Mechanochemical feedback between Neural Crest and Neural Plate cells regulates cephalic Morphogenesis through ECM remodeling

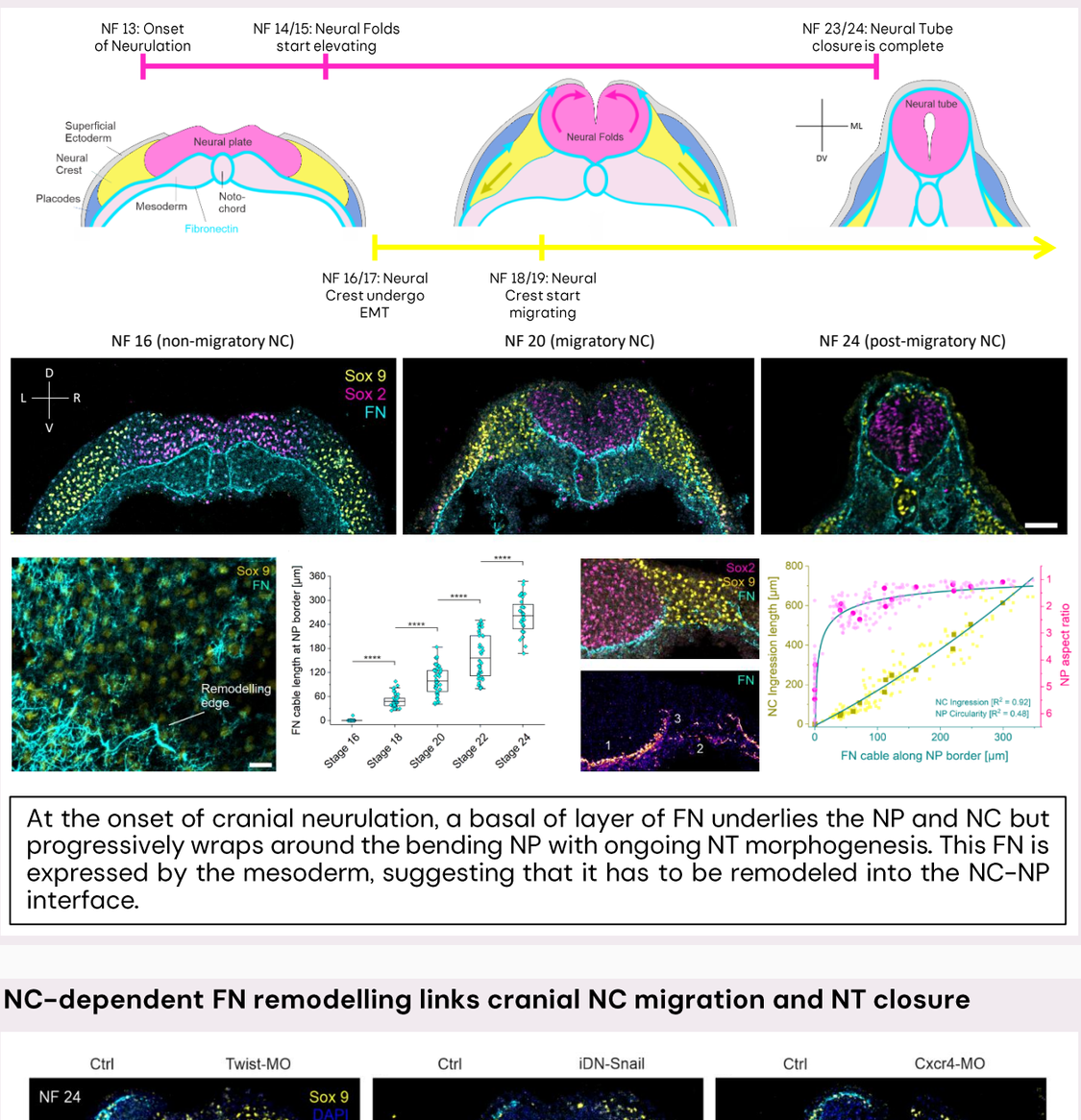
Kai Weißenbruch and Roberto Mayor

Department of Cell and Developmental Biology
University College London
Gower Street, London WC1E 6BT, UK

