Department of Neuroscience
Strategic Research Plan 2022

A. History of the Department of Neuroscience
The current Department of Neuroscience evolved from a successful independent research entity, the Arizona Research Laboratories Division of Neurobiology (ARLDN), which was founded in 1985 and led by current National Academy of Sciences member John Hildebrand. At the time of the transition from a research unit to an academic department (2010), the unit had a total of 15 tenure-track faculty, 3 research faculty and three full time technical staff with probably as many as 12 postdoctoral researchers distributed amongst its different PIs.

To illuminate the kind of funding that can be generated by a well populated and pro-active faculty engaged in basic neuroscience research, the following examples from the period circa 1990 until today may be illustrative:

1. Successive and highly competitive collaborative NIH Program Project Grants, awarded for a period of 10 years total. These grants provided research funds totaling more than $10 million for 5 faculty, four of whom obtained their own additional NIH RO1 funding in parallel. Other faculty not in the program, but whose research reciprocally benefitted from it, were funded consecutively for 4 years or longer.
2. A second example involved RO1 NIH, NSF, and DD grants that from 1989-2010 amounted to US$ 8.5 million. Comparable rates of extramural support were achieved by at least 4 faculty during that period. All faculty during that time were engaged in basic research on non-vertebrate systems.

These data illustrate the significant extramural funding that can be generated by a relatively small group of highly active research faculty, which share intellectual goals and maximize their efforts in collaborative research programs. Since the transition, the department's academic personnel declined to just twelve: three assistant professors (one with a shared appointment), two associate professors, five full professors, a lecturer, and an associate research scientist. Currently, only seven faculty generate extramural funding. Thus, we are presently without the critical mass that could enable copious extramural support.

Our immediate strategic goals are (1) to recreate a vibrant research community with shared research goals by adding new faculty in strategic areas of contemporary neuroscience, and (2) to build on the existing strengths of our department to attract substantial extramural funding for collaborative ventures within the College of Science and across the university.

B. Current Strengths and Challenges
The Department of Neuroscience has a long history of foundational discoveries in neurobiology, with a focus on understanding mechanisms of the brain and integrating them with behavior. Our department employs a broad approach using various models to separate species specializations from generalized brain function to allow us to uncover canonical rules by which the brain develops, functions, and maintains flexibility. The department's research spans diverse levels of inquiry, from genes to neurons, from neurons to circuits, and ultimately to the level of behavior. One premise for this approach is clear: advancements in understanding and treating human neurological and neuropsychiatric disorders cannot be achieved without basic research that seeks to understand the underlying ground rules of how brains process and use the information from the world around them. This integrative, multidisciplinary approach sets us apart from other neuroscience departments. Moreover, understanding the integrative activity of the brain is one of

the stated priorities of federal funding agencies such as the NIH, NSF, and DoD – agencies that currently fund a wide variety of projects in the department.

The department is currently in a period of transition, with multiple faculty members retiring soon. We see this as an opportunity to retool the department, and to expand our approach to neuroscience research while continuing to focus on understanding fundamental brain mechanisms. Contemporary neuroscience is driven by a rapid technological advancement combined with rigorous basic science, a synergy already exploited in our department for big data molecular approaches analyzing gene expression profiles, multi-unit recordings of neuronal activity, opto- and neurogenetics, cutting edge microscopy for both live imaging of neural activity and whole-brain imaging for phylogenetic reconstruction, and wireless devices for stimulating neurons and recording their activity in freely behaving animals. Through this combined, multi-level approach to neuroscience, the department covers a wide breadth of topics and has a broad foundation that will continue to serve the department's research and teaching missions well.

Research in the department includes the following fields of neuroscience: neurogenetics, molecular and cellular neuroscience, neuronal circuitry and computational properties of the brain, and brain evolution. Many faculty have research programs that integrate several of these areas. Because of this breadth, the faculty currently collaborate throughout the university, including within the College of Science (the Departments of Ecology and Evolutionary Biology, Molecular and Cellular Biology, Psychology, Speech, Language and Hearing Sciences). In addition, we collaborate with faculty in the Colleges of Agriculture and Life Sciences (Animal and Comparative Biomedical Sciences, Entomology), Engineering (Biomedical Engineering), Medicine (Neurology, Pharmacology, Physiology) at the University of Arizona Health Sciences (UAHS), the Center for Innovation in Brain Sciences, the College of Optical Sciences, and the BIO5 Institute. These collaborations have led to interdisciplinary grants that connect our department to a diversity of departments across campus, and also enable national and international collaborations.

