

SUMMARY STATEMENT

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(Privileged Communication)

Release Date: 11/29/2016

Revised Date:

Application Number: 1 R41 AI131784-01

Principal Investigator

WAGNER, DAVID H

Applicant Organization: OP-T-MUNE, INC.

Review Group: ZRG1 EMNR-W (10)
Center for Scientific Review Special Emphasis Panel
Small Business: Endocrinology, Metabolism, Nutrition and Reproductive Sciences

Meeting Date: 11/15/2016
Council: JAN 2017
Requested Start: 04/01/2017

RFA/PA: PA16-303
PCC: I5E

Dual IC(s): DK, HD

Project Title: Developing a small peptide to control autoimmune inflammation in type 1 diabetes

SRG Action: Impact Score:10
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 10-No human subjects involved
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

| Project Year | Direct Costs Requested | Estimated Total Cost |
|--------------|------------------------|----------------------|
| 1 | ██████████ | ██████████ |
| TOTAL | ██████████ | ██████████ |

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R41AI131784-01 Wagner, David

ADMINISTRATIVE NOTE

RESUME AND SUMMARY OF DISCUSSION: The investigators seek to develop a peptide therapy to modulate CD40 expressed T cells to mitigate autoimmune inflammation for the treatment of Type 1 diabetes. Reviewers have high praise on this strong application and consider the objective of the project highly significant. If successful, this novel therapeutic peptide will not only hold promise to reverse or prevent the development of Type 1 diabetes but also have broad impact to apply to the treatment of other autoimmune disorders. Many strengths mentioned include the strong scientific premise of the project which is based on solid published data and the compelling preliminary result, the straightforward and rigorously designed experimental approaches, the experienced and productive investigators, and the outstanding research environment. In addition, the testing of each amino acid of the peptide to determine individual amino acid's importance to the whole peptide adds rigor to the study design. Use of various ages of animals in pre-diabetic to diabetic conditions in the approach is also highlighted. Few weaknesses are mentioned and all considered minor. For example, it will be good to investigate whether this peptide allow beta cell regeneration. Only female mice will be used for proposed study and is not sufficiently justified in accounting for sex as a biological variable. However, reviewers also note that female mice have a higher chance to develop into diabetic condition than male, a limitation of this animal model, so the use of female animals only is acceptable. In sum, the proposed study is viewed as being very exciting and likely to have a high impact potential for the treatment of Type 1 diabetes.

DESCRIPTION (provided by applicant): Type 1 Diabetes (T1D) affects an ever growing population. While this disease typically has been associated with juveniles, the disease in adult populations is rapidly increasing. The defining clinical component is insulin loss, which occurs because of sustained inflammation in the islets. At present there is no means to prevent or reverse insulin loss. A major inflammatory pathway in T1D that contributes to insulin loss is the CD40 – CD154 dyad. CD40 is expressed on a wide array of cells and when engaged by CD154 creates localized inflammation. This pathway is decisive in T1D; blocking the interaction prevents diabetes onset and reverses hyperglycemia in new onset diabetic mice. A major impediment to drug development in diabetes has been the failure of therapeutics to translate from mouse to human. Mindful of this, we discovered that CD40 provides a link between mouse and human during T1D. We discovered that NOD mice, the industry standard model for T1D, increase CD40 expression, including on a sub population of T cells during diabetes development. Those cells, termed Th40, not only expand in number as diabetes develops but Th40 cells are singularly capable of transferring T1D to scid recipients. In a translational approach, we discovered that Th40 cells become prominent in human T1D patients, regardless of the age, HLA haplotype, auto-antibody status, or duration of disease. Like in the mouse model, Th40 cells start at low percentages but increase as human subjects progress to T1D and remain at high levels even up to 40 years after diagnosis. New onset as well as long – term diabetic patients have highly expanded numbers of Th40 cells when compared to non-autoimmune, or type 2 diabetic controls. A portion of TrialNet defined Pre-T1D subjects also have expanded Th40 cell numbers, suggesting that these cells become pathogenic over time, depending upon CD40 expression. Controlling CD40 therefore will be therapeutically advantageous. Methods to control CD40 have relied upon monoclonal antibodies or randomly generated, small organic molecules. Both those options have failed clinically. To address this, we developed a series of peptides derived from the CD154 protein sequence that are designed to target CD40 binding sites. These peptides do not function like antibodies and unlike the random generated organic molecule approach, have high specificity for CD40. In preliminary work we determined that some of the peptides prevent diabetes onset in NOD mice and one of the peptides (thus far) reversed hyperglycemia in new onset diabetic mice. The goals of this grant are to establish clinical parameters that will allow further development of a lead candidate for therapeutic development.

