Emerging voices in the evaluation of animal research:

Who decides, and who decides who decides?

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Locating the Animal Research Nexus in our work

- Animal research is a space of innovation in science and technology **and** innovation in forms of research governance, which can be studied by:
  - Understanding **entanglements** between animal research and governance historically
  - Developing **conversations** across biomedical research and its stakeholders today
  - Identifying **connections** to regulatory processes and opportunities for innovation
- We want to illustrate our approach with two stories and end with two questions

Focusing on decision-making practices

- Background of work in **multi-criteria and deliberative decision-making methodologies**
- Chair of the UK Animals in Science Committee **Review of Harm-Benefit Analysis** 2017
- AnNex work focuses on **patient representatives** who are reviewing research proposals that use animals
- Gorman RSPCA Fellowship explores the extension of the 3Rs to the **use of horseshoe crabs in endotoxin testing**

Two tales of Alzheimer's in mice

- ***Breakthrough***: end of ‘decades of failure’ and a step towards ‘a new era of drugs to treat Alzheimer's’ (BBC News, 2022)
- ***Hesitation***: The drug could only be given to people with early Alzheimer’s disease who had evidence of amyloid plaques from scans or spinal fluid analysis, excluding the 98% of people who were untested, many other types of dementia, and those in the later stages of disease
- With thanks to Richard Milne for his work on the history of and patient entanglements in dementia research

