

meducator

MCMMASTER UNDERGRADUATE HEALTH SCIENCES JOURNAL

TARGETED THERAPY OF
GLIOBLASTOMA
MULTIFORME

IN COLLABORATION WITH SABCR

CROSSING SPECIES LINES:
THE CLINICAL FUTURE OF
XENOTRANSPLANTATION

SMILING PILLARS:
COMMUNITY SOLUTIONS TO
COMBAT HEATWAVE CRISES



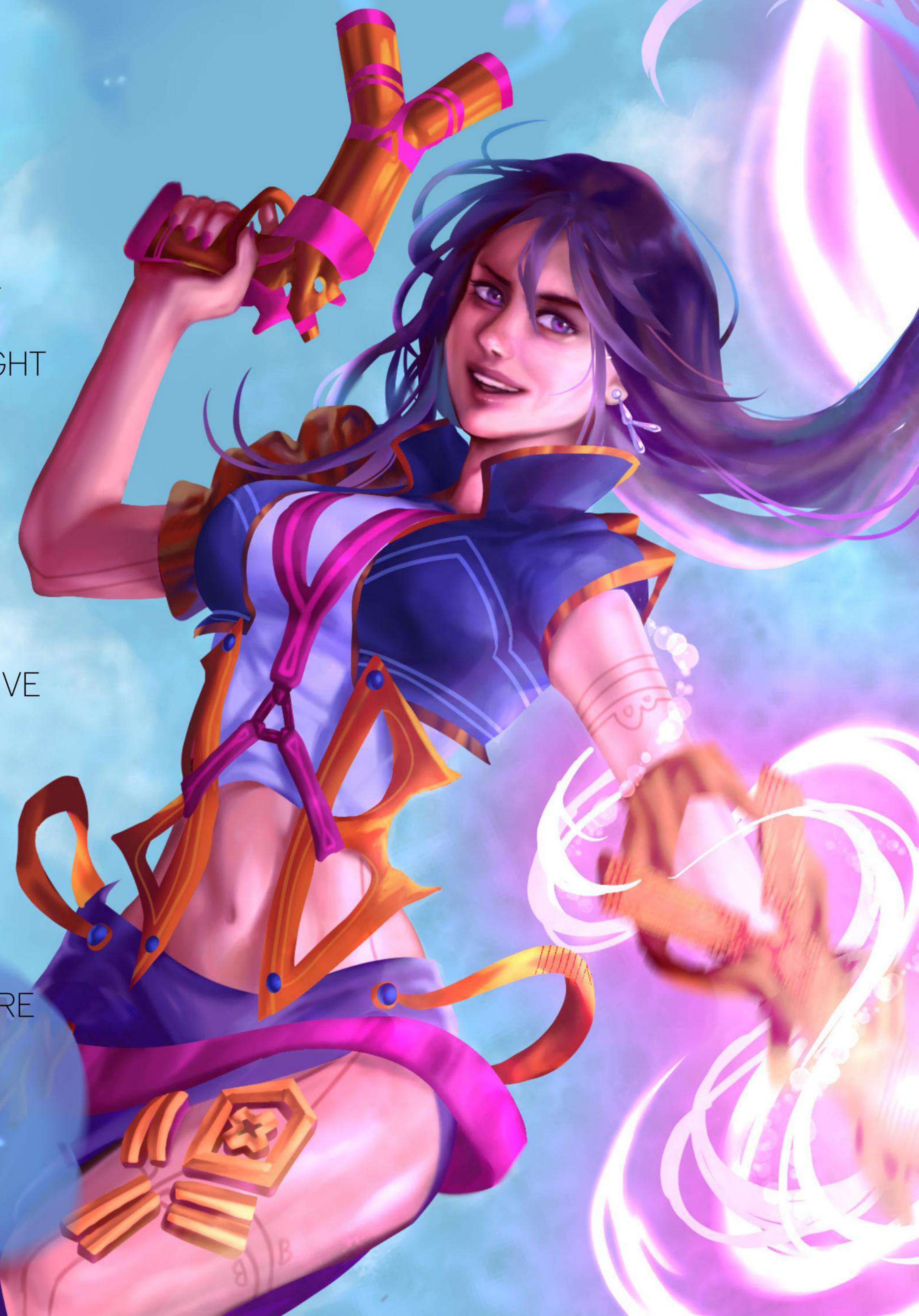
TABLE OF CONTENTS

COVER ARTIST:
MICHELLE WAN

Bachelor of Health Sciences (Honours),
Class of 2027, McMaster University

- 01** INTRODUCTION
- 02** MEDPULSE
- 04** RESEARCH INSIGHT
- 08** INTERVIEW SPOTLIGHT
- 10** CRITICAL REVIEW
- 14** PATHOPROFILE
- 16** CRITICAL REVIEW
- 20** SABCR & IWCH
- 22** GLOBAL PERSPECTIVE
- 26** EDITOR PROJECT
- 30** CRITICAL REVIEW
- 34** MEDUGALLERY
- 36** MEDUAMPLIFY
- 40** VIDEO TEAM FEATURE
- 41** CONTRIBUTORS

TABLE OF CONTENTS:
PARISA MISHAL HOSSAIN
Bachelor of Health Sciences (Honours),
Class of 2025, McMaster University





DEAR READER,

As we unveil Issue 47 of The Meducator, we delve into a world characterized by the delicate balance between progress and consequence. Inspired by Arcane, the theme of Issue 47 explores the interplay between science and power, forces shaping both medicine and society. Scientific discovery drives medical advancement, but accessibility, ethics, and unintended ramifications remind us that innovation must be wielded with responsibility. Arcane's distinctive artistic style—bold contrasts, vivid lighting, and painterly textures—embodies the tensions existing within the art and science of medicine. In this issue, we dissect these tensions, understanding how scientific advancements push the limits of possibility, and the simultaneous ethical and societal obligations that accompany progress.

Issue 47 opens with editors Atta Yazdy, Liza Nooristani, and Nirujah Sutharasan crossing international borders to discuss novel healthcare findings, while Sarah Mohamed Musatheek and colleagues explore adherence to CSEP 24-hour movement guidelines. David Gou, Jia Lu, and Matthew Olejarz delve into the pertinent measles virus, while Alyssa Bocskay and Owen Liu critically review xenotransplantation, and Cynthia Duan and Arvan Kayal discuss Zosurabalin in antimicrobial resistance.

We are honoured to interview Dr. Marnix E. Heersink, philanthropist and ophthalmologist who has generously supported various institutions at McMaster and whose impact has graciously touched The Meducator community. Highlighting a critical biotechnology in the treatment of zoonotic bacterial disease, Cynthia Duan, Evan Sun, and Will Zhang review bacteriophage therapy. In a perspective shift to the future, Derek Kuo and Jennifer Chen review spatial transcriptomics as a novel approach to cancer research.

Stepping outside the walls of McMaster University, authors Sahith Rajkumar, Muhsin Nishath, and Kapilan Sivapatham describe their contributions to heatwave health crises in Hamilton. In a call to action to the McMaster community, editors Aarani Selvaganesh, Kathy He, and Zahrah Talawala review implications of food insecurity on social determinants of health. In a stunning work illustrated by Sophie Li, we glimpse into the societal perceptions of prosthetics.

We are deeply thankful for our 100 talented and dedicated staff, executive members, faculty reviewers, and the McMaster community for their unwavering commitment throughout the publication cycle. We are honoured to welcome Dominic Gangemi and Veronica Grignano as the Editors-in-Chief for the upcoming academic year. With their boundless potential and passion, we are confident that they will take The Meducator to new heights. We would like to extend a special thanks to our sponsors, Dr. Marnix E. Heersink, KRP LLP Chartered Professional Accountants, the McMaster Students Union, and the Honours Health Sciences Program without whom Issue 47 would not be possible. Finally, we extend a heartfelt appreciation to you, our reader, for the ongoing support of our publication.

FLORENCE DENG
Bachelor of Health Sciences
(Honours) Class of 2026

AUDREY DONG
Bachelor of Health Sciences
(Honours) Class of 2026

MEDPULSE

3D-printed brain-like environment promotes neuron growth THE NETHERLANDS | October 2024

Researchers from Delft University of Technology in the Netherlands attempted to recreate the properties of the brain microenvironment that support neuronal elongation.¹ Nanopillar arrays, which are pillar-shaped nanostructures, were designed using a 3D laser-assisted printing technique.¹ By tuning their dimensions and resistance to deformation, a property sensed by cells, the researchers simulated a soft brain-like environment.¹ This helped demonstrate the way neurons mature, which has the potential to provide insight into neurodegenerative disorders, such as Alzheimer's disease.¹

AUTHORS:
LIZA NOORISTANI¹, NIRUJAH SUTHARSAN², & ATTA YAZDY³

¹Bachelor of Science in Nursing, Class of 2025, McMaster University

²Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

³Bachelor of Science Kinesiology (Honours), Class of 2026, McMaster University

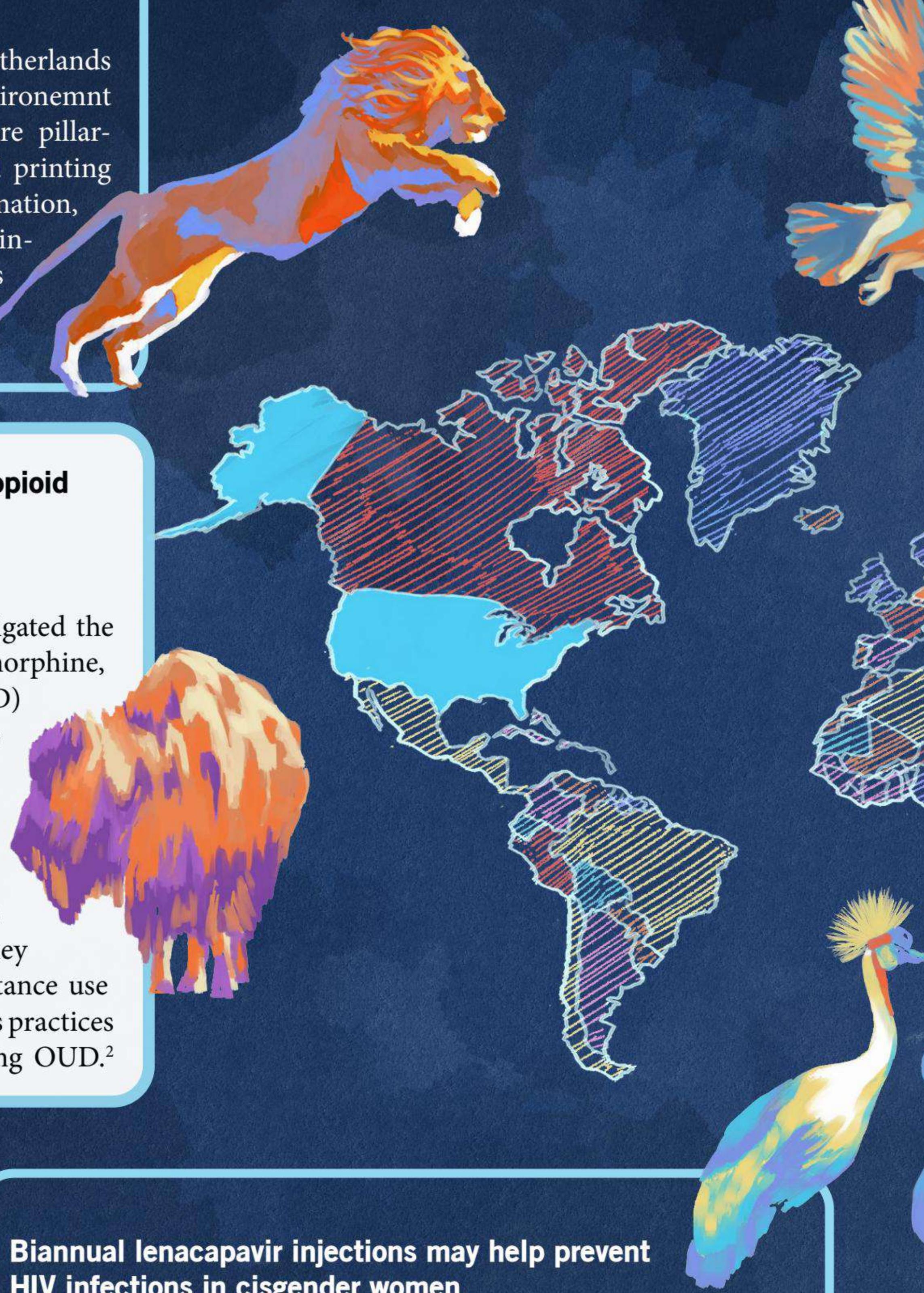
ARTISTS:
YUEWEN GAO² & IRIS QIAN²

Mindfulness training may enhance outcomes for those with opioid use disorder UNITED STATES OF AMERICA | January 2025

A recent randomized controlled trial in the United States investigated the effects of mindfulness training on adults being treated with buprenorphine, a synthetic opioid used to mitigate opioid use disorder (OUD) withdrawal symptoms.² The training encouraged participants to be cognizant of their breathing, thoughts, and emotions, while also teaching them mindful behaviour change skills.² Participants receiving mindfulness training experienced significant reductions in opioid use and OUD cravings compared to the control group.² Participants in the intervention group were at lower risk of relapsing or dropping out of treatment if they experienced residual opioid cravings, anxiety, or comorbid substance use disorder. These findings highlight the need to integrate mindfulness practices into treatment plans to improve outcomes for those experiencing OUD.²

Advancement in tissue engineering with the discovery of new skeletal tissues UNITED STATES OF AMERICA | October 2024

Researchers from the University of California Irvine discovered new skeletal tissue known as 'lipocartilage' found in the throats and noses of mammals.³ Due to its supportive and elastic qualities, lipocartilage has the potential to be used for regenerative tissue engineering in cases such as burn-related injuries or facial defects.³ The current process for cartilage reconstruction is invasive and requires tissue from the patient's rib. Instead, lipocartilage can be obtained from peripheral blood stem cell collection. With the help of 3D printing, lipocartilage can be tailored to the patient's specific needs.³



Biannual lenacapavir injections may help prevent HIV infections in cisgender women UGANDA & SOUTH AFRICA | July 2024

Lenacapavir, an antiretroviral medication, has demonstrated potential to prevent human immunodeficiency virus (HIV) acquisition.⁴ A recent phase III, double-blind, randomized controlled trial evaluated the efficacy of biannual lenacapavir subcutaneous injections compared to daily oral HIV drugs. The study population was comprised of 5,338 young cisgender women in South Africa and Uganda who tested negative for HIV.⁴ None of the participants in the lenacapavir group acquired an HIV infection, whereas 55 infections were observed in the oral drug group.⁴ These findings suggest that lenacapavir may overcome the challenge of adherence associated with oral drugs, decreasing HIV incidence.

Perioperative chemotherapy may be a better approach to esophageal cancer treatment

GERMANY | January 2025

Esophageal cancer is the eighth most prevalent cancer worldwide and is a leading cause of cancer-related deaths.⁵ A recent clinical trial from Germany compared the two most common treatment approaches for esophageal cancer: perioperative chemotherapy and preoperative chemoradiotherapy. Results showed that patients in the perioperative group had a lower mortality rate compared to the preoperative group (3% vs. 6%) within 90 days after surgery.⁶ Additionally, three years post-treatment, the progression-free survival rate in the perioperative group was 52% compared to 35% in the preoperative group.⁶ This research could improve treatment outcomes, while also protecting patients from the more harmful side effects of chemoradiotherapy.

Psilocybin demonstrates promise as a treatment option for MDD

POLAND | December 2024

A recent systematic review of studies in Poland examined the effects of psilocybin, a hallucinogen, on major depressive disorder (MDD) with a focus on determining safe dosing for treatment.⁷ The study analyzed data from three randomized controlled trials, involving a total of 389 patients.⁷ Findings indicated that a 25 mg dose of psilocybin elicited a rapid onset of antidepressant effects due to its ability to enhance neuroplasticity.⁷ However, this dosage was also associated with a significantly higher risk of nausea, headaches, and dizziness, compared to the control.⁷ Psilocybin shows promise as an effective treatment for MDD, however its dosing and side effect profile must be carefully considered for clinical application.

Microplastics in the bloodstream could have severe implications on vascular health

CHINA | January 2025

Microplastics (MPs) are becoming increasingly prevalent within the environment, yet their physiological impacts are less known. A recent study investigating the effects of MPs in the bloodstreams of mice demonstrated that MPs are phagocytosed by immune cells, forming obstructive clusters that block cerebral microvessels.¹⁰ These obstructions lead to reduced blood perfusion and neurobehavioural abnormalities in mice, suggesting that MPs contribute to vascular impairment and may exacerbate cardiovascular conditions.¹⁰ While the direct impact on humans remains uncertain, these findings raise urgent concerns about the infiltration of MPs into the human circulatory system.

Artificial cells altered by DNA nanorobots

GERMANY | September 2024

Scientists from the University of Stuttgart used DNA origami, a technique where DNA strands are designed to fold in a specific way, to control the function of biological membranes.⁸ The folding of DNA creates origami structures known as nanorobots that can reversibly alter the shape and functions of synthetic cells. Giant unilamellar vesicles, which mimic living cells, are coupled with the nanorobots to form synthetic channels that allow for the passage of large molecules.⁸ This new synthetic biology tool can open up new ways for targeted drug administration and other medicinal interventions.

Researchers develop a new tool for epigenome editing

CHINA | January 2025

Researchers in China have developed a powerful new tool for CRISPR-based epigenome editing (CRISPRepi), allowing scientists to modify gene activity without changing the DNA.⁹ CRISPRepi consolidates information on single-guide RNAs (sgRNAs) to analyze editing outcomes, assess off-target effects, and predict the efficiency of newly designed sgRNAs.⁹ By combining data from 671 experiments on 87 cell types, CRISPRepi addresses the challenge of scattered data in epigenome editing, enabling researchers to optimize sgRNA design for functional studies.⁹ CRISPRepi aims to improve the accuracy of gene editing, making it easier to study gene regulation and develop potential treatments for diseases.

RESEARCH INSIGHT

A young child with short hair, wearing a light-colored shirt, is seated in a wheelchair. The child is looking upwards and slightly to the right with a neutral expression. The background is a soft-focus blue.

**Adherence to the
CSEP 24 Hour
Movement Guidelines
In Children with a
Chronic Medical
Condition or
Disability**

ARTIST:
Jessica Palfy¹

¹Bachelor of Health Sciences (Honours),
Class of 2028, McMaster University

doi: 10.35493/medu.47.04

SARAH MOHAMED MUSATHEEK²²Bachelor of Science Kinesiology (Honours),
Class of 2026, McMaster University**INTRODUCTION**

Physical activity (PA), sleep duration (SD), and sedentary time (ST) are movement behaviours that significantly impact children's health. Recent research has demonstrated that PA, SD, and ST interact "collectively and synergistically" to improve physical and psychological health and reduce disease incidence. As a result, researchers now consider how the proportion of time spent being physically active, sleeping, or sedentary over a 24-hour period impacts health, rather than analyzing each behaviour's effect in isolation.¹ Such studies have impacted national guidelines for movement behaviours, including the Canadian Society for Exercise Physiology's (CSEP) recommended movement guidelines for children aged 5-17. These guidelines are associated with health benefits, including improved body composition, cardiorespiratory and musculoskeletal fitness, academic achievement and cognitive function, emotional regulation, and overall quality of life.² Adherence to the CSEP 24-hour movement guidelines is associated with improved health outcomes and a lower risk of disease in children.³ A 2016 study of 6218 children aged 9-11 from 12 countries who met the CSEP movement guidelines were 72% less likely to be obese than those who did not.³

Despite these benefits, it is unclear whether the guidelines are appropriate for children with chronic medical conditions and disabilities. Previous literature has shown that children with chronic conditions and disabilities are significantly less likely to meet all three CSEP movement guidelines than children without chronic conditions. A 2020 study assessing 24,405 children with and without chronic conditions found that 5.4% of children with chronic conditions met all three guidelines, compared to 8.2% of children without chronic conditions ($p < 0.05$).¹ Among these guidelines, adherence to the moderate-to-vigorous physical activity (MVPA) recommendations was particularly low, while compliance with sleep and screen time guidelines were relatively high.^{1,4,5} However, many of these studies used data from the National Survey for Children's Health, an American national health survey, which only uses parent-reported information.^{1,5,6} Therefore, it is unclear whether the parent's responses accurately depict their child's activity. Additionally, there is no evidence of a significant difference or a variation in meeting the guidelines by age.^{1,6} Given the rapid physical and developmental changes throughout childhood and adolescence, adherence may differ even within the same sub-group (e.g. 12-year-olds vs. 17-year-olds). Additionally, barriers for PA may be greater among older children with chronic conditions as differences in ability between children with chronic conditions and healthy children may increase with age.⁷

The research methodologies in the existing literature on movement behaviours within this group were appraised and used to discuss the preliminary findings of MOMENTUM, a pilot study and health survey.

THE MOMENTUM STUDY AND ITS METHODS

In the MOMENTUM study, a child and one of their parents complete two surveys each, 24 hours apart. The MOMENTUM

research team has created their own novel health survey for use in this study, as a result of prior research indicating a lack of an appropriate measurement tool to accurately assess PA in this population.⁸ This survey's psychometric properties and feasibility can be assessed to determine if it is an appropriate and valid measurement tool for future research in this area.

The surveys ask how much time the child spends, sleeping, sitting, and being physically active while also asking questions about the child's mental health and quality of life. The survey also asks children and parents which topics they believe are the most important for researchers to study regarding PA, SD, and ST. Children also have the option to wear an accelerometer, a device that accurately captures time spent being physically active, sleeping, and sitting, for seven days before completing the two surveys. This insight assesses MOMENTUM's first child-reported survey between ages with a focus on adherence to the CSEP movement guidelines. This insight will only use data from the child-reported surveys as children's direct responses likely provide a more precise measure than those of parents, who serve as secondary observers. The more valid association between child-reported data and outcomes has been reflected in the past literature.^{9,10}

RESULTS

Children aged 12-17 (mean = 14.80 years; n = 79) in the MOMENTUM study were assessed for their adherence to the CSEP guidelines and their average times spent being physically active, sleeping, and sitting. PA guidelines recommends at least 60 minutes/day of MVPA and 3 days/week of aerobic activities. SD guidelines state an uninterrupted 9 to 11 hours of sleep per night for ages 5-13 years and 8 to 10 hours per night for those aged 14-17, with consistent bed and wake-up times. ST guidelines state less than two hours of recreational screen time per day.

Children were recruited from the McMaster Children's Hospital and the Children's Hospital of Eastern Ontario in Ottawa. 8.9% of all children met the screen time guidelines, 7.6% met the PA guidelines, and 6.3% met the sleep guidelines. 16.5% of all children met at least one guideline, 5.4% met two guidelines, and none met all three. There were no clear patterns between the average time spent on each movement behaviour and age except for sleep, where children aged 12-13 got more sleep per night than children aged 14-17.

Table 1. Prevalence of meeting individual and multiple movement behavior guidelines between ages 12-17.

	% of all children: (n = 79)	% of all 12-year-old children: (n=8)	% of 13-year-old children: (n = 11)	% of 14-year-old children: (n = 13)	% of 15-year-old children: (n = 18)	% of 16-year-old children: (n = 15)	% of 17-year-old children: (n = 14)
<u>At least one guideline met:</u>	16.5%	12.5%	18.2%	15.4%	11.1%	20%	14.3%
<u>Two guidelines met:</u>	5.1%	12.5%	0%	0%	0%	6.7%	0%
<u>All three guidelines met:</u>	0%	0%	0%	0%	0%	0%	0%

Table 2. General participant characteristics

	% of all children: (n = 79)	% of all 12-year-old children: (n=8)	% of 13-year-old children: (n = 11)	% of 14-year-old children: (n = 13)	% of 15-year-old children: (n = 18)	% of 16-year-old children: (n = 15)	% of 17-year-old children: (n = 14)
Sex (male):	39.2%	62.5%	54.5%	38.5%	44.4%	13.3%	35.7%
Primary Condition Type:							
Physical	13.9%	12.5%	18.2%	15.4%	16.7%	13.3%	7.1%
Immunological	13.9%	12.5%	9.1%	7.7%	16.7%	13.3%	21.4%
Hematological	11.4%	37.5%	9.1%	15.4%	11.1%	6.7%	N/A
Endocrine	10.1%	N/A	N/A	N/A	22.2%	20.0%	7.1%
Neurological	7.6%	25.0%	18.2%	N/A	N/A	13.3%	N/A
Musculoskeletal	7.6%	N/A	9.1%	7.7%	11.1%	N/A	14.3%
Congenital or Chromosomal Abnormality	5.1%	N/A	9.1%	N/A	5.6%	N/A	14.3%
Respiratory	5.1%	N/A	N/A	7.7%	5.6%	13.3%	N/A
Digestive	2.5%	N/A	N/A	N/A	N/A	6.7%	7.1%
Developmental	1.3%	N/A	N/A	N/A	N/A	N/A	7.1%
Other:	19.0%	12.5%	27.2%	38.5%	11.1%	6.7%	21.4%
More Than One Condition	40.5%	12.5%	55.6%	46.2%	55.6%	40%	28.6%

Table 3. Prevalence of meeting each behavior guideline between ages 12-17.

