

QVR NIH Business System (NBS) Accounting Details

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PI: YU, ANTHONY FY: 2024

Total IMPACII Award Amt: \$322,787

Obligation Details for Project:

1R44DK141341-01

External Organization:

SYNTIS BIO INC

Accounting System Totals

PMS Account Type: Subaccount:domestic(P)**Award Document
Number:** RDK141341A*Click hyperlink for accounting details for all projects with this document number*

TIMING INFORMATION: QVR gathers disbursement data from NBS/nVision on a nightly basis. As of April 2021, PMS disbursement data is uploaded to NBS nightly.

Accounting System

IC	CAN	Budget FY	Latest Obligated Dt	Latest Disburse. Dt	NBS Obligated \$	NBS Disbursed \$	Obligated Balance
DK	8469933	2024	2024-09-12	2024-11-20	\$ 322,787.00	\$ 121,891.74	\$ 200,895.26

Accounting System Transactions

Accounting System Transactions

IC	CAN	Budget FY	OCC	NBS Doc Num	NBS Transact. Dt	Obligation Amt	Disbursement Amt
DK	8469933	2024	41021	380RDK141341A	2024-11-20	\$ 0.00	\$ 43,434.74
DK	8469933	2024	41021	380RDK141341A	2024-10-31	\$ 0.00	\$ 78,457.00
DK	8469933	2024	41021	380RDK141341A*10001	2024-09-12	\$ 322,787.00	\$ 0.00
Grand Totals:						\$ 322,787.00	\$ 121,891.74



Recipient Information

1. Recipient Name

SYNTIS BIO INC
135 MORRISSEY BLVD
BOSTON, MA 02125

2. Congressional District of Recipient
08**3. Payment System Identifier (ID)**
1880608856A1**4. Employer Identification Number (EIN)**
880608856**5. Data Universal Numbering System (DUNS)****6. Recipient's Unique Entity Identifier**
NG1VDVBHC87**7. Project Director or Principal Investigator**
Anthony Yu

anthony@syntis.bio
415-734-1428

8. Authorized Official

Matt Lanchantin
matt@Syntis.bio
508-561-3080

Federal Agency Information

9. Awarding Agency Contact Information
Kaitaia Fu

NATIONAL INSTITUTE OF DIABETES AND
DIGESTIVE AND KIDNEY DISEASES
fukai@niddk.nih.gov

10. Program Official Contact Information

Dwayne Lunsford
Program Director
NATIONAL INSTITUTE OF DIABETES AND
DIGESTIVE AND KIDNEY DISEASES
robert.lunsford@nih.gov
301-402-1379

Federal Award Information

11. Award Number
1R44DK141341-01**12. Unique Federal Award Identification Number (FAIN)**
R44DK141341**13. Statutory Authority**
42 USC 241 15 USC 638 42 CFR 52**14. Federal Award Project Title**
Development of an Oral Pill to Mimic the Effects of Gastric Bypass Surgery**15. Assistance Listing Number**
93.847**16. Assistance Listing Program Title**
Diabetes, Digestive, and Kidney Diseases Extramural Research**17. Award Action Type**
New Competing (REVISED)**18. Is the Award R&D?**
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 09/15/2024 – End Date 08/31/2025

20. Total Amount of Federal Funds Obligated by this Action	\$0
20 a. Direct Cost Amount	\$0
20 b. Indirect Cost Amount	\$0

21. Authorized Carryover**22. Offset**

23. Total Amount of Federal Funds Obligated this budget period \$322,787

24. Total Approved Cost Sharing or Matching, where applicable \$0

25. Total Federal and Non-Federal Approved this Budget Period \$322,787

26. Project Period Start Date 09/15/2024 – End Date 08/31/2025

**27. Total Amount of the Federal Award including Approved Cost
Sharing or Matching this Project Period** \$322,787

28. Authorized Treatment of Program Income
Additional Costs**29. Grants Management Officer - Signature**
Sunshine Wilson**30. Remarks**

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.



SMALL BUSINESS INNOVATION RESEARCH PROG
Department of Health and Human Services
National Institutes of Health

Notice of Award



NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

SECTION I – AWARD DATA – 1R44DK141341-01 REVISED

Principal Investigator(s):

Anthony Yu

Award e-mailed to: matt@syntis.bio

Dear Authorized Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to SYNTIS BIO INC in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 15 USC 638 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number R44DK141341. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website <http://grants.nih.gov/grants/policy/coi/> for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Sunshine Wilson
Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)
Salaries and Wages

Itemized Cost

Fringe Benefits
Personnel Costs (Subtotal)
Consultant Services
Materials & Supplies
Other

Federal Direct Costs
Federal F&A Costs
Approved Budget
Fee

Total Amount of Federal Funds Authorized (Federal Share)
TOTAL FEDERAL AWARD AMOUNT

Itemized Cost

\$322,787
\$322,787

AMOUNT OF THIS ACTION (FEDERAL SHARE)

\$0

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	THIS AWARD	CUMULATIVE TOTALS
1	\$322,787	\$322,787

Fiscal Information:

Payment System Identifier: 1880608856A1
Document Number: RDK141341A
PMS Account Type: P (Subaccount)
Fiscal Year: 2024

IC	CAN	2024
DK	8469933	\$322,787

NIH Administrative Data:

PCC: NRL SBGI / OC: 41021 / Released: 10/17/2024

Award Processed: 10/18/2024 12:04:54 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R44DK141341-01 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm>

SECTION III – STANDARD TERMS AND CONDITIONS – 1R44DK141341-01 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

- The grant program legislation and program regulation cited in this Notice of Award.
- Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
- 45 CFR Part 75.
- National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
- Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
- This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at <http://grants.nih.gov/grants/policy/awardconditions.htm> for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part § 75.2. As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-

research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This award is subject to the life cycle certification requirements set forth in Section 18.5.5.4 of the NIH Grants Policy Statement and NOT-OD-19-025. Effective January 1, 2019, Awardees are required to submit this certification within the I-RPPR and the F-RPPR under Section G.1: Special Notice of Award and Funding Opportunity Announcement Reporting Requirements and maintain it on file in accordance with the records and retention policy in Section 8.4.2 of the NIH Grants Policy Statement.

A certification is required at the following times:

- For SBIR/STTR Phase I Awardees: At the time of receiving final payment or disbursement from the Payment Management System.
- For SBIR/STTR Phase II Awardees: Prior to receiving more than 50% of the total award amount and prior to final payment or disbursement from the Payment Management System.

If the grantee cannot complete this certification or cannot ensure compliance with the certification process, it should notify the GMO immediately. If resolution cannot be reached, the GMO will void or terminate the grant, as appropriate.

The certification form is available in fillable format at: <http://grants.nih.gov/grants/forms.htm#sbir>.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See <http://grants.nih.gov/grants/policy/awardconditions.htm> for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R44DK141341. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see <http://grants.nih.gov/grants/policy/awardconditions.htm> for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: <http://publicaccess.nih.gov/>.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: <http://grants.nih.gov/grants/policy/policy.htm#gps>.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the Payment Management System (PMS) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, <http://grants.nih.gov/grants/policy/policy.htm#gps>, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the real-time cash drawdown data in PMS. NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: <http://grants.nih.gov/grants/forms.htm>. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71, DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51, R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as

well. Instructions for preparing an Interim or Final RPPR are at:

https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience.*

NIH requires electronic submission of the final invention statement through the Closeout feature in the Commons.

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and must be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See <https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html> and <https://www.hhs.gov/>.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see <https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html> and <https://www.lep.gov>.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see <http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html>.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see <https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html>. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see <https://grants.nih.gov/grants/policy/harassment.htm>.
- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see <https://www.hhs.gov/conscience/conscience-protections/index.html> and <https://www.hhs.gov/conscience/religious-freedom/index.html>.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than \$10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – DK SPECIFIC AWARD CONDITIONS – 1R44DK141341-01 REVISED

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

REVISION # 1: Lifting Restriction

This revised award reflects the Office of Laboratory Animal Welfare (OLAW) approval of an Animal Welfare Assurance for the recipient and/or all performance sites and removes the restrictive term on the Notice of Award issued on 09/12/2024.

The following terms from the previous Notice of Award also apply to this award:

Other Support

NIDDK has received the updated other support information provided for all key personnel as identified by the applicant. Only other support information for the PD/PI(s) and any individual(s) named as key personnel on the Notice of Grant Award have been reviewed for overlap. It is the responsibility of the recipient to make sure no overlap of budget, effort, or aims exist for all personnel devoted to this grant.

Award Budget

To meet current NIDDK objectives and based on the relative scientific merit ranking of this application, the budget for the initial period has been programmatically reduced. Although specific budget adjustments have been made, the Institution and Principal Investigator retain standard re-budgeting authorities for this mechanism of support.

See the budget information below for additional information.

FUTURE FAST TRACK FUNDING CRITERIA

Funding for the Phase II application will be contingent upon (1) assessment of the Phase I

progress report and determination that the Phase I milestones were achieved, (2) review and approval of other documents necessary for continuation, and (3) availability of funds.

The Fast-Track Phase II application may be funded following the submission of an updated Product Development Plan Appendix and an original or fax or electronic PHS 2590 application form. The applicant should follow the PHS 2590 instructions, specifically sections 1, 2, and 6. All Phase II application should include the following:

1. A Progress Report Summary, excluding the research plan. Use the instructions detailed in Section 6 of the PHS 2590.
2. A section labeled Milestones must be included, describing the progress achieved in Phase I: (1) identifying either the milestones described in the original Phase I application as approved by the peer reviewers or the milestones modified by the peer reviewers and negotiated with the grantee; and (2) describing the progress achieved relative to the milestones.
3. A one-page abstract describing the research plan for Phase II. If the aims have not been modified from the original Phase II application, state this. If they have been modified, give the reviewed aims and the reason for the modifications.
4. An updated Commercialization Plan as necessary, if changes have been made from the original submission.

The continuation application package is due 2 months prior to the anticipated start date of Phase II, which is 07/01/2025. It should be submitted electronically as a complete PDF file to the assigned Program Officer and Grants Management Specialist listed on the Notice of Award.

The Phase II continuation application will be reviewed by the appropriate grants management and program staff of the awarding component. If the continuation request is not approved, written notification will be sent to the applicant.

Prior to drawing down funds for this award from the payment management system, you are required to have in place written policies and procedures for financial and business management systems. Your systems must comply with the standards included in the attachment to the letter/email "Requirements for Financial and Business Management Systems Requirements for SBIR/STTR Awardees" which was sent to your organization's Business Official on **05/31/2024**. The policies and procedures must remain in effect for the duration of this project.

The fee provided as part of this grant award is in addition to the allowable direct and indirect costs. An adjustment of the fee will be made in the event the grant is terminated. The fee should be drawn down from the DHHS Program Support Center's Payment Management System (PMS) in increments proportional to the draw-down of funds for costs. Questions concerning access to the PMS should be directed to (877) 614-5533.

Allowable costs of activities conducted by for-profit organizations will be determined by applying the cost principles of the Federal Acquisition Regulation set forth in 48 CFR, Subpart 31.2.

Intellectual property rights: Normally, the awardee organization retains the principal worldwide patent rights to any invention developed with United States government support. Under Title 37 Code of Federal Regulations Part 401, the government receives a royalty free license for its use, reserves the right to require the patent holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

Rights and obligations related to inventions created or reduced to practice because of this award are detailed in 35 U.S.C. 205 and 37 CFR Part 401. These inventions must be reported to the Extramural Invention Reporting and Technology Resources Branch, OPERA, NIH, 6705 Rockledge Drive, MSC 7980, Bethesda, MD 20892-7980, (301) 435-1986. For additional information, access the NIH link on the Interagency Edison (iEdison) web site which includes an electronic invention reporting system, reference information and the text to 37 CFR 401.

To the extent authorized by 35 U.S.C., Section 205, the government will not make public any information disclosing an NIH-supported invention for a 4-year period to allow the awardee organization a reasonable time to file a patent application, nor will the government release any information that is part of that patent application.

Prior approval to implement budgetary and programmatic changes, where required by NIH Policy, (See the NIH Grants Policy Statement Section 8.1.2 for Prior Approval Requirements) must be obtained in writing from the Grants Management contact shown on this Notice of Award. A letter signed by the Principal Investigator and a Business Official of the Grantee Institution and should include an explanation and justification for the action(s). Requests may be made via e-mail provided they are routed through these same officials. If there are questions as to whether an action requires prior approval, contact the Grants Management Specialist.

The grantee is required to establish a positive time and effort reporting system.

SBIR Awards:

None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the current salary cap (Executive Level II). Therefore, this award and/or future years are adjusted accordingly, if applicable. See the Salary Cap

Summary for the current and historical record of the salary cap, including effective dates.

Prior to drawing down funds for this award from the payment management system, you are required to have in place written policies and procedures for financial and business management systems. Your systems must comply with the standards included in the attachment to the letter/email "Requirements for Financial and Business Management Systems Requirements for SBIR/STTR Awardees" which was sent to your organization's Business Official on 06/02/2024. The policies and procedures must remain in effect for the duration of this project.

The fee provided as part of this grant award is in addition to the allowable direct and indirect costs. An adjustment of the fee will be made in the event the grant is terminated. The fee should be drawn down from the DHHS Program Support Center's Payment Management System (PMS) in increments proportional to the draw-down of funds for costs. Questions concerning access to the PMS should be directed to (877) 614-5533.

Allowable costs of activities conducted by for-profit organizations will be determined by applying the Contract Cost Principles and Procedures of the Federal Acquisition Regulation set forth in 48 CFR, Subpart 31.2.

Intellectual property rights: Normally, the awardee organization retains the principal worldwide patent rights to any invention developed with United States government support. Under Title 37 Code of Federal Regulations Part 401, the government receives a royalty free license for its use, reserves the right to require the patent holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

Rights and obligations related to inventions created or reduced to practice as a result of this award are detailed in 35 U.S.C. 205 and 37 CFR Part 401. These inventions must be reported to the Extramural Invention Reporting and Technology Resources Branch, OPERA, NIH, 6705 Rockledge Drive, MSC 7980, Bethesda, MD 20892-7980, (301) 435-1986. For additional information, access the NIH link on the Interagency Edison (iEdison) web site which includes an electronic invention reporting system, reference information and the text to 37 CFR 401.

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Prior approval to implement budgetary and programmatic changes, where required by NIH Policy, (See the NIH Grants Policy Statement Section 8.1.2 Prior Approval Requirements) must be obtained in writing from the Grants Management contact shown on this Notice of Award. A letter of request signed by the Principal Investigator and a Business Official of the Grantee Institution should include an explanation and justification for the action(s). Requests may be made via e-mail provided they are routed through these same officials. If there are questions as to whether an action requires prior approval, contact the Grants Management Specialist.

The grantee is required to establish a positive time and effort reporting system.

Data Management and Sharing Policy: Applicable

This project is expected to generate scientific data. Therefore, the Final NIH Policy for Data Management and Sharing applies. The approved Data Management and Sharing (DMS) Plan is hereby incorporated as a term and condition of award, and the recipient shall manage and disseminate scientific data in accordance with the approved plan. Any significant changes to the DMS Plan (e.g., new scientific direction, a different

data repository, or a timeline revision) require NIH prior approval. Failure to comply with the approved DMS plan may result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action. See NIH Grants Policy Statement [Section 8.2.3](#) for more information on data management and sharing expectations.

Budget	Year 1
DMS Costs	\$0

SPREADSHEET SUMMARY

AWARD NUMBER: 1R44DK141341-01 REVISED

INSTITUTION: SYNTIS BIO INC

Budget	Year 1
Salaries and Wages	Itemized Cost
Fringe Benefits	
Personnel Costs (Subtotal)	
Consultant Services	
Materials & Supplies	
Other	
FEE	
TOTAL FEDERAL DC	
TOTAL FEDERAL F&A	
TOTAL COST	\$322,787

Facilities and Administrative Costs	Year 1
F&A Cost Rate 1	Itemized Cost
F&A Cost Base 1	
F&A Costs 1	



PI: Yu, Anthony		Title: Development of an Oral Pill to Mimic the Effects of Gastric Bypass Surgery																		
Received: 01/03/2024		Opportunity: PA-23-230	Council: 05/2024																	
Competition ID: FORMS-H		FOA Title: PHS 2023-2 Omnibus Solicitation of the NIH, CDC and FDA for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44] Clinical Trial Not Allowed)																		
1R44DK141341-01		Dual:	Accession Number: 4934968																	
IPF: 10072794		Organization: SYNTIS BIO INC																		
Former Number:		Department:																		
IRG/SRG: ZRG1 EMS-S (10)B		AIDS: N	Expedited: N																	
<u>Subtotal Direct Costs</u> (excludes consortium F&A) Year 1: Year 2: Year 3:		Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N Special Topics: Data Management Sharing	New Investigator: Early Stage Investigator:																	
<table border="1"> <thead> <tr> <th>Senior/Key Personnel:</th> <th>Organization:</th> <th>Role Category:</th> </tr> </thead> <tbody> <tr> <td>Anthony Yu</td> <td>SYNTIS BIO INC</td> <td>PD/PI</td> </tr> <tr> <td rowspan="5">Redacted by agreement</td> <td></td> <td>Co-Investigator</td> </tr> <tr> <td></td> <td>Consultant</td> </tr> <tr> <td></td> <td>Consultant</td> </tr> <tr> <td></td> <td>Other (Specify)-Scientific Advisor</td> </tr> <tr> <td></td> <td>Other (Specify)-Scientific Advisor</td> </tr> </tbody> </table>				Senior/Key Personnel:	Organization:	Role Category:	Anthony Yu	SYNTIS BIO INC	PD/PI	Redacted by agreement		Co-Investigator		Consultant		Consultant		Other (Specify)-Scientific Advisor		Other (Specify)-Scientific Advisor
Senior/Key Personnel:	Organization:	Role Category:																		
Anthony Yu	SYNTIS BIO INC	PD/PI																		
Redacted by agreement		Co-Investigator																		
		Consultant																		
		Consultant																		
		Other (Specify)-Scientific Advisor																		
		Other (Specify)-Scientific Advisor																		

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE		State Application Identifier	
1. TYPE OF SUBMISSION*		4.a. Federal Identifier DK138550	
☐ Pre-application ☒ Application ☐ Changed/Corrected Application		b. Agency Routing Number	
2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number	
5. APPLICANT INFORMATION		UEI*: NG1VDVGBHC87	
Legal Name*: SYNTIS BIO INC			
Department:			
Division:			
Street1*: 69 RICHMOND ST			
Street2:			
City*: DORCHESTER			
County*: MA			
State*: MA: Massachusetts			
Province:			
Country*: USA: UNITED STATES			
ZIP / Postal Code*: 021240000			
Person to be contacted on matters involving this application			
Prefix:	First Name*: Matt	Middle Name:	Last Name*: Lanchantin Suffix:
Position/Title:	Director, Corporate Development		
Street1*:	50 Adams Street		
Street2:	Suite 870073		
City*:	Milton		
County:			
State*:	MA: Massachusetts		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	021870000		
Phone Number*: 5085613080	Fax Number:	Email: matt@Syntis.bio	
6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*		88-0608856	
7. TYPE OF APPLICANT*		R: Small Business	
Other (Specify):			
Small Business Organization Type		☐ Women Owned ☐ Socially and Economically Disadvantaged	
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es).	
☒ New ☐ Resubmission		☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration	
☐ Renewal ☐ Continuation ☐ Revision		☐ D. Decrease Duration ☐ E. Other (specify):	
Is this application being submitted to other agencies?*		☐ Yes ☒ No What other Agencies?	
9. NAME OF FEDERAL AGENCY*		10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER	
National Institutes of Health		TITLE:	
11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*			
Development of an Oral Pill to Mimic the Effects of Gastric Bypass Surgery			
12. PROPOSED PROJECT		13. CONGRESSIONAL DISTRICTS OF APPLICANT	
Start Date*	Ending Date*	MA-008	
05/01/2024	04/30/2027		

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Anthony Middle Name: Last Name*: Yu Suffix:
Position/Title: Associate Director, R&D
Organization Name*: SYNTIS BIO INC
Department:
Division:
Street1*: 50 Adams Street
Street2: Suite 870073
City*: Milton
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 021870000
Phone Number*: 4157341428 Fax Number: Email*: anthony@syntis.bio

15. ESTIMATED PROJECT FUNDING

- a. Total Federal Funds Requested*
b. Total Non-Federal Funds*
c. Total Federal & Non-Federal Funds*
d. Estimated Program Income*

Itemized Cost

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

- a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:
b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR
☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ I agree*

* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION

File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Matt Middle Name: Last Name*: Lanchantin Suffix:
Position/Title*: Director, Corporate Development
Organization Name*: Syntis
Department:
Division:
Street1*: 50 Adams Street
Street2: Suite 870073
City*: Milton
County: MA
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 021870000
Phone Number*: 15085613080 Fax Number: Email*: matt@syntis.bio

Signature of Authorized Representative*

Matthew Lanchantin

Date Signed*

01/03/2024

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name:

424 R&R and PHS-398 Specific

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Project/Performance Site Location(s)**Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Syntis Bio
UEI: NG1VDVGBHC87
Street1*: 135 Morrissey Blvd
Street2: Unit E301
City*: Dorchester
County: Massachusetts
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02125-3393
Project/Performance Site Congressional District*: MA-008

Additional Location(s)

File Name:



RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ☐ Yes ☒ No	
1.a. If YES to Human Subjects	
Is the Project Exempt from Federal regulations? ☐ Yes ☐ No	
If YES, check appropriate exemption number: 1 2 3 4 5 6 7 8	
If NO, is the IRB review Pending? ☐ Yes ☐ No	
IRB Approval Date:	
Human Subject Assurance Number	
2. Are Vertebrate Animals Used?* ☒ Yes ☐ No	
2.a. If YES to Vertebrate Animals	
Is the IACUC review Pending? ☒ Yes ☐ No	
IACUC Approval Date:	
Animal Welfare Assurance Number none	
3. Is proprietary/privileged information included in the application?* ☒ Yes ☐ No	
4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ☐ Yes ☒ No	
4.b. If yes, please explain:	
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No	
4.d. If yes, please explain:	
5. Is the research performance site designated, or eligible to be designated, as a historic place?* ☐ Yes ☒ No	
5.a. If yes, please explain:	
6. Does this project involve activities outside the United States or partnership with international collaborators?* ☐ Yes ☒ No	
6.a. If yes, identify countries:	
6.b. Optional Explanation:	
7. Project Summary/Abstract*	Filename GB01a_-_Abstract_vf_[Uploaded_08.17].pdf
8. Project Narrative*	GB01b_-_Narrative_vf_[Uploaded_08.17].pdf
9. Bibliography & References Cited	GB09_-_Bibliography_[UPLOAD_01.02].pdf
10. Facilities & Other Resources	GB07a_-_Syntis_Facilities_Vf_12.11.pdf
11. Equipment	GB07b_-_Equipment_vf_[Uploaded_08.17].pdf

PROJECT SUMMARY

Obesity is a complex disease that disrupts hormonal and metabolic pathways, increasing the risk of chronic co-morbidities like diabetes, cardiovascular disease, and cancer. Obesity itself afflicts more than 1 billion globally and, when combined with its associated risk factors, contributes to over \$480 billion in direct annual healthcare spending. Roux en Y Gastric bypass surgery (RYGB) leverages duodenal nutrient exclusion (DNE) to achieve best-in-class weight loss results; however, the high costs, extensive procedural risks, and limited reimbursement have greatly limited access to care. Further, pharmacotherapies and weight loss devices have failed to strike a balance between affordability and efficacy, which has both limited adoption and widened socioeconomic access disparities. As such, there is a pressing need to develop novel weight loss interventions that can achieve best-in-class results while maintaining attractive safety and cost profiles. Using technology licensed from MIT, Syntis Bio has created a gastrointestinal synthetic epithelial lining (GSEL) that is administered orally and leverages endogenous enzymes to form a robust muco-adhesive coating specific to the duodenal epithelium. When co-formulated with cross-linking nanoparticles, GSEL creates a semi-permeable barrier capable of blocking nutrient absorption (GSEL-Barrier). The goal of this proposed project is to create a once-daily oral pill that blocks nutrient absorption in the duodenum, thereby mimicking the effects of RYGB. Thus far, GSEL-Barrier has demonstrated the ability to reduce glucose absorption by 70% in pigs when challenged with an oral glucose tolerance test (OGTT). In this Fast-Track SBIR proposal, we seek to expand on this early pig work to further optimize GSEL composition for barrier formation, engineer GSEL into solid tablet formulations, and test efficacy in beagles which more closely reflect human gastric emptying times. Successful completion of these aims will yield optimized solid dosage form tablets that have been validated in large animals and are ready for first-in-human testing. Syntis will then be ready to start scaling GMP manufacturing as well as initiate GLP pre-IDE studies in preparation for first-in-human trials.



NARRATIVE

Obesity is a global disease with significant healthcare spending and co-morbidities, highlighting the need for effective, non-invasive, and affordable weight loss solutions. Roux-en-Y gastric bypass surgery (RYGB) the gold standard for weight loss, but is limited by its high cost and procedural risks. Syntis Bio has created a gastrointestinal synthetic epithelial lining (GSEL) that is orally administered and transiently blocks nutrient absorption in the small intestine, thereby safely mimicking the effects of RYGB. This project aims to further develop the GSEL as an effective, safe, and affordable therapeutic weight loss intervention.



FACILITIES

Laboratory: Syntis labs are currently located in a shared co-working Biosafety Level 2 space managed by Portal Innovations, a venture capital firm that “helps exceptional life sciences innovators build their companies where they live. We surround these entrepreneurs with the resources and community they need: Seed capital, fully equipped lab space, and expertise and introductions to other investors and partners”. Portal Innovations is located at 135 Morrissey Blvd, Unit E301, Dorchester, MA 02125. Syntis is leasing shared office and laboratory space from Portal Innovations. Syntis has access to 10 office desks, 6 lab benches, and one laboratory suite [Square] located at this facility. Within this space there are 2 ventilated fume hoods for chemical use, multiple fridges and -20 °C freezers, 1 -80 °C freezers, 4 flammables cabinets, and 2 incubators.

Office: Shared space at 135 Morrissey Blvd is roughly [Square Footage] and houses a large community/open office area, one kitchen, and three meeting/conference rooms with video and audio-conferencing equipment, as well as copy, scan and fax equipment. There is high speed dedicated ethernet throughout the office and lab. Office amenities include parking for members, access to a gym membership, and snacks and drinks within the office kitchen.

The research team at Syntis occupies 6 laboratory benches and 10 desks in the community office area.

Biohazardous Facilities: Biohazardous waste is disposed of in designated containers, boxed and sealed, and removed by Portal Innovations on a bi-weekly basis or as needed. Portal Innovations sources the proper pickup, treatment, and disposal of biohazards. Per OSHA requirements, Portal Innovations stores all tracking and treatment waste records on-site in a designated binder. The relevant parts of the facilities have been certified by the city of Boston and every precaution is taken to ensure the safety of members and their work.

Other Resources: The rent includes utilities, cleaning and maintenance services and other general support to meet security and regulatory requirements. Portal Innovations maintains the permits for all laboratory operations, provides mandatory Environmental, Health and Safety training and compliance for all laboratory personnel, maintains all equipment and provides technical support.

These facilities comply with applicable local, state, and federal laws and the work will be performed under all required safety conditions.



EQUIPMENT

Syntis Laboratory Equipment

Syntis leverages in-house lab equipment for a majority of its benchtop development work (Table 1). In addition to those items listed in Table 1, Syntis also has access to an autoclave, ice machines, deionized water, vacuum and gas supply on-site. Syntis also currently has access to certain lab resources (e.g. scanning electron microscope, thermogravimetric analysis, x-ray powder diffraction, etc.) at MIT's Nanotechnology Materials Lab in the Koch Institute for Integrative Cancer Research, which will support polydopamine particle synthesis and characterization. Syntis also has access to a shared printer/fax/scanner, multiple laboratory laptops, and secure cloud-based storage space through Microsoft Office Suite.

All in vivo work described in the proposed workplan will be conducted through the [Redacted by agreement] at Tufts University located at [Redacted by agreement] Through a contract research agreement, Syntis has full access to research to facilities and equipment at Tufts, including 8 live pigs and 12 beagle dogs for in vivo development work.

Table 1. Syntis Laboratory Equipment			
Item	Make/Model	Quantity	Location
Dynamic light scatterer	DynaPro® Plate Reader III (Wyatt Technology, Santa Barbara CA)	1	[Redacted by agreement]
Plate reader	BioTek Synergy H1 (Agilent Technologies, Santa Clara CA)	1	
Franz cell heater stages	V9-CB (PermeGear, Hellertown PA)	6	
Oven	Digital Incubator (Southern Labware Inc., Cumming GA)	2	
Chemical hoods	Fume hood (Erlab, Rowly MA)	2	
-20 C freezer	FisherBrand Isotemp GT05LFEEF8A (Thermo Fisher, Waltham, MA)	1	
2-8 C fridge	TSV Value Lab Refrigerator (Thermo Fisher, Waltham, MA)	1	
-80 C freezer	NuAire Glacier -86C Ultra-low Temperature Freezer (Plymouth, MN)	2	
Lyophilizer	VirTis Benchtop Pro (SP Scientific, Warminster PA)	2	
Ultracentrifuge	Sorvall LYNX 6000 (Fisher Scientific, Waltham MA)	1	
pH meter	pH Meter (Fisher Scientific, Waltham MA)	1	
Ultrasonicator bath	CPX3800 (Fisher Scientific, Waltham MA)	1	
Probe sonicator	1800W U.S. Solid Ultrasonic processor (Cleveland, OH)	1	
Optical microscope	AmScope T720 (Microscope Central, Feasterville, PA)	1	
Analytical balances	Mettler Toledo ME104T (Thermo Fisher, Waltham, MA) Mettler Toledo XSE105 (Thermo Fisher, Waltham, MA) Mettler Toledo ML3002T (Thermo Fisher, Waltham, MA)	3	
Deionized water system	RiOs-DI Clinical Water Purification System (Millipore Sigma, Munich Germany)	1	
Plate washer	Biotek ELx405 Select (Agilent Technologies, Santa Clara CA)	1	
High Speed Centrifuge	Sorvall ST-16R (Fisher Scientific, Waltham MA)	1	
Microcentrifuge	Sorvall Micro17R (Fisher Scientific, Waltham MA)	1	
Benchtop Mill	IKA A 10 (IKA, Wilmington NC)	1	

No additional equipment is needed onsite for the project.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator			
Prefix:	First Name*: Anthony	Middle Name	Last Name*: Yu
Position/Title*:	Associate Director, R&D		
Organization Name*:	SYNTIS BIO INC		
Department:			
Division:			
Street1*:	50 Adams Street		
Street2:	Suite 870073		
City*:	Milton		
County:			
State*:	MA: Massachusetts		
Province:			
Country*:	USA: UNITED STATES		
Zip / Postal Code*:	021870000		
Phone Number*: 4157341428	Fax Number:		
E-Mail*: anthony@syntis.bio			
Credential, e.g., agency login	eRA Commons User Name		
Project Role*: PD/PI	Other Project Role Category:		
Degree Type:	Degree Year:		
Attach Biographical Sketch*:	File Name:	GB04a_-_Biosketch_A._Yu_(PI)_vf_[Uploaded_08.17].pdf	
Attach Current & Pending Support:	File Name:		



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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Yu, Anthony

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Director, R&D

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
New York University, New York, NY, USA	BS	06/2015	Chemistry
Stanford University, Stanford, CA, USA	PhD	06/2020	Materials Science & Engineering
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA	Post-doctoral	09/2021	Biomedical Engineering

1. Personal Statement

I am a biomedical engineer with the appropriate research and development experience to lead and carry out the proposed work. I received my BS in Chemistry from New York University and my PhD from Professor Eric Appel's laboratory at Stanford University. In my PhD work, I developed injectable and sprayable biomaterials for targeted and sustained drug delivery. During this time, I gained experience spanning disciplines, including materials science, chemical and biomedical engineering, rheology, and environmental science. Consequently, in addition to my biomaterials work, I also leveraged this expertise to invent and develop a novel materials platform for prevention of wildfires that is currently commercialized and in use. Following my PhD, I completed my post-doctoral training at the Brigham and Women's Hospital working with Professor Jeffrey Karp and then joined Moderna's formulation sciences team where I focused on developing novel lipid nanoparticle technologies for targeted macromolecule delivery and gene editing. I am passionate about using materials engineering to create products that positively impact society.

With my extensive experience working both at the bench and in biotech, I have the expertise and leadership skills necessary to successfully lead the proposed work as PI on this application. Along with the rest of the team at Syntis, we are highly motivated to help make a difference in the lives of patients.

1. **Yu, A.C.**, Lin, H., Kong, X., Lopez, H., Appel, E.A. (2021). Physical networks from entropy-driven non-covalent interactions. *Nature Communications*, 12, 746. DOI: 10.1038/s41467-021-21024-7
2. Kasse, C.M., **Yu, A.C.**, Powell, A.E., Roth, G.A., Liong, C.S., Jons, C.K., Buahin, A., Maikawa, C.L., Zhou, X., Youssef, S., Glanville, J.E., Appel, E.A. (2023). Subcutaneous delivery of an antibody against SARS-CoV-2 from a supramolecular hydrogel depot. *Biomaterials Science*, DOI: 10.1039/D2BM00819J
3. **Yu, A.C.**, Lopez, H., Kim, A.H., Stapleton, L.M., Brand, R.J., Mellor, E.T., Bauer, C.P., McCurdy, G.D., Wolff, A.J., Chan, D., Criddle, C.S., Acosta, J.D., Appel, E.A. (2019) Wildfire prevention through prophylactic treatment of high-risk landscapes using viscoelastic retardant fluids. *Proceedings of the National Academy of Sciences*, 116, 42. DOI: 10.1073/pnas.1907855116
4. **Yu, A.C.**, Chen, H., Chan, D., Agmon, G., Stapleton, L.M., Sevit, A.M., Tibbitt, M.W., Acosta, J.D., Zhang, T., Franzia, P.W., Langer, R., Appel, E.A. (2016) Scalable manufacturing of biomimetic moldable hydrogels for industrial applications. *Proceedings of the National Academy of Sciences*, 113, 50. DOI: 10.1073/pnas.1618156113

B. Positions and Honors

Positions

2022-present Associate Director, R&D, Syntis Bio Inc. Boston, MA
 2021-2022 Formulation Scientist, Moderna Inc. Cambridge, MA
 2020-2021 Post-doctoral Fellow, Professor Jeffrey Karp's Laboratory, Brigham and Women's Hospital
 2015-2020 Ph.D. Candidate, Professor Eric Appel's Laboratory, Stanford University
 2012-2015 Research Assistant, Professor Michael Ward's Laboratory, New York University

Honors

2019-2020 Accel Innovation Scholar
 2017-2020 Eastman Kodak Research Fellow

C. Contributions to Science

1. A significant part of my PhD work focused on developing design criteria for injectable and sprayable polymer-nanoparticle biomaterials for drug delivery. These materials allow for minimally invasive administration, while maintaining materials properties required for functional properties like elastic film formation, sustained drug delivery, and tissue-compatible stiffness. In this work, I elucidated several fundamental insights into design criteria that may help guide future development of these novel materials.
 - a. **Yu, A.C.**, Lin, H., Kong, X., Lopez, H., Appel, E.A. (2021). Physical networks from entropy-driven non-covalent interactions. Nature Communications, 12, 746. DOI: 10.1038/s41467-021-21024-7
 - b. **Yu, A.C.**, Smith, A.A.A., Appel, E.A. (2020) Structural considerations of physical hydrogels based on polymer-nanoparticle interactions. Molecular Systems Design and Engineering, 5, 1. DOI: 10.1039/C9ME00120D
2. Another focus of my PhD work was to use the fundamental insights I elucidated to engineer highly translatable materials for controlled drug delivery. The two challenges I sought to address were (1) patient adherence to injections or infusions of macromolecule drugs and (2) prophylactic treatment of wildlands for the prevention of wildfire ignition. In both challenges, developing a highly processable, viscoelastic hydrogel enabled dynamic administration (injection or spraying), while providing a molecular network to sustain release of antibody or retardant. The macromolecule work led to a demonstration of passive immunization against SARS-CoV-2 by sustaining delivery of antibodies within a hydrogel. The fire-retardant technology was ultimately licensed to a company and the technology is currently being used by Perimeter Solutions, the global leader in wildfire prevention.
 - a. Kasse, C.M., **Yu, A.C.**, Powell, A.E., Roth, G.A., Liong, C.S., Jons, C.K., Buahin, A., Maikawa, C.L., Zhou, X., Youssef, S., Glanville, J.E., Appel, E.A. (2023). Subcutaneous delivery of an antibody against SARS-CoV-2 from a supramolecular hydrogel depot. Biomaterials Science, DOI: 10.1039/D2BM00819J
 - b. **Yu, A.C.**, Reinhart, M., Lu, K., Maikawa, C.L., Rajakaruna, N., Acosta, J.D., Stubler, C., Appel, E.A. (2021). Seasonal impact of phosphate-based retardants on soil chemistry following prophylactic treatment of vegetation. Environmental Science and Technology, 55, 4. DOI: 10.1021/acs.est.0c05472
 - c. **Yu, A.C.**, Lopez, H., Kim, A.H., Stapleton, L.M., Brand, R.J., Mellor, E.T., Bauer, C.P., McCurdy, G.D., Wolff, A.J., Chan, D., Criddle, C.S., Acosta, J.D., Appel, E.A. (2019) Wildfire prevention through prophylactic treatment of high-risk landscapes using viscoelastic retardant fluids. Proceedings of the National Academy of Sciences, 116, 42. DOI: 10.1073/pnas.1907855116
 - d. **Yu, A.C.**, Chen, H., Chan, D., Agmon, G., Stapleton, L.M., Sevit, A.M., Tibbitt, M.W., Acosta, J.D., Zhang, T., Franzia, P.W., Langer, R., Appel, E.A. (2016) Scalable manufacturing of biomimetic moldable hydrogels for industrial applications. Proceedings of the National Academy of Sciences, 113, 50. DOI: 10.1073/pnas.1618156113
3. Following my doctoral work, I worked on engineering lipid nanoparticles that could cross the blood brain barrier to deliver siRNA. Delivery across the blood brain barrier has long been a difficult challenge for all types of drug-nanocarriers. My contribution was to optimize an existing technology to achieve in vivo demonstration of siRNA across the blood brain barrier in a rodent model. Furthermore, I evaluated

additional coating chemistries and their ability to stably encapsulate siRNA and pass the blood brain barrier.

At Moderna, I worked on engineering lipid nanoparticles (LNPs) for tissue targeted delivery of mRNA. Currently, most injected LNP technologies transit directly to the liver or spleen due to biological affinity to the LNPs, cardiac output, protein corona, and additional biological attributes. Creating LNPs that could target specific tissues would greatly broaden the diseases that LNPs could address. My contribution was to develop new LNP formulations that could increase circulation time by avoiding liver or spleen uptake. These formulations would then enable a tissue-targeting strategy by adding ligands onto the LNP that targeted specific tissue. My contributions led to multiple animal studies evaluating new LNP formulations and their ability to increase circulation time and targeted delivery to desired tissues.

