National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

# The use of human tissue in asthma research

## Background

Respiratory conditions such as asthma and COPD remain areas of significant unmet medical need, with few new drugs making it to the clinic in the past 50 years. Many promising drugs that perform well in preclinical animal studies fail in humans due to lack of safety and/or efficacy; suggesting the current preclinical testing strategy, focussing on *in vivo* models which do not recapitulate the complexity of the human disease, is not sophisticated enough to meet today's respiratory drug development needs. A new approach to drug discovery and development in this area is necessary.

Recognising this need, the NC3Rs organised a joint workshop with the MRC in 2009 where delegates were tasked with devising a framework to support the development and application of more physiologically relevant models of the disease for basic and applied research. To move these aspirations forward, we convened the NC3Rs Asthma Advisory Group (AAG) to help establish a programme of work to translate these ideas into practice and to ensure that the activities undertaken by the NC3Rs accurately represent the needs of the asthma research community.

Asthma is a disease unique to humans, and as such the development and application of human tissue-based approaches with which to study the disease was considered a priority by the AAG.

## Survey – Summary of Method

To understand the current level of human tissue use in asthma research and drug development, the NC3Rs, in collaboration with Asthma UK, the UK Respiratory Research Collaborative (UKRRC) and the UK Human Tissue Authority (HTA), conducted a survey of asthma research scientists. The questionnaire was devised by the AAG and distributed as an online survey through the partner networks and others, including the British Thoracic Society and the British Association for Lung Research. The survey was divided into sections to capture information on (i) the way human lung tissue is currently used in asthma research, (ii) the level of knowledge surrounding the regulatory requirements and guidance on human tissue use, and (iii) the perceived barriers to wider uptake of human tissue-based approaches in asthma research.

For the purpose of this survey, human tissue was defined as:

*Human tissues/cells obtained from surgical procedures or from bronchoscopy, or from people that have died and which is surplus to clinical requirement and which has been obtained with the consent of the next of kin. This does not include immortalised cells or cryopreserved material readily available from cell/tissue repositories.*

The data from this survey will be used to develop a strategy to encourage greater adoption of this research tool.

A total of 59 responses were received from academia, pharmaceutical companies, biotech institutes, small and medium enterprises (SMEs) and the NHS. The breakdown of respondents according to sector and position held is provided (figure 1).

The majority of respondents were principal investigators from academia.

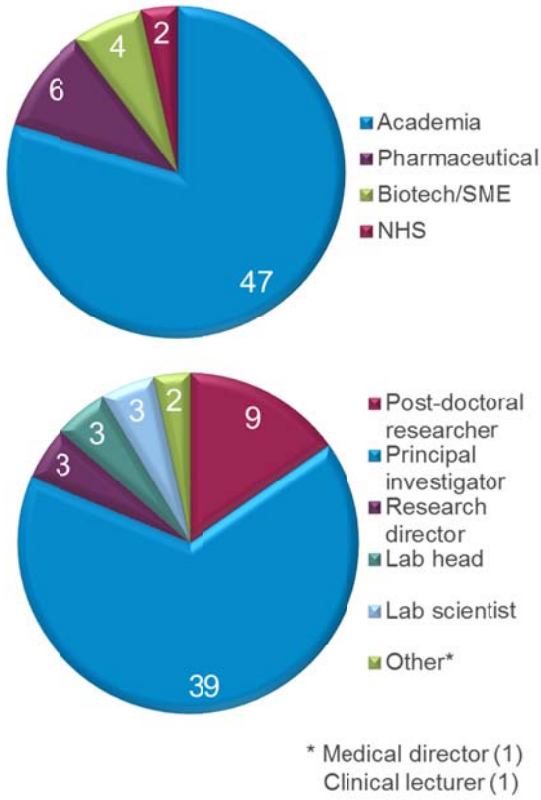


Figure 1. Breakdown of respondents by sector in which they work, and position they hold.

## Results

### Current use

The use of human tissue is already widespread throughout the asthma research community, with over 86% of respondents reporting that they use human tissue in some capacity. Most commonly this is used alongside immortalised cells and cryopreserved material (41%), or in combination with animal research (32%).

The survey indicated that a variety of research questions are currently answered using fresh human tissue. The areas studied using this research tool include immunology, physiology, pharmacology, genetics and epigenetics, and compound evaluation.

The most commonly used human material (figure 2), both diseased and normal, is primary cells followed by tissue sections and, to a smaller extent, sputum and biofluids. This reflects the ease of obtaining this type of tissue in comparison to larger, more complex tissues such as whole lung and tissue slices, which can only be gained from operations or post-mortem.

