Transdisciplinary Research Initiative (TRI)
Spire of Excellence Proposal

February 19, 2010

Multi-Scale Integrative Bioscience

Working Group
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1. EXECUTIVE SUMMARY

At the University of Vermont (UVM) a unique opportunity exists to develop a Spire of Excellence in Multi-Scale Integrative Bioscience. The field of Multi-Scale Integrative Bioscience is concerned with understanding and utilizing functional aspects of biological organisms that emerge from interactions between simpler components and evolve over multiple spatial and temporal scales. Reductionism has been astonishingly successful at advancing our knowledge of the natural world, i.e. the elucidation of the human genome. However, this seminal achievement represents not the culmination but the beginning of understanding complex diseases. We are still faced with trying to understand how the genetic network functions as a dynamic system, and how this function becomes abnormal in disease. Thus, while reductionism will continue to be the yin of biology and medicine’s future, there will need to be a better understanding of and appreciation for the yang represented by multi-scale integrative system-level study of interactions and dynamics.

A comparison between reductionist and multi-scale integrative approaches is exemplified by the beating heart. Although the tiny myosin motors that generate the force and motion required to power this amazing pump have been characterized at the molecular level by Dr. Warshaw’s laboratory at UVM [1], understanding how the more than 10 trillion such motors are activated and synchronized in a beating heart is a challenge that only a multi-scale integrative systems approach could tackle. Another interesting example under study by Dr. Wright and his collaborators at UVM [2] involves ciliated protozoa that inhabit animal rumens and have organelles, hydrogenosomes, that produces hydrogen. This hydrogen is used by archaea, single-celled ancient organisms, to reduce carbon dioxide to methane in the gut. Methane produced by livestock contributes 20% of the world’s methane emissions. Reducing the density and/or activity of the rumen ciliates is one strategy to improve agricultural sustainability and reduce global greenhouse gases. This cadence, involving six biological scales (atoms, molecules, cells, organs, organisms and populations) in four of the six phylogenetic domains and with
the potential to affect them all, will stimulate ongoing basic science research, but understanding and resolution of these complexities will require the interpretation and insight of Multi-Scale Integrative Bioscience.

The overarching goal of this Spire of Excellence is to train the scientist of the future to utilize Multi-Scale Integrative Bioscience approaches to address important research questions within multi-tiered complex systems to elucidate emergent macroscopic behavior. The skills required to undertake this kind of research are not provided by a typical graduate or post-doctoral training, but can be amassed through exposure to the appropriate combination of disciplines including both quantitative and biological sciences. Concomitantly, we will consolidate our extant multi-disciplinary strengths in bioscience into a series of multi-scale clusters, each with a recognized identity defined by common interests and goals. These clusters will be enhanced by: 1) strategic hiring of new faculty members with combinations of biological and quantitative skills required to integrate across multiple scales and systems, 2) fostering transdisciplinary research tracks that cross existing divides through pilot funding, seminar series and meeting venues, 3) developing a set of core graduate courses leading to a new PhD program in Multi-Scale Integrative Bioscience, and 4) leveraging these exciting endeavors to enliven undergraduate education and research experience.

II. DESCRIPTION OF THE PROPOSED TRANSDISCIPLINARY SPIRE OF EXCELLENCE

a. Definition of the Spire of Excellence in Multi-Scale Integrative Bioscience.

