



RETRAINEE - JOB CREATION
Critical Proposal Proposal for:
Audentes Therapeutics, Inc.
Agreement Number: ET16-0477

Panel Meeting of: May 26, 2016

ETP Regional Office: San Francisco Bay Area

Analyst: A. Nastari

PROJECT PROFILE

Contract Attributes:	Critical Proposal Retrainee Job Creation Initiative Priority Rate SB <100	Industry Sector(s):	Biotechnology/Life Sciences Priority Industry: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Counties Served:	San Francisco, San Mateo	Repeat Contractor:	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Union(s):	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
Number of Employees in:	CA: 66	U.S.: 66	Worldwide: 66
<u>Turnover Rate:</u>	6%		
<u>Managers/Supervisors:</u> (% of total trainees)	N/A		

FUNDING DETAIL

Program Costs	-	(Substantial Contribution)	(High Earner Reduction)	=	Total ETP Funding
\$411,840		\$0	\$0		\$411,840

In-Kind Contribution:	100% of Total ETP Funding Required	\$1,000,000
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TRAINING PLAN TABLE

Job No.	Job Description	Type of Training	Estimated No. of Trainees	Range of Hours		Average Cost per Trainee	Post-Retention Wage
				Class / Lab	CBT		
1	Critical Proposal Priority Rate SB<100	Commercial Skills, Continuous Impr	40	8-280	0	\$4,680	\$18.00
				Weighted Avg: 180			
2	Critical Proposal Job Creation Priority Rate SB<100	Commercial Skills, Continuous Impr	48	8-280	0	\$4,680	\$23.00
				Weighted Avg: 180			

Minimum Wage by County: \$17.02 per hour for San Francisco and San Mateo Counties

Health Benefits: Yes No This is employer share of cost for healthcare premiums – medical, dental, vision.

Used to meet the Post-Retention Wage?: Yes No Maybe

Although employer provides health benefits, they are not being used to meet Post-Retention Wage.

Wage Range by Occupation

Occupation Titles	Wage Range	Estimated # of Trainees
Job Number 1		
Administrative Assistant		6
Administrator		1
Engineer 1		1
Maintenance Worker		1
Manager		5
Manufacturing Supervisor		3
Research Associate		2
Scientist		4
Senior Technical Staff		17
Job Number 2		
Administrator		3
Engineer 1		2
Engineer 2		2
Maintenance Worker		4
Manager		8
Manufacturing Supervisor		4

Manufacturing Worker		10
Project Manager		4
Quality Assurance Worker		6
Research Associate		3
Scientist		2

Critical Proposal

This proposal for Audentes Therapeutics, Inc. (Audentes) is designated as a “Critical Proposal”, as defined in Title 22, California Code of Regulations (CCR) 4402.2, by the Governor’s Office of Business and Economic Development.

INTRODUCTION

Audentes Therapeutics, Inc. (Audentes), founded in San Francisco in 2012, is a biotechnology company dedicated to the development and commercialization of “gene therapy” for rare and serious diseases caused by the loss of protein. Gene therapy, while still in the research stage, treats patients by introducing functional copies of genes through vectors (genetically engineered viruses). Once introduced, the copied genes direct cells to produce new genetic materials; in this case, proteins.

The Company has two facilities in California: a headquarters in San Francisco and a manufacturing facility in South San Francisco. Both locations will participate in this proposal. The Company develops, manufactures, and tests vectors at both locations. Clinical testing is scheduled for later this year, pending final approval by the Food and Drug Administration (FDA).

PROJECT DETAILS

Audentes currently has four vector strains in which it is developing processes and formulas required to produce non-clinical (animal testing) and clinical (human testing) studies. To meet FDA requirements, Audentes must first develop consistent processes for the manufacturing of gene therapy products and demonstrate unchanging formulas in its manufacture of vectors. Processes must be brought to scale in a manner that is consistent and re-producible and meets FDA standards. The four vector strains are as follow:

1. AT132 for the treatment of X-Linked Myotubular Myopathy (XLMTM). This is a very rare, inherited disorder affecting approximately one in 50,000 newborn males worldwide. Its effects consist of profound muscle weakness, severe respiratory impairment, and high mortality—almost half of affected children die before 18 months of age. Children with XLMTM who survive beyond infancy suffer significant morbidities and poor quality of life, often requiring supportive care that includes ventilator assistance, motorized wheelchairs and feeding tubes. There is currently no approved treatment for XLMTM. The goal of gene therapy with AT132 is delivery of a specific gene to a patient’s muscle cells, and long-term production of functioning enzyme.
2. AT342 for the treatment of Crigler-Najjar Syndrome Type 1. This is a very rare, inherited disease characterized by severely high levels of bilirubin in the blood. This disease risks irreversible neurological damage and death. It is currently estimated to affect approximately one per million newborns worldwide. With appropriate intervention—typically phototherapy and/or liver transplantation-- life expectancy is around 30 years of age. Left untreated, neurological dysfunction will typically cause death before 2 years of age. The goal of gene

therapy with AT342 is the long-term expression of a protein, leading to restoration and maintenance of normal levels of bilirubin.

3. AT307 for the treatment of Catecholaminergic Polymorphic Ventricular Tachycardia. This is a very rare, inherited cardiac disease, which usually manifests in the first or second decade of life. Physical or emotional stress may cause abnormal heartbeats that can rapidly progress to cardiac arrest and sudden death. It is estimated to affect one in 10,000 people. The disease is caused by mutations in a gene that encodes a protein which plays a key role in the calcium release in cardiac muscle cells. The goal of gene therapy with AT307 is the long-term expression of the calcium in cardiac muscle cells and prevention of life-threatening abnormal heartbeats.
4. AT982 for the treatment of Pompe disease. This is a very rare, inherited neuromuscular disease with variable ages of onset. It is estimated to affect approximately one in every 40,000 births worldwide. Clinical symptoms consists of severe, progressive muscle weakness and respiratory impairment. When untreated, the natural course of this disease leads to wheelchair and ventilator dependence, and death. Patients with the most severe form of Pompe disease usually die before the age of one year, if untreated. The disease is caused by mutations in a gene that encodes the protein needed to break down glycogen – a stored form of sugar used for energy. The goal of gene therapy is long-term expression of the protein to reduce build-up of stored glycogen.

Audentes is one of a few companies in the U.S. working to move gene therapy from pure research to the trial stage for the treatment and potential cure of specific diseases. The Company hopes to receive FDA approval of vectors for non-clinical and clinical trials in the fourth quarter of 2016. If approved, production of XLMTM and AT342 clinical trials will be delivered for FDA approval as the next step.

Extensive training is needed for developing processes and formulas required to produce non-clinical and clinical studies, designing and creating vectors, and using new equipment and technologies to produce genetic paths and genetic material.

Retrainee - Job Creation

With the expected approval for clinical trials, Audentes must ramp up production capacity. The Company's facility in South San Francisco, currently 21,960-square-feet, will be expanded an additional 17,000 square feet in June 2017 to make room for future growth.

Audentes is committed to hiring 48 new employees (Job Number 2). The date-of-hire for all newly hired trainees will be within the three-month period before contract approval or within the term-of-contract. These trainees will be hired into "net new jobs" as a condition of contract.

Training Plan

Commercial Skills (80%): Training will be offered to all occupations. Training will focus mainly on the Company's newly developed Standard Operating Procedures (SOPs), Good Manufacturing Practices (GMPs) and regulatory requirements. Additional Commercial Skills in the area of Clinical Trials, Process Development, Program Management, R&D, Production, Quality Control, Maintenance, will be delivered as required according to occupation.

Continuous Improvement (20%): All occupations will receive one or more courses in Continuous Improvement consisting of team building, troubleshooting, and monitoring quality.

Training Hours Limitation

Audentes is requesting a modification to the maximum hours cap to allow up to 280 hours of training (weighted average of 180 hours per trainee). The Company's extensive training program requires approximately 900 hours, with 42 trainees each receiving an average of 641 hours. Any hours over 280 will be covered by the Company. Workers will be in full-time training sessions between June and November 2016.

The high number of training hours is attributed to the complex nature of process development, implementation, and ultimately the production of testing products. The Company has a third-party team that is developing Standard Operating Procedures (SOPs) and Good Manufacturing Practices (GMPs) to control its processes and systems.