NOTE: Dr. Yu's scientific publications during this time were limited due to his employer's policies.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/anthony.yu.2/bibliography/public/>



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Withheld pursuant to exemption

Redacted by agreement ; Biographical Sketch
of the Freedom of Information and Privacy Act



RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: NG1VDVGBHC87
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: SYNTIS BIO INC

Start Date*: 05-01-2024 End Date*: 04-30-2025 Budget Period: 1

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Dr.	Anthony	Yu		PD/PI		EFFORT			Itemized Cost		
2.	Redacted by agreement					Research Consultant						
3.						Research Consultant						
4.						Regulatory Consultant						
5.						Development Strategy						
6.						In Vivo Consultant						

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Total Senior/Key Person Itemized Cost

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
# OF EMPLOYEES	Secretarial/Clerical						
	Scientist	EFFORT				Itemized Cost	
	Research Associate						
Total Number Other Personnel							Itemized Cost
Total Other Personnel							
Total Salary, Wages and Fringe Benefits (A+B)							

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2024

End Date*: 04-30-2025

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment** 0.00**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost 0.00**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs** 0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2024

End Date*: 04-30-2025

Budget Period: 1

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Glucose assay kits	
9. Glucometers and strips	
10. Ex vivo porcine tissue	
11. Chemicals	
12. In vivo pig work	
13. Data Management and Sharing Costs	
14. Histology materials and services	
15. Bioanalytical services	
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type			
1. Rent, utilities, and general and administrative expenses	Itemized Cost		Itemized Cost
Total Indirect Costs			
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee	Funds Requested (\$)*
	Itemized Cost

K. Total Costs and Fee	Funds Requested (\$)*
	Itemized Cost

L. Budget Justification*
File Name: GB06a_- _Budget_Justification_[01.02].pdf

RESEARCH & RELATED Budget (F-K) (Funds Requested)

Obtained via FOIA by White Coat Waste Project (WCW)

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RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: NG1VDVGBHC87
Budget Type*: ☒ Project ☐ Subaward/Consortium
Enter name of Organization: SYNTIS BIO INC

Start Date*: 05-01-2025 End Date*: 04-30-2026 Budget Period: 2

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Dr.	Anthony	Yu		PD/PI		EFFORT					Itemized Cost
2.	Redacted by agreement				Research Consultant							
3.					Research Consultant							
4.					Regulatory Consultant							
5.					Development Strategy							
6.					In Vivo Consultant							

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Total Senior/Key Person Itemized Cost

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
# OF EMPLOYEES	Scientist	EFFORT			Itemized Cost		Itemized Cost
	Research Associate						
Total Number Other Personnel					Total Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)							

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2025

End Date*: 04-30-2026

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment** 0.00**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

Itemized Cost

E. Participant/Trainee Support Costs**Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2025

End Date*: 04-30-2026

Budget Period: 2

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Glucose assay kits	
9. Glucometers and strips	
10. Ex vivo porcine tissue	
11. Chemicals	
12. Tablet engineering	
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type			
1. Rent, utilities, and general and administrative expenses	Itemized Cost		Itemized Cost
Total Indirect Costs			
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee	Funds Requested (\$)*
	Itemized Cost

K. Total Costs and Fee	Funds Requested (\$)*
	Itemized Cost

L. Budget Justification*
File Name: GB06a_- _Budget_Justification_[01.02].pdf

RESEARCH & RELATED Budget (F-K) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Enter name of Organization: SYNTIS BIO INC

Start Date*: 05-01-2026 End Date*: 04-30-2027 Budget Period: 3

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary (\$)	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits (\$)*	Funds Requested (\$)*
1.	Dr.	Anthony	Yu		PD/PI							
2.	Redacted by agreement					Research Consultant						
3.						Research Consultant						
4.						Regulatory Consultant						
5.						Development Strategy						
6.						In Vivo Consultant						

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

Itemized Cost

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
	Scientist						
	Research Associate						
Total Number Other Personnel					Total Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)							

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2026

End Date*: 04-30-2027

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment** 0.00**Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

Itemized Cost

E. Participant/Trainee Support Costs**Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

0.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: NG1VDVGBHC87

Budget Type*: ☒ Project ☐ Subaward/Consortium

Organization: SYNTIS BIO INC

Start Date*: 05-01-2026

End Date*: 04-30-2027

Budget Period: 3

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	Itemized Cost
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Glucose assay kits	
9. Glucometers and strips	
10. Chemicals	
11. In vivo work	
12. Bioanalytical services	
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	Itemized Cost

H. Indirect Costs	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
Indirect Cost Type	Itemized Cost		Itemized Cost
1. Rent, utilities, and general and administrative expenses			
Total Indirect Costs			
Cognizant Federal Agency			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	Itemized Cost

J. Fee	Funds Requested (\$)*
	Itemized Cost

K. Total Costs and Fee	Funds Requested (\$)*
	Itemized Cost

L. Budget Justification*
File Name: GB06a_- _Budget_Justification_[01.02].pdf

RESEARCH & RELATED Budget (F-K) (Funds Requested)

Budget Justification

Key Personnel

Dr. Anthony C. Yu (Associate Director of R&D): Dr. Yu will serve as the Principal Investigator. Dr. Yu will oversee the work being performed within the lab, coordinate in vivo work, provide technical oversight to the CROs, and supervise the team in duties as described in the proposal. Dr. Yu has extensive technical experience in overseeing projects in formulation development, polymer film engineering, and large animal work. Dr. Yu is therefore well-qualified to manage and contribute significantly to this project. The budget includes payment for the following level of effort for Dr. Yu:

Funding period	Calendar months
Phase I	EFFORT
Phase II Y1	
Phase II Y2	

Redacted by agreement

Personnel

Redacted by agreement

Travel

Travel funds for Phase I will not be paid by funds requested in this grant application.

For Phase II, travel expenses to and from the animal facility in North Grafton, MA are requested. Travel will be round trips from the Boston, MA offices to North Grafton, MA. Travel will occur 2-3 times per month over the 19 months of animal work (7 in Phase I; 12 in Phase II). Each round trip will be 2-2.5 hours long by car. Additionally, travel funds are also requested for one scientist traveling to 1 conference (e.g. Society for Biomaterials) to present the data.

Funding period	Funds requested
Phase I	Itemized Cost
Phase II Y1	
Phase II Y2	

Equipment

No equipment with a value greater than \$5000 is needed to complete this project.

Materials and Supplies

The tables below break down the purchases.

Phase I:

ITEM	COST	VENDOR
Lab Supplies	Itemized Cost	Various
Chemicals		Various
Glucose assay kits		Sigma Aldrich
Glucometers and strips		Various
Ex vivo tissue		
TOTAL		

Phase II Y1:

ITEM	COST	VENDOR
Lab Supplies	Itemized Cost	Various
Ex vivo porcine tissue		Animal Biotech Industries
Chemicals		Various
Glucose assay kits		Sigma Aldrich
Glucometers strips		Various
TOTAL		

Phase II Y2:

ITEM	COST	VENDOR
Lab Supplies	Itemized Cost	Various
Chemicals		Various
Glucose assay kits		Sigma Aldrich
Glucometers strips		Various
TOTAL		

Lab supplies: Sample bottles, sample vials, pipette tips, well plates, microcentrifuge tubes, Franz cells, capsules, scalpels, ultracentrifuge vials, serum separation tubes, endoscope tubing, gloves.

Chemicals: Dopamine hydrochloride, hydrogen peroxide, phosphate buffered saline, tris salts, glucose solution, ethanol, ammonium hydroxide, FaSSIF, FaSSGF, various excipients.

In vivo animal studies Redacted by agreement

Redacted by agreement

provides a wide variety of services accredited by the American Animal Hospital Association and actively collaborates with pharmaceutical, medical device, and biotechnology companies with animal model development and pre-clinical testing. They have several veterinary experts that manage the facility and help with animal housing, large animal models, and imaging. Syntis utilizes this vendor for vivarium services. The budget will support a fee-for-service contract for purchasing animals, housing, vivarium facilities, and technical services (e.g. anesthesia, venipuncture, etc.). Likewise, the attached quote accounts for 4 pigs or 4 dogs, so the values estimated in the quote are scaled to account for the 8 pigs and 8 dogs proposed in the grant. The requested funds are as follows:

Funding period	Funds requested
Phase I	Itemized Cost
Phase II Y1	
Phase II Y2	

Tablet engineering (Crystal Pharmatech): will be spent on prototype tablet formulation development, tablet lead selection, probe batch manufacturing, and formulation development reports in Phase II as a fee-for- service-model. This value is lower than the quote because we would only run stability tests for the probe batch over 1 year instead of 3 years. This expense will yield lead tablet formulations that will stably incorporate all GSEL components that we will validate in our ex vivo and benchtop assays. The tablet manufacturing and engineering equipment in addition to the tablet formulation expertise provided by Crystal Pharmatech will significantly advance this program.

Histology services (The David H. Koch Institute for Integrative Cancer Research): The budget will support a fee-for-service contract for histology sample processing, staining, and imaging. These samples will be used in Phase II Specific Aim 1 to assess tolerability of lead formulations in in vivo pig terminal studies. An estimated 24 pig samples samples will be required for analyses in Phase I total).

Bioanalytics The budget will support a fee-for-service contract for HPLC and LC- MS sample analysis. These analysis tools will support quantifying serum levels of GLP-1, GIP, ghrelin, insulin, and PYY in Phase I Specific Aim 2 and Phase II Specific Aim 2 has two analytical laboratories fully equipped to measure any biological and chemical compound. They routinely analyze ~40,000 samples weekly and have over 40 Agilent 1260/1290 Infinity II HPLC/UHPLCs available. They are well equipped to handle our HPLC and LC-MS needs. An estimated 320 samples will be required for assessing metabolic homeostasis. The requested funds are as follows:

Funding period	Funds requested
Phase I	Itemized Cost
Phase II Y1	
Phase II Y2	

Consultant Services

Indirect Cost

The provisional indirect cost rates are:

Funding period	Indirect rate
Phase I	Itemized Cost
Phase II Y1	
Phase II Y2	

Fee

Company is requesting a fee of



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Consultant Info ; Redacted by agreement
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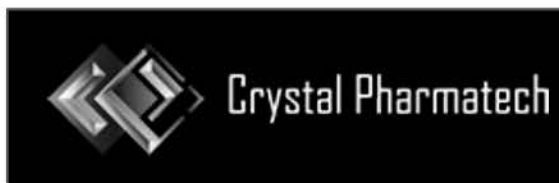
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QUOTATION

March 1, 2023

ATTN: Anthony Yu, PhD

RE: Formulation of proprietary composition

Service Type	Activity	Price (\$)	API need	Timing	Comments
Prototype tablet formulation development and lead formulation selection	Analytical method development for prototype formulation study	Itemized Cost	n/a	Proprietary Info	Assay/deq, XRPD, BR and biorelevant and QC dissolution, water content
	SDI-Excipients compatibility				Stability for 4 weeks
	Prototype formulation development	Itemized Cost			Stability for 4 weeks or longer to make the decision on the top prototype formulations for animal study
	Animal study	Actual charge + sample shipping and handling fee Itemized for ambient condition and itemize for controlled temperature)	n/a		Recommend conducting animal PK study with top prototype formulations
	Lead tablet formulation selection	N/A	N/A	N/A	Based on the results from animal study and in-vitro dissolution results.
Probe batch manufacturing for the lead formulation	Tablet manufacturing and testing at time 0	Itemized Cost		Proprietary Info	2 strengths with the lead formulation
	Stability test for probe batch for 3 years		n/a	n/a	The client will be charged for the actual stability study performed (# of time points)
Formulation development report	Include all information listed above		n/a	Proprietary Info	
Total					

TUFTS UNIVERSITY RESEARCH SERVICE AGREEMENT

This Agreement is entered into as of October 5, 2022 by and between Syntis Bio, Inc. (“Company” and “Sponsor”), having its principal place of business at 50 Adams St, Suite 870073, Milton, MA 02187 and Trustees of Tufts College, a/k/a Tufts University (“Tufts”), a Massachusetts not-for profit corporation with a principal place of business at 136 Harrison Avenue, Boston, MA 02111.

WHEREAS, the Company and Tufts University wish to collaborate on Syntis Pig and Dog (“Project”), as fully described in Appendix A hereto, which Project is of mutual interest and benefit to the Company and Tufts, will further the instructional and research objectives of Tufts in a manner consistent with its status as a non-profit, tax-exempt, educational institution.

Proprietary Info

Proprietary Info

Proprietary Info

Proprietary Info



Proprietary Info



Proprietary Info



Proprietary Info

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WASTE
PROJECT



Proprietary Info

17. Entire Agreement and Amendment. This Agreement constitutes the entire agreement between the parties with respect to its subject matter and supersedes all prior oral and written agreements or understandings between the parties relating to this subject matter. This Agreement can only be amended by a written instrument signed by both Parties.

IN WITNESS WHEREOF, the hands and seals of the parties are affixed hereto:

TRUSTEES OF TUFTS COLLEGE

By: Redacted by agreement
Signature
Redacted by agreement
Typed Name
Associate Director, Pre-Award
Title
Oct 5, 2022
Date

COMPANY

By: Redacted by agreement
Signature
Redacted by agreement CFO & Treasurer
Typed Name
Title
October 5, 2022
Date

Appendix A Statement of Work

Study Design: Pig Studies

- Objectives – confirm repeatability of previous studies
- N=4 Yorkshire pigs (either sex) used for survival studies in series, time frame before euthanasia ~6 months
- Dose under anesthesia/endoscopic guidance to the stomach or SI every 2 weeks for the duration of the period above
- (12 compounds or iterations/animal) – liquid/capsule/tablet formulations
- Read out – blood collection for 1-2 days (for drug carrying formulations) or OGTT (barrier formulations)

For each animal:

- Anesthetic periods – 36 (12 for endoscopic delivery/24 sedations for blood collection for PK)
- Endoscopic use – 12 (for delivery of formulations for the stomach/SI)
- Blood collection – 24 (2/animal/study every 2 weeks for 6 months)
- OGTT – 12 (dosed orally x mins after GSEL and blood collected while under anesthesia ~2 hours)
- Housing – 6 months, no special requirements, no hazards used

Study Design: Dog Studies

- Objectives – utilize a model more mimicking human conditions (oral delivery without sedation and gastric forces more similar to humans)
- N=4 Beagles (either sex)
- Dogs would be used for survival studies in series over 6 months
- Optimized formulations from previous swine studies would be given orally every 2 weeks for the duration of development (~6 months)
- Read out – blood collection for 1-2 days (for drug carrying formulations)/OGTT (barrier formulations)

For each animal:

- Blood collection – 24 (2/animal/study every 2 weeks)
- OGTT – 12 (dosed orally x mins after GSEL and blood collected over 1-2 hours)
- Housing – 6 months or longer depending on needs, no special requirements, no hazards used

LAMS will be responsible for:

- Animal procurement
- Husbandry and care
- Technical assistance for stated procedures
- Euthanasia (pig studies)
- Rehoming (canine studies)

Appendix B – Fixed Price Budget and Payment Schedule

This is a Fixed Price award payable in US dollars

Animal Procurement and Per diems:

Qty:

Rate:

Subtotal:

Cost of Animal(s): (vendor rates)	4.00	@	Itemized Cost	each		Itemized Cost
LAMS Animal Order Fee: (applies to each order)	1.00	@		each		
Vendor Animal Transport Fee: (estimated - TBD)	1.00	@		each		
Per diem rate: (quarantine/acclimation)	56.00	@		each		
Per diem rate: (per animal per day)	800.00	@		each		

Facilities and Technical Services:

Qty:

Rate:

Subtotal:

LAMS Procedure room use:	12.00	@	Itemized Cost	each		Itemized Cost
LAMS Technologist Services:	12.00	@		each		
LAMS Technician Services:	12.00	@		each		
LAMS Blood Collection Services:	24.00	@		each		

Pharmaceuticals and Consumables:

Qty:

Rate:

Subtotal:

General consumables: (per timepoint)	24.00	@	Itemized Cost	each		Itemized Cost
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Additional Services

Qty:

Rate:

Subtotal:

Animal Rehoming Fee:	1.00	@	Itemized Cost	each		Itemized Cost
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Per Study Estimated Total:	Itemized Cost	Proprietary Info	
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IACUC and Project Management Fees:

Qty:

Rate:

Subtotal:

IACUC Processing fee: (per protocol)	1.00	@	Itemized Cost	each		Itemized Cost
IACUC Writing and Review Process: (LAMS DVM)	0.00	@		each		
IACUC Amendment: (per amendment)	0.00	@		each		
LAMS Technical Services Coordinator:	4.00	@		each		

Startup fees; not charged per study:	Itemized Cost	
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Animal Procurement and Per diems:

Qty:

Rate:

Subtotal:

Cost of Animal(s): (estimated - vendor rates)	4.00	@	Itemized Cost	each		Itemized Cost
LAMS Animal Order Fee: (applies to each order)	1.00	@		each		
Vendor Animal Transport Fee: (estimated - TBD)	1.00	@		each		
Per diem rate: (4 pigs x 183 days)	732.00	@		each		

Facilities and Technical Services:

Qty:

Rate:

Subtotal:

LAMS Surgical Suite - 1st 4 hours	12.00	@	Itemized Cost	each		Itemized Cost
LAMS Surgical Suite additional hours: (4 hours)	48.00	@		each		
LAMS Technologist Services: (6 hrs x 12 sessions)	72.00	@		each		
LAMS Technician Services: (2 hour x 12 sessions)	24.00	@		each		
LAMS Blood collection services: (24 sessions)	24.00	@		each		

Pharmaceuticals and Consumables:

Qty:

Rate:

Subtotal:

General consumables: (per session)	36.00	@	Itemized Cost	each		Itemized Cost
Sedation/Induction pharmaceuticals: (4 pigs x 36 sessions)	144.00	@		each		

Rev. – 08/31/2022

Euthanasia pharmaceuticals: (per animal)	4.00	@	Itemized Cost	each	Itemized Cost
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Additional Services

Qty:

Rate:

Subtotal:

Farm Services: (disposal)	2.00	@	Itemized Cost	each	Itemized Cost
LAMS Endoscope use: (per use)	12.00	@		each	
Hospital Imaging: (CT use per session)	0.00	@		each	
Hospital Pathology Incineration: (charged by weight per animal)	4.00	@		each	

Proprietary Info

IACUC and Project Management Fees:

Qty:

Rate:

Subtotal:

IACUC Processing fee: (per protocol)	1.00	@	Itemized Cost	each	Itemized Cost
LAMS Technical Services Coordinator:	4.00	@		each	

Proprietary Info

Itemized Cost

Proprietary Info

Itemized Cost

Proprietary Info

Date	Deliverable	Payment due upon receipt of deliverable and/or invoice from Tufts
Upon execution of this agreement	Invoice from Tufts	100%

Payments made to Tufts under this agreement are not returnable.

Payment Instructions: SPONSOR shall make payment within sixty (60) calendar days from receiving the applicable invoice submitted in accordance with the payment schedule below.

If sending funds via ACH (US) or wire transfer (international):

Proprietary Info



Quote

159 Discovery Drive
Storrs, CT 06269
Phone: (860) 428-6020

Quote #	DATE
Syntis Bio	3/09/2023

BILL TO

Syntis Bio

Prepared By

Personal Info

fentonwoodsconsulting.com

Description of Service or Item	QTY	Price	Amount
HPLC Standard Curve Preparation Preparation of 11-point calibration curves with ISTD in sample media for HPLC/UHPLC analysis. Includes preparation of 4 blanks (2 blanks and 2 double blanks), and this includes all analytical fees.	1	Itemized Cost	
HPLC/UHPLC Analysis HPLC/UHPLC analysis with standard report and data analysis. Includes sample preparation. Data management is non 21CFR-11 compliant. Includes sample preparation, QC standards on every plate, and storage into sealed micronic 96-well plate and 6-months storage. Samples stored for 6 months at -80.	1		
LC-QQQ Standard Curve Preparation (Agilent 6495 / Waters TQ-s mic) Preparation of 11-point calibration curves with ISTD in sample media for LC-MS/MS on an Agilent 6495B QQQ. Includes preparation of 4 blanks (2 blanks and 2 double blanks), and this includes all analytical fees.	1		
LC-QQQ Analysis (Agilent 6495 / Waters Xevo TQ-S micro) LC-MS/MS analysis with standard report and data analysis. Includes sample preparation. Data management is non 21CFR-11 compliant. Includes sample preparation, QC standards on every plate, and storage into sealed micronic 96-well plate and 6-months storage. Samples stored for 3 years at -80.	1		
LC-QQQ Standard Curve Preparation (Sciex 6500/7500) Preparation of 11-point calibration curves with ISTD in sample media for LC-MS/MS on a Sciex 6500/7500 QQQ. Includes preparation of 4 blanks (2 blanks and 2 double blanks), and this includes all analytical fees.	1		
LC-QQQ Analysis (Sciex 6500/7500) LC-MS/MS analysis with standard report and data analysis. Includes sample preparation. Data management is non 21CFR-11 compliant. Includes sample preparation, QC standards on every plate, and storage into sealed micronic 96-well plate and 6-months storage. Samples stored for 3 years at -80.	1		
Thank you for your business!		TOTAL	Itemized Cost

PROPOSAL

Proposal Date	2023-04-25
My Reference	Redacted by Syntis Bio Milton, MA, 02186

FROM:
Koch Institute at MIT
77 Massachusetts Avenue, 76-158
Cambridge, MA 02139 MIT TAX ID: 04-2103

Qty	Description	Unit Price	Total
10	Snap frozen samples for 1 unstained slide each	Itemized Cost	
10	H and E from above unstained slides		
10	20 X digitally scanned slides transferred to user provided external hard drive formatted to a PC		

Subtotal	Itemized Cost
Tax	
Total Quote	

SEND PAYMENT TO	PAYMENT INSTRUCTIONS
Koch Institute at MIT 77 Massachusetts Avenue, 76-158 Cambridge, MA 02139 Attn.: Redacted by agreement	Please make check payable to: Massachusetts Institute of Technology

NOTES

If you have any questions, please contact Redacted by agreement at Redacted by agreement@mit.edu or Redacted by agreement

