BIOGRAPHICAL SKETCH

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NAME: Marcus Stanley Cooke

eRA COMMONS USER NAME (credential, e.g., agency login): MARCUSCOOKE

POSITION TITLE: Professor and Head of Department

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Liverpool Polytechnic, Liverpool, UK	BSc (Hons)	07/91	Biomedical Science
Leicester University, Leicester, UK	MSc	12/93	Molecular Pathology and Toxicology
Leicester University, Leicester, UK	PhD	07/98	Free radical biochemistry
Royal College of Pathologists, London, UK	FRCPath	01/08	Free radical biochemistry

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

I completed my PhD ("Immunochemical investigation of UV-induced DNA damage") in 1998, at the University of Leicester (UK), in the Medical Research Council's Centre for Mechanisms of Human Toxicity. After three post-doctoral positions, in the fields of UV radiation, antioxidants and oxidative stress, I became an Assistant Professor at the University of Leicester. Continued productivity, in terms of grants and papers, lead to an acceleration of my three year mandatory probationary period, with early confirmation in appointment (full tenure May 2003). Less than a year after this, I was promoted to Associate Professor, with joint membership with the University of Leicester's prestigious Department of Genetics. In 2005 I became the Group Lead of the Oxidative Stress Group, which I developed to become one of the foremost groups in the UK undertaking oxidative stress research, specifically studying DNA damage and repair. My area of expertise is oxidative stress, in particular formation and repair of oxidatively damaged DNA (nuclear and mitochondrial) and the dNTP pool: from basic mechanisms to translational application of validated biomarkers. On July 1st 2014 I assumed the position of Professor and Head of the Dept. Environmental and Occupational Health, at Florida International University. Since ~2000 I have held a long-standing interest in the genome-wide study of DNA damage at nucleotide resolution and we were amongst the first to develop methodology to achieve this and reveal differential sites and rates of repair, together with differential sensitivities to damage across the genome. I am internationally recognized as a leader in demonstrating the source and significance of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine, a non-invasive biomarker of oxidative stress. I continue to Chair the EU-funded, European Standards Committee on Urinary (DNA) Lesion Analysis, an international project comprising some of the world's top oxidative stress laboratories and SMEs, the goal of which is the validation urinary DNA lesions as important biomarkers for future large-scale human studies. Over my career to date, I have mentored 11 postdoctoral fellows; 12 technicians; two assistant professors; two data entry clerks; two research midwives and one clinical research fellow. I have successfully supervised one MD student, six PhD students, at least 18 M.Sc students, and at least 20 B.Sc students through their research project placements in my laboratory.

B. Positions and Honors

Positions and employment

2014- present Professor and Head of Department, Dept. Environmental and Occupational Health, Florida International University
2012 – 2014 Associate Professor, Group Leader, Oxidative Stress Group, University of Leicester
2011 – 2012 MRC Research Leader Fellow, Oxidative Stress Group, University of Leicester
2005 – 2010 Group Leader, Oxidative Stress Group, University of Leicester
2004 – 2010 Associate Professor, Radiation and Oxidative Stress Section, University of Leicester
2001 – 2004 Assistant Professor, Department of Clinical Biochemistry, University of Leicester
2000 – 2001 Post-doctoral Research Associate, Oxidative Stress Group, University of Leicester
1999 – 1999 Post-doctoral Research Associate, Division of Chemical Pathology, Univ. Leicester
1998 – 1999 Post-doctoral Research Associate, Division of Chemical Pathology, Univ. of Leicester
1996 – 1998 Research Assistant, Division of Chemical Pathology, University of Leicester

Other experience and Professional Memberships

2010 – 13 Committee member of the Society for Free Radical Research (Europe)
2008 - present Fellow of the Royal College of Pathologists
2006 – present Founding Chair of the European Standards Committee on Urinary (DNA) Lesion Analysis (ESCULA)
2006 – 09 Committee member of the United Kingdom Environmental Mutagen Society

Honors

2010 Society for Free Radical Research (Europe) Catherine Pasquier award.
2009 The Professors' Prize Association for Clinical Biochemistry. Awarded by the UK Heads of Academic Departments of Clinical Biochemistry for an outstanding scientific contribution to the field.
2007 Diploma from the Polish Ministry of Science and Higher Education recognizing the contribution to oxidative stress research in lung cancer.
2003 European Environmental Mutagen Society, Young Scientist Award.

