The ULTRA-DD project: delivering new tools and resources to speed up the development of truly innovative medicines

PSWC – May 2017

Michael Sundström
Scientific Director of European Initiatives, SGC and ULTRA-DD

www.thesgc.org
www.ultra-dd.org

SGC & ULTRA-DD

Translational Medical Research for Early Drug Discovery

1. High Throughput Structural Biology & Protein Science (2004 -)
Proteins of relevance to drug discovery. ~2000 structures deposited to date

2. Chemical Probes (2008 -)
HighQ epigenetic and kinase chemical probes for disease studies

3. Research Tool Antibodies & Biological Probes (2011, 2015 -)
Generation of recombinant antibodies using phage display technologies

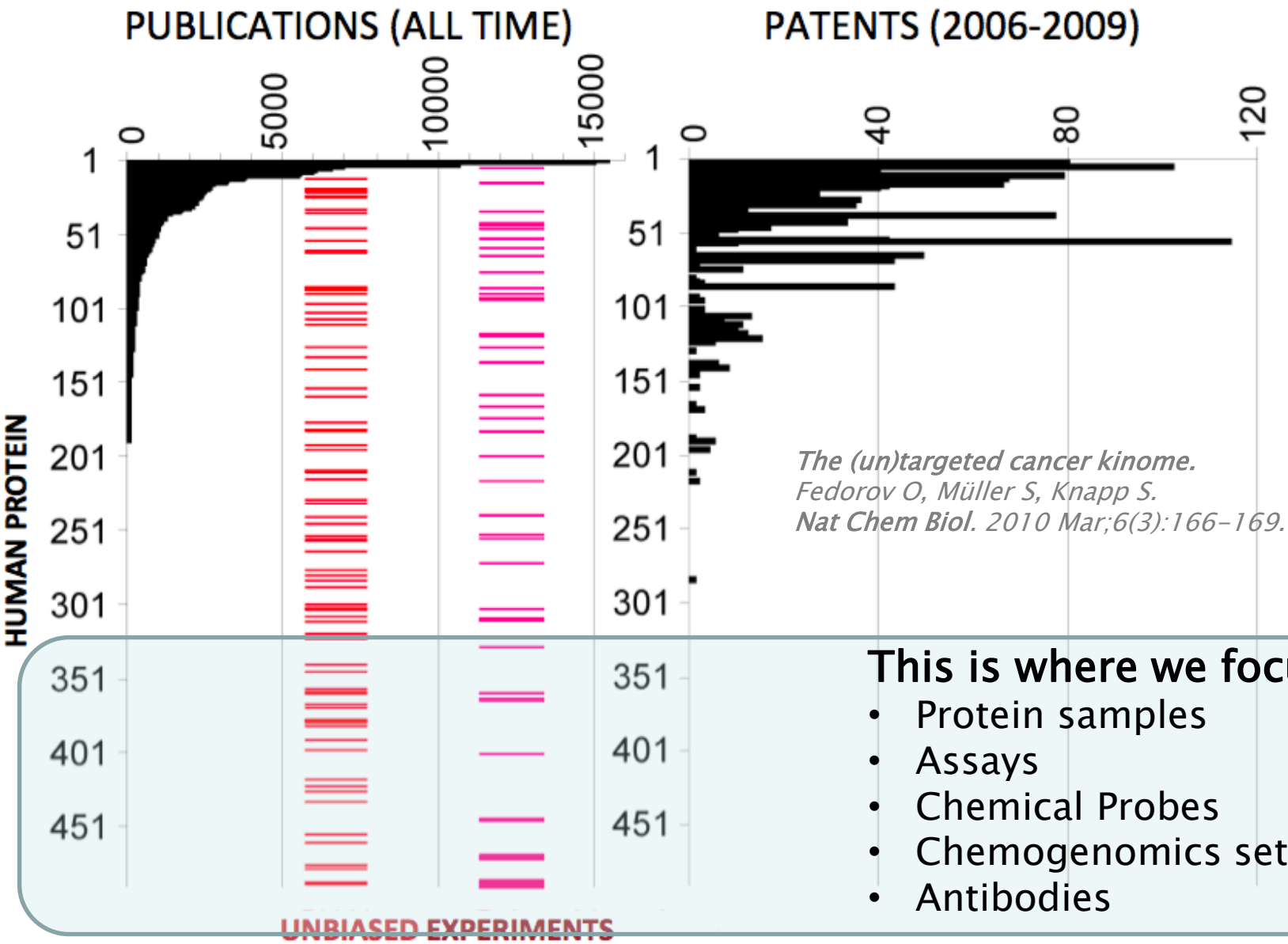
4. Target Enabling Packages (2015 -)
For disease associated & under-explored targets

