Circulating Brain-Enriched microRNAs as Biomarkers of Neurodegenerative Diseases

Kira Sheinerman, PhD
Chief Executive Officer

ISTAART / AABC Webinar on Fluid Biomarkers for AD

May 17, 2017

DIAMIR

DiamiR portfolio of biomarkers in development

Neurodegenerative diseases

MCI, AD, PD, FTD, ALS, TBI

Healthy aging

Monitoring of brain aging

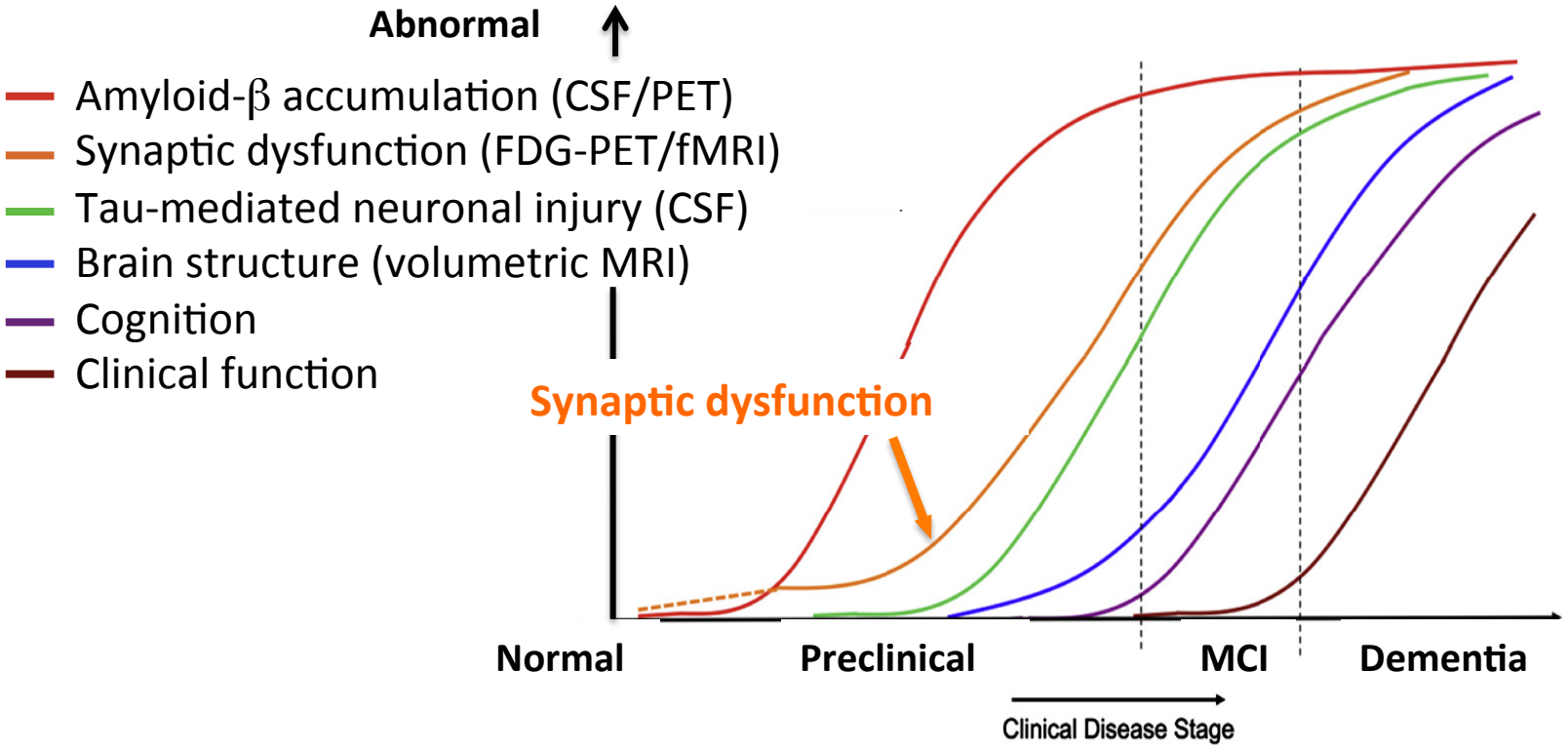
Neurodevelopmental diseases

Rett syndrome

Universal screening test

Early detection of organ pathology

Stages of neurodegeneration



Synaptic dysfunction precedes clinical symptoms

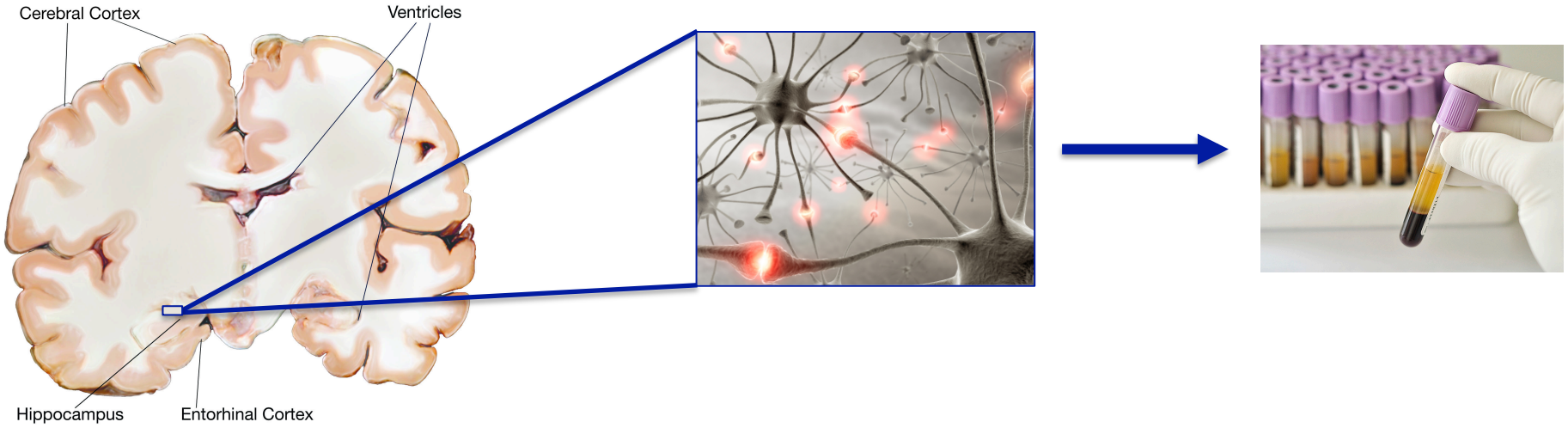
Jack et al. (2010) *Lancet Neurology*
Sperling et al. (2011) *Alzheimer & Dementia*

microRNAs: novel biomarkers detectable in blood

- >2,000 human miRNAs
- miRNAs are short, non-coding, regulatory molecules whose levels change in disease
  - based on sequence complementarity a miRNA can bind to and regulate >100 mRNAs and a mRNA can be regulated by multiple miRNAs
- miRNA sequences are highly conserved across species
- miRNAs appear in blood
  - secreted / excreted into extracellular space; cross body barriers, incl. blood-brain barrier; stable in circulation
