

UIDP London Forum 2023

NPL Teddington | Oct. 17, 2023



Malcolm Skingle CBE PhD
Director Academic Liaison
GSK

“Collaborating with
Public Sector Research Establishments (PRSEs)”

Collaboration with NPL



- Black-tie dinner – Courtney Tuffin
 - Initial visit to NPL in early 2012
 - GSK need for higher spatial resolution **unlabelled** imaging
 - Initial OrbiSIMS discussions with Ian Gilmore were in 2013
-

Sir Colin Dollery (GSK Senior Consultant)



- Visited NPL mass spec imaging lab in 2012
- Concerned about attrition in drug discovery
- Need to know the location and fate of medicines:
 - Does it get to the site of action?
 - How long does it stay there?
 - What is the final fate of the molecule?



Different skills required to drive Innovation

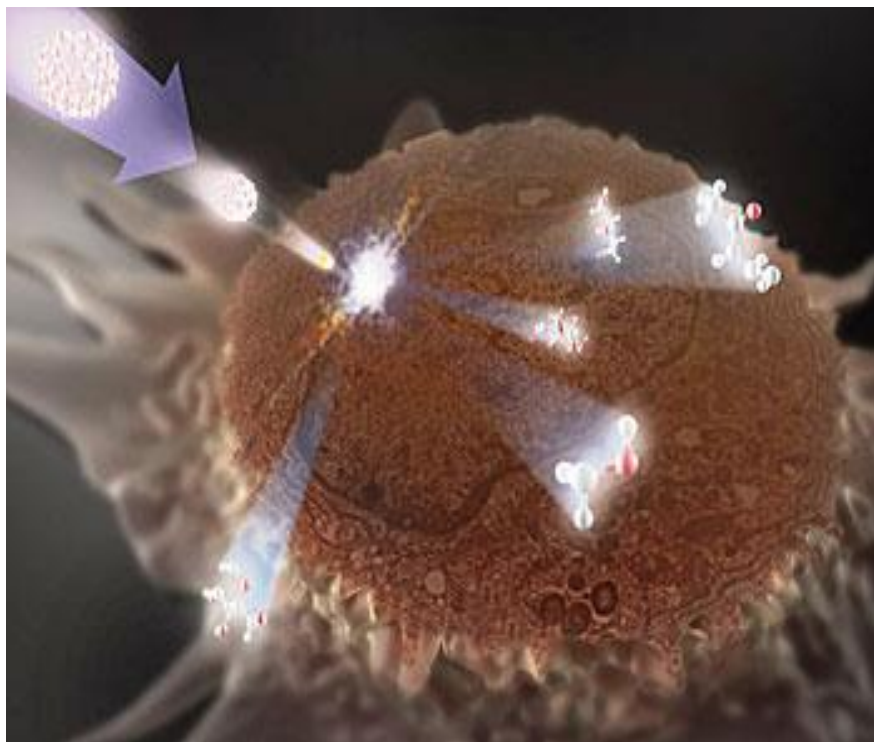
- PRSE - NPL
 - Two equipment manufacturers IONTOF & Thermo.
 - Pharma – GSK
 - Academic consultants – Nottingham University

 - **Prof Ian Gilmore** – scientific champion

 - Spatial resolution of secondary ion mass spectrometry (SIMS) + High mass resolution of Orbitrap mass spectrometer.
-



3D imaging on biological surfaces

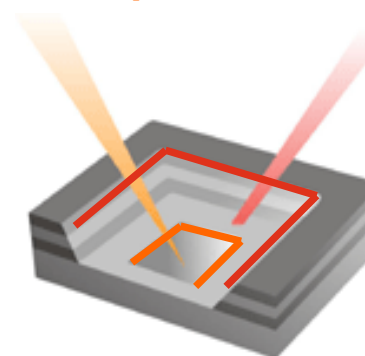


Artist's illustration showing HeLa cell with its top already "milled" off being probed by a secondary ion mass spectrometry (SIMS) beam. Ions from the cell are seen ejecting from the surface in response. The spectra from these molecules are used to map the cell sections from which they originate.