RESEARCH & RELATED BUDGET - Cumulative Budget

Section A, Senior/Key Person

Section B, Other Personnel

Total Number Other Personnel

Total Salary, Wages and Fringe Benefits
(A+B)

Section C, Equipment

Section D, Travel

1. Domestic

2. Foreign

Section E, Participant/Trainee Support
Costs

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other

6. Number of Participants/Trainees

Section F, Other Direct Costs

1. Materials and Supplies

2. Publication Costs

3. Consultant Services

4. ADP/Computer Services

5. Subawards/Consortium/Contractual
Costs

6. Equipment or Facility Rental/User Fees

7. Alterations and Renovations

8. Other 1

9. Other 2

10. Other 3

11. Other 4

12. Other 5

13. Other 6

14. Other 7

15. Other 8

16. Other 9

17. Other 10

Section G, Direct Costs
(A thru F)

Section H, Indirect Costs

Totals (\$)

OF
EMPLOYE
ES

Itemized Cost

Itemized Cost

Itemized Cost

Section I, Total Direct and Indirect Costs
(G + H)

Section J, Fee

Section K, Total Costs and Fee (I + J)

Itemized Cost

WHITE COAT
WASTE
PROJECT



SBIR/STTR Information

Agency to which you are applying (select only one)* ☐ DOE ☒ HHS ☐ USDA ☐ Other:	
SBC Control ID:* Proprietary Info	
Program Type (select only one)* ☒ SBIR ☐ STTR ☐ Both (See agency-specific instructions to determine whether a particular agency allows a single submission for both SBIR and STTR)	
Application Type (select only one)* ☐ Phase I ☐ Phase II ☒ Fast-Track ☐ Direct Phase II ☐ Phase IIA ☐ Phase IIB ☐ Phase IIC ☐ Commercialization Readiness Program (See agency-specific instructions to determine application type participation.)	
Phase I Letter of Intent Number: * Agency Topic/Subtopic:	

Questions 1-8 must be completed by all SBIR and STTR Applicants:	
1a. Do you certify that at the time of award your organization will meet the eligibility criteria for a small business as defined in the funding opportunity announcement?*	☒ Yes ☐ No
1b. Anticipated Number of personnel to be employed at your organization at the time of award.*	# OF EMPLOYEES
1c. Is your small business majority owned by venture capital operating companies, hedge funds, or private equity firms?*	☒ Yes ☐ No
1d. Is your small business a Faculty or Student-Owned entity?*	☐ Yes ☒ No
2. Does this application include subcontracts with Federal laboratories or any other Federal Government agencies?*	☐ Yes ☒ No
If yes, insert the names of the Federal laboratories/agencies:*	
3. Are you located in a HUBZone? To find out if your business is in a HUBZone, use the mapping utility provided by the Small Business Administration at its web site: http://www.sba.gov *	☐ Yes ☒ No
4. Will all research and development on the project be performed in its entirety in the United States?*	☒ Yes ☐ No
If no, provide an explanation in an attached file.	Explanation:*
5. Has the applicant and/or Program Director/Principal Investigator submitted proposals for essentially equivalent work under other Federal program solicitations or received other Federal awards for essentially equivalent work?*	☐ Yes ☒ No
If yes, insert the names of the other Federal agencies:*	
6. Disclosure Permission Statement: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and email address of the official signing for the applicant organization to state-level economic development organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?*	☒ Yes ☐ No
7. Does the application include a request of SBIR or STTR funds for Technical and Business Assistance (TABAs)? If yes, please follow the agency specific instructions to provide the budget request and justification. (Please answer no if you plan to use the agency TABA vendor, which does not require you to include a request for TABA funds in your application.)*	☐ Yes ☒ No
8. Commercialization Plan: The following applications require a Commercialization Plan: Phase I (DOE only), Phase II (all agencies), Phase I/II Fast-Track (all agencies). Include a Commercialization Plan in accordance with the agency announcement and/or agency-specific instructions.* Attach File:* GB08_-_Commercialization_Plan_[UPLOAD_01.02].pdf	

SBIR/STTR Information**SBIR-Specific Questions:**

Questions 9 and 10 apply only to SBIR applications. If you are submitting ONLY an STTR application, leave questions 9 and 10 blank and proceed to question 11.

9. Have you received SBIR Phase II awards from the Federal Government? If yes, provide a company commercialization history in accordance with agency-specific instructions using this attachment.* ☐ Yes ☒ No

Attach File:*

10. Will the Project Director/Principal Investigator have his/her primary employment with the small business at the time of award?* ☒ Yes ☐ No

STTR-Specific Questions:

Questions 11 - 13 apply only to STTR applications. If you are submitting ONLY an SBIR application, leave questions 11 - 13 blank.

11. Please indicate whether the answer to BOTH of the following questions is TRUE:* ☐ Yes ☐ No

(1) Does the Project Director/Principal Investigator have a formal appointment or commitment either with the small business directly (as an employee or a contractor) OR as an employee of the Research Institution, which in turn has made a commitment to the small business through the STTR application process; AND

(2) Will the Project Director/Principal Investigator devote at least 10% effort to the proposed project?

12. In the joint research and development proposed in this project, does the small business perform at least 40% of the work and the research institution named in the application perform at least 30% of the work?* ☐ Yes ☐ No

13. Provide UEI of non-profit research partner for STTR.*

Commercialization Plan

A. Value of the SBIR/STTR Project, Expected Outcomes, and Impact

1. Project Goal and Objectives

The goal of this SBIR Fast-Track project is to develop an oral therapeutic that mimics the effects of gastric bypass surgery by blocking nutrient absorption in the small intestine. Syntis' Gastrointestinal Synthetic Epithelial Lining (GSEL) technology is a synthetic tissue platform that enterically delivers a therapeutic polymer coating to the small intestine. In preliminary work led by scientific founders [Redacted by agreement] at MIT, GSEL demonstrated the ability to block 70% of glucose absorption in pigs when administered as an oral solution¹.

In SBIR Phase I of this project, Syntis will identify lead compositions for nutrient barrier function through ex vivo testing, as well as determine the density coverage needed to ensure nutrient barrier function in pigs. By the end of Phase I, we will have demonstrated tolerability and nutrient barrier function using capsule formulations, with a target endpoint of 15-25% glucose reduction by GSEL compared to controls.

In Phase II, Syntis will engineer tablets that demonstrate optimal stability and performance ex vivo, while also optimizing functionality of these tablets in beagles, which have more human-relevant gastric emptying times than pigs. Following the success of Phase II of this project, Syntis will be ready to start scaling manufacturing through GMP processes while also completing GLP pre-IDE studies in preparation for first-in-human trials.

2. Clinical Need

The obesity epidemic is a significant public health issue linked to chronic diseases such as type 2 diabetes, heart disease, and cancer. Roux-en-Y Gastric Bypass surgery has long been heralded as the gold-standard for Obesity treatment, yielding over 30% total bodyweight loss (TBWL) in just 52 weeks¹. However, RYGP has had limited clinical utility due to the invasive nature of this expensive surgery. GLP-1 drugs, like Wegovy, have significantly advanced the field by achieving unprecedented pharmacologic efficacy (17.4% TBWL), with many next generation drugs positioned to bring that number even higher². Yet, of the 90M eligible obese adults in the US, only 5M receive these treatments monthly, a number which has plateaued since May 2023^{3,4}. This stagnated uptake is largely due lack of insurance coverage, tolerability concerns, variable efficacy, and a high discontinuation rate, with 45.2% of patients stopping treatment within 12 months⁵. Additionally, supply chain issues stemming from complex manufacturing processes have led to shortages, high costs, and counterfeit products⁶. From a mechanistic perspective, GLP-1 drugs are highly effective at inducing satiety however they fail to restore native intestinal nutrient sensing and neuroendocrine signaling, key drivers of metabolic homeostasis and sustained weight loss^{7,8}, resulting in rapid weight rebounding after treatment discontinuation⁹. To provide treatment for the 85M eligible US adults not served by GLP-1 drugs, next generation interventions must look beyond higher short term TBWL and instead focus on improving tolerability and access while restoring underlying metabolic hormonal balances to ensure long-term health benefits.

3. Technology Solution

Syntis' GSEL platform is an orally administrable pill that creates a thin polymer lining along the mucosal epithelium of the small intestine. This mucoadhesive lining is naturally cleared out of the GI tract every 18-24 hours, making it highly transient and reversible. Syntis' lead program, GSEL-Barrier (GSEL-B), is designed to restrict nutrient absorption in the duodenum thereby mimicking the effects of gastric bypass surgery without invasive surgery. A prototype of GSEL-B has demonstrated strong efficacy in pig models and is comprised of biocompatible, inexpensive materials⁴. Evidence gathered to date supports GSEL-B as a highly effective, safe, and low-cost intervention for weight-loss, positioning it as a potential revolutionary solution for obesity management.

Furthermore, the underlying GSEL technology can be engineered to solve a multitude of therapeutic objectives. Current GSEL use cases under investigation include increasing systemic absorption of co-formulated drugs, improving digestive enzyme efficiency, and even interventions targeting new tissues.

4. Commercial Impact

In 2016, the United States spent approximately \$260 billion on direct healthcare costs related to obesity⁵. Moreover, obesity as a risk factor is by far the greatest contributor to the burden of chronic diseases in the U.S., accounting for 47.1% of the total cost of chronic diseases nationwide⁶. These chronic diseases in aggregate drive \$480.7 billion in direct healthcare spending, with an additional \$1.24 trillion in indirect costs due to lost economic productivity⁷.

RYGB remains the most effective intervention (30% TBWL), however fewer than 1% of qualifying patients receive any form of surgical intervention due to high costs and perceived risks⁹. GLP-1 RA drugs, like Wegovy, have been a highly effective pharmacologic solution (17.4% TBWL), however uptake has stagnated at 6% of eligible patients due to lack of insurance coverage, tolerability concerns, variable efficacy, poor adherence, and supply chain issues^{10,11}. In total, this has left roughly 85M Obese US adults without a viable solution¹². If GSEL can modestly recapitulate the metabolic control and weight loss seen in RYGB (10-20% TBWL), while offering higher tolerability, lower costs, and easier manufacturing than GLP-1 drugs, then it will be well positioned to both address a high unmet medical need and make a multi-billion-dollar impact on annual US healthcare spending.

5. Scientific and Societal Impact

To date, GSEL-B development has demonstrated proof of principle that pre-polymer formulations can reliably and specifically target designated tissues to deliver therapeutic benefit. Now, Syntis has the foundational tools to answer more complex questions regarding the feasibility of controlling metabolic function and hormonal responses through non-invasive, mechanical means. Specifically, this project will yield new strategies for metabolic control while helping the greater scientific and medical communities understand the impact of glucose and other nutrient absorption on metabolic health. There will also be an opportunity to better understand the pathophysiology of metabolic diseases like obesity and diabetes, and how they are driven by nutrient absorption in the duodenum.

In addition to affecting physical health, obesity has also contributed to a severe decline in mental health and economic productivity in the US. Adults with excess weight have shown a 55% higher risk of developing depression over their lifetime compared to those without excess weight¹⁰. Obesity also has been associated with an increased risk of temporary work loss such as sick leave and has reduced overall productivity. Moreover, these affects are most severely felt by Black and Hispanic adults who are continually disproportionately affected by this disease.¹¹ Providing a more accessible, safer obesity intervention will help alleviate the mental and economic hardships that currently burden all racial and ethnic groups in our society.

6. Role of SBIR Funding in Business Strategy

Proprietary Info

B. Company

1. Description and Objectives

Syntis Bio was co-founded by MIT Professors [Redacted by agreement] along with veteran [Redacted by agreement]. [Redacted by agreement] Syntis was created with the purpose of developing simple, accessible solutions for the world's most prevalent diseases. The core platform technology, GSEL, is an oral pill that creates a transient synthetic tissue lining in the small intestine. GSEL can be engineered to perform different therapeutic functions such as up-regulating or down-regulating the absorption of nutrients and/or drugs. Syntis' flagship program, GSEL-B, is an oral pill that creates a barrier in the small intestine to block nutrient absorption by coating the small intestine, thereby mimicking the effects of gastric bypass surgery. Additional projects are investigating the use of GSEL to

increase oral bioavailability of drugs by extending their contact time with the epithelial mucosa in the small intestine.

2. Company Background

The original academic work to develop the underlying GSEL technology received philanthropic support from the Private Source in the form of \$6 million in grant funding to MIT. The original project aim was to design a drug delivery device that could provide more efficient, sustained delivery of anti-parasitic medications in developing countries. To this end, GSEL was designed to be co-formulated with therapeutic agents, delivered orally, and then polymerize in situ creating a mucoadhesive drug depot in the lumen of the small intestine. The drug would then slowly diffuse through the polymer coating toward the epithelium, increasing both the half-life and total absorption of the target compound. Variations of the GSEL formulation were also engineered to sustain biologic activity of enzymes in the small intestine as well as block duodenal absorption of nutrients. Results of these experiments were successful and published in *Science Translational Medicine* in 2020¹².

In 2022, Syntis was founded to further develop GSEL as a commercial therapeutic platform. While there were many potential development paths, Syntis selected GSEL-B as its flagship program given its potential for broad healthcare impact, rapid path to market, and ability to lay the foundation for future drug-device combinations. In the Fall of 2022, Syntis secured seed funding and obtained lab space in Boston's Seaport district, where it now houses primary R&D operations. In addition to its operating staff, Syntis is additionally supported by its highly engaged board of directors and scientific advisors.

3. Team and Core Competencies

Redacted by agreement

has over 20-years of experience in commercializing medical devices.

Prior to Syntis, Redacted by served as the founding president and CEO of Sherlock Bio where he successfully commercialized the first-ever CRISPR-based product, diagnostic or therapeutic, to be authorized by the FDA. Prior to Sherlock, Redacted by spent 10 years at T2 Biosystems where, as the VP of Corporate Development and Marketing, he helped grow the company from an early-stage venture-backed startup to a commercial leader in infectious disease diagnostics.

Redacted by agreement

has over 20-years of experience in the pharmaceutical industry with interests focused on novel drug development and delivery mechanisms. During her career, Redacted by has provided technical/CMC support to 30+ regulatory filings worldwide, including submission of an NDA for aripiprazole lauroxil in 2014 (approved as Aristada®). Redacted by current leads R&D at Syntis full time and will apply her rich experience in therapeutics development to oversee the GSEL-Barrier program.

Anthony Yu, PhD (PI, Associate Director of Research) – Dr. Yu is an expert in novel drug delivery methods and will serve as PI on this project. During his PhD at Stanford, Dr. Yu engineered injectable hydrogels for long-term antibody delivery for passive immunization, macular degeneration, and glaucoma. After Stanford, Yu was a postdoctoral research fellow at Brigham and Women's Hospital where he focused on novel delivery vehicles for therapeutics for CNS and lung diseases. Prior to Syntis, Dr. Yu was a Respiratory Delivery scientist at Moderna.

Consultant Info

Redacted by agreement

is an Associate Professor in the Department of Mechanical Engineering at the Massachusetts Institute of Technology (MIT) and a Gastroenterologist in the

Division of Gastroenterology, Brigham and Women's Hospital (BWH), Harvard Medical School. [Redacted by agreement] founded over 6 companies in the gastrointestinal space and is actively advising the Syntis on the development of GSEL-B in addition to other ancillary programs.

[Redacted by agreement]

[Redacted by agreement] is an institute professor at MIT who is widely regarded as a pioneer in biotechnology and materials science. He has contributed greatly to the development of drug delivery systems and tissue engineering, which have important applications in metabolic health. [Redacted by agreement] has founded over 40 companies in his career and actively advises Syntis on its R&D strategy.

Syntis has assembled a team of employees, consultants and advisors who are well positioned to successfully execute the studies described in this SBIR Fast-Track proposal and ultimately commercialize the GSEL-Barrier product. [Redacted by agreement] are world-class pioneers in both drug delivery and materials science and consistently guide the team with their deep technical know-how and company building experience. [Redacted by agreement]

[Redacted by agreement] has a track record of leading teams from early company formation to commercial success and provides the focused leadership necessary to grow Syntis into a commercial enterprise. Consultants [Redacted by agreement]

[Redacted by agreement] bring their respective expertise in both in vivo analysis and regulatory strategy, which complements the core Syntis R&D team's record of successful pharmaceutical entrepreneurship and product development.

4. Previous Federal and Non-federal Funding

Since incorporation, Syntis has been capitalized by a \$15 million seed financing which closed in Q4 2022. This Seed round was led by [Proprietary Info]

[Proprietary Info]

[Redacted by agreement] among others. Syntis is currently pursuing non-dilutive capital through the NIH to capitalize multiple applications of the GSEL technology and accelerate its path to market.

5. Long-term Vision & Growth Strategy

Syntis is committed to developing effective, yet accessible tissue-targeted therapies that treat conditions affecting hundreds of millions of patients all over the world. The first step on this journey is to develop GSEL-B into a highly effective, affordable treatment for all obesity patients, most importantly, those who suffer from socioeconomic or racial/ethnic disparities.

Beyond GSEL-B, Syntis is committed to realizing the full value of the GSEL platform by developing a pipeline of therapeutic programs that will include both novel interventions as well as safer, more effective reformulations of existing compounds. Each successive program is designed to lay the foundation for future applications and attract new revenue and new investments as Syntis grows from a small R&D company into a commercial corporate entity. Further, we look forward to leveraging our deep relationships with local universities and the greater Boston life sciences ecosystem to continually hire top talent that will support a technically and culturally strong and inclusive organization from within.

6. Partnerships

Strategic partnerships will be a critical factor for ensuring the developmental and commercial success of GSEL-B. As such, Syntis will leverage a broad range of partnerships to support GSEL-B as it is driven from a preclinical project to a widely adopted solution for patients. Below are a few examples that illustrate the types of partnerships Syntis is currently pursuing.

TABLE B.6.1 - Strategic Partnership Types

Partnership Type	Purpose	Example Companies
Preclinical Development	Optimize GSEL formulation, scale manufacturing processes	[Proprietary Info]
Clinical Development & Sales	Support clinical development and/or provide market launch expertise with direct reach to prescribing physicians (PCPs, Endocrinologists, etc.)	
Additional Commercial Distribution	Increase patient access through telehealth prescribing services and/or subscription-based delivery offerings	

[Proprietary Info]

C. Market, Customer, and Competition

1. Target Market

Proprietary Info

2. Customer Profile

Proprietary Info

3. Commercialization Hurdles

Proprietary Info

4. Competition Landscape & Advantages

Outside of lifestyle changes, current obesity interventions can be broadly categorized into four main groups: Bariatric Surgeries, Pharmacologic Drugs, Transient Devices, and Implantable Devices. While each category offers a unique approach to losing weight, none of the current interventions simultaneously solve for efficacy,

safety, and affordability (Table C.4). GSEL-B aims to fill this gap by offering best-in-class duodenal nutrient exclusion (DNE), a strong safety profile, and affordable price. In this way, GSEL-B will dramatically lower the barriers to effective weight management.

Proprietary Info

TABLE C.4 - Obesity Intervention Comparisons by Category			
	EFFECTIVE	SAFE	AFFORDABLE
GSEL-B	✓	✓	✓
Bariatric Surgery	✓	-	-
Pharmacologic Drugs	✓	✓	-
Transient Devices	-	✓	✓
Implantable Devices	Mixed	Mixed	-

Bariatric Surgeries. Bariatric surgery includes Roux-en-Y Gastric Bypass (RYGB), Sleeve Gastrectomy, and Adjustable Laparoscopic Banding. Broadly, these surgeries have proven highly effective, yet are associated with severe complications. Fatality within the first year of surgery has been reported to be around 1%, primarily due to therapeutic complications such as pulmonary embolisms, coronary heart disease, and sepsis²⁰. Further, chronic complications often include strictures, internal hernias, fistulas, ulcers and many more²¹. Despite these concerns, RYGP remains the gold-standard for weight-loss, attributed largely to duodenal nutrient exclusion (DNE) which, in addition to altering hormonal responses to induce satiety, has been associated with improved glucose metabolism²². Sleeve Gastrectomy and laparoscopic surgery restrict stomach size, which combats overeating but does not impact duodenal absorption. GSEL-B however leverages DNE and is anticipated to mirror the effects of RYGB without the risks or costs associated with invasive procedures (Table C.4.1).

