ABNEXUS

Special Topic – Quantum and Human Health

AI-Quantum Computing for Drug Optimization in Precision Oncology

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PROJECT SUMMARY

Project Overview: Since 2023, quantum technology has rapidly emerged on the global stage. Colorado, through Elevate Quantum (EQ), has been designated as one of two U.S. quantum tech hubs, securing $127M in funding to establish Colorado as a global leader in quantum innovation. While quantum technology holds immense promise for solving complex challenges, including applications in human health (quantum-health), real-world progress remains limited. Drug discovery is frequently cited as a transformative quantum-health application, yet practical advancements have been scarce [1,2]. This proposal aims to launch Colorado's first quantum-health initiative, focusing on colorectal cancer (CRC) drug discovery.

CRC is the third leading cause of cancer-related deaths worldwide, with chemotherapy serving as the primary treatment option. However, only about 50% of CRC patients respond to standard chemotherapy [3,4], highlighting a significant unmet need for therapies that can enhance treatment efficacy. Chromodomain helicase DNA-binding protein 1-like (CHD1L), a novel oncogenic protein, plays a critical role in tumor progression and resistance to therapy (***Fig 1A***) [5,6]. We have shown that CHD1L inhibitors (CHD1Li) synergize with chemotherapy, increasing their potency against tumor organoids by up to 1,000 times [7,8]. Despite this promising activity, there are no approved therapies targeting CHD1L, making the expedited optimization of CHD1Li an urgent priority for advanced therapeutic development for CRC.

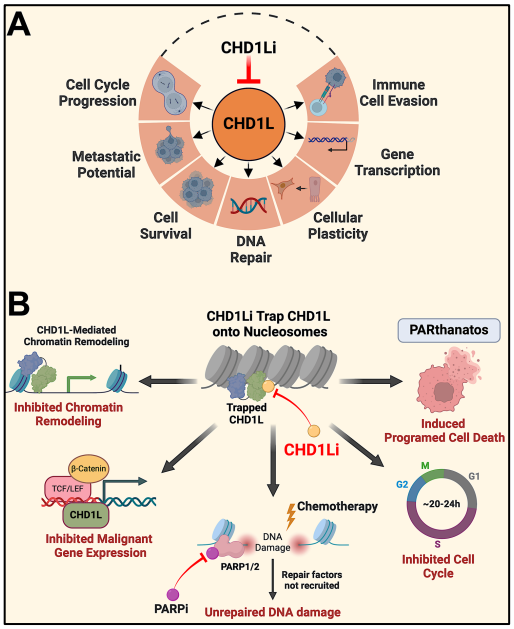

Fig 1. (A) *Oncogenic functions of CHD1L.* ***(B)*** *CHD1Li bind allosterically and inhibit CHD1L ATPase, trapping it onto chromatin, preventing chromatin remodeling. This entrapment suppresses malignant gene expression, disrupts cancer survival, and induces PARthanatos, a unique form of cell death.*

Our project will leverage artificial intelligence (AI) driven quantum computing to optimize CHD1Li, accelerating the discovery of compounds with superior potency and drug-like properties. Integrating generative AI with quantum computing offers an unprecedented opportunity to explore vast chemical space, but this ambitious endeavor presents significant challenges. Quantum computing for drug discovery requires precise algorithms to model complex protein-drug interactions while addressing limitations such as noise and scalability. To overcome these hurdles, we have assembled a multidisciplinary team, with expertise in ***cancer drug discovery and development*** (D. LaBarbera, PI), ***structural biology and biochemistry*** (K. Luger, Co-PI; and J. Rudolph Co-I), ***AI and computer science*** (F. Banaei-Kashani, Co-I), and IQM a global ***quantum computing*** leader (K. Rezai, IQM team lead).

This project aims to show how AI and quantum computing can speed up drug optimization for advanced and metastatic CRC. By addressing the urgent need for more effective CRC treatments and pioneering a new quantum-health approach, we aim to improve patient outcomes, lay the foundation for broader drug discovery applications, and position the University of Colorado (CU) as a leader in quantum-health innovation. With an exclusive license agreement between the CU and Onconaut Therapeutics Inc., CHD1Li have a clear translational pathway to the clinic. If successful, this project could deliver a lead clinical candidate investigational new drug (IND) within two years, advancing to first-in-human trials at UCHealth.

