Research quality in industry vs academia

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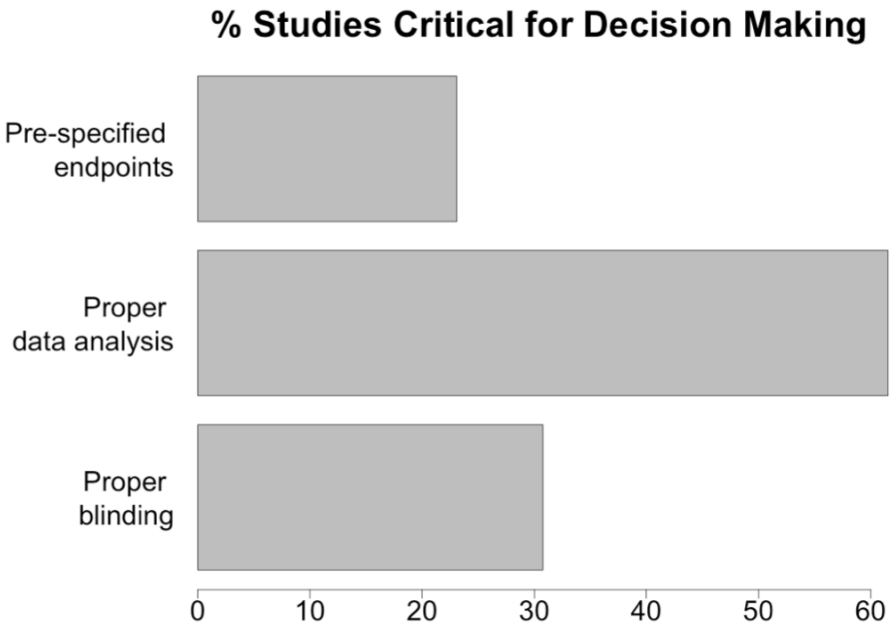
What am I going to talk about?

- As research quality in industry and academic cannot and should not be compared directly, main focus is on the differences in existing needs and motivation and how they evolve over time

- Drug discovery as an area of applied biomedical research where industry and academic closely interact and where adequate quality is essential for the ultimate benefit of patients

In-licensed projects (2015-2017): Research rigor



Post-licensing analysis of „critical“ studies

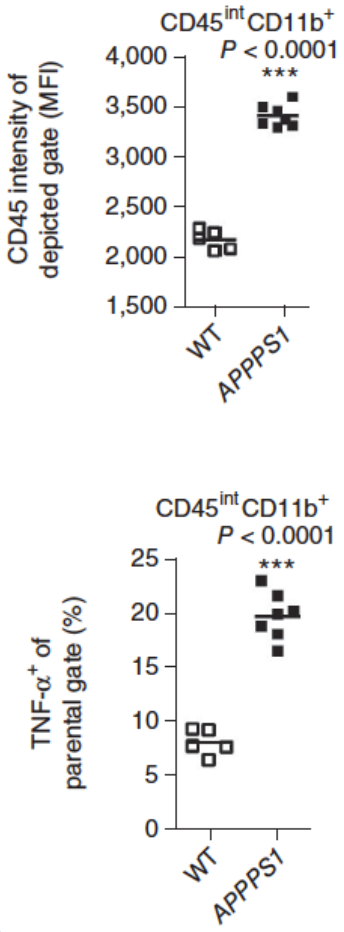
- 12 drug discovery projects
- 3 drug companies
- 26 „critical“ studies

PAASP data on file

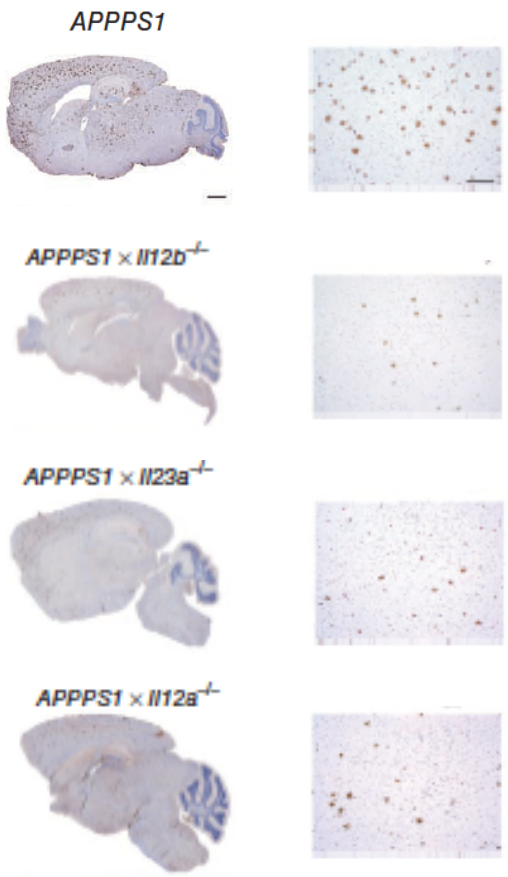
PAASP estimates that at least 30% of early-stage innovative drug discovery projects licensed by pharma companies critically depend on data that do not meet minimum quality criteria

