Project Plan: Pre-Clinical AD Biomarker Validation in ApoE4 Carriers with High Polyomic Risks.

Executive Summary

This project aims to comprehensively evaluate early biomarkers of Alzheimer's disease (AD) in a high-risk population: ApoE4 heterozygotes with elevated polygenic and lifestyle risk scores. The study will assess a multimodal panel of biomarkers including autoantibodies, senescent memory CD8+ T cells (anti-APP and anti-tau specific), blood pTau217, circular RNAs (circRNAs), metabolites, inflammatory cytokines (IL-6, IFN-γ, IL-10, TNF-α), and tissue-specific exosomes in both peripheral blood and cerebrospinal fluid (CSF).

Study Duration: 36 months (3 years)
Estimated Enrollment: 120 participants
Study Type: Longitudinal observational cohort with matched controls

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1. Background and Rationale

1.1 Scientific Foundation

ApoE4 heterozygotes represent a substantial proportion of individuals at elevated AD risk, with a 2-4 fold increased lifetime risk compared to non-carriers[1]. When combined with high polygenic risk scores incorporating additional genetic variants (BIN1, PICALM, CLU, SORL1, ABCA7, etc.), these individuals may represent an optimal population for early biomarker detection and intervention strategies[2].

Recent advances have established plasma pTau217 as a highly accurate blood-based biomarker for AD pathology, with diagnostic accuracy approaching 90% for detecting amyloid positivity[3]. However, comprehensive immune-mediated biomarkers, including senescent T cells and autoantibodies, remain underexplored in preclinical populations[4].

1.2 Innovation

This study uniquely integrates:

- Immunological profiling of senescent memory CD8+ T cells with antigen specificity (anti-APP, anti-tau)
- Autoantibody profiling against AD-related proteins

- Next-generation biomarkers (circRNAs, tissue-specific exosomes)
- Inflammatory cytokine panels
- Established biomarkers (pTau217)
- Comparative analysis between peripheral blood and CSF compartments

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2. Study Objectives

2.1 Primary Objectives

1. **Characterize the immunological signature** of early AD in ApoE4 heterozygotes with high PRS, focusing on senescent CD8+ T cell populations and autoantibody profiles
2. **Evaluate the diagnostic performance** of a multimodal biomarker panel for detecting preclinical AD pathology
3. **Assess longitudinal changes** in biomarker profiles over 24 months

2.2 Secondary Objectives

1. Compare biomarker profiles between peripheral blood and CSF compartments
2. Identify correlations between immune biomarkers and established AD biomarkers (pTau217, amyloid-PET, tau-PET)
3. Develop a predictive model combining genetic risk (ApoE4 + PRS) with multimodal biomarkers
4. Evaluate the relationship between inflammatory cytokine profiles and cognitive decline
5. Assess circRNA and exosomal cargo as novel diagnostic markers

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3. Study Design

3.1 Population

Inclusion Criteria:

- Age 55-75 years
- ApoE4 heterozygote (one ε4 allele)
- High polygenic risk score (top quartile based on validated AD-PRS including non-APOE variants)
- Cognitively normal (CDR = 0, MMSE ≥ 27)
- Willing to undergo CSF collection via lumbar puncture
- Willing to undergo amyloid-PET and tau-PET imaging

- No contraindications to MRI

Exclusion Criteria:

- Diagnosis of dementia or MCI
- Active autoimmune disease (e.g., rheumatoid arthritis, lupus, multiple sclerosis)
- Current immunosuppressive therapy
- Active malignancy or history of malignancy within 5 years
- Significant psychiatric disorder
- Use of investigational drugs within 30 days
- Contraindications to lumbar puncture (anticoagulation, spinal abnormalities)

Control Groups:

Group	Description	N
Primary Cohort	ApoE4 heterozygotes, high PRS	60
Control 1	ApoE3/3, low PRS, age-matched	30
Control 2	ApoE4 heterozygotes, low PRS, age-matched	30
Total		**120**

