Research priorities for preventing & treating dementia-Alzheimer syndrome

[Remarks on key questions & major challenges]

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Define the 'Problem'

*'…the **formulation of the problem** is often more essential than its solution, which may be merely a matter of mathematical or experimental skill…' -**Albert Einstein***

★★★★

- *Four decades of research has generated an abundance of data about dementia but, the **translation of ideas-facts into knowledge**, re: 'clinically meaningful' interventions, has been problematic.*
- *The need to delineated different questions and novel paradigms for research based on lessons learned.*

Key Talking Points

- *Emerging Challenges :*
  - ✓ *Polygenic origins*
  - ✓ *Heterogeneous condition*
  - ✓ *Mixed pathology*
  - ✓ *Specificity of pathobiology - Selective vulnerability of neural circuits*
  - ✓ *Inconsistent/nonlinear relation between biology and behavior*
  - ✓ *Mechanistic interaction among the etiologic factors/risk/susceptibility genes etc*
  - ✓ *Emergent behavior – 'Complexity'*
- *Needs:*
  - ✓ *New 'thinking' [e.g., focus on zeroing disability vs disease eradication*
  - ✓ *Conceptual framework to connect dots [translate data into knowledge]*
  - ✓ *Multiscale modelling systems to address complexity of the disorder*
  - ✓ *Discovery-Validation of biomarkers for individualized prognosis*
  - ✓ *Very large multi-national well-characterized cohorts for longitudinal studies*

Some 'Knowns'

- *Complex polygenic disorder* with multiple putative etiological factors and upstream risks [e.g., age, family history, genetics, metabolic, inflammation, ethnicity, gender, lifestyle and, co-morbid conditions].
- *Heterogeneous* condition [re: age of onset/expression, cluster & pattern of behavioral-clinical symptoms, mixture of neuropathological features, family history, genetic, risks, lifestyle, and other co-morbid conditions].

Some 'Knowns' [II]

- *Prolonged progression* of neurodegenerative process with unknown starting point; including *asymptomatic pre-clinical stage* that precedes the expression of detectable signs.
- An array of putative *risk, susceptibility genes* and *biomarkers associated* with the disorder.
- *Specificity of pathobiology* - *Selectivity vulnerability* of neural circuits.

Unresolved Issues

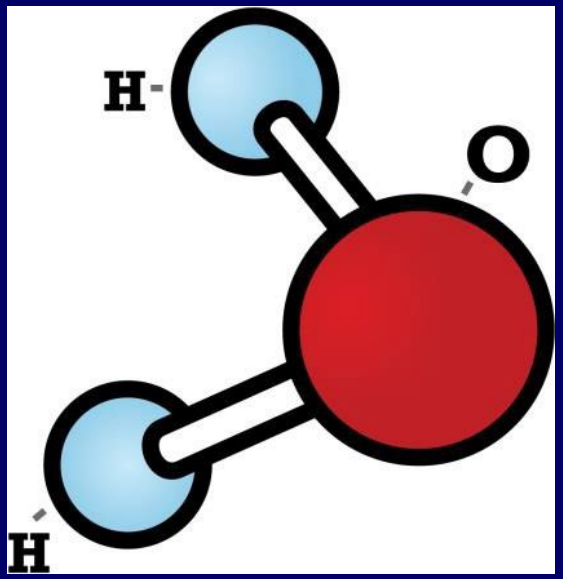
- More *precise characterization* of the disorder is '*dementia-Alzheimer syndrome*' - *AD is a cluster of syndrome, rather than* ***a disease*** *with a distinct cause.*
- *Inconsistent* /or/ *nonlinear* relationships between the neurobiological and the clinical phenotype is not well understood.
- The *mechanistic interaction* among the putative etiological factors risk [e.g., age, family history, genetics, metabolic, inflammation, ethnicity, gender, lifestyle and, co-morbid conditions] is not well understood.

Unresolved Issues [II]

- *Unifying conceptual framework* to connect the dots and links known facts about the disease is hinderance to progress.

- *Models/modeling system* to address *emergent behaviors* and *complexity* of the condition [e.g., integration of existing and emerging information into a cohesive body of knowledge for effective interventions].

