Methods to improve survival from heart failure in chronic hypertension and to prevent arterial stenosis

Team 3 (Vandana Kaul, Melanie Huttner, Tom Lenk, Linda Molnar)

1. Technology Description, Status and Landscape

Heart failure affects 5.1 million people in the United States and is at least partially responsible for one in nine deaths. The projected medical cost of treating heart failure in the US is $32.4 billion in 2015, and is expected to top $77 billion by 2030.1 Stanford inventor and professor Dr. Daria Mochly-Rosen has developed methods for slowing or preventing the progression to heart failure in patients with hypertension. Protein kinase C (PKC) isozymes βII and ε have been implicated to play a role in maladaptive cardiac responses, including those associated with progression to heart failure.ii,iii The Mochly-Rosen lab has utilized peptide inhibitors with high specificity for βII PKC and εPKC isozymes in order to impede the physiological responses of activated PKC in rat hypertension models. mRNA labeling indicated elevated levels of βIIPKC in cardiomyocytes from human heart failure patients, and activation of the enzyme in vivo has been found to correlate with an increase in hypertrophic cardiomyopathy and myocardial dysfunction.iv Inhibition of βIIPKC in rats has improved cardiac function and lifespan and attenuated collagen deposition in the myocardium of post-myocardial infarction in hypertension-induced heart failure.v εPKC plays a critical role in regulating fibroblast adhesion and migration, and activation led to cardiomyocyte hypertrophy in feline cardiomyocytes, while inhibition suppressed cardiac fibrosis.vi

The εPKC inhibitor together with an angiotensin II receptor blocker (ARB) showed improved survival outcomes in rats over treatment with the ARB alone and therefore the inhibitors might be administered alone or as part of a combination therapy.vii The latter strategy may be of particular interest for companies with antihypertensive therapeutics that are facing patent expirations (Table I). This technology may be applicable for several indications affecting large populations currently facing unmet medical needs such as late stage heart failure, diabetes-induced cardiomyopathy, aortic stenosis, and heart disease due to Chagas disease. Alternatively, the inventor and future collaborators may be able to apply for rare/orphan disease designation by pursuing indications such as peripartum cardiomyopathy, patients with severe heart failure awaiting heart transplants, chemotherapy induced cardiomyopathy or carcinoid heart disease. In the latter two cases patients may be too ill to undergo major cardiovascular surgery, but nonetheless are at risk to succumbing to heart failure and therefore would benefit from a treatment that slows or reverses the progression to heart failure that does not require a major medical procedure. Additionally, the PKC inhibitor may have an additive effect in treating both heart failure and cancer.viii For patients awaiting a transplant, we believe this technology has the potential to improve the survival rate of those on the waitlist, and possibly negate the need for a transplant.

Innovative aspects of this technology include targeting a protein-protein interaction (PKC and its receptor for activated c-kinase, RACK) with a peptide inhibitor derived from one of the PKC isozyme of interest. In this manner, the peptide inhibitor is highly selective in blocking its parent isozyme’s interaction with RACK, causing a selective loss of function without interfering with the functions of other PKC isozymes in the cells. While the use of synthetic small molecules as kinase inhibitors is popular in cancer treatments, these PKC inhibitors are often found to have undesirable off-target toxicity and a lack of specificity.ix Current treatments for hypertension and heart failure center on treating patients with a cocktail of drugs for years and hoping something
works. This SOC suffers from harmful and ineffective drug-drug interactions as well as uncertainty over which drug(s) the patients are actually responsive to.x Therefore, treatment with βIIPKC and εPKC inhibitors should be strongly considered for the treatment of maladaptive cardiac remodeling and heart failure, including the possibility of actually inducing positive remodeling.

Future hurdles that will be faced in order to further develop this technology include a lack of preclinical studies amongst different animal species. While studies have been conducted in Dahl salt-sensitive hypertensive rat-models and post-myocardial infarction (MI) rats in vivo, studies with larger animal models have yet to be initiated. Larger animals such as dogs, monkeys and pigs have been used in the past as models for hypertension, but the inventor’s lab at Stanford does not have access to these models, and therefore the studies would need to be contracted or licensed out.xi Another hurdle is the generally high cost and size of clinical trials for cardiovascular diseases. The optimal method of administration and the choice of endpoints still need to be determined.

Table 1. FDA approved top selling hypertension drugs.

<table>
<thead>
<tr>
<th>Brand, Generic Names</th>
<th>Use</th>
<th>Manufacturer</th>
<th>Peak Sales</th>
<th>Patent Expiration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benicar, Olmesartan medoxomil</td>
<td>High blood pressure; ARB</td>
<td>Daiichi Snakyo, Inc.</td>
<td>$2.6 billion in 2011</td>
<td>2016</td>
<td>-5th-top selling cardio drug in 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Prescribed to 1.8 million patients in the U.S. 2013^ii</td>
</tr>
<tr>
<td>Diovan, Valsartan</td>
<td>High blood pressure; congestive heart failure; ARB</td>
<td>Novartis</td>
<td>$6.05 billion in 2010</td>
<td>2012</td>
<td>-Prescribed to 12 million patients in the U.S. in 2005^iii</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-10th most prescribed drug in the U.S. in 2014</td>
</tr>
</tbody>
</table>

2. Intellectual Property Landscape

United States Patent 7,741,290 was approved on June 22, 2010 and covered methods for slowing or inhibiting the progression of heart failure in mammalian subjects suffering from chronic hypertension through the administration of peptide inhibitors conjugated to cell penetrating peptides with or without combination therapy with olmesartan. United States Patent 8,426,364 was approved on April 23, 2013 and was an expansion of the previous patent to include peptide inhibitors containing at least 80% sequence identity to the polypeptides in the previous patent. There is potential for new IP regarding method of administration and combination therapies. Competing patents are summarized in Table 2.

