FOCUS ON: **BioPACIFIC MIP**

A Major Grant for Bio-Based Plastics

National Science Foundation awards UCSB and UCLA $23.7 million to develop high-performance bio-based polymeric materials

Synthetic polymers — think plastic and its chemical cousins — are among the foundations of modern life. The ubiquity of such petroleum-based materials has everything to do with their combination of strength, flexibility, and chemical inertness, the last of which also makes them durable. Given the environmental impact of plastics, however, and the fact that petroleum deposits are finite, one grand challenge is to develop a new realm of sustainable bio-based, high-performance alternatives to petroleum-based polymers. Harnessing nature to make these materials will be a huge undertaking requiring a fundamental change in how polymers are made.

To support such an effort, the National Science Foundation (NSF) has named UC Santa Barbara and UC Los Angeles joint partners in the **BioPolymers, Automated Cellular Infrastructure, Flow, and Integrated Chemistry: Materials Innovation Platform** (BioPACIFIC MIP). The five-year, $23.7 million collaboration is part of the NSF Materials Innovation Platforms (MIP) Program and has a scientific methodology reflecting the broad goals of the Materials Genome Initiative, which was established with the aim of developing new materials "twice as fast at a fraction of the cost." BioPACIFIC MIP is one of two MIPs awarded this year.

The BioPACIFIC MIP leverages the facilities, expertise, and experience of UCSB and UCLA, partners since 2000 in the California NanoSystems Institute (CNSI), which has headquarters at both campuses. It will include faculty and affiliates — thirteen from UCSB and seven from UCLA, supported by seven scientific staff. BioPACIFIC MIP will impact a large number of students and researchers at UCSB, UCLA, and across the country in the fields of materials science, biology, chemistry, and engineering.

The project is aimed at developing bio-based plastics having properties superior to those of existing petroleum-based polymeric materials. It is envisioned as a closed-loop scientific system comprising every aspect of such research, from discovery of microorganisms that can be used as biological "factories" to generate building blocks for polymers, through simulation, design, building, testing, and learning, with feedback loops built into the system. Guest researchers will be welcomed to develop, characterize, and engineer new materials based on merging synthetic biology with materials synthesis.

"Nature has an expansive range of functional building blocks, and we now know that it's possible to synthesize them into better macro-materials, like polymers," says BioPACIFIC MIP director and principal investigator (PI) **Javier Read de Alaniz,** a UCSB professor of chemistry and associate director of the CNSI in the College of Engineering. "We will be extracting blocks from nature that you can't access in any other way and then using synthetic routes to combine them into materials having properties that no other material has."

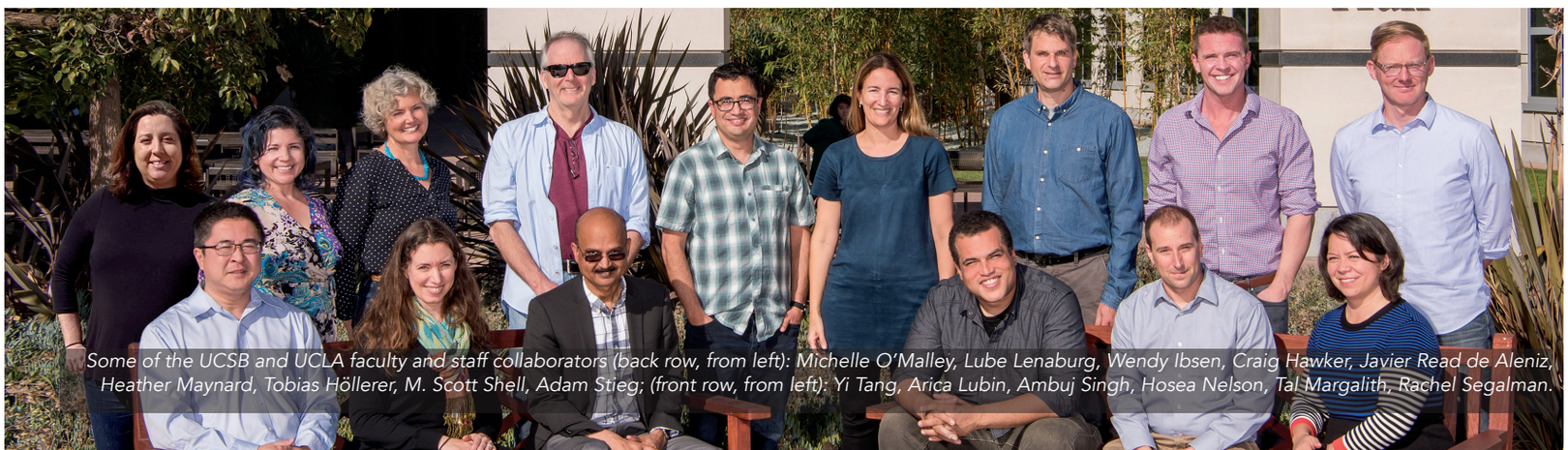
"Our goal is to be the bridge between fundamental and applied research, driving collaboration with industry and establishing Southern California as an economic engine of biomaterials research and innovation," says materials professor **Craig Hawker,** co-PI on the BioPACIFIC MIP and director of the CNSI at UCSB. "It has been our goal for many years to take advantage of our connection with UCLA to land a transformative project such as this."

It is hoped that the BioPACIFIC MIP will support more than a thousand academic researchers and over two hundred companies annually and yield hundreds of peer-reviewed publications each year.

"I see this as a perfect partnership, because UCLA and UCSB have complementary characterization tools and complementary expertise, and when we put them together, we can make a user facility that will be unprecedented in the science it will enable and the services it will provide," said MIP co-director **Heather Maynard,** a UCLA chemistry and biochemistry professor and associate director of the CNSI there.

The collection of expertise at UCSB and UCLA will be coupled with an automated, high-throughput living bioreactor platform and robotic automation to rapidly prepare libraries of bio-based polymer materials. Integration of these platforms with computer modeling and machine learning, as well as user access to a robust facility infrastructure at UCSB and UCLA, will further the process of optimizing plastics derived from living organisms.

The BioPACIFIC MIP will be broken into four sections — In-House Research, External Users, Education, and Knowledge Sharing — while the scientific mission will be organized into four interconnected Elements, each described in one of the following sections.



Some of the UCSB and UCLA faculty and staff collaborators (back row, from left): Michelle O'Malley, Lube Lenaburg, Wendy Ibsen, Craig Hawker, Javier Read de Aleniz, Heather Maynard, Tobias Höllerer, M. Scott Shell, Adam Stieg; (front row, from left): Yi Tang, Arica Lubin, Ambuj Singh, Hosea Nelson, Tal Margalith, Rachel Segalman.

Finding the Bio Building Blocks

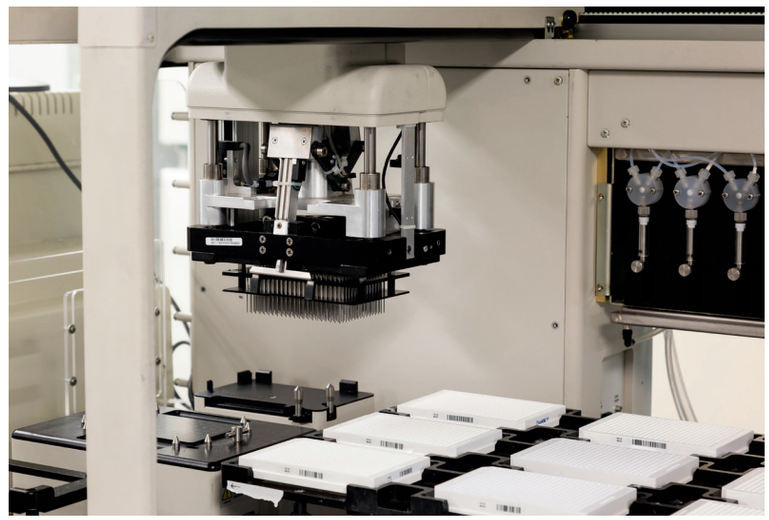
ELEMENT 1:
Synthesis Biology and Living Bioreactors

Synthesis biology lies at the heart of the BioPACIFIC MIP. Researchers in Element 1 will focus on identifying and developing promising biomolecule building blocks and new cell-based polymerization methods. They will explore and expand the chemical space of monomers accessible through synthetic biology and engineer cells to serve as production and polymerization "chassis" for bio-derived polymers.

The group's approach will be to engineer biocompatible polymerization tools in living organisms for the production of biopolymers from renewable feedstock. This will be done with a focus on altering how yeast, fungi, and bacteria use their internal mechanisms to generate building blocks. The engineered organisms can be added to a Materials Library and then screened to determine their potential value as starting systems for an array of new high-performance polymer biomaterials to be developed in Element 2.

"Biology makes a lot of cool little building blocks in the form of molecules, peptides, and proteins, and often, we look at the chemistry of those building blocks and don't know how useful they are," says UCSB chemical engineer **Michelle O'Malley,** who is part of the Element 1 team. "That is mostly because people who have the expertise to make them are often not the people who look at them through the lens of a materials scientist. This effort is bringing people together to make that translation."

"We envision the synthesis biology being fluid, so that people can use both places depending on their priorties," says **Heather Maynard**. "If someone is more interested in synthetic biology, looking at how microorganisms can make certain kind of molecules or monomers and how to characterize them in two and three dimensions, then they'll



An example of the kind of high-throughput system that will allow a substantial acceleration of time-consuming lab-experiment set-up processes.

Artist's concept illustration refers to the BioPACIFIC MIP goal of identifying biological building blocks that can be engineered and assembled to create high-performing polymers.

mostly be at UCLA. If they have monomers already or want to use something from the library to make polymers, they'll be at UCSB."

O'Malley explains that she will be working to build a pipeline to identify organisms that have the potential to make chemically diverse building blocks. She and her Element 1 colleagues will then partner with materials scientists to determine "whether those building blocks are actually worth the time and effort to develop them, perhaps to make polymers, coatings, or maybe even drugs," she says.

At the heart of the Element 1 research will be a high-throughput living bioreactor platform system — that is, a reactor that can change and adapt in its task of producing products made from cells — developed to conduct automated experiments in synthetic biology. Normally, experimental work is exceedingly time consuming. But, as the first user-facility in the nation to link automation and high-throughput experimentation across both synthetic biology and material synthesis for rapid biomaterial discovery and development, BioPACIFIC MIP will reduce lab times dramatically, accelerating the design-build-test-learn (DBTL) cycle from yielding one sample per week to more than five hundred per week.

> "As the first user-friendly facility in the nation to link automation and high-throughput experimentation... BioPACIFIC MIP will reduce lab times dramatically."

Fast Track to New Materials

ELEMENT 2:

Automation speeds the process dramatically

Artist's concept illustration: high-speed research ahead.

"We'll be exploiting BioPACIFIC in two ways," says **Craig Hawker,** co-PI of Element 2 at UCSB. "The first is to take advantage of bacteria and nature's other cellular factories to make existing materials much more efficiently. The second is to exploit nature's ability to prepare complex, multifunctional molecules and direct that machinery to new designer materials, materials that synthetic chemists cannot prepare using traditional techniques."

Using organisms to make new polymeric organisms, he explains, saves researchers from having to produce them under high pressure or at high temperature using toxic chemicals to drive reactions, as is required to make petroleum-based polymers.

"If you go to a major chemical plant, you'll see multiple highly complex systems for each step of the process," says Hawker, who is also the Alan and Ruth Heeger Professor of Interdisciplinary Studies and Clarke Professor. "But, in organisms, nature already takes care of all these separate processes within the same cell. We're trying to make use of that cellular machinery, so that instead of a large, energy-intensive chemical plant that makes, perhaps, a million pounds of a polymer, we'll have hundreds of billions of microbes making a similar, if not a better, polymer much more efficiently — at room temperature, with no toxic chemicals and with little, if any, waste."

Equally important, Hawker notes, is to maintain a careful perspective with regard to scale. "For certain applications, such as polyesters used in packaging, you may need millions of pounds," he says. "For some functionalized materials that may not be used in a bulk setting but as, say, a coating, worldwide production might be only a thousand pounds, so, you can tolerate a smaller yield because it adds such a high value. It's a real Goldilocks kind of calculus for materials design that we are keeping in mind from the get-go."

Like her colleagues in Element 2, **Rachel Segalman,** chair of the Chemical Engineering Department and Edward Noble Kramer Professor at UCSB, will likely find herself working closely with researchers in both Element 1 and Element 2. In her work, she examines how hierarchical polymer structure affects the thermodynamics of self-assembly and macroscopic properties. That fits in Element 1, but she also has significant expertise in producing bioinspired polymers via robotic synthesis, which leans toward Element 2.

Like Element 1, Element 2 will employ a high-throughput system to scale up processes. "We may do ten polymerizations at once in a flow system, so that you set up the system, and it directs the components to the ten different reaction systems, and you get your ten products," says BioPACIFIC MIP co-director and UCSB professor of chemistry and biochemistry **Javier Read de Alaniz,** adding, "We're automating how we do polymer synthesis."

"Right now, a student in my group can carry out about two reactions a day" says UCLA professor and BioPACIFIC MIP co-director **Heather Maynard,** whose expertise lies in the synthesis, characterization, and medical application of biopolymers and bioinspired materials. "With the rapid-throughput system, we'll be able to do fifty to one hundred experimental reactions per day. A student will be able to prepare the number of polymers in a week that had previously taken them more than half a year."

Further, robotic handling and automation of synthetic and purification steps are safer than traditional methods requiring each experiment to be set up by hand, and eliminate user-to-user variability. And, explains Maynard, who earned a master's degree at UCSB, "It allows people who may have an idea for a material but are not polymer chemists to become involved and use the facilities. And if a visiting researcher sees something in the library of monomers and thinks, *I could do something with that,* MIP staff scientists can steer them through the relevant processes."

Element 2 researchers will also be linked forward to Element 3 (computation) and back to Element 1. "We can perhaps figure out ways to use enzymes and proteins to polymerize some of those monomers and then bring these new polymers back to Element 1," says Maynard. "So, maybe we make two hundred polymers and then see which have the properties we want. The computational part will be really important as a feedback. We'll have both, which is why it's so exciting. Experimental science is informed trial and error. It is time-consuming to set up experiments and then await processes to occur that generate results. This allows a massive acceleration of the entire laboratory process."

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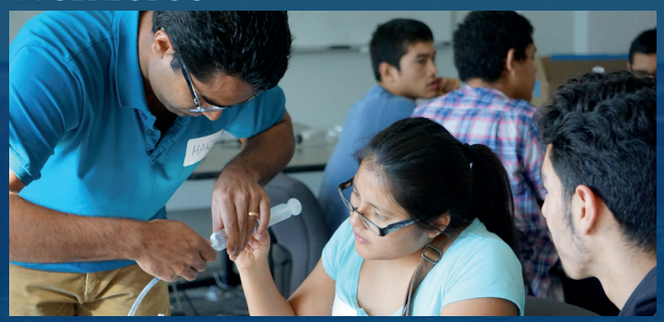
Training the Next-Generation Workforce



An important component of the MIP is to prepare the next generation of scientists and engineers in interdisciplinary biomaterials discovery and high-throughput experimentation, such as that being pioneered in the BioPACFIC MIP. A focus on outreach and fellowships will bring graduate students and postdoctoral scholars into BioPACIFIC MIP facilities to receive training and help drive investigations.

The project team will proactively engage budding researchers who represent California's diversity, with the goal of assembling a cohort in which half the fellows are women and underrepresented minorities. Fellows will have access to a cluster of educational offerings and mentorship opportunities.

One component, a weeklong "summer school" led by experts from industry, academia, and national laboratories, will provide guidance to fellows, facility users, undergraduate and graduate students, and postdoctoral fellows. The school will serve not only as a training ground, but also as a recruitment tool to attract a diverse cohort of users into the MIP.

Currently, a huge training gap exists between academia and industry in terms of training for such high-throughput automated science; industry has invested heavily in automation and big data and has, as a result, a critical need for university graduates who have this experience. The undertaking will involve a multi-pronged approach, but a key element will be to provide training on how to set up and analyze experiments that leverage automation and large data sets.

"A lot of industry would like more training in automation and related skills; they're very interested in it," says MIP co-director and UCLA professor of chemistry and biochemistry **Heather Maynard.** "But in traditional labs you don't get that component, so, this will be an additional tool for broadening their training. Imagine a company being able to hire someone out of university who arrived at work already knowing how to do this without months of training. That would be very valuable to a company."

The training will be coupled with programs to develop students' "soft" skills, such as communication and project management. Overall, the center will provide a clear connection between students' training and their career aspirations, empowering trainees from diverse backgrounds to become the next-generation workforce at the frontier of engineering and science.

Data Narrows the Design Space

ELEMENT 3:

Combining computer simulations and artificial intelligence to explore a vast universe of possibilities

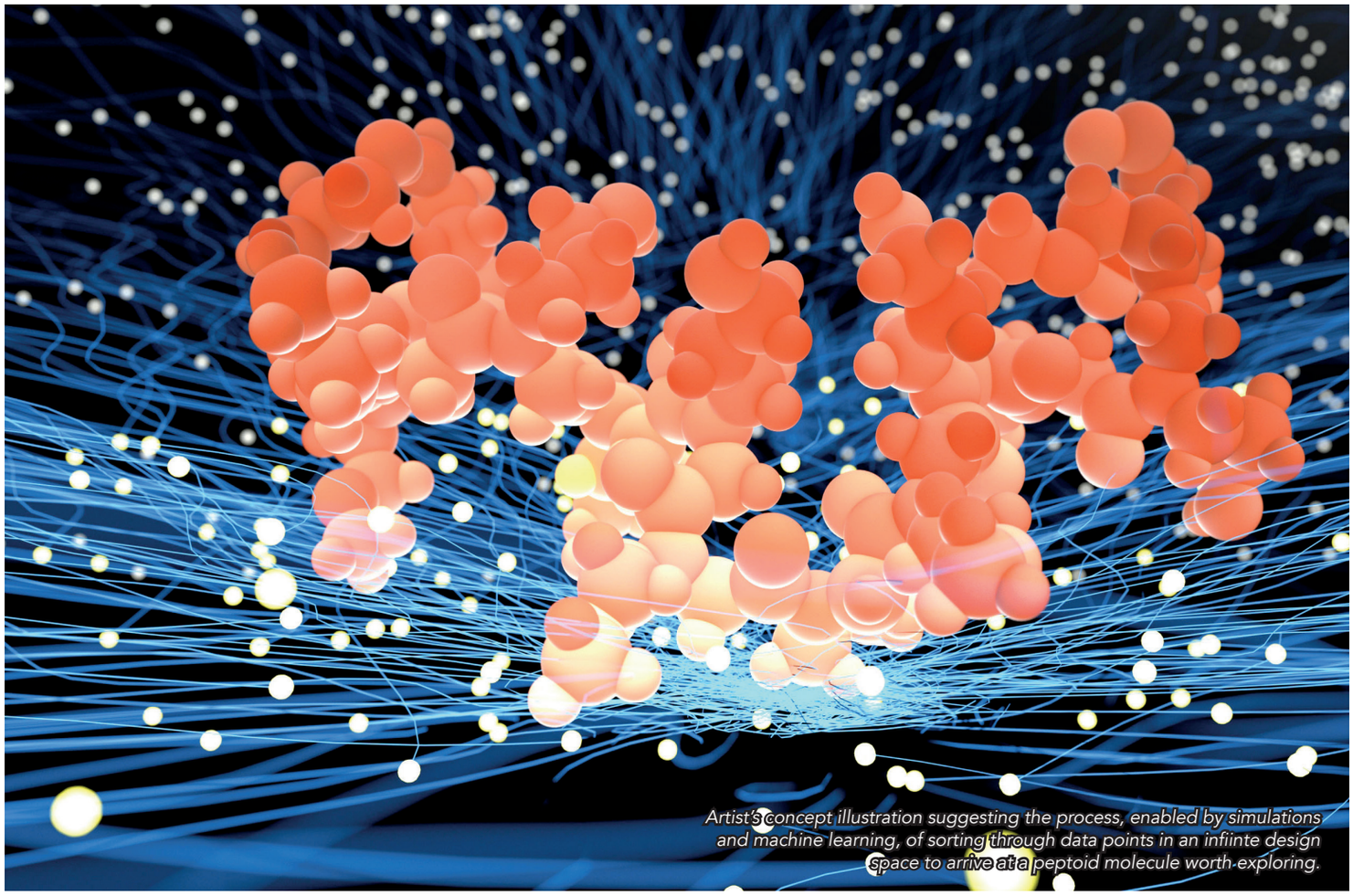
Processing and profiling the properties of new biomaterials — whether they are derived from microorganisms that produce complex building material blocks or are entirely synthetically produced bio-polymers — are time- and labor-intensive processes, and that is without exploring the nearly limitless design space enabled by rapid-throughput development of new bio-molecules. Element 3 researchers will use computational tools, including simulation and machine learning (ML), to characterize new monomers and polymers, improve existing ones, identify and specify desirable material properties, and suggest appropriate chemistries and processes to achieve desired form and function or to improve the effectiveness of the living bioreactors used to produce targeted bio-materials.

Two members of the UC Santa Barbara team — chemical engineering professors **Glenn Fredrickson** and **M. Scott Shell** — have expertise in creating simulations that will be valuable to the project. Fredrickson has developed field-theoretic computer simulation models that enable studies of structure and thermodynamics across a wide range of complex fluids and soft materials at large, supramolecular length and time scales. Shell develops molecular simulation methods for detailed, atomistic-resolution modeling of bio-based and synthetic soft materials, complex interfaces, and water-mediated and hydrophobic interactions that underly many material self-assembly processes. By combining these two approaches to predict properties from the atomistic to macroscopic scales, Fredrickson and Shell provide a powerful framework enabling the MIP to generate molecular insight and predictive materials modeling across scales.

"The high-level role of computational and simulation work as part of BioPACIFIC is to provide guidance to the experimental and synthetic groups as to what to make," Shell says. "Let's say you need a polymer that has this toughness, this refractivity, these kinds of mechanical properties. What should the ingredients be? What should the molecules look like? The idea is to use computations as intelligent ways of exploring the huge range of options and coming up with relationships that allow us to predict, for instance, what the properties will be if we make a particular kind of polymer."

Broadly accessible databases overlaid with machine-learning algorithms using both simulation and experimental data of structure-property relationships will be integrated to help close the design loop, optimize materials design, and provide feedback among explorations of the design space and desirable material properties.

"The challenge in this project is that the design space is huge," says UCSB computer science professor **Ambuj Singh,** who leads the ML effort. "The number of possible molecules is such that there is no



Artist's concept illustration suggesting the process, enabled by simulations and machine learning, of sorting through data points in an infiinte design space to arrive at a peptoid molecule worth exploring.

way to explore the entirety of the possible design space, so, one needs a strategy to probe the most meaningful subspaces. This probing can be based on your own data or on data you have from the public domain. So, the question is, how do you get this data and build the model of this space so that you can try to identify substances that are potentially fruitful and should be probed in order to design new materials?"

To do that, he continues, "You need to be able to probe, you need to be able to store the results of your probing, and you need to store the results of your reactions, so this design is not going to be a one-step process. It's going to be multistep reactions, and each reaction has certain conditions under which it happened. The multistep process makes it much more difficult to explore the design space."

"There are robust techniques that Ambuj and others are working on now that allow you to start organizing, interrelating, and interpreting rich data sets from materials that have interesting measured properties, from a spectrum of different experiments and simulations having slight variations," notes Shell, the Dr. John E. Myers Founder's Chair in Chemical Engineering. "Machine learning is very good at identifying the key factors that are important, as well as making predictive models that allow you to then say 'OK, now if I make this new system, what do I expect for this property?' It's a much more rapid way of exploring the space than can be done using brute-force, expansive simulations alone, since each individual simulation run requires a significant number of compute cycles.

"They're complementary approaches," he adds, "in the sense that our simulations provide a detailed molecular picture that gives a tremendous amount of physical insight into how to think about the interactions that drive the properties of the materials, which machine learning can then use to derive predictive structure-property relationships."

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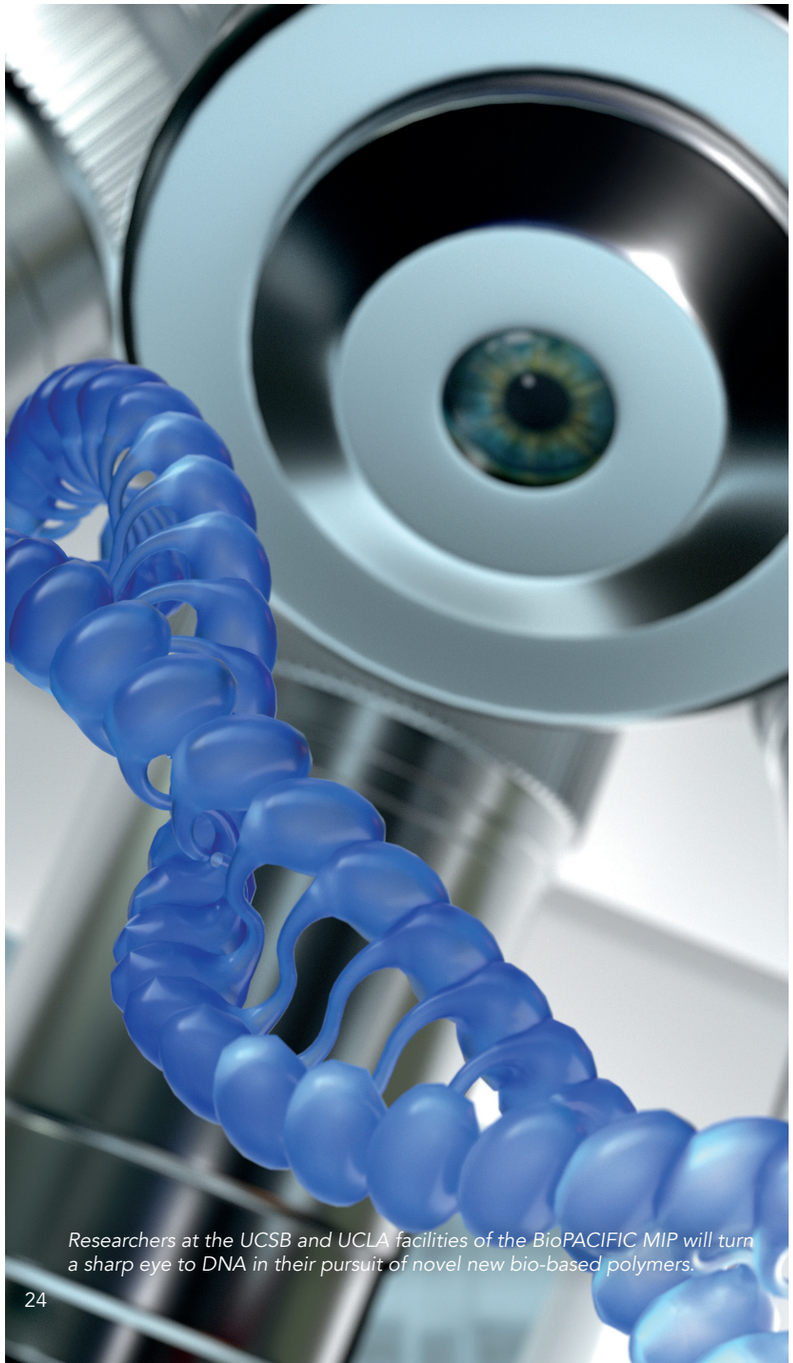
Eye on Application

ELEMENT 4:

Characterizing materials to describe potential and inform future directions



Researchers at the UCSB and UCLA facilities of the BioPACIFIC MIP will turn a sharp eye to DNA in their pursuit of novel new bio-based polymers.

Once new engineered microorganisms, monomers, and polymers are discovered, they need to be characterized to determine whether their chemical structure and resulting properties are as expected or as needed to inform further material development or refinement.

Element 4 researchers will overlap significantly with Elements 1 and 3 "to develop a predictive and mechanistic understanding of how composition influences structure and properties to improve the synthesis and formulation," says UCSB mechanical engineering professor and group lead **Megan Valentine,** an expert in the design, development, and implementation of customized tools for microscale characterization of biological and bio-inspired soft materials using rheology, mechanical testing, and imaging.

Element 4 researcher and UCSB chemistry professor **Songi Han** brings expertise in developing novel techniques in electron paramagnetic, nuclear magnetic resonance, and dynamic nuclear polarization that enable the study of biomolecular structure, dynamics, and interaction with unprecedented sensitivity, resolution, and information content.

"Element 1 folks will be developing processes for making molecules, many of which will be intended for making material," says chemical engineering associate professor **Matthew Helgeson,** a member of Element 4 who brings expertise in the structure and the dynamics of complex soft matter, including biomaterials, surfactants, polymers, and gels. "If someone wants to engineer a molecule or a protein to make something like artificial spider silk, what we envision coming out of that side of the center are literally hundreds of proteins in which ninety-nine percent of the sequence is the same, with small variations here and there to try to make a better material."

The question then, he says is, "How do you screen all those hundreds of proteins for the property that you want? Our expertise in my lab is characterizing the mechanical properties of materials."

Helgeson and his colleagues are developing a rapid-screening tool for microrheology, a process used to examine flow and plasticity characteristics at extremely small scales. UCSB will have a state-of-the-art x-ray scattering instrument for that work, providing an unparalleled fifty-fold increase in speed and sensitivity compared to existing non-synchrotron-based systems.

Another example of new technology is found at UCLA, where researchers are developing a new cryo-electron-microscopy technique called microcrystal-electron diffraction (MicroED). It will enable researchers to take the semi-crystalline form of a bio-derived natural product monomer and generate high-resolution data on its chemical structure within minutes, in contrast to the hours or even days needed to capture the same data using conventional techniques.

"Through BioPACIFIC, we will develop new tooling, new processes, and new materials to meet the needs of diverse applications, with the specific tasks of members evolving as the project progresses," says Valentine. "This adaptation and flexibility set this award apart: through BioPACIFIC, we will develop the infrastructure necessary to tackle many critical questions in biomaterials science, including new questions that weren't envisioned at the outset."

Finally, she notes, "Unlike many of our collaborative grants, which solely support on-campus efforts, BioPACIFIC will focus on building enabling tools and knowledge bases to bolster the biomaterials community across the nation and the world. This is exactly the kind of collaborative, cross-cutting research upon which I built my career, and I am excited to work with scientists and engineers at UCSB, UCLA, and across the nation to advance biomaterials innovation to meet important societal needs."

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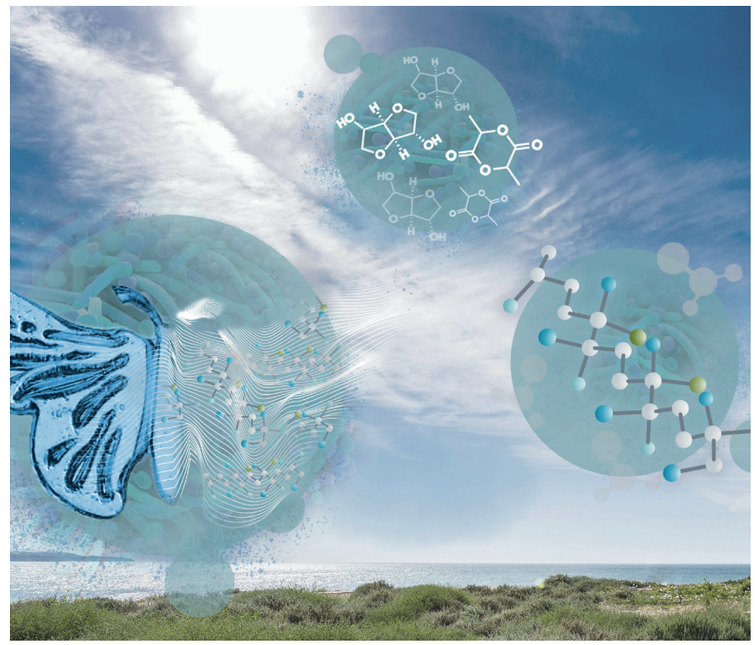
Sharing the Knowledge



Recognizing the importance of collaboration in materials research and the key role of user facilities in allowing the community to access cutting-edge tools, theBioPACIFIC MIP management team, led by executive directors **Tal Margalith** at UCSB and **Adam Stieg** at UCLA, has engaged with a wide range of national centers-of-excellence to design a user facility that avoids reproducing existing infrastructure. This integration is also critical in identifying and implementing best practices in user support, education, and outreach.

While preparing their proposal to NSF, various team members made multi-person visits to the Caltech Center for Catalysis and Chemical Synthesis, the Illinois Biological Foundry for Advanced Biomanufacturing, and the Stanford Nanocenter and Molecular Foundry. Those forays, together with long-standing relationships with such international centers as the Materials Innovation Factory (University of Liverpool), the Center for Integrated Nanotechnologies (Sandia National Laboratories), and the Institute for Complex Molecular Systems (Eindhoven University of Technology) were instrumental in developing the extensively collaborative model that is the foundation of the BioPACIFIC MIP and that will enable it to take a leadership role in the global materials community. A strategic consequence of this network will be the fostering of a culture of truly international knowledge sharing.