Project Notes

Analyzing HLA Sequences to Predict Organ Rejection and Find Optimal Targets for Precise Immunosuppression

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Project Notes:

Project Title: Analyzing HLA Sequences with Machine Learning to Find Optimal Targets for Selective T-Cell Inhibition to Prevent Organ Rejection

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Note Well: There are NO SHORT-cuts to reading journal articles and taking notes from them. Comprehension is paramount. You will most likely need to read it several times, so set aside enough time in your schedule.

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Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
Different Transplant Methods	Reading articles about different transplant methods	Article 6 (stem cells before) and Article 8 (thymus tissue)	September 3
Stem Cells	Read articles about transplanting bone marrow cells	Article 15 (Organ Transplants Without Life-Long Drugs)	September 18
How Organ Rejection Occurs	Learned about the cause of rejection and the different types	Article 17 (understanding rejection) and Article 18 (chronic rejection)	September 20
Current prevention methods	Learned about TCMR and ABMR	Article 13 (kindney therapies)	October 15
Mismatch Organ Transplants	Read articles about abnormal transplantations	Article 7 (ABO incomaptible) and Article 24 (HIV+ to HIV-)	September 31
Immunosupressors	Read about immunosupressors	Article 16 (calcineuron inhibitors)	September 20
Thymus Function	Read about thymus and how to works for T cells	Article 25 (T cell differentiation)	October 14
Rejection Patterns	Read articles about patterns noticed in specific populations	Article 14 (Deleted Gene) and Article 27 (racial disparity)	September 18
Organ Matching	Read about MHC, HLA, and Tissue typing	Article 9 (tissue typing)	September 16
T-Cell Activation	Watched a Video on T cell activation	Video 1 (activation and differentiation)	October 12
Genes/proteins present during rejection	Read/presented articles about selective T Cell inhibition for rejection	Article 11 (IL-6) and article 21 (CTLA4-Ig)	October 16

Personalized Medicine	Reading on precision medicine for immunosupression	Article 12 (personalized medicine)	October 2
Gene Therapy	Learned about Gene therapy in other forms/conditions.	Article 1 (Vjuvek eye drops) Article 2 (collagen) and Article 20 (organ transplants)	October 1
Organ Rejection Monitors	Read a patent about an implant to monitor rejection in kidneys	Article 19 (monitoring device) - Patent	October 13
Technology in Organ Rejection	Read about how AI and machines are used during organ trasnplants	Article 26 (AI model to predic drug dosage) Article 21 (AI in transplants) and Article 19 (monitoring device)	October 14
Extent of Problem	Looking at statistics and death rates of people on wait lists	Article 24 (organ supply vs. demand) and article 27 (race disparity)	October 14
Costimulatry Blockade	Read an article from Dr.Harlan about the costimulatory blockade	Article 29 (costimulatory blockade to prevent rejection) and Article 30 (anti-asialo)	November 13
PCT Microstructures	Watched a Video about role of PCT in kidneys	Video 2 (Function of Proximal Convoluted Tubule)	November 12
Chronic Rejection	Read an article about CTR and difficultly in treatment/research	Article 18 (CTR with pictures)	September 20
HLA mismatches and Machine Learning	Read an article about predicting rejection with HLA and ML	Article 34 (predicting kidney viability with partial HLA data)	November 26
Antibody Induced Therapy	Read an article about mAbs and antibody induced therapy	Article 31 (mAbs therapy in kidneys)	November 26
Machine Learning	Read an article about different AI models	Article 35 (AI and precision medicine)	November 30

Literature Search Parameters:

These searches were performed between **08/20/23** and **10/16/2023**
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
LIVE Science	Organ Rejection/Organ Transplant	Article 6 - kidney transplants with stem cell transplant Article 7 - universal ABO incompatible transplant Article 8 - heart transplant with thymus tissue transplant
Google	Organ Matching	Article 9 - Tissue Typing
Google Scholar	Rejection Therapies	Article 13 - kidney rejection therapies
Google	Organ Rejection Monkey	Article 22 - CTLA4-Ig study on monkeys
Connected Papers	CTLA4-Ig	Article 11 - IL-6 and CTLA4-Ig study on mice
Google	Personalized medicine Organ Transplant	Article 12 - recent advances in personalized medicine for immunosuppression
Google	Organ Transplant Genetics	Article 14 - deleted gene association with organ rejection
Google	Stem cells organ rejection	Article 15 - organ transplant without immunosuppressive drug
Google	Immunosupressors	Article 16 - calcineurin inhibitors
Google	Organ Rejection	Article 17 - understanding organ rejection Article 18 - chronic rejection
Google Patents	Organ Rejection Monitor	Article 19 - Non-Invasive implant to monitor kidney rejection
Google	Organ transplant Gene Therapy	Article 20 - Gene therapy and solid-organ transplantation
Google	AI Organ Rejection	Article 21 - AI for solid organ transplantation Article 26 - Predicting drug dosage with AI algortihm

Google	Organ Shortage	Article 23 - Organ supply vs. demand problem
Google	HIV Positive Organ Transplants	Article 24 - HIV+ to HIV- organ transplant in South Africa Johns Hopkins *HIV-Positive to HIV-Positive Transplant*
Google	Thymus tissue T cells	Article 25 - thymus and tolerance

These searches were performed between **10/17/23** and **12/8/2023**
List of keywords and databases used during this project.

Database/search engine	**Keywords**	**Summary of search**
Google	CAR T cell therapy, organ rejection	Article 28 - Successful CAR T Cell Therapy in a Heart and Kidney Transplant Recipient With Refractory PTLD
Google	Costimulatory Blockade	Article 29 - Can T-Cell Costimulatory Pathway Modifiers Revolutionize the Prevention of Graft Rejection? Article 30 - Asialo GM1+ CD8+ T cells play a critical role in costimulation blockade–resistant allograft rejection
Google	Monoclonal Antibodies	Article 31 - Monoclonal Antibody Therapy and Renal Transplantation: Focus on Adverse Effects
Google	Precision Medicine	Article 32 - Pharmacogenomics: a new paradigm to personalize treatments in nephrology patients Article 35 - Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine
Google	Organ Rejection Prediction	Article 34 - Predicting kidney transplant outcomes with partial knowledge of HLA mismatch Article 33 - DONOR CYTOKINE GENOTYPE INFLUENCES THE DEVELOPMENT OF ACUTE REJECTION AFTER RENAL TRANSPLANTATION
Gene Expression Omnibus	HLA Organ transplant	GSM2309925 and GSM1964076
European Bioinformatics	HLA Organ rejection	E-GEOD-14328 - has multiple GEO datasets

Institute		related to gene expression in rejection
Google Patents	Organ rejection diagnosis	Article 37 - Non-invasive diagnosis of graft rejection in organ transplant patients
ISEF Abstract Search	Organ rejection, transplant, allograft	Demetri Maxim's Biomarker Organ rejection project Article 36 - Portable instrument for in vitro detection and quantification of biomarkers

Tags:

Tag Name	
#Examples	#SummerReading
#Introduction	#PotentialResearch
#Information	#Methodologies
#Background/Stats	#Backup

Article Notes - A-Term:

Article #1 Notes: **Gene-therapy drops restore teen's vision after genetic disease left his eyes clouded with scars**

Source Title	Gene-therapy drops restore teen's vision after genetic disease left his eyes clouded with scars

Source citation (APA Format)	Lanese, N. (2023b, July 26). Gene-therapy drops restore teen's vision after genetic disease left his eyes clouded with scars. *Live Science*. https://www.livescience.com/health/genetics/gene-therapy-drops-restore-teens-vision-after-genetic-disease-left-his-eyes-clouded-with-scars
Original URL	https://www.livescience.com/health/genetics/gene-therapy-drops-restore-teens-vision-after-genetic-disease-left-his-eyes-clouded-with-scars
Source type	General Article
Keywords	Gene therapy, butterfly disease
#Tags	#Examples
Summary of key points + notes (include methodology)	Antonio was born with dystrophic epidermolysis bullosa, which made him blind. Vyjuvek eye drops deliver collagen to people's eyes. His sight was restored when he started using gene therapy eye drops and gel.
Research Question/Problem/ Need	How do the Vyjuvek eye drops treat blind people?
Important Figures	N/A
VOCAB: (w/definition)	**dystrophic epidermolysis bullosa**: genetic condition that prevents cells from making a specific type of collagen. Causes erosion and scarring of skin and eyes **Vyjuvek**: topical gel that users rub on their blistered skin, and it works by delivering working copies of the broken collagen gene into their cells
Cited references to follow up on	https://apnews.com/article/gene-therapy-blindness-rare-diseases-58f81838894dfb8568affde0b7e4d2f1 https://www.livescience.com/butterfly-disease-gene-therapy-phase-three
Follow up Questions	Can the eye drop work for blind people with other conditions? How long do people need to use the gel before they permanently restore their vision? Can the gel be made to deliver copies of other genes?

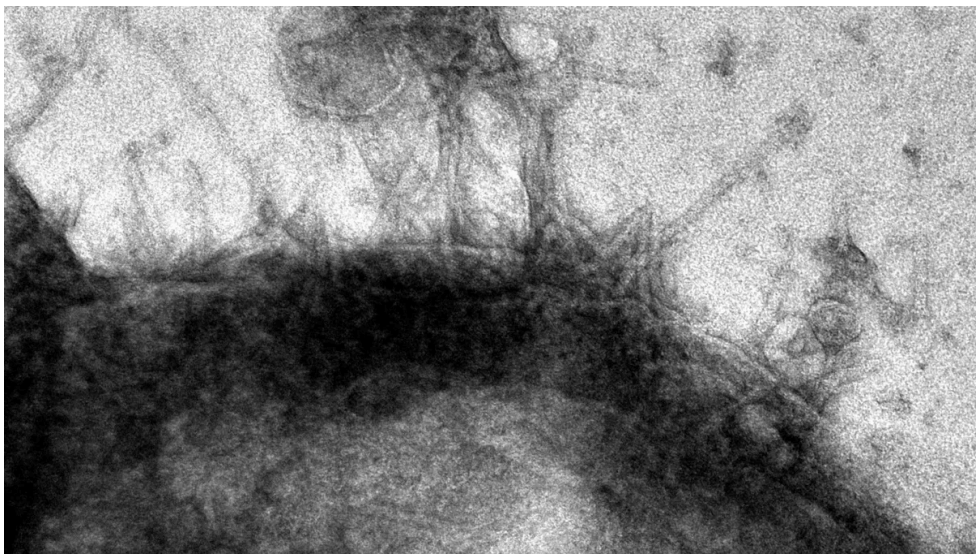
Article #2 Notes: **1st UK child to receive gene therapy for fatal genetic disorder is now 'happy and healthy'**

Source Title	1st UK child to receive gene therapy for fatal genetic disorder is now 'happy and healthy'
Source citation (APA Format)	Lanese, N. (2023, February 16). 1st UK child to receive gene therapy for fatal genetic disorder is now "happy and healthy." *Live Science*. https://www.livescience.com/1st-uk-child-to-receive-gene-therapy-for-fatal-genetic-disorder-is-now-happy-and-healthy
Original URL	https://www.livescience.com/1st-uk-child-to-receive-gene-therapy-for-fatal-genetic-disorder-is-now-happy-and-healthy
Source type	General Article
Keywords	Gene therapy, metachromatic leukodystrophy, genetic disorder, nervous system, stem cells
#Tags	#Examples
Summary of key points + notes (include methodology)	Teddi had gotten gene therapy to treat her MLD, which is a genetic disorder that destroys brain and nerve cells. Gene therapy inserts working copies of the correct genes via stem cells. Doctors did this by removing the child's stem cells and replacing the faulty gene that causes MLD before re-injecting the treated cells into the patient.Teddi is happy and healthy now.
Research Question/Problem/ Need	What are the results of using gene therapy to treat metachromatic leukodystrophy?
Important Figures	N/A
VOCAB: (w/definition)	**MLD:** disrupts cells' ability to break down sulfatides. Sulfatide buildup destroys brain and nerve cells, resulting in cognitive problems, a loss of motor control and sensation, seizures, paralysis and blindness **Stem cells:** self-renewing and able to duplicate, or clone, themselves. These special cells are used in the rapidly growing field of regenerative medicine to halt or even reverse chronic diseases **Libmeldy:** works by inserting into the body working copies of the genes that are

	faulty in MLD, thus restoring the ability to break down sulfatides
Cited references to follow up on	https://www.england.nhs.uk/2023/02/first-baby-receives-life-saving-gene-therapy-on-nhs/
Follow up Questions	How long is gene therapy effective in treating MLD? What are some possible side effects of using gene therapy? Can gene therapy work on people who have severe MLD symptoms?

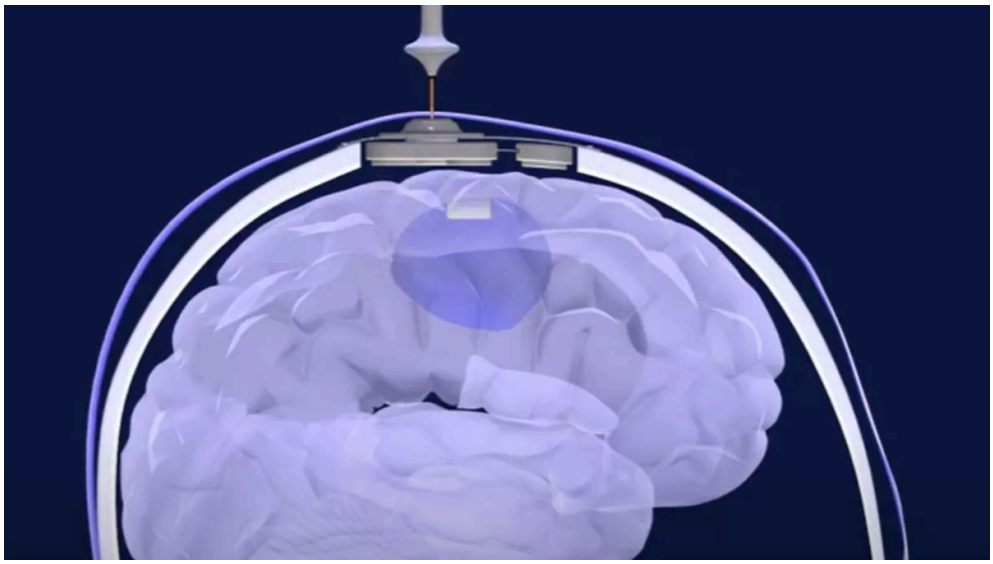
Article #3 Notes: **DeepMind's AI used to develop tiny "syringe" for injecting gene therapy and tumor-killing drugs.**

Source Title	DeepMind's AI used to develop tiny "syringe" for injecting gene therapy and tumor-killing drugs.
Source citation (APA Format)	Lanese, N. (2023b, March 29). DeepMind's AI used to develop tiny "syringe" for injecting gene therapy and tumor-killing drugs. *Live Science*. https://www.livescience.com/deepminds-ai-used-to-develop-tiny-syringe-for-injecting-gene-therapy-and-tumor-killing-drugs
Original URL	https://www.livescience.com/deepminds-ai-used-to-develop-tiny-syringe-for-injecting-gene-therapy-and-tumor-killing-drugs
Source type	General Article
Keywords	Artificial intelligence, proteins, CRISPR-Cas9, cancer
#Tags	#SummerReading
Summary of key points + notes (include methodology)	Scientists used an artificial intelligence program called AlphaFold to develop a molecular "syringe" that can inject proteins directly into human cells. Researchers modified a syringe-like protein found in Photorhabdus asymbiotica. To kill an insect, P. asymbiotica secretes syringes that carry toxic proteins. Small tails at the base bind to the proteins on the surface of an insect's cell. Then, the syringe stabs a needle through the cell membrane to release the toxins. Using AlphaFold, scientists quickly predicted the structures of the tail fibers and how to modify them. They used CRISPR-Cas9 and syringes with DNA-snipping scissors to deliver toxins to cancer cells inside mice. They found that the toxins stayed in the targeted area and didn't give the mice an adverse reaction. Research shows that these syringes can provide better control in gene therapy and cancer treatment.
Research Question/Problem/ Need	Are modified proteins from bacteria effective in administering medicine against cancer cells?

Important Figures	 Microscopy image shows programmed syringes bound to the surface of a cancer cell. Once bound, they injected toxic proteins through the cell's membrane.
VOCAB: (w/definition)	**P. asymbiotica:** grow inside roundworms called nematodes. When a nematode invades an insect larva's body, the bacteria kill the insect's cells, allowing the nematode to eat the insect.
Cited references to follow up on	https://www.livescience.com/artificial-intelligence-protein-folding-deepmind.html
Follow up Questions	How can the syringes be programmed to fight disease-causing bacteria? How well can the syringes diffuse through different tissues and organs? How does the immune system react to the new protein delivery system?

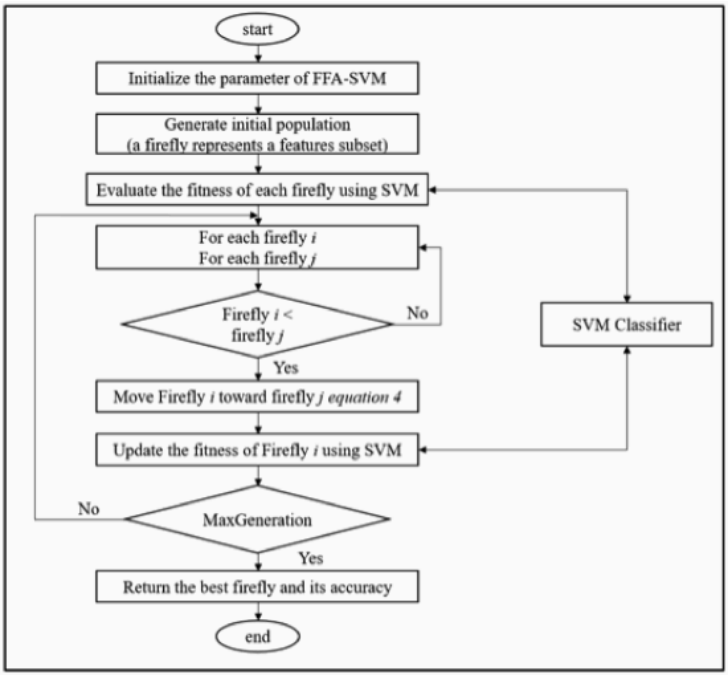
Article #4 Notes: **New ultrasound device helps powerful chemo reach deadly brain cancers, human trial shows**

Source Title	New ultrasound device helps powerful chemo reach deadly brain cancers, human tril shows
Source citation (APA Format)	Lanese, N. (2023, May 2). New ultrasound device helps powerful chemo reach deadly brain cancers, human trial shows. *Live Science*. https://www.livescience.com/health/brain-cancer/new-ultrasound-device-helps-powerful-chemo-reach-deadly-brain-cancers-human-trial-shows
Original URL	https://www.livescience.com/health/brain-cancer/new-ultrasound-device-helps-powerful-chemo-reach-deadly-brain-cancers-human-trial-shows
Source type	General Article
Keywords	Brain, cancer, ultrasound, chemo
#Tags	#SummerReading
Summary of key points + notes (include methodology)	In the brain, there is a wall composed of tightly packed cells that lines the blood vessels. This barrier allows nutrients and hormones to pass but stops toxins and bacteria. However, this barrier can also prevent cancer-killing medicine and drugs from entering. Therefore, scientists made a new ultrasound device that temporarily opens the barrier, allowing medicine to reach the brain. A study conducted by scientists aimed to implant the ultrasound device to help deliver potent chemotherapy drugs into the brain. In the trial, seventeen adults had cancer that spreads quickly and is almost impossible to remove completely through surgery. To use the device, doctors inject microbubbles into the patient's bloodstream,which eventually travel to the blood vessels of the brain. The ultrasound implant emits a sound wave that shakes the microbubbles, disrupting the barrier. After the barrier is damaged, scientists give the medicine up to six times, within 3-week intervals. The results showed that the ultrasound can significantly boost the amount of medicine that crosses the barrier. Paclitaxel and carboplatin crossed the brain tissue 3.7 and 5.9 times more, respectively, in regions of the brain exposed to ultrasound. An hour

	after the ultrasound disrupted the barrier, it closed and restored itself with no serious side effects.
Research Question/Problem/ Need	How can ultrasound overcome the brain vessel barrier to deliver chemo drugs to brain cancer cells?
Important Figures	 An ultrasound device implanted in the skull can help chemotherapies reach tumors in the brain
VOCAB: (w/definition)	**Microbubbles**: gas spheres **paclitaxel and carboplatin:** chemo drugs
Cited references to follow up on	https://www.livescience.com/using-zika-virus-to-treat-brain-cancer.html https://www.livescience.com/ultrasound-jump-start-brain-minimally-conscious.html
Follow up Questions	What is the ultrasound's effectiveness in increasing a patient's survival rate? What are the drug combinations, dosing and schedule that are most effective for this treatment method?

Article #5 Notes: **New Firefly-based Gene Selection Algorithm for Microarray Cancer Classification**

Source Title	New Firefly-based Gene Selection Algorithm for Microarray Cancer Classification
Source citation (APA Format)	Almugren, N., & Alshamlan, H. (2019). FF-SVM: New FireFly-based Gene Selection Algorithm for Microarray Cancer Classification. 2019 IEEE Conference on Computational Intelligence in Bioinformatics and Computational Biology (CIBCB), 1–6. https://doi.org/10.1109/CIBCB.2019.8791236
Original URL	https://ieeexplore.ieee.org/document/8791236
Source type	Research Paper
Keywords	Gene expression, cancer, classification, algorithms
#Tags	#SummerReading
qa	Gene expression profiles provide valuable results that can help solve complicated microarray data analysis problems, such as cancer classification. Gene selection algorithms are commonly used for cancer classification. Hybrid algorithms use a filter technique to reduce the number of selected genes while maintaining maximum accuracy. Scientists are proposing a new hybrid algorithm that combines the f-score and the firefly algorithm with an SVM to make an FFF-SVM classifier. This algorithm will select the most informative and predictive genes that cause cancer. There are three stages to the FFF-SVM algorithm: filtering, gene selection, and classification. The f-score filter reduces data dimensionality, while the firefly method selects more predictive genes that maximize the classification performance. The firefly method simulates the attraction behavior of fireflies, where the firefly's attractiveness will increase depending on the brightness of its light. It compares each firefly in the swarm to every other firefly and chooses the best firefly as a solution based on its brightness. The algorithm considers the variation of the brightness intensity and how the attractiveness is formulated. In cancer classification, the "firefly" is a

	biomarker gene in the search space. This classification method works best when it classifies many genes in a small number of samples. In the study, five different cancer data sets were studied. They found that the FFF-SVM hybrid outperformed other algorithms in almost all data sets tested.
Research Question/Problem/ Need	A new hybrid algorithm for cancer classification
Important Figures	 FF-SVM algorithm flow chart.

	Gene Selection Algorithms	Binary Class Datase			Multi Class Datase	
		Colon	Lung	Leukemia1	SRBCT	Leukemia2
Wrapper Approche	FF-SVM	92.7(22)	100(2)	99.5(11)	97.5(14)	92.6(19)
	PSO-SVM [5]	93.55(78)	94.79(65)	95.83(53)	93.97(68)	95.83(61)
	GA-SVM [5]	93.55(83)	95.83(62)	91.99(51)	92.77(74)	94.44(57)
	ABC-SVM [5]	92.44(20)	93.7(8)	92.5 (14)	91.5(10)	93.1(20)
	ACO-SVM [19]	91.5(8)	-	-	-	-
	GA-SVM [19]	84.6(8)	-	91.5(5)	-	-
	MOBBA-LS [9]	-	-	-	85(6)	-
	HS-GA [20]	95.9(20)	-	97.5(20)	-	-
	BPSO-CGA [21]	99.964(214)	-	-	-	100(196)
	HPSO-LS [22]	84.38 (60)	-	89.28(100)	-	-
Hyprid Approche	IDGA [23]	-	-	100(15)	100(18)	-
	IG/SGA [24]	85.48 (60)	100(9)	97.06 (3)	-	-
	CLA-ACO [8]	-	-	95.95(3)	-	-
	RFR-BBHA-Bagging [25]	91.93(3)	-	-	-	-
	ICA+ABC [10]	98.14(16)	-	98.68(12)	97.33(15)	-
	SU-HSA [26]	87.53(9)	-	100(26)	99.89(37)	100(24)
	mRMR-ABC [27]	96.77 (15)	100 (8)	100 (14)	100 (10)	100 (20)
	MIMAGA [6]	83.41(202)	-	-	88 .64 (207)	-

Comparison of the classification accuracy of FF-SVM with other gene selection algorithms using five of the microarray datasets (the number between parentheses represents the number of selected genes)

VOCAB: (w/definition)	**Gene expression profiles**: give valuable results that can solve difficult microarray data analysis problems such as cancer classification. **Hybrid algorithm**: uses a filter technique to reduce computational time and reduces the number of selected genes, while having a higher classification performance. **Filtering**: f score filter was used to reduce data dimensionality **Gene-selection**: firefly wrapper feature selection method **Classification**: calculates the fitness function to maximize classification accuracy
Cited references to follow up on	https://ieeexplore.ieee.org/document/6971078/ https://ieeexplore.ieee.org/document/6774857/
Follow up Questions	Would the FF-SVM algorithm be efficient in other areas, such as the heart or the brain?