Table 2. Competing IP.

<table>
<thead>
<tr>
<th>Patent</th>
<th>Approved</th>
<th>Inventors</th>
<th>Title</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Eplerenone is a steroid</td>
</tr>
</tbody>
</table>
3. SWOT Analysis

**STRENGTHS**
- Specific isozyme activity (ε, βII)

**WEAKNESSES**
- Requires significant preclinical work
  - Immunogenicity
  - Multiple animal models
- Mode of action not well understood
- Cannot use oral delivery

**OPPORTUNITIES**
- Combination therapy with ARBs or ACE inhibitors
- Could develop delivery IP, especially around a combination drug
- Large treatment population

**THREATS**
- Regulatory requirements on clinical study design
  - Endpoint? (does not lower blood pressure)
  - Timing of study to demonstrate effectiveness
- Other treatments?
- PKC-δ “popularity”
  - Success could overshadow
  - Failure could suggest “another one bites the dust” backlash

4. Market analysis

A. Primary Research- Interviews and surveys

**KOLs in the order that they were interviewed:**
Sara Nakashima, laughter@stanford.edu
Stanford OTL senior licensing associate
- Need more data
  - More preclinical data will help to expand markets and open doors for new IP
- Companies that were briefly interested:
Dr. Leon Chen, ChenL@OrbiMed.com  
Venture Partner at OrbiMed; Co-Founder of KAI (2002); Former Mochly-Rosen student (1998-2001)

- Very concerned about a peptide therapeutic for a chronic indication
  - No cell-penetrating moieties FDA approved or in PIII
  - Peptidic delta PKC inhibitor worked because it was for an acute treatment and was delivered intracoronary
  - Small molecule would decrease company’s risk in pursuing this project
  - Not concerned about targeting protein-protein interactions
- Pharmacological questions to answer:
  - How many PKC/RACK interactions do you need to inhibit?
  - How many myocytes do you need to reach?
  - Can a patient’s HF stage be improved with this treatment?
- Did not choose to license this technology with KAI because of cost issues and risks; may want to consider ophthalmology indications
- Potential to treat diabetics but challenges around clinical development and a way to measure efficacy

Dr. Kevin Grimes, kgrimes@stanford.edu  
Physician and Associate Professor at Stanford; Senior Director of Clinical Research at KAI Pharmaceuticals (2004-2007); Co-Director of SPARK (2008-present)

- Standard of care
  - Lots of competition for antihypertensives but how much of HF is related to hypertension?
  - Treating hypertension:
    - Diuretic and Ca^{2+} channel blocker and ARB
    - Don’t know which patient is responding to which drug(s)
  - Treating HF:
    - ACE/ARB and beta blocker and spironolactone (particularly for the elderly)
    - Goal: decrease blood pressure, decrease strain on heart, prevent negative cardiac remodeling, decrease heart rate
- Delivery of therapeutic (the biggest issue right now!)
  - Subcutaneously: how much do you need to administer for efficacy?
  - Pump: going to limit treatment people with very bad HF but may be best way of administration
  - Peritoneal: risk of bad infection
  - What would the organ and tissue distribution be?
- Using a peptide as a therapeutic is okay but may create additional barriers for funding
- Technology is at too early a stage for a startup
  - Suggests a grant for funding
- Combination therapy
  - Touch clinical trials -> target refractory patients but they may be less like to respond
  - Endpoints: would want change in the number of hospitalization and/or death rate but can possibly get away with ECHO and 6 minute walk
Dr. Lihan Sun, lsun1219@gmail.com
Investment Analyst at Cormorant Asset Management; Former Mochly-Rosen student (2005-2011)

- Translating preclinical work to the clinic
  - Early success based on chemodynamic parameters (ejection fraction, heart size, etc.) but in humans need to see clinical benefit
  - Some human data necessary for VC to invest
    - Some VCs willing to license from well known labs based on early robust data (i.e. Third Rock)
  - Always people willing to bet early and cheap (i.e. $5 million to do initial studies)
  - Study is in too early a stage for big companies and HF is “not sexy” right now
    - Lower hurdle for rare/orphan disease
    - Getting orphan designation is generally easy
    - Look for severe conditions with limited treatments and an imminent need
  - Showing reversal of disease would be a “game changer” and “revolutionary”

- A peptide as a therapeutic is not a big hurdle as long as you know dose and frequency of administration
  - Subcutaneous delivery okay but more than once a week can lead to compliance problems

Dr. Joel Karliner, Joel.Karliner@va.gov
Cardiologist at the VA; Professor Emeritus at UCSF; Former Mochly-Rosen collaborator

- Not entirely convinced that PKC is responsible for HF because despite tremendous interest in PKC for HF over several years, targeting PKC did not work consistently in human trials
  - Concerned about effect on PKC due to ischemic preconditioning in animal and human studies
  - Suggested reading: NEJM ID 26436028 and 26436029
- Suggested additional animal models: spontaneously hypertensive rats (Japan) and Goldblatt models
- Suggested narrowing the target population as much as possible
  - Preselect patients based on their biopsies or genomic data?
  - Stage 4/end stage may be a good target
- Need delivery method to be effective and patient friendly
  - Pump may be best but need to establish formulation method