We propose to determine how candidate peptides impact glucose tolerance testing, serum insulin levels and c-peptide levels.

PUBLIC HEALTH RELEVANCE: Methods to control CD40 CD154 interaction have failed because heretofore they have depended upon monoclonal antibody or randomly generated organic molecules. We designed CD40 targeting peptides that prevent diabetes onset and reverse hyperglycemia in new onset diabetic mice.

CRITIQUE 1:

Significance: 1
Investigator(s): 2
Innovation: 2
Approach: 1
Environment: 1

Overall Impact: The primary investigator has extensive experience with CD40 T cells and has numerous publications in the area. The scientific premise is that D40 T cells are significantly increased in T1D patients and blocking CD40-CD154 interactions can lower CD40 T cell numbers and control T cell mediated inflammation. They are taking the novel approach of using natural peptides derived from CD154 that directly bind to CD40 and have shown that the peptides prevent diabetes in the NOD mice and one peptide reverses diabetes in the NOD mouse. Reversal of diabetes in humans would be highly significant. Certainly the CD40 peptide would be a candidate for drug development especially if the peptide does not cause adverse reactions, such as antibodies already tested clinically, do. The goals of the project are straightforward to determine the lead peptide to consider for peptide drug development. The environment is excellent for the work and the team is already experienced having worked in this field for some time. Usually peptides are degraded rapidly, but one of the peptides the one that reverses diabetes is quite stable. They tested each amino acid in the peptide to determine its importance to the whole and they are using various ages of mice both pre-diabetic and diabetic for experiments attesting to scientific rigor. The enthusiasm is high for this project.

1. Significance:

Strengths

- The scientific premise of the project is significant because CD40 T cells appear to be involved in the development of diabetes and blocking increased numbers of CD40 T cells would lead to a block of inflammation. Increased numbers of CD40 T cells are observed in autoimmune diabetes and MS, significantly above numbers in control individuals. Furthermore, the numbers of CD40 T cells remain high even after years of being diabetic.
- The peptide developed is able to block the development of diabetes in NOD mice something that is seen with many different treatments in these mice. The 15mer however, was also successful for an over 50% reversal of diabetes in new onset diabetic mice. Reversal is obviously a key point.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Dr. Wagner has worked on CD40 T cells (a subpopulation of CD4 T cells) in autoimmune inflammation for 15 years and has had important discoveries associated with this area of research. His discoveries concerning the CD40 molecule include: CD40 is functionally expressed on CD4+ T cells; CD40 is involved through RAG 1 and RAG2 induction leading to TCR revision in peripheral T cells; self-antigen exposure in the thymus promotes CD40 expressing T cells, CD40 is an alternative T cell co-stimulatory molecule, and CD40 expression negatively impacts T cell tolerance; CD40 expressing T cells are significantly expanded in MS and T1D in humans and mouse models; CD40 targeted peptides control and reverse T1D in NOD mice.
- Dr. Wagner has numerous publications in the area of the grant proposal and has had support from ADA, MS and NIAID on CD40 T cell projects.
- Dr. Wagner is an Associate Professor in the Dept. of Neurology, Section Head of the Immunology Section at the Webb-Waring Center at the U of Colorado Denver School of Medicine, and Chief Scientific Officer of Op-T-Mune.
- Dr. Yussman is the Chief Medical Officer at Op-T-Mune. Dr. Yussman has had a successful career as a clinical Cardiologist.

