Reversal of cognitive decline: natural approaches

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“There is nothing that will prevent, reverse, or slow the progress of Alzheimer’s disease.”

“Everyone knows someone who is a cancer survivor; no one knows an Alzheimer’s survivor.”

The perfect Alzheimer's drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.

20th century evaluation of cognitive decline

- **"MRI of the brain and blood for CBC, metabolic panel, thyroids, B12."**
- **"I asked the patient and his wife to keep an eye on his disabilities to manage money, medications and transportation."**
- **"I prescribed donepezil 5mg once per day."**
- **No genetics (no ApoE status, TREM2, CD33, NALP1, PS1, etc.), no hs-CRP or IL-6 or anything re inflammation, no homocysteine, no fasting insulin, no hormonal status, nothing re toxin status, nothing re innate immune system status, nothing on gut health, no microbiome, no blood-brain barrier analysis, no MRI volumetrics, etc., etc., etc…**
- **Prescribing donepezil without diagnosis.**
- **BMI was 33—nothing even noted, no plan to address this.**
- **Pre-diabetes, a key risk factor—nothing to address this.**

67 y.o. F with 3-year history of cognitive decline

- **Amyloid PET-positive**
- **ApoE4+ (heterozygous)**
- **MMSE 24**
- **Onset with depression**
- **Non-amnestic presentation: executive dysfunction, paraphasic errors, dyscalculia**
- **Low zinc (49), low TG (29), high Cu:Zn (1.6)**
- **Anti-amyloid Rx failed (and exacerbated symptoms)**
- **C4a high, TGF-β1 high, MARCoNS+**

67 y.o. F with 3-year history of cognitive decline (2)

- 1 year on protocol
- MMSE 24 → 29
- Marked subjective improvement
- C4a 7790 → 460 (normal < 2830)

Email from patient, MMSE 24 → 29

Thanks!!!
You have made my Christmas!

I am religious and in my mind you are a miracle from God that He has given me.

Words are not adequate to express how I feel.
Thanks is too simple a term for the joy I feel when I can now think clearly - in contrast to struggling with basic thought processes.

May you have a wonderful Christmas!
Sally

“Alzheimer’s disease” is a *protective* response

The ReCODE Protocol

- **We have mapped the many molecular mechanisms of cognitive decline and AD onto a network evaluation, subtype determination, and personalized treatment protocol.**
- **First determine all potential contributors and subtype(s); this allows you to prioritize interventions in the program.**
- **No one intervention is curative: not a silver bullet, silver *buckshot*.**
- **Continue to optimize.**
- **Improvement typically requires 3-6 months.**
- **Compliance is important; health coaching helpful.**

Why Memory Loss? Files and ReCODE

Evaluation Step 1: Determine Subtype(s)

- **Presymptomatic vs. SCI vs. MCI vs. AD.**
- **Several different metabolic syndromes are called "Alzheimer's disease:"**
- **Type 1: Inflammatory ("Hot")**
- **Type 2: Atrophic ("Cold")**
- **(Type 1.5: Glycotoxic ("Sweet" combines 1 and 2))**
- **Type 3: Toxic ("Vile")—a fundamentally different problem.**
- **Type 4: Vascular ("Pale")**
- **Type 5: Traumatic ("Dazed")**

Characteristics of type 1 AD

- **Inflammatory (Ayurvedic pitta).**
- **Increase in hs-CRP and/or other inflammatory markers (e.g., increases in IL-6, IL-8, TNFα, etc.)**
- **Reduction in A/G ratio.**
- **Increase in M1/M2 ratio; reduction in MFI.**
- **ApoE4 is important risk factor.**
- **Presentation is typically amnestic.**
- **Hippocampal atrophy is common.**
- **Seek cause(s) of inflammation (e.g., gut leak, AGEs, diet, poor oral hygiene, etc.)**

