

The Cell Therapy Catapult UK Preclinical Research Database as of June 2015

The UK Preclinical Research Database covers cell therapy research projects that the Cell Therapy Catapult considers to be two or less years from clinical studies. We believe that projects at this stage are sufficiently advanced to merit inclusion, in order to build a picture of the future cell therapy pipeline based on research being undertaken in the UK.

The database, updated annually, has been compiled and verified by the Cell Therapy Catapult team, and includes:

- **academic research in UK universities**
- **commercial research projects ongoing in the UK, where such information has been supplied to the Cell Therapy Catapult for the database, regardless of nationality of the sponsor.**
- **projects aimed at developing a therapeutic, rather than platform projects**

The purpose of the Cell therapy Catapult UK Preclinical Research Database

As a centre of translational excellence in the UK, the Cell Therapy Catapult is progressing a portfolio of projects with the UK and international community. The UK Preclinical Research Database gives us a valuable mechanism for tracking cell therapy trends and enables us to plan activities appropriately and identify research funding needs for the sector going forwards. It complements and leads into our UK Clinical Trials Database. The database is intended to be of use to academics, researchers and commercial organisations operating in the cell therapy space by allowing them to appreciate both the rich science base in the UK and future directions of the cell therapy activity.

For the 2015 database, data was collected in a slightly different format with projects aligned to technology readiness level (TRL) definitions (below) in order to better satisfy the stage of development of projects. Additional data such as funding source and whether/how a cell is gene modified was also collected to allow additional richness.

| Development stage | TRL | Description of activities covered |
|--------------------------|------------|--|
| Early preclinical | 3 | Hypothesis testing and initial proof-of-concept demonstrated in a limited number of <i>in vitro</i> and <i>in vivo</i> models. |
| Mid preclinical | 4 | Establishment of proof-of-concept of candidate therapy demonstrated in defined laboratory or animal models. Initial assessment of scale GMP manufacturing requirements, preclinical data requirements and regulatory environment. |
| Late preclinical | 5 | Preclinical safety and toxicity studies (including GLP studies) sufficient to support application to regulatory authorities for an initial (Phase I or Phase I/II) clinical trial. Development of GMP manufacturing process for therapy, assessment of reimbursement potential and design of initial clinical trial. |

A number of investigators requested that information about projects, supplied to the Cell Therapy Catapult, was kept confidential. Therefore, despite this data being included in the analysis reported here, these projects are not listed on the published preclinical database.

The interesting trends, highlighted within the database, are discussed below.

Commentary on Key findings

1) Number of Projects

A progressive increase in the number of projects listed, within the Preclinical Research Database, can be observed in the graph below (**Figure 1**). 55 projects were included for analysis within this report, an increase of 18 projects from the 2013 database and 10 projects from the 2014 database. Where possible, data is directly compared to the 2013 and 2014 Preclinical Research Databases and it is worth noting that 2 projects on the 2014 preclinical database have now progressed onto the clinical database, as they are now in first-in-man studies.

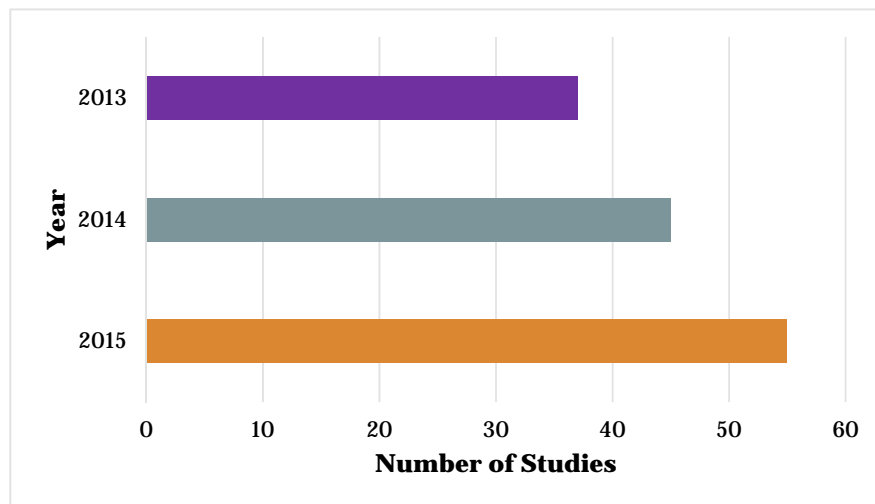


Figure 1. Number of studies listed in the Preclinical Research Database from 2013-2015

