RESEARCH Matters

Summer 2023

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Association for the Accreditation of Human Research Protection Programs, Inc.
Full AAHRPP Accreditation

McLaren

RESEARCH AROUND McLAREN

McLAREN HEALTH CARE RECEIVES FULL AAHRPP REACCREDITATION

McLaren Health Care's Human Research Protections Program (HRPP) has once again been awarded a full reaccreditation by the Association for the Accreditation of Human Research Protections (AAHRPP). MHC first achieved this prestigious accreditation in 2013 and has been accredited continuously for the past ten years.

An HRPP is a system of interdependent groups and individuals interacting to achieve a common aim to protect research participants in the conduct of human research. Chandan Gupte, Vice President of Clinical Excellence and Research states, "It is a common misconception is that an HRPP is a department, when it is actually a comprehensive program involving everyone participating in human research at McLaren. The protection of human subjects participating in research is a shared responsibility of researchers and the institution."

AAHRPP (pronounced "ay-harp") is an independent, non-profit accrediting body that sets rigorous standards for quality and protection of research study participants. As the "gold seal", AAHRPP accreditation offers assurances to research participants, researchers, sponsors, government regulators, and the general public that an HRPP is focused first and foremost on excellence.

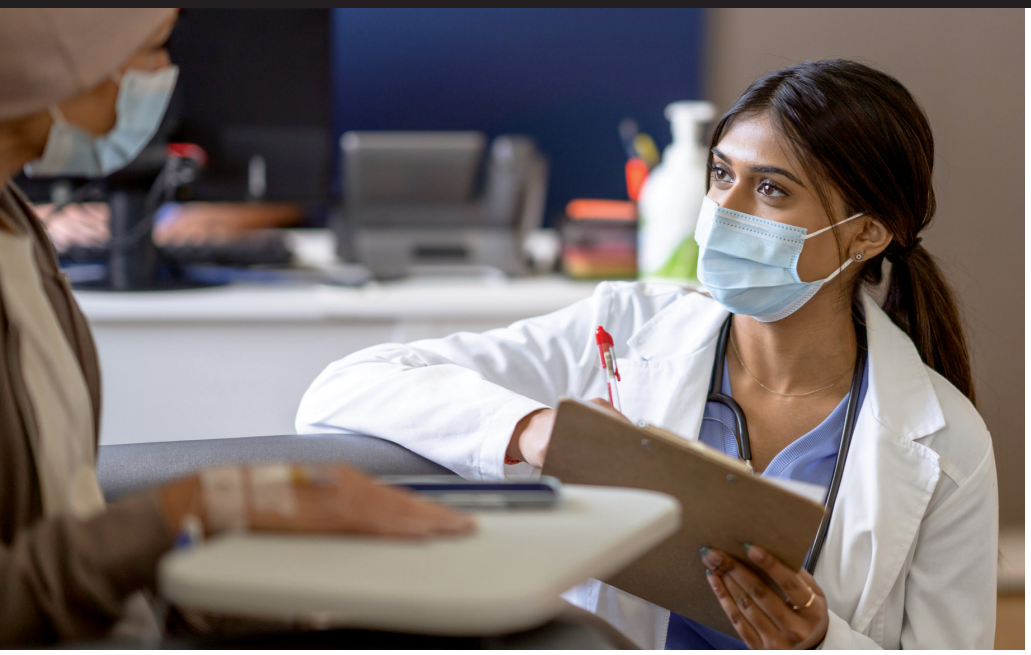
Dr. Justin Klamerus, Chief Clinical Officer, serves as the McLaren Health Care institutional Official. He states, "AAHRPP reaccreditation demonstrates McLaren Health Care's ongoing commitment to the most comprehensive protections for human research participants and the highest quality of ethically sound research".

The reaccreditation process is labor intensive and requires a great deal of self-assessment. Practices are often improved on the road to accreditation or reaccreditation. To maintain accreditation, organizations must provide tangible evidence through policies, procedures and practices of their commitment to scientifically and ethically sound research and to continuous improvement.

At MHC, we are committed to the continuous improvement of our HRPP. "Reaccreditation is evidence of our commitment to the highest level of quality and to upholding our mission of protecting the rights and welfare of human research subjects," according to Patricia Ivery, Corporate Manager of Research Integrity.

Dr. Ammar Hatahet, Chairman of the MHC Institutional Review Board, thanked everyone involved in the reaccreditation process. "The dedication of the staff and our researchers who participated in this reaccreditation process was a testament to the positive culture of collaboration and the care with which our investigators approach their human subjects research."

Congratulations to everyone involved in this intensive process!



STUDY START-UP AT MCRI

New study opportunities come to McLaren through a variety of avenues. Sometimes you as the investigator may be approached by a colleague at a conference, a representative in the cath lab, or receive an email directly from a drug or device manufacturer, asking if you would be interested in participating in a clinical trial. Other times, study opportunities get funneled in through the staff at the sites, the management staff in the Administration Office or even cold calls to our general research line. Whichever way a study gets to us, McLaren Center for Research and Innovation has a systematic study start up management plan.

As soon as a new opportunity comes to our attention, it gets sent directly to the Corporate Research Manager in charge of study start up. The study is entered into to a tracking system, then the work begins. The manager reaches out to the sponsor, telling them who we are, what we have to offer and why they should choose McLaren as a research site. From this, we often get a Confidentiality Disclosure Agreement (CDA) from the sponsor. The CDA is executed on behalf of McLaren Health Care so our whole team can receive confidential study information. Once we have a CDA, the sponsor will provide us with a study synopsis, or brief description of the trial opportunity.

The manager sends this information out to the research coordinators at all active McLaren research locations: Macomb, Flint, Bay Region, Greater Lansing and Northern Michigan. The site staff review it and see if any of their local physicians would have a particular interest in conducting the trial. Once we identify interested investigators, the manager works with the sponsor and sites to get initial feasibility questionnaires completed. The sponsor often wants to do an on-site or remote qualification visit with each site to complete their evaluation of our institution's capabilities. The sponsor will then use this information to determine if we are a suitable site for their study.

