



STING at a Crossroads: Untapped Potential for Innate Immunity

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Society for Immunotherapy of Cancer

#SITC2019

Disclosures

- Thomas W. Dubensky, Jr. is a paid employee of Tempest Therapeutics and holds stock options in the company, and is an inventor on multiple patents and pending applications related to the STING pathway.

STING at a Crossroads: Overview

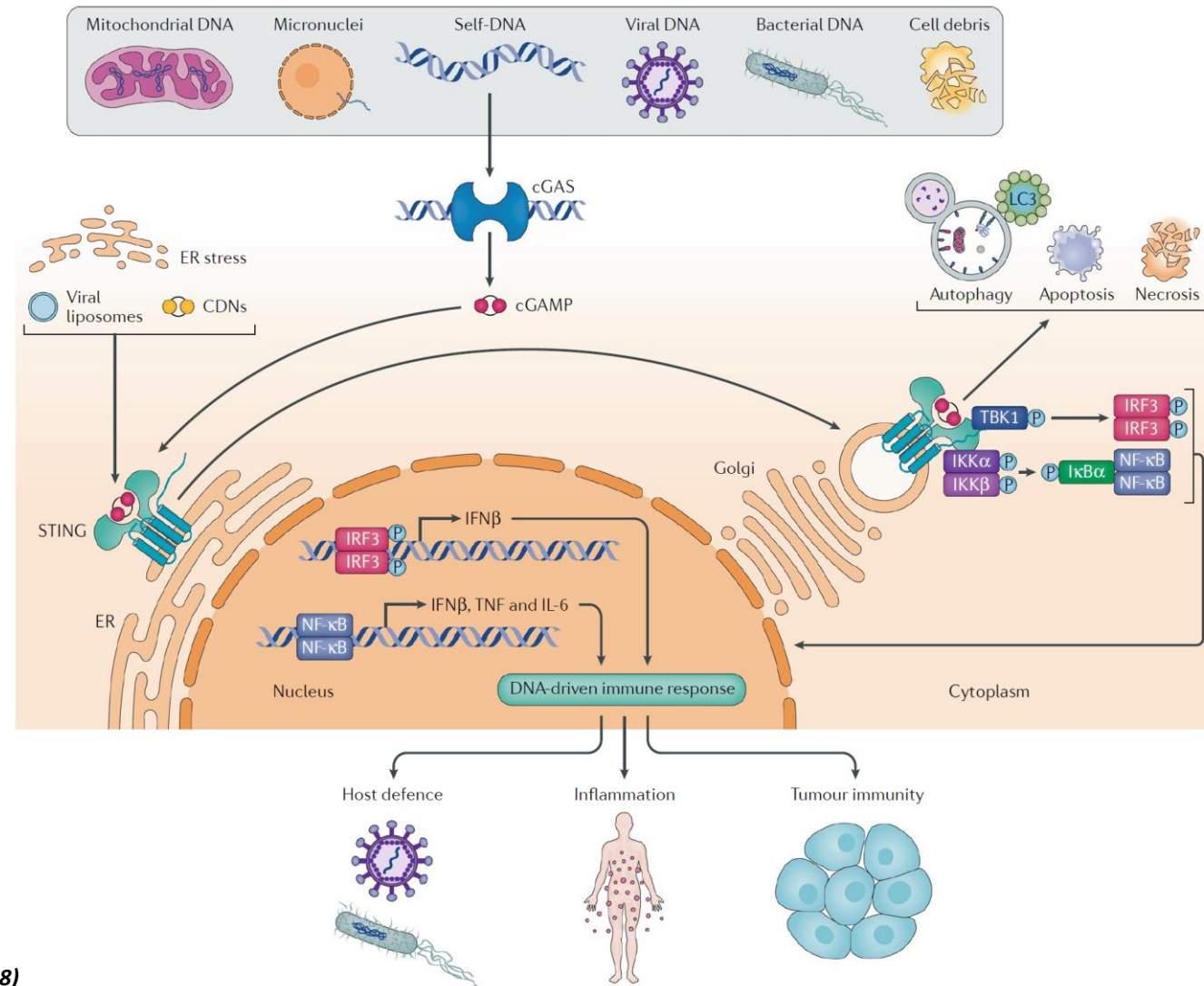
- Scientific rationale for targeting STING, revisited
- Clinical-staged STING agonists, status and results
- Have expectations been met—is STING at a crossroads?
- Other approaches and rationale for targeting STING
- Concluding remarks

Rationale for Targeting STING

Cytosolic DNA sensing pathway

STING (Stimulator of Interferon Genes):

- Innate immunity is activated in response to sensing nucleic acids in the cytosol
- Downstream signaling is triggered through binding of cyclic dinucleotides (CDNs)
- CDNs are synthesized by bacteria or host enzyme cGAS in response to binding cytosolic DNA
- Bacterial and host-produced CDNs have unique structures which informs drug design

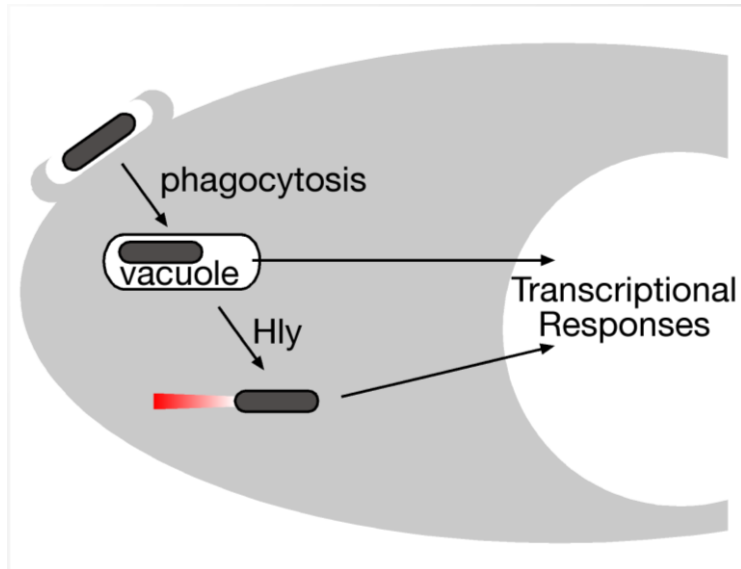


Ishikawa et al., *Nature* (2009); Burdette and Vance, *Nature* (2011); Motwani et al., *Nat Rev Genetics* (2018)

