Summary of the

Knowledge Agenda

Transition towards Animal-free Innovations

ZonMw

Summary

The need for this Knowledge Agenda

Over the past centuries, animal experimentation has greatly contributed to the understanding of how our body works, how diseases arise and how they can be treated. However, it turns out that laboratory animals are often not such good models for studying human physiology or a disease in humans. Partly because of this there is a growing negative sentiment in society about the use of laboratory animals for scientific research. Support for this view has grown as it has become clear that many new therapies, which are effective in laboratory animal models, work less well or even not at all in humans[1,2]. Because of this turnaround, **new methods and models that are more translatable to humans** are actively being sought. The traditional approach in which laboratory animal models are regarded as the "gold standard" is (slowly) giving way to an approach in which humans are put at the centre of research. The development and application of models and methods that are more representative of humans and do not use laboratory animals is referred to as the **Transition Programme for Innovation without the use of animals (TPI)**. This transition is expected to produce results that are more relevant to humans, leading to a reduction in the number of laboratory animals used. This is a long-term process as it runs counter to both past habits and existing interests, and requires trust in animal-free methods to grow. These are not simple challenges and require a collective effort from all stakeholders in the scientific and research communities around animal testing and animal-free innovations.

What is the objective of this Knowledge Agenda?

This Knowledge Agenda identifies the **obstacles** within broader biomedical research that hinder the (continued) development and widespread use of animal-free innovations. In addition, we formulate potential **solutions** and provide concrete **recommendations** to stimulate this transition. The focus of this Knowledge Agenda is primarily the discovery and development phase of animal-free innovations (i.e. innovations with a low technology readiness level (TRL); for further explanation see Chapter 5.1). This concerns fundamental and applied research, and research that focuses on applicability, implementation and validation of an innovation. Obstacles and solutions at the level of further commercialization of animal-free innovations (higher TRLs) are outside the scope of this Knowledge Agenda. This Knowledge Agenda therefore focuses primarily on the academic research field, as well as (resulting) start-ups and small and medium-sized enterprises. We also focus herein on developments and opportunities in The Netherlands, but we are aware that the challenges and solutions are also influenced by international developments. The Netherlands wants to be a catalyst in the (inter)national transition to animal-free innovations[3] and we believe that with the right initiatives, funding and mindset we can inspire other countries to join this transition.

The recommendations of this Knowledge Agenda do not directly aim to achieve a sharp reduction in animal testing in the short term, although such a reduction is desirable in the eyes of many. Indeed, we expect that a forced and/or too rapid strategy to reduce laboratory animal use will result in much resistance and inhibit scientific progress. It will also lead to the relocation of animal testing to other countries, making it more difficult to control the wellbeing of the animals and the quality of the experiments. Moreover, it is important to realize that European regulations stipulate that The Netherlands cannot unilaterally ban animal testing, and that animal testing is required by law for toxicity and safety assessment. Therefore, this Knowledge Agenda rather focuses on **stimulating high-quality research with and into animal-free innovations** that provide results that are reliable and relevant to humans. Reducing animal testing is thus not a goal in itself, but a logical consequence of the major steps that can be taken in the transition. Given the complexity of the issue and the major international forces at play, we therefore advise great caution in setting specific targets for the annual number of animal experiments in the Netherlands, or concrete deadlines for phasing out animal experiments. A steady decline in the number of animal tests needs to be preceded by implementation of and confidence in well-validated animal-free innovations. Such an approach will have several benefits: in addition to encouraging excellent human-centered science to gain greater support in the field, it will also be a more sustainable long-term solution and may also give rise to new commercial opportunities. Moreover, we expect that investments made will be of great added value and will generate significant savings in the development of new

therapies, as research results can be better translated to humans. Ultimately, these positive effects should favour a decline in animal testing.
In order to address the solutions and recommendations from this Knowledge Agenda, ZonMw wants to set up an **ambitious, long-term knowledge and innovation program.** By providing a broad repertoire of funding opportunities that tackle the various obstacles identified in this Knowledge Agenda, we hope to effectively and efficiently accelerate the transition. We will do this in close cooperation with the many national and international parties that (can) play a role; these include not only universities and knowledge institutes, but also industry, regulatory bodies and other stakeholders.

