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AI-Assisted Drug Repurposing System for Pediatric Oncology: The TAKUYA Framework

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Abstract

This research/review analyzes several AI-assisted drug repurposing systems, with particular focus on the TAKUYA framework, an artificial intelligence-assisted system for drug repurposing in pediatric oncology that implements a human-in-the-loop approach, and illustrates its potential through preliminary case studies. The system integrates a Large Language Model with more than fifty atomic bioinformatics tools, assigning the model the role of orchestrator while the system's knowledge is derived from data contained in the authoritative databases it queries.

Keywords: Pediatric oncology; TAKUYA framework; AI-assisted drug repurposing systems; Pediatrics, Research

Introduction

The Pharmacological Gap in Pediatric Oncology

Pediatric cancers represent one of the leading causes of disease-related mortality in childhood in developed countries. According to the most recent data from the National Cancer Institute, between 2003 and 2019, 248,749 cases of pediatric neoplasms were recorded in the United States, with an incidence rate of 178.3 cases per million children per year [1]. Despite this epidemiological significance, the development of drugs specifically intended for the pediatric population remains dramatically insufficient, constituting what the scientific literature defines as the "pharmacological gap in pediatric oncology". The extent of this gap was quantified by Nishiwaki and Ando in a comparative study examining regulatory approvals in the United States, Europe, and Japan: out of 103 oncology drugs approved for adult patients, only 19 received a pediatric indication [2]. This disparity reflects the economic characteristics of the pediatric oncology market, which represents less than one percent of the overall oncology market and therefore offers insufficient commercial incentives to justify the investments required for the development of new molecules [3]. Das and colleagues analyzed the

expected returns of a hypothetical pediatric oncology drug portfolio, estimating values ranging from -24.2% to +10.2%, figures that clearly demonstrate the need for alternative funding models involving the public and philanthropic sectors [4]. Regulatory initiatives have attempted to address this issue by introducing incentive mechanisms. In the United States, the Research to Accelerate Cures and Equity for Children Act of 2017, commonly known as the RACE Act, required pharmaceutical companies to evaluate new oncology agents in pediatric populations whenever the molecular target is relevant to childhood cancers [5]. Liu and Kesselheim analyzed the impact of this regulation, observing that drugs approved after the implementation of the RACE Act were associated with a significantly greater number of pediatric trial requirements, with trials initiated a median of 2.8 years before adult approval compared with 0.04 years after approval for drugs approved before the regulation [6]. However, as highlighted by Laetsch and colleagues, substantial challenges remain in clinical translation due to the biological complexity of pediatric tumors and the difficulty of conducting clinical trials in numerically limited populations [7]. A further critical issue is the shortage of essential chemotherapeutic drugs. A study conducted across Children's Oncology Group institutions documented shortage rates between 73% and 80% for daunorubicin and between 56% and 66% for methotrexate [8]. These disruptions in the supply chain may compromise adherence to standardized therapeutic protocols, with potential consequences for clinical outcomes. DeCamp and colleagues emphasized that managing chemotherapy drug shortages requires a coordinated approach involving clinicians, pharmacists, families, and regulatory institutions [9].

Drug Repurposing as a Therapeutic Strategy

In this context of limited dedicated therapeutic options, drug repurposing emerges as a promising strategy to accelerate access to new treatments. Drug repurposing, defined as the identification of new therapeutic indications for drugs already approved or in advanced stages of clinical development, offers significant advantages over the de novo development of new molecules [10]. These advantages include the availability of already characterized safety profiles, a reduction in development costs estimated at 50–60%, and a shortening of the time required to obtain regulatory approval from 10–17 years to 3–12 years [11]. The biological rationale for drug repurposing is based on the concept of polypharmacology: many drugs interact with multiple molecular targets beyond their primary therapeutic target, and these secondary interactions may prove therapeutically relevant in pathological contexts different from the original indication [12]. Tumors, in particular, frequently exhibit alterations in molecular pathways that are also implicated in other diseases, creating opportunities to repurpose drugs originally developed for non-oncological conditions. The history of pharmacology offers paradigmatic examples of successful repurposing. Thalidomide, originally marketed as a sedative and withdrawn from the market in the 1960s because of its teratogenicity, was later rediscovered as an active agent against multiple myeloma. In 1999, Singhal and colleagues documented thalidomide's ability to induce objective responses in patients with refractory myeloma, with reductions in the monoclonal component exceeding 50% in 30% of treated cases [13]. This observation paved the way for the development of an entire class of immunomodulatory drugs that today represent fundamental pillars in the treatment of multiple myeloma [14].

Metformin, a first-line antidiabetic drug for more than sixty years, has attracted considerable interest as a potential antineoplastic agent based on preclinical evidence demonstrating its ability to modulate critical pathways involved in tumor proliferation, including AMPK and mTOR [15]. The randomized MANSMED study evaluated the addition of metformin to androgen deprivation therapy in patients with advanced prostate cancer, observing a significant prolongation of

progression-free survival to castration-resistant disease [16]. However, the overall results of clinical trials investigating metformin in oncology remain heterogeneous, highlighting the complexity of translating preclinical evidence into demonstrable clinical benefits [17].

