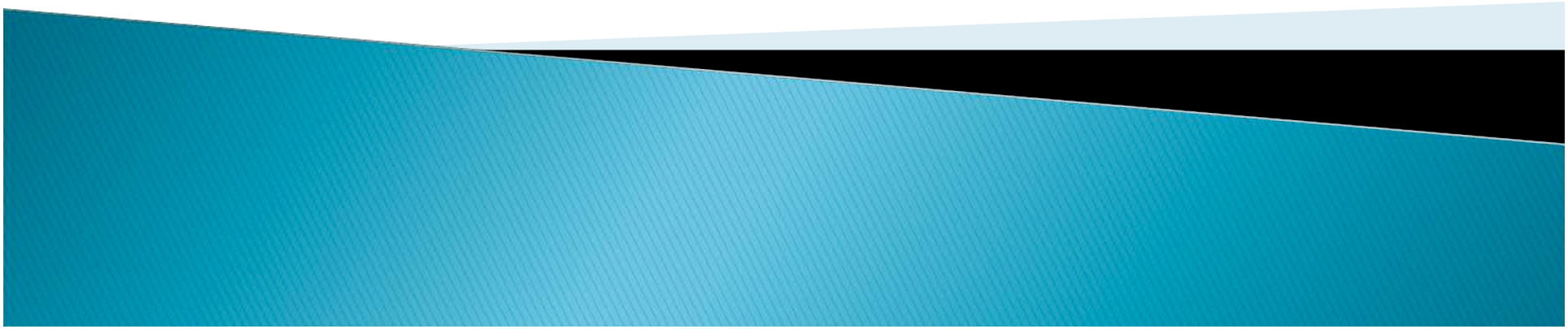
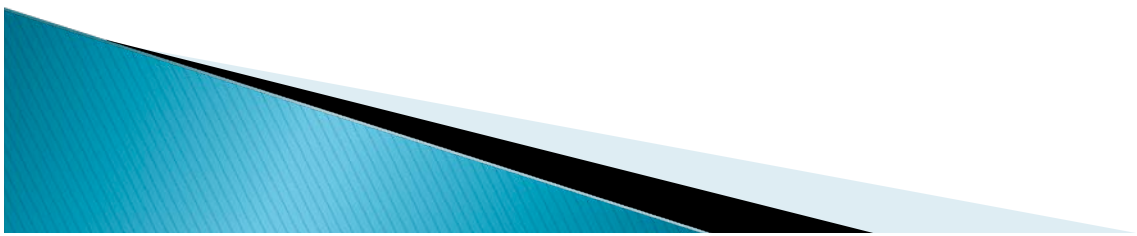
Alzheimer's: Inhibiting Plaque Formation

Immunoliposome directed drug delivery



Alzheimer's Impact

- Alzheimer's lowers quality of life
- Importance of memory
- Longer life (Alzheimer's is ultimately fatal)
- An estimated 26.6 million people 65 years and older had Alzheimer's worldwide in 2006



Beta Amyloid Protein

- Strong correlation between Alzheimer's and beta-amyloid plaques
- Causes neural degeneration
- Beta amyloid protein vs. beta pleated sheets

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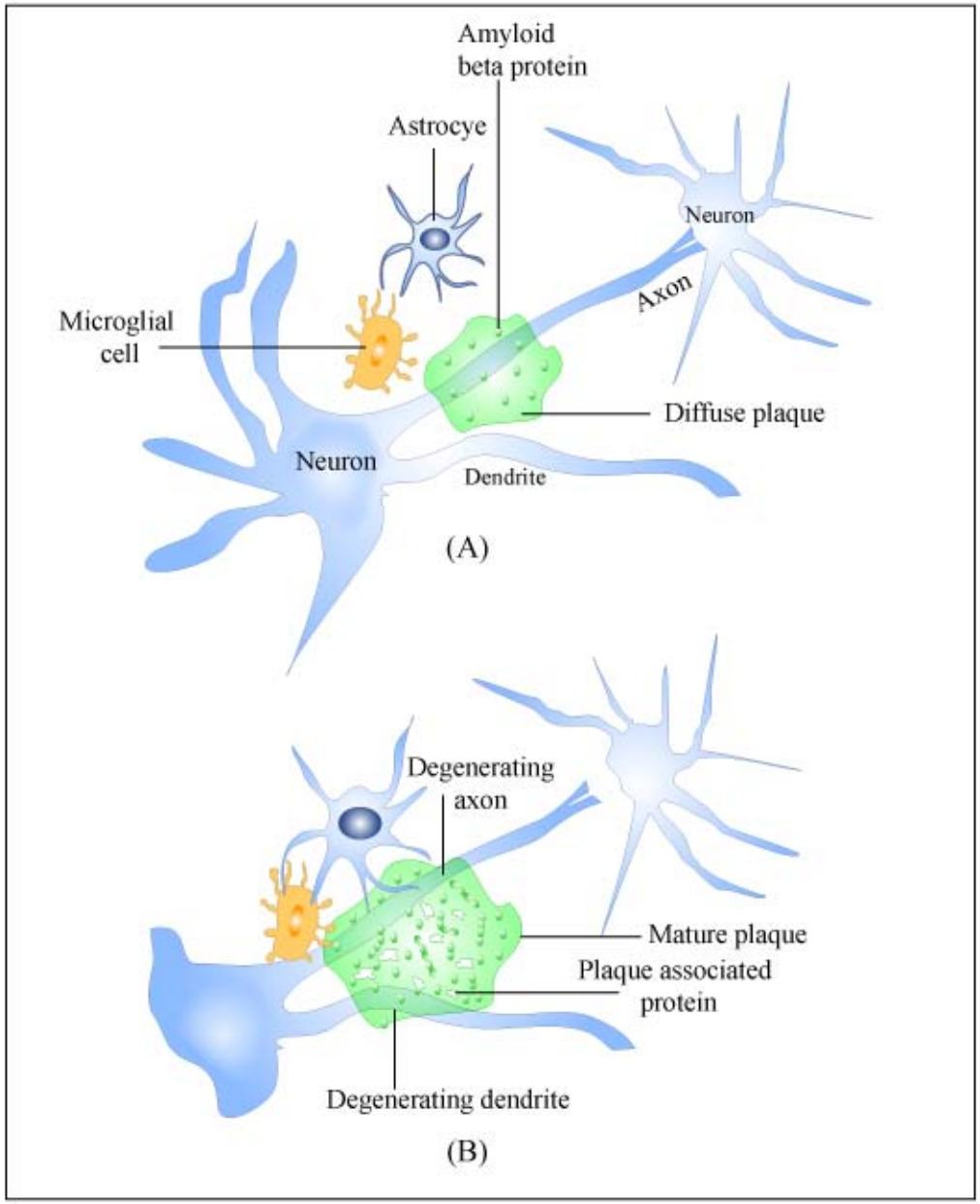
Purpose

