Alix VENTURES

Market Deep Dive Report

Quantum Aided Drug Development

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Contents

1. Summary

The application of quantum technologies towards drug discovery can be classified into two focus areas: quantum mechanics and quantum computing. Technologies utilizing quantum mechanics refer to the use of improved physical models to describe drug target interactions, resulting in accuracy improvements over traditional molecular mechanics models. Quantum computing is a new paradigm of computing that offers improved speed and efficiency for particular computational pain points including simulation of quantum mechanics and simulation of large molecules and biologics.

Quantum aided drug development strategies are immature, and as a result, companies have taken a hybrid approach, combining quantum inspired algorithms with classical computing architectures. These algorithms currently have limited use cases, and the majority of which have provided improvements over existing computational drug design strategies primarily the *de novo* design of protein therapeutics. The hardware and infrastructure allowing the scalable utilization of quantum computing is still > 3 years away and currently has problems in both accuracy and compute power. Successful teams have utilized a hybrid approach, utilizing 'quantum inspired' algorithms and concepts on classical computing machinery that can be readily translated to quantum hardware once available.

Overall, the quantum aided drug development market is young and provides significant potential to add value to drug discovery pipelines. A large majority of startups are at seed stages or below, with only one at series B. The investment space is uncharted territory and thus, investments into this space need to be made only on strong teams with the ability to pivot or reapply their technology to an adjacent need. Teams that have demonstrated research potential and expertise are required in order to make any progress in the field, and must be led by skilled operators that can prove the utility and integrability of their quantum technology. Menten AI, ProteinQure, Rahko AI, and PolarisQB are promising startups to watch in this space.

2. Market Overview

The quantum computing market is small, yet growing rapidly. It was valued at $93 million USD in 2019, and is projected to grow 24.9% YoY through 2024 to $283 million USD. The global drug discovery market is currently worth $10.7 billion and is expected to grow at a CAGR of 12.1% to reach $19.1 billion in 2025. Fast paced growth in quantum computing will be driven by R&D efforts at major labs to increase computing capacity and reduce error rates.

Meanwhile, drug discovery has become a central need for large biopharma companies due to the increasing need to control drug discovery & development costs and the impending patent expiry of blockbuster drugs. Computer aided drug design strategies especially those that are computationally intense such as those integrating quantum mechanics have become further enabled by the rising adoption of cloud-based applications & services.

2.1 Major Stakeholders

Major stakeholders in this space include small quantum technology companies that invent new technologies and license or provide services, large biopharma companies that license such technology and partner with smaller companies, and academics that are primarily responsible for propelling quantum mechanics theory forward. Quantum chemistry research that provides new innovation is largely led by academic institutions. As a result, new companies are often formed from the same researchers and teams that were formed in academic settings. Quantum computing research on the other hand is largely led by tech giants such as IBM, Google, and Microsoft owing to the large upfront investment required to build a quantum computer.

The industry leader in the startup space is XtalPi, a B stage company that has raised $67.7 million from investors including Sequoia China, Tencent, SIG China, Google, Morningside VC, and ZhenFund. The company was founded in 2014 by quantum physicists from MIT, and their CEO is Jian Ma. In 2018, XtalPi engaged in a research partnership with Pfizer to develop their Intelligent Digital Drug Discovery and Development (ID4) platform. With tightly interwoven quantum physics, artificial intelligence, and high-performance cloud computing algorithms, XtalPi's ID4 platform provides more accurate predictions on the physiochemical and pharmaceutical properties of small-molecule candidates for drug design.

Pharmaceutical giants are in wait and see mode in regards to research collaborations with quantum computing startups. AstraZeneca, Biogen, Merck, GSK, and Pfizer (above) have engaged in exploratory stage research collaborations with emerging startups in recent years, but all have just gotten started (past 3 years). However, as large biopharma companies have increasingly searched for new ways to support R&D platforms with declining productivity, it is reasonable to expect more frequent future partnerships once the value proposition has been more fully demonstrated.

