

NSF Engineering Research Center for Integrated Mechanobiology for Women's Health (IMWEL)

1. VISION

Informed by biomechanics and mechanobiology research, the NSF Engineering Research Center for Integrated Mechanobiology for Women's Health (IMWEL) will apply engineering innovations to overcome women's health challenges, attracting and training inclusive next generation engineers focused on a women-centered approach. IMWEL's mission is to bridge the current gaps between computational tools and *ex vivo* systems, focus on women-centric physiology, build a system of devices and models, and train engineers at the interface of mechanobiology and women's health. IMWEL will advance engineering innovations to focus on three Testbeds: **Preterm Birth, Pelvic Floor Disorders, and Healthy Aging of cardiac and Musculoskeletal Systems.** A diverse team of researchers from Columbia University (CU), East Carolina University (ECU), University of California, Irvine (UCI), and University of Pittsburgh (Pitt) unite to integrate biomechanics and mechanobiology insights, a women-centered approach, and engineering innovation to advance women's healthcare (Fig. 1).

Pregnancy demands the uterus grow, remodel, and stretch to many times its original size. Birth requires pelvic tissues to stretch beyond their functional capacity. IMWEL will uncover how cells respond to mechanical loads and how they orchestrate dramatic tissue remodeling to build resilient, tough, and healthy organs, as exemplified in these processes. To explore such a complex biological and mechanical system, IMWEL will use mechanobiology to characterize the physiologic, biomechanically active properties of the female reproductive, pelvic floor, cardiovascular, and musculoskeletal systems. IMWEL will integrate these insights into multiscale biomechanical models, and then create engineering systems to address the proposed three Testbeds.

IMWEL will overcome key challenges to accomplish this mission: 1) The complexity of fast-modeling and resilient biomaterials, exemplified by the female tissue systems targeted, requires a convergent and holistic approach; 2) The paucity of researchers in female reproductive bioengineering demands a dedicated and inclusive education program; 3) The failure of industry to take a women-centered approach in commercialization, from ideation to design to marketing creates an opening to demonstrate a more effective approach.

First, IMWEL's expertise spans from biomechanics to mechanobiology, from experimental to computational, from basic science to clinical, from pregnancy to orthopedics, complemented by depth in psychology, innovation, evaluation and Team Science. IMWEL's core group of pioneering women's health researchers will focus on tissue-level biomechanics. Specifically Center Deputy Director Myers (CU), Co-PI Abramowitch (Pitt), and Co-PI Oyen (ECU) have led in this unique women's health field for the last decade and a half. Investigators from UCI, led by Director of Integration Liu, bring expertise in molecular-to tissue-level mechanobiology. Lead PI and Center Director Guo (CU), a leading bioengineer in osteoporosis and bone microstructure in women, instigated IMWEL and brings extensive managerial experience as CU's Chair of Biomedical Engineering. Deputy Director Kam, a leading mechanobiology expert, brings additional managerial experience of multidisciplinary teams. The full complement of 33 investigators' competency is detailed in the Emerging Technologies, Research Thrusts, and strategies for



Fig. 1: IMWEL's community guides its mission to infuse engineering research and innovation into three realms of women's health.

Engineering Workforce Development (EWD), Diversity Culture of Inclusion (DCI), and Innovation Ecosystem (IE) programs. IMWEL will partner with UCI's Team Scholarship Acceleration Lab (TSAL) to infuse Team Science through the Center.

Second, an integrated and inclusive education program will address the paucity of researchers, entrepreneurs and executives focused on female reproductive bioengineering, especially women and underrepresented minority (URM) engineers. Using a research-based approach to education and team dynamics, DCI Co-Directors Drs. Purdie-Greenway (CU) and Chesler (UCI), with EWD Co-Directors Drs. Downing (UCI) and Oyen (ECU), will implement a series of educational programs that quantitatively focus on training and providing opportunities for a diverse community of researchers. IMWEL's EWD and DCI programs will seek to build best practices to foster discussion about biomedical research that involves gender and sex that some people may find potentially uncomfortable. IMWEL will expose all undergraduates, graduates and postdocs to Team Science principles and practices, as well as training and opportunities created by the IE program.

Third, IMWEL will design and promote engineered products for women's health that take a women-centered approach from ideation to design to commercialization. IMWEL's IE program, led by Dr. Reuther (CU), leverages highly successful entrepreneurial programs and will support projects in women's health and, critically, integrates researchers, physicians, and venture capitalists. Engagement of physicians, research hospitals, industry, patient advocate groups, and community stakeholders throughout this process will further support delivering solutions to the clinic and home.

IMWEL 2032. Within a decade, IMWEL intends to **integrate mechanical forces into the lexicon of diseases disproportionately affecting women.** IMWEL envisions an initial cohort of researchers having established careers spanning academia, medicine, and industry that can leverage the advanced, actionable models the Center will develop. This community will exploit strong connections with all of IMWEL's stakeholders. A sustainable commercialization framework will promote devices and technology that allow stakeholders to incorporate concepts of biomechanics and mechanobiology for women's health with an initial set of technologies that are nearing human testing. IMWEL will also expand its engineering reach beyond the three initial Testbeds, to address more physiological systems for the promotion of health.

IMWEL is a compelling convergence of **science, technology, engineering, entrepreneurship, and mathematics (STEEM)** with education, and mentorship. Only the ERC mechanism can make this possible, providing a core structure and focus that is not achievable through a collection of other projects.

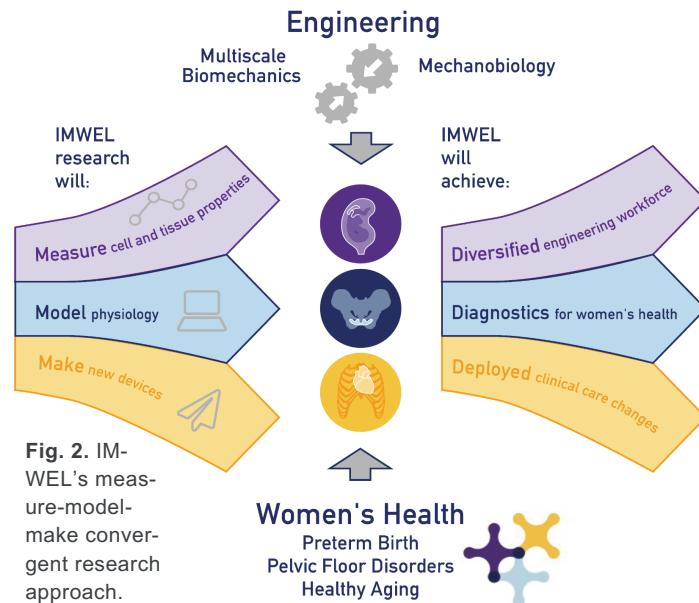


Fig. 2. IMWEL's measure-model-make convergent research approach.

2. STRATEGIC PLAN

IMWEL will nurture a community of researchers, students, educators, developers, and practitioners to unite multiscale biomechanics with mechanobiology around women-specific physiology. The Convergent Research section below details the core research strategy wherein a team of engineers, physicians, physical and social scientists, educators, and entrepreneurs will drive the execution across the four IMWEL sites. Notably, **18 of the 33 IMWEL team members are women**, including several of the world's experts in this nascent field. The integrated EWD and DCI pillars will expand the community, deploying a quantitative educational science framework. The IE strategy utilizes world-class technology transfer programs of the partners to provide training on successful commercialization from research to point of care.

Convergent Research (CR). IMWEL envisions **an engineered system of technologies to restore and support the biomechanical form and function of the female reproductive, cardiac and musculoskeletal physiology.** IMWEL's research components will converge to *measure* and *model* the unique biomechanical adaptations associated with human reproduction, postpartum repair, and aging and

make devices to address clinical diagnosis and intervention (Fig. 2). The top-level of IMWEL's engineering system (detailed in 4. Convergent Research) is a set of physiological Testbeds, each representing a health challenge that uniquely or disproportionately affects women and has origins in biomechanics and mechanobiology. A female physiology-specific knowledge base (Research Thrusts) will inform solutions within the Testbeds. The Enabling Technologies layer bridges these two layers, by defining experimental targets for basic research and feeding the results back to the Testbeds.

The female body's ability to drastically modulate mechanical properties of tissues and organs during pregnancy, childbirth, postpartum repair, and aging drives IMWEL's focus on the mechanical function and cell and tissue mechanical crosstalk [1–3]. For example, during pregnancy and birth, the uterus volume expands from 10 mL to 5 L, the cervix must decrease its tensile stiffness by three orders of magnitude [4–5], and the fetal membranes and placenta that isolate the fetus from infection while negotiating a vital supply exchange with the mother must be built from scratch [6]. IMWEL will develop new engineering devices to *measure* directly the properties of these tissues, informing *ex vivo* cell and tissue systems on the properties that these must *model*. Linking back to improve computer representations will allow IMWEL to *make* devices that use this new information, for example to predict normal or preterm birth (Fig. 1, Innovation), as well as tools to incorporate biomechanics into medical visits. IMWEL's Year 5 milestone for all three Testbeds is a proof of principle in the use of this approach, looking to an initial clinical trial by Year 10. Evaluation of the Year 5 milestones will inform which solutions to pursue to Year 10.

EWD and DCI Programs. IMWEL's EWD and DCI strategies work in tandem to develop a diverse community of researchers at the intersection of women's health with emphasis on biomechanics, and mechanobiology. The DCI strategy will promote communication between groups and enable scientific discussion around potentially uncomfortable subjects including biomedical research focusing on one sex. IMWEL will engage students and trainees across multiple stages of the engineering workforce pipeline, from middle school to postdoctoral mentoring. IMWEL will test whether targeted interventions around women's health can increase student interest in STEEM. Graduate students, postdocs, and fellows will be co-mentored in two-year fellowships. In addition, IMWEL aims to quickly change the EWD landscape by attracting "traditionally trained" STEEM postdoctoral fellows and providing training in biomechanics and mechanobiology of women's health. Dr. Purdie-Greenaway will also conduct a novel quantitative self-study to determine whether practices to respect DCI build a better engineering workforce geared for the next century of technological innovation.

The combined EWD and DCI program Year 5 milestones include completion of quantitative evaluation of specific interventions at middle-school and undergraduates, and examination of diversity at all levels through faculty to determine progress. By Year 10, this program will identify educational interventions that are quantitatively proven to enhance DCI and women's health in academic environments across IMWEL.

IE Program. Emerging engineering technologies and discoveries have significant potential to address many of the challenges in women's health. The IE program supports translation of academic discoveries from the lab to market, across the "valley of death" [7-8], by incorporating sensitivity to commercialization from initiation of research projects to deployed products. Milestones of IE follow the Testbeds; by Year 5, support early device development towards proof of concept. By Year 10, develop an ecosystem that supports successfully translated devices for women's health.

3. INFRASTRUCTURE

Leadership Team. Drs. Guo (CU), Myers (CU), Kam (CU), Abramowitch (Pitt), Oyen (ECU), and Liu (UCI) form the **Executive Committee** (EC) of IMWEL. A broader Leadership Team adds Drs. Purdie-Greenaway (CU) and Chesler (UCI) as Co-Directors of DCI, Dr. Downing (UCI) as Co-Director of EWD with Dr. Oyen, and Dr. Reuther (CU) as Director of IE (Fig. 3). Dr. Guo, in consultation with the EC, is responsible for day-to-day management and sets overall Center direction, adaptation, financial and policy development, and communications. Dr. Guo with the EC will review monthly progress from each basic Research Thrust and applied Testbed, help resolve conflicts, evaluate and select new projects funded by the Center, and select graduate students and other trainees to receive Center funding. As IMWEL's Director of Integration, Dr. Liu will shepherd the integration among Research Thrusts, Technology, and Testbeds. Dr. Liu will approve and validate plans, results, and outcomes from Research Thrusts to converge into the various Enabling Technologies and apply to Testbeds. The Leadership Team commits to Team Science principles and practices, aided by support from the experts at UCI's TSAL.

An Administrative Director (AD) will focus on financial management, operations, personnel, communications, reporting to Dr. Guo. The AD will organize all NSF Site Visits. To assist the AD, a

Programs Manager and two Special Projects Coordinators will manage communications, events, and outreach for EWD, DCI, and IE.

Management Plan, Enabling Convergent Team Science. IMWEL will partner with TSAL led by team science scholars, Drs. Gary and Judith Olson, Campo, and Stokols [9-11] to deliver convergence science training and consultation to ERC members. TSAL will lead a workshop during the kick-off meeting and focused audits will occur at the end of Years 2-4. TSAL will work with IMWEL to develop a team collaboration plan [12] to help guide the Center’s collaborative processes (e.g., specifying agreements for developing and sharing credit on research reports; procedures for resolving collaborative conflicts; sharing leadership activities across institutions to effectively integrate IMWEL’s research; and developing strategies to leverage the team’s diverse composition to enable maximum innovation).

