



# 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

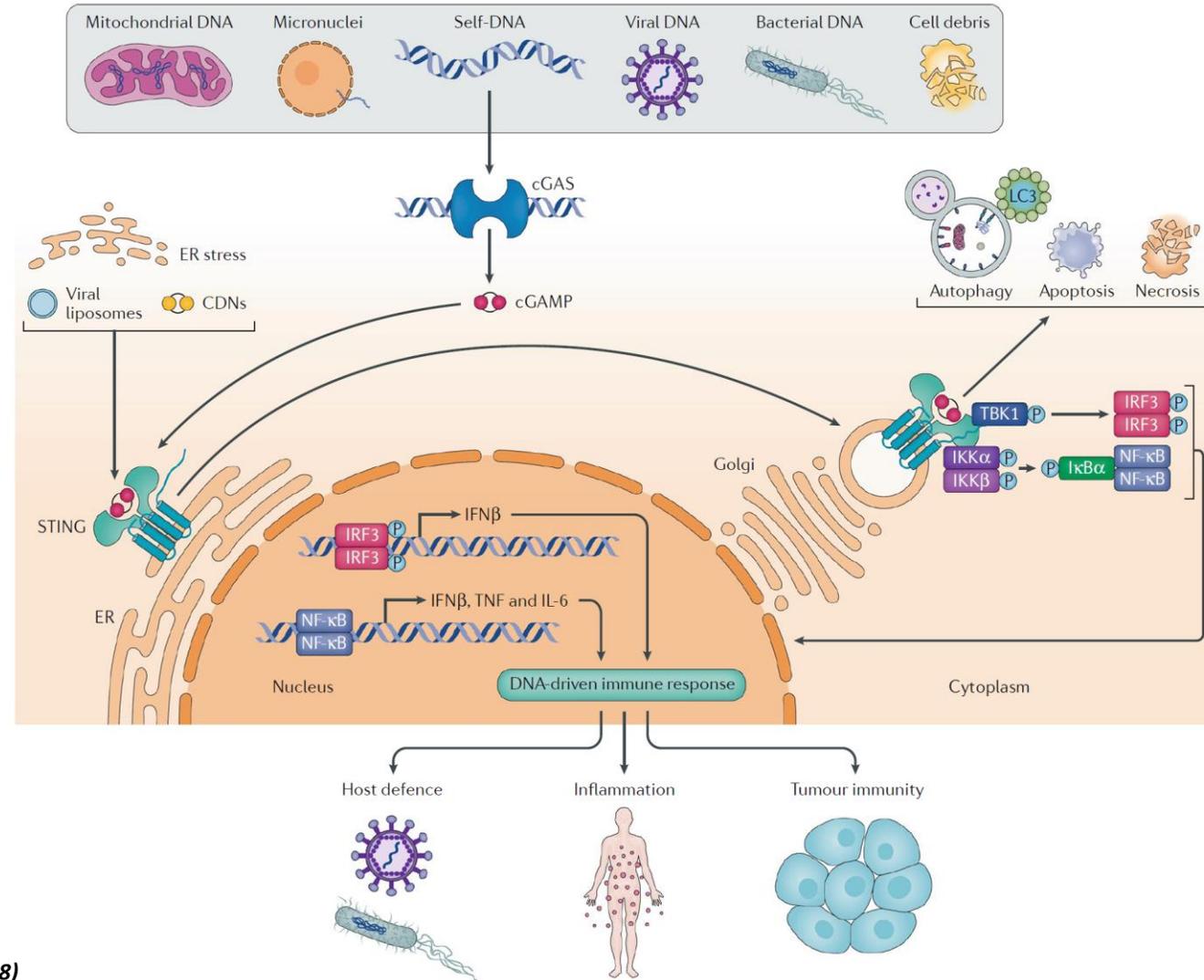
- Scientific rationale for targeting STING, revisited
- Clinical-staged STING agonists, status and results
- Have expectations been met—is STING at a crossroads?
- Other approaches and rationale for targeting STING
- Concluding remarks

# 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

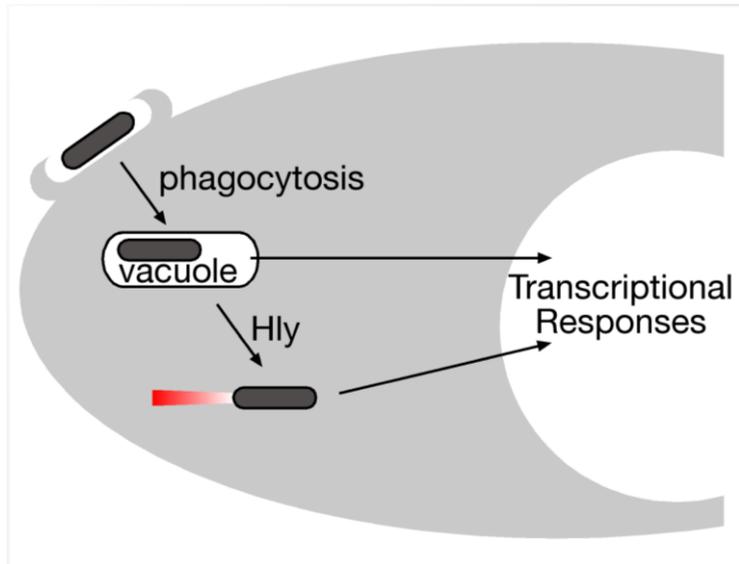


Ishikawa et al., Nature (2009); Burdette and Vance, Nature (2011); Motwani et al., Nat Rev Genetics (2018)

