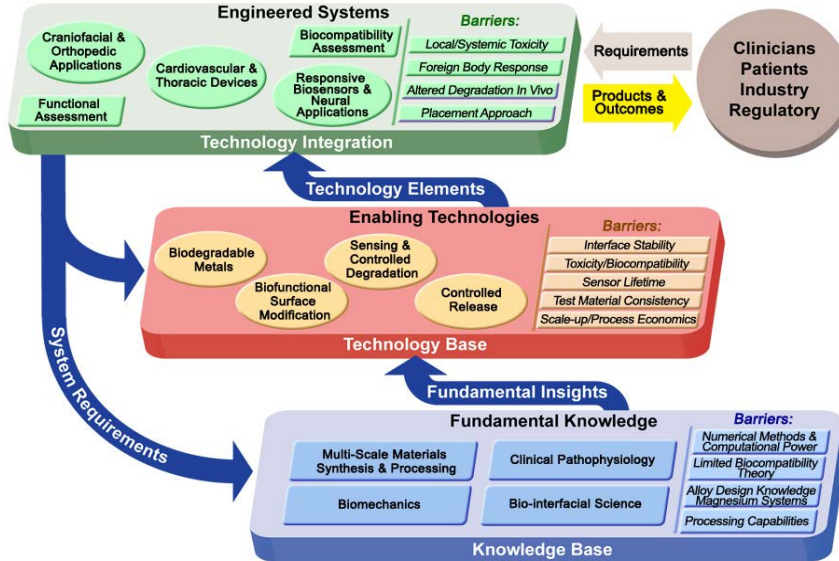


Year 10 Executive Summary

Research efforts within Engineering Research Center for Revolutionizing Metallic Biomaterials (ERC RMB) continue to mature and evolve, emphasizing: 1) synergy of research efforts across ERC RMB institutions and engineered systems (ESs) driven by the research strategic plan; 2) excellence in education; and 3) dynamic outreach activities that highlight the quality and diversity of the ERC RMB.

A. ACHIEVEMENTS IN THE REPORTING YEAR

RESEARCH SYNOPSIS



ERC-RMB 3-Plane Strategic Framework with Barriers

The strategic research plan emerged in Years 01 and 02 from the 3-plane chart and feedback by science advisors to identify device specific test beds within each engineered system (ES). A device focus emerged that enabled strategic decision-making regarding research projects and science projects to address *in vivo* performance of degradable alloys as devices. Year 03 through Year 05 efforts were dedicated to the development of science and research thrusts to support device test beds within each ES. Materials development Thrust (Red Team), Materials processing/characterization coatings and modeling Thrust (Blue Team), and Biocompatibility Thrust (Green Team) provided the fundamental knowledge to advance the development of device prototypes/testbeds moving forward.

Advances in ERC-RMB science have been matched by ERC-RMB achievements in education and outreach, which are highlighted by the awarding of the first baccalaureate and master degrees in biomedical engineering by a historically black college and university. In Year 09, the NCAT BMEN program was successful in Fall 2016 in obtaining approval for the BS programs after its first ABET accreditation visit in Fall 2015. ERC-RMB is facilitating transformational education, outreach, informal education, and diversity. Details are given in the appropriate sections of this report.

Year 09 research efforts continue to build on the substantial progress made in Years 03-08 with greater engagement with industry collaborators to focus opportunities for translation. In particular, the development, processing and testing of novel degradable alloy systems has

emerged as an area of strategic interest among ERC-RMB member companies, including new IAB members. The underlying premise is that ERC-RMB sustainability is intimately tied to the intellectual strength of the team's basic research, translational opportunities for our technologies and the commercial interest developed around this potential, as well as the educational impacts associated with next generation, diverse workforce quality and development.

Research

Integrated Systems:

Craniofacial and Orthopedic Applications – Orthopedic device projects continue to mature, including the ACL-ring project. Currently, the device is being validated in a preclinical animal study with goats, which is supported by Naton Medical Group, a China based orthopedic company, and the Coulter Program. The study is expected to be completed this summer. The ACL ring was originally part of an option to license held by InCube Labs, Inc. However, given interest from Naton, a carve-out was negotiated with InCube (spring, 2016) whereby it would relinquish rights to this particular application. Discussions are underway regarding the possible formation of a U.S. based company that would be supported in part by Naton.

Cardiovascular and Thoracic Devices – The AV-Fistula Stent project continues to move forward, exploring novel stent designs and the use of drug-eluting/non-thrombogenic elastomer coatings. Preliminary data suggests reduced neointimal hyperplasia using uncoated stents. An R21 grant has been received and an R01 involving resorbable stents in combination with ERC-RMB non-thrombogenic coatings to address hyperplasia are underway for this project. The start-up company Innovasc has been established to explore the commercial potential of ERC technologies surrounding this project.

