Dietary Soy Isoflavones in Chronic Pancreatitis

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Research Plan. Study Design/ Overview. (See Figure 1: Flow Diagram, Appendix)
Specific Aim 1: To evaluate the compliance and tolerability of soy bread in patients with chronic pancreatitis enrolled in a Phase I dose escalation clinical trial. A single group, open-labeled *dose escalation study* of soy bread intervention will be conducted in patients with chronic pancreatitis. We hypothesize that the soy bread formulation will be well-tolerated with high compliance in CP patients. This study will be guided by dosing from prior clinical experience with this soy bread in patients with prostate cancer. The use of bread as a food-based delivery vehicle is advantageous as compared to administration of a supplement as it provides the opportunity for delivery of multiple complex bioactive agents in an appropriate matrix. This is the first study designed to determine the Grade 1 and 2 toxicities, (Dose Limiting Toxicities (DLTs), compliance and tolerability of soy bread in human chronic pancreatitis. Once the Maximum Tolerated Dose (MTD) or target dose is reached, 10 subjects will undergo a 4 week *verification study* [Section b, below] to confirm tolerance and safety. Overall, this small clinical trial will provide the necessary clinical data required to move this intervention forward in the setting of a future placebo controlled trial for patients with CP. In addition, it will provide us with valuable biologic material to assess changes in inflammatory biomarkers relevant to CP and to facilitate future study of individual differences in soy isoflavone metabolism within this patient population.

a. Dose Escalation Phase. (n=15-25 CP subjects) This dose escalation study of soy isoflavones will enroll chronic pancreatitis patients from a single academic medical center in Columbus, Ohio. All participants will be informed about the study and potential risks and required to provide written informed consent prior to undergoing study-related procedures. Here a traditional 3+3 design will be used to determine the compliance, tolerability and dose limiting toxicities in this unique patient population. [Table 1: Dose Escalation; Appendix] Dose escalation with soy bread will be continued until dose-limiting toxicities are observed in >33% of the participants or the daily target dose of 4 slices of bread [132 mg soy isoflavone] is reached. [Table 2: Toxicity Grades; see Appendix].

Subject Enrollment. Successive cohorts of patients (3 patients / cohort) will be started on a fixed dose of 33 mg isoflavones (IF) for this study [1 slice of soy bread; 33 mg isoflavones/85 gram slice] for 1 week. CP patients will be accrued in cohorts of 3 and dose escalation will be increased by 1 slice of bread in each successive cohort based on a modified Fibonacci sequence: 50% [2 slices; 66 mg IF], 33% [3 slices; 99 mg IF], 25% [4 slices; 132 mg IF] in which dose increments become gradually lowered until the target of 4 slices of bread or a MTD is determined. Subjects will be enrolled in the study for 7 days and will be seen in the clinic on Day 0 and Day 7. After enrollment (Day 0) subjects will start a legume free diet through the completion of their enrollment (Day 7).

An estimated 15-25 CP patients will be needed for this initial dose escalation phase.

Monitoring. Subjects will be monitored for toxicities defined based on type(s), grade(s) and duration (s) of symptoms using a daily diary that will be reviewed by study staff *before* and *after* each dose escalation. Toxicities will be graded using the Common Toxicity Criteria Version 3.0 (CTC 3.0). If the CTC 3.0 did not apply to an adverse event, it will be graded as mild, moderate or severe. DLT will be defined as any CTC 3.0 Grade 3 or 4 adverse event determined to be related to the soy bread. Our prior experience in prostate cancer patients indicates Grade 1-2 GI discomfort as primary adverse events following bread consumption.

