1,2,3,4,5], Leon Stefanovski[1,2], and Petra Ritter[1,2,3,4,5] **

[1]Berlin Institute of Health (BIH) at Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117, Berlin, Germany
[2]Department of Neurology with Experimental Neurology, Charité, Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Charitéplatz 1, 10117, Berlin, Germany
[3]Bernstein Focus State Dependencies of Learning and Bernstein Center for Computational Neuroscience, Berlin, Germany
[4]Einstein Center for Neuroscience Berlin, Charitéplatz 1, 10117, Berlin, Germany
[5]Einstein Center Digital Future, Wilhelmstraße 67, 10117, Berlin, Germany

* Corresponding Author

December, 2024

Abstract

INTRODUCTION: The synergy of structured knowledge and large language models (LLMs) may contribute to identifying drugs for Alzheimer's disease (AD) drug repurposing (DR). This paper developed a software pipeline that uses LLMs to translate knowledge stored in natural language (such as in scientific texts) to an applicable DR information structure.

METHODS: AD-related entries in Gene Ontology and DrugBank were integrated into a Knowledge Graph database to inform LLM prompts. Based on the biological process impact, the LLM provided a suitability rating for DR, taking into account the inhibitory effect of drugs on AD driving processes..

RESULTS: Drugs with a high potential for DR were identified and manually reviewed, also considering adverse effects. Ripretinib and Pertuzumab (both kinase inhibitors) had the highest DR applicable rating across all iterations.

DISCUSSION: We propose retrospective analyses, considering the high-rated drugs and their effect on AD patients as a starting point for further (prospective) research.

0 Background

In the field of Alzheimer's Disease (AD) and dementia research, the amount of data on biological processes and functional relationships has been growing over the last decades.[1] However, the increased information has not translated into an improved understanding of the disease relative to the degree of the data expansion. In more than 110 years of AD research and over 222,000 studies listed on PubMed on AD, no generally verified AD hypothesis has been confirmed.[2,3]

While the expanding amount of data on AD and drugs facilitates insights into neural processes[4], it also hinders the synergy of all available knowledge since individual researchers cannot consider the entire knowledge systematically at once.

This development requires novel approaches for organizing, accessing, and using data. The availability of large language models (LLMs) provides the scientific community with tools for gaining new insights and developing treatments based on large-scale natural language processing.[5]

Perhaps there are applicable drugs for AD treatment that currently have other indications.[6,7] Such drugs are subject to drug repurposing (DR).[8] DR comes with the advantage that patients may be treated sooner (since repurposed medications do not have to go through a shortened approval procedure),[9] costs for drug development may be reduced, and animal trials can be avoided (according to the 3R principle for replacement of animal trials[10]). Also, the safety profile of drugs that are already in clinical use is more established than the safety profile of an entirely new drug.

This paper aims to apply artificial intelligence technologies to move towards data-driven AD DR.

0.1 Ontologies and Large Language Models

An ontology is a hierarchically organized representation of knowledge that shows the relation of properties in a subject or area.[11] Domain-specific ontologies have been widely used in biology[12], chemistry[13], and medicine[14] to allow for the formal organization of data. Ontologies are designed to be interoperable.[11] Large language models (LLMs) may be applied to connect ontologies and knowledge resources.[15]

Ontologies and LLMs are complementary technologies. While LLMs are able to process high quantities of data in a way that would otherwise require manual, human work, they possibly *hallucinate* and do not work with the newest available data.[16] *Hallucinations* of LLMs describe output with content that either has no factual basis or is inconsistent.[17] LLMs operate on (at least partially) outdated knowledge due to their training using world data (usually data on the internet that was available when the model training started). They often provide plausible answers by predicting the next most probable token (next word or part of the next word).[18] However, their likelihood of

correctness depends heavily on the specific prompt and the knowledge embedded in the model. Scientific data is being published constantly, and it would be challenging to establish an LLM training process that catches up with scientific progress in real-time. Even in such a setup, hallucinations are still likely to occur, the more specific the information one has to ask for as the LLM. This is due to the setup in which the LLM will always provide some response, as they predict the most probable next token, but the likelihood of a correct or valuable answer becomes lower if the information is a detail that rarely occurs in the training dataset or was not included in the first place.[19]

Those described weaknesses are the fields in which ontologies and other highly structured knowledge resources have strengths and complement LLMs. LLMs may serve as a translation layer. They can transform natural language stored in databases (such as biological processes and pharmacodynamics in the DrugBank) along with semantic knowledge stored in ontologies to standardized output (such as a numeric rating). This rating may then be used in virtual DR screening to advance the research in AD.

1 Methods

As a starting point for the DR pipeline, a database containing information on biological processes (GeneOntology[20]), drugs (DrugBank[21]), and AD pathology, as shown in Figure 1, was created. Gene Ontology (GO) provides a comprehensive collection of biological processes (among other entities).[22] The ARUK-UCL dataset contains GO terms relevant to the development of AD based on the literature with a focus on microglial proteins and microRNAs involved in AD.[20,23]

Each entry corresponds either to a biological process from GO associated with AD according to the ARUK-UCL biological process subset or a drug listed in the DrugBank that has an impact on these processes. This information was embedded in prompts to the LLM to rate the potential of drugs to be repurposed for AD to get the reasoning for its decisions based on the biological process. That data worked as a translation layer between the natural language-based knowledge in the DrugBank (which contains mechanisms of action, pharmacodynamics, and biological processes described in GO terms) and the formalized biological processes in GO that are connected to the drugs that interact with them. Finally, the drugs with the top 20 ratings of the LLM were reviewed based on the literature published on them to discuss medications that are promising for DR. Drugs applicable for DR (drugs among the top 20 average ratings that are not yet considered AD medications) were also screened for adverse effects based on the literature. The reasonings provided by the LLM for the ratings were manually reviewed to identify hallucinations supplied in the output.

Figure 2 depicts the Study Protocol, showing each step from the graph database creation to the manual review of DR candidates. For results interpretation, the drugs were classified by the GO process they work on. To set the ratings in perspective, the rating of the drugs was compared with the registered

clinical trials on clinicaltrials.gov. This provided insights regarding the relationship between the number of trials and the ratings the drugs received. To test if the results of the DR pipeline were applicable to all patient groups (ethnicity, nationality, environment) to the same degree, the ratings of drugs were plotted on a map to indicate where the respective drug trials were run and what rating the drugs that had each trial got. As the LLM was trained on world data (including published drug trial studies), this provided a perspective on how the world population is represented by the studies that provided data for the drugs (world data) considered for DR and how the LLM responded to the drugs in dependence on where the trials were conducted.

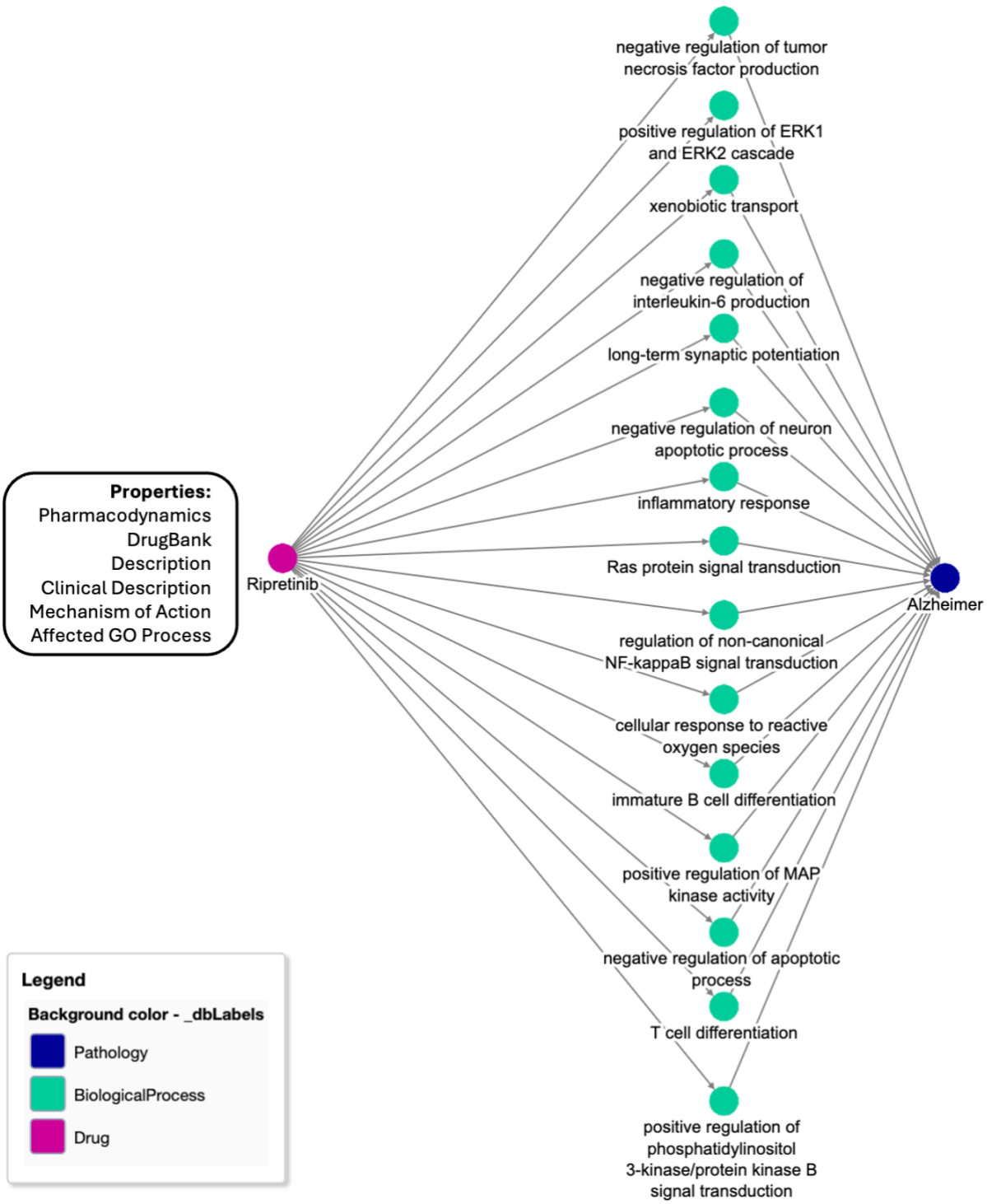

Figure 1: **Sample Graph of the Alzheimer's Drug Repurposing Database**

This is an example graph from the graph database containing a (manual) selection (15 of 76) of processes (green), AD pathology (blue), and the drug Ripretinib (pink). The arbitrary selection of 15 biological processes was done to enhance clarity and readability in this sample plot. The graph design can be used to retrieve the Pharmacodynamics, DrugBank Description, Clinical Description (if available), Mechanism of Action, Affected GO Processes and name of the drug and its associated biological processes (as shown in the figure above). The prompts provided to the LLM followed this principle – a drug and its impacted

biological processes are provided along with information about that drug. All the biological processes are associated with AD pathology (according to the ARUK-UCL dataset as described in Methods **1.1**).

