REQUEST FOR APPLICATIONS

THE ASAP COLLABORATIVE RESEARCH NETWORK

ROUND TWO | SEPTEMBER 2020

asap Aligning Science Across Parkinson's

Table of Contents

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Round Two | September 2020

Opportunity

The Aligning Science Across Parkinson's (ASAP) Initiative invites applications to join the ASAP Collaborative Research Network, an effort to support international, multidisciplinary, multi-institutional research teams to address key knowledge gaps in the basic disease mechanisms that contribute to PD development and progression. **Applications that focus primarily on Circuitry and Brain-body Interactions**, inclusive of genetic and neuro-immune contributors to disease, will be considered.

Goals of the ASAP Collaborative Research Network

We believe that the recent appreciation of PD as a multisystem disorder encompassing motor and non-motor symptoms compels a collaborative and multidisciplinary approach to significantly increase our molecular understanding of disease. We seek to establish an international, multidisciplinary network of collaborating investigators who will address high-priority basic science questions. Further, we seek to:

- **Support** productive, meaningful collaborations to achieve goals that supersede the expertise or capabilities of any one lab
- **Attract** diverse talent from relevant fields outside of PD and neurodegeneration, as well as young investigators who will infuse fresh ideas and perspectives to PD research
- **Drive** intense focus to the selected research themes to accelerate discovery
- **Embrace** the values of openness and transparency as a means of accelerating outcomes and improving the reproducibility and impact of research findings

We encourage a forward-thinking approach to research that is not constrained by long-held hypotheses and dogma, and that is conducted in an environment of trust. As such, we seek to bring together investigators who are enthusiastic about working transparently in a highly collaborative network -- one that includes field experts working with investigators with no previous record of PD research, who prioritize innovation over safe bets, and who are willing to risk testing unconventional ideas.

Background

About Parkinson's Disease

PD is the most common neurodegenerative movement disorder that affects the lives of more than six million people around the world. There are currently no treatments that can slow or

stop its relentless progression. As a progressive disorder, PD increasingly robs patients of coordinated movement while also inflicting several non-motor symptoms ranging from cognitive impairment to gastrointestinal issues. Its pathological hallmarks include the irreversible death of dopamine neurons in the substantia nigra pars compacta (SNpc) region of the brain, as well as the aberrant accumulation and aggregation of the protein alpha-synuclein.

Genetic discoveries have expanded our understanding of PD heredity and broadened insights into spontaneous disease. Efforts like the BRAIN Initiative have supported tools development to image neural activity and interrogate networked brain regions with more clarity and resolution than ever before. Capitalizing on this momentum through strategic investment in discovery science, infrastructure and research tools are essential for continued progress. The opportunity is ripe to expand our limited understanding of basic PD-relevant disease biology and explore brain-wide activity that may precede and contribute to disease progression. Further, elucidating the interplay of genetics, neuro-immune mediators, and circuit activity across the central and enteric nervous systems (CNS and ENS), will bolster future drug discovery efforts as well as sound translational and clinical research.

About the ASAP Initiative

ASAP is a disease-focused, basic research program that will address key knowledge gaps to accelerate the pace of discovery for PD. Led by Nobel Laureate, Dr. Randy Schekman, and Dr. Ekemini Riley, ASAP is working with The Michael J. Fox Foundation for Parkinson's Research (MJFF) to implement its programs. This partnership enables ASAP to leverage the Foundation's grant administration and grantmaking infrastructure to receive applications, administer the review process and make grant awards to projects selected for funding.
To learn more, please visit our website and read this article about the initiative.

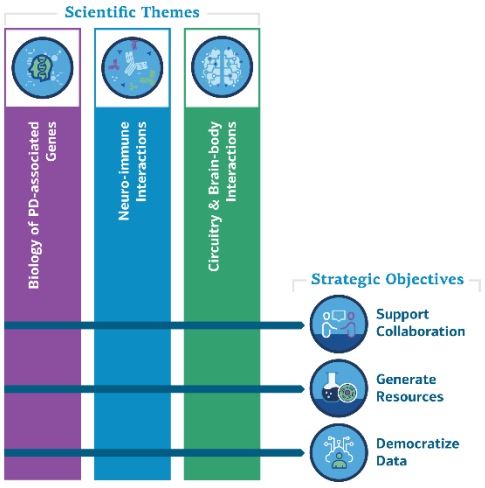

Figure 1. ASAP Research Roadmap
Image depicting the scientific themes and strategic objectives that underpin the ASAP Initiative.