Credit: Donald Bliss, National Library of Medicine, National Institutes of Health

Bi_3^+
400 x 400 μm

Ar^+_{2000} cluster
Crater 650 x 650 μm



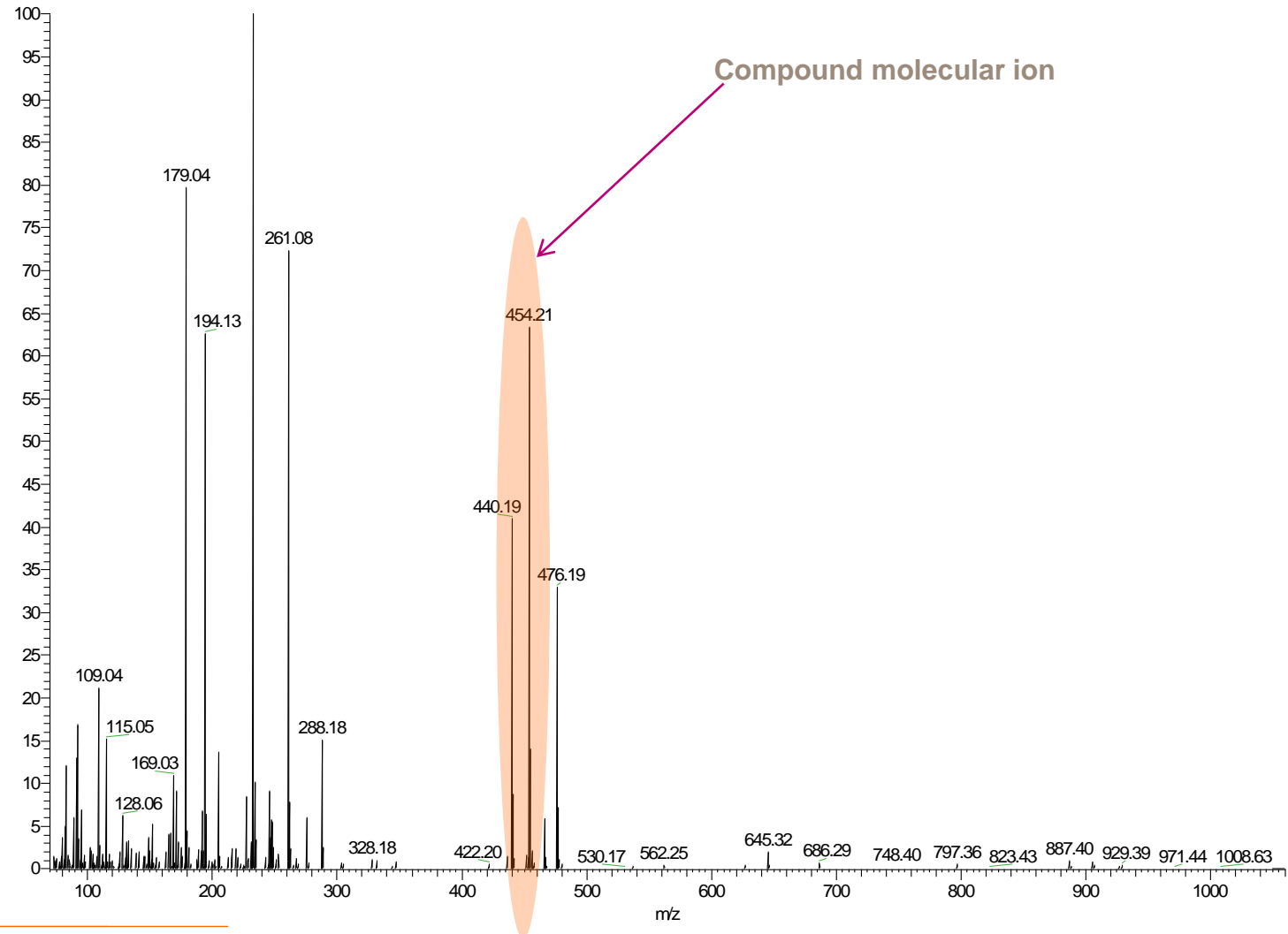
Depth Profile

Depth profiling

