

JANUARY 2023

MONASH HEALTHCARE INNOVATION SUMMER SCHOLARSHIPS

Project Impetus



Monash Partners
Academic Health Science Centre



**MONASH
YOUNG
MEDTECH
INNOVATORS**

Current Team: Dan Lin

Clinical Champion: Dr. Brad Gardiner

Affiliations MYMI, MIME, Monash Health

Executive Summary

The organ transplantation process has advanced significantly during recent times. However, immunosuppressive dosing - a crucial component of the post-transplant process - remains a crude and extremely approximate procedure. Patients are required to take immunosuppressive medication after undergoing a transplant operation to prevent the immune system from treating the organ as a foreign tissue and ultimately attacking itself. There is a significant lack of personalisation when administering immunosuppressive medications, and this increases the likelihood of infection and organ rejection - both contribute to long-term morbidity and mortality. This problem arises since measuring immune level function is difficult and not routinely available, resulting in approximations and rough estimates when prescribing medications.

This project aims to improve precision when administering immunosuppressive medication dosages. The goal is to individualise immunosuppression management in transplant recipients so that patients have a minimal chance of being both under-immunosuppressed, leading to organ rejection, and over-immunosuppressed, leading to infections and drug toxicity. Ideally, the tool being designed should be able to reliably identify overly immunosuppressed patients at higher risk of infection. This would improve the likelihood of reducing serious opportunistic infections, hospitalisations, and overall survival.

Acceptance Criteria

- The solution should be able to identify patients at high risk for developing infections
- The solution should allow for more accurate and precise measurement of immunosuppression
- Implementation of the solution should result in lower rates of infections and rejection than current methods

Gaps analysis

Immunosuppression remains the primary method of treatment in transplant patients. Given the level of personalisation within the healthcare industry, the ability to measure individuals' immunosuppression state is become even more important.

The current method in place to monitor immunological function relies on clinical judgement and measuring immunosuppressive drug levels. However, these measurements do not provide an accurate representation of the immunosuppression status of transplant recipients [1] and only act as a surrogate marker of actual immunosuppression level in patients.

To directly assess graft (transplant tissue) status, biopsies may also be performed. However, this procedure is invasive and is not suitable for continuous monitoring [2].

Another method to monitor patients is through biochemical tests, such as complete blood count (CBC), urinalysis, and hormone levels. However, these tests also have low sensitivity and specificity as graft rejection markers, and do not correlate with the severity of histopathological findings [2].

The inaccuracies of these methods can increase the likelihood of a patient becoming either over- or under-immunosuppressed. The most common threat to transplant patients within 30-180 days post-transplant is opportunistic infections [3].

Thus, there remains a need to find a method that can reliably measure immunosuppression levels, at least more accurately than current approaches.