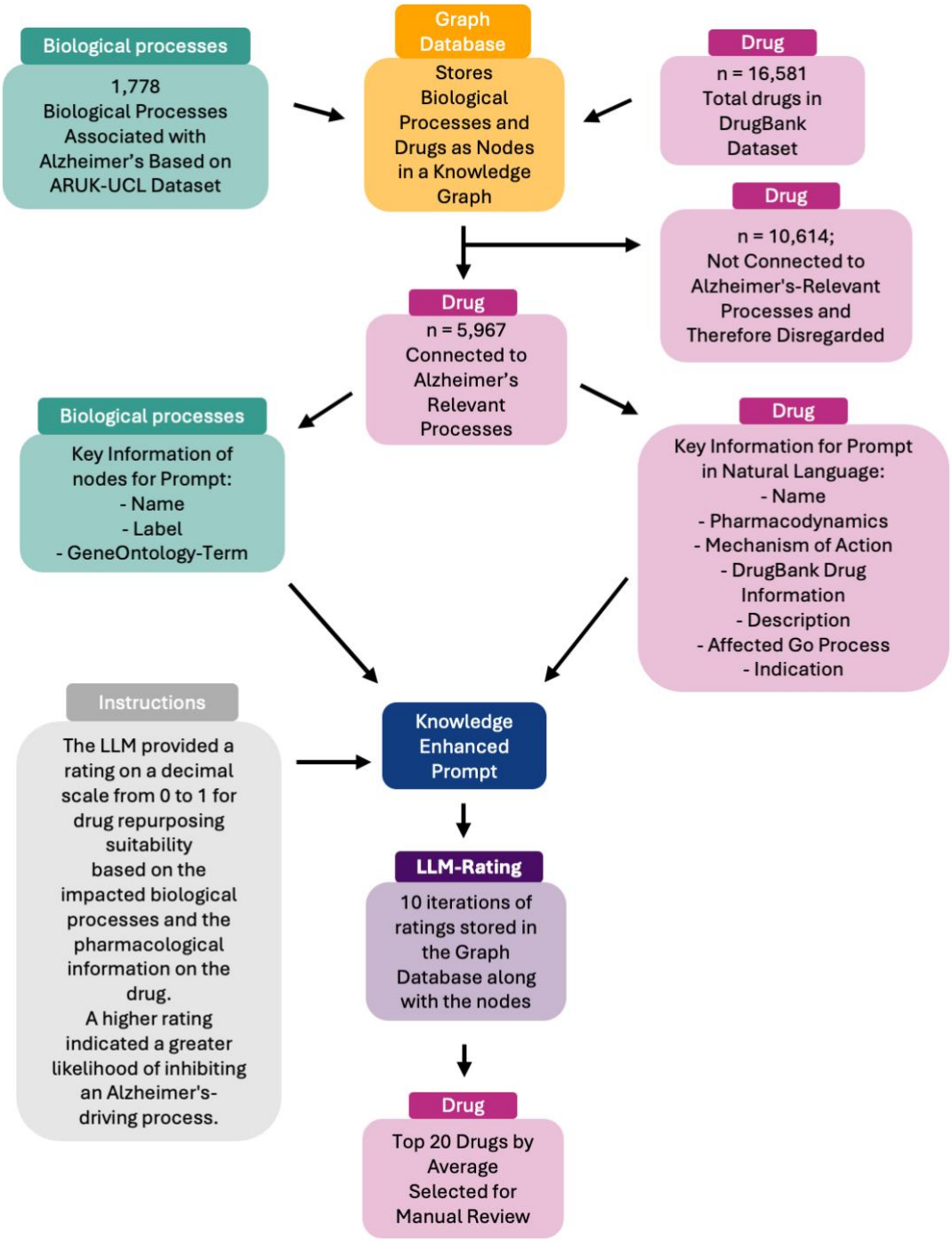

Figure 2: **Study Protocol**

This chart describes how the Alzheimer's Disease (AD) Drug Repurposing (DR) database was created and how its content was systematically provided to a Large Language Model (LLM) to analyze information stored in natural language.

The Gene Ontology (GO) biological processes from the ARUK-UCL dataset and the drugs in the DrugBank were included as nodes in the graph database. *5,967* drugs were connected to AD-relevant processes based on the ARUK-UCL dataset. *10,614* drugs had no connection to the biological processes listed in the ARUK-UCL dataset and were therefore disregarded.

For each of the *5,967* AD biological process-connected drugs, a prompt for the LLM was generated. This prompt contained the key information of the drug from the DrugBank stored in natural language (such as 'Mechanism of Action', 'Pharmacodynamics', and 'Affected GO Processes') and the biological processes associated with it (that were introduced based on the ARUK-UCL dataset earlier).
That information was contextualized by detailed instructions for the LLM to explain its task, input, and required output format. It was tasked to consider the input data (particularly the connection between the AD biological processes and the mechanisms of action of the drug) and analyze, based on that connection, the potential for drug repurposing of a drug.
The data on the drugs, their associated biological processes, and the instructions provided in the knowledge enhanced prompt that was provided to the LLM. The LLM provided a reason, explaining its decision as to why it considers a drug qualified for AD drug repurposing or not, and provided a rating from 0-1 (decimal numbers allowed), translating its reason in numbers.

1.1 Database Setup

The drugs of the DrugBank and the biological processes (based on the ARUK-UCL dataset) were stored in a graph database. In such a database, information is stored as a network with nodes and their relations to each other. Each biological process, drug, and pathology become nodes connected by their relationship, as shown in Figure 1. Since this investigation concerns DR and gathering new insights into treatment by connecting knowledge, a graph database is suitable for retrieving such information systematically.

The DrugBank contains 16,581 drugs along with extensive information on them structured by mechanism of action, indication, and other pharmacological key data.[24] There are descriptions of the mechanisms of action of the drugs and the Gene Ontology (GO) processes they impact.[21,25] The indication of each drug is provided as well, which enables the selection of drugs indicated for AD treatment and medications with other indications specifically.

1,778 biological processes from GO and 16,581 drugs from the Drugbank were included. 7,590 drugs in the DrugBank dataset had associated GO-terms and were therefore applicable to possibly be connected with the ARUK-UCL terms. 5,967 drugs were added to the database that had GO terms associated with them that were considered AD relevant in the ARUK-UCL dataset. All drugs without connections to the (AD-specific) biological processes (10,614) were deleted from the database. Therefore, all drug nodes present in the database at that point had a relationship towards AD-relevant processes but not necessarily AD as an indication for administering the drug. 44 of these 5,967 drugs either had AD as an indication (such as Memantine[26]) or were under investigation for AD (such as VP025[27]), according to the DrugBank dataset. While they were included in the following steps to check their performance in the LLM rating, they are no candidates for DR since AD is already

considered to be their (primary) use. The supplementary document provides technical details regarding the database setup in *Appendix A*.

1.2 Large Language Model (LLM) Approach

The LLM was locally hosted for improved accessibility of the data and to be able to reproduce results with the very same model configurations (which may change in a non-open-source cloud-hosted model). Llama3:8b is an open-source LLM by Meta, suitable for the reproducibility and accessibility of results.[28,29,30] The open-source (open-weights of the LLM) approach was chosen to have more granular control over the model and its parameters. We have used the Llama 3 model with 8 billion parameters. The technical details of the LLM are specified in *Appendix B*.

To move towards virtual DR candidate selection, the drug nodes in the graph database were retrieved along with their associated biological process nodes. The model was prompted by the properties of the drug node and its biological processes. The LLM worked as a translation layer from the knowledge provided in describing natural language (text in the DrugBank) and standardized knowledge (in GO) to a ranked output. For a drug like Ripretinib, its pharmacodynamics, DrugBank description, clinical description, mechanism of action, and name (all-natural language) were provided to the LLM along with the affected GO processes (also natural language but formalized).

The model had to analyze the biological effect of the drug by comparing the GO terms and the data on the drug and to provide a "reason" why it considers the drug to be a high potential candidate for DR or not. To reduce the complexity of the dataset and for enhanced analyzation possibilities, the model additionally had to rate the repurposing potential – based on its reason - of each drug on a decimal scale from 0 to 1. The rating and reason were stored in the database. The model was explicitly instructed to base its reasoning and rating on the information it was provided with from the graph database (biological processes impacted by the drug and data on the drug).

All drugs were rated over ten independent iterations. Each rating within the ten runs was independent of the other (the LLM did not "know" about the ratings provided before and after). Each run through the entire dataset was independent of the others, too. The model did not store any data from any run and was not trained on it either. All iterations were run under equal conditions. The repetitions were performed to account for the variable output of the LLM that provides responses based on probability distributions. Descriptive statistics (minimum, maximum, variance, mean) for each drug across all ten rating iterations were calculated.

We applied the Friedman test for one-way repeated LLM-rating analysis of variance by ranks to test if the ratings per drug were consistent across the rating iterations.[31] Averaging the scores across the 10 iterations led to the final total rating results. Also, it allowed the comparison of each independent run with another to test if the rating was comparable or if it seemed to be random. The authors reviewed the 20 drugs with the highest rating by average for manual review by collecting background

information on the drugs in literature. This included checking if the drugs were already researched for their potential on AD or even indicated for AD (as in both cases, these would not be candidates for DR). The LLM-reasoning output for the drugs remaining was additionally checked for hallucinations (further described in 1.4).

