PRECLINICAL SERVICES AND CLINICAL BIOMARKER INDUSTRY SURVEY REPORT

Introduction

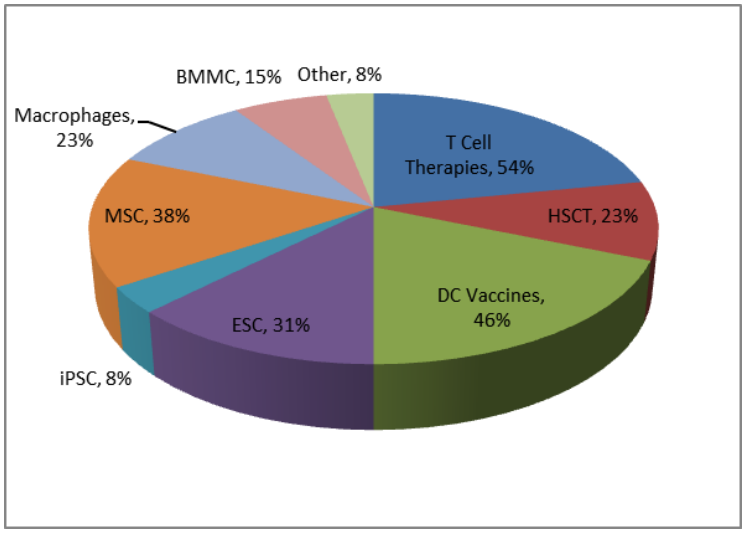
The Cell Therapy Catapult is working to make the UK a global leader in the development, delivery and commercialisation of cell therapies. The Cell Therapy Catapult, in conjunction with the HealthTech and Medicines Knowledge Transfer Network, has recently conducted a survey to develop an understanding of the UK Preclinical Services and Clinical Biomarker Industry available to support cell therapy programmes.

Thirteen organisations participated and the survey findings are summarised. The Cell Therapy Catapult hopes that this report will be of use to academics, researchers and commercial organisations operating in the cell therapy space by allowing them to appreciate the breadth of preclinical services and clinical biomarker service provision available within the UK to support the development of cell therapy products.

Organisational Profile and Experience

The UK has a breadth of preclinical services and clinical biomarker contract research organisation (CRO) facilities, from large multi-national organisations (multiple disciplines) to specialist CROs (biomarkers, immunology, histology and pathology, animal models and surgical). UK CROs have a range of laboratory accreditation (GLP, GCLP, GMP, GCP, HTA, ISO9001 and AALAC), with over half of the organisations registered on the UK GLP compliance monitoring programmes.

Figure 1 Breadth of cell therapy experience within the UK preclinical services and clinical biomarker industry, showing % of CROs with experience of different classes of cell therapies.



As Figure 1 shows, UK CROs have worked on programmes for a diverse range of cell therapies and while T cell therapies and dendritic cell (DC) vaccines dominate, experience is being established in the newer pluripotent cell therapies. All organisations performing animal research do so in accordance with UK Animals (Scientific Procedures) Act 1986 to ensure that research and testing using animals is safe and reasonable.

Preclinical Assessment of Cell Therapy Products

The design and conduct of the preclinical programme helps inform regulatory decisions regarding the safe administration of a novel cell therapy product into humans. Cell therapies cover a broad range of products and as such there is no one-size-fits-all development strategy from bench to clinic. There is variety in type of cell therapy (pluripotent cell therapies, adult stem cell therapies, immune cell therapies and other somatic cell therapies), source of cell therapy (embryonic cells, bone marrow, adipose tissue, peripheral blood, etc.), autologous versus allogeneic donation and disease indication.

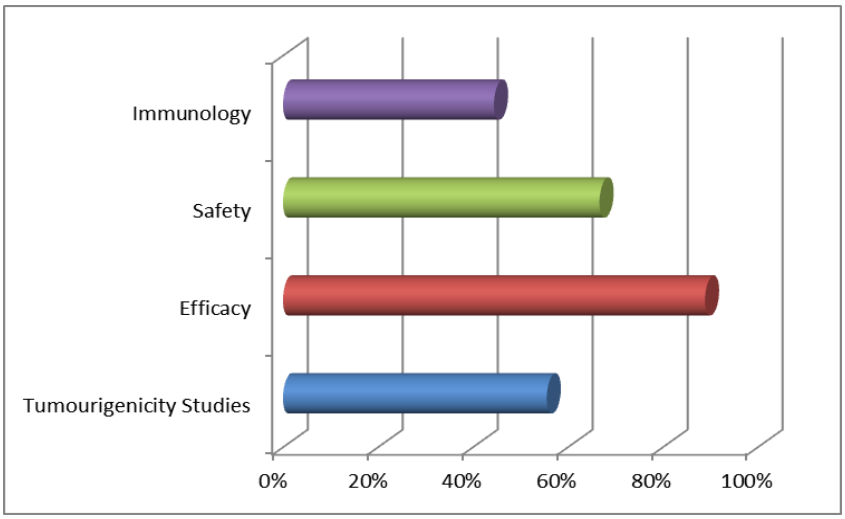
The development strategy is therefore specific for each individual project. The types of studies required for a given programme will be cell therapy specific and scientifically driven and an extensive package of animal studies may not always be appropriate. There are however, common goals; a balance between potential risk and the ability to assess that risk, proof of concept studies and an assessment of safety. Key to the design of the scientifically robust programme is an understanding of the specific product characteristics, the mechanism of action and clinical application.

