HB-EGF to prevent radiation-induced oral mucositis

Peter Santa Maria, MD, PhD – Assistant Professor of Otolaryngology, Head and Neck Surgery; Associate Director, Stanford SPARK, Stanford University

Susan Knox, MD, PhD – Professor of Radiation Oncology, Stanford University

Clinical Need

The clinical indication we are targeting is the prevention and treatment of radiation-induced oral mucositis (severe mouth ulcers). Oral mucositis is often a dose-limiting toxicity preventing optimal radiation therapy for patients. It causes pain and also septicaemia in neutropenic patients. The incidence is approximately 80% in head and neck radiation and 40% in standard radiation. Annually, there are approximately 400,000 cases of treatment-induced damage to the oral cavity.

Solution

We deliver a topical growth factor as a mouth wash that enhances epithelial migration, proliferation and keratin thickness during the 2-3 week period following radiation therapy. This will increase patient compliance with radiation protocols and increase cancer survival.

Competitive Advantage

There remain limited treatment options for this indication. These include oral care, analgesia and anti-inflammatories (e.g. Benzydamine), and cryotherapy (e.g. swallowing ice chips immediately before treatment). Keratinocyte Growth Factor (KGF) (Palifermin / Kepivance. Amgen) ceased manufacturing in 2017. Kepivance (Amgen) was delivered systemically and was poorly adopted clinically as the cost was thought to outweigh the benefits achieved. There were also difficulties surrounding the systemic administration. There is an unmet need for a topical therapy that has high efficacy. HB-EGF as a treatment option can be provided topically, has a potentially high efficacy for oral squamous proliferation and low potential for toxicity and systemic side effects.

Target Market

Head and neck cancer patients are at greatest risk for developing oral mucositis. There were an estimated 65,000 newly diagnosed cases in the U.S. alone in 2017, and an estimated 700,000 worldwide. By 2030, the global incidence is expected to exceed 1M per year. For head and neck cancer patients only, the market has been estimated to range from between $500 million and $1.5 billion on an annual basis. The market extends to all forms of chemoradiation where the incidence of oral mucositis ranges between 20% and 40%. There was thought to be a mean per patient saving of $3,595 when using Kepivance (Amgen) for chemoradiation-induced mucositis in hematological malignancy.

Regulatory Pathway

Biologic - IND with CBER as lead agency

Intellectual Property

A patent (US20170232065A1) covering the method is currently at the PCT stage. (2015) A second patent is at the non-provisional stage. Another patent covering the delivery is at the provisional stage. An independent analysis of patentability and freedom to operate identified no concerns.

Topical HB-EGF for oral mucositis after chemoradiation

P Santa Maria[1], J Lin[1]; J Chen[1]; S Massa[1]; L Bekale[1]; K Khomtchouk[1]; Z Cao[1]; S Ning[2]; S Knox[2]
[1]Department of Otolaryngology, Head and Neck Surgery, Stanford University
[2]Department of Radiation Oncology, Head and Neck Surgery, Stanford University

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UNMET CLINICAL NEED

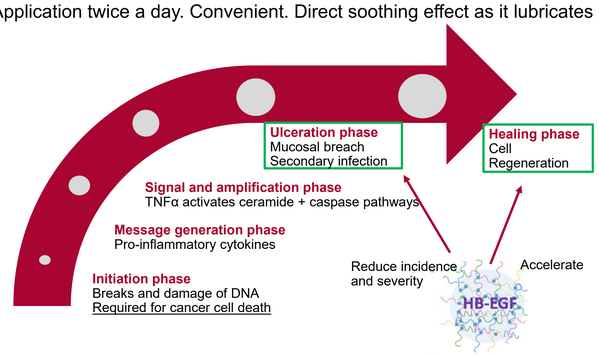
We are developing the only topical regenerative treatment for the oral cavity after chemo/radiation. It does this by protecting the oral epithelial structure and adhesion

A common problem in cancer therapy

It has a 40-80% incidence across most protocols leading to >450k cases/year[1], It begins 2 weeks after therapy stats and continues for 2 weeks after therapy ends. It leads to pain, dehydration, malnourishment, infections and ultimately cessation of therapy. It leads to health costs of $18-40k/patient[2]

Solution

Topical HB-EGF (Heparin Binding Epidermal Growth Factor Like-Growth Factor)
Stimulates EGFR (HER 1 and 4)
Potent Keratinocyte Regeneration (Proliferation + Migration)
Temporarily increases keratin layer to act as protective barrier
Formulation
Mucoadhesive formulation attaches to epithelium and release HB-EGF
Topical Application twice a day. Convenient. Direct soothing effect as it lubricates



MARKET ANALYSIS

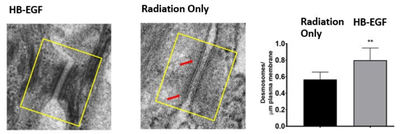
Lack of Approved Treatments on the Market Today

Treatment Option	Topical HB-EGF	KGF	Hydration Protocols	Lubricants	SOD mimetics
Topical Delivery	✓	✗	✓	✓	✗
Lubricates	✓	✗	✗	✓	✗
Active Regeneration	✓	✓	✗	✗	✗
Prevent Degeneration	?	?	✗	✗	✓
Thicker Oral Epithelia	High	Moderate	✗	✗	✗