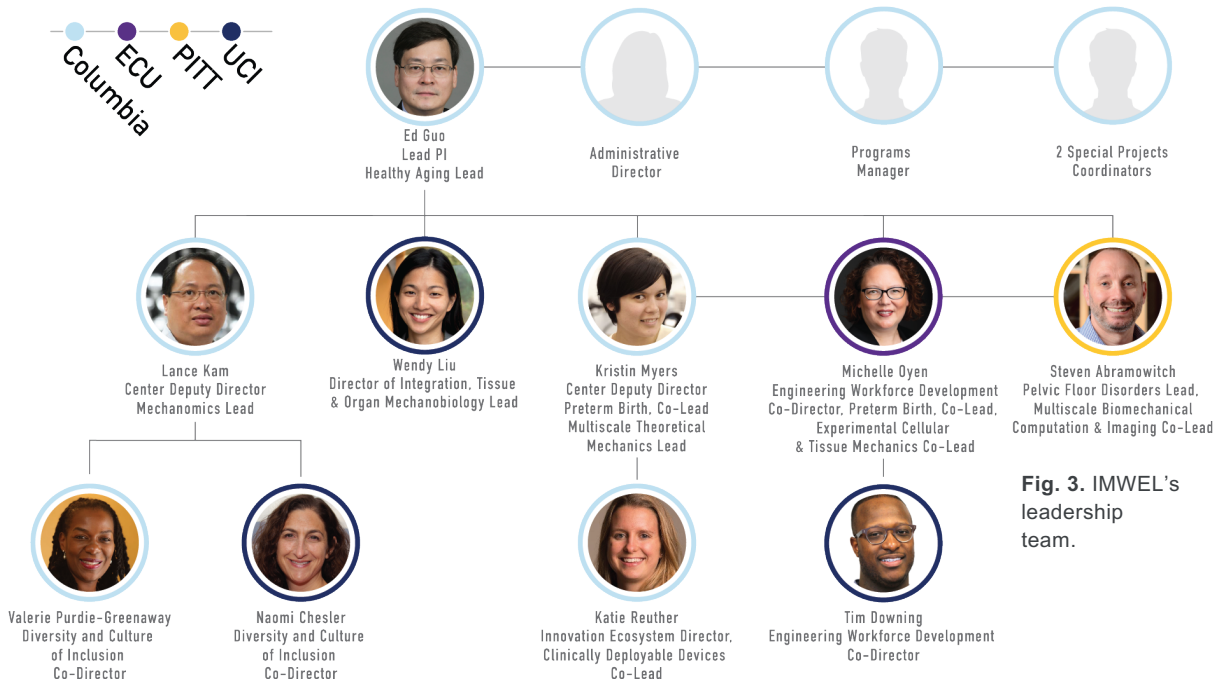


Fig. 3. IMWEL’s leadership team.

Council of Deans. The Council will meet every semester with the Leadership Team to advise on high-level issues related to institutional commitments, new institutional partnerships, and new strategic initiatives. Each spring, the Council will develop 5-10 questions—of both immediate and long-term strategic natures—that will be divided across all IMWEL committees and advisory boards. These questions will assist in the development of Strengths, Weaknesses, Opportunities, and Threats (SWOT) analyses to incorporate into a single “*IMWEL Annual Report*” to be distributed to stakeholders and presented at IMWEL’s annual meeting.

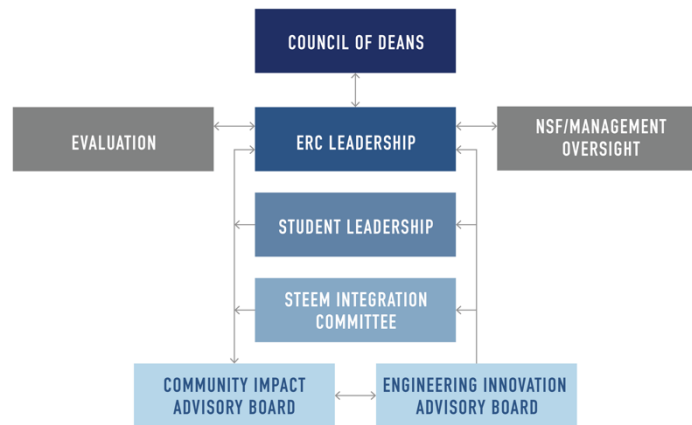
STEEM Integration Committee. All Thrust and Testbed Leads will meet every semester with the EC for a STEEM Integration Committee (led by Dr. Liu). This meeting will have one rotating lead present for 30 minutes on group development and pose operational questions to other leads, with 30 minutes for the larger team to ask questions and identify emerging collaborative opportunities.

Engineering Innovation Advisory Board. This advisory board (led by Dr. Reuther) will include representatives from partner companies and domain-specific business mentors (including women’s health tech entrepreneurs such as partners NextGen Jane, Materna, and Pregnolia AG), investors (e.g., partner Deerfield), policymakers in women’s health, regulatory specialists, and other industry representatives. A representative from each partner institution’s technology transfer offices will staff this advisory board, which meets biannually. The advisory board will provide feedback to translational research initiatives and help evaluate and select projects for translational pilot grants.

Student Leadership Committee. This committee (advised by Dr. Kam) will meet monthly and will include IMWEL-funded undergraduate and graduate students across the four partner institutions. Members will serve for two years and will self-elect a President and Co-President who will liaise with the other committees and advisory boards. The SLC will prepare an annual SWOT analysis to present at the annual NSF visit.

Community Impact Advisory Board.

This advisory board (led by Dr. Myers and including members of the DCI team) envisions a safe, inclusive, and resilient social community, and includes translational research faculty, public policy practitioners, and community stakeholders (e.g., patient advocacy group partner, Iris Fund). The board will stress communication of all research and non-research activities to the general public. The board will orchestrate outreach events to medical, government, women's advocacy groups, and general public communities, to collaboratively create new science literacy and bioethics around mechanobiology and women's health.



IMWEL Annual Meeting. An annual meeting will convene all stakeholders every summer to review the Center's progress and SWOT analyses, make course corrections, and update goals. CU will host the annual meeting in Years 1-5 and the site will rotate between core institutions in Years 2-4.

Institutional Configuration. CU in a large urban city and Pitt in a medium-size midwestern city have world-leading medical centers and engineering schools, including leading mechanobiologists and bioengineers. Pitt's medical partner, Magee-Women's Research Institute, is the leading clinical and research center dedicated to women's health. UCI brings expertise and leadership in cardiovascular bioengineering and mechanobiology, and expertise in Team Science. Located in a west coast suburban county, its designation as a Hispanic-serving institution broadens the impact and reach of IMWEL. ECU, in a relatively small southern town, is the only institution within the North Carolina system with a medical school, dental school, and engineering department on the same campus, and is developing a strong biomedical engineering program with significant clinical-engineering collaborations in women's health. ECU has won the Higher Education Excellence in Diversity Award for the ninth consecutive year and serves a substantial number of first-generation students.



4. CONVERGENT RESEARCH

Research Strategy. Biomechanics and mechanobiology factor into many aspects of pregnancy, including the physical properties of uterine tissues, blood flow and oxygen diffusion in and around the placenta, and the considerations of how and when the fetus exits the womb. Over time, acute pregnancy-related complications affect women's health, including pelvic floor disorders and chronic musculoskeletal and cardiovascular disease. The three Testbeds for IMWEL—Preterm Birth, Pelvic Floor Disorders, and Healthy Aging—form the top layer and unifying themes of the proposed convergent research, supported by four fundamental knowledge Research Thrusts and four Enabling-Technology Thrusts (Fig. 5, the IMWEL 3-plane diagram). This strategic framework aims to overcome the significant barriers that have hampered women's health research and lead to solutions for clinical intervention: diagnosis, treatment, and prevention. The timing and integration of research and design activities for these strategic thrusts are mapped in Fig. 6 and detailed here.

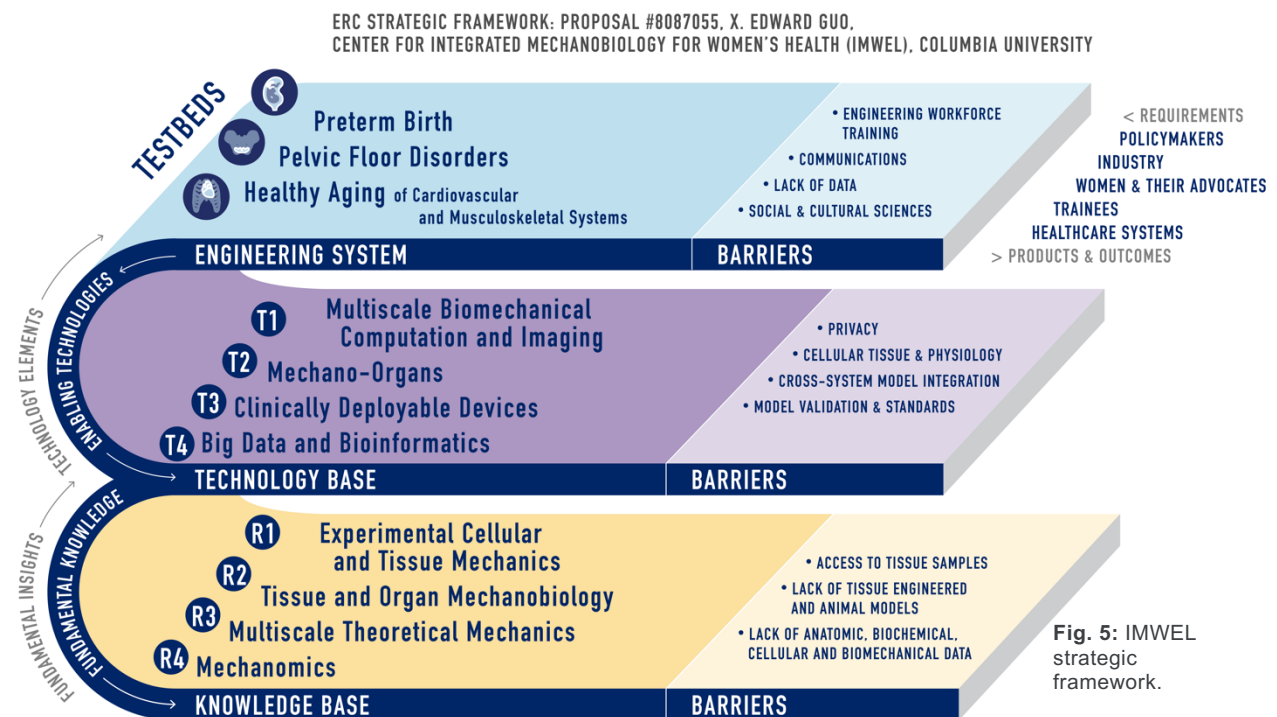
A lack of suitable physiological *in vivo* models complicates research into human reproduction, as no non-primate mammals have anatomy and physiology similar enough to humans to serve as effective animal models. Ethical challenges associated with research on pregnant women also encumbers the field to develop alternative research approaches. The timescales of research compared with the timescales of clinical outcomes observed with pelvic floor disorders and healthy aging creates a second challenge as chronic conditions can appear many years or even decades following childbirth. Significant hormonal change associated with menopause, which systematically affects tissues throughout the body, adds additional complexity. IMWEL's *in silico* models seek to capture key facets of physiology for each testbed that can translate animal and *ex vivo* living experiments into an actionable representation.

Women's health impacts more than half of the world's population and all children, but until recently was not a mainstream topic of dedicated research. Clinical trials omitted female participants for many years due

to fears that hormonal fluctuations would obscure other effects [13]. In current, fast-breaking news cycles, the differential effects of COVID-19 and its vaccines on women have just started to gain widespread attention [14]. This proposal addresses specific issues within women’s health that significantly impact the U.S. healthcare climate, both financially and in terms of morbidity and mortality in both current and future generations of women.

Each of the four Research Thrusts underlying this effort can transform women’s health care in their own right, but a synergistic approach will have outsize impact. Although cell and tissue biomechanics as a field has existed for many years, sports injury and male aging research has dominated research. Current knowledge in multiscale biomechanical theory emphasizes relatively small mechanical strains compared with those experienced during pregnancy. The small amount of women’s health research that does exist has yet to fully incorporate the relatively new fields of “-omics” technologies and mechanobiology.

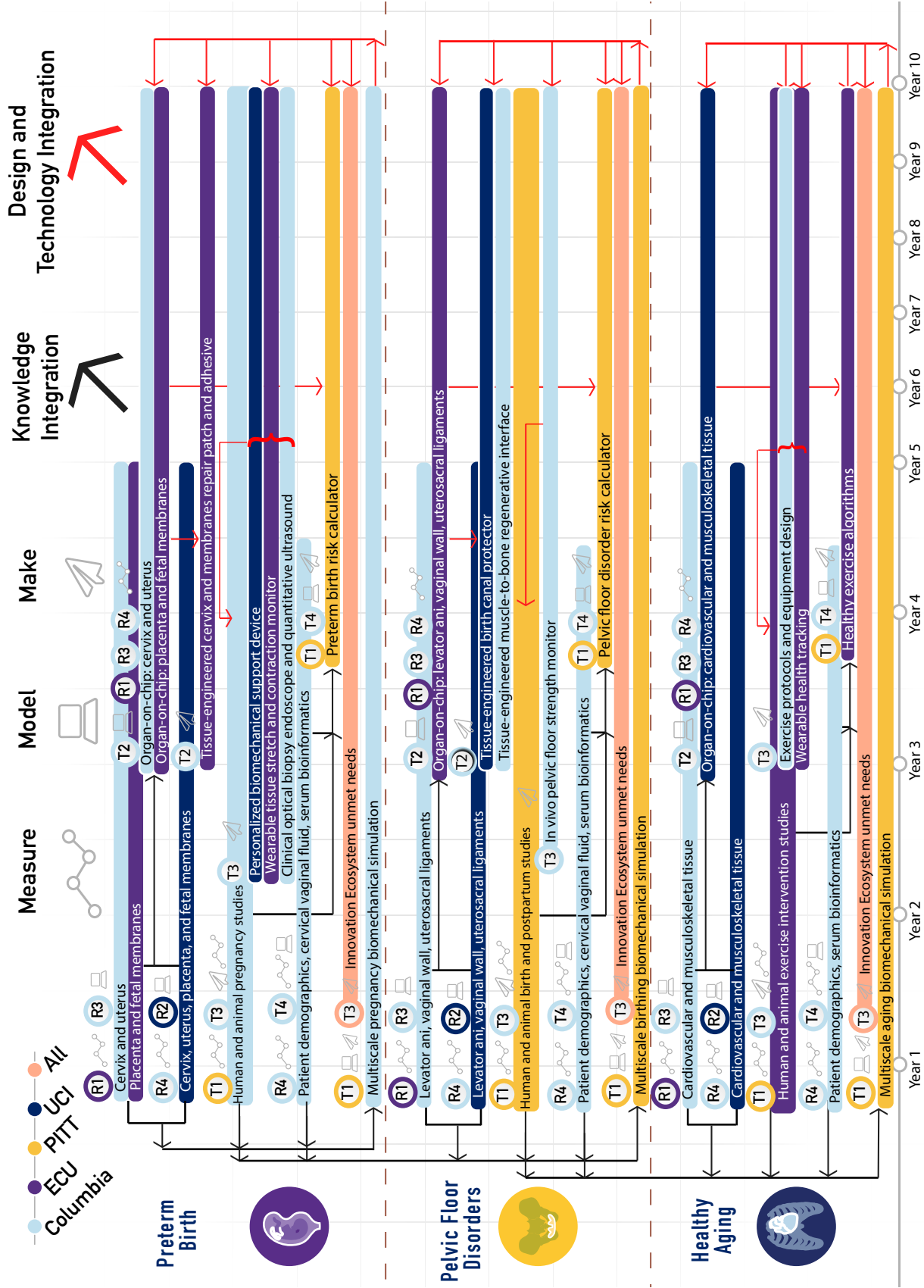
The potential for major technological impact in women’s health mechanobiology is immense. All women undergo hormonal variations that impact general health, particularly in the normal time-course of events associated with aging and menopause. The burden of human reproduction falls disproportionately on women, an increasingly clear issue as other barriers to women’s involvement in science and engineering have emerged.