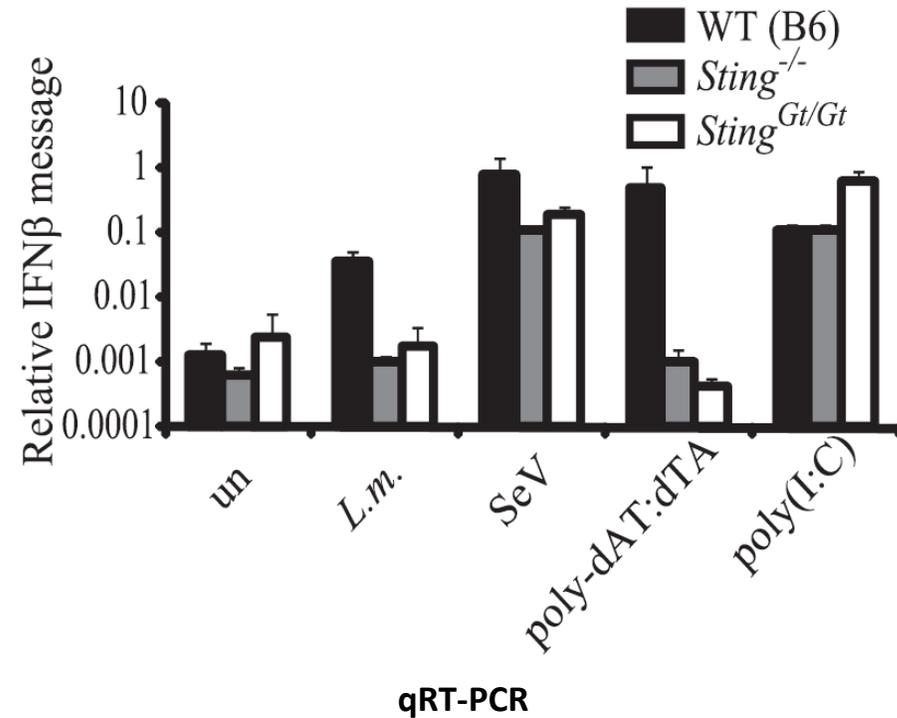
# Rationale for Targeting STING

Cytosolic DNA sensing pathway

## Listeria (*Lm*) intracellular infection



## Induced IFN- $\beta$ expression

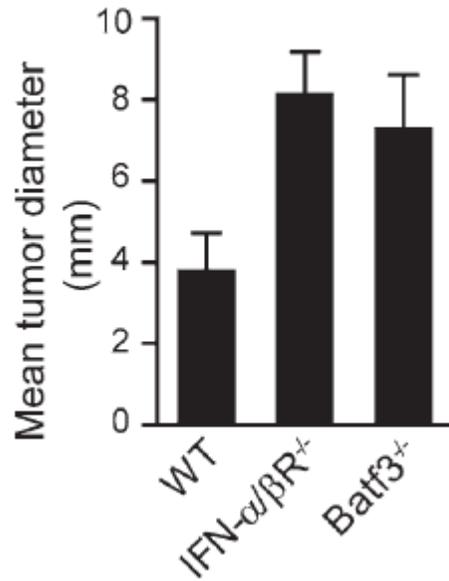


Luster, Moors and Portnoy, 1994 (unpublished); Woodward et al., *Science*, (2011);  
Burdette et al., *Nature*, (2011); and, Sauer et al., *Infection and Immunity*, (2011)

# Rationale for Targeting STING

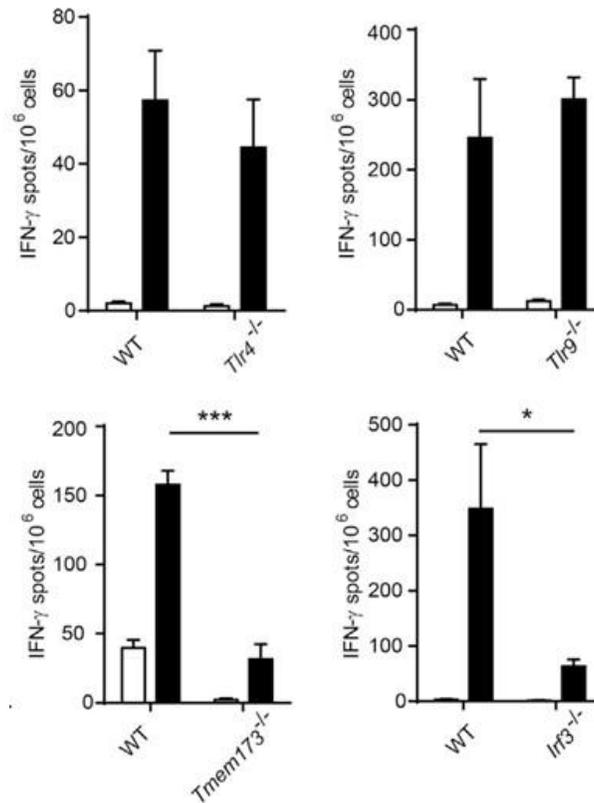
*Tumor-initiated T cell priming is STING-dependent*

**CD8 $\alpha^+$  DC production of IFN- $\beta$  in TME required for tumor inhibition**

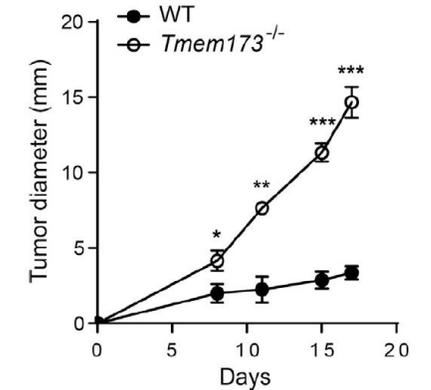
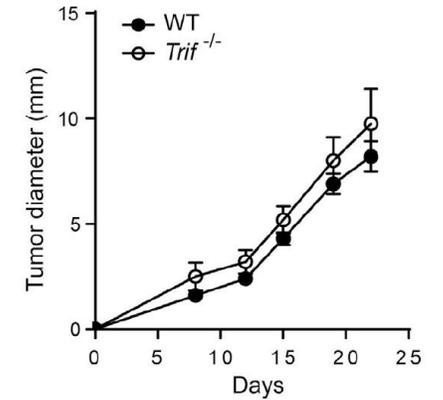


Fuertes et. al., JEM (2011); Woo, Gajewski, Immunity, (2014)