Alzheimer's drug lecanemab hailed as momentous breakthrough

30 November 2022

By James Gallagher
Health and science correspondent

The first drug to slow the destruction of the brain in Alzheimer's has been heralded as momentous.

The research breakthrough ends decades of failure and shows a new era of drugs to treat Alzheimer's - the most common form of dementia - is possible.

Yet the medicine, lecanemab, has only a small effect and its impact on people's daily lives is debated.

And the drug works in the early stages of the disease, so most would miss out without a revolution in spotting it.

Lecanemab attacks the sticky gunge - called beta amyloid - that builds up in the brains of people with Alzheimer's.

For a medical field littered with duds, despair and disappointment, some see these trial results as a triumphant turning point.

Alzheimer's Research UK said the findings were "momentous".

Focusing on the amyloid cascade hypothesis

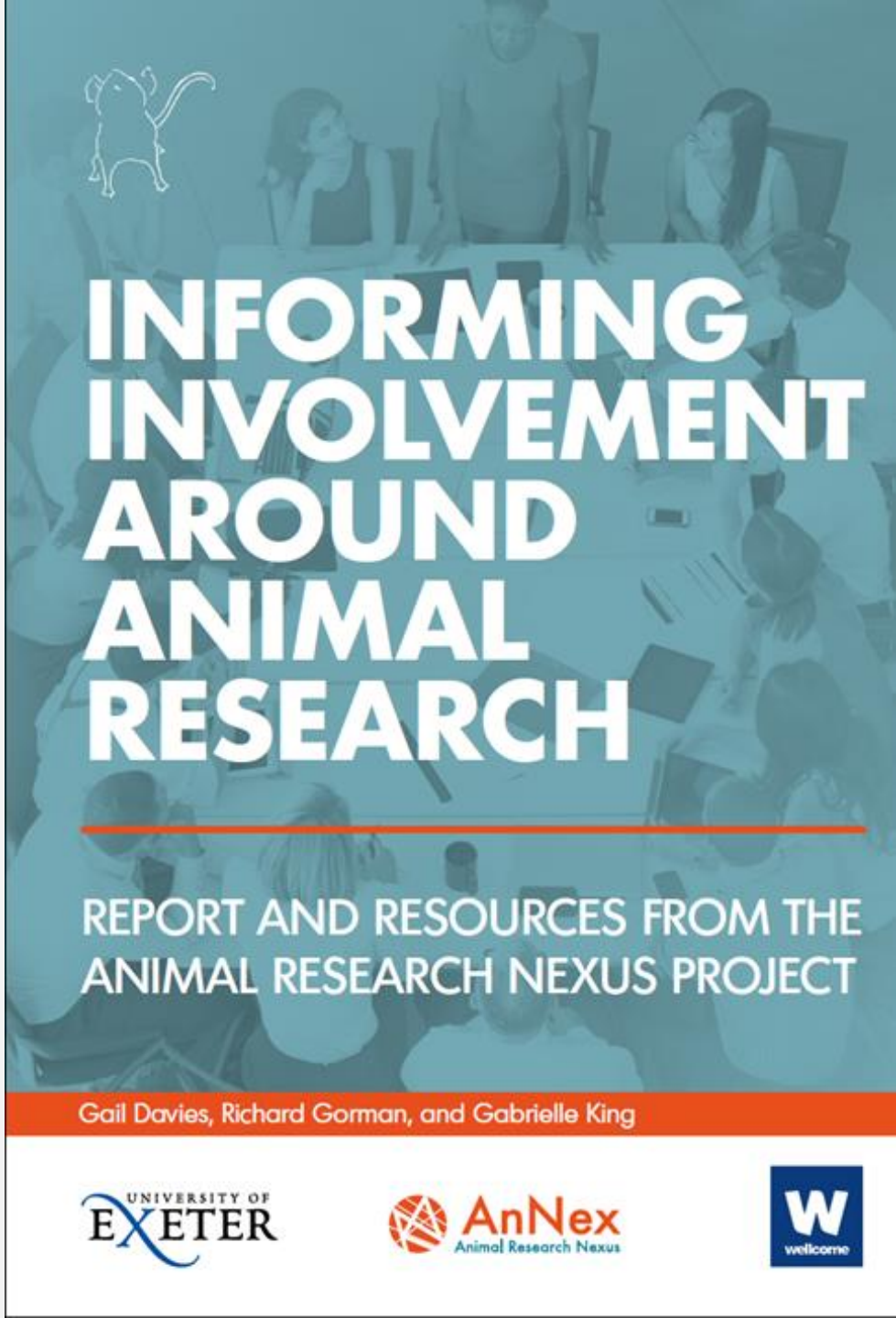
- By the 1980s, Alzheimer's disease settled on a '**theory-methods' package**, combining the techniques of molecular biology and the theory of disease causation known as the 'amyloid cascade hypothesis' (ACH)
- By 2012, 'we can cure amyloidosis in transgenic mice with hundreds of compounds', there are no '**animal models** of a neurological or psychiatric disease that are faithful to the disease itself.' (Greenberg, 2012, p. 58)
- By 2020, the failure of drug trials has been integral to the redefinition of **diagnostic criteria** for Alzheimer's disease, establishing measures such as abnormal levels of beta-amyloid and tau proteins as biological markers of disease that precede cognitive and behavioural symptoms (Milne and Latimer 2020)

