ALZHEIMER DISEASE

Color Index:

- Main Topic
- Main content
- Important
- Extra info, Drs' notes
- Only in girls' slides
- Only in boys' slides

Editing File

Objectives:

- Define neurodegenerative disorders.
- Identify the clinical picture and diagnostic criteria of Alzheimer's disease.
- Understand the different ways of processing of amyloid precursor protein leading to amyloid generation and accumulation.
- Differentiate between the neuritic plaques, neurofibrillary tangles and tau protein and their role in the pathogenesis of the disease.
- Understand the genetics of Alzheimer's disease.
- Discuss ongoing research and therapeutic approach to treat these disorders.

Neurodegenerative Diseases

Diseases of gray matter characterized principally by the progressive loss of neurons.

The pattern of neuronal loss is selective affecting one or more groups of neurons leaving the others intact

The diseases arise without any clear inciting event in patients without previous neurological deficits

A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation.

The aggregated proteins are generally cytotoxic

Alzheimer's Disease

A degenerative disease with the prominent involvement of the cerebral cortex.

Its principal clinical manifestation is dementia.

Dementia: the progressive loss of cognitive function independent of the state of attention.

Patients rarely become symptomatic before 50 years of age but the incidence of disease rises with age.

Most cases are sporadic.

In 5-10 years, the patient becomes profoundly disabled, mute and immobile.

At least 5-10% are familial.

The disease becomes apparent with

- Gradual impairment of higher intellectual function
- Progressive disorientation
- Alterations in mood and behavior
- Memory loss

Diagnosis

1. Combination of clinical assessment and radiologic methods MRI
2. Pathologic examination of brain tissue is necessary for definitive diagnosis
3. Major microscopic abnormalities include: neuritic (or senile) plaques, neurofibrillary tangles and amyloid angiopathy[1]

1- it will cause rupture → hemorrhage

Microscopic findings

Neuritic Plaques

- Spherical with 20-200 µm in diameter.
- Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria.
- The amyloid core contains several abnormal proteins.
- The dominant component of the plaque core is Aβ , a peptide derived from a larger molecule, amyloid precursor protein (APP).
- The two dominant species of Aβ, called $A\beta_{40}$ and $A\beta_{42}$[1] share an N-terminus and differ in length two amino acids.

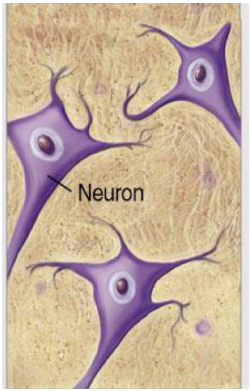
Other less abundant proteins in the plaque:

- Components of the complement cascade
- Proinflammatory cytokines
- α_1-Antichymotrypsin (Protease inhibitor)
- Apolipoproteins

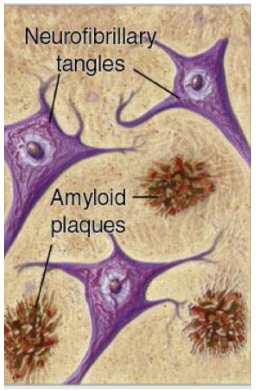
Neurofibrillary Tangles

- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus.
- These filaments mainly contain:
  - ➔ Hyper-phosphorylated forms of the tau protein
  - ➔ A protein that enhances microtubule assembly

Normal



Alzheimer's



Amyloid Angiopathy

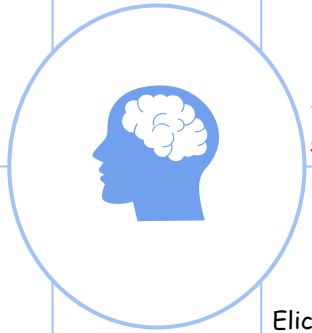
- Amyloid proteins build up on the walls of the arteries in the brain.
- The condition increases the risk of hemorrhagic, stroke and dementia.
- An almost invariable accompaniment of Alzheimer's disease but not specific for Alzheimer's.

