

Characterising the spotty osteomalacia in Phospho1 knockout mice

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Introduction

- Recent evidence has implicated PHOSPHO1, a soluble cytosolic phosphatase, in the initiation of biomineralisation.
- Phospho1* deficient bones are less mineralised and contain smaller mineral crystals, leading to hyperostoidosis, spontaneous fractures, and bowed long bones.
- The consequences of *Phospho1* ablation on the microscale structure of mineralised bone are not yet fully elucidated: such information might help to understand the function of PHOSPHO1 in biomineralisation.

Methodology

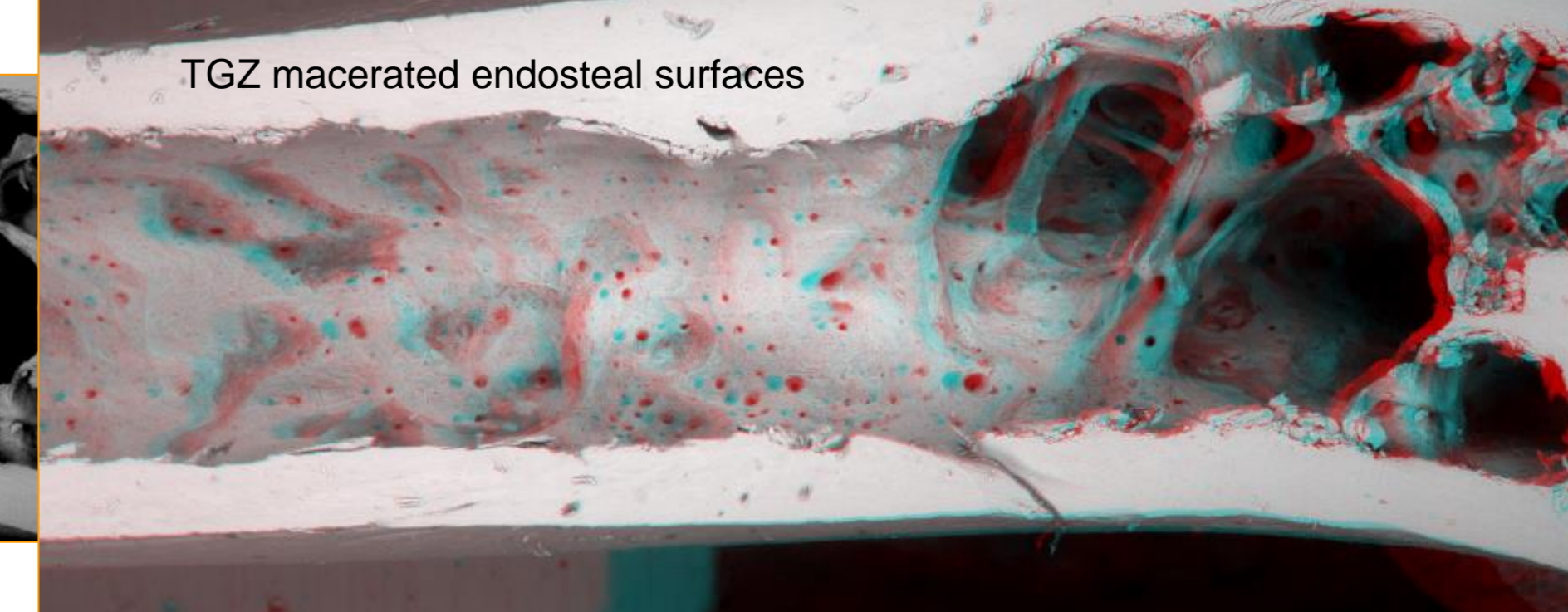
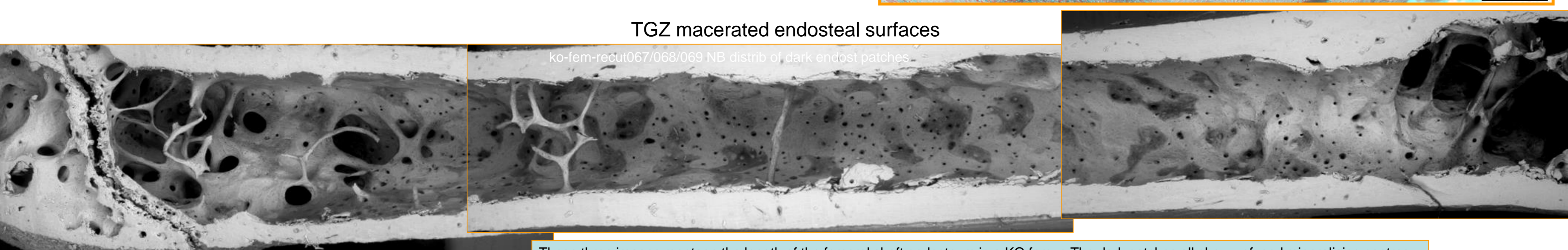
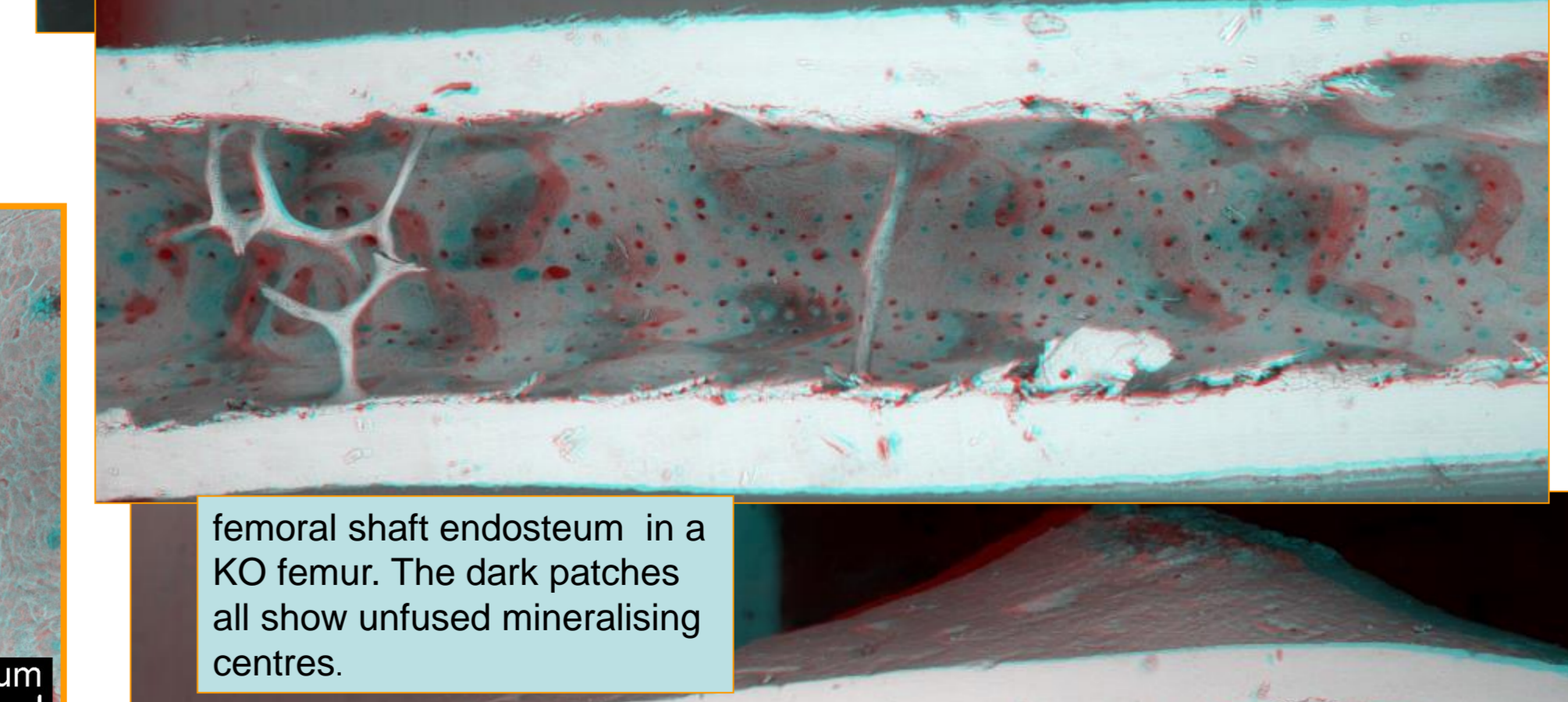