Article #6 Notes: **3 kids receive kidney transplants without need for immuno-suppressing drugs**

Source Title	3 kids receive kidney transplants without need for immuno-suppressing drugs
Source citation (APA Format)	Lanese, N. (2022, June 17). 3 kids receive kidney transplants without need for immune-suppressing drugs. *Live Science*. https://www.livescience.com/kidney-transplants-no-immunosuppression
Original URL	https://www.livescience.com/kidney-transplants-no-immunosuppression
Source type	General Article
Keywords	Immunosuppressors, organ transplant/rejection, stem cells, graft vs host disease
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	There were three kids who had a genetic disorder and needed an immediate kidney transplant. Doctors used unique transplantation technique Normally, after an organ transplant, patients use immunosuppressive drugs for life to stop organ rejection. This puts them at risk for infections and does not guarantee them a rejection-free life. Previously, doctors have tried transplanting stem cells from donor bone marrow to the recipient. Stem cells mature into blood cells and reduce risk of rejection (cell would think the organ is familiar) - risk of new lympocyte attacking original body Now, doctors have performed a new procedure that has had no side effects so far. The doctors transplanted stem cells from the parents into the children. This time, they waited for the body to recover for a few months before transplanting kidneys from the same parents. The procedure worked successfully, and the children do not need immunosupressors.
Research Question/Problem/ Need	What is another way to transplant stem cells and organs without using immunosuppressors?
Important Figures	N/A
VOCAB: (w/definition)	**SIOD:** chronic kidney disease that requires kidney transplant and causes bone marrow failure - need stem cell transplant **Stem Cells:** cells from which all other cells with specialized functions are

	generated. Under the right conditions in the body or a laboratory, stem cells divide to form more cells called daughter cells.
Cited references to follow up on	https://www.livescience.com/how-long-can-donated-organs-last-before-transplant.html
Follow up Questions	Does this method work for other types of organ transplants? Does the surgery procedure have an effect on organ rejection?

Article #7 Notes: **Creating 'universal' transplant organs: New study moves us one step closer.**

Source Title	Creating 'universal' transplant organs: New study moves us one step closer.
Source citation (APA Format)	Lanese, N. (2022, February 16). Creating “universal” transplant organs: New study moves us one step closer. *Live Science*. https://www.livescience.com/universal-blood-type-transplant-lungs-study
Original URL	https://www.livescience.com/universal-blood-type-transplant-lungs-study
Source type	General Article
Keywords	Organ transplant, universal, ABO incompatible, universal transplant
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Scienctists successfully developed a new technique that allowed lungs to be trnsplanted to any recipient, regardless of blood type Organ size and blood type are primary factors used to match organ donors and recipuients Patients with O blood wait the longest and have the biggest shortage They have 20% greater chance of dying while waiting When red blood cells and vessels carry sntigens, plasma contains antobodies that react to other antigens Scientiss found a group of enzymes in the human gut that could stig antigens from blood cells (make them type O) Used FpGalNac deacetyase and FpGalactosaminidase to donor lungs with type A Lungs have the enzymatic treatment in EVLP Eliminated 97% of A antigens in 4 hours Perused organ with type O on treated side, and non treated side and looked for rejection. Lungs with enzymatic treatment had no rejection However, after the transplant, the cells of thetreated lungs will likely start producing bloos antigens. Scientists think rejection will not happen because of accomodation. The recipient would have to undergo a procedure to have their blood group anitbodies removed They would return later, but dont damage the donor organ - reason unknown
Research Question/Problem/ Need	Blood type incompatible organ transplants using enzymes
Important Figures	N/A

VOCAB: (w/definition)	**EVLP** = ex vivo lung perfusion device keeps lungs alive outside of the body **Antigens** = sugar molecules on the surface of cells **Accomodation** = if an organ can avoid rejection in the first few days after transplant, it can accommodate or develop resistance against future attacks from the recipient's immune system
Cited references to follow up on	https://www.science.org/doi/10.1126/scitranslmed.abm7190 https://pubmed.ncbi.nlm.nih.gov/30366846/
Follow up Questions	How would the enzymatic treatment be implemented to human trials? Can it lead to chronic rejection?

Article #8 Notes: **1st-of-its-kind heart transplant could prevent organ rejection**

Source Title	1st-of-its-kind heart transplant in infant could prevent organ rejection
Source citation (APA Format)	Rettner, R. (2022, March 11). 1st-of-its-kind heart transplant in infant could prevent organ rejection. *Live Science*. https://www.livescience.com/infant-heart-thymus-transplant
Original URL	https://www.livescience.com/infant-heart-thymus-transplant
Source type	General Article
Keywords	Organ transplant/rejection, immunosuppressors, T-cells, thymus
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Baby received new heart that can stop organ rejection without immunosuppressors Child got heart transplant with implantation of thymus tissue from same donor Could allow the patient to allow the transplanted organ to recognize as self Thymus works to produce T-cells in the recipient's body
Research Question/Problem	Can implanting another type of tissue decrease the risk of organ rejection?
Important Figures	 Thymus located in the chest, between the lungs and behind sternum
VOCAB: (w/definition)	**Thymus**: important for the immune system; teached the body to recognize its own cells and tissues versus foreign invaders
Cited references to follow up on	https://www.livescience.com/how-long-can-donated-organs-last-before-transplant.html https://www.livescience.com/universal-blood-type-transplant-lungs-study https://www.livescience.com/restoring-cell-function-dead-pigs
Follow up Questions	Can implanting thymus tissue allow the patient to not need immunosuppressors? Can this approach work for other transplants? Can it work for people with a more developed immune system?

Article #9 Notes: **Tissue Typing**

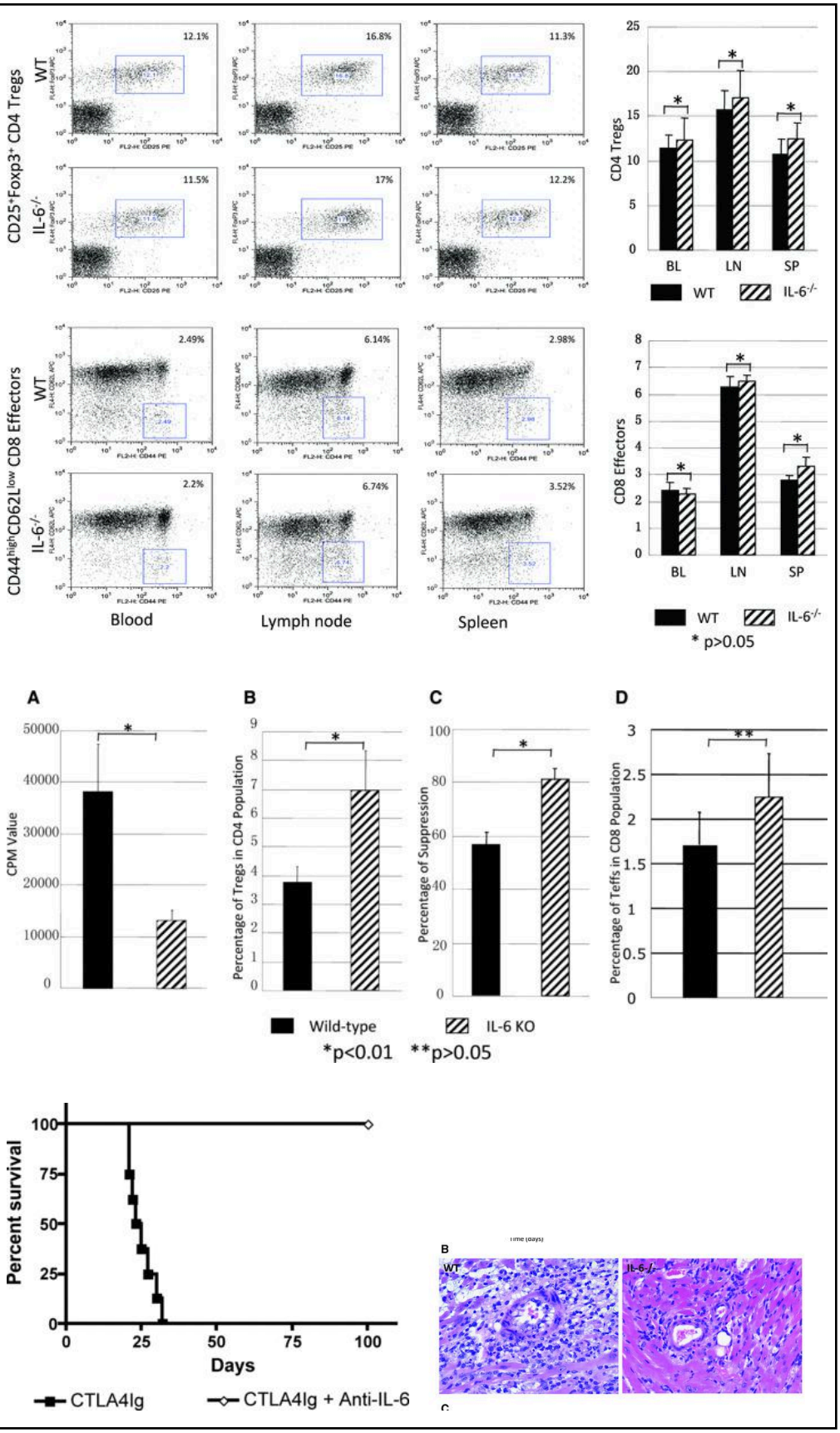
Source Title	Tissue Typing
Source citation (APA Format)	stratech.co.uk. (n.d.). *Stratech*. Stratech. Retrieved September 18, 2023, from https://www.stratech.co.uk/jackson_immunoresearch/tissue-typing/
Original URL	https://www.stratech.co.uk/jackson_immunoresearch/tissue-typing/
Source type	General Article
Keywords	Tissue Typing, HLA, antibodies
#Tags	#Information
Summary of key points + notes (include methodology)	Testing compares the HLA expression between the donor and the recipient to see how similar the two antigen patterns are better match - means less rejection Recipients blood is also screened for DSA, which could stimulate an adverse immune response MHC is on chromosome 6 and is in 3 regions 1st and 2nd region - present T cells 3rd region encodes immune regulatiry molecules Immune system used HLA to distinguish between self and non self Different HLA are seen as invaders System is polymorphic Previous tissue typing methods mix antibodies with certain cells But they couldn't tell the difference between specific typews of proteins on the cell surface
Research Question/Problem	What is Tissue Typing, and how are its challenges being addressed?
Important Figures	N/A
VOCAB: (w/definition)	**Tissue Typing**: process of determining whether a donated tissue/orgam will be compatible with its intended host. **HLA**: human leukocyte antigen - **MHC**: major histocompatibility complex - large group of genes found on the vertebrate DNA that encode cells with proteins that regulate the immune response **DSA**: Donor-specific antibodies **Polymorphic**: occuring in several forms
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/17326240/ https://pubmed.ncbi.nlm.nih.gov/34479742/
Follow up Questions	How can we make tissue typing more accurate?

Article #11 Notes: **Critical Role of Proinflammatory Cytokine IL-6 in Allograft Rejection and Tolerance**

Source Title	Critical Role of Proinflammatory Cytokine IL-6 in Allograft Rejection and Tolerance
Source citation (APA Format)	Zhao, X., Boenisch, O., Yeung, M., & Mfarrej, B. (2012). Critical Role of Proinflammatory Cytokine IL-6 in Allograft Rejection and Tolerance. *American Journal of Transplantation*, *12*(1), 90–101. https://doi.org/10.1111/j.1600-6143.2011.03770.x
Original URL	https://www.sciencedirect.com/science/article/pii/S1600613522272700
Source type	Journal Article
Keywords	Allograft tolerance, CD4, costimulation blockade, CTLA4Ig, IFN-γ, IL-6IL-17, rejection, transplantation
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Many proinflammatory cytokines such as IL-17 play a key role in T cell immunity by connecting Innate immunity to adaptive immunity. IL-6 is a pleiotropic cytokine produced by APCs. Shown to prolong T-cell survival via maintenance of Bcl-2 expression and the downregulation of Fas ligands to promote activation of antigen-specific T cells. T helper (Th) cells separate into different phenotypes that are defined according to the condition and cytokines requires for their differentiation into T-cell subsets and their function. IL-6 is critical for Th17 development. Th17 is associated with inflammation. In the past, scientists showed that hearts with IL-6 deficiency survived longer. Using a mismatched MHC mouse model of heart transplant to prove that targeting Il-6 or its signals will help for tolerance. Made sure the IL-6 deficient mice did not have naturally fewer T cells and more regulatory cells than WT mice by checking for the percentages of t cells in different body parts. Single dose of CTLA4-Ig was given on the day of the transplant Neutralizing IL-6 was given at a daily dose and then every other day. Hearts were recovered either at rejection or at specific times. Used H&E stains to

	look at the cellular infiltration. And MLR to see allorecognition IL-6 enhances the life of T cell activation and promotes the differentiation of CD4 T cells into Th17 cells and imparirs T cell regulatory differentiationAbsence of IL-6 stops the growth of lymphocytes and encourages CD4 T cell to transform into a regulatory form. To determine the function of IL6 they stimulated IL6 deficient lymphocytes with other mice cells and analyzed T cell differentiation and proliferation. The proliferation from IL6 deficient was significantly less than those from WT animals (in vitro) IL6 alone does not prolong allograft survival, but changes the cytokine profile in recipients. Both WT and IL6 deficient mice rejected grafts within 1 week of transplant. However, IL6 deficient blood had less CD8 t cells, but had no significant different of T regulator cells. (in vivo) T cell differentiation varies depending on whether environment is in vivo or in vitro.IL6 dificiency is connected with costimulator blockade to facilitate tolerance in recipients treated wit CTLA4-Ig CTLA4 is a protein that interferes with costimulatory signals to regulate the immune system. To test the hypothesis, they treated WT with IL-6 monoclonal antibody with CTLA4. In control, alowed graft to live for 22 days. With IL6, lives for 100+ days. Significant infiltration present in WT in 3 weeks. In our previous studies using T-bet/-recipients, we found that, in the absence of Th1 responses, CD4 Th17 cells mediate aggressive proinflammatory responses that lead to accelerated rejection and severe vasculopathy in a model of chronic cardiac allograft rejection that IL-17-producing CD8 T cells are resistant toward the induction of tolerance by combined blockade of the CD28-B7 and CD40-CD154 pathways in a fully MHC-mismatched model using the same T-bet /- recipients IL-6 production is closely associated with an inflammatory response. Due to its strong anti-apoptotic properties, IL-6 can increase the effector/memory T-cell population.
Research Question/Problem/ Need	What is the role of IL-6 in organ rejection and tolerance?

Important Figures



VOCAB: (w/definition)	**Innate** = general response to any antigen. It is non-specific and fights any foreign invader. **Adaptive** = specialized immune system that responds to specific antigens. Created in response to exposure to a foreign substance. **Cytokine** = signaling proteins that help regulate the immune system **pleiotropic cytokine** = cytokine that affects the activity of multiple cell types. **Bcl-2** = protein that regulates cell death **Fas ligand** = protein that induced cell death in a cell that has its Fas receptor target
Cited references to follow up on	https://scholar.google.com/scholar_lookup?title=A%20novel%20role%20of%20CD4%20Th17%20cells%20in%20mediating%20cardiac%20allograft%20rejection%20and%20vasculopathy&publication_year=2008&author=X%20Yuan&author=J%20Paez-Cortez&author=I%20Schmitt-Knosalla https://scholar.google.com/scholar_lookup?title=Targeting%20Tim-1%20to%20overcome%20resistance%20to%20transplantation%20tolerance%20mediated%20by%20CD8%20T17%20cells&publication_year=2009&author=X%20Yuan&author=MJ%20Ansari&author=F%20D%E2%80%99Addio
Follow up Questions	What is the significance of the CD8 count in vitro? Is this prevalant in adaptive or innate immune response? How can this be replicated fro human studies? What are the main factors of the difference in results fro in vivo vs. in vitro?

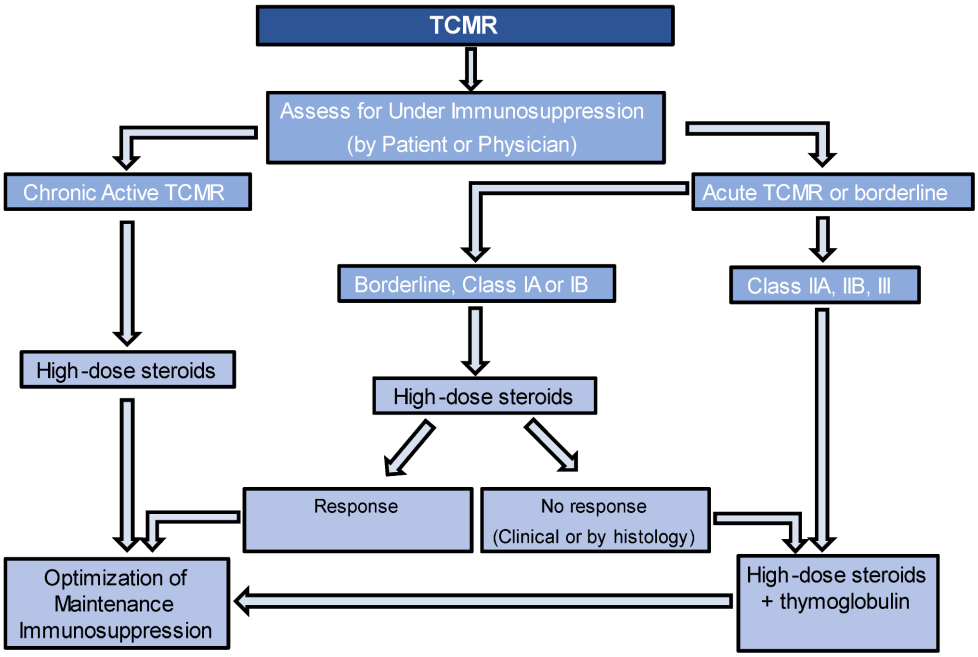
Article #12 Notes: **Recent advances in precision medicine for individualized immunosuppression**

Source Title	Recent advances in precision medicine for individualized immunosuppression
Source citaton (APA format)	Fu, S., & Zarrinpar, A. (2020). Recent advances in precision medicine for individualized immunosuppression. *Current Opinion in Organ Transplantation*, *25*(4), 420–425. https://doi.org/10.1097/MOT.0000000000000771
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7723319/
Source type	Journal Article
Keywords	tacrolimus, pharmacogenomics, personalization, precision medicine
#Tags	#Potential Research
Summary of key points + notes (include methodology)	Therapeutic drug monitoring, particularly measuring blood levels of calcineurin or mTOR inhibitors, is the standard for immunosuppression management. Tacrolimus, a commonly used calcineurin inhibitor, has a high variability which often leads to inaccurate dosing. Genetic polymorphisms of CYP3A5 are predictors of drug dosages. Different alleles contribute to variable tacrolimus. Enzymes are involved with metabolizing tacrolimus. Genotypic allelic differences between African Americans and Caucasians that contribute to differences in tacrolimus metabolism, a generally higher tacrolimus dose requirement for African Americans, and worse outcomes after transplantation in African American patients. Phenomapping uses genotypic information to predict the phenotypic response or phenomic outcome. Tolerance to kidney transplantation correlates with the increase in B cell specific genes IGKV1D-13 and IGLL-1
Research Question/Problem/ Need	What are the recent advances of immunosupression to decrease the side-effects of under/over immunosuppression?
Important Figures	N/A
VOCAB: (w/definition)	**Under-immunosuppression** = immunoe system is not suppressed enough, and is

	still competent **Over-immunosuppression** = immune system is excessively supressed and is weak **Tacrolimus** = immunosuppressive agent used for prophylaxis of organ rejection post-transplant. **mTOR** = protein, an enzyme which regulates cell growth, cell division, cell movement, cell survival, protein synthesis, autophagy, and transcription. **Calcineurin** = protein that plays a role in T-cell activation
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4012056/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6283088/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6283088/
Follow up Questions	How can precision medicine be used to make HLAs similar? How can it be used to make more accurate organ matches?

Article #13 Notes: **Current Therapies in Kidney Transplant Rejection**

Source Title	Current Therapies in Kideny Transplant Rejection
Source citation (APA Format)	Alasfar, S., Kodali, L., & Schinstock, C. A. (2023). Current Therapies in Kidney Transplant Rejection. *Journal of Clinical Medicine*, *12*(15). https://doi.org/10.3390/jcm12154927
Original URL	https://www.mdpi.com/2077-0383/12/15/4927
Source type	Journal Article
Keywords	Rejection, transplantation, kidney transplant
#Tags	#Basics
Summary of key points + notes (include methodology)	Banff system categorizes rejection into different types of T cell mediated rejection r antibody mediated rejection. Takes into account acute and chronic tissue features to diagnose rejection. Acute rejection include inflammation, tubulitus, arthritis, and more. TCMR: Majority of acute rejection within 1st year transplants are TCMR. First line treatment is corticosteroids. T-cell depleting agents are recommended for steroid-resistant cases. Borderline changes typically involve immunopsupressors ABMR: caused by antibodies in recipient blood that bind to donor tissue antigens on graft cells. Chronic ABMR is ongoing antibody damage. Plasmaphoresis andother therapies are used to trat ABMR. In cases where patient presents both types of rejection, there is concern on how to treat it. Banff id commonyl used to diagnose rejection.
Research Question/Problem/ Need	What are the current methods to prevent rejection in Kidney transplants?

Important Figures	 Algorithm for T Cell mediated rejection
VOCAB: (w/definition)	**Subclinical** = lacks evident symptoms or laboratory abnormalites. Identofied through biopsies **Clinical** = has symptoms **Banff** = classification system that grades and categprizes kidney transplant rejection based on tissue findings **TCMR** = infiltration of T cells **ABMR** = recipient immune system produces antibodies that target organ **Borderline Changes** = changes in rejection that lie between normal graft histology and acute cellular rejection
Cited references to follow up on	https://scholar.google.com/scholar_lookup?title=Long-term+kidney+transplant+graft+survival%E2%80%94Making+progress+when+most+needed&author=Poggio,+E.D.&author=Augustine,+J.J.&author=Arrigain,+S.&author=Brennan,+D.C.&author=Schold,+J.D.&publication_year=2021&journal=Am.+J.+Transpl.&volume=21&pages=2824%E2%80%932832&doi=10.1111/ajt.16463 https://scholar.google.com/scholar_lookup?title=Identifying+specific+causes+of+kidney+allograft+loss&author=El-Zoghby,+Z.M.&author=Stegall,+M.D.&author=Lager,+D.J.&author=Kremers,+W.K.&author=Amer,+H.&author=Gloor,+J.M.&author=Cosio,+F.G.&publication_year=2009&journal=Am.+J.+Transpl.&volume=9&pages=527%E2%80%93535&doi=10.1111/j.1600-6143.2008.02519.x
Follow up Questions	What are other systems that can diagnose rejection? How to treat borderline changes? How to improve treatment for patients with both forms of rejection?

