Investing in the Future of Physiatry through RESEARCH
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PRESIDENT'S MESSAGE: URGENT CALL TO SUPPORT THE FUTURE OF PMR RESEARCH

Ross Zafonte, DO

As we navigate the ever-evolving landscape of healthcare, I want to underscore the critical importance of supporting Physical Medicine and Rehabilitation (PM&R) research via the Foundation for PM&R.

Investment in research and development has been the cornerstone of progress in scientific and technology fields. PM&R is no exception, and our collective investment in its future is paramount. Our field is facing urgent, multifaceted challenges and threats ranging from evolving healthcare needs due to demographic shifts and the rising burden of chronic conditions, to the necessity of adapting to rapidly advancing technologies. To effectively navigate these challenges and position ourselves for success, we must champion innovation through research and evidence-based practices. Embracing discovery not only enables us to address current gaps in patient care but also equips us with the tools needed to proactively tackle future challenges.

Prioritizing and supporting PM&R research lays the groundwork for transformative advancements in treatment modalities, rehabilitation strategies, assistive technologies, and interdisciplinary collaborations. This not only enhances patient outcomes but also strengthens the standing of our field within the broader spectrum of healthcare.

Therefore, I urge each one of us to recognize the urgency of this moment and pledge our support to the future of PM&R research via the Foundation for PM&R. Let us come together - harnessing our collective expertise, resources, and passion for innovation - to drive positive change and chart a course toward a future where evidence-based practices and groundbreaking discoveries redefine the landscape of Physical Medicine and Rehabilitation.
Thank you for your dedication and commitment to advancing our field. Your support and contributions are pivotal in shaping the future of PM&R and your practice.

SUPPORT THE FOUNDATION:
DONATE NOW

RESEARCH GRANTS AVAILABLE

The Foundation for PM&R has several grants available in our spring 2024 cycle, with an application deadline of May 1. Information about them can be found on the Foundation website (www.foundationforPMR.org/research-grants-2/); applications must be submitted online at https://foundationforPMR.submittable.com/submit. Opportunities include:

Encompass Midcareer Investigator Grant - One grant of $20,000 for an experienced physiatric investigator to pursue a new line of inquiry. *Special thanks to Encompass for their ongoing support of this grant!*

Richard Materson ERF New Investigator Grant – Up to 3 career-development grants of $10,000 each for a research project by a physiatric investigator 5 years or less out of training (residency or fellowship).

Gabriella Molnar Pediatric PM&R Research Grant – One grant of $10,000 for a pilot study in pediatric rehabilitation.

Scott Nadler PASSOR Musculoskeletal Research Grant – One grant of $30,000 for a pilot study in musculoskeletal rehabilitation.

NEW! Tactile Medical Cancer Rehabilitation Research Grant - One grant of $10,000 for research in rehabilitative care of cancer patients. *Special thanks to Tactile Medical for their support of this grant!*

Questions about our research grants program can be directed to Phyllis Anderson, panderson@foundationforPMR.org or 847-737-6062.

VOLUNTEERS NEEDED!

With only one full-time employee, the Foundation for PM&R is primarily powered by volunteers – and we need your help! There are many opportunities available, including:

Research Grant Reviewers – Each year we receive dozens of research grant applications for consideration. To keep the time commitment reasonable, we only assign 2-3 applications to each reviewer. But that means we need more reviewers, and are always looking for a variety of subspecialty experts as well. You would have 3-4 weeks in mid-May to June to complete the reviews, which are done online through our grants portal (Submittable.com.)

Communications Strategy Committee – This committee oversees our many communications vehicles, from this newsletter

to our regular column in the AAPM&R member magazine *The Physiatrist*, and our digital communications (emails, social media and website.) We are undertaking a website rebuild in 2024 and need volunteers to help not only with the regular communications, but the website review as well.

The Foundation also has committees that manage our fundraising, financial management, programs such as the Rehab 5k and Proof of the Pudding debate, and more. To volunteer or for more information, contact Phyllis Anderson, Executive Director at panderson@foundationforPMR.org or call 847-737-6062.

CALL FOR NOMINATIONS

The Foundation for PM&R welcomes nominations for Directors-At-Large on our Board of Directors. Candidates can be physiatrists or other individual committed to physiatric research (PhD investigator, grateful patient, business executive, legal expert, etc.) Please send the individual(s) name(s), a brief explanation of why you believe they would be valuable candidates for a position on the Foundation Board, and a copy of his/her CV to Phyllis Anderson, Executive Director at panderson@foundationforPMR.org by March 15, 2024.