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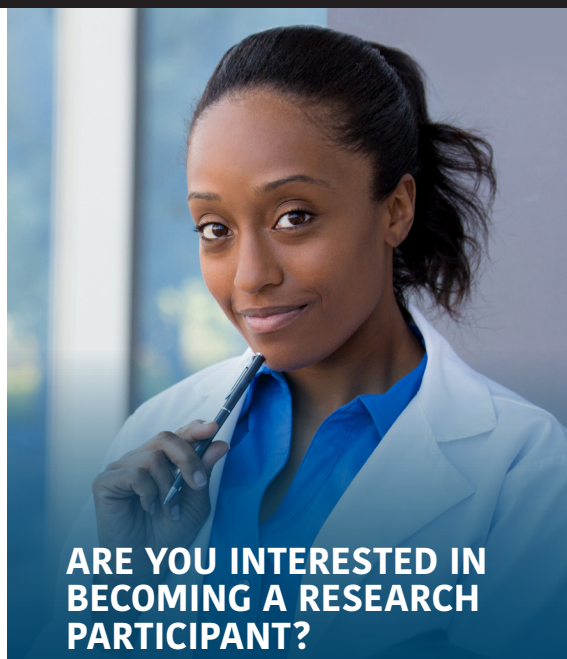

ARE YOU INTERESTED IN BECOMING A RESEARCH PARTICIPANT?

For information on enrolling in a clinical trial please visit our website at **www.mclaren.org/main/clinical-research-trials**. Here you will find a list of open enrolling studies at McLaren, including which hospital the research is being done at and contact information for each study.

We have enrolling studies for the following conditions (not a complete list):

- Diabetes
- Orthopedic Surgery
- COVID-19
- High Blood Pressure (Hypertension)
- Stroke
- Heart Attacks / Heart Failure / Heart Disease
- Kidney Diseases
- Lung Diseases
- Peripheral Artery Disease
- Carotid Artery Disease
- Mastectomy
- Various Cancers
  - Breast
  - Lung
  - Prostate
  - Multiple Myeloma
- Patients who underwent intracranial aneurysm coiling
- Drug study for patients with recent acute coronary syndrome

For a complete list of conditions, please visit our website listed above.

RESEARCH AROUND McLAREN

McLAREN HEALTHCARE NURSES ACHIEVE ADVANCED PRACTICE DEGREES

Seven McLaren nurses have recently graduated from Grand Valley State University with advanced practice degrees! McLaren Health Care and Grand Valley State University have a strong partnership in offering these degree programs funded by the HRSA Advanced Nursing Education Workforce Grant and the HRSA Nursing Workforce Diversity Grant.

The graduates are:

Advanced Nursing Education Workforce Grant earning NP degrees:
Shawn McNally – McLaren Bay Region
Caleb Migda – McLaren Northern Michigan
Lindsay Marlatt – McLaren Port Huron
Erin Russell – McLaren Oakland
Sarah Hunger – McLaren Macomb

Nursing Workforce Diversity Grant earning health systems leadership DNP degrees:
Clara Beaver – Karmanos Cancer Institute
Nina Hudgins – Karmanos Cancer Institute

We asked the graduates to share their experiences, research projects, career goals and to offer some advice for other nurses considering pursuing advance degrees.

Clara Beaver completed a project titled, *Increasing Caregiver Awareness of LGBTQI Cancer Patients Through Self-identification and Staff Education*. She reports the program at Grand Valley helped to increase her knowledge and confidence in leadership. Clara's DNP project sparked her interest

in nursing research and improving patient outcomes. Her future career goals are to continue to pursue nursing leadership positions and work on improved outcomes for cancer patients while making a difference in the LGBTQ cancer patients' lives by increasing awareness and education of staff.

Nina Hudgins completed a project titled, *Improving the Work Environment Among the Registered Nurse and Unlicensed Assistive Personnel*. When asked to offer advice to other MHC nurses considering an advanced degree, she had this to say, "Obtaining an advanced degree will not only enhance you as a nurse, but it will also allow you to make a positive impact on the nursing profession. Nurses are needed in every aspect of the healthcare system. Having an advanced degree will put you in a position to help improve the care patients are receiving and allow you a "seat" at the table when decisions are being made. Take your time and think about your long-term goals. Then decide on which advanced degree program will suit you."

Lisa Zajac, DNP, RN, ANP-BC, OCN, FNAP, Corporate Director of Clinical Informatics, and the graduates.

Sarah Hunger completed a project titled, *Improving Adherence to Annual Retinal Screening Among Adult Diabetics in Rural Midwest*. She states she has become much more interested in learning about the whole patient and has begun including family in clinical decision making in the Emergency Department. Sarah feels more independent in her ability to provide care and much more confident in her critical thinking, as well as her ability to apply evidence-based care. She will be starting as an advanced practice nurse in a rural primary care practice upon completion of certification. Sarah looks forward to providing the best possible care to the community in which she will be serving.

Erin Russell completed a project titled *Type 2 Diabetes Nutrition: A Video-Based Education Approach*. She offered advice to MHC nurses who are pondering returning to school for an advanced degree, "have a vision and a passion for something you care about and pursue it to its fullest potential. You will get more out of your experience if you enter an advanced degree program with an idea of how you want to use your skills to benefit a specific population or a cause you are passionate about". Erin has a passion for weight management and nutrition. She plans to help patients struggling to achieve their wellness goals.

Congratulations to all our graduates!

RESEARCH AROUND McLAREN

INVESTIGATOR'S CORNER

There are lots of ways to get involved in research at McLaren!

- Join one of our research committees:
  - Feasibility Review Committee – Volunteer to review protocol feasibility at your facility within your scope of practice
  - Protocol Review Committee – Participate as a committee member or volunteer to conduct and present scientific reviews of protocols in your therapeutic area
  - Research Operations Councils – Service line based councils charged with guiding research operations within a given service line to promote growth and successful enrollment.
- Participate as an Investigator:
  - Become a Sub-Investigator on a locally conducted trial
  - Become a lead investigator at your subsidiary on a study conducted at a System Level
  - Become a Principal Investigator on a clinical trial at your location
- Have a research idea?
  - Contact MCRI to create an action plan for conducting your own investigator-initiated trial
- New to research, not sure where to start?
  - Talk to your local pharmaceutical or device reps! Let them know you are interested in doing research with their product!
  - Reach out to your local MCRI research coordinators to see what kind of sponsored trials you might be able to take part in
  - Contact MCRI to see how you can get involved

What is required to get involved?

