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NON-TECHNICAL SUMMARY

# Biological and lifestyle influences on fibrosis across organs

**Project duration**

5 years 0 months

**Project purpose**

- (a) Basic research

**Key words**

Fibrosis, Scarring, Repair, Diagnosis, Therapy

| Animal types | Life stages |
|---|---|
| Mice | Embryo and egg, Neonate, Juvenile, Adult, Pregnant adult, Aged animal |
| Rats | Adult |

## Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is required, and should be submitted within 6 months of the licence's revocation date.

### Reason for retrospective assessment

This may include reasons from previous versions of this licence.

- Contains severe procedures

# Objectives and benefits

Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

**What's the aim of this project?**

The aim of this project is to extend our understanding of how scarring (or fibrosis) occurs and progresses during chronic disease affecting different organs, and how in some cases this leads to organ failure and cancer. By improving knowledge of these processes, the project aims to support earlier diagnosis of fibrosis and the development of improved treatments to limit disease progression.

## A retrospective assessment of these aims will be due by 28 March 2032

The PPL holder will be required to disclose:

- Is there a plan for this work to continue under another licence?
- Did the project achieve its aims and if not, why not?

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

**Why is it important to undertake this work?**

Fibrosis, or scarring of tissues, is a common process associated with many long-term diseases affecting organs such as the liver, lung, kidney and heart. Over time, this scarring can reduce how well an organ works, eventually leading to organ failure. Fibrosis is also a significant risk factor for developing cancer in some conditions. Together, these complications represent a major cause of illness and death worldwide and place a significant burden on healthcare systems.

A key challenge is that fibrosis often develops slowly and without obvious symptoms in its early stages. As a result, many people are only diagnosed when damage is already advanced and treatment options are limited. There is therefore an urgent need to better understand how fibrosis starts, why it progresses in some individuals but not others, and how biological factors and lifestyle influences contribute to these differences.

Undertaking this work will help identify the mechanisms that drive fibrosis across different organs and disease settings. Understanding shared and organ-specific processes may reveal opportunities for earlier detection, for example through improved disease indicators, and may also highlight new targets for treatment. This could ultimately support the development of strategies to slow or prevent disease progression, reduce the risk of organ failure and cancer, and improve patient outcomes.

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In the longer term, improved understanding of fibrosis may also help guide public health and lifestyle interventions aimed at reducing disease risk. By addressing a common process that underlies many chronic conditions, this research has the potential to benefit a broad range of patients and contribute to reducing the overall burden of chronic disease.

**What outputs do you think you will see at the end of this project?**

This project is expected to generate new knowledge about how fibrosis develops and progresses in different organs. These findings will be shared through publications in peer-reviewed scientific journals and presentations at scientific and clinical meetings. Sharing results in this way will allow other researchers and healthcare professionals to build on the work and help advance understanding in this area.

The research may also identify biological markers (measurable signs of disease in blood or tissues) associated with fibrosis or disease progression. These could inform the future development of improved diagnostic approaches to detect fibrosis earlier or to better monitor patients over time. In addition, the work may highlight biological pathways that could be explored as potential targets for new treatments aimed at reducing or preventing scarring.

While not all findings will directly lead to clinical applications, the knowledge generated is expected to contribute to the longer-term development of new diagnostic tools, preventative strategies, or therapies designed to improve outcomes for people with chronic diseases associated with fibrosis.

**Who or what will benefit from these outputs, and how?**

In the short term, the scientific and medical research communities will benefit from new knowledge about how fibrosis develops and progresses across different organs. These findings will help guide further research, support collaboration, and refine approaches to studying chronic disease. The outputs may also help clinical researchers design studies aimed at improving early detection and monitoring of fibrosis.

This work builds on previous research from our group that has already informed patient-orientated studies and helped identify potential diagnostic targets. Earlier findings have contributed to the development and evaluation of approaches for detecting liver disease in clinical settings. By extending this research to fibrosis affecting multiple organs and cancer progression, we aim to further identify markers and mechanisms that could be explored for improved diagnosis and monitoring in patients.

In the medium term, healthcare professionals and clinical researchers may benefit from improved understanding of which biological and lifestyle factors influence disease progression. This knowledge may help decide who is at higher risk and lower risk, identify individuals who may benefit from closer monitoring, and guide the design of future clinical trials.