Emergent Characteristics of H_20



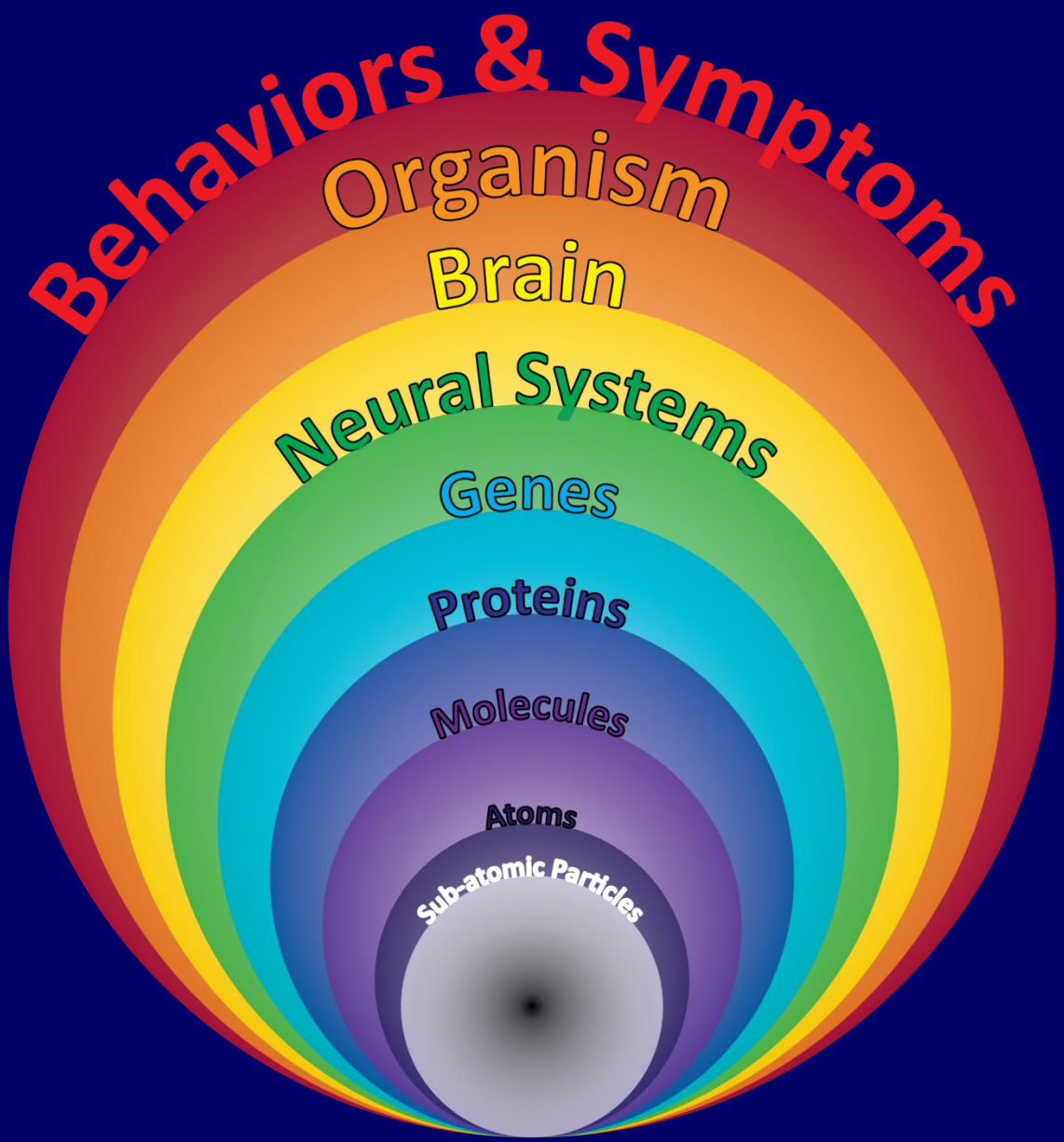
Concept of 'Emergent Behaviors'