2.2 Business Model

Unlike data driven computational platforms utilized for drug screening such as deep learning, quantum aided drug development platforms do not need large amounts of data to demonstrate efficacy. Since calculations are physics based and only requires confirmation of structure to validate accuracy, there is not a need for the in-vitro, in-vivo, or clinical data that large biopharmas have. Therefore, startups do not need to partner with large biopharmas to

make technical progress. Rather, their relationships can focus more on needs discovery and how to design services to best integrate into existing discovery pipelines.

There are several commercialization strategies that quantum technology startups have employed. Due to the difficulty of integrating quantum based solutions into existing pipelines (because of rapid changes and improvements in technology), common approaches have been shared research or service based contracts that startups can execute internally. Startups with more mature technology and self-contained software packages also have licensed technology or utilized a software-as-a-service subscription model.

2.3 Pitchbook Market Statistics

- Quick stats (All time)
  - No. Companies: 22
  - No. Deals: 63
  - No. Investors: 112
  - Largest deal: $50 M (Cambridge Quantum Computing)
- Deal count (TTM): 14
- Funding per quarter
  - Last 3 years: $12.5 million
  - Annual Total: $24.5 million
- Most active VCs by deal count: AI Seed Fund, Prelude Ventures, WorldQuant Ventures, Creative Destruction, Eniac Ventures, Pillar VC

Stage	**Average Round Size**	**Average Post Valuation**
Seed	$2.76 M	$9.86 M
A	$10.17 M	$62.34 M

3. Technology Overview

3.1 Quantum Computing

Quantum computing was first described in the early 1980s, but only recently with the attention of tech giants including Google and IBM, has it gained momentum as a potentially transformative technology. It relies upon quantum-mechanical phenomena such as superposition and entanglement to perform computation, with units of information transmitted in quantum bits (qubits). Unlike traditional computing, qubits can be in a 0 state, a 1 state, or in

between the two states, as a superposition of the 0 and 1 states. This is a probabilistic approach that can much better represent atoms and molecules in comparison to existing 'ball and stick' models. Quantum computing has an advantage over traditional computing especially when many factors or elements are considered due to efficiency in combinatorial optimization. Massive parallelism that can be achieved by modelling many solutions simultaneously: indeed, the number of solutions that can be modelled simultaneously doubles with each additional quantum bit, or qubit, added to the system, allowing exponential scaling far beyond anything achievable with classical computers for certain classes of search problems.

Quantum Bits (qubits)	Equivelant Classical Bits
3	8
10	1024
20	1,048,576
...	...
300	2.037035976...E90

The Quantum Advantage

The first low scale prototypes of quantum computing systems are available. However, it is still an immature technology with minimal usage in the short term due to high costs, high error rates, and low compute power. Limited molecular simulations have been done on simple structures such as a chain of hydrogen atoms by Google in late 2019, or simple 3 atom molecules like beryllium hydride (BH_2) by IBM in 2017. As a comparison, the largest reported molecule simulated using classical computing was pentacene, 36 atoms total. The size of most small molecule compounds are between 50 and 80 atoms, with biologics and protein therapeutics orders of magnitude larger than that. Thus, quantum computing solutions for drug design are still years away.

The state-of-the-art today includes quantum computers with 53 and 72 qubits in size available from IBM and Google respectively, with an expected doubling in the number of qubits every one to two years. Scientists are estimating that the penicillin molecule that would have required 10^{86} classical bits could be simulated with a quantum computer that has 286 qubits. If the current pace of development holds, quantum computers of that size should be available later this decade.