1.3 Prompt Engineering

The prompt (requests to the LLM) blueprint that remained the same for each drug is provided in *Table 1*. For standardized information processing and drug potential rating of the LLM, we used chain-of-thought prompting, which has shown improved reasoning in LLM decisions.[32] However, the strictly standardized chain-of-thought protocol did not sufficiently discriminate between high and low-potential drugs. Therefore, for the final rating, an associative prompt was used that gave the model criteria for its rating without forcing it to follow a certain protocol. The different states of prompts and their results are also provided in *Appendix C* in the supplementary material.

We followed a so-called "Zero-Shot" knowledge-augmented approach with information retrieved from a knowledge graph.[33] This means that the LLM was provided with specific information retrieved from the graph to improve its performance (such as mechanisms of action and pharmacodynamics of the drug). However, it was provided with that information just once within the prompt and did not receive additional information while it was generating an output.

Prompt Blueprint
Introduction (the same for all drugs)
You are a careful pharmaceutical scientist responsible for selecting drugs to repurpose for Alzheimer's disease. You have strictly limited resources and can only select the most promising drugs. You need to rate the drug on a scale from 0 to 1 to classify how promising you consider the repurposing of the drug to be based on careful assessment. The higher the number (1 at max), the more promising you will consider the drug. You will receive information on a drug that has an impact on biological processes. These biological processes have an association with Alzheimer's. You have to decide - based on the information you receive concerning the drug - what impact the drug has on the biological processes given along. You also have to consider if the biological processes impacted by the drug are sufficiently specific to be impacted by a drug. Your resources are highly limited, so you can only provide high ratings to drugs that are very likely to succeed in treating Alzheimer's. Also you have to base your reason on the information you have on the drug and the biological processes it impacts. Be very careful with what you consider to be promising since this has a direct impact on patients. Let your assessment be guided by these questions:

1. Are the biological processes the drug targets relevant for driving Alzheimer's? 2. Does the directionality of the impact of the drug on the biological processes - based on the information you have on the drug - have a preventing or curing effect on Alzheimer's? 3. Is it highly likely that the drug can be taken by patients to prevent or treat Alzheimer's? Provide your reasoning in 'reason_rating' in your JSON output. This is the mandatory form for your JSON output: "{\n" ' "reason_rating\n": "your reason here"\n' ' "rating\n": number from 0 to 1,\n' "}" Follow these instructions and always provide your response as JSON in this format.
Knowledge Enhancement (DrugBank properties for each individual drug)
Pharmacodynamics, **Description**, **Clinical Description (if available)**, **Mechanism of Action**, **Affected GO Processes**, **Name**, **Label**
Outro (the same for all drugs)
You have to base your reason on the information you have on the drug and the biological processes it impacts. This is the mandatory form for your JSON output: "{\n" ' "reason_rating\n": "your reason here"\n' ' "rating\n": number from 0 to 1,\n' "}"
Table 1: **Large Language Model Prompt Blueprint**
This table describes the prompt that was provided to the LLM for each drug. The **bold** printed titles in this table were not part of the prompt but only serve as captions in this table to enhance clarity. The model received one JSON (data format for standardized processing) input file per drug. The **Introduction** was the same for all drugs as it describes the system prompt (explaining the model its role) and the required output to work with the data. This standardized output was a JSON format that allowed seamless integration of the output in the graph database. The **Knowledge Enhancement** content was retrieved for each drug individually. With that, each prompt contained (if available in the DrugBank) the pharmacodynamics, description, clinical description, mechanism of action, affected GO process, name and label of each drug. The **Outro** was – as the **Introduction** – the same for all prompts and "reminded" the model of the mandatory JSON output described in the **Introduction** that was required for further processing the data.

1.4 Hallucination Analysis

For drugs applicable for DR (in the upper top 20 average ratings and no established AD research history), all reasonings for the rating that were provided by the LLM were manually reviewed to identify hallucinations. *Hallucination* in this context was defined as either:

a) A factually wrong statement in the reasoning

AND/OR

b) A self-contradictory statement

Speculative statements (based on correct information from the knowledge enhanced prompt) were not considered hallucinations, as the task of evaluating biological mechanisms' impact for possible DR applicability itself is exploratory and, to some degree, necessarily speculative. Results were reported as booleans, representing if there was either a hallucination concerning the drug during the ratings or not.

1.5 Drug Classification

For interpretation of the results on the chemical level, the drugs were analyzed for their chemical class listed in the DrugBank (e.g., organoheterocyclic compounds or benzenoids). Since many drugs stored in the DrugBank are still (or will always remain) in their experimental phase and there is no pharmacological classification of them, the LLM was asked to classify each drug based on the biological GO processes annotated with it that was considered to be most important in the reason for why it was selected or not. This classification run was done once for each drug and is independent of the rating iterations.

1.6 Clinical Trials Data

Following procedures established in the literature, we complemented the interpretation of the rated drugs by retrieving the registrations of clinical trials from clinicaltrials.gov.[34] This gave the number of studies for each drug and the clinical trial phase in which they were registered. In addition, the characteristics of the study population, such as sex and geographic location, were analyzed to address potential bias in the data and LLM rating. Details regarding the sex ratio in the studies are provided in *Appendix F* in the supplementary document (most studies included all sexes, more studies included only females, and fewer studies included only males). The geography of the institutions involved in the studies was then projected on a geographic map to provide insights into the regional distribution of the medications. This step was taken to determine if the results are applicable to all populations to the same degree. Therefore, it was investigated in what regions the drugs were studied in the first

place and if the drug rating is correlated to a geographic region. This approach addressed the biases in the training data of the LLM when advocating for an AI-supported Drug Repurposing approach. The map represents the number of studies per region and their rating by making use of a color-graded score. The 'Study Score' was calculated by the *number of studies * rating of drug * 10* to account for the region and study population and also for the rating the LLM gave for each drug. The **10* in the calculation was done to always get to natural (whole) numbers that are applicable to the plotting.

1.7 Reproducibility of Results

The entire study setup was repeated twice to ensure the reproducibility of the results. As described above, the rating of the drugs was repeated ten times to account for randomness in LLM responses and to address the variability of the output statistically (Friedman test). In the replication step, these iterations were only done three times since that process was mainly for setting up the database and the following rating processes. The ten iterations in the final results database themselves are already independent of each other. Therefore, another seven runs in the replication database would not have provided any benefit compared with the actual run of 10 iterations.

Author Contributions were reported according to CRedit standards.[35]

2 Results

2.1 LLM Approach Results

The rating distribution between the iterations remained consistent as the Friedman test that tested for differences across rating iterations for each individual drug was insignificant (*p-value=0.24*). This indicates no strong evidence for significant differences in drug ratings across all iterations.

In 135 of 5,967 (~ 2%) drugs rated by the LLM, the input prompt exceeded the context window of Llama (the prompt consisted of more than 8,000 tokens). For 4 (out of 5,967) drugs, the LLM provided at least one non-numeric rating. These four drugs were therefore excluded from the Friedman test, and the plots were based on the rating (but remained in the database).

2.2 Best-Performing Drugs

Table 2 lists the 20 drugs with the highest ratings across all iterations. Drugs with AD as an indication scored the highest but are no candidates for DR (as AD is their indication already).

CTS-2166 is a beta-secretase inhibitor under investigation for AD disease treatment.[36] Lecanemab is an amyloid beta-targeting antibody approved by the FDA for AD treatment.[37] Verubecestat was under investigation for AD treatment[38]; its development, however, was put on hold in 2017.[39] The drug with the highest rating that is not under explicit investigation for AD disease is Ripretinib, a tyrosine kinase inhibitor indicated for the treatment of advanced gastrointestinal stromal tumors.[40] Ten drugs of the 20 highest rating medications have neither been indicated for AD nor been under investigation for it.

20 Highest-Rating Drugs by Average across 10 Rating-Iterations						
Name	Average Rating	Variance	Max	Min	Reasoning in the first iteration	State of research and background
CTS-21166	0.90	0.00024	0.95	0.9	CTS-21166, as a beta-secretase inhibitor, targets the proteolytic process involved in Alzheimer's pathology. The biological processes impacted by CTS-21166, such as protein catabolic process and membrane protein ectodomain proteolysis, are relevant to driving Alzheimer's disease. Additionally, the directionality of the impact suggests a preventive or curative effect on Alzheimer's. With excellent pharmacokinetic properties, it is highly likely that patients can take this drug to prevent or treat Alzheimer's.	Under investigation for AD[36]
Lecanemab	0.90	0.00191	0.95	0.8	Based on the information provided, Lecanemab targets amyloid-β plaques in a dose- and time-dependent manner, which is highly relevant for driving Alzheimer's disease. The directionality of its impact suggests a preventing or curing effect on Alzheimer's. Additionally, it can be taken by patients to prevent or treat the disease, as demonstrated by its clinical trials and FDA approvals.	AD indicated[37]
Verube-cestat	0.88	0.00224	0.95	0.8	Verubecestat's mechanism of action in inhibiting BACE, a key enzyme in amyloid β peptide production, suggests a potential therapeutic effect on Alzheimer's disease. The biological processes it impacts, such as proteolysis, protein catabolic process, and membrane protein ectodomain proteolysis, are relevant to driving Alzheimer's pathology.	Was investigated for AD[38,39]
CAD106	0.84	0.00266	0.9	0.8	The drug CAD106 has a mechanism of action that directly targets the formation of beta-amyloid plaques in the brain, which is considered a hallmark of Alzheimer's disease. This suggests a strong potential for treating the underlying pathology. The impacted biological processes are also relevant to Alzheimer's disease, including neuron remodeling and apoptosis, which supports the drug's potential for preventing or curing the disease.	Under investigation for AD[41]
NGX267	0.84	0.00266	0.9	0.8	NGX267 has a high potential for repurposing as it targets biological processes relevant for driving Alzheimer's, such as synaptic transmission and signal transduction. Additionally, its mechanism of action on	Was investigated for AD[42]