Emergent behaviors

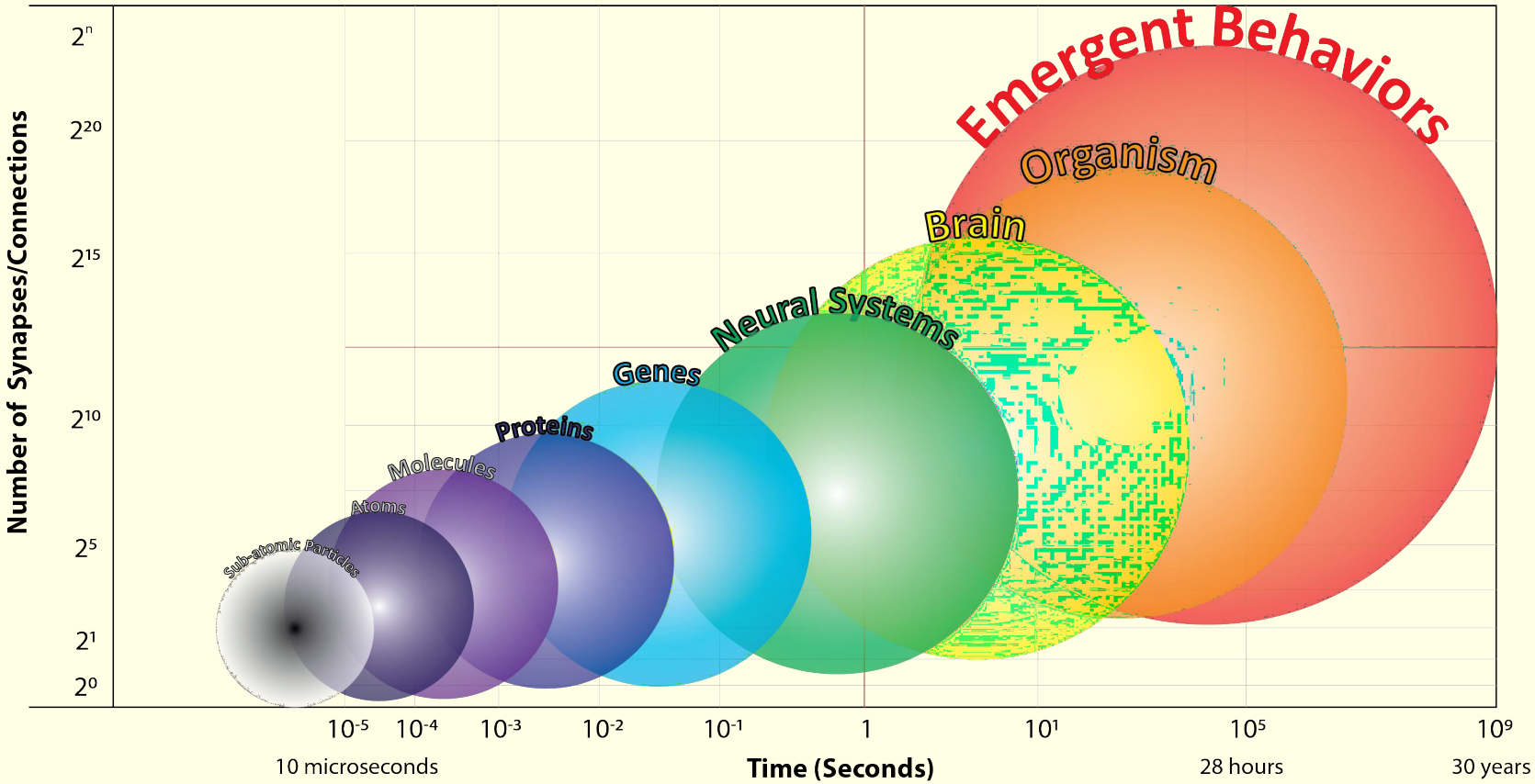
- Key feature of 'Complexity'
- Typically, context-dependent
- Span from clinical symptoms to proteins
- Indicate:

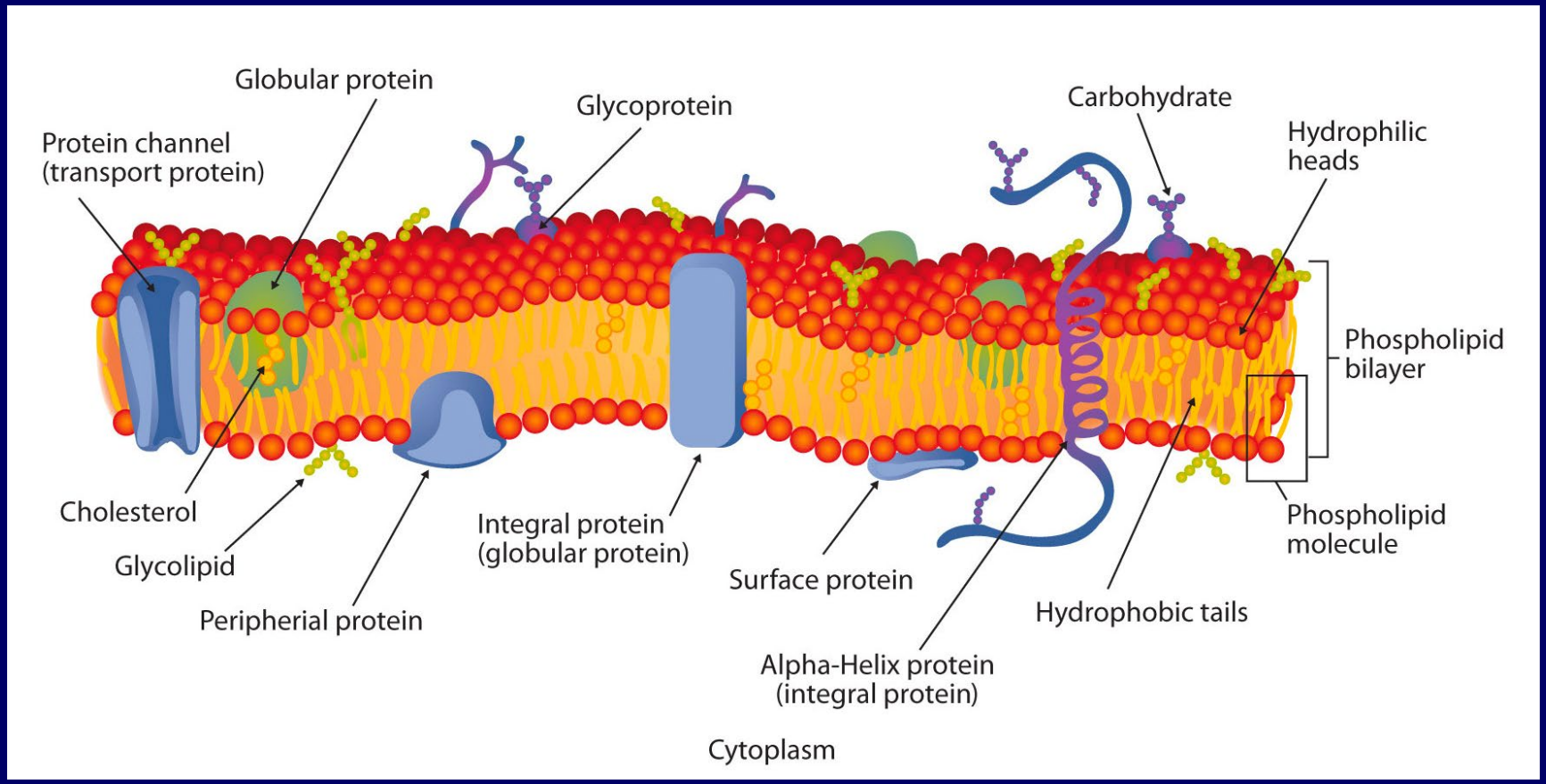
✓ the *whole* is more than the *sum of the parts*

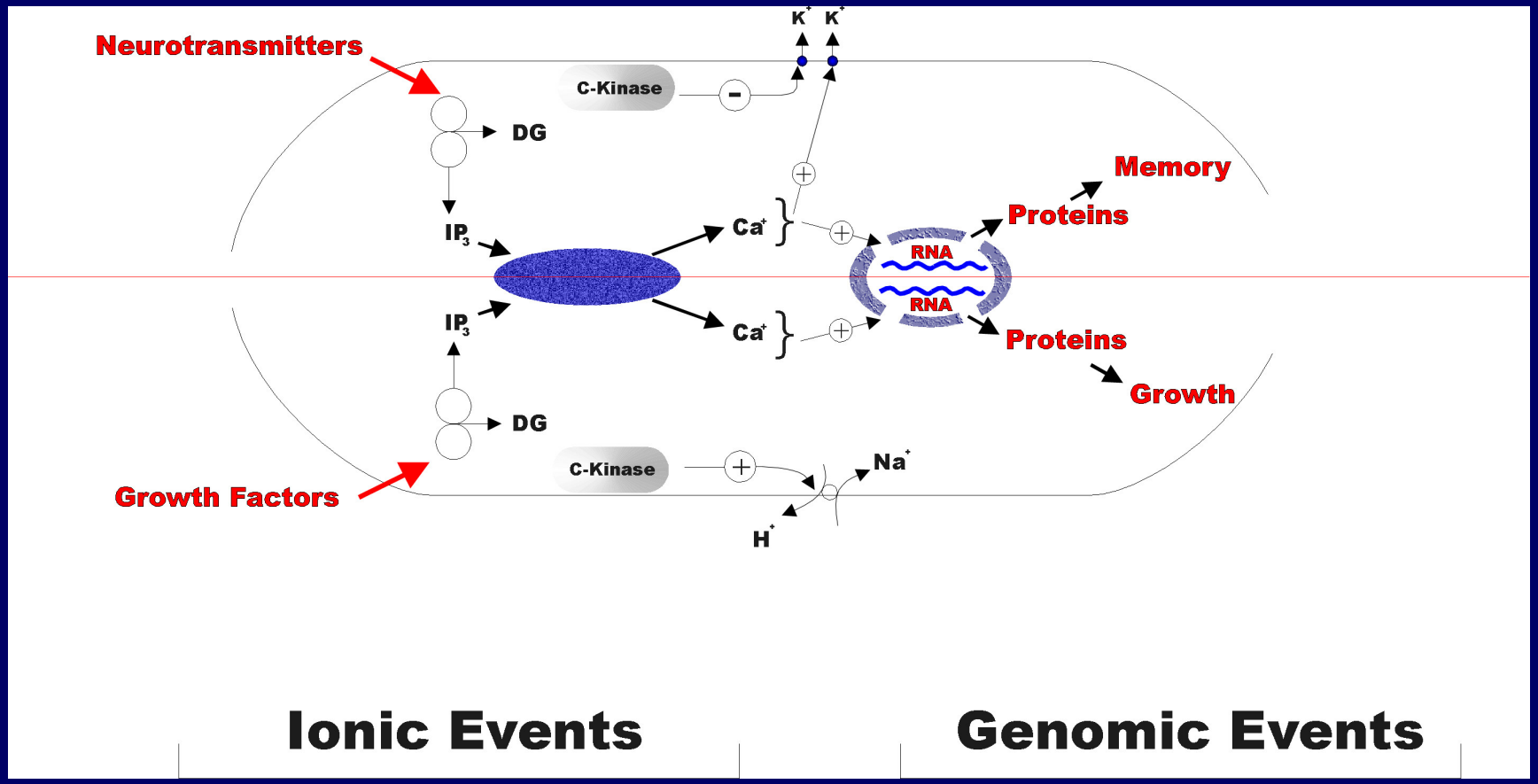
✓ Study of any single component does lead to understand the entire system