Weaknesses

- Dr. Wagner and Dr. Yussman have not published together. Dr. Yussman has few publications, although he is a first author in a Nature Medicine publication.

3. Innovation:

Strengths

- Trying to block the interaction between CD40 and CD154 to block inflammation is not novel; however the approach of making peptides of the areas from CD154 that bind CD40 is novel.
- The 15-mer peptide remains for over a 100 hours in the body and is stable for 6 weeks in solution. This is much better than most peptides that are degraded rapidly. This appears to be an excellent candidate for drug development.
- Antibodies to CD154 did not work in clinical trials because CD154 is expressed on platelets in high levels and antibody treatment caused platelet coagulation leading to thrombosis. It is mentioned in the grant that the 15-mer peptide does not affect normal coagulation time in humans.
- The 15-mer comes from an endogenous protein and therefore may be recognized as normal. In mice it does not elicit antibodies or cause T cell proliferation.

Weaknesses

- None noted.

4. Approach:

Strengths

- Excellent preliminary data showing that two peptides (6-mer and 15-mer) designed from the sequence of the CD154 protein where it binds to the CD40 receptor prevent the development of diabetes in NOD mice. The 15mer also had a 50% success rate in reversing diabetes. They tested each amino acid on the 15-mer and found that positions 2, 9, 11, and 12 were critical to prevent diabetes. This attests to scientific rigor that each amino acid was tested to determine its importance to the whole peptide.

- The goal of phase 1 is to determine the lead candidate peptide 1) based on treatment and impact on glucose tolerance testing (GTT) since a diagnosis of diabetes is based on high glucose in the serum and failed glucose tolerance testing, 2) sustained insulin production (serum and islets), and 3). Impact on insulin and c-peptide levels.
- The first aim will give a single lead compound and will determine if GTT after therapeutic treatment is an appropriate monitor that can be used eventually in human trials. The dose will be used that was preventative previously and route of administration will be varied and different ages of animals (young and older pre-diabetic and when become diabetic) will be tested as well as controls. Using various ages of mice in pre-diabetic to diabetic states attests to scientific rigor.
- The second aim will determine the duration of protection to maintain euglycemia with the two different peptides. Various doses, various routes and if a single dose or multiple doses are needed.
- Aim 3 will determine the maintenance of insulin and c-peptide in the serum based on the peptide injections and may translate for another clinical measure during human trials.
- Very straightforward goals, very doable, experience already in place to carry out the experiments. Timeline is doable.

Weaknesses

- They have looked at the insulinitis and the effect of the peptides on insulinitis, but have not looked to see if the peptides are allowing beta cell regeneration.
- There is no mention of using female or male mice for biological variables, but with the NOD model 80% of the females (in their hands) become diabetic and they are purchasing directly from Jackson labs for the experiments. It is recognized that in this strain, females are used most frequently for experimentation.

5. Environment:

Strengths

- The environment appears to be excellent to carry out the proposed studies. The Wagner lab is now housed in the College of Pharmacy and he has joined the Pharmaceutical Sciences and Toxicology group and this will add further instrumentation including mass spec and ion source mass spec capabilities.
- Plans are in place should they move to phase II wherein Dr Carpenter who worked with them on Structure Activity Relationships will be recruited as a collaborator since he is an expert in peptide drug development. Op-T-Mune also hired a consulting firm to advance IND filing. Patent coverage is in place for the developed peptides and the patent will be awarded in the US and Europe.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all four points addressed

- All four points addressed in detail.