An unreasonable expectation that all pregnancies conclude with the birth of healthy, full-term offspring becomes even less accurate as the average age of mothers increases. Media ignores life-altering medical conditions, such as uterine prolapse, that impact quality of life in a shocking fraction of women; its existence relegated to hushed discussions. Obstetricians and gynecologists are not trained in basic physics and mechanics, unlike their colleagues in medical specialties such as Orthopedics. The preponderance of males in science and especially in engineering, contribute to the neglect of women’s health challenges in public discourse, research funding, and training of the next generation of researchers and product developers.

IMWEL grounds its approach to women’s health research in Measure-Model-Make (Fig. 2): researchers will measure multiscale aspects of genetics and cell biology and tissue biomechanics; they will construct *in silico* models of both normal and pathological conditions in all three Testbeds; researchers and companies will make new devices to deploy for use in both research and clinical treatment, improving the lives of half the world’s population and all future children.

Fig. 6 (next page): Timing and integration of IMWEL research activities. Refer to IMWEL 3-plane Strategic Framework for knowledge and technology activity codes R1-R4 and T1-T4.



SYSTEMS TESTBEDS



PRETERM BIRTH

Background. Childbirth is mechanically complex and insufficiently understood. Preterm birth (prior to 37 weeks of gestation), occurs via different biophysical and biochemical mechanisms, including maternal, fetal, and maternal-fetal (placental) factors [15-16]. Failure of the cervix to remain closed until term contributes to preterm birth, and is accompanied by abnormal growth and distension of the fetal membranes that contain the fetus and amniotic fluid. The mechanical rupture of the membranes prior to full-term gestation occurs in 3-4% of pregnancies [17]. No real treatment or recourse following membrane rupture and loss of amniotic fluid surrounding the fetus exists. The fetal-maternal interface occurs at the placenta (Fig. 7), which physically attaches to the uterine wall. Poor trophoblast invasion in the first trimester is associated with disorders that manifest later in pregnancy, such as pre-eclampsia and fetal growth restriction [18]. Although the fetal circulation is closed, with blood cycling between the placenta and fetus, the maternal circulation is open. As such, disruption of the interface in placental abruption due to physical forces associated with delivery can result in significant maternal blood loss and even death [19]. Thus, macroscale tissue mechanics and cellular mechanics—including cell migration [20] and cell-matrix interactions [21]—are critical in the placenta’s development and function. The complex immunology associated with fetal cells traversing maternal tissue complicates the issue.

Milestones. The Preterm Birth Testbed will coordinate research in the biomechanics and mechanobiology of pregnancy to diagnose and prevent the causes of preterm birth. IMWEL will focus on maternal and maternal-fetal contributions to preterm birth, including cervical insufficiency [22], placental abruption [19], pre-eclampsia [23], preterm premature rupture of membranes [17], and fetal growth restriction [24] due to placental insufficiency. By 10 years, this Testbed aims to provide validated and patient-centered solutions for diagnosis and intervention to prevent preterm birth. Within five years, IMWEL will define the biomechanical health of pregnant patients, and create a ‘biomechanical check-up’ to identify preterm birth risks and possible prevention.

Specifically, IMWEL will build device prototypes to continuously monitor excessive mechanical stretch, such as a bio-compatible wearable strain gauge, and image tissue constituents through a nondestructive endoscopic ‘optical biopsy’ using optical coherence tomography (Enabling-Technology Thrust: Clinically Deployable Devices). IMWEL will leverage tissue engineering approaches to intervene in cervical insufficiency and fetal membrane rupture (Enabling-Technology Thrust: Mechano-Organs). IMWEL will advance basic science by studying cellular mechanisms of trophoblast invasion and placental development (Research Thrust: Tissue and Organ Mechanobiology). Organ-on-a-chip approaches will consider the maternal-fetal interface and the movement of chemical and biological agents across the placental interface (Enabling-Technology Thrust: Mechano-Organs). Within three years, laboratory investigations and device development will occur in tandem with *in silico* approaches to create multiscale virtual models of the uterus and placenta from the cell scale within the uterine environment through tissue scale up to the full pregnant pelvis (Research Thrusts: Multiscale Theoretical Mechanics and Experimental, Cellular and Tissue Mechanics). The computational modeling approach intimately connects to the acquisition of medical imaging datasets from ultrasound imaging and MRI (Enabling-Technology Thrust: Multiscale Biomechanical Computation and Imaging). This lays the foundation both to investigate preterm birth mechanisms and to trial possible clinical interventions in patient-specific models, representing a game-changing paradigm in preterm birth research.

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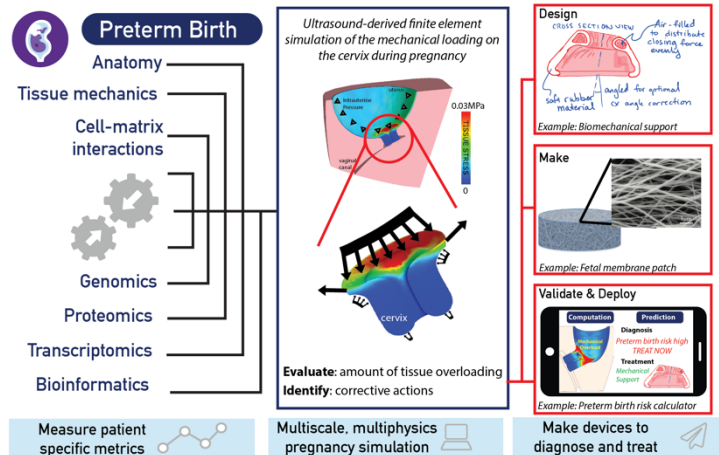


Fig. 7: Preterm Birth Testbed engineering workflow.

Social Impact. Every biological mother and child deserve a safe and full-term pregnancy. Preterm birth before 37 weeks of gestation creates a major long-lasting public health problem. The latest report of global births estimates over 14.5 million babies arrived preterm in 2014; preterm birth leads as the cause of childhood (<5 years old) death [25-26]. Eighty percent of preterm births are spontaneous and cannot be predicted. Preterm birth rates vary by state within the US, with higher rates in the south, where the greatest racial disparities exist [27]). An estimate of the cost of preterm birth in 2016 was \$25.2 billion—on average \$64,815 per preterm birth—a value that is rapidly increasing [28]. Conditions such as pre-eclampsia and maternal hemorrhage can lead to significant maternal morbidity and mortality, especially in African American women [29-30].

The historical lack of interactions between bioengineers and women’s health practitioners has limited biomechanical and mechanobiological interventions into preterm birth. This innovation gap has resulted in a lack of understanding of normal and pathophysiological pregnancy changes and stagnation of the decline of preterm birth rates [31]. Current therapies fail 95% of such preterm births, which suggests that society needs substantial further research [32]. IMWEL aims to identify high-risk women early in their pregnancy [33], and to develop etiology- and patient-specific interventions while simultaneously identifying low-risk women to avoid unnecessary and costly interventions [34-35].



PELVIC FLOOR DISORDERS

Background. Pelvic floor disorders include descent of the pelvic organs (bowel, bladder, uterus) into the vagina (pelvic organ prolapse); urinary dysfunction (e.g., stress urinary incontinence); and defecatory dysfunction (e.g., anal incontinence and obstructed defecation disorders). The majority result from injury to structural supportive tissues (muscle and connective tissue) during vaginal delivery. The primary identifiable injury for patients with pelvic organ prolapse is an avulsion of the enthesis of the pubovisceral muscle (Fig. 8)[36]. This injury and others are mostly internal and not observable to the caregiver at the time of delivery; thus, doctors almost never diagnose injuries until the symptoms develop later in life. Even if a doctor does diagnose internal injury, no treatment strategies exist.

The prevention of pelvic floor disorders starts with the prevention of injury at the time of delivery. While studies have observed that the female body changes during pregnancy in preparation for delivery (e.g., remodeling of the pelvis resulting in wider hips, pelvic tissues become more pliant) and have elucidated some of the mechanisms responsible for these processes, the mechanical implications of such changes have received relatively little attention [37-45]. Elastin, a key structural protein in the vagina, degrades in preparation for delivery and then resynthesizes (unique to female reproductive tissues) as a part of recovery [46,47]. An understanding of such unique processes will enable the intervention prediction.

Milestones. The ten-year goal of this Testbed is to focus fundamental knowledge and enabling technology efforts to deploy devices to promote muscle-to-bone healing, *in silico* tools to predict a woman’s injury potential resulting from vaginal delivery, and therapeutics and interventions to minimize risk of maternal injury during delivery (Figs. 6 and 8). Specifically, IMWEL will capitalize on this team’s existing expertise in recapitulating the soft tissue interface to bone [48–50] by creating a therapeutic that promotes reattachment and regeneration of the pubovisceral muscle enthesis (i.e., the connective tissue interface between the pubovisceral muscle and bone). Within five years, the IMWEL CR team will define and validate, via imaging, human anatomical and functional markers of pregnancy and injury-induced remodeling. This strategy of defining the precise remodeling events that afford successful vaginal birth as well as the events

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H. Lu	Biomed. Eng.	CU	H. West	Mech. Eng	CU

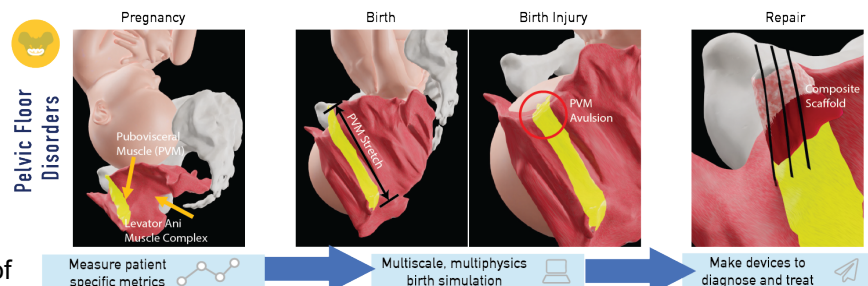


Fig. 8: Computer simulations highlight the significant tissue deformations during childbirth – particularly to the pubovisceral muscle (yellow), a pubovisceral muscle avulsion from the bone, and an envisioned 3-phase composite scaffold to repair the soft-tissue-to-bone interface (moving left to right).

that signal insufficient preparation for delivery, will enable the development of therapeutic interventions that overcome remodeling deficiencies. IMWEL will develop *in silico* biomechanical models of delivery including damage and growth and remodeling, identify mechanics of pregnancy induced remodeling and muscle injury at the time of delivery, and develop initial prototypes of devices to promote healing at muscle-to-bone interface. Such a prevention strategy will require comprehensive analyses of pelvic bones, connective tissues, muscles, and ligaments in a bottom-up approach that incorporates transcriptomics, proteomics, mechanics, along with comprehensive imaging and computational analyses. IMWEL will create animal models for pregnancy-induced remodeling and pubovisceral muscle avulsion. It will map multiscale tissue anatomy, morphology, material properties quantified and spatially and temporally. It will characterize pregnancy and injury-induced remodeling and healing in terms of cell-matrix interactions. Lastly, IMWEL envisions using its big data efforts to help drive fast, accurate, patient-specific, and clinically deployable computational simulations into the hands of clinicians for diagnosis and surgical planning.

Social Impact. Each year in the U.S., 4 million women give birth primarily vaginally. Unfortunately, vaginal birth substantially increases the probability that a woman will develop pelvic floor disorders later in life [51-52]. Pelvic floor disorders negatively impact the physical, psychological, and social wellbeing of affected women [53-55]. It represents a major public health burden with more than 12.6% of women in the United States undergoing major surgery to repair a disorder by age 80, [51-52] at an estimated cost of > \$10 billion annually. Surgeries to treat pelvic floor disorders generally have disappointing success rates leading women to anticipate multiple repairs over a lifespan [51-52]. The aging population implies the demand for care to treat pelvic floor disorders will increase ~50% by 2050 [56]. To date, practice has done little to minimize the risk of damage to the levator ani muscles. Most injuries go unrecognized until symptoms develop years later, likely because the underlying defect was not addressed [57]. Cesarean delivery (CD) is not an attractive option as it increases immediate neonatal and maternal morbidity, and the likelihood of future repeat CD with the attendant risks of uterine rupture, future abnormal placentation, viscus injury, and hemorrhage [58-60]. CD also costs more than spontaneous delivery. Many mothers will not accept CD unless it is medically necessary [61]. Thus, the U.S. should make it a national health care priority to identify methods that reduce levator ani muscles injury at the time of vaginal birth.