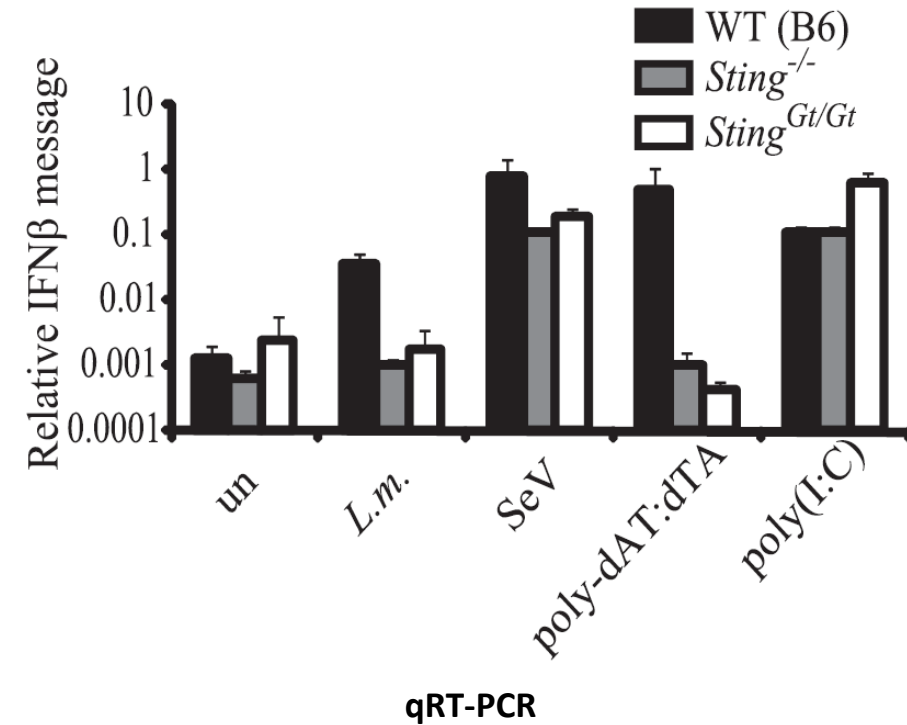
Rationale for Targeting STING

Cytosolic DNA sensing pathway

Listeria (*Lm*) intracellular infection



Induced IFN- β expression

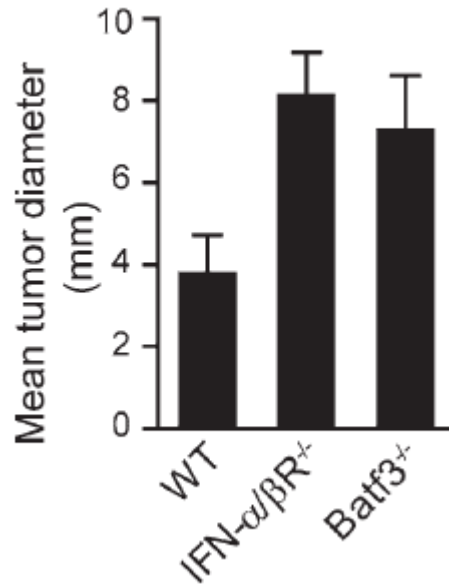


Luster, Moors and Portnoy, 1994 (unpublished); Woodward et al., *Science*, (2011);
Burdette et al., *Nature*, (2011); and, Sauer et al., *Infection and Immunity*, (2011)

Rationale for Targeting STING

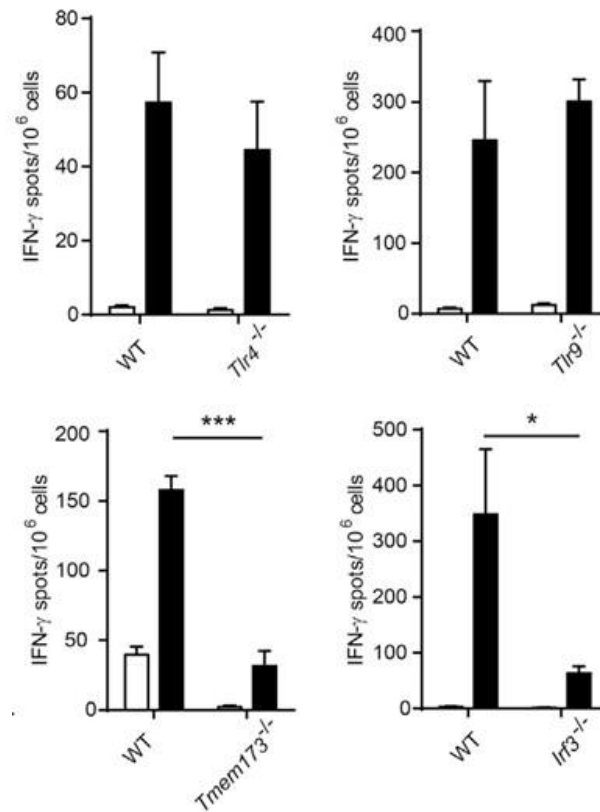
Tumor-initiated T cell priming is STING-dependent

CD8 α^+ DC production of IFN- β in TME required for tumor inhibition

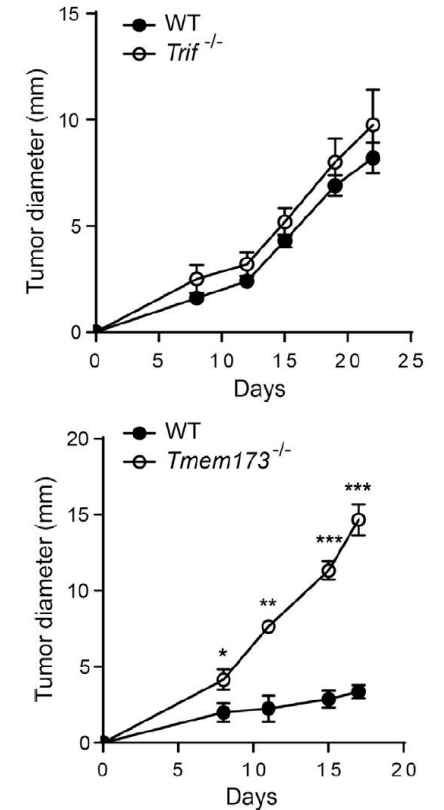


Fuertes et. al., JEM (2011); Woo, Gajewski, Immunity, (2014)