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



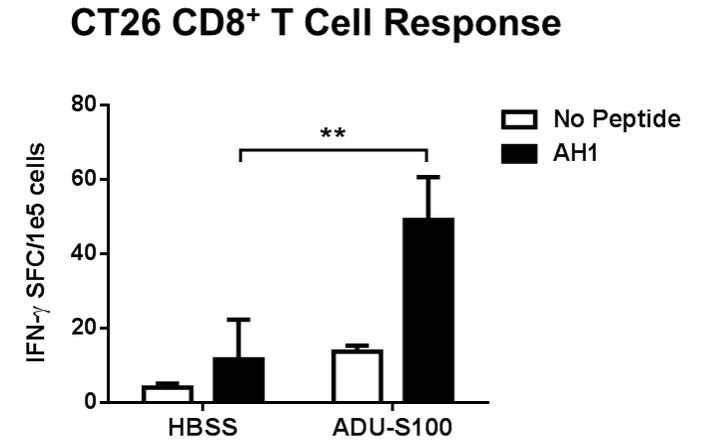
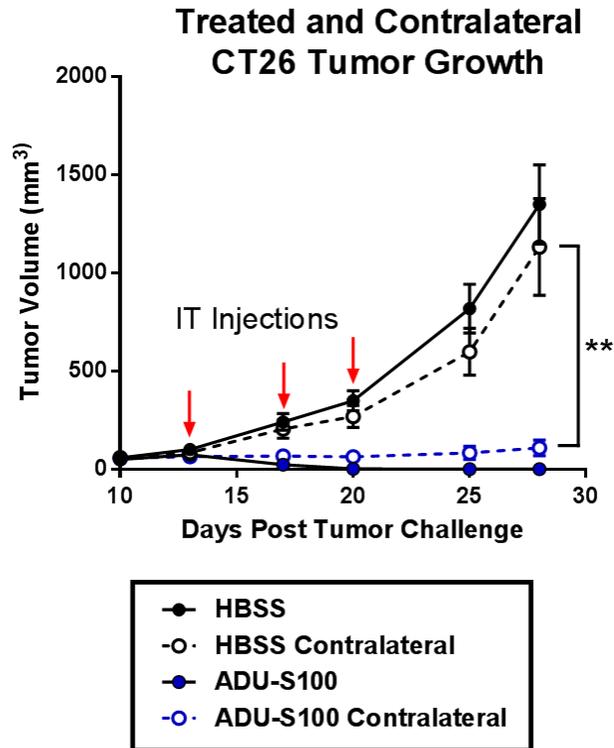
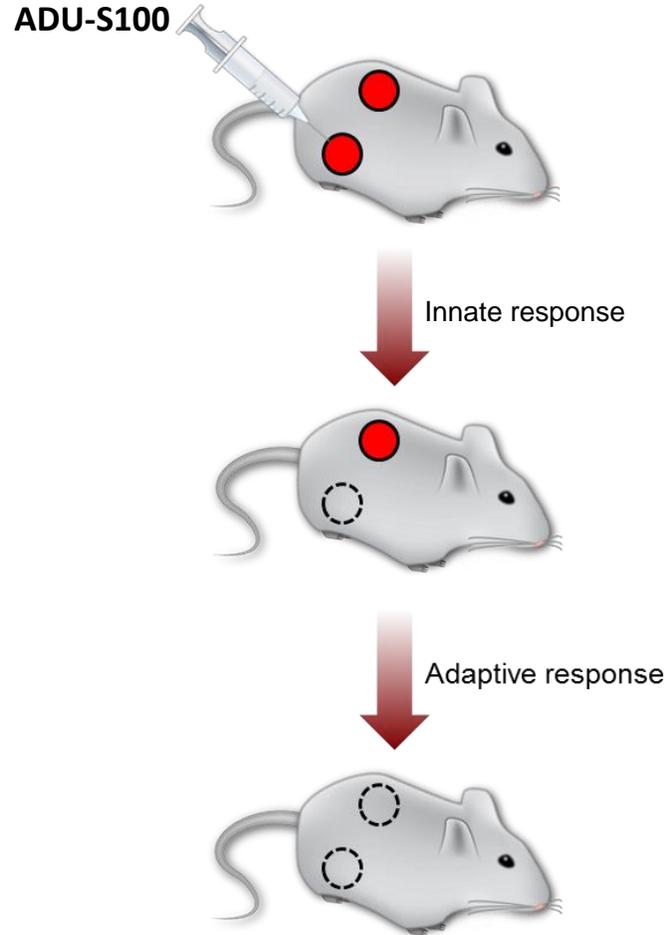
**CD8 T cell priming**



**Tumor control**

# Rationale for Targeting STING

*Synthetic cyclic dinucleotides induce in situ priming and abscopal effect*

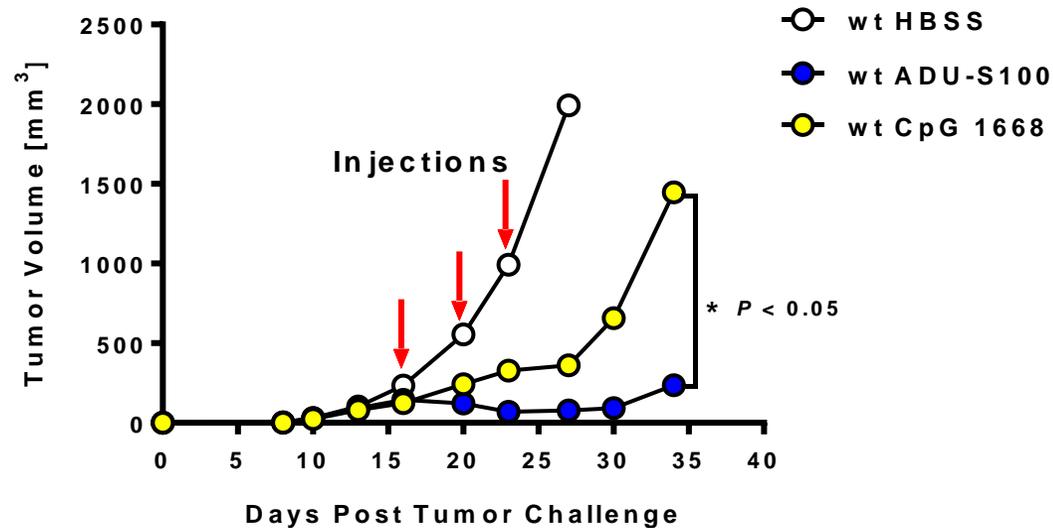


Corrales and Hix Glickman et al, Cell Reports (2015)

