Celladon Corporation (CLDN)

LifeSci Capital Initiates Coverage of Celladon Corporation

LifeSci Investment Abstract

Celladon (NasdaqGM: CLDN) is a clinical-stage biopharmaceutical company developing MYDICAR, a gene therapy for the treatment of advanced heart failure. The Company is conducting a 250 patient Phase IIb trial of MYDICAR; enrollment is complete and data are expected in April 2015. The FDA has granted Breakthrough Therapy Designation to the MYDICAR program. The Company is conducting several additional proof-of-concept trials to expand the potential label for MYDICAR therapy to include additional patient groups.

Key Points of Discussion

- **Celladon is Developing MYDICAR Gene Therapy for Advanced Heart Failure.** Celladon is focused on developing therapies that modulate the activity of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2) enzymes through both small molecule and viral vector strategies. The Company's lead candidate, MYDICAR, is an adeno-associated virus (AAV)-mediated gene therapy in Phase IIb development for the treatment of heart failure (HF). The treatment is designed to introduce and overexpress SERCA2a protein in cardiac muscle cells via intracoronary infusion. Upregulation of SERCA2a expression in the heart has been shown to improve contractility and relaxation of the heart muscle. Clinical data from the Company's CUPID 1 Phase I/IIa clinical trial indicate effective delivery of SERCA2a into cardiomyocytes and improved ventricle function in HF models and patients.

- **MYDICAR is Intended to be Used in Combination with other HF Treatments.** MYDICAR is being developed for use in addition to the current standard of care for HF patients. Therefore, new potential entrants into the HF market such as Novartis's (NVS) LCZ969 would not affect the market potential for MYDICAR.

- **Phase I/II Clinical Trial Data Indicated Improvement in Perfusion.** Results from the CUPID 1 clinical trial indicate that high-dose MYDICAR delivered by intracoronary infusion may improve patient symptoms as well as reduce clinical events and time to hospitalizations. If this effect is confirmed in CUPID 2, then the cost-savings for hospitals and payers could make this therapy a very attractive option. This would increase both market penetration and eligible patient population as MYDICAR could be considered in less advanced disease as a means of slowing the progression of heart failure.

Expected Upcoming Milestones

- Q4 2014 – Initiation of Phase I/II trial of MYDICAR with plasmapheresis for HF patients with neutralizing antibodies.
- April 2015 - Data expected from CUPID 2 trial evaluating MYDICAR in systolic HF.
- 2015 – Expected meetings with FDA and EMA to discuss potential expedited approval pathway
- 2015 – Top-line data expected from Phase I/II MYDICAR in AV-Fistula maturation failure and Phase I/II MYDICAR with plasmapheresis trials

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Market Data

Price	$9.88
Market Cap (M)	$228
EV (M)	$136
Shares Outstanding (M)	23.1
Fully Diluted Shares (M)	26.1
Avg Daily Vol	161,522
52-week Range:	$7.45 - $17.16
Cash (M)	$102.3
Net Cash/Share	$3.98
Annualized Cash Burn (M)	$26.1
Years of Cash Left	4.0
Debt (M)	$10.0
Short Interest (M)	0.22
Short Interest (% of Float)	2.1%

Financials

FY Dec		2013A	2014A	2015A
EPS	Q1	(3.99)A	(0.60)A	NA
	Q2	(8.98)A	(0.38)A	NA
	Q3	(6.17)A	NA	NA
	Q4	(7.96)A	NA	NA
	FY	(27.10)A	NA	NA

- **Enrollment Complete in CUPID 2 Phase IIb Trial; Data Expected in April 2015.** Celladon announced on March 5, 2014 that it had completed enrollment for its CUPID 2 Phase IIb clinical trial. The study, titled Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease, or CUPID 2, is a randomized, double-blind, placebo-controlled study in 250 advanced HF patients testing the efficacy of a high-dose of MYDICAR compared to placebo. In this study, HF patients receive either a single MYDICAR dose of 1 x 10^{13} AAV particles via epicardial coronary artery infusion or placebo and are observed for 12 months with a 2 year follow-up.

  The primary endpoint of this study is time to recurrent HF-related hospitalization, which was accepted by the FDA in 2012 in a Special Protocol Assessment as an acceptable endpoint for pivotal trials. Secondary endpoints include time-to-first terminal event, symptoms, exercise capacity, quality of life, and safety. Additionally, based on scientific advice that the Company received from the European Medicines Agency (EMA) in November 2013, MYDICAR may be eligible for an accelerated approval pathway. If the treatment demonstrates significant efficacy results without adverse effects, the EMA may accept a regulatory filing without the need for a Phase III clinical program. On April 10, 2014, the Company announced that the FDA has granted Breakthrough Therapy Designation to the MYDICAR development program. This designation, for innovative drugs that threat conditions with high unmet need, has the potential to greatly accelerate the regulatory process. Top-line data from this study are expected in the second quarter of 2015.

- **Successful CUPID 1 Phase I/IIa Trial Supports Development of MYDICAR.** Celladon reported positive results from its CUPID 1 Phase I/IIa clinical trial testing the safety and effectiveness of MYDICAR in advanced systolic HF patients. Phase I of this study was a multi-center, open-label, sequential dose-escalation study examining intracoronary infusion of MYDICAR in 9 advanced HF patients already receiving optimal medical and device therapy. These patients were dosed in 3 cohorts, which received either low-dose (1.4 x 10^{11}), mid-dose (6 x 10^{11}), or high-dose (1 x 10^{12}) of AAV1/SERCA2a viral particles. There were also 3 advanced HF patients that were treated with a placebo. Phase I of the CUPID 1 trial demonstrated a favorable safety profile in 12 advanced HF patients across 3 escalating doses and showed improvements in a range of efficacy endpoints, such as functional six-minute walk test, oxygen consumption, quality of life questionnaire, biomarker activity, and left ventricular size and function. These positive results were used as a lead-in to the Phase IIa portion of the CUPID 1 trial.

  The Phase II portion was a randomized, double-blind, placebo-controlled, dose-ranging clinical trial of MYDICAR in systolic HF patients. Thirty-nine advanced HF patients received an intracoronary infusion of placebo, low-dose, mid-dose, or high-dose MYDICAR on top of their existing, optimized heart failure therapy. These patients were monitored for 12 months with an additional 2 years of telephone follow-ups, using the same efficacy criteria to that used in Phase I. Patients receiving the high-dose MYDICAR treatment exhibited lower levels of biomarker signatures of heart failure, had higher maximum oxygen concentrations (VO_2max), and had a lower end-systolic volume than that of controls. Most importantly, after three years of follow-up, there was a significant 82% reduction in the frequency of non-terminal events, as measured by hospitalizations and myocardial infarctions, for MYDICAR treated patients compared to placebo ($p=0.048$). No safety concerns were noted during the three year follow up period for patients who received MYDICAR.

- **Heart Failure Represents a Significant Market Opportunity.** According to the American Heart Association, there are about 6 million people in the United States and over 23 million people worldwide who suffer from heart failure (HF). We estimate that the target market for MYDICAR as currently indicated is around 360,000 patients in the US, with another 900,000 in Europe. HF is a severely debilitating condition, whereby the pumping of the heart cannot keep up with demands of the body that comes to affect all aspects of a patient's life.

Present therapies only aim to slow the progression of the disease, particularly during the early stages. This leaves an enormous opportunity for any therapy that can significantly reverse the disease course and reduce the number of cardiac events. If data from pivotal Phase III clinical trials supports approval, MYDICAR is positioned to potentially become the first disease-modifying therapy for advanced HF to enter the market. Such a treatment would not only greatly improve patients' lives, it has the potential to dramatically reduce costs associated with HF. The resulting pharmacoeconomic benefits would also further drive adoption of the product. Successful development of an efficacious disease-modifying treatment for advanced HF would likely be in high demand and drive significant value for Celladon.

- **Celladon Planning MYDICAR Trial with Plasmapheresis.** Roughly 60% of HF patients have been excluded from MYDICAR clinical trials to date because they possess antibodies against AAV in their blood. Since AAV is a naturally-occurring virus, many people are not eligible for MYDICAR treatment. Celladon plans to conduct a pilot study in 24 HF patients possessing neutralizing antibodies against AAV to determine whether a plasma exchange procedure known as plasmapheresis can effectively filter these antibodies out of circulation just prior to MYDICAR administration. Celladon expects to initiate this Phase I/II trial in the fourth quarter of 2014 with top-line data expected in 2015. Successful results in this study would greatly expand the indicated patient population potentially eligible for MYDICAR therapy.

- **Celladon Initiated Trial Evaluating MYDICAR in LVAD Patients.** MYDICAR is an adeno-associated virus (AAV)-mediated gene therapy designed to introduce and overexpress SERCA2a protein in cardiac muscle cells. The CUPID 1 Phase I/IIa trial for MYDICAR as an HF treatment excluded HF patients that had previously received a left ventricular assist device (LVAD) implant. On August 11th, Celladon announced the initiation of a follow-up Phase I/II trial to establish the safety of MYDICAR use in this patient population. This study is a step towards fulfilling the Company's goal of expanding the scope of HF patients eligible for MYDICAR use. The trial is partially funded by the British Heart Foundation and sponsored by the Imperial College London.

- **Additional Indication for MYDICAR Targeting an Un-met Need in Dialysis Patients.** Over 500,000 Americans have end-stage renal disease requiring dialysis and approximately 100,000 arterio-venous fistulae (AVF) are placed yearly. An AVF, which is a surgically created connection between an artery and a vein, is provides access in the arm for hemodialysis. The clinical problem that has resulted from this practice is that following surgery to create the fistula approximately 50% fail to mature to a usable state for hemodialysis. Furthermore, as many as 25% of hospital admissions in the dialysis population have been attributed to vascular access problems, including fistula malfunction and thrombosis. The biology of SERCA2a in both vascular smooth muscle and endothelial cells provides a unique opportunity to positively impact the pathological processes driving fistula failure. Celladon plans to initiate a Phase IIa trial to evaluate MYDICAR in 100 end-stage renal failure patients with data expected in 2015.

- **Option Agreement with Servier for Small Molecule SERCA2b Inhibitors for Metabolic Diseases.** On February 24, 2014, Celladon announced an option agreement with Servier, granting exclusive outside-the-US licensing rights to use its small molecule SERCA2b modulators in future treatments of diabetes and metabolic disorders. Celladon will receive upfront, research, and milestone payments, in addition to royalties on sales, if the option is exercised by Servier. Both Servier and Celladon will jointly support the discovery effort. Additionally, Servier will handle all development costs associated with non-US regulatory approval and commercialization, while Celladon will retain US rights to commercialize any compound or lead candidate produced through this collaboration.

Financial Outlook

Initial Public Offering and Financing Activity. On January 29, 2014, Celladon Corporation announced the pricing of its initial public offering of stock, and the Company began trading on the NASDAQ Global Market on February 4. Celladon sold 5,500,000 shares of common stock at an offering price of $8.00 to bring in gross proceeds of $44 million. The Company later announced that the underwriter had exercised its overallotment option of an additional 825,000 shares. With this option, total gross proceeds to Celladon were $50.6 million.

On August 1st, Celladon announced the closing of a credit facility agreement with Hercules Technology Growth Capital (NYSE: HTGC) and its affiliates. The Company has drawn $10 million from the first tranche of the credit facility and is eligible to draw another $15 million prior to May 31, 2015 if CUPID 2 data supports continued development or registration of MYDICAR.

On August 18th, Celladon announced the closing of a public offering to sell 4,600,000 shares of common stock, which includes the underwriter's option. The shares were offered at a price of $9.50 per share to yield gross proceeds of $43.7 million.

Recent Financials. On August 7th, Celladon reported financial results for the second quarter of 2014. The Company reported total operating expenses of $7.0 million for the quarter, compared to $5.0 million for the same period of 2013. This reflected increases both in research and development costs from $4.2 million to $5.0 million and general and administrative expenses from $0.8 million to $2.0 million. The Company had a consolidated net loss of $7 million for the quarter compared to a $4.9 million loss in the same period in 2013. As of June 30, 2014, Celladon had cash and cash equivalents of $51.2 million on hand. After drawing the first tranche of debt financing from the credit facility and the closing of the August financing, Celladon has roughly $100 million cash and cash equivalents on hand.

Expected Upcoming Milestones

- H2 2014 - File IND for AV Fistula program.
- Q4 2014 – Initiation of Phase I/II trial of MYDICAR with plasmapheresis for HF patients with neutralizing antibodies.
- April 2015 - Top-line data expected from CUPID 2 trial evaluating MYDICAR in systolic heart failure.
- 2015 – Expected meetings with FDA and EMA to discuss potential expedited approval pathway for MYDICAR
- 2015 – Initiate diastolic heart failure trial, if supported by pre-clinical data
- 2015 – Top-line data expected from Phase I/II MYDICAR in AV-Fistula maturation failure
- 2015 – Top-line data expected from Phase I/II MYDICAR with plasmapheresis trial
- 2016 – Expected completion of MYDICAR with LVAD trial
- 2016 – Data expected from investigator-initiated AGENT-HF study to assess whether HF-induced remodeling of the heart reverses after MYDICAR treatment.

Company Description

Celladon is a clinical-stage biotechnology company developing MYDICAR gene therapy for the treatment of advanced heart failure. The Company is investigating small molecule and gene therapy vectors to target sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2) enzymes. These enzymes are involved in the regulation of intracellular levels of the important signaling ion calcium. Calcium deficiency is associated with many disease states, including heart failure, neurodegenerative diseases, and diabetes. SERCA2a, in particular, is associated with the progression of heart failure. The Company's lead development candidate is a gene therapy named MYDICAR that can deliver a replacement SERCA2a gene into heart muscle cells with the goal of correcting the SERCA2a protein deficiency that exists in advanced heart failure patients. Replacement of the faulty enzyme has the potential to improve cardiac function. Celladon is currently testing MYDICAR for the treatment of advanced heart failure in a randomized, placebo-controlled Phase IIb clinical trial known as CUPID 2. Results from the trial are expected in the second quarter of 2015.

In addition to treating advanced heart failure, Celladon plans to develop MYDICAR for additional indications such as diastolic heart failure, blood vessel disorders including arteriovenous (AV)-fistula maturation failure and pulmonary arterial hypertension, and advanced heart failure with implanted left ventricular assist device (LVAD). The Company has also developed first-in-class small molecule therapies to modulate the activity of the SERCA2b enzyme, which may correct calcium imbalances that may underlie a wide range of systemic disease. The SERCA2b modulators have shown disease-modifying potential in preclinical studies.

MYDICAR: SERCA2a Gene Therapy for Severe Heart Failure

MYDICAR, Celladon's lead candidate, is a gene therapy that uses proprietary viral vector technology to introduce healthy replacement copies of the SERCA2a gene into heart muscle cells to compensate for a pronounced decrease in SERCA expression and/or function that manifests in heart failure.[1] The goal of MYDICAR gene therapy is to improve the clinical symptoms of heart failure by inducing heart cells to increase production of the SERCA2a protein. MYDICAR is delivered by an adeno-associated virus and carries a replacement copy of the SERCA2a gene to increase SERCA2a levels in cardiac myocytes. MYDICAR is currently being tested in a Phase IIb trial known as CUPID 2. The primary efficacy endpoint for the trial is time to recurrent cardiovascular events. Patient enrollment in this trial is complete and data are expected in the second quarter of 2015.

Sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) enzymes are proteins that are present in all muscle cells and function as a pump that modulates intracellular calcium levels. Calcium signaling is an important modulator across the human body, and within heart muscle cells its release and uptake is a critical component in the cycling of muscle contraction and relaxation. Most of the calcium that induces contraction of the heart is released from the sarcoplasmic reticulum. Therefore, regulation of the calcium content within the sarcoplasmic reticulum is extremely important. This is particularly true since the amplitude of the calcium transient, which is what ultimately activates muscle contraction, is mathematically related to the calcium concentration within the sarcoplasmic reticulum.[2]

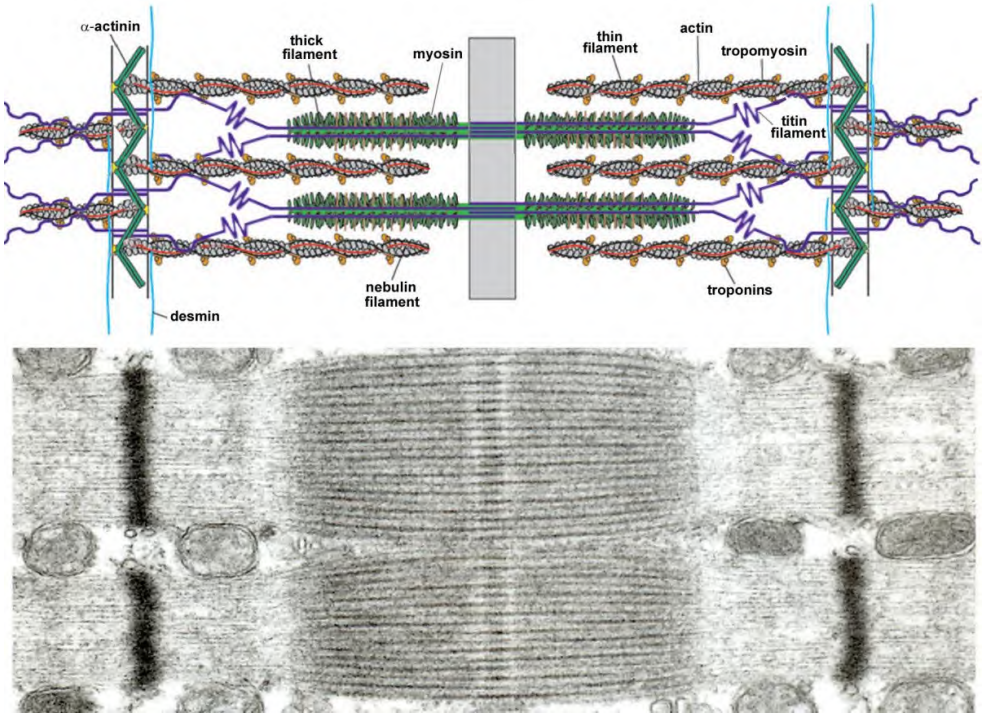
[1] Arai, M, et al., 1993. Alterations in sarcoplasmic reticulum gene expression in human heart failure: a possible mechanism for alterations in systolic and diastolic properties of the failing myocardium. *Circulation Research*, 72, pp463-469.
[2] Díaz, ME, et al., 2005. The control of sarcoplasmic reticulum Ca content in cardiac muscle, *Cell Calcium*, 38, pp391-396.

In advanced heart failure, disturbances to the normal ups and downs of intracellular calcium, resulting from decreased SERCA activity, diminish the contractile force and efficacy of the heart in pumping blood systemically. For patients, this translates into heart muscle that is progressively less able to keep up with the body's physiological demands. In human ventricular myocytes isolated from patients with end-stage heart failure, overexpression of SERCA2a enhanced contraction and relaxation velocities.[3] Since these experiments in 1999, there has been increasing attention and excitement over the potential for targeting SERCA2a to improve the clinical features of heart failure.

Physiology of Muscle Cells

The human body produces movement through the contraction of muscle fibers, whereby electrical impulses are converted into mechanical force in a physiological process known as excitation-contraction (E-C) coupling. While there are several different types of muscle tissue in the human body, they all function in a similar manner. The contractile force of a muscle is generated by the interaction between thick filaments of myosin and thin filaments of actin. In striated muscle, which makes up both skeletal and cardiac muscle tissue, chains of myosin and actin are repeated in a regular arrangement known as the sarcomere, which is the basic unit that is repeated throughout muscle fibers. The structure of the sarcomere is illustrated in **Figure 1**, showing a repeating arrangement of overlapping thin and thick filaments. The image shows the repeating sarcomeres within an actual muscle fiber.

Figure 1. Sarcomere – the Basic Unit of a Muscle



Source: Ottenheijm et al., 2008[4]

[3] del Monte, F, 1999. Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation*, 100, pp2308–2311.
[4] Ottenheijm et al., 2008. Diaphragm adaptations in patients with COPD. *Respiratory Research*, 9:12, pp12-25.

Myosins are a family of ATP-dependent motor proteins that are nearly ubiquitous across eukaryotic cells. There is a vast family of isoforms, many with unique designs adapted to cell-specific functions, although their binding domains are highly conserved across species.[5] Myosins have a head domain that contains an actin binding site and there are many myosin proteins on each thick filament. A contraction is generated by a repeated cycle of binding and releasing between thick and thin filaments, whereby the myosin heads essentially walk or slide down the thin filaments. This sequence is made possible by and continues for the duration of time that calcium is present. Calcium produces a conformational change that exposes the thin filament binding sites, enabling the myosin head to bind to form what is known as a cross-bridge between myosin and actin filaments. In the process of binding, the myosin head flexes to move along the thin filament. Adenosine triphosphate (ATP) binding and hydrolysis enables the myosin head to release from the thin filament and begin the cycle again. The result is a force that contracts the sarcomere. Summed over many muscle cells, enough force is generated to fulfill vital bodily functions. At the end of a contraction, the spike in intracellular calcium, known as a calcium transient, subsides as proteins transport calcium back into storage.

Intracellular Calcium and SERCA Proteins

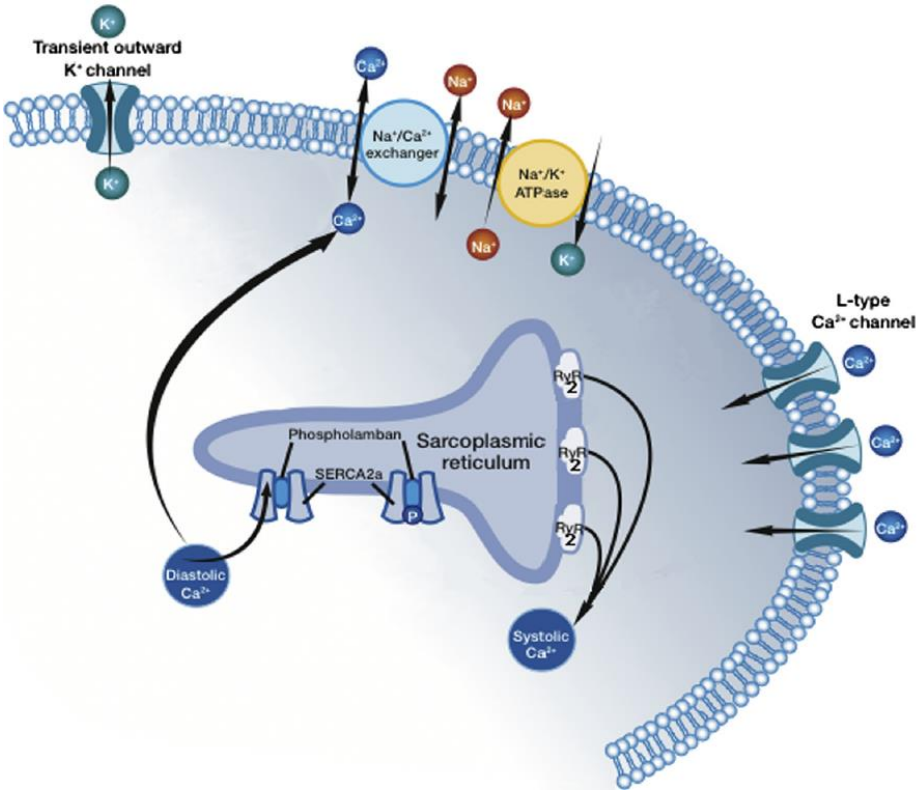
Large stores of calcium are kept in muscle cells in an organelle called the sarcoplasmic reticulum (SR). When muscle cells are activated these stores of calcium are released, producing a sharp spike in the intracellular calcium concentration that triggers contraction of the sarcomere.[6] Calcium release from the SR is mediated by ryanodine receptors (RyRs), triggered by depolarization in skeletal myocytes and Ca^{2+} influx in cardiac myocytes. At the end of a contraction, calcium is returned into the SR by SERCA proteins. These proteins are embedded in the SR membrane and use energy released from ATP hydrolysis to transport calcium ions across the SR membrane and back into storage.

The contraction of muscle tissue is the result of precisely timed electrical and chemical signaling and this takes slightly different forms in different types of muscle. Contraction of cardiac muscle is generated by the sinoatrial (SA) node, which operates as the primary pacemaker of the heart. From the SA node, electrical activity spreads in a precisely coordinated manner to ensure the correct ordering and timing of contractions. There are extensive gap junctions in myocytes, which electrically couple neighboring cells and ensures that they activate together. As this wave of electrical activity spreads, myocytes undergo a change in membrane potential that activates L-type calcium channels, leading to an influx of calcium into the cell. This results in calcium-induced calcium release (CICR), whereby the initial influx of calcium ions activates ryanodine receptors on the SR membrane, resulting in an amplified surge in intracellular calcium levels. Thus, SERCA proteins act to reverse the activity of ryanodine receptors and prepare myocytes for the start of the next cycle. This process of Ca^{2+} influx, release, and recycling across systolic and diastolic phases of heart contraction is illustrated in **Figure 2**.

[5] Cope, MTV, 1996. Conservation within the myosin motor domain: implications for structure and function. *Structure*, 4, pp. 969-987.

[6] Bers, D, 2002. Cardiac excitation-contraction coupling. *Nature,* 415, pp198-205.

Figure 2. Calcium Cycling and the Role of SERCA2a in Cardiomyocytes



Source: Greenberg et al., 2014

SERCA2a and Heart Failure

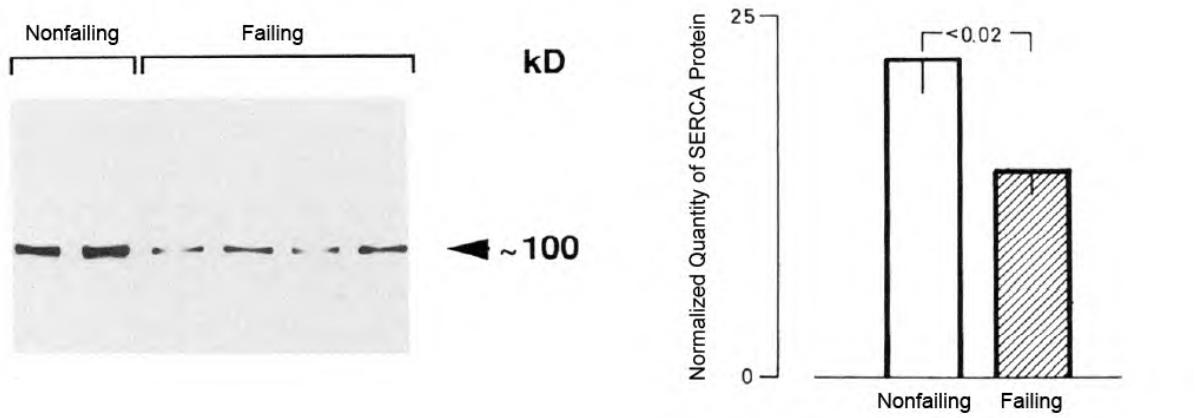
Heart failure is a complex condition resulting from structural changes in the muscle tissue of the heart that diminishes its capacity to pump and fill with blood. There are a variety of characteristics that enable the heart to efficiently pump blood. These include

- A delay between atrial and ventricular contraction allows the atria to fully empty prior to ventricular contraction.
- Coordinated contraction of ventricular myocytes maximizes systolic pressure, forcing blood through the circulatory system.
- Absence of tetany, or persistent activation, since the heart necessarily must relax in order to completely fill up again.

At the cellular level, advanced heart failure is characterized by impaired calcium signaling in cardiac myocytes and has been linked to a decrease in expression and activity of SERCA2a. This has been observed in animal models of myocardial hypertrophy and failing human hearts at the mRNA and protein level.[7,8]

Figure 3 shows a western blot gel illustrating a normalized quantification of the amount of SERCA2a found in failing and non-failing hearts, indicating a reduction in SERCA2a expression in failing hearts. A western blot analysis is a laboratory procedure used to separate proteins isolated from a sample according to molecular weight. In this study, samples from failing hearts showed a weak band compared to non-failing heart samples at ~100 kD, corresponding to SERCA and indicative of a decrease in SERCA protein expressed in the myocardium of failing hearts. Quantifying the amount of protein revealed a significant difference in the amount of SERCA protein present in failing and non-failing heart muscle ($p<0.02$).

Figure 3. Decreased SERCA Protein Expression in Heart Failure and Control Patients



Source: Hasenfuss et al., 1994

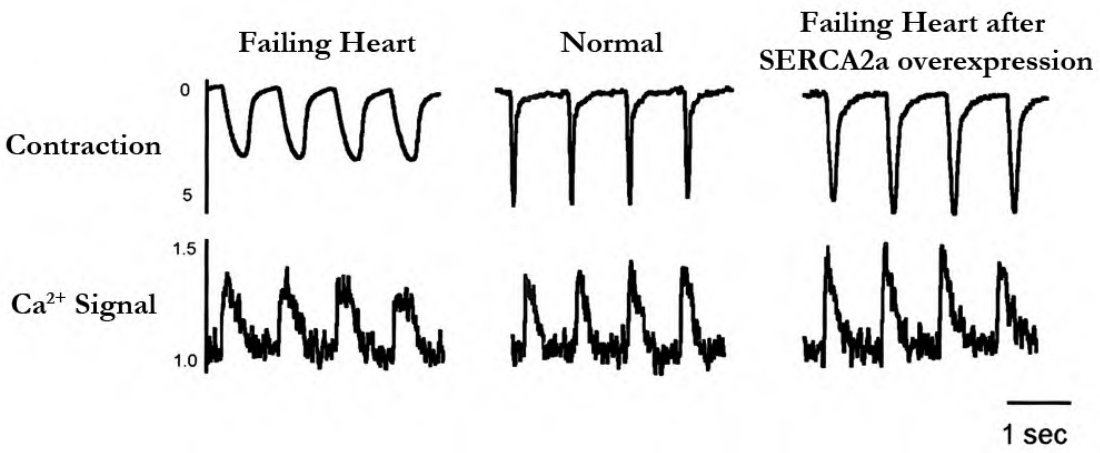
Since the 1980s, animal studies have demonstrated an altered time course in the systolic calcium transient.[9] However, in 1994, it was demonstrated that the degree of change in heart contractile function correlated with the loss of SERCA proteins.[10] Further investigation has shown that these low levels of SERCA impair relaxation of the heart by slowing the decay of the calcium transient. Since the role of SERCA is calcium reuptake, it makes sense that a SERCA deficiency would lead to a slower rate of calcium clearing. The consequence of this is a longer active period for the myocytes and a more gradual relaxation. As a consequence of the decreased calcium content in the SR, also resulting from poor reuptake, the amplitude of the calcium transient and thus the contraction become smaller.