The immediate goal for the next phase of our departmental trajectory is to recruit faculty who further expand our scientific horizon while maintaining and strengthening our emphasis on basic research. The resulting transformative and translational research is generated by diverse perspectives and collaborations, both within the neuroscience community and across disciplines. We are in a fortunate position: the current diversity of neuroscience research in the department serves as a broad foundation on which to connect with other scientists. With the hire of a new department head this year, and further faculty as current members retire, we are well poised to begin a stimulating phase of our research that further intertwines our own programs while establishing new connections across the university.

C. Vision

We have divided our departmental vision into two primary areas of focus. The rationale and vision for these foci are described in the subsections below.

Vision 1 – Transformative Discovery in Neuroscience based on Comparative Approaches

At its inception, all researchers in the Department of Neuroscience (including its years as the ARLDN dating back to 1985) had insects as their common denominator. Within this realm, the focus was comparative, each lab using species particularly well-suited to address their respective research questions. As a group, the department covered major topics in Neuroscience: sensory processing (visual and olfactory), central brain functions (learning and memory, higher order cognition), motor/movement control, synaptic function and plasticity. The research questions were addressed at different and often integrated levels: molecular / subcellular (synapses, neurotransmitters and neuromodulators), cellular (structure and function of neurons or glia), anatomy and physiology of brain compartments, control of animal behavior, brain development, and brain evolution.

With our continuing historical strength in the study of invertebrate brains at all levels, there are opportunities to leverage allied strengths with the Departments of Ecology and Evolutionary Biology (EEB) and Entomology to develop collaborative proposals that would lead to transformative discovery in contemporary invertebrate neuroscience (and beyond). These directions would be primarily funded by the National Science Foundation (NSF) and would match proposed foci of EEB and Entomology. Foci would include:

(1) Brain Evolution (synergy with EEB focus on "Evolution of Complex Systems" and MCB). Research topics of primary interest are how regional specialization of brains originated, and why certain evolutionary lineages evolved stunningly divergent organization yet perform at similar levels of sentience. For example, one topic of primary interest addresses whether networks of coordinated gene expression, crucial for partitioning the brain into functional regions and in establishing proper neural circuits, are a result of convergent evolution or common origins. We will deploy comparisons across a broad spectrum of taxa elucidate whether the organization and computations of diverse brains follow the same structural/functional logic. Current faculty in the Department of Neuroscience would be able to deploy a broad palette of strategies, from comparative neuromorphology and circuit analysis, to high resolution imaging and spatial gene expression profiling to provide a compelling multidisciplinary research program suitable for large-scale National Science Foundation support.

(2) Pest Control and Disease Vectors (synergy with Entomology and EEB; UA “Grand Challenges” pillar). Insects are by far the most important agricultural pests as well as significant human disease vectors. Most insecticides interfere with the function of nervous systems to eradicate insects or to modify their behavior (e.g., mosquitoes not approaching humans). As disease vectors are an extremely relevant topic in the current era, and because of our expertise in analyzing the nervous systems and behavior of insects and those that predate upon them (bats), we are uniquely poised for timely collaborations that will attract significant investment from both NSF (agricultural focus) and also likely from NIH (disease vector focus).

(3) Microbe-Brain-Behavior Axis (synergy with School of Plant Sciences (CALS) and with Neurology (UAHS)): Another exciting area of future investigation may include an evaluation of how the behavior of animals is modified by environmental exposure to fungi and other pathogens. As we learn to navigate a world in which we are increasingly aware of emerging pathogens, studies of how they influence animal behavior are ripe for investigation, and we believe our department is a nexus for such cross-disciplinary research. Examples of possible avenues of research include:

- Parasitic fungi that can control insect brains and manipulate their behavior.
- The protozoan species Toxoplasma gondii, which infects the human brain, contains enzymes that can make dopamine, a neurotransmitter influencing impulsivity and also implicated in Schizophrenia.
- The parasitic tapeworm Taenia solium, which can infect the human brain and cause neurocysticercosis, a disease that can result in premature death.