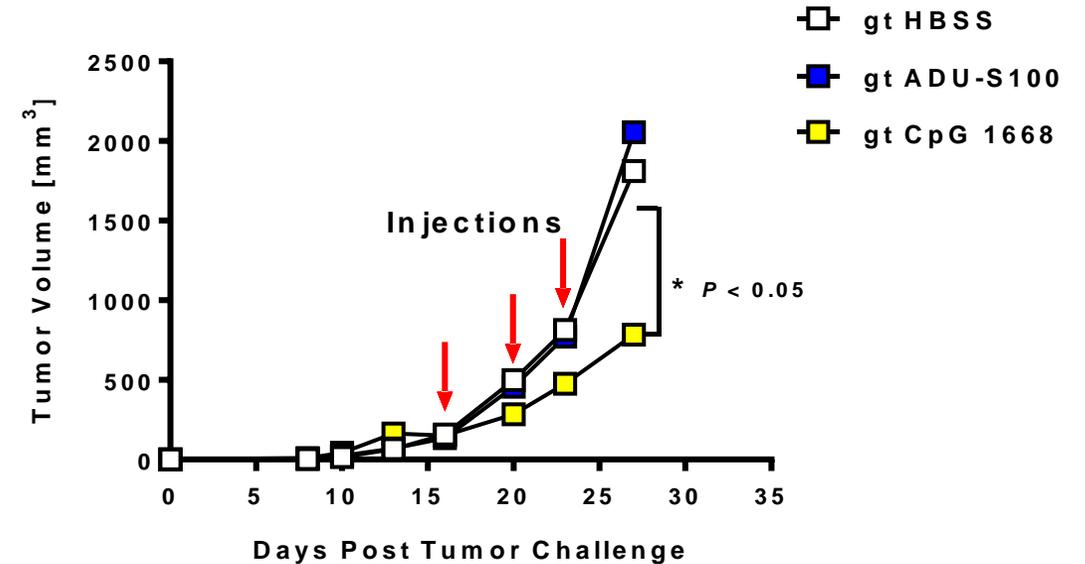
# Rationale for Targeting STING

*CDN induced anti-tumor efficacy is STING-dependent*

Wild-Type C57BL/6 Mice



STING<sup>-/-</sup> (Goldenticket) Mice



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

# Multiple Groups are Targeting STING

Pre-clinical and clinical programs

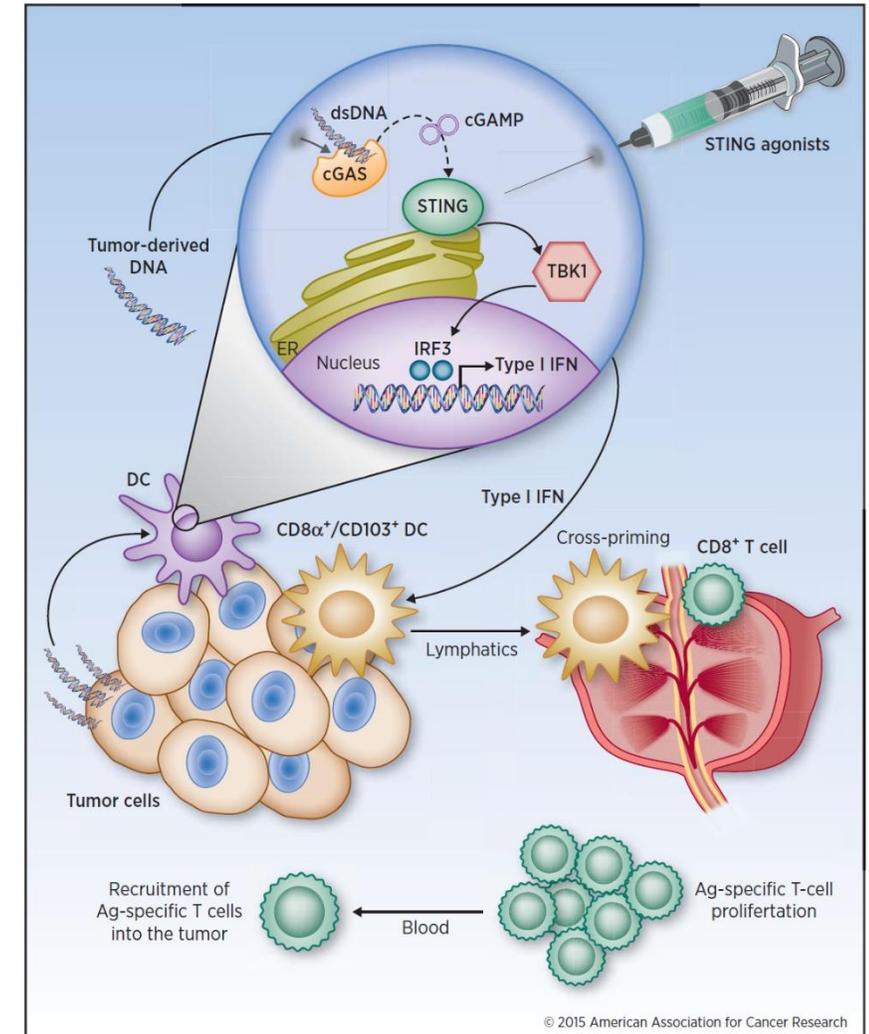
IT Intratumoral Systemic

| 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  | Precl/ Disc |
| Takeda                     | TAK-676        | Unknown  | Small-molecule STING agonist  | Precl/ Disc |
| Takeda/ Curadev            | CRD5500        | Unknown  | Small-molecule STING agonist / “amendable to biconjugation as ADC”      | Precl/ Disc |
| Abbvie (Mavupharma)        | MAVU-104       | Oral     | ENPP1 inhibitor   | Precl/ Disc |
| Synlogic                   | SYNB1891       | IT       | E. coli engineered to produce high levels of the STING agonist c-di-GMP | Precl/ Disc |
| Spring Bank                | SB11325/ 11396 | IV       | Antibody conjugated STING agonists (Targets Unknown)                    | Precl/ Disc |
| Trillium Therapeutics      | TTI-10001      | Unknown  | Small-molecule STING agonist  | Precl/ Disc |
| Codiak Biosciences         | exoSTING       | Unknown  | Engineered exosome  | Precl/ Disc |
| Venn Therapeutics          | VTX-001        | IT       | Adenovirus that produces the bacterial STING agonist c-di-GMP           | Precl/ Disc |
| iTeos Therapeutics         | Unnamed        | IV       | Small-molecule STING pathway activators                                 | Precl/ Disc |
| Nimbus Therapeutics        | Unnamed        | Unknown  | Small-molecule STING agonist  | Precl/ Disc |
| Bicycle Therapeutics       | Unnamed        | Systemic | Bicycle conjugate   |             |
| Selvita                    | Unnamed        | Unknown  | Small-molecule to activate STING  | Precl/ Disc |
| Stimunity                  | Unnamed        | Unknown  | Vectorized cGAMP – “virus like particle”                                | Precl/ Disc |
| StingInn                   | Unnamed        | Unknown  | Small-molecule STING agonists/ nucleic acid-based STING activators      | Precl/ Disc |
| StingInn/ Vyriad           | Unnamed        | Unknown  | Oncolytic viruses encoding STING pathway activators                     | Precl/ Disc |
| Venenum Biodesign          | Unnamed        | Unknown  | Small-molecule STING agonist  | Precl/ Disc |

# First Clinical Approach to Target STING: Intratumoral (IT)

| Sponsor            | NCT#            | Agent               | Molecule | Phase / Title   |
|--------------------|-----------------|---------------------|----------|---|
