The Target Discovery Institute
Cellular High Throughput Screening

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HIDI
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TDI Cellular Screening Facility & CRISPR Screening

1. Target Discovery

2. CRISPR/Cas 9 Cell Screening Facility

   Introduction

   CRISPR/Cas9 technology is ideally suited for genome-wide screening applications due to the ease of generating guide RNAs (gRNAs) and the versatility of Cas9 or Cas9 derivatives to knockdown, repress, or activate expression of target genes. Several pooled lentiviral CRISPR libraries have been developed and are now publicly available. Here at the TDI we have Pooled Lentiviral CRISPR genome knockout and CRISPRa gain of function libraries.

   Daniel Elmer, Elena Novoa-Guerrero and Dylan Jones
1. TDI Cellular HTS Screening

If you are interested in initiating a screen, just send me an email:

daniel.ebner@ndm.ox.ac.uk

http://www.tdi.ox.ac.uk/high-throughput-screening
"Negative autoregulation of BMP dependent transcription by SIN3B splicing reveals a role for RBM39." Faherty et al., Bhattachary - RDM

"The retinoid agonist Tazarotene promotes angiogenesis and wound regeneration" ZEN - RDM

"A genome-wide IR-induced RAD51 foci RNAi screen identifies CDC73 involved in chromatin remodeling for DNA repair" Helleday – Oncology

"Systematic Functional Characterization of Candidate Causal Genes for Type 2 Diabetes Risk Variants" Thomsen, Ceroni,

"Benzimidazoles promote anti-TNF induced regulatory macrophage formation and potentiate therapeutic effect in vivo model of IBD" Wildenberg - Academic Medical Center, Amsterdam

"BET inhibition as a new strategy for the treatment of gastric cancer" Montenegro et al. Müller – TDI/SGC
Open Assay Calls

This is an open call for phenotypic assay proposals funded by the Phenomics Discovery Initiative (PDi). PDi is a public-private partnership between industrial pharmaceutical companies and NPSC. PDi seeks to identify, develop, screen and validate innovative phenotypic assays that are relevant to human disease.

Selected proposals are screened free of charge. The deadline for the next round of selections is Autumn 2017 (date TBD).

[Find out more about PDi](http://npsc.ac.uk/) *We use the EU Commission definition of SMEs that can be found here.*

**How to apply?**

Phenotypic assays are recruited from academic, clinical and SME communities through an online applications portal. Assays can be at various stages of development, from an early concept to a screening format, the well / 384-well. Assays are assessed and selected by the PDi scientific committee, which is made up of a panel of industry and academic experts. Important characteristics for selection are scientific.
Phenotypic assays that accurately model the complexity of the tumour microenvironment. These should allow screening to be carried out in more relevant immune contexts, and be more representative of the pathophysiology of the disease.

Novel assays for intracellular (or even extracellular) immune-regulatory mechanisms that cannot be targeted by current monoclonal antibody-based approaches. These assays should help broaden the potential mechanisms that can be targeted by new therapies.

Assays that allow the discovery of small molecules that synergise with known therapeutics (biologics or CAR-T) to extend their scope and efficacy.

Models for immunologically "warming" up "cold" tumours, including ones involving infiltration of 3D tumour spheroids by T cells. It is expected that these models will be complex in order to accurately represent the disease model.

Models that can explore novel ways of activating exhausted intra-tumoral T cells.

Models involving the manipulation of immunosuppressive Treg cells and/or key cytokines.

Assays that involve other immunosuppressive cell types (for example, MDSCs, dendritic cells and TAMs).

Models that could uncover new targets in innate immune system cell types (eg. NK cells, dendritic cells and macrophages).

http://npsc.ac.uk/open-assay-calls
3. Oxford CRISPR/Cas9 Screening Facility

CRISPR/Cas 9 Cell Screening Facility

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Cellular HTS

High Throughput Screening

CRISPR Pooled Screening
- CRISPR loss of function screening
- CRISPR gain of function screening

Mouse CRISPR Activation Library (SAM - 3 plasmid system)
(Pooled Libraries #1000000375)

Human CRISPR Knockout Pooled Library (GeCKO v2)
(Pooled Libraries #1000000048, #1000000049)

Mouse Genome-wide CRISPRa-v2 Libraries
(Pooled Libraries #63866, #1300000001)

Human Genome-wide CRISPRi-v2 Libraries
(Pooled Libraries #8366, #1000000000)
A quick review of CRISPR/Cas9 Screening and iPSCs:

iPSCs are derived by reprogramming somatic cells of patient donors to obtain stem cell lines that retain the genetic background of the donor and have a normal karyotype, yet can replicate indefinitely and be instructed to differentiate into a wide variety of cell types.
Target Discovery Institute Cell Screening Facility Personnel

Nuffield Department of Medicine

CRISPR Cas9 Screening Facility

CRISPR/Cas9 LOF and GOF Screening
Arrayed CRISPR Screening Development

Students/Visiting Fellows

Co-supervised Student – RDM/OCDEM
Functional Genomics of T2D

Junior Research Fellow – 3D Oncology

NPSC/PDi

PDI Image Analysis Specialist

Cellular HTS

ODDI Neurodegeneration Assay Development Platform

Oncology Screening

OTDI TDI Cellular Screening Facility