[7] Mercadier, JJ, et al., 1990. Altered sarcoplasmic reticulum Ca2+-ATPase gene expression in the human ventricle during end-stage heart failure. Journal of Clinical Investigation, 85, pp305-309.
[8] de la Bastie, D, et al., 1990. Function of the sarcoplasmic reticulum and expression of its Ca^{2+} ATPase gene in pressure overload-induced cardiac hypertrophy in the rat. *Circulation Research*, 66, pp554-564.
[9] Gwathmey, GK, Morgan JP, 1985. Altered calcium handling in experimental pressure overload hypertrophy in the ferret. *Circulation Research*, 57, pp836–843.
[10] Hasenfuss, G, et al., 1994. Relation between myocardial function and expression of sarcoplasmic reticulum Ca2+-ATPase in failing and nonfailing human myocardium. *Circulation Research*, 75, pp434-442.

Preclinical studies have been conducted investigating the reintroduction of SERCA2a into cardiac cells. An i*n vitro* study demonstrated improved cardiomyocyte function, both in the amplitude of the calcium transient and contractile force generated. For this study, failing human ventricular tissue was obtained from 10 explanted hearts and 3 healthy donor hearts. Two different gene delivery adenoviruses were used, one encoding green fluorescent protein (GFP) to label the cells and another encoding the SERCA2a gene. Both vectors are under the control of the active cytomegalovirus (CMV) promoter to drive high levels of protein expression. After transfection with these viruses, cardiomyocytes were incubated in a solution containing a calcium indicator, Fura-2, whose fluorescence rises proportionally with rises in intracellular calcium levels. Myocytes were then excited with a 0.2 Hz biphasic pulse at 50% above threshold and measurements on the contraction and changes in fluorescence were recorded.

The traces in **Figure 4** represent the three conditions studied: normal, failing heart, and failing heart after SERCA2a overexpression. Relative to the normal heart tissue, the failing heart had a reduced total contractile force and prolonged relaxation time that was visible on both contractile force and $Ca2^{+}$ signal traces. Overexpression of SERCA2a via adenovirus-mediated delivery of the transgene under regulation by a strong, constitutive promoter generated faster contractile velocities than untreated failing heart tissue. In addition, the diastolic intracellular Ca^{2+} concentration decreased in SERCA2a-treated failing heart tissue to 270 ± 26 nmol/L from 347 ± 30 nmol/L ($p<0.005$), and systolic intracellular Ca^{2+} concentration rose to 601±38 nmol/L from 508±25 nmol/L ($p<0.05$). This experiment provides clear preclinical evidence supporting SERCA2a gene therapy as an important therapeutic target.

Figure 4. Reintroduction of SERCA2a *in vitro* Improves Contraction and Calcium Cycling



Source: del Monte et al., 1999[11]

Over the last decade, calcium dysregulation has been recognized as a hallmark of heart failure and has become an important therapeutic target. Regardless of the initial cause of heart failure, the disease progression eventually leads to a SERCA2a deficiency. Since the underlying problem is a protein deficiency, it is very difficult to treat the condition with standard pharmacological interventions. Effective treatment requires an increase in SERCA2a protein levels, and modifications to the genetic expression of the cell are necessary to accomplish this goal.

[11] del Monte, F, 1999. Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation*, 100, pp2308–2311.

Gene Therapy

Gene therapy has been around for decades but researchers in the field are only now gaining the level of sophistication needed to successfully and safely implement this technology in a clinical setting. While some diseases can be treated with drugs, in other cases this is simply not possible, particularly when the underlying cause of a disease is the lack of a protein. Excessive amounts of a protein can be targeted with conventional drugs, but adding in a missing enzyme requires a different approach. Gene therapy is the process of introducing DNA into a target group of cells to alter an underlying genetic anomaly, whether inherited or acquired. With gene therapy, a patient can receive replacement copies of missing or defective genes, genes that may aid in healing and growth, or genes that aid in the destruction of cancer cells. This field represents an enormous untapped potential to revolutionize treatment for a vast array of diseases.

Viral Vector Delivery. Gene therapy is primarily accomplished through the use of modified viruses. In general, viruses bind to their host and inject their genetic material into the host cell, making them a natural choice for delivering specifically-tailored genes. Once injected, the viral DNA instructs the cell to make proteins, essentially appropriating the cellular machinery for protein synthesis to manufacture whatever the virus encodes. In natural viruses, the viral DNA is encoding the proteins necessary to make more viruses so that it can continue to spread. However, with recombinant DNA technology, scientists can delete viral genes and insert new genes, using the virus as a delivery mechanism for the therapeutic gene. Importantly, since the virus no longer has viral genes within its genome, it is unable to make more viruses and is known as replication-deficient.

There are a staggering number of different types of viruses, some better suited than others for use in gene therapy. There is no 'one-size-fits–all' approach, since different viruses preferentially target certain cells, have different expression strengths, undergo different cellular processing, and have wildly different pathogenic potentials. As a result, a great deal of research has been necessary to uncover and correctly match parameters for optimal transfection of the target tissue. There are three main types of viruses commonly used in gene therapy: adenoviruses, retroviruses, and adeno-associated viruses. The parvovirus adeno-associated virus (AAV) and lentivirus, a form of retrovirus, are emerging as the preferred viruses used in gene therapy trials. AAV is the virus of choice for non-dividing cells such as cardiomyocytes, while lentiviral vectors are best suited for rapidly dividing cells such as hematopoietic stem cells. The properties of the viral vectors used for gene therapy are summarized in **Figure 5**. Roughly 80-90% of adults have been exposed to wildtype AAV and it has not been found to produce symptoms or disease and evokes a limited immune response.

Figure 5. Comparison of Viral Vectors

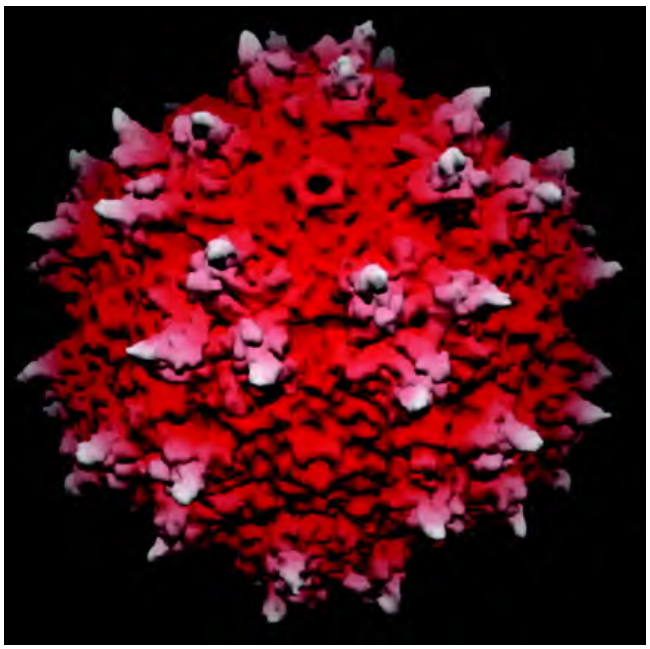
	Retrovirus	Adenovirus	AAV	Lentivirus
Genetic Material	RNA	Double-stranded DNA	Single-stranded DNA	RNA
Insertion Capacity	8 kb	30 kb	< 5 kb	10 kb
Gene Expression	Stable	Transient	Stable	Stable
Integrates into Genome	Yes	No	No	Yes
Risk of Adverse Effects	Moderate	High	Low	Moderate

Source: LifeSci Capital

Adeno-associated virus is a small, nonenveloped virus that packages a linear single-stranded DNA genome of about 4,700 base pairs. The virus is classified within the genus *Dependovirus*, since productive infection of a host cell can only occur in the presence of a helper virus, either adenovirus or herpes virus.[12] Lacking this, AAV is unable to replicate further. AAV exists as a variety of serotypes, which are defined by the expression of certain capsid, or coat, proteins on the surface of the virus. Since the surface proteins determine interactions with glycoproteins on the surface of target cells, these coat proteins play an essential role in defining the AAV cell affinities. **Figure 6** depicts a surface rendering of an AAV particle, revealing the presence of these coat proteins on the virus surface. Recent advances in molecular biology have allowed for the design of recombinant hybrid AAVs. Most often, these recombinant AAVs contain a pairing of the ITRs of AAV2 with the coat proteins of another serotype, thereby altering the virus's cell affinity.

[12] Daya, S, et al., 2008. Gene Therapy Using Adeno-Associated Virus Vectors. *Clinical Microbiology Reviews*, 21, pp583-593.

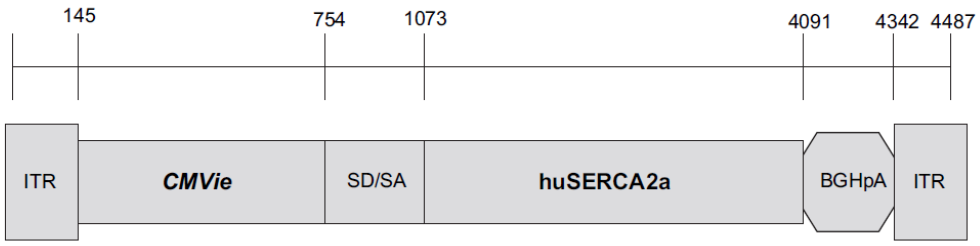
Figure 6. Surface Rendering of Adeno-Associated Virus Particle



Source: Xie et al., 2002[13]

Gene Therapy for Heart Failure. In the case of heart failure, there is a known gene-based target in cardiac myocytes, SERCA2a. Upregulation of this enzyme has been shown in a preclinical setting to improve cardiac function, and so a gene therapy strategy that can elevate the expression of this protein may be effective in improving systolic heart function. Celladon has demonstrated proof of this concept with their promising CUPID 1 Phase I/IIa trial results. Celladon has designed an AAV viral vector intended to drive expression of the human SERCA2a gene (huSERCA2a), the construct of which is shown in **Figure 7**.

Figure 7. MYDICAR Viral DNA Construct



Source: Greenberg et al., 2014

The construct contains the cytomegalovirus immediate early enhancer/promoter (CMVie), which is a very active promoter utilized in molecular biology to generate high levels of protein expression. The promoter sits directly

[13] Xie, Q, et al., 2002. The atomic structure of adeno-associated virus (AAV-2), a vector for human gene therapy. *Proceedings of the National Academy of Sciences*, 99:16, pp10405-10410.

upstream of the huSERCA2a transgene and regulates its transcription into messenger mRNA for protein synthesis. The flanking inverted terminal repeats (ITRs) from the AAV2 serotype are necessary genetic elements required for the proper formation and packaging of AAV viral particles. The ITRs are the only genetic element required to *in cis* next to the therapeutic transgene.

Safety Profile

AAV vectors have been extensively studied in hundreds of patients and have shown a consistently strong safety profile. AAV is not known to cause human disease, despite broad exposure (80 – 90%) to wild-type AAV, indicating a low likelihood of risk to patients from the therapy. To date, the overall safety of AAV has been demonstrated in more than 400 subjects enrolled in clinical trials with up to 8 years of follow-up.[14] The lack of viral genes makes an immune response less likely, allowing it to persist and continue to express the introduced gene. AAV does not randomly insert genes into the genome, so there is no risk of insertional mutagenesis with this vector. Furthermore, the AAV1 serotype has a number of advantages for the treatment of heart failure; after infusion into the coronary arteries, it passes through the blood vessels and through the interstitial space providing broad distribution to the heart.

In CUPID 1, MYDICAR demonstrated a favorable safety profile during the 12 month observation period, as well as during the subsequent two year follow-up period. There was no increase in adverse events, disease-related events, or laboratory abnormalities found in any MYDICAR-treated subjects as compared to placebo. There was also no indication in this study of any unexpected illness associated with MYDICAR administration. No changes were found with cardiac enzymes, serum chemistries and hematology, liver or kidney function, or heart rate in MYDICAR-treated patients. In addition, electrocardiograms did not show any significant changes in rhythm, intervals, or QRS morphology.

Some pre-existing human immunities to certain types of AAV do exist, so patients' immune responses have to be monitored. In MYDICAR clinical trials to date, patients have been screened for preexisting antibodies that would neutralize the AAV particles and have been excluded from the study. Celladon's CELL-005 trial, set to begin in 2014, will test the safety of delivering MYDICAR in patients who possess neutralizing antibodies to AAV particles.

Glybera Offers Validation for Adeno-Associated Viruses. It is worth noting that the EMA has already approved use of an AAV1 vector, uniQure's *Glybera* (alipogene tiparvovec), a gene therapy treatment to restore lipoprotein lipase (LPL) enzyme activity in adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) confirmed by genetic testing, and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. Since MYDICAR uses a vector that is used in an approved product, the pathogenic potential of the virus has already been tested and validated, which bodes well for the safety and potential approval of MYDICAR. As they are both AAV1 and have AAV1 coat proteins and antigens, their capacity for pathogenic and immunogenic responses are likely to be very similar.

[14] Carter, B, et al., 2005. Adeno-associated virus vectors in clinical trials. *Human Gene Therapy*, 16, pp541-550.

Pre-clinical Data

Celladon first tested MYDICAR in preclinical animal studies, using a porcine model of heart failure induced by mitral regurgitation.[15] A single dose of MYDICAR (1 x 10^{12} viral particles) was administered by epicardial coronary artery perfusion and functional and safety parameters were assessed. Eight weeks after treatment, increased levels of SERCA2a protein and mRNA were found in heart tissue and there was an increase in cardiac performance. The median ejection fraction increased by 16% in AAV1/SERCA2a treated animals as compared to controls. In addition, the amount of blood remaining in the ventricle, known as the end-systolic volume, trended upward in control animals as a consequence of the insufficient contractile force. Meanwhile, AAV1/SERCA2a treatment decreased end-systolic volume. Whereas the end systolic volume increased by roughly 35% in the control group, AAV1/SERCA2a treated animals experienced a 14% decrease. This is indicative of a reversal of the remodeling process that the heart undergoes and potentially a slower disease process in treated animals. Safety parameters, including histopathologic analysis, hematology, and clinical chemistry, did not indicate any signs of organ damage or inflammatory response.

Celladon also examined AAV1/SERCA2a therapy in a sheep model of heart failure induced by rapid pacing and found favorable effects on ventricle contractility.[16] In this study, AAV1/SERCA2a was administered in adult sheep after 4 weeks of pacing. Left ventricular mechanics were monitored by echocardiography and conductance catheter measurements during an additional 4 weeks of pacing. Left ventricular function was significantly improved in AAV1-SERCA2a-treated HF animals as compared to untreated HF animals.

Heart Failure

Heart failure (HF) is a progressive condition where the heart cannot sufficiently generate the flow of blood necessary to meet the body's demands. HF is associated with a number of symptoms including shortness of breath, leg swelling, and exercise intolerance. In the early stages, heart failure may primarily manifest as being tired often, feeling weak, and having shortness of breath. Myocardial infarctions, coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy are all causes of HF. Other conditions that can lead to heart failure include diabetes, disease of the pericardium, arrhythmia, long-term alcohol use, or congenital heart defect.