The intellectual focus of the Spire will be the development and dissemination of novel and effective approaches to inform experimental design and to integrate information derived from research carried out in vivo, in vitro, or in silico, bidirectionally across a range of biological scales (atoms, molecules, cells, organs, organisms and populations). Examples of bioscience investigators at UVM who work at these different scales are listed in Table 1 (page 8). The majority of scientists tend to work primarily at one scale, some at two, and few at three or more. In discussions within the Biosciences Working Group, and repeatedly in conversations with colleagues, the same dilemma was encountered – even if investigators were involved in laboratory groups
or program projects that operate at multiple scales, the approach to integrating across scales was usually perceived to be patchy or inadequate. Yet there was unanimous agreement that the ability to integrate across scales offered the greatest hope for better understanding of the biology involved and the potential for targeted interventions at multiple levels of scale. These concepts are illustrated by the work of Dr. Bates’ laboratory group at UVM. One of the key features of an asthmatic attack is excessive and inopportune bronchoconstriction. Bronchoconstriction begins at the molecular level with the activation of the smooth muscle cells that surround the pulmonary airways. Activation (e.g. by binding of acetylcholine to cell receptors, neural stimulation, or activation of histamine receptors) leads to intra-cellular signaling events that result in cyclic binding of myosin to actin causing the smooth muscle cells to shorten. Smooth muscle shortening causes a narrowing of the airway lumen. Understanding bronchoconstriction thus requires an understanding of events that span the scale range from individual molecules all the way up to the entire lung. Importantly, the features of the various events that manifest during bronchoconstriction at these various ranges of scale are qualitatively different, each being determined by the behavior of events at lower levels of scale. This presents opportunities to modulate the degree of bronchoconstricton by interfering with processes at all these different scale levels (i.e. pharmacological block of receptors on the smooth muscle cell, increasing the stiffness of the tissue against which the muscle has to contract by increasing lung volume, decreasing the amount of mucus in the airways with drugs, or increasing ventilation by using specialized breathing maneuvers). Thus multi-scale integrative approaches provide not only a deeper understanding of the interdependence of component parts, but also the potential to compare or combine therapeutic approaches at multiple scales.

b. The Elements of the Proposed Research and Graduate Education Program

Faculty. There are approximately 100 UVM faculty members located in twenty one departments across four colleges whose research is in biosciences. Many of these individuals have backgrounds of strong multi-disciplinary training and conduct research on two or three scales. Although the apex of this Spire is focused and
narrow, the base on which it rests is broad and offers opportunities for many faculty members to align with Multi-Scale Integrative Bioscience focus groups. These individuals may work predominantly in their chosen scale within their discipline, but could extend their interests and activities to incorporate other scales or disciplines. Obvious synergies include nanotechnology within Material Sciences and from interactions with theorists involved in Complex Systems. The Spire will be further strengthened by hiring new faculty members who will work interactively and specifically to bridge multiple disciplines and scales, and provide a transdisciplinary experience for undergraduate and graduate students, and post-doctoral associates.

**Graduate Students.** High quality graduate students will be both the glue and the lifeblood of the Spire. While several strong graduate programs in biosciences exist at UVM, training of students in these programs is specific to a discipline. However, several programs - a PhD in Clinical and Translational Science, a PhD in Cell and Molecular Biology, a PhD in Neuroscience and a pending PhD in Bioengineering - are, by definition, transdisciplinary and transcollegial. Ongoing discussions seek how these programs, and the emerging doctoral program in Complex Systems, can be leveraged to foster doctoral education within this Spire. In time, we will build a specific Multi-Scale Integrative Bioscience graduate program to provide the training and skill sets necessary to train future transdisciplinary scientists (as endorsed by the NSF and NIH) [3]. To train students to become adept at moving across multiple scales of biological and allied sciences, the curriculum for this program will require course work within the first two years in biological and bioengineering disciplines, and in quantitative and computer sciences.

**Undergraduate Students.** One of the goals of the TRI process is to attract and retain excellent undergraduates by creating opportunities for them to interact with scholars in the Spires. We will introduce a new sophomore-level Honors College seminar on Multi-Scale Integrative Bioscience that will produce high quality undergraduates to work on research projects across UVM. We will provide research opportunities for undergraduate students using programs such as the NSF Research Experiences for Undergraduates (REU)
program, the NSF Summer Undergraduate Research Fellowship (SURF), and the T02 and T90 Interdisciplinary Research Undergraduate Program at NIH.

Focus Groups. It is expected that focus groups will emerge within the broad overarching umbrella of Multi-Scale Integrative Bioscience. These focus groups will crystallize around a central champion(s) who will serve as an initial nucleus to attract and engage scientists working at multiple scales in multiple disciplines and colleges. Their participation will be driven by their intellectual interest in the specific focus group. Modest infrastructure (list serves, blogs, on-line fora, a meeting place, a speaker’s budget, etc.) will be provided to help further these interactions. Likely examples include Cardiovascular, Lung, Immunobiology, Neuroscience and Environmental Health. This approach allows groups to emerge organically through a self-organizing process rather than by trying to impose top-down organization.