| Aduro/<br>Novartis | NCT03172<br>936 | ADUS100<br>/ MIW815 | CDN      | Study of the Safety and Efficacy of MIW815 With PDR001 to Patients With Advanced/Metastatic Solid Tumors or Lymphomas                                   |
| Aduro/<br>Novartis | NCT02675<br>439 | ADUS100<br>/ MIW815 | CDN      | Safety and Efficacy of MIW815 (ADU-S100) +/- Ipilimumab in Patients With Advanced/Metastatic Solid Tumors or Lymphomas                                  |
| Aduro/<br>Novartis | NCT02675<br>439 | ADUS100<br>/ MIW815 | CDN      | Efficacy and Safety Trial of ADU-S100 and Anti-PD1 in Head and Neck Cancer  |
| Merck              | NCT03010<br>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<br>680 | BMS-<br>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<br>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<br>(Spartalizumab qmo)            | Results   |
|---|--------------------------------|---|---|
| 41 pts with cutaneously accessible lesions (10 melanoma, 2 uveal pts) | 11/40 SD (28%)<br>2/40 PR (5%) | 53 pts (q3wk, 1 wk off)<br>30 pts (q monthly) | 12/53 SD (23%); 4/53 PR (8%); 1/53 CR (2%);<br>3/8 ≥PR (38%) in PD1-naive TNBC pts; 2 PR in IO relapsed/refractory melanoma pts;<br>6/30 SD (20%) with q monthly CDN dosing |

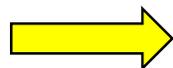
## Merck (MK-1454): NCT03010176

| Monotherapy   | Results       | Combination<br>(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%);<br>3/8 PR (38%) in PD1-naive 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  $\alpha$ -PD-1 mAb
- Some encouraging results:
  - **Aduro/Novartis: 3/8  $\geq$ PR (38%) in PD1-naive 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  $\alpha$ -PD-1 mAb
- Some encouraging results (single armed studies):
  - **Aduro/Novartis: 3/8  $\geq$ PR (38%) in PD1-naive 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 naive 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

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

#### Doses Studied

10 µg → 1600 µg

### *Merck: NCT03010176*

#### Dosing Schedule

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

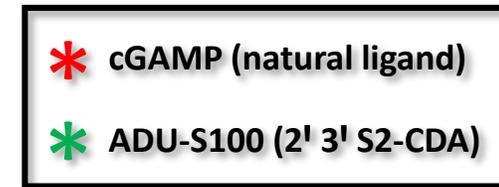
#### Doses Studied

10 µg → 3000 µg

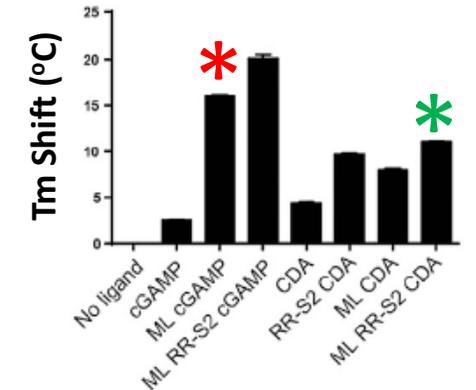
# STING at a Crossroads: Interpretation of Initial Clinical Results

## Deciphering the data

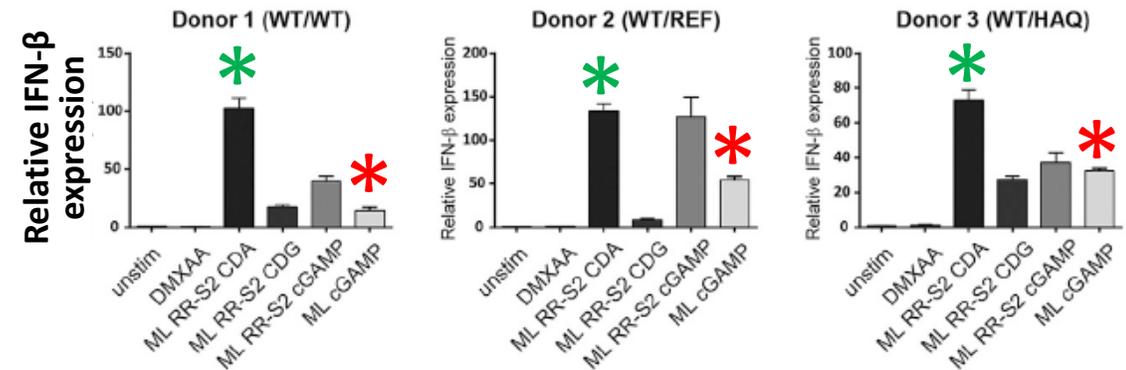
- Differences among molecules in clinical development
  - Aduro, Merck and BMS (IFM) molecules are CDNs
  - Springbank molecule an SMNH
  - Head-to-head studies have not been conducted
  - CDN avidity and signaling can vary according to STING allele
  - Molecules are not formulated—uptake among phagocytes, 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)