Enabling Technologies and Cross-cutting Activities:

Novel Material Processing – Methods for extrusion and thermal treatment of novel alloys developed at NCAT were applied ERC wide to enhance alloy properties. In Year 9, ERC fabricated Mg-alloy wire products for medical application using unique processing and manufacturing techniques.

Biocompatibility – Advanced basic research to identify the molecular mechanisms for improved bone and wound healing from Mg-based alloys. *In vivo* experiments using Mg alloys have suggested stimulatory effects on the growth of new bone tissues. This implies that Mg ion is a potential candidate involved in the intracellular pathway of new bone formation.

Emerging Regulatory Science Focus (ASTM/ISO) – Participation with ATSM work group continues and the new ASTM and ISO standards for testing both metallurgical characterization of absorbable metallic materials for medical implants and biological evaluation of absorbable metals are advancing. The ERC has been active in reviewing and commenting on improvements for both sets of standards and insuring consistency in testing for degradation and provision of relevant materials suitable for biological evaluation. A new guide for in vitro degradation testing of absorbable metals (ASTM WK52640) is open for balloting until May 17, 2017 and is crucial for standardizing the approach for producing extracts for proper biological testing. The ISO standard TC194 was approved as a technical report and is now open for review and balloting as ISO/DTR 37137-2: Biological Evaluation of Absorbable Metals. This document provides standards for in vitro and in vivo biological testing.

Fundamental Science:

Corrosion Science – Data acquired from Year 9 experiments using bioreactors and microfluidic systems have helped to understand the degradation behavior for new materials developed by the ERC. These results are contributing to the establishment of a new ASTM standard for bioresorbable metals as well as novel stent and scaffold designs.

Materials Science -The materials team developed series of Mg-based novel ERC alloys (including expandable alloys) using strengthening functions of alloying elements, grain refinement ability of alloying elements and understanding the functions of alloying elements in corrosion. In addition, new REs were investigated to achieve moderate-to-high mechanical strength, ductility and low degradation/corrosion rates. Improvement in strength and ductility, as well as in corrosion resistance were observed in alloys using these new RE elements. The ductility of some alloys reached as high as 28% in as-cast condition. The corrosion resistance of alloys in as-cast condition were better than or as good as WE43. ERC has also explored the effects of specific alloying elements on *in-vitro* cytotoxicity and osteogenic differentiation. New alloy systems containing Sr added to Mg-Y and Mg-Zn alloys successfully reduced the corrosion rate while also increasing the micro-hardness.

Education and Workforce Development: University Education:

- NCAT history-making enrollment/graduation of BS (with ABET accreditation visit completed in Fall 2015 and full ABET accreditation granted in Fall 2016) and MS students as 1st seamless offering of undergraduate and graduate bioengineering programs at an HBCU.
- 9 BS and 6 MS students graduated from the NCAT BMEN program during the current reporting period; some of them participated in ERC-RMB activities.
- 5 BS, 4 MS and 6 PhD students associated with ERC-RMB (regardless of major) completed their degrees during the current reporting period.
- Between 2009 and 2016, RMB's REU programs have served a total of 56 unique (i.e. non-returning for a second time) participants, plus return summer REUs by 3 of these (total of 59, 4 in Year 09). They have attracted a diverse population in terms of gender, race, and ethnicity, from 14 states and 29 total institutions. An emphasis was placed on recruitment from RMB's principal outreach partners including California State University – Los Angeles (an HSI) and Guilford Technical Community College (GTCC) in Greensboro.

Education and Workforce Development: Pre-college Education:

- Between 2009 and 2016, RMB's YS programs have served a total of 28 unique participants, plus return summer YSs by 3 of these (total of 31, 5 in Year 09). They have attracted a diverse population in terms of gender, race, and ethnicity, from 17 total secondary institutions in North Carolina. An emphasis was placed on recruitment from RMB's principal K-12 outreach partner: Guilford County Schools.
- Between 2009 and 2015, RMB's RET programs have served a total of 29 unique (never participated before) participants, plus return summer RETs by 17 of these (46 total, 4 in Year 09). They have attracted a diverse population in terms of gender, race, and ethnicity, from 21 total secondary institutions, most in North Carolina and two schools in Illinois. An emphasis was placed on recruitment from RMB's principal K-12 outreach partner: Guilford County Schools.