In the longer term, patients with chronic diseases affecting organs such as the liver, lung, kidney, or heart are expected to benefit. Insights from this project may contribute to the development of improved diagnostic tools, preventative strategies, or treatments aimed at reducing scarring and preventing organ failure. Although translation from discovery research to clinical application can take several

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years, this project is designed to build directly on existing work that has already begun to influence patient-focused research, increasing the likelihood of future clinical benefit.

Wider society may also benefit through reduced healthcare burden, earlier intervention, and improved quality of life for people living with chronic disease.

**How will you look to maximise the outputs of this work?**

We will maximise the outputs of this work through collaboration, open dissemination of findings, and engagement with both the scientific community and the public. We collaborate with national and international researchers across a range of disciplines, and these partnerships will continue throughout the project. Such collaborations help ensure that knowledge, methods, and insights are shared efficiently and that findings can be validated and extended by others.

Results from the project will be published in peer-reviewed scientific journals to reach a wide audience. We will also present findings at scientific and clinical meetings. This will include sharing preliminary data where appropriate, often through conference abstracts, so that new ideas and approaches can be communicated early. Reporting both successful and less successful approaches can help avoid duplication of effort and support progress across the field.

Where appropriate, we will contribute to wider dissemination by sharing knowledge with clinical researchers and healthcare professionals to support the translation of findings toward patient benefit. We also engage with patient and public involvement (PPI) groups focused on conditions associated with fibrosis, including those affecting different organs. These interactions help ensure that research priorities remain aligned with patient needs and that outputs are communicated in an accessible way.

Together, these approaches will help ensure that the knowledge generated is widely shared, informs future research, and supports long-term progress toward improved diagnosis and treatment of fibrosis-related diseases.

**Species and numbers of animals expected to be used**

- Mice: 13750
- Rats: 1050

# Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

**Explain why you are using these types of animals and your choice of life stages.**

This project will use mice and rats because they are well-established models for studying fibrosis and chronic disease. These species are widely used in biomedical research, and there is a strong existing body of knowledge, validated methods, and background data that allow findings to be interpreted

reliably. Many of the biological processes involved in scarring, inflammation and tissue repair are shared between rodents and humans, and these models have contributed to our current understanding of diseases affecting organs such as the liver, lung, kidney and heart. Using established models helps ensure that the minimum number of animals is used while still obtaining meaningful results.

Where experiments focus on obtaining tissues or cells for laboratory studies, rats may be used because their larger size allows more material to be collected from a single animal. Cells isolated from a single rat can be grown (cultured) and used for multiple laboratory experiments or experimental conditions. This reduces the overall number of animals required, as samples from one animal can replace the need to use several animals. It also allows paired comparisons within the same animal, reducing variability and improving statistical robustness.

Mice will also be used because they offer well-characterised systems for studying biological mechanisms, including models where specific genes or pathways can be altered. These approaches are important for understanding how fibrosis develops and progresses. Standardised protocols and reagents are widely available for mice, which helps improve reproducibility and reduces unnecessary animal use.

Fibrosis is typically associated with chronic disease that develops during adulthood. Therefore, adult animals will primarily be used to model disease processes that are relevant to human conditions. Using animals at this life stage helps ensure that the biological processes being studied reflect those occurring in adult-onset disease and improves the relevance of the findings.

**Typically, what will be done to an animal used in your project?**

To study fibrosis, animals will be used in established models that cause controlled tissue injury, as scarring typically develops following damage to an organ. In some studies, animals may also be aged naturally to investigate how ageing influences tissue repair, inflammation, and the development or progression of fibrosis over time. Depending on the organ being studied, this may involve injections of substances, inhalation of agents, changes to diet, or surgical procedures. Surgical procedures may include operations performed under general anaesthesia to temporarily or permanently alter part of an organ or its function in order to trigger tissue damage and repair responses associated with fibrosis. Following surgery, animals may experience short-term discomfort, however this will be minimised by giving appropriate pain killers after surgery. These approaches are commonly used to model chronic disease and allow researchers to study how fibrosis develops and progresses over time.

Some animals may undergo a single procedure, while others may receive more than one intervention during the course of a study. For example, animals may receive injections or dietary modifications, such as high-fat or specialised diets that mimic aspects of human disease, to induce fibrosis. These diets are designed to reproduce changes that occur in conditions such as obesity, metabolic dysfunction or nutrient imbalance, allowing researchers to investigate how these factors contribute to tissue scarring. Animals may later receive potential treatments to assess whether scarring can be slowed, halted or reversed.

