



UNDERGRADUATE SUMMER STUDENT RESEARCH PROGRAM (SSRP) 2022 PROJECT LIST

Content updated: **February 10, 2022**

Projects are posted in the order in which they are received. **Please keep checking the website as this list may be added to until the application deadline**

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Summer Student Research Program Project Description

Project #: SSRP22-Page-01

Supervisors: Brent Page

Project Title: Developing new anti-cancer therapies using state of the art chemical biology techniques

Hypothesis or Research Question being addressed: State-of-the-art chemical biology techniques have become essential components of the modern drug discovery and development landscape. The overarching hypothesis for this project is that using these techniques will help our research team to identify and optimize novel chemical compounds that can be applied as therapeutic agents.

Project Description: A project is available focused on the design, synthesis and preliminary testing of novel chemical compounds to target dysfunctional signaling networks in cancer cells. This project has evolved from high-throughput screening campaigns and have employed state of the art chemical biology techniques including cellular thermal shift assays (CETSA), thermal proteome profiling (TPP), fluorescence tagging and other cutting-edge techniques. Compounds that are synthesized within this project will be analyzed for their ability to bind specific proteins in cancer cells and for their ability to halt the growth and proliferation of cancer cells using the latest models and technologies.

Summer students will gain exposure to a breadth of topics in drug discovery and development within these projects and will learn the basics of medicinal and organic chemistry (including synthesis and characterization of new compounds), chemical and cell biology techniques (including CETSA and cell proliferation assays), and will interact with a network of collaborators who will further assess the anti-cancer activity of newly synthesized compounds.

Additional information for potential students: An educational background and/or laboratory experience with organic or medicinal chemistry, biochemistry and/or molecular biology is preferred.

Summer Student Research Program Project Description

Project #: SSRP22-Min/Leung-01

Supervisors: Jason Min; Larry Leung

Project Title: Indigenous Student Safety in Pharmacy

This project is only eligible for the Indigenous Undergraduate-SSRP (IU-SSRP) funding stream (i.e. only eligible Indigenous undergraduate students are invited to apply).

Hypothesis or Research Question being addressed:

- What is the state of Indigenous student safety in pharmacy?
- What factors determine whether a student openly identifies as Indigenous to peers and Faculty?
- What are the opportunities to improve Indigenous pharmacy student safety?

Project Description:

Indigenous identity, or Indigeneity, is a commonly used colonial method to systematically deploy resources and benefits. However, the use of Indigeneity as a prerequisite to these benefits undermines the complex and racially steeped consequences of openly identifying as Indigenous. To this date, there is a dearth of understanding of current Indigenous student safety in pharmacy education, what factors lead to a student openly identifying or not, and what could be done to improve safety.

The student will be integrated into the UPROOT team and expected to collaborate with the Indigenous Curriculum Advisory Committee, consisting of Indigenous and non-Indigenous experts, Indigenous community members and healthcare providers from participating Nations and undergraduate pharmacy students.

In this SSRP position, the student will address the research questions by participating in the following activities:

- Conducting a thorough literature review on Indigenous student safety in post-secondary education and pharmacy
- Working with project leads and Indigenous partners in the development of a survey or talking circle process for data collection
- Successfully receiving ethics approval for this study
- Collecting and analyzing quantitative and qualitative data
- Thematically analyzing findings and creating a summary report
- Making recommendations on strategies to improve Indigenous student safety in E2P PharmD programming

Qualifications:

- An Indigenous undergraduate student enrolled in an undergraduate program at the University of British Columbia
- Proficient knowledge of basic office computer software (e.g. Microsoft Word, Excel)
- Ability to show initiative, good judgement, time management skills, and professionalism
- Be able to work independently, and meet deadlines as agreed upon
- Excellent communication skills, both written and verbal

Summer Student Research Program Project Description

Project #: SSRP22-Wisnovsky-01

Supervisor: Simon Wisnovsky

Project Title: Identification of druggable targets for modulating cancer-associated glycosylation

Hypothesis or Research Question being addressed: Dr. Wisnovsky's lab studies the cell surface glycome, a dense network of sugar molecules that coats the surface of every living cell. The glycome plays a fundamental role in regulating the activity of our immune system, helping immune cells to distinguish normal, healthy cells from abnormal cells and invading pathogens. In diseases like cancer, the structure of the cell-surface glycome becomes profoundly altered, allowing tumour cells to escape immune detection. The overarching goal of this research project is to identify specific signaling pathways that can be targeted to reverse these changes in cancer cell glycosylation, generating new therapeutic options for the treatment of cancer.

