



synlogic

## A Novel Class of Living Medicines

Synthetic Biotic™ medicines to perform and deliver  
critical therapeutic functions to treat diseases  
throughout the body

**Using Synthetic Biotic™ Medicines to Activate Innate  
and Adaptive Immunity and Drive Antitumor Immune  
Response**

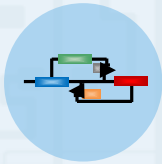
FOCIS 2018 Annual Meeting  
June 20-23, 2018, San Francisco

# Disclosures:

I am an employee of and stockholder in Synlogic Pharmaceuticals, Inc.

# Synthetic Biotic Medicines:

## A Novel Class of Living Medicines



### Synthetic

- **Engineered** bacteria
- With **designed genetic circuits**
- To **degrade metabolites** that induce disease or **synthesize substances** to treat disease



### Biotic: *E. coli* Nissle as chassis:

- Widely-used **oral probiotic**
- **Leverage the safety** of probiotic
- Found within natural human **microbiome**
- **Amenable to genetic manipulation**

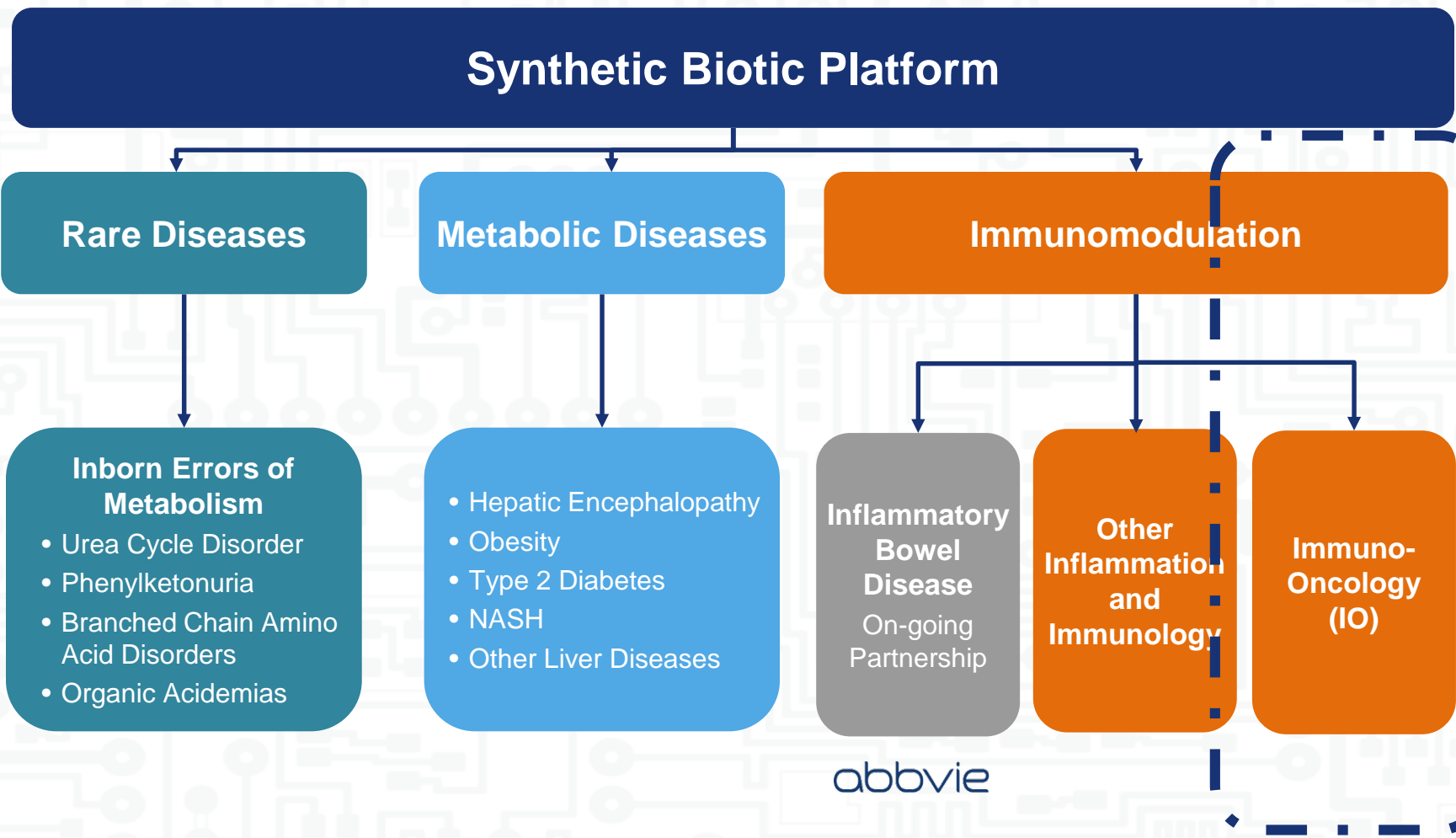
**Synthetic Biology + Bacteria =  
Synthetic Biotic Medicine**

**Therapeutic** delivered locally  
to treat systemic diseases



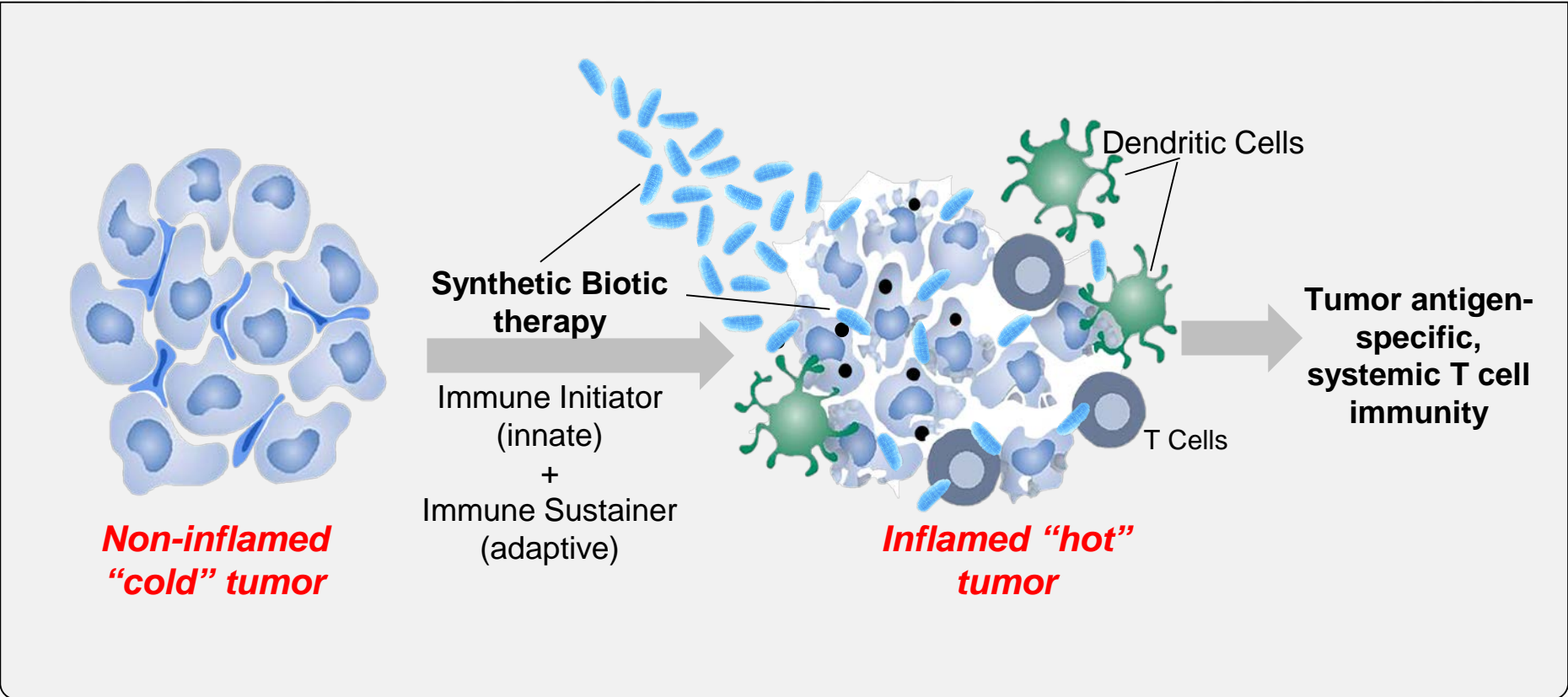
# Synthetic Biotic Platform Breadth and Potential:

## Initial Clinical Focus on Orphan Metabolic Diseases



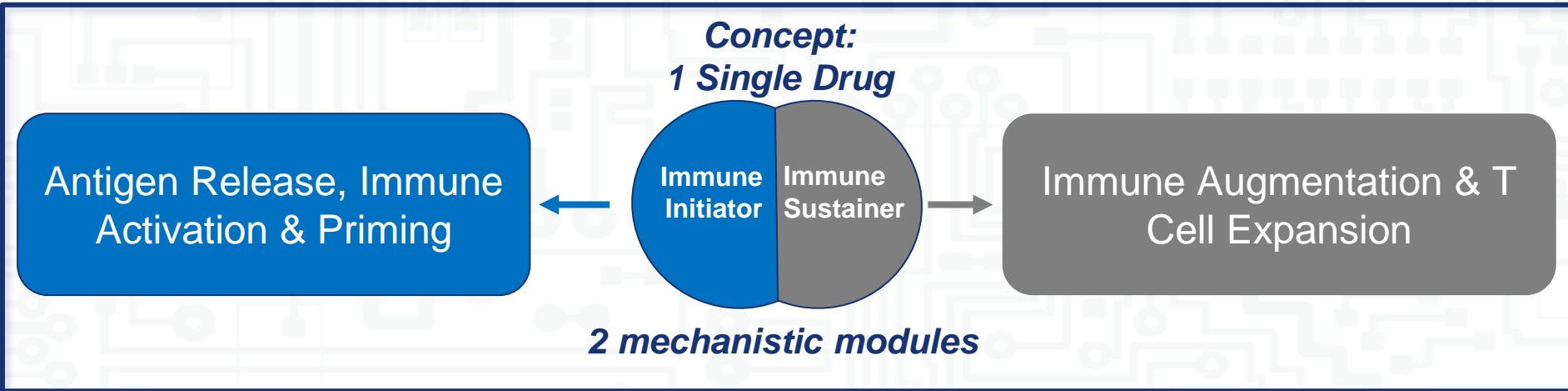
# Synlogic Vision for Immuno-Oncology:

Living Medicines to Turn a “Cold” Tumor “Hot”



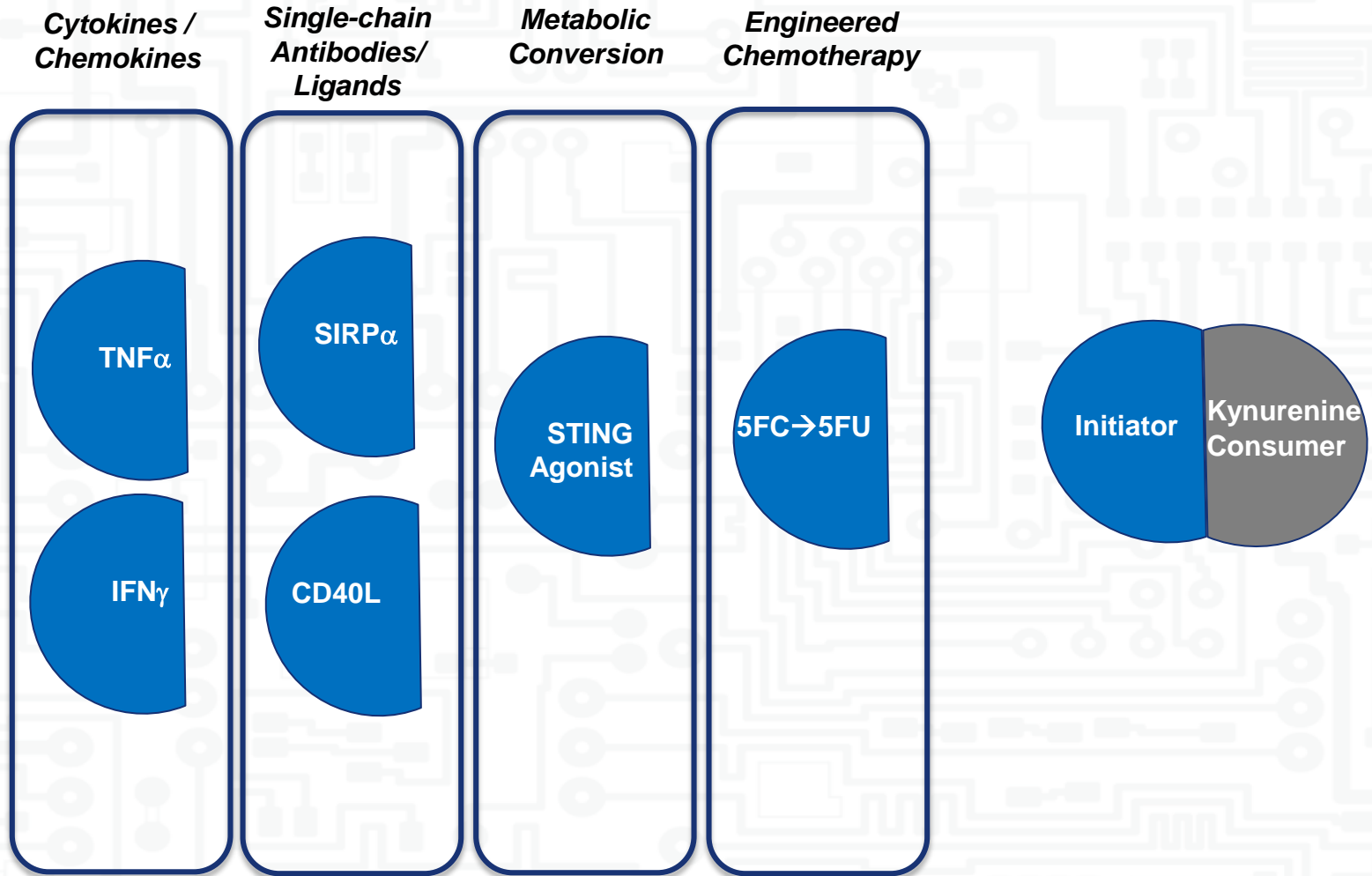
# Synlogic Vision for Immuno-Oncology:

Living Medicines with High Response Rates and Abscopal Effect as Single Agents



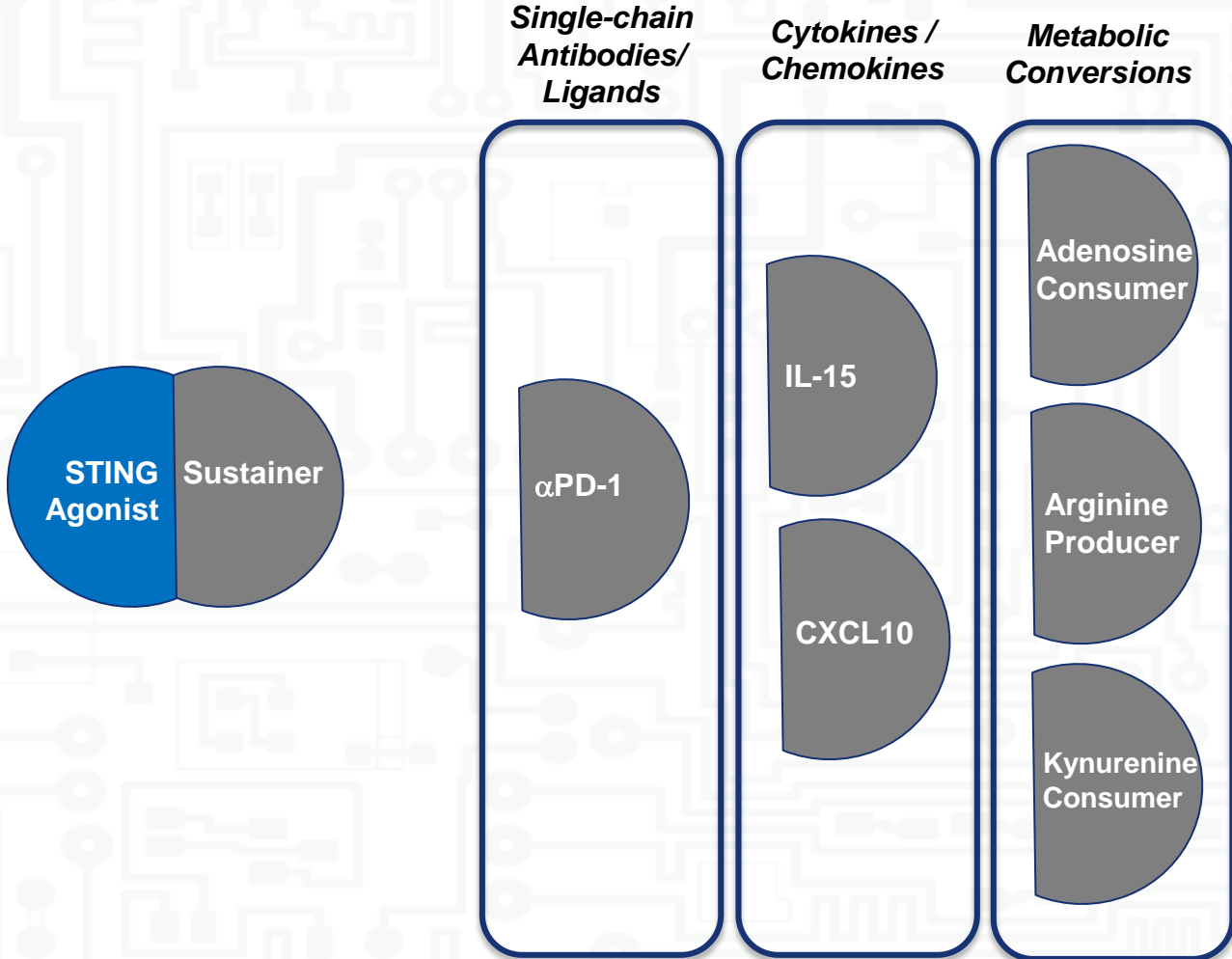
# Immune Initiators:

Rational Design of Immune Pathways for Antigen Release, Immune Activation & Priming