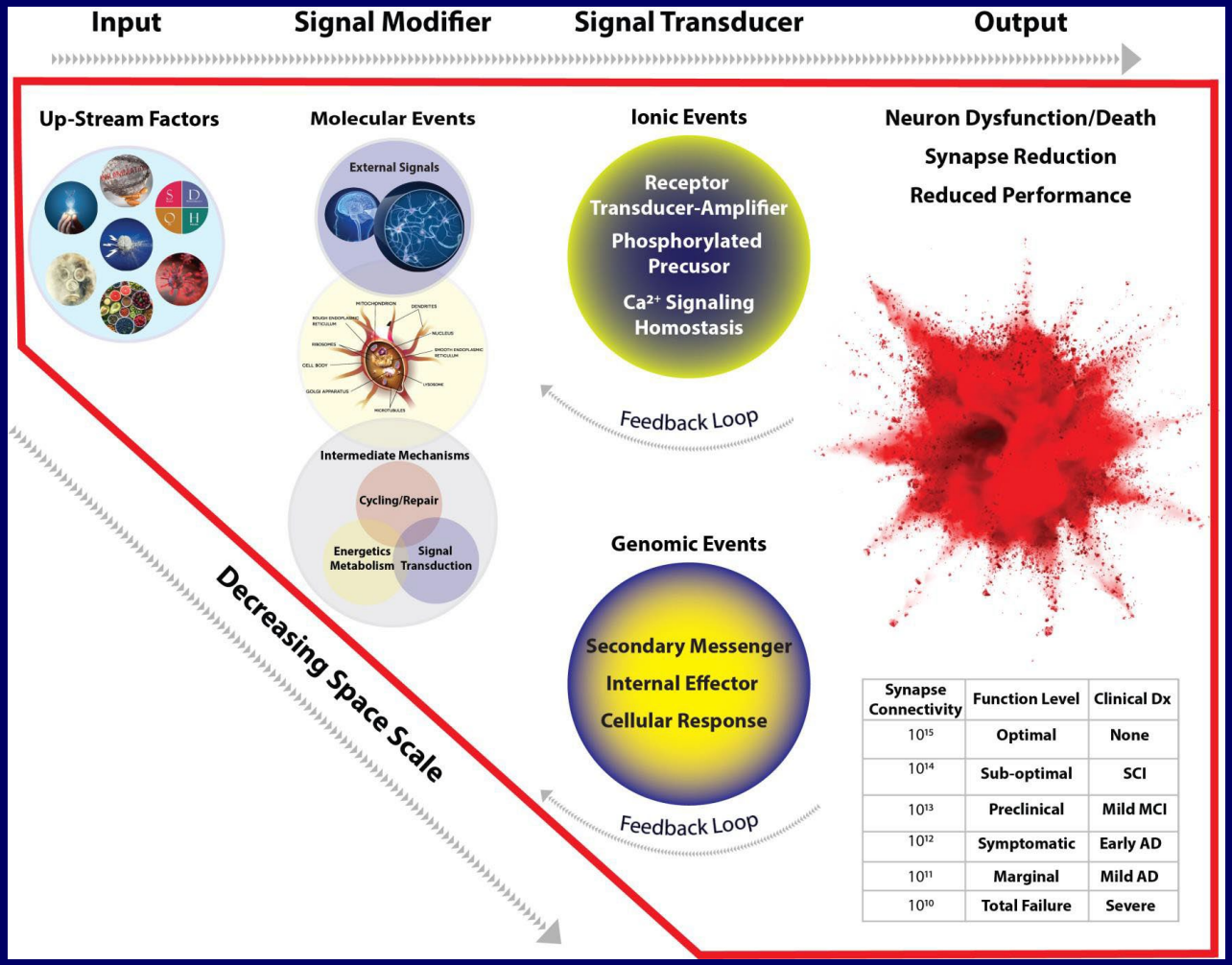
Multiscale of Time and Space




Globular protein
Glycoprotein
Carbohydrate
Protein channel
(transport protein)
Hydrophilic
heads
Phospholipid
bilayer
Cholesterol
Glycolipid
Peripherial protein
Integral protein
(globular protein)
Surface protein
Phospholipid
molecule
Hydrophobic tails
Alpha-Helix protein
(integral protein)
Cytoplasm


Neurotransmitters
C-Kinase
K+ K+
DG
IP3
Ca+
Memory
Proteins
RNA
RNA
IP3
Ca+
Proteins
Growth
DG
C-Kinase
Na+
H+
Growth Factors
Ionic Events
Genomic Events

Four Major 'Buckets' of data with differing granularity of information



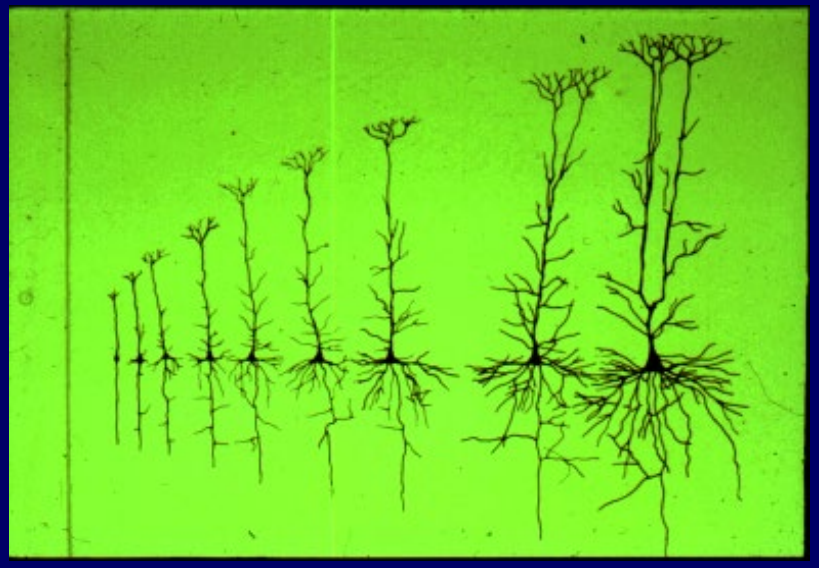
Synapse Connectivity	Function Level	Clinical Dx
10^{15}	Optimal	None
10^{14}	Sub-optimal	SCI
10^{13}	Preclinical	Mild MCI
10^{12}	Symptomatic	Early AD
10^{11}	Marginal	Mild AD
10^{10}	Total Failure	Severe

A 'conceptual framework'

Mapping key components of neurodegenerative cascade

- *Input – Upstream variable* [e.g., risk factors, susceptibility genes, co-morbid conditions, life-style, trauma, toxins, infectious agents etc.]
- *Signal Modifiers* – [e.g., energetics/metabolic, cell-cycles/repair, endocrine factors, inflammation or other variables that modulate signaling paths]
