How to Write a Letter of Intent

Sarah A. Holstein, MD, PhD
Associate Professor, Internal Medicine
Division of Oncology and Hematology
Director, Pilot Projects Program, Great Plains IDeA-CTR Network
University of Nebraska Medical Center

UNMC

Disclaimers

- These are my opinions
- I have had more grant proposals rejected than funded

Outline

- Overview of LOI’s
- Key sections of the LOI
- NIH biosketch

What is the purpose of a LOI?

- From the funding agency perspective:
  - Ensures project is in line with funding mechanism
  - Weeds out the proposals least likely to be promising
- From the applicant perspective:
  - Introduces the investigator to the funding agency
  - Allows the applicant to present their proposed research in a focused, concise manner highlighting the aims, approach and study team
- From the funding agency and applicant perspective:
  - Limits wasted time/effort

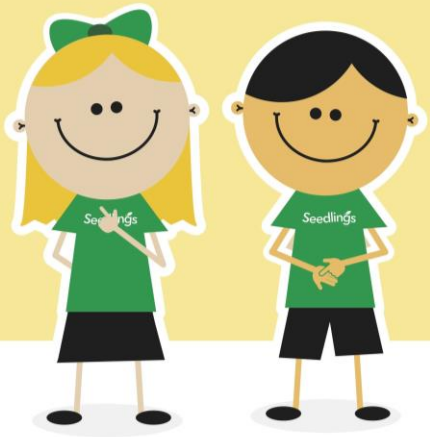
What a LOI is not

- A specific aims page
- A full grant squeezed into 1-2 pages

What does the reviewer of a LOI consider?

- Appropriateness of the subject matter
- Is there a sound rationale
- Are the aims clearly stated
- Is the approach reasonable
- Is there an analytic plan
- Is the timeline reasonable
- Is the investigative team appropriate

I can follow directions.



I

follow
Tap hand twice with pointer finger

Seedlings
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Follow directions

- Use template if provided
- Use specified font type/size
- Use specified margins
- Follow page length requirements
- Provide the requested information (don’t skip sections or include sections that were not requested)

Consider the reviewer

- Reviewer may not be a content expert
- A sea of densely packed text without breaks/spaces encourages the urge to skim
- Make it easy on the reviewer—if they are skimming, can they quickly identify your central hypothesis, your overarching goal, the unmet need in the field?
- If a figure is included—does it serve an important purpose? Can all aspects (legend, axis labels, etc) be clearly read without resorting to the use of a magnifying glass?

Your reviewer: unlikely to be The Doctor

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Grant writing-induced pathological emotive syndrome (GRIPES), characterized by intense feelings of dread, depression, panic attacks, rage and existential crisis, is a disorder that affects nearly all women and men engaged in academic research. Currently there are no proven strategies to prevent or treat GRIPES, although there are anecdotal reports of this syndrome being cured following investigators winning the Mega Millions lottery. However, for the vast majority of academic researchers, GRIPES represents a serious threat to mental health, productivity and career longevity. *Thus there is an urgent unmet need to better understand the pathophysiology of GRIPES so that effective preventative and therapeutic strategies can be developed, leading to the amelioration of suffering of millions of individuals worldwide*. It is our **underlying hypothesis** that there are multiple factors which interact in a synergistic manner to cause GRIPES, including sleep deprivation, perfectionism, procrastination, vitamin D deficiency, administrative burden, cutthroat study sections and infinitesimally small paylines. To begin to develop preventative and therapeutic strategies for GRIPES we propose the following **specific aims**: 1) to develop and validate a GRIPES-specific symptom score, 2) to investigate the impact of modifying one vs multiple GRIPES-mediating factors on GRIPES severity and 3) to determine whether the strategy of providing a service animal to an investigator will reduce GRIPES severity. For the latter, a randomized control study will be conducted in which investigators are randomized to either receive a service animal or a stuffed toy for a period of twelve months.