Dr. Carol Karp, ckarp2155@yahoo.com
Regulatory Advisor to Biotech and Pharma Companies; Regulatory Advisor to SPARK; Previously worked as VP or Sr. VP at Esperid Therapeutics, JANSSEN Alzheimer Immunotherapy, CV Therapeutics, PowderJect Technologies and VIVUS Inc

- Application of this therapeutic to orphan diseases?
  - FDA orphan designation allows for subset of disease
    - Stage 4 HF population may be too high
    - Transplant patients would probably be credible if peptide is studied this way
    - Pregnant women at risk for HF would be too difficult to study -> should try to get approval for different indication first
Pediatric cardiomyopathy would need to be studied in adults first anyway but has a lower barrier to succeed than the above indication
  - FDA concerned with gamesmanship (approving for orphan, then expanding treatment population)
  - If peptide therapeutic has the potential for treating advanced HF, why not treat other stages too?
- To push forward, suggests opening conversations with companies pursuing treatments for population subsets
  - Also can look for resources for treating subset populations from advocacy groups and grants, then consider licensing it out after phase I or II

Dr. Todd Lorenz, tlörenz@stanford.edu
Clinical Development Consultant, Kinexum LLC; Previously worked as CMO or VP at Portola Pharmaceuticals, Catalyst Biosciences, Johnson & Johnson, ALZA Corporation, Orexigen, and Corgentech; Clinical development consultant for SPARK
- Need to get clear answers from companies on what type of preclinical studies they are looking for
  - Which companies are actively looking at HF? (Resource: Bob Herrington)
    - Dr. Adrian Hernandez (Duke) suggests Novartis, Amgen, GSK, BMS, Merck, Gilead and Bayer
  - Look for early development group in a large company
  - Look for a small company willing to develop a peptidomimetic
    - Longer half life, can be taken orally
- Based on animal models, what stage does this therapy work best for?
  - Does stage III/IV heart already have too much damage?

Dr. Julio Ferreira, jcesarbf@usp.br
Assistant Professor at University of Sao Paolo; Mochly-Rosen collaborator; former Mochly-Rosen post-doc (2007-2009)
- Unmet need for highly specific intracellular inhibitors because the industry is mainly using GPCR drugs now and there is a poor five year survival rate for patients with chronic disease
- The peptide inhibitors have the potential to return PKC isoform levels to normal levels and to affect cardiac remodeling, contractility of cardiomyocytes, and Ca²⁺ transient. Not concerned having a peptide as a therapeutic
- Dr. Ferreira has access to Dahl, MI and aortic stenosis rat models and has co-workers with large CVD animal models but requires funding to pursue further studies
  - Suggested money from a company or VC firm
  - Would do more toxicity and combination studies in <6 months (suggested choosing disease with shortest path to study)
  - Need to figure out what dose needs to reach target before deciding on delivery method
- Potential applications: Chagas disease, HF produced by MI, aortic stenosis
Potent therapeutics
- $\beta$IIPKC
  - Connection to diabetes
  - Activation inhibits proteasomes and myocardial infusion causing a lack of energy in cells (Ferreira)
  - Inhibitor shows reversal of disease
- $\varepsilon$PKC
  - Increases cardiac fibrosis (Sun)
- Inhibitors are not a cure but are a significant way to modify the disease and possibly take patients off of a transplant list
- Potential to create peptidomimetics although this was tried by Pfizer 15 years ago and failed
- Possibility for a reversal in cardiac functioning/positive remodeling
- Current SOC drugs have drug-drug interactions that are a huge problem

Delivery
- Changing the carrier:
  - But inhibition in other tissues isn’t bad
  - Nanoparticles require more studies on release and formulation and are not well studied with peptides
  - Antibodies would go to the lysosome and are too expensive
- IP: not acceptable in humans
- IV: too expensive, required a very high dose for $\delta$PKC inhibitor in clinical trials
- Subcutaneous: could provide sustained delivery through a small surgery or a implant under the skin
  - Precedence with insulin pump

Potential for combination therapy
- But ACE and ARBs are given orally so formulation with a peptide would be complicated and would require more FDA testing
- Would combination therapy limit the potential use/application of the peptides?
- Could consider a chimera of the $\varepsilon$ and $\beta$ peptide inhibitors as a new chemical entity

Immunogenicity
- At KAI took two years to raise antibodies to the peptide inhibitor
  - Peptide was non-immunogenic even at high doses, likely due to its quick internalization
- Future tests to do: ELISPOT assay, antibody titer
- Could conduct single dose ascending trial where the roof would be the cost

Future animal studies
- Mochly-Rosen lab unable to contribute more studies to this project
- USC-Charleston: Swine
- Ferreira: human samples, rats
- Safety studies

Targeting subsets of populations
African Americans or Asians (Japan, China)
- End stage HF, too sick for surgery and waiting for a transplant
  - During transplant can check for heart improvement
- Chagas disease: inhibitors would not take care of the parasite & why would this treatment only benefit them?
- Aortic stenosis: why would this treatment only benefit them?
- Postpartum cardiomyopathy: strong potential, very interested but needs more info on numbers and SOC
- Cancer causing cardiomyopathy: inhibitors may also be beneficial for cancer treatment
- Post-MI patients with HF: easier to get their consent!