1- 40 & 42 refers to the number of amino acid in the proteins.

Pathogenesis of Alzheimer's

Still being intensively studied.

Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques.



Loss of synapses best correlates with severity of dementia.

The Aβ peptide forms β-pleated sheets and aggregates.

Resistant to degradation & Can be directly neurotoxic.

Elicits a response from astrocytes and microglia.

★ Biochemical markers correlated to degree of dementia include:

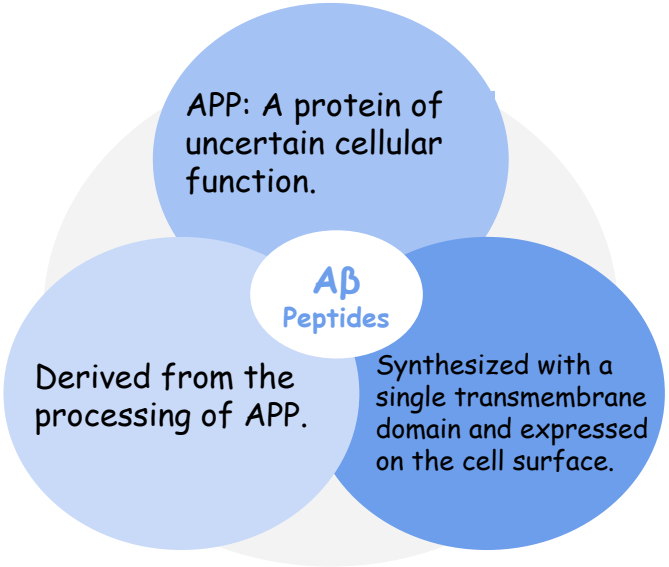
01 Loss of choline acetyltransferase

02 Synaptophysin immunoreactivity

03 Amyloid burden

Aβ Peptides

Aβ: A critical molecule in the pathogenesis of Alzheimer's disease.



Two Pathways for APP Processing

How is Amyloid precursor protein cleaved?

Amyloid precursor protein has 3 cleaving sites for 3 different enzymes: **(α, β, and γ-secretases)**

