

Professor Nicholas D. Mazarakis B.Sc., Ph.D.

Chair of Gene Therapy and Head of Department of Gene Therapy, Division of Medicine, Imperial College London, St Mary's Campus

Professor Nicholas D. Mazarakis obtained his B.Sc. in Applied Biology from the University of East London and his Ph.D. in Biochemistry/Molecular Biology at King's College University of London, where he worked on mammalian molecular genetics. For his doctorate he was the first to isolate, characterise, map and publish the mouse t-complex gene *tcp-11*, a gene important in sperm function and fertility for it encodes the receptor of fertilisation-promoting peptide, a molecule that stimulates capacitation and inhibits spontaneous acrosome reaction. He subsequently worked through two postdoctoral fellowships at the National Institute for Medical Research, Mill Hill, in the departments of Gene Structure and Expression, and Neurobiology. His research spanned neuronal gene expression of Zn finger transcription factors, immortalisation studies in transgenic mice, gene transfer in neural cells using retroviral vectors and transplantation in animal models of spinal injury. He then joined the department of Paediatrics and Neonatal Medicine at the Royal Postgraduate Medical School in London, where he investigated the role of apoptosis in neonatal brain injury. In 1997, he was recruited by Oxford BioMedica, a start-up company specialising in gene therapy, where he served as Vice President of Neurobiology until July 2006. In August 2006 he was head-hunted and appointed as Chair of Gene Therapy and Head of Department of Gene Therapy in the Division of Medicine, Imperial College London, St Mary's Campus.

Together with his team at Oxford BioMedica, he developed a novel lentiviral vector system based on the non-primate lentivirus -Equine Infectious Anaemia Virus (EIAV) and successfully demonstrated that it mediates efficient gene transfer to neuronal cells both *in vitro* and *in vivo*. Using these vectors he developed a dopamine replacement therapy for late stage Parkinson's disease (ProSavin[®]), and completed proof-of-principle experiments in rodent and primate models of the disease. A Phase I/II clinical trial of this therapy is underway since December 2007 at the Henry Modor Hospital in Paris France. In addition in collaboration with researchers at the Bristol Medical School he developed a gene replacement approach that resulted in long-term correction of an animal model of Diabetes Insipidus. He has also discovered that pseudotyping the EIAV vectors with the rabies virus envelope, allows retrograde axonal transport of the viral vector and expression in neurons distal to the site of injection, such as motoneurons after delivery into muscle. Successful proof-of-principle gene therapy experiments have now been completed using these retrogradely transported vectors in animal models of Amyotrophic Lateral Sclerosis (MoNuDin[®]), Spinal Muscular Atrophy (SMN-1G[®]) and Nerve Injury (Innurex[®]). Other work that his group in Oxford BioMedica did and published on includes: (i) use of regulated vectors expressing neuroprotectives for the treatment of early stage Parkinson's disease (ii) use of shRNA vectors for the treatment of Familial Amyotrophic Lateral Sclerosis (iii) target validation experiments using neuroprotective gene therapy in *in vivo* models of stroke and neurodegeneration (iv) drug discovery experiments using *in vitro* models of stroke and (v) drug discovery experiments using *in vivo* models of nerve regeneration.

In his new department of Gene Therapy at Imperial College London (refurbished labs inaugurated April 26, 2007), viral based gene transfer vectors are utilised both for research and gene therapy applications. Research is focused on elucidating the molecular pathways of neurodegeneration associated with Parkinson's disease and Motor Neurone Diseases. On the therapy front novel therapeutic strategies are being developed for the treatment of neurodegenerative diseases (Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Huntington's Disease and Parkinson's Disease), brain tumours (glioma), neuromuscular disease (Duchenne Muscular Dystrophy) and CNS infections (HIV Associated Dementia).

Central to this is the use of models of disease and the potential of such models in validating new therapeutic strategies. He has appointed a number of key staff including Dr Amin Hajitou (lecturer in gene therapy of neurodegeneration) whose team utilises phage-AAV hybrid vectors for systemic gene targeting of glioma and neuromuscular diseases and Dr Veronica Tisato (research associate-Huntington's disease). The Gene Therapy Department has received substantial funding thus far from the *Motor Neurone Disease Association (UK)*, *HighQ Foundation (US)*, *Medical Research Council (UK)*, *Howard Hughes Medical Institute (US)*, *Association Française contre les Myopathies (FR)*, *European Research Council (2008 Advanced Investigators Grant)* and the *Leverhulme Trust (UK)*.

Key Publications:

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