Company: Daichii-Sankyo
Hisashi Nakagaki, hnakagaki@dsi.com

- Although it is reasonably believed that PKC isoforms are related to disease progression, they are also involved in physiological functions and therefore there is safety concern. Compounds like KAI-9803 which can be used with a single administration may be okay, but it would be difficult to target chronic diseases such as CHF with multiple dosing.
- Unlike Eli-Lilly’s ruboxistaurin, even if βIIPKC is selectively inhibited, there is still safety concern. We may reconsider the opportunity if a wide safety margin is established with animal toxicity studies.
- If we remember correctly, your technology is to selectively inhibit PKC translocation with peptides. Subcutaneous administration of peptides may not be suitable for chronic treatment.
- If there are some more data coming out from future studies which would change our thoughts mentioned above, please let us know.

Responded but declined interview and/or didn’t follow up after viewing slide deck:
Erin Denny (edenny@amgen.com); Jay Parrish (Jay.Parrish@gilead.com); Gregory Naeve (Gregory.Naeve@pfizer.com); Dr. Marcelo Kazanietz (marcelog@gmail.med.upenn.edu); Dr. Karl Handelsman (karl@codoncapital.com)

Did not respond:
Christopher Starr (cstarr@raptorpharma.com); Dr. Tom Quetermous (cby@stanford.edu); Dr. Yuen Ashley (euan@stanford.edu); Alan Mathiowetz (alan.m.mathiowetz@pfizer.com); SC Wilkie (scwilkie@lilly.com); Joerg Knaeblein (joerg.knaeblein@bayer.com)
B. Secondary Research

1) Benchmark against existing technologies, products and companies^{xiv,xv,xvi,xvii,xviii,xix,xx}

<table>
<thead>
<tr>
<th>Drug/ Company</th>
<th>Disease condition</th>
<th>Patent</th>
<th>Clinical Trials/ FDA Approval</th>
<th>Market sales</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docket 06-137 (this work)</strong></td>
<td>Hypertension / Cardiac Stenosis</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Peptide Inhibitor of PKCII-β, PKC-ε Isozymes</td>
<td>No serious side effects in rats, human trials not done</td>
</tr>
<tr>
<td>Benicar, Olmesartan medoxomil / Daiichi Sankyo</td>
<td>High blood pressure; ARB</td>
<td>Yes, Expires 2016</td>
<td>Yes</td>
<td>$0.729B, 2012</td>
<td>Angiotension 2 Receptor Blocker</td>
<td>Dizziness, lightheadedness</td>
</tr>
<tr>
<td>Diovan, Valsartan/ Novartis</td>
<td>High blood pressure; congestive heart failure; ARB</td>
<td>Expired 2012</td>
<td>Yes</td>
<td>$1.97B, 2012</td>
<td>Angiotension 2 Receptor Blocker</td>
<td>Headache, dizziness, flu symptoms, musculoskeletal pain</td>
</tr>
<tr>
<td>Atacand/ Astrazeneca</td>
<td>Anti-hypertensive</td>
<td>Expired 2013</td>
<td>Yes</td>
<td>$1.009B, 2012</td>
<td>Angiotension 2 Receptor Blocker</td>
<td>Stuffy nose, sore throat, cough, back pain, joint pain, stomach pain, diarrhea, headache, dizziness, tiredness</td>
</tr>
<tr>
<td>Avapro/ Sanofi</td>
<td>Anti-hypertensive</td>
<td>Expired 2012</td>
<td>Yes</td>
<td>$0.330B, 2012</td>
<td>Angiotension 2 Receptor Blocker</td>
<td>Dizziness, lightheadedness, upset stomach</td>
</tr>
<tr>
<td>Micardis/ Boehringer Ingelheim</td>
<td>Anti-hypertensive</td>
<td>Expired 2014</td>
<td>Yes</td>
<td>$2.098B, 2012</td>
<td>Angiotension 2 Receptor Blocker</td>
<td>Dizziness, stomach pain, back pain</td>
</tr>
<tr>
<td>Norvasc</td>
<td>Anti-hypertensive</td>
<td>Expired 2007</td>
<td>Yes</td>
<td>$3.001B, 2007 global</td>
<td>Calcium channel blocker</td>
<td>Breathing difficulty, dizziness</td>
</tr>
</tbody>
</table>
Cozaar Anti-hypertensive Expired 2010 Yes $1.28B, 2012 global Angiotension 2 Receptor Blocker URT infection, musculoskeletal pain, dizziness

2) Companies that have recently failed in cardiovascular drugs  

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug Candidate</th>
<th>Clinical trial phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>Dalcetrapib</td>
<td>2012</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Darapladib</td>
<td>Phase III, 2014</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Evacetrapib</td>
<td>Shut down Global Phase III, 2015</td>
</tr>
</tbody>
</table>