Seminars. The Multi-Scale Integrative Bioscience Seminar Series will stimulate communication among faculty and students across the institution. The seminars will inform the university community of research conducted by colleagues on campus through presentations by existing faculty, and stimulate cross-fertilization of research programs and unleash new ideas by inviting external speakers. These speakers (e.g. Nobel Laureates, National Academy members, Howard Hughes Medical Institute Investigators) will be expected to spend at least a day meeting and interacting with post-docs, and graduate and undergraduate students to provide stimulation, mentoring and the creation of future research opportunities.

Pilot Funding. New transdisciplinary research initiatives and the development of novel research projects will be fostered through yearly competitions for multi-year seed grants that bring together faculty from two or more academic units and scales. This mechanism has been used successfully at Bio-X at Stanford University to grow the number of extramurally funded cross-disciplinary projects [4].

Technology Transfer. UVM is fortunate to have access to innovative high-tech companies in the private sector with ties to campus faculty. Several of these companies were founded by UVM faculty members
predicated on their patented Intellectual Property or have executives who trained or studied at UVM. There is capacity to develop research partnerships with these companies to provide unique opportunities for graduate students or post-doctoral associates to work in the private sector and broaden their opportunities.

c. Program Relevance to Critical Issues in 21st Century Society

There has been a groundswell of interest in multi-disciplinary research which is usually embodied in interactions between scientists grounded in multiple different disciplines. This trend, which can be considered as horizontal integration, has been useful and important. However, it is our contention that the full benefits of multi-disciplinary research can be reaped more efficiently by the addition of the vertical integration afforded by multi-scale integrative approaches. For therapeutic interventions, the national focus has been on Comparative Efficacy Research wherein multiple different modalities are compared, often utilizing combinations of approaches, to determine which “cocktail” of interventions is superior. It is hard to imagine how this will be achieved in the absence of more robust and systematic abilities to apply Multi-Scale Integrative Bioscience to these endeavors. Moreover, this integrative systems approach offers the brightest hope for understanding biology and pathobiology at a level sufficiently profound and complete to allow for interventions to perpetuate health and forestall the development of disease. Students will be empowered to engage society’s issues with a broader and more complete vision of transdisciplinary approaches. Lastly, it is likely that advances in this field will allow us to learn and utilize the evolutionary wisdom of natural systems in our own designs for prostheses and robotics, and broadly for energy generation and transfer.

d. Opportunity for a World-Class Niche in Scholarship

Biology and bioengineering sciences at UVM already includes several distinct areas with outstanding faculty members who are nationally-renowned. Examples include: Josh Bongard (Computer Science), designated top innovator under 35 by MIT Technology Review; James Iatridis (Engineering), Presidential Early Career Award from the NIH; Stuart Kauffman (Medicine), MacArthur Genius Award and Professor at the Santa
Fe Institute; and Mark Nelson (Pharmacology), recipient of an NIH Merit Award and University Distinguished Professor with a lifetime citation index of over 12,000. These four constitute merely a few examples of the many talented investigators in biosciences. It can be expected that the pursuit of research that takes advantage of new transdisciplinary opportunities will continue to advance the national reputation of this body of work. However, a main goal of our Spire is to augment our extant strength with a cadre of transdisciplinary scientists charged with examining the interdisciplinary interstices between its disciplines, and designing and exploring novel ways to relate information across multiple scales of biological systems. This novel approach is expected to further enhance the reputation of the Spire as the home of world-class scholars.

e. **UVM/VT Competitive Edge for Potential Resources**

The first consideration is the extant strength of the faculty and its funding in biosciences. Although UVM is a small university, approximately 50% of the faculty are involved in the study and teaching of life sciences. The small scale of the UVM community is also advantageous in that all nine colleges and our affiliated teaching hospital, Fletcher Allen Health Care, are located within a 10-minute walk on one central campus. The compact nature of the campus has already proved beneficial in recruiting new faculty members and in fostering emerging multi-disciplinary research. Lastly, in the absence of a large endowment and with minimal funding from the state, faculty committed to research careers have, of necessity, developed strong track records of obtaining extramural funding.

f. **The Effect of Formation of a Transdisciplinary Faculty on Future Outcomes**

Many of the cutting-edge research programs in biology have achieved their success by exploiting multi-disciplinary approaches. There is a widespread belief nationally amongst scientists and within national funding agencies that work at the interstices of disciplines will provide novel insights and thus should be encouraged. To date, such multi-disciplinary efforts have largely arisen spontaneously and tend to bridge only two or three of the six scales of biological systems described earlier. A deliberate attempt to build a diverse faculty in Multi-
Scale Integrative Bioscience is expected to amplify and increase the rate of multi-disciplinary interactions across multiple scales to realize truly transdisciplinary programs.

