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CENTER FOR DISRUPTIVE MUSCULOSKELETAL INNOVATIONS

Development of Novel Impedance Sensor to Monitor Fracture Healing

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Clinical Need and Industrial Relevance

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15M fracture injuries/year in the U.S. [1]

20% fractures result in delayed or non-union [2]

46% when in conjunction with vascular injury [3]

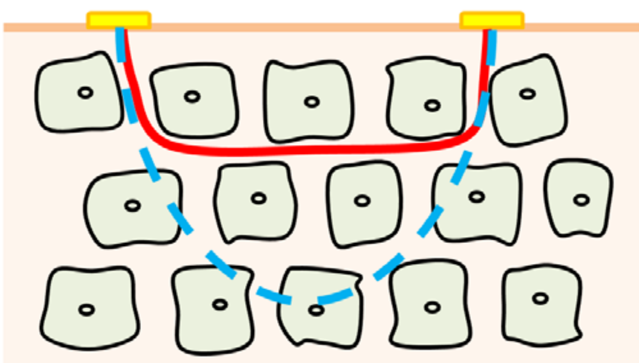
Current Methods of Monitoring

- X-ray: cannot detect soft tissue
- CT scan: high radiation, expensive
- Observation: subjective

[1] Schenker, 2014 [2] AAOS, 2008 [3] Einhorn, 1995

Technique: Impedance Spectroscopy

- Impedance: $Z = R + jX = R + j\frac{-1}{\omega C}$
  - Resistance: intra and extra-cellular environment
  - Capacitance: cell membrane



— Low frequencies: primarily reflect extracellular environment

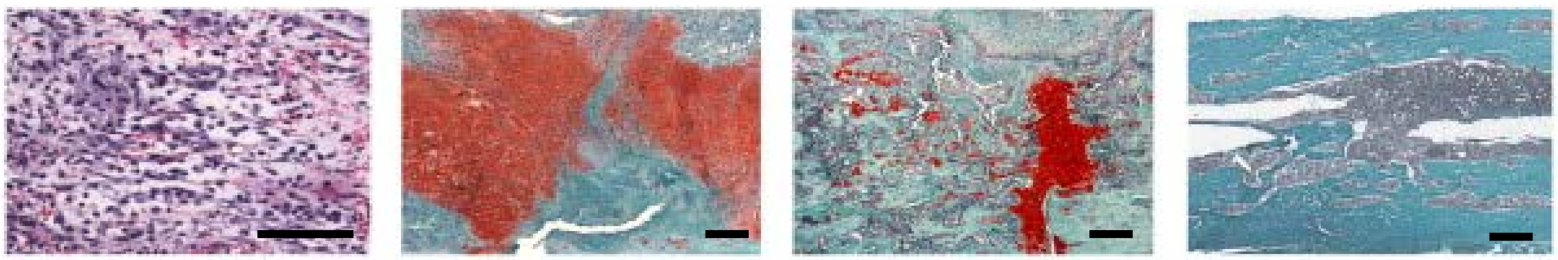
– – High frequencies: reflect both intra- and extracellular environment

Fracture Healing

Endochondral ossification:

4-stage model

Stage 1	Stage 2	Stage 3	Stage 4
Inflammation	Cartilage callus	New Bone	Remodeling



Non-union can occur

Mouse model

<table>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td><td>27</td><td>28</td></tr>
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<tr><td></td><td></td><td></td><td></td><td colspan="8">Cartilage Callus</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="12">Trabecular/New Bone Formation</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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Measurement time points

Project Aims

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1 Quantitatively assess fracture healing in an *in vivo* murine model

1a. Develop sensors for *in vivo* stabilized fracture model
1b. Monitor healing: serial impedance measurements compared to radiographs & histology

2 Determine earliest time point of detecting fracture non-union

2a. Monitor healing in *in vivo* non-union fracture model
2b. Compare normal and non-union measurements: determine when complications can be detected

Hypothesis:

Impedance can be used to track fracture healing and detect non-union early

Impedance Correlates to Cartilage and Bone Fractions in Fracture Calluses

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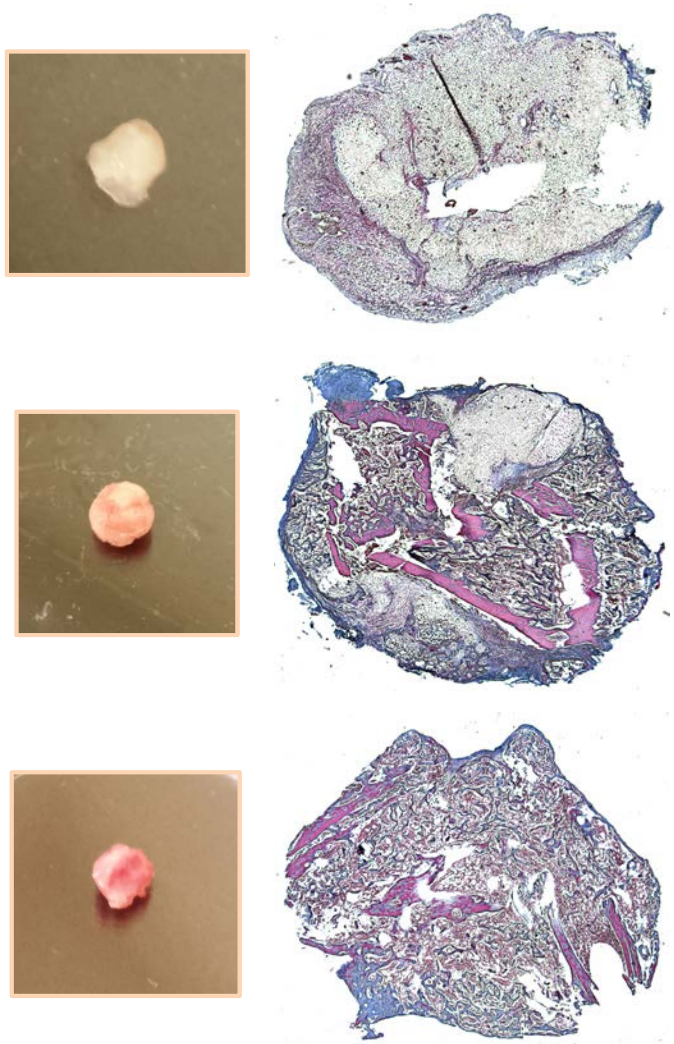
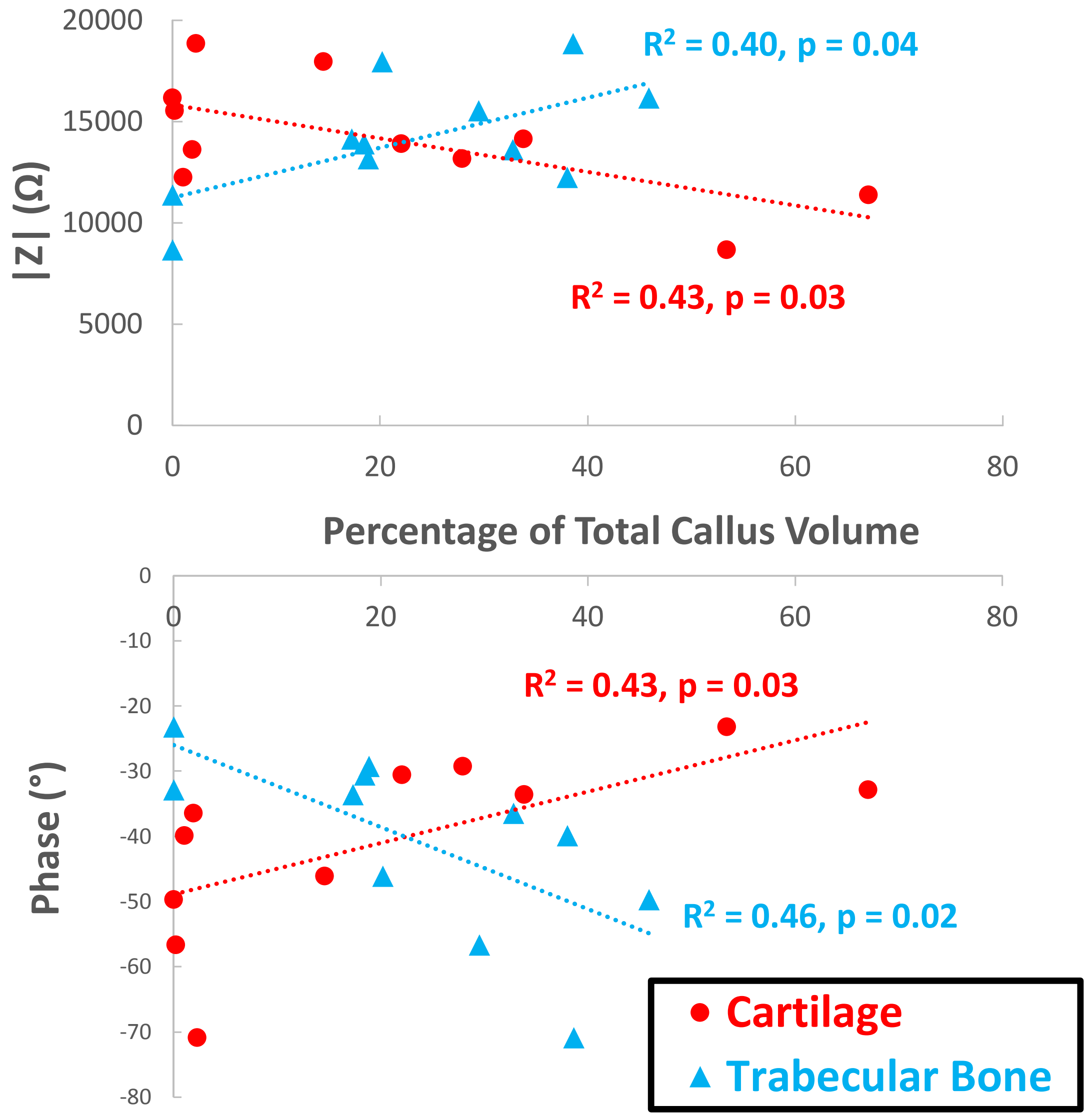
Day 8