# Immune Sustainers:

Rational Design of Immune Pathways Immune Augmentation & T Cell Expansion





# Design of Initiator SYN-STING and Sustainer SYN-Kyn

Antigen Release,  
Immune Activation  
& T cell Priming

Immune Initiator    Immune Sustainer

Immune Augmentation & T Cell Expansion

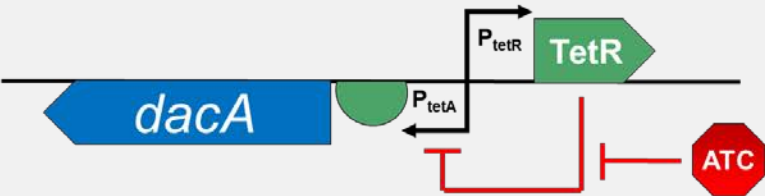
SYN-STING



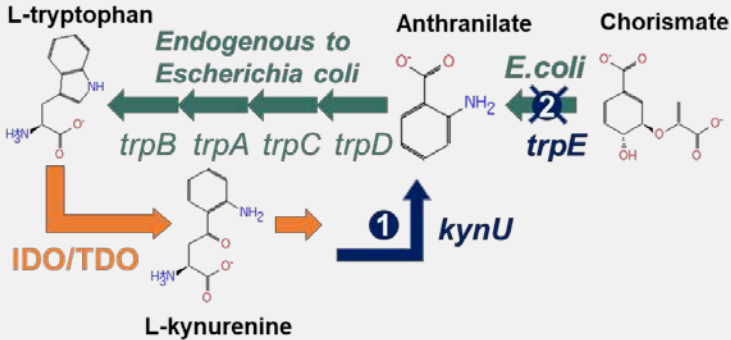
SYN-Kyn

Inducible STING Agonist

Constitutive Kynurenine Consumption



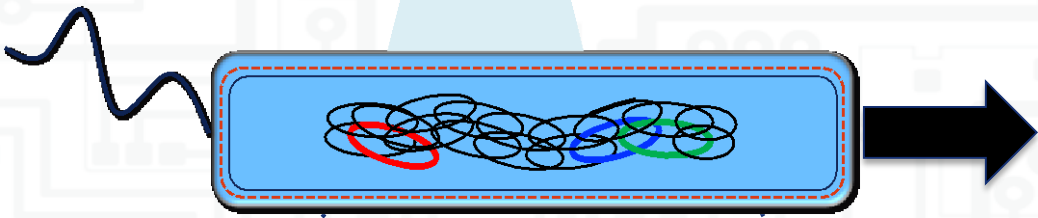
*dacA*, a diadenylate cyclase gene from *Listeria monocytogenes*, driven by *Ptet*



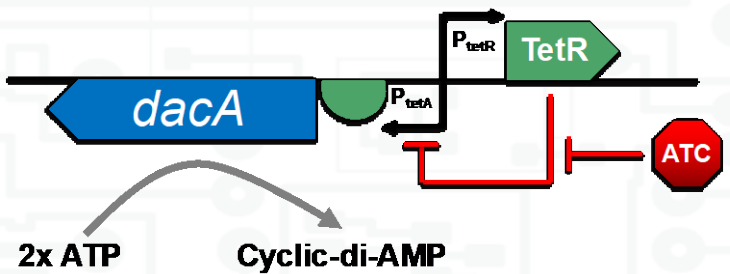
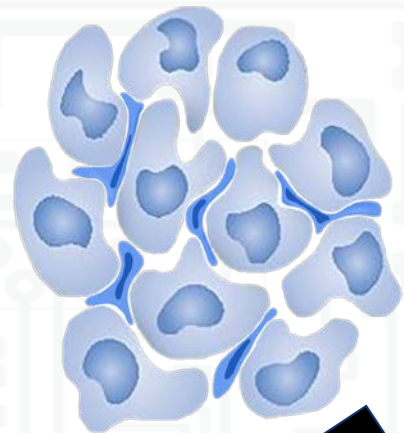
*kynU*, a kynureninase gene from *Pseudomonas fluorescens*, constitutively expressed

# Delivery of STING Agonist to Induce Anti-tumor Immunity: Engineering SYN-STING to Robustly Activate STING Pathway in the TME

## SYN-STING

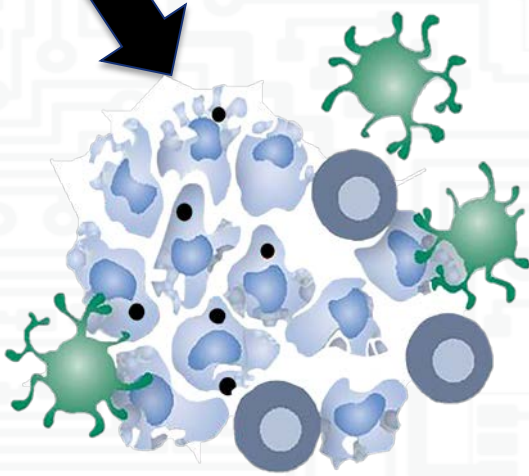


## “Cold Tumor”



*dacA*, a diadenylate cyclase gene from *Listeria monocytogenes*, driven by Ptet

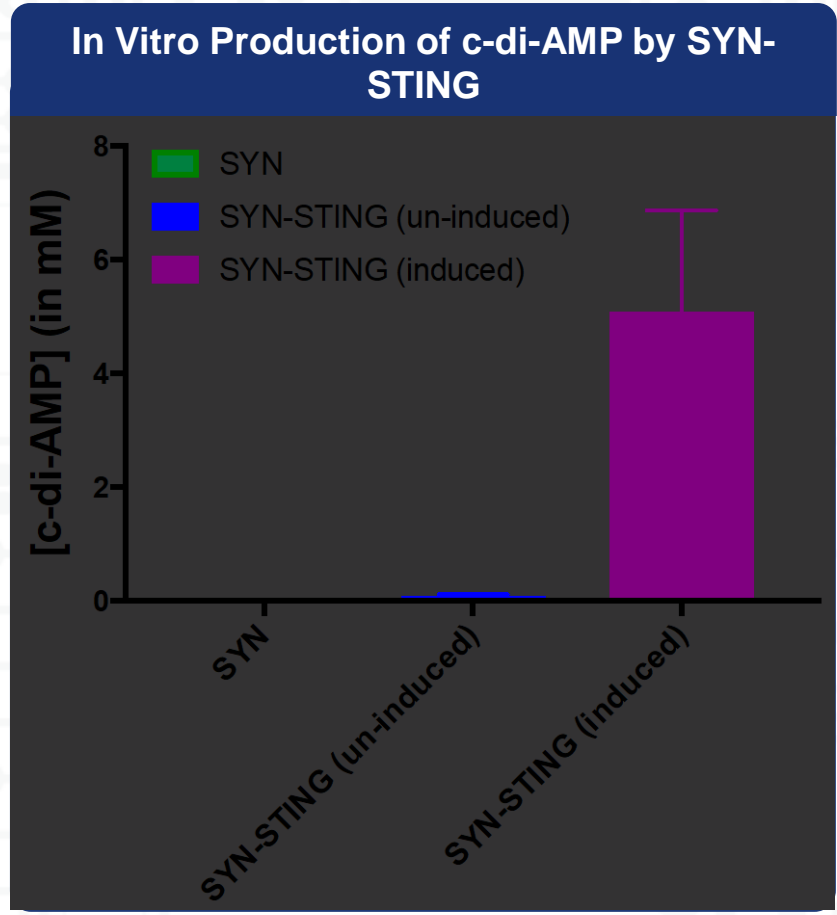
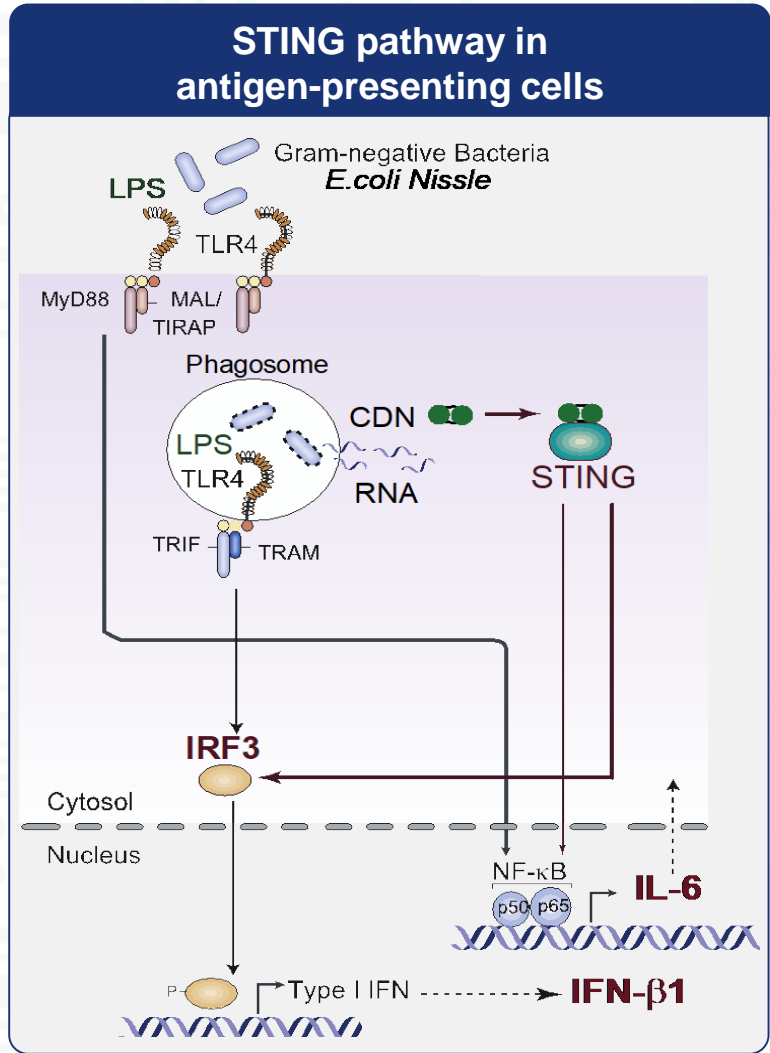
STING PATHWAY ACTIVATION IN INNATE CELLS



