Research Roadmap: Quantum Catalyst for Alzheimer's Drug Discovery

Strategic Plan for Novel Research Contributions and Academic Publications

Version 1.0 | December 2025

🎯 Mission Statement

Establish quantum computing (specifically VQE) as a transformative tool for Alzheimer's drug discovery by achieving chemical accuracy (<1 kcal/mol) in Amyloid-beta (Aβ) inhibitor binding energy calculations—a precision level classical methods fundamentally cannot reach.

📊 Current Project Status

✅ Completed (Foundation Phase)

1. **Core VQE Implementation**
    - Mock VQE engine with convergence tracking
    - Support for multiple ansätze (EfficientSU2, TwoLocal)
    - Optimizer integration (SLSQP, COBYLA)
    - Chemical accuracy validation framework
2. **Quantum Chemistry Pipeline**
    - Hamiltonian construction (mock + PySCF integration)
    - Molecular builder for benchmark systems
    - Energy unit conversion utilities
    - Basis set support (STO-3G, 6-31G, 6-31G*)
3. **Binding Energy Calculator**
    - ΔG calculation with thermodynamic corrections
    - Solvation and entropy estimates
    - Kd/IC50 prediction from ΔG
    - Drug candidate ranking system
4. **Documentation & Open-Source**
    - Comprehensive README with scientific context
    - CONTRIBUTING.md for research collaborations
    - LITERATURE_SURVEY.md (50+ papers)
    - MIT License for open access

🔄 In Progress

1. **Proof-of-Concept Demo**
    - Alzheimer's-specific VQE demonstration script
    - H_2, LiH, H_2O validation benchmarks
    - Visualization generation (PES curves, convergence)

❌ Not Started (Research Priorities)

Listed below in roadmap sections...

🗺️ Research Roadmap (12-24 Month Timeline)

Phase 1: Method Validation (Months 1-3)

Goal: Establish VQE accuracy for small molecules

1.1 Benchmark Suite Development

Tasks:

- ☐ Create standardized molecular test set (H_2, LiH, H_2O, NH_3, CH_4)
- ☐ Implement PySCF real calculations (replace mock mode)
- ☐ Compare VQE vs exact FCI for 2-6 qubit systems
- ☐ Measure convergence: iterations, energy error, wall time

Deliverable: `benchmarks/small_molecules/` with reproducible results

Metrics:

- Energy error < 1 kcal/mol (0.0016 Ha) ✓ Chemical accuracy
- Convergence < 100 iterations for 4-6 qubit systems
- VQE within 5× cost of CCSD (classical comparison)

Publication Opportunity: Supporting data for all papers

1.2 Ansatz Comparison Study

Tasks:

- ☐ Implement UCCSD ansatz (gold standard, but deep circuits)
- ☐ Test ADAPT-VQE (problem-specific ansatz construction)
- ☐ Compare hardware-efficient vs chemically-inspired ansätze
- ☐ Measure expressibility vs trainability trade-off

Novel Contribution: First systematic ansatz study for drug-binding calculations

Publication: *Quantum* or *PRX Quantum* (quantum algorithm focus)

1.3 Optimizer Benchmarking

Tasks:

- ☐ Test gradient-free: COBYLA, SLSQP, Nelder-Mead, Powell
- ☐ Test gradient-based: SPSA, Adam, L-BFGS-B
- ☐ Implement parameter shift rule for quantum gradients
- ☐ Compare convergence speed, accuracy, robustness to noise

Key Question: Which optimizers work best for drug-sized molecules?

Deliverable: `src/optimizers/` module with performance analysis

Phase 2: Fragment-Based VQE (Months 4-6)

Goal: Scale VQE to Aβ fragment sizes (50-100 atoms)

2.1 Fragment Molecular Orbital (FMO) Integration

Tasks:

- ☐ Implement FMO fragmentation algorithm
- ☐ Define Aβ binding site fragments (residues 16-21, 31-35)
- ☐ VQE for fragment-fragment interaction energies
- ☐ Many-body expansion (2-body, 3-body corrections)

Novel Contribution: ⭐⭐⭐ **First FMO-VQE hybrid method**

Publication Target: *JCTC* (method paper)

- Title: "Fragment-Based Variational Quantum Eigensolver for Protein-Ligand Binding"
- Expected Impact: High (IF: 5.5, method development)

Technical Challenges:

- Fragment boundary definitions (avoid dangling bonds)
- Charge embedding scheme
- Convergence of many-body expansion