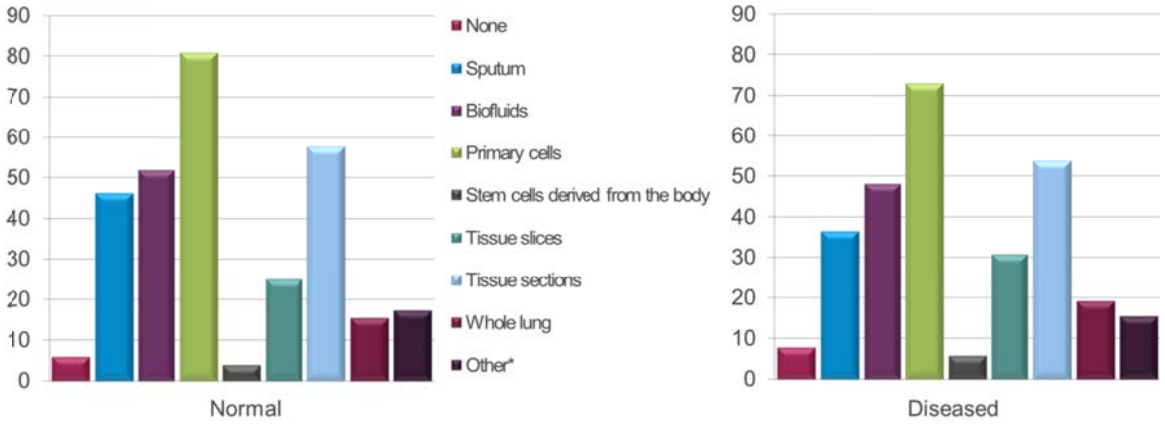


Figure 2: The type of normal and diseased human material that is currently used in asthma research. *87% of respondents answered this question.*

Respondents were then asked which tissue types they would *like* to use if they could access it (figure 3). The most common response was whole lung, followed by tissue slices, demonstrating that larger pieces of tissue are perceived to offer greater benefits to understanding the disease. The results differ significantly from those shown in figure 2 where 70-80% of respondents currently use primary cells, but only 13% feel this is a tissue type they would *like* to use for their research if other options were available to them.

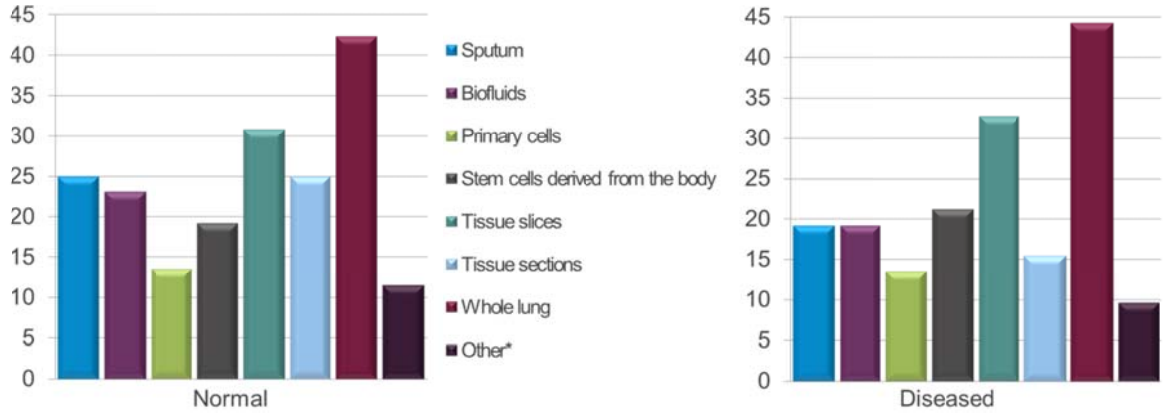


Figure 3: The type of normal and diseased human material that respondents would *like* to use in their asthma research programmes. *87% of respondents answered this question.*

Respondents were encouraged to leave additional comments regarding the tissue they would like to use. Responses demonstrated that tissue is currently difficult to access, with normal tissue being in such high demand that there is not enough available to support studies. Respondents also indicated a desire to use larger tissue samples, such as wedge resections, in order to provide enough tissue for multiple experiments.