Summary

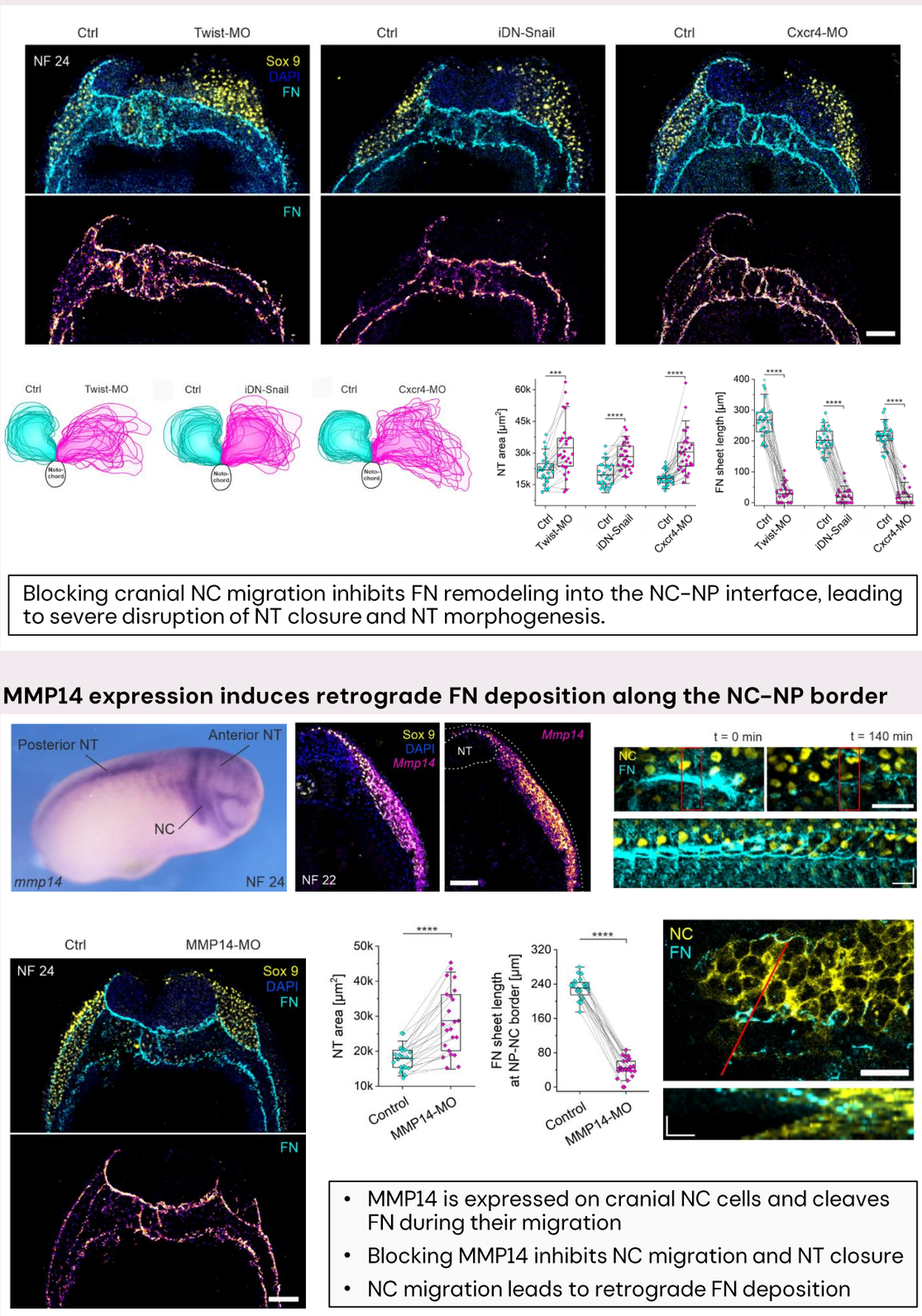
Neural Tube (NT) closure and Neural Crest (NC) migration are two major morphogenetic processes during early embryonic development, laying the foundation for the formation of the future head. Although considered functionally distinct processes, spatiotemporal overlap exists between both across many species. Using *Xenopus laevis* as a model, we show that NC migration is a prerequisite for NT morphogenesis. NC invasion into fibronectin (FN) extracellular matrix leads to FN remodelling along the NC-NT border, which is required for NT closure. To facilitate this, NC cells express the membrane-bound matrix metalloproteinase MMP14. Strikingly, NC-specific MMP14 expression is mechanosensitive and amplified by compressive forces, which arise due to neurulation itself, as the bending motion of the NT spatially confines NC cells between the underlying mesoderm and superficial ectoderm. Thus, at least in *Xenopus*, cranial neurulation is steered by a mechanochemical feedback loop, resulting from the interdependence of NT morphogenesis and collective NC cell migration.

A primary layer of FN is progressively deposited along the NC-NP border and segregates both cell populations during cranial Neurulation



At the onset of cranial neurulation, a basal of layer of FN underlies the NP and NC but progressively wraps around the bending NP with ongoing NT morphogenesis. This FN is expressed by the mesoderm, suggesting that it has to be remodeled into the NC-NP interface.

