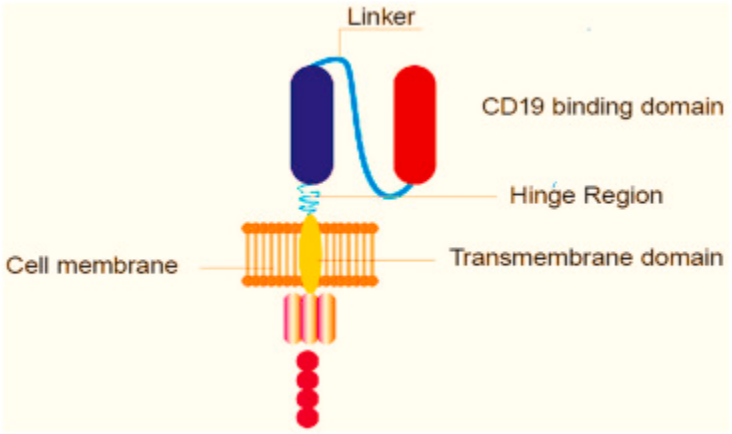
- What's in the name?
    - CD19 CAR T-cell therapy
    - CD19 = protein
        - https://ehoonline.biomedcentral.com/articles/10.1186/2162-3619-1-36
        - https://www.sciencedirect.com/science/article/pii/S0268960X22000765#:~:text=CD19%20is%20ubiquitously%20expressed%20in,no%20other%20available%20treatment%20options.
- How does CAR T-cell therapy work?
    - https://www.nature.com/articles/s41408-021-00459-7
    - Cars are receptors that redirect t-cells to eliminate cells expressing a specific antigen
    - https://www.sciencedirect.com/science/article/pii/S2667394022000090#:~:text=It%20has%20four%20domains%3A%20an,treatment%20against%20many%20hematological%20malignancies.
    - T lymphocytes that are genetically engineered with artificial t cell receptors
        - What are t lymphocytes?
            - https://www.nature.com/articles/s41392-023-01471-y
        - How is the CAR made?
        - How to receptors work
    - Pros and cons?
    - What are antigens?
    - Synthetic receptor
    - 4 parts of a CAR:



    - https://www.sciencedirect.com/science/article/pii/S2667394022000090#:~:text=It%20has%20four%20domains%3A%20an,treatment%20against%20many%20hematological%20malignancies.
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC10835665/
        - Antigen binding
            - Outside the cell
            - scFv that binds to the target
            - When it binds, it activates the anti tumor effect of the t cell
        - Hinge region
        - Transmembrane domain

        - Signaling domain
            - Signals immune response
    - Antigens
        - https://pmc.ncbi.nlm.nih.gov/articles/PMC10835665/
        - Target tumor specific antigens/antigens upregulated on tumor cells
    - Treatment process
        - https://pmc.ncbi.nlm.nih.gov/articles/PMC10835665/
    - Population
    - Limitations
        - https://www.nature.com/articles/s41408-021-00459-7
        - Antigen resistance
            - T-cells that only target a specific antigen are very successful at first, but the cancer eventually stops expressing the antigen
            - IE 70-90% of ALL patients showed response to the CARs (targeting CD19 antigen), but in 30-70% of patients the antigen was downregulated after relapse
            - Strategies to treat involve targeting many different antigens
                - Dual or tandem
        - Off tumor effects
            - In solid tumors, the antigens are sometimes also found in healthy, normal tissue
            - CARs may attack other tissue as well
                - “On-target off-tumor toxicity”
            - Potential solution is to target post-translational markers instead
    - Car t cell exhaustion
        - https://pmc.ncbi.nlm.nih.gov/articles/PMC9773844/
        - Main obstacle in remission
        - CAR t-cell exhaustion contributes to therapy failure
        - T-cell expansion
            - To get sufficient CAR t-cell numbers, cells need to be expanded before being infused
            - Culture affects cell exhaustion
            - Observed that the cytokine IL2 causes exhausgen, while IL15 or IL2+IL4 increases cell efficaincy
        - https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-022-03442-3
    - Reasons for no response
        - https://pmc.ncbi.nlm.nih.gov/articles/PMC8214555/#:~:text=First%2C%20CAR%20T%20cell%20failures,persistence%20in%20vivo%20is%20a
        -
    - Bone marrow and car t-cells
        - https://onlinelibrary.wiley.com/doi/10.1111/sji.13273
        - BM = sticky tissue in bone cavity
            - Blood vessels, nerves, cells

