

Developing a Clinical Research Programme

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UCD School of Medicine
& Medical Science



Scoil an Leighis agus
Eolaíocht An Leighis UCD



Disclosures

Speaker Bureau / Honoraria:

ViiV Healthcare, Merck Sharpe and Dohme, Gilead, Janssen Cilag (Tibotec), Bristol Myers Squibb

Research funding / educational grants:

GlaxoSmithKline

Gilead Sciences

Bristol Myers Squibb

Janssen Cilag (Tibotec)

Merck Sharpe and Dohme

Science Foundation Ireland

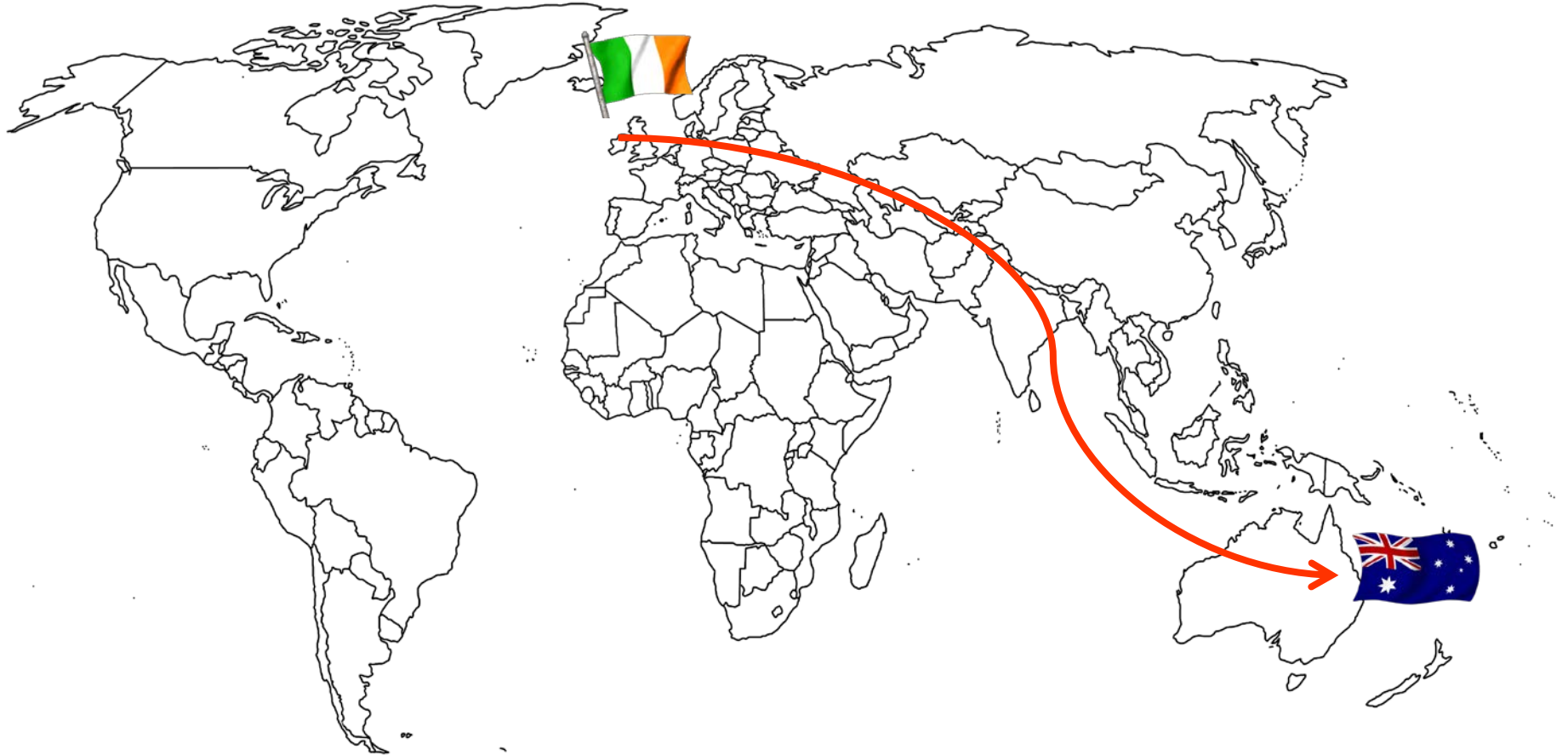
Health Research Board (Ireland)

Molecular Medicine Ireland

Wellcome Trust

NIH

1999.....



Clinical and Academic Training



Kirby Institute



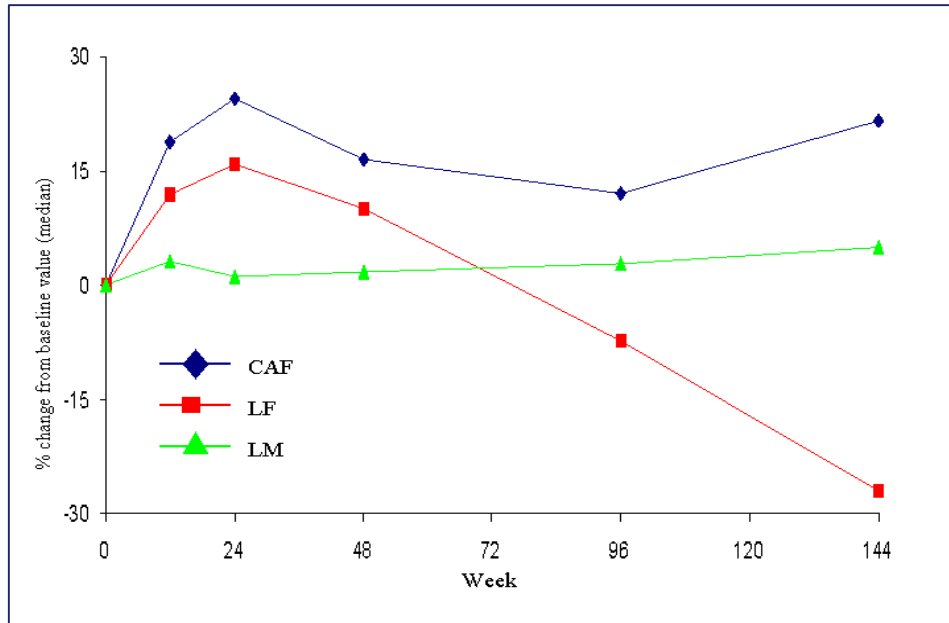
UNSW
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The Royal Australasian
College of Physicians



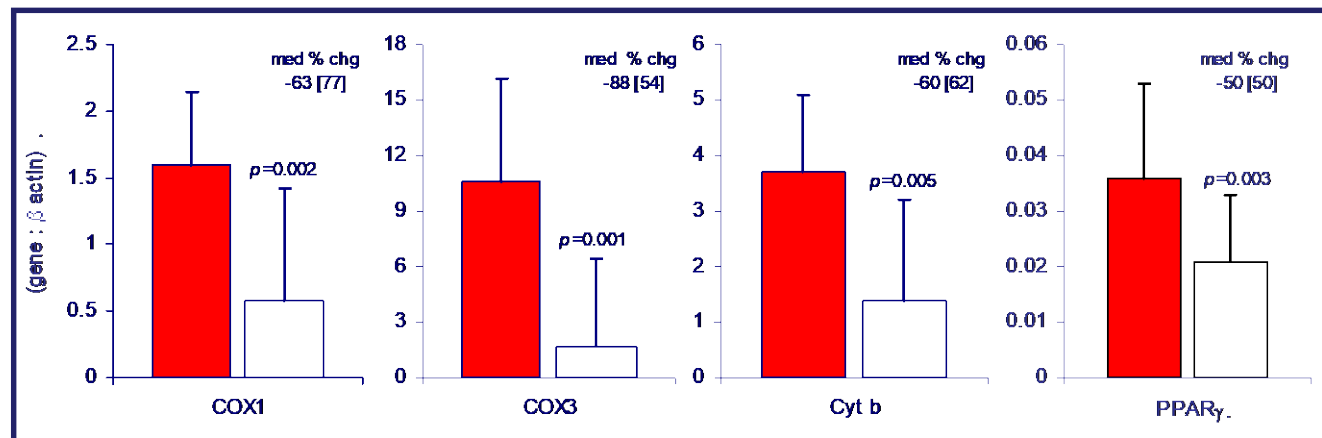
HIV- associated lipodystrophy



Mallon et al. *AIDS* 2003



Antiretroviral Guidelines



Mallon et al. *JID* 2005

2007.....