WELCOME, NEW SUMMIT CLUB MEMBERS!

The following individuals have recently joined their philanthropic colleagues in the Summit Club by pledging to donate at least $1,000 per year for five years. Thank you for your support and your commitment to investing in the future of physiatry through research!

- Joshua J. Alexander, MD
- David X. Cifu, MD
- Janna L. Friedly, MD
- Peter Lim, MD
- Preeti Raghavan, MD
- David Steinberg, MD

CONGRATS, REHAB 5K AND RESIDENCY PROGRAM CHALLENGE WINNERS

Thank you all for joining us in New Orleans (or virtually) in November for a wonderful 5k event! Congrats to our winners:

Male:

1st - Eric Jones (17:41)

2nd - Andy Kramer (17:43)

3rd - Joshua Martin (17:50

Female:

1st - Kaitlyn Vanias (18:59)

2nd - Audrey Adler (21:39)

3rd - Maureen Ginsburg (21:50)

Winners in the Residency Program Challenge are:

Fastest Team - Medstar Georgetown with an average time of 25:66 among its top 3 runners

Most Team Spirit - University of Miami (our sponsor!) with the most social media posts

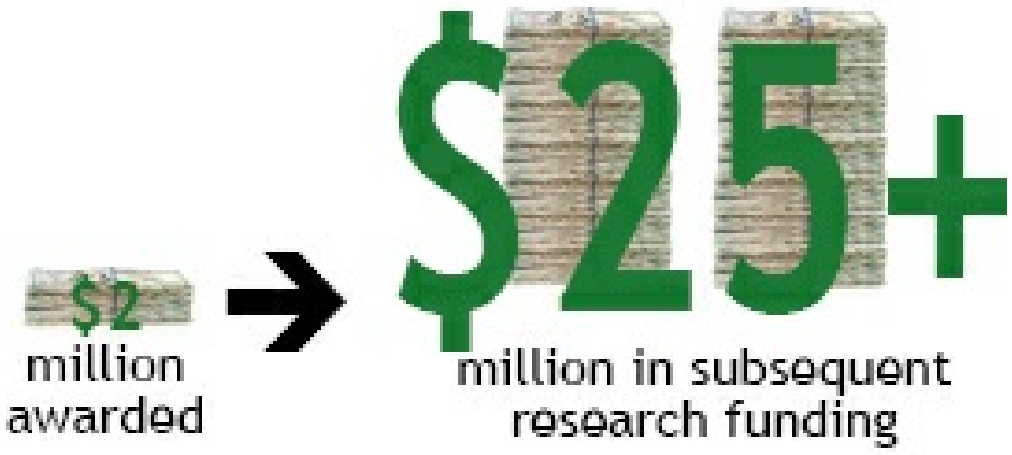
Largest Team - University of Michigan with ten team members

Thanks to our sponsor:

UHealth Jackson Rehabilitation Care

THANKS TO YOU, OUR DONORS!

The Foundation for PM&R relies on donations from individuals like you to allow us to support physiatric research with vital pilot grants. Your generosity has made our success possible – thank you!



SUPPORT THE FOUNDATION:
DONATE NOW

VISIT US AT THE AAP MEETING

The Foundation for PM&R will be in Booth #117 in the Exhibit Hall at the AAP Annual Meeting in Orlando, February 22-24, 2024. Stop by to meet Board members, sign up for the Summit or Ascent Clubs, and get information about research grant funding. Hope to see you there!

REPORT FROM A PAST GRANT RECIPIENT: KUNTAL CHOWDHARY, MD

2020 Scott Nadler PASSOR Musculoskeletal Research Grant, “From Platelet Dust to Extracellular Vesicles: Mechanistic Study of Platelet-rich Plasma and Its Role in the Treatment of Osteoarthritis”