Systems Map

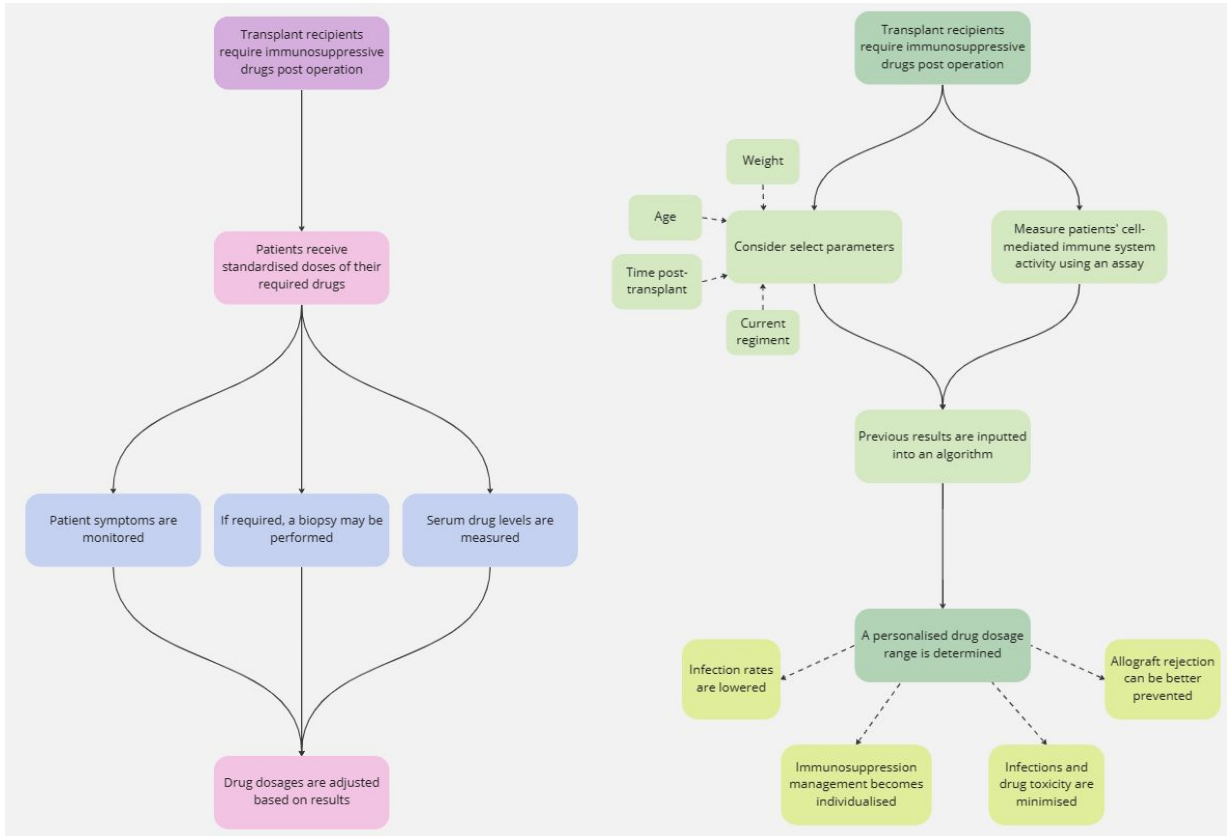


Figure 1: Two separate flowcharts comparing the current process of measuring immunosuppressive drug dosages and the ideal process after introducing the proposed solution. Left - a flowchart demonstrating the timeline of patients after their transplant operation to adjustment of their immunosuppressive drug dosages. Right - a flowchart demonstrating the process of producing a personalised drug dosage range through the proposed solution.

Link for miro board:

https://miro.com/app/board/uXjVP0CmjbU=?share_link_id=923989432289

Stakeholder Map

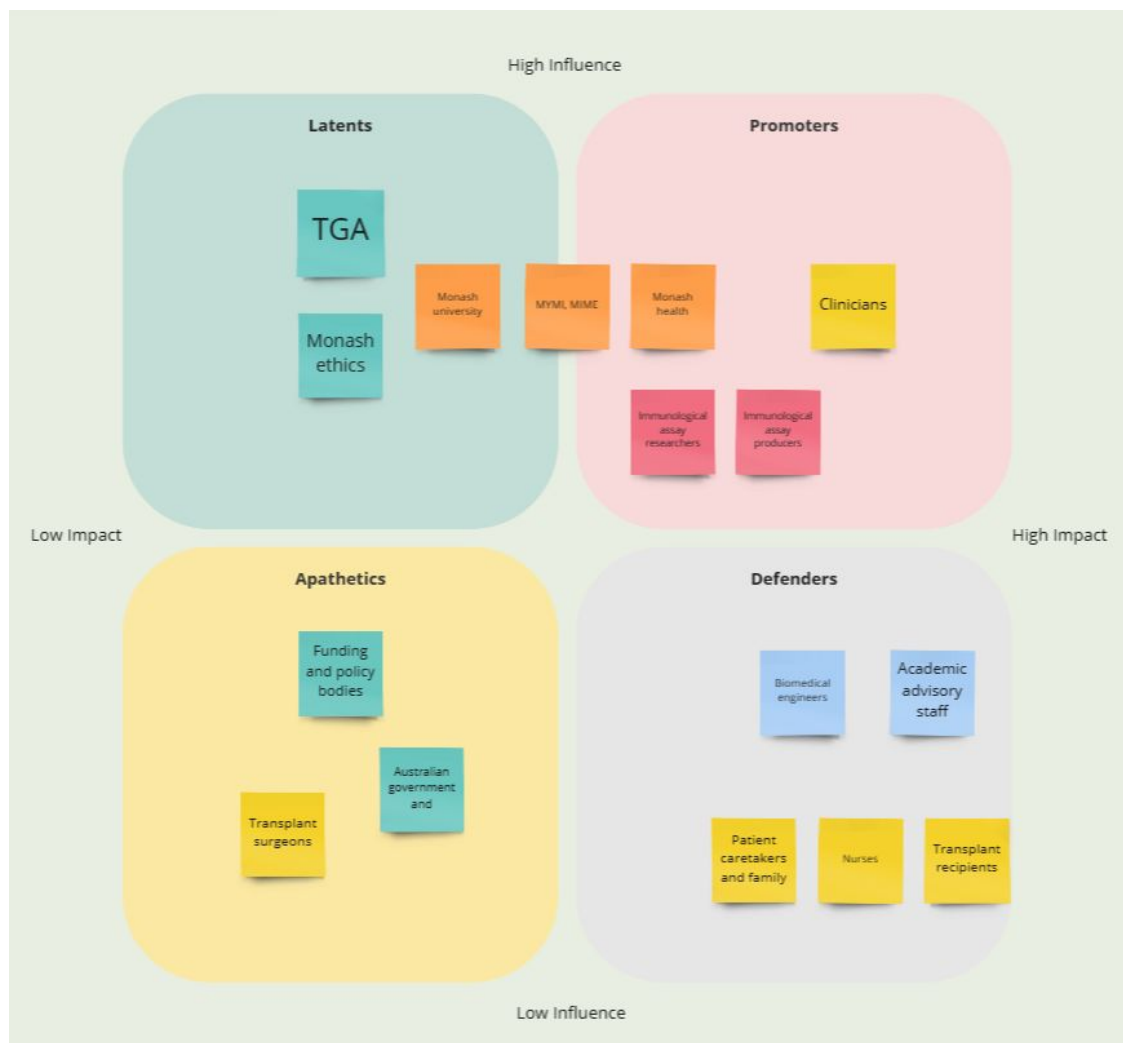


Figure 2. Stakeholder Map. Depicts the range of stakeholders and the position they hold in terms of the direct influence they have on the project, and the impact the project will have on them. There are five major stakeholder categories: stakeholders who are involved in the research of the problem and development of the solution (blue), beneficiaries of the solution (aqua), HISS program contacts (orange), individuals directly involved in the hospital setting (yellow), and immunological assay producers/researchers (red).

Link for miro board:

https://miro.com/app/board/uXjVP0CmgD4=?share_link_id=370496205744

Outcomes of Qualitative and Quantitative Research

The process of organ transplantation has improved over time, but the way immunosuppressive medication is dosed remains imprecise. After a transplant, patients must take immunosuppressive drugs to prevent the immune system from rejecting the new organ. However, there is little personalization in this process, which increases the risk of infection and organ rejection and contributes to long-term morbidity and mortality [4]. This is because it is difficult to measure immune function, so dosing is often based on rough estimates.

The current method for monitoring immunological function is based on clinical judgement and measuring serum drug levels, but these measurements do not provide an accurate representation of immunosuppression status and only serve as a surrogate marker [2]. Biopsies, which can directly assess graft status, are invasive and not suitable for continuous monitoring [2]. Other methods, such as biochemical tests, have low sensitivity and specificity as markers for graft rejection and do not correlate with the severity of histopathological findings [2]. The inaccuracies of these methods can increase the risk of a patient becoming over- or under-immunosuppressed. The greatest threat to transplant patients in the first 30-180 days post-transplant is opportunistic infections [5], so there is a need for a more reliable method of measuring immunosuppression levels.