- Human Subjects Protection Training www.citiprogram.org (renew every 2 years)
- Good Clinical Practice (GCP) Training www.citiprogram.org (renew every 2 years)

- Conflict of Interest Training www.citiprogram.org (renew every 3 years)
- Current and updated CV, signed and dated (renew every 2 years)
- Professional License (if applicable)
- Disclosure of Potential Conflicts of Interest (having a conflict does not disqualify you from participating in research but must be disclosed!)

Contact **MCRI@mclaren.org** or call or text Jill George, Corporate Research Manager **(248) 672-9580** with questions or for more information.

DO YOU HAVE A RESEARCH PROJECT THAT NEEDS FUNDING?

McLaren Health Care has formed a corporate level Research Funding Committee. This committee has been created to establish a system-wide strategic plan and process for awarding research funding to investigators. One goal of this committee is to support and strengthen investigator-initiated research within the corporation. Awards of up to $5,000 will be awarded to individuals involved in Graduate Medical Education Research (Residents and Fellows). Awards of up to $20,000 will be awarded to non-GME individuals interested in pursuing Investigator-Initiated research. Non-GME awards are open to all McLaren employees or affiliated providers. These funds are to be used for the conduct of the observational or interventional research study and will be awarded on a quarterly basis. Due dates for application submissions are January 1st, April 1st, July 1st, and October 1st of each year. The application process can be accessed at: **www.McLaren.org/FundingApplication**. Required information for the application includes a detailed description of the research project, as well as a proposed budget.

RESEARCH AROUND McLAREN

Michael Simon, MD

PUBLISHED REVIEW FOCUSES ON CARDIOVASCULAR DISEASE AND BREAST CANCER

Michael Simon, MD, MPH, medical oncologist, co-leader of the Breast Cancer Multidisciplinary Team, and member of the Molecular Therapeutics and the Populations Studies and Disparities Research Programs at Karmanos Cancer Institute, recently co-authored a review with colleagues across the country. “A review of research on the intersection between breast cancer and cardiovascular research in Women’s Health Initiative (WHI)” was published in Frontiers in Oncology in March. The researchers focused on “cardio-oncology,” where cancer and cardiovascular disease intersect.

“Heart disease is the number one killer in our breast cancer population,” said Dr. Simon. “The studies emphasize the importance of taking care of all aspects of the medical care of our breast cancer patients, including diabetes, hypertension, smoking, among others, which are all essentially risk factors for heart disease.”

Consolidating this research into one article can open doors for other research questions and raise awareness of the work done on this topic.

“Many risk factors for heart disease not only lead to increased risks of breast cancer but can also lead to an increased risk of death and poorer outcomes in our breast cancer survivors,” said Dr. Simon. “It is relevant to consolidate the research in this area of cardio-oncology – at least for breast cancer.”

Dr. Simon’s co-authors include Sreejata Raychaudhuri, MD, Hillman Cancer Center, University of Pittsburgh Medical Center; Christina M. Dieli-Conwright, PhD, MPH, Dana-Faber Cancer Institute and Harvard Medical

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KARMANOS RESEARCHERS STUDY PERSONALIZATION OF HORMONE-POSITIVE BREAST CANCER TREATMENT

Researchers at Karmanos Cancer Institute have published a review article in the *American Journal of Clinical Oncology* on the standard of care for hormone receptor-positive, early-stage breast cancer. The study, "A Review of Endocrine Therapy in Early-Stage Breast Cancer: The Journey from Crudeness to Precision," discusses how treatment models for hormone-positive breast cancer need to be more personalized.

"This article summarizes the milestone trials of a new era in treating hormone-positive breast cancer with more precision medicine involved by focusing on testing the tumor sensitivity to treatment before surgery so we can predict future outcomes," said Jailan Elayoubi, MD, medical oncologist, member of the Breast Cancer, Phase 1 Clinical Trials and Sarcoma Oncology Multidisciplinary Teams.

Co-authors of the published article include Karmanos and Wayne State University researchers Jie Chi, MD, Abdurahman Alloghbi, MD, Hadeel Assad, MD, Malathy Shekhar, PhD, and Michael Simon, MD, MPH, along with Amr A. Mahmoud, MD, of Kafr Elshiekh University in Egypt.

Jailan Elayoubi, MD

RESEARCH AROUND McLAREN

Suresh Balasubramanian, MD

TOP PAPER AWARDED TO TWO KARMANOS RESEARCHERS IN MOLECULAR THERAPEUTICS RESEARCH PROGRAM

The Molecular Therapeutics (MT) Research Program at the Barbara Ann Karmanos Cancer Institute honors two research members with the Top Paper Award: Suresh Balasubramanian, MD, member of the Hematology Oncology and Multiple Myeloma and Amyloidosis Multidisciplinary Teams at Karmanos, as well as assistant professor of oncology at Wayne State University's (WSU) School of Medicine, and Guojun Wu, PhD, associate professor in basic science at WSU. Both were awarded during the 2023 Molecular Therapeutics Annual Research Symposium in May.

"This award recognizes the outstanding science done by MT Research Program members," said Asfar Azmi, PhD, leader of the MT Research Program and associate professor of oncology at WSU School of Medicine. "In order to foster high-quality science and promote high-impact publications, the MT Program leadership instituted the Top Paper Award recognizing one basic science paper and one clinical science paper."

The MT program advisory committee and program co-leaders selected the awardees from papers published in the previous 12 months. Criteria included the impact of the journal, the clinical impact of the research, and its relevance to Karmanos' mission as a National Cancer Institute-designated comprehensive cancer center.

