Non-Viral Aquaporin-1 Gene Therapy to Restore Salivary Flow in Patients Suffering from Radiation-Induced Xerostomia

CLINICAL NEED

In the treatment of head and neck cancers, radiotherapy is commonly prescribed in conjunction with other modalities such as surgery and/or chemotherapy. Because of the anatomical proximity, salivary glands receive secondary damage, where xerostomia is one of the common effects of this damage. While intensity-modulated radiotherapy has significantly reduced the incidence of radiation-induced xerostomia, a pressing need exists for the remaining patients, especially for those in whom amifostine leads to significant side effects.

SOLUTION

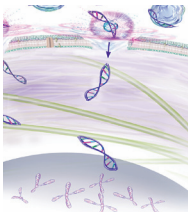
A team of researchers at the Allegheny Health Network led by Michael Passineau, PhD, has developed an ultrasound-assisted gene transfer technique (UAGT), to deliver AQP1 gene for the amelioration of radiation-induced xerostomia. This non-viral gene delivery is based on sonoporation generated by the ultrasound, enabling gene transfer as cell membrane permeability is altered. The delivery of AQP1 to the parotid glands in a mini-swine model has restored salivary flow to pre-treatment levels, demonstrating the efficacy of non-viral AQP1 gene transfer.

COMPETITIVE ADVANTAGE

While a recent clinical trial using AQP1 gene delivery demonstrated increase in saliva production, this approach has not advanced beyond a successful Phase I/II trial to regulatory approval due to the utilization of the adenovirus vector for gene delivery. With the preclusion of a virus for gene transfer, this approach is anticipated to provide enhanced safety and enable serial dosing to provide patients with the benefit of the AQP1 gene transfer throughout their lifetime.

ITP SUPPORT

The long-term objective of this research program is to improve the quality of life in patients who have suffered from radiation-induced xerostomia. In collaboration with Dr. Isabelle Lombaert at the University of Michigan, the ITP program will support the continued validation and characterization of UAGT for the delivery of AQP1 gene towards enabling FDA submission.



MICHAEL PASSINEAU, PHD
Allegheny Health Network

ISABELLE LOMBAERT, PHD
University of Michigan

"We are working to develop a safe gene therapy to provide lifelong relief from dry mouth in patients whose salivary function has been damaged by radiotherapy for head and neck cancers."

http://media.dent.umich.edu/labs/lombaert

CLINICAL TRANSLATION PATHWAY

Publications:
Ultrasound-assisted nonviral gene transfer of AQP1 to the irradiated minipig parotid gland restores fluid secretion. Gene Ther 2015.

Intellectual Property:
In development with MPWRM Core

Regulatory Pathway:
Anticipated: Biologic, IND to enable PMA

Commercialization Strategy:
In development with the MPWRM Commercialization/ Market Needs Core

Product Launch Strategy:
In development with the MPWRM Commercialization/ Market Needs Core

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Contact Information:
Mutsumi Yoshida, PhD | Managing Director, U-M site | yoshidam@umich.edu | **www.doctrc.com**

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Michael Passineau and Isabelle Lombaert

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DOCTRC DENTAL, ORAL, & CRANIOFACIAL TISSUE REGENERATION CONSORTIUM

Michigan - Pittsburgh - Wyss Regenerative Medicine Resource Center

Annual Retreat 2020 | December 8, 2020

UNMET CLINICAL NEED

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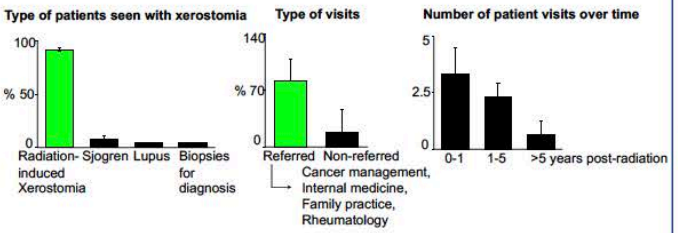
Here, we aim to move this new therapy forward towards towards clinical trials by performing market assessment, preparing FDA regulatory documents, prepare for commercialization, and finalize GLP studies.

MARKET ANALYSIS

STEAKHOLDERS: ENT's, head-and-neck surgeons, oral surgeons



STEAKHOLDERS: Patients

- Only 10% is satisfied with current prescriptions to mitigate xerostomia (e.g. oral hydration, artificial saliva, steroids, pilocarpine, amifostine)
- Current cost for patients ranges from $20-$500 per month

CONDITIONS FOR IMPLEMENTATION OF NEW THERAPY

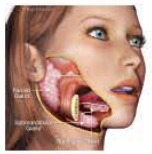
- Phase I/II trial needs to demonstrate
  - Objective increase in saliva
  - Fewer dental issues, reduction in dental decay and improved QOL
- Coverage by insurance based on reimbursement for small amount of procedure time
- Updated training session required for retro-ductal cannulation of the salivary gland by physicians per center or institute
- Evaluate the condition of the duct beforehand

- Objective (e.g. saliva measurements) and/or subjective (e.g. questionnaires) measurement of hyposalivation necessary

INCLUSION / EXCLUSION OF PATIENTS

Inclusion: 18 months post-radiotherapy treatment

Exclusion: children, parotidectomy, history of ductal pathology (e.g. strictures, stones), active cancer



NECESSARY EQUIPMENT

- Ultrasound device with probe transducer
- 2 vials (microbubbles and vector)
- catheter
- mixing tool

MARKET OPPORTUNITY

- 50,000 newly diagnosed patients per year in addition to already radiated patients
- Current competitors are

A) pilocarpine (generates side-effects, doesn't cure xerostomia)
B) mouthwashes (doesn't cure xerostomia)
C) Phase I/II trial of AQP1 via adeno-associated virus (unlikely to provide successive treatment modules)

RESULTS

Milestones accomplished since entry into the program:

1) Manufacture and acquisition of clinic-ready ultrasound device.
2) Design of 3 GLP-compliant preclinical studies to support IND submission.
3) Completion of first GLP Study.
4) Term sheets obtained for license to microbubbles and vector.
5) Market analysis.

MANUFACTURING

The three components of our therapeutic system include: 1) the ultrasound transducer, 2) microbubbles and 3) vector.
(1) has been manufactured and is in our possession.
(2) has been manufactured according to GMP standards and is in our possession.
(3) has been manufactured according to GMP standards by other groups, but is not yet in our possession.

1) 
2) 
3) 

INTELLECTUAL PROPERTY

- A number of issued patents cover aspects of the vector, microbubbles and ultrasound device.
- We have agreements in process to license this portfolio of patents in our field of use.
- We also plan to leverage the 12-year data exclusivity rule for new biologics.

REGULATORY PATHWAY

- We intend to obtain FDA approval to initiate a Phase I clinical study through a Investigational New Drug (IND) application.
- To this end, we have retained Kay Fuller, President of Medical Device Regulatory Solutions as a member of our team.

TIMELINE & FUTURE DIRECTIONS

Our goals for 2021 include the following:

1) Complete GLP Study #2
2) Complete GLP Study #3
3) Finalize and Submit IND
4) Graduate from the ITP program.

REFERENCES