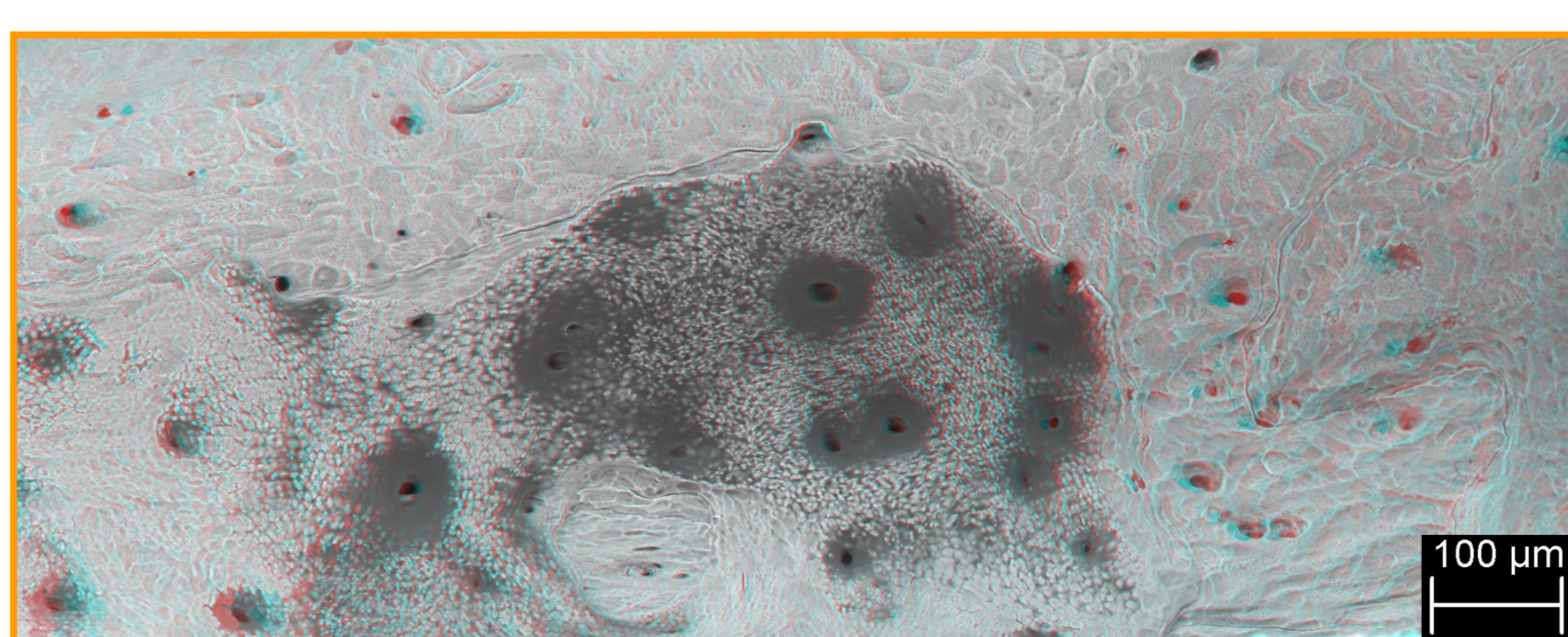
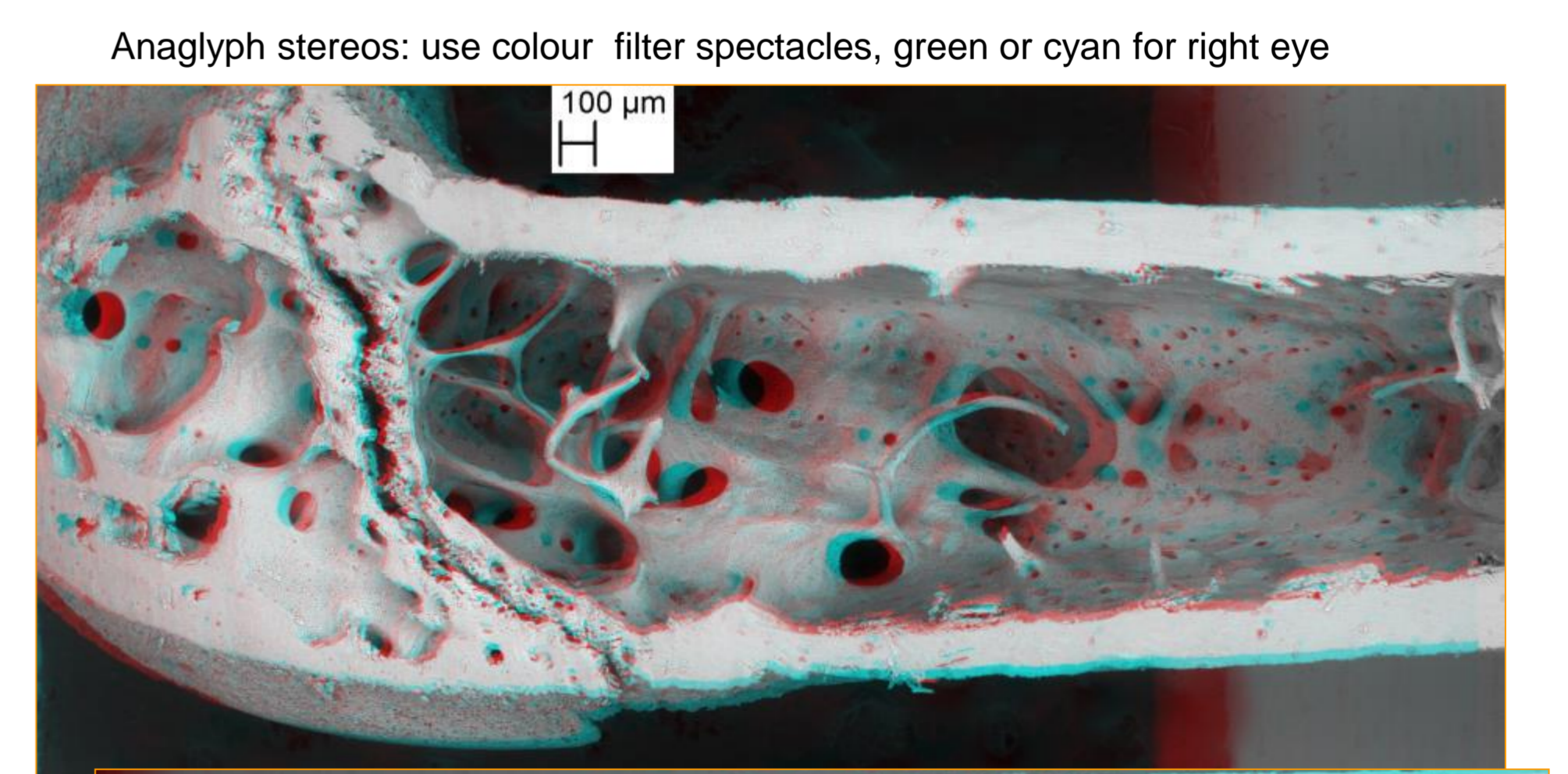
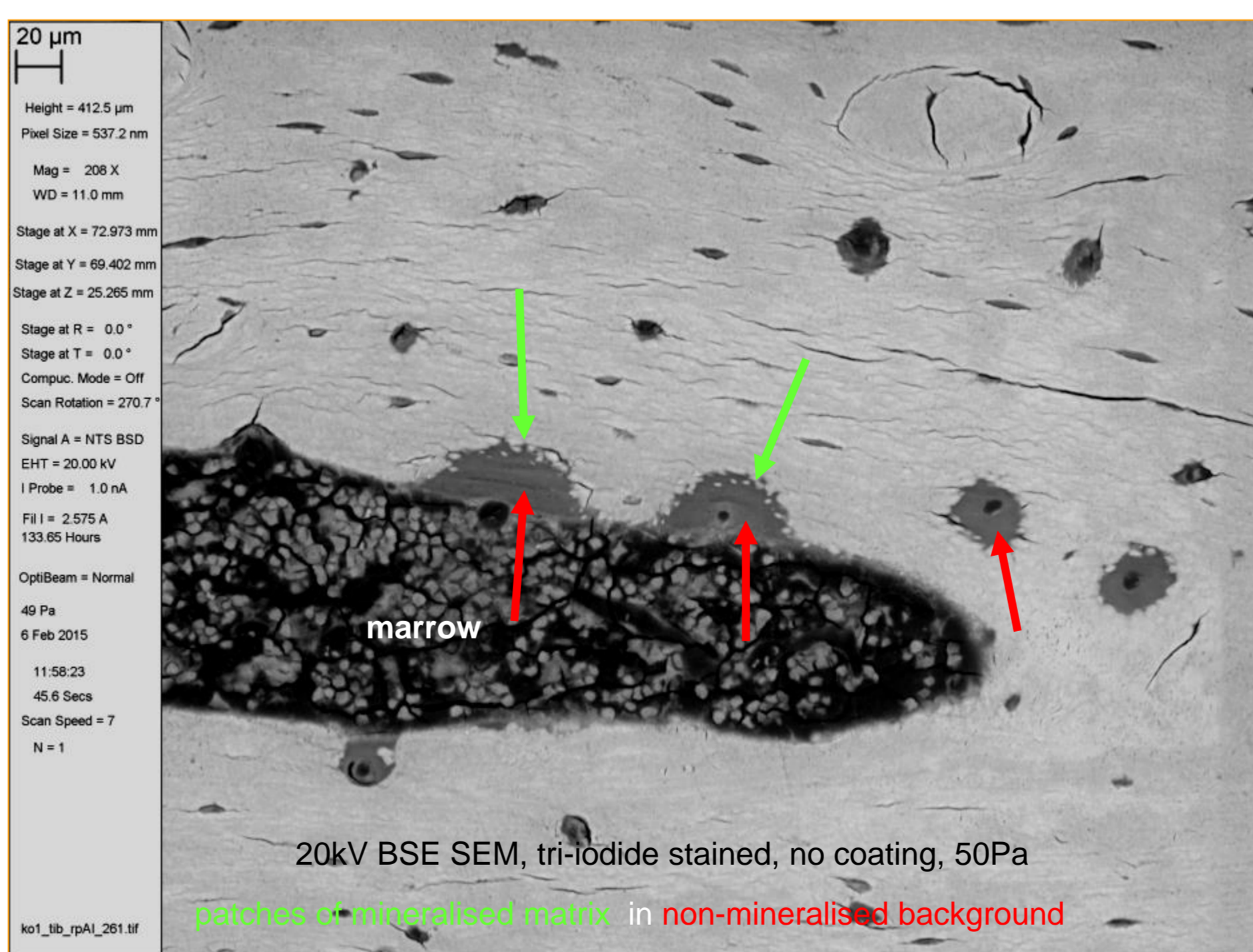
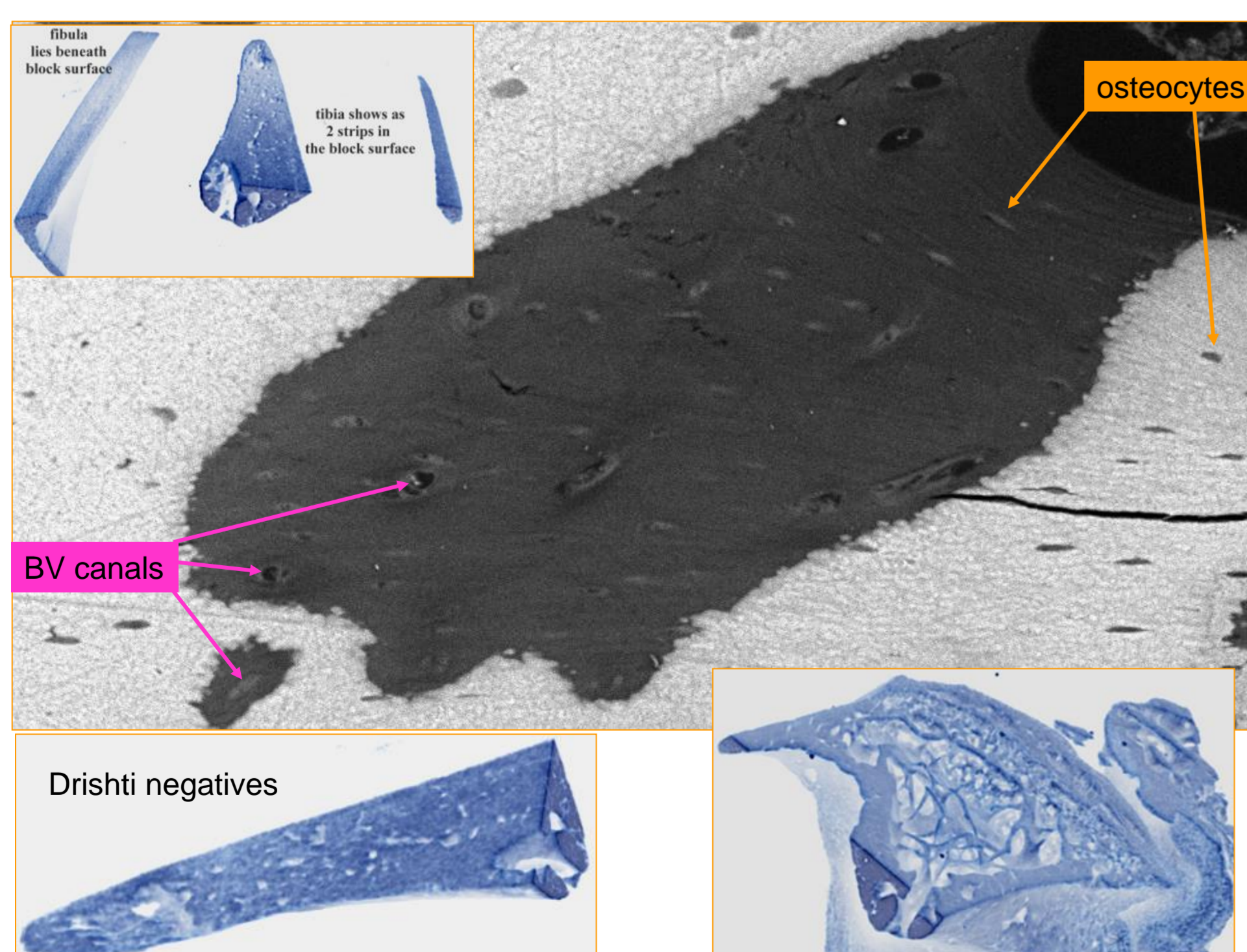
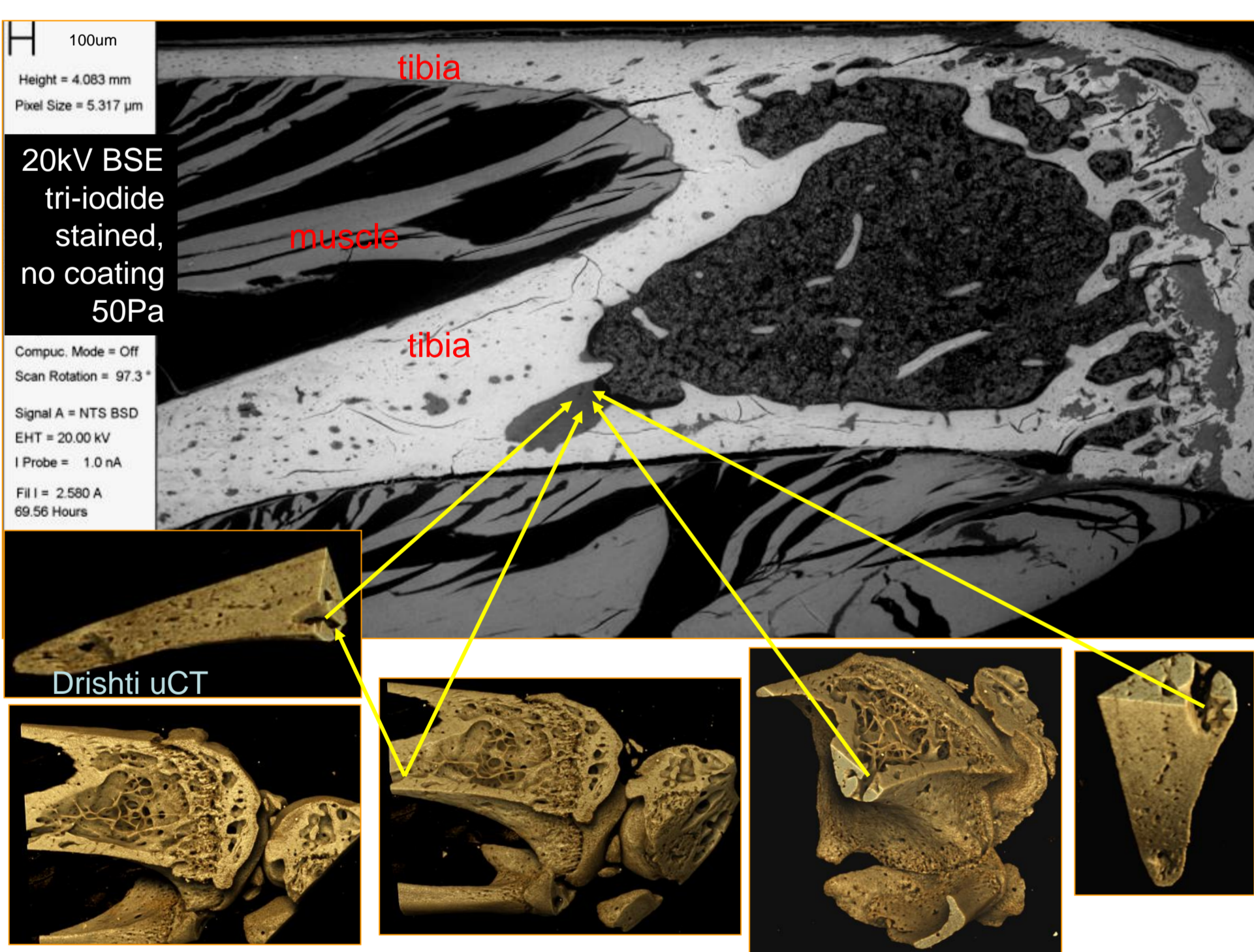
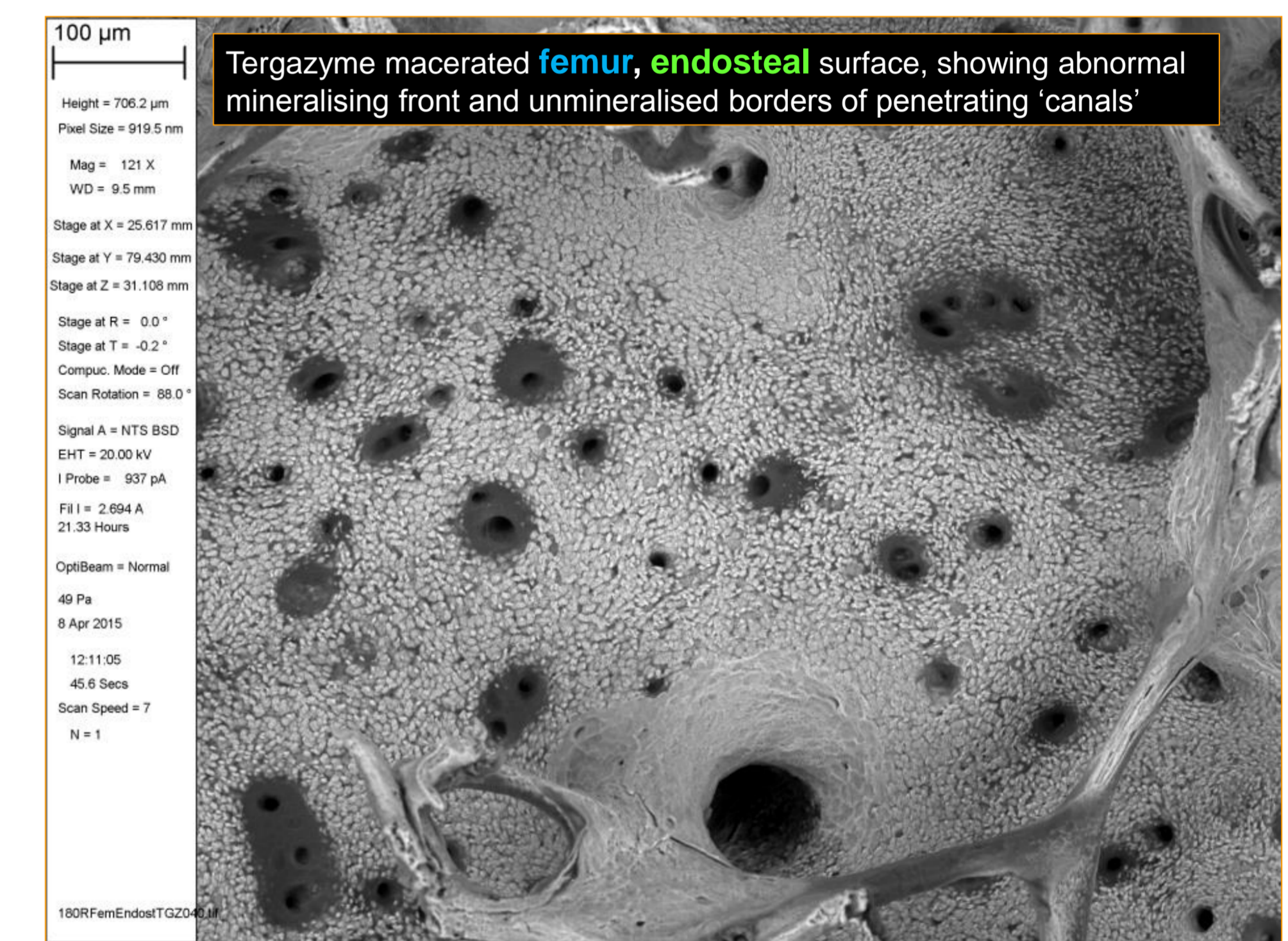
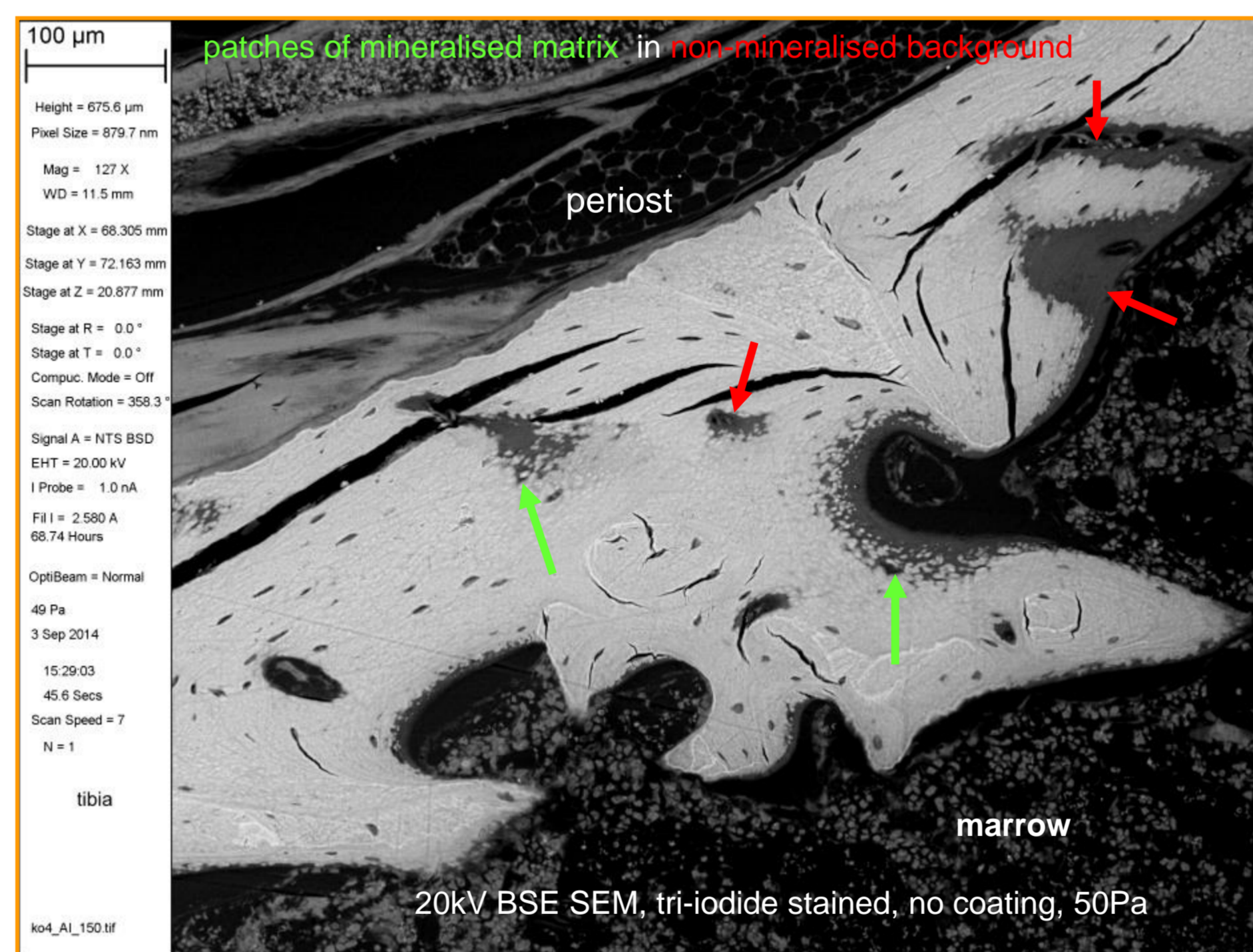
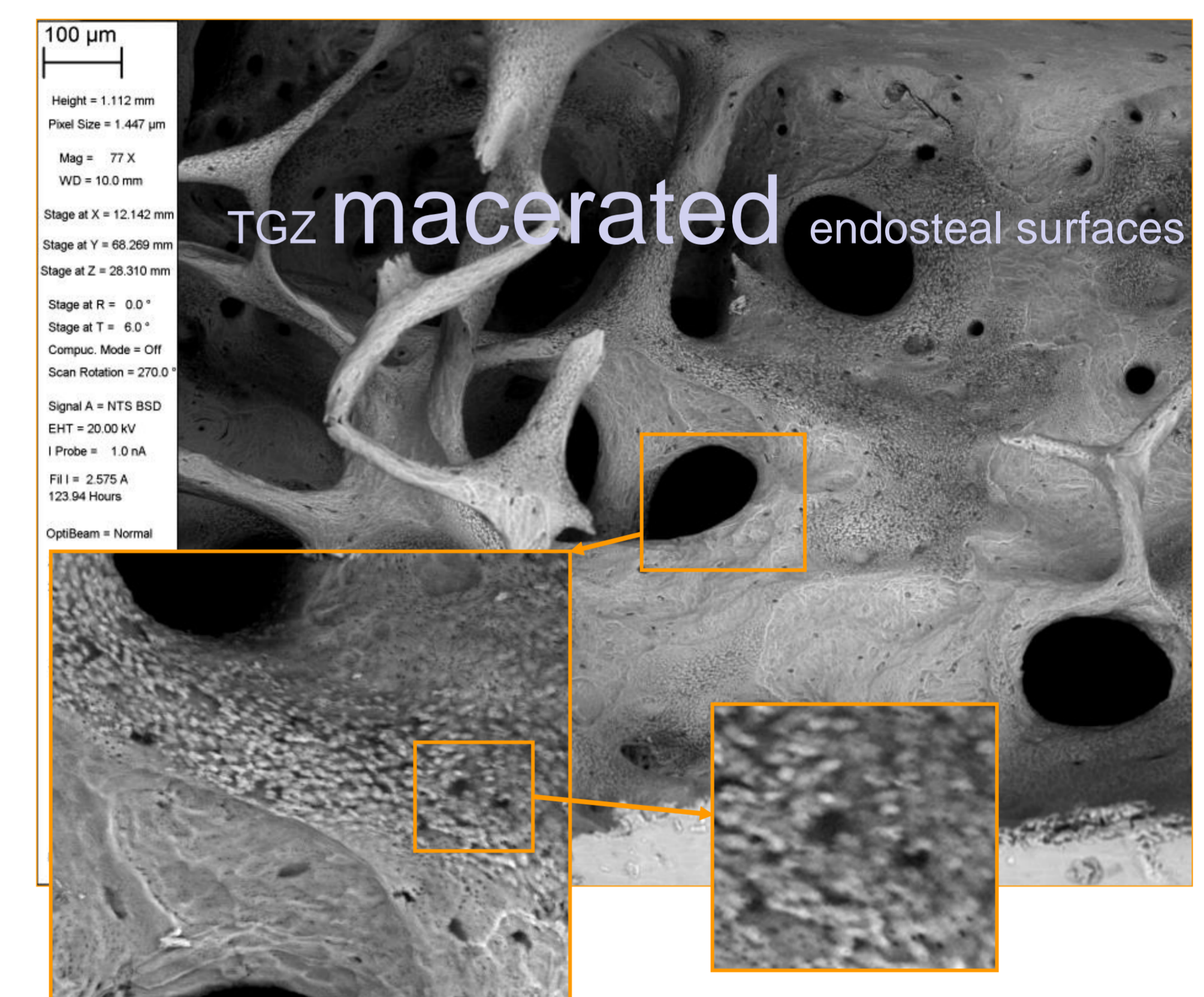
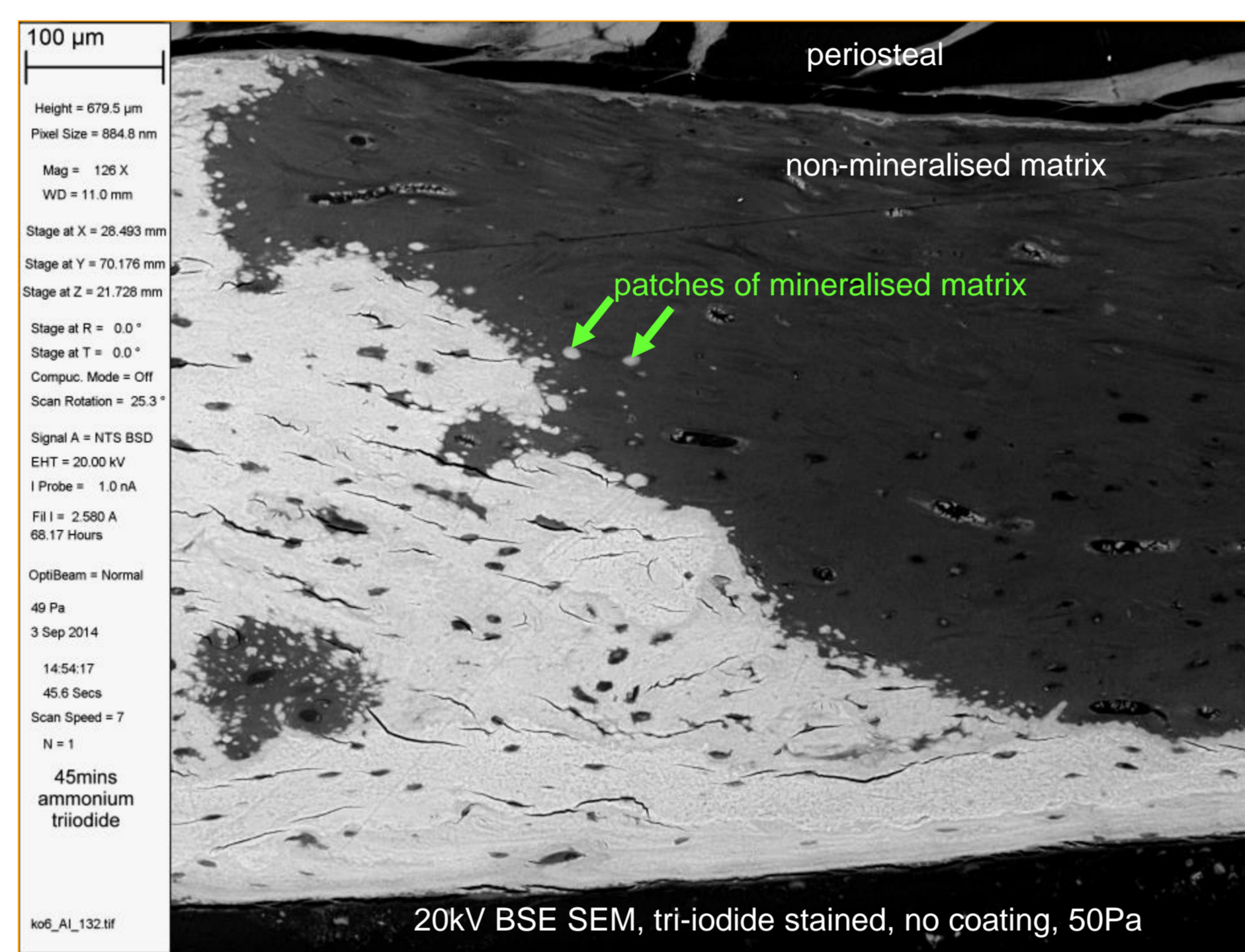
