CARD an NIA and NINDS Initiative

National Institutes of Health
Center for Alzheimer's and Related Dementias

structural opportunity

We have stable, generous resources

We have secure employment

Our review is not entirely prospective

There is the potential for us to define our own metrics of success

structural responsibility

- Take on critical projects others can’t easily address
- Focus on complementing current research activities
- Address critical resource and research gaps
- Focus exclusively on research progress

mission

Initiate, Stimulate, Accelerate, & Support research in AD/ADRD, leading to the development of improved treatments and cures

programmatic priorities

- Projects that require a high tolerance for failure
- Rapidly emerging opportunities; quick & nimble investigation
- Projects that require long-term & stable commitment
- Challenges centered on platform, infrastructure & capability building
- Projects that require a high-level of collaboration and coordination
- Projects that span disease and methodological boundaries

scientific themes

Molecular Pathogenesis Anchored in Genetics

Disease Subtyping, Prediction of Risk, Progression

De-Risking of AD/ADRD Therapeutic Approaches

Development and Application of Precision Therapeutics

Diversifying the Research Endeavor

Democratization of Data

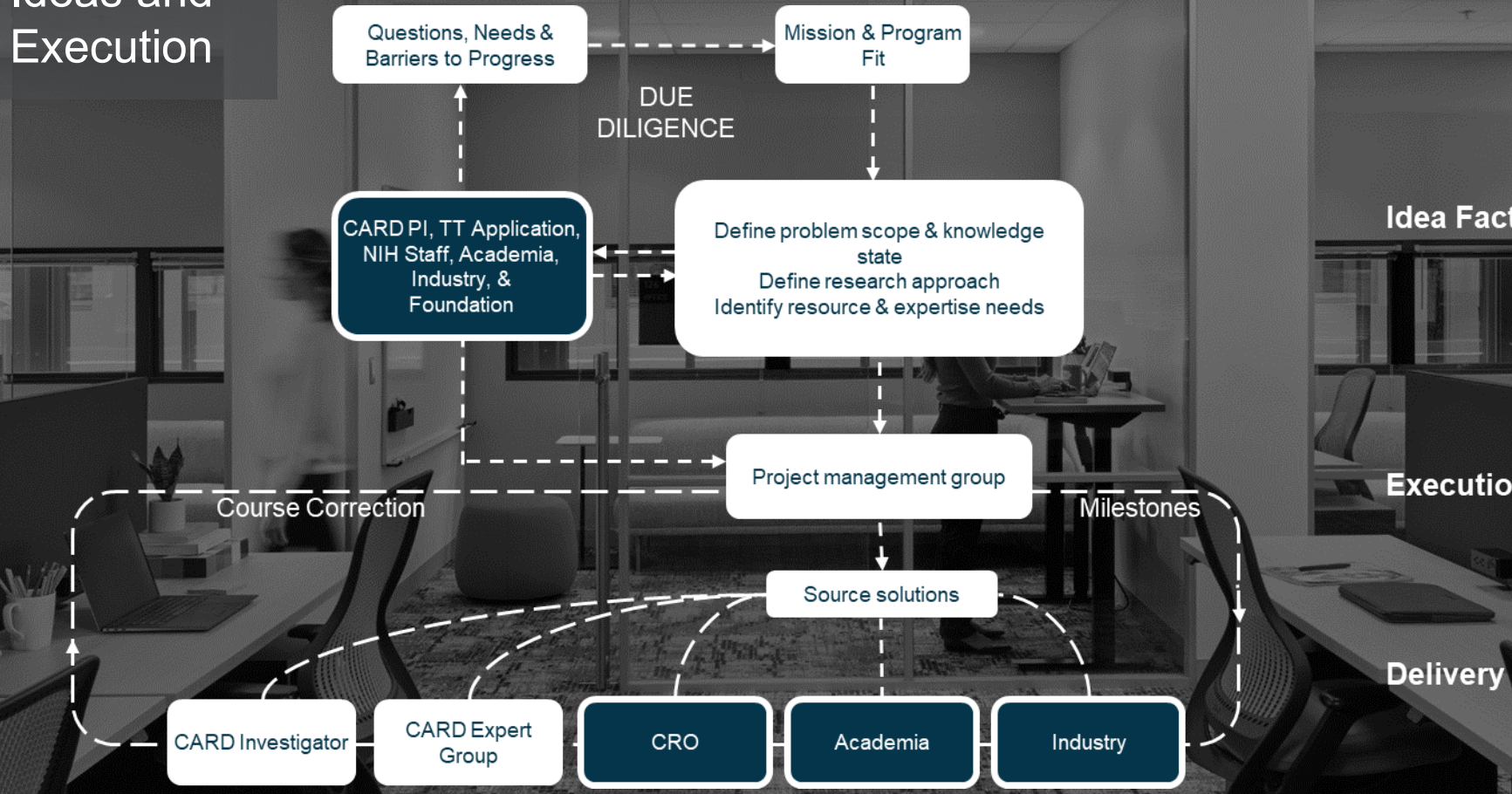
Collaboration and Cooperation

Transparency & Reproducibility

Foundational, Actionable Resource Production

organizational priorities

Ideas and Execution



CARD Challenge

National Institutes of Health
Center for Alzheimer's and Related Dementias

Research Programs | Data and Resources | Job and Training Opportunities | News and Events | About