The alpha secretase pathway

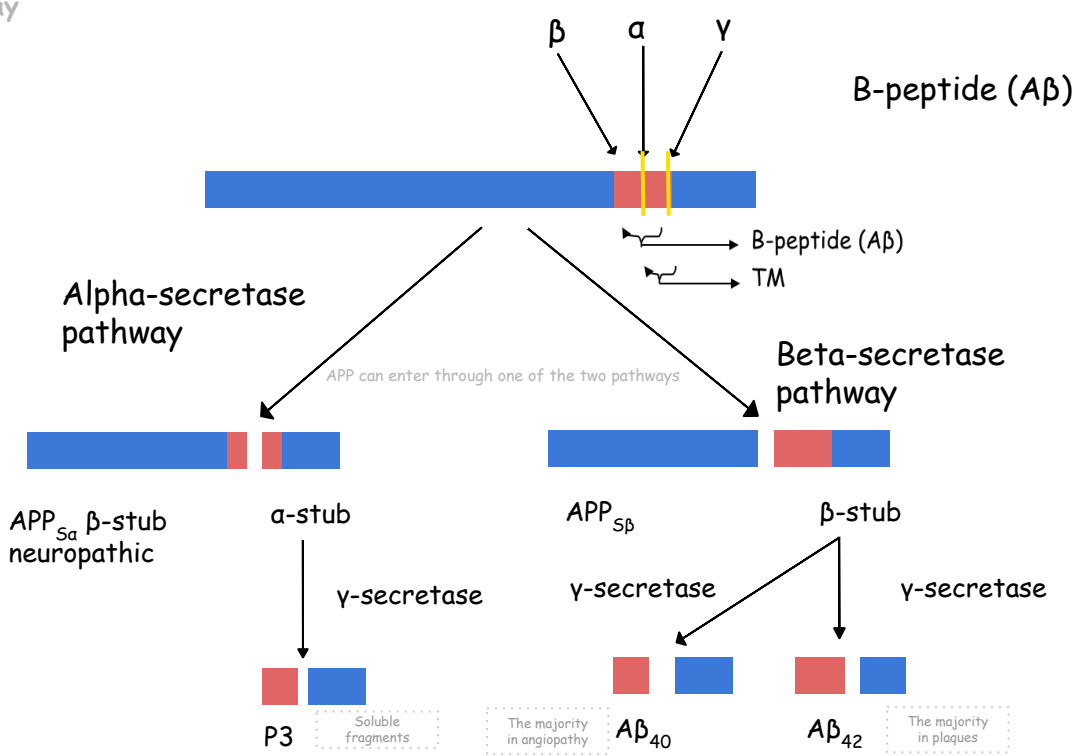
The 1st cleavage is done by α-secretase

↓

This cleavage leads to the formation of a soluble alpha fragment

↓

The 2nd cleavage is always done by γ-secretases which gives us another 2 soluble fragments



Neurotoxic

The beta secretase pathway

The 1st cleavage is done by β-secretase which gives us an insoluble beta fragment

↓

The 2nd cleavage is always done by γ-secretase

↓

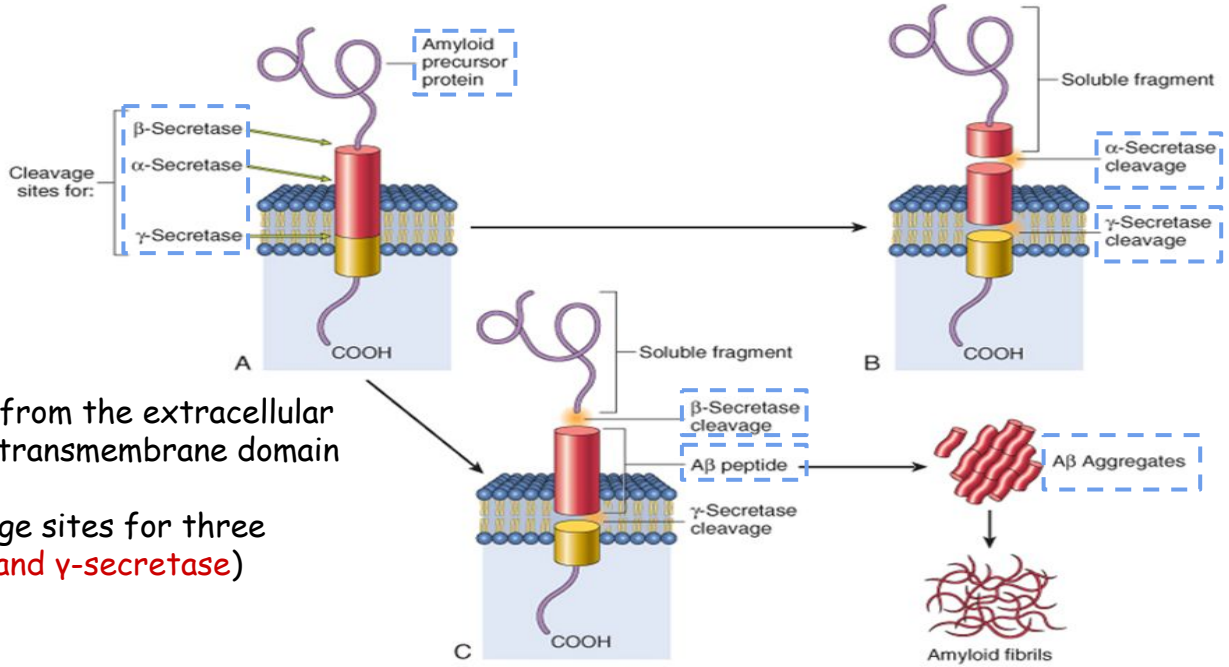
The 2nd cleavage gives us 2 insoluble fragments Aβ$_{40}$ and Aβ$_{42}$

↓

Aβ$_{42}$ is more hydrophobic because of its shape as beta pleated sheet

This is the most prominent pathway in alzheimer's

Mechanism of Amyloid Generation



This figure shows how it's a transmembrane and the cleavage process.