5. Tissue Platforms (2015 -)
Patient-Derived Cell Assays at Karolinska, Oxford, Montreal and Toronto

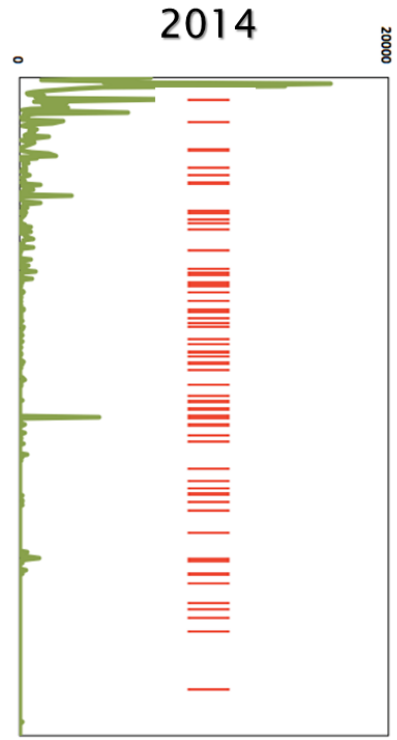
Founded 2003, 300 Staff members, strict open-source, 25 MUSD/annum

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Global Research is Heavily Biased



The (un)targeted cancer kinome.
Fedorov O, Müller S, Knapp S.
Nat Chem Biol. *2010 Mar;6(3):166-169.*



This is where we focus

- Protein samples
- Assays
- Chemical Probes
- Chemogenomics set
- Antibodies

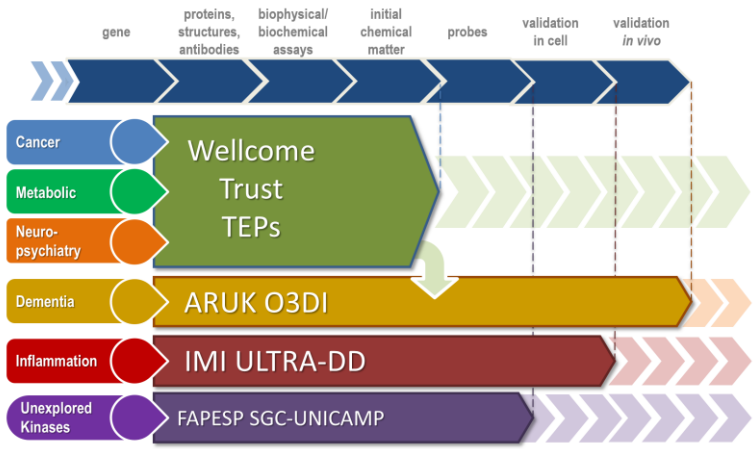
Open Source Partnership Concept

CREATIVE COMMONS

PROPRIETARY

Public–Private Partnership	Public Domain	Commercial
Tools & Basic Knowledge **NOVEL Proteins only!**	**Discovery and Exploration**	**Drug Discovery and Development**
• Structure • Chemistry • Antibodies • Screening • Cell Assays	• No patent • No restriction on use • Open access to tools and data. • Target identification & validation	Facilitated by access to increased amount of information in the public domain – (re)Screening – Lead Optimisation – Pharmacology – Metabolism – Pharmacokinetics – Toxicology – Chemical development – Clinical development

TEPs
Probes
PDCAs



Weigelt J. EMBO Reports **10**:941-5 (2009)

HQ Chemical Tools

innovative
medicines
initiative

SGC

The Inception of Open-Source Chemistry

COMMENTARY

Nature Chemical Biology 5:436 (2009)

- Small molecules to explore biology
- PPP = sharing expertise
- Open tools = exploration by all

Open access chemical and clinical probes to support drug discovery

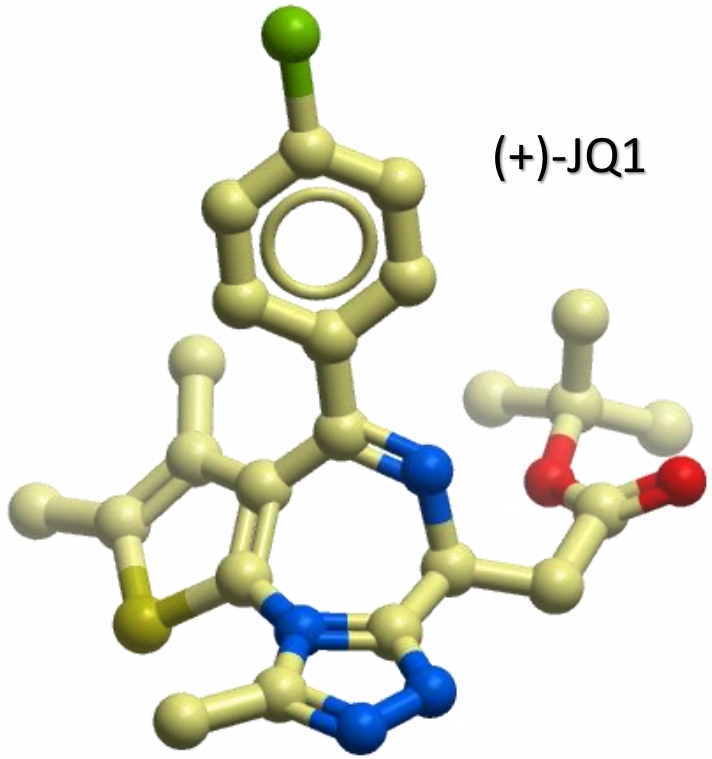
Aled M Edwards, Chas Bountra, David J Kerr & Timothy M Willson

Drug discovery resources in academia and industry are not used efficiently, to the detriment of industry and society. Duplication could be reduced, and productivity could be increased, by performing basic biology and clinical proofs of concept within open access industry-academia partnerships. Chemical biologists could play a central role in this effort.