        - The bone marrow produces haematopoietic stem cells, which then differentiate into other cell lines
        - However, in a tumor state, Myeloid-derived suppressor cells do not differentiate further, causing accumulation of stem cells in the bone marrow
            - These accumulated stem cells produce arginase-1, reactive oxygen species, and iNOS that reduce CAR t-cell efficiency
        - Tregs = CD4+ cells that decrease IL-2
            - Results in inhibitory BM environment
        -
        - https://pmc.ncbi.nlm.nih.gov/articles/PMC7058784/#:~:text=is%20less%20established.-,Structural%20Components,and%20allow%20for%20immune%20escape.
        -

Nov 10

- I'm changing my sf plans last minute
- The original plan was to predict gvhd in bone marrow transplants, but the dataset I found doesn't provide actual read counts
- I wanna stay in this field so I'm thinking of doing something similar to my original idea
- Did some basic research on car t cell therapy

Nov 15

- Potential datasets?
    - https://doi.org/10.1126/sciadv.abj2820
    - https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE246342
    - https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE153670
- Also I need to figure out how gene expression even works
    - From different project, see: galaxy project server
        - Tool for gene expression analysis?

Nov 16

- Tutorial for galaxy project server
    - http://bio3.giga.ulg.ac.be/archana_bhardwaj/userfiles/downloads/2017/GBIO0002/Lecture9/Gene%20expression-v3.pdf
- Did research on CAR proteins and how car t cells work

Nov 20

- I picked out my dataset
    - I'm going with the BM one. The other two are pretty cool, but there is a lot of research already on car t cell relapse and not so much on BM

    - Read counts (what are those?) seem to be in a cvs file
    - Still figuring out galaxy project server
        - All the tutorials seem to be processing raw read counts, but I don't have that???
        - Dataset says normalized, so its processed already?

Nov 23

- TLDR what are read counts
    - So basically in rna sequencing, the rna gets chopped up into tiny pieces, and the base pairs are matched with the other end to find the gene the rna expresses
        - Rna chunks are called read sequences
        - The read counts of a gene is how many rna chucks match up to the gene
        - More read counts = more expression
- Ig differential gene expression is just running a t-test on the read counts two groups, and whatever gene has a significant p value is differently expressed
    - Why do I need all this software if I could just run a t test in python???

Nov 30

- After further exploration, heres why I can't just run a t-test:
    - Too many false positives in the p-value
        - What is adjusted p-value?
    - Degseq2 uses linear modeling to account for the expression levels of other genes to determine sig genes
    - Also many papers run gene ontology on top of differential expression, I need different software for this
- I found a tutorial vid on how to run DE in R
    - https://www.youtube.com/watch?v=OzNzO8qwwp0&t=113s
    - Never coded in r before, this should be interesting…

Dec 4

- Found a much better tutorial
    - https://www.youtube.com/watch?v=Ul-9s8YOOSk&t=821s
- Adj p-value
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC6099145/
    - https://www.youtube.com/watch?v=rZKa4tW2NKs&t=320s&pp=ygULYWRqIHAgdmFsdWU%3D
        - Benjamini and Hochberg method
        - P vals are first ordered by value from smallest to larget
        - Then multiplied by (m/k) where k is the rank of the p value and m is the number of total p values
            - The product is the adjusted p value
        - This method controls the False Discovery Rate
            - What is this?

- FDR = Expected (FalsePositive/ (FalsePositive+TruePositive))
- Expected proportion of false positives among all positives, try to limit this number

Dec 10

- Did more research on car t-cell therapy
  - I need to find the misc infor for my dataset
  - Curretnyl the GEO page only tells me the naming convention and that theres non demographic data, but it doesn't tell me what participants were given, how they were diagnosed etc
  - There is a paper associated w the data. I should get access to it

Dec 15

- Found paper!
- Participants were treated w car t cells from nova
- I also found the study associated with the data, its has been helpful in providing info about dosage, etc
- What is Wald's test?
  - https://medium.com/@analyttica/understanding-wald-test-2e3fa7723516
  - Determines if a variable is significant to the model
    - Does this variable add value to the model?
  - If walds = 0, can remove model

- If MLE is significantly different from 0 (null hypothesis is that

Where

$\hat{\beta}$: maximum-likelihood estimation (MLE) of co-efficient

β_0 : Parameter of interest, usually 0 as we want to test whether the coefficient is different than zero or not.