## Barriers

The following survey questions were designed to understand the reasons for the differences between what is currently used (see figure 2) and what researchers would like to use (see figure 3). Respondents were provided with a series of statements concerning potential barriers, and were asked to select all that applied.

| What are the main barriers to using fresh human tissue in asthma research? | Percentage |
|---|---|
| Lack of access to a regular supply of good quality, fresh normal tissue | 69.5% |
| Lack of access to a regular supply of good quality, fresh diseased tissue | 62.7% |
| The practical issues related to the acquisition and storage of human tissue | 59.3% |
| The regulatory requirements for the removal, storage and use of human tissues | 44.1% |
| There is insufficient funding available to support research programmes using fresh human tissue | 32.2% |
| Difficulty in predicting activity in isolated tissue compared to the complex integrated *in vivo* situation | 25.4% |
| Difficulty in publishing human tissue-based research in high-impact journals | 23.7% |
| Comparability of data generated using human tissue with existing animal data | 20.3% |
| Requirement by the regulatory authorities for *in vivo* animal efficacy/ safety data in pharmaceutical development to support human trials | 11.9% |
| Lack of specific expertise in human tissue-based research | 5.1% |
| I am not aware of any barriers | 5.1% |

Table 1: The main barriers to using fresh human tissue in asthma research. *100% of respondents answered this question.*

As highlighted in table 1, the main barrier to using fresh human tissue is the availability of material. Another widely perceived barrier is the practical issues related to the acquisition and storage of tissue. Given the number of respondents using human tissue already, it may be possible to overcome these barriers by providing some guidance and sharing experiences. Overall, the barriers can be divided into practical, scientific and regulatory groups.

As a related question, respondents were asked what would enable them to use more human tissue in their research (Table 2). The majority believed that greater access to tissue would have the biggest impact. Increased funding and evidence that human

tissue-based approaches are more predictive than animal models were also selected by a large number of respondents.

| What would enable you to use more human tissue as part of your asthma research programme? | Percentage |
|---|---|
| Access to a reliable supply of functional normal tissue | 71.2% |
| Access to a reliable supply of functional diseased tissue | 71.2% |
| Increased specific funding for human tissue research programmes | 55.9% |
| Evidence that human tissue-based methods are more predictive than current animal models | 45.8% |
| More opportunities for dialogue with the agencies that regulate the removal, storage and use of human tissues for research | 35.6% |
| A change in journal publishing policies to more readily publish human tissue-based research | 30.5% |
| Clearer guidance on the regulatory requirements for the removal, storage and use of human tissues | 25.4% |
| Greater acceptance by the pharmaceutical industry regulatory authorities of efficacy/ safety data generated using human tissue | 18.6% |
| Nothing, my research requires the use of complex, integrated whole animal systems | 3.4% |

Table 2: Changes that would enable greater use of fresh human tissue in asthma research. *100% of respondents answered this question.*

## Regulatory framework

The following section was designed to better understand the asthma research community's view of the regulatory framework around accessing and using human tissue for research. Respondents were asked questions regarding the level of information within the framework (Figure 4), and were presented with a series of statements on the guidelines and asked to indicate the level of their agreement with each statement (Figure 5).

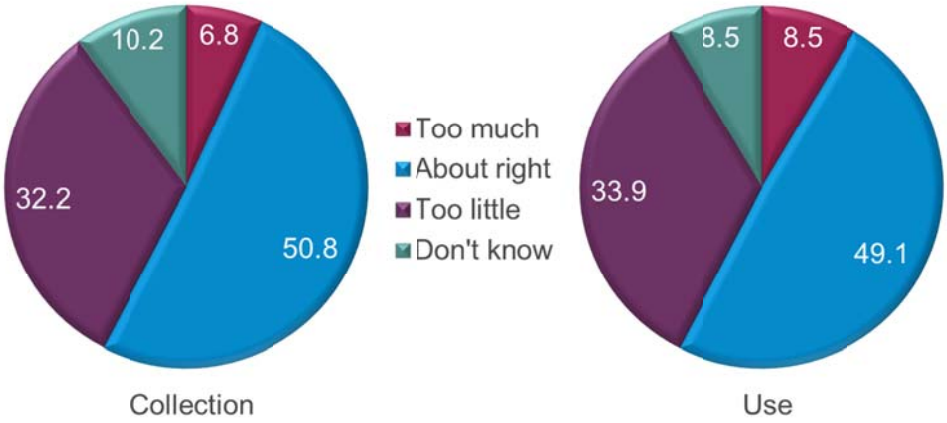


Figure 4: Impressions on the level of information available about the regulatory framework surrounding the collection and use of human tissue. *100% of respondents answered this question.*

