Session VII: Addressing Barriers to Research Translation in AD/ADRD

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Complexity of Age-Related Cognitive Decline

$$Cog_i = \alpha_0 + \begin{pmatrix} X_i^{P_1} \\ \vdots \\ X_i^{P_k} \\ X_i^{P_u} \end{pmatrix}^t \times \begin{pmatrix} \beta_{P_1} \\ \vdots \\ \beta_{P_k} \\ \beta_{P_u} \end{pmatrix} + \begin{pmatrix} X_i^{R_1} \\ \vdots \\ X_i^{R_m} \\ X_i^{R_u} \end{pmatrix}^t \times \begin{pmatrix} \beta_{R_1} \\ \vdots \\ \beta_{R_m} \\ \beta_{R_u} \end{pmatrix} + \begin{pmatrix} X_i^{P_k \times P_l} \\ \vdots \\ X_i^{R_m \times R_v} \\ X_i^{P_k \times R_m} \end{pmatrix}^t \times \begin{pmatrix} \beta_{P_k \times P_l} \\ \vdots \\ \beta_{R_m \times R_v} \\ \beta_{P_k \times R_m} \end{pmatrix} + \varepsilon_i$$

Cog_i: observed cognitive score for participant *i*,

$X_i^{P_k}$: observed pathology *k* for participant *i*, and β_{P_k} is the coefficient,

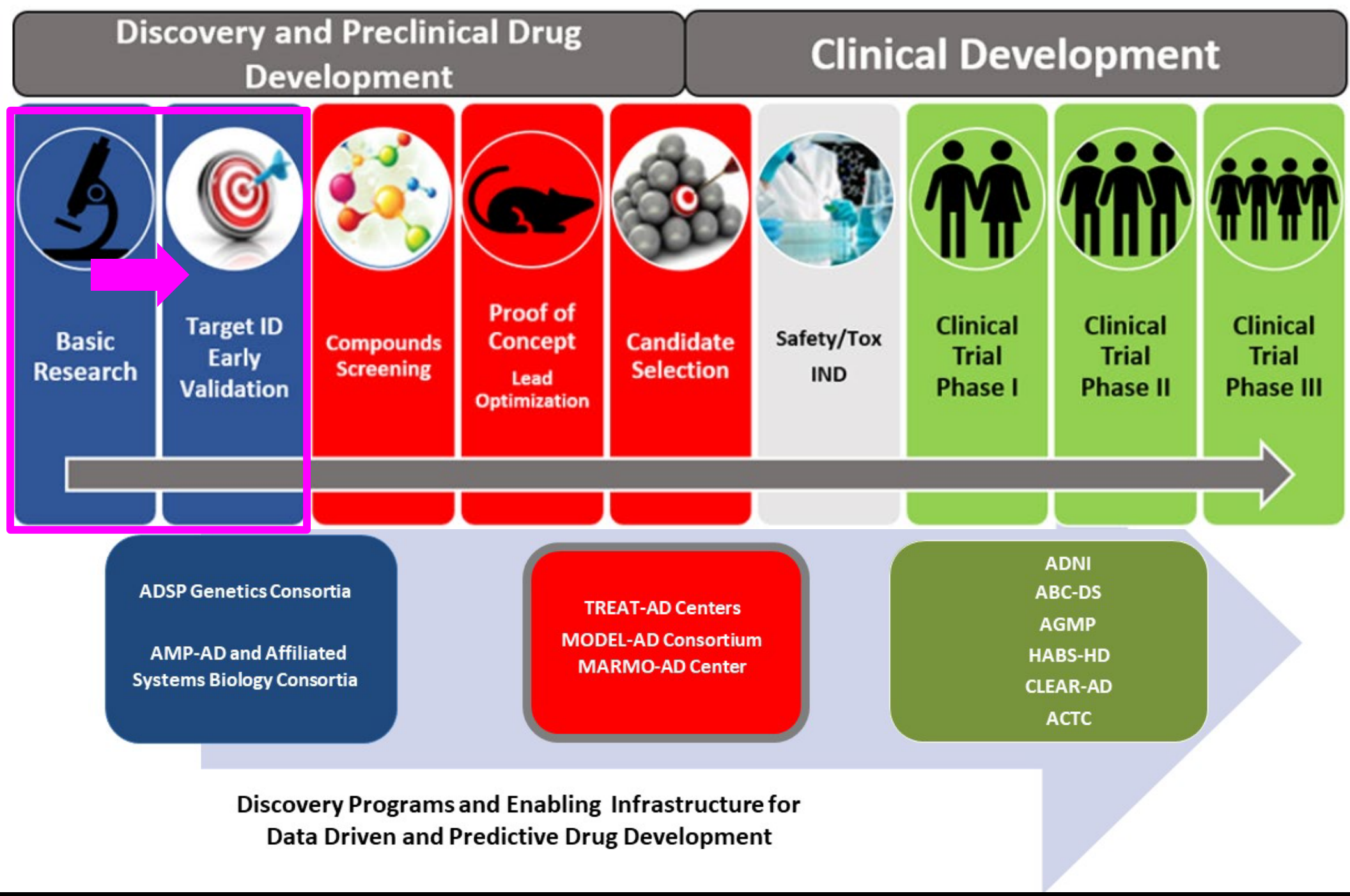
$X_i^{R_m}$: observed measure of resilience *m* for participant *i*, and β_{R_m} is the coefficient,

