Industry
Biologics

Key Features
Keren is developing first-in- class treatment for sarcopenia, cachexia and Alzheimer's; addressing unmet need and a blockbuster market. Company's intellectual property provides clinical utility claims with protection through 2034. Research and Development to date benefited from $7 million in grant funding. KEREN plans to file an IND within 18 months from funding and exit upon completion of Phase II trial within 6 years from funding. GMP-grade material for late pre-clinical and early clinical trials will be produced by Genscript. Phase IIa clinical trial will focus on use of osteocalcin as therapy for sarcopenia and is expected to enroll 60 patients over 12 months.

Company Resources
Exclusive License Agreement between Columbia and Keren will be executed upon funding. Company currently benefits from an NIH grant.

Awards/Recognition

Gerard Karsenty, M.D., Ph.D.
Richard Lounsbery Award, National Academy of Science (USA), French Academie des sciences, 2010
Lee C. Howley Prize for Arthritis Research, Arthritis Foundation, 2008
Schaefer Award, Columbia University Medical Center, 2007
Drieu-Cholet Award, The French National Academy of Medicine, 2006
Edith and Peter O'Donnell Award, The Academy of Medicine, Engineering and Science of Texas, 2006

Business Description: Keren Therapeutics (Keren) is a spin off from Columbia University focusing on pre-clinical and early clinical development of recently discovered hormone osteocalcin as treatment for sarcopenia, cancer cachexia, Alzheimer's and cognitive impairment due to aging. Osteocalcin is a biological construct that can be synthesized on commercial scale and delivered via depot administration. Development of osteocalcin benefited from more than $7 million in grant support. Columbia patented the composition of matter and its utility through 2034 and 2031, for muscular and cognitive impairment indications, respectively. KEREN intends to file an IND within 18 months from funding. Cost of development through completion of first-in-man studies is expected to be $8,200,000. Osteocalcin is addressing blockbuster market with unmet medical need in case of sarcopenia. We anticipate selling KEREN or executing a co-development agreement with pharma within 6 years from funding. The Company's value at that time could exceed $50 million, providing investors with 6x ROI.

Market size and growth:

- Sarcopenia
  Sarcopenia is characterized first by a decrease in muscle mass, muscle function with a reduction in muscle tissue quality, characterized by such factors as replacement of muscle fibres with fat, an increase in fibrosis, changes in muscle metabolism, oxidative stress, and degeneration of the neuromuscular junction. Among adults with an average age of 70.1 years the prevalence of sarcopenia is 36.5%. It is estimated that 7 million Americans suffer from sarcopenia. As of July 2015, there are no approved pharmaceuticals for the treatment of sarcopenia. Growth hormone increases muscle protein synthesis and increases muscle mass, but does not lead to gains in strength and function in most studies. Testosterone has some positive effects on muscle strength and mass, but increases risk of prostate cancer in men and virilization in women. (Wikipedia)

- Cancer Cachexia
  Cachexia or wasting syndrome is loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite in someone who is not actively trying to lose weight. Cachexia is seen in patients with cancer, AIDS, celiac disease, chronic obstructive pulmonary disease, multiple sclerosis, Rheumatoid arthritis, congestive heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia) and hormonal deficiency. It is a positive risk factor for death. (Wikipedia) In the industrialized world, the overall prevalence of cachexia is growing and it currently affects around 1 % of the patient population, i.e. around 9 million people. Cachexia is currently not treated with pharmaceuticals.

- Alzheimer's disease and age-related decrease in cognition
  Alzheimer's disease (AD), leads to loss of bodily functions and ultimately to death. Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years. No treatments stop or reverse its progression. In 2015, there were approximately 48 million people worldwide with AD. It most often begins in people over 65 years of age. It affects about 6% of people 65 years and older. In 2010, dementia resulted in about 486,000 deaths (Wikipedia).

Scientific Expertise: *Osteocalcin is the most abundant non-collagenous protein found in mineralized bone matrix. It is comprised of 46 amino acid residues, including three gamma carboxylated glutamic acid residues. Osteocalcin needs to be decarboxylated to become active as a hormone In the periphery undercarboxylated osteocalcin (osteocalcin) improves uptake of glucose by muscle and increases fatty acid oxidation and protein synthesis in muscle. Osteocalcin is also capable of crossing the blood-brain barrier and has also been shown to influence a number of neurological pathways. This technology aims to use osteocalcin to prevent muscle wasting and neuronal apoptosis, and in doing so, preserve physical and cognitive functions.*

Sarcopenia-related facts:
- Osteocalcin circulating levels increase after exercise and decrease with age
- We have observed that mice lacking osteocalcin or its receptor present at 3 months of age a phenotype of muscle wasting as seen in aged mice. This phenotype includes decreased muscle mass and decreased muscle function.

Total External Capital Invested
The academic laboratory expended more than $7 million on identification and characterization of the hormone and relevant druggable targets

Financing Sought:
$8,200,000 tranched

Scientific Advisors

***Ronald C. Kahn,* MD**
Professor
Harvard Medical school,
Boston, MA

***Eric N. Olson,* Ph.D.**
Professor and Chairman
Department of Molecular Biology,
UT Southwestern, Dallas, TX.

- The same phenotype is observed in mice lacking osteocalcin receptor in myoblasts only that do not have any of the metabolic perturbations seen in Osteocalcin-/- mice thus indicating that the functions of osteocalcin in muscle is not secondary to its role in insulin secretion and sensitivity
- A simple injection of osteocaclin in 12 month-old WT mice restores the muscle function to level of a 3 month-old mice.