Rationale: The past decade has witnessed a revolution in cancer research. In 2018 the Nobel Prize in Medicine recognized the impact of *cancer immunotherapies*, new drugs that stimulate the immune system to find and destroy cancer. To date, the majority of academic and pharmaceutical research into immune checkpoints has focused on a small number of protein-protein interactions that occur at cell-cell interfaces. However, the landscape of the cell surface is not just decorated with proteins. All living cells are also coated with a dense matrix of carbohydrate molecules that influence every aspect of cell function. This diverse set of structures (called *glycans*) can be covalently linked to proteins at asparagine residues (N-linked glycosylation) or serine/threonine residues (O-linked glycosylation). Some glycans are also directly linked to cell membrane lipids. Cell surface glycosylation is profoundly altered during cancer progression. In epithelial tumours, for example, O-linked glycans that normally are highly branched and elongated often become truncated to simple oligosaccharides. These truncated glycans form distinct structures (the Tn, Sialyl-Tn and T antigens) that are collectively referred to as tumor-associated carbohydrate antigens (TACAs). TACAs are found in abundance across a range of tumour tissues but are minimally expressed by healthy cells. Elevated TACA expression is also associated with poor patient outcomes in a number of tumour types, implying a link between TACAs and cancer progression. Recent work has also shown that TACAs can engage immune checkpoint receptors to inhibit anticancer immunity *in vivo*. The intracellular signaling pathways and genetic changes that lead to altered cell-surface glycosylation in cancer, however, are not well defined. **The goal of this project is to use a targeted CRISPR screening approach to mine the “druggable genome” for specific genes whose knockout reduces TACA expression by cancer cells.**

Approach: Students will work to infect multiple Cas9-expressing cancer cell lines with pooled libraries of sgRNAs targeting known “druggable” genes (e.g., kinases, phosphatases, hormone receptors). Cells will then be stained with fluorescently labelled glycan-binding proteins that detect cell-surface expression of common TACAs. Using a magnetic isolation/sorting based approach, cells exhibiting reduced TACA expression will be isolated from pooled libraries. Next-generation sequencing strategies will subsequently be used to define sgRNAs enriched in this cell population, leading to identification of genes whose ablation reduces TACA expression. Students will follow up on possible hits by performing targeted gene knockout and small molecule inhibition experiments coupled to cell-surface staining with glycan-binding proteins.

Expected Project Outcomes: At the end of this project, students will have produced a genomic database of possible druggable targets for modulating expression of several TACAs. These studies thus have the potential to spark multiple new research directions in immunotherapeutic drug discovery. As part of their training, students will gain experience with cutting-edge CRISPR screening techniques and data analysis workflows, as well as experience with fundamental molecular biology laboratory techniques (e.g., cell culture, flow cytometry, PCR, etc.).

Additional information for potential students: Some prior experience with basic laboratory techniques is preferred, although not required. The specific project would be well-suited for a student interested in pursuing graduate-level research in a cell biology, molecular biology and/or immunology-related field.

Summer Student Research Program Project Description

Project #: SSRP22-Frankel-01

Supervisor: Adam Frankel

Project Title: Yeast-based hPRMT2 assay development for high-throughput screening

Hypothesis or Research Question being addressed:

Human PRMT2 enzymatic activity is too low to support activity-based screening efforts to identify inhibitors, but we surmise that more active variants of the enzyme can. We aim to develop a yeast-based screening method for more active variants of hPRMT2.

