AWARD NUMBER: W81XWH-19-1-0061

TITLE: Development of Glucose-Responsive Insulin

PRINCIPAL INVESTIGATOR: Danny Chou

CONTRACTING ORGANIZATION: University of Utah
Salt Lake City, UT 84112-9023

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TYPE OF REPORT: Annual Technical Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Danny Chou

E-Mail: dchou@biochem.utah.eu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Utah, The, 201 S. President Circle, Rm. 408
Salt Lake City, UT 84112-9023

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)
DoD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Technical Abstract

This project proposes to develop glucose-responsive insulin derivatives as next-generation insulin to combat diabetes.

Rationale

One therapeutic limitation of current insulin therapy in people with diabetes is that there is no control of insulin action once insulin is injected. That is, currently available injected insulin analogs can cause severe hypoglycemia if overdosed and remain biologically active, even when blood sugars are falling into dangerously low levels. Thus, hypoglycemia is the rate-limiting step in the glycemic management of diabetes due to the narrow therapeutic window of current insulin therapies. To reduce the risk of hypoglycemia, a glucose-responsive insulin (GRI) derivative is needed that is active when blood glucose levels are high, yet is inactivated when blood glucose levels start to decline. Such a "smart insulin" will eliminate the barrier of hypoglycemia for insulin-treated people with diabetes. To achieve this goal, it is proposed to develop new glucose-responsive insulin therapies such that the risk of hypoglycemia can be minimized.

15. SUBJECT TERMS: NONE LISTED

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Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

One therapeutic limitation of current insulin therapy in people with diabetes is that there is no control of insulin action once insulin is injected. That is, currently available injected insulin analogs can cause severe hypoglycemia if overdosed and remain biologically active, even when blood sugars are falling into dangerously low levels. Thus, hypoglycemia is the rate-limiting step in the glycemic management of diabetes due to the narrow therapeutic window of current insulin therapies. To reduce the risk of hypoglycemia, a glucose-responsive insulin (GRI) derivative is hat is active when blood glucose levels are high, yet is inactivated when blood glucose levels start to decline is proposed in this work. Such a "smart insulin" will eliminate the barrier of hypoglycemia for insulin-treated people with diabetes. To achieve this goal, it is proposed to develop new glucose-responsive insulin therapies such that the risk of hypoglycemia can be minimized.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Insulin, diabetes, hypoglycemia, glucose control, glucose-responsive insulin

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

k

Achieving glucose responsiveness using PBA-modified insulin glargine derivatives	Months	Completion
Synthesis and characterization of PBA-modified insulin glargine derivatives	1-6	12/31/2019. 100%
In vivo characterization of PBA-modified insulin glargine derivatives	7-18	50%
Milestone(s): In vivo evaluation of 6 glucose-responsive insulin derivatives	18	
Specific Aim 2		
Excipient-based glucose-responsive insulin glargine derivatives		
Synthesis and characterization of PBA-modified cucurbit[7]uril-insulin glargine complex	1-6	12/31/2019. 100%
In vivo characterization of insulin glargine complex	7-18	50%
Milestone(s): Identification of PBA-modified cucurbit[7]uril that can lead to glucose responsiveness in vivo	18	

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) major activities

Our major activities include 1) chemical synthesis of PBA-modified insulin glargine derivatives; 2) in vitro characterization of newly synthesized PBA-modified insulin glargine derivatives; 3) animal studies of insulin derivatives; 4) chemical synthesis of PBA-containing peptides for CB7 modifications. Specific details for all 4 activities are described in section 3.

2) specific objectives

The specific objectives are to 1) access next generation glucose-responsive insulin derivatives using chemical protein synthesis, 2) measure the glucose-dependent solubility to confirm glucose responsiveness in vitro, 3) measure insulin receptor activation potency to ensure that bioactivity is retained and 4) perform animal experiments to demonstrate that the insulin derivatives indeed can prevent hyper- and hypoglycemia.

