

2020

## Costas T. Lambrew Research Retreat at Maine Medical Center - Abstracts from 2020

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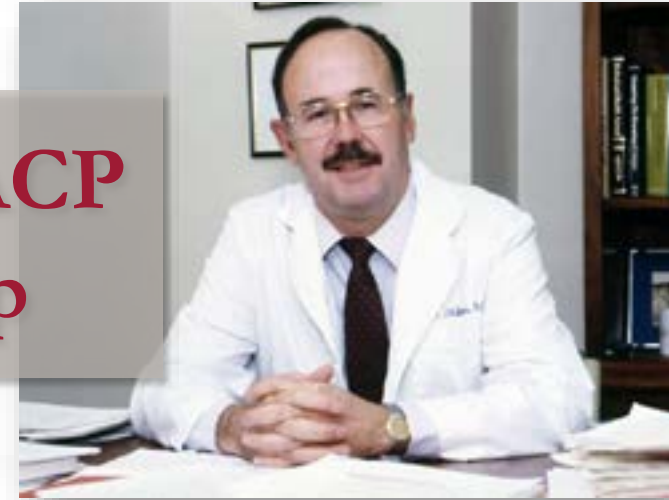
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## Costas T. Lambrew Research Retreat at Maine Medical Center - Abstracts from 2020

The Costas T. Lambrew Research Retreat is an annual gathering celebrating the accomplishments of a diverse group of students, trainees, faculty, scientists, statisticians and others from a wide range of disciplines including Medicine, Nursing, Nutrition, Social Work, Public Health, Education and many others. This year, researchers from across MaineHealth, the University of Southern Maine, the University of New England, and several other institutions submitted abstracts describing their work in basic/translational, clinical/population health, quality improvement, and health professions education categories. The abstracts below were chosen as winners in their respective categories, with selections from both trainees and faculty for each. We are pleased to present this work and are grateful to have had the opportunity to come together virtually on May 6 as a community to foster collaboration and nurture our scholarly environment.

## Robert S. Hillman, MD, MACP Clinical Research Fellowship



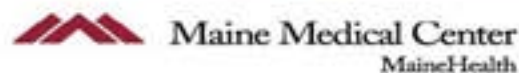
Announcing 2020-2021 Recipient...



### Abdimajid "Majid" Mohamed

*Maine Track Class of 2022 | Portland, ME*

Congratulations to Majid Mohamed for being selected as the inaugural Robert S. Hillman Clinical Research Fellow! Majid's research project will examine frailty as an assessment tool of plausible adverse outcomes in the elderly surgical patient. This research aims to decrease post-surgical complications in elderly patients and the associated financial burden of hospitals, as well as improve mortality rates in complex upper GI surgery.


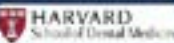


**Thomas Maciag Award for Excellence in Basic & Translational Science**

**Trainee 1st Place Award - Scientific Talk**

Eben Estell, PhD, Research Fellow, Clifford J. Rosen Lab, Maine Medical Center Research Institute, for: *The myokine irisin stimulates osteoclast differentiation and function*

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## Irisin Stimulates Osteoclast Differentiation and Function

Eben Estell, PhD<sup>1</sup>, Phuong Le<sup>1</sup>, Yosta Vegting<sup>1</sup>, Hyeonwoo Kim, PhD<sup>1</sup>, Roland Baron, PhD<sup>1</sup>, Bruce Spiegelman, PhD<sup>2</sup>, Clifford Rosen, MD<sup>1</sup>  
 Maine Medical Center Research Institute, Scarborough, ME<sup>1</sup>; Dana-Farber Cancer Institute, Boston, MA<sup>2</sup>; Harvard School of Dental Medicine, Boston, MA<sup>3</sup>

### Introduction


The myokine irisin, the cleaved product the membrane protein FNDC5 expressed in skeletal muscle, is elevated in human serum after exercise.

