



## Spine Biologics Overview and EBM Update

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Department of Orthopaedic Surgery  
Northwestern University Feinberg School of Medicine

2/15/2017 Park City, UT

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Entity	Consulting	Advisory Board	Royalties	Research Grant
Medtronic	X			
Stryker	X		X	
Ceramtec	X			
Lifenet		X		
Xtant		X		
Globus		X		
Bioventus		X		
Mirus		X		
Graftys	X			
LSRS		X		
OREF				X

2/15/2017 Park City, UT

Disclosures

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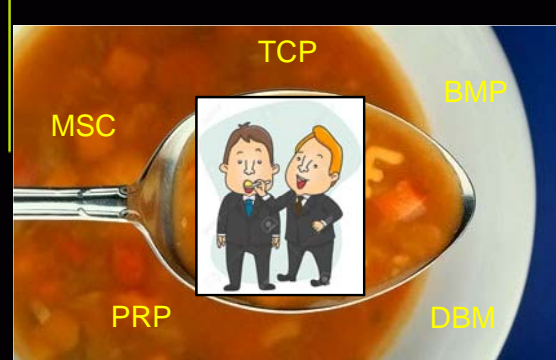
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TCP

MSC BMP

PRP DBM



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**GLOBAL SPINE JOURNAL**

### Improving the Clinical Evidence of Bone Graft Substitute Technology in Lumbar Spine Surgery

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 J. A. Youssef<sup>6</sup> D. S. Brodke<sup>7</sup> C. M. McCullough<sup>8</sup>

- Posterolateral spinal fusion
- 1-3 levels
- Adult degenerative conditions
- Plain radiographs / CT scan
- LOE I-IV



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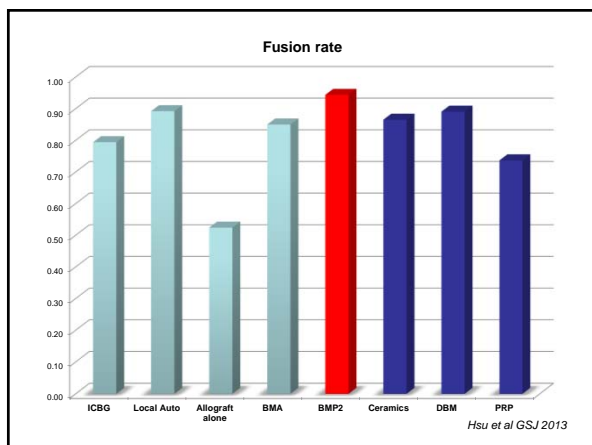
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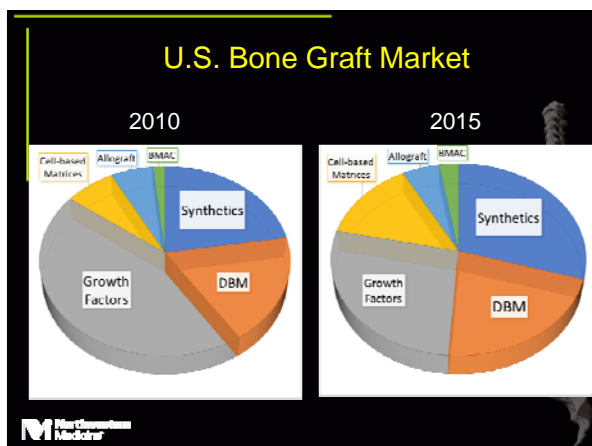
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## Where we have been...

**Short-Term Adverse Events, Length of Stay, and Readmission Following Iliac Crest Bone Graft for Spinal Fusion.**  
 Dombay JA\*, Bassous BA, Bost CD, Webb M, Grauer JN

ICBG comprises 6% of spine fusions...