Movement Guideline:	% of all children who met the guideline: (n = 79)	% of all 12-year-old children who met the guideline: (n=8)	% of 13-year-old children who met the guideline: (n = 11)	% of 14-year-old children who met the guideline: (n = 13)	% of 15-year-old children who met the guideline: (n = 18)	% of 16-year-old children who met the guideline: (n = 15)	% of 17-year-old children who met the guideline: (n = 14)
Physical Activity:	7.6%	12.5%	9.1%	15.4%	0%	6.7%	7.1%
Sleep:	6.3%	0%	0%	23.1%	0%	6.7%	7.1%
Sedentary Time:	8.9%	12.5%	9.1%	0%	11.1%	13.3%	7.1%

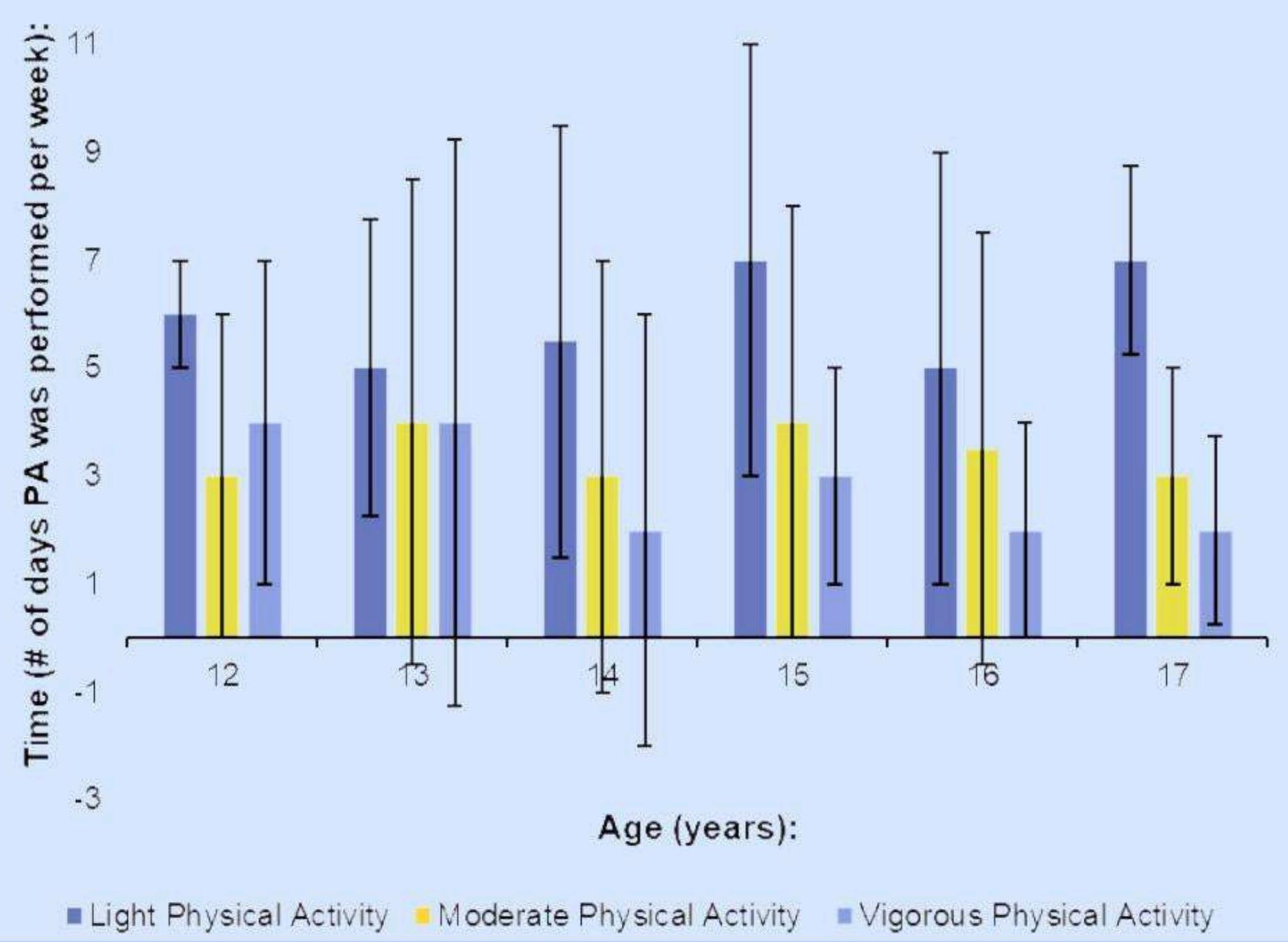


Figure 1. Comparison of Light, Moderate, and Vigorous PA (# of days PA was performed per week) between ages 12-17 (n = 79). Bars represent the group median, error bars represent interquartile ranges.

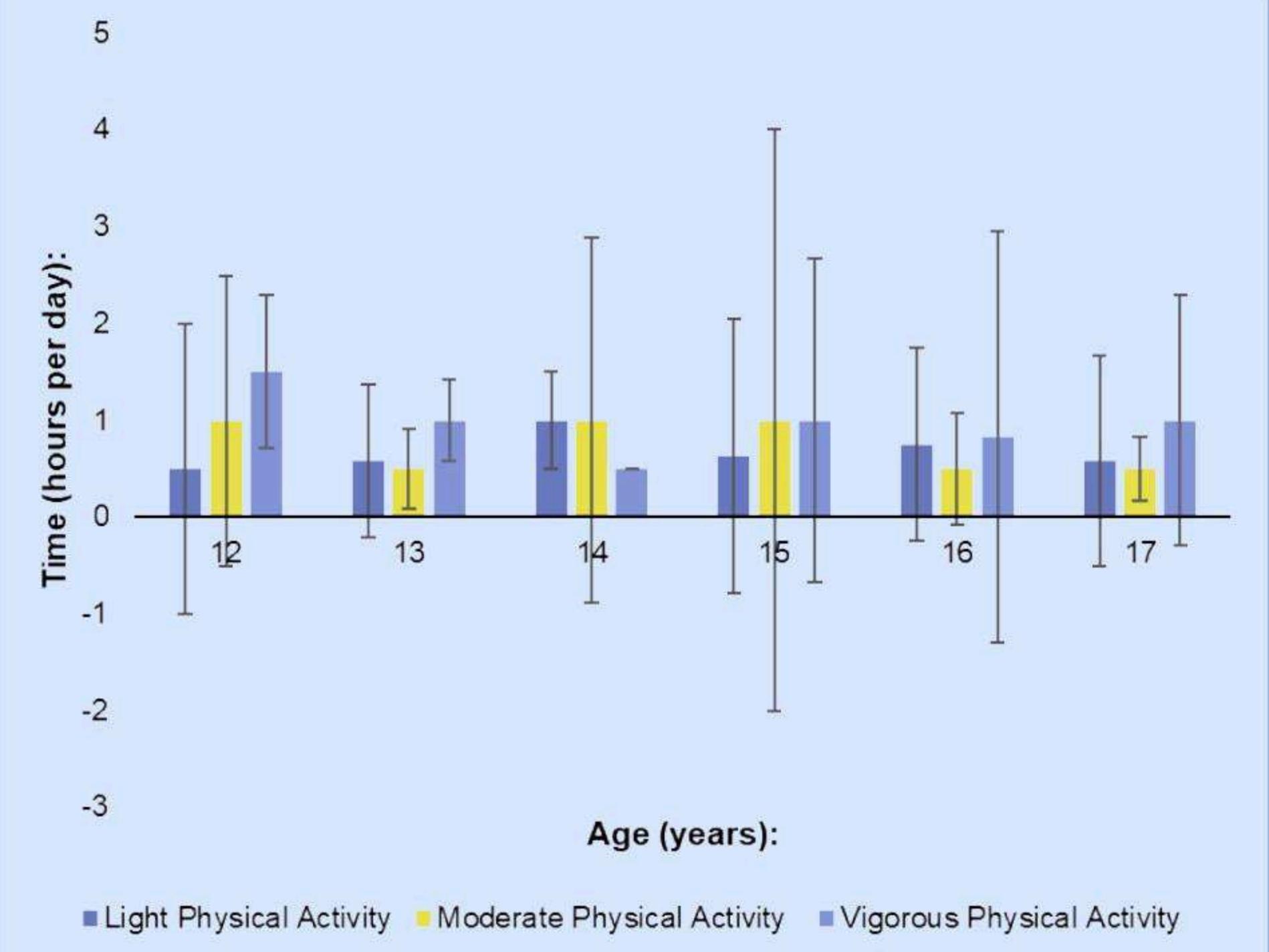


Figure 2. Comparison of Light, Moderate, and Vigorous PA (hours per day) between ages 12-17 (n = 79). Bars represent the group median, error bars represent IQR. IQR, interquartile range.

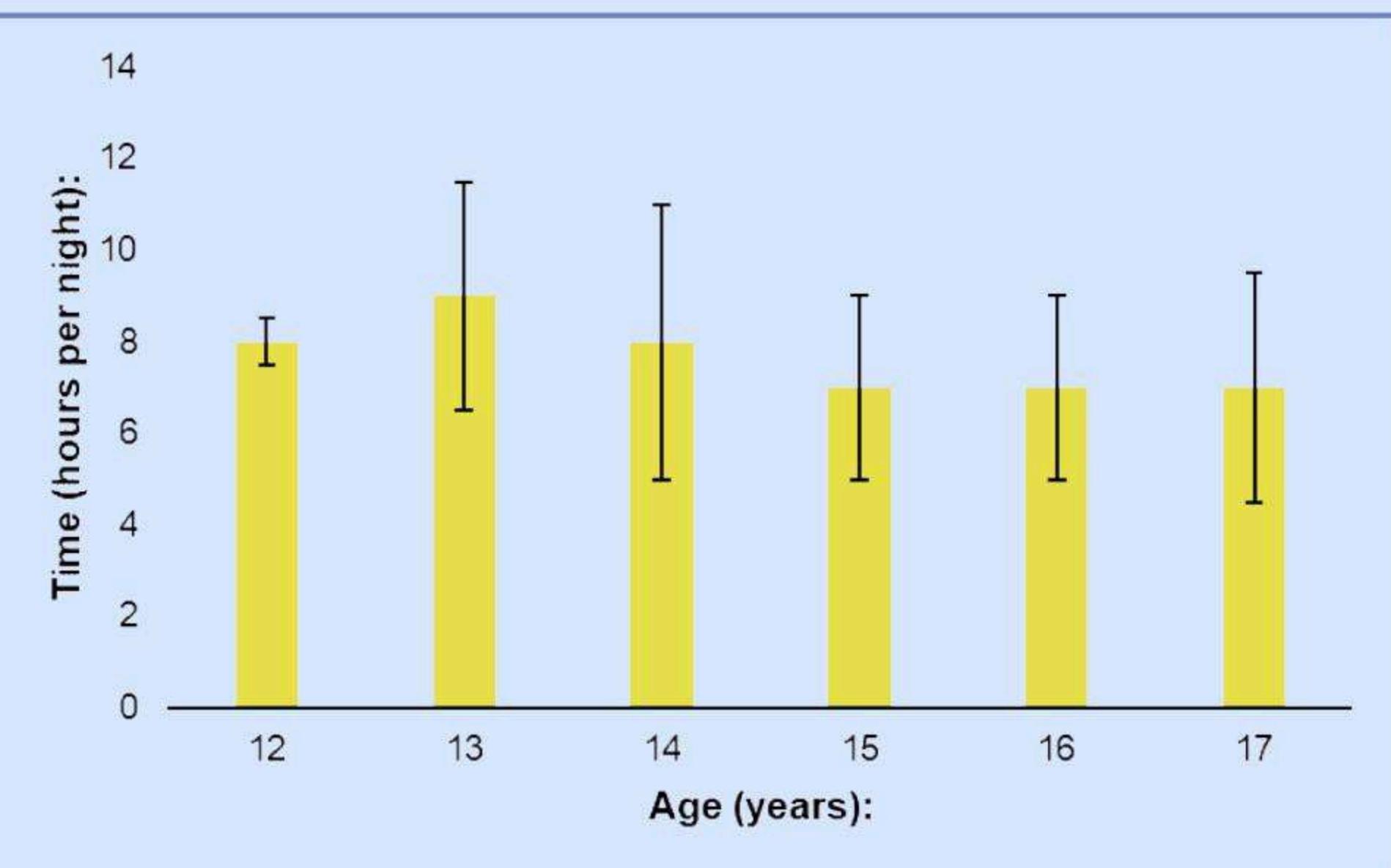


Figure 3. Comparison of Sleep (hours per night) between ages 12-17 (n = 79). Bars represent the group median, error bars represent interquartile range.

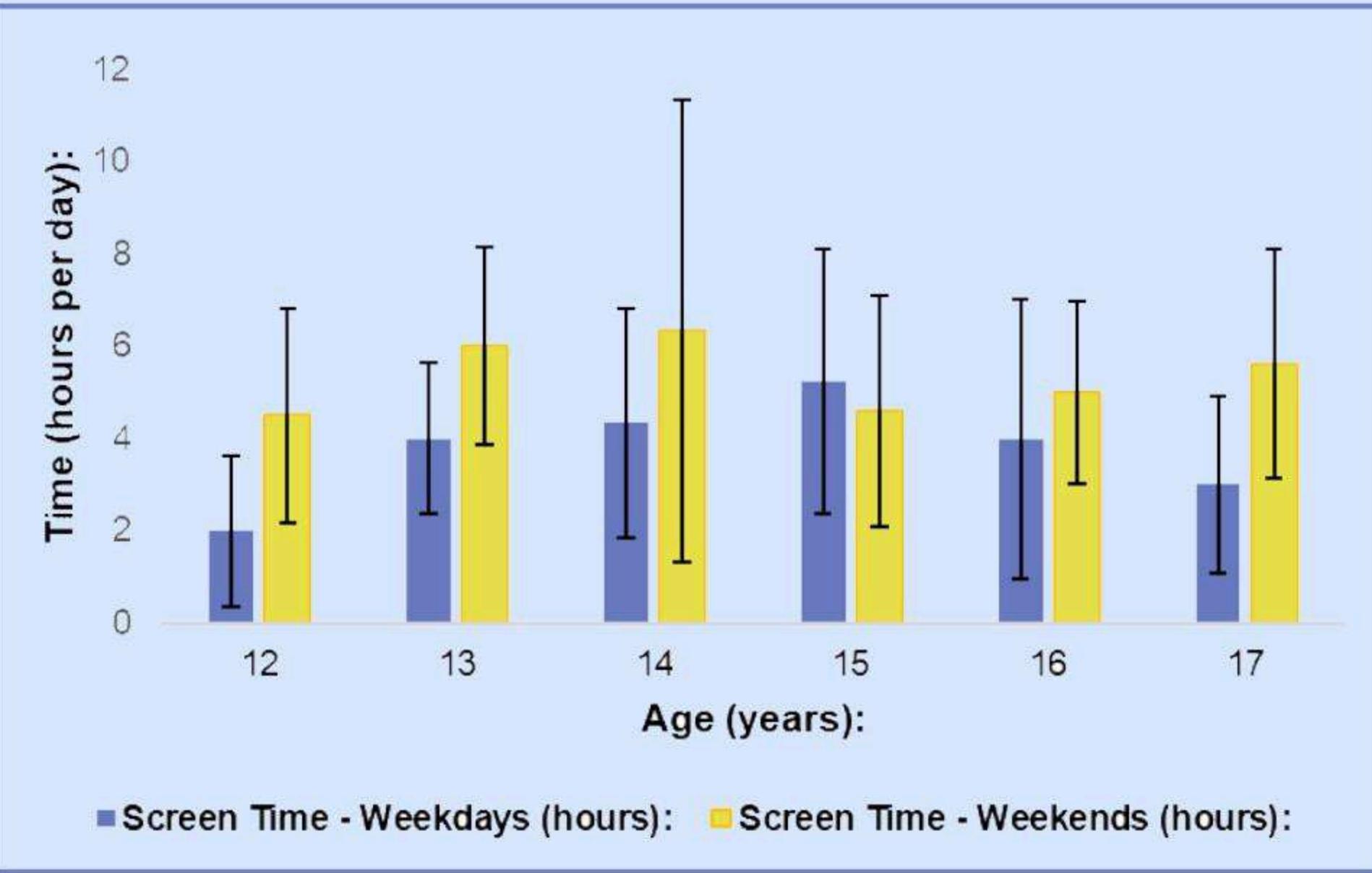


Figure 4. Comparison of Screen Time on Weekdays and Weekends (hours per day) between ages 12-17 (n = 79). Bars represent the group median, error bars represent interquartile range.

DISCUSSION

Children were most likely to meet the guidelines for screen time out of all three guidelines. However, other studies have found that children with chronic conditions were most likely to meet the guidelines for sleep.^{1,6} This discrepancy suggests that the CSEP guidelines may not be equally suitable for all condition types or that adherence can vary depending on the condition type.

Additionally, children were least likely to meet the guidelines for sleep in this study, which contradicts past literature. Moreover, none of the children in this study met all three movement guidelines, in contrast to past studies that concluded that approximately 5-7% of children with chronic conditions met all three guidelines.^{1,5,6} One explanation for these differences could be that the MOMENTUM study is currently in its preliminary stages and had a much smaller sample size ($n = 79$) compared to past completed studies, which had hundreds of participants. As MOMENTUM continues to recruit participants and as the sample size increases, the adherence patterns observed may shift. Also, the majority (60.8%) of participants in this study were female, whereas most past studies had even numbers of male and female participants.^{1,5,6} If a more balanced sample size were used, results might have been more similar to those seen in the past literature.

There were no clear patterns between the average time spent doing each movement behaviour and age, except for sleep, where children aged 12-14 got more sleep per night than children aged 15-17 (Figure 3). Although past studies have not identified a relationship between sleep times in children with chronic conditions and age, the lower SD observed in children aged 15-17 could be attributed to the increase in schoolwork with high school. However, this is not specific to children with chronic conditions. A lack of children meeting the sleep guidelines, and an inconsistency in the average times children of different ages spent sleeping, could prompt the current CSEP guidelines to be tailored even more for specific ages or age groups, as well as more age-based comparisons in future research.

For PA (# of days per week), light PA was the most common type, with moderate and vigorous PA being lower and more variable (Figure 1). However, vigorous PA was the most common type of PA performed (in hours per day) by 12, 13, 16, and 17-year-old children (Figure 2). This is not reflected in the literature and suggests the need for more research.

Furthermore, Figure 4 shows that children of all ages get more screen time on weekends than on weekdays. However, there were no analyses made comparing screen time on weekdays versus weekends in the past literature.^{1,5,6}

The sparse adherence observed in this study suggests that the current CSEP guidelines may not be suitable for children with chronic conditions and disabilities. This prompts the need for modifications to the current guidelines, including age and conditions-based differentiation that considers the barriers children face towards meeting these recommendations. Further research using large sample sizes and accelerometry data should be done to improve the results' reliability, generalizability, and validity. This study, along with future work in the field, can help to refine the current movement guidelines to better accommodate children with

chronic conditions and disabilities, ensuring that the guidelines are both achievable and supportive of children's health and well-being.

LIMITATIONS AND FUTURE DIRECTIONS

Limitations of this study include its small sample size and lack of disease-based comparisons. Future directions include recruiting a larger sample size to increase generalizability, allowing for more equal representation of different ages, genders, and condition types among participants, and stronger statistically powered results. Additionally, further studies should explore the associations between movement behaviours and condition severity and duration to address disease-based associations. Finally, objective measures like accelerometry should be further incorporated to supplement subjective survey data to confirm validity and assess reliability.

REVIEWED BY: SAMANTHA MORIN

Samantha Morin is a PhD student in the Child Health & Exercise Medicine Program at McMaster University. Her research focuses on the links between movement behaviours and health indicators in youth with inflammatory bowel disease.

EDITED BY: IAN KIM & ADITYA MISRA

1. Haines J, Neumark-Sztainer D, Hannan P, Robinson-O'Brien R. Child versus parent report of parental influences on children's weight-related attitudes and behaviors. *J Pediatr Psychol.* 2008;33(7):783-8. Available from: doi:10.1093/jpepsy/jsn016.
2. Healy S, Foley J, Haegele JA. Physical activity, screen time, and sleep duration among youth with chronic health conditions in the United States. *Am J Health Stud.* 2020;4(5):505-11. Available from: doi:10.1177/0890117120915687.
3. Roman-Viñas B, Chaput JP, Katzmarzyk PT, Fogelholm M, Lambert EV, Maher C, Maia J, Olds T, Onywera V, Sarmiento OL, Standage M, Tudor-Locke C, Tremblay MS. Proportion of children meeting recommendations for 24-hour movement guidelines and associations with adiposity in a 12-country study. *Int J Behav Nutr Phys Act.* 2016;13(1):123-23. Available from: doi:10.1186/s12966-016-0449-8.
4. Canadian Society for Exercise Physiology. Canadian 24-hour movement guidelines for the children and youth (5-17 years): An integration of physical activity, sedentary behaviour, and sleep [Internet]. 2021. Available from: <https://csepguidelines.ca/guidelines/children-youth/> [cited 2025 Feb 3].
5. Elmesmari RA, Reilly JJ, Paton, JY. 24-Hour movement behaviors in children with chronic disease and their healthy peers: A case-control study. *Int J Environ Res Public Health.* 2022;19(5):2912-12. Available from: doi:10.3390/ijerph19052912.
6. Wang W, Haegele, JA, Wu Y, Li C. Meeting the 24-hour movement guidelines and outcomes in adolescents with ADHD: A cross-sectional observational study. *Int J Environ Res Public Health.* 2022;19(4):2132-32. Available from: doi:10.3390/ijerph19042132.
7. Shields N, Synnot A. Perceived barriers and facilitators to participation in physical activity for children with disability: A qualitative study. *BMC Pediatr.* 2016;16(9):9-9. Available from: doi:10.1186/s12887-016-0544-7.
8. Lew SM., Hewlett CKL, Anderson D, Finberg M, Spence AL, Maiorana A, Shetty VB, Davey RJ. Questionnaires measuring physical activity in clinical pediatric populations: A systematic review. *Pediatr Exerc Sci.* 2023;35(1):48-60. Available from: doi:10.1123/pes.2022-0003.
9. Haegele JA, Zhu X, Healy S, Patterson, F. Proportions of youth with visual impairments meeting 24-h movement guidelines. *Child Care Health Dev.* 2020;46(3):345-51. Available from: doi:10.1111/cch.12747.
10. Jozefiak T, Larsson B, Wichstrøm L, Mattejat F, Ravens-Sieberer U. Quality of Life as reported by school children and their parents: A cross-sectional survey. *Health Qual Life Outcomes.* 2008;6(1):34-34. Available from: doi:10.1186/1477-7525-6-34.

DR. MARNIX HEERSINK

AUTHORS:

JOEL ABRAHAM¹, ANGELA HONG², & RUHANI KHATTR²

¹Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

²Bachelor of Health Sciences (Honours), Class of 2026, McMaster University

ARTIST:

ELAINE WANG²

COULD YOU INTRODUCE YOURSELF?

My name is Marnix Heersink, and I'm a physician, an entrepreneur, and a philanthropist. I'm 77 years old, but I'm very delighted and fortunate to be healthy enough to continue doing things that I hope are relevant and useful. I was born in the Netherlands, and my family immigrated to Canada a long time ago, where I spent most of my youth in the beautiful city of Burlington, Ontario. I have a great deal of history and connection with McMaster; ever since moving to the United States, I've kept that connection through friends, colleagues, and others whom I know particularly well. One of my dear friends, Dr. John Kelton—the former Dean of McMaster University—is a leader and a wonderful person, so I'm honoured to be here today.

WHY DID YOU DECIDE TO PURSUE OPHTHALMOLOGY AND HOW HAVE YOU SEEN THE FIELD EVOLVE THROUGHOUT YOUR CAREER?

Going through medical school, I had many choices for specialization. I was an athlete and loved the idea of fixing people with sports injuries, so while I didn't get into all the research opportunities, I could be involved in interventional work. My older brother, who's an ophthalmologist himself, said, "Why don't you think about something lifelong? You don't have to be dependent on a hospital and you have a bunch of colleagues. It would be interesting, you will tangibly do things, and of course, you'll be well-compensated." So all of these things inspired me to realize that while I wasn't particularly interested in ophthalmology, I was interested in all of those things that make my life so much better—it was an inspirational thing for me to think about the eyes.

Ophthalmology has transformed remarkably. Fifty years ago, we had tools that were rather barbaric compared to what we do now. Now, we have tools, lasers, and diagnostic instruments that have transformed our work. That transformation has been a wonderful benefit to myself, the profession as a whole, and most importantly, the patients—they're the ones who intimately benefit from advancements.

My career in ophthalmology has been my main driver and passion. When I go to a meeting, I spend most of my time listening; I've learned that you can gain immense wisdom and energy from colleagues and peers by simply listening. This has been particularly influential for me, and it has inspired and allowed me to continue to enjoy my practice. I'm lucky to still be able to work, whereas a lot of people my age have packed it up. I'm at the point now where I say every day, "Isn't this great?", and this is still possible because of what I've learned in ophthalmology and in other areas throughout the years.

WITH THE RISE OF ARTIFICIAL INTELLIGENCE (AI) AND DIGITALIZED HEALTH, HOW ARE YOU ADAPTING TO AND INCORPORATING AI INTO YOUR PRACTICE AND PHILANTHROPIC PURSUIT OF BIOMEDICAL INNOVATION?

In our practice, we're very cutting-edge. We realize that the important thing is patient care; however, we also pursue



research in clinical studies, teaching, and other opportunities to engage with the community. AI will be another essential within this. To stay current and ready for the future, you must figure out a way to incorporate AI. I've realized that while the capabilities of human intelligence are wonderful, we can do even more with AI. Physicians in the United States, myself included, are rather frustrated because we spend probably 20 to 30% of our time doing paperwork and administrative tasks. They're necessary, but the time it takes separates the patient from the doctor. The doctor feels like there are two entities in the room necessitating attention: the computer and the person. Most doctors want to allocate their full attention to the patient but cannot proceed before managing administrative tasks. In the long term, this leads to physician failure, resignation, or retirement. I think a partner in all of this could be AI, helping us with that administrative transcription and translation. Still, there are going to be errors, and there are many questions that have yet to be answered: "Who is going to regulate AI? Is it the government, industry stakeholders, or a 3rd party?" These are tools, rather than our master, and it is an exciting prospect in biomedical innovation.

IN 2022, YOU CONTRIBUTED A TRANSFORMATIVE GIFT TO MCMASTER, ALLOWING US TO ESTABLISH THE MARNIK E. HEERSINK SCHOOL OF BIOMEDICAL INNOVATION AND ENTREPRENEURSHIP. WHAT MADE YOU WANT TO SPONSOR MCMASTER SPECIFICALLY, AND WHAT DO YOU HOPE TO SEE FROM THIS?

I've learned that in my current stage of life, if I have the opportunity, I'll find a way to make meaningful and impactful contributions. What inspired me was realizing I have a lot to be grateful for. I was thinking about "Why do I give? Where do I give? What do I want to expect?" So, I developed an acronym called GIVE. The G stands for gratitude: I hold so much gratitude, and I'm very aware that it motivates me to give. The I stands for investment: a wonderful thing that allows me to inspire and bring innovation to things I stand for. The V stands for vision and values: when I make donations, I like to make sure that the values between the recipient and the donor are the same. The letter E stands for excellence: something I try to involve in everything I do in this stage of life. This acronym evolved as I started to accumulate things and got to a point where my family was financially sustainable. GIVE does two things: it illustrates values and it inspires others.

CREATING YOUR OPHTHALMOLOGY CLINIC, EYE CENTER SOUTH, DID YOU EXPERIENCE ANY CHALLENGES OR RISKS IN PURSUIT OF ITS SUCCESS? HOW WOULD YOU ADVISE YOUNG PEOPLE FACING SIMILAR ISSUES?

After finishing medical school, I was very lucky to go to the wonderful Philadelphia institution, Wills Eye Hospital—one of the leading teaching hospitals for ophthalmologists. As I was training, I began to think about what was going to happen after I left, raising questions like, "Where do I want to live? What kind

of ophthalmologist do I want to be? What are my goals? Would I consider doing philanthropic or innovative things?" I thought about combining these things. Ophthalmology would give me a great opportunity to think outside the box and start something entrepreneurial. When my wife and I moved to Dothan, Alabama, 47 years ago, we realized that it was a terrific community, but there were not many ophthalmologists there, and I was bringing new technology. There was a bit of a challenge in that. New things required a purchase of equipment, and we had to convince people to do things novelly. I started to take some risks, I think you'll learn from risks.

