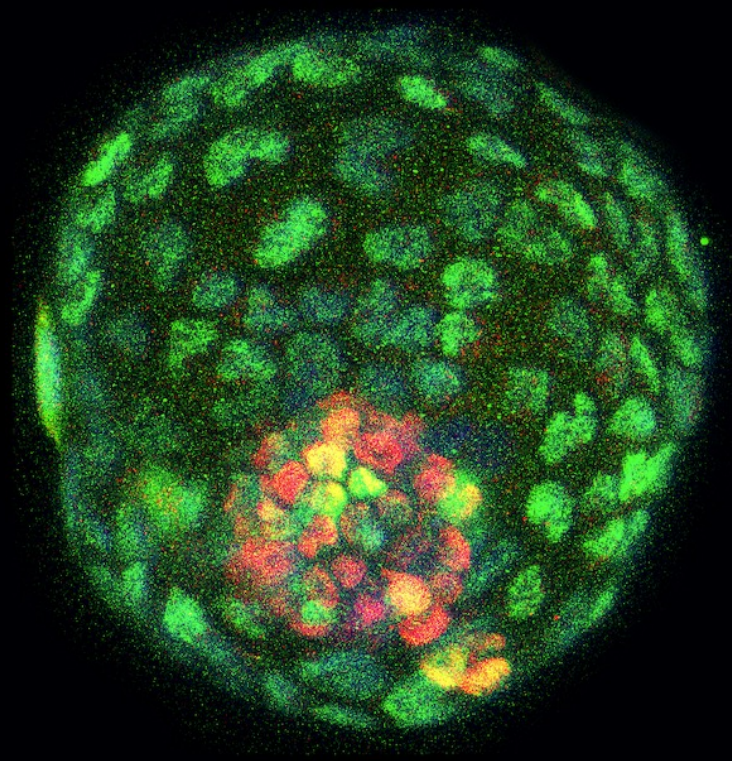
HUMAN CELL MODELS OF AGING CORE

- SD-NSC HUMAN COHORT
- CELLULAR MODELS OF AGING

Co-Leaders:

Anthony Molina (UCSD)

Rusty Gage (Salk)



SAN DIEGO NATHAN SHOCK CENTER

2022 WORKSHOP

salk
Where cures begin.

Sanford Burnham Prebys

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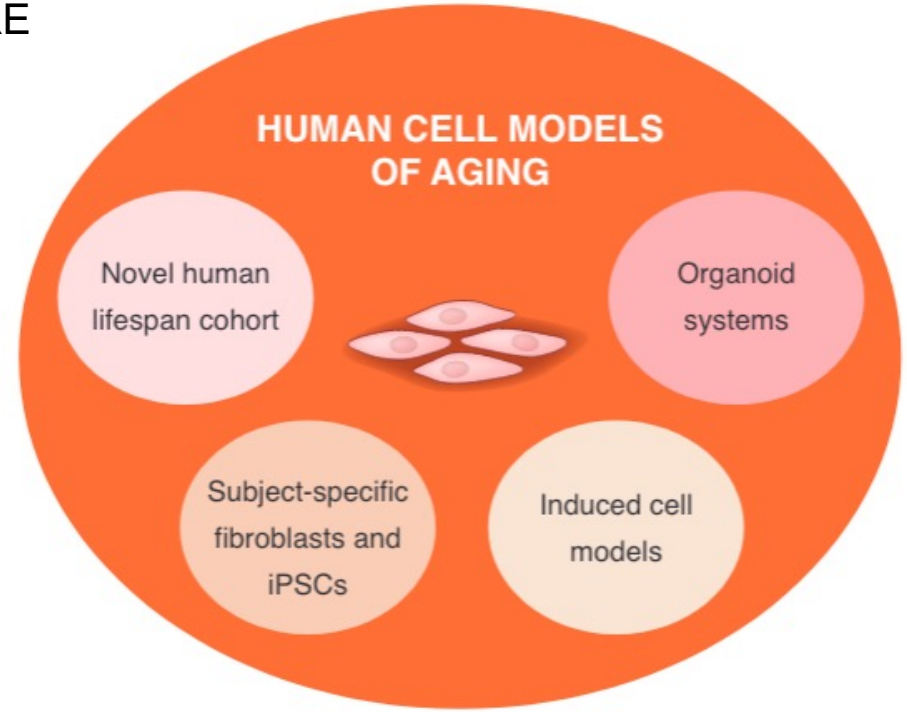
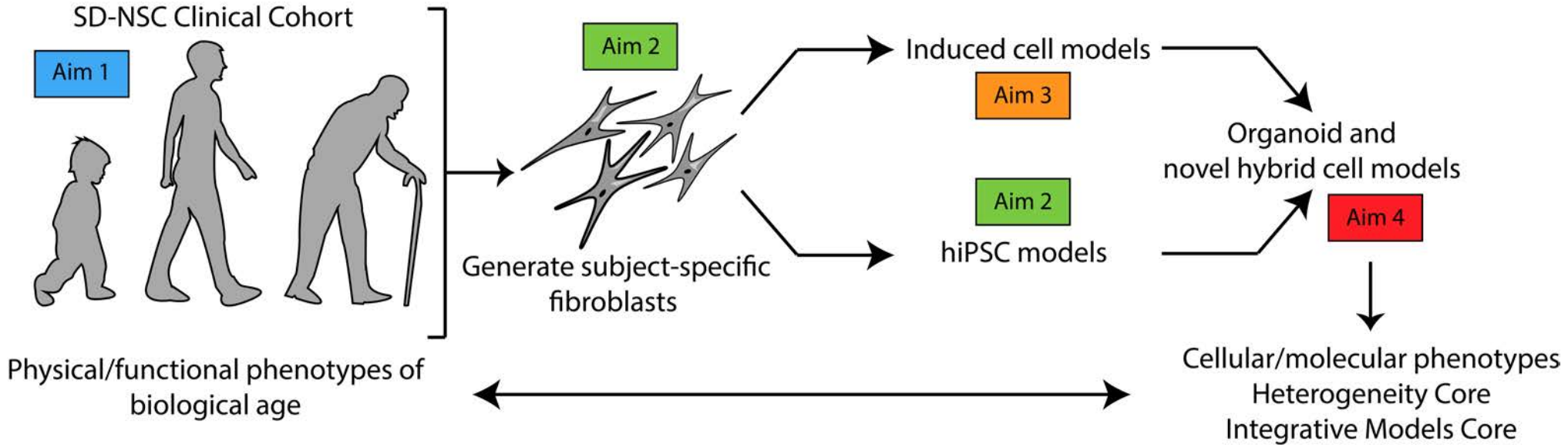
School of Medicine

HUMAN CELL MODELS OF AGING CORE

- INTRODUCTION TO HUMAN CELL MODELS OF AGING CORE
- OVERVIEW OF **SD-NSC HUMAN LIFESPAN COHORT**
- OVERVIEW OF **CELL MODELS**



A WELL PHENOTYPED COHORT POWERS NOVEL CELL MODELS



- **SD-NSC Cohort will represent the adult human lifespan** and be extensively phenotyped for functional metrics of biological aging
- Subject-specific fibroblast used to generate ***iCell models (capture age related phenotypes)*** and hiPSCs
- hiPSCs used to generated ***niche specific multi-cellular organoid models***
- ***iCell and hiPSC models combined*** into novel hybrid models of human aging

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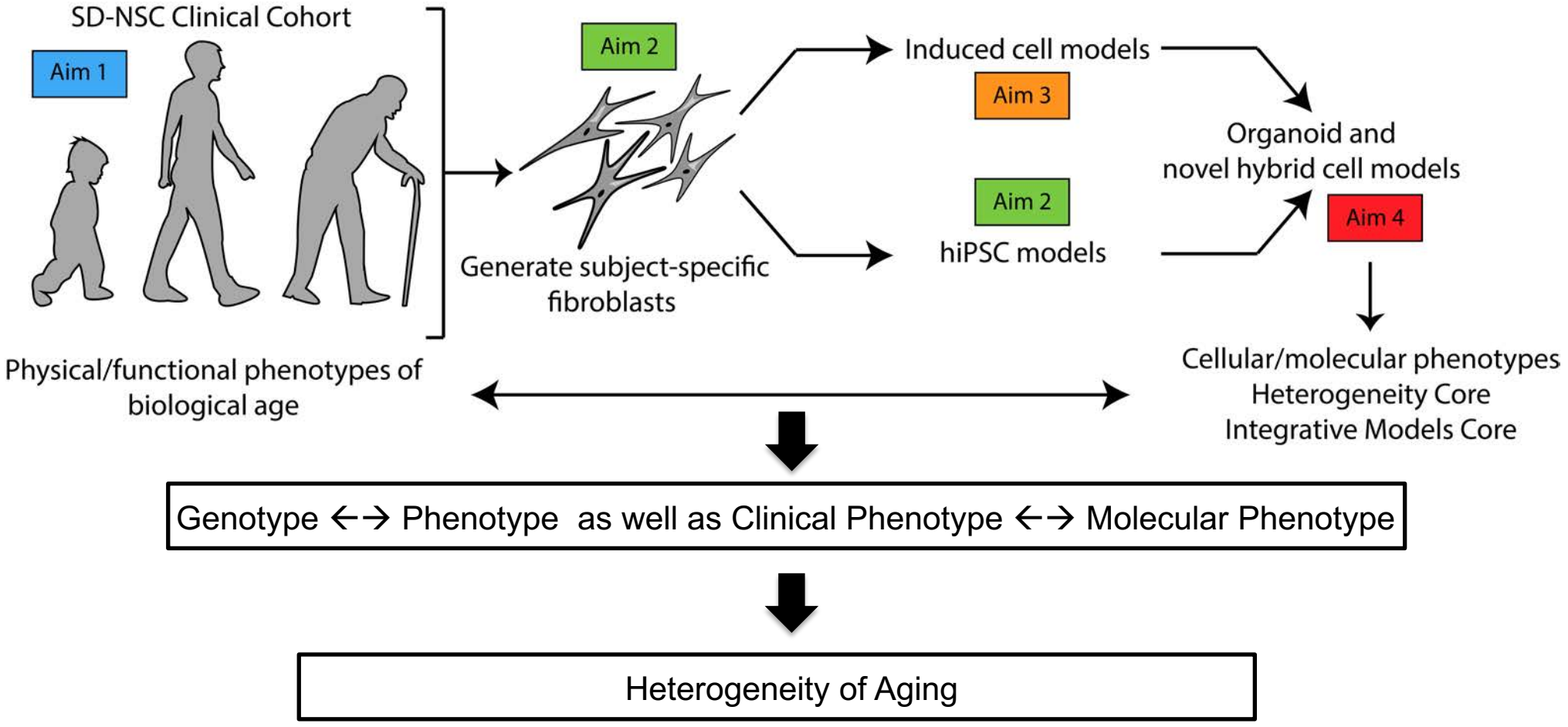

What is “representative” or “normal” when it comes to aging?