- *Signal Transduction Paths* – [e.g., cascade of **molecular events** in signal process including *ionic & genomic* steps [e.g., receptors, phosphorylation, [Ca^{2++}] homeostasis, second-third messenger etc.]
- *Output – Downstream outcomes* – [e.g., cellular responses, synaptogenesis, loss of synapse/dendrite etc; most proximal neurobiological events to the **Expression of behavior** – clinical features]

Fundamental neurobiology of 'Dementia'



- Gradual transition from *optimal functionality* to *dysfunction of specific neural circuits*

- Progressive pruning of *dendrites* and *axons*

- Massive *loss of synapses*

- '*Systems Failure*' in connectivity of neural network

Final common path between brain & behavior

- Virtually all ideas on dementia-Alzheimer syndrome invoke the *loss of synaptic connectivity* as the *vital link* between the *biology* and *behavioral* expression of the condition.
- But the precursor role of failures to ensure constant supply of energy for optimal neuronal functions is overlooked
- Numerous upstream variables potentially can affect the efficiency of brain perfusion; thus, can modulate energy supply leading to systems failure. [e.g., changes in BBB, small vessel disease, mitochondrial dysfunction, deficiencies in glucose-transporter proteins, hypoperfusion due to mineralization vessel walls or some other micro-vessel pathology, etc.]

