ONM-501, a dual-activating polyvalent STING agonist, enhances tumor retention and demonstrates favorable preclinical safety profile

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Zirong Chen[1], Gang Huang[2], Katy Torres[2], Fiona Stavros[1], Alessandra Ahmed[2], Jason Miller[1], Tian Zhao[1], Jinming Gao[1,2,‡] , Ruolan Han[1,‡]

[1]OncoNano Medicine, Inc., Southlake, TX 76092;

[2]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas 75390

[‡]Corresponding authors: Ruolan Han, PhD (rhan@onconanomed.com); Jinming Gao, PhD (jinming.gao@utsouthwestern.edu)

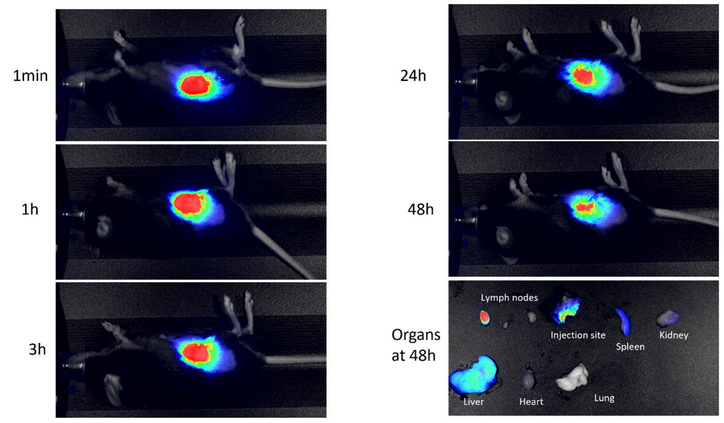
Introduction

The **St**imulator of **In**terferon **G**enes (STING) plays a central role in innate immune response against infection and cancer. ONM-501, a dual-activating STING agonist employs PC7A, a synthetic polymer that induces polyvalent STING condensation and prolongs innate immune activation has been recently developed. ONM-501 encapsulates the endogenous STING agonist cGAMP with the PC7A micelles offering a dual 'burst' and 'sustained' STING activation. The anti-tumor efficacy and pharmacodynamic analysis of ONM-501 in multiple tumor models has previously been demonstrated[1]. Here we report the pharmacokinetic (PK) and biodistribution (BD) analysis of ONM-501 in mice and safety evaluation of ONM-501 in mice, rats and primates.

Methods

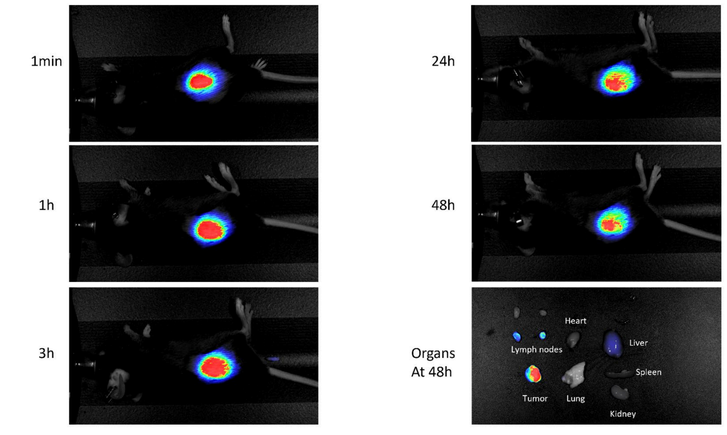
PC7A polymers conjugated with LiCOR 800CW were mixed with unlabeled PC7A to form PC7A-CW800, and cGAMP was encapsulated into the micelles to generate the "always-on", fluorescently labelled ONM-501-CW800. Naïve or tumor-bearing mice were injected subcutaneously (SC) or intratumorally (IT) with ONM-501-CW800, respectively, and plasma and multiple organ samples were collected; the whole tissue specimens were first imaged ex vivo using a LiCOR Pearl Imaging system, and then homogenized and the fluorescence quantified against standard curves prepared by spiking ONM-501-CW800 into a homogenate of the relevant matrix. Tissue and plasma cGAMP concentrations were quantified by LC-MS/MS. PK parameters were calculated using non-compartmental methods. Safety and tolerability were evaluated following single- and multiple-dose SC injections in naïve animals up to the highest feasible doses.

In vivo and ex vivo organ images collected from a naïve mouse injected SC with 50 µg PC7A-CW800 micelles



SC

In vivo and ex vivo organ images collected from a tumor bearing mouse injected IT with 50 µg PC7A-CW800 micelles

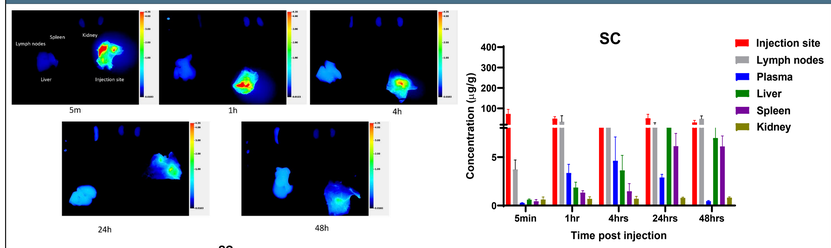


IT

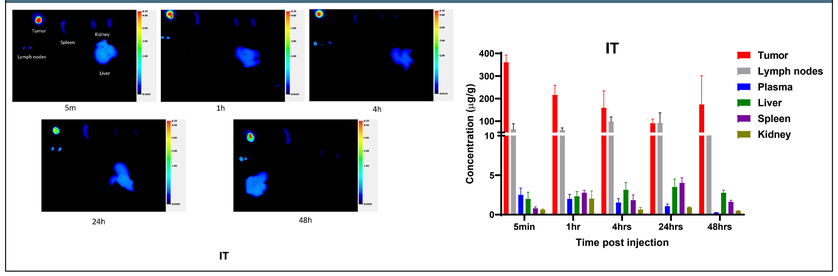
Schematic illustration of ONM-501

ONM-501 encapsulates endogenous cGAMP within PC7A micelles. PC7A is a pH-sensitive synthetic polymer that induces polyvalent STING condensation and prolonged innate immune activation[1,2]

