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Intravenous administration of the small molecule STING agonist CRD5500 elicits potent anti-tumor immune responses in cold tumors

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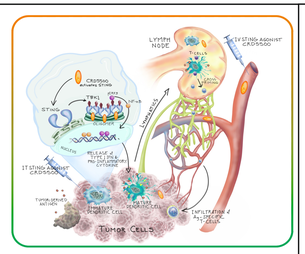
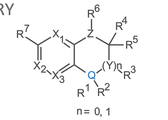
ABSTRACT

- **St**imulator of **In**terferon **G**enes – (STING) is an innate immune mediator that activates Type I interferon and pro-inflammatory responses to drive **anti-viral and anti-tumor immunity**
- STING is activated as part of an early warning mechanism in many cell types by cyclic dinucleotides that are formed when the enzyme cGAS detects cytosolic DNA
- CRD5500 is a potent, first-in-class classical small molecule STING agonist with a distinctive binding site that is outside the CDN pocket. It displays strong anti-tumor effects against multiple tumor types in human STING knock-in mice when administered systemically by the IV route or directly by IT route.

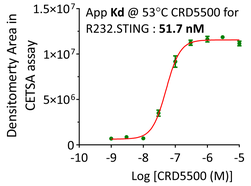


ATTRIBUTES

CHEMISTRY



BINDING



In-vitro ADMET Propertise				In-vitro ADMET Propertise			
Assays		Unit	CRD5500	Assays		Unit	CRD5500
Aqueous Solubility (Kinetic)	pH 3.0	µM	50	Recombinant human CYP$_{450}$ Phenotyping ($T_{1/2}$)	3A4	(min)	15
	pH 7.4	µM	50		2D6	(min)	121
	pH 8.4	µM	50		2C9	(min)	93
Aqueous Solubility (@24h)	pH 3.4	(%)	100	CYP inhibition (DDI) IC_{50}	1A2	µM	> 30
	pH 7.4	(%)	100		2C9	µM	4.1
	pH 8.4	(%)	100		2D6	µM	> 10
Biological Fluid Stability (@24h)	SGF (pH 1.6)	(%)	99		3A4	µM	7.1
	SIF (pH 6.5)	(%)	99	Hepatocyte Stability ($T_{1/2}$)	Human	(min)	21
Plasma Stability (@24h)	Human	(%)	100		Monkey	(min)	18
Mouse		(%)	100		Rat	(min)	16
hERG Binding @10	Human	(%)	8		Mouse	(min)	14

STING ACTIVATION ACROSS VARIANTS IN REPORTER GENE ASSAY

	HEK293T cells					THP-1 Dual cells		HEK293T cells
	IRF axis					*IRF axis*	*NF-kB axis*	*IRF axis*
STING Variants	*R232*	*H232*	*HAQ*	*AQ*	*Q*	*HAQ*	*HAQ*	*Monkey*
EC_{50} (nM)	9.2 (+2.6)	18.1 (+3.4)	12.1 (+5.5)	35.9 (+7.9)	62.2 (+12.7)	65.1 (+32.2)	76.5 (+64.5)	43.6 (+10.7)

CYTOKINE STIMULATION IN PBMCs

PBMC (EC_{50} ± SD) in µM		
Cytokines	**Human EC_{50} (n^*)**	**Monkey EC_{50} (n^*)**
IFNβ	0.22 ± 0.1 (4)	1.87 ± 0.93 (4)
IFNα	1.48 ± 1.09 (7)	2.15 ± 0.88 (4)
IL6	0.13 ± 0.06 (4)	1.94 ± 1.45 (4)
CXCL10	0.04 ± 0.02 (6)	0.15 ± 0.04 (3)

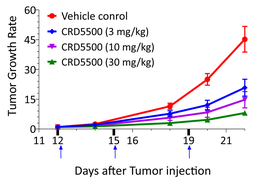
n^* = number of human donors or animals

CRD5500:

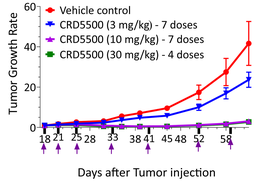
- Induces thermal stabilization of cellular STING with a Kd of 52 nM
- Potently activates all the major human STING variants
- Potently stimulates pro-inflammatory cytokine release from human and monkey PBMCs
- Exhibits good drug like properties

MONOTHERAPY BY IV ROUTE

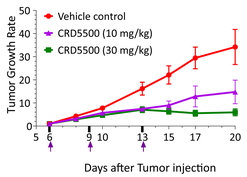
A: B16F10 (Melanoma)



