Novel Gram + Therapeutics

BUSINESS SUMMARY

Overview

Dr. Fred Buckner and Dr. Erkang Fan's labs have discovered novel antibiotic compounds (UW MetRS inhibitors) that have great oral bioavailability and potency against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococcus (VRE), streptococcus strains, and other drug-resistant Gram-positive bacterial strains, have shown no observed toxicity in mice tests, and can be administered via IV or oral pill. We have consulted with an expert in antibiotic drug discovery who has recommended a number of additional experiments to prepare the compounds for licensing to a commercial partner. This summary details the problems faced by skin and soft tissue infections, solutions and technologies, market analysis, competition & differentiation, traction, intellectual property, preliminary financial analysis, an introduction to the management team, and a technical plan & timeline with needs and benefits of funding support.

Problem

MRSA, VRE, streptococcus strains, and many other types of bacteria are the cause of skin and soft tissue infections, as well as catheter, bloodstream, surgical site, heart valve, and orthopedic hardware infections, to just name a few. These infections are responsible for over 20,000 deaths and healthcare costs upwards of $10 billion every year in the United States alone. Many of these strains of bacteria are becoming even more resistant to antibiotics available on the market and continue to spread around the world. Unfortunately, approval of new antibiotics to fight these infections has declined over the past few decades. Making matters worse, all approved antibiotics available on the market and in the clinic use mechanisms of action that bacteria have a known resistance to. New antibiotics are urgently needed to treat patients in hospitals and in the community with these resistant infections. Realizing the global nature of this problem, over 80 international biopharmaceutical firms at the 2016 World Economic Forum in Davos urged governments around the world to join in the effort to fight drug-resistant superbugs that could within a few decades be responsible for killing tens of millions of people unless advancements are made and new antibiotics are discovered.

Solution/Technology

The UW MetRS inhibitors discovered by the Buckner/Fan group have highly potent antibacterial activity on MRSA and other strains of Gram-positive bacteria. They target methionyl-tRNA synthetase (MetRS) in Gram-positive bacteria. They target MetRS for a few reasons. First, it's required for protein synthesis, and is thus essential for cell growth. Second, it is an exploitable difference between Gram-positive bacteria cells and human cells, thus ensuring that these compounds are non-toxic to mammalian and mice cells.

The Buckner/Fan group has two primary selective small molecule inhibitors under development. They have great oral bioavailability and potency. They have excellent in vitro activity against Gram-positive bacteria and not Gram-negative bacteria, which bodes well for gut flora. At this point, there has been no observed toxicity in mice tests. The compound could be administered via IV or oral pill. The compound works by a novel mechanism of action, which means it is unlikely that bacteria circulating in the community will have any resistance. If approved, this would be the only first-in-class antibiotic approved since 2003.

In addition to the technology, the regulatory environment is part of the solution. In 2012 President Barack Obama added provisions for Generating Antibiotic Incentives Now (GAIN) to the Food and Drug Administration Safety Innovation Act. The GAIN provision adds an additional five years of sales exclusivity without generic competition for antibiotics that treat serious infections. This time extension allows for innovative companies to have a better chance at recouping their investment costs. In addition to the time extension during the approval process, these drugs would be fast tracked and given priority review during the regulatory approval process with the FDA.

Market

The global systemic antibiotics industry is currently being driven by the increasing aging population and the emergence of resistant bacteria. The total addressable market for global systemic antibiotics industry is estimated to be $41.2 billion in 2018. In the US, more than 6 million visits to ERs and doctors' offices occur per year for skin and soft tissue infections. MRSA, VRE, Streptococcus strains, and other Gram-positive bacteria are the primary cause for these infections, which result in 20,000 deaths and approximately $10 billion in healthcare costs every year just in the US. The comparable products on the market to combat these infections include:

- Dalvance - Actavis, Approved 2014 - Projected sales of $449M in 2019
- Orbactiv - The Medicines Company, Approved 2014 - Projected sales of $200M in 2021
- Sivextro - Merck, Approved 2014 - Projected sales of $400M in 2020
- Teflaro - Actavis, Approved 2010 - Projected sales of $426M in 2016
- Vibativ - Theravance/Astellas, Approved 2009 - Actual sales of $18M in 2015
- Tygacil - Pfizer, Approved 2005 - Actual sales of $335M in 2012
- Cubicin - Merck, Approved 2003 - Actual sales of $1B in 2015
- Zyvox - Pfizer, Approved 2000 - Actual sales of $1.4B in 2014 (Zyvox characteristics most comparable to UW MetRS inhibitors)

All things being equal, the sum of these sales equate to an estimated serviceable addressable market potential of approximately $4 billion. Three of the four most recently approved drugs used to treat these infections estimate about a 10% market share 6 years after approval. With that said our serviceable obtainable market is estimated at $400 million 6 years after FDA approval.