You should take risks at an early age, rather than when you're sixty, fifty, or forty. You start to think, "If I am an entrepreneur, how can I move forward?" There were challenges when I first came to Dothan, and we've had some failures. However, I always knew that if I had a good family life and worked hard to stay healthy, I'd be able to recover. With time, patience, and hard work, it turns out that we've been successful, and I'm delighted now because that allows me to go from being an entrepreneur to a philanthropist. I get a great deal of joy in that.

WHAT ADVICE WOULD YOU GIVE TO YOUNGER MEDICAL STUDENTS WANTING TO MAKE A LASTING IMPACT IN HEALTHCARE ENTREPRENEURSHIP?

Medical students who want to have an impact need to have drive, discipline, curiosity, and most importantly, kindness. Kindness is what our patients expect and deserve from our community, and as a physician, one should start with that mindset. Being an entrepreneur, there are ways to combine innovation, philanthropy, and clinical care. A young person entering medicine with the right mindset, as an entrepreneur in spirit, has a good opportunity to succeed—and I hope they consider philanthropy.

CREATING YOUR OPHTHALMOLOGY CLINIC, EYE CENTER SOUTH, DID YOU EXPERIENCE ANY CHALLENGES OR RISKS IN PURSUIT OF ITS SUCCESS? HOW WOULD YOU ADVISE YOUNG PEOPLE FACING SIMILAR ISSUES?

I would like to be seen as a person who did things, shared things, and inspired people. However, there are many people who have done so much, if not more than me. Even a small deed can be so impactful and meaningful, and I don't want to put myself above anybody else. If I knew I made the world better because of a tiny action, I would be happy to think that was my mission in life. I've been blessed, like many of us, who have been given something that we may not necessarily deserve. There's an old Native American saying that goes, "We are all warmed by fires that we did not start," and I think that rings true. In my life, I have been warmed by the fires of others: my parents, family, teachers, colleagues, and friends. The world blessed me, so it's my turn to do something else for others.

EDITED BY: PARTH ARORA & EVAN ZHAO

Crossing]Species Lines: The Clinical Future of Xenotransplantation

doi:10.35493/medu.47.10

AUTHORS:

ALYSSA BOCSKAY¹ & OWEN LIU²

¹Bachelor of Health Sciences (Honours Biochemistry), Class of 2027, McMaster University

²Bachelor of Health Sciences (Integrated Biomedical Engineering & Health Sciences), Class of 2028, McMaster University

ARTIST:

CAMELA TEMACINI¹

ABSTRACT

Organ transplantation provides a considerably safe and increasingly effective treatment for patients experiencing late-stage organ failure. However, increasing demand for organ donations has caused waitlist numbers to surge, preventing patients from receiving life-saving transplants and resulting in over 250 annual deaths in Canada alone. With less than 25% of Canadians registered as organ donors, donation numbers from deceased donors continue to fall short of demand. A solution being investigated is xenotransplantation, the transplantation of non-human organs into a human recipient. While rejection remains a major concern following xenotransplantation, genetic engineering of the donor animals using CRISPR-Cas9, an endonuclease system used to precisely alter DNA sequences, has demonstrated decreased levels of hyperacute rejection (HAR), with two recent cases of cardiac xenotransplantation demonstrating promise in overcoming HAR. Despite current advancements, there are ongoing limitations to consider and further research to conduct before widespread implementation.

INTRODUCTION

Xenotransplantation, derived from the Greek prefix ‘*xeno*’, meaning strange or foreign, is the process by which tissues or organs are transplanted between species.¹ Although fascination with allotransplantation, the transplant of organs between humans, has been documented for centuries, the widespread use of tissue grafts and organ transplants has only recently been deemed clinically acceptable.² Xenotransplantation, an even more recent concept, remains a topic

of ongoing debate. Nonetheless, the ever-growing demand for transplants has put organ donation networks under immense strain, with thousands of patients on waitlists in Canada alone.³ In 2022, 270 Canadians died while on a transplant waitlist, an 8% increase from the previous year.² Xenotransplants may have the potential to sustainably supply a large number of viable organs, providing an alternate course of treatment for the thousands of patients awaiting a life-saving donation. Despite this potential, the field of xenotransplantation remains in its infancy, requiring foundational research, N-of-1 trials, and clinical trials prior to its implementation. This review aims to provide an understanding of recent xenotransplantation developments and forthcoming challenges.

BACKGROUND

Early xenotransplants, such as Dr. Keith Reemstma's renal xenografts from chimpanzees in 1963, often resulted in organ rejection and failure to achieve long-term patient survival despite increased doses of immunosuppressants.^{1,4,5}



Although early attempts of xenotransplantation proved unsuccessful, continual advancements in medical technology and the growing knowledge of immunological tolerance have improved patient outcomes, such as donor gene editing to mitigate hyperacute rejection (HAR).¹

HAR is a type II hypersensitive reaction characterized by rapid and violent graft destruction due to foreign epitopes on donor endothelial cells targeted by human antibodies. The activation of the complement cascade results in a robust immune response against these foreign antigens, ultimately leading to HAR in human recipients.^{6,7} HAR is the most immediately life-threatening type of graft rejection and occurs within minutes of transplantation, making it the first immunological hurdle that scientists had to overcome. In contrast, chronic rejection develops months or years after transplantation, and its mechanisms are poorly understood in the context of xenografts due to the limited number of documented cases.⁷ HAR can have several adverse effects on the recipient patient including graft thrombosis, hemorrhage, and oxygen depletion through ischemia.^{7,8} Fortunately, these effects can be mitigated through immunosuppression, donor gene editing, and blood type crossmatching.¹

While physiological and taxonomic similarities with humans paint non-human primates (NHPs) as the ideal xenotransplant donor, it is scientific consensus that pigs are the preferred donor for the purposes of xenotransplantation. Most large primate species are endangered, and their genetic similarity would make it easier for zoonotic pathogens such as simian immunodeficiency virus, simian-T-lymphotropic virus, and foamy virus to cross species barriers and infect humans.^{9,10} As such, pigs are the preferred donor species due to their high reproductive rate, their use being deemed more ethical, and the scientific community's knowledge of porcine gene editing.⁴

Despite the potential capabilities of xenotransplantation, several challenges must be considered prior to the practice's clinical implementation. Recent research has been directed towards the genetic engineering of donor animals to prevent HAR by the deletion or inactivation of xenoantigens, a technique known as genetic knockout.^{6,11}

XENOANTIGEN GENE KNOCKOUT VIA CRISPR-CAS9

The porcine xenoantigen α-1,3-galactose (α-Gal) has been identified as the main target of human antibodies in HAR.¹² Since this antigen is not present in humans, α-Gal residues on donor cells are targeted by human anti-Gal antibodies, inducing an immune response that leads to HAR.¹² Similarly, the cytidine monophosphate-N-acetylneurameric acid hydroxylase (CMAH) porcine xenoantigen and xenoantigen-synthesizing protein β1,4-N-acetylgalactosaminyltransferase (β4GalNT2) have also been associated with the occurrence of HAR.¹³

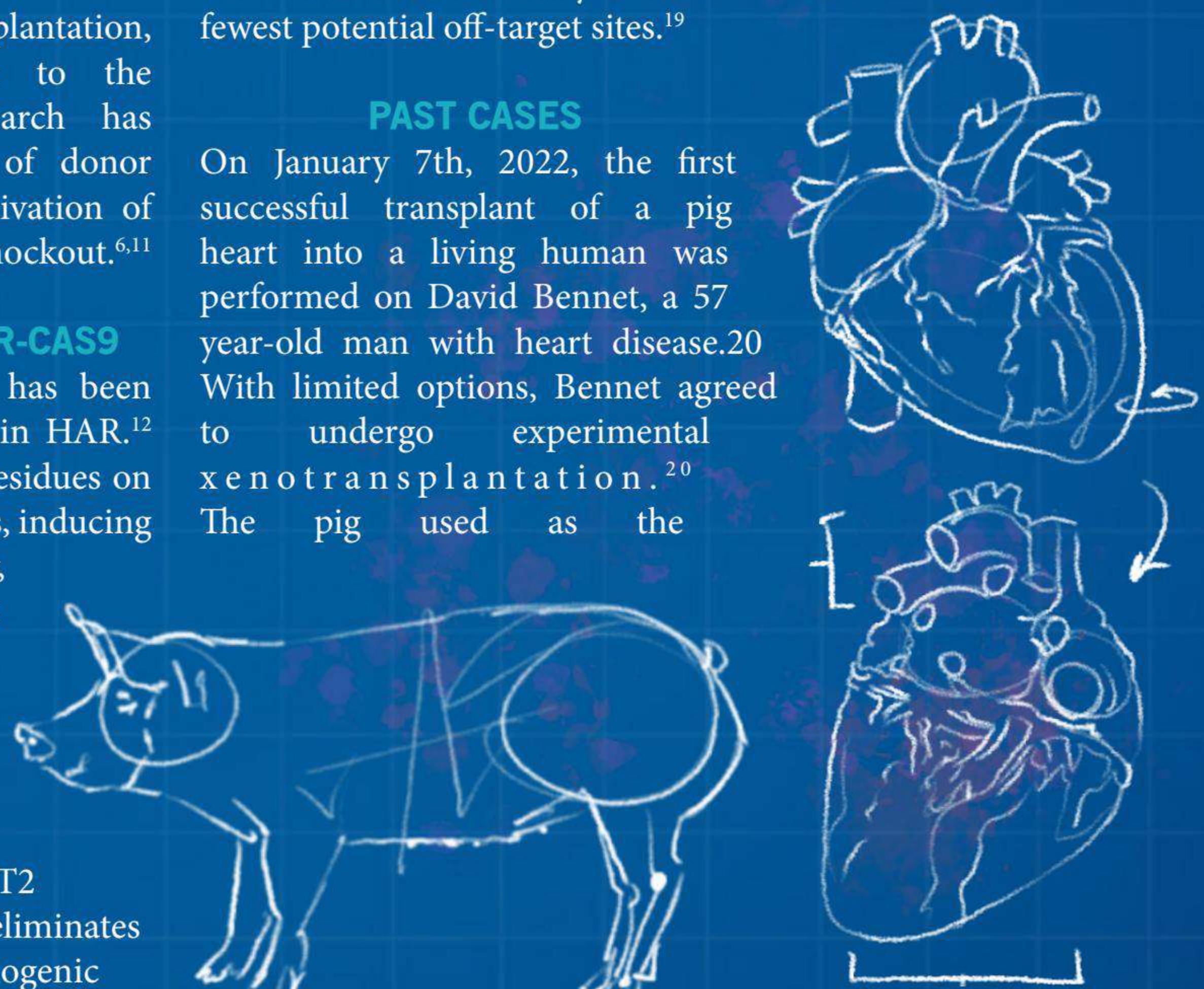
¹⁵ Recent findings demonstrate that the knockout of genes encoding for α-Gal, CMAH, and β4GalNT2 (GGTA1, CMAH, and β4GalNT2, respectively) eliminates antigen expression, thereby overcoming their immunogenic

effects.¹¹ The advent of the clustered regularly interspaced short palindromic repeats (CRISPR) Cas9 endonuclease system has allowed researchers to overcome HAR following xenotransplantation.¹¹ The CRISPR-Cas9 system uses guide RNAs to specifically target a certain sequence and cuts the DNA at that location with a Cas9 enzyme, allowing for natural repair processes to modify the gene. In 2015, Estrada and colleagues used CRISPR-Cas9 to create the first GGTA1/β4GalNT2/CMAH triple-knockout pig, preventing the expression of their respective xenoantigens.¹¹ The study found that cells from GGTA1-/-/β4GalNT2-/-/CMAH-/- pigs exhibited reduced binding of human immunoglobulin M (responsible for acute-phase immune response) and immunoglobulin G (responsible for long-term protection) antibodies across 90% of tested samples.¹¹ These findings suggest that triple-gene knockout in porcine xenografts elicits a diminished immune response in human recipients and reduces the likelihood of organ rejection.¹¹

Another barrier that CRISPR-Cas9 has helped overcome is the transmission of retroviral disease from porcine organs to humans. Notably, porcine endogenous retroviruses (PERVs) have posed a major concern due to their potentially tumour-inducing and immunosuppressive effects on human cells.¹⁶ Unlike other zoonotic pathogens, PERVs are integrated into the pig genome and cannot be eliminated with antiviral drugs.¹⁷ Yang and colleagues used CRISPR-Cas-9 to disrupt copies of the PERV pol gene and eradicate virtually all PERVs in a porcine kidney cell line.¹⁸ When the genetically modified porcine kidney cells were cocultured with human embryonic cells, there was a 1000 fold reduction in PERV infection compared to the wild-type porcine kidney cells.¹⁸ However, a potential limitation with the CRISPR-Cas-9 system is the risk of off-target mutations – unintended changes to DNA outside of the target locus. Current research aims to improve the specificity of CRISPR-Cas9 by developing modified nucleases and using bioinformatics to identify the loci with the fewest potential off-target sites.¹⁹

PAST CASES

On January 7th, 2022, the first successful transplant of a pig heart into a living human was performed on David Bennet, a 57 year-old man with heart disease.²⁰ With limited options, Bennet agreed to undergo experimental xenotransplantation.²⁰ The pig used as the





technique showed no cytomegalovirus to have been absent previous testing—was

blood.²¹ It is uncertain Bennet's xenograft failure, but past studies have linked pCMVs to xenograft injury in NHPs. Mueller and colleagues evaluated the effects of pCMV activation with nine pig-to-baboon cardiac xenotransplants, and found that baboon recipients with pCMV-infected xenografts had reduced median survival times and a greater incidence of consumptive coagulopathy, a condition related to increased bleeding due to the loss of hemostatic factors.²²

Despite its short course, Bennet's transplant highlights years of developments in xenotransplantation research. The absence of HAR demonstrated the efficacy of immunosuppressive treatments including an anti-CD40 antibody that doctors incorporated in Bennet's post transplant medication regimen.²² Past work on baboon xenograft recipients demonstrated that anti-CD40 antibody therapy, which blocked the CD40/154 pathway involved in immune rejection, significantly prolonged graft survival.²³

Postmortem examination of Bennet's case showed that the xenoheart doubled in size and exhibited damage to endothelial cells, myocytes, and erythrocytes inconsistent with typical HAR.²⁰ The presence of pCMV was unexpected and may have initiated inflammatory responses in the graft. Additionally, it was suggested that when doctors administered intravenous immunoglobulin to treat the infection, it reacted with the endothelium of the xenograft and possibly induced antibody-mediated rejection (AMR).²⁰

Following this case, doctors successfully performed another xenoheart transplant on September 20, 2023 on Lawrence Faucette, a 58-year-old male with a history of heart problems. Due to severe atherosclerotic vascular disease and gastrointestinal bleeding, he was ineligible for an allograft, opting for the xenotransplant as a final resort. Previous pCMV surveillance used in Bennet's case was deemed insufficient,

tion of 6 human genes to combat rejection.²¹ Bennet was closely monitored and the xenograft initially functioned without any evidence of rejection.

However, 43 days post-transplant, a chest radiograph showed evidence of infection in Bennet's lungs.²¹ Bennet's health and heart function started deteriorating until he passed away 60 days post-transplant. Although subsequent polymerase chain reaction testing, a used for gene amplification, PERV transmission, porcine (pCMV) – a virus thought from the donor pig based on unexpectedly detected in the if pCMVs directly led to

resulting in an enhanced screening protocol. For several weeks, the xenoheart maintained excellent function, until it showed a similar pattern of graft failure to Bennet's case. Faucette passed away six weeks post-transplant. Since pCMV replication was not detected throughout Faucette's case, the development of AMR is believed to be the cause of xenograft failure.²⁴

Both cases of cardiac xenotransplantation involve AMR as an inferential cause of death. Incidentally, AMR is the most common cause of xenograft failure in NHPs.²⁵ While AMR can be reversed with allografts, there have been no cases of AMR being reversed in xenografts.²⁵ With the scarcity of existing research, doctors do not have a well-defined post-transplant regimen or method to measure the progression of xenograft AMR in humans. Future research directions include a deeper understanding of xenograft rejection mechanisms in humans, testing additional immunotherapy combinations, and further genetic engineering of organ-source pigs.²⁵ Moreover, both xenotransplants were performed on patients with suboptimal health conditions, disqualifying them from receiving an allograft. This questions whether these patients were ideal candidates for assessing the viability of xenotransplantation or if their cases represent disproportionately worsened outcomes.

FUTURE DIRECTIONS

Despite the reported promise of xenotransplantation in improving organ availability, there are several logistical limitations to consider prior to its implementation, as successful xenotransplants in the past have been isolated occurrences. Following fundamental research studies and individualized trials, it will be essential to run numerous clinical trials to explore the efficacy and potential repercussions of xenotransplantation on a more generalized population. These clinical trials will likely involve renal or heart xenotransplants in patients ineligible for other common treatments or an allograft.²⁶ Another issue is the transmission of xenozoonotic introducing complications in obtaining informed consent from patients. Due to the risk of xenozoonotic infection following transplantation, participants must agree to undergo life-long clinical evaluations, complicating participant

consent and becoming a contractual obligation.

Participants would be unable to rescind consent at any time due to the potential

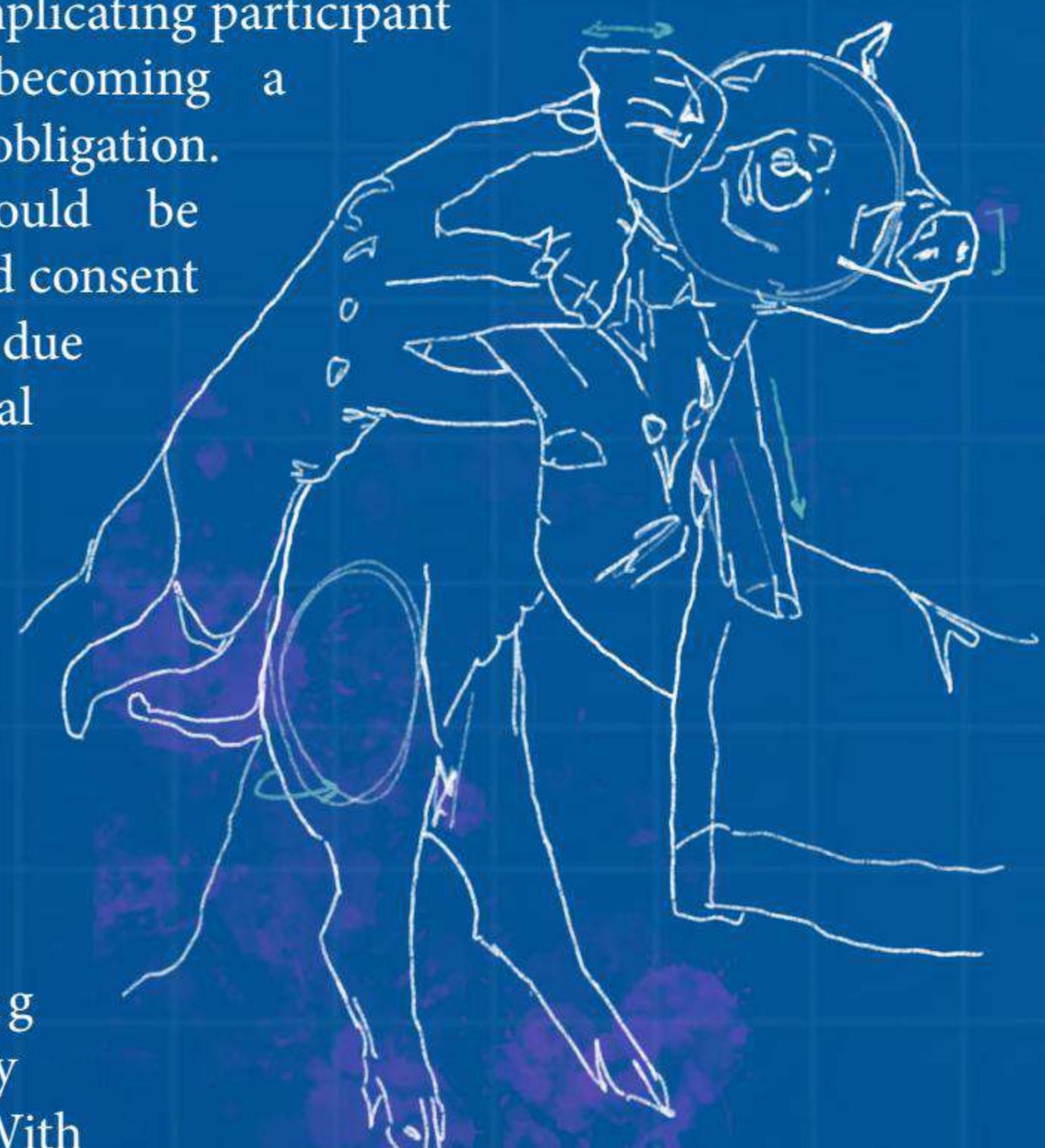
public health risk. It may also be necessary to monitor

the close contacts of the patient,

compromising confidentiality

and privacy. With

the highly limited scope



of past human cases, researchers and healthcare providers cannot accurately communicate all risks to participants, as some animals may carry undetected pathogens that were not readily observed during donor animal screening.²⁷ This poses an additional complication for informed consent, introducing ethical ambiguity into future studies. Future efforts should focus on addressing these complications and later developing a structured clinical trial that works to mitigate these factors.

CONCLUSION

While xenotransplantation shows potential as an allograft alternative in future years, previous cases resulting in premature deaths highlight limitations that must be addressed. The advancement of CRISPR-Cas9 genetic engineering has improved xenotransplant viability by allowing for the development of xenoantigen-knockout pigs to be used for organ donation. Research into past cases highlights potential areas of improvement and successful transplant methods, though the frequency of these cases is sparse. Furthermore, the public health risks related to xenotransplantation must be addressed prior to its mainstream clinical use. Although recent years have shown substantial developments, the clinical implementation of xenotransplantation lies beyond reach for the time being.

REVIEWED BY: DR. JIGISH KHAMAR (MD) AND STEPHEN JUVET (MD , PhD, FRCPC)

Dr. Jigish Khamar is a general surgery resident at McMaster University. His focus is on minimally invasive and upper gastrointestinal surgery. This piece was also reviewed anonymously by a nephrologist at The Children's Hospital of Eastern Ontario. Dr. Stephen Juvet is a respirologist and physician-scientist with the Toronto Lung Transplant Program.

EDITED BY: PARTH ARORA & EVAN ZHAO

INTERESTED IN LEARNING MORE ABOUT XENOTRANSPLANTATION?

Watch our video
“The first successful pig heart transplant”
using the QR code below!



