Development of Synthetic Biotic™ Medicines in Oncology

Designed for life

Aoife Brennan, M.B., B.Ch.,
President and CEO

SITC 2018- Washington, DC
November 10th, 2018

synlogic

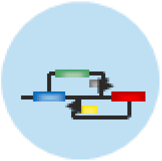
Forward Looking Statements

This presentation contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this presentation regarding strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. In addition, when or if used in this presentation, the words "may," "could," "should," "anticipate," "believe," "estimate," "expect," "intend," "plan," "predict" and similar expressions and their variants may identify forward-looking statements. Examples of forward-looking statements include, but are not limited to, the approach we are taking to discover and develop novel therapeutics using synthetic biology; statements regarding the potential of our platform to develop therapeutics to address a wide range of diseases including: inborn errors of metabolism, liver disease, inflammatory and immune disorders, and cancer; the future clinical development of Synthetic Biotic medicines; the potential of our technology to treat hyperammonemia and phenylketonuria; the expected timing of our anticipated clinical trial initiations; the benefit of orphan drug and fast track status; the adequacy of our capital to support our future operations and our ability to successfully initiate and complete clinical trials; the results of our collaborations; and the difficulty in predicting the time and cost of development of our product candidates. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation: the uncertainties inherent in the preclinical development process; our ability to protect our intellectual property rights; and legislative, regulatory, political and economic developments, as well as those risks identified under the heading "Risk Factors" in our filings with the SEC. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in our quarterly Report on Form 10-Q filed with the SEC on August 9, 2018. The forward-looking statements contained in this presentation reflect our current views with respect to future events. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our view as of any date subsequent to the date hereof.

Agenda

12:30 pm - 12:40 pm	Introductions and intro to Synlogic platform and approach *Aoife Brennan, MB, ChB* *President & CEO, CMO,* *Synlogic Inc.*
12:40 pm - 12:55 pm	Unmet medical need in solid tumor immunotherapy *Filip Janku, MD, PhD* *MD Anderson Cancer Center*
12:55 pm - 1:10 pm	Role of Type I IFN in tumor immune recognition and therapy *Dmitriy Zamarin, MD, PhD* *Memorial Sloan Kettering Cancer Center*
1:10 pm 1:40 pm	Review of SYNB1891 data and program *Jose Lora, PhD* *VP, Research,* *Synlogic Inc.*
1:40 pm 2:00 pm	Q&A and closing remarks *Aoife Brennan*

Synthetic Biotic™ Medicines: A Novel Class of Living Medicines

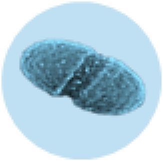


Synthetic

Designed genetic circuits

Degradation of disease-causing metabolites

Production of therapeutic molecules



Biotic

Bacterial chassis

Non-pathogenic

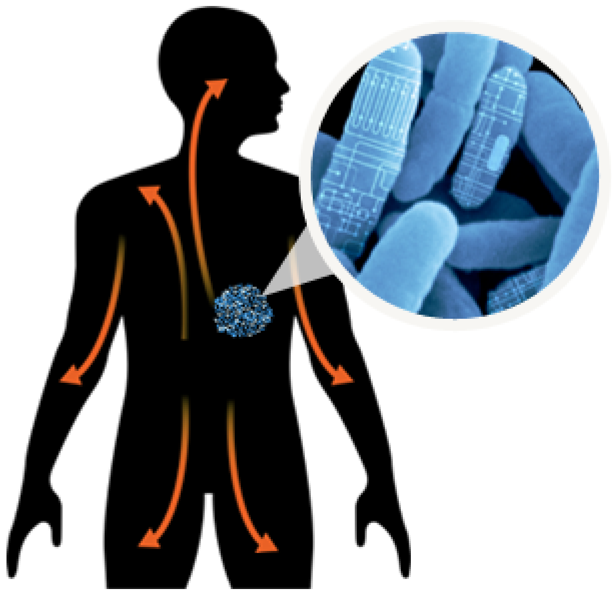
Amenable to genetic manipulation

PROGRAMMABLE POTENCY

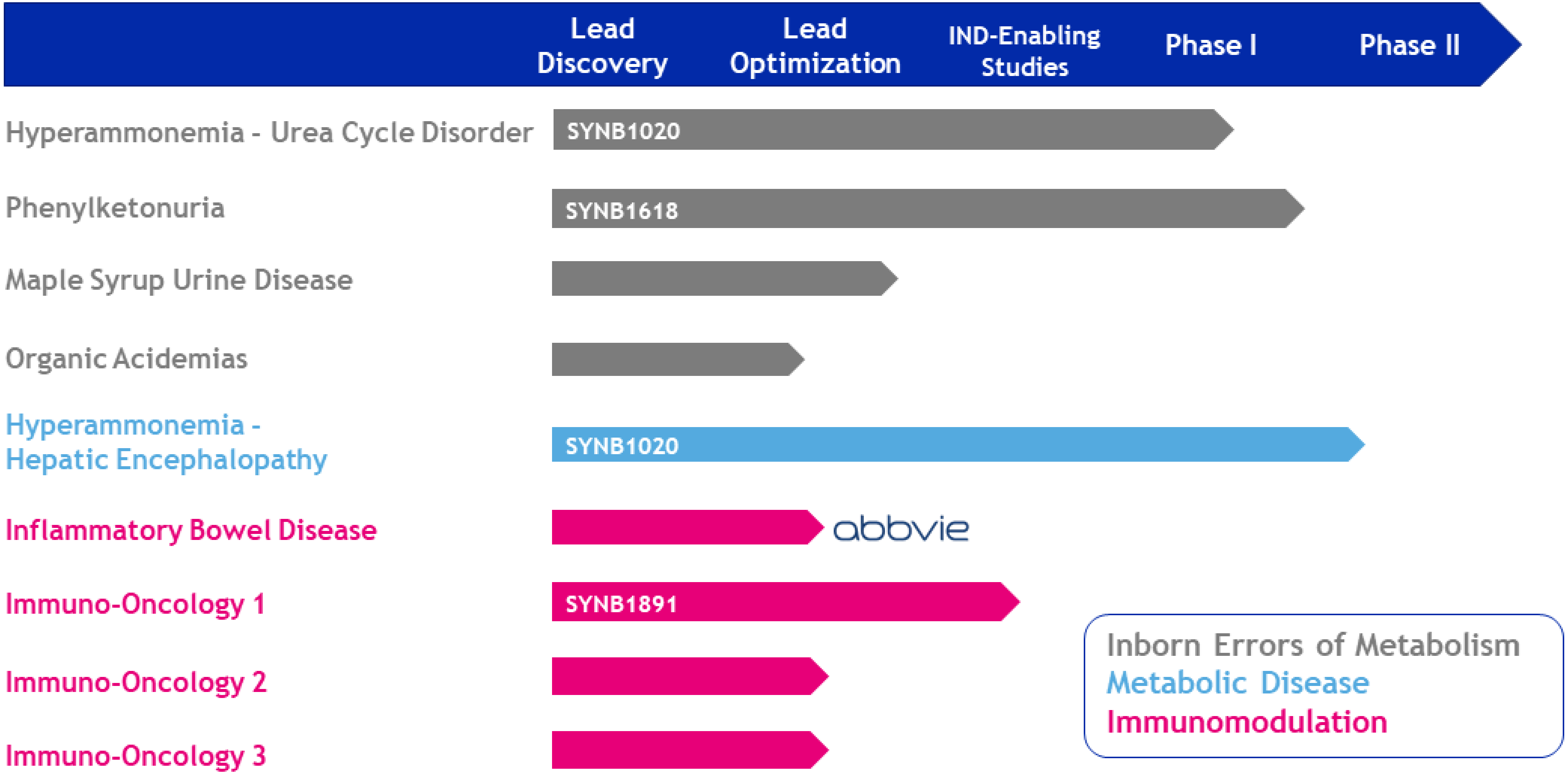
Pathways, Combinations, Biomarkers

SWITCHES FOR CONTROL, TUNING

LOCAL, REDUCED SYSTEMIC TOXICITY



Synthetic Biotic Platform Breadth and Potential: Pipeline Focused on Three Therapeutic Areas



Synlogic Immuno-Oncology Approach

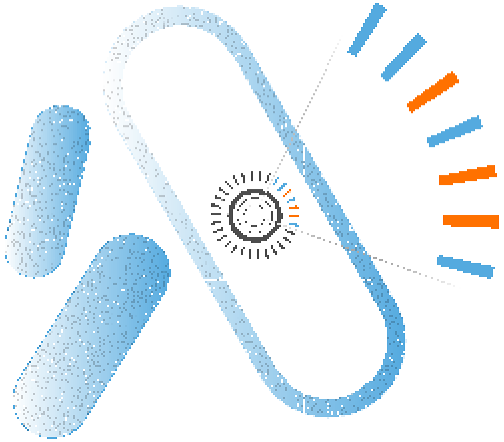
Reimagining Early Immunotherapy for Combinatorial Effect

Bacteria Recognized as Earliest Immunotherapy

"Nature often gives us hints to her profoundest secrets, and it is possible that she has given us a hint in which, if we will but follow, may lead us on to the solution of this difficult problem."

Dr. William B. Coley
Immuno-Oncology Pioneer

Engineer a Living Solution: Synthetic Biotic Medicines



Rationally Designed for Combinatorial Effect

Locally Inflame the TME

Systemically Drive Tumor Antigen-Specific Immunity

In Situ Vaccination: Neo-antigen Priming and Sustained Immune Response

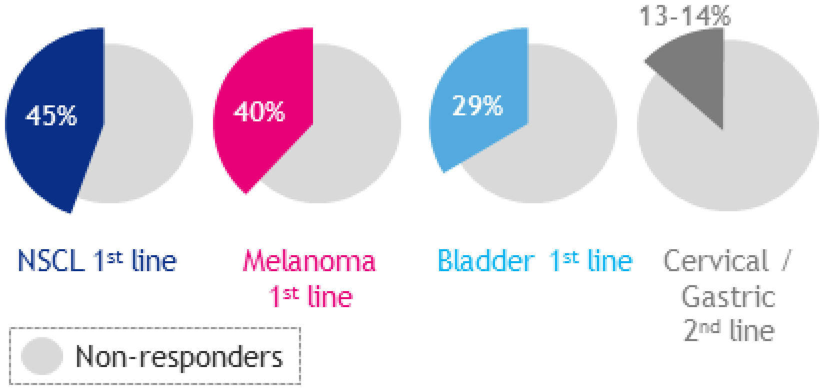
Synlogic Vision for Immuno-Oncology

Expand the benefits of immunotherapy broadly across tumor types

TREATMENT FAILURES

For indications where immune checkpoint inhibitors are indicated, only 13-45% of patients respond

ORR for Select FDA approved CPI Monotherapy



UNRESPONSIVE TUMORS

Other tumor types show little-to-no response to checkpoint inhibitors, for example:

Colorectal - MSS

Pancreatic

Prostate - castrate resistant

Breast - ER+, hormone therapy refractory

Enable broad response and remission through engagement of multiple immunomodulatory pathways to enhance tumor inflammation and promote robust T cell responses

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THE UNIVERSITY OF TEXAS
MD Anderson ~~Cancer~~ Center
Making Cancer History®

Unmet medical need in solid tumor immunotherapy

Filip Janku, MD, PhD
Associate Professor
Clinical & Translational Research Center Medical Director

Investigational Cancer Therapeutics
(Phase I Clinical Trials Program)
MD Anderson Cancer Center
Houston, TX

Bench to Bedside & Back

FDA-approved Immune Checkpoint Inhibitors*

Drug	Immune Checkpoint(s)	FDA-approved tumor-type**
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma
		Non-small cell lung cancer
		Small cell lung cancer
		Renal cell carcinoma
		Classical Hodgkin lymphoma
		Squamous cell carcinoma of the head and neck
		Urothelial carcinoma
		Hepatocellular carcinoma
		Mismatch repair deficient and microsatellite instability high metastatic colorectal cancer
Pembrolizumab	PD-1	Melanoma
		Non-small cell lung cancer
		Squamous cell carcinoma of the head and neck
		Classical Hodgkin lymphoma
		Urothelial carcinoma
		Gastric or gastroesophageal junction
		Microsatellite instability-high or mismatch repair deficient solid tumors
		Cervical cancer
Atezolizumab	PD-L1	Urothelial carcinoma
		Non-small cell lung cancer
Durvalumab	PD-L1	Urothelial carcinoma
		Non-small cell lung cancer
Avelumab	PD-L1	Merkel cell carcinoma
		Urothelial carcinoma
Nivolumab with Ipilimumab	PD-1 and CTLA-4	Melanoma
		Renal cell carcinoma
		Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer

*List of FDA-approved immune checkpoint inhibitors as of September 14, 2018.

Adapted from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm

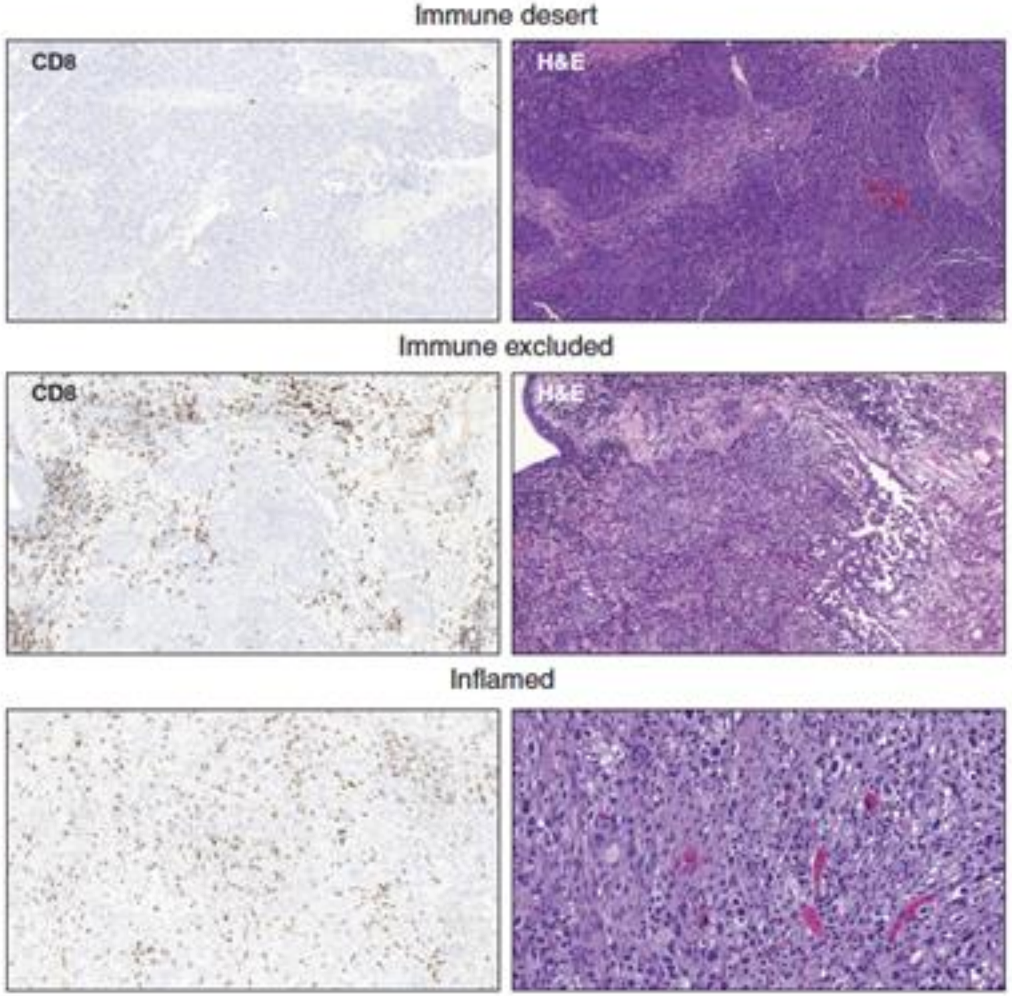
**Tumor type must meet the criteria listed in the above-mentioned website.

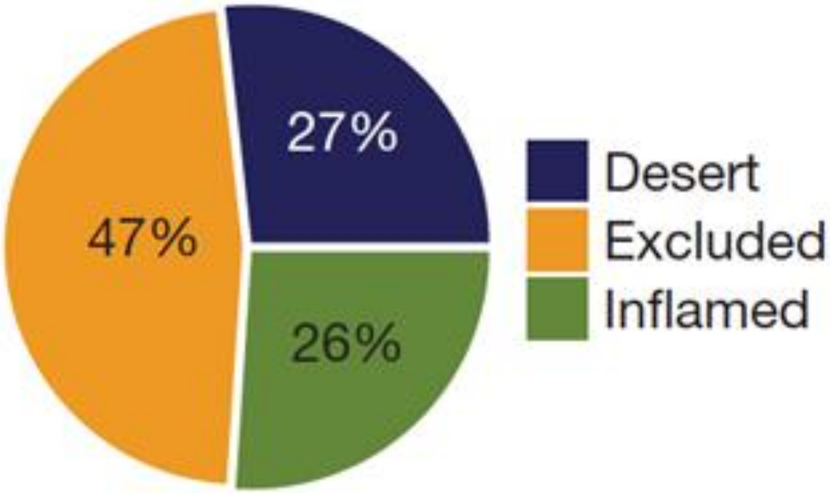
Response rates to checkpoint inhibitors in approved indications

- **Melanoma**
  - Pembrolizumab: RR ~ **30%**
  - Nivolumab/ipilimumab: RR ~ **50%**
- **Non-small lung cancer**
  - Pembrolizumab: RR ~ **20%-40%**
  - Nivolumab: RR ~ **20%**
- **SCC of head and neck**
  - Pembrolizumab: RR ~ **18%**
  - Nivolumab: RR ~ **13%**
- **Urothelial cancer**
  - Pembrolizumab: RR ~ **21%**
  - Nivolumab: RR ~ **28%**
  - Atezolizumab: RR ~ **15%-26%**

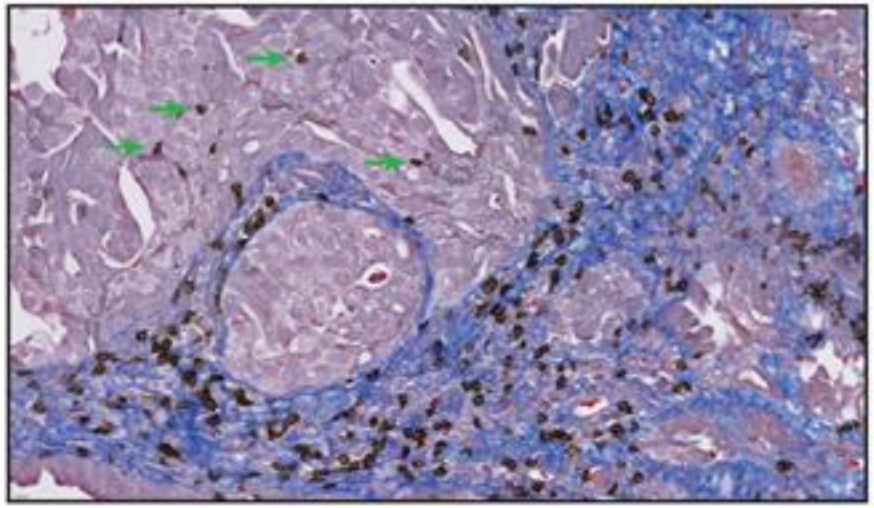
Robert NEJM 2015
Wolchok NEJM 2013
Garon NEJM 2015
Reck NEJM 2016
Ferris NEJM 2016
Chow J Clin Oncol 2016
Bellmunt 2017
Rosenberg 2016

Classification by tumor immune phenotype in urothelial cancers





Immune excluded (CD8 trichrome stain)



Mariathasan S. Nature 2018

Immunotherapy: unmet need

Estimated New Cases

Males			Females		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**	**All Sites**	**878,980**	**100%**

MSI-H: ~5% of mCRC

Siegel CA J Cancer Clin 2018

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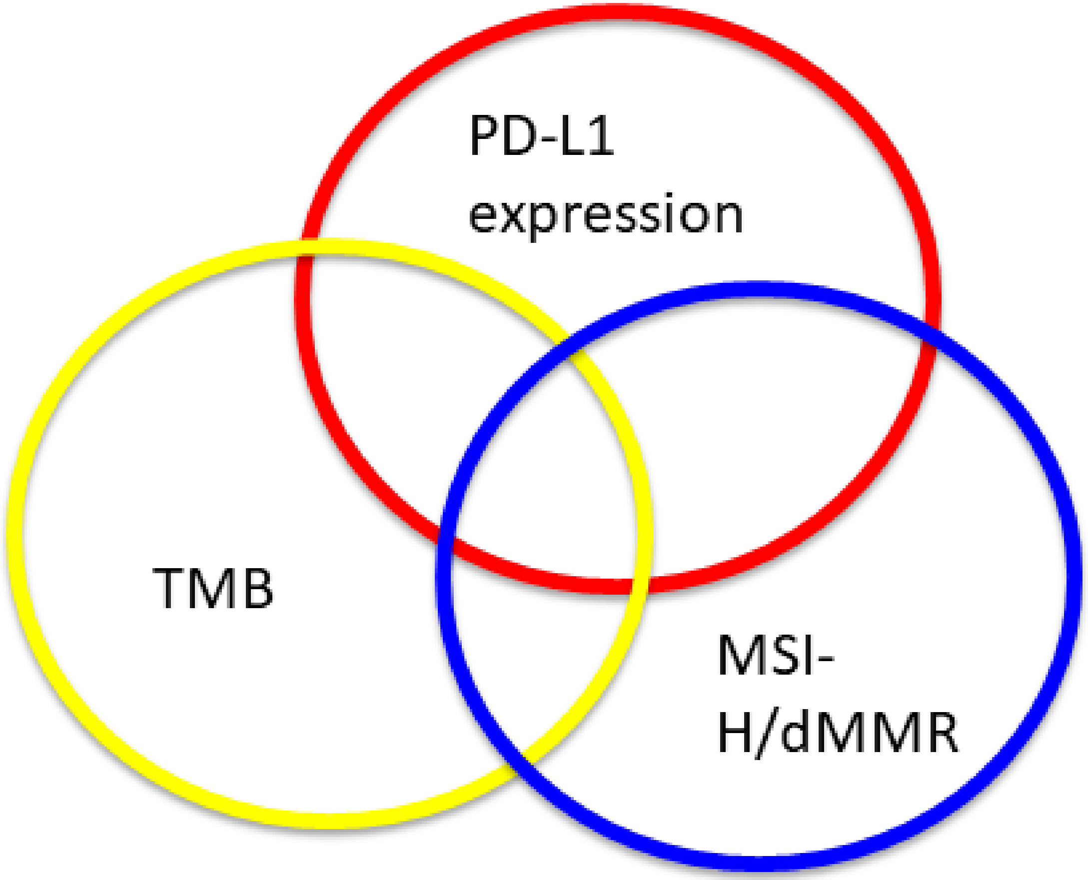
MSI-H: ~5% of mCRC