The duration of experiments will vary depending on the stage of disease being studied. Investigations focused on early changes may last only a few days, for example up to approximately 72 hours. Studies examining long-term progression of fibrosis will last longer, often several weeks to months. Some

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chronic models may take around 12 weeks to develop substantial fibrosis, and in certain cases where progression to more advanced disease is studied, experiments may extend for longer periods, potentially up to approximately 60 weeks. In some studies investigating the effects of ageing, animals may be maintained for longer periods so that age-related changes in tissue repair and fibrosis can be assessed.

Throughout the study, animals may be monitored regularly, and some may receive medicines or other interventions intended to test new approaches for reducing fibrosis. At the end of the experiment, tissues will be collected for further analysis to understand how fibrosis developed and how it responded to any treatments.

**What are the expected impacts and/or adverse effects for the animals during your project?**

In some instances, animals will be treated with agents that cause fibrosis. Although transient discomfort may occur at the time of administration the animals appear normal soon afterwards. Similar to humans, animals can sustain fibrotic injury for a long period of time with no apparent symptoms. In the rare scenario that an animal shows signs of organ failure the animal will be humanely killed to ensure the animal does not exceed the severity limits set out in the project. Some animals will undergo surgery to induce fibrosis, but these are not life-threatening procedures. For surgical induced models animals receive post operative care including pain reducing agents. For some chronic disease models associated with scarring, the most common adverse effect is weight loss usually toward the end of the experiment. However these are typically within the shorter time periods of experiments (up to 2 weeks) and generally, aside from this, animals typically appear well. In lung fibrosis, shortness of breath can occur but is unlikely in the timescale of our experiments (up to 28 days). For the liver, liver fibrosis commonly leads to liver cancer in human. We have an experimental model to investigate this in mice using an injected chemical. These animals will develop tumours specifically in their liver typically towards the end of the experiment. Following completion of each project, animals will be humanely killed and tissue collected for studies in the laboratory.

Expected severity categories and the proportion of animals in each category, per species.

**What are the expected severities and the proportion of animals in each category (per animal type)?**

The expected overall severity for the majority of this project is moderate, and animals will be closely monitored throughout the studies. Humane endpoints and monitoring criteria will be applied to ensure that any adverse effects are identified early and managed appropriately.

For both mice and rats used in this project, it is estimated that approximately 50% of animals will experience procedures classified as mild severity. These animals may undergo interventions associated with transient discomfort, such as injections or short-duration studies, with minimal lasting effects.

Approximately 40% of animals are expected to fall within the moderate severity category. These animals will typically be involved in longer-term fibrosis studies, where gradual changes such as mild weight loss or organ-related effects may occur but remain within acceptable limits.

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A smaller proportion, estimated at around 10% of animals, may reach the severe severity category, primarily associated with significant weight loss. This is primarily associated with long-term models where advanced disease features, such as more pronounced physiological effects associated with severe fibrosis, occur toward the end of the study. These animals will be subject to enhanced monitoring and strict humane endpoints to minimise suffering.

**What will happen to animals used in this project?**

- Killed
- Used in other projects

## A retrospective assessment of these predicted harms will be due by 28 March 2032

The PPL holder will be required to disclose:

- What harms were caused to the animals, how severe were those harms and how many animals were affected?

# Replacement

State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.

**Why do you need to use animals to achieve the aim of your project?**

Despite advances in understanding scarring (fibrosis), many discoveries have not yet led to new treatments for patients. Fibrosis and cancer develop slowly over time and involve complex interactions between different types of cells, the immune system, and the body’s natural repair processes. These conditions are also influenced by other illnesses affecting the body (sometimes called multi-morbidity).

These processes occur across the whole body and rely on communication between many different cell types. At present, these interactions cannot be fully reproduced using cells or tissues grown in the laboratory. While studies using isolated cells or small pieces of tissue are helpful, they cannot mimic the long-term and whole-body responses that occur during chronic injury, scarring, and cancer development.

For this reason, animal models are still required to study how fibrosis develops over time, how different cell types interact, and how disease in one part of the body can influence another. These models currently provide the most practical way to investigate these complex processes in a way that reflects what happens in patients.

