EURL ECVAM Recommendation on Non-Animal-Derived Antibodies

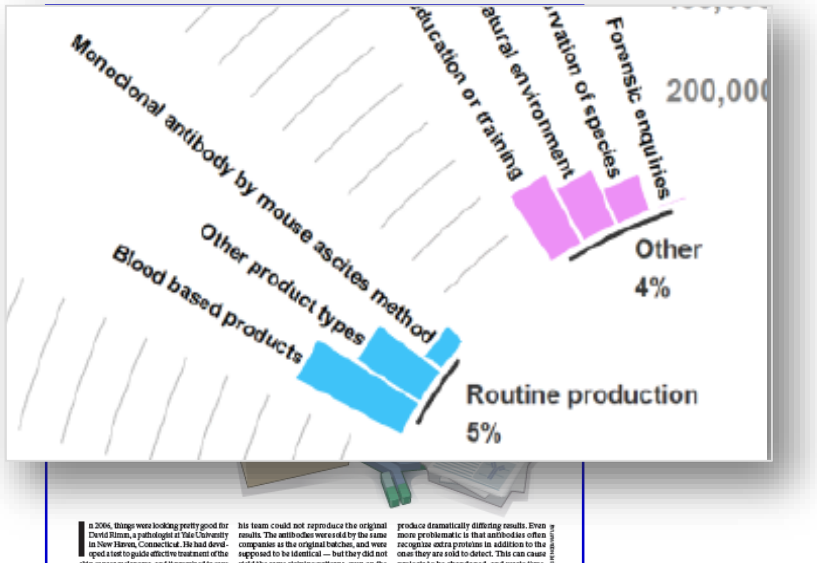
The scientific validity of non-animal-derived antibodies

João Barroso (Joint Research Centre, EURL ECVAM)

16 September 2020

Use of animals

Animals are still used for the generation of monoclonal and polyclonal antibodies as well as other types of affinity reagents.



Mouse ascites method in EU

- 2015 – 27,333 mice
- 2017 – 45,024 mice

Severe procedure

ESAC statement in 1998:

For all levels of monoclonal antibody production, scientifically acceptable in vitro methods (hybridomas technology) are available.

These methods are either better than, or equal to, the in vivo (ascites) production method in terms of antibody quality. Therefore, the in vivo production of monoclonal antibodies by the ascites method is no longer scientifically necessary, except in rare cases.

Note: Production was not covered in 86/609/EEC

ESAC review of the scientific validity of non-animal-derived antibodies

Working Group meeting on 8-9 November 2018
Opinion endorsed on 3-5 June 2019

Core members: Rebecca Clewell (*Chair*); Carl Westmoreland
Ad-hoc members: Carl Borrebaeck; Andrew Bradbury; Stefan Dübel; Alison Gray; Achim Knappik; Andreas Plückthun

Expertise covering…

- Antibody generation with animal and non-animal technologies
- Antibody engineering
- Antibody use in many research applications including diagnostics, therapeutics and research
- Academia and industry

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ESAC review process

- Declarations of interests submitted and analysed to identify potential conflicts of interest (DOIs publicly available at: https://ec.europa.eu/transparency/regexpert/).
- Reports produced by ESAC Working Groups are always peer reviewed by the whole ESAC before publication; final Opinion endorsed by the whole ESAC in plenary.

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Name: ECVAM Scientific Advisory Committee (E03602) Active

Type A - Individual expert appointed in his/her personal capacity

Name	Nationality	Professional Title	Membership Status
Aldert Piersma	Netherlands		Member
Alison Gray	United Kingdom	Dr	Member
Andreas Georg Plückthun	Switzerland	Professor	Member
Andrew Bradbury	United States of America	Dr	Member
Annette Kopp-Schneider	Germany		Member
Carl Borrebaeck	Sweden	Professor	Member
Carl Westmoreland	United Kingdom		Member
Chantra Eskes	Netherlands		Member
Emanuela Corsini	Italy		Member
Hans-Joachim Knappik	Germany	Dr	Member
Ian Cotgreave	Sweden	scientific advisor	Member
José M Navas	Spain		Member
Paula Marques Alves	Portugal		Member
Rebecca Clewell	United States of America		Member
Stefan Dübel	Germany	Professor	Member