HEALTHY AGING

Background. This Testbed will develop strategies and technologies to maximize the effects of physical exercise to maintain and improve women’s health during their entire lifespan (Fig. 9). Exercise benefits the whole body, particularly the cardiovascular and musculoskeletal systems. Currently, science poorly understands the molecular mechanisms induced by exercise to support an aging female body. IMWEL will use the mechanics approach to identify and isolate molecular factors involved in the pro-health of the cardiovascular and musculoskeletal systems, with a specific focus on pregnancy, delivery, and the postpartum period. The Testbed will concentrate on the cardiovascular system and musculoskeletal system with an emphasis surrounding women’s reproductive systems such as pelvic floor and lower extremities. Physical exercise has been promoted to support a healthy pregnancy and mechanically prime the pelvic floor in preparation for childbirth, including the popular Kegel exercises. However, the basic science is poorly understood and their rigors have not been tested.

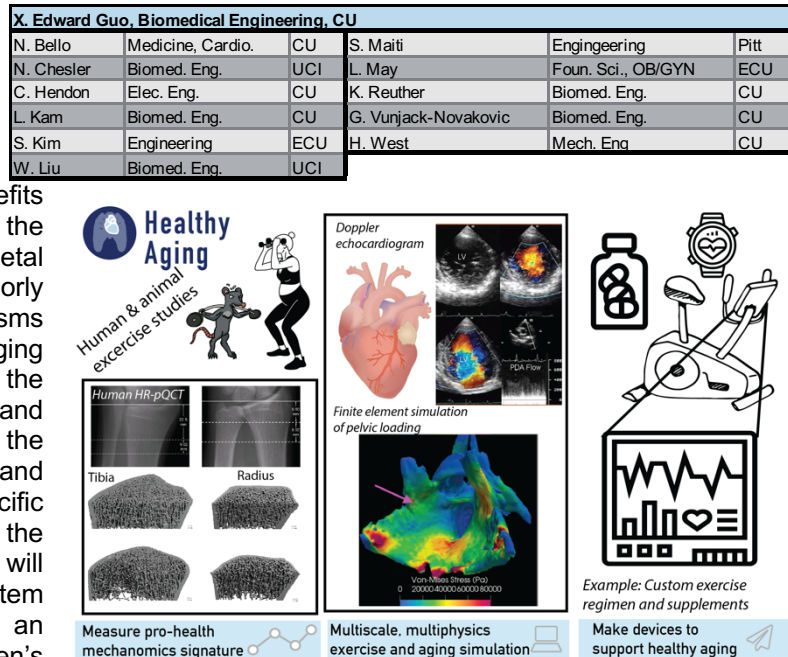


Fig. 9: Healthy Aging Testbed engineering workflow (exercise cartoon courtesy of Ms. Abramowitch, 11-year-old aspiring woman bioengineer in women’s health).

Milestones. The ten-year goal is to develop and test novel exercise models for enhancing pelvic floor health (e.g., squatting and Kegel exercise) based on mechanistically defined pathways (Fig. 6). For example, IMWEL envisions exercise protocols and UX-designed apps for a healthy pregnancy, delivery, and aging. IMWEL intends to integrate these tools with other FemTech apps and devices with consideration of the menstruation cycle. Such strategies will capitalize on expertise in experimental and cellular tissue mechanics and mechanomics to focus on exercise models that help to prevent injurious deliveries and help to build postpartum and post-repair rehabilitation strategies to restore pelvic floor function and obviate the risk of future pelvic floor disorders.

The five-year goal is to define the basic science of exercise on female health using appropriate rodent models (such as rats or mice). IMWEL will utilize Interventions such as treadmill exercises to measure their impact on the biomechanics of female reproductive system (uterus, cervix, vagina, pubocaudalis muscle, and the structural properties of the vagina-supportive tissue complex [62–66]) in both pregnant and non-pregnant animals. In addition, IMWEL will collect tissues from the cardiovascular system (e.g., ventricle & aorta). The team will conduct similar studies in male animals to elucidate sex-specific differences. Finally, IMWEL will measure proteomics and genomics to identify mechanomics factors induced by exercise through blood and serum samples.

Based on these outcomes, IMWEL will conduct a human subject study. Briefly, a *four-arm*, randomized controlled trial will assess the mechanomics of a prescribed exercise intervention. The Center will study (1) premenopausal women (18-45 years old), (2) current pregnant women, and (3) peri-menopausal women (~45-55 years old) in an exercise program and assign participants from each group to one of four regimens: Aerobic Exercise, Resistance Exercise, Aerobic+Resistance Exercise, and no exercise controls. The proposed exercise intervention, which abides by the guidelines of the American College of Obstetricians and Gynecologists, American College of Sports Medicine, and the American Heart Association, builds on previous studies with positive findings [67] conducted by Center researchers (May), supported by consultants: Dr. Ellen Casey of the Hospital for Special Surgery, sport medicine specialist, and Dr. Sherry Liu from the University of Pennsylvania, a pregnancy bone expert. IMWEL will acquire blood samples for mechanomics studies to identify and isolate molecular factors associated with healthy biomechanical function.

Social Impact. Pregnancy in women not only exerts tremendous stresses on the female reproductive system, but also rigorously stresses other organ systems. For example, cardiac output increases by 50% during pregnancy [68]. The growing baby and softening of pelvic muscle exert great strain and stress on the pelvic floor musculoskeletal system. These extraordinary burdens on the cardiovascular and musculoskeletal system during pregnancy impose significant risk factors to women’s health such as hypertension, diabetes, and pelvic floor disorder. Too little attention has been paid to diagnosis and treatment of cardiovascular health in women although cardiovascular diseases rank as the leading cause of morbidity and mortality among women worldwide. The pathophysiological basis of cardiovascular health among men and women is not identical. This leads to variable cardiovascular responses to stimulus and presentation of cardiovascular disease symptoms, both of which can have a direct effect on health and disease outcomes. In addition, women, unfortunately, suffer more musculoskeletal disorders such as osteoporosis and osteoarthritis. This Testbed will provide a roadmap and associated technologies using physical exercise to improve and maintain the health of women throughout their lifespan.

ENABLING TECHNOLOGIES

T1 MULTISCALE BIOMECHANICAL COMPUTATION & IMAGING

IMWEL envisions accurate yet robust computational *models*. Development of these models faces several challenges

given the materials’ ability to deform multi-fold over timescales of hours to decades. The multiscale image of the cardiovascular system (Fig. 10) highlights these challenges, which apply to all three IMWEL Testbeds. Although individual components of this physiology resemble those throughout the body, the female pelvis organizes in unique ways that optimize form and function. For example, “ligaments” that support the pelvic organs consist of collagen and elastin. However, unlike traditional ligaments, they also contain smooth muscle and significantly more nerve and vasculature, providing complex biomechanical

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functions that effective models must include. The levator ani is histologically similar to other skeletal muscles but are mostly under autonomic control and maintains constant tension- without tiring- until an individual decides to relax to allow for elimination of waste. To develop a functional model framework of the female pelvis, IMWEL seeks to understand (1) *how sub-tissue scale structural changes can alter organ scale biomechanics*, and (2) *how physiological and pathological changes at the organ level influence tissue structure and biomechanical behavior*. This research will leverage the knowledge bases that are fundamental to this proposal, extend existing multiscale mechanical theories [69–78], develop novel multiscale growth and remodeling biomechanical theories, and advance quantitative imaging techniques and mechanobiology. IMWEL aims to develop a biology-based, imaging-informed multiscale *in silico* modeling paradigm.

Multiscale, Multimodal Image Analysis. Detailed, mechanics-focused imaging of the female pelvis, quantifying the structure and mechanical properties of load bearing components, will inform the models. High resolution micro-CT, MRI, ultrasound imaging and elastography, serially calibrated frozen cryosection imaging, confocal and multi-photon microscopy will gather 3D data on tissue structure and organization, thickness variations, and overall shape. Techniques currently under development in IMWEL’s laboratories will generate finite element structures of organ geometries.

Finite Element Modeling of the Pelvic Floor Organ Incorporating Microstructural Information. A custom finite element code capable of describing failure based on a microstructural modeling strategy will simulate the biomechanical behavior of female pelvic organs and their supportive tissues. Once developed and tested, IMWEL will implement the tools into FEBio (University of Utah and CU), a software suite developed by an IMWEL team member and used extensively in biomechanics, to promote access by the broader scientific community. IMWEL will calibrate model parameters to match the displacements observed via imaging. Studies will systematically alter geometric shape, fiber structure, and other model parameters to identify parameters that drive these models, which will be tested in cellular and tissue level systems.

Coordination and Milestones. Drs. Abramowitch and Maiti will coordinate IMWEL’s activities in multiscale biomechanical computation and imaging to provide a framework to unite cellular and tissue biomechanics with multi-organ function as well as a set of specific models representing the systems targeted by the three high-level Testbeds. The fundamental knowledge required to accurately describe individual biological components of these models will be drawn from the *ex vivo* experiments of cellular and tissue level mechanics, informed by IMWEL’s Research Thrusts.

Initial studies in Years 1-2 will focus on gaining structural, mechanical, and cellular insight into the target physiologies. IMWEL will image strategic samples from animal and human models, identified by the Testbeds, by the end of this first phase. These data will inform computational models. This first phase will also identify opportunities to develop imaging technologies that more accurately inform these experiments. IMWEL will patent protectable aspects of these technologies for subsequent commercialization. IMWEL will distribute knowledge gained in this first phase through the open FEBio platform. Years 3-5 will leverage the discoveries of phase 1 to demonstrate devices, procedures, and practices to improve human health. As specific milestones, IMWEL will develop at least two interventions to detect and prevent Preterm Birth. For Pelvic Floor Disorders and Healthy Aging, IMWEL will demonstrate modeling of these longer-timescale processes, using the framework described for the female pelvis above and further developed for Preterm Birth. Years 5-10 will approach IMWEL’s long-range goal by applying models for all Testbeds to human physiology.

T2 MECHANO-ORGANS

One of the most fundamentally challenging problems in tissue engineering is to capture the mechanical integrity of native tissues in replacements grown in the laboratory. Reproductive tissues increase the

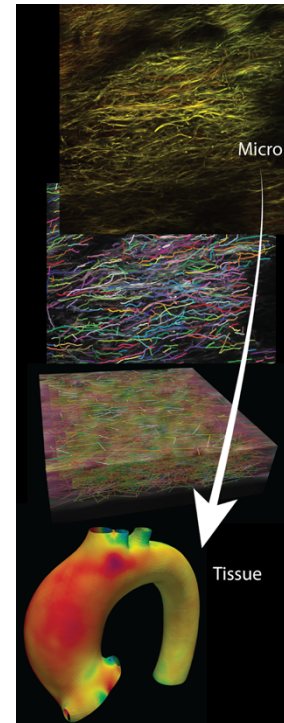


Fig. 10: Workflow demonstrating the incorporation of microstructural imaging into tissue level models to simulate organ level mechanics.

complexity, given the large deformations encountered during pregnancy and birth, as well as the more gradual yet significant changes that occur over a woman's lifetime. With a focus on molecular- to tissue-level mechanics, IMWEL will leverage a set of *ex vivo* technologies to gain insight into how tissues of the reproductive system remodel and repair. These insights will lead to improved techniques for growing tissues for reproductive systems, complementary to development of Clinically Deployable Devices.

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G. Vunjack-Novakovic	Biomed. Eng.	CU

Organ-on-a-Chip Models. Cervical insufficiency, pre-eclampsia, and preterm premature rupture of membranes are known contributors to preterm birth. IMWEL will use organ-on-a-chip models to first understand the role of mechanical forces in establishment, function, and potentially repair of these complex structures, including the maternal-fetal interface, then create interventions. IMWEL will leverage systems developed within the Center for other interfaces, including a recently demonstrated platform for capturing neuromuscular junctions [79], to accelerate studies in this direction. IMWEL will conduct animal studies of muscle tissues involved in the female pelvis and reproductive tissues to enable controlled studies of diverse patient populations (age, genetic background, disease conditions).

Biomaterials for Tissue Integration. The most common injury associated with pelvic organ prolapse involves avulsion of the pubovisceral muscle at its enthesis with the pubic bone, which contributes to muscle atrophy and the onset of prolapse later in life. Leveraging Center expertise in engineering soft tissue-bone integration (ligament-bone, tendon-bone and cartilage-bone) and guided by understanding of the muscle-to-bone interface (Multiscale Models Thrust and the Pelvic Floor Testbed) IMWEL will develop biomaterial-based solutions to replace muscle-bone integration. This will leverage current preclinical studies in IMWEL towards a nanotechnology-based biphasic scaffold to re-establish organized collagenous transition and exercise spatial control over mineralization. Both *in vitro* and *in vivo* models will test the potential of the biphasic nanofibrous scaffold to guide collagen production (tangential insertion) and promote osseointegration.