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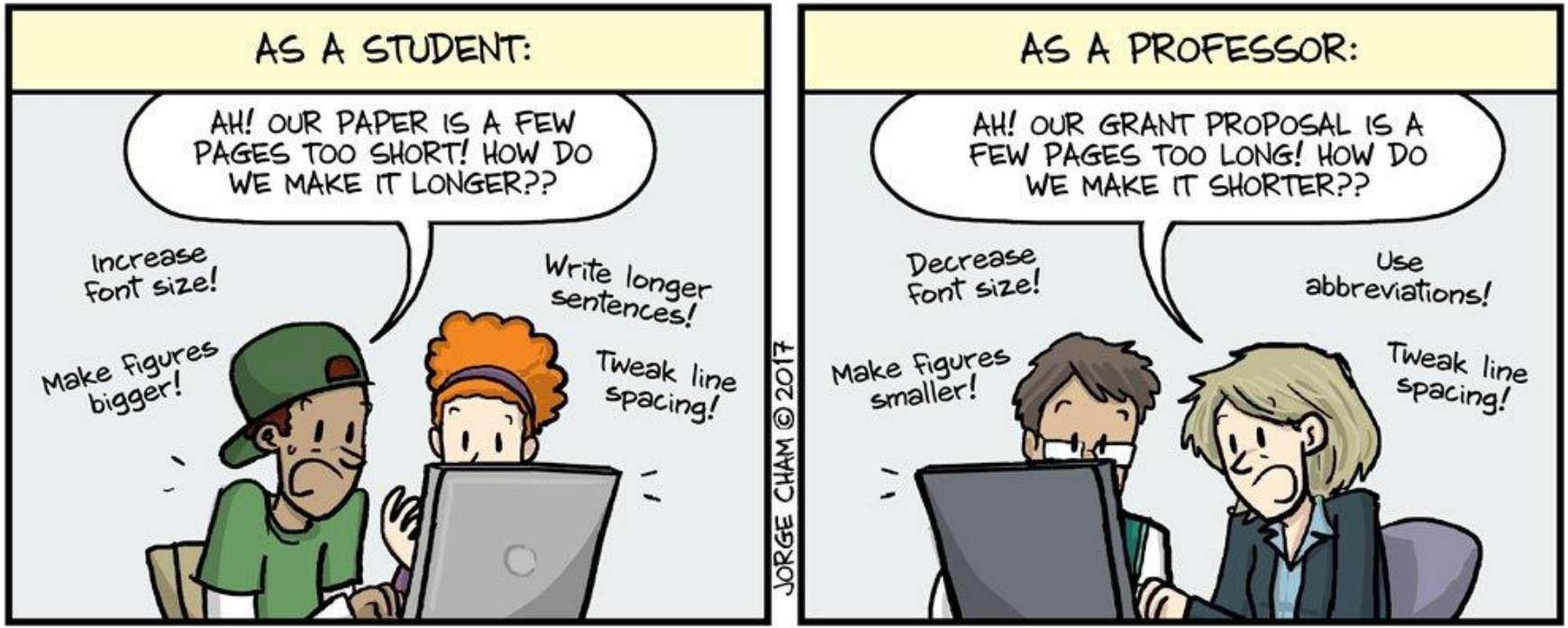
PAGE LIMITS



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GGDPS Inhibitors: Initial efforts at GGDPS inhibitor(s) (GGDPSi) development yielded digeranyl bisphosphonate (DGBP, **1**, **Fig 3**), with cellular activity at ≥ 1 μM.[30,31] Crystallographic studies showed that DGBP's V-shaped structure occupied the enzyme's active site, with the bisphosphonate (BP) group complexing with magnesium ions and the two prenyl side chains occupying the FPP (substrate) and the GGPP (product) sites.[32] Subsequent efforts focused on modification of the V-shaped motif.[22,32-34] The only two previously published reports of the *in vivo* assessment of GGDPSi.[35,36] The inhibitor used in the hydroxyl derivative (**Fig 3**),[37] was initially prepared as a prodrug. These efficacy of this GGDPSi, commenting on effects regarding toxicity of the drug previously on a daily basis (1.25 mg/kg).

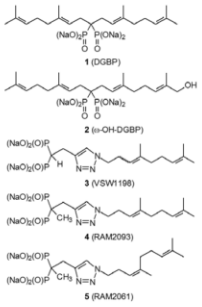
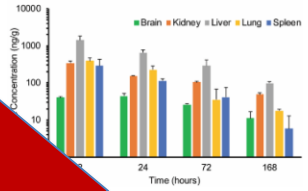


Figure 3. Structures of key GGDPSi.