2.2 ONIOM-VQE Hybrid

Tasks:

- ☐ Implement 2-layer ONIOM: VQE (high) + DFT (low)
- ☐ Test on medium molecules (20-40 atoms): naphthalene, small peptides
- ☐ Validate ONIOM error vs full VQE
- ☐ Define optimal layer boundaries for Aβ systems

Application: Aβ binding pocket = VQE layer, rest = classical

Deliverable: `src/fragmentation/oniom_vqe.py`

2.3 Active Space Selection Automation

Tasks:

- [ ] Implement orbital localization (Boys, Pipek-Mezey)
- [ ] Automatic active orbital selection based on entanglement
- [ ] Benchmark: does active space match chemist's intuition?
- [ ] Reduce qubit requirements by 30-50%

Novel Contribution: Machine learning for active space selection (future)

Phase 3: Aβ Inhibitor Screening (Months 7-12)

Goal: Apply VQE to real Alzheimer's drug candidates

3.1 Aβ Structure Database

Tasks:

- [ ] Curate Aβ structures from PDB (5OQV, 2LMN, 2BEG, etc.)
- [ ] Prepare conformational ensemble (10-20 structures)
- [ ] Extract binding site fragments for VQE calculations
- [ ] Validate against experimental structures (cryo-EM, NMR)

Deliverable: `data/amyloid_beta/structures/` directory

Collaboration Need: Structural biologists, Alzheimer's researchers

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3.2 Known Inhibitor Library

Tasks:

- [ ] Literature survey: known Aβ aggregation inhibitors
  - Curcumin, EGCG, resveratrol (natural products)
  - KLVFF peptides, β-sheet breakers
  - Small molecule inhibitors from clinical trials
- [ ] Collect experimental binding data (IC50, Kd from ITC/SPR)
- [ ] Create molecular structures (SMILES, MOL2, PDB)
- [ ] Initial docking to Aβ fragments (define binding poses)

Target: 20-30 inhibitors with experimental validation data

Deliverable: `data/inhibitors/` with structures + experimental_data.csv

Publication: Dataset paper in *Scientific Data* or supplementary info

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3.3 VQE Binding Energy Calculations

Tasks:

- ☐ Calculate ΔG for all inhibitor-Aβ complexes
- ☐ Fragment-VQE for binding site (10-15 qubits)
- ☐ Compare VQE vs DFT (B3LYP) vs CCSD(T) when feasible
- ☐ Correlate computed ΔG with experimental IC50

Key Metric: $R^2 > 0.8$ for VQE ΔG vs experimental affinity

Novel Result: ⭐⭐⭐ **If R^2 > classical DFT, demonstrates quantum advantage**

Publication Target: *JCIM* (drug discovery journal)

- Title: "Quantum Computing for Alzheimer's Drug Discovery: VQE-Calculated Binding Energies"
- Expected Impact: High (IF: 5.6, pharmaceutical relevance)

3.4 Novel Inhibitor Prediction

Tasks:

- ☐ Use VQE to screen virtual compound libraries
- ☐ Identify candidates with ΔG < -300 kJ/mol (strong binders)
- ☐ Propose 3-5 novel Aβ inhibitors for synthesis
- ☐ (Stretch) Wet-lab validation via collaborators

Highest Impact Scenario: Predict inhibitor, experimentally validate, show quantum guided discovery

Publication Target: *Nature Communications* or *Science Advances*

- Title: "Quantum-Guided Discovery of Alzheimer's Therapeutics"
- Expected Impact: ⭐⭐⭐ Breakthrough (IF: 16+)

Phase 4: Quantum Hardware Deployment (Months 13-18)

Goal: Move from simulation to real quantum computers

4.1 IBM Quantum Access

Tasks:

- ☐ Apply for IBM Quantum Hub access (academic program)
- ☐ Transpile circuits for IBM hardware (127-qubit systems)
- ☐ Deploy VQE on ibmq_guadalupe or ibmq_montreal
- ☐ Compare simulator vs hardware accuracy

Required: Institutional collaboration or grant funding

4.2 Error Mitigation Implementation

Tasks:

- ☐ Implement Zero-Noise Extrapolation (ZNE)
- ☐ Clifford Data Regression (CDR)
- ☐ Measurement error mitigation
- ☐ Benchmark error mitigation impact on chemical accuracy

Novel Contribution: Error mitigation optimized for binding energies (not just energies)

Publication: *PRX Quantum* or *Quantum Science and Technology*

4.3 Noise Characterization for Chemistry

Tasks:

- ☐ Measure T1, T2 times for molecular Hamiltonians
- ☐ Identify noise-sensitive vs noise-resilient molecules
- ☐ Develop noise-aware ansatz selection strategy

Application: Guide which molecules to run on hardware vs simulator

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Phase 5: Advanced Features (Months 19-24)

Goal: Push boundaries of quantum drug discovery

4.1 Thermodynamic Rigor

Tasks:

- ☐ Implement Poisson-Boltzmann solvation (replace empirical)
- ☐ Vibrational entropy via quantum harmonic oscillator
- ☐ Conformational entropy via MD sampling + VQE ensembles
- ☐ Temperature-dependent ΔG calculations

Goal: Achieve <0.5 kcal/mol error (beyond chemical accuracy)

4.2 Machine Learning Integration

Tasks:

- ☐ Surrogate models: ML predicts VQE results (reduce quantum calls)
- ☐ Transfer learning: pre-train on small molecules, fine-tune on Aβ
- ☐ Active learning: intelligently select next molecules for VQE
- ☐ Bayesian optimization for ansatz parameters

Novel Contribution: Quantum-classical-ML hybrid workflow

Publication: *JCIM* or *Machine Learning: Science and Technology*

4.3 Multi-Target Extension

Tasks:

- ☐ Extend beyond Aβ to tau protein (another AD target)
- ☐ Apply to other neurodegenerative diseases (Parkinson's α-synuclein)
- ☐ Generalize platform for any protein-ligand system

Long-Term Vision: Universal quantum drug discovery platform

📈 Publication Strategy

Timeline Overview

Month	Milestone	Publication Target
3	Benchmark suite complete	Preprint (arXiv)
6	FMO-VQE method validated	*JCTC* submission
9	Aβ inhibitor dataset ready	*Scientific Data*
12	VQE screening results	*JCIM* submission
15	Hardware deployment	Conference (ACS, APS)
18	Error mitigation study	*Quantum* submission
24	Novel inhibitor prediction	*Nat. Commun.* (if validated)

Target Journals (Ranked by Impact)

Tier 1 (Breakthrough Results)

- *Nature*, *Science* (IF: 40+) — Only if experimental validation + clear quantum advantage
- *Nature Communications* (IF: 16.6) — Novel inhibitor prediction
- *Science Advances* (IF: 14.1) — Major methodological advance

Tier 2 (Strong Method/Application Papers)

- *JACS* (IF: 15.0) — Chemistry community, VQE for drug discovery
- *PNAS* (IF: 11.2) — Interdisciplinary (quantum + biology)
- *Physical Review X* (IF: 12.9) — Quantum computing focus
- *Quantum* (IF: 6.4) — Open access, quantum algorithms

Tier 3 (Solid Method Development)

- *J. Chem. Theory Comput.* (IF: 5.5) — Computational chemistry methods
- *J. Chem. Inf. Model.* (IF: 5.6) — Drug discovery applications
- *J. Phys. Chem. Letters* (IF: 5.7) — Rapid communication

- *PRX Quantum* (IF: 9.5) — Quantum computing methods

Tier 4 (Educational/Dataset Papers)

- *Scientific Data* (IF: 6.8) — Aβ inhibitor database
- *SoftwareX* (IF: 2.5) — Open-source software description
- *J. Open Source Software* — Software paper

🤝 Collaboration Opportunities

Required Collaborations

1. **Experimental Validation** (Critical for high-impact publications)
    - Partners: University biochemistry labs, pharma companies
    - Techniques: ITC, SPR, BLI for binding measurements
    - Timeline: 6-12 months for synthesis + assays
2. **Quantum Hardware Access**
    - IBM Quantum Hub (academic program)
    - AWS Braket, Azure Quantum, IonQ cloud access
    - Google Quantum AI (collaboration opportunity)
3. **Structural Biology**
    - High-resolution Aβ structures (cryo-EM, X-ray)
    - Molecular dynamics simulations (conformational ensembles)
4. **Alzheimer's Domain Experts**
    - Clinical relevance validation
    - Inhibitor design guidance
    - Interpretation of biological results

Desirable Collaborations

1. **Quantum Algorithm Developers**
    - ADAPT-VQE experts (Harper Grimsley, Nicholas Mayhall)
    - Error mitigation specialists
    - Quantum hardware engineers
2. **Computational Chemistry Groups**
    - FMO method developers (Dmitri Fedorov)
    - Free energy calculation experts
    - Solvation model developers
3. **Machine Learning Researchers**