Article #14 Notes: **Gene deletion raises risk of kidney transplant rejection**

Source Title	Gene deletion raises risk of kidney transplant rejection
Source citation (APA Format)	Reynolds, S. (2019, May 31). *Gene deletion raises risk of kidney transplant rejection*. National Institutes of Health (NIH). https://www.nih.gov/news-events/nih-research-matters/gene-deletion-raises-risk-kidney-transplant-rejection
Original URL	https://www.nih.gov/news-events/nih-research-matters/gene-deletion-raises-risk-kidney-transplant-rejection
Source type	Short Journal Article
Keywords	Gene deletion, organ rejection, risk, prediction
#Tags	#Information
Summary of key points + notes (include methodology)	If a person with a deleted portion of a gene receives a kidney with one who has gene, immune system could see it as foreign methods: scanned 50 common DNA deletions from 705 kidney transplants. ppl with a deletion near gene LIMS1 had 80% higher risk of rejection analyzed more than 2,000 donor-recipient pairs. people with the deletion near LIMS1 who received a kidney from a donor with at least one intact gene had a 58% higher risk of rejection than people without this genetic mismatch. tested blood from 300 transplant recipients. Found antibodies targeting LIMS1 in all the recipients with the gene deletion who'd experienced transplant rejection. antibodies weren't found in the other recipients. LIMS1 mismatches could be avoided by pre-transplant genetic screening
Research Question/Problem/ Need	Can the absence of a gene in the recipient affect their probability of rejecting the organ?
Important Figures	N/A

VOCAB: (w/definition)	**LIMS1**: Involved in the regulation of cell survival, cell proliferation and cell differentiation. **Deletion**: type of mutation that involves the loss of one or more nucleotides from a segment of DNA.
Cited references to follow up on	https://www.nih.gov/news-events/nih-research-matters/biomarkers-early-organ-transplant-rejection https://pubmed.ncbi.nlm.nih.gov/31091373/ https://www.nih.gov/news-events/nih-research-matters/organ-transplants-without-life-long-drugs https://www.nih.gov/news-events/nih-research-matters/urine-test-detects-kidney-transplant-rejection
Follow up Questions	What does LMS1 have to do with organ rejection? What other genes can help predict the risk of organ rejection?

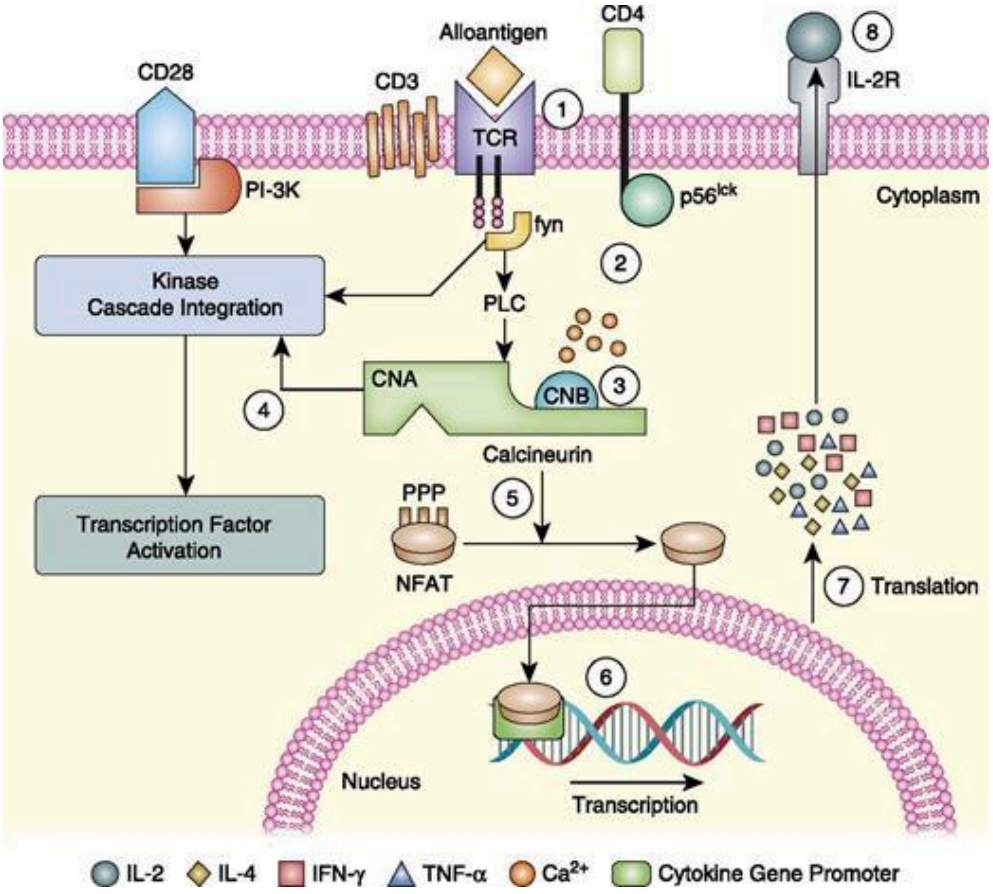
Article #15 Notes: **Organ Transplants Without Life-Long Drugs**

Source Title	Organ Transplants Without Life-Long Drugs
Source citation (APA Format)	Contie, V. (2015, May 15). *Organ Transplants Without Life-Long Drugs*. National Institutes of Health (NIH). https://www.nih.gov/news-events/nih-research-matters/organ-transplants-without-life-long-drugs
Original URL	https://www.nih.gov/news-events/nih-research-matters/organ-transplants-without-life-long-drugs
Source type	Short Journal Article
Keywords	Organ rejection, bone marrow, graft facilitating, graft-host disease, chimeism
#Tags	#Background
Summary of key points + notes (include methodology)	For a time, infusing donor bone marrow can make patients better tolerated the donated organs and survive drug-free. Scientists tried to create long-term chimerism in kidney recipients. The organs came from unrelated or highly mismatched donors. Methods: A day after transplant surgery, 8 patients received infusions of from the donor's bone marrow. mixture had blood-forming stem cells and graft facilitating cells The researchers removed donor immune cells likely to attack the transplant recipient's own body. all 8 patients had a variety of immune cells derived from the kidney donor in their bloodstream 5 of the 8 patients had achieved long-lasting chimerism, with the donated immune cells eventually crowding out the recipient's own immune cells. patients had stopped taking immunosuppressant drugs, transplanted organs continued to thrive. No signs of graft-versus-host disease.
Research Question/Problem	Can bone marrow infusions from the donor decrease the risk of organ rejection?

Important Figures	N/A
VOCAB: (w/definition)	**Chimera** = person who has two totally different sets of DNA inside their body. graft facilitating cells: thought to help foreign stem cells get established in recipient bone marrow.
Cited references to follow up on	https://www.nih.gov/news-events/nih-research-matters/gene-pattern-marks-transplant-patients-who-can-avoid-lifelong-drugs
Follow up Questions	How long would the chimerism last? What are the other potential side effects?

Article #16 Notes: **Calcineurin Inhibitors: 40 Years Later, Can't Live Without**

Source Title	Calcineurin Inhibitors: 40 Years Later, Can't Live Without
Source citation (APA Format)	Azzi, J. R., Sayegh, M. H., & Mallat, S. G. (2013). Calcineurin Inhibitors: 40 Years Later, Can't Live Without …. The Journal of Immunology, 191(12), 5785–5791. https://doi.org/10.4049/jimmunol.1390055
Original URL	https://journals.aai.org/jimmunol/article/191/12/5785/39682/Calcineurin-Inhibitors-40-Years-Later-Can-t-Live
Source type	Journal Article
Keywords	Calcineurin, immunosuppressors, cytotoxicity, cyclosporine
#Tags	#Infromation
Summary of key points + notes (include methodology)	Immunology lab was made to identify an immuosuppressive agent without major cytotoxicity. Used mouse model to test immunosupressive activity of the drug and tumor growth measured cytotoxic activity. Cyclosporine had weak myelotoxicty, avoiding a major side effect of other immunosuppressors. Doctors isolated another similar molecule called tacrolimus, which shares the same property of T cell activation by inhitibit calcineruin. Calcinerin inhibitors bind to immunophillins, which bins to calcinuerins to inhibit its activity. Calcinwuein is formed by 2 subunits: CnA and CnB. T ceel activation increases the concentration of calcium and activated CnB, which unleashes CnA. However, inhibiting calcineurin can also have a negative effec on Treg function. Initial trials had some success, but eventually found superior results for cyclosporine for graft survival. It is also used to treat autoimmune diseases. Cyclosporine's nephrotoxcitiy remains a concern. It can have sideeffects as chronic injuries can show up about 10 years after transplant. Kiney structure are affected with irreversible damage. Many factors, including drug concentration and dosage Tacrolimus has different toxicity profiles. Although there is no evidence that tacrolimus is less nephrotoxic, it is more commonly used. Some trials show that it has a lower risk of acute rejection.

	Many trials have tried to reduce calcineurin inhibitors, especially cyclosporine, because of their association with renal injury.
Research Question/Problem/ Need	How are calcineurin inhibitors used as immunosuppressors?
Important Figures	
VOCAB: (w/definition)	**Cytotoxic** = toxic to living cells **Cyclosporine** = drug with immunosuppresive propertive **Calcineurin** = protein that activated T cells in the immune system **Nephrotoxcitiy** = toxic to kidneys
Cited references to follow up on	http://www.ncbi.nlm.nih.gov/pubmed/8627154 http://www.ncbi.nlm.nih.gov/pubmed/19857752
Follow up Questions	How can CNIs be used without renal injury? What are the renal side effects of tacrolimus? What are the side effects on other organs?

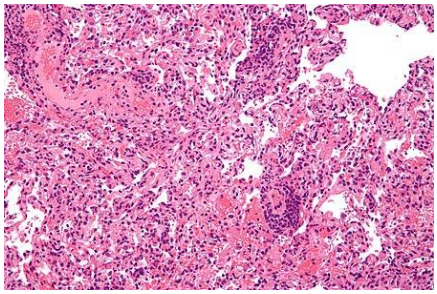
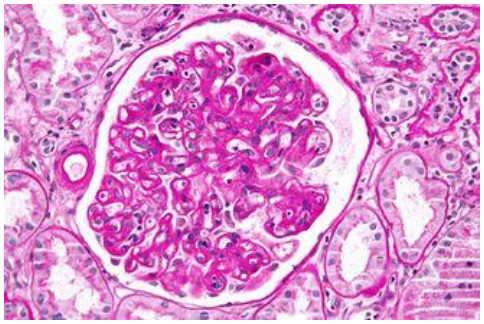
Article #17 Notes: **Understanding Transplant Rejection**

Source Title	Understanding Transplant Rejection
Source citation (APA Format)	Stony Brook University Hospital. (n.d.). *Stony Brook Medicine*. Stony Brook Medicine. Retrieved October 1, 2023, from https://www.stonybrookmedicine.edu/patientcare/transplant/rejection
Original URL	https://www.stonybrookmedicine.edu/patientcare/transplant/rejection
Source type	Informational Website
Keywords	Transplant rejection, symptoms, types of rejection
#Tags	Background Information
Summary of key points + notes (include methodology)	Everyone has different DNA Immune system separates self cells from foreign cells and destroys foreign cells System can try to reject the organ as it sees that it is foreign, and produces cells/antibodies that invade and damage the organ Patients take immunosupressors to prevent organ rejection 3 Types of Rejection: 1. **Hyperacute Rejection**: rare, can be prevented by tissue cross matching a. Caused by the pre-formed antibodies b. Occurs within minutes-hours of transplant, completely destroys organ and has to be removed 2. **Acute:** can occur any time, commonly 1 week- 3 months a. <15% of patients that get organ from dead donors have an episode of acute rejection b. Can be reversible if treated early 3. **Chronic**: over time, due to scarring within organ, month-years after a. Controlling BP, sugar and cholesterol can help prevent this b. Usually no symptoms, diagnosed by changes in lab tests] c. No medication used to reverse this type d. Organ can last some times after diagnosis, and may need another transplant after
Research Question/Problem	What is Organ Rejection?
Important Figures	N/A
VOCAB: (w/definition)	**Tissue-cross matching** = tissue testing for HLA matches

Cited references to follow up on	https://www.stonybrookmedicine.edu/patientcare/transplant/surgery https://www.stonybrookmedicine.edu/patientcare/transplant/medication https://www.stonybrookmedicine.edu/patientcare/transplant/post-transplant
Follow up Questions	How can Acute rejection be reversed? How are BP and cholesterol linked to chronic rejection?

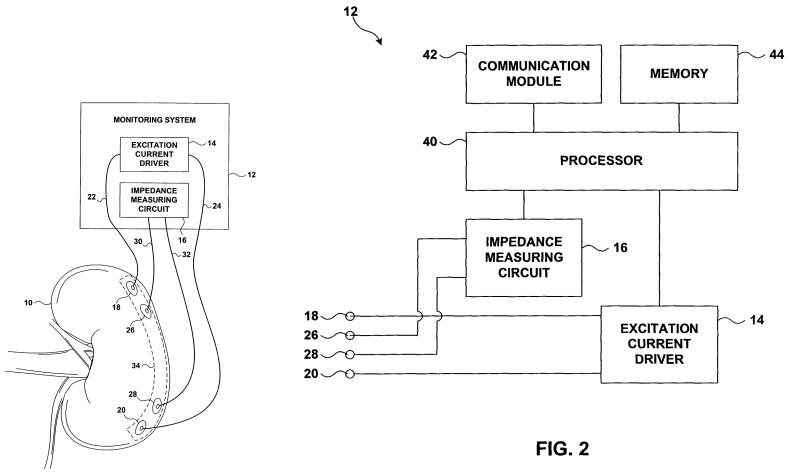
Article #18 Notes: **Chronic Transplantation Rejection**

Source Title	CHronic Transplantation Rejection
Source citation (APA Format)	Justiz Vaillant, A. A., & Mohseni, M. (2023). Chronic Transplantation Rejection. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK535435/
Original URL	https://www.ncbi.nlm.nih.gov/books/NBK535435/
Source type	Informational Article
Keywords	Rejection, chronic, types of rejection, symptoms
#Tags	Introduction, Background
Summary of key points + notes (include methodology)	Acute rejection, caused by recipient lymphocytes recognizing human leukocyte antigens (HLA), emerges days or weeks post-transplantation. The cause of chronic rejection is not entirely understood, but vascular disease is suspected, especially in cardiac allograft vasculopathy (thickening of blood vessels). Chronic kidney allograft rejection is identified as interstitial fibrosis and tubular atrophy. Chronic rejection is a leading cause of graft rejection. The incidence and prevalence of chronic allograft nephropathy vary based on graft biopsy timing and indication. Pathophysiological mechanisms include antibody-dependent complement activation, cell arteritis, and factors like calcineurin inhibitor toxicity. Histopathologically, rejected organs exhibit arteriosclerosis, causing luminal narrowing and graft tissue fibrosis. Chronic rejection symptoms vary by organ but may include fatigue, flu-like symptoms, anuria, edema, and pain. Evaluation involves various laboratory tests, including urine collection, blood tests, electrocardiogram, imaging, and histological studies. HLA typing assesses histocompatibility between donor and recipient. Complications of chronic organ rejection include infections, BK polyomavirus, recurrence of the original disease, and malignancies. Patient compliance with immunosuppressive drugs is crucial to avoid rejection. An interprofessional team, including primary care, specialists, nurses, and pharmacists, is vital for educating and managing patients with chronic rejection.

	Collaboration among team members enhances patient care and outcomes.
Research Question/Problem/ Need	What is organ rejection?
Important Figures	No figures, but pictures below are from other websites  Lung Transplant Rejection  Glomerulus with glomerulopathy https://en.wikipedia.org/wiki/File:Lung_transplant_rejection_-_high_mag.jpg https://en.wikipedia.org/wiki/Transplant_rejection#/media/File:Transplant_glomerulopathy_-_very_high_mag.jpg
VOCAB: (w/definition)	**Vasculopathy** = affects the blood vessels that carry oxgen throgh the body **Allograft** = tissue graft from a donor (other tissue) **Ischemia and fibrosis** = not enough oxygen going to organ **Machine perfusion** = uses machine to temporaily maintain the function of organ Connected with pumps and oxygenators
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6247110/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994504/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728651/
Follow up Questions	Why is there not much research dont on chronic rejection? How dramatic are the effects of chronic rejection compared to other rejections? What demographic is organ rejection most common?

Article #19 Notes: **Organ Rejection Monitoring**

Source Title	Organ Rejection Monitoring
Source citation (APA Format)	Parsonnet, V., & Combs, W. J. (2006). Organ rejection monitoring (Patent US7130679B2). https://patents.google.com/patent/US7130679B2/en
Original URL	https://patents.google.com/patent/US7130679B2/en
Source type	Patent
Keywords	Organ rejection, detection, implant, device, electricity
#Tags	#Examples
Summary of key points + notes (include methodology)	Non-invasive technique for monitoring organ rejection directly Device monitors rejection and provided early warning of rejection Implant has 2 electrodes connected to the organ (conductors) Device delivered excitation current to organ by electrodes and monitors the response to the current Monitors the different voltage that develop as a response to the excitation current The impedance of the organ is related to organ rejection A rejected organ experiences inflammation and edema Fluid buildup causes impedance of organ differently Impedance measuring circuit measures the impedance Need to wait for rhe organ to be accustomed to the electrode to obtain a baseline
Research Question/Problem/ Need	How can we monitor organ rejection?

Important Figures	 FIG. 2
VOCAB: (w/definition)	**Electrodes** = a conductor which electricity can pass through **Impedance** = resistance of an eclectic current **Edema** = swelling caused by fluid (surrounding cells) trapped in the body's tissue **Excitement current** = current that flows through to energize
Cited references to follow up on	US5246008A - Method for monitoring a patient for rejection reactions to an implanted heart
Follow up Questions	How to improve the device? How to decrease the outside factors?

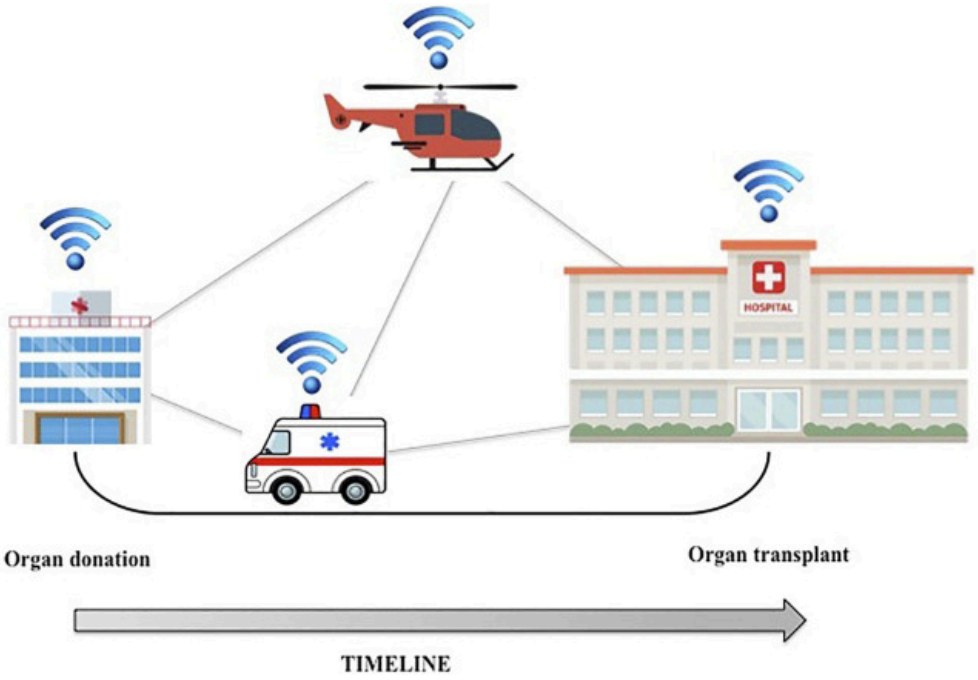
Article #20 Notes: **Gene therapy and solid-organ transplantation**

Source Title	Gene therapy and splid-organ transplantation
Source citation (APA Format)	Bromberg, J. (2002). Gene therapy and solid-organ transplantation. *Kidney International*, *61*(1), S56–S60. https://doi.org/10.1046/j.1523-1755.2002.0610s1056.x
Original URL	https://www.sciencedirect.com/science/article/pii/S0085253815482110
Source type	Journal Article
Keywords	transplantation rejection allograft gene therapy xenotransplantation
#Tags	#PotentialResearch, #Information
Summary of key points + notes (include methodology)	Gene therapy has unique advantages in transplantation as it allows for local production of immunosuppressive molecules and can achieve antigen-specific immunosuppression. For transplantation, transient gene expression may be enough because the potential toxicities and adverse effects of prolonged vector persistence and expression or immunosuppressive molecule production could be avoided. Alloimmune response is T-cell dependent process. Signal 1 is when T cell recognized antigenic peptides in the MHC on the surface of APCs. This signal delivers intracellular signals to the immune response. Signal 2 is the costimulatory signal and is provided by interactions between TCR and ligands on APCs. Antigen-specific tolerance can be achieved by exposing donor MHC antigens through thymus or stem cells. Systemic administration of certain proteins can help. Immunomodulatory cytokines has shown promise, and targeting chemokine functions can be new approaches. ICAM-1 is crucial in cell adhesion and T-cell costimulation. Ex vivo hyperbaric transfection of ICAM-1 blockers reduces chronic graft vascular disease and reperfusion injury in rat cardiac allografts.
Research Question/Problem/ Need	How can gene therapy be used to combat organ rejection?
Important Figures	N/A

VOCAB: (w/definition)	**Antigen-specific-immunosupression** = selectively suppress the immune response against specific antigens (proteins or molecules) while leaving the rest of the immune system intact. **Immunogencity** = medicine that causes an immune response **Transient** = temporary **Antigen** = molecule that the immune system recognizes as foreign **Allotransplantation** = removal of tissues from one individual and offers the possibility of treating cells or organs ex vivo (outside the body) with gene transfer vectors (DNA vehicles) prior to implantation. **Immunomodulators** = medications that change the immune system. They can increase or decrease the immune response.
Cited references to follow up on	https://www.sciencedirect.com/science/article/pii/S0085253815467316
Follow up Questions	Which of these methods decreases organ rejection best? What factors should be considered when determined the best method? What are the long-term effects of these methods?

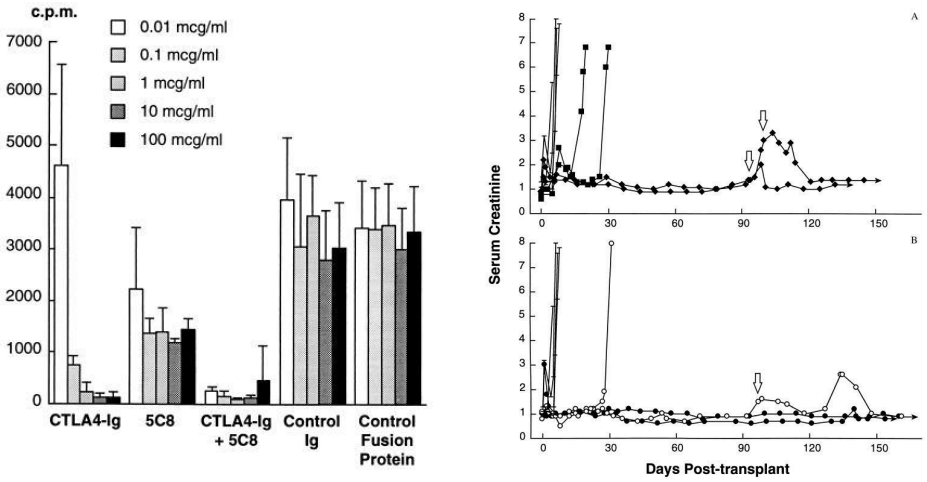
Article #21 Notes: **Artificial Intelligence: Present and Future Potential for Solid Organ Transplantation**

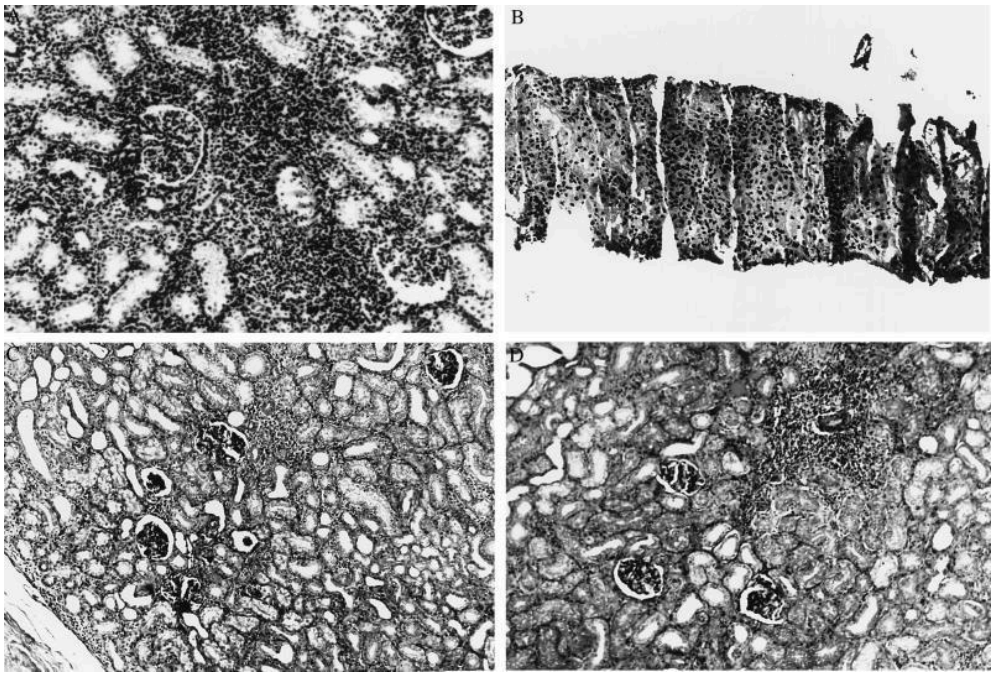
Source Title	Artificial Intelligence: Present and Future Potential for Solid Organ Transplantation
Source citation (APA Format)	Peloso, A., Moeckli, B., Delaune, V., Oldani, G., Andres, A., & Compagnon, P. (2022). Artificial Intelligence: Present and Future Potential for Solid Organ Transplantation. *Transplant International : Official Journal of the European Society for Organ Transplantation*, *35*, 10640. https://doi.org/10.3389/ti.2022.10640
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9290190/
Source type	Journal Article
Keywords	organ transplantation, machine learning, artificial intelligence, deep learning, result prediction, healthcare 4.0, digital pathology
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	The Child-Pugh classification, the Model of End Stage Liver Disease (MELD), the Kidney Allocation System (KAS) and the Lung Allocation System (LAS) are algorithms currently used for organ matches, but does not take in all factors Optimal Predcition Mortality (OPOM) predicts the probability of a patient's 3 month mortality or waitlist removal given their characteristics. Internet of Things (IoT) is a network of smart devices. Uses senors and processors for real-time tracking of organs during transport AI neural networks analyzed data on 1003 liver transplants for graft matches. Also used machine learning to establish survival predictors in liver transplant recipients with preexisting/post transplant diabetes. Machine learning to predict stable dose of immunosuppresors. AI to analyze pathological slides and analyze organs
Research Question/Problem/ Need	How can AI be used to improve challenges in the organ transplant process?