- Mature technologies are available for miRNA detection
  - microarray, NGSeq, qRT-PCR
- Certain miRNAs are enriched in specific organs (e.g. brain), organ regions or tissues (e.g. hippocampus, cortex), cells (e.g. neurons), cellular compartments (e.g. neurites, synapses)
- miRNA-based tests are being used in oncology clinical practice
  - (Rosetta Genomics, Interpace Diagnostics)

Hypothesis: ratios of circulating synapse/brain-enriched miRNAs can detect early stages of neurodegeneration

Presymptomatic AD/MCI **Synaptic loss** **miRNA in plasma**



- Pre-selection of miRNAs: enriched in the brain; detectable in plasma; and
  i. present in synapses of brain region(s) known to be affected by disease;
  ii. enriched in other brain regions or cell types
- Quantitative RT-PCR analysis of plasma levels of 35-50 brain-enriched miRNAs
- Algorithm-based selection of effective miRNA biomarker ratios (pairs)

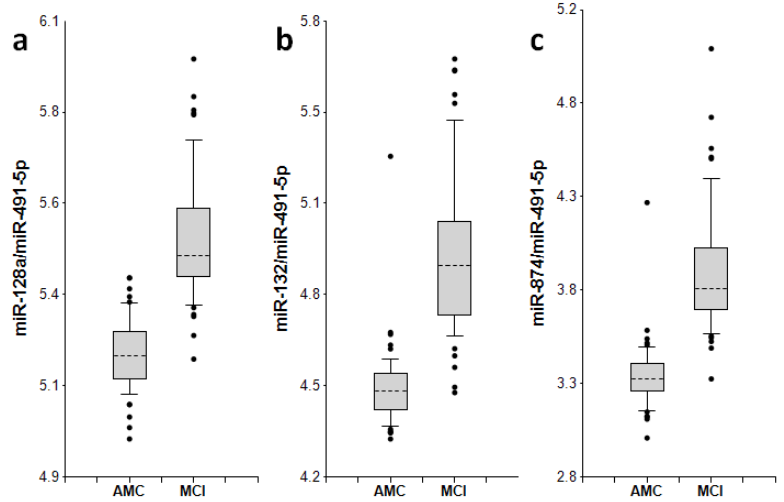
  using pairs of miRNAs increases sensitivity and specificity
- miRNA classifiers (combination of pairs) confirmation in independent cohorts of samples

