CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

UMass Center for Clinical and Translational Science and Voyager Therapeutics Developmental Therapeutics Awards

DATE: November 6, 2017

TO: All UMass Worcester Faculty

FROM: Katherine Luzuriaga, M.D.
Director and PI
UMass Center for Clinical and Translational Science

RE: UMCCTS-Voyager Pilot Project Program 2018 –**Letters of Intent due December 8, 2017**

The NIH has challenged academic medical centers to accelerate the pace at which we integrate research findings into clinical practice. The University of Massachusetts Medical School and its clinical partner UMass Memorial Health Care are committed to this challenge and are aggressively expanding translational and clinical research under the following vision:

To be a national leader in creating the ideal environment to foster interdisciplinary research to enhance the public's health.

A key and enabling element of this commitment is the establishment of the UMass Center for Clinical and Translational Science (UMCCTS). Building upon our strong reputation as a world-class research institution, producing noteworthy advances in clinical and basic research, the UMCCTS will provide the infrastructure necessary to support outstanding clinical and translational investigators and their work.

The UMCCTS, in collaboration with Voyager Therapeutics, is announcing a new round of Pilot Project Programs (PPPs) focused on understanding and optimizing recombinant adeno-associated viral (rAAV) vectors for therapeutic use.

Voyager Therapeutics is developing gene therapies for fatal and debilitating diseases of the central nervous system. Voyager's current lead programs include Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Friedreich's ataxia, Huntington's disease, tauopathies, pain, and additional indications. Voyager is committed to advancing the field of AAV gene therapy by innovating and investing in areas such as vector optimization and engineering, vectorized antibodies, and dosing techniques, as well as process development and production.

Investigators are invited to submit proposals related to the following topics:

1. **Targeted systemic dosing of rAAVs**. Methods of designing rAAV vectors which efficiently transduce target organs or cell types via systemic dosing (e.g. i.v.) while significantly limiting off-target transduction. Target tissues and cells may be in the CNS (preferred), or heart, liver or lung. Methods may include (but are not limited to) modifications to the capsid, the transgene cassette, formulation, dosing route, device or other methods.

2. **Preexisting immunity to rAAV vectors**. Methods of understanding, measuring and avoiding preexisting immunity to rAAV vectors. Topics could include (but are not limited to): 1) understanding the effect of preexisting immunity (cellular and humoral) on rAAV vector activity delivered via multiple routes; 2) assays for characterizing and measuring rAAV-associated pre-existing and acquired

immunity; 3) vectors and methods of designing vectors which can circumvent preexisting immunity; and 4) methods to mitigate pre-existing immunity while preserving transduction of target tissues, in particular CNS. Topics 3 and 4 are of particular interest.

3. **Effect of anti-capsid T cell responses on rAAV expression.** It has been suggested that anti-capsid T cell responses may play a primary role in the limitation on the magnitude and duration of rAAV vector expression after systemic delivery. Studies to determine the effect of such responses on CNS directed delivery and approaches to mitigate those effects would be of interest.

4. **Regulated expression of the transgene product.** Studies that use modern/novel molecular biology tools to regulate the expression of the rAAV transgene product are of interest.

5. **Vectorization of monoclonal antibodies.** Antibodies are a therapeutic class that is showing great potential for the treatment of disease; however, substantial hurdles in delivering antibody across the blood brain barrier and in manufacturing large quantities remain significant hurdles. Studies that explore the optimal expression vector for antibodies and delivery mechanisms both directly to the CNS and in ways that could provide consistent systemic serum levels are of interest.

6. **CNS gene editing using AAV delivery.** New gene editing tools such as CRISPR are a field of incredibly rapid growth. However, CNS delivery, potential immunoreactivity, and off-target effects resulting from constitutive nuclease activity are potential hurdles. We invite proposals for studies that explore the limitations and possible solutions to these, as well as other relevant aspects of gene editing, in the context of AAV-mediated delivery.

Proposal Review

Proposals will be evaluated by a Scientific Review Committee made up of representatives from UMass and Voyager in a two-step process:

1. A brief letter of intent (LOI) will be reviewed.
2. Full proposals will be solicited after LOI review, and reviewed for final decisions on funding.

Funding

In this pilot program between UMCCTS and Voyager, a total of up to $250,000 is available to fund pilot projects (n = 2 – 4). Individual project awards of up to $125,000 over two years will be considered. Smaller "pilot" projects of ~$50,000 are also encouraged.

Projects are expected to be funded in two phases under a sponsored collaboration agreement: Year 1 funding will be provided, and written progress reports will be submitted after 6 and 12 months. At the end of Year 1, the Scientific Review Committee will review the work and determine if sufficient progress has been made to warrant funding for Year 2.

Application Instructions – Letter of Intent due December 8, 2017

LETTER OF INTENT (LOI) INSTRUCTIONS:
Letters of Intent will be peer-reviewed and the most promising projects will be selected for full proposal submission. Please only include non-confidential information.

Please email a Letter of Intent (2 pages or less) as an attachment (PDF) to: nathaniel.hafer@umassmed.edu on or before December 8, 2017 by 5:00 pm (EST).

Describe the research team, appropriate background/scientific rationale and research plan in two (2) pages or less (references are not necessary, but do not count toward page limit).

Selected applicants will be invited to submit full proposals in December 2017.

FULL PROPOSAL INSTRUCTIONS (for selected applicants only):
The full proposal will be submitted under the terms of a confidentiality agreement signed between UMass Medical School and Voyager. The application should adhere to the following template:

1. **Research plan**: This section should not exceed 4 pages (page limit does not count toward references). The format of the research plan should be:
   - Names of investigators, including each investigator's institution and role (e.g. PI, co-investigator, etc.).
   - Executive summary: 1-2 sentence project abstract summarizing what you wish to accomplish, how it will be done, and why you are excited about doing it.
   - Specific aims: Specify 1-3 major aims to be addressed.
   - Background and significance, including discussion of translational significance.
   - Preliminary studies (if applicable; not required).
   - Approach/experimental plan. Explain the "what" and the "how" in sufficient detail to allow the average scientist to assess your idea. Include things like hypotheses to be tested, plans for assay development, proposed analogs, criteria for assessing new models, possible pitfalls and mitigation strategies, etc.
   - Project timeline: identify key project milestones and go/no-go decisions and target timelines for achieving them.
   - Intellectual property considerations (if applicable).
   - Plans for future development.

2. **NIH-format biosketch** (5-page format) for each investigator.
3. **Budget**, broken down by institution, **with budget justification** (complete a PHS 398 form page 4 and 5 for each participating institution). Indirect costs are not allowed. PI/Co-I support up to 10% of the current NIH cap is allowed.
4. Statement of the need for **IUCAC, IRB, COI** or any other review/approval and whether such approvals have been obtained, or the timeline for obtaining necessary approvals. (1 page max).
5. **Letters of support** as appropriate (no page limit).
6. All applicants from UMMS Worcester **must be UMCCTS members**. Membership is free and entails completion of a short online form at http://www.umassmed.edu/CCTS/CCTS-Sign-up-for-Membership/

Full Proposals should be submitted as a single PDF document to Nate Hafer (nathaniel.hafer@umassmed.edu). Full Proposal applications (for selected applicants only) will be due by Friday, January 19, 2018 by 5:00 pm (EST). We anticipate that funding decisions will be made in February 2018.