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Designing for simplicity: Lessons from Mesa Biotech for microfluidic entrepreneurs and early-stage companies

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Abstract

The COVID-19 pandemic has proven the need for point-of-care diagnosis of respiratory diseases and microfluidic technology has risen to the occasion. Mesa Biotech (San Diego, CA) originally developed the Accula platform for the diagnosis of influenza A and B and then extended the platform to SARS-CoV-2. Mesa Biotech has experienced tremendous success, culminating in acquisition by Thermo Fisher for up to \$550M USD. The Accula microfluidics platform accomplished the leap from the lab to commercial product through clever design and engineering choices. Through information obtained from interviews with key Mesa Biotech leaders and publicly-available documents, we describe the keys to Mesa's success and how they might inform other lab-on-a-chip companies.

Introduction

Mesa BioTech was founded in 2009 by Hong Cai, PhD and Bruce Cary, PhD to commercialize work begun at Los Alamos National Laboratory. Drs Cai and Cary started working on a field-deployable diagnostic test for pandemic preparedness following the SARS-CoV-1 outbreak in 2003. By 2009, they had developed a working PCR microfluidic prototype, but it took a further 9 years to fully develop a commercial product and receive

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Conflicts of interest

There are no conflicts to declare.

Our first in this series discusses the development and commercialization of the Mesa Biotech Accula point-of-care PCR test.

Wilbur Lam, MD, PhD co-leads the ACME POCT with Oliver Brand, PhD and Greg Martin, MD.

regulatory approval for the Accula Point of Care (POC) Flu A/Flu B diagnostic test (1). By 2020, the company was selling the Accula platform on the market for influenza diagnosis and had grown to 60 employees, half of which were engaged solely in manufacturing.

On January 10, 2020, the first SARS-CoV-2 genome sequence was released publicly online(2). The Accula platform was designed for exactly this scenario: rapid POC diagnosis when the existing laboratory infrastructure is insufficient. Mesa Biotech leadership was concerned that pivoting to developing a new diagnostic could distract from production of the Flu test and divert resources from the flu effort.

Despite uncertainty about how the epidemic would evolve, on January 23rd, 2020, the company decided to pursue making a test for SARS-CoV-2, ordered the necessary primers and probes, and by February 14th had a working assay with synthetic targets. After testing the assay against the RNA from the Washington strain and performing verification and validation studies, the company submitted for Emergency Use Authorization (EUA) which was granted on March 20, 2020.

Description of the Accula System: Dock and Test Cassette

The Accula test is a semi-automated, colorimetric, multiplex reverse-transcription polymerase chain reaction (RT-PCR) test to qualitatively detect viral RNA from unprocessed nasal swabs. The system integrates nucleic acid extraction, reverse transcription, a novel Mesa Biotech PCR nucleic acid amplification technology named OscARTM, and hybridization-based visual detection into a completely self-contained and automated system.

The Accula Dock is an electronic module which executes in vitro diagnostic tests on compatible Mesa Biotech Test Cassettes. It consists of an electro-mechanical interface to a single Test Cassette. The Dock contains all electrical systems, controls and logic necessary to orchestrate the assay.

Upon insertion of a Test Cassette, the Dock will detect and identify the Cassette type. After the user transfers a clinical test sample into the Cassette and closes the Dock lid, embedded firmware in the Dock will control fluid flow of the sample into the various chambers of the Cassette, apply controlled voltage signals to the various Cassette heaters (monitored by sensors within the Dock), and provide visual status to the user with critical information such as estimated time to read, and various error states, should they be encountered.

Development & Commercialization Path

The path from idea to product to revenue for a microfluidic device can be long and expensive(3). Significant funding was required to sustain Mesa Biotech before their first product was available for sale and revenue could be generated. The original idea was to create an instrument-free, self-contained, low cost (<\$20 USD/unit), disposable, rapid (<30-minute, sample-to-answer), nucleic acid POC diagnostic device (MTIDx) capable of detecting influenza A, influenza B, RSV and other relevant respiratory diseases.

The company followed a traditional commercialization pathway (Chart 1) out of academic research starting with a small, locally available seed grant provided by the New Mexico Venture Acceleration Fund administered through Los Alamos National Laboratory. This was followed by an R01 grant from the National Institute of Allergy and Infectious Diseases (NIAID) for \$800,000 USD (R01AI072334).

