

CURRICULUM VITAE

Graham John LAPPIN BSc PhD
(Retired)

CAREER

September 2016 formally retired (retaining Visiting Professor of Pharmacology, University of Lincoln, UK)

Jan 2015 - Sept 2016: Owner of GLappin Consulting

Consulting to the pharmaceutical industry. Member of the Yorkshire Biomedical Consultants Association.

Sept 2012 – Jan 2015: Associate Professor of Pharmacology and Pharmaceutical Science, University of Lincoln, UK

Founder and Programme Leader for BSc Pharmaceutical Science
Chairman of College of Science Ethics Committee

Aug 2001 – Sept 2012: Chief Scientific Officer (from Aug 2010) Xceleron, Ltd and Inc, York UK and Germantown, Maryland, USA

Xceleron is a spinout company from the University of York UK, providing regulatory and exploratory metabolism and pharmacokinetic studies in humans utilising Accelerator Mass Spectrometry.

October 1995-August 2001: Section Manager, Department of Drug Metabolism and Pharmacokinetics, Covance Laboratories Ltd, Harrogate, UK

My section of 25 scientists conducted regulatory ADME and related studies in laboratory animals and in the clinic (Leeds, UK).

1989-1995: Team Leader, Department of Metabolism and Pharmacokinetics, ICI (to become Zeneca, then AstraZeneca) Central Toxicology Laboratory, Alderley Edge, Cheshire, UK

My section of 10 scientists conducted regulatory ADME and related studies in laboratory animals.

1987-1989: Applications Chemist, VG Masslab Ltd

Manufacturer of Quadrupole Mass Spectrometers

1984-1987: Post Doctoral Research Assistant, Glasgow University, UK, Department of Chemistry

Research into the metabolism of naturally occurring fungicides from plants native to Scotland

EDUCATION AND QUALIFICATIONS

PhD Westminster University, London 1981-1984

Thesis entitled "Biotransformation of Monoterpenoids in Axenic Plant Cell Culture"

BSc (2:1) Biochemistry Westminster University, London 1979-1981

PROFESSIONAL

- Visiting Professor of Pharmacology, University of Lincoln UK.
- Fellow of the Institute of Biology (now Royal Society of Biology) until 2013
- Fellow of the Royal Society of Chemistry until Jan 2017
- Emeritus member of the American Society of Clinical Pharmacology and Therapeutics until Jan 2017
- Member of Editorial Board for *Bioanalysis* (until 2014), *Expert Opinion in Drug Metabolism & Toxicology*, *The Journal of Clinical Pharmacology* (until 2017)
- Member of the Scientific Advisory Board at the Karolinska Institute, Stockholm – “Human Regenerative Map”
- Visiting Professor of Pharmacology, University of Vienna, Austria, May-Oct 2010
- Adjunct Professor, Duke University Medical School, North Carolina, USA (2010-2014)
- Member of the Scientific Advisory Board, Xceleron Inc., Maryland, USA (until Jan 2017)

RESEARCH GRANTS RECEIVED

- Consortium for Resourcing and Evaluating AMS Microdosing (CREAM). Industrial funding from Schering, Institut de Recherches Internationales Servier, F. Hoffmann-La Roche, Eli Lilly, and Pharma Bio-Research Group. £1.2M (2004)
- European Microdose AMS Partnership Programme (EUMAPP), FP6, €2.1M (2006)
- BBSRC, Investigation of drug-drug integrations using microdosing. £250,000 (2006)
- Regional Development Agency (Yorkshire Forward) Research and Development Grant. Applications of ¹⁴C-isotopic tracers and accelerator mass spectrometry with therapeutic proteins. £160,000 (2009)

PUBLICATIONS

Burt, T., Yoshida, K., Lappin, G., Vuong, L., John, C., de Wildt, S. N., Sugiyama, Y., and Rowland, M. (2016) Microdosing and Other Phase 0 Clinical Trials: Facilitating Translation in Drug Development, *Clin Transl Sci* 9, 74-88

Lappin, G. (2015) Approaches to Intravenous Clinical Pharmacokinetics: Recent Developments with Isotopic Microtracers. *Journal of Clinical Pharmacology*, in press.