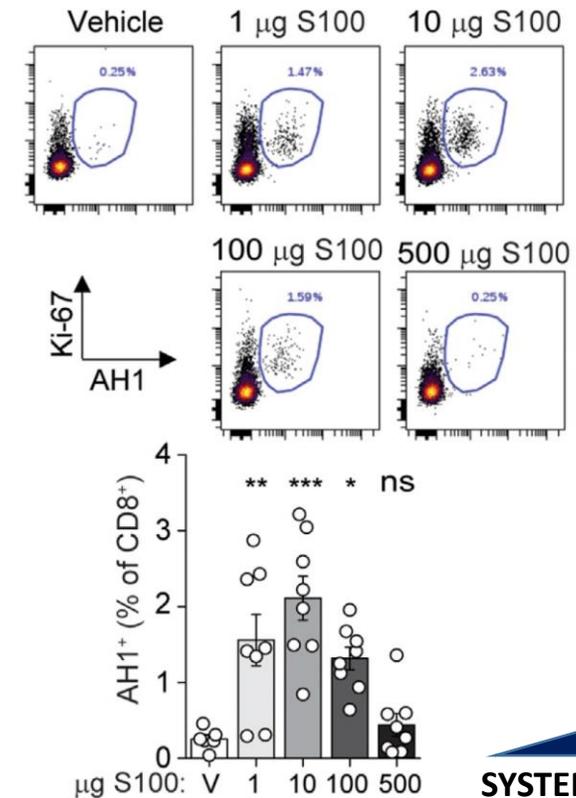
# STING at a Crossroads: Interpretation of Initial Clinical Results

## 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- $\beta$  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- $\beta$  and TNF- $\alpha$  affects priming in the TDLN—a Goldilocks effect

Goldilocks effect of CDN-induced CD8<sup>+</sup> 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

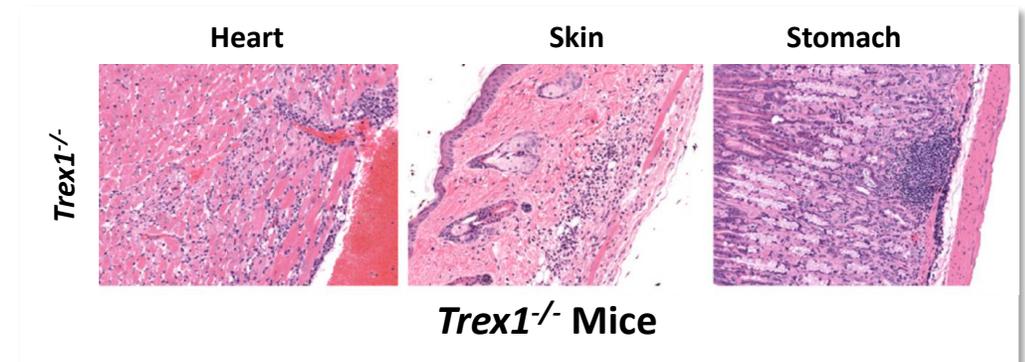
### ➤ Mice:

STING (*TMEM173*)<sup>-/-</sup>: HSV-1 virus infection sensitivity

TREX-1<sup>-/-</sup>: recapitulates human AGS



SAVI



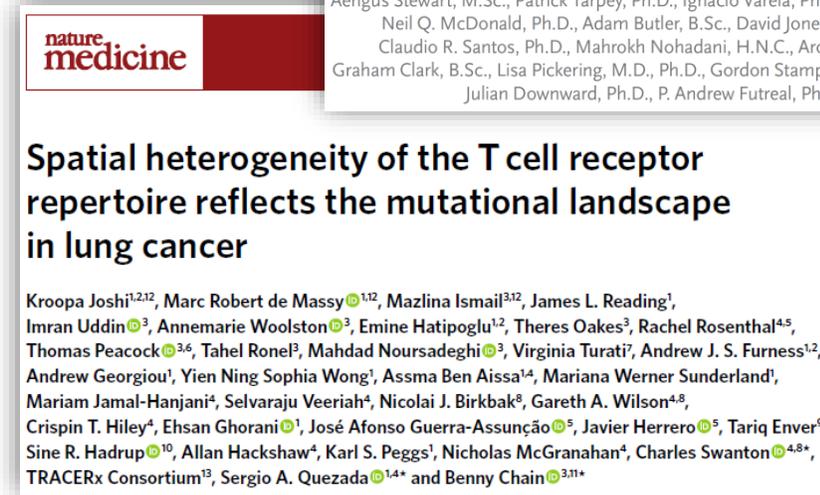
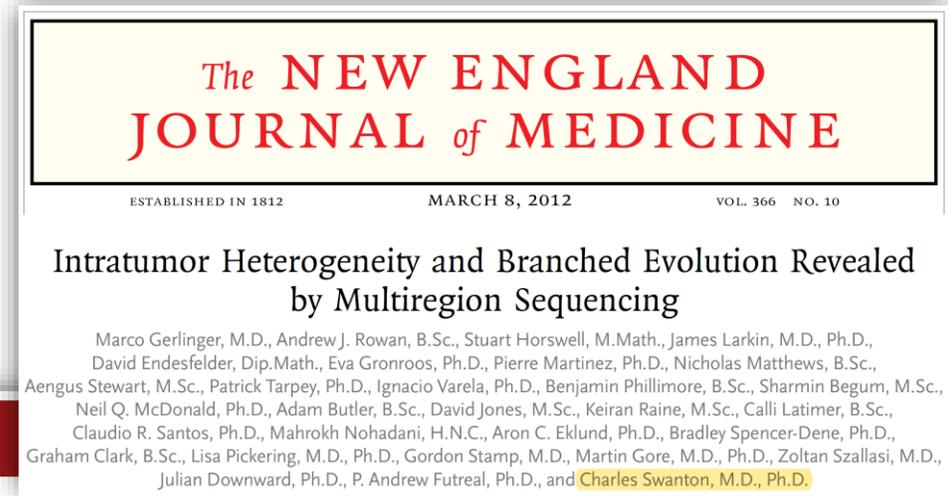
Gray et al., *J. Immunol* (2015); Ishikawa et al., *Nature* (2009); Lau et al., *Science* (2015); Liu et al., *NEJM* (2014); Stetson et al., *Cell* (2008); Xia et al., *Cell Reports* (2016)