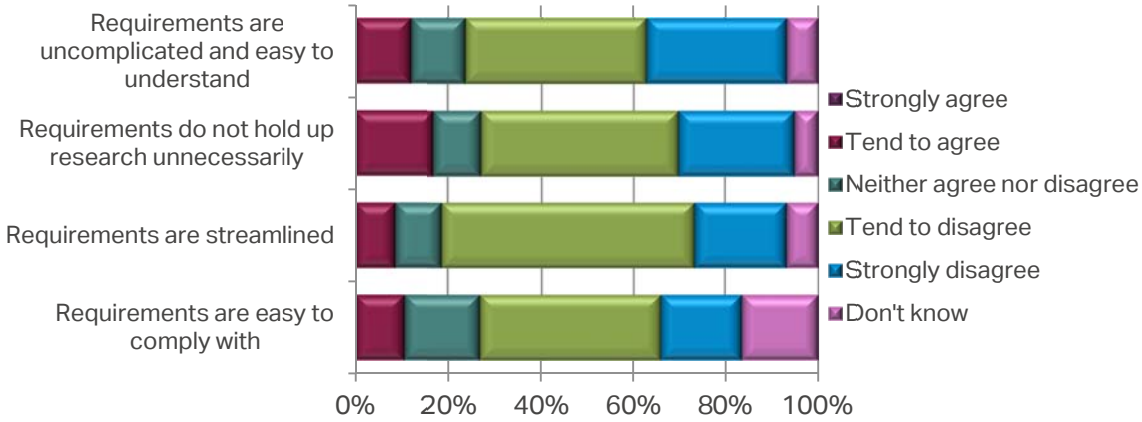


Figure 5: To what extent do respondents agree with the listed statements regarding the regulatory framework surrounding the use of human tissue in research? *100% of respondents answered this question. No respondents selected 'strongly agree' to any of the statements.*

Respondents were invited to leave any additional comments regarding the regulatory framework. Comments were varied with some suggesting that the regulatory framework is difficult to navigate and streamlining is required, and others saying that the requirements are not difficult or unduly complicated but the process is very time-consuming and more clarity in the guidelines is required.

## Knowledge surrounding the regulatory guidelines on human tissue

Respondents were provided with a list of nine types of biological material and asked to indicate which were classified as 'relevant material' covered by the Human Tissue Act, (2004).

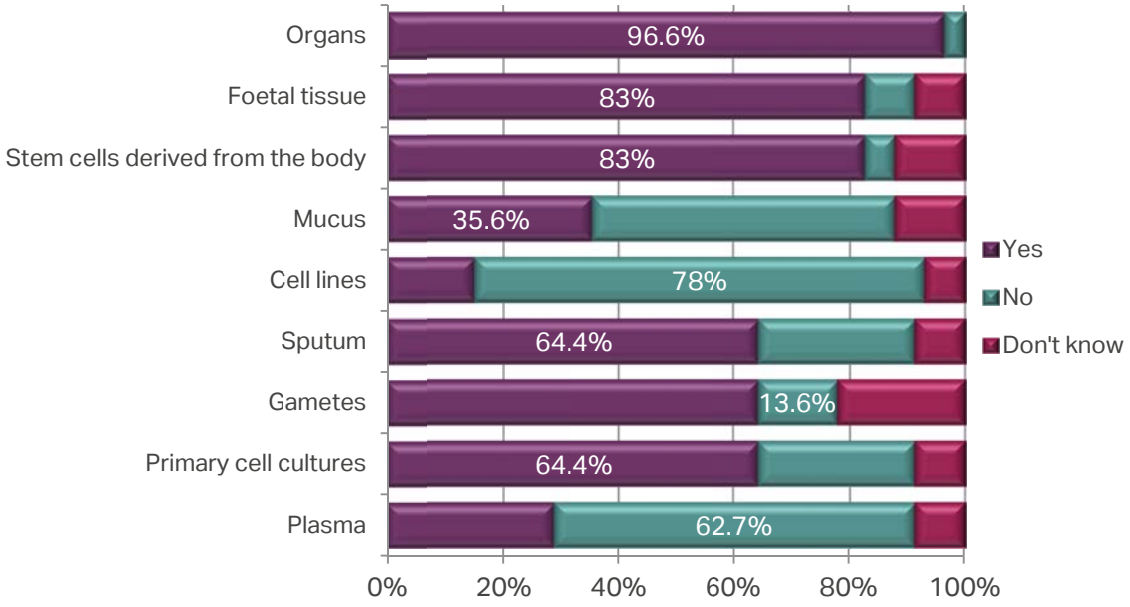


Figure 6: Responses to the question "What is considered relevant material covered by the human Tissue Act 2004?" The percentage of respondents who correctly identified whether a particular material was considered relevant or not is indicated within the appropriate bar. *100% of respondents answered this question.*

In general, there was a high level of awareness among respondents regarding what tissue is classed as 'relevant material' according to the Human Tissue Act (2004). For clarification, 'gametes' are a regulated material, but this is covered by the Human Fertilisation and Embryology Act (1990), not the Human Tissue Act (2004).