Computational Approaches to Drug Repurposing

The advent of omics technologies and the increasing availability of structured biomedical data have catalyzed the development of computational approaches to drug repurposing. These in silico methods enable the rapid and cost-effective screening of thousands of drug–disease combinations, generating hypotheses for subsequent experimental validation [18]. Network-based approaches represent one of the most established computational strategies. These methods integrate heterogeneous information into biological networks that capture relationships among drugs, molecular targets, diseases, and biological processes, enabling the identification of non-obvious connections that may reveal repurposing opportunities [19]. Knowledge graphs have further enhanced these approaches by providing structured representations of biomedical knowledge that support sophisticated forms of reasoning and inference [20]. The signature reversal technique, popularized by the 2006 Connectivity Map study, is based on the principle that an effective drug should induce a gene expression profile opposite to that associated with the disease [21]. This approach quantifies inverse relationships between disease-induced and drug-induced transcriptional signatures through connectivity scores, where negative values indicate therapeutic potential. However, recent critical evaluations have shown that the predictive utility of this approach may be lower than initially reported, suggesting the need to integrate evidence from multiple sources [22]. Machine learning and artificial intelligence have introduced new analytical capabilities into the field of drug repurposing. Deep learning algorithms can identify subtle patterns in high-dimensional data that would escape traditional analysis [23]. Graph neural networks have demonstrated promising performance in inferring new therapeutic indications from the structure of biomedical knowledge graphs [24].

The Emergence of Large Language Models in Drug Discovery

The introduction of Large Language Models has opened unprecedented opportunities for applying artificial intelligence to drug discovery. These models, trained on vast text corpora, demonstrate emerging capabilities in reasoning and natural language understanding that make them potentially useful as interfaces to biomedical knowledge [25]. The function calling paradigm, introduced with more recent versions of these models, overcomes the limitations of purely textual generation by enabling the structured invocation of external tools [26]. Systems such as ChemCrow have demonstrated the feasibility of enhancing an LLM with specialized chemistry tools, enabling the execution of complex tasks requiring the integration of reasoning and action [27]. Agentic architecture represents the most recent evolution of this paradigm. An AI agent is defined by its ability to perceive the environment, plan sequences of actions, and interact iteratively with external tools to achieve a goal [28]. Systems such as DrugAgent and AgentDrug have explored the application of this paradigm to drug discovery, with varying degrees of autonomy and specialization [29]. However, the application of LLMs in biomedical contexts raises significant concerns regarding the phenomenon of hallucinations, namely the generation of plausible but false information [30]. In a domain where the consequences of errors can be serious, validating generated statements becomes critical. Farquhar and colleagues proposed the use of semantic entropy as a method for hallucination detection, but the problem remains unresolved [31]. The debate between fully autonomous systems and human-in-the-loop approaches reflects this tension between computational efficiency and human oversight [32]. While autonomous systems promise greater

throughput, approaches that keep humans at the center of the decision-making loop provide stronger guarantees in terms of accountability and the ability to detect errors. In the context of drug repurposing for pediatric oncology, where decisions concern potential treatments for children with cancer, the architectural choice assumes ethical as well as technical significance.

Research Objectives

Within the scope of this review, we present TAKUYA, an artificial intelligence-assisted system for drug repurposing in pediatric oncology that implements a human-in-the-loop approach, and illustrate its potential through preliminary case studies. The system integrates a Large Language Model with more than fifty atomic bioinformatics tools, assigning the model the role of orchestrator while the system's knowledge is derived from data contained in the authoritative databases it queries.

The specific objectives are:

First, to describe the system architecture, highlighting the design choices that ensure traceability of statements, prevention of hallucinations, and maintenance of human control over critical decisions.

Second, to illustrate the system's potential through preliminary case studies that led to the identification of novel pharmacological candidates for in vitro testing: Dehydroleucodine and Solamargine for medulloblastoma, and Kuraridin and Norkurarinone for osteosarcoma.

Third, to critically discuss the limitations of the approach and future development prospects within the broader context of applying artificial intelligence to drug discovery.

Materials and Methods

Architecture of the TAKUYA System

The TAKUYA system implements a three-layer architecture that clearly separates the responsibilities of presentation, orchestration, and data access. This separation follows a fundamental design principle: the intelligence of the system must derive from data contained in authoritative databases, not from implicit knowledge encoded in the model itself.

The presentation layer consists of a conversational interface that enables users to interact with the system in natural language. Users can formulate complex queries, request further analysis, change the direction of the investigation, and validate or reject the system's proposals at any point in the workflow. This interactivity is essential for implementing the human-in-the-loop paradigm. The orchestration layer consists of GLM-4.5-Air (Z.ai), a Large Language Model optimized for execution speed and cost efficiency. The model receives user queries and decides which tools to invoke through the function calling mechanism. It is essential to understand that the model does not possess up-to-date intrinsic biomedical knowledge: its function is to translate user intentions into sequences of calls to specialized tools, interpret the returned results, and present understandable summaries. Every factual statement produced by the system is traceable to a specific tool response, which in turn derives from an external database.

The data layer comprises more than fifty atomic tools that implement access to public biomedical databases. The principle of atomicity implies that each tool performs a single, well-defined function, enabling flexible composition and facilitating debugging. The main integrated databases include ChEMBL for biochemical activity data [33], DGIdb for drug–gene interactions aggregated from multiple sources [34], PRISM for pharmacological sensitivity data on tumor cell lines [35], cBioPortal for genomic profiles of cell lines, STRING for protein–protein interactions, Reactome for curated biological pathways, and Europe PMC and PubMed for the scientific literature.

