



CGSM Workshop

Graduate Science Education

Rebekah DeVinney, Director for Scholarships
Barsha Rimal, Scholarship and Stipend Officer

Nov 5, 2021

Housekeeping

- Please remain muted with video off unless you would like to ask a question.
- There will be breaks throughout the workshop for questions. You can use the chat or turn your video and mic.
- Slides will be emailed to all registrants and posted on the GSE website.

Agenda

- Background, Eligibility and Timelines
- Adjudication Criteria
- Application parts
 - Application form
 - Common CV
 - Research Proposal
 - Letters of Reference
- General Tips
- Resources

Canada Graduate Scholarship-Masters (CGSM)

- Three agencies (Tri-council)
- CIHR: Health Research
- NSERC: Natural Sciences and Engineering
 - Does not fund human health research
- SSHRC: Social Sciences and Humanities
- \$17,500/year, 1 year, non-renewable
- Uncertain about which agency to apply to? Ask here
<http://www.science.gc.ca/default.asp?lang=en&n=FEE7261A-1>
 - **CIHR** cgsma@cihr-irsc.gc.ca
 - **NSERC** schol@nserc-crsng.gc.ca
 - **SSHRC** fellowships@sshrc-crsh.gc.ca

CGSM Harmonization

- All applicants go through online portal managed by NSERC
 - Research Portal
- Common application for all 3 agencies
- Applications are adjudicated at FGS not nationally
- Universities have a quota of awards
 - CIHR: 40
 - NSERC: 33
 - SSHRC: 32

Scholarship and Stipend Officer

- Barsha Rimal
 - Email(s): awardsgse@ucalgary.ca; gseproj@ucalgary.ca
- Scholarship Support
 - Advertise major scholarship and award programs to CSM graduate students and supervisors
 - Administer a subset of GSE scholarship programs
 - Assist CSM graduate students locate and apply for international, national, provincial, regional, and institutional scholarships and awards (e.g., interpret and navigate application guidelines and processes)
- Stipend Support
 - Set up, revise, terminate all CSM graduate student stipend payments



Eligibility

- Canadian or PR
- Have completed as of Dec 31, 2021
 - Between 0-12 mo full time study
 - M.Sc. Program
 - Doctoral program entering without having a M.Sc. (Direct entry)
 - Not having held a CGSM
 - First class average (3.5 GPA at U of C) in last 2 years of study (full time equivalents)
 - Can only submit 1 application per year to either CIHR, NSERC or SSHRC
 - Significant research component
 - Clinical oriented, joint programs with professional degree if there is significant research
 - Course based usually not eligible

Eligibility

- Eligibility can be tricky.
- Contact FGS Graduate Scholarship Officers with questions—they are the pros!
- CIHR, SSHRC
 - Elsa-Lee Alho (elsalee.alho@ucalgary.ca)
- NSERC
 - Erin Coburn (ecoburn@ucalgary.ca)
- General questions
 - gsaward@ucalgary.ca

Timelines



CGS Masters Deadline:
December 1, 2021
5:59 PM MT/8:00 PM ET

Pay attention to countdown!

Contact REFEREES ASAP

When are results out?

- By April 1, 2022 on Research Portal
- Universities will send out results on same day via email
 - Successful, Unsuccessful, Waiting List
- Students can apply to up to 3 institutions, so there is a tumble down of offers if awards are declined

Questions???

The application

- Application in Research Portal
- Summary of the proposal (Lay Abstract)
- Research proposal (1 page)
 - Bibliography/Citations (1 page)
- CGSM Canadian Common CV
 - Completed on CCV site, and attached to application in Research Portal
- Two referee assessments
- Transcripts
 - Uploaded to Research Portal



Adjudication Criteria

- 50% Academic Excellence
 - Transcripts
 - Awards
 - Reference assessments (x2)
- 30% Research Potential
 - Research proposal
 - Common CV
 - Reference assessments (x2)
- 20% Personal Characteristics and Interpersonal Skills
 - Common CV
 - Reference assessments (x2)