Day 14

Day 21



N = 11



Clear difference in impedance for fractures initially 0.5 mm vs 2 mm in size

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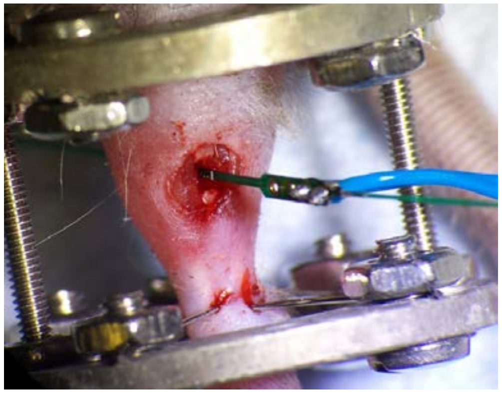
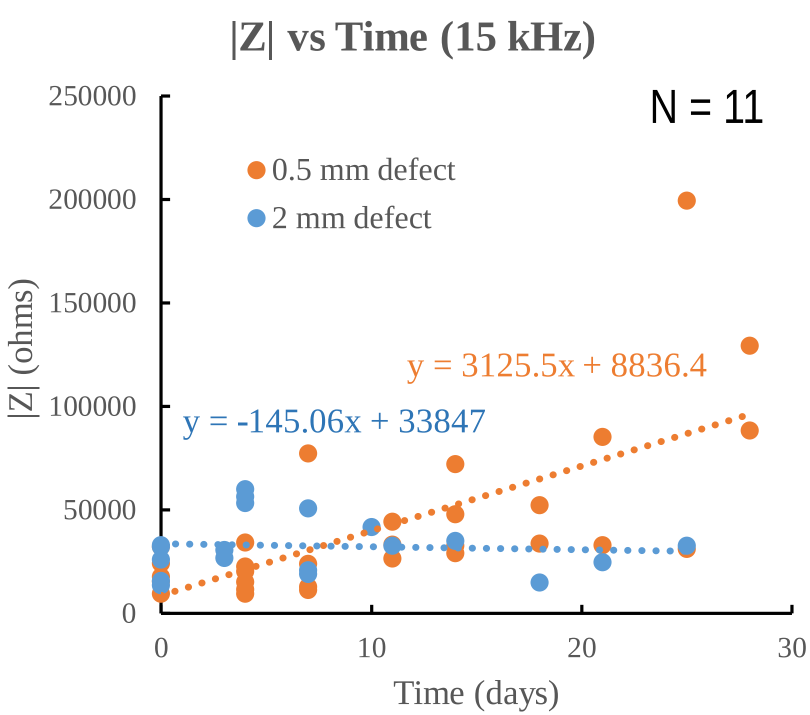
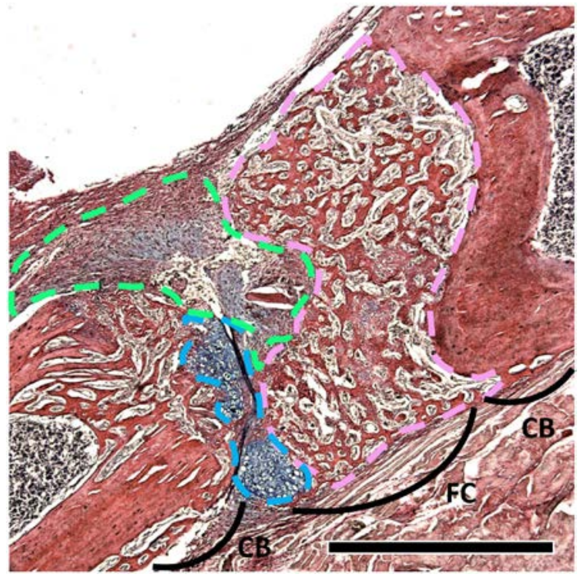


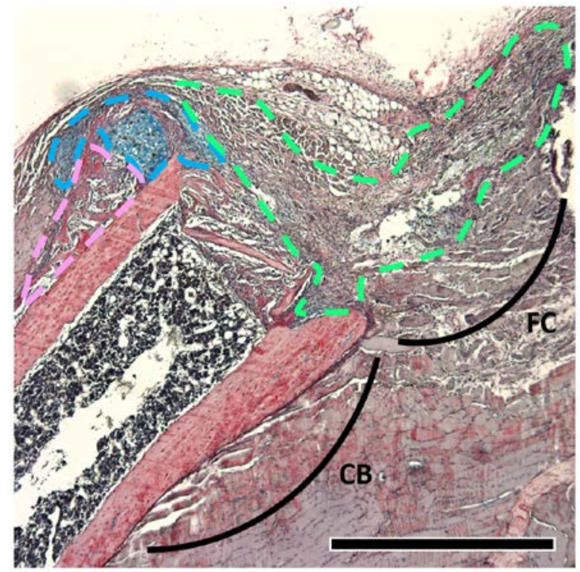
250 um sensor



Histology @ Day 14



0.5 mm defect



2 mm defect

CB	Cortical Bone
FC	Fracture Callus

- Cartilage (blue dashed)
- New Bone (pink dashed)
- Fibrous Tissue (green dashed)

