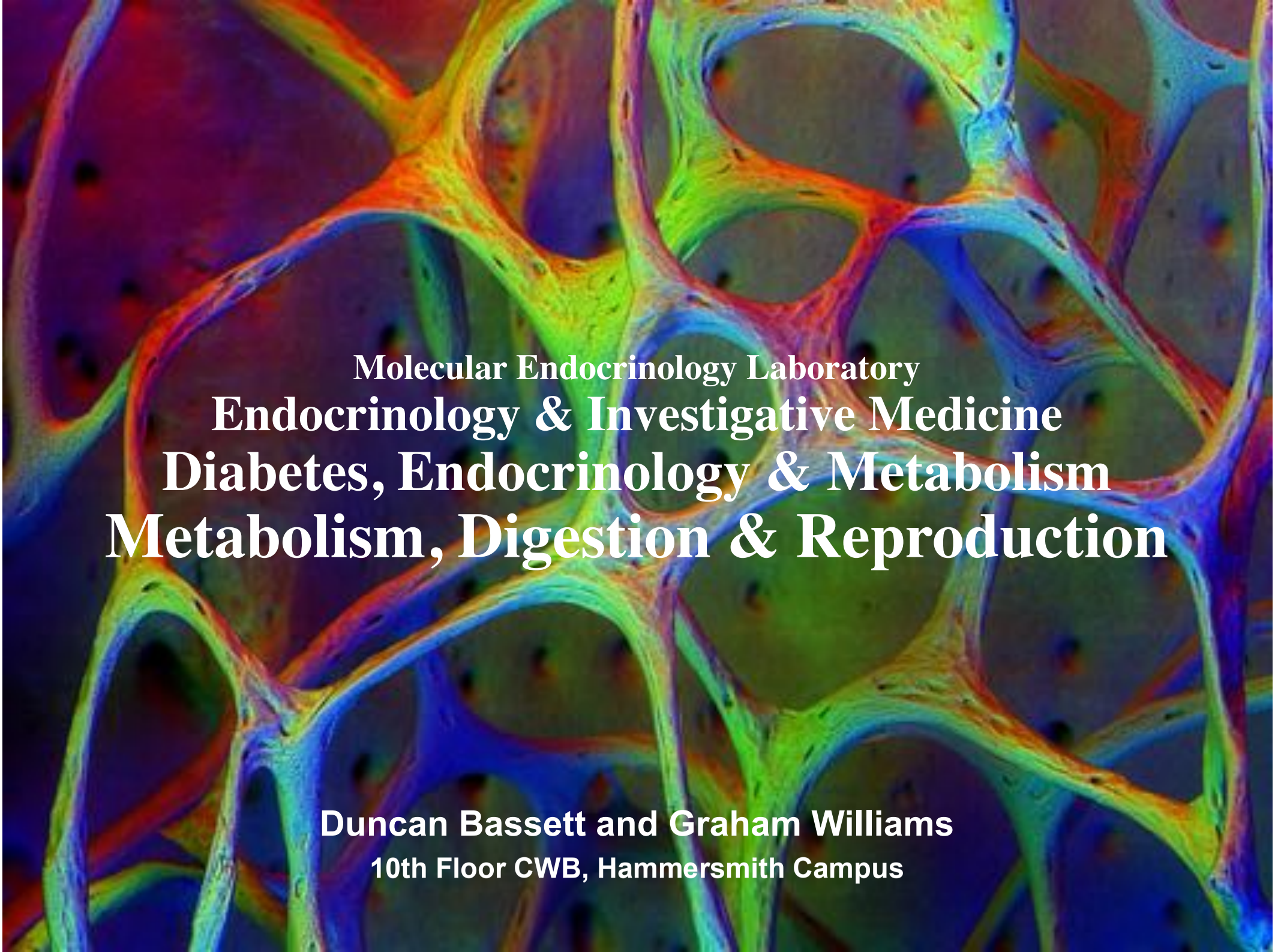
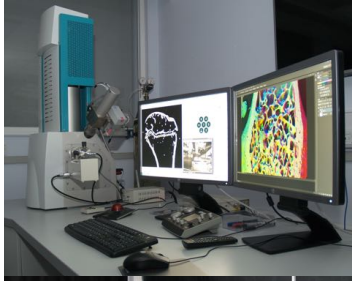
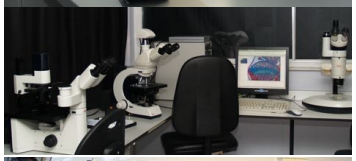
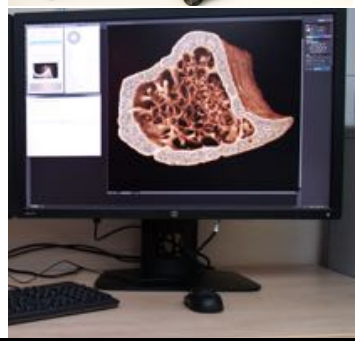