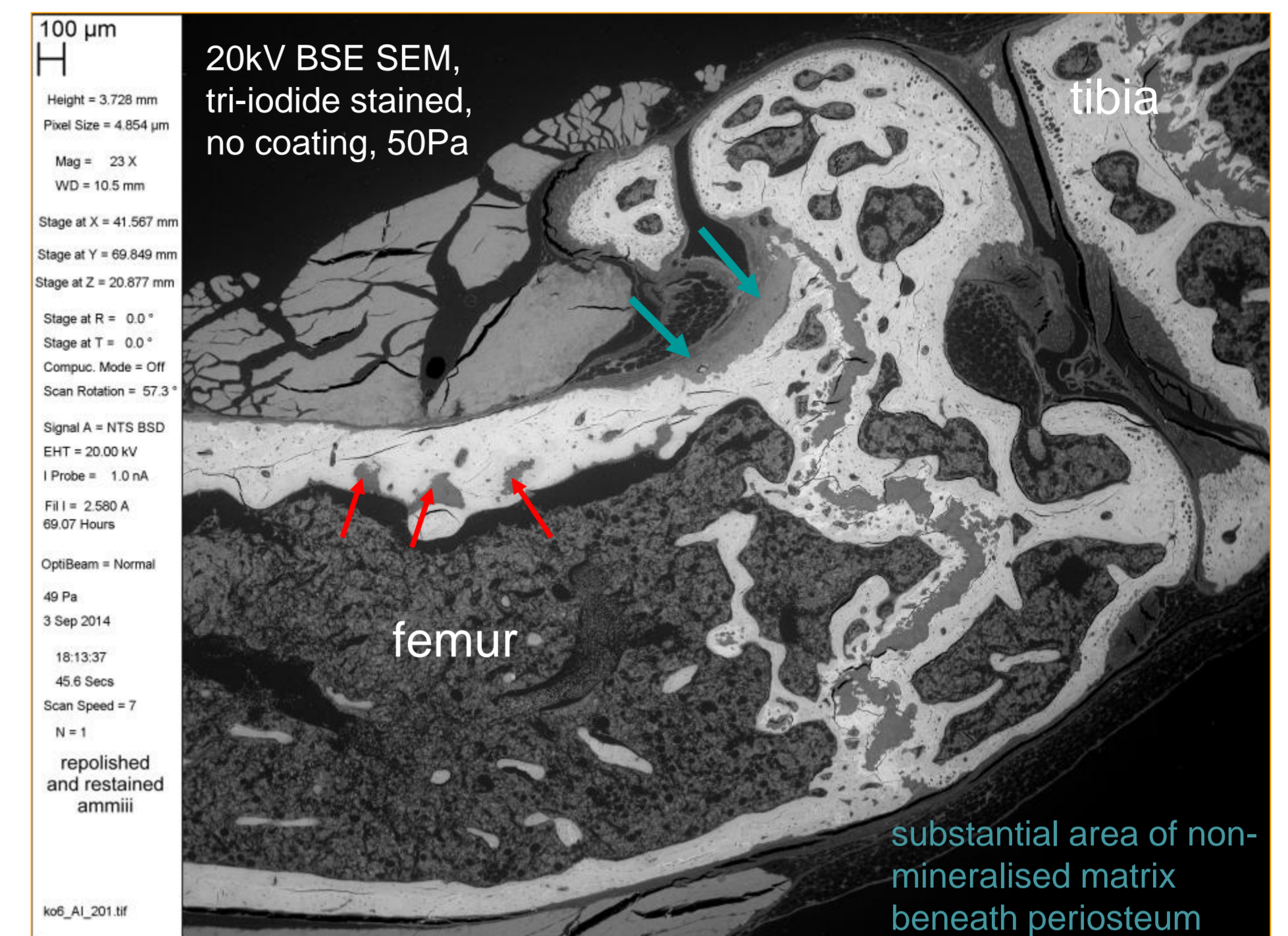
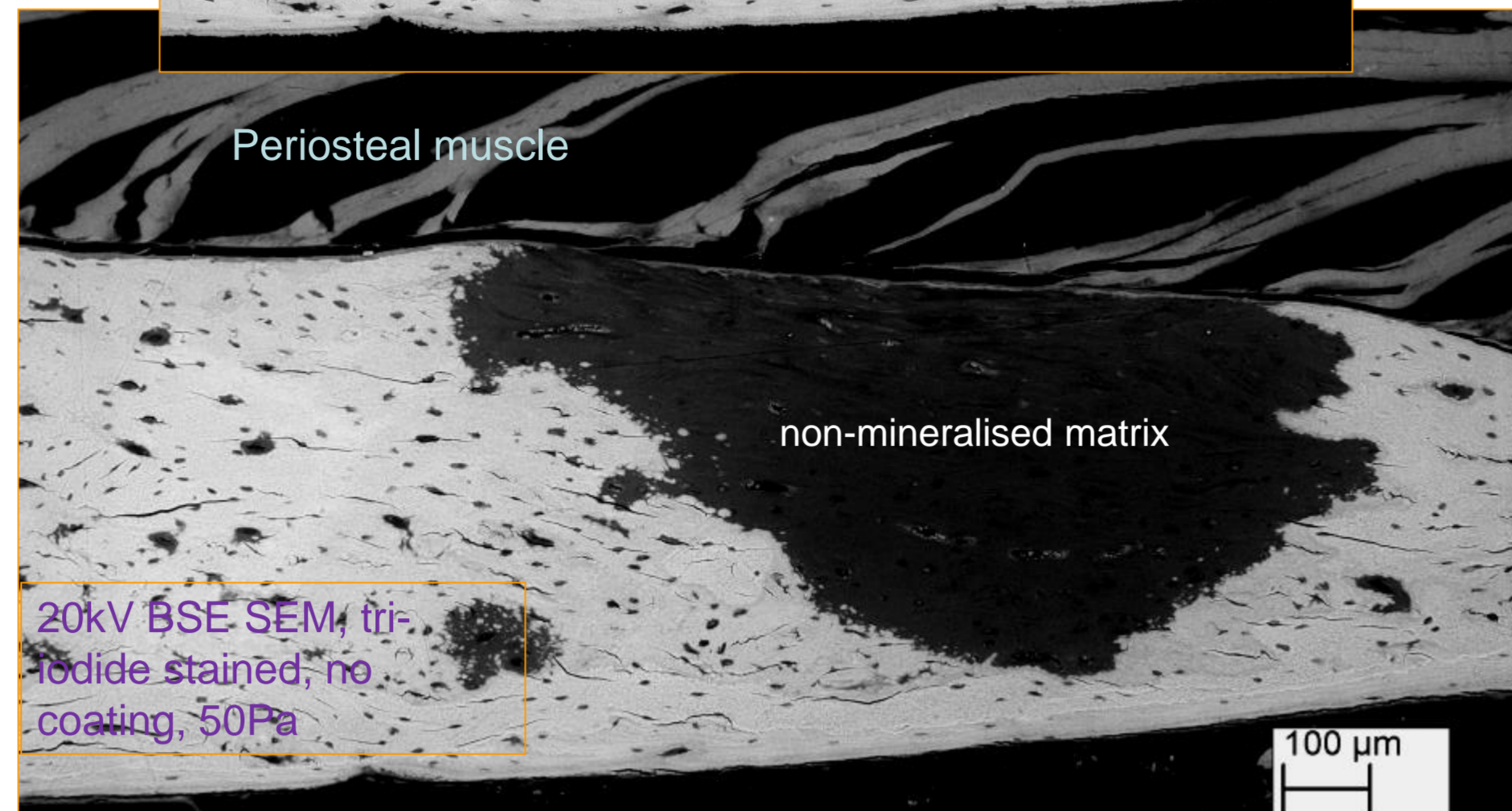
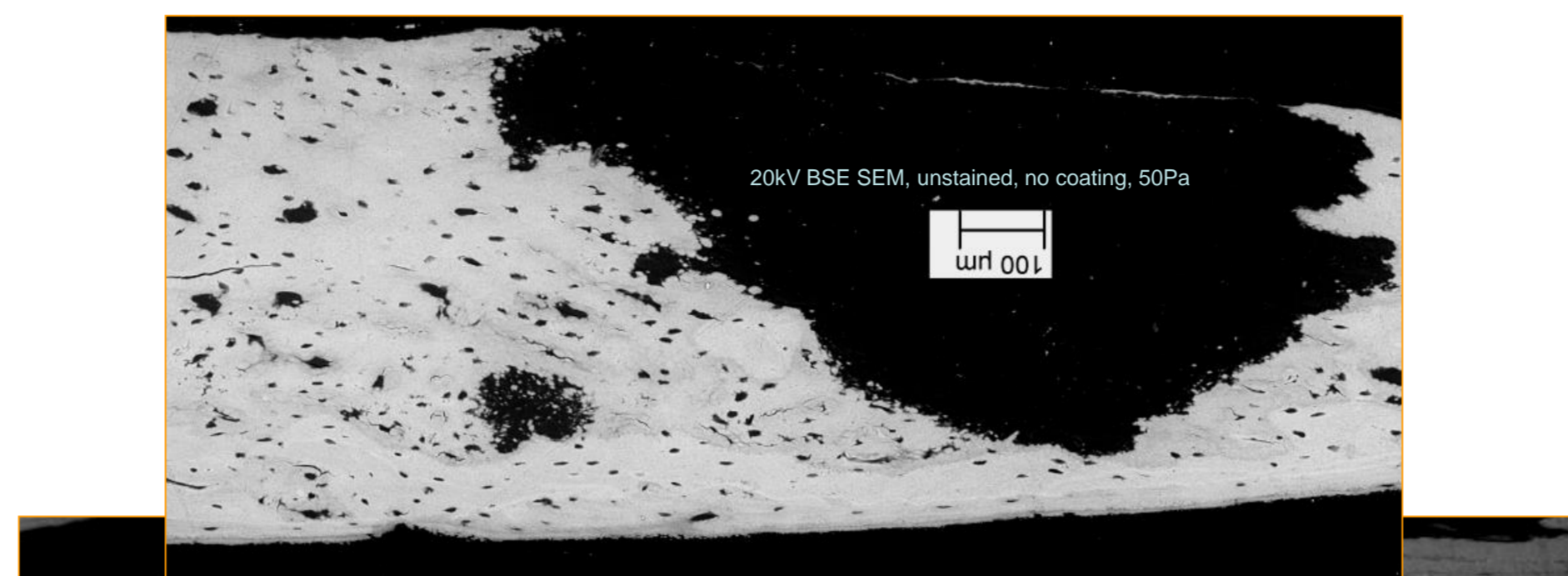
- Bones from wild-type and *Phospho1*^{-/-} mice (25-32 week-old) embedded in PMMA, cut and polished to produce near longitudinal sections.
- 20kV backscattered electron (BSE) imaging, uncoated samples, 50 Pa pressure in the Zeiss EVO