To determine the level of understanding around consent, survey respondents were presented with a series of nine statements and asked to identify which were true and which were false. Responses are shown in Figure 7.

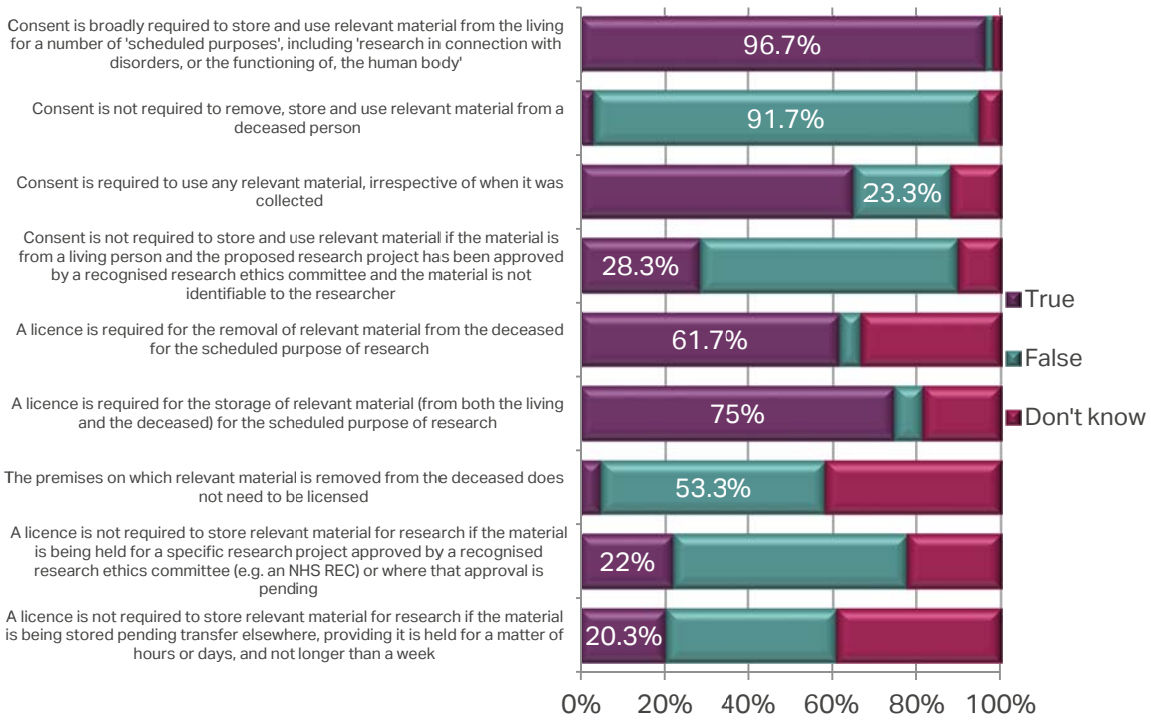


Figure 7: Responses to the question "Which of the following statements regarding consent are true or false?" The correct answer, and the percentage of respondents who correctly identified this, is indicated by a data label within the appropriate bar. *100% of respondents answered this question.*

Figure 8 shows the interaction that respondents have had with the Human Tissue Authority in the 12 months preceding the survey. Respondents were able to select all answers that applied. 71% do not recall any sort of interaction with the HTA. This includes eight respondents who exclusively use human tissue in their research.