Biohazards:

Acceptable

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- This section was not included. No discussion of where peptides were made if in house or externally and purity of peptides although it was mentioned elsewhere that they are patented.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 1

Investigator(s): 1

Innovation: 1

Approach: 2

Environment: 1

Overall Impact: This is an incredibly strong proposal to test novel peptides that have the potential of reversing and/or preventing the development of autoimmune Type 1 Diabetes. The investigators leverage a wealth of understanding of the role of CD40-expressing cells in disease development, and have provided a sound scientific basis for targeting this receptor. Furthermore, monoclonal antibody approaches suffer from severe side effects, necessitating the development of their novel peptides based on the KGYV motif. The planned experiments should elucidate the mechanism of action and establish feasibility in the appropriate models of T1D with respect to glucose tolerance, insulin production, and beta cell preservation. The plan lacks a little rigor with respect to animal numbers and detail, but is otherwise well-conceived. The team and environment are strong and likely to be key determinants in the success of this well-written and exciting proposal.

1. Significance:

Strengths

- There is a strong scientific premise for targeting Th40 expressing T cells for autoimmune diabetes based on mouse adoptive transfer experiments as well as evidence for an increased concentration of these cells in both autoimmune and Type 2 diabetic patients. It is especially

interesting that analysis of a cohort of pre-diabetic subjects had a statistically significant elevation of Th40+ cells.

- In a double blind study measuring the levels of Th40 cells, the researchers were able to identify 97% of T1D subjects from controls or T2D subjects based on Th40 levels.
- There is strong MoA data indicating that blocking CD40-CD154 interaction blocks the onset of T1D in NOD mice.
- There is a strong need to develop alternatives to monoclonal anti-CD40-CD154 antibodies, because of the off-target interactions with platelets.
- Peptides are easy to manufacture at large scale and generally less immunogenic than antibody or other large biologics.
- The lead KGY15 was shown to reverse hyperglycemia in new onset NOD mice, which if translatable to humans, would be a much more practical stage of intervention compared to upstream preventative therapy.

Weaknesses

- While the results demonstrating a reversal of hyperglycemia in new-onset NOD mice after just days are impressive, it calls into question the understanding of MoA and the suitability of the animal models. It does not seem possible to regenerate the lost insulin-producing beta cells so quickly.

2. Investigator(s):

Strengths

- Dr. Wagner brings to the table a wealth of experience on the specific CD40-CD154 biology that is targeted by the novel peptides developed in this proposal.
- Dr. Yussman adds clinical and basic biology expertise to the team.

Weaknesses

- The team could use some advice and expertise from researchers familiar with the NOD disease model and interpretation of the results.
- More expertise in understanding the translation (or lack thereof) from rodent data to clinical applicability is desirable.

3. Innovation:

Strengths

- Targeting the interaction between CD40 and CD154 with engineered peptides is certainly novel, and it is expected that the KGY15 and other peptides are novel compositions of matter.
- SAR data demonstrating the importance of the methionine residue adds to the non-obviousness and patentability of the invention.
- The compounds leverage key learnings developed by the PI over the last decade.

Weaknesses

- There are no obvious weaknesses with respect to innovation.

4. Approach:

Strengths

- Measuring the compounds effects on GTT as well as insulin and c-peptide levels is exactly what is required to further prove out the technology, and evaluating islets for cell infiltration, insulin-producing cells, and inflammation will provide additional support for the mechanism of action.
- With the exception of a few places, the applicants demonstrate careful thought and rigor with each of the planned experiments.
- There is a high likelihood of achieving proof of feasibility at the end of the twelve month study.

Weaknesses

- Animal sex (M/F) as a biological variable was not discussed in the application. It is understandable that only female NODs will be used due to their higher and more reliable disease penetration, but this should have been discussed.
- The approach could have been written with more rigor especially regarding the specific numbers of animals used for Aim 3 and the pancreatic analysis subgroups.
- Although toxicology studies are appropriately noted for Phase 2, it may be worth trying to assess the presence of anti-peptide antibodies with serum collected from the mice as an early readout on immunogenicity potential.

5. Environment:

Strengths

- The PI has access to all the necessary facilities and equipment to conduct the proposed studies.

Weaknesses

- There were no significant weakness noted with this proposal.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all four points addressed

- Investigators should address sex as a biological variable.

