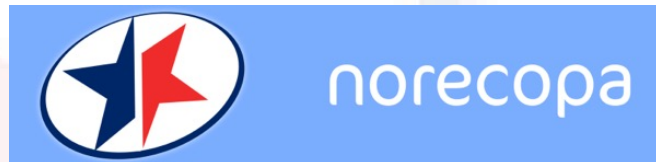


Replacement of animal models in biosciences with non-animal alternatives

[*norecopa.no/Newcastle*](http://norecopa.no/Newcastle)

Adrian Smith

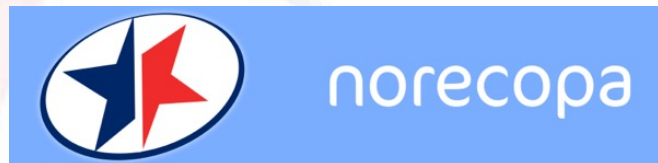
[*adrian.smith@norecopa.no*](mailto:adrian.smith@norecopa.no)



Norecopa: PREPARE for better Science

Norecopa

Norway's National Consensus Platform for the
Three Rs: Replacement, Reduction and Refinement
and a source of global 3R resources



<https://norecopa.no>

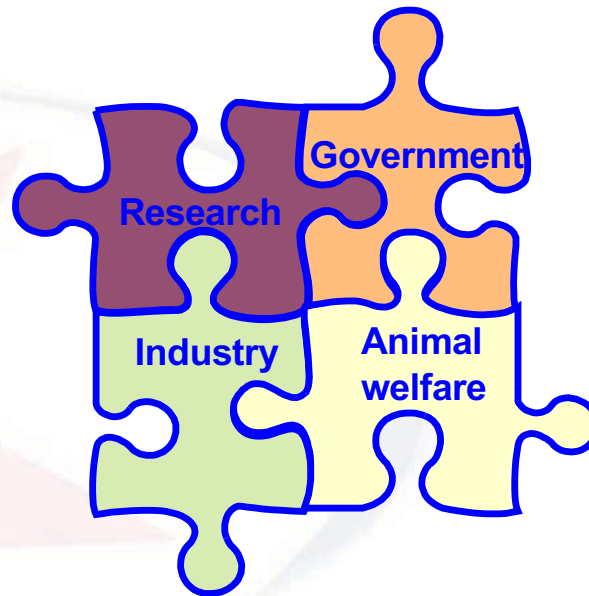
Norecopa: PREPARE for better Science

European Consensus-Platform for Alternatives

ecopa.eu



- Established in 2000
- Recognises National **Consensus Platforms** (NCPs) with 4 stakeholders equally represented:



norecopa.no : an updated overview of global 3R resources



The screenshot shows the norecopa.no website interface. The header features the norecopa logo and navigation links: About Norecopa, Alternatives, Databases & Guidelines, Education & training, Legislation, Meetings, More resources, News, and PREPARE. Below the header is a grid of resource categories including Anaesthesia and analgesia, Animal facilities, Animal welfare organisations, Blood sampling, Culture of, Email discussion lists, Environmental enrichment, Ethics, Experimental design and reporting, Harm-Ben, Health and safety, Health monitoring, Humane endpoints, Humane killing, Journals, Literature searches and systematic reviews, Organisations, Reporting guidelines, and Severity classification. A breadcrumb trail indicates the current page: norecopa.no / More resources / Experimental design and reporting. A sidebar on the right contains search filters: Order by (Relevance), Typo tolerance (Default), Database (3R Guide database (403), Classic AVs database (118), European Commission Inventory of 3Rs Education & Training Resources (567), European Commission Inventory of 3Rs Knowledge Sources (807), European Commission Inventory of NAMs for Respiratory tract diseases (280), NAL records (1688), NORINA database (3141), TextBase database (1501), Website (761)), Browse the databases (eBooks (286), Free (199), Held at NMBU Oslo (contact Kristine Hansen, 67 23 21 89) (431), Key products (68), On loan (6), Reviewed (85)), and Search in the databases (All Text, Title, Author, Publisher, Supplier, Record Number).

- ✓ approx. 9,000 webpages organised as a database with an intelligent search engine tuned to LAS
- ✓ 300,000 hits annually
- ✓ 7-8 detailed newsletters per year

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NORSK ENGLISH

Search:

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[Fish 2005](#) | [Wildlife 2008](#) | [Fish 2009](#) | [Agricultural animals 2012](#) | [Field research 2017](#) | [Past meetings](#) | [Meetings Calendar](#) | [An informal guide to arranging a scientific meeting](#) | [Presentations](#)

norecopa.no / [Meetings](#) / [Meetings Calendar](#)

norecopa.no/meetings/meetings-calendar

Webinar and Meetings calendar

May 2021

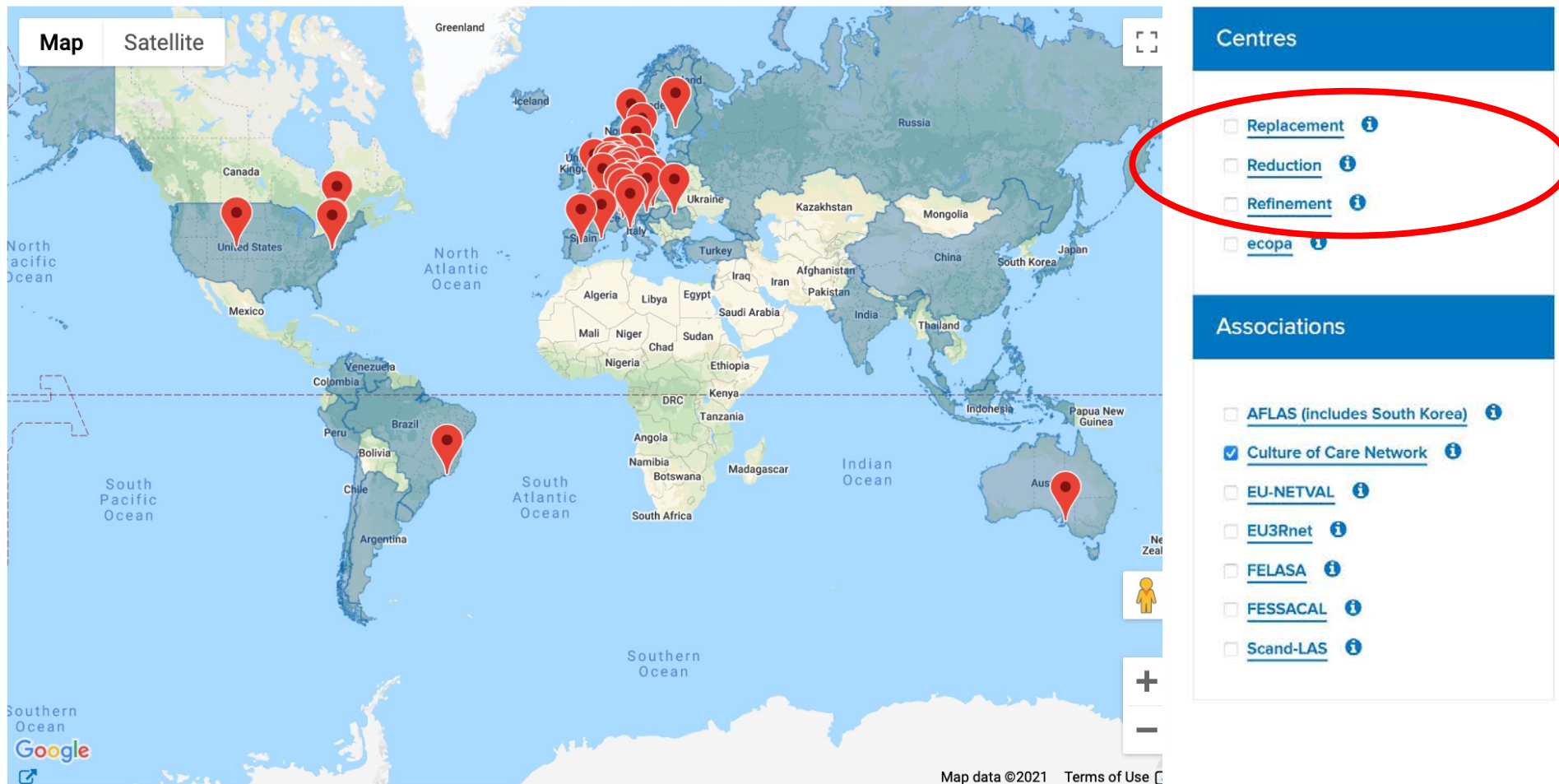
- > [SETAC Europe 31st Annual Meeting](#), online, 3-6 May 2021
- > [Laboratory Animal Science course](#), Porto, 3-14 May 2021
- > [Kick-off meeting, 3R Centre Network in Baden-Württemberg](#) (online meeting in German), 4 May 2021
- > [Avoid Allergies and Infections when Working with Laboratory Animals](#), online course, 5 May 2021
- > [Nordic 3R webinar series](#), 5-6 May 2021
- > [Meeting the Requirements of the US Animal Welfare Act](#), webinar, 6 May 2021
- > [Skin Sensitization](#), Hamburg, 6-7 May 2021
- > [Swedish 3R Center Workshop: Replace strategy and networking activities](#), 10 May 2021
- > [Animal Research: Critical, Challenging & Creative Thinking Course](#), 10-13 May 2021
- > [Dirty or clean mice - What is better for research?](#) Webinar (André Bleich), 11 May 2021
- > [Poultry in biomedical research](#), 6th Meeting of LASA Large Animal Research Network (LARN), 11 May 2021
- > [3rd Pan-American Conference for Alternative Methods](#), Windsor, 12-14 May 2021

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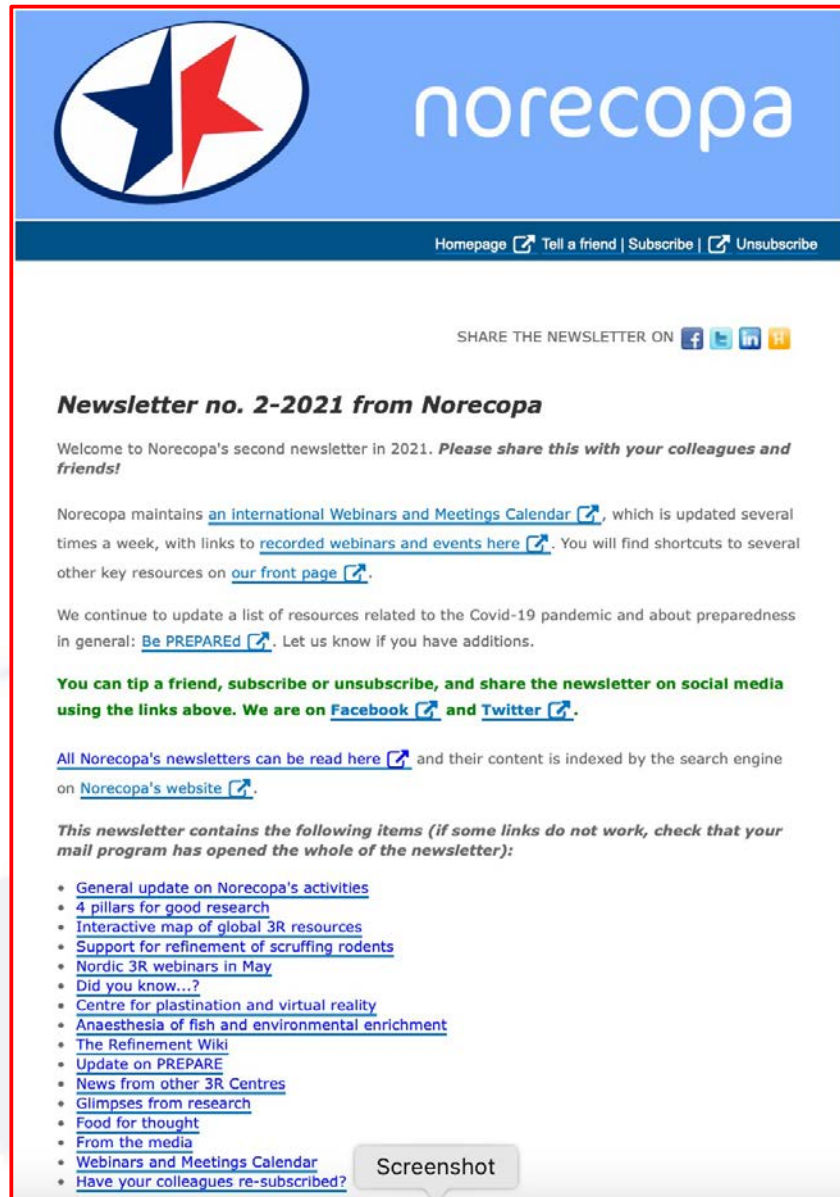
A global map of 3R centres and associations/networks




norecopa.no/global3R



NORECOPA: PÅRBEIÐE FOR BETTER SCIENCE



The screenshot shows the top of a newsletter page. At the top left is the Norecopa logo, which consists of a blue and red star inside a white oval. To the right of the logo is the word "norecopa" in a white, lowercase, sans-serif font. Below the logo and name is a dark blue navigation bar with white text: "Homepage", "Tell a friend", "Subscribe", and "Unsubscribe", each with a small icon. Below the navigation bar is a white section with the text "SHARE THE NEWSLETTER ON" followed by icons for Facebook, Twitter, LinkedIn, and YouTube. The main content area has a heading "Newsletter no. 2-2021 from Norecopa" and a welcome message. It includes several paragraphs of text with hyperlinks to various resources. At the bottom, there is a list of items contained in the newsletter, each with a bullet point and a link. A "Screenshot" label is visible in the bottom right corner of the image.

 norecopa

Homepage [Tell a friend](#) | [Subscribe](#) | [Unsubscribe](#)

SHARE THE NEWSLETTER ON [f](#) [t](#) [in](#) [yt](#)

Newsletter no. 2-2021 from Norecopa

Welcome to Norecopa's second newsletter in 2021. *Please share this with your colleagues and friends!*

Norecopa maintains [an international Webinars and Meetings Calendar](#), which is updated several times a week, with links to [recorded webinars and events here](#). You will find shortcuts to several other key resources on [our front page](#).

We continue to update a list of resources related to the Covid-19 pandemic and about preparedness in general: [Be PREPAREd](#). Let us know if you have additions.

You can tip a friend, subscribe or unsubscribe, and share the newsletter on social media using the links above. We are on [Facebook](#) and [Twitter](#).

All Norecopa's newsletters can be read [here](#) and their content is indexed by the search engine on [Norecopa's website](#).