Why focus on vascular-metabolic factors

- *Vascular-metabolic factors* are *feasible targets for preventive* intervention and a promising area for future therapy development for various forms of other chronic brain disorders in aging.

- *Interventions* for various vascular-metabolic conditions are *widely available* at reasonable costs..

Rationale for targeting 'vascular factors' [II]

The logic is based on evidence that *vascular-metabolic factors are :*

- ✓ *The earliest common pre-cursors leading to various forms neural dysfunction-neurodegenerative processes.*
- ✓ Strong, independent, and *potentially modifiable risk factor* for dementia.
- ✓ Able to *explain the putative neurophysiological mechanisms* that underly the *cause-effect* relationship between vascular changes, cognitive impairments and dementia.

Rationale for targeting 'vascular factors' [I]

- The emerging evidence indicates that *brain vascular-metabolic changes* are *substantially more pervasive* than recognized.
- Structural-functional changes in brain vascular system represent the *common early risk factor* for the neurobiology of cognitive impairments in different forms of dementia.

[See – - Hachinski V et al - *Preventing dementia by preventing stroke: The Berlin Manifesto* - Alzheimer's & Dementia 15 (2019) 961-984 // https://doi.org/10.1016/j.jalz.2019.06.001 // - Khachaturian ZS, Kuller LH, Khachaturian AK - *Strategic goals and roadmap for dementia prevention by stroke prevention* - Alzheimer's & Dementia 15 (2019) 865-869 // https://doi.org/10.1016/j.jalz.2019.06.003

Rationale for targeting 'vascular factors' [III[

- Converging evidence indicate that '*Vascular factors*' are the major upstream contributors to the neurophysiology of cognitive impairments associated with dementia.
- Nearly 80% of autopsy confirmed cases of dementia-Alzheimer syndrome show evidence of cerebrovascular disease
- Evidence that vascular problems in midlife affect brain health decades down the line. The presence of CVD doubles the likelihood of neurodegenerative process of MCI-dementia impairment [MCI] -dementia will start much earlier in life.