Tumor-Initiated T cell priming and tumor control is STING—but not TLR-dependent



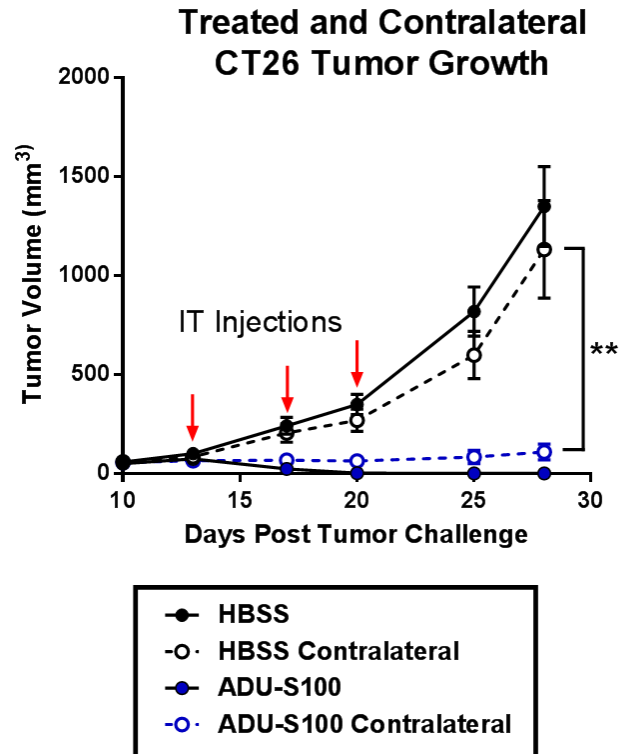
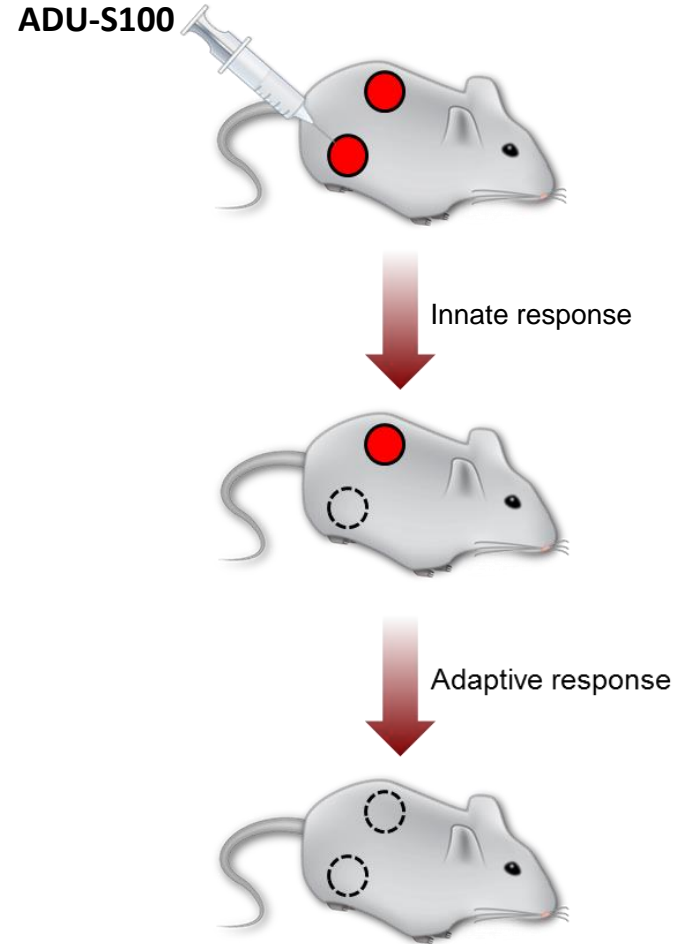
CD8 T cell priming



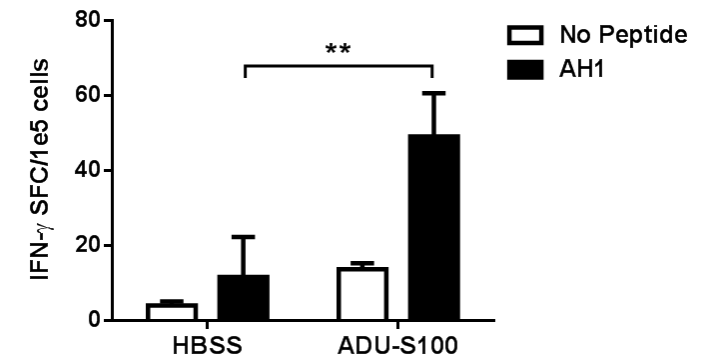
Tumor control

Rationale for Targeting STING

Synthetic cyclic dinucleotides induce in situ priming and abscopal effect



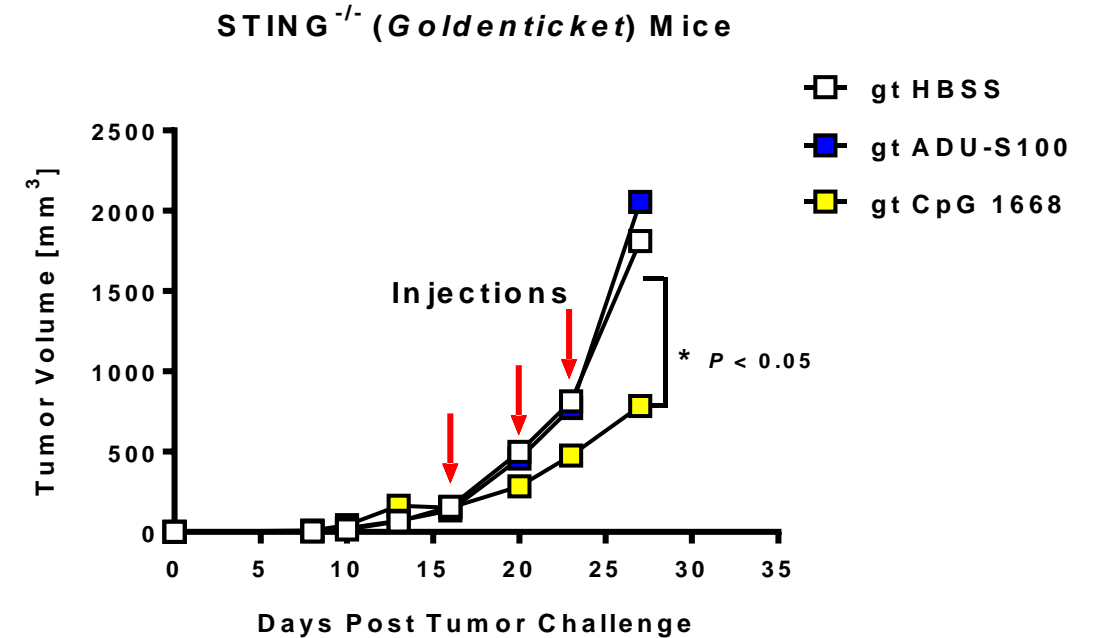
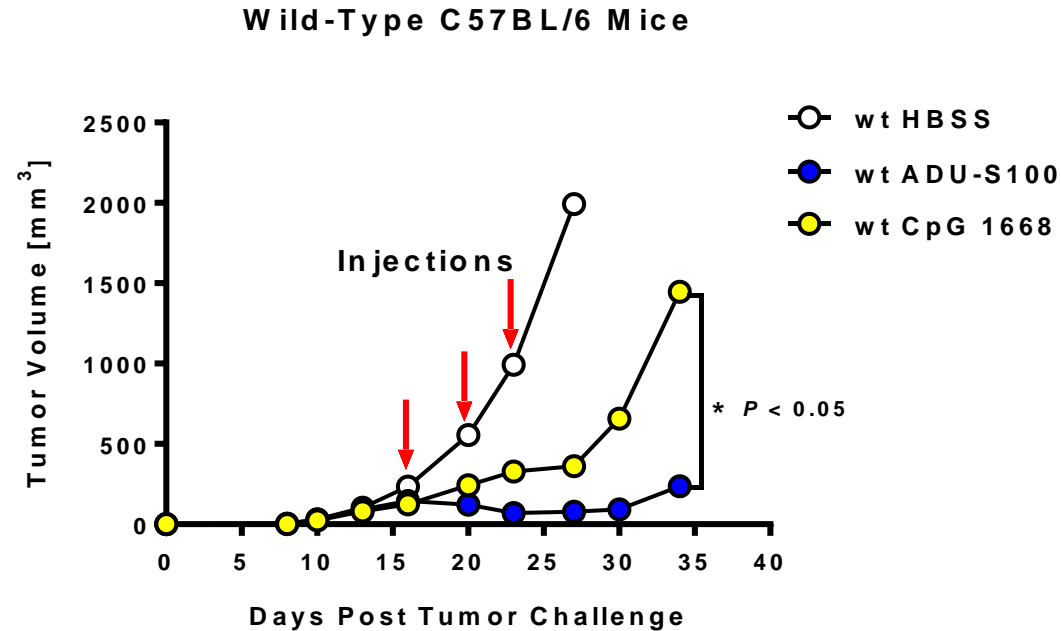
CT26 CD8⁺ T Cell Response