- Irisin injections increase mouse bone formation *in vivo* and exogenous irisin stimulates murine osteoblast differentiation *in vitro*
- FNDC5 knockout blocks resorption driven bone loss after ovariectomy
- Irisin binds to  $\alpha V\beta 5$  integrins on osteocytes, reducing apoptosis and increasing expression of sclerostin and RANKL, key osteoclast factors
- FNDC5 forced expression in muscle suppresses bone formation and increases osteoclast differentiation

*Hypothesis: Irisin directly stimulates osteoclastogenesis. By its direct actions on the osteoclast, osteoblast, and osteocyte, in addition to modulating paracrine signaling between these cell types, it plays a dynamic role in regulating coupled bone remodeling in response to exercise that is yet to be fully elucidated.*

### Methods

**In Vitro Osteoclast Differentiation with Exogenous Irisin Treatment**



- Osteoclast differentiation from primary bone marrow isolated hematopoietic precursors over 7-day culture with 30 ng/ml M-CSF and 100 ng/ml RANKL
- Treatment: +/- 10 ng/ml irisin (ISN), parallel untreated control (CTL), +/- integrin  $\alpha V\beta 5$  antibody (A55)
- TRAP staining & counting for osteoclast number (TRAP+, >3 nuclei/cell)
- Parallel wells for RNA isolation, gene expression via RNAseq & RT-qPCR
- Resorption assays via Outoclay (Corning)
- Statistical analysis via Student's t-test (2 groups) or Two-Way ANOVA with Tukey's Post-Hoc (>2 groups)

### References

1. Baroni, et al. "A PGC1-Dependent Myokine That Drives Brown Fat in the Development of White Fat and Thermogenesis." *Nature* 471(7353): 203-208, 2011. 2. Ishiyama, M, et al. "Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry." *Cell Metabolism* 2(4): 2010, 134-40. 3. Colomero, et al. "Irisin Promotes Osteoblast Differentiation *In Vitro*." *PLoS One* 2014, 9(8): e101111. 4. Kim, H, et al. "Irisin Stimulates Effects on Bone and Fat via  $\alpha V\beta 5$  Integrin Receptors." *Cell* 173(2): 2018, 576-587. 5. Miao, S, et al. "Identification and Culture of Osteoclasts." *Methods* 93: 2014, 579-584. 6. Lee, S, et al. "Irisin Directly Regulates Osteoclastogenesis via a  $\beta$  Integrin Receptor in Vivo and *In Vitro*." *Proceedings of the American Society for Bone and Mineral Research Annual Meeting*, Orlando, FL 2019.

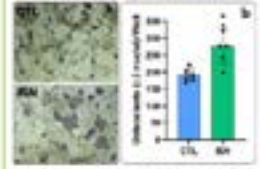
### Acknowledgements

NIDDK U54AG066917 & U54AG015516-D1A1 NIDDK R01 DK112324, NIGMS 1P20GM121301

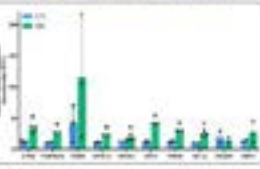
### Results

#### Irisin Stimulates Osteoclast Differentiation

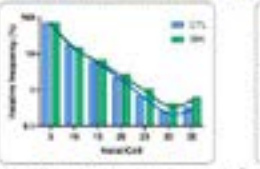
**Increased osteoclast numbers**



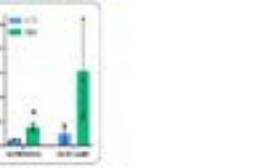
**Upregulated differentiation markers**



**Trend of increased osteoclast size**

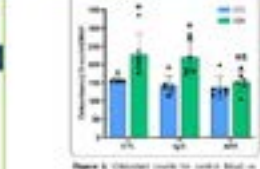


**Upregulated fusion markers**



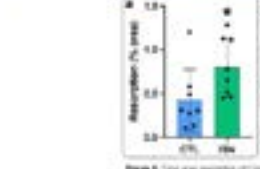
#### Irisin Binds to Integrin $\alpha V\beta 5$

**Blocking  $\alpha V\beta 5$  suppresses irisin effect**

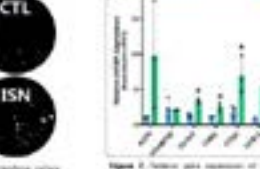


**Irisin Enhances Osteoclast Resorption**

**Increased total resorption**




**Upregulated resorption markers**



#### Irisin Stimulates Cytokine Production


**Increased differentiation gene expression**



**Enhanced resorption and cytokine expression**

| Gene Type                      | Genes   |
|--------------------------------|---|
| Resorption                     | LOX2, MMP2, ADAMTSL, ADAMTSS                        |
| Osteoclast-stimulating Factors | POSTN, IGFBP5, TGF $\beta$ 2, SPARC, CTSCRC3, WNT5a |

