Achieving Therapeutic Success in Alzheimer's Disease: The Case for Refining our Approach

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Welcome to Vancouver….eh !

NB Cross the street with care on Sunday !

Disclosure

- 2012-16 UBC service agreements, or sponsored clinical trials;
  - Eli Lilly, Kyowa Kirin, GE Healthcare, Biogen, Arena, Roche/Genentech, Merck, Eisai, Baxter, Tau Rx
- Peer Reviewed Research Support:
  - NIA, CIHR, Brain Canada, Weston Foundation
  - PI Alzheimer Disease Study Cooperative (From April 1, 2016)

- 2009-2011, on leave from UBC and employed at Bristol-Myers Squibb Company in CT, USA
  - VP and Therapeutic Area Head, Neuroscience Global Clinical Research

Objectives

- **To review the landscape and trajectory of Alzheimer's disease therapeutic development**
- **To provide some reflections on progress to date**
- **To offer a viewpoint on how we can refine our approach to increase likelihood of success**

Global Viewpoint on Therapeutic Goals

- NAPA: Prevent and effectively treat AD by 2025.
- G8 Global Action Against Dementia: Summit declaration

  - The ambition to identify a cure or a disease-modifying therapy for dementia by 2025
  - We will increase the number of people in dementia related research studies

- WHO 2012:

  - Efforts to improve the quality and availability of care, and to seek for a cure, should be coupled with urgent investment in primary prevention measures.

[1] NAPA: http://hhs.gov/daltcp/napa/NatlPlan2013.pdf [2] G8 Summit Declaration RDD 10495 Pub 11/12/2013 [3] Dementia: a public health priority. Geneva, WHO 2012

The State of the Alzheimer Disease Pipeline Report of the Office of Health Economics 2015

- **Pipeline of antidementia drugs vs cancer**
  - **3.8% drugs in discovery vs 31% cancer**
  - **1.2% in phase 3 compared to 24% cancer**

- **Pipeline Analysis (2000 trials all sources over 20 years)**
  - **900 registered compounds commercial R&D source**
  - **Of these 197 in active development**
  - **129 terminated , withdrawn or suspended**
  - **Remainder non active, presumed terminated or discontinued**

Marsden G, Mestre-Ferrandiz https://worlddementiacouncil.files.wordpress.com; Gauthier S et al Alz and Dem 2015

The Need to Learn from Clinical Trials:

- **For terminated trials only 45% provided a reason,**
  - **most commonly recruitment problems**
- **Rationale for d/c products in only 26%**
  - **most common safety and efficacy**

- Insufficient reporting of trial outcomes
- Inability to learn quickly from failures across classes
- Needless exposure of trial participants to products having low probability of success
- Need for clinical trials data sharing for modelling, simulation and hypothesis generation

