**Category**

Best Startup

**Product/Solution Name**

N/A

**Date of Approval**

N/A

**Indications**

N/A

**Therapeutic Categories**

Oncology
Inflammatory diseases

**Background information and need for solution/product**

Biologics, primarily monoclonal antibodies, currently represent many of the top selling drugs due to their transformative treatment to some of our most intractable diseases; improving and lengthening the lives of patients suffering from cancer, autoimmune and other diseases. However, the long development lead times for these therapies means that these transformative therapies were in fact developed in the 80s and 90s using technology from that period.

As these therapies progressed through the clinic, there has been an increasing need to develop novel approaches to antibody therapeutic design that overcame the limitations of the traditional monoclonal antibodies. These next-generation antibodies are some of the most powerful and successful medicines for many intractable diseases promising greater safety and efficacy for patients with rational molecular design. These designs smartly exploit tumor microenvironments, harness cells at disease sites, and resist the evolution of viral variants. However, with these next generation formats (e.g., VHH, CAR-T, scFv, BiTE, etc.), some which have already received regulatory clearance, came new challenges; designing these human engineered antibodies proved to be much more challenging than the traditional monoclonal antibodies and created a demand to find new and more efficient methods to create them.

Traditionally, the development of therapeutic antibodies starts with antibody libraries that are synthetically constructed or obtained from immunized animals. From these libraries, candidate molecules with affinity to the desired target can be selected. However, the initial antibodies found by these display technologies or immunization are rarely clinic-ready and require significant optimization to make a high-quality therapeutic. Currently, this is performed in sequential expert-guided steps to improve primarily one or, at most, a few of the relevant properties. This stepwise approach is not only costly and time-consuming, but also prone to failure because the relevant properties are not independent, making sequential optimization difficult. In addition, these approaches typically only explore a limited number of the antibody molecule during each optimization step, based on data from other engineering campaigns and the literature; thereby likely missing novel and superior antibody

variants.

BigHat's novel AI-guided experimental platform offers an innovative approach using ML techniques ideally suited for multi-parameter optimizations to chart an efficient experimental path to find higher quality variants of the initial antibody. Unlike other platforms that have simply tacked on bioinformatics to their programs, BigHat's platform, Milliner was designed and built from the ground up with a 'fit-for-purpose' philosophy and is based on using machine learning coupled with iterative design-build-test cycles of sequences in an automated wet lab.

At BigHat, every therapeutic program starts with a design blueprint and antibodies generated in our discovery engine or supplied by a partner. These initial molecules are then iteratively transformed into best-in-class next-generation therapies on BigHat's platform through sequential design-build-test cycles. Our machine learning models design hundreds of variants that we build and test in our lab using the latest synthetic biology technologies in each cycle. We measure biophysical properties and impact on disease activity for every variant using cell-based or other functional assays that replicate in vivo disease processes. We then update our models with this new data, iteratively accelerating our predictions. Over multiple cycles, our models quickly identify antibodies that match our design blueprint. By repeating such rapid design-build-test cycles multiple times and using the test data from all previous cycles to inform the design for the next cycle, the platform can guide a highly efficient multi-parameter sequence optimization across an intractably large sequence space.

This AI-guided smart selection of high-value test sequences provides a highly efficient and cost-effective approach to discovering better antibody sequences with the required biophysical properties, allowing BigHat to optimize existing lead therapeutic candidates for more effective treatment and create therapies addressing unmet needs inaccessible to traditional drug design approaches. This unique platform design enables a highly efficient and faster path to drug discovery than other existing platforms as well as enabling novel designs beyond today's capabilities.

BigHat captures the value created by its Milliner platform by developing therapeutic antibodies in two complementary ways: through partnerships with biopharma companies and our pipeline of wholly-owned assets. We currently have two biopharma partnerships that have been made public: a single-target agreement with Amgen and a multi-target agreement with Merck. These multi-year collaborations aim to develop antibodies on the Milliner platform that have proven intractable using conventional antibody discovery and development techniques. These collaborations produce short-term revenue that helps Milliner continue to run and grow, give us invaluable access to our partners' proprietary biological methods and assays, and help us generate the data we need to train the ML models that will be used in the future. In addition, our partners can quickly get these newly developed medicines to patients by utilizing their clinical development and commercialization expertise.

BigHat is also developing a pipeline of wholly-owned therapeutic antibodies. BigHat has quickly assembled a superb team of subject matter experts and scientific luminaries for its therapeutics team and advisory board. This therapeutics group designs our molecules, works with Milliner to create them, and guides their progression through preclinical and clinical testing. Our in-house therapeutic pipeline currently focuses on significant unmet medical needs across various indications, from oncology to inflammation. BigHat has quickly assembled a superb team of subject matter experts and scientific luminaries for its core team and advisory board. For instance, BigHat successfully advanced one of the molecules intended to control inflammation into a disease model based on human blood this year

with remarkably encouraging results. The CRO even commented, “The reduction in [redacted assay] that we see here is really exceptional, better than what we’ve seen with any other compound we’ve tested academically or industrially. You should know that that is really remarkable.”