3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)

1) Chemical synthesis of PBA-modified insulin glargine derivatives

This activity is successfully completed and the results are described as following:

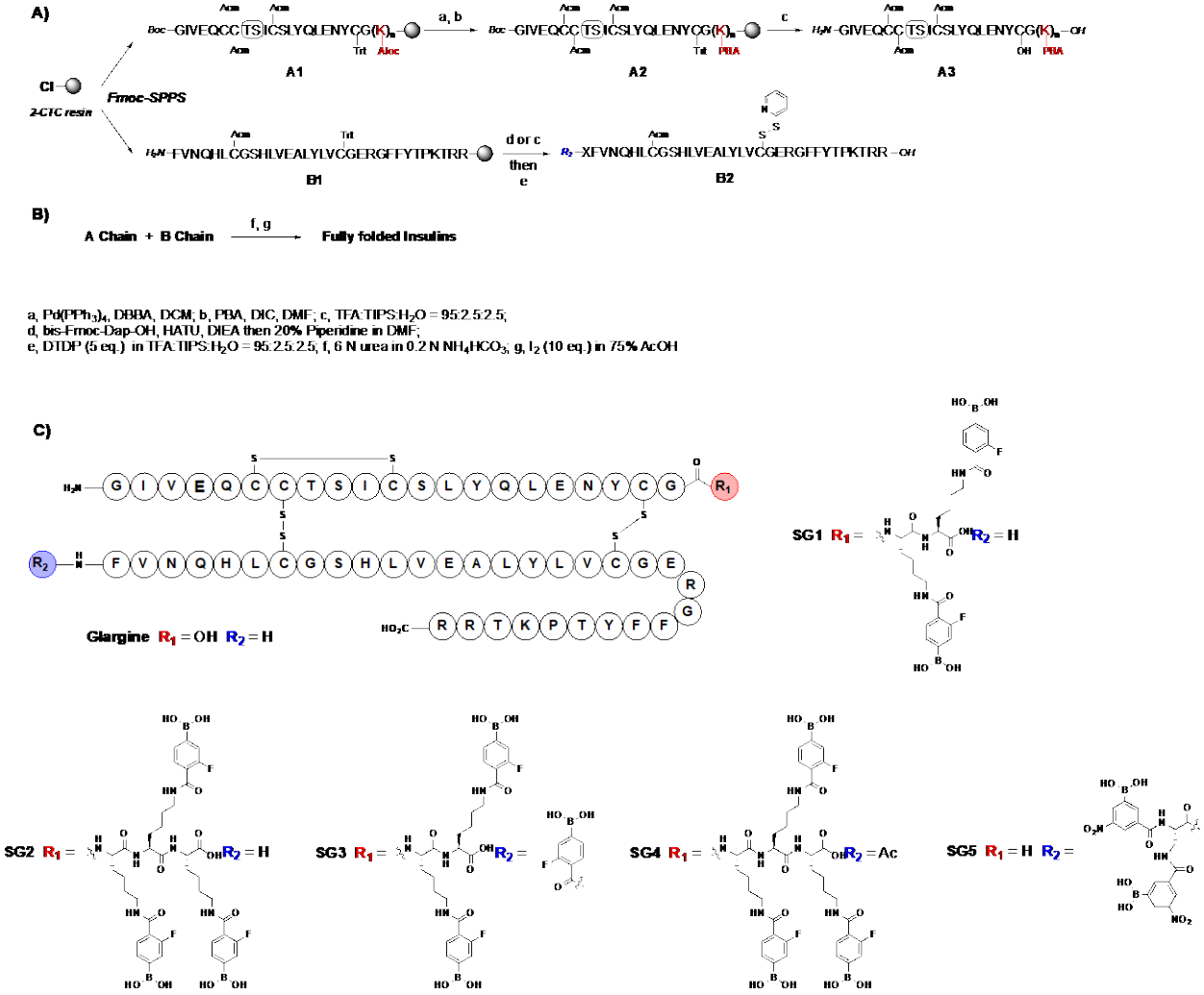

Figure 1. Chemical synthesis of 5 novel PBA-modified insulin glargine derivatives.

Briefly, we were able to identify new chemical methods to insert glucose-sensing PBA groups into C-terminal of A chain and N-terminal of B chain. Previously, we demonstrated the insertion only on C-terminal of B chain (described as preliminary data in the proposal). These five derivatives cover difference in 1) numbers of PBA, 2) types of PBA (nitro vs F modified) and 3) locations of PBA. These five insulin derivatives were then further evaluated for their in vitro activity.

