Biological activity of Pyrrole-Imidazole polyamides *in vivo*.

Thesis by
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ABSTRACT

This thesis focuses on biological activity of pyrrole-imidazole polyamides *in vivo*. The work presented includes experiments underlining sequence selectivity of these compounds in living cells and potential methods to improve it. A large fraction of this thesis is devoted to activity of Py-Im in murine models of cancer. We investigated the pharmacokinetics and biodistribution of two compounds – targeted to 5'-WGGWCW-3' and 5'-WTWCGW-3' sequences – and characterized their activity by measuring their effects on tumor growth, gene expression *in vivo* and in tissue culture, and their effects on physiology of tumors. The initial theoretical studies suggested that a large fraction of genomic sites are bound by Py-Im polyamides non-specifically and experimental data shows that the programmed binding sequence is not a sole determinant of the patterns of gene regulation. Despite the likely presence of non-specific effects of Py-Im polyamides in living cells, *in vivo* administration of Py-Im polyamides resulted in tolerable host toxicity and anti-tumor activity. Py-Im polyamide targeted to Estrogen Receptor Response Element showed downregulation of ER-driven gene expression in tumor cells, while the compound targeted to hypoxia response element reduced vascularization of tumors and their growth rate, induced apoptosis of cells in hypoxic areas and reduced expression of proangiogenic and prometastatic factors. Further studies, showed that polyamides distributed to many of the tested tissues and their FITC-conjugates showed nuclear uptake. The gene expression effects were also present in murine tissues, such as liver and kidneys, indicating a potential for use for Py-Im polyamides in non-cancerous diseases.

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