Lappin, G. (2015) A Historical Perspective on Radioisotopic Tracers in Metabolism and Biochemistry. *Bioanalysis*, 7(5) 531-40

Lappin G, Noveck R, Burt T. Microdosing and Drug Development: Past, Present and Future. *Expert Opin Drug Metab Toxicol*. 2013;9(7): 817-834.

Lappin, G., Boyce, M. J., Matzow, T., Lociuero, S., Seymour, M. and Warrington, S. J. (2013) A microdose study of ¹⁴C-AR-709 in healthy men: pharmacokinetics, absolute bioavailability and concentrations in key compartments of the lung. *Eur J Clin Pharmacol* 69(9) 1673-1682

Duchateau, G., Cochrane, B., Windebank, S., Herudzinska, J., Sanghera, D., Burian, A., Müller, M., Zeitlinger, M. and Lappin, G. (2012) Absolute oral bioavailability and metabolic turnover of β -sitosterol in healthy subjects. *Drug Metab Dispos*. 40(10) 2026-2030.

Lappin, G., Seymour, M., Gross, G., Jørgensen, M., Kall, M. and Kværnø, L. (2012) Meeting the regulatory requirements in MIST: Human metabolism data early in phase-1 using accelerator-MS combined with tiered bioanalytical approach in metabolite quantification. *Bioanalysis*. 4(4): 407-16.

Croft, M., Keely, B., Morris, I., Tann, L. and Lappin, G. (2012) Predicting drug candidate victims of drug-drug interactions using microdosing. *Clin Pharmacokinet* 51(4): 237-46.

- Lappin, G., Seymour, M., Young, G., Higton, D. and Hill, H. (2011). Analysis by accelerator mass spectrometry: proposed method validation pertaining to the quantitation of analytes during pharmacokinetic studies conducted by concomitant extravascular and intravenous administration. *Bioanalysis* 3 (4) 393-405
- Lappin, G., Seymour, M., Young, G., Higton, D. and Hill, H. (2011). Analysis by accelerator mass spectrometry: A method for determining analyte recovery during pharmacokinetic studies conducted by concomitant extravascular and intravenous administration. *Bioanalysis* 3 (4) 407-410
- Wagner, C., Simpson, M., Bauer, M., Karch, R., Abraham, A., Feurstein, T., Zeitlinger, M., Schütz, M., Kletter, K. Müller, M., Lappin, G and Langer, O. (2011). A combined accelerator mass spectrometry - positron emission tomography microdose study to assess the plasma and brain tissue pharmacokinetics of ¹¹C- and ¹⁴C-labeled verapamil in healthy volunteers. *Clin Pharmacokinet* 50 (2) 111-120
- Lappin, G. (2011) Pharmacokinetics II: 14C-labelled microdosing in assessing drug pharmacokinetics at phase-0. In *Pharmacokinetics in Drug development*. Bonate, P. and Howard, D. R. (eds) Springer, New York
- Lappin, G., Shishikura, Y., Jochemsen, R., Weaver, R. J., Gesson, C., Brian Houston, J., Oosterhuis, B., Bjerrum, O. J., Gryniewicz, G., Alder, J., Rowland, M., and Garner, C. (2011) Comparative pharmacokinetics between a microdose and therapeutic dose for clarithromycin, sumatriptan, propafenone, paracetamol (acetaminophen), and phenobarbital in human volunteers. *Eur J Pharm Sci* 43, 141-150.
- Lappin, G. and Seymour, M. (2010) Addressing metabolite safety during first-in-man studies using ¹⁴C-labelled drug and accelerator mass spectrometry. *Bioanalysis*, 2(7) 1315-1324
- Lappin, G. (2010). ¹⁴C -Labelled microdosing in assessing drug pharmacokinetics at phase-0. *Clinical Pharmacology, Current Topics and Case Studies*. Müller, M. (ed) Springer Wien, New York.
- Lappin, G., Simpson, M. and Keely, B. (2010) Development of 2-dimensional chiral chromatography with accelerator mass spectrometry for quantification of 14C-labelled R- and S-verapamil in plasma from a human microdosing study. *Bioanalysis* 2 (3) 397-405
- Lappin, G. (2010) Microdosing, Current and Future. *Bioanalysis*, 2 (3) 509-517
- Bergmann, L., Berns, B., Dagleish, A. G., von Euler, M., Hecht, T. T., Lappin, G., Reed, N., Palmeri, S., Smyth, J., Embacher-Aichorn, S. and Zwierzina, H. (2010) Investigator-initiated trials of targeted oncology agents: why independent research is at risk. *Annals of Oncology*, 21 (8) 1573-1578
- Lappin, G., Shishikura, Y., Jochemsen, R., Weaver, R. J., Gesson, C., Houston, B., Oosterhuis, B., Bjerrum, O. J., Rowland, M. and Garner, R. C. (2010). Pharmacokinetics of fexofenadine: evaluation of a microdose and assessment of absolute oral bioavailability. *Eur J Pharma Sci* 40 125-131
- Coamezoglu, N., Ly, Van T., Zhang, D., Humphreys, W. G., Bonacorsi, S. J., Everett, D. W., Cohen, M. B., Gan, J., Beumer, J. H., Beijnen, J. H., Schellens, M. and Lappin, G. (2009) Biotransformation profiling of [¹⁴C]-Ixabepilone in human plasma, urine and feces samples using Accelerator Mass Spectrometry (AMS). *Drug Metab. Pharmacokinet.* 24 (6): 511–522
- Lappin, G., Wagner, C. C., Langer, O. and van de Merbel, N (2009) New ultra-sensitive detection technologies and techniques for use in microdosing studies. *Bioanalysis* 1 (2) 357-366.
- Lappin, G. and Garner, C. (2008) The utility of microdosing over the past 5 years. *Expert Opin Drug Metab Toxicol* 4 (12) 1499-1506.
- Garner, C. and Lappin, G. (2008) Human ADME studies come early. *International Clinical Trials*, November, 22-24.
- Madan, A., O'Brien, Z., Wen, J., O'Brien, C., Farber, R. H., Beaton, G., Crowe, P., Oosterhuis, B., Garner, R. C., Lappin, G. and Bozigian, H. P. (2008) A Pharmacokinetic evaluation of five H1 antagonists after an oral and intravenous microdose to human subjects. *Br J Clin Pharmacol*, 2008. 67(3) 288-298.

