

The Cell and Gene Therapy Catapult UK preclinical research database

The UK preclinical research database includes cell and gene therapy research projects that the Cell and Gene Therapy Catapult (CGT Catapult) considers to be three 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 and gene therapy clinical pipeline based on research being undertaken in the UK.

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

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

The purpose of the CGT Catapult UK preclinical research database

As a centre of translational excellence in the UK, the CGT 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 and gene therapy trends and enables us to plan activities appropriately and identify research funding needs for the sector going forwards. It also complements and feeds into our UK clinical trials database. The database is intended to be of use to academics, researchers and commercial organisations operating in the cell and gene therapy space by providing insight of the diversity of the types of preclinical studies and demonstrating the rich science base in the UK. It is also used to provide an indication of the likely future directions of cell and gene therapy activity.

Project data was collected and aligned to technology readiness level (TRL) definitions in order to better classify the stage of development of projects (**Table 1**). For the purpose of this study, we have included studies classified at TRL 3-5 only. Additional data such as funding source, cell types used and whether/how a cell is gene modified, amongst other information, were also collected for enhanced data 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 good manufacturing process (GMP) requirements, preclinical data requirements and regulatory environment.
Late preclinical	5	Preclinical safety and toxicity studies (including good laboratory practice 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.

Table 1. Technology readiness level (TRL) definitions.

A number of investigators requested for their project information to be kept confidential. Consequently, despite this data being included in the analysis reported here for all 60 preclinical studies, only 44 of these studies are listed in the published UK preclinical database for 2016. Here in this report, we have quantified the data collected and discussed the interesting trends observed.

There are several challenges involved when collating new data and tracking studies at the preclinical stage of research. This is mainly due to the nature of the project information requested and also breaks in the research as a result of non-continuous funding, and so while this database represents some of the ongoing preclinical research in the UK, it is not exhaustive.

Commentary on key findings

1) Number of preclinical studies

The pipeline of preclinical cell and gene therapy studies in the UK has grown in the past 12 months, we have seen an increase in the number of studies we have been able to capture each year that are approximately three or less years away from the clinic (**Figure 1**). There were a total of 60 studies at TRL 3-5 that have been included in this year's database, which is a 9% increase from last year and a 62% increase from the first UK preclinical database published in 2013. Additionally, two of the preclinical studies that were listed at TRL 5 last year have progressed to clinical trials in the UK and have been included in our 2016 clinical trials database.

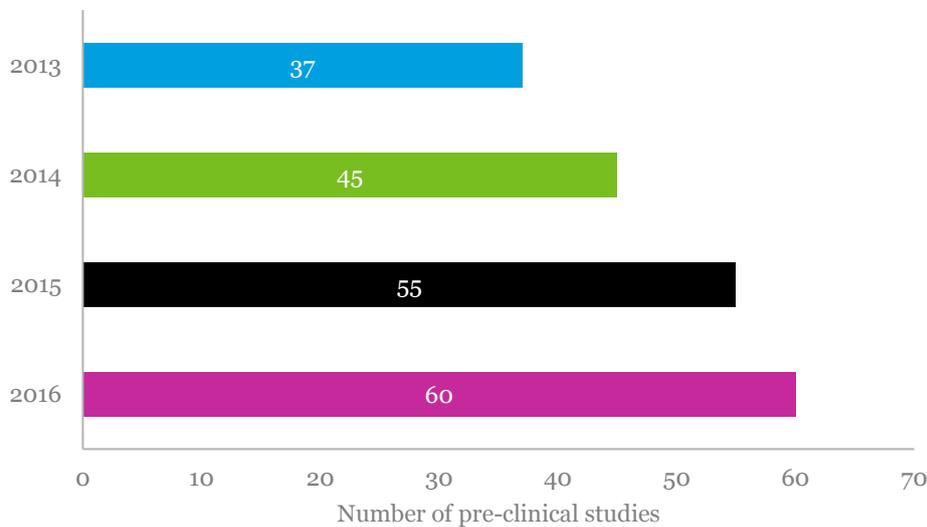


Figure 1. Number of UK preclinical studies identified from 2013-2016

2) Disease area

The preclinical studies that have been identified this year cover a broad range of disease areas, with the majority focusing on ophthalmology (23%), followed by cardiovascular (13%) and neurology and oncology (both 12%) (**Figure 2**).