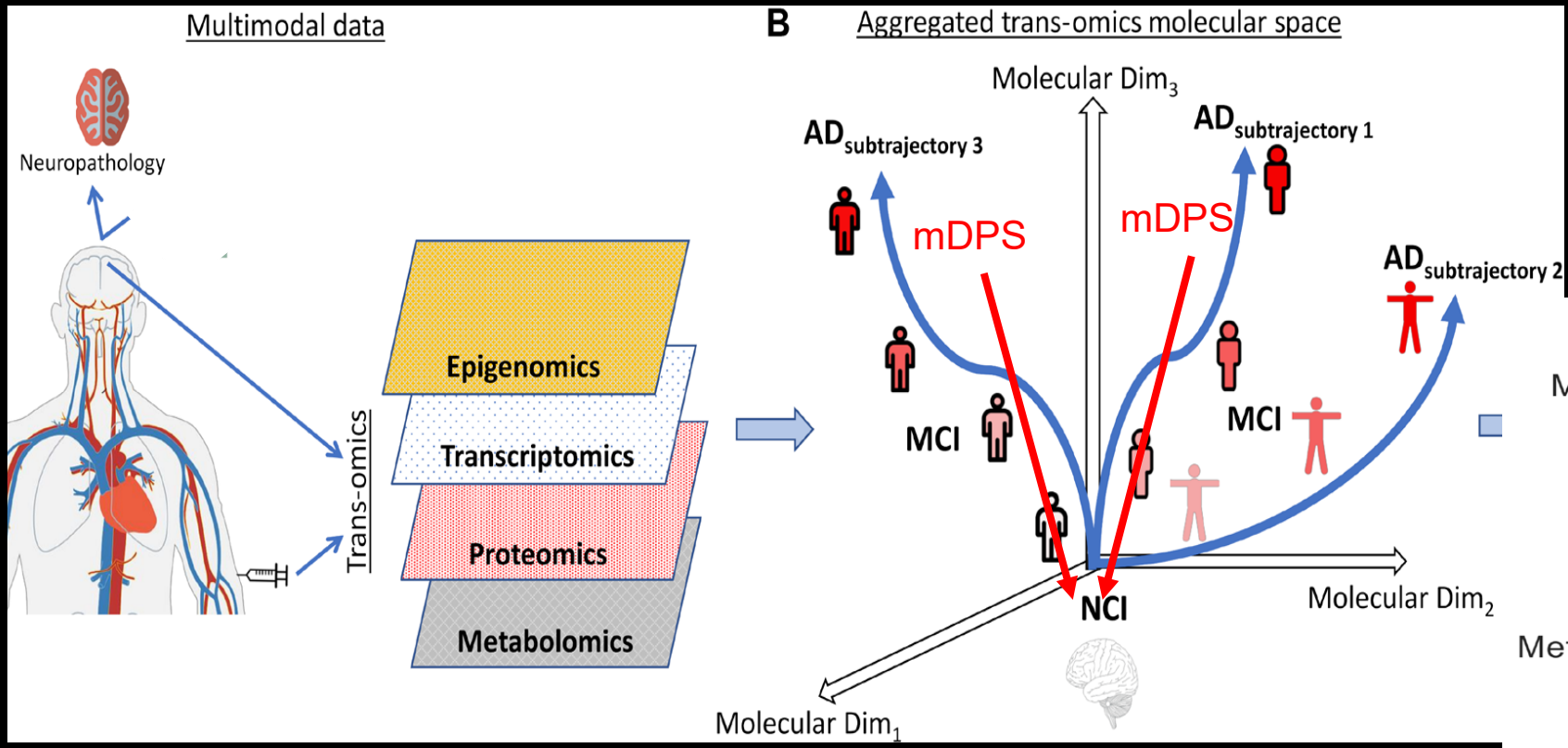
$X_i^{P_k \times P_j}$: an interaction term between pathologies *k* and *j*, and $\beta_{P_k \times P_j}$ is the coefficient,