Important Figures	
VOCAB: (w/definition)	**Computer Algorithms** = Computer algorithms are automated instructions **Machine Learning (ML)** = Machine learning is a subfield of artificial intelligence intended as a sets of automated computer algorithms **Deep-Learning (DL)** = Deep learning is a type of ML that imitates the way humans gain certain types of knowledge including statistics and predictive modeling **Neural Networks (NN)** = Neural networks reflect the behavior of the human brain, allowing computer algorithms to recognize patterns and solve common problems in the fields of AI, ML and DL. **Cyber Physical System** = Cyber Physical System is referred to computer-human networks, controlling physical processes, where physical processes affect computations and vice versa **Internet of Things** = The Internet of Things represents a system of interralated computing devices, capable of operating without human-to-human or human-to-computer interaction
Cited references to follow up on	https://unos.org/resources/allocation-calculators/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6309666/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8862776/
Follow up Questions	How can AI be used to monitor organ rejection? Can AI be used to aid in the organ shortage?

Article #22 Notes: **CTLA4-Ig and anti-CD40 ligand prevent renal allograft rejection in primates**

Source Title	Gene Therapy Approaches to Prevent Corneal Graft Rejection: Where Do We Stand?
Source citation (APA Format)	Kirk, A. D., Harlan, D. M., Armstrong, N. N., Davis, T. A., Dong, Y., Gray, G. S., Hong, X., Thomas, D., Fechner, J. H., Jr, & Knechtle, S. J. (1997). CTLA4-Ig and anti-CD40 ligand prevent renal allograft rejection in primates. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(16), 8789–8794. https://doi.org/10.1073/pnas.94.16.8789
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC23132/
Source type	Research Paper
Keywords	Gene therapy, Costimulation, Inhibitory receptor, Immunomodulation,
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Selective inhibition of T cell signals using protein CTLA4-Ig has proved to help the long-term allograft survival in rodents. T cell molecule CTLA4 downrelgulates costimulation and TC Receptor activation. 5C8 blocks CD80 antibody and can suppress the up regulation These proteins were tested on rhesus white blood cells. Donor-recipeint combis were chosen based on no genetic match. Each animal was tested with other donors to see the best pairs for rejection. Cells were incubated and the positive control was polyclonal stimulation They performed kidney transplants. Graft was attached to blood vessels and was connected to the bladder. Regular checks were conducted Medicine (CTLA4 or 5C8 was given). Blood tests were performed Both proteins were effective in preventing t cell responses CTLA4-Ig peformed better alone, but the combo also helped long-term survival

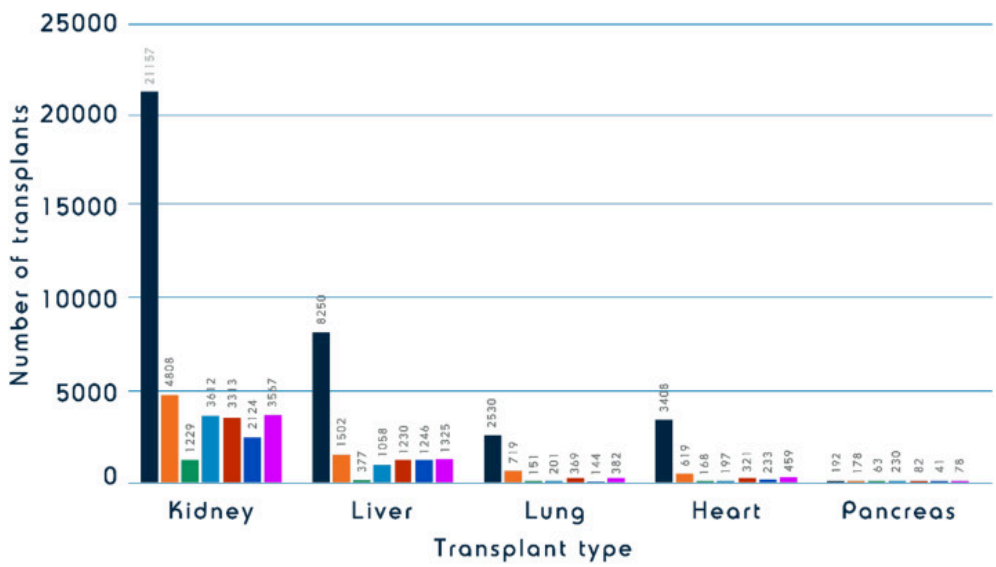
	Both agents stopped lymphocyte reactions, and it was 100x more effective than a drug. CTLA4 was more effective of suppressingT-cells 4 had non immunological medicine. Acute Rejected 5-8 days 1 had 5 days of CTLA4 and 20 day survival (10mg) 1 had 20 mg on the day of transplant. Then a 12 day couse of CT 10mg every other day. Had a 30 day survival 2 had 5c8 alone. 20mg every other day for 14 days. 95-100 day survival There was an acute rejection episode. It was retreated with 7 5C8 doses and both returned back to normal. More than 150 days survival. 2 animals had 20mg of CT and 5C8. 1 survided 32 days, 1 survived100 days. Animal died cause of weight loss No animal had side effects
Research Question/Problem	How can selective inhibition decrease the risk of organ rejection?
Important Figures	

	
VOCAB: (w/definition)	**APC** = antigen-presenting cells **Costimulatory signal** = second signal of T-cell activation. Provided by interactions between specific receptors on T-cells **Ligand** = molecule that binds to another molecule **Antigen-specific** = 1st signal and causes the T-cell to enter the cell cycle **Cytokine** = signaling molecules that are produced by immune system **Upregulation** = increasing a response to a stimulus, such as the activation of the nervous system or an increase in the number of receptors **Downregulation** = returning to a state of relaxation and calm.
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2119166/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2191223/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC46977/
Follow up Questions	What are the long-term effects of this method? Would this allow for universal transplants? Is it possible to inhibit the first signal? If so, what would be the effects?

Article #23 Notes: **Organ donation in the US and Europe: The supply vs demand imbalance**

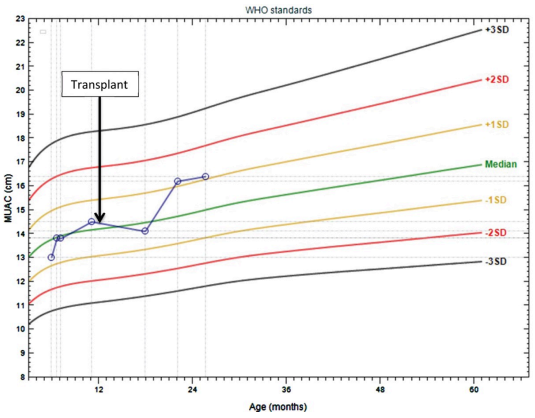
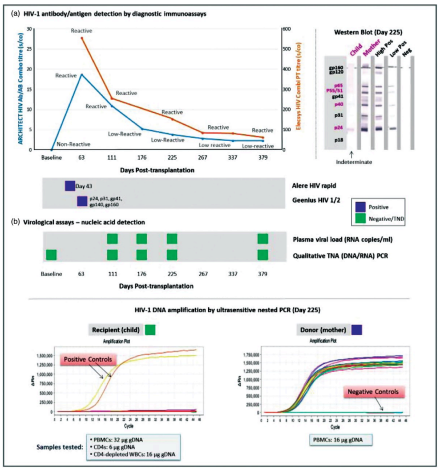
Source Title	Organ donation in the US and Europe: The supply vs demand imbalance
Source citation (APA Format)	Lewis, A., Koukoura, A., Tsianos, G.-I., Gargavanis, A., Nielson, A., & Vassiliadias, E. (2021). Organ donation in the US and Europe: The supply vs demand imbalance. *Transplantation Reviews*, *35*(2). https://doi.org/10.1016/j.trre.2020.100585
Original URL	https://www.sciencedirect.com/science/article/pii/S0955470X20300586
Source type	Journal Article
Keywords	Organ donation, Organ donor, Organ transplant, Donation after brain death, Donation after circulatory death, Organ shortage
#Tags	#Background
Summary of key points + notes (include methodology)	There is a big supply vs demand imbalance in organ donations. Kidneys are the most transplanted organs worldwide. In 2018, 13.8% of donated organs were discarded because of poor organ function or other issues The long wait lists kill many every year: 74.63% of candidates failed to receive a transplant in the US, but only 19.89 in the UK (2018). Preemptive and early transplants help people with kidney disease receive transplants before their dialysis therapy or very shortly after kidney failure. These early transplants have reduced transplant rejection, improved life quality, and avoided dialysis therapy. Donation after brain death (DBD) is very common. When someone goes into an irreversible coma, doctors have to test the organ for any changes in function after brain death. Many ethical concerns. Donation after circulatory death (DCD) is a transplant from a person who has permanent loss of consciousness and brainstem function. DCD is risky and has frequent graft failures. Donor and recipient have to be consistently studied to overcome failure Having to check for age, economic status, and illness causes many waitlist deaths

	There are many governmental organizations in Europe that help hospitals and transplant units represent all members and link ICUs and hospitals with donors. Racial disparities - minorites need more transplants as diseases occur more frequently Early identification of donor eligibility can reduce the risk of injuries after brain death. Can give a resolution and identification on Coronial/Procurator Fiscal problems. However, there is a lack of training and communication in this field In Africa, there were HIV+ to HIV+ donations, which could potentially expand donor criteria. Artificial extracorporeal liver support devices have been developed that perform haemodialysis, TPE and albumin dialysis. US uses the points-based system MELD to ensure that those with the highest need are prioritized and the outcome after transplantation They look at the recipient's history, including their psychiatry, social support system, and addictions. MELD score do not include any of the donor's environmental factors.
Research Question/Problem/ Need	What are some problems with the organ transplantation system, and what are some solutions to decrease the organ supply shortage?
Important Figures	<table><tr><th>Year</th><th colspan="4">Region</th></tr><tr><th></th><th>US</th><th>EuroTransplant[a]</th><th>Scandiatransplant[b]</th><th>UK</th></tr><tr><td>2018</td><td>113,759 (5565)</td><td>14,129 (1289)</td><td>2660 (129)</td><td>6077 (400)</td></tr><tr><td>2017</td><td>115,759 (5850)</td><td>14,773 (1386)</td><td>2629 (111)</td><td>6044 (411)</td></tr><tr><td>2016</td><td>119,362 (6199)</td><td>14,533 (1370)</td><td>2487 (100)</td><td>6388 (457)</td></tr><tr><td>2015</td><td>122,071 (6688)</td><td>14,560 (1437)</td><td>2402 (105)</td><td>6476 (466)</td></tr><tr><td>2014</td><td>123,851 (6727)</td><td>14,928 (1387)</td><td>2280 (99)</td><td>6943 (429)</td></tr><tr><td>2013</td><td>121,272 (6488)</td><td>15,292 (1392)</td><td>2211 (122)</td><td>7026 (456)</td></tr><tr><td>2012</td><td>117,040 (6585)</td><td>15,027 (1543)</td><td>2116 (112)</td><td>7332 (466)</td></tr><tr><td>2011</td><td>112,816 (6786)</td><td>15,499 (1552)</td><td>2093 (118)</td><td>7636 (508)</td></tr><tr><td>2010</td><td>110,375 (6624)</td><td>15,591 (1561)</td><td>2117 (102)</td><td>7800 (511)</td></tr></table> Total waitlist count by year and region Deaths that occurred while on the waitlist are in parenthesis.

	 Total number of transplants in the US and Europe in 2018
VOCAB: (w/definition)	**EuroTransplant** = international collaboration between Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. **ScandiaTransplant** = international collaboration between the following countries: Denmark, Finland, Iceland, Norway, Sweden and Estonia. **Specified donation** = not anonymous donations; could be genetically related **Unspecified donation** = completely anonymous donation to waitlist recipient **Dialysis** = replaces normal filtering function of kidneys when kidney deteriorates. **LOD** = Living Organ Donation transplants when living person donates organ **Xenotransplantation** = pig-to-human transplantation. Genome editing approaches and stem cell technology allow pig breeding free of xenoantigens and retroviruses **TAH** = total artificial heart is a mechanical circulatory support that restores total pulmonary and systemic flow. **TPE** = therapeutic plasma exchange helps patients with acute liver failure.
Cited references to follow up on	https://www.sciencedirect.com/science/article/abs/pii/S0168827804005161 https://www.sciencedirect.com/science/article/abs/pii/S0749070414000566
Follow up Questions	Can we transplant organs between patients with the same disease? What are the problems with transplanting organs from deceased donors?

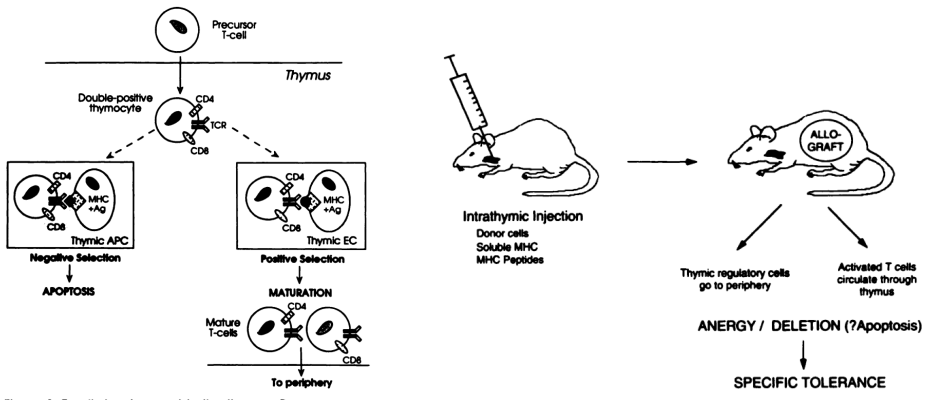
Article #24 Notes: **Living donor liver transplant from an HIV-positive mother to her HIV-negative child opening up new therapeutic options**

Source Title	Living donor liver transplant from an HIV-positive mother to her HIV-negative child opening up new therapeutic options
Source citation (APA Format)	Botha, J., Conradie, F., Etheredge, H., Fabian, J., Duncan, M., Haeri Mazanderani, A., Paximadis, M., Maher, H., Britz, R., Loveland, J., Ströbele, B., Rambarran, S., Mahomed, A., Terblanche, A., Beretta, M., Brannigan, L., Pienaar, M., Archibald-Durham, L., Lang, A., & Tiemessen, C. T. (2018). Living donor liver transplant from an HIV-positive mother to her HIV-negative child: opening up new therapeutic options. *AIDS*, *32*(16), F13. https://doi.org/10.1097/QAD.0000000000002000
Original URL	https://journals.lww.com/aidsonline/fulltext/2018/10230/living_donor_liver_transplant_from_an_hiv_positive.1.aspx
Source type	Journal Article
Keywords	antiretroviral therapy, HIV serodiscordant, liver transplant, liver/hepatitis, living donor, pediatrics, reservoirs
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Unique liver transplant case from HIV+ mother to HIV- child. After one year, the child and the mother are both healthy. Involved LOD liver donation from someone with HIV. In the past, there were some successful HIV+ to HIV+ transplants, but the donors have died. However, these programs allowed HIV+ transplants to be legal. This process puts HIV+ donors at a higher risk and is not ethically best Involved controlled transplant: they prevented the HIV transmission as much as possible with prophylaxis. In the past, HIV transplants were from deceased donors, and seroconversion occurred.

	Child had end stage liver cancer. Both parents had HIV. Mother went on PMTCT and child was HIV-. Had no choice but to transplant mother's liver. She have CD4+ count of >200 cells and suppressed HIV virus for at least 6 months before. Child was 13 months old. Performed the transplant as normal, but the monitored the child with medications and check ups. To prevent HIV, child was started on ART on the evening before the transplant and is still on the regimen. After transplant, child was tested for HIV. Had no short-term effects. Doctors believe on the causes could be that the child developed HIV immune cells when she was in the womb.
Research Question	How to transplant a liver from an HIV-positive mother to her HIV-negative child?
Important Figures	  Fig 1:Recipient catch-up growth based on middle-upper arm circumference. Fig 2: Time course showing recipient HIV seroconversion, undetectable plasma HIV RNA and cellular DNA reservoir
VOCAB: (w/definition)	**ART** = antiretroviral treatment is a durg regimen treatment for people with HIV **PMTCT** = prevention of mother-to-child transmission is a treatment that helps HIV+ pregant women decrease the risk of vertical transmission, or prevent the HIV transmission to their children **Prophylaxis** = refers to all the methods used to prevent disease **Seroconversion** = time between exposure ot virus and when antibodies show up in your blood **CD4+** = helper T cells that signal other immune system cells how and when to fight
Cited references to follow up on	https://journals.lww.com/aidsonline/fulltext/2020/07010/organ_transplantation_in_persons_with_hiv.2.aspx https://journals.lww.com/co-transplantation/abstract/2023/08000/immunosuppression_in_hiv_positive_kidney.8.aspx
Follow up Questions	Is it possible to transplant organs with other diseases? Would this same procedure be successful in adults?

Article #25 Notes: **The thymic way to transplantation tolerance**

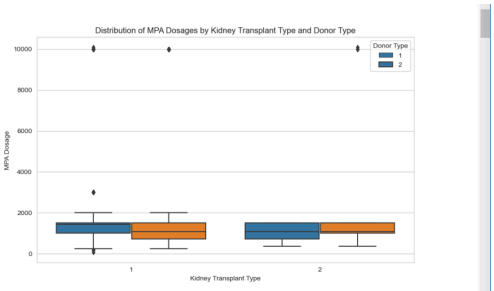
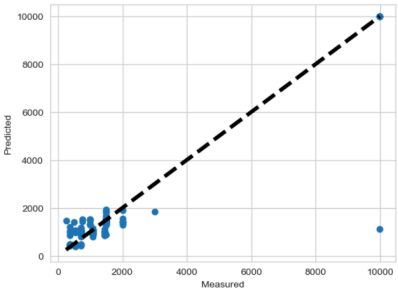
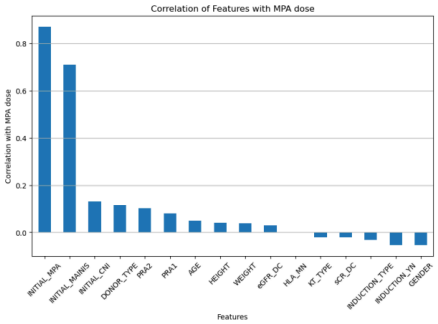
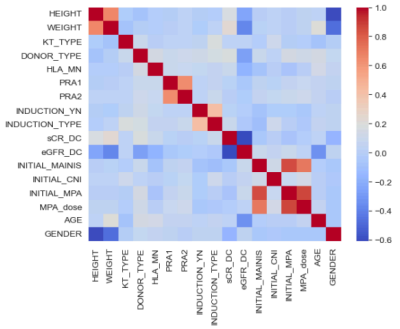
Source Title	The thymic way to transplantation tolerance
Source citation (APA Format)	Chin, Y. M., Takahashi, Y., Chan, H. T., Otaki, M., Fujishima, M., Shibayama, T., Miki, Y., Ueno, T., Nakamura, Y., & Low, S.-K. (2021). Ultradeep targeted sequencing of circulating tumor DNA in plasma of early and advanced breast cancer. *Cancer Science*, *112*(1), 454–464. https://doi.org/10.1111/cas.14697
Original URL	https://pubmed.ncbi.nlm.nih.gov/7780051/
Source type	Journal Article
Keywords	Thymus, self-tolerance, acquired tolerance, pancreatic islets, kidney, MHC allopeptides, transplantation
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Previous research shows that the thymus may play a role in the induction of acquired tolerance to external antigens Foreign antigens are recognized after they are processed and presented as peptides in the binding groove of cell surface molecules encode by the MHC genes to the TCR. The TCR on each T cell are identical and specific fro a given MHC and antigenic peptide complex. TCR are selected to react with foreign antigens. Self/nonself discrimination is established early in life and dependent on the thymus. TCR are not secreted after antigen stimulation, but remain on the surface of T lymphocutye in proteins forms. Antigen receptors are generated by random rearrangement of DNA segments encoding variable parts of the alpha/beta chains of TCR with specificity fro self and nonself antigens. The capacity to distinguish self/nonself is acquired through T cell development Precursor T lymphocytes reach thymus in early life. Immature T cells in the cortex have no TCR, CD4 or CD8 molecules. Cells undergo growth, TCR gene arrangement and surface expression of CD4 and CD8.

	These cells interact with bone marrow derived APCs with MHC molecules and undergo a process that shape the T cell to self-tolerance. Negative selection delects the T cells that are not self-tolerant Then, they move to the medulla and have increased TCR expression and become MHC class II helper or Class 1 cytotoxic and go outside. Only 1-5% of total thymocyte population completes maturation, the remaining are deleted in thymus Scientists induced specific tolerance to skin allografts in mice by injecting stem cells. Intrathymic inactivaton or deletion of T cells may contribute to the unresponsiveness. Mice with stem cells at birth deleted donor-reactive T cells in the thymus. Injecting soluble antigens into the thymus induced systemic unresponsiveness. Renal allografts survived indefinitely with preserved function after subsequent transplantation. The intrathymic injection of donor cells expressing MHC Class I and Class II antigens induced tolerance to renal allografts, showing that acquired thymic tolerance is not tissue-specific. Whole donor cells are not needed, MHC molecules was enough to induc unreponsiveness.
Research Question/Problem/ Need	What is the role of the thymus in T cell formation and organ rejection?
Important Figures	
VOCAB: (w/definition)	**Tolerance** = recipient does not reject donor organ, but immune system remains competent to fight infection without immunosupressors **Islets** = a portion of tissue structurally distinct from surrounding tissues. **acquired tolerance** = lack of immunological reactivity to a specific antigen. **Heterodimeric** = something is composed of two nonidentical simpler molecules **Thymocyte** = lymphocyte within the thymus **Self tolerance** = the ability of the immune system to recognize self-produced antigens as a non-threat

Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/9469488/ https://pubmed.ncbi.nlm.nih.gov/2119056/ https://pubmed.ncbi.nlm.nih.gov/8154045/
Follow up Questions	What is the waiting time between intrathymic injection and transplantation? What is the impact of immunosupressive drugs on the unresponsive state? How can this be used in adults with a competent immune system?