NC-dependent FN remodelling links cranial NC migration and NT closure

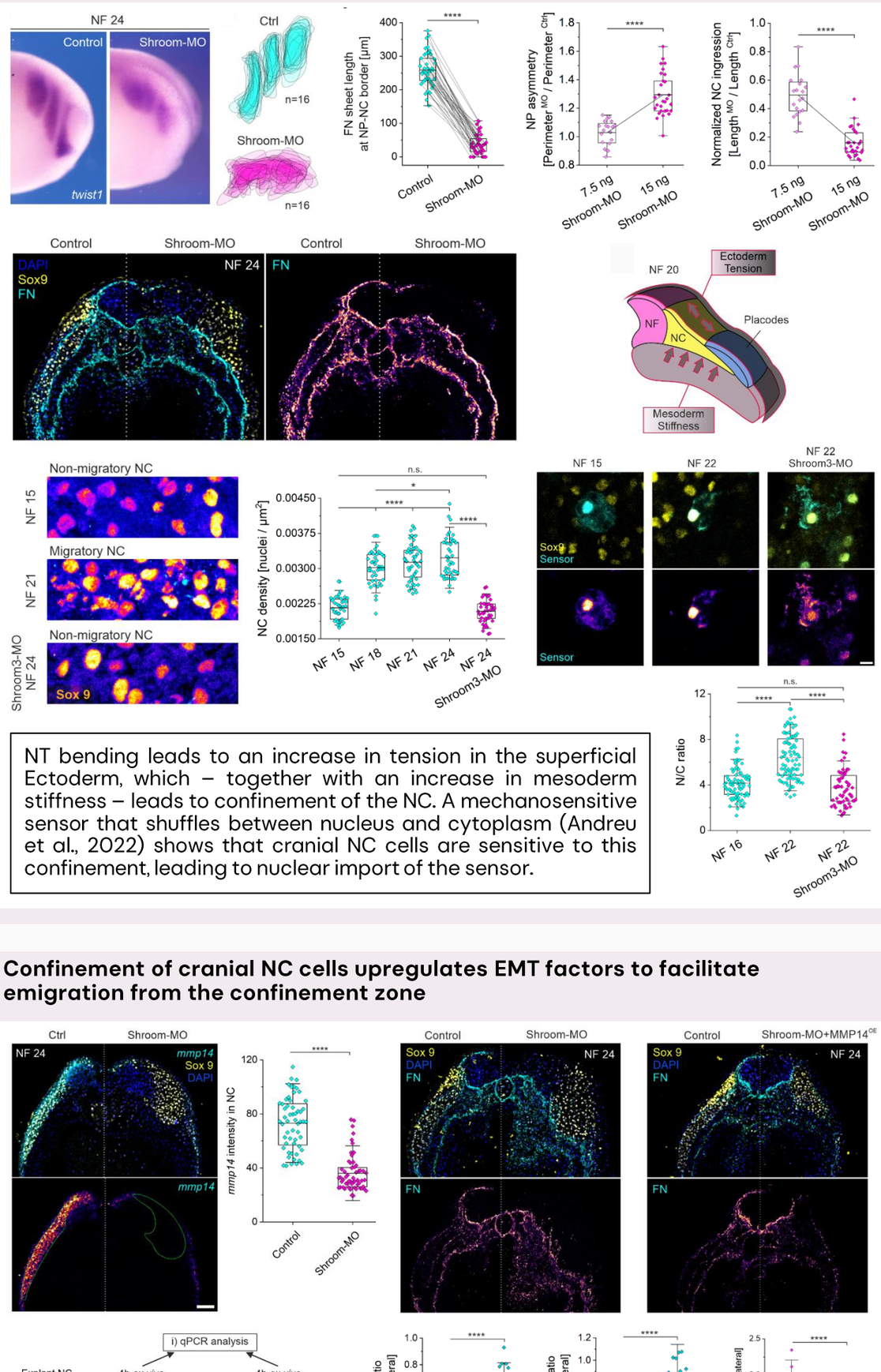


Blocking cranial NC migration inhibits FN remodeling into the NC-NP interface, leading to severe disruption of NT closure and NT morphogenesis.

MMP14 expression induces retrograde FN deposition along the NC-NP border

- MMP14 is expressed on cranial NC cells and cleaves FN during their migration
- Blocking MMP14 inhibits NC migration and NT closure
- NC migration leads to retrograde FN deposition

Bending of the Neural Plate confines mechanoresponsive cranial NC cells to induce their migration



NT bending leads to an increase in tension in the superficial Ectoderm, which – together with an increase in mesoderm stiffness – leads to confinement of the NC. A mechanosensitive sensor that shuffles between nucleus and cytoplasm (Andreu et al., 2022) shows that cranial NC cells are sensitive to this confinement, leading to nuclear import of the sensor.

Confinement of cranial NC cells upregulates EMT factors to facilitate emigration from the confinement zone

- Blocking NT bending reduces MMP14 expression in cranial NC cells
- Overexpression of MMP14 mRNA in Shroom-MO embryos partially rescues the migration defect of cranial NC cells.
- *Ex vivo* compression is sufficient to upregulate MMP14 and other EMT-related genes in cranial NC cells
- Mechanically primed (compressed) cranial NC cells are able to migrate when transplanted in migration-deficient Shroom-MO embryos

The working model: A mechanochemical feedback loop

This study is supported by grants from the Medical Research Council (MR/W001292/1 to Roberto Mayor), the Biotechnology and Biological Sciences Research Council (BB/T013044/1 to Roberto Mayor), and the Wellcome Trust (220209/Z/20/Z to Roberto Mayor).

Kai Weißenbruch. acknowledges support from the Deutsche Forschungsgemeinschaft (DFG) via the Walter Benjamin Fellowship (513518868).

DFG Deutsche Forschungsgemeinschaft German Research Foundation