**Initiative C**

**Title**
Deep-mining into multi-cellular human samples: a workflow to analyse macromolecular structures in Health and Disease

**Initiators**

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<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Expertise</th>
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<tr>
<td>Peter Peters</td>
<td>Maastricht University</td>
<td>Cryo-electron microscopy, Nanoscopy, Cell Biology, organoids</td>
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<td>Jacob Hoogenboom</td>
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<td>3D correlative Light and Electron Microscopy</td>
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<td>Imaging, engineering, integration, marketing</td>
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**Description**

Cryo-electron microscopy (cryo-EM) has emerged as a powerful enabling technology to visualize the 3D structure of macromolecular complexes, providing fundamental insight in structure-function relationships needed to develop novel nanomedicines. It has resolved many novel isolated macromolecular complexes at ultra-high resolution. However, to fully understand the role of such complexes in Health and Disease, we need to study them in a complex multi-layered cell environment, such as a biopsy or an organoid.

Organoids are now used to study human physiology and pathology in a dish. They act as a potential replacement of animals in scientific research, and have been used to study disease such as cancer and infectious diseases. Typical sizes are a few hundred micrometers: 4 orders of magnitude larger than the size of important macromolecular players that can derail the development of a healthy organoid. Cryo-EM has the potential to provide deep structural and functional insight into these macromolecular player, within the context of such complex human environment.

However, next generation user-friendly high tech equipment would be needed for doing so. In this proposal, we will develop, demonstrate and validate the machinery needed to vitrify multi-layered samples, target regions of interests, trim those under cryogenic conditions, collect cryo-electron tomograms, segment these and apply sub-tomogram averaging techniques. Artificial intelligence will be used to identify regions of interest both within the original samples as well as the final tomograms, and AI-driven feedback loops will be developed to maximise throughput. If successful, our equipment will provide an unprecedented insight into life itself.

**Needed expertise**

This project will require expertise in organoid research, vitrification, multi-modal imaging, structural biology, data processing, engineering, artificial intelligence, advanced mechatronics, sociology (of the cell and between cells), industrial design and business administration.

**Contact person**

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