Summary: The global geriatric population is rapidly expanding, posing unprecedented challenges linked to age-related pathologies, including metabolic disorders, cardiovascular diseases, neurocognitive decline, and physical deconditioning. In the United States alone, the number of individuals aged 65 and older is expected to rise from 50 million to 72 million by 2030. While increased life expectancy is positive, the corresponding surge in age-associated disabilities raises the question of whether aging itself can be considered a disease. Focusing on musculoskeletal health, cartilage injuries, particularly in the context of osteoarthritis (OA), present significant clinical challenges. Cartilage, with its limited healing properties, undergoes degeneration during the aging process, leading to OA - a prevalent chronic condition characterized by articular cartilage degradation and joint inflammation. Symptomatic OA affects over 15% of individuals aged 56-84 and often results in invasive surgical procedures like knee arthroplasties, which have seen a substantial increase in recent years. Addressing the intrinsic challenges of cartilage healing, platelet-rich plasma (PRP) has gained popularity as a therapeutic intervention for OA. PRP, a highly concentrated autologous mixture of platelets, is believed to stimulate cartilage regeneration through the release of growth factors, influencing chondrocyte recruitment, proliferation, and differentiation. In vitro studies consistently demonstrate the positive effects of PRP on chondrocyte proliferation and inflammation reduction. Animal models also support its healing capacity for joint defects. Despite these promising findings, there is a significant gap in research regarding the efficacy of PRP in the geriatric population, where OA is most prevalent. Furthermore, the impact of PRP on mitochondrial integrity and function in OA cartilage remains unexplored. This project aimed to investigate the age-dependent role of platelet-rich plasma (PRP) in mitigating declines in cartilage integrity associated with osteoarthritis (OA). The overarching goal was to understand the mechanisms underlying PRP's potential to reverse age- and disease-related changes in cartilage. The research aims to bridge the existing gap in knowledge and contribute valuable insights into developing clinical interventions for this high-risk demographic.

Results: In the in vitro studies, human cadaveric male chondrocytes were obtained from donors spanning different age groups (19 years, 68 years, and 73 years), and platelet-rich plasma (PRP) samples were derived from young individuals aged 18 to 35 and older individuals aged 65 or older. Chondrogenic markers, specifically type II collagen and SOX-9, were quantified in co-culture cell models. The results indicated that older chondrocytes displayed a modest decrease in these markers compared to young counterparts, with osteoarthritis-affected chondrocytes showing a significantly reduced expression. When osteoarthritis-affected cells were exposed to young PRP, there was a rejuvenation of the chondrogenic profile, evidenced by increased type II collagen and SOX-9 expression. However, this beneficial effect was attenuated in the presence of PRP derived from aged donors. In the in vivo PRP injections using a mouse model, knees treated with young male PRP exhibited lower Osteoarthritis Research Society International (OARSI) scores and decreased cartilage surface roughness compared to those treated with old male PRP. Additionally, PRP from aged male donors led to increased cartilage surface disruption and chondrocyte lacunes. Young PRP, not aged PRP, significantly decreased OARSI scores compared to saline controls. The study also found a correlation between synovial thickness and OARSI scores, indicating that treatment with old PRP not only failed to provide chondro-protection but also potentially induced an inflammatory response. In the realm of regenerative medicine, platelet-rich plasma (PRP) has garnered attention, yet its efficacy remains a topic of controversy. The lack of standardization in PRP preparation protocols, evidenced by various classification systems, has been a major criticism in current literature. The impact of patient characteristics, particularly age, on PRP's effects is a less-explored aspect. Through a series of in vitro and in vivo studies, we discovered that young PRP, but not old PRP, induced restorative properties in osteoarthritic chondrocytes, generating a chondrogenic profile resembling that of young and healthy chondrocytes. In vivo studies further indicated that injection of young PRP had a chondroprotective effect in aged mice. Paradoxically, the study found that PRP efficacy is attenuated with age and may even provoke an inflammatory response. Notably, recent clinical trials lacked consideration of patient characteristics, such as age, in evaluating PRP efficacy for knee and ankle osteoarthritis. Moreover, the impact of adiposity and sex on PRP outcomes is also notable, with increased adiposity linked to a higher incidence of osteoarthritis and significant differences in PRP composition observed between men and women. This complexity underscores the need for a comprehensive evaluation of patient characteristics to optimize the effectiveness of PRP treatments. The

study findings emphasize the significance of age as a critical patient characteristic influencing the efficacy of platelet-rich plasma (PRP) in osteoarthritis (OA) treatment. The rejuvenating effects of young PRP on osteoarthritic chondrocytes in vitro and murine chondrocytes in vivo enhancing cartilage integrity stand in contrast to the potentially harmful impact of PRP derived from older individuals on the knee joint. The results highlight the need for further investigation into age-dependent factors affecting PRP efficacy in mitigating OA.

