

A. Agent-generated Query to get Abstracts from PubMed

Using the query below, we have filtered 1000 abstracts from PubMed to mine the drug targets using the Abstract Mining Agent.

```
'''("Alzheimer's disease"[MeSH Terms] OR "Alzheimer's disease") AND ("drug target" OR "therapeutic target" OR "molecular target" OR biomarker OR pathway OR mechanism) AND ("protein" OR "gene" OR "enzyme" OR "receptor" OR "kinase" OR "transporter") AND ("small molecule" OR inhibitor OR agonist OR antagonist OR modulator)'''
```

B. Building Agents for Target Discovery

The *Abstract Mining Agent* quickly skims through the abstract and extracts the potential targets with a self-reported confidence score. We have used `gemini-2.5-flash-lite` to build this agent, as this is very fast and cheap, and capable enough to solve this task effectively.

```
model="gemini-2.5-flash-lite",

contents=f'''
    From the following abstract, extract all **protein-coding genes or proteins** that are explicitly described as potential or validated **drug targets**, particularly for small-molecule therapeutics (e.g., inhibitors, agonists, antagonists, modulators).

    For each identified target, return an object with:
    - "name": the official gene/protein symbol (HGNC if possible)
    - "confidence": a float between 0 and 1 indicating how certain you are that this is a small-molecule druggable target in the given context.

    If there is no explicit mention of drug targets, return:
    {"drug_target": []}.

    Output only valid JSON in the exact form:
    {"drug_target": [{"name": "GENE", "confidence": 0.95}], ...}}.

    Abstract: {result["abstract"]}
    ...
```

For the *Target Evaluator Agent*, we have used `gemini-2.5-pro` as we need more reasoning power to get the best set of targets for parallel drug discovery. Besides the self-reported confidence score, the agent also returns the novelty score and evidence score, using the search tool to get the scientific evidence to evaluate the targets.

```
model="gemini-2.5-pro",

contents=f'''
    You are an expert biomedical research assistant
    specializing in drug discovery for Alzheimer's Disease (AD).
    You have access to recent scientific literature and
    reasoning capabilities.

    TASK:
    Validate whether the following protein/gene is a promising
    **small-molecule drug target** for Alzheimer's Disease.

    Target: {target}

    INSTRUCTIONS:
    1. Use your search capabilities to find **recent
    (2020-2025)** peer-reviewed studies, reviews, or authoritative sources
    mentioning this target in the context of Alzheimer's Disease and
    small-molecule drug discovery.
        - Prefer experimental evidence (e.g., inhibition,
        activation, modulation, animal models, human studies).
        - Consider clinical trial data or high-quality preclinical
        studies.
        - Discard vague, speculative mentions without strong
        evidence.
    2. Evaluate the evidence considering:
        - **Confidence Score (0-1):** How likely this target is
        genuinely druggable by small molecules in AD (explicit
        experimental/clinical support, reproducibility).
        - **Novelty Score (0-1):** How recent and original the
        target is in the AD drug discovery landscape.
            - 1 = very novel/emerging,
            - 0 = heavily studied / saturated.
        - **Evidence Score (0-1):** Quality and robustness of
        evidence.
            - 1 = strong experimental/clinical validation,
            - 0 = anecdotal or speculative.
    3. Provide a **short reasoning trace** (2-3 sentences max)
```

summarizing your judgment.

```
OUTPUT FORMAT (JSON only, no explanations outside JSON):
{{
  "target": {target},
  "confidence_score": 0.0-1.0,
  "novelty_score": 0.0-1.0,
  "evidence_score": 0.0-1.0,
  "reasoning": "Brief justification with supporting
evidence."
}}
```

C. Results

From the *Abstract Mining Agent*, we have found the top 10 targets sorted by *average confidence*, reported by the agent shown in Table S1. Also, we can see the number of times the target was present in the abstracts in the *count* column.

Table S1. Top targets from the *Abstract Mining Agent* with count and average confidence score (before evaluation).

target	count	average confidence
MAO-B	7	0.96
SGLT2	8	0.96
BCHE	17	0.95
CGAS	8	0.95
GLP-1 RECEPTOR	6	0.95
SEH	7	0.95
GLP1R	10	0.95
DYRK1A	7	0.94
ACHE	42	0.94
HDAC	7	0.94

Evaluating the targets from *Abstract Mining Agent* based on novelty, evidence and self-reported confidence by the *Target Evaluation Agent*. The targets are sorted based on novelty score and top 5 are selected to develop novel inhibitors.

