Contribution ID: **15** Type: **not specified**

Alpha-particle nanotherapeutics against recurrent, chemoresistant Triple Negative Breast Cancer

Metastatic and/or recurrent chemoresistant Triple Negative Breast Cancer (TNBC) is currently incurable. TNBC accounts for 12-17% of breast carcinomas with the lowest 5-year survival rates among all breast cancer patients due to high proliferation and reoccurrence outside the breast combined with lack of effective targeted therapeutic modalities. For such cases, key to the progression of the disease is the choice of therapeutics which need to be both tumor selective and potent against cancer cells. Given the vast heterogeneity of the disease identified as TNBC, this choice could be a major challenge.

Alpha-particle radiopharmaceutical therapy has already been shown to be impervious to most resistance mechanisms. However, historically, the short range of α-particles in tissue has hampered the use of α-particle emitters for the treatment of solid tumors; the diffusion-limited penetration depths of radionuclide carriers combined with the short range of α-particles result in only partial tumor irradiation. This is quite unfortunate given the killing power of α-particles.

In the past we have had remarkably promising initial results in effectively controlling the growth of TNBC tumors in vivo and in prolonging survival using α-particle nanoradiotherapy (lipid nanoparticles loaded with α-particle emitters)[1]. The key design element of these nanoradiotherapeutics to enable uniform tumor irradiation, was to engineer nanoparticles ('releasing' NPs) that upon their uptake by tumors they release highly-diffusive forms of the α-particle emitters within the tumor interstitium, resulting in uniform distribution of emitters within tumors, and uniform irradiation of tumors without - as we demonstrated - additional toxicities.

In this work, to maximize the fraction of emitted energy retained by tumors we designed NPs ('adhering' NPs) that, in addition to interstitial release, they adhere on the extracellular matrix and on cancer cells but DO NOT become internalized; this has the potential to enable slower clearance of NPs from tumors increasing the time-integrated delivered doses.

We systematically varied the release and adhesion properties on NPs loaded with the alpha-particle emitter Actinium-225 and present the effect of these properties on the dose response of large TNBC MDA-MB-231 spheroids used as surrogates of solid tumors' avascular regions. Preliminary data on SCID mice demonstrate the translational potential of this approach on controlling the growth rate of orthotopic TNBC xenografts and on delaying the spreading of spontaneous metastases.

Our findings demonstrate the potential of this 'diffusion-based' approach to lead to a new class of α-particle nanoradiotherapy as a platform technology to control tumor growth and/or spreading for a variety of difficult-to-treat tumors.

References

[1]. Zhu, C.; Sempkowski, M.; Holleran, T.; Linz, T.; Bertalan, T.; Josefsson, A.; Bruchertseifer, F.; Morgenstern, A.; Sofou, S. Alpha-particle radiotherapy: For large solid tumors diffusion trumps targeting. Biomaterials 2017, 130, 67-75.

Funding Agency

American Cancer Society, National Science Foundation, Elsa Pardee Foundation

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Presentation Type

Contributed Oral

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