Metabolism and Cognition Go Hand in Hand

Association	Yes/No
ApoE4? Heterozygote? Homozygote?	Yes (4/3)
Homocysteine >7?	Yes (15.1)
Vitamin B12 < 500?	Yes (328)
CRP > 1.0?	Yes (9.9)
A/G ratio < 1.8?	Yes (1.6)
HgbA1c > 5.6? Fasting insulin > 6 uIU? GTT insulin?	HgbA1c 5.5 Insulin 32
Simple CHO in diet?	Yes
FBS > 90?	Yes (96)
Thyroid: TSH > 2.0?	Yes (2.21)
Free T3 < 3.2? RT3 > 20?	Yes (2.4)
Free T4 < 1.3?	Yes (0.8)
Sleep apnea/hypopnea?	No
Low androgen? Total T < 500? Free T < 6.5?	Yes (264) Yes (41, 4.1)
Low estradiol? Post-menopausal? E2<100? E2:P >300? Hysterectomy at <41 y.o.?	NA
Low pregnenolone? <20?	Pd.
Vitamin D < 30?	Yes (21)
History of head trauma? LOC?	No
Diabetes?	No, but insulin resistant
Neuroactive medications? Which?	No
History of illicit drug use?	No
Metabolic syndrome?	Yes (TG, BP, glu, insulin)
Cholesterol > 225? < 150?	Yes
Abnormal HDL:LDL ratio?	Yes
Post-menopausal?	NA

Characteristics of type 2 AD

- Atrophic ("cold;" Ayurvedic vata).
- Patients tend to be older than type 1.
- Typically amnestic presentation; patients often protest that nothing is wrong.
- Reductions in trophic support (e.g., estradiol, progesterone, testosterone, vitamin D, pregnenolone, thyroid, NGF, BDNF).
- ApoE4 is risk factor.
- Rapid reductions in support are most concerning (cf. oophorectomy at <41 without HRT), c/w depR mismatch.
- Hippocampal atrophy is common.
- Optimizing support may be complicated by receptor response, HRT controversy, trophic factor delivery (intranasal vs. peptides vs. indirect, etc.).

75 y.o. psychiatrist with 2-yr history of memory loss: Dx

- Severe difficulty retaining new information.
- No problems with organizing, calculating, dressing, or speaking.
- ApoE3/3.
- FDG-PET c/w Alzheimer's. MRI with HC volume 16%ile.
- On-line cognitive assessment 9%ile for age.
- Low vit D, pregnenolone, progesterone, estradiol, fT3, B12.
- Dx: type 2 MCI.

75 y.o. psychiatrist with 2-yr history of memory loss: Rx

- **Began protocol, but left out several parts.**
- **Cognitive assessment from 9%ile to 55%ile over 9 months.**
- **Significant other said her memory went from "disastrous to just lousy." Now he says it is "normal."**
- **Patient noted marked improvement in her memory.**
- **Improvements in vit D, pregnenolone, progesterone, estradiol, fT3, and B12; homocysteine reduced 14→8.**
- **Optimizing protocol as of 2/17.**
- **Follow-up hippocampal volume, neuropsych pending.**

Characteristics of type 1.5 AD

- Glycotoxic (“sweet”).
- Inflammatory part from AGEs (via RAGE, glyoxals, etc.) and related.
- Atrophic part from insulin resistance (e.g., IRS1 S/T phos.).
- Goetzl noted insulin resistance in 100% of the neural exosomes from AD patients (measured via IRS1).
- ApoE4 is an important risk factor.
- Amnestic presentation is common.
- Hippocampal atrophy is common.
- Paradox of insulin sensitization and trophic requirement.

69 yo businessman

- 3-yr history of poor memory and orientation.
- MRI read as normal, without volumetrics.
- Fasting insulin 14, hemoglobin A1c 5.8, fbs 102.
- hs-CRP 0.1.
- ApoE3/3.
- BMI 33.
- Normal Cu:Zn, Mg, vit D, Hg, hormones.
- Dx: type 1.5 AD.

Characteristics of type 3 AD

- Age at symptom onset < 65.
- ApoE4-negative (often).
- Negative family history (or only older).
- Low triglycerides and/or zinc.
- HPA dysfunction.
- Depression.
- Problems with math or organization or word finding.
- Exposure to toxins (mercury, mycotoxins, CIRS-related such as Lyme, MARCoNS, surgical implants, others).
- Precipitation or exacerbation by stress.
- “Atypical Alzheimer’s,” often with frontal effects and imaging.