Major Considerations:

-Healthy vs Normal

-Majority of patients over 65 present with multiple comorbidities

Inclusion	Exclusion
-Over 20yrs of age **-Able to consent and participate in the study using English** **-BMI ≥ 18.5 and ≤30 kg/m2.** **-Weight stable for the prior 6 weeks** **-Normal cognitive function** **-Willing and able to attend two in-person study visits that will include vigorous exercise testing, blood draw, and skin biopsy.** **-Willing to wear a wireless accelerometer (Actigraph GT3X) for 14 days**	-Are pregnant -Diabetes (fasting glucose >126 mg/dl) -Uncontrolled hypertension (BP > 140/90 mmHg) -Heart or cardiovascular condition, including coronary artery disease, congestive heart failure, diagnosed abnormality of heart rhythm, atrial fibrillation, and/or a history of myocardial infarction -Cancer or history of cancer -Dementia or other conditions that may affect cognitive ability -Sensory or physical impairment that would prevent participation -Parkinson’s disease, multiple sclerosis, or other neurological condition, including a previous stroke, which may be causing impaired muscle function or mobility -Medications and supplements that may interfere with measurements or biological outcomes including, but not limited to: metformin, CoQ, glucocorticoids, and medications that may alter cardiac and hemodynamic responses to exercise -Respiratory disease -Answers “yes” to one or more questions in the American College of Sports Medicine’s Physical Activity Readiness Questionnaire (PAR-Q) and/or report two or more risk factors for exercise testing

Defining Biological Age – Function Based

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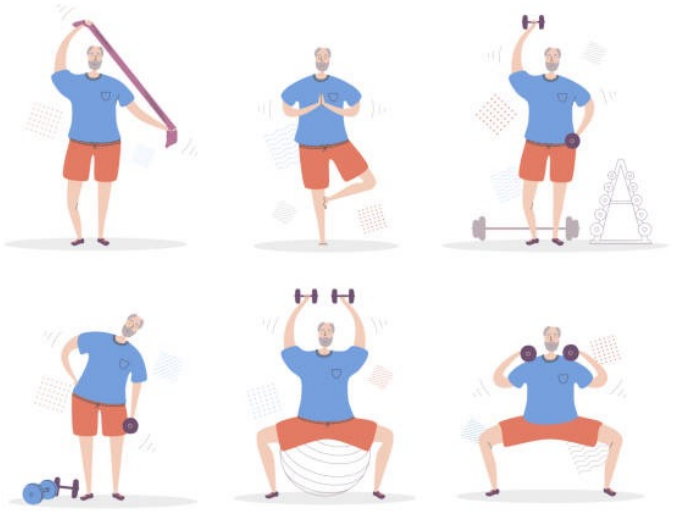
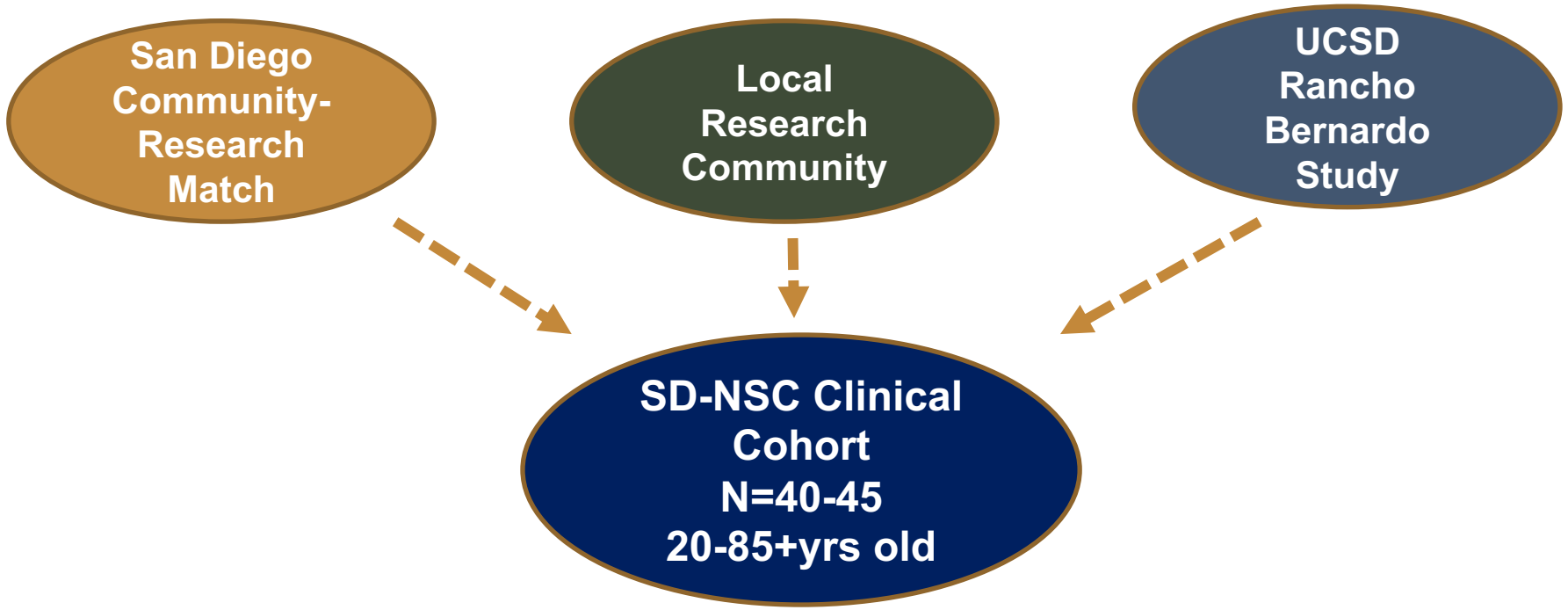
Physical

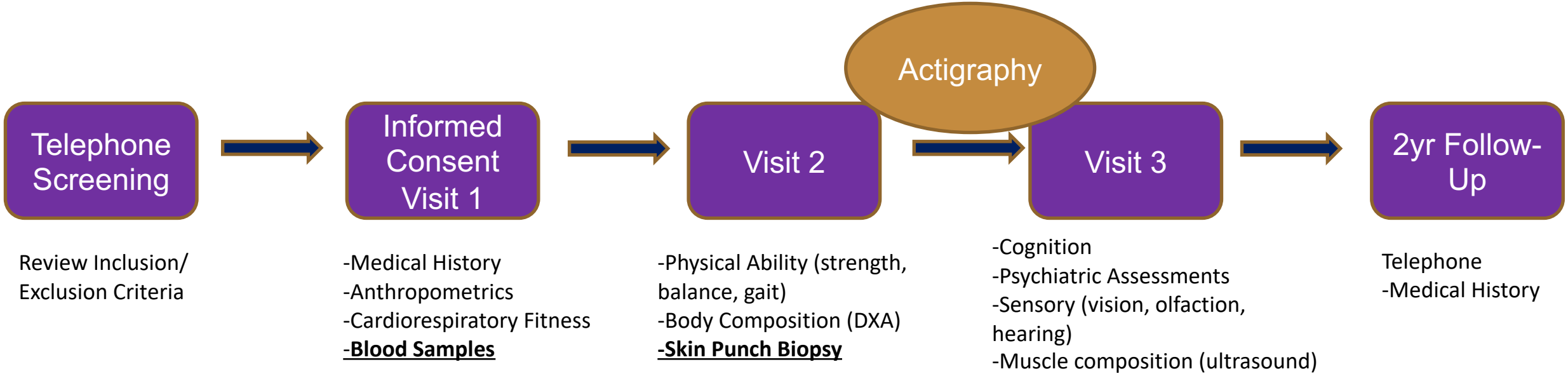


Cognitive

Sensory

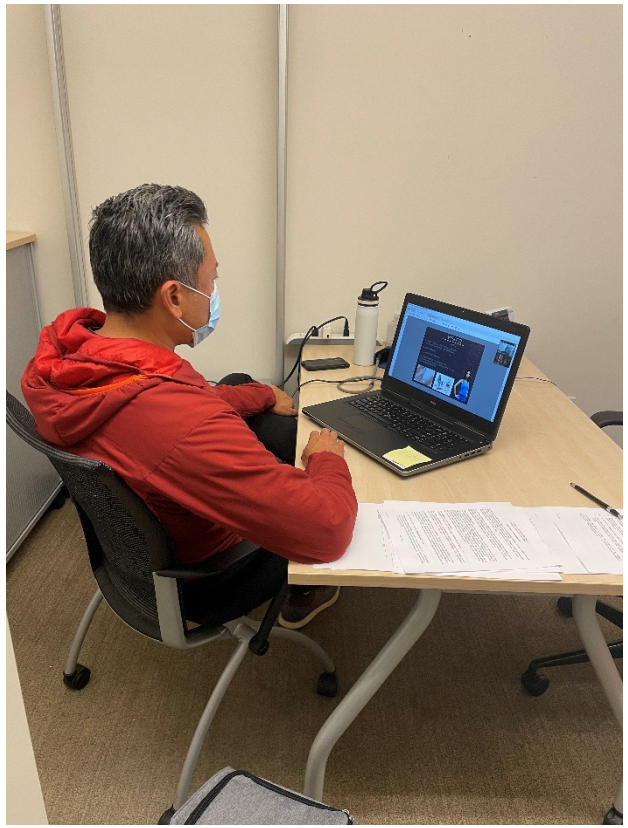
Additional Measures : Activity, Wisdom, Loneliness