A lot of variability between mice in stabilized model with 250 um sensor

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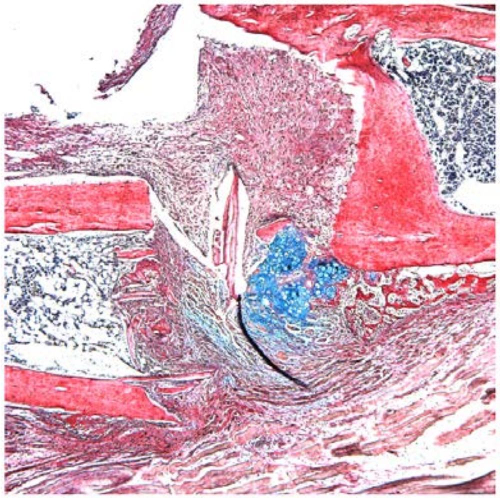
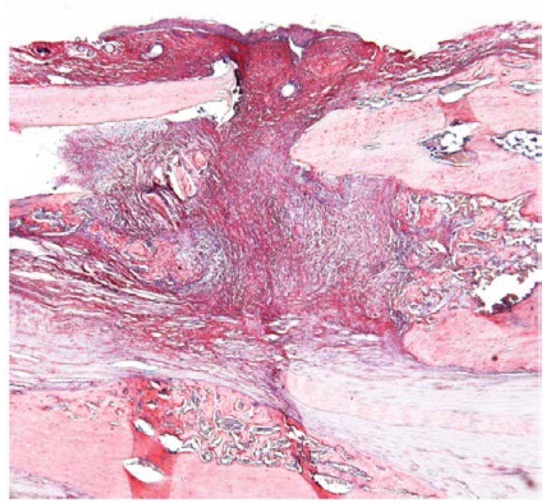
Day 14



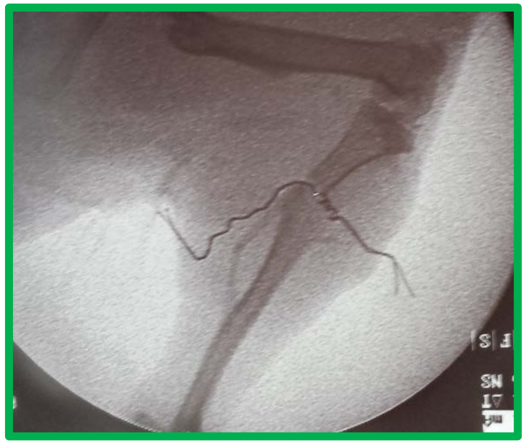
Day 28



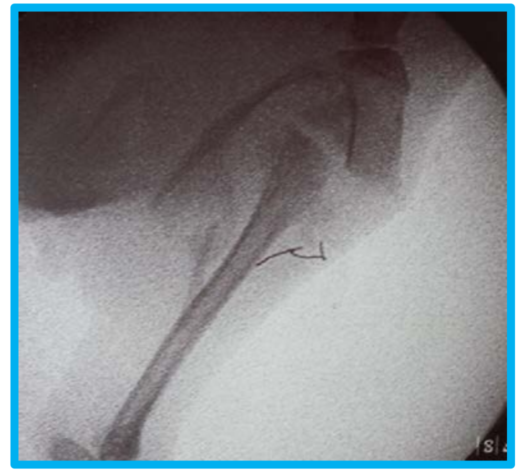
- Sensor too large relative to fracture callus
- Motion of rigid sensor causes soft tissue damage

Move to <u>unstable model</u>: **larger callus**
<u>New prototype</u> of sensor: **smaller, flexible**