Home › Research Programs › Propose a CARD Research Challenge

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Research Programs

- All Research Programs
- iPSC Neurodegenerative Disease Initiative
- Long-read Sequencing
- AutoTAC (Tau Protein Aggregates)
- Brain Atlas
- TDP-43
- **Propose a CARD Research Challenge**

Propose a CARD Research Challenge

The AD/ADRD research field is a thriving and productive one. CARD aims to complement this work and fill critical gaps and needs in the research pipeline with an emphasis on projects that are not easily supported by traditional extramural funding mechanisms. Formed as part of NIH's Intramural Research Program (IRP), CARD is committed to working closely with NIH staff to develop critical programs of research and infrastructure development in the AD/ADRD space.

CARD Facility (1)

National Institutes of Health
Center for Alzheimer's and Related Dementias

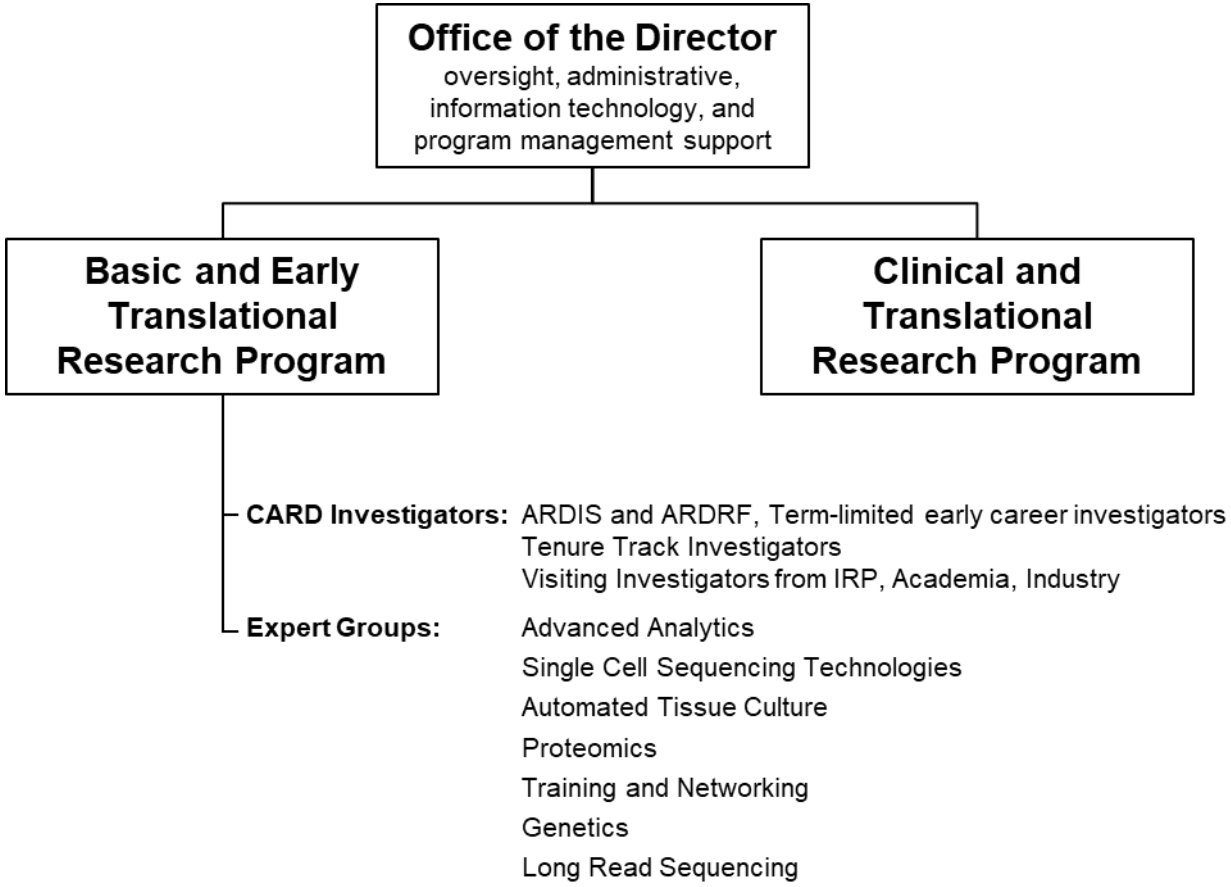
CARD Facility (2)