Table 1: Study enrollment by group

3.2 Study Schema

Visit	Screening	Baseline	Month 6	Month 12	Month 24
Informed Consent	X				
Demographics	X				
Medical History	X				
Physical Exam	X	X		X	X
Cognitive Testing	X	X	X	X	X
Blood Draw	X	X	X	X	X
CSF Collection		X		X	X
Amyloid-PET		X			X
Tau-PET		X			X
MRI		X		X	X

Table 2: Study visit schedule and procedures

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4. Biomarker Assessment Strategy

4.1 Peripheral Blood Biomarkers

4.1.1 Senescent Memory CD8+ T Cells

Sample Requirements:

- 50 mL whole blood in sodium heparin tubes
- Process within 4 hours of collection

Methodology:

1. Peripheral blood mononuclear cell (PBMC) isolation via density gradient centrifugation
2. Flow cytometry panel for senescence markers:
    - CD3, CD8, CD45RA, CD45RO, CD27, CD28, CD57
    - KLRG1, PD-1, CD160
    - Ki-67 (proliferation marker)
3. Senescence-associated β-galactosidase (SA-β-gal) staining
4. Antigen specificity assessment:
    - APP peptide tetramers (epitopes from Aβ region)
    - Tau peptide tetramers (phospho-tau epitopes)
    - IFN-γ ELISPOT with APP/tau peptide stimulation
5. Telomere length measurement by qPCR
6. Gene expression profiling of sorted senescent CD8+ populations (RNA-seq)

Key Phenotypes to Quantify:

- CD8+CD28-CD57+ (senescent)
- CD8+CD45RA+CD27- (TEMRA)
- APP-specific CD8+ cells
- Tau-specific CD8+ cells

4.1.2 Autoantibodies

Sample Requirements:

- 10 mL serum (collected in SST tubes)

Methodology:

1. Multiplex bead-based immunoassay (Luminex platform)
2. Target antigens:
    - Aβ40, Aβ42

    - Tau (full-length, phospho-tau epitopes: pT181, pT217, pT231)
    - APP (full-length and fragments)
    - GFAP (glial fibrillary acidic protein)
    - Neurofilament light chain (NfL)
    - Myelin basic protein (MBP)
    - S100B
3. Immunoglobulin isotype determination (IgG, IgM, IgA subclasses)
4. Antibody avidity assessment for major hits
5. Epitope mapping for tau and APP autoantibodies

4.1.3 Plasma pTau217

Sample Requirements:

- 5 mL plasma (EDTA tubes, centrifuged within 2 hours)
- Store at -80°C

Methodology:

- Quantification using validated immunoassay platforms:
    - Lumipulse G pTau217 assay (FDA-cleared)[5]
    - ALZpath pTau217 immunoassay
- Single-molecule array (Simoa) as confirmatory method
- Calculate pTau217/Aβ42 ratio

4.1.4 Circular RNAs (circRNAs)

Sample Requirements:

- 5 mL whole blood in PAXgene RNA tubes
- 2 mL plasma (EDTA)

Methodology:

1. RNA extraction from whole blood and plasma
2. RNase R treatment to enrich for circRNAs
3. RNA-seq (targeted or whole transcriptome)
4. Quantitative RT-PCR validation of candidate circRNAs:
    - circRNA.2837
    - circHIPK2
    - circNF1-419
    - Additional AD-associated circRNAs from literature
5. Bioinformatics analysis:
    - Differential expression analysis

- circRNA-miRNA-mRNA network construction
- Functional enrichment analysis

4.1.5 Metabolites

Sample Requirements:

- 5 mL plasma (EDTA, fasting sample preferred)
- 5 mL serum

Methodology:

1. Targeted metabolomics panel:
    - Amino acids and derivatives
    - Acylcarnitines
    - Organic acids
    - Sphingolipids and ceramides
    - Cholesterol metabolites
2. Untargeted metabolomics (LC-MS/MS)
3. Lipidomics profiling
4. Focus on AD-associated pathways:
    - Sphingolipid metabolism
    - Oxidative stress markers (8-isoprostane, F2-isoprostanes)
    - Energy metabolism (lactate, pyruvate, TCA intermediates)

4.1.6 Inflammatory Cytokines

Sample Requirements:

- 5 mL plasma (EDTA)
- 5 mL serum

Methodology:

1. Multiplex cytokine assay (Mesoscale Discovery , Luminex platform, or **EVERGREEN Health**)
2. Target cytokines:
    - IL-6
    - Interferon-gamma (IFN-γ)
    - IL-10
    - TNF-α
    - Additional inflammatory markers: IL-1β, IL-8, IL-12p70, IL-17A, IL-18
    - Chemokines: MCP-1, IP-10, MIP-1α, MIP-1β
3. High-sensitivity assays for low-abundance cytokines

4. Calculate inflammatory index scores
5. Correlate with cognitive and imaging measures

4.1.7 Tissue-Specific Exosomes

Sample Requirements:

- 10 mL plasma (EDTA)
- Process within 4 hours or freeze immediately

Methodology:

1. Exosome isolation:
    - Differential ultracentrifugation
    - Size exclusion chromatography (SEC)
    - Immunoaffinity capture for tissue-specific exosomes
2. Tissue-specific exosome isolation and characterization[6]:
    - Neuronal-derived exosomes (NDEs): L1CAM (CD171) capture
    - Astrocyte-derived exosomes (ADEs): GLAST (EAAT1) capture
    - Microglia-derived exosomes: CD11b capture
    - Oligodendrocyte-derived exosomes: MOG capture
3. Exosome characterization:
    - Nanoparticle tracking analysis (size and concentration)
    - Transmission electron microscopy (morphology)
    - Western blot for exosomal markers (CD9, CD63, CD81, TSG101)
4. Cargo analysis:
    - Protein profiling: Aβ42, total tau, pTau (T181, T217, T231), α-synuclein, neurogranin, synaptotagmin, SNAP-25
    - miRNA profiling- upregulation of miR-16-5p, miR-25-3p, miR-92a-3p, and miR-451a
    - circRNA content - (e.g., circNF1, circTLK1, circPGD, circPSD3) , circLPAR1, circAXL, circGPHN (high-risk) and circPCCA, circHAUS4, circKIF18B, circTTC39C (protective-associated)
5. Functional assays:
    - Exosome uptake by recipient cells
    - Assessment of neurotoxic vs. neuroprotective cargo

4.2 CSF Biomarkers

Sample Requirements:

- 20 mL CSF collected via lumbar puncture
- Aliquot into polypropylene tubes

- Store at -80°C within 2 hours

CSF Collection Protocol:

- Standardized LP procedure (L3/L4 or L4/L5 interspace)
- Patient in lateral decubitus position
- Discard first 2 mL
- Collect in polypropylene tubes (avoid adhesion of proteins)
- Gently invert tubes to mix
- Centrifuge at 2000g for 10 min at 4°C
- Aliquot 0.5 mL per tube

Biomarker Assessment in CSF:

1. **Senescent CD8+ T cells**:
    - Flow cytometry with same panel as peripheral blood
    - Compare phenotypes between CSF and blood
    - Assess APP/tau-specific cells
    - Measure TEMRA (CD45RA+ effector memory) expansion
2. **Autoantibodies**: Same panel as blood
3. **pTau217**: ALZpath or Lumipulse assay
4. **Additional CSF AD biomarkers**:
    - Aβ42, Aβ40, Aβ42/40 ratio
    - Total tau, pTau181, pTau231
    - Neurofilament light chain (NfL)
    - Neurogranin
    - YKL-40 (neuroinflammation marker)
    - sTREM2 (microglial activation)
5. **Cytokines**: Same inflammatory panel as blood
6. **CircRNAs**: RNA extraction and profiling
7. **Exosomes**:
    - Direct isolation from CSF (no need for tissue-specific capture)
    - Cargo analysis similar to plasma exosomes
8. **Metabolomics**: Targeted and untargeted approaches

4.3 Imaging Biomarkers

4.3.1 Amyloid-PET

- Tracer: [18F]florbetapir, [18F]florbetaben, or [18F]flutemetamol
- Standardized uptake value ratios (SUVRs)

- Centiloid scaling for harmonization
- Visual read by certified readers (positive/negative)

