Transdermal deferoxamine for treatment of irradiated soft tissue

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Clinical Need

Approximately one-third to one-half of all patients with cancer receive radiation therapy, and greater than 90% of patients experience radiation-induced collateral soft tissue injury including severe, debilitating chronic fibrosis. Current therapeutic approaches for patients with radiation-induced soft tissue fibrosis are limited. A mechanism to improve local perfusion and skin quality would help to address the pathophysiologic limitation preventing rehabilitation in these patients.

Solution

We have developed a transdermal patch delivery system for an FDA-approved medication, deferoxamine, to treat chronic, fibrotic radiation-injured soft tissue. Preclinical studies demonstrated that serial direct injection of this medication into irradiated tissue results in improved blood flow and tissue quality. However, translation for this route of administration is limited by logistical challenges of repeat injections as well as potential for poor patient tolerance. A transdermal patch delivery system is far more attractive to both clinicians and patients. Given the frequency and severity of debilitating radiotherapy side effects and limited available treatment options, our novel approach meets a large clinical need with potential for rapid clinical adoption.

Competitive Advantage

There are no approved topical formulations or transdermal delivery patches for deferoxamine in the EU or US. This transdermal deferoxamine patch would be a new product that could bring significant improvement in the care of post-radiation patients without encountering any therapeutic competition for quite some time.

Target Market

The largest targeted market would likely be represented by breast cancer reconstruction, with current market size estimated to be $526.5M worldwide in 2017. Breast reconstruction typically involves silicone or saline implants, and radiation is associated with increased implant exposure/failure risk and scar formation. A second potential target market would be head and neck cancer reconstruction. There are over 60,000 new cases diagnosed each year in the US, and 27,898 reconstructive procedures were performed in 2017 alone.

Regulatory Pathway

Combination product (Drug-Device) with the PMOA being the drug so the regulatory pathway will be an IND with CDER as the lead agency. Deferoxamine is already FDA approved and in clinical use for other indications. Therefore, the team may ultimately go through a 505(b)(2) application pathway.

Intellectual Property

Deferoxamine is off-patent. Application for improvement of radiation-induced fibrotic tissue represents a new indication. We have filed a patent for transdermal delivery of deferoxamine for wound healing and a patent application on the use of transdermal deferoxamine patch delivery to improve irradiated tissue to facilitate subsequent reconstructive procedures. US12/577,006, US20100092546A1, PCT/US2018/050626, WO2019055490A1

Related Publications

Duscher D, Neofytou E, Wong VW, et al. (2015) Transdermal deferoxamine prevents pressure-induced diabetic ulcers. Proc Natl Acad Sci USA 112(1): 94-99. PMID: 25535360. / Flacco J, Chung N, Blackshear CP, et al. Deferoxamine preconditioning of irradiated tissue improves perfusion and fat graft retention. (2018) Plast Reconstr Surg 141(3): 655-665. PMID: 29135894.

Transdermal Deferoxamine to Enhance Fat Graft Retention For Reconstruction of Irradiated Soft Tissue Defects

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UNMET CLINICAL NEED

Over half of all patients with cancer receive radiation therapy as part of their treatment, and while this improves overall survival, over 90% of patients experience radiation-induced collateral soft tissue injury. Late effects of radiation therapy may include development of radiation fibrosis, characterized by dermal thickening and loss of vascularity, leading to hypoperfusion and hypoxia. When radiation fibrosis is severe, significant cosmetic and functional consequences may result which can substantially impact quality of life. Furthermore, reconstruction of soft tissue defects following cancer resection are challenging owing to hypovascular changes and poor tissue compliance.

Current therapeutic approaches are limited to physical therapy, pentoxyfilline, and vitamin E. However, poor compliance and variable outcomes have been reported with these regimens. Therefore, a commercially available mechanism to improve local perfusion and tissue quality using an FDA-approved medication would help to address the fundamental pathophysiologic limitation preventing successful rehabilitation of patients following radiation therapy. Given the frequency and severity of debilitating radiotherapy side effects and with limited available treatment options, a novel treatment strategy would meet this large clinical need with potential for rapid clinical adoption.

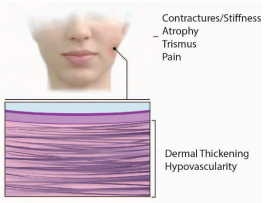

Figure 1. Schematic showing symptoms and histologic effects of radiation fibrosis

MARKET ANALYSIS

Cancers of the head and neck account for 3% of all malignancies in the United States. With an estimated 60,000 new cases each year, and rising, annual health care expenditure exceeds $3.6 billion for treatment of this condition (1). And beyond the head and neck region, a potentially even larger market for our product exists among patients with breast cancer, with over 250,000 newly diagnosed patients annually. Over one in five women with breast cancer with receive adjuvant radiation therapy.

