1. TECHNOLOGY DESCRIPTION, STATUS AND LANDSCAPE

A. Background

1) Problems trying to solve: inefficient drug design (cryogenic temperature, prolonged time, inaccuracy)

2) Time to develop a drug = 10 to 15 years
   (http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf)

3) Amgen 2014 report (http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NTc0NTMzfENoaWxkSUQ9Mjc3Njc2FRI5cGU9MQ==&t=1); Discovery research and translational sciences, $1212 million: R&D from early research through completion of phase I clinical trials

B. Idea Description

Pharmaceutical companies and research laboratories need a way to accurately obtain physiologically relevant structural information about drug targets in order to accelerate drug discovery and design. The MESH innovation is a fluidic microjet used for serial femtosecond crystallography (SFX) with X-rays. SFX is an emerging method for determining the 3D structure of nano- to micron-sized crystals at room temperature. The method relies on intense X-ray pulses that pass through a sample before causing significant damage. Sample consumption can be reduced by 60-100 times, and structures less than 2 angstrom can be resolved. This innovation promises to break the correlation between radiation damage, sample size, and resolution in the field of structural biology. Furthermore it will lead to a previously elusive understanding of dynamic structures and their intermediates at room temperature.

C. Potential Commercial Applications of Technology

1) With an X-ray laser or synchrotron
   a. Early drug discovery from lead identification to optimization
   b. Mechanisms of drug efficacy and toxicity
   c. Structural biology research, e.g. protein-drug imaging

2) Without an X-ray laser or synchrotron (potential future markets)
   a. Mass spectrometry sample delivery
   b. 3D printing

D. Features and Benefits

1) Not damaging to sample
2) Room temperature drug design
   a. Current drug target structures are studied at cryogenic temperatures where overall structure is attainable, but dynamics are lost
   b. Room temperature structure is dynamic
   c. Technique does not require cryogenic temperatures thus allowing for room temperature structures
3) Low sample consumption
   a. Legacy tech requires milligrams-grams of protein at $30,000/10 grams
   b. Legacy tech requires dozens of facility hours to solve a structure at $25k/hr
   c. Legacy tech requires $40-50k/yr for consumables
   d. Legacy tech requires one dedicated technician minimum to prepare and create consumables
   e. New tech requires micrograms and can solve a complex room temperature structure in 2 hr
   f. New tech does not require technician after brief training
   g. New tech consumables are $5-10k/year

E. Innovative Aspects

1) Room temperature
2) Low sample consumption
3) Modularity and ease of integration and automation

F. Regulatory Hurdles: none
G. Development Status
1) Prototype complete
2) LCLS experiments showed that this new method offered 33-53 times reduction in sample consumption rate without compromising data acquisition.
3) Continued research to explore suitable buffer conditions, perform experiments with the apparatus at LCLS, and optimize the design
4) Compatible with XFELS
   a. Vacuum compatible
   b. Uses modular off-the-shelf parts
   c. Testing in-air experiments this November
5) Further compatibility
   a. Testing compatibility with synchrotrons at SSRL (SLAC)
   b. Promising results with LCP and sponge phase (2012 Nobel Prize)
   c. Testing in new facility (Japan) in late November
6) Needs automation and beamtime for high throughput
   a. MFX (crystallography-focused beamline at LCLS)
   b. Japan SFX

2. INTELLECTUAL PROPERTY LANDSCAPE

A. Patent Status
1) Published application 11/21/2013
2) Responded to first USPTO rejection
3) Recently responded to second USPTO rejection (adjusted claims to focus on X-ray probing)

B. Patent Coverage
1) Fluidic microjet used for serial femtosecond crystallography (SFX) with X-ray lasers
2) Does not address non- X-ray applications like 3D mass spectrometry sample delivery and 3D printing

C. Competing IP
1) https://desy.cfel.de/cid/research/serial_femtosecond_crystallography/ using Gas Dynamic Virtual Nozzle (GDVN)
2) Apparatus and methods for lipidic cubic phase (lcp) injection for membrane protein investigations (PCT/US2014/035627)

3. SWOT ANALYSIS

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Helpful</th>
<th>Harmful</th>
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| Strengths: | ● Margin on disposables  
● Revenue stream on disposables  
● Potential revenue for black box/instrument  
● Hard to replicate  
● New, enabling technology  
● Cost advantage compared to the | Weaknesses: |
|           |         | ● SLAC contracting and logistics  
● XFEL facility hours are low supply and high demand  
● Few customers  
● Few facilities  
● Facility expense  
● Switching cost is high (customers |