Molecular Endocrinology Laboratory
Endocrinology & Investigative Medicine
Diabetes, Endocrinology & Metabolism
Metabolism, Digestion & Reproduction
Duncan Bassett and Graham Williams
10th Floor CWB, Hammersmith Campus



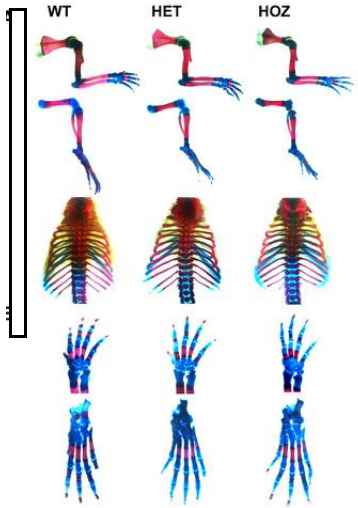


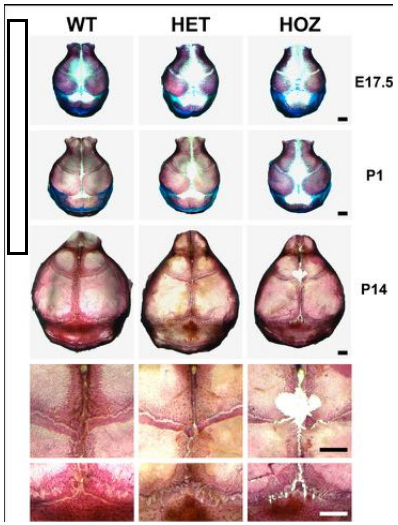
>20 years studying hormone action and skeletal biology using mouse genetics

- Mouse genetics
  - KO, knock-in, Cre-lox, inducible Cre, Crispr
- World leading state-of-the-art skeletal phenotyping
  - X-ray microradiography
  - High resolution micro-CT
  - BSE-SEM
  - Static and dynamic histomorphometry
  - Biomechanical testing
  - *in vitro* primary culture systems

