SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

BIOPHARMA

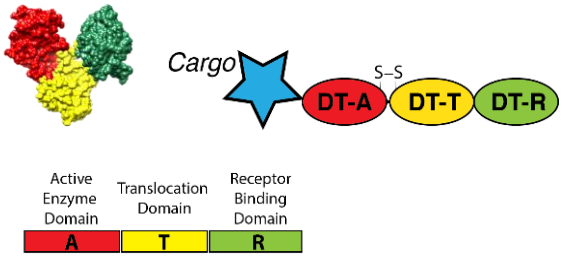
A novel cell-penetrant delivery platform applied to a pan-Ras targeting anti-cancer therapy

BACKGROUND

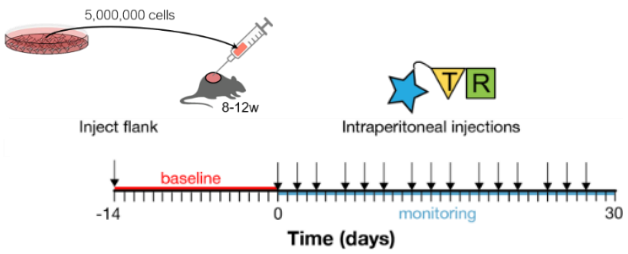
Ras proteins belong to a class of small GTPases that play a critical role in signal transduction, differentiation, cell growth, proliferation, and survival. Mutations in the *ras* gene lead to constitutively active signaling, causing unrestrained cell growth, division, and cancer. Mutations in *ras* are found in up to 30% of all human tumors and are present in 3 of the most lethal cancers (colon, lung, pancreatic), making this one of the most important oncogenes in humans. However, there are currently no effective inhibitory therapeutics targeting intracellular Ras proteins as the vast majority of biotherapeutics fail to penetrate the cell membrane. As a result, there is a growing need to develop protein carriers to traverse the plasma membrane barrier to target “undruggable” intracellular targets, such as mutant Ras.

DESCRIPTION OF THE INVENTION

Many bacteria secrete toxins that target and inactivate small GTPases, including Ras, as part of their strategy to disable the host immune system. Using these toxins as therapeutics, however, has not be possible since, until recently, none have been shown to be highly specific for Ras. Our team has discovered an effector enzyme (RRSP) that specifically targets and inactivates intracellular Ras in human cells. Ectopic expression of this enzyme was shown to cleave mutant Ras protein and inhibit cell growth. To deliver RRSP into cells, a chimera was generated with an intracellular protein delivery platform based on diphtheria toxin that has evolved a sophisticated mechanism for crossing the plasma membrane with high efficiency (RRSP-DTB). *In vitro* work has shown that RRSP-DTB can effectively degrade total Ras levels in colorectal cell lines (HCT-116).

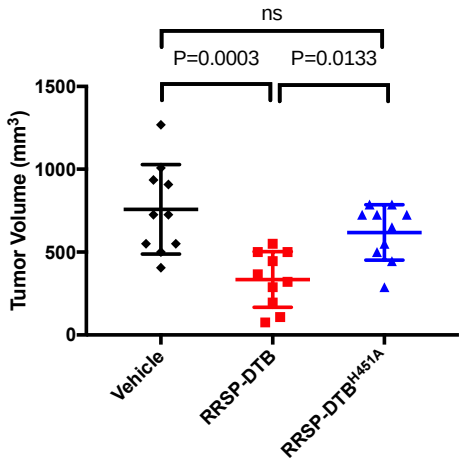


In addition, *in vivo* preclinical assessments have revealed that tumor growth and volume is significantly attenuated following RRSP-DTB administration in nu/nu immunodeficient mice who have receive either HCT 116 or breast cancer cell line (MDA-MB-436) injections.

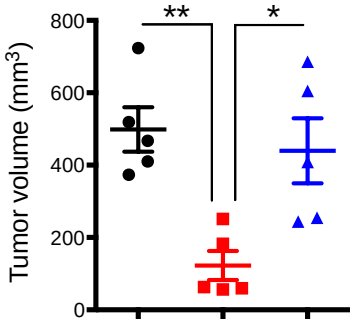


KEYWORDS
Cancer, RAS, diphtheria toxin, intracellular drug delivery

RRSP-DTB attenuates tumor growth in mice injected with HCT-116 cells



RRSP-DTB attenuates tumor growth in mice injected with MDA-MB-436 cells



COMMERCIAL APPLICATIONS & ADVANTAGES

This invention is a platform technology which permits the targeted delivery of a wide range of cargo into cells that have been previously unachievable.

- Ras proteins are implicated in one third of all cancers and mutated in 3 of 4 of the most lethal human malignancies (colon, lung and pancreatic cancers), making it a highly prized cancer drug target.
- There are two developing Ras inhibitors in clinical trial phases that target *KRAS G12C*. *KRAS* is a member of the Ras family, and the *KRAS G12C* mutation is present in 1-3% of colorectal and other solid tumors, and 13% of non-small cell lung cancer (NSCLC) patients.
- Unlike the two developing KRAS inhibitors, this invention targets all Ras mutants and isoforms.
- Versatility of the drug delivery platform will enable it to be easily redirected specifically to cancerous cells, and for additional applications (e.g. enzyme replacement therapy).
- Anticipate superior potency and safety over existing therapies (antibody-drug conjugates, immunotoxins) based on mechanism of action.

DEVELOPMENT STAGE

In vivo assessments of RRSP-DTB effects on tumor growth are completed.

PATENT STATUS

- US 2016/003053 A1 covers the enzyme (Satchell)
- US 10,597,663 (issued) covers the diphtheria toxin delivery system (Melnyk et al)
- US 2018/0080033 A1 covers the combination of enzyme and delivery platform (Melnyk et al)

IP&C intends to create a spin-off company and is seeking venture capital investment and/or a strategic partnership with a pharmaceutical company.

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