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Chapter 1 : Calando Pharmaceuticals | RONDEL siRNA drug delivery system - In the Clinic

Transforming unprecedented RNAi technologies into treatment realities. Developing the promise of a siRNA therapeutic candidate. CALAA, Calando's leading drug candidate, is a combination of RONDELâ„¢ and a patented siRNA targeting the M2 subunit of ribonucleotide reductase, a clinically-validated cancer target.

Solid cancers are considered by many the most important near-term value driver for RNAi Therapeutics. It is this flexibility of the platform that makes RNAi Therapeutics ideally suited to satisfy the demands of a genetically such heterogeneous disease group as cancer. All of these rely on the particles being able to circulate sufficiently long in the blood stream and being small enough so that they can passively accumulate through EPR in the solid tumors as these lack an effective way of draining them through lymphatics. While particle stability and ability to accumulate through EPR is a critical first step where we should also expect to see important differentiation between the technologies, once there, the nanoparticles then have to be taken up by the cancer cells and moreover mediate the cytoplasmic release of the RNAi trigger into the cytoplasm. Although the so called RACE assay used for this analysis is not quantitative, in my experience, you have to get sufficiently robust RNAi to cleanly detect such products. It is in fact the pioneering work with RONDEL-siRNA delivery from which this pharmacokinetic model has been derived and that is now informing quite a bit our thinking of how to design siRNA-nanoparticles for solid cancer applications. For example, it was work on CALAA that showed that the utility of the transferrin targeting ligand is in enhancing the cellular uptake of the nanoparticles, not so much in concentrating them in the tumors in the first place, and should be influential in the selection of targeting ligands being contemplated now for all types of delivery technologies, including SNALPs. For a more thorough molecular background on this program, please refer to a previous entry here that was part of a 3-part collaborative series with Tobias Wolfram on the first RNAi Therapeutics solid cancer candidates. Briefly, CALAA is a self-assembled nanoparticle system based on a cationic co-polymer containing cyclodextrin complexed with siRNA targeting RRM2, a gene involved in DNA replication, and that like most of the advanced nanoparticle-siRNA systems is stabilized through pegylation some of these carry the transferrin targeting ligand. While Tobias and I had cautioned about a relative lack of preclinical in vivo characterization of CALAA, particularly not having directly demonstrated that CALAA can knock down genes via RNAi in solid tumors following intravenous administration, it seems that the gamble of skipping some of the pre-clinical proof-of-concept has paid off for the investigators and Arrowhead Research of which Calando is a subsidiary. It was also a clever move that, amongst other tumor types, a number of melanoma patients were enrolled as such tumors can be easily accessed through biopsy and thus represent good material for molecular analysis of a clinical candidate. Despite the limited sample size, a number of conclusions can be drawn from the data: Clearly, these are highly encouraging results and call for the continuation of the phase I studies and further investigation of the modular RONDEL delivery platform. Importantly for shareholders, it should put Arrowhead in a better position to fulfill their stated goal of monetizing RONDEL either through licensing or outright sale. Part of the value would derive from the pioneering position of the RONDEL technology and from representing a complementary approach to lipid-based delivery which is currently dominating RNAi Therapeutics development programs. With such progress, urgency to invest in RNAi Therapeutics, particularly in enabling delivery technologies should return. Considering the generally weak share prices of RNAi Therapeutics companies, all the ingredients seem to be in place to see related deal activities, with a significant portion of the value being driven by the solid cancer opportunity for RNAi Therapeutics. Update May 29, More details about the study, including the safety profile was published recently in an abstract for the upcoming ASCO cancer conference: Systemic delivery of siRNA via targeted nanoparticles in patients with cancer: Results from a first-in-class phase I clinical trial Author s: Ribas and colleagues Background: Systemically delivered small interfering RNA siRNA would allow targeting oncogenic molecules beyond current approaches. We report on the first siRNA trial with a targeted nanoparticle delivery system. Open-label, dose- escalation trial in pts with solid refractory cancers receiving 4 i. The 70 nm particles were designed to minimize renal clearance and allow tumor vasculature permeation

with binding to tumor hTf receptors TfR. Primary endpoints safety, MTD determination were based on the first cycle. GI 4 , melanoma 3. Dose escalation progressed with no DLTs. Most common treatment-related AEs: No objective tumor responses were seen; 1 pt at highest dose had stable metastatic melanoma for 4 mo, a change from prior course. Biopsies in 3 pts melanoma showed particles in tumors. TfR was not downregulated in cancer cells. This approach could be expanded to any currently undruggable cancer therapy target.