2) in vitro characterization of newly synthesized PBA-modified insulin glargine derivatives

All five novel derivatives were further evaluated for their solubility in various glucose concentrations. As a control, the parent insulin glargine molecule is included. As shown in Figure 2, insulin glargine has the same solubility in all conditions, which makes sense since it has no glucose sensing group. Among the 5 novel derivatives, SG2 and SG4 have the largest glucose-dependent solubility fold changes. Both have 3 PBA groups on the C-terminal A chain of inuslin. These results suggest that 1) more PBA groups indeed lead to more glucose responsiveness, a key hypothesis in

our proposal and 2) modifications on insulin A chain led to desired enhanced glucose responsiveness.

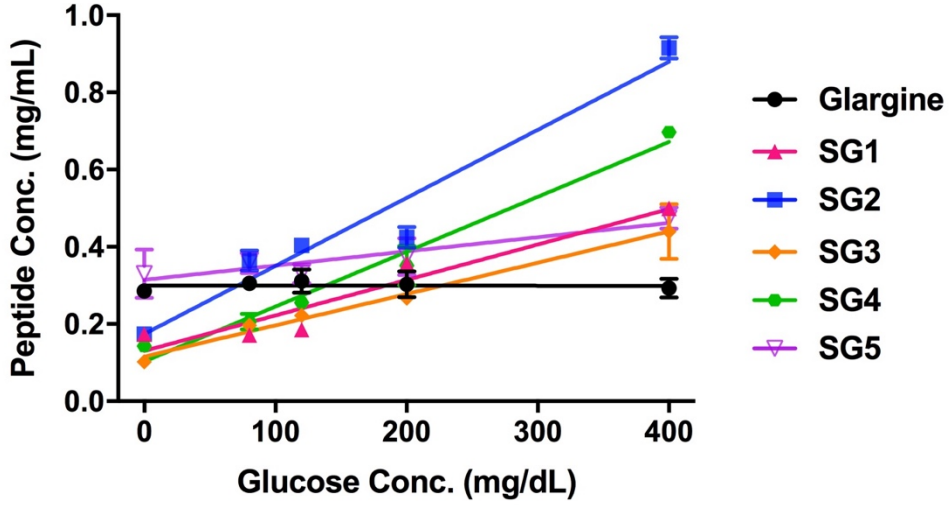

Figure 2. Solubility profile of insulin glargine and 5 more novel derivatives

After confirming the glucose responsiveness in vitro, we performed cell activity assay to measure the potency. As show in figure 3, SG3 has roughly 2-dolf reduction of bioactivity compared to native insulin and is in line with insulin glargine. These results indicate that modifications on insulin C-terminal A chain do not interfere with insulin bioactivity.

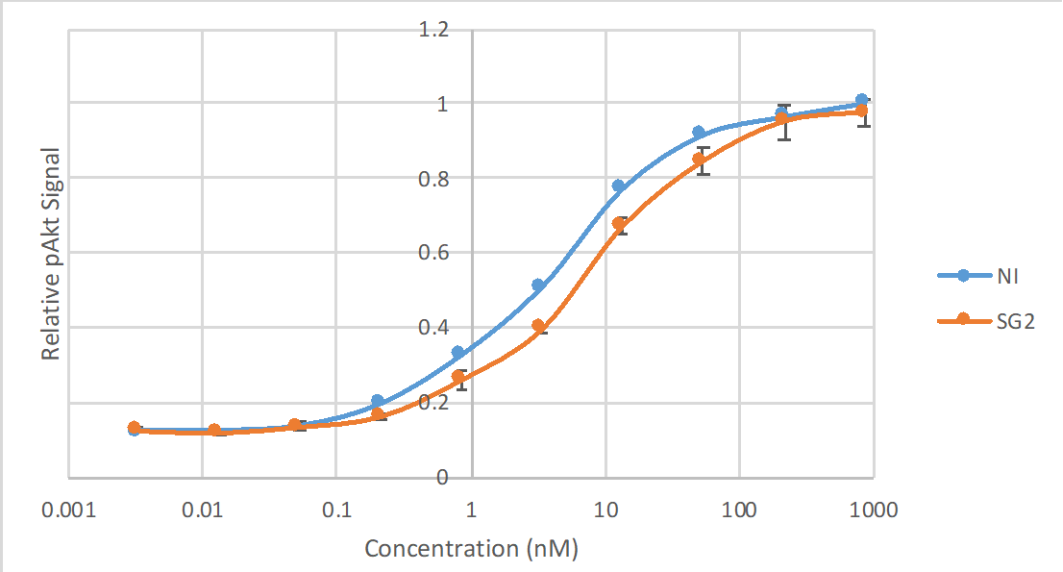

Figure 3. Cell-based assays to measure insulin bioactivity.