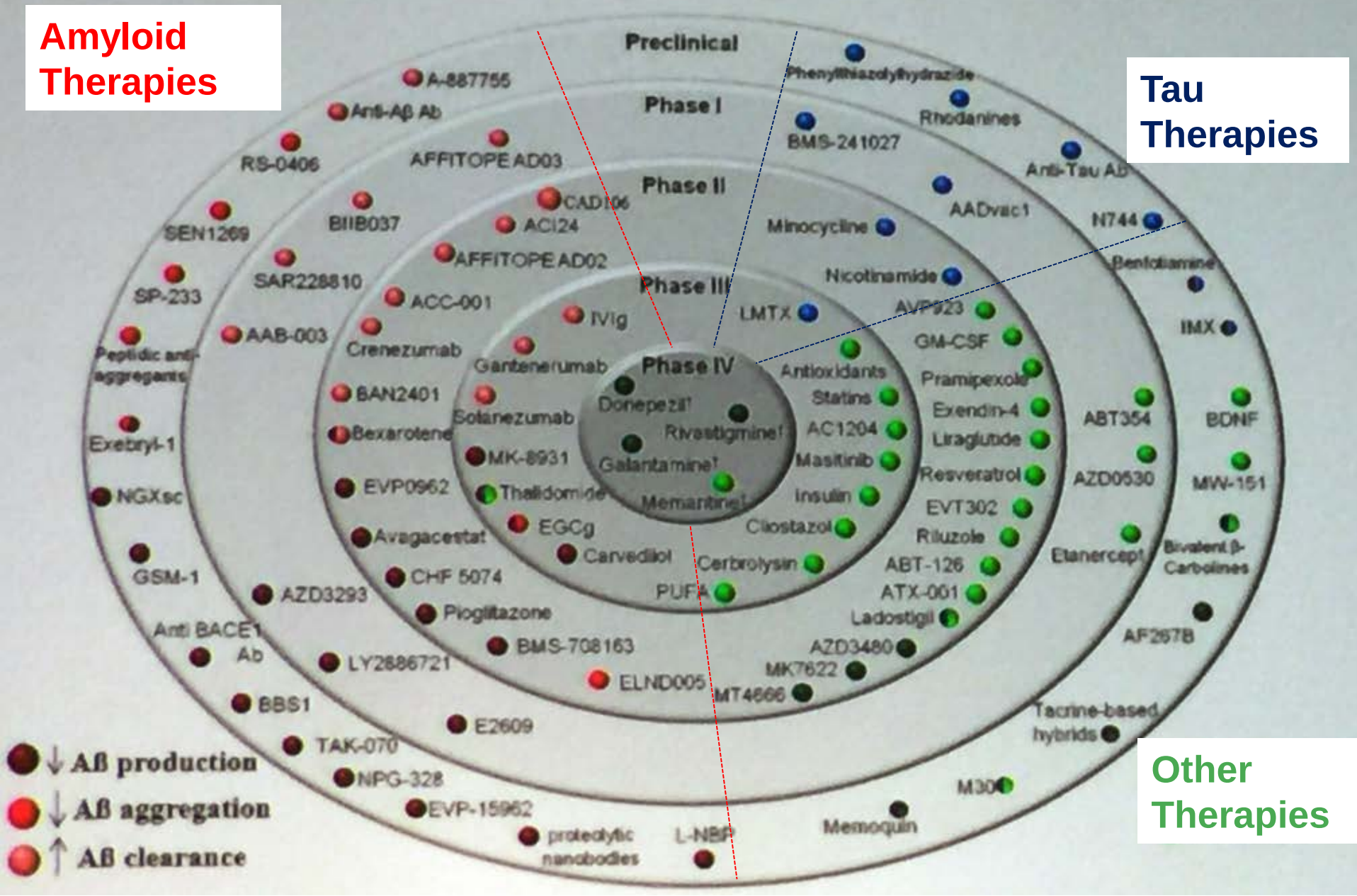
1 Marsden G, Mestre-Ferrandiz https://worlddementiacouncil.files.wordpress.com 2 Gauthier S et al Alz and Dem 2016

2014 Report on the Milestones for the US National Plan to Address AD

- **To achieve a cure….**
  - **30 new therapeutic drugs need to reach early clinical testing**
  - **3 diverse classes of drug targets**
  - **12 new drugs advancing from first in man to phase 2 trials**