Dr. Balasubramanian's Top Paper

Dr. Balasubramanian was the corresponding author of "Efficacy analysis of different FLT3 inhibitors in patients with relapsed/refractory acute myeloid leukemia and high-risk myelodysplastic syndrome," published in the November 2022 issue of eJHaem.

Dr. Balasubramanian played a role in the study's design, analysis, and completion, which focused on comparing the two biological classes of

FLT3 inhibitors as monotherapy in cases of relapsed or refractory acute myeloid leukemia.

"There is no data if one is better than the other, so we conducted a meta-analysis of all FLT3 inhibitors that were tested in clinical trials as a monotherapy," said Dr. Balasubramanian. "Our analyses showed that there was a trend toward a higher pooled ORR in patients treated with type 2 FLT3 inhibitors."

The most recent information shows that Gilteritinib (type 1 inhibitor) as a post-transplant maintenance therapy wasn't as effective as Sorafenib (type 2 inhibitor).

"These results underscore the need for prospective studies," said Dr. Balasubramanian. "I am happy that our work is recognized amongst the various high-impact submissions from my colleagues."

Dr. Wu's Top Paper

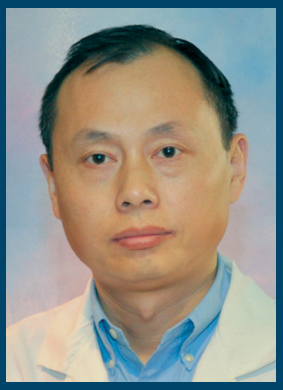
Dr. Wu is the corresponding author of "FOXQ1 recruits the MLL complex to activate transcription of EMT and promote breast cancer metastasis," published in Nature Communications in November 2022.

He designed and oversaw the project, which took around ten years to finish. The team's studies explored the possibility of targeting FOXQ1, a pan-cancer driving oncogene, to benefit patients' treatment outcomes across six cancer types, including triple-negative breast cancer (TNBC).

"We identified a novel protein-to-protein interaction that is responsible for FOXQ1-promoted in TNBC progression," said Dr. Wu. "Targeting this interaction, instead of the protein itself, will provide an unprecedented strategy to combat tumor progression driven by FOXQ1 in many cancer types."

Dr. Wu credits the many faculty at Karmanos Cancer Institute, departments of WSU and other universities who have contributed at different stages of this decade-long project.

"I am honored to be granted this award and would like to thank the MT Program leadership for their acknowledgment of the importance of our research."



Guojun Wu, PhD

PUBLISHED REVIEW

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School; Richard K. Cheng, MD, MS, University of Washington; Ana Barac, MD, PhD, FACC, Inova Schar Cancer Institute, Inova Heart and Vascular Institute; Kerryn W. Reding, PhD, MPH, RN, University of Washington; Alexi Vasbinder, PhD, RN, University of Michigan; Katherine L. Cook, PhD, Wake Forest University School of Medicine, Winston-Salem; Vidhya Nair, Ascension Providence Hospital, Michigan State University College of Human Medicine; and Pinkal Desai, MD, MPH, Weill Cornell Medical College.

RESEARCH AROUND McLAREN

Surgery for gynecologic cancer and pelvic floor disorders:

KARMANOS RESEARCHERS INVESTIGATE BENEFITS OF ONE VERSUS TWO PROCEDURES FOR CANCER PATIENTS

Researchers at Karmanos Cancer Institute completed a study that looks at the rate of concurrent surgery for locoregional gynecologic cancers and pelvic organ prolapse-urinary incontinence (POP-UI), as well as the rate of surgery for patients who have POP-UI but did not get the surgery concurrently with the removal of their cancer. Understanding that many gynecologic oncology patients also have risk factors for pelvic floor disorders, including obesity and age, scientists wanted to know if it would benefit the patient to have both procedures simultaneously. Their study, "Concurrent surgery for locoregional gynecologic cancers and pelvic floor disorders in a population of patients with Medicare insurance," is listed on the cover of the April publication of Obstetrics and Gynecology.

"Previously published literature had established that concurrent surgery for gynecologic cancer and pelvic floor disorders was feasible and safe, but it was unclear as to how often these surgeries were performed together in practice," explained Logan Corey, MD, a gynecologic oncology fellow at the Barbara Ann Karmanos Cancer Institute and Wayne State University (WSU) School of Medicine.

Corey trains with Ira Winer, MD, PhD, FACOG, gynecologic oncologist, Gynecologic Oncology and Phase 1 Clinical Trials Multidisciplinary Teams member, and Molecular Therapeutics Research Program member at Karmanos. Dr. Winer is the senior and corresponding author of the study.

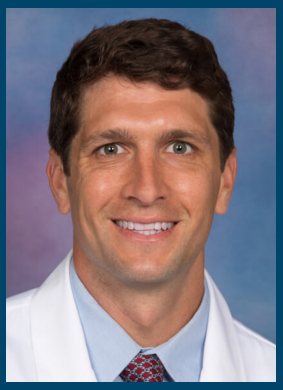
The team used the SEER-Medicare database to collect data by diagnosis, procedure codes and pelvic floor disorder identifiers. They found over 30,000 patients who fit the criteria they were looking for.

From that data, they discovered that around 5.5% of the patients who had surgery for gynecologic cancer also had concurrent surgery for pelvic floor disorders. Those diagnosed with pelvic floor disorders before their cancer diagnosis had simultaneous surgery at a higher rate (21%) than those without a known diagnosis.

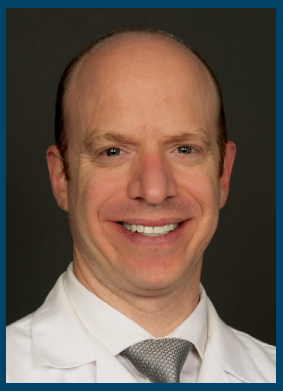
“This is important because 5% of those patients with pelvic floor disorders and gynecologic cancers who only underwent surgery for their cancer ultimately underwent a second surgery for their pelvic floor disorder within five years,” added Dr. Corey.