VSW1198 showed comparable metabolic stability in studies utilizing human liver microsomes (HLM) and mouse S9 cells to assess Phase I and II metabolism (**Fig 5**).[50] We performed a pharmacokinetic (PK)/tissue distribution study. Metabolic stability of VSW1198 in human and mouse S9. Data are mean ± SD, n=3. blood and tissue samples were collected over a period from 5 min to 7 days post-injection of VSW1198 at 0.5 mg/kg IV, n=5 per time point. We have developed a methodology to measure VSW1198 in plasma and tissue samples. VSW1198 was extracted from plasma and tissue samples, derivatized by reaction with diazomethane, and analyzed via liquid chromatography (LC)-mass spectrometry (MS)/MS. The maximum concentration (C_0) is 829.4 (± 135.2) ng/mL, the area under curve ($AUC_{0-\infty}$) is 2748.5 (±95.4) hr*ng/mL, and the plasma elimination half-life ($t_{1/2}$) is 47.7 (±7.4) hrs.[50] Analysis of the tissue samples revealed highest accumulation in the liver, with persistence of the drug in all tested tissues at 7 days (**Fig 6**).



Concentrations of 98 in mouse tissue es after 0.5 mg/kg IV ministration (mean ± SD, n=5).

Research Design and Methods

Study Population and Setting. R/R DLBCL or ALL patients (n=20) scheduled to receive commercial CAR-T therapy will be recruited from the University of Nebraska Medical Center (UNMC) Fred & Pamela Buffett Cancer Center (FPBCC) in Omaha, NE. The inclusion criteria are: (1) R/R DLBCL or R/R ALL diagnosis; (2) scheduled to receive commercial CAR-T therapy (Axi-cel or Tisa-cel); (3) ≥19 years of age; (4) legally licensed to drive for at least 5 years; (5) previously drove an average of 50 miles/week or at least 1 hour/week; (6) normal visual acuity (20/40 or better); (7) fluent in English. Patients presenting with severe neurocognitive impairment prior to T-cell apheresis will be excluded. *Study Design*. Patients will undergo T-cell apheresis, lymphodepleting chemotherapy, and CAR-T infusion per commercial guidelines of CAR-T products (see Table 1). Patients will concurrently undergo longitudinal evaluation for the current study. Each patient will complete: (1) blood collection for immunological evaluation; (2) EEG to assess electrophysiological evidence of NT/CRES; (3) MRI to assess radiological evidence of NT/CRES sequelae; and (4) driving assessment using a standardized on-road driving evaluation. All study procedures will be completed during primary study visits: prior to apheresis (T0) and 8-weeks post-infusion (T6). Secondary study visits will include EEG and immunological evaluation each week between CAR-T infusion and discharge (T1-T5) to monitor changes in CRS and NT/CRES.

Table 1: Study Procedures Schema

Week on Study	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
CAR-T Therapy														
Consent	■													
Apheresis		■												
Lympho. Chemo.					■									
CAR-T Infusion						■								
Discharge										■				
Study Procedures		***T0***				***T1***	***T2***	***T3***	***T4***	***T5***				***T6***
Consent	■													
Blood Panel		■				■	■	■	■	■				■
EEG		■				■	■	■	■	■				■
MRI		■												■
Driving Assessment		■												■

Courtesy of David Anderson, PhD

The Title

- Often the very first thing a reviewer will see—sets the stage and establishes the initial level of enthusiasm
- Not too vague but also not too long/complex
- Don’t use abbreviations in the title

- *Vague and uninformative*: “A study of chronic fatigue in cancer patients”
- *Overly detailed*: “Determining the utility of the Multidimensional Fatigue Inventory, the Fatigue Severity Scale, the Profile of Fatigue-Related Symptoms, and the ME/CFS Fatigue Types Questionnaire in evaluating the severity of fatigue experienced by women undergoing paclitaxel-based adjuvant chemotherapy for ER/PR-negative stage II breast cancer”

The “Lay Summary”

- Scientific reviewer may read, but often times this will be what is disseminated to the public/community advisory board/foundation advisory board.
- Could your family member who knows very little about science/medicine understand the summary?

