ALZFORUM | Celebrating 20 Years of Alzforum (1996 - 2016)

EVOLUTION OF ALZHEIMER'S DISEASE RESEARCH

1900 | 1910 | 1960 | 1970 | 1980 | 1990 | 1995 | 2000 | 2005 | 2010 | 2015

Alois Alzheimer describes case of Auguste Deter at meeting in Tuebingen

Oskar Fischer describes Alzheimer pathology in dementia cases

Robert Terry, Michael Kidd revive interest with electron microscopy of neuropathologic lesions

Aggregated neurofilaments | Amyloid aggregated material in plaques

"Miliary foci", later known as amyloid plaques, seen in Auguste Deter's cortex

Emil Kraepelin coins the term "Alzheimer's disease"

Early brain imaging detects brain atrophy and reduced perfusion in AD

First report | 1976-1980 | 1981-1988

Neurofibrillary tangles and component proteins first isolated from AD brain

Sir Martin Roth equates pathology and cognitive decline of common senile dementia to that of AD — then considered a rare, presenile dementia

The consistent, progressive memory loss in early AD is different from the mild memory loss in healthy aging

National Institute of Aging founded, boosts AD research funding

Mini-mental State Exam (MMSE) developed to screen mental status

Robert Katzman raises awareness that AD is common disease of aging

First reports of hippocampal atrophy and reduced brain metabolism hint that MCI may predict AD

CONTROL | DEMENTIA

Cholinergic hypothesis of Alzheimer's disease

George Glenner (shown), Colin Masters isolate Aβ peptide from human brains

Tau identified as main component of tangles

Entorhinal cortex is key site of AD pathology, already has profound neuron loss in mild AD

CDR = 0.5

CERAD established to standardize diagnostic procedures

Alzheimer's Association founded

U.S. network of federally funded ADRCs starts with initial sites in Baltimore, Boston, LA, NYC, and San Diego

Innate immune system implicated in AD

NINCDS-ADRDA criteria of "possible", "probable", "definite" AD

Inge (shown) Grundke Iqbal and Khalid Iqbal, and other groups found that tau is abnormally phosphorylated in AD

In brain, glial cells synthesize ApoE, secrete it in HDL particles

Alpha cleavage of APP precludes Aβ formation

APP cloned and sequenced, Aβ42 and 43 fragments identified

Braak staging of AD neuropathology defined

First APP transgenic mouse model

Concept of cognitive reserve articulated

APP Dutch mutation causes autosomal-dominant cerebral amyloid angiopathy

APP London; first mutation found to cause autosomal-dominant AD

Tau cloned

Evidence for activated microglia in AD brain

Oligomers reported as bioactive Aβ species

NIA launches ADCS, founded on Leon Thal's tacrine trial

The New England Journal of Medicine

Cognitive impairment correlates with synaptic damage

Dr. Robert Terry

Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Aβ peptide toxic to cultured neurons

Aβ release is part of normal cell metabolism

MCI or early AD? Controversy over psychometric norms vs intra-individual decline

Amyloid hypothesis marks conceptual shift from descriptive to mechanistic view

APP Swedish mutation found at BACE cleavage site

Anti-inflammatory treatment approach articulated

Alzforum launched

Donepezil approved

Protofibrils reported as bioactive Aβ species

FDG-PET in ApoE carriers and non-carriers reveals AD signature of brain hypometabolism

PDAPP, Tg2576 mice express Indiana, Swedish mutations, respectively, develop plaques

Aβ release into CSF prompts search for fluid biomarker assays

AD signature found in CSF: tau increased, Aβ42 decreased

Microvasculature in brain is damaged in AD

Family history is a major risk factor for late-onset AD

ApoE4 major risk factor for late-onset AD; risk up 3fold with one allele, 12fold with 2; ApoE2 protective

Mutations in presenilin-1 and presenilin-2 cause autosomal-dominant AD; Colombian kindred largest in the world