- Advantages of our strategy include:
  - First-in-class
  - Minimal safety/toxicology drug risk as deferoxamine is FDA approved
  - Addresses acute medical need
  - No drug product developed or commercialized to specifically address post-cancer radiation market segment
- The largest potential market is breast cancer, with a total world-wide addressable population of 1 million and medical expenditures exceeding $16.5 billion annually (2,3).
- Likely targeted population in United States 20,000 breast cancer patients based on 40% of addressable population, growing to 50% based on awareness and availability over time.

INTELLECTUAL PROPERTY

- Deferoxamine originally trademarked as Desferal by Novartis in 1962 and is now off-patent.
- Application of deferoxamine for radiation-induced hypovascular tissue represents a new indication for an existing drug.
- IP / Licensing Status:
  - **"Topical and transdermal delivery of hif-1 modulators to prevent and treat chronic wounds"**
    - USPTO Patent # 2010/0092546 – filed October 9, 2009
  - **"Conditioning irradiated tissue for fat graft retention"**
    - Provisional Application filed September 14, 2017 - #62/558,698
    - International Application for Patent Filed September 12, 2018 - #PCT/US2018/050626
    - Recorded with USPTO October 31, 2018 at Reel 04737, Frame 0095
  - **"Prophylactic skin treatment for radiation therapy"**
    - Provisional Application filed November 22, 2019

RESULTS

Local delivery of deferoxamine to mouse skin has been shown to chelate iron (**Fig. 2a**) and stabilize HIF-1a (**Fig. 2b**) (4,5). This results in downstream activation of pro-angiogenic growth factors (**Fig. 2c**) and restoration of perfusion in irradiated tissue **(Fig. 2d).** Iron also catalyzes formation of reactive oxygen species (ROS) via the Haber-Weiss and Fenton reactions, which results in oxidative stress and cellular apoptosis. Formation of ROS has been established as an etiopathogenic feature of radiation fibrosis. Transdermal deferoxamine reduces ROS in irradiated mouse skin, as shown by decreased dihydroethidium staining (**Fig. 2e**).

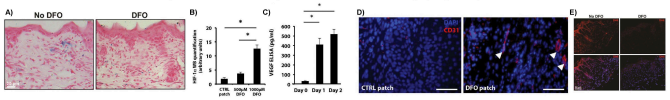

Figure 2. (A) Prussian blue-stained mouse skin shows decreased iron with DFO treatment. (B) DFO increases HIF-1a protein locally in skin, as well as (C) downstream VEGF levels. (D) CD31 staining (red) showing increased vascularity in DFO treated mouse skin (right). (E) Dihydroethidium shows decreased ROS with DFO (right).

Chronic, radiation-injured mouse scalps also demonstrated reduced perfusion, however deferoxamine was noted to improve perfusion as seen on laser doppler analysis (**Fig. 3a**) (4). Histologic analysis of treated irradiated mouse skin also revealed decreased dermal thickness on H&E staining and improvement in collagen deposition on picrosirius red staining (**Fig. 3b**).

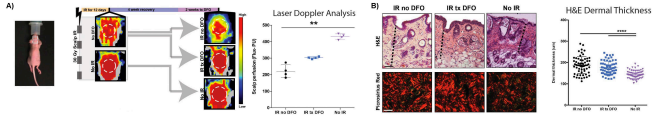

Figure 3. (A) Laser doppler analysis (left) and quantification (right) revealed increased perfusion with deferoxamine. (B) H&E (top) and picrosirius red (bottom) demonstrated decreased dermal thickness and collagen deposition following DFO patch treatment.

A large animal red Duroc pig model was developed to evaluate effects of transdermal deferoxamine on irradiated tissue more similar to human skin. Pigs were treated with 30 Gy radiation delivered to each flank and then were allowed to recover for 8 weeks to develop chronic fibrosis (**Fig. 4A**). Regions (5x5cm, 3x3cm, and 1x1cm) were treated with no patch, a control patch with no deferoxamine, or the transdermal deferoxamine patch (1mg/cm2). Patches were changed daily for four weeks. No adverse reactions were appreciated with either the control or transdermal deferoxamine patch at any treatment size (**Fig. 4b**). Clinical assessment of irradiated skin demonstrated improvement in pliability over four weeks of treatment using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grading for radiation injury (**Fig. 4c**).