Biohazards:

Acceptable

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- An authentication plan is not provided.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 1
Environment: 1

Overall Impact: The proposed innovation are a series of peptide modulators of CD40 for the prevention and treatment of autoimmune diabetes. The broad impact of this product extends to other autoimmune conditions. The objective of the proposal is to extend the initial observations in vivo to determine the impact of the lead candidates on glucose tolerance improvement in autoimmune diabetic mice, the duration and stability of the therapeutic outcome in vivo and to identify possible cellular mechanisms affected by the treatment in the pancreas of autoimmune diabetic recipients. The scientific premise of the application is based on sound published data as well as the compelling preliminary data provided and experience of the applicants in the space of using this proposed innovation in diabetes. The scientific rigor is implied in the approach in the research work-plan in terms of considering replicates in vitro and in vivo. The consideration of female mice only is based on the experimental NOD model where only 20% of males develop T1 diabetes and therefore and therefore this proposal for females only is justified. There are considerable strengths in this application. The applicant is a solid and experienced scientist with significant and long-term expertise in the specific molecular pathway and disease, with well-supported research programs that demonstrate interest, productivity, and support feasibility to develop the innovation. The research work-plan is excellent, well-designed, and builds upon the previous work. The products are protected by patent, and the molecular targets are viable and innovative niches for which there is no other competition in terms of class of modulator, or drug/peptide target. The weaknesses are rectifiable and are as follows: 1) Absence of a team of business leaders in the space of peptide therapeutics in immunological disease; 2) Absence of a business development plan to translate the STTR into a viable small business; 3) an astonishing absence of letters of interest from key industry stakeholders.

1. Significance:

Strengths

- Immunomodulators that prevent and treat autoimmune diabetes have significant toxicities that the proposed product could obviate.
- Novel molecular target offers a niche without any competition.
- Immunomodulation offers an opportunity to prevent and treat new onset disease.
- The scientific premise of the application is based on sound published data as well as the compelling preliminary data provided and experience of the applicants in the space of using this proposed innovation in diabetes.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Well-established, experienced, and productive scientist with novel discoveries in the field of diabetes autoimmunity.

Weaknesses

- None noted.

3. Innovation:

Strengths

- Targeting CD40 by small peptides is novel
- CD40 is a critical pathway in the balance between tolerance and autoimmunity
- Product would represent a first-in-line class of modulator.
- Broad applicability to other autoimmune conditions.

Weaknesses

- None noted.

4. Approach

Strengths

- Experimental work-plan is generally sound and well-designed
- The scientific rigor is implied in the approach in the research work-plan in terms of considering replicates in vitro and in vivo.

Weaknesses

- None noted.

5. Environment:

Strengths

- Outstanding overall.

Weaknesses

- None noted.

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- No information on how peptide purity will be verified (measurements of potential contaminants that may affect outcomes).

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMAL (Resume): ACCEPTABLE

Please see the new NIH guideline for vertebrate animal section requirement ([NOT-OD-16-006](#)). Only 4 points of the vertebrate animal welfare concerns are required to address.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

ADMINISTRATIVE NOTE:

- (1) Applications submitted for due dates on or after January 25, 2016 are required to include a new PDF attachment describing plans for Authentication of Key Biological and/or Chemical Resources that will be used in that research study (see [NOT-OD-16-011](#)). Reviewers were asked to consider information provided in this attachment as part of their evaluation of your application. This attachment was missing from your application and could not be assessed.
- (2) During the review of this application, reviewers and/or NIH staff noted that one or more biosketches did not comply with the required format ([NOT-OD-15-032](#)). An electronic notification has been sent to the contact Program Director/Principal Investigator and Signing Official for this application, to ensure that future applications use the correct biosketch format. NIH has the authority to withdraw such applications from review or consideration for funding.

Footnotes for 1 R41 AI131784-01; PI Name: Wagner, David H

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html>. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER
Center for Scientific Review Special Emphasis Panel

CENTER FOR SCIENTIFIC REVIEW
Small Business: Endocrinology, Metabolism, Nutrition and Reproductive Sciences
ZRG1 EMNR-W (10)
11/15/2016 - 11/16/2016

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