What is in this Knowledge Agenda?

For this Knowledge Agenda, almost 60 acadamic and commercial researchers, regulators, students and lecturers from various Dutch universities and institutes with extensive experience with laboratory animals and/or animal-free innovations were consulted. Together, we inventoried why existing animal-free methods do not yet find their way to **implementation** (for example, in regulations or in the daily practice of universities and companies), and in what respects there is still a need for the **(further) development of new models** and technologies. Additionally, stakeholders were asked to provide input on other factors required for a successful transition, such as **education, infrastructure provision**, and the **disclosure of existing knowledge** about animal-free innovations. The information from the consulation sessions forms the basis for this Knowledge Agenda, and is divided into obstacles and solutions on either an **scientific/technical** or an **educational/political/ societal/cultural** level. Surprisingly, the current and upcoming generations of researchers are very united on the challenges and possible solutions required to accelerate the transition:

– **Obstacles and solutions on a scientific or technical level**
The complexity of the human body is a major limiting factor in the development and application of animal-free innovations. For simple research questions, reasonably performing, animal-free methods have now been developed, but complex physiological processes are difficult to model outside the body, and therefore still require **in vivo** testing (in animals or humans). Furthermore, too few animal-free innovations are validated and applied; validation is often less important for fundamental research, but is vital for translational/applied and safety research. Lack of validation and implementation of new animal-free models is due to both lags in standardization and replication, but also to historical barriers in scientific culture. Logistical and legal issues are also impeding factors in replacing animal testing with the use of human or animal residual tissue. Finally, although much information that can accelerate the transition is available, it is very fragmented and difficult for researchers to find.

– **Obstacles and solutions that are driven by education, politics, society and culture:** In training courses the dominant line of thinking is from the perspective of the laboratory animal as a primary tool, with little attention being paid to animal-free innovations. We see in the workplace that the current mindset about laboratory animal use is maintained by tradition, and that researchers are not always as familiar with or have confidence in newly developed animal-free methods. This status quo is maintained in part by scientific journals and regulatory bodies, and in part by the tendency of academia to be competitive, holding back the transition. Particularly the competitive nature of career opportunities in academia or industry, can make multi- and interdisciplinary research a difficult path to take, as does the exchange of expertise, knowledge and materials. Developing new animal-free models represents a significant investment in time and resources, which lends itself against sharing in a competitive environment. On a societal and political level, there is a lack of substantive discussion about the usefulness and necessity of laboratory animal use, and the risks of testing new treatments using animal experiments versus animal-free methods. Finally, there is a need for 'slow science' in order to have sufficient space to develop, improve and validate useful models and ways of thinking/procedures, instead of the current focus on having to move forward regardless (the current 'publish or perish' model of science). In light of this, this part of the transition also fits well with the implementation of the national **Recognition and Rewards program**[6], because it acknowledges the added value of less popular but important and relevant research.

6 With the 2019 position paper "Room for Everyone's Talent," UNL, KNAW, NFU, ZonMw and NWO aim to achieve a better balance in recognizing and valuing researchers. Since then, the organizations have been working together in the national Recognition and Rewards program to implement the proposals.

The eight key recommendations from this Knowledge Agenda

Based on the consultation sessions and additional conversations with experts, we propose the following eight recommendations:

1. Encourage fundamental research into complex physiological processes, fund (continued) development of animal-free models that simulate complex biological systems, and invest in multidisciplinary consortia in which scientists with diverse expertise can work closely together for longer periods of time.
2. Fund appropriate parallel and replication studies for the validation of animal-free models, invest in unlocking information regarding the use or validation of animal-free innovations, and map out an implementation trajectory for the development and validation of animal-free innovations for new pharmaceuticals.
3. Involve potential end users of animal-free methods at an early stage of scientific research, encourage public-private collaborations for the development or validation of animal-free innovations and promote early consultation between scientists and regulators on new testing strategies.
4. Coordinate the use of existing biobanks with human tissue, facilitate obtaining and working with human tissue, and investigate the added value of biobanks with animal tissue.
5. Provide objective and good quality information about laboratory animals and animal-free innovations to the general public, and facilitate and encourage the public's ability and willingness to participate in scientific research/medical studies.
6. Encourage online pre-registration of animal studies in international databases, disclose the results of these studies, and encourage the publication of neutral or negative data from animal studies and animal-free innovations.
7. Promote change in the mindset of current and new generations of researchers and technicians regarding the use of laboratory animals and facilitate training at MBO, HBO and WO, as well as continuing education of professionals (technicians, animal caretakers, teachers, members of animal experimental committees, scientific staff, legislators and regulators) in the field of animal-free innovations.
8. Encourage, especially with inter- and transdisciplinary research, a new approach to scientific practice aimed at propelling the field as a whole (replication, validation, development of robust methods, etc).