The authors suggest future directions will be identifying patients who benefit from concurrent surgery, determining why these simultaneous procedures do not occur, and investigating how adjuvant treatment for gynecologic cancers, including chemotherapy and radiation, affects the development of pelvic floor disorders.

Additional co-authors on this paper include Randell Seaton, MPH, WSU School of Medicine; Julie J. Ruterbusch, MPH, director of the Epidemiology Research Core (ERC) and member of the Population Studies and Disparities Research Program at Karmanos; Carol Emi Bretschneider, MD, Northwestern Medicine; Alex Vezina, MD, Ochsner Clinic Foundation; Trieu Do, MD, who at the time of this publication was a resident in the Department of Obstetrics & Gynecology, WSU School of Medicine; and Deslyn Hobson, MD, urogynecologist, WSU School of Medicine. This study was supported by the ERC and the National Cancer Institute grant awarded to Karmanos and WSU.



Logan Corey, MD



Ira Winer, MD

RESEARCH AROUND McLAREN

Nerissa Viola, PhD

RESEARCHERS AT KARMANOS DISCOVER POSSIBLE SOLUTION TO SUPPRESS PROSTATE CANCER TUMOR GROWTH

A collaborative preclinical study between researchers at Karmanos Cancer Institute, Wayne State University (WSU), Beaumont Health, the National Institutes of Health, and Curemeta, LLC, has succeeded in finding a way to potentially suppress tumor growth for patients with prostate cancer. Their study, "Selective ablation of TRA-1-60+ pluripotent stem cells suppresses tumor growth of prostate cancer," was published in Volume 13, Issue 7 of Theranostics (Impact Factor: 11.6).

"The study demonstrates that by using radiopharmaceutical therapy targeting the biomarker TRA-1-60, selective ablation of pluripotent cancer stem cells suppressed the progression of prostate cancer. We have also further shown that these TRA+ cells are culprits of tumor regrowth and require targeted treatment to prevent relapse and metastasis," explained Nerissa Viola, PhD, leader of the Molecular Imaging Research Program at Karmanos, associate professor at WSU School of Medicine, and co-author of the study.

The team explored how targeting TRA-1-60+ (TRA) can be used clinically for prostate cancer. They used an antibody specific to TRA, radiolabeled with zirconium-89, an isotope that is used for positron emission tomography (PET) imaging to detect these cells within the prostate tumors. After detection, they substituted the isotope with Lutetium-177, an isotope that emits beta particles that causes single and double-strand DNA breaks. The team injected this drug in mice with prostate cancer cells following the guidelines established by Wayne State University's Institutional Animal Care and Use Committee. They then subsequently looked at tumor growth delay over time.

"Preclinical studies using rodents, such as mice, allow us to test the efficacy of drugs like TRA-targeted RPT (radiopharmaceutical therapy). Once we validate and confirm the potency of the drugs, we can move forward to clinical trials in prostate cancer patients," said Dr. Viola.

From the experiments, researchers came to three conclusions: there is a clinical significance of TRA expression in prostate cancer, engineered and tested radiotheranostic agents can image and treat TRA+ prostate cancer stem cells, and the ablation of the TRA+ cancer stem cells did suppress the growth of prostate cancer. Their findings lead to the potential of future studies.

"The next step would be to look at targeted drug combinations with TRA RPT that will not only suppress growth but completely eradicate the tumor and prevent relapse," concluded Dr. Viola.

Jordan White, PhD, a graduate of the Cancer Biology Program at WSU School of Medicine and a mentee of Dr. Viola, is the study's lead author. Additional co-authors include Karmanos Molecular Therapeutics Research Program members and professors at WSU School of Medicine Steve Patrick, PhD, Seongho Kim, PhD, and Elisabeth Heath, MD, FACP, medical oncologist, member of the Tumor Biology and Microenvironment Research Program, leader of the Genitourinary Oncology Multidisciplinary Team (MDT), member of the Phase 1 Clinical Trials MDT, associate director of Translational Sciences, and the Hartmann Endowed Chair for Prostate Cancer Research at Karmanos.

Nicholas Ramos and Allen-Dexter Saliganan were both research assistants with Dr. Viola at the time and they contributed to the study. Jacob Lindquist, graduate student research assistant in the Cancer Biology Program at WSU; Kayla Conner, PhD, a graduate of the Cancer Biology Program; Wendy Wiesend, MD, Beaumont Health System; Michael Schopperle, Curemeta, LLC; and Joon-Yong Chung, PhD, Meghan Bell and Freddy Escorcia, M.D., PhD, from the National Cancer Institute and the National Institutes of Health are also co-authors of the study.

The research team would like to acknowledge the WSU Cancer Biology Program for supporting the three graduate students who worked on the project, including the DeRoy Testamentary Foundation Fellowship.

EQUIP CORNER

Susmita Jain, MS

WHEN RESEARCH PAYMENT BECOMES "UNDUE INFLUENCE"

By Susmita Jain, MS, Research QI and Education Specialist, McLaren Health Care

For over 200 years, payments have been offered as a commonly acceptable practice to research participants for various reasons. These reasons include alluring them to participate to meet target recruitment goals, motivating them to stay until the study completion, or compensating for loss of daily wages and relieving them from financial sacrifice, as appreciation for contribution to medical science, targeting recruitment where target population is difficult to reach or targeting individuals with rare conditions or certain races. Payment for participation in research makes many IRB members nervous because of their concerns about when monetary compensation for the study exerts undue influence on those who would otherwise not consent to participate and whether it could lead to harm. This article will explore payment models, Federal guidance on undue influence, and the attitude and role of the IRB in managing undue influence.

Defining Undue Influence

An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. This article will focus on undue influence.