Implemented Repurposing Logic

The system encodes repurposing logic specific to pediatric oncology both in the model's system prompt and in the internal logic of the tools.

The INN filter represents a critical mechanism for identifying genuinely "repurposed" candidates from non-oncological indications. The system automatically excludes drugs whose names end with suffixes characteristic of modern oncology drug classes according to the WHO International Nonproprietary Names nomenclature: -tinib for tyrosine kinase inhibitors, -mab for monoclonal antibodies, -ciclib for cyclin-dependent kinase inhibitors, -rafenib for RAF inhibitors, -zomib for proteasome inhibitors, and -parib for PARP inhibitors. This exclusion is necessary because the goal of drug repurposing is to identify drugs developed for other diseases that may have unexpected antitumor activity, rather than simply extending the use of drugs that are already oncological to new indications. The pathway novelty assessment quantifies the degree of exploration of a given molecular pathway in the context of a specific tumor cell line. The system queries PubMed using structured queries and classifies the results into four levels: unexplored when there are no publications associating the pathway with the cell line, understudied when there are between one and five publications, studied when there are between six and twenty publications, and saturated when there are more than twenty publications. Unexplored or understudied pathways represent opportunities of greatest interest for repurposing, since the absence of previous studies suggests that any discoveries would be genuinely innovative.

The novelty verification of pharmacological candidates follows a similar logic applied to individual compounds. For each drug identified as a potential candidate, the system checks through PubMed queries for publications associating it with the specific cell line, the tumor type, and cancer in general. A drug is classified as "experimentally_tested" if publications exist with experimental data (IC50, viability assays) on the specific cell line, "mentioned_together" if publications of co-occurrence exist without experimental testing, and "novel" if no publications exist either on the cell line or the tumor type. The integration of the Cancer Gene Census makes it possible to annotate every gene with its functionally validated role according to the scientific community [36]. The database, curated by the Wellcome Sanger Institute, classifies genes as oncogenes, tumor suppressors, or genes involved in oncogenic fusions, with two levels of evidence. This annotation is critical to prevent the language model from incorrectly assigning functional roles to uncharacterized genes: when a gene is not present in the Census, the system explicitly reports that its functional role has not been determined.

Operational Workflow

The standard TAKUYA workflow follows a logical progression that replicates the reasoning of an expert drug discovery researcher.

The first phase consists of genomic characterization of the cell line of interest. The system resolves the cell line name into the corresponding Cellosaurus and DepMap identifiers, then queries cBioPortal to obtain the profile of somatic mutations and copy number alterations. Each alteration is annotated with the gene's functional role according to the Cancer Gene Census. The second phase involves target selection based on the identified genomic alterations. The system prioritizes genes with defined functional roles and high levels of evidence, assessing pathway novelty to identify unexplored opportunities. The selection logic considers the appropriate therapeutic direction: for mutated or amplified oncogenes, the objective is inhibition, whereas for lost tumor suppressors, the objective is to target downstream effectors that become hyperactive as a consequence of the loss. The third phase consists of exploring the molecular network of the selected target. The system queries STRING for protein-protein interactions and Reactome for biological pathways, identifying upstream regulators and downstream effectors that may represent alternative therapeutic targets with better druggability. The fourth phase involves searching for

pharmacological modulators. The system sequentially queries ChEMBL for biochemical activity data with documented mechanisms, DGIdb for drug-gene interactions aggregated from multiple sources, and PRISM data for empirical evidence of cytotoxic efficacy. Candidates that pass the INN filter undergo novelty verification. The fifth phase consists of validating the biological rationale. For candidates classified as novel, the system verifies the existence of a plausible biological connection between the drug's mechanism of action and the genomic alterations of the cell line by querying the literature and pathway databases.

At every stage of the workflow, users can intervene to modify the research direction, explore specific aspects in greater depth, exclude candidates based on considerations not encoded in the system, or request additional verification. This interactivity is at the heart of the human-in-the-loop approach.

Sources of Empirical Data: The PRISM Dataset

The Broad Institute's PRISM dataset represents a unique resource for evidence-based drug repurposing. PRISM, an acronym for Profiling Relative Inhibition Simultaneously in Mixtures, uses a molecular barcoding technology that allows hundreds of cell lines to be tested simultaneously in pooled format, dramatically increasing throughput compared to traditional screening [35]. The public dataset in version 24Q2 contains screening results for 6,790 compounds across 919 tumor cell lines. Activity is quantified as Log Fold Change, where negative values indicate reduced cell viability and values below -1 are generally considered indicative of significant cytotoxic activity. Of the tested compounds, 1,593 have recognized drug names that enable cross-referencing with other databases. The integration of PRISM into the TAKUYA workflow enables triangulation of pathway-based predictions with empirical evidence of efficacy. A drug that demonstrates both a plausible biological rationale and cytotoxic activity in the PRISM dataset achieves a higher level of confidence than candidates supported by only a single line of evidence.