2) Disease area

Studies within the 2015 Preclinical Research Database cover a diverse range of disease indications, with the majority focusing on ophthalmology (31%), followed by neurology (18%) and oncology (11%) (**Figure 2**). Ophthalmology has predominated the preclinical database since 2013, which is likely attributed to the suitability of ophthalmic-based studies for translation into stem cell-based regenerative therapies. This is followed by cardiovascular (16% in 2014, 22% in 2013), and oncology (16% in 2014, 16% in 2013), owing to the continued burden of these non-communicable diseases. Interestingly, there has been a reduction in the number of orthopedic studies and an increase in neurological studies from 2013 to 2015. This is due to a

gradual shift in research efforts from bone and cartilage-based cell therapies towards neurological diseases and ischemic damage.

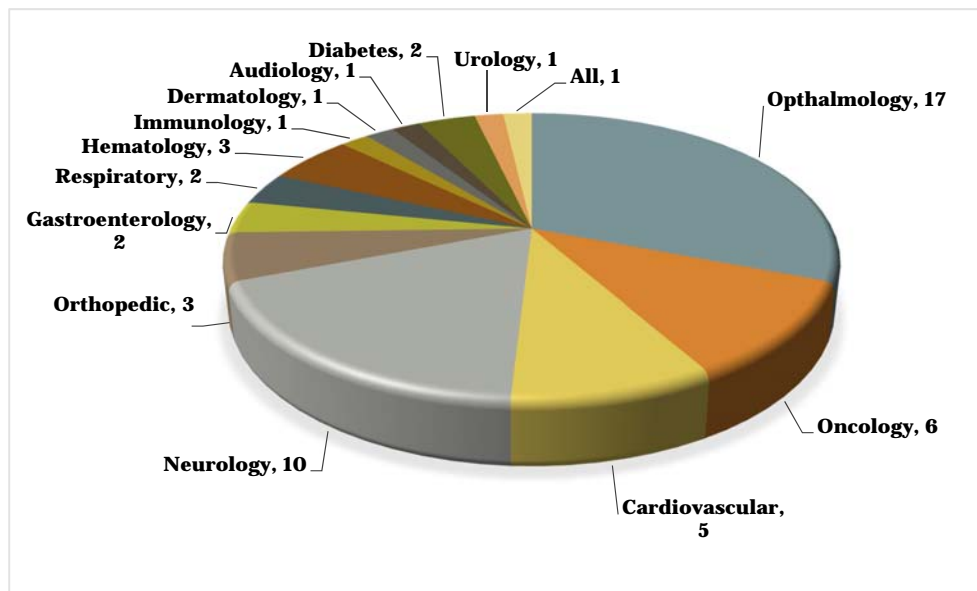


Figure 2. Disease areas represented by projects in the 2015 Preclinical Research Database

3) Cell type

Similarly to disease area, a wide range of cell types are being pursued in preclinical research. As seen below, mesenchymal stromal/stem cells (18%) and endothelial-based cell types (18%) are the most common within the 2015 database, followed by T-cells (11%) (**Figure 3**). The diversity in cell types being used in pre-clinical studies has increased from 15 in 2013 to 17 in 2015, as a result of scientific advancements and a growing number of research interest within the field. In general, the number of mesenchymal stromal/stem cells and endothelial cell-based studies has increased since 2013, whereas the number of T-cell therapies has slightly reduced. This could be attributed to an increasing focus on mesenchymal stromal/stem cells for immunotherapeutic purposes and endothelial cells for both ophthalmic and oncological indications. Furthermore, since 2013 there has been a continuous increase in the number of studies that are using retinal cells for the treatment of inherited retinal diseases, in addition to neural cells for ischemic and neurodegenerative conditions.