San Diego Community-Research Match
Local Research Community
UCSD Rancho Bernardo Study
SD-NSC Clinical Cohort
N=40-45
20-85+yrs old


Actigraphy
Telephone Screening
Informed Consent Visit 1
Visit 2
Visit 3
2yr Follow-Up
Review Inclusion/ Exclusion Criteria
-Medical History
-Anthropometrics
-Cardiorespiratory Fitness
-Blood Samples
-Physical Ability (strength, balance, gait)
-Body Composition (DXA)
-Skin Punch Biopsy
-Cognition
-Psychiatric Assessments
-Sensory (vision, olfaction, hearing)
-Muscle composition (ultrasound)
Telephone
-Medical History

Visit 1

Informed Consent During the Covid-19 Pandemic



Blood Sample Collection

Visit 1

Cardiorespiratory Fitness (CPET)

-VO2 max is generally regarded as the best indicator of cardiorespiratory fitness.

-Safety

-Persons with counterindications will be excluded from the study

-Monitoring (Physician, Exercise Physiologists)

-EKG, Blood Pressure

-Age/Ability appropriate

-Exercise Modalities

Additional measurements: RMR, Pulmonary function (spirometry)

Visit 2

Short Physical Performance Battery

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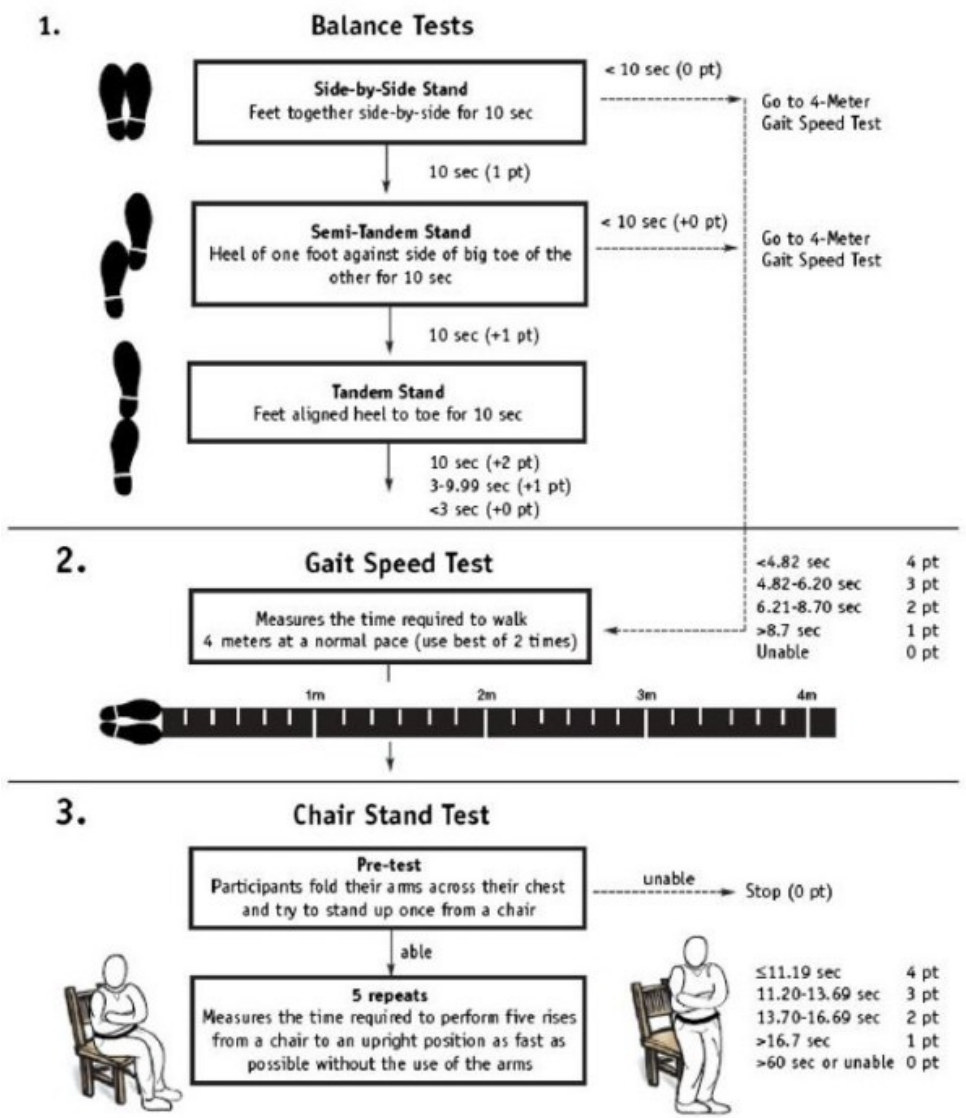
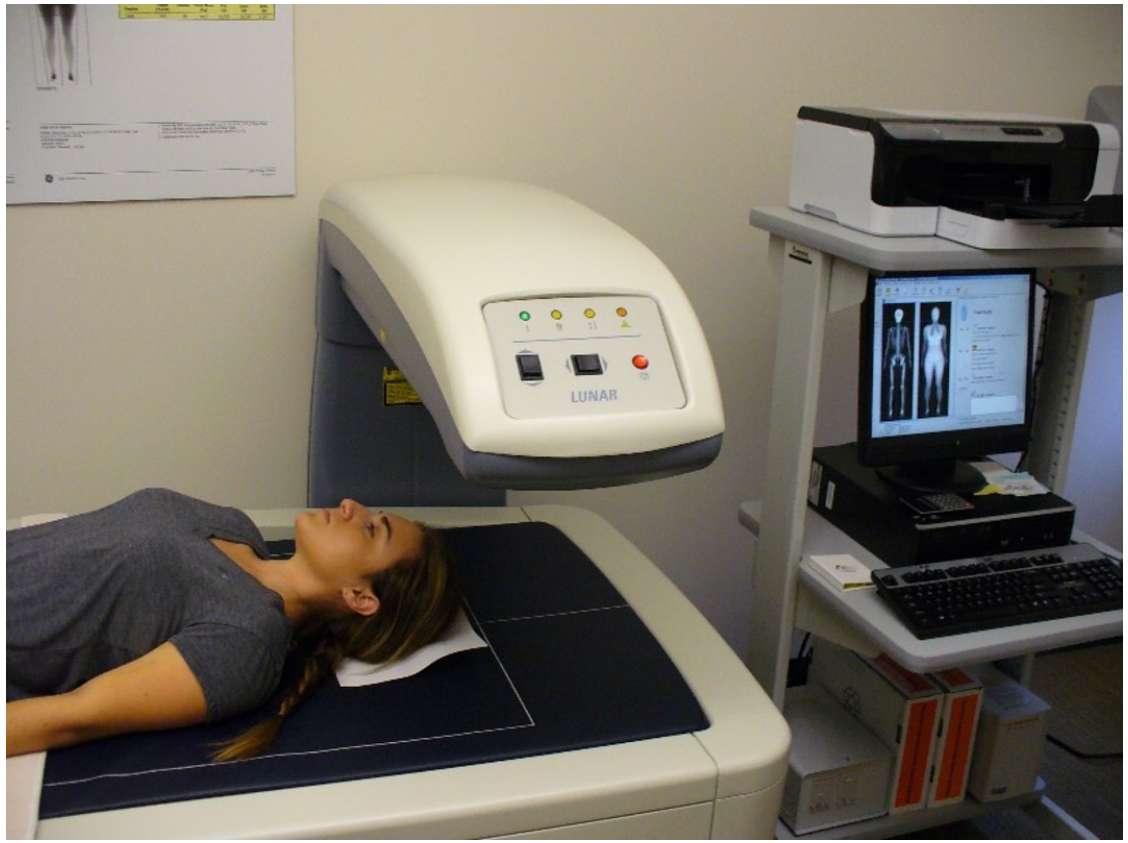


Limitations

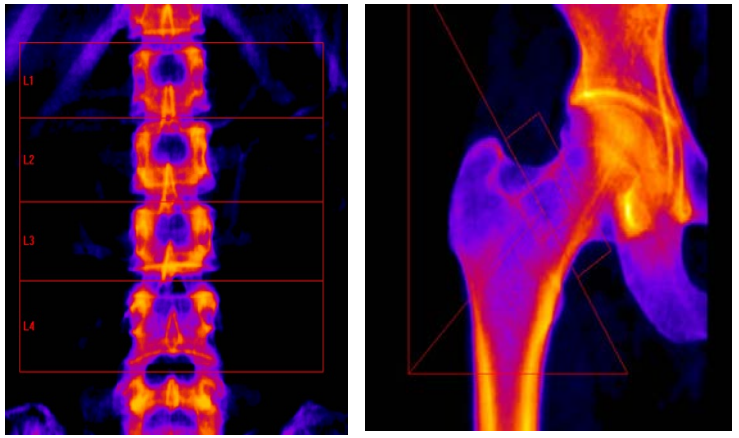
-Ceiling Effects

Visit 2

Dual-energy X-ray absorptiometry (DXA)