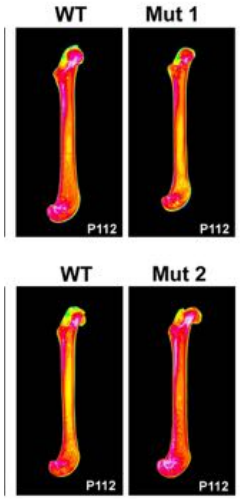


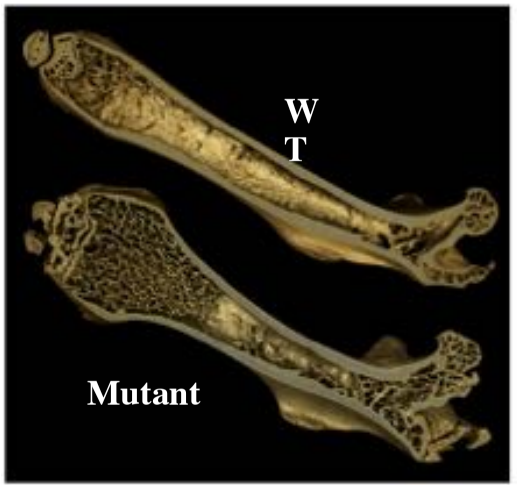
Skeletal development



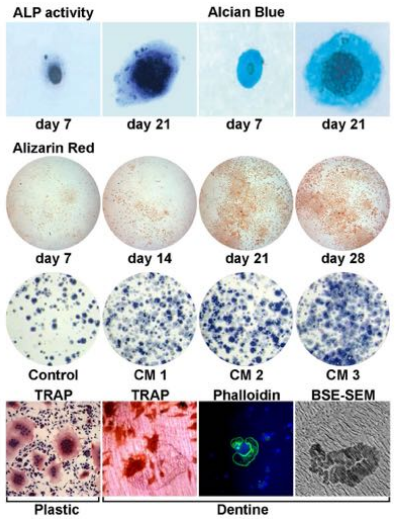


Adult bone structure and strength





Cellular mechanism



Strategy

Diversify

- **International networking**
- **Endocrinology and skeletal biology**
- **Mouse and human**
- **Technical (scientists, industry)**
- **Funders**

- **Collaboration**

- **Marketing and cutting-edge capability**
- **Skills**
- **Resources**
- **Infrastructure**

Focus

Ageing and chronic disease

Network

- **Osteoporosis/osteoarthritis**
  - Imperial
- **Neurodegeneration**
  - Paris (Demeneix), Budapest (Fekete, Gereben)
- **Sarcopenia**
  - Naples (Salvatore, Dentice)
- **Human ageing cohorts**
  - Leiden (van Heemst), Copenhagen (Westendorp)
- **Targeted drug development**
  - Leiden (Pepscan)

Skills

- **Diverse phenotyping capability**
- **Human cohorts**
- **Chemistry**

Resources

- **Exchange un… …ouse mod…**
- **Share reagen… …ocols and…**

Michael Dack

Andrea Pollard

Siobhan Guilfoyle

Davide Komla-Ebri

European Commission Horizon 2020 (2016-2021)

"THYRAGE: resetting the THYRoid axis for prevention of AGE-related diseases and co-morbidities"

Mechanisms of chronic skeletal disease

Network

Industrial partners

- Scanco (µCT)
- Deben/Tescan (SEM)
- Faxitron (X-ray microradiography)

Skills

- Develop novel phenotyping methods
- Develop provocation models
  - Fracture repair (Maes, Leuven)
  - DMM (Kennedy Institute)

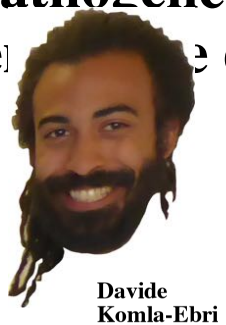
Resources

- Tissue-specific gene targeting
- Mouse models of human genetic polymorphisms
- Analysis of thyroid hormone metabolism
- Share reagents, protocols and data


Ann-Kathrin Schörding


Andrea Pollard


Hannah Dewhurst


Davide Komla-Ebri

Wellcome Trust Joint Investigator Award

(2016-2021)

"Cellular thyroid hormone availability: regulation of development and tissue repair, and pathogenesis of lege[illegible] disease"

Origins of Bone and Cartilage Disease

Network

High throughput skeletal phenotyping (>1250 KO mice)

Imperial

RNAseq and bioinformatics

Sydney (Croucher, Mattick)

Human GWAS

Brisbane (Evans), Montreal (Richards), Rotterdam (Rivadeneira), UKBiobank, GEFOS

Munich (Zeggini)

Mouse Genetics Pipeline

Sanger Institute (Adams)

