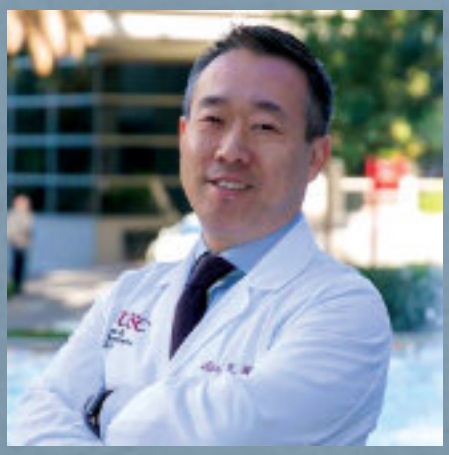
3dTH fibronectin therapy for non-healing irradiated head & neck skin wounds



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Clinical Need

Over 500,000 individuals develop head & neck cancer annually and up to 70% of these patients require radiation to treat their disease. Despite improvements in delivery, unintended cutaneous damage from radiation to the head & neck can result in chronic non-healing wounds which are painful, disfiguring, and at risk for infection. Basic wound care, such as moist dressing changes, may be effective for a small fraction of irradiated wounds but most require advanced wound care strategies or surgical debridement and reconstruction with non-irradiated vascularized skin flaps. However, not all patients are eligible surgical candidates, which in the case of a non-healing wound, presents an unsolvable clinical scenario.

Solution

Our proposal is an innovative solution to this difficult problem. We have demonstrated that treating irradiated skin with topically-applied fibronectin (FN) in a murine model led to improved rates of wound healing by >20%. The next phase will be to incorporate a FN into a patented 3-D transglutaminase hydrogel (3dTH) which allows for controlled delivery of FN. This prototype will be tested in minipig in order to study its therapeutic effects and work toward the development of a prefabricated wound dressing. Since the current standard of care involves frequent, costly, and painful office visits for wound care and debridement, development of a user-friendly dressing would improve patient outcomes and reduce the healthcare burden. Ideally, this technology could be exported beyond the craniofacial area to any irradiated location on the body.

Competitive Advantage

Fibronectin is a naturally occurring human protein. The hydrogel drug delivery system is biocompatible and offers predictable slow release that increases the drug's wound healing efficacy.

Target Market

It is estimated that 50% of head and neck cancer patients who receive radiation have some form of delayed wound healing, which would equal 250,000 patients per year in the US alone. However, this drug-device has the potential to be applied to non-healing radiation wounds all over the body (not limited to head & neck) thus significantly increasing market potential. A conservative estimate would be 10% of the total wound healing market – which will be $35B by 2025.

Regulatory Pathway

Combination product (drug-device) with the PMOA being the drug. Regulatory pathway will be IND with CDER as the lead agency. PMOA is well defined so no Request for Designation should be necessary.

Intellectual Property

Systems and Methods of Cell Activated, Controlled Release Delivery of Growth Factors for Tissue Repair and Regeneration (US20130202564A1)

Related Publications

Johnson MB, Pang B, Gardner DJ, et al. (2017) Topical fibronectin improves wound healing of irradiated skin. Sci Rep 7(1):3876.

Fibronectin Hydrogel For Non-healing Irradiated Head & Neck Wounds

DOCTRC DENTAL, ORAL, & CRANIOFACIAL TISSUE REGENERATION CONSORTIUM

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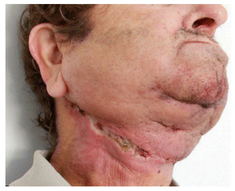
UNMET CLINICAL NEED

- **Non-healing radiation wounds**: A sub-type of chronic wound open for >6 weeks seen in patients requiring therapeutic radiation for treatment of cancer. Currently, there is NO effective FDA approved topical agent for radiated wounds.
- **At risk population**: Approximately 400,000 new head and neck (H&N) cancers are diagnosed annually worldwide. Radiation therapy is utilized in >70% of patients with malignant tumors of the H&N. Acute and chronic skin injury as a consequence of radiation occurs in 95% of patients.
- **Complexity**: Irradiated wounds do not respond to traditional wound care modalities. In the H&N region, there is a high chance that open wounds put critical anatomic structures at risk. Radical surgical wound debridement and vascularized flap reconstruction is a treatment option but is often too morbid and risky for elderly patients. In addition, wound recurrence is common due to wide fields of radiation injury.