If no DLTs are observed for 1 week after administration of soy bread, a new cohort will be enrolled at the next planned dose level. If DLTs are observed in one participant in the cohort, another three participants will be treated with the same dose level. The maximum tolerated dose (MTD) will be defined as one dose level below the dose in which DLTs were observed in >33% of the participants who are at least 80% adherent to the soy bread intervention, as evidenced by the number of empty packets received. In other words if DLTs are observed in a least 2 of 3 participants, the MTD will be determined to be the dose administered to the previous cohort. Similarly, in a cohort of 6 participants, 3 of the 6 participants would have to experience DLTs to determine the MTD.

Data collection. Subjects will be seen in clinic on Day 0 and at the end of the study on Day 7. A physical exam, vital signs, a blood draw to assess complete blood count with differential, cytokines, and comprehensive metabolic profile, and a urinalysis, will be completed at both of these visits. Blood and Urine will be collected and stored at -80C to complete batch testing. Urine isoflavones and their metabolites will also be analyzed from the urine collected at enrollment.

Subjects will be given a container to collect a urine sample starting at 24 hours prior to Day 7 (Day 6) and ending with the urine collected the morning of their Day 7 clinic visit. The subject will bring the sample with them to their visit for urine isoflavones analysis.

Symptoms, toxicity, compliance, and acceptance of the soy bread will be assessed ***before*** and ***after*** each dose escalation and maintained in a secure case report form. Soy bread tolerability, a diet record, and consumer acceptance will be measured throughout the subject's enrollment via a booklet and maintained in a secure case report form.

Dietary compliance: Adherence to the soy bread diet and legume restriction will be measured using daily diary entries (see DEG phase I SMc Appendix) as well as a count of empty packets returned. Additionally, isoflavones in the urine will be used to verify the subject's self-reported compliance. A detailed list of foods to avoid for the legume restricted (peas, beans, soy, sprouts, and foods made with these items as well as peanut butter limited to 1 tablespoon/week) diet will be provided. We have developed a checklist of the most common food sources of isoflavone-rich foods based on the USDA Isoflavone Database (release 2.0, September 2008) which will be included in the daily dairy. Subjects will be instructed on the proper storage, handling, and consumption of the soy bread slices (see Soy Bread Instruction Appendix).

Three day diet record: Subjects will be instructed by the research team with detailed instructions of how to approximate food quantities and record all foods and beverages consumed for three days during a given week. The three days will be assigned by the study coordinator (typically two weekdays and one weekend day). Each participant will be provided with an instruction booklet (see DEG phase I SMc Appendix) and examples of data collection. When subjects return for their visit, the study coordinator will review the three day diet record with the participant to ensure thoroughness and resolve any ambiguities. Subjects enrolled in this group will complete this one time over 3 days during their enrollment. The dietary records will be used to assess compliance to the legume restricted diet and analyzed using the Nutrition Data System for Research (NDS-R; University of Minnesota, Minneapolis, MN).

Soy bread tolerability and consumer acceptance: Soy bread tolerability and consumer acceptance will be measured using the sensory evaluation questionnaire and visual analogue scale to determine satiety. This will be completed at least once a day.

b. MTD Verification Phase (n= up to 10). After the Phase I study has been completed, an additional 10 chronic pancreatitis patients will then be treated at the best tolerated dose for 4 weeks to further verify safety and toxicity.

Subject Enrollment: Subject enrollment will begin 14 days prior to the start of eating the soy bread. Total enrollment time for this group is 6 weeks. During the first two weeks of enrollment subjects will undergo a legume-free washout period and will be asked to refrain from eating legumes during this time. Subjects will continue the legume free diet until they complete the study (total of 6 weeks). Subjects enrolled in this phase will be asked to stop any multivitamins that they are taking and all will be asked to start a multivitamin with a mineral supplement (MVI) each day. This multivitamin with mineral supplement will be provided to the subjects enrolled in this phase for consistency.