While the PD field has seen significant advancement in recent years, key scientific and systemic barriers continue to impede research progress, namely the lack of scale, multidisciplinary expertise, collaboration, and coordination. ASAP intends to address these gaps to catalyze transformational progress in the field.

Our research roadmap is a tri-part strategy to (1) support multidisciplinary research within three scientific focus areas, (2) generate research-enabling resources for the field, and (3) democratize data to lower the barrier of entry to the field (see Fig 1).

This funding opportunity serves to implement the first part of the overall Initiative strategy.

Research Focus and Scope

This RFA is aimed at investigations focused solely on underlying disease biology. While research phases (i.e., basic, translational, and clinical) are broad and may overlap, we see the modified definition of basic research used by the National Institute of Neurological Disease and Stroke (NINDS) as the most appropriate for this program; that is,

Basic Research: aimed at understanding the structure and function of the nervous system and related physiological systems. Can involve studies performed *in vitro*, in animals, or in humans.

- **Basic/Disease-Focused:** focused on understanding disease mechanisms that contribute to PD.

Given the multidisciplinary remit of ASAP, we have adapted the definition above to capture the nervous system as well as other related/contributing physiological systems.

Research Tools

Human cellular and animal models

It is important to note that fundamental/foundational/basic science aimed at elucidating human disease mechanisms can benefit from the use of any model organism. However, it is important that the work is grounded in human biology and disease pathology. For reference, there are several PD research tools available, including but not limited to: animal models, human cell lines (including induced pluripotent stem cells [iPSCs]), antibodies, biochemical assays, plasmids, viral vectors, and recombinant protein. While not an exhaustive list, available tools can be searched on these databases:

- US-based: MJFF – Research Tools Catalog, iPSCs, biosamples; AlzForum's PD Research Models Database; NINDS Human Cell and Data Repository; BioSEND Human Biosample Repository; PPMI Data Repository (contains neuroimaging data on deeply phenotyped study participants)
- EU-based: European Bank of induced pluripotent Stem Cells (EBiSC); Human Pluripotent Stem Cell Registry (hPSCreg)

Innovative tools

Within the past decade, the field has seen advances in imaging techniques with optogenetics and CLARITY, as well as understanding dynamics of key neuromodulators and the ability to manipulate specific circuit elements with next-generation sensors and reporters. Further, techniques to assess neuronal activity across brain-wide networks using high-density recording, multi-fiber photometry, designer receptor exclusively activated by designer drug (DREADD) technology, and DREADD-assisted metabolic mapping (DREAMM) are of interest. Investigators are encouraged to use these and other cutting-edge tools to define circuits and their constituent cells (e.g., single-cell RNA sequencing) in their proposals to interrogate PD-relevant mechanisms of dysfunction and degeneration.

About the Scientific Themes

ASAP is focused on three scientific themes: (1) Biology of PD-associated Genes, (2) Neuro-immune Interactions, (3) Circuitry and Brain-body Interactions, with the role of these processes on the progression of PD as an important cross-cutting theme.

This RFA will focus predominately on the third theme. While RFAs focused exclusively on the biology of PD-associated genes and neuro-immune interactions have closed, aspects of genetic and/or neuro-immune contribution to circuit dysfunction are within scope. This RFA is seeking laboratory assessments of PD-relevant neuronal circuitry, including efforts to:

- Assess the contribution of circuit activity and anatomy to selective vulnerability in neurodegeneration
- Define cell-type-specific mechanisms and function of key neuromodulatory effectors on neuronal and non-neuronal cells
- Define circuit dysfunction and its relation to specific motor and non-motor symptoms

THEME 3: CIRCUITRY AND BRAIN-BODY INTERACTIONS

Contributions of circuit activity to selective vulnerability in neurodegeneration
Some neurons are vulnerable to degeneration in PD while others are not. These neurons are embedded in brain circuits whose activity directs specific functions. Activity and anatomical connectivity of these circuits may contribute to differential susceptibility to degeneration. To assess the contribution of circuit activity to neuronal dysfunction and degeneration, projects should aim to:

- Map, across a range of spatial scales, the input and output circuits into which vulnerable neurons & non-neuronal cells are embedded across the central and/or enteric nervous systems.
- Manipulate activity or connectivity within identified circuits and assess effects on vulnerable neurons.
- Explore convergence or divergence of these vulnerable populations & circuits across species (e.g., rodent, non-human primate [NHP], human).