This newsletter contains the following items (if some links do not work, check that your mail program has opened the whole of the newsletter):

- [General update on Norecopa's activities](#)
- [4 pillars for good research](#)
- [Interactive map of global 3R resources](#)
- [Support for refinement of scruffing rodents](#)
- [Nordic 3R webinars in May](#)
- [Did you know...?](#)
- [Centre for plastination and virtual reality](#)
- [Anaesthesia of fish and environmental enrichment](#)
- [The Refinement Wiki](#)
- [Update on PREPARE](#)
- [News from other 3R Centres](#)
- [Glimpses from research](#)
- [Food for thought](#)
- [From the media](#)
- [Webinars and Meetings Calendar](#)
- [Have your colleagues re-subscribed?](#)

Screenshot

English-language newsletters

norecopa.no/news/newsletters

7-8 times a year

nearly 1,000 international subscribers

What do we mean by Replacement?

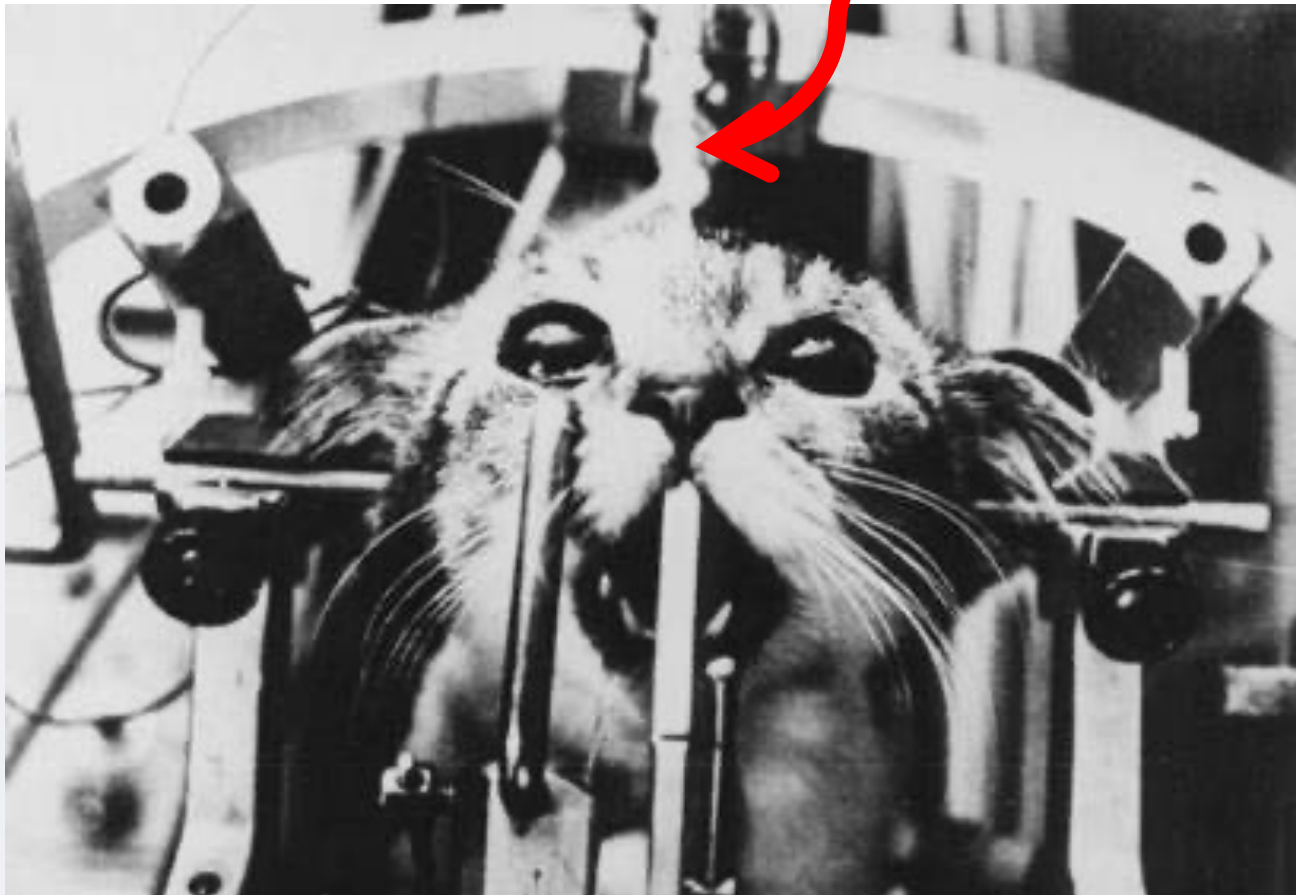
Russell and Burch (1959):

'The substitution for conscious living higher animals of insentient material.'



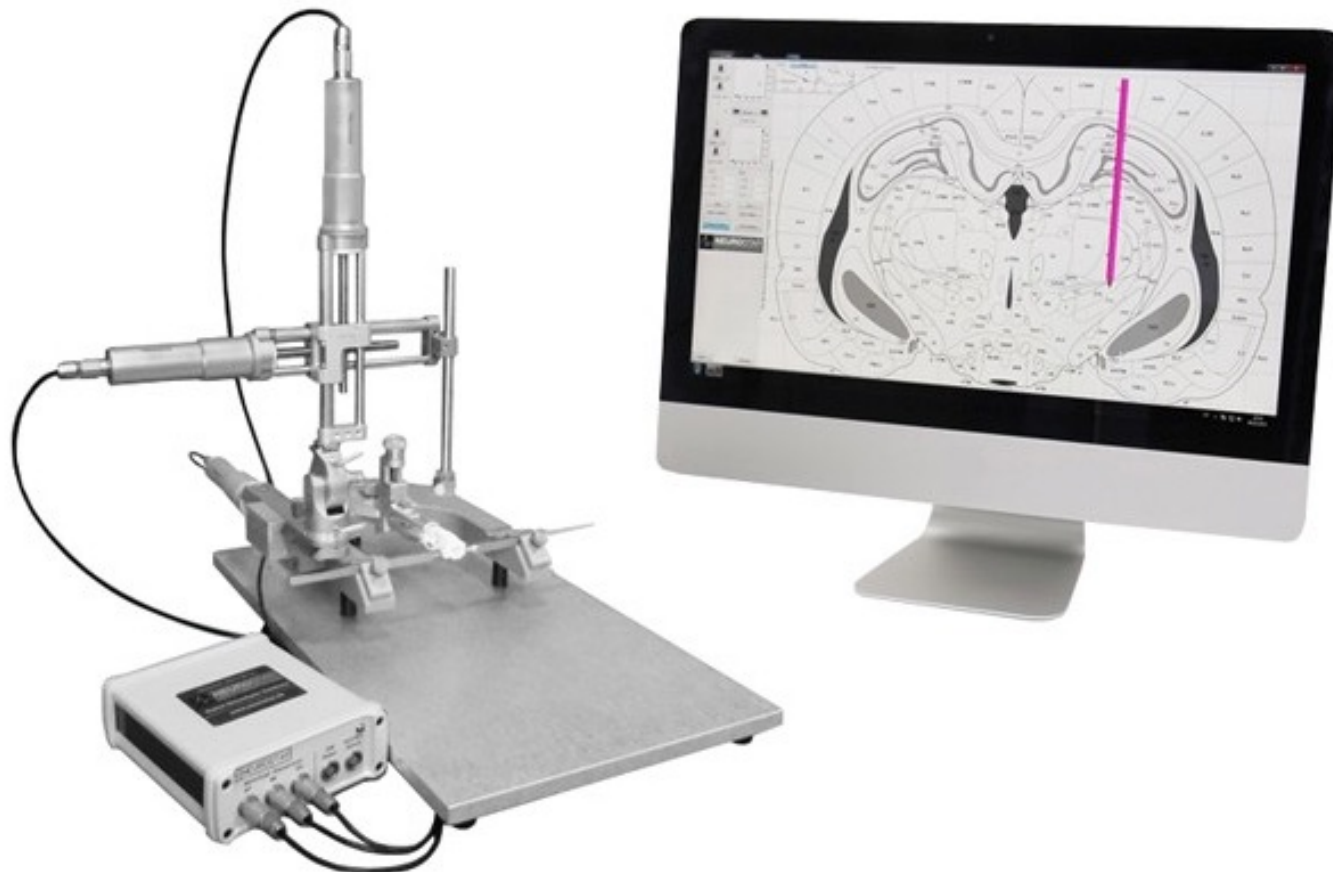
Appearances can be misleading

Brain electrode



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<http://www.all-creatures.org/anex/cat-res-07.html>



<http://www.agnthos.se/stereotaxic-equipment/stereotaxic-frames/model-900-motorized/small-animal-stereotaxic-instrument-motorized.html>

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Russell and Burch (1959):

'The substitution for conscious living higher animals of insentient material.'

Contemporary definition:

Methods which permit a given purpose to be achieved without conducting procedures on animals.

NC3Rs:

	Standard	Contemporary
Replacement	Methods which avoid or replace the use of animals	Accelerating the development and use of models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals

<https://norecopa.no/alternatives/the-three-rs>

Full Replacement:

No use of any research animals

Partial Replacement:

Use of animals not considered to be sentient

e.g. immature vertebrates

Cells or tissue taken from animals killed solely for that purpose and without any prior treatment

Fruit flies, worms

Neither fish nor cephalopods (octopus) are an alternative to mammals! (nor are decapod crustaceans in some countries)

- What is an alternative, and what types do we have?
- Where and how do we find information about them?
- What can we do about it?
- Alternatives to bad experiments

What is an alternative?

A method without the use of animals that gives the same answers as an animal experiment.

Are these alternatives?

- Cell cultures
- Use of bacteria to test carcinogenicity
- Chemical analysis of biologically active compounds

The potential for using alternatives

Basic research: + / -

Toxicological research ++

Education & training +++ (very dependent upon objectives)

Production and testing +++++

1) Replacement alternatives – in the broadest sense

Computer simulations
Films, video, virtual reality
Models, manikins, simulators, robots
QSAR (Quantitative Analysis of Structure/Activity Relationships)
Cell and tissue cultures, organoids, organ perfusion
 High Throughput Screening (HTS), organs-on-a-chip
Biochemical & immunological methods (RIA, ELISA)
Hybrid DNA technique, Genetically altered microorganisms
Trials on “lower” organisms, including plants
Acute experiments (terminal anaesthesia)
Trials on dead animals (ethically sourced cadavers, slaughterhouse material)
Observation of animals in their natural setting or a brief period of captivity
Animals in need of clinical veterinary care
Research animals that will be used anyway
Surplus breeders from lab animal suppliers
Trials on humans (microdosing and medical imaging)
Synthesis of new evidence from experiments that have already been
 performed
Replacement with a theoretical session

Home

ARTICLES

THE RAPID RAT TEST FOR PREGNANCY: THE OVARIAN HYPEREMIA RESPONSE AS A ROUTINE DIAGNOSTIC PROCEDURE*

GARDNER M. RILEY, Ph.D., MARJORIE H. SMITH, B.S. and PEARL BROWN, B.A.

Author Affiliations

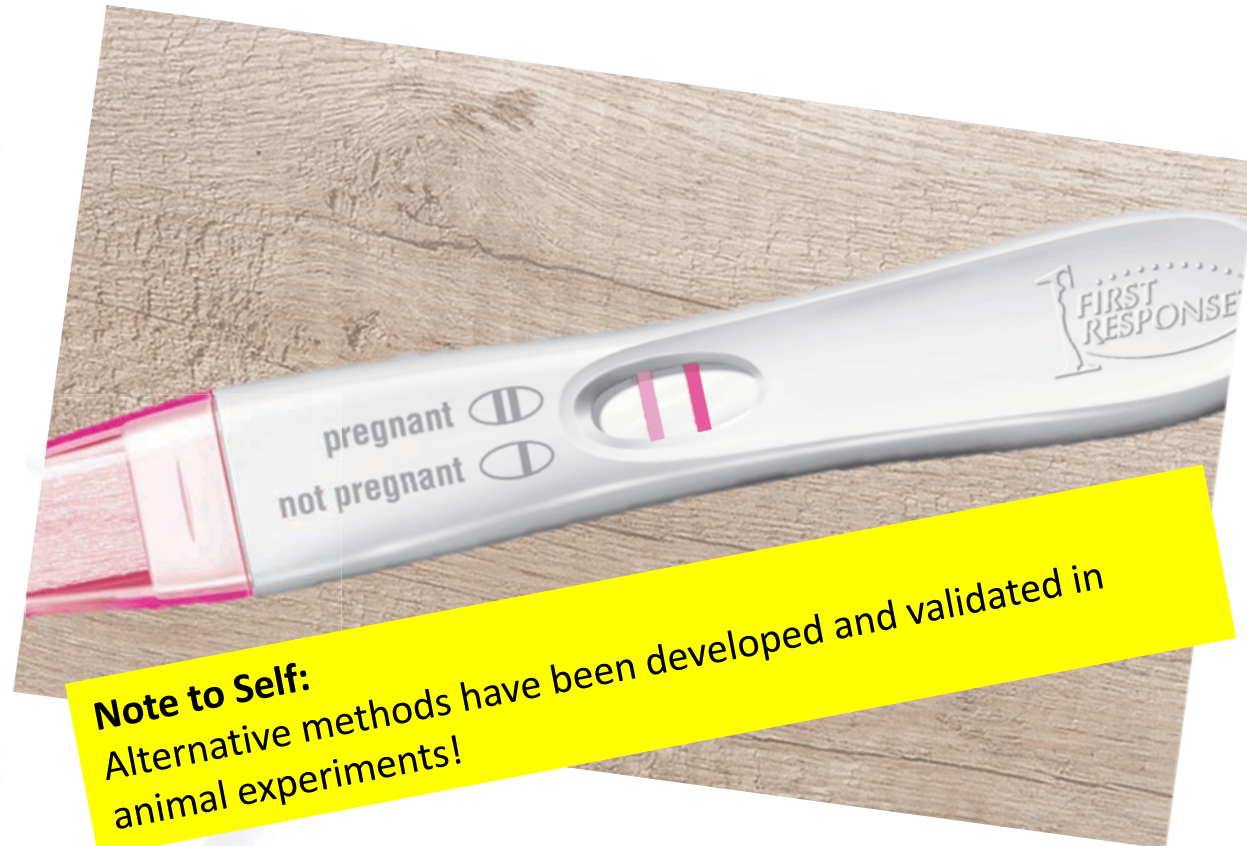
Department of Obstetrics and Gynecology, University of Michigan Medical School Ann Arbor, Michigan

Excerpt

SEVERAL authors have described rapid tests for pregnancy based on the hyperemic response of the immature rat ovary to pregnancy urine gonadotropin. Salmon and associates (1) observed that ovarian hyperemia was produced within six hours following a subcutaneous injection of pregnancy urine and suggested this as a test for pregnancy. Kupperman, Greenblatt and Noback (2) reported that the duration of the test could be reduced to two hours provided the urine was injected intraperitoneally.