Data Collection: Data and bio-specimen collection will be obtained at enrollment, when they start eating the soy bread and then weekly through the end of the study. Subjects will be seen in clinic at enrollment (Day -14), when they start eating the soy bread (Day 0), Week 1, Week 2, Week 3, and at the end of the study on Week 4. A physical exam and vital signs will be completed at each of these visits. A blood draw for complete blood count with differential, cytokines testing, comprehensive metabolic profile will be completed at Day 0 and Week 4. A urinalysis will be completed weekly starting with Week 0 and ending with Week 4.

Subjects will be given a container at Day -14 to collect a urine sample starting at 24 hours prior to Day 0 and ending with the urine collected the morning of the Day 0 visit. The subject will bring the sample with them to their Week 0 visit. They will also be given a container at Week 3 visit to collect a urine sample starting at 24 hours prior to their last study visit (Week 4 visit) and ending with the urine collected the morning of the Week 4 visit. Urine isoflavones and their metabolites will be analyzed with this urine collection.

Dietary adherence: Adherence and tolerability to the soy bread diet and legume restriction will be measured using daily diary entries, sensory evaluation questionnaire, and visual analogue scale measuring the subject's satiety (see MTD Phase II SMc Appendix) as well as count of empty packets returned. Additionally, isoflavones and their metabolites in the urine will be used to verify the subject's self-reported adherence. A detailed list of foods to avoid for the legume restricted (peas, beans, soy, sprouts, and foods made with these items as well as peanut butter limited to 1 tablespoon/week) diet will be provided. We have developed a checklist of the most common food sources of isoflavone-rich foods based on the USDA Isoflavone Database (release 2.0, September 2008) which will be included in the daily dairy, Appendix. Subjects will be instructed on the proper storage, handling, and consumption of the soy bread slices, Appendix.

Three day diet record Subjects will be instructed by the research team with detailed instructions of how to approximate food quantities and record all foods and beverages consumed for three days during a given week. The three days will be integrated into the booklets (see MTD Phase II SMc Appendix) provided. Each participant will be given written instructions and examples of diet record data collection. When subjects return for their visit, the study coordinator will review the three day diet record with the participant to ensure thoroughness and resolve any ambiguities. Two 3 day diet records will be administered in the MTD phase, once between enrollment (Day -14) and Day 0 and once between Week 3 and Week 4. The dietary records will be used to assess compliance to the legume restricted diet and analyzed using the Nutrition Data System for Research (NDS-R; University of Minnesota, Minneapolis, MN).

Soy bread tolerability and consumer acceptance: Soy bread tolerability and consumer acceptance will be measured using the sensory evaluation questionnaire and visual analogue scale to determine satiety. This will be completed at least once a day while subjects are eating the bread.

Sensory testing of soy breads will be used to assess the acceptance and physical characteristics of the soy bread and will be conducted during the first day of soy bread consumption. The information gained will be used to assess the effects of soy bread consumer acceptance (liking) to soy bread. In our previous studies, acceptance of the soy bread was excellent surrogate measures of adherence. Overall acceptance of the soy bread will be conducted using a nine point hedonic scale (1=dislike extremely to 9=like extremely) whereas a five point Just About Right (JAR) scale (1=much too little to 5=much too much) will be used to optimize the soy bread formulation for future trials with this cohort, Appendix. Descriptive analysis will be used to characterize the organoleptic qualities (saltiness, sweetness, beaniness, hardness, and brown color) of the soy bread. A horizontal line scale (6 inch) ranging from 1 to 10 will be used to measure the intensity of each attribute. At the last clinic appointment (week 4) general consumer questions regarding the soy bread will be collected.

The satiety scale will determine the subjects hunger levels after they eat the bread. Measures of satiety (perceived fullness or lack of hunger) will be conducted using visual analogue scale (VAS) adapted from Hill and Blundell (1983)[41] and will be used to examine the impact of satiety on soy bread compliance. Subjects will be asked to rate their satiety (hunger, fullness, satisfaction, and thoughts of food) as well rate their nausea, thirst, and energy. VAS will be completed prior to the first slice of soy bread consumed and immediately after bread consumption, 240 minutes after consumption of the soy bread as well as before going to bed.