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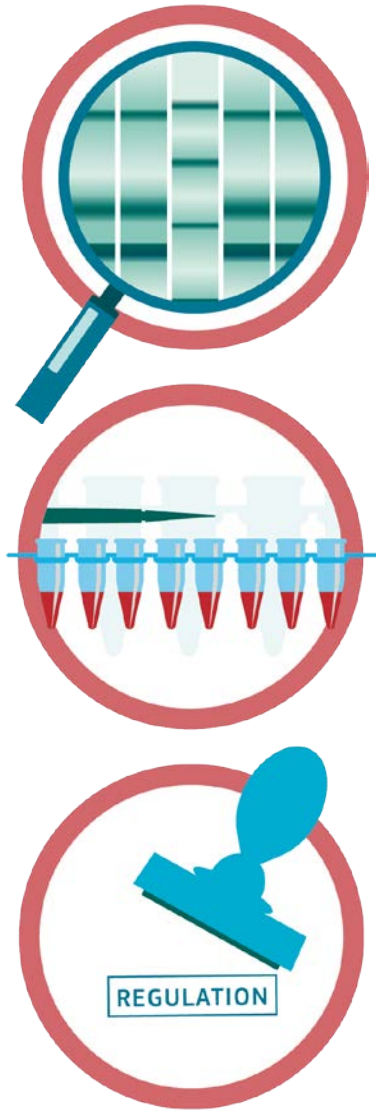
Charge question

Review the available proof of the **scientific validity** of antibodies and non-antibody **affinity reagents**, used in **research**, **diagnostics** and **regulatory applications**, **generated using animal-free technologies**



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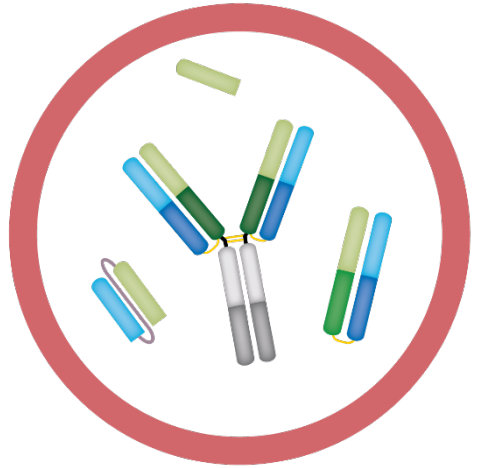
Final scope of the ESAC review



ESAC focused on non-animal-derived antibodies:

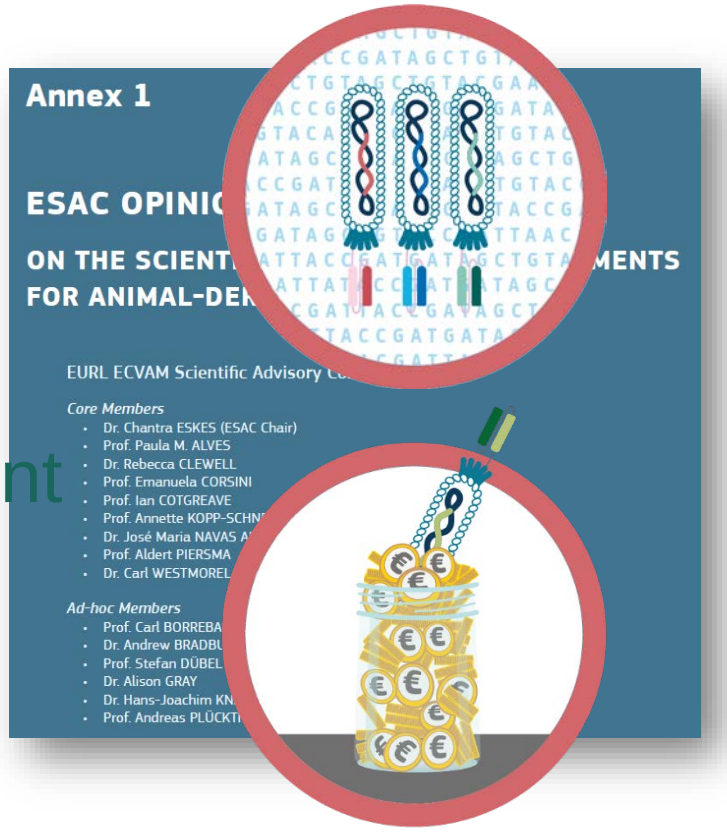
- are relatively mature technologies,
- have large bodies of evidence supporting their utility,
- have been used in a broad range of applications, and
- have few perceived hurdles to rapid implementation (e.g., cost, patents).

It was noted, however, that there would be value in convening a separate review of non-antibody affinity reagents as replacements for animal-derived antibodies.

