Academic Drug Discovery within the UK - a reassessment.

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In 2011 and 2014, Frye *et al* [1] and Tralau-Stewart *et al* [2] published an account of academic screening undertakings within the USA and UK, respectively. Tralau-Stewart *et al* observed that academic screening within the UK is comparable to the USA with regard to primary therapeutic focus, (with cancer, infectious disease and cardiovascular disease constituting the most highly prioritised therapeutic indications) and areas of unmet medical need. Parallels were also drawn between the motivational drivers and annual operating costs. However, regarding infrastructure, it was reported that most drug discovery programmes (DDPs) in academic screening groups (ASGs) within the UK were conducted within a 'traditional' research group (i.e. a team of postdocs, Ph.D. students and technicians led by a single Principal Investigator), with only 13% operating within a drug discovery-dedicated centre. The most surprising finding was that "access to HTS facilities and associated compound libraries was not reported by any UK group" [2]. The authors were clear to state that responses provided a "snapshot" of academic research at the time of surveying (2013), and not a comprehensive analysis. However, we feel centre-led ASGs and industry standard DDPs conducted within an academic environment in the UK has been grossly understated.

Academic Screening Groups and Drug Discovery Units within the UK

We have identified 23 dedicated drug discovery units/facilities across the United Kingdom (Table 1), each applying the drug discovery tenet to different clinical indications within a pharmaceutical/biotechnology infrastructure. These facilities have a range of operational frameworks: some are academic facilities operated by universities with several sources of funding, several are operated by charitable organisations, while others are industrial facilities sited on or near academic campuses. The common theme linking them is they are all open-access drug discovery facilities, accessible by UK-wide academic groups and each facility employs some personnel from academia thereby strengthening links to the UK academic community. These groups may therefore be better referred to collectively as academic and not-for-profit screening groups. However, for simplicity's sake, we will hereon refer to them as ASGs.

The scale of undertaking and the resourcing of these groups vary according to the objectives of each facility. Some groups provide dedicated support for distinct aspects of the drug discovery pipeline, for example target discovery or identification of chemical starting points for nominated disease indications, and are resourced with the relevant expertise/technical knowledge. At least six ASGs conduct industry-standard drug discovery resourced largely by professionals with substantial industrial experience and incorporate extensive in-house medicinal chemistry expertise and DMPK resource.

All of the identified groups reported the execution of multiple HTSs in the past year (Table 1). They actively pursue primary screen hits for further validation or drug development, and regularly publish their results in peer reviewed scientific journals. Additionally, we found that all of the groups employ industry standard liquid handling/readout instruments, and have research staff dedicated to each step of the drug discovery pipeline (i.e. compound management, assay development/screening, data analysis, etc.) suggesting their facilities are well equipped in both instrumentation and personnel. These facilities represent a major investment in UK drug discovery research. The similarity in facility

numbers between the UK and the USA, highlights a clear commitment within the UK to provide the infrastructure necessary to support academic screening.

Funding and Collaboration

Currently, the majority of funding for the major UK ASGs is provided by the UK government with considerable support coming from universities, UK and international charitable organizations (Cancer Research UK supports programs at 5 of the 23 facilities), and the UK Medical Research Council. In addition to governmental and charitable funding streams, we have recently experienced a paradigm shift in the perception of academic screening by the industrial sector. Pharmaceutical companies now recognise the potential of academic alliances and have entered into partnerships with UK ASGs. Collaborative efforts to address a broad range of disease areas (Table 1) are underway, through provision of well characterised compound collections (GSK and Pfizer) and/or engaging closely with academic partners to enhance their own drug discovery capacity. Notable examples include AstraZeneca's Open Innovation Initiative, GSK's Centre for Therapeutic Target Validation (CTTV), and the Eisai-UCL collaborative drug discovery alliance. These partnerships are evidence that the UK academic screening community is held in high esteem by global pharmaceutical companies.