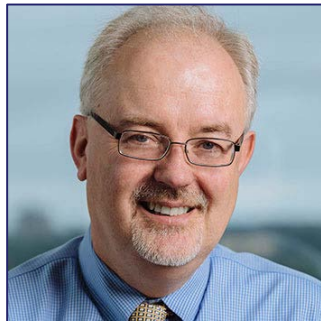
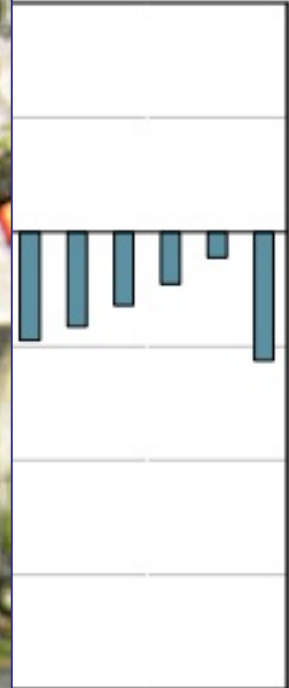




Figure 9: Irish employment growth



0

Q1 2011

My environment.....

Mater Misericordiae University Hospital (MMUH)



What is going on in our department?

- How many PLWH in the clinic?
- Who are these PLWH?
- How many are on treatment?
- Which treatments?
- What is happening to them?

....who cares?

Establishing research....

There are two types of people!

‘Mmmmm...I don’t think you can’t do that....!’



Establishing research....

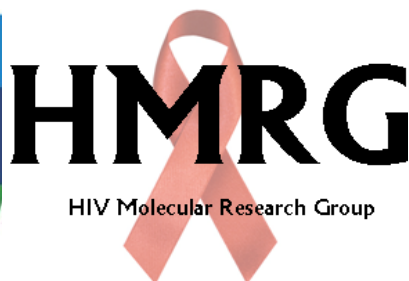
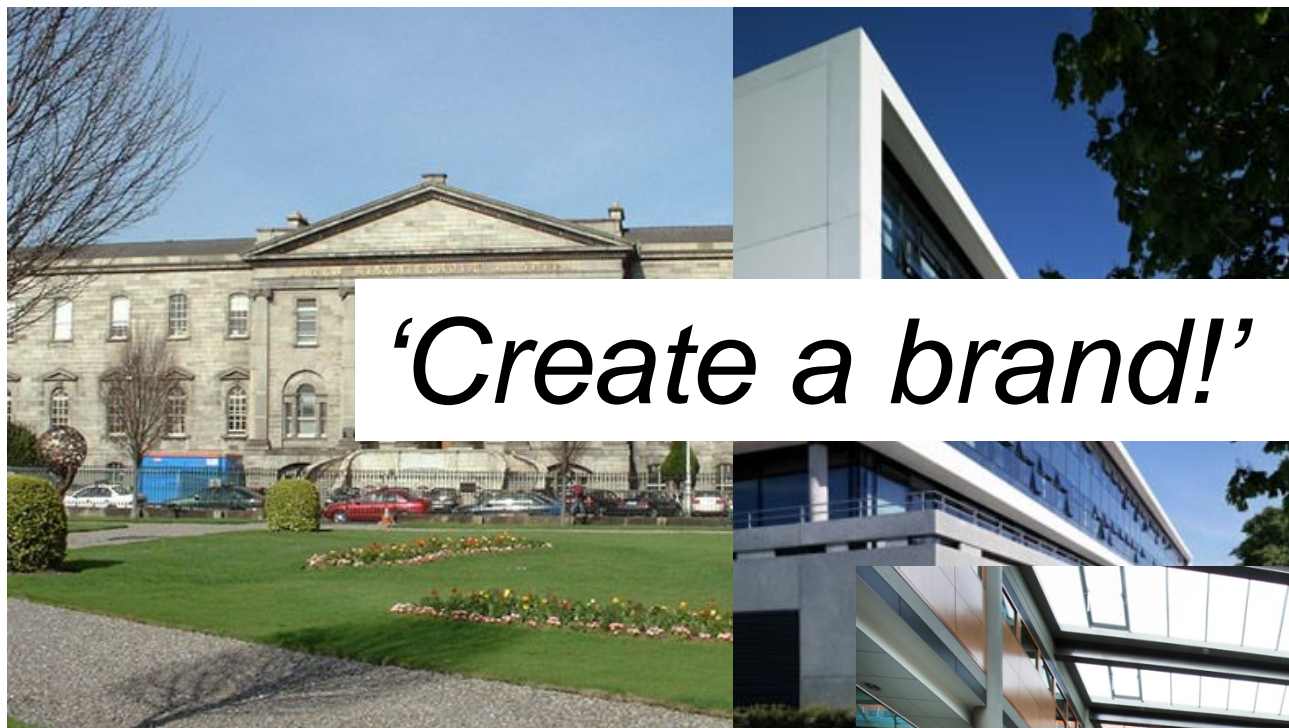
‘Yes we can!’



© Image supplied by Capital Pictures

The MMUH ID Cohort

Mater Misericordiae University Hospital (MMUH)



Steps to becoming an investigator....

1. Build up your c.v. – publications / presentations
2. Develop a broad area of expertise
3. Develop a track record
4. Co-applicant on research grants
5. Seek 'soft' money –
 - Scholarships
 - Institutional grants
 - Pharmaceutical funding
6. Fellowship or new investigator grants (supervisor)
7. Project grants (P.I.) / Large Pharma awards
 - Demonstrate ability to supervise (MD / PhD)
 - Develop collaborations / establish research team
8. Programme grants (P.I.)

What is going on in our department?

- How many PLWH in the clinic?
- Who are these PLWH?
- How many are on treatment?
- Which treatments?
- What is happening to them?

....who cares?

What do I need to answer my questions?

DATA!

Institutional grant



Alan Macken
Data Manager, HMRG

.....from County Mayo!

Why you don't want to be from Mayo.....



Sports-related
https://en.wikipedia.org/wiki/2017_GAA_Football_All-Ireland_Championship_Finals

Why utilise routine clinical data?

- Enhances patient care
 - Audit
 - Access to therapies – feasibility for clinical trials
- So that you can record what you're doing!!
- Builds research capacity / expertise
 - Basis for funding applications
- Streamlines research
 - One protocol covers all analyses / audits
 - Avoids unnecessary duplication of effort
- Enables collaboration

Conducting local research

- Access to appropriate patient population
- Have a good data collection tool
- Get appropriate approvals
- Store samples
- Motivating colleagues to do research (share the workload)
- Exploit available data sources
- Sharing data and getting results

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Electronic records and research

START

MATER MISERICORDIAE UNIVERSITY HOSPITAL
INFECTIOUS DISEASES OUTPATIENT DATABASE

The data contained on this database is the property of the HIV Molecular Research Group (HMRG). Any prohibited. All users of this database agree to abide by university, hospital, and government legislation, privacy and patient confidentiality. Any unauthorised use or distribution of all or part of the data contained in this database is prohibited. Any unauthorised change to the design, or replication or distribution of part or all of the database is prohibited. The design of this database is copyright Logicielle 2005. Use is restricted to approved personnel. By clicking on the bar below, the user agrees to abide and to use this database in the knowledge that failure to abide by the above rules could result in

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>1,900 subjects
recruited

FRONT SHEET HIV

PATRICK MALLON

DOB: 02-Jan-45

Age: 70

MRN: 1234123

Year diagnosed: 2010

Consultant: Mallon

Referring hospital: Mater Private Hd

AIDS diagnosis:

CDC stage:

Last updated:

HIV 33

Currently active diagnoses:

Diagnosis: Start date: AE/SAE:

DIABETES MELLITUS 01/01/2004 No

CEREBROVASCULAR ACCID 01/01/2014 No

CHANGE / ADD DIAGNOSES

Previous diagnoses:

Diagnosis: Date: AE/SAE:

Previous clinic visits:

20-Jan-15 Mallon

Mr Mallon is clinically stable. Adherent to medications. He is up to date with vaccinations and all his bloods are stable.