Next the company applied for and received a two-year Small Business Innovation Research (SBIR) phase I grant from NIAID for ~\$600,000 USD to transition to injection molding prototypes which enabled short-run production for rigorous characterization and laboratory testing (R43AI093018). The company incorporated the development of lyophilized reagents for amplification and detection, developed stable buffer reagents and capsulation methods, started design for manufacturing optimizations to facilitate future high-volume production, and conducted initial testing to identify design refinements required to attain performance objectives.

Following this, the company applied for and received an SBIR phase II grant for \$3M USD to optimize their design for a low complexity, CLIA-waved product (R44AI093018). The company also focused on design for manufacturing optimizations and conducted performance evaluations on clinical samples.

Up to this point, the company was funded exclusively through non-dilutive grant mechanisms but now, with design for manufacture complete, the company needed funding to build a manufacturing capacity and raised \$27M USD in venture capital.

Next, the company applied for regulatory approval of the Accula platform as a class II device with CLIA waiver using the 510k pathway. The company received approval for the “Accula Flu A/Flu B Test” in February 2018. This was followed quickly with approval for a test to detect respiratory syncytial virus (RSV) called the “Accula RSV Test” in November 2018 and the “Accula Strep A Test” to aid in the rapid diagnosis of Group A Streptococcus bacterial infections in November 2020. As described previously, the company created a SARS-CoV-2 test for the platform which led directly to an additional \$16M USD in funding to scale up manufacturing capacity (contract No. 75N92020C00014, 75A50120C00019). Finally, in 2021, it was announced that Mesa Biotech would be acquired by Thermo Fisher for up to \$550M USD(4).

Expedited Regulatory Pathway During the SARS-CoV-2 Pandemic

During a public health emergency, the United States Food and Drug Administration (FDA) continually assesses the risk: benefit ratio in the context of safety (e.g. is the product safe to use?) & efficacy (e.g. how well does the product perform?) but also critically takes into consideration the timing of how quickly the technology can enter the market as well as supply chain issues and shortages of existing technologies on the market. Accordingly, during a public health emergency, the FDA assesses the availability of tests in the different contexts of clinical use, such as use in central laboratories, at the POC, or over-the-counter (OTC, e.g. in the home). Therefore, during the SARS-CoV-2 pandemic, the FDA prioritized assays that fill market gaps in POC and OTC contexts. Specific to Mesa Biotech, the Accula

system was one of the first PCR assays authorized for POC use and the assay was prioritized because it met a clear unmet clinical need as few POC assays were available at the time. As such, unlike typical times, during public health emergencies, regulatory agencies stay attuned to the market at hand and constantly assess the availability of the specific type of technologies to the patient populations at risk, which, in turn, informs their authorization decisions.

Keys to Success

It is a considerable challenge moving from a benchtop prototype to a diagnostic product manufactured at production scale. Through interviews with Mesa Employees, “keys to success” were identified by the company spanning strategy, technical decisions, and design decisions.

Strive for “Elegantly Simple” Design Through Iterative Development

A key strategy that contributed to the success of the Accula platform (Chart 2) is the focus on design simplicity. The company knew they wanted to use gold standard PCR technology but were inspired to make the test as “easy to use as a pregnancy test”. This design simplicity applied to the visual read lateral flow assay user experience but also to the internal design of the system.

One specific design decision that simplified the test is the inclusion of lyophilized reagents in the fluidic cassette. This allows not only a room temperature stable product with a long shelf life but also renders the system very easy to use by placing all the critical reagents in the test cassette, thus avoiding any need for the user to handle sensitive reagents.

Force Fast Failure

This concept is often antithetical to the academic mindset that focuses on scientific exploration and perseverance when problems arise. In contrast, forcing fast failure involves data collection to inform rapid go/no go decision making that ultimately saves time and financial resources and can be applied for technical as well as business-related decisions,

From a technical perspective, Mesa made extensive use of rapid prototyping approaches to fuel frequent iterative cycles of testing and refinement early on. Enabled by technologies such as laser cutting and 3D printing, the company was able to quickly evaluate the impact of small design changes to the cassette and fluidics channels to optimize performance and address problems that emerged during testing. This was particularly important as the company moved toward more manufacturable designs where seemingly small changes to accommodate manufacturability had unanticipated impacts to the performance of the test that needed to be quickly resolved. Relying solely on modifying injection molding would have been prohibitively cumbersome especially earlier in the design process. Once design for manufacture of the cassette was complete, the company also iterated on the injection molding process using many different materials and adhesion methods. Each rapidly produced prototype, many of which “failed,” ultimately improved the performance and form factor of the cassette and led to the simple design of the laminated cassette and associated channels and chambers.