Chemical Probes Programme

- Produced in partnership with pharma
- Publicly available & no patents
- No restriction on use
- Well characterised, not yet drugs
- Interrogate biological function
- Target & Pathway validation

- Potent: *in vitro* IC_{50} /K_D< 100nM
- Selective: 30 fold over near family members
- Cell Permeable: activity IC_{50} <1 µM
- Clean in wide profiling panels (*e.g.* CEREP, DiscoveRx)
- Costs around 2MUSD/probe to develop



(+)-JQ1

Other target families have their specific criteria

BRD Chemical Probe

nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video | For

Archive > Volume 468 > Issue 7327 > Articles > Abstract

NATURE | ARTICLE

previous abstract next abstract

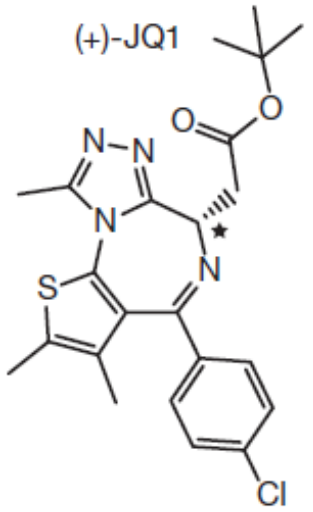
Selective inhibition of BET bromodomains

Panagis Filippakopoulos, Jun Qi, Sarah Picaud, Yao Shen, William B. Smith, Oleg Fedorov, Elizabeth M. Morse, Tracey Keates, Tyler T. Hickman, Ildiko Felletar, Martin Philpott, Shonagh Munro, Michael R. McKeown, Yuchuan Wang, Amanda L. Christie, Nathan West, Michael J. Cameron, Brian Schwartz, Tom D. Heightman, Nicholas La Thangue, Christopher A. French, Olaf Wiest, Andrew L. Kung, Stefan Knapp & James E. Bradner

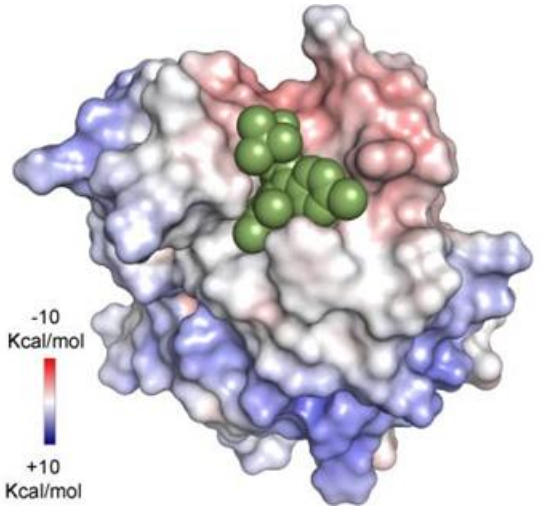
Affiliations | Contributions | Corresponding authors

Nature **468**, 1067–1073 (23 December 2010) | doi:10.1038/nature09504

Received 05 May 2010 | Accepted 17 September 2010 | Published online 24 September 2010

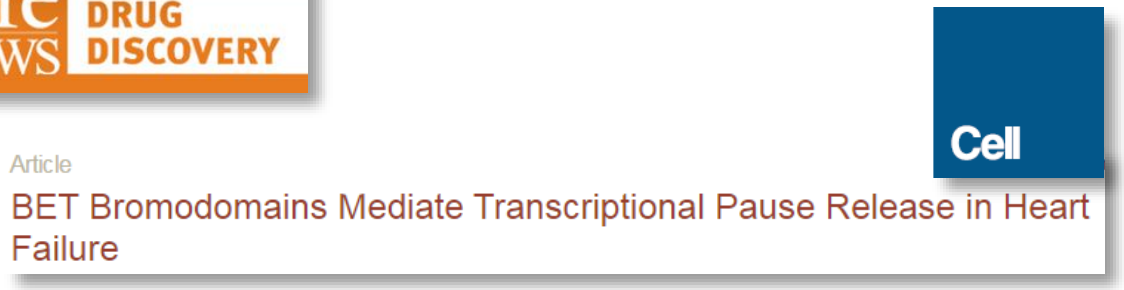


Co-crystal (JQ1 + BRD4)



Disease Agnostic Exploration

- NUT midline carcinoma
- Septic Shock / Inflammation
- Myeloma
- Leukemia
- MYC regulation
- HIV infection
- Male Contraception
- Pathologic Cardiac hypertrophy