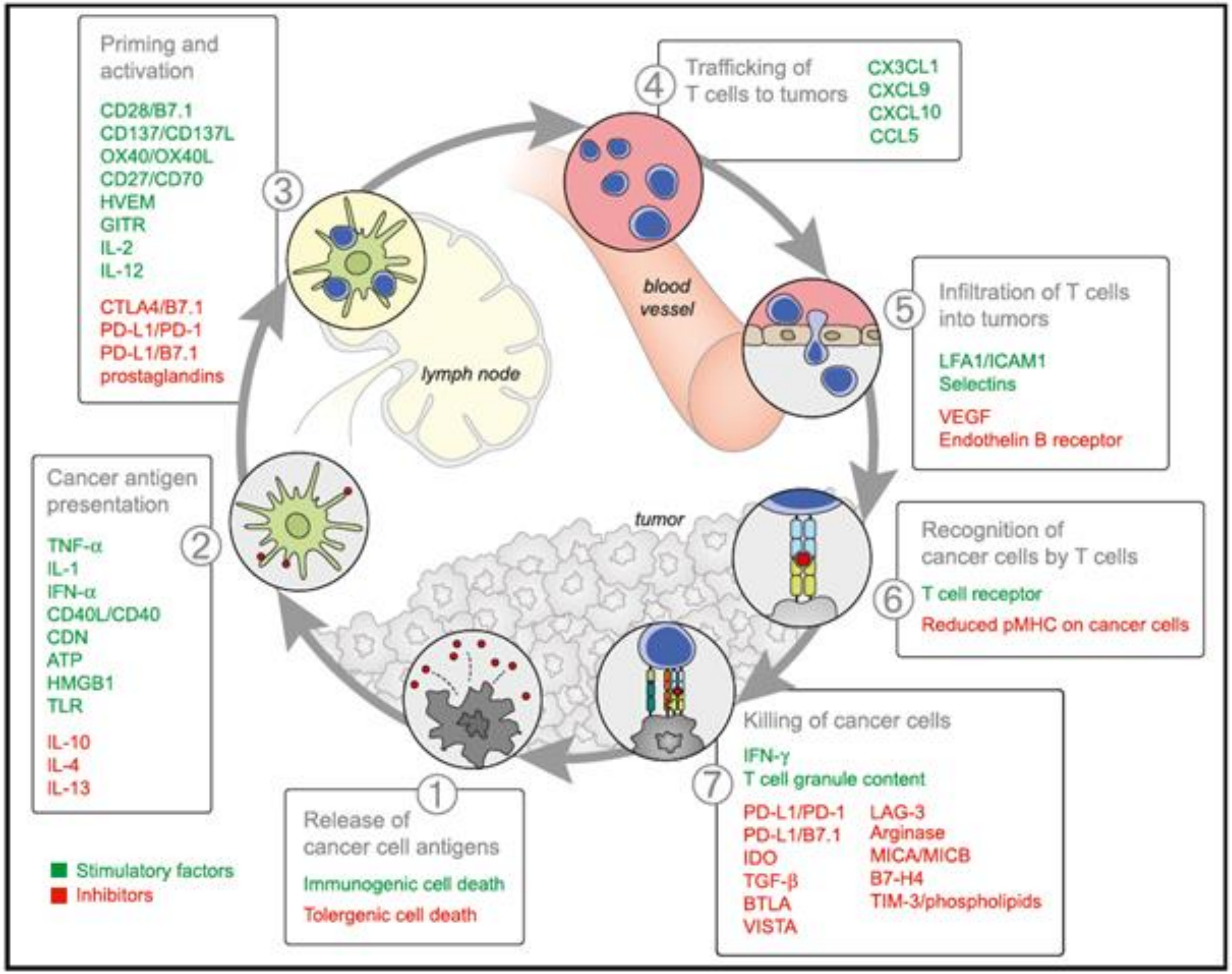
- Ovarian cancer
- Soft tissue sarcomas
- Glioma
- Myeloma

Siegel CA J Cancer Clin 2018

Predictive factors for response to immune checkpoint inhibitors

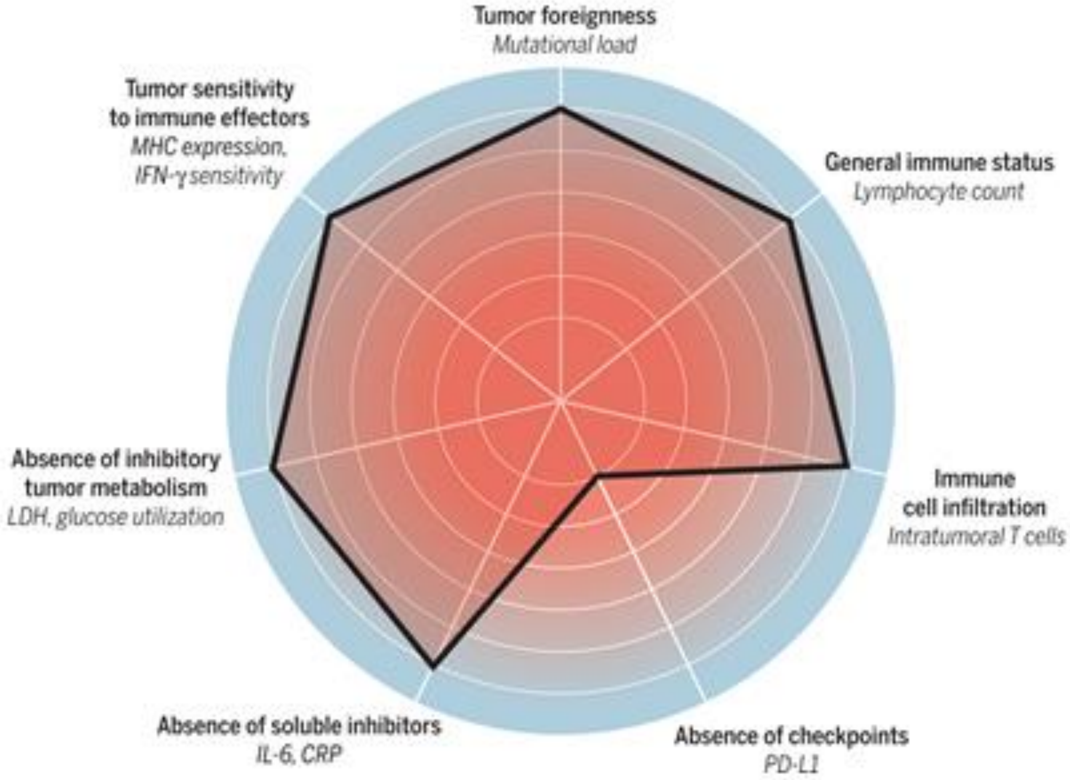


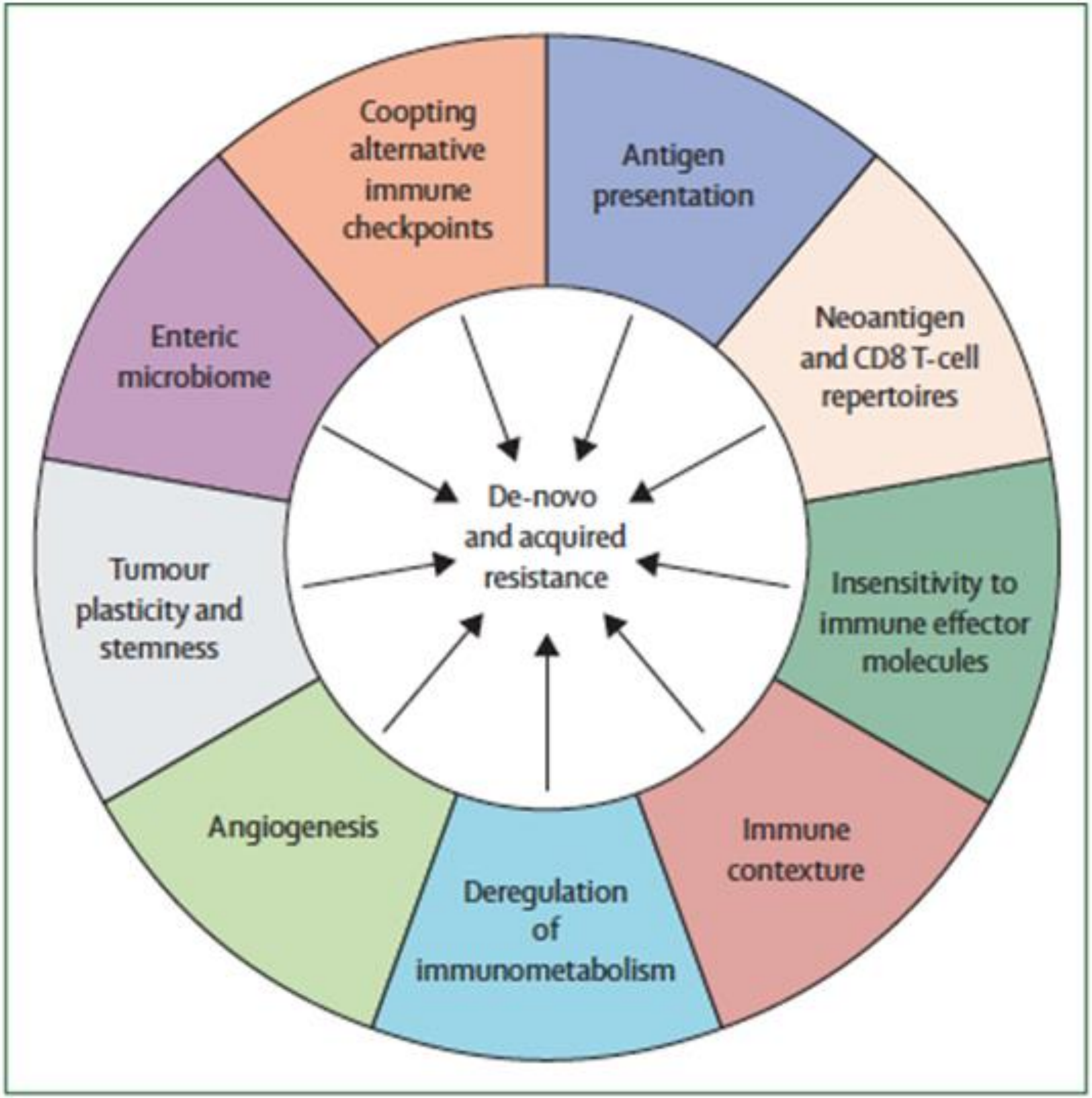
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Chen DS. Immunity 2013

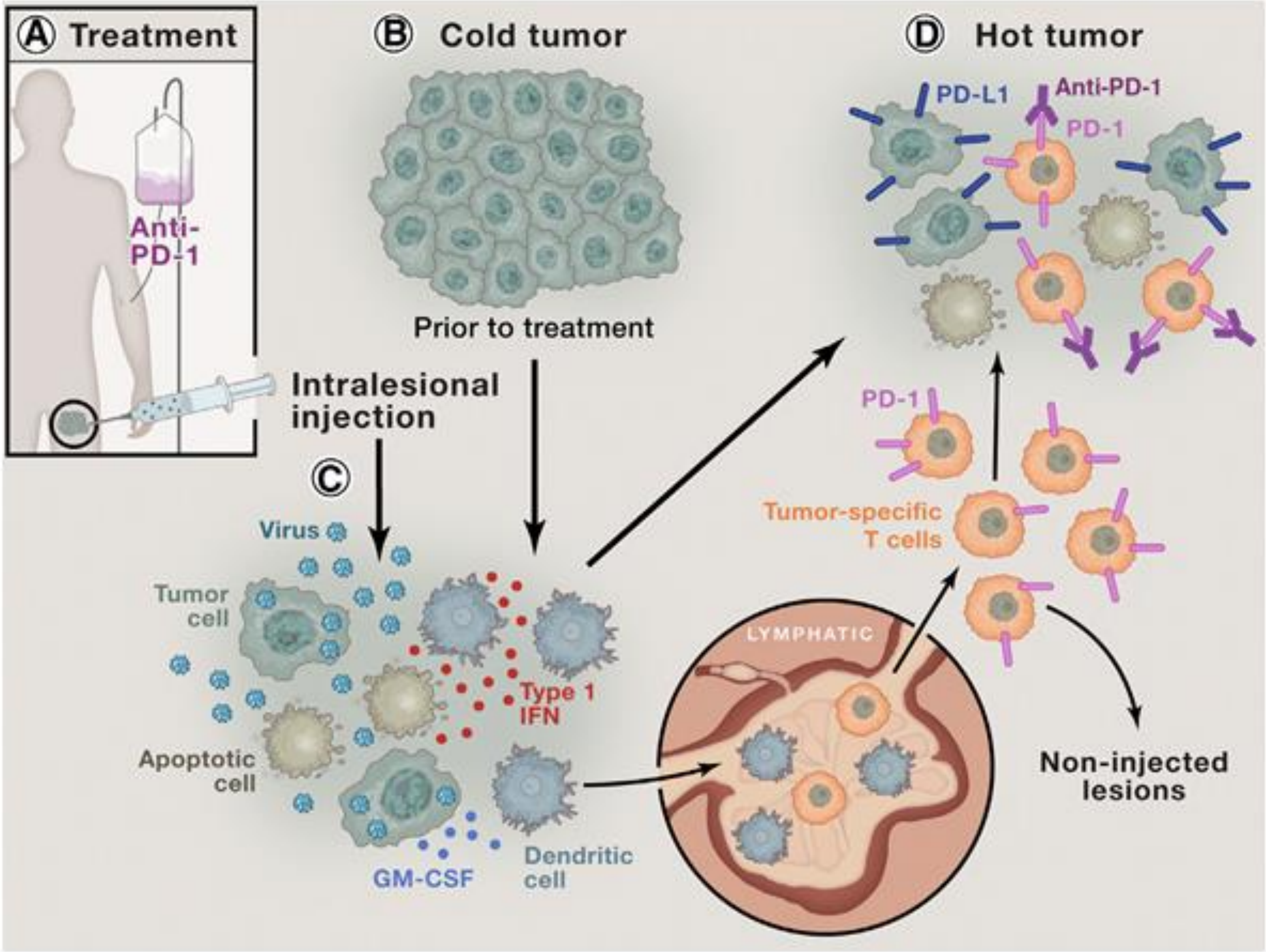
Mechanisms of immunoresistance





Syn Lancet Oncol 2017
Blank Science 2016

Converting Cold Tumors into Hot

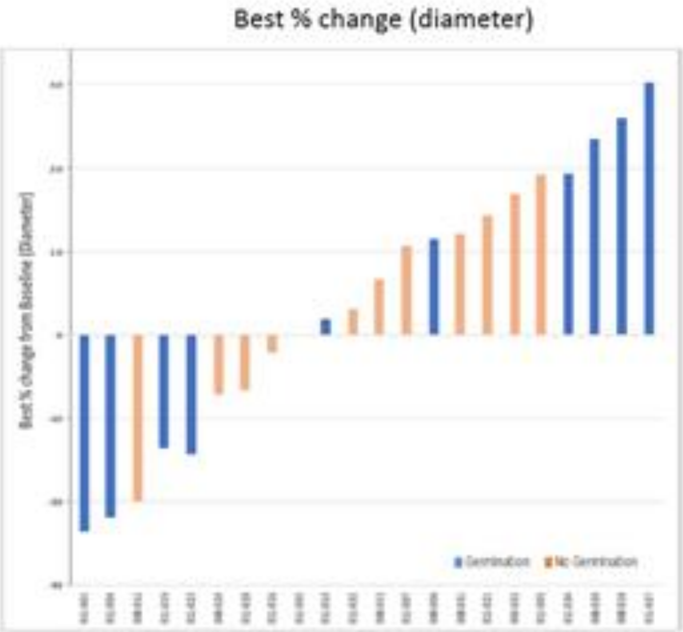


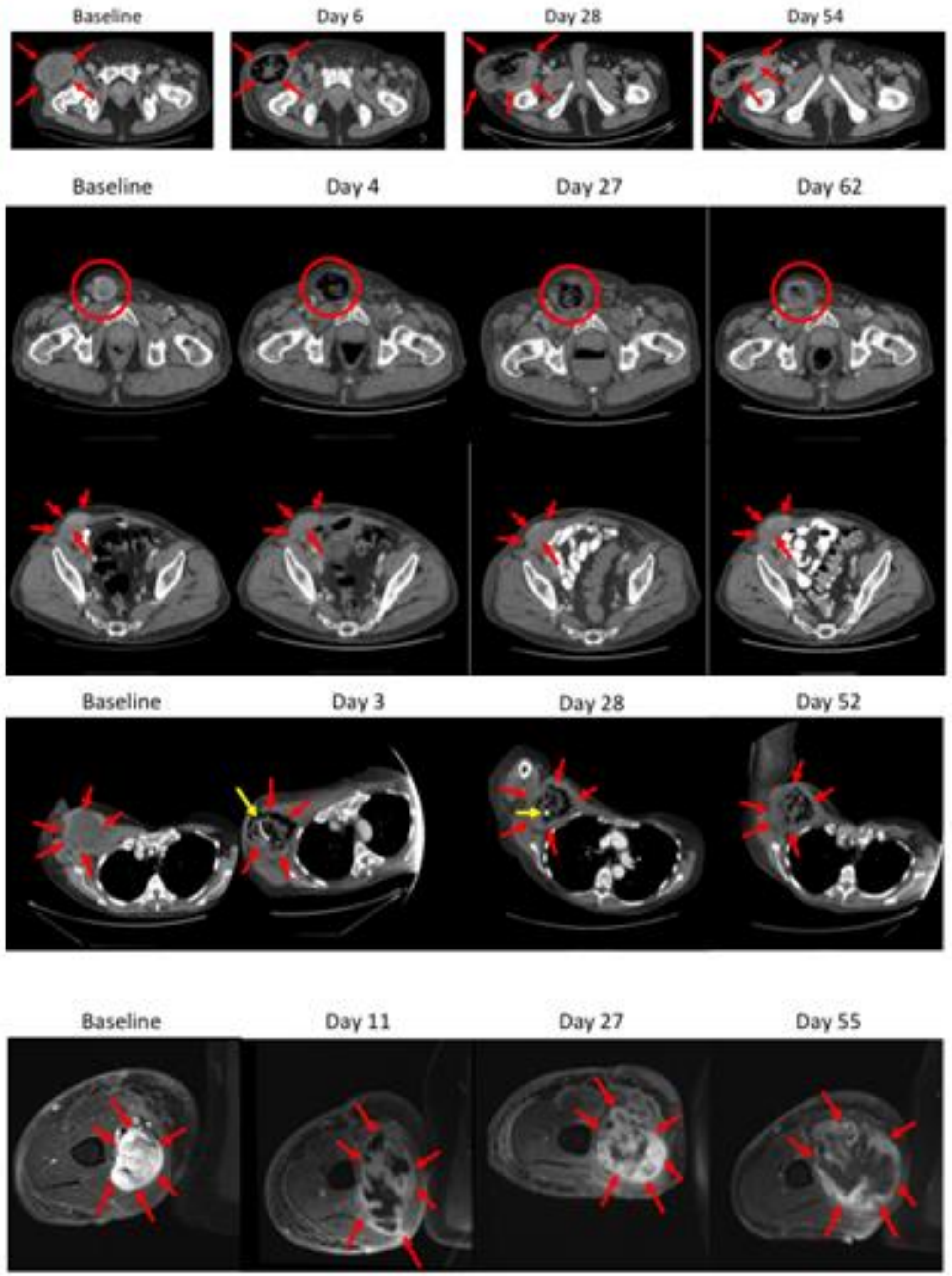
Haanen Cell 2017

Patient with MPNST (sarcoma) with spontaneous remission after prolonged infection with coagulase negative staphylococcus and *Klebsiella Pneumoniae*

Prolonged infection with bacteremia
January to February 2013

Anticancer activity of single intratumor injection of *Clostridium Novyi-NT*





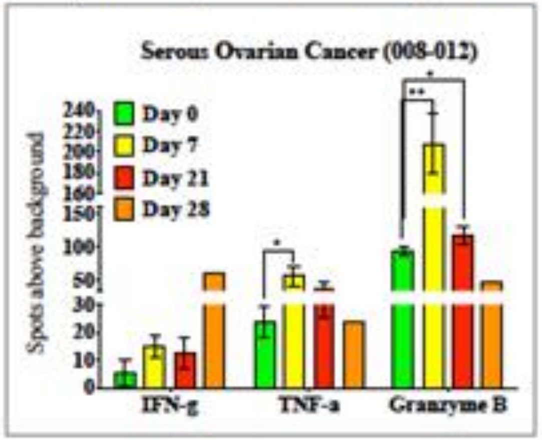
Janku

CRI-CMIT-EATI-AACR 2018

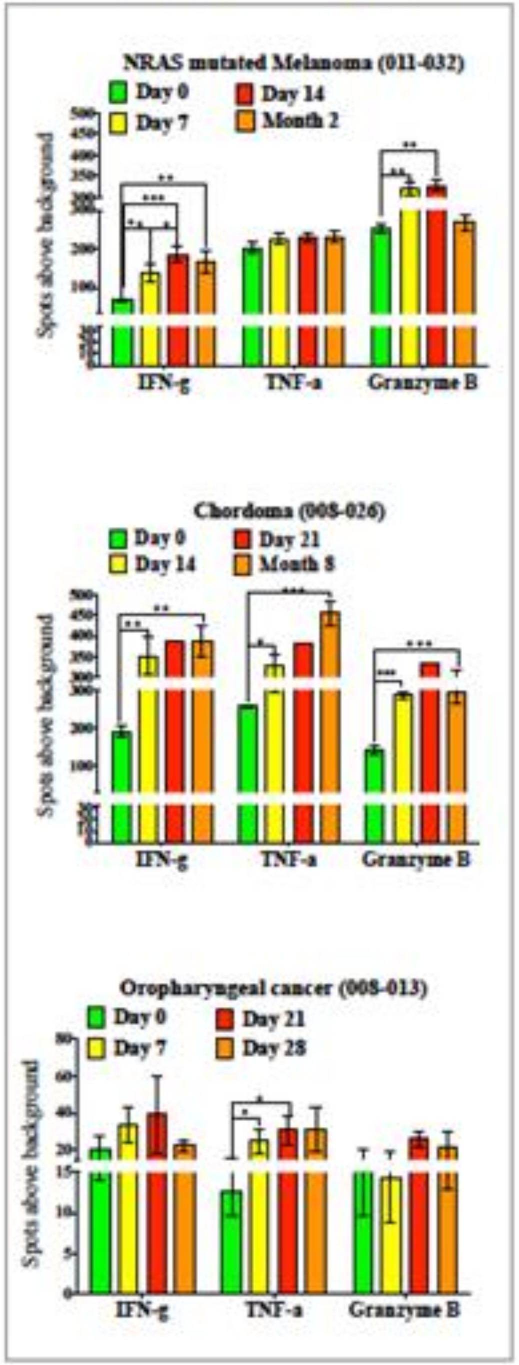
Cytokine response after single intratumor injection of *Clostridium Novyi-NT*

Figure 3. Release of IFN-γ, TNF-α, and Granzyme B by patients' T-cells before and after stimulation with compatible tumor antigens. Patients are categorized by general cytokine response and clinical germination. ELISPOT assays were in triplicate. *p<0.05, **p<0.01, ***p<0.001, student T –test.