Technical abstract

…We will prepare and screen a rationally designed library of potential GGSI and evaluate the compounds for potency and specificity as GGSI as well as metabolic stability. Compounds that meet our carefully specified criteria will be carried forward to *in vivo* studies evaluating their toxicology, pharmacokinetic and biodistribution profiles. The GGSI which are determined to have suitable *in vivo* pharmacological properties will then be assessed for efficacy in mouse models of myeloma. The ultimate goal of these studies will be to identify a lead GGSI for an IND application.

Lay abstract

…Therefore, we propose to prepare and screen a library of compounds we have designed as potential anti-myeloma drugs to identify a lead inhibitor which could be carried forward to animal testing and later to human testing. The ultimate goal of these studies is the development of novel drugs which can be used to safely and effectively treat multiple myeloma so that these patients may live longer and develop fewer complications from their disease.

Specific Aims

- Concise but informative
- Realistic, achievable within study period, not too ambitious
    - Aim 1: To determine the molecular mechanisms underlying the pathogenesis of cancer
- Success of one aim should not be dependent on the success of another aim
    - Aim 1: To develop a drug (“MagicCure”) that selectively kills all myeloma cells but does not affect any normal cells
    - Aim 2: To evaluate MagicCure in a phase I clinical trial

Investigators/study team

- Why are you the right person to lead this study?
- Have you assembled a study team that includes the requisite areas of expertise?
- Have you described how each study team member will be contributing to the project?

The PI, Susan Smith, MD is a fellowship-trained palliative care physician with extensive research experience in the field of symptom management in patients with advanced malignancies. She will be responsible for the scientific direction of this project and will coordinate the efforts of her co-investigators (Drs. Jones, Rhodes and Wells). Jason Jones, PharmD is a pharmacist whose research focuses on the use of pain medications in the chronically ill. Dr. Jones will participate in the multi-disciplinary rounds evaluating the medication regimens of the research subjects. Robin Rhodes, MD is a geriatrician and will conduct the geriatric assessments. Wallace Wells, PhD, is a clinical psychologist and will be responsible for directing the counseling sessions involving the research subjects and their family members. Dr. Theresa Todd is the biostatistician for this project. Dr. Todd has assisted in the study design and will conduct all statistical analyses.

Patient/subject information

- Clearly describe the key characteristics of the patients/subjects that will be included in your study
- Don't make the reviewer question whether this population exists in sufficient numbers
    - *Reasonable*: Men and women enrolled in undergraduate programs at UNL, UNO or Creighton who have at least one social media account will be recruited. It is anticipated that a total of 50 subjects will be recruited over a six-month period.
    - *Unreasonable*: Adult left-handed males (ages 42-45) with heterochromia iridium, dog dander allergies and port wine stain birthmarks born in Alaska but living in Omaha will be eligible for this study. It is anticipated that 80 subjects will be recruited over a two-month period.
- Provide justification for why your expected accrual (numbers of patients/subjects over specified period of time) is feasible.
    - The FPBCC is the only NCI-designated cancer center in the state of Nebraska and has a large referral base throughout Nebraska and neighboring states. In 2018, 250 patients underwent mastectomy for breast cancer at the FPBCC. Therefore, it will be highly feasible to enroll 25 breast cancer patients whose treatment plan includes mastectomy within the accrual period of 12 months.

Analytic plan

- Unless you are a biostatistician, consult with a biostatistician
- Even for a pilot study, where the *n* may be small because of time and funds, the study still needs to be designed to allow for analyzable data
- Specify what the primary endpoint is and how this will be measured
- Specify any secondary/exploratory endpoints
- Justify the numbers of participants that will be enrolled
- For intervention studies: what is the hypothesized effect size and what is the expected difference between the intervention and the control (or historical control)?


Don't
Touch

Biosketch

- First, follow the instructions
  - no more than 5 pages
  - no more than five sections under the contribution to science section; no more than four publications/abstracts/other works of scholarship under each of those sections
  - up-to-date completed research support section
- What do reviewers actually read?
  - The personal statement
  - Skim the contributions to science section
    - Relevance to current grant proposal
    - Breadth of publications
  - Ongoing and completed research funding