Opening up questions from patient perspectives

- **Translatability**: “What I think they should be researching is why does it work so well in a mouse and not translate into humans, instead of carrying on doing all the basic research they’re doing into tau and amyloid and all that sort of stuff […] I want to come back as a mouse! Then I know if I get Alzheimer's as a mouse, they’re going to cure me!” (Tabitha, interview 2018)
- **Equity**: “It’s trying not to just do a job where you're representing people with FTD but where you’ve got some awareness of all the dementias’ (Rachel, interview, 2018)
- **Balance**: ‘Because of our involvement as carers, we encouraged research, and the research programme, to be on the care side, not only medication based, or 100% the science and pathology of dementia. So over 10 or 15 years, we helped to balance it, to about 30% each of care, cure, and medicine, so these are all spread out.’ (Win, interview, 2018)

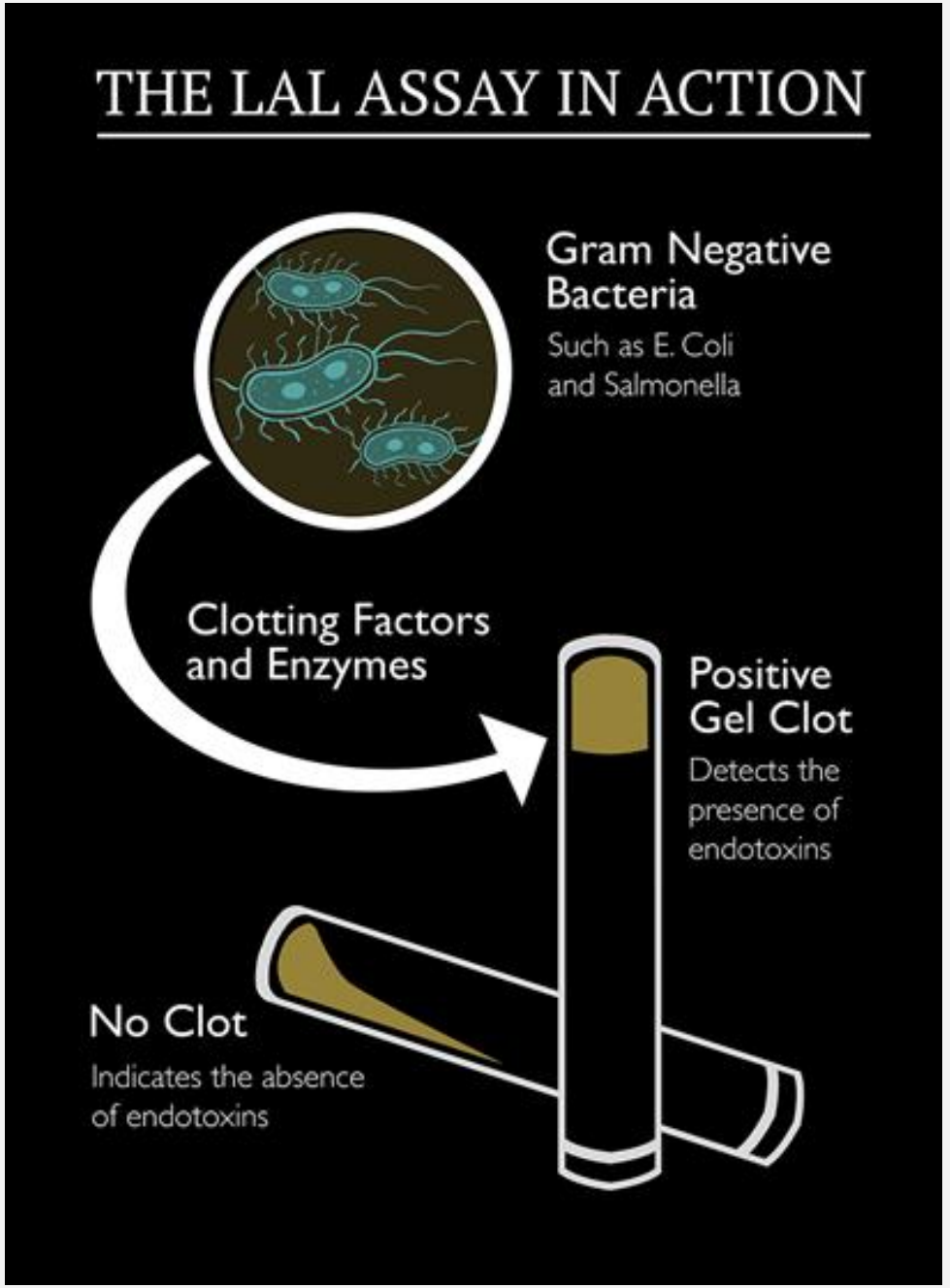
How can this work inform decision-making?

- Recognising that there are **two kinds of harm-benefit analysis** being enacted in two different contexts
- Acknowledging the **differently situated motivations** and languages through which these are carried out
- Exploring the forms of **dialogue that can connect them** and the different contributions they can make
- Locating these within the wider **'biomedical decision-making network**' (Caron-Flinterman, Broerse and Bunders, 2007)



Two stories of ‘replacement’ in endotoxin testing

- **Rabbit pyrogen test (1942 – present):** Adopted as a regulatory requirement by US Pharmacopeia in 1942
- **LAL test using horseshoe crab blood (1987 – present):** Potential identified 1960s. Draft guidelines published 1980. Regulatory use finalised 1987
- **Synthetic LAL replacement (2021 – present):** A synthetic substitute was introduced in 2001 and has been available commercially since 2003. European Pharmacopoeia guidance approved this as an alternative in 2021, but it remains an alternative non-pharmacopoeia test in the US



The invisibility of a ‘less of an animal test’