A blood immune function assay was recently developed - the Quantiferon®-Monitor (QFM, Qiagen, Germantown, MD, USA) which measures plasma interferon- γ levels. There are increasing numbers of clinical studies emerging on this biomarker [6]. In a cohort of liver transplant recipients, the QFM levels of patients were measured early after their operations. Lower QFM values were associated with infection, while high values were associated with rejection. Although, cutoffs were not easily identified due to the high numbers of false positives and false negatives [7]. A larger prospective cohort study consisted of 137 transplant recipients (50 lung, 44 kidney, 42 liver, 1 small bowel) that underwent testing at 1, 3- and 6-months post-transplant. This study identified that there was an association between low QFM values and higher prednisolone doses and thymoglobulin use. Patients who developed infections had lower QFM values prior to their infection, but there was no association with organ rejection [8].

Solution Concept Discussion

- top 2

The solution landscape currently depends on monitoring patients' clinical presentations and immunosuppressive drug levels by performing either biopsies or standard biochemical tests. However, biopsies are an invasive procedure and are not suitable for continuous monitoring. Biochemical tests have low sensitivity and specificity as markers for graft rejection and show poor correlation with the severity of histopathological findings.

#1 - Modify dosage of an immunosuppressive drug based on measuring serum levels of an assay

Recently however, many biomarkers have been identified that may help individualise the immunosuppression approach. One of them is the Quantiferon-Monitor, a whole blood immune function assay aiming to measure the net state of immunosuppression for individual patients. Recent data suggest that this assay can predict patients at higher risk of serious opportunistic infections.

#2 - Develop an implant that can monitor serum levels of drugs in patients

Implantable drug delivery devices have several benefits over traditional systemic delivery methods. They allow for targeted drug release, resulting in higher concentrations in specific areas and maintaining drug levels in the therapeutic range [9,10]. Additionally, the extended use of these devices eliminates issues of poor patient compliance and reduces discomfort associated with other forms of treatment, making it a more effective option for managing chronic diseases [10].

Final Concept

The final concept will be solution #1 - Modifying the dosage of an immunosuppressive drug based on measuring serum levels of an assay. Recent research is demonstrating that there is a link between higher immunosuppression dosages, low QFM values, and infections. My clinician is currently analysing the data obtained from a prospective cohort study of 80 lung transplant recipients from August 2015 to July 2017, testing QFM before and at 2, 6, 12, 24 and 52 weeks post-transplant [11]. From the data, he has identified that patients with QFM values <10 and <60 IU/mL were more likely to develop serious opportunistic infections between 3-6 months and 6-12 months post-transplant respectively. However, this is only the beginning of the research, and more analysis is required to understand the mechanisms of QFM in the long term.

The concept is more reasonable than the implant solution (#2), since the goal is to create a web-based immunosuppression dose modification calculator. As this is a piece of software, regulatory considerations will be far less than working on an implant. The proposed solution will ideally be integrated into real-time clinical decision-making in hospitals. As it will possibly be an online tool, there will be no need to install separate software on company devices. It will be designed for clinicians, with a simple user interface, allowing for a very small learning curve to operate the software. As such, the clinical adoption process should not be too complex.

A technical risk is that the correlation between drug dosage and immunological assays may be affected by novel or undiscovered factors, possibly affecting predicted drug dosages. To address this, irregular patient symptoms after administration can be observed. A dedicated team can be on board to determine whether the abnormalities are random or related with certain factors.

Currently, data analysis is being undertaken to determine whether there is a correlation between certain immunosuppressive drugs levels and QFM levels. If a relationship can be determined, an algorithm can be created to relate QFM to the certain drug, and it will hopefully output a more personalised dosage range for patients

Business Model

In hospitals, the shift to adopting online systems and databases leaves potential for our software to be easily integrated into existing workflows. The software will be designed to be operated by clinicians and doctors, but no specialist training will be required. As this software solution does not meet the criteria of defining a medical device, there are very few regulatory barriers to overcome.