As part of the disease progression, the body tries to compensate for the insufficient blood flow by retaining salt and water, which increases the amount of circulating blood, heart rate, and eventually the size of the heart. These mechanisms compensate for the heart's deteriorating performance, at least for a while, but reinforce a negative feedback loop that contributes to the disease progression. In advanced HF, the insufficient pumping of blood results in poorly oxygenated blood to flow to the organs in the body, eventually leading to a breakdown of vital systems.

In developed countries, HF affects approximately 2% of the adult population[17] and it's the leading cause of hospitalization in patients over the age of 65. There are roughly 5 million people in the United States who have heart

[15] Ly, H, et al., 2007. Cardiac function improvement following in vivo intracoronary adeno-associated virus type 1 vector gene transfer of SERCA2a in a pre-clinical model of heart failure. *Circulation*, 116, pp46.
[16] Mariani, JA, 2011. Augmentation of left ventricular mechanics by recirculation-mediated AAV2/1-SERCA2a gene delivery in experimental heart failure. European Journal of Heart Failure, 13, pp247-253.
[17] McMurray, JJV, et al., 2005. Marc A Pfeffer. Heart failure. *The Lancet*, 365, pp1877-1889.

failure and the total cost of heart failure is estimated to exceed $32 billion each year.[18] Although survival rates have improved considerably, currently the 5 year survival rate for heart failure patients is approximately 50%.[19] A treatment that effectively improves the condition of HF patients would have significant direct value for patients as well as major pharmacoeconomic benefits.

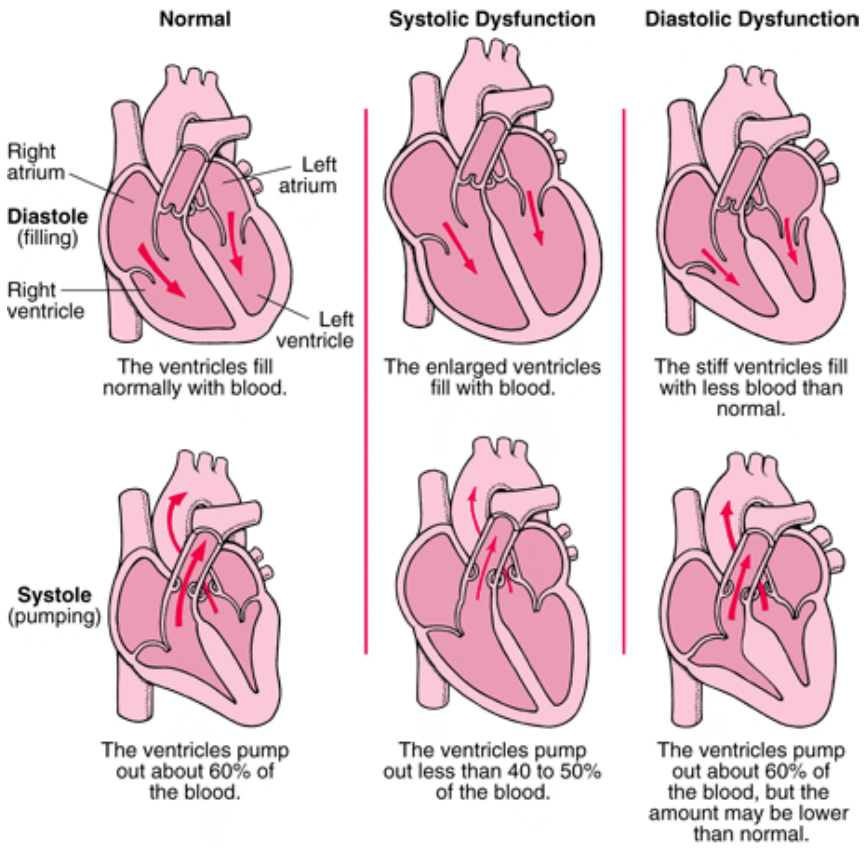
Causes & Pathogenesis of Heart Failure

A variety of causes can progress to heart failure, a condition where the heart is not meeting the body's demand for oxygenated blood. There are two types of HF, systolic and diastolic, each of which affects roughly half of HF patients and has a different underlying pathology. In systolic HF, the heart muscles weaken and cannot pump sufficient amounts of blood to keep up with the body's demands. It is characterized by a reduced ejection fraction (< 40%), which is the percentage of blood that gets ejected from the ventricle of the heart. The heart muscle can be weakened by a variety of medical disturbances, which can also lead to progression of heart failure. Progressive damage from HF is reflected at the level of the myocytes; many congenital causes of heart failure involve alterations of the arrangement and function of myocytes. Celladon is developing MYDICAR for the treatment of advanced systolic heart failure.

In diastolic heart failure, the heart muscle becomes rigid and cannot properly relax, resulting in improper refilling with blood. This causes a backup of fluid entering the heart, which puts stress on the venous system and tissue surrounding the heart. The differences between normal conditions and systolic and diastolic heart failure are illustrated in **Figure 8**. In a normal heart, the blood flowing into the ventricles from the atria is efficiently pumped out of the heart into systemic circulation. However, a heart in systolic HF pumps a smaller percentage of the blood out of the ventricles, which both strains the heart further and reduces the efficacy of systemic blood circulation. In diastolic HF, the ventricles have a reduced capacity to fill with blood, and so end up pumping less blood through circulation despite normal ventricular function. In either case, the general effect is reduced cardiac output and greater strain on the heart. This puts the patient at a greater risk of cardiac arrest from ventricular dysrhythmias and reduces systemic blood circulation, which can have a wide array of downstream consequences on other organ systems that progressively worsen as poor flow and oxygenation persist. The process accelerates as the body's attempts to compensate for low cardiac output further strain an already taxed heart. Celladon is planning preclinical activities of MYDICAR for the treatment of diastolic heart failure. If the studies support further development, Celladon expects to initiate clinical trials with MYDICAR for diastolic heart failure in 2015.

[18] Heidenreich PA, et al., 2011. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, 123, pp933–944.
[19] Go AS, et al., 2013. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*, 127, pp6–245.

Figure 8. Heart Function in Normal and Dysfunctional States



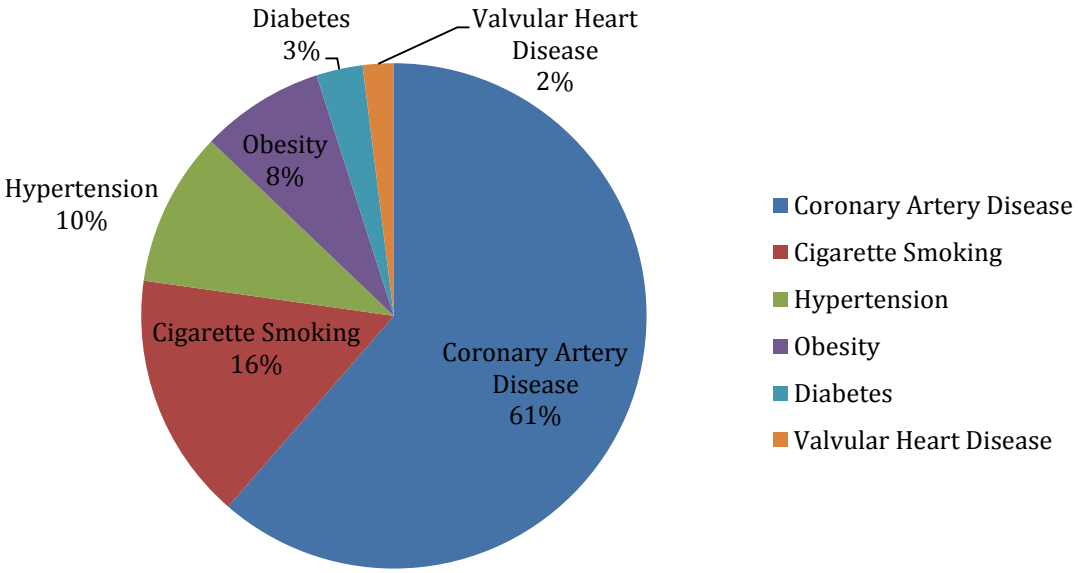
Source: Arnold, 2013 [20]

The most common cause of heart failure is coronary artery disease, where the buildup of fatty deposits in arteries that supply blood to the heart muscle itself, a process known as atherosclerosis, hampers the flow of blood to and proper oxygenation of cardiac muscles. Coronary artery disease underlies over 60% of heart failure cases in the United States adult population.[21] Heart muscle can also be weakened from a heart attack, usually itself a result of atherosclerosis, where a blockage in a coronary artery results in damage and death to heart muscle tissue that becomes starved for oxygen. Other contributing factors that can lead to heart damage and failure include faulty heart valves, either from damage or defect, high blood pressure, cardiomyopathy, which is damage to heart muscle that can be incurred from infections, alcohol abuse or toxic drug effects, viral infections, congenital heart defects, and heart arrhythmias. The breakdown of causes of HF in the United States is shown in **Figure 9**.

[20] Arnold, MO, 2013. Heart Failure. In *Merck Manual Online*. Retrieved from http://www.merckmanuals.com/home/heart_and_blood_vessel_disorders/heart_failure/heart_failure.html

[21] He J, et al., 2001. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Archives of Internal Medicine, 161, pp996-1002.

Figure 9. Causes of Heart Failure in US Adults



Source: He et al., 2001

Diagnosis, Classification, & Official Treatment Guidelines

Diagnosis of heart failure is based on symptoms, a physical exam, and tests to identify the cause of HF. All of these factors contribute to a decision regarding the correct treatment regimen. The necessary tests may include blood tests, chest x-ray, electrocardiogram (ECG), cardiac catheterization, and a stress test to look for coronary artery disease. An echocardiography is the likely first step that allows doctors to measure key benchmarks of the heart's performance, such as stroke volume and ejection fraction, with an ejection fraction less than 40% indicating impaired left ventricular systolic function. There is no single gold standard for screening heart failure; commonly used procedures include the Framingham Criteria, Boston Criteria, and Duke Criteria, which have standards for diagnosing heart failure based on the combinations of symptoms presented. Functional classification of the disease relies on designations described by the New York Heart Association, as shown in **Figure 10**.

Figure 10. Functional Classification of Heart Failure Stages by New York Heart Association

Class	Description
Class I	No limitations in activity are experienced; no symptoms in ordinary activities
Class II	Slight limitations but comfortable at rest and mild activity
Class III	Increased limitations; comfortable only at rest
Class IV	Physical activity brings discomfort; symptoms occur even at rest

Source: New York Heart Association

Treatment for heart failure focuses on improving symptoms and preventing the progression of the condition in a multi-pronged effort. To prevent the condition from worsening, it is necessary to identify the underlying cause of the heart failure and to treat it. The goal of treatment is also to reduce symptoms and thus improve the quality of life that a patient experiences. Treatments include lifestyle changes, medicines, and ongoing care; in severely debilitating cases not responsive to treatment, surgical interventions, such as implanting a pacemaker or left ventricular assist devices (LVAD) or undergoing a heart transplant may become necessary.

Yet, while these changes may elicit positive effects on the patient's health, these therapies are not disease-modifying, with the exception of a heart transplant, and act mainly to reduce the heart's workload. The first line of defense in heart failure is the use of an angiotensin-converting enzyme (ACE) inhibitor, a drug that dilates blood vessels, reducing how hard the heart has to work to circulate blood. Beta-blockers, which are drugs that block the β adrenergic receptor, are also used in treating heart failure, due to their ability to slow down the heart rate and reduce strain on the heart. In addition to medicines, treatment commonly involves lifestyle changes, such as changing diet to be more heart-friendly, quitting smoking, exercising more, limiting alcohol, and reducing weight.

The standard course of treatment for a systolic HF patient usually involves initiating treatment with an angiotensin-converting enzyme (ACE) inhibitor, which is titrated to optimal clinical outcome or maximum tolerated dose. ACE inhibitors work by blocking the production of angiotensin II, a potent vasoconstrictor and increasing production of the vasodilator bradykinin. This drug class has consistently shown beneficial effects on mortality, morbidity, and quality of life. ACE inhibitors may be used as early as Class I HF in order to prevent the progression of the disease. This will often be paired with a beta-adrenergic receptor antagonist, or beta-blocker, in stable patients with systolic dysfunction, in order to decrease the workload of the heart. If symptoms persist while a patient is receiving both ACE inhibitors and beta-blockers, then an aldosterone inhibitor is usually added into the regimen.

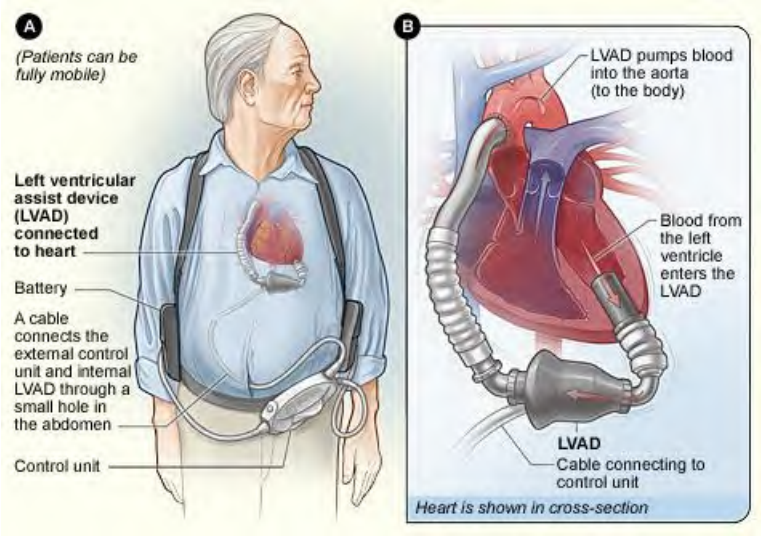
An aldosterone inhibitor blocks binding of aldosterone, a hormone released by the adrenal glands, which reduces the systemic buildup of fluid and strain on the heart. As a last pharmacological resort, in patients not responding to the cocktail already described, a cardiac glycoside called digoxin is taken. This drug acts to slow conduction of the AV

node in the heart, allowing for a greater fill time for the ventricle. Once pharmacological interventions fail, more invasive surgical interventions often become necessary to counteract the disease progression. In patients with severe cardiomyopathy, an automatic implantable cardioverter-defibrillator (ICD) is often considered to reduce the risk of life-threatening arrhythmias.

The target patient population for MYDICAR is advanced HF patients with NYHA class III and IV symptoms of heart failure and who might also be eventual candidates for heart transplant or left ventricular assist device (LVAD), both of which are end-stage treatments available to a small percentage of the heart failure population. Only about 3,500 heart transplants performed each year, about 2,500 of which take place in the US. In end-stage HF, a heart transplant is the only curative option presently available. Yet, its use as a treatment is severely hampered by the scarcity of donor hearts. The five and 10 year survival rate after a heart transplant is 75% and 56%, respectively. An LVAD, once a temporary fix while a patient waited for a heart transplant, has become long-lasting and small enough to work as a long-term therapy.

In 2012, over 5,000 LVADs were implanted worldwide, with roughly 1,000 procedures in the United States. The design of an LVAD, containing both an internal implanted pump connected to the heart and an external control and battery pack, is shown in **Figure 11**. With an LVAD device, a tube connects the left ventricle to one end of a pump and another tub connects the other end of the pump to the aorta. Thus, an LVAD pump reduces strain on the heart by helping the left ventricle pump oxygenated blood into systemic circulation. There are also right ventricular assist devices (RVAD), which can be used in conjunction with LVAD. In this case the system is referred to as a bilateral ventricular assist device (BIVAD). The daily charging that the device requires for its battery pack is an additional inconvenience on top of a very invasive and risky procedure. The one year survival rate after LVAD implantation is 85%, which is a considerable improvement over the 25-50% one year survival rate for advanced heart failure with medical therapy alone.