4.3.2 Tau-PET

- Tracer: [18F]MK-6240 or [18F]RO948 (second-generation tracers preferred)
- Regional SUVRs (entorhinal cortex, temporal lobe, neocortex)
- Braak staging correlation

4.3.3 MRI

- 3T MRI with standardized protocol
- T1-weighted structural imaging (volumetric analysis)
- T2-FLAIR (white matter hyperintensities)
- DTI (diffusion tensor imaging) for microstructural integrity
- Resting-state fMRI (optional)

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5. Cognitive and Clinical Assessments

5.1 Cognitive Battery

- **Global cognition**: MMSE, MoCA
- **Episodic memory**: Logical Memory (WMS-IV), RAVLT
- **Executive function**: Trail Making Test A/B, Stroop Test
- **Language**: Category fluency, Boston Naming Test
- **Attention/Processing speed**: Digit Span, Symbol Digit Modalities Test
- **Functional assessment**: FAQ (Functional Activities Questionnaire)

5.2 Clinical Scales

- CDR (Clinical Dementia Rating) and CDR-SB
- NPI (Neuropsychiatric Inventory)
- GDS (Geriatric Depression Scale)

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6. Statistical Analysis Plan

6.1 Sample Size Justification

Based on literature suggesting medium effect sizes (d = 0.5-0.7) for blood biomarker differences between amyloid-positive and amyloid-negative individuals, a sample size of 60 in

the primary cohort and 30 in each control group provides 80% power to detect meaningful differences at $\alpha = 0.05$[7].

6.2 Primary Analyses

6.2.1 Cross-sectional Analysis (Baseline)

1. Compare biomarker levels across the three groups (ANOVA or Kruskal-Wallis)
2. Correlation analyses between:
    - Senescent CD8+ T cells and cognitive performance
    - Autoantibody levels and amyloid/tau-PET
    - pTau217 and imaging biomarkers
    - Inflammatory cytokines and neurodegeneration markers
    - CircRNAs and other biomarkers
    - Exosomal cargo and CSF biomarkers
3. ROC curve analysis for diagnostic accuracy:
    - Individual biomarkers vs. amyloid-PET positivity
    - Multimodal biomarker panel
4. Machine learning approaches (Random Forest, SVM) for biomarker panel optimization

6.2.2 Longitudinal Analysis

1. Linear mixed models for trajectory analysis:
    - Change in biomarkers over 24 months
    - Group × time interactions
    - Covariate adjustments (age, sex, education, baseline cognition)
2. Rate of cognitive decline assessment:
    - Composite cognitive score change
    - CDR-SB progression
3. Predictive modeling:
    - Baseline biomarkers predicting 24-month cognitive decline
    - Baseline biomarkers predicting amyloid/tau accumulation
4. Survival analysis for progression to MCI

6.3 Exploratory Analyses

- Network analysis of cytokine-immune cell interactions
- Mediation analysis (e.g., do senescent T cells mediate the relationship between amyloid and cognitive decline?)
- Subgroup analyses by sex, age, baseline cognitive reserve

- Blood-CSF concordance for shared biomarkers
- Integration of genetic variants with biomarker profiles (GxB interactions)
- Pathway enrichment analysis for metabolomics and transcriptomics data

6.4 Missing Data and Quality Control

- Multiple imputation for missing data (assuming MAR)
- Sensitivity analyses excluding participants with missing CSF or imaging data
- Longitudinal data quality checks (outlier detection, drift correction)
- Batch effect correction for multi-platform assays

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7. Project Timeline

Phase	Timeline
Year 1 (Months 1-12)	
Regulatory approvals (IRB, IND if needed)	Months 1-3
Site initiation and staff training	Months 2-4
Assay validation and optimization	Months 1-6
Participant recruitment (target: 60 enrolled)	Months 4-12
Baseline assessments	Months 4-12
Data collection and biobanking	Ongoing
Year 2 (Months 13-24)	
Continued recruitment (target: 120 total)	Months 13-18
6-month and 12-month follow-up visits	Months 10-24
Biomarker assay execution (batched)	Months 13-24
Interim data analysis	Months 18-24
Year 3 (Months 25-36)	
24-month follow-up visits	Months 25-36
Complete biomarker assays	Months 25-32
Statistical analysis	Months 30-36
Manuscript preparation	Months 33-36
Final report and dissemination	Month 36