Another early example of forcing fast failure that led to a simpler design was the decision to design the Mesa Accula to be a reusable dock/disposable cassette model completely as opposed to a disposable single use unit model. Initially, the company initiated the design for a stand-alone unit wherein the entire system including electronics was for single use. While the design process progressed, however, Mesa quickly observed that the approach not only raised environmental concerns but also unnecessarily increased cost. The company then pivoted and altered the design to comprise an inexpensive but reusable dock to limit waste and reduce cost.

Forcing fast failure also applied to digital interpretation of results by the Accula dock. The Accula cassette is a visual read assay. To improve performance and consistency, the company began developing a second-generation dock that included the ability to read and interpret the results from the Accula cassette. However, after designing, prototyping, and testing the new dock, the team decided to halt development of the project, despite having invested considerable time and resources. A more complex and expensive dock would not have fit the deployment model of the company and instead the team pivoted product development towards a mobile application-based solution that maintained the systems low barrier to deployment. While this pivot was a setback for the company, a quick failure during development was far less costly than a failure in the marketplace.

A final example of forcing fast technical failure was the development of the PCR heater interface. The original heating element was mounted to a PCB board with surface mounted resistors. First, the company underwent a series of failed iterations attempting to achieve a reproducible thermal interface to the cassette, a necessity for reliable PCR chemistry. The company tried multiple attempts at interfacing a disposable PCB directly to the cassette, placing the heater in the base, and pressing the disposable cassette against the heater elements and finally succeeded by designing a flex circuit heating element which improved test reproducibility and reliability.

Collectively, the aforementioned iterative development processes culminated in a product that was simple to use and manufacture while maintaining reliability and reproducibility.

The model of quick decision making through fast failure extended beyond product development to the financing of the company. Investors, especially venture capital (VC) funds, use a rigorous metric to fail fast when assessing a company that is raising money by, for example, assessing strategic fit, stage of financing, competitive positioning, and intellectual property position, eliminating potential companies quickly so they may focus on promising investments. The company took the same approach and developed a metric that was specific to selecting the best lead investor by, for example, assessing the fund lifecycle timing, the portfolio companies within the fund, expertise, and even cultural fit. The same process was used to assess interested investors who were interesting in joining the funding round. For example, if a fund was already at its later stage in its lifecycle, the fit would have been suboptimal since we were looking for long-term investors. A VC fund that is either in its early years or an evergreen-fund (a fund with continuous investment funding) was a better fit for the company because of the long product development timeline of regulated diagnostics. The company also prioritized funds whose portfolio companies were not in

potential conflict with Mesa but rather could provide synergies such as data and cloud computing services, e-commerce, etc. This quick decision model helped the company to focus and quickly eliminate investment mismatches for both the company and the investor.

Stay True to the Company Vision

The guiding principle of the Accula platform was to be a field deployable CLIA waived test for emerging pathogens that could be sold for comparatively nominal cost to a small clinic or practice. The company had an opportunity to offload technical challenges into a more complex instrument to solve engineering problems, but this would have increased the cost of the platform, creating an undifferentiated product compared to existing competitors. This strategy was derived from the original conception of the company to develop field deployable tests in the context of a pandemic. The Accula platform consists of a relatively inexpensive dock and interchangeable test cassettes. This design allows for new test cassette types to be created while maintaining the dock and overall system function, changing only the primers and probes within the test. This split design provides two important benefits that are aligned with the company vision: first, the dock is relatively inexpensive, allowing quick field deployment and second, the interchangeable cassette design allows the company to react quickly to emerging pathogens, allowing many different tests to be run using the same installed equipment.