Pressure-generating hypothesis

Elevated glial cytokines in AD



Deletion of IL12/23 subunits reduces Aß plaque load



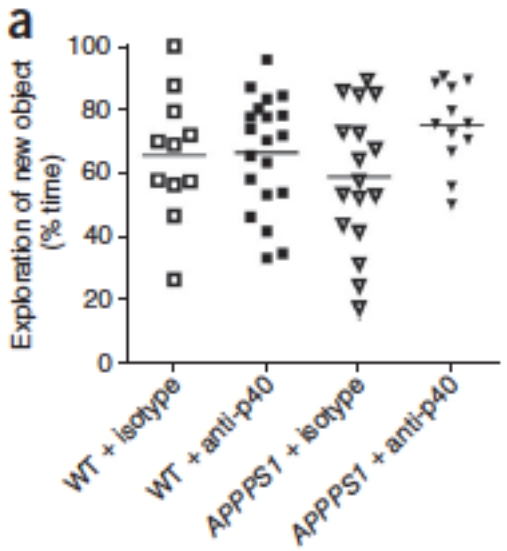
Functional outcome

ICV delivery of p40 antibody reversed cognitive deficits in aged APP/PS1 mice

vom Berg et al (2012) Nat Med 18:1812-9

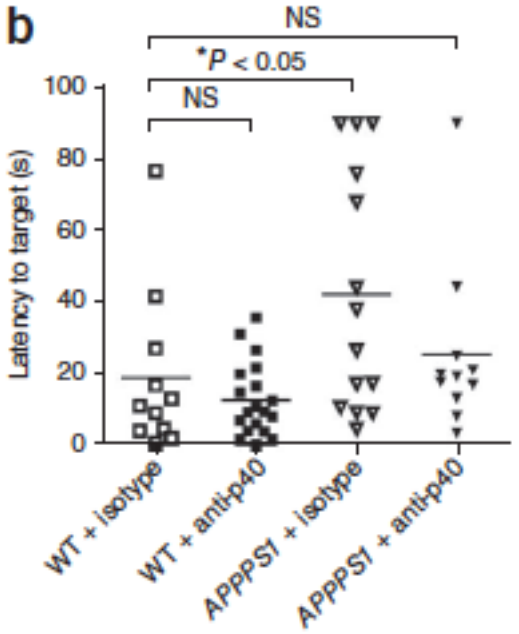
Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease–like pathology and cognitive decline

Novel object recognition



One-way ANOVA: „P<0.05“
Post hoc: not shown

Barnes maze



ANOVA: not shown
Post hoc: Dunnett's

Fear conditioning

Stated in the text:
„... performance in the contextual fear conditioning test did not differ between p40-antibody–treated and isotype-treated APPPS1 mice (data not shown)“

vom Berg et al (2012) Nat Med 18:1812-9

Heads I win, tails you lose

Scenario	Positive control worked	Positive control failed
My drug worked		???
My drug failed		

If one does not pre-specify how the study outcomes will be interpreted and used in decision-making, studies can be designed to bias the interpretation in a favored direction

Cummings et al. Alzheimer's Research & Therapy 2014, 6:37
http://alzres.com/content/6/4/37

alzheimer's research&therapy

RESEARCH Open Access

Alzheimer's disease drug-development pipeline: few candidates, frequent failures

Jeffrey L Cummings[1*], Travis Morstorf[2] and Kate Zhong[1]

Abstract

Introduction: Alzheimer's disease (AD) is increasing in frequency as the global population ages. Five drugs are approved for treatment of AD, including four cholinesterase inhibitors and an *N*-methyl-D-aspartate (NMDA)-receptor antagonist. We have an urgent need to find new therapies for AD.