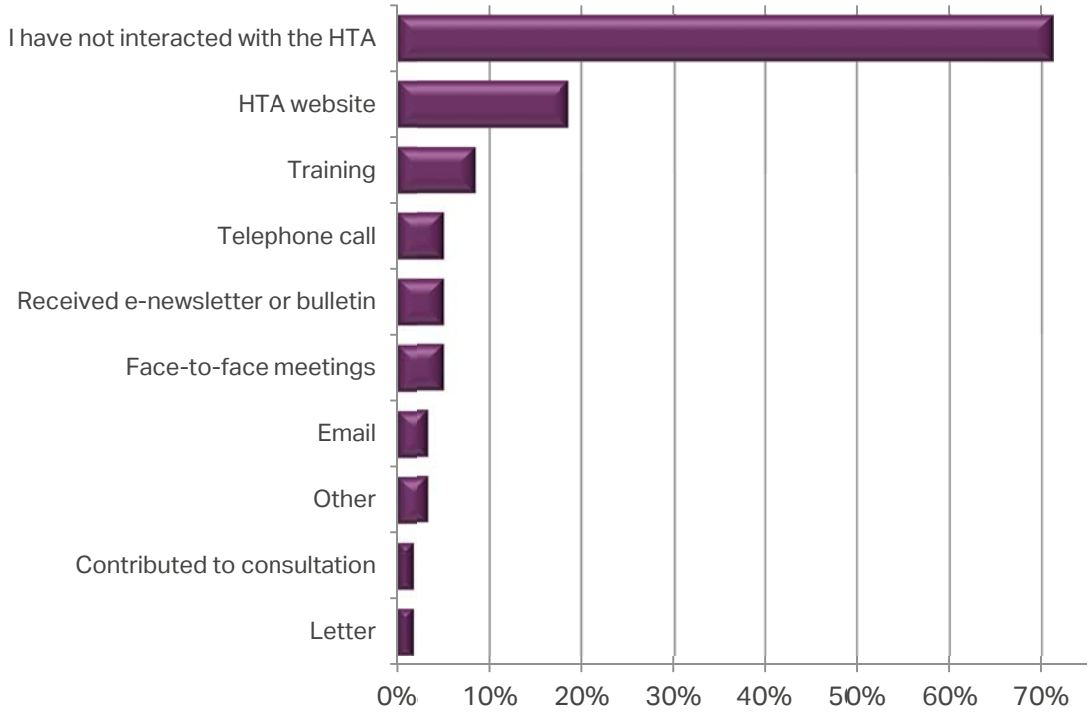


Figure 8: Responses to the question: "What interaction have you had with the human Tissue Authority in the last 12 months?" *100% of respondents answered this question.*

## Access to human tissue

This section of the survey initially asked two questions regarding knowledge of biobanks and tissue repositories. The first was "how much, if anything, do you know about the existence of biobanks/tissue repositories?" (Figure 9) and the second "how much, if anything, do you know about what fresh human material is available in biobanks/tissue repositories?" (Figure 10). Respondents were asked to choose a single option from the five available.

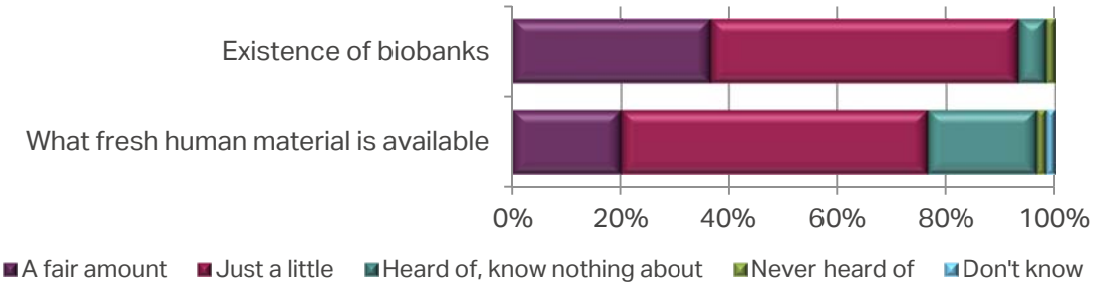


Figure 9: How much, if anything, do you know about the existence of biobanks/tissue repositories and what fresh human material is contained in them? *100% of respondents answered this question.*

Over 95% of researchers questioned were aware of the existence of biobanks, and almost 80% have some knowledge (know a fair amount or know just a little) of what material is available in them.

The survey then asked which resources they currently used to access human tissue for their asthma research. Respondents were able to select multiple options for this question, and 70% of respondents who currently use human tissue indicated they used more than one resource to access their tissue. The results indicate that researchers generally access human tissues from volunteers enrolled in their own research programmes or in the research programmes of collaborators. Less tissue is obtained from tissue banks/repositories. Taken together with the results from figures 9 and 10, this may suggest that there may currently be a lack of lung tissue available in biobanks.