Chapter 2 : START - South Texas Accelerated Research Therapeutics - START NEWS

The trial, which is investigating the safety and efficacy of drug candidate CALAA and the broader RONDEL nanoparticle delivery system, represented the first time siRNA was systemically.

It is thought to be the first ever demonstration in humans of targeted siRNA-containing nanoparticle delivery to tumors using systemic administration, delivery of functional siRNAs, and achievement of specific mRNA and protein reductions via RNAi. Thus far in the trial, no significant drug-related toxicities, known as serious adverse events SAEs , have been observed that may limit use. The article, titled, "Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles" and further discussion of the article and the data may can be viewed on the Nature website. The study was led by Professor Mark E. Davis and a team of scientists at Caltech. For the past decade, the field of RNAi therapeutics has been the focus of much investigational effort and investment. RNAi as a platform is widely considered a potentially revolutionary new way of treating a wide array of diverse diseases, including many conditions that are currently considered "undruggable. As a result, investment in RNAi therapeutics has been widespread and is a major focus by most large pharmaceutical companies. However, the promise of RNAi as a new therapeutic class has not yet been realized. This has been, in large part, due to the lack of an effective and safe system for delivering highly fragile siRNA to intended tissues and cells. With its deep expertise and long experience in drug delivery technology, Calando recognized this opportunity to create significant value, and the current data suggest that it has capitalized on that opportunity. We believe we are nearing the time when siRNA therapeutics can begin to make a historic leap from science to applied medicine, where it can truly make a difference as viable treatments for patients with a variety of prevalent unmet medical needs. Effective systemic delivery of siRNA has been referred to as the Holy Grail of RNAi therapeutics, and we have now shown that we can accomplish this in humans. We have always believed that great value would be created by the first company to demonstrate the following in humans: We have now shown these, so we continue to see Calando as an attractive candidate for partnering and licensing opportunities both with respect to CALAA as a specific drug candidate, as well as with RONDEL as a broad, flexible siRNA delivery system for delivering virtually any other oncology-related siRNA sequence. Importantly, we are not seeing drug-related SAEs, so while we have entered a dose range capable of triggering RNAi, we believe we are still far from a maximum tolerated dose MTD. We intend to continue to escalate doses in search of that MTD," Dr. Importantly, the sugar-based system has not shown the immune system activation caused by other lipid-based siRNA delivery systems in pre-clinical and clinical development. Pacific time to discuss the data and its implications. To participate in the conference call, please dial toll free from the US or Canada, or from outside the US. A replay of the webcast will be available approximately two hours after the conclusion of the call. The webcast replay will remain available for 90 days. An audio replay will also be available approximately two hours after the conclusion of the call and will be made available until Friday, March 26, The audio replay can be accessed by dialing toll free from the US or Canada, or internationally, and entering account number and encore passcode number Comprised of three components and siRNA, the system is engineered to form targeted, stabilized, siRNA-containing nanoparticles of less than nm in diameter that target specific tissues and fully protect the siRNA from degradation in serum. Upon delivery to the target cell, the nanoparticle binds to membrane receptors on the cell surface and the siRNA-containing nanoparticle is taken into the cell by endocytosis. There, chemistry built into the system unpacks the siRNA from the delivery vehicle. The siRNA is deposited into the cytoplasm of the cell where it can access the cellular machinery for RNA interference. Benefits of the RONDEL system include more effective delivery, modular design to allow easy exchange of the active siRNA ingredient and targeting agent, fewer immune reactions and increased stability. Ribonucleotide reductase catalyzes the conversion of ribonucleosides to deoxyribonucleosides and is necessary for DNA synthesis and replication; it is a critical component in the proliferation of cancer cells. Transferrin receptors have been shown to be up regulated in many types of cancer cells. A cycle consists of four infusions administered on days 1, 3, 8, and 10 followed by 11 days of rest. If safe, a second day cycle is administered consisting of