- Baxter, M., Castle, L., Crews, H. M., Rose, M., Garner, C., Lappin, G. and Leong, D (2009) A sensitive method for the determination of chlorine-36 in foods using accelerator mass spectrometry. *Food Additives & Contaminants: Part A* 26 (1) 139 – 144.
- Lappin, G. and Stevens, L. (2008) Accelerator Mass Spectrometry: applications in pharmacokinetics and metabolism. *Expert Opin Drug Metab Toxicol* 4 (8) 1-13.
- Lappin, G., Simpson, M., Shishikura, Y. and Garner, C. (2008) High Performance Liquid Chromatography Accelerator Mass Spectrometry: correcting for losses during analysis by internal standardisation. *Analytical Biochemistry* 378 93-95.
- Wagner, C. C., Müller, M., Lappin, G. and Langer, O. (2008) Positron emission tomography for use in microdosing studies. *Curr Opin Drug Discov Devel* 11 (1) 104-110.
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- Lappin, G. and Garner, R. C. (2006) A review of human phase 0 (microdosing) clinical trials following the US food and drug administration exploratory investigational new drug studies guidance. *Int J Pharma Med* 20 (3) 159-165.
- Garner, R C and Lappin, G (2006) Commentary: The phase 0 microdosing concept. *Br J Clin Pharmacol* 61 (4) 367.
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- Lappin, G., Garner, R. C., Meyers, T. and Powell, J. (2006) Novel use of accelerator mass spectrometry for the quantification of low levels of systemic therapeutic recombinant protein. *J Pharmaceutical and Biomedical Analysis* 41 1299-1302.
- Lappin, G., Rowland, M. and Garner, R. C. (2006) The use of isotopes in the determination of absolute bioavailability of drugs in humans. *Expert Opin Drug Metab Toxicol* 2 (3) 419-427.
- Klem, B., Lappin, G., Nicholson, S., van de Wetering, J., de Vries, D. E., Oosterhuis, B. and Garner R. C. (2006) Determination of the bioavailability of [¹⁴C]-hexaminolevulinate using accelerator mass spectrometry after intravesical administration to human volunteers. *J Clin Pharmacol* 46 456-460.
- Sarapa, N., Hsyu, P. H., Lappin, G., and Garner, R. C. (2005) The application of accelerator mass spectrometry to absolute bioavailability studies in humans: simultaneous administration of an intravenous microdose of ¹⁴C-nelfinavir mesylate solution and oral nelfinavir to healthy volunteers. *J Clin Pharmacol* 45, 1198-1205.
- Lappin, G. and Garner, R. C. (2005) The use of accelerator mass spectrometry to obtain early human ADME/PK data. *Expert Opin Drug Metab Toxicol* 1(1) 23-32.
- Lappin, G. (2004) Animal experimentation, the worst form of science? Editorial in the *Biologist* 51 (1).
- Lappin, G. and Garner R. C., Current perspectives on ¹⁴C isotope measurement in biomedical accelerator mass spectrometry (2004). *Analytical and Bioanalytical Chemistry* 378 (2) 356-364.
- Lappin, G. and Garner, R. C. (2003) Ultra-sensitive detection of radiolabelled drugs and their metabolites using accelerator mass spectrometry in: *Handbook of analytical separations*. Series Editor Roger M. Smith, Volume Editor, Ian Wilson, Elsevier, Amsterdam.
- Bacon, J. R., Williamson, G., Garner, R. C., Lappin, G., Langouët, S. and Bao, Y. (2003) Sulforaphane and quercetin modulate PhIP-DNA adduct formation in human Hep G2 and hepatocytes. *Carcinogenesis* 24 (12) 1903-1911.
- Lappin, G. (2003) Biology meets nuclear physics *Biologist* 50 (4) 183-187.
- Lappin, G. and Garner, R. C. (2003) Big physics, small doses – The use of AMS and PET in human microdosing of development drugs. *Nature Reviews (Drug Discovery)* 2 (3) 233-240.