ESAC Opinion

In June 2019, the ESAC concluded:

- ✓ Non-animal-derived antibodies are mature reagents generated by a proven technology
- ✓ Non-animal-derived antibodies offer significant scientific advantages and economic benefits
- ✓ Non-animal-derived antibodies should be promoted



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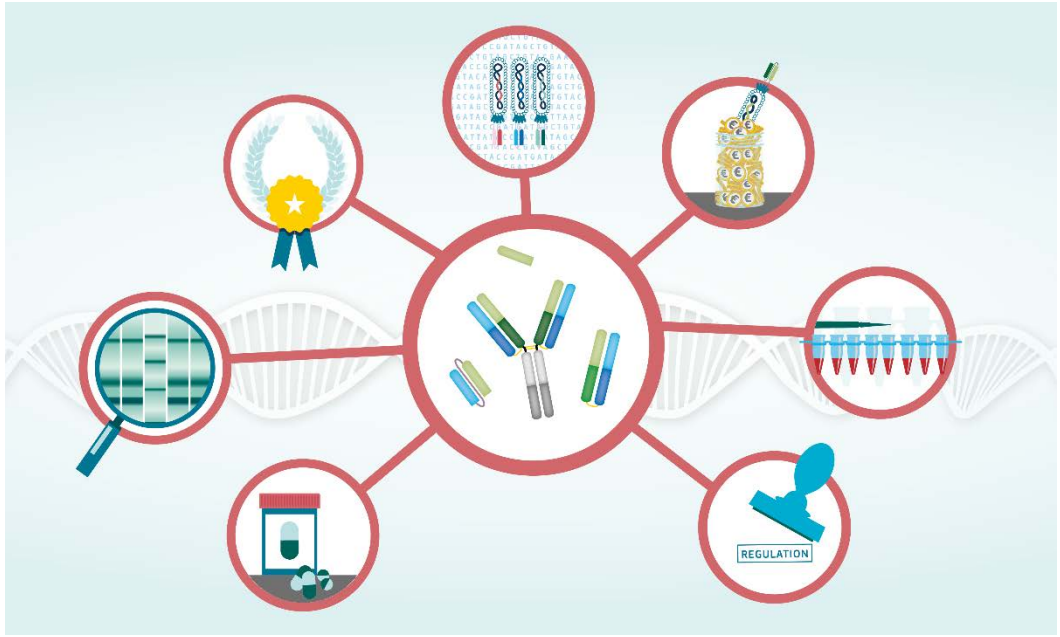
ESAC unanimous conclusion

Non-animal-derived antibodies are able to replace animal derived antibodies in the vast majority of applications.

Well-characterised, recombinant affinity reagents **will improve the reproducibility of science** and positively impact society.

EURL ECVAM Recommendation



“Animals should no longer be used for the development and production of antibodies for research, regulatory, diagnostic and therapeutic applications”

Authorisation for the use of animals should systematically be challenged and rejected where robust scientific justification is lacking

Available at: *https://ec.europa.eu/jrc/en/science-update/better-antibodies-without-using-animals*

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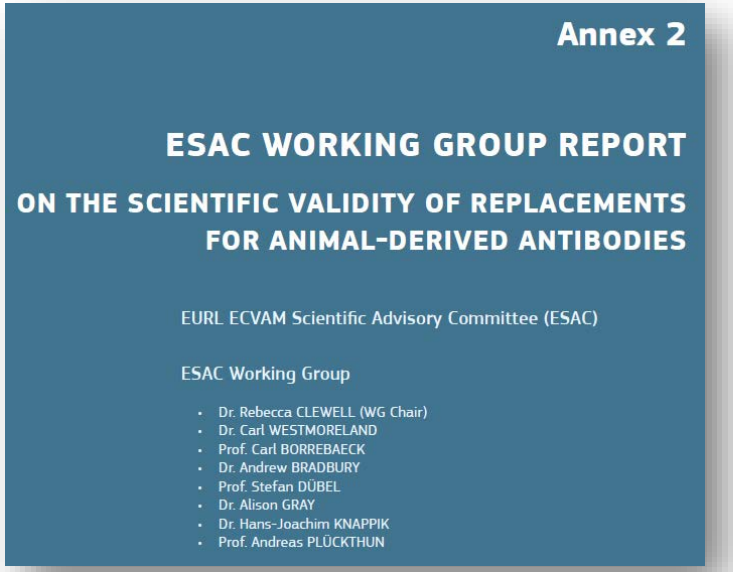
Availability, quality and relevance of NAD Abs