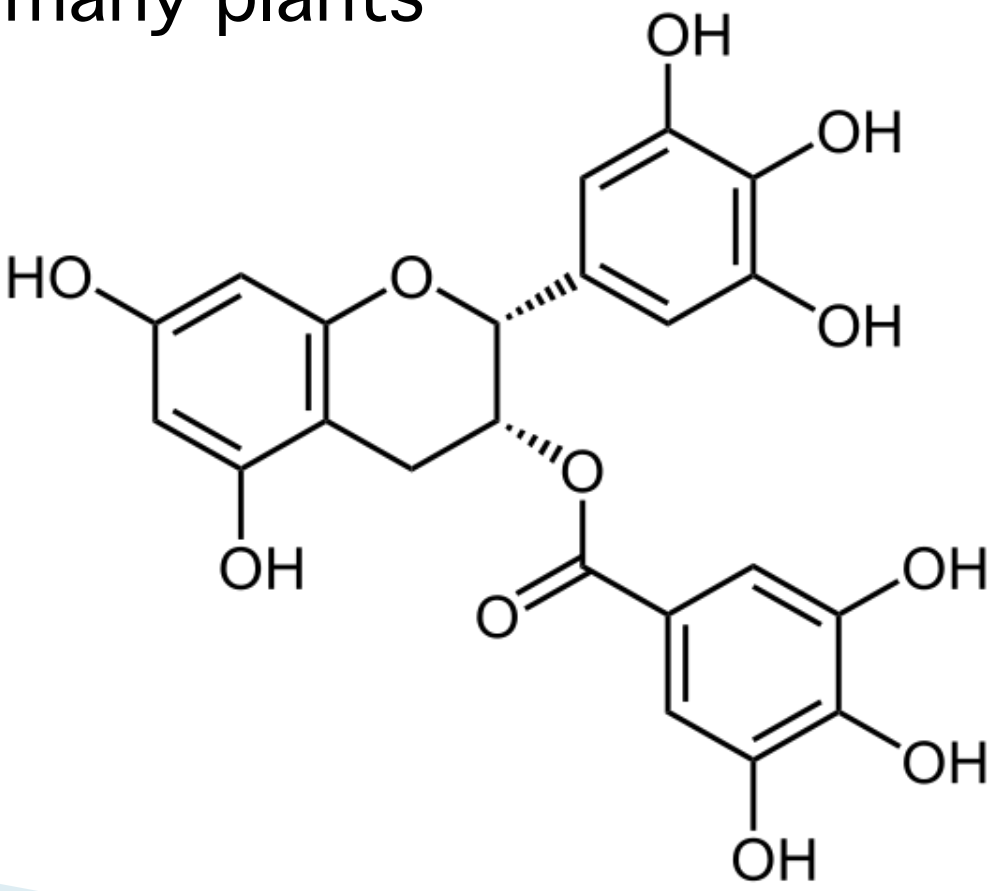
- To target a specific component of Alzheimer's
  - Beta-amyloid protein
- Reduce neural damage
  - By inhibiting the formation of plaques



Epigallocatechin gallate (EGCG)

- A polyphenol with many antioxidant properties found in many plants

• Binds to BA precursor protein, prevents it from taking final shape with its potent iron chelating abilities