Corrales and Hix Glickman et al, Cell Reports (2015)

Rationale for Targeting STING

CDN induced anti-tumor efficacy is STING-dependent



Corrales and Hix Glickman et. al, Cell Reports (2015)

Multiple Groups are Targeting STING

Pre-clinical and clinical programs

IT Intratumoral

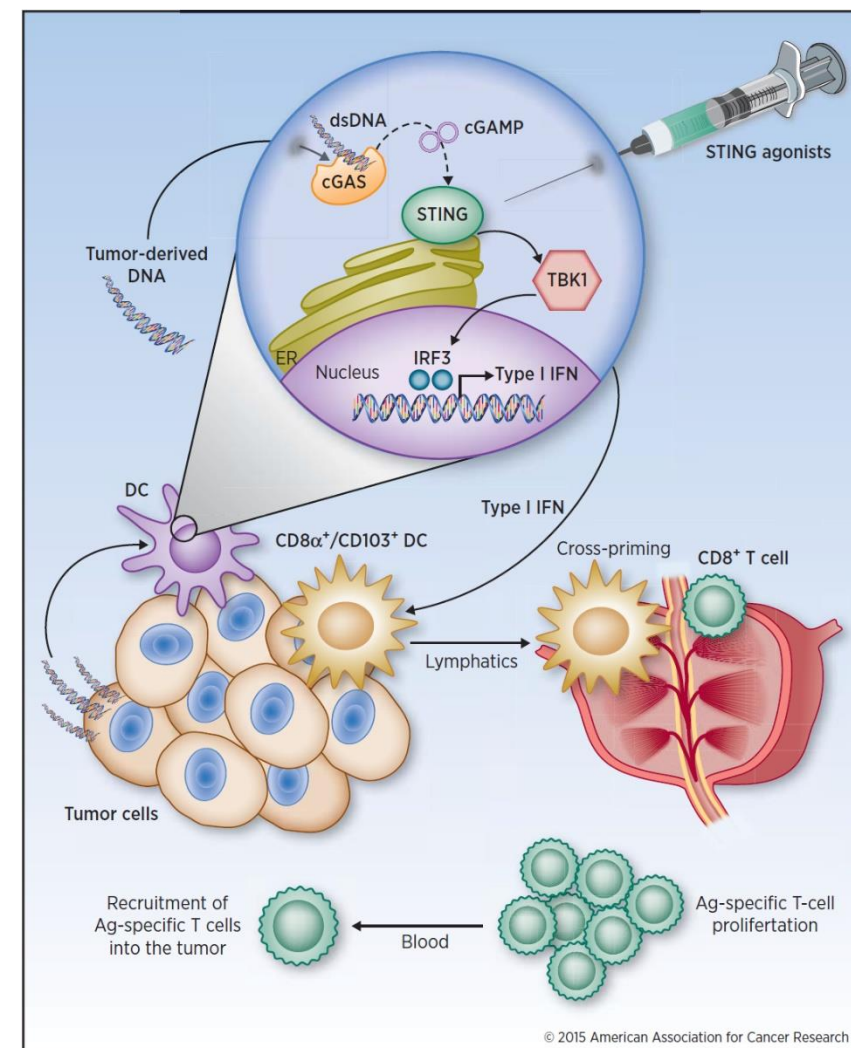
Systemic

Company	Agent	Delivery	Program	Stage
Aduro/ Novartis	ADU-S100	IT	Small-molecule STING agonist	Ph1/2
Merck	MK-1454	IT	Small-molecule STING agonist	Ph1/2
Merck	MK-2118	IT/ SubQ	Small-molecule STING agonist	Ph1
Spring Bank	SB11285	IT/ IV	Small-molecule STING agonist	Ph1
GSK	GSK3745417	IV	Small-molecule STING agonist	Ph1
Bristol-Myers Squibb (IFM)	BMS-986301	IT	Small-molecule STING agonist	Ph1
Eisai	E7766	Unknown	Small-molecule STING agonist	Prec/ Disc
Takeda	TAK-676	Unknown	Small-molecule STING agonist	Prec/ Disc
Takeda/ Curadev	CRD5500	Unknown	Small-molecule STING agonist / “amendable to biconjugation as ADC”	Prec/ Disc
Abbvie (Mavupharma)	MAVU-104	Oral	ENPP1 inhibitor	Prec/ Disc
Synlogic	SYNB1891	IT	E. coli engineered to produce high levels of the STING agonist c-di-GMP	Prec/ Disc
Spring Bank	SB11325/ 11396	IV	Antibody conjugated STING agonists (Targets Unknown)	Prec/ Disc
Trillium Therapeutics	TTI-10001	Unknown	Small-molecule STING agonist	Prec/ Disc
Codiak Biosciences	exoSTING	Unknown	Engineered exosome	Prec/ Disc
Venn Therapeutics	VTX-001	IT	Adenovirus that produces the bacterial STING agonist c-di-GMP	Prec/ Disc
iTeos Therapeutics	Unnamed	IV	Small-molecule STING <i>pathway</i> activators	Prec/ Disc
Nimbus Therapeutics	Unnamed	Unknown	Small-molecule STING agonist	Prec/ Disc
Bicycle Therapeutics	Unnamed	Systemic	Bicycle conjugate	
Selvita	Unnamed	Unknown	Small-molecule to activate STING	Prec/ Disc
Stimunity	Unnamed	Unknown	Vectorized cGAMP – “virus like particle”	Prec/ Disc
StingInn	Unnamed	Unknown	Small-molecule STING agonists/ nucleic acid-based STING activators	Prec/ Disc
StingInn/ Vyriad	Unnamed	Unknown	Oncolytic viruses encoding STING <i>pathway</i> activators	Prec/ Disc
Venenum Biodesign	Unnamed	Unknown	Small-molecule STING agonist	Prec/ Disc

First Clinical Approach to Target STING: Intratumoral (IT)

Sponsor	NCT#	Agent	Molecule	Phase / Title
Aduro/ Novartis	NCT03172 936	ADUS100 / MIW815	CDN	Study of the Safety and Efficacy of MIW815 With PDR001 to Patients With Advanced/Metastatic Solid Tumors or Lymphomas
Aduro/ Novartis	NCT02675 439	ADUS100 / MIW815	CDN	Safety and Efficacy of MIW815 (ADU-S100) +/- Ipilimumab in Patients With Advanced/Metastatic Solid Tumors or Lymphomas
Aduro/ Novartis	NCT02675 439	ADUS100 / MIW815	CDN	Efficacy and Safety Trial of ADU-S100 and Anti-PD1 in Head and Neck Cancer
Merck	NCT03010 176	MK-1454	CDN	Study of MK-1454 Alone or in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/Metastatic Solid Tumors or Lymphomas (MK-1454-001)
BMS (IFM)	NCT03956 680	BMS- 986301	CDN	An Investigational Immunotherapy Study of BMS-986301 Alone or in Combination With Nivolumab, and Ipilimumab in Participants With Advanced Solid Cancers
Springbank	NCT04096 638	SB11285	SMNH*	Evaluating Safety and Efficacy of SB 11285 Alone and in Combination With Nivolumab in Patients With Advanced Solid Tumors