Competition & Differentiation

Pharmaceutical and biotechnology companies are working to develop new drugs for MRSA and other infections caused by drug resistant organisms. However, few companies have programs to develop drugs acting by entirely new mechanisms of action. As seen in the table below, the antibiotics in clinical trials are mainly filled by “me too” drugs that are likely to become ineffective in short time by resistance mechanisms already present in circulating bacterial strains.

Drug Interventions	Sponser	Condition	Phase	Novel Mechanism
Delafloxacin, Vancomycin, & Aztreonam	Melinta Therapeutics, Inc.	SSTIs	Phase 3	No
Omadacycline & Linezolid	Paratek Pharmaceuticals, Inc	SSTIs	Phase 3	No
Cholecalciferol & Placebo	Peter Bergman; et al	SSTIs	Phase 2	No
Daptomycin & Vancomycin	Singapore General Hospital; et al	SSTIs	Phase 2	No
Fosfomycin & Daptomycin	Miquel Pujol; et al	SSTIs	Phase 3	No
Ceftaroline & Vancomycin	Wayne State University; et al	SSTIs	Phase 4	No
New Mexico Honey & Bactrim DS	R. Stephen Rankin, M.D.	SSTIs	Phase 2	No
Chlorhexidine Gluconate & Saline Placebo	Thrasher Research Fund; et al	SSTIs	Phase 2	No

Our advantage is having compounds that act by a novel mechanism, which are thus likely to be active against resistant strains in the community and hospitals. In addition, our compounds have excellent oral bioavailability, meaning they can be developed as drugs for oral administration. This is a distinct advantage compared to widely used drugs such as daptomycin and vancomycin that can only be given by injection as seen below in the table.

Drug	Mfg	MRSA	VRE	Route of administration	Side effects + mild ++++ major	Lab monitoring	Year of introduction	First in class?
Vancomycin	Baxter/Pfizer	Yes	No	IV only	++	Weekly	1956	Yes
Daptomycin	Merck	Yes	Yes	IV only	+	Weekly	2003	Yes
Ceftaroline	Allergan	Yes	No	IV only	+	Weekly	2010	No (5th gen.)
Linezolid	Pfizer	Yes	Yes	IV/oral	+++	Weekly	2000	Yes
Tedizolid	Merck	Yes	Yes	IV/oral	++	Weekly	2014	No (linezolid)
Bactrim	Roche	Yes	No	IV/oral	++		1968	Yes
MetRS inhibitor	UW	Yes	Yes	IV/oral	To be determined	To be determined	2022?	Yes

Effective IV/oral drugs can help reduce hospitalizations, shorten the time to hospital discharge, avoid antibiotic complications post discharge, and thereby save healthcare dollars.

Traction

The UW MetRS inhibitors are more potent on MRSA and VRE strains than vancomycin by a factor of 10. The lead compounds **1614** and **1717** are small, easily synthesized molecules with good aqueous solubility. When administered to mice, **1614** has >85% bioavailability and achieves high peak and sustained plasma concentrations. Both **1614** and **1717** are non-toxic to mammalian cells *in vitro* and have been administered to mice at high doses (50 mg/kg twice per day) for up to 20 days without evidence of toxicity. Through support from CoMotion, we have presented our data to Dr. Lynn Silver, an expert consultant on antibiotic drug development, for her feedback. Overall, she expressed enthusiasm for the project. She recommended a brief panel of additional experiments that will help establish our portfolio before pursuing commercial partners. The six sets of recommended experiments are enumerated below in the Technical Plan.

Intellectual Property

The University of Washington has filed International Patent Application no. PCT/US2015/046357 on August 21st, 2015. No national stage applications have been filed yet. The patent application covers multiple uses including antibacterial applications as well as for treating various parasitic diseases such as trypanosomiasis.