Isoflavone Metabolism and Adherence to Soy Bread Intervention Patients with pancreatitis may have altered metabolism which can cause significant changes in glycated hemoglobin. HbA1c and is often times closely monitored in these patients. Advanced glycation end products as well as individual differences in activity, nutritional status, and smoking have shown to affect isoflavone metabolism and expression of novel isoflavone metabolites[42 43]. For these reasons, subjects most recent HbA1c will be recorded. This HbA1c may be completed prior to enrollment in the study or after as their standard medical treatment for Chronic Pancreatitis. Furthermore, factors such as activity level, nutritional status, and smoking affect the absorption and metabolism of isoflavones within and among individuals and over time their biological activity[44]. Therefore a standardized vitamin will be provided to participants in the MTD phase of the study as well daily activity and daily exposure to smoking will be monitored.

Specific Aim 2: To determine the effect of soy bread intervention on pro-inflammatory cytokine expression in serum and urine from patients with chronic pancreatitis. Cytokine and lipid biomarkers relevant to inflammation will be assessed at baseline and following soy bread intervention in patients' serum and urine. We hypothesize that dietary soy will be associated with reduced levels of key pro-inflammatory cytokines that drive the pathogenesis of CP including IL-6, CRP, IL-1β and TNF-α, among others

Blood sampling. At enrollment, patients will present for a blood draw at the Outpatient Clinic. In addition to standard-of-care blood work ordered by the physician, a phlebotomist will collect another 30 ml (1 ounce) into sodium-heparin Vacutainer tubes (Fisher) and a clean catch urine sample for our study. Blood and urine will be immediately processed, and stored at -80°C for analyses. The same procedure will be used on 1 subsequent visit at the end of study, for a total

of two blood draws to monitor changes in cytokine profile over time. *Cytokine biomarkers will be assessed at [1] Baseline and [2] upon completion of the study.*

Immune Biomarkers. Studies investigating the effect of dietary soy on immune parameters in patients with CP are non-existent. This trial will fill a critical gap in understanding how dietary soy affects key biomarkers of inflammation in CP patients. Blood from patients will be processed via centrifugation with ficoll-paque. Our primary objective will be to assess the change in three pro-inflammatory cytokines (IL-6, CRP, IL-1β) known to be important in the pathogenesis of pancreatitis via a Luminex-based assay (Affymetrix). However, our high-throughput analytical platform will allow for an assessment of other factors that regulate inflammatory processes including: [1] inflammatory cell mobilization expansion: G-CSF, GM-CSF; [2] inflammatory cell trafficking: IP-10, MCP-1, M-CSF, MIG, RANTES, SDF-1; [3] Th1-type CD4+ T cell responses: IFN-γ, IL-1β, TNF-α; [4] Th2 or Th17-type CD4+ T cell responses: IL-4, IL-6, IL-10, IL-17; [5] Other measureable factors relevant to inflammation as they relate to pancreatic carcinogenesis: IL-11, IL-13, TGFβ, PGE_2, HMGB1. Sufficient volume of samples will also be available for validation by a second method in the event interesting trends are observed (i.e. ELISA). All samples will be analyzed in a batched manner to assess changes across the four individual time points per each patient. These data will provide us with a comprehensive understanding of how dietary soy alters the expression of soluble factors implicated in inflammatory processes.

Lipid Biomarkers Pro-inflammatory markers from adipose (adiponectin, leptin, and resistin) and lipid metabolism (triglycerides, total cholesterol, LDL, HDL) will be collected for subjects enrolled in the MTD group at enrollment (Day 0) and at the end of study visit (Week 4), as they are related to pancreatitis and soy exposure. This will be obtained from blood collected after a 12 hour fast. One serum separator (10 mL) will be collected for these analyses. Serum lipids (total cholesterol, HDL, LDL, triglycerides, adipokines, and leptin) will be batch analyzed by the CRC Core Laboratory using Dimension Xpand Clinical Chemistry analyzer or Immulite 1000 (Siemens Medical Diagnostics, Decatur, GA.).