Quantum Computing Vendors

Rigetti	Rigetti Computing is a Berkeley, California-based developer of quantum integrated circuits used for quantum computers. The company also develops a cloud platform called Forest that enables programmers to write quantum algorithms.
IBM Q	IBM has developed Qiskit, an open-source quantum programming framework which allows access to IBM Q simulators and quantum devices over the cloud. Basic quantum computing resources are available through the cloud, with advanced use given to Q network clients.
D-Wave	D-Wave provides access to cloud quantum computing resources and also ships their own quantum annealing system to commercial users. Quantum annealers are able to contain many more qubits than universal quantum computers, but lacks some functionality important for factoring problems.
Xanadu	Xanadu is a photonic quantum computing and advanced artificial intelligence company based in Toronto that designs and integrates quantum silicon photonic chips into existing hardware to create full-stack quantum computing.

3.2 Quantum Mechanics

The use of quantum mechanics to more accurately predict molecular interactions is not new, in fact, it was born in 1926. Quantum chemistry is required in order to derive a 3D representation of molecules based on electrostatic, steric, and hydrophobic interaction fields from quantum mechanics calculations. Incorporating such considerations provide much higher accuracy compared to alternative approaches, such as viewing molecules according to a 'balls and sticks' model. However, efficiently incorporating such factors has required far greater complexity and computational power, which was not available until very recently with the rise of cloud based computing. Screening drug target interactions (DTIs) for thousands of molecules makes efficiency and speed very important. Even today, the largest molecule we can simulate via full configuration interaction is pentacene, which is 36 atoms and takes more than 9 days.

The important point to understand is that full and exact analysis of molecular mechanics is not feasible for a pharmaceutical screening platform. However, quantum chemistry has provided insight into which features to prioritize during screening, making the accuracy versus computation tradeoff more favorable. Startups in drug discovery utilizing quantum chemistry are designing algorithms that improve upon accuracy, but still likely utilizing more computational effort. However, computing resources are now a ubiquitous commodity and the industry is looking for new methodologies to find a new wave of New Molecular Entities. Hence, there is definitively an increase in the applicability of this fine grain theory in drug discovery.

4. Historical Context, Key Trends, & Future Development

4.1 Historical Context

The biopharma industry already applies quantum mechanics for energy calculations and structural optimization, especially in molecular docking and quantitative structure-activity relationship (QSAR) analyses. Quantum mechanics–enabled synthetic chemistry gives researchers the tools to preclude potentially inactive compounds. But the usefulness of virtual tools depends on their ability to accurately predict hits, especially for complex molecules. Classical computing techniques to 'brute force' the calculations by simulating the atomic behavior of molecules is slow and inefficient. The industry has been trending towards the use of AI to learn how to most efficiently convert compute power into accurate insights, but these are still in development and have a ceiling to how accurate and fast they can be.

Quantum computing has the potential to transform virtual screening through physically precise modeling of drug-target interactions and efficient screening of massive virtual libraries. The qubit based computing architecture most closely emulates the probabilistic quantum mechanics models that are used to describe molecules, and the strengths of quantum computing including multiparameter optimization, linear algebra, and search make the technology an ideal engine for several use cases. Summarized below are common tasks in computational drug design and bolded are applications where quantum computing will begin to have a major impact.

Structure Based	Ligand Based	Other Algorithms
Binding site identification **Pharmacophore modelling** **De novo protein modelling** **Docking** / virtual screening Molecular dynamics / FEP	Ligand similarity search / scaffold hopping **Conformational search** Ligand-based virtual screening Library design QSAR	ADME/Tox prediction pKa prediction Membrane permeability Decision-making algorithms **Statistical modelling** Electronic structure calcs.

Protein-protein docking		Sequence alignment / homology modelling Crystal structure prediction

4.2 Present Status

Currently teams are waiting on hardware. The response has been to develop algorithms that work on both classical and quantum computing architectures, so that when error free quantum hardware arrives, the algorithms will be the same but accuracy and speed will improve. Microsoft, which has dubbed these new techniques "quantum-inspired," has just released a quantum-inspired chemistry library with 1QBit to run on Azure Quantum. Quantum-inspired approaches, often in combination with machine learning, are used to achieve quicker and more-accurate drug discovery.