The accuracy of the two-hour test (excluding observations in ectopicpregnancy) has recently been reported by Kupperman and Greenblatt (3) to be 99.5 per cent in a total of 752 tests. Bunde (4) using either the twohour test with intraperitoneal injections or the six-hour test with subcutaneous injections, obtained an accuracy of only 84.5 per cent in 108 tests. A test developed by Zondek, Sulman and Black (5) consists of two subcutaneous injections of pregnancy urine at an interval of one hour. The accuracy of this test was 69 per cent at two hours, 92.2 per cent at six hours and 99 per cent at twenty-four hours.

Screenshot



Note to Self:
Alternative methods have been developed and validated in
animal experiments!

The long and winding road to replacement...



The Mouse Bioassay for shellfish toxins

- International regulations
- Costs
- Validation and detection
- of novel toxins



Choose your objectives!

You can't decide whether or not there is an alternative until you know the aim of the experiment.

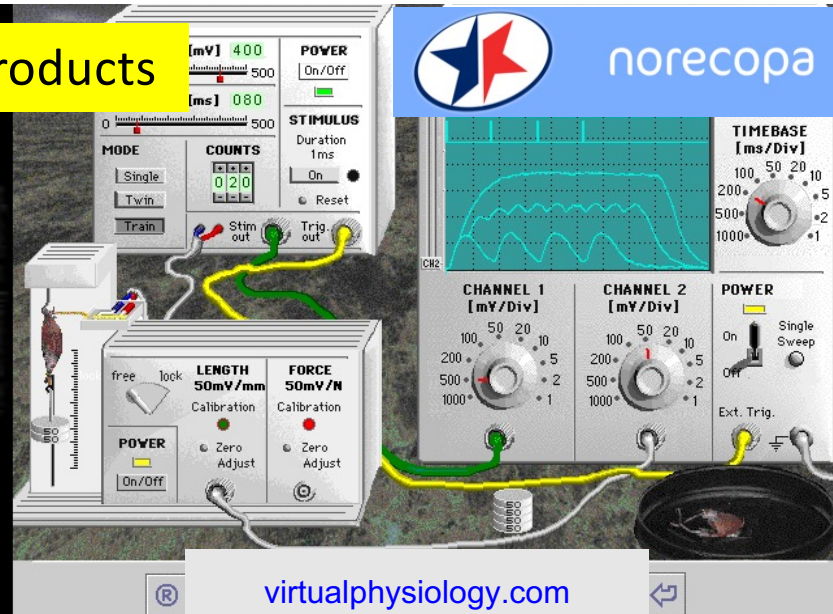
An example: animal use in education and training

- Teaching and practising:
 - laboratory skills
 - general animal handling skills
 - preparation-specific animal skills
- imparting good ethical thinking
- new knowledge and reinforcing existing
- data handling skills
- experimental design skills
- communication skills (oral, written)
- group work
- staff-student interaction

NORINA database: approx. 3,000 products



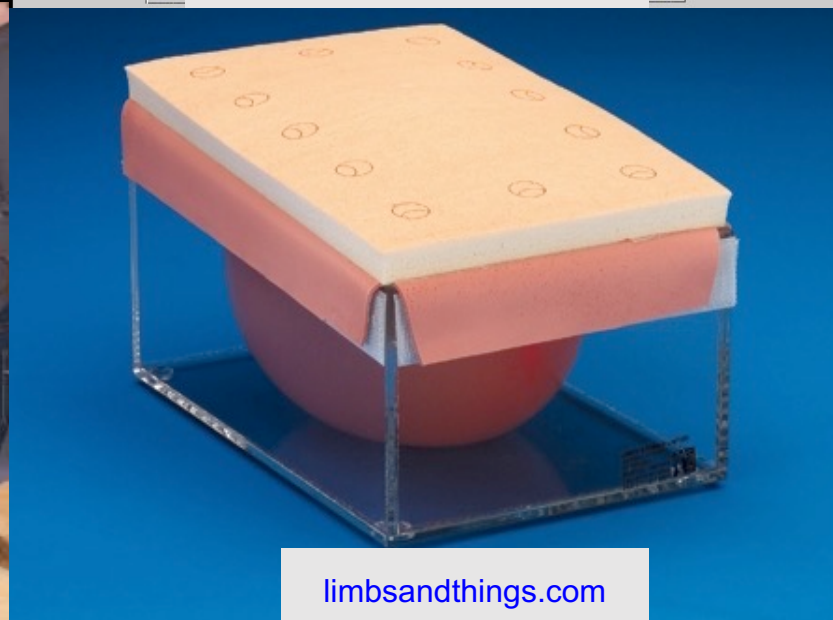
3dglasshorse.com



virtualphysiology.com



rescuecritters.com



limbsandthings.com



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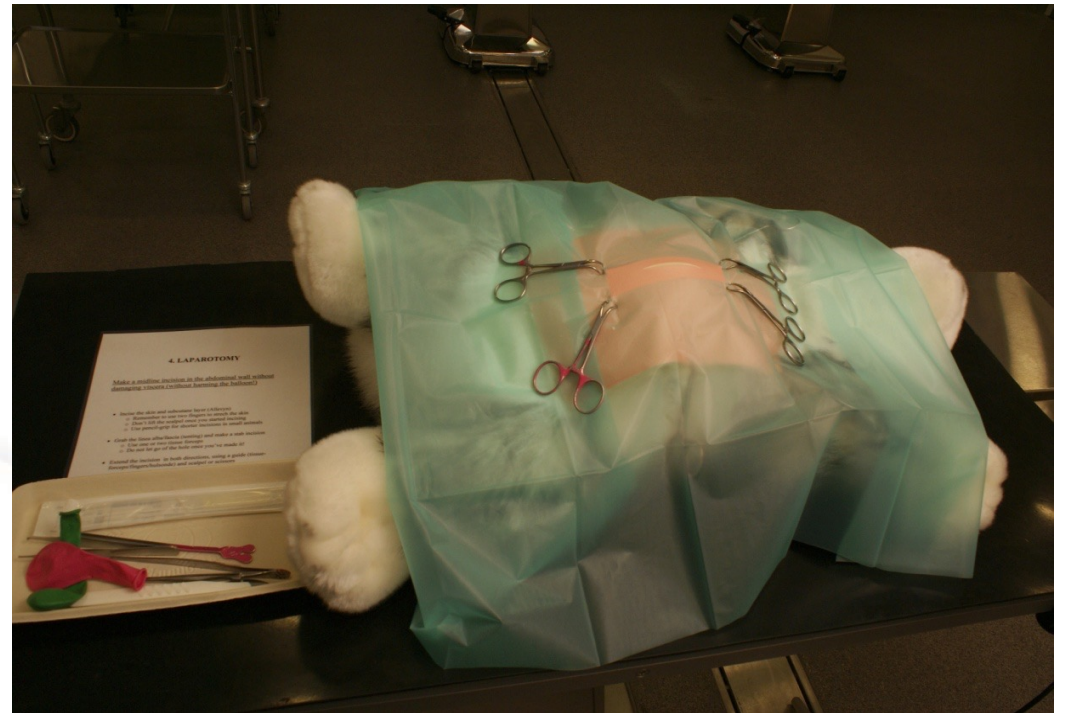
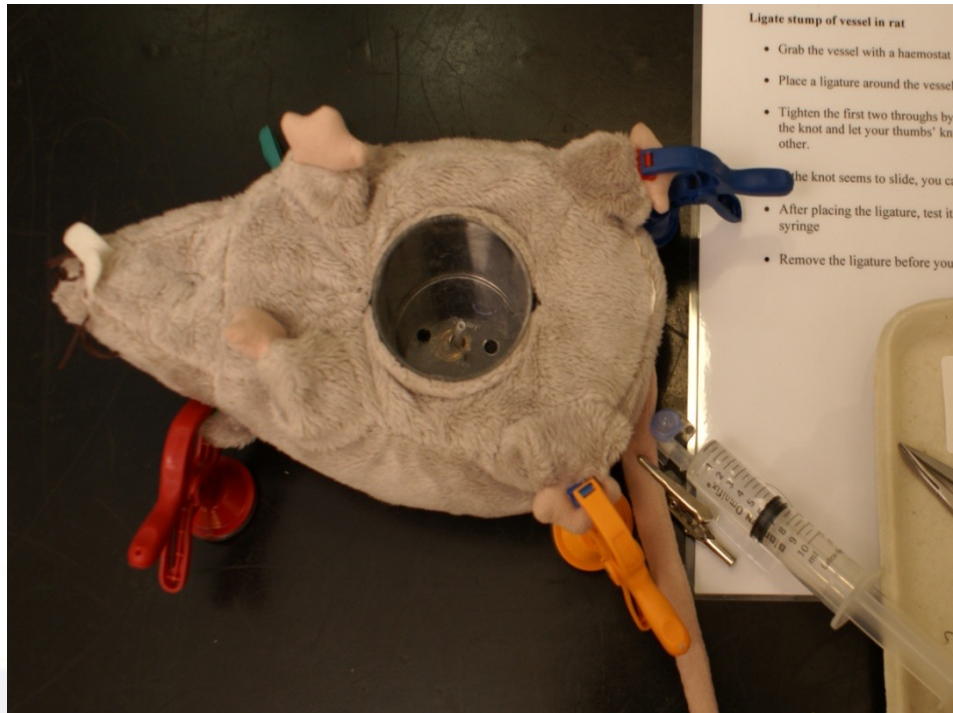
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Rikke Langebæk, University of Copenhagen



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Rikke Langebæk, University of Copenhagen



<https://norecopa.no/education-training/homemade-educational-materials>

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'We may need the animals, as it were, on the night; but the machines will do very well at rehearsals'

"Alternatives" may be too poor to replace animals totally, but may be excellent as briefing or debriefing aids.

*Learning new information **without animal experiments** by Synthesis of Evidence:*

Systematic Reviews of ones that have already been published!

Radboudumc

Systematic Review Center for Laboratory animal
Experimentation
SYRCLE

Systematic Reviews and Synthesis of Evidence



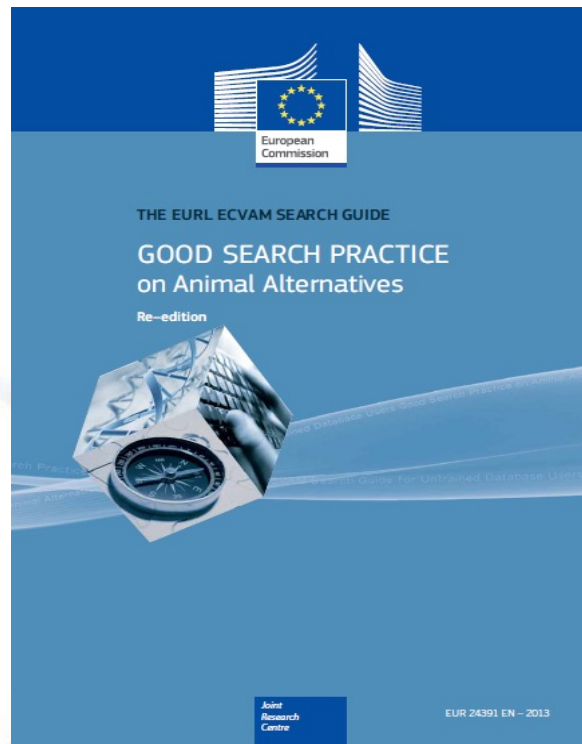
Why is 3R literature hard to find?

- Bibliographic databases are often not used adequately (poor overlapping between the databases)
- Too few scientists are aware of the specialist 3R-databases
- Scientists rarely use "3R" words when they write titles/abstracts/keywords for their papers
- Databases rarely flag 3R-papers with explicit thesaurus terms
- We have no single "Journal of Alternatives"

The EURL ECVAM Search Guide

Can be ordered free of charge from

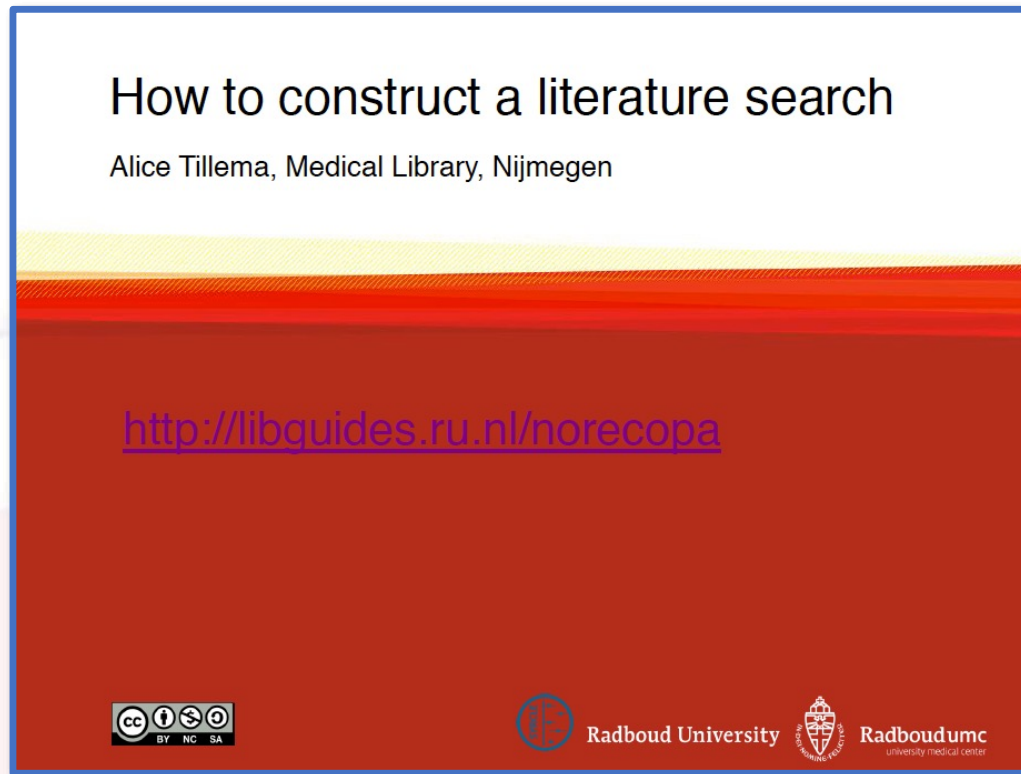
bookshop.europa.eu



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Alice Tillema, Radboud University

<http://norecopa.no/how-to-construct-a-literature-search.pdf>



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Perspective | Open Access | Published: 10 January 2017