Cross-departmental collaborative proposals will be submitted to the NSF IOS (Division of Integrative Organismal Systems) Core Program, spanning the Developmental Systems, Neural Systems, and Behavioral Systems clusters. Research involving fungi and pathogens would also be likely to attract support from the USDA.

Vision 2 – Neuroscience that Identifies the Roots of Disease

In Neuroscience, as in many biological sciences fields, genomics has opened a window into the complexity of the cells making up the brain and ensuring its function. The regulation of gene expression in neurons and glia governs every aspect of their capabilities. New technologies such as single cell RNA sequencing, genetically targeted labeling of newly synthesized proteins, and spatial genomics (transcript identification from defined regions of the brain) enable detailed understanding of baseline states and their transitions into diseases of development, cognition, or degeneration. In addition, genomics allows the study of diseases originating from many coordinating mutations, as it is the case for complex diseases. The Department of Neuroscience's vision is to facilitate and/or lead intra- and extramural collaborative teams focused on understanding the genomic and/or epigenomic roots of disease in gene networks as well as homeostatic regulatory gene networks that evolved to counter disease.

We specifically envision joint ventures with campus work being done in understanding the aging brain (collaborations with Psychology, McKnight Brain Institute), degenerative disorders such as ALS and Parkinson's Disease (collaborations with MCB, Neurology, and Pharmacology/Center for Innovation in Brain Science (CIBS)), and cognitive, eating, and anxiety disorders (collaborations with CIBS, Pharmacology, Optical Sciences). We also foresee collaborations with the Department of Computer Science, the Center for Biomedical Informatics and Statistics (UAHS) and Research Computing (RII) to jointly accomplish the informatics, statistical evaluation and programming necessary to analyze genomic and high-throughput data. Our Departmental expertise in neurogenetics and genomics puts us in the position to have a substantial impact on these collaborative ventures, which would attract significant funding from the National Institutes of Health (please see appendix). Areas of focus are expanded upon below.

1) <u>The Aging Brain in Health and Disease:</u> As we approach our senior years, cognitive abilities can be negatively altered, even among those that are not diagnosed with clinical dementia. To understand the backdrop upon which age-related changes are occurring, the department offers collaborations to take a neurogenomic view of this process. Together with research on functional and behavioral human brain changes done by faculty in Psychology, the department can employ its genetic and genomic expertise to identify genomic signatures of the aging brain, experimentally perturb these signatures and investigate the affected neural circuits in animal models such as birds, mice, and flies.

2) <u>Sensory, Motor, Eating and Degenerative Disorders</u>: To understand the root of such disorders, the department is actively studying the basic mechanisms underlying the function of sensory, motor, and eating systems as well as mechanisms preventing and/or causing neurodegeneration at the molecular, cellular, systems and/or behavioral level using various species including mice, bats, songbirds, and flies. The expertise of the department includes genetic approaches to manipulate genes and thereby all or selected cells; immunohistochemical, biochemical, genomic and proteomic approaches to analyze gene and/or cellular function; optogenetic approaches to manipulate selected neurons and/or glia; electrophysiological and imaging approaches to analyze the function

of neurons or glia individually on the level of single circuit, or a neuronal network (Bhattacharya, Cai, Miller, Strausfeld, Wohlgemuth, Zinsmaier). Our collective expertise will provide a foundation for collaborative grants with others on campus using orthogonal toolsets and expertise (MCB, CBC, Neurology, Psychology, Physiology, Pharmacology, CIBS). Such a multi-faceted approach is poised to attract significant NIH funding in the form of Multi-PI or Project-level grants.