Coordination and Milestones. Dr. Lu will coordinate IMWEL's development of mechano-organs to the 10+ year goal of demonstrating constructs with mechanical integrity characteristic of the native tissues they are replacing. For Years 1-2, IMWEL will focus on translating the mechanical properties of tissues such as the cervix, placenta, and supportive tissues of the pelvic floor into an *ex vivo* system that allows for exploration of the underlying mechanobiology. Informed by the advances in those sections, Years 3-5 will reverse this knowledge flow to produce tissues that reach new levels of control over compositional and mechanical properties. This includes tissues for fetal membrane repair, smooth muscle constructs for uterine tissues, and a biphasic nanofibrous scaffold tailored for use in the female pelvis. Years 5-10 will scale up these initial constructs and design complete systems for implementation to target animal testing in year 10. Throughout the project, the Mechano-organs component will coordinate development of bioreactors, high-throughput culturing systems and animal models. Human organ-tissue-cell benchmarks identified by all three Testbeds will validate these new technologies, comparing molecular markers as well as structural and ultrastructural properties.

T3 CLINICALLY DEPLOYABLE DEVICES

IMWEL will *make* new biomaterials, sensors, imaging tools, software, and technologies based on mechanobiology to support the development of clinically deployable devices to enhance healthcare for women. IMWEL will support deployment of these technologies using good technology development practice and emphasizing *women-centered design* and *early stage commercialization guidance*, both points of weakness in today's pipeline.

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C. Hendon	Elec. Eng.	CU	K. Myers	Mech. Eng.	CU
S. Kim	Engineering	ECU	J-S. Vink	OB/GYN	CU
C. King	Biomed. Eng.	UCI	R. Wapner	OB/GYN	CU
J. Mauney	Urology	UCI	H. West	Mech. Eng.	CU
L. May	Foun. Sci., OB/GYN	ECU			

Women-Centered Design. A lack of attention to specific needs of women's anatomy and physiology contributes to deficits in women's healthcare. Examples include the automobile seat-belt, which designers created for the average man, leaving women more likely to be injured in a car crash [80]. Healthcare repurposed mesh for hernia repair as a vaginal mesh to treat pelvic organ prolapse in women without consideration for their unique physiological needs, leading to significant complications and costly removal surgeries [81]. IMWEL will apply *women-centered design* throughout technology development, from benchtop testing to clinical trials and commercialization.

Early Stage Commercialization Guidance. An understanding of clinical trials, manufacturing under quality systems, and the pathway toward regulatory approval will underpin technology development and eventual transfer through the IE. IMWEL will lower the traditional boundaries between technology development and commercialization by exposing researchers to and soliciting advice from entrepreneurs and other commercialization partners throughout ideation and development.

Coordination and Milestones. Dr. Reuther will coordinate IMWEL’s development of Clinically Deployable Technologies and Devices to advance devices to market. Specifically, Years 1-2: initiate device development based on Research Thrusts and aligning new fundamental research with clinically-defined needs. Milestones: assessment of the number and quality of projects launched around each Research Thrust and initial pilot grants awarded. Years 3–5: ready prototypes for pre-clinical and clinical testing, iterative redesign, intellectual property filing. Milestones: design finalization of two devices. Years 5–10: establish partnerships for design verification and validation, clinical trials, technology transfer and/or commercial manufacturing, regulatory clearance and approval, deployment and commercialization of new women’s health technologies.

IMWEL’s Women-Centered Devices. IMWEL will develop technologies for diagnosis, treatment and prevention across the three Testbeds. Industry partners (e.g., Materna, Renovia, Pregnolia, and Alydia) will accelerate technology development. IMWEL targets as five-year goals: For Preterm Birth: devices to monitor stretch of reproductive tissues as part of biomechanics-based standard-of-care screening, and a patch sensor to monitor the cervical remodeling remotely and provide alerts for urgent events [82-83]. For Pelvic floor disorders: *in silico* tools to predict a woman’s potential injury from vaginal delivery, devices to promote muscle-to-bone healing including promoting reattachment and regeneration of the pubovisceral muscle enthesis, interventions to minimize risk of maternal injury during delivery, and a responsive uterine tamponade to provide adaptive treatment for uterine atony. For Healthy Aging: devices to measure the biomechanics of exercise beyond heart rate, and as a ten-year goal, science-based biomechanics-driven protocols for exercise for women at different stages of life and life-events including pregnancy. Unmet clinical needs and fundamental knowledge being pursued in the Research Thrusts will drive the device development direction.

T4 BIG DATA AND BIOINFORMATICS

Personalization of treatment and recognition of diversity between individuals in Women’s Health lag behind other areas of medicine. IMWEL will harness the predictive power of Big Data and Bioinformatics analysis to provide mechanistic insight into preterm birth and pre-eclampsia specifically in the areas of biomechanics and mechanobiology. IMWEL will develop representations of large-scale genomic, clinical and mechanistic (“Big”) data that, combined with recent deep learning frameworks and multiscale computational models of physiology, will facilitate accurate and interpretable tools for predicting negative pregnancy outcomes. IMWEL will exploit resources, technologies, and approaches including:

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S. Kim	Engineering	ECU

The nuMoM2b Consortium. This prospective cohort study enrolls racially, ethnically, and geographically diverse pregnant women through 8 clinical research sites and 12 subsites around the U.S., to study predictive models for preterm birth and pre-eclampsia based on biomarker data and genome-wide genetic profiling. Model components utilize transformer models [84] (i.e., Google’s BigBird framework [85]), trained on large, diverse collections of data to improve work across multiple genomics applications. Additional training data include genetic single nucleotide polymorphism array data, vaginal microbiome profiling, and single-cell RNA sequencing. Advanced GPU hardware will provide easier access to highly parameterized models [86]. Lastly, this Thrust will adapt predictive models of preterm birth that are currently based on association to features such as age, genetics, stress, nutrition and hormones, to identify causation instead, thus devising potential interventions.

Auto Encoding Multi-Omics and Mechanobiology Data Modalities. Bioinformatic data will include profiling of cervical samples by single cell RNA sequencing (Dr. Azizi) along with vaginal and gut microbiome compositions through metagenomics (Dr. Pe’er.) IMWEL will also incorporate data from the other Enabling Technology arms—data from sensors in Clinically Deployable Devices and structural and mechanical data from Multiscale Biomechanics Computation and Imaging. Finally, it will incorporate clinical attributes from electronic health records, questionnaire responses and genetic information. Each data source is very high dimensional, with a complex distribution of datapoints. IMWEL will process each source

using variational autoencoders, a computational technology of deep neural networks, to reduce dimensionality effectively in a non-linear fashion.

Pre-training Generative Transformers on Integrated Datastreams. Generative Pre-trained Transformers (GPTs) are probabilistic models that learn the distribution of datapoints by optimizing neural networks for accuracy of predicting held-out pieces of data. The state-of-the art GPT-3 family of models provides revolutionary success across multiple domains, and IMWEL will leverage their flexibility in integrating multiple datastreams, each of which may be noisy and incomplete. IMWEL will pre-train these models to learn the patterns of individual-level data across modalities.

Interpretability for Interventions Through Counterfactuals. The GPT initially outputs black-box prediction. Yet, the unique setting of IMWEL allows a much more interpretable deliverable in two ways. First, interacting with the IMWEL components of Multiscale Biomechanics Computation and Imaging, Experimental Cellular and Tissue Mechanics, and Mechanomics, IMWEL will integrate known and investigated connections between measured quantities, through computational tools for evaluating feature importance. This will identify generalizable, human-understandable and clinician-approvable rules and risk factors the Center can understand, implement, and use in practice. Second, devices developed by IMWEL directly intervene and modify the data. The Big Data Enabling Technology will support this process as GPTs facilitate posing counterfactuals to explore what-if scenarios, predicting outcomes of devices. An interactive feedback loop between the device development and data analysis will improve performance and avoid negative side-effects.

Coordination and Milestones. Dr. Pe'er will coordinate IMWEL's integration of Big Data and Bioinformatics to the 10+ year goal of incorporating human individuality into the Center's fundamental knowledge Research Thrusts as well as interpretable rules guiding therapy. This will coordinate with the other Emerging Technology components, directed ultimately by the three systems Testbeds. Advancing the Preterm Birth Testbed, GPTs can pre-learn data patterns even without a particular focus. After pre-training, IMWEL will refine the GPT to focus on predicting each of the negative outcomes that define the Testbeds for IMWEL. Most importantly, IMWEL will develop predictors of preterm birth where the preliminary data already identifies key risk factors. Such factors assist prediction as highlighted input features, such as demographic attributes, nutritional information and associated genetic variants, but also as mechanistic or functional proxies for preterm birth that would be the predicted output, such as collagen remodelling or stress response. Focusing on Pelvic Floor Disorders and Healthy Aging, milestones mirror that of the Preterm Birth Testbed-model development and discovery in Years 1-3, leading to a possible intervention in Year 5 and by Year 10 guiding the design of therapeutic interventions (from biomaterials to exercise protocols) based on the patient's history and individuality.

RESEARCH THRUSTS

R1 EXPERIMENTAL CELLULAR AND TISSUE MECHANICS

Tissues combine biological cells with extracellular matrix. IMWEL will measure their properties as the issues associated with pregnancy research and very-long-term sequelae point to exciting opportunities for *in vitro* and *in silico* bioengineering-based approaches to women's health research. The projects discussed here are experimental, but the information obtained from these experiments link directly into the Enabling-Technology Thrust of Multiscale Biomechanical Computation and Imaging. Further, IMWEL will use these data to calibrate material models in the Theoretical Multiscale Modeling Thrust, feed into the design of assays in the Tissue and Organ Mechanobiology Thrust, and inform other computational models generated across Enabling-Technology Thrusts and Systems-Testbeds.

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K. Knight	Bioengineering	Pitt	P. Mcalli	Uryo/Gyn	Pitt

Exemplar Project. Preterm Birth Testbed—Trophoblast Invasion and Migration. The placenta's unusual status as a temporary organ, and one that changes continuously throughout the pregnancy, complicates its study. A significant challenge in pregnancy research arises in that placenta-related complications in the third trimester of gestation are rooted in developmental issues that occur in the first trimester [18]. Although early invasion of the uterus by trophoblast cells plays a critical role in reproductive outcome, a limited understanding of the mechanisms controlling trophoblast invasion remains a significant obstacle to progress in pregnancy research [87]. The mechanics of trophoblast migration have been investigated in a hydrogel microfluidics platform [20]. The IMWEL collaborative framework will expand upon these studies by characterizing hydrogel properties compared with those of the maternal decidua, to

develop an improved hydrogel system better mimicking *in vivo* implantation conditions [21]. This will enable a deeper understanding of the mechanobiology of implantation and early placental development. It will also provide data to help diagnose preterm births that are associated with suboptimal placentation, particular in third-trimester complications such as pre-eclampsia and fetal growth restriction.

Exemplar Project. Pelvic Floor Testbed—Pelvic Floor Injury During Childbirth. Maternal injury resulting from vaginal childbirth is considered the greatest risk factor for the development of short- and long-term complications. IMWEL hypothesizes that mechanical stresses and strains in the pelvic floor are exceeded in some women due to deficient functional adaptations, thus contributing to the high incidence of instrumented delivery, dystocia's, and maternal birth injury. This project proposes to define the biomechanical, biochemical, and histomorphological changes that occur in the vaginal supportive tissues during pregnancy up to delivery, and to determine whether a simulated birth injury impacts their ability to return to a pre-pregnancy state. To enable IMWEL to overcome problems associated with procurement of human tissue, the Center has established a rodent model as a testing protocol. Investigators will employ rigorous mechanical testing to define the mechanical behavior of vaginal supportive tissues in virgin, pregnant (mid and late), vaginally delivered (with and without simulated birth injury), and abdominally delivered rats. IMWEL will also examine biochemical and histomorphological changes of the extracellular matrix. Ultimately, the data obtained from these proposed studies will help support future research priorities to identify factors that mediate pelvic tissue adaptations during pregnancy and the postpartum period, correlate findings with clinical data from women, and finally identify strategies to maximize distension of these tissues at the time of delivery and enhance recovery following birth injury.

R2 TISSUE & ORGAN MECHANOBIOLOGY

Mechanical properties of tissues and external mechanical forces not only result from physiology and biological activities, but they can actively *drive* biological responses.

In many tissues throughout the body including bone, heart, and blood vessels, studies have well established that mechanical cues are important for regulating healthy function of resident cells, as well as healing response after injury [88-89]. In comparison, the role of mechanical cues in the function of the cells within the female reproductive system remain obscure. In addition, the effects of female hormone profiles on the musculoskeletal system remain poorly understood. The Tissue and Organ Mechanobiology Research Thrust will advance the understanding of how tissue properties and mechanical forces coordinate with hormone and cytokine changes during pregnancy, childbirth, and aging to regulate the female reproductive, musculoskeletal and cardiovascular systems. With this knowledge, IMWEL will endeavor to understand the impact of pregnancy, lactation, aging, and exercise on mechanobiology of the female reproductive, cardiovascular, and musculoskeletal systems. Cell-material interactions are critical in this endeavor, including methods to harvest and culture primary cells from reproductive organs, to differentiate relevant cell populations from patient-specific induced pluripotent stem cells (iPSCs), and materials that mimic the native extracellular matrix composition and mechanical properties of reproductive tissues. Bioreactors combine cells, materials, and mechanical forces into *in vitro* mechano-organs, modeling reproductive tissues. IMWEL will use these to *measure* and manipulate how mechanical forces regulate reproductive system cells.

Exemplar Project. Preterm Birth and Pelvic Floor Testbeds—Mechanoregulation of Uterine and Cervical Tissue Remodeling. Pregnancy and childbirth are associated with massive changes in the mechanical environment of the female reproductive system and major fluctuations in the systemic and local hormone and cytokine milieu. The uterine wall grows over 300% the non-gravid size during pregnancy [90-91] to accommodate the growing fetus, and the cervix softens three orders of magnitude in stiffness prior to the onset of childbirth [4-5]. Estrogen, progesterone, as well as many cytokines also increase [4]. In addition, the clinically deployable devices used to treat pelvic floor disorders also dramatically change the mechanical environment of the tissue. This project will investigate how acute biophysical stretch coordinates with hormone and cytokine fluctuations during pregnancy and childbirth to regulate uterine and cervical tissue remodeling.