Characteristics of type 3 AD (cont'd)

- High C4a (>2800), TGF-beta-1 (>2380); low MSH (<35).
- HLA-DR/DQ with "dreaded" multiple biotoxin sensitive or pathogen-specific (4-3-53, 11-3-52B, 12-3-52B, 14-5-52B).
- MARCoNS (multiple-antibiotic resistant coagulase-negative Staphylococcus, deep nasopharyngeal culture)—biofilm assessment.
- Visual contrast sensitivity abnormalities.
- Surprisingly, most do NOT have allergic symptoms.
- Most do not fulfill criteria for CIRS, yet have laboratory values compatible with CIRS—thus "ISIS" (innate system immune stimulation).
- Potential relationship to Lewy body disease.
- Most difficult type of AD to treat successfully.

50 yo woman with depression post-hysterectomy

- **Over the ensuing 4 years, developed word-finding difficulty, disorientation, difficulty following recipes, difficulty driving.**
- **Declined markedly with stress, sleep deprivation, and viral illness.**
- **Neuropsych: poor semantic fluency, paucity of speech, confabulation; frontal, temporal, and parietal deficits.**
- **FDG-PET: temporal and parietal > frontal reduced glucose utilization, compatible with Alzheimer's disease.**
- **Seen at university dementia center, started on antidepressant and donepezil.**
- **ApoE3/3, negative family history, hs-CRP 0.2, C4a 5547, TGF-β1 7037, VCS failed, anti-Lyme negative, anti-thyroglobulin antibodies 1:2000.**
- **Treated with ReCODE, intranasal VIP. Improvements in memory, interaction, following directions, MoCA.**

HLA-DR/DQ haplotypes in type 3 AD

Table 1. HLA-DR/DQ haplotypes in patients with type 3 Alzheimer's disease

Age at symptom onset (years)	Major symptoms	HLA-DR/DQ	Comment
50	Dyscalculia, executive	10-3-52B 10-5 (low MSH)	ApoE3/3
54	Executive, visual	11-3-52B ** 7-2-53 *	ApoE3/3
72	Executive, dyscalculia	4-3-53 ** 15-6-51 * (Lyme)	ApoE3/3
65	Spatial > verbal memory, attention, irritability, depression	11-3-52B ** 13-6-52B *	ApoE3/3
54	Executive, visuospatial, memory, depression	17-2-52A * 1-5 (low MSH)	ApoE4/4
59	Aphasia, executive, dyscalculia, depression	12-3-52B ** 15-6-51 * (Lyme)	ApoE2/3
59	Headache, executive	4-3-53 ** 15-6-51 * (Lyme)	ApoE ND
66	Headache, executive, memory	11-3-52B ** 13-6-52C *	ApoE ND

*Pathogen-specific HLA-DR/DQ-related sensitivity (mold or Lyme).
**Multiple-biotoxin-sensitive HLA-DR/DQ association.

Basic concepts of the protocol

- **Identify all contributors to the imbalanced plasticity network (from 100, e.g., copper:zinc ratio > 1.3, RBC Mg < 5.2, hs-CRP > 1.0, homocysteine > 7, fasting insulin > 4.5, C4a > 2800, free T3 < 3.2, TSH > 2.0, Cyrex Array 2 +, etc., etc., etc.). From these, we use a software algorithm to construct a "why memory loss" table weighted for each type.**
- **Determine the degree of contribution to types 1 (inflammatory ("hot")), 1.5 (glycotoxic ("sweet")), 2 (atrophic ("cold")), 3 (toxic ("vile")), 4 (vascular ("pale")), or 5 (traumatic ("dazed")).**
- **For each abnormality identified, we want to go beyond simply normalizing the test, we want to optimize the value.**
- **We want to address as many of the abnormalities as possible, not just one, and the earlier in the process, the greater chance for success.**
- **For each treatment we include, the goal is to design the treatment so that it will be as physiological and upstream as possible.**
- **The program is personalized.**

Lessons we are learning

- **If we can identify all of the key contributors to cognitive decline, we can improve cognition even relatively late in the course (e.g., MoCA=10).**
- **Patients with type 3 AD are exquisitely sensitive to stress, sleep loss, and hormonal loss.**

Sensitivity to stress and hormonal loss

- 54 yo F, ApoE3/3, with type 3 AD, beginning with depression followed by executive dysfunction.
- FDG-PET typical for AD, with temporal and parietal reductions in glucose utilization.
- High C4a, HLA-DR/DQ mold-sensitive and post-Lyme.
- Responded well to protocol, with increased MoCA, able to remember directions again, more engaged, able to read and remember once again.
- After improvement, repeated stressful travel and went off BHRT.
- Lost much (not all) of what she had gained.
- Back on HRT, reduced stress and travel, now once again improving.