Two algorithms that have been published that utilize this approach include the Variational Quantum Eigensolver (VQE) and also the Quantum Approximate Optimization Algorithm (QAOA). These algorithms have been designed to take advantage of noisy intermediate-scale quantum (NISQ) computers and can be used to solve a variety of drug optimization problems. NISQ devices are a step up above current quantum computing machines in terms of qubits (~50-300 qubits vs 72 currently), but have high error rates. NISQ devices increasingly will be able to perform useful, discrete functions, but will also be plagued by high error rates that limit their functionality. In three to five years, error mitigation techniques, along with better hardware and algorithms, should begin to support useful applications such as *de novo* molecular design to fit certain parameters.

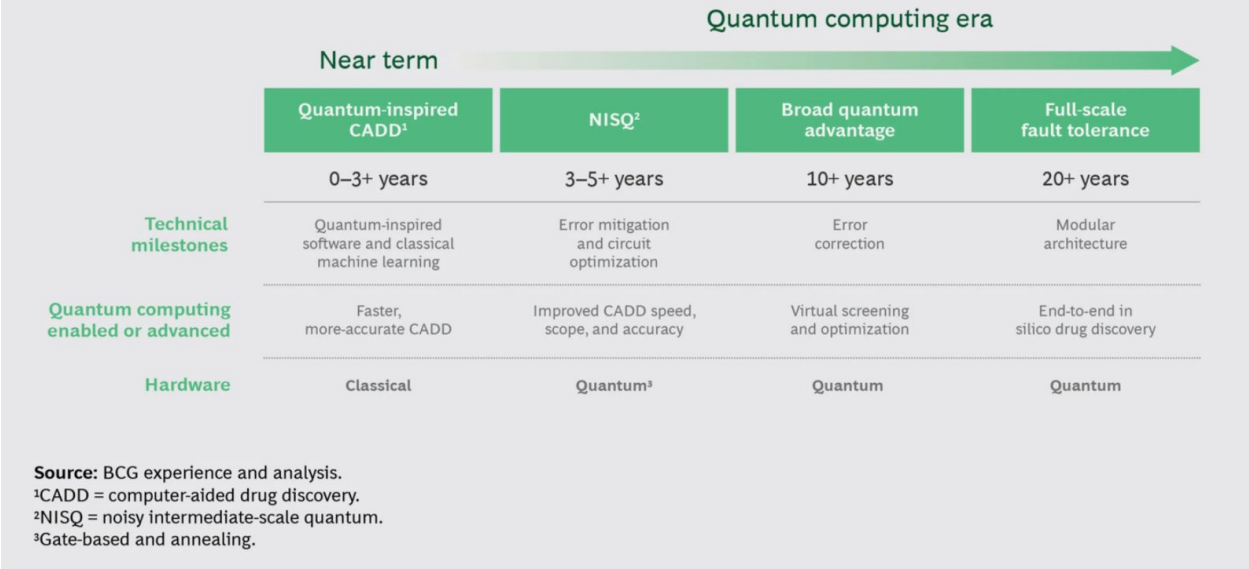
Another promising approach has been quantum machine learning (QML). QML is most valuable for applications with sparse data and complicated probability distributions. Quantum versions of machine learning can learn from data faster and with higher precision, producing more accurate predictions, given that data can be formatted into quantum format and accurately interpreted. These are current pain points. However, they hold promise especially for drug discovery programs for rare indications and binding targets because of the lack of historical data.

Finally, there has also been promising work done with digital/quantum annealers. Annealers solve optimization problems, which are useful in *de novo* drug design because of the many parameters that need to be satisfied for any given compound. Quantum-inspired Digital Annealers (DA) solve this problem using classical computing in a smarter fashion than brute-force enumeration. The DA uses a heuristic technique for solving hard optimization

problems by mimicking quantum mechanical effects such as quantum tunneling, a promising approach with a potential to harness quantum mechanical concepts to solve hard optimization problems. The DA can thus be used for single or multi-objective optimization problems, allowing optimization over multiple dimensions and thus an efficient global search for promising solutions.