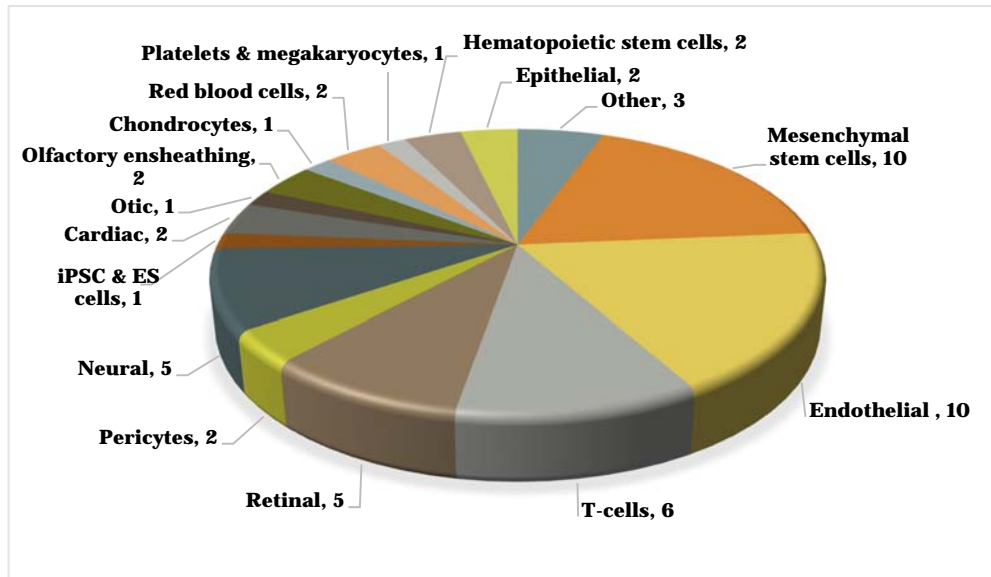


Figure 3. Projects within the 2015 Preclinical Research Database arranged by cell type
 iPSC & ES cells: induced pluripotent and stem cells & embryonic stem cells; BM mononuclear cells: bone marrow mononuclear cells. Other: islet cells, mesangioblasts, urothelial cells.

4) Cell source

Although the proportion of autologous to allogeneic cell-based projects has varied slightly from 2013 to 2015, there continues to be a higher proportion of autologous (49%) to allogeneic (38%) projects within the 2015 database due a minimised risk of systemic immunological reactions (**Figure 4**). The number of studies that utilise both cell types has increased since 201, which included 1 study, and has remained constant since 2014 with 7 studies.

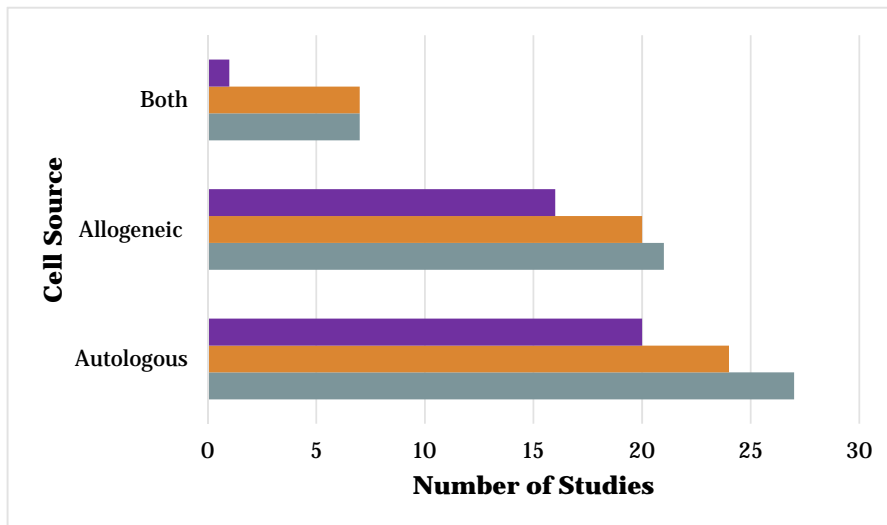


Figure 4. Number of preclinical studies using autologous, allogeneic or both cell types within the UK

2015 preclinical database (blue); 2014 preclinical database (orange); 2013 preclinical database (purple)

5) Gene Modification

In recent years, there has been an increase in the number of gene modification studies due to advancements in our understanding and the development of novel gene editing methods. Although the majority of studies do not incorporate gene-modification (83%) (**Figure 5**), 8 studies employ various methods of gene modification; 7 studies used retroviral vectors or microRNAs to influence cell gene expression, whilst 2 studies involved both retroviral gene transduction and gene-editing via CRISPR or human artificial chromosome-mediated gene replacement.