Lessons we are learning

- If problems remain, continue to search for contributors.
- ISIS (innate system immune stimulation) is a very common and critical part of AD.
- Break in protocol is associated with decline within 1-2 weeks.
- Potential relation to type 3 AD; response.
- Key Rx parameters for type 3:

Responses in type 3

- IV glutathione.
- Cholestyramine.
- Intranasal VIP (after MARCoNS neg.).
- Striking effect of exercise.
- Sleep, stress minimization.
- BHRT.
- Removal of exposure.
- IQ Air/HEPA filter.

Concerns for removing Aβ prematurely

- 58 yo M, ApoE4/4, presented with driving difficulty; PET scan +.
- MoCA 24.
- 2-year trial of antibody to Aβ; with each injection, he became very confused for several days.
- MoCA 24 → 6.
- Subsequently found to have both high Hg and mold exposure, mold-sensitive HLA-DR/DQ.
- Improved on chelation followed by CIRS Rx.

Troubleshooting

“I am not getting better—why?”

- How long on the protocol? Slow decline, stop decline, minor improvements, major improvements.
- How well documented is the problem? AD-related?
- Have the suboptimal lab values been optimized?
- Has mild ketosis been achieved? Good fats-based diet?
- How advanced was the process on presentation?
- Most common cause is lack of compliance; health coach?
- 2nd most common cause is type 3 AD.
- “Rich man’s syndrome.”

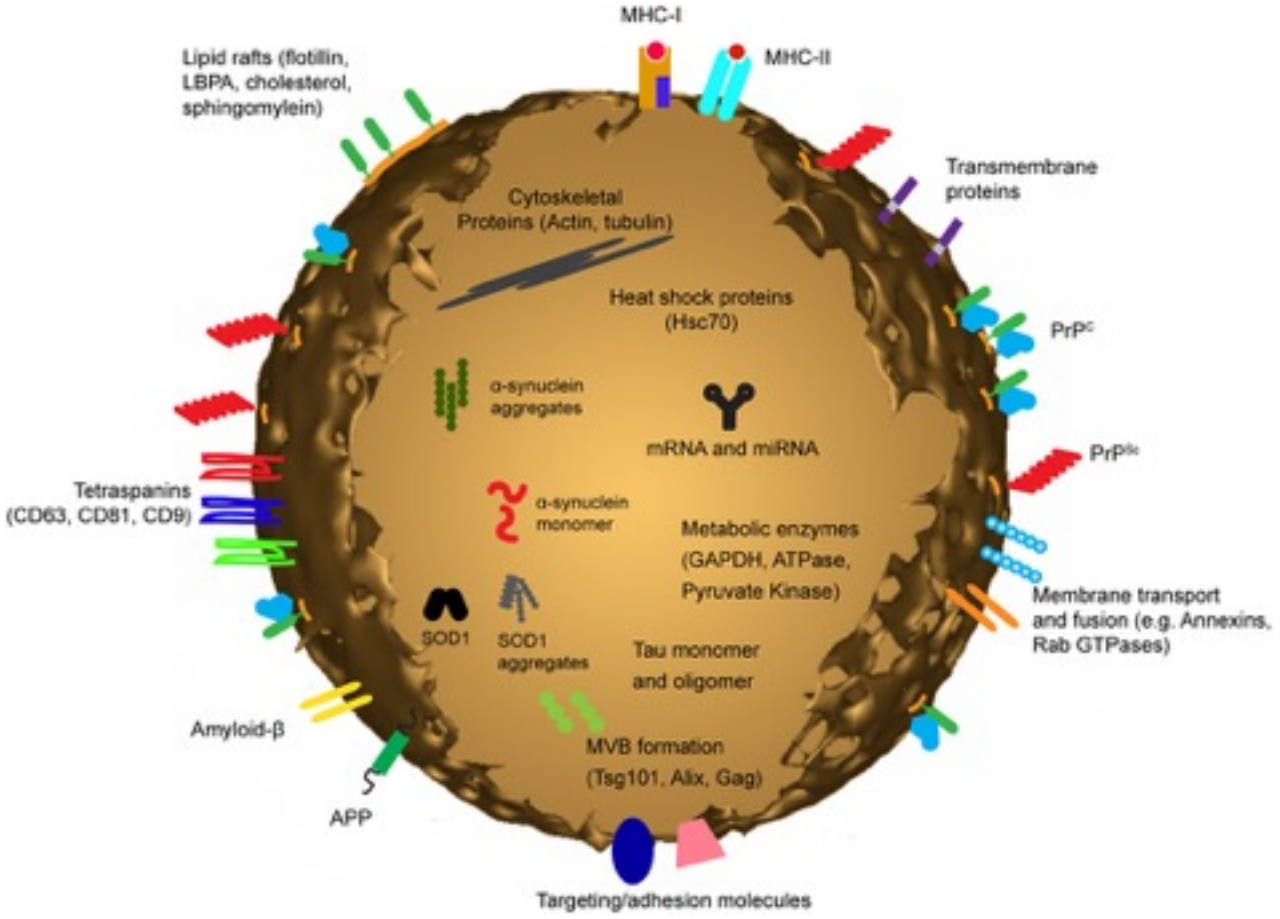
“I am not getting better—why?” (cont’d)