Table 3: Project timeline by phase

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8. Budget Overview

8.1 Personnel Costs (36 months)

Position	Estimated Cost
Principal Investigator (20% effort)	$180,000
Co-Investigators (2 × 10% effort)	$160,000
Project Manager (100% effort)	$210,000
Research Coordinators (2 FTE)	$300,000
Biostatistician (25% effort)	$90,000
Laboratory Technicians (2 FTE)	$240,000
Bioinformatics Analyst (50% effort)	$135,000
Total Personnel	**$1,315,000**

8.2 Laboratory and Biomarker Costs

Assay/Service	Estimated Cost
Flow cytometry (senescent T cells)	$240,000
Autoantibody panels (Luminex)	$180,000
pTau217 assays (blood and CSF)	$144,000
CircRNA sequencing and validation	$200,000
Metabolomics (targeted + untargeted)	$180,000
Cytokine multiplex assays	$120,000
Exosome isolation and analysis	$250,000
CSF core biomarkers (Aβ, tau)	$120,000
DNA extraction and genotyping	$60,000
RNA-seq for CD8+ T cells	$150,000
Reagents and consumables	$200,000
Total Laboratory	**$1,844,000**

8.3 Imaging Costs

Imaging Modality	Estimated Cost
Amyloid-PET (240 scans)	$960,000

Tau-PET (240 scans)	$960,000
MRI (360 scans)	$360,000
Image processing and analysis	$120,000
Total Imaging	**$2,400,000**

8.4 Other Direct Costs

Category	Estimated Cost
Participant compensation	$180,000
Recruitment and advertising	$60,000
Data management system	$90,000
Equipment and supplies	$150,000
Travel and meetings	$60,000
Publication costs (open access)	$30,000
Total Other	**$570,000**

8.5 Total Budget Summary

Category	Amount
Personnel	$1,315,000
Laboratory/Biomarkers	$1,844,000
Imaging	$2,400,000
Other Direct Costs	$570,000
Direct Costs	**$6,129,000**
Indirect Costs (50% of MTDC)	$3,064,500
Total Project Cost	**$9,193,500**

Table 4: Total budget summary for 36-month project

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9. Regulatory and Ethical Considerations

9.1 IRB Approval

- Full IRB review required (greater than minimal risk due to lumbar puncture and PET scans)
- Annual continuing review
- Adverse event reporting plan
- Data Safety Monitoring Board (DSMB) for participant safety oversight

9.2 Informed Consent

- Comprehensive consent process covering:
    - Genetic testing and results disclosure (ApoE4 status)
    - Return of research results policy
    - Biobanking and future use of samples
    - PET radiation exposure
    - Lumbar puncture risks
- Separate consent for optional future contact

9.3 Data Privacy and Security

- HIPAA compliance
- De-identification procedures
- Secure data storage (encrypted, access-controlled)
- Data sharing plan with appropriate protections
- Certificate of Confidentiality

9.4 Genetic Counseling

- Pre-test counseling for ApoE genotyping (if not previously known)
- Post-test result disclosure with genetic counselor available
- Discussion of implications for family members

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10. Data Management and Quality Assurance

10.1 Data Management Plan

- Electronic data capture (EDC) system (REDCap or similar)
- Standard operating procedures (SOPs) for all procedures
- Real-time data validation and range checks
- Regular data quality reports

- Central monitoring of data completeness
- Biospecimen tracking system (LIMS)

10.2 Quality Assurance

- Staff training and certification
- Inter-rater reliability for cognitive assessments
- Calibration and maintenance of equipment
- Proficiency testing for laboratories
- Internal audits (quarterly)
- Protocol deviation tracking and corrective action

10.3 Biobanking

- Establish comprehensive biobank with aliquots for:
    - Current planned analyses
    - Future exploratory studies
    - Validation studies
    - Assay optimization/troubleshooting
- Storage at -80°C for plasma, serum, CSF, PBMCs
- Liquid nitrogen storage for long-term cell banking
- Detailed sample inventory and tracking

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11. Expected Outcomes and Impact

