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Targeted CT contrast agents for molecular imaging of cancer based on cathepsins' elevated activity

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In this study, we generated new classes of cathepsin targeted probes based on different sizes of GNP for functional CT imaging of cancer. ABPs are small molecules that have been engineered to covalently modify enzyme targets in an activity dependent manner. These novel probes enable detection of the elevated cathepsin activity within cancerous tissue using a CT instrument, thus creating a direct link between imaging signals and biological process. X-ray CT instruments are among the most available, efficient and cost-effective imaging modalities in hospitals. The field of CT molecular imaging agents is emerging relying mainly on detection of gold and bismuth nanoparticles, iodine and gadolinium labeled compounds. However, the low sensitivity of CT scanners to contrast reagents in comparison to other imaging modalities makes this a challenging task.

We have generated chemical scaffolds of GNP-ABPs with combination of different protective layers of PEG studied in terms of length (3 or 5 kDa) and ratio (10, 50, and 100%). Efficiency of targeting moiety, based on different PEG coatings, was evaluated for tumor accumulation and enzyme inhibition effectiveness. After chemical and biochemical evaluations we selected the most potent and stable probes to proceed to non-invasive imaging in cancer mice models. Micro-CT scans performed at various time points post probe injections showed significantly higher CT contrast from the tumor injected with targeted (T) GNP compared to non-targeted (NT) particles. Contrast agent concentrations and sub-cellular localization within the tumor cells was detected using ICP-MS and transmission electron microscopy (TEM). In conclusion, we were able to generate molecular imaging probes that report on cathepsin activity within tumors bearing mice using a CT modality.

Biography

Darya Tsvirkun began her career oriented towards the development and evaluation of PET ^{11}C-tracers for imaging and quantification of myocardial perfusion, receiving the Dean's Excellence Award. Her contemporary research focuses on development and synthesis of new libraries of activity based probes (ABPs) labeled with various CT contrast agents for cysteine proteases for cancer imaging. This project will significantly advance the molecular imaging field that is rapidly developing worldwide by creating dramatically enhanced imaging reagents. Having tools that can allow non-invasive imaging of protease activity *in vivo* is a powerful research tool. The use of ABPs to investigate biological regulation is an exceptionally powerful method as it enables real time monitoring of enzymatic activity and localization *in vivo*. Most importantly, CT probes that identify cathepsin activity can be widely applied to image human tumor location and grade, and can also be used to determine therapy efficacy.

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