Green Metabolic Factories Collaborative

***Strategic Plan Theme*: Global Impact, Global Impact**

***Funding Level*: Between $1-5 million, Between $1-5 million**

***Facility Needs*: Adjustments to existing facilities will be needed, Adjustments to existing facilities will be needed**

***Submitting Unit*: COM/CHM/CVM, NA**

Collaborating colleges/departments/units involved with this proposal.

Departments include: BMB, PHM, MMG, CEM, PLB, HRT, PED, PSL, FSHN, and RTSF. Colleges represented include: CNS, COM, CHM, CVM, and ANR, Departments: BMB, PHM, MMG, CEM, PLB, HRT, PED, PSL, FSHN, and RTSF. Colleges:CNS, COM, CHM, CVM, and ANR

What is the proposal's big theme or idea?

We will harness and extend the unique ability of plants to generate complex and valuable chemicals for translation from field to bedside and back to field. We will accomplish this by building a collaborative which coalesces tremendous strengths at MSU in plant biology, biochemistry, and pathway discovery with our expanding expertise in synthetic biology and strong biomedical research and drug discovery enterprises to develop novel technologies that create compounds addressing key biomedical and agricultural and environmental needs.

Plants are the ultimate chemical factories, absorbing ~120,000 million metric tons of CO2 per year, more than 20 times all anthropogenic carbon emissions, using only solar energy. They feed directly or indirectly every animal on Earth and assemble some of the most abundant and useful polymers, including lignin (wood) and cellulose (paper, cotton). They also produce a myriad of specialty chemicals (estimated at several million) that serve as building blocks for more than 30% of the pharmaceuticals currently on the market. These same compounds also harbor valuable nutritional properties with potential as functional foods. This chemical diversity also furnishes plants with a singular opportunity to adapt to the inevitable upcoming climate changes, including developing durable resistance to pathogens and herbivores expanding in range as consequence of global warming.

Michigan State University has been at the forefront of plant biology and biochemistry worldwide. To maintain this leadership position, it is imperative to invest in emerging technologies and talent. This cross-disciplinary initiative will foster a hotbed for innovation for novel, bioactive, natural and new-to nature compounds, while contributing to the development and adoption of innovative technologies that will permit MSU to continue to be at the forefront of the field. This collaborative will also advance MSU's land-grant mission by applying basic knowledge to practical needs in health (inflammatory diseases, cancer, and antimicrobial resistance) and to enhance sustainable production of agrichemicals and to generate unique plant strains with enhanced resilience., We will harness and extend the unique ability of plants to generate complex and valuable chemicals for translation from field to bedside and field back to field. We will accomplish this by building a collaborative which coalesces tremendous strengths at MSU in plant biology, biochemistry, and pathway discovery with our expanding expertise in synthetic biology and strong biomedical research and drug discovery enterprises to develop novel technologies that create compounds addressing key biomedical and agricultural and environmental needs.

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What is the proposal's goal?

Our goals are to:

Sustain world leadership in plant biology and biochemistry

Develop new approaches for the production, purification, structural characterization, and diversification of plant-derived bioactive chemicals

Exploring medical uses of these novel plant-derived/plant-inspired chemicals to tackle areas of high unmet medical need

Develop novel intellectual property and catalyze the translation of basic discoveries to practical applications in medicine and agriculture

To achieve these goals, we will undertake:

Pathway, gene, and compound discovery – Barry, Grotewold, Hamberger, and Last have strong programs in small molecule discovery, pathway identification, cloning, and enzyme purification and in situ expression in plants or other model organisms.

Synthetic biology/pathway engineering to optimize production of novel plant products – Draths and Walker also use enzymes isolated from plant and microbial biosynthetic pathways to build in vitro production factories with enzyme combinations. Using both known pathways and novel enzyme combinations we will produce new-to-nature chemicals.

Combining synthetic biology and chemistry (SynBxC) to create new-to-nature molecules. We will design and synthesize novel substrates for enzymes and derivatize enzyme products to diversify and enhance biological activity and drug-like properties. In an MSU strategic partnership grant, Hamberger and Ellsworth developed patent-pending technology (WO 2021/092200 A1 - "Biosynthesis of chemically diversified non-natural terpene products"). Expanding this approach. Last, Walker, and Draths, will utilize their expertise in pathways. They will join the SynBxC team with Ellsworth, Tepe, and Lee. We will also recruit a new faculty member in chemistry/chemical biology. They will extend the SynBxC approach to new pathways and new chemical structural targets.

Analytical chemistry – We also need to be able to determine structures of new compounds developed by our team. Thus, we will recruit a new tenure-track analytical chemist with expertise in complex small molecule analysis (NMR, CryoED, or MS). Also, core leaders (Parent, Schilmiller, Staples, and Ellsworth) will be able to enhance their cores' technologies (see impact).

Explore the activity of novel compound collections for value in diseases with high unmet medical need - We will engage faculty on therapeutics for cancer (Bachmann, Bernard, Doseff, Liby, Neubig), inflammatory and immunologic diseases (Lee, Pestka, Doseff, Neubig), and antimicrobial resistance (DiRita, Hammer,

Abramovitch, Olive). This utilizes resources of MSU Drug Discovery, integrating novel compounds from this collaborative into the screening collection of the ADDRC. Each lab will use technologies already in place to identify active compounds. These will enter our robust pipeline for testing (ADDRC in vitro and In Vivo Facility) and optimization for specificity, and pharmacokinetic properties in the Med Chem core., Our goals are to: 1) Sustain world leadership in plant biology and biochemistry 2) Develop new approaches for the production, purification, structural characterization, and diversification of plant-derived bioactive chemicals 3) Exploring medical uses of these novel plant-derived/plant-inspired chemicals to tackle areas of high unmet medical need 4) Develop novel intellectual property and catalyze the translation of basic discoveries to practical applications in medicine and agriculture

To achieve these goals, we will undertake:

Pathway, gene, and compound discovery – Barry, Grotewold, Hamberger, and Last have strong programs in small molecule discovery, pathway identification, cloning, and enzyme purification and/or in situ expression in plants or other model organisms. This serves as the starting point for the novel elaboration and semi-synthetic diversification of unique plant products.

Synthetic biology/pathway engineering to optimize production of novel plant products – In addition to Hamberger and Last, Draths and Walker use enzymes isolated from plant and microbial biosynthetic pathways to build in vitro production factories with enzyme combinations. Existing pathways plus mixed-and-matched combinations can produce new-to-nature chemicals. Studies of enzyme mechanisms allow rational enzyme combinations use of distinct natural and synthetic substrates.

Combining synthetic biology and chemistry (SynBxC) to create new-to-nature molecules by: design and synthesize novel substrates for enzymes, derivatize enzyme products to diversify and enhance biological activity and drug-like properties. In a collaboration catalyzed by an MSU strategic partnership grant, Hamberger and Ellsworth developed patent-pending technology (WO 2021/092200 A1 - "Biosynthesis of chemically diversified non-natural terpene products"). Here, we will expand this approach. Last, Walker, and Draths, are all experts in plant or bacterial pathway applications to the generation of complex chemical materials. The will join the SynBxC team with Ellsworth, Tepe, and Lee. We will also recruit a new new faculty member in chemistry/chemical biology. They will extend the SynBxC approach to new pathways and new chemical structural targets.

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Define the significance, or impact of your big idea.

This program will:

- Develop novel technologies to mix and match synthetic enzymes from plant and bacterial sources to optimize green synthesis of known and new-to-nature small molecule products.
- Combine this with synthetic organic chemistry methods to rapidly diversify outputs from these synthetic biology approaches – creating a new field – Synthetic biology x Chemistry (SynBxC)
- Create unique MSU plant-derived/-inspired chemical collections for in vitro screening
- Apply these novel collections to address critical biomedical areas of need and generate novel IP

In addition, we will support the goals of MSU to enhance NIH funding and to build recognition for faculty and students

- Obtain center grants for basic research (e.g., NSF, NIGMS) or translation (e.g., NCI, NIAID, USDA)
- Maintain plant sciences at MSU among the top five in the country
- Obtain training grants (e.g., T32 and NRT) to train "small molecule biochemists" – a disappearing breed

Benchmarks of Success

- Grant funding (P01, Center grants, NSF programs, other)
- National Recognition
- Training programs/new combined degree (Molecular Plant Sciences, Chemistry, PharmTox)
- Intellectual property – in novel plant strains, chemical matter, and therapeutics
- DEI/Outreach and public engagement
- Opportunity to support student industrial internships, Objectives to be Achieved • Obtain center grants for basic research (e.g., NSF, NIGMS) or translation (e.g., NCI, NIAID, USDA) • Maintain plant sciences at MSU among the top five in the country • Obtain training grants (e.g., T32 and NRT) to train "small molecule biochemists" – a disappearing breed • Create unique MSU plant-derived/-inspired chemical collections for screening and applications • Apply these novel collections to address critical biomedical areas of need and generate novel IP Benchmarks of Success • Grant funding (P01, Center grants, NSF programs, other) • National Recognition • Training programs/new combined degree (Molecular Plant Sciences, Chemistry, PharmTox) • Intellectual property – in novel plant strains, chemical matter, and therapeutics • DEI/Outreach and public engagement • Opportunity to support student industrial internships

Who will be impacted?