Bromodomain Inhibitors in the Clinic - 2015

Company	Compound		Named Indications	Stage	Initated	Status
Abbvie	ABBV-075	1	Advanced Cancer; Breast Cancer; Non-Small Cell Lung Cancer; Acute Myeloid Leukemia; Multiple Myeloma	Phase I	2015	Ongoing
Bayer	BAY1238097	1	Neoplasms	Phase I	2015	Ongoing
Gilead	GS-5829	1	Solid Tumors; Lymphomas	Phase I	2015	Ongoing
GSK	GSK525762	1	Elapsed, Refractory Hematologic Malignancies	Phase I/II	2013	Ongoing
		2	NUT Midline Carcinoma (NMC) and Other Cancers	Phase I	2012	Ongoing
Merck (Oncoethix)	OTX015	1	Acute Myeloid Leukemia	Phase I	2014	Ongoing
		2	NUT Midline Carcinoma; Triple Negative Breast Cancer; Non-small Cell Lung Cancer With Rearranged ALK Gene/Fusion Protein or KRAS Mutation; Castrate-resistant Prostate Cancer (CRPC); Pancreatic Ductal Adenocarcinoma	Phase I	2014	Ongoing
		3	Acute Leukemia; Other Hematological Malignacies	Phase I	2012	Ongoing
		4	Glioblastoma Multiforme	Phase IIa	2014	Ongoing
Constellation	CPI-0610	1	Acute Leukemia, Myelodysplastic Syndrome, or Myelodysplastic/Myeloproliferative Neoplasms	Phase I	2013	Ongoing
		2	Previously Treated Multiple Myeloma	Phase I	2014	Ongoing
		3	Progressive Lymphoma	Phase I	2013	
Tensha	TEN-010	1	Acute Myeloid Leukemia and Myelodysplastic Syndrome	Phase I	2014	Ongoing
		2	Solid Tumors	Phase I	2013	

- 7 compounds and 14 trials mid-2015
- 2016 update: 14 compounds in 30 trials mid-2016 (+BI, BMS, FORMA, Incyte, Plexxicon, Roche, Zenith)

HQ Test Systems

innovative
medicines
initiative

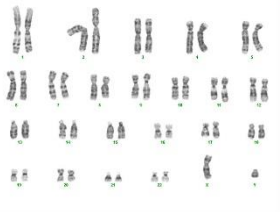
SGC

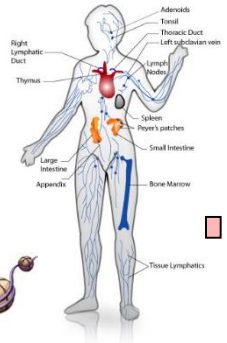
Changing the Treatment Approach

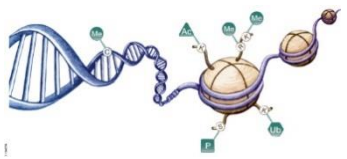
Needed ← Current

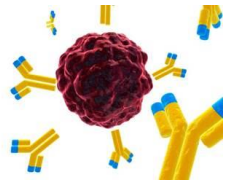
Genes, environment → Immune system activation → Immune attack → **Inflammation** → Tissue destruction Organ failure

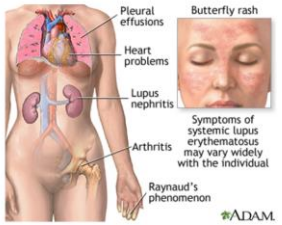
- Early detection
- More Specific
- Treating the disease not symptoms
- Patient tailored intervention
- Aiming for cure and prevention
- Collaborative and iterative process



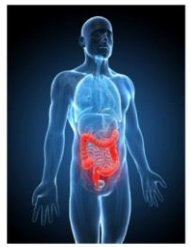




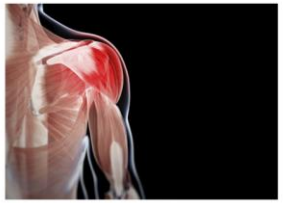




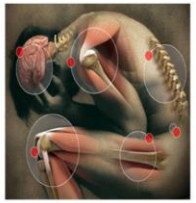
Lupus



IBD



Myositis



RA

Late disease detection and unspecific treatment options

No cures - symptomatic relief and bad long-term outcomes

Current therapies associated with many side-effects

Major healtcare concern and health economic burden

Affect ~5% of the population, most patients are women

No signs and symptoms → Unspecific symptoms → Disease diagnosis → Disability

At risk for inflammation | **Pre-Disease Symptoms and biomarkers** | **Early Disease** | **Disease**

Nature Reviews Drug Discovery, 2015

Preclinical target validation using patient-derived cells

*Aled M. Edwards[1], Cheryl H. Arrowsmith[1], Chas Bountra[2], Mark E. Bunnage[3], Marc Feldmann[4], Julian C. Knight[5], Dhavalkumar D. Patel[6], Panagiotis Prinos[1], Michael D. Taylor[7], and Michael Sundström[8] on behalf of the SGC Open Source Target-Discovery Partnership**

The Structural Genomics Consortium (SGC) and its clinical, industry and disease-foundation partners are launching open-source preclinical translational medicine studies.