National Institutes of Health
Center for Alzheimer's and Related Dementias

CARD Facility (3)

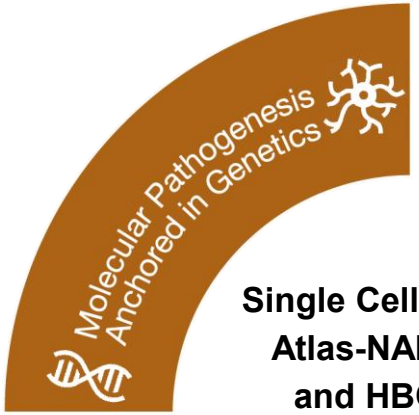
National Institutes of Health
Center for Alzheimer's and Related Dementias

Organizational Structure



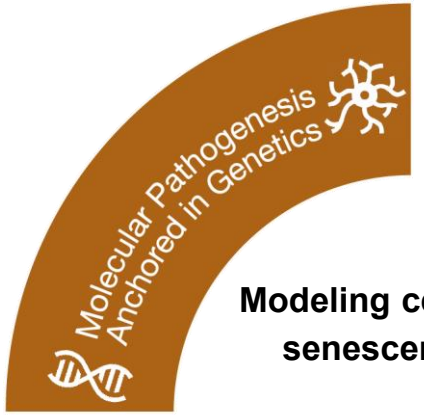
CARD Scientific Priorities

CARD Project Example 1



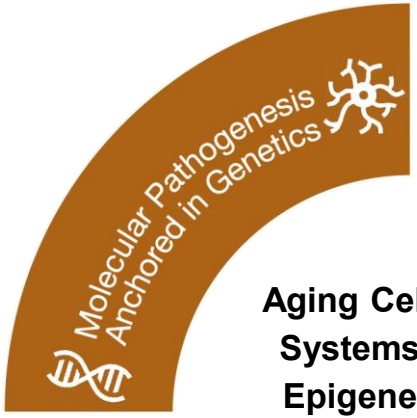
Single Cell Brain Atlas-NABEC and HBCC

CARD Project Example 2



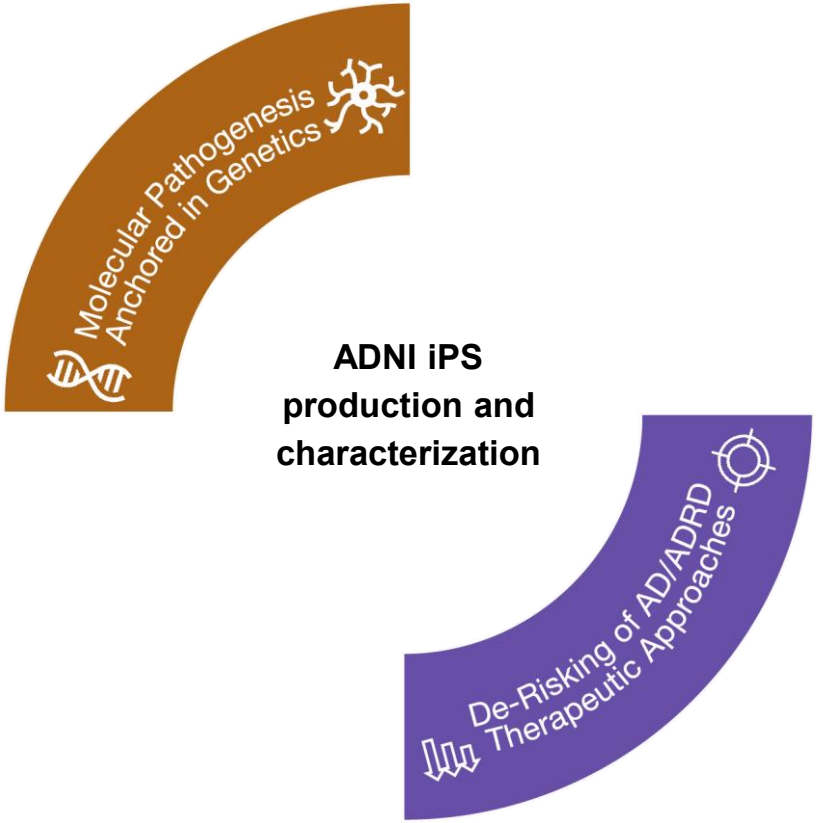