DIAMIR

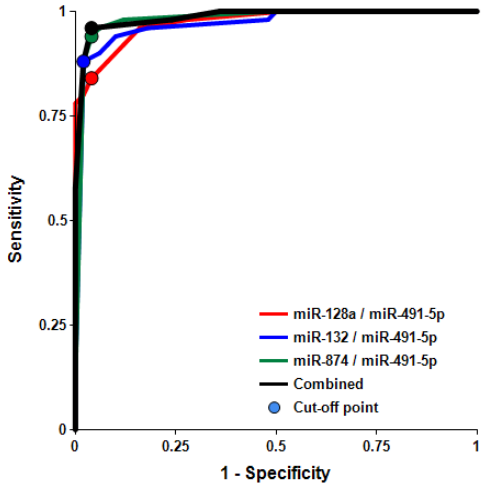
Two families of brain-enriched miRNAs detect MCI

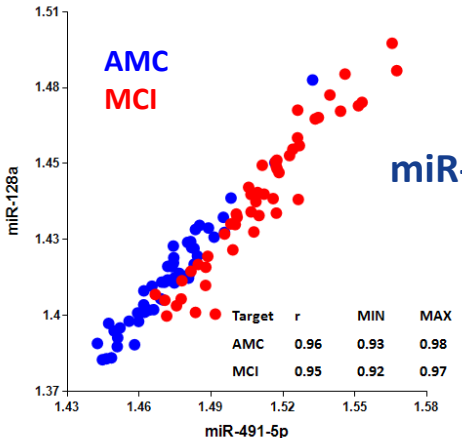
miR-132 and miR-134 biomarker families

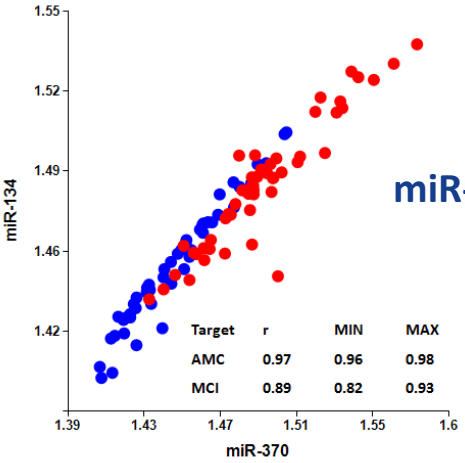
miR-132 family



MCI: Mild Cognitive Impairment patients; **AMC:** age-matched control







Sheinerman et al. (2013) Aging, ***5****:925*
Sheinerman & Umansky (2013) Front. Cell Neurosci. ***7****:150*

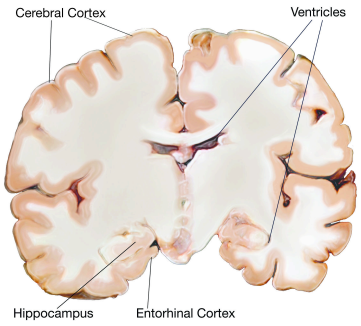
DIAMIR

Clinically relevant questions

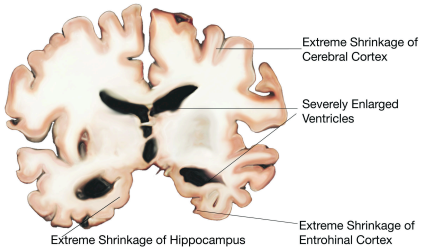
- Detection of MCI / AD in presymptomatic participants
- Prediction of pre-MCI / MCI to AD progression
- Differentiation between neurodegenerative diseases (AD / FTD / PD…)
- Association of miRNA biomarkers with imaging and CSF biomarkers
- Longer term goal: disease and treatment monitoring

CogniMIR™ program status

Presymptomatic AD



Severe AD



Source: National Institute on Aging

- Assay development
  - 24-miRNA classifier
  - Protocol optimization, incl. plasma prep tailored to miRNAs
  - Potential “feature reduction”
  - Analytical validation, SOP
  - Clinical validation in multi-site biomarker study in prodromal AD, MCI, AD, control participants
- Initial application
  - Targeted profiling of brain-enriched miRNA classifiers in plasma
  - Clinical Trial Assay (CTA) for patient selection, monitoring of progressors and responders

DIAMIR

Summary

- Novel targeted approach to identification of miRNA classifiers of brain and synaptic health in the blood; >1,000 plasma samples analyzed
- Brain-enriched miRNAs detectable in plasma as promising and patient friendly biomarkers complementary to other biomarkers
- CogniMIR™: clinical assay in development for early AD with initial application in clinical trial support
- Research collaborations with pharma, academic and medical centers, disease foundations to analyze multiple independent cohorts
- Larger, longitudinal studies are planned
- Organ-enriched miRNA technology holds potential for diseases beyond neurodegeneration

Kira Sheinerman, PhD
ksheinerman@diamirbio.com

DIAMIR