Form B: Full Proposal Template

Form B: IGEM-HERC Full Proposal Cover Sheet

Idaho State Board of Education

PROPOSAL NUMBER: (to be assigned by HERC after submsiion)	TOTAL AMOUNT REQUESTED: $100,000

Proposal Track (select one):

- **Proof of Concept**

NSF I-Corps participation:

Have you participated in, or plan to participate in the NSF I-Corps Program? plan to participate

Is so, when did you or will you?" Jun-Jul 2026

TITLE OF PROPOSED PROJECT:

Artificial Intelligence Guided Discovery of Dual-Mechanism Cyclin-Dependent Kinase 12 and Cyclin K Modulators for Targeted Osteosarcoma Therapy

SPECIFIC PROJECT FOCUS:

Biotechnology/Biomedicine and Artificial Intelligence/Machine Learning

PROJECT START DATE: July 1, 2026	PROJECT END DATE: June 30, 2027

NAME OF INSTITUTION: Idaho State University	DEPARTMENT: Biomedical and Pharmaceutical Sciences

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PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR	Dr. Solomon Zeleke	Assistant Professor	Solomon T. Zeleke
CO-PRINCIPAL INVESTIGATOR			

NAME OF PARTNERING COMPANY:	COMPANY REPRESENTATIVE NAME:
SIGNATURE:	

Authorized Organizational Representative	NAME: Dave Harris	SIGNATURE: Dave B. Harris

1. **Name of Primary Idaho Public Institution**:

Idaho State University (ISU)

2. **Project Title**:

Artificial Intelligence Guided Discovery of Dual-Mechanism Cyclin-Dependent Kinase 12 and Cyclin K Modulators for Targeted Osteosarcoma Therapy

3. **Principal Investigator(s) and Key Personnel**

Principal Investigator:

Solomon Zeleke, BPharm, MSc, PhD
Department of Biomedical and Pharmaceutical Sciences
College of Pharmacy, Idaho State University

Key Personnel:

Graduate and undergraduate research trainees (medicinal chemistry, AI/ML, and pharmacology)
External collaborators providing specialized services:

1) Jesse Wheeler, PhD, Idaho State University – Supports machine learning model development, biostatistical design, data analysis, and statistical interpretation.
2) Robert Mancini, PharmD, St. Luke's Health System, Idaho – Clinical advisor offering oncology expertise.
3) Joanna Burdette, PhD, University of Illinois Chicago – Provides strategic guidance on translational model development and definition of study endpoints.
4) Elizabeth Kaweesa, PhD, University of Illinois Chicago – Serves as a bioassay specialist, supporting assay development, optimization, and data interpretation.
5) Reaction Biology Corporation, Contract Research Organization – Conducts kinase profiling and provides downstream pharmacology and signaling pathway support.

Total Amount Requested: $100,000

Significance of Project and Project Objective(s)

What if a single small molecule could simultaneously shut down a cancer cell's ability to repair its deoxyribonucleic acid (DNA) and silence the transcriptional engines that keep it alive?

5.1. Significance of the Project

Osteosarcoma is a rare but highly aggressive bone cancer that primarily affects children and young adults.[1] Despite intensive multimodal treatment, including surgery and intensive combination chemotherapy, survival outcomes for relapsed or metastatic disease have remained essentially unchanged for more than four decades, underscoring a profound and persistent unmet medical need. A defining biological feature of osteosarcoma is its reliance on transcriptional resilience and highly active DNA damage response pathways, which enable tumor cells to tolerate genomic instability and evade the cytotoxic effects of standard therapies.[2] This reliance on coordinated transcription and DNA repair represents a compelling yet underexploited therapeutic vulnerability.

This project advances a first-in-class, dual-mechanism therapeutic strategy designed to collapse both transcriptional maintenance and DNA repair capacity in osteosarcoma. The proposed approach integrates CDK12 inhibition with targeted degradation of Cyclin K within a single small-molecule chemical entity.[3,4] CDK12 is a master regulator of transcriptional elongation for genes involved in homologous

recombination and DNA damage repair, while Cyclin K serves as an essential regulatory partner required for CDK12 stability and activity. Disruption of the CDK12-Cyclin K axis therefore produces a coordinated "double strike," simultaneously suppressing DNA repair gene transcription and destabilizing the kinase complex that sustains transcriptional elongation.

Previous CDK-targeted strategies have achieved limited clinical success due to pathway redundancy, incomplete target suppression, and resistance mechanisms associated with retinoblastoma pathway alterations.[5,6] Catalytic inhibition alone often results in transient pathway suppression without eliminating the underlying protein scaffold. By combining enzymatic inhibition with targeted protein degradation (TPD), the proposed strategy moves beyond reversible kinase blockade to physically eliminate Cyclin K protein, thereby preventing complex reassembly and adaptive resistance. This integrated mechanism is expected to produce deeper and more durable antitumor responses than either modality alone.

TPD has emerged as a transformative therapeutic paradigm by harnessing the ubiquitin-proteasome system to selectively eliminate disease-driving proteins.[7] Among TPD approaches, molecular glue degraders are particularly attractive due to their favorable physicochemical properties, oral bioavailability potential, and clinical scalability. However, their discovery has historically relied on serendipity or large-scale phenotypic screening, limiting systematic development. This project directly addresses that bottleneck by integrating artificial intelligence-enabled molecular design, structure-informed medicinal chemistry, and chemical biology validation into a unified discovery framework. A central innovation is the AI-guided design of dual-function small molecules that both inhibit CDK12/13 kinase activity and induce Cyclin K degradation. Through predictive modeling, degradation propensity scoring, and iterative structure-activity optimization, this approach establishes a rational pathway for engineering kinase-bound molecular glue degraders. The result is a reproducible strategy to achieve sustained disruption of transcriptional elongation programs in osteosarcoma and other transcription-dependent malignancies.

Strategic Capacity Building to Develop Expertise and Translational Technologies that Increase Idaho's Competitiveness

Although osteosarcoma is a rare malignancy, it carries substantial morbidity and treatment intensity, particularly among pediatric and adolescent patients who require aggressive multimodal therapy. Survival outcomes for relapsed or metastatic disease remain poor, underscoring the need for innovative therapeutic strategies. This project establishes and experimentally validates a dual-mechanism platform integrating CDK12 inhibition and Cyclin K degradation within Idaho's public research system, generating rigorous preclinical data to support competitive federal translational funding and future commercialization pathways. Beyond osteosarcoma, transcription-dependent malignancies, including breast, ovarian, and hematologic cancers, contribute significantly to Idaho's overall cancer burden. Therapeutic strategies that disrupt transcriptional elongation and DNA repair pathways therefore have broad oncologic relevance. By advancing expertise in TPD and dual-mechanism kinase modulation, this project develops a scalable platform applicable across multiple cancer indications rather than a single-disease solution.

Importantly, establishing AI-enabled drug discovery capabilities within Idaho strengthens the state's capacity to participate in early-stage oncology innovation rather than relying exclusively on external pharmaceutical discovery pipelines. The integration of AI-guided molecular design, structure-informed medicinal chemistry, and targeted protein degradation directly aligns with IGEM-HERC priorities in *Biotechnology/Biomedicine and Artificial Intelligence/Machine Learning*. These activities build durable translational research infrastructure, enhance workforce training capacity, and increase Idaho's competitiveness in high-value biomedical innovation sectors.

The project strengthens Idaho State University's ability to operate at the intersection of computational modeling, synthetic chemistry, and quantitative biological validation within a coordinated translational research framework. *By developing these capabilities in-state, the program generates protectable intellectual property, validated lead compounds, and mechanistically characterized datasets suitable for federal translational funding mechanisms.*

This work represents a foundational step toward expanding translational drug discovery infrastructure in Idaho, including future development of the Idaho Center for Translational Therapeutics (I-CT). IGEM-HERC support will establish core capabilities, de-risk early-stage innovation, and enable strategic progression toward intellectual property protection and competitive translational funding. Subsequent phases will evaluate commercialization pathways based on data maturity, regulatory positioning, and market opportunity. In parallel, the project contributes directly to *workforce development by training graduate and professional students in AI-guided drug design, synthetic medicinal chemistry, and mechanistic cancer biology*. Over a three-year period, multiple trainees will gain interdisciplinary research experience, exposure to intellectual property strategy, and familiarity with federal translational funding processes. Collectively, this integrated approach strengthens Idaho's biotechnology and artificial intelligence ecosystem while building sustainable, data-driven translational research capacity within the state.

5.2. Project Objective(s)

The overarching objective of this project is to establish a rational, AI-enabled framework for developing dual-function small molecules that disrupt DNA repair and transcriptional addiction in osteosarcoma by simultaneously inhibiting CDK12 and inducing targeted degradation of Cyclin K. To achieve this objective, the project will pursue the following aims:

Aim 1. Develop an AI-driven generative design platform for de novo discovery of dual-action CDK12 inhibitors and Cyclin K molecular glue degraders.