Modeling cellular senescence

CARD Project Example 3

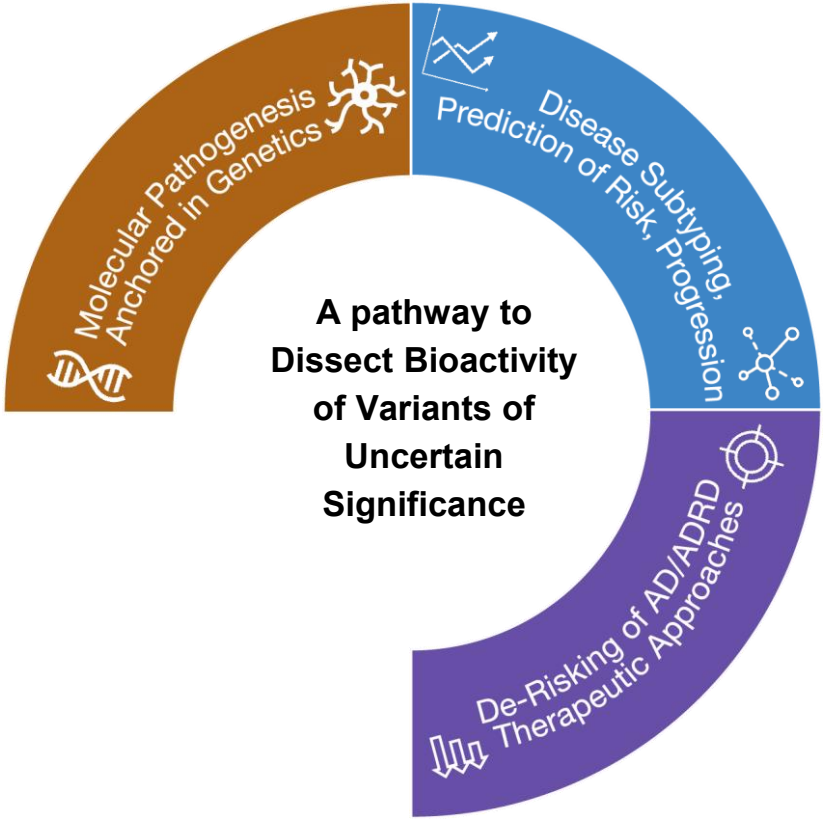


Aging Cellular Systems via Epigenetics

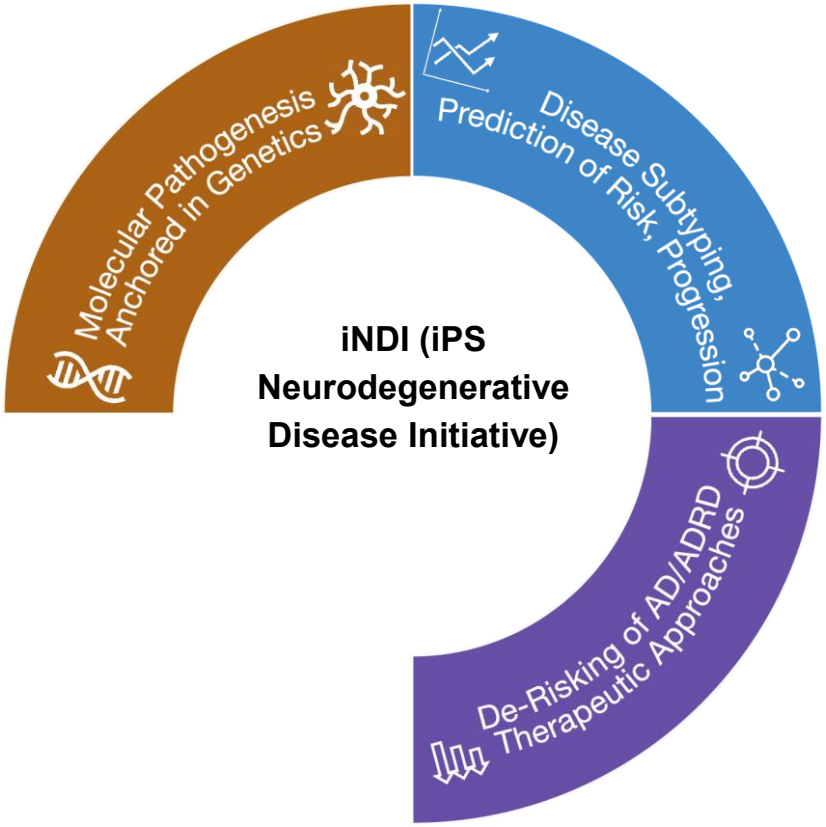
CARD Project Example 4



CARD Project Example 5

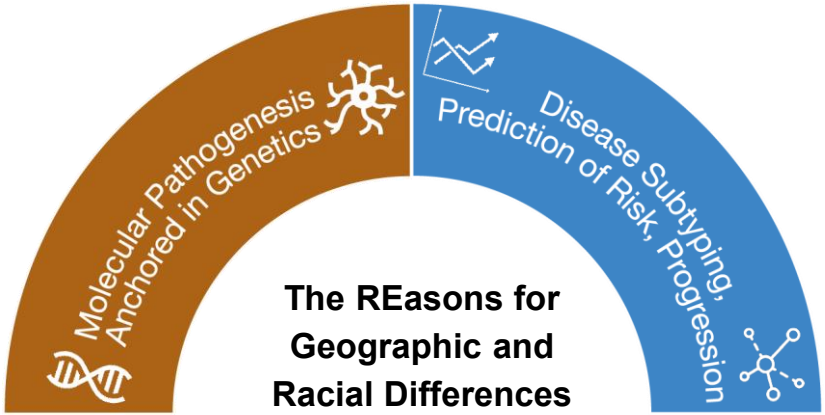


CARD Project Example 6

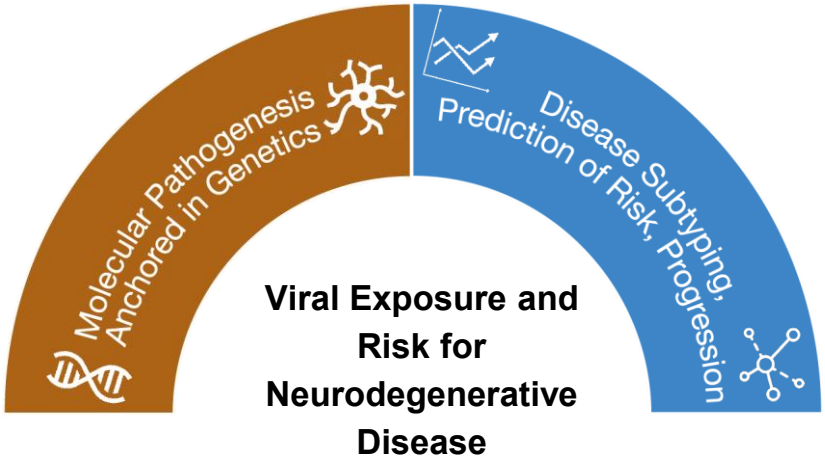


CARD Project Example 7

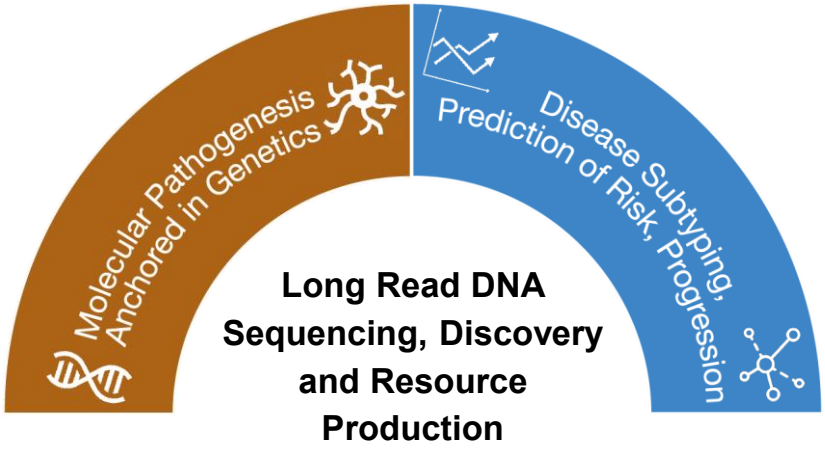
CARD Project Example 8



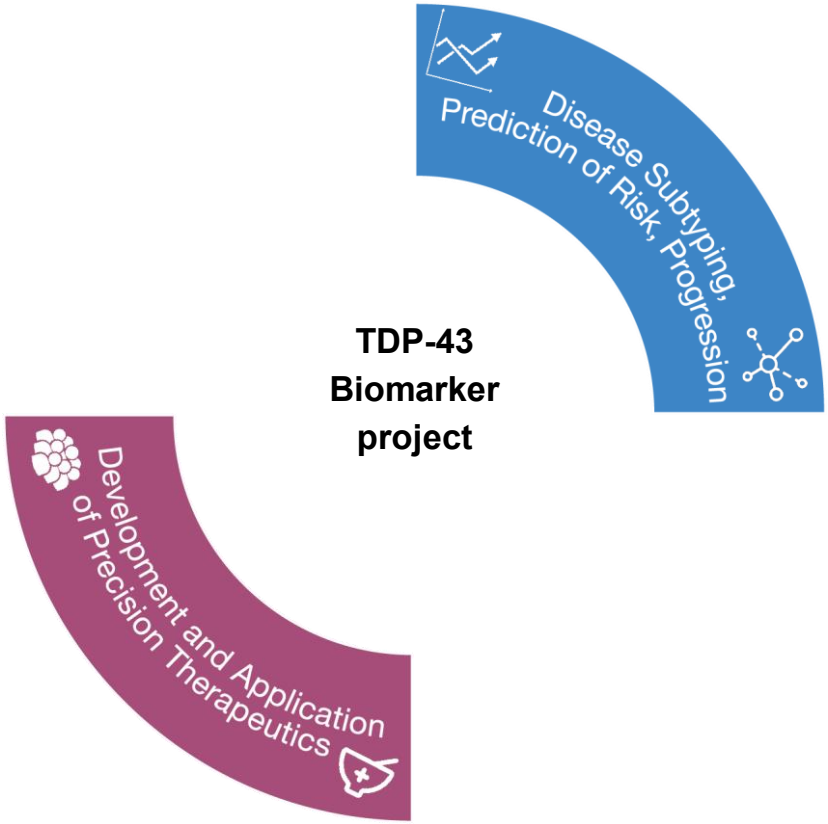