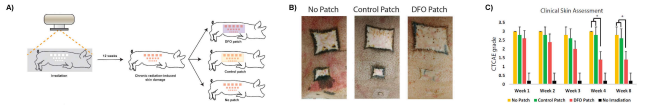

Figure 4. (A) Schematic of radiation patch and treatment in red Duroc pigs. (B) Photographs of treated sites showing no adverse reactions. (C) Clinical assessment revealed decreased stiffness with DFO patch (red bars).

Dose response was evaluated in irradiated pigs at three different concentrations (0.5 mg/cm2, 1.0 mg/cm2, and 2.0 mg/cm2) **(Fig. 5a).** Similar improvements in irradiated skin were appreciated with patches containing 1.0 mg/cm2 and 2.0 mg/cm2, both of which were greater than observed with patches containing deferoxamine at 0.5 mg/cm2 (**Fig. 5b**). These observations support proceeding with a transdermal patch dosage of 1.0 mg/cm2. Furthermore, systemic distribution of deferoxamine was also evaluated by mass spectrometry of pig venous blood samples. At all time points following deferoxamine patch application, systemic concentration was observed to be no greater than 12 ng/ml (**Fig. 5c**).

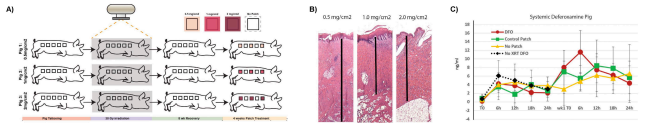

Figure 5. (A) Schematic of radiation and patch treatment with different deferoxamine dosages. (B) H&E revealed similar decreased in dermal thickness with 1.0 mg/cm2 (middle) and 2.0 mg/cm2 (right) dosages. (C) Mass spectrometry of venous blood following patch application showing deferoxamine concentration in ng/ml range.

MANUFACTURING

- Our transdermal deferoxamine patch is purchased through a third-party company and is manufactured in compliance with GMP guidelines.
  - Deferoxamine is USP grade and is obtained from supplier listed in the Orange Book
  - Surfactants used for construction of reverse micelles are GRAS and have been tested for impurities and stability.
  - Patches sterilized using Ebeam in a validated process.
  - 12-month stability testing at 25C on sterilized patches completed by manufacturer

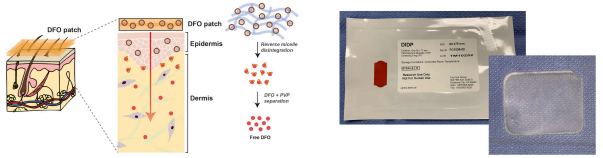

Figure 6. Illustration of deferoxamine patch and delivery of reverse micelles through the epidermis into dermis with release of free deferoxamine (left). Image of transdermal delivery patch and sterile packaging (right).

REGULATORY PATHWAY

- Our strategy integrates deferoxamine into a transdermal patch delivery system and will be viewed as a combination product regulated by the FDA **Center for Drug Evaluation and Research**.
- A **505(b)(1) pathway** to approval of an NDA is planned. Reference to IND 135603 submitted by the Tautona Group for Deferoxamine Intradermal Delivery Patch (DIDP) will be included with the IND submission.
- Objectives of Pre-IND meeting:
  - Confirm proposed indication for treatment of chronic, radiation-induced soft tissue injury
  - Define key study design considerations regarding proposed clinical trial including efficacy endpoint and secondary endpoints for measuring treatment effects
  - Determine whether additional conduct of *in vivo* toxicology or pharmacology studies in animals is necessary
  - Establish specifications for both the drug substance and the drug product
  - Obtain guidance from the FDA to consider breakthrough, fast track, or other submissions for expedited programs related to rare and/or unmet medical needs

TIMELINE & FUTURE DIRECTIONS

- **Milestone 1 (Q1 2021) –** Formatting and submission of Pre-IND packet to FDA including nonclinical pharmacology, dosage analysis, pharmacokinetics, and toxicology studies. Additional data from IND 135603 to also be included.
- **Milestone 2 (Q2-3 2021) –** Completion of additional GLP toxicology/pharmacology studies as necessary. Previous GLP animal studies performed by Care Research LLC.
- **Milestone 3 (Q4 2021) –** Design of Clinical Trial and IRB approval for a randomized, double blinded, placebo-controlled Phase II study of transdermal deferoxamine patch treatment in patients with radiation fibrosis.

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Funding sources: NIH NIDCR 5 U24 DE026914, NIH NIDCR 5 R01 DE027346