SE: Standard error of MLE

VAR: Variance of MLE

χ^2_1 : Chi-Square distribution with 1 degree of freedom

B0=0), MLE improves model fit and is significant
    - Maximum likelihood distribution -maximise the chance that process described by model is actually observed

Dec 30

- Found the clinical trial the data came from!
- https://clinicaltrials.gov/study/NCT02228096
- https://clinicaltrials.gov/study/NCT02435849
    - Used CTL019 (tisagenlecleucel)
    - 2-5 million cells/kg for patients under 50kg
    - 100 - 250 million cells/kg for patients above 50kg
- Still no demographic data????

Jan 6-10

- Finished background research on CAR t-cell therapy
- Working on the writeup- putting my background research, variables and hypothesis into words
- I'm using the tutorial I found to start writing code in R

Hypothesis: If gene expression in BM of ALL patients recieving CAR t cell therapy is measrued, there will be differently expressed genes because studies have shown BM microenvironment has an impact on car t cell therapy success

Jan 15

- Found sig genes and pathways!
    - Enriched pathways in NR seem to be related to cardiac functions…hmmmmm
- Writing variables and methodology rn

Jan 20

- Something interesting I found is Interleukin-10 is an enriched pathway 👀
    - IL-10 is related to IL2 and IL6, two heavily studied cytokines. I wonder if IL10 is sig in CAR t cell therapy
    - Found paper on IL10 and immunosurpression???

Jan 30

- Code is done and I'm putting in the results now
- IL10 is related to tcells. Perhaps I can mention this in paper?
- Still not sure about the cardiac signaling thing. Could it have something to do with pathways

Feb 1-17

- Worked on my writeup
- I also got Josh and Dr Morin to take a look. They both dont have many outstanding comments

Fed 27

- Writeup is finished! School SF is on March 11 so I'm cutting it pretty close here 😅
    - Got sylvan to look at it
- Starting to work on my trifold printout
    - (too many words and not enough space on the trifold ahhh!)

March 5

- Presented my tedtalk but in other news I got my trifold
    - I'm going for a blue theme this year…

March 6-9

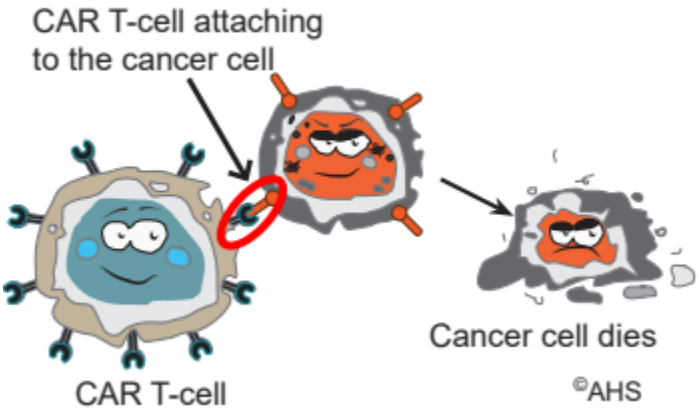
- Practiced my speech w sylvan and my parents
    - Wish me luck tomorrow 🙏

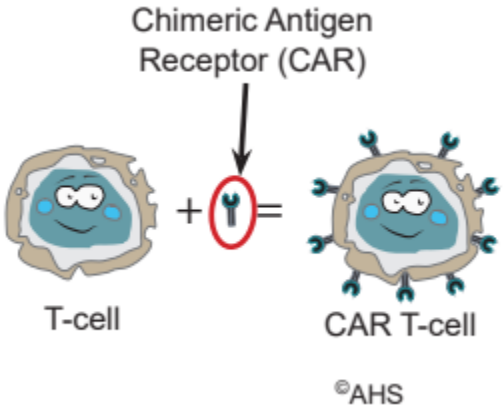
March 13

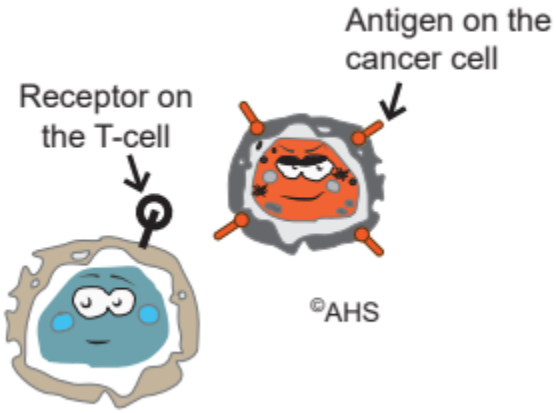
- Got into CYSF 🙂
- Todo
    - Review feedback from judges
    - Email mentor with updates and questions
    - Redo speech - put more emphasis on relevance
    - Present for ms ghanem (do buy mar 21)
    - Film video for the platform
- **Platform submission is due on march 21, the last day of school**