Article #26 Notes: **Predicting Dosage of Immunosuppressant Drugs After Kidney Transplantation Using Machine Learning**

Source Title	Predicting Dosage of Immunosuppressant Drugs After Kidney Transplantation Using Machine Learning
Source citation (APA Format)	Panda, K., & Mazumder, A. (2023, August 22). *Predicting Dosage of Immunosuppressant Drugs After Kidney Transplantation Using Machine Learning*. arXiv.Org. https://arxiv.org/abs/2308.11167
Original URL	https://arxiv.org/pdf/2308.11167.pdf
Source type	Journal Article
Keywords	machine learning, artificial intelligence, kidney transplantation, immunosuppressants, predictive analytics
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Algorithm predicts exact dosage of immunosupressant drugs to be administered after kidney transplant. Random FOrest Regression algorithm was used and trained on different subsets of data containing various features and data points. Python was used to write and compile the code. Data was divided by age, gender, height, weight. Missing variables were inputted by replacing tem with average value of that category. Only used number data. Exploratory data analysis was conducted to understand if there was a correlation between dosage and variables in dataset. There was a clear correlation. Patients who received a kidnet from living donor needed higher dosages. Random forest algorithm helped mitigate outliers in data. More balanced approach. Reduces irrelevant features automatically. The mean absolute error shows that the algorithm fits the training data, it only gives average values that are moderate distance from true dosage. Could be explained by outliers. Correlation analysis showed what variables were most predictive ofthe final optimized dosage Need to use more data to make the model more precise and accurate.

Research Question/Problem/ Need	How can AI and ML be used to predict immunosupressive dosage?
Important Figures	 Fig. 2: MPA dosages based on kidney and donor types  Fig. 3: Predicted Output vs. Actual Output  Fig. 4: Feature correlation with the MPA dosage  Fig. 1: Correlations between each variable
VOCAB: (w/definition)	**Random Forest Regression algorithm** = creates multiple decision trees, each trained on a random subset of the dataset, using different features and data points.
Cited references to follow up on	https://pubmed.ncbi.nlm.nih.gov/31682262/ https://pubmed.ncbi.nlm.nih.gov/26834463/ https://pubmed.ncbi.nlm.nih.gov/28846737/
Follow up Questions	What other algorithms could be used? How much more data is needed to make it accurate? How could the algorithm be modified to consider outliers?

Article #27 Notes: **Hispanics And Native Americans Are More Likely To Have Heart Transplant Rejection.**

Source Title	Hispanics And Native Americans Are More Likely To Have Heart Transplant Rejection.
Source citation (APA Format)	Ahmed, I., & Amoateng, R. (2023). Hispanics And Native Americans Are More Likely To Have Heart Transplant Rejection. *Journal of Cardiac Failure*, *29*(4). https://doi.org/10.1016/j.cardfail.2022.10.178
Original URL	https://www.sciencedirect.com/science/article/pii/S1071916422009101
Source type	Short Journal Article
Keywords	Rejection, demographics
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Investigate racial disparities in heart transplant complications Retrospective cohort study using NIS database to identify adults with complications from 2019 Majority of heart transplants were Caucaisans and males. Hispanic and Native AMerican had rejection rates of 18.92% and 2.7% There was an association between heart rejection and Hispanic race, Native Americans, young age, and increased hospital cost
Research Question/Problem	What populations are more likely to present organ rejection?

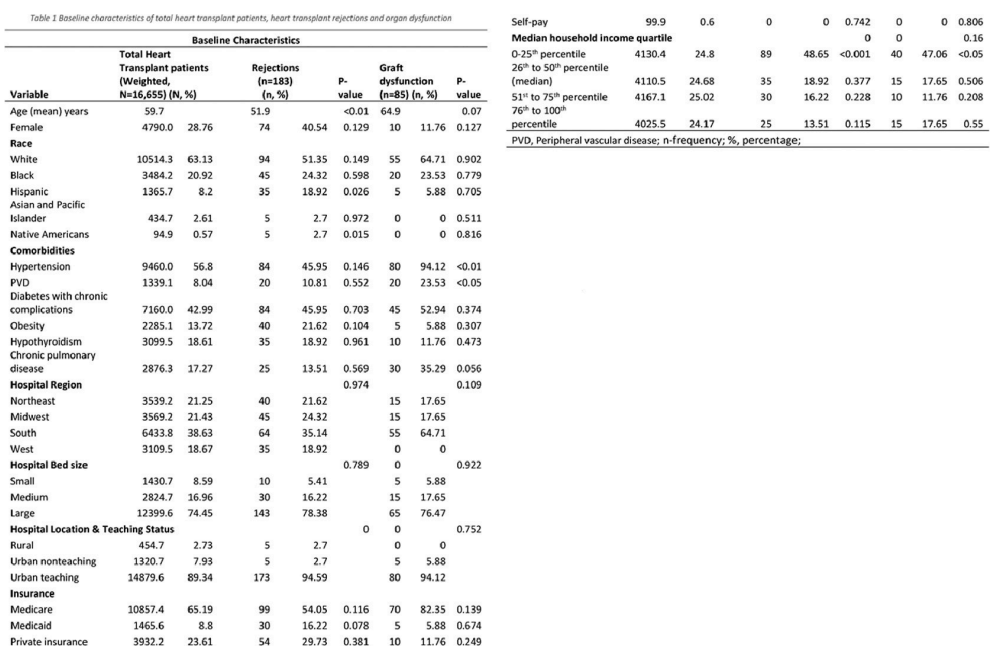
Important Figures	
VOCAB: (w/definition)	**Retrospective Cohort Study** = observational research that uses existing data to examine relationship between exposure and outcome **Graft dysfunction** = severe lung injury that occurs within the 1st 72 hrs of transplantation. Common cause of early mortality **cardiac allograft vasculopathy** = causes blood vessels to become narrowed and blocked
Cited references to follow up on	https://www.sciencedirect.com/science/article/pii/S2772993122000705 https://www.sciencedirect.com/science/article/pii/S2666501823000089
Follow up Questions	Why is a main cause for this association? What is the demographic profile for immunosuppression side effects?

Table 1 Baseline characteristics of total heart transplant patients, heart transplant rejections and organ dysfunction

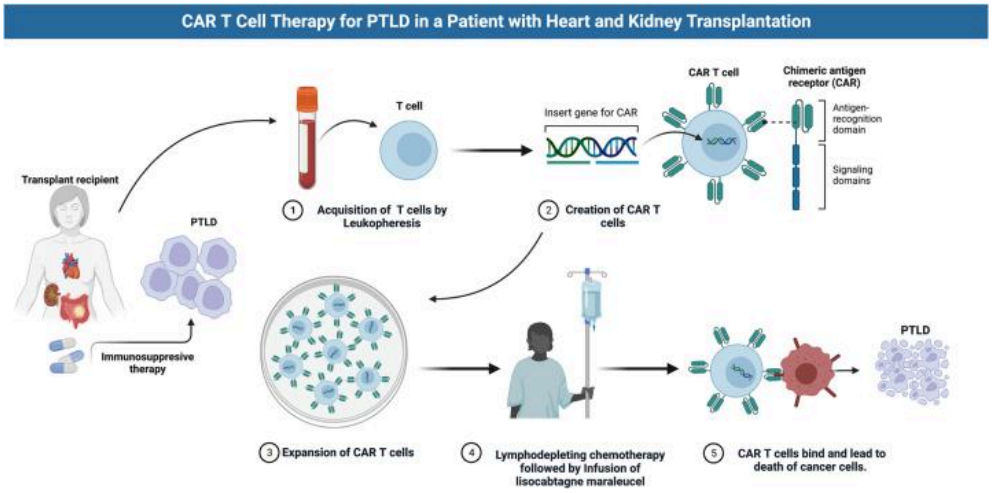
Baseline Characteristics								
Variable	Total Heart Transplant patients (Weighted, N=16,655) (N, %)		Rejections (n=183) (n, %)		P-value	Graft dysfunction (n=85) (n, %)		P-value
Age (mean) years	59.7		51.9		<0.01	64.9		0.07
Female	4790.0	28.76	74	40.54	0.129	10	11.76	0.127
Race								
White	10514.3	63.13	94	51.35	0.149	55	64.71	0.902
Black	3484.2	20.92	45	24.32	0.598	20	23.53	0.779
Hispanic	1365.7	8.2	35	18.92	0.026	5	5.88	0.705
Asian and Pacific Islander	434.7	2.61	5	2.7	0.972	0	0	0.511
Native Americans	94.9	0.57	5	2.7	0.015	0	0	0.816
Comorbidities								
Hypertension	9460.0	56.8	84	45.95	0.146	80	94.12	<0.01
PVD	1339.1	8.04	20	10.81	0.552	20	23.53	<0.05
Diabetes with chronic complications	7160.0	42.99	84	45.95	0.703	45	52.94	0.374
Obesity	2285.1	13.72	40	21.62	0.104	5	5.88	0.307
Hypothyroidism	3099.5	18.61	35	18.92	0.961	10	11.76	0.473
Chronic pulmonary disease	2876.3	17.27	25	13.51	0.569	30	35.29	0.056
Hospital Region					0.974			0.109
Northeast	3539.2	21.25	40	21.62		15	17.65	
Midwest	3569.2	21.43	45	24.32		15	17.65	
South	6433.8	38.63	64	35.14		55	64.71	
West	3109.5	18.67	35	18.92		0	0	
Hospital Bed size					0.789	0		0.922
Small	1430.7	8.59	10	5.41		5	5.88	
Medium	2824.7	16.96	30	16.22		15	17.65	
Large	12399.6	74.45	143	78.38		65	76.47	
Hospital Location & Teaching Status					0	0		0.752
Rural	454.7	2.73	5	2.7		0	0	
Urban nonteaching	1320.7	7.93	5	2.7		5	5.88	
Urban teaching	14879.6	89.34	173	94.59		80	94.12	
Insurance								
Medicare	10857.4	65.19	99	54.05	0.116	70	82.35	0.139
Medicaid	1465.6	8.8	30	16.22	0.078	5	5.88	0.674
Private insurance	3932.2	23.61	54	29.73	0.381	10	11.76	0.249
Self-pay	99.9	0.6	0	0	0.742	0	0	0.806
Median household income quartile						0	0	0.16
0-25th percentile	4130.4	24.8	89	48.65	<0.001	40	47.06	<0.05
26th to 50th percentile (median)	4110.5	24.68	35	18.92	0.377	15	17.65	0.506
51st to 75th percentile	4167.1	25.02	30	16.22	0.228	10	11.76	0.208
76th to 100th percentile	4025.5	24.17	25	13.51	0.115	15	17.65	0.55

PVD, Peripheral vascular disease; n-frequency; %, percentage;

Article Notes - B-Term:

Article #28 Notes: **Successful CAR T Cell Therapy in a Heart and Kidney Transplant Recipient With Refractory PTLD**

Source Title	Successful CAR T Cell Therapy in a Heart and Kidney Transplant Recipient With Refractory PTLD
Source citation (APA Format)	Oren, D., DeFilippis, E. M., Lotan, D., Clerkin, K. J., Fried, J., Reshef, R., Fernandez, H., Lin, E., Amengual, J., Sayer, G., Uriel, N., & Raikhelkar, J. K. (2022). Successful CAR T Cell Therapy in a Heart and Kidney Transplant Recipient With Refractory PTLD. JACC: CardioOncology, 4(5), 713–716. https://doi.org/10.1016/j.jaccao.2022.09.002
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9830195/
Source type	Journal Article
Keywords	CAR T cell, heart transplantation, immunotherapy, kidney transplantation, post-transplant lymphoproliferative disorder
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Even though organ transplant patients have been living longer, there have been more cases of EBV that cause problems after the first 18 months of transplant. In 2018, 2 out of 1000 patients had this. Trials have demonstrated the effectiveness of CAR T-cell therapy in providing a durable response against NHL. However, data was limited. 23-year old women had heart transplant at 11 months of age (no EBV) Had kidney transplant at 20 years old (EBV). 5 years before, she had rejection of her cardiac allograft. But she had no vasculopathy or donor-specific antibodies and maintained graft function. Increased immunosupression by three times. Had worsened symptoms, and she was PTLD positive. Medicine did not help. She received 2 cycles of GemCo. Disease got worse. Treated with polatuzmab vedotin.

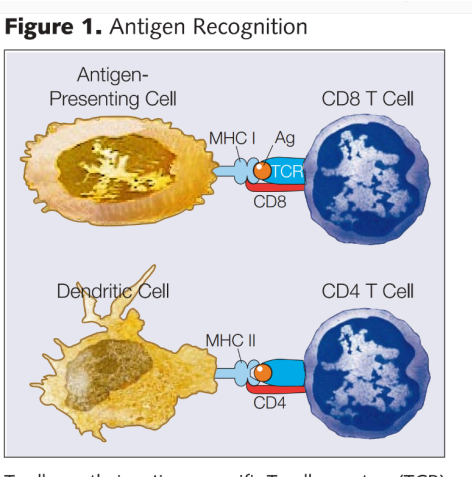
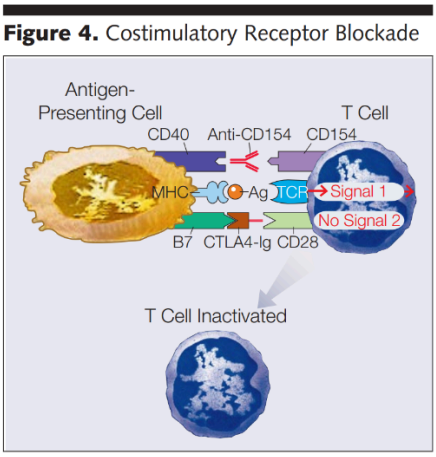
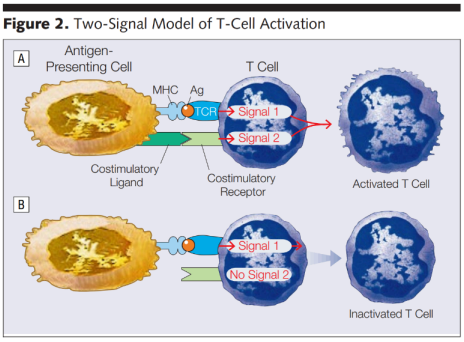
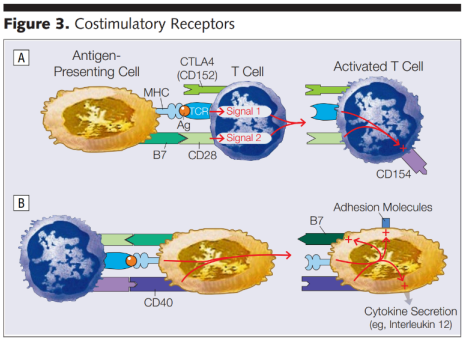
	PBMC were collected to manufacture lisocabtagene maraleucel, a CD19 targetting CAR T cell product. However, patient blood cultures had E coli, and was treated until there was no evidence of contamination. CAR T cells were infused, and had no evidence of cytokine release syndrome. After infusion, patient had COVID, but only had mild symptoms and had a complete metabolic response. Doing well after CAR t cell therapy
Research Question/Problem/ Need	How can CAR T cell therpay be safely used in heart transplant recipients with refractory PTLD?
Important Figures	 CAR T Cell Therapy for PTLD Flow chart depicting the development of post-transplant lymphoproliferative disorder (PTLD) following immunosuppressive therapy, percurrent of T cells followed by generation of chimeric antigen receptor (CAR) T cells, clone expansion, and infusion with subsequent binding of CAR T cells to cancer cells
VOCAB: (w/definition)	**PTLD** = Post-transplant lymphoproliferative disorder refers to a wide array of immunosupression related complications following solid organ transplantation **Epstein-Barr virus (EBV)–negative PTLD** = PTLD that are late-onset and have poor prognosis **diffuse large B cell lymphoma** = type of fast-growing non-Hodgkin lymphoma **NHL** = Non-Hodgkin lymphoma is a type of cancer that develops in the lymph nodes and lymphatic tissue **Tacrolimus** = decreases the activity of your immune system **GemCo** = gemcitabine and carboplatin, common chemo combo **polatuzmab vedotin** = monoclonal antibody used to trate PTLD **peripheral blood mononuclear cells** = immue cells are PBMC **lisocabtagene maraleucel** = combo of CD4+ and CD8+ cells. Works by binding to CD19 expressed on the cell surface of tumor ad normal B cells, and induces activation and proliferation of CAR T cells **CD19** = biomarker for B cell development and lymphoma diagnosis

Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8211027/ https://pubmed.ncbi.nlm.nih.gov/32265077
Follow up Questions	How can this therapy be used to prevent organ rejection? What are the long-term outcomes? Do ther external conditions have any influence in results?

Article #29 Notes: **Can T-Cell Costimulatory Pathway Modifiers Revolutionize the Prevention of Graft Rejection?**

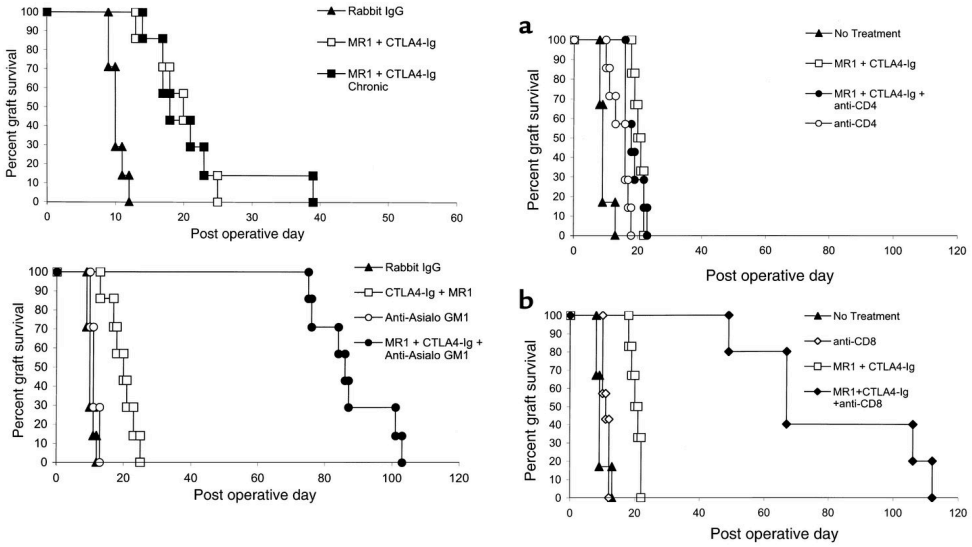
Source Title	Can T-Cell Costimulatory Pathway Modifiers Revolutionize the Prevention of Graft Rejection?
Source citation (APA Format)	Harlan, D. M., & Kirk, A. D. (1999). The Future of Organ and Tissue Transplantation: Can T-Cell Costimulatory Pathway Modifiers Revolutionize the Prevention of Graft Rejection? JAMA, 282(11), 1076–1082. https://doi.org/10.1001/jama.282.11.1076
Original URL	https://jamanetwork.com/journals/jama/article-abstract/191586
Source type	Journal Article
Keywords	Costimulatory, T cells, organ rejection, transplant
#Tags	#Information
Summary of key points + notes (include methodology)	Important factors shown to be symptomatic of chronic rejection are acute rejection episodes, donor organ quality, certain immunosupressive drugs, elevated blood pressure, and serum lipid levels. The immune system is divided into 2 systems: innate system and adaptive immune systems. Innate system has phagocytic cellsthat use a variety of clues to recognie, engulf, and digest invading pathogens. In mammals, this system has dendritic cells Adaptive immune system has T and B lymphocytes. The surface of these cells have antigen specific receptors that are desigfned to recognize only 1 target. B cells make antigen-specific antibodies and T cells do the cell-mediated immune response. This response is mainly responsible for rejection. T cells direct the immune response that recognizes and destroys cells damaged by toxins or viruses. Each T cell can recognize only 1 target. TCRs recognize small peptide fragments of whole antigens presented by the MHC proteins on the cell surfaces. Class I MHC molecules are present on all tissue cells and present fragment of proteins made within the cell. MHC II are found only on specilized APCs and

	present fragments of antigens made outside the cells which are digested and presented by the specialized APC. MHC molecules are polymorphic, so 2 unrelated ppl probably dont have identical MHC types. This disparity causes rejection. T cells have 2 subgroups based on the presen of other protein complexes on their surfaces. CD4+ recognized MHC II (cells of the innate immune system) and CD8+ recognizes MHC class I antigens. Approximately 1% of person's T cells are unmatched for another. When the hosts innate immune system encounter damaged cells within the transplant, those damaged donor cells are ingested and antigens from there are presented to the host T cells. TCRs recognize MHC presented, but its not enough. There is a 2nd signal. The costimulator signal is rewuitred to activate the T cell. A costimuatory signal delivered without antigen recognition was neutral. But is the t cell recognize the MHC but didnt have the 2nd signal, the T cell would die or not activate in future. Immunosupressors block signal 1. Indiscriminately impair signal 1. Impairing the 2nd signal can inactivate the t calls for that antigen, leaving the other ones unaffected. The CD28-B7 counter receptor group has 4 unique receptors. 2 B7 receptors (CD80 and CD86) were clones and are known to be expressed by activated APC. The interaction with B7 and CD28 can costimuate T cell activation if a TCR signal is also delivered. T cells also express another receptor called CTLA4 (CD152) that is a counter receptor for both of the B7 receptors. CD28-B7 stimulate T cell activation and CD152-B7 restrains immune response. Combining CTLA4 with an IgG, is CTLA4-Ig.
Research Question/Problem/ Need	Can T-Cell Costimulatory Pathway Modifiers Prevent Organ Rejection?

Important Figures	   
VOCAB: (w/definition)	**Vasculopathy** = a general term for any disease that affects blood vessels. **CD28** = a protein expressed on T cells that provides co-stimulatory signals required for T cell activation and surviv **IgG** = the most common type of antibody in the blood and other body fluids. Antibodies are proteins made by plasma cells when the body feels under attack.
Cited references to follow up on	https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2811462?widget=personalizedcontent&previousarticle=191586 https://jamanetwork.com/journals/jama/article-abstract/1029038?widget=personalizedcontent&previousarticle=191586 https://jamanetwork.com/journals/jama/article-abstract/1844849?widget=personalizedcontent&previousarticle=191586
Follow up Questions	Why does the costimulatory signal inactivate T cells but the first signal have a neutral effect? How does the MHC mismatch plah a role in rejection?

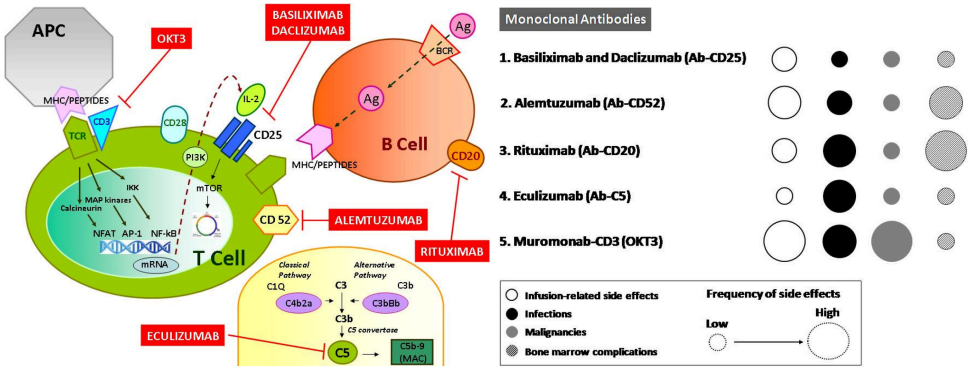
Article #30 Notes: **Asialo GM1+ CD8+ T cells play a critical role in costimulation blockade–resistant allograft rejection**

Source Title	Asialo GM1+ CD8+ T cells play a critical role in costimulation blockade–resistant allograft rejection
Source citation (APA Format)	Trambley, J., Bingaman, A. W., & Lin, A. (1999). Asialo GM1+ CD8+ T cells play a critical role in costimulation blockade–resistant allograft rejection - PMC. The Journal of Clinical Investigation, 104(12). https://doi.org/10.1172/JCI8082
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC409885/
Source type	Journal Article
Keywords	T cells, costimulatory blockade, organ rejection
#Tags	#Background
Summary of key points + notes (include methodology)	Previous studies had that anti CD40L and CTLA4 dramitally prolong survival. However, there was only minimal prolongation during their initial tests Thought it was cause insufficient blockade, so they did the regimen for as long as complete rejection occurred. Survival was not significantly improved with chronic trial. Shows that B6 mice can effectively reject allografts via pathways that are independent of the CD40 and CD28 costimulatory pathways Asialo GM1+ cells are important mediators of the rejection that is resistant to costimulaotry blockade. NK cells infiltrate cardiac allografts during acute rejection responses. They wanted to study role of Nk cells in costimulatory-blockade resistance rejection. Used anti-asialo GM1 to deplete NK cells Flow cytometry shoes that 20% of CD8 expressed GM1 93% on Nk cells and aboiut 1% on CD4 cells. Wanted to see if Anti-asialo was depleting CD8 or NK cells In a CD4 vs. CD8 study, they saw that depleting CD8 has a bigger impact on preventing organ rejection. Data is limited to B6 mice, and more research is needed because the immune response may depend on both the genetic background of the recipient and the

	organ being transplanted
Research Question/Problem/ Need	How effective are costimulation blockade therapies, and what do they tell us about the role of certain cell types in the immune system?
Important Figures	
VOCAB: (w/definition)	**GM1** = molecule found on surface of cells and can aid in immune system signalling
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2192869/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2188638/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2198972/
Follow up Questions	Can CD8 costimulatory pathways decrease rejection even more? What other molecules can be targeted to decrease rejection?