Figure 11. Implantable Left Ventricular Assist Device (LVAD)



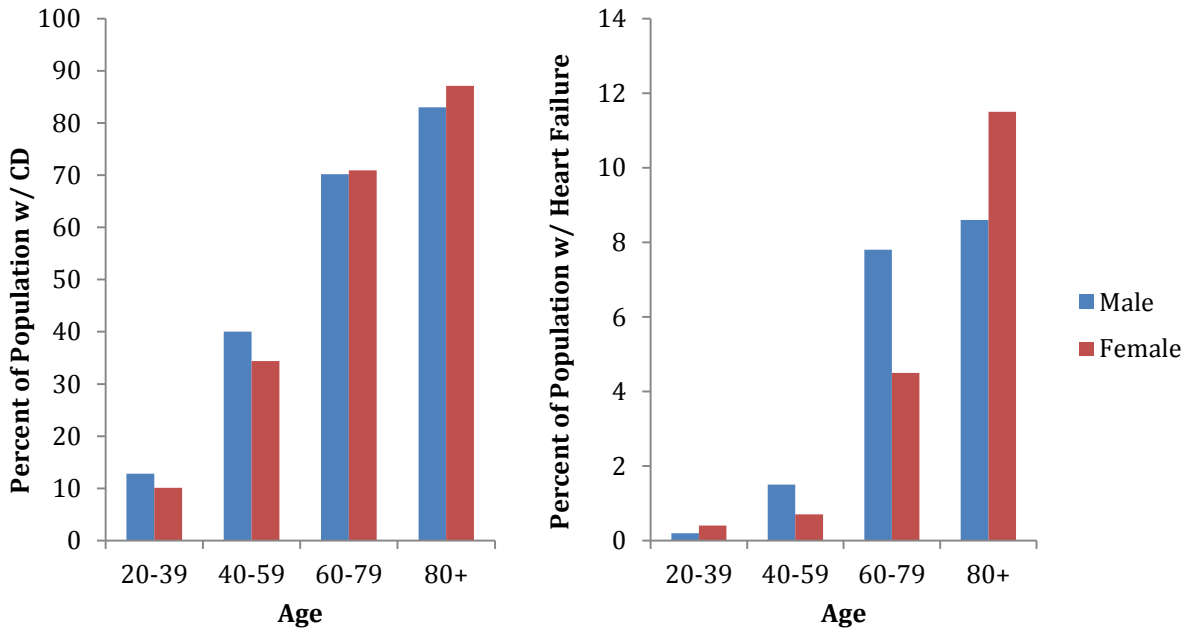
Source: NIH, National Heart, Lung, and Blood Institute

When heart failure progresses to an advanced stage, the present landscape for treatment involves highly invasive procedures that carry grave risks for the patient. While pharmacological interventions may be able to mitigate symptoms and reduce strain on the heart initially, the progression of heart failure is such that eventually the patient's condition reaches a point where pharmacology is not enough. There is an enormous potential market here for any heart failure therapy that can steal market share from heart transplant and/or LVAD therapy or can significantly delay the need for such therapies. This is particularly true for a new therapy that can accomplish improvements in cardiac function in a less invasive manner.

Heart Failure Market Information

There are over 5 million people in the United States afflicted by congestive heart failure, and an additional 18 million worldwide.[22] About half of HF patients die within 5 years of diagnosis,[23] indicating significant room for improvement in the management of the disease. Cardiovascular disease and the risk of HF increase substantially with age; by 80 years of age, over 80% of adults have some form of cardiovascular disease, and increasing incidence of HF. The prevalence rates of cardiovascular disease and heart failure in the US adult population can be seen in **Figure 12**.

Figure 12. Prevalence of Cardiovascular Disease and Heart Failure by Age



Source: National Heart, Lung, and Blood Institute & LifeSci Capital

A disease-modifying therapy that can significantly slow or reverse the natural progression of heart failure may potentially affect millions of patient. Present treatments are only able to counteract the failing heart and reduce strain

[22] Bui, AL, et al., 2011. Epidemiology and risk profile of heart failure. *Nature Reviews Cardiology*, 8, pp30-41.
[23] Go AS, et al., 2013. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*, 127, pp6–245.

on the muscle but without much disease-modifying capacity. With gene therapy there is enormous potential to alter the course of this progressive condition for millions of people and prevent an otherwise slow deterioration of health resulting from a weakened heart. The potential pharmacoeconomic benefits of a successful treatment for HF could be profound, as HF carries a heavy economic burden with annual costs exceeding $30 billion.[24]

Market Estimates

MYDICAR, a gene therapy to elevate SERCA2a expression levels in cardiomyocytes, has the potential to treat a subset of the HF patient population. Estimates from the American Heart Association indicate that there are about 6 million patients are affected by heart failure in the United States.[25] About half of HF cases stem from systolic heart failure, and these are the patients who are eligible for MYDICAR treatment as presently indicated. MYDICAR is currently being tested in patients with NYHA Class III, and IV symptoms of heart failure. According to the National Heart, Lung and Blood Institute, Class II, III, and IV HF patients make up 35%, 25%, and 5% of the HF patient population, respectively.[26] Additionally, as presently indicated, patients are screened for neutralizing antibodies against adeno-associated virus (AAV) and excluded from treatment if detected. Since it is estimated that about 40% of patients do not possess the neutralizing AAV antibodies, we believe approximately 264,000 HF patients comprise the initial target patient population for MYDICAR. The calculation is outlined in **Figure 13**.

Figure 13. Market Estimate of Target US Patient Population

Criteria	Patients
Have Heart Failure	6,000,000
Have Systolic Heart Failure	x 50% (3,000,000)
Are NYHA Classes III or IV	x 30% (900,000)
Don't Possess Neutralizing Antibodies	x 40% (360,000)
Target Patient Population	**= 360,000**

Source: LifeSci Capital

Among a population of roughly 900 million spread across 51 countries, there are estimated to be about 15 million HF patients in Europe.[27] Assuming similar distributions of systolic HF, NYHA Classes, and neutralizing antibodies among European HF patients, the European target population consists of 900,000 HF patients.

[24] Yancy, CW, et al., 2013. ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, 128, pp. 240-327.
[25] Heidenreich, P.A. et al., 2013. Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. *Circulation: Heart Failure*, 6, pp606-619.
[26] Ahmed, A, et al., 2006. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. *American Heart Journal*, 151:2, pp444-450.
[27] Dickstein, K, et al., 2008. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *European Journal of Heart Failure*, 10(10), pp933-989.

A clinical trial to test the safety of administering MYDICAR in patients that possess neutralizing antibodies against AAV is scheduled to begin in the second half of 2014. If demonstrated to be safe, this represents a sizeable increase in the target patient population.

Results from the CUPID 1 clinical trial indicate that high-dose MYDICAR delivered by intracoronary infusion may improve patient symptoms as well as reduce clinical events and time to hospitalizations. If this effect is confirmed in CUPID 2, then the cost-savings for hospitals and payers might make this therapy a very attractive option. This would increase both market penetration and eligible patient population as MYDICAR came under consideration in less advanced disease as a means of slowing the progression of heart failure.

This market estimate is based solely on MYDICAR's potential in the treatment of systolic heart failure and does not factor in other indications presently under investigation and entering clinical trials. Celladon is also preparing to test MYDICAR in the treatment of diastolic heart failure and blood vessel disorders, such as AV-fistula maturation failure and pulmonary arterial hypertension. Additionally, MYDICAR is being evaluated as a means of weaning HF patients off of an left ventricular assist device (LVAD). These represent future growth areas for Celladon after potential launch of MYDICAR in the primary systolic HF population.

Clinical Data Discussion

Celladon is pursuing a comprehensive clinical program that includes multiple Phase II trials to test their MYDICAR therapy in a variety of HF conditions. The trials that have been completed to date support MYDICAR's strong safety profile and ongoing development efforts. In the CUPID 1 Phase I/II clinical trial, MYDICAR was shown to be safe and well-tolerated. MYDICAR reduced heart failure-related hospitalizations and improved symptoms, quality of life, serum biomarkers, key cardiac predictors of survival, such as end systolic volume. Based on this success and prior clinical and preclinical results, Celladon has advanced MYDICAR to a 250 person Phase IIb clinical trial, referred to as CUPID 2. On March 5, 2014, the Company announced that enrollment was completed and that top-line results are expected in April of 2015. In 2012, the Company received a Special Protocol Assessment, or SPA, whereby the FDA agreed to time-to-recurrent hospitalization as the primary endpoint for the pivotal Phase III trial for MYDICAR. On April 10, 2014, Celladon announced that the FDA granted Breakthrough Therapy Designation to MYDICAR, which confers numerous regulatory advantages. There is a possibility that strong CUPID 2 data could support a regulatory filing in Europe.

CUPID 1 Phase I Trial

CUPID 1 was a Phase I/II clinical trial that included a dose escalation and safety Phase I portion followed by a larger Phase II portion that explored the initial efficacy of a single dose of MYDICAR in treating systolic HF patients.

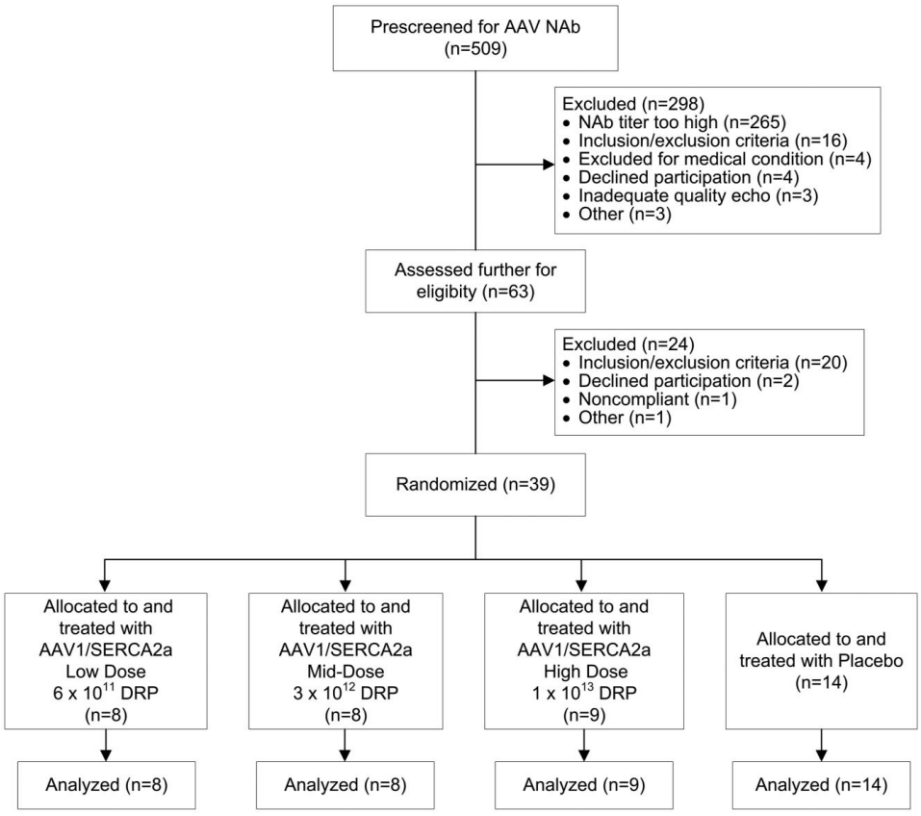
Trial Design. The CUPID 1 Phase I trial was an open-label dose escalation study in 12 patients that was designed primarily to investigate the safety of a single intracoronary infusion of MYDICAR. Key inclusion criteria for the trial included: NYHA Class III or Class IV heart failure, an implantable cardiac defibrillator, a left ventricular ejection less than 30%, and stability on outpatient therapy for at least 30 days prior to beginning treatment. Patients received a single intracoronary infusion of low-dose, mid-dose, or high-dose MYDICAR (1.4×10^{11}, 6×10^{11}, or 3×10^{12} virus particles) in addition to optimized HF therapy. Nine patients received MYDICAR (3 per dose group) and 3 received placebo. The primary endpoint for this Phase I trial was the safety of a single intracoronary infusion, while also

exploring parameters of efficacy. Safety monitoring was performed weekly for the first six weeks, then during months 2, 3, 6, 9, and 12. Patients received follow-up telephone calls every 6 months for an additional two years, for a total of 3 years of follow-up.

Phase I Results. This trial demonstrated positive safety results and served as the basis for continuing into the Phase IIa portion of the CUPID 1 trial. No consistent clinically meaningful changes in safety parameters were observed in any organ systems; measured vital signs such as blood pressure, heart rate, or body temperature; electrocardiographic parameters such as interval, rhythm, or QRS morphology; or blood chemistries such as electrolytes, liver, or kidney enzymes. In addition, Celladon found improvements in a number of efficacy parameters from baseline to 6 months. With these positive results, the Company moved into the Phase II portion of this study.

Phase II Trial Design.
The Phase II CUPID 1 trial was a randomized, placebo-controlled, double-blind, parallel group dose-ranging study in 39 patients with systolic heart failure. Patients received an epicardial coronary artery infusion of one of three doses of AAV1/SERCA2a or placebo over a 10 minute period in a cardiac catheterization laboratory. While continuing optimal medical therapy for their heart failure, patients were observed for 12 months for efficacy and safety endpoints and periodically completed a long-term follow-up by phone questionnaire. A schematic of the trial design as completed is shown in **Figure 14**.

Figure 14. Protocol for CUPID 1 MYDICAR Trial



Source: Jessup et al., 2011

Seven efficacy parameters were assessed in four domains:

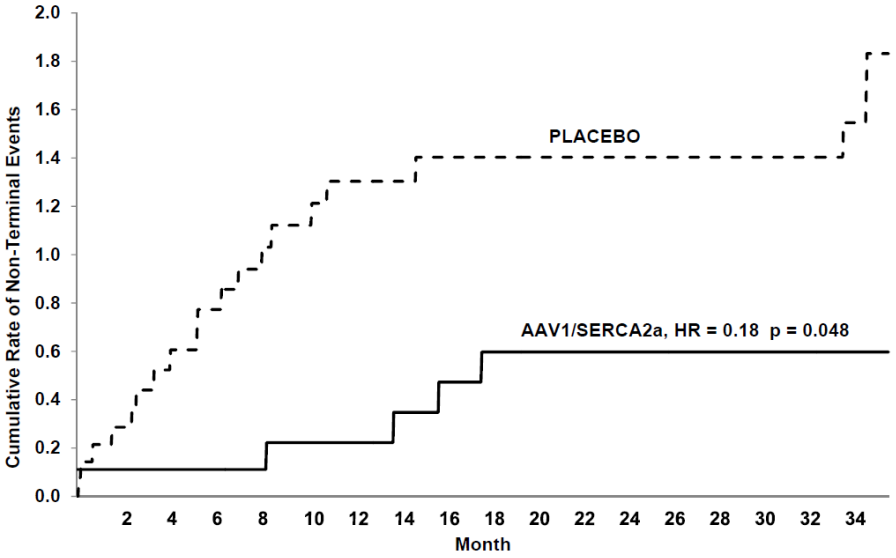
- LV function recovery determined by ejection fraction and end-systolic volume
- symptom improvement scored by New York Heart Association and Minnesota Living with Heart Failure Questionnaire
- improved cardiac function tested with a six-minute walk test and peak maximum oxygen consumption
- reductions in N-terminal prohormone brain natriuretic peptide (NT-ProBNP) levels, a biomarker for cardiovascular disease

The study was designed with a primary endpoint of efficacy, measured by improvement in multiple categories without worsening in any of them, and a secondary endpoint of safety.