The working hypothesis is that generative deep learning models can identify novel chemical scaffolds capable of high-affinity CDK12 engagement and neomorphic E3 ligase recruitment, thereby inducing selective ubiquitination and degradation of Cyclin K, destabilizing the CDK12 transcriptional elongation complex, and producing coordinated suppression of DNA damage response and gene transcription. This aim will establish an AI-first platform that operates beyond existing compound libraries to explore previously inaccessible chemical space, accelerating the discovery of dual-mechanism candidates suitable for experimental validation.

Aim 2. Identify and validate chemical features that convert CDK12 inhibitors into molecular glue degraders of Cyclin K.

The working hypothesis is that selected heterocyclic and aromatic moieties (e.g., benzimidazole-, thiazole-, and phenylpyridyl-derived groups) can function as E3 ligase-engaging elements when appended to CDK12 inhibitor scaffolds. *Rationale.* Prior studies across oncology have demonstrated that small molecules bound to kinases can create novel composite interfaces that engage ubiquitin ligase adaptors, particularly members of the Cullin 4 (CUL4) DNA damage-binding protein 1 (DDB1) family. In this context, CDK12-bound inhibitors provide a structured scaffold capable of orienting appended chemical moieties toward E3 ligase recognition without disrupting kinase engagement. *The proposed heterocyclic motifs are selected based on known E3-ligase compatibility, favorable physicochemical properties, and precedent in molecular glue systems, making this a biologically plausible and experimentally testable strategy*. Compounds generated under this aim will be evaluated for their ability to promote formation of a CDK12-Cyclin K-E3 ligase complex, leading to selective Cyclin K degradation in osteosarcoma cells. This represents a novel, non-PROTAC (PROteolysis TArgeting Chimera) approach to TPD design with significant translational potential.

By integrating kinase inhibition and targeted protein degradation into a single chemical entity, this project redefines the functional role of CDK12-targeted therapeutics and establishes a transferable platform for transcriptional kinase degradation. Successful completion will (i) deliver first-in-class chemical matter for osteosarcoma, (ii) generate patentable discovery assets suitable for follow-on funding and industry engagement, and (iii) position Idaho State University as a contributor to next-generation AI-enabled oncology drug discovery.

6. Specific Project Plan and Timeline (1 Year)

6.1. Current Technology Readiness Level (TRL)

At project initiation, the technology sits at Technology Readiness Level (TRL) 2–3, where foundational scientific principles underlying dual CDK12 inhibition and Cyclin K degradation are established and early feasibility is demonstrated (Figure 1). We designed and synthesized a benzimidazole-modified dinaciclib analog, MR-1226, which exhibits potent dual functionality. MR-1226 selectively inhibits CDK12 (half-maximal inhibitory concentration [IC_{50}] = 100 nM) while inducing robust Cyclin K degradation (half-maximal degradation concentration [DC_{50}] = 53 nM; maximum degradation [D_{max}] > 95%). This coordinated target modulation produces significant antiproliferative activity in U2OS osteosarcoma cells (50% growth inhibition [GI_{50}] = 780 nM).[8,9] Together, these findings establish technical feasibility and mechanistic validity for the dual-acting CDK12 inhibition and Cyclin K degradation strategy and provide a strong foundation for structured proof-of-concept development and iterative optimization of next-generation dual-mechanism modulators.

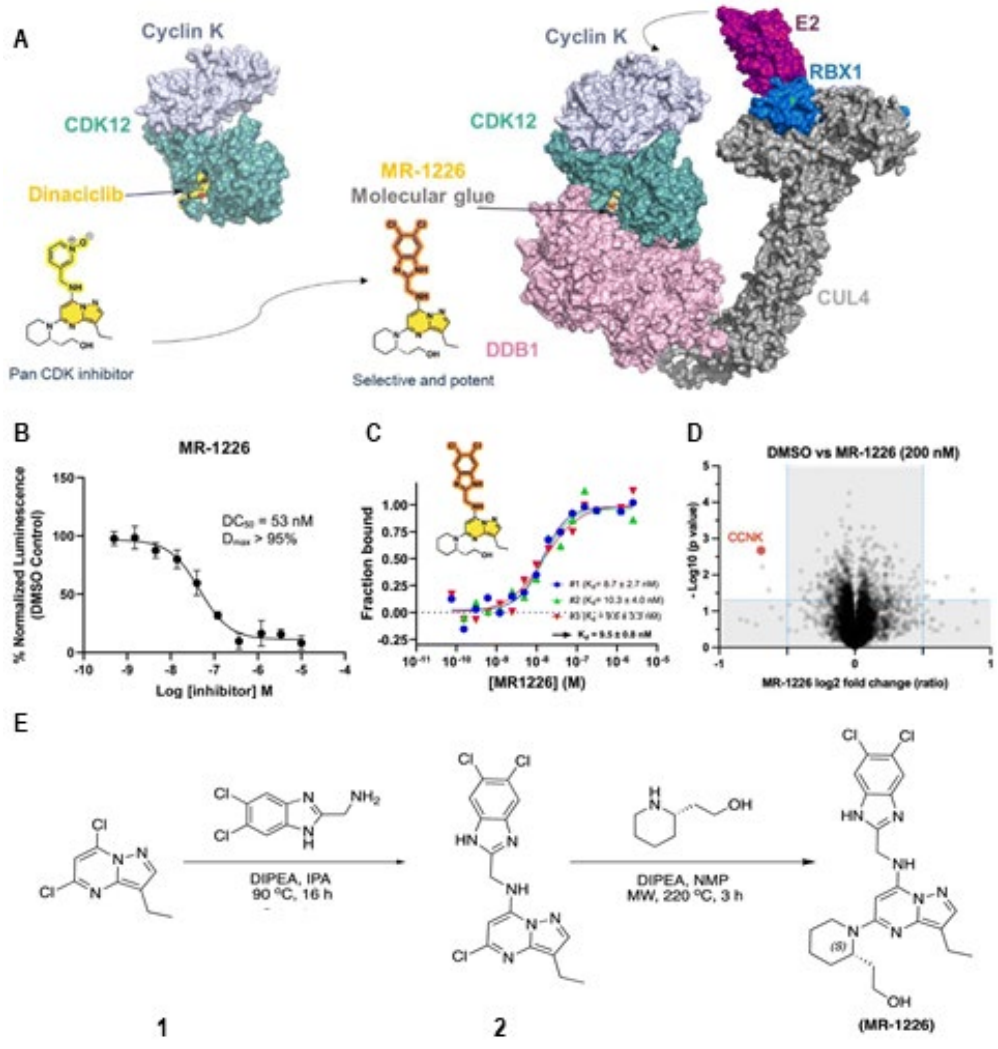

Figure 1. Feasibility study results. (A) *De novo* design of cyclin K molecular glue degraders from pan-CDK inhibitor dinaciclib. Cyclin K is degraded through a ubiquitin-dependent pathway mediated by the damage-specific DNA-binding protein 1-cullin 4 (DDB1-CUL4) E3 ubiquitin ligase complex. In this mechanism, DDB1 acts as an adaptor that recognizes and recruits Cyclin K, often facilitated by molecular glues (MR-1226), enabling the CUL4 scaffold to promote polyubiquitination and subsequent proteasomal degradation of Cyclin K. (B) Microscale thermophoresis studies assessing CDK12-Cyclin K-DDB1 ternary complex formation induced MR-1226. (C) Degradation of HiBiT tagged Cyclin K using with MR-1226 (A549 cell lines). (D) Label-free TMT-based quantitative proteomics upon treatment with MR-1226 (200 nM) at 2 h. Plot shows the significantly differentially abundant proteins ranked according to their p value (Y-axis) as −log10 and their relative abundance log2 ratio (X axis) between DMSO control and the compound of interest. All samples were generated in triplicates and 0.5-fold changes cut off were used for avg log2 ratio's to analyze the data. The p values < 0.05 were considered as significant. (E) Synthesis of MR-1226.

Although proof-of-concept chemical matter has been identified, the program currently lacks a systematic, design-driven discovery framework and mechanistically validated lead prototypes suitable for translational advancement. Support from IGEM-HERC will advance the technology from TRL 2–3 to TRL 3–4 by delivering structurally defined, mechanistically validated dual-activity lead compounds supported by reproducible *in vitro* kinase inhibition and targeted degradation datasets. Progression to TRL 5, encompassing *in vivo* validation and pharmacokinetic characterization, is anticipated through subsequent translational funding mechanisms.

6.2. Task Breakdown and Timeline (12 Months)

Two tightly integrated aims/workstreams will operate in parallel:

Aim 1. Develop an AI-driven generative design platform for de novo discovery of dual-action CDK12 inhibitors and Cyclin K molecular glue degraders.