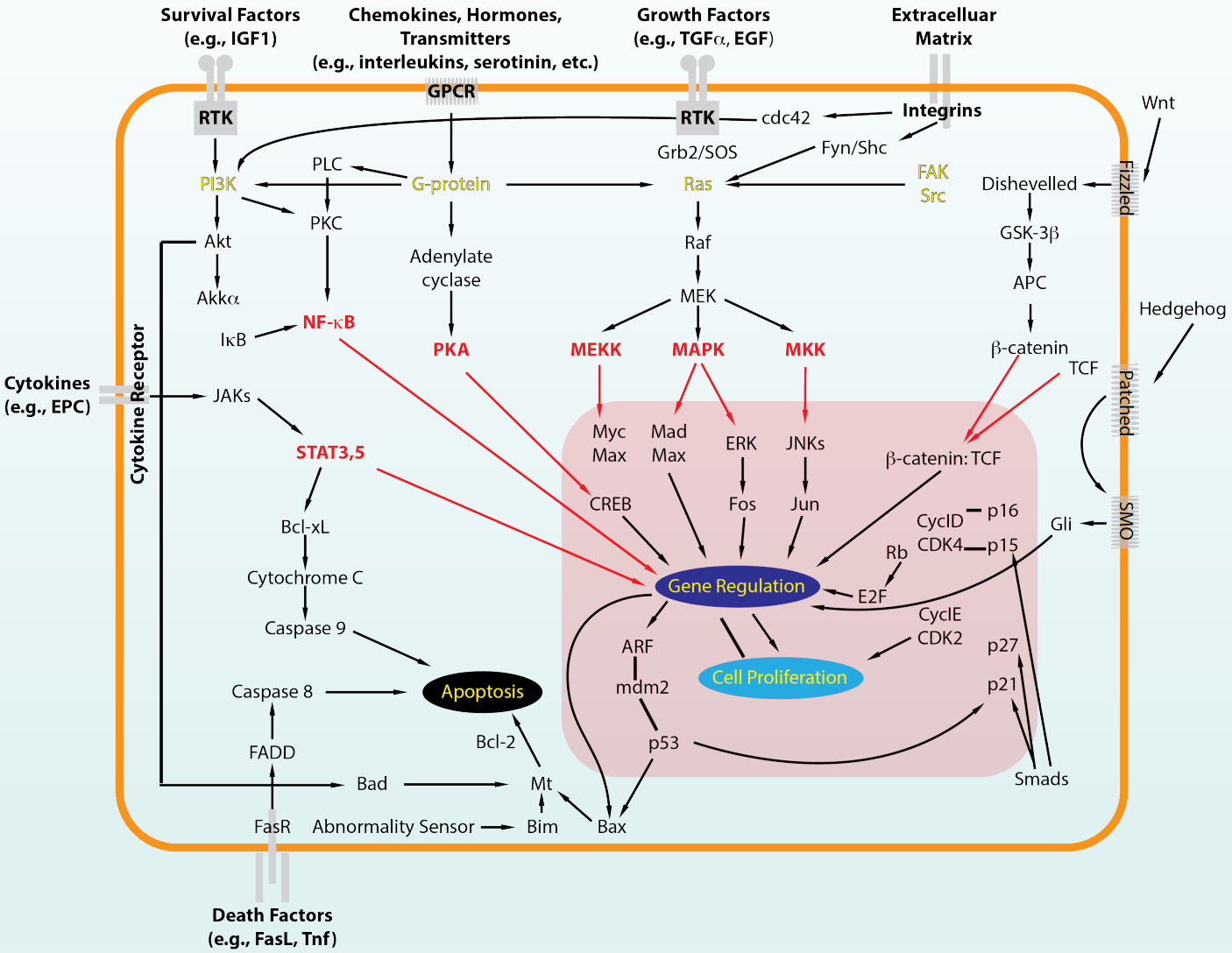
Major Scientific Challenges

Early Detection of :

- *asymptomatic people at elevated risk for cognitive impairments*

Novel Therapeutic Targets to:

- *maintain vitality of synaptic function*
- *prevent synapse loss/dendrite pruning*


Survival Factors
(e.g., IGF1)
Chemokines, Hormones,
Transmitters
(e.g., interleukins, serotinin, etc.)
Growth Factors
(e.g., TGFα, EGF)
Extracelluar
Matrix
GPCR
RTK
RTK
cdc42
Integrins
Grb2/SOS
Fyn/Shc
PLC
PI3K
G-protein
Ras
FAK
Src
Wnt
Fizzled
Dishevelled
PKC
Akt
Raf
GSK-3β
Adenylate
cyclase
APC
Akkα
MEK
Hedgehog
IκB
NF-κB
PKA
MEKK
MAPK
MKK
β-catenin
TCF
Cytokines
(e.g., EPC)
Cytokine Receptor
JAKs
Myc
Max
Mad
Max
ERK
JNKs
β-catenin: TCF
Patched
STAT3,5
CREB
Fos
Jun
CyclD
CDK4
p16
p15
Gli
SMO
Bcl-xL
Rb
Cytochrome C
Gene Regulation
E2F
Caspase 9
CyclE
CDK2
ARF
p27
Caspase 8
Apoptosis
Cell Proliferation
mdm2
p21
FADD
Bcl-2
p53
Smads
Bad
Mt
FasR
Abnormality Sensor
Bim
Bax
Death Factors
(e.g., FasL, Tnf)

10 Questions Key to Solving Alzheimer's

1.	Association with Age	Does it explain the relationship between the biology of aging and the biology of Alzheimer's pathology?
2.	Risk Factors	Will it explain the relationships between known risk or protective factors and the neurobiological mechanisms which then modify risk?
3.	Progression	How to account for the progression of the disease--from limbic to neocortical, the asymmetry and non-linear changes of clinical severity? Can we describe the mechanism of disease progression through contiguity, axonal transport, prion-like mechanisms, etc.?
4.	Sequence of Events	What is the observable sequence of measurable or observable events that contribute to disease?
5.	Selective Vulnerability	What is a plausible explanation for the anatomical specificity of early lesions associated with the syndrome?
6.	Pathogenic Interactions	How to account for the interactions of specific pathologic features including tau metabolism/NFTs, amyloid metabolism/senile plaques, inflammation within the CNS, synapse function and connectivity, disconnection syndromes, projection systems, structure (blood-brain barrier and endovascular cell function, CSF dynamics) and whole brain physiology (cellular metabolism and clearance mechanisms, resting state connectivity)?
7.	Mixed Pathology	What is the justification for mixed pathologies and comorbid conditions (e.g., Lewy bodies, vascular pathology, TDP-43)?
8.	Multiple Clinical Phenotypes	What explains the clinical heterogeneity of the syndrome, especially the non-amnestic manifestations of Alzheimer's pathology? (e.g., behavioral (FTD), visuospatial (PCA), aphasic (PPA))?
9.	Biomarkers	Does the putative theory account for the puzzles in diagnostic biomarker relationships?
10.	Translational Potential	Can a new theory lead to novel therapeutic targets or diagnostic technologies?