Page 3 of 7
existing methods
● Faster than the existing methods
● appealing to the biological users’ pain points on sample consumption

unwilling to try new technology and deal with SLAC
● Revenue gated by customers’ grant funding

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<tr>
<th>Extrinsic</th>
<th>Opportunities:</th>
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<td></td>
<td>● Increasing cost of drug discovery</td>
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<td>● Increasing needs of analysis of protein 3D structure</td>
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<td>● Increasing needs of precise analysis of protein 3D structure</td>
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<td></td>
<td>● Increasing needs of protein analysis in usual temperature</td>
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<td></td>
<td>● Improved structural knowledge leads to improved drug efficacy</td>
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<table>
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<th>Threats:</th>
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<td>● Technology advancement of the existing X-ray facilities</td>
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<tr>
<td>● Emergence of direct competitors using the same technology</td>
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<td>● Development of cheaper way of drug discovery (other than 3D structure analysis)</td>
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<td>● Alliance/relationship between clients and existing players</td>
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<td>● Cryo-EM</td>
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Strategic Implications
- Strength x Opportunity:
  - Focus R&D and Marketing on growing market/clients
  - Seek/expand applications with deepening client relationship
  - Price discrimination strategy depends on users’ cost of substitutes
  - Price the reduced time of clients’ R&D
- Strength x Threats:
  - Find clients who most benefit from our technology (and ignore others)
  - Make R&D alliance with major clients to develop technology and expand application
- Weakness x Opportunity:
  - Consulting service/fo following up/after service, including contracting and logistics with SLAC, to reduce switching cost
  - Select clients to maximize the revenue/profit growth in the limited SLAC resource
- Weakness x Threats:
  - If competing technologies get better and become real threats, total solution provider (providing both methods) is a strategic option

4. **MARKET ANALYSIS**

A. Primary Research – Interviews and Surveys
1) Expert opinions: Hasan believes there is a market for this technology.
2) Inventors: Ray believes there is a market for this technology.
3) Distinguished Japanese professor So Iwata saw our demo and believes this can be a breakthrough in how membrane proteins are solved
4) Chinese head of iHuman thinks this can increase the throughput of structural biology
5) Beamline Scientists at LCLS, SSRL and SACLA (Japan) are in tune with a structural biologists needs and have expressed interest in adapting our technique to their instruments
6) People to contact for interview:
a) Brian Kobilka - Stanford (http://med.stanford.edu/kobilkalab/)
   (kobilka@stanford.edu) - emailed 11/17
b) Tom Patapoff - Genentech (http://www.gene.com/scientists/our-scientists/tom-patapoff) (patapoff.thomas@gene.com) - emailed 11/17
c) Roger Kornberg - Stanford (http://kornberg.stanford.edu/)
   (kornberg@stanford.edu) - emailed 11/17
d) Molecular Dimensions, Ltd. “guy” - (http://www.moleculardimensions.com/)
e) Douglas Whittington - Amgen (http://www.amgen.com/)
f) Aina Cohen’s colleague - SLAC (http://smb.slac.stanford.edu/staff/)
g) George Martin - Roche (https://www.linkedin.com/in/george-martin-78114a1)
h) Nick Grupido - Rigaku (Conn.Mallett@Rigaku.com emailed 11/17; Nick.Grupido@Rigaku.com)
i) Ivan Simardiev - Pfizer (https://www.linkedinvy.com/in/ivan-samardiev-8045a011)
j) Jerome Riebman - Novartis (jerry.riebman@novartis.com); visited SLAC 11/17
k) Mary Ann Ramirez - Novartis (maryann.ramirez@novartis.com); visited SLAC 11/17
l) Rajiv Chopra - Novartis (rajiv.chopra@novartis.com)
m) Michael Romanowski - Novartis (michael.romanowski@novartis.com)

B. Secondary Research – Internet, Printed Documents
   1) Benchmark against existing technologies, products and companies
   2) Sources: BCC, GSB library – ABI-Inform and Thomas One, PrivCo, LuxEx, Knowledge Express, ISIS, data monitor reports, SEC filings/10k/annual reports
   5) Protein Crystallization & Crystallography Market worth $1,253 Million by 2018 with 10.15% CAGR from 2013-2018

5. INDUSTRY ANALYSIS – PORTER'S FIVE FORCES

   A. Threat of New Entrants - Barriers to Entry: There are considerable barriers to entry in this market. Notably there are limited customers and limited facilities, and those facilities are expensive to access.