III. JUSTIFICATION FOR STRATEGIC INVESTMENT

IIIa. Existing UVM Strengths that Support the Program

i, ii and iii. Faculty, Grants and Program Recognition

A non-exhaustive sample of successful faculty members who work predominantly in biosciences, and their annual funding (90 grants to 55 faculty members for a total of $39,270,676), is shown in Table 1 (next page). These examples, which account for 30% of total extramural funding at UVM, were chosen to illustrate the multiple scales at which they work. Also shown are respective lifetime citations which attest to the reputation of these investigators [5]. Listing of their names in no way confers on them special advantages nor does it commit them to the Spire in any way.

iv. Facilities: Infrastructural grants to UVM that support the Spire:

<table>
<thead>
<tr>
<th>Infrastructural Grant Funding</th>
<th>PI</th>
<th>Annual Funding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5P20 Translational Research in Lung Biology</td>
<td>Irvin</td>
<td>$2,118,617</td>
</tr>
<tr>
<td>P20 Vermont Genetics Network – Vermont INBRE</td>
<td>van Houten</td>
<td>$1,048,847</td>
</tr>
<tr>
<td>1P20 VT Immunobiology/Infectious Diseases Center</td>
<td>Budd</td>
<td>$2,166,298</td>
</tr>
<tr>
<td>5P20 Center for Neuroscience Excellence</td>
<td>Parsons</td>
<td>$2,120,470</td>
</tr>
<tr>
<td>5M01 General Clinical Research Center</td>
<td>Galbraith</td>
<td>$2,377,997</td>
</tr>
<tr>
<td>5K30 A Curriculum for Clinical Research Training in VT</td>
<td>Littenberg</td>
<td>$ 300,000</td>
</tr>
<tr>
<td>VT EPSCoR Research Infrastructure Improvement</td>
<td>van Houten</td>
<td>$2,244,291</td>
</tr>
</tbody>
</table>

Total $12,376,520

Key to the success of many endeavors are the graduate student and post-doctoral training programs at UVM including seven NIH-funded T32 grants: Immunology/Infectious Diseases Training Grant, Behavioral
### Table 1. Examples of Investigators in Biosciences