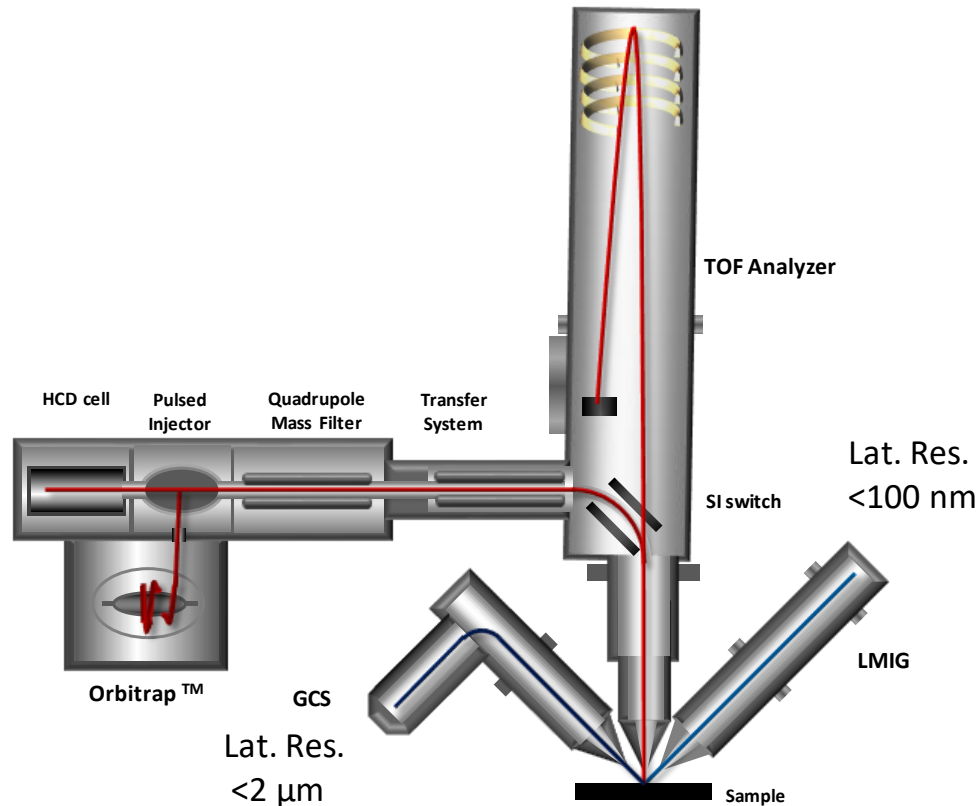
Bi_3^+ generates mass spectra

Ar^+_{2000} cluster "sputters" away ~5nm layer

DpRE1_058_10_pos #2-240 RT: 0.05-5.01 AV: 239 NL: 1.34E4
T: FTMS + pMALDI Full ms [70.0000-1050.0000]