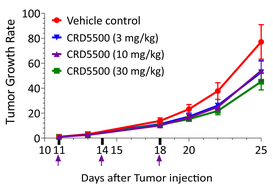
B: PAN02 (Pancreatic)



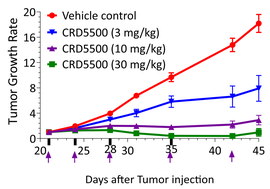
C: C1498 (AML)



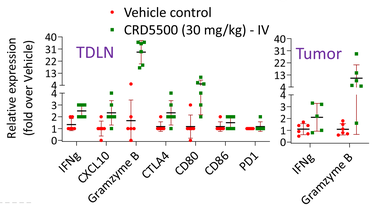
D: LL/2 (Lung)



E: MOC1:(HNSCC)

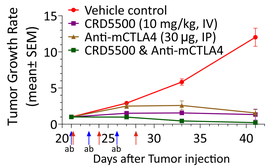


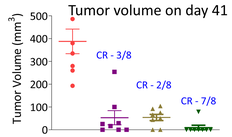
F: MOA in MOC-1 tumor bearing mice



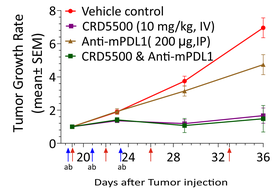
COMBINATIONS WITH CPI in MOC-1

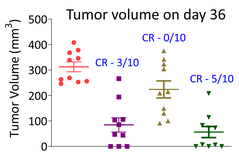
G: Anti-tumor efficacy in combination with mCTLA-4





H: Anti-tumor efficacy in combination with mPDL1



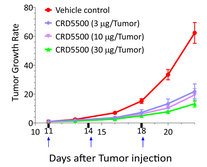


IV dosed CRD5500 :

- **A-E**: Displays robust dose dependent anti-tumor effects against multiple subcutaneously implanted tumor types as monotherapy
  - Regimen followed: Bi-weekly for the 1st week followed by once a week till the end of the study
- **F**: Induces change in tumor and TDLN immune contexture with a marked increase in the activated cytotoxic CD8 T-cell marker Granzyme B
- **G-H**: Combines with anti-CTLA-4 and anti-PD-L1 to completely eradicate established MOC-1 tumors in several mice

MONOTHERAPY BY IT ROUTE

A: B16F10 (Melanoma)



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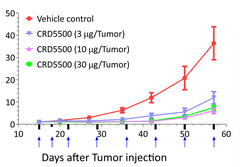

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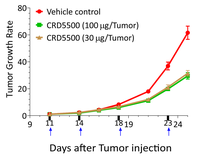
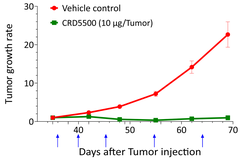


D: MOC-1 (Head & Neck)

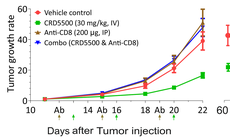


IT dosed CRD5500:

- **A-D**: Displays robust dose dependent anti-tumor effects in multiple tumors as monotherapy with complete eradication of MOC -1 tumors in several mice
- Regimen followed: Bi-weekly for the 1st week followed by once a week till the end of the study

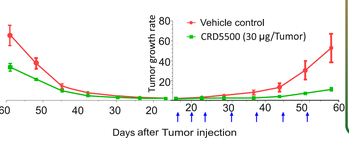
MECHANISM OF ACTION

CD8 dependent anti-tumor effect



Abscopal Effect in PAN02

(contralateral flank) (ipsilateral flank)



- The administration of anti-CD8a T cell blocking antibodies reverses the anti-tumor effects of CRD5500
- Intratumoral administration of CRD5500 into ipsilateral tumors causes regression of the contralateral tumor
- Effect is due to induced anti-tumor immunity and not due to direct effects of drug leaking into vasculature (*AACR 2019*)

CONCLUSIONS

- Agonists of STING, an innate immune mediator that activates pro-inflammatory Type I interferon responses are being pursued as a novel anti-tumor modality in the clinic
- CRD5500 – clinical candidate: (*Supporting in-vitro and ex-vivo functional data had been presented at AACR'2019, Annual Meeting*)
  - Potent, first-in-class classical small molecule STING agonist with a distinct binding site outside the cGAMP binding region
  - Demonstrates robust anti-tumor effects in multiple syngeneic murine tumors in human STING-knock in mice when administered either IV or IT as monotherapy or in combination with CPI
  - Displayed excellent systemic tolerability in 28-day repeat dose GLP studies in non-human primates
  - **Scheduled for FIH trials in Q3 2022**