IMWEL will seed uterine and cervical fibroblasts, smooth muscle and epithelial cells within bioreactors that mechanically stimulate cells with stretch. IMWEL will initially use cells obtained from commercial sources, while Drs. Vink and Vunjak-Novakovic develop new methods to differentiate cells from patient-specific iPSCs. In addition, IMWEL may use cells from animal sources such as mice for platform

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J. Mauney	Urology	UCI	G. Vunjak-Novakovic	Biomed. Eng.	CU

development, recognizing that murine pregnancy involves similarities but also many differences compared to humans, especially with regard to changes in the mechanical environment. Drs. Mauney and Lu will seed cells onto synthetic and natural biomaterials that are designed to mimic the material properties of the natural female reproductive tissue. Dr. Liu will incubate the cell-seeded scaffold with estrogen, progesterone, and/or cytokines relevant to pregnancy, and stretch using a mechanically active bioreactor. A histological and cell-based assay will measure tissue growth to determine the effects of mechanical cues on cells.

Exemplar Project. Healthy Aging Testbed—The Role of Hormones in Mechanoregulation of Musculoskeletal and Cardiovascular Systems. It is widely appreciated that mechanical forces play a major role in the regulation of musculoskeletal and cardiovascular systems. Women’s musculoskeletal and cardiovascular health declines with age through mechanisms that remain ill-defined and not therapeutically targetable. Loss of endogenous estrogen with menopause may further exacerbate age-related declines [1]. Age, sex and endogenous estrogen likely have independent and dependent effects on musculoskeletal and cardiovascular systems at multiple scales – from subcellular to cellular, tissue, organ and to the organism itself [2]. The benefits of exercise on cardiovascular and musculoskeletal health are similarly well known and multiscale, but poorly understood [3]. This project aims to investigate the mechanobiological mechanisms by which age, sex, and endogenous estrogen affect vascular and musculoskeletal mechanobiology, including the mechanisms by which exercise preserves musculoskeletal and cardiovascular structure and function. Studies have primarily explored the impact of mechanical stimuli on function of cells in the musculoskeletal and cardiovascular systems using cells of unknown donor age or sex [4]. Since sex differences have been identified in multiple other cell types [92–95], IMWEL anticipates sex differences are also relevant to mechanical sensing as well as subsequent biological signaling. Age and loss of endogenous estrogen may independently affect musculoskeletal and cardiovascular cell mechanobiology. Investigation of the impact of sex, age, and endogenous estrogen on structural and functional responses will provide insight into the healthy aging in women.

The Tissue and Organ Mechanobiology Thrust will fill a gap in knowledge about how mechanical forces influence the female reproductive and musculoskeletal tissue and organ systems. Significant barriers in this field include (1) lack of multiscale mechanical characterization of tissues during pregnancy and childbirth, and (2) lack of appropriate tissue culture models to study the female reproductive system. Led by Dr. Liu, this Thrust will integrate new knowledge and tools gained from the Multiscale Biomechanical Computation and Imaging and Mechano-Organs Enabling-Technology Thrusts to address these knowledge gaps and barriers, and advance the understanding of how mechanical cues regulate female reproductive, cardiovascular, and musculoskeletal physiology.

R3 MULTISCALE THEORETICAL MECHANICS

This Research Thrust enables IMWEL to mathematically implement the information *measured* in the Experimental Cellular Tissue Mechanics and Tissue and Organ Mechanobiology Research Thrusts into the tissue- and organ-scale models described in the Multiscale Biomechanical Computation and Imaging Enabling-Technology Thrust. Leveraging current advances in quantitative imaging techniques and mechanobiology, this Thrust will aim to develop biology-based, imaging-informed multiscale modeling paradigms to describe biomechanical behaviors spanning the sub-micron scale to the organ scale. This work will generate fundamental insight into the synergy between microstructural mechanisms at the sub-tissue scale and emergent biomechanics of the female reproductive and aging cardiovascular and musculoskeletal systems. This modeling Thrust will provide a library of material constitutive models appropriate for each model system researched in the Center. The tissues for each model system are unique in their drastic and robust ability to stretch, grow, remodel, and repair. To describe and predict this unique behavior, IMWEL will formulate new and novel material equations based on experimental evidence. The modeling effort here will overcome long-standing challenges in biomechanics and mechanobiology to mathematically describe: 1) how sub-tissue scale structural changes alter tissue and organ scale biomechanics; 2) how evolving microstructural constituents, driven by hormone-, chemical- and stretch-mediated processes, remodel tissue and alter its biomechanical function; and 3) how pathological changes to these remodeling processes influence tissue biomechanical behavior. Such research will extend the following modeling work of the IMWEL team: linear and nonlinear elasticity [96–98]; fiber-based anisotropy [69,71-72,76,78,99-103]; time-dependence including poroelasticity [104–106] and poro viscoelasticity [107]; fatigue damage and fracture mechanics

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[70,75,77,108–111], and hormone-, chemical-, and stretch-mediated mixture models for evaluation of tissue growth and remodeling [4,112].

Exemplar Project. All Testbeds—Formulation of a Hormone- and Stretch- mediated Mixture Theory to Describe the Growth and Remodeling of a Time-dependent, Anisotropic, Fibrous Tissue.

IMWEL will develop a general mixture theory material modeling framework to describe the evolving tissue properties of the tissues of all of the Testbeds [112]. For example, the Center will model the cervix as a porous hyper elastic fiber composite material with an intrinsically viscoelastic solid compartment and a continuously distributed fiber network [98,103,106,113]. The modeling choice here reflects the availability of experimental evidence, where the mechanobiological characteristics will drive the temporal changes in the material behavior of the tissue. The postulated constitutive equations offer a starting framework to decipher the complexities of the 3-D geometric and material behavior. As IMWEL collects experimental evidence, the forms of these equations will either be validated or alternative modeling equations will be employed. For example, cervical tissue during pregnancy results from a complex cascade of upstream signaling mechanisms, with many of these molecular signaling pathways still being elucidated. IMWEL will base this modeling framework on the strong evidence that levels of estrogen and progesterone play a key role in regulating cervical tissue composition during pregnancy [4, 114-115]. This compositional state variable approach offers the flexibility to integrate experimental data and can be widely applied to other tissue systems where the extracellular matrix is rapidly remodeling.

Exemplar Project. Preterm Birth and Pelvic Floor Testbeds—Formulation of a Chemo-Degradation Material Model to Describe Fracture and Injury.

Damage to the human body can occur when it is subjected to excessive physical forces, leading to injuries. In stark contrast, labor and delivery require the rupture of membranes (“breaking of waters”) [116]. However, idiopathic mechanical rupture prior to full-term gestation presents in approximately 3-4% of all pregnancies and factors into 40-50% of preterm births [17] leading to approximately 20% of perinatal deaths [116]. Although engineers have for decades considered the process of bone fracture [117], crack-propagation in soft tissues has been poorly studied. IMWEL will examine the fundamental theories of soft tissue fracture mechanics. IMWEL will subject collagenous soft tissue membranes to a battery of fracture mechanics experiments in different geometrical configurations and at different applied loading rates. Research will study combined chemical-mechanical failure, investigating how collagen-attacking enzymes in tissues cause a process analogous to stress corrosion cracking. The theory will consider enzymatic degradation in concert with mechanical loading. IMWEL will deploy a multiscale approach to model and interpret experimental observations modeling fracture in discrete materials based on mechanics of individual fibrils [118]. In addition to the mechanical failure of fibril elements due to excessive mechanical straining, IMWEL will incorporate an additional component for element failure in the context of mechanical breakdown of the elements due to chemical enzymatic attack. The Center will model degradation as diffusing through the tissue, and a chemical reaction rate constant will govern the kinetics of bond rupture for collagen molecules using a Monte Carlo approach [119]. The results of these coupled experimental and modeling investigations will together form the first comprehensive set of fracture resistance data for soft tissues and provide fundamental insights into failure mechanisms in injury, preterm birth, and fatigue failure of aged tissues.

R4 MECHANOMICS

Contemporary compositional analysis technologies provide unprecedented views into physiological systems. To profile and understand the complexity and diversity of functional tissues in female-specific systems, IMWEL will deploy high-throughput analysis techniques with single-cell precision, such as next-generation sequencing and mass cytometry. Conversely, the focus of IMWEL on mechanobiology will develop the use of -omic technologies to study the role of mechanical forces in driving cell and tissue function. Dr. Kam will lead this Research Thrust, coordinating the use of these technologies across IMWEL research initiatives, and building upon rapidly growing efforts by the team to understand molecular and epigenetic changes associated with cells interpreting their environment. As guided by the physiology of all three Testbeds and the Research Thrusts of Experimental Cellular and Tissue Mechanics and Tissue and Organ Mechanobiology, the Mechanomics Thrust will identify signaling pathways and genomic signatures associated with cell-level mechanosensing. IMWEL will integrate this information into Multiscale Computation and Big Data and Bioinformatics Thrusts to more accurately capture the role of mechanical forces in directing and mediating tissue level and organ

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K. Leong	Biomed. Eng	CU			

level responses, as well as provide a mechanobiology context with which to interpret single cell -omics data collected from physiological tissues and patients.

Technologies include single cell transcriptomics and proteomics resources across the Institutes. IMWEL will use these technologies to provide key information regarding the composition and state of cells and tissues, as guided by the Testbeds and other Center components.

Exemplar Project. Preterm Birth Testbed. In the context of preterm birth, this Testbed targets capturing in multiscale models the dynamics of cervical and placental tissues observed during normal and preterm birth. It will bring together Organ/tissue systems and mechanobiology to create reductionist systems that will inform these models, allowing integration of modern understanding of biological signaling cues, which must accurately reflect the physiology of interest. Additional interaction with Big Data and Bioinformatics will inform interpretation of our results. Mechanomics is distinct from those efforts with a specific integration on cellular and molecular mechanosensing and will support these efforts in two directions. First, it will identify the cells and proteins that drive tissue remodeling in both normal and preterm birth, guiding creation of and interpretation of results from cell and tissue systems. The Testbed will use flow, proteomics, and next generation sequencing approaches (including single-cell and spatially resolved approaches), on tissues from both human and rodent models. Conversely, these approaches will guide design of *ex vivo* models to capture real physiologies. Second, the Preterm Birth Testbed will develop -omics signatures that reflect mechanical changes in tissues, such as strain-induced remodeling and stress damage (cervical tissue) or incomplete integration of cellular interfaces (placenta). IMWEL will verify these against cell culture, acute tissue, and cultured organ models, developing signatures of mechanical activity, similar to inflammation or tissue state. These advances will inform, implement, and improve the models that predict preterm birth. In addition, IMWEL envisions mechanobiological signatures detected from diagnostic samples, such as those indicated by biomechanics-inspired check-ups over the course of pregnancy, improving the information that these samples can offer.

Exemplar Project. Healthy Aging Testbed. Mirroring the role of mechanomics in Preterm Birth, this Research Thrust will serve the Healthy Aging Testbed by guiding development of *ex vivo* models and identifying new signatures that change in response to aging and exercise. Primarily rodent models but some human volunteers will provide the reproductive and cardiovascular tissues. IMWEL will use next generation sequencing and proteomic approaches to identify cell systems that are critical to aging and exercise response of these animals. Later in the Center, IMWEL will apply these approaches to human participants in the exercise trials. IMWEL will analyze diagnostic samples from blood and, to a lesser degree, swabs of reproductive tissues and fluids on the basis of signatures developed in the animal and *ex vivo* cellular and tissue level models. From the insights gained, IMWEL envisions assays using technologies such as genomic and proteomic swabs.

In the short term, this Research Thrust will focus on the characterization of key tissues across all three Testbeds, including cell and tissue source identification, and consideration of the potential utility of animal and *in vitro* models for capturing the complex human physiology of interest. Within these model systems, the Research Thrust will generate curated data sets around mechanobiology, leading to a “mechanomics profile” for each healthy and pathological condition within each Testbed. In the longer term, IMWEL will integrate these profiles into the annual ‘biomechanical check-up’ to use the mechanomics signatures in clinical diagnosis and treatment. IMWEL will share the mechanomics profile data across other Testbeds, Research and Enabling-Technology Thrusts to benefit the convergent research workflow of all systems.

5. ENGINEERING WORKFORCE DEVELOPMENT

The IMWEL EWD team will train engineers, basic scientists, educators, students, and entrepreneurs at the nexus of biomechanics, mechanobiology, and women’s health. **Through this ecosystem, IMWEL seeks to create a language and conceptual framework for talking about women’s health with ease, comfort and clarity.**

IMWEL’s EWD will engage trainees across multiple stages of the engineering pipeline, starting with early middle school where the academic trajectories can be shaped towards science and engineering [120–122]. High school, undergraduate, graduate, and postgraduate training, critical junctures where individuals gain specialization and expertise within subfields of engineering, will further nurture these careers. This engagement will focus on recruitment, retention,

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T. Ibrahim	Bioeng, Rad., Psych.	Pitt	V. Purdie-Greenaway	Psychology	CU
A. Kyle	Biomed. Eng.	CU	R. Wapner	OB/GYN	CU

technical advancement, and diversification of a highly talented engineering workforce, poised to develop the next generation of biomedical applications for women's health and healthcare.

IMWEL EWD will combine with IMWEL DCI to create a module-based curriculum, develop and test a series of randomized controlled longitudinal interventions in middle school and undergraduate classrooms, and run a multi-site Research Experiences for Teachers (RET) for high school teachers. These activities build on psychological and curricular-based interventions research previously conducted by Dr. Purdie-Greenaway (described also in 6. DCI). These interventions are designed to increase awareness, interest, and retention in STEEM and to create inroads to diversify the broader engineering community and the types of problems that engineers solve. The ecosystem will also include rich and inclusive research experiences, including a multi-site Research Experiences for Undergraduates (REU), graduate and post-graduate fellowships incorporating culturally aware mentor training, exposure to the IE training, pilot funding opportunities (described in Sec. 7), and community building using UCI TSAL expertise.