Mar 18

- Looked at judging feedback
    - Need to tell judges that I don't have a control group, but nonrespoders are the group of interest
    - Looked at feedback on writeup
- I found the cutest diagram from AHS for car t cell therapy
    - I might use it in april





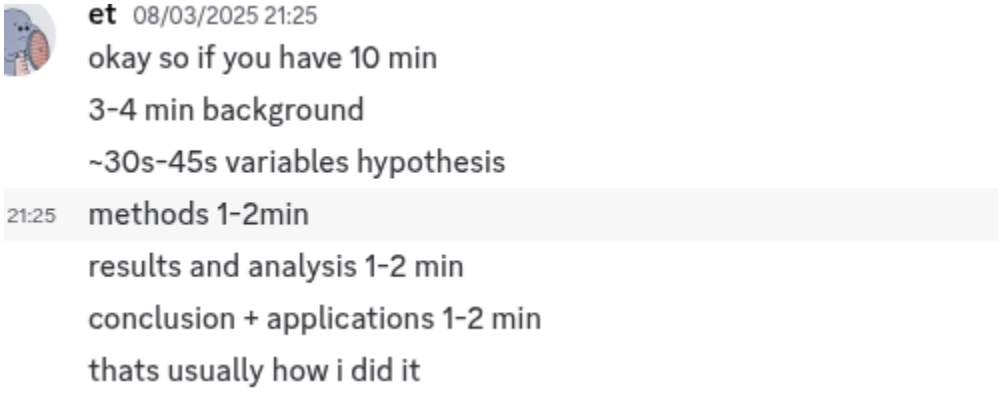


March 19

- Worked on presentation for the CYSF platform
    - I switched to figma instead of slides
- Will present to Ms Ghanem tomorrow
- Judging questions that made me tweak out:
    - Where are stem cells found?
    - What is the cause of IL-10 levels?

March 20

- Finished uploading everything to the website including video



Time limit is 10 minutes

EMAILS TO MENTORS

Hello!

My name is Andi, and I'm a grade 10 student at Webber Academy. I have been doing science fairs for six years, and last year I won the top life science award at the Calgary Youth Science Fair for my project on statistics and dementia. This year, my project is on bioinformatics and hematology. I want to use differential gene expression, and software like Limma, to find biomarkers of graft-vs-host disease in gene expression data. I am seeking a mentor experienced in bioinformatics and microarrays for this project.

Any advice is greatly appreciated. My resume is attached below.

Thanks for your time!

Andi Liu

Thread with Dr Morin:

Sent: Friday, January 17, 2025 21:39
To: Ryan Morin <rdmorin@sfu.ca>
Subject: Re: Science Fair Mentorship

•••

Andi <andulo2021@gmail.com> Thu, Feb 20, 8:00 AM
to Ryan

Hi Dr Morin,

Happy February! I'm working on the results and discussion portion of my writeup right now. I was wondering if you could read through some of my thoughts/outline for my discussion (highlighted in yellow) and go over the write-up as a whole. Some of my results are pretty exciting, and some are unexpected.

Thank you,

Andi

WRITEUP_2025

•••

One attachment • Scanned by Gmail

WRITEUP_2025

Andi <andulo2021@gmail.com> Fri, Jan 17, 10:39 PM
to Ryan

Hello Dr Morin,

Wow, its the new year, hope you had a great 2025 so far! Apologies for not updating in so long, my school has midterms right now. I have several big updates: the first is that I switched my focus from GvHD to CAR t-cells. The GvHD dataset I mentioned had very poor documentation, and I am more interested in CAR t-cell therapy anyway. The dataset I'm looking at has data from the bone marrow of B-ALL patients before receiving CD19 CAR t-cell therapy, and I have found 38 genes that are biomarkers of remission :) The software I'm using is Deseq2 in R. I'm looking to do some gene ontology analysis and make volcano plots.

This is an update, I will try my best to send you my writeup closer to the end of the month when exam season is over.