11.1 Primary Deliverables

1. Comprehensive characterization of immune-mediated biomarkers in early AD among high-risk individuals
2. Diagnostic performance metrics for a multimodal biomarker panel
3. Longitudinal trajectories of biomarker changes preceding cognitive decline
4. Blood-CSF biomarker concordance data to inform future blood-based screening approaches
5. Validated assays for senescent T cell quantification and antigen-specific responses
6. CircRNA and exosomal biomarker signatures

11.2 Scientific Impact

This study will address critical knowledge gaps:

- **Immune dysfunction in early AD**: Define the role of senescent CD8+ T cells and autoimmunity in preclinical disease
- **Multimodal biomarker integration**: Move beyond single biomarkers to comprehensive biological profiles
- **Blood-based accessibility**: Evaluate which biomarkers can be reliably measured in blood, reducing the need for invasive CSF collection
- **Personalized risk stratification**: Combine genetic (ApoE4 + PRS) with biological markers for precision medicine approaches
- **Therapeutic target identification**: Senescent T cells and inflammatory pathways may represent actionable targets for intervention

11.3 Clinical Translation Potential

- Development of point-of-care or laboratory-developed tests for early AD screening
- Identification of participants for clinical trials of disease-modifying therapies
- Stratification biomarkers for immunomodulatory interventions (e.g., senolytic therapies targeting senescent T cells)
- Foundation for future intervention studies in high-risk, biomarker-positive individuals

11.4 Publications and Dissemination

Planned Publications:

1. Primary manuscript: "Multimodal biomarker profile of early Alzheimer's disease in ApoE4 heterozygotes with high polygenic risk" (target: *Nature Medicine*, *JAMA Neurology*, or *Alzheimer's & Dementia*)
2. Immune profiling manuscript: "Senescent CD8+ T cells and autoantibodies in preclinical Alzheimer's disease"
3. CircRNA biomarkers manuscript
4. Exosome cargo analysis manuscript
5. Blood-CSF concordance analysis
6. Methodological paper on senescent T cell isolation and characterization

Conference Presentations:

- Alzheimer's Association International Conference (AAIC)
- Clinical Trials on Alzheimer's Disease (CTAD)
- Society for Neuroscience (SfN)
- American Academy of Neurology (AAN)

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12. Risk Mitigation Strategies

Risk	Likelihood	Mitigation Strategy

Slow recruitment	Medium	Multi-site expansion plan; targeted recruitment through registries; flexible inclusion criteria if needed
High attrition rate	Low-Medium	Minimize participant burden; provide adequate compensation; maintain regular contact
Technical failures in novel assays	Medium	Extensive validation phase; backup assays; collaboration with expert laboratories
Batch effects in biomarker measurement	Medium	Randomized sample processing; use of internal standards; statistical batch correction
Low proportion of amyloid-positive participants	Low	Target high-risk population; may extend follow-up if needed
Insufficient CSF volume	Low	Train experienced clinicians; have re-consent process for repeat LP if necessary

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13. Future Directions

Following completion of this foundational study, logical next steps include:

- **Validation cohort**: Independent replication in a separate cohort
- **Intervention studies**: Test immunomodulatory or senolytic therapies in biomarker-positive individuals
- **Point-of-care device development**: Translate key biomarkers (e.g., pTau217, autoantibodies) into accessible testing platforms
- **Expanded PRS analysis**: Refine polygenic risk models incorporating novel variants and biomarker data
- **Multi-ethnic cohorts**: Extend findings to diverse populations
- **Earlier intervention**: Study younger individuals (40-55 years) in ApoE4 homozygote populations

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14. Project Team and Expertise

14.1 Required Expertise

- **Principal Investigator**: Expertise in Alzheimer's disease, clinical research, biomarker development

- **Co-Investigators**:
  - Neurologist with AD specialization
  - Immunologist with T cell biology expertise
  - Biochemist/Molecular biologist for circRNA and exosome work
- **Collaborators**:
  - Flow cytometry core director
  - Bioinformatics expert
  - Imaging specialists (PET, MRI)
  - Biostatistician with longitudinal data expertise
  - Genetic counselor