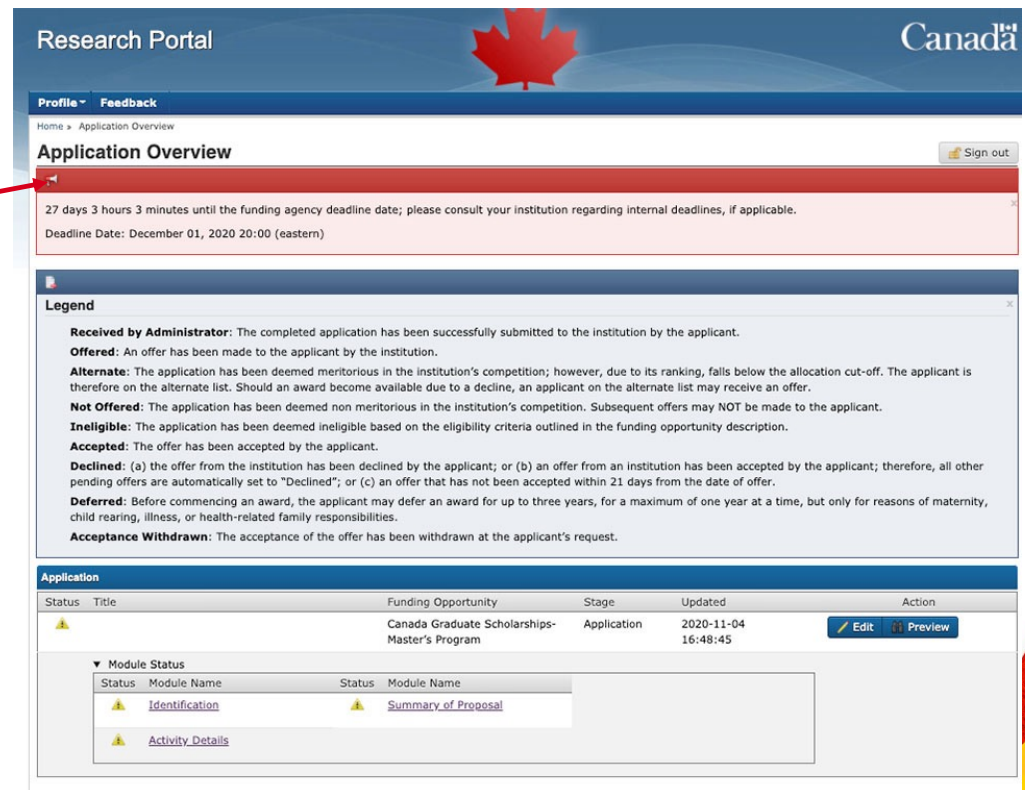




Top Reasons Good Students Don't Get Funded

- Not applying.
- A generic reference--the assessment is positive but gives no specifics and does not address criteria
- Content, context and/or impact of research not clearly stated. "So what?"
- Not following instructions by stretching the rules
- Frustrating evaluators by making material hard to find
- Diluting genuinely important/impressive material by describing generic material at length
- Not addressing possible weaknesses in the application

Application portal

- What you will see when you log in
- Timer
- Application info
 - Identification
 - Activity Details
 - Proposal summary



Research Portal  **UNIVERSITY OF CALGARY** 

Profile **Feedback**

Home > Application Overview

Application Overview [Sign out](#)

27 days 3 hours 3 minutes until the funding agency deadline date; please consult your institution regarding internal deadlines, if applicable.

Deadline Date: December 01, 2020 20:00 (eastern)

Legend

Received by Administrator: The completed application has been successfully submitted to the institution by the applicant.

Offered: An offer has been made to the applicant by the institution.

Alternate: The application has been deemed meritorious in the institution's competition; however, due to its ranking, falls below the allocation cut-off. The applicant is therefore on the alternate list. Should an award become available due to a decline, an applicant on the alternate list may receive an offer.

Not Offered: The application has been deemed non meritorious in the institution's competition. Subsequent offers may NOT be made to the applicant.

Ineligible: The application has been deemed ineligible based on the eligibility criteria outlined in the funding opportunity description.


Accepted: The offer has been accepted by the applicant.

Declined: (a) the offer from the institution has been declined by the applicant; or (b) an offer from an institution has been accepted by the applicant; therefore, all other pending offers are automatically set to "Declined"; or (c) an offer that has not been accepted within 21 days from the date of offer.




Deferred: Before commencing an award, the applicant may defer an award for up to three years, for a maximum of one year at a time, but only for reasons of maternity, child rearing, illness, or health-related family responsibilities.

Acceptance Withdrawn: The acceptance of the offer has been withdrawn at the applicant's request.

Application

Status	Title	Funding Opportunity	Stage	Updated	Action
		Canada Graduate Scholarships-Master's Program	Application	2020-11-04 16:48:45	Edit Preview

Module Status

Status	Module Name	Status	Module Name
	Identification		Summary of Proposal
	Activity Details		

Identification

- If field of research is “Health” you will need a CIHR PIN
 - Natural Sciences
 - Social Sciences other options
- Register with CIHR here:
<http://www.cihr-irsc.gc.ca/e/38201.html>
- Start early, it can take 1 full working day to get CIHR PIN

Application - Canada Graduate Scholarships-Master's Program Sign out

Identification

Applicant

To modify this information, update the User Profile page.