The business model of Project Impetus will likely follow a B2B structure where hospitals and institutions that utilise the software will be billed annually. Each dosage calculation will incur a small fee, ultimately determining the annual cost, which is the total number of operations performed in the hospital. The majority of revenue will come from subscriptions and additional reimbursement will hopefully be sourced from sponsors.

To advertise the product, team members will approach clinical directors, IT staff, and front-line clinicians in hospitals. There will be demonstrations on using the software, and this could be in the form of live in-person demonstrations, video snippets, or brochures and posters. The aim of these demonstrations will be to emphasise the ease of use, its efficiency, and how it will improve patient care and reduce risks. Depending on the target audience, supporting data from clinical trials could also be displayed to demonstrate the reliability of the product.

The most likely exit strategy of this project will be through acquisition, where the stake is sold to a partner or investor. The most suitable teams would be those that include data modellers with experience in the medical and biomedical space. One of the risks associated with this project is that the correlation between drug dosage and immunological assays may be affected by novel or undiscovered factors. A disease modeller would be highly beneficial in monitoring the current health landscape and addressing problems concerned with the relationship between drug dosage and assays.

Market Analysis

A large market exists for both transplants and immunosuppressive medications. However, the market for precision dosing of the medications seems to be relatively untapped.

TAM:

To produce an estimate of the total addressable market (TAM), the number of individuals requiring immunosuppressive treatment will be multiplied by the frequency of dosages they require and the cost per dosage. The following assumptions will be made in the calculation:

- Population: the estimated number of organ transplants worldwide is 144,000 (in 2020) [12]
- Dosage frequency: immunosuppressive drug dosages are modified with a different frequency for each patient depending on their needs and response to treatment, and other factors. We will assume that the average patient requires their dose to be modified twice each week following their transplant, for a period of a year
 - Two modifications per week for one year = $2 \times 52 = 104$ modifications per patient per year
 - Cost: the fee-per-use business model can adopt a cost of \$30 per dosage modification

The TAM will therefore be: Population x dosage frequency x cost = $144,000 \times 104 \times 30 = \$450M$

SAM:

The serviceable available market will be calculated the same way, except the population now only encompasses transplant recipients in Australia. There are 1750 Australians on the waiting list for an organ transplant [13]. The remaining assumptions are unchanged.

The SAM will therefore be:
Population x dosage frequency x cost = $1750 \times 104 \times 30 = \$5.5M$

SOM:

Assuming the realistic reach of the software will initially be in Victoria, the SAM is divided by the number of states and territories in Australia (8).
 $\$5.5M / 8 = \$690K$

This is a conservative estimate, since Victoria manages a larger proportion of transplant procedures compared to other states and territories.

Proposed KPIs

Given that the proposed solution will most likely be closely intertwined with healthcare services, and will be influenced by forces within Monash, we have considered how the solution fits within Monash and MIME’s KPIs.

The following are the domains within Monash Health:

Domain	Indicators
Safety and Effectiveness	Mortality, unplanned hospital readmission, hospital acquired infections, safety of maternity services and cancer
Equity and Access	Emergency Department (ED) wait length, specialist care wait length
Efficiency/Value for money	Cost and length of stay
Patient Centered/Experience	Maternity and in-patient personal needs

The solution will hopefully lower mortality, unplanned hospital readmission rates, emergency department wait length, and specialist care wait length.

One of the aims is to reduce the cost of patient stays. The end goal is for less complications to occur post-transplant resulting from inaccurate dosage, and thus less medical interventions will be required. It will also hopefully reduce the time of patient stay, also indirectly reducing the cost.

More personalised dosages can also result in lower unplanned hospital readmission rates, alongside emergency department wait length and specialist care wait length since treatments are not generalised, and are more tailored to the individual patients.

It will also improve the quality of specialist care since patients that are at high risk of infection will hopefully be identified earlier, allowing for more preparation of specialist care.

Ultimately, the cumulation of these factors will result in lower morbidity and mortality.