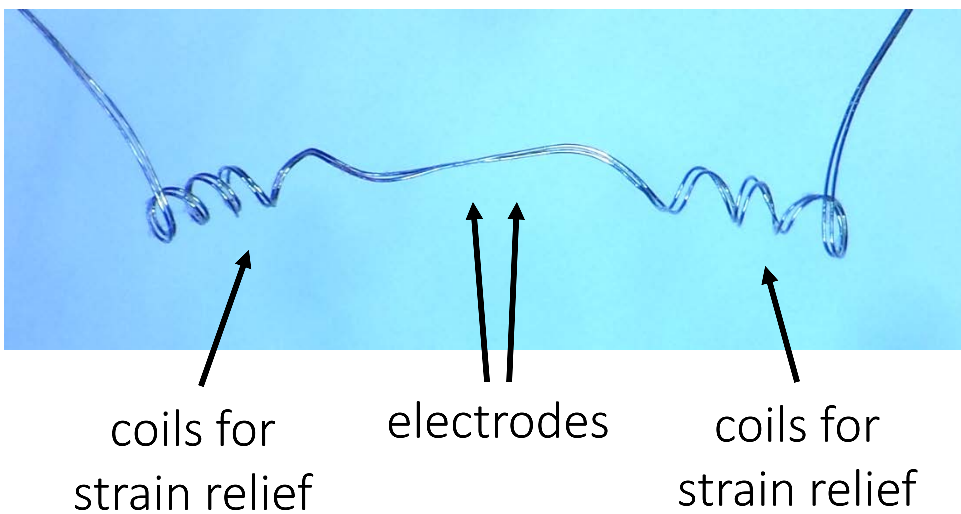
50 um sensors break in unstable model



Day 0



Day 14



- 3 rounds of experiments
- N = 12

Sensor always broken or pulled out of leg by Day 14

Small 50 um sensors in stabilized external fixator model

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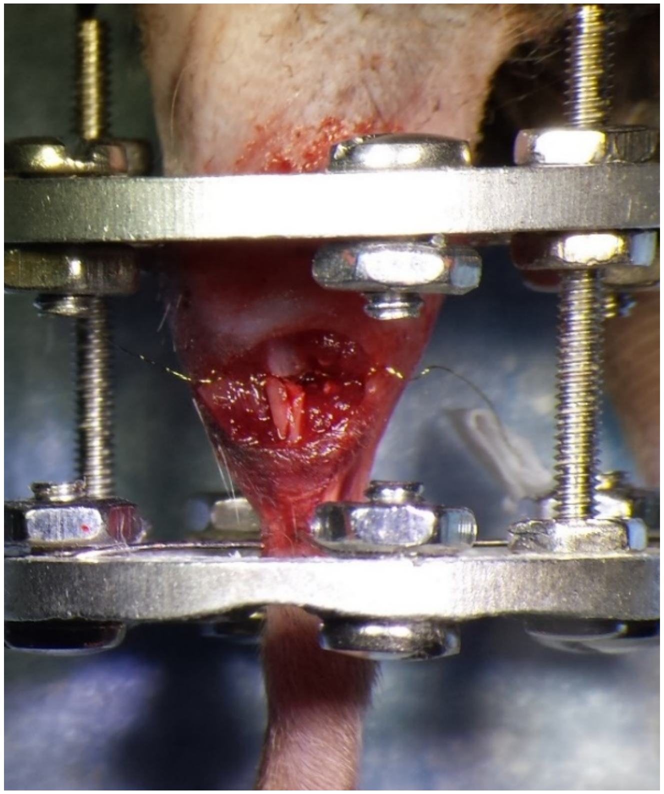
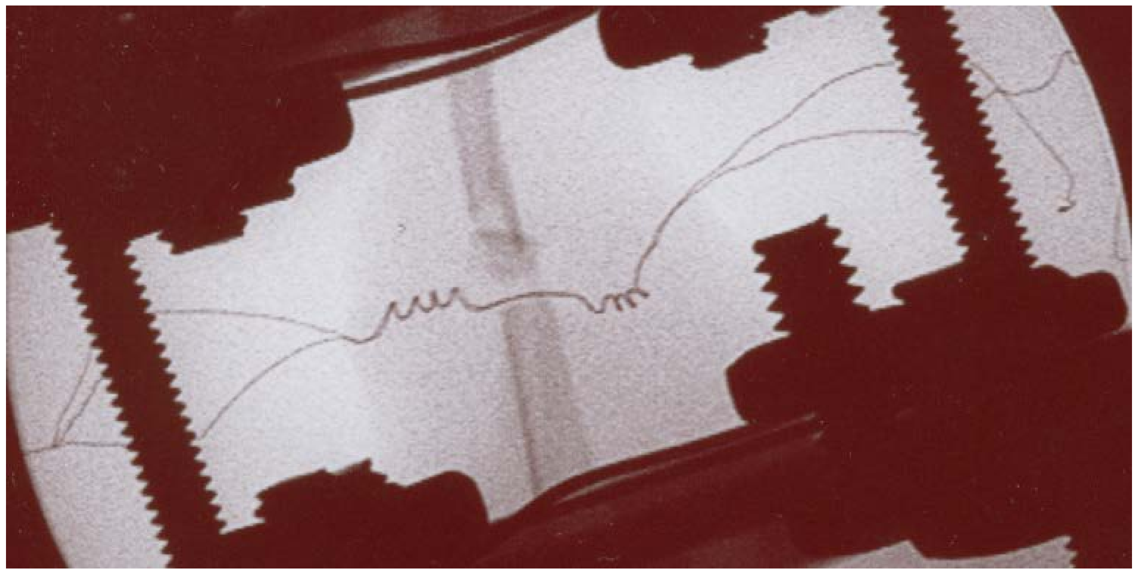
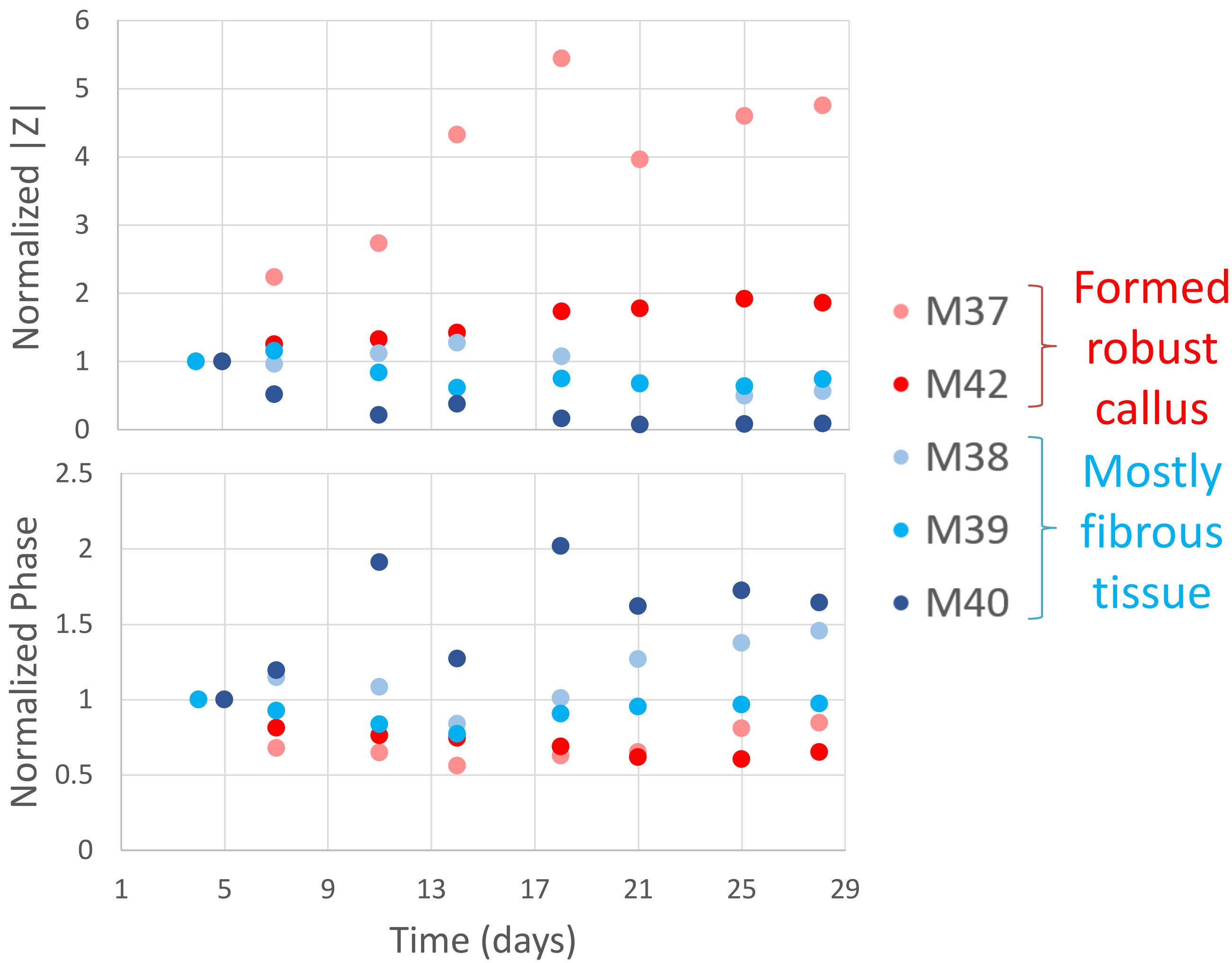
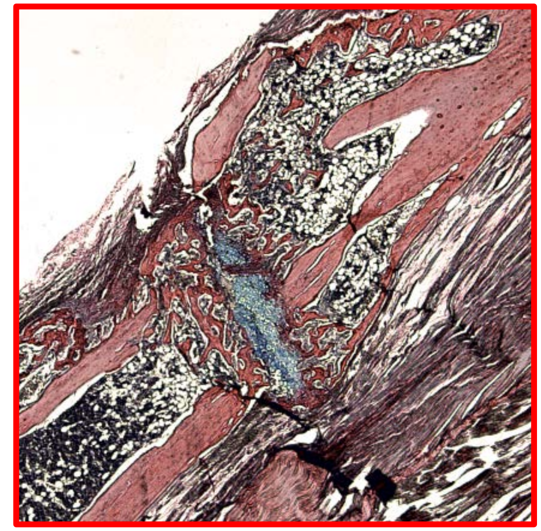
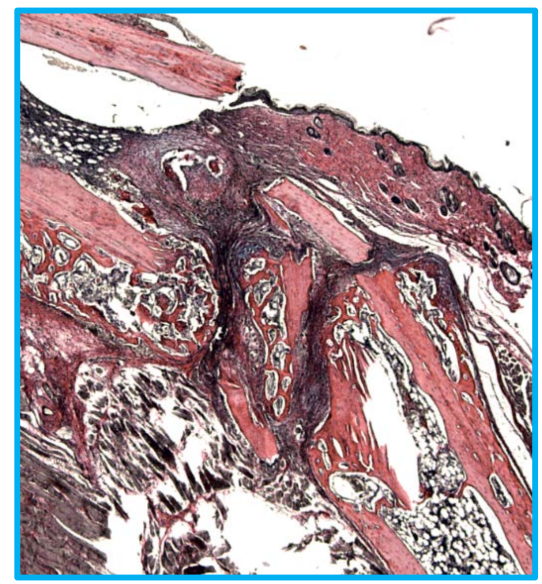




Difference in impedance between fractures forming robust callus vs. fibrous tissue







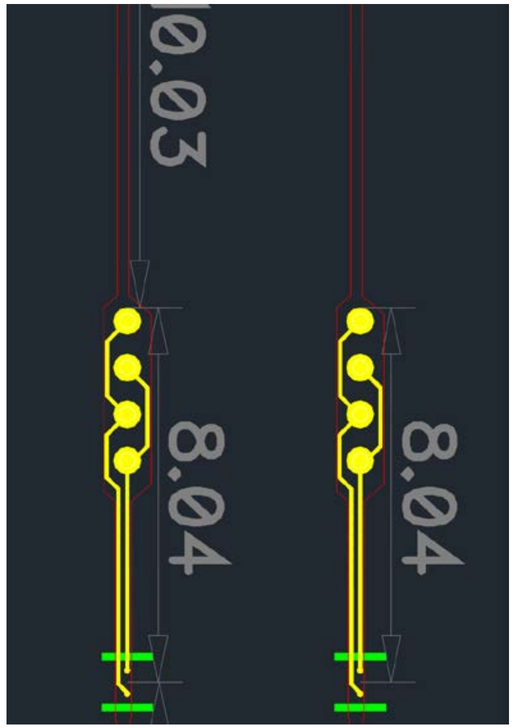
Deliverables

UCSF INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

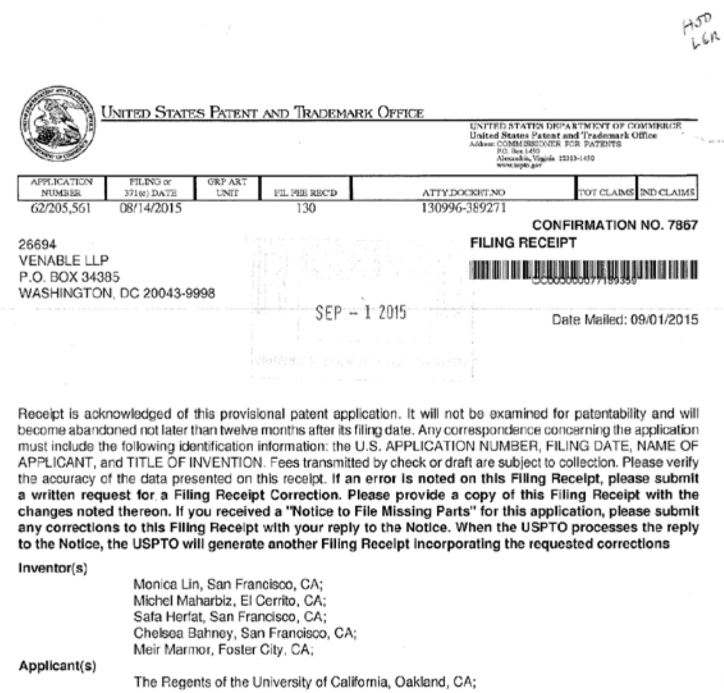
ACCREDITED BY: aaalac INTERNATIONAL — WHERE SCIENCE AND RESPONSIBLE ANIMAL CARE CONNECT.

AN143402-01

Mouse model development



Prototype sensors



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
62/205,561	08/14/2015		130	130996-389271		

CONFIRMATION NO. 7867

26694
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WASHINGTON, DC 20043-9998

FILING RECEIPT

SEP - 1 2015

Date Mailed: 09/01/2015

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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Meir Marmor, Foster City, CA;

Applicant(s)

The Regents of the University of California, Oakland, CA;

Provisional patent

Publications & Presentations

Conferences

- M.C. Lin, F. Yang, S.T. Herfat, C.S. Bahney, M.M. Maharbiz, M. Meir. *"Novel Impedance Spectroscopy Device Detects Fracture Progression in Mice".* Orthopaedic Research Society (ORS) Annual Meeting: Orlando, FL (Mar. 2016). [podium talk]
- M.C. Lin, F. Yang, S.T. Herfat, C.S. Bahney, M.M. Maharbiz, M. Meir. *"Impedance Measurements Correlate to Callus Maturation of Mice Tibia Fractures".* OTA Annual Meeting: National Harbor, MD (Oct. 2016). [podium talk]
- M.C. Lin, D. Hu, F. Yang, S.T. Herfat, C.S. Bahney, M.M. Maharbiz, M. Marmor. *"Using Impedance to Characterize Fracture States in Externally-Stabilized Mouse Tibia Fractures vs. Critical-Sized Defects."* ORS 2017 Annual Meeting. [abstract submitted Aug 29, 2016]

Manuscripts

- M.C. Lin, F. Yang, S.T. Herfat, C.S. Bahney, M. Meir, M.M. Maharbiz. *"Ex Vivo Evaluation of Impedance Spectroscopy to Distinguish Different Phases of Fracture Healing."* [article in preparation]

Intellectual Property

- Monica Lin, et al. "*Quantitative tool using impedance spectroscopy to monitor fracture healing.*" PCT International Application. Filed Aug 11, 2016.

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2016-2017 Project Proposal:

Smart Implant to Detect Fracture Healing

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TRAUMA
CROSS TABLE
L
REJ

Can you make this heal faster?

How fast will this heal?

Will this heal?

6 weeks post op

Can I start weight bearing?

Is there an imaging study I can do?

Is there a blood test I can take?

Impedance Signatures Differ Between Tissue Types

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Tissue types present in healing fractures

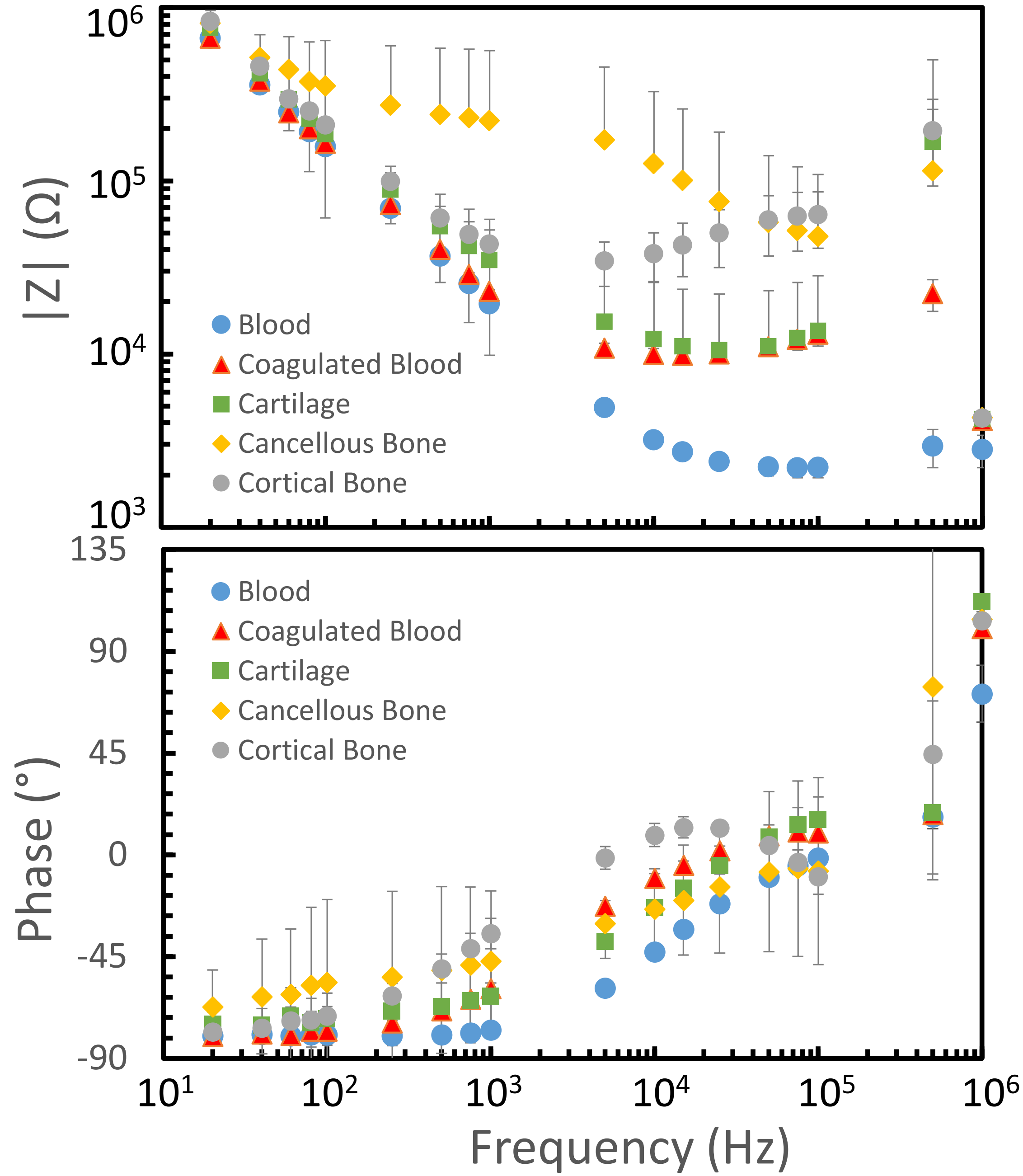

Blood


Coagulated Blood

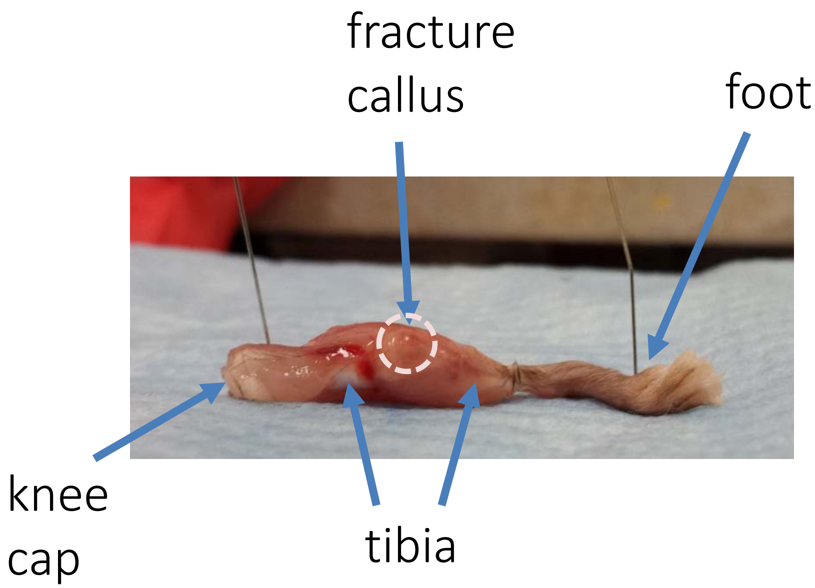

Cartilage

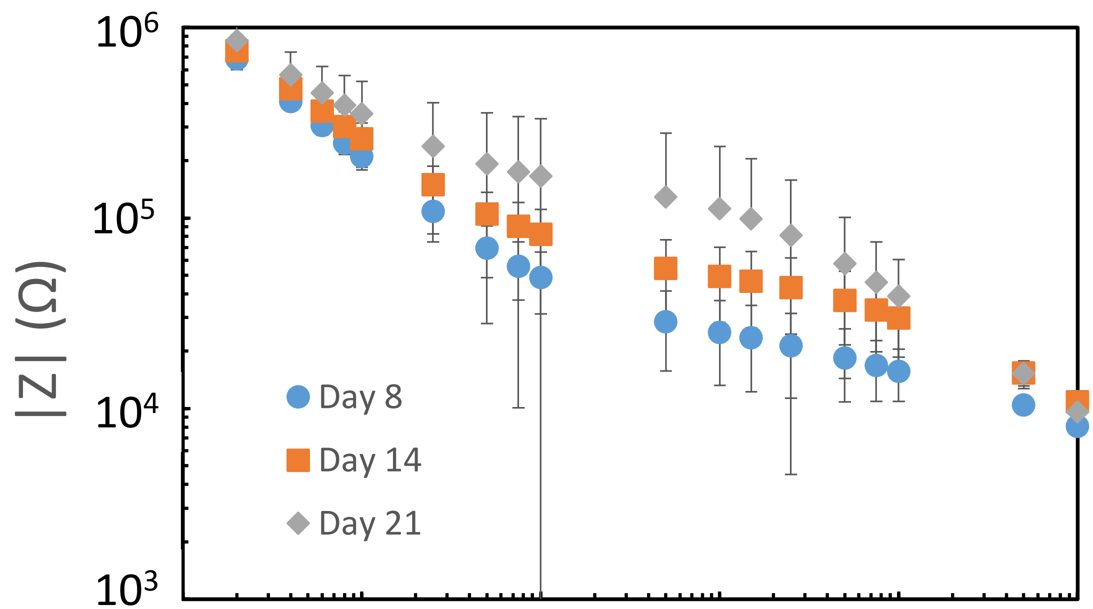

Cancellous Bone


Cortical Bone

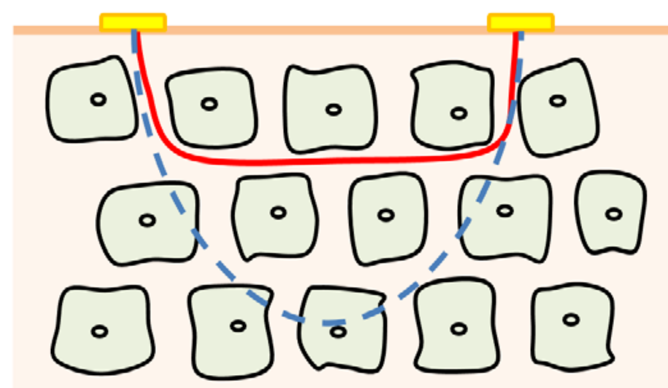


Impedance Tracks with Healing Progression

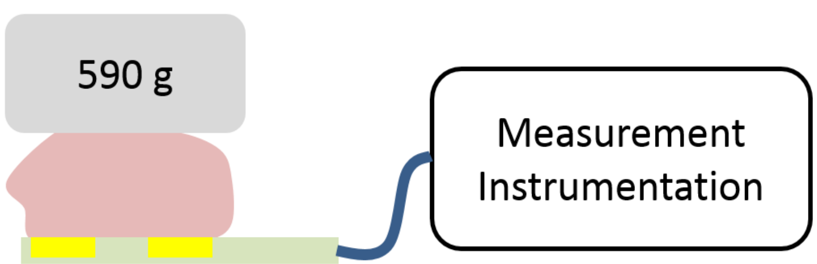




Day 8 Day 14 Day 21



|Z| ≈ conductivity of tissue



Difference in impedance between fractures forming robust callus vs. fibrous tissue

