The Team

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- Leading experts in the underlying physiology of food intake control, emesis/nausea and development of therapeutic peptides and conjugates.
- Extensive Research, IP development and licensing experience.
- Experience with multiple ‘Big Pharma’ companies (research, consulting and scientific advisory board)
Large market given lack of available pharmacotherapies to treat nausea, vomiting (emesis) and cachexia in cancer patients (with some estimates link 1/3 cancer deaths to cachexia). Nausea and emesis are frequently occurring symptoms in chronic diseases and their treatment.

Projected 5 year CAGR of 4.3%

https://www.mordorintelligence.com/industry-reports/cancer-cachexia-market
• Growth differentiation factor 15 (GDF15), also known as MIC-1, is a stress response protein cytokine that shows increased expression (up to 1000-fold) and rise in blood concentration in response to obesity, diabetes, pregnancy, cancer and chemotherapy (and can indicate poor prognosis).

• GDF15 specifically targets the GFRAL-Ret receptor complex, that is shown to be only expressed in the area postrema (AP) and nucleus tractus solitarius (NTS) of the brainstem – two nuclei essential for the control of energy balance and nausea/emesis.
GDF15 increases following chemotherapy (cisplatin treatment) and correlates with the severity of the anorectic response induced by chemotherapy.
GDF15 induces pica (kaolin consumption; behavior correlated with nausea in rodents), anorexia and conditioned taste avoidance (CTA) in rats.

All measures of illness-like behavior and shows that GDF15 (Mic-1) signaling causes the animals to feel sick.

N=40, fully within-subject
GDF15 induces profound emesis and anorexia in the Asian house musk shrew (Suncus murinus)
Chemotherapy (using Cisplatin) induces neural activation in GFRAL-expressing cells in the AP and NTS, as read out by c-Fos co-localization.
Ahead of the Competition

All major Big Pharma is looking at both agonists and antagonists of GFRAL (Pfizer, Novo Nordisk, NGM Pharma, Boehringer-Ingelheim, BMS, Novartis, etc).

**Cons:** Such Companies are further down the pipeline with their antibody-based technology.

**Pros:** Competition has focused on generation of antibody based technologies.

- The antibody route is much less adaptable (limiting both ability to translate, to adapt and to discover), is considerably more costly to produce and store long-term, and, critically, will not target brainstem GFRAL receptors as efficiently due to a lack of penetrance into such tissue.
GDF15 can be derived endemically at the blood brain barrier of the NTS/AP from endothelial cells forming the blood brain barrier, as well as microglia. These “central” sources of GDF15 might represent a crucial contributing source for NTS/AP GFRAL signaling in response to energy balance perturbations and emetic stimuli. Like most antibodies, anti-GDF15 antibodies under clinical development by the pharmaceutical industry will not readily access the hindbrain and thus will not effectively block the NTS site of action for local GDF15 production.

In contrast, GRASP technology does penetrate into the hindbrain.

Rat NTS endothelial cells (RECA) and microglia (IBA1) express GDF15 under unstimulated (vehicle) conditions – providing a potential direct central source for emetic and/or anorectic stimuli to increase central GDF15-GFRAL signaling at the blood brain barrier directly.
Systemic treatment with current anti-emetics, like ondansetron (Ond) are not able to block GDF15 induced nausea-like behaviors and only slightly attenuate the anorexia – suggesting the GDF15-GFRAL system as a potential novel drug target.
We use rational design and in silico modelling to design target peptide libraries.

For GRASP, we focused on GDF15 interactions with the GFRAL receptor (binding) and subsequent RET interactions (recruitment) to design antagonists.

In addition, regions of GDF15 known to be critical for GFRAL receptor specificity were incorporated into the initial library.

Screening of the library in vivo in the rat led to confirmation of a lead peptide antagonist of GFRAL (GRASP).

Overall, we believe GRASP is a non-competitive peptide-based antagonist of the GFRAL-Ret complex that is capable of penetrating into the brain.
GFANT-05 (GRASP) (300 pmol) attenuates pica (nausea-like behavior) induced by GDF15 (a.k.a MIC-1)
**GRASP Technology – a GFRAL-Ret Receptor Antagonist**

for the treatment of cachexia, nausea, and emesis

Image shows GRASP peptide technology co-localizing with the GFRAL receptor in the brainstem (a major source of illness behaviors in disease and/or disease treatments). This technology provides a new route to treat cachexia and chemotherapy induced nausea/vomiting by uniquely blocking the GDF15-GFRAL signaling in the brainstem.