Conclusion. We have assembled a multi-disciplinary research team to assess compliance, toxicity and changes in pro-inflammatory cytokine expression from a soy based dietary bread product using a classic 3+3 dose escalation study design in subjects with chronic pancreatitis. This novel non-pharmacologic intervention has a high likelihood of being tolerable and safe in patients with chronic pancreatitis and in down-regulating the pro-inflammatory cytokine cascades that drives the pathobiology of this debilitating illness.

References

1. Peery, A.F., et al., *Burden of gastrointestinal disease in the United States: 2012 update.* Gastroenterology, 2012. **143**(5): p. 1179-87 e1-3.
2. Steer, M.L., I. Waxman, and S. Freedman, *Chronic pancreatitis.* N Engl J Med, 1995. **332**(22): p. 1482-90.
3. Maule, W.F., *Chronic pancreatitis.* N Engl J Med, 1995. **333**(18): p. 1221.
4. Yadav, D. and A.B. Lowenfels, *The epidemiology of pancreatitis and pancreatic cancer.* Gastroenterology, 2013. **144**(6): p. 1252-61.
5. Whitcomb, D.C., et al., *Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2).* Pancreatology, 2008. **8**(4-5): p. 520-31.
6. Whitcomb, D.C., *What is personalized medicine and what should it replace?* Nat Rev Gastroenterol Hepatol, 2012. **9**(7): p. 418-24.

7. Talukdar, R. and R.K. Tandon, *Pancreatic stellate cells: new target in the treatment of chronic pancreatitis.* J Gastroenterol Hepatol, 2008. **23**(1): p. 34-41.
8. Sikkens, E.C., et al., *The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis.* Pancreatology, 2013. **13**(3): p. 238-42.
9. Tignor, A.S., et al., *High prevalence of low-trauma fracture in chronic pancreatitis.* Am J Gastroenterol, 2010. **105**(12): p. 2680-6.
10. Rickels, M.R., et al., *Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: Recommendations from PancreasFest 2012.* Pancreatology, 2013. **13**(4): p. 336-42.
11. Yadav, D., et al., *Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis.* Arch Intern Med, 2009. **169**(11): p. 1035-45.
12. Lowenfels, A.B., P. Maisonneuve, and P.G. Lankisch, *Chronic pancreatitis and other risk factors for pancreatic cancer.* Gastroenterol Clin North Am, 1999. **28**(3): p. 673-85, x.
13. Gold, E.B. and J.L. Cameron, *Chronic pancreatitis and pancreatic cancer.* N Engl J Med, 1993. **328**(20): p. 1485-6.
14. Rebours, V., et al., *The natural history of hereditary pancreatitis: a national series.* Gut, 2009. **58**(1): p. 97-103.
15. Pandol, S., et al., *Epidemiology, risk factors, and the promotion of pancreatic cancer: role of the stellate cell.* J Gastroenterol Hepatol, 2012. **27 Suppl 2**: p. 127-34.
16. Apte, M.V. and J.S. Wilson, *Stellate cell activation in alcoholic pancreatitis.* Pancreas, 2003. **27**(4): p. 316-20.
17. Masamune, A., et al., *Fibrinogen induces cytokine and collagen production in pancreatic stellate cells.* Gut, 2009. **58**(4): p. 550-9.
18. Hisada, S., et al., *Peroxisome proliferator-activated receptor gamma ligand prevents the development of chronic pancreatitis through modulating NF-kappaB-dependent proinflammatory cytokine production and pancreatic stellate cell activation.* Rocz Akad Med Bialymst, 2005. **50**: p. 142-7.
19. Logsdon, C.D. and B. Ji, *Ras activity in acinar cells links chronic pancreatitis and pancreatic cancer.* Clin Gastroenterol Hepatol, 2009. **7**(11 Suppl): p. S40-3.
20. Stimac, D., et al., *Prognostic values of IL-6, IL-8, and IL-10 in acute pancreatitis.* J Clin Gastroenterol, 2006. **40**(3): p. 209-12.
21. Khanna, A.K., et al., *Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis.* HPB Surg, 2013. **2013**: p. 367581.
22. Pooran, N., et al., *Cytokines (IL-6, IL-8, TNF): early and reliable predictors of severe acute pancreatitis.* J Clin Gastroenterol, 2003. **37**(3): p. 263-6.
23. Chen, J. and X.F. Huang, *Interleukin-6 promotes carcinogenesis through multiple signal pathways. Comment on: Clinical significance of interleukin-6 gene polymorphism and IL-6 serum level in pancreatic adenocarcinoma and chronic pancreatitis.* Dig Dis Sci, 2009. **54**(6): p. 1373-4.
24. Mroczko, B., et al., *Diagnostic usefulness of serum interleukin 6 (IL-6) and C-reactive protein (CRP) in the differentiation between pancreatic cancer and chronic pancreatitis.* J Clin Lab Anal, 2010. **24**(4): p. 256-61.
25. Zhang, H., et al., *IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality.* J Clin Invest, 2013. **123**(3): p. 1019-31.
26. Clayton, H., et al., *Anti-TNF Therapy in the Treatment of Psoriasis in a Patient with Acute-on-Chronic Pancreatitis.* Dermatology, 2013. **227**(3): p. 193-6.
27. Mace, T.A., M. Bloomston, and G.B. Lesinski, *Pancreatic cancer-associated stellate cells: A viable target for reducing immunosuppression in the tumor microenvironment.* Oncoimmunology, 2013. **2**(7): p. e24891.