Bone Mineral Density



Body Composition

Visit 2

Physical Performance

Gait Speed

-6mwd (fast)

-2.5 mwd (usual)

Leg Strength (Biodex)

Grip Strength

Visit 2

Skin Punch Biopsy

SD-NSC Cell Models Core @Salk

Actigraphy

Visit 2-3

monitoring rest/activity cycles
2 weeks

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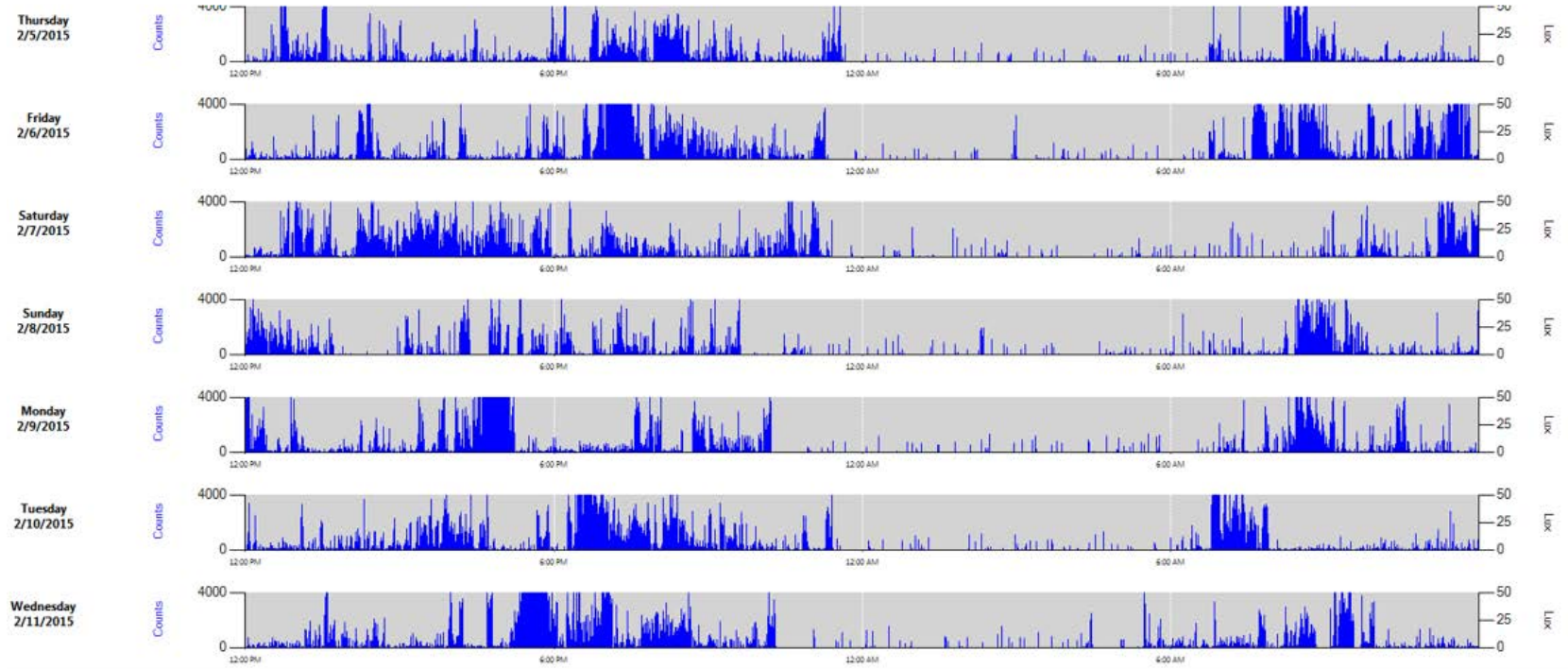
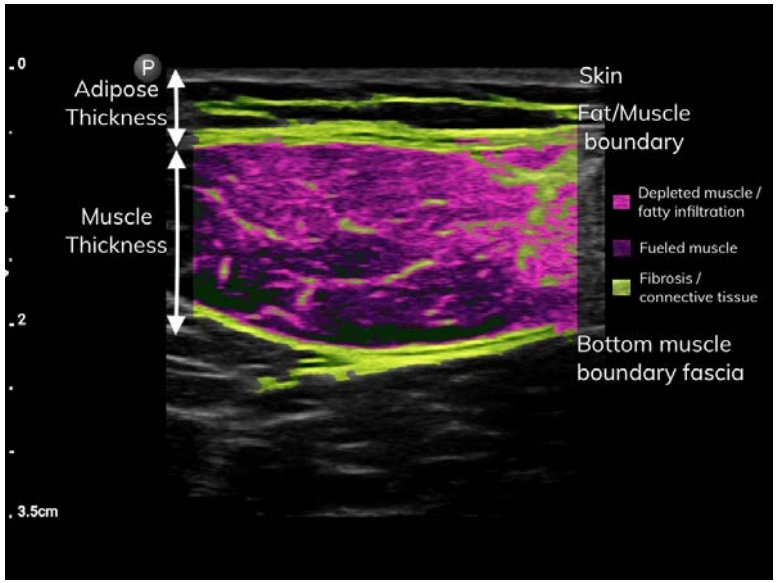


Visit 3

Muscle Composition

Size and Adiposity



Visit 3

Sensory Abilities

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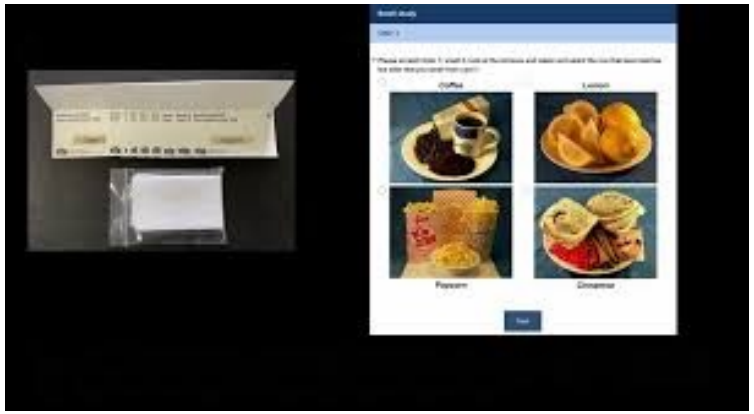
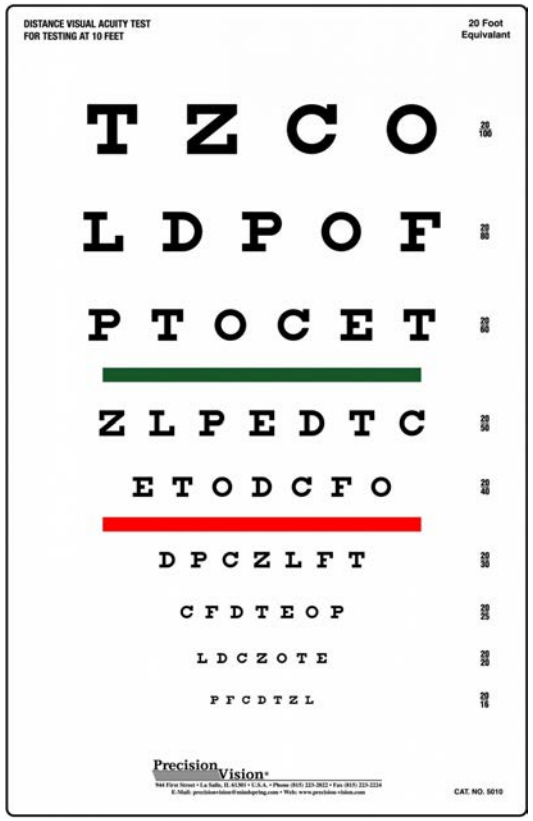
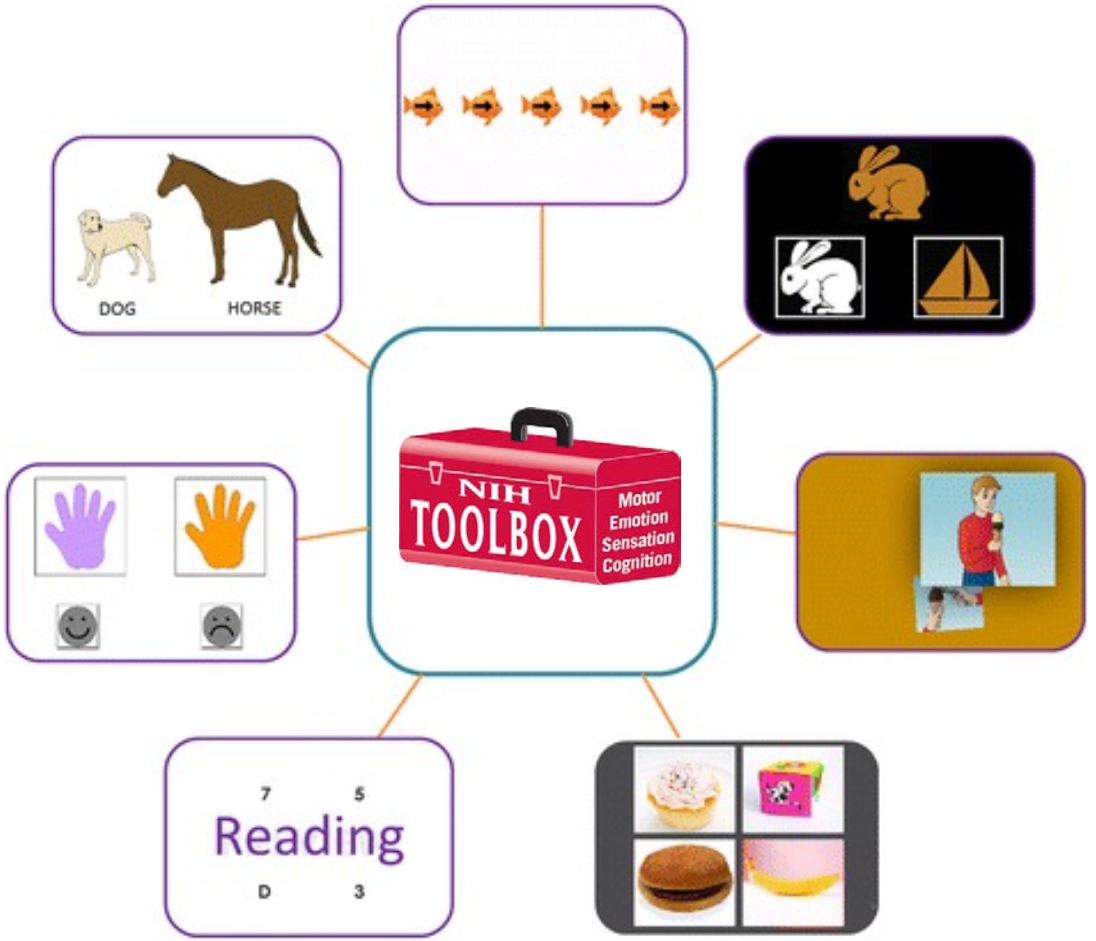