Ophthalmology has been the most common disease area in the preclinical database each year since 2013, which is likely attributed to the suitability of ophthalmic-based studies for translation into cell-based regenerative therapies. In previous years this was followed by neurology (18% in 2015, 7% in 2014) and oncology (11% in 2015, 16% in 2014), owing to the continued burden of these non-communicable diseases. These trends were also reflected in the clinical database where the three main disease areas were oncology, neurology and ophthalmology.

Compared to last year's preclinical activity, the number of studies in cardiovascular and oncology areas has grown. Interestingly, there has also been an increase in the number of projects in the area of the neurology in the last two years, from a total of 17 in 2016 and 2015, compared with six in 2014 and 2013.

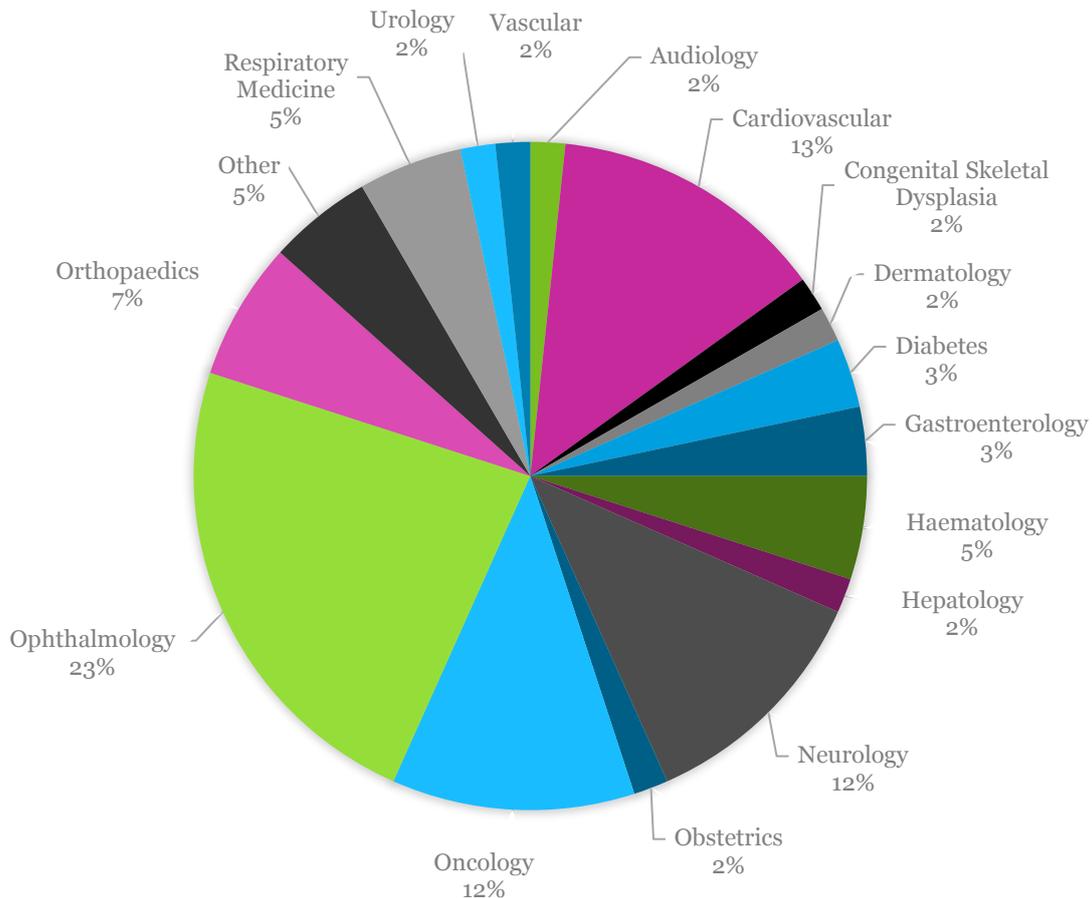


Figure 2. Disease areas studied in UK preclinical projects in 2016

3) Cell type

In line with the range of disease areas represented by the identified preclinical research undertaken in the UK, there was a wide range of therapeutic cell types being explored. Figure 3 shows that 20% of listed preclinical studies explored the use of mesenchymal stromal/stem cells, which was the most common cell type explored within the 2016 database, followed by induced pluripotent stem cells/embryonic stem cells (15%) and T-cells (10%) (**Figure 3**). Similar to last year's findings, there are 16 different cell types being investigated for preclinical stage cell and gene therapy research. In general, the number of mesenchymal stromal/stem cell-based studies has increased since 2015, with their application predominantly in the area of cardiovascular and orthopaedics this year. The preclinical studies exploring the use of pluripotent stems cells are mainly in the area of ophthalmology.