3D OrbiSIMS – Launched Nov 2016



Nature Methods 2017

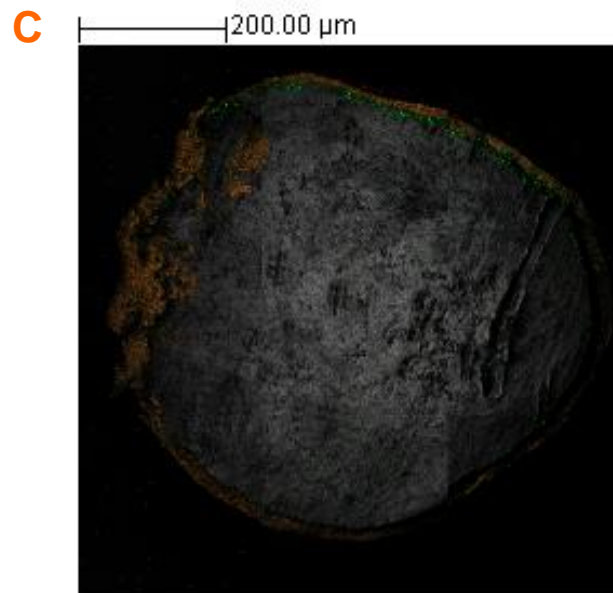
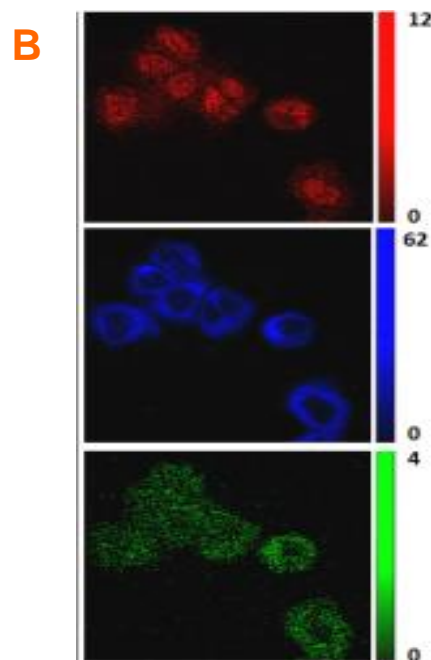
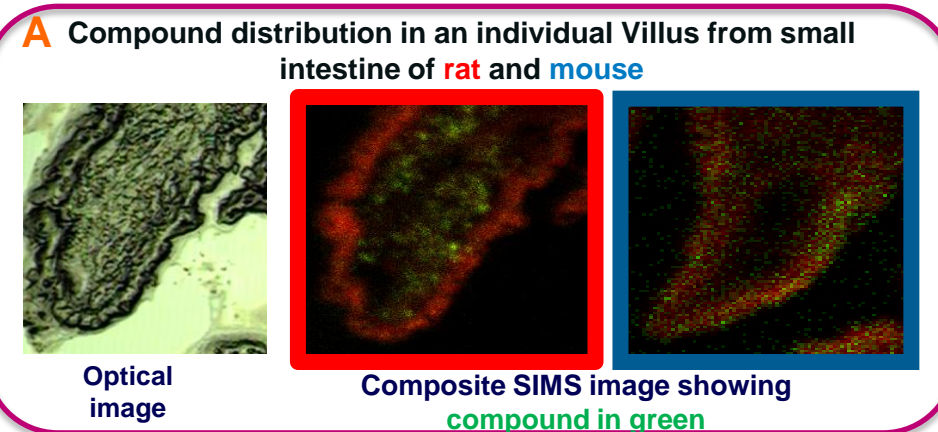


Thermo Scientific™
Q Exactive™ HF

How OrbiSIMS has helped GSK

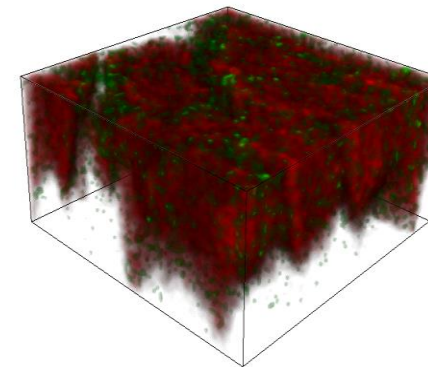
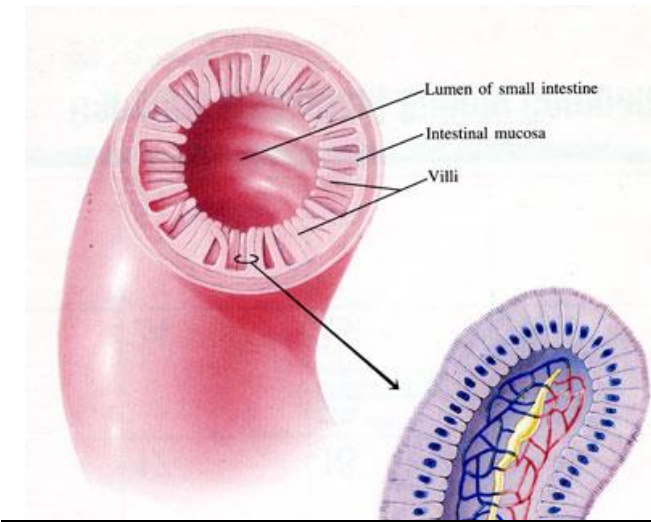