## “Hot Tumor”

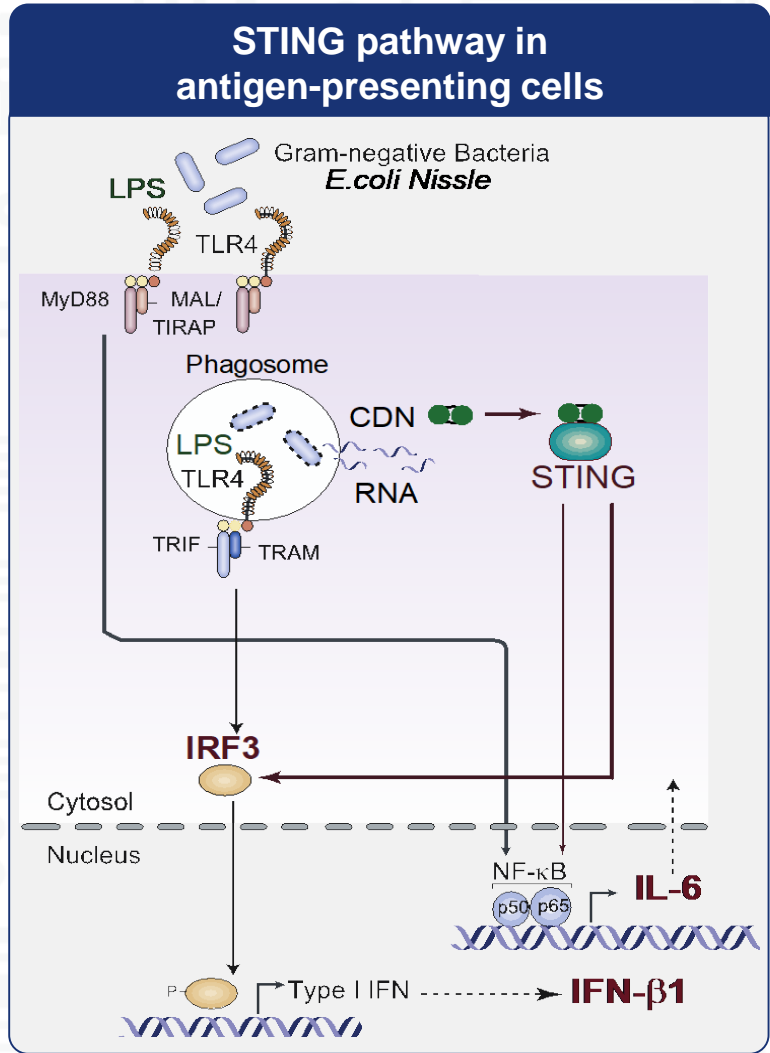
# STING Initiator Module In Vitro Characterization:

## STING Pathway and SYN-STING Activity In Vitro

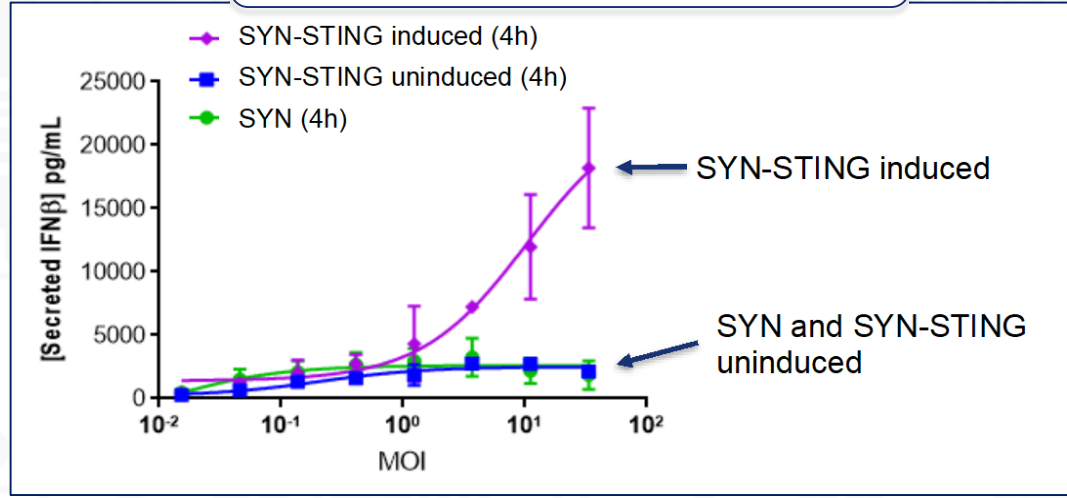


# STING Initiator Module In Vitro Characterization:

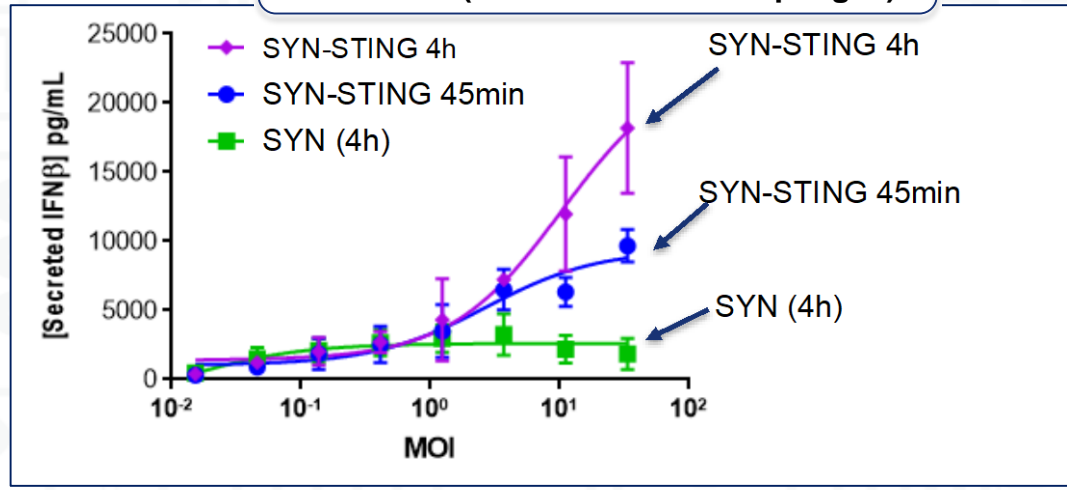
## STING Pathway and SYN-STING Activity In Vitro



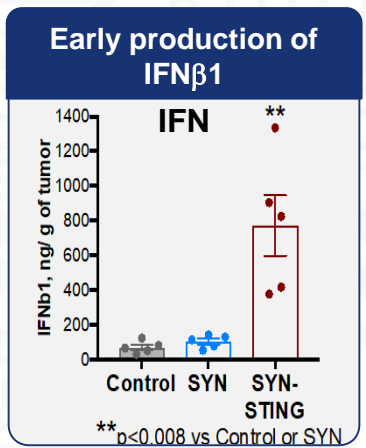
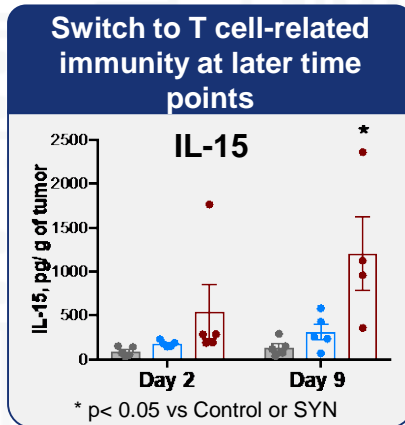
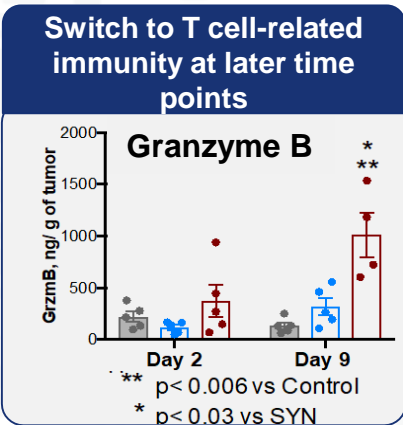
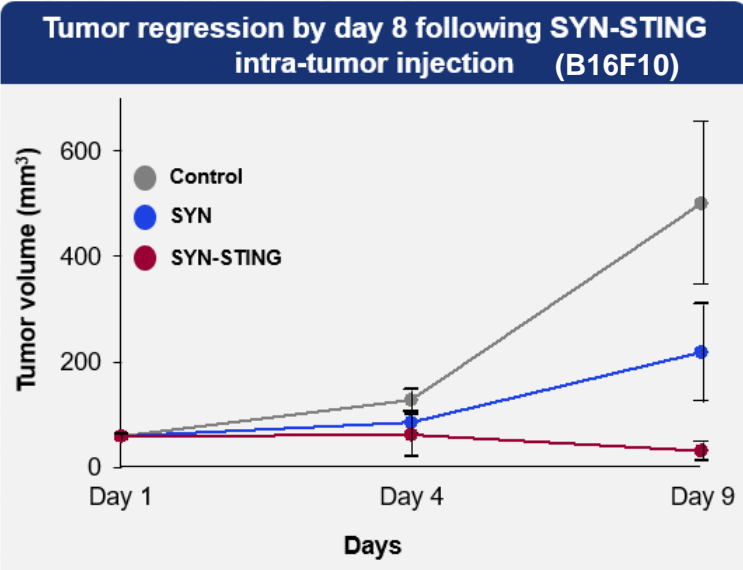
**Induced vs Un-induced RAW cells (immortalized macrophages)**



