Brief Report

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Archives in Cancer Research
ISSN 2254-6081

2016
Vol.4 No.3:95

DOI: 10.21767/2254-6081.100095

Specific Accumulation of a Cell Penetrating Peptide Targeting AAC-11 in Melanoma Tumors

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Received: 21 July 2016; **Accepted:** 25 July 2016; **Published:** 30 July 2016

Citation: Kotula E, Jagot-Lacoussiere L, Bruzzoni-Giovanelli H, et al. Specific Accumulation of a Cell Penetrating Peptide Targeting AAC-11 in Melanoma Tumors. Arch Can Res. 2016, 4: 3.

Brief Report

Melanoma is the most serious and potentially dangerous form of skin cancer with a rapid increase in prevalence, especially among western countries. The prognosis for patients with the more advanced form of the disease, metastatic melanoma, remains poor with survival rates ranging from 6.7% to 8% at 5 years, and a median survival of 6 to 9 months [1]. Therefore, there is a clear unmet clinical need to identify new drugs to combat melanoma.

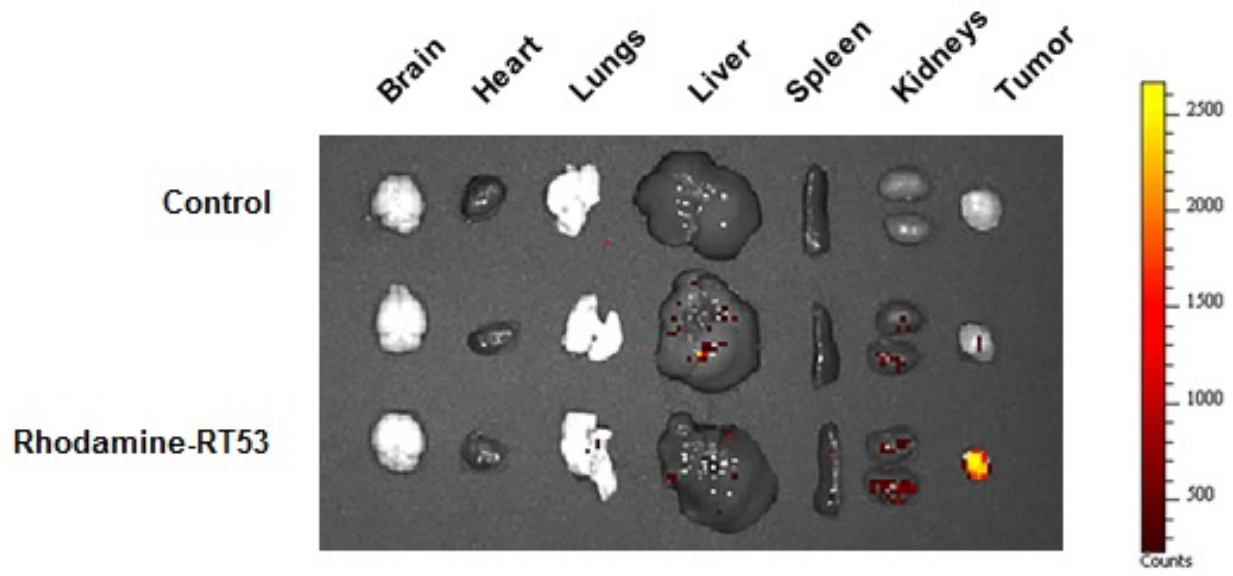

Figure 1 Mice bearing subcutaneous C8161 melanoma tumors were injected IP with either saline solution (top), rhodamine-labelled control peptide (middle) or wild-type peptide (bottom) (5 mg/kg). 1 h post injection, the mice were dissected and the excised organs imaged using an IVIS 100 imaging system (Xenogen).

The survival protein AAC-11 has previously been shown to be overexpressed in multiple cancer cells, including melanoma, and contribute to tumor invasion and metastases [2]. We and others have shown that AAC-11 is critically involved in tumor survival, through inhibition of apoptosis, by inhibiting Acinus–mediated DNA fragmentation and in an E2F-dependent manner [3,4]. Silencing of AAC-11 sensitizes tumor cells to chemotherapeutic drugs whereas its overexpression drastically increases tumor cells migration and invasiveness [3,5]. Recently, AAC-11 has been identified as a novel immune escape gene in tumors that promotes immune resistance to antigen-specific T cells [6]. Thus, inactivation of AAC-11 might constitute an attractive approach for developing cancer therapeutics.

AAC-11 is involved in multiple protein-protein interactions [3,7,8]. Recent data indicate that the heptad leucine repeat domain of AAC-11 is crucial for its biological functions, probably by acting as a protein-protein interaction module [3,9-11]. Therefore, targeting the heptad leucine repeat domain of AAC-11 might prevent its binding to its protein partners, thus inhibiting AAC-11 function as signal transducer.

We have developed a cell penetrating peptide, called RT53, spanning the heptad leucine repeat region domain of AAC-11 (residues 363-399) fused at the N-terminus to the transmembrane-penetrating sequence penetratin that exhibits selective cytotoxicity toward cancer cells, but not normal cells. RT53 can induce membranolysis of cancer cells, leading to rapid, necrotic death, probably through its selective interaction and accumulation in cancer cells plasma membranes, suggesting binding with a membrane partner(s) that is absent or minimally present in the membranes of untransformed cells [12]. Moreover, RT53 was able to inhibit tumor growth *in vivo* in human melanoma xenograft models, BRAF wild type and V600E mutant, with limited to non-existent off-target toxicity [12].

To better understand the *in vivo* performance of RT53, we studied the bio-distribution of rhodamine-labelled wild-type RT53 and a control peptide in which in which two conserved leucines were substituted by glycines [12] in nude mice bearing subcutaneous C8161 human melanoma tumors with an IVIS imaging system (Xenogen). Very interestingly, efficient homing and accumulation of the fluorescent conjugate in the tumor was clearly evident at 1h postadministration for the wild-type peptide, but not the control peptide **(Figure 1)**. These results indicate that RT53 is able to target and accumulate in melanoma tumors *in vivo*.

In conclusion, our data demonstrate that the RT53 exhibits potentially desirable features as novel anticancer class of drug in melanoma and constitutes a promising anti-cancer molecule worthy of further evaluation and development.

Acknowledgement

This work was supported by the INSERM and a grant from INSERM Transfert and SATT IDF Innov.

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