The traditional, standardized approaches for preclinical testing, which were developed for drug development and device testing, are often not appropriate for the preclinical evaluation of cell therapy products. UK CROs have a wealth of scientific experience across multiple disciplines that can help facilitate the design and delivery of appropriate preclinical programmes for a given cell therapy. Some aspects of the preclinical programme such as efficacy and safety apply to all therapies, for some cell therapies however, specific safety aspects need to be considered (e.g.):

- Allogeneic cell therapies - an assessment of potential for unacceptable immune responses
- Pluripotent cell therapies – an assessment of tumorigenic potential

While efficacy and safety studies dominate, the UK preclinical services industry has experience across the range of study types, as Figure 2 shows.

Figure 2 The percentage of UK preclinical in vivo CROs that have experience in the major study formats that may be used to assess the safety and efficacy of cell therapy products. The types of studies required for a given programme will be cell therapy specific and scientifically driven



Models of Disease

Unlike safety programmes for traditional small molecules, where established in vivo safety studies are appropriate, for a given cell therapy, the appropriate efficacy and safety studies will typically be evaluated scientifically on a case by case basis. Where possible, safety studies are conducted together with efficacy measures in the most suitable and translatable animal model of the human disease state to be treated. This brings with it unique challenges; the inherent variability of the models, limited historical data and complex pathology. By careful design of programmes and engagement with pathology specialists it is possible to maximise the predictive value of preclinical studies and take the opportunity to incorporate the principles of the 3Rs (refine, replace, reduce animal use) into the preclinical programme. Well characterised models provide a depth of knowledge of the historical characteristics of the disease models facilitating the design and interpretation of studies. Although many highly specialist animal disease models reside within academic facilities, a range of animal models are also available and validated within the UK commercial setting (Table 1).

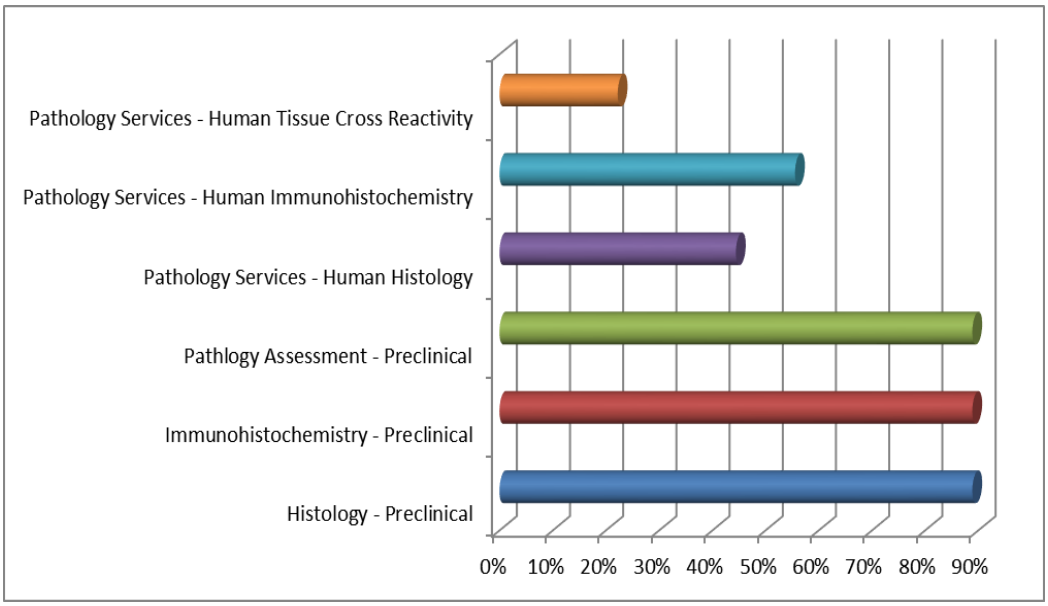
Table 1 Commercially available animal models cover a wide range of major disease areas.

Animal Models	
Oncology	Immunology
Surgical	Infectious Disease
Pain	Wound Healing
Inflammation	

Pathology Services

UK CROs have extensive experience in both preclinical and human tissue services (Figure 3). The pathologist has a pivotal role in the preclinical development programme of many cell therapy products particularly those employing animal models of disease; from the characterization of tissue responses in complex models, to helping to distinguish optimal from deficient regeneration/repair.

Figure 3 Pathology activities to support cell therapy clinical trials utilise both clinical and preclinical tissues, dependent on the development programme. The graph represents the percentage of UK in vivo CROs with experience in different pathology techniques.