Workforce Intervention Curriculum. IMWEL will design curriculum modules that focus on tissues of the female reproductive system to build familiarity in applying engineering to women's reproductive health. IMWEL will create and adapt this "Workforce Intervention Module for Engaging the Next generation (WIMEN)" over the project period based on IMWEL's DCI intervention research. The WIMEN module has four core goals: 1) Prioritizing women's voices throughout the process (e.g., Women-centered Design), 2) Expanding language consistency to promote communication between engineers and OBGYN clinicians, 3) Encouraging a growth mindset, and 4) Promoting convergence of research and training. The EWD team will work with instructors at each intervention site to adapt the WIMEN module to each community, and will work with evaluators to test the effectiveness of this intervention in increasing interest in STEEM education and careers.

Targeted and Tested Interventions in the STEEM Workforce Pipeline. The goal of these interventions is a framework and language for communicating about women's health within the engineering community. *5th Grade/Middle School Intervention.* A compelling facet of the EWD ecosystem is a series of school-based randomized interventions that will take place in middle schools in Orange County (CA), and NYC over Years 1-5, and then expand to Pittsburgh and Greenville in Years 6-10. IMWEL will 1) conduct a needs assessment by surveying students and teachers in participating schools to identify psychological (e.g., embarrassment communicating about women's bodies), pedagogical (e.g., lack of curricula) and institutional (e.g., few educators with STEEM training) barriers that face students and teachers as well as anticipate areas of opportunity (e.g., interest in health at younger ages); 2) develop and test a series of randomized double-blind longitudinal interventions designed to increase engagement, interest and academic performance in STEEM courses; and 3) identify best-practice strategies for the interventions. Intervention materials will consist of 1) content related to biomechanics of "what's going on inside a growing belly" during pregnancy, 2) activities designed to attenuate anxiety and promote a growth mindset, and 3) interactive activities designed to deepen learning (e.g., flipped classrooms). The "control" condition consists of content focused on biological material (e.g., tissue samples) with no mention of women's health. All interventions include random assignment of students to treatment or control conditions. Intervention materials will be embedded in video modules and complement classroom instruction and rigorous methods to rule out alternative causal explanations (e.g., block randomization by gender and ethnicity; teachers unaware of condition; students unaware of participating in an experiment; pre-registration of data collection and analysis). IMWEL will follow cohorts longitudinally over multiple years with access to relevant grades (classwork, report cards) and survey data. Survey measures include interest in STEEM careers, knowledge about women's health, and motivation. *Undergraduate Intervention.* IMWEL will tailor the WIMEN Module for college first-year students enrolled in Biomedical Engineering or Bioengineering programs or concentrations at each partner institution, leveraging the book proposal MIT has contracted from Drs. Myers and Oyen "Expecting Ingenuity. Human Pregnancy through an Engineering Lens." IMWEL will test the impact of this module on increasing student technical knowledge in women's reproductive health and their interest in applying engineering principles, tools and technology to meet these challenges. Rigorous intervention methods will be used as specified above. The core partners will deploy the module, follow student cohorts longitudinally, and measure outcomes including grades, student engagement and success in downstream elements of EWD (e.g., REU and Senior Design Projects in Women's Reproductive Health). The EWD/DCI team will analyze outcomes.

RET for High School Teachers. IMWEL will establish an NSF RET at high schools local to each IMWEL site, starting with UCI and CU, to partner with teachers to create and integrate WIMEN module concepts into their curriculum. By asking teachers "How can we make this intervention work?" within their existing curriculum requirements, while also enhancing student readiness for STEEM education in college, IMWEL will address barriers of rigid curriculum standards and timelines of high school curriculums [123]. UCI's Orange County STEM Ecosystem Institute will coordinate the RET, which provides existing infrastructure, staff, and national reach for the program.

Supporting IMWEL EWD Pipeline Success. IMWEL will implement the REU across the four IMWEL institutions, starting with UCI and CU in Year 2, and then expanding to ECU and Pitt in Year 3, IMWEL will promote interaction and interdisciplinary collaborations between the different institutions' students through joint scheduled learning times, virtual lab tours, team research projects, participation in the Annual Meetings, and networking events. *Graduate Student, Postdoc and Early Career Development.* IMWEL's IE component will support entrepreneurial endeavors in Women's Health through programs such as W.Spark (UCI, promoting women's success in SBIR/STTR grants) and DICE (CU, supporting underrepresented groups in life science entrepreneurship) and mentored training, adopting resources from the National Academies-endorsed Center for the Improvement of Mentored Experiences in Research (CIMER) program, which includes training modules on culturally aware mentoring [124] (see Sec. 7).

EWD Milestone Achievements. The long-term, 10-year goal of IMWEL's EWD is to deploy a quantitatively-proven set of interventions that build an informed, effective, and robust engineering workforce. By Year 10, IMWEL will implement programs described above at all four IMWEL sites, informed by the successes and challenges identified at the other locations. Implementation of a Women's Health Engineering Concentration at all IMWEL universities will be complete. IMWEL also anticipates that institutions currently outside of IMWEL will adopt these programs, led by former IMWEL fellows and graduates. IMWEL will have completed blueprints for implementing all intervention curriculum modules. Toward this goal, IMWEL's Year 3 milestones are to have completed intervention studies in the initial set of middle schools (100-200 students at each of the two partnered middle schools), developed new high school curriculum through RET across our 8 partnered high schools, and established an inaugural class of IMWEL Postdoctoral Fellows. The collaboration of RET teachers and IMWEL scientists will complete two years of design and development of intervention materials. Year 5 milestones include completion of a second full cycle of data collection; Completion of cycle one data analysis, and completion of expanding intervention research sites. IMWEL will have partnerships with K-12 and post-secondary institutions for design verification and outlets for dissemination.

6. DIVERSITY AND CULTURE OF INCLUSION

DCI is a foundational research pillar of IMWEL's multifaceted strategy to address existing challenges facing women's health. The first aim is to ensure that IMWEL is a diverse, equitable, and inclusive Center suited to train the next generation of scholars and women's health care executives.

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L. Kam	Biomed. Eng.	CU	R. Wapner	OB/GYN	CU
K. Knight	Bioengineering	Pitt			

and women's health care executives. The second aim is to broaden participation of members of underrepresented groups (e.g., women, ethnic minorities, persons with disabilities, first generation) in the engineering workforce and expand the types of problems engineers solve. IMWEL will achieve these aims by successful recruitment, mentoring and retention strategies, and conducting an innovative self-study designing "best in class" practices for diversity, equity and inclusion. While EWD and DCI activities are described separately, these teams will coordinate on all activities. For instance, Drs. Chesler and Purdie-Greenaway, provide deep expertise on interventions while EWD team leads will leverage inclusive and equitable recruitment and mentoring strategies for their programs.

IMWEL's DCI Ecosystem. The IMWEL broader institutional context makes it well situated to create a "best in class" diverse and equitable IMWEL ecosystem. UCI is a Hispanic-Serving Institution and received the AAAS 2021 STEMM Equity Achievement Change Bronze Award; within the Samueli School of Engineering is the Stacey Nicholas Office of Access and Inclusion, an endowed office that facilitates the recruitment, retention, and graduation of students from historically excluded populations with strong ties to other HSIs as well as HBCUs. CU was awarded an NSF ADVANCE in STEM and has successfully developed a blueprint for implementing inclusive practices throughout their STEM community. In April 2021, ECU and UCI were named to the 2021-22 class of First-gen Forward, the nation's first recognition program

acknowledging higher education institutions for their commitment to first-generation student success. IMWEL will not only draw from these schools to recruit and mentor top talent, but will draw heavily on their successful strategies for achieving diverse and inclusive institutions. [Recruitment and retention strategies](#) will take advantage of institutional infrastructure and pipeline programs (e.g., NSF LSAMP, UC LEADS, OAI's HBCU Accelerate Pathways Doctorate Program) to target schools from diverse communities for the RET and middle school intervention and to recruit a diverse group of the brightest students nationally for the REU program and Ph.D. research and to cultivate an environment to improve their persistence in engineering. Students who participate in research show an increased interest in pursuing a research career and obtaining a Ph.D., and women and URM engineers can thrive in REUs with peer networks and a critical mass of students they identify with [125-126].

IMWEL designed the DCI ecosystem study to 1) understand the policies, practices and procedures that may inadvertently prevent women and ethnic minorities within the ecosystem from thriving in STEEM (Yrs. 1-3); 2) identify best-practice strategies developed by NSF ADVANCE institutions and team science that might be tailored to fit IMWEL's context (yrs. 4-5); and 3) develop and implement a 5-year IMWEL STEEM strategic plan to promote and accelerate an inclusive and diverse workforce across IMWEL. The [design data collection](#) includes focus groups with post-docs and faculty and staff (separate) and 1-1 interviews with scientists and policy makers in [Year 1](#), social network analysis and daily diary surveys for two week intervals administered to all scientists, students and staff in the IMWEL ecosystem in [Years 2-4](#) (gather 3 years of data), data compilation and analysis in [Year 5](#), and policy recommendations and implementation for [Years 6-10](#).

While IMWEL will integrate best practices and conceptual frameworks gleaned from NSF ADVANCE institutions (including UCI and CU) and team science into the IMWEL ecosystem, IMWEL also has the opportunity to address a number of unique challenges specific to bioengineering. First, basic physiologic understanding of women's bodies is *immature as a science* and many disparities in women's health differentially impact ethnic minority women. Second, the IMWEL ecosystem itself features unparalleled functional, demographic, disciplinary and regional diversity. Third, IMWEL explicitly intends to create a new kind of citizen-scientist, citizen-engineer who is ready to address these scientific gaps while engaging in a diverse intellectual ecosystem with ease. These unique challenges present an opportunity to study and then cultivate and accelerate an empirically-grounded "best in class" diverse and inclusive leadership culture.

DCI Milestone Achievements. Self-study Milestones. By [Year 3](#), IMWEL will have collected two years of data for the self-study designed to understand the policies, practices and procedures that may inadvertently prevent women and ethnic minorities from thriving in STEEM. By [Year 5](#), IMWEL will have developed a rigorous empirically validated 5-year strategic-plan to promote and ensure inclusive, equitable and diverse leadership. IMWEL will also have identified best-practice strategies developed by NSF Advance institutions. By the end of [Year 10](#), IMWEL will have implemented and refined evidence-based policies, procedures and practices throughout the IMWEL ecosystem achieving the: [diversity goal](#) - meeting or exceeding established metrics for demographic diversity in each Research Thrust and EWD activities; [equity goal](#) - empirical evidence of no disparities in participation and career progression metrics among every Research Thrust between members of historically underrepresented groups in STEEM (e.g., publication rates); [inclusion goal](#) - empirical evidence that all members in the IMWEL ecosystem perceive that their expertise is valued and feel belonging (functional diversity). Moreover, IMWEL will have published (peer reviewed) blueprints designed for other similarly structured STEEM centers in both research and practitioner outlets.

7. INNOVATION ECOSYSTEM

IMWEL will address challenges facing women's health by creating an environment conducive to successful translational work and facilitating industry and community partnerships along the entire product development process. IMWEL will build upon the robust translational record of four institutions. Each year, CU alone manages more than 400 disclosures, 100 licenses, and 20 startups, the majority in life sciences. It has particular strength in medical devices including startups: EpiBone, Singular Genomics, Auris, and Tara Biosystems; and licenses: Biomet, Acuseal, Floseal, Teleflex, and Microline.

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C. King	Biomed. Eng.	UCI	K. Myers	Mech. Eng.	CU
K. Knight	Bioengineering	Pitt	M. Oyen	Engineering	ECU
E. Konofagou	Biomed. Eng., Rad.	CU	G. Vunjak-Novakovic	Biomed. Eng.	CU
A. Kyle	Biomed. Eng.	CU	H. West	Mech. Eng.	CU
H. Lu	Biomed. Eng.	CU			

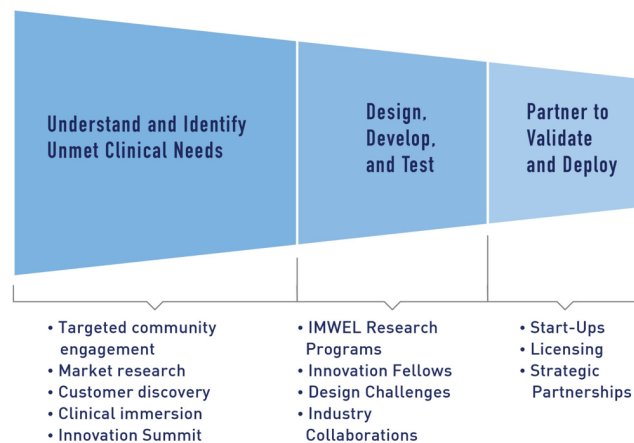
Needs-Driven Innovation Pipeline. Unmet needs around IMWEL’s research will be focused through engagement with women’s groups (e.g., Iris Fund), clinicians, and other stakeholders. New technologies will be designed, developed, and supported within the IE through four mechanisms, described below. *Innovation Fellowships, Design Challenge, and Summit.* IMWEL will launch an Innovation Fellowship, building on institutional programs (CU’s DICE program) that equip aspiring innovators with experience and skills in women-centered medical innovation. Fellowships will be open to graduate, postdoctoral and clinical trainees from partner institutions, with an emphasis on under-represented groups. Fellows will help drive a year-long project alongside the IMWEL multidisciplinary team. Fellows will broaden clinical, engineering, and business skills. Fellows will also participate in a virtual reality clinical immersion experience (UCI) and receive a stipend.