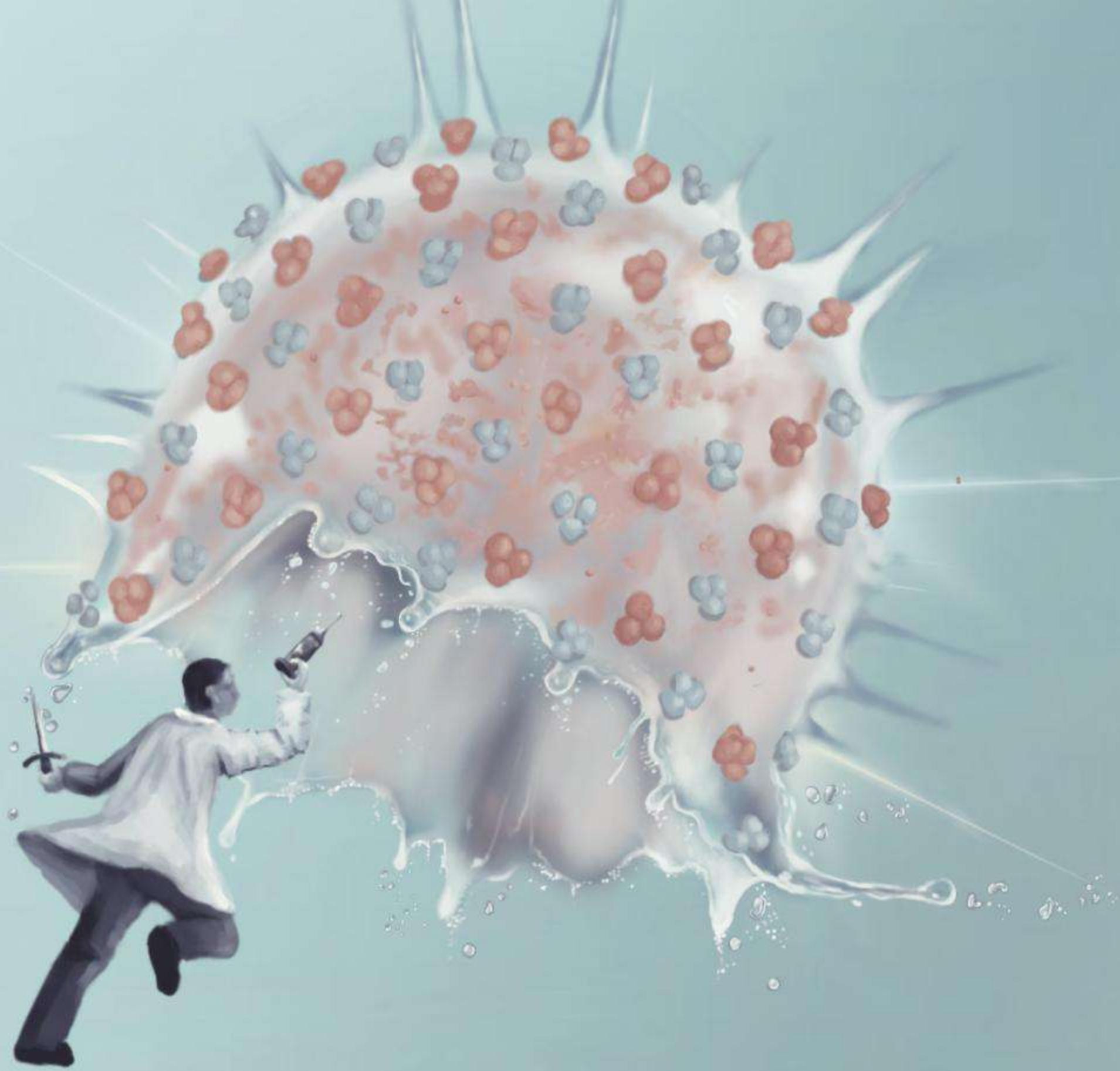
1. Nordham KD, Ninokawa S. The history of organ transplantation. *Proc (Bayl Univ Med Cent)*. 2022;35(1):124–8. Available from: doi:10.1080/08998280.2021.1985889.
2. Canadian Blood Services. Organs and tissues: System progress data reporting [Internet]. Available from: <https://professionaleducation.blood.ca/en/organs-and-tissues/reports/system-progress-data-reporting> [cited 2024 Nov 6].
3. Government of Canada. Organ and tissue donation [Internet]. Available from: <https://www.canada.ca/en/health-canada/services/healthy-living/blood-organ-tissue-donation/organ-tissue.html> [cited 2024 Dec 19].
4. Cooper DKC. A brief history of cross-species organ transplantation. *Proc (Bayl Univ Med Cent)*. 2012;25(1):49–57. Available from: doi:10.1080/08998280.2012.11928783.
5. Reentsma K. Xenotransplantation: A historical perspective. *ILAR J*. 1995;37(1):9–12. Available from: doi:10.1093/ilar.37.1.9.
6. Stevens RB, Platt JL. The pathogenesis of hyperacute xenograft rejection. *AJKD*. 1992;20(4):414–21. Available from: doi:10.1016/S0272-6386(12)70310-4.
7. Platt JL. Xenotransplantation. Berlin, Heidelberg: Springer, Berlin, Heidelberg; 1997. 8–16 p.
8. Bradley JA, Hamilton DNH. *Transplantation Surgery*. London: Springer, London; 2001. 1–21 p.
9. Knowledge Project. Non-human primates, retroviruses, and zoonotic infection risks in the human population [Internet]. 2012. Available from: <https://www.nature.com/scitable/knowledge/library/non-human-primates-retroviruses-and-zoonotic-infection-59119998/> [cited 2025 Jan 27].
10. Rollin BE. Ethical and societal issues occasioned by xenotransplantation. *Animals (Basel)*. 2020;10(9):1695. Available from: doi:10.3390/ani10091695.
11. Estrada JL, Martens G, Li P, Adams A, Newell KA, Ford ML, et al. Evaluation of human and non-human primate antibody binding to pig cells lacking GGTA1/CMAH/B4GALNT2 genes. *Xenotransplantation*. 2015;22(3):194–202. Available from: doi:10.1111/xen.12161.
12. Eisenson DL, Hisadome Y, Yamada K. Progress in xenotransplantation: Immunologic barriers, advances in gene editing, and successful tolerance induction strategies in pig-to-primate transplantation. *Front Immunol*. 2022;13. Available from: doi:10.3389/fimmu.2022.899657.
13. Cooper DK, Ekser B, Ramsoondar J, Phelps C, Ayares D. The role of genetically engineered pigs in xenotransplantation research. *J Pathol*. 2016;238(2):288–99. Available from: doi:10.1002/path.4635.
14. Lutz AJ, Li P, Estrada JL, Sidner RA, Chihara RK, Downey SM, et al. Double knockout pigs deficient in N-glycolylneuraminc acid and galactose β -1,3-galactose reduce the humoral barrier to xenotransplantation. *Xenotransplantation*. 2013;20(1):27–35. Available from: doi:10.1111/xen.12019.
15. Byrne G, Ahmad B, Villiers S, Du Z, McGregor C. B4GALNT2 and xenotransplantation: A newly appreciated xenogeneic antigen. *Xenotransplantation*. 2018;25(5). Available from: doi:10.1111/xen.12394.
16. Chan JCY, Chaban R, Chang SH, Angel LF, Montgomery RA, Pierson RN. Future of lung transplantation. *Clin Chest Med*. 2023;44(1):201–14. Available from: doi:10.1016/j.ccm.2022.11.003.
17. Denner J. Monitoring for PERV following xenotransplantation. *Transplant International*. 2024;37. Available from: doi:10.3389/ti.2024.13491.
18. Yang L, Güell M, Niu D, George H, Lesha E, Grishin D, et al. Genome-wide inactivation of porcine endogenous retroviruses (PERVs). *Science*. 2015;350(6264):1101–4. Available from: doi:10.1126/science.aad119.
19. Ryczek N, Hryhorowicz M, Zeyland J, Lipiński D, Stomski R. CRISPR/Cas technology in pig-to-human xenotransplantation research. *Int J Mol Sci*. 2021;22(6):3196. Available from: doi:10.3390/ijms22063196.
20. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, et al. Genetically modified porcine-to-human cardiac xenotransplantation. *NEJM*. 2022;387. Available from: doi:10.1056/nejmoa2201422.
21. Kuehn BM. First pig-to-human heart transplant marks a milestone in xenotransplantation. *Circulation*. 2022;145:1870–1. Available from: doi:10.1161/circulationaha.122.060418.
22. Mueller NJ, Kuwaki K, Dor FJMF, Knosalla C, Gollackner B, Wilkinson RA, et al. Reduction of consumptive coagulopathy using porcine cytomegalovirus-free cardiac porcine grafts in pig-to-primate xenotransplantation. *Transplantation*. 2004;78(10):1449–53. Available from: doi:10.1097/01.TP.0000141361.68446.1F.
23. Mohiuddin MM, Singh AK, Corcoran PC, Thomas III ML, Clark T, Lewis BG, et al. Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO-hCD46.hTBM pig-to-primate cardiac xenograft. *Nat Com*. 2016;7(1). Available from: doi:10.1038/ncomms11138.
24. Griffith BP, Grazioli A, Singh AK, Tully A, Galindo J, Saharia KK, et al. Transplantation of a genetically modified porcine heart into a live human. *Nat Med*. 2025. Available from: doi:10.1038/s41591-024-03429-1.
25. Habibabady Z, McGrath G, Kinoshita K, Maenaka A, Ikechukwu I, Elias GF, et al. Antibody β -mediated rejection in xenotransplantation: Can it be prevented or reversed? *Xenotransplantation*. 2023;30. Available from: doi:10.1111/xen.12816.
26. Hawthorne WJ, Thomas A, Pierson RN. Ethics and theoretical issues in kidney xenotransplantation. *Semin Nephrol*. 2022;42(4):151288. Available from: doi:10.1016/j.semnephrol.2022.151288.
27. Daar AS. Ethics of xenotransplantation: Animal issues, consent, and likely transformation of transplant ethics. *World J Surg*. 1997;21(9):975–82. Available from: doi:10.1007/s002689900336.



MEASLES

doi: 10.35493/medu.47.14

AUTHORS:

DAVID GOU¹, JIA LU², & MATTHEW OLEJARZ¹¹Bachelor of Health Sciences (Honours), Class of 2026, McMaster University²Bachelor of Health Sciences (Honours), Class of 2027, McMaster UniversityARTIST:
ALEEYA LI¹

INTRODUCTION

Measles is a highly contagious viral infection caused by the measles virus (MV), a negative-sense RNA virus which belongs to the *Morbillivirus* genus of the *Paramyxoviridae* family.^{1,2} Although MV likely evolved from a domesticated cattle virus, it has become a uniquely human pathogen, emerging from the rise of densely populated cities.²⁻⁴ Measles is characterized by a prodromal phase followed by a characteristic rash.^{5,6} Adults tend to experience a more severe course of infection than children, with common complications including pneumonia and acute encephalitis.⁷ Despite the availability of a safe and effective vaccine, measles remains a critical public health concern, particularly in regions with low vaccine availability and declining vaccination rates.⁸

PATHOGENESIS

The pathogenesis of measles begins with the entry of MV into the host, which is primarily transmitted through airborne particles in the respiratory tract. Based on in vivo studies, MV likely targets alveolar macrophages and dendritic cells (DC) in the lungs and respiratory submucosa.⁹ MV binds to the signaling lymphocyte activation molecule family member 1 (CD150, also known as SLAMF1) surface receptors found on macrophages and DCs, although they can also bind to the nectin cell adhesion molecule 4 (nectin-4, also known as PVRL4) receptors, more commonly expressed by epithelial cells.⁹ Another potential point of MV entry is the infection of myeloid and lymphoid cells in the conjunctiva.⁹ Regardless of the entry route, MV-infected immune cells migrate to tertiary lymphoid tissues, allowing for further propagation of the virus.⁹

Owing to their high quantity of CD150⁺ lymphocytes (primarily B-cells and memory CD4⁺ and CD8⁺ T-cells), lymphoid tissues are principal sites for MV replication.⁹ Subsequently, cell-to-cell mechanisms allow lymphocytes and dendritic cells to transmit MV to neighbouring nectin-4⁺ epithelial cells and keratinocytes.^{11,12} Through this mechanism, the virus mainly spreads through the circulatory system to the gastrointestinal tract, kidney, liver, and skin, although endothelial cells, neurons, astrocytes, and oligodendrocytes may also be infected.⁹ In these organs and tissues, MV

infection stimulates the activation of several antigens, permitting the adherence of infected migrating cells to local endothelial cells and enabling transmission of the virus into these tissues.^{13,14}

The initial incubation period of MV is typically 11 to 12 days, followed by prodromal symptoms (those that occur prior to rash onset), including high fever, cough, runny nose, and conjunctivitis.⁶ However, symptoms can appear anytime between 7 to 21 days following infection.¹⁵ Two to four days after symptom onset, the characteristic maculopapular rash appears on the head and face and spreads to the trunk and limbs, lasting five to six days.⁶ The rash is likely caused by the host's immune response to the infection of dermal endothelial cells and keratinocytes.⁹

Due to the widespread infection of immune cells, measles causes profound immune suppression, which increases the risk of opportunistic infections, especially in children.¹⁸ Immunosuppression may last years and contributes to susceptibility to tuberculosis and other infections. MV infection initially causes a notable decrease in circulating and resident T- and B-cells and rapidly exhausts B-cells in germinal centers.⁹ This is especially impactful in tertiary bronchus-associated lymphoid tissue and gut-associated lymphoid tissues, which typically increase protective immunity against mucosal pathogens.⁹ Destruction of these sites can facilitate the infiltration of existing pathogens.

Long-term complications as a result of measles are rare but can occur upon infection of the central nervous system (CNS). Acute disseminated encephalomyelitis occurs in 0.1% of measles cases, where demyelination leads to ataxia (poor coordination of movements), sensory loss, changes in mental status, and potential death.¹⁹ Measles inclusion body encephalitis (MIBE) most frequently occurs in patients with preexisting immunodeficiencies and has a mortality rate of 75%.²⁰ MIBE often causes altered consciousness and seizures, leading to epilepsy, aphasia, hemiplegia, and ataxia.²¹ An extremely rare neurological complication of measles is subacute sclerosing panencephalitis, which presents as progressive mental deterioration, affecting scholastic performance and behaviour, eventually leading to myoclonic seizures, ataxia, and death.^{9,22}

DIAGNOSIS

The first detectable symptom of measles is a high, long-lasting fever and can be accompanied by a cough, runny nose, watery eyes, and rash.²³ Measles can also be diagnosed through serologic testing and RNA detection via PCR of respiratory specimens or urine.^{24,25}

A clinician may recommend a serologic test involving a detection assay trying to identify specific IgM antibodies in the serum. A more robust testing method for the measles virus is via PCR.²⁶ The specimen can either be collected with a nasopharyngeal/throat swab or a urine sample. Genetic analysis can provide significant contextual information in diagnosis and the course of the disease, including identification of the strain or source of the infection.

VACCINATION

Based on the recommendations provided by the U.S. Centers for Disease Control and Prevention, the measles vaccine is administered alongside immunizations for mumps and rubella, together forming the measles, mumps and rubella vaccine (MMR).²⁸ In Canada, it is typically advised that vaccinations are completed during childhood, with one dose given at 12-15 months, and another given at 3-5 years. The measles vaccine incorporates an attenuated form of the virus creating a dampened version of the infection with few, if any of the effects, although it may cause severe disease in immunocompromised children. This results in the vaccine being 93% effective after the first dose, and 97% effective after the second.²⁹ Despite the effectiveness of the measles vaccine, not all individuals are eligible to receive such a treatment. Allergies, pregnancy, immunocompromise, susceptibility to bleeding and bruising, and active TB infection are contraindications to receiving the MMR vaccine.²⁸

EPIDEMIOLOGY

Measles has an approximate R_0 (average number of incident secondary cases produced by one case in a completely susceptible population) of 12 to 18, which is high compared to other viruses such as seasonal influenza (1.2–1.4) and COVID-19 (2.8–3.8).^{30–32} Notably, there have been some rare documented cases of a single patient infecting over 200 others in superspreading events.³³

The highly contagious nature of MV can be attributed to multiple factors. Tracheobronchial epithelial cells are susceptible to MV infection, allowing viral particles to ascend to the upper respiratory tract via mucociliary escalation, followed by subsequent discharge by coughing.³⁴ Additionally, MV particles may survive in the air or on surfaces for a few hours, particularly when found in larger droplets.⁹ Infected patients shed large quantities of viral particles, with only 0.2 viral particles necessary for transmission.⁹ For these reasons, measles is one of the most infectious diseases in the world with a secondary attack rate of 90%.^{28,35,36} Before the development of the measles vaccine, 10,000 to 90,000 cases of measles were reported annually in Canada.³⁷ However, after the implementation of the single-dose, and later double-dose, routine MMR combination vaccine, the incidence of measles declined by 99% since the 1970s.

The elimination of infectious disease within the context of measles is signified by the absence of endemic measles transmission in a defined geographic area for at least 12 months, under the inspection of a high-quality surveillance system.³⁸ Although Canada eliminated endemic measles transmission in 1998, outbreaks continue to occur mostly as a result of international travel.³⁷ Since the onset of the COVID-19 pandemic, routine vaccination in children has steadily declined, mounting concerns regarding the risk of vaccine-preventable disease

resurgence. In 2-year-old Canadian children, the coverage for one dose of the MMR vaccine decreased from 89.5% in 2019 to 82.5% in 2023.³⁹ To achieve herd immunity for measles, childhood MMR vaccine coverage rates should be as high as 95%.⁴⁰ The impact of this reduction in routine vaccinations on prevention and control of measles is emphasized by the large outbreaks occurring in early 2024, in which 77 cases were reported compared to 12 and 3 cases in 2023 and 2022, respectively.⁴¹

GLOBAL IMPLICATIONS

Despite progress in increasing the measles vaccination coverage, barriers including inequalities in access to vaccines and vaccine hesitancy obstruct the disease's eradication. From 2022 to 2023, estimated measles cases increased by 20% and the number of countries experiencing disruptive outbreaks surged from 36 to 57. Most outbreaks occurred in African, Eastern Mediterranean, and European regions. The distribution of the increased number of cases and outbreaks across more countries with lower measles fatality rates resulted in an 8% decrease in estimated measles deaths from 2022 to 2023. An approach developed by the Pan American Health Organization involves implementing mass immunization campaigns that deliver the measles-containing vaccine to individuals in a specific age group to fill population immunity gaps cost-effectively.⁴²

A loss of public confidence in vaccination is also a major obstruction to measles elimination. According to a retrospective cohort study conducted by Feikin et al., children exempt from measles vaccination on the basis of religious or personal beliefs were 22 times more likely to be infected. Furthermore, at least 11% of vaccinated children in measles outbreaks were infected through contact with a child exempt from vaccination.⁴³ Moreover, the publication of a biased, now-retracted, report positing an association between the MMR vaccine and autism has led to diminished uptake of the MMR vaccine in the United Kingdom, correlating with more frequent measles outbreaks.^{44,45} To combat vaccine refusal, policies proven to increase vaccine acceptance and evidence-based communication are needed.⁴⁶

CONCLUSION

Despite the elimination of endemic disease in Canada through effective vaccination, measles eradication continues to present a challenge due to barriers such as unequal vaccine access, vaccine hesitancy, and incomplete vaccination of children. Strategies are required to control this vaccine-preventable disease worldwide.

REVIEWED BY: DR. MAREK SMIEJA (MD PhD FRCPC)

Dr. Marek Smieja (MD PhD FRCPC) is a Professor at McMaster University, a medical microbiologist and infectious diseases physician. He is a clinician, educator, and researcher with an interest in improving diagnostic testing for respiratory and gastrointestinal infections.

EDITED BY: ZAHRA TAUSEEF & EMILY WANG



Breaking Barriers: Exploring Zosurabalin in Carbapenem-Resistant *Acinetobacter baumannii* Treatment

ARTIST:
FIONA DUYU¹

¹Bachelor of Science (Honours Integrated Science), Class of 2027, McMaster University

doi: 10.35493/medu.47.16

AUTHORS:**CYNTHIA DUAN² & ARVAN KAYAL³**²Bachelor of Health Sciences (Honours), Class of 2027, McMaster University³Bachelor of Health Sciences (Honours Biochemistry), Class of 2027, McMaster University**ABSTRACT**

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is a significant threat within the growing global concern over multidrug-resistant bacteria due to its resistance to most antibiotics and associated high mortality rates. To address this issue, a promising lead compound, Zosurabalin (ZAB), has emerged from the macrocyclic peptide antibiotic class. ZAB targets the lipopolysaccharide (LPS) transport system by inhibiting the function of the LptB₂FGC complex which causes internal LPS to reach toxic levels that induce cell death. ZAB overcomes traditional resistance mechanisms and achieves high specificity against *Acinetobacter baumannii* (*A. baumannii*) by exclusively targeting the CRAB-specific variation of the LptB₂FGC complex, minimizing damage to the gut microbiome. Moreover, Phase I clinical trials demonstrate a strong safety profile unlike current therapeutics that generally have unfavourable side effects. Despite its promise, ZAB faces several challenges, including inevitable antibiotic resistance, high development costs, and limited accessibility in low-income countries. Thus, further research and considerations are needed before ZAB can be approved.

INTRODUCTION

Over the past few decades, multi-drug resistant (MDR) bacteria have emerged as one of the most pressing global health threats, with a growing number of resistant bacterial strains and infected individuals, increasing from roughly 2 million per year in the United States in 2013 to over 2.8 million per year in 2019.^{1,2} Drug resistance in Gram-negative bacteria (GNB) is particularly concerning due to its association with high mortality rates. In a study of 4,437 patients with MDR infections, 26.9% of patients with Gram-negative MDR infections died, compared to only 16.0% of patients with Gram-positive MDR infections.³ In other studies, high levels of multi-drug resistance were found in several GNB, including *A. baumannii* (97.8%), *Pseudomonas aeruginosa* (65.0%), and *Klebsiella pneumoniae* (50.0%).⁴ These bacteria were resistant to common GNB antibiotics, such as fluoroquinolones, β-lactams, and carbapenems.⁴

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) is one such GNB that demonstrates a rapid accumulation of antibiotic resistance mechanisms. Some strains are resistant to all available antibiotic options.^{7,8} This has resulted in increased mortality rates for CRAB infections, with some estimates as high as 50%.⁹ As such, the Center for Disease Control and Prevention has classified CRAB as an “urgent public health threat,” while the World Health Organization has declared antibiotic development for this bacteria to be a “critical priority.”^{8,10}

Thus, the development of macrocyclic peptides (MCPs), which

differ in structure and function from current antibiotics, marks a significant advancement in the fight against CRAB; MCPs could introduce the first new antibiotic class for GNB to the market since the 1970s.^{7,11} Among these, Zosurabalin (ZAB) stands out as one of the most promising candidates for combating CRAB. Identified through whole-cell phenotypic screening of nearly 45,000 MCPs from Tranzyme Pharma, ZAB features a tripeptide subunit and a diphenylsulfide tether that closes the ring, employing zwitterions—molecules with both positive and negative charges—to effectively tether the MCPs.⁷ This review aims to analyze the development of ZAB by examining associated advantages, challenges, and broader implications in the healthcare field.

MECHANISM OF ACTION

The outer envelope of GNB, which consists of the inner membrane, periplasm, and outer membrane, is essential for bacterial protection.¹² A key component of this structure are LPSs, which are glycolipids synthesized near the inner membrane that move and adhere to the exterior of the outer membrane.¹³ LPSs contribute significantly to antibiotic resistance in many GNB by establishing selective permeability of the outer membrane to prevent the entry of various antibiotics. Moreover, LPSs are essential to the survival of almost all GNB, making it an attractive target in antibiotic development compared to conventional inner membrane targets.¹³

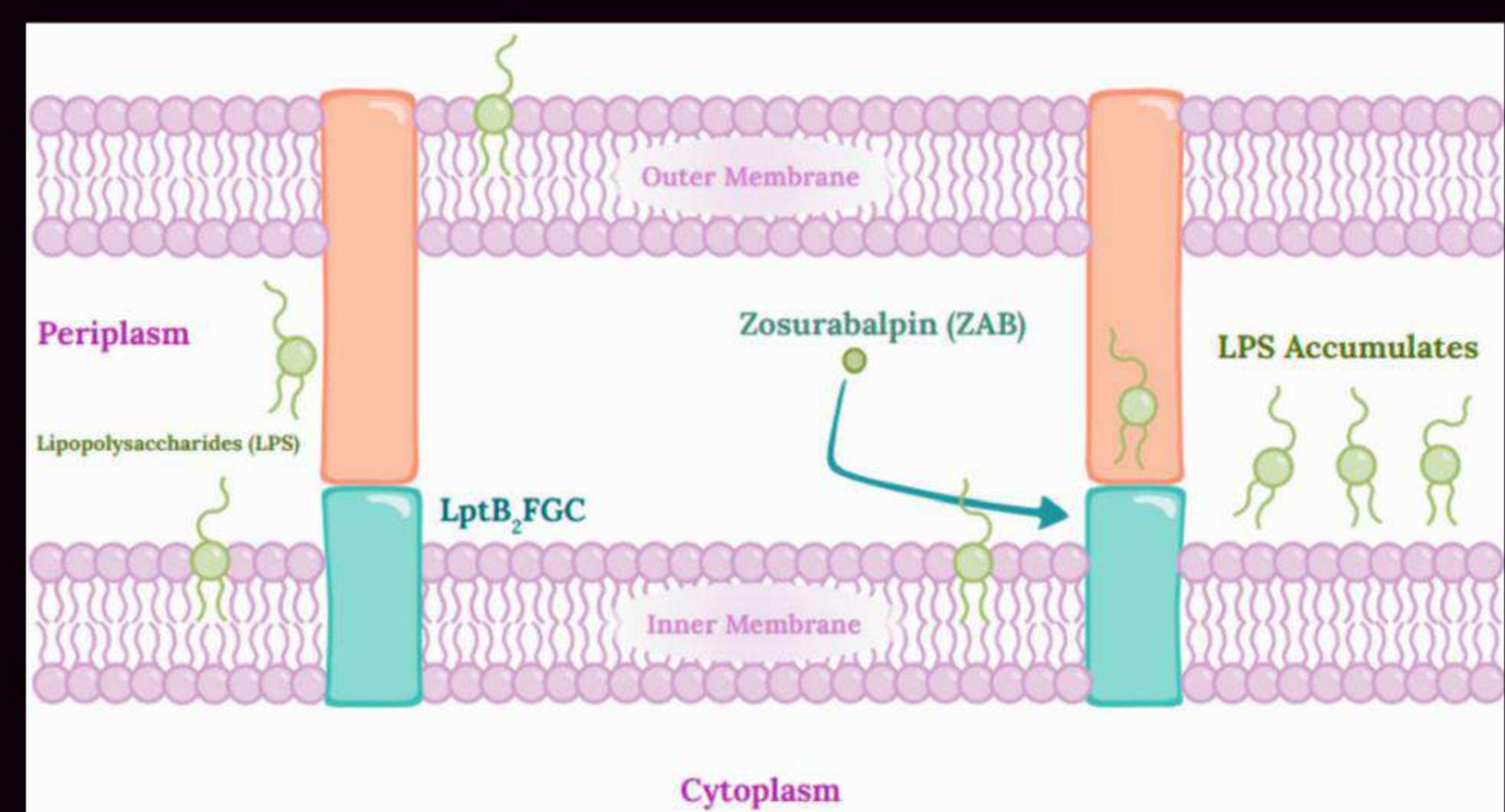


Figure 1. LptB₂FGC, located between the inner and outer membrane, is a protein responsible for LPS transportation across the inner and outer bacterial membranes. ZAB inhibits the LPS transport mechanism and causes LPS to accumulate, leading to cytotoxicity and cell death.

