Antibodies and the reproducibility crisis

The Antibody Society Webcast series - Antibody Validation #2

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Between 2002-2012, Amgen was not able to reproduce the seminal findings from 47of 53 “top tier” publications.

- publications that reported something completely “new”

The major finding was not reproduced!

In the majority, data was not reproduced by the original investigators with their reagents in their lab

Amgen’s experience is not unique….

Begley and Ellis. Nature (2012) 483: 531

Begley's Position Statement.

- These results do not challenge the validity or legitimacy of the scientific method
- Not talking about fraud: the subject is laziness, sloppiness, ignorance, exaggeration, desperation
- The vast majority of investigators want to do the right thing
- This debate, occurring in public, confirms the strength our scientific system

We get what we incentivize

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The advances in medical treatment have been truly outstanding: we have every reason to remain optimistic that research will continue to deliver.

The issue is the "opportunity cost".

This could impacted immediately (solved?) by Funding Agencies

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High-Profile Studies Typically Fail at Multiple Levels

Begley's six criteria for judging scientific reports:

1) Were studies blinded?
   - Almost never

2) Were all results shown?
   - Typically not
     - "representative examples" & data selection bias
     - western blots that show only a slice; no size markers

3) Were experiments repeated?
   - Typically not
     - westerns/immuno-precipitation usually only performed once
     - use 1/2 RNAis and in 1/2 cell lines
     - confusion between replicates and independent experiments

4) Were positive and negative controls shown?
   - Typically not

5) Were reagents validated?
   - Typically not
     - IHC with a polyclonal anti-peptide antibodies
     - small molecule inhibitors

6) Was the analysis appropriate (e.g. cell growth/statistical tests)?
   - Typically not

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Begley. Nature (2013) 497; 433

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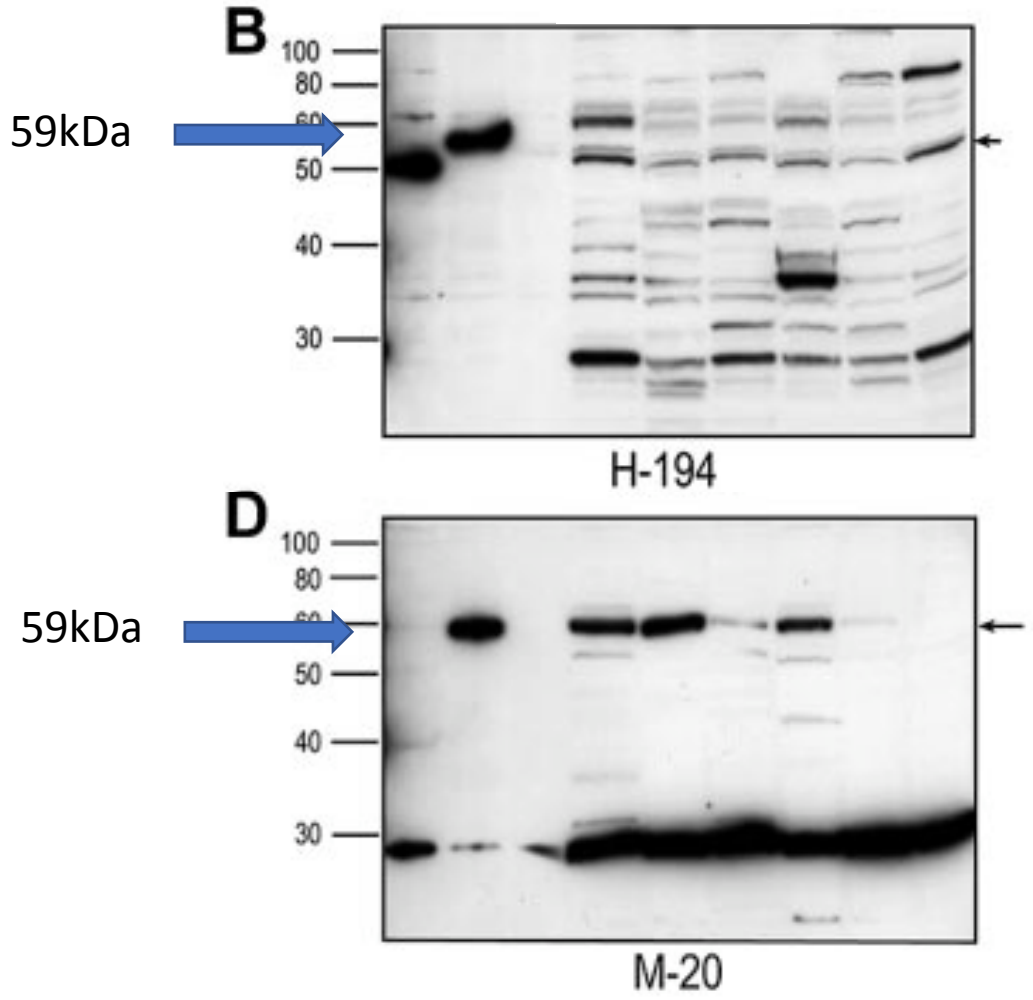
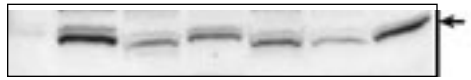
Poor Quality Antibodies Are a Major Problem…one example