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Search: "local bone graft" and "spine fusion"

**ORIGINAL ARTICLE**

**Uni- and bi-lateral Instrumented Posterolateral Fusion of the Lumbar Spine with a local Spine with Local Bone Grafting: a Prospective Study with a 2-Year follow-up**

**Follow-Up**

Suji Ohtori, MD, PhD,\* Takama Koshi, MD, PhD, Munetaka Suzuki, MD, PhD, Masashi Takano M, MD, PhD, Jun Miyagi, MD, PhD, Jun Takamiya, MD, PhD

**Bone Union Rate With Autologous Iliac Bone Versus Local Bone Graft in Posterior Lumbar Interbody Fusion**

Zenya Ito, MD,\* Yukihiko Matsuyama, MD,\* Yoshihito Sakai, MD,\* Shiro Inagama, MD,\* Norimasa Wakano, MD,\* Ken Ando, MD,\* Kenichi Hwang, MD,\* Ryoji Tashiki, MD,\* Akihiro Muramoto, MD,\* Hiroaki Matsui, MD,\* Tomohiro Matsumoto, MD,\* Takumi Kanemura, MD,† Go Yoshida, MD,† Yoshinori Ishikawa, MD,† and Naoki Ishiguro, MD\*

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### Lumbar Spine Fusion Rates with Local Bone in Posterolateral and Combined Posterolateral and Interbody Approaches: Results from a Multicenter Trial

Beaumont Health System  
Orthopaedic Research

*Daniel Park, MD; Kevin Baker; Paul Arnold, MD, FACS; David Kim, MD; Rick Sasso, MD; Jeff Fischgrund, MD*

- Retrospective study
- 241 pt with instrumented PLF or with PLF/interbody at single-level
  - Local autologous bone
  - No extenders/enhancers
- Fusion assessed with
  - < 3 mm translation
  - < 5 degrees angulation on flex/ex
  - CT scan grading of bridging bone
- **18% bilateral fusion rate with PLF alone** (6 months)
  - 24% unilateral fusion
- **44% bilateral fusion rate with PLF alone** (12 months)
- Interbody patients with significantly lower rates of fusion
- Could be volume-dependent

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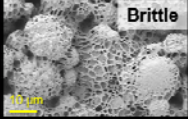
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## Synthetic carriers

- Silicates
- Ceramics
  - Calcium phosphate
  - Hydroxyapatite
- Bioglass
- Collagen-based
  - More flexibility
  - Less variability
  - Better biomechanical properties





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### Ceramics: Clinical evidence for ceramics in spine fusion

Ralph W. Cook, BS, and Wellington K. Hsu, MD\*

Department of Orthopaedic Surgery, Feinberg School of Medicine, Northwestern University, 676 N. St. Clair St., Suite 1350, Chicago, IL 60611

- Bone graft extender
- Non-immunogenic, biologically inert
- Favorable cost profile



**Table 1 – Efficacy of ceramics in posterolateral lumbar fusion (PLF)**

Type of ceramic	Number of studies	Number of patients	Fusion rate (%)
B-TCP <sup>10-15,16-17</sup>	11	755	90.3
HA <sup>18-20,21,22,23</sup>	6	259	95.0
B-TCP/HA <sup>24,25,26,27,28</sup>	5	374	91.2
Calcium sulfate <sup>29-31,32,33</sup>	5	353	87.0
Collagen-based matrices <sup>34,35,36</sup>	3	67	62.7
Silicated calcium phosphate <sup>37</sup>	2	88	77.3
Bioactive glass ceramics <sup>38</sup>	2	33	36.3

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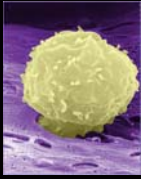
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## Cell-based Strategies

- Mesenchymal stem cells
  - Multipotent
  - Adult source
  - Autologous
  - Survival rates
  - Autocrine effects
  - Paracrine effects
  - Long-term stimulus
  - Unlimited supply





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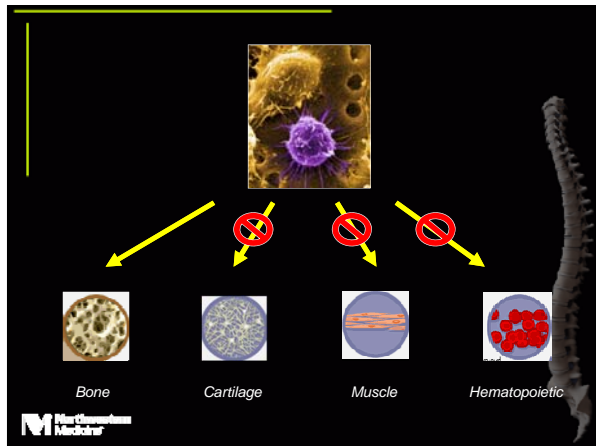
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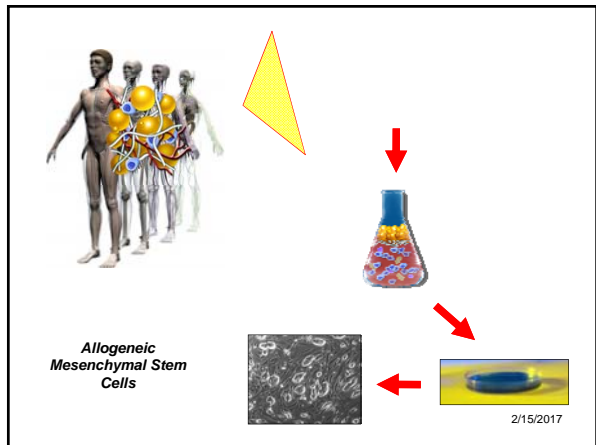
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## Cell-based Matrices