Results

Case Study 1: Dehydroleucodine for DAOY Medulloblastoma

The first case study aimed to identify a novel pharmacological candidate for the DAOY cell line, an established pediatric medulloblastoma model belonging to the SHH (Sonic Hedgehog) molecular subgroup [37]. Genomic characterization of the cell line revealed a profile of alterations including mutations in several genes with defined functional roles in the Cancer Gene Census. Among these, CYLD carries an F610V missense mutation and is classified as a Tier 1 tumor suppressor, the highest level of evidence. SMO carries a mutation and is classified as a Tier 1 oncogene. The cell line also harbors alterations in CDKN2A and TP53, both tumor suppressors involved in cell cycle control. CYLD (Cylindromatosis) encodes a deubiquitinase that acts as a negative regulator of the NF-kB pathway and other pro-inflammatory and pro-survival pathways [38]. The protein removes ubiquitin chains from key substrates including TRAF2, TRAF6, and NEMO, thereby inhibiting NF-kB activation in response to inflammatory stimuli [39]. Loss of CYLD function, such as that presumably caused by the F610V mutation, results in hyperactivation of downstream pathways, promoting cell survival and proliferation [40]. The F610V mutation is located within the USP domain (amino acids 583-956), which contains the catalytic deubiquitinase machinery. Computational predictions using the SIFT and PolyPhen-2 algorithms suggest that the mutation is deleterious (SIFT score 0.02, PolyPhen score 0.939), although these values specific to F610V have not been independently published and represent in silico predictions. The mutation likely affects the deubiquitinase activity of CYLD, although its precise impact on the catalytic site requires experimental characterization. Pathway

novelty verification revealed that CYLD represents a completely unexplored target in the context of DAOY: there are no publications associating pharmacological interventions on this pathway with the specific cell line. The importance of NF-kB signaling in medulloblastoma has been established by multiple studies. Spiller and colleagues demonstrated high constitutive activity of the canonical NF-kB pathway, as shown by Western blot analysis of the NF-kB p65 subunit, in medulloblastoma tumors compared with normal brain tissue **[41].** Pharmacological inhibition of NF-kB in cell lines halts proliferation and induces apoptosis, while expression of a dominant-negative form of the endogenous NF-kB inhibitor (dnIkB) resulted in xenograft tumor volumes 40% smaller than controls **[41].**

The systematic search for CYLD modulators led to the identification of Dehydroleucodine, a natural sesquiterpene lactone isolated from *Artemisia douglasiana* Besser (Argentina) and *Gynoxys verrucosa* (Ecuador). Dehydroleucodine (ChEMBL ID: CHEMBL441260, molecular formula C15H16O3, molecular weight 244.28 g/mol) has been characterized as an inducer of multiple cell death pathways through TP73-dependent transcriptional mechanisms. The key study by Ratovitski demonstrated that Dehydroleucodine induces TP73-dependent transcriptional regulation of multiple cell death target genes in human glioblastoma cells [42]. Following exposure to Dehydroleucodine, total and phosphorylated (p-Y99) TP73 levels were upregulated in U87-MG cells. TP73 silencing resulted in partial rescue of cells from Dehydroleucodine-induced cell death. Critically, Dehydroleucodine induced TP73 binding to specific gene promoters including CDKN1A, BAX, TP53AIP1, CYLD, RIPK1, and APG5L. Exposure to Dehydroleucodine increased protein levels of CYLD, RIPK1, and other pro-apoptotic factors **[42].** The biological rationale for Dehydroleucodine in DAOY is therefore coherent and multilayered. DAOY harbors the CYLD c.1828T>G, p.Phe610Val mutation (reported with reference to transcript NM_001042412.1), meaning the protein is still produced, although the functional impact of the F610V mutation has not been experimentally characterized. In silico predictions suggest a deleterious effect that could translate into reduced catalytic activity, although this hypothesis requires validation. By activating TP73-dependent transcription, Dehydroleucodine increases CYLD expression. This could compensate for the reduced activity per molecule of mutant CYLD by increasing total protein levels. Furthermore, Dehydroleucodine has been shown to inhibit NF-kB signaling in multiple cellular contexts **[42]**, providing a convergent mechanism targeting the pathway dysregulated by CYLD loss.

Additional preclinical evidence supports the antitumor activity of Dehydroleucodine. The compound triggers senescence and apoptosis associated with the accumulation of DNA damage markers such as ATM phosphorylation and focal organization of gammaH2AX and 53BP1 **[43].** Treatment promotes either cell cycle arrest or apoptosis depending on the concentration administered to cells. In a preclinical melanoma model, Dehydroleucodine inhibited tumor growth by inducing cell cycle arrest, senescence, and apoptosis **[44].** Recent studies have shown that Dehydroleucodine exerts antiproliferative effects on human Burkitt lymphoma Daudi cells through SLC7A11-mediated ferroptosis **[45].** Novelty assessment using Europe PMC confirmed that Dehydroleucodine has been mentioned together with DAOY (1 publication) but has never been experimentally tested (0 publications with IC50, viability assays, or dose-response data) in this cell line. Likewise, no experimental studies exist in medulloblastoma in general. The compound has 49 cancer-related publications, indicating established antitumor activity in other contexts.

In summary, the first case study identified Dehydroleucodine as a novel candidate for in vitro testing in DAOY medulloblastoma, with a biological

rationale based on loss of the tumor suppressor CYLD, the documented ability of Dehydroleucodine to upregulate CYLD expression via TP73, and convergent activity on the NF-kB pathway that is dysregulated in this context.