* Small Molecule Nucleic Acid Hybrid



Corrales and Gajewski., 2015, *Clin. Can. Res.*

Clinical Results of Phase 1 Dose Escalation Studies

Publicly disclosed clinical results from ongoing Phase 1 studies with IT STING agonists

Aduro/Novartis (ADU-S100/MIW815): NCT03172936

Monotherapy	Results	Combination (Spartalizumab qmo)	Results
41 pts with cutaneously accessible lesions (10 melanoma, 2 uveal pts)	11/40 SD (28%) 2/40 PR (5%)	53 pts (q3wk, 1 wk off) 30 pts (q monthly)	12/53 SD (23%); 4/53 PR (8%); 1/53 CR (2%); 3/8 ≥PR (38%) in PD1-naïve TNBC pts; 2 PR in IO relapsed/refractory melanoma pts; 6/30 SD (20%) with q monthly CDN dosing

Merck (MK-1454): NCT03010176

Monotherapy	Results	Combination (Pembrolizumab)	Results
20 pts with cutaneously accessible lesions (5 melanoma pts)	4/20 SD (20%)	25 pts	6/25 SD (24%), 6/25 PR (24%); 3/8 PR (38%) in PD1-naïve HNSCC pts

Clinical Results of Phase 1 Dose Escalation Studies

Publicly disclosed clinical results from ongoing Phase 1 studies with IT STING agonists

- Sporadic evidence of single agent activity across diverse tumor types
- No consistent observation of abscopal activity as a single agent
- No clear evidence of increased activity by combination with α -PD-1 mAb
- Some encouraging results:
 - **Aduro/Novartis: 3/8 \geq PR (38%) in PD1-naïve TNBC pts and 2 PR in IO relapsed/refractory melanoma pts**
 - **Merck: 3/8 PR (38%) in HNSCC in PD1-naïve pts**

 **Are these first clinical results with IT STING agonists disappointing?**

Clinical Results of Phase 1 Dose Escalation Studies

Publicly disclosed clinical results from ongoing Phase 1 studies with IT STING agonists

- Sporadic evidence of single agent activity across diverse tumor types
- No consistent observation of abscopal activity as a single agent
- No clear evidence of increased activity by combination with α -PD-1 mAb
- Some encouraging results (single armed studies):
 - **Aduro/Novartis: 3/8 \geq PR (38%) in PD1-naïve TNBC pts and 2 PR in IO relapsed/refractory melanoma pts**
 - **Merck: 3/8 PR (38%) in HNSCC in PD1-naïve pts**

\$MRK human STING data very unimpressive IMHO - 0% ORR as monotherapy, and 24% ORR in combo with pembro for PD-1 naïve pts is not clearly better than pembro alone would be. STING appears to be yet another example of an IO agent that looked great in mice, but flopped in humans...

@ArtKrieg

Injected only 1 lesion mostly. Too early to say in combo. Appears safe and biomarker data is what we want. Looking forward to more!

@jasonlukemd

STING at a Crossroads: Interpretation of Initial Clinical Results

Deciphering the data

- Differences between clinical studies
- Differences among molecules in clinical development
- Is STING being activated in the right cell types in the TME to initiate immunity?
- Is STING a validated target?
- Is intratumoral injection the right approach?

STING at a Crossroads: Interpretation of Initial Clinical Results

Deciphering the data

Differences between clinical studies:

Aduro/Novartis: NCT03172936

Dosing Schedule

<i>IT Injections</i>	Cycle 1+			
	Week 1	2	3	4
Schedule A	X	X	X	
Schedule B	X			

Doses Studied

10 µg → 1600 µg

Merck: NCT03010176

Dosing Schedule

<i>IT Injections</i>	Cycle 1			Cycle 2			Cycle 3			Cycle 4+		
	Week 1	2	3	5	6	7	9	10	11	13	14	15
Schedule	X	X	X	X	X	X	X	X	X	X		

Doses Studied

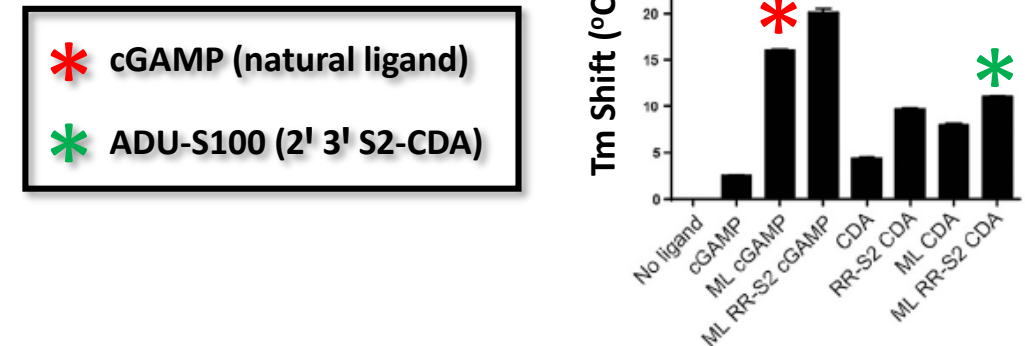
10 µg → 3000 µg

STING at a Crossroads: Interpretation of Initial Clinical Results

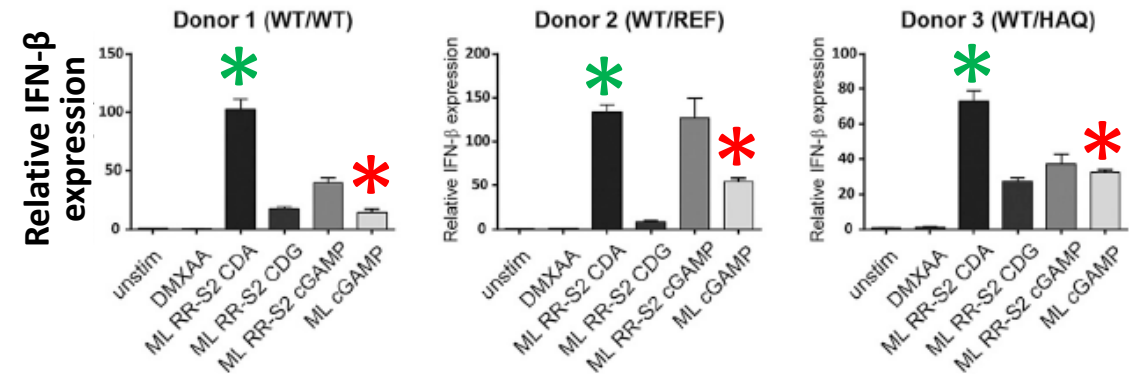
Deciphering the data

- Differences among molecules in clinical development
 - Aduro, Merck and BMS (IFM) molecules are CDNs
 - Springbank molecule an SMNH
 - Head-to-head studies have not been conducted
 - CDN avidity and signaling can vary according to STING allele
 - Molecules are not formulated—uptake among phagocytes, somatic cells and tumor cells can be variable
 - **The most potent STING ligand is not necessarily the optimal CDN for clinical development**

