

Professor Mike Dixon: Understanding the causes of cleft lip and palate

HIGH-QUALITY RESEARCHERS 2005/2006

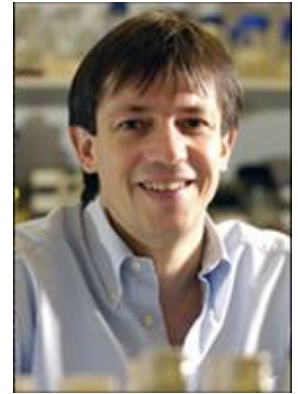
BACKGROUND

Professor Mike Dixon is currently a Professor of Dental Genetics at the University of Manchester, with research interests in normal and abnormal facial development. Originally trained as a dentist, he obtained a PhD in developmental biology. He currently holds **Wellcome Trust programme, project and equipment grants** and received his first funding from the Trust in the 1980s through a fellowship award.

Professor Dixon's research focuses on cleft lip and palate (a malformation affecting the head, face or neck, which causes an opening between the mouth and the nose). There are approximately 400 known syndromes associated with cleft lip and/or palate; these 'syndromic' cases are also associated with other physical problems – in the case of Van der Woude syndrome, for example, missing teeth and a 'pit' in the lip.

Professor Dixon's research has been supported by a number of research funders over the last ten years, including the Wellcome Trust, Action Medical Research, Medical Research Council, the National Institute for Dental and Craniofacial Research, Biotechnology and Biological Sciences Research Council and the European Union.

In 2001, in recognition of his work, Professor Dixon received the International Association for Dental Research Craniofacial Biology Research Award. In 2003, he was awarded a Fellowship in Dental Surgery from the Royal College of Surgeons of England.



Professor Mike Dixon

ADVANCE

Professor Dixon's work integrates genetic analyses in affected individuals and their families, biochemical approaches, developmental analyses, and experimental embryology to dissect the molecular pathways underlying facial development.

The genetic studies by Professor Dixon and colleagues have resulted in the identification of genes that play a crucial role in the fundamental pathways driving craniofacial development, which had not been implicated by alternative approaches. These include the identification of genetic mutations underlying numerous inherited disorders causing cleft lip and palate, including: Treacher Collins syndrome, Papillon-Lefevre syndrome, Van der Woude/popliteal pterygium syndrome, amelogenesis imperfecta and dentine dysplasia.

Professor Dixon – in collaboration with colleagues at the University of Manchester, in the USA and at the Wellcome Trust Sanger Institute – has shown that mutations affecting interferon regulatory factor (IRF6) lead to malformation of the face during prenatal development in Van der Woude syndrome. Work on a mouse model suggests that IRF6 is involved in the control of skin cell (keratinocyte) proliferation and differentiation.

HOW IT'S MAKING A DIFFERENCE

The identification of genes playing a crucial role in the fundamental pathways driving craniofacial development has opened up new avenues of research. Importantly, these studies have also helped to improve the quality of life of patients, as the results have impacted directly on the clinical management of affected individuals and their families. For example, the elucidation of the range of mutations underlying Treacher Collins syndrome has allowed Professor Dixon's team to perform both pre- and postnatal molecular diagnoses for affected families. By this approach, it is possible to determine unequivocally which family members are affected by Treacher Collins syndrome and which are not.

NEXT STEPS

Ongoing research in the laboratory is focused on dissecting the mechanisms underlying a number of aspects of craniofacial development, using the integrated approach outlined above. Specifically, Professor Dixon's group is engaged in two broad areas of research. Firstly, it is attempting to dissect the molecular cascades essential for normal development of the lip and palate and how these are disturbed in cleft lip and cleft palate. Secondly, in collaboration with Professor Kirkham and Professor Brook, Professor Dixon is hoping to define the role of extracellular organic matrix proteins in biomineralisation – the deposition and controlled growth of inorganic crystals to form skeletal tissues. The developing tooth provides a model system that can be studied in a variety of ways, including human and mouse genetics, biochemistry and structural biology, to help elucidate the role of matrix proteins in biomineralisation and therefore craniofacial development.

REFERENCES

Professor Dixon's research interests: www.dentistry.manchester.ac.uk/staff/74805.

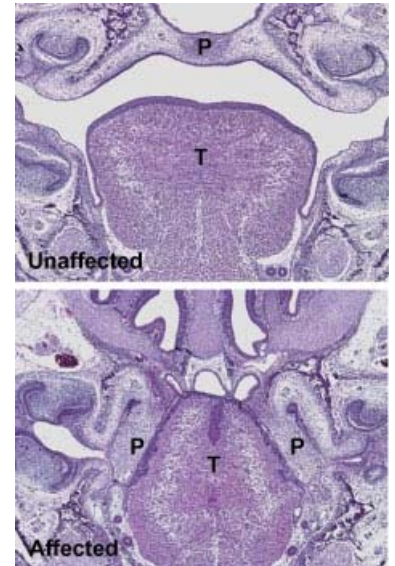
Kondo S et al. [Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes](#). Nat Genet 2002;32:285–9.