<table>
<thead>
<tr>
<th>Scale</th>
<th>Discipline</th>
<th>Annual Funding</th>
<th>Lifetime Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atoms</strong></td>
<td><strong>Pharm:</strong> Nelson, Brayden, Wellman</td>
<td>$2,897,176</td>
<td>19,293</td>
</tr>
<tr>
<td>1. Calcium</td>
<td><strong>Chem:</strong> Case; <strong>Eng:</strong> Sansoz; <strong>Phys:</strong> Headrick</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Nanomaterials</td>
<td><strong>Bio:</strong> Ne</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Molecules</strong></td>
<td><strong>Calcium</strong></td>
<td>$10,337,096</td>
<td>14,795</td>
</tr>
<tr>
<td>1. Flight</td>
<td><strong>Bio:</strong> Vigoreaux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Actin/Myosin</td>
<td><strong>MPBP:</strong> Warshaw, Trybus, Lowey, Berger, Maughan, Palmer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Energy</td>
<td><strong>MPBP:</strong> Radermacher, Ruiz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. DNA Repair</td>
<td><strong>Biochem:</strong> Morrical; <strong>MMG:</strong> Wallace; <strong>Phys:</strong> Yang</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Virus</td>
<td><strong>MMG:</strong> Thali</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Signaling</td>
<td><strong>Pharm:</strong> Dostmann</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Dynamics</td>
<td><strong>Eng:</strong> Dubief</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td><strong>Eng:</strong> Hill; <strong>MMG:</strong> Mintz</td>
<td>$10,019,770</td>
<td>1,840</td>
</tr>
<tr>
<td>1. Bacterial Adhesion</td>
<td><strong>Animal Sci:</strong> Kerr; <strong>Bio:</strong> van Houten; <strong>Chem:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Cytoskeleton/ Cell Motility</td>
<td><strong>CCTS:</strong> Fukagawa, Kien, Pratley; <strong>MED:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Heart</td>
<td><strong>Ob/Gyn:</strong> Osol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Skeletal Muscle</td>
<td><strong>Eng:</strong> Iatridis; <strong>Orthoped:</strong> Beynon, Stokes; <strong>Rehab/Mvmt:</strong> Henry</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organs</strong></td>
<td><strong>RMS:</strong> Wu</td>
<td>$10,230,534</td>
<td>17,655</td>
</tr>
<tr>
<td>1. Smooth Muscle</td>
<td><strong>Med:</strong> Bates, Irvin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Vasculature</td>
<td><strong>N:</strong> Cipolla, Vizzard; <strong>Neurobio:</strong> Mawe; <strong>Ob/Gyn:</strong> Osol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Heart</td>
<td><strong>Med:</strong> LeWinter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Skeletal Muscle</td>
<td><strong>Eng:</strong> Iatridis; <strong>Orthoped:</strong> Beynon, Stokes; <strong>Rehab/Mvmt:</strong> Henry</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organisms</strong></td>
<td><strong>PBIO:</strong> Vogelmann</td>
<td>$2,587,100</td>
<td>5,041</td>
</tr>
<tr>
<td>1. Kinesiology</td>
<td><strong>RMS:</strong> Wu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Muscle/ Metabolism</td>
<td><strong>CCTS:</strong> Fukagawa, Kien, Pratley; <strong>MED:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Fascia</td>
<td><strong>N:</strong> Langevin; <strong>PHYS:</strong> Wu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Photosynthesis</td>
<td><strong>PBIO:</strong> Vogelmann</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Populations</strong></td>
<td><strong>CS:</strong> Bongard; <strong>ME:</strong> Hitt</td>
<td>$3,199,000</td>
<td>135</td>
</tr>
<tr>
<td>1. Robotics</td>
<td><strong>TRC:</strong> Aultman-Hall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Transportation</td>
<td><strong>TRC:</strong> Aultman-Hall</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>55 Faculty; 90 Grants</strong></td>
<td><strong>$39,270,676</strong></td>
<td><strong>58,759</strong></td>
</tr>
</tbody>
</table>

**KEY:**
- **AN:** Anatomy & Neurobiology
- **ASCi:** Animal Science
- **BIOCHEM:** Biochemistry
- **CCTS:** Center for Clinical and Translational Science
- **CHEM:** Chemistry
- **CS:** Computer Science
- **ED:** Education
- **ENG:** Engineering
- **ME:** Mechanical Engineering
- **MMG:** Microbiology and Molecular Genetics
- **MPB:** Molecular Physiology & Biophysics
- **NP:** Neurology and Pharmacology
- **OBGYN:** Obstetrics, Gynecology and Reproductive Sciences
- **OR:** Orthopaedics & Rehabilitation
- **PBIO:** Plant Biology
- **PHARM:** Pharmacology
- **PHYS:** Physics
- **REHAB:** Rehabilitation & Movement Science
- **SE:** School of Engineering
- **TRC:** Transportation Research Center
Pharmacology of Human Drug Dependence, Multi-disciplinary Training in Lung Biology, Post-Doctoral
Cardiovascular Research Training Program, Hemostasis and Thrombosis Program for Academic Trainees,
Environmental Pathology Training Grant, Training Program in the Molecular Basis of Cardiovascular Disease.
Also critical to research endeavors is the support of core facilities at UVM that allow faculty and their students
to compete effectively for extramural funds. Examples of key cores are (1) Multi-Scale Imaging from atoms to
whole animal and fMRI imaging; (2) Computational Power from the state-of-the-art 7.1 teraflop UVM
Advanced Computer Center; (3) RNA and DNA analysis and synthesis; (4) Materials Science Processing and
Analysis; (5) Instrumentation and Model Facility; (6) Bioinformatics; and (7) Proteomics and Mass
Spectrometry.

v. Quality of Graduate Students

Graduate students working in laboratories of faculty members associated with the Spire will initially
matriculate through the Cell and Molecular Biology (CMB) Program. This is an established cross-college
program at UVM that includes over 60 faculty members from the Colleges of Arts and Sciences, Medicine,
Engineering and Mathematical Sciences, and Agriculture and Life Sciences. CMB maintains ~ 45 Ph.D.
students, the majority of which are supported by graduate teaching fellowships for their first year and after that,
by individual faculty grants. During 2009, 12 students graduated with PhDs from the CMB Program and 7
enrolled with a mean GPA of 3.8, and a mean GRE Verbal of 591 and a mean Quantitative of 674. In time, it
may be that the umbrella of Multi-Scale Integrative Bioscience, with its unique focus on both horizontal (multi-
disciplinary) and vertical (multi-scale) integration may prove to be an extremely attractive program to potential
graduate students.