Family Name: DeVinney First Name: Rebekah
Middle Names:

Application

Application Title (required)

Language in which the proposal is written (required) ☐ English ☐ French

Field of Research

Start date or proposed start date of program of study Proposed end date of program of study

Number of months of graduate studies completed as of December 31 of year of application

Months of full-time study Months of part-time study

If you are successful in obtaining a Canada Graduate Scholarship will you consider applying for a Michael Smith Foreign Study Supplement? ☐ Yes ☐ No

Proposed Host Organization

Proposed Host Organization #1

Organization

Faculty

Department/Division

Proposed Host Organization #2

Organization

Faculty

Department/Division

Proposed Host Organization #3

Organization

Faculty

Department/Division

Activity Details

- Sex and Gender portion important
- If yes, it will open window for explanation
 - Basic science: Sex of animals, cell lines.
 - Patient oriented: sex and gender considerations
- CIHR Sex and Gender Modules
- Talk to your supervisor!!

Home > Application Overview > Application

Application - Canada Graduate Scholarships-Master's Program

Sign out

Activity Details

Certification Requirements

Does the proposed research involve humans as research participants? (required)	<input checked="" type="radio"/> Yes <input type="radio"/> No	Does the proposed research involve animals? (required)	<input type="radio"/> Yes <input type="radio"/> No
Does the proposed research involve human pluripotent stem cells? (required)	<input type="radio"/> Yes <input type="radio"/> No	Does the proposed research involve controlled drugs and/or substances? (required)	<input type="radio"/> Yes <input type="radio"/> No

For statistical purposes only

Does this application propose research involving Indigenous people? (required)

☐ Yes ☐ No

Sex- and Gender-Based Analysis

Are sex (biological) considerations taken into account in this proposal? (required)	<input type="radio"/> Yes <input type="radio"/> No	Are gender (socio-cultural) considerations taken into account in this proposal? (required)	<input type="radio"/> Yes <input type="radio"/> No
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Keywords

List up to 10 keywords that best describe the proposal. (required)

-
-
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-

Field of Study

Indicate and rank up to three primary fields of study relevant to your proposal, with #1 the most relevant and #3 the least relevant. (required)

- Select
- Select
- Select

Common CV

- Register for Common CV (CCV) on site.
 - Do this ASAP if you haven't done so already
- Select the CGSM CCV from Funding dropdown menu
- Enter information about
 - Publications and Presentations
 - Awards
 - Extracurriculars/leadership activities
 - Leaves of absence and impact on research
- Keep criteria from each section in mind (Academics, Research Potential, Personal Characteristics).
- Demonstrate that you are well-rounded.
- https://www.nserc-crsng.gc.ca/Students-Etudiants/CCV_CGSM-CVC_BESCM_eng.asp

Summary of Proposal and Attachments

- Summary of Proposal
 - Separate Page
- Research proposal and citations
- Transcripts as a single file
 - Request from FGS TODAY
 - <https://grad.ucalgary.ca/sites/default/files/teams/5/2022%20CGSM%20Transcript%20request.pdf>
- Common CV
- Invite your referees

Attachments				
Status	Title	Document Type	Updated	Action
		Outline of Proposed Research	2020-11-04 16:48:45	Attach
		Transcripts	2020-11-04 16:48:45	Attach

[Export application and attachments to PDF](#)

Canadian Common CVs Attached				
Status	Title	Role	Updated	Action
		Applicant	2020-11-04 16:48:45	Attach

Invitations						
Status	Role	Family Name	First Name	Email	Invitation Status	Updated
	Must provide two references					

[Manage Invitations](#)

[Submit](#) [Delete Application](#)

[Report this page](#)

Version: 25.1.2009.30

COVID and Research

- Well understood that shutdowns due to COVID have impacted progress (academic and research)
- Can use “Leaves of Absence and Impact on Research” in CCV to detail specific impacts on work due to COVID
 - Cancellation of field work due to travel restrictions
 - Inability to do person-person work
 - Inability to get training

Questions???

Adjudication Criteria

- 50% Academic Excellence
 - Transcripts
 - Awards
 - Reference assessments (x2)
- 30% Research Potential
 - Research proposal
 - Common CV
 - Reference assessments (x2)
- 20% Personal Characteristics and Interpersonal Skills
 - Common CV
 - Reference assessments (x2)



Academic Excellence

- As demonstrated by past academic results, transcripts, awards and distinctions:
 - Academic record (first class average)
 - Transcripts
 - Scholarships and awards held
 - Application form, CCV (Awards), reference assessments
 - Type of program and courses pursued
 - Course load
 - Relative standing (if available)
- **Since this is worth 50%, do everything you can to make sure you address all of the selection criteria:**
 - **Reference assessments**
 - **Address potential weaknesses head-on**

Research Potential- 30%

- Refereed Contributions:

- Peer-Reviewed Publications
- Conference Presentations
- Invited Talks.
 - Include local talks too (i.e LIM symposium) as well as international ones.
 - State your role in each.
 - Ex. Conducted in vitro experiments for X publication.

