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Novel anti-cancer binary system activated by bacteriophage HK022 integrase

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Gene therapy is a promising tool for cancer therapeutics. However, a major obstacle that persists is the lack of specificity of the expressed toxic gene against cancer cells. Binary systems based on site-specific recombination are one of the most effective potential approaches for cancer gene therapy. In these systems, a cancer specific promoter expresses a site-specific recombinase/integrase that in turn controls the expression of a toxin gene. We have developed a new HK022 bacteriophage integrase (Int) based binary system that activates a diphtheria toxin (*DTA*) gene expression specifically in cancer cells (Fig 1. A). The efficiency, and specificity of the system were assessed *in-vitro* and *in-vivo* in a lung cancer mouse model. The system presents a significant efficiency and specificity in series of criteria. Strikingly, employment of the developed system to treat mice with lung cancer demonstrates significantly increased longevity (Fig.1 B). The molecular factors that contribute to the system specificity will be described.

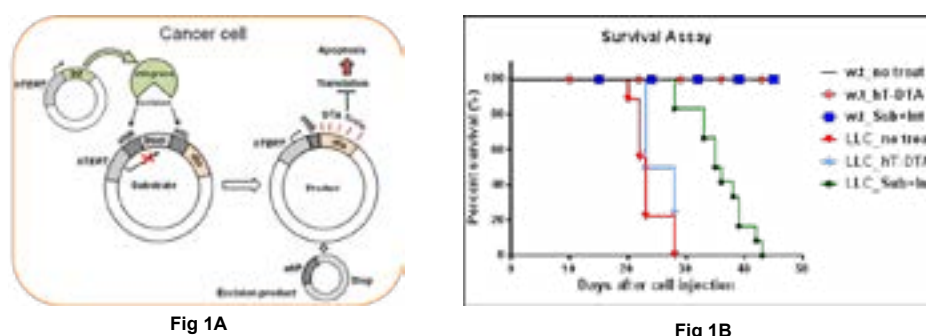


Figure 1: A. Scheme of the Int-based binary system. The recombination substrate carrying a silenced *DTA* toxin gene separated from its hTERT promoter by a transcription terminator (Stop) flanked by attR and attL recombination substrates. The recombination products generated by Int excision reaction: the activated *DTA* gene separated from its hTERT bacterial recombination site attB (top), and the excised circular attP-Stop (bottom). B. Validation of a binary Int-activated cancer cells killing technology advantage over conventional technology (*hTERT-DTA*) in healthy and LLC-Kat cancer mice. The mice were retro-orbital injected after 10 days of LLC-Kat cells injection systemically each 3-4 days with Sub+Int or *hTERT-DTA* (hT-DTA) plasmid DNA complexed with jetPEI.

Recent Publications:

1. Elias A et al. (2016) Cancer-specific binary expression system activated in mice by bacteriophage HK022 Integrase. *Sci. Rep.* 6:24971.
2. Yucheng Xu and Amir Goldkorn (2016) Telomere and telomerase therapeutics in cancer. *Genes* 7:22.
3. Chen X, Scapa J E, Liu D X and Godbey W T (2016) Cancer-specific promoters for expression-targeted gene therapy: ran, brms1 and mcm5. *J Gene Med.* 18:89.
4. Dalit Landesman-Milo, Srinivas Ramishetti and Dan Peer (2015) Nanomedicine as an emerging platform for metastatic lung cancer therapy. *Cancer Metastasis Rev.* 34:291.
5. Hao Yin, Rosemary L Kanasty, Ahmed A Eltoukhy, Arturo J Vegas, J Robert Dorkin, Anderson. (2014) Non-viral vectors for gene-based therapy *Nature Reviews Genetics* 15:541.

Biography

Amer Elias has his expertise in The Genome Editing and Genome Engineering. He established a model system intended to catalyze a reaction of DNA fragment replacement in the human genome known as, "recombinase mediated cassette exchange (RMCE)" that is based on the site specific recombination system of the coliphage HK022 integrase, with the purpose of developing a gene therapy method to cure human deleterious mutations. He is also developing a specific anti-cancer binary system based on site-specific recombination for targeting tumors with specific suicide gene in animal models, demonstrating its high specificity and safety.

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