

UNDERSTANDING THE RULES OF LIFE: PREDICTING PHENOTYPE (UROL)

URoL Funding (Dollars in Millions)			
	FY 2019 Actual	FY 2020 (TBD)	FY 2021 Request
Stewardship Activities (BIO)	\$30.00	-	\$30.00
Foundational Activities	\$108.24	-	\$109.26
BIO	58.80	-	57.00
CISE	7.66	-	4.75
ENG	5.63	-	2.85
GEO	4.00	-	3.80
MPS	27.30	-	37.06
SBE	4.85	-	3.80
Total	\$138.24	-	\$139.26

Overview

The URoL NSF Big Idea aims to create a new paradigm at the convergence of science, engineering, and technology that will elucidate theoretical frameworks, or rules, to enable prediction of the diversity of solutions that biological systems use to support life processes. Advances in understanding life at the fundamental level of the genome will enable re-engineering of cells, organisms, and ecosystems, and innovative biochemicals and biomaterials that sustain a vibrant bioeconomy and strengthen society. URoL also aims to train the next generation of researchers capable of using those rules and theories not only to predict the behavior of living systems, but to design them to benefit humankind.

Associated with URoL, NSF funds convergent research across the Foundation that addresses questions from the molecular to the ecosystem scale, and across biological diversity. These include foundational research on genetic variation and phenotypic emergence; the ethical and social implications and societal acceptance of new biotechnologies, such as tools for genetic engineering and synthetic biology; ecological forecasting; and machine learning to predict phenotype. In addition, in FY 2021, NSF will fund new awards in mathematical and physical sciences that utilize theory and novel experimental tools to address fundamental problems in biological systems and build capacity in a convergent research domain; new programs in synthetic biology that enable creation of novel chemicals, materials, and engineered systems; and infrastructure that further enables URoL research. These associated activities align with the Administration's R&D budgetary priorities and are expected to continue in FY 2022.

In FY 2018, NSF released several Dear Colleague Letters to announce URoL opportunities for catalytic activities. Building on those, in FY 2019, NSF made 38 new awards for 14 collaborative projects in response to two Foundation-wide URoL solicitations: *Understanding the Rules of Life: Building a Synthetic Cell: An Ideas Lab Activity*¹ and *Understanding the Rules of Life: Epigenetics*.² The awards, totaling \$36 million, demonstrate NSF's commitment to applying interdisciplinary approaches to uncovering the rules, and their exceptions, that govern the essential features of life at all scales, from cells to ecosystems. In FY 2020 NSF anticipates funding projects in response to the re-issued *Understanding the Rules of Life: Epigenetics* solicitation, and in response to a new NSF-wide solicitation, *Understanding the Rules of Life: Microbiome Theory and Mechanisms*.³ Also in FY 2020, NSF will invite proposals for research networks to build

¹ www.nsf.gov/funding/pgm_summ.jsp?pims_id=505600

² www.nsf.gov/funding/pgm_summ.jsp?pims_id=505582

³ www.nsf.gov/funding/prgm_summ.jsp?pims_id=505694

capacity in URoL research domains. NSF anticipates that URoL will run through FY 2023.

Goals

1. To support a convergence of science, engineering, and technology in discovery of rules governing the emergence of robust, resilient, and adaptable phenotypes at three levels of biological organization, across the tree of life: (1) cells and cell systems; (2) multi-cellular organisms and their co-dependent microbial associations; and (3) complex networks of organisms and species involving social, ecological, and population dynamics. These rule sets are referred to as, respectively, minimal rules, interaction rules, and complexity rules. Understanding the rules at these three different scales should enable the prediction of the behavior of living systems and how those systems interact with, respond to, and modify the environment, and will facilitate the engineering of biological systems and enable new forms of bio-manufacturing that are ethically sound, societally acceptable, and that can benefit humankind.
2. To support the discovery of scale-invariant rules that govern living systems. These theories will begin to explain the existence of a diversity of solutions that biology creates and uses to solve the essential problems of living systems at all scales: maintenance and transmission of information (genome); capture and conversion of raw materials to make biochemicals and biomaterials that make up a living system; capture and conversion of energy to support all life processes; and reproduction to perpetuate the species. These universal, scale-invariant rules will serve to help improve human health and safety (e.g., agricultural adaptability, food safety, environmental sustainability, and disease prevention).
3. To support networks of researchers, technology developers, and educators engaged in URoL activities and thereby further the development of a robust community, with an impact that is sustained beyond the five-year investment in the URoL Big Idea. The convergent nature of research addressing emergent properties of life should stimulate technological innovation that feeds back to drive the science forward. This includes development of: new and improved techniques in molecular, genomic, and cellular examination and manipulation; improved technologies for the capture of biological, behavioral, and social phenotypic data in free-living organisms, including new sensors and observing capabilities from nano- to macro-spatial and temporal scales; advances in data analysis, such as machine learning, as well as computation and complex modeling to support learning and simulation-driven URoL investigations; more capable cyberinfrastructure to support robust, data- and computational-enabled URoL discovery and sharing of research results; and advances in theory coming from all of these sciences and engineering. The predictive goals of URoL also guide investments in training and workforce development to produce scientists that have a firm grounding in the life sciences as well as the mathematical, physical, computational, behavioral and/or social sciences and engineering that enable them to work collaboratively across disciplinary boundaries. Finally, URoL provides a rich context in which to expand science-literacy efforts, in both formal and informal learning environments, aimed at diverse communities across the nation. Research networks provide a mechanism for sustained support of distributed groups of investigators working to achieve URoL goals.

FY 2021 Investments

URoL activities in FY 2021 will build upon the investments made in FY 2019 and FY 2020. The FY 2020 solicitation supporting microbiome research will continue in FY 2021, enabling deeper exploration of interaction rules (Goal 1). A new solicitation will be developed to support research that addresses convergence approaches for the discovery of scale-invariant rules that govern living systems (Goal 2). The URoL: Research Networks solicitation that will be released in FY 2020 will also continue in FY 2021, supporting networks of researchers, technology developers, and educators in different URoL domains (Goal 3). URoL-associated activities include continued support of convergent programs initiated in FY 2019 and planned for FY 2021 across all directorates, most of which address Goals 1 and 3.