Hepatitis serology: Date tested:

Hep A total Ab:

Hep A IgM:

Hep C Ab:

Hep C RNA (qual):

Hep C RNA (quan):

Hep C RNA date:

Cryptococcal serology

Date tested:

Crypto serology:

Toxoplasma serology

Date tested:

Toxo IgG:

HLA B*5701 Date tested:

HLA B57:

Syphilis Serology

Date tested:

Hep B

HepB cAb:

HepB sAb:

sAb titre:

HepB sAg:

HepB eAg:

CMV serology

Date tested:

CMV IgG:

PPD

Date tested:

Diameter:

TPPA:

EIA:

TP (Abbott):

RPR:

CD4: 440 HIVVL: 40

CD4 nadir: 440

Current medications:

Darunavir	800mg	daily
Ritonavir	100mg	daily
Truvada	One tab	daily
Atorvastatin	10mg	nocte
Aspirin	75mg	daily

Prophylaxis: PCP: Septtrin 1 tab daily

MAC:

CMV:

TB:

Crypto:

Clinical studies: Week 0 Study code Study Arm

HIV UPBEAT 01/01/2010 B001 1

Patient and LMO details	Add a test result	Graphs of results	Review test results	Add new clinic visit	Allied Health OOS	Change Medication	Write a referral	Clinical Outcome	HIV/ID COHORT	Open HepC Form	Open Hep B Form	HIV UPBEAT	IMM Study
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MENU BAR

Conducting local research

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Approvals

- Study Protocol
 - Details the process for enrolment
- Keep the protocol broad – avoid specifics
 - e.g. young people with HIV rather than adolescents
 - Avoid too many restrictions to recruitment
 - Consider wider group outside of HIV? (controls)
- Get the appropriate regulatory approvals
 - Ethics committee
 - National regulatory bodies
- Request approval for collection of all ‘routine’ clinical data
 - Blood results
 - Investigations
 - Medical history

Conducting local research

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- **Store samples**
- Motivating colleagues to do research (share the workload)
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Storing samples

- When designing cohort think of what you want to do, not what you currently can do – aspirations
- Storage of samples facilitates translational research
- Serum, plasma, DNA, PBMC
 - Preferably fasting – standardise
- Build into original consent (? Optional)
- Use of plasma / serum for biomarkers
 - Usually straight forward approval
- Use of DNA for research
 - Consider local regulations around use of DNA
 - Host versus pathogen analyses

Conducting local research

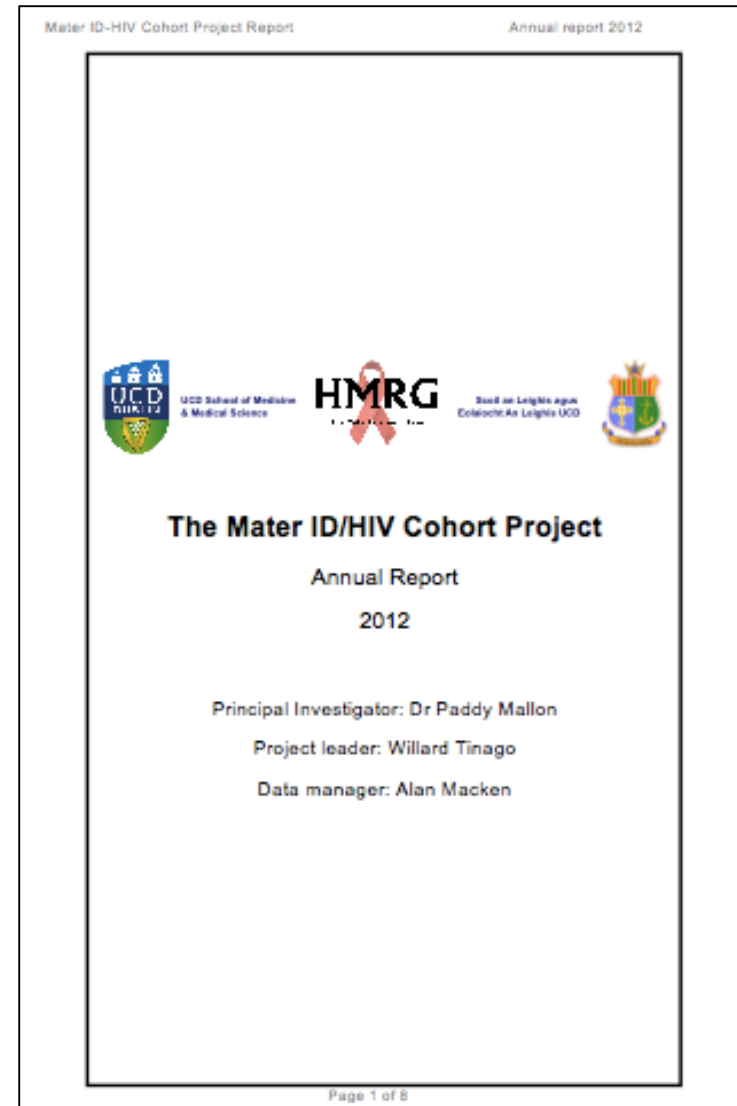
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Incentivise Data Collection

- Database utility to make clinical work easier
 - Clinical summaries
 - Access to results (graphs)
 - Automated letters
- Build in competition to data collection
 - Competitive recruitment
 - Awards / recognition for recruitment
- Regular communication maintains momentum
 - Updates on cohort statistics
 - Quarterly / Annual reports
 - Highlight dissemination (abstracts / manuscripts)

Communication

- Weekly updates from data manager
- Clinic-based recruitment figures
- Monthly recruitment figures
- Milestones celebrated
- Annual report to all stakeholders



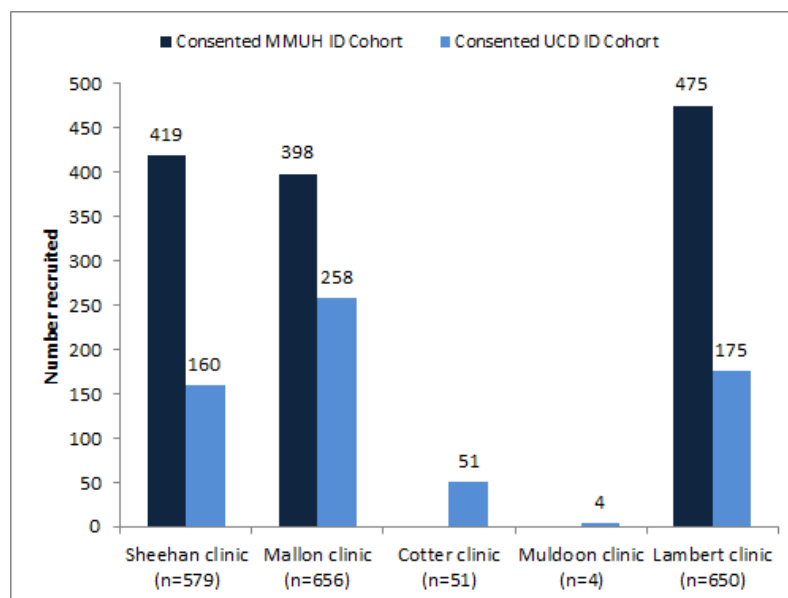
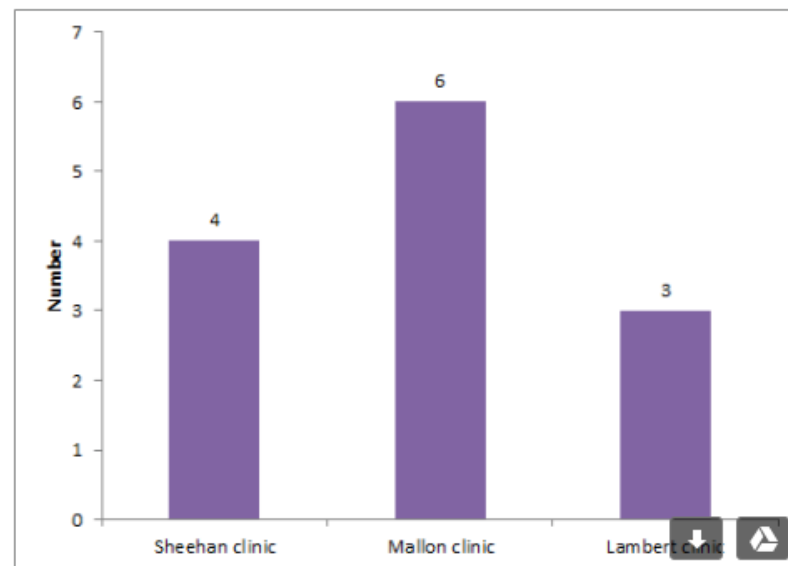
Communication



Well done team, what a milestone! **1001** recruited and still counting.....

Thank you for the continued support with recruitment for the Mater ID Cohort.

Last week recruitment statistics.



Conducting local research

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Exploit available data sources

- Look around for data linkages
- Can save time +++
- Explore opportunities for direct linkage with other databases
 - Laboratory
 - Pharmacy / drug dispensing
 - Government records (deaths)
- Data linkages can be real-time or 'data dumps'
- Consider a 'Source Data Agreement' - GCP

Conducting local research

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- Sharing data and getting results

Sharing data and getting results!

- Develop protocol for sharing data
- Ensure the data is used according to ethics / regulatory approval
 - Important if external requests
- Ensure confidentiality is maintained
 - Emails / print outs
 - Memory sticks
- Ensure you are credited for data collection
 - Clear authorship policy
 - Funding
- Keeps everyone happy!