ZAB inhibits the LptB₂FGC complex, which is responsible for generating the energy required to transport LPSs through the periplasm.^{7,13} Specifically, ZAB interacts with a binding site made up of a LPS and its transporter, trapping LPSs inside the cell, causing toxic accumulation and inducing cell death.^{7,14}

ADVANTAGES OF ZOSURABALPIN

Roughly 75% of existing antibiotics originate from natural sources, which presents challenges when producing them at large scales.^{15,16} In contrast, ZAB is a synthetic molecule, suggesting relative ease and efficiency in bulk production. The synthetic nature of ZAB also allows for chemical modification and adaptability, circumventing potential resistance issues in the future. As such, ZAB is a flexible and scalable option for antibiotic development.⁷

ZAB also showed favourable results in studies that observed its effects on CRAB-induced lung and thigh infections as well as sepsis in various mouse models. The study found that the minimum inhibitory concentration for ZAB in which 90% of bacterial strains were inhibited was 1 mg/L, highlighting its potency.⁷ In two Phase I clinical trials, single intravenous ZAB doses of 10 to 200 mg were effective and generally well-tolerated amongst 64 healthy patients. While some instances of adverse effects were reported, with infusion-related reactions (IRRs) being the most common and occurring in 9 patients, they were reversible and of mild to moderate severity. Furthermore, administration of the drug did not induce any clinically significant changes on vital signs, ECGs, and other laboratory tests compared to placebo trials, demonstrating the strong safety profile of ZAB. Phase II human clinical trials are being initiated to develop this drug as a treatment option for invasive CRAB infections.¹⁷

Finally, LPSs are found almost exclusively in the outer membrane of GNB. Studies testing the efficacy of ZAB on non-CRAB bacteria have shown differences between the LptF helices and LPS binding positions, rendering it ineffective and allowing it to avoid targeting other GNB in addition to Gram-positive bacteria.¹⁸ ZAB's high specificity for CRAB prevents it from disrupting healthy gut microbiota, a common complication with most broad-spectrum antibiotics.¹⁹ Thus, developing more bacteria-specific antibiotics may improve the precision of diagnosis and treatment in clinical settings.¹⁹

LIMITATIONS OF ZOSURABALPIN

Antibiotics targeting single cellular mechanisms like ZAB are more vulnerable to resistance-forming point mutations. Mutations of the LptB2FGC genes can drastically reduce ZAB's bacteria-killing efficiency. In one case, a single-nucleotide mutation in the LptB2FGC gene resulted in a greater than 256-fold decrease in antibiotic activity.⁹ There is also increasing concern regarding the potential development of macrocyclic-degrading enzymes, which could lead to antibiotic resistance against MCPs like ZAB.²⁰ To mitigate this issue, combined therapy with two active agents has been recommended to treat CRAB infections, increasing the genetic barrier to resistance and slowing the development of resistance mechanisms.²¹ However, the benefits of ZAB administration in conjunction with other medications have not yet been demonstrated. Determining the mechanisms through which CRAB and other strains of *A.*

baumannii could develop resistance against ZAB could help create strategies to prevent and reduce related drug resistance.¹⁹

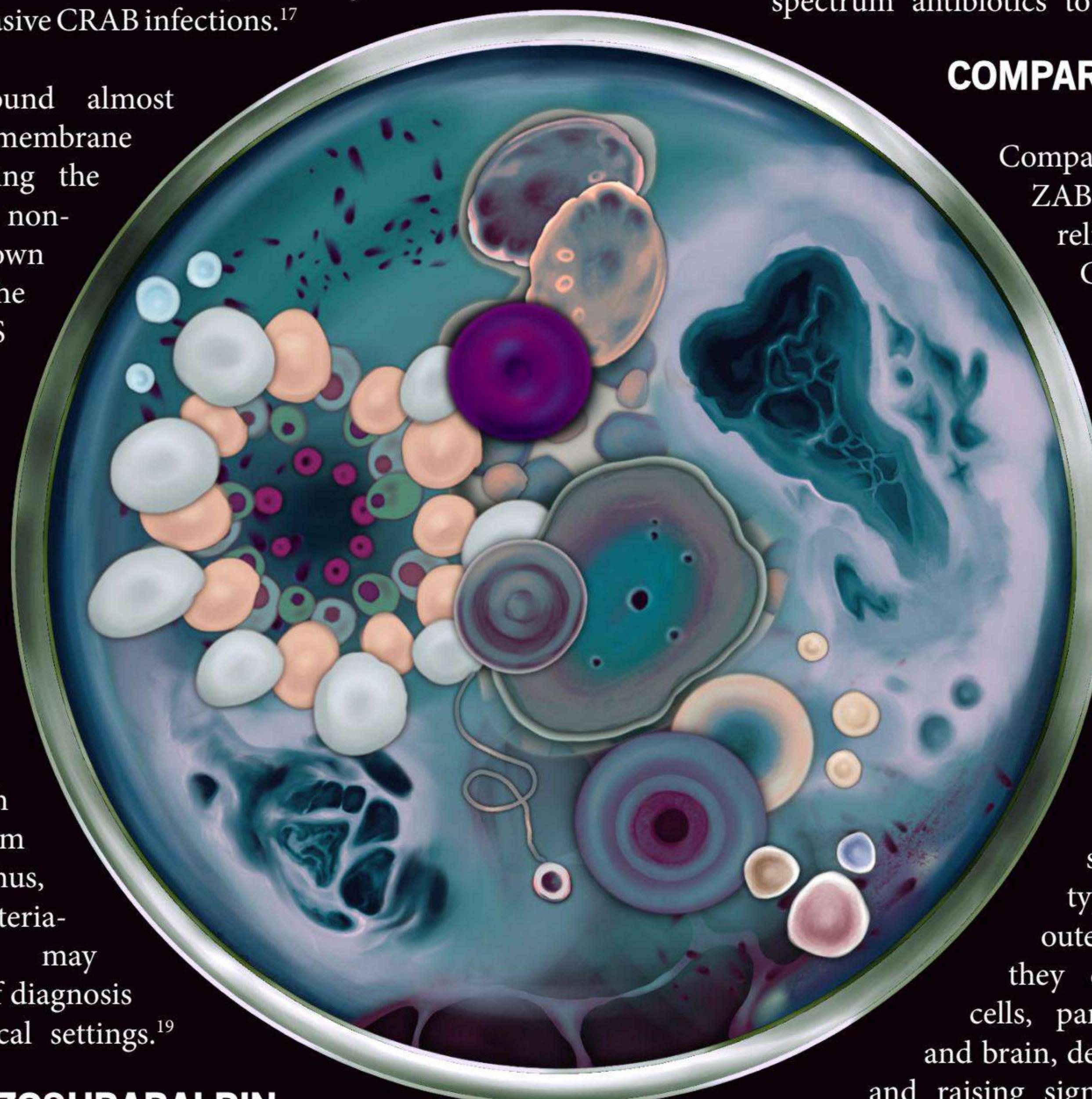
Developing new antibiotics that target a singular species can be costly and inefficient.²² While the potential for high specificity can be appealing, narrow-spectrum antibiotics, like ZAB, pose several challenges in clinical settings, particularly in low- and middle-income countries (LMICs).²³ These antibiotics require accurate species identification prior to treatment, being both expensive and time-consuming in LMICs, where pathogen identification is limited.^{23,24} Furthermore, this additional requirement for accurate identification may increase the burden on already overwhelmed healthcare systems, emphasizing the need for the clinical implementation of narrow-spectrum antibiotics to be carefully evaluated.²³

COMPARISON TO EXISTING ANTIBIOTICS

Compared to existing antibiotics, ZAB prioritizes safety and reliability when combatting CRAB infections. For example, the current primary treatment for CRAB is combination therapy between polymyxin E and other antimicrobial agents like tigecycline.²⁵ Polymyxin E, considered a last-resort antibiotic for MDR GNB, binds to LPS and disrupts the outer membrane, making the bacteria susceptible to antibiotics typically repelled by the outer membrane. However, they can also attack human cells, particularly in the kidney and brain, demonstrating their toxicity and raising significant safety concerns.¹³

β -lactams, another antibiotic commonly used against GNB, works by inhibiting transpeptidase, an enzyme that plays a crucial role in peptidoglycan synthesis.²⁶ The nature of this mechanism allows it to target bacterial cells. However, prolonged use of β -lactams has led to the development of β -lactam-resistant CRAB strains, diminishing its effectiveness and requiring more advanced combination therapies or higher dosages.²⁵

Many other antibiotics used in combination therapies to treat CRAB demonstrate high toxicity or limited effectiveness due to antibiotic resistance.²⁵ Thus, there is a pressing need for antibiotics with novel mechanisms of action that have not yet been targeted by resistance strategies while simultaneously maintaining a favourable safety profile-criteria, which ZAB fulfills.

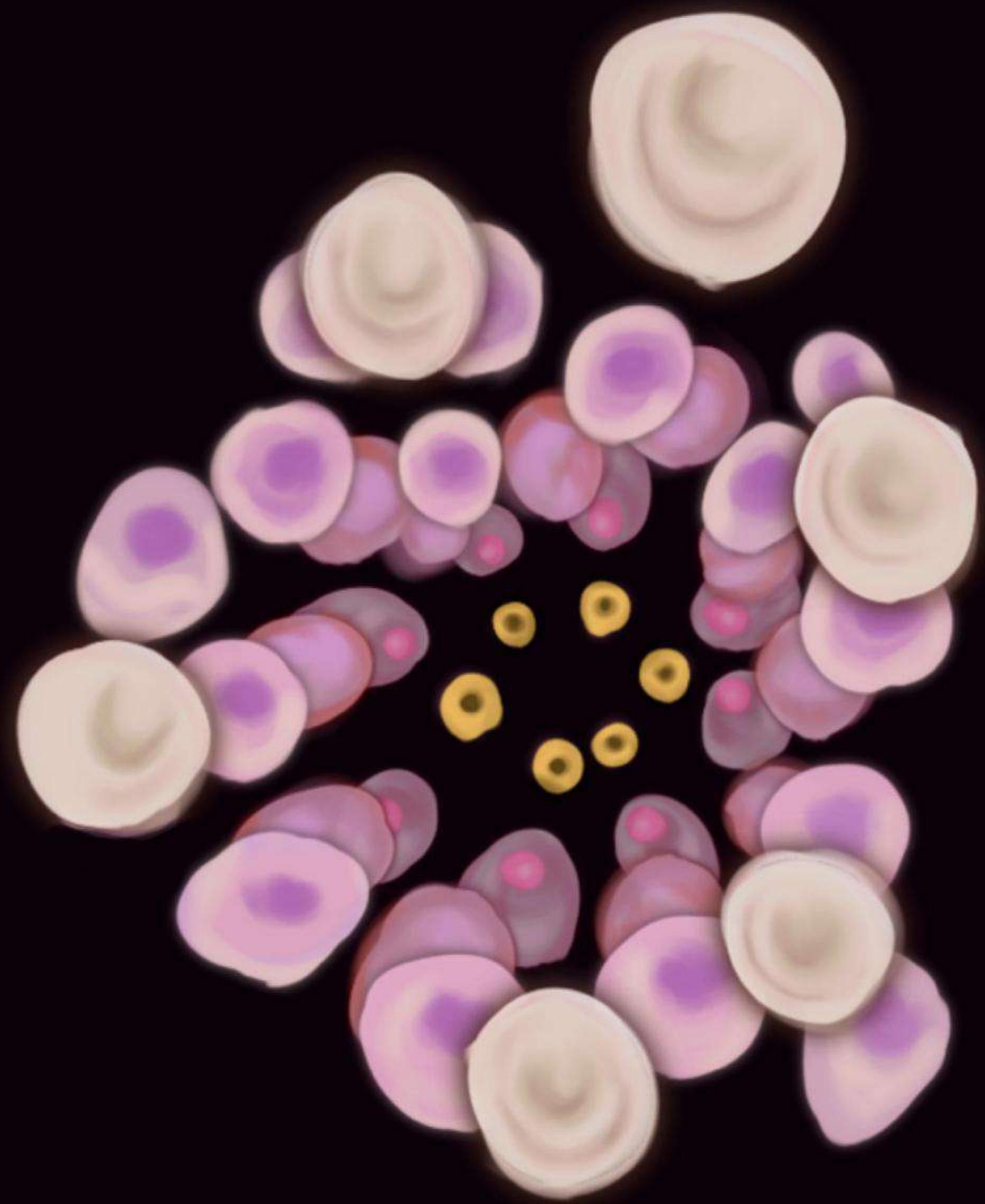


IMPACT ON HEALTHCARE FIELD

Previous attempts to target the LPS system in clinical settings were hindered by drug delivery challenges, such as host toxicity and inadequate intracellular penetration, as well as reduced antibacterial efficacy.¹³ However, the discovery of ZAB has reinvigorated the LptB2FGC complex as a promising target for antibiotic development. This is driven not only by ZAB's efficacy against CRAB, but also by the widespread prevalence of the LPS transport system in GNB.^{9,13} Targeting this system offers a compelling strategy for combating hard-to-treat pathogens, including various MDR-GNB.¹³ As such, further exploration of the components in the LPS transport system across various bacteria could assist in developing other therapeutics modelled after ZAB. Moreover, the development of ZAB could promote the use of macrocycles and peptides in antibiotic discovery, offering a distinct advantage over small molecules, which are often ineffective against certain protein targets.^{26,27} This shift could broaden the scope of druggable targets, opening new avenues for innovative therapeutic approaches across the field of medicine.

CONCLUSION

With the significant health risk posed by CRAB, ZAB offers a promising solution through its unique mechanism of targeting the LPS transport system.⁷ In addition to bypassing common resistance mechanisms, Phase I clinical trials demonstrate ZAB's strong safety profile, showcasing its potential as a therapeutic with advantages over existing antibiotics.¹⁷ However, challenges such as its high cost and the potential emergence of new resistance mechanisms still remain, indicating the need for further research and considerations during drug development.^{20, 24} Despite these limitations, ZAB serves as a groundbreaking advancement in the fight against MDR bacteria.



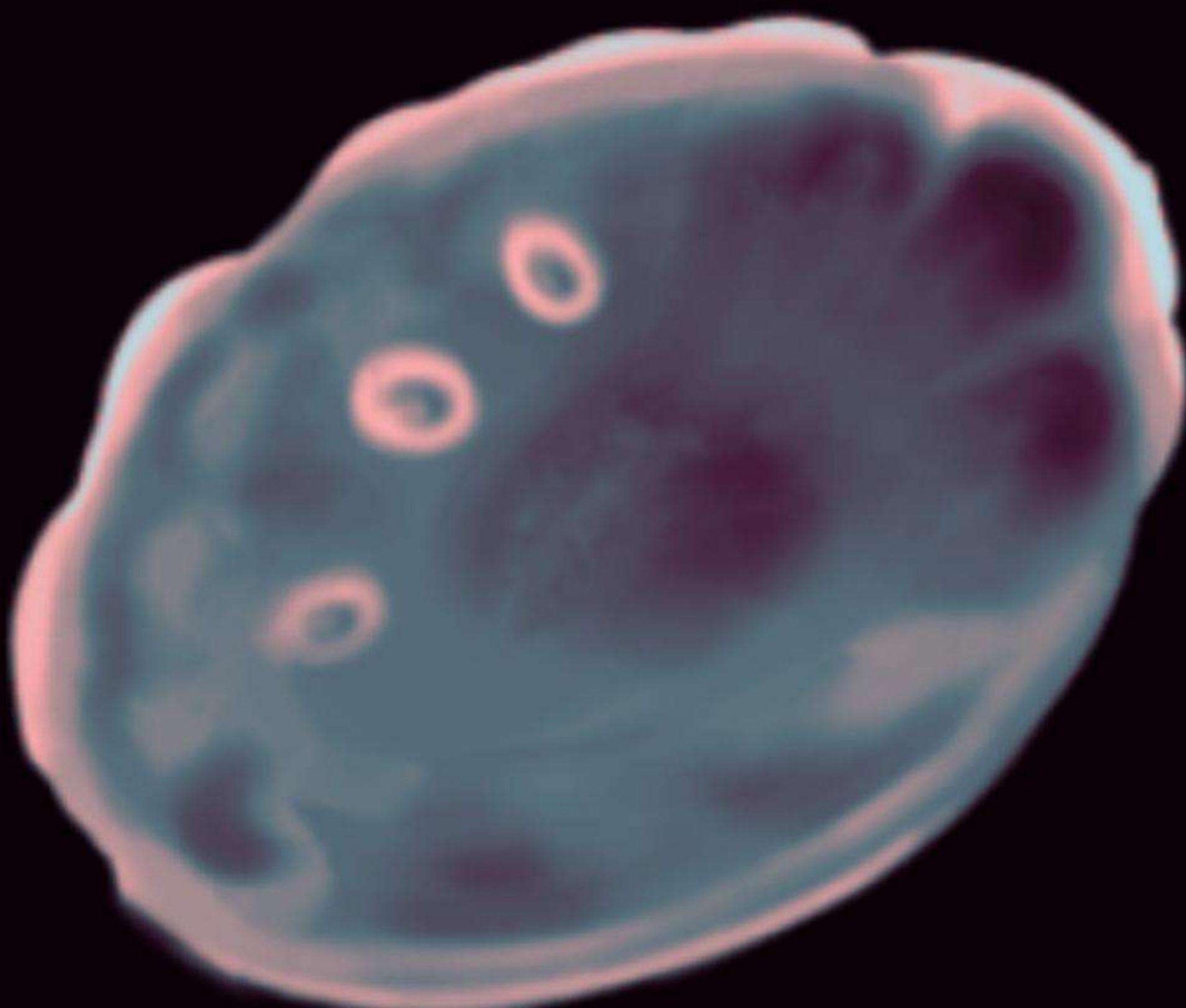
REVIEWED BY:

MANUPREET KAUR (PhD) & JEREMIE ALEXANDER

Manupreet Kaur (PhD) is a postdoctoral fellow in the Wright Lab at McMaster University. She received her PhD from the Academy of Scientific and Innovative Research, India. Her work investigates utilizing novel antimicrobial compounds to work against multidrug-resistant Gram-negative bacteria.

Jeremie Alexander is completing his PhD in the Stokes Lab at McMaster University. His research involves leveraging generative AI models to inform and accelerate drug antibiotic development.

EDITED BY: ZAHRA TAUSEEF & EMILY WANG



Abstract

Integrating Rhosin, Methotrexate, and Focused Ultrasound for Targeted Therapy of Glioblastoma Multiforme

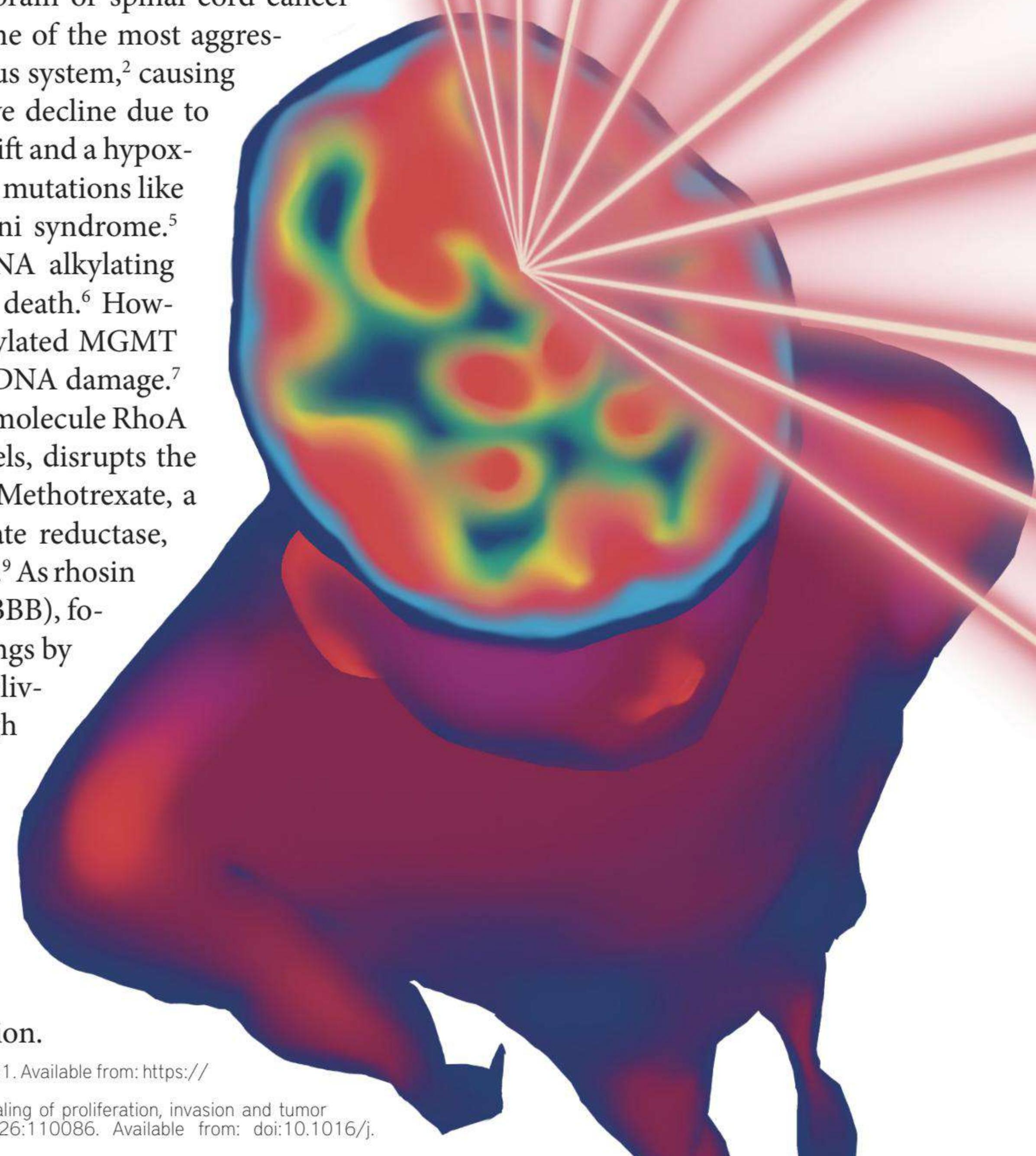
AUTHORS:

DHUSHAN KIRITHARAN¹, SETH (ZE LONG) XUE¹, MARYAM KHATIB¹

¹Bachelor of Engineering & Biomedical Engineering, Class of 2028, McMaster University

Approximately 3,300 Canadians were diagnosed with brain or spinal cord cancer in 2024, with glioblastoma multiforme (GBM) being one of the most aggressive forms.¹ GBM targets astrocytes in the central nervous system,² causing symptoms like nausea, vision impairment, and cognitive decline due to intracranial pressure.³ Imaging often reveals a midline shift and a hypoxic tumour environment.⁴ GBM's progression is driven by mutations like EGFR and TERT, along with disorders like Li-Fraumeni syndrome.⁵ Treatment for GBM has involved temozolomide, a DNA alkylating agent that methylates nucleotides, causing tumour cell death.⁶ However, more than 50% of GBM tumours express unmethylated MGMT promoters capable of reversing temozolomide-induced DNA damage.⁷ A multifaceted approach may be the key. Rhosin, a small molecule RhoA inhibitor that reduces metastases in breast cancer models, disrupts the RhoA/YAP pathway, reducing tumour aggressiveness.⁸ Methotrexate, a chemotherapy alternative to TMZ, inhibits dihydrofolate reductase, blocking DNA and RNA synthesis to slow tumour growth.⁹ As rhosin and methotrexate cannot cross the blood-brain barrier (BBB), focused ultrasounds can create temporary, localized openings by oscillating lipid-encased gas particles, permitting drug delivery.¹⁰ Although there is a risk of damaging the BBB through the microbubble oscillations, they are diminished due to existing edema, which already compromises the BBB.¹¹ While this approach offers hope, ethical and safety concerns remain due to the potential off-target effects of rhosin and the need for further clinical testing. Informed consent and striving for cost-effective methods, equitable access, and careful patent consideration are essential in future research and implementation.

1. Lee S. Brain and spinal cord cancer statistics [Internet]. Canadian Cancer Society. 2021. Available from: <https://cancer.ca/en/cancer-information/cancer-types/brain-and-spinal-cord/statistics>
2. Zhang H, Zhou Y, Cui B, Liu Z, Shen H. Novel insights into astrocyte-mediated signaling of proliferation, invasion and tumor immune microenvironment in glioblastoma. *Biomed & Pharmacother.* 2020;126:110086. Available from: doi:10.1016/j.bioph.2020.110086.
3. Chieffo DP, Lino F, Ferrarese D, Belella D, Della Pepa GM, Doglietto F. Brain tumor at diagnosis: from cognition and behavior to quality of life. *Diagnostics.* 2023;13(3):541. Available from: doi:10.3390/diagnostics13030541.
4. Mendichovszky I, Jackson A. Imaging hypoxia in gliomas. *Br J Radiol.* 2011;84(special_issue_2):S145-58. Available from: doi:10.1259/bjr/82292521.
5. Li-Fraumeni syndrome: MedlinePlus Genetics [Internet]. medlineplus.gov. 2020. Available from: <https://medlineplus.gov/genetics/condition/li-fraumeni-syndrome/>
6. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev.* 2013(4). Available from: doi: 10.1002/14651858.CD007415.pub2.
7. Butler M, Pongor L, Su YT, Xi L, Raffeld M, Quezado M, Trepel J, Aldape K, Pommier Y, Wu J. MGMT status as a clinical biomarker in glioblastoma. *Trends Cancer.* 2020;6(5):380-91. Available from: doi:10.1016/j.trecan.2020.02.010.
8. Tsubaki M, Genno S, Takeda T, Matsuda T, Kimura N, Yamashita Y, Morii Y, Shimomura K, Nishida S. Rhosin suppressed tumor cell metastasis through inhibition of Rho/YAP pathway and expression of RHAMM and CXCR4 in melanoma and breast cancer cells. *Biomedicines.* 2021;9(1):35. Available from: doi:10.3390/biomedicines9010035.
9. Figueiró F, de Oliveira CP, Bergamin LS, Rockenbach L, Mendes FB, Jandrey EH, et al. Methotrexate up-regulates ecto-5'-nucleotidase/CD73 and reduces the frequency of T lymphocytes in the glioblastoma microenvironment. *Purinergic Signal.* 2016;12:303-12. Available from: doi:10.1007/s11302-016-9505-8.
10. Etame AB, Diaz RJ, Smith CA, Mainprize TG, Hyynnen K, Rutka JT. Focused ultrasound disruption of the blood-brain barrier: a new frontier for therapeutic delivery in molecular neurooncology. *Neurosurg Focus.* 2012;32(1):E3. Available from: doi:10.3171/2011.10.FOCUS11252.
11. Solar P, Hendrych M, Barak M, Valekova H, Hermanova M, Jancalek R. Blood-brain barrier alterations and edema formation in different brain mass lesions. *Front Cell Neurosci.* 2022;16:922181. Available from: doi:10.3389/fncel.2022.922181.



ARTIST:
NICOLE KIM²

²Bachelor of Health Sciences (Honours),
Class of 2026, McMaster University

IWCH Abstract

SURGICAL SIMULATORS FOR POSTPARTUM HEMORRHAGE: A SCOPING REVIEW

INTRODUCTION

Postpartum hemorrhage (PPH), characterized by excessive bleeding following childbirth, is the leading cause of maternal mortality worldwide. Surgeries may be required when PPH is refractory to medical management but the high-acuity, low-occurrence of these clinical scenarios leaves *in vivo* opportunities to learn and practice these procedures up to chance. Simulation-based learning therefore provides a safe and controlled environment for healthcare providers (HCPs) to develop adequate surgical skills to manage PPH.

OBJECTIVE

This scoping review aims to map out existing literature on surgical simulators for PPH including evidence of their effectiveness as an educational tool.

METHODS

A literature search was conducted in the electronic databases Cochrane Libraries, PubMed, MEDLINE, and Embase. Eligibility criteria included all study designs regarding surgical simulators for practicing, teaching, or learning compression sutures (eg., B-Lynch, transverse/longitudinal sutures), uterine artery (UA) ligation, and hysterectomy for treating PPH. Studies that only simulated non-surgical management such as medication, bimanual uterine massage, balloon tamponade etc. were excluded.

RESULTS

In total, 825 studies were identified. Ten studies were included for extraction. In all but one, uterine simulators resulted in a positive impact on HCP education on surgical management of PPH. Various methods were used to measure the effectiveness of these simulators as an educational tool, such as objective test scores, preceptor feedback, and self-surveys. With the use of simulators, 6 articles reported increased confidence in responding surgically to a PPH, 2 articles reported an improvement in skill and readiness, and 1 article reported improved knowledge of surgical management based on pre- and post-simulation test scores. Simulator materials varied; 5 studies used animal tissue and 5 studies used non-animal tissue to mimic the uterus. Various surgical techniques were used, with 7 articles assessing compression sutures (B-Lynch, longitudinal, transverse), 2 articles assessing both UA ligation in addition to B-Lynch sutures, and 1 article assessing only hysterectomy.

DISCUSSION

No studies included simulators that supported the use of all 3 surgical techniques. Most taught compression sutures while only 1 supported use of UA ligation, despite its common use as a first-line surgical management for PPH. Models used animal tissue, such as bovine bladders, muscle, and skin. While these may closely mimic human tissue, animal products may be taboo or limited in various countries. Non-animal tissues include cloth, felt, and water bottles. These resources may be more widely accessible and culturally acceptable. Overall, there was insufficient data to compare the effectiveness and outcomes of low vs high fidelity simulators.

CONCLUSION

This scoping review highlights the effectiveness of using simulators to improve HCP readiness to surgically address PPH. The implementation of simulators may help bridge the training gap that exists in being adequately prepared for life-threatening, high acuity low occurrence procedures. Future research should explore and compare the use of low vs high fidelity simulators on PPH management.