Visit 3

Cognition



Biological Samples

SD-NSC Biorepository
Rolling Enrollment (2021-2023)

Blood

-Platelets
-WBCs
-Plasma

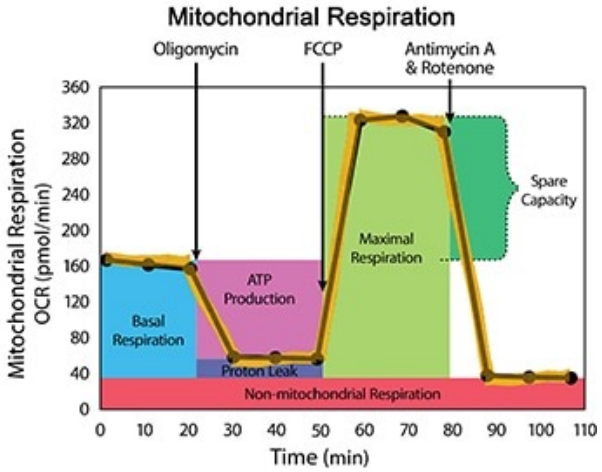
Cells

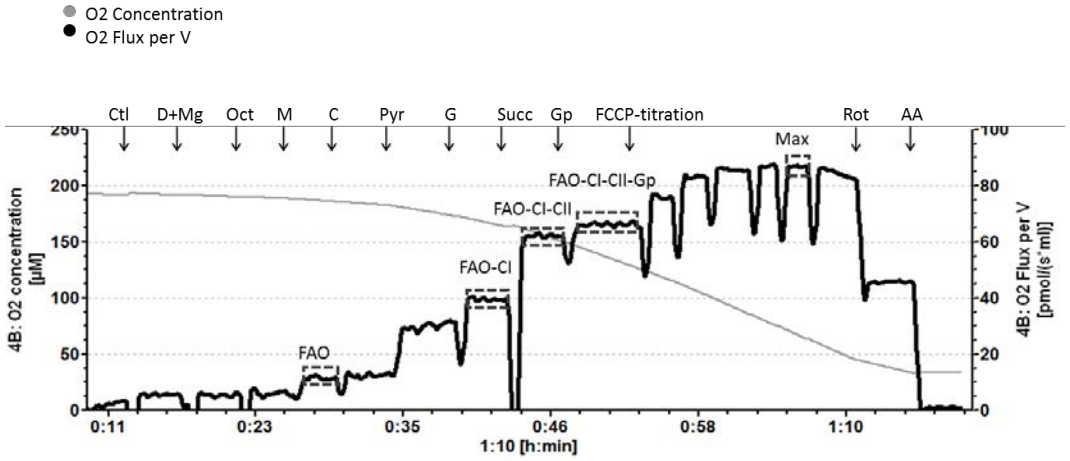
-Primary dermal fibroblasts
-iPSCs (not yet available)

Representation from 20-75+ yrs old is available now

What are we doing with the cells?

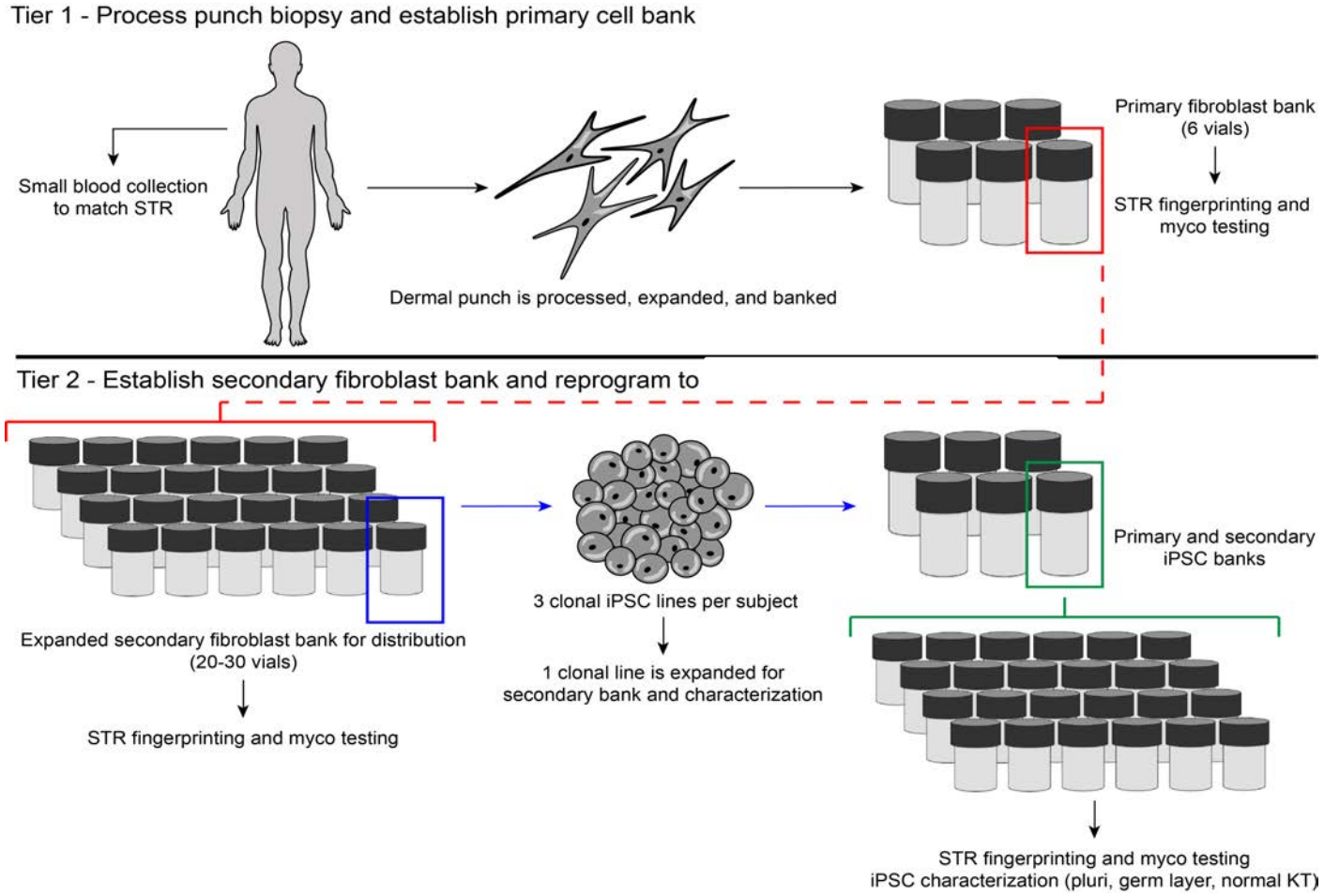
-Profiling age-related mitochondrial bioenergetic decline
Fibroblasts, PBMCs, Platelets, lymphocytes