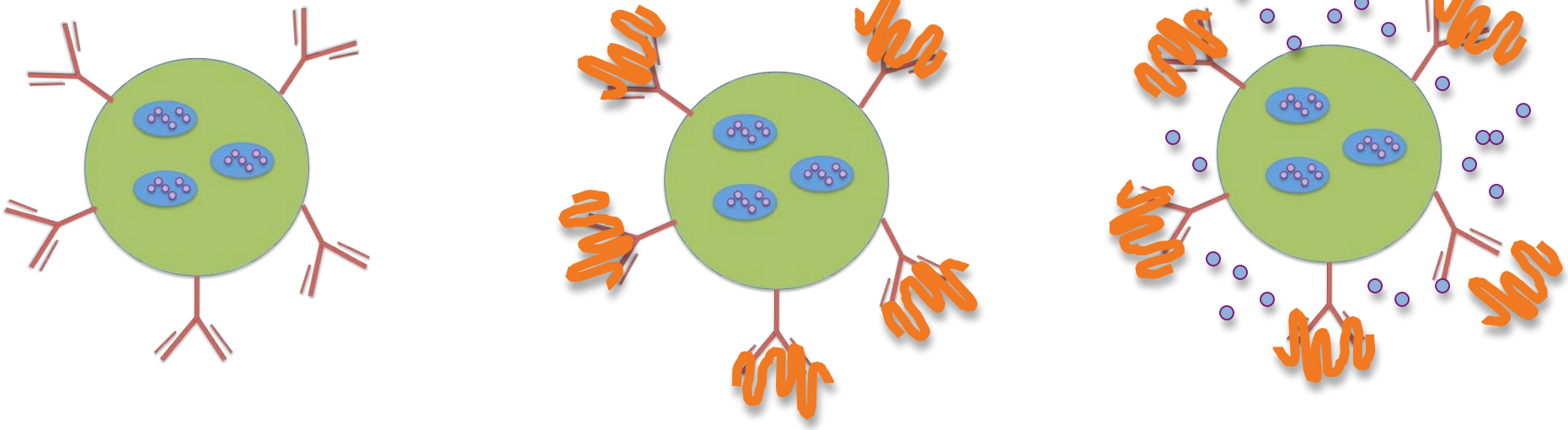
General System Diagram

Immunoliposomes

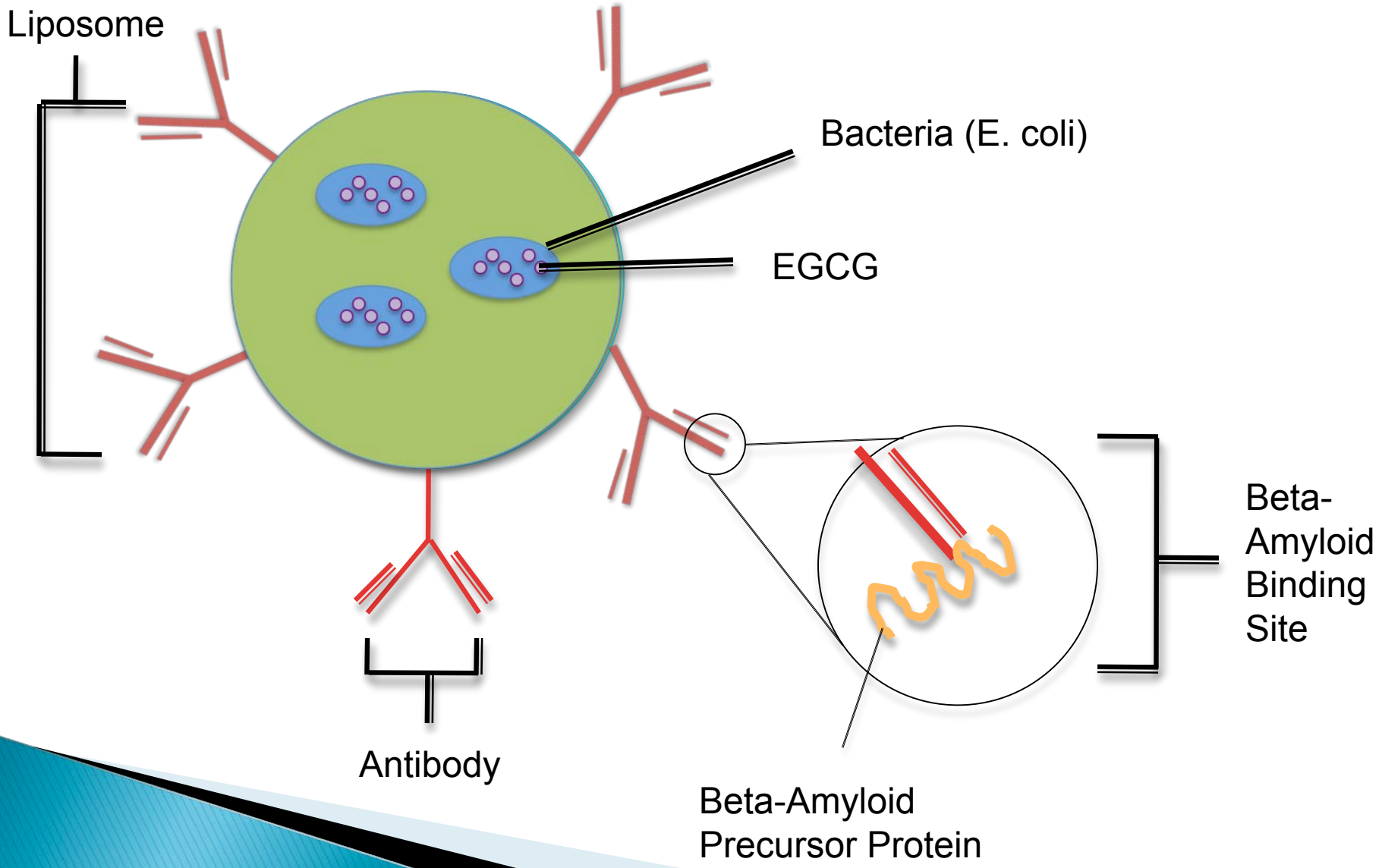
Goes to brain

Attaches to BA precursor protein

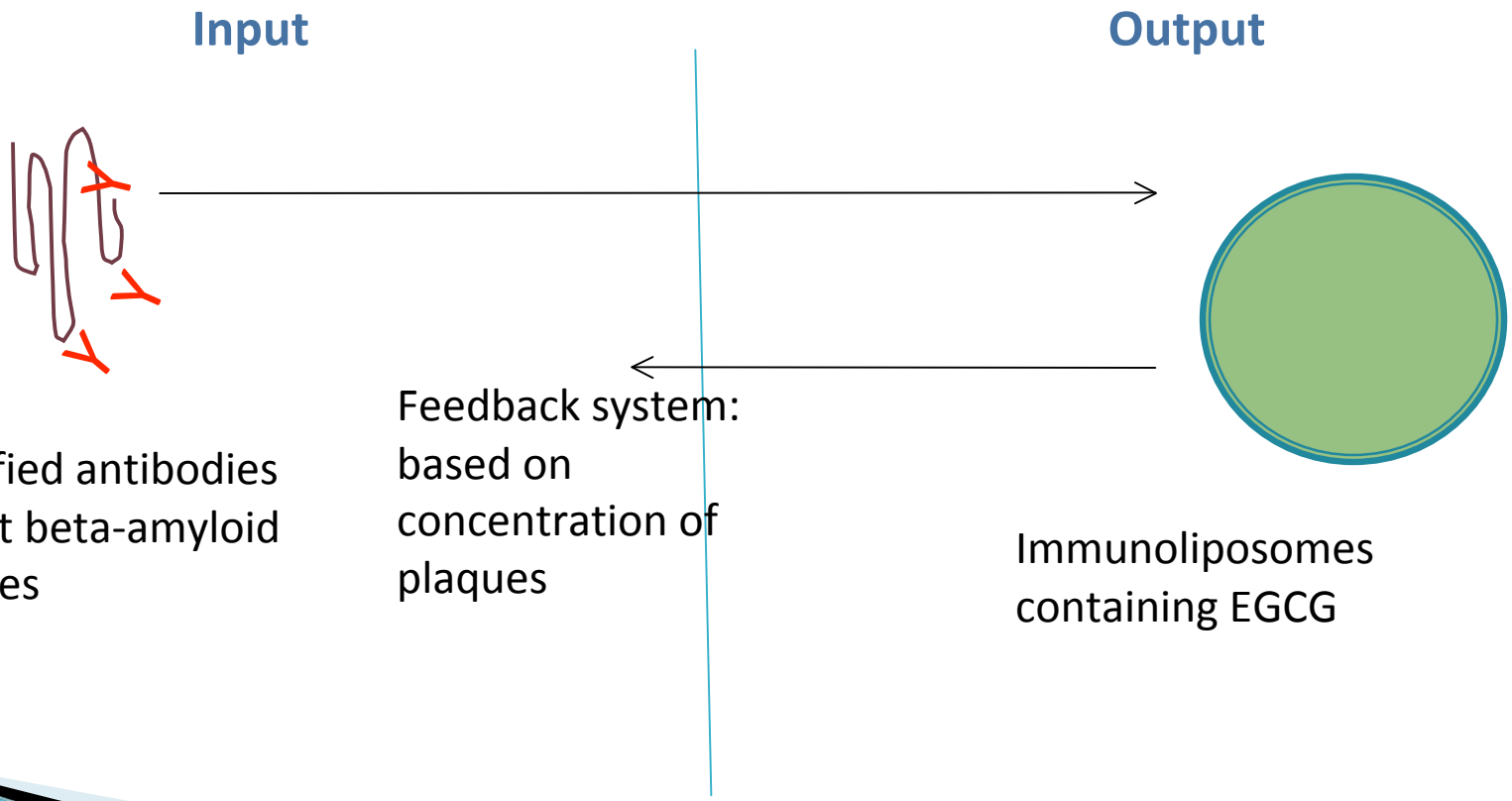
Releases EGCG



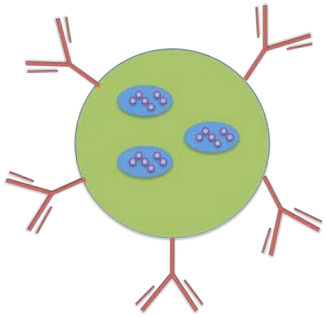
Immunoliposome Structure



Device Diagram



Devices



- Drug Delivery Device
  - -Immunoliposome

