XXXIII JCET LECTURE, 28.03.2014, 9.00

WHEN DWARF MEETS GIANT: NANOPHARMACOLOGY AND NANOTOXICOLOGY OF NANOMATERIALS

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Nanomaterials are tiny devices and structures sized at least in one dimension between 1 to 100 nm[1]. Engineered nanomaterials are developed for novel applications including drug delivery, imaging, tissue scaffolding, tissue regeneration and medical device systems. Indeed, nanomedicine is one of the fastest growing areas in nanotechnology poised to revolutionize diagnostics and therapeutics of human diseases[2].

Our research focuses on pharmacological and toxicological significance of nanomaterials and the use of nanodevices in the R&D. We have introduced the term nanopharmacology to pharmacological sciences to highlight the importance of nanodrugs and nanodrug delivery systems for therapeutics[3]. We have investigated the interactions and biocompatibility of engineered nanomaterials such as carbon nanotubes, amorphous silica and gold nanoparticles in blood platelets, endothelial cells and lung epithelium[4-10] and currently are studying the effects of surface-bound carbon nanotubes in the extracorporeal circuits[11, 12]. Finally, we have used commercially-available and custom-made nanoresolution and microfluidics devices for nanodiagnostics of platelet activation and for studying tumour cell-induced platelet aggregation under flow [8, 13-16].

As with all medical progress the introduction of novel diagnostics and therapeutics carries some risk. In order to mitigate this risk we apply toxicological principles to nanotechnology. Interestingly, humans have been exposed to nanosized materials such as burned fuels throughout evolutionary stages; however the exposure has greatly increased over the past century mainly due to anthropogenic sources[17]. This poses a risk of combined effects of nanomaterials and other xenobiotics (*Inkielewicz-Stepniak et al accepted to Int J Nanomedicine*). Therefore, establishing the risk-benefit analysis of nanomaterials not only in medicine, but also in other environmental sciences including food and agriculture[18], is crucial for successful R&D.

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2. Caruso F, Hyeon T, Rotello VM. Nanomedicine. Chem.Soc.Rev. 2012;41:2537-2538.
3. Medina C, Santos-Martinez MJ, Radomski A, et al. Nanoparticles: pharmacological and toxicological significance. Br J Pharmacol 2007;150:552-8.
4. Radomski A, Jurasz P, Alonso-Escolano D, et al. Nanoparticle-induced platelet aggregation and vascular thrombosis. Br J Pharmacol 2005;146:882-93.
5. Li X, Radomski A, Corrigan OI, et al. Platelet compatibility of PLGA, chitosan and PLGA-chitosan nanoparticles. Nanomedicine (Lond) 2009;4:735-46.
6. Corbalan JJ, Medina C, Jacoby A, et al. Amorphous silica nanoparticles trigger nitric oxide/peroxynitrite imbalance in human endothelial cells: inflammatory and cytotoxic effects. Int J Nanomedicine 2011;6:2821-35.
7. Corbalan JJ, Medina C, Jacoby A, et al. Amorphous silica nanoparticles aggregate human platelets: potential implications for vascular homeostasis. Int J Nanomedicine 2012;7:631-9.
8. Santos-Martinez MJ, Inkielewicz-Stepniak I, Medina C, et al. The use of quartz crystal microbalance with dissipation (QCM-D) for studying nanoparticle-induced platelet aggregation. Int J Nanomedicine 2012;7:243-55.
9. McCarthy J, Gong X, Nahirney D, et al. Polystyrene nanoparticles activate ion transport in human airway epithelial cells. Int J Nanomedicine 2011;6:1343-56.
10. Lesniak A, Salvati A, Santos-Martinez MJ, et al. Nanoparticle adhesion to the cell membrane and its effect on nanoparticle uptake efficiency. J Am Chem Soc 2013;135:1438-44.
11. Gaffney AM, Wildhirt SM, Griffin MJ, et al. Extracorporeal life support. BMJ 2010;341:c5317.
12. Gaffney AM. Blood biocompatibility of polyvinyl chloride surface-modified with multi-walled carbon nanotubes. School of Pharmacy and Pharmaceutical Sciences. Volume PhD. Dublin: Trinity College Dublin, 2012.
13. Santos-Martinez MJ, Prina-Mello A, Medina C, et al. Analysis of platelet function: role of microfluidics and nanodevices. Analyst 2011;136:5120-6.
14. Bazou D, Santos-Martinez MJ, Medina C, et al. Elucidation of flow-mediated tumour cell-induced platelet aggregation using an ultrasound standing wave trap. Br J Pharmacol 2011;162:1577-89.
15. Santos-Martinez MJ. A novel method for the measurement of flow-induced platelet activation at nanoscale resolution level. School of Pharmacy and Pharmaceutical Sciences. Volume PhD. Dublin: Trinity College Dublin, 2009.
16. Santos-Martínez M, Medina C, Prina-Mello A, et al. A nanoscale resolution assay of flow-induced platelet microaggregation. Kardiochirurgia i Torakochirurgia Polska 2010;7:365-375.
17. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 2005;113:823-39.
18. Cockburn A, Bradford R, Buck N, et al. Approaches to the safety assessment of engineered nanomaterials (ENM) in food. Food Chem Toxicol 2012;50:2224-42.