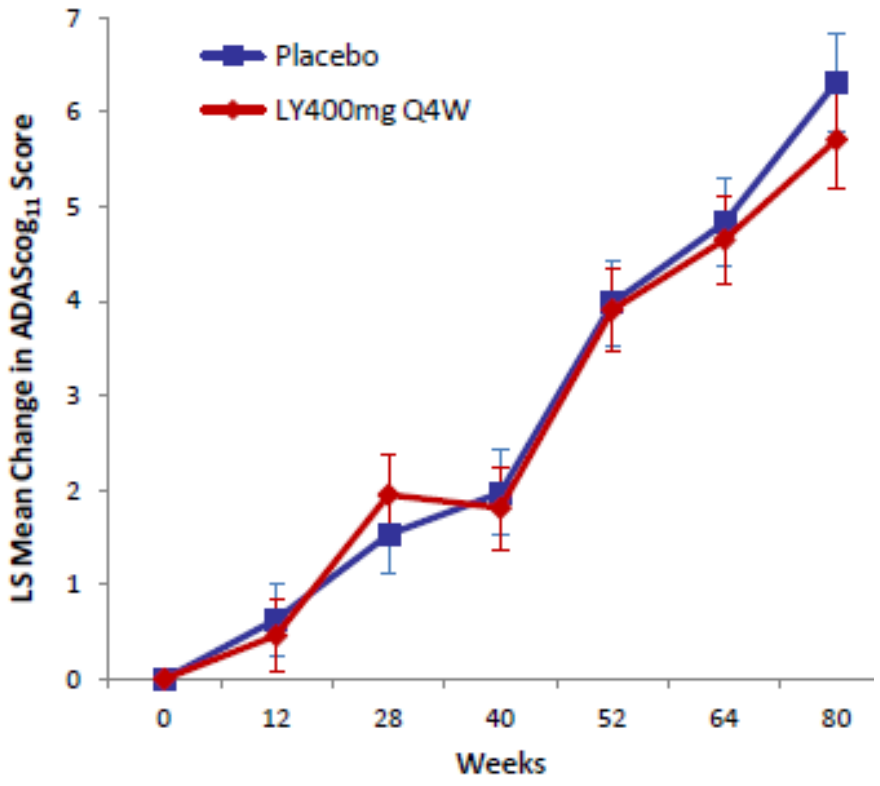
- **A massive underestimate?**

AA National Plan Milestone Alz & Dem 2014; 10 S430-452

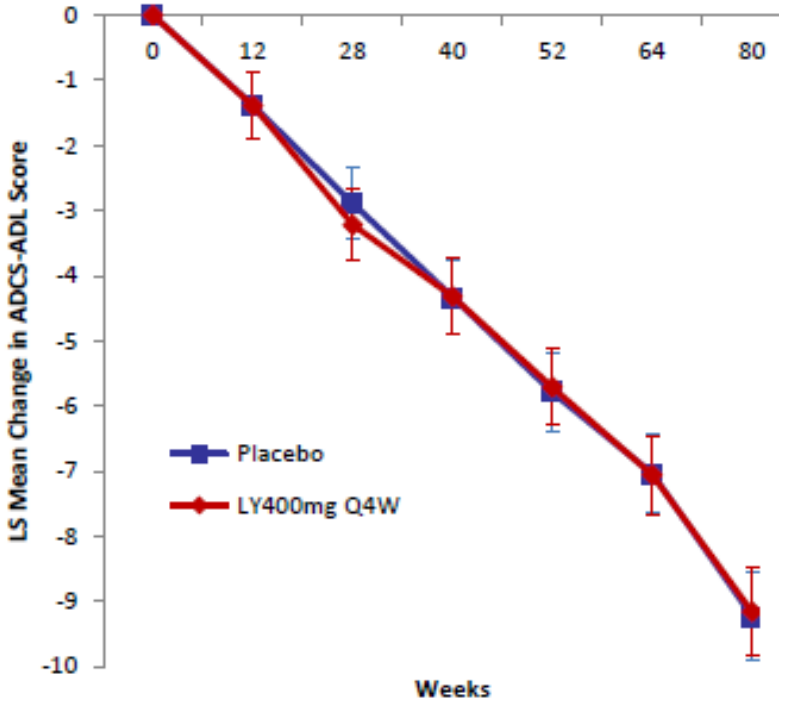

Amyloid Therapies
Tau Therapies
Other Therapies
Preclinical
Phase I
Phase II
Phase III
Phase IV
A-887755
Anti-Aβ Ab
RS-0406
AFFITOPE AD03
SEN1269
BIIB037
CAD106
ACI24
SAR228810
AFFITOPE AD02
SP-233
ACC-001
IVIg
AAB-003
Crenezumab
Gantenerumab
Peptidic anti-aggregants
BAN2401
Solanezumab
Exebryl-1
Bexarotene
Donepezil
Rivastigmine
Galantamine
Memantine
MK-8931
Thalidomide
NGXsc
EVP0962
EGCg
Avagacestat
Carvedilol
GSM-1
CHF 5074
Cerebrolysin
AZD3293
PUFA
Pioglitazone
Anti BACE1 Ab
BMS-708163
LY2886721
ELND005
BBS1
MK7622
MT4666
E2609
TAK-070
NPG-328
EVP-15962
proteolytic nanobodies
L-NBP
Memoquin
M30
Tacrine-based hybrids
AF267B
Bivalent β-Carbolines
MW-151
BDNF
IMX
Bentotiamine
N744
AADvac1
Anti-Tau Ab
Rhodanines
Phenylthiazolylhydrazide
BMS-241027
Minocycline
Nicotinamide
LMTX
Antioxidants
Statins
AC1204
Masitinib
Insulin
Cilostazol
ABT-126
ATX-001
Ladostigil
AZD3480
Etanercept
ABT354
AZD0530
Resveratrol
EVT302
Riluzole
GM-CSF
Pramipexole
Exendin-4
Liraglutide
AVP923
↓ Aß production
↓ Aß aggregation
↑ Aß clearance

Solanezumab: Phase 3 Results
Expedition 1 Trial: Mild to Moderate AD

ADAS-cog 11



ADCS-ADL



http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf

Solanezumab: Expedition Trials: Phase 3 Results: Subanalysis of Mild AD (MMSE 20-26)

