NANOSPONGES TO MAKE IMMUNOLOGICALLY COLD TUMORS HOT

NOVOCHZOL FORMULATION FOR INTRATUMORAL CYTOKINE SPIKES

THE PROBLEM:

Immunotherapy in general and checkpoint inhibition, in particular, rely on pre-existing antitumor immunity – both innate and adaptive - which is absent or suppressed in poorly immunogenic, immunologically cold tumors. Most solid cancers fall into this category.

Immunologically hot tumors, amenable to immunotherapies, differ from cold tumors in two respects: they are infiltrated by cytotoxic immune system cells (CD8+ T lymphocytes being the best studied so far) and their tumor microenvironment produces a variety of pro-inflammatory cytokines that attract, activate and promote the proliferation of additional tumor fighting cells.

It is possible to activate anti-tumor immunity and hence render cold tumors hot by exogenous addition of “master” pro-inflammatory cytokines. But all anti-cancer cytokine therapies, whether established or investigational, have two major limitations: severe dose-limiting toxicities[1] and inability to directly establish tumor tropism that would direct tumor fighting cells where they are needed.

In principle, both limitations may be overcome by confining the introduced cytokines to the tumor microenvironment. The rationale is supported by a recent report where an engineered Interleukin-12 fused to a collagen-binding domain was injected into mice tumors, resulting in dramatic responses[2] However, this and other approaches (superkines, immunokines, PEGylation, etc.) are laborious and limited to only “master” cytokines.

OUR SOLUTION: NOVOCHIZOL

What is it?
Novochizol are pure chitosan nanoparticles that can be rapidly "loaded" with any combination of active substances (small, medium or large, hydrophilic or hydrophobic).
More info: https://www.novochizol.ch/what/

Why?
Novochizol acts as a "sponge" with 2 key properties:

1. Strong adherence to tissues at the site of injection (no systemic distribution)
2. Sustained release over long periods of time (weeks)

More info: https://www.novochizol.ch/why/

We believe that Novochizol can be easily used:

1. To target any anti-cancer compound to tumors
2. To enrich the TME with cytokines that may help transform cold tumors into hot tumors. We could formulate any mixture of the "right" cytokines very rapidly and our formulation could be injected intratumorally , for targeted TME delivery without any systemic distribution.

We believe we have a universal way of doing what is otherwise quite laborious if not impossible.

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[1] Conlon KC, Miljkovic MD, Waldmann TA. Cytokines in the Treatment of Cancer. *J Interferon Cytokine Res*. 2019;39(1):6-21. doi:10.1089/jir.2018.0019

[2] Mansurov, A., Ishihara, J., Hosseinchi, P. et al. Collagen-binding IL-12 enhances tumour inflammation and drives the complete remission of established immunologically cold mouse tumours. Nat Biomed Eng 4, 531–543 (2020). https://doi.org/10.1038/s41551-020-0549-2

TOXICITY/ SAFETY CONSIDERATIONS

Novochizol have been tested extensively in a preclinical setting in human cell lines, mice (intramuscular, intracardial, intestinal injections, brain – dural graft substitutes, ocular applications), pigs (intra-pulmonary aerosols, intracardial and renal artery injections), dogs (brain – dural graft substitutes), chicks (ocular applications), and rabbits (ocular applications).

Of particular relevance are the extensive animal studies we have been conducting on a **Novochizol formulation of botulinum toxin** (**BTN**) with the aim of developing a new treatment to prevent arrhythmia and atrial fibrillation.

1. In preliminary work we demonstrated that free botulinum toxin prevents arrhythmia
2. BTN injections into epicardial fat pads in dogs resulted in extended complete abolition of cardiac vagal responses and increased suppression of atrial fibrillation.
3. Intramuscular injections of BTN in mice ensured localized sustained release of toxin with significantly longer effects where they were needed, without any systemic toxicity
4. BTN formulation antagonizes arrhythmia induced by the activation of Ca, K and Na channels in three different arrhythmia rat models

In all these studies and in all of our unpublished work, we have seen no evidence of any adverse events or undesirable effects of globular chitosan administration, be it topically, ocularly, intramuscularly, subepicardially, intra-arterially or intra-pulmonary.

STRONG POINTS

- A robust proof of concept and toxicity studies using Novochizol-formulated botulinum toxin and other biologically active substances.
- Chitosan has an excellent safety profile
- Easy, one- to two-step manufacturing process.
- Novochizol adheres to endothelial cells that make up the lining of all blood vessels (including arteries)
- Localized presence of cytokines may prevent the development of the development of cytokine neutralizing antibodies that have been observed, e.g. for Interleukin-7 .
- Rapid formulation of any combination of active ingredients of any size and solubility (including insoluble compounds). Ponderated combinations of different agents whether cytotoxic, proinflammatory or chemoattractant are easy to formulate.

OPPORTUNITY

We are seeking partners to conduct preclinical studies that will demonstrate the versatility and ease of our solution in finding the right combination of cytokines for effective combination (immuno)therapies, the “transformation of cold tumors into hot ones” and direct anti-tumor effects.

Please address all inquiries to Vanya Loroch, PhD

https://www.novochizol.ch/
Chemin des Vidies 2
1186 Essertines-sur-Rolle, SWITZERLAND

vanya@loroch.ch Tel/Whatsapp. +41 76 370 73 25 Skype: swissconnexion1