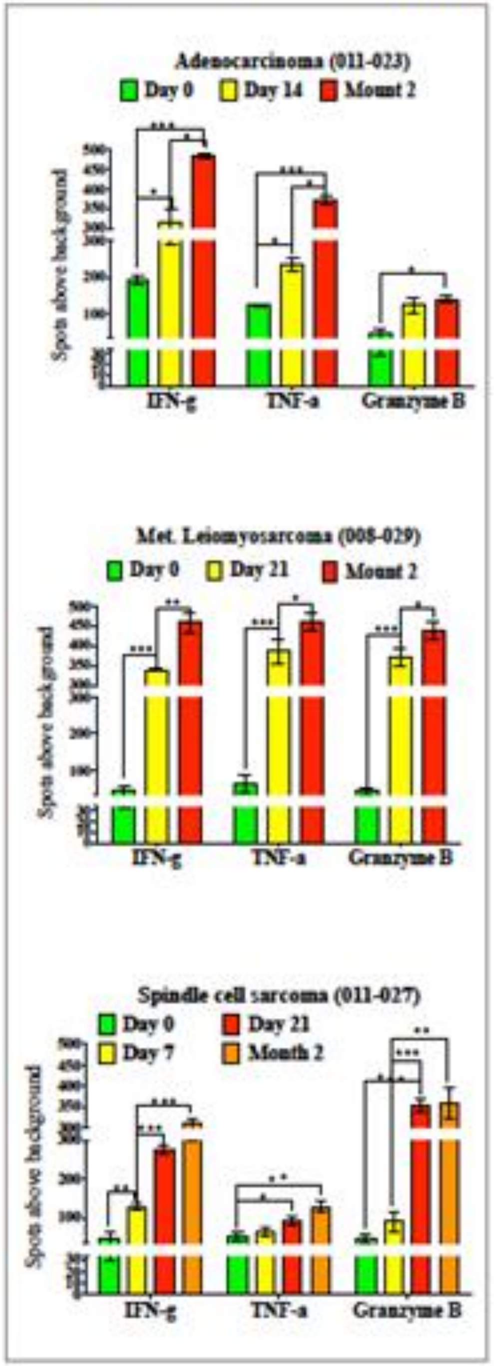
A. "-" Cytokine response / "-" Clinical germination



B. "+" Cytokine response / "-"Clinical germination



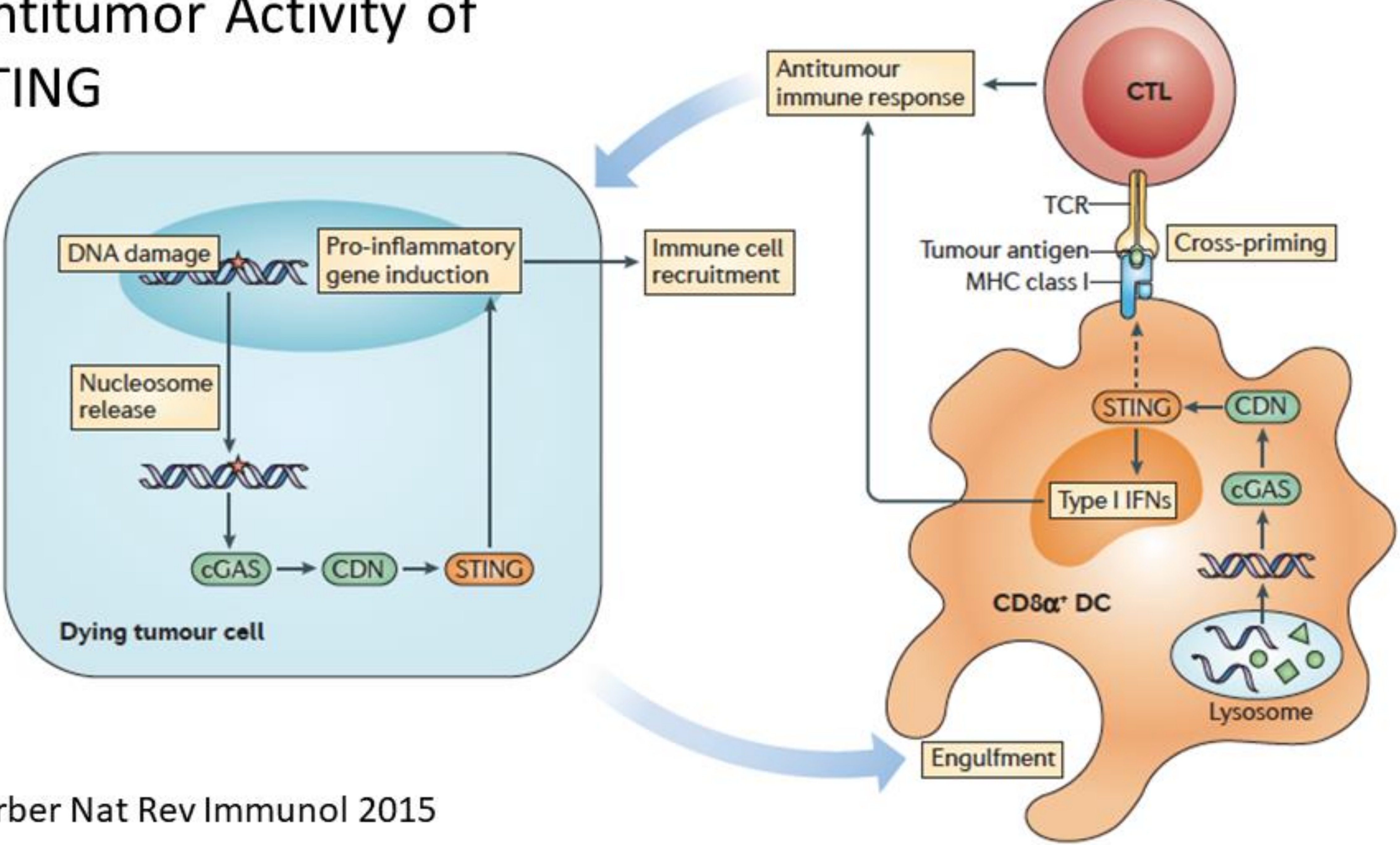
C. "+" Cytokine response / "+" clinical germination



Janku

CRI-CMIT-EATI-AACR 2018

Antitumor Activity of STING



Barber Nat Rev Immunol 2015

Phase I: Intratumor STING agonist MK-1454 +/- pembrolizumab

- Phase I: Accelerated Titration Design -> modified Toxicity Probability Interval
- Endpoints
  - Primary: safety, dose
  - Secondary: PK/PD
  - Exploratory: objective response
- DLTs:
  - Monotherapy (26 patients): G3 vomiting (1)
  - Combination (25 patients): G2 erythema multiforme (1), G3 injection site pain (1), G3 skin/tumor necrosis (1)
- AEs:
  - Pyrexia (65.2%/42.9%), chills (39.1%/25%), injection site pain (47.8%/10.7%), fatigue (34.8/25%)

Harrington ESMO 2018

Phase I: Intratumor STING agonist MK-1454 +/- pembrolizumab

EFFICACY

- Monotherapy
  - Myoepitehlial carcinoma > - 30% (not confirmed as PR)
  - 2 patients with shrinkage of injected lesions

- Combination
  - Partial response: 6 (TNBC, 1; HNSCC, 3; ATC, 2)
  - Shrinkage of injected and noninjected lesions observed
  - PRs were durable (>6 months)
  - Median 83% reduction in size of target lesions for responders

Harrington ESMO 2018

SITC 2018: MIW815 STING agonist

- 41 pretreated patients with solid tumors or lymphomas
- No DLTs
- The most common AEs: pyrexia (7; 17.1%), injection site pain (6; 14.6%), headache (6; 14.6%).
- Grade 3/ 4 AEs: increased lipase (2; 4.9%), elevated
- amylase, tumor pain, dyspnea, respiratory failure,
- and injection site reaction (1 each; 2.4%).
- On-treatment tumor biopsies showed increases in CD8 T cells infiltrating the injected tumors in a subset of patients.
- PR: Merkel cell (CPI naïve), Parotid gland (CPI pretreated), both response appear to be durable

Meric-Bernstam. SITC 2018

STING agonists in the clinic

- MK-1454: early data for monotherapy and combination with pembrolizumab presented at ESMO 2018
- MIW815: early data for monotherapy presented at SITC 2018
- MK-2118: clinical trial ongoing (monotherapy and combination with pembrolizumab)

Conclusions

- Immunotherapy with immune checkpoint inhibitors can be effective in subsets of patients with melanoma, lung cancer and other tumor types

- Immunotherapy with immune checkpoint inhibitors has not shown enough activity resulting in FDA approval in many common cancers including breast cancer, prostate cancer, ovarian cancer, MSS colorectal cancer and sarcomas, which creates unmet need for novel therapeutic approaches

- Turning cold tumors into hot with activators of innate immunity such as STING agonists (and others) offers a new promising approach to increase efficacy of cancer immunotherapy

Role of type I IFN in tumor immune recognition and therapy

Dmitriy Zamarin MD PhD
Assistant Attending Physician
Translational Research Director
Gynecologic Medical Oncology Service
Immunotherapeutics Service
Memorial Sloan Kettering Cancer Center

Type I IFN: the first cytokine

Alick Isaacs

Jean Lindenmann

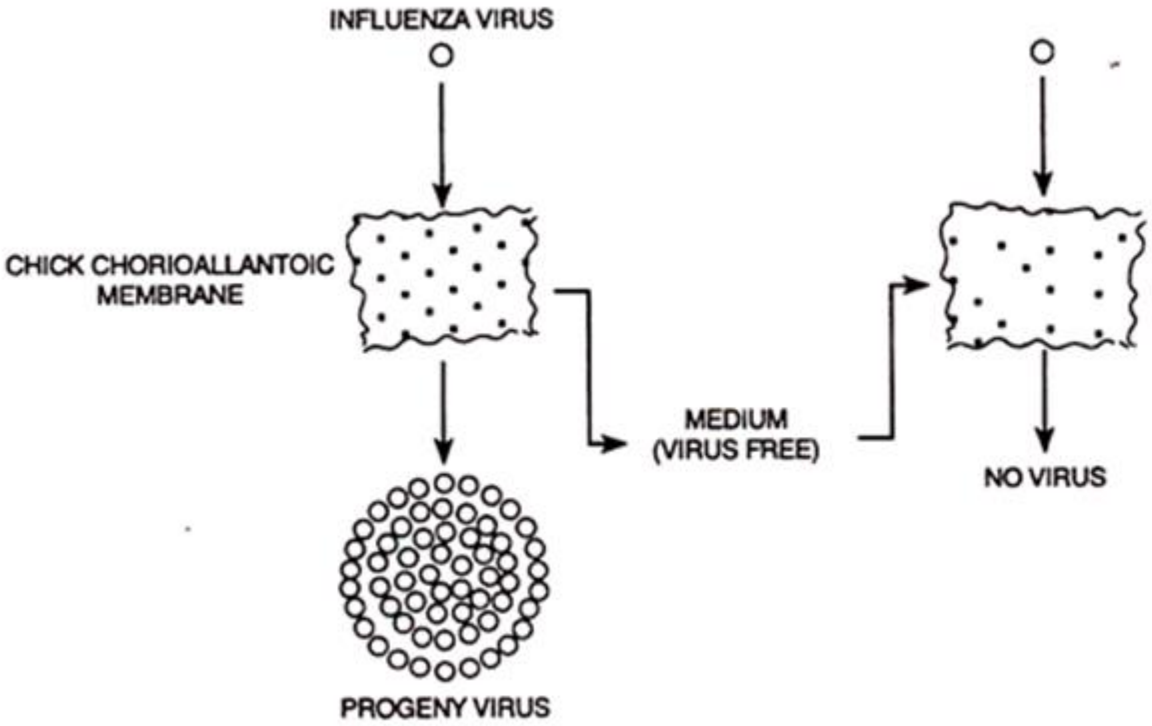
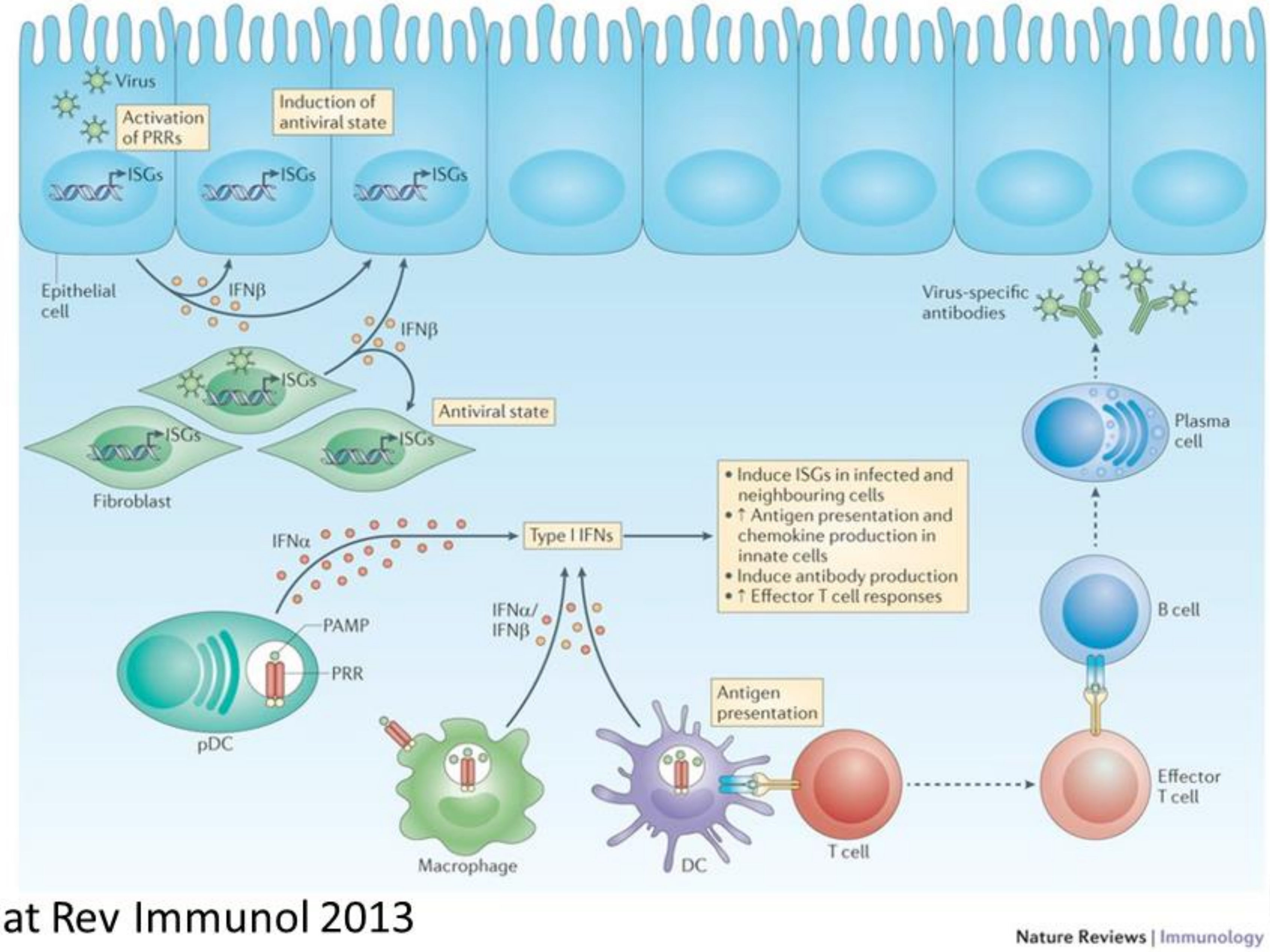


FIG. 11.14. Discovery experiement.

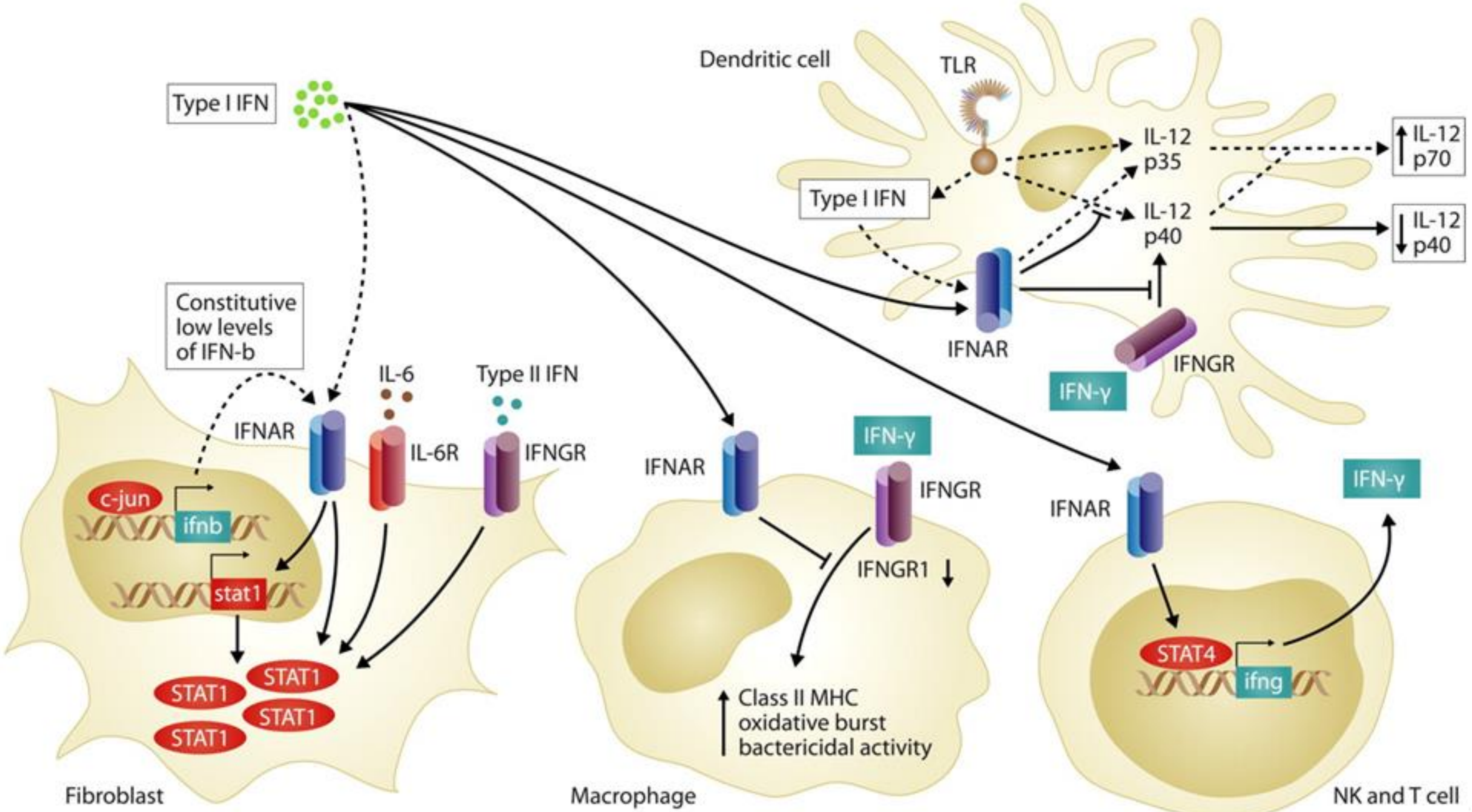
Isaacs, A., and Lindenmann, J., *Proc. Roy. Soc.*, B, **147**, 258 (1957)

