Look back in anger: What clinical studies tell us about the quality of pre-clinical research

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About 1/3 funding each from industry, philanthropy and research funding
Toward evidence-based pre-clinical sciences

Example
Global warming
The problems of the temple

- Dropping numbers of new drugs
- 92% of drugs fail in clinical trials
- Unexpected side effects leading to withdrawals

The problems of the pillars?
Clinical Studies
- Mostly randomized, double-blind, and placebo-controlled
- Usually multi-centric
- Ethical review
- Good Clinical Practice
- Skilled professionals
- Urge to publish / register
- Evidence-based Medicine
A typical thesis…

Learning on the job
Limited resources / supervision
Unclear hypothesis

Redefinition of hypothesis
Changed hypothesis
Cherry-picking of experiments
Different sequence of events

Storyline of a scientific article
Basic Research

- Mostly unblinded, single laboratory
- Learning on the job
- No quality assurance
- Limited replicates
- Pressure to publish
Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

...data from 67 projects, ... This analysis revealed that only in ~20–25% of the projects were the relevant published data completely in line with our in-house findings... In almost two-thirds of the projects, there were inconsistencies between published data and in-house data that either considerably prolonged the duration of the target validation process or, in most cases, resulted in termination of the projects.

We need less research, better research, and research done for the right reasons.
If a study depends on \( n \) experiments with \( p = 0.95 \), the overall probability of a correct result is

- One exp.: 0.95
- Two exp.: 0.90
- Three exp.: 0.86
- Four exp.: 0.81
- Five exp.: 0.77
- Six exp.: 0.74
- Seven exp.: 0.70
The third scientific culture: Toxicology

- Internationally harmonized protocols
- Good Laboratory Practice
- Outdated methods
- Precaution
- Mechanistic thinking as “mustard after the meal”
Learning from experience may be nothing more than learning to make the same mistakes with increasing confidence.

Petr Skrabanek, James McCormick
Follies and Fallacies in Medicine
Tarragon Press, Glasgow, 1989
Source: B. Ames & L. Gold

Alcohol 36-times more dangerous than coffee intake

When using the same threshold levels as for TCDD (dioxin):

One beer in 345 years
R22 harmful if swallowed
\((LD_{50} = 150-200\text{mg/kg in rats})\)
R 36 irritant to eyes
R 37 respiratory irritant
R 38 irritant to skin
Not carcinogenic, but co-carcinogen (promotor)
Unclear mutagenicity
Embryonic malformations in cat, dog, rat, mice, rabbit, monkey

*Unlikely to be brought to the market today*
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

Harry Olson,1 Graham Betton,2 Denise Robinson,3 Karluss Thomas,3 Alastair Monro,1 Gerald Kolaja,4 Patrick Lilly,5 James Sanders,6 Glenn Sipes,7 William Bracken,8 Michael Dorato,9 Koen Van Deun,10 Peter Smith,11 Bruce Berger,12 and Allen Heller13


This survey includes input from 12 pharmaceutical companies with data compiled from 150 compounds with 221 HT [human toxicity] events reported. Multiple HTs were reported in 47 cases. The results showed the true positive HT concordance rate of 71% for rodent and nonrodent species, with nonrodents alone being predictive for 63% of HTs and rodents alone for 43%.
This week in PNAS

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok\textsuperscript{a,1}, H. Shaw Warren\textsuperscript{b,1}, Alex G. Cuenca\textsuperscript{c,1}, Michael N. Mindrinos\textsuperscript{a}, Henry V. Baker\textsuperscript{c}, Weihong Xu\textsuperscript{a}, Daniel R. Richards\textsuperscript{d}, Grace P. McDonald-Smith\textsuperscript{e}, Hong Gao\textsuperscript{a}, Laura Hennessy\textsuperscript{f}, Celeste C. Finnerty\textsuperscript{g}, Cecilia M. López\textsuperscript{c}, Shari Honari\textsuperscript{f}, Ernest E. Moore\textsuperscript{h}, Joseph P. Minei\textsuperscript{i}, Joseph Cuschieri\textsuperscript{i}, Paul E. Bankey\textsuperscript{k}, Jeffrey L. Johnson\textsuperscript{h}, Jason Sperry\textsuperscript{l}, Avery B. Nathens\textsuperscript{m}, Timothy R. Billiar\textsuperscript{l}, Michael A. West\textsuperscript{n}, Marc G. Jeschke\textsuperscript{o}, Matthew B. Klein\textsuperscript{l}, Richard L. Gamelli\textsuperscript{p}, Nicole S. Gibran\textsuperscript{l}, Bernard H. Brownstein\textsuperscript{q}, Carol Miller-Graziano\textsuperscript{k}, Steve E. Calvano\textsuperscript{r}, Philip H. Mason\textsuperscript{e}, J. Perren Cobb\textsuperscript{s}, Laurence G. Rahme\textsuperscript{t}, Stephen F. Lowry\textsuperscript{t,2}, Ronald V. Maier\textsuperscript{l}, Lyle L. Moldawer\textsuperscript{e}, David N. Herndon\textsuperscript{g}, Ronald W. Davis\textsuperscript{a,3}, Wenzhong Xiao\textsuperscript{a,t,3}, Ronald G. Tompkins\textsuperscript{t,3}, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program\textsuperscript{d}

carry new drug candidates forward into clinical trials. Systematic studies evaluating how well murine models mimic human inflammatory diseases are nonexistent. Here, we show that, although acute inflammatory stresses from different etiologies result in highly similar genomic responses in humans, the responses in corresponding mouse models correlate poorly with the human conditions and also, one another. Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts (e.g., $R^2$ between 0.0 and 0.1). In addition to improve-
Evidence-based Toxicology
“Evidence-based medicine goes toxicology!”

Hoffmann and Hartung “Toward an evidence-based toxicology”, Human Exp. Tox., 2006
Mar 2011: US EBTC
Oct 2011: Secretariat at CAAT
Jan 2012: First conference hosted by EPA

Kick-off meeting of the Evidence-Based Toxicology Collaboration (EBTC) Europe

In conjunction with Eurotox Congress 2012 (Stockholm, Sweden)

June 17, 2012
15:30h - 17:30h

Radisson Blu Royal Viking Hotel • Vasagatan 1, Stockholm, Sweden
Complimentary Registration: http://www.ebtox.com
EBT Collaboration Steering Committees
Johns Hopkins is the right environment for EBTC secretariat
Clinical research has undergone changes, which should be a role model for basic research and regulatory sciences:

- Evidence-basation, Documentation and Quality Assurance
- Publish less, but of better quality
Hurt because everything's stayed the same...