Breaking down misconceptions

- NAD Abs are available from catalogues
- Custom generation offered as commercial service
- Abundance of scientific literature
- NAD Abs can be stably produced in unlimited amounts
- NAD Abs are equivalent to animal-derived antibodies for the vast majority of applications
- No known limits concerning the choice of the species for building recombinant antibody gene libraries


Annex 2

ESAC WORKING GROUP REPORT

ON THE SCIENTIFIC VALIDITY OF REPLACEMENTS FOR ANIMAL-DERIVED ANTIBODIES

EURL ECVAM Scientific Advisory Committee (ESAC)

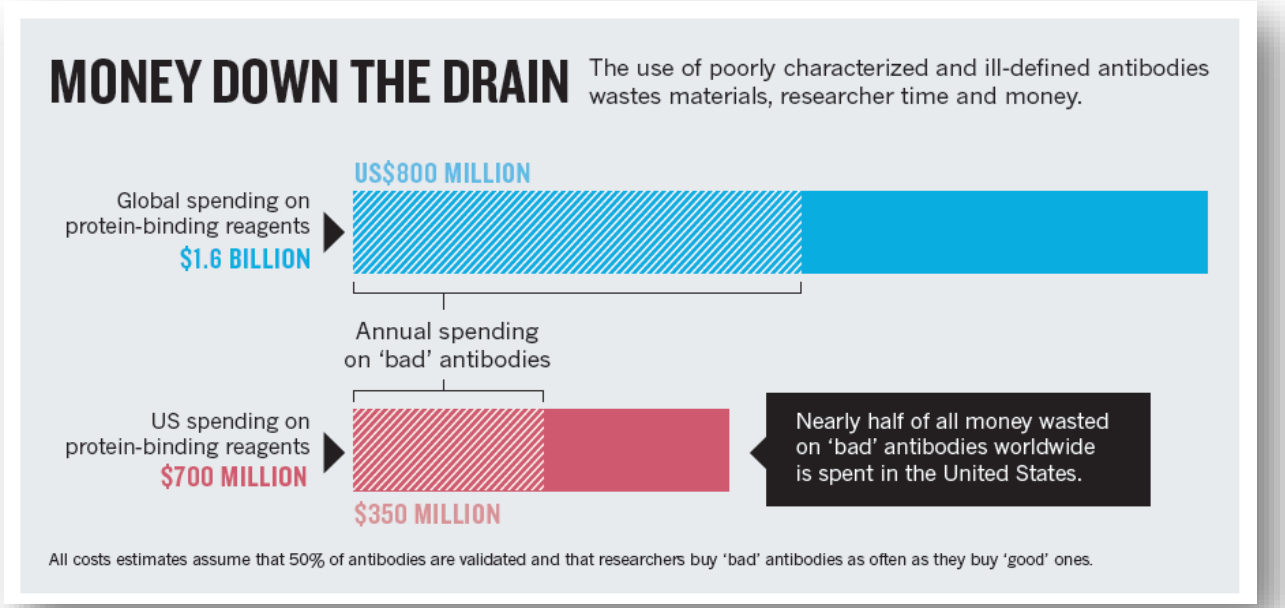
ESAC Working Group

- Dr. Rebecca CLEWELL (WG Chair)
- Dr. Carl WESTMORELAND
- Prof. Carl BORREBAECK
- Dr. Andrew BRADBURY
- Prof. Stefan DÜBEL
- Dr. Alison GRAY
- Dr. Hans-Joachim KNAPPIK
- Prof. Andreas PLÜCKTHUN