Clinical, immunological and treatment-related factors associated with normalization of CD4+/CD8+ T-cell ratio: effects of naïve and memory T-cell subsets

**Tinago W¹, Coghlan E¹, Macken A¹,
McAndrews J², Doak B,² Fuller-Prior C²,
Lambert J^{1,3}, Sheehan G^{1,3}, Mallon P^{1,3}**

¹HIV Molecular Research Group, School of Medicine and Medical Sciences, University College Dublin, Ireland

²Department of Immunology, Mater Misericordiae University Hospital, Dublin, Ireland

³Department of Infections Diseases, Mater Misericordiae University Hospital, Dublin, Ireland

PLOS ONE May 9 2014; 9(5):e97011

The Mater Immunology Study

1. We thought of a research question
2. We explored what collaborations would be required:
 - Immunology Laboratory
 - External advice (Sydney)
3. We explored feasibility - single clinic
4. We sought funding - €10k local pharma
5. We presented and discussed results
 - Spanish cohort

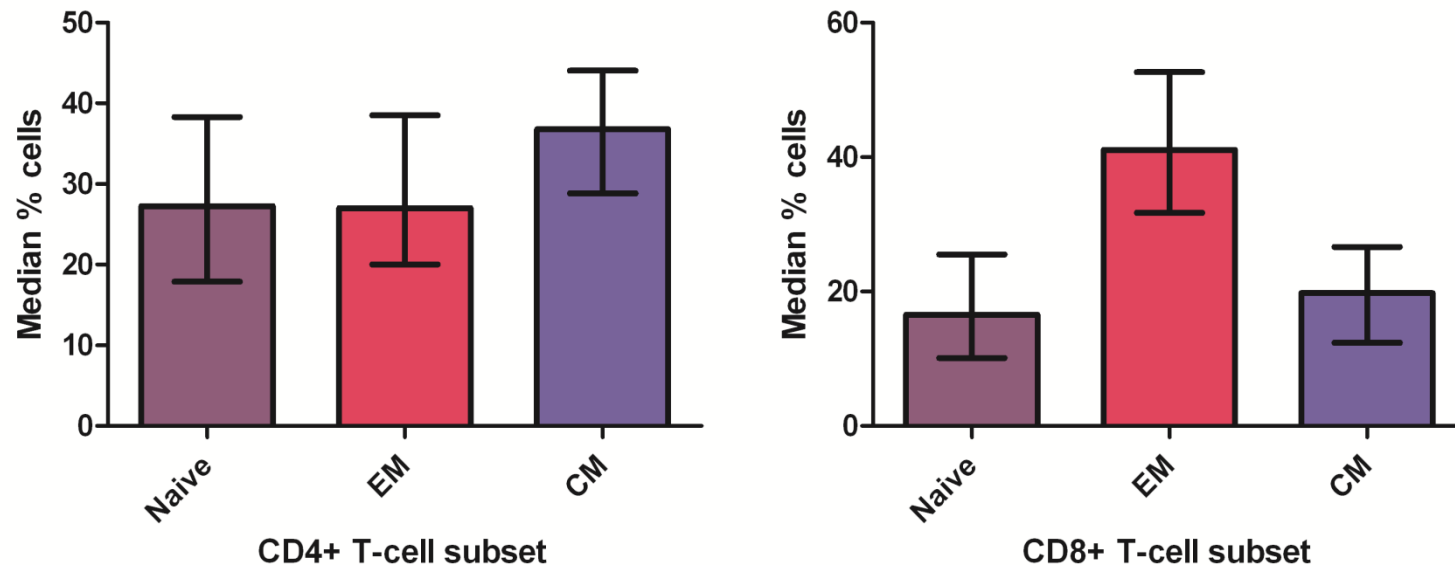
The Mater Immunology Study

- Prospective cohort on ambulatory HIV+ patients attending MMUH ID clinics
- N=190 adults, 42 (36-48) yrs old, 64% male, 65% Caucasian
- CD4+ and CD8+ T-cell subsets:
 - Naïve cells CD45RO-,CD62L+
 - Central memory cells CD45RO+,CD62L+
 - Revertant memory cells CD45RO-, CD62L-
 - Effector memory cells CD45RO+CD62L-

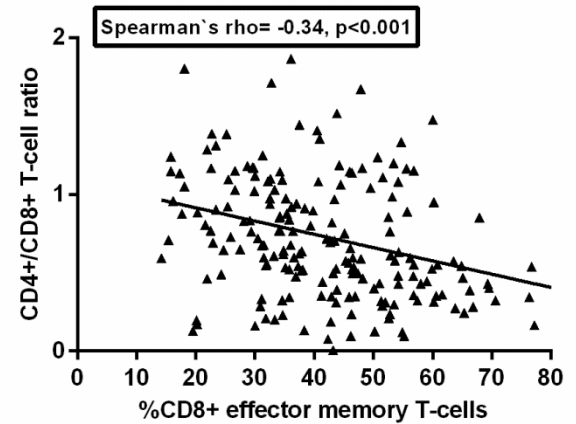
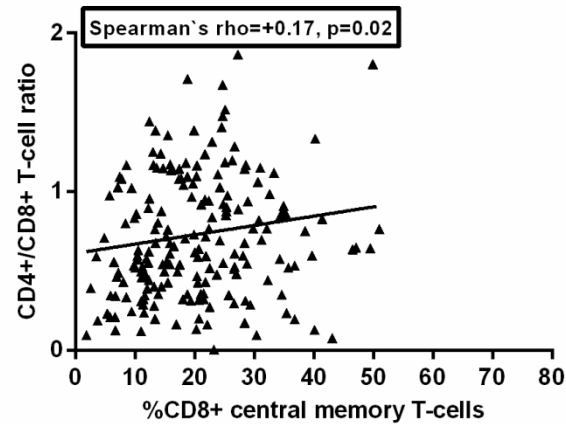
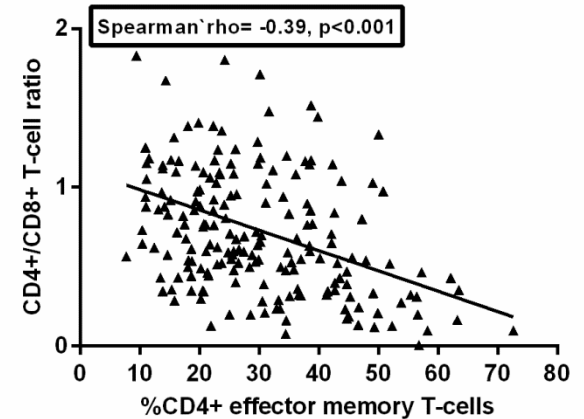
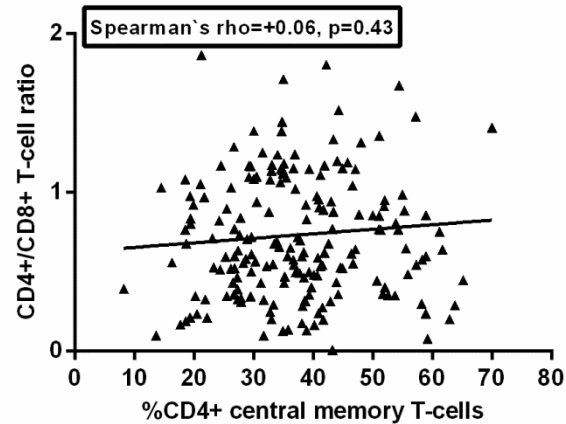
The Mater Immunology Study

- CD4+/CD8+ T-cell ratio 0.6 (0.4-1.0)
- CD4+/CD8+ T-cell ratio ≥ 1 50/190 (26.3 %)