Task 1: Data collection and predictive modeling (Months 1–3). Curated datasets of CDK12 inhibitors, Cyclin K degraders, and inactive compounds will be assembled to support predictive modeling efforts. Few-shot learning architectures (e.g., Siamese networks, Matching networks, Prototypical networks, and Relational networks) will be applied to predict compound potency, selectivity, and degradation efficiency.[10,11]

Model performance for classification tasks (e.g., active vs. inactive, degrader vs. non-degrader) will be evaluated using the Area Under the Receiver Operating Characteristic Curve (ROC-AUC) and the Area Under the Precision-Recall Curve (PR-AUC). For regression tasks (e.g., continuous potency or degradation efficiency prediction), performance will be assessed using the Coefficient of Determination (R^2) and the Mean Absolute Error (MAE). Together, these metrics will provide a comprehensive evaluation of discriminative performance, predictive accuracy, and model generalizability.

To ensure statistical robustness and mitigate overfitting, models will be trained using stratified k-fold cross-validation, with performance confirmed on an independent held-out test set. Hyperparameter optimization will be conducted using nested cross-validation. Bootstrapping analyses will be performed to estimate confidence intervals for key performance metrics. Where feasible, external validation using literature-derived or newly generated experimental datasets will be incorporated to further assess model transferability and predictive stability.

Task 2: Transfer learning and conditional fine-tuning of REINVENT (Months 2–6). REINVENT 4 will be fine-tuned on CDK12 actives and jointly adapted with Mol2Mol for dual-target design. Model performance will be confirmed by SMILES distributions, fingerprint similarity, scaffold coverage, Tanimoto shifts, and enrichment of target-specific substructures.[12,13]

Task 3: Multi-objective curriculum reinforcement learning with composite scoring (Months 2–6). A composite score integrating ML predictors, docking/molecular dynamics (MD) simulations, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) metrics will guide policy-gradient reinforcement learning (RL) with curriculum learning. This will yield a library of ~200 candidate molecules optimized for dual activity, novelty, diversity, synthetic accessibility, and degradation likelihood.[12,14]

Task 4: Synthesis and mechanistic *in vitro* validation of top dual-target candidates (Months 6–9). The top 5–8 candidates will be synthesized and tested as described in Task 2 of Aim 2. Experimental data will retrain predictive models and inform additional RL iterations in a closed-loop workflow.

Aim 2. Identify and validate chemical features that convert CDK12 inhibitors into molecular glue degraders of Cyclin K.

Task 1: Rational design and synthesis (Months 1–9).

Analysis of known Cyclin K degraders identified benzimidazole, 5-methylthiazol-2-amine, 3-methylpiperidine-2,6-dione, and pyridyl groups as key solvent exposed moieties that interact with Arg928 of DDB1 to recruit the DDB1–CUL4–RBX1 E3 ligase. This suggests that CDK12 binders can be engineered into molecular glue degraders by transplanting these moieties. Compounds will be synthesized by assembly of inhibitor cores with ligase-recruiting moieties and characterized (e.g., Figure 1E).

Task 2: *In vitro* biological mechanism of action evaluation of compounds (Months 4–12).

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays will assess the antiproliferative activity of compounds in osteosarcoma cell lines (MG63, OHS, HOS, U2OS, OS-17 PDX model and the metastatic HOS-143B), with the most responsive line used for mechanism-of-action studies. Cyclin K degradation will be evaluated by immunoblotting, and ubiquitin ligase-dependent cytotoxicity will be assessed using MG132 (potent inhibitor of the proteasome) pre-treatment. Proteomics using quantitative mass spectrometry will determine proteome-wide degradation selectivity of the most promising candidate molecule. Kinase inhibition/selectivity will be evaluated using [^{32}P] ATP assay.

Controls and selectivity. An established CDK12 inhibitor (THZ-531) and a Cyclin K degrader (CR8) will be included as activity benchmarks. Normal osteoblasts and fibroblasts will be used to assess selectivity.

Statistical Analysis. All data will be analyzed using GraphPad Prism. Experiments will be performed in triplicate and independently repeated at least three times. Dose-response relationships will be evaluated by nonlinear regression to calculate IC_{50}, DC_{50}, and Dmax values. Group comparisons will be assessed using one-way analysis of variance (ANOVA). Statistical significance will be defined as $p \leq 0.05$. Data will be presented as mean ± standard error of the mean (SEM).

7. Potential Economic Impact

The proposed dual-mechanism CDK12 inhibition and Cyclin K molecular glue degradation platform represents a novel chemical space with translational potential in osteosarcoma and related transcription-dependent malignancies. The project is structured to generate protectable intellectual property, including scaffold architectures, degradation design principles, and mechanistic validation data. A provisional patent application will be filed through the Idaho State University Office of Technology Transfer.

The PI brings prior experience in patent generation and translational drug discovery, including co-invention of kinase inhibitor patents and contributions to a discovery program that led to the formation of Aucentra Therapeutics, a clinical-stage biotechnology company. [15-20] This experience reduces commercialization risk by ensuring that intellectual property strategy, data package development, and translational positioning are integrated from the outset rather than retrofitted after proof-of-concept.

Representative patents illustrating this experience include:

- USRE49850E1 – N-(pyridin-2-yl)-4-(thiazol-5-yl)pyrimidin-2-amine derivatives as therapeutics
- US20250042903A1 – Triazine inhibitors of cyclin-dependent kinases

Follow-on funding will prioritize the IGEM-HERC Initial Startup Track, the Department of Defense Rare Cancer Research Program, and NIH R21 exploratory/developmental mechanisms. Additional support will be pursued through foundation-based programs, including the American Association for Cancer Research (AACR), the American Cancer Society (ACS), and the Sarcoma Foundation of America, to advance translational validation and de-risk the platform for commercialization. These programs are aligned with early-stage, mechanism-driven oncology innovation and provide structured pathways for advancing validated preclinical assets. Following patent filing and generation of reproducible dual-mechanism validation data, non-confidential summaries will be shared with oncology-focused biotechnology partners

for exploratory engagement. Reaction Biology will provide kinase selectivity profiling to ensure industry-standard data quality. Partnership discussions will be driven by data maturity and strategic fit.

Near-term impact centers on intellectual property generation, translational funding leverage, and workforce development rather than immediate revenue (Table 1). Commercialization pathways, including licensing or Idaho-based startup formation, will be evaluated based on technical de-risking milestones. Looking ahead, I intend to establish the Idaho Center for Translational Therapeutics (I-CT) as a statewide nexus for drug discovery, translational science, and industry-academic partnership. I-CT will offer shared infrastructure designed to advance therapeutic candidates, mitigate early-stage development risk, and foster biotechnology startup creation within Idaho. Funding from the IGEM-HERC grant will lay the groundwork for I-CT by supporting proof-of-concept studies and initial commercialization strategy development.

Table 1. Estimated path to profitability

Stage	Time frame	Value-Creating Outcome	Revenue Potential
IGEM-HERC Project	Year 1	Dual-mechanism scaffolds; validated AI-enabled discovery platform	Non-revenue; asset creation
Follow-on Funding	Years 2–4	*In vivo* validation; expanded IP; orphan-drug positioning	Sponsored research, option-to-license deals
Licensing / Spinout	Years 5–7	Lead optimization and IND-enabling studies	Upfront licensing fees; milestones; equity
Clinical Advancement	Years 7+	Orphan-drug clinical development	Royalties, milestone payments

8. Criteria for Measuring Success

Project success will be assessed using concise, quantitative metrics that track advancement of the AI-enabled discovery workflow, and experimental validation of dual-mechanism molecules within the one-year project period. (Table 2).

Table 2. Criteria for measuring success

No.	Metric	Year-1 Target
1	AI-enabled design workflow established and operational	1 functional pipeline
2	Virtual dual-mechanism candidates designed and prioritized	~200 candidates
3	Dual-mechanism compounds synthesized and tested	~ 10 compounds
4	Compounds with confirmed CDK12 inhibition and Cyclin K degradation	≥1 compounds
5	Intellectual property generated	
6	Workforce development	≥2 trainees

Value Inflection Milestones. Advancement from TRL 2–3 to TRL 3–4 through validated dual-mechanism prototypes represents the first major valuation inflection point, as mechanistically confirmed degraders significantly de-risk platform feasibility. Conversion to TRL 4–5 (*in vivo* validation and pharmacokinetics) represents a second inflection milestone typically associated with option-to-license agreements venture formation. These staged advancements align technical milestones with measurable increases in commercial asset value.