**Conditioned media from irisin-treated osteoclasts stimulates osteoblasts**



### Conclusions


**Irisin stimulates osteoclastogenesis**  
 Exogenous irisin at physiologically relevant levels increases osteoclast differentiation (quantity and size)

Irisin effect dependent on  $\alpha V\beta 5$  integrin binding, confirming this receptor as previously established in the osteocyte

Irisin induces differential gene expression that supports increased differentiation, fusion, resorption, and cytokine production

Irisin-induced cytokines may in turn stimulate osteoclast mineralization, suggesting a role in mediating coupled remodeling

By its direct actions on the osteoclast, osteoblast, and osteocyte, as well as paracrine signaling between the key cells in the bone remodeling unit, irisin demonstrates the potential to regulate bone formation and resorption independently, or through coupled remodeling, in differing contexts of disease, fitness, and experimental model. Future work addressing this dynamic functionality (similar to PTH) will be crucial to elucidate the role of irisin in mediating muscle-bone crosstalk during exercise, and its potential role as a therapeutic to treat degenerative bone diseases.



Act with kindness and compassion.

Be an active listener.

Be a role model.

Set high standards.

Take responsibility.

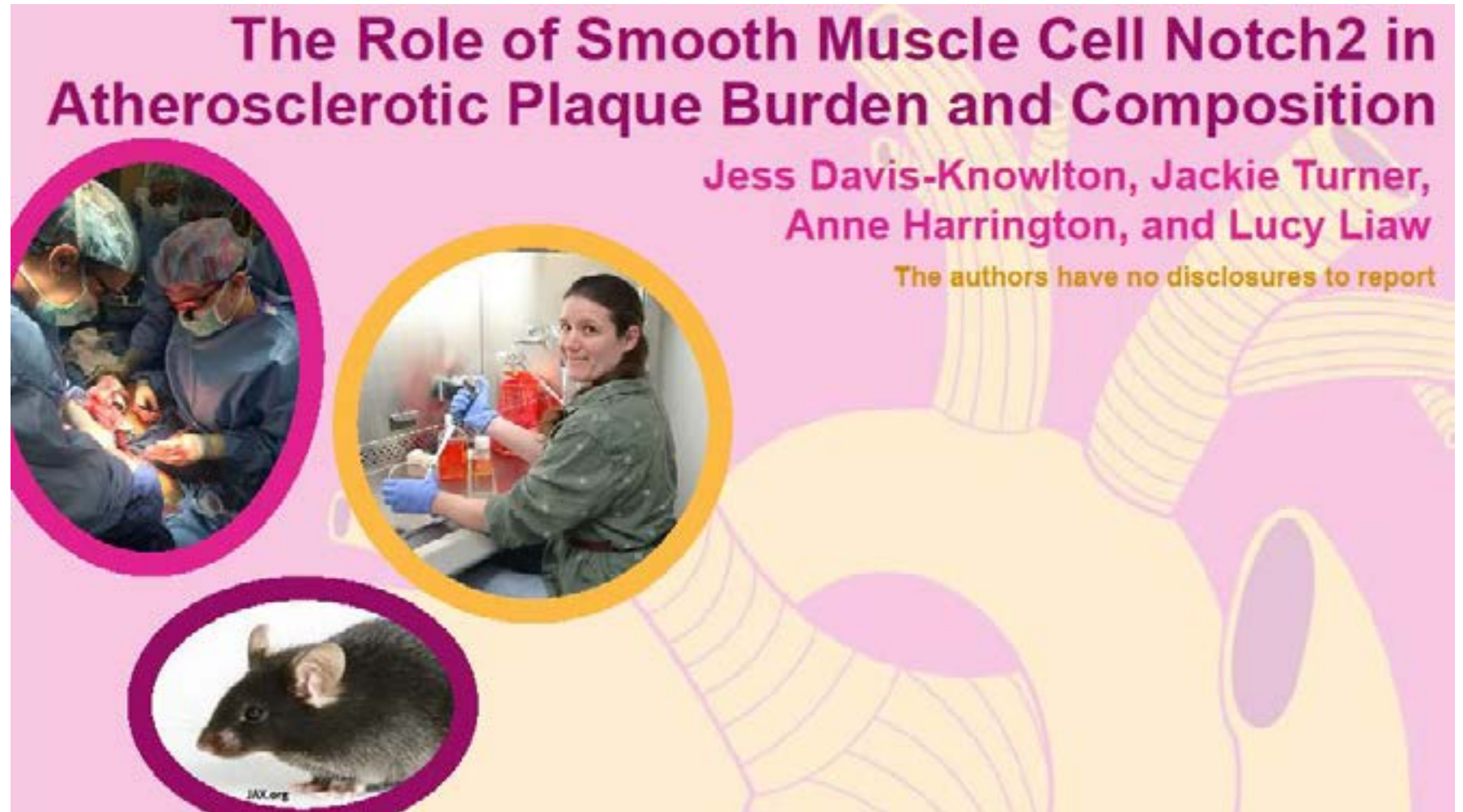
Embrace change.