By whom and for whom is this Knowledge Agenda?

This Knowledge Agenda was prepared by ZonMw, and has been endorsed by NWO. A large group of scientists, policy advisors, regulators and other experts has provided input. This includes members of the **TPI partner program**, an alliance of partners from government, education, society, industry and academia[7].

This Knowledge Agenda focuses on the **entire biomedical research field** and adjacent fields that can contribute to this research, both in fundamental, applied and legally required toxicological and safety research. This includes **researchers and boards** at universities, schools of applied science, academic hospitals, knowledge institutes, small and large **companies, regulators** and **funding agencies (Figure 2)**. Various government **ministries** also have a role, in particular the ministries of Agriculture, Nature and Food Quality (LNV), Education, Culture and Science (OCW), and Health, Wellbeing and Sports (VWS). Also the ministries of Infrastructure and Water Management (I&W), Economic Affairs and Climate Policy (EZK), and Defence are involved via the Interdepartmental Working Group on Alternatives to Animal testing (IWAD).

By its design, this Knowledge Agenda is both widely supported and far reaching. We hope that the entire community surrounding the transition to animal-free innovations will relate to the contents of this document, making this Knowledge Agenda a valuable tool in the transition.

7 https://www.animalfreeinnovationtpi.nl/

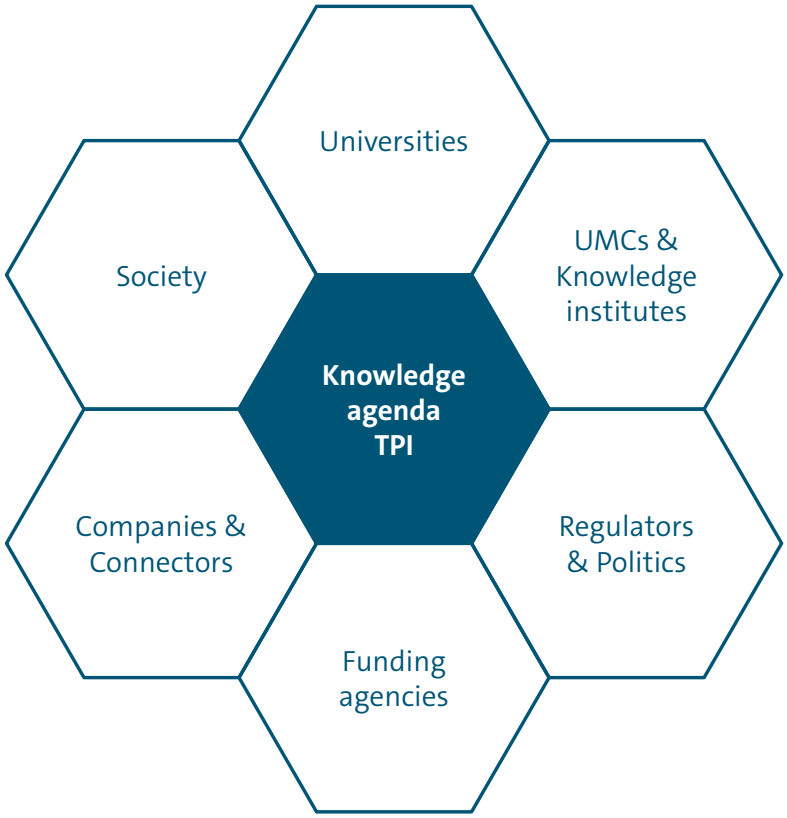

Figure 2: Target audience of the Knowledge Agenda with all key parties playing a role in the transition to animal-free innovations.