9. Anticipated Development Challenges and Mitigation Strategies

The proposed project involves technical and computational risks inherent to early-stage, AI-enabled drug discovery; however, these risks are well understood and mitigated through a modular, iterative design strategy. A primary technical risk is that initial CDK12-targeted designs may fail to induce Cyclin K degradation. To address this, alternative ligase-recruiting moieties will be explored using ligand- and structure-based virtual screening guided by the CDK12-CR8-Cyclin K-DDB1 crystal structure (PDB:

6TD3). This structure-guided approach enables rational prioritization of chemical features that promote productive E3 ligase engagement. Synthetic challenges, including low yields or complex routes, will be mitigated by prioritizing synthetically accessible scaffolds and employing alternative synthetic strategies reported in peer-reviewed literature and databases such as SciFinder and Reaxys.

On the computational side, reinforcement learning (RL) mode collapse may lead to reduced chemical diversity. This risk will be mitigated through the use of diversity filters within REINVENT 4, which penalize repeated scaffolds and overrepresented chemotypes. Because docking and *in silico* filters are approximations, conservative scoring thresholds will be applied to limit false positives while maintaining molecular diversity. Limited training data will be augmented with related kinase inhibitors and degraders, and predictions will be benchmarked against known binders and validated through docking and molecular dynamics simulations. Biological assay variability, including challenges with detecting protein degradation, will be addressed through optimization of sample preparation, antibody selection, and detection protocols, with appropriate positive and negative controls included throughout. Overall, the closed-loop integration of AI-driven design, medicinal chemistry, and experimental validation enables rapid identification of failure modes and timely course correction, ensuring that core project objectives and TRL advancement remain achievable within the proposed timeframe.

10. Budget: Form D (IGEM-HERC Full Proposal Budget Form) is provided as a separate spreadsheet.

11. Budget justification

Requested costs primarily support personnel effort, specialized reagents and assay consumables, limited targeted profiling or outsourced services, and computational resources necessary to deliver validated lead candidates, assay-ready endpoints, and data packages required to advance the project from TRL 2–3 to TRL 3–4 within the project period (Table 3).

Other Personnel

1. *A full-time PhD graduate student* (TBD) is requested and will be supported at 19 hours per week during the academic year and full time during the summer months ($22,800**).** The student will be responsible for the design, synthesis, and biological evaluation of small-molecule compounds in support of the proposed research objectives.
2. *A part-time undergraduate or professional PharmD student* is requested ($5,100). Salary support is not requested during the academic year, as the student will be enrolled in a 3-credit research elective. Summer salary support is requested based on an estimated 20 hours per week in the laboratory. The student will work side by side with a graduate student to design, synthesize, and evaluate small-molecule inhibitors.
3. *Fringe Benefits* ($800) are calculated in accordance with Idaho State University's federally negotiated blended rate for students (2.9%**).**

Equipment **-** BUCHI Rotavapor R-300 Rotary Evaporator, Cost: $22,000

The proposed research involves frequent and time-sensitive solvent removal during compound synthesis, purification, and iterative optimization within medicinal chemistry workflows. Reliable evaporation is essential to maintain compound integrity, ensure reproducibility, and sustain experimental throughput. Although older rotary evaporators are available, they are heavily shared, limited in capacity, and lack the automated pressure control and safety features required for reproducible small-molecule synthesis. These limitations constrain scheduling flexibility and reduce efficiency in synthesis-purification cycles central to the project. The BUCHI R-300 rotary evaporator provides precise temperature and vacuum control, automated pressure regulation, and enhanced operational safety, enabling consistent, high-throughput solvent removal across diverse chemical scaffolds. Dedicated access will allow uninterrupted synthesis-validation cycles, directly strengthening feasibility, experimental rigor, and project timelines, particularly for TRL advancement activities. Beyond the immediate scope of this project, the instrument will serve as a shared

medicinal chemistry resource within the College of Pharmacy and Department of Chemistry. It will support future externally funded drug discovery efforts while providing hands-on training for graduate, PharmD, and undergraduate researchers. The College of Pharmacy will provide maintenance support and laboratory infrastructure to ensure sustained operation beyond the award period, thereby expanding long-term institutional translational capacity.

Other Direct Costs

Research Supplies and Consumables - $20,200
Funds are requested for essential research supplies and consumables required to execute the proposed medicinal chemistry and human cell-based studies ($20,200). These costs include chemical reagents, solvents, purification materials, and analytical consumables for compound synthesis and optimization; cell culture media, sera, plastics, and reagents; assay kits for viability, proliferation, and biomarker analyses; and commercially sourced primary human hematopoietic cells. These supplies are necessary to generate high-quality, reproducible data central to the proposed translational aims.

External Services - $9,600
Funds are requested for external services ($9,600) to support specialized analyses not available in the PI's laboratory. These include kinome selectivity profiling, and advanced analytical characterization. Use of established cores and external providers enhances feasibility and cost efficiency.

Data Analysis, Software, and Computational Resources - $6,000
Modest funds are requested for data analysis and software resources ($6,000), including statistical or computational tools required for data processing, visualization, and interpretation. These resources will support rigorous quantitative analysis of experimental outcomes.

Table 3. Budget justification summary

Line-Item Request	**Justification**	**Total request**
Personnel (salary and fringe)	Salary support is requested for student research assistants who will carry out some of the experimental work.	$28,700
Equipment	See above	$22,000
Other Direct Costs		
1. Research Supplies	See above	$20,200
2. External Services	See above	$9,600
3. Data Analysis, Software, and Computational Resources	See above	$6,000
4. Tuition	See above	$13,500
		$100,000

12. Project Management

The project will be managed by the PI, who will oversee scientific direction, milestone completion, budget management, and reporting (Table 4). The PI will coordinate all project activities, including AI-driven molecular design, medicinal chemistry, and biological evaluation, ensuring alignment with the one-year timeline and advancement goals. Progress will be reviewed monthly, with milestone-based adjustments made as needed to maintain schedule and deliverables.

Table 4. Project management chart and milestones (1-Year Timeline)

No.	**Task / Milestone**	**Months (M) 1–3**	**M4–6**	**M7–9**	**M10–12**
1	AI model development and candidate generation	●	●		
2	Compound synthesis	●	●	●	
3	*In vitro* mechanistic validation		●	●	●
4	Lead selection and TRL assessment				●
5	IP preparation and data packaging			●	●

13. Additional Institutional and Other Sector Support (See Appendix A: Facilities and Equipment)

Institutional Support (Idaho State University).

Idaho State University (ISU) provides substantial institutional support for this project through dedicated laboratory space, shared research infrastructure, protected research time, and administrative support. The Principal Investigator (PI) is housed in a newly renovated >1,500 sq. ft. laboratory in Leonard Hall (College of Pharmacy), fully equipped for medicinal chemistry, cell-based assays, and translational drug discovery. Additional synthetic chemistry space and fume-hood access are provided through the Department of Chemistry. ISU has made significant recent investments in state-of-the-art instrumentation supporting drug discovery, including LC–MS/MS, automated flash chromatography, microwave reactors, solvent-drying systems, organoid bioprinting platforms, and molecular biology and imaging cores. The PI holds an 11-month appointment with 50% protected research time, startup funding, and a fully supported research assistant, representing a substantial in-kind institutional commitment. University core facilities, high-performance computing resources (CPU/GPU clusters), and licensed molecular modeling software further support the AI-enabled components of this project. ISU leadership has formally committed to supporting the PI's research program, student training, and grant development through the Office for Research and the College of Pharmacy.

External and Sector Support.

External collaborations strengthen the scientific and translational rigor of the project. Reaction Biology will provide kinase selectivity profiling under a defined service agreement, ensuring industry-standard data generation to support mechanistic validation and lead optimization. As a contract research organization, Reaction Biology functions strictly as a technical validation partner and does not retain intellectual property rights, preserving full IP ownership within Idaho State University. In addition, the PI maintains active research collaborations with cancer biology experts at the University of Illinois Chicago, providing access to advanced biological expertise and consultation as needed. These partnerships enhance experimental rigor and translational relevance while avoiding duplication of institutional resources and maintaining centralized intellectual property management within Idaho.

14. Future Funding

Completion of this IGEM-HERC project will position the technology for advancement beyond TRL 4 through a staged and disciplined follow-on funding strategy focused on lead optimization and early translational validation.

Planned mechanisms will include:

- Federal programs, Department of Defense rare cancer initiatives and NIH R21 (NCI) awards
- Foundation grants, including the American Association for Cancer Research, American Cancer Society, and Sarcoma Foundation of America, which support translational oncology and rare cancer research.
- State and regional translational programs (e.g., CTR-D, IGEM-HERC mechanisms).
- Industry engagement, potentially leading to sponsored research agreements or option-to-license discussions, contingent upon compelling preclinical data.

This multi-pronged grant-seeking approach is strategically important. Diversifying funding sources reduces reliance on a single mechanism and enables stepwise technical de-risking while strengthening competitiveness for subsequent awards. The phased framework supports responsible TRL progression, preserves intellectual property, and reinforces workforce and economic impact within Idaho without overextending projected outcomes.