Figure 2. Distribution of CD4+ and CD8+ expanded T-cell subsets



The Mater Immunology Study



The Mater Immunology Study

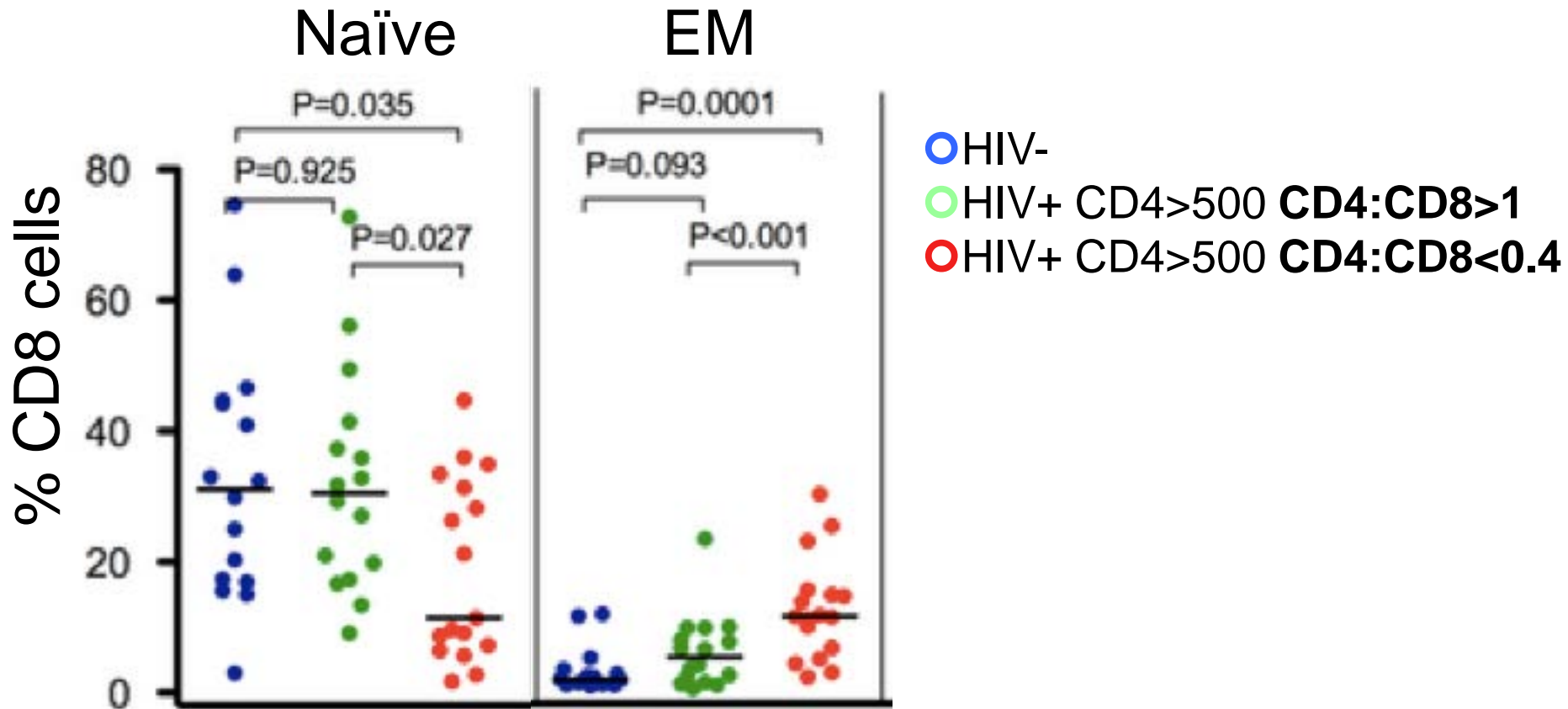
	†All patients (N=190)			‡Patients on ART with HIV RNA<40cp/ml (N=149)		
	Coefficient	95% Confidence Interval	P-value	Coefficient	95% Confidence Interval	P-value
Total cumulative ART exposure (years)	+0.014	0.0042, 0.025	0.006	+0.014	0.0022, 0.026	0.021
Nadir CD4+ T-cell count (per 10cells/mm ³ increase)	+0.011	0.0081, 0.014	<0.001	+0.013	0.0084, 0.017	<0.001
Absolute CD8+ T-cell count (per 10cells/mm ³ increase)	-0.0044	-0.0056, -0.0033	<0.001	-0.0052	-0.0068, -0.0036	<0.001
%CD4+ effector memory (CD45RO+CD62L-)	-0.0036	0.0074, 0.00006	0.054	-0.0057	-0.010, -0.0012	0.014
%CD8+ naive (CD45RO-CD62L+)	+0.0088	0.0044, 0.013	<0.001	+0.0080	0.0028, 0.013	0.003

†Adjusted for age, gender, ethnicity, Hepatitis C status, and HIV RNA,

‡Adjusted for age, gender, ethnicity, Hepatitis C status

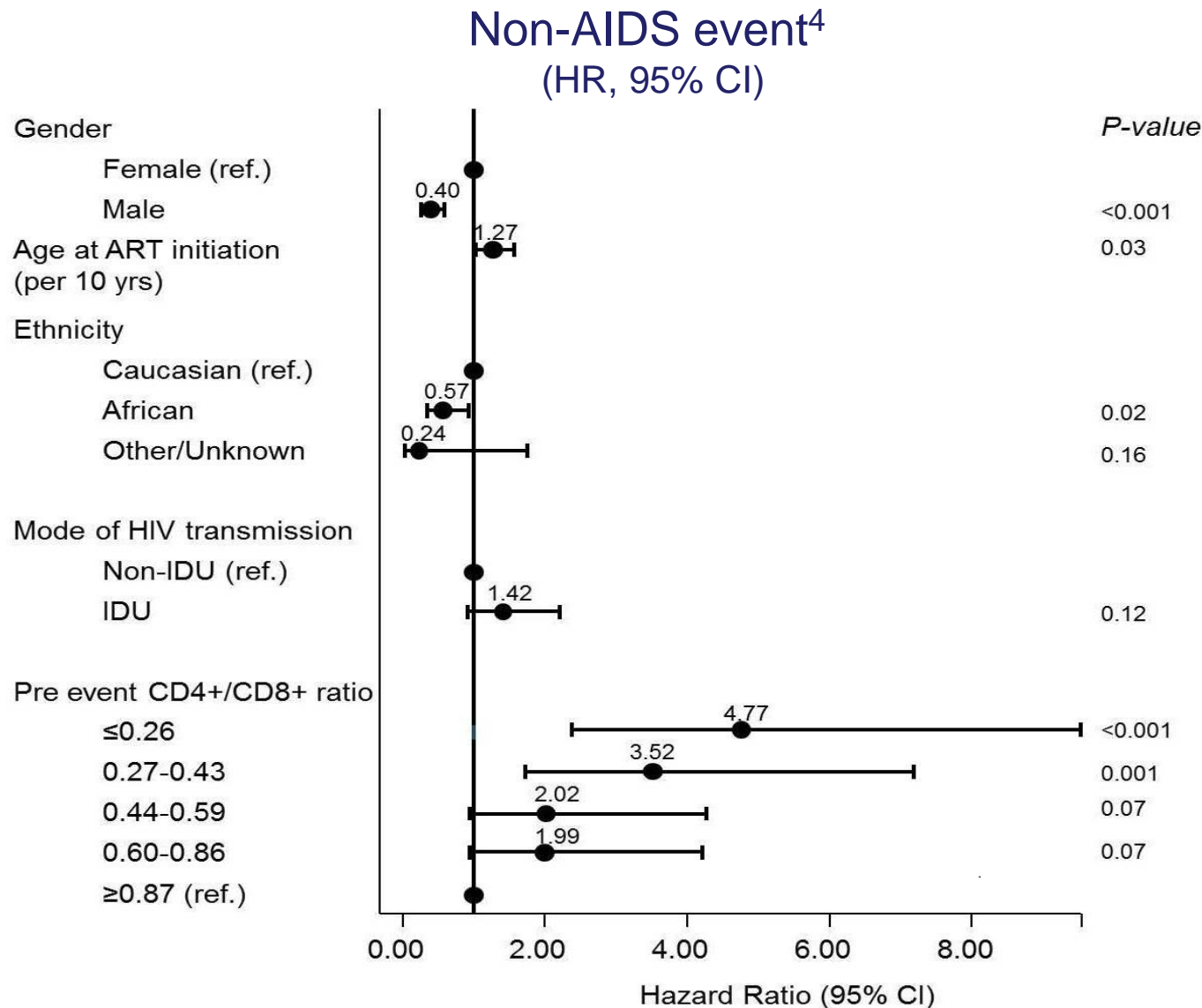
NB: Coefficients of %CD4+, %CD8+ T-cells and their subsets are per 1% increase