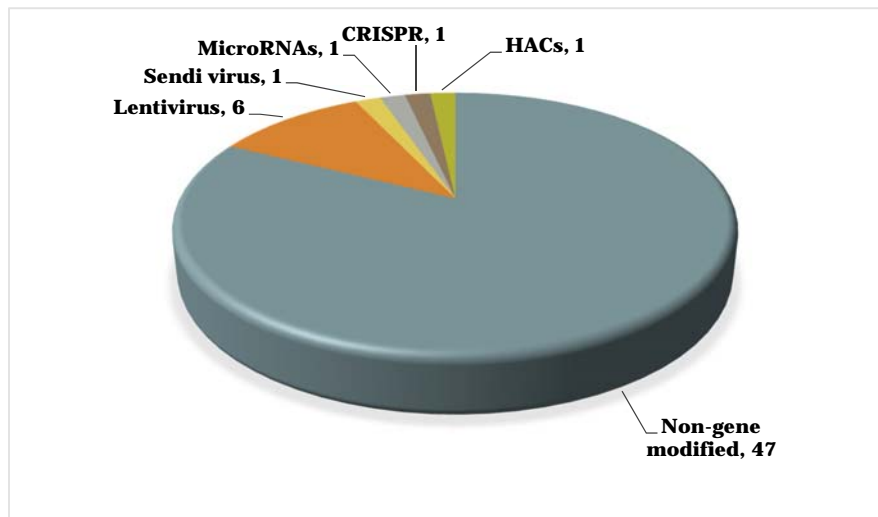


Figure 5. Types of gene editing techniques seen in the 2015 Preclinical Research Database

HACs: human artificial chromosomes

6) Technology readiness level

The major difference to the 2013 and 2014 databases is the way that we have recorded the development stage or project, using TRL definitions. This has allowed us to better stratify the development stage of projects and show that the number of projects at a later stage of preclinical development are increasing, compared to previous years. As seen below (**Figure 6**), the majority of studies within the Preclinical Research Database are TRL 3 (58%), generating initial proof-of-concept data in a limited number of *in vitro* and/or *in vivo* models. 25% of studies are TRL4, where further proof-of-concept data is being generated in addition to initial assessment of scale GMP manufacturing requirements, preclinical data requirements and the regulatory environment. The remaining 17% of projects are TRL 5, where sufficient GLP toxicity and animal safety studies have been undertaken to support application to the regulatory authorities for initial (safety and indication of efficacy) clinical trials.

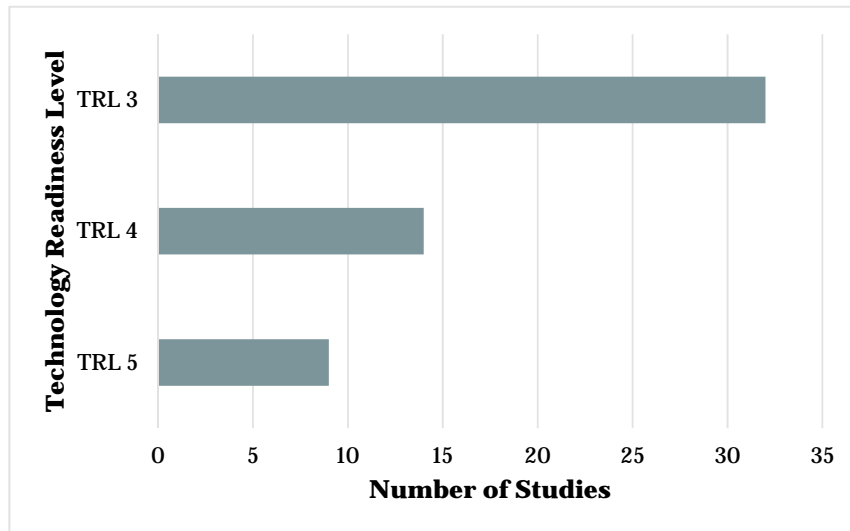


Figure 6. Proportion of projects at different TRL levels within the 2015 Preclinical Research Database

7) Sponsor

The proportion of research institutions has been consistently higher than the proportion of commercial sponsors, within the preclinical database, from 2013 to 2015. In 2015, the proportion of commercial sponsors is 7%, in comparison to 93% being research institutions (**Figure 7**). There are a number of reasons for the vast majority of preclinical research activities taking place in academic institutions, perhaps most predominantly due to public funding opportunities and the sheer volume of research and development that takes place within academic institutions.