3) <u>Behavioral and Cognitive Function and their Complex Disorders</u> (synergy with EEB focus on "Integrative Comparative Organismal Systems" and Psychology foci on "Healthy Mind" and "Healthy Brain"): It is widely recognized that health conditions involving changes in emotion, thinking or behavior (or a combination of these) has roots in genetic changes that can be inherited and/or in epigenetic changes that occur in response to environmental factors including stress. Linking behavior to the function of specific brain regions is a significant strength of the department. We envision to achieve a better understanding of how neural circuit wiring and firing drives behavior in diverse systems establishing the logic used by more complex circuits including human brains. Using our collective expertise, we aim to collaboratively study genomic and epigenomic contributors to various dysfunctions, including cognitive, mood, and anxiety disorders, from the molecular/cellular level to the circuit and network level. As stated above, the department is at a unique nexus for these studies because we can model human diseases in tractable animal models.

D. Current and Future Collaborative Directions

Building upon the historical research expertise in our department, the addition of four new tenure-track faculty between 2014-2020 (Miller, Cai, Bhattacharya, Wohlgemuth) has led to an exciting expansion of our research expertise and thematic foci of mechanisms facilitating cognition-linked motor control, vocalization, itch, degeneration, eating behavior, anxiety, development, and aging (many of these are studied in health and disease conditions). Here, we describe how existing faculty have leveraged extradepartmental collaborations and university core resources to advance their research programs in areas covering sensor-motor systems driving behavior, aging, disease including neurodegeneration, technological advances, and brain evolution. Please see the table attached at the end of this document highlighting current intramural and extramural collaborations (*Appendix 1*).

<u>Anticipated Funding for Collaborative Directions: (please see Appendix 2 for details of funding calls)</u>

Federal funding agencies (National Institutes of Health - NIH, National Science Foundation - NSF) are enthusiastic about basic neuroscience investigations as evidenced by funding opportunities (see Appendix) for team-based multidisciplinary grants that investigate brain circuits and networks driving behavior using innovative methods. With future investment to support pilot studies providing proof of principle for the feasibility of new multi-disciplinary studies and/or to develop new methodological tools, such as wireless brain implant devices, we will be well positioned to accomplish our vision of cross-disciplinary discovery.

The new university initiative on “Innovations in Healthy Aging” offers an exciting opportunity for our faculty to provide important experimental insight into basic brain mechanisms affected with aging. We foresee productive collaborations with math and computer science departments, Psychology, MCB, BIO5, the Evelyn F. McKnight Brain Institute, and Center for Innovation in Brain Science to approach questions in the aging field.
Our facilities provide excellent support for this work, including RII and other cores (University Genetic Core, Proteomics Core, High-Performance Computing). Pioneering studies involving large genomic, proteomic,

epigenomic, electrophysiological, neural imaging, and behavioral datasets are attractive to funding agencies. If supported in expanding our current cohort of departmental faculty with computing and bioinformatics experience, we will be able to take advantage of these timely funding calls in "big-data" approaches in aging research as well as many other areas.

E. Faculty Hires to Support the Strategic Research Plan and Further Departmental Excellence

Need for Growth. The Department of Neuroscience has always been a small but interactive group of faculty working together on essential questions of contemporary Neuroscience. While a small group can be an asset in certain scenarios, the faculty pool of the department needs to grow **a)** to support the growing in-person and online teaching missions, and **b)** to strengthen and expand the existing research expertise to ensure that the outlined vision of the department will be achieved. With the impending retirement of several faculty in 2022 and 2023, the department is currently at a crossroad and facing a contraction instead of an expansion. Accordingly, execution of this strategic plan will require significant investment in new faculty to rejuvenate and expand the department in multiple steps:

Recruitment of a New Head of Department. The department is well underway in its search for a new Head, which is an integrated part of this strategic plan.

Strategic Replacement of Retiring Faculty. Two tenure-track hires are essential to replace faculty retiring in 2022-2023. The new hires will be in research areas of the current focus and vision.

Expansion in Key Collaborative Areas. Five additional tenure-track faculty hires in the Neuroscience Department will tie into our vision and enhance competitiveness for large collaborative awards from NIH, NSF, and DOD. In combination with the strategic replacement of retiring faculty, this will bring 7 total new faculty into the department.