- Beta-amyloid Detector
  - -Receptor sequence on antibody
- Trigger
  - -Release of EGCG

- Stop/Feedback Mechanism
  - -Large amount of EGCG inhibits production of EGCG

DDD Drug Delivery Device (Immunoliposome)

BAPD Beta-amyloid Protein Detection

Trigger Releases EGCG

I Immunoliposomes

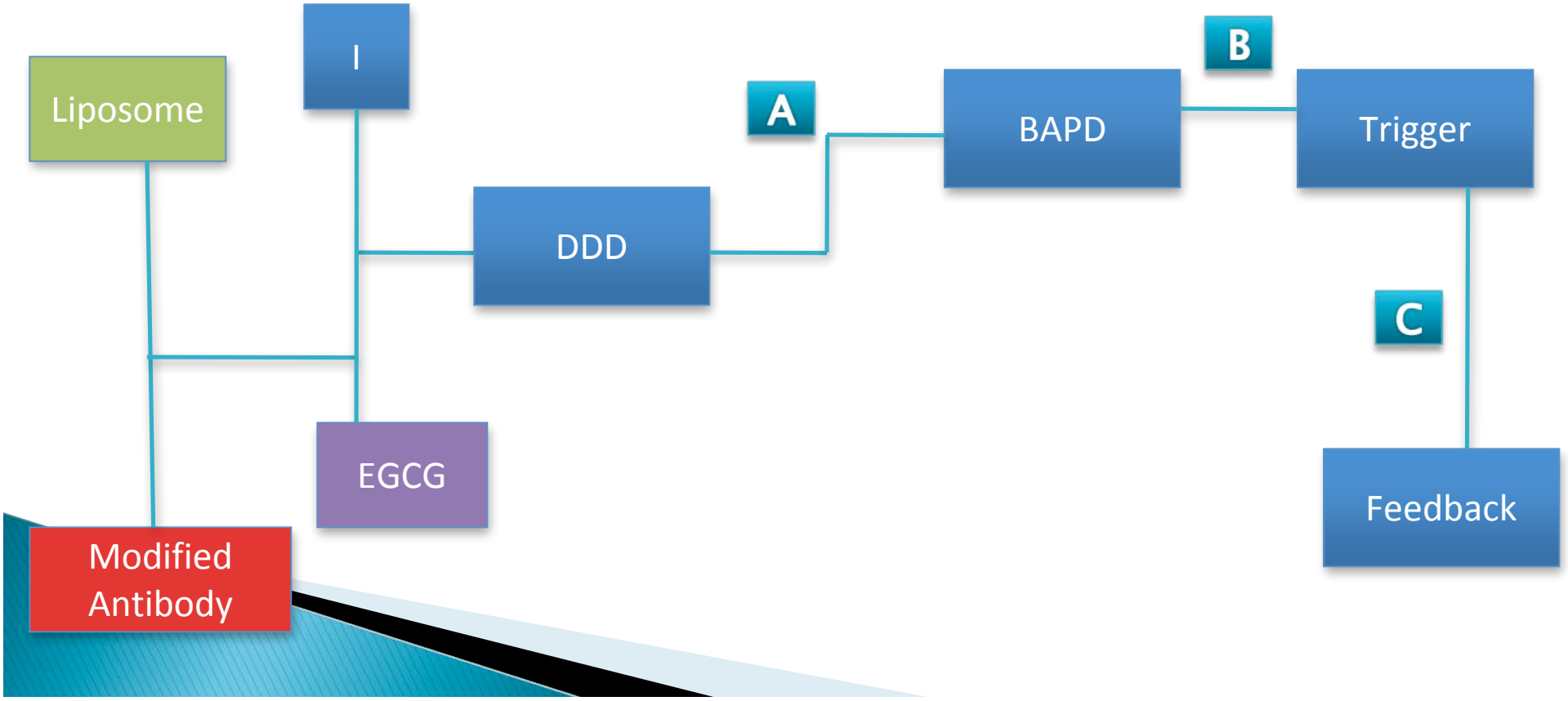
Feedback EGCG inhibits production of more