Table S2. Targets with scores and reasoning after evaluation by the *Target Evaluation Agent*.

target	confidence score	novelty score	evidence score	reasoning
SGLT2	0.8	0.9	0.7	SGLT2 is a highly promising drug repurposing target, with strong evidence from multiple large cohort studies and meta-analyses demonstrating that its inhibition via existing small-molecule drugs is associated with a significantly lower risk of dementia and Alzheimer's Disease. Preclinical studies in animal models provide mechanistic support, showing SGLT2 inhibitors can reduce amyloid-beta deposition, tau pathology, and neuroinflammation. While a recent randomized controlled trial in early AD did not meet its primary endpoint, the target's druggability is confirmed, and the wealth of supportive human observational data justifies the high confidence and novelty.
CGAS	0.7	0.9	0.8	CGAS is an emerging drug target with strong preclinical evidence. Its inhibition is supported by recent studies demonstrating that genetic deletion or administration of small-molecule inhibitors targeting the cGAS-STING pathway can ameliorate both amyloid- β and tau pathologies, reduce neuroinflammation, and rescue cognitive deficits in various mouse models of Alzheimer's Disease. The target is novel and gaining significant attention, though the lack of clinical trial data and some conflicting preclinical results temper confidence.
SEH	0.9	0.8	0.9	Soluble Epoxide Hydrolase (sEH) is upregulated in Alzheimer's Disease (AD) patient brains and animal models. Preclinical studies (2020-2025) robustly demonstrate that small-molecule sEH inhibitors cross the blood-brain barrier, reduce neuroinflammation, decrease amyloid and tau pathology, and reverse cognitive deficits in multiple AD rodent models, thus providing strong evidence and high confidence in this novel therapeutic target.
HDAC	0.8	0.6	0.7	HDACs are a well-validated target class with approved small-molecule drugs for other indications. Recent preclinical studies show that isoform-selective HDAC inhibitors, particularly for HDAC6 and the novel target HDAC11, can modulate core Alzheimer's pathologies including amyloid and tau accumulation, and neuroinflammation, leading to cognitive improvements in animal models. While the general target class is not new, the focus on specific isoforms to improve efficacy and reduce side effects provides a novel therapeutic strategy, though clinical data for Alzheimer's disease is still limited.
GLP-1 RECEPTOR	0.8	0.6	0.9	The GLP-1 receptor is a highly promising drug target for Alzheimer's Disease (AD), supported by robust preclinical evidence and compelling clinical data. While most current agonists are peptides, the development of oral small molecules is underway, confirming druggability. Large-scale Phase 3 clinical trials with the GLP-1 agonist semaglutide in early AD are ongoing, with results expected in late 2025, representing a significant investment in this target. Evidence from real-world patient data indicates that

				treatment with GLP-1 receptor agonists is associated with a significantly reduced risk of AD.
DYRK1A	0.9	0.6	0.9	DYRK1A is a kinase strongly implicated in Alzheimer's Disease (AD) as it phosphorylates both amyloid precursor protein (APP) and tau, contributing to the formation of plaques and tangles. Extensive preclinical evidence from animal models demonstrates that small-molecule inhibitors can reduce both core AD pathologies and reverse cognitive deficits. The target's druggability is high, with multiple small-molecule inhibitors developed and at least one, SM07883, having entered Phase 1 clinical trials, providing strong validation for its therapeutic potential.
GLP1R	0.8	0.3	0.9	GLP1R is a highly validated target supported by extensive preclinical evidence showing that its agonists reduce neuroinflammation, A β deposition, and tau hyperphosphorylation in Alzheimer's Disease (AD) models. This is strongly corroborated by late-stage clinical trials, including pivotal Phase 3 studies for oral semaglutide and positive Phase 2b results for liraglutide in AD patients. While current lead drugs are peptides, the demonstrated clinical potential and active development of oral formulations make it a highly promising target for small-molecule approaches.
BCHE	0.6	0.2	0.8	BCHE (butyrylcholinesterase) is a clinically validated target, as the approved dual AChE/BCHE inhibitor rivastigmine is used for Alzheimer's Disease (AD) treatment. Recent preclinical studies (2022-2025) provide strong evidence, with novel selective BCHE inhibitors demonstrating significant cognitive improvements in transgenic AD mouse models and showing neuroprotective effects. The rationale is further strengthened by findings that BCHE levels increase in the AD brain and are associated with amyloid plaques, while BCHE knockout in mice reduces plaque pathology.
MAO-B	0.8	0.1	0.9	MAO-B is a well-established target with a long history in neurodegeneration, resulting in a low novelty score. However, its role in Alzheimer's-related oxidative stress is well-supported, and it is highly druggable with small molecules. Confidence and evidence are high due to extensive recent preclinical development of novel inhibitors and an ongoing Phase 2a clinical trial for KDS2010, a selective MAO-B inhibitor, in patients with early Alzheimer's disease.
ACHE	1.0	0.1	1.0	ACHE is a clinically validated target with multiple FDA-approved small-molecule inhibitors (e.g., donepezil, rivastigmine, galantamine) that are standard symptomatic treatments for Alzheimer's Disease. Its druggability is therefore certain, but it is not a novel target. Current research (2020-2025) focuses on developing multi-target-directed ligands that combine ACHE inhibition with other disease-modifying mechanisms, such as inhibiting amyloid aggregation or monoamine oxidase, to move beyond purely symptomatic relief.

As we found **GLP-1 RECEPTOR** to be a duplicate of **GLP1R** from **Table S1 and S2**, we did not consider it to move forward. In stead, we have picked **DYRK1A**, along with **SGLT2**, **CGAS**, **SEH**, **HDAC** for our top 5 targets.