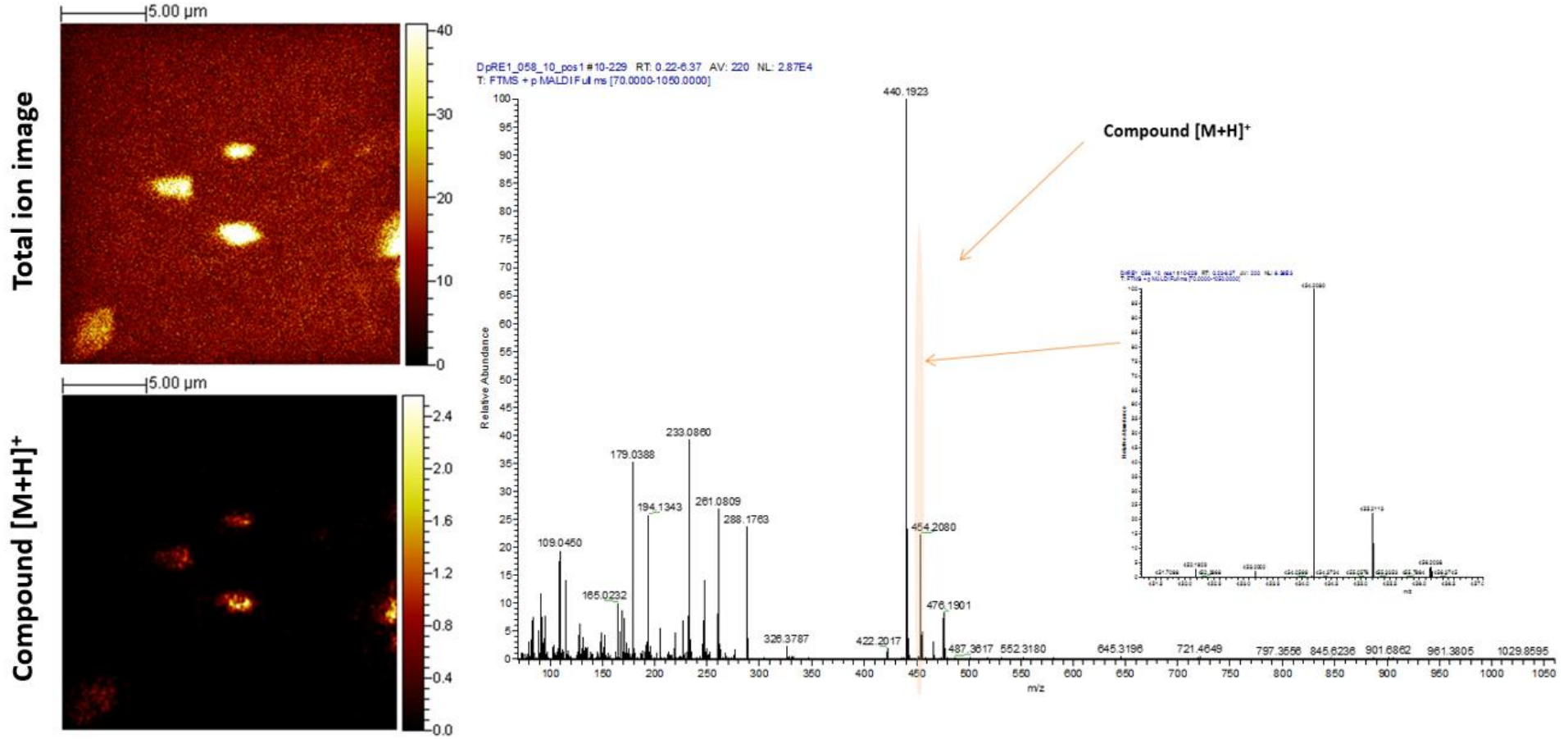
- A. Compound/metabolite distribution in Tissue
- B. Compound/metabolite distribution in Cells
- C. Compound/exciipient distribution in pharmaceuticals



“All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.”