- Van Ravenzwaay, B., Hardwick, T., Needham, D., Pethen, S. and Lappin, G. J. (2003) Comparative metabolism of 2,4-dichlorophenoxyacetic acid in rat and dog. *Xenobiotica* 33 (8) 805-821
- Laird, W. J. D., Gledhill, A. J. and Lappin, G. J. (2003) Metabolism of methyl-(E)-2-[2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl]-3-methoxyacrylate (Azoxystrobin) in rat. *Xenobiotica* 33 (6) 677-690.
- Lappin, G. (2002) Chemical toxins and body defences. *Biologist* 49 (1) 33-37.
- Lappin, G. J., Hardwick, T. D., Stow, R., Pigott, G. H. and van Ravenzway, B. (2002) Absorption, metabolism and excretion of MCPA in rat and dog. *Xenobiotica* 32 (2) 153-163.
- Lappin, G. J. and Ashby, J. (1996) Lack of correlation in CsCl gradients between radioactivity and DNA from ¹⁴C-NMU treated mice: consequences for CBI calculations. *Experim Toxicol Path* 48 (5) 367.
- Lappin, G. J., Pritchard, D., Moore, R. B. and Laird, W. J. D. (1996) Metabolism of 2,3,5,6-tetrachloronitrobenzene in the rat. *Xenobiotica* 26 (1) 65-67.
- Provan, M., Jones, H., Lappin, G., Pritchard, D., Moore, R. and Green, T. (1995) Incorporation of radiolabelled sulphur from captan into protein and impact on a DNA binding Study. *Chem Biol. Interactions* 96 (2) 174-184.
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- Lappin, G. J., Tampion, J. and Stride, J. The biotransformation of monoterpenoids by tissue plant culture. In: *Secondary Metabolism in Plant Cell Cultures*, Cambridge University Press (1989).
- Lappin, G. J., Tampion, J. and Stride, J. (1987) Biotransformation of monoterpenoids by suspension cultures of *Lavandula angustifolia*. *Phytochemistry*, 26 (4) 995-997.

Text Books

Lappin, G and Temple, S. *Radioisotopes in Drug Development*. Taylor Francis CRC Press, Florida, USA. ISBN 0849333474, April 2006

Patents

- Garner, R. C. and Lappin, G. Radioisotope labelled biological compositions and their use in accelerator mass spectrometry. EP Patent 1,868,655
- Garner, R. C. and Lappin, G. Library of compounds labelled with radioisotope. EP Patent 1,597,583. US Patent 10/546,324.
- Quantification of analytes using accelerator mass spectrometry. EP Patent 2,288,635. US Patent 7,985,589.