IIIb. Emerging UVM Strengths that Support the Program

i. Faculty or Prospective Hire Potential.

Faculty members whose primary area of interest is bioengineering have been hired recently in both the
Colleges of Medicine and Engineering and Mathematical Sciences. A joint PhD in Bioengineering is pending
approval by the Board of Trustees. Similarly, the CCTS has recently been constituted as the first UVM Matrix
Center. This administrative/academic structure, reporting directly to the Vice President for Research, sponsors
a PhD in Clinical and Translational Science and can jointly hire faculty. Three new faculty members have already been hired as joint appointees and six more are committed in UVM’s CTSA application to NIH. The CCTS will likely benefit those involved in this Spire. Of particular note are two newly-hired PhDs in Biomedical Informatics who lead a team from Informatics Services at the hospital, the University, the Computer Science Department, and the Vermont Advanced Computing Center. Areas of particular strength and emphasis for this team are linking and mining disparate databases (e.g. DNA sequence, crystallography, clinical records, state registries, insurance claims) to facilitate translational Multi-Scale Integrative Bioscience.

Multi-Scale Integrative Bioscience is inherently complementary to Complex Systems analysis that has been an area of active recruitment in Engineering and Mathematical Sciences. This group has been augmented by Stuart Kauffman, MD, who joined the UVM faculty in 2010, and is widely recognized as a foremost authority in the field of complex biological systems. Trained as a physician, he has studied dynamic Boolean networks as models of gene-gene interactions, the auto-regenerative capacity of auto-catalytic sets of enzymes, and proposed a theory of the cell phenotype as a dynamic attractor in the energy landscape of the genome network.

III. c. Alignment of Funding Availability for the Program

There are rich funding opportunities for a Spire in Multi-Scale Integrative Bioscience. For undergraduates, there is the McNair Postbaccalaureate Achievement Program (Department of Education), and the NSF Programs Research Experiences for Undergraduates, Interdisciplinary Training in Mathematics and Biology, Undergraduate Research Collaboratives, and S-STEM. The Howard Hughes Medical Institute provides undergraduate research training grants such as the Undergraduate Science Education Program. There are also multiple funding opportunities for graduate student training most notably the NIH Training Grants and the NSF’s IGERT, AGEP, and G12K programs.

We envision no shortage of funding opportunities for investigators that participate in this Spire, the research themes of which are consonant with the strategic mission of many federal agencies including the NIH, NSF, DOD, DOE, and NASA. Transdisciplinary research in biological and bioengineering sciences is explicit in the strategic vision of both the NIH and NSF (3) that provide center, partnership, and consortium grants.
appropriate for the transdisciplinary theme of the Spire. For example, the NIH provides the P20 Exploratory Centers for Interdisciplinary Research mechanism and the NSF invests in Science and Technology Centers that support interdisciplinary research and training. Similarly, the DOD provides the Multi-disciplinary Research Initiative which supports university research efforts intersecting across traditional science and engineering disciplines. During preparation of this proposal, two new funding opportunities were announced. First, the NSF IGERT Limited Competition for New Models of Graduate Education in Collaborative Research that Transcends Traditional Disciplinary Boundaries [6] and second, the NIH RC4 ARRA Director’s Opportunity [7] which requires a minimum budget of half a million dollars annually. We plan to apply for both these grants to support this Spire.