- Need a CIRS consultant?
- Undiagnosed sleep apnea?
- Regular brain training?
- Doing supplements only?
- Key is to exceed threshold; if not, keep tweaking.
- Continued exposure?
- Are the major underlying causes—inflammation, trophic withdrawal, insulin resistance, and toxic exposure—all addressed optimally?
- Behavior, purpose, joy, stress reduction.

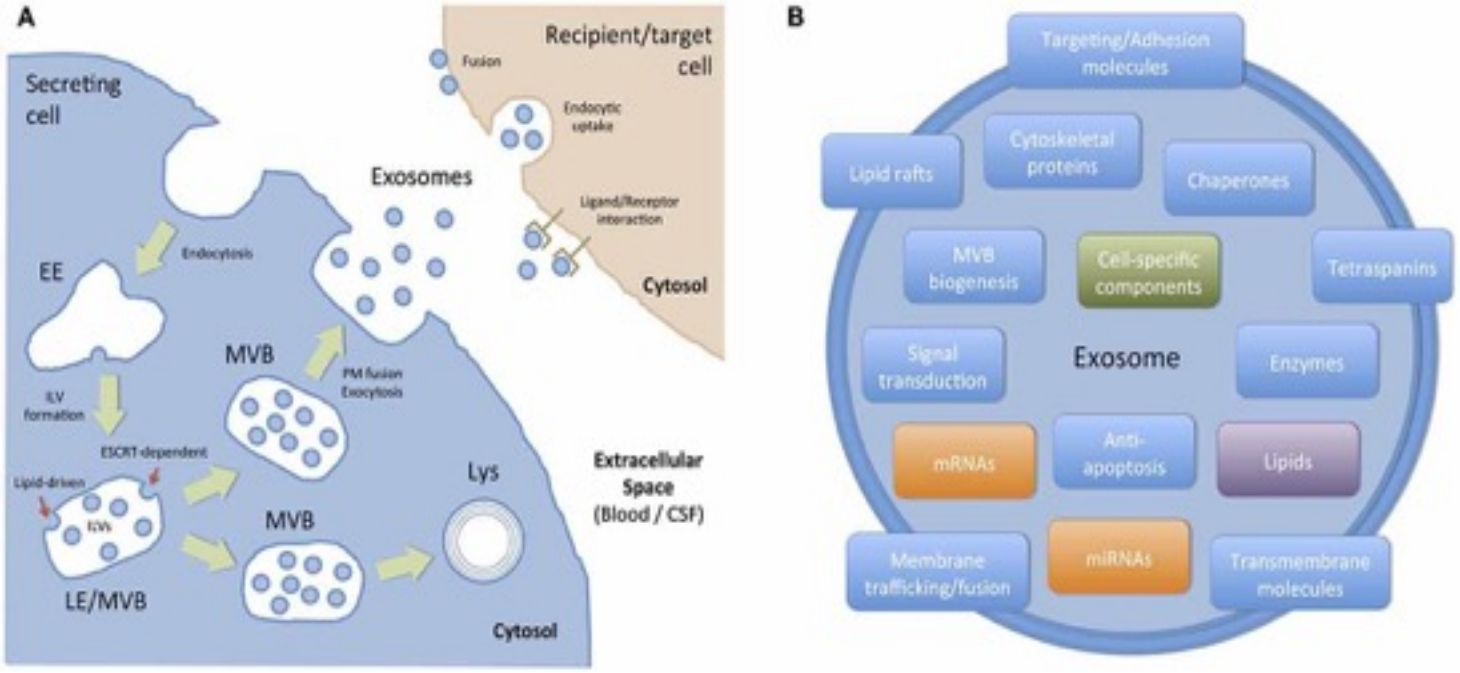
What's coming up?