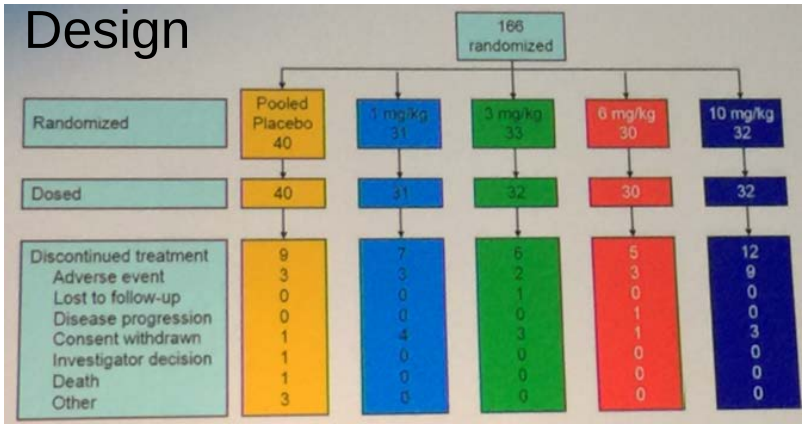
n= 2,052

	EXP1 overall	EXP1 mild		EXP2 overall	EXP2 mild		Pooled overall	Pooled mild
Cognitive								
$ADAScog_{11}$	**.312**	.008		.060	.097		.042	.001
$ADAScog_{14}$	.155	.006		.075	**.120**		.025	.001
MMSE	.067	.002		.004	.099		.002	.001
Functional								
ADCS-ADL	**.931**	.302		.062	.076		.217	.057
ADCS-iADL	.919	.319		.080	.029		.250	.045

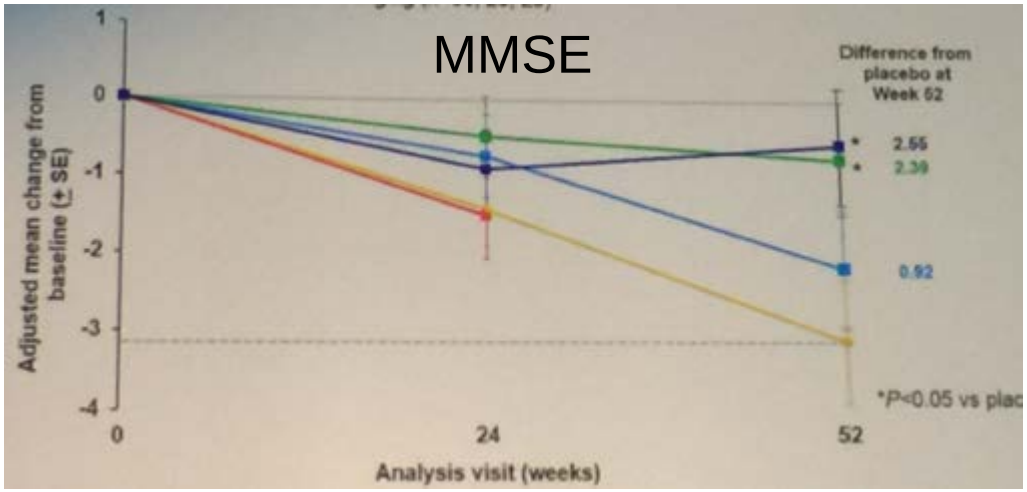
http://files.shareholder.com/downloads/LLY/2110812184x0x604107/6a7ad129-ff1d-4dbc-9e6e-828f09e7b60b/Solanezumab_ANA_Slides_8-Oct-2012.pdf

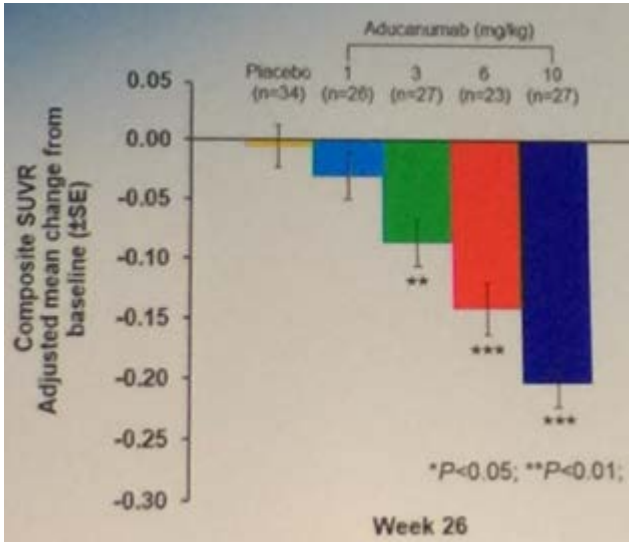
Aducanumab: Phase 1 'Multiple Ascending Dose' PRIME Study in Prodromal or Mild AD