infusions on days 22, 24, 29, and 31 followed by 11 days of rest. Arrowhead is seeking to build value for shareholders through the progress of its subsidiaries and investments. Currently, Arrowhead is focused primarily on its two majority owned subsidiaries; Unidym, a leader in carbon nanotube technology for electronic applications, and Calando, at the forefront of clinical application of RNAi delivery technology. Arrowhead also has minority investments in two privately held nanobiotech companies. About Calando Pharmaceuticals, Inc. Calando, a majority-owned subsidiary of Arrowhead Research Corporation, is a clinical stage nanobiotechnology company at the forefront of RNAi therapeutics. Calando develops nanoparticle therapeutics that use patented sugar cyclodextrin -based polymer technologies as a drug delivery system for siRNA. Engineered to reduce the debilitating effects of cancer treatment, the proprietary molecules are designed to improve the safety and efficacy of cancer therapeutics using siRNA as the active ingredient. The target-agnostic platform technology has the potential to be applied to a wide range of diseases beyond cancer as well as to therapeutic classes beyond siRNA therapeutics. These articles might interest you as well:

Chapter 3 : Arrowhead Completes Enrollment in Phase 1b Trial of RNAi Drug Candidate CALAA | FiercePh

Rationale: CALAA is a targeted therapeutic designed to inhibit tumor growth and/or reduce tumor size. The active ingredient in CALAA is a small interfering RNA (siRNA). This siRNA inhibits tumor growth via RNA interference to reduce expression of the M2 subunit of ribonucleotide reductase (R2).

Metaphor of two companies with large market shares, making a deal. Arrowhead Research has increased its ownership of majority-owned subsidiary Calando Pharmaceuticals through the exchange of Calando Series A preferred stock for Arrowhead warrants. It comprises an siRNA targeting ribonucleotide reductase M2, an enzyme involved in nucleotide metabolism and required for DNA replication. RRM2 is considered a promising target for cell proliferative diseases, especially cancers. An interim analysis of Phase I data from 15 solid tumor patients treated with the drug showed that it was well tolerated, including at the highest dose tested so far. The absence of significant, dose-limiting immune responses furthermore supports that Rondel, even with unmodified siRNAs, is relatively nonimmunogenic and does not function as an immune adjuvant, which is unlike a number of lipid-based delivery approaches, Calando points out. Of the 15 patients enrolled at the time of the analysis, three with melanoma volunteered to have biopsies taken allowing for more detailed molecular analyses of the effects of CALAA The firm was able to confirm the dose-dependent accumulation of CALAA in the melanoma cancer target tissues. This has not been established before for any RNAi therapeutics clinical candidate, Calando notes. Moreover, the knockdown was long lasting and could be detected after more than a month. In aggregate, the data provides first-ever direct proof of target mRNA knockdown through an RNAi mechanism of action in man, Calando reports. A cycle will consist of four infusions administered on days 1, 3, 8, and 10 followed by 11 days of rest. If safe, a second day cycle will be administered consisting of infusions on days 22, 24, 29, and 31 followed by 11 days of rest. Rondel binds to and self-assembles with siRNA to form uniform colloidal-sized particles. Analysis has shown that these particles are spherical and less than nm in diameter, according to Calando, which allows for accumulation at the tumor site. Additionally, Rondel particles have been shown to be stable under physiological conditions. Pursuant to the exchange agreement between Arrowhead and the Calando Series A holders, Arrowhead exchanged a warrant to purchase approximately 3. The Calando preferred stock is convertible into 2. Currently, Arrowhead has four subsidiaries, all of which are involved in nanotechnology. Its second majority-owned firm is Unidym, which provides bulk materials, carbon nanotube-enabled products, and intellectual property to a range of customers and partners. Arrowhead has minority investments in two early-stage companies, Nanotope and Leonardo Biosystems. Nanotope is a regenerative medicine company developing a suite of products customized to regenerate specific tissues including neuronal, vascular, bone, myocardial, and cartilage. It expects to initiate clinical trials later this year. Leonardo Biosystems has a multistage delivery platform that has been shown in animal models to be effective in targeting delivery of siRNA and small molecule drugs. It anticipates entering commercial development partnerships in