For example: Were all the results shown?



"Anti-EPOR" antibodies

Versus



Investigators deliberately hide poor experiments by failing to show all the data

Elliott et al. Blood (2006) 107: 1892

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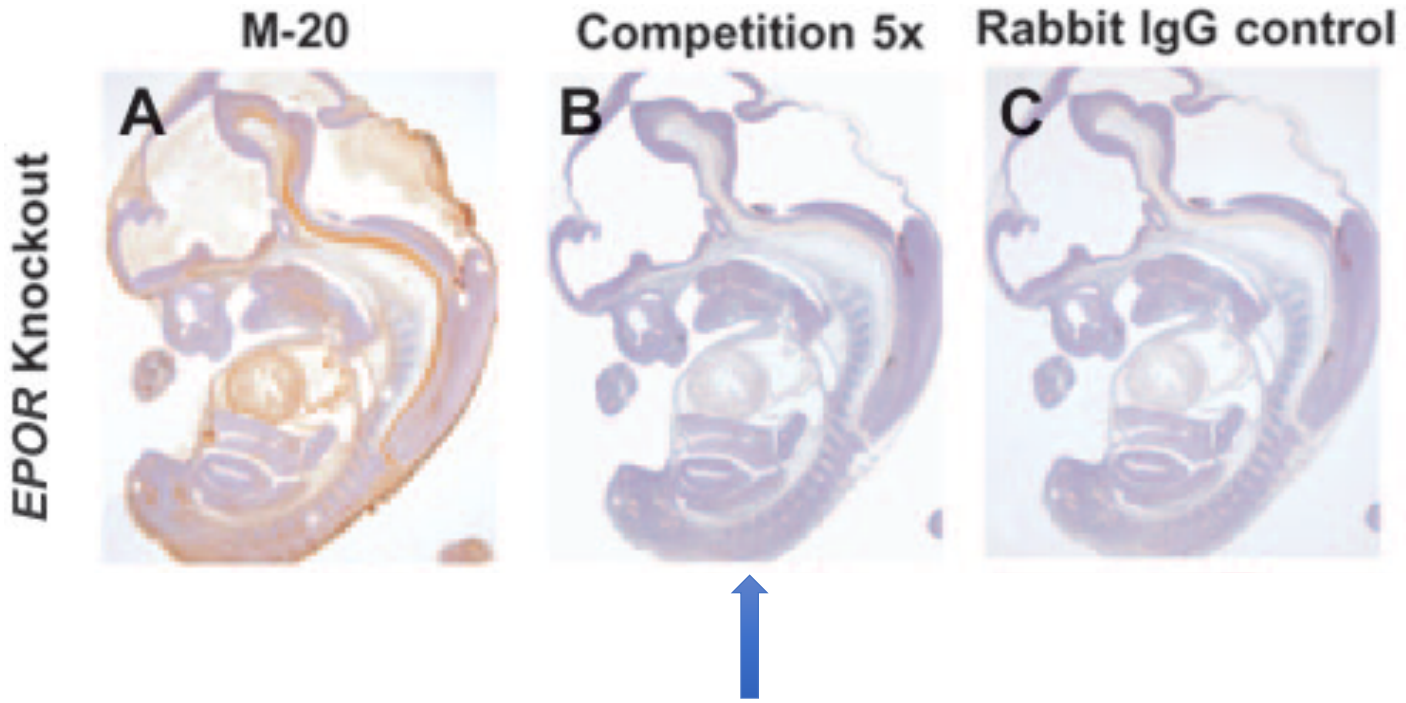
Were Positive and Negative Controls Shown?