Screening Platforms and Technologies

The approaches used across ASGs are multidisciplinary, yet complimentary: target identification and de-risking of potential targets using high throughput functional genomics bridges the often all too apparent translational gap between the academic research and drug discovery disciplines [3, 4]. Platforms such as RNAi screening can support target identification, while concurrently providing novel biological insights. Moreover, dedicated efforts to unearth novel chemical starting points for drug discovery are increasing, supplemented with committed medicinal and/or computational chemistry for development of lead compounds. The re-purposing of existing therapeutics is increasingly complementing the more traditional drug discovery workflow as more groups begin to use screening to explore the potential applications of existing drugs for alternate indications [5].

ASGs have also been a main driver for the development and implementation of high-content imaging and analysis in drug discovery. We found that amongst UK ASGs which are engaged in cell based phenotypic screening; all employ state of the art high content imagers and most employ multiple instruments. Other platforms typically perceived to be restricted to use of pharmaceutical companies such as acoustic dispensing are now well embedded in ASGs, with a total of 19 Echos systems (Labcyte) sited in 14 ASGs.

Tralau-Stewart *et al* also reported an apparent lack of uptake of HTS (defined as screening collections of >100K compounds) in UK-based ASGs. At the time of their review, both the CRUK Cancer Therapeutics Unit at The Institute of Cancer Research and CRT DL were regularly screening >100K compounds. Along with MRCT and DDU Dundee, these centres are fully capable of large-scale screening, though it is still not commonplace in ASGs. Given limitations in funding, this will likely remain so as it is, arguably, unnecessary to duplicate such efforts. Typically, ASGs use high diversity libraries of 10-50K compounds or smaller focussed compound sets. Since the publications of Swinney and Anthony [6, 7], highlighting that phenotypic approaches were more successful than target-based approaches in identifying first-in-class drugs, there has been a dramatic change in the

perception of the necessity of screening vast numbers of compounds in order to identify the most apposite start points for innovative drug development. The focus has shifted to screening fewer, more discrete, well designed and diverse compound libraries. When coupled with advanced computational approaches to virtually explore chemical space *in silico*, it becomes evident that size of screening collections is not necessarily the most critical criterion for success in primary HTS [8, 9].

Discussion

Screening within an academic environment forms an integral part of drug discovery initiatives within the UK, and efforts in this area have undergone dramatic expansion over the last 10 years. Furthermore, the strategic alliance between academia, the UK government and the pharmaceutical industry is exemplified by i) the £8 million investment into the UK National Phenotypic Screening Centre (UKNPSC, 2014), sourced principally from the Scottish Government via the Scottish Funding Council with both academia and industry supporting running costs, and ii) the establishment of the European Screening Centre, which supports researchers and SMEs in screening around 300K compounds, collectively contributed by seven pharmaceutical companies. While sources and timescales of funding continue to evolve, the level of investment in the infrastructure and research of UK-based ASGs may represent an emerging cultural shift in the recognition of the value of academic drug discovery efforts.