5. INDUSTRY ANALYSIS – PORTER’S FIVE FORCES

A. Threat of New Entrants - Barriers to Entry
Potential New entrants that obtained FDA approval in 2015 xxiv

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Target condition</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestalia (perindoprilarginine and amlodipinebesylate)</td>
<td>Symplmed Pharmaceuticals</td>
<td>Hypertension</td>
<td>January 2015</td>
</tr>
<tr>
<td>Savaysa (edoxaban)</td>
<td>Daiichi Sankyo</td>
<td>For the treatment of deep vein thrombosis, pulmonary embolism and risk of stroke and embolism due to atrial fibrillation</td>
<td>January 2015</td>
</tr>
<tr>
<td>Corlanor (ivabradine)</td>
<td>Amgen</td>
<td>Chronic heart failure</td>
<td>April 2015</td>
</tr>
<tr>
<td>Kengreal (cangrelor)</td>
<td>The Medicines Company</td>
<td>For reducing periprocedural thrombotic events</td>
<td>June 2015</td>
</tr>
<tr>
<td>Entresto (sacubitril and valsartan)</td>
<td>Novartis</td>
<td>Chronic heart failure</td>
<td>July 2015</td>
</tr>
<tr>
<td>Praluent (alirocumab)</td>
<td>Sanofi Aventis</td>
<td>For the treatment of heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease</td>
<td>July 2015</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>Amgen</td>
<td>High Cholesterol</td>
<td>August 2015</td>
</tr>
</tbody>
</table>
### B. Threat of Substitutes

**Drugs currently in pipeline (early stage/ Phase I, II, III )**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism</th>
<th>Disease condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omecamtiv mecarbil</td>
<td>Amgen (collab. With Cytokinetics)</td>
<td>small molecule activator of cardiac myosin</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>BAY1067197</td>
<td>Bayer</td>
<td>Partial Adenosine A1 Receptor Agonist</td>
<td>Chronic Systolic Heart Failure</td>
</tr>
<tr>
<td>Beperminogene Perplasmid</td>
<td>AnGes MG, Inc.</td>
<td>Angiogenesis inducing agents; Hepatocyte growth factor stimulants</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Gencaro (bucindolol hydrochloride)</td>
<td>ARCA biopharma, Inc.</td>
<td>beta-blocker and mild vasodilator</td>
<td>atrial fibrillation and chronic heart failure</td>
</tr>
<tr>
<td>BIA-51058</td>
<td>Bial - Portela &amp; Ca, S.A.</td>
<td>Antihypertensives</td>
<td>Heart failure</td>
</tr>
<tr>
<td>RLX030</td>
<td>Novartis</td>
<td>Targets relaxin receptor</td>
<td>Acute Heart Failure</td>
</tr>
<tr>
<td>Tekturna</td>
<td>Novartis</td>
<td>Renin inhibitor</td>
<td>Chronic Heart Failure</td>
</tr>
<tr>
<td>PB1046</td>
<td>PhaseBio Pharmaceuticals, Inc.</td>
<td>VPAC 2 selective Agonist</td>
<td>HF/Cardiomyopathy in DMD/BMD</td>
</tr>
<tr>
<td>SAR439152</td>
<td>Sanofi</td>
<td>Myosin Inhibitor</td>
<td>Hypertrophic Cardiomyopathy</td>
</tr>
<tr>
<td>Stemedyne</td>
<td>Stemedica Cell Technologies, Inc</td>
<td>MSC- allogeneic mesenchymal stem cells for ischemic tolerant properties</td>
<td>Chronic heart failure, acute myocardial infarction</td>
</tr>
<tr>
<td>C-Cure (Cardiopoiesis platform)</td>
<td>Celyad</td>
<td>produce new autologous heart muscle cells</td>
<td>Heart failure</td>
</tr>
<tr>
<td>MPC-150-IM</td>
<td>Mesoblast Limited (collab with Teva Pharmaceutical Industries)</td>
<td>150 million mesenchymal precursor cells (MPCs)</td>
<td>Advanced and end-stage chronic heart failure</td>
</tr>
<tr>
<td>MPC-25-IC</td>
<td>Mesoblast Limited</td>
<td>allogeneic cellular therapy of Mesenchymal precursor cells (MPCs) delivered by intracoronary infusion</td>
<td>Acute myocardial infarction</td>
</tr>
</tbody>
</table>

*Source: Company website showing drugs in pipeline* xxv, xxvi, xxvii, xxviii, xxix, xxx, xxxi, xxxii, xxxiii, xxxiv, xxxv, xxxvi, xxvii, xxxviii, xxxix
C. Supplier Power
D. Buyer Power
E. Degree of Rivalry

1. Multiple equal contributors- Currently, there is at least seven branded and/or generic drugs for heart failure/CVD in the market. These drugs are from the top pharmaceutical companies such as Daichii-Sankyo, Novartis, AstraZeneca, Sanofi, Boehringer Ingelheim, Pfizer and Merck. These pharma giants share the market space based on US and global sales and most of them have more cardiovascular drugs in the pipeline. A huge market in this space played between equivalent competitors makes this a highly competitive arena. Rivalry (as measured by Concentration Ratio, CR); percentage of market share owned by the four largest firms in this industry: The top players in this field are Novartis, Pfizer, Roche and Sanofi. Competing with these giants will be difficult and the best strategy seems to license our candidate drug to one of the interested companies. (Source: http://www.pmlive.com/top_pharma_list/global_revenues)

2. Sluggish growth within industry: FDA approval of new drugs has been slow and only a couple of drugs have seen the light of the day after Phase III trials. Recently approved drugs from Amgen, Novartis, Sanofi-Aventis are a few examples. However, Roche, GlaxoSmithKline and Eli Lilly suffered serious setbacks in late stages of CVD clinical trials, slowing the pace for development of new drugs.