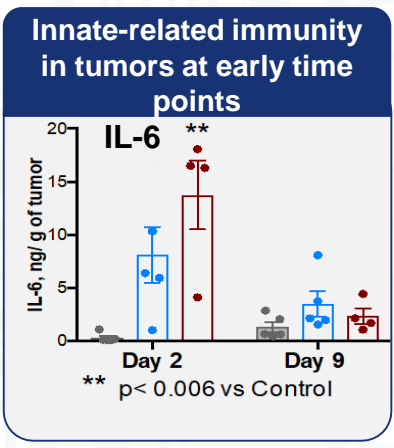
**Time course RAW cells (immortalized macrophages)**



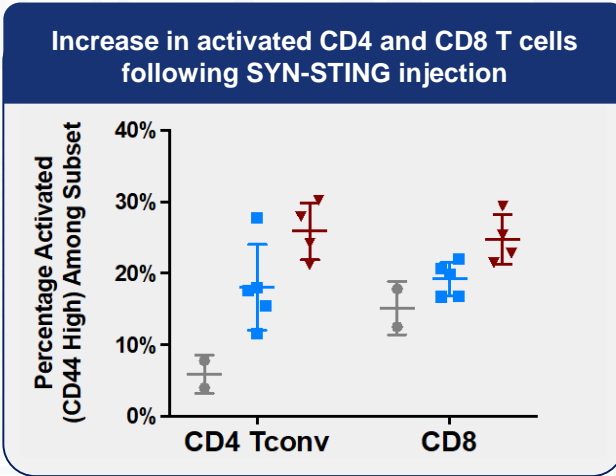
# STING Initiator Module In Vivo Characterization: SYN-STING Strain Delivers Robust Anti-tumor Activity as Single Agent



*Initial robust Type I IFN production*  
*Leads to early innate activation*



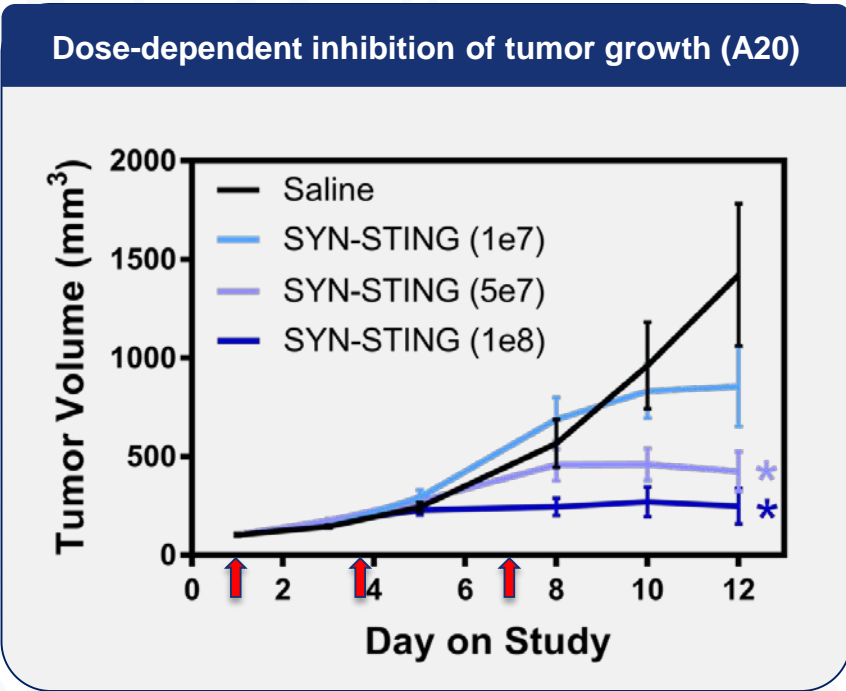
*Followed by*  
*an adaptive T cell response*



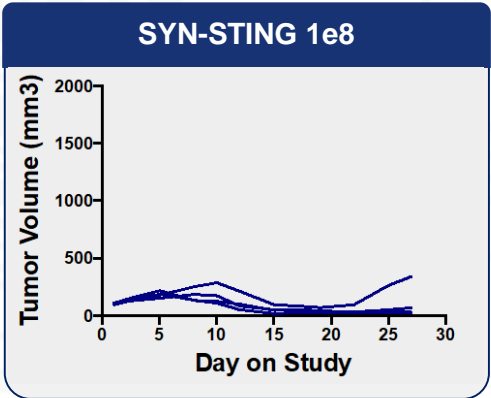
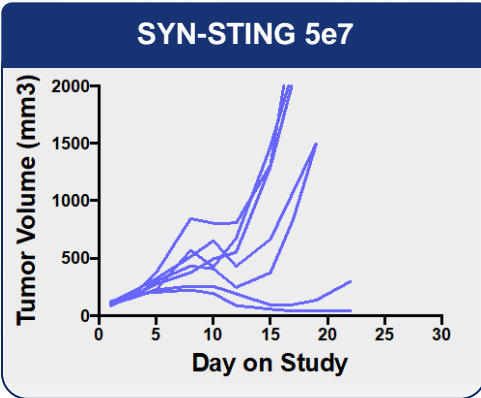
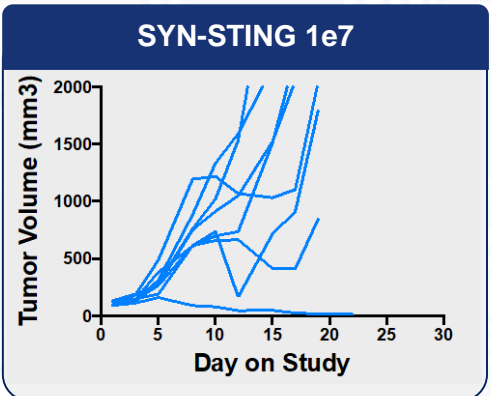
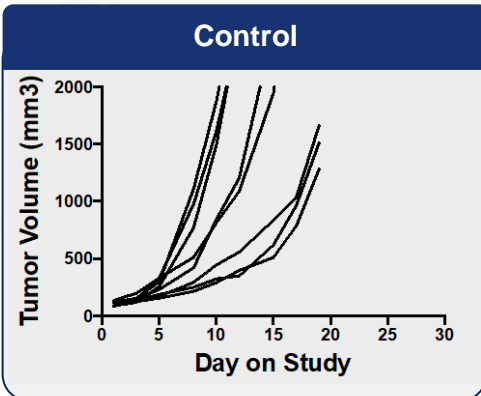
**Sequence of activation following intra-tumor injection of SYN-STING**

# Pharmacological Control of Anti-Tumor Activity:

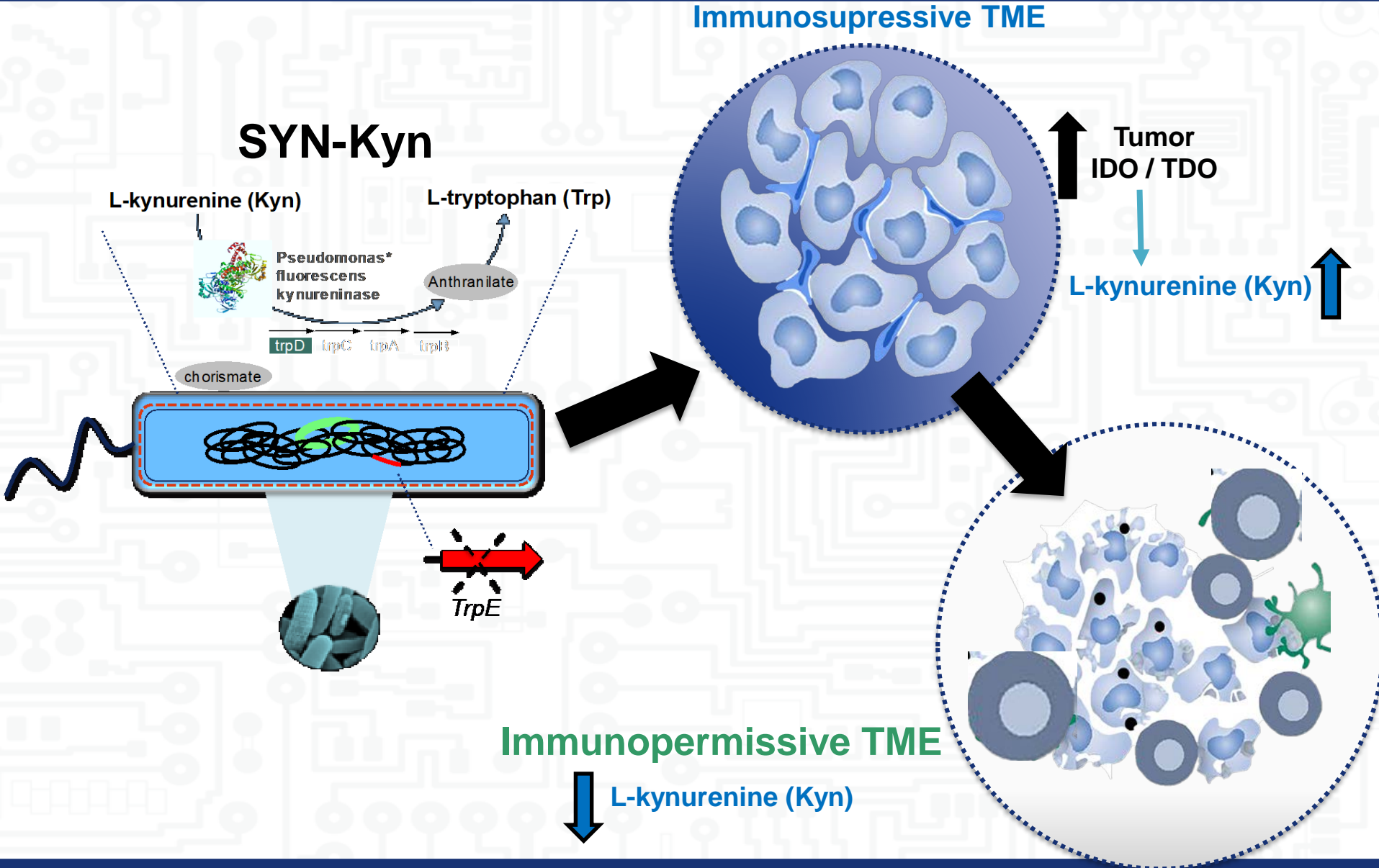
## SYN-STING drives dose-dependent tumor control in A20 lymphoma model