Functions of type I IFN in infection



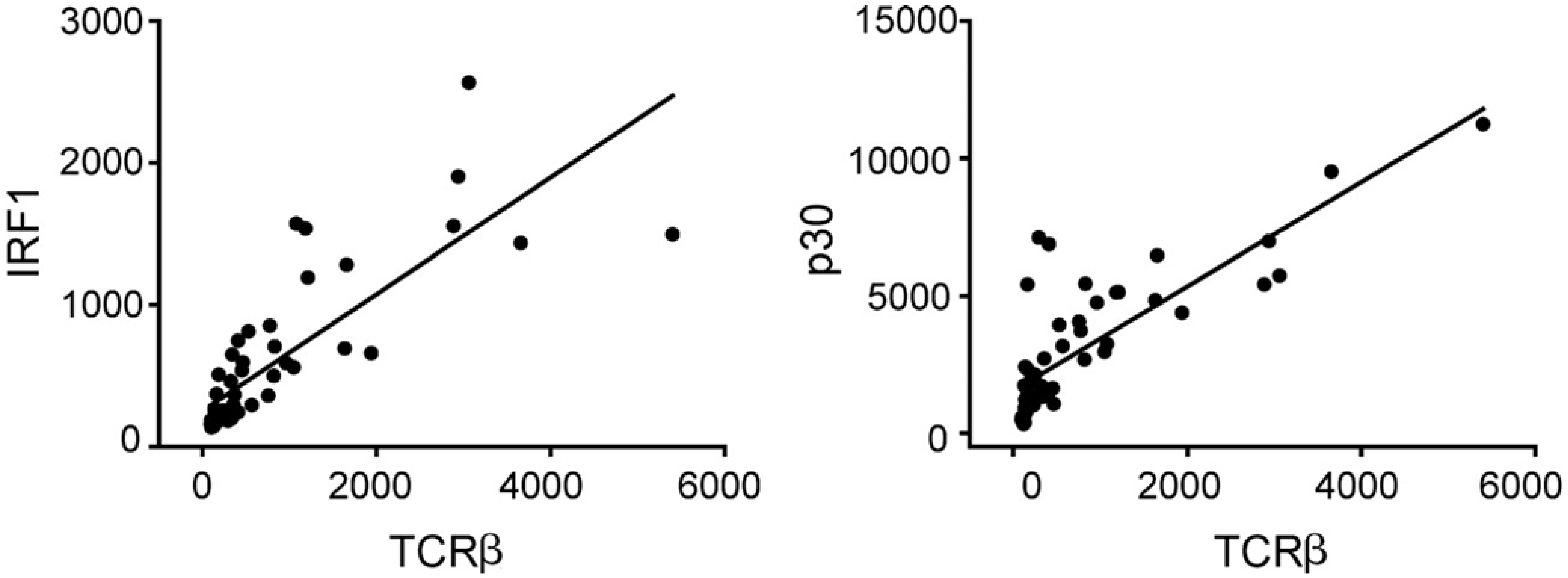
Ivashkiv et al. Nat Rev Immunol 2013

Cross-talk between type I IFN and adaptive immunity



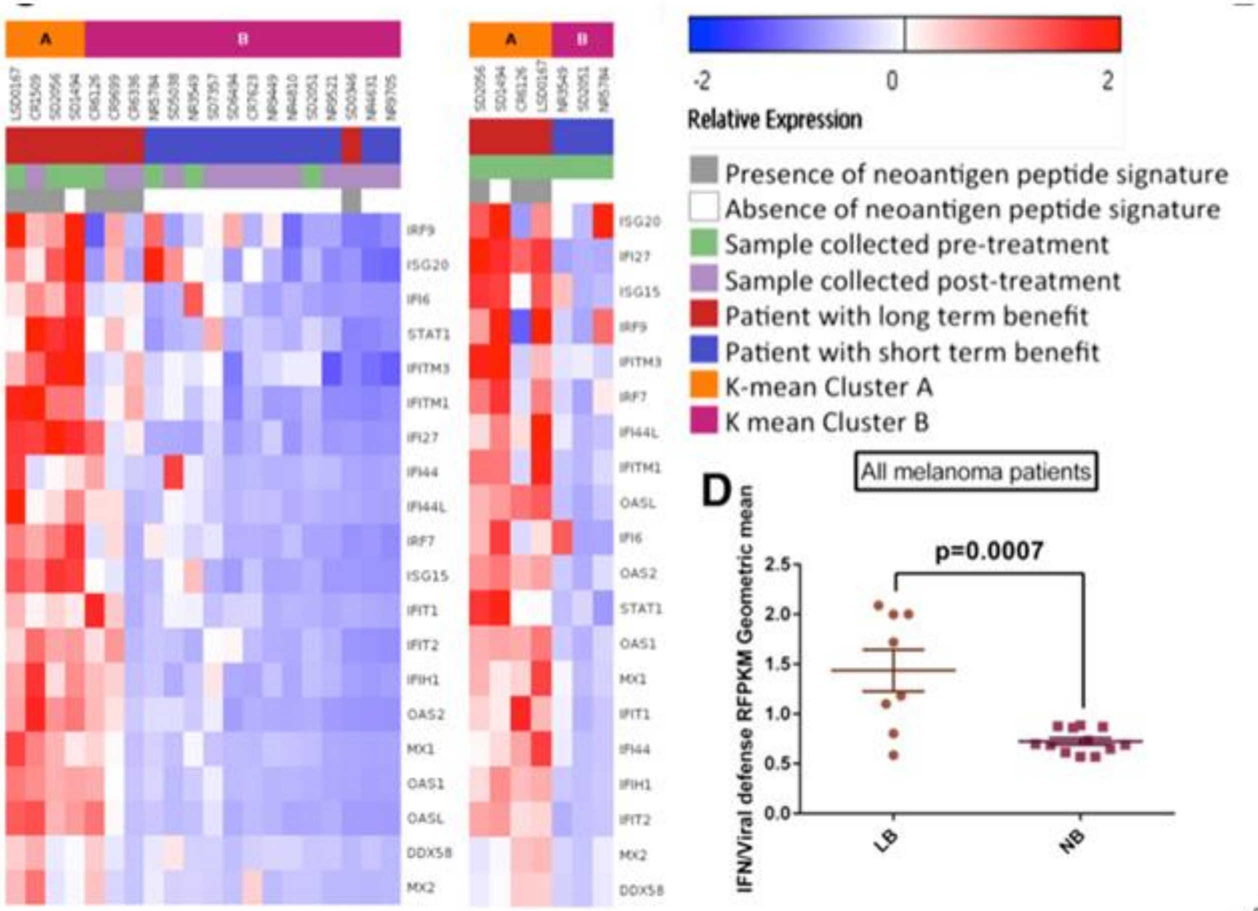
Trinchieri G, JEM 2010.

Type I IFN- related transcripts correlate with T cell infiltration in tumors



Fuertes M.B. et al., JEM. 208:2005-16 (2011)

Type I IFN signature is associated with clinical benefit from ipilimumab in melanoma

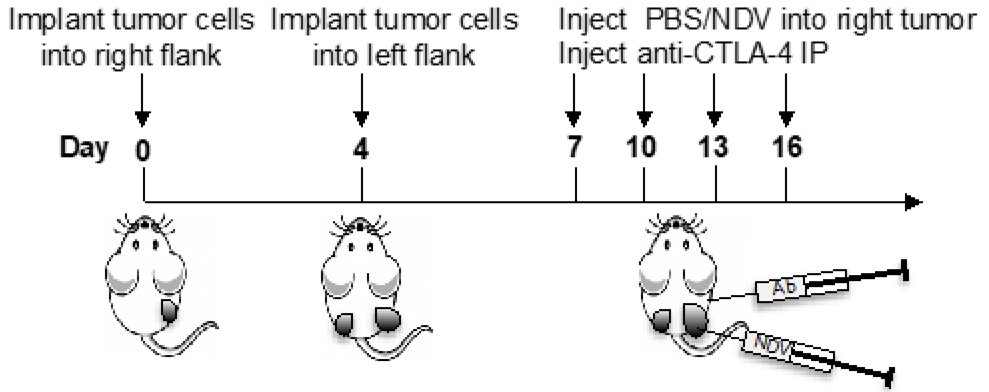


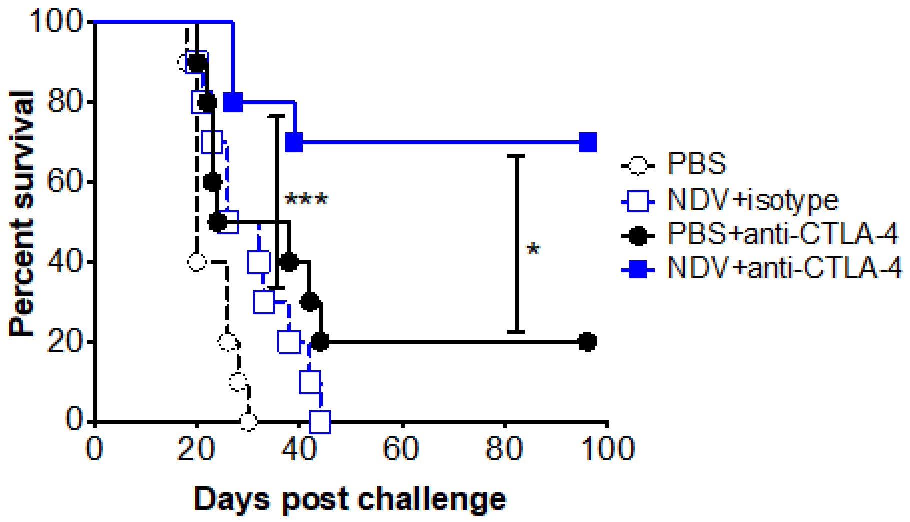
Chiappinelli et al., Cell 2015

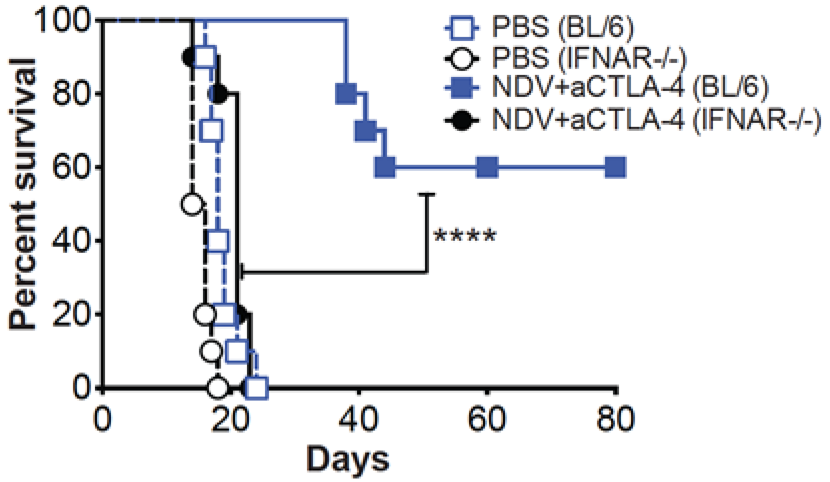
Memorial Sloan Kettering Cancer Center

Type I IFN pathway is essential for the efficacy of cancer immunotherapy

a.





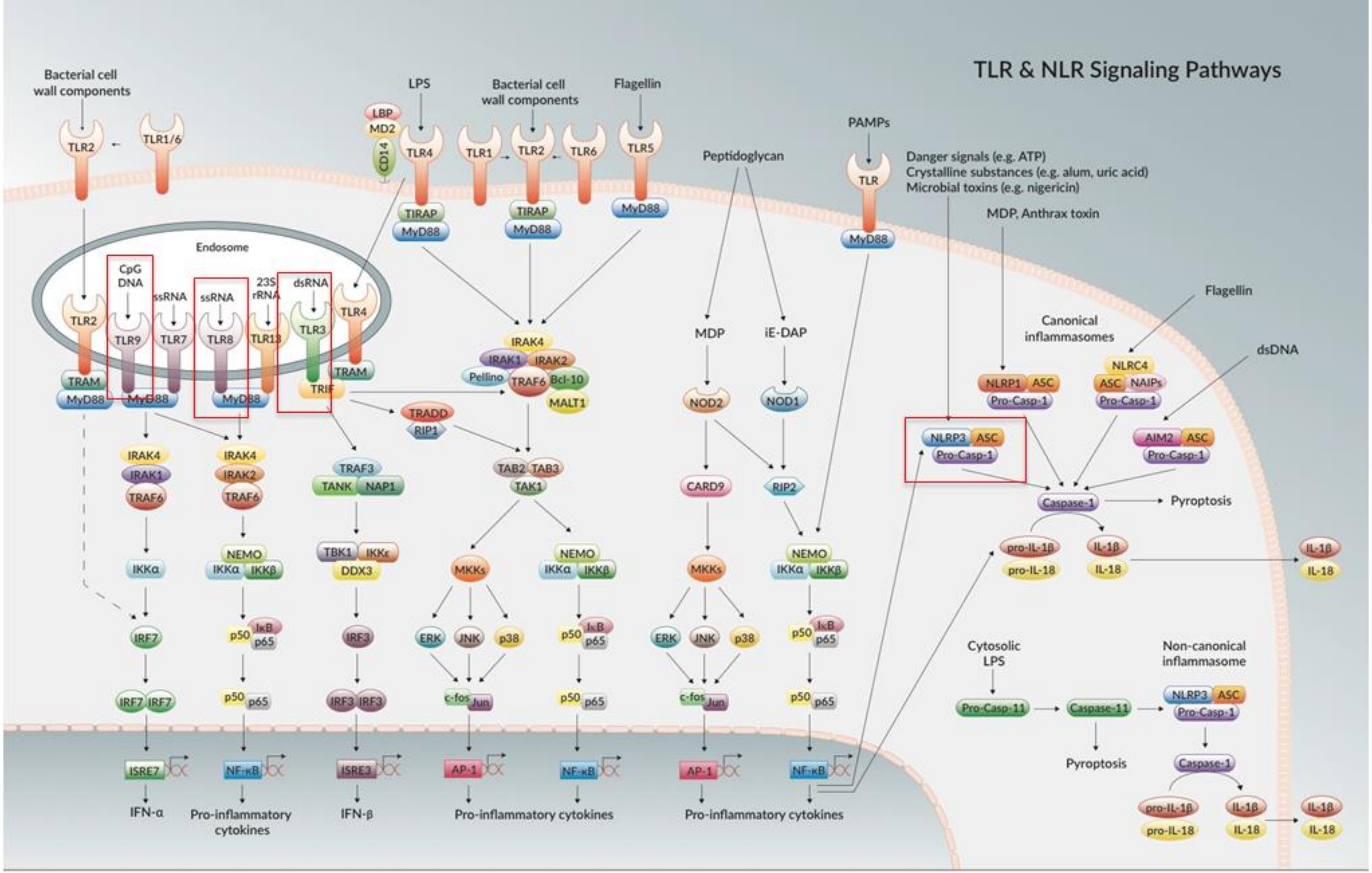


Zamarin D, Wolchok JD, Allison JP. *Sci Transl Med.* 2014 5:226ra

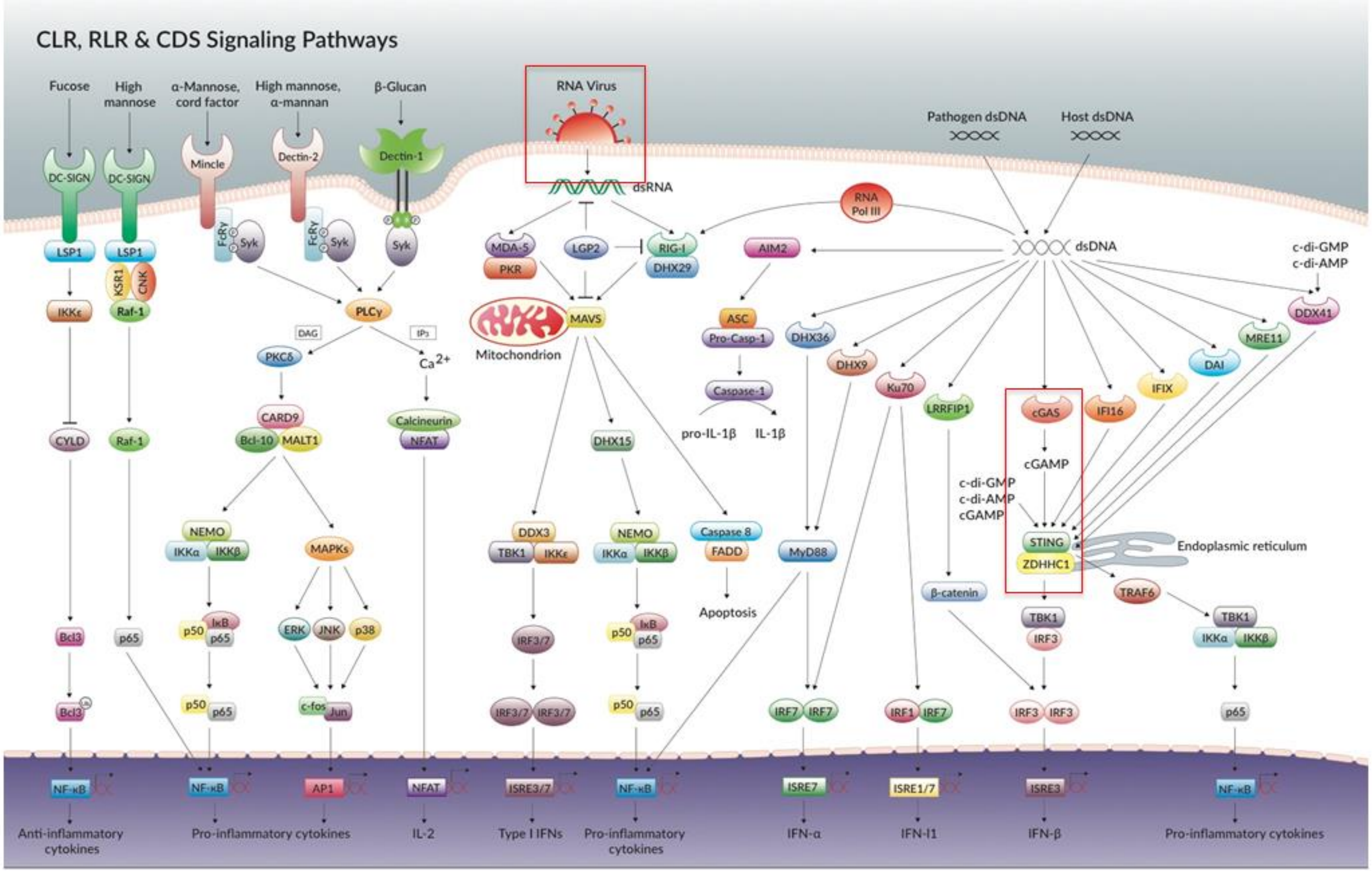
Memorial Sloan Kettering Cancer Center

Mechanisms of activation of type I IFN pathway

Memorial Sloan Kettering Cancer Center

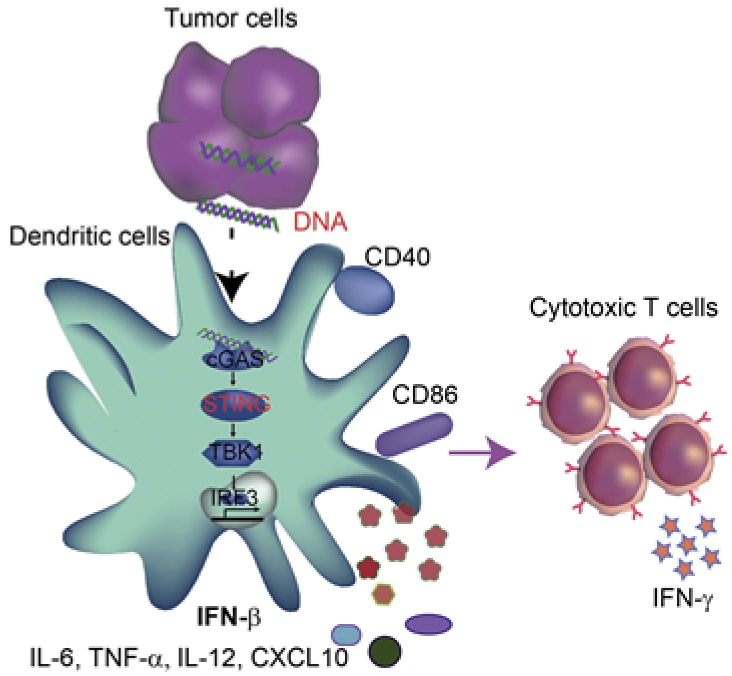

TLR & NLR Signaling Pathways
Bacterial cell wall components
TLR2
TLR1/6
LPS
LBP
MD2
CD14
TLR4
Bacterial cell wall components
TLR1
TLR2
TLR6
Flagellin
TLR5
TIRAP
MyD88
TIRAP
MyD88
MyD88
Endosome
CpG DNA
ssRNA
ssRNA
23S rRNA
dsRNA
TLR2
TLR9
TLR7
TLR8
TLR13
TLR3
TLR4
TRAM
MyD88
MyD88
MyD88
TRIF
TRAM
IRAK4
IRAK1
IRAK2
Pellino
TRAF6
Bcl-10
MALT1
TRADD
RIP1
IRAK4
IRAK1
TRAF6
IRAK4
IRAK2
TRAF6
TRAF3
TANK
NAP1
TAB2
TAB3
TAK1
IKKα
NEMO
IKKα
IKKβ
TBK1
IKKε
DDX3
MKKs
NEMO
IKKα
IKKβ
IRF7
p50
IκB
p65
IRF3
ERK
JNK
p38
p50
IκB
p65
IRF7
IRF7
p50
p65
IRF3
IRF3
c-fos
Jun
p50
p65
ISRE7
NF-κB
ISRE3
AP-1
NF-κB
IFN-α
Pro-inflammatory cytokines
IFN-β
Pro-inflammatory cytokines
Peptidoglycan
MDP
iE-DAP
NOD2
NOD1
CARD9
RIP2
MKKs
NEMO
IKKα
IKKβ
ERK
JNK
p38
p50
IκB
p65
c-fos
Jun
p50
p65
AP-1
NF-κB
Pro-inflammatory cytokines
PAMPs
TLR
MyD88
Danger signals (e.g. ATP)
Crystalline substances (e.g. alum, uric acid)
Microbial toxins (e.g. nigericin)
MDP, Anthrax toxin
Flagellin
Canonical inflammasomes
dsDNA
NLRP1
ASC
Pro-Casp-1
NLRC4
ASC
NAIPs
Pro-Casp-1
NLRP3
ASC
Pro-Casp-1
AIM2
ASC
Pro-Casp-1
Caspase-1
Pyroptosis
pro-IL-1β
pro-IL-18
IL-1β
IL-18
IL-1β
IL-18
Cytosolic LPS
Non-canonical inflammasome
Pro-Casp-11
Caspase-11
NLRP3
ASC
Pro-Casp-1
Pyroptosis
Caspase-1
pro-IL-1β
pro-IL-18
IL-1β
IL-18
IL-1β
IL-18

