<u>C2C ERC-RMB Year 11 (C2C Year 2 Update):</u> US-Ireland- Northern Ireland R&D Partnership Between the NSF-ERC for Revolutionizing Metallic Biomaterials (ERC-RMB) in the US and CÚRAM at NUI Galway, Ireland, NIBEC at Ulster University, Northern Ireland: NSF-SFI-C2C

Overview: Our team shares the goal of developing bioresorbable magnesium alloy systems for clinically-capable orthopedic implant devices. The regulatory landscape, especially for biomedical materials and devices, is highly dependent on intercountry efforts. This tripartite partnership via the C2C program has created a unique convergence of world-leading expertise from academia and industry in the fields of materials processing (ERC-RMB, Fort Wayne Metals), surface modification (ERC-RMB, NIBEC), characterization (ERC-RMB, NIBEC), computational modeling (NUI Galway), and regulatory issues (Ft Wayne Metals, Orthokinetics, C2C universities). Our groups have, with the input of clinician team members, chosen applications ranging from thin wires (for clinical use as "k wires") to thicker pins, rods and elastic stable intramedullary nails (IMs or ESINs) and meshes for the treatment of complex bone fractures.

Materials and Data Exchange: One of the many outcomes of the matured ERC-RMB program is the ability to tailor magnesium (Mg) materials and characterize the resulting materials at the atomic and micro-scale and relate these characteristics to bulk mechanical properties. Unique Mg materials including polycrystalline Mg alloys (Dr Xu, NCAT; Dr Kumta, Pittsburgh), and monocrystalline pure Mg (Dr Shanov, Cincinnati) have been shared with NIBEC for coating studies and analysis. Related microstructural, fatigue, and corrosion data have been sent to NIU Galway for Finite Element Analysis of these materials in application relevant scenarios, developed in conjunction with our clinical partners. Inputs from our C2C partners have helped modify the subsequent rounds of materials produced. NCAT (Dr Yarmolenko) has prepared a living document materials data base distributed to both academic and industrial members. This C2C partnership has demonstrated the efficacy of Mg materials as a K-wire material and resulted in the development of a monocrystalline Mg alloy driven by the demands and needs of the EISN application.

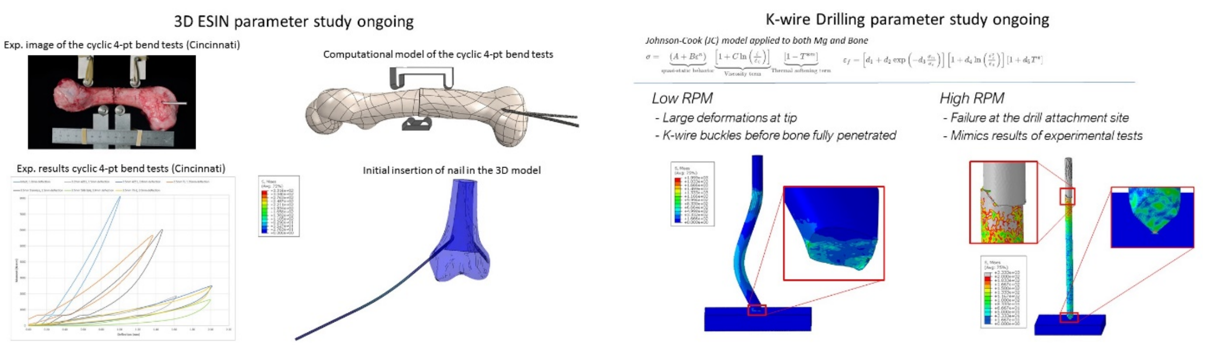

Figure 1. Representative slides presented during webinar meetings illustrating experimental (ERC-RMB) and computational (Cúram, NUI-Galway) approaches to improved application of Mg Biomedical devices.

Center Visits and Meetings: Modern industry is multi-national and so should be the scientific teams and the training of our current and future researchers. An essential component of the collaboration is the efficient exchange of ideas that allows student researchers to operate and succeed in an intercontinental arena. We can communicate person-to-person on the different challenges associated with each country's academic, industrial, and regulatory challenges. We have leveraged this opportunity via student and faculty transatlantic visits and cross-institution webinars and person-to-person communication. ***US to Ireland, August 31-September 2, 2018:***. Drs. Pixley and Little (Cincinnati) visited NIBEC at Ulster University, for collaborative talks and tours of the facilities. Our C2C experience has allowed us to contribute to the international community through participation in the ***NSF sponsored C2C Collaboration Workshop, August 14-15,2018 UCLA, Los Angeles.*** (Drs. Pixley (Cincinnati) and Collins (NCAT)); the **10th Annual Biodegradable Metals for Biomedical Implants, Oxford University, Oxford, England, August 26-31**, Several C2C members presented and met for discussions: Keynote talks: Dr. Kumta (Pittsburgh), Adam Griebel (Ft. Wayne Metals), Dr Pixley (Cincinnati); Presentations: Dr Shanov (Cincinnati), Dr Little (clinician, Cincinnati), Dr Acheson (NIBEC); 03/27-28/2019 – Dr Kumta (Pittsburgh) on behalf of the ERC-RMB attended the **Science Foundation Ireland Site Review for CÚRAM-2,**

Galway, Ireland, March 27-28, 2019; and Drs. Sankar (NCAT) and Dr. Pixley attended the **ERC Workshop on International Center-Level Collaborations to Enhance Research and Workforce Development, NSF, Alexandria, VA, April 11-12, 2019**.

Device Progress via the NSF-SFI-C2C program

K-wires: K-wires of various diameters and tip designs were fabricated and tested in cadaver porcine and rabbit bones at the University of Pittsburgh (ERC-RMB), throughout the C2C time period. These tests have shown that the Mg alloy-based diamond tip K-wires can be used to drill both compact and trabecular porcine and rabbit cadaver bones. A pilot study of K-wires fabricated from proprietary alloys was also performed on a rabbit ulna fracture model. The K-wires showed improved bone growth and complete union of the bone on the fracture sites, demonstrating efficacy of the alloy and the K-wire device technology. Ongoing work is aimed at optimizing the design and strategies involving in control of microstructure, including new coatings to optimize the healing as well as regeneration. Coating strategies are being followed up with NIBEC, Ulster Univ., Ireland. Initial feasibility tests of coating strategies were conducted at NIBEC, using some of the ERC-generated alloy samples. For these initial feasibility tests of coating strategies, samples of a proprietary alloy were supplied by Dr. Kumta's lab at University of Pittsburgh to the NIBEC coating team in Ireland. Pure hydroxyapatite and Sr-substituted hydroxyapatite coatings were deposited by the group at NIBEC on these substrates using primarily RF sputtering deposition techniques. The coating was characterized at NIBEC, using various techniques, including time of flight mass spectroscopy (TOF-MS). In-vitro corrosion tests were also performed by both NIBEC and Pitt teams on these coated samples and the results showed that alteration of the corrosion rate of the substrate is possible by varying the coating thickness and composition. Follow on studies are being planned with additional substrates and plans are in place to conduct cell cytocompatiblity (in vitro) studies on the coated samples. While these efforts are spearheaded by *in vivo* data on K-wires, the findings from all coating studies are applicable to the bone nail project.

Bone Nails: Early in the project Mg Intramedullary Bone nails (IMs), provided by ERC groups (Xu, NCAT; Kumta, Pittsburgh) and industrial partner (Ft. Wayne Metals), were tested for biomechanical properties. All but one type of Mg IMs had sufficient strength to withstand insertion and extraction pressures, using pig cadaveric fore-leg bones (ASTM F1264 standards, with reduced support spacing for smaller specimens). These results have aided CAD model development (Dr Gallagher, NUI Galway) and led to new design criteria in polycrystalline Mg materials (ERC-RMB) for IM applications as well as creating strong and stiff alloy single crystal nails (Shanov, Cincinnati) capable to compete with Ti or Stainless steel. This year, the team has focused on the development of novel WE43 single crystal materials for biodegradable bone nail application. A micro-hardness test of WE43 single crystals revealed an average number of 118.78 Vickers, which was a two-fold increase compared to pure Mg single crystals (Avg. 62.44 Vickers). Optical microscopy, SEM, EBSD and Micro-CT studies found the existence of large size second phases co-existing in the "as grown" WE43 single crystal matrix. Phase homogenization was achieved by proper thermal annealing through varying different parameters to obtain a uniform microstructure throughout the whole WE43 single crystal rod. Our team believes that bone nails created from WE43 single crystals nails will be appropriate in terms of their mechanical properties for orthopedic applications, especially in pediatric patients.

Meshes: Dr. Shanov' s group has produced variety of mesh patterns using photochemical etching of AZ31 magnesium allow sheet with two different thicknesses (250micron and 500micron). These biodegradable meshes and related ribbons are available for testing as surgical collars for enhancing the healing of transverse bone fractures, applied after implanting axially a bone nail. Such tests will be done in collaboration with Drs. Little and Pixley at UC. The meshes could further stabilize and promote bone growth at the fracture site. The UC technology for making Mg mesh by photo-chemical etching has been protected by an US patent (V. Shanov, P. Roy-Chaudhury, M. Schulz, Z. Yin, B. Campos-Naciff, Y. Wang, "*Method for Making Magnesium Biodegradable Stent for Medical Implant Applications",* US Patent 9,655,752, May 23, 2017).