Specific Aims: CHD1Li were discovered and are being developed at the CU Anschutz Center for Drug Discovery in Dr. LaBarbera's lab. We have elucidated their mechanism of action (MOA), demonstrating that CHD1Li allosterically bind, inhibit, and trap CHD1L on chromatin. This entrapment disrupts DNA repair, impairs cancer cell survival pathways, and induces PARthanatos, an irreversible form of tumor programmed cell death (***Fig 1B***) [7-11]. Due to this unique MOA, CHD1Li exhibit unprecedented synergy with chemotherapy and targeted therapy, enhancing tumor cell death by up to 1,000-times [7,8]. While these findings underscore their therapeutic potential, lead optimization is needed to improve drug-like properties and in vivo efficacy for clinical translation.

Hypothesis: AI-driven quantum-classical computing will accelerate CHD1Li optimization, advancing a clinical candidate to IND-enabling studies and first-in-human trials within 2–3 years. Our iterative AI-quantum-classical platform not only integrates in silico modeling, medicinal chemistry, and biological validation but also continuously trains and refines the AI algorithm to enhance CHD1Li potency, selectivity, and drug-like properties (***Fig 2***).

Aim 1: AI-Quantum-Classical Computing Drug Design. Dr. Banaei-Kashani's lab has developed an AI-driven drug design algorithm that will be extended and adapted for quantum computing in collaboration with IQM. This approach will prioritize our in-house CHD1Li lead compounds, which are protected by extensive worldwide patents and licensed to Onconaut, ensuring commercial viability. AI screening of Enamine's "REAL Space library"

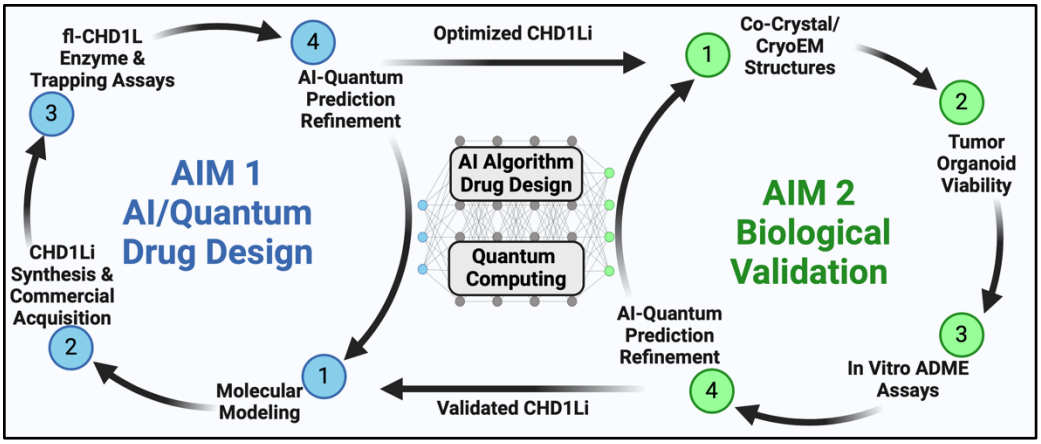

Fig 2. *AI-Quantum drug design approach. ADME = absorption distribution metabolism excretion.*

(>36 billion make-on-demand molecules) will provide novel structural insights and potential backup lead CHD1Li. AI training, quantum integration, and enzyme screening will run in parallel to refine molecular modeling and optimized lead compound selection.