↑ = Dose



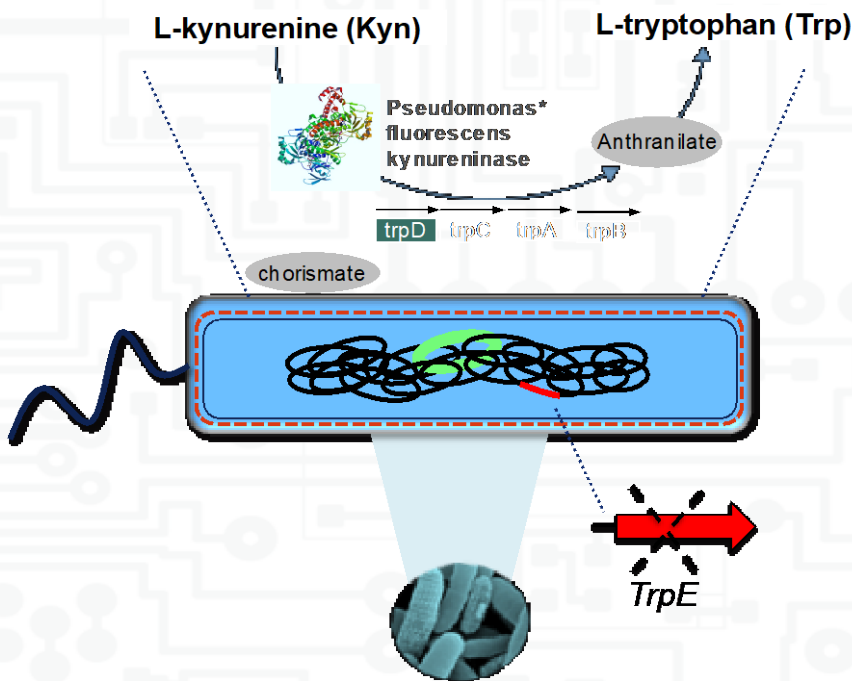
# Removal of Kyn from the TME to Relieve Immunosuppression: Engineering SYN-Kyn to Efficiently Consumes Kynurenine in the TME



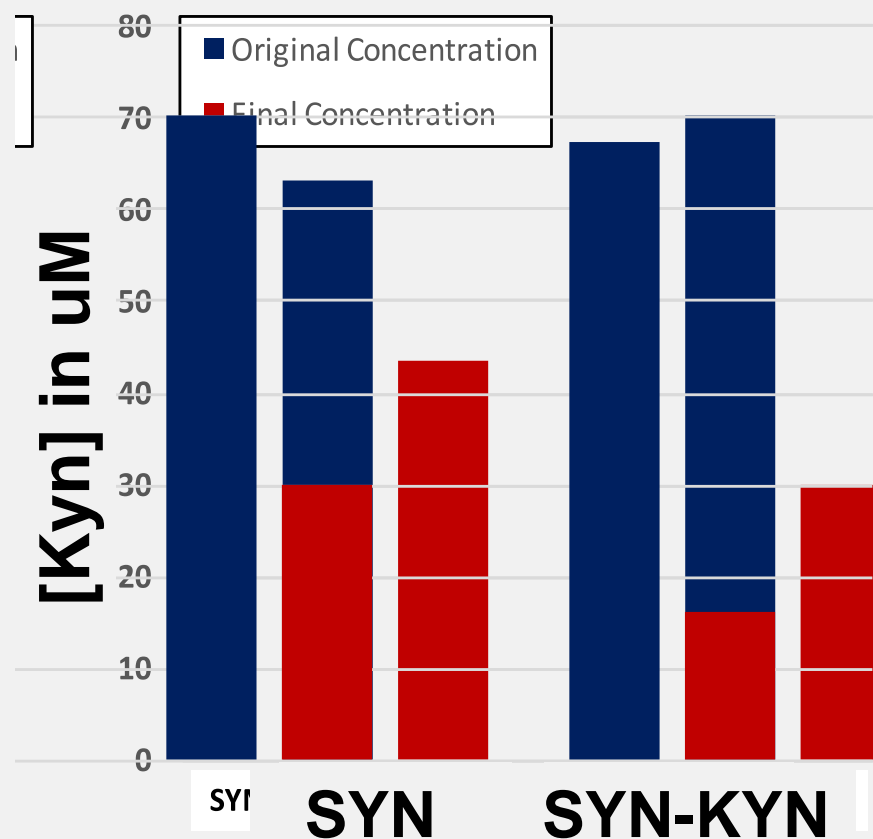
# Kyn Sustainer In Vitro Module Characterization :

SYN-Kyn Efficiently Consumes Kynurenine in the TME and Elicits Anti-tumor Control in Combination with CPIs

## SYN-Kyn



## Kyn-consuming strain efficiently consumes kynurenine in vitro

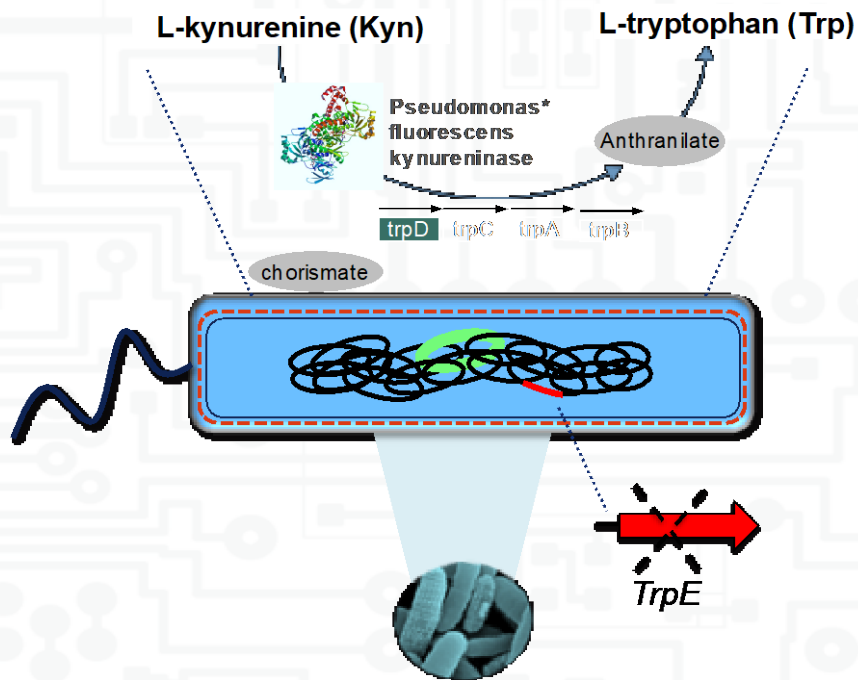




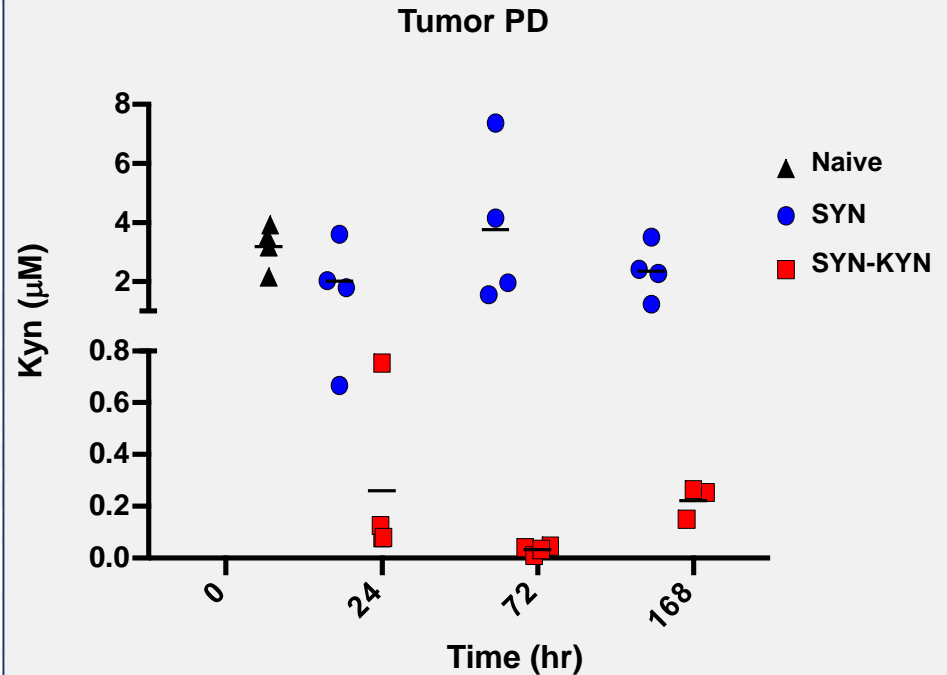
# Kyn Sustainer Module In Vivo Characterization :

