Nanoparticle Delivery to Living Cells Supported by Thermophoresis

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Thermophoresis is the motion of particles towards the colder region of a gas in presence of a temperature gradient. This effect is utilized by thermal precipitators that comprise two parallel plates of different temperatures to collect nanoparticles located in between the plates on the colder side. We have developed a thermal precipitator that is able to deposit nanoparticles onto living cells, called the Cyto-TP (Broßell et al., 2013). The first prototype placed cell monolayers at the air-liquid interface on the cold plate to allow deposition of aerosols. We showed in a proof-of-concept study, that in presence of a temperature gradient, the deposition efficiency scaled with the intensity of the temperature gradient and was enhanced, compared to when the temperature gradient was absent.

In this work, we show the next step in the development process of the Cyto-TP - the implementation of thermal precipitation in the Vitrocell 6/3 CF, a commercial air-liquid interface exposure module. This exposure module comprises a bell-shaped aerosol inlet placed circa one millimetre above the cell monolayer. With volume flow rates in the range of ml/min, nanoparticles can deposit on the cells via diffusion. However, the deposition efficiency for nanoparticles is usually very low. The deposition efficiency can be enhanced by increasing the particle size with droplet formation, enabling the deposition of the nanoparticles via impaction and gravitational settling of the droplets on the cells (Kim et al., 2013).

Thermal precipitation was enabled by mounting a metallic grid on the exit of the aerosol inlet, which can be heated up. Figure 1 shows a layout the basic concept. The temperature gradient is established from the cell monolayer to the grid at the exit of the inlet. The blue arrows show the flow direction and the black arrows show an approximation of the particle trajectories.

With a temperature gradient established between the cell monolayer (37°C) and the slightly warmer grid (40-42°C), A549 cells at the air-liquid interface were exposed to dry aerosols made of barium sulphate ($BaSO_4$) or cerium dioxide (CeO_2) nanoparticles. After exposure, the deposition efficiencies on selected samples were determined and compared to results from exposures in which the temperature gradient was absent.

Dose-response relationships were investigated for both nanomaterials. The dose was expressed in number-, surface- and mass-based metrics, whereas the response was characterized by determining cytotoxicity, cytokine release and production of reactive oxygen species (ROS).

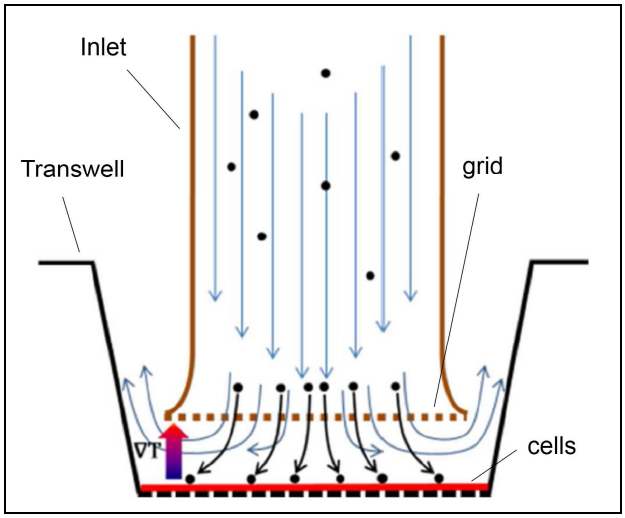

Figure 1: Thermophoresis driven deposition of particles in an insert of the Vitrocell 6/3 CF exposure module.

Broßell et al., (2013), *Journal of Aerosol Science*, **63**:75-86.
Kim et al., (2013), *Toxicol. In Vitro*, **27**(1): 164–173