A manifesto for reproducible science

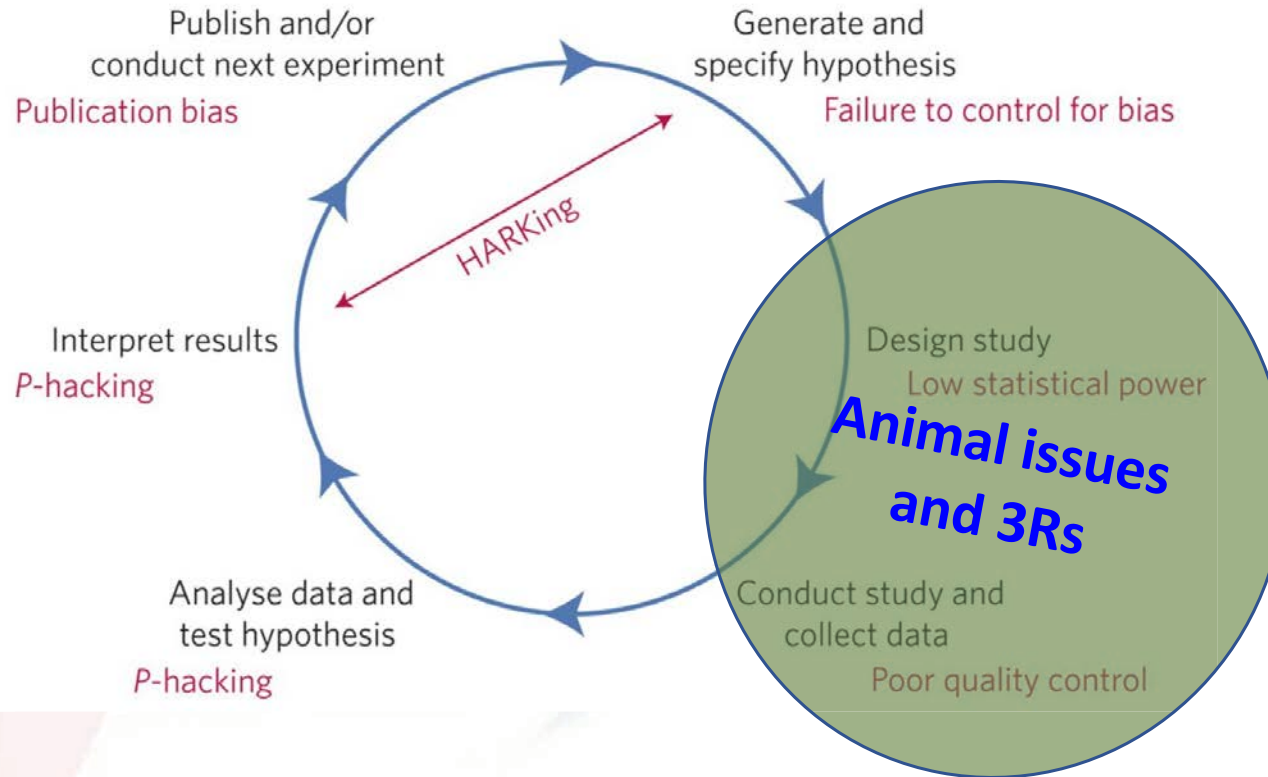
Marcus R. Munafò , Brian A. No-
Button, Christopher D. Chambers,
Jan Wagenmakers, Jennifer J. Wa

Nature Human Behaviour 1, Artic

33k Accesses | 518 Citations |

Figure 1: Threats to reproducible science.

From: A manifesto for reproducible science





Refinement

Reduction

Replacement

Lab animal community -///- Statisticians -///- *In vitro* experts

EU Directive 2010/63

Article 38:

- The project is justified from a scientific or educational point of view or required by law;
- The purposes of the project justify the use of animals;

Article 33 - Non-technical summaries:

Demonstration of **compliance with the requirement** of replacement, reduction and refinement.

Recital no. 10:

This Directive represents an important step towards achieving **the final goal of full replacement** of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so.



<https://publications.jrc.ec.europa.eu/repository/handle/JRC120199>



<https://www.eara.eu/post/eara-efpia-response-to-antibody-recommendation>

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Summary of key points:

- Animal-derived antibodies have unique properties, being based on the immune systems of humans and animals.
- Non-animal-derived antibody technologies still cannot recapitulate many of the properties which make animal-derived antibodies so useful.
- The vast majority of approved therapeutic antibodies are from animal-derived origin.
- In COVID-19 research, we have seen the benefits of animal-derived antibodies which have played a key role in potential therapeutic development and will be essential in the large-scale production of approved therapeutics which counter coronavirus infections.
- Animal health and veterinary medicine requires development of antibodies suitable for a vast range of animal species, which currently is not possible with non-animal-derived methods.
- Restricting the use of animal-derived antibodies would have implications for the competitive nature of EU research, and access of European patients to the best medicines.

https://230099ef-af46-4cc6-b2be-415f0041b55e.usfiles.com/ugd/230099_55a2f8cd94c644eaa699989849b00723.pdf



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FAQs

Frequently asked questions

**EURL ECVAM Recommendation
on Non-Animal-Derived
Antibodies**

<https://ec.europa.eu/jrc/en/science-update/answering-your-questions-about-non-animal-derived-antibodies>

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'The Recommendation does not impose a ban on the use of animals for the development and production of antibodies. Instead, it simply calls for proper adherence to the legal obligations adopted under Directive 2010/63/EU...

This relates in particular to the evaluation process carried out by competent authorities in Member State and the need for **case-by-case scrutiny of project proposals** to ensure that the use of live animals for developing or producing antibodies is scientifically justified.

According to Maurice Whelan, *"It's important to us that people and organisations with an interest in this area take this opportunity to not only appreciate better what's actually said in the ESAC Opinion and our Recommendation, but also to gain a better practical understanding of Directive 2010/63, and the many scientific benefits offered by non-animal alternatives".*'

<https://ec.europa.eu/jrc/en/science-update/answering-your-questions-about-non-animal-derived-antibodies>



Biosciences Institute

Research Impact

Our research generates scientific impact through the creation of a collaborative and multi-disciplinary research environment.



PLOS BLOGS

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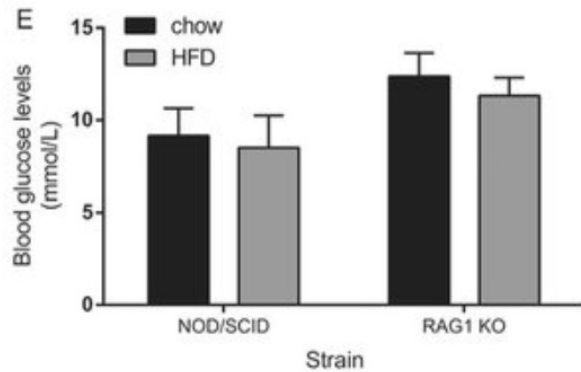
Collaboration on the road to better preclinical research

October 6, 2020 / PLoS ONE Guest Blogger / Guest Post



<https://everyone.plos.org/2020/10/06/prepare>

The scientist



The mouse

Breeding

New social groups

Transportation

Acclimatisation to research facility

Allocation to experimental group

Adaptation to new diet

Handling and immobilisation

Blood samples

often also:

injections, gavaging, surgery

pain and distress

developing illness and death



NASA



cbsnews.com



no.wikipedia.org

- Complex machines/animals create *known or unknown unknown interactions*
- **Design weaknesses** (*which the engineers knew about!*)
- **External pressure to launch** (political, media) - "Publish or perish"
- **Management decisions** (pushing the safety envelope):
"We've got away with it before" / "We've managed to publish this before"
- **A combination of many factors, each of which may appear insignificant**
- **until they occur simultaneously**

We need a Culture of Care!



"because we've always done it that way"

"as often as necessary"

"there are no alternatives"

Shouldn't we as scientists be open for novel methods...?

Closely related to a culture of care is the concept of a **Culture of Challenge** (Louhimies, 2015).

Look for the acceptable, rather than choosing the accepted.



<https://medium.com/the-composite/in-defence-of-the-emperors-new-clothes-dd23b1c04455>

Communication and the Culture of Care

Penny Hawkins, RSPCA Research Animals Department
on behalf of the International Culture of Care Network*

Effective two-way communication between scientists and animal technologists is essential for a good Culture of Care
The European Commission suggests the 'development of formal and informal communication channels, for mutual benefit with respect to science and animal welfare'
Here are some examples from International Culture of Care network members

Regular meetings

Scheduled meetings for scientists, animal technologists, vets, unit managers and AWERB members



Regular refresher/update meetings for all organised by NTCO



Special events

Duo-talks: researcher talks about their science, and animal technologists talk about techniques and animal care within the project



ELH organises an **informal meeting** for all, in which anyone can raise welfare issues



Building communication into existing processes

Each study has a **pre-start** and **wash-up** meeting involving everybody



Three Rs improvements **reported to AWERB & shared** at external user meetings



Other ideas

A **'boxless' event:** anyone can submit 'out of the box' ideas to improve practice



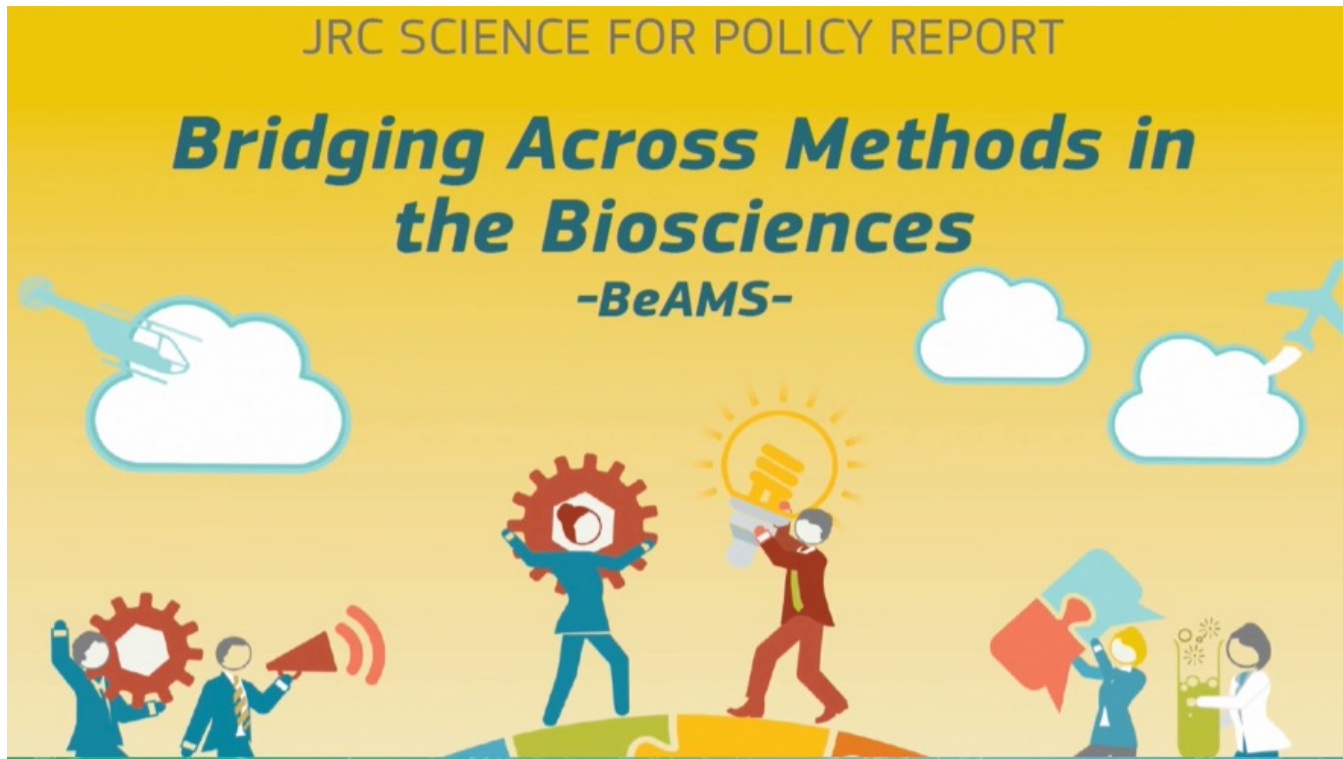
A **staff survey** for all e.g. how much do you agree with statements such as *'in our group we listen to each others' ideas about animal welfare'*




The International Culture of Care Network

A Quick Start Guide and more resources

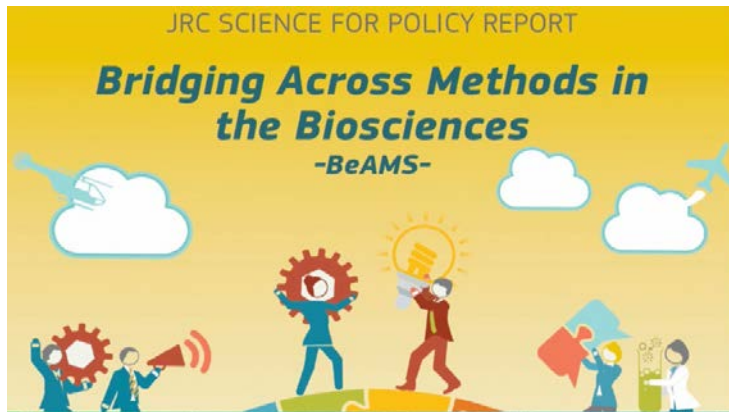
norecopa.no/CoC



ec.europa.eu/jrc/en/news/bridging-silos-biosciences

'Compartmentalisation within biosciences is limiting the potential for new methods to translate from one domain to another.'

This may be a challenge for scientists used to humanising animal models in basic research



'Take Alzheimer's disease for example. There are only 5 drugs approved for treating it, and these only offer minimal benefits in some patients, without any improvement in long-term prognosis.

And to make matters worse, this disease has the highest failure rate in drug development (over 99%) with no new drug appearing in the last 10 years.

Often the type of scientific method used by an investigator, for example based on an animal model (in vivo), a cell-based assay (in vitro) or a computer simulation (in silico), strongly influences the way in which research problems are both formulated and addressed.'