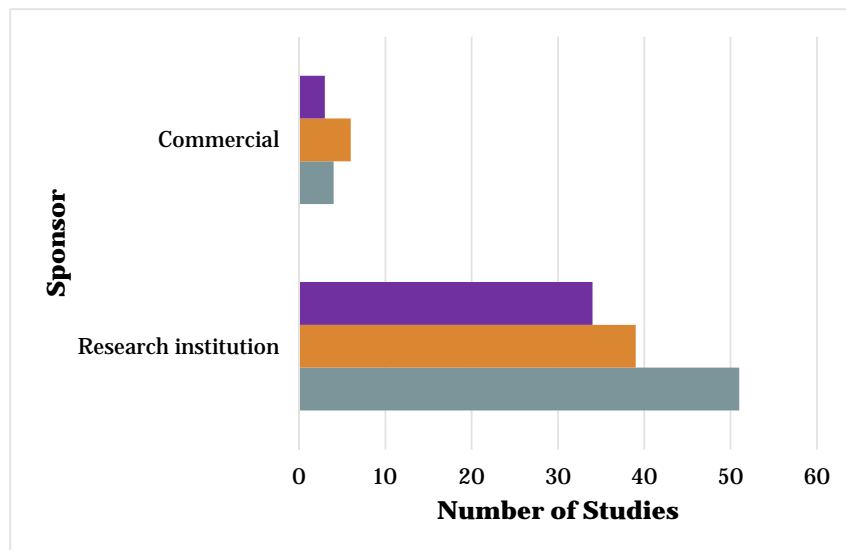


Figure 7. Proportion of commercial and research institution sponsors for project within the Preclinical Research Database

2015 preclinical database (blue); 2014 preclinical database (orange); 2013 preclinical database (purple)

8) Funding

There are a diverse range of funding bodies that have awarded grants to projects within the Preclinical Research Database. However, the clear majority of late-stage preclinical studies are being funded through the Medical Research Council or grants from the European Union (**Figure 7**).

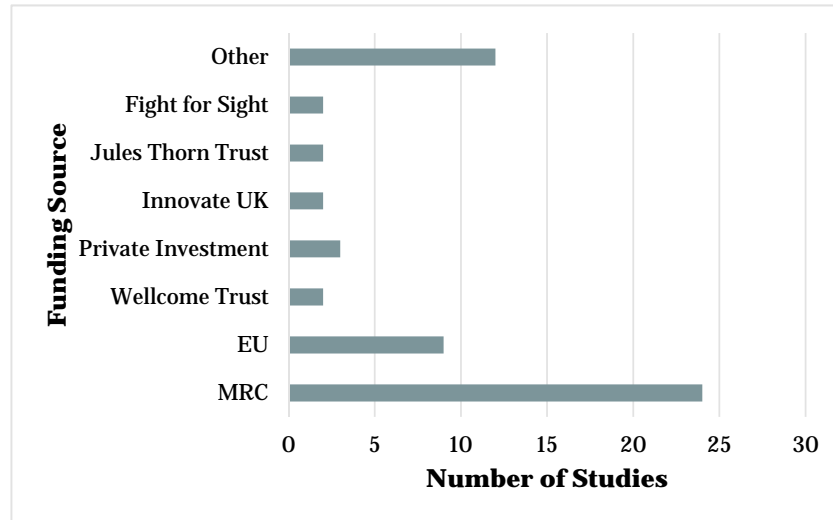


Figure 8. Funding streams obtained by projects within the 2015 Preclinical Research Database

MRC: Medical Research Council; EU: European Union. Other funding sources include: The Biotechnology and Biological Sciences Research Council, The Engineering and Physical Sciences Research Council, National Institute for Health Research, UK Stem Cell Foundation, Cancer Research UK, Scottish Funding Council, Diabetes UK, Juvenile Diabetes Research Foundation, Alzheimer’s Research UK, MS Societies, Biodesign, and the British Heart Foundation.

Obtaining funding for preclinical projects was identified as a specific challenge by a number of respondents and we hope that this database will prove useful for funders in helping them to understand the funding needs of this sector in the coming years, as these projects progress through preclinical development.

Conclusions

The Preclinical Research Database highlights the rich pipeline of cell therapies under development in the UK, which are likely to enter clinical development within the next two years. Many of the trends reflected herein – a dominance of research institution sponsors and a strong focus on neurology and oncology - are also seen in the Clinical Trials Database. Although it is early to be drawing definitive conclusions seen in the Preclinical Research Database, and bearing in mind the inherently speculative nature of the projects therein, it is encouraging to see a diverse range of cell types making their way to clinical trials in addition to successful advancements in neurology-based projects and those involving gene modification including editing technologies.



There has been a continued increase in the number of studies that are coming to the attention of the Cell Therapy Catapult on a yearly basis since the preclinical database was produced in 2013. It is also important to note the encouraging number of early preclinical studies, currently including 32 projects at TRL3, which will undoubtedly provide equally prosperous projects that are worth further pursuit. An important and increasing additional source of therapies entering the clinic in the UK is overseas sponsors, where the UK is selected to conduct the clinical trial based on its NHS clinical trial infrastructure. These projects are not represented currently in the Preclinical Research Database but are included in the Clinical Trials Database, once trials are ongoing. **June 2015.**