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Facility	Host Institution	Location	Principal Disease Indication(s)	Funding	Personnel	Platform(s)	Technology(ies)	# of Screens / year (any size)	Medicinal Chemistry Follow-up	Website
Drug Discovery Unit*	University of Dundee	Dundee	Diseases of the Developing World, Innovative Targets & Pathways	UK government, charities, industry	70+	Biophysical, biochemical, cellular assays	Multiple	N/A	Yes	http://www.drugdiscovery.dundee.ac.uk/welcome-drug-discovery-unit-dundee
UK-National Phenotypic Screening Centre	University of Dundee/University of Oxford/University of Edinburgh	Dundee/Oxford/Edinburgh	All diseases: human > non-human	UK government, charities, industry	25 (estimated)	Small molecules, 3D, tissue, patient cells, iPS, genome engineering	HCI, MPA, label-free, HT flow	10-15	Yes	http://www.sulsa.ac.uk/research-facilities/uk-national-phenotypic-screening-centre
European Screening Centre	Multiple sites across the UK and Europe	UK (Dundee, Lanarkshire) and Europe	All human diseases	Innovative Medicines Initiative, EFPIA participants' in-kind contributions	50	Small molecules (326K (2013) - 500K (2017)), biophysical, biochemical assays	ultra-HTS plate-reader, SPR, label-free.	30	Yes	www.lifesci.dundee.ac.uk/research/esc www.europeanleadfactory.eu
Edinburgh Cancer Discovery Unit	Edinburgh Cancer Research Centre, University of Edinburgh	Edinburgh	Oncology	Industry alliances, MRC, University of Edinburgh	14	Small molecules, chemical library synthesis	HCI, MPA, image informatics, reverse phase protein array, dual ligand	12	Yes	http://www.ecrc.ed.ac.uk/discovery-unit/overview.html
RNAi Screening Facility	CRUK Beatson Institute, University of Glasgow	Glasgow	Oncology	Cancer Research UK	5	Genome-wide human and mouse RNAi, drug repurposing	HCI, MPA, HTS plate reader	8	No	http://www.beatson.gla.ac.uk/advanced-technologies/emma-shanks-rnai-screening.html
Drug Discovery Unit	CRUK Beatson Institute, University of Glasgow	Glasgow	Oncology	Cancer Research UK	24.5	Fragments	NMR/SPR	1-5	Yes	http://www.beatson.gla.ac.uk/drug-discovery/drug-discovery.html
Scottish Bioscreening Facility	Institute of Infection, Immunity and Inflammation, University of Glasgow	Glasgow	Neglected diseases/parasitology.	Wellcome Trust, Scottish Universities Life Science Alliance (SULSA)	3	Small molecules, RNAi	HCI, HTS plate reader	6	Yes	http://www.gla.ac.uk/researchinstitutes/iii/facilities/imaging/sbfglasgow/
Drug Discovery	Queen's University	Belfast	Oncology	Almac, Queen's University, Invest Northern Ireland	20	Fragments, CADD, virtual screening	SPR, thermopheresis, Schrodinger, MOE, HCI, MPA	3	Yes	http://www.qub.ac.uk/research-centres/CentreforCancerResearchCellBiology/Research/EnablingTechnologies/DrugDiscovery
Medicinal Chemistry and Chemical Biology Technology Group	University of Leeds	Leeds	All human diseases	University of Leeds, UK government, charities, industry	5	Small molecules (50K), drug repurposing, fragments, virtual screening	Biochemical, phenotypic, biophysical	5-10	Yes	http://medhealth.leeds.ac.uk/info/1930/medicinal_chemistry_and_chemical_biology_technology_group
BioScreening Technology Group	University of Leeds	Leeds	All human diseases	University of Leeds, UK government, charities, European Commission	2	Genome-wide human and mouse RNAi, miRNA inhibitors and mimics, small molecule screening, drug repurposing	HCI, MPA, HTS plate reader	5-8	Yes	http://http://medhealth.leeds.ac.uk/info/360/facilities/909/bioscreening_technology_group
Adhiron Screening Facility	University of Leeds	Leeds	All human diseases	University of Leeds, UK government, charities, industry	19	Biologics	Phage display, biochemical, biophysical	150	Yes	http://www.fbs.leeds.ac.uk/staff/profile.php?tag=Tomlinson_D
Drug Discovery Unit	CRUK Manchester Institute, University of Manchester	Manchester	Oncology	Cancer Research UK	5	Small molecules, drug repurposing	HCI	5-10	Yes	http://www.cruk.manchester.ac.uk/Research/CRUK-MI-Groups/Drug-Discovery/Home