CARD Project Example 9



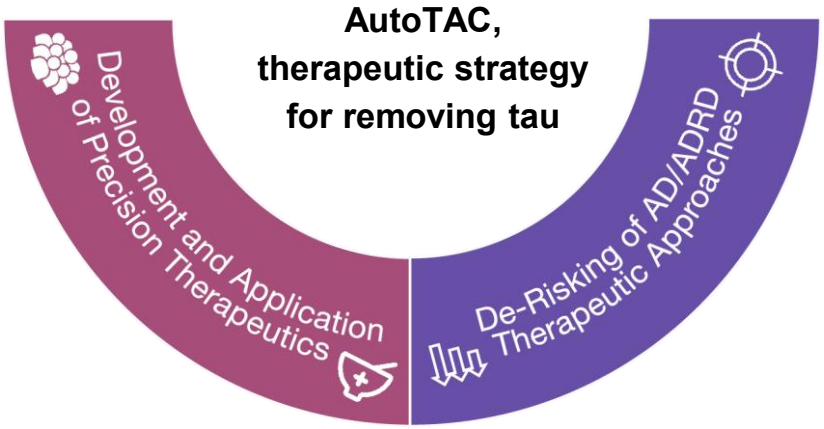
CARD Project Example 10



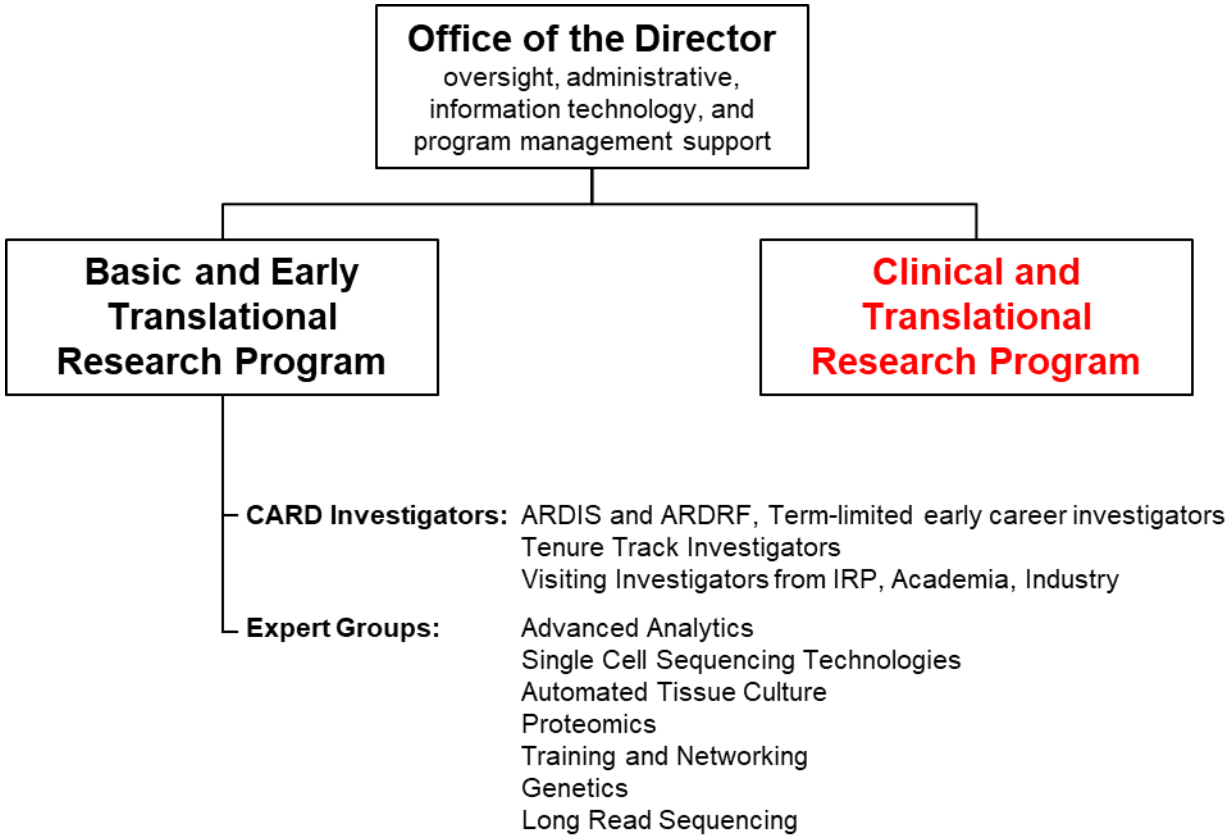
CARD Project Example 11



CARD Project Example 12



Organizational Structure



CARD Clinical Translational Research Program

Right Patient

Right Therapeutic

Right Time

CARD Precision Therapeutics

High-confidence precision therapeutic targets exist
Genomic therapies (ASOs, CRISPR) are effective
Regulatory pathways are becoming clearer for ASOs