CURRICULUM VITAE

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CURRENT POSITIONS:
Professor and Chair of Pharmacology (1979), School of Pharmacy and Pharmaceutical Sciences Trinity College Dublin, Ireland;
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DEGREES:
1978/M.D. Medicine, Jagiellonian University Medical School, Poland (Honours with Distinction)
1983/Ph.D Pharmacology, Department of Pharmacology, Jagiellonian University Medical School, Krakow, Poland, Supervisor: Prof. R.J. Gryglewski
1990/D.Sc. Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

ACADEMIC, RESEARCH AND WORK EXPERIENCE:

Positions held:

1978 -1981	Research Associate (Department of Pharmacology)
1981 -1987	Lecturer (Jagiellonian University Medical School)
1987 -1988	Senior Lecturer (Krakow Poland)
1988 -1991	Senior Lecturer (Polish Academy of Sciences, Warsaw, Poland)
1989 -1993	Senior Scientist (Wellcome Research Laboratories, Beckenham, Kent U.K.)
1993 -1994	Head, Nitric Oxide Research Group (Wellcome)
1998 -1998	Director of Research (Lacer SA, Barcelona, Spain)
1994 -2002	Professor -tenure (Department of Pharmacology, University of Alberta, Canada)
2002-2005	Professor - tenure (Department of Pharmacology, Institute of Molecular Medicine,University of Texas-Houston)
2005-2007	Director of Research (Silesian Centre for Heart Diseases)
2007-2008	Director of Research (School of Pharmacy Trinity College)
2008-2013	Head of School of Pharmacy (Trinity College Dublin)
2011-2013	Director of Cancer Drug Discovery (Trinity College Dublin)

RESEARCH SUPERVISION:
Supervision/co-supervision: total 24 PhD students, currently 3 PhD students, total 18 post-doctoral fellows, 3 research associates.

FUNDING:
Alberta Heritage Foundation for Medical Research (1994-1996), Canada
Alberta Lung Association (1996), Canada
Eli Lilly Pharmaceuticals (1996-1998)
Schwarz Pharma (1996-1997), Germany
Lacer Pharmaceuticals (1996-1997), Spain
Canadian Institutes of Health Research (1997-2002), Canada
Canadian Institutes of Health Research Equipment (group grant) (2002), Canada
Alberta Lung Association (2002-2004), Canada
Health Effects Institute (2004-2005), USA
McDonald Fund (2004-2005), USA
Plx Pharma, 2005, USA
Trinity College Dublin establishment grant (2006-2007), Ireland

Committee for Scientific Research (2005-2008), Poland
Science Foundation Ireland PI (2006-2012), Ireland, *Effects of nanoparticles on human platelets: role of nitric oxide and matrix metalloproteinases*
Science Foundation Ireland PI (Stokes Lecturer, Dr. Carlos Medina (2008-2012)
Science Foundation Ireland Strategic Research Cluster (2007-2011)
Enterprise Ireland (2006-2007), Ireland
Enterprise Ireland, (2007-2009), Ireland
Higher Education Authority (2007) equipment grant, Ireland
Health Research Board PI (PhD Clinical Scientist Scheme, Dr. Alan Gaffney, 2009-2012) Ireland, *Blood biocompatibility of surface-bound carbon nanotubes*
European Union Framewok Project 7 FP7 Multifun research consortium 2011-2014, *Bifunctional nanoparticles for cancer treatment*
PRLTI5 Ireland 2010-2014, infrastructure for co-funding the Trinity Biomedical Sciences Institute, PI of Cancer Drug Discovery Centre one of three centres in the building
Celtic Alliance Nanohealth INTERREG consortium 2011-2013

PUBLICATIONS:
Original: 124, book chapters: 48, reviews: 37, abstracts: 86, invited lectures: 180
Cited in www.isihiglycited.com: search: radomski (Institute of Scientific Information Web of Science).
Citation number (Google Scholar, 01/01/2014): 17344, papers cited ≥ 100 times: 42, h-index: 58 http://scholar.google.com/citations?user=wGSCyU4AAAAJ&hl=en