Sheffield RNAi Screening Facility	University of Sheffield	Sheffield	Oncology, Parkinson's Disease, Myeloproliferative Neoplasms	Wellcome Trust, Yorkshire Cancer Research, University of Sheffield	2	Genome-wide drosophila RNAi, human siRNA, small molecules	HCI, MPA, HTS plate reader	16	No	http://www.rnai.group.shef.ac.uk
SiTraN Drug Discovery Suite	University of Sheffield	Sheffield	Motor Neuron Disease, Parkinson's Disease	Wellcome Trust, MRCT, MNDA, Parkinson's UK	6	Small molecules	HCI, MPA, HTS plate reader, metabolic outputs	2	No	sitran.dept.shef.ac.uk/
Zebrafish Small Molecule Screening Unit	University of Sheffield	Sheffield	Zebrafish models of disease, including epilepsy, inflammation, infection, hypoxia, ototoxicity	MRC, BBSRC, charities, industry	1	Small molecules	HCI, MPA, HTS plate reader, microscopy	5-10	Yes	http://www.bateson.group.shef.ac.uk/research/facilities/small-molecule-screening-unit/
Drug Discovery Priority Group	University of Nottingham	Nottingham	All human diseases	Charities, industry, EU	2	Small molecules	HCI, HTS plate reader	2-4	Yes	http://nottingham.ac.uk/research/priorities/drugdiscovery/index.aspx
Birmingham Drug Discovery Facility	University of Birmingham	Birmingham	Infectious disease (Tuberculosis, Salmonella, S.aureus), Leukaemia and Lymphoma, HBV	MRC, Wellcome Trust and ERC	3	Small molecules	HTS plate reader	5	Yes	http://www.birmingham.ac.uk/facilities/bddf/index.aspx
Cancer Research Technology (CRT) Discovery Laboratory	Babraham Research Campus	Cambridge	Oncology	Industry alliances/CRT/ Cancer Research UK	74	Small molecules (100K+), fragments, RNAi	HCI, MPA, HTS plate reader, MSD technology, SPR, ITC, crystallography	6	Yes	http://www.cancertechnology.co.uk/
Target Discovery Institute	University of Oxford	Oxford	Oncology, Cardiovascular, Neurodegeneration	UK government, University of Oxford, BHF, ARUK, pharmaceutical companies, SRF	50+	Small molecules (50K), drug repurposing, fragments, RNAi	HCI, HTS plate reader, rtPCR, HTFACS	20	Yes	http://www.tdi.ox.ac.uk/home
CRUK Cancer Therapeutics Unit	The Institute of Cancer Research	London	Oncology	Cancer Research UK, The ICR, Wellcome Trust, industrial collaborators	143	Small molecules (210K), fragments (2K), siRNA. Extensive aspects of DD pipeline covered.	HCI, HTS plate reader, mobility shift assays, SPR, ITC, DSF, Xray crystallography	3	Yes	http://www.icr.ac.uk/our-research/our-research-centres/cancer-research-uk-cancer-therapeutics-unit
High-throughput Screening Facility	CRUK London Research Institute	London	Oncology	Cancer Research UK	4	Genome-wide RNAi, small molecules (4K), fragments	HCI, MPA, HTS plate reader, thermal melt, FACS	20-30	No	http://www.london-research-institute.org.uk/technologies/high-throughput-screening
Laboratory for Molecular Cell Biology	University College London	London	Neurodegeneration, Oncology, HIV. General cell biology	Medical Research Council	4	RNAi, cDNA, small molecules, CRISPR	HCI, MPA, HTS plate reader	15-20	Yes	http://www.ucl.ac.uk/lmcb/about-translational-research-resource-center
Medical Research Council-Technology (MRCT)	Medical Research Council	London	All including Oncology, Fibrosis, Neurodegeneration, Inflammation, Anti-infectives, Pain, Autoimmune disease, Cushings disease	Self funded through income from translational activities	70	Small molecule (250K+), phage antibodies. Extensive aspects of DD pipeline covered.	HCI, MPA, HTS plate reader, label free, biophysical (SPR, ITC, Thermal shift)	8-10	Yes	: http://www.mrctechnology.org/about-us/
Translational Drug Discovery Group	University of Sussex	Sussex	Oncology, Neuroscience	Wellcome Trust, Cancer Research UK	18	Structure-based drug discovery	Biophysical, X-ray crystallography, virtual screening, high-throughput electrophysiology	4	Yes	www.sussex.ac.uk/lifesci/drugdiscovery/

* data collated from website
N/A - information unavailable
The authors apologise to any ASG we may have overlooked

Abbreviations

HTS	High Throughput Screening
HCI	High content imaging
MPA	Multiparametric Phenotypic Analysis
SPR	Surface Plasmon Resonance
NMR	Nuclear Magnetic Resonance