Expertise & costs

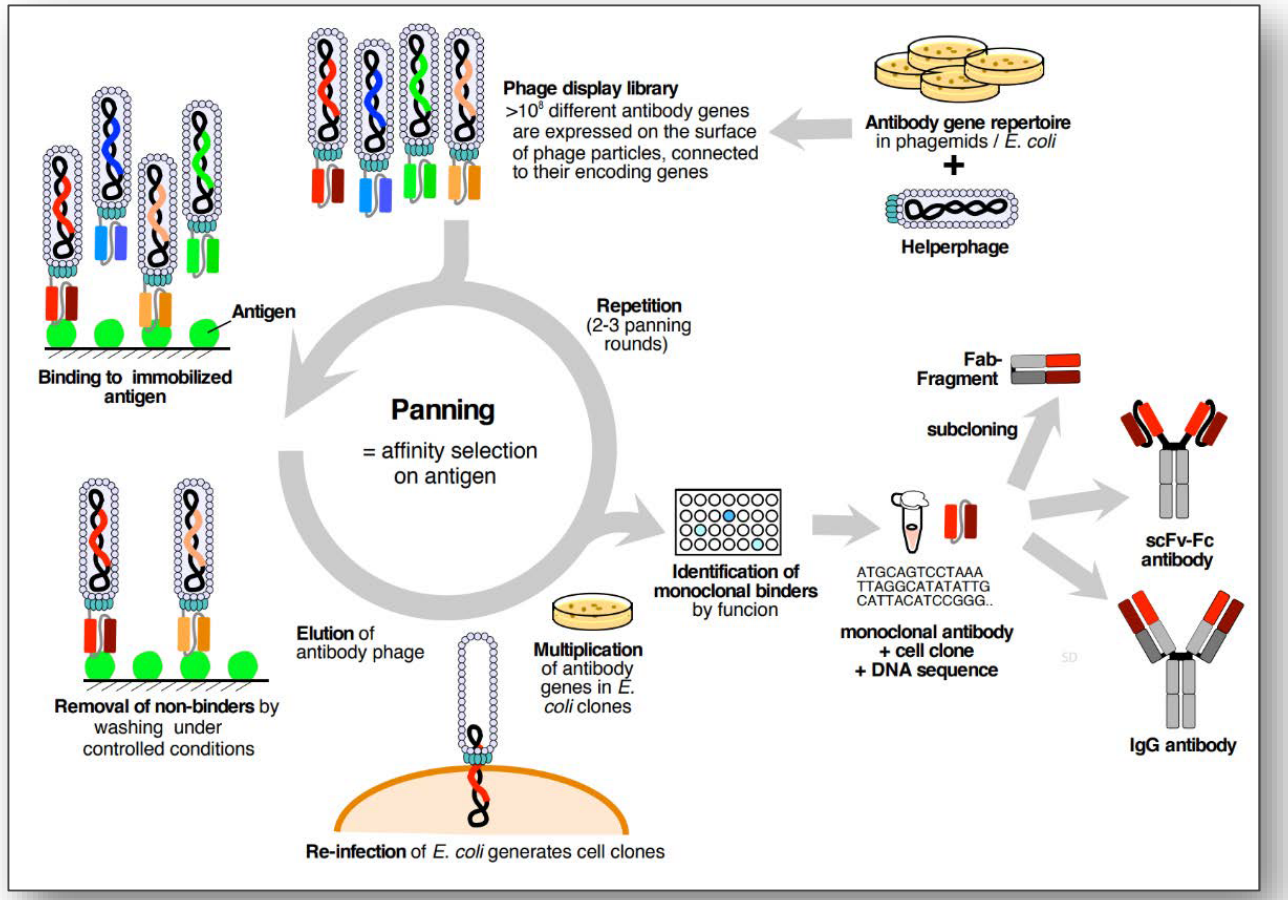
- Only standard laboratory equipment and consumables
- Expertise in modern molecular, cell and microbiology
- Significant time investment required to build a universal recombinant library, however:
  - ✓ supplies a high diversity of antibody candidates
  - ✓ significant benefit in time for selection of new antibodies

- Costs comparable to generation of mAbs by immunisation
- High financial impact of producing and using animal-derived antibodies of questionable quality



Bradbury & Plueckthun, 2015, Nature

Scientific advantages of NAD antibodies



- Sequence defined, i.e. unique identifier, unlimited and sustainable supply, enhance reproducibility of experiments
- Control over affinity selection conditions allowing selection of essential characteristics
- Free choice of detection system and many formats, IgG, fragments

Antibody phage display (according to Tomszak *et al.*, 2016)

How to promote generation and use of NAD Abs

- Education and training
- Project authorization under Directive 2010/63/EU
- Provision of funding

https://www.bio-rad-antibodies.com/hucal-recombinant-antibody-webinars-videos-technical-articles.html

Article 4

Principle of replacement, reduction and refinement

1. Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

Article 13

Choice of methods

1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

What should stakeholders do?

- Manufacturers/suppliers should establish a rapid phasing-out timescale for the use of animals to generate and produce antibodies
  - ✓ Catalogues should unambiguously show whether antibodies are animal-derived or not
- End-users should search for and request well-defined, non-animal-derived affinity reagents
- Where feasible, academic institutions should establish their own development and production services to support research activities
- Editors, reviewers and publishers should demand higher quality in antibody-based research and adopt unified validation standards

Thank you

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