Methods: We examined Clinicaltrials.gov, a public website that records ongoing clinical trials. We examined the decade of 2002 to 2012, to better understand AD-drug development. We reviewed trials by sponsor, sites, drug mechanism of action, duration, number of patients required, and rate of success in terms of advancement from one phase to the next. We also reviewed the current AD therapy pipeline.

Results: During the 2002 to 2012 observation period, 413 AD trials were performed: 124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials. Seventy-eight percent were sponsored by pharmaceutical companies. The United States of America (U.S.) remains the single world region with the greatest number of trials; cumulatively, more non-U.S. than U.S. trials are performed. The largest number of registered trials addressed symptomatic agents aimed at improving cognition (36.6%), followed by trials of disease-modifying small molecules (35.1%) and trials of disease-modifying immunotherapies (18%). The mean length of trials increases from Phase 2 to Phase 3, and the number of participants in trials increases between Phase 2 and Phase 3. Trials of disease-modifying agents are larger and longer than those for symptomatic agents. A very high attrition rate was found, with an overall success rate during the 2002 to 2012 period of 0.4% (99.6% failure).

99.6% failure

Conclusions: The Clinicaltrials.gov database demonstrates that relatively few clinical trials are undertaken for AD therapeutics, considering the magnitude of the problem. The success rate for advancing from one phase to another is low, and the number of compounds progressing to regulatory review is among the lowest found in any therapeutic area. The AD drug-development ecosystem requires support.

Yesterday: no big differences between industry and academia

- The subject of lacking quality is reduced to scientific misconduct
- Significance of suboptimal research practices is not fully understood
- No hard evidence published to document the impact of lacking research rigor
- Trust in the scientific excellence and “gut feeling“
- Options such as GLP or ISO perceived negatively (by scientists) and act as „demotivators“
- Large gap between scientists and quality professionals

Today: differences start to emerge

- Academia:
  - scientists are already overloaded by paperwork
  - scientific freedom is a sacred cow
  - „reproducibility“ is a minor (rare) problem
  - „reproducibility crisis“ is invented by industry
  - lack of incentives to change diminishes the impact of training (even if provided) and existing resources

Why Most Published Research Findings Are False

John P. A. Ioannidis

Corollary 1: The smaller the studies conducted in a scientific field (i.e. N), the less likely the research findings are to be true.

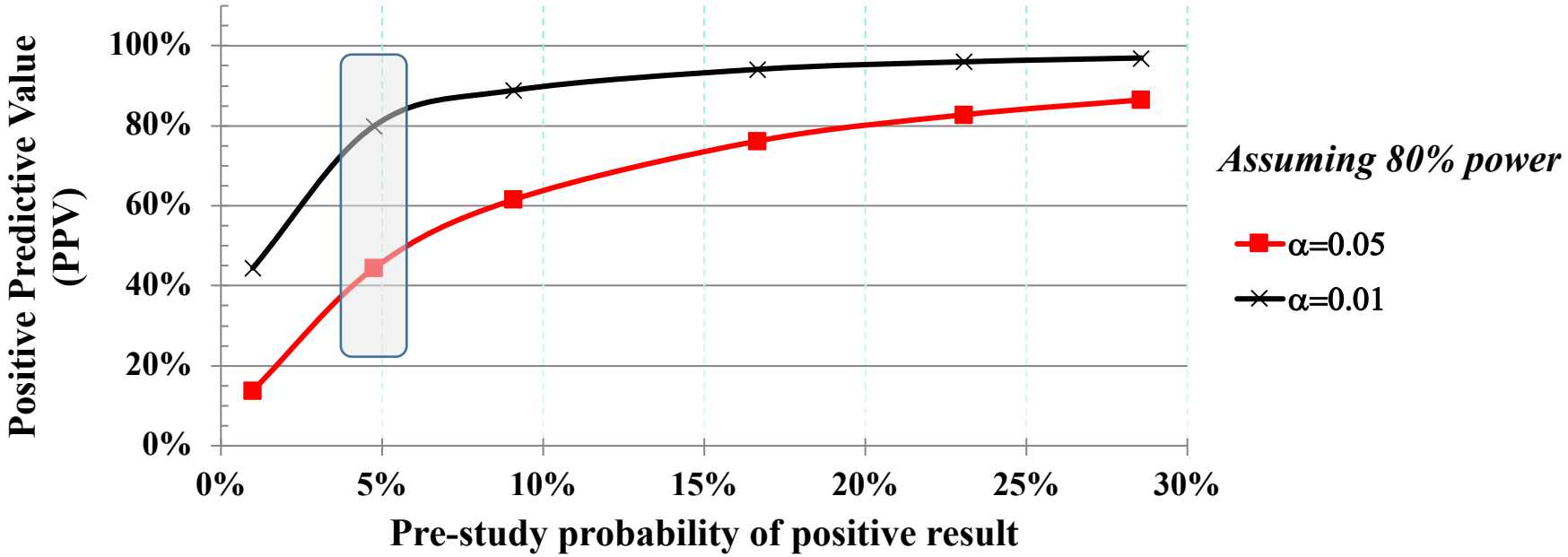
Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.