					phospholipase C-activating G-protein coupled receptor signaling pathway may contribute to delaying disease progression. Furthermore, NGX267 has shown potential to reduce symptoms and slow disease progression in Alzheimer's patients.	
4-{2-[(7-amino-2-furan-2-yl[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino]ethyl}phenol	0.83	0.00233	0.9	0.8	The drug has a positive impact on biological processes associated with Alzheimer's disease, including regulation of synaptic transmission and plasticity, which are key mechanisms underlying the progression of Alzheimer's. Additionally, it affects apoptosis and inflammatory responses, both of which are important in Alzheimer's pathology. However, some of these processes are not specific to Alzheimer's, such as membrane depolarization and locomotory behavior. Nevertheless, the overall profile suggests a potential therapeutic effect on Alzheimer's disease.	Research state unclear[43,44]
Brasofensine	0.83	0.00233	0.9	0.8	Brasofensine's ability to positively regulate ERK1 and ERK2 cascade, long-term synaptic potentiation, neuroblast proliferation, and receptor internalization suggests its potential to promote neuronal health and prevent Alzheimer's disease pathology.	Was investigated for Parkinson's and AD[45,46]
Ripretinib	0.83	0.00788	0.95	0.7	The drug's ability to positively regulate peptidyl-serine phosphorylation, which is relevant to Alzheimer's disease, and its impact on cellular response to thyroid hormone stimulus, which may be related to the disease's underlying biology.	Treatment of advanced gastrointestinal stromal tumors[40]
CX-717	0.83	0.00233	0.9	0.8	CX-717's impact on glutamate receptor signaling pathway, synaptic transmission, and signal transduction suggests potential therapeutic benefits for Alzheimer's disease treatment.	Under investigation for AD[47]
D-glucose	0.82	0.00736	0.95	0.7	The drug D-glucose is a glucose transporter that regulates glucose transmembrane transport, which is involved in the insulin receptor signaling pathway and has been linked to Alzheimer's disease. Additionally, it regulates calcium ion import, which can have neuroprotective effects.	Role in AD investigated[48] , not considered a treatment
Aranidipine	0.82	0.00402	0.9	0.7	The drug Aranidipine targets biological processes related to receptor-mediated endocytosis, retina homeostasis, and transmembrane transport, which are implicated in Alzheimer's disease. Furthermore, it modulates inflammatory response, negative regulation of tumor necrosis factor production, and negative regulation of interleukin-6 production, all of which are key features of the disease. Given its potential to	Under investigation for treatment of hypertension[49]

					influence multiple relevant biological processes, I believe Aranidipine has a high likelihood of being effective in Alzheimer's disease.	
Pertuzumab	0.82	0.00180	0.9	0.8	Pertuzumab's mechanism of action involves the inhibition of HER2-mediated signaling, which is also implicated in Alzheimer's disease. Additionally, Pertuzumab has been shown to have neuroprotective effects and may help prevent neuronal degeneration. The biological processes it impacts, such as signal transduction, protein phosphorylation, and positive regulation of cell growth, are all relevant to the pathology of Alzheimer's disease.	Indicated for HER2-positive metastatic breast cancer[50]
JNJ-37822681	0.82	0.00180	0.9	0.8	JNJ-37822681's ability to positively regulate ERK2 cascade, long-term synaptic potentiation, and neuroblast proliferation suggests its potential to modulate Alzheimer's disease-related pathways, warranting further testing.	Investigated for Schizophrenia treatment[51]
Umifenovir	0.82	0.00236	0.95	0.8	Umifenovir regulates lipid metabolic process, which is associated with Alzheimer's disease pathology, making it a potential candidate for repurposing.	Antiviral agent approved in some countries for prophylaxis and treatment of influenza and other respiratory viral infections[52]
CYT006-AngQb	0.82	0.00124	0.9	0.8	The drug CYT006-AngQb has a significant impact on biological processes related to brain development, cell surface receptor signaling pathway, and intracellular signal transduction, which are all relevant to Alzheimer's disease. Additionally, it regulates inflammatory response, which is also a key feature of the disease. Furthermore, it positively regulates transcription, DNA-templated, phosphoprotein phosphatase activity, nitric oxide biosynthetic process, extrinsic apoptotic signaling pathway, cytokine production, and protein metabolic process, which are all potential mechanisms that could be targeted to treat Alzheimer's.	A therapeutic vaccine in development for the treatment of hypertension by activating the immune system to target Angiotensin II[53]
DPI59	0.82	0.00344	0.9	0.7	DPI59's ability to regulate cell cycle, protein autophosphorylation and Ras protein signal transduction makes it a promising candidate for Alzheimer's disease kinase B signaling repurposing.	Research state unclear[54]
MK-0354	0.82	0.00177	0.9	0.8	MK-0354's ability to positively regulate release of sequestered calcium ion into cytosol, protein phosphorylation, and phosphatidylinositol 3-kinase/protein kinase B signal transduction, which are	Was investigated for Atherosclerosis[55]

					all relevant to Alzheimer's disease regulation of epidermal growth factor receptor signaling pathway.	
Indigotindisulfonic acid	0.82	0.01566	0.95	0.5	The drug Indigotindisulfonic acid has shown promise in regulating neuron differentiation and MAPK cascade, both of which are relevant biological processes for Alzheimer's disease. Additionally, it modulates G-protein coupled receptor signaling pathway, a key pathway involved in neuronal function and survival. Given its potential to impact multiple key pathways, I believe this drug is worth further testing for repurposing as an Alzheimer's treatment.	Contrast agent with cardiovascular effects[56]
Darifenacin	0.82	0.00177	0.9	0.8	Darifenacin's ability to modulate the cholinergic system, which is involved in Alzheimer's disease pathology, makes it a strong candidate for repurposing. Additionally, its impact on lipid metabolic process and xenobiotic transport may also contribute to its potential therapeutic effects.	M3 muscarinic blocker for treating urinary incontinence[57]
Selenious acid	0.82	0.00177	0.9	0.8	The drug Selenious acid has a high potential for Alzheimer's disease drug repurposing due to its impact on biological processes related to apoptosis regulation, inflammation modulation, and oxidative stress response. Its ability to regulate neuron apoptotic process, negative regulation of release of cytochrome c from mitochondria, and negative regulation of oxidative stress-induced intrinsic apoptotic signaling pathway suggests that it may have a therapeutic effect in reducing neuronal death and oxidative damage associated with Alzheimer's disease.	Essential trace element under investigation for AD treatment options[58]

Table 2: **Top 20 drugs across all iterations with a rating and example reason**

This table shows the top 20 drugs, along with their average ratings across all 10 rating iterations by the LLM. Also, it provides the variance across the rating and the maximal and minimal rating per drug across the 10 iterations. The reasoning behind the provided rating was taken from the first iteration to give an example. The third column shows the state of research and indication (if applicable) of each drug based on manual literature review.

Drugs with no indication for AD or AD research background are indicated by purple background as they are potential drug repurposing candidates.

The decision to set '20' as the upper limit for drugs being analyzed more closely was done arbitrarily but based on the the distribution of ratings. The density plot in Figure 2a-Appendix in *Appendix D* shows a maximum of ratings just below 0.8. The top 20 drugs are those drugs that are ahead of this maximum. Drugs applicable for DR (as they are not under investigation for AD) are marked in purple.

Nine of the 20 best-performing drugs have either been under investigation or were investigated for Alzheimer's disease. In two cases ('4-{2-[(7-amino-2-furan-2-yl[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino]ethyl}phenol' and 'DPI59', the state of research was not determinable based on the literature. Nine high-performing drugs had no determinable history of AD consideration. The best performing chemical class of drugs with a relevant number of drugs classified as it was "organoheterocyclic compounds" (*Appendix E* provides a detailed overview of the chemical classes)

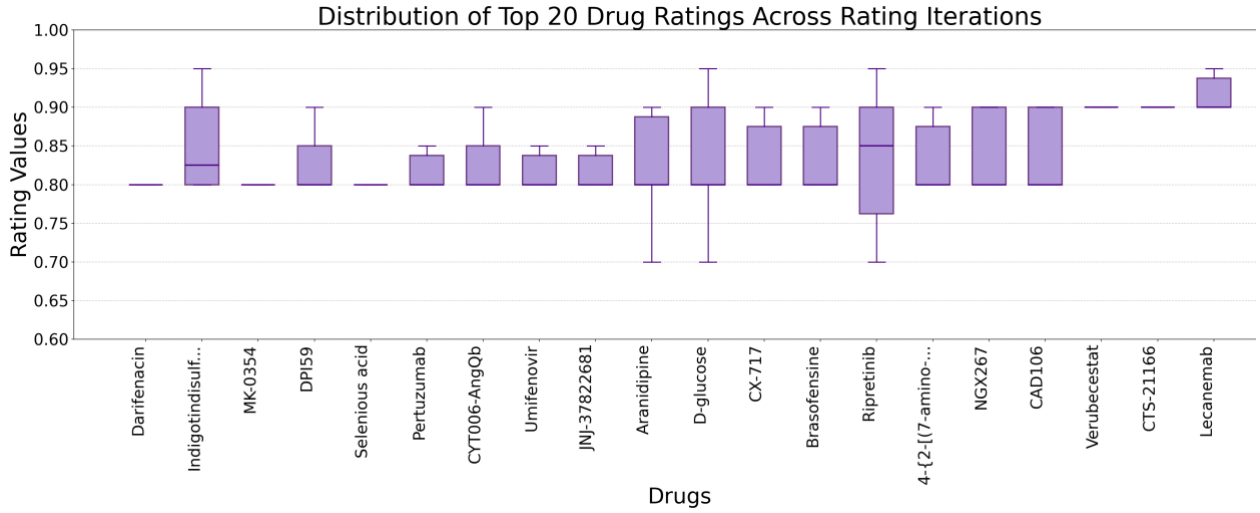

Figure 3: Distribution of Top 20 Drug Ratings Across Rating Iterations
This plot shows the boxplots of the upper 20 drugs sorted by their average rating. As some of the drugs had the same average rating (such as Lecanemab and CTS-21166) the sorting for those drugs is random. Indigotindisulfonic acid has the highest variance at 0.01566. A plot that includes boxplots representing the rating iterations of all drugs is located in the supplement in *Appendix D*. The drug shortened for layout reasons in the plot is: '*4-{2-[(7-amino-2-furan-2-yl[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino]ethyl}phenol*'.