28. Nicholas, C. and G.B. Lesinski, *Immunomodulatory cytokines as therapeutic agents for melanoma.* Immunotherapy, 2011. **3**(5): p. 673-90.
29. Droke, E.A., et al., *Soy isoflavones avert chronic inflammation-induced bone loss and vascular disease.* J Inflamm (Lond), 2007. **4**: p. 17.
30. Llaneza, P., et al., *Soy isoflavones, diet and physical exercise modify serum cytokines in healthy obese postmenopausal women.* Phytomedicine, 2011. **18**(4): p. 245-50.
31. Tovar, A.R., et al., *A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome.* J Nutr, 2002. **132**(9): p. 2562-9.
32. Fanti, P., et al., *Positive effect of dietary soy in ESRD patients with systemic inflammation--correlation between blood levels of the soy isoflavones and the acute-phase reactants.* Nephrol Dial Transplant, 2006. **21**(8): p. 2239-46.
33. Messina, M., S. Ho, and D.L. Alekel, *Skeletal benefits of soy isoflavones: a review of the clinical trial and epidemiologic data.* Curr Opin Clin Nutr Metab Care, 2004. **7**(6): p. 649-58.
34. Messina, M.J., et al., *Soy intake and cancer risk: a review of the in vitro and in vivo data.* Nutr Cancer, 1994. **21**(2): p. 113-31.
35. Borzan, J., et al., *Effects of soy diet on inflammation-induced primary and secondary hyperalgesia in rat.* Eur J Pain, 2010. **14**(8): p. 792-8.
36. Messina, M.J., *Emerging evidence on the role of soy in reducing prostate cancer risk.* Nutr Rev, 2003. **61**(4): p. 117-31.
37. Hsu, A., et al., *Dietary soy and tea mitigate chronic inflammation and prostate cancer via NFkappaB pathway in the Noble rat model.* J Nutr Biochem, 2011. **22**(5): p. 502-10.
38. Messina, M., C. Nagata, and A.H. Wu, *Estimated Asian adult soy protein and isoflavone intakes.* Nutr Cancer, 2006. **55**(1): p. 1-12.
39. Franke, A.A., et al., *Liquid chromatographic-photodiode array mass spectrometric analysis of dietary phytoestrogens from human urine and blood.* J Chromatogr B Analyt Technol Biomed Life Sci, 2002. **777**(1-2): p. 45-59.
40. Busby, M.G., et al., *Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men.* Am J Clin Nutr, 2002. **75**(1): p. 126-36.
41. Hill, A.J. and Blundell, J.E. *Nutrients and behaviour: research strategies for the investigation of taste characteristics, food preferences, hunger sensations and eating patterns in man*. J Psychiatr Res 1983.**17**: p 203-12.