A Immunoliposomes go to brain

B Reaches beta-amyloid protein

C Releases EGCG

Device Diagram 2



DDD Drug Delivery Device

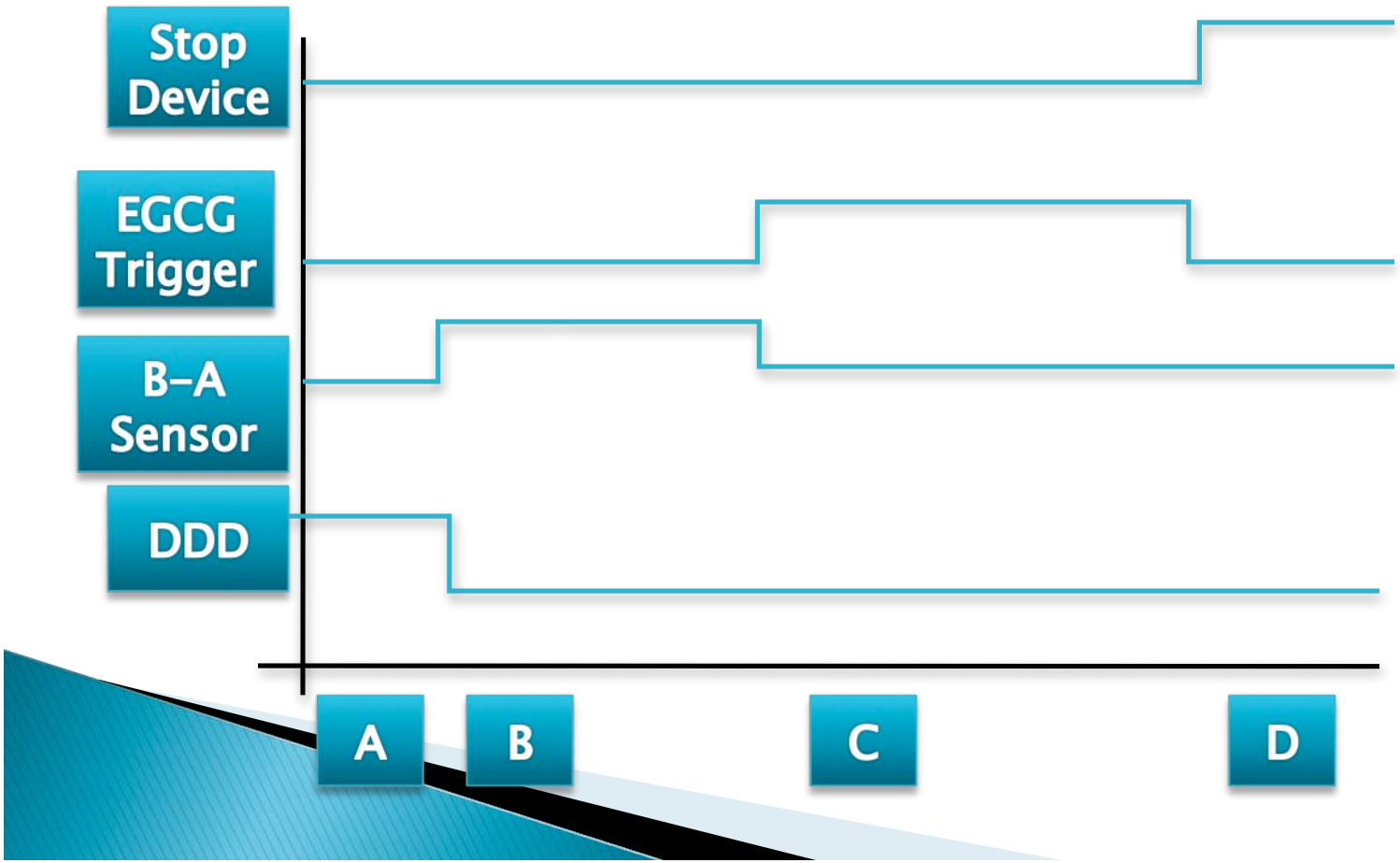
A Immunoliposomes go to brain

B Reaches beta-amyloid protein

C Releases EGCG

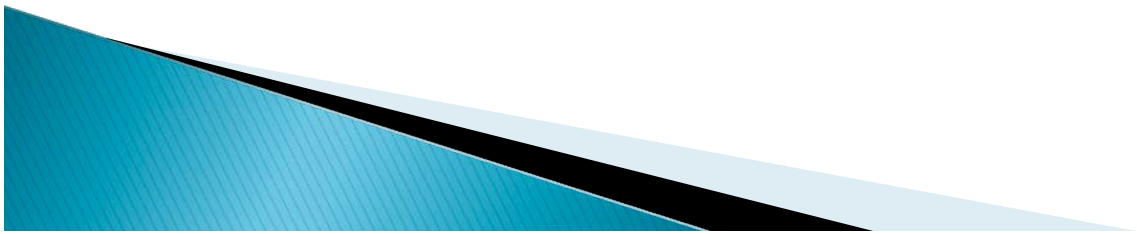
D Excess of EGCG

Timing Diagram



Parts

PARTS	
Liposome	DSPE-PEG
Monoclonal Antibody	OX26
Radioligands	
Beta-Amyloid Sensor	
E. Coli Promoter	PEC3876
EGCG gene	
EGCG Inhibitor Enzyme	
Transcription Terminators	



Parts (Sequence)