★ The Aβ domain extends from the extracellular side of protein into the transmembrane domain

★ APP has potential cleavage sites for three distinct enzymes: (α, β, and γ-secretase)

When APP is cleaved by α-secretase, Subsequent (followed) cleavage by γ-secretase does not yield Aβ.

Cleavage by β-secretase followed by γ-secretase results in production of Aβ

Aβ can then aggregate and form fibrils.

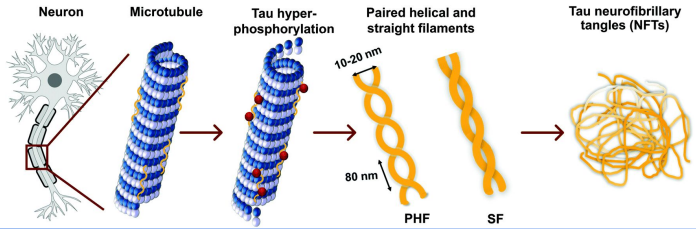
Accumulation of Aβ protein

Accumulation of Aβ protein affects neurons and neuronal function:

- Small aggregates of Aβ alters neurotransmission by sitting between neurons and preventing transmission.
- Aggregates can be toxic to neurons and synaptic endings.
- Larger deposits (plaques) also cause neuronal death.
- Elicit a local inflammatory response leading to further cell injury.

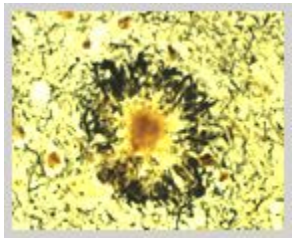
The Tau Protein

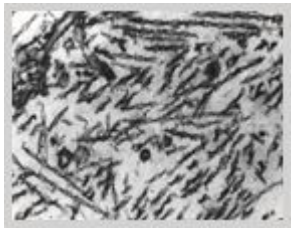
- Presence of Aβ causes **hyper-phosphorylation** of tau protein in neurons.
- This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body).
- The process results in neuronal dysfunction and cell death.



Aβ and tau may both contribute to the pathogenesis Of the Alzheimer's disease

Factors that elevate Aβ





Aβ

Tau

Fibril assembly

Filament assembly

Nerve cell mis-function and death?

Nerve cell mis-function and death?

Genetics of Alzheimer's

- Mutations in APP gene.
- Mutations in γ-secretase (presenilin-1 or presenilin-2). PS-1 PS-2
- Both lead to early onset of **familial** Alzheimer's disease due to high rate of Aβ accumulation.
- Alzheimer's occurs in most patients with Down syndrome (trisomy 21) beyond 45 years of age.
- The gene encoding APP is located in chromosome 21.
- Due to APP gene dosage effects[1].
- Genes associated with typical, sporadic Alzheimer disease are being identified[2].
- This may provide new clues to pathogenesis of the disease.

IMPORTANT

Chromosome	Gene	Consequences
21	Amyloid Precursor Protein (APP)	Early onset FAD[1] Increased Aβ production
14	Presenilin-1 (PS1)	Early onset FAD Increased Aβ production
1	Presenilin-2 (PS2)	Early onset FAD Increased Aβ production
19	Apolipoprotein E (ApoE)	Increased risk for development of AD Decreased age at onset of AD

1. Familial Alzheimer's disease - Since there is an extra gene in down syndrome, there will be extra production of APP.
2. We only know about APO E4.