Case Study 2: Solamargine for DAOY Medulloblastoma

The second case study maintained its focus on the DAOY cell line but addressed the second major genomic alteration: the mutation in SMO (Smoothened), a Tier 1 oncogene that serves as the central transducer of the Sonic Hedgehog (SHH) pathway. The Hedgehog pathway is critically important in medulloblastoma, with SHH subtype tumors accounting for approximately 30% of all medulloblastoma cases **[46].** Under normal conditions, the pathway operates through ligand binding (SHH, IHH, DHH) to the PTCH1 receptor, releasing its inhibition of SMO. Activated SMO triggers an intracellular signaling cascade culminating in the nuclear translocation of the GLI1/GLI2 transcription factors, which activate target genes including PTCH1 (feedback), GLI1 (amplification), MYCN, Cyclin D1, and BCL2, thereby promoting proliferation and survival. In DAOY, SMO is mutated and constitutively active, leading to ligand-independent pathway activation. This results in constitutively active GLI1 and hyperactive Hedgehog signaling. Clinical trials with SMO inhibitors (vismodegib, sonidegib) have shown that patients with SHH subtype medulloblastoma can respond to targeted therapy, although resistance frequently develops through downstream pathway mutations **[47].**

The systematic search for SHH pathway modulators that are not modern oncology drugs (according to the INN filter exclusion criteria) led to the identification of Solamargine, a steroidal glycoalkaloid found in *Solanum* species (eggplant, potato, and other nightshades). A key study by Han and colleagues identified Solamargine as a cisplatin sensitizer through phenotypic screening in cisplatin-resistant NSCLC organoids **[48].** The study demonstrated that Solamargine inhibits the Hedgehog pathway through direct binding to the SMO protein, as shown by the Gli responsive element (GRE) reporter assay and the BODIPY-cyclopamine binding assay. This binding to SMO results in downstream inhibition of GLI1 transcriptional activity. The IC50 for Hedgehog pathway inhibition (GRE reporter) was determined to be 2.66 uM **[48].** The antitumor properties of Solamargine have been comprehensively reviewed **[49].** The compound exhibits antitumor activity through its effects on multiple biological pathways, including cell survival pathways, tumor suppressor pathways, caspase activation pathways, mitochondrial pathways, death receptor pathways, protein kinase pathways, and signaling pathways that promote invasion/migration and multidrug resistance. The mechanism of Solamargine-induced apoptosis involves both the extrinsic and intrinsic pathways. For the extrinsic pathway, Solamargine upregulates the expression of external death receptors such as tumor necrosis factor receptor I (TNFR-I), the Fas receptor, TNFR-I-associated death domain (TRADD), and Fas-associated death domain (FADD) **[50].** For the intrinsic pathway, Solamargine increases the Bax/Bcl-2 ratio by upregulating Bax and downregulating Bcl-2 and Bcl-xL expression, resulting in mitochondrial cytochrome c release and activation of caspases-8, -9, and -3 **[51].**

Particularly relevant for medulloblastoma therapy is Solamargine's ability to sensitize tumor cells to cisplatin, a key chemotherapeutic agent in medulloblastoma treatment protocols [48]. Furthermore, Solamargine has been shown to inhibit growth and induce apoptosis in lung cancer cells through p38 MAPK-mediated suppression of Stat3 phosphorylation and protein expression, followed by induction of the downstream Stat3 effector p21 **[52].**

Novelty assessment confirmed that Solamargine has been mentioned together with DAOY (2 publications) but has never been experimentally tested in this cell line (0 publications with IC50/viability data). No

experimental studies exist specifically in medulloblastoma. However, Solamargine has an extensive cancer literature (401 publications), indicating well-established antitumor activity. The mechanism of direct binding of Solamargine to the SMO protein provides a clear target engagement rationale. By inhibiting SMO, the compound blocks the upstream activator of the Hedgehog cascade, resulting in reduced GLI1 transcriptional activity. This is mechanistically similar to approved SMO inhibitors (vismodegib, sonidegib) but represents an alternative natural compound that has not been tested in the context of medulloblastoma.

In summary, the second case study identified Solamargine as a novel candidate for DAOY medulloblastoma, with a strong biological rationale based on direct binding to the SMO protein leading to Hedgehog pathway inhibition, with additional potential for synergy with standard chemotherapy through cisplatin sensitization.

Case Study 3: Kuraridin and Norkurarinone for MG-63 Osteosarcoma

The third case study shifted the focus to the MG-63 cell line, an osteosarcoma model, with the objective of identifying novel repurposing candidates. This case study also illustrates the critical importance of target validation, as it revealed significant limitations in the biological rationale.

Genomic characterization of MG-63 revealed a profile distinctly different from DAOY. Key alterations involving Cancer Gene Census genes include mutations in ATRX (chromatin remodeler, Tier 1 TSG), SH2B3 (adapter protein, TSG), CHD2 (chromatin remodeler, TSG), PTPN13 (phosphatase, TSG), and PTPRT (phosphatase, TSG). Critically, all of these tumor suppressor genes exhibit a challenging druggability profile.