$X_i^{R_m \times R_l}$: an interaction term between resiliences *m* and *l*, and $\beta_{R_m \times R_l}$is the coefficient,

$X_i^{P_k \times R_m}$: an interaction term between pathology *k* and resilience *m*, and $\beta_{P_k \times R_m}$ is the coefficient,

I include $X_i^{P_u}$ and $X_i^{R_u}$ for unmeasured pathology and resilience indices. However, $X_i^{P_u}\beta_{P_u}$ and $X_i^{R_u}\beta_{R_u}$ are unidentifiable and included in residual ε_i.


Discovery and Preclinical Drug Development
Clinical Development
Basic Research
Target ID Early Validation
Compounds Screening
Proof of Concept
Lead Optimization
Candidate Selection
Safety/Tox IND
Clinical Trial Phase I
Clinical Trial Phase II
Clinical Trial Phase III
ADSP Genetics Consortia
AMP-AD and Affiliated Systems Biology Consortia
TREAT-AD Centers
MODEL-AD Consortium
MARMO-AD Center
ADNI
ABC-DS
AGMP
HABS-HD
CLEAR-AD
ACTC
Discovery Programs and Enabling Infrastructure for Data Driven and Predictive Drug Development



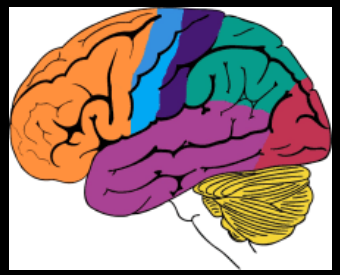
RNA -> HOXC9
Metabolite -> 6-ketoLCA
Protein -> Tau 77G7
DNAm -> PRDM6
RNA -> TCEB3B
DNAm -> NRN1L
Metabolite -> C0
Metabolite -> PC aa C38:3
DNAm -> C3orf55
DNAm -> JAK1
Metabolite -> LCA
RNA -> PFKP
DNAm -> C2orf42
DNAm -> KPNA2
Metabolite -> LCA-3S
DNAm -> DISC1
DNAm -> SLC2A4RG
Metabolite -> Putrescine
RNA -> HS.564153
Metabolite -> NorDCA
DNAm -> TTLL13
Metabolite -> Spermidine

Top molecular markers contributing to pseudotime trajectories include genes, metabolites, proteins, and CpGs

We are integrating many more omic layers

We eventually need to project this onto living persons

Iturria-Medina Y, et al. Sci Adv. 2022 Nov 16;8(46):eabo6764.



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What do we need from the same persons while alive:

- Repeat clinical phenotypes and ante-mortem imaging and biomedical device data from diverse participants
- Biofluid biomarker data
- Biofluid and other relevant peripheral tissues with multiple omic layers that match with the brain omics
- iPSC lines from large numbers of diverse individuals with a range of clinical and pathologic phenotypes and genomic backgrounds
- The computational tools to link the brain and non-brain data in meaningful and actionable way