**Thomas Maciag Award for  
Excellence in Basic &  
Translational Science**

**Trainee 2nd Place Award –  
Poster**

Jessica Davis-Knowlton, PhD,  
Research Fellow, Lucy Liaw  
Lab, Maine Medical Center  
Research Institute

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**Thomas Maciag Award for  
Excellence in Basic &  
Translational Science**

**Faculty/Staff Award -  
Scientific Talk**

Heather Campbell, MS,  
Scientific Manager, Michaela  
R. Reagan Lab, Maine Medical  
Center Research Institute, for:  
*Investigation of the  
relationship between obesity,  
weight cycling, and tumor  
progression in a myeloma  
xenograft model*

Not publically available at this  
time.



**Harold Osher Award for  
Excellence in Clinical and  
Population Health**

**Trainee 1st Place Award -  
Scientific Talk**

Prathusha Yerramilli,  
Student, Tufts University  
School of Medicine-MMC  
Maine Track Program,  
Pediatrics/Pediatric  
Neurology, Maine Medical  
Center

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HOSPITAL BIRTH  
VOLUME IMPACTS  
RESUSCITATION  
AND OUTCOMES OF  
INFANTS AFTER  
THERAPEUTIC  
HYPOTHERMIA

Prathusha Yerramilli,  
Channing Pooley,  
Nabeel Hashmi MD,  
Jay Kerecman MD,  
Misty Melendi MD,  
Alexa Craig MD


2020-04-27 21:08:21

**Harold Osher Award for Excellence in Clinical and Population Health**

**Trainee 2nd Place Award – Poster**

Kaitlin Minnehan, MD,  
Resident, Family/Sports  
Medicine, Maine Medical  
Center

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## Panoramic Ultrasound Measurement of the Vastus Medialis: A Validation Study with NASA

Kaitlin Minnehan, MD<sup>1</sup>, Kaitlyn Chin<sup>2</sup>, James Alex, MD<sup>3</sup>, Jessica Scott, PhD<sup>4</sup>, Megan Downs, PhD<sup>5</sup>, Amy Haskins, PhD<sup>1</sup>, Christina Holt, MD<sup>1</sup>, William Dexter, MD<sup>6</sup>, Dirk Kokmeyer, PT, DPT, PhD<sup>7</sup>

<sup>1</sup>Maine Medical Center, Department of Family Medicine, Portland, ME; <sup>2</sup>University of New England College of Osteopathic Medicine, Biddeford, ME; <sup>3</sup>Wagone Sports and Regenerative Medicine, Wallis, AR; <sup>4</sup>University Space Research Association, Houston TX; <sup>5</sup>Memorial Sloan Kettering Cancer Center, NY, NY; <sup>6</sup>Maine Medical Partners Department of Orthopedics and Sports Medicine, South Portland, ME