- Scholarly Achievements:

- Teaching, Mentorship, Academic Conference participation, Organizational Leadership and Participation, Review Leadership and Participation, Community Involvement.



Research proposal

- Quality of your proposal
 - Specific, focused, feasible and clearly stated research questions/objectives/hypothesis
 - Methodology explained clearly
 - Significance and expected contributions to research
- Think about
 - What is new and important about your work?
 - What is the key question and how will you address it?
 - How does your work fit into the bigger picture?
 - What does success look like for your project?
- Hook your reader early
 - Introduction at "newspaper" level—more general
 - State importance of work quickly

The Proposal

- **How is the proposal scored? Develop sub-sections accordingly.**
- Project ideas should be concise and easily understood.
 - Rationale
 - Aims to address questions
- Spacing = visually appealing
- Ask people outside your lab to review your proposal for clarity, brevity, and comprehension - overall, the more eyes, the better.



Personal Characteristics and Interpersonal Skills (20%)

- Work experience
 - CCV
- Leadership experience
 - CCV, reference assessments
- Project management including organizing conferences and meetings
 - CCV, reference assessments
- The ability or potential to communicate theoretical, technical, and/or scientific concepts clearly in written and oral formats
 - Research proposal, references, awards, CCV
- Involvement in academic life
 - references, CCV
- Volunteerism/community outreach
 - references, CCV

Putting It All Together, Tips for Scientific Writing

- Use minimalism to achieve clarity.
 - Remove filler words.
 - Ex. Immunocompromised patients that contract pneumonia often can develop very severe symptoms and illness.
 - Change to:
 - Immunocompromised patients contract pneumonia and develop severe sickness.
- Have a consistent theme and overall message.
 - Ex. Refer to impact in intro then use it in the conclusion.
- Limit each paragraph to a single message.
 - Question → Aim → What/how/why → conclude.



References

- **Ask early:** Give your referees time to write a good assessment.
- **Choose wisely:** ask your potential referees if they can provide you with a positive, strong reference; one of them should be your current supervisor or someone who is familiar with your academic work. Tri-councils are research awards, so it is best to have researchers write your assessments.
- **Follow up - Don't be shy!**
 - Remind your referees of the deadline a week or more before the reference is due.

Reference Assessment

Do not just ask someone for a reference. Be proactive and make it easy for your referee to write a good assessment:

- Provide the selection criteria.
- Provide transcripts and a CV: highlight areas you wish to have covered in the assessment.
- Meet to discuss: what criteria do you think they should address? Provide examples
- Inform them of the deadline & REMIND them.

Reference Assessments: Tips for Referees

Strong assessments:

- Address the criteria in each sub-field.
- Describe characteristics and abilities. Use extracurricular activities, and describe roles (any leadership roles), address personality traits and comment on where you think this student will end up in their career.
- **Be specific.** Back a point up with an anecdote.

Letters of Reference: The Student Perspective

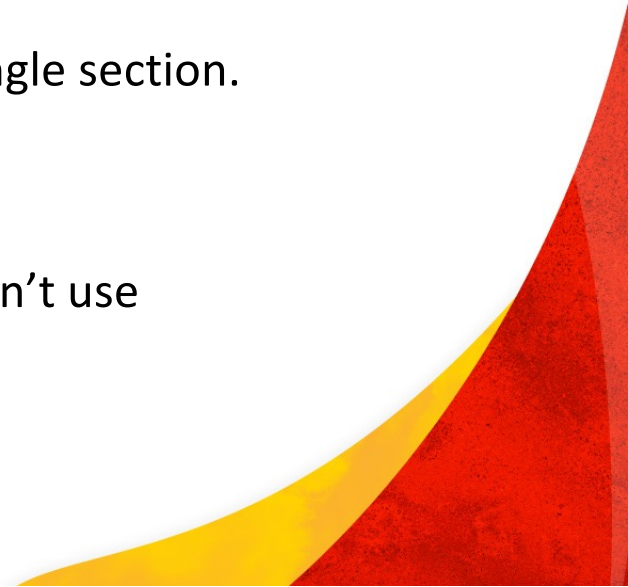
- Carefully choose/suggest terminology
 - Do your research on a 'successful applicant'.
- **How are these letters scored?**
- Total points for each section should correlate approximately with number of examples your referees provide.
 - Introduction – few sentences; describe your relationship capacity and context
 - Research Ability* – Critical Thinking, Independence, Organizational Skills, Originality, Perseverance, Interest in Discovery
 - Leadership Ability – single paragraph
- Give your referee some guidance.
 - List attributes, key words, examples etc.
 - Length and depth in each section.



