CONTROL ID: 2500142

TITLE: Design and development of nanomedicines to treat atherosclerosis: a cross platform head-to-head theranostic study

PRESENTER: Amr Alaarg

ABSTRACT BODY:

Abstract Body: Background: Atherosclerosis is a chronic inflammatory disease of the large arteries and a leading cause of death worldwide. Macrophages are key players in the progression of atherosclerosis and are a compelling target for disease management [1]. Statins, HMG-CoA reductase inhibitors, exhibit anti-inflammatory and anti-proliferative pleiotropic effects [2]. Using a nanomedicine approach these effects can be amplified [3].
Here, we systematically study three different statin-loaded nanoparticles in atherosclerotic apoE -/- mice. Since the nanomedicines also contain diagnostic probes in addition to the encapsulated drug, we can use powerful imaging modalities like positron emission tomography with computed tomography (PET/CT) and near-infrared fluorescence (NIRF) imaging to follow the fate of the theranostics nanoparticles.

Methods: Simvastatin loaded high-density lipoprotein ([S]-rHDL), polymeric nanoparticles ([S]-PN), and liposomes ([S]-lip.) were developed. The three formulations were characterized by transmission electron microscopy (TEM), dynamic light scattering (DLS) for mean size and polydispersity (PDI), as well as for drug entrapment efficiency (EE%) by high performance liquid chromatography (HPLC). The effect of the three formulations on RAW 264.7 macrophage viability was evaluated in vitro. For multimodal imaging, Cy5.5 phospholipid (for NIRF imaging) and desferrioxamine (DFO)-phospholipid (for ^{89}Zr-labeling and PET imaging), were included in the [S]-rHDL and [S]-lip. formulations, while for [S]-PN, Cy5.5 and DFO were covalently conjugated to the polymeric nanoparticles. In apoE -/- mice, the nanoparticles were injected i.v. 24 hours before performing in vivo PET/CT. The radioactivity and dye distribution were assessed by gamma counting, autoradiography and NIRF imaging ex vivo.

Results: The [S] formulations were successfully prepared and had average sizes < 100 nm, with a narrow PDI, and EE > 60% (Fig.1B and C). [S]-PN shows a more potent effect on RAW 264.7 cell viability with IC_{50} of 5 μM, compared to IC_{50} of 10 μM for [S]-HDL and >25 μM for [S]-L (Fig. 1D). Distinct biodistribution profiles for the three nanoparticles were observed by PET/CT imaging, which was corroborated by ex vivo gamma counting (Fig 1E and F). [S]-PN accumulates to a higher degree in spleen and liver compared to [S]-lip. and [S]-rHDL, while the latter [S]-rHDL accumulates to a higher extent in the kidneys. [S]-lip. shows slightly higher concentration in blood at 24 hours. Radioactivity concentration in the aortas was similar for the three nanoparticles. Ex vivo NIRF imaging and autoradiography demonstrated co-localization of ^{89}Zr with Cy5.5 signal in the aortas (Fig. 1G and H).

Conclusions: We have developed three [S]-loaded nanoparticle platforms and labeled them for imaging with PET and NIRF. This allowed us to non-invasively visualize their distinct biodistribution profiles and to assess their plaque targeting ability. Studies are ongoing to evaluate the impact of platforms on the therapeutic outcomes.

References

1.Schulz & Massberg . Sci. Transl. Med. **2014**

2.Tang et al. Sci. Adv **2015**

3.Mulder et al. Sci. Transl. Med. **2014**

AUTHORS (LAST NAME, FIRST NAME): Alaarg, Amr[1, 2]; Perez Medina, Carlos[1]; Tang, Jun[4]; Fay, Francois[1]; Zhao, Yiming[1]; Sanchez-Gaytan, Brenda[1]; Reiner, Thomas[4]; Fayad, Zahi A.[1]; Kok, Robbert J.[5]; Metselaar, Josbert M.[2]; Mulder, Willem J.[3]; Storm, Gert[5, 2]

INSTITUTIONS (ALL):

1. Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, United States.
2. Department of Biomaterials Science and Technology, MIRA Institute for Biomedical Technology and Technical Medicine, Enschede, Netherlands.
3. Radiology, Icahn School of Medicine at Mount Sinai, New York City, NY, United States.
4. Radiology, Memorial Sloan Kettering Cancer Center, New York City, NY, United States.

5. Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS) , Utrecht, Netherlands.
(No Image Selected)