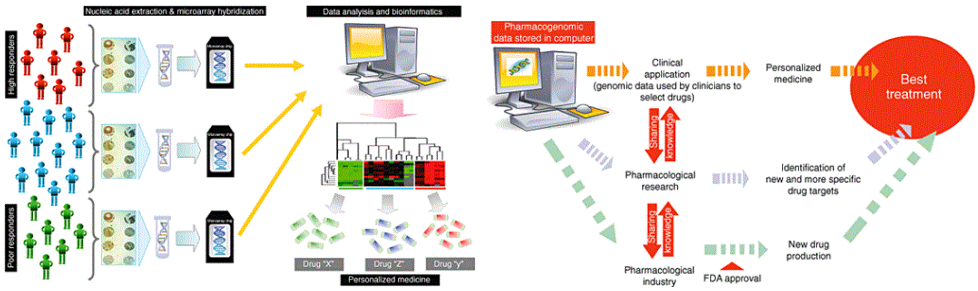
Article #31 Notes: **Monoclonal Antibody Therapy and Renal Transplantation: Focus on Adverse Effects**

Source Title	Monoclonal Antibody Therapy and Renal Transplantation: Focus on Adverse Effects
Source citation (APA Format)	Zaza, G., Tomei, P., Granata, S., Boschiero, L., & Lupo, A. (2014). Monoclonal Antibody Therapy and Renal Transplantation: Focus on Adverse Effects. Toxins, 6(3). https://doi.org/10.3390/toxins6030869
Original URL	https://www.mdpi.com/2072-6651/6/3/869
Source type	Journal Article
Keywords	renal transplantation; adverse effects; toxicity; Basiliximab; Rituximab; Eculizumab; malignancy; infection; toxicity
#Tags	#Background/Stats
Summary of key points + notes (include methodology)	mAbs are commonly used as induction therapy (period of intese immunosupresion befire and immediately after implant) to treat rejection Antbdy induction therapy is used in over 80% of renal transplantations Main objective to reduce early acute rejections Decrease delayed graft function Majority of meds are targeted against CD proteins in T and B cells Provide barrier through effects of cytotoxic/effector cells Basilizimab and Daclizumab bind to IL2 receptier (CD25) and prevent formation of IL2 binding site Alemtuzumab is directed against CD52 which determines lysis of lymphocytes (kill) Rituximab binds to CD20 antigen on B cell surface Eculizumab is against C5 and prevents formation of membrane attack comples OKT3 targets CD3 protein on T cell surface and blocks the generation and function od cytotoxic T cells No universal consensus on the optimal mAb for induction therapy Decisuon is taken into account the balance and risks
Research Question/Problem/ Need	What are different types of monoclonal antibodies used in organ transplants and how do they prevent rejection?

Important Figures	
VOCAB: (w/definition)	**mAbs** = monoclonal antibodies **Lysis** = process of breaking down a cell's membrane. This can happen inside or outside of the cell. Lysis can result in the release of cell contents or the death of the cell **Cytotoxic** = substance or process can damage or kill cells.
Cited references to follow up on	https://scholar.google.com/scholar_lookup?title=Impact+of+renal+cadaveric+transplantation+on+survival+in+end-stage+renal+failure:+evidence+for+reduced+mortality+risk+compared+with+hemodialysis+during+long-term+follow-up&author=Van+Der+Woude,+F.J.&publication_year=1998&journal=J.+Am.+Soc.+Nephrol.&volume=9&pages=2135%E2%80%932141 https://scholar.google.com/scholar_lookup?title=T-cell+alloimmunity+and+chronic+allograft+dysfunction&author=Safinia,+N.&author=Afzali,+B.&author=Atalar,+K.&author=Lombardi,+G.&author=Lechler,+R.I.&publication_year=2010&journal=Kidney+Int.+Suppl.&volume=119&pages=S2%E2%80%93S12
Follow up Questions	What are someways that mAbs can be personalized for organ transplants? Are there any biomarkers that can provide insight on the best mAbs to use?

Article #32 Notes: **Pharmacogenomics: a new paradigm to personalize treatments in nephrology patients**

Source Title	Pharmacogenomics: a new paradigm to personalize treatments in nephrology patients
Source citation (APA Format)	Zaza, G., Granata, S., Sallustio, F., Grandaliano, G., & Schena, F. P. (2009). Pharmacogenomics: a new paradigm to personalize treatments in nephrology patients. *Clinical and Experimental Immunology*, *159*(3), 268–280. https://doi.org/10.1111/j.1365-2249.2009.04065.x
Original URL	https://academic.oup.com/cei/article/159/3/268/6438781
Source type	Journal Article
Keywords	chronic kidney disease, drugs, nephrology, pharmacogenetics, pharmacogenomics
#Tags	#Background/Stats
Summary of key points + notes (include methodology)	The latest methods used to adjust drug dosages result in inadequate, non reproducible and poor predictive efficacy before drug administration Hormonal levels, and pharmacokinetic interactions and genetic variablit in targets may have a predominant role in modulating drug effects. Genetics may account for 20-95% of variability in drug disposition and effect. Even if it is possible to predict therapeutic effectiveness and dosages based on polymorphic drig-related genes, it is not applicable for the majority of drugs Innovative automated genome based research tech from the human genome project may be a tool to weight the genetic/genomic influence in pharmacological outcomes and identify more selective and appropriate targets for drug targets Tailoring the dose of drugs to specific rewuiremet sof the individual patient to minimize toxcicity is hard. Several programmes have been undertaken to analze the genetic influence on the patients reponse to these conventional treatments Azathioprine: genetic polymorphisms hae a major impact on the metabolism of AZA. AZA is mainly catabolized by an enzyme. Enzyme is encoded by TPMT gene. Elevated TPMT was associated with increased risk of acute rejection.

	CNI and TAC: impact of genetic variablity has not been defined completely. Expression of multi drug resitance (MDR-1) gene may be influential. Patients with CYP3A5 gene results in lack of enzyme expression may need lower dosages od CNIs compares to another variant. NEP was most significant upregulated gene in a group of stable renal transplants. Incubation of proximal tubular cells with MPA led to increase in NEP gene expression. More realistic to consider a group of genetic variants rather than one single gene. Several genes have been suggested as potemntially useful [redictors of tolerance. Microarray studies ave been performed to identify genes during rejection. Among those genes selected were those encoding or several chemoknes with porinflammatory and chemotactic activity, interleukin (IL)-8, chemokine (C-C motif) receptor 7 (CCR7), tumour necrosis factor (TNF)-α, chemokine (C-X-C motif) receptor 4 (CXCR4) key regulators of oxidative stress: v-rel reticuloendotheliosis viral oncogene homologue A (RELA) and glutathione synthetase (GSS) those implicated in the mitochondrial oxidative phosphorylation system ATP5O, COX6C, COX7C, NDUFS5, NDUFA6, UQCRH, NDUFA1, ATP5J, UQCRB, NDUFB1 and ATP5I
Research Question/Problem/ Need	How can pharmacogenomics be used to find better biomarkers and genes that are linked to organ rejection?
Important Figures	
VOCAB: (w/definition)	**Chemokine** = ny of a class of cytokines with functions that include attracting white blood cells to sites of infection. **Microarray** = a grid of DNA segments of known sequence that is used to test and map DNA fragments, antibodies, or proteins.
Cited references to follow up on	http://www.ncbi.nlm.nih.gov/pubmed/14673633 http://www.ncbi.nlm.nih.gov/pubmed/15616206
Follow up Questions	How can these genes be used for drug discovery?

Article #33 Notes: **Donor Cytokine Genotype Influences the Development of Acute Rejection After Renal Transplantation**

Source Title	Donor Cytokine Genotype Influences the Development of Acute Rejection After Renal Transplantation
Source citation (APA Format)	Marshall, S. E., McLaren, A. J., McKinney, E. F., Bird, T. G., Haldar, N. A., Bunce, M., Morris, P. J., & Welsh, K. I. (2001). DONOR CYTOKINE GENOTYPE INFLUENCES THE DEVELOPMENT OF ACUTE REJECTION AFTER RENAL TRANSPLANTATION. Transplantation, 71(3), 469. https://journals.lww.com/transplantjournal/fulltext/2001/02150/donor_cytokine_genotype_influences_the_development.22.aspx
Original URL	https://journals.lww.com/transplantjournal/fulltext/2001/02150/donor_cytokine_genotype_influences_the_development.22.aspx
Source type	Journal Article
Keywords	Cytokine, genetics, rejection, kidney transplant
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Both donor and recipient factors contribute to local enviornemtne that inc=fluences rejection reposnse severity. Cytokines are mahor determinant od this. 145 dead renal donors were selected for the analysis according to the presence or absence of graft rejection infirst 30 days after transplantation. DNA was genotypes for 20 polymorphism in 11 cytokine and cytokine receptors genes using PCR with sequence specific primers. Identifying risk factors tha influence the incidence and severity of acute rejection - can be used to develop algorithms to estimate individual patient risk and ultimately allow for development of personalized immunosuppressive regimens T cells are capable of exhibiting a wide spectrum of immune responses after encounter with antigen.

	Cytokines are small, short acting proteins tjat amplify and direct the immune response and are produced by lymphocytes, APC. Controlling cytokine production is important in regulating the immune response. Outcome of immune response can be influenced by individual variation of cytokine receptor genes, Cytokines do not act in isolation but froma complex network of interacting proteins, so the cytokine environment may be the product if a variation in many polymorphic cytokine genes Cytokines produced within the graft mey be derived from both the recipient and the donor. Cytokine genotyping was preformed on 145 organ donors. IL-6 genotype was determines in 209 renal allograft recipients. Donor-recipient pair was considered to be mismatched for a polymorphism if the donor genotype included an allele not identified in therecipient. All donors were genotypes fro 20 polymorphisms in 11 cytokine and cytokine receptor genes: IL-1 α, IL-1 β, IL-1 receptor, IL-1 receptor antagonist, IL-4, IL-4 receptor, IL-6, IL-10 , tumor necrosis factor, lymphotoxin, and TGF-β Not all polymorphism have clear significance, but they may be useful indicators for the involventment of other alleic variants. All genotyping was conducted with PCR-SSP assays that use identical amplification and detection conditions. Phenotype, genotype, and allel frequencies were measure for all polymorphism. Phenotype frequencies were obtained by counting the number of individuals in a population positive for an allele. Revealed an association of a polymorphism in the promotor of the donor IL-6 gene with acute rejection. No other polymorphism was associated with acute rejection according to the stuy criteria. A major genetic determinant of acute rejection after kidney transplantatuon is doner-recipient mismatching at HLA-DR
Research Question	How do cytokines affect the probability rejection?

Important Figures	**Appendix 1: PCR-SSP primer sequences, specificities, and primer mix composition** PCR-SSP primer sequences, specificities, and primer mix composition
VOCAB: (w/definition)	**Polymorphism** = genetic variation that causes multiple different forms of individuals within a single species.
Cited references to follow up on	http://www.ncbi.nlm.nih.gov/pubmed/8154032 http://www.ncbi.nlm.nih.gov/pubmed/10862201 https://journals.lww.com/plasreconsurg/00005531-199701180-00012.fulltext
Follow up Questions	How can a predictive model be made to analyze cytokine genes and predict rejection?

Gene	Allele or haplotype	Sense primer	Conc (μM)	Antisense primer	Conc (μM)	Size (bp)
IL-1 α	−889t	CTTTAATAATAGTAACCAGGCAACAT	13.6	AAGTAGCCCTCTACCAAGGA	3.4	220
	−889c	CTTTAATAATAGTAACCAGGCAACAC	13.6	AAGTAGCCCTCTACCAAGGA	6.8	220
IL-1 β	−511c	CTCATCTGGCATTGATCTGG	3.4	GGTGCTGTTCTCTGCCTCG	1.36	215
	−511t	CTCATCTGGCATTGATCTGG	3.4	GGTGCTGTTCTCTGCCTCA	1.36	215
	+3962t	CATTGTCACCAGAGGTTCGT	3.4	CCTCGTTATCCCATGTGTCA	3.4	336
	+3962c	CATTGTCACCAGAGGTTCGT	3.4	CCTCGTTATCCCATGTGTCG	3.4	336
IL-1 receptor	Pst1 970c	CCAGCCTGGATTTGTCCGG	3.4	GCAGTGGTCGAGTCTGCAG	3.4	288
	Pst1 970t	CCAGCCTGGATTTGTCCGG	3.4	GCAGTGGTCGAGTCTGCAA	3.4	288
IL1 receptor antagonist	MspA1 11100t	CCTTCATCCGCTCAGACAGT	0.68	TGACGCCTTCTGAGGGTC	1.7	297
	MspA1 11100c	CCTTCATCCGCTCAGACAGC	0.68	TGACGCCTTCTGAGGGTC	1.7	297
IL-4	−590c	CTAAACTTGGGAGAACATTGTC	6.8	CACTTGGGGCCAATCAGCA	6.8	447
	−590t	CTAAACTTGGGAGAACATTGTT	6.8	CACTTGGGGCCAATCAGCA	6.8	447
IL4 receptor	1902a	CAGTCCTCTGGCCAGAGAG	3.4	CACCGCATGTACAAACTCCT	5.1	700
	1902g	CAGTCCTCTGGCCAGAGAG	3.4	CACCGCATGTACAAACTCCC	5.1	700
IL-6	Promoter NlaIII −174g	TCGTGCATGACTTCAGCTTTA	3.4	AATGTGACGTCCTTTAGCATC	3.4	156
	Promoter NlaIII −174c	TCGTGCATGACTTCAGCTTTA	3.4	AATGTGACGTCCTTTAGCATG	3.4	156
IL-10	−1082a/−819c/−592c	CTACTAAGGCTTCTTTGGGAA	3.4	CCAGAGACTGGCTTCCTACAGG	3.4	530
	−1082a/−819t/−592a	CTACTAAGGCTTCTTTGGGAA	3.4	GCAAACTGAGGCACAGAGATA	3.4	303
	−1082g/−819c/−592c	CTACTAAGGCTTCTTTGGGAG	3.4	CAAACTGAGGCACAGAGATG	3.4	303
TGF β	−800g to −509c	AGGGACTCTGCCTCCAACG	1.7	GGGCAACAGGACACCTGAG	1.7	291
	−800g to −509t	AGGGACTCTGCCTCCAACG	1.7	GGGCAACAGGACACCTGAA	1.7	291
	−800a to −509c	AGGGACTCTGCCTCCAACA	1.7	GGGCAACAGGACACCTGAG	1.7	291
	−800a to −509t	AGGGACTCTGCCTCCAACA	1.7	GGGCAACAGGACACCTGAA	1.7	291
	aa10L	CCCCAGACCTCGGGCGC	0.68	GCAGCGGTAGCAGCAGCA	0.51	416
	aa10P	CCCCAGACCTCGGGCGC	0.68	GCAGCGGTAGCAGCAGCG	0.85	416
TNF	488g/−238g/−308g	GCATCCCCGTCTTTCTCCAC	0.51	ATAGGTTTTGAGGGGCATGG	0.51	835
	488g/−238g/−308a	GCATCCCCGTCTTTCTCCAC	1.7	ATAGGTTTTGAGGGGCATGA	1.7	835
	488g/−238a/−308g	GCATCCCCGTCTTTCTCCAC	0.85	GAAGACCCCCCTCGGAATCA	0.85	763
	488a/−238g/−308g	GCATCCCCGTCTTTCTCCAT	0.51	GAAGACCCCCCTCGGAATCG	0.51	763
Lymphotoxin	720c/365g/249a	GAGCAGCAGGTTTGAGGG	1.7	GGGGTCGGGGGGTGCTG	1.7	390
	720c/365c/249a	GAGCAGCAGGTTTGAGGG	1.7	GGGGTCGGGGGGTGCTC	1.7	390
	720a/365g/249g	GAGCAGCAGGTTTGAGGT	1.7	GGGGTCGGGGGGTGCTG	1.7	390
	720a/365c/249a	GAGCAGCAGGTTTGAGGT	1.7	GGGGTCGGGGGGTGCTC	1.7	390

Article #34 Notes: **Predicting kidney transplant outcomes with partial knowledge of HLA mismatch**

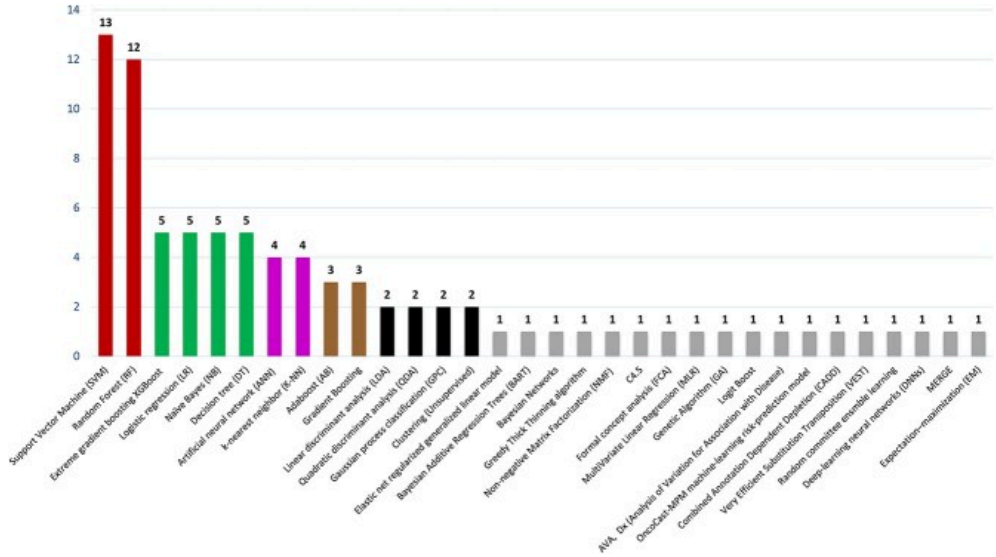
Source Title	Predicting kidney transplant outcomes with partial knowledge of HLA mismatch
Source citation (APA Format)	Manski, C. F., Tambur, A. R., & Gmeiner, M. (2019). Predicting kidney transplant outcomes with partial knowledge of HLA mismatch. Proceedings of the National Academy of Sciences, 116(41), 20339–20345. https://doi.org/10.1073/pnas.1911281116
Original URL	https://www.pnas.org/doi/10.1073/pnas.1911281116#:~:text=Research%20in%20transplant%20immunology%20has,antibodies%20that%20attack%20the%20graft.
Source type	Journal Article
Keywords	HLA, rejection, prediction, mismatches, DSA
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Problem is to predict graft survival hen an organ is transplanted into a recipient, Research in transplant immunology has shown survival varies wth degree of genetic matchbetween donor and recipient (HLA genpotypes) Doctors will benefit from teh accurate prediction of survival conditional on HLA mismatch. Used data from the scientific rehistry of transplant recipients on transplant outcomes on low-resolution HLA types with HaploStats data on the distribution of refined HLA types with specific populaion. Simple tool for prediction of kidney transplant outcomes is KDPI. Only determined by demographics, not HLA mismatch. Higher age and organ KDPI is associated with lower survival probabilities. De novo DSAs play a cumulative role rather than a time invariant role in graft loss. SRTR standard analysis files have ample data. The SRTR dataset is large that it may be possible to get precise nonparametric estimates *** For each organ and recipient, the file records 3 HLA. Humans have 2 antigens on each HLA locus, one from each parent. So, there are 27 possible values for A,B,DR mismatch. There is a possibility that the effect of

	mismatch varies with the specific locus and genotype and not just the number SAF records date of trasplant and the date of graft failure. SAF data does not have data at the C, DP, and DQ locus,
Research Question/Problem/ Need	How can the HLA mismatched between the donor and the recipient be used to predict organ rejection?
Important Figures	N/A
VOCAB: (w/definition)	**KDPI** = The Kidney Donor Profile Index (KDPI) is a numerical measure that combines ten donor factors, including clinical parameters and demographics, to summarize into a single number the quality of deceased donor kidneys relative to other recovered kidneys. **SRTR** = The Scientific Registry of Transplant Recipients (SRTR) is an organization that analyzes organ transplantation data in the United States.
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pubmed/17667803 https://www.ncbi.nlm.nih.gov/pubmed/23838649 https://www.ncbi.nlm.nih.gov/pubmed/19623019
Follow up Questions	How can more HLAs be used to have a more accurate model? How does the model take into account the polynmorphisms of HLA sequences?