CD4:CD8 Ratio – naïve CD8+ T-cells



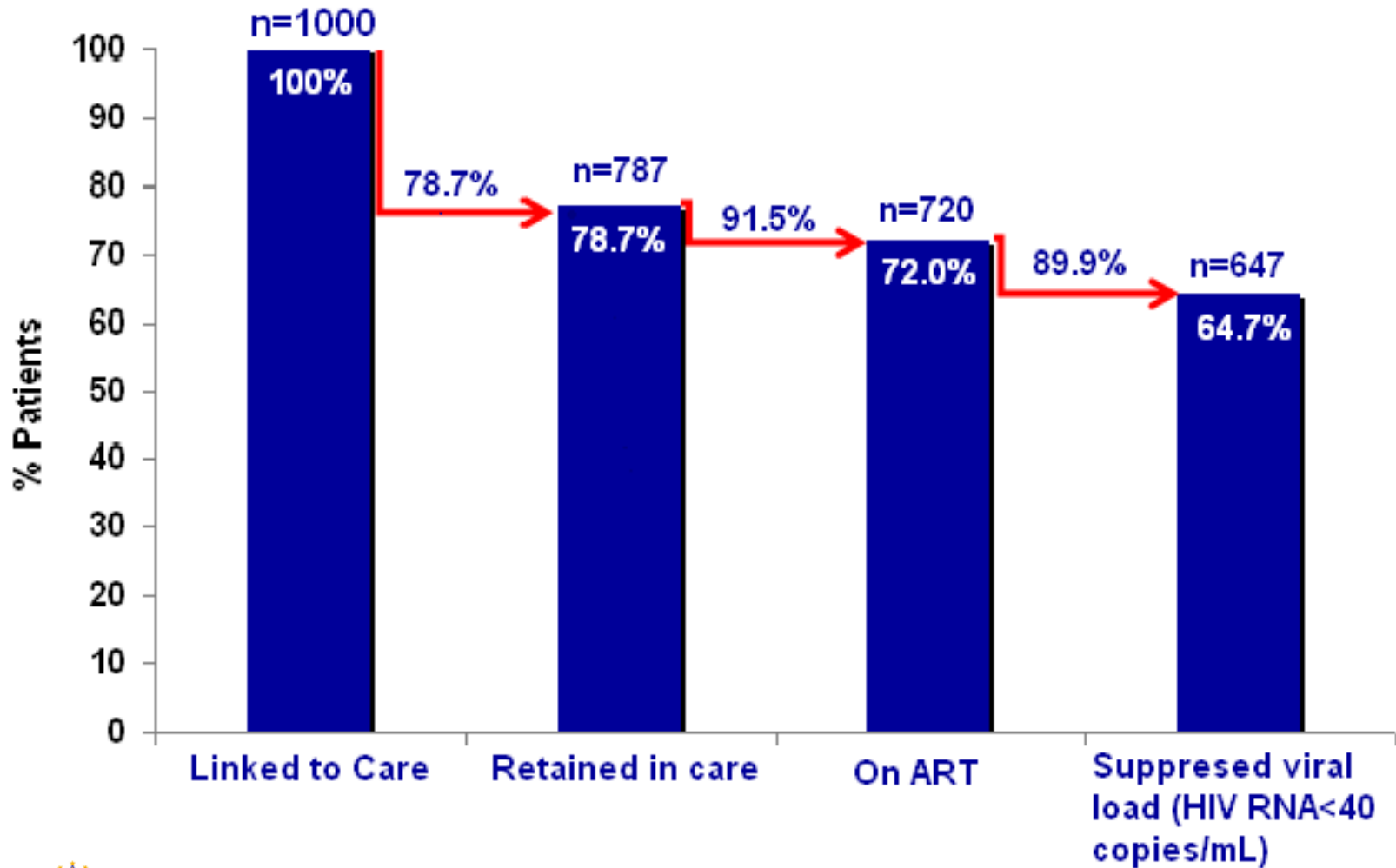
- Each 10% decrease in the CD4/CD8 ratio and each 10% increase in the CD8+ T cell count associated with 48% and 22% higher odds of serious non-AIDS events, respectively.

Biomarkers and outcome – CD4:CD8 ratio



P

HIV care continuum – Ireland



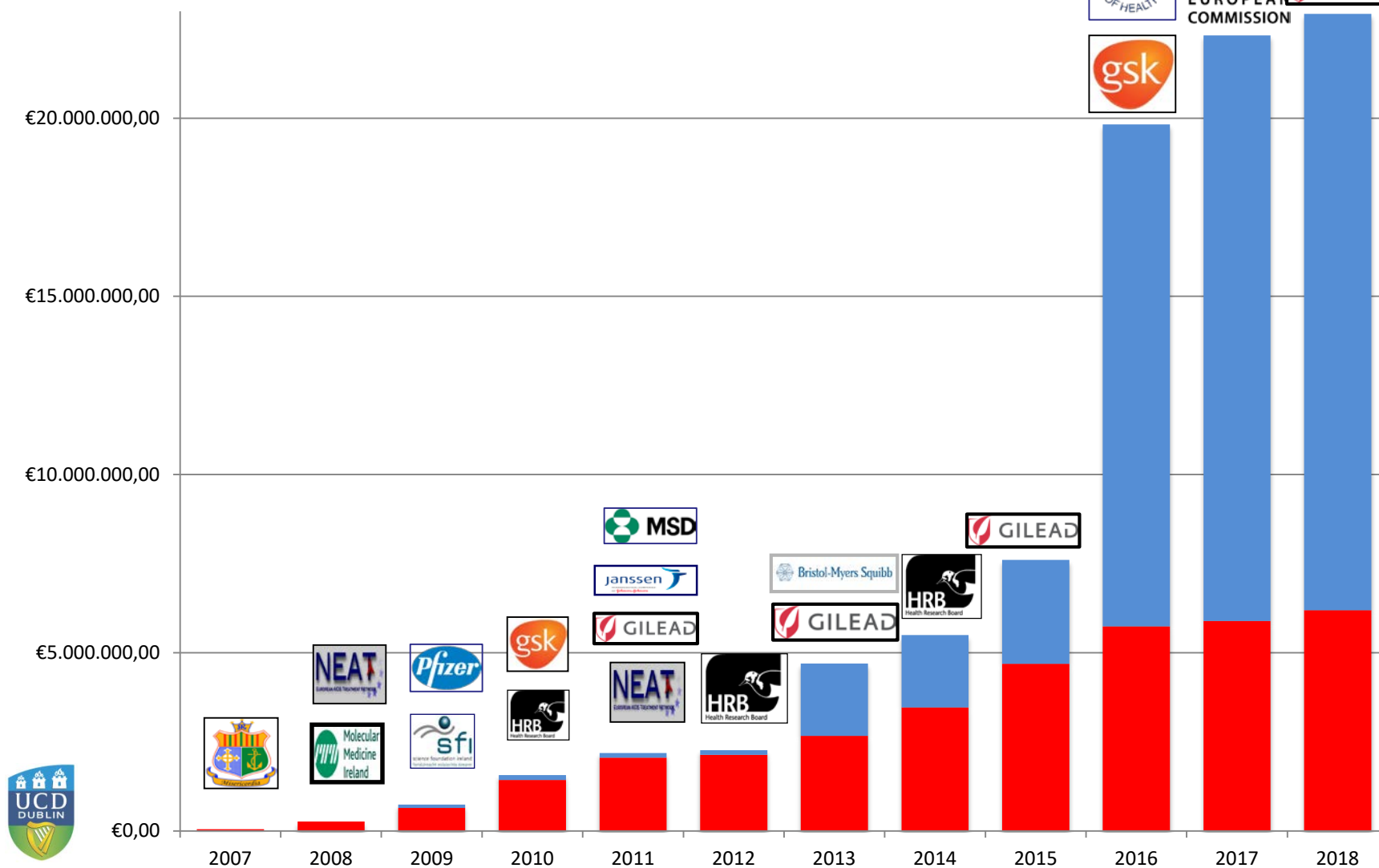
The Mater ID Cohort

- Modified consent to collect viable PBMC
- Flu vaccination immunology
- Spinal infection case series
- TB case series
- Immunoprofiling
- Interferon genotype and immunological outcome
- Prevention Support Service research (PrEP)

Cohorts.....