TABLE C.4.1 - GSEL-B v. Bariatric Surgery							
Intervention	Description	Status	DNE?	ROA	Efficacy*	Cost**	Comparison to GSEL-B
GSEL-B	Daily oral pill that creates a polymer barrier in small intestine, blocking nutrient absorption	Preclinical	YES	Noninvasive Oral Pill (1x Daily)	Proprietary Info		Highly effective duodenal nutrient exclusion achieved safely, conveniently, and at low cost.
Gastric Bypass (RYGB)	The section of the small intestine called the duodenum is removed, reducing the calories and nutrients that the body absorbs	Marketed	YES	Surgical	31% After 52 Weeks ¹⁷	\$23,000 Per Procedure ¹⁸	Invasive & Expensive. Of the 30M qualifying patients in US, fewer than 1% proceed with surgery due perceived risks, costs, and other factors
Sleeve Gastrectomy	Removal of part of the stomach to reduce total food consumption	Marketed	NO	Surgical	25% After 52 weeks ¹⁹	\$14,900 Per Procedure ²⁰	Invasive & Expensive. Of the 30M qualifying patients in US, fewer than 1% proceed with surgery due perceived risks, costs, and other factors
Adjustable laparoscopic banding	Inflatable band placed around the stomach to restrict stomach size, reducing consumption	Marketed	NO	Laparoscopic	14% After 26 weeks ²¹	\$14,500 Per Procedure ²²	Invasive & Expensive. Of the 30M qualifying patients in US, fewer than 1% proceed with surgery due perceived risks, costs, and other factors
*Avg. Bodyweight Loss (%); **Estimated base case, see Section H. Revenue for more information on pricing ***Anticipated. EndoBarrier achieved ~18.9% TBWL at 36 weeks. When extrapolated to 52 weeks we think the ceiling for DNE performance is closer to 20% TBWL. DNE: Duodenal Nutrient Exclusion; ROA: Route of Administration							

Pharmacologic Solutions. Pharmacologic approaches such as GLP1 receptor agonists (GLP1-RA), have recently proven highly effective at treating type Obesity. WeGovy® and Mounjaro®, both GLP-1RAs, have touted impressive bodyweight loss results at 15% and 21% TBWL, respectively, rivaling that of RYGB. Their spike in popularity however has exposed several significant issues including high uninsured costs, supply shortages, and severe side effects associated with thyroid cancer, rapid weight rebounding, excessive muscle loss.

According to the SUMMOUNT-4 Trial data released in July 2023, Mounjaro patients achieved 21.1% TBWL and subsequently regained 14.8% TBW at 52 weeks post-discontinuation for a net TWBL of 5.3% from baseline²⁹. By comparison, a meta-analysis of EndoBarrier® performance reported that patients who were treated with

EndoBarrier® for approximately 9 months and then tracked for 52-weeks post-explant saw a net TBWL of 7.2% from baseline after the 52-week discontinuation period [5.5, 8.9] ($P < 0.0001$) (two studies with 80 subjects)³⁰. In another 2022 study, almost half (45%) of EndoBarrier® patients achieved **complete weight remission** during the 52-week discontinuation period³¹. Compared to GLP1-RAs, the EndoBarrier® has also yielded fewer incidences of Nausea (11% v. 44%), Diarrhea (9% v. 32%), Vomiting (16% v. 25%), and Constipation (9% v. 23%)^{32,33}. Further, **RYGB has shown a two-fold superior retention of muscle mass compared to GLP1-RA** Semaglutide^{34,35}, and has shown reduce cancer risk^{36,37}. It is known in the literature that DNE stimulates natural GLP1 and PYY production^{38,39,40}, and thus we believe the above data supports our hypothesis the Duodenal Nutrient Exclusion offers safer, more sustainable incretin homeostasis and weight management compared to exogenous GLP1-RA administration.

Product	36-Week Efficacy*	52-Week Post-Treatment Maintenance*	Study
Mounjaro®	21.1% TBWL	5.3% Net-TBWL	SURMOUNT-4
EndoBarrier®	18.9% TBWL	7.2% Net-TBWL	Jirapinyo et al., 2018

*From $t=0$ baseline

On the payer side, GLP1-RAs medications require weekly injections and come with a significant price tag at over \$1,000/month. Their popularity has also created manufacturing shortages, leaving many patients unable to receive treatment. GSEL-B's simple components are easily manufactures and anticipated to enable a roughly 10-fold reduction in price which will help increase payer coverage access to patients (see Section H: Revenue Projections). Moreover, orally administered medications are preferred by patients, physicians and payers to increase adherence, compliance and convenience⁴¹. In summary, GSEL-B is well positioned to compete with leading GLP1-RA drugs based on sustained efficacy, tolerability, safety, and access (Table C.4.2).

Table C.4.2 - GSEL-B v. Leading Pharmacologic Drugs

Intervention	Description	Status	DNE?	ROA	Efficacy*	Cost	Comparison to GSEL-B
GSEL-B	Daily oral pill that creates a polymer barrier in the small intestine, blocking nutrient absorption	Preclinical	YES	Oral Pill (1x Daily)	Proprietary Info		Highly effective duodenal nutrient exclusion achieved safely, conveniently, and at low cost.
WEGOVY® (Semaglutide)	GLP1-RA peptide injection for adults with obesity (BMI ≥ 30) or overweight (BMI ≥ 27) with weight-related conditions.	Marketed	NO	Injection (1x Weekly)	15% After 68 weeks ²³	\$1,600 Per month ²⁴	Limited Payer Coverage. Not typically covered by commercial insurance ²⁵ . Patients often required to pay full retail price.
SAXENDA® (Liraglutide)	GLP1-RA peptide injection for adults with excess weight (BMI ≥ 27) who also have weight-related medical problems or obesity (BMI ≥ 30)	Marketed	NO	Injection (1x Daily)	7.4% After 56 weeks ²⁶	\$1,349 Per month ²⁷	Limited Efficacy, Inconvenient Dosing. Saxenda only achieves modest weight loss and requires daily injections.
MOUNJARO® (Tirzepatide)	GLP1/GIP dual agonist injection indicated improve glycemic control in adults with type 2 diabetes mellitus. Projected sales of \$15B NOTE: NOT INDICATED FOR OBESITY ALONE	Phase III	NO	Injection (1x Weekly)	22.5% After 52 Weeks ²⁸	\$1,000 Per month ²⁹	Not Covered for Obesity. Not indicated for Obesity, only Diabetic patients. Patients required to pay full retail price for off-label use.
*Avg. Bodyweight Loss (%); **Estimated base case, see section H. Revenue for more information on pricing ***Anticipated. EndoBarrier achieved ~18.9% TBWL at 36 weeks. When extrapolated to 52 weeks we think the ceiling for DNE performance is closer to 20% TBWL. DNE: Duodenal Nutrient Exclusion; ROA: Route of Administration							

Implanted Devices. Implanted devices have historically seen mixed efficacy while necessitating high priced procedures. ORBERA® has achieved strong short-term results, however it costs over \$8,200, requires a hospital visit, and must be removed after 6 months. The EndoBarrier® most closely mimics RYGB's DNE mechanism by anchoring a plastic sheath in the small intestine and has achieved impressive 18.9% TBWL after an average of 9 months of treatment⁴⁹. However, an abrasive anchoring system has resulted in gastric bleeding incidents and liver abscesses, resulting in it being pulled from the market in 2016. Despite these rampant safety issues, ongoing work is still being done to bring the EndoBarrier® to market⁵⁰. The EndoBarrier®'s reported efficacy orthogonally validates DNE as a critical driver of metabolic control, while the safety issues surrounding the device's implementation highlight the necessity for safer DNE alternatives. **GSEL-B leverages this same DNE mechanism, however with a much stronger safety profile and significantly lower price point** (Table C.4.3).

Table C.4.3 - GSEL-B v. Implanted Devices

Intervention	Description	Status	DNE?	ROA	Efficacy*	Cost**	GSEL Advantage
GSEL-B	Daily oral pill that creates a polymer barrier in small intestine, blocking nutrient absorption	Preclinical	YES	Oral Pill (1x Daily)	Proprietary Info		Highly effective duodenal nutrient exclusion achieved safely, conveniently, and at low cost.
ORBERA®	Endoscopically placed intra-gastric balloon that induces satiety. NOTE: Balloons are not covered by insurance.	Marketed	NO	Endoscopic	10.2% After 26 weeks ³⁰	\$8,200 Per Procedure ³¹	Invasive, Expensive Procedure. Must be removed after 6 months
OBALON®	Endoscopically placed intra-gastric balloon that induces satiety. NOTE: Balloons are not covered by insurance.	Marketed	NO	Endoscopic	6.6% After 26 weeks ³²	\$7,500 Per Procedure ³³	Invasive, Expensive Procedure. Must be removed after 6 months
ENDOBARRIER®	Endoscopically installed sleeve that restricts duodenal absorption. NOTE: NOT INDICATED FOR OBESITY ALONE	Pivotal	YES	Endoscopic	18.9% After 36 weeks ³⁴	\$10,000 Per Procedure ³⁵	Severe Safety Issues. Despite strong efficacy, severe safety issues bleeding events and liver abscesses. Next gen. device currently in trials in US
*Avg. Bodyweight Loss (%); **Estimated base case, see Section H. Revenue for more information on pricing ***Anticipated. EndoBarrier achieved ~18.9% TBWL at 36 weeks. When extrapolated to 52 weeks we think the ceiling for DNE performance is closer to 20% TBWL. DNE: Duodenal Nutrient Exclusion; ROA: Route of Administration							

Transient Devices. While the field of transient weight-loss devices is still in its infancy, Gelesis was the first to make a commercial breakthrough with Plenity®, an oral pill that expands in the stomach to induce satiety. This product is both safe and highly affordable, however it demands high patient adherence (2x daily dosing) and only restricts about 25% of stomach volume⁵⁷. The Elipse® balloon is the first non-endoscopically administered gastric balloon and is naturally excreted 4 months after installment. However, while demonstrating strong weight loss results, this device has had slow market uptake as it requires an outpatient visit for installment, has a high out-of-pocket cost not covered by insurance, and has been associated with severe stomach discomfort, nausea and vomiting^{58,59}. GSEL-B solves the issues faced by devices in this category as it is a simple, once daily pill that can be taken anywhere (Table C.4.4).

TABLE C.4.4 - COMPARISON: GSEL-B v. Transient Devices							
Intervention	Description	Status	DNE?	ROA	Efficacy*	Cost	GSEL Advantage
GSEL-B	Oral pill that creates a polymer barrier in small intestine, thereby blocking glucose absorption and mimicking gastric bypass	N/A	YES	Oral Pill (1x Daily)	Proprietary Info		Highly effective duodenal nutrient exclusion achieved safely, conveniently, and at low cost.
Plenity® (Cellulose)	Oral cellulose pill taken before meals that expands in stomach to induce satiety.	Marketed	NO	Oral Pill (2-3x daily with meals)	6.4% After 48 weeks ³⁶	\$98 Per month ³⁷	Limited Efficacy. Despite commercial availability, Plenity has yielded nominal improvement over placebo (6.4% v. 4.4%).
Elipse®	Gastric balloon system compressed into swallowable vegan capsule that is implanted during outpatient visit and naturally excreted after 4 months. Balloons are not covered by insurance.	Marketed in EU	NO	Oral Pill + Catheter	10-15% After 16 weeks ³⁸	\$4,800 procedure ³⁹	Expensive, Patient Discomfort. Elipse™ requires outpatient visit to install. During first two weeks, patients experience discomfort, nausea and vomiting ⁴⁰
*Avg. Bodyweight Loss (%); **Estimated base case, see Section H. Revenue for more information on pricing ***Anticipated. EndoBarrier achieved ~18.9% TBWL at 36 weeks. When extrapolated to 52 weeks we think the ceiling for DNE performance is closer to 20% TBWL.. DNE: Duodenal Nutrient Exclusion; ROA: Route of Administration							

5. Target Product Profile

To deliver on its promise of marrying efficacy, safety, and affordability, GSEL-B will need to meet a set of baseline product specifications. While the intention is to ultimately make GSEL-B available to all overweight and obese patients, the initial product must be able to, at minimum, adequately impact those qualifying as Obese as they make up the bulk of the prescription weight loss drug market share (See Section H. Revenue Projections).

Proprietary Info

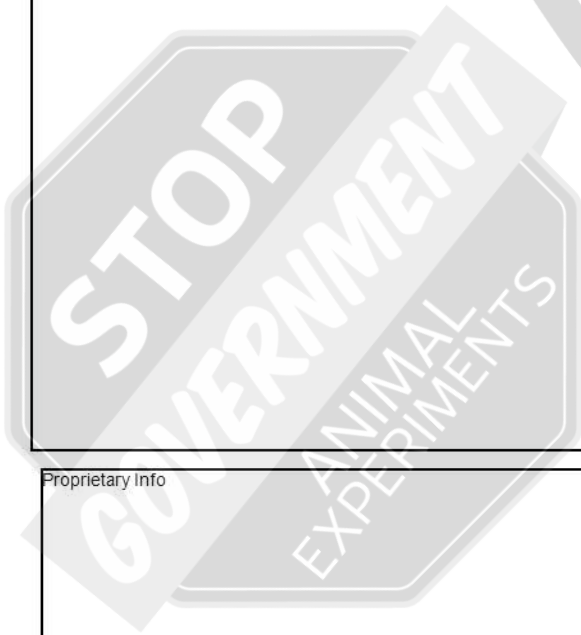
Proprietary Info

D. Regulatory Strategy

1. Regulatory Strategy Overview

Proprietary Info

Proprietary Info



Proprietary Info

Proprietary Info

4. Payer Engagement

Once marketing approval is received from the FDA, Syntis will submit GSEL-B and its price for evaluation by payers. We believe GSEL-B will have favorable results in a cost/benefit analysis done by payers as it is projected to improve patient's quality of life and lower obesity-related healthcare spend, all while being priced at roughly one-tenth of today's leading pharmacologic solutions.

E. Intellectual Property (IP) Protection Strategy

1. Patents

Syntis has licensed Proprietary patents Proprietary which grant Syntis worldwide exclusivity Proprietary Info to develop and commercialize GSEL both within and beyond metabolic health applications:

- Proprietary Info
-

2. New IP

Syntis is continually filing additional IP covering the composition of matter and methods of use of GSEL technology in novel therapeutic applications such as oral macromolecules drug delivery, inflammatory bowel disease (IBD), and many others. Proprietary Info

Proprietary InfoProprietary Info

Strengthening the IP around GSEL and enabling proprietary pipeline programs will help grow the enterprise value of Syntis, making it easier to raise venture financing and support the company as it advances GSEL-B through the clinic.

F. Financing Plan

1. Financing Strategy

Proprietary InfoProprietary Info

G. Production, Marketing and Sales Plan

1. Production

Proprietary Info

2. Marketing

Commercializing a product for the large and growing population of obesity patients will require a large and sophisticated marketing organization. Therefore, Syntis will market its products through a strategic partnership or licensing deal with a pharmaceutical leader who can provide effective marketing and distribution networks. Key to this marketing process will be to reach the prescribing physician, which will likely be a primary care physician and/or endocrinologists.

Proprietary Info

Proprietary Info

3. Acceptance

Driving the overall market acceptance and adoption for GSEL-B will require implementing a multi-pronged commercial strategy. Using the conclusions/results from the proposed clinical studies, a variety of tools will be utilized that include:

Proprietary Info

-
-
-
-
-
-
-
-

H. Revenue Projections

Syntis will generate revenue through licensing partnerships with other pharmaceutical companies which will include upfront payments, sales milestones, and royalty payments once GSEL-B is FDA approved and sold on the market.

Total Addressable Market. Proprietary Info

Proprietary Info

Market Penetration. Proprietary Info

Proprietary Info

Proprietary Info

Global Access. Syntis is dedicated to maximizing global access to its medicines. In developing countries, pricing will be reduced to maximize accessibility, and distribution will likely be pursued in partnership with global specialty pharmaceutical manufacturers.

Selling, General, Administrative Expenses. A simplifying assumption of 30% topline revenue was used as a proxy for selling, general and administrative expenses. In practice, much of this cost would fall to a commercial partner.

Table H.1 PRO-FORMA: Profit & Loss Statement (USD, thousands)

	Proprietary Info
Addressable Market	
Obesity Population (BMI 30-40)	
Drug Treated Population	
Peak Market Penetration	
Market Uptake ⁴⁵	
Total Patients Treated	
Revenue	
Topline Sales	
Cost of Revenue	
COGS	
Gross Profit	
Operating Expenses	
SG&A	
Total OpEx	
Net Income (thousands, USD)	

Table H.2 SENSITIVITY ANALYSIS: Year 5 Topline Sales Post-Launch (millions, USD)

Projected Topline Sales	Price/month
Mkt Penetration	Proprietary Info

PHS 398 Cover Page Supplement**1. Vertebrate Animals Section**

Are vertebrate animals euthanized? ☒ Yes ☐ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

☒ Yes ☐ No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount (\$)	*Source(s)
----------------	--------------------------	------------



3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ☐ Yes ☒ No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ☐ Yes ☒ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ☐ Yes ☐ No

6. Change of Investigator/Change of Institution Section

☐ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

☐ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

Introduction 1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section 2. Specific Aims 3. Research Strategy* 4. Progress Report Publication List	
Other Research Plan Section 5. Vertebrate Animals 6. Select Agent Research 7. Multiple PD/PI Leadership Plan 8. Consortium/Contractual Arrangements 9. Letters of Support 10. Resource Sharing Plan(s) 11. Other Plan(s) 12. Authentication of Key Biological and/or Chemical Resources	
Appendix 13. Appendix	



Specific Aims

Obesity is a complex disease that disrupts hormonal and metabolic pathways, increasing the risk of chronic co-morbidities like diabetes, cardiovascular disease, and cancer. Obesity itself afflicts more than 1 billion globally and, when combined with its associated risk factors, contributes to over \$480 billion in direct annual healthcare spending. Roux en Y Gastric bypass surgery (RYGB) leverages duodenal nutrient exclusion (DNE) to achieve best-in-class weight loss results, however the high costs, extensive procedural risks, and limited reimbursement have greatly limited access to care. Further, pharmacotherapies and weight loss devices have failed to strike a balance between affordability and efficacy which has both limited adoption and widened socioeconomic access disparities. Consequently, there exists a critical unmet need for effective, non-invasive, and affordable weight loss solutions. Using technology licensed from MIT, Syntis Bio has created a gastrointestinal synthetic epithelial lining (GSEL) that is orally administered and achieves DNE by forming a transient, absorption-blocking barrier in the duodenum. In this Fast-Track SBIR proposal, we seek to engineer GSEL into solid tablets and optimize the composition to achieve optimal DNE in beagles. Successful completion of this proposal will result in a demonstration of GSEL tolerability and functionality in beagles and a protocol for manufacturing tablets.

Phase I Specific Aim 1. Identify lead compositions of GSEL for glucose barrier function by altering component ratios, component concentrations, and buffer identity. (5 months)

Milestone: The lead formulation will form a robust film on porcine tissue in less than 30 minutes and prevent at least Proprietary Info glucose permeation through porcine duodenum over 0.5-6 hours in Franz cell studies.

Phase I Specific Aim 2. Determine the density of coverage needed for barrier function after direct placement of GSEL capsules to the duodenum in an *in vivo* pig model. (7 months)

Milestone: Capsules are chosen here to enable rapid compositional changes compared to tablets. Success in this Aim will show that lead capsule formulations deposit GSEL within 60 minutes and retain in the duodenum for at least 6 hours using radiography. After 1-2 days, all signals should be gone as GSEL is eliminated. OGTTs in combination with radiography will inform on the optimal GSEL density of coverage needed for reducing blood glucose concentrations by at least Proprietary Info. Tolerability studies should show no indications of malnutrition or dehydration. Taken together, these results will reduce commercial risk by demonstrating a solid capsule formulation of GSEL can perform as expected.

Phase I -> II transition milestone: By the end of Phase I, we will have demonstrated glucose barrier function in *ex vivo* and *in vivo* experiments using the solid powder and capsule GSEL formulations. In the porcine *in vivo* model, liquid GSEL should reduce blood glucose concentrations by at least 15-25% over 1-2 hours. Finally, we will have created bench-scale solid dosage forms of the lead formulations and demonstrated disintegration and dissolution of GSEL components when exposed to small intestinal tissue in a static assay.

Phase II Specific Aim 1. Engineer tablets that stabilize components for 4 weeks, have the desired disintegration and dissolution properties, and optimize GSEL formation on *ex vivo* tissue. (12 months)

Milestone: In *ex vivo* experiments, the lead formulation will deposit GSEL components over an optimal area as determined by Phase I *in vivo* radiograph results. Disintegration and dissolution will happen within 10-30 minutes and GSEL films should prevent at least Proprietary Info

Final tablet formulations should maintain component stability for 4 weeks (at least 1-3 day stability enables parallel work in Aim 2) and coated with enteric coatings to maintain stability in fasted state simulated gastric fluid at pH <7.4.