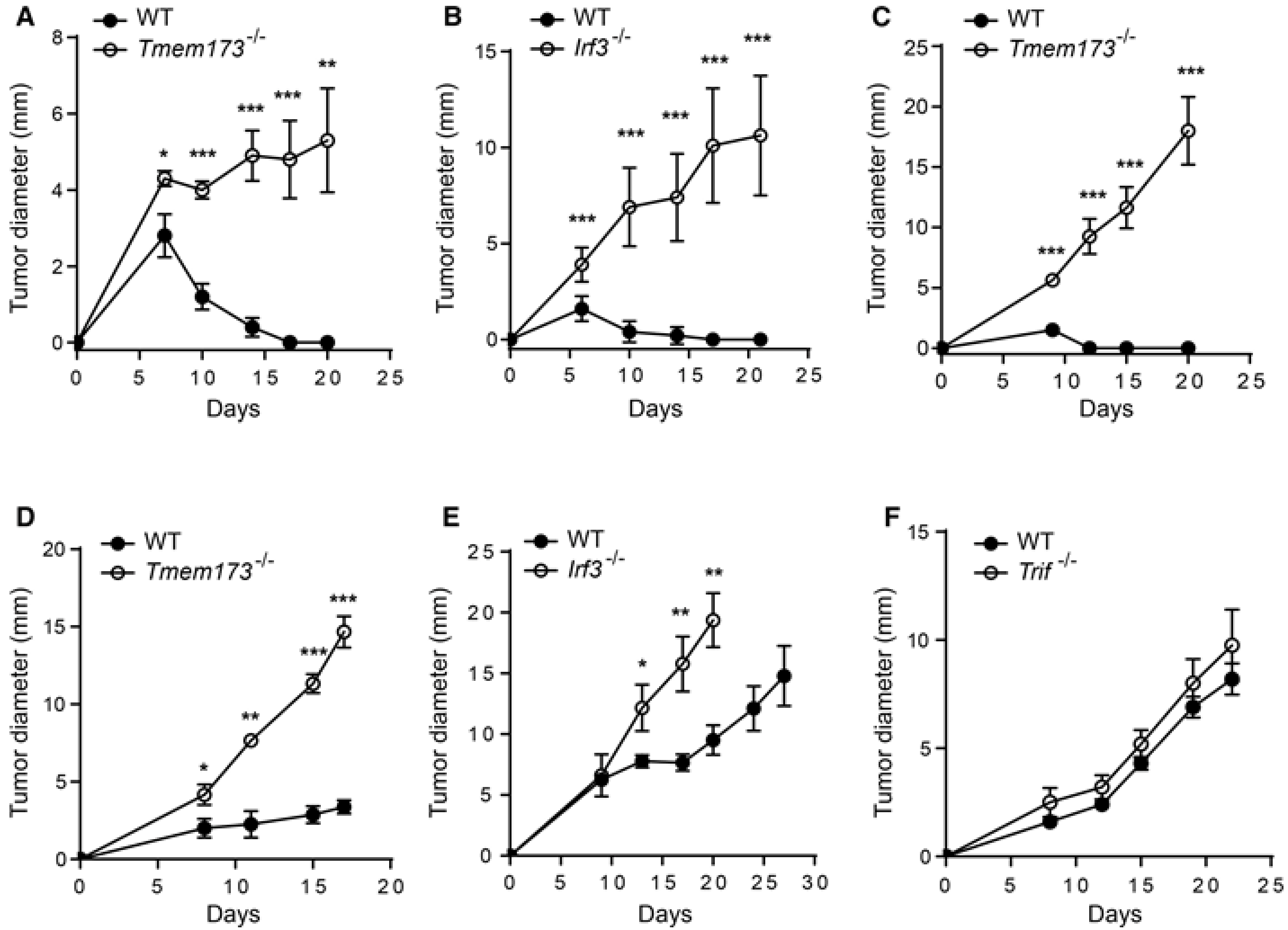
Kettering


CLR, RLR & CDS Signaling Pathways
Fucose
High mannose
α-Mannose, cord factor
High mannose, α-mannan
β-Glucan
RNA Virus
dsRNA
Pathogen dsDNA
Host dsDNA
DC-SIGN
DC-SIGN
Mincle
Dectin-2
Dectin-1
FcRγ
Syk
FcRγ
Syk
Syk
LSP1
LSP1
KSR1
CNK
Raf-1
IKKε
PLCγ
DAG
IP3
PKCδ
Ca2+
CARD9
Bcl-10
MALT1
Calcineurin
NFAT
CYLD
Raf-1
MDA-5
PKR
LGP2
RIG-I
DHX29
RNA Pol III
AIM2
dsDNA
c-di-GMP
c-di-AMP
Mitochondrion
MAVS
ASC
Pro-Casp-1
Caspase-1
pro-IL-1β
IL-1β
DHX36
DHX9
Ku70
LRRFIP1
cGAS
IFI16
IFIX
DAI
MRE11
DDX41
DHX15
cGAMP
c-di-GMP
c-di-AMP
cGAMP
NEMO
IKKα
IKKβ
MAPKs
DDX3
TBK1
IKKε
NEMO
IKKα
IKKβ
Caspase 8
FADD
Apoptosis
MyD88
STING
ZDHHC1
Endoplasmic reticulum
β-catenin
TRAF6
TBK1
IRF3
TBK1
IKKα
IKKβ
Bcl3
p65
p50
IκB
p65
ERK
JNK
p38
IRF3/7
p50
IκB
p65
Bcl3
p50
p65
c-fos
Jun
IRF3/7
IRF3/7
p50
p65
IRF7
IRF7
IRF1
IRF7
IRF3
IRF3
p65
NF-κB
NF-κB
AP1
NFAT
ISRE3/7
NF-κB
ISRE7
ISRE1/7
ISRE3
NF-κB
Anti-inflammatory cytokines
Pro-inflammatory cytokines
IL-2
Type I IFNs
Pro-inflammatory cytokines
IFN-α
IFN-l1
IFN-β
Pro-inflammatory cytokines

n Kettering

STING pathway is required for immune recognition and elimination of tumors.





Woo …. Gajewski. Immunity 2015.

Memorial Sloan Kettering Cancer Center

Therapeutic strategies to target type I IFN pathway in cancer

- TLR agonists
- STING agonists
- Viruses
- Bacteria
- Engineered viruses and bacteria

Development of a STING Agonist-producing Synthetic Biotic™ Medicine to Activate Innate and Adaptive Immunity and Drive Antitumor Immune Responses

Designed for life

Jose M. Lora, PhD
Vice President, Research

SITC 2018- Washington, DC
November 10th, 2018

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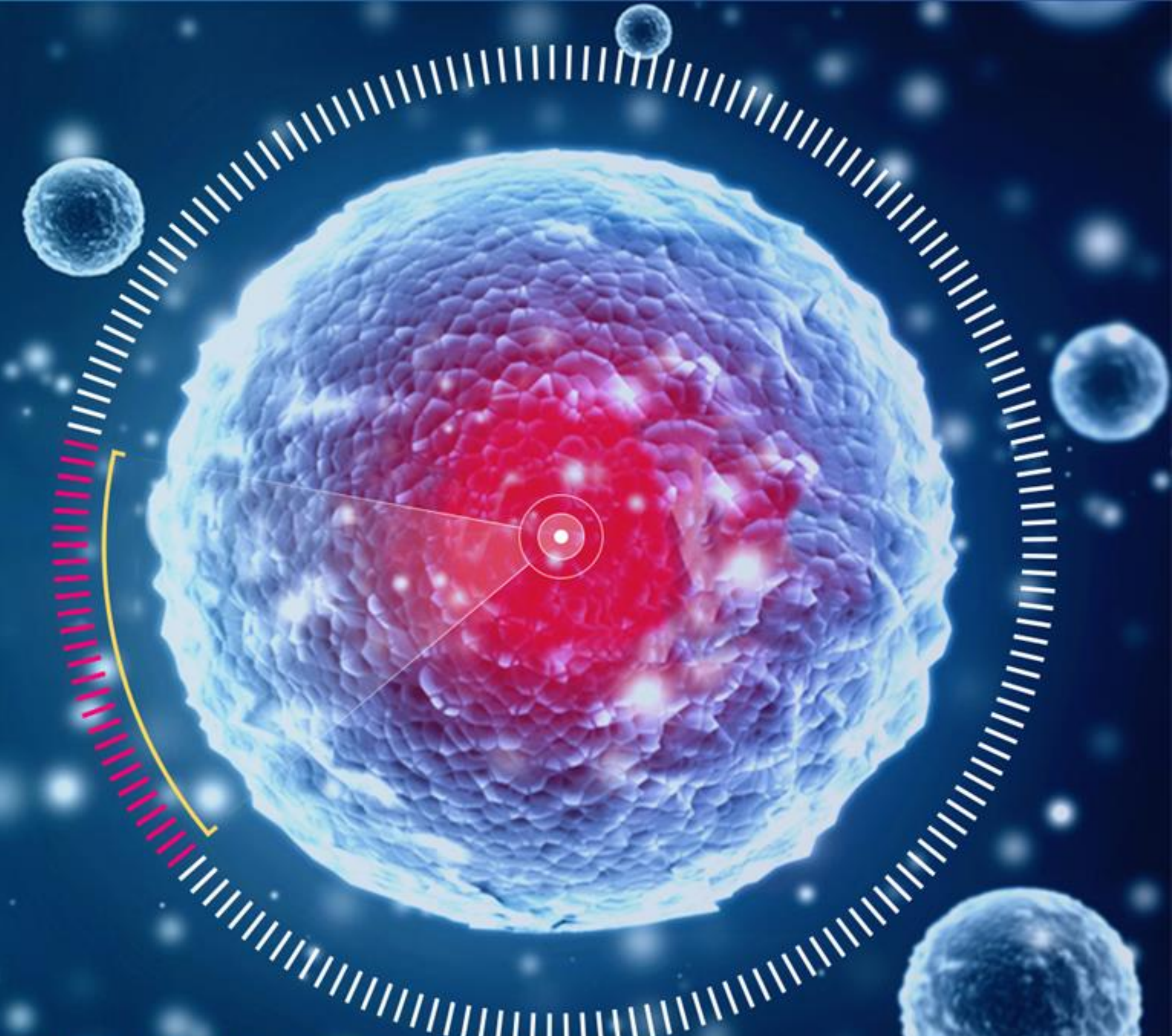
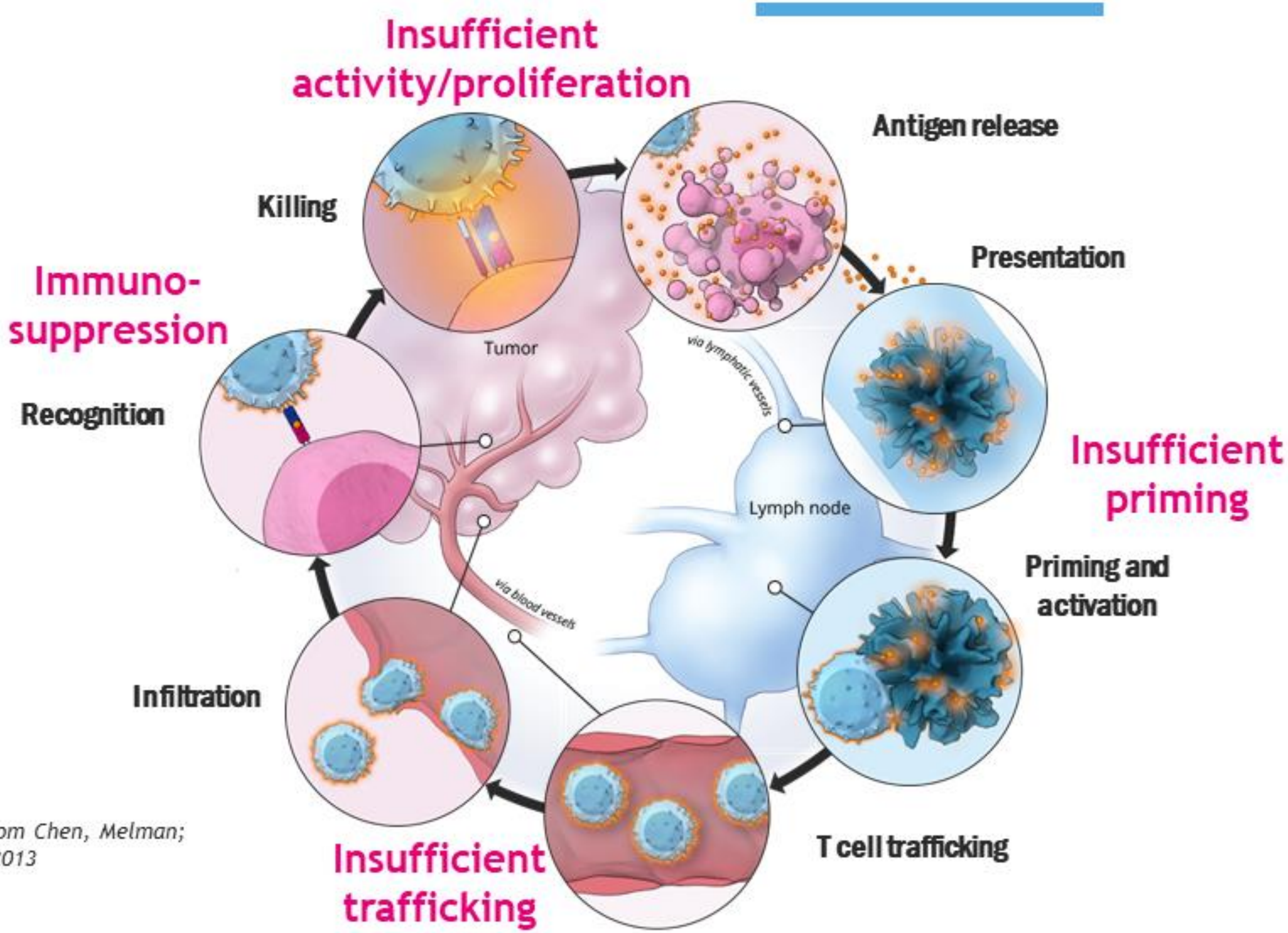


A Tumor Can Evade Multiple Critical Aspects of the Cancer-Immunity Cycle



Adapted from Chen, Melman; Immunity 2013

Monotherapies Often Fail to Overcome Tumor Evasion Mechanisms

Recognized Need to Combine Mechanisms to Broaden the Benefit of Immunotherapy

Synthetic Biotic Medicines Engineered for Efficacy

Rational Design of Key Immunostimulatory Mechanisms in a Bacterial Chassis

Relieve Immunosuppression

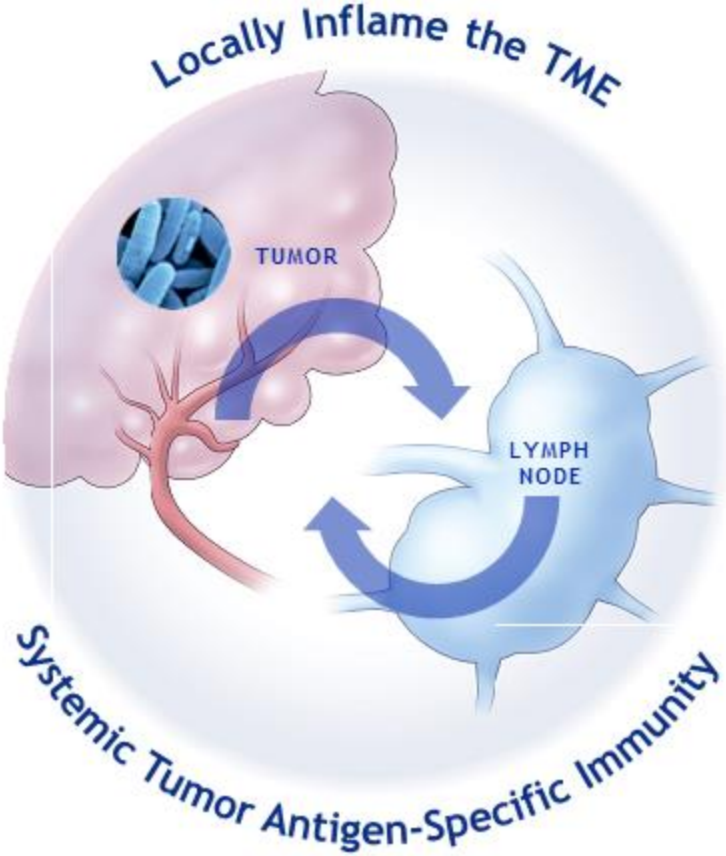
Consume immunosuppressive metabolites

Produce checkpoint inhibitors

Promote Trafficking

Chassis effect

Produce cytokines/chemokines



Promote and Sustain Immune Activation / Proliferation

Produce Immunostimulatory Molecules

Promote Immune Cell Survival and Activity

Prime for Tumor Antigen-Specific Vaccination

Chassis effect

Produce lytic factors

Produce agonists for immune cell activation

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Synthetic Biotics Medicines Attributes

Platform Flexibility to Maximize Efficacy, Control, and Safety

EFFICACY DRIVERS

Sustained Payload Delivery: Persistence in TME
Multiple Mechanisms: Large gene insertion capacity
Cellular Bioreactors: Enzymatic activity

CONTROL

Large Engineering Toolkit: Design to sense / respond to inducer
Manufacturability: No mammalian cell culture

SAFETY

Low Systemic Risk: Initial programs intratumoral
Non Pathogenic: Probiotic chassis, antibiotic deactivation

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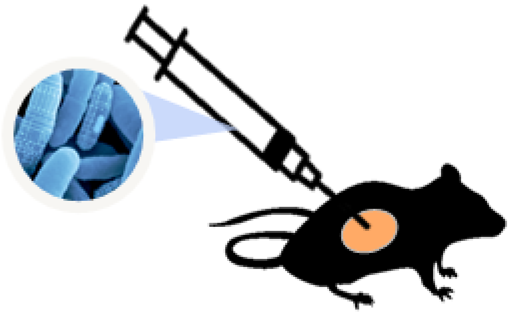
Intra-tumoral Injection of Synthetic Biotic Chassis: Tumor Colonization Without Leakage; Local Innate Immunity

Chassis Distribution



Robust proliferation in tumor.
No significant leakage to tissues

Survival/proliferation in tumors 10-15 days post-single dose.
Potential for limited injections

Elicits **innate responses** (e.g., IL-6, TNFα) **in the tumor,** not in circulation

Intra-tumoral Injection of Synthetic Biotic Chassis: Tumor Colonization Without Leakage; Local Innate Immunity

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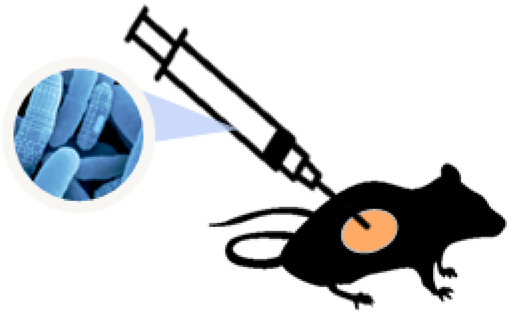

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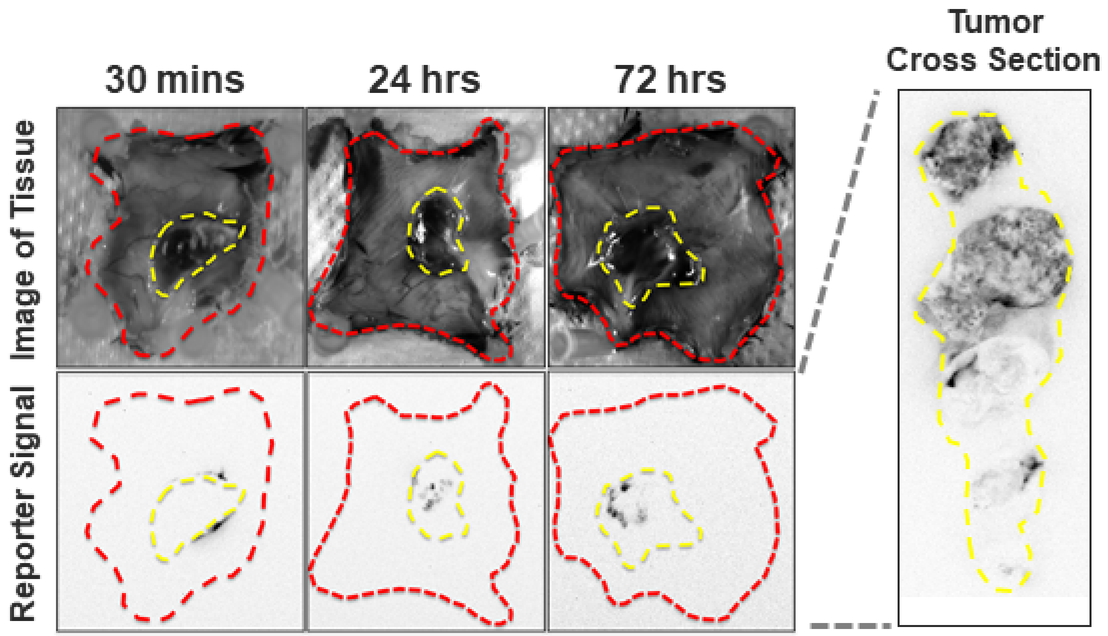
Behavior within TME

in B16.F10 Mice



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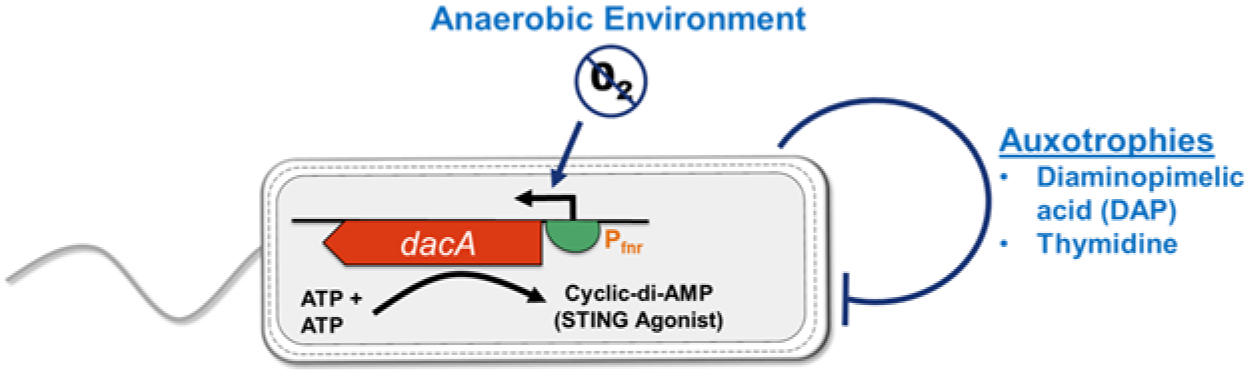
Dual Innate Immune Activator
Synthetic Biotic Medicine Producing STING Agonist: SYNB1891



- Synthetic biology applied to IO programs to confer activities for efficacy and control for safety
- SYNB1891 designed as a dual innate immune activator: Combined benefit of bacterial chassis and STING agonist
- *dacA* gene: Integrated into the genome under the control of inducible promoter (P_{fnr}) to produce c-di-AMP (CDA)
- Dual biosafety feature via auxotrophies
- Learnings inform future combinations

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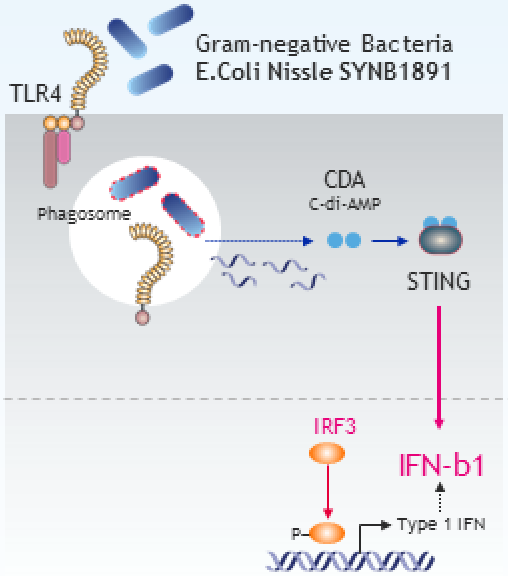
Dual Innate Immune Activator