Grant reviewing

2007 – 2011 World Cancer Research Fund & adviser to their 'Netherlands RFA' programme.
2008 Italian Telethon Foundation.
2008 Biotechnology and Biological Sciences Research Council.
2008 – 2014 Medical Research Council.
2008 EU's Innovative Medicine Initiative Joint Undertaking.
2009 British Skin Foundation.
2009 Wellcome Trust.
2012 National Institute for Health Research, i4i Programme.
2012 French Agence Nationale de la Recherche.
2010 - 2013 Wellbeing of Women.
2014 Health & Medical Research Fund (Government of Hong Kong Special Administrative Region).
2015 External reviewer of Public Health England.
2015 Engineering and Physical Sciences Research Council.
2015 – present National Cancer Institute [ZCA1 SRB-L (J1, M1)] R03 and R21 omnibus.

C. Contribution to Science

The focus of my research is oxidative stress, in particular oxidatively induced damage and repair of nucleic acids. Oxidative stress is implicated in a wide variety of human health issues, such as cancer, diabetes, cardiovascular and neurodegenerative disease, and hence warrants close study.
(Students, under my supervision, contributing to publications are underlined.)

1. *Analysis and sources of urinary nucleic-acid derived biomarkers of oxidative stress.*
I am a leading proponent that the nucleotide pool is the source of damaged 2'-deoxyribonucleotides and ribonucleotides in urine (1). Examples of these damage products are 8-oxo-7,8-2'-deoxyguanosine (8-oxodG)

and 8-oxo-7,8-guanosine (8-oxoGuo), which are widely studied non-invasive biomarkers of oxidative stress. It has been suggested that cell turnover and diet can all contribute to levels of these products in urine, which would confound their interpretation. I conducted a simple, but elegant, experiment which ruled out the contribution of diet, and have argued that precedent in the literature indicates that cell death does not contribute, leaving only DNA repair (2). Many in the field believe that nucleotide excision repair (NER) is the source of the modified 2'-deoxyribonucleotides present in extracellular matrices, although we have proposed that sanitization of the 2'-deoxyribonucleotide pool is a more credible source. In fact, some recent work from my laboratory, together with a considerable number of international collaborators, has convincingly ruled out a contribution from NER, strengthening the pool as the source (3). Facilitating such discoveries has been the continual improvement of assays for the measurement of such biomarkers (4,5).

1. **Cooke, MS.,** Evans, MD., Herbert, KE. and Lunec, J. (2000) Urinary 8-oxo-2'-deoxyguanosine - source, significance and supplements. *Free Rad. Res.,* **32,** 381-397
2. **Cooke, MS.,** Evans, MD., Dove, R., Rozalski, R., Gackowski, D., Siomek, A., Lunec, J. and Olinski, R. (2005) DNA repair is responsible for the presence of oxidatively damaged DNA lesions in urine. *Mutat. Res*. *Fundamental and Molecular Mechanisms in Mutagenesis,* **574,** 58-66.
3. Evans, MD., Misty, V., Singh, R., Gackowski, D., Różalskic, R., Siomek-Goreckac, A., Phillips, DH., Zuod, J., Mullenders, L., Pines, A., Nakabeppu, Y., Sakumi, K., Sekiguchi, M., Tsuzuki, T., Bignami, M., Oliński, R. and **Cooke, MS.** (2016) Nucleotide excision repair of oxidised genomic DNA is not the primary source of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine. *Free Radic. Biol. Med.* **99,** 385-391.
4. ESCULA, Evans, MD., Olinski, R., Loft, S. and **Cooke, MS.** (2010) Towards consensus in the analysis of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine as a non-invasive biomarker of oxidative stress. *FASEB J*. **24,** 1249-1260.
5. Barregard, L., Moller, P., Henriksen, T., Mistry, V., Koppen, G., Rossner, P., Sram, RJ., Weimann, A., Poulsen, HE., Nataf, R., Andreoli, R., Manini, P., Marczylo, T., Lam, P., Evans, MD., Kasai, H., Kawai, K., Li, Y-S., Sakai, K., Singh, R., Teichert, F., Farmer, PB., Rozalski, R., Gackowski, D., Siomek, A., Saez, GT., Cerda, C., Broberg, K., Lindh, C., Hossain, M., Haghdoost, S., Hu, C-W., Chao, M-R., Wu, K-Y., Orhan, H., Senduran, N., Smith, RJ., Santella, RM., Su, Y., Cortez, C., Yeh, S., Olinski, R., Loft, S. and **Cooke, MS.** (2013) Human and methodological sources of variability in the measurement of urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine. *Antioxidants and Redox Signalling* **18,** 2377-2391.