EGCG

Liposome

Antibody

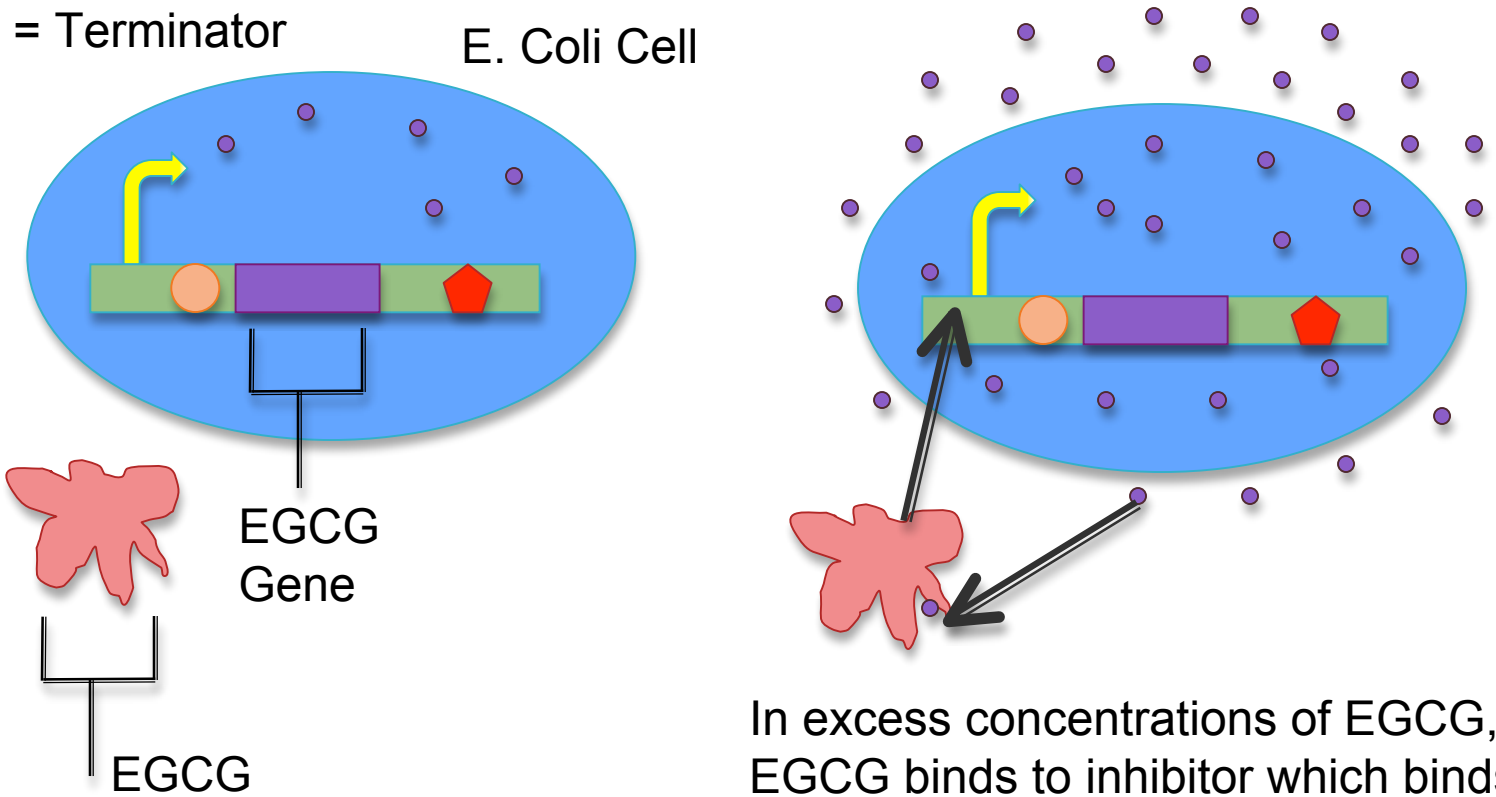
= Promoter

= RBS

= ORF

= Terminator

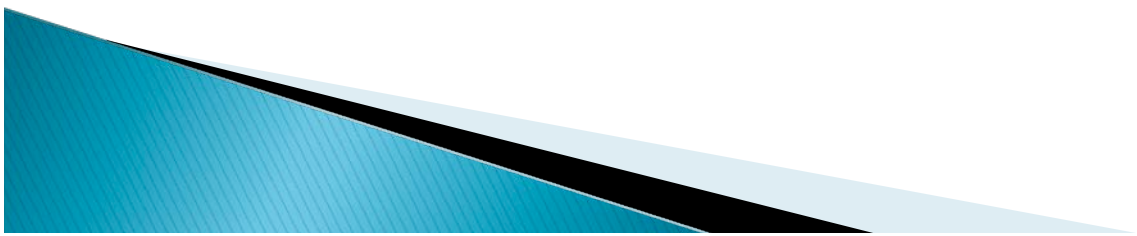
Feedback System



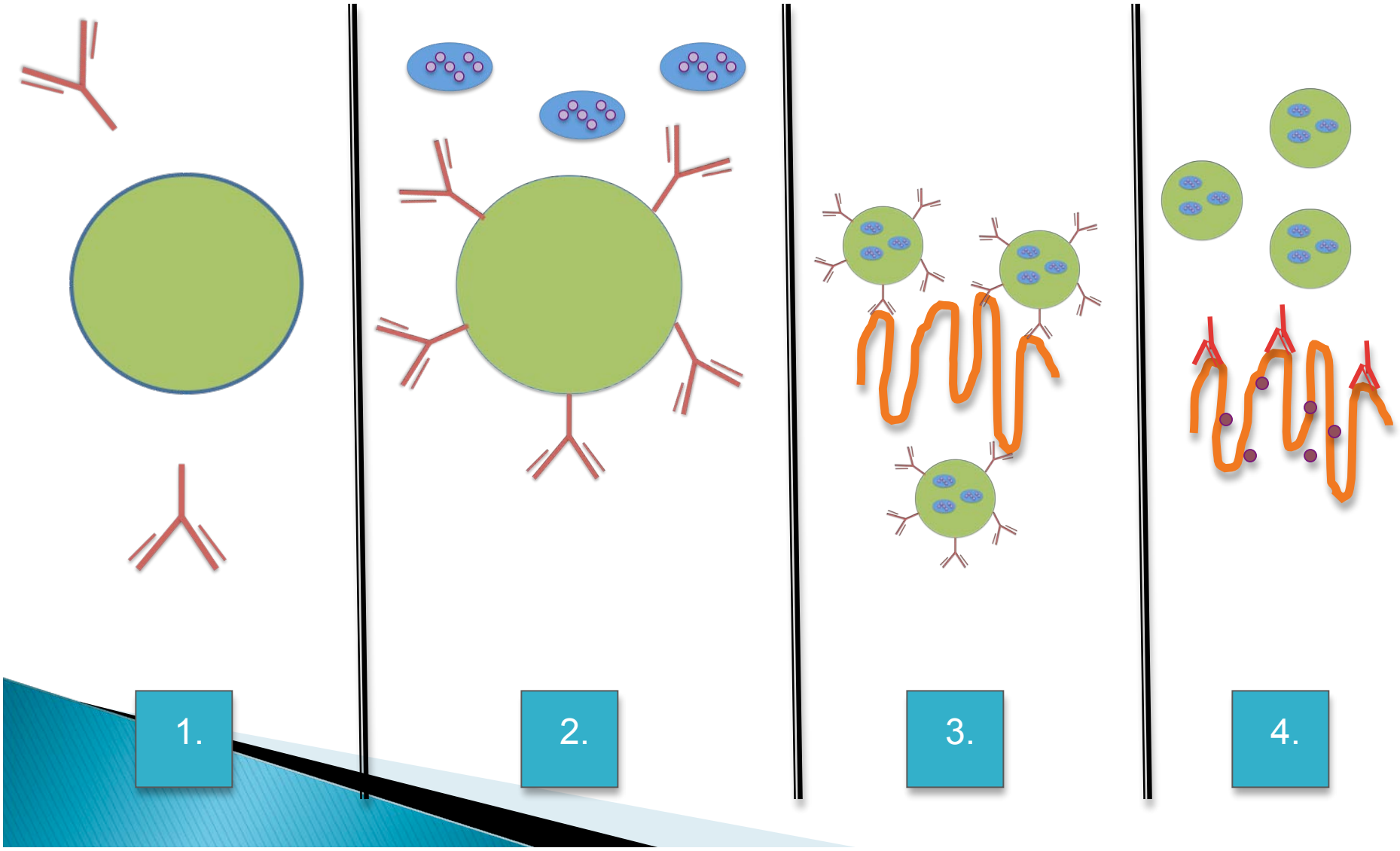
In excess concentrations of EGCG, EGCG binds to inhibitor which binds to the promoter site to prevent the production of more EGCG.