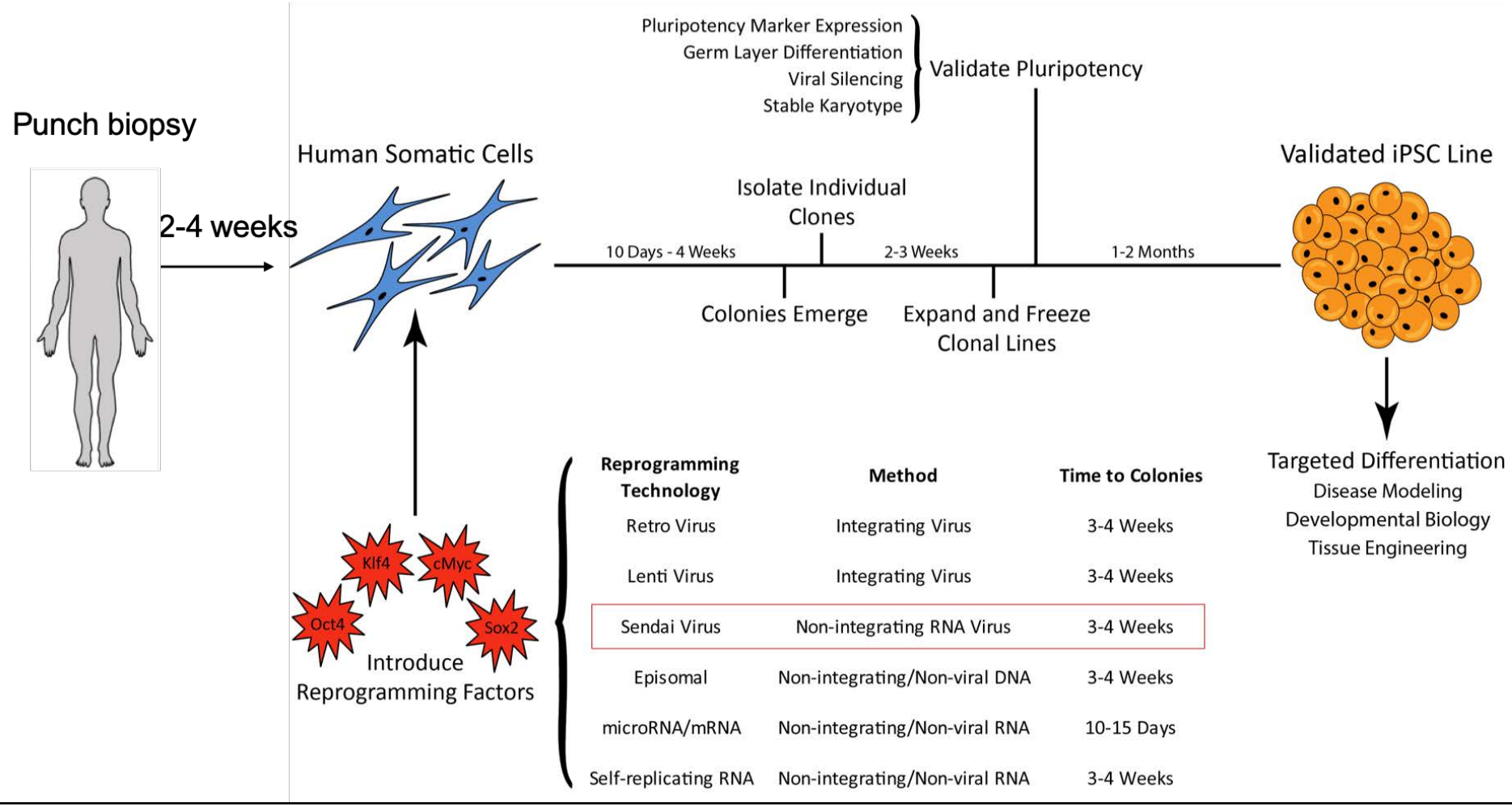


www.molinalab.com

Tiered Banking Ensures Prolonged Access to Cell Resources

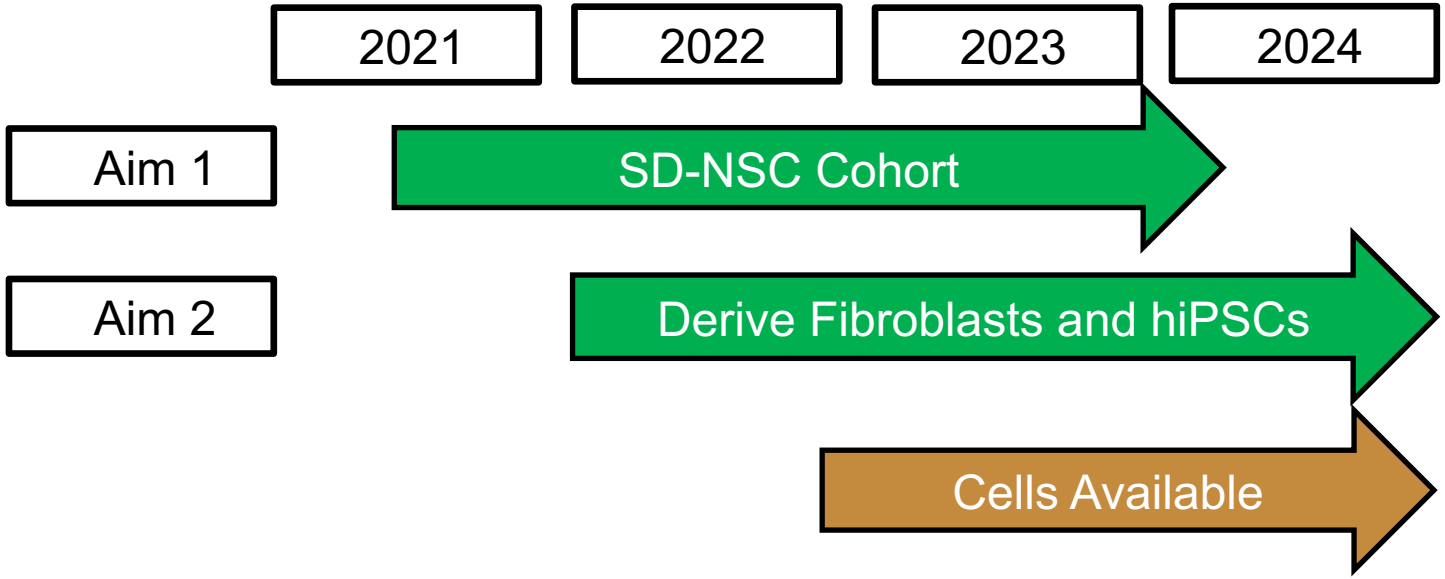


Derive → Bank → Characterize → Model



Reprogramming Technology	Method	Time to Colonies
Retro Virus	Integrating Virus	3-4 Weeks
Lenti Virus	Integrating Virus	3-4 Weeks
Sendai Virus	Non-integrating RNA Virus	3-4 Weeks
Episomal	Non-integrating/Non-viral DNA	3-4 Weeks
microRNA/mRNA	Non-integrating/Non-viral RNA	10-15 Days
Self-replicating RNA	Non-integrating/Non-viral RNA	3-4 Weeks

ESTIMATED TIMELINE FOR CELL RESOURCES



Fibroblasts and hiPSCs available in late 2022

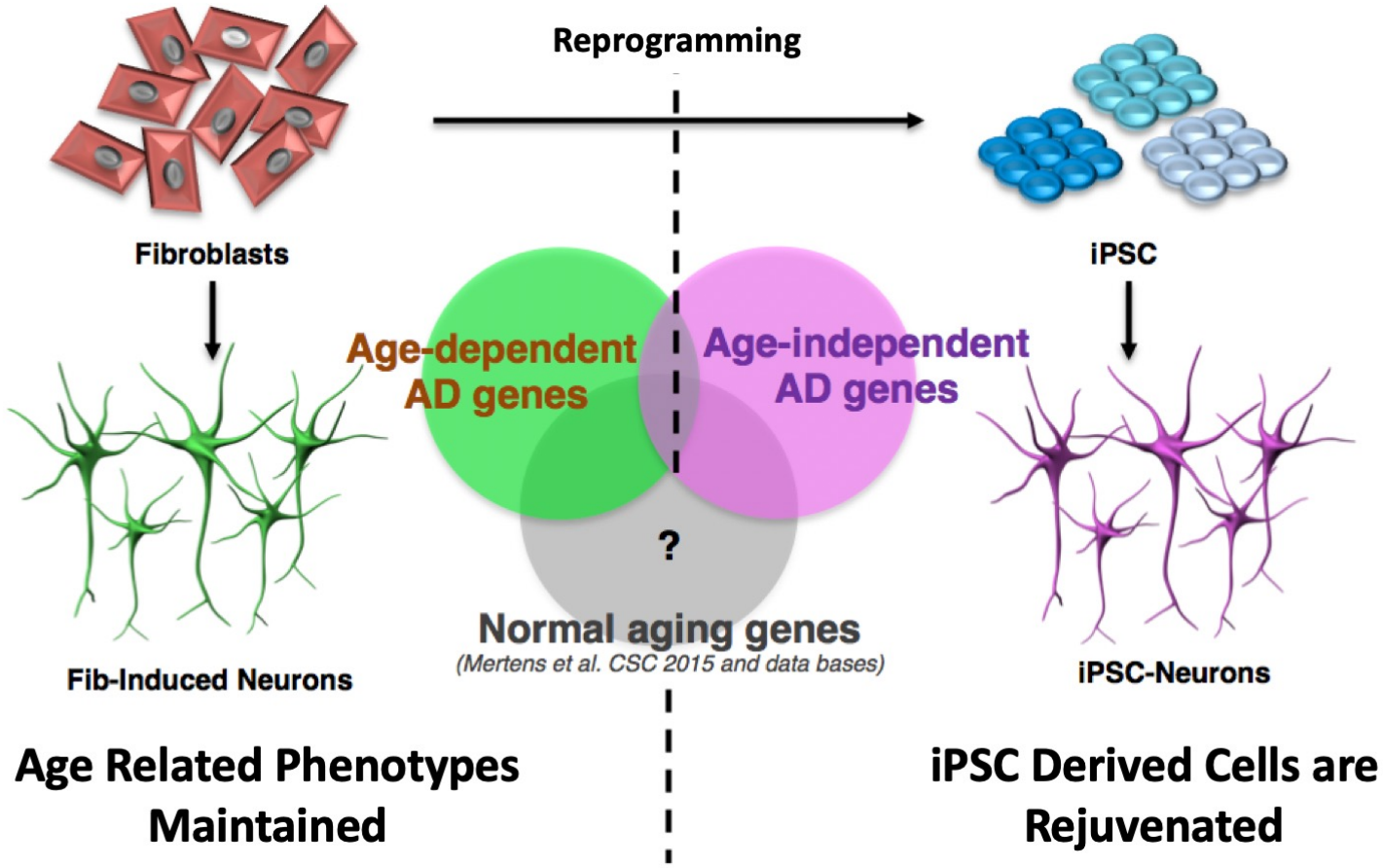
Early sharing through HCMA Core (SD-NSC Website)