Druggability assessment revealed that:

ATRX: GATE 2 FAILED - Target is CHALLENGING (not directly druggable)

SH2B3: GATE 2 FAILED - Target is CHALLENGING

CHD2: GATE 2 FAILED - Target is CHALLENGING

PTPN13: GATE 2 FAILED - Target is CHALLENGING

PTPRT: PREDICTED_DRUGGABLE but no drug found in DGIdb

This pattern presents a fundamental challenge for target-based drug repurposing: when genomic alterations affect genes that are not amenable to pharmacological intervention, the standard workflow cannot identify candidates with a strong biological rationale. The search for modulators targeting the PTPN phosphatase family led to the identification of Kuraridin and Norkurarinone, two lavandulyl flavonoids isolated from the roots of *Sophora flavescens* (Ku Shen in traditional Chinese medicine). Sasaki and colleagues demonstrated that screening of a natural compound library led to the discovery of five lavandulyl flavonoids as novel PTP1B inhibitors: kuraridin, norkurarinone, kurarinone, 2'-methoxykurarinone, and kushenol T **[53].** Both Kuraridin and Norkurarinone exhibit inhibitory activity against PTP1B (protein tyrosine phosphatase 1B, gene PTPN1) with IC50 values below 30 uM. CRITICAL LIMITATION: PTP1B (PTPN1) IS NOT in the Cancer Gene Census**.** The original search targeted PTPRT (a CGC-listed phosphatase found mutated in MG-63), but the identified compounds actually target a different member of the phosphatase family (PTP1B/PTPN1), which has not been validated as an oncological target.

The role of PTP1B in cancer is controversial and context-dependent **[54].** PTP1B may exert both tumor-suppressive and tumor-promoting effects depending on the substrate involved and the cellular context. In some tumors (HER2-overexpressing breast cancer, non-small cell lung cancer), PTP1B overexpression promotes tumor progression by activating the Src and ERK1/2 pathways **[55].** In other contexts (lymphoma, esophageal cancer), PTP1B acts as a tumor suppressor, with PTPN1 mutations leading to reduced phosphatase

activity and increased phosphorylation of the JAK-STAT pathway [56]. Evidence specifically concerning PTP1B in osteosarcoma is limited. A recent multi-omics analysis of the PTPN family in osteosarcoma demonstrated the prognostic importance of the PTPN gene family as a whole but did not specifically validate PTP1B as a therapeutic target [57]. Open Targets database associations link PTP1B primarily to neurodegenerative diseases (Alzheimer's score 0.47, Parkinson's score 0.46), not cancer. Additional evidence for the antitumor activity of Kuraridin and Norkurarinone exists but is not specific to osteosarcoma. One study demonstrated that kuraridin and nor-kurarinone induce mitochondria-mediated apoptosis in human gastric adenocarcinoma SGC-7901 cells by examining mechanisms including G2/M phase arrest [58]. However, this activity was observed in gastric cancer, not osteosarcoma.

Novelty assessment for both compounds confirmed zero experimental publications on MG-63:

In summary, the third case study identified Kuraridin and Norkurarinone as novel compounds never tested in MG-63 osteosarcoma. However, the biological rationale is considerably weaker than that of the DAOY candidates because: (1) the target PTP1B is not included in the Cancer Gene Census; (2) the role of PTP1B in osteosarcoma has not been established; (3) there is no mechanistic connection between PTP1B inhibition and the actual genomic alterations in MG-63. These candidates are therefore classified as exploratory rather than priority candidates.

Discussion

Significance of the Results in the Context of Oncological Drug Repurposing

The case studies presented raise fundamental questions about the nature of AI-assisted drug discovery and the epistemological meaning of "discoveries" generated through such a process. Before discussing limitations and practical implications, it is necessary to ask what it really means to identify a "novel candidate" and what predictive value the collected evidence actually has. The identification of Dehydroleucodine and Solamargine for DAOY medulloblastoma follows an epistemic pattern fundamentally different from the identification of Kuraridin and Norkurarinone for MG-63 osteosarcoma. For the DAOY candidates, the system constructed chains of biological inference linking specific genomic alterations (CYLD F610V, SMO mutation) to compounds with documented mechanisms affecting relevant targets or pathways. These connections, although supported by independent literature for each node in the chain, represent syntheses that have not been experimentally tested in the specific context of medulloblastoma. The system did not "discover" these connections; rather, it assembled fragments of existing knowledge into configurations that had not previously been explored. This distinction is crucial for understanding both the value and the limitations of the approach. For Dehydroleucodine, the literature documents that the compound upregulates CYLD expression via TP73-dependent transcription in glioblastoma cells [42]. The assumption that this mechanism would be operative and therapeutically relevant in DAOY medulloblastoma cells requires direct experimental validation. However, several factors strengthen the rationale: (1) both glioblastoma and medulloblastoma are central nervous system tumors; (2) CYLD is mutated in DAOY with predicted functional impairment; (3) NF-kB signaling has been documented as important in medulloblastoma [41]; (4) DAOY has been confirmed as an SHH-subtype medulloblastoma cell line in which multiple signaling pathways intersect. For Solamargine, the rationale is equally strong but operates through a different mechanism. The compound inhibits Hedgehog signaling through direct binding to SMO [48], which is mutated in DAOY, resulting in downstream inhibition of GLI1 transcriptional activity. DAOY's classification as the SHH subtype has been confirmed by multiple studies [37], and clinical trials have demonstrated that patients

with SHH-subtype medulloblastoma respond to Hedgehog pathway inhibitors [47]. Solamargine's additional cisplatin-sensitizing activity is clinically relevant because cisplatin-based chemotherapy is part of the standard treatment protocols for medulloblastoma.

