The Bredesen Protocol

This protocol has been tested in over 250 subjects to effectively reverse cognitive decline in neurodegenerative diseases such as Alzheimer's Disease and Dementia.

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The Bredesen Protocol was developed by Dr. Dale Bredesen and his team at MPI Cognition. This protocol used to be called the MEND protocol, but now is called ReCODE. The overall goal of this protocol is to fix the following (which in turn reverses cognitive decline and helps with Alzheimer’s and Dementia):

- Insulin resistance
- Inflammation/infections
- Hormone, nutrient, and trophic factor optimization
- Toxins (chemical, biological, and physical)
- Restoration and protection of lost (or dysfunctional) synapses

Protocols like this may never reach global recognition or even FDA consideration for further evaluation.

The problems with most FDA-based studies is that they only look at one aspect of the disease - X causes Y.

Unfortunately, AD is complex and there are many root causes to it.

The ReCODE protocol looks at 45 factors (metabolic markers) that have to be simultaneously optimized (more discussed below).

Amyloid Plaques

Amyloid Precursor Protein

Amyloid precursor protein (APP) is naturally occurring in the brain and depending on how it is cut (either by netrin-1 or other molecules) it can either turn into:

1. Something healthy for the brain (such as sAPPα and αCTF)
   OR
2. Something toxic such as amyloid-beta (as well as Jcasp and C31).
If APP is cut to produce amyloid-beta, then amyloid-beta can continue to cut APP into more amyloid-beta plaques. This creates a positive feedback loop, thus creating more and more amyloid-beta plaques in the brain, instead of creating healthy molecules for the brain.

This positive feedback loop creates a clastic (destructive) effect on the synapses, instead of a blastic (protective) response.

Amyloid-Beta Plaque

The dogma behind amyloid plaque (the sticky plaque that builds up in the brain of Alzheimer's patients) as the main evil in Alzheimer's Disease (AD) is actually incorrect.
In fact, it may be protective:

- Acts as an anti-microbial
- Binds to toxins (like heavy metals)
- Protects against inflammation

If you have been shot, would you just patch up the wound and not remove the bullet?

No, you would treat the underlying problems (remove the bullet) and replace the blood loss.

The Bredesen Protocol first targets the underlying problem.

### 3 Types Of Alzheimer's Disease

There are 3 types of Alzheimer's disease described in the ReCODE protocol.

You can develop one of these or a combination:

#### 1. Inflammation

[Diagram of immune response and inflammation]


Anything that causes inflammation to the brain (low chronic inflammation can do this as well) can contribute to Alzheimer's Disease (AD):
- AGEs
- ApoE4 (and ApoE3) R
- Diet High in Lectins
- Imbalances in fatty acids (omegas)
- Infections
- Insulin Resistance
- Leaky Gut or Leaky Blood Brain Barrier
- Neuroinflammation
- Toxins (incl metals)

1.5 Glycotoxic

Glycotoxicity comes from an imbalance of glucose/insulin usage in the brain.

The pancreas produces Insulin-Degrading Enzyme (IDE, the enzyme that breaks down insulin) to break down amyloid beta.

If IDE is used up by a diet too high in sugar (like someone with insulin resistance), then there is none left to break down amyloid beta.

This type of AD is called 1.5 because it is a combination of AD 1, inflammation and AD 2, trophic loss.

For example, having high amounts of glucose in the blood creates inflammation, and having improper usage of insulin, degrades insulin's ability to act as a neurotrophic (brain growth) promoter.

**Intranasal insulin** may help with this type.

2. Metabolic/Trophins Loss

This type of AD is usually caused by imbalances in the endocrine system (hormones) and nutrient depletion, as well as neurotrophic loss (brain breaking down faster than it can regrow).

This includes:

- ApoE4 R
- Hormone Imbalances (Vitamin D, Sex and Neuro Steroids, Thyroid)
- Insulin Resistance
- Methylation Problems
- Mitochondrial Damage
- Neurotrophic Loss (atrophy in brain)
- Nutrient Depletion

3. Toxins
The *toxin/infectious* type of AD is more *environmental* and can be caused by:

- **ApoE3** (more common)
- Heavy Metals (including amalgams)
- Hormonal Imbalances
- HPA-Axis Imbalances
- Infections (such as mold, Lyme, HSV, active EBV, oral/nasal/gut *dysbiosis*)
- Low Zinc/high copper ratio
- Psychiatric disorders (correlation)
- Toxins (including *haptens*, pesticides, **NSAIDS**, **PPIs**, statins, and other drugs)

This usually occurs after 80 y/o.

**Testing/Biomarkers**

*All the labs and tests for the Bredesen Protocol can be ordered here* (does not include MRI/PET scan).