Ask and Next Steps

Our Team:



Dr. Brad Gardiner
Infectious Diseases
Physician at Alfred
Health
Clinical Champion



Dr. Michael Lydeamore
Infectious Disease
Modeller
Lecturer in Econometrics
& Business Statistics



Dan Lin
Biomedical Science
and Electrical
Engineering Student

Our Clinical Champion, Dr. Brad Gardiner, is an Infectious Diseases Physician and clinical researcher at Alfred Health & Monash University in Melbourne, Australia. He is passionate about the prevention, early diagnosis and optimal treatment of infections in immunocompromised patients, particularly solid organ transplant recipients.

Dr. Michael Lydeamore's current research focuses on quantifying the spread and designing control strategies for the spread of antimicrobial resistance in Victorian hospitals, at Monash University and The Alfred Central Clinical School.

I am working with Dr. Brad Gardiner and Dr. Michael Lydeamore to determine the relationship between QFM and many factors contributing to the immune system.

Moving forward, we would require team members with experience in data modelling, preferably experience in either Matlab or R. This would help with performing statistical analyses on data from clinical trials and working on algorithms to correlate QFM with other factors. We would also require team members with experience in website development to assist in creating an online platform that hosts the software.

Timeline

Feb 2023

Work towards a basic prototype to calculate the dosage of one drug

Jun 2023

Update software for more drug correlations

Oct 2023

Test combinations with patient-specific variables

Feb 2024

2nd version of prototype completed

References

1. Levitsky J. Next level of immunosuppression: drug/immune monitoring. *Liver Transpl.* 2011;17 Suppl 3:S60-5.
2. Lim TY, Heneghan M. Biomarkers of immunosuppression. *Clin Liver Dis (Hoboken).* 2016;8(2):34-8.
3. Singh N, Limaye AP. Infections in Solid-Organ Transplant Recipients. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 2015:3440-52.
4. Srinivas TR, Meier-Kriesche H-U, Kaplan B. Pharmacokinetic Principles of Immunosuppressive Drugs. *American Journal of Transplantation.* 2005;5(2):207-17.
5. Kamaleswaran R, Sataphaty SK, Mas VR, Eason JD, Maluf DG. Artificial Intelligence May Predict Early Sepsis After Liver Transplantation. *Front Physiol.* 2021;12:692667.
6. Sood S, Yu L, Visvanathan K, Angus PW, Gow PJ, Testro AG. Immune function biomarker QuantiFERON-monitor is associated with infection risk in cirrhotic patients. *World J Hepatol.* 2016;8(35):1569-75.
7. Sood S, Cundall D, Yu L, Miyamasu M, Boyle JS, Ong SY, et al. A novel biomarker of immune function and initial experience in a transplant population. *Transplantation.* 2014;97(8):e50-1.
8. Mian M, Natori Y, Ferreira V, Selzner N, Husain S, Singer L, et al. Evaluation of a Novel Global Immunity Assay to Predict Infection in Organ Transplant Recipients. *Clin Infect Dis.* 2018;66(9):1392-7.
9. Pons-Faudoa FP, Ballerini A, Sakamoto J, Grattoni A. Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases. *Biomed Microdevices.* 2019;21(2):47.
10. Fayzullin A, Bakulina A, Mikaelyan K, Shekhter A, Guller A. Implantable Drug Delivery Systems and Foreign Body Reaction: Traversing the Current Clinical Landscape. *Bioengineering.* 2021;8(12):205.
11. Gardiner BJ, Lee SJ, Cristiano Y, Levvey BJ, Sullivan LC, Snell GI, et al. Evaluation of Quantiferon®-Monitor as a biomarker of immunosuppression and predictor of infection in lung transplant recipients. *Transpl Infect Dis.* 2021;23(3):e13550.
12. GODT Home Page [Internet]. GODT. [cited 2023 Jan 8]. Available from: <https://www.transplant-observatory.org/>
13. Statistics in Australia [Internet]. DonateLife. [cited 2023 Jan 8]. Available from: <https://www.donatelife.gov.au/all-about-donation/statistics-in-australia>