IMWEL will launch an annual Design Challenge for women’s health. IMWEL will hold annual Innovation Summits, paired with IMWEL’s annual conferences, as a platform for members to network with academic, industry, community, and investors interested in women’s health. The Summit will feature technologies from IMWEL research programs, and Innovation Fellow Design Challenge teams. It will provide members with exposure to IMWEL technologies, with opportunities to spur partnerships. Select teams will participate in a pitch competition for grants (up to \$10K). *Translational Funding, Lab-to-Market Accelerator.* The IE will leverage

existing programs to accelerate research discovery translation, including CU’s BiomedX program. Over 10 years, BiomedX awarded \$5M to support 60 projects involving clinician-engineer collaborations, with nearly 1/3 exiting and receiving >\$80M in follow-on funding and two are FDA-cleared and in-use. In Years 1-2, BiomedX will fund 1-2 IMWEL projects (~\$100k) to support critical milestones. By Year 3, IMWEL will launch a dedicated women’s health accelerator around pilot grants. Teams will receive training towards the project proposal as well as project management to ensure timely milestone-driven product development. *Innovation Oversight.* The Engineering Innovation Advisory Board will provide feedback and close oversight of IMWEL translational projects, assessing progress and milestones relevant for commercialization, as well as timely direction and connections to industry partners along the product development pipeline. *Product Development Partnerships.* The core institutions have existing programming (e.g., BiomedX, Coulter program, NSF I-Corps) that will inform teams of best practices in launching and managing start-ups. IMWEL will have access to the W.SparkSBIR initiative (UCI) that supports women entrepreneurs. IMWEL spin-outs will leverage existing incubators and lab space for relevant resources. In NYC, Deerfield Catalyst and Harlem Biospace will both provide space and access to resources including their advisory boards. Teams will also have access to Alexandria LaunchLabs @Columbia on site of the ERC. At UCI, start-ups will have access to the Wayfinder Incubator. IMWEL will engage investors (e.g., Deerfield, Upstate Capital), government agencies (e.g., NYSTAR), regulatory and reimbursement consultants (e.g., MSquared Associates, Inc.), clinical research organizations, and industry (e.g., NextGen Jane, Hitlab, Pregnolia, Renovia, Materna, Viscus Biologics, and Alydia) throughout product development. With support from members, the IE will help secure sponsored research for early development and partnerships for clinical deployment of technologies.

Milestones and Metrics. Milestones are around Research Thrusts and innovation pipeline (RTIP), education (E), and partnerships (P). Years 1-2 (Understand, Identify, Build Network). RTIP: 1st annual Innovation Summit, first pilot grants, E: 1st annual Design Challenge, Innovation Fellowship, P: Establish women’s health engineering innovation advisory board Years 3-5 (Develop, Design, Test, Expand Network). RTIP: Complete prototypes, initial testing (pre-clinical, clinical), first university exits (i.e., licensing), women’s health accelerator, E: Fellowship expanded, P: 1st partnerships for sponsored research, 1st start-ups launched. Years 5-10 (Partner to Validate + Deploy, Scale Nationally). RTIP: First FDA clearance and approval, Partnerships for clinical testing and commercial manufacturing. Metrics include # of Programs, Follow-on funding (\$), number of inventions, number of start-ups, number of innovation

Fig. 11: Pipeline for Innovation Ecosystem



fellows, number of full-time jobs, number of agreements with industry, number of start-ups, number of university “exits”, licensing, and number of FDA clearances and approvals.

Intellectual Property (IP). IP protection serves as a crucial step and encourages commercialization. This ERC will operate with multiple entities (academia, industry, and the community) supporting and being actively involved in research. Any IP conceived and/or developed through the ERC will be governed by an IP Management Plan agreed to by academic partners and aligned with the terms of the ERC Membership Agreement. IMWEL will offer members assets like early looks at emerging IP; opportunities to judge innovation competitions or provide mentorship and advice to teams; or early review of publications. Any conflicts of interest must be disclosed to the Center's EC, which works to mitigate potential risk. *Membership Agreement.* IMWEL will have a membership structure to provide partners benefits according to their level of contribution. Member organizations will benefit from close interaction with the ERC's faculty, students, and the innovation ecosystem. Organizations will have access to Testbeds and facilities to design and evaluate the next generation of women's health technologies, as well as to any new innovations. IMWEL has three membership categories to offer benefits appropriate to the depth of collaboration sought: Charter Member (\$150K/year); Standard Member (\$75K/year); and Affiliate Member (\$25K/year; \$5K/year for start-ups).

8. EVALUATION PLAN

Evaluator Qualifications. The Center for Research in Education and Social Policy (CRESP) will serve as the IMWEL evaluator; Dr. Sue Giancola from CRESP will lead and coordinate evaluation efforts. Dr. Giancola has a PhD in Policy Research, Evaluation, and Measurement from the University of Pennsylvania, as well as degrees in management and engineering. With over 25 years of experience, she has evaluated large-scale projects funded through the NIH, NSF, U.S. DHHS and U.S. DOE. She currently leads the evaluation of an NSF MRSEC, as well as the Tracking and Evaluation Core of a multi-site NIH-funded CTR. She has also evaluated NSF REUs, CAREERs, as well as other NSF mechanisms, including ADVANCE, CS4ALL, and FFW. Dr Giancola is a member of the American Evaluation Association, American Educational Research Association, and Association for Clinical and Translational Science, and leads the National CTR Evaluators Network.

Evaluation Overview. The IMWEL evaluation team (EVAL) will work to facilitate the success of projects and the Center as a whole. As such, EVAL will employ a theory-based, participative approach to evaluation. The IMWEL program theory is based on the premise that Center strategies and activities will lead to enhanced engineering systems, increased technology-driven solutions, and a diverse pipeline of women's health engineers, and will ultimately advance women's health. The evaluation is designed around three elements of the theory linking IMWEL strategies to long-term goals: 1) *implementation assessment* to document progress and assess fidelity; 2) *formative evaluation* to inform, shape, and facilitate improvement; and 3) *summative evaluation* to examine effectiveness and measure impact across all elements of IMWEL. Logic modeling will be used to graphically represent the theory linkages between strategies and goals.

Evaluation Aims. In alignment with theory elements, the evaluation will continually assess implementation in order to facilitate the identification of needs and foster Center effectiveness; however, the primary purpose of the IMWEL evaluation is to examine the impact of the Center on advancing women's health. Thus, EVAL will support IMWEL through the following evaluation aims: 1) *define metrics* that guide data collection, analysis, and reporting to aid in directing program improvement and efficient use of resources; 2) *monitor and report* progress towards Center goals, via standardized reports and ongoing formal and informal feedback; 3) *assure quality* of EVAL activities by monitoring processes and implementing process improvements; and 4) develop and *share best practices* in evaluation within and beyond the ERC program.

Evaluation Questions. The IMWEL evaluation includes formative and summative components, in order to provide ongoing feedback to the IMWEL leadership and to assess program outcomes. Theory-based evaluation methods will be used to document the logic relating Center activities to intended outcomes; metrics will be created in alignment with the logic model. These metrics will track program activities, provide ongoing feedback for data-informed evolution and improvement, document program changes, and assess effectiveness and impact. Evaluation findings will be routinely reviewed and collaboratively interpreted with Center leadership to assess their implications for programmatic adjustments and continuous improvement. While the evaluation will address all program phases, Research Thrusts, and foundational components, the following overarching questions will guide the IMWEL evaluation:

Evaluation Question	Evaluation Design and Methods
1. To what extent has the Center <i>successfully integrated</i> CR, EWD, and DCI within an IE?	<ul style="list-style-type: none"> - Internal Coalition Effectiveness (ICE; Cramer, Atwood, & Stoner, 2006) Instrument administered annually to leadership, Thrust and Testbed leads, team members, staff, and advisory board members - Annual interviews with Thrust/Testbed leads, & Leadership Team
2. What factors facilitate <i>effective convergent research</i> ? What barriers hinder CR?	<ul style="list-style-type: none"> - Ongoing, formative, quarterly quick-check assessments with IMWEL team members to inform effective team science and CR - Quarterly facilitated meetings with Thrust and Testbed leads
3. How can these <i>facilitators and barriers</i> inform IMWEL activities in order to improve CR, as well as EWD, DCI, and an IE?	<ul style="list-style-type: none"> - Annual focus groups with leadership, staff, and team members - Annual (and as-needed) team health assessment using research-practice partnership model, focused on alignment, priorities, barriers, and needs - Ongoing examination of CR milestone achievements
4. In what ways have <i>community hubs</i> been leveraged to maximize impact of innovations developed through research thrusts and projects?	<ul style="list-style-type: none"> - Annual survey of stakeholders through Community Hubs of Education, Research, & Innovation, and IMWEL leadership, researchers, and students; annual evaluation of RETs, REUs, and graduate or postdoc programs - Ongoing examination of EWD, DCI, & IE milestone achievements
5. What <i>societal impacts</i> have been fostered by IMWEL through CR, EWD, DCI, and IE? How has IMWEL impacted scientific enterprise, the engineering community, & women's health?	<ul style="list-style-type: none"> - Application of the Translational Science Benefits Model (TSBM) to examine clinical, community, economic, and policy impacts - Ongoing tracking of research facilitators, collaborations, competencies, and achievements (also informs questions 1-4) - Targeted mixed-method case studies of Research Thrust projects

Implementation of the evaluation will be in accordance with IRB protocols and aligned with the guidelines established by the Joint Committee on Standards for Educational Evaluation and the American Evaluation Association's Guiding Principles for Evaluators.

Formative and Summative Evaluation. Formative and summative evaluation will utilize both qualitative and quantitative data collection methods. The *formative evaluation* will track, assess, and inform IMWEL activities, including the availability and use of ERC resources, to provide ongoing feedback for continuous improvement and accountability. The *summative evaluation* will examine the value of ERC resources, as well as assess research productivity, team science effectiveness, and the leveraging of existing resources, as well as measure outcomes as a result of Center activities, including changes in research capacity, infrastructure, results, and broader impacts. An *evaluation matrix* will be used to align strategies, objectives, and goals of the Center with associated indicators, targets, data sources, data collection timelines, and data analysis techniques.

Performance Feedback, Timeline, and Reporting. Evaluation findings will be shared with IMWEL leadership via informal discussions, monthly infographics, supplemental reports, quarterly meetings, and annual evaluation reporting. EVAL will work with leadership to interpret findings and assess their implications for programmatic adjustments and continuous improvement. Lessons learned and best practices will be shared through technical reports, evaluation briefs, presentations at state and national conferences, and publications. As IMWEL is part of the larger ERC program, EVAL will engage in program-level evaluation activities, respond to NSF inquiries, participate in common data collection efforts, and assist in evaluation activities to benefit ERC programs and NSF.

9. FINANCIAL SUPPORT AND FUNCTIONAL ALLOCATION OF RESOURCES

IMWEL is positioned to promote convergent activities by leveraging an array of resources across all partner institutions. Please see below for our Year 1 planned distribution, allocation of resources and committed levels of support, and 5-Year Functional Budget Table:

Functional Budget Table (Years 1-5)	
Function	%
Preterm Birth	11%
Pelvic Floor Disorders	11%
Healthy Aging	11%
Research Total	33%
EWD Programs	4%
DCI Programs	3%
IE Programs	9%
REU Program	2%
General & Shared Equipment	2%
New Facilities/New Construction	1%
General Operating Expenses	0%
Leadership/Administration/Management	7%
Center Related Travel	9%
Other	2%
Indirect Cost	28%
Total	100%

10. RESULTS FROM PRIOR NSF SUPPORT

NSF 1937094 Planning Grant: Engineering Research Center for Integrated Mechanobiology for Women's Health (IMWEL) 09/01/2019 - 05/31/2021, PI X. Edward Guo. This project sought to expand and develop a team of engineers, scientists, educators, entrepreneurs and medical professionals at the intersection of engineering and women's health to refine the vision, mission and strategy. It led directly to this proposed NSF Engineering Research Center for Integrative Mechanobiology for Women's Health (IMWEL). The planning grant outlined three goals: 1) we would visit current NSF-supported Centers to learn best practices on group organization and program management. 2) we would visit the programs of potential partner institutes to get a broad overview of activities and build community. 3) we would attend NSF-sponsored cohort meetings focused on the ERC planning grant opportunity.

COVID-19 shifted our approach and we were able to accomplish the first two goals via Zoom. The generosity of participants in NSF-supported Centers and potential partners were invaluable and advice spanned the spectrum from high-level thinking about research goals to practical day-to-day management practices. Due to these Zoom visits, we have successfully assembled an outstanding team and submitted a pre-proposal, which resulted in an invitation to this full proposal.

Intellectual Merit. As predicted by the discussions with other NSF-supported Centers and the NSF workshop, the work detailing what the Center wished to accomplish and how to pursue those objectives challenged the team. The planning grant enabled the team to develop its ability to strategize across different disciplines, conceptual frameworks, and even vocabulary to develop the proposal that essentially endeavors to infuse engineering insights into the healthcare practices of preterm birth, pelvic floor disorders, and healthy aging. These discussions have resulted in many novel ideas on bioengineering in women's health.

Broader Impacts. Early in the process, the team coalesced on two objectives critical to ensuring the dissemination of its findings. One, to impact healthcare, the Center must build a robust ecosystem of all the players. Two, the Center had to encourage more people—particularly women and underrepresented minorities—to pursue engineering for women's health. This full proposal incorporates innovative strategies for both objectives, including middle school, undergraduate intervention programs in STEEM on women's health, and a self-study of IMWEL for DCI.

11. PROPOSING TEAM TABLE

Please see Supplemental Documents.