Article #35 Notes: **Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine**

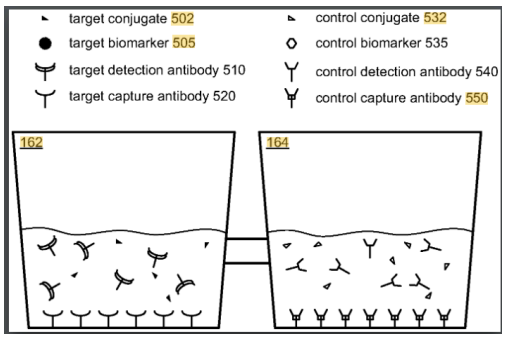
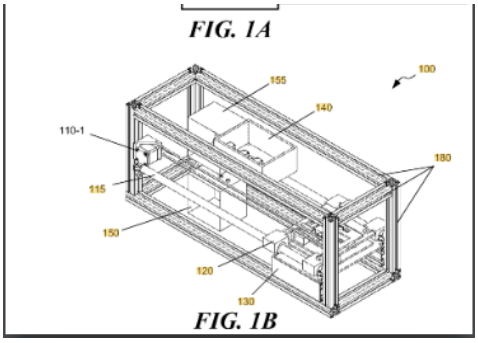
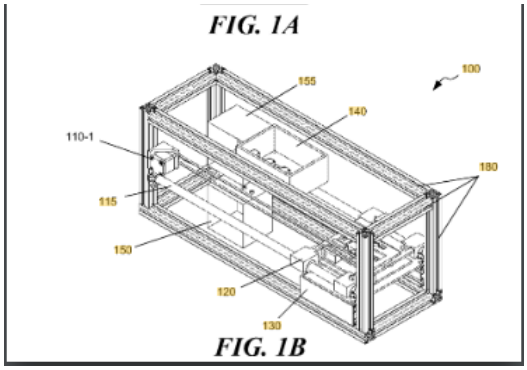
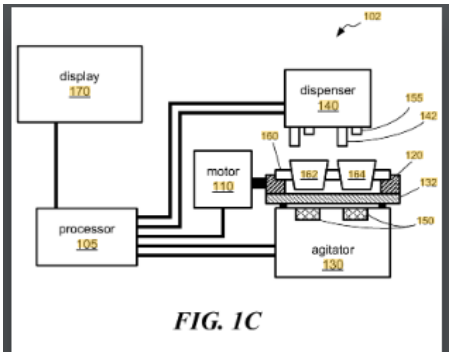
Source Title	Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine
Source citation (APA Format)	Vadapalli, S., Abdelhalim, H., Zeeshan, S., & Ahmed, Z. (2022). Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine. Briefings in Bioinformatics, 23(5), bbac191. https://doi.org/10.1093/bib/bbac191
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10233311/
Source type	Journal Article
Keywords	artificial intelligence, machine learning, gene expression, gene variant, predictive analysis
#Tags	#Information
Summary of key points + notes (include methodology)	Genetic studies can reveal biomarkers that diagnose, determine risk, and predict treatment outcomes for many diseases. Most genetic research uses biological insights and risks by comparing healthy and diseased populations DNA and RNA sequencing are 2 most used methods. Combining multiple gene variants and gene expression differences into multiple biomarkers can increase predictive power. AI has the potential to address the issue of implementing precision medicine for heterogeneous ancestry groups. Example approaches: Random Forest (RF) Support Vector Machine (SVM) Gradient Boosting Extreme Gradient Boosting (XGBoost) Logistic Regression (LR) Artificial Neural Network (ANN) K-Nearest Neighbor (K-NN) Decision Tree (DT)

	Gaussian Process Classification (GPC) Multivariate Linear Regression (MLR) Deep Learning Neural Networks (DNNs) Genetic Algorithm (GA) During the process of choosing and implementing AI/ML algorithms, it is important to measure and avoid algorithmic bias. Disease prediction: SVM Identification of molecular gene expression markers for precise treatment: MERGE, FCA Identification of potential peripheral blood transcriptome biomarkers and development of a prediction model using peripheral blood transcriptomes: SVM, RF, KNN Identification of blood-based gene variant profiles for precise treatment: Clustering, RF Disease model to predicting disease risk by genotypes, utilizing gene expression and rare variant data: SVM, LR Single omics approach is where they study transcriptomic data and its potential in identifying disease genes. Methods include XGBoost, RF, and SVM. MERGE identified gene markers fro precise and targeted treatment. Transcriptomic data from 30 patients were compiled for this study. Drug concentraion and sensitivites fro 53 drugs were collected. Used MERGE on the gene expression data from GEO. MERGE uses the 'MERGE' score which indicates gene drug association.Higher MERGE score means the more number of associations with drugs. Unsupervised FCA multi-omics study tio study drug response Zhao et al. identified and used potential peripheral blood transcriptome biomarkers to develop an MDD prediction model The authors utilized nine different datasets. Clinical data such as age, gender and ethnicity were also recorded. They implemented SVM, RF, K-NN and NB on the gene expression data from GEO, where the RF was used to select the features. The meta-analysis of the genes showed 137 DEGs of which 66 are upregulated and 71 of them are downregulated. These six genes were linked with the immune process, hormonal metabolism and inflammatory response and played an important role in the diagnosis of MDD by acting as a potential biomarker. Authors observed and reported that genes had a significant expression difference with a single-gene diagnostic method, which proves that single-gene model is not efficient.

	Authors then used the transcriptome data from the discovery sets to perform the meta-analysis and it was seen that 114 DEGs were identified. Feature selection of these data resulted in feature set containing 108 genes that were implemented upon with four models. All models produced an average AUC value, whereas the SVM had the highest average AUC with values of average AUC of 0.82, an accuracy of 0.75, a sensitivity of 0.78, and a specificity of 0.74 in the train dataset. SVM had a better predictive performance when compared to the single-gene diagnostic model. This study is limited by lack of knowledge regarding the amount of data needed to demonstrate the model's predictive ability. Additionally, further independent validation is required to determine the accuracy of the model. The authors propose that this model could be used to discover transcriptional markers related to other mental illnesses.
Research Question	How is machine learning used in precision medicine and gene expression analysis?
Important Figures	 Total number of machine learning algorithms applied for predictive analysis.
VOCAB: (w/definition)	**single-gene diagnostic method** = look for changes in only one gene. **Feature selection** = process of isolating the most consistent, non-redundant, and relevant features to use in model construction
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8249859/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7655162/
Follow up Questions	What are criteria that can be used to choose the best model?

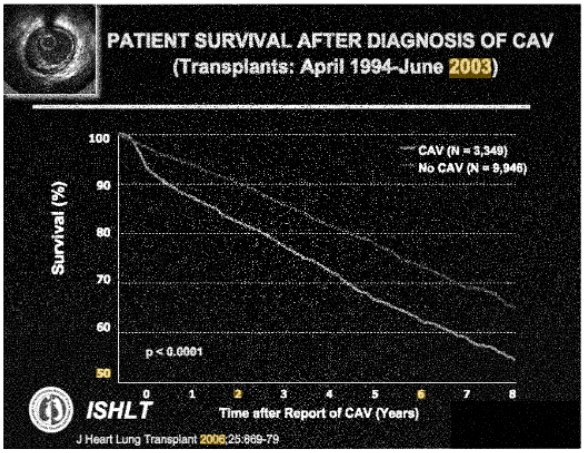
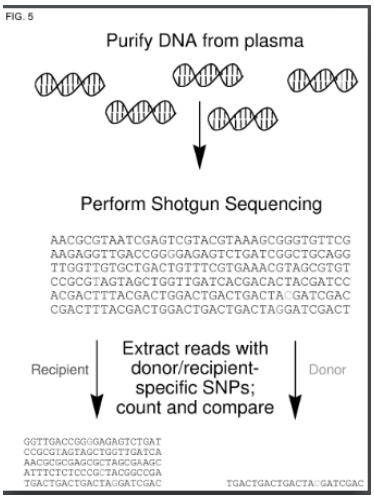
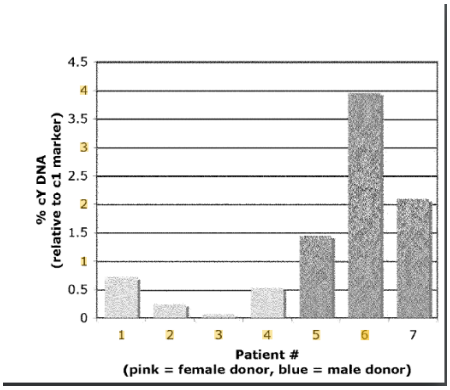
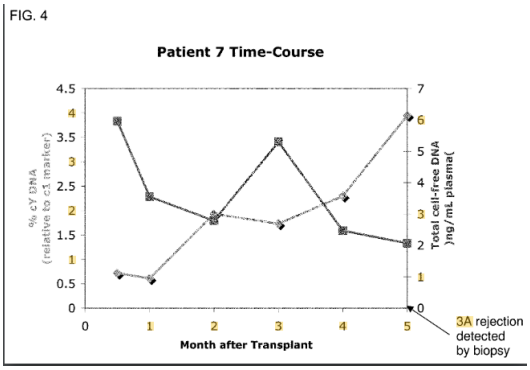
Article #36 Notes: **Portable instrument for in vitro detection and quantification of biomarkers**

Source Title	Portable instrument for in vitro detection and quantification of biomarkers
Source citation (APA Format)	Maxim, D. S. (2021). *Portable instrument for in vitro detection and quantification of biomarkers* (Patent US10908156B2). https://patents.google.com/patent/US10908156B2/en
Original URL	https://patents.google.com/patent/US10908156B2
Source type	Patent
Keywords	Biomarker, rejection, renal transplant
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Some conventional assay tests for medical patients can be inconvenient to the patient and can involve an undesirably long amount of time before results are available. Low-cost, portable instrumentation and associated methods of operation that may be used for rapid quantitative detection of biomarkers. In some embodiments, the instrument automates an assay that targets detection of a particular biomarker. The automation can reduce human error in the assay and provide more reliable detection results. Vascular endothelial growth factor-C (VEGF-C) was seen as an indicator of chronic transplant rejection (CTR). The device has a sample holder, sample wells and a motor. The incubation phase starts when the sample that has a targeted biomarker is put ino the sample wells. Then, a solution that has a dection binding agent for he target biomarker is also put into one of the sample wells. The instrument also has an optical detector that can detect radiation that calculated the detected radiation form the target biomarker. Whole process takes about 30 minutes. The target biomarker can indicate presence of cancer, transplant rejection or renal damage.

Research Question/Problem/ Need	How can a biomarker detector device be used to find biomarkers for rejection?
Important Figures	   
VOCAB: (w/definition)	**Assays** = the testing of a metal or ore to determine its ingredients and quality. **Antibody Conjugate** = also known as antibody labeling, is a technique for modification of antibodies which involves with the attachment of a specific tag to an antibody.
Cited references to follow up on	https://patents.google.com/patent/US5316726A/en https://patents.google.com/patent/US20020172621A1/en
Follow up Questions	How can this device be used to detect rejection without biopsies? Will this device work for other organs?

Article #37 Notes: **Non-invasive diagnosis of graft rejection in organ transplant patients**

Source Title	Non-invasive diagnosis of graft rejection in organ transplant patients
Source citation (APA Format)	Quake, S. R., Snyder, T. M., & Valantine, H. (2022). *Non-invasive diagnosis of graft rejection in organ transplant patients* (Patent US11384389B2). https://patents.google.com/patent/US11384389B2/en
Original URL	https://patents.google.com/patent/US11384389B2/en
Source type	Patent
Keywords	Rejection, diagnosis, transplant
#Tags	#PotentialResearch
Summary of key points + notes (include methodology)	Steps to diagnose includes taking a transplant sample, determining presence of one or more nucleic acids from the donor transplant (the donor nucleic acids were identified based in a predetermined marker profile) and diagnosing the transolatn status based on the presence/absence of the nucleic acids. The marker profile is a polymorphic marker profile. The polymorphc marker profile has one or more SNP, RFLPs, STRs, or VNTRs. The marker profile is determined by genotyping the transplant donor and the recipients and establishidn a profile of markers where the markers are different between the donor and recipient. The genotyping is performed by a method such as sequencing, nucleic acid array and PCR. The transplant graft can be any solid organ or skin. The nucleic acid is selected from double stranded DNA, single stranded DNA, RNA or cDNA.
Research Question/Problem/ Need	How can organ rejection be diagnosed non-invasively using cell DNA?

Important Figures	FIG. 1  FIG. 5   FIG. 4 
VOCAB: (w/definition)	**SNP** = single nucleotide polymorphism: A variation in a single DNA building block, or nucleotide, among individuals. SNPs are the most common type of genetic variation among people. **RFLP** = Restriction Fragment Length Polymorphism is a technique that studies the differences in DNA sequences between individuals. **STR** = Short tandem repeats are DNA sequences that are 2–6 base pairs long and are repeated multiple times. These sequences are scattered throughout the genome and account for about 3% of the human genome. **VNTR** = variable number tandem repeat. It's a location in a genome where a short nucleotide sequence is repeated adjacent to each other.
Cited references to follow up on	https://patents.google.com/patent/US11111544B2/en https://patents.google.com/patent/US11111543B2/en
Follow up Questions	Which nucleotide type would be the best to use to diagnose rejection? How can a similar method be used to find DSAs?

Article # Notes: Title

Article notes should be on separate sheets

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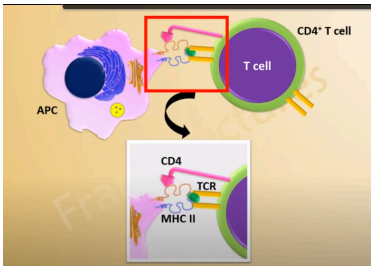
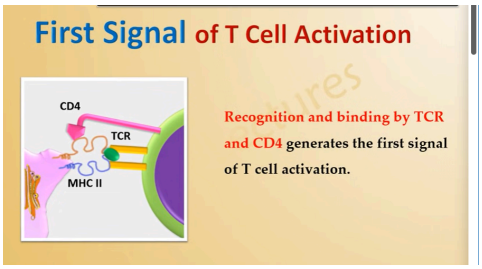
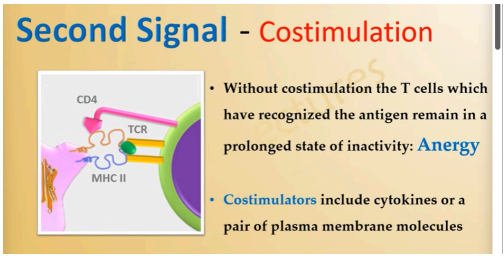
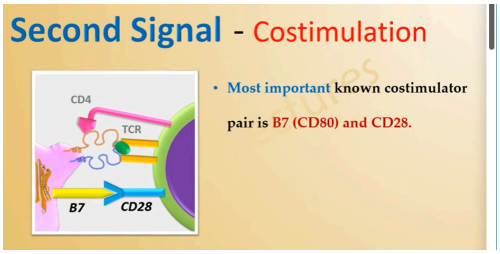
Source Title	
Source citation (APA Format)	
Original URL	
Source type	
Keywords	
#Tags	
Summary of key points + notes (include methodology)	
Research Question/Problem/ Need	
Important Figures	
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

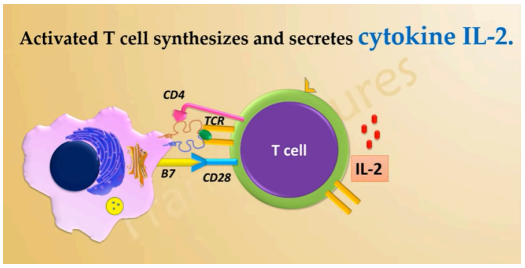
Videos

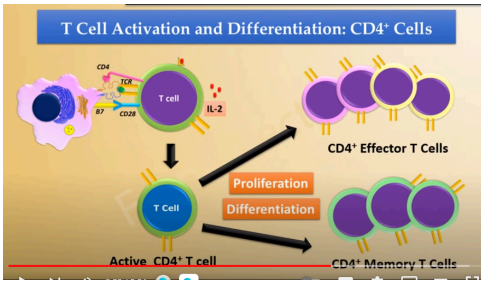
Video #1 Notes: **T cell Activation and differentiation (FL-Immuno/31)**

Source Title	T cell Activation and differentiation (FL-Immuno/31)
Source citation (APA Format)	Frank Lectures. (2017, May 20). T cell Activation and differentiation (FL-Immuno/31). https://www.youtube.com/watch?v=JPh9P1aEfMI
Original URL	https://www.youtube.com/watch?v=JPh9P1aEfMI&t=170s
Source type	Video
Summary of key points + notes (include methodology)	Mature T Cells are of 2 types: CD4+ T cells and CD8+ T cells. These are naive T cells because they have not encountered an antigen yet. CD4+: Once the peptide antigen is present on the surface of an APC, it is called a MHC II-peptide complex. APC goes to lymph nodes. They meet the CD4+ T cells, as it recognized the MHC II antigens. Need 2 signals. Most important costimulator pair is B7 (CD80) and CD28. CD28 acts as a receptor on T cell and B7 is on the APC. After binding, IL-2 is synthesisxes. They bind to its specific receptor on the T cells. IL-2 allows for the proliferation and differentiation of T cells into effector cells and memory cells. CD4+ effector cells develop into diverse subsets of Th. CD4+ memory T cells can quickly generate more T effector in case this antigen is present in future. CD8+: very similar, few differences. CD8+ recognze antigens present by MHC I molecules. CD8+ T effector cells are the cytotoxic T cells that attack the body cells that are affected by the pathogen/antigen.
Important Figures	 

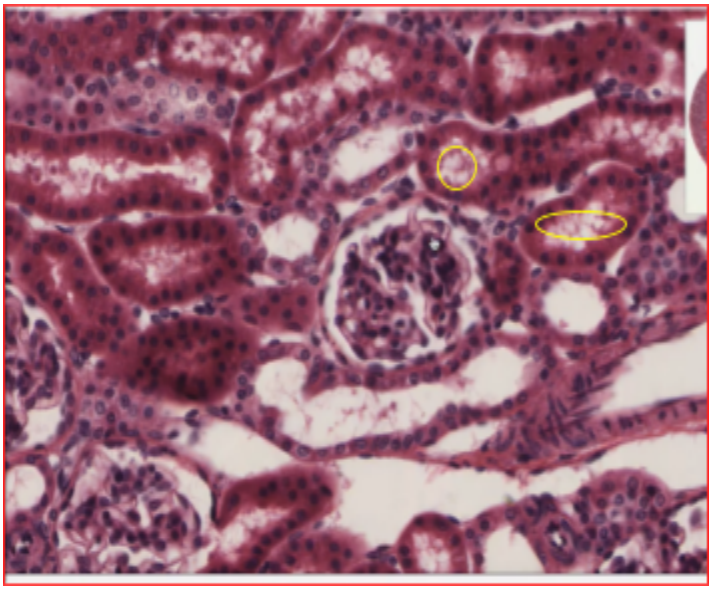

Second Signal - Costimulation
CD4
TCR
MHC II
• Without costimulation the T cells which have recognized the antigen remain in a prolonged state of inactivity: Anergy
• Costimulators include cytokines or a pair of plasma membrane molecules


Second Signal - Costimulation
CD4
TCR
B7
CD28
• Most important known costimulator pair is B7 (CD80) and CD28.

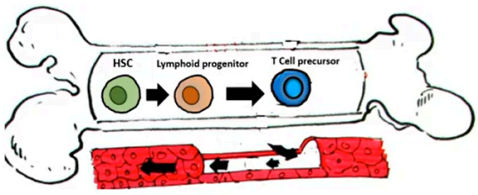
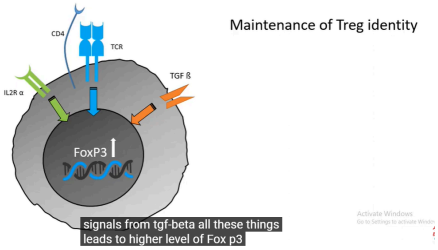
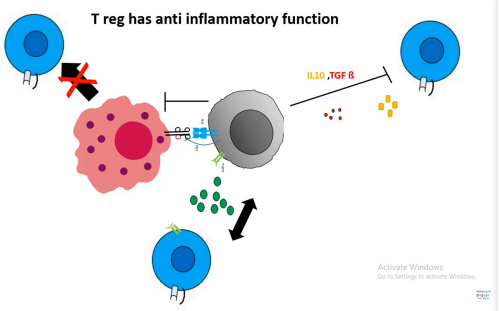
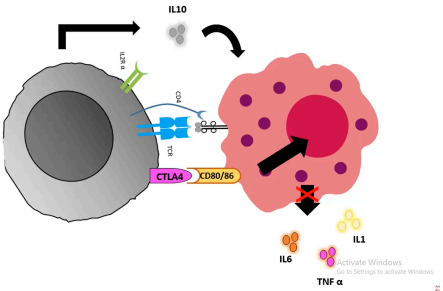

Activated T cell synthesizes and secretes cytokine IL-2.
CD4
TCR
B7
CD28
T cell
IL-2


T Cell Activation and Differentiation: CD4+ Cells
T cell
IL-2
CD4+ Effector T Cells
Proliferation
Differentiation
Active CD4+ T cell
CD4+ Memory T Cells

Video #2 Notes: **Functions & Histology of The Proximal Convoluted Tubule [PCT]**

Source Title	Functions & Histology of The Proximal Convoluted Tubule [PCT]
Source citation (APA Format)	Catalyst University. (2019, November 9). Functions & Histology of The Proximal Convoluted Tubule [PCT]. https://www.youtube.com/watch?v=6_cfjvZhKoQ
Original URL	https://www.youtube.com/watch?v=6_cfjvZhKoQ
Source type	Video
Summary of key points + notes (include methodology)	Urinary system takes waste out of blood or removes fuild if fluid volume is too high Filtration of blood occurs in Glomerulus (filters everything). However, there are some things that we dont want to get rid of. Proximal Convoluted Tublule (PCT) is the nephron site where most reabsorption of the important things that were filtered by the glomerus. Process is called tubular reabsortion. Called Proximals (adjacent to the glomerus) Have peritubular capillaries next to the PCT. Use active transport to move the substances back to the capillaries, and then they are reabsorbed by the blood. If there is excess waste in the capilaries, theu are secreted from the peritiular capillaries into the intersituial area and then into the PCT again. Then, it goes on to the loop of Henle. Called Tubular secretion.
Important Figures	

Video #3 Notes: **Regulatory T cells**

Source Title	Regulatory T cells
Source citation (APA Format)	Animated biology With arpan. (2018, May 30). Regulatory T cells. https://www.youtube.com/watch?v=navE0zgIShU
Original URL	https://www.youtube.com/watch?v=navE0zgIShU
Source type	Video
Summary of key points + notes (include methodology)	Tregs are one of the cousins of CD4+ Th cells. Tregs maintain the homeostasis of immune response, and maintain the balance between inflammatory and anti-inflammatory response Tregs develop in the bone marrow where hemapoietic pluripotent stem cells give rise to lympoid progenitor which create T cell precursors. T cell precursors go to the thymus. In thymus, immature t cells learn to recognize peptides located on MHC II molecules Tregs express IL2 chain (CD25) and express high levels of transcription factor FoxP3
Important Figures	   

Video # Notes: Title

Article notes should be on separate sheets

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	
Source citation (APA Format)	
Original URL	
Source type	Video
Summary of key points + notes (include methodology)	
Important Figures	

https://www.youtube.com/watch?v=DkM3PL-2Rmg
https://www.youtube.com/watch?v=kR4xTGIBDIM

STEM Update Meeting Prep:

STEM MEETING 1:

1: Provide an update on your STEM project:
A: What is going well?

My 3 ideas:

1. Predicting and preventing organ rejection
2. Making gene therapy commercialized
3. Personalized medicine and cancer treatment

The in-class work and brainstorming have been very helpful.
I was able to come up with a lot of ideas and topics that I would never have thought of by myself

The in-class presentations, such as the elevator pitches, are also helpful
Allow me to take the information I know and present it in a way that is understandable and relevant to an audience that doesn't have as much knowledge on the topic.

B: What is challenging?
Genes expressed during teranplanratioj
Correlate with rejectin?

Time-management - finding the time in the day/week to work on STEM

C: What are your goals for the next two weeks?

Read more journal articles related to my project ideas
Read more articles about my other two topics

Read articles from professors who live in my area
Email the professors n

D: Provide evidence for the rubric components (see Bi-Weekly Meeting Assessment Form). How might you document your work?

project notes

Qs: how to make the projects specific?
Did past students look at knowledge gaps and focused on that?
Would it be risky to base whole idea on one article?

General Article 1:

2 pts. Reading & Highlighting w/ APA Citation
(or watching videos)
2 pts. Bulleted notes (notes must be in own words)
1 pt. Questions
1 pt. Vocab. defined
2 pt. Summary (3 sentences explaining goal & findings)
2 pts. Ability to explain/"teach" the material

1st article is general article from live science called 1st of its kind heart transplant could prevent organ rejection by Rachel Retner

Article talks about
A child was born with a heart defect.
He also had a thymus condition which meant he also needed a thymus transplant as well as the heart transplant.

The thymus plays an important role in immune system function.
produces cells that mature into T-cells.
body uses T-cells to help destroy or fight of viruses and forign invaders.
T cells are known to be cause of organ rejection

The child is the first person to receive a heart transplant along with implantation of thymus tissue from the same donor.

Tests show that the donated thymus tissue is working to produce T-cells in the child's body.
No sign of rejection so far

It's possible that this combination transplant could allow the body to accept the new organ as part of itself instead of treating it as a foreign object. (decrease need for drugs)

The child is taking immunosuppressive drugs, but doctors will attempt to take him off the drugs to see how his body reacts.

Transplant patients take Immunosupressive drugs to prevent organ rejection, but it can weaken them and make them prone to other diseases.

Much more research is needed to see if this combination transplant allows the boy to live without immunosuppressive drugs and whether it could work for other transplant recipients such as adults. (child=weak immune system)

General Article 2:

2nd article is a general article from live science called Gene therapy drops restore teen's vision after genetic disease left his eyes clouded with scars by nicoletta lanese

A boy has dystrophic epidermolysis bullosa, a genetic condition that prevents people's cells from making a specific type of collagen.

Collagen provides structural support to connective tissues, helping to maintain their integrity and strength.
Also major component of the cornea

Without collagen, Their skin is weak and can get blisters easily. disease can also lead to blistering, erosion and scarring of the eye and blindness.

A boy was born with this condition that caused scar tissue to build up in his eyes, rendering him legally blind

The first-ever treatment for dystrophic epidermolysis was a gene therapy gell
Vyjuvek is a gel that users rub on their blistered skin, and it works by delivering working copies of the broken collagen gene into their cells.

The treatment helps prevent new blisters from forming as the skin heals. It doesn't permanently change cells' DNA, however, so it must be regularly reapplied.

Scientists made a version of Vyjuvek that worked as eyedrops
(by removing the gel-like ingredient from its formula.)