[1]*Structural Genomics Consortium (SGC), University of Toronto, 101 College Street, Toronto, Ontario M5G 1L7, Canada.*
[2]*SGC, Nuffield Department of Clinical Medicine, University of Oxford, Old Road Campus*

Although the annual number of new drug approvals is trending upwards, the number of 'first-in-class' therapies has remained relatively constant — often fewer than 10 per year. For such new medicines for 'pioneer targets', attrition in Phase II proof-of-concept clinical studies remains the biggest hurdle[1], in large part because the target–disease associations derived from the currently dominant cell-line or animal preclinical models of disease-methods were developed that enabled 90% of the total cells originating from the diseased joint to survive for 5–6 days was it possible to provide the first convincing evidence of the importance of TNF in joint inflammation, which was rapidly confirmed in animal models and then in proof-of-principle trials[3].

The discovery of anti-TNF therapy also provides two other lessons. First, success derived not only from the use

Tissue Platforms - Organization

Scientific Committee
- Independent chair
- Academic KOLs

JMC
- SGC Chair
- Pharma Partners

Working Groups
- Driven by GLs
- Pharma scientists

LMT
- SGC Chair
- Local key PIs & GL

Ethics Committee
- SGC Chair

Pharma TP Meeting
- Boston 2015, Basel 2016

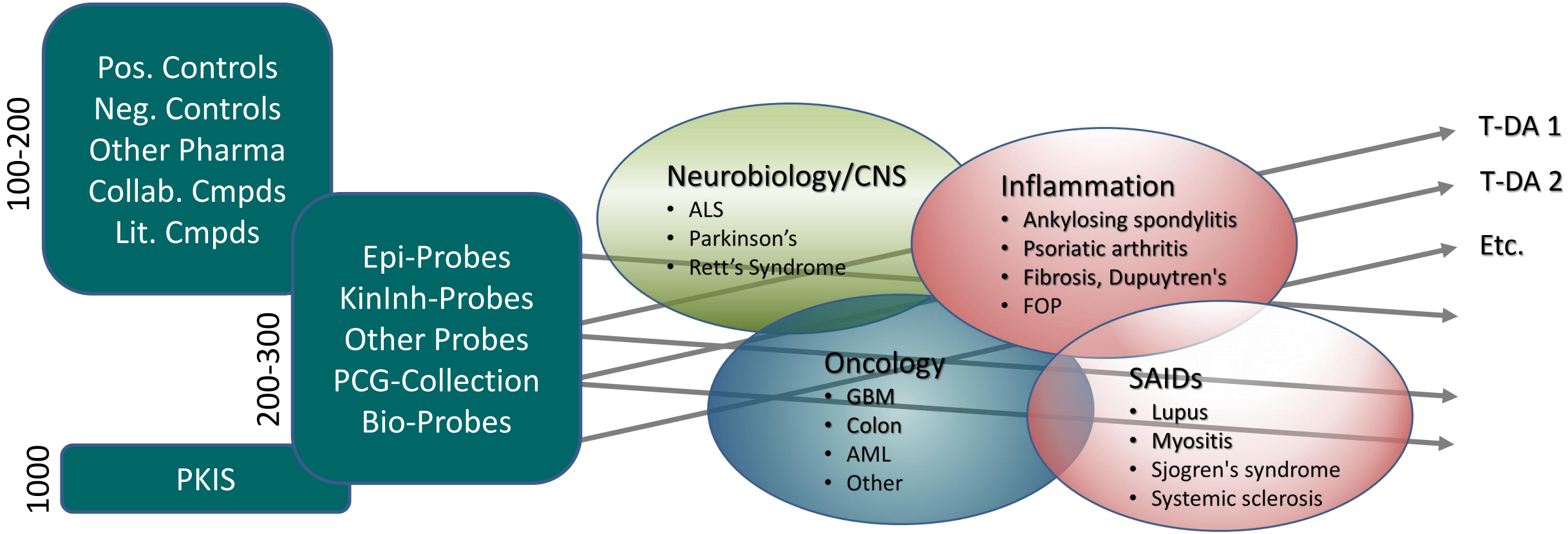
- Group Leader
- Senior Scientist
- 1-2 TAs
- 0.5 Research Nurse

PhDs & PDFs for specific Projects

- Assay Development
- Probe screen
- Verification studies
- Initial data analysis

- Interface to clinicians
- Patient consent
- Sample collection
- Ethical approvals

HQ Probes Meet HQ Assays



Patient Cohorts

Disease	Patients/Controls seen annually	Genetic characterization	Blood	Biopsies
SLE	475/320	HLA, ImmunoChip	yes	Skin (20-30/year)
Myositis	300 (SweMyoNet) 2300 (EuMyoNet)	HLA, ImmunoChip	yes	Skin (10-20/year)
SS	40	-	yes	None
SSc	165/110	HLA, ImmunoChip	yes	Yes (20-30/year)
FOP	30	Genotypes	yes	None
AS	600	HLA, ImmunoChip	yes	Synovial fluid (30)