Plans are underway for broader distribution

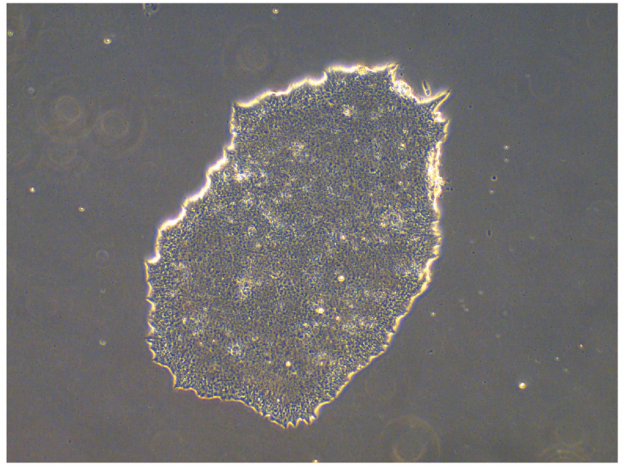
Protocols for basic fibroblast/hiPSC maintenance are now available

Formal written and image-enhanced protocols (SD-NSC Website)

iCell Models Maintain Age Related Phenotypes



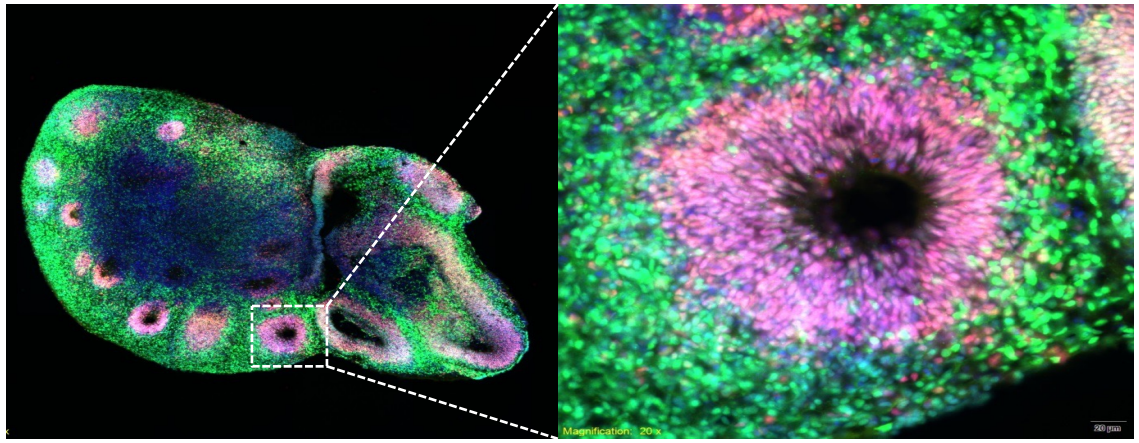
hiPSCs Recreate Niche Specific Dynamics Through Organoid Models



2D hiPSCs

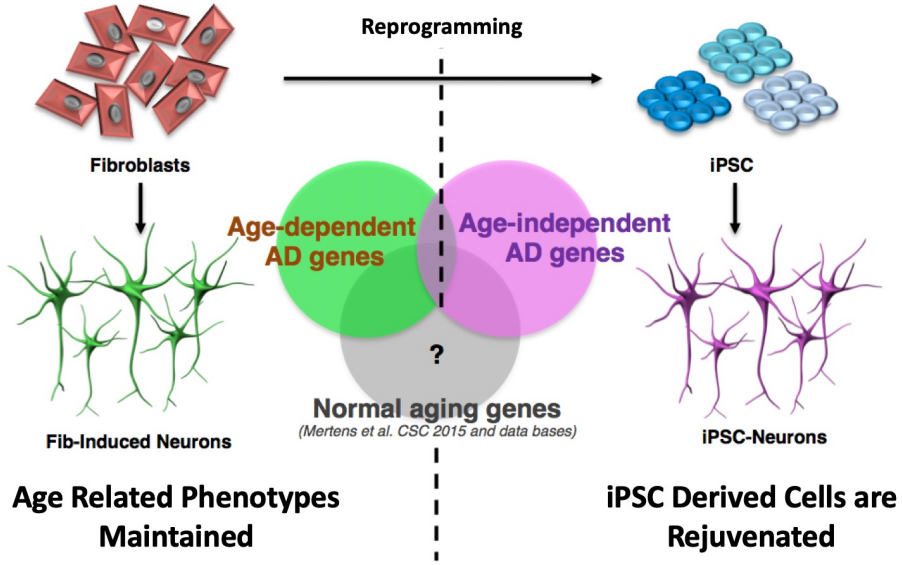
3D, Matrix, Morphogens

Time



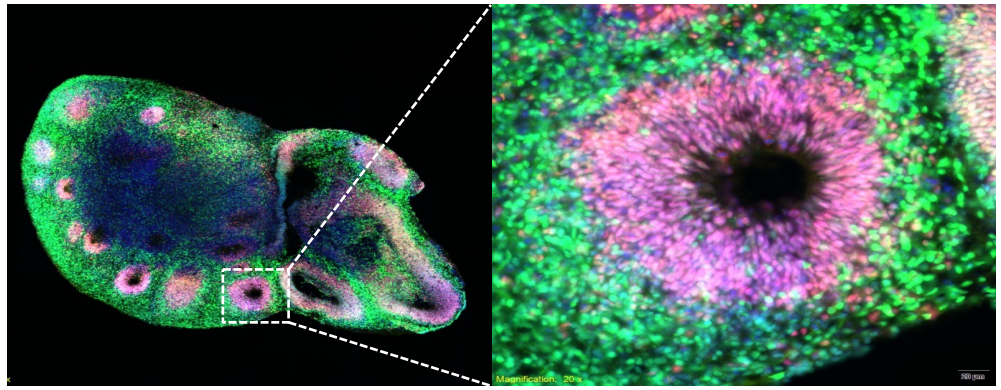
3D Organoids w/Multi-Cellular Structural Complexity

HYBRID MODELS COMBINE THE BEST OF BOTH WORLDS



Age Related Phenotypes

+

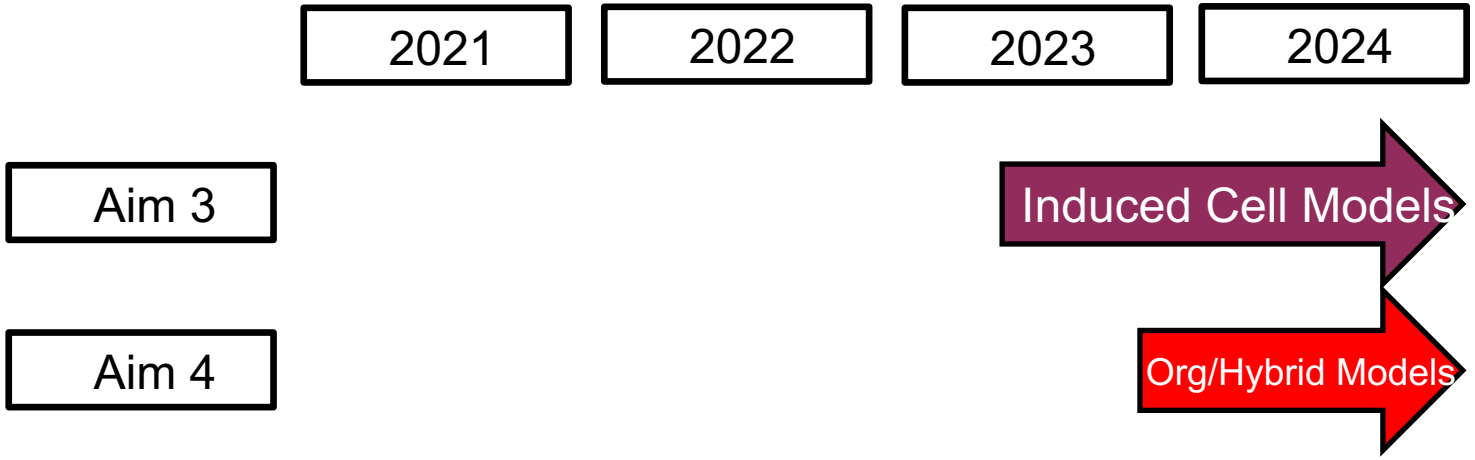


Niche Specific Multi-Cellular Dynamics

Hybrid Models of Human Aging

Aged Niche in a Dish

ESTIMATED TIMELINE FOR CELL MODELS



Induced cell models available in 2023

Neurons (iN) and Vascular Endothial Cells (iVECs)

Detailed Protocols (SD-NSC Website)