Treatment of AD

Currently no effective treatment for AD.

Epidemiological studies show NSAIDs decrease the risk for developing AD, unfortunately Clinical trials of NSAIDs in AD patients are not very fruitful.

Flavonoid supplements may be a new therapeutic approach for AD.

Regulating neurotransmitter activity (eg.enhancing cholinergic function improves symptoms).

Polyphenols "antioxidants" such as flavonoids (found in fruit) reduce proinflammatory responses.

Stem cell therapy offers:

- Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration.
  "by grafting a certain type of neurons in an affected area"
- Neurotrophic support to remaining cells.
- Prevent the production or accumulation of toxic factors that harm neurons.

Continued Research on AD

The small aggregates of Aβ and larger fibrils are directly **neurotoxic**.

They can elicit oxidative damage and alterations in calcium homeostasis.

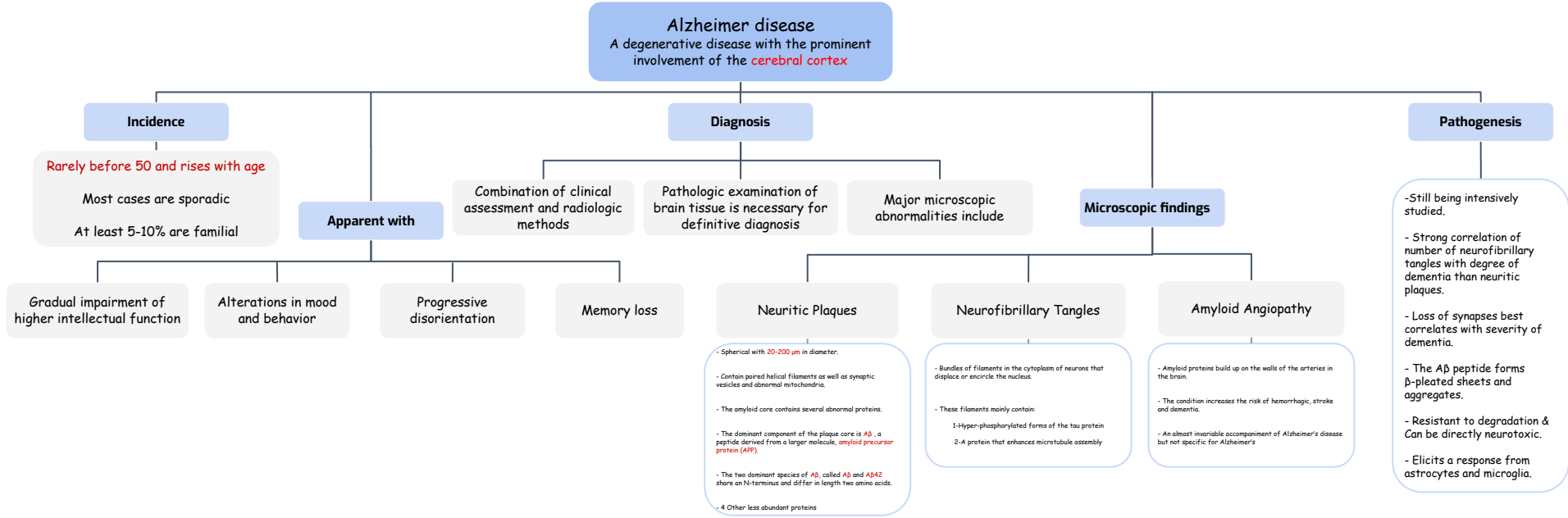
How Aβ is correlated to neurodegeneration in AD? How it is linked to tangles and hyperphosphorylation of tau protein?

All remain open questions.