Challenges: The current studies faced several challenges that should be acknowledged. Notably, the small sample size of platelet-rich plasma (PRP) was a challenge, and to address this, the decision was made to utilize the same samples in both in vitro and in vivo experiments, thereby enhancing the study's rigor. In the face of resource limitations during the COVID-19 pandemic, obtaining adequate samples was challenging. Despite the samples arriving frozen on dry ice from an external vendor, assessing platelet concentrations in the PRP was unfeasible. However, it is important to highlight that the PRP preparation protocol employed, while facing challenges in sample analysis, has been extensively scrutinized and demonstrated a yield of approximately 2 to 3 times higher platelet concentrations compared to whole blood. Additionally, due to the circumstances, the study resorted to a freeze-thaw method using commercially available PRP. Although studies comparing fresh and frozen PRP indicated no significant differences in their effects on chondrocyte health, it is acknowledged that future research would ideally utilize freshly isolated PRP to more closely align with clinical protocols, despite the challenges imposed by the circumstances surrounding the COVID-19 pandemic. FUTURE PLANS Future research aims to explore the long-term regenerative effects of PRP in osteoarthritic joints and establish a mechanism of action to enhance autologous PRP efficacy. The ultimate goal is to develop strategies for assessing PRP quality on a case-by-case basis, potentially leading to testing platforms enabling clinicians to determine the appropriateness of PRP treatment for individual patients. This personalized approach would optimize the targeting of specific patients with tailored PRP formulations for OA treatment. Recent studies emphasize the role of circulating factors in regulating tissue health. Administering young blood to aged cells has been shown to stimulate skeletal muscle cell bioenergetics, but this benefit is absent with aged blood exposure. The study suggests that the positive effects of young blood may be attributed to circulating extracellular vesicles (EVs), lipid-encased nanovesicles containing bioactive molecules. Depleting EVs from young blood eliminates serum-induced benefits on cellular respiration. EVs act as potent mediators of intercellular

communication, yet the impact of age-related alterations in circulating EV structure and cargo on cellular function remains poorly understood. As such, we plan to study EVs within platelet-rich plasma (PRP) across various age groups aimed to enhance our understanding of their role in PRP efficacy, providing insights for the development of meaningful therapeutic strategies for osteoarthritis prevention and treatment. Additionally, we plan to apply for additional funding for EV research in the future to further investigate the role of EVs within PRP across various age groups.

Publications: Chowdhary K, Sahu A, Iijima H, Shinde S, Borg-Stein J, Ambrosio F. Aging Affects the Efficacy of Platelet-Rich Plasma Treatment for Osteoarthritis [published online ahead of print, 2022 Dec 7]. *Am J Phys Med Rehabil.* 2022;10.1097/PHM.0000000000002161. doi:10.1097/PHM.0000000000002161

Chowdhary K, Sahu A, Iijima H, Miller A. Bean A, Ambrosio F. Age Attenuates the Benefits of Platelet-Rich Plasma on Chondrocyte Health. Abstracts of Scientific Papers and Posters Presented at Physiatry ’21, *American Journal of Physical Medicine & Rehabilitation*: April 2021 - Volume 100 - Issue 4 - p a1-a204 doi: 10.1097/PHM.0000000000001696

Presentations:

Chowdhary K., Iijima H., Sahu A., Shinde S., Ambrosio F. Coming of Age – An Investigation into the Impact of Aging on the Efficacy of Platelet-Rich Plasma Treatment in Osteoarthritis. 9th Annual AR3T Symposium. Austin, TX. October 2022.

Chowdhary K., Iijima H., Sahu A., Shinde S., Ambrosio F. Coming of Age – An Investigation into the Impact of Aging on the Efficacy of Platelet-Rich Plasma Treatment in Osteoarthritis. Rehabilitation Medicine Scientist Training Program (RMSTP) Scientific Papers Plenary. Physiatry ’22. New Orleans, LA. May 2022.

Chowdhary K., Sahu A., Iijima H., Shinde S., Ambrosio F. 2020 Scott F. Nadler PASSOR Musculoskeletal Research Grant Recipient: From Platelet Dust to Extracellular Vesicles – Mechanistic Study of Platelet-rich Plasma and Its Role in the Treatment of Osteoarthritis. 2021 AAPM&R Annual Assembly. Nashville, TN. November 2021. (Presented on-demand session virtually given the COVID-19 pandemic)

Chowdhary K., Sahu A., Iijima H., Shinde S., Ambrosio F. Age Attenuates the Benefits of Platelet-Rich Plasma on Chondrocyte Health. 17th Annual Rehabilitation Institute Research Day 2021. Pittsburgh, PA. June 2021.