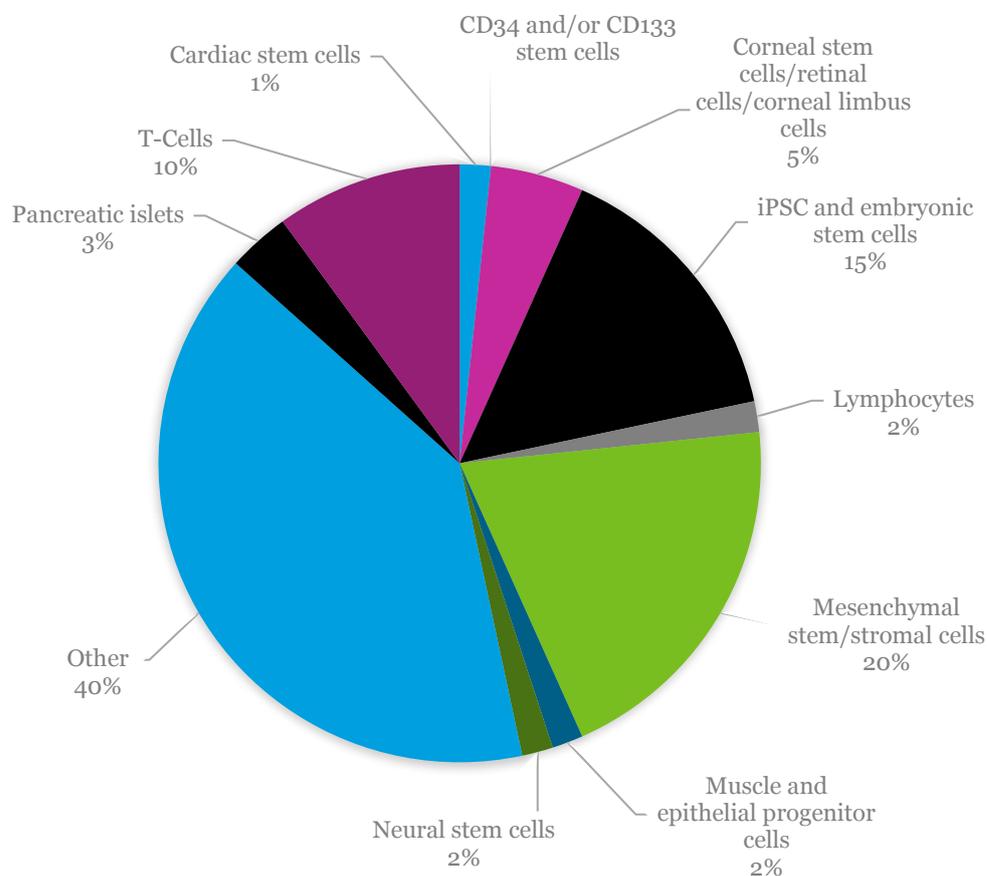


Figure 3. Therapeutic cell types investigated in UK preclinical research in 2016

The 'other' category was comprised of the following cell types: cord blood cells, bone marrow cells, adipose cells, bladder-derived cells, and cells derived from muscle and oral biopsies.

4) Cell source

There has been an increase in the number of autologous and allogeneic projects each year (**Figure 4**). The proportion of autologous to allogeneic studies has remained fairly constant from 2013 to 2016. Although, there has consistently been a greater proportion of autologous projects listed each year, the difference between the number of autologous and allogeneic projects has not been greater than six. This is in contrast to observations in the UK clinical trial database where the ratio of autologous to allogeneic studies was 2:1. The number of studies that explore the use of both autologous and allogeneic cell types as part of one therapy has decreased this year to three from the seven studies identified last year in 2015.