Appendices

Appendix A: Facilities and Equipment

Institutional Environment

Idaho State University (ISU) is a comprehensive public research institution offering Bachelor of Arts, Bachelor of Science, Master's, and Doctoral degrees. In the most recent academic year, ISU enrolled nearly 12,000 undergraduates and 2,105 graduate students, with a substantial proportion being first-generation college students. As the state's designated health sciences university, ISU plays a central role in workforce development, biomedical research, and expanding access to high-quality education in underserved regions.

The College of Pharmacy at ISU is the only provider of professional (PharmD) and graduate education in pharmaceutical sciences within Idaho. The College offers the PharmD, Master's, and Doctoral degrees, alongside residencies and fellowships, and emphasizes hands-on training, clinical practice, and research. In the last academic year, the College enrolled 300 students, with over 30% engaged in research projects under faculty mentorship. Approximately 15% of graduates continue on to doctoral training in pharmaceutical sciences, toxicology, or related health sciences. Recent institutional investment has further strengthened this environment: the College has expanded laboratory space for drug discovery and translational research, launched targeted faculty recruitments in biomedical and pharmaceutical sciences, and acquired state of-the-art instrumentation, including LC–MS, Biotage Selekt chromatography, microwave reactors, and advanced solvent-drying systems, to accelerate cutting-edge research and student training.

The Department of Biomedical and Pharmaceutical Sciences fosters a vibrant research culture across undergraduate, PharmD, and graduate levels. Students participate in research through elective coursework and assistantships, contributing to projects in medicinal chemistry, pharmacokinetics, drug design, and cancer therapeutics. Faculty provide close mentorship from project design through data analysis and publication, while College-sponsored symposiums and travel funds support student dissemination at national and international meetings. Increasingly, students from ISU's Biology and Chemistry programs, as well as nearby institutions such as BYU–Idaho, are joining these efforts, expanding the pipeline of future biomedical scientists. Collectively, these initiatives, combined with new facilities, instrumentation, and faculty expertise, underscore ISU's commitment to building sustainable research capacity, enhancing student training, and advancing pharmaceutical sciences in Idaho and beyond.

Description of institutional resources available for the proposed research

Protected Research Time and Start-Up. Dr. Zeleke was hired in 2023 as a tenure track assistant professor to teach in the ISU College of Pharmacy and establish a drug discovery and development research portfolio using his expertise in drug development. Dr. Zeleke maintains an 11-month appointment with 50% protected time for research. He was provided startup funds and a fully funded research assistant.

Laboratory

Dr. Zeleke's laboratory is housed in the newly renovated Leonard Hall within the College of Pharmacy. The facility features an open-laboratory design adjacent to the department's pharmaceutical core, providing an interactive and collaborative research environment. The PI's primary laboratory space covers approximately 1500 sq. ft. and is equipped for both bioassay studies and chemical synthesis. Dedicated student work stations are outfitted with computers supporting essential research software, including Chemdraw, Chimera, SciFinder, GraphPad Prism, chemical inventory management tools, and the Schrödinger Small Molecule Drug Discovery Suite. Additional computers are available within the lab for data acquisition and student use.

Beyond this primary space, Dr. Zeleke also has access to an additional 200 sq. ft. laboratory area in the Chemistry Department, which includes a fume hood outfitted with a Schlenk line system to support advanced synthetic work.

Office

Dr. Zeleke has a 120 sq. ft. office equipped with standard computer stations with connections to printers and unlimited Box cloud storage. Faculty offices are equipped with a desktop computer and a laptop computer for work conducted outside of the office.

The Zeleke laboratory houses the following:

The laboratory includes a fully equipped, BSL2-certified cell culture facility that supports a wide range of cell culture studies. The facility is equipped with Class II biosafety cabinets, CO_2-controlled incubators, inverted microscopes, and liquid nitrogen cryo storage for long-term preservation of cell lines. Routine mycoplasma testing and sterile technique training ensure cell line integrity and experimental rigor. Our facility houses a BioX bioprinter and an INKREDIBLE+ organoid culturing system, both of which enable reproducible generation of patient- and cancer-derived 3D models. These instruments provide the capacity to perform high-throughput, physiologically relevant assays for cell growth, drug response, and mechanistic validation. A central goal of this project is to train students in cutting-edge preclinical model systems.

The Zeleke laboratory is equipped with advanced instrumentation to support medicinal chemistry and organic synthesis. Major resources include automated flash chromatography systems (Teledyne Isco CombiFlash RF and Biotage Selekt), a CEM Mars 5 microwave reactor, and an MBRAUN solvent drying system with dedicated solvent-drying space. Additional equipment includes rotary evaporators with vacuum pumps and chillers, multiple heating/stirring systems (hotplates, mantles, DrySyn kit), a Welch high-vacuum pump, and a MEL-TEMP apparatus for melting point determination. Three UV spectrophotometers (254/356 nm) are available for compound analysis, and solvents are safely stored in flammable cabinets. Together, this infrastructure enables efficient purification, characterization, and handling of organic compounds and supports training of student researchers in modern synthetic methods.

Biomedical and Pharmaceutical Sciences Core facilities, Pocatello

In general, the Pocatello laboratories includes all necessary equipment for this project including routine laboratory equipment, analytical balances, low temperature freezers, refrigerators, microscopes etc. The following is a list of specialized equipment, primarily located in core laboratory of the department.

1. SCIEX QTRAP 5500 LC-MS/MS.

2. Agilent HPLC with DAD and FLD: This instrument was purchased in 2018. The 1220 Infinity II LC is an integrated system for routine HPLC and UHPLC analysis. This system has high quality and high-performance capability to serve analytical needs.

3. Agilent GC-MS: This is a used system. The Agilent 6890 GC-MS is equipped with a 7683 series autoinjector and controlled by enhanced Agilent MSD ChemStation software. The GCMS will support the mass analysis of small molecules.

4. Aapptec Focus Xi Peptide synthesizer: This instrument was purchased in December 2018 and installed in Feb 2019. The Aaptec peptide synthesizer used solid phase peptide synthesis peptides of pharmaceutical grade purity on a large scale.

5. Surface Plasmon Resonance: The Reichert 2SPR system was purchased in Spring 2018. This system is well known for its ease of use, low-cost maintenance, adaptability and sensitivity. This system allows detection of molecules down to a molecular weight of approximately 90.

6. LKB WALLAC 1277 Gammamaster automatic gamma counter

7. TRI-CARB 2900TR Liquid scintillation counter

8. Sorvall floor mounted highspeed and ultracentrifuges.

9. AutoClave

Other investigators in the department possess a wide variety of equipment to perform research in neurophysiology, pharmacogenomics, immunology, pharmacology, and developmental biology. Available equipment includes agarose electrophoresis and blotting equipment for DNA and RNA, polyacrylamide electrophoresis equipment for proteins, electro-blotting apparatus, ELISA readers, micro-plate washers, glucose analyzers, bench-top microfuges, gel-drying systems, preparative isoelectric unit and other protein purification equipment, lightboxes, homogenizers, rotary shaker baths, microwave ovens, auto-pipette dispensers, dissecting scopes, inverted microscopes, light microscopes, microtomes, liquid nitrogen storage dewars, Geiger counter, and biohazard and radioactive waste containment and disposal supplies, Wallace 1410 liquid scintillation counters, a large walk-in cold room, and several low-temperature freezers. Faculty readily share equipment between laboratories.

Molecular Biology Core Facility (Gale Life Sciences Building, Idaho State University): A molecular core facility is maintained by the office for research and is located in the Gale Life Sciences Building on campus. This is the same building where the vivarium is housed. This core includes instrumentation for support of molecular biology procedures as well as house an imaging core, including a new confocal microscope. Key equipment includes:

Molecular Biology:

1. Illumina MiSeq Next-Gen Sequencer
2. AB 3130xl Sanger Sequencing
3. AATI Fragment Analyzer
4. BioTek Synergy HTX Platereader
5. Veriti 96-Well Thermal Cyclers
6. Bio-Rad CFX96 qPCR Machine
7. Bio-Rad ChemiDoc Gel Imager and Printer
8. NanoDrop
9. Qubit 2.0 Fluorometer
10. Speed-Vac Evaporator
11. Electrophoresis Gel Rigs
12. Multiple Centrifuges, Refrigeration Optional
13. Vortexers

Microscopy Laboratory:

1. FACSCalibur Flow Cytometer, with Cell Sorter
2. Zeiss Transmission Electron Microscope (TEM)
3. Olympus Multiphoton Microscope
4. Olympus Confocal Laser Scanning Microscope
5. Leica DM6B Brightfield Microscope
6. Leica Microtome
7. Leica Cryostat, Motorized

Biomedical and Pharmaceutical Sciences Computational Core facilities, Meridian Campus:

Current Hardware:

o Hybrid CPU/GPU Computing Cluster (GARLIC): 1 head node/file server provides 146TB of disk space and data backup/redundancy; 19 compute nodes provide a total of 236 Intel and AMD CPUs, 36 NVIDIA GTX 1080 Ti GPUs (129,024 CUDA Cores), 1TB RAM, 177TB disk space, connected by Cisco Gigabit network switches.

o Laptop CPU Computing Cluster (YGGDRASIL): 1 head node (HP Compaq 600 Pro) and 86 Acer Aspire laptop compute nodes, which provide a total of 174 Intel and AMD CPUs, 348GB RAM, and 67TB disk space, connected by Cisco Catalyst 2960-S and TP-Link TL-SG108E Gigabit network switches.

o CPU Computing Cluster (BERRY): 1 head node (HP Compaq 600 Pro) and 9 compute nodes (HP Compaq dc5800), which provide a total of 20 Intel CPUs, 40GB RAM, and 4TB disk space, connected by a NetGear GS316 Gigabit network switch.

o Clinical Informatics Servers: (1) WASABI server provides 24 Intel CPUs, 144GB RAM, 6TB of high-speed non-volatile memory express (NVMe) solid state drives (SSDs), 9TB of SATA SSDs, and 20TB of conventional hard drives; (2) NUTMEG server provides 16 AMD CPUs, 64GB RAM, 6TB of high-speed NVMe SSDs, 10TB of SATA SSDs, and 20TB of conventional hard drives; (3) OUTCOME server provides 24 Intel CPUs, 64GB RAM, 10TB of SATA SSDs.

Molecular modeling software licenses to perform computations studies

o Schrödinger
o OpenEye
o AMBER
o ChemAxon
o AutoDock/MGLTools
o Smina/Vina
o MegaDock
o NAMD/VMD
o GROMACS
o ChemFP
o RDKit
o UCSF Chimera
o Modeller
o Python/Scikit-Learn
o DeepChem
o SAS
o JMP Pro
o DNA Star
o SimCYP
o Phoenix WinNonlin

Department of Chemistry: The Chemistry department, located in a nearby building on the Pocatello campus houses a wealth of analytical equipment relevant to this project including:

o BRUKER 400 MHz NMR equipped with autosampler
o High Performance Liquid Chromatograph (HPLC)
o FTIR Spectrometer
o Lambda35 UV/Vis Spectrometer
o Shimadzu GCMS
o Atomic Absorption Spectrometer
o Atomic Force Microscope
o Differential Scanning Calorimeter
o Genesys Spectrometer
o Inductively Coupled Plasma Optical Emission Spectrometer
o J-815 CD Spectrometer
o Raman Microscope
o 1XRD Spectrometer

Animals

ISU's AAALAC certified animal research facility, located in the Gale Life Sciences Building, provides designated space to house mice (100 square feet) and access to a surgical suite for the humane euthanasia and resection of important tissue samples. This facility is maintained by a veterinarian, two full-time, and one part-time animal technician.

Use of special facilities or equipment at other institutions

The research will primarily be conducted in the PI's lab, which is equipped with state-of-the-art facilities for cancer biology research. Through collaboration with Professor Joanna Burdette at the Retzky College of Pharmacy, University of Illinois Chicago (as mentioned in the letter of support), the PI and student researchers will benefit from additional resources, including advanced cell culture and molecular biology equipment. This partnership also offers valuable opportunities to collaborate with specialists in cancer biology, complementing the work being done in the PI's lab and enhancing multidisciplinary research efforts.

Quote for the Requested Büchi R-330 Rotavapor

Please refer to the justification provided above for the rationale supporting the purchase of the requested Büchi R-300 Rotavapor. The quotation reflects the required configuration to support compound purification, solvent recovery, and scalable synthetic workflows essential for the proposed medicinal chemistry activities.

Sales Quotation

*Quote Nbr	Creation Date	Due Date	Page
6007-6664-98	01/07/2026		1 of 2

Payment Terms	Delivery Terms
NET 30 DAYS	DESTINATION
Valid To	Prepared By
02/04/2026	LONGFIELD, MICHAEL
Customer Reference	Sales Representative
SOLOMON ZELEKE R-300E 1.7.26	STEPHEN HANEY

To place an order	Ph: 800-766-7000	Fx: 800-926-1166

Submitted To:	Customer Account: 379880-001
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For complete Terms and Conditions, please click here.

Nbr	Qty	UN	Catalog Number	Description	Unit Price	Extended Price
1	1	EA	05001074	EVAPR R300E 24/40 V I300P 305 BUCHI Rotavapor R-300 Rotary Evaporator with Controller and V-300 Pump, Condenser Type: Vertical, Capacity: 5L, Controller Type: I-300 Pro Interface, Includes: V-300 Vacuum Pump, F-305 Chiller, Electronic Lift, Model: R-300/V-300/F-305, Rotary Evaporator System, Speed: 10 - 280 rpm Vendor Catalog # 11SR300252VP12 Hazardous Material This item is being sold as 1 per each COMMENTS: 6 BUSINESS DAY LEAD TIME	20,656.83	20,656.83
2	1	EA	01258207	START MAINTAIN DIY R-300 Vendor Catalog # 11CSN12026 This item is being sold as 1 per each Product - Non-Returnable	373.67	373.67
3	1	EA	01258209	START MAINTAIN DIY V-300 Vendor Catalog # 11CSN12060 Hazardous Material This item is being sold as 1 per each Product - Non-Returnable	604.24	604.24

Sales Quotation

Fisher Scientific
Part of Thermo Fisher Scientific

Quote Nbr	Customer Reference	Page
6007-6664-98	SOLOMON ZELEKE R-300E 1.7.26	2 of 2

Nbr	Qty	UN	Catalog Number	Description	Unit Price	Extended Price
4	1	EA	01258250	START WARRANTY 1 F-305	242.05	242.05
				Vendor Catalog # 11CSN11505		
				Hazardous Material		
				This item is being sold as 1 per each		
				Product - Non-Returnable		
5	1	EA	01258247	START WARRANTY 1 I-300 PRO	139.58	139.58
				Vendor Catalog # 11CSN11544		
				Hazardous Material		
				This item is being sold as 1 per each		
				Product - Non-Returnable		
6	1	EA	NC2940546	SHIPPING AND HANDLING	N/C	N/C
				Vendor Catalog # 34004868		
				Hazardous Material		
				Original Catalog Number 34004868		

MERCHANDISE TOTAL 22,016.37

NOTES:
Returns are subject to manufacturer terms and conditions.

We now offer highly competitive financing with low monthly payments. Please contact your local sales representative for more information.

Tell us about your recent customer service experience by completing a short survey. This should take no longer than three minutes. Enter the link into your browser and enter the passcode: USA-PGH-CS2
http://survey.medallia.com/fishersci

Effective 05/20/2024 NSF BIOGRAPHICAL SKETCH OMB-3145-0279

IDENTIFYING INFORMATION:

NAME: Zeleke, Solomon Tadesse

ORCID iD: https://orcid.org/0000-0002-9966-2236

POSITION TITLE: Assistant Professor of Biomedical and Pharmaceutical Sciences

PRIMARY ORGANIZATION AND LOCATION: Idaho State University, Pocatello, Idaho, United States

Professional Preparation:

ORGANIZATION AND LOCATION	DEGREE (if applicable)	RECEIPT DATE	FIELD OF STUDY
H. Lee Moffitt Cancer Centre & Research Institute, Tampa, Florida, United States	Postdoctoral Fellow	03/2020 - 02/2021	Drug Discovery and Development
University of South Australia, Adelaide, Not Applicable, N/A, Australia	Postdoctoral Fellow	03/2018 - 01/2019	Drug Discovery and Development
University of South Australia, Adelaide, Not Applicable, N/A, Australia	PHD	02/2014 - 12/2017	Medicinal Chemistry
Addis Ababa University, Addis Ababa, Not Applicable, N/A, Ethiopia	MS	10/2004 - 04/2007	Pharmacognosy
Addis Ababa University, Addis Ababa, Not Applicable, N/A, Ethiopia	BS	09/1998 - 07/2004	Pharmacy

Appointments and Positions

2023 - present Assistant Professor of Biomedical and Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, United States

Products

Products Most Closely Related to the Proposed Project

1. Pandurangan T, Zeleke ST, Iermolaieva A, Ghosh P, Mosior J, Sun L, Grassie D, Schmitz M, Kalaga MN, Albritton W, Rodas MM, Chin Chan S, Frydman S, Sansil S, Geyer M, Schönbrunn E, Roush WR, Duckett DR, Monastyrskyi A. Structure-Activity and Structure-Degradation Relationship Studies of 2-Amino-6-(benzimidazol-2-ylmethyl)-N9-heteroarylpurines as Potent and Selective CDK12/13 Inhibitors and Cyclin K Degraders. J Med Chem. 2026 Feb 12;69(3):2287-2309. PubMed PMID: 41533987.
2. Ghosh P, Schmitz M, Pandurangan T, Zeleke ST, Chan SC, Mosior J, Sun L, Palve V, Grassie D, Anand K, Frydman S, Roush WR, Schönbrunn E, Geyer M, Duckett D, Monastyrskyi A. Discovery and design of molecular glue enhancers of CDK12-DDB1 interactions for targeted degradation of cyclin K. RSC Chem Biol. 2024 Oct 11; PubMed Central PMCID: PMC11494886.