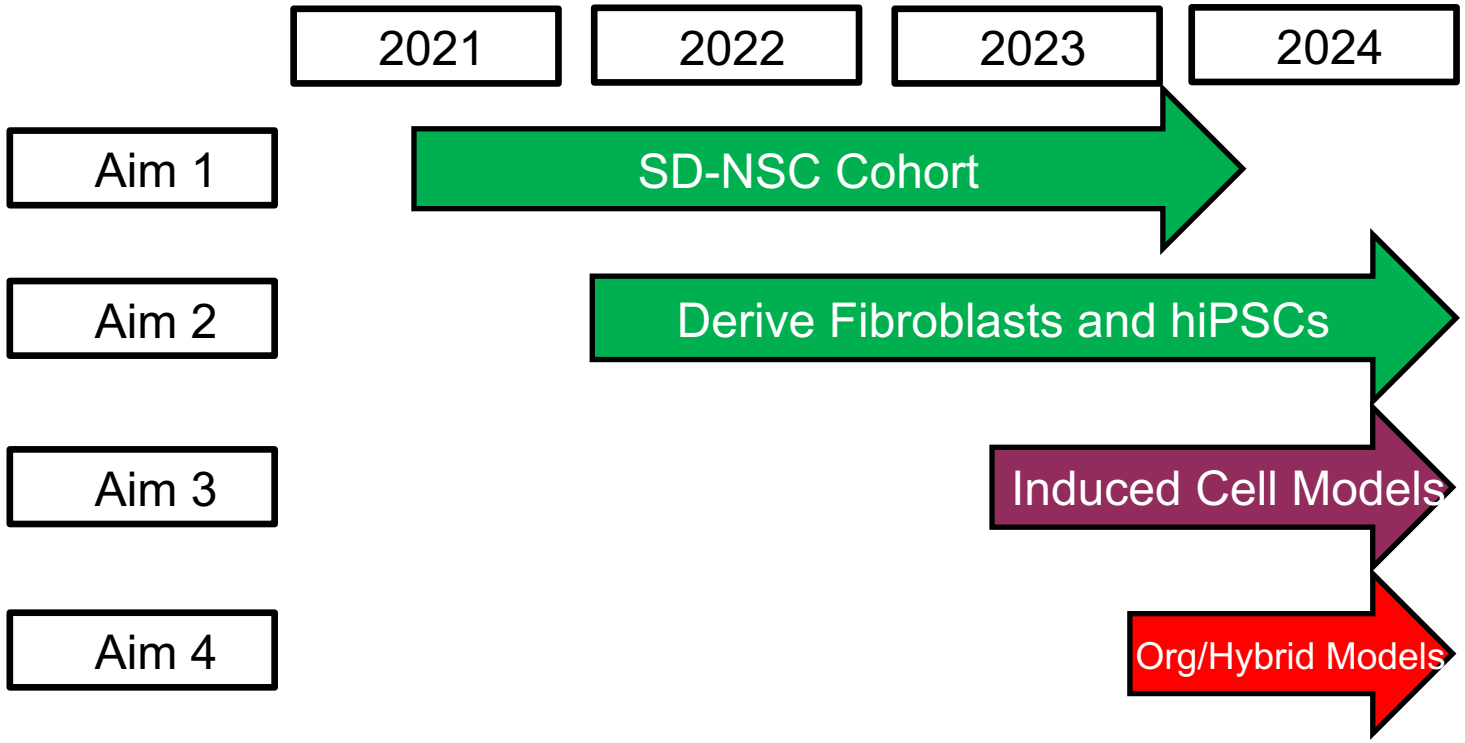
Updates made available (SD-NSC Website)

Organoid and Hybrid Cell Models in 2023-2024

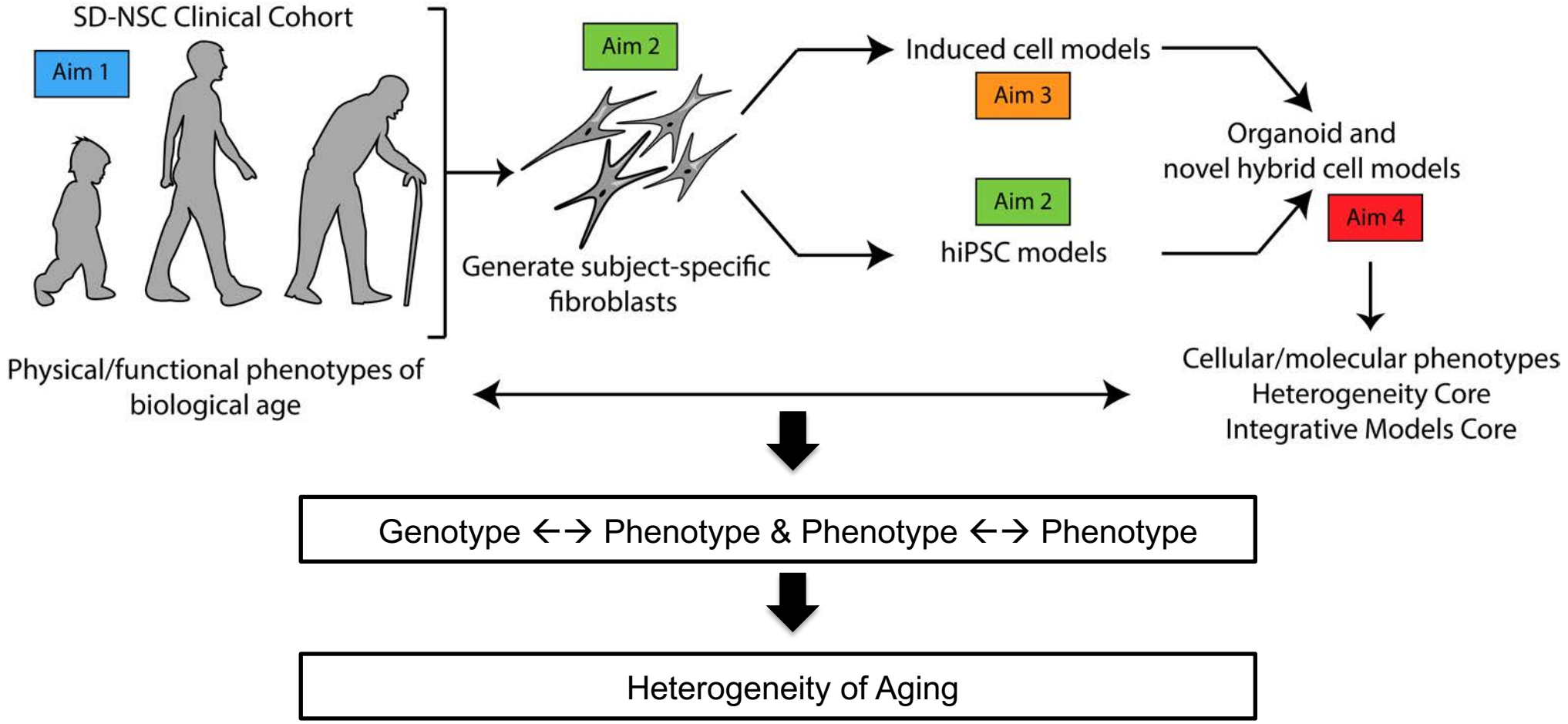
In development – HCMA Core partnering with key SD-NSC researchers (Rusty Gage)

Keep fingers crossed and stay tuned!

ESTIMATED TIMELINE FOR CELL RESOURCES AND MODELS



SD-NSC COHORT POWERS IT ALL…



Overview of Facility, Equipment, and Resources

- 2500 sqft High Volume TC facility
- 13 hoods, 24 incubators
- Vapor-phase cryostorage (3 total)
- Established 2007
- Last renovated in 2012

Overview of Facility, Equipment, and Resources

The Mission: Lower the bar to access advance state of the art human cell based models

- Equipment (Live Imaging, Metabolism)
- Validated Media and Reagents
- Training and Project Support

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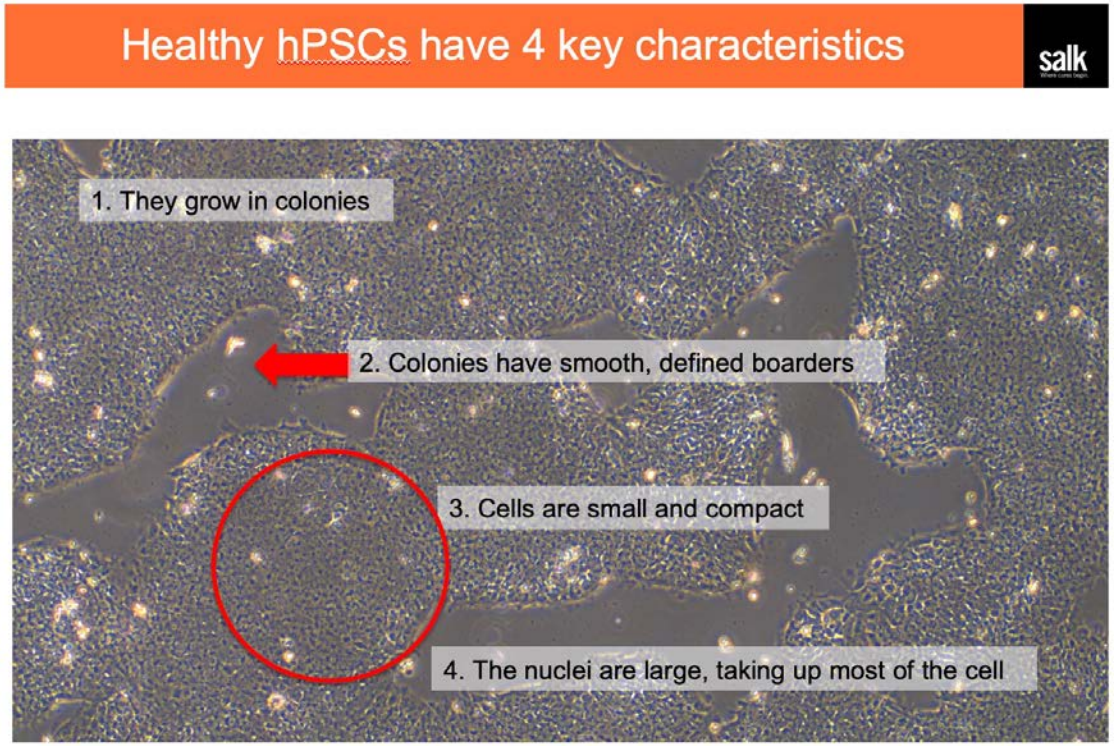

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