Chapter 4 : Cyclodextrin-Containing Polymers: Versatile Platforms of Drug Delivery Materials

Briefly, CALAA is a self-assembled nanoparticle system based on a cationic co-polymer containing cyclodextrin complexed with siRNA targeting RRM2, a gene involved in DNA replication, and that like most of the advanced nanoparticle-siRNA systems is stabilized through pegylation (some of these carry the transferrin targeting ligand).

An abstract with the clinical study data, entitled "Systemic Delivery of siRNA via targeted nanoparticles in patients with cancer: Results from a first-in-class phase 1 clinical trial" Abstract No. Ribas said, "Given the longstanding hurdles with effective systemic delivery of siRNA in humans, these exciting data represent a significant step for the field of RNAi. We have also seen mRNA and protein knockdown as well as the presence of RONDEL inside tumors in a dose-dependent manner, both of which are excellent indications of effective systemic delivery. The trial is an open-label, dose-escalating study of intravenously administered CALAA in adults with solid tumors, who have failed other standard-of-care treatments. One patient at the highest dose level had stable metastatic melanoma for four months, a change from prior course. Biopsies from three patients showed CALAA nanoparticles in tumors in amounts that correlate with dose levels. Additionally, a reduction of target messenger RNA and target protein was observed and at the highest dose, the targeted protein was knocked down with confirmation of mechanism by specific cleavage sequence RACE-PCR. The study is ongoing and patients continue to be enrolled at escalating doses. The Company expects to complete the Phase I study by the end of the calendar year. Comprised of three components and siRNA, the system is engineered to form targeted, stabilized, siRNA-containing nanoparticles of less than nm in diameter that target specific tissues and fully protect the siRNA from degradation in serum. Upon delivery to the target cell, the nanoparticle binds to membrane receptors on the cell surface and the siRNA-containing nanoparticle is taken into the cell by endocytosis. There, chemistry built into the system unpacks the siRNA from the delivery vehicle. The siRNA is deposited into the cytoplasm of the cell where it can access the cellular machinery for RNA interference. Benefits of the RONDEL system include more effective delivery, modular design to allow easy exchange of the active siRNA ingredient and targeting agent, fewer immune reactions and increased stability. Ribonucleotide reductase catalyzes the conversion of ribonucleosides to deoxyribonucleosides and is necessary for DNA synthesis and replication; it is a critical component in the proliferation of cancer cells. Transferrin receptors have been shown to be up regulated in many types of cancer cells. A cycle consists of four infusions administered on days 1, 3, 8, and 10 followed by 11 days of rest. If safe, a second day cycle is administered consisting of infusions on days 22, 24, 29, and 31 followed by 11 days of rest. ARWR is a nanotechnology company commercializing new technologies in the areas of life sciences and electronics. Arrowhead is seeking to build value for shareholders through the progress of its subsidiaries and investments. Currently, Arrowhead is focused primarily on its two majority owned subsidiaries; Unidym, a leader in carbon nanotube technology for electronic applications, and Calando, at the forefront of clinical application of RNAi delivery technology. Arrowhead also has minority investments in two privately held nanobiotech companies. About Calando Pharmaceuticals, Inc. Calando develops nanoparticle therapeutics that use patented sugar cyclodextrin -based polymer technologies as a drug delivery system for siRNA. Engineered to reduce the debilitating effects of cancer treatment, the proprietary molecules are designed to improve the safety and efficacy of cancer therapeutics using siRNA as the active ingredient. The target-agnostic platform technology has the potential to be applied to a wide range of diseases beyond cancer as well as to therapeutic classes beyond siRNA therapeutics. This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties. We disclaim any intent to revise or update publicly any forward-looking statements.