(1) Molecular Modeling – AI will be trained using data from >150 CHD1Li from two distinct chemotypes developed in the LaBarbera lab (published [5-10] and unpublished). Quantum computing will enable large-scale screening of millions of compounds from the Enamine library, but priority will be given to optimizing our in-house CHD1Li. ***(2) Synthesis of Optimized CHD1Li*** – AI-prioritized CHD1Li will be synthesized using our established medicinal chemistry methods [10]. Additionally, commercially available CHD1Li (~100 initial compounds) will be screened as a cost-effective means of identifying high-performing compounds for comparative evaluation. ***(3) CHD1L Enzyme & Trapping Assays*** – CHD1L is distinct from other chromatin remodelers due to the presence of a macro domain, which auto-inhibits its ATPase activity under normal conditions but is activated in cancer cells. While this makes CHD1L an attractive target, it complicates biochemical inhibition assays. Previously, we addressed this challenge by using a truncated ATPase-active CHD1L lacking the macro domain (cat-CHD1L) [10,11]. To improve inhibitor design, CHD1Li will be evaluated for inhibition concentration 50% (IC_{50}) potency using a mutant full-length CHD1L (fl-CHD1L) that maintains ATPase activity [12]. CHD1Li will also be validated using our established cell-based CHD1L trapping assay to confirm chromatin entrapment of CHD1L. Additionally, the Luger Lab will continue to develop functional assays to measure CHD1Li activity in a chromatin context ***(4) AI-Quantum Prediction Refinement*** – The data generated will refine the AI-quantum algorithm, improving predictions and drug optimization. We expect this process to yield 20-50 optimized CHD1Li prioritized for biological validation in Aim 2.

Aim 2: Biological Validation of Optimized CHD1Li Lead Drugs. To advance CHD1Li toward clinical translation, we will experimentally validate their potency, selectivity, and drug-like properties using physiologically relevant models. ***(1) Structural Optimization*** – The Luger lab will produce a co-crystal and/or cryoEM structures of one or more prioritized lead CHD1Li bound to CHD1L, also in complex on chromatin to provide critical structural and mechanistic insights. These data will refine molecular docking studies not only for current CHD1Li but also for AI-identified candidates, feeding back into the AI model to improve predictive accuracy. ***(2) Tumor Organoid Viability*** – 20-50 prioritized CHD1Li will be tested for IC_{50} efficacy in killing CRC tumor organoids using our published protocols [7-11]. ***(3) In Vitro ADME Profiling*** – Lead compounds will be assessed for key drug-like properties, including metabolic stability (>90 min), aqueous solubility, and plasma protein binding (≤97%). ***(4) AI-Quantum Optimization Feedback*** – The data generated will be fed back into the AI-Quantum-classical model to refine CHD1Li drug design, ensuring continuous iterative optimization. Our goal is to identify a clinical CHD1Li candidate with low-nM IC_{50} for CHD1L inhibition, sub-μM IC_{50} for CRC organoid viability, and optimized ADME properties (LogP = 3–4, metabolic stability >90 min, plasma protein binding ≤97%).

Expected Outcomes: This project is expected to yield two major outcomes with broad implications for drug discovery. ***First***, we will develop an AI-driven quantum computing platform that integrates AI, quantum computing, structural biology, and medicinal chemistry to optimize drug candidates. This transformative approach will enable rapid exploration of chemical space, with a goal of refining lead compounds with greater potency and drug-like properties. While initially focused on CHD1Li for CRC, this scalable AI-Quantum framework has the potential to accelerate drug discovery across multiple disease areas, positioning the University of Colorado as a leader in quantum-health innovation. ***Second***, this project will advance CHD1Li lead optimization, potentially delivering a clinical candidate for IND-enabling studies. By iteratively refining AI-Quantum predictions, we aim to identify five optimized CHD1Li compounds with enhanced potency and drug-like properties. Beyond the scope of this project, CHD1Li clinical candidates will undergo preclinical validation, including pharmacokinetics, toxicology, and tumor xenograft efficacy studies, generating critical data for regulatory advancement. Ultimately, our AB Nexus program aims to accelerate CHD1Li clinical translation, addressing an urgent need in CRC patient treatment while demonstrating the real-world impact of AI-Quantum computing in drug discovery.

Potential Impact: *Impact on quantum computing and quantum-health.* The successful development of an AI-driven quantum computing platform for drug discovery will have transformative implications for both academic research and the pharmaceutical industry. While progress has been made in AI-based drug discovery[13] and quantum machine-assisted approaches[14], their integration remains largely unexplored. This AB Nexus project aims to position CU as a national leader in quantum-health innovation applied to drug discovery, leveraging Colorado's status as one of only two federally designated quantum tech hubs. By demonstrating the feasibility of quantum-enhanced drug discovery and design, this project will establish a scalable framework to accelerate therapeutic development across oncology, neurodegenerative, infectious, and other disease areas.