Fibrosis/DD accessed from external sites

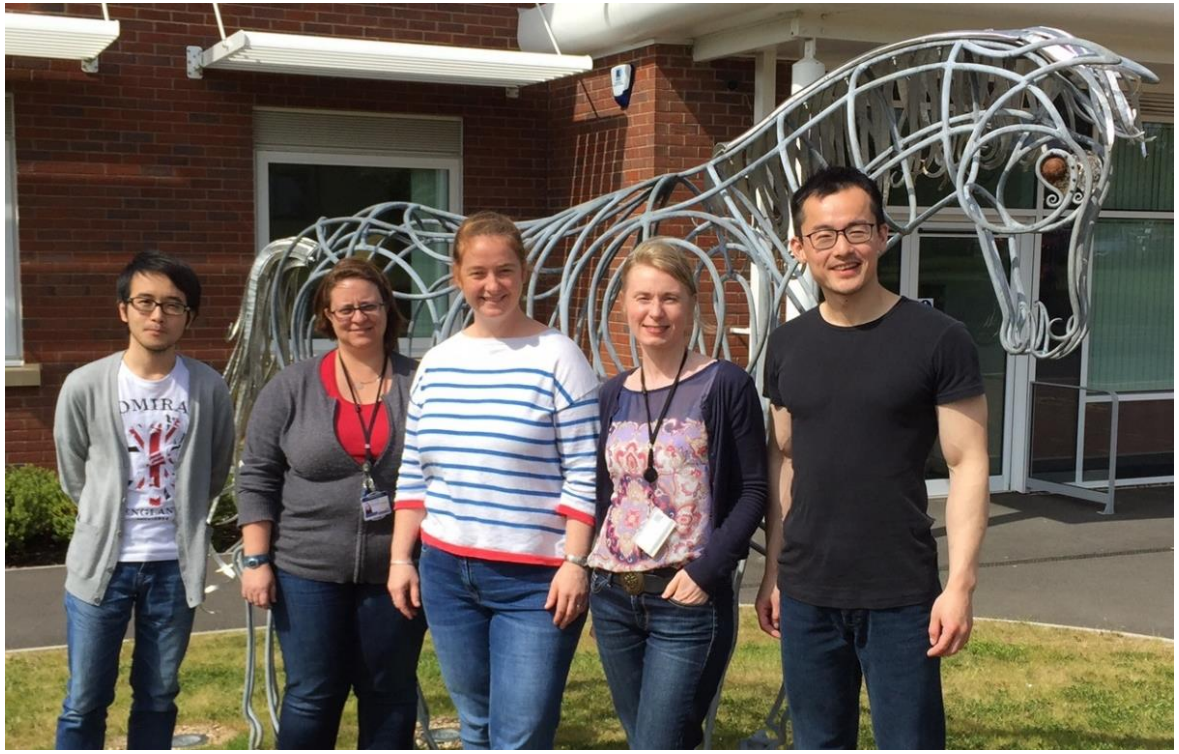
Inflammatory Diseases

Kennedy Institute of Rheumatology

NDORMS Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences

University of Oxford

- Tissue Platform focused on *Fibrosis, AS & FOP*
- 5 staff members in place (GL, Senior Scientist, TA, PDFs)
- Laboratories established at the Botnar Research Centre
- Results to date from patients with AS and Fibrosis



Tak, Marisa, Lynn, Fiona, Liye

Scientific Leadership

Prof. Jagdeep Nanchahal

Prof. Sir Marc Feldmann

Prof. Paul Bowness

Auto-Immune Diseases

- Clinical research in *SLE, myositis, systemic sclerosis, SS (and RA)*
- Well characterized and managed patient cohorts
- Strong and supportive local clinical network
- Team of four staff, recruiting additional positions
- Results to date from patients with Myositis, Lupus and SSc