Beware non-validated polyclonal anti-peptide antibodies



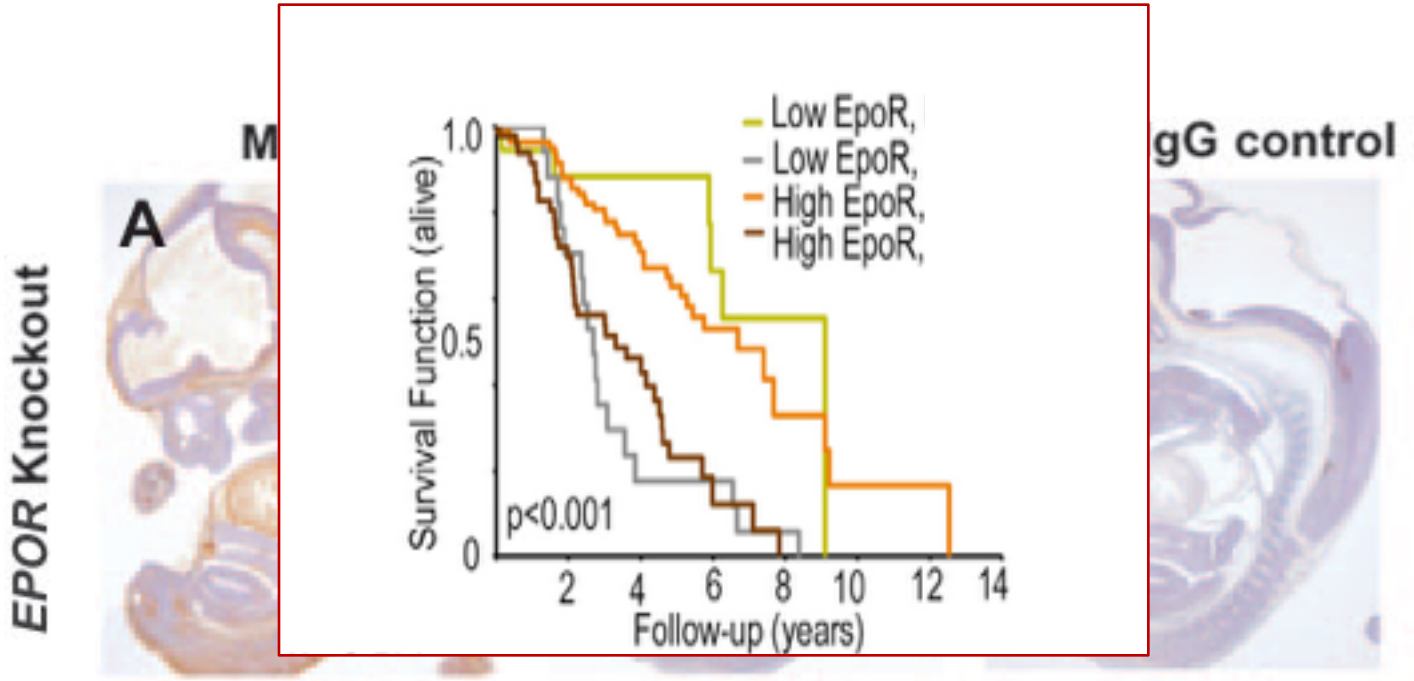
Beware “illegitimate” controls

Here peptide competition experiments are not an appropriate control

Elliott et al. Blood (2006) 107: 1892

Were Positive and Negative Controls Shown?

Beware non-validated polyclonal anti-peptide antibodies



This illegitimate, anti-mouse antibody, M20 was used to "stratify" outcome for breast cancer patients! (Cancer Cell, 2015)

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