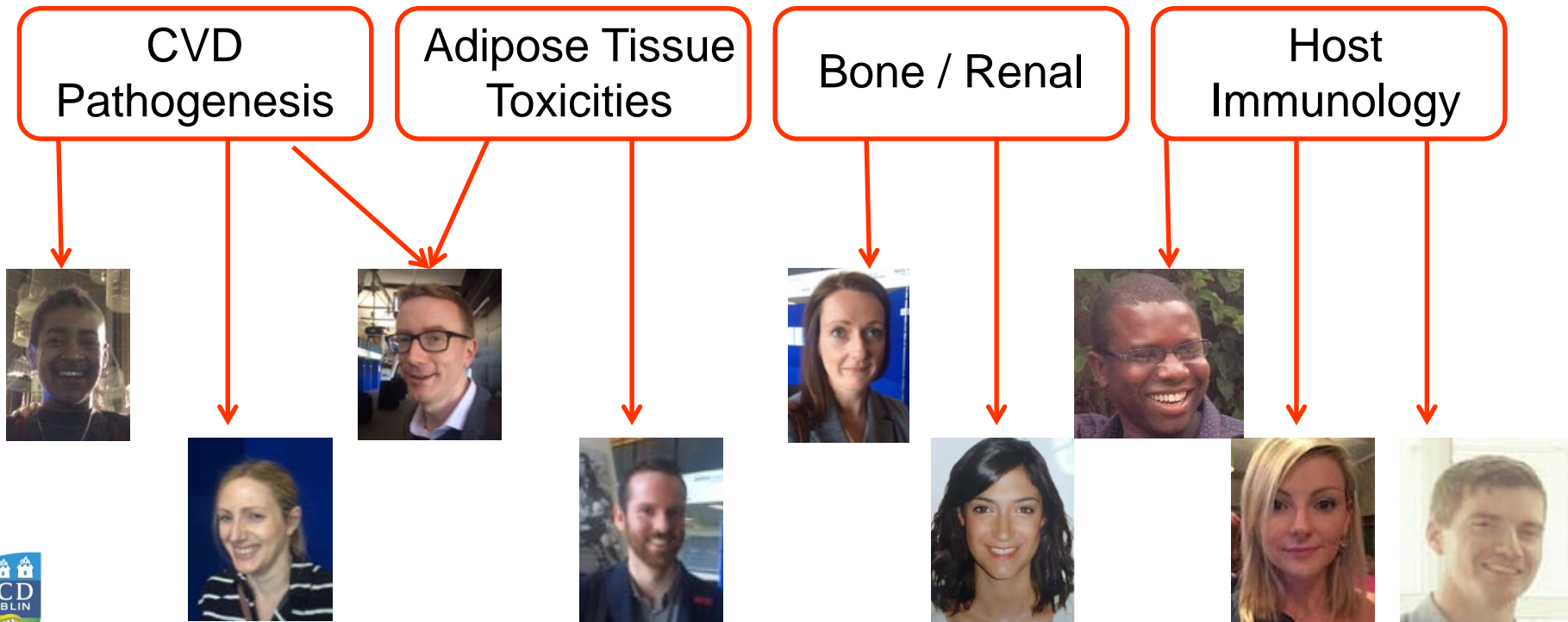
- Putting thought into the design of a cohort study can maximise research opportunities
- Database tool is only one component
- Always think into the future
- Seek consent
- Standardised processes essential
- Always look for opportunities to **collaborate**