In August 2022, the teen underwent surgery to remove scar tissue from his right eye and then began using the eyedrops only in the right eye.

Following surgery, the scarring in the boy's eyes didn't return, and he saw steady improvements, until his vision was a near-perfect 20/25.

Antonio uses the eyedrops once a month and also continues to apply the skin gel version of Vyjuvek. He now feels safe walking again, which he'd struggled to do since his vision deteriorated.

Qs: how long does the gel work for? - not permanent, but can it be?

STEM MEETING 2:

1: Provide an update on your STEM project:
A: What is going well?

Been focusing on my topic
Reading informative articles to really understand my topic
Learned about other transplant methods ABOi and H&E stains, which are commonly used in Histology (study of tissues)

The in-class work has been helpful to help me do more work
Emailed 5-6 professors - yet to hear back from them
    Best one: Martins lab focuses on improving liver grafts with machine perfusion
    Also experimenting with gene silencing
WPI labs?

Focus on chronic rejection - how it works?

Why chronic rejection occurs:
Some think its related to vasculopathy - vascular disease
Ischemis - organ transportation

Personalized medicine as antigen-specific immunosupressors

B: What is challenging?

Fiding gene therapy and organ rejection journal articles - 90$

Genes expressed during teranplanratioj
Correlate with rejectin?

Time-management - finding the time in the day/week to work on STEM WIKI articles?

C: What are your goals for the next two weeks?

Read more journal articles related to my project ideas
Isolate my idea - make it permanent

Read articles from professors who live in my area

D: Provide evidence for the rubric components (see Bi-Weekly Meeting Assessment Form). How might you document your work?

project notes

Qs: how to make the projects specific?
Did past students look at knowledge gaps and focused on that?
Would it be risky to base whole idea on one article?

Ethical to use tissue cells?

CTLA4-Ig and anti-CD40 ligand prevent renal allograft rejection in primates

Allan D. Kirk,

Intro:
Rejection hap[ens because olf T-cells

Ppl need immunosupressive drugs to combat rejection

T cell recognizes the antigenic proteins in the groove of major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs).

This so-called signal 1 delivers signals

The second signal, or “costimulatory signal,” is provided by interactions between specific receptors on the T cells, CD28, CTLA4 (CD152), CD40 ligand, and their respective ligands on APCs, B7-1 (CD80), B7-2 (CD86), and CD40.

T-cells need costimulatory signals
T cell antigen receptor signals and costimulatory signals

*****The first signal is antigen specific and causes the T cell to enter the cell cycle. The second signal is the "costimulatory signal" and is required for cytokine production and proliferation***

Drugs prevent the release of cytokines which are proteins that direct the t cell response system
Impair the t-cell antigen receptor signal,

Prevents the t cell from have an immune response to donor organ
Drusg work on ALL t-cells

Drug effect is not permanent
Ppl need to take it life long

PREVIOUS

Selective inhibition of T cell signals using protein CTLA4-Ig has proved to help the long-term allograft survival in rodents

protein used by the immune system to identify and neutralize foreign objects such as pathogenic bacteria and viruses. The antibody recognizes a unique molecule of the pathogen, called an antigen.

T cell molecule CTLA4 downrelgulated costimulation and TC Receptor activation

Rodent studies hwo that t cell activation can be blocked by the CTLA4 protein
5C8 blocks CD80 antibody that can suppress the up regulation

Upregulation is the process of increasing a response to a stimulus, such as the activation of the nervous system or an increase in the number of receptors. Downregulation is the process of returning to a state of relaxation and calm.**

NOW:
These proteins were tested on rhesus white blood cells

METHODS:
Donor-recipeint combis were chosen based on no genetic match

Mixed lymphocyte reaction were performed on all animals to see how the t cells behave with the t cells of other animals

Each animal was tested with other donors to see the best pairs for transplantation
Cells were incubated and the positive control was polyclonal stimulation

CTLA4-Ig or 5C8 was added to MLR on day 1 at different concentrations from 100 micrograms/mL to 0.1 micrograms/ml, but the 5C8 concentration was at 50 micrograms

researchers tested how cells reacted in the lab before and after transplantation. They used various techniques to measure cell responses, analyzed blood cells, and used flow cytometry (lab test) for detailed examination.

They performed kidney transplants
Performed surgery on them

Graft was attached to blood vessels and was connected to tbe bladder

Regular checks were conducted
Medicine (CTLA4 or 5C* was given)
Blood tests were performed

Both proteins were effective in preventing t cell responses
CT thin peformed beter alone, but the combo also hel;ped long-term survival

RESULTS:

Both agents stopped lymc=pocyte reactions, but it was 100x more effective than a drug

Ct was more effective of suppressing ti cells

12 kidney transplangs
4 = non immunological medicine
Rejected 5-8 days
Acute rejectuin

1 = 5 days of CT 20 day survival (10mg)

1 = 20 mg on the day of trqansplant
12 day couse odf CT 10mg every other day
30 day survival

2 = 5c8 alone
20mg every other day for 14 days
95-100 day survival
Acute rejection episode
Retreated with 7 5C8 doses and both returned back to normal
More than 150 days

2 animals = 20mg of CT and 5C8
1 = 32 days, 1 = 100 days
EROOR: animal died because of weight loss

No animal had side effects

CONCLUSION
Focused on modifying costiukation rather than t cell supressiomn
Anti rejection can exist after rejection

Monkeys are similar to humans (MHC Genes)
Need more research for humans

Need to see for more ling term

STEM MEETING 3:

1: Provide an update on your STEM project:
A: What is going well?

Been focusing on my topic
Reading informative articles to really understand my topic
Learned about T cell activation and the role of thymus in making T cells
Gathered statistics about organ rejection - can use in MSEF proposal
HIV+ to HIV- transplants and the potential of AI in organ tranplants

The in-class work has been helpful to help me do more work
Emailed professors
- Heard back from Dr.Zhang from the Medical FUSION
  - meeting on Friday
  - Made OCT which assess kidneys and their viability for organ transplant
- Heard back from Biomere
  - Meeting on Thursday
- Not heard from Martins lab
  - focuses on improving liver grafts with machine perfusion
  - Emailed other assistant professors
  - Will call sometime this week to talk after few business days

Focus on chronic rejection - how it works

Why chronic rejection occurs:
Some think its related to vasculopathy - vascular disease
Ischemis - organ transportation

Personalized medicine as antigen-specific immunosupressors
Want to focus on long-term effects of these methods

Precision method approach for T cell inhibitors - only change organ, not recipient

Main thing to find out: model, can't use mice or mammals, will talk to Biomere and Zhang about possible metjodologies

B: What is challenging?

Fiding gene therapy and organ rejection journal articles - 90$

Genes expressed during transplantation

Time-management - finding the time in the day/week to work on STEM

C: What are your goals for the next two weeks?

Finalize my idea - decide if I want to focus on CTLA4 only or recipient antigens
Get an idea of a lab
Research how personalized medicine is done, and how the genetic sequence is analyzed

D: Provide evidence for the rubric components (see Bi-Weekly Meeting Assessment Form). How might you document your work?
Would it be risky to base whole idea on one protein that already has little research?
Ethical to use tissue cells?

STEM Meeting 3

Critical Role of Proinflammatory Cytokine IL-6 in Allograft Rejection and Tolerance

By: X. Zhao et al., published in American Journal of Transplantation 2012

Research Question: What is the role of IL-6 in organ rejection and tolerance?

Intro:
T cells are key initiators of graft rejection. Many proinflammatory cytokines such as IL-17 play a key role in T cell immunity by connecting Innate immunity to adaptive immunity.

Innate = general response to any antigen. It is non-specific and fights any foreign invader.
Adaptive = specialized immune system that responds to specific antigens. Created in response to exposure to a foreign substance.

IL-6 is a pleiotropic cytokine produced by APCs. Shown to prolong T-cell survival via maintenance of BcI-2 expression and the downregulation of Fas ligands to promote activation of antigen-specific T cells

Cytokine = signaling proteins that help regulate the immune system
pleiotropic cytokine = cytokine that affects the activity of multiple cell types.
BcI-2 = protein that regulates cell death
Fas ligand = protein that induced cell death in a cell that has its Fas receptor target

T helper (Th) cells separate into different phenotypes that are defined according to the condition and cytokines requires fro their differentiation into T-cell subsets and their function.

IL-6 is critical fro Th17 development. Th17 is associated with inflammation. In the past, scientists showed that hearts with IL-6 deficiency survived longer. Using a mismatched MHC mouse model of heart transplant to prove that targeting Il-6 or its signals will help for tolerance.

Materials and Model:
Had 2 tests
Transplanted hearts into the control and the "knockout"
Monitored and regular check ups

Made sure the IL-6 deficient mice did not have naturally fewer T cells and more regulatory cells than WT mice by checking for the percentages of t cells in different body parts

Single dose of CTLA4-Ig was given o the day of the transplant
Neutralizing IL-6 was given at a daily dose and then every other day

Hearts were recovered either at rejection or at specific times
Used H&E stains to look at the cellular infiltration
ANd Mixed lymphocyte reaction to see allorecognition

Results:
IL-6 enhances the life of T cell activation and promotes the differentiation of CD4 T cells into Th17 cells and imparirs T cell regulatory differentiation.

Absence of IL-6 stops the growth of lymphocytes and encourages CD4 T cell to transform into a regulatory form.

To determine the function of IL6 they stimulated IL6 deficient lymphocytes with other mice cells and analyzed T cell differentiation and proliferation. The proliferation from IL6 deficient was significantly less than those from WT animals (in vitro)

IL6 alone does not prolong allograft survival, but changes the cytokine profile in recipients. Both WT and IL6 deficient mice rejected grafts within 1 week of transplant. However, IL6 deficient blood had less CD8 t cells, but had no significant different of T regulator cells. (in vivo)

T cell differentiation varies depending on whether environment is in vivo or in vitro

IL6 dificiency is connected with costimulator blockade to facilitate tolerance in recipients treated wit CTLA4-Ig

CTLA4 is a protein that interferes with costimulatory signals to regulate the immune system. To test the hypothesis, they treated WT with IL-6 monoclonal antibody with CTLA4. In control, alowed graft to live for 22 days. With IL6, lives for 100+ days. Significant infiltration present in WT in 3 weeks.

In our previous studies using T-bet/-recipients, we found that, in the absence of Th1 responses, CD4 Th17 cells mediate aggressive proinflammatory responses that lead to accelerated rejection and severe vasculopathy in a model of chronic cardiac allograft rejection

that IL-17-producing CD8 T cells are resistant toward the induction of tolerance by combined blockade of the CD28-B7 and CD40-CD154 pathways in a fully MHC-mismatched model using the same T-bet /- recipients

Discussion:
IL-6 production is closely associated with an inflammatory response. Due to its strong anti-apoptotic properties, IL-6 can increase the effector/memory T-cell population (11).
IL-6 has also been shown to skew Th cell differentiation toward a Th17 phenotype and to prevent the development of Tres (12). Our in vitro data presented here indicate that IL-6 deficiency promotes Tre generation and limits T-cell proliferation. However, in vivo data from transplanted animals showed only a significant reduction in effector/memory population in IL-6/- recipients, but no significant increase of Tregs. This might be due to differences in antigen presentation, or to the niches in which the antigen was encountered.

Costimulatory blockade has been shown to be effective in tolerance induction in many different animal models. A mutant version of CTLA4Ig, belatacept (two amino acid mutations in the

extracellular domain), has recently been investigated in human clinical trials to prevent transplant rejection and to treat rheumatoid arthritis

STEM MEETING 4:

1: Provide an update on your STEM project:
A: What is going well?

Been focusing on my topic
Reading more articles
Narrowed idea to costimulatory blockade using precision medicine
CTLA4-Ig is common costimulatory blockade, but has varying results in diff studies
    Human trials = blood clots
Works best when paired with another protein/molecule that aids in preventing immune response

Personalized medicine as antigen-specific immunosupressors
Want to focus on long-term effects of these methods

Precision method approach for T cell inhibitors - only change organ, not recipient

Precision medicine approach: analyze rejection first, and see what connection is most prominent in the rejection process
Use protein to downregulate or suppress the immune system, but to only that one antigen
Keeps immune system competent
If time: use antibody titer or subject complex to other infections and moniter how it reacts

Lab:
Emailed MANY ppl, not many responses
Not many ppl researching rejection
Met with Dr.Harlan
    Focuses on transplanting pancreatic islets to treat T1D
    Kinda lab

No lab:
Computationally
Making proteins computationally or analyze gene editing/gene expression?

Anyone at WPI?
Focus on chronic rejection - unclear how it happens

Backup:
Under Dr.Zhang - Medical Fusion lab
Made an OCT device to monitor kidney pre-transplant
Met few weeks ago
Scans, acoustic waves
PCT AI algorithm
    If backup, maybe make more general
    Analyzie multiple things
Test viability of the organ
Learning MATLAB and AI

Ask about model organisms and methodology

B: What is challenging?

FINDING LABS + METHODOLOGY

C: What are your goals for the next two weeks?

Continue learning MATLAB
Look at more methodologies - computer programs I could use

D: Provide evidence for the rubric components (see Bi-Weekly Meeting Assessment Form). How might you document your work?

In project notes and logbook

STEM Meeting 4

Asialo GM1+ CD8+ T cells play a critical role in costimulation blockade–resistant allograft rejection

Blocking CD40 and CD28 costimulatory pathways can be effective treatment for rejection, but does not lead to permanent survival

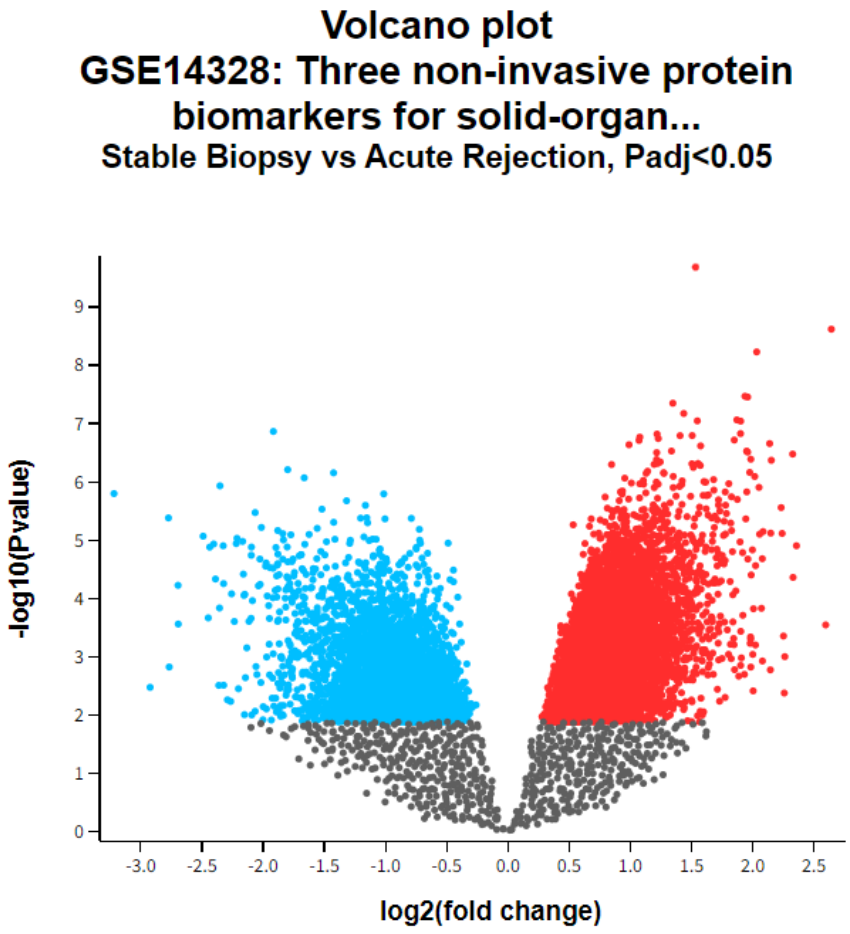
Activated T cells are important in immune response to transplant tissues\
Many studies shoe that CD4+ T cells may be important for survival
Depletion of CD4 t cell sis enough to prompt long term acceptance of heart transplants in mice

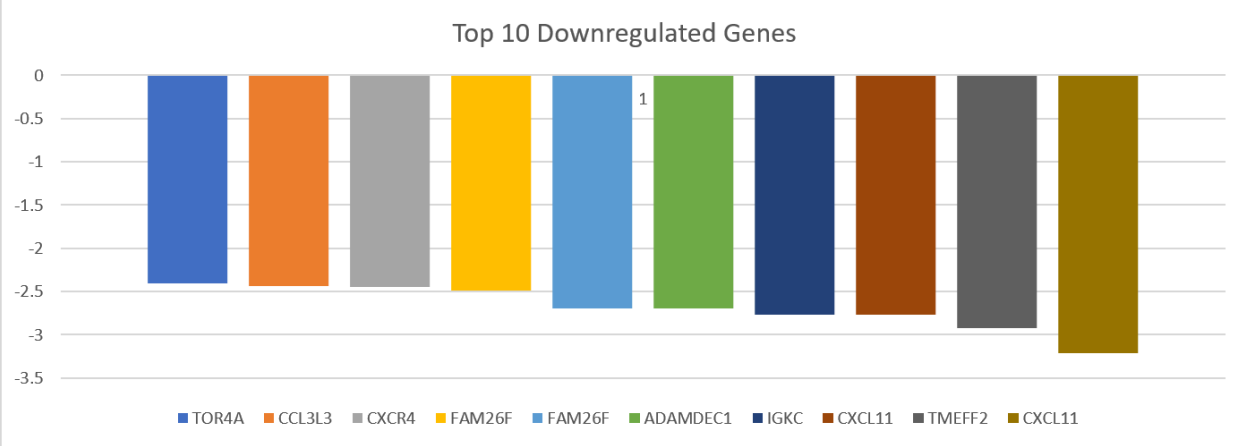
However, in other mcie, CD8 t cells ar enough to reject allografts

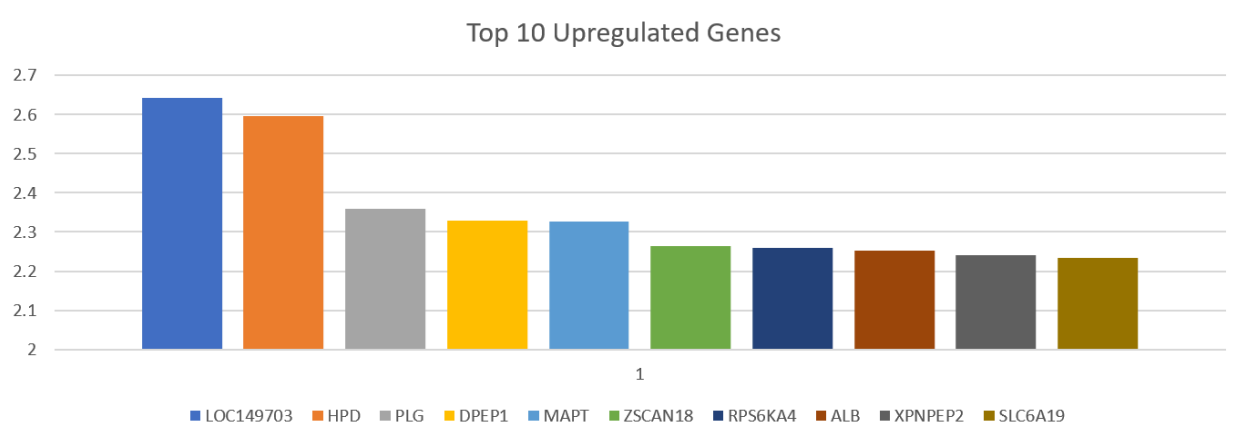
T cell proliferation and cytokinme secretion need costrimulatory signal
CD40 and CD28 are recpetirs for the cotrimulatoy pathways and are crucial fro the development of t cell repnses
Blocking this path can inhibit alloimmune response

Addition of anti-asialo GM1to costmulator blockade delays rejection
B6 mice

STEM MEETING 6:







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209978_s_at	0.002172	1.24e-05	5.007937	3.203502	2.358	PLG	plasminogen
205983_at	0.0030169	4.33e-05	4.608509	2.050545	2.329944	DPEP1	dipeptidase 1 (renal)
225379_at	0.0006775	3.35e-07	6.146199	6.544924	2.3265	MAPT	microtubule associated protein tau
217593_at	0.0107447	9.88e-04	3.564574	-0.818731	2.263167	ZSCAN18	zinc finger and SCAN domain containing 18
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1: Provide an update on your STEM project:
A: What is going well?

Changed project to computationally

Found lab → Dr.Brownwell at WPI
    Works with mAbs

Met with him, said I could use lab and materials
Went over procedure and asked how to do it

Original idea:
    Costimulatory blockade → Harlan said blood clots
    Create rejection, see which cytokines were present, give mAbs against those cytokine

To see cytokine, have to do MULTIPLE tests (30+ cytokines)
Also, have to do lab training, got lab pretty late
    For time frame, wouldnt be accurate cause Im tryna focus on chronic rejectionon
        Long term, dont have that much time

Backup..
Under Dr.XIhan at medical fusion lab
Use MATLAB to create ML to measure PCT structures in kidney to asses viabilty
Reseaching..
    Made a simple algorithm → kinda boring
        Still difficult, but just drawing on X-rays
        Learn ML, wanted to learn more
Also… when looking for kidney X-ray scans, not many cause using OCT scans
    Only DR.Xihan had the images
    Looked for online ones
    2 papers were doing exactly what im tryna do, unoriginal, cant do it

But…
Met with Dr.Stern and Demtri
    Demitri is ISEF 2015 about rejection, biomarker
    Stern works with MHC and T cells, more focused on Tregs

Stern explained mHC-peptide presentation
    Gave databases around that

Gave me idea to focus on peptide presentation

Still focusing on HLAs → can tell us the molecule the peptide would bind to
Can better predict the peptide

Can give more precise treatments
Directly focusing on what actually activates T cells
Personalized medicine

C: What are your goals for the next two weeks?

Continue learning ML
Look at more methodologies - computer programs I could use to test clinical applications

D: Provide evidence for the rubric components (see Bi-Weekly Meeting Assessment Form). How might you document your work?

In project notes and logbook

Questions/Comments

How much justification for focus and methods?
TCMR vs AMR

In build somelting, did competitor analysis, should I bring up in prezi or be more broad?

Issues with Dec fair:
When explain bg, talked about the problem

Tryna talk about activation, made sense in my head, tried to focus more on data/metods and what going to go
Thought that was more important
some judge asked to reexplain

How in-depth should I go
Looked up judge, is actual scientists

Need to keep PCT stuff in entries?

STEM Meeting 6

Analyzing HLA Sequences to Find Personalized Targets for Selective T-Cell Inhibition to Prevent Organ Rejection

Chronic organ rejection is primarily caused by T-cell-mediated rejection (TCMR).

MHC peptide presentation plays a vital role in T-cell activation and can lead to developing strategies to prevent transplant rejection.

The major histocompatibility complex (MHC) is a group of genes that code for MHC molecules found on the surface of cells.

These proteins play a vital role in the immune system's ability to distinguish between "self" and "non-self."

There are two main types of MHC molecules: MHC class I and MHC class II molecules. As MHC class I molecules are present on all nucleated body cells and directly interact with T-cells, this project will focus on MHC class I peptide presentation.

In the case of organ transplantation, the organ cells release proteins called antigens which are broken down into smaller peptides inside the organ cells.

These peptides are transported into the Endoplasmic reticulum and bind to a groove in the MHC class I molecule, forming a peptide-MHC complex.

This complex then travels to the cell surface and is displayed for T-cells to recognize. If a T-cell recognizes a peptide from the transplanted organ on an MHC molecule, it activates, which starts the immune response against the transplanted organ.

STEM MEETING 7:

1: Provide an update on your STEM project:
A: What is going well?

Researched MHC stuff
More experiment with ML

Antigen confusion -> virus
Intracellular proteins

Questions/Comments:
Reference previous entries?

Delete unnecessary entries?
- Too cluttuered with stuff not relevant to project
- Keep adding blurbs?

Judges see code?
- 4 references

Judge rubric: Blank Sample ScoringSheet-Feb2023
- Engineering project
- Prototypes?
- Rubric has research paper, feb 15
- Due feb 21 in canvas

What judged use to compare?
- Presentation?
- Results?

Diff between sensitivity vs specificity

Talk abt AMR, even if judge not know it

STEM Meeting 7

STEM MEETING 8: