BioFrontiers Institute

UNIVERSITY OF COLORADO **BOULDER**

INNOVATION WITHOUT BOUNDARIES:

The Future of Human Health & Welfare

VOLUME I

TRANSFORMATIONAL DISCOVERIES

Dear Friends,

As we continue undaunted in our interdisciplinary exploration of some of the greatest scientific challenges in human health and welfare, we invite you to learn more about how we are pursuing transformational discoveries and educating the science and engineering leaders of the future.

With the support of our generous donors, the University of Colorado, our industry partners, and state and federal funders, our researchers continue to create new knowledge on the frontiers of bioscience. Our thriving community of faculty, postdocs, students and staff remains focused on pursuing collaborations that will lead to new scientific discoveries, new innovations in education, and new start-up companies.

BioFrontiers is experiencing remarkable growth:

- In August of 2017, we celebrated the opening of new BioFrontiers Institute research and active learning facilities, which are located on the second floor of a 56,340 square foot addition to the Jennie Smoly Caruthers Biotechnology Building. These new facilities have also become a hub for CU and non-CU based start-up and established companies, while moving us closer to our vision of promoting increased collaborations among researchers, students, and industry partners.
- We are welcoming five new talented and innovative faculty members who specialize in Computational Biology. Their expertise in developing algorithms and models to better understand various biological systems and relationships is at the leading edge of this field.
- Our prominent faculty members and talented students continue to receive national and international honors and awards that are a testament to the value of our research for the common good.

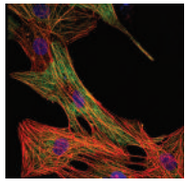
As we look forward to even more success in the future, thank you for your support of our efforts to unlock scientific potential and solve major biological mysteries.

Warm regards,

Thomas R. Cech, Ph.D.
Distinguished Professor, Biochemistry
Investigator, Howard Hughes Medical Institute
Director, BioFrontiers Institute

Leslie Leinwand, Ph.D.
Distinguished Professor, Molecular, Cellular and Developmental Biology
Tom Marsico Chair of Excellence
Chief Scientific Officer, BioFrontiers Institute

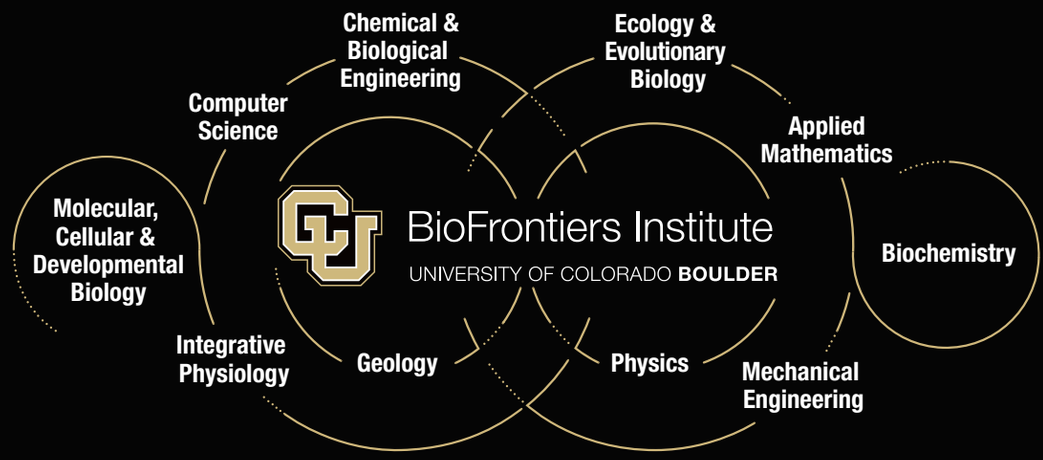
ON THE COVER



Specific disease-inducing mutations can be studied on the molecular and cellular level through a viral expression system. Here, the individual sarcomere bundles of cardiac muscle cells (myocytes) are shown in red. Myocytes expressing the disease-causing protein (shown in green) can be distinguished from those that have not been infected. The nuclei are stained in blue.

Esther Choi | Leinwand Lab, BioFrontiers Institute
Nikon A1R Laser Scanning Confocal
BioFrontiers Institute Advanced Light Microscopy Core Facility

Jennie Smoly Caruthers Biotechnology Building, home of the BioFrontiers Institute: Completed in 2012 and expanded in 2017, the 405,000 square foot Jennie Smoly Caruthers Biotechnology Building was designed to facilitate collaborations between scientists and students from multiple disciplines as they address critical challenges in the biosciences. Generous donors contributed $62 million toward the $206 million cost of the building.



BIOFRONTIERS INSTITUTE:

Integrating Research Across Campus

Our community of **cross-disciplinary scientists and engineers in 10 affiliated departments** are empowered to tackle critical challenges in bioscience through collaborations across academia and industry.

Here, the dissolution of boundaries and resultant sharing of knowledge accelerates discovery and innovation.

TEAMING UP AGAINST DRUG RESISTANCE

Drug resistance is arguably one of the most significant medical challenges of our era, costing millions of lives a year. Antibiotics, once a miracle cure against deadly bacterial infections, have bred antibiotic-resistant bugs that now defy all treatments. Meanwhile, cancers continue to evade even our most advanced treatments and a cure remains elusive. Despite our greatest efforts, these challenges remain beyond the reach of the medical research.

Modern medicine has thus far failed against drug resistance not because our drugs are ineffective, but because a very small fraction of cells can survive these potent treatments. "Rare drug-tolerant cells can survive supra-lethal doses of toxic molecules and appear spontaneously in genetically identical populations," says BioFrontiers' Joel Kralj. These survivor cells drive the resurgence of more aggressive and drug-resistant disease. Yet researchers know very little about them without the tools to identify them from among the masses. Their secrets hold the key to once and for all cure cancers and antibiotic-resistant infections.

Rising to the challenge, BioFrontiers has assembled a dream team of researchers to face off against modern medicine's greatest foe. With their highly innovative and interdisciplinary approach, the team is poised to make headway where others have repeatedly tried and failed. "With experts on the leading edge of four different waves of innovation, we have the convergence of **cutting-edge biotechnology and computational capabilities** required to break new ground," says Liz Bradley. Each team member brings a unique skill-set to the project, wielding powerful new weapons against their formidable opponent.

> "People here can speak many different scientific languages. It is a really big advantage to advance our research." – *Joel Kralj*

Joel Kralj Survivor cells have remained elusive because scientists lack the molecular tools to examine individual cells within living populations—to find the wolves lurking among the sheep. Until now. With innovative molecular biosensors and sophisticated video imaging tools, biologist and physicist Joel Kralj offers unprecedented microscopic surveillance of living cells. **His tools reveal a whole new world** of biology in action, exposing key aspects of cellular dynamics that are lost with traditional biochemical techniques.

Most recently, Joel made the revolutionary discovery that antibiotic resistant bacteria use voltage as a means to sense their environment, similar to mechanisms used by human neurons to relay the sense of touch. Furthermore, these electrical signals play important roles in antibiotic resistance, distinguishing resistant bacteria from their susceptible neighbors. These unique electrical patterns provide a rare clue to resistance mechanisms that might be exploited to target and block resistance. Now Joel aims to investigate whether these unique electrical patterns might reveal survivor cells even before antibiotic treatments, affording a means to target and prevent resistance before it's too late.

In addition, Joel will deploy his arsenal of molecular biosensors to identify novel predictors of bacterial resistance. These may include molecular pathways involved in bacterial transformations like biofilm formation, virulence, and defense against immune attack.

Sabrina Spencer Paralleling Joel's work, biochemist Sabrina Spencer develops similar video surveillance tools for studying human cells, focusing on cancer. Her greatest forte is in programming computers to watch molecular videos and see what the human eye cannot. "A lot of information would be left on the table if we only watched with our own eyes," she says. "We can track and process 30,000 cells per movie run, whereas the current standard in the field is closer to tens of cells. As one of the few labs in the world equipped to do this kind of work, we can see into the molecular world of individual cancer cells like few others can."

With her melanoma pipeline she examines how rare survivor cells emerge from genetically identical populations to seed resistance. "Some research suggests that quiescent, undividing cells may be resistant to drug treatments," she says. Looking for survivor cell 'tells,' she will investigate whether a cell's growth rate might predict its resistance. If so, molecular pathways that control cell division could provide new targets to block cancer relapse.

Since day one Joel and Sabrina forged a synergistic relationship, having joined CU as junior faculty on the same day three years ago. By sharing ideas, algorithms and even students between them, they **accelerate scientific progress** in both of their labs. They are excited to now collaborate on the same biological question for the first time. "We thought, why don't we pool these two diverse topics that are united by a common methodology." says Sabrina.

Dan Larremore After Joel and Sabrina collect microscopy videos, computer scientist Dan Larremore will track down which cells gave rise to resistant lineages. Dan is the perfect man for the job, with dual expertise in microbial resistance and bioinformatics. Dan has honed his applied mathematical skills to track the evolution of the Malaria parasite, which is also notoriously evasive of drug treatments. His experience and computational leadership in this arena will be **invaluable to the mission**. Adapting his computational tools to analyze terabytes of video data, Dan will deconstruct the team's big data into cellular family trees, retracing the roots of resistance. The BioFrontiers High Performance Computing Resources facility, with state-of-the-art data storage and computational clusters, will be crucial to accomplishing this otherwise insurmountable task.

As a newcomer to BioFrontiers and to image processing, Dan is enthusiastic to jump right into the challenge. "The collaboration is a great opportunity to dive in and learn from the very best to grow my expertise. It's a great position to be in," he says. *(Read more about Dan on Pages 10 & 11.)*

Liz Bradley A computer scientist tops off the team with her prowess in **computational geometry and topology**. Her first foray into biological research, Liz has focused on data from other scientific fields, such as astronomy and earth science. She recently drew the connection to biology after hearing that breast cancer cells change shape and motility right before becoming cancerous—which triggered a light bulb in Liz's brain. "It struck me that maybe shape mattered in terms of what a cell is doing, or could do. It got the wheels spinning in my head," she says.

Applying her algorithms to pre-process cell shape, size and movement, Liz will transform the team's complex imaging data into digestible bites for machine learning. Artificial intelligence (AI) will then take the reins, guiding the team to cellular features that serve as red flags for resistance. "We are using machine learning to actually generate scientific hypotheses. Then we can go back and investigate the biology," says Liz.

AI and machine learning offer the team powerful new tools for analyzing dynamic biological processes in the pursuit of drug resistance mechanisms. Pioneering these transformative tools—which remain largely untapped in biomolecular research—will unlock enormous potential against intractable bioscience problems. "As a data scientist, I have a toolbox that can be applied to diverse situations. With this project I saw the opportunity to get a lot of traction on a very real problem with the tools I already have," says Liz. "If the same mathematics works to classify a sunspot that will become dangerous, or a cell that will become pathological or drug-resistant, that's BIG!" she says, "The universality of science is amazing."

A TEAM BORN OF BIOFRONTIERS

The team credits the unique atmosphere of BioFrontiers, with its innovative and cooperative culture, for seeding their **transformative collaboration**. Housing experts across diverse biomolecular and computational disciplines under one roof, BioFrontiers also fosters idea exchange through new programs like grant escape rooms. "We all work on very different things, but sequestered in a room together we came up with this synthesis of unique ideas that we would never have thought of otherwise. It turns out, we came up with something really good, so we thought, well, let's do it!" says Sabrina.

This creativity and drive to take action is a hallmark of BioFrontiers scientists, forming a magical environment where brainstorms become a reality. "As a multidisciplinary institute, people in BioFrontiers are always interested in getting involved in diverse projects," says Joel. He adds that even with the desire, very few teams could pull off such an ambitious goal. BioFrontiers researchers' unique interdisciplinary communication skills will be essential. "People here can speak many different scientific languages—I see this as a really big advantage to advance our research. I can guide my colleagues through my work in their terms, and they have enough interdisciplinary knowledge to extract relevant data and derive new insights," he says.

This creativity and drive to take action is a hallmark of BioFrontiers scientists.

IMPACTING HUMANITY

Interfacing advances in live-cell imaging and machine learning in unprecedented ways, the BioFrontiers team aims to finally unlock the secrets of survivor cells. Their insights will inspire powerful new strategies in the search for a cure against cancers, as well as antibiotic resistance.

"Developing imaging and computational tools to identify new molecular and cellular features of live cells in the context of diabetes, immunology, etc., and having computers make novel biologically relevant hypotheses, would be phenomenal across the board," says Joel. For instance, such tools could crack the code to perplexing neurologic diseases like autism and schizophrenia, by helping to determine how nerves misfire. Ultimately, the project could have widespread impact across all fields of medicine.

BREAKTHROUGHS IN GLOBAL HEALTH

The human papillomavirus (HPV) vaccine was a landmark first in cancer prevention, protecting women against the virus that causes cervical cancers. Yet this life-saving vaccine and many others remain inaccessible to a large part of the developing world due to their high cost and need for refrigeration. Many have tried to overcome these barriers to universal vaccination, but thus far, all have fallen short.

Now BioFrontiers scientist Bob Garcea and collaborator, Ted Randolph, promise to finally **break down these barriers with a fresh, cross-disciplinary approach**. Blending their expertise in virology and chemical engineering, with a dash of ingenuity, they are redesigning low-cost, heat-stable vaccines with unprecedented success. Starting with HPV, their revolutionary vaccine designs could transform vaccine programs worldwide to serve regions that need them most.

Bob Garcea (left) gives Ted Randolph a vial of capsomeres, which Ted's lab will turn into thermostable vaccine powder.

VIROLOGY GURU

Bob Garcea

Bob Garcea has been a transformative force in vaccine development since the 1980s. By studying viral structures, he has discovered new ways to simplify vaccines that drastically reduce their cost and increase their reach. His discovery of virus-like particles (VLPs) led to **next-generation vaccines** that are more affordable and safer than traditional live-attenuated or heat-killed virus vaccines, and have since become the new gold standard in vaccine design.

Now Bob promises to revolutionize vaccines once again with his discovery of viral capsomeres. "You don't need the whole VLP to elicit an immune response," says Bob. "Building blocks of the viral shell, termed capsomeres, are just as good at sensitizing the immune system against HPV." These capsomeres are so simple they can be churned out en masse by bacteria, whereas VLPs require more complex biological production systems that are four times as costly. In addition, complex VLP vaccines are unstable, requiring liquid suspension and refrigeration for preservation. Meanwhile, simple capsomeres are much more stable, lending themselves to a new heat-tolerant formulation.

While Bob had no experience with vaccine formulations himself, he knew someone in a neighboring lab who did. "Our BioFrontiers lab happened to be next to chemical engineers. They come at problems in a very different way than we do. For them, it's about practicality," says Bob. "In particular, Ted Randolph had developed a technique for thermo-stabilizing proteins in powder form."

CHEMICALLY ENGINEERING DRUG FORMULATIONS

Ted Randolph

Ted Randolph specializes in the practical matters of converting molecular discoveries into viable treatments. Biological proteins are notoriously unstable, particularly when exposed to heat. Ted's job is to prevent them from degrading throughout the manufacture, storage, and distribution processes. The stakes are high—any failures can compromise drug safety or efficacy, putting patients' lives at risk.

"Meeting the stringent requirements for chemical and conformational stability during shelf life is a daunting task," says Ted. Exploring how and why proteins go bad, he stabilizes them with chemical engineering solutions. His cutting-edge technique to freeze-dry proteins into powder form has achieved unprecedented heat-stability, enduring temperatures as high as 120 degrees Fahrenheit for 3 to 4 months.

"We brought our capsomeres over to Ted's lab, and his team quickly made thermostable capsomere powders that equaled the ability of the current HPV vaccine to sensitize the immune system," Bob says.

FROM DISCOVERY TO THE REAL-WORLD

Recognizing the revolutionary nature of their breakthrough, and its potential to finally **overcome barriers to universal vaccination**, the duo teamed up with Al Weimer of the Department of Chemical and Biological Engineering in a unique collaboration that secured a $1.1 million grant from the Bill & Melinda Gates Foundation in 2016. The three investigators work in the Jennie Smoly Caruthers Biotechnology Building (JSCBB) at CU Boulder, but their research areas have very different emphases, and the grant has helped them work together and collaborate to translate their discovery into real-world vaccines. “It’s really merging three different people with three different sets of expertise into one project,” Garcea says. Ted adds, “This formulation represents a breakthrough technology previously unattainable for vaccines, allowing for safe and effective distribution wherever needed.”

Bob and Ted also founded the spin-off company VitraVax Inc., turning to CU’s Technology Transfer Office in conjunction with the Innovation Center of the Rockies to get up and running. Offering essential guidance in identifying business drivers, finding equity support and licensing intellectual property, among other new challenges, these resources were instrumental in successfully launching the new venture.

IMPACTING GLOBAL HEALTH

With low-cost, heat-stable vaccines in a single dose, this BioFrontiers inspired team is aiming for the holy grail of vaccination. Their revolution in vaccine design would overcome the barriers to universal vaccination and save millions of lives, particularly in developing nations.

Current disparities in access to HPV vaccination deprive millions of women and men worldwide of this life-saving breakthrough in cancer prevention. “In cancer, an ounce of prevention is worth a pound of cure,” says Bob, explaining that HPV vaccination offers a more realistic strategy to save lives in areas without the resources for cervical cancer screening or treatments.

In addition, the team’s new technique could lead to new, more protective HPV vaccines by lowering R&D costs. “Although a majority of HPV-related cancers result from HPV16 and 18 infections, another 15 different strains can be oncogenic,” Bob says. “Our ability to fight this disease is currently limited by manufacturing and distribution costs as well as the breadth of coverage.”

Beyond HPV, the team is laying the foundation for an entirely new paradigm in vaccinology that could impact all vaccines. “Our decades of work aimed at better HPV vaccines may become more about a process than a product—a way of making many types of vaccines rather than a single vaccine itself,” Bob explains. With their **elegant combination of virology and chemical engineering**, Bob and Ted’s next-generation vaccines have the potential to rewrite the book on disease prevention worldwide. Their admirable work exemplifies the BioFrontiers mission to drive medical advances through innovative cross-disciplinary science.

Ted Randolph (left) and Bob Garcea blend their expertise in virology and chemical engineering, creating low-cost, heat-stable vaccines.

The duo took on the responsibility of translating their discovery into real-world vaccines.

DENVER METRO CHAMBER
LEADERSHIP
FOUNDATION

Each year the Denver Metro Chamber Leadership Foundation sends business and civic leaders on the road for a two-day, one-night “Colorado Experience”, connecting them to big ideas and communities in every corner of the state.

As part of the May 2018 event, nearly three dozen Colorado Experience delegates heard from leaders, faculty, postdoctoral fellows and IQ Biology graduate students, in an afternoon packed with information about the interdisciplinary innovations happening at BioFrontiers.

2018 Colorado Experience participants listen as Anastasia Karabina, a postdoctoral associate in the Leinwand Lab, describes the collaboration between BioFrontiers and Edgewise Therapeutics, a Boulder based start-up biotechnology company. Edgewise is focused on developing novel therapies for diseases involving skeletal muscle.

SECURING THE FUTURE OF BIOSCIENCE

Despite the widespread popularity of "interdisciplinarity" (a major buzz-word in current bioscience research), few programs deliver on its promise. **BioFrontiers' Interdisciplinary Quantative Biology PhD Certificate Program (IQ Biology)** is a rare breed, designed from the ground up to break down academic silos, and foster cross-disciplinary collaboration. This unique program trains the next generation of innovation leaders, laying the foundation for tomorrow's bioscience advances.

Biofrontiers staff join 2018 IQ Biology students to celebrate the receipt of their PhD Certificates: (left to right) Cloe Pogoda, Ryan Langendorf, BioFrontiers Director Tom Cech (rear), Amber McDonnell (staff), David Brazel, Kristin Powell (staff) *Not pictured: students John Nardini and Nora Connor*

To secure the future of the program, BioFrontiers advisory board members *Chris Christoffersen, Ken Hitchner, Jim Linfield*, and *Jeannie Thompson*, along with their families, joined together to fund the Cech-Leinwand Endowed Graduate Fellowship. This diverse group of scientists, entrepreneurs, investors, and legal experts are longtime supporters of BioFrontiers' vision, and they continue to bolster its strength. "The IQ Biology program is an invaluable and indispensable driver of medical breakthroughs benefiting human health. This program is of tremendous value to the University, students, and faculty who are a part of it," says Jeannie.

LAUNCHING A FORWARD-THINKING GRADUATE PROGRAM

The IQ Biology Program was originally launched by a National Science Foundation Integrative Graduate Education and Research Traineeship (IGERT) grant, which provided $3 million over five years. With this funding, Tom Cech, Leslie Leinwand, and BioFrontiers' faculty built a forward-thinking training program. Sustaining and growing the IQ Biology Program requires extensive fundraising efforts. Chris explains, "Programs must be endowed to become independent of the vagaries of politics, etc."

BioFrontiers aims to raise support for ten endowed fellowships for incoming students. These fellowships are essential for attracting top-notch talent and providing the resources to explore scientific frontiers without limitations. This freedom of exploration is a cornerstone of BioFrontiers' success in innovation.

> "It's a hothouse for generating the type of science and scientists who will fertilize medical advances that will revolutionize the way we live." – *Ken Hitchner*

In 2016, the first fellowship was established with a $1 million gift from John Milligan and his wife, Kathryn Bradford-Milligan, in honor of John's PhD mentor, Dr. Olke Uhlenbeck. Following suit in 2017, CU alumnus and advisory board member *Evan Jones* funded a two-year fellowship to begin that fall. Evan explains, "Contributing to an IQ Biology Fellowship is an extraordinary opportunity to affect the lives of emerging professionals. In the future, these students will become key leaders in the life sciences. We are launching the next generation of scientists to catapult us into the future." With the Cech-Leinwand Fellowship, the advisory board hopes to further inspire others to support the cause.

The new fellowship honors Tom and Leslie for their pioneering vision and distinctive brand of leadership. "They have created **a unique environment and culture of collaboration**, which is really hard to do. It's been in the fabric of BioFrontiers since the very beginning, and that's a testament to their leadership, values, and personalities," says Jim.

TRAINING TOMORROW'S BIOSCIENCE LEADERS

For students aiming to forge new frontiers in bioscience, the IQ Biology program is the perfect launching pad, says Jeannie. The unique interdisciplinary training will set IQ Biology graduates up for success. "Whereas most graduate programs silo emerging scientists, stifling their creativity and training them for a very narrowly focused career, the IQ Biology Program is a very unique model that gives students the freedom and breadth to tackle big ideas and big problems during their training and throughout their careers," says Evan. With this foundation, Jim notes, "IQ Biology graduates will rise to leadership positions in both academia and industry thanks to their breadth of skills." IQ Biology alumni build biotech companies, become professors, and receive prestigious postdoctoral fellowships in varied research areas.

In academic realms, their skills in bridging diverse disciplines will provide the insight to solve today's greatest medical challenges. "Their knowledge of other fields and how they interact will lead them to innovative paths that others can't see," says Chris. Jim adds, "It's rare to find a solution to a complex problem within a single discipline." Trained to harness the power of computational sciences to assess biological systems, they will make breakthroughs against leading killers like cancer, and cardiovascular and infectious diseases. "Basic research here touches the most significant health concerns of today, with the potential to help hundreds of millions of people worldwide," says Jim.

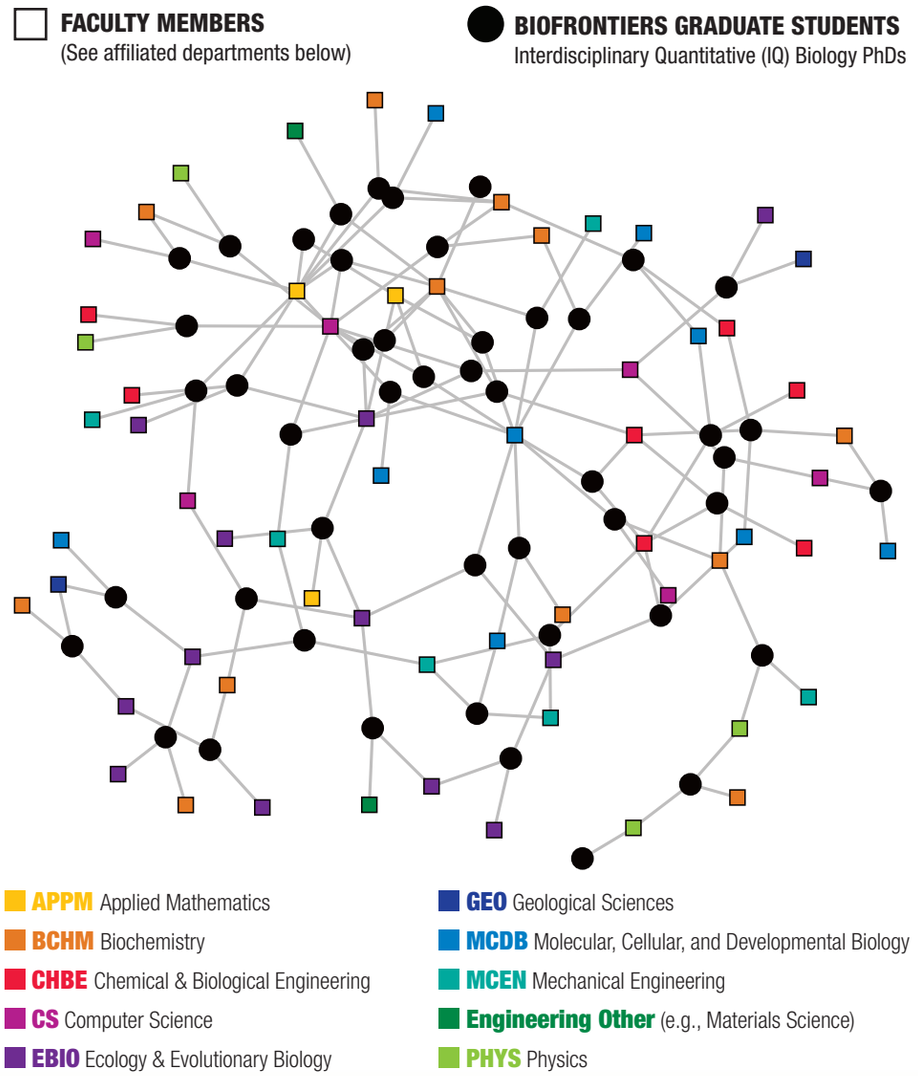
IQ Biology students are also well prepared for diverse aspects of translational science. With mentors like Tom Cech, Leslie Leinwand, and many others on the BioFrontiers team, students learn from the best how to turn discoveries into impactful commercial ventures. "Ultimately to make a difference to people's health, you have to develop a product and take it to market," says Jim. Exposing students to industry operations and opportunities early on trains them to think big picture, and develop translational skills. "Those with interdisciplinary training rise to industry leadership because they see a broader picture. Their interest and knowledge of a wide range of topics, including clinical trial design, patent law, and finance, is extremely valuable for effective senior management," says Jim.

By ingraining interdisciplinary thinking and skills to traverse public and private sectors early, **IQ Biology is educating a new breed of scientists with translational muscle**. "BioFrontiers understands the need to integrate education with commercial development in order to optimize medical progress," says Ken. "It's a hothouse for generating the type of science and scientists who will fertilize medical advances that will revolutionize the way we live." Ken, Jim, Jeannie, and Chris all agree the program has pioneered a unique and essential niche in training that yields not only groundbreaking medical advances but seeds the future of bioscience research. "These students will invent the next set of revolutionary techniques and tools that will drive bioscience forward," says Chris.

IQ Biology Academic Collaborations

The **IQ Biology PhD Certificate Program** attracts talented, diverse, and curious students who conduct research representing three different scientific and engineering disciplines druing their first year rotations. Student exposure to such a rich variety of team-based, interdisciplinary research is rare among U.S.-based scientific PhD programs, especially in the formative first year.

This visualization depicts the academic collaborations between IQ Biology PhD students and the faculty from their affiliated academic departments.



VISION TO REALITY

JOURNEY FROM

Joey Azofeifa came to CU Boulder looking for a challenge. While he applied to many top notch biology programs, the IQ Biology Program spoke to him as the only place he could challenge himself and gain new perspective by delving into a completely new field—computational biology. "IQ Biology brings people in from diverse backgrounds and invests in them. They really took a chance on me and bridged across departments to train me and get me where I wanted to go," says Joey.

The chance paid off, as Joey threw himself into computational studies and interdisciplinary research that **bridged genomics and machine learning** in ways that had never been done before.

Choosing **Robin Dowell** as his mentor, Joey emulated her interdisciplinary research style. "Robin really embodies interdisciplinary science. She asks her own questions, not what the field dictates. She combines disciplines in novel and interesting ways that open up new directions in bioscience. That's the kind of scientist I wanted to be," says Joey. Robin gave Joey the freedom to explore his own path under her tutelage, which took him to the fringes of bioscience knowledge. "By combining fields I pushed myself so far out into the frontier that there wasn't anyone else out there to help me. I grew a lot because I had to figure it out on my own. That's the biggest challenge of interdisciplinary science," says Joey.

Joey credits his peers in the IQ Biology community for helping him develop the mental fortitude, courage and persistence required to navigate the unknown and work through challenges to succeed as an interdisciplinary scientist. This intrepid crew from diverse backgrounds bonded over **tackling unexplored intersections of science together**. Working side by side, they developed the essential communication skills to bridge disciplines that will serve them throughout their careers.

Joey partnered with **Tim Read**, his roommate, who was a wet lab biologist PhD candidate also in Robin's lab. As yin and yang, the duo **built off each other's vastly different knowledge to forge a new frontier** in RNA biology. Examining genomic read-outs called enhancer RNA (eRNA), Tim honed state-of-the-art RNA sequencing assays while Joey built the mathematical modeling and machine learning tools required to decipher the genomic data. Their combined approach brought new perspective to the field. "Before we came along the field was dominated by geneticists, so it was easy for us to make a big impact with new computational tools. The payoff was huge," says Joey. With their innovative approach, they transformed a sea of previously undecipherable genomic data into a goldmine of crucial information for drug development.

Joey Azofeifa (left), 2017 IQ Biology PhD graduate, and his mentor, Robin Dowell, see a bright future using computational biology to solve bioscience challenges.

"Glad to see this is happening in our state."
Daisy Rocha Vasquez, Denver Metro Chamber of Commerce, Colorado Experience Tour Participant

With their innovative approach, they transformed a sea of previously undecipherable genomic data into a goldmine of crucial information for drug development.

Specifically, their platform pinpoints a drug's mechanism of action by distinguishing primary drug targets from aftereffects that can obscure the message. This is priceless information for pharmaceutical companies, which waste millions of dollars and years of R&D on drug candidates that ultimately fail due to misunderstood mechanisms.

> "We realized we had this groundbreaking technology and we wanted to use it for good." – *Joey Azofeifa*

The new insights afforded by Joey's work will help companies choose the right drug candidates to pursue, and which diseases and patient populations to target for success. Overall the platform will accelerate the development of better drugs with fewer side effects at a fraction of the cost.

And so, Arpeggio Biosciences was born. The name resonated with Joey and Tim as musicians: "The eRNA signatures we decipher are like discrete ordered chords that run through the genome and flesh it out. It is the profile, not a single note, that says something interesting," says Joey. Arpeggio truly symbolizes the IQ Biology spirit, Joey explains, because its value lies in the combined approach of **employing mathematical tools to derive meaning from biological data**.

They teamed with **Daniel Weaver**, Boulder scientist and inventor, whose business expertise and connections helped to make their vision a reality. Arpeggio will tackle its first real world oncology pipeline this year with FORMA Therapeutics. Focusing first on cancer drugs, Arpeggio is poised to solve diverse bioscience challenges with its highly adaptable platform. Working from both biological and computational sides gives Arpeggio the dynamic flexibility and nimble approach that sets them up for success in today's rapidly changing research and technology landscape.

ARPEGGIO
BIOSCIENCES

Joey suggests Arpeggio may be particularly insightful against infectious disease, and BioFrontiers may provide a crucial partner in this arena with faculty member Bob Garcea, virology expert and co-founder of the vaccine development company, VitraVax, Inc. Such collaborations will come easily as Arpeggio moves into the new BioFrontiers Hub space, strengthening its bond with the CU community that spawned it. The Hub space will provide the community and resources Arpeggio needs to thrive as a new start-up. With established laboratory equipment and computational services, Arpeggio will hit the ground running in their new, yet familiar, home. "BioFrontiers has been my home for the last 7 years. It's where this journey began, and it only feels right to continue to grow here among our CU friends and family," says Joey.

Interdisciplinary Bioscience Innovation and Discovery (ibid.) Initiative

While many universities are providing space for companies on their campuses, few of them are integrating industrial research alongside academic research in the same building. With Boulder's national reputation for fostering both entrepreneurship and scientific excellence, and the BioFrontiers Institute's ability to integrate the two, CU is uniquely positioned to be a leader in academic-industry research interface.

Currently, five start-up and established biotechnology companies lease offices and research labs adjacent to BioFrontiers researchers. These industry partnerships facilitate the translation of discoveries into leading-edge tools, strategies, and therapeutics. To advance discovery and learning, and to drive the useful application of ideas, entrepreneurship, and economic growth, BioFrontiers plans to construct a first-of-its-kind facility that will promote increased collaborations among researchers, students, and industry partners.

NURTURING A CULTURE OF COLLABORATION

As part of a focused effort to expand the BioFrontiers Institute's research portfolio in Computational Biology, five new faculty were recently recruited. Dan Larremore and John Rinn came on board in Fall 2017, and Orit Peleg arrived in Spring 2018. Ed Choung and Ryan Layer will arrive in Fall 2018 (Stay tuned!). With advances in technology that are providing researchers with vast quantities of biological data to manage and interpret, their expertise and ability to converse in more than one scientific discipline will help identify useful information in large sets of unsorted, disorderly data.

HUNTING FOR TREASURES IN RNA BIOLOGY

John Rinn

"To run your best, you have to run with the best," says John Rinn of his decision to leave his tenured position at Harvard to join the BioFrontiers team last year. John had a booming career in Boston, where he **pioneered innovative genetic techniques to study RNA biology**, but wanted to change the course of his career by moving to CU Boulder. "Everything was perfect back East, but I just could not resist this feeling in my gut that progress would be made here and not there," says John.

John felt a growing gravitational pull towards CU Boulder after visiting for the GoldLab Symposium five years ago. For an RNA biologist, CU Boulder is the Mecca where the field got its start. "Being here is like working in the coliseum of RNA, where all these groundbreaking discoveries were made. You get to soak in that je ne sais quoi of the place, and it really focuses your mind," says John. Indeed, RNA has been an elusive target for biologists who have attempted to uncover its biological functions and mechanisms. Of the few breakthroughs that have been made, CU Boulder has historically led the way with a powerhouse team of RNA researchers spearheaded by Tom Cech, who won the Nobel Prize in 1989 for his discovery of RNA's catalytic functions. John knew he needed to learn from the best if he wanted to unravel the mysteries of RNA biology and expose its roles in disease. "Marv Caruthers, Olke Uhlenbeck, Art Pardi, and the rest of the CU Boulder team are like the Jedis of RNA biology—and I am a little Padawan apprentice. My ideas get shaped through interactions with these master craftsmen, and get a special crafting that you couldn't get anywhere else in the world," he says.

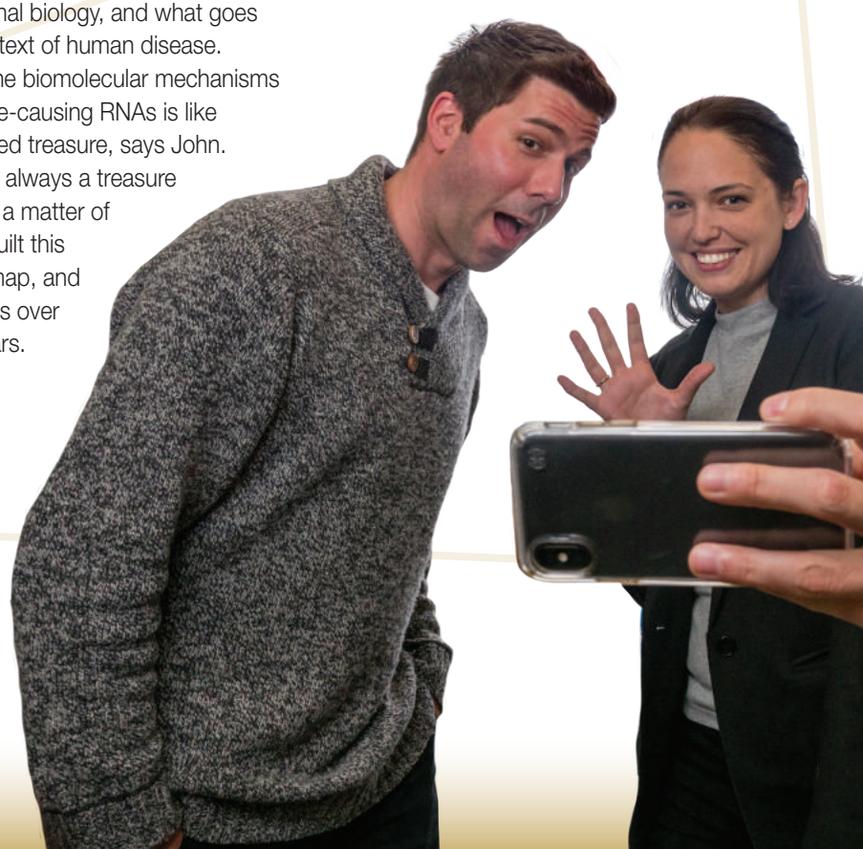
John has his sights set on exposing the functions of two RNA targets in particular. The first, nicknamed "FIRRE," causes inherited epilepsy in patients with dysfunctional copies of the gene. The second, called "TUG1," causes infertility in males. John spent years identifying these targets from among tens of thousands of potential RNA targets in the human genome whose functions remain unknown. To do so required the invention of novel bioinformatic and genetic techniques that have transformed the field.

Now John aims to write the next chapter in his career by exposing how these RNAs function in normal biology, and what goes awry in the context of human disease. Searching for the biomolecular mechanisms of these disease-causing RNAs is like hunting for buried treasure, says John. "There's almost always a treasure in RNA, it's just a matter of finding it. I've built this RNA treasure map, and located a few Xs over the last few years. I moved here for the tools to dig into those Xs," he says. "Now I can't wait to dig in and see what we find!"

QUEEN BEE OF BIOLOGICAL SYSTEMS

Orit Peleg

Orit Peleg is busy as a bee building her new hive at BioFrontiers, literally. This physicist/computer scientist-turned-biologist studies bee swarms, and how the individual behavior of each insect contributes to the collective wellbeing of the whole colony. "I'm interested



"As an alumnus, it was really cool to see the adaptability of the University to migrate to a world class research environment."
Tonya Kaye, ANB Bank, Colorado Experience Tour Participant

in fundamentals of biology that dictate how local rules for individuals achieve global stability in larger groups," she says.

Originally, Orit studied these fundamentals on the microscopic level, examining how the physics of molecular interactions contributed to protein assemblies within biological materials and polymers. Then she started thinking big picture: "In my mind there was a very clear connection between biological structure and function on a small and large scale," says Orit. Indeed, she finds many similarities between honeybee population dynamics and cellular dynamics within tissues, which she hopes to explore further with BioFrontier's Associate Director Kristi Anseth. By working with bees, she aims to inform molecular and cellular dynamics that are fundamental to cancer, Alzheimer's, and many other diseases.

All of these biological systems are comprised of individual components that sense and integrate environmental signals, Orit explains. Their **interactions with their neighbors create a whole that is much more than the sum of its parts**, much like BioFrontiers itself. "The way organisms (and molecules) interact is basically a network," says Orit, enthusiastic that BioFrontiers' network experts like Dan Larremore and Aaron Clauset will bring exciting new insights to her work. In addition, Orit plans to explore applications to swarm robotics with her home department of computer science. These applications could inform the engineering of next-generation "smart" technologies like self-driving cars, search-and-rescue drone squads, or self-stabilizing construction materials that adapt to withstand hurricane-force winds or earthquakes.

TACKLING HEALTH ISSUES FROM NEW ANGLES

Dan Larremore

BioFrontiers welcomes home alumnus, Dan Larremore, who earned his PhD in Applied Mathematics from CU Boulder in 2012. After pursuing training in genetic epidemiology at the Harvard T.H. Chan School of Public Health, he returns with the skills to tackle bioscience and global health challenges from new computational angles.

Capturing the collaborative spirit of BioFrontiers: (left to right) John Rinn, Orit Peleg and Dan Larremore

> "This building is remarkable. I love the fact that my students are sharing a space and mixing with both computer scientists and molecular biologists."
>
> *– Dan Larremore*

Dan's mission is to crack the case against malaria, a mysterious parasite that has evaded humanity's greatest efforts to control it. To curb this continuing global health crisis will require new tools and approaches that combine the fields of genetics, epidemiology, mathematics and experimental biology in novel ways. "These parasites constantly bob and weave to avoid detection. How they do this on a population level is not exclusively within a realm of only genetic epidemiology, math or biology, but falls right in the middle. BioFrontiers is the kind of place where that kind of work is not only tolerated, but encouraged," says Dan. Working with partners in Senegal to procure samples from the heart of the epidemic, Dan will combine cutting-edge genetic sequencing technologies with novel computational algorithms to reveal how these dangerous parasites evolve around immune defenses and drug treatments.

The dynamic intersection of disciplines at BioFrontiers will be critical to Dan's success. He cites the unique atmosphere of the BioFrontiers building, with its unencumbered exchange between groups of diverse expertise, as a major driver for new ideas and innovation that will propel his work forward. "This building is remarkable. I love the fact that my students are sharing a space and mixing with both computer scientists and molecular biologists. There is a community growing here completely separate from anything I work on," says Dan, adding that **tangential conversations often circle back to yield breakthroughs both within and outside of his own research**.

VISIONARY ENTREPRENEURS

Innovative faculty make their mark

As recognition of their pioneering advances in biotechnology, the National Academy of Inventors (NAI) has welcomed five BioFrontiers faculty to its ranks in the last three years. Marvin Caruthers and Larry Gold now join their colleagues Leslie Leinwand (2016), Christopher Bowman (2016), and Kristi Anseth (2015) in this exclusive club.

These distinguished faculty are recognized not only for their leadership in forging new frontiers in biosciences, but also for their noteworthy impacts on quality of life, economic development and welfare of society. All of these BioFrontiers trailblazers have a prolific spirit of discovery, innovation and entrepreneurship that drives them. Implementing their inventions in creative ways to solve real-world problems, they have generated dozens of patents and built numerous biotechnology powerhouses that have transformed the landscape of bioscience research and treatments.

"As exciting as the Big Bang."
Paul Lhevine, Swallow Hill Music, Colorado Experience Tour Participant

Marvin Caruthers

Pioneering discoveries in DNA and RNA biochemistry, Marv Caruthers leveraged his insights to develop automated DNA synthesis techniques. These technologies have made bioscience what it is today, by enabling modern genetic analysis techniques. From DNA sequencing, to genome mapping and everything in between, Marv gave researchers the tools required to understand the genetic material that underlies all life.

With the explosion of genetic research tools, the pace of bioscience advances has accelerated exponentially. By laying the foundation for these technologies, Marv has empowered academic and industry researchers alike to explore the basis of human health and disease. In doing so, **his discoveries facilitated innumerable scientific and clinical advances** across all fields of medicine. From the Human Genome Project to next-generation cancer treatments and personalized medicine approaches, Marv's work has a hand in it all. Now, making similar advances in RNA synthesis, he promises to continue to unravel this new class of biochemical messages that orchestrate biology and disease processes.

> "My career is devoted to developing new approaches for solving important biological problems using synthetic DNA, RNA, and their analogs."
>
> *– Marv Caruthers*

As co-founder of Amgen and Applied Biosystems, Marv has deployed his inventions to break new ground against bioscience challenges and push the boundaries of biosciences. "My career is devoted to developing new approaches for solving important biological problems using synthetic DNA, RNA, and their analogs," he says. Among the many honors for his lifetime of achievements, he has received the National Medal of Science, the National Academy of Sciences (NAS) Award for Chemistry in Service to Society, and is an NAS member.

Larry Gold

Larry Gold has called CU Boulder home since the 1970s when he struck out on a career path that has taken him to the frontiers of biotechnology and beyond. At a time when the mysteries of DNA and RNA were just beginning to be unraveled, Larry opened the world's eyes to whole new dimensions. While the world of these molecules was assumed to be flat, Larry demonstrated that world was in fact round. Discovering that these linear strands folded into complex 3D structures, he exposed biological roles far beyond the genetic messages for which they were known.

With this revelation, Larry and his graduate student Craig Tuerk—who Larry says "did the work"—envisioned manipulating and designing these structures, which he called "aptamers," for bioscience purposes. "We imagined a future in which RNAs were shapes, not tapes," says Larry. Turning his dream into a reality, Larry spent the rest of his career developing innovative technologies to shape RNA and DNA into tools for medical discovery. Founding biotechnology companies NeXstar and SomaLogic, he channeled his academic discoveries into pioneering medical advances that have had widespread impact.

Developing libraries of synthetic "aptamers" to bind cellular proteins, Larry generated high-throughput screens for biomarker and drug discovery. These biochips have proven instrumental in studying, diagnosing, and finding treatments for diverse diseases, from cancers to bacterial infections. They have even led to new classes of drugs against untreatable illnesses, including NeXagen's own Macugen. A first in treating blindness, Macugen binds to and blocks proteins that cause macular degeneration.

> "We imagined a future in which RNAs were shapes, not tapes."
>
> *– Larry Gold*

Even now, Larry continues to dream up new directions. "The future of aptamers is limited only by our imaginations, as is always the case. Already they are used for proteomics, cell sorting, pathology, affinity purification, and pharmaceuticals. And this is just the beginning." he says. To drive further innovations, he has created the GoldLab Foundation, which **aims to solve today's healthcare challenges by leveraging biotechnology advances in inventive ways.**

Larry's visionary career has earned him an impressive collection of accolades. A member of the National Academy of Sciences, he has also received Merit and Career Development Awards from the National Institutes of Health and the Lifetime Achievement Award and Chiron Prize for Biotechnology from the Colorado BioScience Association.

Biotechnology building debuts state-of-the-art E-Wing

As Boulder's biotech community continues to thrive and grow, the Jennie Smoly Caruthers Biotechnology Building debuted its state-of-the-art E-Wing in August of 2017.

The 56,340-square-foot E-Wing features next-generation active learning spaces where students learn by doing rather than by being lectured, as well as laboratory space where current and future faculty in the BioFrontiers Institute and the Department of Chemical and Biological Engineering will be able to continue their groundbreaking interdisciplinary research.

The ribbon-cutting event honored Colorado-based philanthropists John and Anna Sie, whose generous $2 million gift allows for the creation of an industry co-location space on the E-Wing's second floor. The space will be leased to industry partners, allowing local and national biotech companies to bring scientists and resources on-site in order to work side-by-side with university students and researchers.

CU Boulder Chancellor Philip DiStefano, Tom Cech, Nobel laureate and director of the BioFrontiers Institute, and Leslie Leinwand, chief scientific officer for the BioFrontiers Institute, officially opened the Yuan Yung-Foo Interdisciplinary Bioscience Research Neighborhood with members of the Sie family during a celebration that included BioFrontiers donors, friends, faculty and staff.

"The Sies, whose philanthropic generosity is well known in the state of Colorado and around the world, have provided stalwart support for the BioFrontiers Institute for many years and in many ways," said Cech, a Distinguished Professor of Biochemistry at CU Boulder, and a Nobel laureate. "We are truly grateful for their most recent commitment to providing much-needed research facilities where our talented researchers, students and industry partners work together to unravel the complexities of biology with an ultimate goal of enhancing human health and welfare."

"Anna and John are among CU's most generous donors—their gifts are always transformational," DiStefano said. "With their support, we are achieving our vision to become a leader in addressing the humanitarian, social and technological challenges of the 21st century."

Adapted from an 8/31/17 article by Trent Knoss

August 2017 saw the debut of the state-of-the-art E-wing in the Jennie Smoly Caruthers Biotechnology Building. Participating in the ribbon cutting are (left to right) Michelle Sie Whitten, Chancellor Philip DiStefano, John Sie, Anna Sie, Leslie Leinwand and Tom Cech.

AWARDS & RECOGNITION

PhD & POSTDOCTORAL AWARDS & FELLOWSHIPS

GRADUATE STUDENTS

Kelsie Anson and Lara Janiszewski
– Palmer lab
National Science Foundation (NSF) Graduate Research Fellowships

These prestigious fellowships recognize and support outstanding graduate students in NSF-supported science, technology, engineering, and mathematics disciplines who are pursuing research-based master's and doctoral degrees at accredited United States institutions.

> "It's been a wild ride getting into science. I really love it, and I would like to use this fellowship as a springboard to not only advance my career, but also use any publicity I can to advance other scientists."
>
> *– Giancarlo Bruni*

Giancarlo Bruni
– Kralj Lab
Howard Hughes Medical Institute (HHMI) Gilliam Fellowship

The Gilliam Fellowships for Advanced Study support exceptional graduate students who are committed to increasing diversity among scientific leaders, especially those students who will go on to become faculty members at colleges and universities.

Tova Christiansen
– Anseth and Leinwand labs
The American Heart Association (AHA) Pre-Doctoral Fellowship

To enhance the integrated research and clinical training of promising students who are matriculated in pre-doctoral or clinical health professional degree training programs and who intend careers as scientists, physician-scientists or other clinician-scientists, or related careers aimed at improving global cardiovascular health.

Scott Nordstrom
– Melbourne Lab
Evan & Cynthia Jones Fellowship

This fellowship, established by BioFrontiers Institute Advisory Board member Evan Jones and his wife Cynthia, provides funding to promising IQ Biology students.

Daniel Ramirez
– Dowell Lab
Consejo Nacional de Ciencia y Technologia (CONACYT) *National Council of Science and Technology* 5 Year Graduate Fellowship

CONACYT awards fellowships to Mexican nationals, so they may pursue graduate studies in quality scientific research areas. It is Mexico's equivalent of NSF.

Ignacio Tripodi
– Dowell Lab/Hunter Lab
Olke C. Uhlenbeck Graduate Fellowship

The fellowship is established in honor of CU Professor Emeritus Olke C. Uhlenbeck. Dr. Uhlenbeck is a longstanding contributor to RNA biochemistry. His group has shown many important findings, as well as developed important tools for RNA biochemists.

POSTDOCS

Claudia Crocini
– Leinwand Lab
The International Human Frontiers Science Program, Long-Term and Cross-Disciplinary Fellowship (HFSP)

HFSP postdoctoral fellowships encourage early career scientists to broaden their research skills by moving into new areas of study while working in a new country.

Emily Feldman and Cody Warren
– Sawyer lab
National Institutes of Health (NIH) NRSA Postdoctoral Fellowships

The goal of this program is to prepare qualified predoctoral and/or postdoctoral trainees for careers that have a significant impact on the health-related research needs of the nation. The award is named after Ruth L. Kirschstein, who was an icon at the National Institutes of Health (NIH), and who worked on the polio vaccine.

Stephanie Moon
– Parker Lab
Zach Poss
– Old Lab
Sie Postdoctoral Fellowship Program

In affiliation with the Linda Crnic Institute for Down Syndrome at CU's Anschutz Medical Campus, the Sie Fellowship Program funds postdoctoral researchers, and occasionally early-career research assistant professors, who focus on research that will improve the lives of individuals with Down syndrome.

Jens Schmidt
– Cech Lab
Damon Runyon-Dale F. Frey Award for Breakthrough Scientists

The Damon Runyon Fellowship identifies the nation's top Postdoctoral Fellows with potential to become a leader in the field of cancer research.

BIOFRONTIERS FACULTY AWARDS

Mary Ann Allen awarded continued funding by the Sie Postdoctoral Fellowship Program

In recognition of her exceptional work as a Sie Fellow, Mary Ann Allen was awarded further funding for her transition to become a BioFrontiers faculty member, focusing on research that will improve the lives of individuals with Down syndrome.

Edward Chuong (top) **and John Rinn among the first recipients of the prestigious Marvin H. Caruthers Endowed Chair**

Marv Caruthers is a world-renowned chemist, a distinguished professor at CU Boulder, and a biotech giant. In the 1970's Marv developed methods for synthesizing oligonucleotides by solid-phase chemistry, which gave birth to the biotech industry and the human genome project, among other advances.

Inspired by Marv's accomplishments and continued vision, several of his previous students and colleagues endowed these Chairs in his honor. Their hope, and ours, is to attract and support the very best young BioFrontiers faculty using interdisciplinary approaches to solve today's most challenging bioscience and biomedical problems.

Sara Sawyer awarded Innovative Seed Grant to pursue a machine learning approach for predicting cellular targets of the dengue virus

Using a grant from the CU Research & Innovation Office (RIO), Sara Sawyer combines methods from bioinformatics, genomics, and evolutionary theory to investigate emerging human and animal viruses.

DISTINGUISHED CAREER AWARDS

Tom Cech receives CU Boulder's Hazel Barnes Prize

University of Colorado Boulder Distinguished Professor Tom Cech, Colorado's first Nobel Prize winner, has been named the 2017 Hazel Barnes Prize winner – the most distinguished award a faculty member can receive from the university.

"Tom Cech is one of the leading scientists in the world and has been for many years," said Chancellor Philip P. DiStefano. "Equally important is his commitment to teaching. Over the years, he has trained and mentored thousands of undergraduates and graduate students, some of whom are now world-renowned scientists themselves. We are truly honored to have Professor Cech, one of our five Nobel Laureates, working among us."

The Hazel Barnes Prize is awarded to a CU Boulder faculty member who best exemplifies the enriching interrelationship between teaching and research, and whose work has had a significant impact on students, faculty, colleagues and the university.

Leslie Leinwand is CU Boulder's first ever recipient of the American Heart Association's annual Distinguished Scientist award.

This prestigious award recognizes significant, original and sustained scientific contributions to the field of heart research.

Leinwand is also a member of the American Academy of Arts and Sciences, a National Academy of Inventors fellow, and helped found the intercampus University of Colorado Cardiovascular Institute (which integrates cardiovascular research, treatment and discovery across the Anschutz Medical and Boulder campuses). Leinwand attributes much of her success to the interdisciplinary focus at CU Boulder, and at the BioFrontiers Institute in particular.

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Marvin H. Caruthers Endowed Chair for Early-Career Faculty

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August 2018 | HF/CC

SCIENCE IS FUN! As part of BioFrontiers Professor John Rinn's biochemistry class, graduate students perform an RNA-splicing interpretive dance on the west lawn of the Jennie Smoly Caruthers Biotech Building. CU Nobel Laureate and BioFrontiers Director Tom Cech (in the tie-dye T-shirt) played the starring role of the catalytic G, since he discovered and won the Nobel Prize for it. Balloons represent different parts of genes. Here students wear purple for exons (and there are green balloons for introns).

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James and Catherine Patten Endowed Chair
Clinical Professor of Restorative Dentistry
Co-Director of the NSF I/UCRC for Fundamentals and Applications and Photopolymerizations
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MECHANICAL ENGINEERING

Meredith Betterton
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PHYSICS

David Bortz
Associate Professor
APPLIED MATHEMATICS

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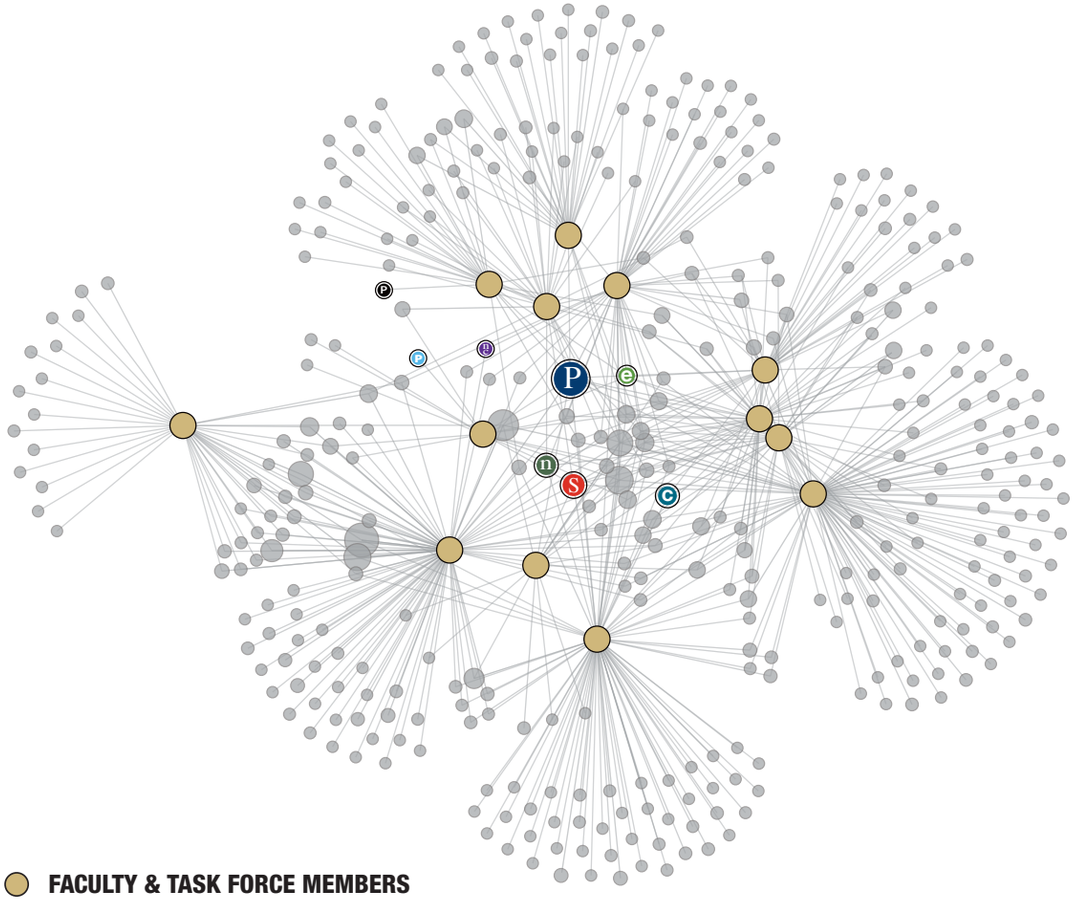
Assistant Professor
BIOCHEMISTRY

Alexis Templeton
Associate Professor
GEOLOGICAL SCIENCES

BioFrontiers Faculty & Task Force Members

ACADEMIC PUBLICATIONS

The breadth and depth of research at BioFrontiers is represented by a wide spectrum of journal publications. The gray circles are journals, with size correlating to Impact Factor (IF) of the publication. Publications with the highest IF are listed below with the number of articles indicated in parentheses.



FACULTY & TASK FORCE MEMBERS
Does not include new faculty

- *Proceedings of the National Academy of Sciences of the United States of America* (37)
- *Science* (18)
- *Nature* (14)
- *Cell* (13)
- *eLife* (9)
- *Nature Chemistry* (4)
- *Physical Review Letters* (2)
- *Public Library of Science* (2)

BioFrontiers Institute

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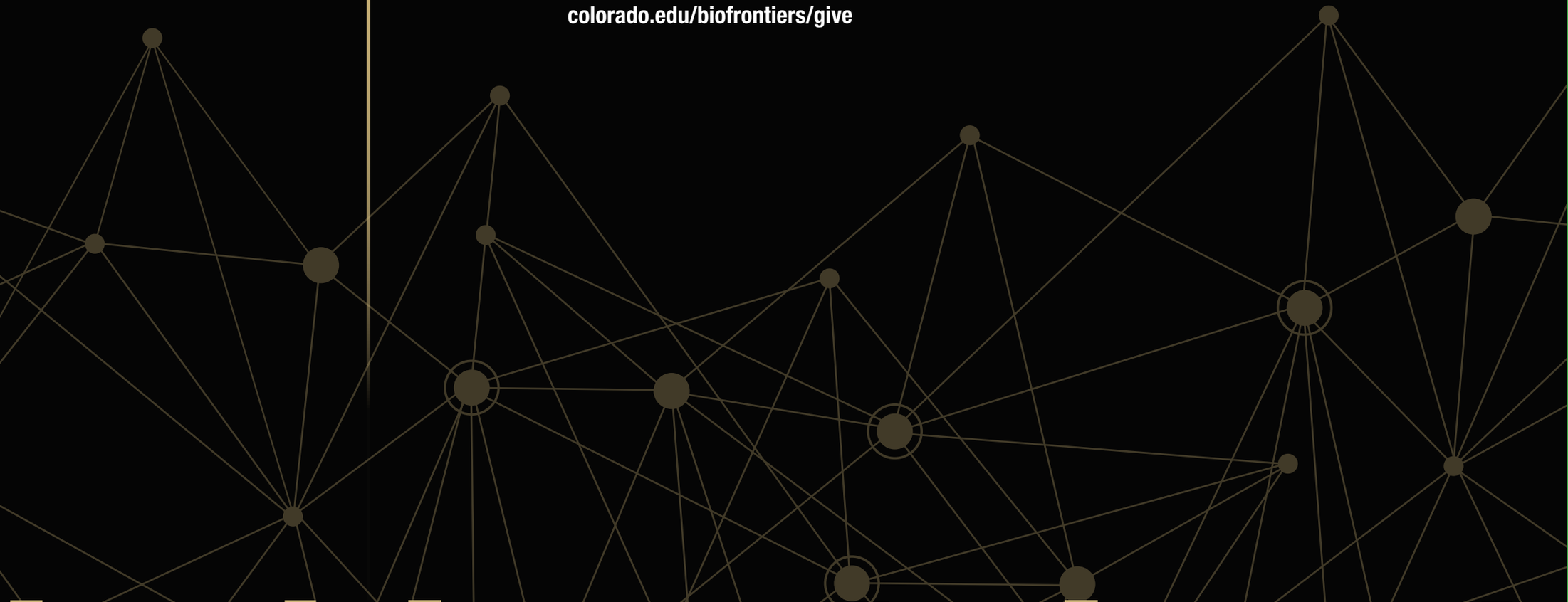

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