SYN-Kyn Efficiently Consumes Kynurenine in the TME and Elicits Anti-tumor Control in Combination with CPIs

## SYN-Kyn



Kyn-consuming strain reprograms the tumor microenvironment by depleting kynurenine

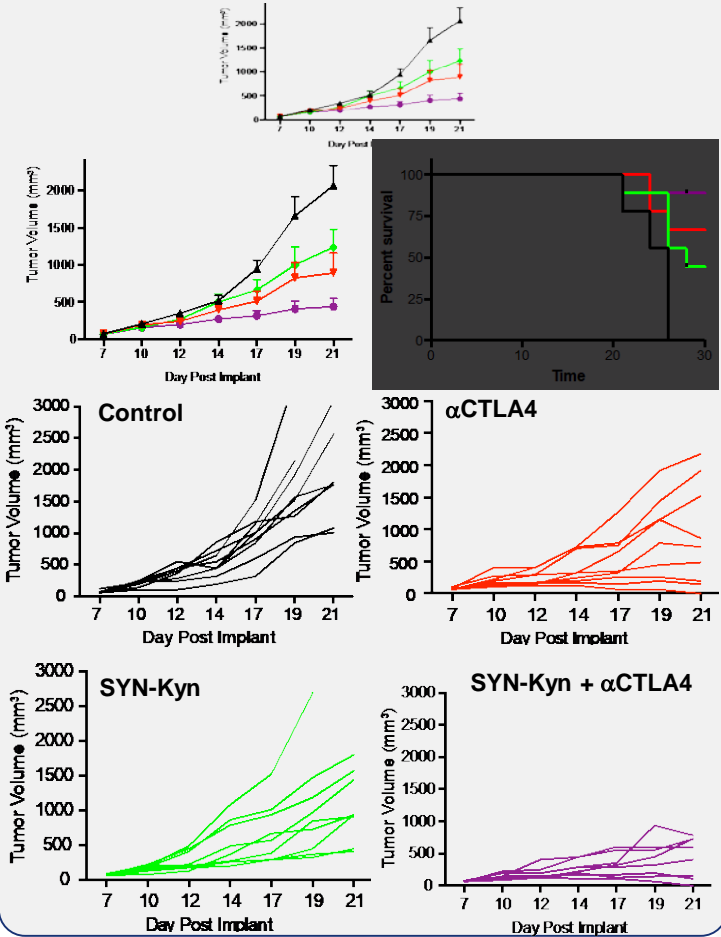




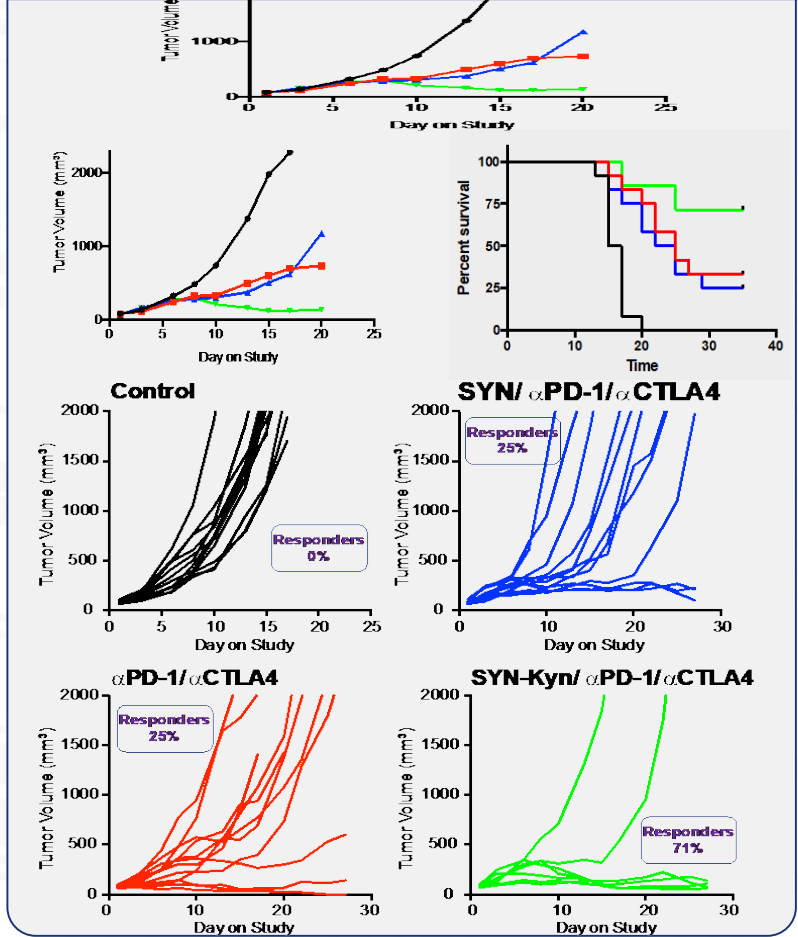
# Kyn Sustainer Module In Vivo Characterization :

SYN-Kyn Efficiently Consumes Kynurenine in the TME and Elicits Anti-tumor Control in Combination with CPIs

## Metabolite reprogramming in the TME and early T cell activation result in significant tumor growth arrest

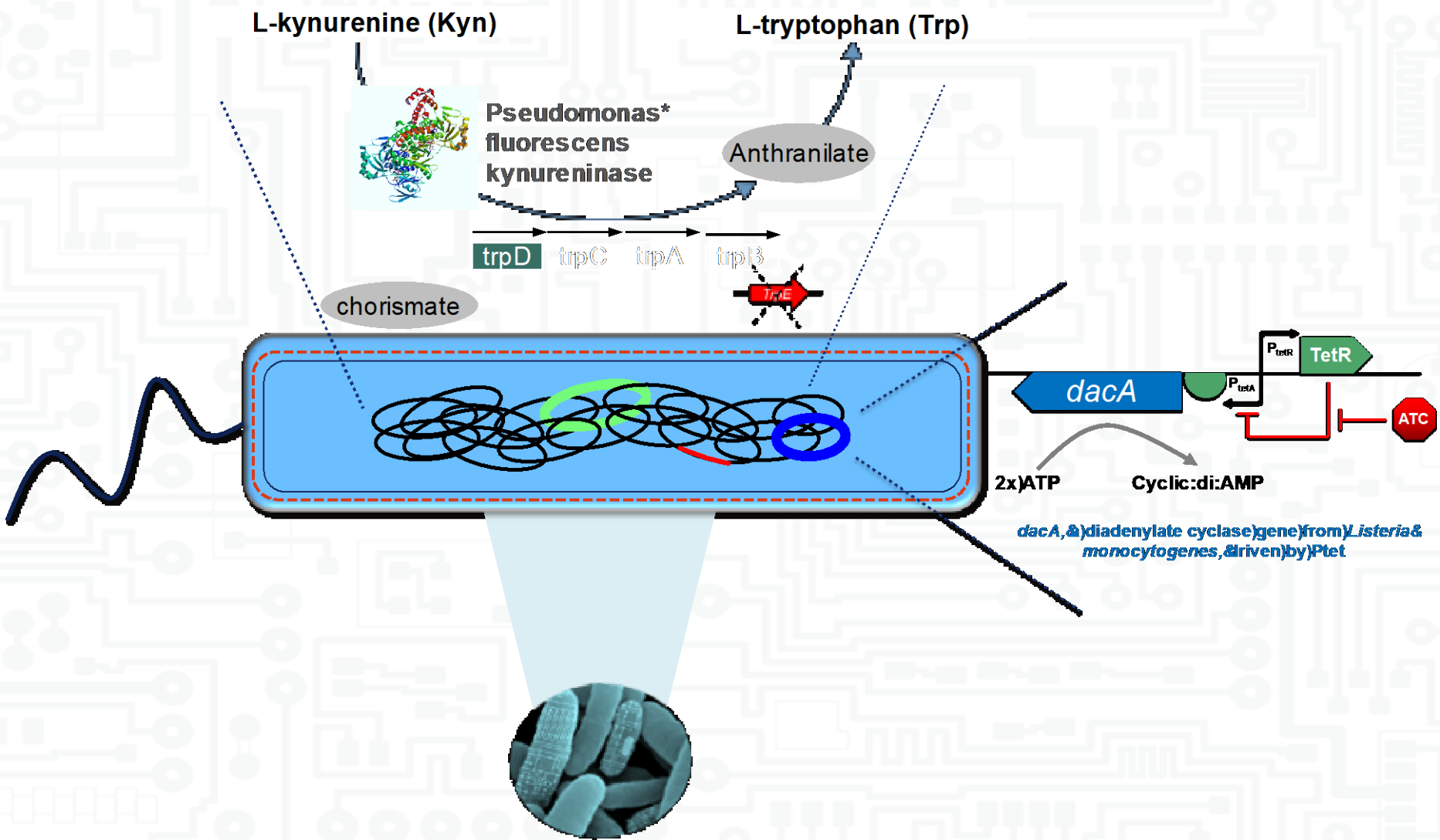


## Metabolite reprogramming in the TME, early T cell activation and reversal of T cell exhaustion drive tumor rejections



# Dual STING and Kyn Module In Vitro Characterization :

Combination of SYN-STING and SYN-Kyn Results in Efficient Activity of both Circuits