Cognitive impairment-related facts:
- Osteocalcin crosses the blood brain barrier
- Osteocalcin favors synthesis of all monoamine neurotransmitters and prevents the one of GABA
- Osteocalcin prevents neuron apoptosis during development
- Osteocalcin binds to and signals in specific neuronal populations in the amygdala and hippocampus that are relevant to cognition
- Osteocalcin is needed for proper cognitive functions
- Peripheral injections of osteocalcin in older wild type mice lowers anxiety and significantly improves memory
- Maternal-derived osteocalcin favors brain development in the embryos and optimizes cognitive functions in the offspring.

Technology: Despite advances in understanding the biology of sarcopenia there is no approved treatment for this disease. The same is true for age-related decrease in cognitive functions and Alzheimer's disease. Administration of osteocalcin is expected to be efficacious in patients as it is in rodents in part because the hormone is endogenous to both species. Furthermore, we would not expect serious side effects because the hormone seems to have mostly positive effect in body such as improved metabolism, cognition, muscle function and male fertility. Moreover, because osteocalcin favors liver gluconeogenesis even when overdosed it does not cause hypoglycemia. Dr. Karsenty's lab identified the osteocalcin receptor in myofibers and β cells of the pancreas that is drugable target for the treatment of sarcopenia and glucose intolerance. His laboratory has also identified a receptor for osteocalcin mediating its functions in the brain. Thus as follow up product Keren will be able to develop a treatments based on synthetic compounds.

Intellectual Property: Two PCT patent applications were filed in March, 2014 and January, 2015. The first patent application titled "Use of osteocalcin for treatment of age-related cognitive decline" has serial numbers PCT/US14/027404 and 14/777,285.
The other patent application titled "Osteocalcin maintains muscle mass and functions" has serial number PCT/US2015/061590.

Regulatory Strategy: Our sarcopenia regulatory strategy is guided by the need for efficacious therapy that improves quality of life and patient's ability to take care of self. We will initially conduct a Phase I trial with a standard 3x3 design to determine the maximum tolerated dose with depot administration. We do not anticipate serious adverse effects of this endogenous hormone. The phase I study will be followed by a Phase IIa single arm clinical trial enrolling approximately 60 patients with the objective to show convincing effects on muscle function with the most efficacious dose for all of patients. There will be an early stopping rule for futility, and robust molecular correlative analyses to pursue potentially patentable biomarker development. Encouraging results will be followed by a phase III trial.

Comparables:

October 1, 2012 - Novartis jumped on board MorphoSys' antibody discovery platform to find BYM338. The treatment reins in myostatin, and investigators have cited its added potential for cachexia, COPD and sarcopenia. Back in the spring of 2014, MorphoSys execs put its peak sales potential at a whopping $4 billion while the FDA has handed out its breakthrough therapy designation alongside its commitment to speed development efforts. Novartis will make an approx. € 9 million investment in MorphoSys by purchasing non-interest bearing convertible bonds of MorphoSys. The convertible bonds can be converted into 490,133 common MorphoSys shares, to be issued from conditional capital. In addition, MorphoSys will receive over US$ 30 million in committed R&D funding and technology license fees over the first three years.

MorphoSys also stands to receive technology license payments, research and developmental milestones, as well as royalties on marketed antibody products.

September 15, 2014 - Scholar Rock, a Cambridge, MA-based developer of niche modulators had raised $20m in Series A funding round led by ARCH Venture Partners, followed with a $36m in Series B round led by Fidelity Management and Research Company. Scholar Rock is developing a myostatin blocker, looking to build muscle in patients suffering from muscle atrophy.

February 21- 2014 - Pronutria revealed a $12.5 million Series B round, with unnamed private investors participating alongside Flagship Ventures. Much of the Series B will be used for clinical trials on two muscle-protecting candidates that preserve strength in frail, elderly people with sarcopenia, the loss of muscle mass that can occur during periods of hospitalization. The candidates, PN-107 and PN-365, are formulations of the amino acid leucine delivered as small "shot"-sized beverages similar to bottled energy products found on supermarket shelves.

Manufacturing: GMP-grade product for late pre-clinical and early clinical development will be produced by Genscript, Piscataway, NJ.

Funding Strategy and Use of Proceeds: We will retain Genscript to produce I kg of GMP compound at cost of $2,400,000. This compound will be used to perform late stage pre-clinical and Phase I clinical studies. Mechanistic studies are funded with existing NIH grant. Construct optimization, depot formulation and depot dose response studies, GMP scale-up, Bioanalytical method, Pk/Pd studies, ADMET and CMC studies will cost $3,870,000. Cost of regulatory and clinical consultants who will prepare IND submissions to the FDA and design clinical studies is expected to reach $250,000. Phase I clinical studies will cost $540,000 and patent prosecution will reach $450,000.
First year of R&D will yield development candidate with appropriate formulation costing about $2,250,000. During the second year we will spend $2,320,000 to generate necessary data to file an IND. Third year R&D activities cost is expected to reach $3,630,000 and will test the lead compound in first-in-man studies.

Contact Information

Jerry Kokoshka, Ph.D., MBA
Columbia Technology Venture
(212) 305-8884
Jk2108@Columbia.edu