Before one can consider payment to participants as an undue influence, the IRBs and researchers should apply the definition of "undue influence." The Office of Human Research Protections (OHRP) defines undue influence as potentially occurring "through an offer of an excessive or inappropriate reward or other overture in order to obtain compliance". The Belmont Report defines undue influence as an "offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance". Additionally, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Payment Models

To explore the ethics of paying participants for research, we must determine the motivation of the researchers in offering payment. Usually, compensation is offered to subjects for their time and effort for participating in the research. Also, as a reimbursement for the expenses incurred by them during participation in the research, such as travel, loss of daily wages, etc. There are several payments models in practice such as:

- **Free Market Model** – subjects are paid for providing services such as completing surveys or undergoing tests and procedures or goods such as blood. Payment is based on amount of goods and services that subjects provide. Compensation is paid to the participants for the studies that offer little or no benefits or the studies for which the target population is difficult to reach. It is based on the principle of supply and demand. High wages allowed under this approach could constitute undue inducement. The lure of money may entice some subjects to undercut efforts to protect them from harm, i.e. lying about medical history.
- **The Wage Model** – suggests that the subjects engaged in similar activities be paid similarly. This model shares some of same concerns as in the free market model.
- **The Reimbursement Model** – Unlike the market or wage model, participants are not paid labor, but as a type of public service. Based on the principle that compensation should only cover the costs incurred by the subject and the time spent away from work for participating in the trial.
- **The Appreciation Model** – offers the payment as a token of gratitude or appreciation at the end of the study completion. Small gifts, such as t-shirts, mugs, gift certificates or money, may be offered to subjects in recognition of their public service.

Since the reimbursement and appreciation models do not accurately reflect the motivations of research subjects, they could lead to difficulties with recruitment.

In summary these models may have advantages like helping in achieving recruitment targets in required timeframes, decreasing financial burden on patients, and helping in resolving the issue of undue inducement to a certain extent. But it may add the disadvantages of subjects compromising risk involved in the research and not paying enough attention during consenting process, may hide important information that could make them ineligible for the study, and creating competing environments among the investigators by paying higher amounts. The researcher needs to carefully weigh the above models and decide which one is best suited for the study at hand.

Does undue Influence impact on the informed consent and data integrity?

Now that we have looked at models of compensation, the question still remains, how does one decide how much compensation to pay to the subject for trial participation? Remember with undue influence a person is induced to “act otherwise than by their own free will or without adequate

EQUIP CORNER

attention to the consequences". In clinical research, paying subjects through an offer of an excessive or inappropriate reward in order to achieve the enrollment targets or to obtain compliance may raise ethical concerns about compromising the decision-making process regardless of the outcome. It also influences the integrity of the research data. Furthermore, it can have a more detrimental impact on some of the vulnerable populations, like children, the mentally challenged population, underprivileged population, and illiterates who have the limited autonomy in making a decision.

Attitudes of the IRB Members

Online surveys have been conducted on IRB members and research ethics professionals to address the lack of systematic data concerning attitudes about payment in general, and to determine how these individuals think about the concepts of coercion and undue influence specifically. Individuals were randomly selected from the Public Responsibility in Medicine and Research (PRIM&R)'s membership database. The survey results concluded 1) persistent ethical concerns about the effect of offering payment to research subjects, 2) divergence between how individuals view the meaning of coercion and undue influence and how they apply these concepts to concrete situations, and 3) more acceptance of payment as reimbursement or compensation for time and inconvenience than as an incentive to participate or as compensation for risk.

What Does the current Regulations, Federal Agencies and Committee say About Undue Influence?

The Federal regulations and guidelines do not explicitly define what would make a payment excessive. As a result, IRBs and investigators bear significant responsibility and discretion for correctly identifying and addressing ethical concerns around paying research participants. However, some general insight is provided for IRBs in their assessment and decision making.

Both the FDA and OHRP recognize that "paying research subjects in exchange for their participation is a common and, in general, acceptable practice." However, IRBs are instructed to be sensitive to whether "any aspect of the proposed remuneration will be an undue influence, thus interfering with the potential subjects' ability to give informed consent." Both OHRP and FDA indicate that "remuneration for participation in research should be just and fair," but OHRP warns IRBs to make sure that payments are not so high that they "could compromise a prospective subject's examination and evaluation of the risks or affect the voluntariness of his or her choices".

The FDA guidance does not consider reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence. The FDA purports that the IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20]. In addition, any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. All information concerning payment,

including the amount and schedule of payment(s), should be set forth in the informed consent document.

The Secretary's Advisory Committee on Human Research Protections (SACHRP) advises IRBs to be sensitive to whether "any aspect of the proposed remuneration will be an undue influence, thus interfering with the potential subjects' ability to give informed consent". SACHRP does recommend that FDA and OHRP issue guidance that recognizes the concerns about unduly influential incentive payments can be managed without necessarily lowering or eliminating the payments, and outlines ways to minimize the possibility of undue influence.

It is essential that researchers and regulatory bodies such as IRBs ensure that research participants are not being exploited.

Some points IRBs should considers while reviewing the research subject payment:

- Payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risks; it is a recruitment incentive.
- Payment for participation in research should be just and fair. However, the specifics of each protocol will influence how those determinations are made. Both researchers and IRBs need to be familiar with the study population and the context of the research to make reasonable judgments about how compensation might affect participation.
- Investigators must justify the compensation being provided as well as why the amount being offered is appropriate.
- The investigator should consider offering prorated payment for the time of participation in the study rather than delayed until study completion depending on the length and number of interactions or interventions.
- IRBs should ensure and carefully review the information in the consent form to be disclosed to potential subjects to ensure the terms of payments, amount, time and the method of payment is described clearly. Presentation of compensation must not detract from important information participants need to consider in order to fully understand the study and assess the risks associated with participation.
- IRBs will also review the informed consent process. Who will be conducting the Informed Consent process? Will the prospective subject feel pressured into acting quickly or be discouraged from seeking advice from others?
- The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
- Providing compensation may require the use of personally identifiable information like email addresses used to email gift cards and/or Social Security Numbers required for tax reporting purposes. The mechanics of compensating participants can contribute to risks associated with a

UPCOMING RESEARCH EDUCATION

OHRP Research Community Forum
September 26-27, 2023
For Registration follow the link:
OHRP Research Community Forum | Research Ethics & Compliance
umich.edu

WCG MAGI Clinical Research Conference – 2023 West
October 18-21, 2023
The Hilton Union Square Hotel
San Francisco, CA
For Registration follow the link:
WCG MAGI Clinical Research Conference – 2023 West | WCG
wcgclinical.com