### Background

- Ultrasound (US) offers a cost-effective and accessible means of evaluating cross-sectional area (CSA) of muscles as compared to the gold standard, MRI
- Vastus medialis (VM) strength is important in knee injury rehab, however strength is difficult to accurately measure
- CSA can be used as an alternative to strength testing
- US CSA accuracy is dependent on muscle and location, often less accurate with smaller muscles




### Methods

**NASA study methods**

- Prospective cohort study
- 27 subjects (26 male, 1 female; age: 34.5 +/- 7.8 years, BMI 24.2 +/- 2.8 kg/m<sup>2</sup>)
- 70 days of bed rest at 6-degree head down tilt
- MRI and US images of right extremity at 13 time points
- Dil-filled templates to identify location

**MWC study methods**

- Secondary data analysis using NASA acquired and de-identified images
- 24 subjects
- Compared US and MRI images from first time point

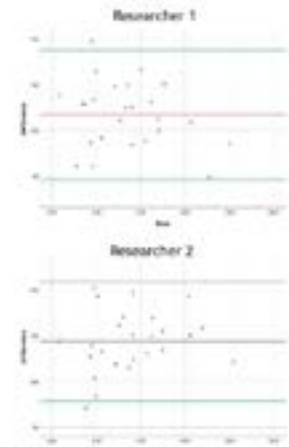


### Results

**Validity:**

|     | ICC  | 95% CI       | P value | SEM (cm <sup>2</sup> ) | MDC (cm <sup>2</sup> ) |
|-----|------|--------------|---------|------------------------|------------------------|
| R 1 | 0.98 | 0.95 to 0.99 | P<0.01  | 0.76                   | 2.1                    |
| R 2 | 0.98 | 0.96 to 0.99 | P<0.01  | 0.77                   | 2.1                    |

**Bland-Altman Plots:**  
Displays the difference between MRI and US CSA measurements along the y-axis vs. the range of the average MRI and US measurements along the x-axis

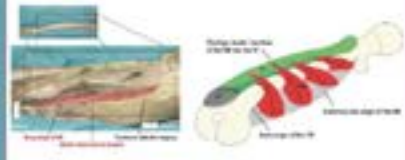


### Conclusions

- Ultrasound is valid and reliable tool to measure the CSA of the vastus medialis when compared to the gold standard, MRI
- There is acceptable intra- and inter-rater reliability
- Ultrasound is a cost-effective option to assist with diagnosis and plan of care

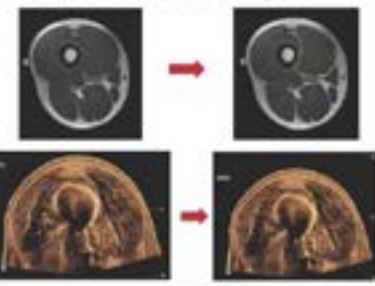
### Study Aims

- To test the validity of panoramic ultrasound measurements of the CSA of the vastus medialis compared to the gold standard MRI.
- To test the inter- and intra-rater reliability of the ultrasound measurements of vastus medialis CSA



### Data Analysis

- Used ImageJ software from NIH
- With freehand function, outlined the VM in all MRI images then in all US images in randomized order (3 measurements each)
- ImageJ calculated CSA in cm<sup>2</sup>
- Trained research assistant on same technique
- Used SPSS to calculate interclass correlation coefficients (ICC), standard error of the mean (SEM), minimal detectable change (MDC) and make Bland-Altman plots



**Inter-rater reliability:**

|                          | ICC  | 95% CI        | P value |
|--------------------------|------|---------------|---------|
| MRI average measurements | 0.94 | 0.94 to 0.98  | P<0.01  |
| US average measurements  | 0.98 | 0.95 to 0.99  | P<0.01  |
| US single measurement    | 0.95 | 0.89 to 0.975 | P<0.01  |

**Intra-rater reliability:**

|                 | ICC   | 95% CI         | P value |
|-----------------|-------|----------------|---------|
| US Researcher 1 | 0.996 | 0.992 to 0.998 | P<0.001 |

### Limitations


- Study population consists of young, healthy subjects with low BMI
- There are anatomic variants that make it difficult to distinguish the VM muscle septum in some subjects

### Next Steps

To determine if 10 weeks of weightlessness creates measurable change in VM CSA as measured by ultrasound.