Questions??

Putting It All Together, Tips for Scientific Writing

- Keep sentences short and precise.
 - Don't overuse transition words.
- Only use an adjective if it is relevant.
 - Don't say the same thing in three different ways in any single section.
- Don't slow the reviewer down.
 - Avoid jargon, buzzwords, or overly technical language. Don't use acronyms.



Putting It All Together, Tips for Scientific Writing

- Spoken language and common sense are generally better guides than a rule book.
 - It is more important to be understood than it is to form a grammatically perfect sentence.
- Commas denote a pause in speaking.
 - Speak the sentence aloud to find pauses. Make it natural.
- Choose concrete language and examples.
- Avoid placing equations in the middle of sentences.



Formatting: Aesthetics

- Don't cram as much text as possible into the document
- Consider using some of the following:
 - Space between paragraphs
 - Indentation
 - Headings
 - Bullets
 - Bold text

How set in stone are the project's and movement's names at this point? To grow faster, the movement needs to make a good first impression, taking advantage of anyone's feeling first exposure to it as a person will want to learn more and believe it could actually offer a possible real solution or they won't bother. But this name, "The Venus Project", rather than encouraging one to listen with an open mind could cause one's antennae to go up, waiting for the crazy, not realistic, but of this world part. I'm guessing the Venus in the Venus Project comes from Jacques being in Venus, Florida, but to any reader "Venus" means something "out there" on other planets, and I think that makes an easily avoidable bad first impression. The "Venus Project" name doesn't sound serious to me, it sounds childish. Also the name of the movement, "Zeitgeist", is not only needlessly non-descriptive (we're wasting valuable exposure time with a mysterious name - losing the opportunity that on each occasion when the name of the organization is mentioned, that in itself could be sending an introduction to a new idea, like if the name were "Technology Solves All Movement for a slippy example), but it will also foster to the movement to what some will call the conspiracy stuff (911, religion, etc.) because of your identically named movie Zeitgeist, and this will only distract and alienate from the RBE prize. I was in the 911 Truth Movement and saw up front & personal so many who had an instinctively negative visceral reaction to any suggestion that 911 was an inside job, that they would hear no more. Also, why alienate those with strong beliefs in their religion? Is it really necessary for us to first convince everyone they've been led to about everything their whole life before introducing a sane alternative to a profit based society when there are no good jobs anyone even in the first world? People are desperate for an alternative and these other things I think are unhelpful distractions to a beginner's introduction to the possibility of another way. Activists for a new system won't get to many likes at the mainstream media exposure apple that we can afford to squander any by trying a hand behind our back with unimportant inconsequential stuff like names and logos. Perhaps if we eliminate these easily changed hurdles, the movement will grow faster and have less back and debanking charges to respond to. Trust me, I know that responding to 911 debunking charges is a full time job in itself, it's a rabbit hole. Unless we get away from the Zeitgeist movie name, we will be linked to the what people call the 'conspiracy' stuff. Of course, this suggestion should not anyway detract from your contribution, Peter. You actually created the movement, right? and probably lots of us learned of it BECAUSE of your movie's addressing of the 'conspiracy' stuff. This is truly only a request for a superficial and easily made change to de-link the V.P. and a R.B.E. with the unrelated items others deem conspiracy and/or non-positive theories. I say easily because people's flyers, old sleeves, logos, stuff that is printed when needed, can be changed digitally on computers. Existing technology generally available to those who print the stuff (just retyping, or simple editing, right?) and there are no stockpiles of stuff with the current names on it that would be wasted I assume? Thanks in advance for your consideration and please also address whom you think such a decision as to the movement's name should be made.

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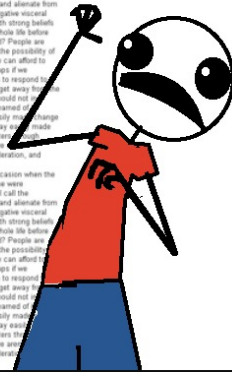