In the ***short term***, the initiative aims to deliver an optimized CHD1Li clinical candidate ready for IND-enabling studies and first-in-human trials within 2–3 years. Over the ***long term***, this approach could lead to a paradigm shift in how new drugs are discovered, designed, tested, and translated into clinical applications, enhancing precision medicine and expanding the drug development pipeline at CU. Establishing CU as a hub for quantum-driven drug discovery will strengthen collaborations between academic institutions, biotechnology startups, and the pharmaceutical industry, fostering innovation, attracting investment, and reinforcing Colorado's position as a global leader in quantum-health. By showcasing real-world applications of quantum computing in medicine, this initiative aims to accelerate clinical translation and commercialization, ultimately improving patient outcomes and shaping the future of next-generation therapeutics.

Impact on patients with colorectal cancer and other cancers. CRC is a global problem, with ~2 million new cases annually and an increasing incidence in adults under 45 (World Cancer Research Fund). At diagnosis, nearly 25% of cases are metastatic, and over 50% progress to become metastatic[1,4], where treatment options remain limited. The survival rate for metastatic CRC is just 13%[15,16], and chemotherapy, the current standard of care, is only effective in about 50% of patients[3], highlighting the urgent need for more effective therapies. Furthermore, CHD1L is implicated as an oncogenic protein and driver in many cancer indications, providing a potentially broader impact in the treatment of cancer [6,17-25].

CHD1Li offer a novel precision medicine approach by targeting CHD1L, an oncogenic chromatin remodeler critical for tumor progression and resistance. By trapping CHD1L on chromatin, CHD1Li prevent DNA repair, disrupt cancer survival pathways, and induce PARthanatos, an irreversible form of programmed cell death. These inhibitors exhibit synergy with chemotherapy, PARPi and other targeted drug therapy, increasing their antitumor potency hundreds to thousands of times by shifting tumor cell death from apoptosis to PARthanatos [7,8,26], a mechanism less prone to resistance. Unlike tumor cells, normal cells remain less affected, as CHD1L is limited in non-cancerous tissues [25,27]. By combining CHD1Li with chemotherapy or PARPi, we anticipate higher response rates, improved patient outcomes, and extended survival. Targeting this oncogenic vulnerability could fundamentally change CRC treatment, offering patients a more effective and durable therapeutic option.

Project Sustainability: *NIH Funding Potential.* In the ***short term*** (2025), this project will support the NIH NCI R01 (CA251361) renewal grant ($2.5M total, 5 years) for CHD1Li development (PI: D. LaBarbera, Co-I: K. Luger), to be submitted in Fall 2025. Additionally, Dr. LaBarbera has submitted an NIH NCI Fast Track STTR grant ($2.5M total, 3 years, submitted Jan 5, 2025) to evaluate up to four CHD1Li lead drugs using in vivo PK, toxicology, and efficacy studies, prioritizing a clinical candidate for IND-enabling studies. CHD1Li leads identified through AB Nexus funding may also undergo further testing via the STTR grant. In the ***long term*** (2026–2028), this work will also support the 2028 NIH NCI R01 renewal grant (CA218255) (PI: K. Luger). We will pursue new R01 and R21 investigator-initiated grants to advance AI-Quantum algorithm development for drug discovery. Additionally, NIH NCATS has a $1.3M Quantum Computing Challenge Prize to support quantum algorithm development in drug discovery. While this opportunity may not be available in 2025, NIH has signaled a strong interest in quantum-driven drug discovery, making future funding prospects promising.

NSF Funding Potential. The NSF supports quantum computing applications in biomedical research through initiatives like the Convergence Accelerator program and grants in computational and quantum sciences. While no specific RFA exists for drug discovery, NSF has funded projects in quantum machine learning and Scalable Quantum AI (SQAI), highlighting its commitment to quantum-driven innovations. This project aligns with NSF's focus on computational advancements in drug discovery, positioning it well for future funding opportunities.

Commercialization Strategy. We anticipate this project will generate novel intellectual property and commercialization opportunities. For the quantum component, potential pathways include the formation of a new CU startup or licensing to an existing company. If a new startup is established, we will pursue SBIR/STTR small business grants, including NOT-EY-24-014, which supports quantum applications in healthcare. This project will also strengthen CU-affiliated Onconaut Therapeutics, which holds an exclusive license to CHD1Li technology, enabling the company to leverage capital investment and partnerships with the pharmaceutical industry.

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