Biosciences Institute

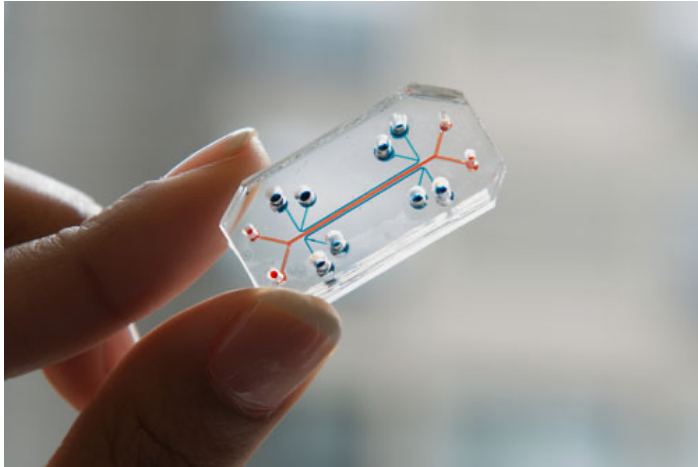
“ Our vision is to unravel basic biological processes and solve major biomedical challenges, generating knowledge that is vital to human health and the next generation of clinical therapies. ”

Professor Joris Veltman, Biosciences Institute Dean

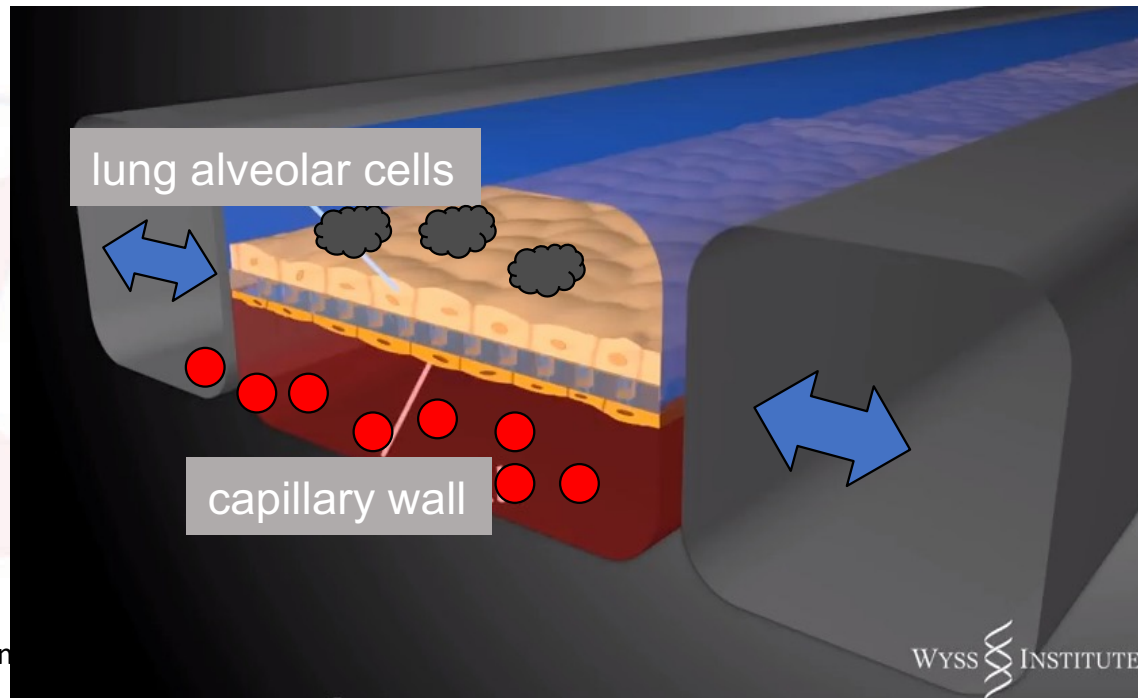


A paradigm shift is underway:

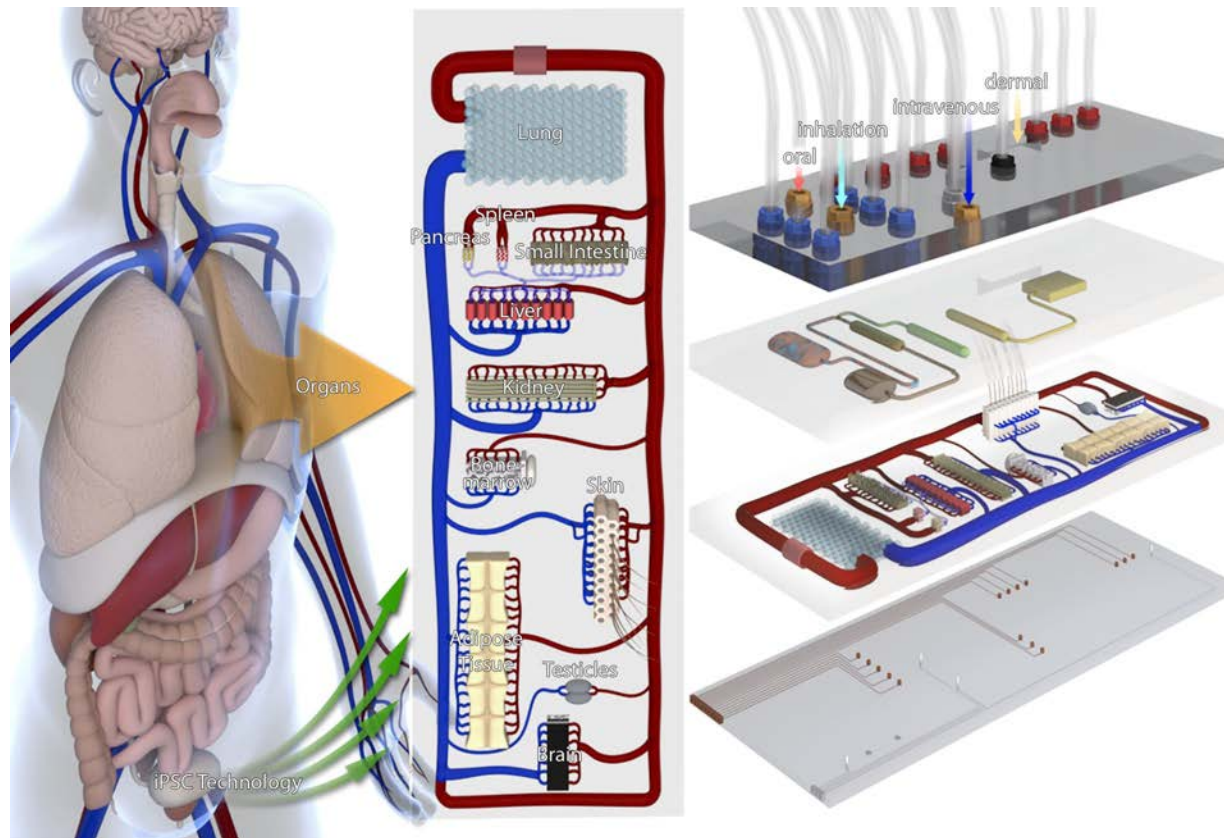
Understand the mechanisms and pathways, rather than trying to understand or humanise an animal model



Lung-on-a-chip
Wyss Institute, Harvard



Next generation Multi-Organ-Chip



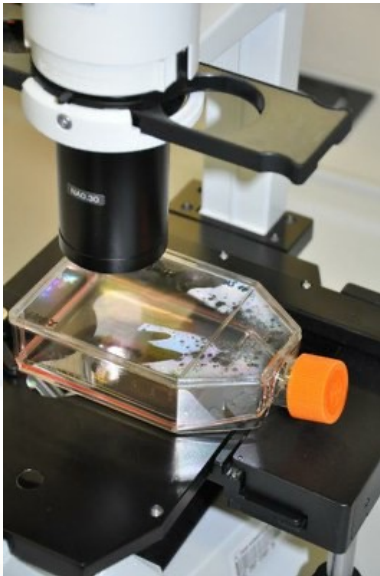
Marx et al., Altern Lab Anim. 2012 Oct;40(5):235-57

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TISSUSE
Emulating Human Biology

High Throughput Screening (HTS)

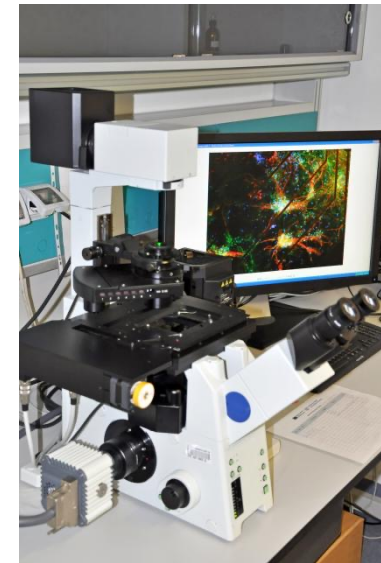


Cell culturing and
compound management
laboratories



Robotic platform with high-throughput
liquid handler for **sample preparation**,
dilution and test-plate treatment.
Supported by optical **plate reader**, plate
washer and incubator

Data management system to trace
and process the test data



Automated **imaging**
microscope can be added
for **high-content screening**

<https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/high-throughput-screening-and-test-development/hts>

Norecopa: PREPARE for better Science

2020 Call: Identifying new regulators of cell invasion in colorectal cancer using the *Drosophila* adult intestine

05/10/2021 | Funded Projects

Project OC-2020-011

Colorectal cancer (CRC) is a cancer of the colon and the rectum. It is the third most prevalent cancer worldwide and is the fourth most common cause of cancer-related deaths. If the cancer is localized, the five-year survival rate is 90%; if the cancer has spread – metastasized – the five-year survival rate drops to 14%. Consequently, it is crucial to understand how CRC cells adopt a metastatic fate.

The predominant CRC signature is hyperactivation of Wnt and RAS signaling plus loss of cellular repair pathways. There have been many attempts to develop metastatic CRC mouse tumor models to define the molecular progression of the disease. Unfortunately, the path to developing these models has heavily relied on “trial and error” mouse screens. Recently however, *Drosophila* researchers have developed the genetics and screening tools to study CRC metastasis in the fly gut.

The project will use the newly established *Drosophila* CRC metastasis model to screen for genes involved with promoting cell invasion, a key initiating step in metastasis. The researchers will then characterize these genes in *Drosophila* and identify which conserved molecular systems are involved with the metastatic pathway.

Dr Jamie Little

University of Zurich

Prof. Konrad Basler

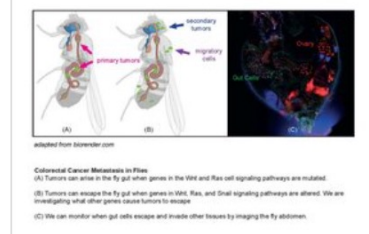
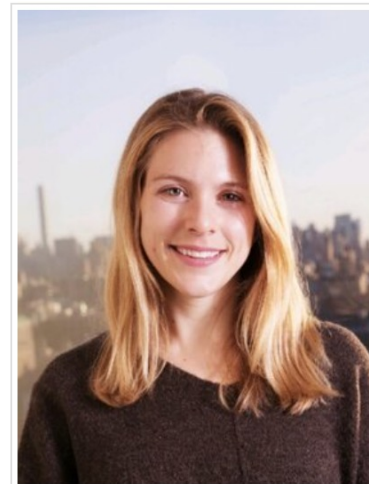
University of Zurich

Dr Erich Brunner

University of Zurich

Dr Hassan Fazilaty

University of Zurich



ds/research-funding/funded-projects

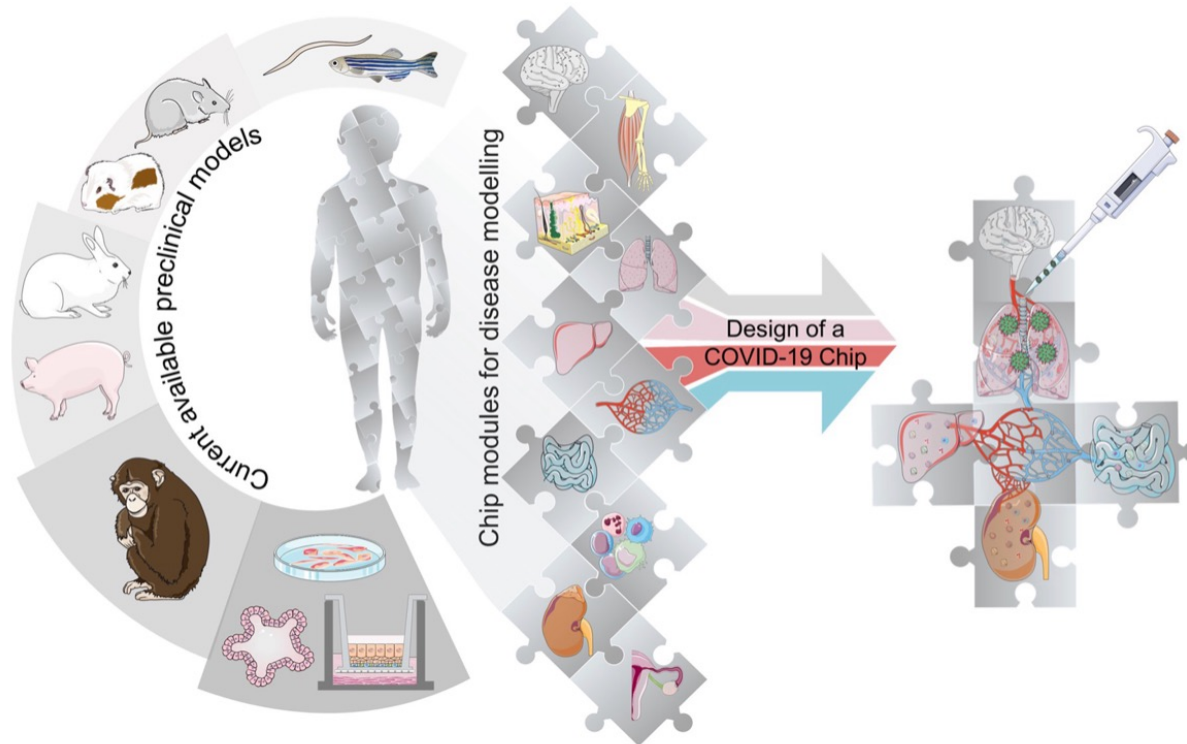


Image © Sarah Hedtrich

8th Annual 3Rs Symposium: Pandemic-Driven Advances

June 3-4, 2021

Norecopa: PREPARE for better Science



VOL. 140, NO. 5

NOVEMBER 1971

NATIONAL GEOGRAPHIC

THE PEOPLE OF CUMBERLAND GAP
JOHN FETTERMAN 591
BRUCE DALE

ANTARCTICA'S NEARER SIDE
SAMUEL W. MATTHEWS 622
WILLIAM R. CURTSINGER

NEPAL'S ROADLESS KARNALI: AN AMERICAN FAMILY EXPLORES IT ON FOOT 656
LILA M. AND BARRY C. BISHOP

CARNIVAL IN TRINIDAD
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FIRST PHOTOGRAPHS OF SNOW LEOPARDS IN THE WILD 702
GEORGE B. SCHALLER

UGANDA, AFRICA'S UNEASY HEARTLAND
HOWARD LAFAY 709
GEORGE F. MOBBLEY



Norecopa: PREPARE for be screenshot

JOURNAL OF THE NATIONAL GEOGRAPHIC SOCIETY WASHINGTON, D.C.