CDN-STING Thermal Stability
(Differential Scanning Fluorimetry)



STING activation in human PBMCs
(IFN- β expression)



Corrales and Hix Glickman et. al, Cell Reports (2015)

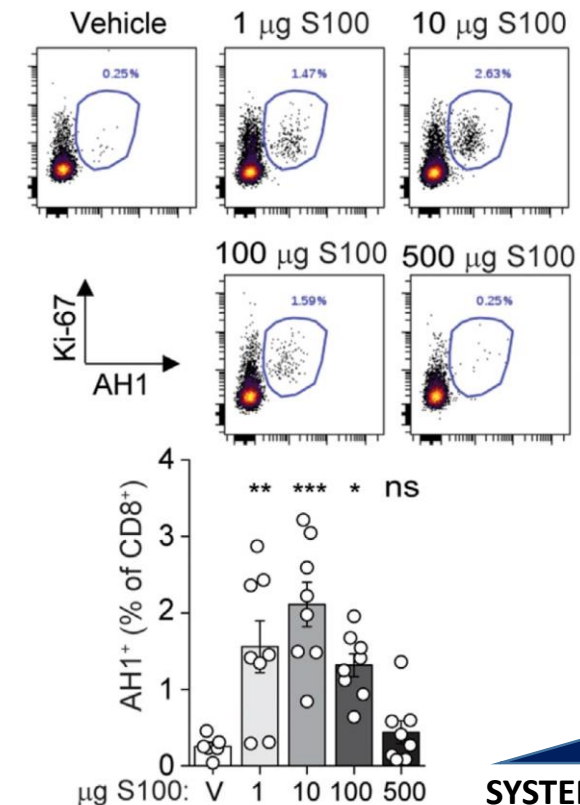
STING at a Crossroads: Interpretation of Initial Clinical Results

Deciphering the data

Is STING being activated in the right cell types in the TME to initiate immunity?

- cGAS/STING is ubiquitously expressed
- STING pathway can be epigenetically silenced in tumor cells
- STING activation, and production of IFN- β leading to anti-tumor immunity can be initiated from diverse cells in the TME:
 - Tumor cells, phagocytes, myeloid cells, stroma, endothelial cells
- Level of STING-induced IFN- β and TNF- α affects priming in the TDLN—a Goldilocks effect

Goldilocks effect of CDN-induced CD8⁺ T cell priming



Baird et al. PLOS (2017); Baird et al. Cancer Res (2015); Corrales et al, Cell Reports (2015); Demaria et al. PNAS (2015); Francica et al., Can Immunol Res (2018); Sivick, et al, Cell Reports (2018)

STING at a Crossroads: Interpretation of Initial Clinical Results

Deciphering the data

Is STING a validated innate immune target?

- Genetic validation—interferonopathies due to dysregulation of STING pathway

➤ Humans:

STING-associated vasculopathy with onset in infancy (SAVI) (ligand-independent activated STING)

Aicardi–Goutieres syndrome (AGS), chilblain lupus (TREX-1 mutation)

Epigenetic silencing of STING in tumor cells

DNA tumor virus inactivation of STING

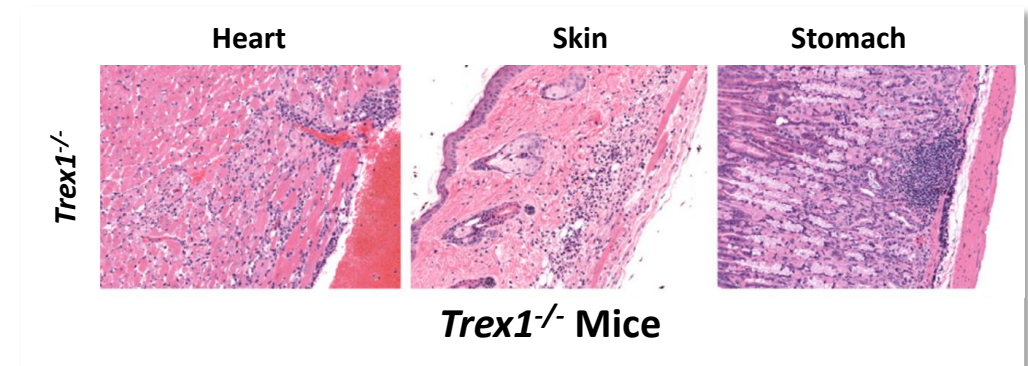
➤ Mice:

STING (*TMEM173*)^{-/-}: HSV-1 virus infection sensitivity

TREX-1^{-/-}: recapitulates human AGS



SAVI



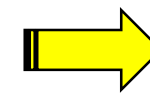
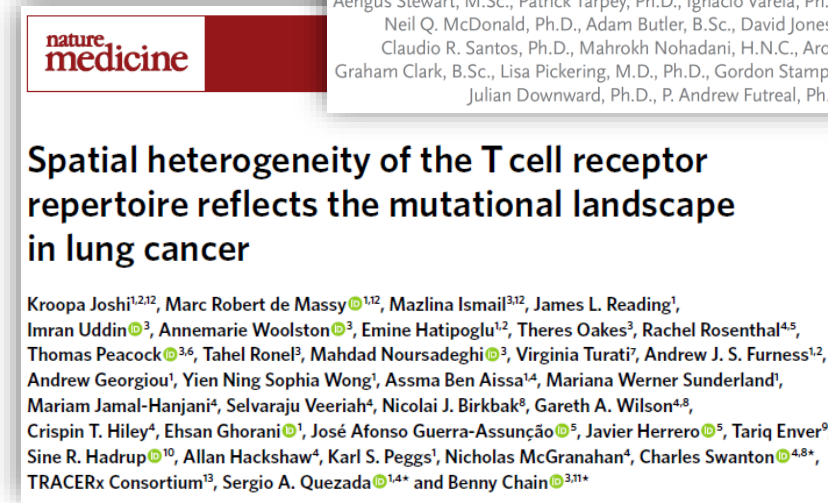
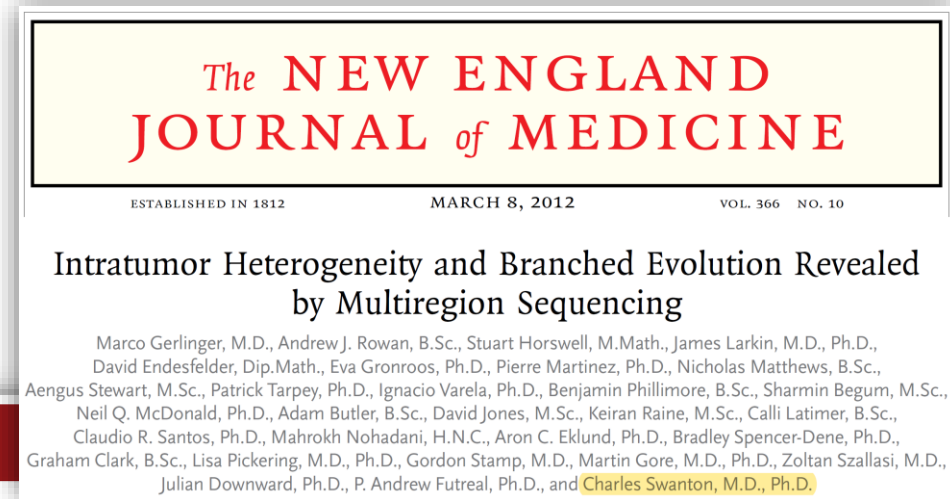
Gray et al., *J. Immunol* (2015); Ishikawa et al., *Nature* (2009); Lau et al., *Science* (2015); Liu et al., *NEJM* (2014); Stetson et al., *Cell* (2008); Xia et al., *Cell Reports* (2016)