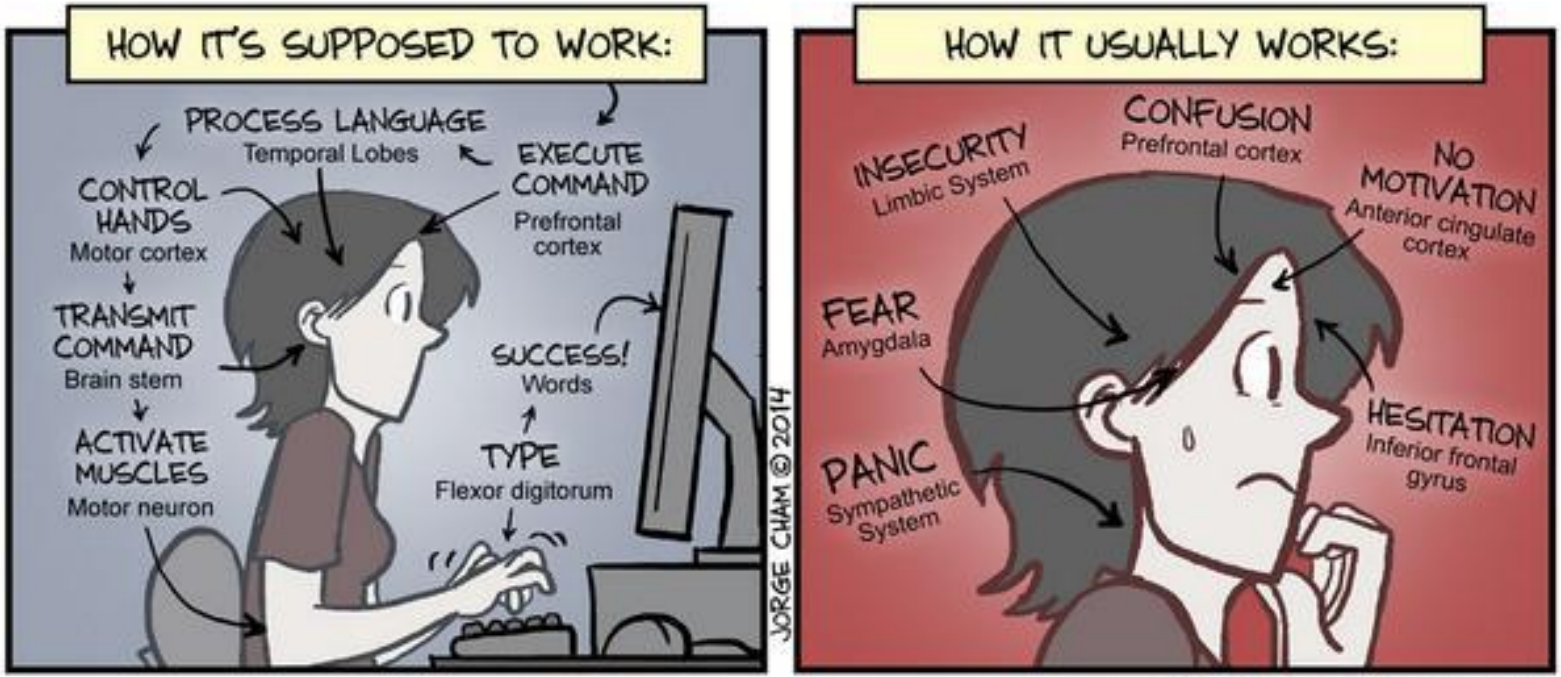
Biosketch—the personal statement

- First 1-2 sentences should provide a concise description of your academic identity and area of expertise, but is also relevant to the funding mechanism you are pursuing
  - We all wear many hats—decide which hat/s is/are most relevant
  - I am a physician-scientist who specializes in the clinical management of multiple myeloma with a research focus in multiple myeloma that encompasses basic science, translational and clinical research.
  - I am a physician-scientist whose research focus is on the development of novel therapeutic agents for cancer. My research training in pharmacology and cancer biology coupled with my clinical training as a board-certified and practicing hematologist-oncologist, has placed me in an ideal position to perform translational research.
- Summary of relevant training or research experience, titles or positions, track record of funding, experience of working with your co-investigators
- After reading this, will the reviewer know why you are well-suited for your role on this project?

Final recommendations

- Remember your audience
  - Make sure your writing is easy to follow
  - Emphasize the importance and feasibility of the project
  - Make sure you have convinced the reader that you are the ideal candidate to lead this project
- Get input from others, both in your field and outside of it
- Follow the instructions!

THE NEUROBIOLOGY OF WRITING



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