3) animal studies of insulin derivatives

In the preliminary data of the proposal, we described that PBA-F-glargine has a 2.9-fold insulin activity difference in vivo using a glucose clamp study in rats. We further performed a large dose study here to demonstrate if PBA-F-glargine can indeed avoid hyper- and hypoglycemia in vivo. Given its reduced bioactivity under lower glucose conditions, we hypothesize that PBA-F-glargine

may be less likely to cause hypoglycemia. To evaluate the potential for insulin-induced hypoglycemia, high dose (1 mg/kg) insulin tolerance tests (ITTs) were performed in streptozotocin (STZ)-induced diabetic rats. In the absence of glycemic clamp conditions, the subcutaneous administration of both insulin glargine and PBA-F-glargine (1 mg/kg) lowered blood glucose levels (Figure 4A). The nadir blood glucose levels reached in insulin glargine-treated rats was 40 mg/dl. An equal dose of PBA-F-glargine resulted in a more gradual lowering of blood glucose and a nadir blood glucose level of 102 mg/dl. To quantify the hypoglycemic potency of these insulins, the duration of time during which the blood glucose remained hypoglycemic (<70 mg/dl) was quantified. PBA-F-glargine-treated rats remained hypoglycemic for a significantly shorter duration as compared to commercial glargine-treated rats (Figure 4B). This 15-fold less hypoglycemic potency demonstrates that PBA-F-glargine portends a reduced risk of causing hypoglycemia as compared to insulin glargine.

To further investigate whether changes in blood glucose level alters the in vivo bioactivity of the two insulin analogs, we again evaluated bioactivity and hypoglycemic potency following rescue glucose administration. In this experiment, an intraperitoneal injection of bolus glucose (4g/kg) was administered to both insulin glargine and PBA-F-glargine insulin-treated rats 150 minutes after subcutaneous insulin injection. The glucose bolus resulted in a spike in blood glucose levels in both experimental groups; however, blood glucose returned to hypoglycemic levels in rats treated with insulin glargine, whereas blood glucose returned to normogylcemic levels in rats treated with PBA-F-glargine (Figure 5A). Evidence of ongoing insulin absorption/action was noted by the maintenance of normal or low glucose levels for greater than five hours in both groups of diabetic animals. This persistent insulin action is particularly noteworthy in the setting of a (likely) counterregulatory response to hypoglycemia. Again, the duration of time during which the blood glucose remained hypoglycemic (<70 mg/dl) following the glucose bolus was significantly shorter in the PBA-F-glargine-treated rats as compared to commercial glargine-treated rats (Figure 5B).