This is in contrast to quantum annealing, where the system looks for the best solution in a massively parallel way with all the states taken into account simultaneously. Quantum annealing is a computing technique that is not a 'complete quantum machine' in that it is not circuit based and cannot solve some factorization problems. However, quantum annealers can utilize up to 2000 qubits now, and thus have been used to success in optimization problems for drug design.

4.3 Future Development



Predictions from BCG

In the short term, drug development will primarily be aided by improvements in quantum chemistry models and limited hybrid computing applications. The results will be incremental improvements in accuracy and speed of screening programs and potentially improved speed of *de novo* drug design algorithms due to better optimization solvers. Proof of concepts using low level quantum computers will be published to demonstrate the potential of use especially in protein optimization and *de novo* drug design. However, practical utility will be limited.

Eventually, as quantum computers become larger and less error prone, they will become part of the computing ecosystem, but will not replace classical computing methods. Quantum

computing infrastructure will be more cost prohibitive and does not have a theoretical advantage over classical computing architectures in all aspects. For example, there can be difficulties in preparing data in a quantum state (the data we are typically familiar with does not work on a quantum computer and must be reformatted), and also difficulties in interpretation of results from a quantum machine. Thus, from a usability and integration perspective, quantum computing will likely be isolated to a few use cases where it can vastly outperform classical computers such as large scale optimization in *de novo* drug design.

5. Opportunities

5.1 Startups to Watch

Qulab - Qulab was founded in 2017 and has since raised $3 million from investors including Cota Capital, Civilization Ventures, and Plug and Play. Qulab is a developer of advanced computational methods intended to automate molecular drug design. The company's methods redesign research and development by integrating advanced computing technology and leverages the power of classical, molecular, and quantum engineering for developing therapeutics, enabling researchers to enhance drug development through artificial intelligence and hardware acceleration.

Menten AI - Menten was founded in 2018 and since has raised 150k by becoming part of YC Class of 2020. Menten AI was the first company that created a peptide using a quantum computer. The start-up is interested in applying their technology to the development of novel peptide therapeutics, small-proteins, antibodies, and active site optimization for enzymes. They are a team of PhDs led by CEO Hans Melo.

ProteinQure - ProteinQure is a Seed stage company founded in 2017 that has raised $4.6 million from investors including Inovia Capital, 8VC, and Felicis Ventures. Their CEO is Lucus Siow (lucas@proteinqure.com). The Toronto-based startup is combining quantum computing, reinforcement learning, and atomistic simulations to design novel protein drugs. Using this mix of technologies they model essential processes, such as protein folding, and the underlying physics of interactions between biomolecules. Using their proprietary algorithms and external supercomputing resources, ProteinQure can design small peptide-based therapeutics, and explore protein structures without known crystal structures.

Rahko - Rahko AI is a seed stage company based in London and founded in 2018 that has raised $1.45 million in venture funding. Rahko is a quantum machine learning company that announced a 3 year research collaboration with Merck in May 2020 and is an early partner of Amazon Quantum Solutions Lab.

Silicon Therapeutics - Silicon is a seed stage company founded in 2016 with $6.2 million in total funding and led by CEO Lanny Sun. The company utilizes physics-based molecular simulations, quantum physics, statistical thermodynamics, and molecular dynamics for the improvement of conventional drug discovery.

ApexQubit - ApexQubit is a seed stage company out of Berkeley backed by Nvidia, Overkill Ventures, and HealthInc. It was founded in 2018 and has raised $370k. Their technology uses a combination of reinforcement learning, generative models and quantum computing and allows them to search for undiscovered small molecules and peptides with the final goal to unlock personalized medicine without side-effects. ApexQubit offers tools for the generation of promising small-size ligands and the estimation of their affinity towards target proteins.