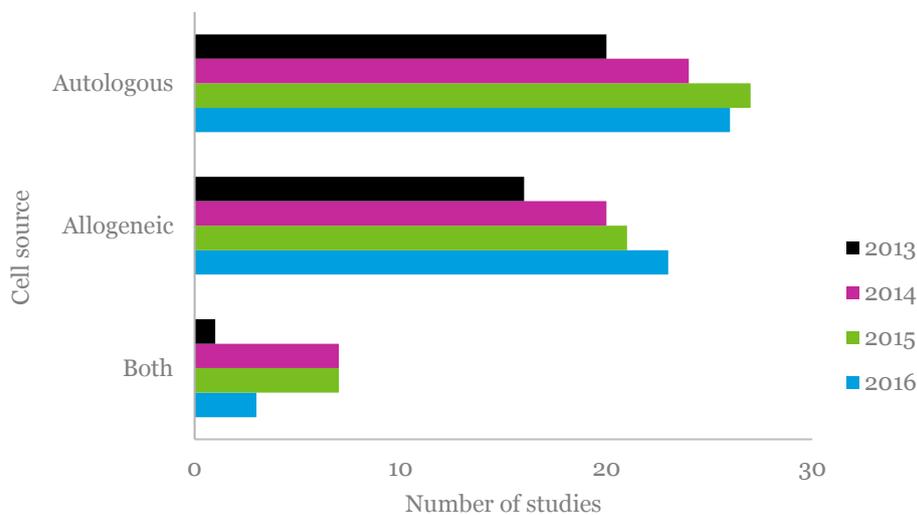


Figure 4. The number of UK preclinical studies exploring the use of autologous, allogeneic or both cell sources

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 modification methods. Although the majority of studies do not incorporate gene-modification (82%) (**Figure 5**), 11 studies employ various methods of gene modification, half of which use lentiviral vectors to modify gene expression.

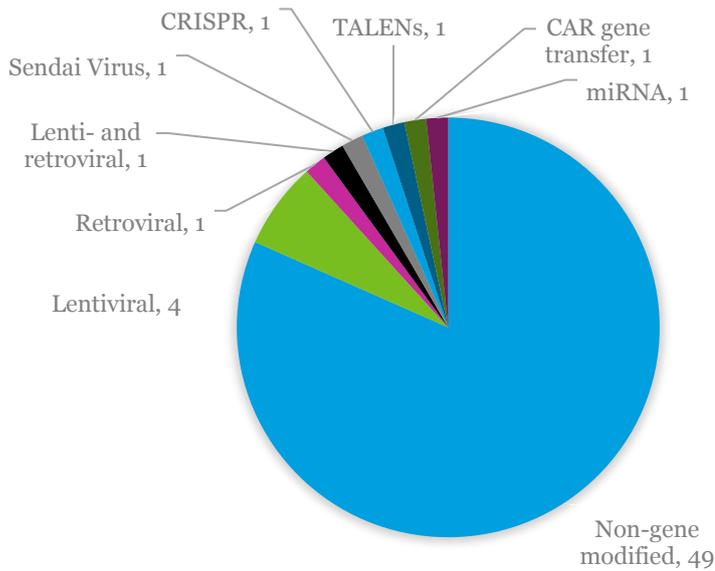


Figure 5. Gene modification techniques used in the identified UK preclinical studies in 2016

6) Technology readiness level

The development stage of the preclinical studies identified have been classified according to their technology readiness level (TRL) (**Table 1**). For the purpose of this study, projects that are defined as TRL 3 and above, which are considered to be no more than three years away from the clinic have been included in this analysis. Figure 6 shows that 60% of studies identified are at the stage of generating initial proof of concept data in a limited number of *in vitro* and/or *in vivo* models (TRL 3), compared to 58% last year. There are fewer projects at TRL 4 this year compared to last year's database, however the number of projects at TRL 5 has increased by 56% this year from the 2015 database (**Figure 6**).