Depth profile through jejunum of the mouse





Aminoacid metabolism

Alanine Metabolism [map00250]
Alanine, Aspartate And Glutamate Metabolism [map00250]
Arginine And Proline Metabolism [map00330]
Arginine And Proline Metabolism [map00330]
Arginine Biosynthesis [map00220]
Cysteine And Methionine Metabolism [map00270]
Glutamate Metabolism [map00250]
Glycine And Serine Metabolism [map00260]
Glycine, Serine And Threonine Metabolism [map00260]
Histidine Metabolism [map00340]
Lysine Degradation [map00310]
Methionine Metabolism [map00270]
Phenylalanine Metabolism [map00360]
Phenylalanine, Tyrosine And Tryptophan Biosynthesis [map00400]
Tryptophan Metabolism [map00380]
Tyrosine Metabolism [map00350]
Valine, Leucine And Isoleucine Degradation [map00280]

158 metabolites identified

Other aminoacid metabolism

Beta-Alanine Metabolism [map00410]
Cyanoamino Acid Metabolism [map00460]
D-Alanine Metabolism [map00473]
D-Arginine And D-ornithine Metabolism [map00472]
D-Glutamine And D-glutamate Metabolism [map00471]
Glutathione Metabolism [map00480]
Phosphonate And Phosphinate Metabolism [map00440]
Selenocompound Metabolism [map00450]
Taurine And Hypotaurine Metabolism [map00430]

32 metabolites identified

Carbohydrate metabolism

Amino Sugar And Nucleotide Sugar Metabolism [map00520]
Ascorbate And Aldarate Metabolism [map00053]
Butanoate Metabolism [map00650]
C5-Branched Dibasic Acid Metabolism [map00660]
Citrate Cycle (TCA Cycle) [map00020]
Citric Acid Cycle [map00020]
Galactose Metabolism [map00052]
Gluconeogenesis [map00010]
Glycolysis / Gluconeogenesis [map00010]
Glycolysis [map00010]
Glyoxylate And Dicarboxylate Metabolism [map00630]
Inositol Phosphate Metabolism [map00562]
Pentose And Glucuronate Interconversions [map00040]
Pentose Phosphate Pathway [map00030]
Propanoate Metabolism [map00640]
Pyruvate Metabolism [map00620]
Starch And Sucrose Metabolism [map00500]

70 metabolites identified

Nucleotide metabolism

Purine Metabolism [map00230]
Pyrimidine Metabolism [map00240]

20 metabolites identified

Lipid and energy metabolism

Carbon Fixation In Photosynthetic Organisms [map00710]
Carbon Fixation Pathways In Prokaryotes [map00720]
Methane Metabolism [map00680]
Nitrogen Metabolism [map00910]
Oxidative Phosphorylation [map00190]
Sulfur Metabolism [map00920]
Glycosaminoglycan Biosynthesis - Heparan Sulfate / Heparin [map00534]
Peptidoglycan Biosynthesis [map00550]
Ether Lipid Metabolism [map00565]
Fatty Acid Biosynthesis []
Glycerolipid Metabolism [map00561]
Glycerophospholipid Metabolism [map00564]
Primary Bile Acid Biosynthesis [map00120]
Sphingolipid Metabolism [map00600]
Steroid Biosynthesis [map00100]
Synthesis And Degradation Of Ketone Bodies [map00072]