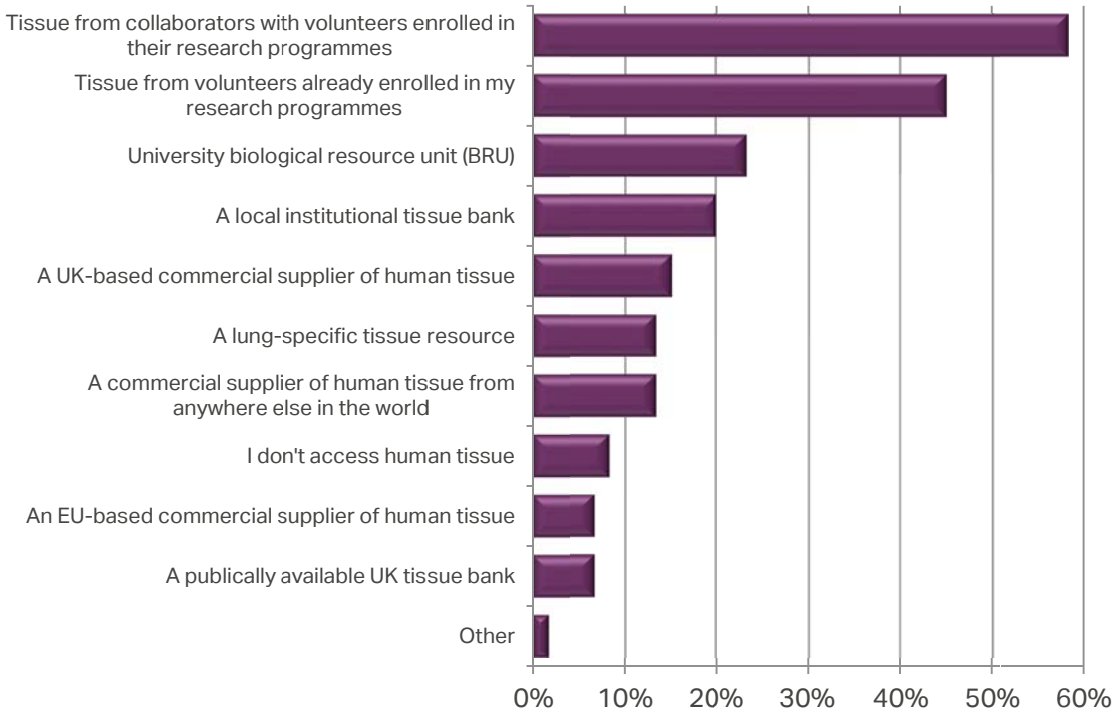


Figure 10: Which resources do you use to access human tissue for asthma research? *100% of respondents answered this question.*

Respondents were asked the question: "If available, how likely would you be to access a UK-based lung tissue bio-resource/tissue network to obtain fresh human tissue for your asthma research programme?" 83% of respondents indicated that they would be likely (selecting either fairly likely or very likely) to access such a resource if it were available.

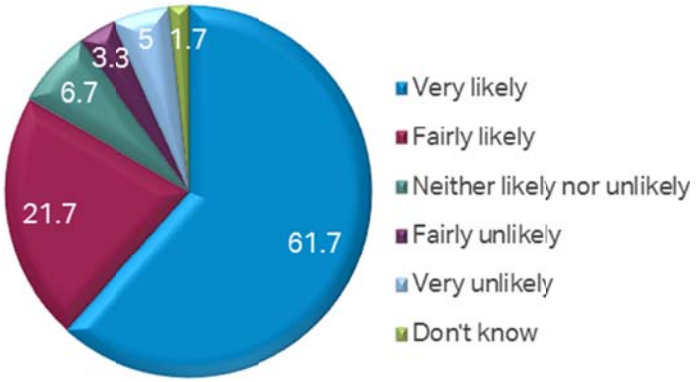


Figure 11. Answers to the question: If available, how likely would you be to access a UK-based lung tissue bio-resource/tissue network to obtain fresh human tissue for you asthma research programme? *100% of respondents answered this question.*

Reasons given for not accessing a bioresource/tissue network included:

- not being short of material, due to working on population based projects or having access locally
- there being a shortage of samples available within such a resource
- lack of trust in a biobank to maintain accurate and detailed information on clinical details of subjects

Finally, the respondents were provided with a series of four statements regarding their opinions on the potential impact of using human tissue in asthma research, and asked to indicate their level of agreement with each statement. As shown in figure 12, the majority of researchers surveyed believe an increased use of human tissue will increase our understanding of the pathobiology of asthma (93.4%), speed up the development of new therapies (88.4%), help develop more predictive animal models of asthma (81.7%) and reduce the number of animals used for asthma research (75.1%).