Project Description:

Protein arginine *N*-methyltransferases (PRMTs) catalyze the transfer of methyl groups from *S*-adenosyl-L-methionine to arginine residues on proteins important for the epigenetic regulation of transcription, RNA processing, and signal transduction.¹ Dysregulation of arginine methylation is implicated in a number of different cancers for which several research groups have developed PRMT-specific inhibitors as potential therapeutics.² In recent years, human PRMT2 was shown to be involved in the pathogenesis of glioblastoma multiforme (GBM), an aggressive brain cancer with a low survival rate.³ Our laboratory showed hPRMT2 *in vitro* activity for the first time in 2009;⁴ however, it is too low to support activity-based screening efforts. We have used *in silico* modelling to identify amino acid residue mutation sites within the hPRMT2 active site that thermodynamically stabilize the overall protein structure. Preliminary evidence using recombinantly-expressed hPRMT2 containing these active site residue changes indicate that the variants are more active than the unmutated enzyme in methylating a glycine- and arginine-rich (GAR) substrate. Our lab is interested in taking advantage of these more active forms of hPRMT2 to develop a high-throughput compound screening assay.

Over twenty years ago, Silver and coworkers created a temperature-sensitive yeast strain mutated in the *NPL3* gene (*np13-1*) that codes for a GAR-containing protein responsible for shuttling mRNA from the nucleus to the cytoplasm, and they found that temperature-sensitive growth was overcome by the overexpression and enzymatic activity of the major yeast methyltransferase Hmt1p/Rmt1p.⁵⁻⁷ It was subsequently shown that the major human homologue of Hmt1p, hPRMT1, was able to functionally rescue the *np13-1* temperature-sensitive growth phenotype, but hPRMT2 was not.⁸ We hypothesize that the low activity of hPRMT2 is responsible for its inability to rescue, but we suspect that more active forms of hPRMT2 may be able to rescue the mutation. For this summer student research project, we plan to use the *np13-1* temperature-sensitive yeast strain to develop a growth-dependent compound screen to target the inhibition of hPRMT2. We want the summer student to subclone hPRMT2 mutants into a yeast expression vector and transform yeast to validate the assay by demonstrating a phenotypic rescue. The outcome of this work represents the first step in the journey to developing a means to target GBM through hPRMT2 inhibition.

Additional information for potential students:

A potential student should have a working understanding of sterile technique in working with microorganisms (i.e., bacteria and yeast), ability to make buffers and media, and foundational knowledge of biochemistry and molecular biology.

References:

1. Blanc, R. S. & Richard, S. Arginine Methylation: The Coming of Age. *Molecular Cell* **65**, 8–24 (2017).
2. Jarrold, J. & Davies, C. C. PRMTs and Arginine Methylation: Cancer's Best-Kept Secret? *Trends in molecular medicine* **25**, 993–1009 (2019).

3. Dong, F. *et al.* PRMT2 links histone H3R8 asymmetric dimethylation to oncogenic activation and tumorigenesis of glioblastoma. *Nat Commun* **9**, 4552 (2018).
4. Lakowski, T. M. & Frankel, A. Kinetic analysis of human protein arginine N-methyltransferase 2: formation of monomethyl- and asymmetric dimethyl-arginine residues on histone H4. *The Biochemical journal* **421**, 253–261 (2009).
5. Henry, M. F. & Silver, P. A. A novel methyltransferase (Hmt1p) modifies poly(A)⁺-RNA-binding proteins. *Molecular and Cellular Biology* **16**, 3668–3678 (1996).
6. Lee, M. S., Henry, M. & Silver, P. A. A protein that shuttles between the nucleus and the cytoplasm is an important mediator of RNA export. *Genes & Development* **10**, 1233–1246 (1996).
7. McBride, A. E., Weiss, V. H., Kim, H. K., Hogle, J. M. & Silver, P. A. Analysis of the yeast arginine methyltransferase Hmt1p/Rmt1p and its in vivo function. Cofactor binding and substrate interactions. *The Journal of biological chemistry* **275**, 3128–3136 (2000).
8. Scott, H. S. *et al.* Identification and characterization of two putative human arginine methyltransferases (HRMT1L1 and HRMT1L2). *Genomics* **48**, 330–340 (1998).

Summer Student Research Program Project Description

Project #: SSRP22-Velenosi-01

Supervisor: Thomas Velenosi

Project Title: Computational methods for improving mass spectrometry-based lipidomics

Hypothesis or Research Question being addressed: Machine-learning algorithms can increase the number of correctly identified lipids when compared to database matching from mass spectrometry-based lipidomics.

Background: Lipidomics is the large-scale analysis of all lipids in a biological matrix and can provide fundamental insights into biological systems. Lipids are analyzed by liquid-chromatography coupled to mass spectrometry and the resulting data is used for identification. However, the process for identifying lipids is highly manual and creates a major bottleneck in the analysis pipeline.