ARTIST:
TITUS TAN¹

¹Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

AUTHORS:
ASHLEY ASSAM (BHS, MSc)², LORI LAI (BSc)², YITING WU (BASc, MASc)³, NOAH STEWART (BMLSc, MASc)³, VINCENT LEVANDIER (BEng, MEng)³, YONG HUI CHAN (BEng, MEng)³, ESTHER CHIN (MD, MGSC, FRCSC)^{2,4}

²Michael G. DeGroote School of Medicine, McMaster University

³School of Biomedical Engineering, University of British Columbia

⁴Department of Obstetrics/Gynecology, McMaster University

Smiling Pillars: Community Solutions to Combat Heatwave Health Crises

doi: 10.35493/medu.47.22

AUTHORS:

SAHITH RAJKUMAR¹, MUHSIN NISHATH¹, & KAPILAN SIVAPATHAM¹

¹Bachelor of Science (Honours Life Sciences), Class of 2028, McMaster University

ARTIST:

TRAM NGUYEN²

²Bachelor of Arts (Honours Media Arts), Class of 2026, McMaster University



INTRODUCTION

The city of Hamilton experiences some of the hottest summers in Canada, and is the fourth city to shatter Canada's heat index, a tool which measures heat in relevance to humidity and air temperature.¹ In response to Hamilton's heat waves Smiling Pillars was founded, a humanitarian outreach program that employs tactics to relieve communities suffering from extreme heat events (EHEs). Through advocacy, community engagement, and direct response efforts, Smiling Pillars promotes long-term systemic changes to help address public health disparities, particularly heat-related issues in Hamilton.

THE CRISIS

Heat-related emergency department visits in Hamilton more than doubled between 2010 and 2020, highlighting its severity as a public health threat.² Climate models predict a rise in both heat wave intensity and duration in the city.² Notably, temperatures in low-income households frequently rise above outdoor temperatures. These difficulties are enhanced by structural barriers, as 30% of citizens reporting lacking access to in-suite air conditioning. Residents of such buildings frequently face installation issues, exorbitant fees, or landlord restrictions. Others turn to makeshift and potentially dangerous cooling techniques such as placing wet towels over electric fans, which has been shown to increase the risk of electrical fires.³

EHEs are becoming more severe, exemplified by average global temperatures rising 1.5°C beyond pre-industrial levels for the first time and Canada frequently reaching temperatures 10°C higher than normal.^{5,6} EHEs put vulnerable human populations such as the elderly, young children, outdoor workers, and underprivileged communities at heat-related risks. Prolonged exposure to high temperature increases the risk of heat strokes, respiratory diseases, and cardiovascular stress.⁴ In addition, rising temperatures are contributing to the growing prevalence of natural disasters, including floods, wildfires, and droughts.⁵ This poses a public health concern with adverse weather events resulting in poor air quality, physical hazards, and unlivable conditions.

During prolonged exposure to heat, the human body relies on sweating to cool and regulate body temperature. However, excessive sweating depletes

water and electrolyte reserves.⁷ The loss of these ions disrupts the electrochemical gradients required for cellular processes, including signal transmission in neurons, which is essential to the survival of cells and muscle fibre activations.⁸ Additionally, depleted electrolyte reserves disrupt the osmolarity of the ions inside and outside the cells, creating a hypertonic environment and leading to abnormal cell function by impairing hydration, oxygen transport, and circulation.

Heat-related illnesses can vary in degree from mild heat cramps, which are characterized by muscle cramps, spasms, and intense pain, to more severe conditions like heat exhaustion.⁹ Heat exhaustion occurs when the body's cooling mechanisms become overwhelmed, leading to symptoms like heavy sweating, weakness, nausea, and headaches. If not addressed, it can escalate into heat stroke, a life-threatening condition where the body's core temperature rises above 40°C, impairing its ability to regulate temperature. This life-threatening emergency state requires immediate medical attention and can result in permanent brain damage, organ failure, and cardiovascular collapse.⁹ Heat exposure significantly increases the risk of cardiovascular mortality and morbidity. A 1°C rise in temperature is associated with a 1.3% increase in cardiovascular-related deaths and heat-related illnesses.¹⁰ Additionally, extreme heat conditions also lead to a significant decline in overall physical activity, poor sleep efficiency, increased fatigue, and a heightened risk of heat-related illnesses.¹¹

ABOUT THE INITIATIVE AND SOLUTION

Smiling Pillars is an organization created to address issues caused by Hamilton's intense summer heat waves. Nearby companies and private donors, many of whom are local to Hamilton, donate water-rich fruits and vegetables, like apples, watermelons, and celery to the program. These foods are packaged into hydration kits alongside cooling towels and heat-safety educational materials, which are then distributed to the local community. Smiling Pillars acknowledges the need for systemic changes to better support areas vulnerable to EHEs. For instance, they focus on prioritizing the older homeless population during heat waves, ensuring greater equity within our community. These initiatives demonstrate the effectiveness of community engagement in tackling health inequalities and how direct efforts are crucial in reducing the long-term effects of public health emergencies.

Smiling Pillars supports over 1000 people every weekend, with the majority being seniors, individuals with disabilities, families with kids, immigrants, and refugees. Every Thursday, donations are collected from local produce companies, including Bimbo Canada, COBS Bread, Speroway Food Education Health, and the Taylor Company, which are preserved in refrigerators overnight at Hillfield Strathallan College. With over 100 volunteers helping each weekend, Smiling Pillars was able to prepare and distribute over 1,100 cups of water-rich foods in the first three months of the project, such as watermelon, cantaloupe, cucumbers, and strawberries. These kits were essential for combatting the negative effects of excessive perspiration, which can reach around 1.5 litres per hour in hot weather periods. During this period, around 2,160 wet towels were also given out. Along with this, informative pamphlets were distributed, including information on the risks of hot weather and the importance of staying safe.

CONCLUSION

Smiling Pillars distributed supplies with great care to help individuals in Hamilton to cope with the hottest weeks of 2024. They hope to expand its efforts by hosting year-round initiatives to tackle other pressing health challenges. These include educating Hamilton communities on all seasonal health precautions through local events. They will also continue this summer's efforts in tackling heat-related health emergencies.

ACKNOWLEDGEMENTS

Our appreciation goes out to Jeffrey Ng, the founder of Gore Park Community Outreach, whose continual vision and commitment have been essential in helping Hamilton's most vulnerable communities during all times of the year. Their support was crucial for Smiling Pillars' success. We would also like to express our gratitude to Linda Watson, Director of Technology, Innovation, and Integration at Hillfield Strathallan College for her assistance in moving our initiative forward with strategic and operational elements. Their combined efforts, along with all the volunteers at Smiling Pillars, have been instrumental in fostering community strength and ensuring this project's long-term role in making a difference in Hamilton.



REVIEWED BY: DR. RACHEL WELDRICK (PhD)

Dr. Rachel Weldrick (PhD) is an Assistant Professor in the Faculty of Health, Aging & Society at McMaster. Their research investigates services for aging individuals experiencing numerous social conditions, with a focus on homelessness.

EDITED BY: FIRDOSE KHAN & DEVLYN SUN

1. ICLEI Canada. Climate science report for the City of Hamilton. Prepared by: ICLEI Canada [Internet]. 2022. Available from: <https://www.hamilton.ca/sites/default/files/2022-10/climate-change-impact-adapation-plan-science-report.pdf>
2. City of Hamilton. Heat Warnings & Heat-Related Illness | City of Hamilton [Internet]. www.hamilton.ca. 2024. Available from: <https://www.hamilton.ca/people-programs/public-health/environmental-health-hazards/he-at-warnings-heat-related-illness>
3. ACORN Canada. ACORN Canada Extreme Heat & Climate Justice Report - ACORN Canada [Internet]. ACORN Canada -. 2023 [cited 2025 Jan 13]. Available from: <https://acorncanada.org/resources/acorn-canada-extreme-heat-climate-justice-report/>
4. Yao H, Zhao L, He Y, Dong W, Shen X, Wang J, et al. Changes caused by human activities in the high health-risk hot-dry and hot-wet events in China. *Commun Earth Environ.* 2024;5(1). Available from: doi:10.1038/s43247-024-01625-y.
5. Paddison L. 2024 was the hottest year on record, breaching a critical climate goal and capping 10 years of unprecedented heat [Internet]. CNN. 2025. Available from: <https://www.cnn.com/2025/01/09/climate/2024-hottest-year-record/index.html>
6. Shingler B. Canada draws link between June heat wave and climate change with new attribution analysis [Internet]. CBC. 2024. Available from: <https://www.cbc.ca/news/climate/canada-eccc-rapid-attribution-heat-1.7257456>
7. Wartenberg L. Dehydration: Causes, Symptoms, Treatment, and More [Internet]. Healthline. 2021. Available from: <https://www.healthline.com/health/dehydration#risk-factors>
8. Baker LB. Sweating rate and sweat sodium concentration in athletes: A review of methodology and intra/interindividual variability. *Sports Med.* 2017;47(S1):111–28. Available from: doi:10.1007/s40279-017-0691-5.
9. Ebi KL, Capon A, Berry P, Broderick C, de Dear R, Havenith G, et al. Hot weather and heat extremes: health risks. *Lancet.* 2021;398(10301):698–708. Available from: doi: 10.1016/S0140-6736(21)01208-3.
10. Liu J, Varghese BM, Hansen A, Zhang Y, Driscoll T, Morgan G, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. *Lancet Planet Health.* 2022;6(6):e484–95. Available from: doi: 10.1016/S2542-5196(22)00117-6.
11. Zhang W, Du Z, Zhang D, Yu S. Quantifying the adverse effect of excessive heat on children: An elevated risk of hand, foot and mouth disease in hot days. *Sci Total Environ.* 2016;541:194–9. Available from: doi: 10.1038/s41598-018-20318-z.



Ontario Society of
Occupational Therapists

Welcome to the profession!

We're here to support you in your
professional practice.

Join your Ontario colleagues at
www.osot.on.ca



EDITOR PROJECT

26 mEducator | April 2025

Bacteriophages for Treatment of Zoonotic Bacterial Diseases



ARTIST:
PARISA MISHAL HOSSAIN¹

¹Bachelor of Health Sciences (Honours), Class of 2025, McMaster University

doi: 10.35493/medu.47.26

AUTHORS:

CYNTHIA DUAN², EVAN SUN³, WILL ZHANG²

²Bachelor of Health Sciences (Honours), Class of 2027, McMaster University

³Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

BACKGROUND

Zoonotic diseases are infectious diseases transmitted from animals to humans. Common human pathogens such as *Salmonella enterica* (*S. enterica*), chickenpox, and human immunodeficiency virus (HIV) are zoonotic diseases that pose significant risks to both human and animal health. With globalization and increased human contact with animals, there is a growing risk of transmission of zoonotic diseases between species. Public health programs cannot adequately determine the identities of zoonotic pathogens circulating in the environment, nor limit human contact with animal populations.

Of these zoonotic pathogens, bacteria are of particular concern with respect to their associated morbidity and treatment costs.¹ As antimicrobial resistance (AMR) becomes increasingly prevalent across the world, conventional treatments lose their effectiveness and accelerate the evolution of drug-resistant bacteria strains. As a result, there is a significant need for an alternative form of therapy against bacterial diseases.² Bacteriophages (phages) are a diverse family of bacteria-specific viruses that demonstrate potential as an alternative therapy for zoonotic bacterial infections. Phages are ubiquitous and function ecologically as a regulator of bacterial population growth and distribution.³ These properties allow applications of phage therapy for the treatment of zoonotic bacterial infections.

MECHANISMS OF BACTERIOPHAGE THERAPY

The most commonly reported phage is the double-stranded DNA (dsDNA) tailed phage that possesses an icosahedral capsid containing viral DNA attached to the tail.⁴ While bacterial entry mechanisms differ between species, the lytic cycle seen in dsDNA phages such as *Caudovirales* is well-described.⁵ Receptor-binding proteins (RBPs) on the phage tail recognize receptors on the bacterial cell wall, pili, and flagella. Phages bind to receptors in two stages: reversible binding, followed by irreversible binding to the same or different receptor.⁶ Phage-RBP binding induces a conformational change that opens channels for the injection of viral DNA from the capsid into the bacterial cytoplasm.⁷ The phage then modifies the host bacteria's metabolism, preventing host gene expression while expressing viral genes to produce new phages. Viral genes that code for lytic enzymes expressed later in the infection cycle rupture the bacterial cell wall, releasing 50–200 phage progeny while killing the bacteria.⁶ Phages that exclusively follow lytic replication are referred to as strictly lytic or virulent. Phages that are also capable of undergoing the lysogenic cycle, where the viral genome is incorporated into host genetic material as a prophage, are called temperate phages.^{4,8} The viral DNA remains dormant and is distributed by cell replication and horizontal gene transfer until conditions are

unfavourable, often when the host DNA is compromised, during which the prophage switches to the lytic cycle.^{6,9} The therapeutic properties of phages present them as a safe and effective treatment. The rate of phage resistance development in bacteria is significantly lower than AMR development.¹⁰ Additionally, when used alongside other antimicrobials, phages often enhance infection treatment more effectively than antibiotics alone.¹¹ The safety has also been demonstrated through studies which show that mice safely tolerated doses 3,500 times higher than the standard human dose.¹¹ Phages can be highly selective, only targeting bacterial families which express the surface molecules required for binding. This selectivity is referred to as the host range and may be broad, where phages infect different bacterial species, or narrow, where a single species or strain is targeted.⁴ Thus, phages have less of a destructive impact on the body's microbiome, unlike antibiotics.⁵

Collections of lytic and temperate phages that target clinically relevant bacterial species have led to the creation of databases documenting their individual therapeutic potentials.¹² For instance, *Staphylococcus aureus* phages have a wider host range, and a comprehensive library could feature only 20–30 phages. Conversely, phages with lower host ranges such as those that infect *Acinetobacter baumannii* require a library of 300 phages for the same coverage.⁴ These properties become clinically significant in "phage cocktails" where a combination of phages are used to treat individual or multi-bacterial infections to reduce the incidence of AMR.¹³ Fixed phage cocktails can destroy a wide spectrum of bacteria through the use of wide host range phages and are simpler to produce and deploy.⁴ However, selective phage cocktails are only effective on a case-by-case basis where the combination of phages is only relevant to the pathogens in a specific infection.¹⁴ Moreover, phage resistance can still develop from the modification of receptors on the cell surface or activation of cellular mechanisms that defend against phage infection.⁶

A primary concern with phage therapy administered for longer periods is the possible induction of immune responses that affect treatment efficacy.¹⁵ One such response involves phage-neutralizing serum antibodies, though the exact mechanism remains unclear.¹⁵ If antibody levels are consistently high, phage therapy should be discontinued; however, this metric may not directly relate to clinical outcomes. Antibody degradation varies between individuals and may take over one year to clear in some patients, posing clinical significance in recurring treatments.¹⁶

APPLICATIONS OF PHAGE THERAPY IN ZOONOTIC DISEASES

Phage therapy has demonstrated potential in combating zoonotic diseases, with several studies highlighting its efficacy in controlling bacterial infections and reducing the risk of animal-to-human transmission. One key application of this therapy was in the control of *S. enterica*, particularly in poultry. Fiorentin

a reduction by $3.5 \log_{10}$ CFU/g in the population of *S. enterica* within the cecum of chickens, following a single dose of three different phages—each at 1,011 plaque-forming units.¹⁷ The study followed disease progression over the course of several weeks, demonstrating the self-replicating nature of phages and their potential for long-term therapeutic effects.^{18,19} However, as phage therapy is often administered orally, physiological conditions such as stomach acidity and gastrointestinal tract enzymes may limit phage viability and efficacy.¹⁷

Another important application of phage therapy is in the treatment of *Escherichia coli* O157:H7, a leading cause of foodborne illness resulting in diarrhea, hemorrhagic colitis, and hemolytic-uremic syndrome in humans. The phage combination of P5, P8, and P11 was successful in reducing fecal shedding of *E. coli* O157:H7 in sheep over the course of 21 days. The results indicated that the populations of total coliforms and *E. coli* were similar in both treated and untreated groups, demonstrating the specificity of phage treatment.^{20,21} The therapy targeted pathogenic bacteria without disrupting the host microbiome, demonstrating a significant advantage over traditional antibiotics.^{20,21} While this specificity can be advantageous, it also indicates that phages must be carefully selected to match pathogenic bacterial species, which can be time-consuming and expensive.

Outside of animal studies, there has been limited approval of phage therapy in humans. A case report following a patient with recurrent *Enterococcus faecium* blood infections, which eventually developed AMR, highlights the potential of combining antibiotics with phage therapy. Following the addition of phage therapy to an antibiotic regime, there were several months of clinical improvement and reduced *E. faecium* intestinal burden, as there was a marked suppression of bacterial growth compared to when either therapy was used alone. Unfortunately, an antibody response eventually neutralized phage activity which, coinciding with the resurgence of antibiotic-resistant *E. faecium*, likely contributed to clinical failure and the discontinuation of treatment.²² Despite these challenges, phage therapy remains a promising avenue for AMR infections, with ongoing research focused on clinical applications and treatment efficacy.

CURRENT REGULATORY GUIDELINES AND KNOWLEDGE GAPS

With the advent of antibiotics, the commercial push for phage therapy has declined. Medical reports have suggested a low efficacy of phage therapy and incorrectly identified phages as enzymes.¹¹ While interest in phage research has returned recently, phage therapy is not available as a treatment in most Western countries, including Canada, but is limited to compassionate use. The experimental status of phage therapy is attributed to the lack of clinical research, as current knowledge is based on theory, physiological evidence, animal models, and accumulated medical experience.²³ The first phage therapy trial in Canada was conducted in 2023 to treat a urinary tract infection caused by a superbug.²⁴ Despite compassionate use status, a second Canadian patient was also treated with phage therapy in 2024 for sepsis caused by an artificial joint infection at the University of Ottawa after approval from Health Canada, leading to a significant recovery.^{25,26}

The Public Health Agency of Canada recently dedicated \$3.2

million CAD to fund the Phage Science, Therapeutics, and Research (PhageSTAR) program. PhageSTAR is affiliated with the Association of Medical Microbiology and Infectious Disease Canada (AMMI) and Health Canada to develop regulatory guidelines for providing national phage therapy with the goal of reducing AMR. The National Research Council Canada has invested an additional \$1 million CAD in the development of antibiotic alternatives such as phage therapy.²⁷ This funding reflects a growing interest in the field and will help accelerate development.

Phage therapy is classified as an experimental treatment under the Declaration of Helsinki, complicating phage therapy efficacy assessments through double-blind, placebo-controlled clinical trials.²³ This contrasts with regulations in Russia and the Republic of Georgia, where phage cocktails can be purchased without prescriptions. In Georgia, personalized phage medicines are classified as pharmaceuticals and are manufactured in pharmacies licensed by the Georgian Ministry of Healthcare through magistral preparation. Western medicine regulatory agencies do not recognize these phage products from Russia and Georgia, making exports difficult.²⁹ Critically, the production of phages must follow strict regulations to ensure quality and safety, and is enforced in the UK by the Good Manufacturing Practices guidelines.^{28,30}

There has been interest in genetically modifying temperate phages to become lytic phages for therapeutic use.⁶ Notably, genetically engineered synthetic phages may modulate the bacterial host response and reduce the transfer of AMR by degrading the bacterial genome.⁵

Knowledge gaps in phage therapy include phage pharmacokinetics and pharmacodynamics for optimizing administration routes, frequencies, and dosage. Phage interactions with other antimicrobials and phage-to-phage interactions are also unclear. While synthetic phage development is novel and relevant in combating phage resistance and bacterial biofilms, phage therapy developers face difficulties in securing long-term funding for their high-risk research and clinical trials.³²

CONCLUSION

With the increasing health risk posed by zoonotic diseases and continued concern regarding AMR, phage therapy offers a promising solution due to its inherent advantages over traditional antibiotics, including its high selectivity and potential efficacy against drug-resistant bacteria. The current body of knowledge demonstrates a robust understanding of phage molecular mechanisms, but more clinical evidence is required before phage therapy can be implemented into widespread medical practice.

REVIEWED BY: DR. RABIA FATIMA (PhD)

Dr. Rabia Fatima is a PhD graduate in the Hynes Lab at McMaster University, specializing in bacteriophage research. Her work focuses on combating multi-drug-resistant pathogens by developing innovative strategies that harness phage-antibiotic synergy.

EDITED BY: JACQUELINE CHEN & SAEJIN HUR



1. Dafale NA, Srivastava S, Purohit HJ. Zoonosis: An emerging link to antibiotic resistance under "One Health approach". *Indian J Microbiol.* 2020;60:139–152. Available from: doi:10.1007/s12088-020-00860-z.
2. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet.* 2022;399(10325):629–55. Available from: doi:10.1016/S0140-6736(21)02724-0.
3. Garvey M. Bacteriophages and the One Health approach to combat multidrug resistance: Is this the way? *Antibiotics.* 2020;9:414. Available from: doi:10.3390/antibiotics9070414.
4. Strathdee SA, Hatfull GF, Mutualik VK, Schooley RT. Phage therapy: From biological mechanisms to future directions. *Cell.* 2023;186(1):17–31. Available from: doi:10.1016/j.cell.2022.11.017.
5. Pires DP, Cleto S, Sillankorva S, Azeredo J, Lu TK. Genetically engineered phages: A review of advances over the last decade. *Microbiol Mol Biol Rev.* 2016;80(3):523–43. Available from: doi:10.1128/mmbr.00069-15.
6. Hibstu Z, Belew H, Akelew Y, Mengist HM. Phage therapy: A different approach to fight bacterial infections. *Biologics.* 2022;16:173–86. Available from: doi:10.2147/BTT.S381237.
7. González-García VA, Pulido-Cid M, García-Doval C, Bocanegra R, Van Raaij MJ, Martín-Benito J, et al. Conformational changes leading to T7 DNA delivery upon interaction with the bacterial receptor. *J Biol Chem.* 2015;290(16):10038–44. Available from: doi:10.1074/jbc.M114.614222.
8. Wetzel KS, Aull HG, Zack KM, Garlena RA, Hatfull GF. Protein-mediated and RNA-based origins of replication of extrachromosomal mycobacterial prophages. *mBio.* 2020;11(2):e00385-20. Available from: doi:10.1128/mbio.00385-20.
9. Howard-Varona C, Hargreaves KR, Abedon ST, Sullivan MB. Lysogeny in nature: Mechanisms, impact and ecology of temperate phages. *ISME J.* 2017;11(7):1511–20. Available from: doi:10.1038/ismej.2017.16.
10. Carlton RM. Phage therapy: Past history and future prospects. *Arch Immunol Ther Exp (Warsz).* 1999;47(5):267–74.
11. Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. *Antimicrob Agents Chemother.* 2001;45(3):649–59. Available from: doi:10.1128/aac.45.3.649-659.2001.
12. Bacteriophage.news. Phage banks & collections [Internet]. 2021 Nov 21. Available from: <https://www.bacteriophage.news/phage-banks-collections/> [cited 2025 Feb 2].
13. Tekle mariam AD, Al Hindi R, Qadri I, Alharbi MG, Hashem AM, Alrefaei AA, et al. Phage cocktails – an emerging approach for the control of bacterial infection with major emphasis on foodborne pathogens. *Biotechnol Genet Eng Rev.* 2024;40(1):1–29. Available from: doi:10.1080/02648725.2023.2178870.
14. Brives C, Pourraz J. Phage therapy as a potential solution in the fight against AMR: Obstacles and possible futures. *Palgrave Commun.* 2020;6(1):100. Available from: doi:10.1057/s41599-020-0478-4.
15. Jerne NK, Avegno P. The development of the phage-inactivating properties of serum during the course of specific immunization of an animal: Reversible and irreversible inactivation. *J Immunol.* 1956;76(3):200–8. Available from: doi:10.4049/jimmunol.76.3.200.
16. Łusiak-Szelachowska M, Międzybrodzki R, Rogoź P, Weber-Dąbrowska B, Żaczek M, Górska A. Do anti-phage antibodies persist after phage therapy? A preliminary report. *Antibiotics (Basel).* 2022;11(10):1358. Available from: doi:10.3390/antibiotics11101358.
17. Gigante, A, Atterbury, RJ. Veterinary use of bacteriophage therapy in intensively-reared livestock. *Virol J.* 2019;16:155. Available from: doi:10.1186/s12985-019-1260-3.
18. Fiorentin, L, Vieira, ND, Barioni Jr W. Oral treatment with bacteriophages reduces the concentration of *Salmonella Enteritidis* PT4 in caecal contents of broilers. *Avian Path.* 2005;34(3):258–263. Available from: doi:10.1080/01445340500112157.
19. Loc-Carrillo C, Abedon ST. Pros and cons of phage therapy. *Bacteriophage.* 2011;1(2):111–114. Available from: doi:10.4161/bact.1.2.14590.
20. Gigante, A, Atterbury, RJ. Veterinary use of bacteriophage therapy in intensively-reared livestock. *Virol J.* 16:155 (2019). Available from: doi:10.1186/s12985-019-1260-3.
21. Bach, SJ, Johnson, RP, Stanford, K and McAllister, TA. Bacteriophages reduce *Escherichia coli* O157:H7 levels in experimentally inoculated sheep. *Can J Anim Sci.* 2009;89:285–293. Available from: doi:10.4141/CJAS08083.
22. Stellfox ME, Fernandes C, Shields RK, Haidar G, Hughes Kramer K, Dembinski E, et al. Bacteriophage and antibiotic combination therapy for recurrent *Enterococcus faecium* bacteremia. *mBio.* 2024;15:e03396-23. Available from: doi:10.1128/mbio.03396-23.
23. Verbeken G. Towards an adequate regulatory framework for bacteriophage therapy [Internet]. 2015 Sept 28. Available from: <http://rgdoi.net/10.13140/RG.2.1.3875.9924> [cited 2025 Feb 2].
24. CTV News. First Canadian trial successfully uses phage therapy to stop life-threatening UTI caused by superbug [Internet]. 2023 July 4. Available from: <https://www.ctvnews.ca/health/article/first-canadian-trial-successfully-uses-phage-therapy-to-stop-life-threatening-uti-caused-by-superbug> [cited 2025 Feb 20].
25. uOttawa. First patient in Canada treated with phage therapy for artificial joint infection [Internet]. 2024 Mar 22. Available from: <https://www.uottawa.ca/research-innovation/news-all/first-patient-canada-treated-phage-therapy-artificial-joint-infection> [cited 2025 Feb 2].
26. CBC. 'This was my last resort,' Ottawa-area woman says of experimental phage therapy to treat infection [Internet]. 2024 Mar 28. Available from: <https://www.cbc.ca/news/canada/manitoba/phage-therapy-infection-1.7156333> [cited 2025 Feb 2].
27. Canada.ca. Pan-Canadian action plan on antimicrobial resistance: Year 1 progress report (June 2023 to May 2024) [Internet]. 2024 Sept 26. Available from: <https://www.canada.ca/en/public-health/services/publications/drugs-health-products/pan-canadian-action-plan-antimicrobial-resistance-year-1-progress-report-2023-2024.html> [cited 2025 Feb 2].
28. Justice Laws Website. Food and drug regulations [Internet]. 2024 Dec 14. Available from: https://laws.justice.gc.ca/eng/regulations/c.r.c._c_870/page-80.html [cited 2025 Feb 2].
29. Yang Q, Le S, Zhu T, Wu N. Regulations of phage therapy across the world. *Front Microbiol.* 2023;14:1250848. Available from: doi:10.3389/fmicb.2023.1250848.
30. Yang Y, Luo M, Zhou H, Li C, Luk A, Zhao G, et al. Role of two-component system response regulator bceR in the antimicrobial resistance, virulence, biofilm formation, and stress response of group B *Streptococcus*. *Front Microbiol.* 2019;10:10. Available from: doi:10.3389/fmicb.2019.00010.
31. Luong T, Salabarria AC, Roach DR. Phage therapy in the resistance era: Where do we stand and where are we going? *Clin Ther.* 2020;42(9):1659–80. Available from: doi:10.1016/j.clinthera.2020.07.014.
32. Turner PE, Azeredo J, Buurman ET, Green S, Haaber JK, Haggstrom D, et al. Addressing the research and development gaps in modern phage therapy. *Phage.* 2024;5(1):30–9. Available from: doi:10.1089/phage.2023.0045.