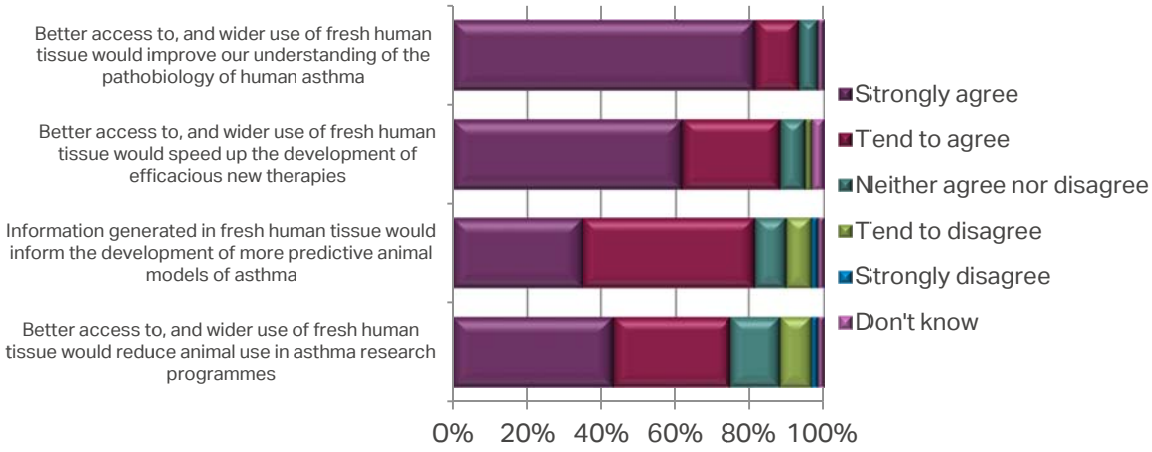


Figure 12: Potential impact of using more human tissue-based approaches in asthma research. *100% of respondents answered this question.*

## Summary

### Moving forward

The data presented in this report indicates that asthma researchers already use a range of human tissues as part of their research programmes and that there is a desire to utilise more, especially larger tissue sections or whole lungs, which are difficult to source. Respondents believe that the benefits of this include advancing our understanding of asthma and potentially reducing reliance on current animal models.

However, despite the widespread use of human tissues, the survey has highlighted a number of barriers, both real and perceived, to the wider adoption of human tissue-based approaches. The main barriers are the complex regulatory framework around using human tissue for research, and access to a reliable supply of normal and

diseased tissue. Overall, the barriers can be broadly grouped into several topics: access, funding, regulations, and validation.

Tackling these barriers has the potential to improve the uptake of human tissue-based approaches for respiratory disease research as a whole, and we suggest that the following steps should be considered:

- Publishing the survey results in a peer reviewed journal

The aim of this would be to raise awareness and provide some guidance on how to overcome some of the barriers to wider adoption of human tissue for asthma research. The article would include the survey results and case studies of how researchers are applying human tissues in their studies. The case studies would focus on how the barriers highlighted in the survey have been overcome.

- A workshop for sharing experiences

Working with the Human Tissue Authority, the aim would be to bring together the asthma community, the regulators, and researchers already using human tissue to provide a forum to share information on how to overcome the barriers highlighted in the survey. This would provide an opportunity to explore what flexibility exists to streamline the regulatory framework.

Case studies for the publication may come from this workshop.

- Engaging with journal editors to encourage publishing human tissue studies

The survey highlighted that researchers experience difficulty publishing studies using human tissues, preventing valuable information on the utility of these approaches entering the public domain. Engaging with the relevant journal editors to understand their views on human tissue studies and encouraging a change in practice, if necessary, would begin to address this barrier

- Promoting a more networked approach to tissue supply

The survey results show that some researchers are able to access the necessary tissue locally, whereas others are not able to do this. There are activities ongoing by others (e.g. MRC and UK Clinical Research Collaboration - http://www.ukcrc.org/research-infrastructure/experimental-medicine/funders-vision-for-human-tissue-resources/) to network together the publically available tissue banks and tissue repositories and a similar initiative, the Lung Tissue Research Consortium (LTRC), was launched by the U.S. National Institutes of Health (NIH). Therefore, rather than develop a separate programme of work, we should explore opportunities for engaging with these groups and focus on disseminating the output to relevant stakeholders. We believe that by implementing the above steps, a number of the barriers indicated in this survey can be addressed, allowing for more widespread uptake of human tissue-based approaches by the asthma research community.