   B. Threat of Substitutes: Legacy technologies and protocols can be substitutes. Simple off-the-shelf design may be “engineered around.” Patent aims to protect the core of the technique to limit designing around the beneficial aspects. Is biosimulation a substitute?

   C. Supplier Power: MESH has very little power outside of being a possible gatekeeper for SLAC. As additional global sites open, MESH’s supplier power will decrease. A key to future success might be to secure the first-to-market position and to leverage synchrotrons.
D. Buyer Power: Potential customers have large financial resources and are used to spending large sums on drug discovery; pharma and large structural biology research consortiums.

E. Degree of Rivalry: Given the number of synchrotrons and potential for revenue, it seems likely that some customers and competitors might seek to develop their own competing technologies. ASU is already an expert at pedaling their technology, people are willing to pay for a $7k device which is flawed but the best out there. Our aim is to increase signal quality and sample consumption by orders of magnitude, while maintaining simplicity and user-friendliness.

6. REGULATORY ANALYSIS

A. Hurdles: none
B. Timeline: none

7. OPPORTUNITY ASSESSMENT

A. Industry Assessment for Primary Application
   1) Industry Trends- Globally there are 70 existing synchrotrons and 2 existing X-ray lasers; there are 7 additional synchrotrons and X additional X-ray lasers planned or under construction. The demand for biology beamtimes has grown almost 400% in the past 5 years. Structural biology beamlines around the world continue to be oversubscribed by academic users and have paid spots from industry (e.g. Genentech at SSRL), LCLS is the most intense XFEL at the moment. SACLA (Japan) is the only other hard XFEL to do SFX. Soon, Switzerland, Germany, S. Korea, China, and LCLS-II will be open by ~2020 increasing the supply of beamtimes.
   2) Company Financials- see information regarding 2014 Amgen report in part 1 above. Pharmaceutical companies do not publish details regarding money spent solely on early drug research (discovery and design).
   3) New Investments
   4) Industry Reports- see link from Markets and Markets. Unfortunately these industry reports are too expensive to obtain for the purpose of iFarm.

8. POTENTIAL PARTNERS

A. Company names and contact information if available: The major players operating in the protein crystallization & crystallography consumables market are Rigaku Corporation (Japan), Hampton Research (U.S.), Jena Bioscience GmbH (Germany), Molecular Dimensions Ltd. (U.K.), Formulatrix, Inc. (U.S.), Bruker Corporation (U.S.), and MiTeGen LLC (U.S.). These guys sell little consumables and devices for crystallography. Most structural biology labs buy plates, loops, buffers, and other tools (e.g. acupuncture needles repackaged as crystal pokers).
   1) Consider large pharmaceutical companies who are developing multiple drugs and are embracing crystallography for drug discovery and design:
      a. Pfizer and Bristol-Myers-Squibb, for example
      (https://www.genomeweb.com/pfizer-joins-accelrys-crystallography-consortium)
B. Why company would be a good fit for the technology? Already spending money to use synchrotron and X-ray laser facilities. Potential to increase relevancy of drug discovery and design data.

C. Startup potential: Sample delivery consulting. Build Customer base and begin to further understand pain points of users. Begin to develop user-focused techniques and products that are packaged for ease-of-use. Alternatively research customer needs prior to startup. Then

9. IFARM TEAMS TECHNOLOGY SUMMARY AND RECOMMENDATION

A. Where did you mainly focus your efforts for this technology? biopharma
B. How have you contributed to the licensability of this invention? vetted different options for licensure and determined biopharma to be most viable
C. Did you address the associate’s comments from the iTIP? yes
D. If you had more time to work on this project, what areas would you plan to further investigate? more feedback from potential licensees and industry experts (only received feedback from Douglas Whittington, Principal Scientist at Amgen, Inc.)
E. How do you recommend OTL should proceed with this technology? advertise for licensure to start-up, biopharma companies, and HW/SW or protein crystal manufacturers that serve the biopharma industry