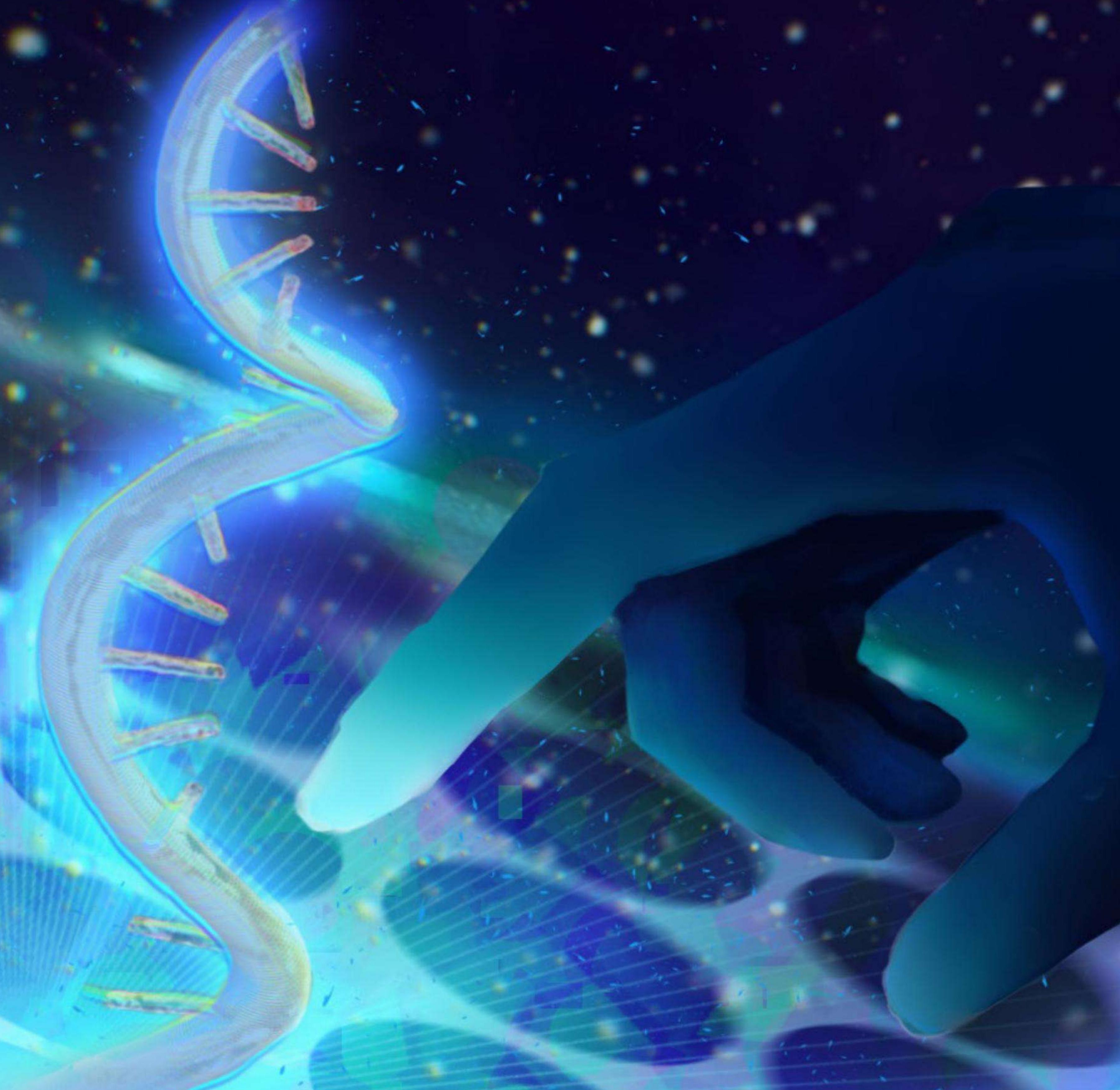
CRITICAL REVIEW

CRITICAL REVIEW
30 mEducator | April 2025

SPATIAL TRANSCRIPTOMICS: A PROMISING NEW APPROACH TO CANCER RESEARCH

ARTIST:
HENIN YE¹

¹Bachelor of Science (Honours), Class of 2026, McMaster University



doi: 10.35493/medu.47.30

AUTHORS:

DEREK KUO² & JENNIFER CHEN³

²Bachelor of Health Sciences (Honours), Class of 2028, McMaster University

³Bachelor of Science (Honours), Class of 2028, McMaster University

ABSTRACT

Transcriptomics are techniques that track gene expression by detecting gene transcripts, which include ribonucleic acid (RNA) found in cell and tissue samples. Integrating transcript detection methods with spatial technologies identifies which genes are transcribed and the precise location of transcript products. Researchers can use this information to identify biomarkers, cell communication patterns, and gene expression variations, which can improve treatments and prognostic judgements, within the field of oncology. The spatial information can identify particular genes and pathways in metastasis as it helps pinpoint areas for therapeutic targets in cancer treatment. Despite being in its early stages of growth, spatial transcriptomics (ST) has already been used to better understand cancer function and identify potential treatments. This review aims to assess the state of ST in cancer research and consider its potential as an emerging technology. Each of the studies reviewed highlights a different area for ST to contribute to the understanding and treatment of cancer.

INTRODUCTION AND ST TECHNIQUES OVERVIEW

Spatial transcriptomics (ST) encompasses a wide variety of techniques involving the localization of gene products within a tissue.¹ ST can be categorized into four categories: sequencing-based, probe-based, imaging-based, and image-guided spatially resolved.²

Sequencing-based methods are characterized by the extraction of transcripts from tissues while preserving spatial information.^{1,2} Microarrays containing barcoded oligonucleotides—small deoxyribonucleic acid (DNA) sequences that contain spatial information—are arranged in a grid. Oligonucleotides then bind to messenger RNA (mRNA) from the tissue sample, which are used to sequence complementary DNA (cDNA) strands. The barcodes are preserved and transferred to the cDNA, which researchers then use to trace the transcript's past position in the sample.² These techniques are high-throughput, meaning they can process large numbers of transcripts at once. Importantly, they are also less biased, as they do not require researchers to manually select the targets. However, a limitation of these techniques is their lack of sensitivity; researchers are currently unable to detect transcripts present in low concentrations.²

Probe-based techniques also use barcoded oligonucleotides as probes to capture specific target RNA transcripts.² Probes are applied to a region of interest (ROI) and bind to any target transcripts present.¹ This process uses a form of *in situ* hybridization, a technique for studying spatial gene expression within the tissue.² Compared to sequencing-based methods, these techniques involve a read-out in digital counts of RNA expression and have higher sensitivity. However, they are more susceptible to bias, as they may miss transcripts outside of the targeted set or outside the ROI.^{1,2} Additionally, they

are lower throughput than the sequencing-based methods.²

Imaging-based methods are similar to probe-based techniques in that they visualize transcripts *in situ*.^{1,2} However, instead of barcoded oligonucleotides, they use complementary fluorescent probes that bind to specific target RNA sequences that are captured with imaging technology. This approach allows for high spatial resolution, sometimes down to the subcellular level.² Unlike sequencing-based methods, which can capture the entire transcriptome in a single experiment, this method involves the preselection of targets. This could potentially exclude important genes and may introduce selection bias. Furthermore, imaging-based methods are limited by the number of distinct fluorophores that are accurately detected and quantified simultaneously in a single experiment. This is due to the overlapping wavelengths of fluorescence emitted by different fluorophores.

The final method described is image-guided spatially resolved single-cell transcriptomic sequencing. This relatively new method involves selecting spatially different cells or ROIs, followed by single-cell RNA sequencing (scRNA-seq). In contrast to most existing techniques, these methods allow for a high throughput at high resolution.²

FINDINGS

ST is a field with broad applications for a diverse range of cancers. One example is its potential to address tumour heterogeneity: the cellular diversity present throughout the tumour. Current research suggests that this heterogeneity causes some cancers to resist treatment.⁴⁻⁶ A 2023 study by Arora et al. utilized ST to analyze heterogeneity in HPV-negative oral squamous cell carcinoma (OSCC).⁷ Using 10X Genomics Visium, an industry-standard sequencing-based technique,² they investigated differences in gene expression at the tumour's leading edge (LE) and the tumour core (TC).⁷ The LE displayed higher mRNA abundance of cell cycle- and protein translation-related genes, which may contribute to OSCC's invasive tendencies.⁷ Conversely, upregulated genes in the TC were involved in cell differentiation- and immune-related pathways, suggesting that these cells may alter the body's nearby immune response and thus control tumour growth. Upon analysis of drug response data, Arora and colleagues found that effective OSCC therapeutics targeted the LE by "inducing reversal from the LE state" and encouraging cells to exhibit more TC-like gene expression.⁷ ST allowed researchers to identify spatially distinct transcriptomic profiles and provided crucial insight into the mechanisms of certain cancer drugs.⁷

ST has also shown the potential to further elucidate the mechanisms of cancer cell metabolism. More specifically, ST may help us understand the dynamic changes which occur during metastasis, the process in which cancer cells break free from the original tumour and spread using the bloodstream or the lymphatic system.⁸ This was observed in a 2023 study by Liu and colleagues, which investigated metabolic changes in breast

cancer during early dissemination into the axillary lymph nodes by applying scRNA-seq and ST.⁸ The researchers observed a transition from glycolysis to oxidative phosphorylation occurred as clusters of cells on the LE of the tumour disseminated into the lymph node.⁸ This suggests that the oxidative phosphorylation pathway might play a vital role in the metastatic process.⁸

A 2022 study by Qi et al. demonstrated the potential of ST in highlighting specific cell interactions as new therapeutic targets. The paper investigated the expression of FAP+ (fibroblast activation protein) in fibroblasts and SPP1+ (secreted phosphoprotein 1) in macrophages, both associated with poor colorectal tumour prognosis.⁹ Through combined analyses of scRNA-seq, ST, and other cellular techniques, the researchers observed that most FAP+ fibroblasts and SPP1+ macrophages were found to be colocalized. This provided strong evidence of physical interaction between the two cell types. Researchers believe various proteins may be involved in this interaction, which could result in the creation of structures that limit immune cell infiltration, contributing to immunotherapy resistance. Hence, targeting FAP+ fibroblast and SPP1+ macrophage communication mechanisms is a strong potential therapeutic target.¹⁰

In 2023, Ferri-Borgogno et al. investigated the heterogeneity of cancer tissues in high-grade serous ovarian cancer (HGSC), which accounts for 70% of all ovarian cancer-related deaths. Only 15% of patients diagnosed with the advanced form of HGSC survive for more than seven years. The study aimed to discover biomarkers that predicted long-term survival in this treatment-resistant cancer.^{11,12} In tumour samples from short-term survivors (<24 months), some cell clusters expressed high levels of CDK1, periostin, and LGR5—genes associated with the cell cycle, cancer stem cell maintenance, and cell adhesion—respectively.¹¹ These genes have been associated with cancer proliferation and growth, and thus their upregulation correlates with poor prognosis.^{13–15} Integration of ST and scRNA-seq allowed researchers to determine that these transcripts were concentrated in specific clusters, opening the door to further investigation.

FUTURE DIRECTIONS AND LIMITATIONS

A future goal for the ST field is expanding to larger studies with more samples and building holistic spatial images of a wider range of cancers. All studies analyzed through this article had a limited sample size; for example, the paper by Arora and colleagues only analyzed 12 surgically resected OSCC samples from 10 patients.^{7,8,10,11} Advanced analysis on large sample sizes is extremely costly,³ restricting the scope of the study.

Previous RNA sequencing methods, such as scRNA-seq have allowed the profiling of immune cells localized in tumors. However, these methods often miss spatial information, which is crucial for understanding the interaction within the tumour microenvironment. ST could be applied to investigate how the spatial organization of the tumour influences the mRNA profiles of immune cells.

ST could also play a key role in precision oncology: personalized therapies designed based on individual tumour profiles and gene expression.^{16–18} Transcriptomic techniques have already

enhanced genomic investigations by improving biomarker identification.¹⁶ Though revolutionary, the emergence of precision oncology could simultaneously increase the disparities in healthcare related to treatment access.¹⁷ Specialized treatments may become prohibitively expensive, raising questions regarding accessibility. Scientists and policymakers will have to work in tandem to solve these issues.^{17,18}

Another limitation involves current algorithms for ST as they can only analyze small sections of tissue at a time.¹ The broader health applications of ST can only become available to scientists with further development in computation.² Similarly, the sheer volume of data, even from a single individual, is difficult for present-day systems to handle. More sophisticated methods of integration computation and biology are yet to be discovered. It is these findings that will pave the way for more complex applications of ST.^{3,16}

CONCLUSION

This paper demonstrates that while ST is in its infancy, it has already yielded promising results. Researchers have used it extensively to identify biomarkers and gain a more thorough understanding of the tumour microenvironment. These discoveries have a range of clinical applications and could fundamentally change cancer therapeutics. However, several limitations exist in the ST field, including economic and technological challenges in ST research and concerns surrounding accessibility in ST-driven therapeutics. Further developments in the field are highly anticipated.

ACKNOWLEDGEMENTS

Throughout our writing process Devlyn Sun, Raymond Qu, and Zahra Tauseef have been instrumental through their guidance, for which we would like to extend our sincere gratitude. We would also like to thank Dr. Lovaye Kajiura for her assistance during the planning and research process of this article.

REVIEWED BY: DR. KATHLEEN (KATIE) HOULAHAN

Katie Houlahan is an Assistant Professor in the Department of Biochemistry and Biomedical Sciences (BBS) and a Principal Investigator at the Centre for Discovery in Cancer Research (CDCR) at McMaster University.

EDITED BY: JACQUELINE CHEN & SAEJIN HUR

1. Williams CG, Lee HJ, Asatsuma T, Vento-Tormo R, Haque A. An introduction to spatial transcriptomics for biomedical research. *Genome Med.* 2022;14(68). Available from: doi:10.1186/s13073-022-01075-1.
2. Chen TY, You L, Hardillo JAU, Chien MP. Spatial Transcriptomics Technologies. *Cells.* 2023;12(16):2042. Available from: doi:10.3390/cells12162042.
3. Wu Y, Cheng Y, Wang X, Fan J, Gao Q. Spatial omics: navigating to the golden era of cancer research. *Clin Transl Med.* 2022;12(1):e696. Available from: doi:10.1002/ctm2.696.
4. Lewis SM, Asslein-Labat ML, Nguyen Q, Berthelet J, Tan X, Wimmer VC, et al. Spatial omics and multiplexed imaging to explore cancer biology. *Nature Methods.* 2021;18:997-1012. Available from: doi:10.1038/s41592-021-01203-6.
5. Marusyk A, Janiszewska M, Polyak K. Intratumor heterogeneity: the Rosetta stone of therapy resistance. *Cancer Cell.* 2020;37(4):471-84. Available from: doi:10.1016/j.ccr.2020.03.007.
6. Cajal SR, Sesé M, Capdevila C, Aasen T, De Mattos-Arruda L, Diaz-Cano SJ. Clinical implications of intratumor heterogeneity: challenges and opportunities. *J Mol Med.* 2020;98(2):161-77. Available from: doi:10.1007/s00109-020-01874-2.
7. Arora R, Cao C, Kumar M, Sinha S, Chanda A, McNeil R, et al. Spatial transcriptomics reveals distinct and conserved tumor core and edge architectures that predict survival and targeted therapy response. *Nat Commun.* 2023;14:5029. Available from: doi:10.1038/s41467-023-40271-4.
8. Liu YM, Ge JY, Chen YF, Liu T, Chen L, Liu CC, et al. Combined single-cell and spatial transcriptomics reveal the metabolic evolution of breast cancer during early dissemination. *Adv Sci.* 2023;10(6):2205395. Available from: doi:10.1002/advs.202205395.
9. Liu X, Qin J, Nie J, Gao R, Hu S, Sun H, et al. ANGPTL2+ cancer-associated fibroblasts and SPP1+ macrophages are metastasis accelerators of colorectal cancer. *Front Immunol.* 2023;14. Available from: doi:10.3389/fimmu.2023.1185208.
10. Qi J, Sun H, Zhang Y, Wang Z, Xun Z, Li Z, et al. Single-cell and spatial analysis reveal interaction of FAP+ fibroblasts and SPP1+ macrophages in colorectal cancer. *Nat Commun.* 2022;13(1):1742. Available from: doi:10.1038/s41467-022-29366-6.
11. Ferri-Borgogno S, Zhu Y, Sheng J, Burks JK, Gomez JA, Wong KK, et al. Spatial transcriptomics depict ligand-receptor crosstalk heterogeneity at the tumor-stroma interface in long-term ovarian cancer survivors. *Cancer Res.* 2023;83(9):1503-1516. Available from: doi:10.1158/0008-5472.CAN-22-1821.
12. Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong STC, Mok SC. Cellular and molecular processes in ovarian cancer metastasis. A review in the theme: cell and molecular processes in cancer metastasis. *Am J Physiol Cell Physiol.* 2015;309(7):444-56. Available from: doi:10.1152/ajpcell.00188.2015.
13. Izadi S, Nikkhoo A, Hojjat-Farsangi M, Namdar A, Azizi G, Mohammadi H. CDK1 in breast cancer: implications for theranostic potential. *Anticancer Agents Med Chem.* 2020;20(7):758-67. Available from: doi:10.2174/1871520620666200203125712.
14. Sung PL, Jan YH, Lin SC, Huang CC, Lin H, Wen KC. Periostin in tumor microenvironment is associated with poor prognosis and platinum resistance in epithelial ovarian carcinoma. *Oncotarget.* 2015;7(4):4036-47. Available from: doi:10.18632/oncotarget.6700.
15. Cao HZ, Liu XF, Yang WT, Chen Q, Zheng PS. LGR5 promotes cancer stem cell traits and chemoresistance in cervical cancer. *Cell Death Dis.* 2017;8(9):3039. Available from: doi:10.1038/cddis.2017.393.
16. Senft D, Leiserson MDM, Ruppin E, Ronai ZA. Precision oncology: The road ahead. *Trends Mol Med.* 2017;23(10):874-98. Available from: doi:10.1016/j.molmed.2017.08.003.
17. Prasad V, Fojo T, Brada M. Precision oncology: Origins, optimism, and potential. *Lancet Oncol.* 2016;17(2):81-6. Available from: doi:10.1016/S1470-2045(15)00620-8.
18. Mateo J, Steuten L, Aftimos P, André F, Davies M, Garralda E, et al. Delivering precision oncology to patients with cancer. *Nat Med.* 2022;28:658-65. Available from: doi:10.1038/s41591-022-01717-2.
19. Bressan D, Battistoni G, Hannon GJ. The dawn of spatial omics. *Science.* 2023;381(6657):eabq4964. Available from: doi:10.1126/science.abq4964.

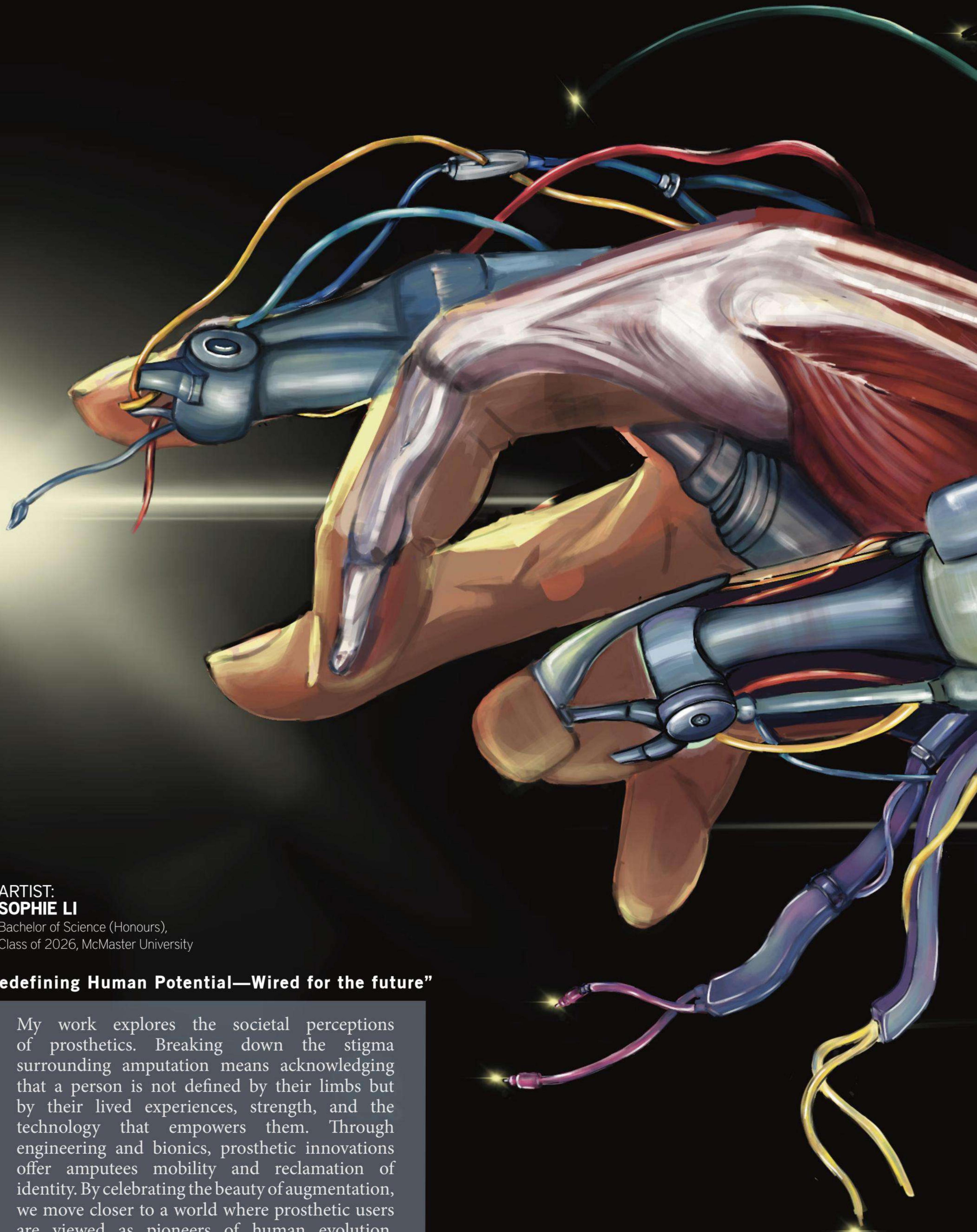
Proud
to be a part of
your medical journey

Cambridge Memorial Hospital has
immediate openings for:

- Endocrinologist
- Hospitalist (*full time and locum*)
- Anesthesia
- Geriatrician
- Dermatologist
- Neurology
- Psychiatry
- Pathology
- Family Medicine
- Obstetrician/Gynecologist
- Emergency (*full-time, part-time, urgent care and locum*)
- General Internal Medicine (*full time and locum*)
- Respirologist
- Psychiatrist
- Pediatrician
- Surgical Assist
- Plastic Surgeon
- Pediatrics
- Urology
- Orthopedics
- Emergency
- Surgical Assist