Kuano AI - Kuano AI is a seed stage company founded in 2020 with $191k from the AI Seed Fund in the U.K. The company's Nautilus platform combines quantum simulation and machine learning approaches to create enzyme inhibitors.

ChemAlive - Founded in 2014, Switzerland-based company ChemAlive is focused on applying a mix of technologies, including quantum mechanics calculations and machine learning, for accurate prediction of chemical reactions and molecular properties, as well as modeling processes for drug discovery research. The company develops a range of cloud-based software products, available via APIs, including InteraQt (Structure-based quantum dynamics and quantum mechanics/molecular mechanics docking tool), ConstruQt (High throughput quantum chemistry for designing chemical libraries), and other packages for chemical reaction modeling and spectroscopy predictions.

Cloud Pharmaceuticals - Founded in 2014, Cloud Pharmaceuticals is a North Carolina based company that has raised $1.5 million. The company is applying a set of computational technologies, including cheminformatics, machine learning, and quantum mechanics, to accelerate and improve the drug discovery process. Their research platform Quantum Molecular Design (QMD) generates drug-like hits and leads for a wide range of biological targets, including previously "undruggable" ones. It uses an artificial intelligence engine and quantum mechanics to accurately predict ligand binding affinities in solvents and in protein environments. In 2018 it signed a research deal with GSK to discover novel small molecule leads.

Pharmacelera - Pharmacelera is a seed stage company founded in 2015 with $2.23 million in funding. The company is applying quantum theory to boost drug design via their two primary software packages: PharmScreen and PharmQSAR. PharmScreen is a virtual screening software package to find candidate molecules with larger chemical diversity from compound libraries. PharmQSAR is a 3D Quantitative Structure-Activity Relationship (QSAR) software package that builds predictive models based on data from experimental assays. The products are offered on a

licensing basis: a cloud-based Software-as-a-Service monthly subscription or a yearly license for companies willing to execute the technology on their own IT infrastructure.

QSimulate - QSimulate is a privately held research company that has redesigned how quantum mechanics calculations are performed so that they can be run in the cloud in a cost and time efficient manner. They are supported by partnerships with the Amazon Quantum Solutions Lab, the Google AI Quantum Lab, and in April 2020 announced a partnership with Amgen to integrate large-scale, accurate, quantum mechanics with drug discovery.

Polaris Quantum Biotech - PolarisQB was founded in 2020 as a spinout from Cloud Pharmaceutics with 485k in Seed funding. They have developed a drug discovery platform combining quantum-inspired technology, machine learning, hybrid quantum mechanics and molecular mechanics simulations (QM/MM). PolarisQB has partnered with Fujitsu to scan and identify de novo molecules starting with dengue fever. Fujitsu's quantum-inspired Digital Annealer has enabled the platform to search an exponentially larger molecular space (over 1 billion molecules) compared to current market techniques. The list of lead molecules identified by the Digital Annealer is then analyzed by Polarisqb's proprietary machine-learning algorithm and QM/MM for rapid assessment of the molecule's potential to be a viable drug. The resulting high-quality lead molecules are then synthesized, tested, and finally licensed to pharmaceutical partners for further development.

5.2 Industry challenges

The two largest challenges in the quantum drug discovery space are talent and infrastructure. Quantum computing is currently an exceedingly niche field that requires deep specialization in physics to understand hardware deployment and machine learning to develop effective algorithms and applications.

Current quantum computing offerings are early stage and expensive. The largest quantum computers are error prone and have not demonstrated supremacy over classical computing systems. Better suited to solve almost all drug discovery problems currently are domain expertise or the application of AI techniques on classical computing architectures. While current complete quantum computers have only reached a maximum size of 72 qubits, computers in the range of 300 qubits or more are necessary to outperform classical computers. Furthermore, the more qubits a computer has, the further the risk of calculation errors. Thus, there must be significant strides to improve both size and accuracy of quantum computers.