Do Not Push the Envelope on Miniaturization

One technical decision that had multiple downstream effects is the sample volume used within the cassette. The company originally developed a smaller cassette design using a 40-microliter sample volume but increased the size of the reaction to 60-microliters and increased the size of the chambers to improve sensitivity. After this lesson, the company specifically used larger sample volumes going forward and did not try to “push the envelope” on miniaturization of the system. This decision allows for larger channels within the cassette that are harder to foul with biological samples and improves manufacturing reproducibility because the channel tolerances are less strict. Additionally, highly miniaturized platforms require a high degree of sample concentration because the volumes are small and unless the device concentrates the sample, a significant amount of sensitivity can be lost.

Don't Ignore Basic Business Challenges

During the development of the SARS-CoV-2 diagnostic, the company faced three major challenges that it had to overcome. These challenges stemmed directly from effects of the SARS-CoV-2 pandemic but apply generally to operating a diagnostics business. First, like any company, Mesa Biotech could not run out of money to keep operating and developing tests. The company continually sought additional capital both in the form of grants and dilutive funding. Second, hiring talented people to scale up quickly was not easy during a global pandemic. The company hired an exceptional Chief People Officer (CPO) who had experience in scaling organizations quickly and attracting talent. In addition, many employees were attracted to the company by the cause of having a meaningful impact in the fight against the pandemic. And third, supply chains were disrupted by the pandemic which required geographic supplier flexibility. Different countries had different capabilities at any

given time due to the pandemic. As an example, China recovered its supply capabilities earlier than Europe or the US. In addition, the company validated alternative materials and suppliers, as an example swabs. The original swab supplier for the Accula test kits could not deliver the volumes needed so the company subsequently validated additional swabs and updated the product labeling to allow for use of a variety of swabs, rather than only one.

Conclusions

Mesa Biotech's foresight to develop an adaptable and robust diagnostic platform positioned the company to respond quickly to the COVID-19 pandemic. The company's technical and commercial success was derived from a few key strategies that can be used by future microfluidic companies and entrepreneurs:

- Strive for "Elegantly Simple" Design Through Iterative Development
- Force Fast Failure
- Stay True to the Company Vision
- Do Not Push the Envelope on Miniaturization
- Don't Ignore Basic Business Challenges

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The NIH-funded Atlanta Center for Microsystems Engineering POC Technologies (ACME POCT) is focused on microsystems-based and microfluidics-based diagnostics. The center's experience with the Rapid Acceleration of Diagnostics (RADx) program to speed the development, validation, and commercialization of innovative SARS-CoV-2 point-of-care and home based tests has brought the ACME POCT team into contact with amazing leaders of diagnostic technology companies. This experience has taught the team tremendously about the business and technology of microfluidics commercialization. As such, we aim to disseminate this knowledge to our microfluidics community by publishing a series of "lessons learned" case studies focused on the technical, clinical validation, regulatory, and commercialization lessons that led to company success or company failure.

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Chart 1 –.
Mesa Biotech Commercialization Pathway

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Chart 2 –
Accula Cassette and Dock Platform

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Table 1 -

Funding Raised by Mesa Biotech

Date (M/D/Y)	Amount (USD)	Cumulative (USD)	Funding Source
2003–2009	Pre-Company	Pre-Company	Los Alamos National Laboratory
9/11/09	\$ 100,000	\$ 100,000	Seed Grant
4/20/09	\$ 727,411	\$ 827,411	R01
9/16/09	\$ 82,460	\$ 909,871	R01
7/13/11	\$ 298,218	\$ 1,208,089	STTR Phase I
6/26/12	\$ 285,395	\$ 1,493,484	STTR Phase I
6/5/14	\$ 1,000,000	\$ 2,493,484	STTR Phase II
5/14/15	\$ 1,000,000	\$ 3,493,484	STTR Phase II
7/11/16	\$ 1,000,000	\$ 4,493,484	STTR Phase II
2/13/18	\$ 12,000,000	\$ 16,493,484	Venture Capital
7/9/18	\$ 12,000,000	\$ 28,493,484	Venture Capital
10/28/19	\$ 3,000,000	\$ 31,493,484	Venture Capital
3/19/20	\$ 561,000	\$ 32,054,484	RADx
6/21/20	\$ 15,400,000	\$ 47,454,484	RADx
2/6/21	\$ 450,000,000	\$ 497,454,484	Exit - Sale to Thermo Fisher