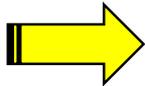
# STING at a Crossroads: Interpretation of Initial Clinical Results

## 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

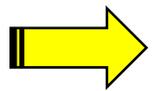


 Rejection Ag(s) in (injected) tumor X may be different from tumor X + 1

# Systemic Targeting of STING: Next Step in Therapeutic Development?

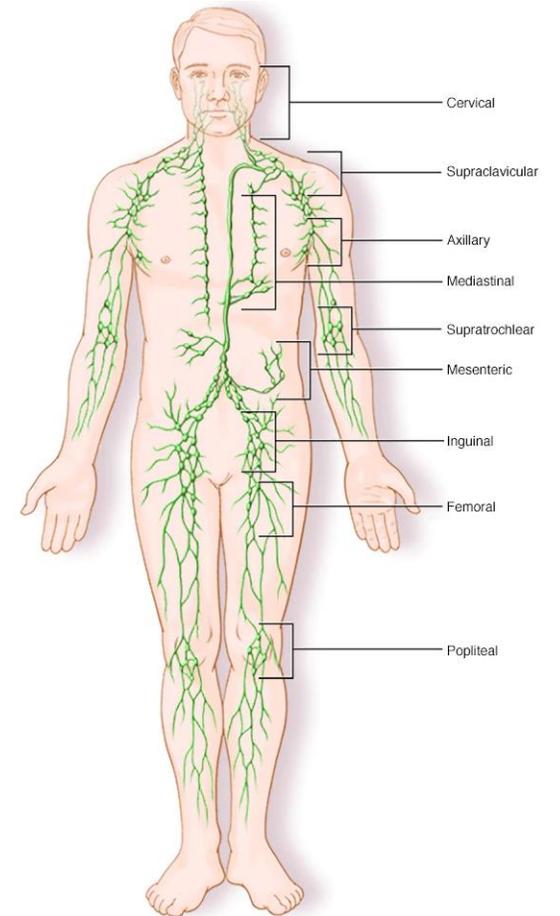
- Important next step in therapeutic advancement of innate immunity
- Activation of STING in TME globally leading to T cell priming in multiple TDLNs
- Challenge with systemic delivery may be therapeutic index given ubiquitous expression of cGAS/STING