Design



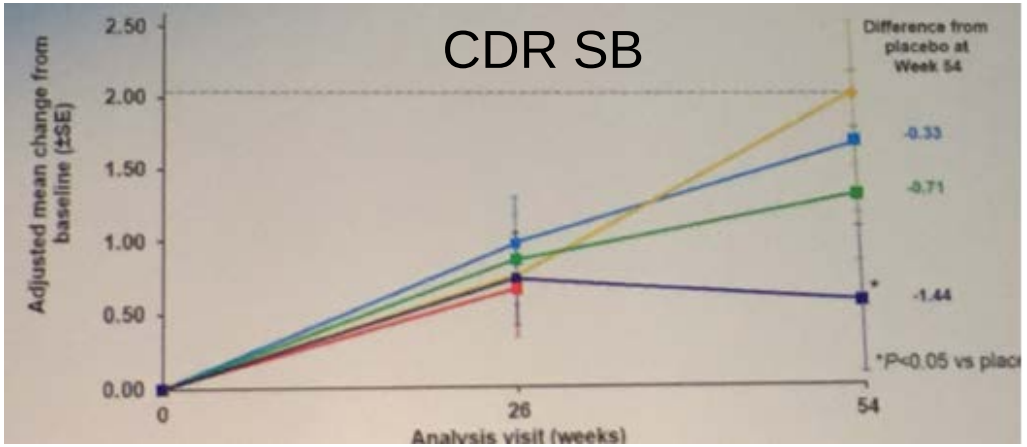
MMSE





PET SUVR (OC)