Education and Workforce Development: General Outreach:

- # STEM teachers: Visiting / visited by RMB researchers: 152
- # Community college teachers/Students: 80/20
- # K-12 students: Visiting / visited by RMB researchers: 839
- Visitors from industry/legislative/executive/entrepreneur/academia to RMB (~100)

Education and Workforce Development: Diversity Advances in the Center:

- The current (Spring 2017) enrollments in the ERC-RMB-initiated BS and MS programs in bioengineering at NCAT are MS: 17 (59 % female, 35 % African-American and 65 % students choosing not to provide race/ethnicity information to the University), and BS: 95 (65 % female, 69 % African-American). Since their inception in Fall 2010, the BMEN degree programs have graduated: MS 27 (52 % female) and BS 24 (71 % female). Many students have successfully found employment in industry (Baxter International, BioMet, Medtronic, St. Joseph's, Veterans Administration), graduate and/or professional schools and post-doctoral fellowships (Pitt, Pennsylvania State Univ., UC, Univ. of North Carolina – Chapel Hill, Univ. of Utah, Univ. of Virginia, Rutgers).
- Continuation of special efforts to promote diversity at Pitt and UC by Drs. Wosu and Pixley
- Special efforts by Dr. Harvey Borovetz to secure Pitt Swanson School of Engineering support and work with Dr. Pai / Knisley to organize a clinical field trip to the University of Pittsburgh Medical Center by NCAT students in Dr. Borovetz's trans-ERC course Artificial Organs-1.

Technology Transfer and Commercialization (Innovation Ecosystem):

1. In the present reporting year, the ERC has produced 2 additional Disclosures, bringing the total to 67, including topics involved in all Engineering Platforms.
2. During the reporting period, ERC-RMB filed 4 patent applications (2 provisional and 2 full patents) and 3 patents were awarded.
3. Revisions to the Membership Agreement implemented at the end of the previous reporting period have resulted in an increased dialog with industry. 2 new members have signed, and several more are in active discussions.
4. Interactions with, Dentsply, have led to additional research contracts to support further development of their product opportunity.
5. Work continues with inCube to characterize and qualify alloys for prototype device development.
6. A novel biodegradable Sternotomy Closure and Fixation Device activity was initiated with Luiminal Solutions, Inc., based out of Atlanta., USA with interest expressed from Germany (Doctors as well as a Venture Capital group). Activities are underway for a key presentation,
7. New SBIR- Phase II -SECO award was received to work with Koli, Inc, Fremont, CA. The activities are related to evaluating the filtering effectiveness of our implant with varying implant diameters and gallstone sizes using *in vitro* testing. In addition, the ERC will help

evaluate the mechanical durability of the nitinol implant under cyclic expansion and contraction of the gallbladder using FEA and fatigue analysis.

International Partnerships/Collaborations:

- Dr. Witte, University Professor at Charite, Universitätsmedizin Berlin, continued the ERC global activities through participation in AC-87 Biodegradable Metals Standardization Committee and co-organizing the 8th Biometals Conference in Montreal, Canada.
- Dr. Witte continues to have active research interaction with various ERC technical team members

Center Infrastructure, Including Personnel:

- NCAT College of Engineering has provided BMEN teaching and research laboratory space in Hines Hall (Rooms 217, 218, 219), McNair Hall, and Cherry Hall to the Bioengineering programs. These spaces have been fully utilized for bioengineering curricular and faculty research activities. The Hines Hall facility has been renovated and research/instructional lab infrastructure and equipment are in place.
- An additional research space for ERC-RMB materials characterization and analysis facility was provided in Room #007 of the Fort IRC building (basement of the ERC research building) with appropriate infrastructural modifications and is almost in the final stages of getting completed with all functionality during the reporting year.

B. HIGH-LEVEL RESPONSE AND STATUS TO SWOT FINDINGS OF YEAR 09

Selected initiatives undertaken to address weaknesses, opportunities and threats include

- revisions to the Industrial Affiliates Membership agreement designed to enhance industrial engagement are fully executed and bearing promising results
- In Year 09, all project proposals and priority ideas were shared with the CSAB and IAB Chairs, and as well as with appropriate CSAB and IAB members based on their research/development interest. Further, the project activities were continuously tweaked based on the participation and involvement of the entire ERC team (including students and post-doctoral scholars) via our joint (ERC+CSAB+IAB) Friday 4:00 PM webinar series.
- ERC-RMB has initiated during this reporting year an infrastructure user fee charging mechanism, which has already proven successful, with multiple ongoing requests.
- engaged with the Global Community through ASTM-ISO (Committee AC-87) to develop biodegradable metals testing standards
- progressed further in establishing more focused activities with Industrial Advisory Board members specific to device projects of their interest.

Publications / Patents / Key Meetings

- The impact of ERC RMB's science continues to be demonstrated through a strong publication record and presence at key symposia, including as invited/keynote speakers. Invention disclosures and patent applications are increasing with more focus and credibility.
- For the reporting period, 35 journal papers and 5 peer-reviewed conference proceedings papers were published from ERC-supported projects, 5 journal articles, 2 peer-reviewed

conference proceedings papers and 1 book chapter from the associated projects, and 5 journal articles from sponsored projects.

- ERC members attended/led 47 scientific conferences/workshops and gave 50 seminars/colloquia/invited talks.
- During the reporting period ERC-RMB filed 2 invention disclosures, have been 4 patent applications (2 provisional and 2 full). Many of invention disclosures and patents include researchers from the all core partner universities.