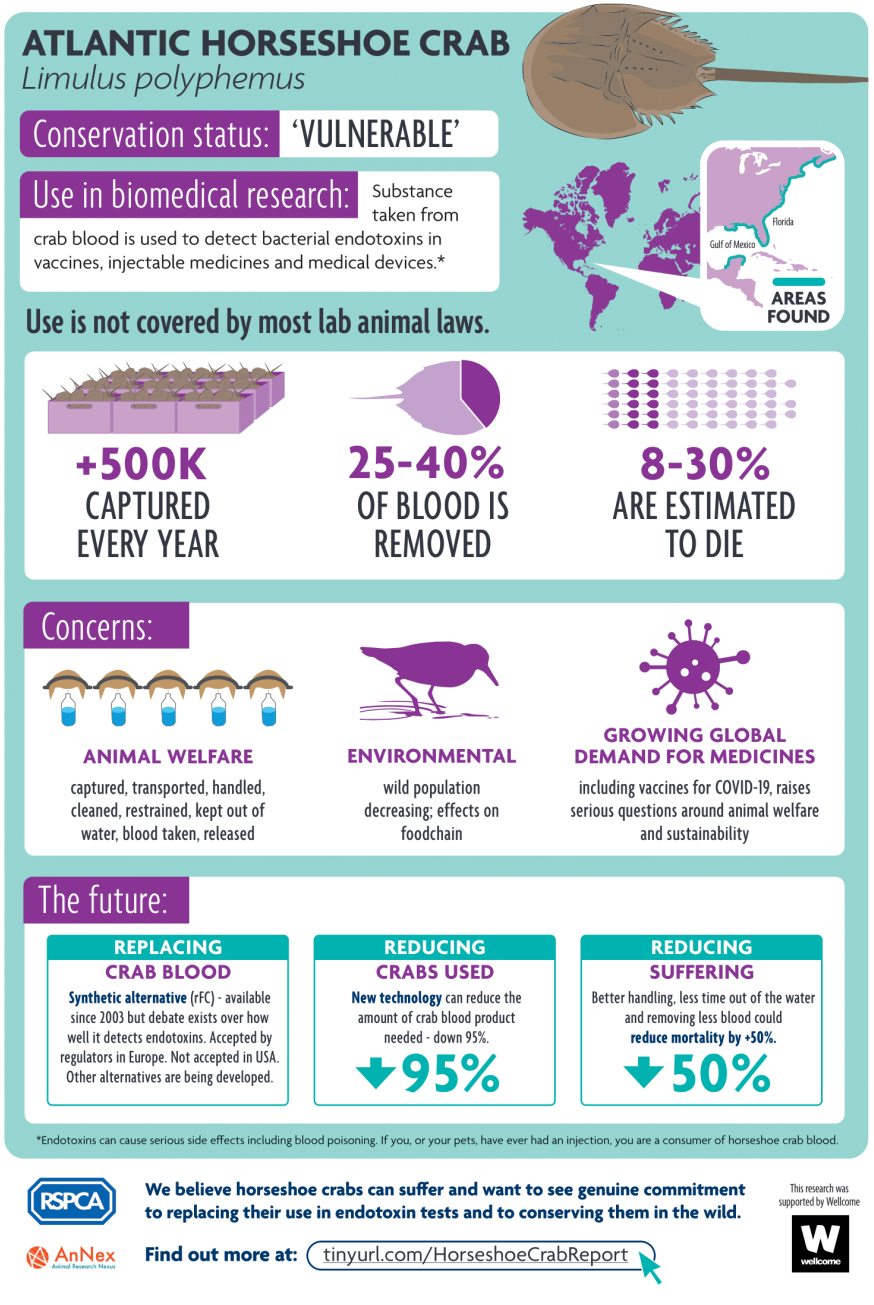
- “We knew obviously that the LAL test was a move away from the rabbit pyrogen test, that had been the requirement beforehand, so **it was seen as less of an animal test than perhaps the rabbit pyrogen test and other whole animal testing**.” (Interview, pharmaceutical sector, 2020)
- “I would say it’s probably not even irrational to say that **95% of the people using LAL don't know its origin** and that’s probably our fault for not educating them.” (Interview, biotechnology sector, 2020)
- “Since those horseshoe crabs are invertebrates and arthropods**, I guess the whole concept of pain and so on is not applied to them that much**. I guess just because they’re not as similar to us as other vertebrates.” (Interview, biotechnology sector, 2020)

An expanding circle of ethical concern

- “**Any responsible organization will go through a process of reducing, refining and replacing as part of its operational and strategic growth plans. The LAL industry is no different** and in fact is expected to be constantly getting better at doing this, hence waste is reduced, consumption is reduced and we can offer alternatives to customers.” (Interview, biotechnology sector, 2020)
- “**I think what’s been really good for the industry over the past few years is that the discussion is there on the table**, which it wasn’t prior to 2016, everyone was just sort of taking it for granted. There was a bit but it was just people went merrily on their way so I think it’s good that we’ve got the discussion on the table.” (Interview, pharmaceutical sector, 2020)

How can this work inform decision-making?

- The **3Rs in this context opens up a space of discussion**, even when animals are outside of regulation
- This helps drive the **identification of opportunities for replacement, reduction, and refinement**, including discussion of invertebrate suffering
- The application of **the 3Rs does not remove controversies**, but it starts to connect conversations about animal testing with ethical discussions around *in vitro* research and environmental conservation



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- Decision support techniques for animal research like Harm-Benefit Analysis and the 3Rs are **flexible technologies for ethical governance** that can be adapted to new contexts and purposes
- As social scientists we are interested in how this **flexibility can be used to facilitate dialogue and knowledge exchange across different settings**
- Power to affect change **is materially shaped by research trajectories, as well as framed discursively by the way that power is distributed in conversations** and connected to decision-making processes

Selected references and resources

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