2. *Role of oxidative stress in disease.*

I have extended our knowledge of the involvement of oxidative stress in a number of pathological conditions. For example, I showed that a particular sub-group of renal transplant patients were under greater oxidative stress, and these were also at greater risk of developing squamous cell carcinoma (1). Screening this vulnerable population would offer an opportunity for clinical intervention. Spinning off from my large, UK Food Standards Agency-funded project examining the risk to the fetus of caffeine consumption during pregnancy (2), I used urine samples collected at 12 and 28 weeks gestation to quantify levels of 8-oxodG. I discovered that women that went on to have a baby which was small for gestation age (growth restricted), had higher levels of 8-oxodG in their urine, compared to mothers who had a baby whose weight was average for gestational age. This finding was particularly evident at 12 weeks (3), presenting an opportunity for the development of a screening test to identify at-risk mothers, early on in pregnancy, and provide closer clinical monitoring (at present there is no intervention for fetal growth restriction). This also implies a potential role for oxidative stress in fetal growth restriction, and hence an opportunity for the development of an intervention. Arguably the most profound single contribution to human health was the study with Grigg (Queen Mary University of London) in which measuring urinary 8-oxodG revealed a role for oxidative stress in idiopathic pulmonary haemosiderosis, a condition that, though repeated bleeding, leads to scarring of the lungs, and ultimately respiratory failure (4). With the link to oxidative stress shown, the patient in question was treated with a clinically approved antioxidant, her episodes of bleeding stopped and she was eventually weaned off the aggressive standard treatment. Although a relatively rare condition, this precedent has been adopted by clinicians worldwide.

1. **Cooke, MS.,** Osborne, J., Singh, R., Mistry, V., Farmer, PB., Evans, MD. and Hutchinson, PE. (2007) Oxidative stress is a risk factor for the development of squamous cell carcinoma in renal transplant patients. *Free Radic. Biol. Med*. **43,** (9) 1328-1334.

2. Potdar, N., Boylan, S., **Cooke, MS.,** Greenwood, D., Hay, A., Kirk, S., Konje, JC., Simpson, N., Taub, N., White, K., Cade, J. on behalf of the CARE Study Group. (2008) Maternal caffeine intake during pregnancy and the risk of fetal growth restriction: a large prospective observational study. *British Medical Journal* **337,** a2332-
3. Potdar, N., Singh, R., Mistry, V., Evans, MD., Farmer, PB., Konje, JC. and Cooke, MS. (2009) First trimester increase in oxidative stress and risk of fetal growth restriction. Brit. J. Obs. Gynae. 116, 637-642.
4. Panicker, J., **Cooke, MS.** and Grigg, J. (2007) "Evidence for oxidative stress in idiopathic pulmonary haemosiderosis". *New Eng. J. Med.,* **356,** (22) 2329-2330.

3. *Urinary thymine dimers, biomarkers of in vivo UVR exposure*

Not all urinary biomarkers of interest are oxidatively generated. In 1999 I became the first person to identify the presence of cyclobutane thymine dimers in urine, and develop a novel enzyme-linked immunoassay for their quantification (1). Thymine dimers are formed in DNA when cells are exposed to UVR, and discovering their appearance in urine, following their repair from cells, offered the potential to non-invasively assess an individual's exposure to UVR (2). This offers a number of advantages over current method for UVR biodosimetry, such a film badges, which require compliance as they can be taken off, or covered up, limiting their reliability. In fact this finding led to the funding of three major projects by the European Union, UK Department of Health and Cancer Research UK, and I have been involved in all of them, including as a principal investigator. More recently, we have developed a mass spectrometry-based assay for CPD (3). This work is complimented by studies investigating the cellular DNA damage response to UVR exposure (4).

1. Ahmad, J., **Cooke, MS.,** Hussieni, A., Evans, MD., Burd, RM., Patel, K., Bleiker, TO., Hutchinson, P. and Lunec, J. (1999) Urinary thymine dimers and 8-oxo-2'deoxyguanosine in psoriasis. *FEBS Letts.* **460,** 549-553.
2. **Cooke, MS.,** Evans, MD., Burd, RM., Patel, K., Barnard, A., Lunec, J. and Hutchinson, PE. (2001) Induction and excretion of UV-induced 8-oxo-2'-deoxyguanosine and thymine dimers *in vivo*: implications for PUVA. *J. Invest. Dermatol*. **116,** 281-285.
3. Felton, SJ., **Cooke, MS.,** Kift, R., Berry, JL., Webb, AR., Lam, PMW., de Gruijl, FR., Vail, A. and Rhodes, LE. Concurrent impact of low level summer sunlight exposures and vitamin D production and cutaneous DNA damage in people of light and dark skin. Br. J. Dermatol. (Submitted)

