The European Commission's science and knowledge service

Joint Research Centre

João BARROSO

European Commission

Scientific Validity of Replacements for Animal-Derived Antibodies

João Barroso (Joint Research Centre, EURL ECVAM)

SACATM Meeting

Washington, D.C., USA, 19 September 2019

European Commission

ESAC review of the scientific validity of replacements for 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

European Commission

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**

Final scope of the ESAC review

ESAC focused on nonanimal-derived antibodies, as they:

- are relatively mature technologies,
- have large bodies of evidence supporting their utility,
- have been used in broad ranging 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.

Advantages of nonanimal-derived antibodies

- Control over affinity selection conditions (e.g. selection under defined biochemical conditions selects only antibodies that are functional at these conditions)
- Free choice of detection system (e.g. fusion to tags, enzymes, etc.)
- Nonanimal-derived antibodies are sequence-defined:
  - Polyclonals not sequence-defined
  - Hybridomas only sequence-defined with substantial effort
- Duplicate antibody with identical binding and specificity profiles can be reconstituted easily
- Unlimited reproducibility of scientific results:
  - Reproducibility of antibodies over time and across labs
  - No batch to batch variation
  - No irretrievable loss of clone


BLAME IT ON THE ANTIBODIES

Antibodies are the workhorses of biological experiments, but they are littering the field with false findings. A few evangelists are pushing for change.

Misconceptions about limitations of nonanimal-derived antibodies

- Perceptions that nonanimal-derived antibodies have low affinity due to wrongly comparing avidity of animal-derived antibodies to monovalent affinity of nonanimal-derived antibodies
  - After selection, nonanimal-derived antibodies similar to rat and mouse monoclonal affinity
  - After affinity maturation, nonanimal-derived antibodies similar to rabbit monoclonal affinity
- Few providers perceived as lack of utility, but actually more related to cost/demand (majority focused on therapeutic applications)
- Some of the same limitations as conventional antibodies
  - Antigen specific difficulties: carbohydrates, complex biological samples, etc.
  - *These limitations represent areas that have not been fully explored, not necessarily impossibilities*

ESAC opinion

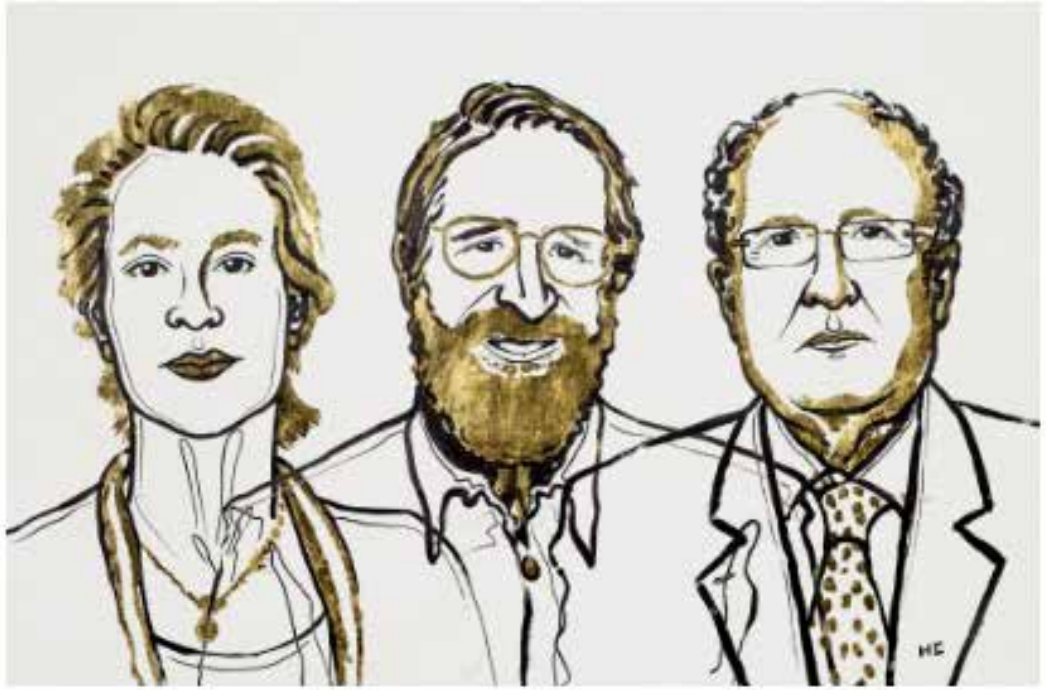
1. **Nonanimal-derived antibodies are mature reagents generated by a proven technology**
   - No general or systematic disadvantages with respect to affinity, stability/shelf life and specificity
   - Used in approved therapeutic & diagnostic applications
   - Available from catalogues as research reagents and generated as commercial service
   - Thousands of nonanimal-derived affinity reagents generated in EU- & NIH-funded programmes

Phage display: the technology that has revolutionised anima-free antibody production

The 2018 Chemistry Laureates

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry 2018 with one half to Frances H. Arnold "for the directed evolution of enzymes" and the other half jointly to George P. Smith and Sir Gregory P. Winter "for the phage display of peptides and antibodies".

Read the press release



Ill. Niklas Elmehed. © Nobel Media

European Commission

ESAC opinion

2. Nonanimal-derived antibodies offer significant additional scientific benefits

- Knowledge of the sequence provides a unique identifier as well as unlimited and sustainable supply, which will improve experimental reproducibility
- Phage display technology allows the guided selection of essential properties, such as specificity, compatibility to certain assay conditions, cross-reactivities, stability or affinity

ESAC opinion

3. There is a need to promote accessibility to nonanimal-derived antibodies within the research, diagnostic and regulatory communities

- Most key patents have expired
- Similar cost to generate nonanimal-derived recombinant reagents as animal-derived mAbs
- Lack of awareness leads to scientific misconceptions: Education is needed!

ESAC unanimous conclusion

The experts conclude on the scientific evidence that **nonanimal-derived antibodies are able to replace animal derived antibodies in the vast majority of applications**. Moreover, well-characterised, recombinant affinity reagents **will improve the reproducibility of science** and positively impact society

European Commission

JRC Science for Policy Report

- **Awareness raising** and **dissemination of information**: availability, cost, scientific benefits
- **Education and training**: webinars, e-learning, hands-on training courses
- **Project authorisation**: use of animals to generate antibodies should be rejected or seriously challenged by authorising bodies
- **Review of EU funded projects**: new funding applications should not propose the use of animals for antibody generation (in the interst of ethical standards and quality of science)
- **Provision of funding** to fully **characterise affinity reagents** generated in EU- (and US NIH)-funded programmes

European Commission

Any questions?

You can find me at @JoaoFBarroso & Joao.BARROSO@ec.europa.eu

European Commission