These diseases and the illness-behaviors from the current treatment of these diseases are in desperate need of new pharmacopeia to block nausea and emesis. Further, cachexia alone is projected to have an additional CAGR of 4.3% over the next five years.
Adult male Sprague Dawley rats were treated with GRASP (100 nmol/kg) or Saline vehicle (intraperitoneal injections) 30 min prior to a 6mg/kg (IP) dose of the chemotherapy drug, cisplatin. Pica behavior, the ingestion of non-nutritive substances in response to visceral malaise, in this case measured by the intake of Kaolin clay (aluminum silicate) occurred 6 hrs later. Consistent with extensive literature, cisplatin alone induces pica behavior, indicating nausea/malaise. Confirming our hypothesis, the novel GFRAL receptor antagonist GRASP is able to attenuate this cisplatin-induced pica.
Joint Penn/Syracuse University (SU) Intellectual Property with the three PI’s as named inventors

PCT International Application No. PCT/US2020/016844

UPENN is the IP and Commercialization Lead

Patent being exclusively optioned to Cantius Therapeutics LLC, of whom all five inventors are sole members.
Characterize brainstem anatomy/ cellular circuitry for endogenous GDF15 production and GFRAL-RET-expressing neuronal phenotypes. Through immunohistochemical (IHC) and fluorescent in situ hybridization (FISH) 3-dimensional confocal analyses, we will characterize the phenotype(s) of GFRAL-RET-expressing neurons in the AP/NTS. Building on exciting preliminary data we also will determine whether emetic stimuli and perturbations to energy balance alter expression of endogenous GDF15 production in brainstem endothelial cells and microglia cells. Finally, we will trace deductive neural outputs of GFRAL-expressing cells to CNS nuclei implicated in energy balance and nausea/emesis.

Further characterize GDF15-induced emesis, nausea-like behavior, and anorexia as well as characterize GRASP against these behaviors with a multi-species approach. Our preliminary data suggest that exogenous GDF15 causes vomiting and behaviors indicative of nausea prior to exerting anorectic effects in musk shrews (*Suncus murinus*) and rats, respectively. This aim will test whether GRASP functions *in vivo* as an anti-emetic and/or anti-anorectic/anti-cachexic agent using multiple behavioral pharmacology assays and automated behavioral recordings.

Rationally design, develop, and conduct *in vitro* and *PK in vivo* screens for a GRASP-based peptide library. This aim will build upon our successful development, using rational design, of a small peptide antagonist of the GFRAL receptor (‘GRASP’), and subsequent solving of the solution state structure of GRASP via Nuclear Magnetic Resonance spectroscopy. This aim will develop new iterations of GRASP to refine the pharmacodynamics. Once second-generation *in vitro* leads are identified, they will then be tested anatomically and behaviorally.
The Path: Preclinical development

- **2018 Jan**: Idea Conceived
- **2018 May**: Provisional patent filed
- **2019 Sept**: Proof of Concept
- **2020 Feb**: PCT filed
- **2020 July**: Secure $2 million
- **2020 Dec**: Complete PK & cell assays
- **2021 Feb**: Expand in Vivo Behavior/function
- **2021 Mar**: Clinical Development Plan; Pre-IND FDA meeting request
- **2021 Nov**: Data collection For Human Safety/ADME

**Timeline**

- **2018 Jan**
- **2018 May**
- **2019 Feb**
- **2019 May**
- **2019 Sept**
- **2020 Feb**
- **2020 July**
- **2020 Dec**
- **2021 Feb**
- **2021 Mar**
- **2021 Nov**
Funding and Exit

- Cantius Therapeutics, LLC was founded September 5th 2019, based on IP generated via capital and Intellectual investment from the owners and their host institutions.

- Initial round of funding requested is $2 million dollars to enable a second round of funding to translate IP into human screening. See ‘immediate next steps’ slide.

- Likely exit strategy is acquisition by larger pharmaceutical company with whom we are already in contact or currently in collaboration with on other projects (Novo Nordisk, Pfizer, BI, BMS) at IND filing or start of Phase I clinical trial.

Technology is likely to generate multiple exits (cachexia alone and/or in combination with another drug; Use to expand chemo-therapeutic drug tolerance; treat morning sickness; ‘other’ GDF15 associated illness behaviors (new field with new areas Opening up regularly).