International Mouse Phenotyping Consortium

Jackson Laboratories, University of Connecticut, Helmholtz Munich

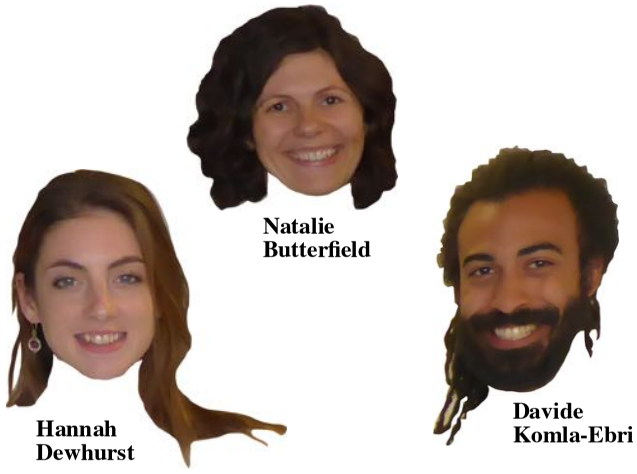
Rare diseases

X-linked juvenile osteoporosis (*PLS3*), Omodysplasia (*GPC6*), Gray platelet syndrome (*NBEAL2*), Idiopathic epilepsy (SLC20A2)

Wellcome Trust Strategic Award

(2014-2019)

"Origins of bone and cartilage disease"



Resources

Funding and collaboration seeds opportunity

EU COST Network

(2019-2024)

"GEnomics of MusculoSkeletal traits TranslatiOnal Network GEMSTONE"

MRC Clinical Training Fellowship (2017-2020)

Bernard Freudenthal

"The role of PLS3 in the pathogenesis of osteoporosis"

MRC Research Grant (2016-2020)

Jacques Behmoaras

"Control of macrophage multinucleation in health and disease"

Wellcome Imperial 4i Clinician Scientists (2017-2020)

Laura Watts

"The role of FUBP3 in the pathogenesis of osteoporosis"

Bernard Freudenthal

Riikka Mäkitie

Jeong-Hun Ko

Marie Pereira

Jacques Behmoaras

Laura Watts

Collaboration is highly productive

ARTICLES
https://doi.org/10.1038/s41588-018-0302-x
nature genetics

An atlas of genetic influences on osteoporosis in humans and mice

John A. Morris[1,2,34], John P. Kemp[3,4,34], Scott E. Youlten[5], Laetitia Laurent[2], John G. Logan[6], Ryan C. Chai[5], Nicholas A. Vulpescu[7], Vincenzo Forgetta[2], Aaron Kleinman[8], Sindhu T. Mohanty[5], C. Marcelo Sergio[5], Julian Quinn[5], Loan Nguyen-Yamamoto[9], Aimee-Lee Luco[9], Jinchu Vijay[10], Marie-Michelle Simon[10], Albena Pramatarova[10], Carolina Medina-Gomez[11], Katerina Trajanoska[11], Elena J. Ghirardello[6], Natalie C. Butterfield[6], Katharine F. Curry[6], Victoria D. Leitch[6], Penny C. Sparkes[6], Anne-Tounsia Adoum[6], Naila S. Mannan[6], Davide S. K. Komla-Ebri[6], Andrea S. Pollard[6], Hannah F. Dewhurst[6], Thomas A. D. Hassall[3], Michael-John G. Beltejar[12], 23andMe Research Team[13], Douglas J. Adams[14], Suzanne M. Vaillancourt[15], Stephen Kaptoge[16], Paul Baldock[5], Cyrus Cooper[17,18,19], Jonathan Reeve[19], Evangelia E. Ntzani[20,21], Evangelos Evangelou[20,22], Claes Ohlsson[23], David Karasik[24], Fernando Rivadeneira[11], Douglas P. Kiel[24,25,26,27], Jonathan H. Tobias[28], Celia L. Gregson[28], Nicholas C. Harvey[17,18], Elin Grundberg[10,29], David Goltzman[9], David J. Adams[30], Christopher J. Lelliott[30], David A. Hinds[8], Cheryl L. Ackert-Bicknell[31], Yi-Hsiang Hsu[24,25,26,27], Matthew T. Maurano[7], Peter I. Croucher[5], Graham R. Williams[6], J. H. Duncan Bassett[6], David M. Evans[3,4,35*] and J. Brent Richards[1,2,15,32,33,35*]

NATURE GENETICS | VOL 51 | FEBRUARY 2019 | 258–266 | www.nature.com/naturegenetics

PNAS

Optimal bone strength and mineralization requires the type 2 iodothyronine deiodinase in osteoblasts