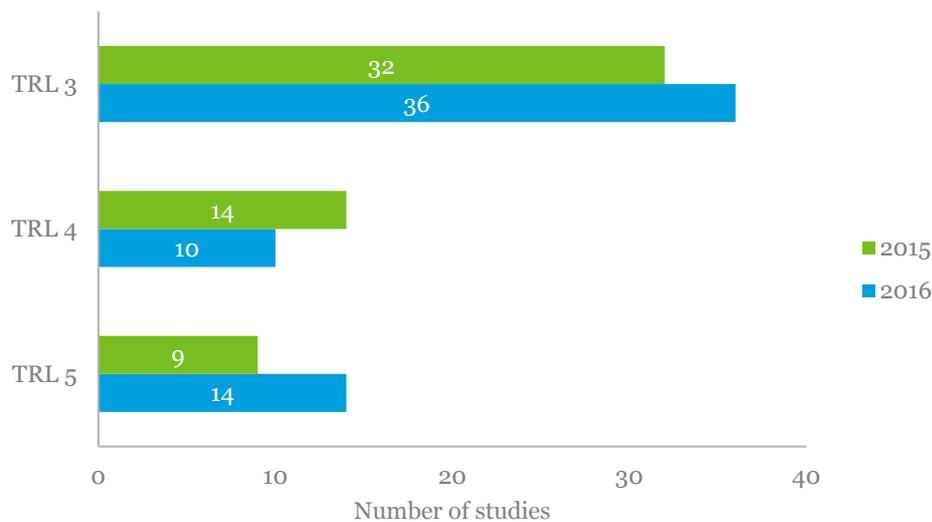


Figure 6. The number of projects at TRL 3, 4 and 5 in 2015 and 2016 (data not available for previous years)

7) Sponsor

The proportion of identified projects carried out at research institutions has been consistently higher than the proportion carried out at commercial organisations each year. In the 2016 UK preclinical research database commentary, 15% of the preclinical projects were carried out at commercial organisations, compared to 85% at research institutions (**Figure 7**). The number of preclinical studies at research institutions has remained the same as last year, while the number of preclinical studies at commercial organisations has increased since last year by 5 projects. Interestingly, in 2016, the majority of projects carried out at research institutions were early-stage studies with 67% at TRL 3, compared with 22% of studies at commercial organisations classified to be at TRL 3. In contrast, the majority of studies at commercial organisations were late-stage studies, with 56% classified at TRL 5, compared to 18% at TRL 5 at research institutions.