53 metabolites identified

Vitamin and co-factor metabolism

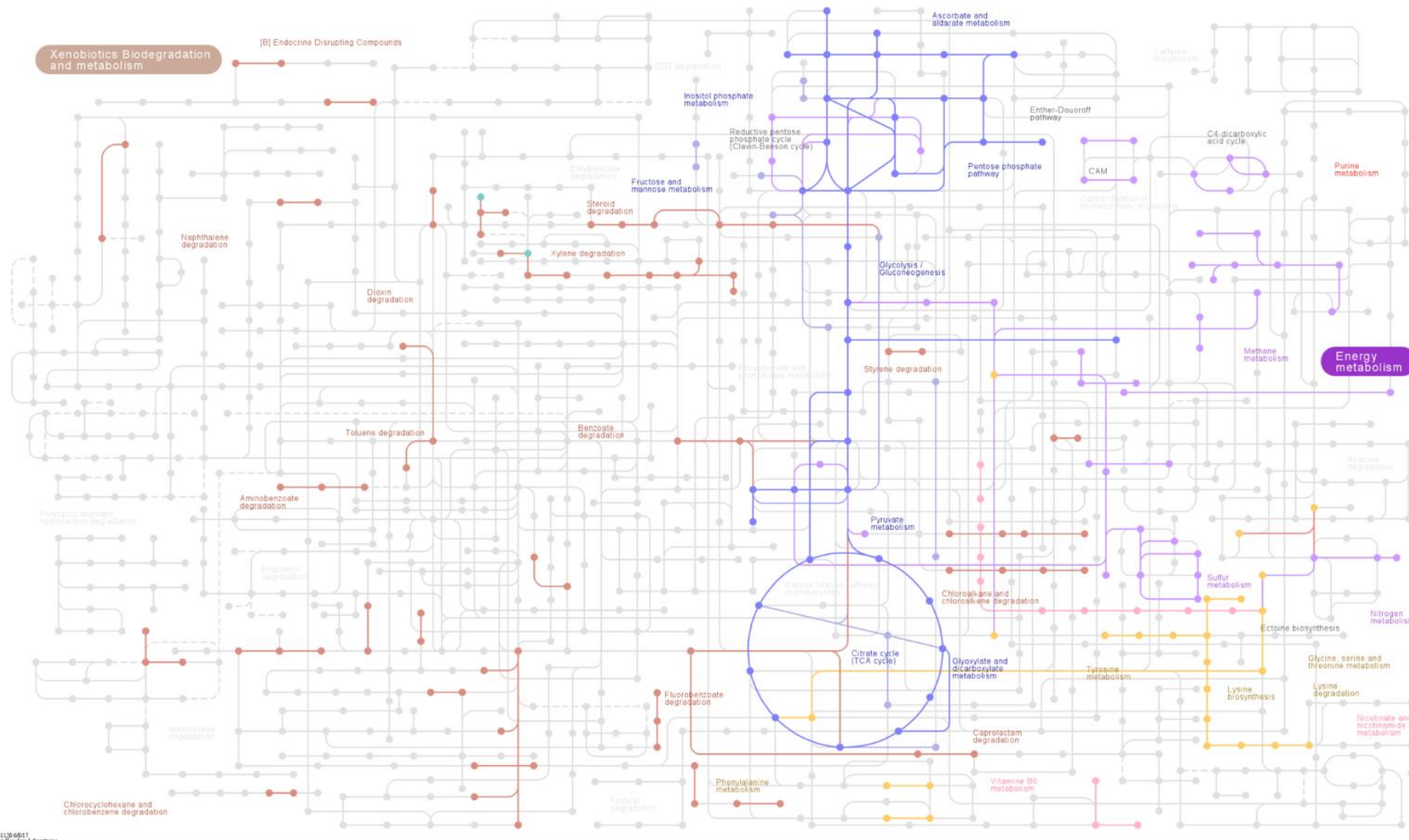
Biotin Metabolism [map00780]
Folate Biosynthesis [map00790]
Nicotinate And Nicotinamide Metabolism [map00760]
One Carbon Pool By Folate [map00670]
Pantothenate And CoA Biosynthesis [map00770]
Porphyrin And Chlorophyll Metabolism [map00860]
Riboflavin Metabolism [map00740]
Thiamine Metabolism [map00730]
Ubiquinone And Other Terpenoid-quinone Biosynthesis [map00130]
Vitamin B6 Metabolism [map00750]

37 metabolites identified

BCG Metabolite pathways Identified from KEGG (Kyoto Encyclopaedia of Genes and Genomes)



Metabolite clusters identified from OrbiSIMS data shown in colour



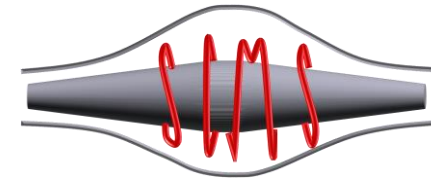
NiCE-MSI timeline (2013-2018)

New recruits:
Josephine Bunch
Mischa Zelzer
Rory Steven

Jose joins
Sep 2013



Roy Soc Scientific Meeting
22-23 November 2005



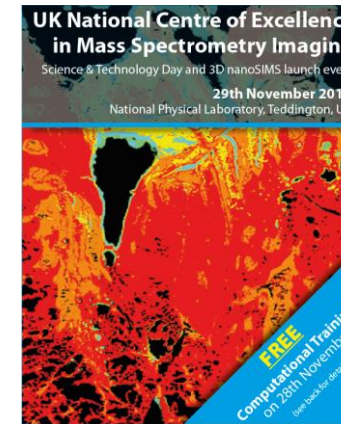
Science & Technology Day
OrbiSIMS launch
29 Nov 2016