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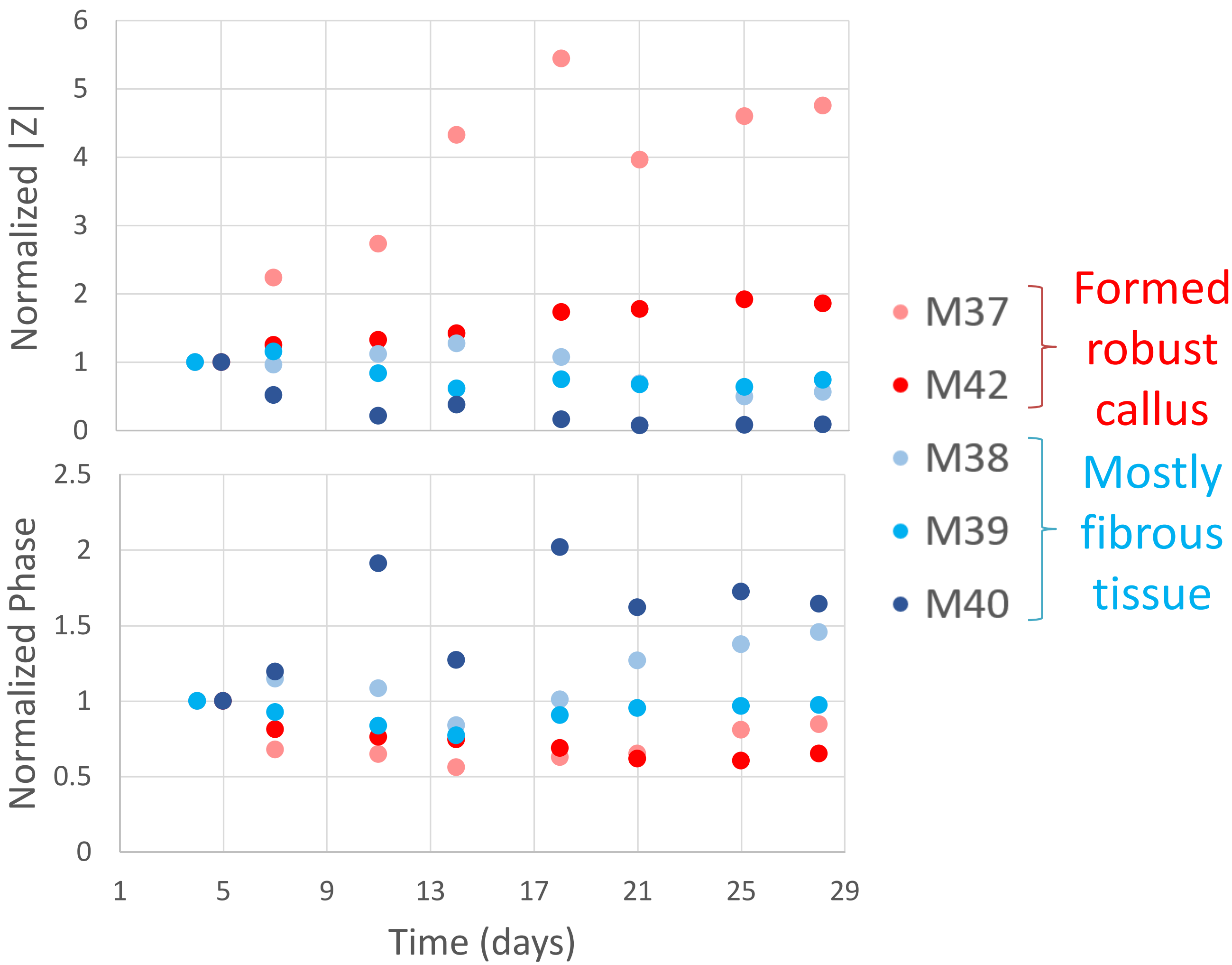
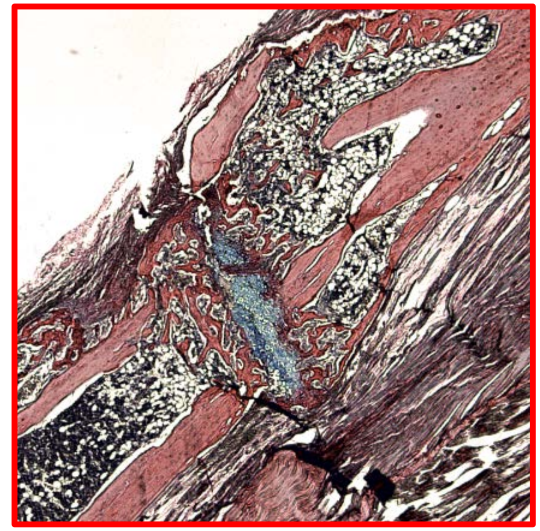
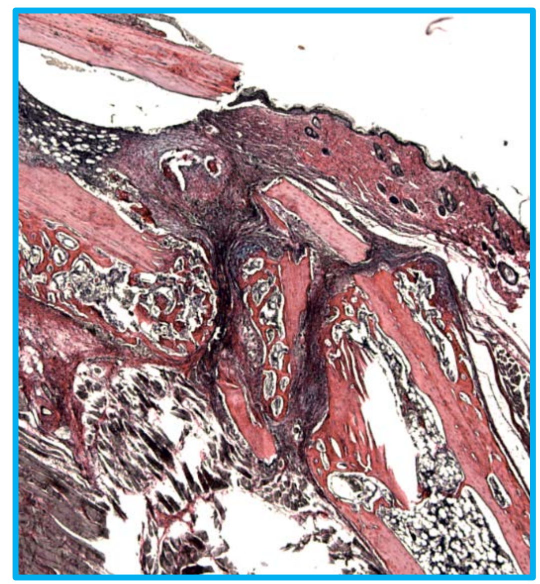
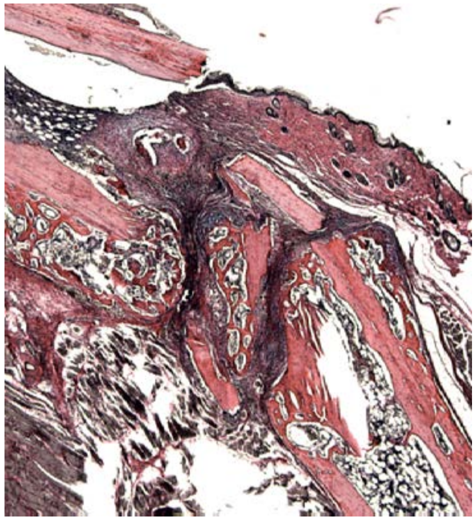
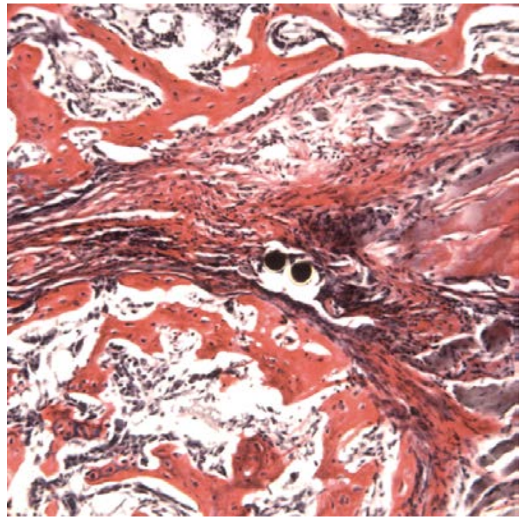






Clinical Need and Industrial Relevance



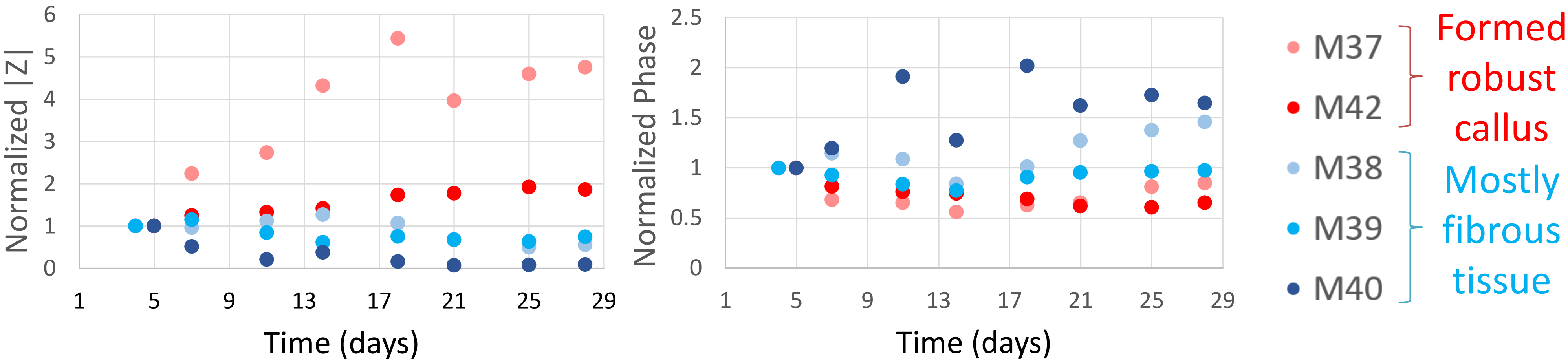


0.05 mm sensors in stabilized fracture model cause prevailing fibrous tissue & delayed healing

- Due to excess motion of the sensor relative to bone ends
- Many challenges with small scale of mouse tibia

→ Scaling-up to a larger animal model will address these issues

Clinical Need and Industrial Relevance



Changes in impedance are correlated with stages of fracture healing in cadaveric, *ex vivo*, and *in vivo* models

Scaling-up to a larger animal model will provide increased control of fracture stability and sensor movement & progress towards clinical use

2016-2017 Project Proposal

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1 Develop sensor electronics integrating impedance measurements & wireless capability

1a. Replace LCR meter with impedance measurement chip solution
1b. Establish wireless communication, data transfer, and power transfer

2 Prototype sensor for a larger animal model

2a. Use cadaveric tibias to model size restrictions and determine necessary dimensions
2b. Fully implant sensors in cadaveric rabbit hind limb to verify ability to collect data wirelessly

Methods

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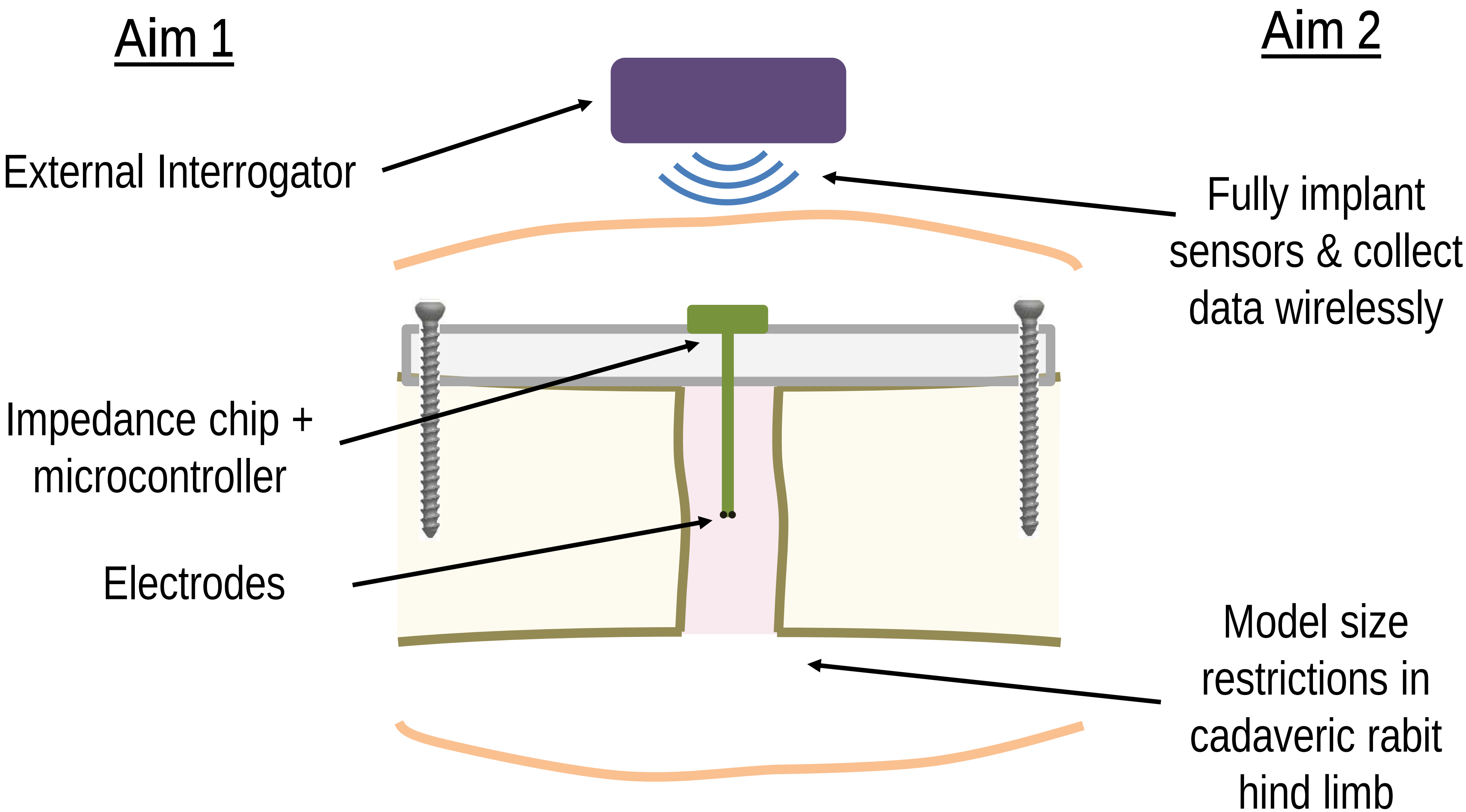

Milestones & Timeline

	Oct 2016	Nov 2016	Dec 2016	Jan 2017	Feb 2017	Mar 2017	Apr 2017	May 2017	Jun 2017	July 2017	Aug 2017	Sept 2017
Aim 1 Sensor Electronics	Tune impedance chip for use in monitoring fractures (Aim 1a)						Build prototype for rabbit model					
			Design board incorporating wireless capabilities (Aim 1b)									
Aim 2 Cadaveric Rabbit Model					Initial studies in cadaveric rabbit hind limb to determine dimensions (Aim 2a)							
							Fully implant sensors in cadaveric rabbit (Aim 2b)					
Writing				EMBC Conference Submission						Write journal manuscript		

Deliverables

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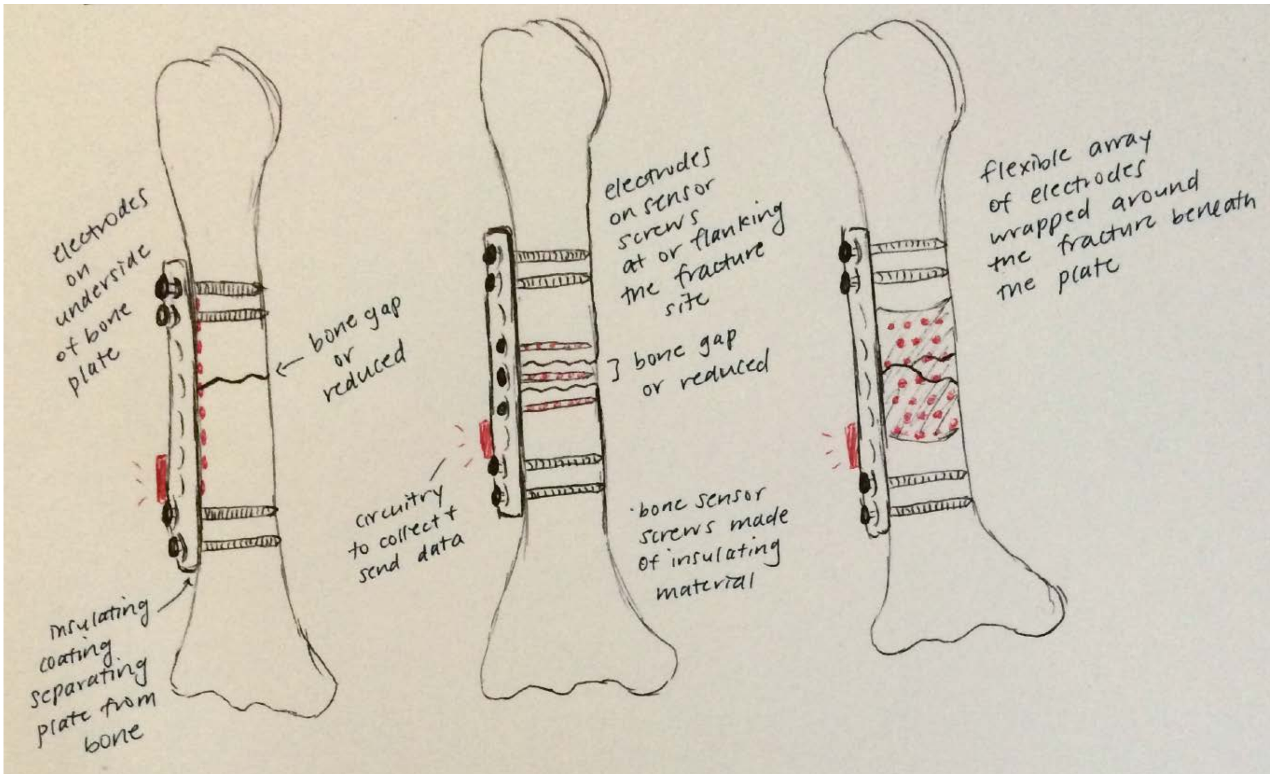
- Prototype for larger animal model



- Journal article
- Application for full U.S. patent

Proposed Budget

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Personnel	$ 8,000	Monica Lin (PhD student)
Supplies	$ 5,000	Electronic components, precision sensor fabrication
Prototyping	$ 10,000	Laser cutting, 3D printing, machining
Specimens/Implants	$ 10,000	Rabbit specimens, implant hardware
Total Directs	*$ 33,000*	
Indirects (10%)	*$ 3,300*	
Total	**$ 36,300**	