Cell-type-specific mechanisms and function of key neuromodulatory effectors
An overt loss of neurons in the SNpc is a hallmark of PD, resulting in dopaminergic circuit malfunction. However, cellular degeneration is also seen brain-wide, thereby implicating other neuromodulatory effectors (e.g., serotonergic, noradrenergic, etc.). Further, recent evidence suggests a link between the gut-brain axis in PD; however, a deep understanding of the cellular and neuromodulatory landscape of the ENS is lacking as well as any potential feedback to the CNS. To assess cellular and neuromodulatory system dysfunction in PD – throughout the brain and periphery – projects should aim to:

- Define activity and spatiotemporal profile of dopamine and other neuromodulators across projection targets.
- Identify and characterize regional and brain-wide activity patterns induced by key neuromodulatory systems, and their changes in the context of PD-like dysfunction.

- Explore the interplay of the circuit activity and anatomical connectivity across the central and enteric nervous system.

Defining circuit dysfunction and relation to specific motor and non-motor symptoms in PD
Motor and non-motor symptoms of PD are likely the result of pathological patterns of circuit activity across multiple brain regions that may precede overt symptomatology. Loss of dopaminergic signaling and other striatal neuromodulatory tone may trigger aberrant activity in other interconnected circuits. Additionally, ENS neuronal circuit dynamics is an understudied area that may be implicated in PD symptomatology. To better understand how altered circuit activity relates to PD symptoms – throughout the brain and periphery – projects should aim to:

- Characterize regional and brain-wide activity patterns that correlate with emergence of PD motor and non-motor symptoms.
- Explore the interplay of the circuit activity across the central and enteric nervous system.
- Assess the impact of circuit manipulations on motor and non-motor symptoms.

CROSS-CUTTING COMPONENT: PROGRESSION

At the time of clinical PD diagnosis, nearly 60-80% of SNpc neurons have already degenerated. Importantly, non-motor symptoms can precede the onset of overt motor symptoms by up to 20 years, during a period known as the prodrome, raising the possibility that PD may be detectable before SNpc neuronal degeneration. This leads to the broader question of whether intervening during the prodromal period may delay or prevent SNpc neuronal degradation and other late stage symptoms like cognitive difficulties and dementia. **The challenge remains in understanding the interplay of heredity, neuro-immune factors, and circuit-level alterations during the prodromal period and how these factors are altered during the progression to overt disease.** This RFA is seeking to understand the network signatures of motor and non-motor disease progression from earliest triggers (e.g., genetic mutation/variation, immune-targeted perturbagen, and environment) to progressive degeneration and dysfunction.

Award Overview

Funding Available

Applicants may request funds up to $3 million USD total costs per year per Team to support up to a three-year research plan, for a total of up to $9 million USD in total costs over three years. Total costs are inclusive of a 15% indirect cost rate for all entities. There will be a two-year extension opportunity with commensurate funding for select Teams.

Applicants who propose to use NHPs for their studies may request an additional $1 million USD only for the year(s) in which the NHPs are proposed for use. As such, these Teams may request up to $4 million USD per year of NHP use.

Final funding will be determined based on submission and review of an invited full proposal and budget detailing rationale, key project milestones, and timeline for completion of project goals.