GSK Master Service
Agreement
2014



Summer meeting II
25 June 2015



Launch event
Bushy House
9 July 2013



NiCE-MSI group
June 2015



2013

2014

2015

2016

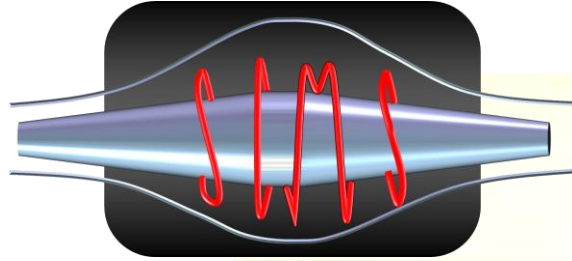
2017

2018

3D OrbiSIMS launched Nov 2016

NPL 
National Physical Laboratory




NICE-MS 
National Centre of Excellence
in Mass Spectrometry Imaging



Many OrbiSIMS around the world



The dietary sweetener sucralose is a negative modulator of T cell-mediated responses **nature**

[Fabio Zani](#) , [Julianna Blagih](#) , [Tim Gruber](#), [Michael D. Buck](#), [Nicholas Jones](#), [Marc Hennequart](#), [Clare L. Newell](#), [Steven E. Pilley](#), [Pablo Soro-Barrio](#), [Gavin Kelly](#), [Nathalie M. Legrave](#), [Eric C. Cheung](#), [Ian S. Gilmore](#), [Alex P. Gould](#), [Cristina Garcia-Caceres](#) & [Karen H. Vousden](#) 


nature methods

The 3D OrbiSIMS—label-free metabolic imaging with subcellular lateral resolution and high mass-resolving power

Angewandte
International Edition **Chemie**



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German
Chemical Society

Communication |  Open Access |  

Cryogenic OrbiSIMS Localizes Semi-Volatile Molecules in Biological Tissues[†]

Mechanisms of lipid preservation in archaeological clay ceramics revealed by mass spectrometry imaging

[Simon Hammann](#)^{a,b,1} , [David J. Scurr](#)^c , [Morgan R. Alexander](#)^c , and [Lucy J. E. Cramp](#)^a 

PNAS

Elucidating the molecular landscape of the stratum corneum




[Nichola J. Starr](#), [Mohammed H. Khan](#) , [Max K. Edney](#) , , and [David J. Scurr](#)  

March 17, 2022 | 119 (12) e2114380119 | <https://doi.org/10.1073/pnas.2114380119>

PNAS


ScienceAdvances

The use of nanovibration to discover specific and potent bioactive metabolites that stimulate osteogenic differentiation in mesenchymal stem cells

[Tom Hodgkinson](#) , [P. Monica Tsimbouri](#), [Virginia Llopis-Hernandez](#) , [Paul Campsie](#) , [David Scurr](#) , [Peter G. Childs](#) , [David Phillips](#) , [Sam Donnelly](#) , [Julia A. Wells](#) , [L.J. Matthew J. Dalby](#) ,  +9 authors | [Authors Info & Affiliations](#)

nature communications

Protein identification by 3D OrbiSIMS to facilitate in situ imaging and depth profiling

[Anna M. Kotowska](#), [Gustavo F. Trindade](#), [Paula M. Mendes](#), [Philip M. Williams](#), [Jonathan W. Aylott](#), [Alexander G. Shard](#), [Morgan R. Alexander](#) & [David J. Scurr](#) 

Win-win

- Publications e.g Passarelli et al, Nature Methods (2017)
- Drug development go/no go decisions
- Equipment sales
- Pushes back the frontiers of science

Trust Develops resulting in New & Diverse Collaborations

- Reference the umbrella agreement
- Call off process
- Fixed price list for trial run/ quick look & see experiments

Conclusions :



- Scientific advances made at the interfaces of scientific disciplines
 - No single organisation has all the skills & knowledge to effectively deliver innovation.
 - Collaborating with partners who have complementary skills is essential
 - PRSEs are an important part of the innovation jigsaw
-

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Thank you!

Acknowledgments

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Acknowledgements: Dr Andy West & Professor Ian Gilmore