Clinical Example: A patient with a history of squamous cell carcinoma who had right neck lymph node dissection and post-operative radiation suffers from a non-healing right neck open wound. Typical wound characteristics include erythema, drainage, yellow fibrinous non-healing tissue**.** Current wound care options include daily wet to wet gauze, Silvadene, alginate, etc. but none reliably facilitate stable wound closure.

MARKET ANALYSIS

- **Global market** for wound care estimated at $19.8 billion in 2020 and forecasted to be $24.8 billion in 2024.[1]
- **Cancer survivorship** is on the rise and will increase by 31% in the next 10 years due to early detection and innovation in treatments. More patients will be living with post-oncologic morbidities such as non-healing radiation wounds.[2]
- **Target market**: Patients of any age with non-healing radiation wounds, margins free of tumor, & non-infected. While initial target will be head & neck wounds this technology will be expanded to wounds in any anatomic region. In addition to radiated wounds, fibronectin hydrogel may also improve other chronic wounds due to diabetes, venous stasis, etc.
- **Foresight Technology Niche Analysis®**:
  - Confirmed significant unmet need
  - Identified hyperbaric oxygen as a non-topical/non-biologic alternative
  - Randomized controlled clinical trials essential for adoption
  - Other biologics such as amniotic/placental membranes, are being used off-label with variable success but are considered competitors
  - Price point critical ($25-40 per application)

INTELLECTUAL PROPERTY

- IP landscape review identified several outdated patents regarding fibronectin and wound healing however none are specific to radiated non-healing wounds.
- Biocompatible 3D-transglutaminase hydrogel (3dTH) system for fibronectin delivery is protected by **US9393267B2** (Bo Han, PhD / USC Viterbi School of Engineering).
- Peer-reviewed publication describes systematic identification of fibronectin as a key molecule downregulated in irradiated wounds and significant functional benefit after topical application in a murine irradiate wound model[3]
- Topical fibronectin normalizes TGF-β & Smad-3; decreases pathologic inflammation, and supports angiogenesis in healed irradiated murine wounds
- IP has not been licensed to a 3rd party for human use
- Topical therapy for non-healing radiated wounds was determined to be a '**viable application**' by Foresight Technology Niche Analysis®

RESULTS

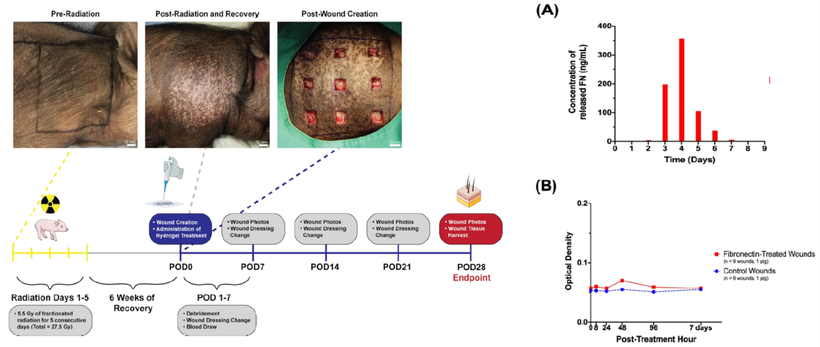


Fig 1 (left): Overview of current validated mini-pig irradiated wound testing platform (right = cranial); Fig 2 (right): a) *In vitro* FN sustained release kinetics; b) No significant systemic distribution observed after topical fibronectin treatment.