### Acknowledgements

Supported by the Maine Medical Center Mentored Research Grant. Partnered with the University Space Research Association and KBRhyle through NASA.



### Literature Cited

1 Scott, J., Martin, D., et al. Panoramic ultrasound: a novel and valid tool for monitoring change in muscle mass. *J Cachexia Sarcopenia Muscle*, 4(2):481 (2017)

2 Grib, K., Alexander, M., Filgenis, L. et al. The interaction between the vastus medialis and vastus intermedius and its influence on the extensor apparatus of the knee joint. *Knee Surg Sports Traumatol Arthrosc* 24, 127-138 (2016)



**Harold Osher Award for  
Excellence in Clinical and  
Population Health**

**Faculty/Staff Award -  
Scientific Talk**

Kinna Thakarar, DO, MPH,  
Infectious Disease, Maine  
Medical Center, for: *Injections  
and infection: understanding  
harm reduction utilization in a  
rural state*

Not publically available at this  
time.

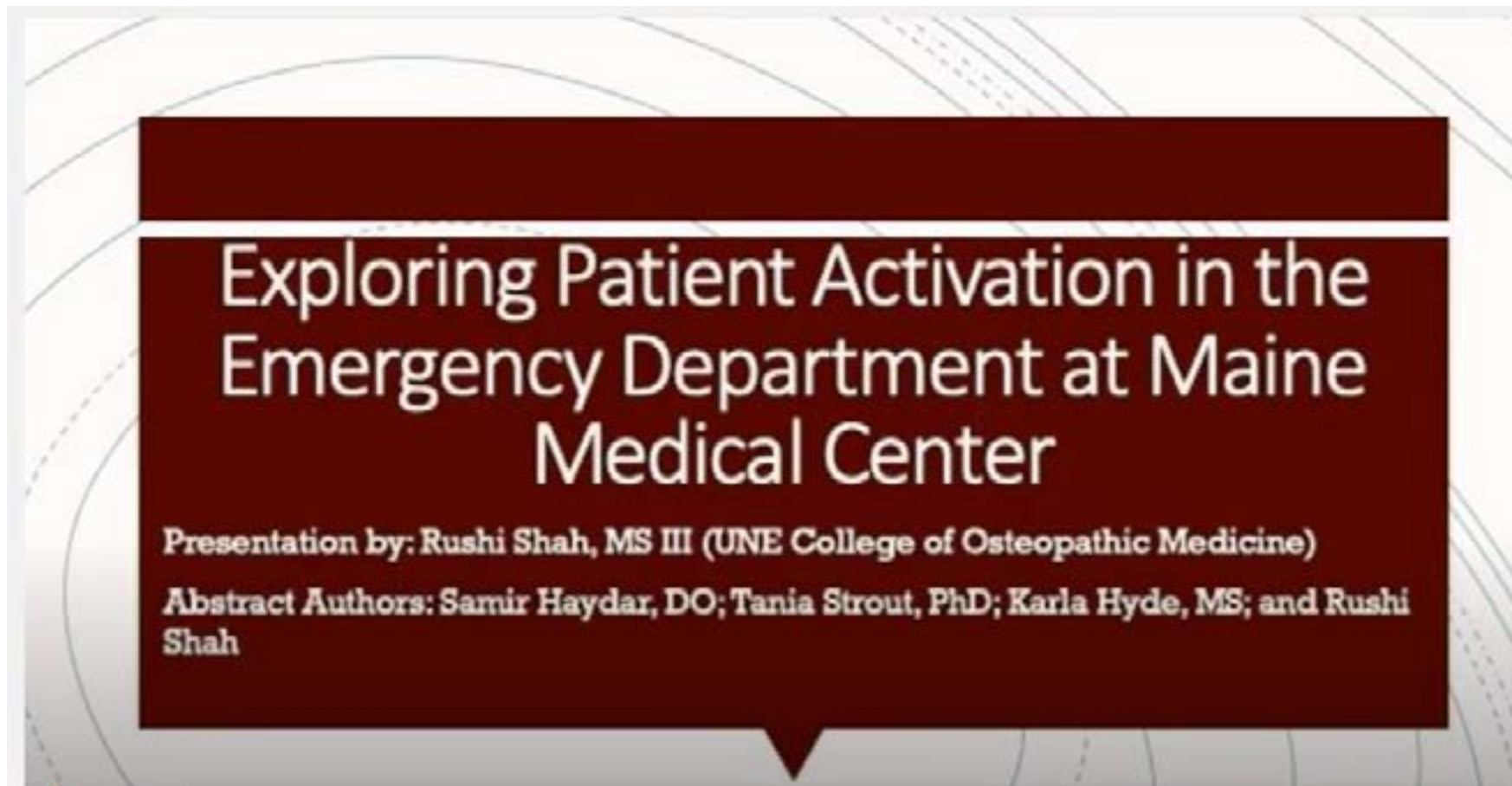


**Award for Excellence in  
Quality Improvement  
Research**

**Trainee 1st Place Award -  
Scientific Talk**

Rushi Shah, MS, Student, UNE  
College of Medicine,  
Emergency Medicine, Maine  
Medical Center

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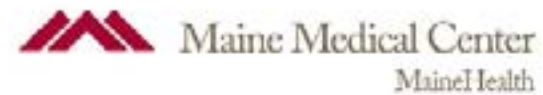
**Award for Excellence in  
Quality Improvement  
Research**

**Trainee 2nd Place Award –  
Poster**

Kayla Harris, PharmD,  
Resident, Ambulatory Care,  
Maine Medical Center

\*This abstract also won the  
2020 Maine Nephrology  
Associates Himmelfarb  
Research Prize

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**Impact of pharmacist-led medication  
reconciliation and education at an  
outpatient dialysis center**

**Costas T. Lambrew Research Retreat  
May 6, 2020**

**Primary Investigator: Kayla Harris, PharmD**

**Co-Investigators:**

Marizela Savic PharmD, BCPS

Corinn Martineau PharmD, BCACP, CDOE

**Award for Excellence in  
Quality Improvement  
Research**

**Faculty/Staff Award -  
Scientific Talk**

Lauren Tate, RD, Clinical  
Dietician, Nutrition Services,  
Maine Medical Center