Currently, Engineers and Manufacturing Workers must execute each process until competence is demonstrated, which may result in various "practice runs" of the genetic material. Trainees will first produce non-clinical batches that will be discarded upon completion, based on step-by-step processes. Trainees will then produce non-clinical batches that will be used for trials. Non-clinical testing must be FDA approved before the Company can move to developing clinical products. Once the clinical products are approved by FDA, it will then be able to begin manufacturing the gene therapy treatments for commercial use.

During this training time, processes may change, which will result in updating SOPs and GMPs, thereby requiring additional training.

Commitment to Training

Audentes represents that ETP funds will not displace the existing financial commitment to training. Safety training is, and will continue to be, provided in accordance with all pertinent requirements under state and federal law.

As a new company, Audentes has been limited to a training budget of \$100,000, which has been used to provide informal, on-the-job training and attend educational conferences and meetings. Also, mandatory company-sponsored training has been delivered to all occupations based on job-specific skills.

➤ Training Infrastructure

Audentes will utilize internal trainers to deliver most of its proprietary training. Classroom training will consist of its SOPs, GMPs, regulatory requirements, process development, R&D, and Quality Control. Afterwards, the Company will provide training in a simulated, non-production laboratory setting to develop formulas, based on step-by-step processes, for non-clinical batches. These batches will be discarded upon completion of training. Once the processes are finalized, the Company will develop the actual batches that will be provided to the FDA for review. It will then use these same processes to create vectors for clinical trials. At the end of clinical trials, the Company will have to resubmit for approval. If approved, the Company may then begin commercial manufacture of vectors.

Third-party vendors may be considered during which time the Company will notify ETP. Company personnel will schedule training activities and document training on rosters. Approximately four people will work together to administer this project. The Company will be ready to begin training once the ETP Proposal is approved.

Impact/Outcome

Audentes' ultimate goal is to produce FDA approved gene therapy products that will lead to improved quality of life and/or cures for affected persons.

RECOMMENDATION

Staff recommends approval of this proposal including modifying the cap from 200 to 280 hours.

DEVELOPMENT SERVICES

Audentes retained Steve Duscha Advisories in Sacramento to assist with development of this proposal for a flat fee of \$17,500.

ADMINISTRATIVE SERVICES

Audentes also retained Steve Duscha Advisories to perform administrative services in connection with this proposal for a fee not to exceed 10% of payment earned.

TRAINING VENDORS

To Be Determined

Exhibit B: Menu Curriculum**Class/Lab Hours**

8 – 280

Trainees may receive any of the following:

COMMERCIAL SKILLS

Clinical Trials

- ✦ Creating and following standard operating procedures
- ✦ Following Good Clinical Practice
- ✦ Following regulations for clinical trials
- ✦ Conducting site qualification visits to assess clinical trial sites
- ✦ Working with clinical research organizations
- ✦ Monitoring and auditing clinical trials
- ✦ Managing investigational supplies
- ✦ Documenting clinical trials
- ✦ Identifying, assessing, and implementing appropriate corrective actions
- ✦ Managing local labs and supplies
- ✦ Reporting adverse events
- ✦ Creating protocols for preclinical animal studies
- ✦ Analyzing preclinical data

Process Development

- ✦ Developing processes for production of gene therapy vectors
- ✦ Assessing equipment needs
- ✦ Equipment procurement and layout
- ✦ Optimizing cell growth and productivity
- ✦ Using bioreactors
- ✦ Developing downstream processing steps and methodology to ensure high yield, potency and purity
- ✦ Producing research drug products for animal studies
- ✦ Evaluation procedures of production process
- ✦ Working in a GMP (FDA Good Manufacturing Practice) environment
- ✦ Meeting regulatory requirements
- ✦ Integrating processes
- ✦ Managing production of research drug products
- ✦ Assessing and implementing new manufacturing technologies

Program Management

- ✦ Managing drug product development
- ✦ Developing project plans
- ✦ Setting timelines
- ✦ Budgeting
- ✦ Contingency planning
- ✦ Risk mitigation
- ✦ Tracking milestones
- ✦ Managing internal and external partners
- ✦ Managing suppliers