CDR SB

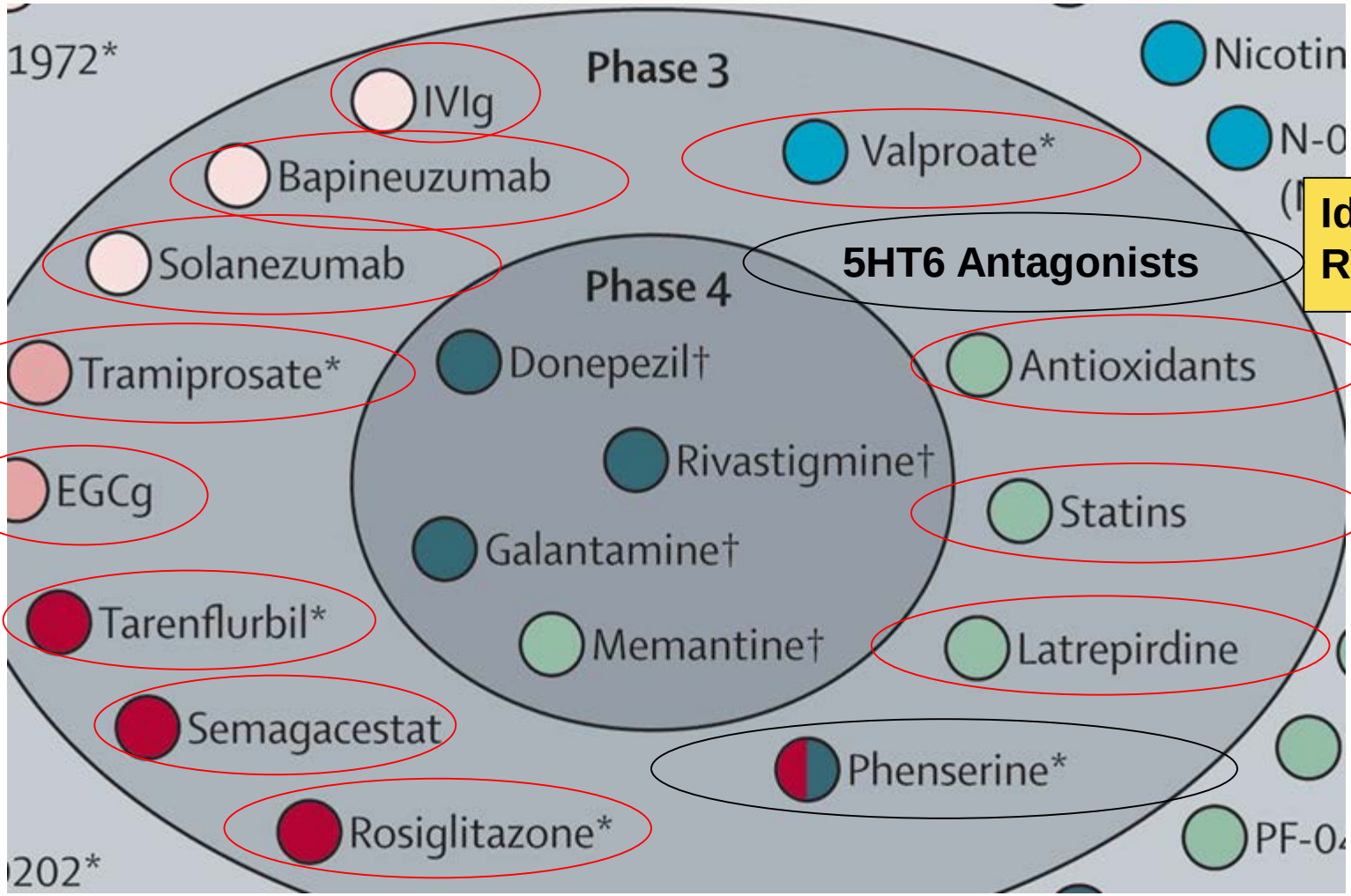


Next Up for Amyloid Related Phase 3 Trials

Small Molecules	Other names	Background	Target Type	Phase 1-2 data in AD	PD effects at selected doses	Clinical POC	Comment
ALZT-OP1	Cromolyn Na Intal + Ibuprofen	2 FDA approved drugs	Amyloid related inflamm ation	N/A	N/A	N/A	No phase 1 or phase 2 trials, no PD biomarkers
Azeliragon [1]	TTP 488 PF 04494700	High dose stopped, + futility analysis in phase 2	Amyloid related inflamm ation	Available	N/A	N/A	No consistent or clinically meaningful effect on plasma levels of Aβ, or on inflamm biomarkers
Verubecestat[2]	MK8931	Mild to mod AD (n=1960); Prodromal (n=1500)	BACE inhibitor	Phase 2-3	Y	N/A	Dose proportional plasma and CSF exposure and dose dependent lowering of Aβ