ACRP Webinar
Upper Midwest Chapter: Navigating, Surviving, and Thriving Through Clinical Research Contract and Budget Negotiations
July 20, 2023 • 12:00 pm-1:00 pm
For Registration follow the link:
Upper Midwest Chapter: Navigating, Surviving, and Thriving Through Clinical Research Contract and Budget Negotiations | ACRP
acrpnet.org

ACRP Webinar
Suncoast chapter: regulatory summer days: don't forget your sunscreen, training logs, and delegation logs
July 25, 2023 • 12:00 pm-1:00 pm
For Registration follow the link:
Suncoast Chapter: Regulatory Summer Days: Don't forget your Sunscreen, Training Logs, and Delegation Logs | ACRP
acrpnet.org

ACRP Webinar
How do IRBs Review Virtual Trial Technology?
August 9, 2023 • 12:00 pm-1:00 pm
For Registration follow the link:
Webinar–How do IRBs Review Virtual Trial Technology? | ACRP
acrpnet.org

SOCRA
2023 Annual Conference
Advancing Innovation and Integrity: A Time for Transformation in Clinical Research
September 29-October 1, 2023
Montreal, QC Canada
Palais des congres de Montreal
(Montreal Convention Center)
1001 Place Jean-Paul-Riopelle
Montreal, QC H2Z 1H5
For registration follow the link:
2023 Annual Conference Information
socra.org

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loss of privacy or breach of confidentiality. Researchers should develop mechanisms to minimize such risks.

- McLaren IRB prohibits payments to professionals in exchange for referrals of potential subjects ("finder's fees") and payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
- Recruitment techniques (e.g., advertising) should not focus on compensation as a means of attracting potential participants. The IRB should review all advertising materials – flyers, print ads and internet postings – to ensure that they are appropriately written and displayed.
- Researchers may offer payments and compensation to vulnerable populations. Determining appropriate compensation for these populations raises difficult issues, as IRBs try to balance ethical principles including respect for participants' autonomy, prevention of undue influence and providing protection for vulnerable persons.

CONCLUSION

The future guidelines should be more focused on establishing and discussing those circumstances in detail around which offers of payment may be ethically acceptable, addressing concerns related to the amount, mechanism, timing, and context of payment.

Knowing where to draw the line between appropriate and inappropriate incentives is a challenge for IRBs and the research community. Because different benefits, such as payment amounts, impact people differently, it may often be wise to address the underlying concern while preserving the integrity of research. Helping the research community speak about their concerns regarding offers of payment will enable a more concrete separation of ethically acceptable and unacceptable payment structures, which may have the effect of improving trial recruitment and promoting fair compensation of research participants with new attention paid to the problem of underpayment.

Resources:

McLaren policy on payment to research participants and Undue Influence
MHC_RP0110_Additional Consideration during IRB Review and Approval of Research
Link: Policy Title: (mclaren.org)

FDA guidance on Payment and Reimbursement to Research Subjects
Link:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects

OHRP guidance on the payment to research participants.
Link: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html

GCP guidelines
Link:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1

STUDY START-UP AT MCRI

CONTINUED FROM PAGE 3

Once we are selected by the sponsor, we receive a contract and a budget and this starts the clock on our "study start up timeline". MCRI's goal is 90 days from contract receipt to IRB approval. Study sponsors expect a tight timeline to get studies enrolling as this process can be costly for them. The contract and budget specialist, in conjunction with McLaren's research legal team, begins reviewing the contract and budget while regulatory specialists begin drafting consents and collecting regulatory documents for the sponsor. Meanwhile, the Feasibility Review Committee, chaired by Chandan Gupte, VP of Clinical Excellence and Research, gets to work with the site staff to tease out the operational details of the protocol. FRC exists to ensure that each site has the manpower, equipment, space and local hospital resources to adequately conduct the study. The study is also evaluated for financial impact to the institution.

In the background, MCRI's contract and budget specialists and regulatory specialists are working to get study budgets, contracts, consents and other related material reviewed, prepared and ready for final execution and IRB submission. Our research informatics team and research finance teams are also on high alert during this time to prepare our Clinical Trials Management System and patient payment system for the new study.

The final step before IRB submission is Protocol Review Committee. PRC, as chaired by Mark Zainea, MD, reviews research protocols for scientific merit. This committee is charged with ensuring McLaren embarks on research that has value to the scientific community and can be of potential value to our patients. The committee is made up of primarily McLaren physicians who conduct peer reviews of research protocols. This is a wonderful forum for scientific discussion and research related collaboration.

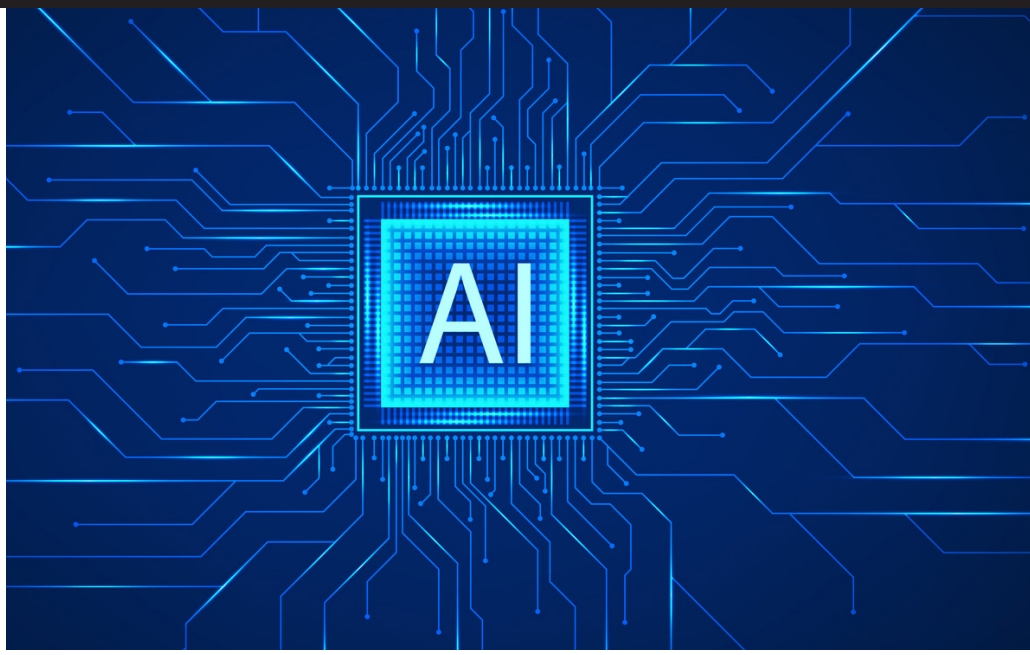
After PRC approval, the study can be released for IRB submission. Typically, once submitted, we can anticipate about 3 weeks to approval. Once the study is IRB approved, each participating site will have a Site Initiation Visit to ensure they are ready to begin enrollment. The SIV is conducted by the sponsor and includes detailed training on the study protocol, FDA regulations and responsibilities of the investigator and research team. This is also when study drug, devices or other study supplies will be shipped out to the study sites. Once the sponsor gives us the go ahead, we can begin the enrollment phase of the study.