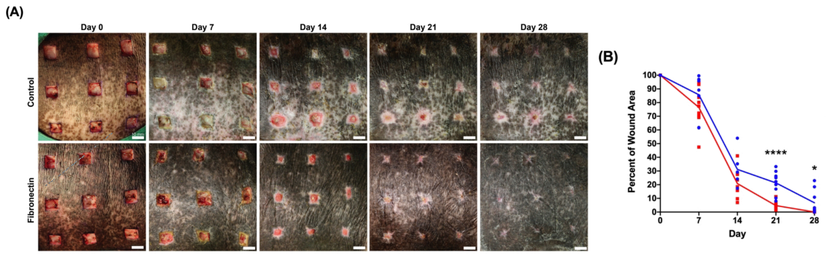


Fig 3: a) Photographs of full thickness radiated wound healing in mini-swine; control hydrogel only (top) FN hydrogel (bottom). b) Graphical summary of % wound wound healing vs. time indicating statistically significant improvement in rate of wound healing after single application of fibronectin hydrogel on POD #0 (blue = control; red = FN).

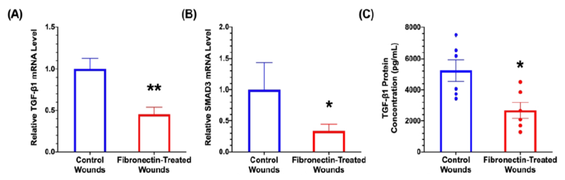


Fig 4: Fibronectin hydrogel normalizes radiation associated increases in a) *TGF-β1 &* b) *Smad-3* gene expression, & *TGF-β1* protein in mini-swine

MANUFACTURING

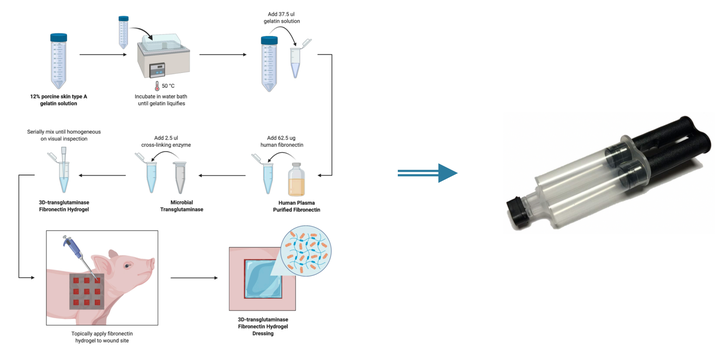


Fig 5: Transition from laboratory-based fibronectin hydrogel protocol to scaled up standardized production clinician/end user friendly dual chamber mixer/applicator using GMP sourced materials.

REGULATORY PATHWAY

- Our regulatory expert has advised that FN hydrogel is a **combination drug/biologic device product** as defined by 21 CFR 3.2(e)
- Evaluation will be conducted by FDA Center for Biologics Evaluation and Research (CBER)
- Standard operating procedures (SOPs) are being finalized to ensure scalability
- Price quotation and contract manufacturing of **GMP source materials** has been secured from at least 2 different vendors
- FDA documents to address product description, target disease to be treated, product development, manufacturing, control requirements, and toxicology are in final draft form
- Planned consultation with Regulatory Professionals, Inc. to identify regulatory gaps, generate clinical protocol synopsis, and develop pre-IND meeting information package and briefing book
- Plan to schedule non-binding INTERACT (initial targeted engagement for regulatory advice on CBER products) meeting to obtain preliminary guidance and determine extent of GLP testing required prior to pre-IND meeting

TIMELINE & FUTURE DIRECTIONS

- **Milestone 1**: Finalize product specification, titrate fibronectin to minimal effective dose to ensure final production cost is commercially viable
- **Milestone 2**: Engage regulatory consultant team and complete non-binding INTERACT meeting
- **Milestone 3**: Secure GMP source materials and agreement with contract research organization to conduct GLP assays
- **Milestone 4**: Compile GLP data and prepare pre-IND meeting packet

Month	Milestone 1	Milestone 2	Milestone 3	Milestone 4
1				
2				
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11				
12				

- **Future Directions:** Submit Phase I/II fast track STTR application to support final proof of concept studies and early clinical trials

REFERENCES

1.https://www.marketsandmarkets.com/Market-Reports/wound-care-market-371.html
2. American Cancer Society. *Cancer Treatment & Survivorship Facts & Figures 2019-2021.* Atlanta: American Cancer Society; 2019.
3. Johnson MB, et. al. Topical Fibronectin Improves Wound Healing of Irradiated Skin. *Sci Rep.* 2017 Jun 20;7(1):3876.

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