Phase II Specific Aim 2. Optimize film formation, residency time, and glucose barrier efficacy of GSEL tablets in a beagle model. (12 months)

Milestone: Lead formulations will deposit GSEL primarily in the small intestine after oral ingestion and a barrier will form within 20 minutes. Blood glucose concentrations will be reduced by Proprietary Info compared to the untreated control in an oral glucose tolerance test. GSEL components will be eliminated in 24 hours. Beagle models are used here due to ease of tablet administration and more human-relevant gastric emptying times for transit of the tablet to the small intestine.

Next steps: At the end of Phase II, we will have a formulated tablet, tablet manufacturing protocol, and demonstration of oral administration in beagles that prevents Proprietary Info. The next steps will be to finalize the sourcing of raw materials for GMP manufacturing, initiate GLP toxicity studies with a CRO, and finalize a clinical plan for a first-in-human study. GSEL tablets aim to be an effective, non-invasive, and affordable weight loss solution.

Research Strategy

1. SIGNIFICANCE

1.1. Problem

According to the World Health Organization (WHO), the global prevalence of obesity has more than doubled since 1980, affecting more than 1 billion people today with a CAGR of roughly 16.7%¹. In the US, 41.9% of all adults are obese, with roughly 30M of that population qualifying as severely obese. The obesity epidemic is a complex global challenge that requires innovative solutions to address its impacts on society and the economy. While there are many different causal drivers of obesity, its pathophysiology involves severe disruption of hormonal and metabolic pathways, which has been found to increase risk for chronic diseases such as diabetes, cardiovascular disease, and cancer². Moreover, adults with excess weight have a 55% higher risk of developing depression over their lifetime compared to control groups³. In aggregate, obesity and its associated chronic conditions contribute \$480.7 billion in direct annual healthcare spending, with an additional \$1.24 trillion associated with indirect costs due to lost economic productivity⁴.

Roux-en-Y Gastric bypass surgery (RYGB) has long been heralded as the gold standard for weight loss, achieving upwards of 30% total body weight loss (TBWL) after just 52 weeks⁵. Despite this impressive efficacy, the highly expensive and invasive nature of RYGB has limited access to fewer than 1% of severely obese individuals⁶. Within the last several years GLP-1 receptor agonist (GLP-1) drugs have ushered in a new era of pharmacologic obesity treatment with the intent on making effective weight loss more accessible. Market leader Wegovy® (semaglutide) reports an average of 17.4% TBWL in clinical studies, which has in turn inspired an entire pipeline of next generation GLP-1 products poised to push that number ever higher⁷. Of the 90M eligible US obese patients however, only 5M are prescribed a GLP-1 therapy each month, a rate which has plateaued since May 2023⁸. Further, overstimulation of GLP-1 receptors has been shown to cause severe GI symptoms as well as secretion of stress hormones in the brain leading to an investigation for linkage to suicidal thoughts⁹. As a result, semaglutide has seen a 45% twelve-month drop-out rate as well as a widening gap between reported clinical efficacy (17.4% TBWL) and real-world efficacy (4.4% TBWL)^{10,11} as the majority of people who take GLP-1 RAs gain most of the weight back within a year of stopping the medication^{12,13}. Next generation products are not a perfect solution either; in August 2023, Eli Lilly was sued over safety concerns related to its recent blockbuster GLP-1 ZepBound™, and in December Pfizer pulled a highly anticipated danuglipron from Phase IIb development due to severe GI symptoms^{14,15}. Complex manufacturing of injectable pens has also proven to be a headwind, creating supply shortages that have driven higher prices and created markets for unsafe counterfeit products¹⁶. Taken together, these tolerability, manufacturing, and pricing concerns have left over 85M Obese US adults unserved and looking for better solutions. To urgently address the Obesity crisis, it's imperative to shift our focus beyond higher, short term weight loss and instead focus on building effective products that improve patient access, promote adherence, and yield more sustainable results.

1.2. Current State of the Art

The current state of the art for obesity treatments includes a variety of approaches, including lifestyle interventions, bariatric surgery, pharmacotherapy, and devices. However, to date none of these solutions have been able to effectively balance efficacy, safety, and affordability.

Lifestyle interventions. Diet and exercise have been shown to produce modest weight loss, but long-term adherence can be challenging, especially without the careful monitoring of a trained professional. Further, these interventions may not be suitable or accessible for all individuals, particularly those with severe obesity.

Bariatric surgeries. Roux en Y Gastric Bypass (RYGB) and Sleeve Gastrectomies have produced the most significant average bodyweight loss at 31% and 25% respectively¹⁷. RYGB best-in-class efficacy is largely driven by its duodenal nutrient exclusion (DNE) mechanism¹⁸. Despite the efficacy reported for RYGB and other bariatric surgeries however, these procedures are highly invasive and expensive which has limited their access to fewer than 1% of severely obese individuals¹⁹.

Pharmacotherapy solutions like GLP1RAs have generated efficacy data rivaling certain bariatric surgeries, however these injectable drugs are accompanied by their own set of unwanted side effects, expensive price tags, and limited insurance coverage for obesity indications²⁰.

Implantable devices. Gastric Balloons like the Orbera® have seen mixed results ranging from ~6-10% average body weight loss, however each of these invasive endoscopic procedures are expensive, have been reported to create severe discomfort, and must be replaced every 6 months²¹.

Transient devices. Transient satiety devices like Plenity® absorbent capsules and Elipse™ gastric balloons, which non-invasively occupy stomach capacity to prior to being naturally excreted, are perhaps the most well tolerated weight loss devices. Despite their benign nature however, Plenity®'s results have been limited at around 6% average bodyweight loss²² and Elipse™ has out of pocket costs running an average of \$4,800 per surgery²³, highlighting the existing tradeoff between affordability and efficacy.

As such, to meaningfully address the obesity epidemic, novel weight loss solutions are needed that are effective, safe, and reduce disparities being accessible to the growing population of suffering individuals.

1.3. Proposed Solution

Duodenal Nutrient exclusion (DNE) is an empirically demonstrated weight loss mechanism that achieves equally efficacious results compared to Roux-en-Y Gastric Bypass Surgery (RYGB), demonstrating a 30% TBWL after 52 weeks²⁴. Studies have shown that nutrient sensing and the **rate of duodenal nutrient absorption** is a key factor in metabolic regulation via mechanisms such as improving glucose homeostasis, stimulating natural GLP-1 secretion, and suppressing plasma glycerol levels²⁵. In Obesity, duodenal nutrient sensing defects are acquired which dampen native hormonal responses and therefore leaves nutrient intake unchecked, hepatic glucose production uncontrolled²⁶, and energy expenditure muted²⁷. DNE has been proven to streamline ingested nutrients to the jejunum and ileum where nutrient receptors are more sensitive and can more tightly regulate energy intake (satiety), energy expenditure, and glucose production through secreted gut hormones (GLP-1, PYY, OXM, etc.)²⁸. This mechanism is empirically supported by the association of RYGB surgery with restoring postprandial gut hormone secretions in Obese and diabetic patients.²⁹ Further, nutrients are still absorbed in the distal small bowel, including glucose, which is significant as this prevents accumulation and/or fermentation in the gut³⁰. Moreover, prolonged non-surgical DNE stimulates villus hyperplasia, restoring native duodenal nutrient sensing³¹ and providing a long-term physiological benefit. This contrasts GLP-1 drugs, which rapidly induce satiety through exogenous GLP-1 stimulation yet fail to sustain this benefit upon treatment discontinuation, resulting in rapid weight regain³².

While first clinically seen in RYGB, DNE has additionally been validated by non-surgically implanted duodenal bypass liners, like the EndoBarrier®™, which has shown 18.9% TBWL in 9 months³³. Further, one year post-EndoBarrier™ removal, 39% of patients demonstrated fully sustained improvement with another 39% retaining partial improvement. Compared to semaglutide, EndoBarrier® achieved 2.4x improved weight loss remission^{34,35}. Together, these findings point toward DNE as a possible best-in-class mechanism for long-term weight management and metabolic control. Further, DNE mechanisms, such as RYGB and Duodenal Bypass Liners have demonstrated superior lean mass retention, and toxicity compared to exogenous GLP-1 drugs^{36,37,38,39}. It is important to note that the EndoBarrier® was pulled from the market in 2016 due to safety concerns surrounding bacterial infections and liver abscesses, however these issues were directly attributed to the devices mechanical anchoring system and not it's therapeutic mechanism⁴⁰. Even in light of this recall, compelling data surrounding its efficacy has given the EndoBarrier® new life as it has since been rebranded as RESET™ and is currently in Pivotal Trials in the US^{41,42,43}. While the mechanical safety and clinical utility of the EndoBarrier® as a product remains to be seen, its reemergence points toward the clinical importance of DNE as a highly effective and highly regarded mechanism for metabolic control. Syntis is leveraging recent advances in synthetic tissue technology developed at MIT to create an oral pill, GSEL, that delivers a robust, mucoadhesive polydopamine barrier to the small intestine to restrict duodenal nutrient absorption. This intestinal barrier is composed of simple, biocompatible components that are safely excreted from the body within 24 hours allowing for periodic nutrient supplementation and medication administration, which minimize concerns with malnutrition. Further, GSEL's DNE mechanism is designed to restore postprandial neuroendocrine signaling. This approach is intended to provide a more balanced and sustainable solution to metabolic control compared to GLP-1 drugs, or

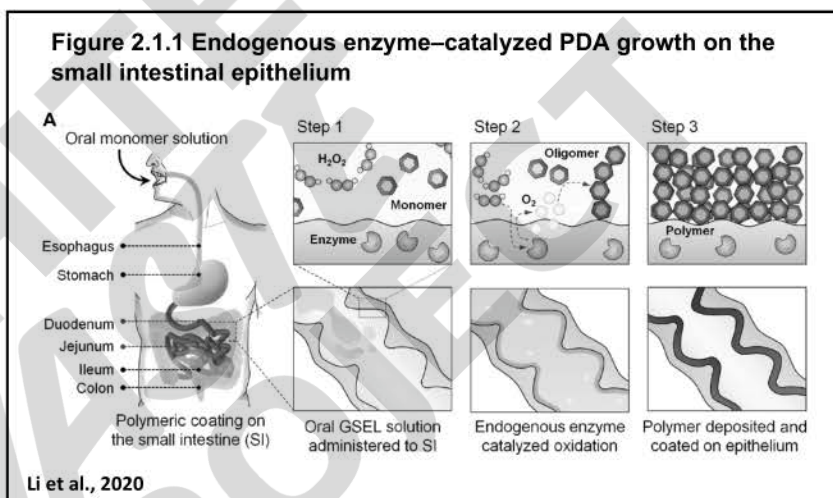
combinations thereof, which are limited by the number of metabolic signaling pathway they can address⁴⁴. As such, GSEL is a noninvasive, low-cost DNE weight loss device designed to be more accessible and deliver more sustainable results than GLP-1 drugs, bariatric surgeries, or implanted devices.

2. INNOVATION

2.1. Gastrointestinal Synthetic Epithelial Lining (GSEL) leverages polydopamine to develop temporary linings adherent to the small bowel that are safe and easily administered

Polydopamine (PDA) is a highly mucoadhesive material that complexes with a variety of biological surfaces, including mucus membranes, making it an attractive material in biomedical applications⁴⁵. PDA formation occurs when dopamine monomers are reduced by oxygen resulting in PDA formation and trace, clinically insignificant levels of hydrogen peroxide⁴⁶. In general, PDA polymerization is a slow process, with the reaction limited by low oxygen concentrations⁴⁶. PDA polymerization reactions can be rapidly accelerated in the presence of the enzyme catalase, which breaks down hydrogen peroxide to release oxygen, thereby accelerating the forward reaction by several orders of magnitude. Further, catalase enzymes (CAT) are highly enriched in the duodenum of the small intestine, a critical site for nutrient absorption and digestive activity.

The above findings taken together present a unique opportunity to create novel means of modulating nutrient and/or drug absorption in the small intestine through an oral pill. In 2020, Dr. Giovanni Traverso's Lab at MIT published results demonstrating that formulations containing dopamine monomers and trace amounts of hydrogen peroxide can be administered orally to create robust PDA linings along the epithelial surface of catalase-rich porcine duodenal tissues⁴⁶. Figure 2.1.1. illustrates the in situ polymerization of GSEL in the presence of H_2O_2 under endogenous CAT catalysis, forming PDA coating on the small intestinal epithelium.



2.2. The GSEL-Barrier represents an innovative device that combines the efficacy of DNE and RYGB with the convenience of a once daily oral pill that replicates the effects of DNE

GSEL overcomes many of the limitations of current tissue-targeting strategies, including invasive transplantation, potential immunogenicity, toxicity, and inconvenience⁴⁶. Further, the GSEL platform has thus far demonstrated the ability to restrict or enhance systemic absorption of substrates depending on the porosity of the PDA lining. Given the urgent need for better obesity interventions and the strong evidence behind duodenal nutrient exclusion as an effective therapeutic mechanism, GSEL is first being developed as a novel therapeutic for weight management (GSEL-Barrier or GSEL-B). This therapy will come in the form of a once daily oral dopamine pill that is delivered to the duodenum where it polymerizes in situ to form mucoadhesive barrier to block duodenal nutrient absorption.

2.3. Team

Syntis was formed in 2022 to develop and commercialize GSEL-based technologies and has an exclusive license to the relevant patents from MIT. The Syntis team is comprised of experts with diverse backgrounds in drug development and delivery. Dr. Anthony Yu, Associate Director of R&D and PI for this project, is a specialist in novel drug delivery methods. Dr. Yu's PhD work at Stanford focused on developing injectable hydrogels for the long-term delivery of antibodies for passive immunization, macular degeneration, and glaucoma. Dr. Yu later worked as a postdoctoral research fellow at Brigham and Women's Hospital where he developed novel delivery vehicles for the CNS and lung diseases and then as a formulation scientist at Moderna, where he developed lipid nanoparticles for targeted tissue delivery. [Redacted by agreement] brings over 20 years of experience

in the pharmaceutical industry, with a focus on novel drug development and delivery mechanisms. [Redacted by agreement] has supported more than 30 regulatory filings worldwide and led the NDA submission for aripiprazole lauroxil (approved as Aristada®) while at Alkermes in 2014.

Syntis is also supported by [Redacted by agreement] our respective in vivo and regulatory consultants. [Redacted by agreement] is a current Senior Clinical/Surgical Veterinarian in the [Redacted by agreement] lab with over 20 years of experience in laboratory animal medicine and has deep expertise in regulatory affairs governing animal use in research, IACUC administration, and GLP regulations for device assessment. [Redacted by agreement] has over 40 years of experience providing regulatory and clinical support for medical device companies, implemented regulatory and clinical strategies from development through commercialization, and completed 510(k) submissions in women's digital health, orthopedics, endoscopy, neurology, and ENT products. Additional consulting support is provided by [Redacted by agreement] is a gastroenterologist and researcher at Massachusetts General Hospital and has been recognized for his expertise in areas of liver disease, IBD, and GI cancer. [Redacted by agreement] is a gastroenterology specialist at the University of Maryland of Baltimore Washington Medical Center and is an expert in gut microbiology, gut motility, and IBD. Both [Redacted by agreement] will provide the Syntis team with their clinical expertise, specifically in terms of better understanding both the patient journey and what prescribing physicians consider when recommending interventions targeting the GI tract.

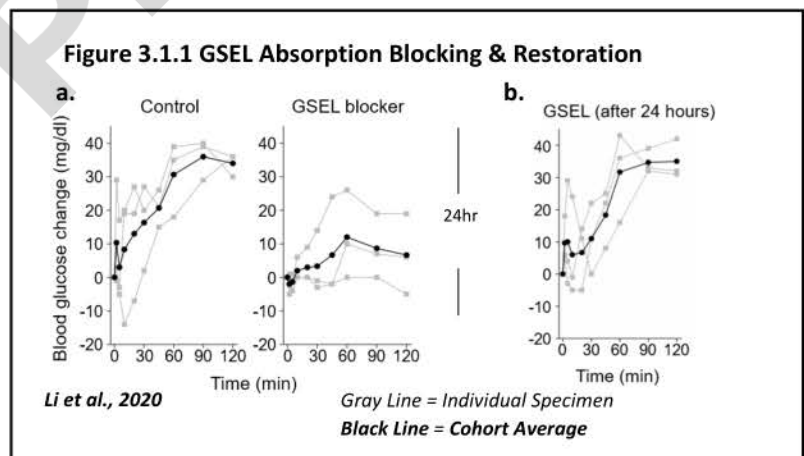
[Redacted by agreement] Syntis co-founders and co-inventors of the GSEL technology, will also continue to provide advisory support to the Syntis team for this project. [Redacted by agreement] is a David H. Koch Institute Professor at MIT and renowned for both his work in drug delivery systems and track record launching successful companies (Moderna, PureTech, etc.). [Redacted by agreement] is a physician scientist who splits time as a gastroenterologist at Brigham and Women's Hospital and as a faculty member in MIT's Department of Mechanical Engineering. Together, Syntis has assembled a team of scientists, consultants, and advisors who possess the depth and breadth of experience necessary to take the GSEL platform from a benchtop concept to a commercial therapeutic platform.

3. APPROACH

3.1. Current State of Technology

The GSEL technology was developed with the goal of enabling targeted therapeutic deposition and intervention in the small intestine. The discovery and characterization of GSEL for tissue-directed polymerization, and proof-of-concept applications in drug delivery, enzymatic immobilization for digestive supplementation and nutritional modulation in pigs have been described⁴⁶, and key results relevant to nutrient barrier formation are highlighted below.

Efficacy of Barrier Function (Glucose). To validate intestinal barrier function, a GSEL solution with PDA nano-crosslinkers was administered endoscopically to the small intestine (clamped) of three anesthetized Yorkshire pigs. For the three control pigs, 500 ml of water was administered in the same way. Standard oral glucose tolerance tests (OGTT) were initiated 20 minutes after GSEL/control administration. Changes in blood glucose level were recorded at each time point and averaged for comparison (Figure 3.1.1a). Quantitative comparison of blood glucose showed an average 73.3% reduction in glucose concentrations in GSEL vs. control (Figure 3.1.1a), indicating effective reduction of postprandial glucose absorption.



Quantitative comparison of blood glucose showed an average 73.3% reduction in glucose concentrations in GSEL vs. control (Figure 3.1.1a), indicating effective reduction of postprandial glucose absorption.

For the three pigs that received GSEL solution, OGTT was performed again 24 hours after initial GSEL administration. OGTT results demonstrated that these pigs recovered normal glucose absorption after 24 hours, demonstrating that the GSEL coating is transient (Figure 3.1.1b).

Tissue Specificity (Porcine GI Tract).

Tissue specificity of GSEL was evaluated by comparing the GSEL coating in different parts of the porcine GI tract, including the esophagus, stomach, duodenum, jejunum, ileum, and colon. Strong PDA polymerization in the duodenum and jejunum relative to other segments of the GI tract was observed (Figure 3.1.2a; PDA depots present a natural dark brown color) and then confirmed via quantitative signal analysis (Figure 3.1.2b). Statistical analysis using one-way analysis of variance (ANOVA) and post hoc Bonferroni test showed that there were statistically significant intensity differences between the small intestine and other tissues ($P < 0.05$) such that GSEL preferably adhered to the duodenum and jejunum compared to other parts of the GI tract. The data are presented as means $\pm$ SD and were obtained from three different tissue samples. This GSEL-tissue specificity correlates strongly to the relative CAT activity within each porcine tissue type as measured through CAT activity analysis (Figure 3.1.3.).

