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An Industry Viewpoint on Clinical Trial Designs for Disease Modification in Alzheimer's Disease: Challenges

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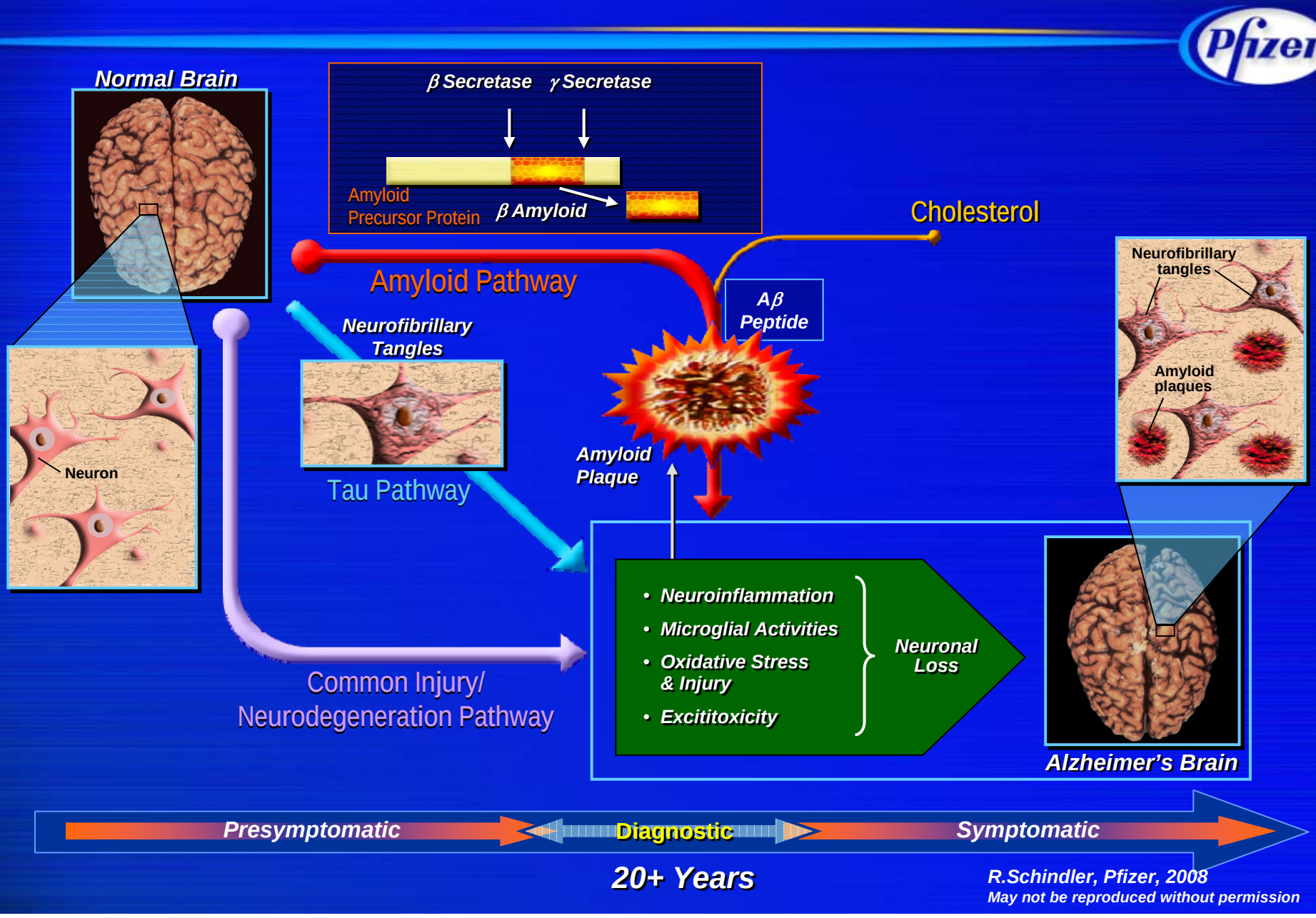
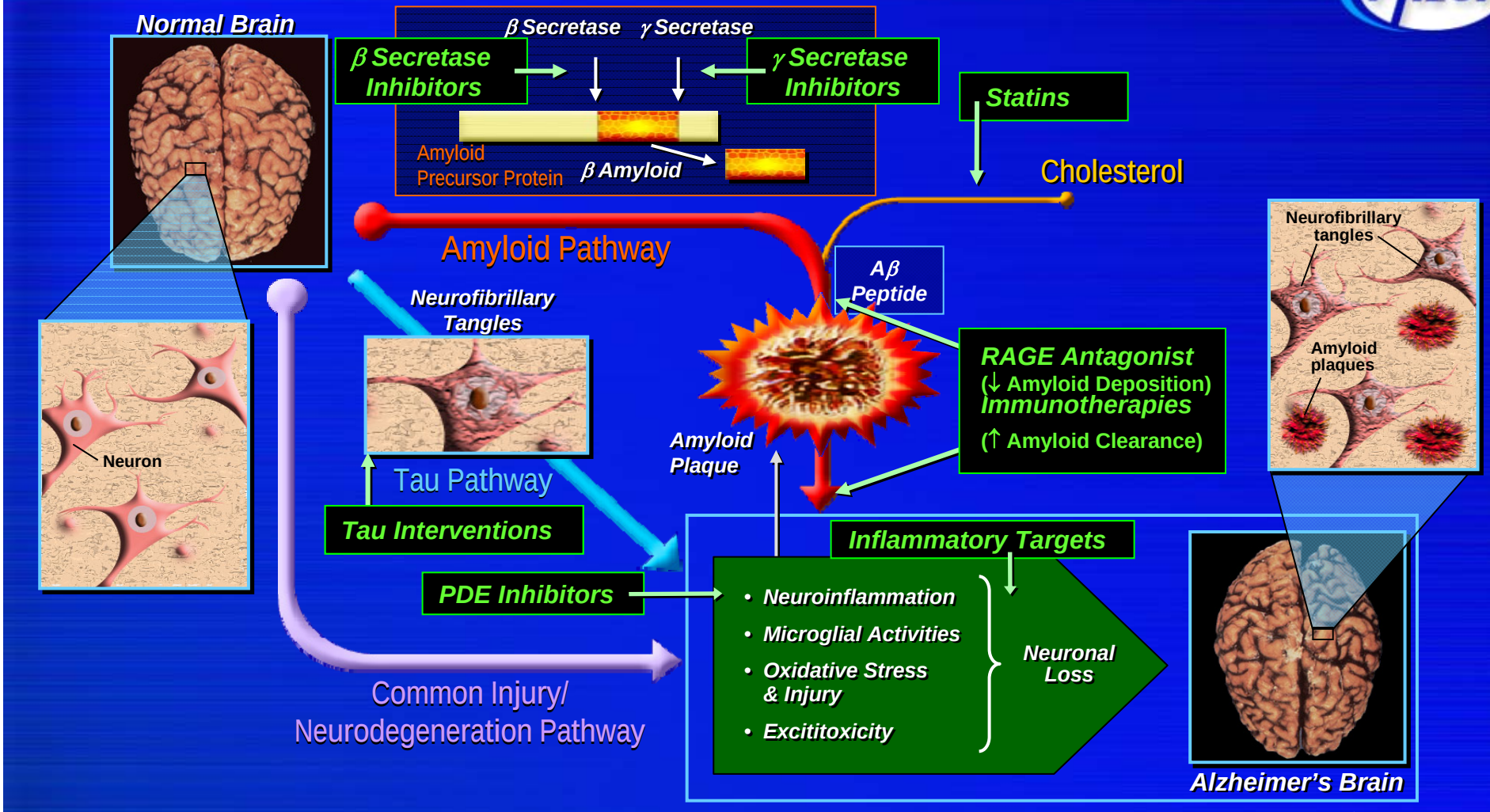
Key Challenges