Selected Papers:
1. Radomski, M.W., Palmer, R.M.J., Moncada, S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. The Lancet ii:1957-1058(1987).
2. Radomski, M.W., Palmer, R.M.J., Moncada, S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. Proc. Natl. Acad. Sci. USA 87:10043-10047(1990)
3. Radomski, M.W., Palmer, R.M.J., Moncada, S. An L-arginine/nitric oxide pathway present in human regulates aggregation. Proc. Natl. Acad. Sci. USA, 87:5193-5197(1990)
4. Radomski, M.W., Palmer, R.M.J., Moncada, S. The antiaggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. Br. J. Pharmacol.92:639-647(1987)
5. Radomski, M.W., Palmer, R.M.J., Moncada, S. Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide and prostacyclin in platelets. Br. J. Pharmacol.92:181-187(1987)
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7. Fernandez-Patron, C., Radomski, M.W., Davidge, S.M. Vascular matrix metalloproteinase- 2 cleaves big endothelin-1 yielding a novel vasoconstrictor. Circ. Res. 85: 906-911 (1999).
8. Fernandez-Patron, C., Martinez-Cuesta, M.A., Salas, E., Sawicki, G., Wozniak, M., Radomski, M.W., Davidge, S.T. Differential regulation of platelet aggregation by matrix metalloproteinase-9 and –2. Thromb. Haemostas. 82:1730-1735 (1999).
9. Cheung, P-Y., Sawicki, G., Wozniak, M., Wang, W., Radomski, M.W., Schulz, R. Matrix metalloproteinase-2 contributes to the ischemia-reperfusion injury in the heart. Circulation 101:1833-1839 (2000).
10. McNaughton, L.E., Puttagunta, L., Martinez-Cuesta, M.A., Kneteman, N., Mayers, I., Radomski, M.W. Expression and localization of nitric oxide synthase in normal and diseased human liver. Proc.Natl.Acad.Sci. USA 99:17161-17166(2002).

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12. Medina, C., Santos-Martinez, M.J., Radomski, A., Corrigan, O.I., Radomski, M.W. Nanoparticles: pharmacological and toxicological significance. Br.J.Pharmacol.,150:552-555(2007) ***(This paper has been downloaded 3523 times in 2007, one of 3 most downloaded papers in Br J Pharmacol in 2007)***.
13. Li, X., Radomski, A., Corrigan, O.I., Tajber, L., De Sousa Menezes, F., Endter, S., Medina, C., Radomski, M.W. The Platelet Compatibility of Poly(lactide-co-glycolide) (PLGA), Chitosan and PLGA- Chitosan Nanoparticles. Nanomedicine 4:735-746(2009) (cited 9 times).
14. Gaffney, A.M., Wildhirt, S.M., Griffin, M.J., Annich, G.M., Radomski, M.W. Extracorporeal Life Support. British Medical Journal, 341:c5317(2010).
15. Santos-Martinez, M.J., Prina-Melo, A., Medina, C. Analysis of platelet function: role of microfluidics and nanodevices Analyst DOI: 10.1039/c1an15445a(2011).
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17.Santos-Martinez, M.J., Inkielewicz-Stepniak, I., Medina, C., Rahme, K., D'Arcy, D., Holmes J.D., Zhang, H., Radomski, M.W. The use of quartz crystal microbalance with dissipation for studying nanoparticle-induced platelet aggregation. International Journal of Nanomedicine 7:243-255(2012).
18. Radziwon-Balicka, A., Medina, C., O'Driscoll, L., Bazou, D., Inkielewicz-Stepniak, I., Radomski, A., Treumann, A., Jow, H., Radomski, M.W. Platelets increase survival of adenocarcinoma cells challenged with antcancer drugs: mechanisms and implications for chemoresistance. Br. J. Pharmacol. 167:787-804(2012)
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20.Lesniak, A., Salvati, A., Santos-Martinez, M.J., Radomski, M.W., Dawson, K.A., Aberg, C. Nanoparticle adhesion to the cell membrane and its effect on nanoparticle uptake efficiency. J.Am.Chem.Soc. 135:1438-1444(2013).
21. Radziwon-Balicka, A., Santos-Martinez, M.J., Corbalan, J.J., O'Sullivan, S., Treumann, A., Glimer, J.F., Radomski, M.W., Medina, C. Mechanisms of platelet-stimulated colon cancer invasion: role of clusterin and thrombospondin-1 in regulation of the P38MAPK-MMP-9 pathway. Carcinogenesis 35:324-332(2014).

PATENTS:

1. The use of S-nitrosoglutathione for the treatment of restenosis with J.F. Martin and S. Moncada, London, U.K., 1995. 2. The use of metalloproteinase inhibitors as inhibitors of platelet activation with E. Salas, Edmonton, Canada 1997. 3. Novel tolerance-free organic nitrates with Department of Research and Development Lacer Laboratories, Barcelona, Spain 1998. 3. Aspirin-PC as antiplatelet drug with Plx Pharma, USA 2005. 4. Tumour cell-induced platelet aggregation using an ultrasound standing wave trap, Trinity College Dublin, 2010.

SELECTED AWARDS:

1991 Honorary Award of the Central University of Ecuador
1994 Alberta Heritage Foundation for Medical Research Scholar (five salary support and operating)
1999 The University of Alberta McCalla Research Professor
2000 Canadian Institutes of Health Research Scientist (five year salary support)
2001 The Alta-Pharm International Senior Scientist Award, Pharmacological Society of Canada
2002 State Professorship (Republic of Poland) presented by President of Poland A. Kwasniewski.
2004 Outstanding Pioneers of Physiology Medal awarded by the Polish Physiological Society.
2005 World Innovation Foundation Fellow
2007 Fellow of Trinity College Dublin
2008 Doctor Honoris Causa, Complutense University, Madrid, Spain