14.2 Clinical Site Requirements

- Access to Memory Clinic or Research Cohort with ApoE4+ individuals
- Clinical laboratory (CLIA-certified for some assays)
- Flow cytometry facility
- Neuroimaging center with PET and MRI capabilities
- Biobanking facility with -80°C storage

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15. Conclusions

This comprehensive project plan outlines a rigorous, hypothesis-driven study to evaluate early biomarkers of Alzheimer's disease in a genetically high-risk population. By integrating cutting-edge immunological profiling, established biomarkers, and novel molecular signatures, this study has the potential to:

1. **Transform our understanding** of immune dysregulation in preclinical AD
2. **Identify accessible blood-based biomarkers** for early detection and risk stratification
3. **Reveal therapeutic targets** for disease-modifying interventions
4. **Accelerate clinical trial recruitment** by identifying biomarker-positive, at-risk individuals
5. **Advance precision medicine** approaches to AD prevention and treatment

The multimodal biomarker strategy positions this study at the forefront of AD research, bridging basic immunology, systems biology, and clinical neuroscience to address one of the most pressing challenges in medicine.

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EAJM_October_2023 (1)-208-212.pdf - Exosomal Circular Ribonucleic Acid–Microribonucleic Acid Expression Profile from Plasma in Alzheimer's Disease Patients by Bioinformatics and Integrative Analysis

Alzheimer's Disease Genetics Fact Sheet | National Institute on Aging

Can digital replicas of patients help personalize Alzheimer's treatment? | Penn State University

Award Details - NSF Award Search

Longitudinal blood biomarker trajectories in preclinical Alzheimer's disease - PubMed

Alzheimer's disease and inflammatory biomarkers positively correlate in plasma in the UK-ADRC cohort - PMC

TSPO PET BRAIN INFLAMMATION IMAGING: A TRANSDIAGNOSTIC SYSTEMATIC REVIEW AND META-ANALYSIS OF 156 CASE-CONTROL STUDIES | International Journal of Neuropsychopharmacology | Oxford Academic

Table 3 Replication of the LOAD-associated proteins from AGES (n = 5,127) in the ACE cohort (n = 719)

Frontiers | Why Senescent Cells Are Resistant to Apoptosis: An Insight for Senolytic Development

BCL-xL Targeting to Induce Apoptosis and to Eliminate Chemotherapy-Induced Senescent Tumor Cells: From Navitoclax to Platelet-Sparing BCL-xL PROTACs - PubMed

Fig. 1: The multifaceted effect of GLP-1RAs on different brain cells to mitigate AD phenotypes. | Nature Aging

GLP-1R agonists protect against Alzheimer's disease by rewiring energy regulation - PubMed

Transcriptomic Profiling Identifies CD8+ T Cells in the Brain of Aged and Alzheimer's Disease Transgenic Mice as Tissue-Resident Memory T Cells - PMC

CD103–CD8+ T cells promote neurotoxic inflammation in Alzheimer's disease via granzyme K–PAR-1 signaling | Nature Communications

Spatiotemporal Analysis of Remyelination Reveals a Concerted Interferon-Responsive Glial State That Coordinates Immune Infiltration

Altered Extracellular Vesicle miRNA Profile in Prodromal Alzheimer's Disease

Altered T-cell reactivity in the early stages of Alzheimer's disease | Brain | Oxford Academic

Aging reshapes the adaptive immune system from healer to saboteur | Nature Aging

Look And Listen: Cognito And WVU Imagine A Future Beyond Alzheimer's

Advancing T-cell immunotherapy for cellular senescence and disease: Mechanisms, challenges, and clinical prospects - ScienceDirect

Guidelines for T cell nomenclature | Nature Reviews Immunology

S41577-025-01238-2.pdf

A wearable repetitive transcranial magnetic stimulation device | Nature Communications

Targeted clearance of senescent cells using an antibody-drug conjugate against a specific membrane marker | Scientific Reports

Detection of Alzheimer's disease at mild cognitive impairment and disease progression using autoantibodies as blood-based biomarkers - PubMed

Altered Extracellular Vesicle miRNA Profile in Prodromal Alzheimer's Disease

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