Tacrine is the first drug approved for AD

Mutations in APP and presenilins change Aβ42/40 ratio

ApoE influences amyloid deposition in mouse models

Lysosomal degradation impaired early on in AD

Neuropathologists formulate NIA-Reagan consensus criteria

Presenilin involved in processing APP, mutations change Aβ generation

γ-secretase cleaves Notch

Most people accumulate brain Aβ with age, more with AD

Tau mutations cause neurofibrillary pathology, neurodegeneration, FTD, but not AD

First double-transgenic mice expressing mutant APP and PSEN1

CSF Aβ, CSF Aβ/tau ratio predict decline in cognitively normal elderly and FAD mutation carriers

Rivastigmine approved

Age biggest risk factor: incidence doubles every 5 years after 65

Toxicity attributed to pre-fibrillar tau aggregates

Presenilin contains catalytic core of γ-secretase

BACE1 cloned and identified as β-secretase

Plaque, tangle pathology begin more than decade before symptoms, represent 'preclinical' AD

Syndrome of mild cognitive impairment (MCI): amnestic, non-amnestic forms

First mice expressing FTD tau mutations

BACE1 knockout mice are viable

Aβ fibrils accelerate tangle formation in mice

Galantamine approved

Tacrine is the first drug approved for AD

First Aβ active immunotherapy in mice

Cognitive decline correlates with soluble Aβ

Morphology of neurites around plaques is distorted

3-D structure of BACE

Neprilysin and other enzymes degrade Aβ in vivo

Complement implicated in AD

Midlife hypertension increases risk

Certain NSAIDs modulate γ-secretase to produce less Aβ42

FDG-PET tracks normal-MCI-AD progression, becomes marker for neurodegeneration and differential diagnosis

Multiphoton microscopy through cranial window enables observation of plaque clearance by immunotherapy

Reactive astrocytes crowd near plaques, degrade Aβ

Successive ε-, ζ-, γ-cleavages of APP release Aβ peptides

Dendritic tau mediates Aβ-induced synaptic toxicity, circuit abnormalities

Complement eliminates Aβ in vivo

Stages of amyloid pathology published

Mixed brain pathology commonly discovered at autopsy

Memantine approved for AD

First anti-Aβ vaccine affects pathology and atrophy, but fails in phase 2 over encephalitis

Four proteins make up active γ-secretase complex

BACE cuts many substrates besides APP

Activity-dependent Aβ release linked to synaptic depression

Head injury increases risk

Clioquinol fails in phase 2

Phenserine fails in phase 3

Midlife obesity increases risk

Default mode network activity is impaired in symptomatic and preclinical AD, overlaps with regions of amyloid

Videos show dynamic microglial surveillance, interaction with plaques

t0 | t1

Gene transfer of human ApoE changes amyloid deposition, neurotoxicity

AAV4-GFP | AAV4-APOE2 | AAV4-APOE3 | AAV4-APOE4

Retromer implicated as pathogenic player, drug target

VPS29 | VPS35

APP duplication causes autosomal-dominant AD with CAA

Low CSF Aβ reflects brain amyloid deposition

First transgenic rat models

Non-human primate models

ApoE4 genotype influences timing and amount of amyloid deposition in human brain

Physical activity protects against AD

Alzheimer's Disease Neuroimaging Initiative launched

Amyloid PET visualizes Aβ pathology in living human brain with Pittsburgh Compound B (PiB)

Aβ seeds induce β-sheet structure, cerebral amyloidosis

AD prevention trial of Celecoxib and Naproxen halted

Somatic transgenics via AAV gene transfer

AD neurotoxicity attributed to tau mis-sorting to dendritic compartment and interaction with Aβ oligomers

Aβ stress affects excitatory and inhibitory circuits

First demonstraton of tau immunotherapy in mice

Atorvastatin fails in phase 3

First AD GWAS

Sorl1 variants increase risk of LOAD

International Working Group revises AD diagnosis, uses biomarkers to capture early stage