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

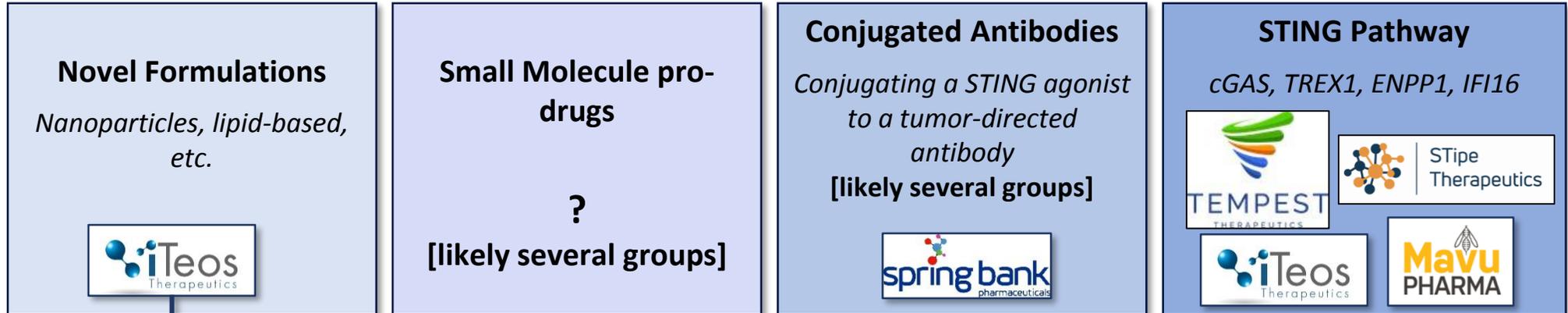
Intratumoral

1<sup>st</sup>  
Generation



Systemic

2<sup>nd</sup>  
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*

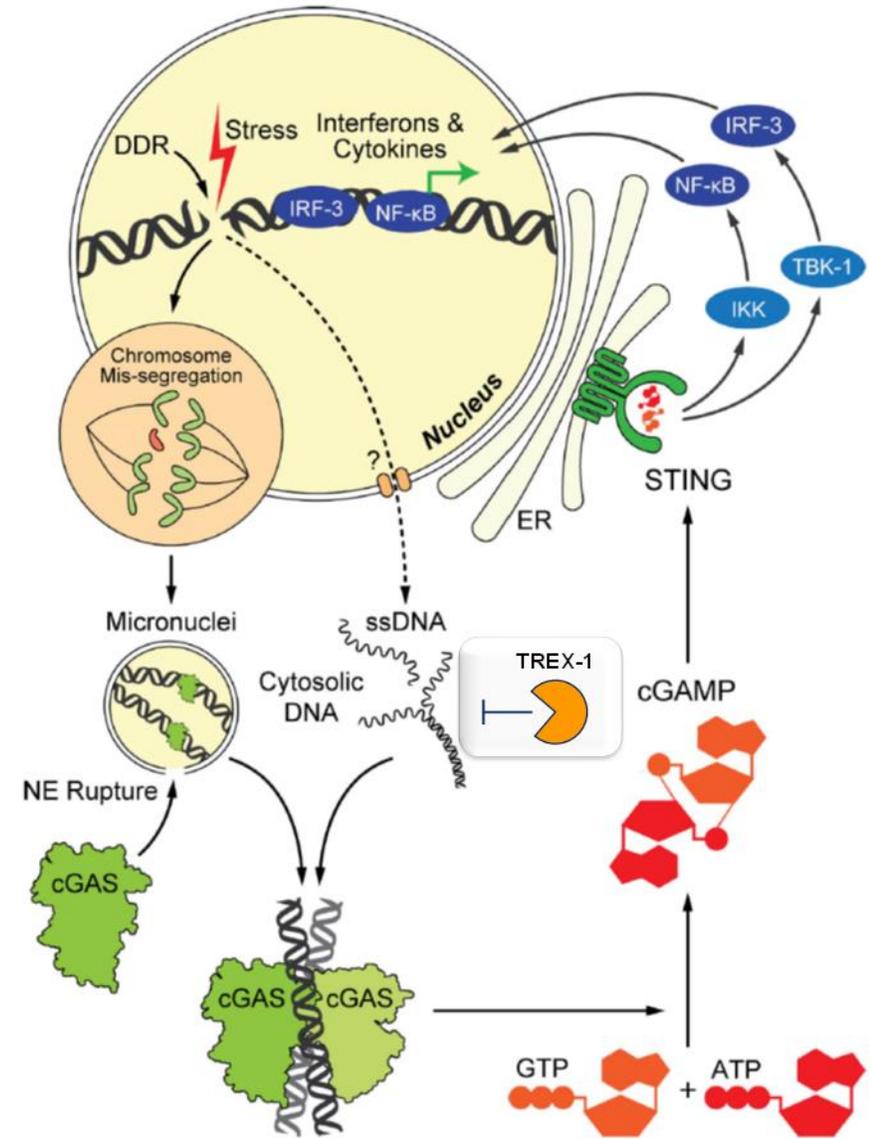
“iTeos CEO Michel Detheux says... the target is **instead another protein upstream of STING**”  
*Source: C&EN article\**

“...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



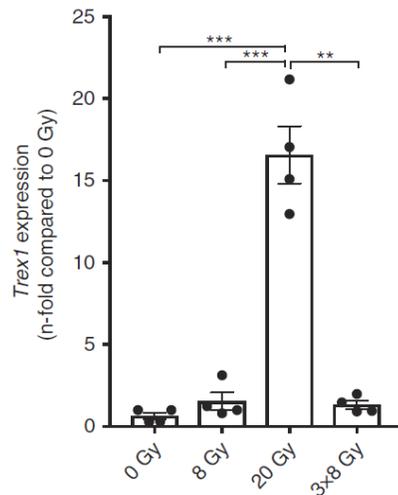
Adopted from Li and Chen, JEM (2019)

# TREX-1 Inhibitor Rationale

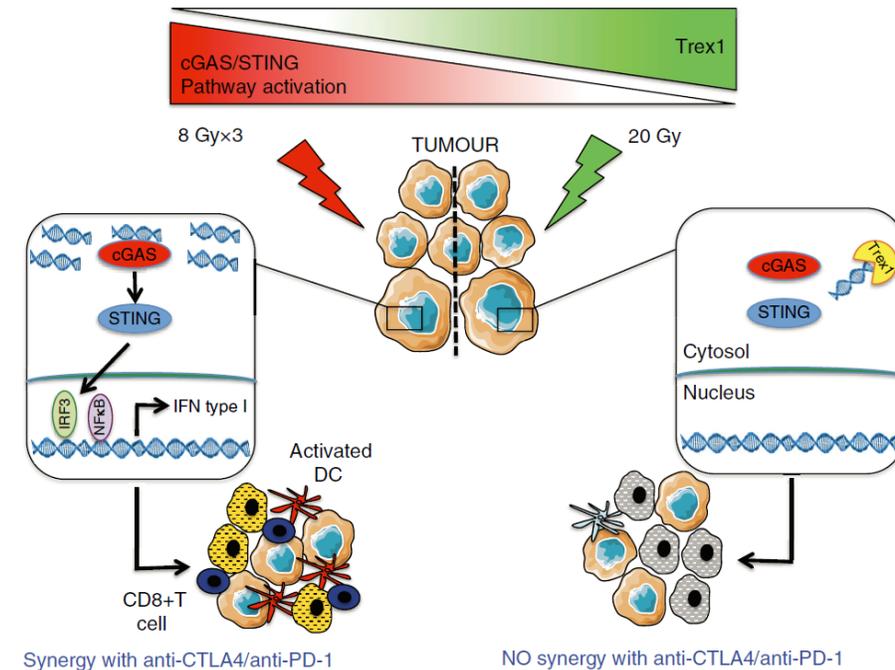
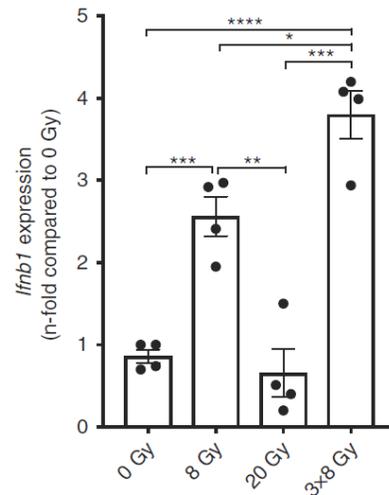
Systemic approach for targeting STING

Radiation dose level has opposite effects on TREX-1 expression and IFN- $\beta$  levels

High Dose RT induces  
Trex1 expression



Fractionated RT  
induces IFN $\beta$



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