Thank you

Andi

•••

Ryan Morin <rdmorin@sfu.ca> Sat, Jan 18, 11:26 AM
to me

Happy new year.
Sounds good. Let me know how I can help.

Ryan

From: Andi <andulo2021@gmail.com>
Sent: Friday, January 17, 2025 21:39
To: Ryan Morin <rdmorin@sfu.ca>
Subject: Re: Science Fair Mentorship

•••

Ryan Morin <rdmorin@sfu.ca> Mon, Nov 25, 2024, 1:42 PM
to me

I did. What is your timeline for this project?

Get Outlook for iOS

From: Andi <andulo2021@gmail.com>
Sent: Monday, November 25, 2024 11:01:38 AM
To: Ryan Morin <rdmorin@sfu.ca>
Subject: Fwd: Science Fair Mentorship

•••

Andi <andulo2021@gmail.com> Thu, Nov 28, 2024, 11:12 AM
to Ryan

Dear Dr Morin,

My school fair is in March and the city fair is in April. I plan to use data from a GEO dataset with differential gene expression analysis to find biomarkers. Right now, I am downloading the data and doing background research on gene expression analysis. I plan to analyze my results in January.

December: run data through Limma
January: analyze identified genes/pathways
February: work on science fair writeup

I was hoping you could check if my methodology and analysis are sound and up to industry standards and give feedback on my writeup closer to science fair.

Thank you,

Andi

Andi <andulo2021@gmail.com> Fri, Jan 17, 10:39 PM
to Ryan

MBB Manager Administrative Services Mon, Nov 25, 2024, 10:27 AM
Hello Andi, I have forwarded your email to our faculty whose expertise includes bioinformatics. I have told them to respond directly to you. Hopefully one of th

Ryan Morin <rdmorin@sfu.ca> Mon, Nov 25, 2024, 10:30 AM
to me

Dear Andi,
I was forwarded your email by a colleague but your resume was not attached. Could you please send it along?
Your project idea sounds appealing to me and is within my area of expertise.

Thanks
Dr. Morin

From: MBB Manager Administrative Services <mbbmas@sfu.ca>
Sent: Monday, November 25, 2024 09:24
To: Sophie Sneddon <sophie_sneddon@sfu.ca>; Ryan Morin <rdmorin@sfu.ca>; Fiona Brinkman <brinkman@sfu.ca>; William Hsiao <wwhsiao@sfu.ca>; Amy Lee <amy_lee_10@sfu.ca>
Subject: FW: Science Fair Mentorship

Hi all,

Please respond directly to this student if you feel you would like to help them.

Thanks,

Christine Beauchamp
Manager, Academic and Admin Services
Department of Molecular Biology and Biochemistry
778-782-3991

Science Fair Mentorship Inbox ×

Andi <andulo2021@gmail.com> Mon, Nov 25, 2024, 8:00 AM
to mbbmas

Dear Ms Beauchamp,

My name is Andi, I am a grade 10 student in Calgary. I have been participating in the Calgary Youth Science Fair for four years, and am interested in hematology and bioinformatics. Last year, I won the top Life Science award for my project on dementia and statistics. This year, I want to determine the biomarkers of graft-vs-host disease in hematopoietic stem cell transplants using statistics. I am seeking a mentor who is experienced in bioinformatics for this project.

If anyone in the department is interested in mentoring me, it would be invaluable. Any advice is greatly appreciated. My resume is attached below.

Thank you for your time!

Sincerely,

Andi Liu

One attachment • Scanned by Gmail

MBB Manager Administrative Services Mon, Nov 25, 2024, 10:27 AM
Hello Andi, I have forwarded your email to our faculty whose expertise includes bioinformatics. I have told them to respond directly to you. Hopefully one of th

Dear Dr Morin,

Happy March! I recently attended my school fair, and have advanced to the regional competition 🙂. I have a question about CAR T-cells and enriched pathways. Some of the most enriched pathways I found in the bone marrow of nonresponders to therapy were related to cardiac muscle signaling and activation gradient. Could cardiac cell signaling (or just cell signaling in general) create an immunosuppressive BM microenvironment that impacts CAR T-cells? Or is there a more technical explanation like poor quality sequencing? These pathways are pretty enriched so I have some of my own theories, but what are your thoughts on this?

The city fair is on April 10. I will be working on my speech and poster until then. My school's spring break is from March 22-April 5, so I was wondering if you would be interested in hearing me present my speech to you over a virtual call and provide some feedback (perhaps between April 7 and 10th, or before then?).

Thank you for your time,

Andi