In contrast, the MG-63 case presents epistemologically different characteristics. The primary evidence does not derive from target-pathway reasoning but from the identification of compounds that inhibit a phosphatase (PTP1B) belonging to a different family member than the phosphatases actually mutated in MG-63 (PTPN13, PTPRT). The connection is indirect and hypothetical. While the PTPN family has been associated with osteosarcoma prognosis [57], there is no evidence that PTP1B specifically is relevant to MG-63 biology or that its inhibition would have a therapeutic effect.

Comparative Analysis: Strong versus Weak Rationale

The contrast between the DAOY and MG-63 case studies illustrates a fundamental principle in target-based drug repurposing: the strength of the biological rationale depends critically on whether the proposed target is validated in the specific tumor context.

For DAOY (Medulloblastoma):

Criterion	Dehydroleucodine	Solamargine
Target	CYLD	SMO
Status CGC	Oncosuppressor Tier 1	Oncogene Tier 1
Alteration in DAOY	Mutation missense p.Phe610Val	Activating Mutation
Compound Mechanism	Upregulates CYLD via TP73	Directly binds SMO (IC50 2,66 µM)
Target-Compound Connection	DIRECT	DIRECT
Pathway validated in tumor	YES (NF-κB) [41]	YES (SHH, 30% cases) [66]
Rationale	STRONG	STRONG

For MG-63 (Osteosarcoma):

Criterion	Kuraridin	Norkurarinone
Target	PTP1B (PTPN1)	PTP1B (PTPN1)
Status CGC	NOT present	NOT present
Alteration in MG-63	PTPN1 not mutated	PTPN1 not mutated
Compound Mechanism	Inhibits PTP1B (IC50 < 30 µM)	Inhibits PTP1B (IC50 < 30 µM)
Target-compound Connection	INDIRECT (different family)	INDIRECT (different family)
Pathway validated in the tumor	No	No
Rationale	WEAK	WEAK

This comparison highlights that the novelty of a compound (never tested on a specific cell line) is necessary but not sufficient for prioritization. The TAKUYA system correctly identified novel compounds for both cell lines, but the scientific rationale differs dramatically in strength.

The Value of Human-in-the-Loop for Critical Evaluation

The architectural choice to implement a human-in-the-loop approach proved essential in this study. The automated novelty assessment correctly identified all four compounds as never having been experimentally tested on their respective cell lines. However, the

automated system alone could not distinguish between the strong rationale for the DAOY candidates and the weak rationale for the MG-63 candidates. The critical assessment that PTP1B is not included in the Cancer Gene Census, and that no mechanistic connection exists between PTP1B inhibition and the genomic alterations in MG-63, required expert human judgment. An autonomous system could have presented all four candidates as equivalent opportunities, potentially leading to the misallocation of experimental resources. This observation supports the position that, particularly for high-risk decisions in pediatric oncology, human oversight remains essential even as AI systems become more sophisticated. The IQ Consortium position paper on AI in pharmaceutical development emphasized that maintaining human oversight is essential to ensure regulatory compliance and decision traceability **[32].** The present study provides empirical support for this position.

Study Limitations and Sources of Error

An honest analysis of TAKUYA's limitations must distinguish between contingent limitations, which may be overcome through future developments, and intrinsic limitations of the approach. Among the contingent limitations, incomplete database coverage represents the most significant issue. ChEMBL, while containing over 2 million compounds and 20 million bioactivity measurements, has systematic gaps for natural compounds, older drugs, and secondary pharmacological interactions **[33].** The Cancer Gene Census, with approximately 700 annotated genes, covers less than 4% of all human protein-coding genes **[36].** These gaps may eventually be addressed through the ongoing expansion of databases, but for now they limit the completeness of the search. The MG-63 case study exemplifies a situation in which genomic alterations involve genes that are predominantly "CHALLENGING" in terms of druggability (chromatin remodelers, adaptor proteins). In such cases, the target-based approach cannot identify candidates with a strong rationale, and alternative strategies (phenotypic screening, synthetic lethality approaches) may be more appropriate. The intrinsic limitations are more fundamental. The system operates exclusively on structured data and cannot extract information from non-indexed sources. The principle of atomic tools, while ensuring traceability, limits the ability to perform creative inferences that would require unforeseen combinations of information. Although sophisticated in reasoning, the language model lacks causal understanding of biology and may propose connections that appear plausible but are biologically nonsensical. Publication bias represents a particularly insidious source of systematic error. Novelty verification based on PubMed queries implicitly assumes that the absence of publications is equivalent to the absence of studies. In reality, many studies with negative results are never published, a phenomenon well documented in the meta-science literature **[59].** A compound classified as "novel" may have been tested and found ineffective in unpublished studies.