3. Undifferentiated product: A number of drugs currently available in the market are Angiotensin II Receptor Blockers (ARBs). Some of these drugs have similar and potentially serious side-effects. Our proposed PKC-inhibitor is specific for PKC-IIβ and ε and thus the mechanism of action is highly selective for this new drug candidate, a highly differentiating factor form the current drug strategies. If this new therapy can succeed in reducing off target toxicity/side effects compared to current therapies, this may be a competitive advantage.

4. Switching costs: Branded drugs are accessible to well insured patients or patients who do not respond to generics. Since switching costs for going from one drug treatment strategy to another are high for the end user, this can be a major factor when determining pricing of the drug and the target market segment.

5. Strategic focus: Most CVD drug companies target huge populations of patients within the US and globally. Hence, the CVD market is considered highly profitable in terms of number of sales. It is of importance to note here that a number of blockbuster drugs are losing exclusive patents within the next few years and it will be beneficial for these companies to focus on combination therapies, and generating new IP to extend the life and market shares of their blockbuster drugs. Also, targeting specific pockets of global population with high effectivity of the drugs can be another strategy to maximize gains, minimize the numbers needed for huge clinical trials, and to reduce the time taken for FDA approval (by gaining potential fast-track approval).

6. Barriers to exit: High cost of drug development and clinical trials in CVD domain is a huge investment for pharmaceutical companies. A clinical trial failure or cessation of a drug program can cost the company billions of dollars. An example is Eli Lilly which recently stopped the trials of its drug Evacetrapib, which was projected to reach $632.7 million in sales in 2020. The company’s shares fell 7.1% after the announcement and Eli Lilly will take a charge of $90 million, or 5 cents a
share after taxes as R&D costs. This high-risk high-reward game in the CVD drug market makes this field highly competitive, with high barriers to exit and tremendous losses for failed attempts at new drugs.\textsuperscript{xl}

6. Regulatory Analysis

Hurdles

- **Indication** – The indication for use will need to be decided, particularly whether this should be a combination therapy (where it seems to fit best, but would also be more amenable to specific partners) and whether there is a subset of hypertensive patients who form the initial or full target population.

- **Endpoint** – The drug does not change an easily measurable parameter such as blood pressure and its purpose is to slow the progression to heart failure in hypertensive patients. As this is an extended phenomenon, timely assessment of the drug will require choosing a surrogate marker(s) such as thickening of the atrial wall or other blood markers indicative of heart disease or damage. The choice of surrogate marker may influence both the cost of the trial and the available clinical population.

- **Adherence** – Adherence to medication for a chronic disease is often problematic, especially when the disease does not cause immediate everyday effects. Adherence to a combination therapy for this type of disease, especially in the context of a clinical trial where some participants will be receiving a placebo, will likely need to addressed in the design and sizing of the clinical trial.

- **Safety** – Because the specific mode of action is not fully understood, because the impact is not a prevention of immediately imminent death, and because there have been previous issues with unintended effects of PKC inhibitors, it is likely that the expectation for demonstration of safety will be on the more stringent side.

Timeline

- **Preclinical animal models (6-12 months)**
- **Phase 0: pharmacokinetics (3-6 months)**
- **Phase 1: Safety screening (12 months)** – because the mode of action is not fully understood, and some previous issues occurred with PKC inhibitors, it is likely that this Phase would have to be completed before Phase 2 could be started rather than running parallel.
- **Phase 2: Efficacy (18-24 months)** – this will depend a great deal on the specific indication and the markers chosen; however as it will be a combination therapy and “failure” will simply result in standard-of-care treatment, it may be possible to make an argument for expanded access to the drug during Phase 2, especially if the Phase 1 safety data is convincing.
- **Phase 3: Confirmation (6-18 months)** – this will depend a great deal on the results of Phase 1 and 2, particularly whether there is any evidence of safety concerns. If safety data is good, it could be possible to make a strong argument for expanded access during Phase 3 if the indication being tested is as a combination therapy.
- **Total estimated timeline: 45-72 months**, with possible expanded access to the drug as early as 27-39 months if presented as a combination therapy and safety results are good.
7. Opportunity Assessment

According to statistics from 2008, around 1,000,000,000 people worldwide (including 80,000,000 in the US) suffer from hypertension, with significant population sizes in both first and third world countries.\textsuperscript{xiii} The lifetime risk of hypertensive patients in the US developing heart failure is 25-29% depending on age, while 70% of patients with chronic heart failure had antecedent hypertension.\textsuperscript{xii} The HF drug market is anticipated to grow at a compound average growth rate of 9.47% over the next five years, as the incident of HF continues to increase around the globe.\textsuperscript{xiii}

While the industry for cardiovascular disease has expanded in recent years to include biologics, it is still highly dominated by orally administered small molecule inhibitors (see table below). Few of the companies investigated for this report appeared to be currently pursuing antihypertensives, while all companies appear to have therapeutics that treat a diverse number of indications in their pipeline. With the number of heart failure patients expected to increase over the coming decades due to lifestyle choices and aging populations, the major pharmaceutical companies are continuing to seek novel molecular entities, mechanisms of actions, and combination therapies for patients with CVD including HF. Startups with therapeutics appear to be uncommon, although several such as CardioKinetix, CVRx, InterValve and more are working on medical devices for CVD.\textsuperscript{xliiv}