Based on our vision, the multiple hires will include the following research topics:

- **Neural Circuits underlying Sensory - Motor Integration (two hires).** These new faculty will complement and expand our strength in the analysis of neural circuits that coordinate the translation of sensory input cues into appropriate motor outputs and behavior. We foresee that these hires will use vertebrate systems that are already in use in the department to maximize collaborative potential.
- **Neural Circuit Analysis with Expertise in Development of Neuroimaging Technology (one hire).** This hire will expand the department's expertise of neural circuits to brain regions that are currently not explored in the department. This faculty member would also collaborate on technology development for live imaging of the brain in action. This hire will bridge efforts of current faculty with those in Optics and Engineering, and may create a cutting-edge imaging center that would be poised to make fundamental discoveries and compete successfully for federal investment.
- **Molecular and Cellular Neuroscience (two hires).** These faculty members are expected to utilize genetic and/or epigenetic approaches in animals to better understand molecular/cellular mechanisms of neuronal and/or glial function in health and disease. These hires will expand the set of molecular neuroscience-oriented faculty in the department, which is critical to both the research and the undergraduate teaching mission. At least one hire is envisioned to facilitate collaborative capabilities in analyzing large scale quantitative transcriptomic and proteomic data to understand fundamental neuroscience questions.

- **Animal Models of Neurological and Complex (neuropsychiatric) Diseases (two hires).** One faculty member would be hired with a translational focus on mechanisms underlying complex neuro-developmental, neuropsychiatric, or neurodegenerative diseases. A key area of interest for this hire are pathogenic interactions of glial cells (astrocytes, microglia, oligodendrocytes, or Schwann cells) with neurons in an *in vivo* context. Another key area of technical interest for a second hire is someone employing human induced pluripotent stem cell-derived neurons or organoids, which is a critical technology for translating findings of basic research to a pre-clinical level. Acquiring this expertise is critical for the department's collective ability to move projects from a basic to a preclinical level, and successfully execute vision 2.

Appendices

Appendix 1: Intramural and Extramural Research Collaborations of Neuroscience Department Faculty

Faculty Members	Collaborators & Affiliations	Project Areas
Martha Bhattacharya	Rajesh Khanna, Tally Largent-Milnes, Pharmacology/UAHS Anita Koshy, Neurology & Immunobiology/UAHS; Fei Yin, Pharmacology/UAHS and CIBS Daniela Zarnescu, Molecular and Cellular Biology/CoS Sean Sweeney, University of York, UK	pain and itch behavior spinal cord gene expression laser capture microscopy of nervous tissue neuron-glia interactions in Alzheimer's Disease *Drosophila* motor behavior Endosomal maturation pathways
Haijiang Cai	Shaowen Bao, Physiology/UAHS Anita Koshy, Neurology & Immunobiology/UAHS Rongguang Liang, Leilei Peng/OSC Philipp Gutruf, Biomedical Engineering/COE	determining how inflammation affects auditory sensory integration and emotion behaviors behavioral and cellular outcomes of T. gondii-neuron interactions developing novel microscopy system for large scale brain imaging developing novel wireless tools for *in vivo* brain imaging and stimulation
Wulfila Gronenberg	Daniel Papaji, Ecology & Evolutionary Biology/CoS	social communication
Julie Miller	Haijiang Cai, Stephen Cowen, Neuroscience & Psychology/CoS; Arthur Riegel, Pharmacology/UAHS; Lalitha Madhavan, Neurology & CIBS/UAHS Fiona McCarthy, Animal and Comparative Biomedical Sciences/CALS; Robin Samlan, Speech, Language and Hearing Sciences/CoS; Beate Peter, School of Health Solutions/Arizona State University; Michelle Ciucci, Surgery/University of Wisconsin-Madison Philipp Gutruf, Biomedical Engineering/COE	molecular and cellular mechanisms of Parkinson's disease associated with vocal function molecular mechanisms of aging and vocal function developing novel wireless tools for *in vivo* brain imaging and stimulation in vocal behavior
Nicholas Strausfeld	Todd Oakley, UC Santa Barbara Gabriella Hanna Wolff, Case Western U. Marcel Sayre, Macquarie University, Sydney, Australia Frank Hirth, King's College London Marcel Ethan Sayre, Lund University, Sweden Xianguang Hou, YKLP, Yunnan University, Kunming PRC	Evolution of learning and memory centers. Transphyletic brain evolution
Melville Wohlgemuth	Philipp Gutruf, Biomedical Engineering/COE, University of Arizona	Developing novel wireless tools for *in vivo* brain imaging and stimulation 2-photon imaging in the echolocating bat