42. Xie et al. Glycation of plasma proteins in type II diabetes lowers the non-covalent interaction affinities for dietary polyphenols. Integr Biol 2012. **4**: p.502-7
43. Lebon et al *Additive effects of isoflavones and exercise training on inflammatory cytokines and body composition in overweight and obese postmenopausal women: a randomized controlled trial*. Menopause 2012:21(8):p.869-75
44. Hoshida et al *Different effects of isoflavones on vascular function in premenopausal and postmenopausal smokers and nonsmokers: NYMPH study.* Heart Vessels 2011. **26**(6):p.590-9
45. Ahn-Jarvis, J.H., et al. *Impact of food matrix on isoflavone metabolism and cardiovascular biomarkers in adults with hypercholesterolemia*. Food Funct 2012. **3**: p.1051-8.

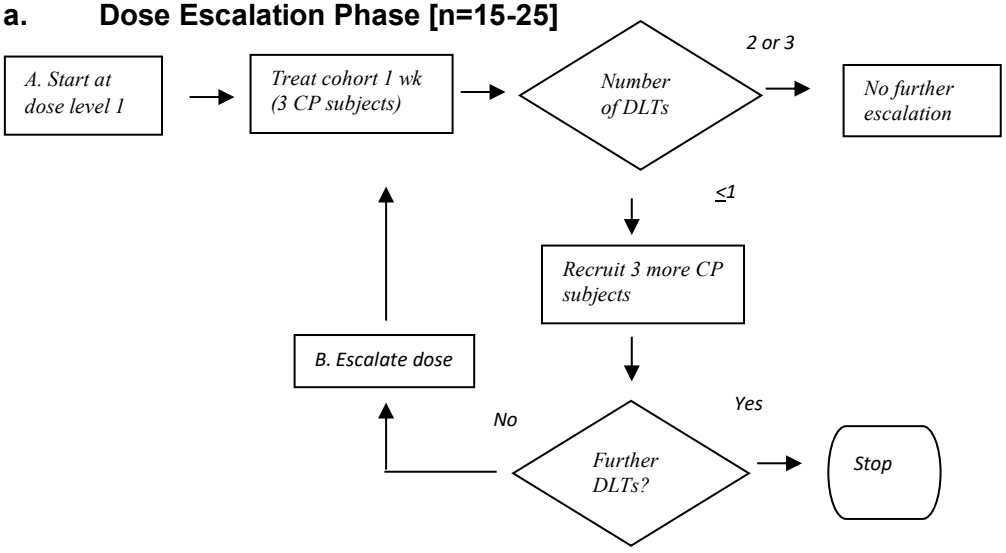
Budget – uploaded

D. Other Support – uploaded
E. IRB Approval Letter – pending submission
F. Conflict of Interest – uploaded
G. Curriculum Vitae – uploaded
H. Supporting Letters - uploaded

I.Appendix

Figure 1: Study Flow Diagram

a. Dose Escalation Phase [n=15-25]



b. MTD Verification Phase [n=10]