Rajpar MH. et al. [Mutation of the signal peptide region of the bicistronic gene DSPP affects translocation to the endoplasmic reticulum and results in defective dentine biomineralisation](#). Hum Mol Genet 2002;11(21):2559–65.

Dixon J et al. [Tcof1/Treacle is required for neural crest stem cell formation and proliferation through its role in mature ribosome production, deficiencies in which cause craniofacial abnormalities](#). Proc Natl Acad Sci USA 2006;103(36):13403–8.

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Above: Mice in which the function of IRF6 is knocked out exhibit cleft palate as a result of the palatal shelves (P) adhering to the tongue (T).

M Dixon

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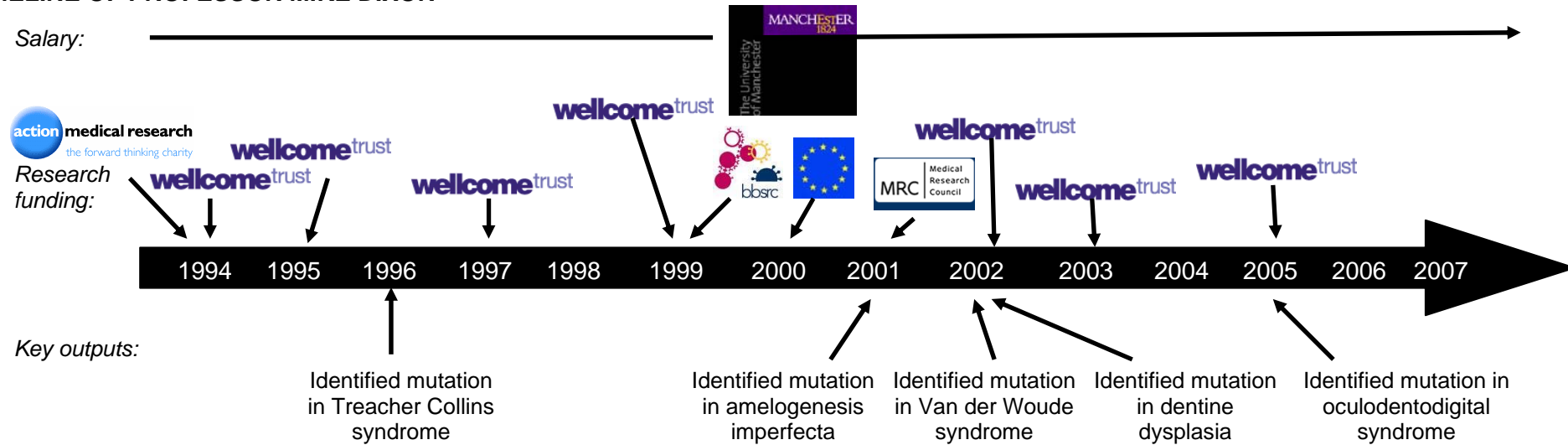


TABLE OF ACHIEVEMENTS

Inputs	Key activities/outputs	Outcomes
<ul style="list-style-type: none"> Seven Wellcome Trust project grants (1994, 1995, 1997, 1997, 2002, 2002, 2003) One Wellcome Trust programme grant with Professors Kirkham and Brook (2005–2010) Two Wellcome Trust equipment grants (1995, 1999) Wellcome Trust support for a transgenic animal unit (1999) BBSRC project grant (1999) European Union project grant (2000) Supervisor for a MRC Research Training Fellowship (2001) 	<ul style="list-style-type: none"> Publications in: <i>Nature Genetics</i>, <i>Proceedings of the National Academy of Sciences USA</i>, <i>American Journal of Medical Genetics</i>, <i>Human Molecular Genetics</i> and <i>Genomics</i> In 2002, in collaboration with colleagues in the USA, Professor Dixon showed that a common form of cleft lip and palate results from mutations affecting a protein called interferon regulatory factor 6 Identified mutations in Treacher Collins syndrome, Van der Woude/popliteal pterygium syndrome, amelogenesis imperfecta, dentine dysplasia and oculodentodigital syndrome. Involvement in initiatives to raise awareness of science (e.g. Outstanding Achievement Award from the Treacher Collins Syndrome Family Support Group) A number of guest lectures and conference proceedings at international meetings (e.g. 'Molecular Genetics Studies of Treacher Collins Syndrome', Gordon Research Conference on Craniofacial Morphogenesis, Ventura Beach, California, 2004) Primary supervision of a PhD project for a MRC-funded clinical academic Clinical management of affected patients and their families (e.g pre- and postnatal molecular diagnoses) 	<ul style="list-style-type: none"> Establishment of a transgenic animal unit with five colleagues Establishment of a semi-automated, integrated DNA sequencing facility Progression from senior lecturer to professor International prizes and fellowships awarded (International Association for Dental Research Craniofacial Biology Research Award and appointed a Fellow in Dental Surgery from the Royal College of Surgeons of England)