BigHat anticipates these molecules will enter first-in-human clinical trials in the next few years. BigHat is fulfilling its mission to "make better antibodies faster" in just five years from its founding, a remarkable achievement in drug discovery and development, where a typical drug takes more than ten years to develop.

**History of the development of the solution/product**

BigHat was founded upon the premise that deep learning innovations in the late 2010s weren't having nearly as much of an impact on biomedicine as they were on high-tech. In biomedicine, AI/ML essentially served as a data analysis tool that was stuck at the tail end of the laborious traditional experimental workflow. Even at Google AI, where Mark DePristo oversaw a genomics research team, and Stanford, where Peyton Greenside was a Schmidt Science Fellow, most AI/ML in the life sciences was just fancy data analysis.

BigHat’s co-founders, Mark and Peyton imagined a brand-new kind of biological research lab built from the ground up to incorporate and enable AI/ML technologies. An integrated, quick-turnaround wet lab for designing antibodies was at the heart of BigHat's plan. It could produce vital data and verify the predictions made by machine learning models, allowing for data-driven engineering of safer and more effective antibody drugs. Peyton left a promising academic career, while Mark left his group leader position at Google to realize this vision and founded BigHat Biosciences in 2019.

Receiving its seed funding mere 8 weeks from inception, BigHat developed the first iteration of the platform, demonstrating its ability to engineer an antibody and enhance its characteristics. BigHat was accepted into the MBC Biolabs incubator program, which provided a sandbox environment where BigHat built its prototype platform, and early iterations of the lab in 2019. After raising a preempted Series A financing led by prestigious venture capital firm a16z, BigHat received early market traction via a collaboration with the biopharma giant Amgen, with BigHat completing Phase 1 of the collaboration significantly ahead of schedule in December 2021. Concretely, this milestone was to improve the affinity of several high value lead molecules where significant traditional antibody optimization efforts had failed. In doing so, BigHat publicly demonstrated that its unique combination of machine learning, laboratory automation and synthetic biology was able to create better antibodies, where significant traditional antibody optimization efforts had failed.

In the same year, BigHat graduated from shared bench space at the MBC BioLabs incubator into its first global headquarters, a brand new 30,000 sq ft flexible laboratory and coworking space at 1900 Alameda de las Pulgas in San Mateo, CA in the heart of the Bay Area life sciences cluster. The market traction driving expansion of BigHat’s innovative platform led BigHat to acquire Frugi Biotechnology, an Aimes, Iowa-based SBIR-supported company that produces advanced cell-free protein synthesis (CFPS) reagents, in January 2022. Catalyzed by growth of the team and the new space, BigHat expanded its antibody development throughput 5-fold, from around 100 antibodies per week to nearly 500 weekly designs.

In July of 2022, BigHat Biosciences raised a $80 million Series B financing, led by global investment firm Section 32, with participation from pharma giants Amgen Ventures and Bristol Myers Squibb as

well as Quadrille Capital, Gaingels, among others, while prior investors a16z, 8VC, and AME Cloud Ventures also contributed to the round. With this infusion, BigHat has been rapidly operationalizing on its Series B promise of scaling Milliner to tackle thousands of new antibody designs each week, advance therapeutic programs toward clinical trials, continue recruiting world-class drug discovery and development experts and to accelerate strategic collaborations with flagship partners. In late 2022, BigHat inked a collaboration partnership with biopharma giant Merck to optimize up to three proteins by leveraging BigHat's platform to synthesize, express, purify, and characterize molecules, further solidifying its market traction.

BigHat also tracks across a variety of metrics to measure growth of our platform:

Platform capacity - One of the most significant metrics that has been tied to the growth of BigHat's platform, Milliner, is its output capacity measured in the number of molecules produced per week. Milliner has gone from producing 100 molecules in the beginning of last year to over 1000 molecules per week today.

Number of Supported Programs - Milliner has increased its capacity to support multiple programs simultaneously reflecting an advanced level of sophistication of the platform. Milliner's ability to simultaneously support multiple programs have increased from supporting only 2 programs last year to more than 9 today.

Assay Onboarding - The speed at which BigHat can onboard fully customizable assays into our lab infrastructure management software (Reccy) has increased tremendously. This process that took months during the early days of Milliner now only takes a few seconds today.

Weekly Average of Protein synthesized - Over a year ago an RA at BigHat could only synth-purify-quant 1 plate of samples per week. Following the growth of the platform and added levels of automation and manufacturing innovation that BigHat has implemented, a single RA can now synth-purify-quant >500 samples in a 24 hr period.