Preliminary Financials

The UW MetRS inhibitors will have to go through the FDA approval process which is a time and capital intensive process. Projected financials were forecast until the the drug hits peak sales in 2028. Using recently approved antibiotics as a benchmark, the UW MetRS inhibitors are projected to capture 10% of the $4 billion global Gram-positive infection therapeutics market 6 years after FDA approval. Additional assumptions are detailed below.

($) in M	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Revenue	0	0	0	0	0	0	0	67	133	200	267	333	400
COGS (35% of Rev)	0	0	0	0	0	0	0	23	46	69	92	115	138
Gross Profit	0	0	0	0	0	0	0	44	87	131	175	219	262
R&D (8% of Rev)	0	5	15	23	66	43	2	6	11	17	22	28	33
SG&A (37% of Rev)	0	0	0	0	10	10	10	34	59	73	98	122	146
EBIT	(0)	(5)	(15)	(23)	(76)	(53)	(12)	4	18	41	55	69	83
Tax (35%)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	1	6	14	19	24	29
EBIAT	(0)	(5)	(15)	(23)	(76)	(53)	(12)	2	11	27	36	45	54
Future Cash Flows	(0)	(5)	(15)	(23)	(76)	(53)	(12)	2	11	27	36	45	54
Terminal Value													421
NPV	$14												

Based on biopharmaceutical industry benchmarks for financial projections we used a discount rate of 15%, COGS of 35% of revenue, R&D costs of 8% of revenue, and SG&A costs of 37% of revenue. Included in the R&D costs before FDA approval are the costs to move the compounds from the lab through the IND, clinical trial, and NDA processes. Using industry benchmarks we estimated that this entire process would cost $131 million spread out unevenly over 7 years. Included in the SG&A cost we estimated that launch costs for the approved drug would cost approximately $50 million spread out evenly over 5 years with prep beginning in 2020. We also estimate that since this drug could utilize the benefits of the GAIN provision it would be fast tracked and given priority review during the FDA regulatory process with approval occurring in early 2023. These estimates are not meant to be taken as a company valuation. They are meant show the potential that this product could become cashflow positive in the future based on benchmarks in the biopharmaceutical industry. With regards to pricing, we plan to price the therapy in line with current competition in the market at approximately $2,000 for full treatment.

Management Team

Student Team

Ryan Delacruz is pursuing his Doctorate of Pharmacy at the University of Washington. He is also part of the technological entrepreneurship program associated with the Foster School of Business. He has a strong interest in business and healthcare and looks to work in the pharmaceutical industry after graduating. He received his Bachelor of Science degree in Biology from the University of Nevada Las Vegas.

Omeed Faghih recently graduated from the University of Washington with a Bachelor of Science degree in both Biochemistry and Neurobiology. While at UW, he was an 8 time recipient of the Dean's Academic Scholarship and was in both the Biochemistry and Interdisciplinary Honors Programs. His past experience includes over 3 years of research at the Center for Emerging and Re-emerging Infectious Diseases and a TA position for the Introduction to Systems and Behavioral Neurobiology course. Omeed is currently working as a Technician in Dr. Buckner's lab and will be dedicated fulltime to the UW MetRS inhibitors project.

Colin Johnston worked at Harborview Medical Center before returning to school to pursue his MBA, managing research projects in the intensive care units. He is passionate about healthcare delivery and helping organizations provide high-value care to the patients and communities they serve. After graduating, he will serve healthcare delivery organizations through ECG Management Consultants. He received his Bachelor of Science degree from the University of Washington.

Christopher Joyce is pursuing a dual degree, Master of Business Administration and Master of Pharmaceutical Bioengineering, at the University of Washington. He is a Global Health Innovation Fellow at the Arthur W. Buerk Center for Entrepreneurship. His prior experience includes over 8 years of consulting for early and late stage biotechnology companies which helped him hone his expertise in Operational Risk Management. Chris is focusing his studies on strategy, finance and entrepreneurship in the biotechnology industry and he received his Bachelor of Science degree in Biology from Loyola Marymount University.

Advisory Board

Principal Investigator: Fred Buckner, MD, is a professor in the UW Department of Medicine, Division of Allergy & Infectious Diseases, with nearly 20 years' experience in antimicrobial drug discovery research. He has >100 peer reviewed publications. He has helped develop an antimalarial drug that is now in Phase II clinical trials and several compounds in preclinical stages of development for other protozoan infections. Dr. Buckner is a Board certified infectious diseases specialist.