CUPID 1 Phase II Results

The high dose group, containing 9 patients, reached the primary endpoint at 6 months as compared with controls and confirmed again at 12 months.[28] Change in LV end-systolic volume from baseline to 6 months was 18±39 mL as compared to -10±28 mL in placebo controls, indicating an improvement in an important HF parameter. Patients in the active treatment group showed improvements or stabilization in all four efficacy categories being studied. As can be seen in **Figure 15**, high-dose MYDICAR markedly reduced the cumulative occurrence of clinical events as compared with the baseline exhibited in placebo-treated heart failure patients. Clinical events were categorized as incidents of worsening heart failure (WHF), myocardial infarction, use of chronic IV inotrope, heart transplant, LVAD implantation, or death. WHF contained a range of signs and symptoms, including hospitalization as well as treatment with IV diuretics, vasodilators/positive inotropes, intra-aortic balloon pump, or mechanical fluid removal.

Figure 15. Rate of Clinical Events During CUPID 1 Phase II Trial Over 3 Year Period



Source: Zsebo, K. et al., 2014

[28] Zsebo, K. et al., 2014. Long-term effects of AAV1/SERCA2a gene transfer in patients with severe heart failure: analysis of recurrent cardiovascular events and mortality. *Circulation Research*, 114(1), pp101-108.

While all doses of MYDICAR reduced the frequency of clinical events, this reduction only persisted in the high-dose group 36 months after treatment, as demonstrated in a long-term follow-up of MYDICAR-treated patients. However, even in low and mid-doses, there was a longer delay until experiencing a cardiovascular event, compared with placebo. The placebo group had 26 clinical events, despite optimized heart failure treatment, compared with 15 in the low-dose cohort, 13 in the mid-dose cohort, and 4 in the high-dose cohort.

In patients treated with high-dose MYDICAR, there was an 82% reduction in the frequency of non-terminal events ($p=0.048$) as compared to controls at three years follow-up. This reduction over the span of three years is a promising result that supports ongoing investigation into MYDICAR's efficacy. In heart tissue samples examined, when available, from patients that later died or had an implant or transplant, investigators performed a quantitative polymerase chain reaction (qPCR) assay which enables quantification of DNA copies in a sample. They found that the SERCA2a transgene introduced from AAV1/SERCA2a injection had persisted long-term in the target tissue in 2 patients – one at 31 months and one at 22 months – while a third patient still possessed AAV DNA at month 23. All three of these patients were from the high-dose group, suggesting that this dose delivered a sufficient virus concentration to ensure reliable transfection. Yet, importantly, they confirmed stable, long-term expression of the transgene which can ensure long-term therapy from a single injection. No safety concerns were noted during the three year follow up period for patients who received MYDICAR.

CUPID 2: Phase IIb Trial with MYDICAR in Patients with Advanced Heart Failure

CUPID 2 is a double-blind, placebo-controlled Phase IIb trial evaluating MYDICAR in the treatment of heart failure.[29] 250 patients will be enrolled across 60 sites worldwide and randomized in a 1:1 fashion to treatment with MYDICAR or placebo. This trial is only using the high-dose (1×10^{13} particles) from CUPID 1 since this was found to be most effective at yielding viral transfection of cardiomyocytes and achieved primary and secondary endpoints. Inclusion criteria call for patients 18 to 80 years of age with systolic heart failure, ejection fraction measurements below 35%, having Class III and Class IV symptoms of HF on the NYHA scale, negative for AAV neutralizing antibodies (nAbs), and at high-risk of HF related hospitalizations. Patients will receive a single intracoronary infusion of high-dose MYDICAR or placebo and will be observed for 12 months. There is a five year follow up period for all patients enrolled in the trial.

The primary efficacy endpoint of this study is time-to-recurrent HF related hospitalizations in the presence of terminal events, which includes all-cause death, LVAD implantation, and heart transplant. Secondary endpoints are time-to-first terminal event, symptoms, exercise capacity, quality of life, and safety. The time-to-recurrent hospitalizations was accepted by the FDA in 2012 as an approvable endpoint in a Special Protocol Assessment. The Company announced on March 4, 2014 that enrollment is complete and top-line data is expected in April of 2015. Safety will be evaluated by determining the prevalence and severity of adverse clinical events and changes in laboratory parameters in MYDICAR-treated as compared to placebo-treated subjects.

[29] Greenberg, B, 2014. Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients with Advanced Heart Failure. *Journal of American College of Cardiology: Heart Failure*, 2:1, pp84-92.

MYDICAR in HF Patients with an LVAD

The CUPID 1 Phase I/IIa trial excluded HF patients that had previously received a left ventricular assist device (LVAD). On August 11th, Celladon announced the initiation of a follow-up Phase I/II trial to establish the safety of MYDICAR in this patient population.

Trial Design. The study will be a randomized, double-blind, placebo controlled Phase I/II trial evaluating percutaneous MYDICAR infusion in 24 stable chronic heart failure patients who have an LVAD implant. Patients will receive a dose of either $1x10^{13}$ viral particles or placebo over a 10 minute infusion period. The primary endpoint of the study will be the safety and feasibility of administering MYDICAR to LVAD patients. Safety measures will be defined according to incidence of death, major adverse cardiovascular events, or out-of-range laboratory values. Secondary endpoints will include the presence of viral DNA in the myocardium detected by quantitative PCR (qPCR), echocardiography of left ventricular function, SERCA2a protein levels, protein expression of other HF-related protein biomarkers, and function of isolated myocytes. The Company expects to complete this trial in May 2016.

AGENT-HF Trial

The AGENT-HF study aims to determine whether MYDICAR administration in patients with severe HF experience any changes in ventricular remodeling in response to treatment. The study will employ CT scans before and after treatment to assess a range of heart function metrics. This Phase II trial began enrolling patients in December 2013 and is expected to be completed in 2016.

Trial Design. The AGENT-HF study is a randomized, placebo controlled, double-blind Phase II trial assessing the effects of MYDICAR on cardiac volume and function in 44 patients with NYHA III/IV severe HF. Patients are randomized to receive either $1x10^{13}$ MYDICAR or placebo as a single intracoronary infusion. The primary endpoint is the change in the left ventricular end-systolic volume measured by a 256 slice CT-scan pre-injection and at 6 months. The secondary endpoints include a range of physiological, functional, quality of life, and rate of hospitalization metrics that were previously utilized in CUPID 1 and CUPID 2. Celladon is conducting this study in collaboration with the Assistance Publique - Hôpitaux de Paris and expects to complete the trial in 2016.

Other Treatments in Development

There are several other therapies in development to treat heart failure patients, many of which take a similar gene-based strategy. Perhaps the most important treatment currently under development is Novartis' (NVS) LCZ696, which is a combination of angiotensin-receptor blocker valsartan and the neprilysin inhibitor sacubitril. In August 2014, Novartis presented results at the Annual Congress of the European Society of Cardiology (ESC) from a large trial indicating that the treatment produced a significant survival advantage over the ACE inhibitor *Vasotec* (enalapril). LCZ696 will likely become the standard of care for heart failure patients. MYDICAR is designed to be used in addition to treatments like LCZ696. Therefore the potential market for MYDICAR should not be affected by approval of LCZ696

Other gene therapy development candidates are highlighted in **Figure 16**. Many of these therapies are AAV based and are targeting the same cell in the heart, the cardiac myocytes; where they differ is in the gene that they are introducing. While it is too early to tell which of these gene targets will be most-effective in improving heart failure symptoms, we will examine the potential benefits and drawbacks of each. Moreover, recent advances in the field of stem cell biology have opened up new potential avenues for HF treatment. These therapies aim to repair damaged heart tissue by introducing healthy cardiomyocytes into the heart and allowing them to graft themselves into the damaged tissue.

Figure 16. Ongoing HF Development Programs

Company	Product	Target Gene	Stage
Novartis	LCZ696	n/a	NDA
Renova Therapeutics	AC6 Gene Therapy	AC6	I/II
Juventas Therapeutics	JVS-100	SDF-1	II
Cardio3 Biosciences	C-Cure	n/a	III
Medistem	ERC-124	n/a	II
uniQure	AAV-S100A1	S100A1	Preclinical
NanoCor	Carfostin	Protein Phosphotase-1 inhibitor	Preclinical
VentriNova	VN-100	Cyclin A2 Gene	Preclinical
Beat BioTherapeutics	BB-R12	dATP	Preclinical

Source: LifeSci Capital

LCZ696 - Novartis. In a large, 8,442 patient trial known as PARADIGM-HF,[30] LCZ696 produced a significant survival advantage over *Vasotec* (enalapril), which is a very commonly used treatment for heart failure. The study measured the difference between treatment groups in death from cardiovascular causes and hospitalization for HF, as well as numerous secondary outcomes. The trial LCZ696 was significantly better than enalapril in terms of the primary outcome at 21.8% compared to 26.5% for enalapril ($p<0.001$). There were significantly fewer deaths in the LCZ696 arm (17.0% vs. 19.8%, $p<0.001$), and fewer deaths from cardiovascular causes (13.3% vs. 16.5%, $p<0.001$).[31]

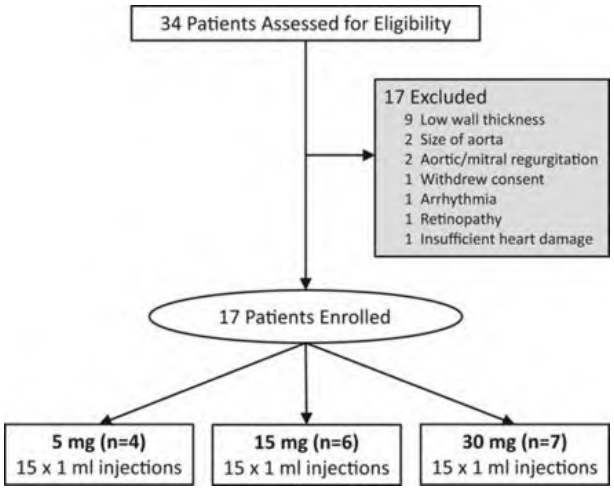
As mentioned above, if both treatments were approved then MYDICAR would likely be used in combination with LCZ696 and the two would not compete. Also noteworthy, MYDICAR is being developed for patients with advanced HF with NYHA classes III and IV whereas the LCZ696 trial enrolled patients in Classes II-IV. Only about one-fourth of the PARADIGM-HF study participants had NYHA Class III or IV HF, so the result is primarily an indication of the drug's effectiveness in treating earlier-stage HF patients. However, the difference in treatment effect between NYHA classes was not statistically significant. It appears that LCZ696, if approved, will become an important armament against HF, especially in patients with mild to moderate HF. Regardless of what happens with LCZ696, MYDICAR has the potential to be an important addition to the standard of care for treating HF.

JVS-100 – Juventas Therapeutics. Juventas is conducting one Phase I/II and one Phase II clinical trial on its lead candidate non-viral plasmid, JVS-100, which introduces and overexpresses the stromal cell-derived factor-1 (SDF-1)

[30] http://clinicaltrials.gov/ct2/show/NCT01035255
[31] McMurray, J.J.V., et al., 2014. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. *The New England Journal of Medicine*, 371(11), pp993-1004.

gene in heart muscle cells. SDF-1 upregulation has been shown in preclinical research to increase cell survival, promote the formation of new vasculature to improve the performance of the heart, and activate the proliferation of stem cells. Juventas' Phase I trial was an open-label, dose-escalation study with 12 months of follow-up in 17 NYHA Class III HF patients with ischemic cardiomyopathy.[32] These HF patients were divided into three cohorts receiving 1 of 3 doses−5 mg, 15 mg, or 30 mg JVS-100 doses−given in one session of 15 endomyocardial injections into the region of infarcted heart tissue. The study design is depicted in **Figure 17**.

Figure 17. Study Design for Open-Label, Dose-Escalation Phase I Study for JVS-100



Source: Penn et al., 2013

The trial demonstrated that the therapy so far is safe and well-tolerated, consistent with prior preclinical and clinical non-viral gene delivery.[33, 34, 35] Data from 15 mg and 30 mg cohorts showed statistically significant improvements at in several efficacy parameters at 4 months that were still present at 12 months, indicating the persistence of changes induced by JVS-100.

In October 2013, Juventas completed enrollment for its Phase II STOP-HF clinical trial, which is a randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy of JVS-100 in treating symptomatic HF. In STOP-HF, 93 patients have received a 15 mg JVS-100, 30 mg JVS-100, or placebo dose via endomyocardial injection in a 1:1:1 randomization. In addition to safety, primary endpoints include efficacy parameters such as heart failure related hospitalizations, major adverse cardiac events, and changes in 6 minute walk distance test, MLWHQ scores, and ejection fraction.

[32] Penn, MS, et al., 2013. An Open-Label Dose Escalation Study to Evaluate the Safety of Administration of Nonviral Stromal Cell-Derived Factor-1 Plasmid to Treat Symptomatic Ischemic Heart Failure. *Circulation Research*, 112, pp816-825.
[33] Shah, PB, Losordo, DW, 2005. Non-viral vectors for gene therapy: clinical trials in cardiovascular disease. *Advances in Genetics*, 54, pp339–361.
[34] Fortuin, FD, et al., 2003. One-year follow-up of direct myocardial gene transfer of vascular endothelial growth factor-2 using naked plasmid deoxyribonucleic acid by way of thoracotomy in no-option patients. *American Journal of Cardiology*, 92, pp436–439.
[35] Kusano, KF, et al., 2005. Sonic hedgehog myocardial gene therapy: tissue repair through transient reconstitution of embryonic signaling. *Nature Medicine*, 11, pp1197–1204.

On May 6th, Juventas announced top-line interim data from the STOP-HF trial, which was presented at the European Society of Cardiology Heart Failure Congress (ESC-HF). Efficacy data at four months elicited a dose-dependent improvement in echocardiographic metrics and biomarkers. Patients receiving the high dose of JVS-100 experienced a significant improvement in left ventricular end systolic volume ($p<0.05$). Other measures, such as left ventricular end diastolic volume, left ventricular ejection fraction, and NTproBNP biomarker levels were not significantly affected by treatment. While this is a positive development for Juventas, it is not yet clear how the drug affected other study endpoints.

This follows the completion of a first-in-man, double-blind, placebo-controlled Phase IIa clinical trial for JVS-100 in treating critical limb ischemia (CLI), referred to as STOP-CLI. Juventas expects to complete primary data collection by October 2014.

The Phase I portion of their RETRO-HF clinical trial, which began enrollment in October 2013, was an open-label dose-escalation study of a single-dose of JVS-100 administered via retrograde delivery. The first cohort of 6 patients received a 30 mg dose, before escalating to a 45 mg dose in the second cohort. Upon completion of this Phase I trial, Juventas immediately led into the Phase II RETRO-HF trial. In February 2014, Juventas announced the initiation of the Phase II portion of its RETRO-HF clinical trial to evaluate the safety and efficacy of JVS-100 in treating advanced heart failure secondary to ischemic cardiomyopathy. The study is a randomized, double-blind, placebo-controlled trial that will enroll 60 HF patients to receive 30 mg, 45 mg, or placebo doses of JVS-100 via retrograde infusion of the drug in the coronary sinus. The RETRO-HF trial represents the first retrograde delivery of a gene into the heart in a clinical setting. In addition to treating heart failure, the SDF-1 repair pathway is highly-conserved across organ systems, so there is the potential for JVS-100 to ultimately impact many disease modalities.