- Disease etiology: not fully elucidated
  - Primary etiological trigger(s) unclear
  - Where to best direct interventions?
- “Disease Modification” concept: evolving
  - What does “modification” look like?
  - Is a robust, durable effect “good enough”?
- Regulatory Guidance: evolving
- Biomarkers: none validated
- Trial design issues

The Brain: From Normal to AD



Alzheimer's Disease: Potential Intervention Points



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Disease Etiology

- Target rich area based on expanding understanding of pathophysiology
  - But unclear where to best intervene
  - Single point or multiple points of intervention needed?
- Translational models (eg, tg mice) lend support to specific targeted interventions (particularly those targeting Abeta and tau)
  - But no specific “AD” animal model exists
- Clinical relevance still unknown
  - “Proof of Mechanism” has not yet translated into robust “Proof of Concept” (eg, bapineuzumab results)

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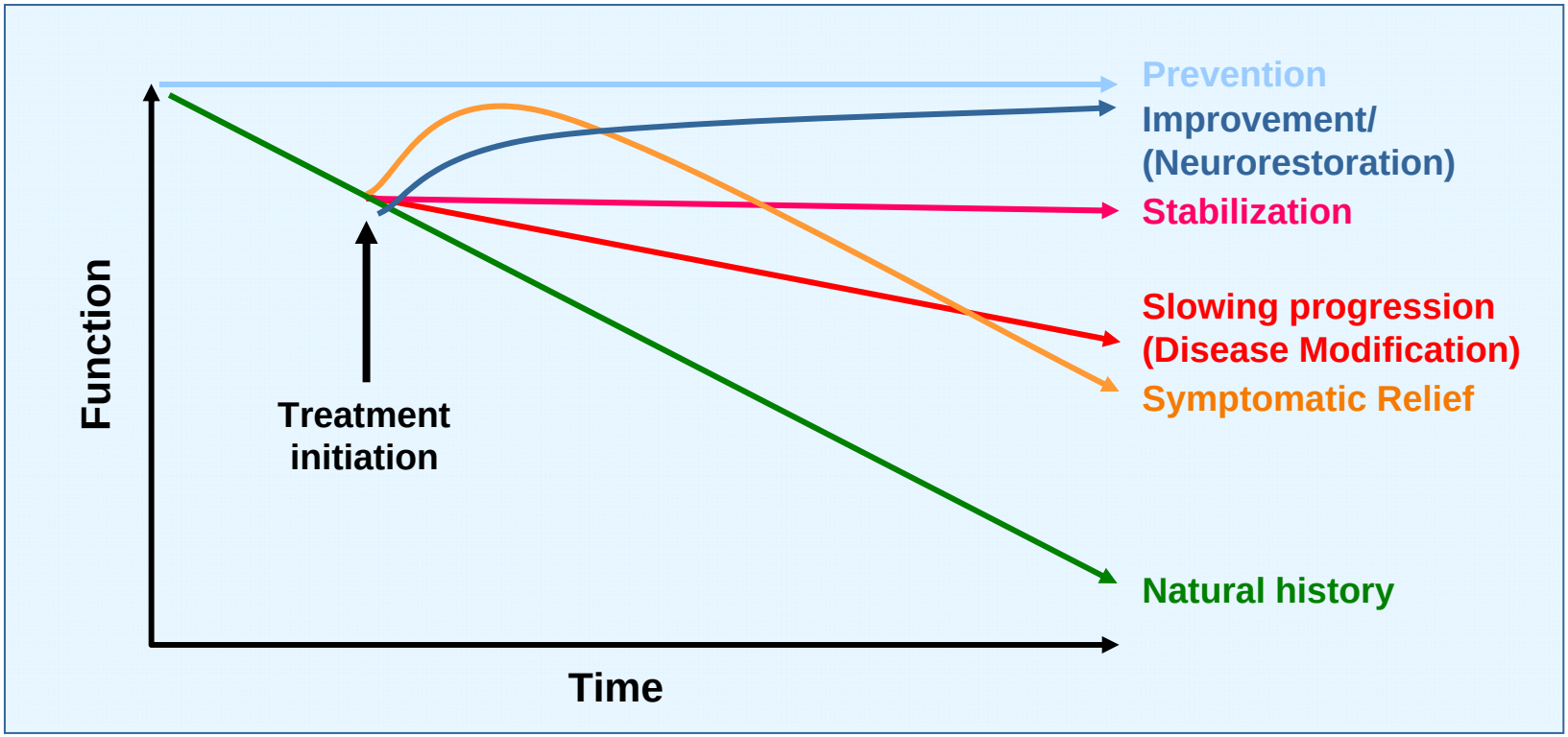
Disease Modification

- What does disease modification look like?