…

Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true.

PLoS Med. 2, e124; 2005

Post-study probability of confirming positive result vs Pre-study probability of positive result

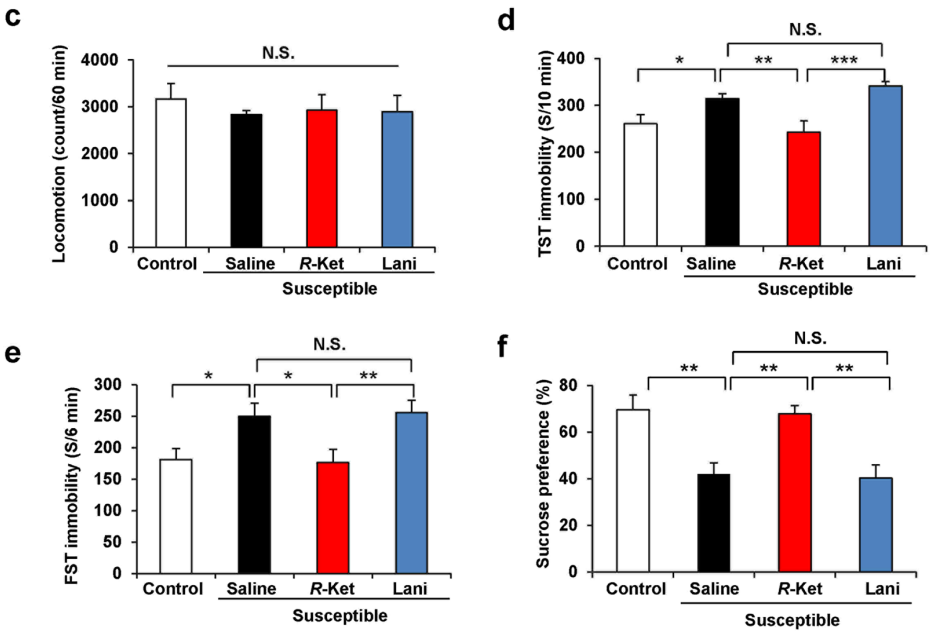


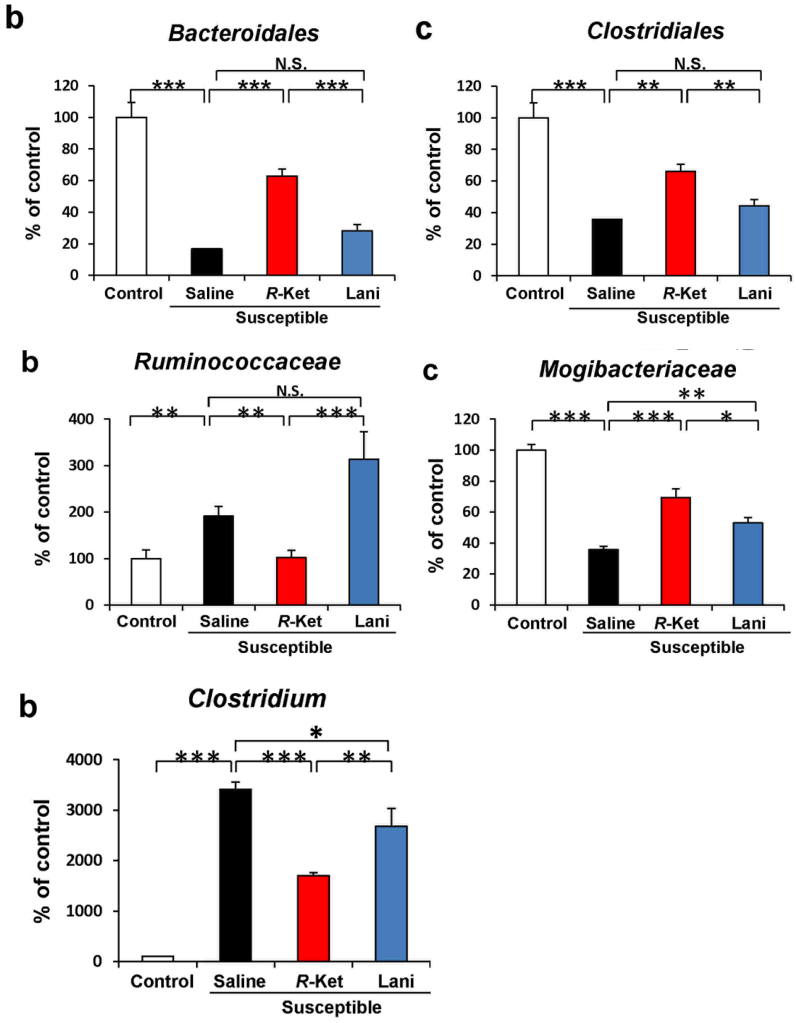
If pre-study probability is 5%, post-study PPV is only ~ 40% for 5% Type-1 error (alpha) & 80% power