Figure 3.1.2 GSEL Tissue Specificity

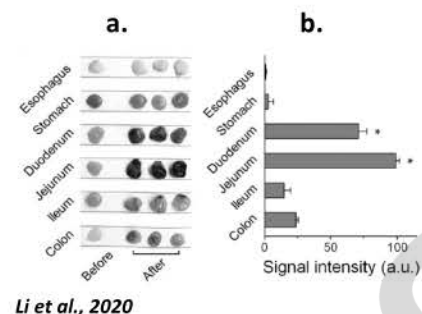
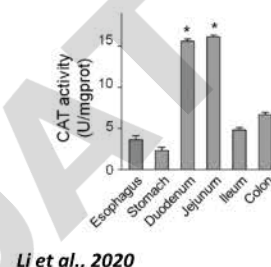
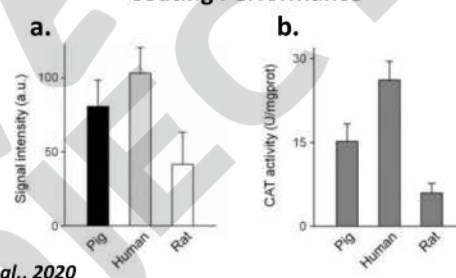


Figure 3.1.3 CAT Expression in GI



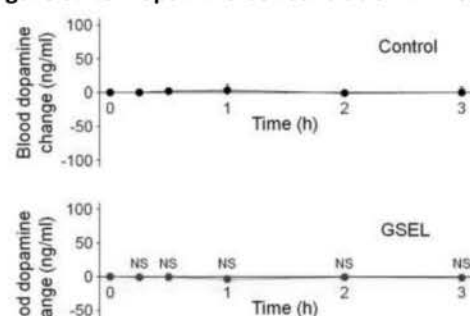
Tissue Specificity (Cross-species). To further investigate GSEL coating density and CAT expression, intestinal tissues from three species (porcine, human, and rat) were analyzed. The selected tissue was coated with GSEL, and the GSEL coating density was measured by analyzing the PDA signal intensities (Figure 3.1.4a). CAT activity was then quantified across each tissue type (Figure 3.1.4b). Consistent trends were observed between GSEL density and CAT activity, with the highest CAT activity and GSEL density being exhibited by human specimens compared to rat and pig. The data are reported as means $\pm$ SD over three replicates.

Figure 3.1.4 Cross-Species GSEL Coating Performance



Safety - Biodistribution. In vivo biodistribution of GSEL was evaluated using anesthetized Yorkshire pigs. GSEL solution was directly administered to the small intestine and/or stomach through a catheter under endoscopic visual guidance. During the study, there was no detectable increase in dopamine or PDA observed in the submucosa or blood after GSEL coating by microscopy (Li et al., 2020, Fig. S10), UV-Vis spectroscopy (Li et al., 2020, Fig. S15), or liquid-chromatography-tandem mass spectroscopy (Figure 3.1.5). Additionally, we did not observe any clinically relevant changes in blood pressure or heart rate in animals throughout the procedures (data not shown), demonstrating the lack of dopamine absorption and supporting the early safety of the GSEL technology.

Figure 3.1.5 Dopamine Concentration in Blood



Safety – Prolonged Intestinal Retention. GSEL demonstrated safe and prolonged intestinal retention of PDA coating. Kinetics of GSEL retention were monitored radiographically by PDA-encapsulated X-ray contrast agents. A solution containing GSEL and the PDA-encapsulated probe was administered to healthy pigs and a strong X-ray signal was observed. As a control, conventional contrast agent alone was administered to pigs. After both imaging areas in the duodenum were subsequently rinsed, the signal of the conventional contrast agent was barely detectable whereas the PDA probe had an almost 9-fold higher signal intensity (data not shown). Additionally, during this experiment pigs were assessed clinically and radiographically for evidence of GI perforation and obstruction (e.g., inappetence, abdominal distension, lack of stool, or vomiting). *There was no clinical or radiographic evidence of GI perforation and obstruction observed during the study.*

Safety – Toxicity. GSEL has demonstrated a strong safety and biocompatibility profile in rat in vivo and human in vitro toxicity studies. Oral toxicity was assessed by following guidelines issued by the Organization for Economic Co-operation and Development (OECD) with minor modifications. Specifically, rats were exposed to the GSEL solution over a period of 4 weeks, on the basis of a repeated dose 28-day toxicity study. There were no significant bodyweight changes of rats following the oral administration of water (control), PDA, or GSEL solution separately. Further, histology of heart, lung, liver, kidney, splenic, stomach, and intestinal tissue were collected from rats after sacrifice and demonstrated no signs of tissue damage across all conditions. Cytotoxicity of PDA was also evaluated on multiple human cell lines: HeLa, COLO320DM, Caco-2, Hep3B, and HS 895.T. No obvious cytotoxicity was observed after 6-48 hour in vitro incubation of GSEL (data not shown).

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3.2. Phase I Research Plan

The goal of Phase I is to demonstrate the feasibility of GSEL as a solid formulation and define the dose and density of coverage required for barrier function. Currently, the GSEL technology has one lead composition that functions in in vivo and static ex vivo tests as a liquid. In anticipation of developing a solid dosage form as final product, our strategy in Phase I is to develop lead formulation compositions for solid formulations of GSEL and demonstrate equivalent or superior barrier function in a pig model when compared to the liquid formulation. This work will significantly reduce commercialization risk by demonstrating the feasibility of GSEL to be delivered as a solid capsule or tablet.

By the end of Phase I, we will have a lead solid dosage composition of GSEL that has demonstrated feasibility in a pig model when delivered as a capsule and a target density of coverage for proper barrier function.

3.2.1 Phase I Specific Aim 1: Identify lead solid compositions of GSEL for barrier function by altering component ratios, component concentrations, and buffer identity. (5 months)

Strategy: Using our ex vivo porcine tissue model, we will optimize solid compositions of GSEL for film formation kinetics, film mechanical robustness, and barrier function. Compositions will be altered by changing dopamine to polydopamine ratios, overall concentration of dopamine components, and the buffer strength and identity.

Method and analysis: In this aim, solid compositions of GSEL will be made by simple addition of each component (dopamine hydrochloride, polydopamine particles, urea hydrogen peroxide, and tris salts) into a sample container. Milling will be considered if powders are heterogeneously distributed or sized. Compositions will be altered by changing dopamine to polydopamine ratios (e.g. 1:1, 1:2.5, 1:5), overall concentration of dopamine components (e.g. 25, 35, 45 mg/mL), and the buffer concentration (e.g. 25, 37.5, 50, 75 mM) and identity (e.g. tris, carbonate, phosphate buffers). We will use Franz cells to test the barrier function of different GSEL compositions across porcine small intestinal tissue. These cells are designed to measure permeation of contents from a donor chamber to a receiving chamber over time and can assess intact, resected tissue⁴⁷. Stir bars are

placed in the receiving chamber to provide uniform distribution of the permeating test article and the entire cell is kept at 37 °C. Fresh (12-24 hours after resection) small intestinal porcine tissue obtained from Animal Biotech Industries (Doylestown, PA) will be rinsed with antibiotic/antimycotic solutions before mounting onto Franz cells to limit bacterial activity. Solid GSEL formulations will be added to the tissue and allowed to react with tissue catalase for 5-20 minutes. To test permeability, glucose will be introduced on top of the GSEL film at 500 mg/mL (250 uL), which is the concentration used in standard oral glucose tolerance tests. Three to five samples will be taken from the receiver chamber over 24 hours to be analyzed using Amplex™ Red Glucose Assays (ThermoFisher). We choose to focus on glucose because of the relatively low molecular weight, which will provide insight into the permeabilities of larger nutrients like lipids or proteins. We anticipate if we can demonstrate decreased glucose absorption, then absorption of macromolecules (10,000 Da) and complex carbohydrates (1,000,000 Da) will also be blocked.

Rigor: To assess how compositional changes affect the kinetics of robust GSEL formation, different incubation times will be used when loading Franz cells with GSEL and barrier function against glucose will be measured. To assess GSEL adhesive strength after different incubation times, GSEL will be incubated on tissue for different durations (5, 10, 20, 30, 40 minutes) and then rinsed with Fasted State Simulated Intestinal Fluid (FaSSIF, BioRelevant). The control group will be tissue mounted on the Franz cell with no treatment added before adding glucose solution. All experimental groups will also be compared to the original GSEL liquid composition as a control. To limit regional and animal specific variation in all tests, tissue samples from 4 different male and female donor pigs will be randomized across tested groups and experiments will be repeated 2-3 times. Statistical analysis will be done using one-way and two-way ANOVA of diffused glucose at each timepoint, followed by a post-hoc analysis to compare specific groups..

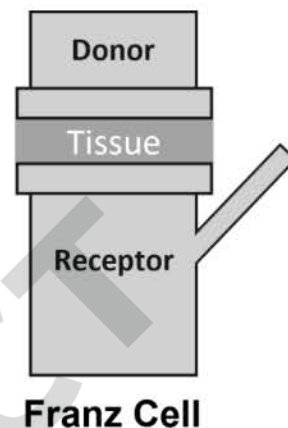


Figure 3.2.1 Franz cell setup for permeability studies.

Milestone: Proprietary Info

Proprietary Info

Proprietary Info

Expected outcomes, risks, and alternative strategies: The primary objective of this Aim is to (1) determine if solid formulations have different GSEL film forming kinetics than liquid formulations, and (2) identify lead solid compositions that can form GSEL quickly and prevent glucose permeation through porcine tissue. Since all components are highly soluble, we do not expect solid formulations to significantly slow GSEL forming kinetics. Furthermore, solid formulations by default are interfacing the mucosa (as opposed to fluid, suspension formulations) and form a hypotonic interface, suggesting film density and robustness should significantly improve compared to liquid formulations. As a result, glucose permeability should be lower for solid formulations and compositions may require less polydopamine concentrations to achieve similar barrier functionality.

An important aspect we are considering is the translatability of ex vivo experiments for both GSEL formation and glucose permeation given that sodium-glucose transport proteins may have lower activity in the Franz cells. For GSEL formation, the risk is that the lack of moisture in dead tissue will slow GSEL dissolution and formation to 30+ minutes. An alternative strategy to address this risk is to rinse the dead tissue with simulated intestinal fluid before adding GSEL formulations. As for the risk of glucose permeation being underestimated using dead tissue, data that is generated in Aim 2 will quickly inform on this risk and allow us to determine if rank ordering of lead formulations still correlates with in vivo data. This iterative data cycle will allow us to confidently rank order formulations in Aim 1, while using the in vivo model in Aim 2 to confirm in vivo performance. Furthermore, GSEL works by physically preventing diffusion of glucose across the mucosa, so we expect successful GSEL film formation to generally provide a more tortuous path for glucose to reach sodium-glucose transport proteins near the epithelium.

Lastly, ex vivo tissue may have reduced catalase activity compared to in vivo tissue. However, because we have existing data (see above) demonstrating successful formation of GSEL on ex vivo tissue, we are not concerned that using ex vivo tissue will preclude GSEL formation. In anticipation for in vivo studies where GSEL may form faster because of increased catalase activity, the lead formulations in this Aim that are tested on ex vivo tissue will include compositions that have a range of GSEL formation kinetics.

3.2.2 Phase I Specific Aim 2: Determine the density of coverage needed for barrier function after direct placement of GSEL capsules to the duodenum in an in vivo pig model. (7 months)

Strategy: The purpose of this Aim is to determine the proper density of coverage needed for barrier function and which solid GSEL composition best creates that coverage when delivered directly to the small intestines. We will use pigs to determine the density and area of GSEL coverage needed for barrier function because their intestinal anatomy is most like humans⁵¹. An overtube with endoscopic guidance will be used to directly place GSEL-filled capsules into the small intestines of pigs under anesthesia. This direct placement will be done to avoid the long gastric emptying time of pigs when compared to humans. Furthermore, direct placement will allow for quicker iteration of GSEL compositions without the need to enterically coat the capsules. Capsules are chosen over tablets because it is much easier to rapidly change compositions in capsules compared to tablets. In vitro dissolution experiments in simulated intestinal fluid and ex vivo tissue will be used to rank order capsule types before the in vivo experiments. We will include radiograph tests to image GSEL formation and use oral glucose tolerance tests (OGTTs) and mixed meal tolerance tests (MMTTs) to assess blockade and post-prandial hormonal responses.

Method and analysis: Formulations will be tested by taking the lead compositions from Specific Aim 1 and hand-filling capsules. In vitro dissolution experiments with simulated intestinal fluid and ex vivo intestinal tissue will be done to rank order capsule types (e.g. gelatin, hypromellose, coated capsules etc.) based on dissolution time and powder escape behavior. In these experiments, capsules will be placed on ex vivo duodenal tissue and incubated with 4-12 mL of FaSSIF until capsules disintegrate and GSEL is released.

For in vivo experiments, a total of 8 Yorkshire pigs (4 male and 4 female to address Sex As a Biological Variable) weighing 40-80 kg each over 7 months' time will be used for these in vivo tests. In these experiments, the following variables will be evaluated: body weight, clinical variables (heart rate, appetite, lethargy); blood glucose, glucagon-like peptide (GLP-1), peptide YY (PYY), ghrelin, insulin, and glucose-dependent insulintropic polypeptide (GIP) concentrations before and after oral glucose administration. Clinical variables will be primary readouts to assess tolerability of the formulations and any indications of malnutrition (water or nutrients).

For OGTTs and MMTTs, blood will be taken according to the following schedule:

Procedure:	Deliver Capsule	Deliver Glucose or Nutrition solution	Blood sample collection (1-2 mL)									
Time (min):	-60	0	5	10	15	20	25	30	45	60	90	120

OGTT doses will be in a standard range of 1.7 g/kg for seeing a response in pigs within 2 hours^{52,53}. Blood will be collected in serum separation tubes and drawn from an indwelling marginal ear vein catheter. Blood glucose concentrations will be immediately measured from fresh blood samples using handheld glucometers. Serum samples will be analyzed using Amplex™ Red Glucose Assays after the experiment as a secondary confirmation of results. Relevant pharmacodynamic characteristics related to metabolic homeostasis will be assessed using LC-MS to measure serum levels of GLP-1, PYY, ghrelin, insulin, and GIP.

MMTTs will be used on lead formulations to assess barrier performance in the presence of diverse macronutrients. The protocol will follow the same procedure as the OGTT, but instead of a pure glucose solution, a nutrition solution (e.g. Ensure®) containing fat, cholesterol, carbohydrates, fiber, protein, minerals, and vitamins will be used. For these formulations, blood samples will be submitted for comprehensive chemistry, complete blood count, and nutrient panel tests for assessment of nutrient absorption and tolerability.

To conduct radiograph experiments, barium sulfate will be encapsulated into PDA particles to act as a contrast agent. For radiography, pigs will be administered GSEL capsules using the same process as for OGTTs: using an overtube with endoscopic guidance directly to the small intestines.

Terminal studies will be done with lead compositions and include tolerability assessments where intestinal tissue will be harvested for analyses. These tissues will be visually inspected by our veterinary consultant and then processed and sent for histological analyses to assess epithelial layer integrity and tissue toxicity.

Rigor: In vivo test results will be reported with fold-change of blood glucose concentration (or other analytes) vs time plots, t_{max} (time to peak concentration), and AUC (area under the curve). Serum samples will be analyzed in duplicate. Control groups will be untreated before the OGTT or MMTT. Prior to radiograph experiments, to ensure the inclusion of barium sulfate does not change GSEL formation, we will use Franz cell control experiments to confirm barrier function of barium sulfate-containing PDA particles. We will also conduct in vitro contact time control experiments where GSEL formulations are incubated on tissue for different amounts of time and then analyzed for film formation using fluorescence to ensure GSEL formation kinetics of barium sulfate-containing PDA particles are the same. A power analysis approach was taken to calculate the minimum sample size to assess effects of different formulations (alpha value <0.05).

Milestone:

Proprietary Info

Proprietary Info

Expected outcomes, risks, and alternative strategies: In this aim, we examine how delivery as a capsule may change GSEL performance because the delivery and spreading of solid GSEL is likely different compared to previous results from a liquid formulation. The primary variable to measure for this study is the blood glucose concentration after an OGTT or MMTT when administering GSEL capsules to pigs. Based on previous liquid formulation results, we would expect 2-3 one-gram capsules to achieve 15-25% reduction in blood glucose concentrations compared to the control. The secondary endpoints we will measure are post-prandial hormonal responses. We expect there to be an increase in post-prandial levels of GLP-1 and PYY as seen by patients who have undergone metabolic surgery like RYGB and a decrease in blood insulin levels. Variability in *in-situ* polymerization kinetics and tissue coverage across multiple different pigs will allow us to benchmark GSEL performance across possible patient-patient variability seen in future human patients. If the range of these metrics seen in tissue samples are such that the lower end of GSEL performance is well below 1 standard deviation of the average, we will draw from our library of formulations to use a formulation with less variability.

By choosing to use capsules, we have already limited the risk of solid dosage formation because the capsule chemistry and coating will be highly modular across commercially available products. If we observe that spreading of GSEL components is not efficient after delivery into the small intestines, we will consider using formulations that have slower polymerization rates (>30 minutes) to enable bulk flow from peristalsis of unreacted components. Since the goal of this Aim is to determine the proper coverage density of solid formulations, we may also consider the strategy of increasing the number of capsules and address the spreading properties in Phase II aims using tablets and super disintegrants.

While we do not anticipate challenges with the OGTT because our preliminary results illustrated that 1.7 g/kg dose of glucose creates a wide dynamic range when comparing GSEL containing groups to the control, we can lower the glucose dose if the GSEL capsule dose is less than what we previously observed. To mitigate the risk of solid GSEL formulations being unable to reach our barrier function criteria, we will alter the ratio and concentrations of polydopamine, dopamine, and hydrogen peroxide, as we have previously demonstrated that we can tune the barrier density and kinetics to optimize film formation in vivo⁵⁶.

3.3. Phase I -> II transition milestone

By the end of Phase I, we will have demonstrated barrier function in ex vivo and in vivo experiments using solid powder GSEL and solid capsule-filled formulations.

Proprietary Info

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Proprietary Info

3.4. Phase II Research Plan

The goal of Phase II is to prepare for the next steps of commercialization by engineering tablets and demonstrating barrier function in a beagle model. A beagle model is chosen because it is the best in vivo model to iterate through enterically-coated solid dosage formulations.

3.4.1 Phase II Specific Aim 1: Engineer tablets that stabilize components for 4 weeks, have the desired disintegration and dissolution properties, and optimize GSEL formation on ex vivo tissue. (12 months)

Strategy: This Aim will focus on generating a tablet that can stabilize components for at least 4 weeks and properly disintegrate and form GSEL on ex vivo tissue with the same level of blockade as Phase I lead candidates. Tablets are chosen due to downstream benefits related to manufacturing, stability, spreading of materials in vivo, and dosing.

Method and analysis: Using the results from Phase I Specific Aim 2, we will define critical tablet attributes needed for optimal GSEL formation and glucose barrier function. These attributes will include powder flow properties, kinetics of disintegration and dissolution, and area of spreading. Additional critical tablet attributes, such as compressibility, moisture resistance, and enteric coating chemistry will be evaluated by a powder flow rheometer, thermogravimetric analysis, and two-stage dissolution tests, respectively. Tablets will be made by Crystal Pharmatech (East Windsor, NJ) and they will use standard two-stage dissolution tests to assess disintegration and dissolution times under different physiologically relevant pHs. In these tests, tablets will be submerged in Fasted State Simulated Gastric Fluid (FaSSGF) and then Fasted State Simulated Intestinal Fluid (FaSSIF) and kinetics of disintegration and dissolution will be measured. Flow properties and excipients (such as glidants) will be evaluated to optimize the tablet formation process. Syntis will then assess disintegration and dissolution kinetics of the tablets on ex vivo small intestinal porcine tissue (Animal Biotech Industries). These ex vivo tests will also be critical to assess spreading behavior of GSEL when delivered as a tablet. In these tests, the tablet will be placed on resected small intestinal tissue and incubated for up to 60 minutes. To simulate dilution due to pockets of intestinal fluid⁵⁷, we will introduce 4-12 mL of FaSSIF on top of the tablet at an early timepoint (0-20 minutes). GSEL adhesiveness will be tested by undergoing an additional rinse step with FaSSIF as described by Phase I Specific Aim 1 and measuring the total area of coverage as determined visually by GSEL's black color (Figure 3.1.2). Functional performance of GSEL will be determined by mounting these treated tissues onto Franz cells and testing glucose permeability as described in Phase I Specific Aim 1. Stability of the components will be determined by evaluating GSEL formation kinetics, GSEL adhesiveness, and barrier function from tablets that have been stored for various amounts of time at room temperature or 4 °C. These metrics are all assessed by Syntis using the methods described above.

Animal Bridging and Justification: In anticipation for Phase II Specific Aim 2, we will also acquire small intestinal beagle tissue (BioChemed Services, Winchester VA) to quantify the differences in GSEL formation on porcine

versus beagle tissue. As mentioned previously, we optimize on porcine tissue in our ex vivo tests because the gastrointestinal tract of pigs is most like humans, so all the metrics and formulation-function relationships developed will be more directly applicable towards a future first-in-human study not part of this grant. However, beagles have more human-like gastric emptying times than pigs and are therefore used in optimizing tablets.