3. Tadesse S, Duckett DR, Monastyrskyi A. The promise and current status of CDK12/13 inhibition for the treatment of cancer. Future Med Chem. 2021 Jan;13(2):117-141. PubMed PMID: 33295810.
4. Tadesse S, Bantie L, Tomusange K, Yu M, Islam S, Bykovska N, Noll B, Zhu G, Li P, Lam F, Kumarasiri M, Milne R, Wang S. Discovery and pharmacological characterization of a novel series of highly selective inhibitors of cyclin-dependent kinases 4 and 6 as anticancer agents. Br J Pharmacol. 2018 Jun;175(12):2399-2413. PubMed Central PMCID: PMC5980294.
5. Tadesse S, Yu M, Mekonnen LB, Lam F, Islam S, Tomusange K, Rahaman MH, Noll B, Basnet SK, Teo T, Albrecht H, Milne R, Wang S. Highly Potent, Selective, and Orally Bioavailable 4-Thiazol-N-(pyridin-2-yl)pyrimidin-2-amine Cyclin-Dependent Kinases 4 and 6 Inhibitors as Anticancer Drug Candidates: Design, Synthesis, and Evaluation. J Med Chem. 2017 Mar 9;60(5):1892-1915. PubMed PMID: 28156111.

Other Significant Products, Whether or Not Related to the Proposed Project

1. van der Noord VE, McLaughlin RP, Karuntu JS, He J, Timmermans AM, Basnet SKC, Long Y, Diab SAH, Tadesse S, Proost N, van Gerwen B, Siteur B, van de Ven M, Pont C, Le Dévédec SE, Martens JWM, Wang S, Zhang Y, van de Water B. Disrupting CDK9 activity suppresses triple-negative breast cancer and is enhanced by EGFR Inhibition. Cell Oncol (Dordr). 2026 Jan 8;49(1):20. PubMed Central PMCID: PMC12783313.
2. Tadesse S, Kaweesa E. Targeting the gate: The rise of Sec61 inhibitors in cancer therapy. J Pharmacol Exp Ther. 2025 Nov;392(11):103721. PubMed PMID: 41110331.
3. Shrestha J, Blanchard J, Tadesse S. Cyclin-Dependent Kinase 11: Cellular Functions and Potential Therapeutic Applications. ChemMedChem. 2025 Oct 15;20(20):e202500305. PubMed PMID: 40627000.
4. Bantie L, Tadesse S, Likisa J, Yu M, Noll B, Heinemann G, Lokman NA, Ricciardelli C, Oehler MK, Beck A, Pradhan R, Milne R, Albrecht H, Wang S. A first-in-class CDK4 inhibitor demonstrates in vitro, ex-vivo and in vivo efficacy against ovarian cancer. Gynecol Oncol. 2020 Dec;159(3):827-838. PubMed PMID: 32958271.
5. Tadesse S, Zhu G, Mekonnen LB, Lenjisa JL, Yu M, Brown MP, Wang S. A novel series of N-(pyridin-2-yl)-4-(thiazol-5-yl)pyrimidin-2-amines as highly potent CDK4/6 inhibitors. Future Med Chem. 2017 Sep;9(13):1495-1506. PubMed PMID: 28795589.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that

meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Certified by Zeleke, Solomon Tadesse in SciENcv on 2026-02-18 17:12:26

Appendix C: Senior Personnel

1. Joanna E. Burdette, PhD

Professor of Pharmaceutical Sciences
Associate Dean for Research and Graduate Education
University of Illinois Chicago

Qualifications

Dr. Burdette is an NIH-funded cancer biologist with extensive expertise in transcription-driven malignancies, tumor signaling pathways, and mechanistic oncology. She co-leads the Cancer Biology Program at the University of Illinois Cancer Center and has maintained continuous federal and foundation support for over a decade

Her laboratory utilizes advanced translational platforms, including patient-derived systems, 3D models, and mechanistic signaling analyses, to interrogate tumor initiation, DNA damage response pathways, and therapeutic vulnerabilities. These capabilities are directly relevant to CDK12 biology, which regulates transcription elongation and homologous recombination gene expression.

She has mentored over 15 postdoctoral fellows and more than 20 PhD trainees and previously co-led an NIH K12 IRACDA program, demonstrating strong experience preparing investigators for independent NIH funding.

Services to the IGEM–HERC Project

Dr. Burdette will serve as Expert Translational Mentor and provide:

- Guidance on mechanistic validation of CDK12 inhibition and Cyclin K degradation in cancer-relevant systems
- Input on DNA damage response biomarkers, transcriptional stress pathways, and HR-deficiency phenotypes
- Strategic oversight for positioning feasibility data toward future NIH R21/R01 submissions
- Quarterly structured mentorship meetings, with additional consultation during milestone transitions

Her expertise ensures that the AI-designed small molecules are validated within biologically rigorous and clinically meaningful frameworks.

2. Elizabeth Kaweesa, PhD

NIH MOSAIC Postdoctoral Research Associate
University of Illinois Chicago

Qualifications

Dr. Kaweesa specializes in advanced human-relevant biological models, including 3D organoid systems and pathway-engagement assays. She has experience integrating medicinal chemistry outputs with functional biological validation to support translational decision-making. Her expertise is particularly relevant for evaluating transcriptional kinase inhibition and degradation strategies in physiologically meaningful systems.

Services to the IGEM–HERC Project

Dr. Kaweesa will support:

- Functional validation of AI-prioritized CDK12/Cyclin K candidates in advanced biological systems
- Evaluation of pathway suppression, apoptosis induction, and transcriptional disruption
- Mechanistic interrogation of degradation versus catalytic inhibition phenotypes
- Cross-disciplinary training of Idaho State University trainees in translational assay platforms

Her contributions strengthen biological rigor and translational depth beyond standard 2D screening systems.

3. Jesse Wheeler, PhD

Assistant Professor
Idaho State University

Qualifications

Dr. Wheeler provides expertise in quantitative modeling, statistical inference, and experimental design applicable to AI-driven medicinal chemistry campaigns.

Services to the IGEM–HERC Project

Dr. Wheeler will provide:

- Statistical validation of predictive modeling outputs (e.g., ROC–AUC, PR–AUC, R^2, mean absolute error benchmarking)
- Design-of-experiments support for structure–activity relationship (SAR) refinement
- Multivariate analysis of structure–degradation relationships (SDR)
- Data visualization and inferential support for publication and follow-on funding

His role ensures quantitative rigor in AI model evaluation and medicinal chemistry decision-making.

4. Robert Mancini, PharmD, BCOP, FHOPA

St. Luke's Health System

Qualifications

Dr. Mancini is an oncology pharmacist and residency director with clinical expertise in kinase inhibitor therapy and toxicity management

Services to the IGEM–HERC Project

Oncology Clinical Advisor

Dr. Mancini will serve as Clinical Translational Advisor and provide:

- Input on therapeutic index considerations for CDK-targeted agents
- Guidance on anticipated hematologic toxicities and clinical development challenges
- Strategic insight into translational positioning toward IND-enabling studies
- Clinical benchmarking against approved CDK inhibitors

His advisory role ensures early alignment with clinical feasibility and commercial viability.

Appendix D: Other

Idaho State University

February 23rd, 2026

Dear Dr. Zeleke,

The Office for Research at Idaho State University (ISU) is pleased to support your proposal, *Artificial Intelligence Guided Discovery of Dual-Mechanism Cyclin-Dependent Kinase 12 and Cyclin K Modulators for Targeted Osteosarcoma Therapy*, for the IGEM-HERC award. ISU strongly supports this project and is fully committed to providing the institutional resources, infrastructure, and coordination necessary to ensure its success. The Office for Research, in collaboration with relevant academic units and research centers, will actively support this effort as it establishes advanced capabilities in AI-enabled drug discovery and translational oncology within Idaho's public research system, key priorities of Idaho's Higher Education Research Strategic Plan.

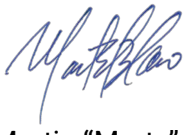
To ensure the success of your proposed project, ISU will facilitate access to shared research infrastructure, including computational resources, newly renovated laboratory facilities, and access to Core facilities. ISU will also support cross-disciplinary collaboration through its Office of Research Development. This Office will help coordinate interactions among investigators and support applications for external funding to ensure that you can focus on high-value discovery and validation activities. Through its Office of Technology Transfer, ISU will also support the project's goal of producing protected intellectual property suitable for future commercialization.