This Collaborative engages MSU's strong initiatives, facilities, institutes, and centers including the DOE-funded Plant Research Laboratory (PRL), the Plant Resilience Institute (PRI), the Assay Development and Drug Repurposing Core (ADDRC), the Medicinal Chemistry Facility, the Mass Spectrometry and Metabolomics Core, the Cryo-EM facility, the NMR facility.

The participants in the Green Metabolic Factories Collaborative belong to 10 departments and 5 colleges. The project was developed by: Rick Neubig – an expert in signal transduction and academic drug discovery (voice-person for this initiative); Erich Grotewold - an expert on the biosynthesis and regulation of plant specialized metabolism; Bjoern Hamberger – an expert in plant pathway discovery and metabolic engineering. Participating faculty e-mails are listed in the proposal form; their departments include: BMB, PHM, MMG, CEM, PLB, HRT, PED, PSL, FSHN, and RTSF. Colleges represented include: CNS, COM, CHM, CVM, and ANR. We also plan an open-door policy to expand beyond this initial group as the collaborative develops. Two new faculty will be recruited, one with analytical expertise and another with a medicinal chemistry or chemical biology focus.

A major component of our funding request is to enhance the capabilities of core facilities – Mass Spec (MALDI imaging system and prep-LCMS), CryoEM (Cryo electron diffraction camera for small molecule structure elucidation), Medicinal Chemistry (additional chemical synthesis hood). In addition to the faculty in the collaborative, these upgrades will have broad benefits for faculty and students across the East Lansing Campus. To ensure progress on the proposed work, we also request funds for joint graduate students or postdocs (4-5 FTE for 2 years) to bridge 2 or 3 labs in the collaborative to obtain preliminary results for successful grant applications.

Enhancing DEI
Our new faculty recruitments will identify and recruit outstanding faculty from under-represented groups. We also plan to heavily recruit under-represented students to build a pipeline for future faculty recruitment. This will build on active programs in student diversity training led by faculty in our collaborative. The Success in Graduate Education (SiGuE) Postbaccalaureate program (Grotewold and Doseff) has run for ~10 years and

channels URM students to graduate school. BMB is starting to recruit Michigan native American students and diversity recruiting efforts by Pharmacology and Toxicology are an emphasis of IPSTP/T32 training grant (Neubig) and the EHS R25 grant (Luyendyk and Bernard). Also, Barry and Last have led an NSF REU program on its 4th consecutive award cycle. It recruits under-represented students into plant biology and MSU graduate programs. Thus, we already have and will expand strong programs to generate a pipeline for diverse undergraduate and graduate students and will extend that to our recruiting efforts for faculty., This Collaborative engages MSU's strong initiatives, facilities, institutes, and centers including the DOE-funded Plant Research Laboratory (PRL), the Plant Resilience Institute (PRI), the Assay Development and Drug Repurposing Core (ADDRC), the Medicinal Chemistry Facility, the Mass Spectrometry and Metabolomics Core, the Cryo-EM facility, the NMR facility.

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What does sustainability for your proposal look like?

The most effective way to sustain this program and to support research activities is to obtain multi-PI or center grants (NIH RM1, P01, P30 or P50 grants or NSF center grants). Also, new training grants to support students would be valuable to enhance cohesion and generate joint publications. Based on priorcollaborative work by Hamberger and Ellsworth, an R01 has been submitted. A larger group (Neubig, Hamberger, Ellsworth, Last, Parent, and Jian Hu) extended the SynBxC concept and submitted an NIGMS RM1 grant ($10M total costs). While that was not funded, aspects of this proposed Collaborative would directly address some of the key critiques – not having joint publications and lack of instrumentation/expertise in small molecule structural elucidation. The requested upgrades for core facilities and funding for joint students or postdocs will directly address the critiques of the submitted RM1 grant., New training and large center grants to support students and research activities