<table>
<thead>
<tr>
<th>Company</th>
<th>Stock Price</th>
<th>CVD Drug (Status)</th>
<th>Method &amp; Administration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>$88.53</td>
<td>Entresto (approved 2015)</td>
<td>-Blocks angiotensin II receptor -&gt; vasodilation and reduction of extracellular fluid via sodium excretion - Oral 2x daily</td>
<td>-FDA fast track designation - Reduced rate of death and hospitalizations compared to enalapril - Combination drug (1:1 ARB &amp; neprilysin inhibitor) - Cannot use in combination with ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>$212.11B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$5.93B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serelaxin</td>
<td></td>
<td></td>
<td>-Relaxin receptor agonist -&gt; vasodilation and reduction in fluid buildup - 48 h infusion during an acute HF (AHF) episode</td>
<td>-AHF (Phase III) and chronic HF (Phase II) - Breakthrough therapy designation - Reduction of the rate of worsening of heart failure - 6 kDa recombinant form of a naturally occurring hormone</td>
</tr>
<tr>
<td>Tekturna</td>
<td></td>
<td></td>
<td>-Lowers blood pressure by targeting an enzyme (renin) in the bloodstream that narrows blood vessels - Oral 1x daily</td>
<td>-Chronic heart failure - Not safe for diabetics or for patients taking ARBs or ACE inhibitors - Small molecule</td>
</tr>
<tr>
<td>(approved 2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company</td>
<td>Price</td>
<td>Medication</td>
<td>Mechanism</td>
<td>Phase</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Amgen        | $159.63    | Corlanor (approved 2015)                         | - Inhibits a pacemaker ion current in a dose-dependent manner to slow the heart rate  
                     | $120.41B   | - Oral 2x daily                                  | - Used in combination with beta blockers; decreases CV death rate and hospitalizations  
                     | $31.12B    |                                                      | - Small molecule                                                 |
|              |            | Repatha                                         | - mAb that inhibits PCSK9  
                     |            | - Monthly injection                              | - Phase III for the treatment of high cholesterol  
                     |            |                                                      | - Being developed in Japan                                      |
|              |            | AMG 899                                         | - Cholesteryl ester transfer protein inhibitor  
                     |            |                                                      | - In Phase II for dyslipidemia  
                     |            |                                                      | - Small molecule                                                |
|              |            | Omecamtiv mercabil                               | - Activates cardiac myosin  
                     |            |                                                      | - In Phase II for HF  
                     |            |                                                      | - Developed in collaboration with Cytokinetics  
                     |            |                                                      | - Small molecule                                                |
| Eli Lilly    | $79.36     | Evacetrapib                                      | - Cholesteryl ester transfer protein inhibitor  
                     | $84.04B    | - Oral                                          | - In Phase III for the prevention of CV events                          |
|              | $4.32B     | LY3015014                                        | - mAb that inhibits PCSK9  
                     |            | - infusion                                       | - In Phase II for hypercholesrolaemia  
                     |            |                                                      | - Not applicable for diabetics                                  |
| Bayer        | $120.75    | Rivaroxaban                                      | - Factor Xa inhibitor  
                     | $99.85B    | - Oral, 1x daily possible                        | - In Phase III for the prevention of major CV events and for CHF  
                     | $3.94B     |                                                      | - Improved in 2011 for prophylaxis of deep vein thrombosis and stroke prophylaxis  
                     |            |                                                      | - Small molecule                                                |
|              |            | Finerenone                                       | - Blocks mineralocorticoid receptors  
                     |            | - Potassium sparing diuretic                      | - In Phase III for CHF and diabetic kidney disease  
                     |            | - Oral                                           | - Nonsteroidal antimineralocorticoid small molecule               |
|              |            | Riociguat                                         | - Stimulates soluble guanylate cyclase independent of nitric oxide (NO)  
                     |            | - Acts in synergy with NO to produce anti-aggregatory, anti-proliferative and vasodilatory effects  
                     |            | - Oral                                           | - In Phase II for worsening CHF and Phase I for hypertension      |
8. Potential Partners

A. Company names and contact information if available

<table>
<thead>
<tr>
<th>Company</th>
<th>Contact person</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Erin Denny</td>
<td><a href="mailto:edenny@amgen.com">edenny@amgen.com</a></td>
</tr>
<tr>
<td>Bayer</td>
<td>Joerg Knaeblein</td>
<td><a href="mailto:joerg.knaeblein@bayer.com">joerg.knaeblein@bayer.com</a></td>
</tr>
<tr>
<td>Daichii-Sankyo</td>
<td>W. Kuziel</td>
<td><a href="mailto:wkuziel@dsi.com">wkuziel@dsi.com</a></td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>SC Wilkie</td>
<td><a href="mailto:scwilkie@lilly.com">scwilkie@lilly.com</a></td>
</tr>
<tr>
<td>Gilead</td>
<td>Jay Parrish</td>
<td><a href="mailto:Jay.Parrish@gilead.com">Jay.Parrish@gilead.com</a></td>
</tr>
<tr>
<td>Novartis*</td>
<td>Dr. Carlos Garay</td>
<td><a href="mailto:carlos.garay@novartis.com">carlos.garay@novartis.com</a></td>
</tr>
<tr>
<td>Novartis*</td>
<td>Edward Vander Veen</td>
<td><a href="mailto:edward.vanderveen@novartis.com">edward.vanderveen@novartis.com</a></td>
</tr>
<tr>
<td>Novartis*</td>
<td>Loretta Boyd</td>
<td><a href="mailto:loretta.boyd@novartis.com">loretta.boyd@novartis.com</a></td>
</tr>
<tr>
<td>Novartis*</td>
<td>Hui Liu</td>
<td><a href="mailto:hui.liu-phd@novartis.com">hui.liu-phd@novartis.com</a></td>
</tr>
<tr>
<td>Pfizer</td>
<td>Gregory Naeve</td>
<td><a href="mailto:Gregory.Naeve@pfizer.com">Gregory.Naeve@pfizer.com</a></td>
</tr>
<tr>
<td>Raptor</td>
<td>Christopher Starr</td>
<td><a href="mailto:cstarr@raptorpharma.com">cstarr@raptorpharma.com</a></td>
</tr>
<tr>
<td>Regeneron*</td>
<td>Michael Aberman</td>
<td><a href="mailto:michael.aberman@regneron.com">michael.aberman@regneron.com</a></td>
</tr>
</tbody>
</table>