ISU is proud to offer its strong support for this project as it is closely aligned with IGEM-HERC priorities. The proposed research will advance two of the five areas targeted for development: Biomedical and Healthcare Sciences, and Data Science, Computer Science, and Cybersecurity. ISU is home to Idaho's only College of Pharmacy and is the state's designated lead institution in health professions and medical education. Your project leverages that strength and builds on our institution's growing research profile in Computer Science. In further alignment with the Higher Education Research Strategic Plan, this project is poised to advance the commercial potential of research in Idaho. This is evidenced by your partnership with Reaction Biology.

Beyond immediate project needs, ISU is committed to sustaining the capabilities developed through this work. ISU will support efforts to leverage project outcomes toward external funding and will ensure that its Technology Transfer Office is available to support commercial applications of your work. This long-term institutional commitment reflects ISU's strategic focus on research programs that generate broad impact, economic value, and improved health outcomes for Idahoans.

Thank you for your consideration, and please do not hesitate to contact me with any questions.

Sincerely,



Martin "Marty" Blair, PhD
Vice President for Research and Economic Development
Idaho State University

REACTION BIOLOGY
1 Great Valley Parkway, Suite 2, Malvern, PA 19355, USA
1-610-722-0247 • www.reactionbiology.com

Haiching Ma, PhD
Chief Science Officer
Haiching.ma@reactionbiology.com

Feb. 22nd, 2026

Higher Education Research Council (HERC)
Idaho State Board of Education
IGEM–HERC Program

Re: Letter of Support for Dr. Solomon T. Zeleke – IGEM–HERC Proposal

Dear Members of the Higher Education Research Council,

Reaction Biology is pleased to provide this letter of support for the IGEM–HERC proposal submitted by Dr. Solomon T. Zeleke, Assistant Professor in the Department of Biomedical and Pharmaceutical Sciences at Idaho State University.

Reaction Biology is a recognized provider of industry-standard kinase profiling and selectivity screening services. We have previously collaborated with Dr. Zeleke and are familiar with his research program focused on cyclin-dependent kinase (CDK) inhibition and targeted protein degradation strategies for oncology applications. Our prior engagements have involved kinase selectivity profiling and mechanistic validation studies supporting translational medicinal chemistry efforts.

For the proposed IGEM–HERC project, Reaction Biology commits to:
1. Providing comprehensive kinase selectivity profiling services to support validation and lead optimization of novel CDK-targeted compounds.
2. Delivering high-quality, reproducible biochemical data suitable for downstream regulatory, licensing, and commercialization discussions.
3. Offering academic discounted pricing to support the feasibility and budget efficiency of the proposed work.

Our role will be that of a technical validation partner operating under a defined service agreement. Reaction Biology will not claim intellectual property ownership arising from the project. All IP generated will remain with Idaho State University in accordance with institutional policies and any applicable agreements.

We believe this project aligns strongly with IGEM–HERC objectives to accelerate technology maturation, strengthen commercialization pathways, and enhance economic development through biotechnology innovation in Idaho. Rigorous kinase profiling will be essential to de-risk the technology, define selectivity windows, and support advancement along the Technology Readiness Level (TRL) continuum.

Reaction Biology looks forward to continuing our collaboration with Dr. Zeleke and supporting the successful advancement of this program.

Sincerely,

Haiching Ma, Ph.D.

UNIVERSITY OF ILLINOIS CHICAGO
College of Pharmacy

2/23/2026

Re: **IGEM–HERC Proposal – AI-Enabled CDK12/Cyclin K Translational Therapeutic Platform**

Dear IGEM–HERC Review Committee Members,

I am pleased to provide this letter of support as an external expert and scientific advisor for Dr. Solomon Zeleke in connection with his IGEM–HERC proposal focused on the development of an AI-enabled CDK12/Cyclin K therapeutic platform for translational oncology applications. I am a Professor of Pharmaceutical Sciences, the Edward and Josephine Mika Professor, and Associate Dean for Research and Graduate Education in the College of Pharmacy at the University of Illinois Chicago. I also co-lead the Cancer Biology Program at the University of Illinois Cancer Center. My laboratory maintains a long-standing NIH-funded research program centered on translational cancer biology and therapeutic target validation.

As an external expert and scientific collaborator, I commit to the following defined contributions:

1. I will provide structured scientific consultation on experimental design, translational model selection, and mechanistic interrogation of CDK pathway modulation.
2. I will advise on selection and interpretation of appropriate in vitro and in vivo models to ensure that feasibility data generated under IGEM–HERC meet translational relevance standards expected for subsequent federal funding and industry engagement.
3. I will advise Dr. Zeleke on framing project outcomes for competitive external funding and potential industry partnership discussions.

The IGEM–HERC mechanism provides an important opportunity to advance this technology from early-stage feasibility toward translational validation and commercialization readiness. Dr. Zeleke has demonstrated strong leadership in drug discovery and medicinal chemistry innovation. I am confident that, with IGEM–HERC support, this project will generate high-quality validation data that strengthen Idaho's biomedical innovation ecosystem and position the technology for competitive follow-on funding and partnership development.

I fully support this IGEM–HERC application and am committed to contributing meaningful scientific and strategic mentorship throughout the project period.

Sincerely,

Joanna Burdette, PhD
Professor of Pharmaceutical Sciences
Edward and Josephine Mika Professor
Associate Dean for Research and Graduate Education
College of Pharmacy
University of Illinois Chicago

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February 18, 2026

Re: IGEM–HERC Proposal

Dear Review Committee Members,

I am writing to express my strong support for Dr. Solomon Zeleke's application to the IGEM–HERC project focused on the development of an AI-enabled CDK12/Cyclin K translational therapeutic platform. I have had the opportunity to collaborate closely with Dr. Zeleke on a multidisciplinary research effort focused on the development and translational evaluation of CDK–targeted therapeutic strategies, and I am enthusiastic about continuing this collaboration as part of his proposed CDK12/Cyclin K project.

As a postdoctoral research associate in Dr. Joanna Burdette's laboratory at the University of Illinois Chicago, I contribute specialized biological expertise that complements Dr. Zeleke's strengths in translational science. My role focuses on the implementation and execution of advanced human-relevant biological assays, including three-dimensional organoid systems, which provide physiologically meaningful platforms for evaluating compound efficacy, mechanism, and therapeutic potential.

Within the context of the proposed project, my contributions will support translational evaluation of candidate molecules by applying these advanced biological platforms to interrogate antitumor activity and mechanistic effects in clinically relevant systems. This collaborative framework strengthens the project by ensuring that medicinal chemistry optimization is informed by functional biological outcomes, thereby increasing rigor, reproducibility, and translational relevance.

An important aspect of this collaboration is its strong emphasis on training and workforce development. Dr. Zeleke's laboratory at Idaho State University actively engages PharmD, graduate, and undergraduate students in hypothesis-driven research spanning compound design, synthesis, and biological evaluation. Through our collaboration, these trainees will gain exposure to advanced biological systems and translational experimental design, including organoid-based assays and data interpretation. This cross-disciplinary training is especially impactful at Idaho State University, which serves a largely rural and under-served population and includes many first-generation students. By participating in this collaborative research environment, students develop technical skills, critical thinking, and scientific communication abilities that prepare them for careers in translational research, directly supporting IGEM–HERC's workforce development goals.

Sincerely,

Elizabeth Kaweesa, Ph.D.
NIH MOSAIC Postdoctoral Research Associate
College of Pharmacy
University of Illinois Chicago

Idaho State University

February 20, 2026

Solomon Zeleke. BPharm, MSc, PhD
Department of Biomedical and Pharmaceutical Sciences
LS Skaggs College of Pharmacy
Idaho State University
921 S 8th Ave Stop 8288
Pocatello, ID 83209

Dear Dr. Zeleke:

Please consider this letter as support for your proposed IGEM–HERC project focused on the development of an AI-enabled CDK12/Cyclin K translational therapeutic platform. After reviewing your proposal and discussing the project with you in detail, I am confident that the study design will yield significant, high-impact data. The proposed experimental framework and analytical techniques are expertly aligned with the project aims. I anticipate that the success of this proof-of-concept pilot will provide the essential data needed to secure larger federal funding in the future.

In addition to supporting your project design, my expertise in data analysis and statistics will prove valuable as we collaborate on the analysis of data resulting from your studies. Specifically, I will provide my support in helping you and the students who participate in the proposed project analyze and perform inference on data that arise from experiments. I will also aid in experimental design, data visualization, and implementation of machine learning algorithms as the need arises.

I look forward to our collaborative work.

Sincerely,

Jesse Wheeler, PhD
Assistant Professor
Department of Mathematics and Statistics
Idaho State University

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