Ketamine and gut microbiota: Can it get hotter?

- Acute (!) ketamine is confirmed in clinical studies to be effective in treatment-resistant depression
- Gut microbiota was demonstrated to be altered in disease states such as depression
- Hypothesis: acute injection of ketamine to chronically stressed mice restores normal gut microbiota within 3 days post-injection

Ketamine and gut microbiota





4 groups
x 6 mice each

Qu et al (2017) Sci Rep 7: 15725

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- Industry:
  - most (!) companies have dedicated efforts focusing on enhancing quality standards in non-regulated research
  - external validity is recognized as the problem
  - more open to collaborate and share information

NATURE MEDICINE

PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease

Kuti Baruch[1], Aleksandra Deczkowska[1], Neta Rosenzweig[1], Afroditi Tsitsou-Kampeli[1], Alaa Mohammad Sharif[1], Orit Matcovitch-Natan[1,2], Alexander Kertser[1], Eyal David[2], Ido Amit[2] & Michal Schwartz[1]

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GLIA
WILEY

RESEARCH ARTICLE

Systemic immune-checkpoint blockade with anti-PD1 antibodies does not alter cerebral amyloid-β burden in several amyloid transgenic mouse models

Martine Latta-Mahieu[1] | Bradford Elmer[2] | Alexis Bretteville[3] | Yaming Wang[4] | Mati Lopez-Grancha[1] | Philippe Goniot[1] | Nicolas Moindrot[1] | Paul Ferrari[5] | Véronique Blanc[5] | Nathalie Schussler[1] | Emmanuel Brault[1] | Valérie Roudières[1] | Véronique Blanchard[1] | Zhi-Yong Yang[2] | Pascal Barneoud[1] | Philippe Bertrand[1] | Bart Roucourt[6] | Sofie Carmans[6] | Astrid Bottelbergs[3] | Liesbeth Mertens[3] | Cindy Wintmolders[3] | Peter Larsen[3] | Caroline Hersley[4] | Tyler McGathey[4] | Margaret M. Racke[4] | Ling Liu[4] | Jirong Lu[4] | Michael J. O'Neill[4] | David R. Riddell[4] | Andreas Ebneth[3] | Gary J. Nabel[2] | Laurent Pradier[1]

