

Figure 4: Localization of membrane protrusions in mitochondrial outer membranes. A group of mitochondria was located in a melanoma cell that displayed membrane structures protruding from mitochondria (A). The black dots in the image represent quantum dots taken up by the cell that was used in this experiment. The boxed area is shown in (B) as a sequence of surface images collected in the process of imaging the cellular volume. (C) Another example of a mitochondrion with membrane protrusion found in the same volume. Inter-image spacing: 30 nm, in-plane pixel size 3.1 nm. Scale bar is 1  $\mu\text{m}$ .

Figure 5: Detection of melanosome distribution in cultured human melanocytes. (A) Segmented 3D representation of image stack from a cultured melanocyte cell showing the position and distribution of melanosomes (in color) within the cell body (magenta) and outside the nucleus (purple). A single 2D image is shown below the 3D image. (B–D) Selected, serial 2D cross-sections of individual segmented melanosomes (indicated by colored arrows) from (A) showing differences in internal membrane organization and pigmentation. The melanosome in column (B) has the beginnings of internal membrane organization that is further advanced in the melanosome in column (C), and completed in the melanosome in column (D). Inter-image spacing: 30 nm, in-plane pixel size 6 nm. Scale bars are 0.5  $\mu\text{m}$  in (B–D).

## APPENDIX A: SUPPLEMENTAL MATERIAL

Supplemental Movie 1: 3D image stack from MNT-1 melanoma cell interior displaying detailed view of intracellular architecture including mitochondria, Golgi and other internal membranes using in-plane pixel size of 3.1 nm, and section spacing of 20 nm.

Supplemental Movie 2: Segmented rendering of melanoma cell imaged at 30-nm resolution in the cutting direction, and in-plane spacing of 12 nm. Mitochondria are depicted in red, endoplasmic reticulum in yellow, nucleus in light purple, and the cell envelope is in grey.

Supplemental Movie 3: View into the interior of an MNT-1 melanoma cell that has taken up Quantum dot particles with a core size of  $\sim 7$  nm, imaged with in-plane pixel size of 3.1 nm, and section spacing of 20 nm. The quantum dots can be seen as bright specks in the images. Only a 100 nm wide z-stack (corresponding to six slices) of the interior is shown to reduce movie size.

Supplemental Movie 4: Morphology of mitochondria and their proximity to membranes of the endoplasmic reticulum. Membranes appear as white contours. The 3D representation of this image stack is shown in Fig. 2F. Inter-image spacing: 30 nm, in-plane pixel size 3.1 nm.