	Kishore Kuchibhotla, Dept of Psychological and Brain Sciences, Johns Hopkins University Tobias Bruckmann, Dept of Mechantronics, Universitat Duisburg-Essen Bertram Shi, School of Engineering, Hong Kong Science and Technology University	Cable robot solutions to 3D target tracking in the laboratory Computational modeling of the external auditory system
Konrad Zinsmaier	Sreeganga S Chandra, Yale University, New Haven, CT Yihong Ye, NIH/NIDDK, Bethesda, MD	Animal models of Adult-Onset Neuronal Ceroid Lipofuscinoses Lysosomal secretion of aggregating and pathological proteins

Table is organized alphabetically based on last names. Abbreviations: CALS: UA College of Agriculture & Life Sciences, CIBS: UA Center for Innovation in Brain Sciences; CoS: UA College of Science, COE: UA College of Engineering, OSC: UA James C. Wyant College of Optical Sciences, UAHS: UA Health Sciences

Appendix 2: Identified Funding Opportunities Matching our Strategic Plan

1. NIH Brain Initiative: R01s, U01s:
https://braininitiative.nih.gov/brain-programs/understanding-circuits

BRAIN Initiative: Exploratory Team-Research BRAIN Circuit Programs (U01) – eTeamBCP:
https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-20-029.html

BRAIN Initiative: New Technologies and Novel Approaches for Recording and Modulation in the Nervous System (R01 Clinical Trial Not Allowed):
https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-21-026.html

BRAIN Initiative: Targeted BRAIN Circuits Projects- TargetedBCP (R01 Clinical Trial Not Allowed)
https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-21-013.html

Innovation Grants to Nurture Initial Translational Efforts (IGNITE): Development and Validation of Model Systems to Facilitate Neurotherapeutic Discovery (R61/R33 Clinical Trial Not Allowed)
https://grants.nih.gov/grants/guide/pa-files/PAR-21-123.html

2. NSF:

Integrative Organismal Systems, NeuroNex Program: https://beta.nsf.gov/funding/opportunities/next-generation-networks-neuroscience-neuronex-0)

Integrative Strategies for Understanding Neural and Cognitive Systems (NCS)
https://www.nsf.gov/pubs/2021/nsf21517/nsf21517.htm

Integrative Organismal Systems, Neural Systems Cluster (NSC) program:
https://beta.nsf.gov/funding/opportunities/neural-systems-0

Emerging Frontiers in research and Innovation, section 2: Brain Inspired Dynamics for Engineering https://www.nsf.gov/pubs/2021/nsf21615/nsf21615.htm

3. Department of Defense

Peer-Reviewed Medical Research Program (Discovery Award, Focused Program Award, or Technology/Therapeutic Development Award): https://cdmrp.army.mil/funding/archive/prmrparchive

DARPA: Biological Technologies Program https://sam.gov/opp/ae37f3e27f364e58a6742384f5739c36/view

4. Office of Naval Research

Cognitive Neuroscience of Perception and Attention: https://www.onr.navy.mil/en/Science-Technology/Departments/Code-34/All-Programs/human-bioengineered-systems-341/cognitive-neuroscience-of-perception-and-attention

5. Private Foundations

Chan-Zuckerberg Institute Biohub Networkmulti-institutional grand challenges addressing how to cure or manage disease in the 21st century, https://www.czbiohub.org/investigator-competition-2021/

Human Frontiers Science Program: **innovative basic research** into fundamental biological problems with emphasis placed on **novel and interdisciplinary approaches** that involve scientific exchanges across national and disciplinary boundaries https://www.hfsp.org/funding/hfsp-funding/research-grants

Example of Parkinsons funding from Michael J Fox foundation: https://www.michaeljfox.org/funding-opportunities