Protein/Biomolecule quality in Life Science Research

The scale of the problem:

PLOS | BIOLOGY

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

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Abstract

Low reproducibility rates within life science research undermine cumulative knowledge production and contribute to both delays and costs of therapeutic drug development. An analysis of past studies indicates that the cumulative (total) prevalence of irreproducible preclinical research exceeds 50%, resulting in approximately US$28,000,000,000 (US $28B)/year spent on preclinical research that is not reproducible—in the United States alone. We outline a framework for solutions and a plan for long-term improvements in reproducibility rates that will help to accelerate the discovery of life-saving therapies and cures.

OPEN ACCESS

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COMMENT

POLICY Climate engineering research and governance needs to start small p.29

HISTORY Mysterious defection of cold war physicist revisited p.32

CORRESPONDENCE Lessons from terrible toll of workaday Typhoon warning p.35

OBITUARY Mary F Lyon, pioneer of mouse genetics, remembered p.36

ILLUSTRATION BY PETE ELLIS/DRAWGOOD.COM

PHARMA

RESEARCH

Standardize antibodies used in research

To save millions of dollars and dramatically improve reproducibility, protein-binding reagents must be defined by their sequences and produced as recombinant proteins, say **Andrew Bradbury**, **Andreas Plückthun** and 110 co-signatories.

Economic Impact

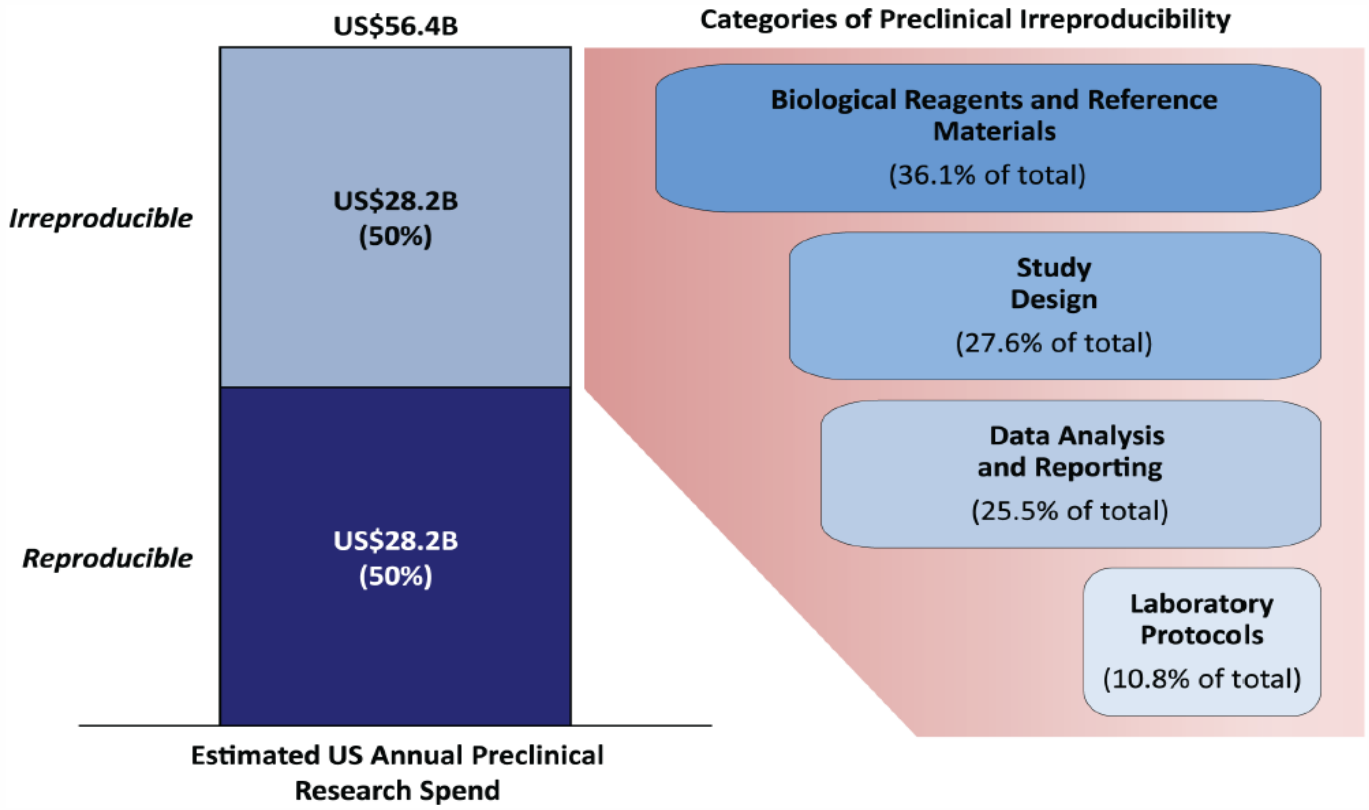
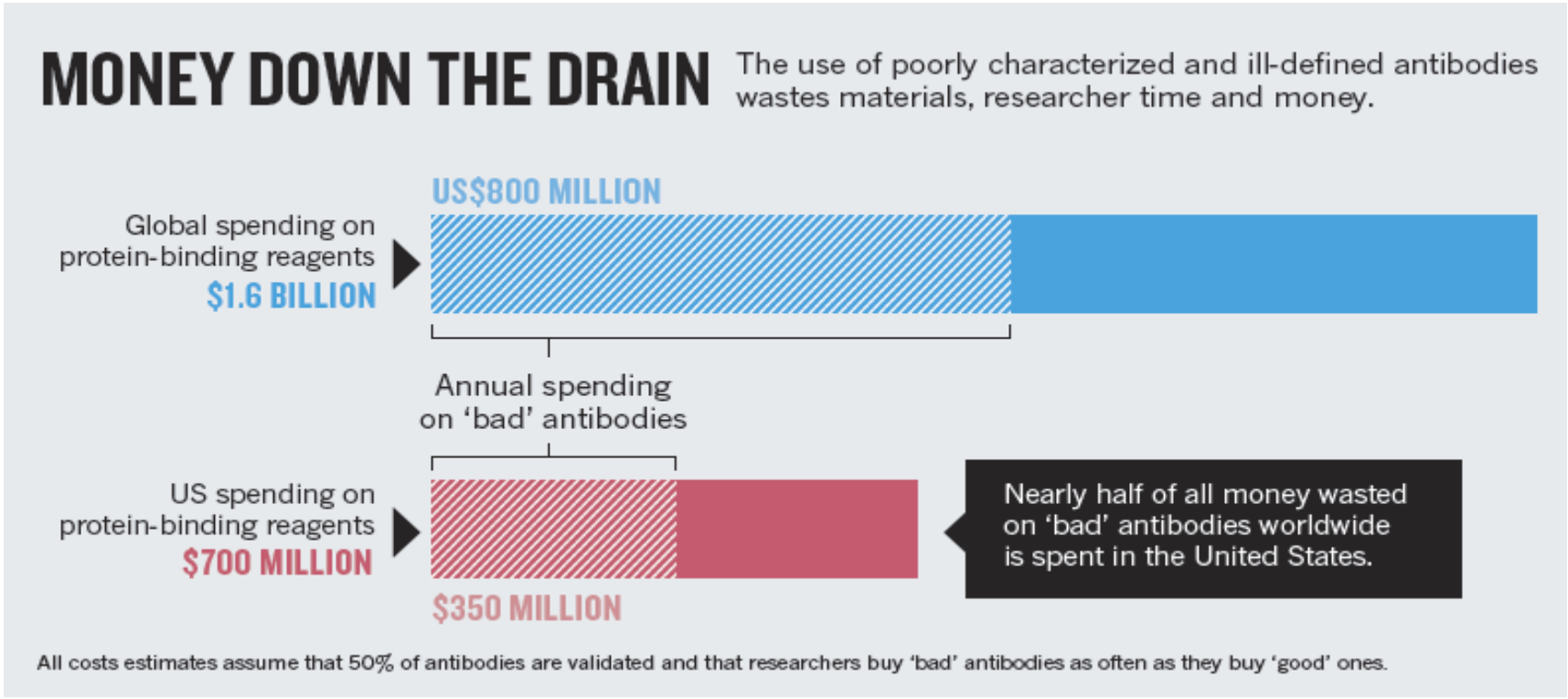


Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates (see S1 Dataset). Source: Chakma et al. [18] and the American Association for the Advancement of Science (AAAS) [19].

Are we wasting 50% of EU pre-clinical research budget?

Estimated $350M on Commercial Abs alone in US!

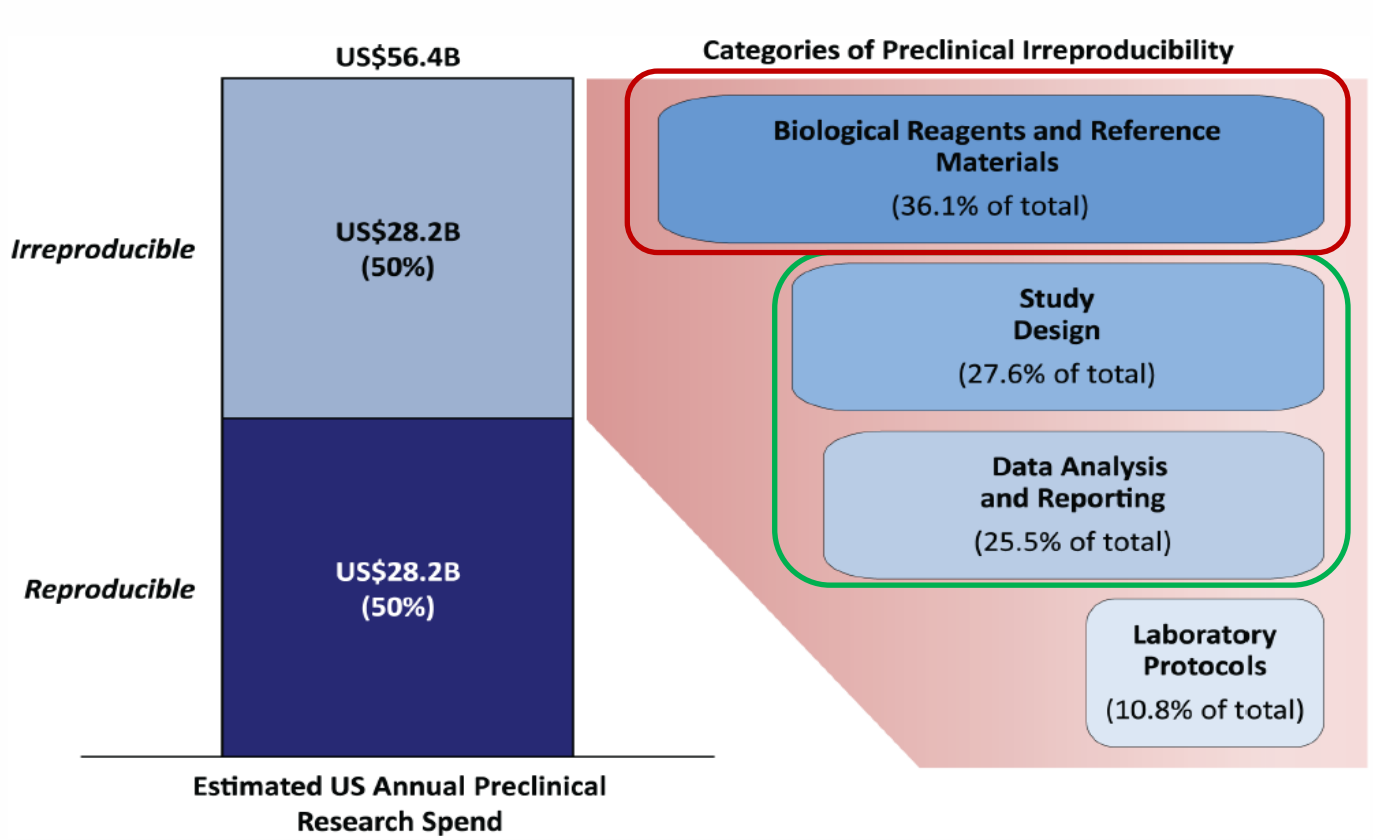


Simple examples

- Poorly characterized protein X.
- Incorrect size on SDS-PAGE? No MS data/ID. No SEC data.
- Different activity to full length protein observed-experimental artifact!
- Loss of 2 years post-doc work

- Poorly characterized protein Y.
- No SEC data.
- Used in Biacore assay/pull-down expts.
- Different binding characteristics due to aggregation/dimerization.
- -artifactual binding?
- -artifactual K_D!
- Wrong conclusions from data?

What can we do?



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Improve Experimental Design/data Analysis!

Improve Quality Control and Characterization of Protein Reagents!

Joint P4EU/ARBRE ‘Protein Guidelines’

We hope to:

Publish joint guidelines on ‘minimal’ and ‘recommended’ data on protein production, quality and characterization for proteins used to derive data for publications.

Reverse the trend for less and less information available in mainsteam journals on the production and purification of laboratory reagents. Lobby editors to encourage/oblige more extensive use of supplementary data. Improved reproducibility between labs.

Your experiments are only as good as your reagents!

Association of Resources for Biophysical Research in Europe

Protein Production and Purification Partnership in Europe

PECF Minimal Checklist

Tryptic digest/MS or intact MS (depending on protein size) to confirn identity.

SDS-PAGE or Caliper data/image to confirm integrity/relative purity.

SEC is generally included in our purification protocols-monomer/ dimer/aggregate. Analytical SEC will be available in PECF.

Complementary Checklist

Dynamic Light Scattering (Crystallography platform instrument).


10
YEARS
2005-2015
IRB
BARCELONA
INSTITUTE
FOR RESEARCH
IN BIOMEDICINE

CRISPR endonucleases available ‘in-house’ soon

Direct use of enzymes has advantages over expression of enzymes in target cells:

- No ‘delay’ due to transcription and translation of endonucleases-immediate protection of guide RNAs from degradation. Removes necessity for ‘protected’ RNAs, less guide RNAs required.
- Less off-target effects reported?
- Higher overall efficiencies?

Endonucleases vailable on request:
Cas9 (tested) and Cas9 D10A (Nickase-in testing)

Planned Endonucleases:
Cpf1 (two isoforms)-can be used in AT rich regions of genes