AC6 Gene Therapy – Renova Therapeutics. Renova is developing a gene therapy targeting the AC6 gene in moderate and advanced heart failure patients that is currently in randomized, double-blind, placebo-controlled Phase I/II clinical trial. AC6, or adenylyl cyclase type-6 is a transmembrane protein in cardiac myocytes that has been shown to improve cardiac function when overexpressed in the myocardium. Renova has been recruiting subjects for this study since July 2010 and expects to complete enrollment in December 2014 with an estimated total of 56 HF patients. Subjects receive either intracoronary infusion of an adenovirus encoding the human AC6 gene (Ad5.hAC6) or placebo in a 3:1 randomization. The study will assess primary endpoints of include exercise treadmill time, LV function, and rate of LV pressure change and secondary endpoints of symptoms and hemodynamics. At present, only preclinical data is available in mice and pigs with cardiomyopathy, which showed an increase in heart function, survival, and reduction in heart dilation. Renova has yet to report data from this therapy in human subjects.

***C-Cure*® by Cardio3 Biosciences.** *C-Cure* (C3BS-CQR-1) is a clinical-stage treatment in development by Cardio3 Biosciences for the treatment of chronic heart failure secondary to ischemic cardiomyopathy. It based on proprietary stem cell technology developed at the Mayo Clinic. *C-Cure* begins with harvesting multipotent cells from the patient's bone marrow. These are undifferentiated, immature cells capable of forming a wide range of specialized cells in the body. With *C-Cure* treatment, they apply the appropriate growth factors to induce the harvested cells to differentiate into cardiomyocytes and then inject these cells into the heart. This treatment carries both potential direct benefit from the proliferation and grafting of healthy cardiomyocytes into the heart muscle and possible indirect benefit from the signaling factors excreted from these healthy cells.

Cardio3 Biosciences obtained positive results in an open-label, randomized Phase II clinical trial in patients with advanced HF secondary to ischemic cardiomyopathy, finding that *C-Cure* showed a significant improvement in the

left ventricular ejection fraction of HF patients compared to a baseline control group receiving standard of care. In addition, *C-Cure*-treated HF patients had a significant improvement in exercise capacity as measured by the standard 6-minute walking test. Cardio3 Biosciences commenced a double-blind, multi-site Phase III clinical trial for *C-Cure* called CHART-1, standing for Congestive Heart Failure cArdiopoietic Regenerative Therapy. The primary endpoint is a composite endpoint measured 9 months post-procedure that includes mortality, morbidity, quality of life, 6-minute walking test, and left ventricular structure and function. On July 7th, the Company announced the enrollment of the 120th patient, which represents the halfway point in study enrollment. Cardio3 Biosciences expects to complete enrollment by December 2014, with topline data reported by the end of 2015.

ERC-124 – Medistem. In 2007, Medistem (OTCQB: MEDS) identified a new type of mesenchymal-like stem cell that they named Endometrial Regenerative Cells (ERCs), derived from menstrual blood, that can be pharmacologically induced to differentiate into cardiomyocytes.[36] Since the lining of the uterus, or endometrium, from where the ERCs originate, undergoes rapid angiogenesis monthly during menstruation, Medistem hypothesized and preclinical studies confirmed in 2008[37] that ERC-based cell therapy has strong angiogenic potential. In an animal model of critical limb ischemia, induced by ligation of the femoral artery in mice, intramuscular injection of 1 million ERCs below the level of ligation reversed the course of necrosis. While 8 control mice in the study experienced limb necrosis by day 14, all 8 treated mice had intact limbs, indicative of substantial angiogenesis. In a nude rat model of myocardial infarction (MI) induced by ligating the left anterior coronary artery, ERC transplanted cells integrated into infarcted heart tissue and improved LV systolic function.[38]

In January 2012, Medistem launched a double-blind, placebo-controlled, dose-escalation Phase II clinical trial, named RECOVER-ERC, testing efficacy and safety of ERC doses on HF patients. In total, the study will enroll 60 patients with advanced congestive heart failure, divided into 3 escalating dose cohorts with 15 HF patients receiving treatment and 5 receiving placebo. Treated patients will receive 1 of 3 possible ERC doses − 50 million, 100 million, or 200 million ERCs − via retrograde coronary sinus delivery. Retrograde delivery, compared with anterograde coronary artery infusion or intramyocardial injection, has been shown in preclinical studies to have better safety and efficiency for protein, cell, or gene delivery.[39, 40, 41, 42] At the time of publication of a peer-reviewed study update in 2013, 17 patients have been dosed, no serious adverse effects have been reported, and a preliminary review of data has allowed the study to continue as planned.[43] In December 2013, Medistem was acquired by Intrexon Corporation and is

[36] Meng, X, et al., 2007. Endometrial regenerative cells: a novel stem cell population. *Journal of Translational Medicine*, 5, pp57-66.
[37] Murphy, MP, et al., 2008. Allogeneic endometrial regenerative cells: An "Off the shelf solution" for critical limb ischemia? *Journal of Translational Medicine*, 6, pp45-52.
[38] Hida, N, et al., 2008. Novel Cardiac Precursor-Like Cells from Human Menstrual Blood-Derived Mesenchymal Cells. *Stem Cells*, 26:7, pp1695-1704.
[39] von Degenfeld, G, et al., 2003. Selective pressure-regulated retroinfusion of fibroblast growth factor-2 into the coronary vein enhances regional myocardial blood flow and function in pigs with chronic myocardial ischemia. *Journal of American College of Cardiology,* 42:6, pp1120–1128.
[40] Thompson, CA, et al., 2003. Percutaneous transvenous cellular cardiomyoplasty. A novel nonsurgical approach for myocardial cell transplantation. *Journal of the American College of Cardiology*, 41:11, pp1964–1971.
[41] Tuma, J, et al., 2011. Safety and feasibility of percutaneous retrograde coronary sinus delivery of autologous bone marrow mononuclear cell transplantation in patients with chronic refractory angina. Journal of Translational Medicine, 9, pp183-189.
[42] Uzuki, K, et al., 2004. Targeted cell delivery into infarcted rat hearts by retrograde intracoronary infusion: distribution, dynamics, and influence on cardiac function. *Circulation*, 110:11s1, pp225–230.
[43] Bockeria, L, et al., 2013. Endometrial regenerative cells for treatment of heart failure: a new stem cell enters the clinic. *Journal of Translational Medicine*, 11, pp56-63.

continuing its operation as a wholly-owned subsidiary of Intrexon. While the Company has delivered promising preclinical work showing therapeutic potential for ERCs, they have not yet reported human data.

AAV-S100A1 – uniQure. In August 2014, uniQure (NasdaqGS: QURE) acquired InoCard GmbH, a private development-stage biotechnology company that has developed a gene therapy for HF. The acquisition was completed in a shares and cash upfront deal valued at approximately €3 million ($3.9 million) with the potential for additional milestone and royalty payments. InoCard developed a novel HF therapy targeting the S100A1 protein and has generated positive proof-of-concept data in a porcine HF model. The S100A1 protein, like SERCA2a, is involved in the regulation of Ca^{2+} signaling in cardiomyocytes and is downregulated in HF patients.[44,45]

Inocard's founders, Professors Patrick Most and Hugo Katus, discovered that the S100A1 protein had an important role as a regulator of cardiomyocyte function. S100A1 functions by enhancing the activity of ryanodine receptors (RyRs) and SERCA2a. Preclinical work in rodent and porcine HF models provides proof-of-concept for AAV-S100A1 as a HF treatment.[46] In pigs with induced HF, AAV-S100A1 introduced safe, stable S100A1 expression and appeared to reverse heart remodeling and cardiac deterioration. The S100A1 gene also had beneficial effects on contractile force, growth control of heart muscle cells, rhythm stability, and more efficient excitation-coupling.[47]

InoCard has used both AAV serotype 6 and serotype 9 in preclinical studies which are known to have a cardiotropism. InoCard has also used a cardiomyocyte-specific promoter, a CMV-enhanced myosin light chain promoter (CMV-MLC), in the development of the construct. Both of these features make the AAV-S100A1 more specific than Celladon's AAV-SERCA2a for cardiomyocyte infection by design. However, the AAV serotype 1 has broad tropisms that include cardiomyocytes and Celladon has not generated any data suggestive that this will be a problem. It is also not yet clear which serotype uniQure will use in clinical development, considering that *Glybera* was designed with the AAV1 construct much like MYDICAR.

***Carfostin* – NanoCor Therapeutics.** NanoCor is developing a heart failure therapy, *Carfostin* that is also based on the delivery of genes via AAV particles. In this case, the viral vector is used to introduce genes for phosphatase-1 inhibitors into cardiac myocytes. In preclinical studies in pig and rodent models, NanoCor reported improvements in both the contractility of the heart and the morbidity and mortality associated with heart failure. Researchers also reported a reduction or slowing in the remodeling process that takes place as the body compensates for heart failure. *Carfostin's* downstream effect on the cell is an improvement of calcium cycling that underlies contraction. However, *Carfostin* has yet to be tested in humans, and so, it is far behind Celladon in progress towards approval.

BB-R12 – Beat BioTherapeutics. Beat BioTherapeutics is developing BB-R12, an AAV-based gene therapy, to increase expression of ribonucleotide reductase, a protein that synthesizes dATP, or 2-deoxy-ATP. By increasing dATP levels in the myocytes, which acts as a "superfuel" for the cardiomyocytes' contractile machinery, there is greater force generated and more myofilament cross-bridge cycling, and thus, greater contraction and heart performance.[48] dATP can also be used by other ATPases besides myosin, so its mechanism of action may include a variety of

[44] Remppis, A et al., 1996. Altered expression of the Ca(2+)-binding protein S100A1 in human cardiomyopathy. *Biochimica et Biophysica Acta*, 1313, pp253-257.
[45] Brinks, H et al., 2011. S100A1 genetically targeted therapy reverses dysfunction of human failing cardiomyocytes. *Journal of American College of Cardiology*, 58, pp966-973.
[46] Ritterhoff, J and Most, P, 2012. Targeting S100A1 in heart failure. *Gene Therapy*, 19, pp613-621.
[47] Pleger, ST, et al., 2011. Cardiac AAV9-S100A1 Gene Therapy Rescues Post-Ischemic Heart Failure in a Preclinical Large Animal Model. *Science Translational Medicine*, 92(3), pp92.
[48] Regnier, M, 2000. 2-deoxy-ATP enhances contractility of rat cardiac muscle. *Circulation Research*, 86:12, pp1211-1217.

enzymatic byproducts in the cell including greater activation of SERCA2a protein, which is the biochemical pathway targeted by MYDICAR. Beat BioTherapeutics closed series A financing in April 2013 to finish IND-enabling preclinical studies and embark on a Phase I clinical trial in humans.

VN-100 – VentriNova. VentriNova is performing preclinical trials on VN-100, a viral vector that delivers the cyclin A2 gene into cardiac myocytes to stimulate heart cell regeneration. The company plans to apply for an IND so that it can begin studies in large animals.

Competitive Landscape

The current treatment landscape is largely defined by therapies that aim to reduce strain on the heart and prevent the disease progression from reaching a point that necessitates a heart transplant. In terms of disease-modifying potential in congestive heart failure, there are two broad strategies that can be employed. The existing heart muscle tissue has to be fixed or it has to be replaced. While heart transplant remains the *de facto* end-of-the-line treatment for advanced heart failure patients, developments in molecular biology have renewed interest in other less invasive means of altering the course of this disease.

Celladon has chosen a viral gene delivery mechanism to express the SERCA2a transgene in cardiomyocytes, targeting a known deficiency that correlates with advanced HF. There are several other companies presently developing viral gene strategies for treating HF, targeting other transgenes, but they are mostly still in preclinical development. One exception to this is Renova Therapeutics, which has begun enrollment for a Phase II trial of its gene delivery of the adenylyl cyclase type-6 (AC6) gene into cardiomyocytes, which has shown promise in preclinical studies. However, Renova has yet to report data from clinical trials in humans. The adenovirus used by Renova is known to generate an immune response and other adverse effects, which may detract from the safety profile of this therapy when compared with MYDICAR. In addition, the transgene being targeted in their therapy is a broad signaling molecule that has effects across a range of biochemical pathways in the cell. This means the potential for unintended cellular side effects due to the broad signaling capacity of adenylyl cyclase. Celladon has targeted a protein that is more closely linked to the signaling underlying muscle contraction by modulating cellular calcium dynamics.

One company, Juventas, has developed a non-viral gene therapy strategy that uses a plasmid encoding stromal cell-derived factor-1 (SDF-1) gene. Juventas has completed enrollment for one Phase II trial, STOP-HF, and has begun enrollment for the Phase II portion of its RETRO-HF Phase I/II trial. This therapy uses a more recently developed retrograde delivery method from the coronary sinus, which may increase its uptake over traditional intracoronary, or anterograde, infusion. However, this is also necessary to compensate for the lower transduction efficiency obtainable with non-viral strategies. Due to its viral design, MYDICAR will likely have a greater transfection efficiency and thus would be expected to affect a greater portion of the heart tissue from a single treatment. Juventas has targeted a gene related to the cell-repair machinery and has shown promising results in its early clinical trials. This company is likely to offer the most direct and immediate competition to Celladon and MYDICAR in the realm of gene delivery, since it is also in Phase II trials and likely has a similar timeline to commercialization. Juventas has also begun testing retrograde delivery in their RETRO-HF study as a potentially safer alternative to the series of intracardial injections employed during STOP-HF.

UniQure's recently acquired AAV-S100A1 candidate may have the greatest similarity to MYDICAR in this space, but it is still in preclinical development. The MYDICAR program has been de-risked in several important ways that the

AAV-S100A1 program has not. First and foremost, MYDICAR's positive safety profile has been established in humans in the CUPID1 Phase I/II trial, whereas the uniQure program is still in preclinical development. With data from the CUPID 2 Phase IIb trial expected in 2015, Celladon may complete its second Phase II trial prior to AAV-S100A1 entering clinical development. Second, MYDICAR utilizes the same AAV serotype 1 as uniQure's *Glybera*, which has been approved by the EMA. If uniQure proceeds with clinical development using a different serotype, they may face additional scrutiny of their safety data representing an added hurdle to obtaining approval.

Third, AAV-S100A1 uses a recombinant promoter that has not been tested in humans before. While InoCard generated preclinical data in a porcine HF model, interspecies variation in serotype tropism, promoter strength, and other factors can substantially alter the virus' safety and efficacy. Fourth, the effects of S100A1 are directly related to SERCA2a function. Since SERCA2a expression is also diminished in HF patients, S100A1 may not have as strong an effect as expected based on its success in an experimentally-induced animal model of HF. These clinical risks, combined with the Celladon's headstart, make uniQure's program unlikely to threaten the MYDICAR program or its attractiveness as a potential HF treatment in the near term.