Image copyright Ally Brosh
<http://hyperboleandahalf.blogspot.ca/>

Aplastic Anemia (AA) is a bone marrow failure disease where in approximately 20% of patients, the AA evolves into a myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), clonal disorders of hematopoietic cells. Studies have shown there is an association between shortened telomeres, advanced AA and increased risk of progression to MDS and AML. However, the mechanism on how shortened telomeres impact disease progression and response to treatment is not well understood. Progressive telomere shortening triggers cellular senescence but in a small proportion of cells, this is bypassed by activating the enzyme telomerase. Preservation of telomere length requires the activation of the telomerase complex, consisting of telomerase reverse transcriptase (hTERT) and an intrinsic RNA template (hTR). In the case of AA, telomerase activation and shortened telomeres may lead to an accumulation of chromosomal aberrations, evading senescence and apoptosis, providing a proliferative advantage of leukemic clones. Heterozygous mutations in the gene encoding the telomerase protein component hTERT are seen in approximately 10-15% of AA patients and result in short telomeres. We will investigate how mutations lead to telomere shortening and telomere dysfunction in cells in order to improve our understanding of the role telomerase plays in the pathogenesis of these disorders. Hypothesis: Aberrant telomerase activity from naturally occurring hTERT mutations in AA and AML, results in telomere shortening and genomic instability, contributing to bone marrow failure and disease progression. We will test this under the following aims: Aim 1. Biochemical characterization of hTERT mutants associated with AA and AML. Telomerase regulates telomere length at several levels. First, hTERT and hTR are transcribed, processed, and in the case of hTERT, translated. Second, telomerase localizes in the nucleus and assembles into an active complex. Third, the enzyme recognizes and is recruited to the telomere. Telomerase then catalyzes de novo addition of the telomeric sequence. Since each of these steps is indispensable, disruption of any one would decrease the efficiency of telomerase function. To understand the biochemical properties of these naturally occurring mutants, we have generated expression constructs bearing hTERT mutations found in patients with AA and AML and will test each biochemical activity in vitro. Catalytic activity will be measured using the telomeric repeat amplification protocol (TRAP), processivity measured using the conventional telomerase assay and the ability to interact with telomeric DNA measured with a primer binding assay. Aim 2. Generation of cell lines as surrogate models of human disease state. To better understand the effect of hTERT mutations in a cell culture model, we will utilize various cell models to create human cell lines that over-express the naturally occurring hTERT proteins. 2a. Hematological Cell Line: For initial characterization, we will stably express our mutants in a leukemic cell line, THP-1. 2b. Senescent Cell Line: We will also examine the effects of expressing our mutant hTERT proteins in BJ fibroblast cell, a telomerase negative cell line. These cells do not express telomerase and telomeres shorten with each division. This allows us to address whether expression of hTERT mutants are able to elongate telomeres and bypass senescence. 2c. Hematological Stem Cells: To address the function of mutant telomerase in hematopoiesis we will utilize a long term culture method using CD34+ hematopoietic stem cells. CD34+ cells will be collected from apheresis bone marrow transplant products and transfected with either a control vector or specific hTERT variants. In all 3 models, we will examine the effects of mutant hTERT on telomerase activity (TRAP assay), telomere length (Terminal Restriction fragment analysis), senescence (growth curves and B-galactosidase activity), chromosomal instability (cytogenetics and telomere induced foci assays), apoptosis (Annexin V staining) and the DNA damage response (DDR, clonogenic survival assays, and activation of the DDR via phosphorylation of ATM, Chk2, and p53). Aim 3. Affect of therapeutics on mutant telomerase. In addition to examining the contribution of hTERT mutations on disease progression, our cell model systems can be used to assess therapeutic responses. Each of our stable cell lines expressing either wt or mutant hTERT proteins will be treated with a selective chemotherapeutic panel from MDS and AML treatment protocols to determine how expression of mutant telomerase and difference in telomere lengths affects the viability of the cells via alamar blue viability assay. Outcomes such as cellular differentiation, telomerase activity and apoptosis will also be measured. By considering the role telomeres, telomerase and genomic stability play in the hematopoietic system, we can determine the replicative capacity of hematopoietic stem cells during tumour progression. This will provide insight in predicting response to therapeutics, determining most suitable treatment plan and a mechanism to monitor disease progression. Our studies will advance our understanding of bone marrow failure and AML disease progression in patients with hTERT mutations as well as lead to novel therapeutics for bone marrow failure syndromes.

Aplastic Anemia (AA) is a bone marrow failure disease where in approximately 20% of patients, the AA evolves into a myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), clonal disorders of hematopoietic cells. Studies have shown there is an association between shortened telomeres, advanced AA and increased risk of progression to MDS and AML. However, the mechanism on how shortened telomeres impact disease progression and response to treatment is not well understood. Progressive telomere shortening triggers cellular senescence but in a small proportion of cells, this is bypassed by activating the enzyme telomerase. Preservation of telomere length requires the activation of the telomerase complex, consisting of telomerase reverse transcriptase (hTERT) and an intrinsic RNA template (hTR). In the case of AA, telomerase activation and shortened telomeres may lead to an accumulation of chromosomal aberrations, evading senescence and apoptosis, providing a proliferative advantage of leukemic clones. Heterozygous mutations in the gene encoding the telomerase protein component hTERT are seen in approximately 10-15% of AA patients and result in short telomeres. We will investigate how mutations lead to telomere shortening and telomere dysfunction in cells in order to improve our understanding of the role telomerase plays in the pathogenesis of these disorders. **Hypothesis: Aberrant telomerase activity from naturally occurring hTERT mutations in AA and AML, results in telomere shortening and genomic instability, contributing to bone marrow failure and disease progression.** This will be tested via the following:

Aim 1. Biochemical characterization of hTERT mutants associated with AA and AML. Telomerase regulates telomere length at several levels. First, hTERT and hTR are transcribed, processed, and in the case of hTERT, translated. Second, telomerase localizes in the nucleus and assembles into an active complex. Third, the enzyme recognizes and is recruited to the telomere. Telomerase then catalyzes de novo addition of the telomeric sequence. Since each of these steps is indispensable, disruption of any one would decrease the efficiency of telomerase function. To understand the biochemical properties of these naturally occurring mutants, we have generated expression constructs bearing hTERT mutations found in patients with AA and AML and will test each biochemical activity in vitro. Catalytic activity will be measured using the telomeric repeat amplification protocol (TRAP), processivity measured using the conventional telomerase assay and the ability to interact with telomeric DNA measured with a primer binding assay.

Aim 2. Generation of cell lines as surrogate models of human disease state. To better understand the effect of hTERT mutations in a cell culture model, we will utilize various cell models to create human cell lines that over-express the naturally occurring hTERT proteins. 2a. Hematological Cell Line: For initial characterization, we will stably express our mutants in a leukemic cell line, THP-1. 2b. Senescent Cell Line: We will also examine the effects of expressing our mutant hTERT proteins in BJ fibroblast cell, a telomerase negative cell line. These cells do not express telomerase and telomeres shorten with each division. This allows us to address whether expression of hTERT mutants are able to elongate telomeres and bypass senescence. 2c. Hematological Stem Cells: To address the function of mutant telomerase in hematopoiesis we will utilize a long term culture method using CD34+ hematopoietic stem cells. CD34+ cells will be collected from apheresis bone marrow transplant products and transfected with either a control vector or specific hTERT variants. In all 3 models, we will examine the effects of mutant hTERT on telomerase activity (TRAP assay), telomere length (Terminal Restriction fragment analysis), senescence (growth curves and B-galactosidase activity), chromosomal instability (cytogenetics and telomere induced foci assays), apoptosis (Annexin V staining) and the DNA damage response (DDR, clonogenic survival assays, and activation of the DDR via phosphorylation of ATM, Chk2, and p53)

Aim 3. Affect of therapeutics on mutant telomerase. In addition to examining the contribution of hTERT mutations on disease progression, our cell model systems can be used to assess therapeutic responses. Each of our stable cell lines expressing either wt or mutant hTERT proteins will be treated with a selective chemotherapeutic panel from MDS and AML treatment protocols to determine how expression of mutant telomerase and difference in telomere lengths affects the viability of the cells via alamar blue viability assay. Outcomes such as cellular differentiation, telomerase activity and apoptosis will also be measured. By considering the role telomeres, telomerase and genomic stability play in the hematopoietic system, we can determine the replicative capacity of hematopoietic stem cells during tumour progression. This will provide insight in predicting response to therapeutics, determining most suitable treatment plan and a mechanism to monitor disease progression. **Our studies will advance our understanding of bone marrow failure and AML disease progression in patients with hTERT mutations as well as lead to novel therapeutics for bone marrow failure syndromes**



Aplastic Anemia (AA) is a bone marrow failure disease where in approximately 20% of patients, the AA evolves into a myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), clonal disorders of hematopoietic cells. Studies have shown there is an association between shortened telomeres, advanced AA and increased risk of progression to MDS and AML. However, the mechanism on how shortened telomeres impact disease progression and response to treatment is not well understood. Progressive telomere shortening triggers cellular senescence but in a small proportion of cells, this is bypassed by activating the enzyme telomerase. Preservation of telomere length requires the activation of the telomerase complex, consisting of telomerase reverse transcriptase (hTERT) and an intrinsic RNA template (hTR). In the case of AA, telomerase activation and shortened telomeres may lead to an accumulation of chromosomal aberrations, evading senescence and apoptosis, providing a proliferative advantage of leukemic clones. Heterozygous mutations in the gene encoding the telomerase protein component hTERT are seen in approximately 10-15% of AA patients and result in short telomeres. We will investigate how mutations lead to telomere shortening and telomere dysfunction in cells in order to improve our understanding of the role telomerase plays in the pathogenesis of these disorders. **We hypothesize that aberrant telomerase activity from naturally occurring hTERT mutations in AA and AML, results in telomere shortening and genomic instability, contributing to bone marrow failure and disease progression.** This will be tested via the following:

- Aim 1. Biochemical characterization of hTERT mutants associated with AA and AML.
- Aim 2. Generation of cell lines as surrogate models of human disease state.
- Aim 3. Affect of therapeutics on mutant telomerase

Telomerase regulates telomere length at several levels. First, hTERT and hTR are transcribed, processed, and in the case of hTERT, translated. Second, telomerase localizes in the nucleus and assembles into an active complex. Third, the enzyme recognizes and is recruited to the telomere. Telomerase then catalyzes de novo addition of the telomeric sequence. Since each of these steps is indispensable, disruption of any one would decrease the efficiency of telomerase function. To understand the biochemical properties of these naturally occurring mutants (**Aim 1**), we have generated expression constructs bearing hTERT mutations found in patients with AA and AML and will test each biochemical activity in vitro. Catalytic activity will be measured using the telomeric repeat amplification protocol (TRAP), processivity measured using the conventional telomerase assay and the ability to interact with telomeric DNA measured with a primer binding assay.

To better understand the effect of hTERT mutations in a cell culture model, we will utilize various cell models to create human cell lines that over-express the naturally occurring hTERT proteins (**Aim 2**). **2a. Hematological Cell Line:** For initial characterization, we will stably express our mutants in a leukemic cell line, THP-1. **2b. Senescent Cell Line:** We will also examine the effects of expressing our mutant hTERT proteins in BJ fibroblast cell, a telomerase negative cell line. These cells do not express telomerase and telomeres shorten with each division. This allows us to address whether expression of hTERT mutants are able to elongate telomeres and bypass senescence. **2c. Hematological Stem Cells:** To address the function of mutant telomerase in hematopoiesis we will utilize a long term culture method using CD34+ hematopoietic stem cells. CD34+ cells will be collected from apheresis bone marrow transplant products and transfected with either a control vector or specific hTERT variants. In all 3 models, we will examine the effects of mutant hTERT on telomerase activity (TRAP assay), telomere length (Terminal Restriction fragment analysis), senescence (growth curves and B-galactosidase activity), chromosomal instability (cytogenetics and telomere induced foci assays), apoptosis (Annexin V staining) and the DNA damage response

In addition to examining the contribution of hTERT mutations on disease progression, our cell model systems can be used to assess therapeutic responses (**Aim 3**). Each of our stable cell lines expressing either wt or mutant hTERT proteins will be treated with a selective chemotherapeutic panel from MDS and AML treatment protocols to determine how expression of mutant telomerase and difference in telomere lengths affects the viability of the cells via alamar blue viability assay. Outcomes such as cellular differentiation, telomerase activity and apoptosis will also be measured. By considering the role telomeres, telomerase and genomic stability play in the hematopoietic system, we can determine the replicative capacity of hematopoietic stem cells during tumour progression. This will provide insight in predicting response to therapeutics, determining most suitable treatment plan and a mechanism to monitor disease progression. ***Our studies will advance our understanding of bone marrow failure and AML disease progression in patients with hTERT mutations as well as lead to novel therapeutics for bone marrow failure syndromes.***



Putting It All Together, A Final Word

Take breaks

Read out loud

Ask for input and edits



Questions??

Application support



Internal review by CSM postdocs

- Students writing Tri-council doctoral scholarships matched with postdoc reviewers
- Contact me at rdevinne@ucalgary.ca for link
- Or click here [CGSM Application Support](#) to access form for both postdoc review and peer mentors.

FGS resources

- Plan your **support network**: your supervisor, your program (is there a department workshop?)
- Consult current scholarship holders in your program
- **Peer review**: Scholarship Cafés & Drop-In Mentoring (Zoom)
- gradlead@ucalgary.ca

Scholarship Café #1	Tuesday, November 9, 2021	10:00am - noon
Scholarship Café #2	Tuesday, November 24, 2021	10:00am - noon
Drop-in #1	Friday, November 12, 2021	1:00pm - 2:30pm
Drop-in #2	Thursday, November 25, 2021	1:00pm - 2:30pm
Drop-in #3	Monday, November 29, 2021	10:00am - noon

**Good luck on your
application!!!**

Links

- Agency website.
 - https://www.nserc-crsng.gc.ca/Students-Etudiants/PG-CS/CGSM-BESCM_eng.asp
- Transcripts: Due end of day Nov 5
 - <https://grad.ucalgary.ca/sites/default/files/teams/5/2022%20CGSM%20Transcript%20request.pdf>
- FGS link
 - <https://grad.ucalgary.ca/awards/award-opportunities/canada-graduate-scholarships>
- Common CV
 - <https://ccv-cvc.ca/>