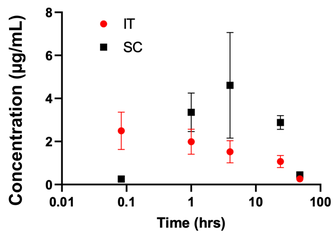
Ex vivo tissue distribution of PC7A-CW800 following SC injection of ONM-501-CW800



Ex vivo tissue distribution of PC7A-CW800 following IT injection of ONM-501-CW800



PC7A-CW800 plasma concentrations following IT or SC administration of 50 µg ONM-501-CW800



Route	IT	SC
Timepoint (h)	PC7A-CW800 (µg/mL)[1]	
0.08	2.5 ± 0.87	0.26 ± 0.04
1 h	1.99 ± 0.58	3.36 ± 0.89
4 h	1.52 ± 0.52	4.61 ±2.45
24 h	1.07 ± 0.28	2,89 ±0.32
48 h	0.27 ± 0.02	0.45 ± 0.07

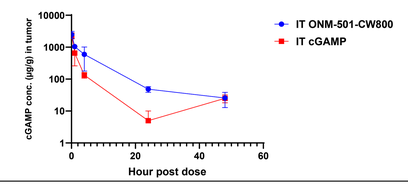
[1] Mean ±SEM; N=3

PC7A-CW800 pharmacokinetic parameters following a single SC or IT injection of 50 µg ONM-501-CW800

Parameter	Plasma (SC)	Plasma (IT)	Tumor
Cmax (µg/mL)	4.63	2.5	361
Tmax (h)	4.0	0.08	0.08
AUC(0-t) (h*µg/mL)	129	49.4	4,992
AUC(0-inf) (h*µg/mL)	137	56.2	6,716
λz (1/h)	0.0538	0.0399	0.0275
t ½ (h)	12.9[1]	17.4	25.2

[1] Value derived from 3 datapoints including Cmax

cGAMP concentrations in tumor tissue following a single IT injection of 50 µg ONM-501-CW800 (containing 2.5 µg encapsulated cGAMP) or 2.5 µg unencapsulated cGAMP



Higher cGAMP concentrations at later timepoints and higher AUC(0-t) in the tumor tissue following injection of ONM-501-CW800 suggest slower elimination of cGAMP by PC7A-CW800 encapsulation

cGAMP pharmacokinetic parameters following a single SC or IT injection of 50 µg ONM-501-CW800 and IT injection of 2.5 µg unencapsulated cGAMP

	Tumor		Plasma
Parameter	IT ONM-501-CW800	IT cGAMP	SC ONM-501-CW800
Cmax (ng/mL)	2492	2325	109
Tmax (h)	0.08	0.08	4
AUC(0-t) (h*ng/mL)	11492	4390	4256
AUC(0-inf) (h*ng/mL)	11862	NC	6110
λz (1/h)	0.0698	NC	0.0225
t ½ (h)	9.93	NC	30.8

NC not calculated due to lack of a log-linear decay

ONM-501 demonstrates a strong safety profile in preclinical models

The highest tolerated SC doses in different species

Species	Mice	Rats	Monkeys
MTD (**HED**) (mg/kg) in single-dose studies	74 (**6**)	45 (**7.3**)	30 (**9.7**)
HNSTD (**HED**) (mg/kg/dose) in 2-week QW dosing studies	-	30 (**4.8**)	30 (**9.7**)
HNSTD (**HED**) (mg/kg/dose) in 4-week, QW dosing GLP studies	-	30 (**4.8**)	7.5 (**2.4**)

MTD: maximum tolerated dose; HNSTD: highest non-severely toxic dose; HED: human equivalent dose; QW: once weekly

The toxicity profile of ONM-501 was evaluated in mice, rats and monkeys in several toxicology studies using SC injection as a surrogate for IT injection in healthy animals. The highest tolerated doses in each species and their human equivalent doses are summarized in the table.

The average efficacious IT dose of ONM-501 in mice is ~0.001mg/dose/(mm^3 of tumor), assuming similar activity with the same local drug concentration, the estimated efficacious dose in a minimally injectable human tumor of 10mm in diameter would be ~0.5mg/dose, or 0.007mg/kg/dose in a 70 kg adult, indicating a large potential therapeutic window and safety margin in the proposed first-in-human clinical study of ONM-501.

Summary

Systemic exposure to ONM-501 was lower after IT than SC administration, consistent with increased retention of both active moieties of ONM-501 (PC7A and cGAMP) within tumors. Combined with preclinical toxicology studies, ONM-501 showed a favorable pharmacokinetic, tolerability and safety profile that supports its continued development in cancer patients via IT delivery.

References

[1] Li S, *et al*. Nature Biomedical Engineering. 2021;5: 455-466.
[2] Bennett Z, *et al*. Seminars in Immunology. 2021; p.101580.

Acknowledgement

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