| Título del Proyecto | Activity and connectivity drive neuronal vulnerability and <br> disease progression in Parkinson's disease |
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| $N^{\circ}$ de expediente asignado / grant number | ASAP-020505 |
| Abstract | Specific brain circuits that are highly melanized with age are <br> primarily affected, particularly early in Parkinson's disease <br> (PD). Models incorporating this aspect of PD have only been <br> developed recently and show that increased neuromelanin <br> (NM) production causes neurodegenerative changes |
| consistent with PD. The regulators of cellular NM metabolism |  |
| have not been determined, the effect of NM on normal activity |  |
| in these pathways has not been defined (circuitry assessment), |  |
| the potential for NM aggregates to increase a-synuclein (aSyn) |  |
| accumulation has not been evaluated, and the impact of |  |
| extracellular NM on detrimental inflammatory processes has |  |
| not been assessed (brain-body interactions). We will test |  |
| whether activity in melanized brain circuits is a dominant factor |  |
| in the initiation of PD and sustains its progression by seeding |  |
| pathology in connected regions and providing the stimulus for |  |
| chronic inflammation. We will also assess whether |  |
| manipulating NM production and/or brain circuit activity can |  |
| ameliorate these deficits. |  |


|  | Aligning Science Across Parkinson's (ASAP) is a coordinated research <br> initiative to advance targeted basic research for Parkinson's disease. Its <br> mission is to accelerate the pace of discovery and inform the path to a |
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| cure through collaboration, research-enabling resources, and data |  |
| sharing. The Michael J. Fox Foundation for Parkinson's Research is |  |
| ASAP's implementation partner and issued the grant. |  |