- Source of cells
  - Adipose
  - Bone Marrow
- Processing method
  - Retention of bone, GF, cells
  - "Dirty DBM"
- Mechanism of action
  - Non-cell-based
  - Creating a microenvironment

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"spine fusion" and "allogeneic stem cells"

The role of Osteoecel Plus as a fusion substrate in minimally invasive instrumented transforaminal lumbar interbody fusion  
 Joshua M. Ammerman<sup>1,2,\*</sup>, Joseph Librizzi<sup>3</sup>, Matthew D. Ammerman<sup>1,2</sup>  
<sup>1</sup>Department of Neurological Surgery, George Washington University School of Medicine, Washington, DC, United States  
<sup>2</sup>Department of Surgery, Valley Memorial Hospital, Washington, DC, United States

*Clinical Study*  
**Allograft Cellular Bone Matrix in Extreme Lateral Interbody Fusion: Preliminary Radiographic and Clinical Outcomes**  
 Antelme G. Tuhmei,<sup>1</sup> Blake Watson,<sup>1</sup> Mirna Tuhmei,<sup>1</sup> and Xavier J. Zielinski<sup>2</sup>

**The Use of Osteo-conductive Stem-Cells Allograft in Lumbar Interbody Fusion Procedures: An Alternative to Recombinant Human Bone Morphogenetic Protein**  
 Subhansu J. Kerr III, MD, Ajay Jaiswal, MD, MS, Terry Wooten, RT, Stephen Kay PA-C, David A. Cavanaugh, MD, and Pierce D. Nunley, MD




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Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis  
 Steven J. McAnany, MD<sup>1</sup>, Junyoung Ahn, BS<sup>2</sup>, Islam M. Elboghady, BS<sup>3</sup>, Alejandro Marquez-Lara, MD<sup>4</sup>, Nomaan Ashraf, MD,MBA<sup>5</sup>, Branko Svovrlj, MD<sup>6</sup>, Samuel C. Overley, MD<sup>7</sup>, Kern Singh, MD<sup>8</sup>, Sheeraz A. Qureshi, MD, MBA<sup>9\*</sup>

- Retrospective review of ACDF
  - 57 patients
  - 1- or 2-level ACDF between 2010-12
  - Osteoecel, allograft, anterior plate
  - Compared to control of allograft (Vertigraft)
  - 1-year f/u
- 50 of 57 (87.7%) fused in Osteoecel group
- 54 of 57 (94.7%) fused in control, p=0.19




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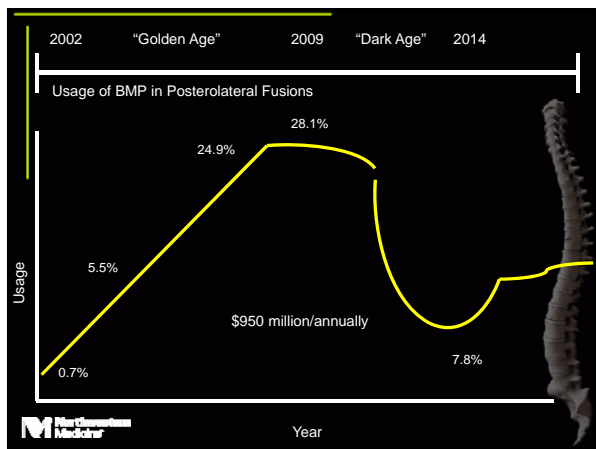
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DISREVIEWS

Wellington K. Hsu, MD

*Investigation performed at the  
Department of Orthopaedic Surgery,  
Feinberg School of Medicine,  
Northwestern University, Chicago,  
Illinois*

### RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 IN SPINE SURGERY

- ICBG is gold standard, but there is morbidity
- No clinical advantage for BMP and similar complication rates (not including ACDF)
- In some surgical cases, may not make sense to assume any increased risk, no matter how small
- In others, the small risks of cancer and other complications may be reasonable to take
- Patients should be counseled on this information



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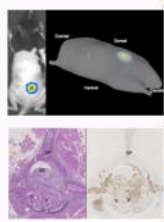
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### Effect of Recombinant Human Bone Morphogenetic Protein-2 on a Novel Lung Cancer Spine Metastasis Model in Rodents

Kevin A. Sonn, Abhishek S. Kannan, Sharath S. Bellary, Chawon Yun, Sohaib Z. Hashmi, John T. Nelson, Jason H. Ghodadra, Michael S. Nickoli, Vamsi Parimi, Anjan Ghosh, Nicholas Shawen, Amruta Ashtekar, Stuart R. Stock, Erin L. Hsu, Wellington K. Hsu

- 36 athymic rats intraosseous injection of lung CA cells
  - Group A - control
  - Group B - cells exposed to BMP
- BLI used to confirm tumor size and signal
- BMP no difference in
  - Tumor burden
  - BLI radiance
  - Amount of osteolysis



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### Cancer Risk from Bone Morphogenetic Protein Exposure in Spinal Arthrodesis

Mick P. Kelly, BS, Jason W. Savage, MD, Soren M. Bentzen, PhD, Wellington K. Hsu, MD, Scott A. Ellison, MBA, and Paul A. Anderson, MD

*Investigation performed at the Department of Orthopedics and Rehabilitation, University of Wisconsin, Madison, Wisconsin*

- SEER cancers
- Population-based study
- 2005-2010
- 5-year f/u
- Medicare/PearlDiver
- ICD-9-CM codes
- 467,916 patients
  - 110,808 pt with rhBMP-2
- Relative risk reduction with rhBMP-2
  - 6.2%

	% Dx		Incidence		RR (95% CI)
	BMP	Non-BMP	BMP	Control	
Overall	5.9	6.5	2076	2212	0.938
Male	7.5	8.0	2674	2722	0.982
Female	4.9	5.4	1699	1823	0.932

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### Bone Morphogenetic Protein Use and Cancer Risk Among Patients Undergoing Lumbar Arthrodesis

A Case-Cohort Study Using the SEER-Medicare Database

Daniel C. Beachler, PhD, MHS, Elizabeth L. Yanik, PhD, ScM, Brook I. Martin, PhD, MPH, Ruth M. Pfeiffer, PhD, MA, Sohail K. Mirza, MD, MPH, Richard A. Deyo, MD, MPH, and Eric A. Engels, MD, MPH

- Case-cohort study
- SEER Program-Medicare
  - 7278 patients > 65 yo, Lumbar arthrodesis 2004-11
    - 3627 random subcohort (191 with cancer)
    - 3651 with cancer
- Weighted Cox prop-hazards regression for hazard ratios based on BMP exposure
- 31% of lumbar fusions used BMP
- No association of BMP and cancer
- BMP not associated with new cancer with prior diagnosis of cancer
- BMP not associated with mortality after cancer diagnosis

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MENU	
ICBG.....	\$1600
Allograft.....	\$300
DBM.....	\$900
Ceramics.....	\$1100
Stem cells.....	\$2600
rhBMP-2.....	\$4000

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### What do I use?

Approach	Biologic
Open lumbar	Local bone graft + synthetic
ACDF	Allograft
Posterior cervical	DBM
MIS TLIF	BMP
ALIF/LIF	BMP