2.3 Hallucination Check

The hallucination check of reasonings of the DR candidates was done manually. One hallucination was detected across all rating iterations of the DR candidates (Pertuzumab). The LLM reported, "Pertuzumab has been shown to have neuroprotective effects and may help prevent neuronal degeneration", which is a wrong statement.[59]

While D-glucose does not fall in the category of DR applicable drugs as it has an AD research history and is not considered a treatment,[48] it has to be pointed out that a hallucination occurred for D-Glucose as well (provided in reasoning in *Table 2*). The LLM called D-Glucose a "glucose transporter", which is factually wrong.

2.4 Adverse Effects

The Adverse Effects check was done to exploratively assess the risk of repurposing the drugs. While we do not recommend based any prospective studies that put patients at risk solely based on the results presented in this paper, it remains important to keep a perspective on the medications' safety profiles.

Name	Adverse Effects (Selection)	Any FDA Approval
Ripretinib	Dermatologic Toxicities, Primary Cutaneous Malignancies, Hypertension, Cardiac Dysfunction, Impaired Wound Healing, Embryo-fetal toxicity[60]	Yes[60]
Aranidipine	Headache, ankle edema, alvo adstricta, apex linguae hot sensation, neck pain[49]	No[61]
Pertuzumab	Fatigue, Asthenia, Edema peripheral, Mucosal inflammation, Pyrexia, Alopecia, Rash, Diarrhea, Nausea, Vomiting, Stomatitis, Neutropenia, Leukopenia, Headache, Dysgeusia, Peripheral Sensory Neuropathy, Myalgia, Arthralgia, Decreased Appetite, Insomnia[59]	Yes[59]
JNJ-37822681	Insomnia, Akathisia, Anxiety, Somnolence, Agitation, Headache, Extrapyramidal Symptoms, Nausea[51]	No[62]
Umifenovir	Diarrhea, Nausea, safety profile not well investigated[52]	No[63]
CYT006-AngQb	Erythema, Oedema, Pain (at injection site), Mild Headache[64]	No[65]
DPI59	No safety profile studies available[66]	No[54]
MK-0354	Flushing, ALT Increase[67]	No[68]
Indigotindisulfonic acid	Nausea, Vomiting, Constipation, Abdominal Pain, Pyrexia, ALT Increase, Dysuria[69]	Yes[69]
Darifenacin	Constipation, Dry Mouth, Headache, Dyspepsia, Nausea, Urinary Tract Infection, Accidental Injury, Flu Symptoms[70]	Yes[70]

Table 3: **Adverse Effects Screening**

The table depicts a selection of adverse effects of the drugs applicable for DR. If available, an FDA report of the safety profile of the drug was used as reference for the adverse effects. For drugs that were too experimental to have an FDA safety profile report, a literature search was done on Pubmed. The list of adverse effects makes no claim of completeness but aims to provide an overview what drugs are generally safer than others among the DR high potential candidates.

2.5 Studies on the Drugs

We retrieved data for all drugs associated with AD from clinicaltrials.gov (on 07/26/2024). However, of the 5,967 drugs with AD-associated GO processes, only 2,918 had retrievable trials available. The data contained information on the phase of the drug trial and the geographic location of the research facilities investigating the drug (such as a hospital).

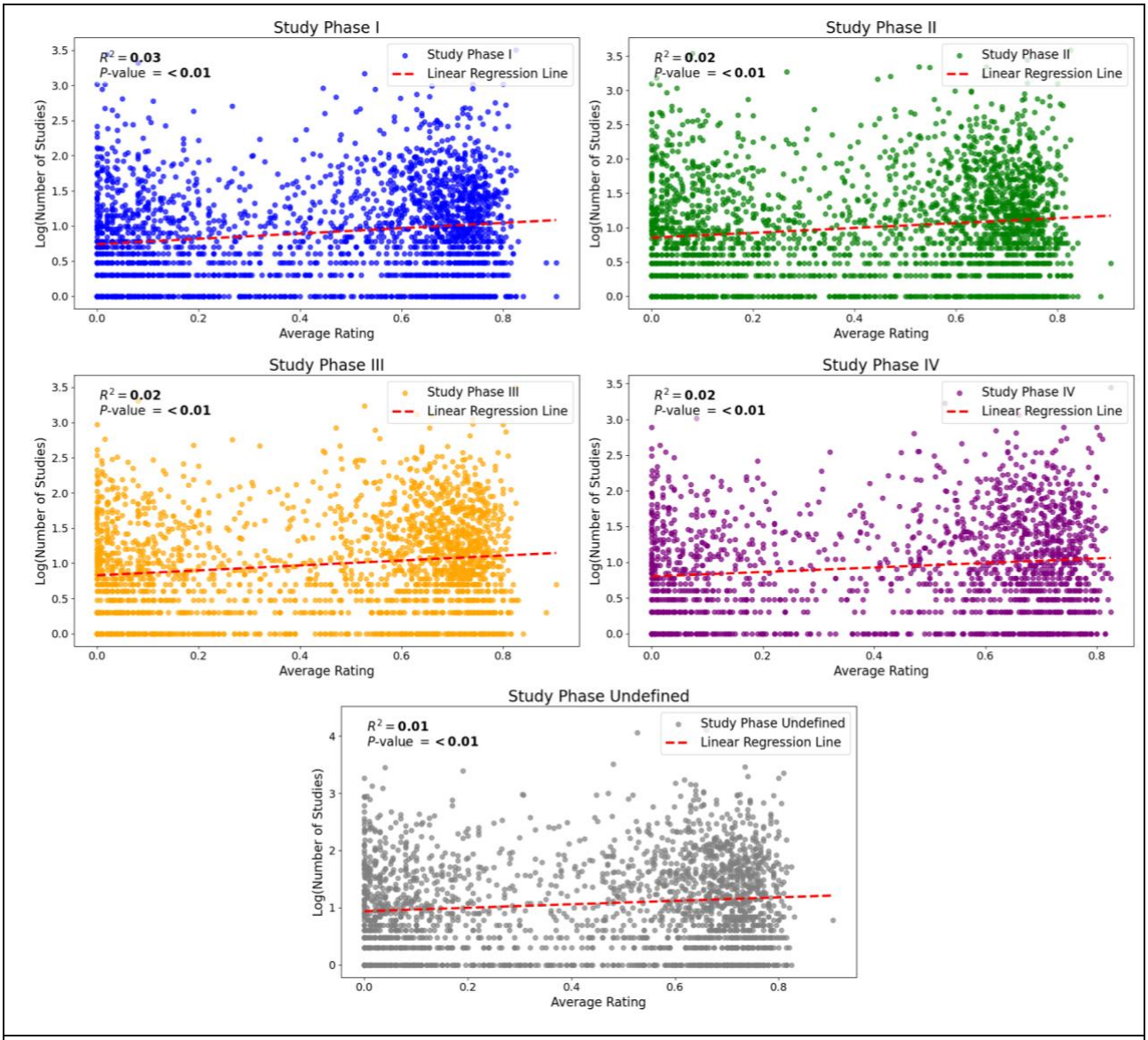

Figure 4a: **Rating of Drugs in Dependence of Study Phases and Number of Studies**

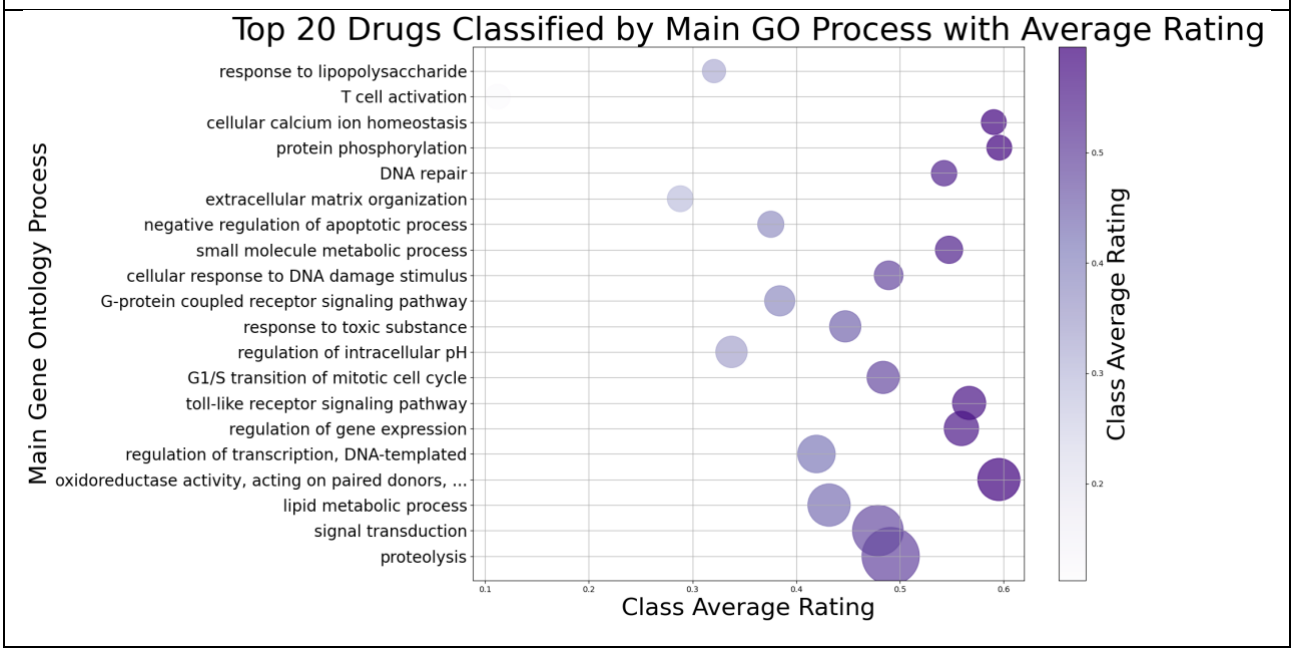

Figure 4b: **Classification of Rated Drugs by Gene Ontology (GO) Process**
Figure **4a**) Each plot shows the base-10 logarithm of the number of studies associated with each drug in dependence on the average rating the drug received across all rating iterations. Each subplot stands for one Study Phase according to the registration of the studies on clinicaltrials.gov. A linear regression line was fitted to the individual data points using the least square method. The analysis suggests a tendency towards higher average ratings for drugs that have a greater (log-transformed) number of (registered) studies associated with them. For all phases, the p-values associated with the regression coefficients were lower than 0.05, indicating that the relationships are statistically significant at the 5% significance level. However, the R^2 values for all regression models were also lower than 0.05 showing that less than 5% of the variance in the log-transformed number of studies is explained by the average drug ratings. Consequently, while the linear regression suggests a significant relationship, the average drug rating is a weak predictor of the number of studies associated with each drug. As there were only 2918 (retrievable) registered studies for the drugs investigated in this study, 3049 drugs are not shown on the graphs. Figure **4b**) In this plot, the drugs were classified by the LLM according to the GO process that was most relevant for the drug repurposing (DR) (based on the reason provided). The size of the bubble depends on the number of drugs whose AD treating mechanism was considered mostly driven the the respective GO process. The x-axis shows the average rating of drugs classified with that GO term. The average rating is also color-graded, deeper purple indicating a higher class average rating. Only the 20 most classified GO-terms are shown for readability purposes. The full GO-term at the fourth position from the bottom (which was truncated for layout reasons) is: *'oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen'*.