Testing/Debugging

- Clinical trials with mice with Alzheimer's
- Need to determine:
  1. Amount of EGCG needed
  2. Side effects of excess EGCG
- Test that:
  1. Liposome binds to antibody
  2. Insertion of bacteria
  3. Immunoliposome attaches to BA proteins
  4. EGCG is released

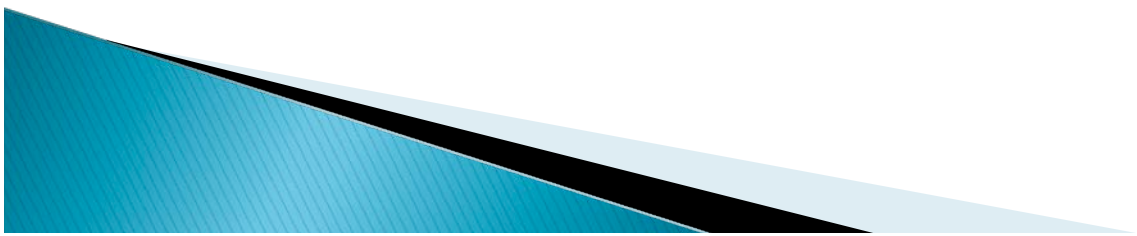


Debugging Steps



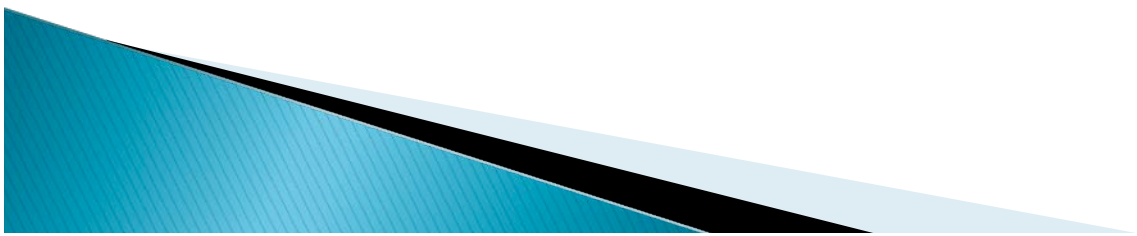
Overall System

- Image brain for beta-amyloid plaques
  - If plaques have not formed
    - Overall system has the desired effect
  - If plaques have formed
    - Overall system is not working
    - Check individual parts of the system for problems



1. Formation of Immunoliposome

- Test in vitro
  - Chromatography
    - Separates liposomes, antibodies, and bonded antibody-liposomes
    - Bonded immunoliposomes heaviest
    - Select for attached antibody-liposomes



2. Insertion of Bacteria

- Test in vitro
  - Set-up: Known amount of bacteria into solution with immunoliposome
  - Chromatography:
    - Immunoliposomes with bacteria will be heavier and travel a shorter distance than immunoliposomes without bacteria

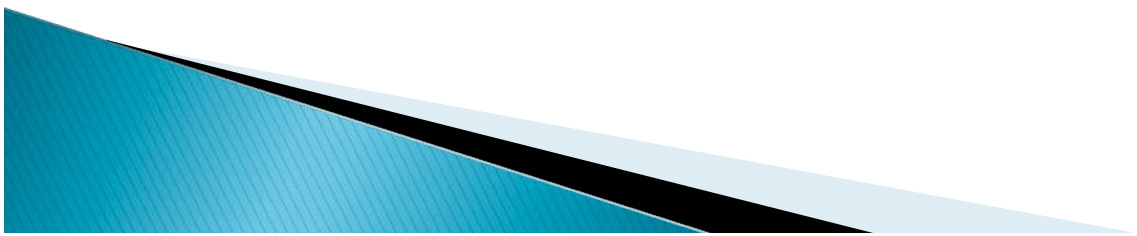
3. Beta-Amyloid Detection

- Isolate BA precursor protein from brain
- Introduce known amount of immunoliposomes in culture
- Determine change in immunoliposome levels

- “Radioligands” – probe that can pass through blood-brain barrier and detect/label plaques, which can then be imaged

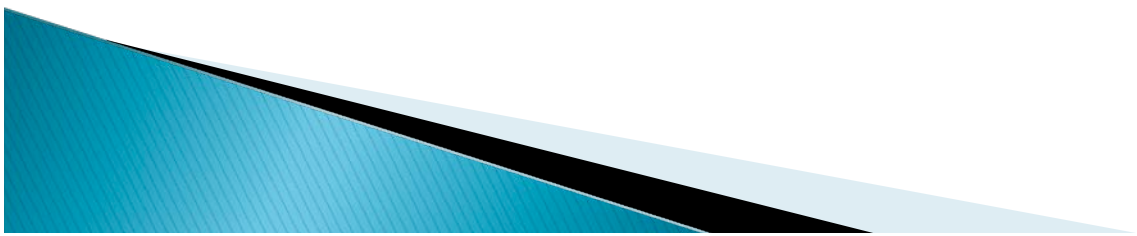
4. Drug Release

- Place immunoliposomes with EGCG-containing bacteria in solution with beta-amyloid precursor protein
- If all previous steps work
  - Concentration of EGCG in solution should increase when beta-amyloid protein introduced
  - If concentration of EGCG does not increase check trigger device