For information,
contact Nina Grealy,
Medical Affairs,
ngrealy@cmh.org



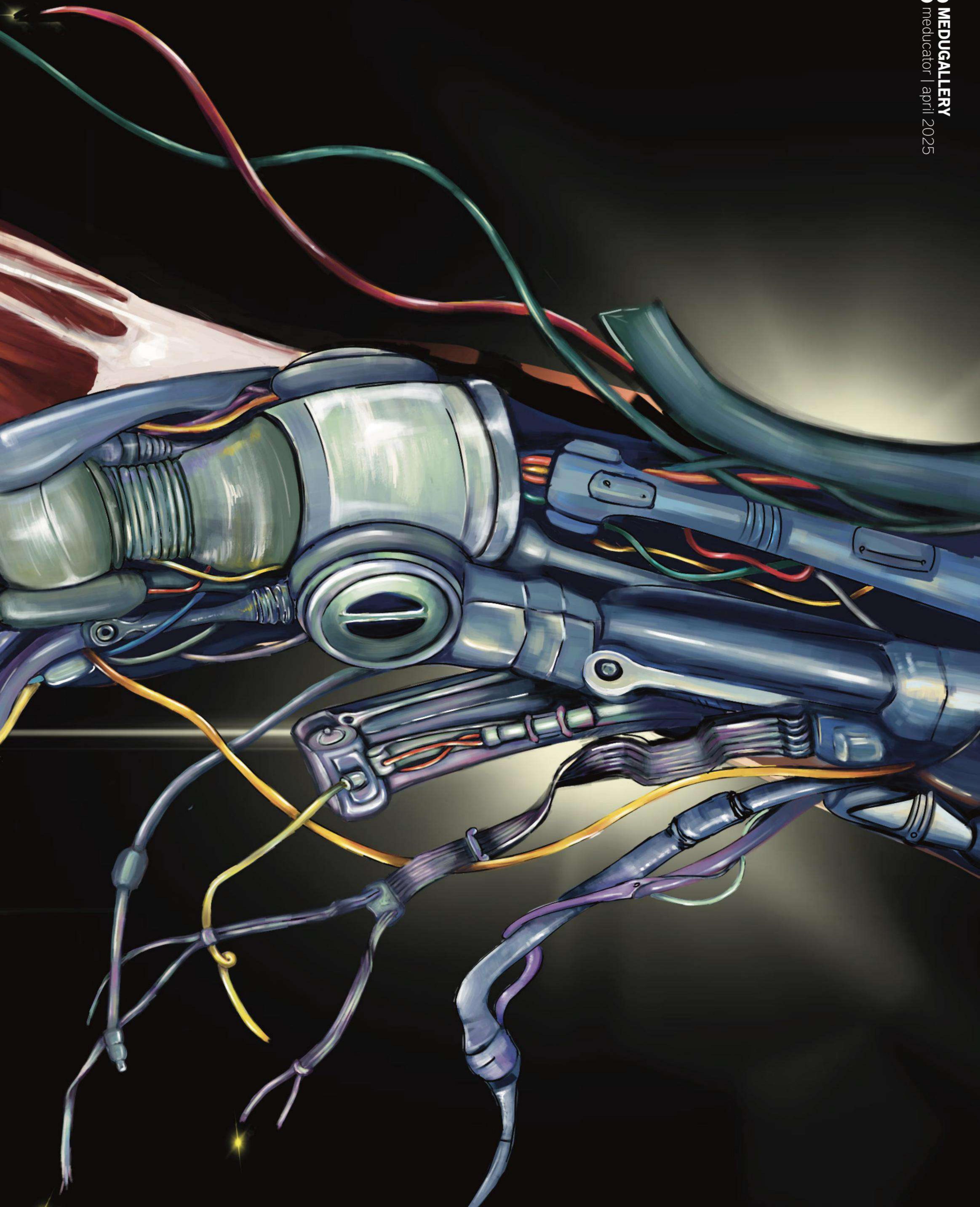


**ARTIST:
SOPHIE LI**

Bachelor of Science (Honours),
Class of 2026, McMaster University

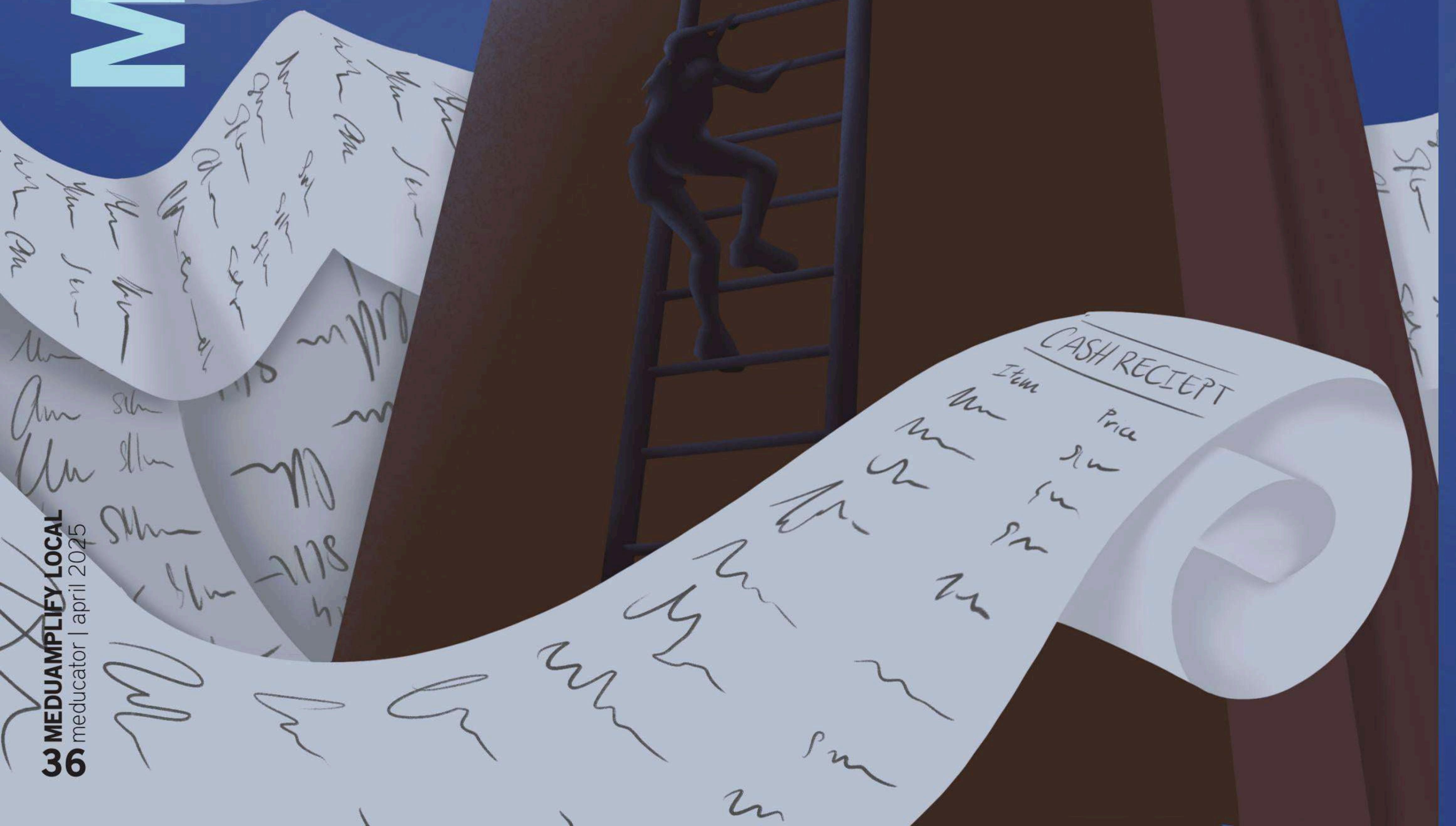
"Redefining Human Potential—Wired for the future"

My work explores the societal perceptions of prosthetics. Breaking down the stigma surrounding amputation means acknowledging that a person is not defined by their limbs but by their lived experiences, strength, and the technology that empowers them. Through engineering and bionics, prosthetic innovations offer amputees mobility and reclamation of identity. By celebrating the beauty of augmentation, we move closer to a world where prosthetic users are viewed as pioneers of human evolution.



MEDUAMPLIFY

Food Insecurity in Hamilton



doi: 10.35493/medu.47.36

AUTHORS:

KATHY HE¹, AARANI SELVAGANESH², & ZAHRAH TALAWALA³

¹Bachelor of Health Sciences (Honours Biochemistry), Class of 2027, McMaster University

²Bachelor of Arts & Science (Honours), Class of 2027, McMaster University

³Bachelor of Health Sciences (Honours), Class of 2025, McMaster University

ARTIST:

SABRINA VILORIA⁴

⁴Bachelor of Science (Honours Biology), Class of 2025, McMaster University

ISSUE

Hamilton was once the home to many steel mining companies and was a site of economic prosperity. However, in the early 2000s, the steel industry declined, with a gradual drop in the proportion of people employed in manufacturing jobs.¹ Hamilton, now home to 570,000 people, faces several growing socioeconomic challenges.²

One such issue is food insecurity: the inability and uncertainty related to obtaining a diet sufficient to maintain a healthy lifestyle.³ As of 2023, 27.3% of Hamilton households are currently facing food insecurity, a notable increase from 18.1% in 2022.⁴ The increased use of food banks is a key indicator of worsening food insecurity, with Hamilton being the city with the second-highest per-capita food bank access in Ontario.⁵ There are approximately 800 people reaching out for food support everyday in Hamilton, over 300 of which are children.⁵

Policies aimed at financially supporting low-income households have been noted to reduce food insecurity, suggesting that this issue may be a product of financial constraints.^{4,6} Though the cost of food has drastically increased over the past years, the income of residents have not.⁷ For example, if the Ontario Works program, which provides financial and employment assistance, adjusted their payouts to the 21% inflation that accumulated over six years in 2024, recipients would receive \$884 CAD per month.⁷ However, financial aid rates have not increased since 2018, with single adults receiving \$733 CAD per month, a nearly 20% reduction in purchasing power.^{7,8} However, food insecurity is more than an economic issue. It is also associated with adverse health outcomes, such as diabetes and hypertension, necessitating an interdisciplinary solution.

HEALTH IMPACT AND IMPLICATIONS

The majority of individuals experiencing food insecurity are unable to prioritize nutritious foods and report skipping or reducing the size of their meals.⁹ Episodes of food insecurity are typically short, but can lead to permanent dietary changes in the anticipation of future food insecurity.⁹ For example, individuals may decrease dietary variety and consume energy-dense foods of poor nutritional quality with lower levels of micronutrients such as B complex vitamins, magnesium, zinc, and calcium.⁹ One study examined household food security data for people up to age 70 from the Canadian Community Health Survey. They used a 24-hour recall survey to assess the correlation between nutrient intake and food security status.¹⁰ Findings illustrate that food insecurity indicated systematically lower nutrient consumption through fewer servings of dairy, fruits, vegetables, and meat or protein alternatives.¹⁰

A major limitation in food insecurity research is the inability to isolate the impacts of food insecurity from other determinants of health, such as poverty and stress.¹¹ Despite this, Tarasuk and colleagues assert that food insecurity is still a strong predictor of

poor physical and mental health, independent of other factors.¹²

In children, food insecurity is associated with adverse health outcomes including compromised immune systems, chronic illnesses, poor physical quality of life, poor physical development, poor cognitive development, and worsened mental health.^{13,14} One review by Ke and Jones describes how low prenatal iron levels, a condition correlated with food insecurity, can lead to poor performance on comprehension exams in children up to five years of age.¹⁵ Iron is essential for neurotransmitter formation and the metabolism of nervous tissue and glial cells. Thus, chronic iron deficiency can lead to permanent changes in dopamine metabolism, impacting brain function.^{15,16} One study by Anderson and colleagues found that children and adolescents with food insecurity had a 55% higher prevalence of outpatient health service contact, and 74% higher prevalence of acute care contact for mental and substance use disorders.¹⁷ Early life toxic stress, which is correlated with repeated episodes of hunger, is associated with future chronic illnesses.¹⁸

Food insecurity in adults is also associated with various chronic conditions, especially in individuals with comorbidities.¹⁹ Ziliak and Gunderson's 2021 report for Feeding America found that adults with food insecurity were more prone to diabetes, high blood pressure, congestive heart failure, heart attacks, gingivitis, asthma, and were three times more likely to have depression.²⁰ In addition, food insecurity can exacerbate infectious diseases such as human immunodeficiency virus (HIV).²¹ Cox and colleagues explain that the prevalence of food insecurity is more than 70% in individuals living with HIV, and is correlated with lower HIV treatment adherence and low CD4+ T cell counts.²¹ This is due to the worsened side effects of HIV treatment when individuals are hungry and immunosuppression caused by nutritional deficiencies.²¹ A retrospective cohort study by Men and colleagues also identified that severely food insecure households were more likely to require emergency department visits, caused by incidents including unintentional and/or self-harm.²²

Household food insecurity is also correlated to increased health care utilization and government spending. Researchers reviewed administrative health data and data from the Canadian Community Health Survey to identify health care costs and food insecurity in Ontario. They found that there was a significant effect of food insecurity on health care spending.¹² As the study was conducted on the basis of universal health care and the coverage of prescription drugs through the Ontario Drugs formulary, they noted that their results were independent of selection issues, a huge confounder in American based studies.¹² Additionally, they found that adjusted annual health care costs were 49% higher in moderate food insecurity cases, and 121% higher in severe food insecurity.¹² Berkowitz and colleagues also describe how food insecurity exacerbates diet-dependent illnesses such as obesity, type 2 diabetes, and congestive heart failure, leading to competing demands between food and health care such as medication and transportation.²³

HAMILTON'S CURRENT RESPONSE

In response to Hamilton's growing need for food assistance programs, the Emergency Food Strategic Planning Committee requested increased funding from the municipal government.²⁴ In October 2023, the city agreed to invest an additional \$1.25 million CAD to support hunger relief programs.^{24,25} The proposed distribution was to be split equally between the Hamilton Food Share for purchasing food, as well as covering staffing and facility management costs at partnering food organizations.²⁶ The 2024 Hunger Report by Hamilton Food Share revealed a 4.4% increase

in hot meals served since 2022, from 27,978 meals to 29,218 meals per month.^{5,27} However, the number of households visited per month since 2022 increased by 22.8%, rising from 8,525 to 10,468 households in 2024.^{5,27} This suggests that the increase in food distribution is not sufficient to meet growing demands. With this consideration, Hamilton Food Share continues to advocate for more donations, volunteers, and grants, while also working towards optimizing their distribution methods.²⁸

Most recently, on June 8th, 2024, the City of Hamilton, Halton Region, and Peel Region presented a collaborative resolution at the Federation of Canadian Municipalities (FCM) Annual Conference to gain federal support for food banks. The proposal called on the federal government to distribute more emergency funding to local food rescue organizations, in light of a 40% increase in Hamilton food bank use. As such, 69.4% of the FCM members voted in favour of the proposed settlement.²⁵ With this resolution approved, significant changes are to be expected in Hamilton's food support services in the upcoming years.

CALL TO ACTION

Currently, the specific allocation of the additional FCM funding has not been disclosed. We call upon the City of Hamilton to increase their transparency and communicate detailed, accessible plans for citizens to remain informed. Transparency and accountability will foster greater community involvement and trust, leading to stronger support of local organizations and their services. Organizations such as Hamilton Food Share have been operating for over 30 years, and their latest 2024 Hunger Report shows that 79.9% of their funds come from community-donated foods.²⁷ This highlights the substantial role that individual and collective community efforts play in addressing food insecurity. Beyond material contributions, engaging in advocacy is critical in influencing systemic change. Through community participation, Hamilton Food Share continues to improve their initiatives through revised plans of equitable food distribution among diverse and socioeconomically marginalized groups.²⁸ In feedback, the community unwaveringly supports their efforts to provide for more families through donations at annual events.

However, despite the proactive efforts of individual advocacy and support for local initiatives, food insecurity remains a complex issue that demands large-scale legislative solutions. Food banks are often considered a temporary solution as they fail to tackle the underlying causes of food insecurity, including high costs of living and rising energy costs, leading to poverty.^{29,30} The government has treated the food bank system as an incomplete solution, subsidizing government budgets instead of investing in affordable housing and reducing inflation rates.³⁰ One solution implemented by the United Kingdom to overcome the limitations of food banks is community markets. These markets operate by prioritizing social inclusion and sustainability, offering food at subsidized prices or with vouchers for those in need.²⁹ Unlike food banks, community markets encourage the act of purchasing. However, unlike grocery stores, they collaborate with local businesses to prioritize local socioeconomic goals over profit gains.²⁹ While community markets present a promising alternative to food banks by addressing both immediate needs and socioeconomic sustainability, a holistic approach that tackles the root causes of food insecurity is still necessary.

CONCLUSION

Food insecurity is a growing issue in Hamilton as it often leads to malnutrition and other serious health complications. Addressing this challenge requires a solution that lies beyond food banks as the persistent challenge of systemic disparity must be resolved at the legislative level first. A combined approach that considers individual action, community advocacy, and policies to induce systemic change will be critical in achieving food security for all.

REVIEWED BY:

DR. KIRSTEN BELL (PhD) & DR. JOSH NEDERVEEN

Dr. Kirsten Bell (PhD) is an Assistant Professor in the Department of Kinesiology at McMaster. She is the Principal investigator of Bell's Laboratory, exploring the relationship between adipose tissue and metabolic health. Specifically, she is interested in the mechanisms of lipid-induced insulin resistant through diet interventions and novel techniques to non-invasively measure muscle fat infiltration in humans.

Dr. Josh Nederveen (PhD) is an Assistant Professor in the Department of Kinesiology at McMaster. His research focuses exercise and skeletal muscle physiology, using biochemical techniques to discover novel interactions on a cellular level. He is involved in many studies on a variety of conditions such as spinal muscular atrophy and metabolic syndrome.

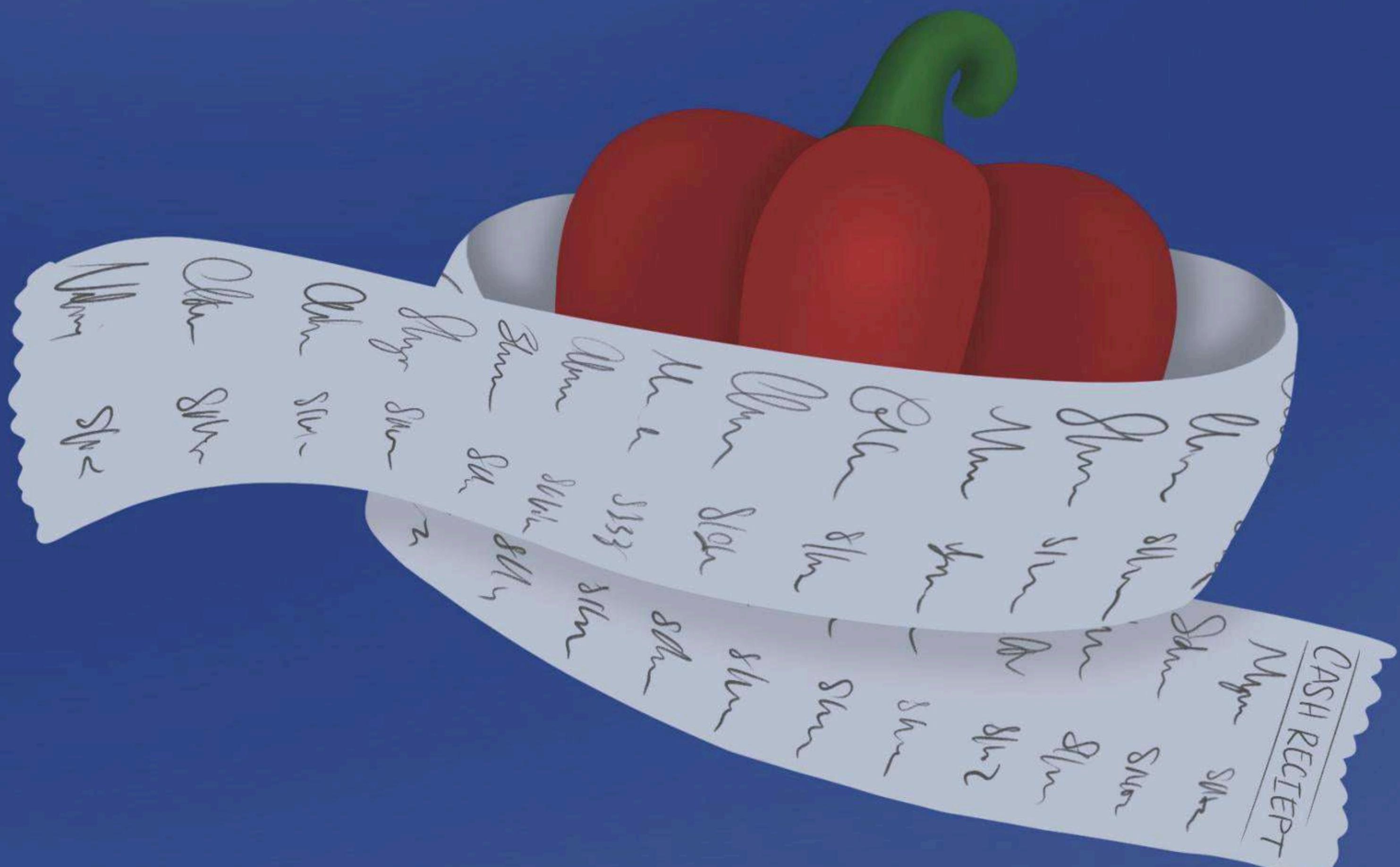
EDITED BY:

LIZA NOORISTANI, NIRUJAH SUTHARSEN, & ATTA YAZDY

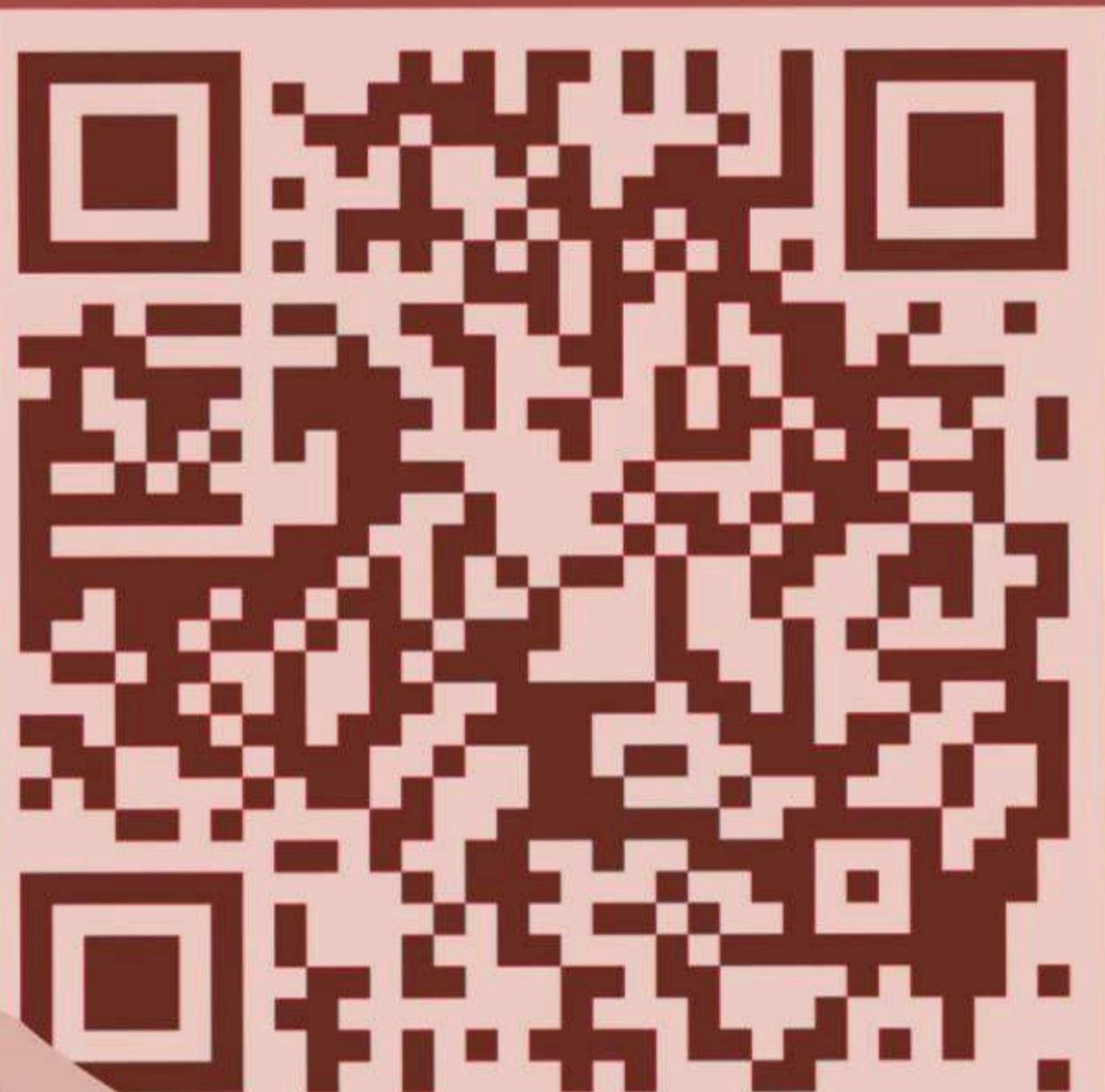
NOMINATIONS ARE NOW OPEN FOR MSU VICE-PRESIDENTS *Administration • Finance • Education* & MSU SPEAKER

ELECTIONS WILL BE HELD APRIL 5 & 6
INSIDE COUNCIL CHAMBERS, GH 111

VISIT MSUMCMMASTER.CA/ELECTIONS TO LEARN MORE DEADLINE: 10AM ON APRIL 5
NOMINATIONS AND QUESTIONS CAN BE SENT TO SPEAKER@MSU.MCMASTER.CA



VIDEO TEAM





STAFF

EDITORS-IN-CHIEF

Florence Deng & Audrey Dong

EDITORIAL BOARD

Managing Editors

Dominic Gangemi, Veronica Grignano, &
Ria Patel

Editors

Aarani Selvaganesh
Aditya Misra
Angela Hong
Atta Yazdy
Cynthia Duan
David Gou
Devlyn Sun
Emily Wang
Evan Sun
Evan Zhao
Firdose Khan
Ian Kim
Jacqueline Chen

GRAPHICS & DESIGN

Creative Directors

Elaine Wang & Henin Ye

Graphic Designers

Aymen Saeed
Aleeya Li
Ameya Gupta
Camela Temacini
Fiona Duyu
Iris Qian
Jessica Luo
Jessica Palfy
Michelle Wan

Jia Jia Lu
Joel Abraham
Kathy He
Liza Nooristani
Matthew Olejarz
Nirujah Sutharsan
Parth Arora
Ruhani Khattra
Saejin (Grace) Hur
Will Zhang
Zahra Tauseef
Zahrah Talawala

Krish Devgan
Noelle Di Perna
Michelle Giang

Nicole Kim
Parisa Mishal
Hossain
Sabrina Viloria
Sophie Li
Titus Tan
Tram Nguyen
Yuewen Gao

Aiza Baano
Angeline Vo

Olivia Kim & Aarani Selvaganesh
Meduevent Planners
Hemtoj Deo
Morgan Puusaari

SENIOR ADVISORS
Nishaad Sheth & Natalie Chu

VIDEO TEAM

Video Managers

Cindy Lin, Ryan Liu, & Nishaad Sheth

Video Producers

Mahitaj Rashid
Megan Lee
Shauna Vanderhorst
Sophie Ying
Tiffany Vo

MEDUPROMO

Director

Serena Wei

Medupromoters

Jessica Li
Tenzin Tsarong

MEDUCOLLAB

Directors

Raymond Qu & Zahra Tauseef

MEDUFINANCE

Directors

David Gou & Eric An

MEDUEVENTS

Directors

Olivia Kim & Aarani Selvaganesh

Meduevent Planners

Hemtoj Deo
Morgan Puusaari

ADDRESS

The Meducator, Honours Health Sciences Program
Michael G. DeGroote Centre for Learning and Discovery
Room 3308
Faculty of Health Sciences
1280 Main Street West
Hamilton, Ontario L8N 3Z5

CONTACT US THROUGH EMAIL

the.mediator@gmail.com

VISIT OUR WEBSITE FOR PAST ISSUES

www.themeducator.org/issues

FOLLOW UPDATES ON INSTAGRAM

www.instagram.com/the_mediator

FIND US ON YOUTUBE

Meducator Official Channel

INTERESTED IN WRITING FOR OUR NEXT ISSUE?

Visit www.themeducator.org/submissions

WE WOULD LIKE TO THANK OUR SPONSORS FOR THEIR GENEROUS SUPPORT



Honours Health Sciences Program



McMaster Student Union



Bachelor of Health Sciences Society



Office of the President



ISSN 1929-4220

A standard one-dimensional barcode is positioned vertically on the left side of the page. It is used for tracking and identification purposes.

9 771929 422471