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Disease Modification

- Outstanding issues
  - How do we best define “disease modification”?
  - How long will it take to observe a treatment difference?
  - How large an effect can we expect from our interventions?
  - How relevant are “minor” changes that take upwards of 18-24 months to confirm (to paraphrase the FDA)?
  - Are disease modifying therapies likely to benefit those patients already diagnosed with AD?
    - How do we drive academic and regulatory consensus for earlier intervention in populations “at risk”?
    - How do we define these populations?

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Regulatory Guidance

- Outstanding issues
  - Biological evidence of disease modification required, but no regulatory endorsed biomarker to-date
  - Imaging measures alone will not suffice
    - Clinical outcomes + vMRI, once validated, may meet regulatory hurdle
  - FDA/EU divergence re: acceptance of comparison of slopes (rate of change) using standard parallel arm study
  - Randomized start/withdrawal may be “more convincing” way of demonstrating DM
  - Probable need for replication, unless results “robust” (possibility of 1 large study + “confirmatory evidence”)

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Biomarkers

- Outstanding issues
  - No “Framingham” study in Alzheimer’s exists
    - Initiatives ongoing (eg, ADNI)
  - Validation of biomarkers may end up being confirmed *in* long-term treatment trials, not *prior to* trial initiation
  - Characteristics of subpopulations may influence behavior of specific markers
  - Utility of biomarkers may vary across disease stage, from “pre-AD” through AD stages
  - Still unknown: will changes in biomarker translate into meaningful clinical benefit?

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Trial Design (1)

- General Design
  - Parallel arm appropriate?
  - Randomized start or withdrawal necessary?
- Population
  - Should we include the same population as in standard symptomatic treatment trials?
    - Disease modification may only be apparent in earlier stage patients
    - How do we facilitate trials in “pre-AD” populations?
    - How do we define populations “at risk”?
  - How do we manage background symptomatic therapy?
- Study Duration
  - What is the appropriate length of study required to demonstrate disease modification?
    - Differences between bapienuzemab and control (ICAD July ’08) didn’t separate till week 37
  - Expectation is that treatment differences associated with disease attenuation will evolve slowly and increase over time—how long an observational period needed to capture a meaningful separation?
- Clinical Endpoints
  - Are current endpoints, eg ADAS-cog and global measures, applicable to longer-term trials with disease modifying interventions?

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Trial Design (2)

- Imaging/biochemical Endpoints
  - What are the most appropriate measures?
    - vMRI to assess cortical atrophy appears most likely candidate
  - What is the minimum timeframe to capture change with reasonable precision?
  - How do we both define and ensure standards?
- Safety Endpoints
  - Are there specific safety concerns, based on unique treatment interventions, that will require greater monitoring efforts (eg, micro hemorrhaging, vasogenic edema associated with certain immunotherapies)?
- Statistical Analysis
  - Given natural disease progression and unknown degree of change associated with novel interventions, what assumptions should be used to power long-term trials?
  - What are the appropriate statistical methods to apply to the long-term study of a progressive, degenerative disease?
  - Should we stratify population based on genotype? Baseline severity?

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Summary

- Implications to Industry
  - Large, long, costly studies required
  - Significant risk yet to be resolved
    - Unprecedented MOA's
    - Limitations of current translational models
    - Biomarker yet to be validated
    - Awaiting robust POC results, particularly for therapies based on amyloid hypothesis
  - Regulatory guidance not "written in stone"
  - Value of Disease Modification treatments to payers a huge unknown

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Thank You