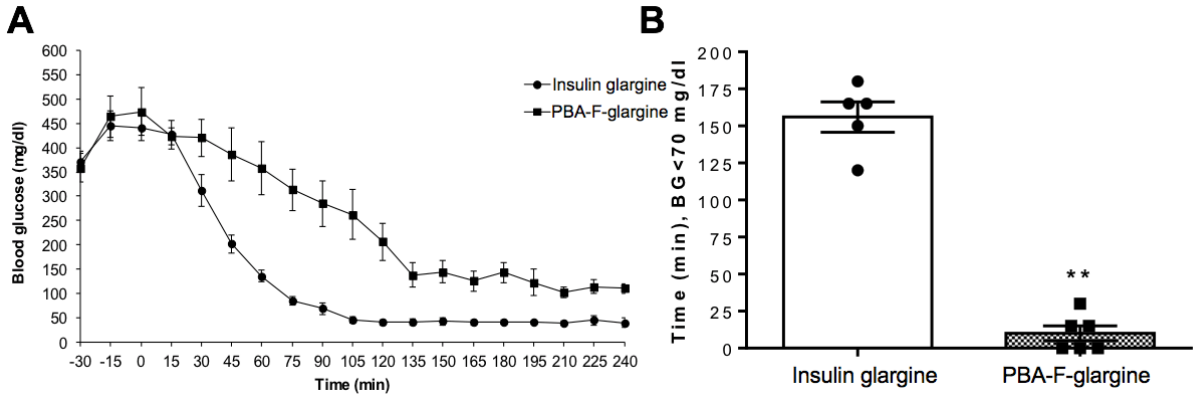

Figure 4. Insulin tolerance test. A) Blood glucose levels (mg/dl) during insulin tolerance tests (ITTs) performed in STZ-diabetic rats. After obtaining baseline blood glucose readings, rats were injected at time zero with either insulin glargine (1 mg/kg) or PBA-F-glargine (1 mg/kg) subcutaneously. Data are expressed as mean ± SEM (n=5-6/group). Statistics were calculated by repeated measures ANOVA (two-way) followed by post-hoc test with Tukey's comparisons. B) Time (min) during which the blood glucose levels remained below 70 mg/dl during the ITT in rats injected with either insulin glargine (1 mg/kg) or PBA-F-glargine (1 mg/kg). Data are expressed as mean ± SEM (n=5-6/group). **P<0.01 vs Glargine; Student 't' (unpaired) test.

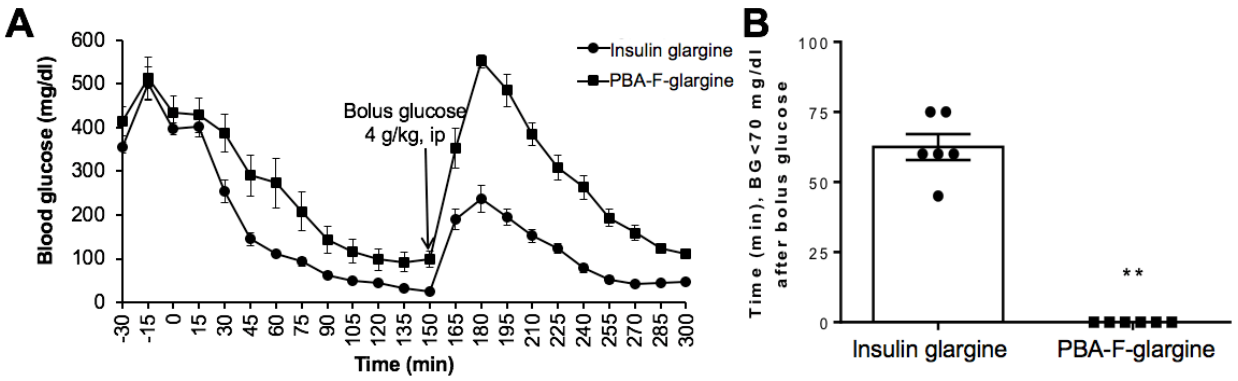

Figure 6. Insulin tolerance test with glucose challenge. A) Blood glucose levels (mg/dl) during insulin tolerance test (ITT) followed by a glucose challenge performed in STZ-diabetic rats. After baseline blood glucose readings, rats were injected at time zero with either insulin glargine (1 mg/kg) or PBA-F-glargine (1 mg/kg) subcutaneously and both groups were subsequently injected with a glucose bolus (4 g/kg, ip) 150 minutes following insulin injection. Data are expressed as mean ± SEM (n=6-7/group). B) Time (min) during which the blood glucose levels remained below 70 mg/dl after bolus glucose in rats injected with either insulin glargine (1 mg/kg) or PBA-F-glargine (1 mg/kg). Data are expressed as mean ± SEM (n=6-7/group). **P<0.05 Vs Glargine; Student 't' (unpaired) test.

4) chemical synthesis of PBA-containing peptides for CB7 modifications
Toward the second aim of our proposal, we have successfully synthesized various PBA conjugated alkynes, which will be coupled with CB7 (Figure 7). Initially, we were facing some challenges to achieve this as our typical methodology for introducing PBA groups does not work in this case (see Figure 1). We were able to use an alternative protecting group (Mtt in this case) to achieve this goal. We are in the process of determining the glucose-dependent solubility similar to the case of part 2.