**Blood tests:**

- **Albumin/Globulin Ratio** *(A:G Ratio)*
  - ≥ 1.8
  - >4.5 (albumin)
- **Alpha-MSH**
  - 35–81 pg/ml
- **Arsenic**
  - <7 mcg/L
- **Cadmium**
  - <2.5 mcg/L
- **Calcium**
  - 8.5-10.5 mg/dl
- **Cholesterol**
  - 150
- **Complement C4a**
  - < 2830 ng/ml
- **Copper**
  - 90-110 mcg/dL
- **Copper:Zinc Ratio** *(also look at ceruloplasmin ≤ 30)*
  - 0.8-1.2
- **Cortisol** *(morning)*
  - 10-18 mcg/dL
- **DHEA**
  - 350-430 (women) mcg/dL
  - 400-500 (men) mcg/dL
- **Estradiol** *(Estrogen)*
- **Folate**
  10-25 ng/ml
- **Glucose (fasting)**
  70-90 mg/dL
- **Glutathione**
  5-5.5 micromolar
- **HbA1C**
  ≤5.6%
- **HDL**
  >50
- **HLA-DR/DQ**
  negative
- **Hs-CRP**
  ≤0.9 ng/dL
- **Il-6**
  ≤3 ng/ml
- **Insulin (fasting)**
  ≤4.5 microIU/ml
- **LDL-p**
  700-1000
- **Lead**
  <2 mcg/dL
- **Leptin**
  - 0.5-13.8 ng/mL (male)
  - 1.1-27.5 ng/mL (female)
- **Mercury**
  <5 mcg/L
- **MMP9**
  85-332 ng/mL
- **Omega 6:3 Ratio**
  0.5-3.0
- **Osmoality**
  280-300 mosmol
- **Oxidized LDL**
  <60 U/l
- **Pregnenolone**
  50-100 ng/dL
- **Progesterone**
  1-20 ng/ml
- **Potassium**
  4.5-5.5 mEq/L
- **RBC Magnesium**
• **RBC Thiamine Pyrophosphate**
  100-150 ng/ml

• **sdLDL**
  <20 mg/dL

• **Selenium**
  110-150 ng/ml

• **T3**
  - 3.2-4.2 pg/ml (free)
  - <20 ng/dL (reverse)

• **T4**
  1.3-1.8 ng/dL (free)

• **TSH**
  <2 microIU/ml

• **Testosterone**
  - 500-1000 ng/dL (total)
  - 6.5-15 ng/dL (free)

• **TGF-β1**
  < 2380 pg/ml

• **TNF-alpha**
  ≤6pg/ml

• **Triglycerides**
  <150

• **Vasopressin**
  1.0-13.3 pg/ml

• **VEGF**
  31-86 pg/mL

• **VIP**
  23-63 pg/mL

• **Vitamin B6**
  60-100 mcg/L

• **Vitamin B12 (MMA test can complement, but isn't a replacement)**
  500-1500 pg/ml

• **Vitamin C**
  1.3-2.5 mg/dL

• **Vitamin D**
  50-80 ng/ml

• **Vitamin E** (as Alpha-Tocopherol)
  12–20 mcg/ml

• **Zinc**
  90-110 mcg/mL

It's also a good idea to test for **leaky gut, leaky brain**, and **food sensitivities**:
- **Cyrex Array 2** - leaky gut
- **Cyrex Array 3/4** - food sensitivities and gluten intolerance
- **Cyrex Array 5** - autoantibodies
- **Cyrex Array 20** - leaky blood brain barrier

**Infections** can travel to the brain (via a leaky brain) through the **nose, vagus nerve, or eye** such as:

- Aspergillus
- CIRS
- Gingivitis
- Lyme (Borrelia)
- HSV
- Syphilis (neurosyphilus)

This can also cause meningitis.

For **mitochondrial** function testing, use an **organic acids test** or look at **8-oxo-dg**.

A **urine culture** should be **free of mycotoxins**.

All microbiomes shouldn't have **dysbiosis** or **infections**.

Imaging can be done with:

- **PET** (FDG-PET, Amyloid PET, or Tau PET)
- **MRI** with volumetrics (**Neuroreader** or **NeuroQuant**).

**Body mass index** (BMI) should be 18–25; waistline < 35 inches (women) or < 40 inches (men).

Here are some cognitive tests:

- **MMSE** (Mini-Mental State Examination)
- **MoCA** (Montreal Cognitive Assessment) - A normal MoCA score is 26 to 30
- **SAGE** (Self-Administered Gerocognitive Examination)

**Genetics**
ApoE4 (epsilon 4) is the most common genetic variable for predicting Alzheimer's.

What does ApoE4 do?

