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Preclinical development of folate receptor-targeted radiopharmaceuticals for ovarian cancer

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Ovarian cancer represents the most common cause of gynecological cancer death with a 5-year relative survival rate of 29% for patients diagnosed at a metastasized stage (1). The development of new treatment options is urgently needed to treat patients with refractory disease and platinum-resistance (1).
The folate receptor (FR) is overexpressed on the cell surface of a variety of tumors including ovarian cancer (>80%), being therefore a promising target for radiotheragnostics (2). The vitamin folic acid has been chemically derivatized for the delivery of radionuclides to FRpositive tumors. The overexpression of FR in the kidneys has been, however, the main obstacle towards the development of effective and safe radiofolates for therapeutic applications.
Different strategies have been used to increase the accumulation of radioactivity in the tumor and dicrease the kidney uptake (3). At PSI, a radiofolate was functionalized with an albumin-binding entity (AB) for the first time, which resulted in a reduced glomerular filtration of the radioligand and, consequently, a 6-fold higher tumor-to-kidney ratio, enabling the first therapy study in mice with a 177Lu-AB-folate. Further modification in the linker part led to even superior pharmacokinetic properties. The developed radiofolates were radiolabeled also with 47Sc and 44Sc as well as with 161Tb and 155Tb, potentially enabling the realization of the radiotheragnostic principle.
Based on the results reached so far, further pharmacokinetic optimization is necessary and studies are ongoing at PSI to develop safe and effective radiofolates for the management of ovarian cancer patients.

References:

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2. Low PS et al., Curr Opin Chem Biol. 2009;13:256-262.
3. Siwowska K et al., Q J Nucl Med Mol Imaging. 2015;59:269-286.

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