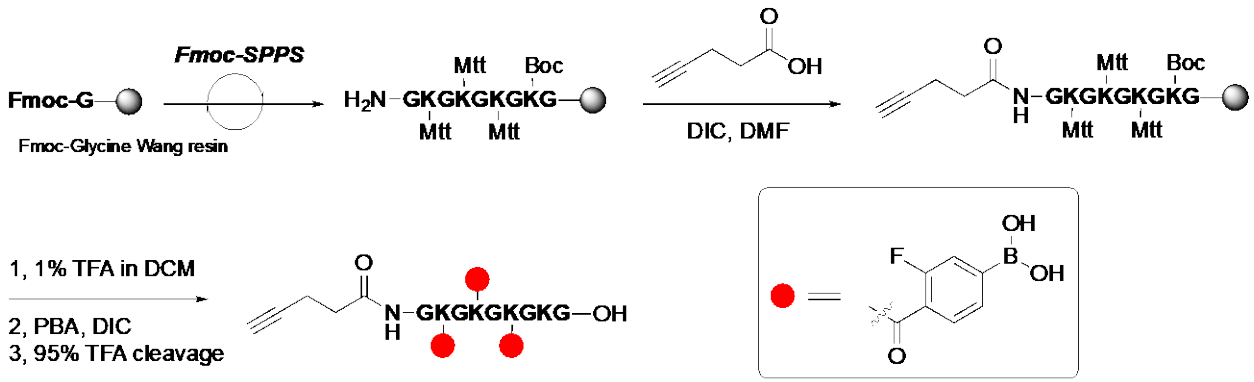

Figure 7. Synthetic scheme for PBA-modified peptide for CB7 conjugation.

4) other achievements.

Part of the reported results is published in the following paper: Qiu, Yibo, et al. "Long-Lasting Designer Insulin with Glucose-Dependent Solubility Markedly Reduces Risk of Hypoglycemia." Advanced Therapeutics 2.11 (2019): 1900128.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Trainees attend weekly Biochemistry department research in progress seminar series. They present their research progress to other department members. Trainees also participate in the weekly seminar in metabolism series and share their progress with the metabolism community within University of Utah.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Members in our lab participate in events with the local JDRF chapter. These are people or families with type 1 diabetes connections, who are interested to know the latest development of this insulin research project.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We plan to finish the in vivo animal experiments and finish the PBA-CB7 conjugation studies.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Our current findings demonstrate that 1) phenylboronic acids (PBAs) can indeed to be used as a glucose sensor to modify the behavior of insulin and 2) PBA-modified glargine can further improve the most widely used insulin therapeutic and lead to better glycemic control. For the diabetes research field, the project suggests that novel therapeutics can be achieved by inserting glucose sensor on currently available therapeutics.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

For the peptide research field, this project suggests that a similar peptide modification approach may be extended to other therapeutic peptides.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*

- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

University of Utah is currently filing a patent application for this project and is in discussion with a biotech company for licensing.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

It is still too early for us to make claims as this is only basic science research. However, our project has the potential to improve the life quality for people with diabetes as frequent check-up of glucose levels may not be required in the future.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Our lab was shut down since late March due to the COVID-19 pandemic. Things will be delayed but we will do our best to stick to the plans.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

The current shutdown may lead to increased expenditures on personnel. We will need to wait until the shutdown is over to measure the extent of the increased expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

NA

Significant changes in use or care of vertebrate animals

NA

Significant changes in use of biohazards and/or select agents

NA

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Qiu, Yibo, et al. "Long-Lasting Designer Insulin with Glucose-Dependent Solubility Markedly Reduces Risk of Hypoglycemia." Advanced Therapeutics 2.11 (2019): 1900128.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

NA

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

NA

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

NA

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

NA

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Patent application is undergoing at University of Utah.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

NA

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	*Danny Chou*
Project Role:	*PD/PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-9110-614X*
Nearest person month worked:	*0.6*
Contribution to Project:	*design and supervise overall research acitivities*
Funding Support:	*(Complete only if the funding support is provided from other than this award.)*
Name:	*Surbhi Verma*
Project Role:	*Post Doctoral Associates*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Verma has provided research support for the project aims and has also assisted with lab organization and management.*
Funding Support:	*N/A*
Name:	*Landa Purushottan*
Project Role:	*Post Doctoral Associates*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4*
Contribution to Project:	*Ms. Purushottan has conducted research experiments for the proposed aims 2 and 3*
Funding Support:	*N/A*
Name:	*Nai-Pin Lin*
Project Role:	*Graduate Students*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.13*
Contribution to Project:	*Ms. Lin has assisted with research experiments for the project.*
Funding Support:	*N/A*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