Scientific Leadership

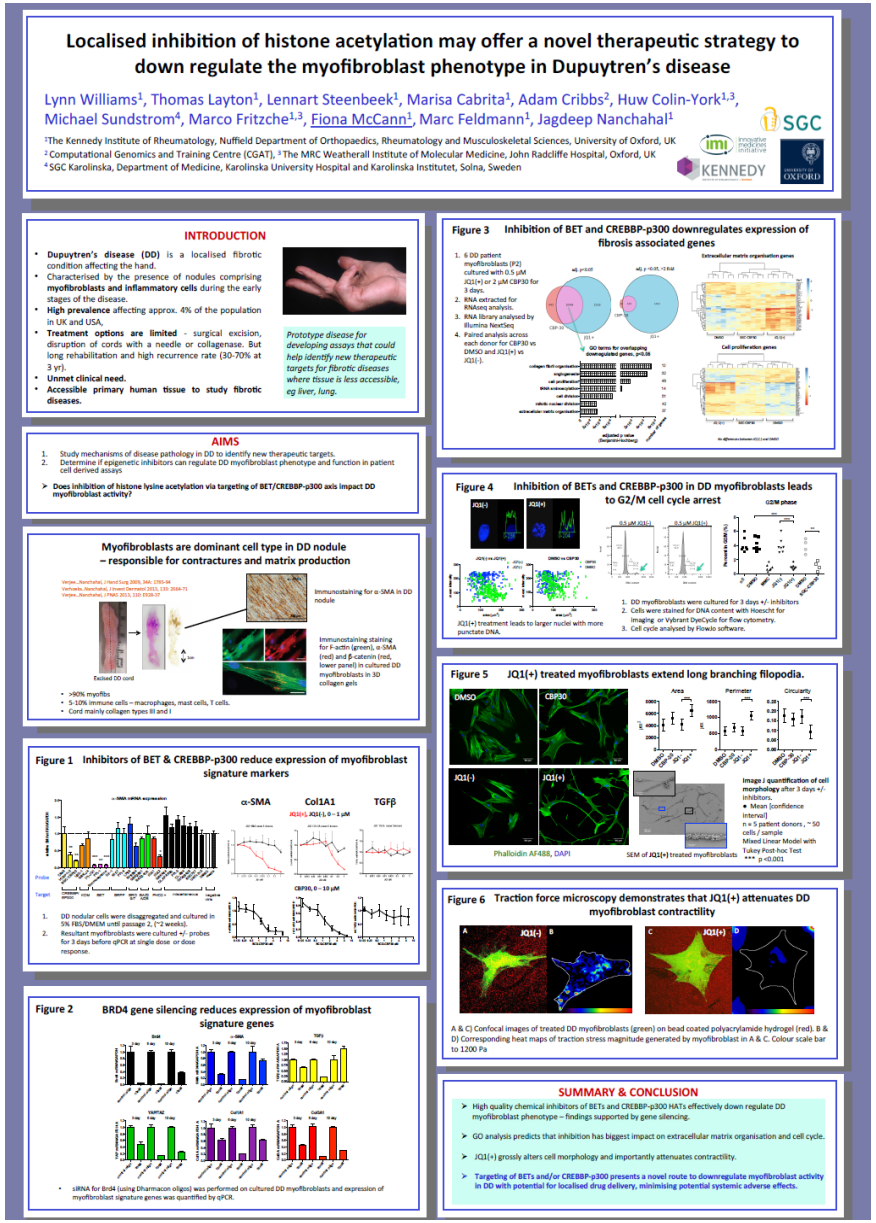
Prof. Lars Klareskog

Prof. Per-Johan Jakobsson

Prof. Ingrid Lundberg

Dr. Louise Berg

Open Translational Medicine Resources



Localised inhibition of histone acetylation may offer a novel therapeutic strategy to down regulate the myofibroblast phenotype in Dupuytren's disease

Lynn Williams[1], Thomas Layton[1], Lennart Steenbeek[1], Marisa Cabrita[1], Adam Cribbs[2], Huw Colin-York[1,3], Michael Sundstrom[4], Marco Fritzche[1,3], Fiona McCann[1], Marc Feldmann[1], Jagdeep Nanchahal[1]

[1]The Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK
[2] Computational Genomics and Training Centre (CGAT), [3] The MRC Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK
[4] SGC Karolinska, Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Solna, Sweden

INTRODUCTION

- **Dupuytren's disease (DD)** is a localised fibrotic condition affecting the hand.
- Characterised by the presence of nodules comprising **myofibroblasts and inflammatory cells** during the early stages of the disease.
- **High prevalence** affecting approx. 4% of the population in UK and USA.
- **Treatment options are limited** - surgical excision, disruption of cords with a needle or collagenase. But long rehabilitation and high recurrence rate (30-70% at 3 yr).
- **Unmet clinical need.**
- **Accessible primary human tissue to study fibrotic diseases.**

Prototype disease for developing assays that could help identify new therapeutic targets for fibrotic diseases where tissue is less accessible, eg liver, lung.

AIMS

1. Study mechanisms of disease pathology in DD to identify new therapeutic targets.
2. Determine if epigenetic inhibitors can regulate DD myofibroblast phenotype and function in patient cell derived assays

➢ **Does inhibition of histone lysine acetylation via targeting of BET/CREBBP-p300 axis impact DD myofibroblast activity?**

Myofibroblasts are dominant cell type in DD nodule – responsible for contractures and matrix production

Immunostaining for α-SMA in DD nodule

Immunostaining staining for F-actin (green), α-SMA (red) and β-catenin (red, lower panel) in cultured DD myofibroblasts in 3D collagen gels

- >90% myofibs
- 5-10% immune cells – macrophages, mast cells, T cells.
- Cord mainly collagen types III and I

Figure 1 Inhibitors of BET & CREBBP-p300 reduce expression of myofibroblast signature markers

α-SMA Col1A1 TGFβ

1. DD nodular cells were disaggregated and cultured in 5% FBS/DMEM until passage 2, (~2 weeks).
2. Resultant myofibroblasts were cultured +/- probes for 3 days before qPCR at single dose or dose response.

Figure 2 BRD4 gene silencing reduces expression of myofibroblast signature genes

- siRNA for Brd4 (using Dharmacon oligos) was performed on cultured DD myofibroblasts and expression of myofibroblast signature genes was quantified by qPCR.

Figure 3 Inhibition of BET and CREBBP-p300 downregulates expression of fibrosis associated genes

1. 6 DD patient myofibroblasts (P2) cultured with 0.5 μM JQ1(+) or 2 μM CBP30 for 3 days.
2. RNA extracted for RNAseq analysis.
3. RNA library analysed by Illumina NextSeq
4. Paired analysis across each donor for CBP30 vs DMSO and JQ1(+) vs JQ1(-).