MA10 SEM, revealed large patches with no mineral deposition.
- To characterise this further, block surfaces were stained with ammonium tri-iodide to reveal non-mineralised matrix and cellular components before further BSE SEM.
- For 3D characterisation, we used x-ray microtomography of whole bones before, and of trimmed PMMA blocks after SEM. We also opened bones with carbide milling tools to expose endosteal surfaces - macerated to produce 3D surfaces for study with 3D BSE SEM.

Findings

- Extensive regions of both compact cortical and trabecular bone matrix in *Phospho1*^{-/-} mice contained no significant mineral and/or showed arrested mineralisation fronts (failure of fusion of the separately mineralising micro-volumes) at trabecular, endosteal and periosteal surfaces.
- Osteoclastic resorption of the uncalcified matrix was attenuated compared with surrounding normally-mineralised bone.
- The extent and position of this aberrant biomineralisation varied considerably between animals, contralateral limbs and anatomical sites.
- The most frequent manifestation lay in the nearly complete failure of mineralisation in the bone surrounding the numerous transverse blood vessel canals in the cortices.

Conclusion

- Extensive histological osteomalacia, varying widely in extent, is found in *Phospho1*^{-/-} lower limb bones.



These three images montage the length of the femoral shaft endosteum in a KO femur. The dark patches all show unfused mineralising centres.