***Changes notated with an ***

CURRENT

5-CDA-2018-572-A-N (**Chou**, PI) 06/01/2018-05/31/2023 2.0 calendar
Juvenile Diabetes Research Foundation $127,000 direct cost per year
Synthesis of ultra-fast acting insulin for the treatment of diabetes
In this project, we are developing monomeric insulin to be used in artificial pancreas.
Program Officer: Sanjoy Dutta, sdutta@jdrf.org
JDRF: 26 Broadway, 14th Floor, New York, NY-10004
Aims:
Aim 1: Development of UFI candidates from characterization of novel cone snail insulin molecules
Aim 2: Biochemical and in vitro characterization of ultrafast-acting human monomeric insulin analogs
Aim 3: In vivo evaluations of UFI molecules in animal models
Overlap with current application: None

1 R35GM125001-01 (**Chou**, PI) 09/01/17-08/31/22 4.9 calendar
NIH/NIGMS $250,000 direct cost per year
Studies on insulin receptor isoforms
The major goal of this application is to develop novel insulin molecules specific to insulin receptor isoforms to learn the roles of each insulin receptor in vivo. Successful outcome will lead to new strategies for treating human diseases.
Program Officer: Sailaja Koduri, sailaja.koduri@nih.gov
NIGMS: 45 Center Drive MSC 6200, Bethesda, MD 20892
Aims:
Project 1: Develop insulin receptor isoform-specific agonists
Project 2: Explore the signaling transduction of insulin receptor isoform A and B
Overlap with current application: None

*1 R01 DK120430-01 (**Chou**, PI) 12/01/18-11/30/22 2.4 calendar
NIH/NIDDK
Development of concentrated, stable ultra fast-acting insulin
In this project, we are developing stable insulin formulation that can optimize artificial pancreas performance.
Program Officer: Aaron Pawlyk, pawlykac@mail.nih.gov
NIDDK: 9000 Rockville Pike, Bethesda, MD 20892
Aims:
Aim 1: Development of UFI candidates with fast-on, fast-off properties responsiveness
Aim 2: Development of concentrated and stable insulin formulation
Overlap with current application: None

* W81XWH-17-1-0413 (**Chou**, PI) 09/30/2017-09/29/2021 0.5 Calendar Months
Army Medical Research Acq (DoD)
Novel Strategies for Accelerating Non-Opioid Drug Discovery
In this project, my lab is involved in synthesizing macrocyclic RgIA4 peptides with enhanced pharmacological properties to target nicotinic receptors.
Program Officer: Congressionally Directed Medical Research Program Office, usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil
DoD: 1120 Fort Detrick, Frederick MD 21702
Aim: Synthesis of macrocyclic RgIA peptide derivatives
Overlap with current application: None

* W81XWH1910061 (**Chou**, PI) 03/01/2019-08/31/2020 0.6 calendar months
Army Medical Research Acq (DoD)
Development of Glucose-Responsive Insulin
This project proposes to develop glucose-responsive insulin derivatives as next-generation insulin to combat diabetes
Program Officer: Congressionally Directed Medical Research Program Office, usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil
DoD: 1120 Fort Detrick, Frederick MD 21702
Aims:
Aim 1: Achieving glucose responsiveness using PBA-modified insulin glargine derivatives
Aim 2: Excipient-based glucose-responsive insulin glargine derivatives
Overlap with current application: None

Completed Research Support

*3-SRA-2015-120-Q-R (**Chou**, PI) 10/01/15-09/30/18
JDRF/Sanofi Aventis
Development of Glucose-Responsive Insulin Analogues
In this project, we are developing insulin analogues with glucose-dependent affinity to insulin receptor.

*3-SRA-2015-120-Q-R (**Chou**, PI) 10/01/15-09/30/18 4.0 (year 1) calendar
2.0 (years 2-3) calendar
JDRF/Sanofi Aventis $225,000 direct cost per year
Development of Glucose-Responsive Insulin Analogues
In this project, we are developing insulin analogues with glucose-dependent affinity to insulin receptor.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

NA

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.