- ✚ Reporting
- ✚ Managing supply chains
- ✚ Managing inventory
- ✚ Record keeping
- ✚ Warehouse management
- ✚ Sourcing raw materials and equipment
- ✚ Meeting regulatory requirements

Research and Development

- ✚ Conducting assays
- ✚ Assays to detect residual impurities
- ✚ Assays for titration and residual impurity quantification
- ✚ Cell-based in-vitro potency assays for AAV products
- ✚ Biochemical assays
- ✚ Shake flask culturing
- ✚ Cell line maintenance
- ✚ Mammalian cell transfection
- ✚ Mammalian cell transduction
- ✚ Fluorescent microscopy
- ✚ Supply management
- ✚ Preparing standard operating procedures
- ✚ Optimizing Adeno-Associated Virus vector production and potency
- ✚ Standardizing assays for vector genome production
- ✚ Vector system design
- ✚ Engineering cells for performance
- ✚ Evaluating production experiments and system designs
- ✚ Isolation and characterization of stable cell lines
- ✚ Developing novel assays to assess viral vector attributes based on nucleic acid chemistry
- ✚ Using analytical assays to support process development
- ✚ Developing and maintaining laboratory quality control systems and reports
- ✚ Coordinating internal and external research activities
- ✚ Creating reference standards

Production

- ✚ Producing AAV in shake flasks and bench-scale bioreactors
- ✚ Developing and implementing process sampling plan to monitor process development
- ✚ Interpreting analytic data from in-process and final production quality data
- ✚ Process optimization
- ✚ Creating pilot production scale cell culture operations
- ✚ Preparing cell culture media and reagents
- ✚ Sterile handling
- ✚ Monitoring and sampling of lab scale cultures
- ✚ Scheduling research scale production batches
- ✚ Selecting and implementing new technologies and instrumentation
- ✚ Generating and managing laboratory documentation
- ✚ Managing data
- ✚ Troubleshooting operations

- ✦ Performing cell culture activities
- ✦ Thawing, feeding, passaging, cell banking, transfecting and harvesting cell lines
- ✦ Qualifying equipment and instruments
- ✦ Calibrating and maintaining equipment and instruments
- ✦ Creating manufacturing policy and procedures
- ✦ Creating documentation systems
- ✦ Following GMP and ISO requirements
- ✦ Set-up, inspection and use of production equipment
- ✦ Establishing and following safety protocols
- ✦ Developing and implementing corrective action plans
- ✦ Installing and using control and automation systems
- ✦ Designing, engineering, and commissioning of new systems
- ✦ Conducting trial runs
- ✦ Creating qualifying lots
- ✦ Minimizing process deviations and unplanned equipment downtime
- ✦ Transferring cell culture and purification technologies from development into production
- ✦ Starting up the production facility
- ✦ Starting up and qualifying equipment

Quality Control

- ✦ Developing and using standard operating procedures for quality functions
- ✦ Analyzing and interpreting test results
- ✦ Identifying deviations
- ✦ Conducting equipment qualification and validation studies
- ✦ Testing raw materials for conformance
- ✦ Quality assurance during design, commission, validation and startup of new manufacturing processes and facilities
- ✦ Resolving discrepancies
- ✦ Implementing change control policies

Maintenance

- ✦ Managing calibration and calibration services
- ✦ Creating standard operating procedures for planned maintenance
- ✦ Creating standard operating procedures for repairs
- ✦ Develop calibration testing procedures for temperature, pressure, level, flow and analytical instruments
- ✦ Testing electronic components to determine functionality level and capacity
- ✦ Maintaining records
- ✦ Maintaining mechanical systems
- ✦ Preventive maintenance
- ✦ Troubleshooting
- ✦ Conducting safety checks
- ✦ Setting up and testing equipment

CONTINUOUS IMPROVEMENT

- ✦ Development of standard operating procedures
- ✦ Use of standard operating procedures
- ✦ Monitoring quality
- ✦ Measuring reproducibility
- ✦ Working in teams
- ✦ Selecting team members
- ✦ Troubleshooting
- ✦ Corrective Action

Note: Reimbursement for retraining is capped at 280 total training hours per trainee, regardless of the method of delivery.