The preclinical development programme may also employ the use of donated human tissue samples (e.g. tissues for characterisation of antigen expression). The European Union Tissue and Cells Directive (EUTCD) has established a harmonised approach to the regulation of tissues and cells across Europe. The Directives were fully implemented into UK law via the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations). In the UK all human tissues donated for research activities are collected under these provisions of the Human Tissue Act 2004 (England, Wales and Northern Ireland) or Human Tissue (Scotland) Act 2006 to ensure that human tissue is used safely and ethically, and with proper consent/authorisation. Where human tissues are stored the establishments are suitably HTA licensed.

Distribution and Persistence

An important efficacy and safety consideration for cell therapy products is the biodistribution of the administered product, with a need to understand the potential for trafficking, homing and persistence of cells in both target and non-target tissues. Distribution potential will be impacted by the route of administration, use of scaffolds and matrices and whether the cell

therapy exerts biological function via trophic mechanisms (e.g. home to specific tissues particularly when the tissues are damaged or diseased).

Understanding the distribution and persistence of a cell therapy is a major technical challenge and developing novel imaging modalities remains an area of active academic research (for example; UK Regenerative Medicine Platform – Safety and Efficacy, focussing on Imaging Technologies [Universities of Liverpool, Manchester, Edinburgh and University College London] and the MRC award of £2.77 Million for the establishment of a state of the art imaging facility at the University of Bristol [October 2103]). A further challenge is to expedite clinical translation of the technologies to enable the distribution and behaviour of transplanted cells to be monitored in both model systems and in man.

Table 2 Range of technologies available for assessment of biodistribution and persistence of cell therapies from molecular techniques to live cell imaging.

Imaging Technologies	
QPCR	MRI
Quantum Dots	PET
Flow Cytometry	Autoradiography
Fluorescent Imaging Microscopy	CT Scanning
Fluorescent Whole Body Imaging	

There currently is no one single satisfactory method for assessing biodistribution and a pragmatic approach is recommended on a per project basis. A wide variety of techniques are being employed within UK CROs for use in preclinical studies (Table 2), from in vivo live cell imaging to QPCR assessments of tissues.

Immunology Services

A cell therapy may be derived from an immune cell, may modulate immune function or may induce an immune reaction (intentionally or unintentionally). An immunology assessment therefore forms a critical component of cell therapy preclinical development packages. However immunogenicity and immunotoxicity may be difficult to address in preclinical models.

Table 3 Assays are offered to enable the assessment of the breadth of immune system activity.

Range of Assays Available for Assessment of Immune Responses	
Natural Killer Cell	Flow Cytometry
Multiplex Cytokine	Cytokine Storm Assay
Cytokine Release	HLA Typing
Intracellular Cytokine	Phagocytosis
Extracellular Markers	MHC Peptide Binding
Apoptosis	MHC Multimer Staining
Cytotoxicity	ELISPOT
ELISAs	Peptide/Protein Ligand Binding
Cell Activation	Biacore
Cell Proliferation	Bespoke Services

Administration of the clinical product into an immune competent animal is a xenogeneic situation and any responses generated may not reflect the clinical setting. Studies in an immune deficient animal will also not reflect potential clinical responses. Therefore many programmes comprise a comprehensive in vitro panel of assays as part of the risk-benefit assessment of the product. A number of UK CROs support preclinical and/or clinical immunogenicity testing, from establishing bespoke assays to running routine immunological assessments (Table 3). Assays developed to support preclinical studies can frequently be cross validated for analysis of the same endpoints in clinical samples.

Biomarker Services

In 1998, the US National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Biomarkers are by definition objective, quantifiable characteristics of biological processes. The range of biomarker endpoints and assays available within UK CROs are extensive (Table 4). Biomarker assays are performed on a wide variety of matrices and may be critical to assessing the efficacy and safety of cell based therapies in both animal models of disease and the clinical population. The use of animal models to evaluate pharmacodynamic biomarkers is ideal for transfer of this knowledge for predictive biomarker analysis in human tissues from proof of concept clinical trials. Indeed the use of animal models of disease provides the opportunity for possible identification of activity-risk biomarkers that may be applicable for clinical monitoring.

Table 4 A broad spectrum of assays are available to provide measures of a biological state

Range of Biomarker Assays and Panels	
Oncology	Biomarker Panels
Renal	Cell Signaling Pathways
Hepatic	Cardiac
Prediction Analysis	Metabolic
Multiplex Platforms	Toxicity
IHC Protein Biomarkers – Clinical	Vascular and Growth Factor
IHC Protein Biomarkers - Preclinical	Target Protein Expression

Summary

Cell based therapies represent an exciting therapeutic class that could revolutionise the treatment of multiple diseases. As with any medicinal product a thorough examination of efficacy and safety is essential prior to progression into the clinic. UK preclinical and clinical biomarkers CROs with a wealth and breadth of experience are well placed to support the development of these novel programmes.

Cell Therapy Catapult, February 2014

Contact Information:

Organisations looking to design preclinical packages and looking for service providers can get advice / contacts from the Cell Therapy Catapult: info@ct.catapult.org.

Acknowledgements:

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