GO terms for overlapping downregulated genes, p<0.05

Extracellular matrix organisation genes

Cell proliferation genes

Figure 4 Inhibition of BETs and CREBBP-p300 in DD myofibroblasts leads to G2/M cell cycle arrest

JQ1(-) JQ1(+)

JQ1(+) treatment leads to larger nuclei with more punctate DNA.

G2/M phase

1. DD myofibroblasts were cultured for 3 days +/- inhibitors
2. Cells were stained for DNA content with Hoescht for imaging or Vybrant DyeCycle for flow cytometry.
3. Cell cycle analysed by FlowJo software.

Figure 5 JQ1(+) treated myofibroblasts extend long branching filopodia.

DMSO CBP30 JQ1(-) JQ1(+)

Area Perimeter Circularity

Phalloidin AF488, DAPI

Image J quantification of cell morphology after 3 days +/- inhibitors.
Mean (confidence interval)
n = 5 patient donors , ~ 50 cells / sample
Mixed Linear Model with Tukey Post-hoc Test
*** p <0.001

SEM of JQ1(+) treated myofibroblasts

Figure 6 Traction force microscopy demonstrates that JQ1(+) attenuates DD myofibroblast contractility

A & C) Confocal images of treated DD myofibroblasts (green) on bead coated polyacrylamide hydrogel (red). B & D) Corresponding heat maps of traction stress magnitude generated by myofibroblast in A & C. Colour scale bar to 1200 Pa

SUMMARY & CONCLUSION

- High quality chemical inhibitors of BETs and CREBBP-p300 HATs effectively down regulate DD myofibroblast phenotype – findings supported by gene silencing.
- GO analysis predicts that inhibition has biggest impact on extracellular matrix organisation and cell cycle.
- JQ1(+) grossly alters cell morphology and importantly attenuates contractility.
- **Targeting of BETs and/or CREBBP-p300 presents a novel route to downregulate myofibroblast activity in DD with potential for localised drug delivery, minimising potential systemic adverse effects.**

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ULTRA-DD Annual Conference and SGC Immunology Day

at Karolinska Institutet, Stockholm

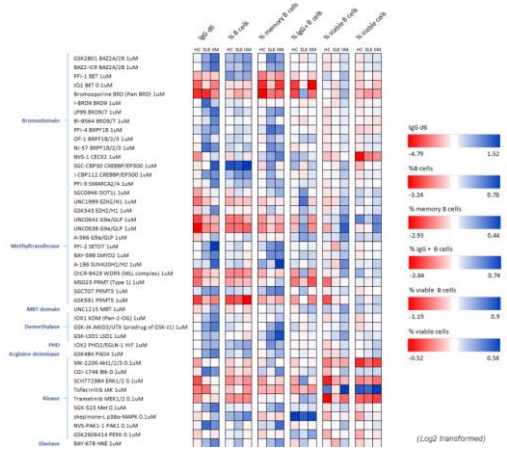
1st of June 2017

The Project

ULTRA-DD

Unrestricted Leveraging of Targets for Research Advancement and Drug Discovery

Funded by the European Union and



(Log2 transformed)

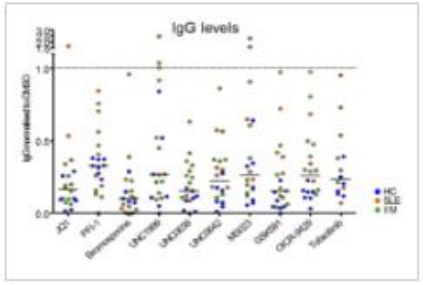


Fig 2a IgG levels

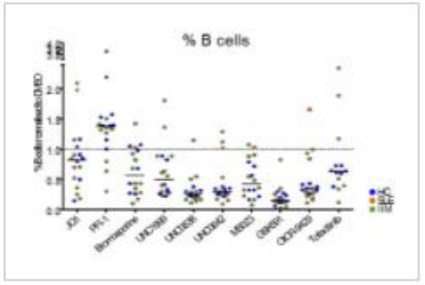


Fig 2b %B cells

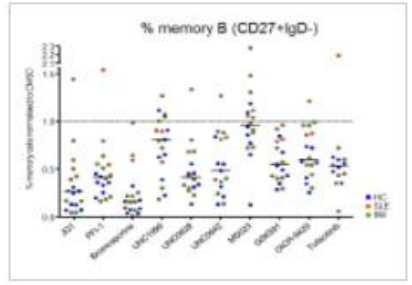


Fig 2c %memory B

Thanks to all contributors !

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FUNDING PARTNERS
The SGC is a registered charity (number 1097737) that receives funds from AbbVie, Bayer Pharma AG, Boehringer Ingelheim, Canada Foundation for Innovation, Eshelman Institute for Innovation, Genome Canada, Innovative Medicines Initiative (EU/EFPIA), Janssen, Merck & Co, Novartis Pharma AG, Ontario Ministry of Economic Development and Innovation, Pfizer, São Paulo Research Foundation-FAPESP, Takeda, and Wellcome Trust