STING at a Crossroads: Interpretation of Initial Clinical Results

Deciphering the data

Is intratumoral injection the optimal approach?

- Limited scope of indications: IT is a first step in clinical development
- Consistency of injection
- Difficult to commercialize
- Unique antigenic repertoire between tumors may limit effectiveness of abscopal effect
- Broad activation of STING in TME globally leading to priming in multiple TDLNs
- Challenge with systemic delivery may be therapeutic index

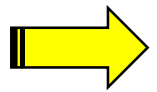


Rejection Ag(s) in (injected) tumor X may be different from tumor X + 1

Systemic Targeting of STING: Next Step in Therapeutic Development?

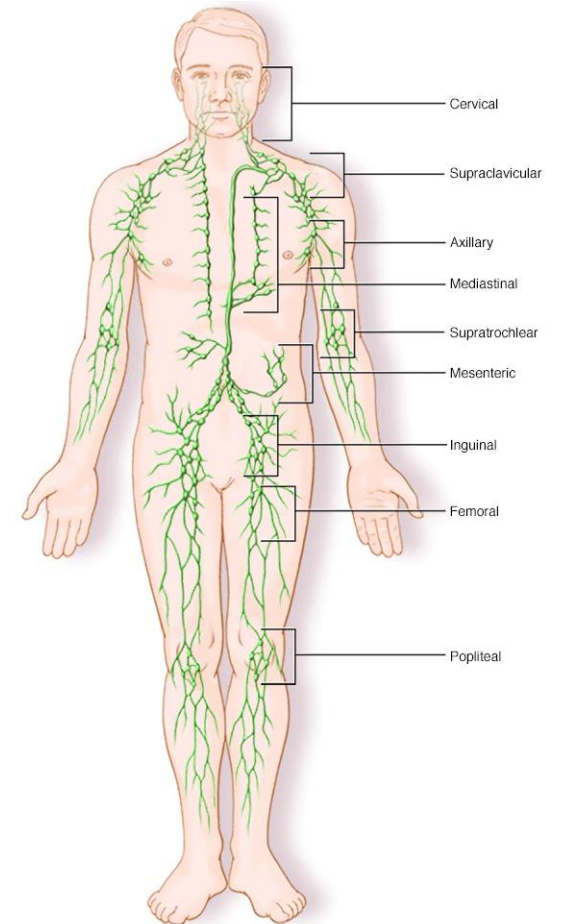
- Important next step in therapeutic advancement of innate immunity
- Activation of STING in TME globally leading to T cell priming in multiple TDLNs
- Challenge with systemic delivery may be therapeutic index given ubiquitous expression of cGAS/STING

Possible exception: Phase 1 First Time in Humans (FTIH), Open Label Study of GSK3745417 Administered to Subjects With Advanced Solid Tumors (NCT03843359)



IV administration (amidobenzimidazole)

Ramanjulu et al., Nature (2018)



The Race is On for Systemic Delivery

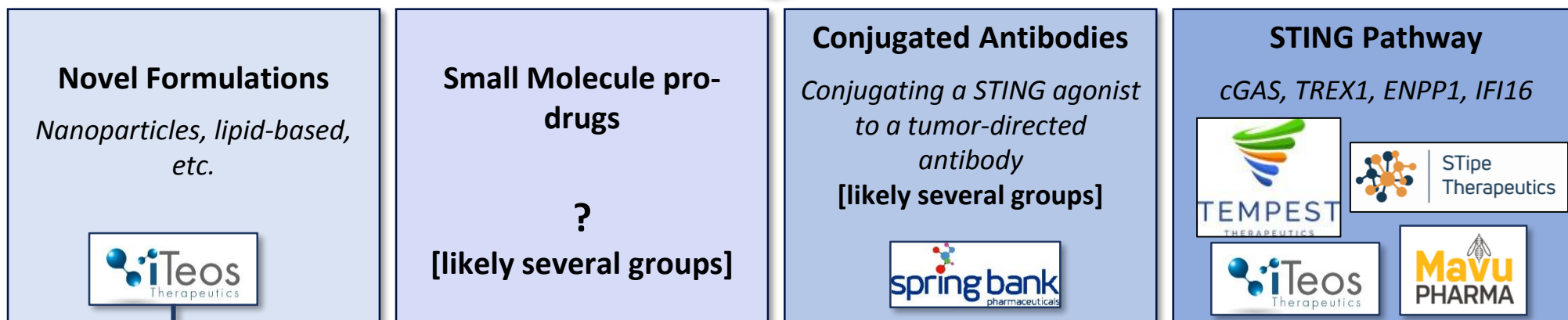
Intratumoral

1st
Generation



Systemic

2nd
Generation



“To improve the therapeutic window of STING agonist, iTeos selected Cristal Therapeutics **nanoparticle** technology to control the delivery towards the tumor microenvironment”

Source: Company Website

“iTeos CEO Michel Detheux says... the target is **instead another protein upstream of STING**”