Take Home Messages

- Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons.
- Extracellular deposition of normally soluble proteins in certain tissues in the form of insoluble fibrous aggregates known as amyloid. The deposition of amyloid interferes with normal cellular function, resulting in cell death and eventual organ failure.
- **The dominant component of amyloid plaque that accumulates in Alzheimer's disease is amyloid β42 (Aβ42) peptide.**

Summary


Alzheimer disease
A degenerative disease with the prominent involvement of the cerebral cortex
Incidence
Rarely before 50 and rises with age
Most cases are sporadic
At least 5-10% are familial
Apparent with
Gradual impairment of higher intellectual function
Alterations in mood and behavior
Progressive disorientation
Memory loss
Diagnosis
Combination of clinical assessment and radiologic methods
Pathologic examination of brain tissue is necessary for definitive diagnosis
Major microscopic abnormalities include
Microscopic findings
Neuritic Plaques
- Spherical with 20-200 µm in diameter.
- Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria.
- The amyloid core contains several abnormal proteins.
- The dominant component of the plaque core is Aβ , a peptide derived from a larger molecule, amyloid precursor protein (APP).
- The two dominant species of Aβ, called Aβ and Aβ42 share an N-terminus and differ in length two amino acids.
- 4 Other less abundant proteins
Neurofibrillary Tangles
- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus.
- These filaments mainly contain:
1-Hyper-phosphorylated forms of the tau protein
2-A protein that enhances microtubule assembly
Amyloid Angiopathy
- Amyloid proteins build up on the walls of the arteries in the brain.
- The condition increases the risk of hemorrhagic, stroke and dementia.
- An almost invariable accompaniment of Alzheimer's disease but not specific for Alzheimer's
Pathogenesis
-Still being intensively studied.
- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques.
- Loss of synapses best correlates with severity of dementia.
- The Aβ peptide forms β-pleated sheets and aggregates.
- Resistant to degradation & Can be directly neurotoxic.
- Elicits a response from astrocytes and microglia.

Quiz

MCQs :

Q1: Which one of the following is the main component of neuritic plaques?

a) Amyloid precursor protein **b)** Tau proteins
c) Aβ peptides **d)** All of them

Q2: Which one of the following biochemical markers is NOT correlated with the degree of dementia in Alzheimer patients?

a) Choline Acetyltransferase **b)** Synaptophysin
c) Amyloid burden **d)** Troponin I

Q3: Neurofibrillary tangles are composed of:

a) Amyloid beta **b)** Tau protein **c)** APP

Q4: Most of conditions of alzheimer disease are due to:

a) Familial **b)** Sporadic **c)** MS

Q5: Alzheimer disease usually associated with which condition?

a) Spina bifida **b)** Down syndrome **c)** MS

Q6: Alzheimer's Disease is diagnosed with:

a) Clinical assessment **b)** Radiologic methods
c) Pathologic examination of brain tissue **d)** All of them

SAQs :

Q1: Name 3 major microscopic abnormalities for Alzheimer's disease

Q2: What is dementia?

Q3: What are the main genes affected in Alzheimer disease?

Q4: APP has potential cleavage sites for three distinct enzymes, name them

★ **MCQs Answer key:**

1) C 2) D 3) B 4) B 5) B 6) D

★ **SAQs Answer key:**

1) neuritic (or senile) plaques, neurofibrillary tangles and amyloid angiopathy.

2) The progressive loss of cognitive function independent of the state of attention.

3) Amyloid Precursor Protein (APP), Presenilin-1 (PS1), Presenilin-2 (PS2), Apolipoprotein E (ApoE).

4) α, β, and γ-secretase.

Team members

Girls Team:

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Arwa Al Emam
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

Boys Team:

- Abdulrahman Bedaiwi
- Alkassem Binobaid
- Naif Alsolais
- Omar Alyabis
- Rayyan Almousa
- Sultan Alhammad
- Tariq Alanezi

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ The harder you work for something, the greater you'll feel when you achieve it.

438 BIOCHEMISTRY TEAM

We hear you