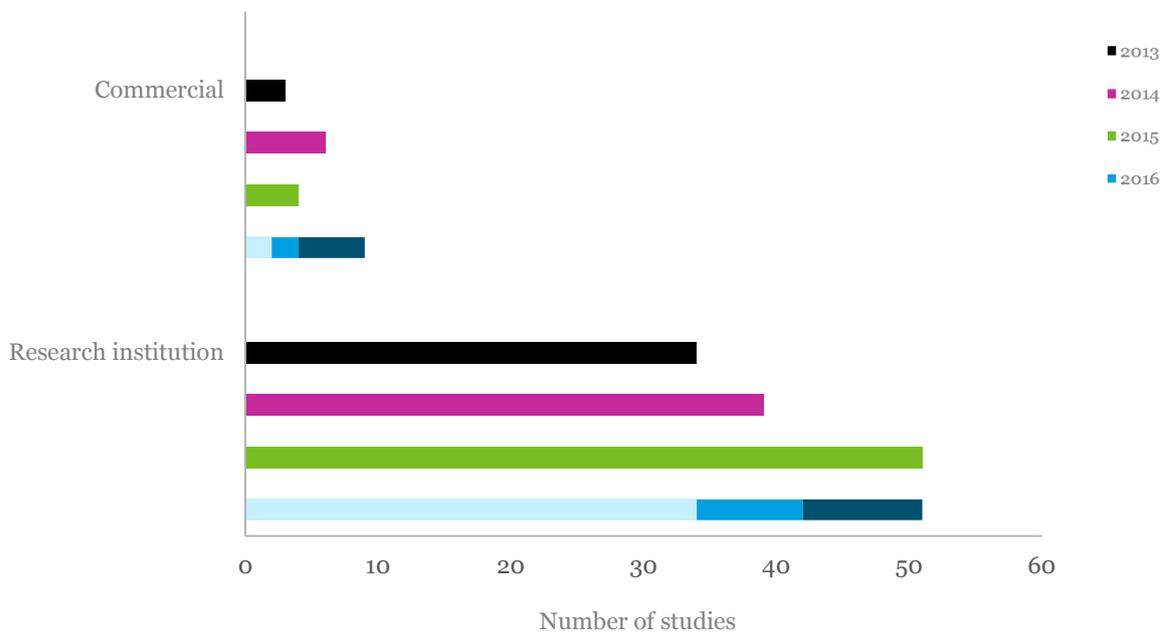


Figure 7. The number of preclinical studies carried out in commercial organisations and research institutions
For the bar representing 2016: light blue represents TRL 3 studies, medium blue represents TRL 4 and dark blue represents TRL 5 studies.

8) Funding

The identified preclinical projects are supported by several different funding bodies and from private investment (**Figure 7**). The majority of the 14 late-stage preclinical studies are solely or co-funded by EU grants (five projects) and private investment (three projects). The following bodies each supported two late-stage projects: Innovate UK, Medical Research Council, British Heart Foundation and the Wellcome Trust.

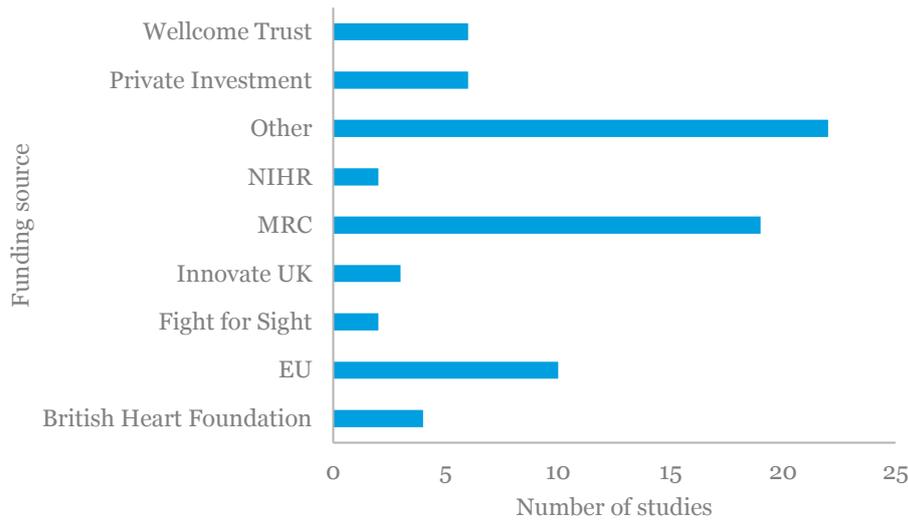


Figure 8. Funding streams obtained by identified preclinical projects in 2016

MRC: Medical Research Council; EU: European Union; NIHR: National Institute for Health Research. Other funding sources include: UK Stem Cell Foundation, Cancer Research Wales, Scottish Funding Council, Diabetes UK, Alzheimer's Research UK, MS Societies, Rosetrees Trust, Stonegate Trust, Great Ormond Street Hospital, Scottish National Blood Transfusion Service, University College London Hospital Biomedical Research Centre, Imperial Confidence in Concept Fund, Leverhulme Trust, UK Regenerative Medicine hub, Jules Thorn Foundation, Innovation and Knowledge Centre Medical Technologies, Defense Science and Technology Laboratory, Cure Huntington's Disease Initiative Foundation, and Juvenile Diabetes Research Foundation.

Conclusions

The 2016 preclinical research database commentary showcases the diversity of the UK cell and gene therapy pipeline, which are likely to enter clinical development within the next three years. In the last year, two of the identified projects in last year's database have progressed into clinical development but despite this reduction, the number of identified preclinical studies have increased by five projects. The majority of preclinical studies are exploring therapies for the following disease areas: ophthalmology, cardiovascular, neurology and oncology (**Figure 2**).

The number of ongoing cell and gene therapy projects tracked and identified in the preclinical research database and commentary has increased each year. The growth of the preclinical database is also representative of the progression of research in the cell and gene therapy space in the UK, with new activity in the areas of oncology and cardiovascular research this year. Please do note that while effort was made to capture and include information for as many preclinical studies as possible, the database is not complete and does not include all ongoing UK preclinical studies.