J. H. Duncan Bassett[a], Alan Boyde[b], Peter G. T. Howell[b,c], Richard H. Bassett[d], Thomas M. Galliford[a], Marta Archanco[a], Holly Evans[e], Michelle A. Lawson[e], Peter Croucher[e], Donald L. St. Germain[f], Valerie Anne Galton[f], and Graham R. Williams[a,1]

7604–7609 | PNAS | April 20, 2010 | vol. 107 | no. 16

nature metabolism
ARTICLES
https://doi.org/10.1038/s42255-018-0005-8

Transferrin receptor 2 controls bone mass and pathological bone formation via BMP and Wnt signalling

Martina Rauner[1,2,17*], Ulrike Baschant[1,2,17], Antonella Roetto[3], Rosa Maria Pellegrino[3], Sandra Rother[4], Juliane Salbach-Hirsch[1,2], Heike Weidner[1,2], Vera Hintze[4], Graeme Campbell[5], Andreas Petzold[6], Regis Lemaitre[7], Ian Henry[8], Teresita Bellido[9], Igor Theurl[10], Sandro Altamura[11], Silvia Colucci[11], Martina U. Muckenthaler[11], Georg Schett[12], Davide S. K. Komla-Ebri[13], J. H. Duncan Bassett[13], Graham R. Williams[13], Uwe Platzbecker[2,14,15] and Lorenz C. Hofbauer[1,2,15,16]

NATURE METABOLISM | VOL 1 | JANUARY 2019 | 111–124 | www.nature.com/naturemetab

PNAS

Noncanonical thyroid hormone signaling mediates cardiometabolic effects in vivo

G. Sebastian Hönes[a], Helena Rakov[a], John Logan[b], Xiao-Hui Liao[c], Eugenie Werbenko[b], Andrea S. Pollard[b], Stine M. Præstholm[d], Majken S. Siersbæk[d], Eddy Rijntjes[a], Janina Gassen[a], Sören Latteyer[a], Kathrin Engels[a], Karl-Heinz Strucksberg[a], Petra Kleinbongard[f], Denise Zwanziger[a], Jan Rozman[g,h], Valerie Gailus-Durner[g], Helmut Fuchs[g], Martin Hrabe de Angelis[g,h,i], Ludger Klein-Hitpass[j], Josef Köhrle[a], David L. Armstrong[k], Lars Grøntved[d], J. H. Duncan Bassett[b], Graham R. Williams[b], Samuel Refetoff[c,l,m], Dagmar Führer[a], and Lars C. Moeller[a,1]

PNAS | Published online December 11, 2017 | E11323–E11332

JCI The Journal of Clinical Investigation
RESEARCH ARTICLE
The Journal of Clinical Investigation

Type 2 deiodinase polymorphism causes ER stress and hypothyroidism in the brain

Sungro Jo,[1] Tatiana L. Fonseca,[2] Barbara M. L. C. Bocco,[3] Gustavo W. Fernandes,[3] Elizabeth A. McAninch,[1] Anaysa P. Bolin,[1,3] Rodrigo R. Da Conceição,[1,4] Joao Pedro Werneck-de-Castro,[1] Daniele L. Ignacio,[1] Péter Egri,[5] Dorottya Németh,[5] Csaba Fekete,[5] Maria Martha Bernardi,[6] Victoria D. Leitch,[7] Naila S. Mannan,[7] Katharine F. Curry,[7] Natalie C. Butterfield,[7] J.H. Duncan Bassett,[7] Graham R. Williams,[7] Balázs Gereben,[5] Miriam O. Ribeiro,[8] and Antonio C. Bianco[2]

jci.org Volume 129 Number 1 January 2019 JCI

OPEN ACCESS
PLOS GENETICS

Rapid-Throughput Skeletal Phenotyping of 100 Knockout Mice Identifies 9 New Genes That Determine Bone Strength

J. H. Duncan Bassett[1*], Apostolos Gogakos[1], Jacqueline K. White[2], Holly Evans[3], Richard M. Jacques[4], Anne H. van der Spek[1], Sanger Mouse Genetics Project, Ramiro Ramirez-Solis[2], Edward Ryder[2], David Sunter[2], Alan Boyde[5], Michael J. Campbell[4], Peter I. Croucher[3,6*], Graham R. Williams[1*]