Source: C&EN article*

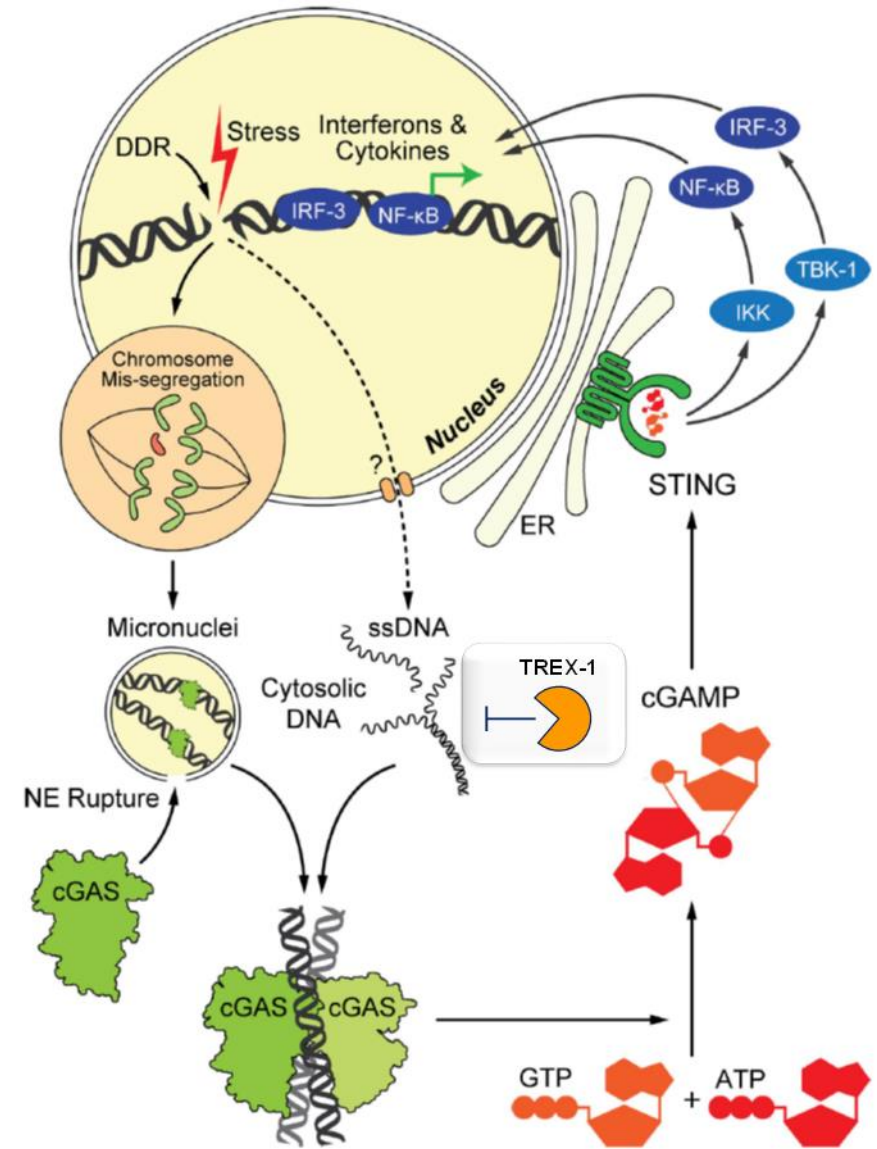
“...non-nucleotide small molecules to indirectly and conditionally modulate the pathway, and we are leveraging this technology to develop **orally bioavailable** STING activators with **first-in-class potential**”

Source: Financing PR – \$20M Series A

TREX-1 Inhibitor Rationale

Systemic approach for targeting STING

- STING is ubiquitously expressed in immune and somatic cell populations
- TREX-1 maintains homeostasis by limiting activation of cGAS-STING in normal cells
- TREX-1 is **induced** by cytosolic DNA resulting from inflammation, DNA repair deficiency, and chemo/radiotherapy
- TREX-1 inhibition enhances dsDNA activation of cGAS and enzymatic production of cGAMP
- TREX-1 **inhibitor** is a systemic approach to localize / partition STING activation in the TME



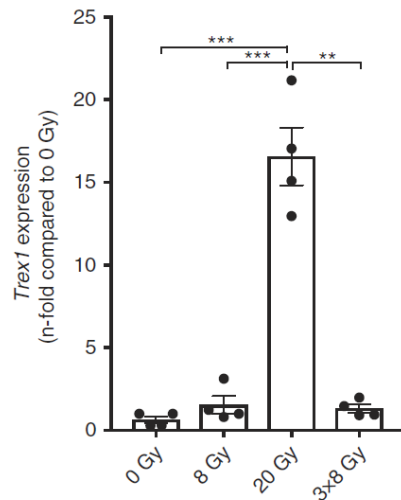
Adopted from Li and Chen, JEM (2019)

TREX-1 Inhibitor Rationale

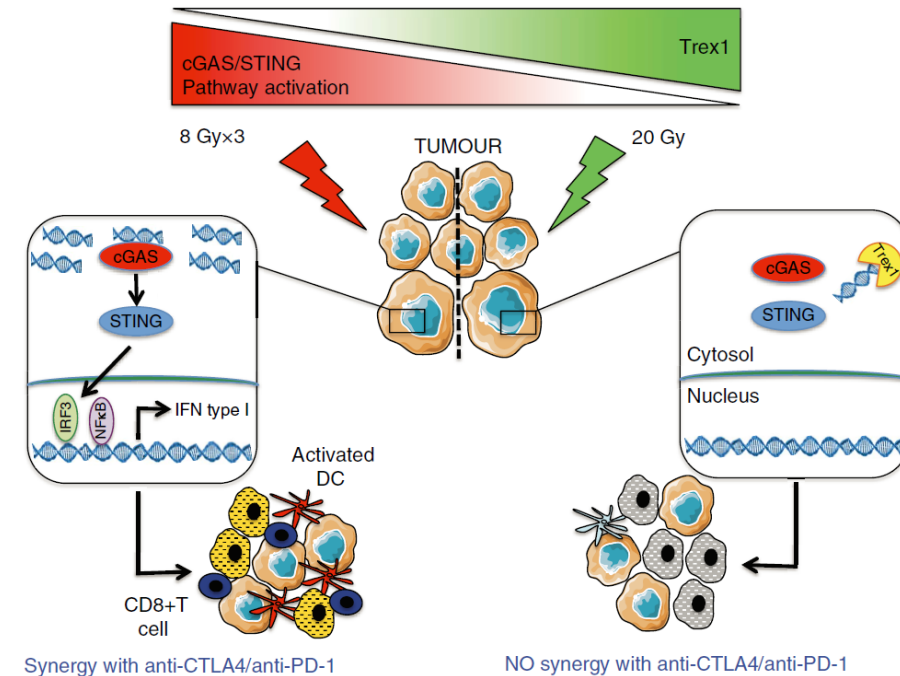
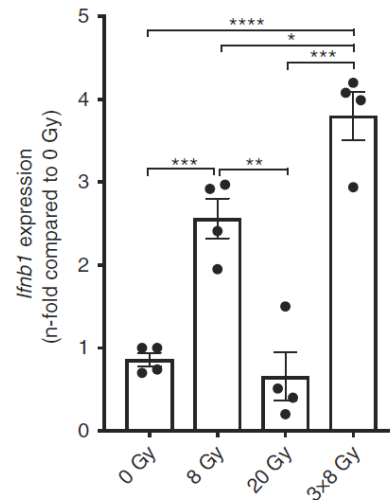
Systemic approach for targeting STING

Radiation dose level has opposite effects on TREX-1 expression and IFN- β levels

**High Dose RT induces
Trex1 expression**



**Fractionated RT
induces IFN β**



Demaria. *Nature Com*, (2017), *TREX1 regulates RT induced tumor immunogenicity*

Concluding Remarks

- STING is at a crossroads—early monotherapy clinical results did not reflect promise of preclinical studies
- Compelling genetic evidence in humans demonstrates that STING is a central mediator of cancer and autoimmunity
- Multiple players and approaches may reveal a better clinical approach for targeting the STING pathway—*it's the approach not the target*
- Selective activation of innate immunity in the TME in metastatic disease with systemic therapies may be an optimal clinical approach for effectiveness