The study start-up process is vital to the success of research at McLaren. Selecting studies that match our abilities and interests provides us a strong foundation to conduct valuable scientific inquiry and provide sponsors with high quality data. When we meet our contractual obligation with these high -profile industry leaders, they value McLaren as a partner in research and come back with future contracts. If MCRI continues to refine and improve our study start-up process, we can provide McLaren opportunity to grow research at our institution in ways we have yet to imagine.

FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

Carlos F. Rios-Bedoya, ScD



SCHOLARLY ACTIVITY AND ARTIFICIAL INTELLIGENCE

By Carlos F. Rios-Bedoya, ScD, MPH

Several weeks ago, an Artificial Intelligence (AI) tool was made freely available on the internet called ChatGPT. This tool is capable of writing programming code, news reports, term papers, legal documents, etc. with minimal instructions from a human being. Its user adoption increased to 120 million in less than two months. It did not take long for some people to start using it to write their scholarly activity papers. The use of AI to complete scholarly work bring to our attention at least two important aspects of any scholarly activity: ethics and trust.

Regarding the ethical aspects of using AI to make up scholarly activity manuscripts, we are dealing with the moral compass of professionals trained to treat human pain and suffering compassionately. Using AI in this manner could disseminate false and inaccurate information that might lead to wrong diagnoses, treatments, and negative health outcomes. Furthermore, the dissemination of scholarly activity projects is based on an honor system where everyone is supposed to uphold the highest ethical principles. It is expected that dissemination of findings come from original work, free of conflict of interests; financial or otherwise, and each researcher should have significantly contributed to the creation of that dissemination.

Trust is another major component in the dissemination of findings from scholarly activity projects. The submission, review, and publication process is based on trust. The scientific community, journal editors, and peers trust that authors of medical or scientific literature have not plagiarized the work of others, have given credit to others that have contributed to the subject matter, and disclosed any source of funding supporting the scholarly activity. Elsevier is one of many journal publishers that has instituted policies

regarding the use of AI in scientific writing. Other publishers/journals are following Elsevier.

Moreover, there is currently at least one website (https://zerogpt.net/) that can review any write-up and produces a probability that the written document was generated using AI. Similarly, researchers at Kansas University have developed a model to identify papers written by human beings with 100% accuracy and 92% accuracy for AI written manuscripts. Another current limitation of AI is that its database was created in 2021 and thus AI written manuscripts cannot cite work beyond 2021. Also, AI can create references that do not exist in any database. Therefore, journal editors and reviewers can quickly run the references cited through several databases and identify those that were generated by AI.

Currently, the Division of Scholarly Inquiry strongly discourages the use of AI on any scholarly activity project. The Division of Scholarly Inquiry is committed to supporting and facilitating scholarly activity for McLaren residents, fellows, and faculty. For additional information contact Dr. Carlos F. Ríos-Bedoya at carlos.rios@mclaren.org.

Resources:

Desaire H, Chua AE, Isom M, Jarosova R, Hua D. Distinguishing academic science writing from humans or ChatGPT with over 99% accuracy using off-the-shelf machine learning tools. Cell Reports Physical Science, 2023;4:6(1-11)

ANNOUNCEMENTS AND WHAT'S NEW

Clinical Trials Day was celebrated internationally on May 20, as it is each year to commemorate the date that English surgeon Dr. James Lind began the first randomized clinical trial to combat scurvy in 1747. Dr. Lind's research took place on a British naval ship where he divided ill soldiers into six groups, provided each group with various dietary supplements, and was able to determine a positive connection between Vitamin C and scurvy. This clinical trial laid the foundation for modern clinical research.

Clinical Trials Day is a celebration of clinical research professionals and participants, by recognizing their contributions to public health and medicine. It is a well-deserved time out to honor those who make clinical trials possible and raise awareness of clinical trials in the community. Clinical Trials are research studies with human volunteers that are intended to add to overall medical knowledge. Behind every medication and medical intervention are thousands of patients that volunteered to participate in Clinical Trials. Without Clinical Trials, devastating diseases like polio would not be all but eradicated in the United States. Nor would we have seen a 50 percent decline in coronary artery mortality rates between 1980 and 2000. Clinical Research Professionals and patients are the unsung heroes in the development of new drugs, devices, biologics and treatments to improve the care of all Americans.

Patients involved in clinical trials are often provided choices for their care beyond the standard available treatment. This care is coordinated and provided by our highly skilled clinical research professionals. At McLaren, research matters for our patients, our organization, and our physicians. Growing our research program gives our patients access to the latest clinical trials and the confidence they are receiving the best treatments, proven by research conducted in our own hospitals, by physicians they know and trust.

Clinical Trials at McLaren Health Care are conducted by the McLaren Center for Research & Innovation and the Karmanos Cancer Institute.

Office of Clinical Excellence

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