1 Sabbagh M et al Alz Dis AssocDis2011, 2 Forman M et al Alz Dement 2013 P690

AD Drug Development Results 2010-present

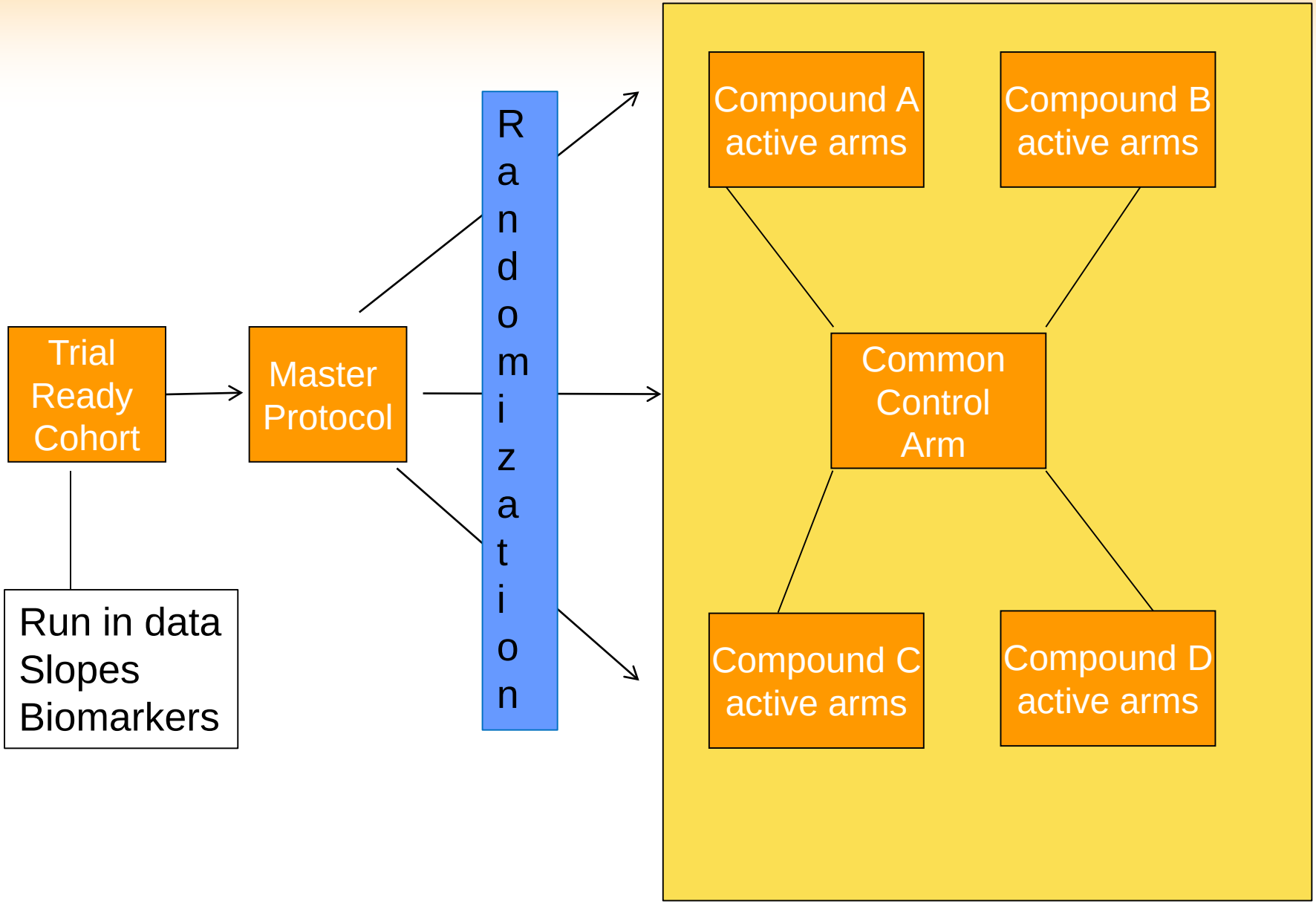


Adapted from Mangiolasche F, et al. *Lancet Neurology* July 2010

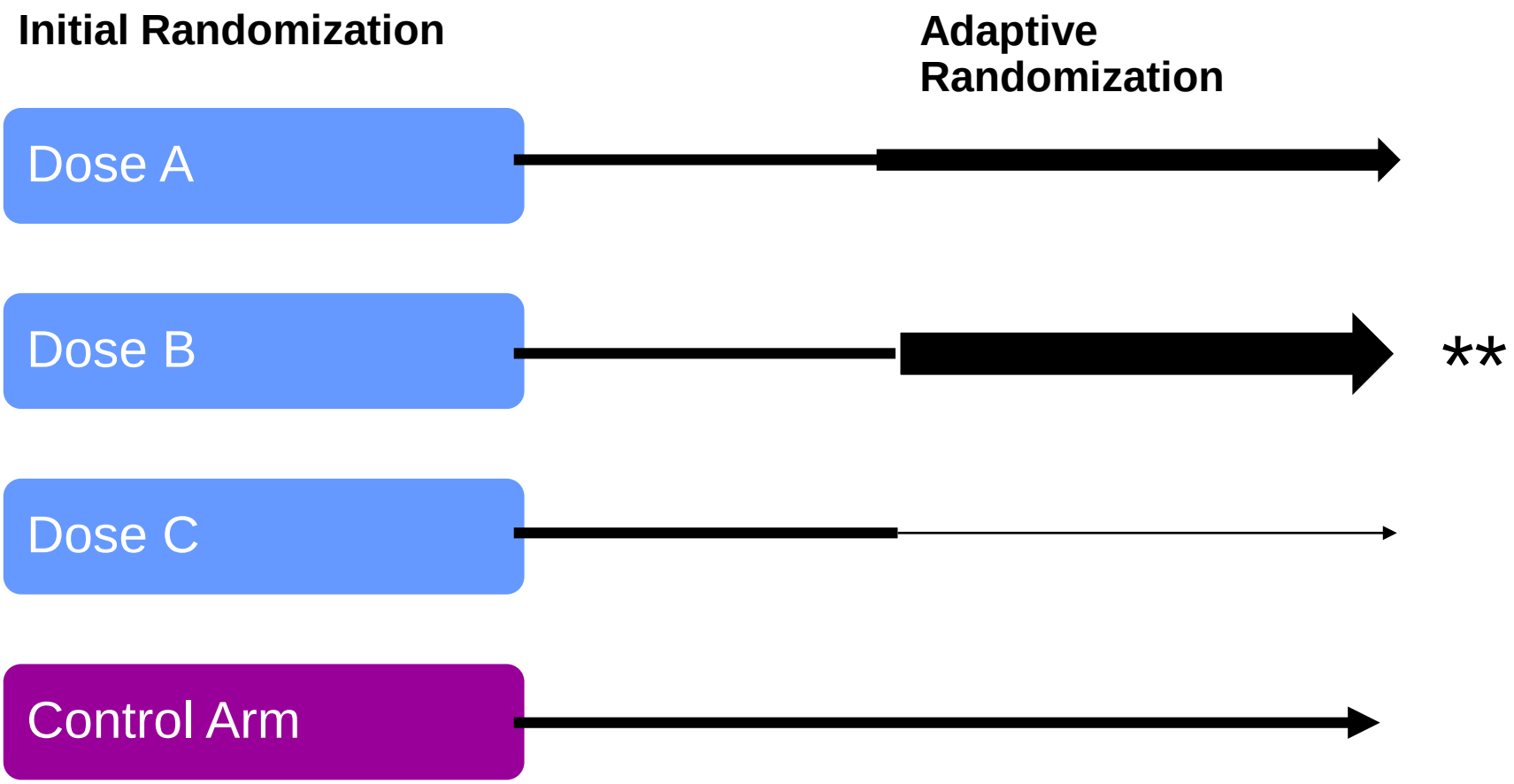
Regrouping and Refining the Approach

- **Pharmacology matters**
  - **First principles: PK, PD, biological effects**
- **Achieving clinical POC is difficult but needs our creativity to achieve**
  - **Novel designs, seemless studies, sensitive and ecologically interesting outcome measures**
- **Effect sizes: updating our approach to trials**
  - **Bigger samples are not necessarily better…….**
  - **Aim for ES that are clinically important not just statistically significant**
  - **More programs enabled**
    - **Investment in more front end costs**
  - **Attention to the therapeutic product profile**