The geographic data concerning the rating of the LLM led to a map that has most of its data points in North America and Europe. Each dot represents a research-facilitating institution (such as a hospital). Most retrieved studies were conducted on those continents, but the LLM rating for drugs tested in these areas was also higher. The color density depended – as described in the Methods – on the number of studies per area *and* the average rating of the drugs.

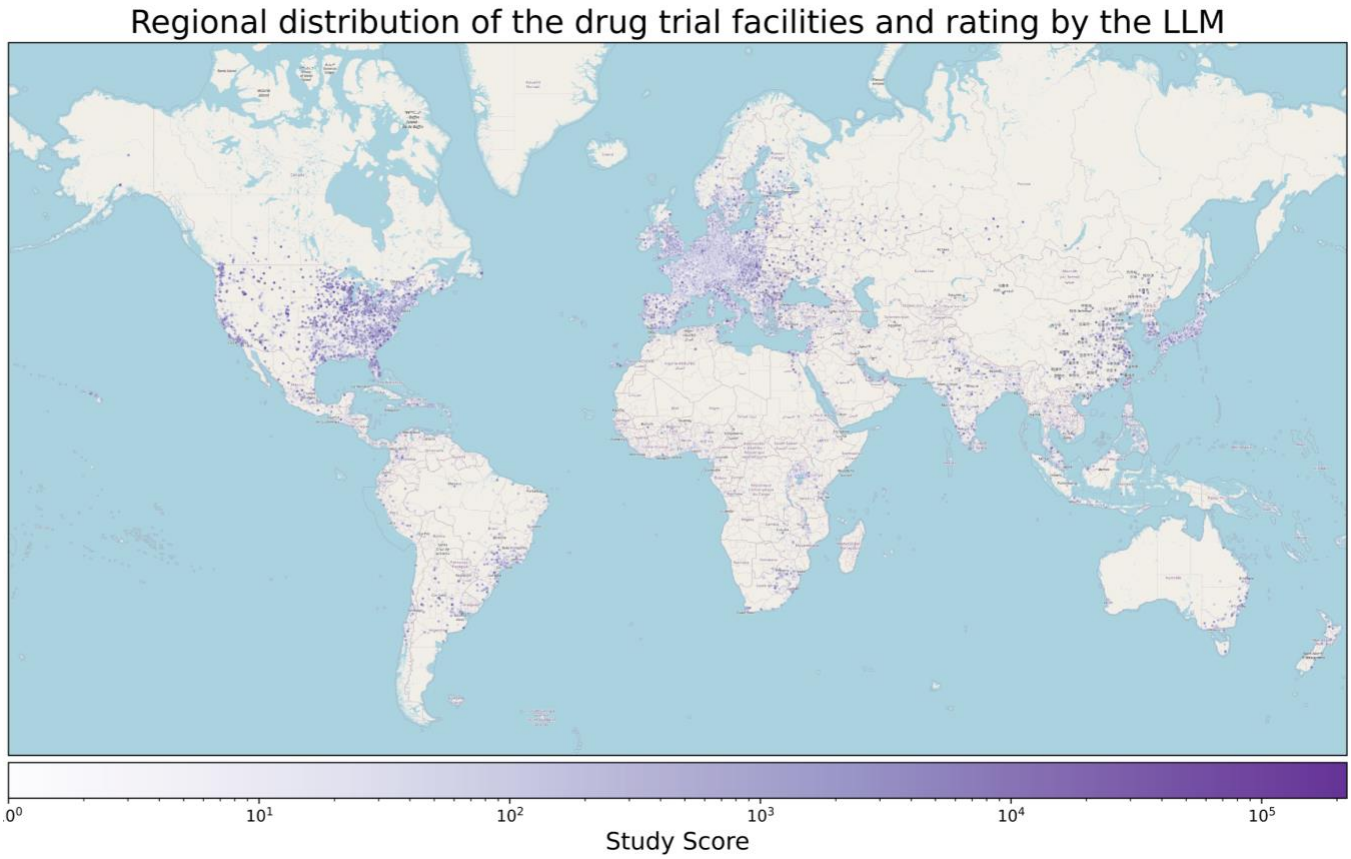

Figure 5: **Regional distribution of the drug trial facilities and rating by the LLM**

The map[71,72] shows the regional distribution of the drug trial facilities and the LLM's ratings. Each dot on the map represents a drug trial facility provided in the trial registrations. The color intensity corresponds to the 'Study Score', which was calculated using *number of* studies * *average rating* * *10* to obtain natural (whole) numbers. Therefore, darker purple indicates higher ratings and/or more conducted studies in an area.

For multicentered studies (e.g., several hospitals) all research facilities are shown on the map. A logarithmic normalization was applied to the 'Study Score' to allow for color-differentitation. This provides a more interpretable representation of the score across all regions.

The Alzheimer's associated drugs from the DrugBank were mainly studied on populations in the Northern Hemisphere and those drugs also received a higher rating by the LLM. This may indicate that the output of the LLM is not applicable to populations to the same degree. Possibly, region-specific influences on the effects of the drugs (such as climate, nutrition, ethnicity, healthcare system) have a biased representation in the drug repurposing pipeline and need to be considered when interpreting and applying the results.

3 Discussion and Conclusion

3.1 Summary of Main Results

A systematic network creation was performed that unifies information from biology (GO) pharmacology (DrugBank) and their interplay. 5,967 drugs were rated for their DR potential. The rating of the individual drugs did not vary significantly (according to the Friedman test conducted)

across the rating iterations of the LLM. The ratings remained fairly stable across all iterations with the highest variance of 0.01566 for Indigotindisulfonic acid. The highest-rated drugs were either indicated or investigated for AD treatment. However, in the upper twenty drugs, ten drugs were applicable for DR consideration since they have not been associated with AD in the literature. The number of registered drug trials had a slightly increasing impact on the rating of the LLM, which may be caused by more training data on these drugs. Drugs with high ratings and many associated trials were mostly investigated in North America and Europe, which may indicate that the results are not applicable to all patient groups equally.

3.2 Drug Research Facilitation

Due to the graph database design, results can be queried quickly and deployed for individual project purposes. This may include domain-related queries for specific use cases or an improved understanding of the interplay of drugs in polypharmacy if different medications target the same biological processes.

While the current results do not justify prospective DR clinical trials, we propose to conduct retrospective analyses, considering the performance of the high-rated drugs and their effect on AD patients. Analyzing the effect of Ripretinib and Pertuzumab – the highest-rated medicines that are not AD-related by their indication - on patients across AD stages may be a starting point for this. However, limiting such a study to those two drugs is arbitrary, and more high-rating drugs may be considered, too. If a retrospective study indicates a significant, positive effect on AD for some of the high-rated drugs, those medications may be tested in RCTs. Actual drug trials that test the proposed medications are the only way to validate the concept.

This study took the GO ARUK-UCL dataset as a biological basis, although the pipeline may be easily adapted to set proteins as a starting point since proteins have annotated biological processes (for example, in the UniProt[73] resource). That way, one can get from the protein to the biological processes and from there to the drugs and their effects. However, when choosing such an approach, the directionality of the processes needs to be considered. The GO terms imply a directionality within their name (e.g., positive regulation of x, negative regulation of y, etc.). If one starts with a manually selected set of processes, this directionality was – ideally – already accounted for. However, the mere name of a protein does not imply a directionality. If directionality is provided, a set of proteins is also a valid starting point for the pipeline. The LLM-driven drug repurposing pipeline may also be employed for other pathologies as long as there is a systematic biological entity set at the starting point.

While we do not recommend prospective studies based on these exploratory results, if clinical trials are considered in the future, a thorough safety profile check has to be done that exceeds the overview in *Table 3*.

3.3 Limitations

Since the AD driving processes are not yet known/fully understood, the ARUK-UCL dataset, which was used as a starting point, may lack important GO terms or also include terms that are not significant to the pathology's etiology. While the DrugBank is one of the most established datasets for drugs, it may not include all experimental and new drugs that are possibly applicable for drug repurposing for AD. Also, only 7,590 of the drugs have annotated GO terms. Those without annotated GO terms were excluded from our approach since it was based on the applicability of the preselected biological terms from ARUK-UCL.

While we tested different prompts to find one that brings valuable outputs from the LLM, prompt engineering is always imperfect since the number of possible prompts is infinite. Excerpts from the prompt engineering are given in the secondary supplementary material.

The Large Language Model we used (Llama3:8b) had 8 billion parameters and a context length of 8.2k tokens. While such a model would have been considered highly advanced only a few years ago, larger models have emerged. Shortly before the research on this paper was concluded, Meta launched the larger (open source) Llama3:400b 400 billion parameter model. In the future, LLM-driven drug repurposing should also consider such models. However, one also has to keep in mind that a larger model is not equivalent to better outcome performance, and improved results based on a larger model are not guaranteed at all.[74] Currently, the number of openly available LLMs is limited, and this study only used Llama3 by Meta and no models by other providers. Future research should extend the model selection to a diverse set of open-source LLMs.

The LLM-driven DR approach itself is debatable since addressing DR with an LLM is not established. LLMs work by predicting the next likely token (usually a word or a part of a word). They have no consciousness of the matter they are dealing with and are easily impacted by keywords and minor variations in the prompt that is addressing them. Further research that analyses the scientific value of the ratings is required to validate such an approach.