Rigor: For two-stage dissolution and disintegration tests, at least 5 replicates will be done to ensure statistical confidence in the kinetics. In the ex vivo tests, small intestinal porcine and dog tissue will be sourced from 4 male and female individual animals. Tissues will be cut into 10-20 pieces and randomized for all test groups to ensure there is no regional heterogeneity within a length of tissue. Statistical analysis will be done using one-way or two-way ANOVA, followed by a post-hoc analysis to compare specific groups.

Milestone:	Proprietary Info
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Proprietary Info

Expected outcomes, risks, and alternative strategies: We expect glidants and filler excipients such as silicon dioxide will be required to enable optimal powder flow and compressibility for tablet formation. Once these uncoated tablets are formed, we expect the disintegration and dissolution at pH 7.4 to happen faster because there is no capsule to dissolve. Upon coating with enteric coatings, we expect >45-minute stability at pH 2-4 and 10-30 minute disintegration and dissolution of GSEL components in a two-stage dissolution test (described above). We expect larger spreading of components because of the stored potential energy in creating a tablet.

One of the main risks we anticipate is the stability of urea hydrogen peroxide being insufficient for the 4-week stability target. We anticipate this risk because urea hydrogen peroxide is hygroscopic and may prematurely start reacting in the tablet during storage. We have several alternative strategies to mitigate this risk: (1) add additional desiccants to the storage containers, (2) create bilayer tablets to separate urea hydrogen peroxide from other components, and (3) encapsulate urea hydrogen peroxide in another matrix (e.g. polymer excipient matrix) before incorporating it with other GSEL components. Depending on the strategy used, we will either work with Crystal Pharmatech, or develop some in-house methods first (e.g. encapsulation of urea hydrogen peroxide in another matrix) prior to incorporation into the tablet.

Another risk is generating coated tablets that have the right two-stage dissolution properties for oral delivery. This risk is largely mitigated by tuning the enteric coating chemistry and tablet excipients; however, we could alternatively consider creating tablets-in-capsule dosage forms or mini-tablets within a capsule. These two alternatives will leverage capsules to achieve the desired two-stage dissolution metrics, while keeping the tissue spreading benefits of tablets. While we have the capability to hand-fill capsules for creating tablets-in-capsule or mini-tablets within capsule formulations, the mini tablets will need to be manufactured by Crystal Pharmatech.

3.4.2 Phase II Specific Aim 2: Optimize film formation, residency time, and barrier efficacy of GSEL tablets in a beagle model. (12 months)

Strategy: We will use beagle dogs (Cummings School of Veterinary Medicine) to determine the optimal tablet formulation for GSEL deposition, residency time, and barrier function. At this final stage, beagles are chosen over pigs because beagles are routinely trained for oral delivery of drugs and have a gastric residency time more like humans⁵⁸.

OGTTs will be used to quantify functional performance of different GSEL tablets by comparing the reduction of blood glucose concentrations when compared to the control. We will also measure serum levels of GLP-1, GIP, ghrelin, PYY, and insulin to assess postprandial metabolic homeostasis. Radiography will be done with GSEL compositions with barium-sulfate-encapsulated PDA particles to determine residency time of GSEL as described in Phase I Specific Aim 2.

Method and analysis: The primary objective of this Specific Aim is to optimize tablets in the beagle model to enable an orally delivered product. The metrics for barrier function will be defined by the percent of glucose reduction seen in pigs in Phase I Specific Aim 2, where delivery conditions were optimal because capsules were placed in the small intestines via endoscopy. A total of 12 beagles (6 male and 6 female to address Sex As a Biological Variable) weighing 8-12 kg will be used over 8 months for these studies with a two-week washout period between GSEL dosing. For radiograph tests, tablets formulated with PDA particles encapsulating barium sulfate will be delivered orally, and dogs will be anesthetized and imaged over 24 hours. Syntis will determine the area of coverage and time for excretion by using image analysis software (ImageJ) on the radiograph images.

For barrier function tests, tablets will be administered orally by feeding while beagles are awake after overnight fasting. Water will be withheld 1 hour prior to dosing. After feeding the tablet, a post-dose flush of 15 mL of water will be administered. After 1 hour, baseline blood will be taken and then glucose (1.7 g/kg) will be orally administered via gavage as a 50% solution for the OGTT. Blood will be taken over 2 hours via cephalic

venipuncture at 15-30 minute intervals. Blood glucose concentrations will be immediately measured using handheld glucometers and then collected into serum separation tubes for analysis by Syntis using Amplex™ Red Glucose Assays for secondary confirmation of results. Levels of GLP-1, GIP, ghrelin, PYY, and insulin will be measured using LC-MS.

In all in vivo experiments, the following variables will be evaluated: clinical variables (heart rate, appetite, lethargy), baseline blood glucose concentrations, blood glucose concentration following oral glucose administration, and body weight. Metabolic homeostasis will be evaluated by measuring serum levels of GLP-1, GIP, ghrelin, PYY, and insulin. Tolerability endpoints around water absorption and nutrients uptake will be assessed via stool quality, emesis, appetite, lethargy, and prolonged survival monitoring. We will work with our veterinary consultant and clinical consultant to analyze these data.

Rigor: The lead formulation testing will be repeated three times in different dogs. The controls will be untreated dogs. The area under the curve (AUC) of these data calculated using MATLAB will be a metric to compare the relative bioavailability of each group. The colony of 12 beagles was determined using a resource equation approach to calculate a minimum sample size to keep degrees of freedom to 10-20.

Proprietary Info

Expected outcomes, risks, and alternative strategies: Based on the data from Phase I Specific Aim 2, we expect to need 2-3 500 mg tablets to achieve 15-30% reduction in blood glucose concentrations compared to the control over the monitoring period. We anticipate that oral delivery will introduce two main risks: (1) the gastric emptying time may lead to premature tablet disintegration, and (2) upon reaching the small intestines, spreading behavior of the tablet is not optimal for barrier function.

For the first main risk, the mitigation will come from Phase II Specific Aim 1 results, where we will have developed several lead formulations with different enteric coating chemistries that demonstrate >40-minute dissolution times at pH 2-4. If none of those coatings work in vivo, we will consider a tablet-in-capsule or mini-tablets-in-capsule solid dosage form to leverage enteric protection of capsules, while keeping the spreading advantages of tablets. For the second main risk, there are two mitigation strategies. If it is a kinetics-driven problem due to the pH of gastric fluid reducing the local pH of the GSEL tablet during dissolution, we will adjust the buffer strength and ratio of components to increase GSEL formation kinetics. If it is a physical spreading problem, we will adjust tablet disintegrant excipients to increase spreading kinetics and spreading area.

If no barrier function is seen, we will leverage radiograph tests to investigate if the issue is density of coating or area of coating. These issues can be solved by increasing the overall dosage or adjusting the formulation for more optimal coating areas, respectively.

Next Steps: At the end of Phase II, we will have a formulated tablet, tablet manufacturing protocol, and demonstration of oral administration in beagles that prevents 15-30% glucose absorption over 1-3 hours. The next steps will be to finalize raw materials sourcing for GMP manufacturing, initiate GLP toxicity studies with a CRO, and finalize a clinical plan for a first-in-human study.

3.5. Timeline

PROGRAM TIMELINE	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Phase I												
Aim 1: Capsule optimization												
Aim 2: Capsule feasibility study												
Phase II												
Aim 1: Tablet engineering												
Aim 2: Oral delivery demonstration												

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *

☐ Yes

☒ No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

☐ Yes

☒ No

Is the Project Exempt from Federal regulations?

☐ Yes

☐ No

Exemption Number

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

Other Requested Information



Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

WHITE COAT
WASTE PROJECT



VERTEBRATE ANIMAL SECTION

1. Description of Procedures

Aim	Study	Species	Strain	Age	Sex	Total # Animals	Procedures
Phase I Specific Aim 2	Determine the density of coverage needed for barrier function after direct placement of GSEL capsules	Swine	Yorkshire Pig	4-9 months	M&F	8	Endoscopy, oral glucose tolerance test, blood collection, radiographs
Phase II Specific Aim 2	Optimize film formation, residency time, and glucose barrier function of GSEL tablets	Canine	Beagle	6-14 months	M&F	12	Blood collection, oral glucose tolerance test, radiographs

Phase I Specific Aim 2: A total of 8 (4 male 4 female to address Sex As a Biological Variable) Yorkshire pigs, weighing 40-80 kg each over 7 months and approximately 4-9 months of age will be used. Following routine preoperative fast, pigs are anesthetized and intubated and maintained on isoflurane anesthesia during the procedure. An endoscope guided overtube is placed into the small intestine to allow for safe delivery of GSEL or control capsules. 1 hour following administration of the test articles, a glucose solution will be administered to the small intestines via endoscope guided overtube. An indwelling marginal ear vein catheter will be inserted for blood collection, which will occur immediately after administration of the glucose solution over 2 hours. Blood will be immediately analyzed using handheld glucometers and then spun down in serum collection tubes. Serum will be isolated and frozen for additional analysis. Following collection of blood, the pigs will be removed from isoflurane and monitored until recovery. For radiograph experiments, pigs will be dosed with GSEL containing barium sulfate-encapsulated polydopamine particles and imaged over 24 hours (0, 0.5, 1, 2, 4, 6, 24 hours). Dose levels will be selected based off prior pharmacology and pharmacokinetics data of previous studies. Since all studies are survival studies, 8 pigs will allow for the most efficient number of experiments over 7 months and enable at least 10 experiments per pig.

A power analysis approach was taken to calculate the appropriate number of animals. Taking previous porcine results (mean and standard deviation), an alpha value of 0.05 would require a minimum of $n=3$ animals per group. The proposal of 8 pigs (4 male 4 female) is a sufficient sample size to assess the effects of different formulations.

Phase II Specific Aim 2: A total of 12 (6 male 6 female to address Sex As a Biological Variable) beagles, weighing 9-12 kg each over 12 months and approximately 6-14 months of age will be used. Dogs will be trained to swallow tablets and test articles will be administered orally following an overnight fast. Following dosing, 15 mL of saline will be administered as a post-dose flush using a syringe. 1 hour after administration, a glucose solution bolus will be given orally. Blood will be collected over 2 hours via the cephalic venipuncture. Blood will be immediately analyzed using handheld glucometers and then spun down in serum collection tubes. Serum will be isolated and frozen for additional analysis. Dose levels will be selected based off prior pharmacology and pharmacokinetic data on safe levels of dopamine infusions. This selection is to create an upper bound on the dose because we do not expect any free dopamine to diffuse into the blood stream given how GSEL forms. If any emesis is observed within 40 minutes, the dog will not be bled and will be monitored for adverse effects. For radiograph experiments, dogs will be anesthetized and imaged after being administered GSEL formulations containing barium sulfate-encapsulated polydopamine particles. Over 12 months, 12 dogs will allow for at least 24 experiments per dog.

Since existing beagle data does not exist for GSEL, a resource equation approach was used to determine appropriate sample sizes. Using this approach, the minimum sample size to keep the degrees of freedom to 10-20 is 6 animals per group for a total sample size of 12. Given this number, the colony of 12 beagles is planned.

2. Justifications

Phase I Specific Aim 2: The purpose of this study is to determine the optimal GSEL coverage needed for glucose barrier function. Swine are critical to use because the size of the gastrointestinal tract allows for direct delivery of materials to the small intestines. Furthermore, swine have similar physiological and anatomical

gastrointestinal characteristics compared to humans, making them an ideal model for these studies. While our *ex vivo* models can recapitulate formation of GSEL, they are unable to capture the full dynamic physiological environment (e.g. peristalsis, catalase activity, microbial activity, etc.). Moreover, a literature search of benchtop models of the gastrointestinal environment demonstrates that *in vitro* to *in vivo* translation is not predictive, not to mention the confounding factor of how physiology of an animal model might affect GSEL formation. Lastly, pigs provide the optimal animal model to directly place capsules into the small intestines, therefore bypassing the stomach and allowing us to isolate effects of compositional changes on GSEL distribution and function. For all these reasons, we have chosen pigs for this Aim and have chosen the minimum number of pigs that would allow for efficient use of the animals while providing the necessary experimental data.

Justification for Canine Model: The purpose of using a canine model is to enable testing of orally administered solid dosage formulations in anticipation of optimizing tablet coatings to bypass the acidic pH of the stomach. Pigs are the best model for human gastrointestinal function, which is why we use pigs in Phase I to establish feasibility of the product. However, for solid dosage form optimization, pigs are non-optimal because their gastric emptying time is highly variable spanning 0.25-28 days compared to the human gastric emptying time of 0.25-2 hours. Beagles fill this gap by having gastric emptying times of 0.5-1 hours. Moreover, beagles can be trained to swallow solid dosage forms without chewing, whereas pigs would likely require anesthesia for endoscope-guided placement of the solid dosage form in the stomach. For these reasons, canines are the more relevant animal model for Phase II, where the goal is to engineer and optimize a solid dosage form.

Phase II Specific Aim 2: The purpose of this study is to iterate on tablet compositions to optimize GSEL formation, residency time, and glucose barrier efficacy. For this Aim, we will iterate on tablet coatings to enable stable passage through the stomach. Consequently, dogs are the ideal animal model because the gastric emptying times are comparable to humans, whereas pigs have a prohibitively long gastric emptying time. Furthermore, dogs can be trained to orally ingest tablets, precluding the need for endoscopy and anesthesia. While our benchtop assays using simulated gastric fluid may aid in tablet engineering, there is no benchtop model that can sufficiently test the delivery, formation, and function of GSEL tablets. For all these reasons, beagle dogs are the optimal model for this Aim and we have chosen the minimum number of dogs that would allow for efficient use of the animals while providing the necessary experimental data.

3. Minimization of Pain and Distress

This study will comply with all appropriate parts of the Animal Welfare Act Regulations: 9 CFR Parts 1, 2 and 3. All procedures are expected to cause minimal, momentary, or no pain or distress. All formulations are comprised of known components delivered at concentrations known to be non-toxic. Blood collection procedures are executed by trained staff to minimize trauma. For the pigs, if blood cannot be collected from an indwelling catheter, samples may be taken from the pigs' ear using a lance.

As stated in Tufts' Corporate Policy on Animal Welfare and the Humane Treatment of Animals, prior to study start, each study protocol and corresponding animal use proposal is submitted to the site Institutional Animal Care and Use Committee (IACUC) for review and approval. In studies where there is potential for pain and/or distress from either test material administration and/or procedures, humane endpoints (the criteria to end experimental studies earlier to avoid or terminate unrelieved pain and/or distress) will be employed whenever possible. The use of humane endpoints is a key component of refinement of animal studies. Study Directors and other professional personnel conducting studies should use the earliest possible endpoint that will satisfy the scientific objectives of a study while minimizing potential negative effects on the well-being of the research animals involved. A team consisting of the veterinary staff, study director, and sponsor is involved in making these decisions. Whenever possible, these decisions are based on prior agreements with the study director and sponsor and are reflected in the animal use proposal. Identification of early humane endpoints in advance can lead to more timely intervention when serious adverse effects are seen.

All animals will be monitored closely for signs of toxicity and/or recovery. Each animal will be observed for mortality, inappetence, abdominal guarding, fever, diarrhea, mobility, hunched posture, weight loss, any abnormalities, and signs of pain and distress at least once daily (nominally twice daily during the normal work week and once on weekends and holidays). Examinations can include evaluation of external surface areas (visual inspection and palpation) for detectable "masses", orifices, and excretory products. During the examination, animals could also be observed for common signs relating to neurological effects, including, but not limited to, piloerection, respiratory abnormalities, posture, involuntary motor movements (clonic or tonic), stereotypy, bizarre behavior, gait abnormalities, and vocalizations. Abnormal findings or an indication of normal will be recorded and scored to determine if the animal will recover or rebound. In the event adverse reactions

indicate pain or distress (e.g. infection, respiratory distress, failure to eat, hunched, scruffy), the study director, a veterinarian, and if possible, the sponsor will be contacted promptly.

The following are examples of supportive care that may be utilized as needed: a towel/blanket, dosing holiday, supplemental water source, fluid therapy, provision of supplemental heat, supplemental feed, and feed regimen changes.

The animals will be treated or euthanized, based upon their specific circumstances, according to the professional judgment of a veterinarian in consultation with the study director and sponsor will be notified. Animals experiencing severe or chronic pain/distress that cannot be relieved will be humanely euthanized.

4. Euthanasia

All animals will be euthanized by methods that comply with the 2020 AVMA Guidelines on Euthanasia and that are species appropriate and consistent with study objectives. Animals will be anesthetized prior to euthanasia. An IV injection of pentobarbital-based euthanasia solution such as Euthasol will be used. Euthasol contains 390 mg/mL pentobarbital and 50 mg/mL phenytoin so that 1 mL/10 lbs equates to 86 mg/kg pentobarbital and 11 mg/kg phenytoin and is administered as a dose of 1 mL/5 kg to effect.



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Resource Sharing Plan

Syntis recognizes that promising new materials, methods, reagents and technologies may arise during the course of the proposed research. We agree to abide by the principles for sharing research resources as described by the *Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources* issued in December, 1999 and revised December, 2021.

The proposed research aims to generate data sets including in situ polymerization kinetics of GSEL formation in vivo, proprietary GSEL solid dosage formulations and manufacturing processes, and GSEL glucose blocking performance data derived from ex vivo permeability assays and in vivo postprandial glucose testing. These datasets consist of proprietary and confidential information that will be the basis for obtaining future funding towards the next stage in drug development. The company has networked data servers that allow for appropriate control of data quality and distribution in accordance with federal policies. These are state-of-the-art systems that include automatic back-up protection.

Syntis plans to file patent applications on this dataset in order to protect the company's intellectual property position. We then plan to publish the work in respected peer-reviewed journals in order to disseminate the information to the broader scientific community.

In addition, company representatives will present the findings at scientific conferences. Data sharing prior to patent filing may be delayed for 30-60 days to allow for time to prepare and file the application to protect the company's rights to the invention.

For each publication that results from this grant, research, an acknowledgment of NIH grant support will be included. Information on each publication resulting from this work will be included in the annual and/or final progress report submitted to the NIH awarding office.

For unpatented methods or reagents developed during this award, **Syntis** will allow access under an appropriate material transfer agreement (MTA). Material transfers will be made with no more restrictive terms than in the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach through requirements. Should any intellectual property arise which requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with the NIH *Principles and Guidelines* document.



NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.



Authentication of Key Biological and/or Chemical Resources

The following methods will be used to ensure the identity and validity of the key biological and chemical resources used in the proposed studies:

- All MSDS, product fact sheets, certificates of analysis, and compound information/specification sheets are kept in a central location in the laboratory and can be referred to at any time
- Authentication data will be assessed with each product to ensure that the information from the vendor meets the needs of the user. If not, then the vendor will be contacted to obtain the necessary information before proceeding with the experiment.
- Manufacturer/source, catalog number and lot numbers of all reagents are noted in the relevant laboratory notebook.
- All acquired compounds and reagents will be authenticated for both identity and purity using standard techniques and methods for the characterization of small molecules according to the guidelines of the American Chemical Society. Experimental techniques employed routinely in the lab for the authentication of chemicals could include NMR, EPR, and UV-visible absorption spectroscopy, mass spectrometry, X-ray diffraction analysis, cyclic voltammetry, magnetometry, and combustion analysis.
- Reagents are aliquoted and stored according to manufacturer's specifications such that they are stable and retain function/activity.
- Reagents/test compounds will be aliquoted into single use tubes, and a new tube will be used for each assay to avoid any loss of activity between assays.
- Proper control compounds, conditions and/or reagents will be used in all experiments and replicates so as to repeat data that was obtained previously.
- In-house methods will be authenticated using these control compounds prior to performing an experiment.

Experimental design

- Proper control compounds, conditions, and/or reagents will be used in all experiments and replicates so as to compare to data that was obtained previously.
- Study designs will include sample collections to allow for validation endpoints as required.
- When possible, materials from the same production lot will be utilized.

Polydopamine Particles

- Batch records will verify particle identity and quality upon receipt from manufacturer.
- For internally synthesized polydopamine nanoparticles, spectroscopy will be used to authenticate and evaluate particle quality (hydrodynamic radius, polydispersity, % unreacted monomer).
- Optical microscopy methods will be used to validate nanoparticle morphology.

Animal Tissue

- Batch records will be inspected for all ex vivo tissue to validate the identity of the specimen as well as verify its timely collection and integrity.

Animals

- Authenticity of all in vivo pig and dog species used will be verified through documentation provided by Tufts University Cummings School of Veterinary Medicine. This documentation may include but is not limited to animal health records, chain of custody documentation, animal welfare records.