1 Billion dollar market for oral mucositis
>450,000 potential patients in US alone.
25% market share times 450,000 times $10,000/treatment (cost of Kepivance)
= $1.1 billion/year US only sales

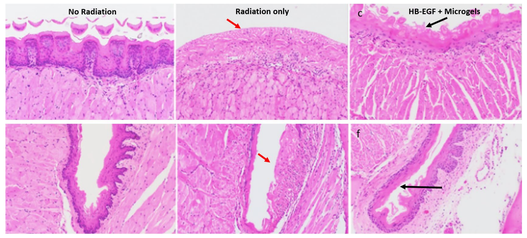
RESULTS

HB-EGF protects and regenerates the epithelia



HB-EGF[3]
Mouse model
Preserves of intercellular adhesion (desmosome quantity and quality)
Increased new epithelial cells
Chen, J. et al Sci Reports 2020

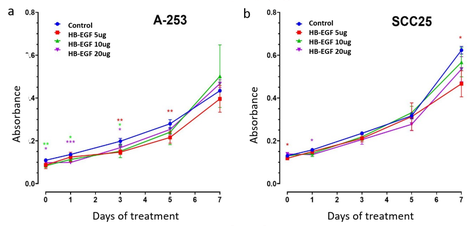
HB-EGF protects against oral mucositis



HB-EGF
Mouse model
Preservation of basement membrane
Epithelial preservation
Protects from Ulceration

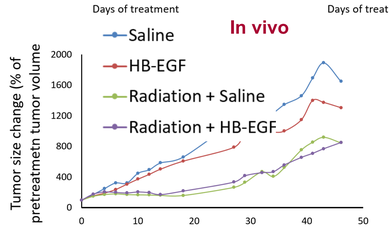
HB-EGF safety

In vitro

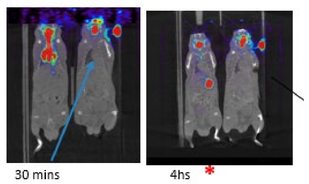


No in vitro or in vivo Tumorigenicity
All available ATCC and UM cell lines tested in vitro
(9 head and neck SCCs)
4 representative cell lines chosen for in vivo
No significant growth compared to control

In vivo



Non GLP Toxicology completed
No toxicity concerns
Rat oral application
Mouse oral gavage



No significant systemic exposure
Oral administration: follow-up for 4hr Formulation maintains HB-EGF in the oral cavity for 3 ½ t ½'s
Prevent systemic absorption at any meaningful dose

INTELLECTUAL PROPERTY

More information available with NDA. Covering method, accessory indications and novel mucoadhesive formulation. 10 year biologic protection in the US

FTO

Independent analysis conducted in 2019. No issues.

Patentatbility

Independent opinion on patentability 2019

REGULATORY PATHWAY

Kepivance™ (Palifermin)
Amgen sold to Sobi
IV administration
Hematological malignancy
*likely eligible for fast track approval (SOD recently granted)
Discussions with Amgen's regulatory scientist

TIMELINE & FUTURE DIRECTIONS

Our aim, for the next year, is to work through the IND enabling studies after completing GMP manufacturing. We aim to hold a pre-IND meeting with the FDA to gain agreement on the study requirements we will need to meet for an IND approval.

GMP manufacturing
We have identified and confirmed a scale up manufacturer for HB-EGF.
Formulation / Delivery System manufacturing and biocompatibility
We have identified two formulation manufacturers who have confirmed the ability to provide scale up delivery systems for us. We are currently evaluating their proposals to scale up into phase 1.
Confirmation of efficacy of GMP materials
Once we have completed first batch GMP manufacturing of HB-EGF and the formulation we aim to repeat efficacy studies to confirm activity and support the pharmacological component of the IND filing.
Toxicity
GMP / GLP toxicology studies in mouse and non-rodent large animal as required, based on our initial FDA interactions.,
CMC
Stability and accelerated stability studies..
Packaging / Sterilization
We plan to further define transport, storage conditions and packaging together with our manufacturer.
GLP Pharmacokinetics
Pending a pre-IND discussion, pharmacology data (in vitro effect of drug on human and mouse keratinocytes, in vivo (mouse model) efficacy dose response in animal model), pharmacokinetics after single administration and distribution may be required.
Clinical trial design
We will begin to have discussions on clinical trial design and endpoints with consultants. The KGF and Galera products provide acceptable trial design and endpoints and we will use these as a basis to frame our phase 1 and 2

REFERENCES

1 Naidu MU et al. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. Neoplasia. 2004.
2 Nonzee NJ et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis Cancer. 2008
3 Chen, J. Bekale, LA. Khomtchouk, KM. Xia, A. Cao, Z. Ning, S. Knox, SJ. **Santa Maria, PL**. Locally Administered Heparin-Binding Epidermal Growth Factor-Like Growth Factor Reduces Radiation-Induced Oral Mucositis in Mice. Sci Reports 2020

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