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What is Bystander Effect and Bystander Protein

AdIFN-α2b (Instiladrin, nadofaragene firadenovec, Adenoviral vector expressing interferon protein α2b) is in FDA Pending FDA approval on New Biologic Gene therapy. During its pre-clinical and Phase I study, Dr William Benedict lab observed "AdIFN-α Bystander Effect". When infected with AdIFN-α2b, tumor cells and normal urothelial (NHU) cells can produce soluble bystander factors, which are toxic to various cancer cells (bladder cancer, breast cancer, lung cancer and prostate cancer). This potent bystander factor(s) can be found in conditioned medium (CM) obtained from AdIFN-α2b infected cells. This toxicity is specifically and unique to cancer cells, but not to normal cells.

During 2001-2017, Dr Benedict lab had used several approaches to identify these bystander factors. Initial work had proved those factors are heat sensitive indicating they are proteins. Later comparing the Ad-IFNα2b CM vs control CM using iTRAQ, and focusing peaks seen in the AdIFN-α2b CM that are not present in the control CM. A Gelectin-3 Binding Protein (LGALS3BP) was identified as the highest score among several candidate proteins. After preparing a large volume CM from the AdIFN-α2b infected NHU cell, fractionating the CM with ultrafiltration and FPLC, the resulting fractions were then assessed for cytotoxicity comparison between different fractions. siRNA inhibition assay was also done with LGALS3BP specific siRNA, and found those siRNA can decrease cytotoxicity significantly. Those works provide clues to consider LGALS3BP as an important player in AdIFN-α2b bystander effectors. Similar results were seen on AdIFN-beta infected cells.

The LGALS3BP is a cell-adhesive protein, widely expressed, secreted 90 kD glycoprotein in serum found in normal individuals and at elevated levels in cancer patients. It is a well-known tumor marker since it was reported in 1996. Much evidence supports a role for LGALS3BP in tumor invasion and metastasis. The expression level is proved to be associated with the patient's prognosis. LGALS3BP is an independent prognostic indicator of poor outcome for some tumor types. Until today, no report on LGALS3BP direct cancer toxicity, and this makes our cloning effort for this cancer cytotoxic LGALS3BP protein gene difficult.

During effort to obtain both 5’ and 3’-end cDNA sequence using RACE methodology, it was found difficult to get 5’-end with LGALS3BP primer. There might be at least three different isoforms of LGALS3BP, and it would be very difficult to clone the cancer toxic isoform that we are hunting for.

We hypothesize the one isoform of LGALS3BP protein has a novel mechanism of cancer cell toxicity. It potentially could be developed as a new cancer therapeutic agent itself. It’s also possible for this LGALS3BP to be a fusion protein. We hope that the transcriptome analysis with RNA-seq would provide critical information for hunting LGALS3BP gene.