PLoS Genetics | www.plosgenetics.org August 2012 | Volume 8 | Issue 8 | e1002858

ARTICLES
nature genetics

Identification of 153 new loci associated with heel bone mineral density and functional involvement of GPC6 in osteoporosis

John P Kemp[1,2,25], John A Morris[3,4,25], Carolina Medina-Gomez[5,6,25], Vincenzo Forgetta[3], Nicole M Warrington[1,7], Scott E Youlten[8,9], Jie Zheng[2], Celia L Gregson[10], Elin Grundberg[4], Katerina Trajanoska[5,6], John G Logan[11], Andrea S Pollard[11], Penny C Sparkes[11], Elena J Ghirardello[11], Rebecca Allen[11], Victoria D Leitch[11], Natalie C Butterfield[11], Davide Komla-Ebri[11], Anne-Tounsia Adoum[11], Katharine F Curry[11], Jacqueline K White[12], Fiona Kussy[12], Keelin M Greenlaw[3], Changjiang Xu[13], Nicholas C Harvey[14,15], Cyrus Cooper[14,15,16], David J Adams[12], Celia M T Greenwood[3,4,17,18], Matthew T Maurano[19], Stephen Kaptoge[20,21], Fernando Rivadeneira[5,6], Jonathan H Tobias[10], Peter I Croucher[8,9,22], Cheryl L Ackert-Bicknell[23], J H Duncan Bassett[11], Graham R Williams[11], J Brent Richards[3,4,24,26] & David M Evans[1,2,26]

VOLUME 49 | NUMBER 10 | OCTOBER 2017 NATURE GENETICS

ENDOCRINE REVIEWS

Role of Thyroid Hormones in Skeletal Development and Bone Maintenance

J. H. Duncan Bassett and Graham R. Williams

Endocrine Reviews, April 2016, 37(2):135–187

…… and translates to clinical care

RESEARCH

OPEN ACCESS

BMJ

Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study

Katerina Trajanoska,[1,2] John A Morris,[3,4] Ling Oei,[1,2] Hou-Feng Zheng,[5,6] David M Evans,[7,8] Douglas P Kiel,[9,10] Claes Ohlsson,[11] J Brent Richards,[3,4] Fernando Rivadeneira,[1,2] on behalf of the GEFOS/GENOMOS consortium and the 23andMe research team

the bmj | BMJ 2018;362:k3225 | doi: 10.1136/bmj.k3225

THE LANCET

Articles

Iodine status of UK schoolgirls: a cross-sectional survey

Mark PJ Vanderpump, John H Lazarus, Peter P Smyth, Peter Laurberg, Roger L Holder, Kristien Boelaert, Jayne A Franklyn, on behalf of the British Thyroid Association UK Iodine Survey Group*

Lancet 2011; 377: 2007-12

CLINICAL ENDOCRINOLOGY

Guidelines for the management of thyroid cancer

Third edition

Perros P, Colley S, Boelaert K, Evans C, Evans RM, Gerrard GE, Gilbert JA, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold KL, Taylor J, Thakker RV, Watkinson J, Williams GR

British Thyroid Association

July 2014

JIM Original Article

Association between subclinical thyroid dysfunction and change in bone mineral density in prospective cohorts

D. Segna[1], D. C. Bauer[2], M. Feller[1], C. Schneider[1], H. A. Fink[3,4], C. E. Aubert[1], T.-H. Collet[5], B. R. da Costa[6], K. Fischer[7,8], R. P. Peeters[9], A. R. Cappola[10], M. R. Blum[1], H. A. van Dorland[1], J. Robbins[11], K. Naylor[12], R. Eastell[12], A. G. Uitterlinden[6], F. Rivadeneira Ramirez[6], A. Gogakos[13], J. Gussekloo[14], G. R. Williams[13], A. Schwartz[2], J. A. Cauley[15], D. A. Aujesky[1], H. A. Bischoff-Ferrari[7,8], N. Rodondi[1,6] & for the Thyroid Studies Collaboration