Mobilizing an Adaptive Clinical Trials Platform

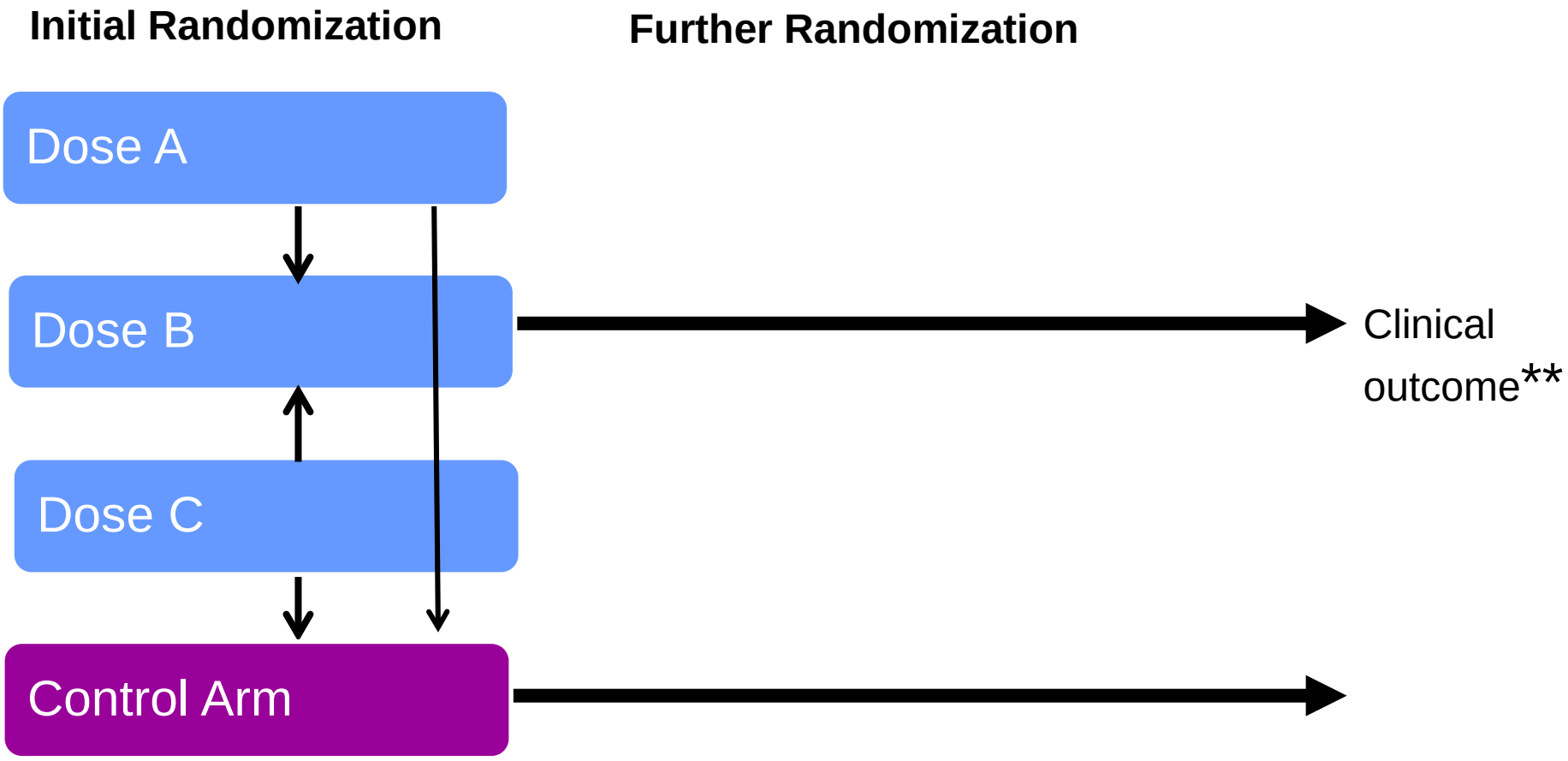


Adaptive Trial Design Phase 1



Study sample powered for significant results on biomarker primary outcome
Study duration 3-6 months n=50 tbd

Adaptive Trial Design Phase 2



Study sample powered for significant results on clinical outcome measure
Study duration further 6 – 12 months n=500 tbd

Evolving our Approach

- **Precision medicine:**
  - Intensive analytics around endophenotypes and biomarker panels to predict who may respond
    - Inflammatory endophenotype for an inflammatory therapeutic
    - Metabolic, vascular to specific interventions
  - Novel individualized treatment screening response
    - iPSC cell systems and models to find responders before trials

- **Taking a broader approach to define responders**
  - Including more real world populations
    - comorbid cerebrovascular and other neurodegenerative pathologies
    - Seek responding populations more intensively
    - Adjust designs adaptively
    - Value genetic models for genetic disease but sporadic ?

“Skate where the puck is going to be……..”

- The Canadian Philosopher Wayne Gretzky

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