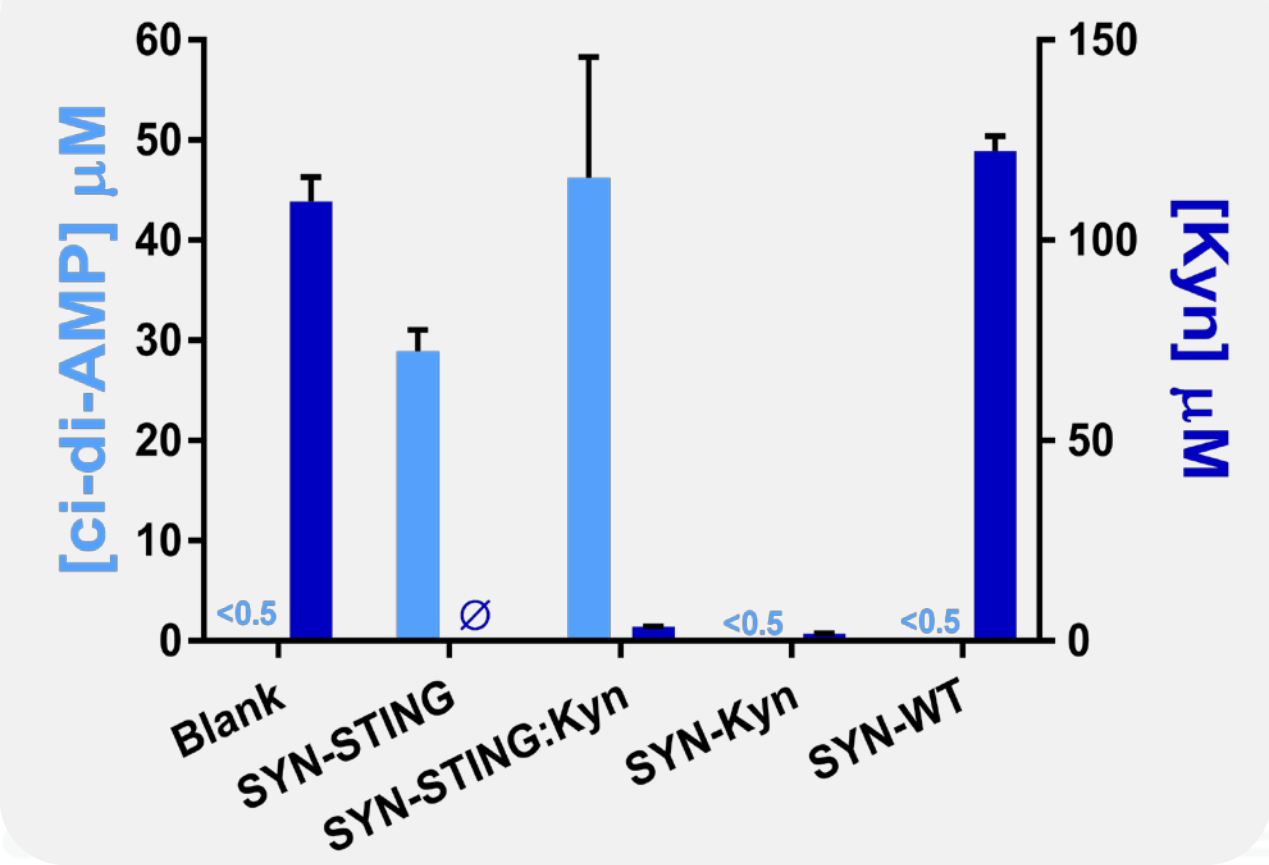


# Dual STING and Kyn Module In Vitro Characterization :

Combination of SYN-STING and SYN-Kyn Results in Efficient Activity of both Circuits

Simultaneous ci-di-AMP production and Kyn consumption by SYN-STING:Kyn

Immune Initiator



Immune Sustainer

# Synlogic Synthetic Biotic Platform:

Bringing Rational Drug Development to Synthetic Biology



## Build Potency

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### Rational design:

- Synthetic biology tools applied
- Engineer potency
- Exceed endogenous bacterial activity



## Apply Pharmacological Principles

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### Pharmacologically tractable:

- Non-colonizing
- Measurable dose-response



## Develop Reliable Manufacturing

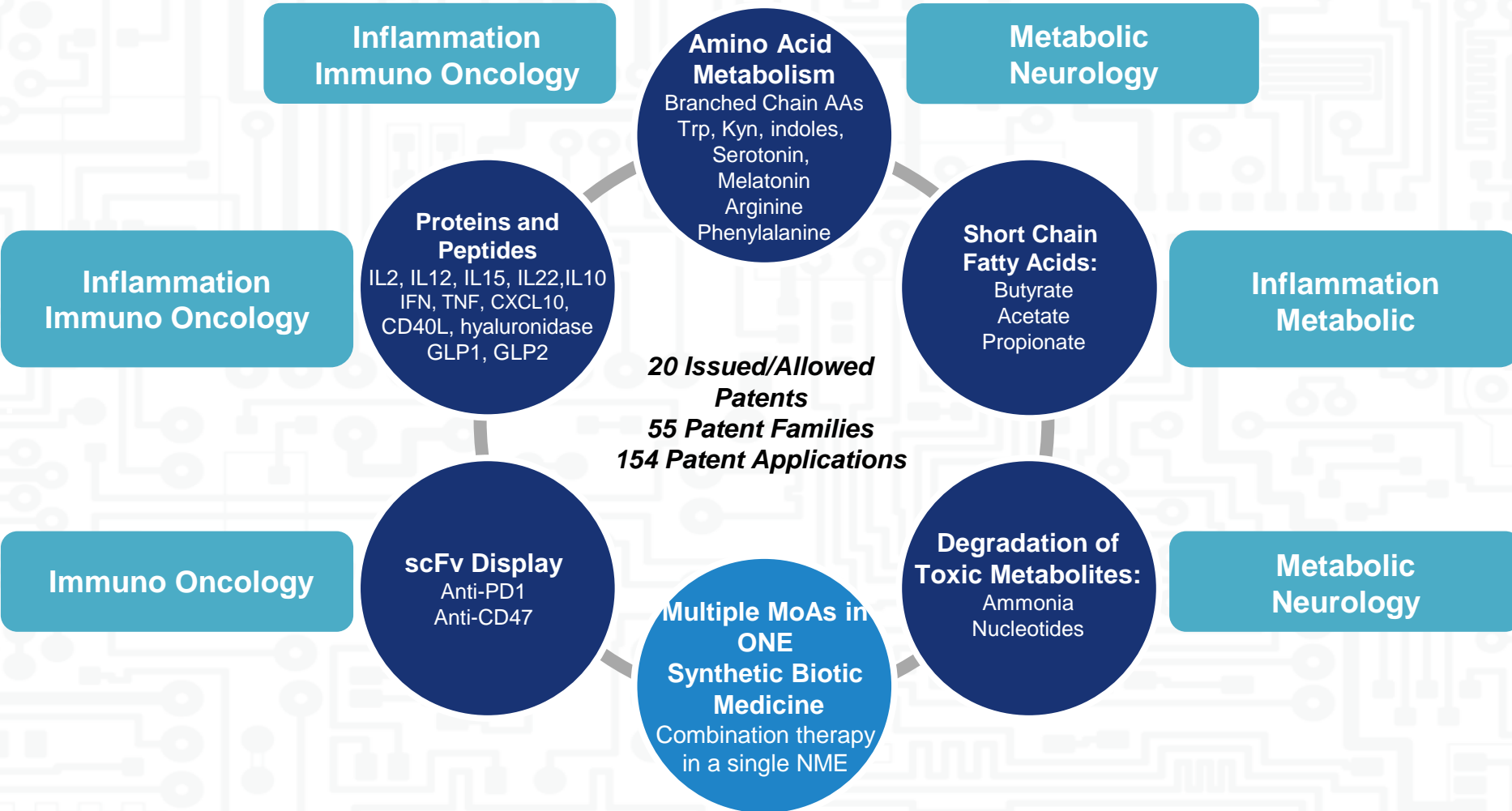
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### GMP manufacturing:

- Single strain
- Reproducible yield
- Formulation & delivery
- Control switches
- Portfolio applicability

# Synthetic Biotic Medicines:

Broad Applicability Across Multiple Disease Areas



# synlogic



# Thank You!