III. d. Opportunities for UVM in the Next Five Years

i. Competitive Faculty Recruitment: UVM continues to have success in recruiting high quality faculty to the various areas of excellence in biology and bioengineering. The additional opportunities offered through this Spire in Multi-Scale Integrative Bioscience is an exciting opportunity for transdisciplinary foci for emerging multi-dimensional scientists.

ii. Competitive Graduate Student Recruitment: The existing Cellular and Molecular Biology Program continues to recruit high quality graduate students as do the relatively newly created doctoral programs in Bioengineering and Clinical and Translational Science. Our goal is to evolve to the point where graduate students can apply, perhaps through a central portal or “umbrella” system to do doctoral work in specific disciplines but also to a newly created transdisciplinary PhD program focused on Multi-Scale Integrative Bioscience.

iii. Competitive Position for Funding: UVM faculty have convincingly demonstrated their ability to obtain extramural funding not least by their success in the recent ARRA funding from the NIH where they received three of the 200 nationally available challenge grants and $20.6 million in total, a disproportionately large share of the total dollars available given UVM’s small size. The transdisciplinary focus on Multi-Scale
Integrative Bioscience positions us well to compete successfully for the federal, private, and non-profit funding described above (Section IIIc).

iv. **Coordination with VT Economic Development:** Companies established in Vermont based on patents awarded to COM and CALS faculty members or that have added to existing product lines based on faculty patents include: Biotek, Microstrain, Med Associates/Catamount Research/Living Systems Instrumentation, Chroma Technologies, Creative Microsystems, IBM, Green Mountain Antibodies, Hemetek, and Vermedex. In total, UVM has 209 invention disclosures, 54 patents, and 21 licensing agreements in the biological and bioengineering sciences domain.

v. **Contribution to Service and Outreach Mission:** The expectation that UVM will be able to translate the fruits of this transdisciplinary research in the Spire to improving the health and reducing the disease burden of the population of the State of Vermont is supported by the fact that UVM is the only university and its affiliated teaching hospital, Fletcher Allen Health Care, is the only tertiary hospital in the state. In addition, the areas of biological study are not solely confined to human physiology and disease but also include the study of animals and plants, both major foci of the College of Agriculture and Life Sciences and the Extension Service which provides consultation to farmers involved in livestock and crop growth to provide food. It is expected that going forward, as it has been in the past, the scientific work at UVM will significantly impact thought and practice in the agricultural sector of the state.

### III.e. Expected Faculty/Programmatic Facilities Needs (Additions/Renovations) over Next Five Years

i. **Space (Individual/Collaborative):** The Spire will leverage the existing substantial strengths in Biological and Bioengineering Sciences at UVM, so the additional space requirements for the Spire are directed at consolidating these strengths and supporting additional hires. For the purposes of consolidation, we require office space for a Director and an Administrative Assistant, and a modest area for meetings involving Spire faculty, focus groups and research trainees. The additional faculty hires will require office and laboratory space as dictated by their specific research needs. Ideally, space for new hires should be in the immediate vicinity of the Spire Director and other faculty to foster a sense of Spire cohesion and identity.
ii. **Equipment:** Additional equipment will be required to serve the research needs of the new faculty hires as per their specific research interests and cannot be predicted prior to identification of the new faculty.

iii. **Computational/IT:** The Spire will stimulate major computational modeling efforts. Some of these models are likely to be sophisticated and will require substantial computing power. Consequently, we believe the principal IT resource for the Spire will eventually become the Vermont Advanced Computing Facility at UVM. This is a state-of-the-art computing facility that will be constantly developing as new hardware and software tools become available. The Spire will contribute to this development, as will the CCTS Bioinformatics Core.

iv. **Faculty:** Modest investment in this Spire will empower the existing faculty to realize its full potential. We propose that eight new faculty lines be dedicated to this Spire to foster intellectual cross-fertilization among the disciplines over the next 5 years. These hires should possess experience and expertise in experimental or theoretical aspects of Multi-Scale Integrative Bioscience. They will be quantitatively trained scientists with knowledge of modeling, a strong grounding in biology and an understanding of complex information on multiple scales; they must also be able to communicate and collaborate across disciplines. These individuals will be expected to collaborate with other investigators within the Spire and to build an extramurally (i.e. NIH/NSF) funded research program capable of supporting both faculty and students from multiple colleges at multiple academic levels (undergraduate, graduate, and postgraduate) within 5 years. Selection of new faculty members will follow an internal RFA where various units (i.e. Matrix Centers of Multi-Scale Integrative Bioscience Focus Groups) respond, within well-defined guidelines designed to ensure multi-scale and multi-disciplinary scope, and compete for faculty positions.