Ethical Considerations in the Pediatric Context

The application of drug repurposing to pediatric oncology raises specific ethical considerations that deserve discussion. Children represent a vulnerable population with additional regulatory protections that reflect both their inability to provide autonomous informed consent and the uncertainties surrounding the safety of drugs not specifically studied in this population **[60]**. In the context of drug repurposing, this tension takes on specific forms. On one hand, repurposed drugs offer the advantage of already-characterized safety profiles, at least for their original indications. On the other hand, extrapolating safety data from adult to pediatric populations is problematic due to pharmacokinetic and pharmacodynamic differences **[61].** Children are not simply "small adults": they differ in hepatic metabolism, renal function, body composition, and tissue sensitivity to pharmacological effects. For drugs such as Dehydroleucodine and Solamargine, which have not

been studied in pediatric populations, dedicated pediatric phase 1 studies would be required before any efficacy trials. A further ethical consideration concerns resource prioritization. Pediatric clinical trials are expensive, require specialized infrastructure, and compete for access to numerically limited patient populations. The decision to invest resources in validating a repurposed candidate carries opportunity costs: those same resources could instead be devoted to other potentially more promising candidates. Systems such as TAKUYA can help rationalize these decisions by providing structured evidence to support prioritization, but ultimate responsibility remains with clinical experts and regulatory institutions.

Future Perspectives and Development Directions

Experience with TAKUYA suggests several directions for the future development of AI-assisted drug repurposing systems, positioned along a continuum between incremental improvements and more radical architectural transformations. In the short term, integrating additional data sources could significantly expand the search space. Adverse event databases such as FAERS contain signals of unintended pharmacological activity that could reveal repurposing opportunities [62]. Real-world evidence databases derived from electronic health records could enable the identification of epidemiological associations between drug use and cancer incidence [63]. Integrating gene expression data from resources such as GEO and TCGA would enable signature reversal approaches complementary to pathway-based reasoning. In the medium term, incorporating predictive pharmacokinetic and toxicity models could enable more sophisticated candidate filtering. Tools such as ADMET-AI can predict pharmacokinetic and toxicological properties from molecular structures, allowing the early exclusion of compounds with unfavorable characteristics [64]. Integrating these tools into the TAKUYA workflow would add a layer of validation that is currently lacking.

In the long term, evolving toward multi-agent systems with planning and metacognitive capabilities could radically transform the approach. Specialized agents focused on different aspects of the problem—tumor genomics, pharmacology, toxicology, regulation—could collaborate toward integrated solutions, with human oversight exercised at a higher level of abstraction [65]. However, this evolution raises fundamental questions regarding accountability and responsibility that the scientific and regulatory communities will need to address. Applying the framework to other therapeutic areas represents a natural direction for expansion. Rare non-oncological diseases present a pharmacological gap similar to pediatric oncology, with insufficient commercial incentives and limited patient populations. The architectural principles of TAKUYA—tool atomicity, statement traceability, and human-in-the-loop—are generalizable to these contexts with adaptations specific to the relevant databases and selection criteria.

Conclusions

This review has presented TAKUYA, an artificial intelligence-assisted system for drug repurposing in pediatric oncology that implements a human-in-the-loop approach based on integrating a Large Language Model with atomic bioinformatics tools. The effectiveness of the system was validated through case studies that led to the identification of four novel drug candidates for potential in vitro testing:

Dehydroleucodine for DAOY medulloblastoma – A sesquiterpene lactone that upregulates expression of the tumor suppressor CYLD via TP73-dependent transcription, targeting the CYLD F610V mutation present in this cell line. Scientific rationale: STRONG.

Solamargine for DAOY medulloblastoma – A steroidal glycoalkaloid that inhibits the Hedgehog pathway at the level of the GLI1 effector, downstream of the mutated SMO oncogene. Additional value derives from its potential to sensitize cells to cisplatin. Scientific rationale: STRONG.

Kuraridin for MG-63 osteosarcoma – A lavandulyl flavonoid that inhibits the phosphatase PTP1B. However, PTP1B is not included in the Cancer Gene Census and has no validated role in osteosarcoma. Scientific rationale: WEAK.

Norkurarinone for MG-63 osteosarcoma – A structural analog of Kuraridin with similar inhibitory activity against PTP1B and similar limitations. Scientific rationale: WEAK.

The contrasting results between the DAOY and MG-63 case studies highlight a critical principle in computational drug repurposing: the novelty of a compound (never tested on a specific cell line) is necessary but not sufficient for prioritization. The strength of the biological rationale—determined by whether the target is included in the Cancer Gene Census, whether genomic alterations in the cell line involve that target, and whether preclinical evidence supports the proposed mechanism—is essential for distinguishing high-priority candidates from exploratory hypotheses. The results demonstrate the feasibility of an approach that combines the computational efficiency of AI with the critical judgment of human experts. The architectural choice to keep humans in the decision loop, although reducing throughput compared with fully autonomous systems, provides superior guarantees in terms of controllability, traceability, and the ability to detect errors—qualities that are essential when decisions concern potential treatments for children with cancer.

Drug repurposing, supported by AI tools such as TAKUYA, represents a sustainable strategy for bringing therapeutic options to pediatric populations that are otherwise neglected by the commercial incentives of the pharmaceutical market. Integrating multichannel evidence—theoretical pathways, empirical data, and the scientific literature—increases the likelihood of identifying genuinely promising candidates while reducing the false positives that affect approaches based on a single line of evidence.

The identified candidates await experimental validation. Confirmation of in vitro activity would represent the first concrete validation of the approach and pave the way for subsequent clinical development. The DAOY candidates with a strong rationale (Dehydroleucodine and Solamargine) should receive experimental priority over the MG-63 candidates with a weak rationale (Kuraridin and Norkurarinone). Regardless of the outcome of these specific tests, the methodological framework developed remains applicable to identifying new candidates for other cell lines and other pediatric tumors, contributing to reducing the pharmacological gap that disadvantages the youngest patients.

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