4. *Novel methods for studying DNA damage*

More recently I have incorporated the single cell gel electrophoresis assay (comet assay) into my repertoire of assays (1), and have made a number of paradigm-changing advances. The convention was that, in order to use the comet assay to study DNA damage in blood samples, the white blood cells would first have to be isolated – a time-consuming and relatively skilled procedure. Also, for storage, these cells have to be combined with a specific solution to prevent artefactual formation of damage. I showed that a pin-prick of whole blood could be used directly in the comet assay, and furthermore, when storing such small volumes of blood (a pin-prick is up to 250 µL), no freezing mix is required, and no artefact is generated (2). This will hugely simplify human studies. The second innovation was based upon my discovery that the slides, used as the platform for cell electrophoresis, could be placed in a vertical orientation, rather than the conventional horizontal, and electrophoresis successfully performed. The benefit of this is that multiple slides can be held in this orientation in a rack and manipulated simultaneously through the multiple sample workup step, increasing throughput and decreasing assay time and footprint of the electrophoresis tank (3). This discovery (patent pending) has been licensed to a company who are manufacturing and selling a product based upon my original designs. Other, related patents have been submitted, or are in preparation. For a long time we thought that measurement of damage and repair at the sequence level is likely to be informative that global genome levels of DNA damage. Early attempts were limited to single, small intra-genic regions (4). More recently, NGS has allowed us to extend this approach, allowing us to identify differential sites and rates of damage induction, together with differential rates of repair across the entire genome (5).

1. **Cooke, MS.,** Duarte, TL., Cooper, D., Chen, J., Nandagopal, S. and Evans, MD. (2008) Combination of azathioprine and UVA irradiation is a major source of cellular 8-oxo-7,8-dihydro-2'-deoxyguanosine. *DNA Repair* **7,** 1982-1989
2. Al-Salmani, K., Abbas, HHK., Schulpen, S., Karbaschi, M., Abdalla, I., Bowman, KJ., So, KK., Evans, MD., Jones, GDD., Godschalk, R. and **Cooke, MS.** (2011) Evaluation of storage and DNA damage analysis of whole blood by Comet assay. *Free Radic. Biol. Med.*, **51,** 719-725.
3. Karbaschi, M. and **Cooke, MS.** (2014) Novel method for the high-throughput processing of slides for the comet assay. *Scientific Reports* **4,** 7200 DOI:10.1038/srep07200

4. Karakoula, A., Evans, MD., Podmore, ID., Hutchinson, PE., Lunec, J. and **Cooke, MS.** (2003) Quantitative analysis of UV-induced DNA damage: global versus gene-specific levels of thymine dimers. J. Immunol. Meth. 277, 27-37.
5. Al-Salmani, ASM. Jones, GDD. and Cooke, MS. (2016) Genome-wide analysis of DNA damage and repair reveals differential sites and rates of repair, together with differential sensitivities to damage. Cancer Res., 76, DOI: 10.1158/1538-7445.AM2016-LB-163.

Complete List of Published Work in My Bibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/1VgOxZHwqORki/bibliography/47226589/public/?sort=date&direction=ascending

D. Recent Research Support

Current Research Support

"Sandbox Grant", Biomolecular Sciences Institute, FIU. Tempest (PI) 2015 - 2016
Investigation of the genome-wide, sequence-specific distribution of DNA damage and repair, and its association with chromatin organization.
To apply sequencing-based methodology to study the induction and repair of DNA damage, and chromatin remodeling, following exposure to UVR. Role: Co-PI.

Selected Completed Research Support

C30431/A13128 (Cancer Research-UK) Cooke (PI) 2012 - 2015
Biomarkers of UVR exposure: tools for determining the relationship between the benefits and hazards of UVR.
The aim of the project is to determine whether sufficient vitamin D can be generated from simulated sunlight exposure, with minimal induction of DNA damage. Role: PI.

(Department of Health, UK) Webb (PI) 2012 - 2014
Modelling approach to determine the duration and intensity of sunlight exposure required to maintain and achieve adequate vitamin D status in winter in 'at risk' population groups.
Using pre-existing data, the aim is to determine the duration and intensity of sunlight exposure required to maintain and achieve adequate vitamin D status in winter in 'at risk' population groups e.g. the elderly. Role: Co-PI.

G101808/1 (Medical Research Council, UK) Cooke (PI) 2011-2012
Development of validated assays for the evaluation of oxidative stress in health and disease. People Exchange Programme – Research Leader Fellowship.
The aim was to develop novel methodology for evaluating oxidative stress *in vivo*. Role: PI.

University of Leicester Innovation Fellowship. Cooke (PI) 2012 - 2013
Methodology for the point-of-collection treatment of extracellular, biological matrices to account for possible analyte loss/degradation during the sample processing chain and correction for sample concentration. Role: PI.

Cleaver Scientific Ltd, UK. Cooke (PI) 2014 - 2014
High throughput single cell gel electrophoresis assay. Role: PI.