Co-Investigator: Erkang Fan, PhD, is an associate professor in the UW Department of Biochemistry who will oversee the chemistry component of the project. His laboratory has made nearly 500 MetRS inhibitors and has the expertise to provide the chemical materials necessary for the proposed experiments.

Technology Manager: Jennifer McCullar, PhD with CoMotion. She has a doctoral degree in Molecular and Cellular Biology and has extensive experience with developing life sciences technologies.

Patent/Legal Manager: Andrew L. Laughlin, JD, with CoMotion. He is an expert in patent law and preparation and has a Masters of Science in Chemistry.

Entrepreneur in Residence: Steve Runnels, PhD, MBA, has more than 28 years of business management experience in the healthcare industry. He has led drug discovery and product development activities in diverse therapeutic areas.

Antibiotic Drug Development Consultant: Lynn Silver, PhD, has 21 years of experience working in antibiotic drug discovery at Merck Research Laboratories. She started her own independent consultancy (LL Silver Consulting, LLC) in 2003 in the area of antibacterial discovery and pre-clinical development. She has provided recommendations for additional steps to strengthen this research program (see technical plan) and is on retainer for ongoing discussions as the project advances.

Faculty Advisor: Lance Young, Phd, MS, MBA, CPA is a Senior Lecturer of Finance and Business Economics at the Foster School of Business. His expertise is in asset pricing, behavioral finance, business valuation, financial markets, growth management, small business finance, and venture capital. He is currently researching empirical asset pricing, behavioral finance, and capital market anomalies. Lance has numerous publications and has been voted Professor of Year on many occasions.

Technical Plan & Timeline

We plan to identify a potential pharmaceutical/biotechnology partner in late Q3 2016 to help develop the UW MetRS inhibitors for clinical trials.The following experiments and activities were recommended by our expert consultant, Dr. Lynn Silver, to address important areas of concern

to potential commercial partners and will be completed before we identify our partner. These experiments will answer some detailed questions about the potential for the current lead compounds to be developed for clinical trials.

1. Resistance frequency determination: The purpose of these experiments is to establish whether resistance to the MetRS inhibitors occurs at a high or low frequency compared to known drugs.
2. Perform serum shift assays to determine the role of protein binding on compound potency.
3. Screen more bacterial strains to determine the range of MICs to various strains of *Staphylococcus, Enterococcus, Streptococcus,* and *Clostridium.*
4. Screen "permeable" strains of *E. coli* to determine if the compounds have potential activity on Gram-negative bacteria.
5. Perform "cidality" assays to better characterize if the compounds have a "static" or "cidal" mechanism of inhibiting bacterial growth.
6. Test compounds **1614** and **1717** in the *Staph aureus* target organ model in mice to determine the efficacy of compounds in this alternative animal model.
7. Market research for potential development partners.

Needs/benefits of Health Innovation Funding Support

This project on antibiotics arose from research in the Buckner/Fan labs relating to antiparasitic drug discovery, specifically for trypanosomiasis. The NIH-funded research led to the discovery of highly potent compounds against trypanosomes that we recently found to have excellent activity on Gram-positive bacteria. Trypanosomes and Gram-positive bacteria share the same biochemical target for the compounds, specifically a Type 1 methionyl-tRNA synthetase (MetRS). The antibiotic component of this research is not supported by the NIH grants to the Buckner/Fan labs, hence, we have a critical need to secure funding to further advance this project.

As noted previously, we have a defined plan as recommended by an industry expert for additional experiments to be completed before approaching commercialization partners. The planned experiments will establish the proof of concept that the compounds are viable and promising candidates for clinical development. It is important to move forward with this research in a timely manner as we are in a period in which few pharmaceutical and biotechnology companies have truly novel antibiotics in their pipelines and the call for new antibiotics is scaling up. Although the proposed experiments are critical for advancing the compounds to the next stage of development, it is not necessarily easy to procure funding from NIH or other public sources for this type of research since the experiments are fairly "boilerplate" in nature. Funding from the Health Innovation Challenge will enable us to get through this translational step (sometimes referred to as the "valley of death") to a position where future commercial partners will view the product as sufficiently de-risked to consider partnering for downstream development. Our end goal is to reduce the spread of these infectious diseases while at the same time lowering the associated healthcare costs for treatment resulting in greater health and wellness to the populous.

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