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ORIGINAL ARTICLE

Endocrine Care

Thyroid Function within the Upper Normal Range Is Associated with Reduced Bone Mineral Density and an Increased Risk of Nonvertebral Fractures in Healthy Euthyroid Postmenopausal Women

Elaine Murphy, Claus C. Glüer, David M. Reid, Dieter Felsenberg, Christian Roux, Richard Eastell, and Graham R. Williams

J Clin Endocrinol Metab, July 2010, 95(7):3173–3181

ORIGINAL ARTICLE

JBMR

Slc20a2, Encoding the Phosphate Transporter PiT2, Is an Important Genetic Determinant of Bone Quality and Strength

Sarah Beck-Cormier,[1,2*] Christopher J Lelliott,[3*] John G Logan,[4*] David T Lafont,[3*] Laure Merametdjian,[1,2,5] Victoria D Leitch,[4] Natalie C Butterfield,[4] Hayley J Protheroe,[4] Peter I Croucher,[6,7] Paul A Baldock,[6,7] Alina Gaultier-Lintia,[8] Yves Maugars,[1,5] Gael Nicolas,[9,10,11] Christopher Banse,[12] Sébastien Normant,[13] Nicolas Magne,[13] Emmanuel Gérardin,[13] Nina Bon,[1,2] Sophie Sourice,[1,2] Jérôme Guicheux,[1,2,5] Laurent Beck,[1,2†] Graham R Williams,[4†] and J H Duncan Bassett[4†]

Research

JAMA

Original Investigation

Subclinical Thyroid Dysfunction and Fracture Risk
A Meta-analysis

Manuel R. Blum, MD; Douglas C. Bauer, MD; Tinh-Hai Collet, MD; Howard A. Fink, MD, MPH; Anne R. Cappola, MD, ScM; Bruno R. da Costa, PhD; Christina D. Wirth, MD; Robin P. Peeters, MD, PhD; Bjørn O. Åsvold, MD, PhD; Wendy P. J. den Elzen, PhD; Robert N. Luben, PhD; Misa Imaizumi, MD, PhD; Alexandra P. Bremner, PhD; Apostolos Gogakos, MD, PhD; Richard Eastell, MD; Patricia M. Kearney, MD, PhD, MPH; Elsa S. Strotmeyer, MD, PhD; Erin R. Wallace, PhD; Mari Hoff, MD, PhD; Graziano Ceresini, MD, PhD; Fernando Rivadeneira, MD, PhD; André G. Uitterlinden, PhD; David J. Stott, MD, PhD; Rudi G. J. Westendorp, MD, PhD; Kay-Tee Khaw, MD; Arnuf Langhammer, MD, PhD; Luigi Ferrucci, MD, PhD; Jacobijn Gussekloo, MD, PhD; Graham R. Williams, MBBS, PhD; John P. Walsh, MBBS, PhD; Peter Jüni, MD; Drahomir Aujesky, MD, MSc; Nicolas Rodondi, MD, MAS; for the Thyroid Studies Collaboration