Number of characterization assays - A year ago, an RA at BigHat would need a week to run an ELISA and Thermostability assay for 1 plate of 96 samples. Today, a single operator at BigHat can run a suite of characterization assays (ELISA, Thermostability, CE-SDS (purity), Kinetics, and Cell Based Assays) on 8 96 sample plates in the same amount of time.

Number of experiments per month - The number of experiments run on the Milliner platform has increased by more than a 100% (from ~1000 to ~2200 experiments/month) from last year to today.

Number of observations tracked over time - The number of observations the Milliner platform is observing has increased from ~20,000 last year to over 100,000 today.

Number of Datasets - The number of datasets generated has increased from ~2000 last year to almost 20,000 today.

Number of Pipelines - The number of pipelines we have run over time that do automatic data processing has increased from ~500 last year to well over 2000 today.

Publications at ML conferences: BigHat published its first peer-reviewed article, Effective Surrogate Models for Protein Design with Bayesian Optimization at the prestigious International Conference for Machine Learning (ICML) Workshop on Computational Biology (WCB). Specifically, BigHat researchers collaborated with advisor and Bayesian deep learning expert, Andrew Gordon Wilson of NYU, to develop a framework for protein design that requires only a small amount of labeled data. The real-world utility of these methods were demonstrated by optimizing the Stokes shift of green fluorescent protein (GFP). This paper served as the first public illustration of how BigHat leverages its rapid design/build/test platform for data-driven antibody discovery and engineering.
In summary, BigHat is enjoying a phase of rapid organic growth. In just three and a half years, BigHat has developed partnerships with top biopharmas like Amgen and Merck, invented the essential science and technologies needed to run and support its platform, and nurtured an internal therapeutics team using our Milliner platform to develop tomorrow's therapies today.

**Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition**

Licensing cutting-edge technology from a research lab is the traditional starting point for biotech startups. BigHat, unlike the majority of biotechs, invented its platform technologies after establishing the company. BigHat's organic research and development has led to advancements in various fields of science and technology, from affordable cell-free protein synthesis to novel active learning algorithms. As pioneers in successfully integrating these technologies into the Milliner platform, BigHat has become a leader in applying AI/ML to drug discovery. Milliner allows BigHat to develop a unique pipeline of therapeutics for patients suffering from today’s worst diseases in addition to significantly reducing the development cost and timeline associated with discovering new therapeutics. This approach will not only reduce the cost-burden on some of the most intractable and costly diseases but also improve patient outcomes by introducing more effective drugs than what is available today. Our work has received numerous awards for innovation, has been featured in top trade journals, and has been published in prestigious AI/ML conferences. BigHat has become a trailblazer in shifting today’s empiric approach to drug discovery to that of an engineering one. BigHat is fundamentally changing the way humans will look at today’s most challenging diseases in the future, which will become more tractable and reduce cost burdens on economies worldwide as BigHat broadens its pipelines of these next generation therapeutics.

**Please provide appropriate references (ie Pubmed links)**

Intros:

BigHat non-confidential deck: https://bighat.docsend.com/view/z3x6gnvrn9vr29kj
One-page overview: https://docsend.com/view/jhi3dya6enr584jy
Antibody Engineering and Therapeutics 4Q22 talk: https://www.bighatbio.com/news/bighats-cso-presents-at-antibody-engineering-and-therapeutics-conference
Pitchbook profile: https://pitchbook.com/profiles/company/366556-33

Publications:

Effective Surrogate Models for Protein Design with Bayesian Optimization: https://icml-compbio.github.io/2021/papers/WCBICML2021_paper_61.pdf

Disclosed partnerships:

BigHat and Amgen: https://www.bighatbio.com/news/bighat-biosciences-completes-first-stage-of-research-collaboration-with-amgen
BigHat and Merck: https://www.bighatbio.com/news/bighat-biosciences-announces-research-collaboration-with-merck

Financing:

Section 32-led $75M Series B: https://www.bighatbio.com/news/bighat-raises-xxxxxxxx
a16z-led $19M Series A: https://www.bighatbio.com/news/bighat-raises-19m-series-a
8VC-led $5M seed: https://www.bighatbio.com/news/bighat-closes-oversubscribed-seed-round

Media:

Fierce Biotech 4Q22: https://www.fiercebiotech.com/biotech/exclusive-bighat-cherry-picking-opportunities-amid-stormy-market-pens-pact-big-pharma-merck
Fierce Biotech 3Q22: https://www.fiercebiotech.com/biotech/bighat-protects-against-stormy-market-conditions-big-pharmas-joining-80m-series-b
AWS Summit 2Q22: https://www.bighatbio.com/news/bighats-cso-and-vp-engineering-speaking-at-aws-summit-san-francisco
Pharma's Almanac 1Q22: https://www.bighatbio.com/news/bighat-in-pharmas-almanac-q1-2022-issue
BIOS Builders 1Q22: https://www.bighatbio.com/news/bighats-ceo-and-cso-on-bios-builders-podcast