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The screenshot shows a video player interface. The main content is a presentation slide with the following text:

**Improving Vitamin D  
Management in an Adult  
Cystic Fibrosis Program**

Stefanie DiLoreto, PharmD  
Alicia Murry, RN  
Tegan Swift, RD  
Lauren Tate, RD

May 6<sup>th</sup>, 2020

The slide also features the Maine Medical Center logo and several award logos at the bottom, including 'BEST' and 'MAGNET'. A video player control bar at the bottom shows a timestamp of 0:00 / 6:57 and various playback controls. A small video inset in the top right corner shows a woman speaking.

**Peter W. Bates Award for  
Excellence in Health  
Professions Education  
Research**

**Trainee 1st Place Award -  
Scientific Talk**

Richard Byrnes, Student,  
Tufts University School of  
Medicine-MMC Maine Track  
Program, Medical Education,  
Maine Medical Center

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*(video presentation by Leah  
Mallory, Medical Director,  
The Hannaford Simulation  
Center, Maine Medical  
Center)*

The screenshot shows a video player interface. The main content is a presentation slide with the following text and logos:

- Maine Medical Center** (Maine Health logo)
- Tufts** | School of Medicine
- The Barbara Bush Children's Hospital** (At Maine Medical Center)
- Factors correlating with interprofessional engagement in debriefing following pediatric simulation-based team training**
- Richard Byrnes, Zachary Priest, Christine Schreiber, Justin Michaud, Tracie Barbour, Michael Ferguson, Micheline Chipman, Wendy Craig, Leah Mallory
- Hannaford Center for Safety, Innovation & Simulation

At the bottom of the slide, there are several award logos: BEST REGIONAL HOSPITALS (U.S. News & World Report), YAFF (Yale Award for Family Fellowship), and a gold medal. The video player controls at the bottom show a timestamp of 0:00 / 14:30 and a date of 2020-04-25 02:05:01.

**Peter W. Bates Award for  
Excellence in Health  
Professions Education  
Research**

**Faculty/Staff Award -  
Scientific Talk**

Rebecca Hutchinson, MD,  
Hospice & Palliative  
Medicine, Maine Medical  
Center

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