Window on the mind: *neural exosomes*

Window on the mind: *neural exosomes*



Cell-to-cell communication

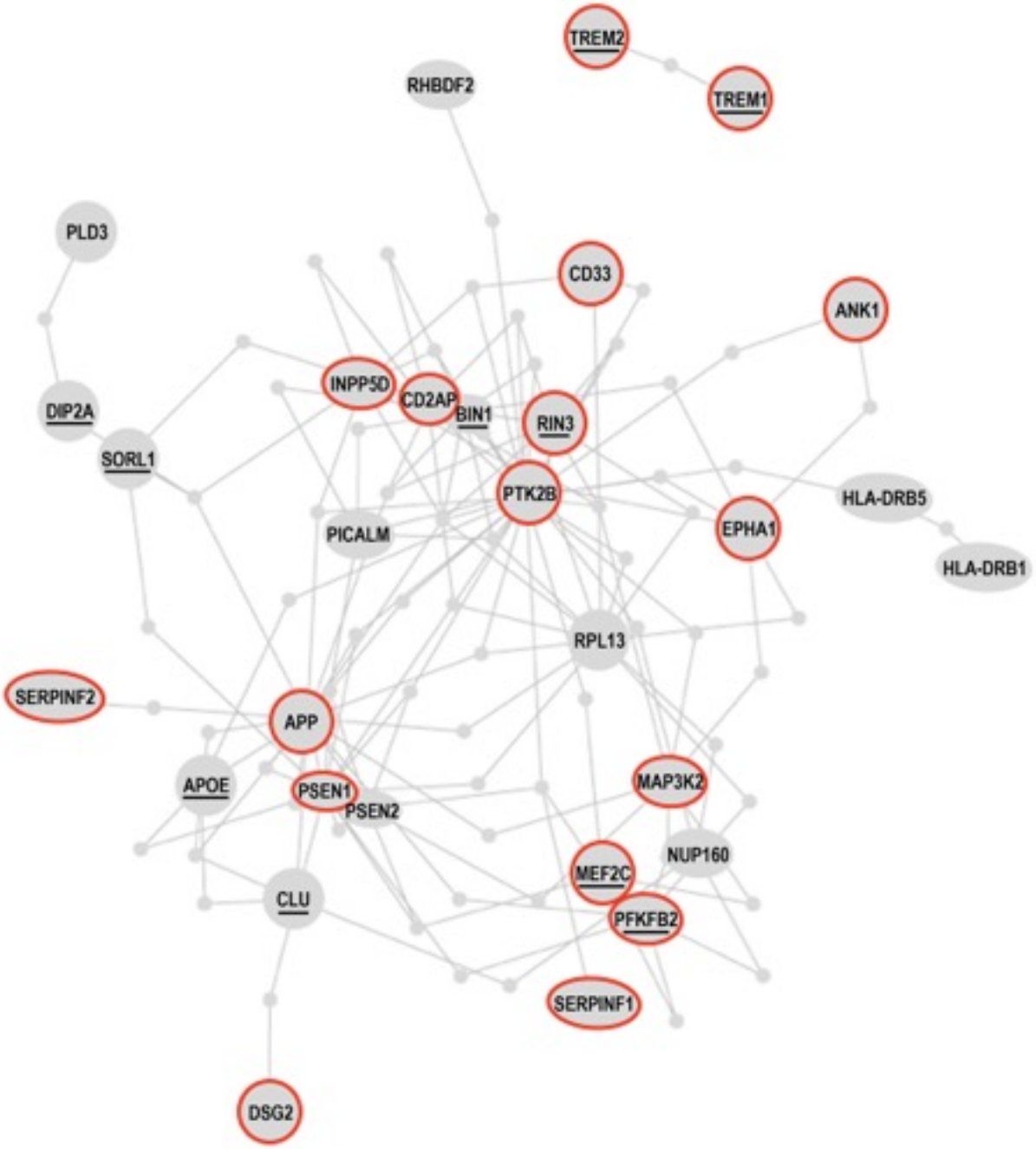


Enhancements on the way: exosomes

- Neural exosomes (e.g., Nanosomix):
- 1.2 billion exosomes per ml of blood; multiple origins.
- About 10% are of neural origin.
- Two-way traffic to/from brain: diagnostic and therapeutic?
- Indicator of Alzheimer's: Aβ42, p-tau.
- Indicator of insulin resistance: specific Ser/Thr phos:Tyr phos.
- Indicator of trophic signaling: REST.
- Indicator of proteolytic function: cathepsin-D.
- Abnormalities up to 10 years prior to diagnosis of AD.
- Promise as longitudinal measure of efficacy.
- Should be available clinically in 2017.

Continued development of ReCODE

- **Addressing multiple neurodegenerative diseases.**
- **Larger data sets: inclusion of whole genome data, lipidomics, metabolomic data.**
- **More accurate and extensive network dissection for each individual.**


TREM2
TREM1
RHBDF2
PLD3
CD33
ANK1
INPP5D
CD2AP
BIN1
RIN3
DIP2A
SORL1
PTK2B
HLA-DRB5
PICALM
EPHA1
HLA-DRB1
RPL13
SERPINF2
APP
APOE
PSEN1
PSEN2
MAP3K2
NUP160
MEF2C
CLU
PFKFB2
SERPINF1
DSG2

Continued development of ReCODE (2)

- More rapid determination of response, with anatomically-based functional testing, MFI, exosomes, metabolic data.
- Simplification of protocols.
- Focus on priorities based on rank order of subtype contribution and overall list of contributors.
- Troubleshooting function.

Clinical issues arising

- **Striking effects of exercise, stress, and BHRT on type 3—mechanism?**