Aim: To develop computational methods for identifying lipids from mass spectrometry-based lipidomics data.

Research approach: To reduce the manual burden of identifying lipids, we are developing software tools that will systematically optimize lipid identification for individual lipid classes and further increase confidence in the lipid identity by using R software. The goal of this approach is to develop a software package that will bridge the gap between lipidomics data and lipid identification while seamlessly integrating into the analysis pipeline.

Project activities: The summer student will analyze raw lipidomics data and contribute to the optimization of a machine learning algorithm for identifying lipids. This project will be entirely computer-based using R for software development and Github for version control. If necessary, the project can be conducted virtually. The student will be provided guidance by the supervisor through regular meetings, but will be expected to work independently on the project. This project will contribute to the development of an R software package and lay the groundwork for a future manuscript. At the end of the program, the student will be expected to prepare a poster presentation.

Additional information for potential students: Potential students should have prior programming experience in R or similar programming language.

Summer Student Research Program Project Description

Project #: SSRP22-Velenosi-02

Supervisor: Thomas Velenosi

Project Title: Developing a stable cell line reporter model for evaluating chemotherapy effects on gene expression

Hypothesis or Research Question being addressed: Chemotherapy effects on enzyme gene expression can be evaluated through CRISPR/Cas9 knock-in of a polycistronic GFP reporter.

Background: Chemotherapy drugs can have a profound effect on cellular metabolism, generating metabolites that can indicate effective drug response. These effects can be mediated by altering the gene expression of enzymes involved in key metabolic pathways for cancer growth and proliferation. However, characterizing the mechanisms by which chemotherapy drugs alter metabolite production at the level of enzyme gene expression remains a challenge.

Aim: To develop a stable cell line reporter model for evaluating enzyme specific gene expression in response to chemotherapy treatment.

Research approach: We will develop a stable cell line model containing a polycistronic green fluorescent protein (GFP) reporter using CRISPR/Cas9 mediated knock-in. This model will be validated to ensure that enzyme function is retained and enzyme gene expression is represented by GFP fluorescence.

Project activities: The summer student will perform several wet-lab techniques including bacteria and cell culture, cell transfection, PCR and fluorescence assays. They will also learn to validate CRISPR/Cas9 mediated homology directed recombination as well as the associated analysis to quantify and summarize findings. The projected outcome of this project is a validated stable cell-line to characterize gene regulation in response to chemotherapy treatment. The student will be required to take UBC biosafety and chemical safety training. At the end of the program, the student will be expected to prepare a poster presentation.

Summer Student Research Program Project Description

Project #: SSRP22-Ross-01

Supervisor: Colin Ross

Project Title: Quantification of CRISPR/Cas9 base editing efficiency in a novel reporter mouse model

Hypothesis or Research Question being addressed: We hypothesize that CRISPR/Cas9 base editing can successfully repair the mutation in the mouse model and the editing efficiency can be quantified with enzyme assay and sequencing.

Background: Genome sequencing has aided our ability to understand and diagnose genetic diseases and cancer. However, less than 5% of human genetic diseases have approved treatments. Previously, gene therapies have focused on the treatment of genetic diseases by inserting functional copies of a gene into patient cells. While this approach has been successful, critical limitations remain.

Project Overview: To overcome these limitations, we are investigating the potential of using novel CRISPR/Cas9 gene editors to specifically repair pathogenic mutations directly in the DNA sequence of the gene of interest. In order to optimize this novel approach, we have developed an *in vivo* reporter model system that utilizes a repairable mutation in luminescence gene to evaluate nanotechnology-based approaches to deliver therapeutic components into cells.

Methods: This project will require UBC biosafety and chemical safety training. The project involves handling of animal tissues, a wide variety of lab-based molecular biology techniques and bioinformatics-based analyses. Students will learn techniques involving animal tissue processing and luminescence enzyme assays. In addition, the project will require quantitative data analyses and the application of statistics to summarize laboratory findings. Finally, the project will require detailed presentations of findings in weekly lab meetings and reporting of project findings.