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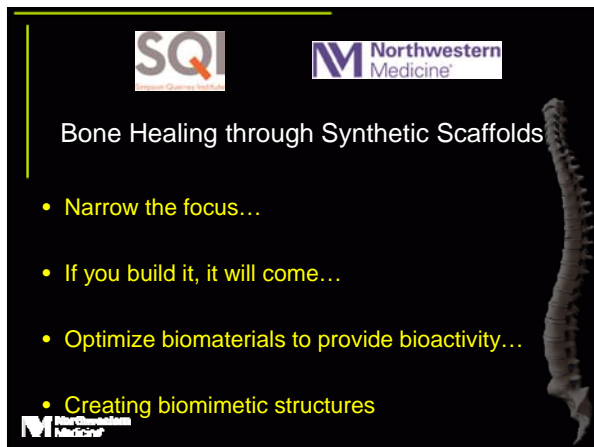
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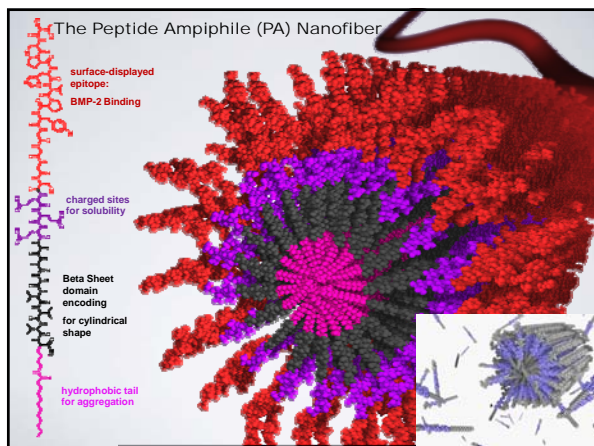
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### Complexity in Self-Assembling Structures

Forces Controlling Self-Assembly

- Hydrophobicity
- Molecular Packing
- Van der Waals force
- Hydrogen bonding
- Polar force
- Ionic charge
- pi-pi stacking (aromatic molecules)

**M** McGraw-Hill  
Medicine

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### Adding Osteoinductive Properties to the PA Nanofiber

Bone Morphogenetic Protein (BMP-2)  
Growth Factor

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### Adding Osteoinductive Properties to the PA Nanofiber

Bone Morphogenetic Protein (BMP-2)  
Growth Factor

surface-displayed epitope: BMP-2 Binding

charged sites for solubility

Beta Sheet domain encoding for cylindrical shape

hydrophobic tail for aggregation

*Advanced Healthcare Materials* 4(1), (2015) 131-141.

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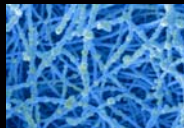



### Gel Scaffolds of BMP-2-Binding Peptide Amphiphile Nanofibers for Spinal Arthrodesis


Sungsoo S. Lee, Erin L. Hsu, Marco Mendoza, Jason Ghodadra, Michael S. Nickoli, Amruta Ashtekar, Mahesh Palavarapu, Jacob Babu, Rehan M. Riaz, Joseph D. Nicolas, David Nelson, Sohaib Z. Hashmi, Stuart R. Kaltz, Jeffrey S. Earhart, Bradley R. Merk, Jeff S. McKee, Shawn F. Bairstow, Ramille N. Shah, Wellington K. Hsu, and Samuel I. Stupp\*



Only gelled



Gelled then exposed to BMP-2 in solution



**M** Multiple Views **Medicine**

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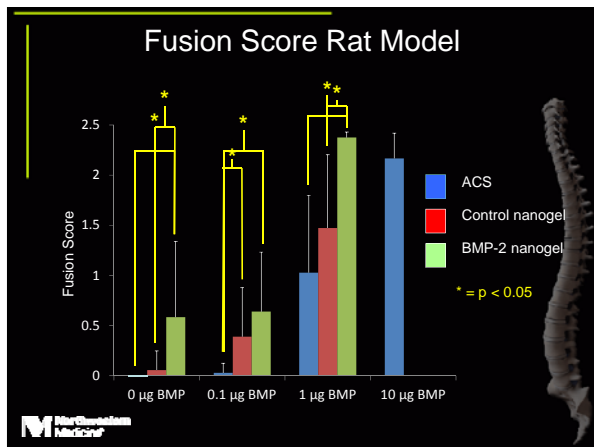
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## Conclusions

- Technologies behind spinal biologics continue to evolve
- Almost all products available are extenders vs. substitutes
- Synthetics gaining market share
- Increasing our understanding of CBMs
- BMP likely does not increase risk of cancer



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## Acknowledgements

### Current Contributors *(Pictured left to right)*

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 Erin Hsu, PhD  
 Ralph Cook, MD Candidate  
 Erin Hsu, PhD  
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 Michael Schallmo, MD Candidate  
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 Jonghwa Yun (not pictured)  
 Sameer Singh, MD Candidate (not pictured)  
 Andrew George, MD Candidate (not pictured)  
 Stuart Stock, PhD (not pictured)

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 Marco Mendoza, MD  
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 Jason Ghodadra, MD  
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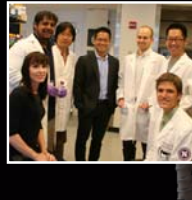
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