JAMA. 2015;313(20):2055-2065. doi:10.1001/jama.2015.5161

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ORIGINAL ARTICLE

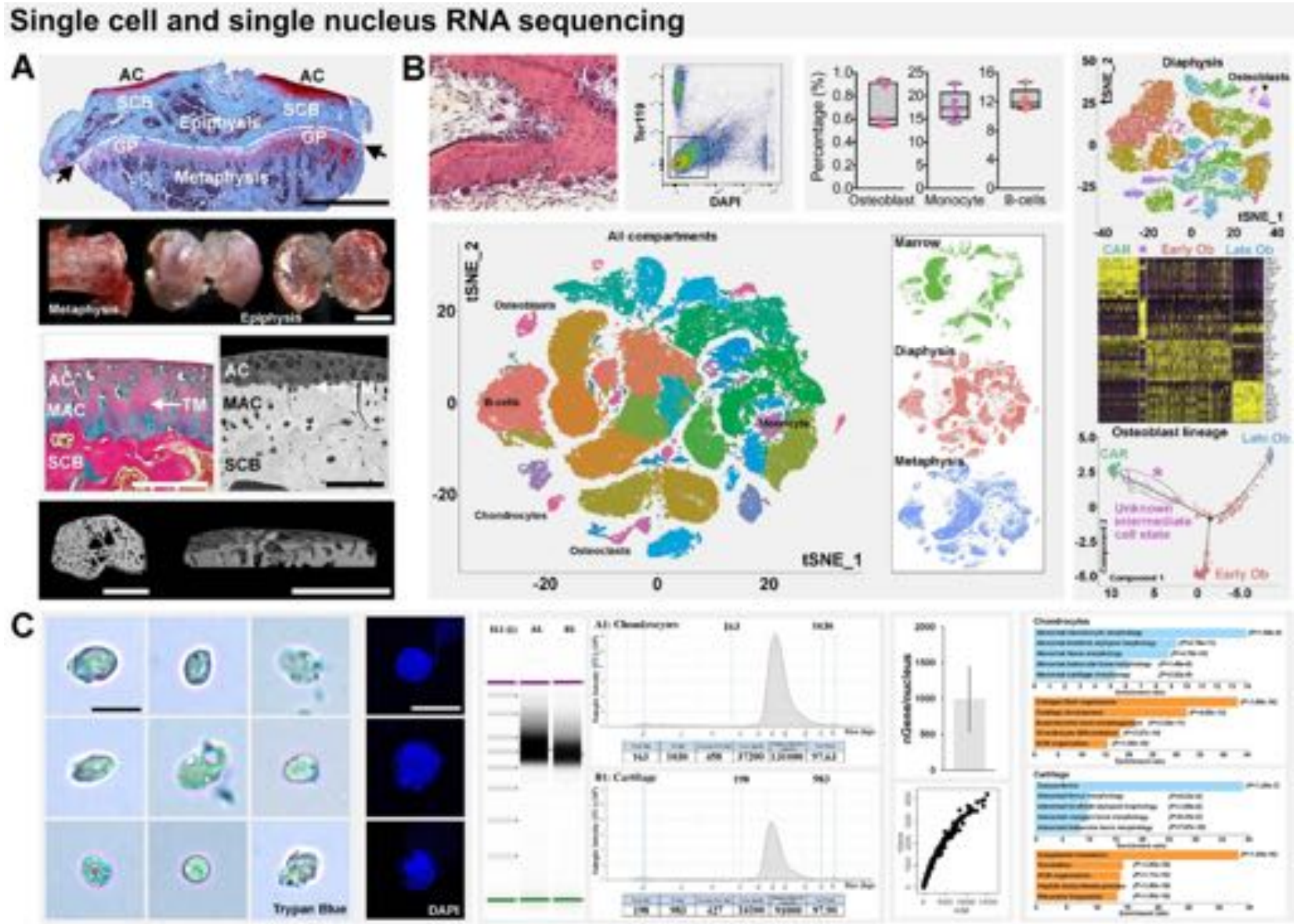
Endocrine Research

Bone Turnover and Bone Mineral Density Are Independently Related to Selenium Status in Healthy Euthyroid Postmenopausal Women

Antonia Hoeg,* Apostolos Gogakos,* Elaine Murphy, Sandra Mueller, Josef Köhrle, David M. Reid, Claus C. Glüer, Dieter Felsenberg, Christian Roux, Richard Eastell, Lutz Schomburg, and Graham R. Williams

J Clin Endocrinol Metab, November 2012, 97(11):4061–4070

Current development of cutting edge methodology



Future

Funding

- In discussions with Wellcome Trust
  - Clinical and Physiological Systems (Sara Marshall)
    - Align research plans to latest novel research questions
    - Using state-of-the-art technology

Development of new methods to address cellular and disease mechanisms

- RNAseq
  - sc and sn development
    - Peter Croucher (Garvan Institute, Sydney)
    - Sam Behjani (Teichmann lab, Sanger Institute)
    - Jacques Behmoaras (Dept Immunology & Inflammation, Imperial)
  - Data analysis and bioinformatics
    - John Marioni (Sanger Institute)
    - Terry Meehan (EBI)
  - Big data management, integration with human disease, leverage, visualisation
    - John Marioni