CSF Aβ/tau signature identifies prodromal AD within MCI cohorts, predicts cognitive decline

The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing launched

First report of amyloid PET in autosomal-dominant AD

First reports of amyloid PET in differential diagnosis; first F-18 tracer

Live CSF monitoring shows Aβ clearance is reduced in LOAD

Alzheimer's Prevention Initiative launched

Staging diagram for successive biomarker change proposed

Flurizan™, Xaliproden fail in phase 3

Dominantly Inherited Alzheimer Network launched

DIAN

Dimebon fails in phase 3

Rosiglitazone, Valproate fail in phase 3

Solanezumab enters phase 3

Ibuprofen fails in phase 2

Sleep affects Aβ clearance, plaques, dementia risk

Tau propagation hypothesis articulated

Congress passes National Alzheimer's Project Act

First DIAN prevention trial in ADAD

Avagacestat, Ponezumab, Tideglusib fail in phase 2

DIAN-TU forms Pharma Consortium

NIA-AA diagnostic criteria for AD dementia, MCI due to AD, and preclinical AD

Gantenerumab enters phase 2/3 in prodromal AD

Semagacestat fails in phase 3

FDA approves first amyloid tracer, florbetapir

NIA-AA updates consensus criteria, uncoupling AD pathology from dementia symptoms

First Bayesian adaptive trial, BAN-2401

Gamunex enters phase 2/3

Bapineuzumab fails in phase 3

AVP-923 enters phase 2 for agitation in AD

Induced pluripotent stem cells from AD patients recapitulate aspects of disease

A4 starts, first secondary prevention trial for LOAD

BACE inhibitor AZD3293 enters phase 2/3

Type 2 diabetes increases risk

TREM2 mutation found in FTD, AD

Icelandic APP mutation protects against AD

Verubecestat, TRx0237, Masitinib, Nilvadipine enter phase 3

Inflammasome implicated in AD

GAP launched

Meta-analysis of four GWAS identifies 22 susceptibility loci: confirms previous, finds new variants

FDA issues guidance for therapy development in early AD

Crenezumab enters Colombian ADAD prevention trial

Gammagard® fails in phase 3

BACE inhibitor LY2886721 fails in phase 2

Idalopirdine, Brexpiprazole enter phase 3

Tau PET ligands enter human testing

Brak 0 | Brak I/II | Brak III/IV | Brak V/VI

G8 holds Dementia Summit

Prospective biomarker study finds 20-year prodrome in late-onset AD

Incidence of dementia decreases in developed countries

Amyloid load, ApoE, subjective memory complaints predict fastest decline in preclinical AD

Active immunotherapy CAD106; BACE inhibitor CNP520 enter phase 2/3 in cognitively normal ApoE4/4 carriers

AGB101 to enter phase 3

CERE-110 fails in phase 2

Azeliragon enters phase 3

Carriers of an autosomal-dominant AD mutation develop brain changes in childhood

Comphrensive meta-analyses of fluid AD biomarkers

Complement and microglia eliminate synapses in aging and AD brain

APP knockin mice recap only some phenotypes, pointing to overexpression artifacts

Longitudinal study tracks biomarkers in same ADAD mutation carriers for 11 years

European Prevention of Alzheimer's Dementia Consortium launched

Prospective biomarker studies find 20-year prodrome in autosomal-dominant AD

Microdialysis tracks tau in vivo in brain interstitial fluid

Prevalence of plaques precedes prevalence of AD dementia by 15 years, starting earlier in ApoE4 carriers

Vanutide cridifirac discontinued in phase 2

Blood-borne factors modulate synaptic plasticity and cognitive function in aging mice

First atomic structure of human γ-secretase

Approximately 80 therapeutics in phases 1, 2, or 3 trials

CATEGORIES

- Biology of Disease
- Biomarkers
- Diagnosis
- Epidemiology / Risk Factors
- Genetics
- Neuropathology
- Research Models
- Therapeutics
- Community Initiatives
- Hypotheses

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