Enorm isklump festet seg til reinsdyrets radiohalsbånd



SMERTER: Denne villreinen måtte avlives i Nordfjella. En isklump på GPS halsbåndet hadde vokst seg større enn hodet på reinen.

Av **TOR-HARTVIG BONDO** og **LINN K. YTTERVIK**
(VG) 22.01.2016 20:27

49

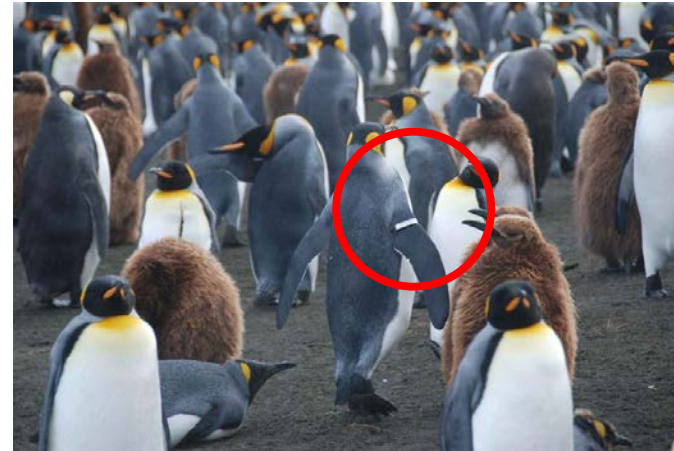
annonse

*"Simple" identification methods?
Do they affect the animal?*



Photo: T. Poppe, NMBU

Norecopa: PREPARE for better Science



http://blogs.discovermagazine.com/notrocketscience/2011/01/12/flip-per-bands-impair-penguin-survival-and-breeding-success/#.VLU6_8Y7_wo



Photo: colourbox.com

Using DNA technology to monitor the movement of wildlife without invasive tracking and tagging systems



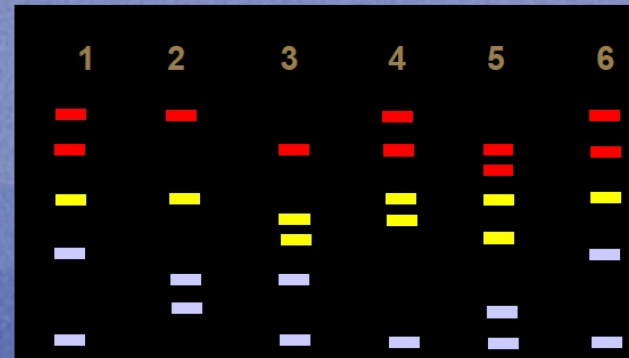
Øystein Flagstad

<https://norecopa.no/Nordic-webinars>

DNA-based monitoring Scandinavian carnivores

DNA-profiles from the scat samples provide unique ID-codes (1=6), that can be traced back to certain individuals in the target population(s)

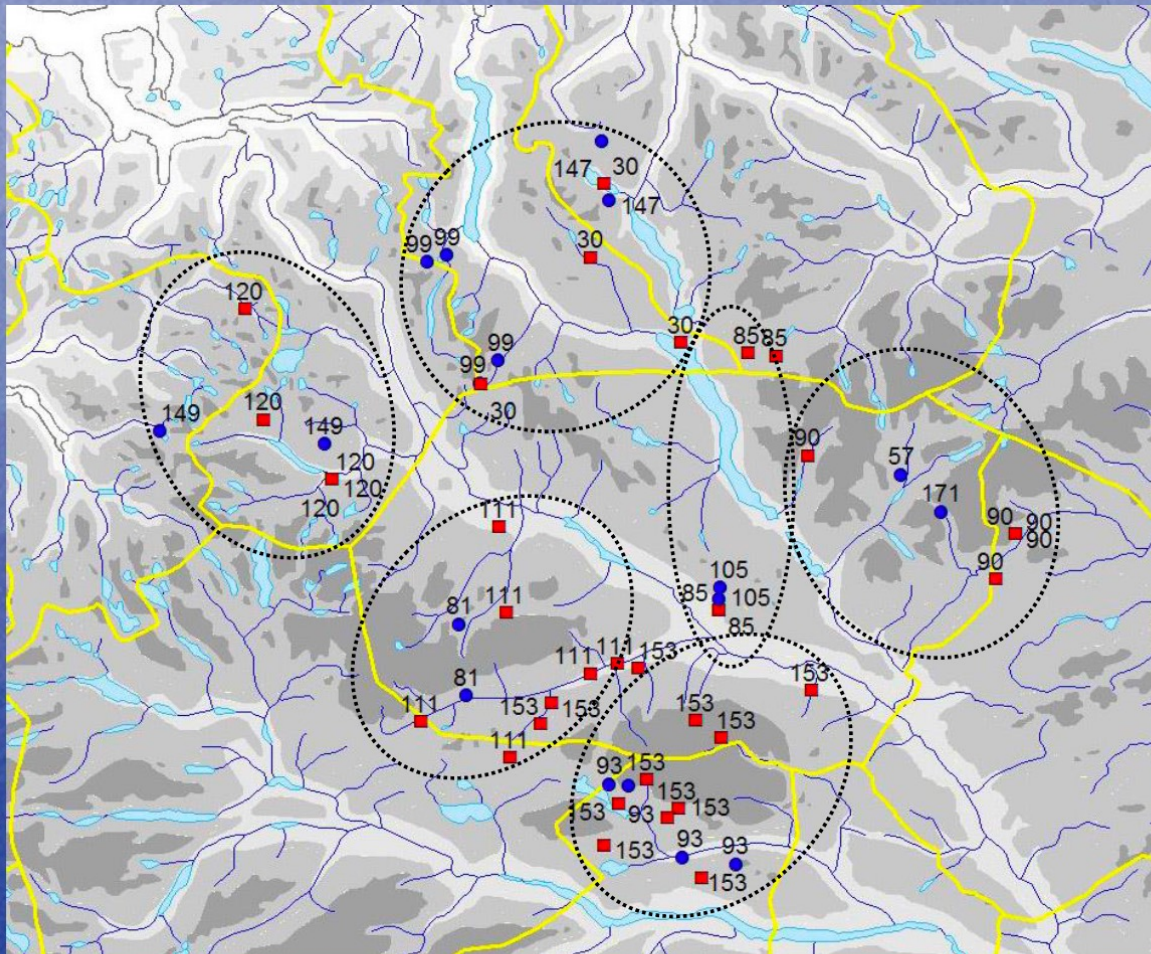
Yearly sample collection allow us to follow the same individuals during a period of several years



mapping=>

- home range and territories
- reproduction
- dispersal and migration patterns
- population size and - dynamics
- genetic structure; levels of isolation

Mapping territorial wolverines



Nor

Screenshot



Home ranges and movements

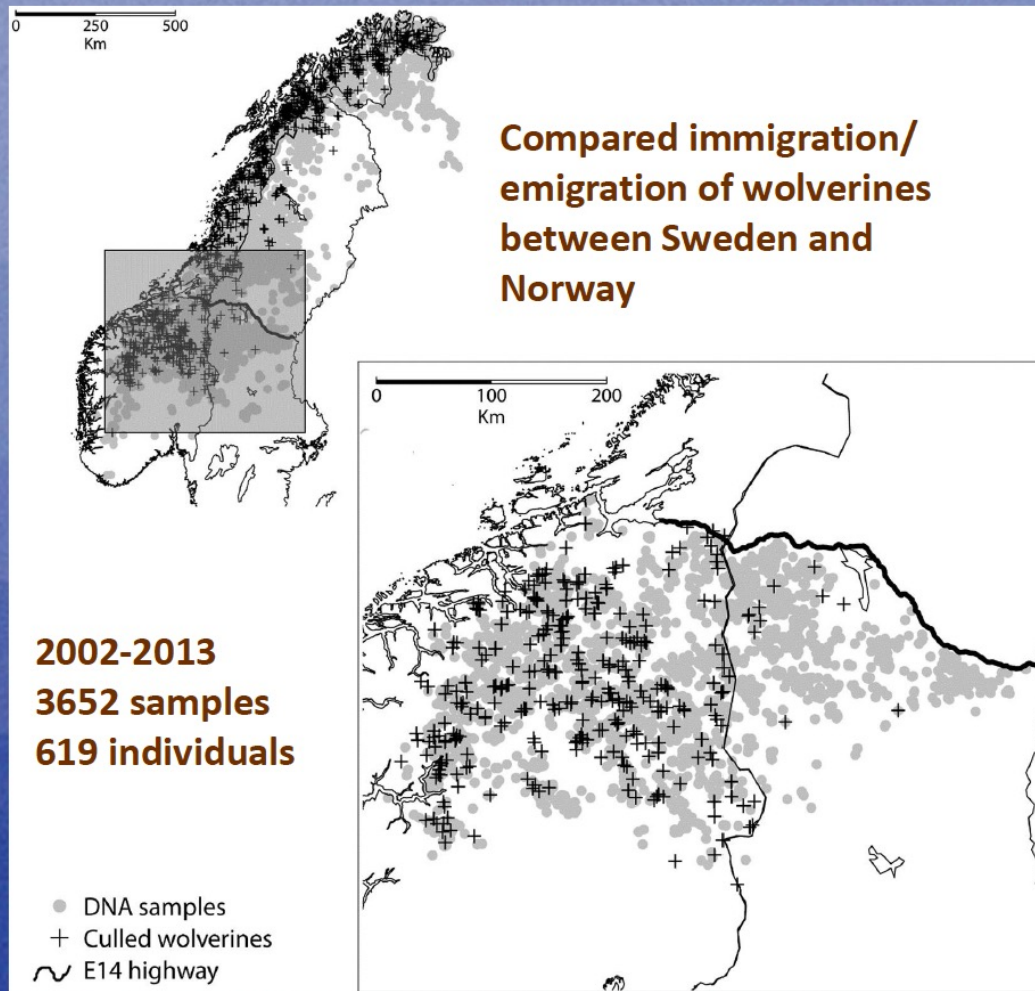


Norec

Screenshot



Patterns of emigration/immigration in a managed population

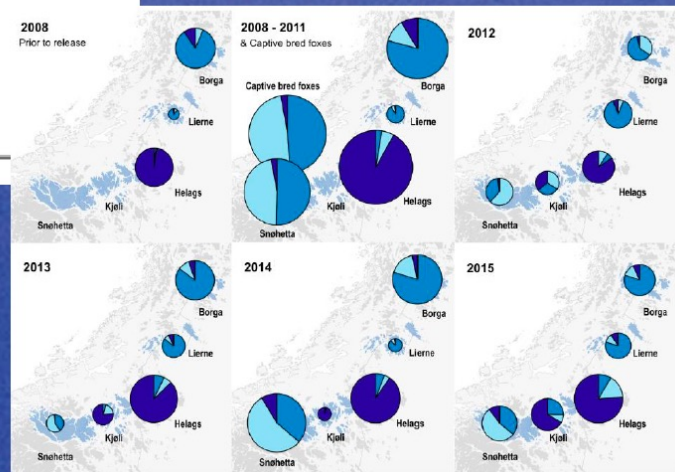


Gervasi et al. 2015 (*Biological Conservation* 191, 632-639)

Genetic structure and dispersal patterns

Population	2008/2009		
	Immigration rate	95% CI	Proportion admixed
Borga	0.046	0.036–0.055	0.139
Lierne	0.290	0.271–0.309	0.000
Helags	0.032	0.023–0.040	0.000
Kjøli			
Snøhetta	0.285	0.271–0.299	0.050

Population	2014/2015		
	Immigration rate	95% CI	Proportion admixed
Borga	0.057	0.044–0.070	0.218
Lierne	0.149	0.122–0.176	0.143
Helags	0.067	0.055–0.080	0.167
Kjøli	0.219	0.196–0.241	0.050
Snøhetta	0.229	0.220–0.238	0.312



2020 Call: Reducing the need for lethal health monitoring in trout

05/10/2021 | Funded Projects

Project OC-2020-003

Proliferative Kidney Disease (PKD) is a deadly parasitic fish disease that is classified as reportable and that has to be monitored in Switzerland. For this purpose, 15'500 potentially healthy pre-reproductive brown trout were electrofished and euthanized since 2000 to determine their PKD status by the applicant at the Centre for Fish and Wildlife Health (FIWI) alone.

This project aims to establish an alternative, non-lethal and animal-independent monitoring method based on pathogen DNA detection from water samples (an approach also called “eDNA” – environmental DNA). By establishing sensitive and reliable technical methods, and by evaluating them in the field, we will generate spatio-temporal detection probability maps and will provide the necessary expertise and tools for our implementation partners in cantonal and federal fish health and water quality monitoring to replace current monitoring practices.