Chapter 5 : Calando Pharmaceuticals | RONDEL siRNA drug delivery system - About

R2 is the gene targeted by Calando's lead siRNA-containing nanoparticle therapeutic, CALAA, which is currently in a Phase I clinical trial for patients with non-resectable or metastatic solid tumors.

It is thought to be the first ever demonstration in humans of targeted siRNA-containing nanoparticle delivery to tumors using systemic administration, delivery of functional siRNAs, and achievement of specific mRNA and protein reductions via RNAi. Thus far in the trial, no significant drug-related toxicities, known as serious adverse events SAEs , have been observed that may limit use. Further discussion of the article and the data may also be viewed at: The study was led by Professor Mark E. Davis and a team of scientists at Caltech. For the past decade, the field of RNAi therapeutics has been the focus of much investigational effort and investment. RNAi as a platform is widely considered a potentially revolutionary new way of treating a wide array of diverse diseases, including many conditions that are currently considered "undruggable. As a result, investment in RNAi therapeutics has been widespread and is a major focus by most large pharmaceutical companies. However, the promise of RNAi as a new therapeutic class has not yet been realized. This has been, in large part, due to the lack of an effective and safe system for delivering highly fragile siRNA to intended tissues and cells. With its deep expertise and long experience in drug delivery technology, Calando recognized this opportunity to create significant value, and the current data suggest that it has capitalized on that opportunity. We believe we are nearing the time when siRNA therapeutics can begin to make a historic leap from science to applied medicine, where it can truly make a difference as viable treatments for patients with a variety of prevalent unmet medical needs. Effective systemic delivery of siRNA has been referred to as the Holy Grail of RNAi therapeutics, and we have now shown that we can accomplish this in humans. We have always believed that great value would be created by the first company to demonstrate the following in humans: We have now shown these, so we continue to see Calando as an attractive candidate for partnering and licensing opportunities both with respect to CALAA as a specific drug candidate, as well as with RONDEL as a broad, flexible siRNA delivery system for delivering virtually any other oncology-related siRNA sequence. Importantly, we are not seeing drug-related SAEs, so while we have entered a dose range capable of triggering RNAi, we believe we are still far from a maximum tolerated dose MTD. We intend to continue to escalate doses in search of that MTD," Dr. Importantly, the sugar-based system has not shown the immune system activation caused by other lipid-based siRNA delivery systems in pre-clinical and clinical development. Pacific time to discuss the data and its implications. To participate in the conference call, please dial toll free from the US or Canada, or from outside the US. This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties. We disclaim any intent to revise or update publicly any forward-looking statements. A replay of the webcast will be available approximately two hours after the conclusion of the call. The webcast replay will remain available for 90 days. An audio replay will also be available approximately two hours after the conclusion of the call and will be made available until Friday, March 26, The audio replay can be accessed by dialing toll free from the US or Canada, or internationally, and entering account number and encore passcode number About Arrowhead Research Corporation Arrowhead Research Corporation is a nanotechnology company commercializing new technologies in the areas of life sciences and electronics. Arrowhead is seeking to build value for shareholders through the progress of its subsidiaries and investments. Currently, Arrowhead is focused primarily on its two majority owned subsidiaries; Unidym, a leader in carbon nanotube technology for electronic applications, and Calando, at the forefront of clinical application of RNAi delivery technology. Arrowhead also has minority investments in two privately held nanobiotech companies. About Calando Pharmaceuticals, Inc. Calando develops nanoparticle therapeutics that use patented sugar cyclodextrin -based polymer technologies as a drug delivery system for siRNA. Engineered to reduce the debilitating effects of cancer treatment, the proprietary molecules are designed to improve the safety and

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