Cell therapy has emerged as another strategy for repairing and even replacing damaged heart tissue and two companies, Cardio3 Biosciences and Medistem, are presently developing stem cell-based therapies for treating HF. While these therapies may ultimately prove effective, cell therapies carry several potential risks as well. Stem cell transplantation carries a risk of abnormal cellular differentiation, and since cells transplanted into the heart may end up in several different organ systems, this can be difficult to detect. Although studies to date have not shown an increased rate of tumor formation in transplant recipients, they have only included a small number of patients and have not fully assessed longer-term risks that may present. It remains to be determined whether grafted stem cell-derived cardiomyocytes or viral induction of transgenes will offer longer-term modification of the heart in HF patients. Celladon has found stable expression up to Month 31 in their CUPID 1 Phase II trial of viral DNA in explanted cardiomyocytes.

Additional Development Opportunities for MYDICAR

Celladon has developed MYDICAR, an AAV-based gene therapy delivering a complimentary copy of the human SERCA2a transgene, to treat systolic HF by elevating SERCA2a protein expression levels and consequently improving the calcium dynamics that underlie muscle contraction. The calcium cycle in cardiomyocytes is an important therapeutic target for a variety of heart conditions beyond systolic HF and modification of SERCA2a expression may have therapeutic value for a wide range of heart conditions. Celladon plans to evaluate MYDICAR for additional indications including advanced HF with an implanted left ventricular assist device (LVAD), diastolic HF, pulmonary arterial hypertension (PAH) and arteriovenous (AV) fistula maturation failure. In addition, Celladon has recently acquired rights to develop gene therapies that target the membrane bound stem cell factor. This therapeutic strategy is currently under evaluation in preclinical studies.

Diastolic Heart Failure. Diastolic HF, where the heart fails to sufficiently relax and thus cannot properly fill with and pump blood, is also characterized by a SERCA2a deficiency. Since SERCA2a functions to clear Ca2+ ions from the cytoplasm into storage in the sarcoplasmic reticulum, the slower decay of the calcium transient in HF patients could be a cellular correlate of the dysfunctioning heart and therefore a therapeutic target. Celladon is initiating preclinical activities for the use of MYDICAR in diastolic heart failure. If these activities support further development, Celladon plans to initiate clinical trials in 2015.

Pulmonary Arterial Hypertension. Pulmonary arterial hypertension (PAH) is an increase in blood pressure within the arteries supplying the lungs, which can progressively weaken the right ventricle. Preclinical studies have shown improvements in animal models of PAH after MYDICAR intratracheal administration, finding decreased pulmonary artery pressure and vascular remodeling compared with control animals. Additional toxicology and formulation studies will be necessary prior to any clinical trials and the Company expects to file a separate IND for this indication. Celladon co-owns a family of patents with Mount Sinai relating to gene-based treatment of PAH, including SERCA2a.

AV-Fistula Maturation Failure. Arteriovenous (AV)-fistula is a surgically created connection between an artery and a vein in the arm to allow repeated vascular access for hemodialysis in end-stage renal failure. Roughly 40% of the 100,000 surgically-created AV-fistulas fail due to rapid growth of vascular smooth muscle cells. Preclinical studies indicate that MYDICAR infusion may prevent rapid smooth muscle cell growth and help stabilize the AV-fistula. Celladon does not expect that additional formulation studies would be required before evaluating this indication in a clinical setting. Celladon plans to initiate a Phase IIa trial to evaluate MYDICAR in 100 end-stage renal failure patients with data expected in 2015.

Therapies Based on Membrane Stem Cell Factor Gene. Celladon has reported an exclusive, global in-license deal with Enterprise Partners Venture Capital. The deal allows for Celladon to develop potential therapies based on the membrane-bound stem cell factor (mSCF) gene. The mSCF protein, expressed by the mSCF gene, is an important cytokine that modulates the migration and proliferation of cardiac stem cells. Researchers at the Icahn School of Medicine at Mount Sinai have demonstrated the efficacy of mSCF gene therapy to reverse heart damage in an animal model of myocardial infarction.[49] The mSCF gene modulates the activity of cardiac precursor cells, thus promoting a regenerative response in damaged heart muscle. Celladon plans to develop a clinically-acceptable viral vector and build on this data with additional preclinical studies.

SERCA Small Molecule Program

Celladon is also developing a small molecule platform of SERCA2b enzyme modulators. Preclinical pilot studies have been completed in the treatment of heart failure, diabetes, and neurodegenerative diseases. The Company has an exclusive license to the University of Minnesota's jointly-owned family of patents covering the screening of SERCA small molecule modulators and pays an annual fee of $120,000 to the University of Minnesota as part of the licensing agreement. In February 2014, Celladon announced an option agreement with Servier, granting exclusive ex-US licensing rights to its small molecule SERCA2b modulators in diabetes and metabolic disorder treatments. Servier and Celladon will jointly support the discovery effort, while Servier will handle all development costs associated with non-US regulatory approval and commercialization. Celladon will retain US rights to commercialize any compound or lead candidate produced through this collaboration. If the option is exercised by Servier, Celladon will receive upfront, research, and milestone payments plus royalties from sales outside the United States.

[49] Yaniz-Galende, E, et al., 2012. Stem Cell Factor Gene Transfer Promotes Cardiac Repair After Myocardial Infarction via In Situ Recruitment and Expansion of c-kit+ Cells. *Circulation Research*, 111, pp1434-1445.

Intellectual Property & Licensing

Celladon is the owner or licensee of a portfolio of patents and patent applications, largely focused on the clinical development of MYDICAR, their gene therapy to treat heart failure patients. The Company owns two patent families related to the delivery of AAV vectors to the heart as a therapy in the United States with corresponding patents in Europe and Israel, and patent applications are pending in Europe, Austrailia, Hong Kong, India, and Japan. These patents and applications, if granted, would have expiration dates in 2027 or 2028. Relating to the hybrid composition of MYDICAR, which contains different elements from several AAV serotypes, Celladon holds a sublicense with the University of Pennsylvania (UPenn) via an exclusive agreement with AmpliPhi (formerly Targeted Genetics) and a non-exclusive licensing agreement with AskBio LLC. The Company expects, upon commercialization of MYDICAR, to pay royalties to both UPenn and AskBio, until expiration of these patent families−U.S. Patent Nos. 6,759,237, 7,186,552 and 7,172,893−in November 2019 and February 2021. Celladon also holds an exclusive licensing agreement with AmpliPhi covering aspects of the AAV manufacturing process.

On top of the trade secrets the Company possesses, these patents and licensing agreements represent additional proprietary protection by restricting competitors' access to the methods of AAV production. In the United States, these patents (U.S. Patent Nos. 6,566,118, 6,989,264, 6,995,006 and 6,475,769) are set to expire in September 2018 with corresponding foreign patents in Europe, Canada, Japan, and Austrailia expiring in September 2018 or 2019. Celladon has also licensed certain patent rights from The Regents of the University of California relating to gene therapy treatment of heart failure by targeting the SERCA2a gene, although these patents will expire in the United States in 2015, prior to commercialization of MYDICAR.

On top of their IP protection, Celladon expects a 12 year period of regulatory exclusivity from the FDA according to the Biologics Price Competition and Innovation Act. This exclusivity period, if granted, will start at the point of FDA regulatory approval and provide an additional barrier to entry for a potential competitor

Aside from patent protections relating to MYDICAR as a heart failure therapy, Celladon has developed patents and licensing agreements for a wide range of products in their development pipeline. These rights include co-ownership of a patent family related to treating pulmonary artery hypertension (PAH) with Mount Sinai School of Medicine, co-ownership of a portfolio of patents with the University of Minnesota related to high-throughput screening of small molecule modulators of SERCA proteins, in-licensing of a patent family related to AAV-based delivery of SERCA2a to treat heart arrhythmias, and exclusive in-licensing with Enterprise Partners Venture Capital for use of the membrane-bound stem cell factor (mSCF) gene in developing novel therapies.

Management Team

Krisztina M. Zsebo, Ph.D.
Director and CEO

Dr. Zsebo has served as Celladon's President, Chief Executive Officer and a member of the board of directors since 2004. From 2004 until 2007, Dr. Zsebo was a venture partner at Enterprise Partners Venture Capital. Prior to joining Enterprise Partners, Dr. Zsebo held executive positions at Remedyne Corporation, Connetics Corporation, ALZA Corporation, Cell Genesys, Inc., and Amgen Inc. Dr. Zsebo received a B.S. in Biochemistry from the University of

Maryland, an M.S. in Biochemistry and Biophysics from Oregon State University and a Ph.D. in Comparative Biochemistry from the University of California, Berkeley.

Paul Cleveland
President and CFO

Mr. Cleveland has served as our President and Chief Financial Officer since June 2014. From February 2013 to August 2013, Mr. Cleveland served as Executive Vice President, Corporate Strategy and Chief Financial Officer of Aragon Pharmaceuticals, Inc. From April 2011 to February 2013, Mr. Cleveland served as General Partner and Chief Operating Officer of Mohr Davidow Ventures. From January 2006 to February 2011, Mr. Cleveland served as Executive Vice President, Corporate Development and Chief Financial Officer of Affymax, Inc., a biopharmaceutical company. From 1996 to 2005, he served as a managing director at investment banks Integrated Finance, Ltd., J.P. Morgan Chase and Co and a predecessor firm, Hambrecht & Quist. From 1981 he was a corporate attorney at Cooley LLP, at Sidley Austin LLP and at Davis Polk & Wardwell LLP. Mr. Cleveland received an A.B. from Washington University and a J.D. from Northwestern University School of Law.

Rebecque J. Laba
Vice President, Finance and Administration

Ms. Laba has served as Celladon's Vice President, Finance and Administration since 2007, and before that, served as a consultant to the Company on finance and administrative matters since 2005. From 1999 to 2005, Ms. Laba served in various financial and operational roles at Idun Pharmaceuticals, Inc. until Idun was acquired by Pfizer Inc., in 2005. From 1997 to 1999, Ms. Laba worked at Asset Management Group, where she served in various financial and operational roles.

Jeffrey J. Rudy
Vice President, Clinical Operations

Mr. Rudy has served as Celladon's Vice President, Clinical Operations since joining us in 2006. From 1997 to 2006, Mr. Rudy worked at Agouron Pharmaceuticals where he served in roles of increasing responsibility within its clinical research operations, including portfolio manager of the ophthalmology franchise and director of development operations. From 1995 to 1997, Mr. Rudy was at Gilead Sciences, Inc., where he was clinical program manager in the clinical research department overseeing a number of antiviral compounds in early development. From 1991 to 1994, Mr. Rudy was at Amgen, where he worked in clinical affairs on a number of antiviral programs. Mr. Rudy received his B.S. in Microbiology from Ohio State University.

Fredrik Wiklund
Vice President, Corporate Development and Investor Relations

Mr. Wiklund has served as Celladon's Vice President, Corporate Development and Investor Relations since 2013 and before that, as the Company's Head of Corporate Development. From 2009 to 2012, Mr. Wiklund served as a consultant to Celladon on business development matters. From 2003 to 2008, Mr. Wiklund was head of corporate development and investor relations at Tercica, Inc., until its acquisition by the Ipsen Group in 2008. From 2001 to 2003, Mr. Wiklund was at Lehman Brothers, Inc., where he served in the Investment Banking Health Care Group.

From 1996 to 2000, Mr. Wiklund served as an antiviral specialist at Gilead Sciences. Mr. Wiklund received his M.B.A. from the University of Southern California and his B.A. in International Relations from the University of San Diego.

Ryan K. Takeya
Vice President, Manufacturing

Mr. Takeya has served as our Vice President, Manufacturing since April 2012. From 1996 to 2009, Mr. Takeya served in the Manufacturing Group at Targeted Genetics Corporation, where he oversaw in-house and contract manufacturing of clinical gene therapy products, including clinical supplies used in the MYDICAR clinical program. From 1993 to 1996, Mr. Takeya held various process development and process transfer roles at Immunex Corporation. In 2011, Mr. Takeya was at Dendreon Corporation, where he was involved with the transfer of the PROVENGE antigen manufacturing process to a secondary commercial manufacturing site. Mr. Takeya received his B.A. in Chemistry from the University of Washington.

Risk to an Investment

We consider an investment in Celladon to be a high risk investment. Celladon is currently in clinical-stage development, has never generated product revenue, and does not have any marketed or approved products. Celladon is primarily focused on its MYDICAR clinical program, using gene therapy to introduce and overexpress a SERCA2a transgene. Celladon has not completed any pivotal clinical trials for MYDICAR or its small molecule SERCA2b platform and is several years, if ever, away from having a candidate ready for commercialization. Failure to show convincing results in a pivotal Phase III clinical program or failure to reach FDA or EMA approval could adversely affect Celladon's stock price. As a clinical-stage company, Celladon is not profitable and may need to seek additional financing from the public markets, which may result in dilution of existing shareholder value.

	1Q12A	2Q12A	3Q12A	4Q12A	FY12A	1Q13A	2Q13A	3Q13A	4Q13A	FY13A	1Q14A	2Q14A
REVENUES												
Total Revenues	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
COGS												
Gross Profit	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Gross Margin												
G&A	$	1,383.00	$	1,248.00	$ 2,631.00	$	1,328.00	$	1,709.00	$ 3,037.00	$	1,706.00	$	2,024.00
R&D	$	7,867.00	$	5,447.00	$ 13,314.00	$	7,136.00	$	9,791.00	$ 16,927.00	$	5,218.00	$	4,981.00
Total Operating Expense	**$**	**9,250.00**	**$**	**6,695.00**	**$ 15,945.00**	**$**	**8,464.00**	$	11,500.00	**$ 19,964.00**	**$**	**6,924.00**	**$**	**7,005.00**
Operating Income	**$**	**(9,250.00)**	**$**	**(6,695.00)**	**$ (15,945.00)**	**$**	**(8,464.00)**	**$**	**(11,500.00)**	**$ (19,964.00)**	**$**	**(6,924.00)**	**$**	**(7,005.00)**
Operating Margin												
Interest Income (expense)											$	8.00	$	21.00
Interest Expense											$	(59.00)		
Other income (expense)	$	(161.00)	$	(689.00)	$ 74.00	$	5.00			$ (127.00)	$	(4.00)	$	(8.00)
Change in Fair Value of Warrant Liability											$	(183.00)		
Unrealized gain (loss) on investments					$ 9.00	$	(7.00)				$	(2.00)	$	18.00
Total Other Income (expense)	**$**	**(161.00)**	**$**	**235.00**	**$ 83.00**	**$**	**(2.00)**	**$**	**(125.00)**	**$ (127.00)**	**$**	**(240.00)**	**$**	**31.00**
Net Income (loss) Before Taxes	**$**	**(9,411.00)**	**$**	**(6,451.00)**	**$ (15,862.00)**	**$**	**(8,466.00)**	**$**	**(11,625.00)**	**$ (20,091.00)**	**$**	**(7,164.00)**	**$**	**(6,974.00)**
Income Tax	$ -	$ -	$ -	$ -	$ -	$	-	$	-	$ -	$	-	$	-
Tax Rate												
Net Income	**$**	**(9,411.00)**	**$**	**(6,451.00)**	**$ (15,862.00)**	**$**	**(8,466.00)**	**$**	**(11,625.00)**	**$ (20,091.00)**	**$**	**(7,164.00)**	**$**	**(6,974.00)**
EPS - Basic	**$**	**1.03**	**$**	**0.55**	**$ 1.58**	**$**	**1.04**			**$ 27.09**	**$**	**(0.60)**	**$**	**(0.38)**
Shares Out - Basic		9,470.9			10,261.5		11043.541			884.2		11,939.9		18511.889

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