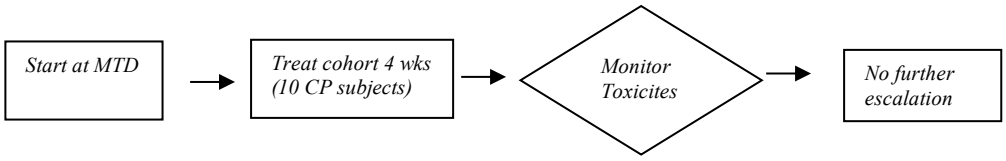


Table 1: Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined below in Table 2.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

Table 2: Definition of Toxicity Grades

a. **Dose Limiting Toxicity (DLT) –** Appearance of side effects during treatment that are severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level.
b. **Grade –** a numeric scale used to rate the severity of toxicity associated with a treatment. Each side effect is separately rated from "0" to "4." "0" = side effect not present. "1"= present but minor. "2"=present, moderate effect. "3"= present, with significant effect. "4" = potentially life threatening effect. G. "3" or "4" toxicity usually results in further treatment being delayed or stopped. If resumed, treatment may be at lower dosage or frequency.

Table ___

Nausea, Vomiting, Diarrhea, Abdominal pain, Bloating	**Management/Next Dose for *[Soy Bread]***	**Management/Next Dose for *[Soy Bread]***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a delay of > 1 week should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.		
Recommended management: Nausea / vomiting (antiemetics); diarrhea (loperamide); abdominal pain (acetaminophen, NSAID)		

For the purposes of this Phase I trial, side effects rated >= 3, lasting > 1 week are considered dose limiting. Side effects will be managed with standard medications such as anti-diarrheals, antiemetics and non-narcotic analgesics.

Appendix A

Inclusion criteria

1. Diagnosis of chronic pancreatitis by fulfilling any **one of the following three** clinical scenarios (i.e., a or b or c):
    a. **Presence of pancreatic calcifications** - Pancreatic parenchymal or ductal calcifications (≥1) seen on abdominal imaging study
    b. **Suggestive for chronic pancreatitis** – fulfillment of any of the following 3 criteria (i.e., i or ii or iii):
        i. EUS demonstrating lobular appearing pancreas (≥3 continuous lobules) and ≥3 minor EUS criteria
            1. Minor EUS criteria (aka Rosemont criteria) include: lobular appearing pancreas (1-2 lobules), hyperechoic foci without shadowing, cysts, hyperechoic stranding, irregular main pancreatic duct contour, dilated side branches, main pancreatic duct dilation, or hyperechoic main pancreatic duct walls
        ii. EUS demonstrating ≥ 5 minor EUS criteria
        iii. Presence of ≥ 3 abnormal pancreatic duct side branches visualized on MRCP or ERCP (derived from Cambridge criteria for mild chronic pancreatitis)
    c. **Indeterminate EUS findings for chronic pancreatitis with evidence of exocrine pancreatic insufficiency (EPI)** (i.e., i + [ii or iii or iv or v])
        i. Presence of 3-4 minor EUS criteria (listed above)
        ii. Abnormal fecal fat collection (>15g fat per day)
        iii. Abnormal endoscopic pancreas function test (i.e., maximum duodenal bicarbonate concentration <80 meq/L)
        iv. Decreased serum trypsin (<20 ng/mL)
        v. Decreased fecal elastase level (<200 microgram/gram stool)
2. Age ≥18 years

Exclusion criteria

1. Inability to provide written consent
2. Inability to comply with the study protocol
3. Soy allergy
4. Pancreatic cancer
5. History of prior pancreatic surgery (this does not include endoscopic therapies)
6. Comorbid diseases characterized by a chronic inflammatory state, including, but not limited to rheumatologic diseases, chronic kidney disease, extra-pancreatic malignancy (these conditions would confound the measurement of inflammatory mediators)
7. Pregnancy (based on verbal history alone; the study intervention does not have known harmful effects to a mother or fetus, and therefore, pre-study pregnancy testing will not be mandated).