Above features enable rapid target->trial pathway

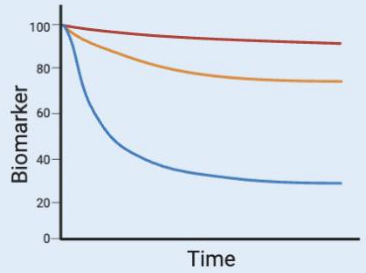
IRP advantages

Existing clinic/hospital infrastructure
Experience in genomic medicine
Funding available at front end – speed + equity
Link to existing CARD projects and infrastructure

CARD Precision Therapeutics Clinical Program

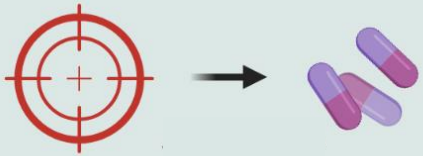
Natural History

Deep phenotyping of AD/ADRD patients



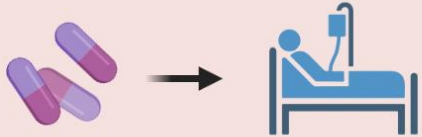
Translational

Developing & de-risking precision therapies

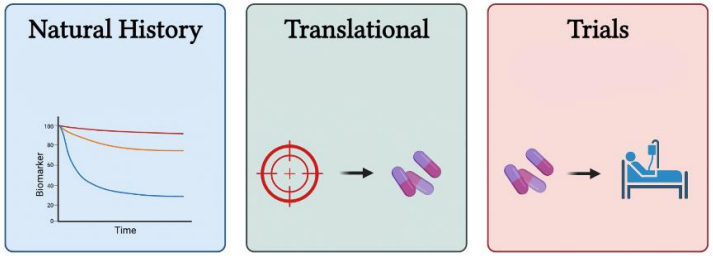


Trials

Precision therapy application



CARD Precision Therapeutics Clinical Program Components: Natural History



Natural History

Deep phenotyping of AD/ADRD patients

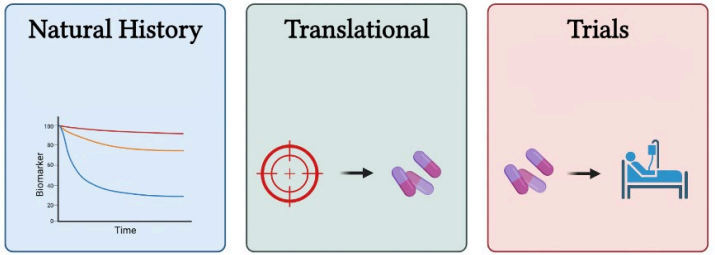
Patients

- New and longitudinal
- Complex and Monogenic
- Leveraging existing efforts

Characterization

- History and Physical
- Neuropsych.
- Imaging
- Biospecimens
- Genetic
- Digital