Dr Heike Schmidt-Posthaus

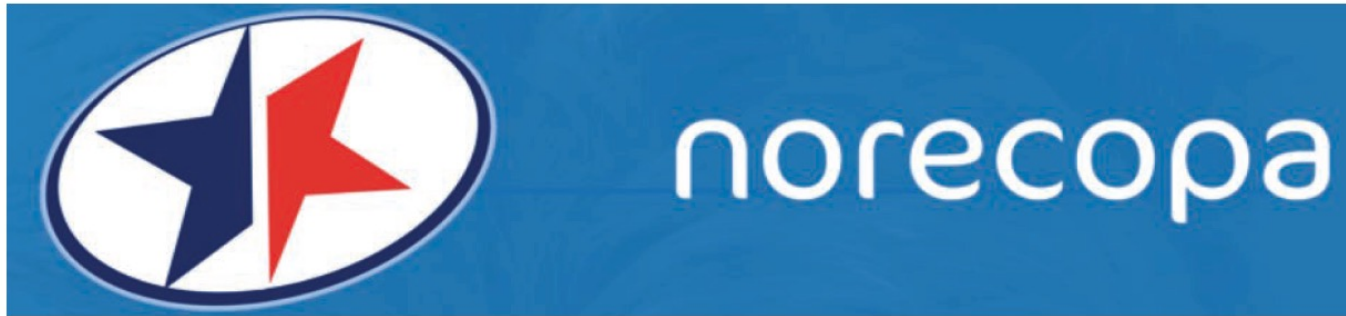
University of Bern

Prof. Irene Adrian-Kalchhauser

University of Bern



<https://www.swiss3rcc.org/en/funding-awards/research-funding/funded-projects>



Novel human-cell based models to study neurodegeneration

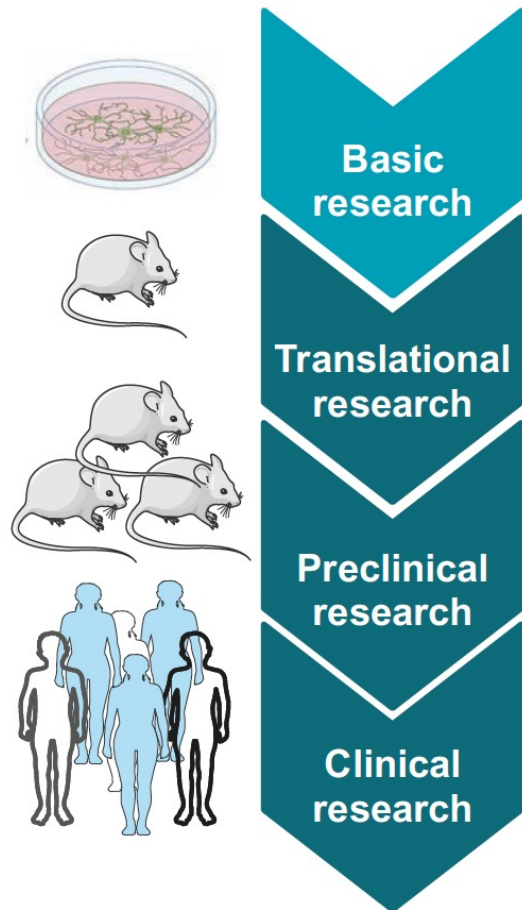
<https://norecopa.no/Nordic-webinars>

Šárka Lehtonen, PhD, Docent in Neuropharmacology

Head of Human brain disease modelling group



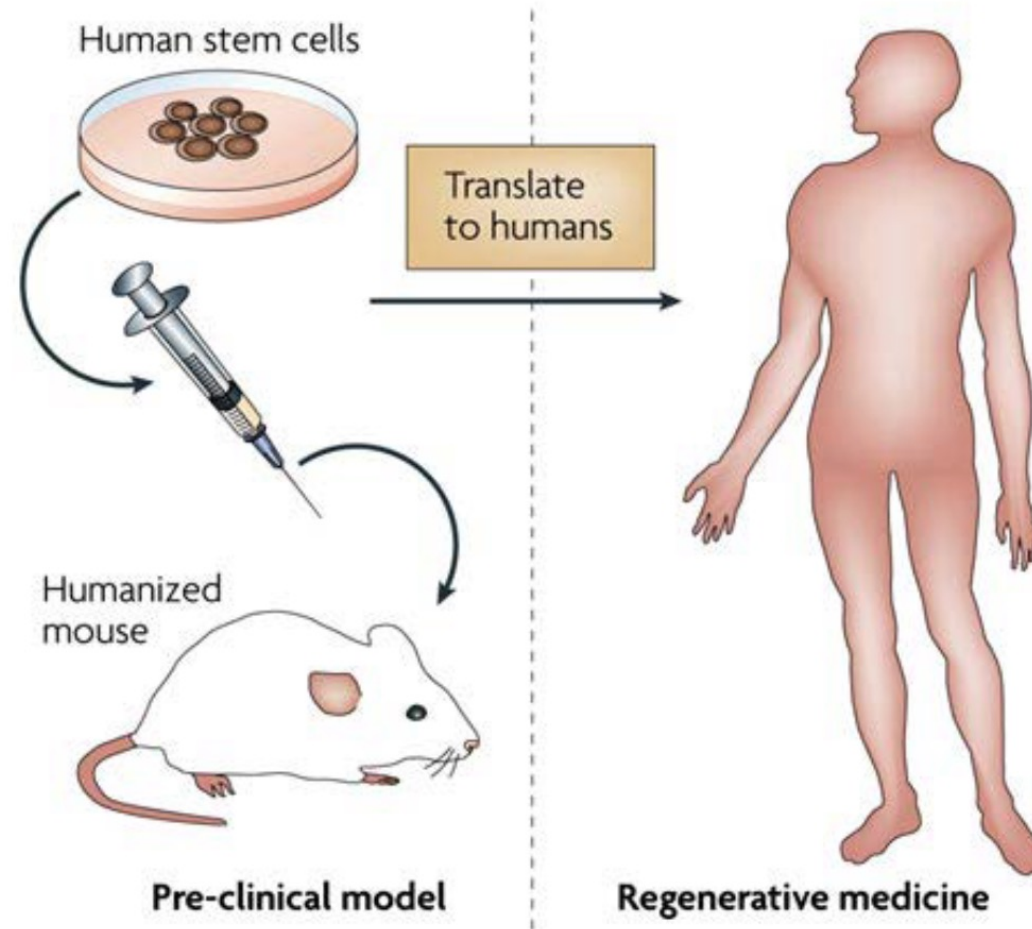
Current in vivo approach does not necessary predict human effects



- Traditional drug success rate from preclinical stage to phase I clinical trials is only 30 % and in clinical trials 10%.
- Clinical trials of CNS drugs have shown a very low overall success rate (6.2% vs. 13.3% for non-CNS drugs)
- For AD, only 1 out of 244 experimental compounds in Alzheimer's clinical trials was approved during a 15-year period

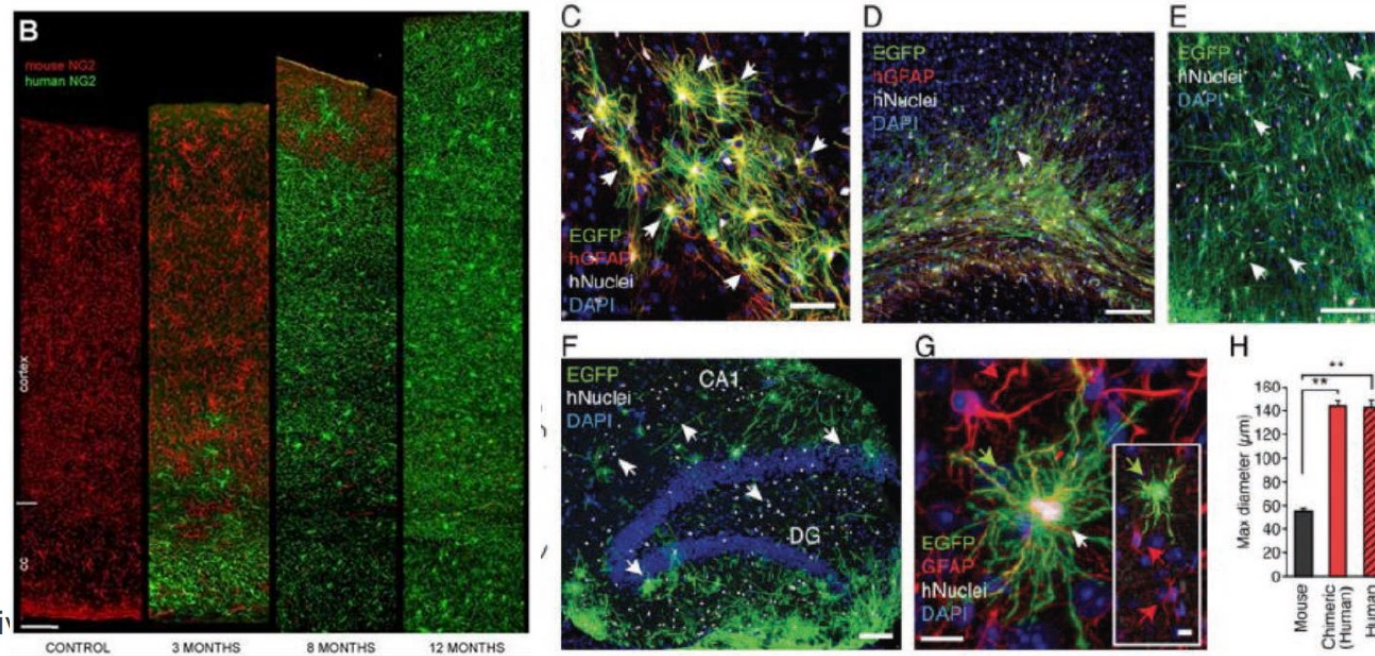
Average cost for approved drug: over \$ 2 billion
Average time: 10 years

Humanized mouse



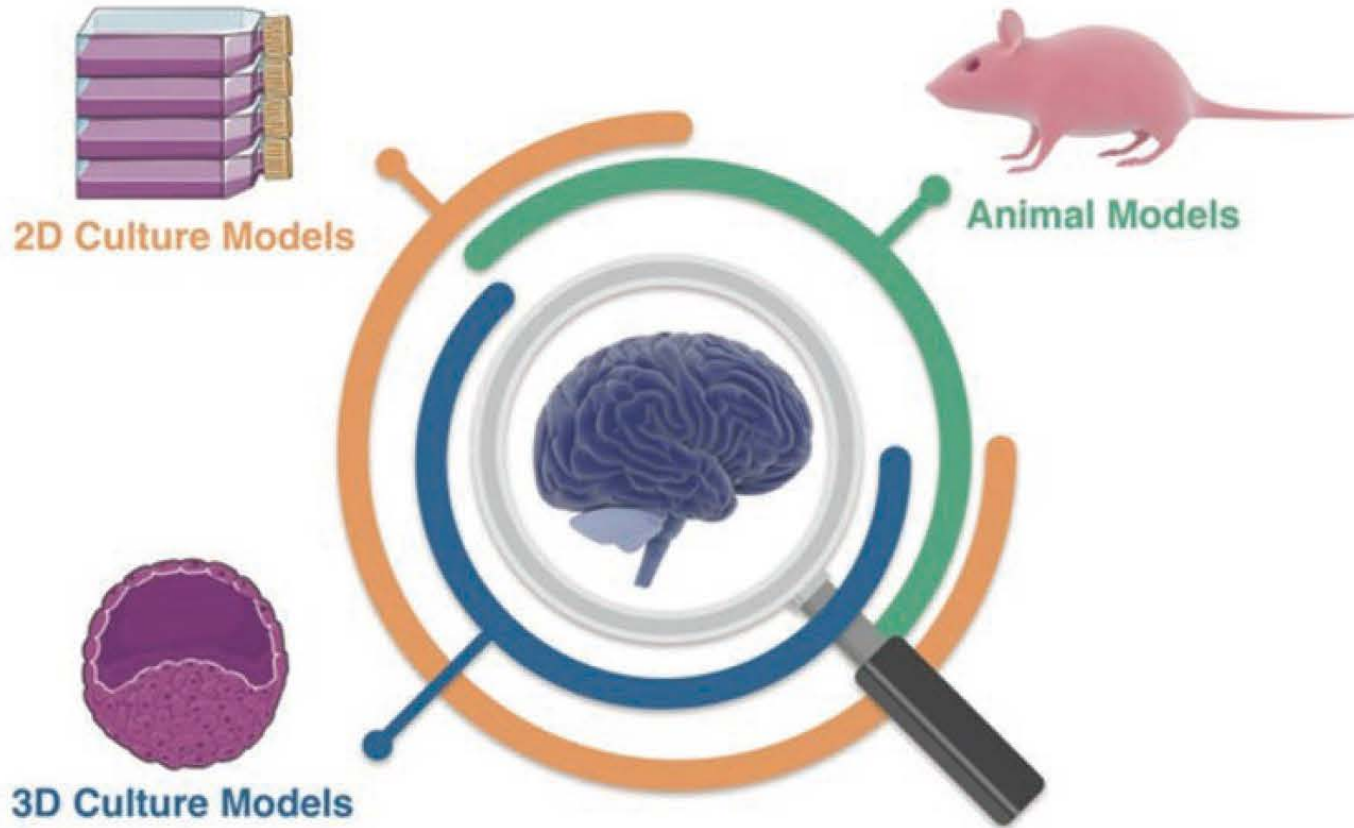
Humanized mouse model_forebrain

Type of study	Transplanted human cell type	Outcome of transplantation	References
rag2 ^{-/-} or rag1 ^{-/-} immunodeficient mice	A2B5+/PSA-NCAM ⁻ (from human 17-22-week old fetuses); transpl. to forebrain 2 locations; 100,000 cells	↑ Calcium propagation, gap junction-coupled to host astroglia, ↑ LTP; improved cognition functions (learning and memory)	Han et al. 2013, Cell Stem Cell 12: 342-353



Human glial progenitor cells outcompete and ultimately replace resident mouse glial progenitor cells.

MODELING HUMAN NEURODEGENERATIVE DISEASES

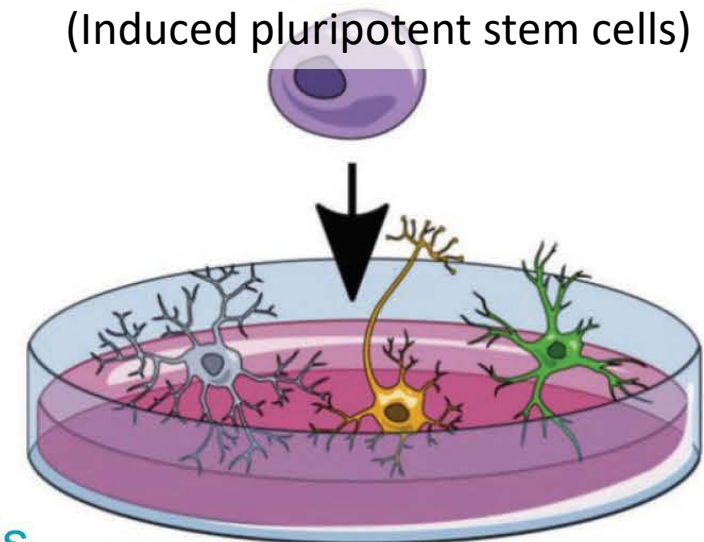


Where do we go from here?



iPSCs

(Induced pluripotent stem cells)



In vitro models

iPSCs can give advantages over traditional animal models in that they more accurately represent the human genome

UEF // University of Eastern Finland

Albert et al., 2021 *IJMS* 22(9), 4334.