TUMOR

1 CDA-STING Activation



SYN-STING	✓
Naked STING Agonist	✓

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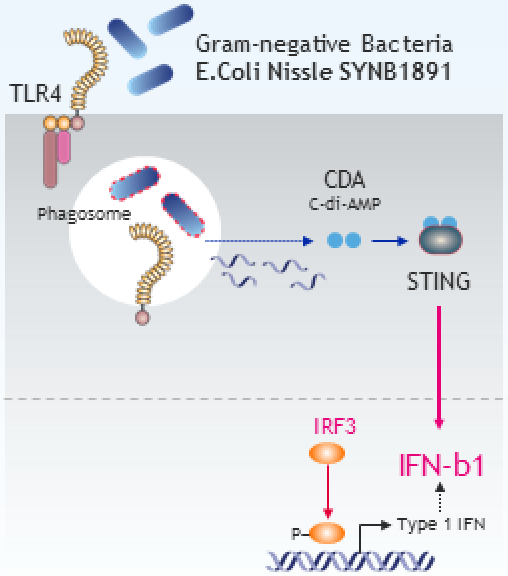
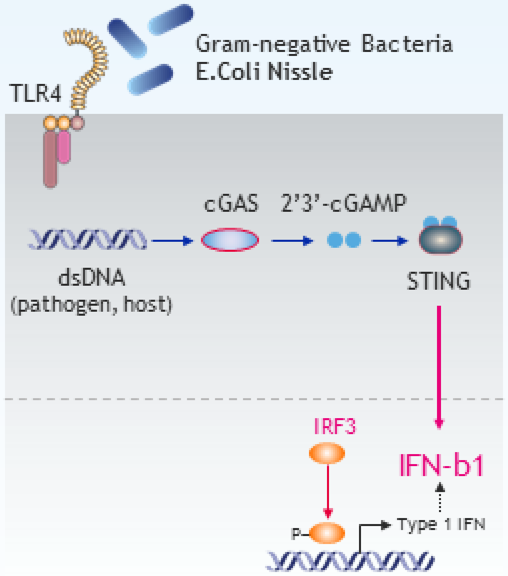
Dual Innate Immune Activator

TUMOR

1 CDA-STING Activation



2 Bacterial cGAS-STING Activation



	1 CDA-STING Activation	2 Bacterial cGAS-STING Activation
SYN-STING	✓	✓
Naked STING Agonist	✓	✓ ⊗

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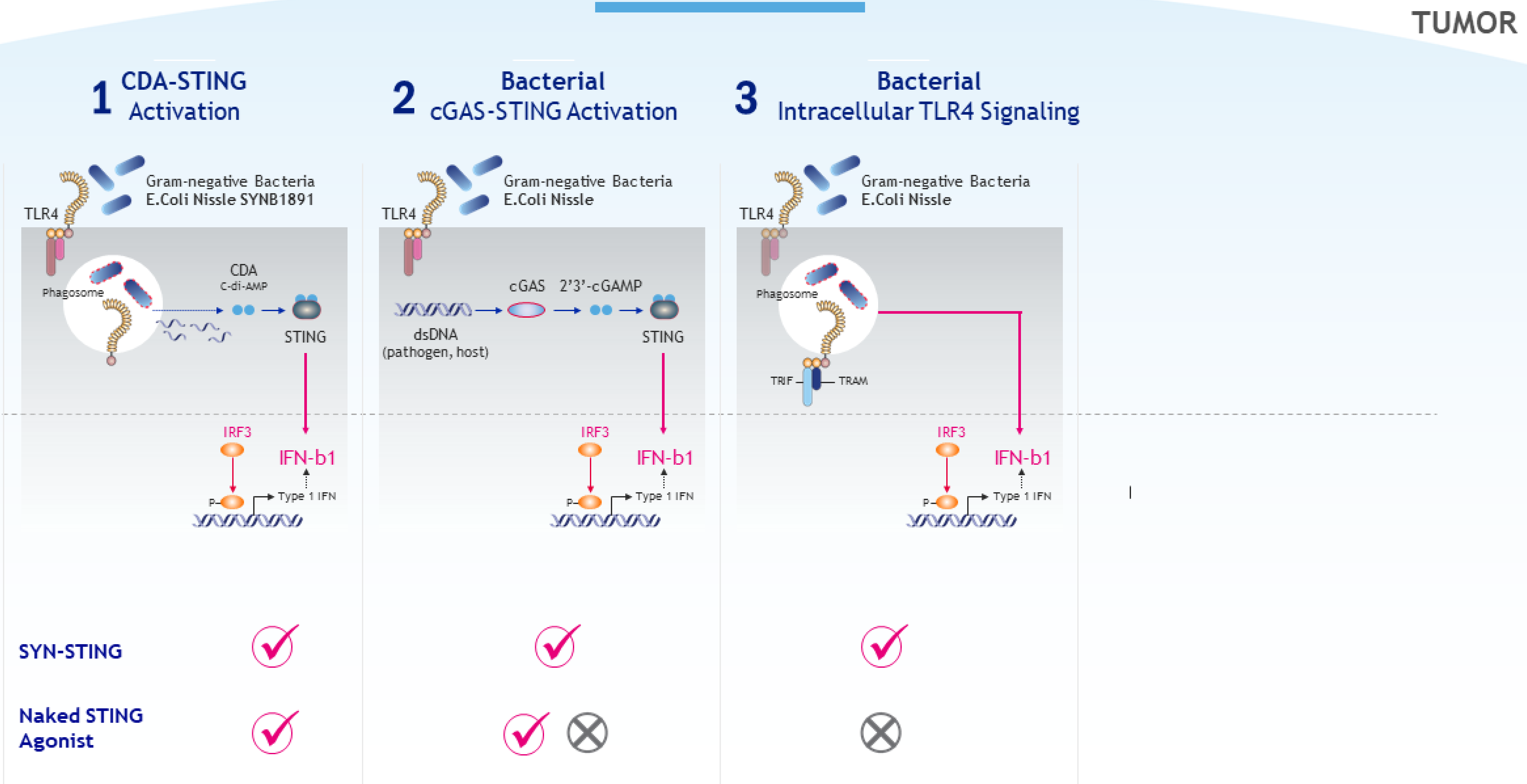
Dual Innate Immune Activator



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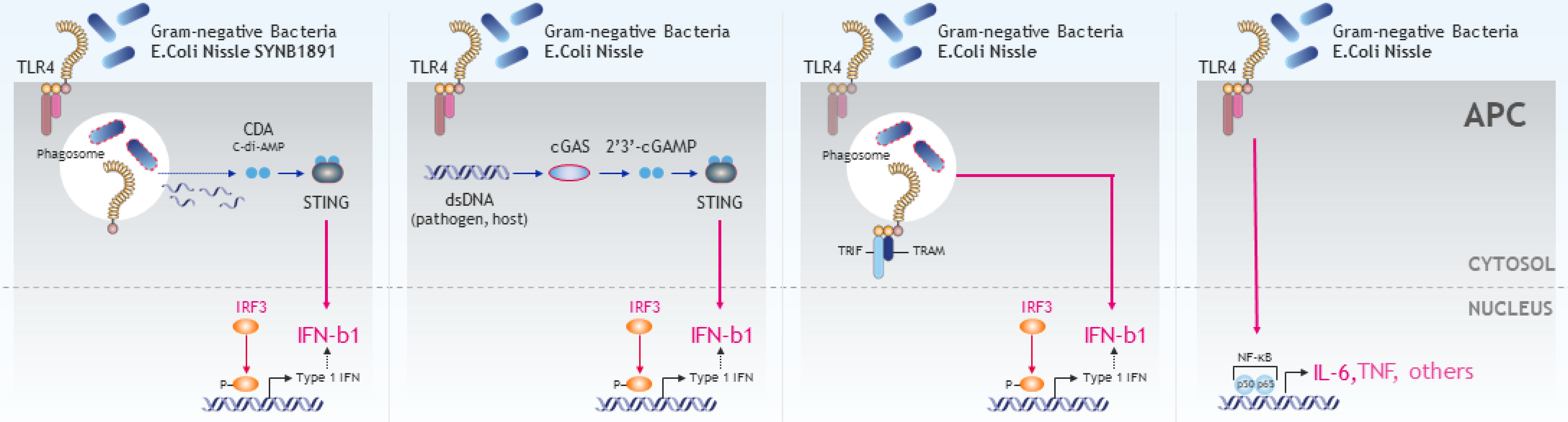
Dual Innate Immune Activator

TUMOR

1 CDA-STING Activation | **2** Bacterial cGAS-STING Activation | **3** Bacterial Intracellular TLR4 Signaling | **4** Bacterial TLR/MyD88 Signaling



	1	2	3	4
SYN-STING	✓	✓	✓	✓
Naked STING Agonist	✓	✓ ⊗	⊗	⊗

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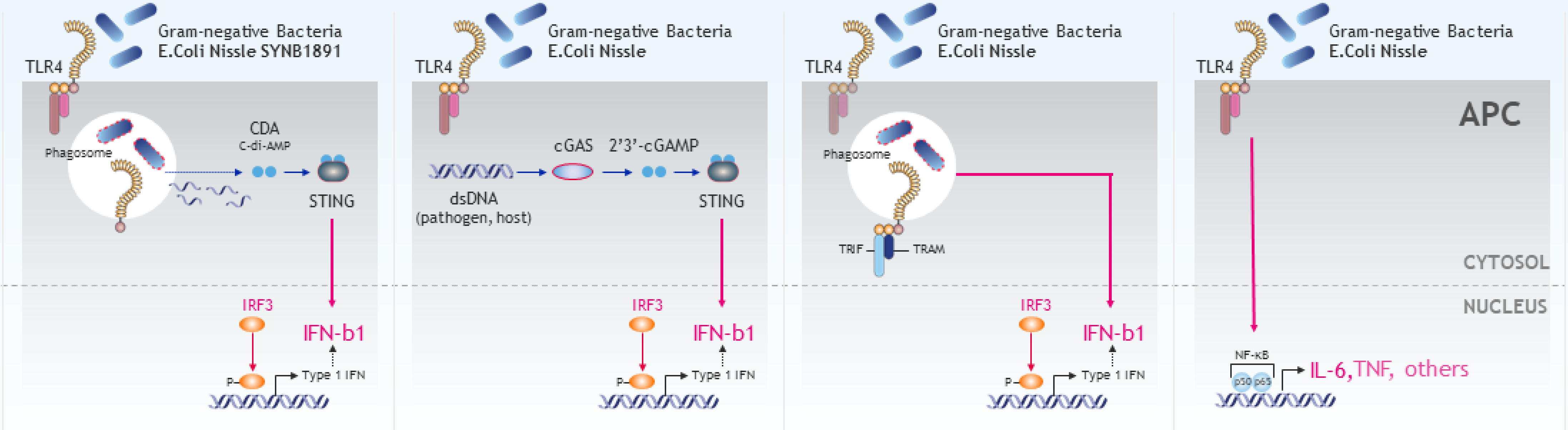
Dual Innate Immune Activator

TUMOR

	1 CDA-STING Activation	2 Bacterial cGAS-STING Activation	3 Bacterial Intracellular TLR4 Signaling	4 Bacterial TLR/MyD88 Signaling

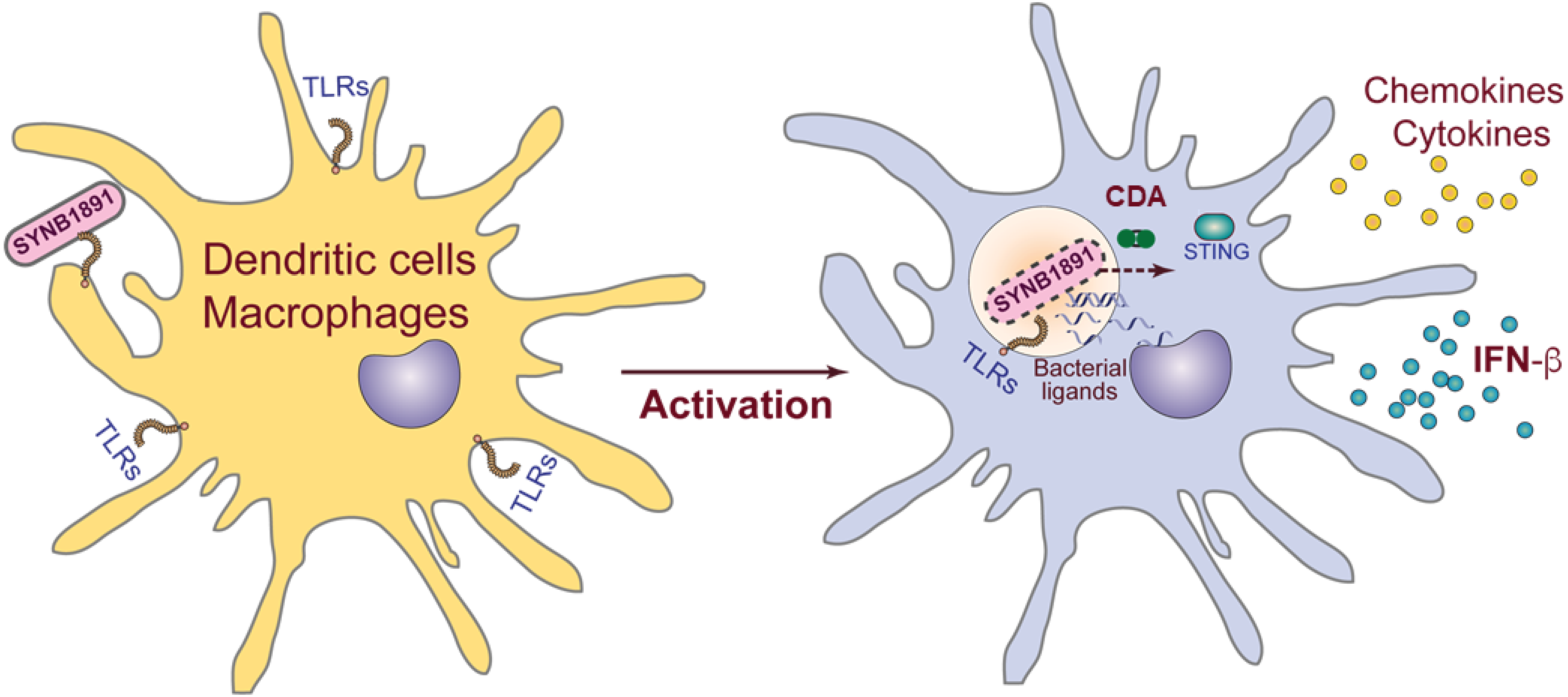


Promotes Trafficking, Immune Activation/Proliferation, Priming

	1	2	3	4
SYN-STING	✓	✓	✓	✓
Naked STING Agonist	✓	✓ ⊗	⊗	⊗

SYNB1891 Leverages Natural Phagocytic Activity of Antigen Presenting Cells

Agonizes STING in Natural Context



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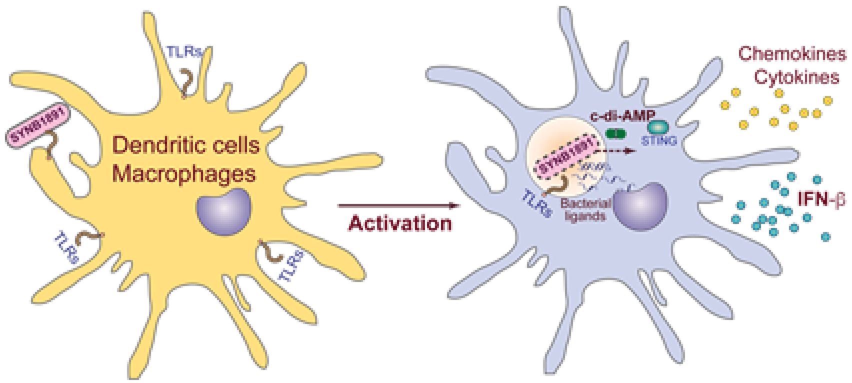
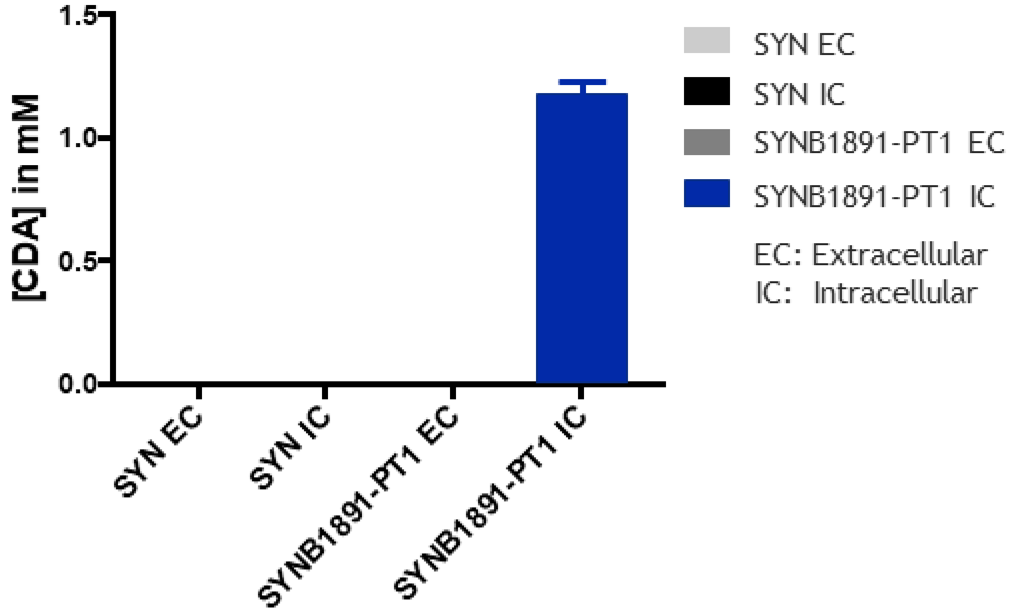
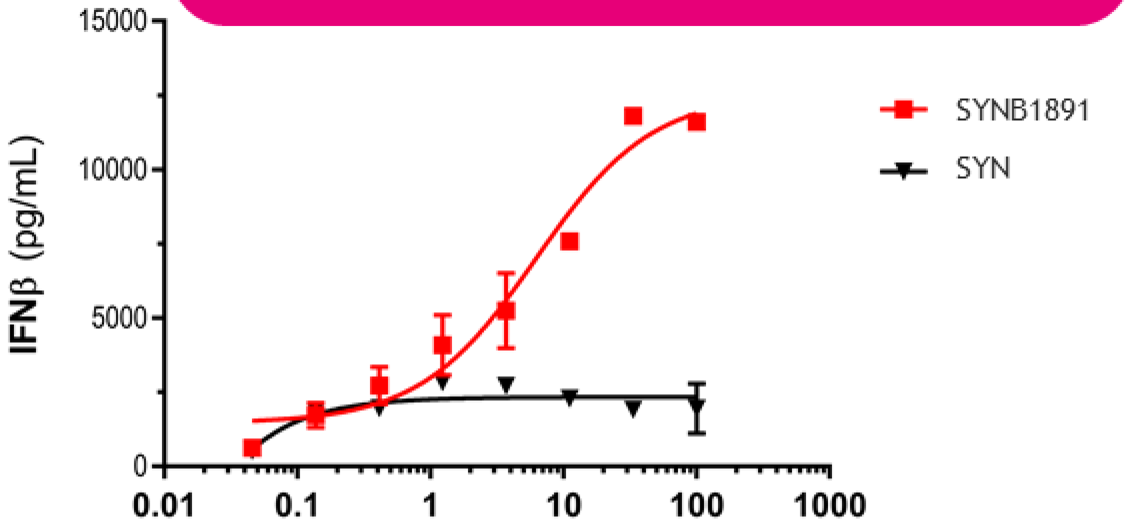
In Vitro Characterization of SYNB1891



STING Agonist Not Released to Extracellular Space



Dose-dependent Activity in Mouse APCs



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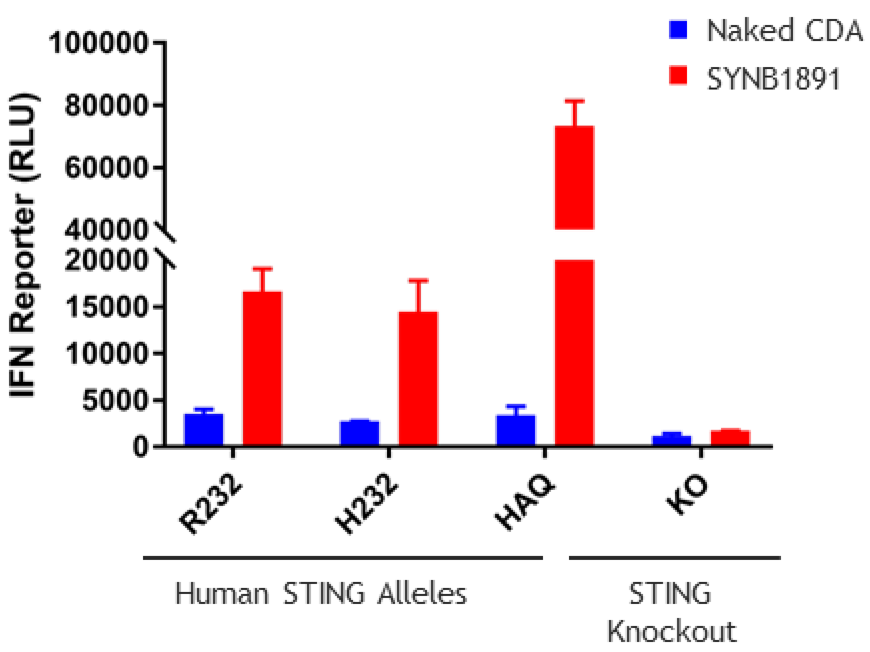
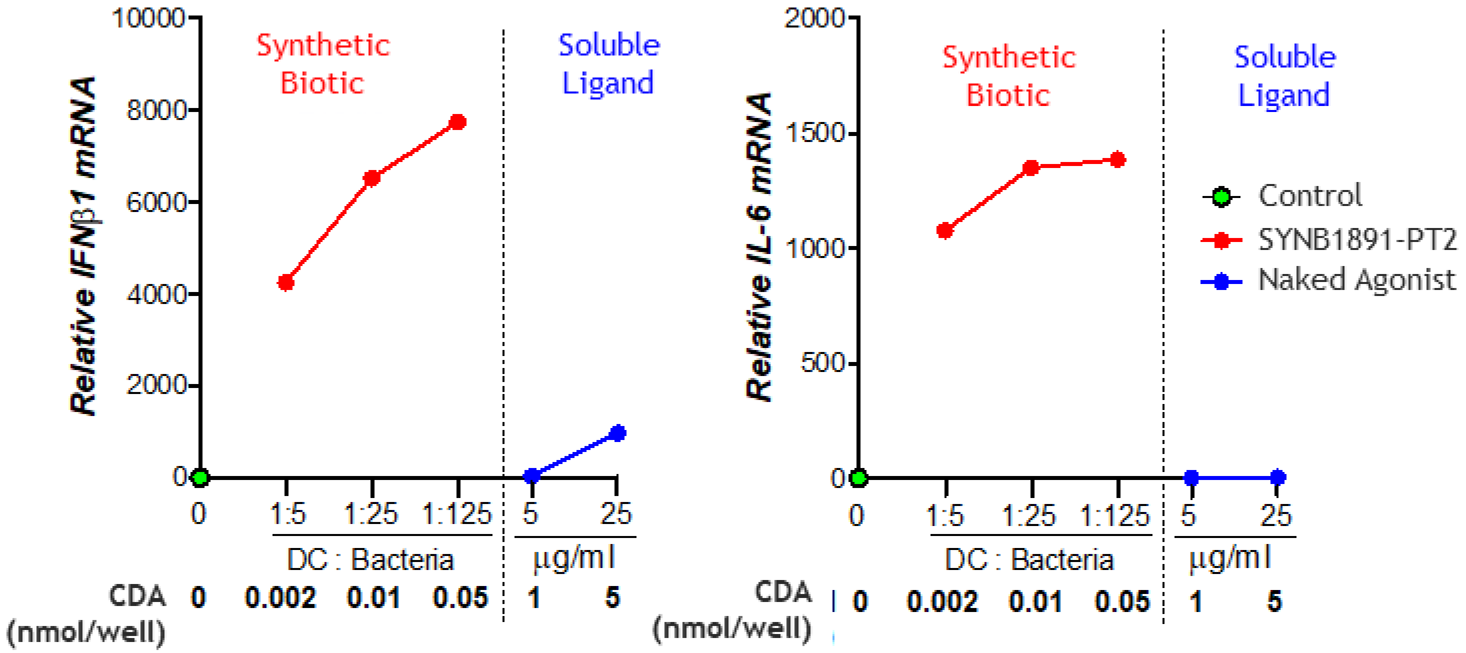
In Vitro Characterization of SYNB1891