*Have not reached out to them yet

B. Which company would be a good fit for the company? Companies that have a well-established Cardio-vascular drug (CVD) pipeline, have recently have some success in FDA approvals of their CVD drugs and run Phase II or Phase III clinical trials will be a good fit for our technology.

<table>
<thead>
<tr>
<th>Company</th>
<th># CVD drugs in pipeline</th>
<th>Responded to initial email?</th>
<th>Followed up with us?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>3</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Daichii-Sankyo</td>
<td>8</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Gilead</td>
<td>4</td>
<td>Yes</td>
<td>-</td>
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<tr>
<td>Bayer</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Regeneron</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pfizer</td>
<td>8</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: Company websites for drugs in pipeline

C. Start-up potential

Limited

Since this technology is at a pre-clinical stage, any startup venture will face considerable challenges for funding that can successfully support further research using non-primate animal models such as swine. Also, clinical trials for CVD treatments tend to involve thousands of patients and several hundred million dollars. These limitations make it difficult for a stand-alone start-up technology. However, a startup that can further take this technology to a stage (additional Pre-clinical data or Phase I trials) with positive results would make it lucrative for big players to step in and license this technology.
9. iFarm Teams Technology Summary and Recommendation

The first half of the quarter was spent deciding between two technologies. We proceeded by reading through the patents and recent literature related to the technologies, as well as by meeting with both inventors. Docket 06-137 was ultimately chosen based on interest on our behalf, ideas for how to move the technology forward, and a good rapport with the inventor. After this docket was chosen, our efforts focused on identifying and talking to KOLs, and summarizing the technology in the form of a progress report and a slide deck.

We feel that we have contributed to the license ability of this invention through the following: a) identifying that there is still a need for therapeutics that prevent the progression to heart failure in patients with chronic hypertension, b) identifying several companies which may be interested in this technology by asking for their input on what would make this technology most attractive and c) formulating plans to address the concerns (immunogenicity, lack of animal models, method of delivery, identifying best indication/target populations) of this technology in order to help it progress from its current preclinical stage.

With more time and resources to work on this project, we would develop a plan for more preclinical tests based on feedback from companies. For example, through interviews with companies we would hope to gain a better understanding of which animal models are most acceptable as hypertension models. Using this information, we would then identify an academic lab that has this model, and formalize an academic contract between that lab and the Mochly-Rosen group in order to complete the preclinical animal studies. However, we have not been able to interview any companies. Additionally, if we had more time we would like to delve deeper into the issue of delivery through literature searches and interviews in order to identify the absolute best indication of this therapeutic.

We recommend that the OTL remains in contact with the companies who have expressed interest and identify which animal models they would like to see the peptides tested in. Then we recommend that OTL utilizes Dr. Mochly-Rosen’s connections to set up mutually beneficial collaborations to finish the preclinical studies on efficacy and immunogenicity. This would require choosing an indication and finding a funding source, such as SPARK (at Stanford) or industry/VC-based funding. Lastly, we recommend that OTL considers promoting and/or licensing this technology to international companies located in countries with significant populations suffering from hypertension and the resources to bring this therapeutic to the clinic, such as China or Japan.

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βIIPKC inhibition reduces post-myocardial infarction induced end-stage heart failure in rats (unpublished).


xv http://www.fiercepharma.com/special-reports/avapro

xvi http://www.drugs.com/stats/top100/2012/sales


xxiii http://www.pmlive.com/pharma_news/lilly_drops_evacetrapib_on_failed_atherosclerosis_trial_840531

xxiv http://www.centerwatch.com/drug-information/fda-approved-drugs/

xxv http://www.trialdetails.com/detail/NCT02040233/Multiple-Dose-Study-in-Heart-Failure-of-BAY-1067197

xxvi http://www.amgenpipeline.com/pipeline/

xxvii http://adisininsight.springer.com/drugs/800015980


xxix http://adisininsight.springer.com/drugs/800033043

xxx https://clinicaltrials.gov/ct2/show/NCT02151994

xxxi http://www.arcabiopharma.com/science/


xxiv http://www.gilead.com/research/pipeline

xxv https://www.novartis.com/our-work/research-development/clinical-pipeline#ui:id=1=1

xxv http://www.pfizer.com/research/science_and_technology/product_pipeline