Summary

Development of human brain cell platforms for improved clinical translation

Astrocytes or microglia in 2D system:

- manifestation of disease pathology
- platform for drug trials

3D co-cultures with neurons:

- mimicking in vivo complexity
- different functional behavior

Brain organoids:

- complex cellular interactions
- modelling of brain networks
- immunocompetent (microglia)
- vascularization (endothelial cells)

Humanized models:

- studying contribution to the disease pathogenesis
- elucidate mechanism of neurodegenerative diseases

PREPARE:

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

PREPARE covers 15 topics:

Formulation of the study

1. Literature searches*
2. Legal issues*
3. Ethical issues, harm-benefit assessment and humane endpoints
4. Experimental design and statistical analysis*

Dialogue between scientists and the animal facility

5. Objectives and timescale, funding and division of labour
6. Facility evaluation
7. Education and training*
8. Health risks, waste disposal and decontamination

Methods

9. Test substances and procedures*
10. Experimental animals*
11. Quarantine and health monitoring*
12. Housing and husbandry
13. Experimental procedures*
14. Humane killing, release, reuse or rehoming
15. Necropsy

Items in pink are
not typically
highlighted in
reporting guidelines

***Replacement opportunities**



PREPARE



The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Adrian J. Smith¹, R. Eddle Clutton², Elliot Lilley³, Kristine E. Aa. Hansen⁴ & Trond Brattfeldt⁵

¹Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750 Sentrum, 0106 Oslo, Norway; ²Royal (Dick) School of Veterinary Studies, Easter Bush, Midlothian, EH25 9RG, U.K.; ³Research Animals Department, Science Group, RSPCA, Wilberforce Way, Southwater, Horsham, West Sussex, GU10 2PH, U.K.; ⁴Section of Experimental Biomedicine, Department of Production Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian School of Veterinary Science, P.O. Box 8146 Dep., 00333 Oslo, Norway; ⁵Division for Research Management, Norwegian School of Veterinary Science, 5020 Bergen, Norway.

PREPARE¹ consists of planning guidelines which are complementary to the ARRIVE² guidelines. PREPARE covers the three broad areas which determine the quality of research: 1. Formulation of the study 2. Dialogue between scientists and the animal facility 3. Quality control of the components in the study

The topics will not always be addressed in the order in which they appear in the checklist, since in-house experiments are dependent upon their specific circumstances. The management of animal facilities, since in-house experiments are dependent upon their specific circumstances. The PREPARE guidelines are available on the Norecopa website, with links to global resources, at <https://norecopa.no/PREPARE>.

The PREPARE guidelines are a dynamic set which will evolve as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

Three Rs

Topic	Recommendation
(A) Formulation of the study	
1. Literature searches	<input type="checkbox"/> Form a clear hypothesis, with primary and secondary outcomes. <input type="checkbox"/> Consider the use of systematic reviews. <input type="checkbox"/> Decide upon databases and information specialists to be consulted, and construct search terms. <input type="checkbox"/> Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and to welfare needs. <input type="checkbox"/> Assess the reproducibility and translatability of the project.
2. Legal issues	<input type="checkbox"/> Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. <input type="checkbox"/> Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	<input type="checkbox"/> Construct a lay summary. <input type="checkbox"/> In dialogue with ethics committees, consider whether statements about this type of research have already been produced. <input type="checkbox"/> Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). <input type="checkbox"/> Consider pre-registration and the publication of negative results. <input type="checkbox"/> Perform a harm-benefit assessment and justify any likely animal harm. <input type="checkbox"/> Discuss the learning objectives, if the animal use is for educational or training purposes. <input type="checkbox"/> Allocate a severity classification to the project. <input type="checkbox"/> Define objective, easily measurable and unequivocal humane endpoints. <input type="checkbox"/> Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	<input type="checkbox"/> Consider pilot studies, statistical power and significance levels. <input type="checkbox"/> Define the experimental unit and decide upon animal numbers. <input type="checkbox"/> Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.

Topic	Recommendation
(B) Dialogue between scientists and the animal facility	
5. Objectives and timescale, funding and division of labour	<input type="checkbox"/> Arrange meetings with all relevant staff when early plans for the project exist. <input type="checkbox"/> Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. <input type="checkbox"/> Discuss and disclose all expected and potential costs. <input type="checkbox"/> Construct a detailed plan for division of labour and expenses at all stages of the study.
6. Facility evaluation	<input type="checkbox"/> Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. <input type="checkbox"/> Discuss staffing levels at times of extra risk.
7. Education and training	<input type="checkbox"/> Assess the current competence of staff members and the need for further education or training prior to the study.
8. Health risks, waste disposal and decontamination	<input type="checkbox"/> Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. <input type="checkbox"/> Assess, and if necessary produce, specific guidance for all stages of the project. <input type="checkbox"/> Discuss means for containment, decontamination, and disposal of all items in the study.
(C) Quality control of the components in the study	
9. Test substances and procedures	<input type="checkbox"/> Provide as much information as possible about test substances. <input type="checkbox"/> Consider the feasibility and validity of test procedures and the skills needed to perform them.
10. Experimental animals	<input type="checkbox"/> Decide upon the characteristics of the animals that are essential for the study and for reporting. <input type="checkbox"/> Avoid generation of surplus animals.
11. Quarantine and health monitoring	<input type="checkbox"/> Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel.
12. Housing and husbandry	<input type="checkbox"/> Attend to the animals' specific instincts and needs, in collaboration with expert staff. <input type="checkbox"/> Discuss acclimatization, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing).
13. Experimental procedures	<input type="checkbox"/> Develop refined procedures for capture, immobilisation, marking, and release or rehoming. <input type="checkbox"/> Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques.
14. Humane killing, release, reuse or rehoming	<input type="checkbox"/> Consult relevant legislation and guidelines well in advance of the study. <input type="checkbox"/> Define primary and emergency methods for humane killing. <input type="checkbox"/> Assess the competence of those who may have to perform these tasks.
15. Necropsy	<input type="checkbox"/> Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples.

References

- Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattfeldt T. PREPARE Guidelines for Planning Animal Research and Testing. *Laboratory Animals*, 2017, DOI: 10.1177/0023677217724823.
- Kilkenny C, Browne WJ, Cuthill IC et al. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PLoS Biology*, 2010, DOI: 10.1371/journal.pbio.1000412.

Further information

<https://norecopa.no/PREPARE> | post@norecopa.no | [@norecopa](https://twitter.com/norecopa)

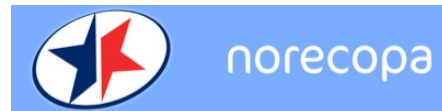


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Checklists

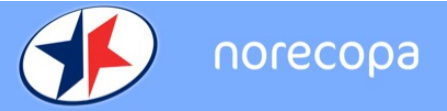
- Reduce risk of **forgetting** to carry out vital actions
- Ensure checks are carried out in the **correct sequence**
- Encourage **cooperation** and **cross-checking** between crew members
- Make sure that everyone is "**on the same page**"

Too late to read the checklists when you have ARRIVED!



colourbox.com

Norecopa: PREPARE for better Science



In addition to the checklist, much more information is available on:

norecopa.no/PREPARE



A screenshot of the norecopa.no website. The header is blue with the Norecopa logo and the word "norecopa" in white. To the right, there are language options for "NORSK" and "ENGLISH", and a search bar with the text "Search: Q". Below the header is a navigation menu with items: "About Norecopa", "Alternatives", "Databases & Guidelines", "Education & training", "Legislation", "Meetings", "More resources", "News", "PREPARE", and "Species". The "PREPARE" item is circled in red. Below the navigation menu is a list of links for the PREPARE Checklist, including: "1-Literature searches", "2-Legal issues", "3-Ethical issues, Harm-Benefit Assessment and humane endpoints", "4-Experimental design and statistical analysis", "5-Objectives and timescale, funding and division of labour", "6-Facility evaluation", "7-Education and training", "8-Health risks, waste disposal and decontamination", "9-Test substances and procedures", "10-Experimental animals", "11-Quarantine and health monitoring", "12-Housing and husbandry", "13-Experimental procedures", "14-Humane killing, release, re-use or re-homing", "15-Necropsy", and "Comparison with ARRIVE". At the bottom of the page, there is a breadcrumb trail "norecopa.no / PREPARE" and social media icons for Facebook, Twitter, Email, and a plus sign for more options.

Norecopa: PREPARE for better Science



The screenshot shows the top section of the norecopa website. It features a blue header with the norecopa logo and name. Below the header is a navigation menu with links for 'About Norecopa', 'Alternatives', 'Databases & Guidelines', 'Education & training', 'Legislation', 'Meetings', 'More resources', 'News', 'PREPARE', and 'Species'. A search bar is also present. Below the navigation menu is a list of links for the PREPARE Checklist, including '1-Literature searches', '2-Legal issues', '3-Ethical issues, Harm-Benefit Assessment and humane endpoints', '4-Experimental design and statistical analysis', '5-Objectives and timescale, funding and division of labour', '6-Facility evaluation', '7-Education and training', '8-Health risks, waste disposal and decontamination', '9-Test substances and procedures', '10-Experimental animals', '11-Quarantine and health monitoring', '12-Housing and husbandry', '13-Experimental procedures', '14-Humane killing, release, re-use or re-homing', '15-Necropsy', and 'Comparison with ARRIVE'.

norecopa.no / PREPARE



Harm-Benefit Assessment

[Harm-Benefit assessment](#), an evaluation of the likely sources and level of suffering of a planned procedure, followed by an assessment of the potential benefits of the research weighed against these harms, lies at the heart of [legislation in the EU](#) and elsewhere. [A framework for severity assessment and severity classification](#) must be established and justified. The likely adverse effects of each procedure should be described, along with their likely incidence and methods of recognising them, with indications of how these effects can be mitigated by implementing refinement. This necessitates the involvement of personnel with the relevant expertise to recognise, assess and reduce animal suffering, especially severe suffering. [Guidance on this is available on the RSPCA website](#). Specific justification of all unavoidable animal suffering must be provided. An estimate must be made of the maximum amount of pain, distress or lasting harm to which an individual can be

Links to quality guidelines worldwide on e.g. blood sampling, injection volumes, housing and husbandry, analgesia, humane endpoints, experimental design

Clicker training

Clicker training is an operant conditioning based on positive reinforcement. When the animal offers the desired behavior, a *click* or another distinctive sound (secondary reinforcer) is delivered and within the following few seconds the reward is presented (primary reinforcer)^[1]. The *click* bridges the time between the desired behavior and the presentation of the reward^[1]. A target stick providing a visual guide for the animal can be used for the training.

Animals are usually trained individually, though it is also possible to perform clicker training in a groups, e.g. in mice, rats, and rabbits. For rats, it was demonstrated that they learned tasks by observing the clicker training of their cage mates^[2].

Clicker training can be used to train animals in a stress-free way. The following behaviours are examples for what this technique can be used for:

Mice: entering a tunnel, following a target stick, climbing on the palm of the hand^[3]

Rats: following a target stick, voluntarily change to a cage, observational learning^[2]

Rabbits: following a target stick, rearing/standing up to inspect the abdomen, approaching a human, being touched and lifted by a human, trimming nails, coming on command

Pigs: Pigs can be easily trained to cooperate if they are treated empathetically and desired behavior is reinforced by providing food stuff in form of treats and apple juice^[4].



Clicker training with mice using a target stick. *Left:* The mouse is following the target stick and is climbing on the experimenter's hand. If the hand is lifted, the mouse will remain on the palm of the hand. *Right:* The mice are trained in a group. Two mice are following the target stick on the palm of the experimenter's hand.

- ↑ ^{1.0} ^{1.1} Feng, Lynna C.; Howell, Tiffani J.; Bennett, Pauleen C. (1 August 2016). "How clicker training works: Comparing Reinforcing, Marking, and Bridging Hypotheses". *Applied Animal Behaviour Science*. **181**: 34–40. doi:10.1016/j.applanim.2016.05.012. ISSN 0168-1591.
- ↑ ^{2.0} ^{2.1} Leidinger, Charlotte Sophie; Kaiser, Nadine; Baumgart, Nadine; Baumgart, Jan (25 October 2018). "Using Clicker Training and Social Observation to Teach Rats to Voluntarily Change Cages". *JoVE (Journal of Visualized Experiments)* (140): e58511. doi:10.3791/58511. ISSN 1940-087X. PMC 6235608. PMID 30417890.
- ↑ Leidinger, Charlotte; Herrmann, Felix; Thöne-Reineke, Christa; Baumgart, Nadine; Baumgart, Jan (6 March 2017). "Introducing Clicker Training as a Cognitive Enrichment for Laboratory Mice". *JoVE (Journal of Visualized Experiments)* (121): e55415. doi:10.3791/55415. ISSN 1940-087X. PMC 5408971. PMID 28287586.
- ↑ "Positive Reinforcement Training in Large Experimental Animals" (PDF).

Experts for clicker training in mice and rats: TARC, Mainz, Germany

This page was created and edited by KH191219 (talk).

This page was last edited on 27 May 2020, at 11:23.

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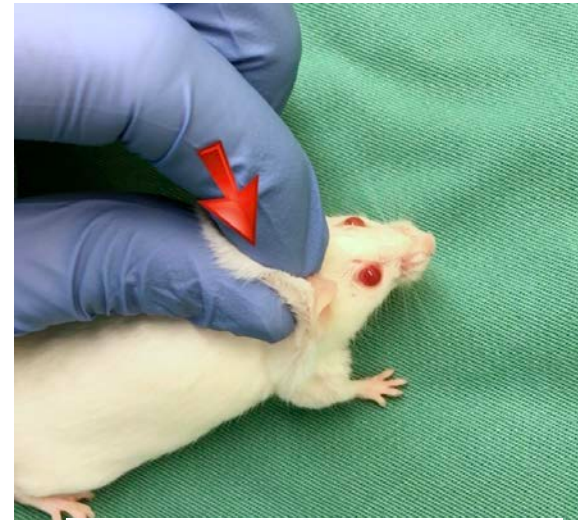
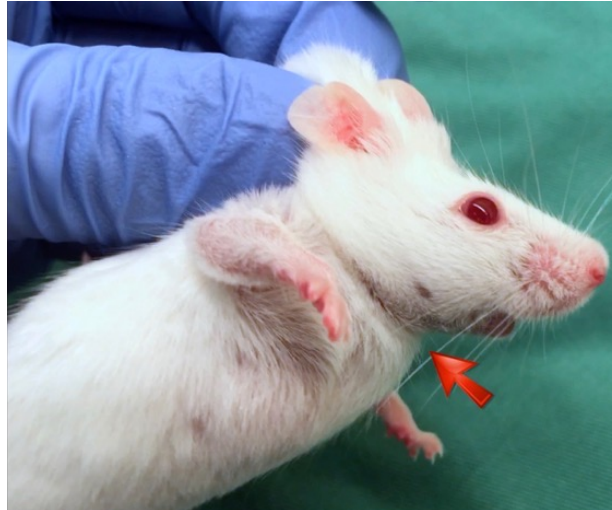


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Refinement Wiki

Refinement of scruffing mice

norecopa.no/scruff



Three fingers better than two

Baseline



Immobilizing
Sinus bradycardia, VEC






Reprinted with permission. Labitt RN, Oxford EM, Davis AK, Butler SD, Daugherty EK. 2021. A Validated Smartphone-based Electrocardiogram Reveals Severe Bradycardias during Immobilizing Restraint in Mice of Both Sexes and Four Strains. *J Am Assoc Lab Anim Sci* 60:201–212. DOI: 10.30802/AALAS-JAALAS-20-000069

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