**III f. Potential Barriers to Success in this Field and Proposed Solutions**

i. **Institutional:** Like many universities, UVM’s research enterprise is conducted by academic units whose organizational home was established by historical events rather than by disciplinary considerations. The dispersal of besciences investigators across four colleges and schools inhibits cross-unit collaborations for reasons of base unit funding, reporting, and faculty promotion and tenure. Models to remove this institutional
barrier have been proposed (e.g. UVM Matrix Centers) but there remains a lack of clarity about how to create mechanisms that sustain their transdisciplinary research.

ii. **Pedagogical:** Both undergraduate and graduate education tend to align strictly along disciplinary lines. Models for truly transdisciplinary, cross-collegial educational programs have been developed successfully at UVM: for undergraduate teaching, the Honors College; and for graduate teaching, the Cell and Molecular Biology, Bioengineering, Neuroscience and the CCTS Graduate Programs. Implementation of procedures that reward programs for the tuition and grant dollars that they generate could motivate faculty to participate in transdisciplinary initiatives. Another means would be to redistribute graduate teaching and research assistantships to stimulate and foster transdisciplinary research.

iii. **Professional:** Significant problems are evident in the procedures surrounding hiring, promotion, and tenure of faculty that often present real barriers to transdisciplinary research. Other than through the approaches outlined in Matrix Centers, these problems have remained intractable.

**IIIg. Projected Metrics for Success in Five Years**

The traditional metrics for success are increases in the numbers of grants, extramural funding, publications and citations. However, these measures do not necessarily speak to the success of the Spire as an integrated transdisciplinary enterprise so much as to the individual success of faculty members within the Spire. Metrics to assess the success of transdisciplinary initiatives are more difficult to define but include increases in the numbers of authors from different fields who participate in writing grants and authoring manuscripts. Interdisciplinary or emerging fields may be indicated by funding of grants with multiple PIs or from non-traditional agencies, or in response to specific transdisciplinary RFAs, or by authorship in journals without strong disciplinary boundaries or those involving either new or infrequently cited library “MeSH” terms.

In the programs of graduate study relevant to the Spire, one would expect to see increased competition for entry into the program, an increase in the number of theses written under the auspice of co-mentors from different disciplines or scales or in new emergent disciplines, and an interest, ability and record of students taking courses and rotating through laboratories pertaining to widely divergent and non-traditional disciplinary foci. The establishment and funding of transdisciplinary graduate training programs specific to this Spire is also
expected. There are several integrated metrics for research and graduate educational programs and one of the most cited is the National Research Council (NRC) Assessment of Doctoral Programs [8]. At UVM the research doctoral programs ranked in the second quartile by the NRC in 1995 [9] were physiology; pharmacology; ecology, evolution and behavior; cell and developmental biology; and psychology. Biochemistry and molecular biology, and chemistry were ranked at the third quartile. Arguably, because of the breadth and diversity of the content areas of the Spire, all of the above research doctoral programs could be considered to be contributory. An additional metric of success would therefore be an increase in the ranking of the above research doctoral programs. Finally, the reputation of the faculty, their scientific contributions and the increasing numbers of high quality graduate students is expected to attract increasing numbers of undergraduate students to learn about and participate in the intellectual foment of the Spire.

IV. CONCLUSION

Strategic investment in research utilizing Multi-Scale Integrative Bioscience is a tremendous opportunity at UVM to focus expertise in highly recognizable and productive areas of excellence in Bioscience. The Spire is founded on successful and well-funded investigators with access to outstanding infrastructural support and core facilities. Moreover, the efforts of these core faculty members will be augmented by other scientists in other spires, particularly in Complex Systems and Neurosciences. We anticipate that the existence, growth and relevance of Multi-Scale Integrative Biosciences in integrating complexities from multiple scales will galvanize prospective faculty and post-doctoral, graduate and undergraduate students challenging them to reach beyond the confines of a traditional channeled educational or research experience.

It should be noted that the approaches outlined for Multi-Scale Integrative Bioscience are not exclusive or exhaustive. New approaches or concepts may arise organically from foundations laid earlier. Thus, if this Spire is selected, the foregoing high-level, visionary overview of the potential program will require refinement by a coalition of the willing prepared to devote time and effort towards its fulfillment. The anticipated input of diverse opinion from faculty, students, staff and administrators is anticipated to further strengthen the concept and actualize the reality of this Spire of Excellence.
REFERENCES


[5] Search conducted 1/7/10 in Web Science, 1982 to present, using the following strategy: Author last name/Author first and middle initials AND UVM or VT or Vermont[address]