The upper seven drugs that had the highest rating for drug repurposing potential were either indicated for AD already or were/are at least under investigation for treating AD. Since the LLM was prompted to rate all drugs that had AD-driving biological processes associated with them, some of the drugs were necessarily under investigation for AD or even indicated for it in some countries (such as Lecanemab). Also, in cases where the indication was provided in the DrugBank dataset, the LLM received that information as part of the prompt. Ripretinib (ranked 8th) was the highest-rated drug with a determinable research history not investigated for AD. The fact that AD-associated

medications had the highest rating allows for several interpretations. While it may indicate that the LLM is aligned with pharmacological AD research, it may also have rated these medications so highly because it was trained based on world data (which likely contained information regarding these medications). Whatever the specific reason may be why these drugs received the highest ratings, it would have been unexpected if they were – as AD drugs – rated as being less promising than (currently) unrelated drugs. Future LLM DR research using more advanced models that can handle more input than current models may benefit from providing more details about each drug.

The drug classification based on the GO term for Figure 4b was based on the classification of the LLM since there were no pharmacological class categorizations available for many medications (particularly those that are still so experimental that such data is not available). Mistakes in terms of classification may have occurred here. However, since the figure was about giving an overview of the drugs with their rating, a few single wrong classifications would – given the scale - have changed neither the results nor the graph notably.

There were only clinical trials on 2,918 drugs retrievable from clinicaltrials.gov, possibly because there might not have been trials on these drugs. However, it is also possible that for those drugs that do not have a generic name but only an IUPAC classification, the data was not retrievable for technical reasons. The retrieval process and its limitations are extensively discussed in *Appendix F*.

The Alzheimer's associated drugs from the DrugBank were mainly studied on populations in the northern hemisphere and those drugs also received a higher rating by the LLM. As the model was trained on the available data on the internet, we wanted to pay attention to flag this potential bias inherent to the LLM. This may indicate that the DR rating results are not applicable to all populations to the same degree. We took this step to address the biases in the training data of the LLM when advocating for an AI-supported Drug Repurposing approach.

3.4 Conclusions

This advancement may move the synergies of ontologies, databases, and LLMs closer to each other. LLMs make it possible to enhance manual research work by automizing tasks that require low levels of semantic understanding. The time and resources saved may be invested in new research. Therefore, no such pipeline would replace the critical thinking of the researcher, but novel thought experiments and retrospective studies could be made possible by taking up the low-level understanding of knowledge work. This approach should move us toward making better mistakes in the endeavor to find a cure for AD.

4 References

1. Bettencourt C, Skene N, Bandres-Ciga S, et al. Artificial intelligence for dementia genetics and omics. *Alzheimers Dement*. 2023;19(12):5905-5921. doi:10.1002/alz.13427

2. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement Transl Res Clin Interv*. 2018;4(1):575-590. doi:10.1016/j.trci.2018.06.014

3. PubMed. Alzheimer's Disease on PubMed. pubmed.ncbi.nlm.nih.gov. October 31, 2024. Accessed October 31, 2024. https://pubmed.ncbi.nlm.nih.gov/?term=alzheimer%27s+disease

4. Doherty T, Yao Z, Khleifat AA l., et al. Artificial intelligence for dementia drug discovery and trials optimization. *Alzheimers Dement*. 2023;19(12):5922-5933. doi:10.1002/alz.13428

5. Marzi SJ, Schilder BM, Nott A, et al. Artificial intelligence for neurodegenerative experimental models. *Alzheimers Dement*. 2023;19(12):5970-5987. doi:10.1002/alz.13479

6. Das AKK, Sharma D, Sharma L. Drug repurposing strategy for treating Alzheimer's disease. *Alzheimers Dement*. 2021;17(S9):e058503. doi:10.1002/alz.058503

7. Grabowska ME, Huang A, Wen Z, Li B, Wei WQ. Drug repurposing for Alzheimer's disease from 2012–2022—a 10-year literature review. *Front Pharmacol*. 2023;14. doi:10.3389/fphar.2023.1257700

8. Rao PPN, Tin G, Mohamed T, Shakeri A, Pham AT. Drug repurposing for Alzheimer's disease: Selective serotonin reuptake inhibitors. *Alzheimers Dement*. 2020;16(S9):e039163. doi:10.1002/alz.039163

9. Parvathaneni V, Kulkarni NS, Muth A, Gupta V. Drug repurposing: a promising tool to accelerate the drug discovery process. *Drug Discov Today*. 2019;24(10):2076-2085. doi:10.1016/j.drudis.2019.06.014

10. Verderio P, Lecchi M, Ciniselli CM, Shishmani B, Apolone G, Manenti G. 3Rs Principle and Legislative Decrees to Achieve High Standard of Animal Research. *Animals*. 2023;13(2):277. doi:10.3390/ani13020277

11. Berners-Lee T, Hendler J, Lassila O. The Semantic Web: A New Form of Web Content That is Meaningful to Computers Will Unleash a Revolution of New Possibilities. *Sci Am*. 2001;284:34-43.

12. Ashburner M, Ball CA, Blake JA, et al. Gene Ontology: tool for the unification of biology. *Nat Genet*. 2000;25(1):25-29. doi:10.1038/75556

13. Wishart DS, Girod S, Peters H, et al. ChemFOnt: the chemical functional ontology resource. *Nucleic Acids Res*. 2023;51(D1):D1220-D1229. doi:10.1093/nar/gkac919

14. Malhotra A, Younesi E, Gündel M, Müller B, Heneka MT, Hofmann-Apitius M. ADO: A disease ontology representing the domain knowledge specific to Alzheimer's disease. *Alzheimers Dement*. 2014;10(2):238-246. doi:10.1016/j.jalz.2013.02.009

15. Hertling S, Paulheim H. OLaLa: Ontology Matching with Large Language Models. In: *Proceedings of the 12th Knowledge Capture Conference 2023*. K-CAP '23. Association for Computing Machinery; 2023:131-139. doi:10.1145/3587259.3627571

16. Amini R, Norouzi SS, Hitzler P, Amini R. Towards Complex Ontology Alignment using Large Language Models. Published online April 16, 2024. doi:10.48550/arXiv.2404.10329

17. Chen Y, Fu Q, Yuan Y, et al. Hallucination Detection: Robustly Discerning Reliable Answers in Large Language Models. In: *Proceedings of the 32nd ACM International Conference on Information and Knowledge Management*. CIKM '23. Association for Computing Machinery; 2023:245-255. doi:10.1145/3583780.3614905

18. Vaswani A, Shazeer N, Parmar N, et al. Attention is all you need. In: *Proceedings of the 31st International Conference on Neural Information Processing Systems*. NIPS'17. Curran Associates Inc.; 2017:6000-6010.

19. Jiang Z, Xu FF, Gao L, et al. Active Retrieval Augmented Generation. Published online October 21, 2023. doi:10.48550/arXiv.2305.06983

20. Kramarz B, Huntley RP, Rodríguez-López M, et al. Gene Ontology Curation of Neuroinflammation Biology Improves the Interpretation of Alzheimer's Disease Gene Expression Data. *J Alzheimers Dis*. 75(4):1417-1435. doi:10.3233/JAD-200207

21. Wishart DS, Knox C, Guo AC, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res*. 2006;34(Database issue):D668-D672. doi:10.1093/nar/gkj067

22. The Gene Ontology Consortium, Aleksander SA, Balhoff J, et al. The Gene Ontology knowledgebase in 2023. *Genetics*. 2023;224(1):iyad031. doi:10.1093/genetics/iyad031

23. Gene Ontology, Kramarz B, Lovering RC, et al. QuickGO:: ARUK-UCL Annotation List. Gene Ontology. Accessed June 7, 2024. https://www.ebi.ac.uk/QuickGO/annotations?assignedBy=ARUK-UCL

24. DrugBank. DrugBank Release Version 5.1.12 | DrugBank Online. go.drugbank.com. March 14, 2024. Accessed September 23, 2024. https://go.drugbank.com/releases/latest

25. Vitali F, Zhang J, Wang T, Brinton RD. Computational identification of precision therapeutics for Alzheimer's disease specific to endocrine and APOE genotype status. *Alzheimers Dement*. 2023;19(S21):e080506. doi:10.1002/alz.080506

26. DrugBank. Memantine. go.drugbank.com. Accessed August 25, 2024. https://go.drugbank.com/drugs/DB01043

27. DrugBank. VP025. go.drugbank.com. Accessed August 25, 2024. https://go.drugbank.com/drugs/DB05133

28. Touvron H, Lavril T, Izacard G, et al. LLaMA: Open and Efficient Foundation Language Models. Published online February 27, 2023. doi:10.48550/arXiv.2302.13971

29. Dubey A, Jauhri A, Pandey A, et al. The Llama 3 Herd of Models. Published online August 15, 2024. doi:10.48550/arXiv.2407.21783

30. Meta. Download Llama. Llama. Accessed September 27, 2024. https://www.llama.com/llama-downloads/

31. Friedman M. The Use of Ranks to Avoid the Assumption of Normality Implicit in the Analysis of Variance. *J Am Stat Assoc*. 1937;32(200):675-701. doi:10.1080/01621459.1937.10503522

32. Wei J, Wang X, Schuurmans D, et al. Chain-of-Thought Prompting Elicits Reasoning in Large Language Models. Published online January 10, 2023. doi:10.48550/arXiv.2201.11903

33. Baek J, Aji AF, Saffari A. Knowledge-Augmented Language Model Prompting for Zero-Shot Knowledge Graph Question Answering. Published online June 7, 2023. doi:10.48550/arXiv.2306.04136

34. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement Transl Res Clin Interv*. 2023;9(2):e12385. doi:10.1002/trc2.12385

35. CRediT. CRediT. Accessed November 30, 2024. https://credit.niso.org/

36. Mikulca JA, Nguyen V, Gajdosik DA, et al. Potential novel targets for Alzheimer pharmacotherapy: II. Update on secretase inhibitors and related approaches. *J Clin Pharm Ther*. 2014;39(1):25-37. doi:10.1111/jcpt.12112

37. Qiao Y, Chi Y, Zhang Q, Ma Y. Safety and efficacy of lecanemab for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. *Front Aging Neurosci*. 2023;15:1169499. doi:10.3389/fnagi.2023.1169499