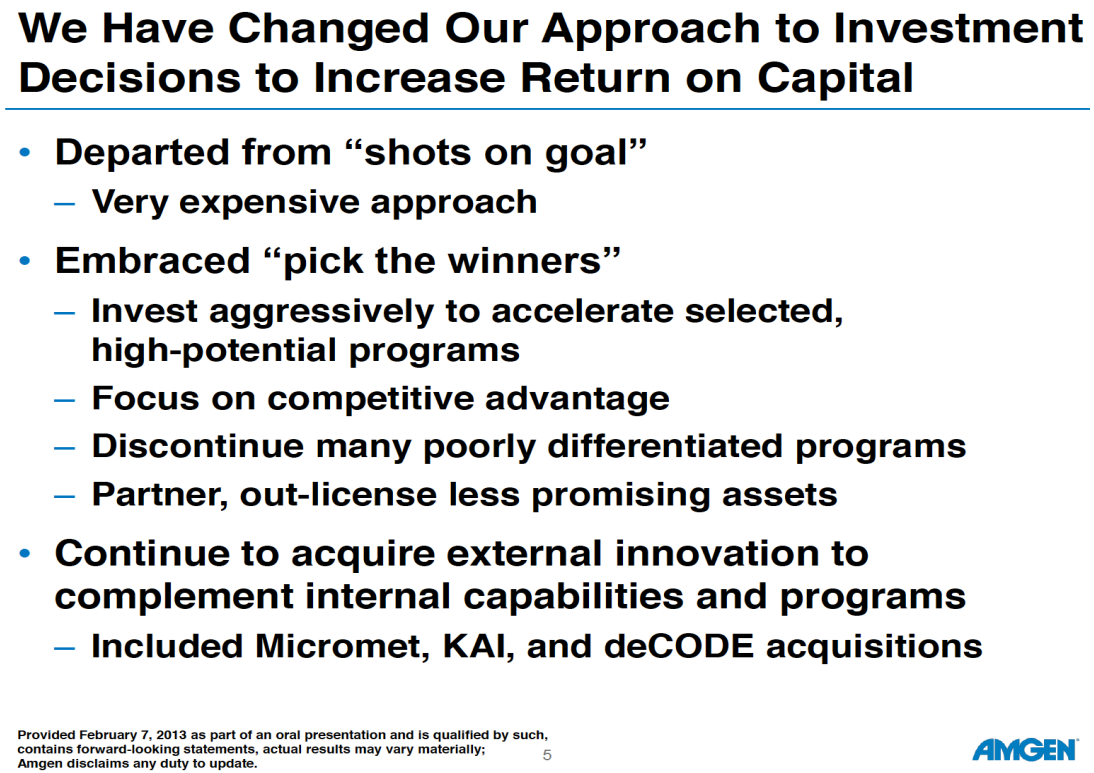
… inhibition of PD1 checkpoint signaling by itself is not sufficient to reduce amyloid pathology and that additional factors might have contributed to previously published results (Baruch et al., (2016): Nature Medicine, 22:135–137). Until such factors are elucidated, animal model ***data do not support further evaluation*** *of PD1 checkpoint inhibition as a therapeutic modality for Alzheimer's disease.*

Future: Industry has an advantage?

- Habit of having quality management
  - GxP – trained personnel, infrastructure, awareness
  - Beyond GxP – biohazards, GMP, unborn life, etc.

Future: Industry has an advantage?

- Habit of having quality management
- Important initiatives can be introduced top-down



We Have Changed Our Approach to Investment Decisions to Increase Return on Capital

- **Departed from "shots on goal"**
  - **Very expensive approach**
- **Embraced "pick the winners"**
  - **Invest aggressively to accelerate selected, high-potential programs**
  - **Focus on competitive advantage**
  - **Discontinue many poorly differentiated programs**
  - **Partner, out-license less promising assets**
- **Continue to acquire external innovation to complement internal capabilities and programs**
  - **Included Micromet, KAI, and deCODE acquisitions**

Provided February 7, 2013 as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

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Future: Industry has an advantage?

- Habit of having quality management
- Important initiatives can be introduced top-down
- All stakeholders within one organization

Industry

Management

Scientists

(both lab leaders & lab associates)

Clinical development

Business development

Biostatistics

Academia

Senior scientists

Junior scientists

Collaborators

University officials

Funders

Publishers

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- Drug discovery is a much narrower field than „biomedical research“ or „life sciences“

Future: Industry has an advantage?

- Habit of having quality management
- Important initiatives can be introduced top-down
- All stakeholders within one organization
- Drug discovery is a much narrower field than „biomedical research“ or „life sciences“
- Industry cannot switch to using only methods such as in silico, zebra fish, …, hIPSCs, etc.

Industry can trigger the change but needs to work together with academia in order to make a real change

Academia should use this opportunity of using industry‘s resources and knowledge to invest into future

Quality in non-regulated drug discovery

European Quality in Preclinical Data

www.eqipd.org

EQIPD develops a quality management system for both industry and academia that is

- Flexible – no ”one-size-fits-all” solutions
- Fit-for-purpose – continuous improvement triggered by specific needs
- Lean – focus on impact, not on paperwork
- User-friendly – continuous improvement driven by scientists

THANK YOU!