Role of the Summer Student: The summer student will work closely with the supervisor, research associates/postdoctoral fellows and graduate students to complete the project. The role of the summer student will be to prepare animal tissues and samples for sequencing and to develop and perform enzyme assays to determine the efficiency of gene editing. The student will also utilize bioinformatic software to quantify gene editing. In addition, the summer student will assist in genotyping assays and help with general mammalian cell culture maintenance and experiments. The summer student will be expected to participate in weekly lab meetings and prepare a final report and poster presentation.

Additional information for potential students: It is preferable that the student have done the UBC biosafety and chemical safety trainings prior to start of the program.

Summer Student Research Program Project Description

Project #: SSRP22-Nicholl/Inglis-01

Supervisor: Tessa Nicholl; Colleen Inglis

Project Title: To evaluate the attainment of confidence, knowledge, competence, and perception of safety secondary to providing pharmacy-specific suicide prevention training in a supportive environment.

Hypothesis or Research Question being addressed: How did the provision of pharmacy-specific suicide prevention training administered in a safe and supportive environment, impact participants and their readiness to identify, support, and refer patients who may present with suicidal ideations? This pharmacy-specific suicide prevention training, delivered in a safe and supportive environment, will increase the conversation about suicide, contribute to stigma reduction, and improve patient safety.

Background: Suicide is an ongoing health crisis in Canada, with an underestimated average of 10 lives lost each day. For every life lost, there are devastating impacts to individuals and communities. Although trusted and available health care professionals, pharmacists are not routinely trained in suicide prevention and therefore represent a potential missed opportunity to identify and support those at risk. Through pharmacy-specific suicide prevention training, delivered in a safe and supportive environment, this research project will increase the conversation about suicide, contribute to stigma reduction, and improve patient safety. Through evaluation and dissemination of this project's effectiveness and security, we aim to embed suicide prevention training in Pharmacy curricula at UBC and beyond.

The research trainee will support the evaluation of participants' attainment of confidence, knowledge, and competence in their ability to help patients at risk of suicide. Additionally, we will investigate participants' perspectives through focus group interviews to evaluate whether the content was delivered in a safe environment and help identify best practices and the necessary supports required for participants when a sensitive subject (i.e., suicide) is discussed. This research will demonstrate that pharmacy-specific suicide prevention training will help participants identify patients at risk, initiate a conversation, provide referrals, and support the community affected by suicide. This research aims to increase patient safety and prevent suicide ultimately.

The SSRP student will participate in the following activities:

- Conduct a thorough literature review
- Submit minimal risk application to UBC's Behavioral Research Ethics Board (BREB)
- Develop an evaluation of the asynchronous pharmacy-specific suicide prevention training
- Design a pre-and post-test to evaluate participant attainment of confidence, knowledge, and competence in preventing suicide
- Create electronic surveys and conduct participant interviews
- Collect and analyze quantitative and qualitative survey data
- Create a summary report of key findings and deliver a poster presentation
- Contribute to manuscript writing
- Collaborate with faculty members to help improve the delivery of pharmacy-specific suicide prevention training to Entry-to-Practice PharmD students

Desired qualifications:

- Proficient knowledge of essential office computer software (e.g., Microsoft Word, Excel)
- Ability to show initiative, good judgment, time management skills, and professionalism
- Be able to work independently and meet deadlines as agreed upon

- Excellent communication skills, both written and verbal
- Previous experience conducting mix-method analysis is an asset

Summer Student Research Program Project Description

Project #: SSRP22-Lynd/Dragojlovic-01

Supervisor: Larry Lynd; Nick Dragojlovic

Project Title: Environmental scan of the in-vivo CAR-T innovation landscape

Hypothesis or Research Question being addressed: What indications are being explored as potential targets for in-vivo CAR-T therapy? For which indications would in-vivo CAR-T therapy have the greatest potential societal impact and strongest value proposition for payers?

Project Description: The impressive potential of nucleotide-based therapies delivered by lipid nano-particles (LNPs) has been powerfully illustrated by the rapid development and global deployment of the Moderna and Pfizer/BioNTech mRNA-based COVID-19 vaccines, the latter of which uses a LNP system developed at UBC. On the heels of that success, there is a race to develop mRNA-based vaccines and therapies for additional indications, including by targeting LNPs to specific cell types or tissues. A promising application of this technology is its use to create chimeric antigen receptor T-cells (CAR-Ts) in-vivo rather than reprogramming the T-cells ex-vivo and infusing them into the patient. This technology would make CAR-T therapy much less costly and less logistically challenging.