CARD Precision Therapeutics Clinical Program Components: Translational



Translational

Developing & de-risking precision therapeutics

Target Causality

- Scalable pooled editing and phenotyping in cells

Target Engagement

- Reversal of cellular phenotypes

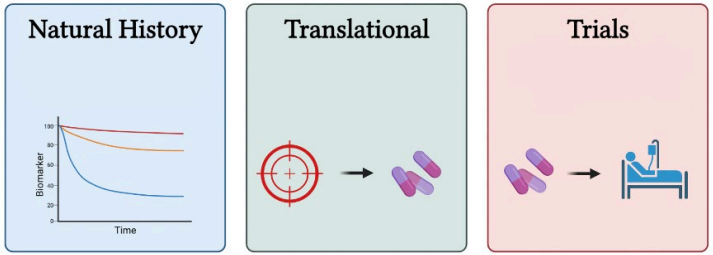
De-risking Therapies

- Xenotransplantation
- Toxicology

Biomarkers

- Mass. spec, somalogic, o-link
- Identify molecular subpopulations of sporadic AD

CARD Precision Therapeutics Clinical Program Components: Trials



Trials

Precision therapy application

ASOs

- Patient recruitment: Regional, national and International
- Initially target well-defined genes/mechanisms (GRN, APOE)
- Broaden to sporadic AD patients sub-grouped based on molecular biomarkers /genetics

CRISPR/prime

- C9ORF72, APOE

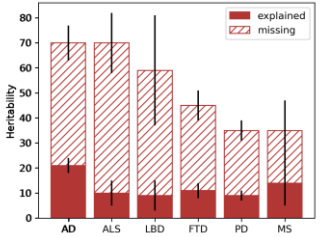
Novel small molecules

- e.g. TDP-43 de-aggregases

CARD Clinical Translation – Challenge Projects

C9 CRISPR therapy

VUS pathogenicity



Wearables/digital health

Synergy with existing efforts in CARD/IRP

Genetics/Genomics
iPSCs (iNDI)

Functional Genomics (iNDI)

Biomarker Development

Data Science

Gene Therapy/ASO Investment

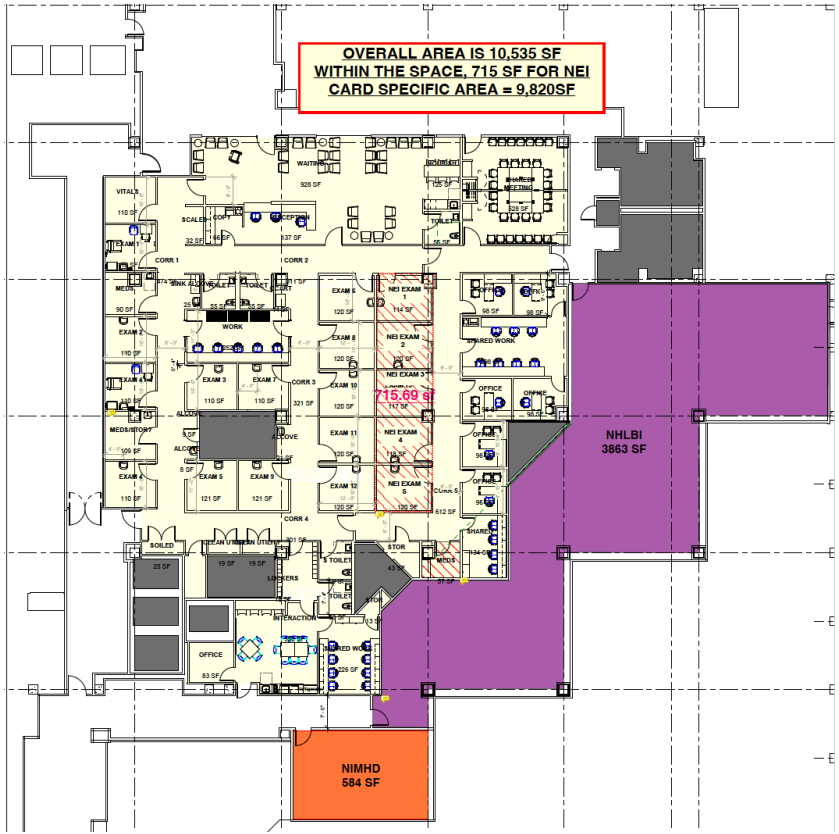
Culture of Rigor, Transparency, Collaboration

Goal: Become destination medical center for precision trials in AD/ADRDs

Identifying Space

Approximately 8,500sf of contiguous space for an outpatient clinic, for eg with

- Examination rooms
- Rooms for neuropsychological evaluations
- Nursing intake room (monitoring vital signs etc.)
- LP and small procedure room
- Conference rooms for discussion with families and case conferences
- Offices for clinical staff
- Patient waiting area



Identifying a Leader

Over the next period, recruitment efforts will begin to identify a Director for the Clinical Translation Program at CARD

- ✓ An individual with a track record in the AD/ADRD space
- ✓ Someone who recognizes the potential of the IRP and the opportunity to work in lock step with the basic and early translational program of CARD
- ✓ A clinician-researcher with a clear vision and the skill necessary to implement this vision