- Reduces the clearance of amyloid-beta plaques
- Regulates over 1,700 different genes (1/20 of human genome)
- Shuts down the gene that makes SirT1, which helps with gene regulation (resveratrol would help this)
- Activates NF-κB, thus promoting inflammation.

ApoE4 (14% of the population) is the worst, followed by ApoE3 (78%), then ApoE2 (8%).

Read more about ApoE here and see if you are ApoE4.

It's also a good idea to check any mutations or polymorphisms in APP, PS1, PS2, CD33, TREM2, CR1, and NLRP1.

Treatment

Treatment is different for everyone, but simply goes like this:

1. Fixing the **underlying cause** (infections, toxin exposure, chronic inflammation)
2. Changing lifestyle to **increase neurotrophic factors** and proper autophagy
3. Using **diet** and treatments to **restore biomes** and **insulin sensitivity** in the brain/body
4. **Optimizing hormones** and other **biomarkers** using bioidentical hormones, supplements, and herbs

Infections

Treat MARCoNs if positive.
Inactivate/excrete pathogens using:

- IV glutathione
- Intranasal VIP
- Cruciferous foods (more listed in diet)

Here are some other useful tools to help remove infections or toxins:

- Activated Charcoal
- Alpha lipoic acid
- Chitosan
- Chlorella
- Cholestyramine
- Guggul
- Maganese
- NRF2 Activation
- Restore4Life
- Sauna
- Vitamin B6
- Vitamin C
- Welchol
- Zinc picolinate

Lifestyle
These are lifestyle requirements for the ReCODE protocol that help reverse AD:

Sleep:
- **8 hours of sleep**/night (also going to bed before midnight)
- No **blue light** at night
- No **EMFs** at night

Brain Stimulation:
- Do brain training games
- Exercise
- Increase neurotrophic factors (BDNF and NGF, but I recommend CNTF, GDNF, CDNF,and MANF as well)

Psychological:
- Keep stress low (for reduced atrophy)

Oral Hygiene:
- **Brush and floss daily**
- **Coconut pulling**

**Diet (Ketoflex 12/3)**

You can find a more in-depth layout of the diet (with how to do it, recipes, and supplements) here.

The ReCODE diet, called "Ketoflex 12/3", consists of being in ketosis, eating high amounts of fiber, eating within a 12 hour window, and stop eating at least 3 hours before bed.

The goals:
- Increases **ketone bodies** (acetoacetate, beta-hydroxybutyrate, and acetone) and BDNF
- **MCT oil** (caprylic acid is the strongest form) is a must for **ApoE4 until insulin sensitivity is restored**, then must switch to MUFAs (like avocado) and PUFAs predominantly (such as **olive oil**)
- Lots of uncooked veggies
- **Fasting** 12 hours/day
- Stop eating 3 hours before bed
- Increase **insulin sensitivity**

**Foods**

Eat frequently:
- Avocados
- Artichokes
- Beets
- Cilantro
- Cruciferous vegetables (such as cauliflower, broccoli/broccoli sprouts, various types of cabbage, kale, radishes, Brussels sprouts, turnips, watercress, kohlrabi, rutabaga, arugula, horseradish, maca, rapini, daikon, wasabi, and bok choy)
- Dandelions
- Garlic
- Ginger
- Grapefruit
- Jicama
- Kimchi
- Leafy greens (such as kale spinach, and lettuce)
- Leeks
- Lemons
- Mushrooms
- Olive oil
- Onions
- Pasture raised eggs
- Resistant starches (such as sweet potatoes, rutabagas, parsnips, and green bananas)
- Saurkraut
- Seaweed
- Tea (oolong, black, and green)
- Wild-caught fish (SMASH fish such as salmon, mackerel, anchovies, sardines, and herring)

Eat less frequently:

- Coffee (such as super coffee)
- Grass-fed beef
- Legumes (such as peas and beans)
- Nightshades (such as eggplant, peppers, and tomatoes)
- Nontropical fruits (low glycemic, such as berries)
- Pasture raised chicken
- Starchy veggies (such as corn, peas, squash, but sweet potatoes are an exception)
- Wine (1 glass/wk)

Avoid:

- Dairy (occasional cheese or plain yogurt is okay, I recommend A2-based dairy)
- Fruits (high glycemic ones especially)
- Gluten
- Grains
- High mercury fish (such as tuna, shark, and swordfish)
• Processed foods
• Sugar and simple carbs (including breads, wheats, rice, cookies, cakes, candies, sodas, etc)

Some important notes about the diet:

• Avoid overheating foods (as it creates AGEs)
• Fish is good, but don't do too much meat.
• Remove all inflammatory lectins. R
• If you do eat fruits, make sure they are higher in fiber and not as juice.
• Include lots good fats in your diet (such as avocados, olive oil, MCT oils like caprylic acid, and if non-lectin sensitive then nuts and seeds oils are okay)
• Use digestive enzymes

MicroBiome

Include probiotics and prebiotics:

• **B. lactis** (fermented dairy)
• **B. longum** (fermented veggies and dairy)
• **L. acidophilus** (fermented dairy)
• **L. brevis** (sauerkraut and pickles)
• **L. plantarum** (kimchi, sauerkraut and fermented veggies)
• **Probiomax**
• **S. boulardii**

If you have any infections with biofilms, you must take care of those as well (may use Bactroban/Mupirocin, SinuClenz, or Xlear).

For the nasal microbiome:

• **Kimchi juice + nasal swab**
• **Restore4Life**

Insulin Resistance

Here are some supplements recommended for decreasing insulin resistance:

• **Alpha lipoic acid**
• **Berberine**
• **Chromium picolinate**
• **Cinnamon**
• **Magnesium Glycinate**
• **Magnesium Threonate**
• **Metformin** (drug)
• **Zinc picolinate**
Supplements And Herbs

Supplements on the ReCODE program that help with cognition and inflammation:

- **ALCAR**
- Citicoline
- **Coffee fruit extract**
- **DHA/EPA** *(fish oil or krill oil)*
- **Nicotinamide riboside** (combines well with resveratrol)
- **Pantothenic acid** (use B6/B12/folate if homocysteine ≥ 6)
- **PQQ**
- **Resveratrol**
- Ubiquinol
- **Vitamin B1**
- **Vitamin C**
- **Vitamin D**
- **Vitamin E**
- **Vitamin K2**

Herbs on the ReCODE program that help with cognition and inflammation:

- Ashwagandha
- **Bacopa**
- **Gotu Kola**
- **Guduchi**
- **Guggul** *(or activated charcoal)*
- **Lion’s Mane**
- **Rhodiola**
- **Skullcap**
- **Triphala** *(Amalaki + Haritaki + Bibhitaki)*

Also, pro-resolving mediators (like **SPM Active**), such as **resolvins**, **protectins**, and **maresins** will also help against inflammation.

**Mechanism Of Action**

Here are all the functions that the ReCODE protocol aims to accomplish:

- Increase **α-cleavage**
- Increase **ADNP**
- Increase **autophagy**
- Improve axoplasmic transport
- Increase **BDNF**
- Increase **cAMP**
- Increase **GABA**
• Increase glutathione
• Increase IDE
• Increase insulin sensitivity
• Improve LTP
• Increase NGF
• Increase microglial clearance of Aβ
• Increase netrin-1
• Increase neprilysin
• Increase PPAR-γ
• Increase phagocytosis index
• Increase PP2A
• Increase resolvins
• Increase SirT1
• Increase synaptoblastic signaling
• Increase telomere length
• Improve vascularization
• Increase VIP
• Increase vitamin D signaling
• Optimize all metals
• Optimize cholinergic neurotransmission
• Optimize cortisol
• Optimize detoxification
• Optimize DHEA
• Optimize E2:P (estradiol to progesterone) ratio
• Optimize estradiol
• Optimize free T3
• Optimize free T4
• Optimize insulin secretion and signaling
• Optimize leptin
• Optimize mitochondrial function and biogenesis
• Optimize pregnenolone
• Optimize progesterone
• Optimize stem-cell-mediated brain repair
• Optimize synaptic components
• Optimize testosterone
• Optimize TSH
• Reduce amyloid-beta oligomerization
• Reduce APPβ-cleavage
• Reduce caspase-6 cleavage
• Reduce caspase-3 cleavage
• Reduce γ-cleavage
• Reduce glial scarring
• Reduce homocysteine
- Reduce inflammation
- Reduce mTOR activation
- Reduce NF-κB
- Reduce phospho-tau
- Reduce oxidative damage and optimize ROS
- Reduce synaptoclastic signaling

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lavandulyl moiety

naringenin moiety

Sophoraflavanone G

C_{25}H_{28}O_6 (MW = 424.49)

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**MULTIPLE TARGETING**

- **GPCR**
  - $H_1R$, $H_2R$, $H_4R$
  - $D_1R$, $D_2R$
  - 5-HT$_4$
  - $MT_1R$, $MT_2R$

- **ENZYME**
  - HMT
  - AChE, BuChE

- **TRANSPORTER**
  - SERT

- **SIGNALLING**
  - NO

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