However, the development of specific therapeutic products based on an innovative technology through to approval and successful commercialization is an expensive and risky process that can slow the translation of biomedical technologies from bench to clinic. As a result, focusing on applications for which there is a large potential market, unsatisfactory existing and emerging solutions, and significant potential to create value for healthcare insurers and other stakeholders can facilitate investment to bring the innovation to market and maximize its societal impact and commercial success once the product is approved. This project aims to describe the technological and commercial landscape for in-vivo CAR-T therapies, with the goal of facilitating an early health technology assessment of proposed applications of new targeted LNP systems.

This environmental scan will have two related components. First, in collaboration with our team the student will conduct a rapid review of the literature on in-vivo CAR-T therapy. This will involve developing a study protocol, conducting exploratory searches in relevant databases, screening sources for inclusion, data extraction, and literature synthesis. The literature summary will focus on creating an inventory of the following information: a) the types of technology platforms being used to develop in-vivo CAR-T (e.g., targeted LNPs, viral vectors); b) the indications being discussed and/or tested in animal models; and, c) the research groups and companies involved in this work. Once this rapid review is complete, for key indications identified in the first step, the research team will also collect estimates of their incidence/prevalence, epidemiology and average cost of care (e.g., mortality rate, healthcare utilization), and information on existing and emerging therapies, including technology, mode of action, effectiveness, safety profile, patent coverage, exclusivity, cost, and cost-effectiveness, where available. This work will ultimately be published as a scientific journal article, and the dataset will be a valuable resource for nanomedicine scientists and health economists aiming to conduct early health technology assessments to inform decisions on which candidate indications to pursue for further development.

Summer Student Research Program Project Description

Project #: SSRP22-Williams-01

Supervisor: Karla Williams

Project Title: Biomarker analysis of extracellular vesicles to improve prostate cancer detection

Hypothesis or Research Question being addressed: Previous work from our lab has identified six transmembrane epithelial antigens of the prostate 1 (STEAP1) extracellular vesicles (EVs) from the plasma of prostate cancer (PCa) patients with diagnostic capabilities far superior to the PSA blood test. However, we need to identify additional biomarkers to improve the prognostication capabilities of our test to support the detection of high-risk PCa. We hypothesize that STEAP1 expressing EVs contain additional biomarkers capable of distinguishing low risk PCa from high-risk PCa. These subpopulations will be detectable by nanoscale flow cytometry and support the development of a high throughput test for PCa screening. For this project, we plan to characterize STEAP1 positive EVs from PCa patient plasma to compare low-risk and high-risk PCa patients.

Project Description: An unbiased approach is required to identify new biomarkers with clinical utility. Given our preliminary work with STEAP1 expressing EVs, we hope to dive deeper into the composition of these EVs and identify additional protein biomarkers. By examining the protein composition of EVs from high-grade and low-grade PCa patients, we hope to identify biomarkers that will support the detection of high-risk PCa patients and distinguish this from low-risk disease

We have recently optimized isolation of STEAP1 EVs from plasma and validated our protocol. Next, we hope to compare isolated STEAP1 EVs from high-grade and low-grade PCa patients using mass spectrometry. Proteins of interest present in the data sets generated from high-risk PCa and low-risk PCa will be used for validation strategies and test development. This unbiased approach will create a dataset of markers that can be subject to nFC in whole plasma or on isolated EVs to validate if the selected biomarkers hold clinical utility. Validation will be performed on our entire PCa cohort (n=121), healthy age matched males (n=50),

This study builds on novel research from our lab that has identified the diagnostic potential of STEAP1 expressing EVs. Our proposed research identifying STEAP1 subpopulations associated with high-risk PCa will accelerate the translation of EVs to clinical diagnostics through advances in characterization and phenotyping. Given the rates of PCa overdiagnosis, improved screening is a significant clinical need. More reliable diagnoses will render health care delivery more efficient and effective with quality-of-life benefits for males and socioeconomic benefits for all Canadians. Through earlier detection and improved prognostication, this study may significantly reduce mortality from PCa in Canadian men.

Additional information for potential students: Prior experience with basic laboratory techniques is preferred, although not required. This position is funded through a Prostate Cancer Foundation of BC Grant-In-Aide Award.