Another consequence of being an emerging technology is that talent is in very short supply. Mastery of quantum technology requires Ph.D. degrees in top academic institutions, in a quantum development environment. Quantum software developers have a very different skill set than 'normal' software engineers because quantum computing is at a far more basic stage of development which requires physical knowledge of the hardware and software interface.

6. Conclusion

Overall, quantum aided drug development is an immature field that requires intense domain expertise in the founding team as well as technology that does not rely on quantum computing hardware upgrades to provide value. The funding environment is favorable, and the startup cycle is young, with most startups at seed stages with less than $3 million in total funding. Technology that utilizes quantum chemistry to improve drug binding models can provide marked improvements over classical molecular mechanics models and have value as part of a screening process. However, these approaches seem better suited as part of an arsenal of tools led by a machine learning driven screening platform rather than as a standalone solution. Quantum computing approaches are years away and will take time to mature. Hybrid approaches applying 'quantum inspired' algorithms towards protein design and other approaches with heavy computational load are promising but still without an example of a scaled proof of concept.

6.1 Vertical Strengths

- Lack of competitors and ample area to avoid competitive overlap
- Favorable acquisition and collaboration environment
- No need to acquire large datasets that are not freely available
- Gap between industry and academia research is small, so R&D will be supported by academic researchers
- Significant amount of funding resources from both the private and public sector has been dedicated towards the growth of quantum computing and applications.

6.2 Vertical Weaknesses

- The development of hardware is limited to tech giants and is currently slow and early stage. Startups need to develop technology that does not depend on advances in hardware capabilities. The size of quantum computers needed to be useful is still > 3 years away
- The field is strongly specialized, and talent will be difficult to recruit due to competition and short supply of quantum software developers (needs heavy specialization in physics and machine learning)
- Total addressable market is not as promising because quantum computing has supremacy only in a limited set of applications.

6.3 Opportunity Cost of Capital

The quantum aided drug development space is severely hindered by immature technology. The entire investment space is uncharted territory and thus, investments into this space need to be made only on strong teams with the ability to pivot or reapply their technology to an adjacent need. Still, the next decade will see drastic improvements in quantum computing speed and accuracy. Startups should validate proof of concepts and ensure that they are on the frontier of high performance computing in order to take advantage of future advancements. Overall, this report finds quantum aided drug development a risky area for investment given challenges in hardware, lack of proof of concepts, and shortage of available talent. Exceptions should be made for strong and proven teams that can consistently produce high quality research on a specific high value use case.

6.4 Investment Theses

This report finds AI drug discovery as a small vertical but with significant opportunity for startups to make technological advances. Specifically, companies that are able to address the following needs will have ample ground to build category defining leadership.

1. **Algorithms for Protein Therapeutics**: Protein therapeutics including peptides, antibodies, and enzymes are the next frontier in terms of HTS and computational based drug discovery. Quantum computing algorithms utilizing quantum annealers have already shown some proof of concept for small molecule structural chemistry problems. Teams that are able to develop technology for simulating protein therapeutics will be category leaders and outpace conventional computing approaches for protein design once quantum hardware arrives.

2. **Structural Chemistry Simulation**: Quantum computing algorithms better approximate the quantum mechanical forces involved in small molecule drug target interactions. In the near term, quantum algorithms will aid in screening, feature creation (to expand ML feature sets), and docking calculations. Structural chemistry characterization is the most attainable value add that quantum offers in the near term.

7. Further Reading

1. Pharmacelera CEO Interview
2. BCG Case Report
3. Juniper Mini Review
4. Quantum Computing in NISQ Era and Beyond
5. Designing Peptides on a Quantum Computer (Menten AI)
6. Quantum Machine Learning