38. Miranda A, Montiel E, Ulrich H, Paz C. Selective Secretase Targeting for Alzheimer's Disease Therapy. *J Alzheimers Dis JAD*. 2021;81(1):1-17. doi:10.3233/JAD-201027

39. Hawkes N. Merck ends trial of potential Alzheimer's drug verubecestat. *BMJ*. 2017;356:j845. doi:10.1136/bmj.j845

40. van de Wal D, Elie M, Le Cesne A, et al. Health-Related Quality of Life and Side Effects in Gastrointestinal Stromal Tumor (GIST) Patients Treated with Tyrosine Kinase Inhibitors: A Systematic Review of the Literature. *Cancers*. 2022;14(7):1832. doi:10.3390/cancers14071832

41. Riviere ME, Langbaum JB, Turner RS, et al. Effects of the active amyloid beta immunotherapy CAD106 on PET measurements of amyloid plaque deposition in cognitively unimpaired APOE ε4 homozygotes. *Alzheimers Dement J Alzheimers Assoc*. 2024;20(3):1839-1850. doi:10.1002/alz.13532

42. Ivanova A, Murphy M. An adaptive first in man dose-escalation study of NGX267: statistical, clinical, and operational considerations. *J Biopharm Stat*. 2009;19(2):247-255. doi:10.1080/10543400802609805

43. DrugBank. 4-{2-[(7-amino-2-furan-2-yl[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino]ethyl}phenol. go.drugbank.com. Accessed August 23, 2024. https://go.drugbank.com/drugs/DB08770

44. Palmer TM, Poucher SM, Jacobson KA, Stiles GL. 125I-4-(2-[7-amino-2-[2-furyl][1,2,4]triazolo[2,3-a][1,3,5] triazin-5-yl-amino]ethyl)phenol, a high affinity antagonist radioligand selective for the A2a adenosine receptor. *Mol Pharmacol*. 1995;48(6):970-974.

45. DrugBank. Brasofensine. go.drugbank.com. Accessed August 23, 2024. https://go.drugbank.com/drugs/DB04857

46. Brasofensine Treatment for Parkinson's Disease in Combination with Levodopa/Carbidopa - Edyta J Frackiewicz, Stanford S Jhee, Thomas M Shiovitz, Jonathan Webster, Christine Topham,

Randy C Dockens, Daisy Whigan, Daniel E Salazar, Neal R Cutler, 2002. Accessed August 23, 2024. https://journals.sagepub.com/doi/10.1345/aph.1A152

47. DrugBank. CX-717. go.drugbank.com. Accessed August 23, 2024. https://go.drugbank.com/drugs/DB05047

48. Kumar V, Kim SH, Bishayee K. Dysfunctional Glucose Metabolism in Alzheimer's Disease Onset and Potential Pharmacological Interventions. *Int J Mol Sci*. 2022;23(17):9540. doi:10.3390/ijms23179540

49. Yan L rong, Li Y shi, Chen G liang, et al. Efficacy and safety of aranidipine enteric-coated tablets compared with amlodipine in Chinese patients with mild to moderate essential hypertension: a multicenter, randomized, double-blind, parallel-controlled clinical trial. *J Cardiovasc Pharmacol*. 2012;60(1):8-14. doi:10.1097/FJC.0b013e318254a566

50. Harbeck N. Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer. *Breast Edinb Scotl*. 2022;62 Suppl 1(Suppl 1):S12-S16. doi:10.1016/j.breast.2022.01.006

51. Schmidt ME, Kent JM, Daly E, et al. A double-blind, randomized, placebo-controlled study with JNJ-37822681, a novel, highly selective, fast dissociating D_2 receptor antagonist in the treatment of acute exacerbation of schizophrenia. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2012;22(10):721-733. doi:10.1016/j.euroneuro.2012.02.007

52. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;323(18):1824-1836. doi:10.1001/jama.2020.6019

53. Nakagami H, Morishita R. Therapeutic Vaccines for Hypertension: a New Option for Clinical Practice. *Curr Hypertens Rep*. 2018;20(3):22. doi:10.1007/s11906-018-0820-z

54. DrugBank. DPI59. go.drugbank.com. Accessed August 23, 2024. https://go.drugbank.com/drugs/DB03217

55. Gaidarov I, Chen X, Anthony T, Maciejewski-Lenoir D, Liaw C, Unett DJ. Differential tissue and ligand-dependent signaling of GPR109A receptor: implications for anti-atherosclerotic therapeutic potential. *Cell Signal*. 2013;25(10):2003-2016. doi:10.1016/j.cellsig.2013.06.008

56. Chang KS, Zhong MZ, Davis RF. Indigo carmine inhibits endothelium-dependent and -independent vasodilation. *Hypertens Dallas Tex 1979*. 1996;27(2):228-234. doi:10.1161/01.hyp.27.2.228

57. Steers WD. Darifenacin: Pharmacology and clinical usage. *Urol Clin North Am*. 2006;33(4):475-482, viii. doi:10.1016/j.ucl.2006.06.007

58. Huo X, Zhang Y, Jin X, Li Y, Zhang L. A novel synthesis of selenium nanoparticles encapsulated PLGA nanospheres with curcumin molecules for the inhibition of amyloid β aggregation in Alzheimer's disease. *J Photochem Photobiol B*. 2019;190:98-102. doi:10.1016/j.jphotobiol.2018.11.008

59. Food and Drug Administration, Amiri-Koredstani L, Wedam S, et al. CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 125409Orig1s051 SUMMARY REVIEW PERTUZUMAB PERJETA. Published online September 30, 2013.

60. Food and Drug Administration, Chen MY, Everhart E, LaCivita C. Risk Assessment and Risk Mitigation Review(s) CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 2139730rig1s000 RISK ASSESSMENT AND RISK MITIGATION REVIEW(S) Drug Approval Package: QINLOCK Established Name: Ripretinib. Published online April 22, 2020. Accessed November 27, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213973Orig1s000RiskR.pdf

61. DrugBank. Aranidipine. Accessed November 27, 2024. https://go.drugbank.com/drugs/DB09229

62. NCATS Inxight Drugs — JNJ-37822681. Accessed November 27, 2024. https://drugs.ncats.io/drug/GJB2URS7NJ

63. DrugBank. Umifenovir. Accessed November 28, 2024. https://go.drugbank.com/drugs/DB13609

64. Ambühl PM, Tissot AC, Fulurija A, et al. A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. *J Hypertens*. 2007;25(1):63-72. doi:10.1097/HJH.0b013e32800ff5d6

65. DrugBank. CYT006-AngQb. Accessed December 1, 2024. https://go.drugbank.com/drugs/DB05739

66. DPI59 - Search Results. PubMed. Accessed November 28, 2024. https://pubmed.ncbi.nlm.nih.gov/?term=DPI59

67. Lai E, Waters MG, Tata JR, et al. Effects of a niacin receptor partial agonist, MK-0354, on plasma free fatty acids, lipids, and cutaneous flushing in humans. *J Clin Lipidol*. 2008;2(5):375-383. doi:10.1016/j.jacl.2008.08.445

68. NCATS Inxight Drugs — MK-0354. Accessed November 28, 2024. https://drugs.ncats.io/drug/4U62D8JYIQ

69. Food and Drug Administration. BLUDIGO T™ (indigotindisulfonate sodium injection), for intravenous use Initial U.S. Approval: 2022.

70. Food and Drug Administration. ENABLEX ® (darifenacin) extended-release tablets Initial U.S. Approval: 2004. Accessed November 28, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021513s010lbl.pdf

71. Met Office, Cartopy. Cartopy: a cartographic python library with a Matplotlib interface. Published online 2015 2010. https://scitools.org.uk/cartopy

72. OpenStreetMap contributors. OpenStreetMap - Planet dump retrieved from https://planet.osm.org. Published online 2017. https://www.openstreetmap.org

73. The UniProt Consortium. UniProt: the Universal Protein Knowledgebase in 2023. *Nucleic Acids Res*. 2023;51(D1):D523-D531. doi:10.1093/nar/gkac1052

74. Li Y, Bubeck S, Eldan R, Del Giorno A, Gunasekar S, Lee YT. Textbooks Are All You Need II: phi-1.5 technical report. Published online September 11, 2023. doi:10.48550/arXiv.2309.05463

5 Author contributions

Taxonomy following CRedit[35]

Name	Contributions
Rico Andre Schmitt	Conceptualization, Software, Investigation, Writing – Original Draft Preparation, Methodology, Formal Analysis, Data Curation, Project Administration, Validation, Visualization
Konstantin Buelau	Conceptualization, Supervision, Writing – Review & Editing, Project Administration, Editing, Visualization
Leon Martin	Writing – Review & Editing, Methodology, Visualizations
Christoph Huettl	Writing – Review & Editing, Visualization, Methodology
Michael Schirner	Writing – Review & Editing, Visualization
Leon Stefanovski	Conceptualization, Supervision, Writing – Review & Editing, Project Administration, Editing, Visualization
Petra Ritter	Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing, Project Administration, Resources, Visualization

6 Acknowledgements

PR acknowledges support by the Virtual Research Environment at the Charité Berlin – a node of EBRAINS Health Data Cloud, by EU Horizon Europe program Horizon EBRAINS2.0 (101147319), Virtual Brain Twin (101137289), EBRAINS-PREP 101079717, AISN – 101057655, EBRAIN-Health 101058516, Digital Europe TEF-Health 101100700, EU H2020 Virtual Brain Cloud 826421, Human Brain Project SGA2 785907; Human Brain Project SGA3 945539, German Research Foundation SFB 1436 (project ID 425899996); SFB 1315 (project ID 327654276); SFB 936 (project ID 178316478; SFB-TRR 295 (project ID 424778381); SPP Computational Connectomics RI 2073/6-1, RI 2073/10-2, RI 2073/9-1; DFG Clinical Research Group BECAUSE-Y 504745852, PHRASE Horizon EIC grant 101058240; Berlin Institute of Health and Foundation Charité. JM acknowledges funding by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 424778381 – TRR 295.

Computation has been performed on the High-Performance Cluster for Research and Clinic of the Berlin Institute of Health, Berlin, Germany.

7 Conflicts of interest/Disclosures

RS, KB, LM, CH, MS, LS and PR have no financial or other conflicts to declare.