**Which non-animal alternatives did you consider for use in this project?**

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A range of non-animal approaches have been considered before undertaking animal studies. This includes regular review of the published scientific literature (using databases such as PubMed), attendance at scientific meetings to identify emerging technologies and replacement methods, and consultation with resources such as the Replacement Checklist (https://replacinganimalresearch.org.uk/resources/replacement-checklist/). These approaches will be used wherever possible. These include:

- Cells grown in the laboratory to study how treatments work and to test safety before animal studies
- Human tissue samples obtained during routine medical procedures (such as biopsies) to help confirm findings
- Short-term culture of tissues outside the body to study cell behaviour and can be used as a pre-screen prior to animal studies
- Organoids (mini tissue models grown in the laboratory) to better mimic some aspects of organs
- Stem cell–based models that can be developed into different cell types for research, useful for testing genetic alterations prior to animal studies
- Computer modelling and analysis of existing datasets

These approaches will be used as a first step where possible to reduce the number of animals required and to ensure that only the most promising approaches progress to animal studies.

**Why were they not suitable?**

Cells that are grown continuously in the laboratory can change over time and may no longer behave like normal cells. They also do not include the range of different cell types and structures found in real tissues, which limits their usefulness for studying fibrosis.

Models using human cells or tissue samples cannot fully reproduce how the whole body responds during disease. Fibrosis involves interactions between many different cell types, the immune system, and signals travelling through the body. These complex processes cannot currently be recreated outside a living organism. In addition, tissues kept in the laboratory can only survive for short periods, so they cannot model diseases that develop slowly over months or years.

Organoid and stem cell models offer promising new approaches, but they still lack important features such as blood supply, immune system involvement, and communication between organs. As a result, they cannot yet fully replicate the development of fibrosis in the body.

Despite these limitations, findings from animal studies will be checked against human tissue samples wherever possible to ensure the research remains relevant to patients and to maximise the use of non-animal approaches.

## A retrospective assessment of replacement will be due by 28 March 2032

The PPL holder will be required to disclose:

- What, if any, non-animal alternatives were used or explored after the project started, and is there anything others can learn from your experience?

# Reduction

Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.

**How have you estimated the numbers of animals you will use?**

Animal numbers are based on our previous experience using similar models and study designs. Our group has extensive experience in this area and has published studies that help guide the number of animals needed to produce reliable results.

Typically, experiments are designed using small groups of animals, including appropriate control groups for comparison. We will always use the minimum number of animals required to answer the scientific question while ensuring results are robust and meaningful.

Although a small proportion of animals (estimated to be around 10%) are expected to experience severe effects due to the nature of advanced chronic disease models, these models are only used where there is no suitable alternative and where they are necessary to answer important scientific questions that cannot be addressed using non-animal methods or less severe approaches. The number of animals reaching this stage will be minimised through careful study design, early intervention and the application of defined humane endpoints.

**What steps did you take during the experimental design phase to reduce the number of animals being used in this project?**

Experiments are carefully planned in consultation with experienced researchers and statisticians. We also make use of guidance tools such as the NC3Rs Experimental Design Assistant to help design studies efficiently and avoid unnecessary animal use.

Where new models are developed, we will seek further advice and refine the design before proceeding to larger studies. This approach helps ensure that only the minimum number of animals are used.

**What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?**

We will use several additional measures to minimise animal numbers:

- Using information and data from previous studies to guide experimental planning

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- Efficient breeding strategies to ensure that only the required number of animals are produced, avoiding unnecessary breeding
- Re-using archived control tissues from earlier experiments where appropriate
- Using both male and female animals where suitable, to maximise the information gained
- Collecting multiple tissues (such as liver, lung, kidney and heart) from a single animal so that more data can be obtained from each animal
- Sharing tissues within the research group to avoid duplication of experiments
- Using advanced computer modelling to predict how genes and cells interact, which can help refine experiments before animals are used
- Making use of existing large datasets, including single-cell studies, to identify the most important targets and reduce the need for exploratory animal experiments
- Using computational approaches to better understand interactions between tissues, which may reduce the need to generate additional genetically altered animals

These approaches ensure that the maximum amount of information is obtained from each animal and that overall animal numbers are kept as low as possible.

### A retrospective assessment of reduction will be due by 28 March 2032

The PPL holder will be required to disclose:

- How did you minimise the numbers of animals used on your project and is there anything others can learn from your experience?

# Refinement

Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.

**Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.**

For studies using cells, rats may be used as they provide sufficient tissue for detailed analysis. For studies in living animals, mice will often be used because genetically altered strains are widely available and allow us to investigate specific disease mechanisms without using larger animals. To alter gene expression, some animals may receive a substance by injection or in food. In many studies these approaches are used to investigate or improve disease outcomes by altering specific biological

pathways. These models are required because the biological pathways being studied cannot currently be replicated adequately in cell-based systems alone.

To induce fibrosis or related disease states, including cancer, animals may receive substances by injection, inhalation, in food or drinking water, or undergo surgical procedures that produce controlled tissue injury. Some animals may also be aged naturally to investigate how ageing influences tissue repair and chronic disease progression, as many fibrotic diseases primarily affect older patients. Where scientifically appropriate, substances will be administered using the least invasive route possible, including voluntary consumption in food or drinking water where suitable, to reduce handling and cumulative procedural burden.

Different organs and causes of fibrosis cannot be reproduced adequately using a single model. For this reason, several complementary models are required to investigate fibrosis caused by different injuries and disease processes and to determine whether potential diagnostic or therapeutic approaches are effective across multiple tissues and clinically relevant disease settings.

Wherever possible, the least severe model capable of answering the scientific question will be selected. However, some severe models are necessary because some models do not reproduce the advanced stages of fibrosis or organ dysfunction seen in human disease. For example, severe liver fibrosis models involving bile duct obstruction produce rapid and reproducible liver injury and fibrosis that cannot be achieved reliably using less severe dietary approaches. These models can be associated with greater disease severity, including significant weight loss, and a small risk of mortality despite careful monitoring and supportive care. Similarly, severe lung fibrosis models are required because they currently provide the most relevant and widely accepted representation of progressive fibrotic lung disease and advanced respiratory fibrosis.

Later stages of disease are sometimes necessary because patients commonly present clinically with advanced fibrosis or organ damage, and potential treatments must therefore be tested in established disease rather than only during early injury. Earlier endpoints would not allow assessment of whether therapies can halt or reverse advanced fibrosis or prevent progression to organ failure or cancer.

The project will continually review emerging refinements in animal welfare and husbandry, including guidance from organisations such as the NC3Rs, RSPCA and other recognised bodies, and will adopt further refinements where scientifically appropriate.

**Why can’t you use animals that are less sentient?**

The research requires a whole-body system where different organs, cells, and the immune system interact over time. Mice and rats were selected as the most appropriate species capable of addressing the scientific objectives, consistent with the principles of Replacement, Reduction and Refinement (the 3Rs).

Less sentient species, for example fruit flies (Drosophila) or nematode worms (Caenorhabditis elegans), do not adequately reproduce the complex interactions between organs, the immune system and tissue repair that occur during chronic fibrosis. They also do not allow the same range of genetically altered mammalian disease models required for this research.

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Using animals under terminal anaesthesia would not be suitable because the project requires studying how disease develops, progresses and responds to treatment over time in living animals.

**How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?**

Procedures will be refined to minimise discomfort and improve recovery. Animals will be closely monitored, and appropriate pain relief will be provided where necessary. Post-procedure care will include supportive measures such as temperature control and careful observation during recovery.

Our group has already refined several procedures. For example, improvements in surgical techniques and post-operative care have reduced mortality in one model of liver fibrosis. The introduction of warming cabinets and enhanced monitoring (including the introduction of scoring sheets) has further improved recovery.

We also use non-invasive monitoring techniques where possible and aim to shorten experiments when the same outcome can be achieved in a shorter time. Participation in collaborative research networks allows sharing of best practice and ongoing refinement of methods.

**What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?**

All procedures will be discussed with the animal care unit and carried out according to established standard operating procedures. We will follow recognised best practice guidance, and regularly review the scientific literature to identify further refinements and ensure that experiments are conducted using the most up-to-date and humane methods available. Resources are available include guidance and publications from the NC3Rs and PREPARE guidelines.

**How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?**

We will keep up to date with advances in the 3Rs through institutional training, newsletters, and guidance from our animal care unit. We will also regularly review information from organisations such as NC3Rs and incorporate new approaches where appropriate. Discussions with collaborators and participation in research networks will also help identify opportunities to further refine procedures.

## A retrospective assessment of refinement will be due by 28 March 2032

The PPL holder will be required to disclose:

- With the knowledge you have now, could the choice of animals or model(s) used be improved for future work of this kind? During the project, how did you minimise harm to the animals?

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