Key Dates

WEEK OF SEPTEMBER 21, 2020	Online application portal opens for pre-proposal submission
DECEMBER 11, 2020	Pre-proposal deadline
WEEK OF MARCH 1, 2021	Notification of invitation to submit full proposals
APRIL 13, 2021	Full proposal deadline
WEEK OF JUNE 21, 2021	Earliest notification of invitation to interview
WEEKS OF JULY 12 & 19, 2021	Finalist virtual interviews held
AUGUST 2021	Funding decisions made
SEPTEMBER 2021	Anticipated funds available

Eligibility Criteria

Institutional Eligibility

- **Type** – Applications may be submitted by public and private non-profit entities, such as universities, colleges, hospitals, laboratories, units of state and local governments, as well as eligible agencies of the federal government. For-profit entities are also eligible and encouraged to apply.
- **Region** – Applications may be submitted by U.S. and foreign entities.
- **Submitting Institution** – The Coordinating Lead PI must be affiliated with the institution submitting the application and grant funds will be awarded to that institution, which will take responsibility for distributing funds to the institutions of the other members of the collaboration.

Core Leadership Eligibility

- **Core Leadership** – Each Team must consist of a minimum of three (3) to a maximum of five (5) PIs. A Coordinating Lead PI must be appointed for each Team, who will be responsible for overall project management and reporting to ASAP/MJFF staff. Team structure and management is discussed in further detail below.
- **Career Stage & Disciplines Represented –** We require the Core Leadership for each Team to consist of at least one (1) early career investigator in the position of Co-I, and for there to be at least two (2) different disciplines represented on each Team.

- **Institutions** – There must be a minimum of two (2), but no more than five (5) participating institutions represented by the Team.
- **Degree** – All Core Leadership must hold a doctorate, such as a PhD, MD, or equivalent degree.
- **Appointment** – The Coordinating Lead PI must have an academic appointment and be in an independent faculty position or equivalent. All other Core Leadership must be in an independent faculty position or equivalent.
- **Time Allocation** – All Core Leadership are expected to allocate a minimum of 25% time and effort to the research project.

Ineligibility

This RFA will not provide funding to develop or characterize patient cohorts. Further, given the basic science remit of this initiative, early drug discovery work and clinical trials are out of scope for this RFA.

Infrastructure support is the second pillar of the ASAP Initiative writ large. There are plans to expand relevant patient cohorts, establish an isogenic iPSC resource expressing key PD-relevant causal/high-risk mutations, as well as deepen genetic analyses by examining PD in ethnically diverse populations around the globe. We will keep the PD community apprised of the development timeline for these infrastructure projects; therefore, proposals focused on these topics are not appropriate for this RFA.

Team Structure and Management

Teams are required to be multidisciplinary and multi-institutional. Unlike "Center Grants" that play to the strengths of a single institution, this research network intends to establish teams comprising the best researcher expertise to address key knowledge gaps, regardless of their geographical location or institutional affiliation.

Preference will be given to teams that exhibit the following:

- **Evidence of past collaborative behaviors** – teams that comprise two or more members who have worked together collaboratively with successful integration of diverse talents and approaches. We seek teams who are eager to share ideas and results across the spectrum of the network and who embrace the principles of transparency and open science in publication and public presentations.
- **Diversity** – Promotion of diverse scientific teams is important to ASAP. We believe that research teams from differentiated backgrounds in terms of gender, race, scientific expertise or discipline, career stage, etc. are poised to enrich the process of discovery. Teams which demonstrate diversity across their members will be considered more favorably.

Please note, these awards are not intended to be conventional research awards. As such, investigators will be asked to interact regularly with ASAP Initiative-associated staff and advisors to discuss any element of the project. Given the ASAP-MJFF partnership, applicants may hear from ASAP or MJFF staff throughout the project duration.

DEFINITIONS:

- **Core Leadership** – Each Team should consist of at least three (3), but not more than five (5) Core Leadership members, including: A Coordinating Lead Principal Investigator (PI) and up to four additional Co-Investigators. All Core Leadership members are required to allocate 25% effort to the project.
- **Coordinating Lead PI.** This person is responsible for the scientific and technical direction of the proposed research project, contractual and financial obligations, and other organizational assurances/certifications. The Coordinating Lead PI must ensure that the Team complies with the terms and conditions of the award and will be the primary contact person for ASAP Scientific Review as well as MJFF Grants Administration staff. Given the complexity of managing multi-institutional collaborations, it is imperative that the Coordinating Lead PI take primary responsibility for managing the project by providing strong, capable leadership and oversight of the project plan and managing Team communication internally as well as with ASAP-Initiative associated staff. The Coordinating Lead PI must be the team member to apply in the MJFF Grant Portal. Preference will be given to lead PIs with a history of open science practices and fruitful collaboration with one or more members of the Team.
- **Co-Investigators.** These investigators will lead a component(s)/subproject(s) of the Team's research project. Please note that at least one of these investigators must be an early career investigator (ECI) within one (1) to seven (7) years of their first independent appointment. For the purposes of this award, an ECI should have attained their first independent appointment no earlier than 9/30/2014 and no later than 9/30/2020. PIs for each Team may be recruited from existing or previous collaborations, or in the case of early career PIs, new talent in areas complementary to those represented by the senior members of the team. Emphasis will be on meaningful collaborations where the senior and junior members of the Team have an equal stake in the planning and goals of the effort and a corresponding share of the credit for discovery.
- **Key Personnel, Collaborators and Consultants.** Additional team members may be named at the full proposal stage, if invited.
- **Team Project Manager.** The Coordinating Lead PI is required to budget for a project manager. This person would assist with the day-to-day coordination of all team efforts to consistently maintain a high level of functionality and communication. The Project Manager is **not** to be named at the pre-proposal stage. If invited to full proposal, the Project Manager will have to be budgeted for and named no later than three months after the award start date.

Grant Terms and Policies

- **Use of Funds** – Funds may be used for scientific and technical personnel, supplies and standard equipment needs directly related to the successful execution of the proposed scope or work. However, funds may not be used for laboratory or facility renovation.
- **Carryover Funding** – Unused research funds may be carried over to the following year, with approval, and requests for no-cost extensions will be considered.
- **Open access** – All data resulting from the Team's work will be available to the scientific community at large at the earliest opportunity on preprint servers, online protocol platforms, and in an open access journal format. Please see ASAP's Open Access Policy here.
    - **Publications** – All publications related to this funded work must be submitted to a preprint server, such as bioRxiv, before or concurrent to the first submission to a journal. An open access journal format is a requirement of this funding opportunity. Experimental protocols should be made publicly available through a protocol sharing service, such as bio-protocol or protocols.io. In addition, early sharing of null and incremental results, within the network and publicly, is encouraged. ASAP requests that scientific publications, preprints, and presentations that result from this award be acknowledged as being supported by this funding.
    - **Data and Code Sharing** – All datasets and code, either curated or generated through the project, should be made publicly available and easily accessible online, as early as possible when feasible. This includes metadata, documentation, and intended computational use cases, as appropriate. ASAP and MJFF will work with grantees to identify appropriate data platforms.
    - **Reagent Sharing** –ASAP requires that all tools or reagents (a) funded by and (b) that result from awarded projects be made readily available to the community through an accessible community repository, such as the MJFF Tools Program (for model systems, cell lines, vectors), Addgene (for plasmids, DNA reagents, viruses), etc. This requirement applies to cell lines, transgenic models, plasmids/clones, antibodies, and other reagents.
- **Reporting Requirements** – Progress reports are due annually or at other times as deemed necessary by ASAP and MJFF for project evaluation. Progress report forms will be provided by MJFF approximately two months before they are due.
- **Intellectual Property** – ASAP will not retain any rights to funded projects, other than right to publicly discuss data, published results, and intellectual property that result from the research.

Application Process

There are three stages for this funding opportunity: (1) pre-proposal, (2) invited full proposal, and (3) finalist virtual interview.

Pre-proposals are due no later than December 11, 2020 by 6pm EST. Following evaluation, teams selected to submit full proposals will be notified during the week of March 1, 2021. Invited full proposals are due no later than Tuesday, April 13, 2021 by 6pm EST. Finalists will be interviewed virtually by ASAP leadership during the weeks of July 12 & 19, 2021. Final funding decisions are anticipated by August 2021 and awardees will be notified.

All applications must be completed and submitted through ASAP online portal at www.parkinsonsroadmap.org/apply. We strongly recommend that applicants familiarize themselves with the online portal in advance of any deadlines. Exceptions will not be made for technical difficulties. For detailed application instructions, please visit the online portal for more information.