Interferon Production Across Multiple Human STING Alleles Greater than Naked STING Agonist
Additional Proinflammatory Pathways Engaged

Reporter THP-1



Primary DCs



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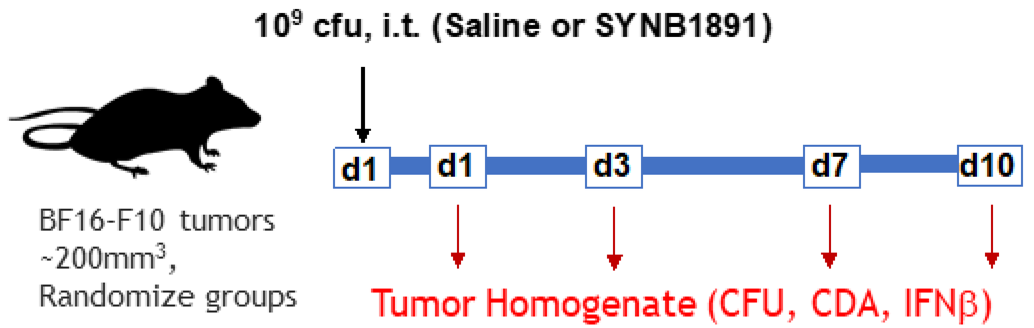
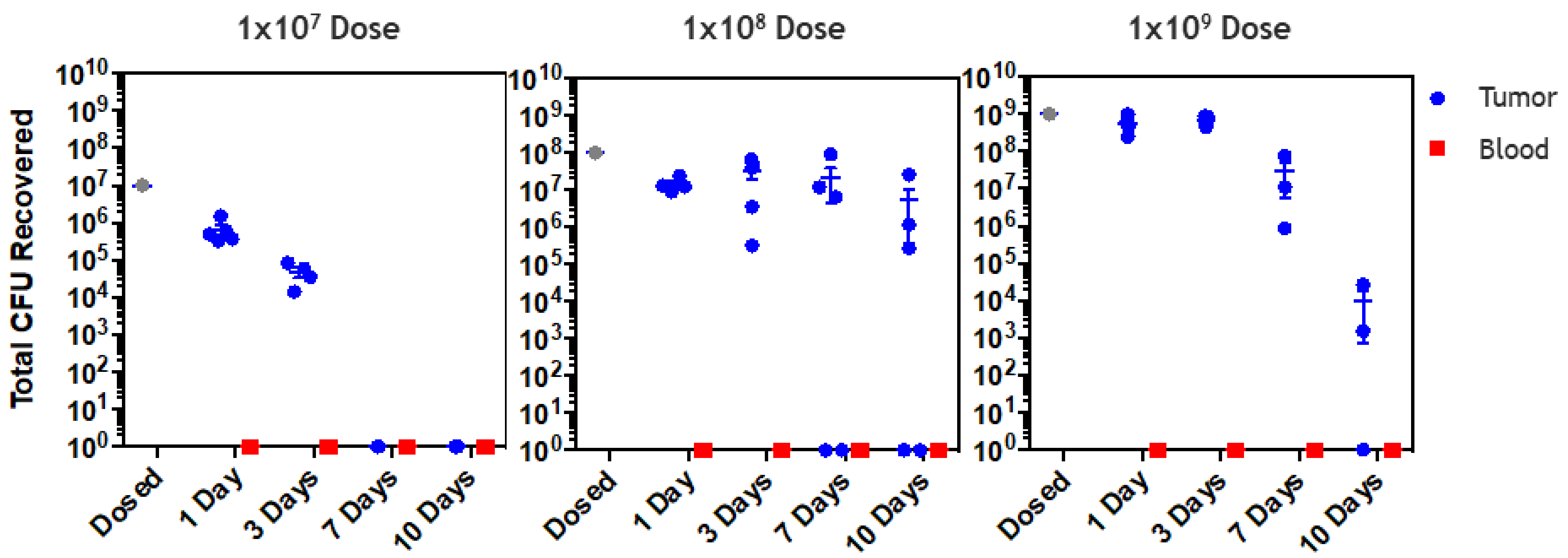
In Vivo Bacterial Kinetics of SYNB1891

Restricted to Tumor and Cleared Quickly

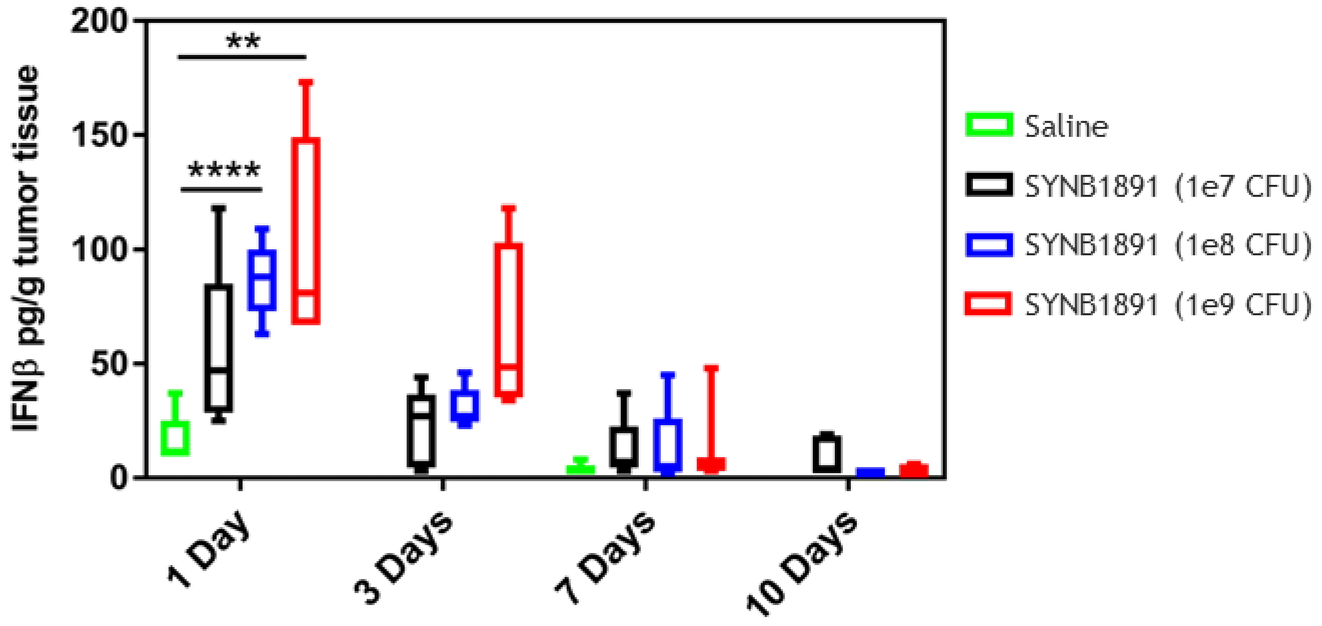




Pharmacodynamic Characterization of SYNB1891

Dose-dependent Increases in Tumoral IFNß and Other Innate Immune Markers

Dose Dependent IFNß Following 1 Injection



Additional Innate Immune Markers

Administration of SYNB1891 Results in Dose-dependent Increase in Tumoral CDA along with Innate Cytokines

Prototype Elicits Inflammation-related Gene Signature in Injected Tumors

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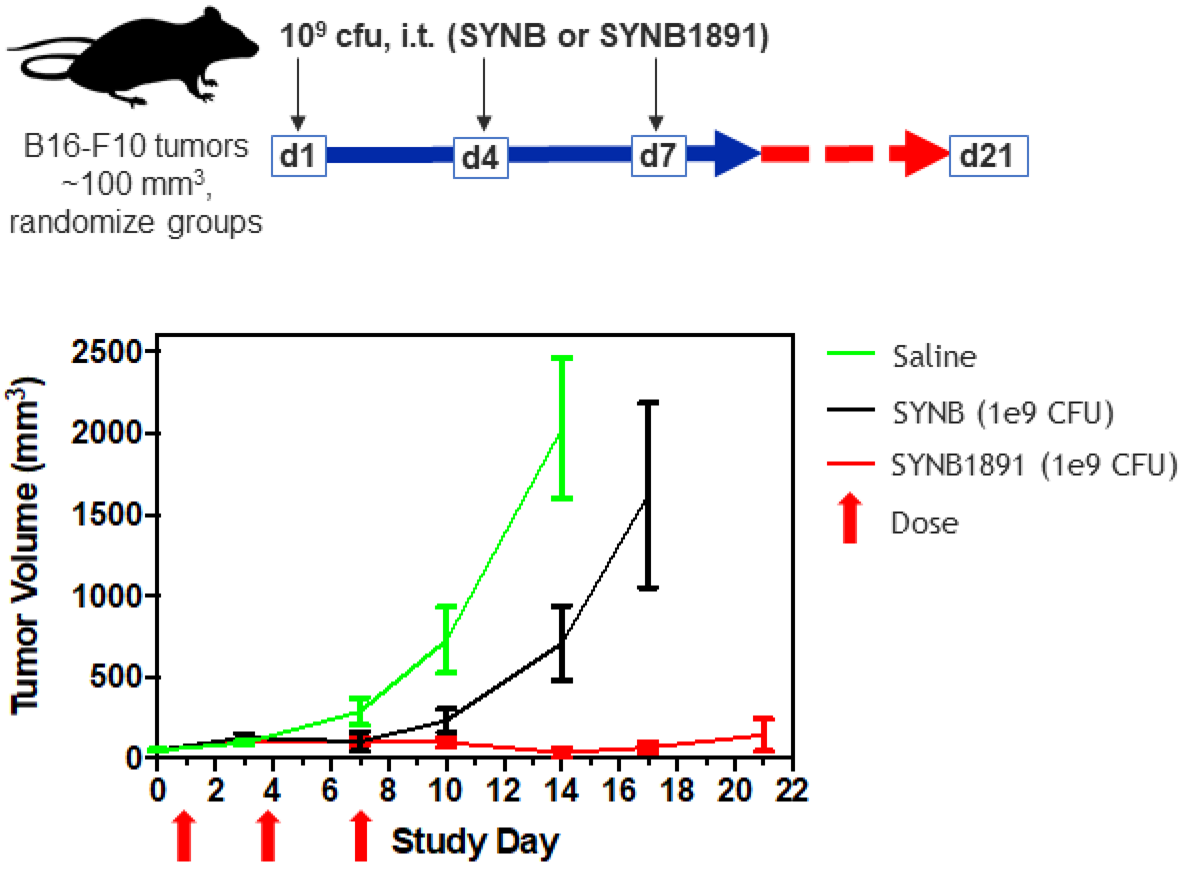
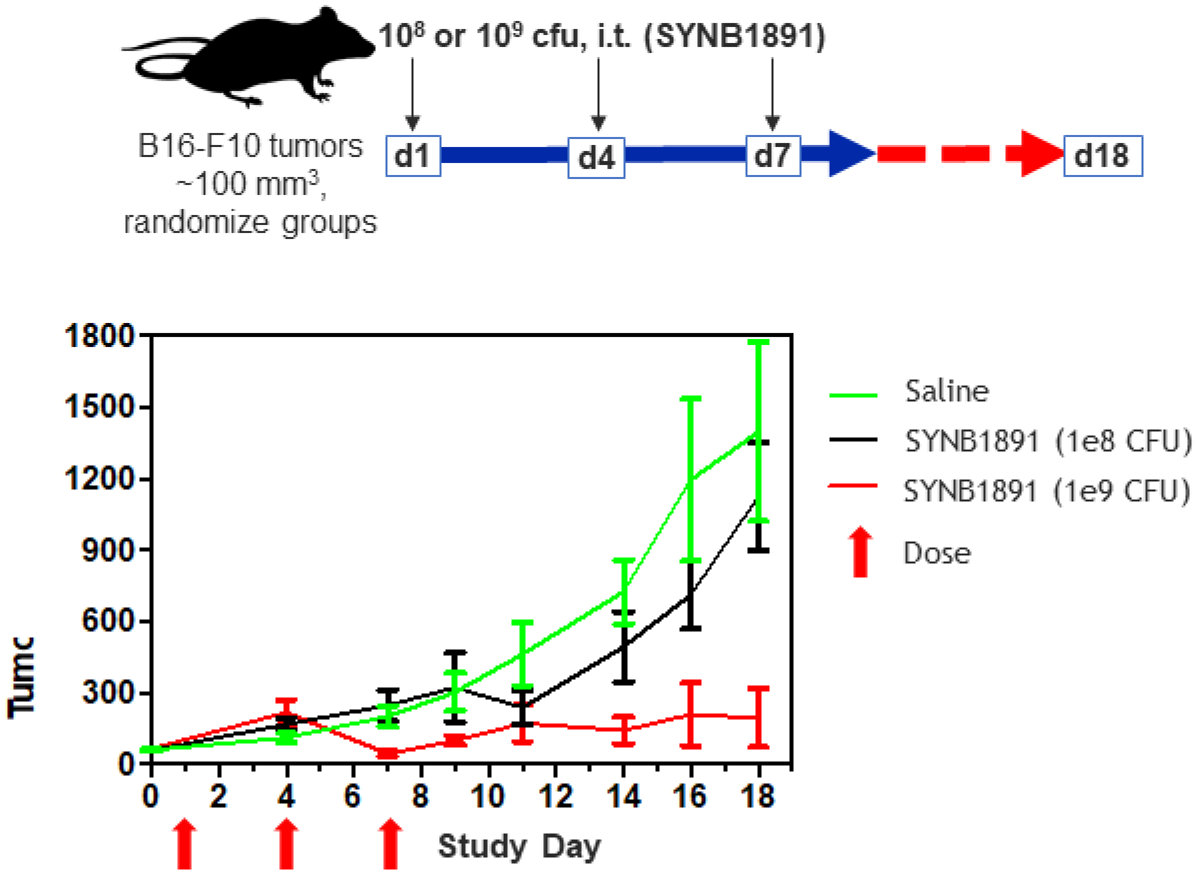
In Vivo Characterization of SYNB1891

Delivers Anti-tumor Activity as a Single Agent





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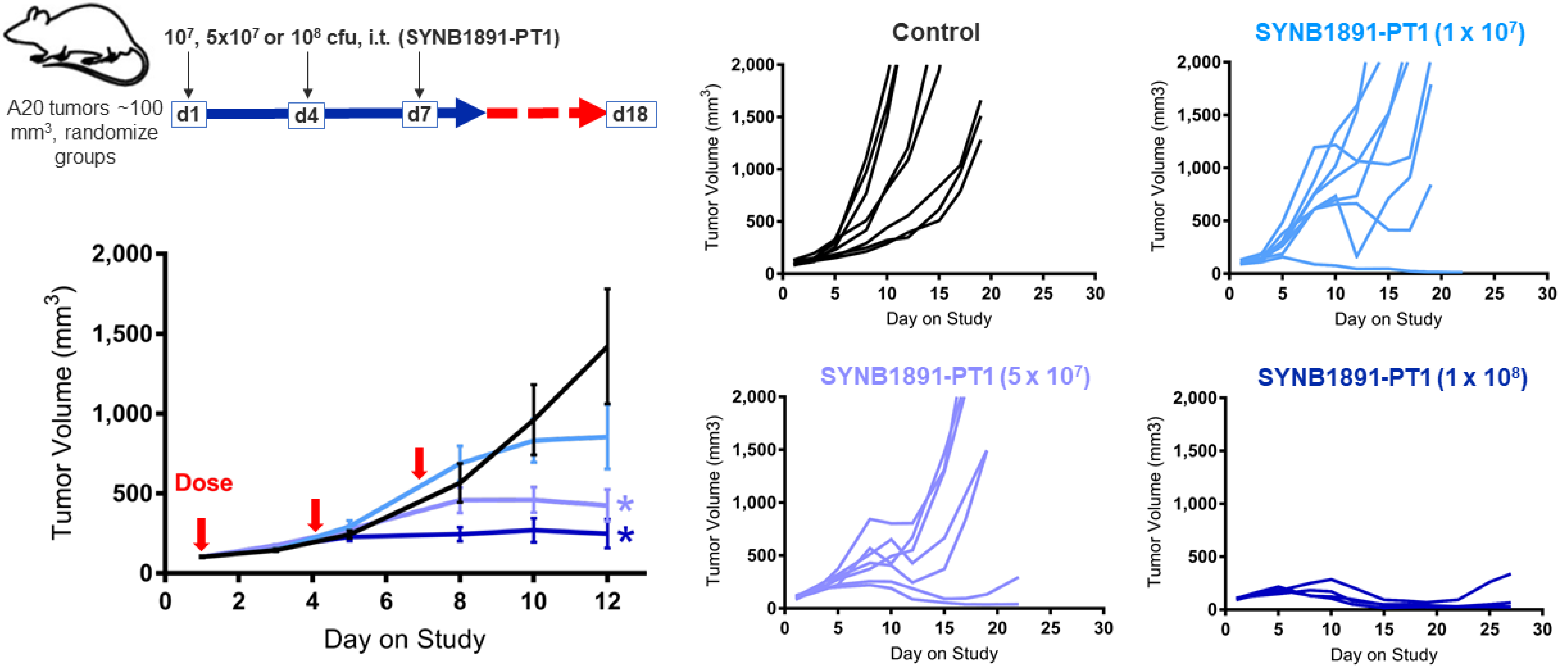
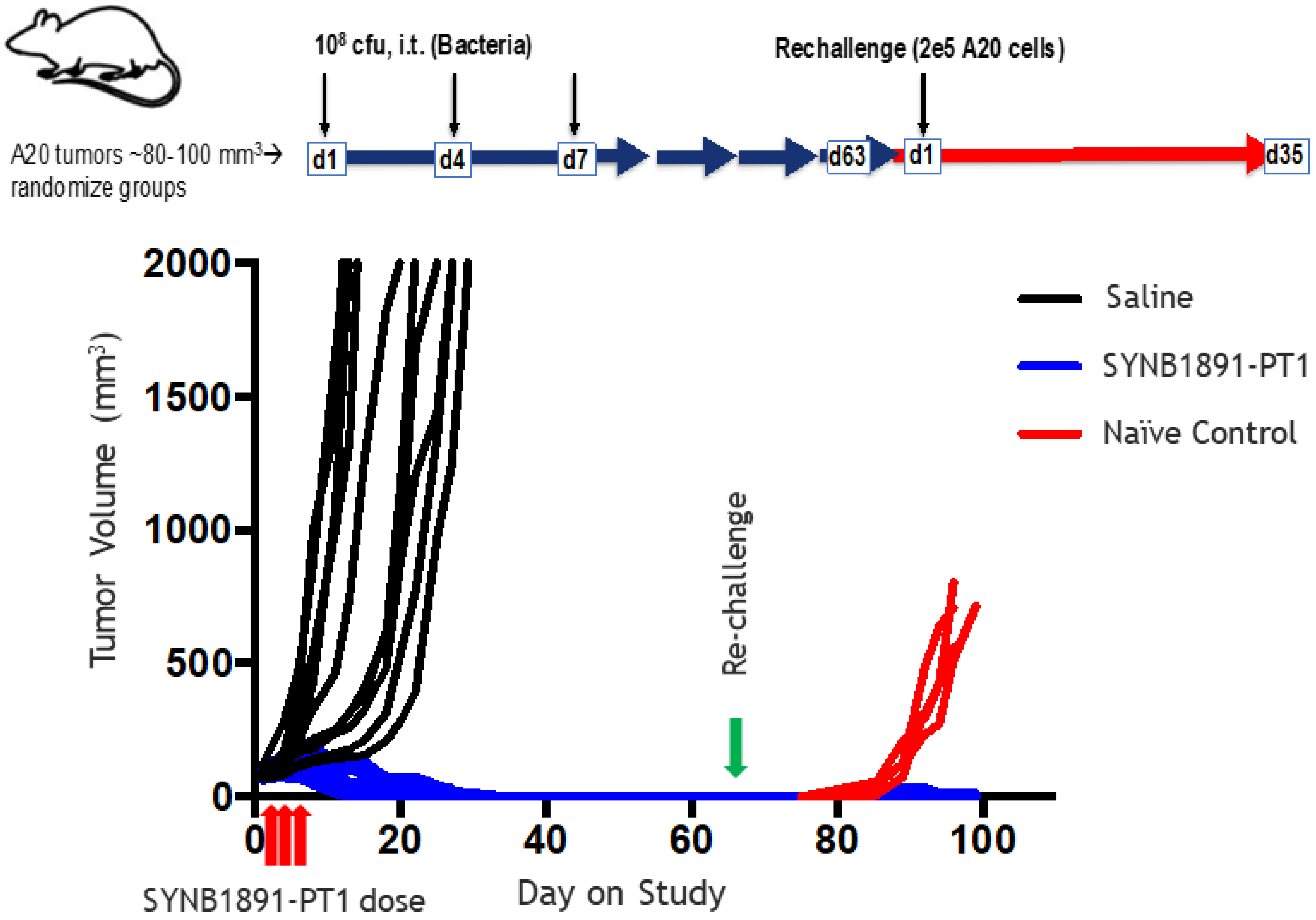
In Vivo Characterization of SYNB1891

Dose-dependent Anti-tumor Activity of SYNB1891 Prototype Strain as a Single Agent