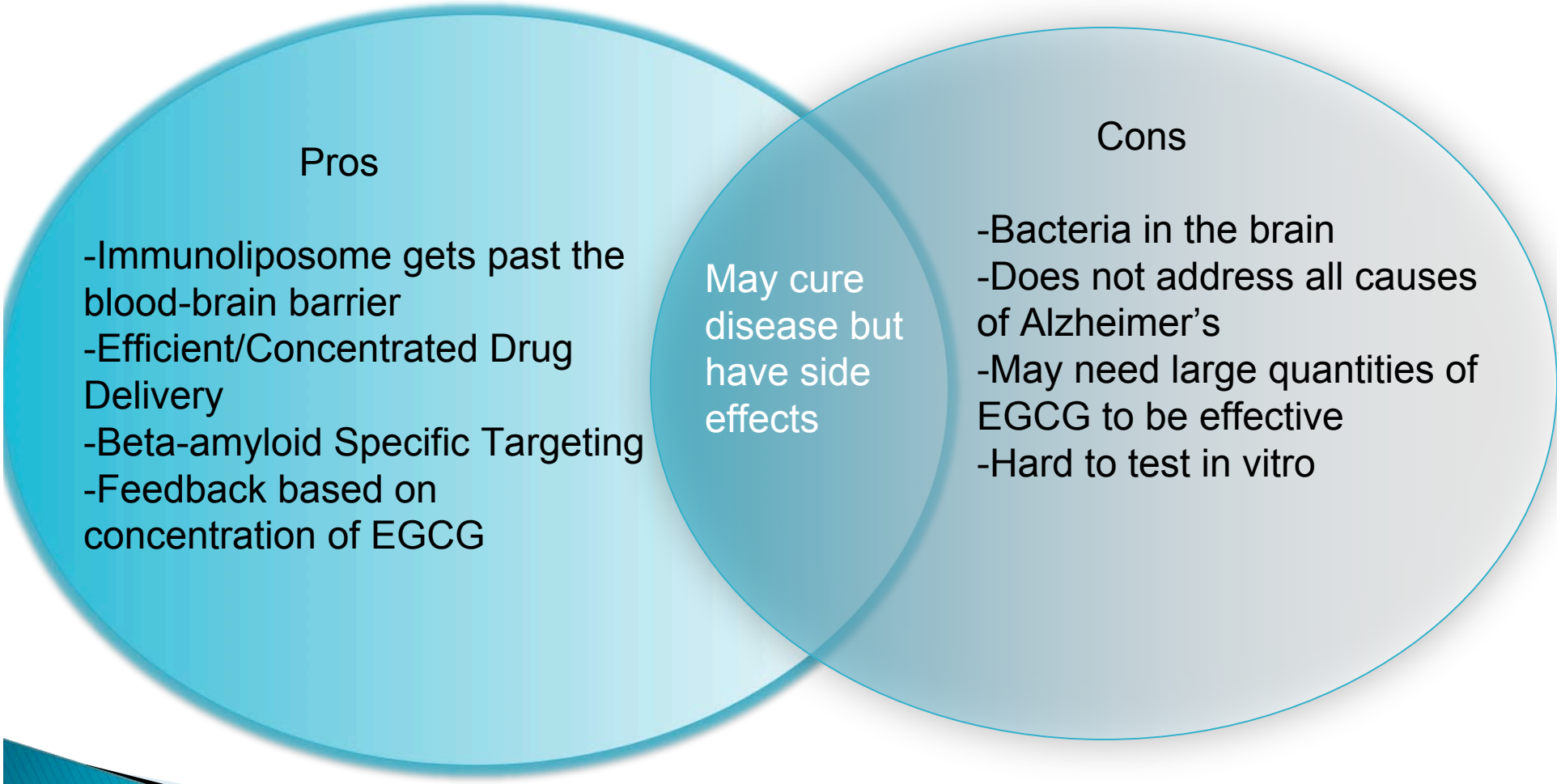


Unknowns/ Possible Issues

Does B-A secrete anything?
Make sure fat degrades in brain and does not build up
How does binding to B-A trigger release of EGCG? (What pathway?)
How do we put the bacteria into the immunoliposome? Polycarbonate membrane extrusion
Can we replicate the parts of immunoliposomes with E.Coli?
Do the antibodies have to be specific to each person?
Can we have the bacteria degenerate with the immunoliposome?



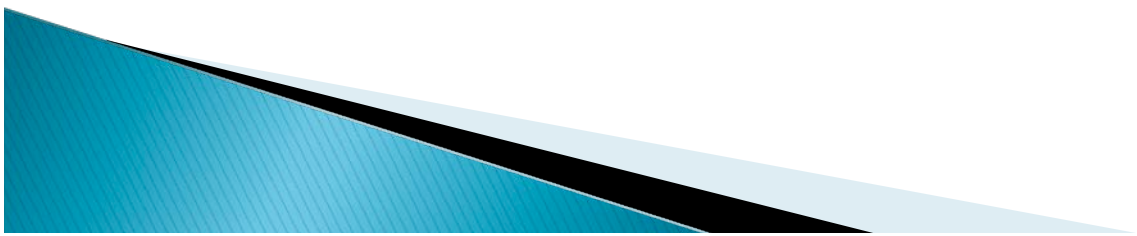
Important Pros and Cons



Costs

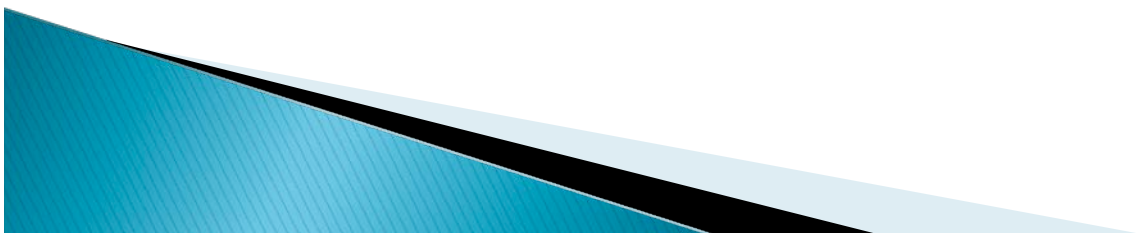
- DSPE-PEG 2000 in Chlorophyll Solution (C) 25mg => $195
- E. coli promoter (PEC3876) => $80
- Radioligands => $150
- Antibodies (OX26) => $3,900

- Estimated Cost: ~$5000



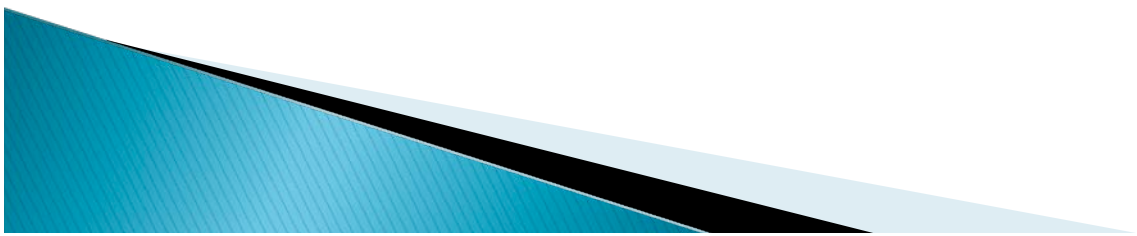
Go?

- Main difficulty: moving substances into brain past blood-brain barrier (BBB)
- Current methods:
  - direct injection into brain
  - surgical implantation/catheters
  - All invasive, dangerous, and have limited effectiveness



No Go?

- Competition – several current techniques in development:
  - drugs to temporarily open BBB
  - attachment to nanoparticles
  - Ultrasound
- Unknowns:
  - Side effects of excess EGCG
  - The base cause of Alzheimer's



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20.020 Introduction to Biological Engineering Design

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