As a reminder, ASAP and MJFF are partnering to implement this RFA. As such, applicants may hear from ASAP or MJFF staff with follow-up needs or questions pertaining to their submissions.

Pre-proposal Instructions

A brief pre-proposal is required for funding consideration (no more than five [5] pages). Applicants must use the template available on the online portal. In addition to the five-page template, applicants must follow each tab within the online portal and fill in the designated areas. The pre-proposal consists of the following sections:

Project Description

- Project title
- Project summary (100 words maximum)
- Scientific goals and strategy (500 words maximum)
- Statement of impact and alignment with ASAP Initiative goals (100 words maximum)

Team Summary

- List of Team investigators
- Description of each investigator's role on the project (100 words maximum per investigator)
- Description of the collective expertise and resources that the investigators bring to the Team
- Collaboration history of each investigator including reference to past intra-Team collaboration where relevant (review the pre-proposal template for specific parameters)
- Historical adherence to open science practices (review the pre-proposal template for specific parameters)

Letter of commitment signed from each investigator.

Full Proposal Instructions

Full proposal submissions are **by invitation only**. A weblink and additional instructions for online submission will be provided to select applicants during the week of March 1, 2021. Full proposals are **due no later than Tuesday, April 13, 2021.**

Review and Selection Process

There is currently no pre-determined number of research teams that will be a part of the ASAP Collaborative Research Network, and there are no specified number of awards currently set aside. Decision-making will be guided by expert peer review; however, ASAP Executive Leadership and the Scientific Advisory Board reserves the right to make ultimate final funding decisions on any application.

Pre-proposals will be reviewed by ASAP Executive Leadership and ASAP Initiative-associated scientific staff, including but not limited to scientific staff at The Michael J. Fox Foundation for Parkinson's Research, Parkinson's Foundation, and Parkinson's UK, as well as relevant external advisors. Full proposals will be reviewed by an external Peer Review Committee comprised of multidisciplinary scientists who are familiar with our program goals and have deep expertise in our program's scientific focus areas, as well as methods proposed in the grant applications. As this RFA intends to bring diverse disciplines together, an equally diverse peer review committee will be essential to this process.

Feedback will not be provided for pre-proposals that are not invited for full application submission. However, feedback will be provided for full proposals that are not selected for funding.

Selection of awardees will be based on the following criteria:

- **Quality** of the proposal, expertise, and capacity of the collaborative group for addressing the proposed project. There should be evidence of synergy and substantive contributions from all assembled members of the research team – i.e., not simply a collection of individual projects.
- **Potential impact** of the research questions being addressed in the application.
- **Focus on basic disease biology**. While the ASAP Initiative is focused on basic science, rather than translational or clinical strategies, the proposed work should have a clear disease context to Parkinson's disease and include the use of existing human biomaterial where appropriate.
- **Degree** to which the proposed work brings in new ideas to the field and stimulates potential new avenues of investigation.
- **Diversity** of the proposed scientific team.

- **Demonstrated collaborative potential** of the proposed Team as evidenced by co-authorships, past collaborations among at least two (2) members of the Team, as well as relevant contributions to other successful research collaborations in the recent past.
- **Commitment to open science and active research community engagement.** These values may be demonstrated through service on committees and editorial boards, past publication of open access articles, use of preprint servers, protocol repositories, etc.
- **Leadership capacity of the Coordinating Lead PI.** This investigator's vision, leadership qualities, willingness to collaborate, and demonstrated ability to bring together and lead a multidisciplinary team of experts to a successful conclusion will be a critical factor.

Confidentiality

The review process will be performed under confidentiality among all parties involved in proposal evaluation. Funded proposals will be shared across the ASAP Collaborative Research Network, as well as the MJFF network, and lay project summaries will be publicly communicated on our website. Unfunded proposals will remain confidential. Application materials will not be returned to applicants.

Contact

Inquiries concerning this funding opportunity are encouraged to avoid submission complications. For administrative and programmatic inquiries, please contact grants@parkinsonsroadmap.org. We encourage questions well in advance of the deadline.