- **WCFE: best for type 2? Length of Rx? Side effects? Withdrawal?**
- **CIRS markers without CIRS in type 3?**
- **Importance of rhinosinal microbiome?**
- **Imaging sinus/nasal-CNS access.**
- **Role of resolvins in type 1; also 1.5, 3?**
- **How to detect and classify CNS biofilms.**

Enhancements on the way

- **Retinal imaging of amyloid, nerve fiber layer thickness.**
- **NeuroTrack and mesial temporal lobe: novel object recognition.**
- **Intranasal trophic peptides (beyond VIP, insulin, ADNP).**
- **Non-intranasal trophic peptides (e.g., IV Cerebrolysin).**
- **Novel PET tracers (beyond tau-binding).**
- **Stem cell improvements.**

Enhancements on the way (2)

- Improved understanding of CIRS-type 3 AD connection, and CIRS-LBD connection.
- Enhanced detoxification protocols.
- Continued optimization of critical nutritional components.
- Role of nitric oxide.
- Genetics: whole genome vs. exome vs. neurodegeneration chip.
- Matching behavioral type to behavioral change method.

New Protocols

- **Lewy body disease: 1 million Americans.**
- **α-synuclein (synuclein from synapse and nucleus) is present in the inclusions. May be mixed with AD. Severe cholinergic and dopaminergic deficits.**
- **Sx: dementia, often with motor deficits of Parkinsonism, visual hallucinations, delusions, fluctuations, sensitivity to medications, late sleeping.**
- **FDG-PET or SPECT: occipital involvement, no medial temporal.**
- **Potential relation to type 3 AD; response.**

Lifting the fog: toward more accurate and complete diagnostics and effective therapeutics for complex chronic illnesses