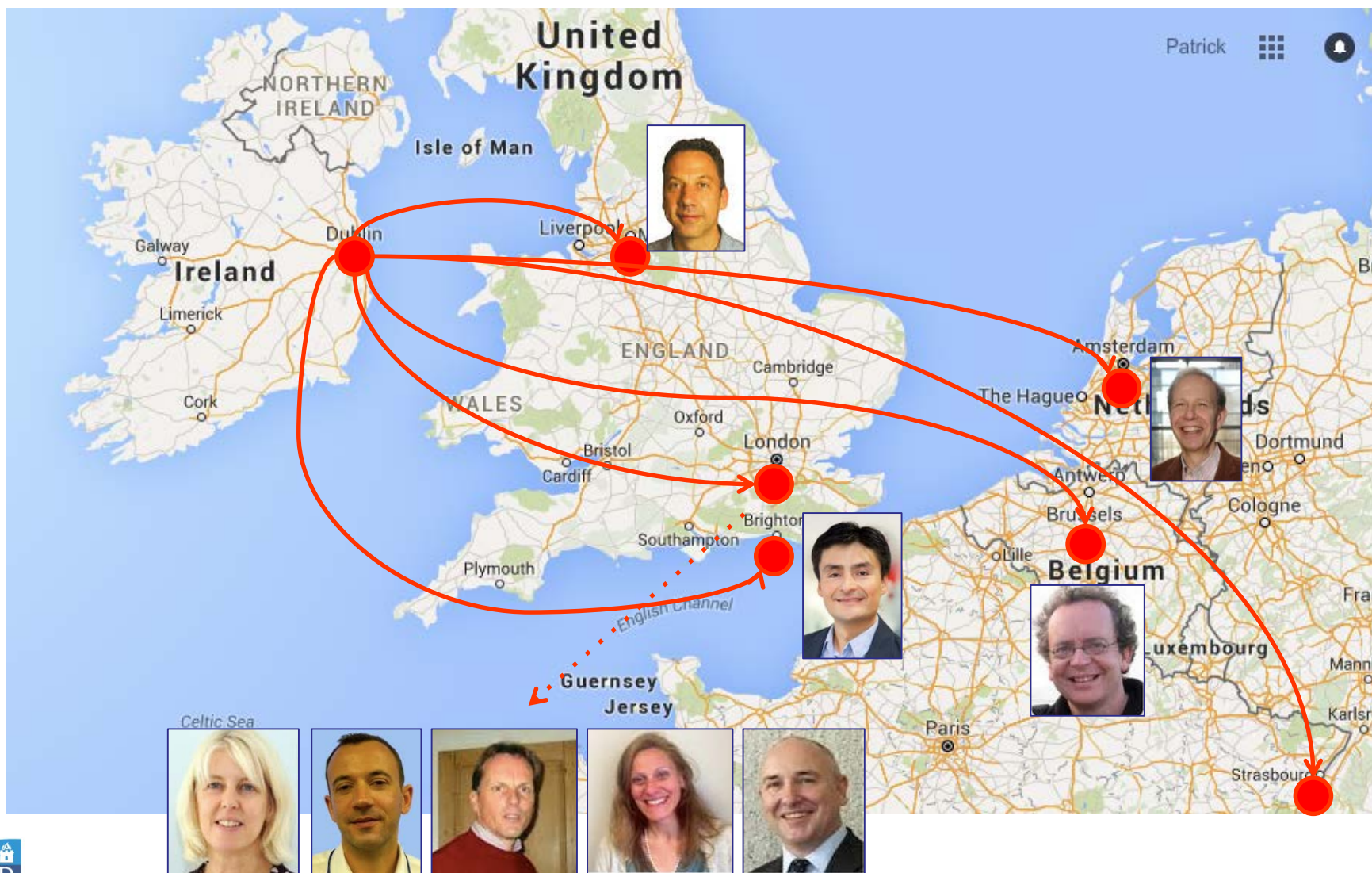
Funding achievements



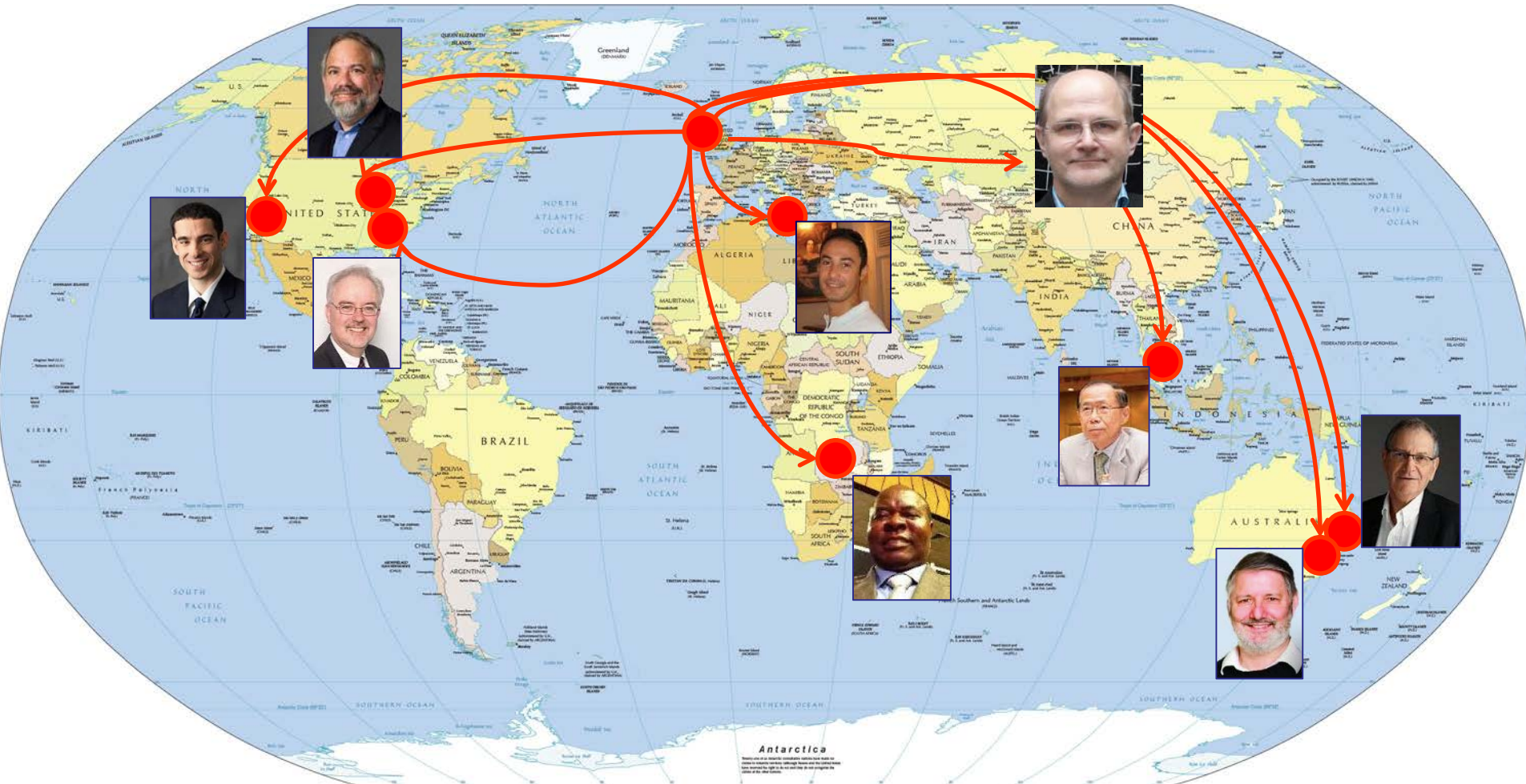
HIV Molecular Research Group

Pathogenesis research into long-term outcomes in HIV using the human host as the research model





HMRG - collaboration



Building research

Building collaborations and growing expertise within the team enables more complex research

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Saved Studies (0)

[Give us feedback](#)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Saved Studies (0)

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Alendronate for Prevention of AntiRetroviral Therapy-associated Bone Loss (APART)

This study is currently recruiting participants.

See [▶ Contacts and Locations](#)

Verified November 2016 by Patrick Mallon, University College Dublin

Sponsor:
University College Dublin

Patient & Public Involvement (PPI)



Dissemination and impact - social media!

Home Moments Search Twitter Have an account? Log in

HIV & AGEING
TOWARDS HEALTHIER AGEING IN HIV
European HIV Seminar
23rd-24th June 2017. Dublin. Ireland

HMRG
HIV Molecular Research Group

Tweets 691 Following 250 Followers 287 Likes 358 Follow

HIVMRG
@HIVMRG

UCD School of Medicine-Mater Hospital based translational research team interested in long-term HIV care and models of HIV testing and prevention. Tweets by Alan

Tweets Tweets & replies Media

Pinned Tweet

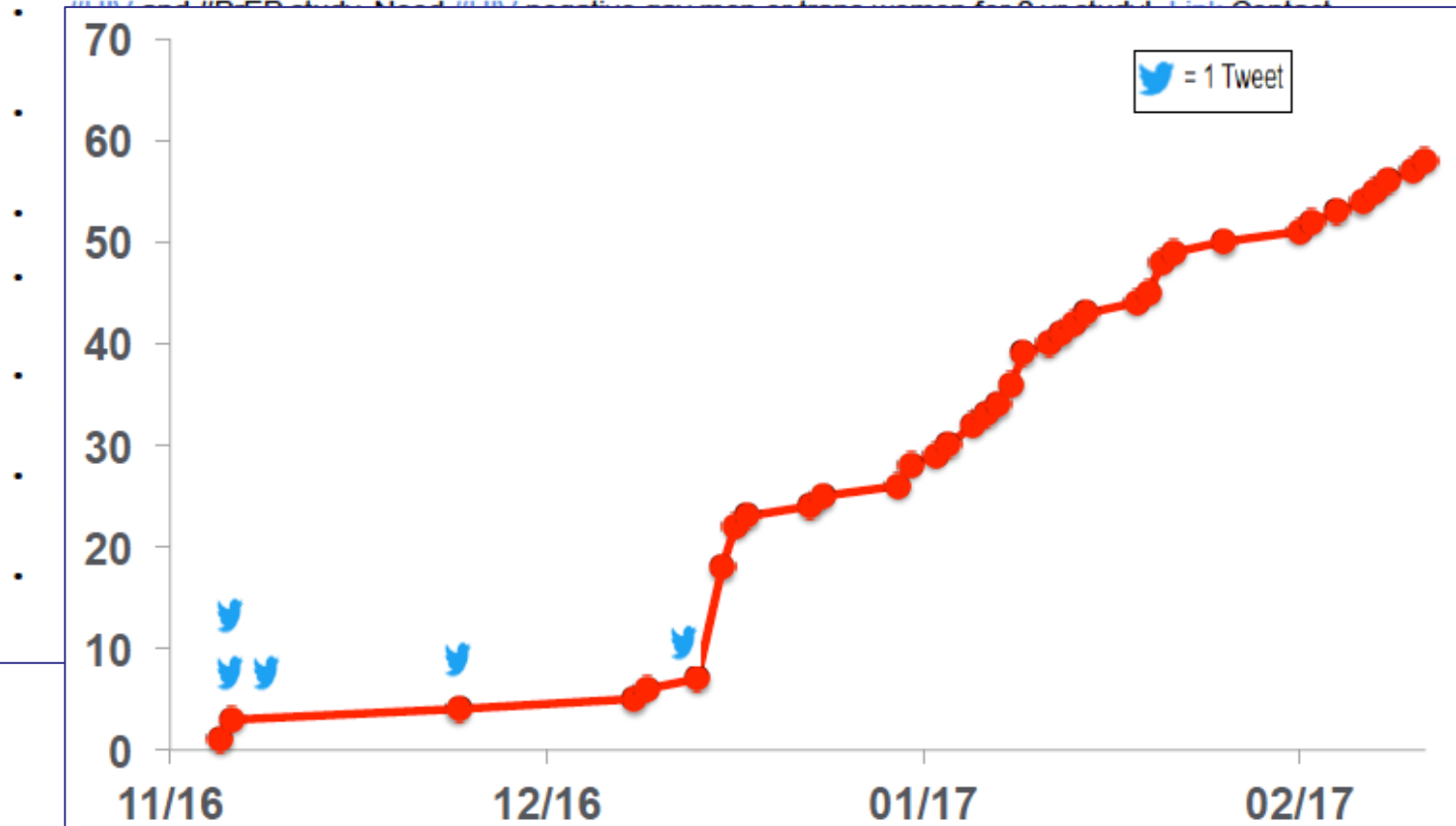
HIVMRG @HIVMRG · May 18
Delighted to announce Inaugural HMRG European HIV Seminar, Dublin 23-24 June 2017. Exciting lineup-Register early!

Home - European HIV Seminars : HIV and Ageing
"Welcome. On behalf of the UCD School of Medicine,

Dissemination and impact - social media!

IRB approved DISCOVER Trial Tweets

- Help us explore [#HIV](#) and [#PrEP](#) in Ireland. Join the DISCOVER study. [#GetInvolved](#) [Link](#) Contact hmrq@ucd.ie or 01-7164584



Implementation of research

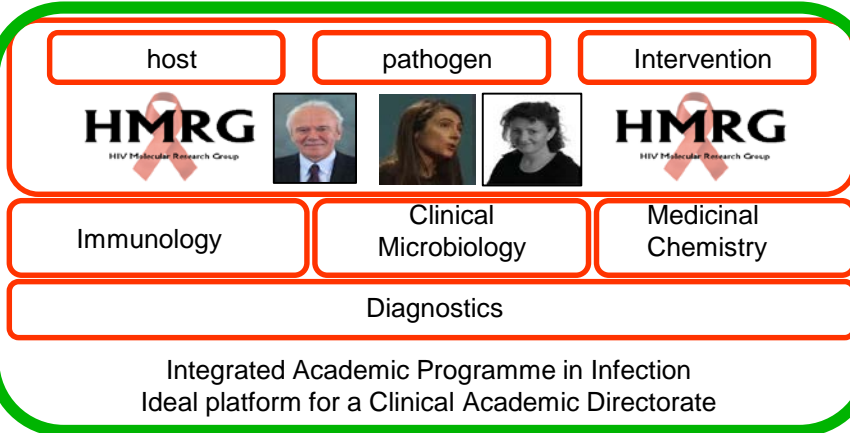


- Challenging aspect of research
- Different kind of discipline
- Stakeholder involvement essential
- Create an '*environment for change*'
- PrEP in Ireland (#PrEP4Ireland)



Always have a plan..... '*CEPHR*'

Centre for Experimental Pathogen Host Research



Policy, development,
preparedness, research



ONE HEALTH

5 year plan.

Framework for growth.

Agreed by all stakeholders.

Maintain flexibility.



EACS
European
AIDS
Clinical
Society



Summary

Research is fun!

Surround yourself with like-minded people

Seek ways to collaborate

Try not to be too focused

Establish links with stakeholders – PPI

Never give up!