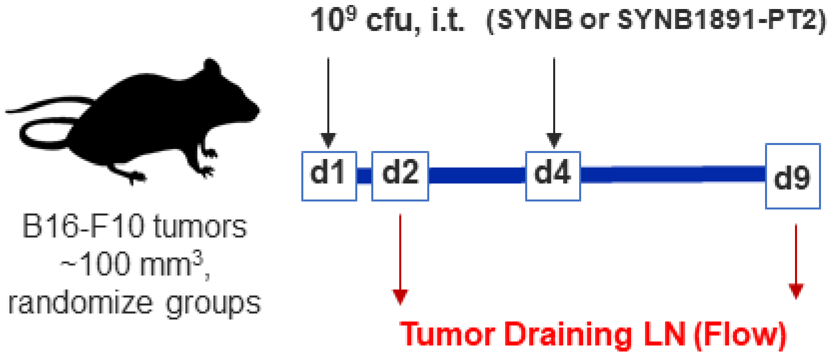
In Vivo Characterization of SYNB1891

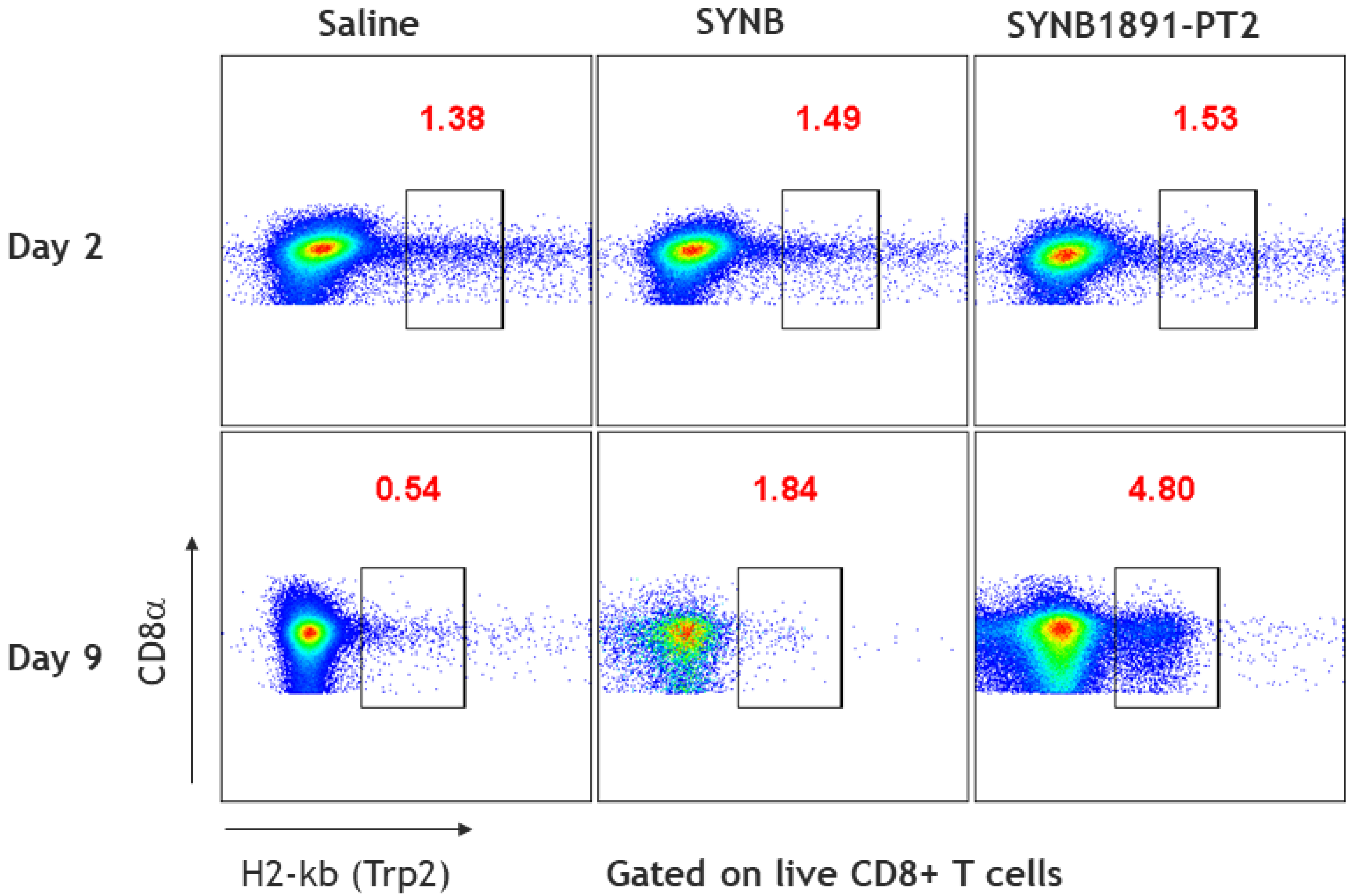
SYNB1891 Prototype Strain Leads to Systemic Anti-tumor Immunity



In Vivo Characterization of SYNB1891

SYNB1891 Prototype Strain Leads to Generation of Tumor Antigen-specific T Cell





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Dual Innate Immune Activator SYNB1891

A STING Agonist-producing Synthetic Biotic Designed to Locally Inflame the TME and Systemically Drive Tumor Antigen-Specific Immunity

Progress Towards the Clinic

Tumor Colonization without Leakage

Enhanced Activity vs. Naked STING Agonist

Intracellular Activation of STING and Bacterial-Induced Immune Pathways Within APCs

Dose-dependent Anti-tumor Activity

Immunological Memory

IND Submission 2H19

Promise Over Other Approaches

STING Agonism in Natural Context

Activation of Multiple Innate Immune Pathways

Low Systemic Risk

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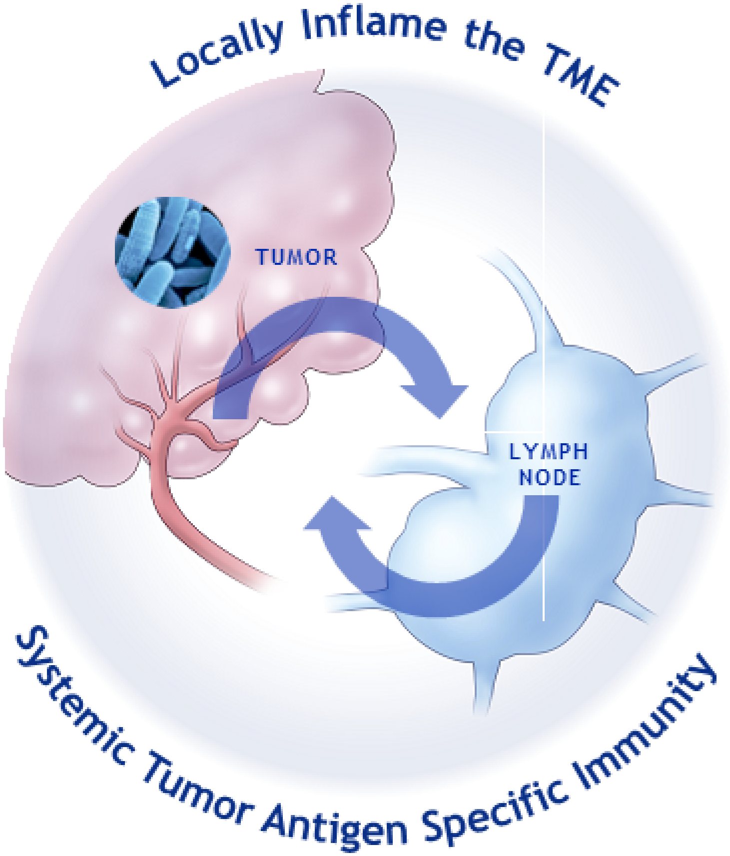
Dual Innate Immune Activator SYNB1891



NEXT STEPS

IND-Enabling Studies On-going

IND Submission 2H19

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Pipeline of Synthetic Biotic Effectors Poised to Deliver

Relieve Immunosuppression

Kyn Consumption

Ade Consumption

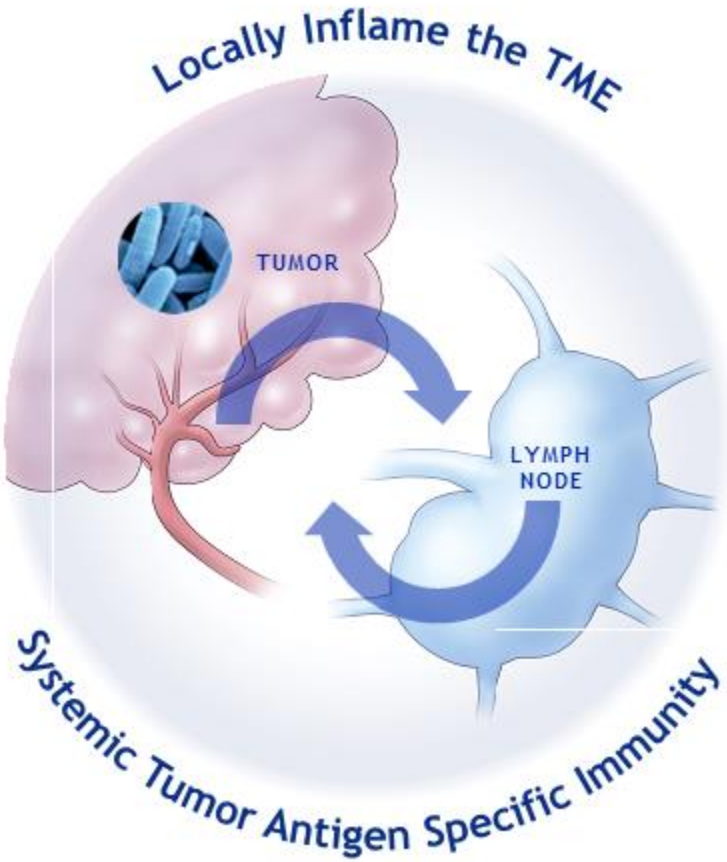
αPD-1 scFv

Promote Trafficking

Chassis effect

CXCL10

Hyaluronidase



Promote and Sustain Immune Activation / Proliferation

IL-15; IL-12

Arg Production

4-1BBL

OX40L

Prime for Tumor Antigen-Specific Vaccination

Chassis effect	TNFα
5FC→5FU	IFNγ
STING	αCD47 ScFv / Sirpα
αCD40 scFv/CD40L	GM-CSF

Development of Synthetic Biotic™ Medicines in Oncology

Designed for life

Aoife Brennan, M.B., B.Ch.,
President and CEO

Jose M. Lora, PhD
Vice President, Research

SITC 2018- Washington, DC
November 10th, 2018

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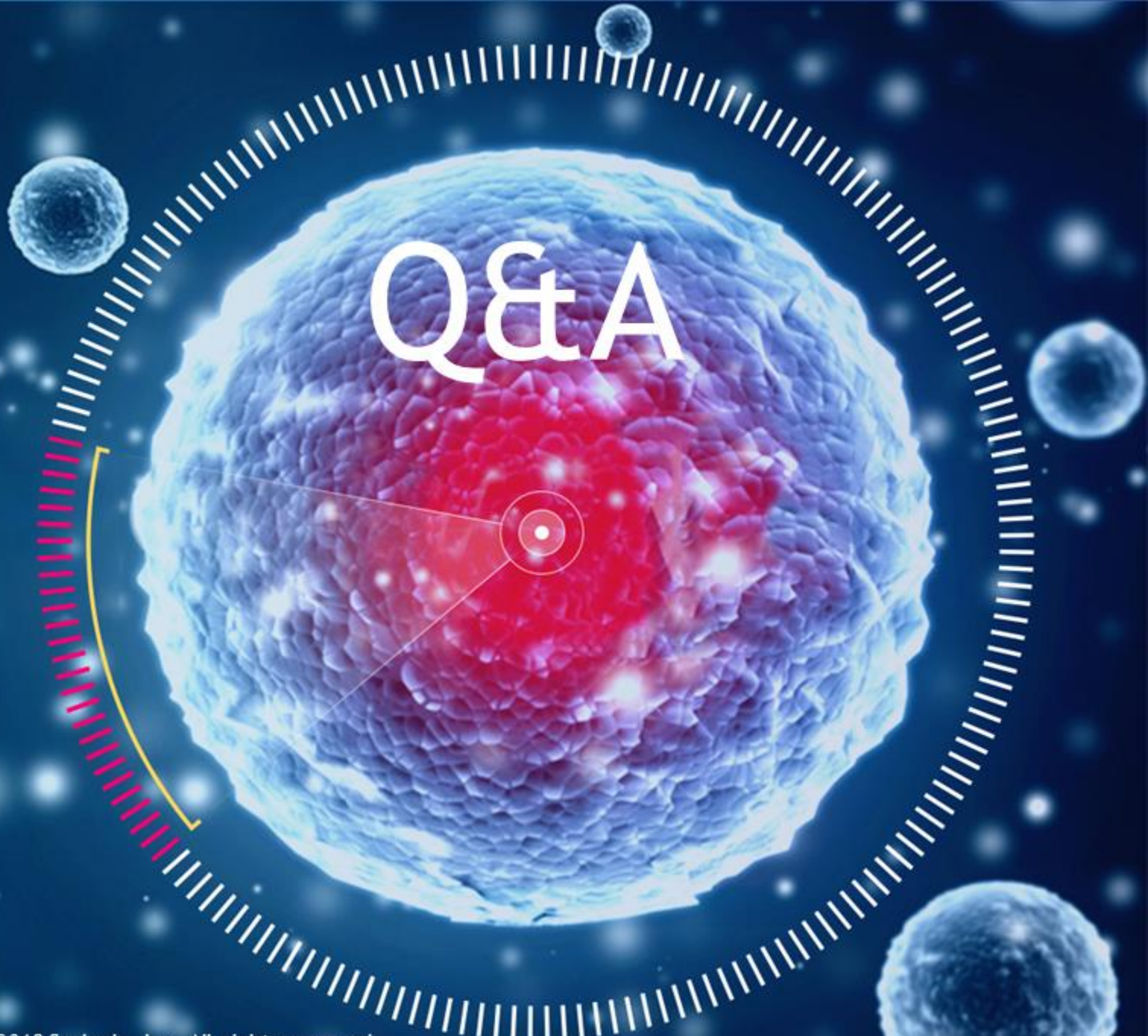

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IND Submission 2H19

Promise Over Other Approaches

STING Agonism in Natural Context

Activation of Multiple Innate Immune Pathways

Low Systemic Risk

Broad Ambitions in Immuno-Oncology

Vision: Expand and Exceed the Effect of Cancer Immunotherapies

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Table of Synthetic Biotic Strains

Strain	Genetic Content
SYN	Un-engineered *E. coli* Nissle:Abx+
SYNB	DAP/Thy dln EcN (no dacA insert):Abx+
SYNB1891-PT1	DAP dln EcN:dacA$_{plasmid}$:FnR-inducible:Abx+
SYNB1891-PT2	DAP/Thy dln EcN:dacA$_{integrated}$:FnR-inducible:Abx+
SYNB1891	DAP/Thy dln EcN:dacA$_{integrated}$:FnR-inducible:Abx-

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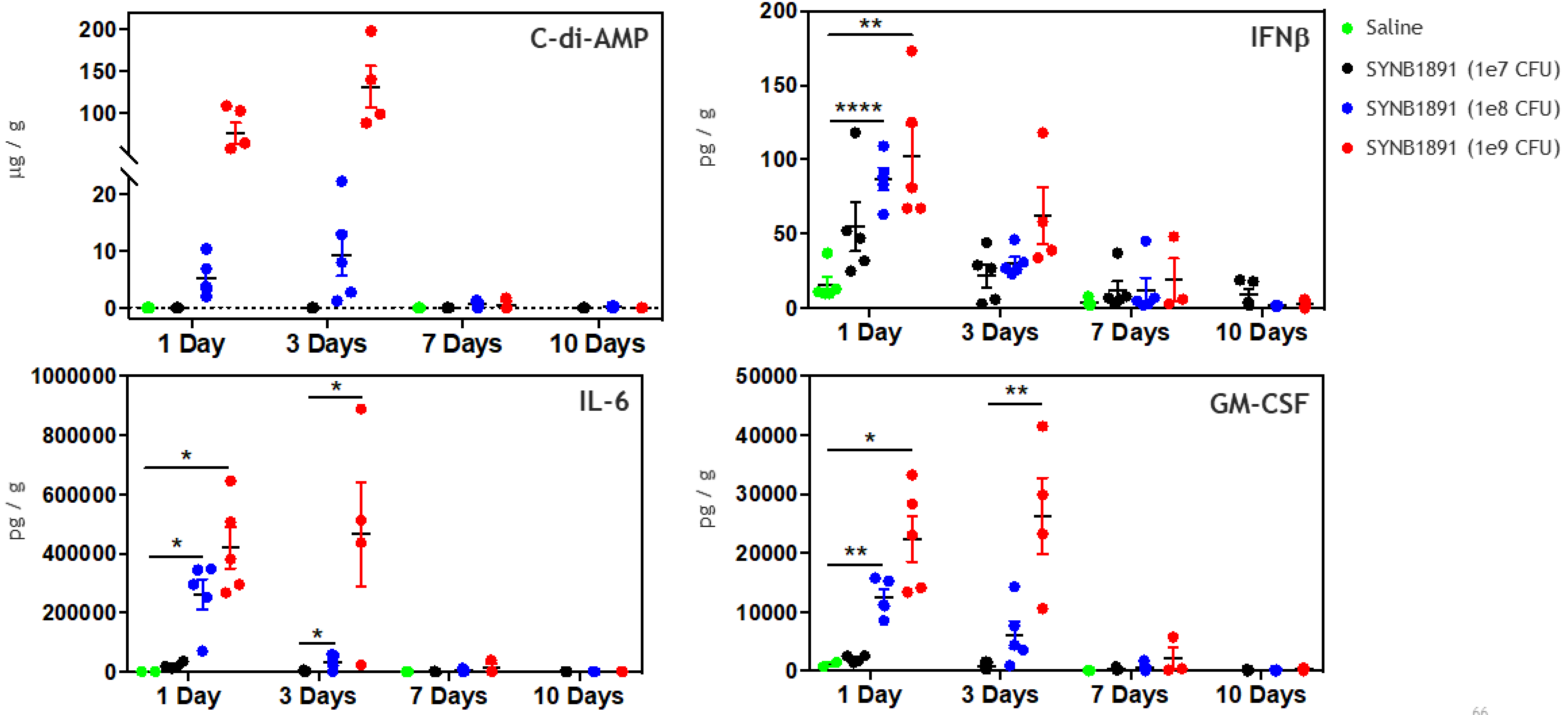
Pharmacodynamic Characterization of SYNB1891

Administration of SYNB1891 Results in Dose-dependent Increases in Tumoral CDA, Cytokines

Production in Tumor Tissue



Pharmacodynamic Characterization of SYNB1891

Prototype Elicits Inflammation-related Gene Signature in Injected Tumors

B16-F10 or CT-26 tumors ~100 mm^3, randomize groups

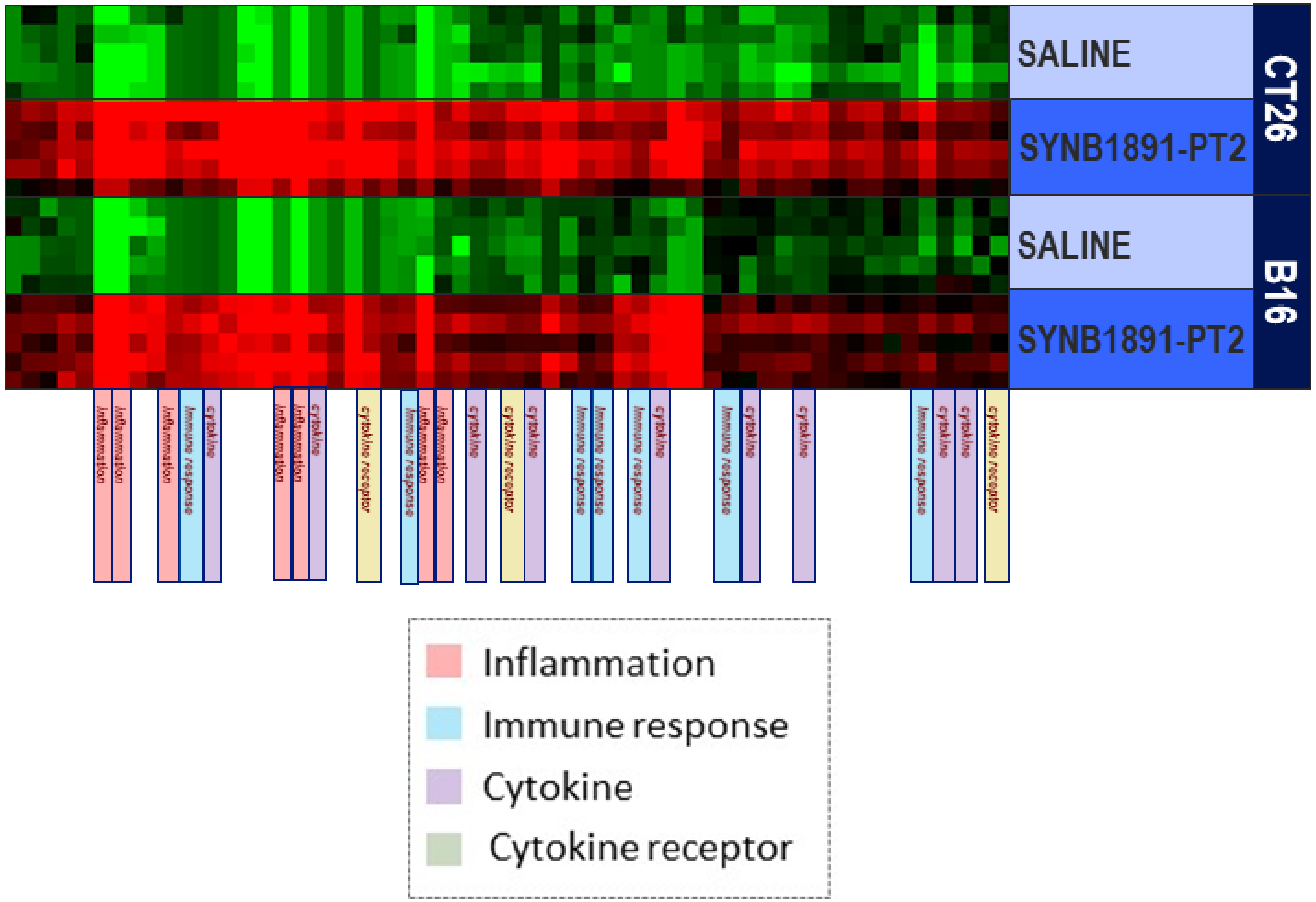
Saline or 10^9 cfu SYNB1891-PT2, i.t.

d1 — **d4**

Harvest Tumor Tissue

Isolate Tumor Infiltrating Lymphocytes

Perform RNAseq on Purified T cells



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