- Quantum machine learning applications
- Surrogate modeling for expensive calculations
- Active learning for drug discovery

💰 Funding Opportunities

Grant Targets

US Funding Agencies:

1. **NSF Quantum Leap Challenge Institutes** ($25M, 5 years)
   - Focus: Quantum computing applications
   - Proposal: "Quantum Computing for Drug Discovery"
2. **NIH R01** ($250K/year, 5 years)
   - Focus: Alzheimer's disease research
   - Proposal: "Quantum Methods for Aβ Inhibitor Discovery"
3. **DOE Quantum Information Science** ($1M, 3 years)
   - Focus: Quantum algorithms for chemistry
   - Proposal: "VQE for Molecular Binding Energies"
4. **DARPA Quantum Benchmarking** ($500K, 2 years)
   - Focus: Demonstrating quantum utility
   - Proposal: "Quantum Advantage in Drug Discovery"

Industry Partnerships:

- IBM Quantum Network (academic membership)
- Google Quantum Research Awards
- Microsoft Quantum computing grants
- Pharmaceutical companies (Roche, Pfizer, Novartis quantum initiatives)

Estimated Budget Needs:

- Personnel: 2 postdocs + 3 PhD students = $400K/year
- Quantum hardware access: $50K/year
- Experimental validation: $100K/year
- Travel/conferences: $30K/year
- **Total**: ~$600K/year for 3-5 years

🎓 Educational & Outreach

Tutorial Development

- ☐ Jupyter notebooks for each major feature
- ☐ Video tutorials (YouTube series)
- ☐ Workshop materials for conferences
- ☐ Online course module (Coursera/edX)

Conference Presentations

- **ACS National Meeting** (American Chemical Society)
- **APS March Meeting** (American Physical Society)
- **QIP** (Quantum Information Processing)
- **Q2B** (Quantum for Business)
- **Alzheimer's Association International Conference**

Community Building

- ☐ Monthly online seminars (quantum drug discovery series)
- ☐ Hackathons (quantum chemistry challenges)
- ☐ Summer schools (quantum computing for chemists)

📊 Success Metrics

Short-Term (6 months)

- ✅ 3+ papers submitted/published
- ✅ 10+ GitHub contributors
- ✅ 500+ repository stars
- ✅ 1 conference presentation

Medium-Term (12 months)

- ✅ VQE achieves <1 kcal/mol error on Aβ inhibitors
- ✅ 5+ papers published
- ✅ Hardware deployment on IBM Quantum
- ✅ 1 grant proposal submitted

Long-Term (24 months)

- ✅ Experimental validation of VQE-predicted inhibitor
- ✅ Demonstrate quantum advantage (VQE > classical DFT)
- ✅ High-impact publication (*Nat. Commun.* or higher)
- ✅ Established research community (100+ users)
- ✅ 1 grant funded

🚧 Risk Assessment & Mitigation

Technical Risks

Risk 1: VQE fails to achieve chemical accuracy on real hardware

- *Mitigation*: Focus on error mitigation, use simulator for method development

Risk 2: Aβ fragments too large for current quantum devices

- *Mitigation*: Aggressive fragmentation, active space reduction, await hardware improvements

Risk 3: No correlation between VQE ΔG and experimental data

- *Mitigation*: Rigorous thermodynamic corrections, ensemble averaging, validate on small molecules first

Scientific Risks

Risk 4: Classical methods improve faster than quantum (DFT functional development)

- *Mitigation*: Emphasize quantum advantage is fundamental (not incremental), target systems where DFT fails

Risk 5: Amyloid hypothesis loses favor in AD research community

- *Mitigation*: Generalize platform to other AD targets (tau), other diseases

Publication Risks

Risk 6: Reviewers demand expensive experimental validation

- *Mitigation*: Establish collaborations early, include preliminary experiments, frame as computational methods paper

Risk 7: "Quantum hype" bias from reviewers

- *Mitigation*: Be rigorous, transparent about limitations, avoid overclaiming, compare to realistic classical baselines

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📞 Contact & Leadership

Project Lead: [Your Name/Institution]
Research Area: Quantum Computing + Alzheimer's Drug Discovery
Collaboration Inquiries: [Email]

Advisory Board Needed:

- Quantum computing expert
- Computational chemist
- Alzheimer's disease researcher
- Pharmaceutical industry representative

This roadmap is a living document. Updates quarterly based on research progress and community feedback.

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Next Review: March 2026