Патогенез легочного туберкулёза: Экспериментальный иммуногенетический анализ

Игорь Крамник

Бостонский Университет
Центр Заболеваний Легких

Юбилейная научно-практическая конференция с международным участием, посвященная 100-летию ФГБНУ «Центральный научно-исследовательский института туберкулеза»

28 сентября 2021 года

Igor Kramnik, MD, PhD
National Emerging Infectious Diseases Laboratory
Pulmonary Center Boston University School of Medicine

BOSTON UNIVERSITY

NEIDL National Emerging Infectious Diseases Laboratories

Особенности противотуберкулёзного иммунитета в лёгких чувствительных к туберкулёзу хозяев

Lung-specific aspects of host resistance to TB

Immunology 1991 **73** 173–179

ADONIS 001928059100133V

Regulation of T-cell proliferative responses by cells from solid lung tissue of *M. tuberculosis*-infected mice

A. S. APT, I. B. KRAMNIK & A. M. MOROZ *Experimental Immunogenetics Laboratory, Central Institute for Tuberculosis, Moscow, USSR*

Accepted for publication 24 January 1991

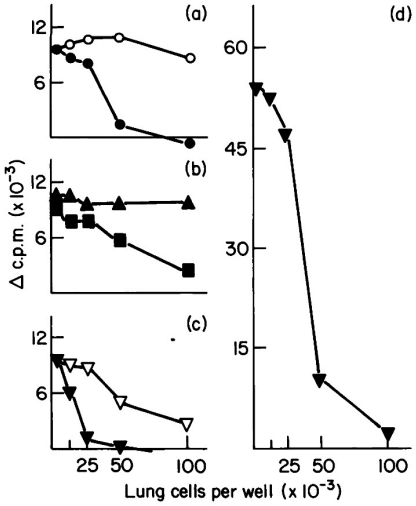

Figure 2. The proliferative response of FCA-immune lymph node cells is suppressed by the PA lung cells. 4×10^5 lymph node cells were co-cultured for 48 hr (Con A) or 72 hr (PPD) with indicated numbers of mitomycin-C-treated lung cells from infected (closed symbols) or intact (open symbols) mice in the presence of PPD (a, b, c,) or Con A (d). The

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EDITORIAL

Man and mouse TB: Contradictions and solutions

Alexander Apt*
Central Institute for Tuberculosis, Russian Academy of Medical Sciences, Laboratory for Immunogenetics, 107564 Moscow, Russia
* Corresponding author. Tel.: +7 499 785 9072.
E-mail address: asapt@aha.ru

Igor Kramnik**
Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA 02115, USA
** Corresponding author. Tel.: +1 617 432 3243.
E-mail address: ikramnik@hsph.harvard.edu

21 January 2009

Чем отличаются миелоидные клетки лёгких при туберкулёзе?

Are myeloid cells in pulmonary TB lesions different?

Какова их роль в иммунитете и иммунопатологии?

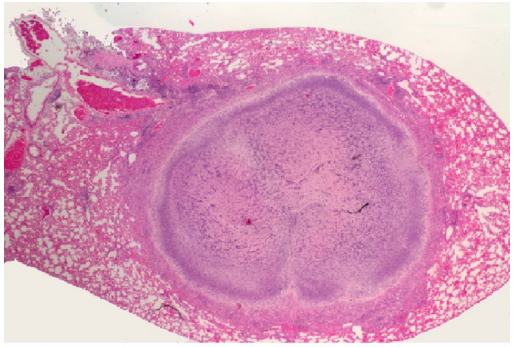
What are their specific roles in immunity and immunopathology?

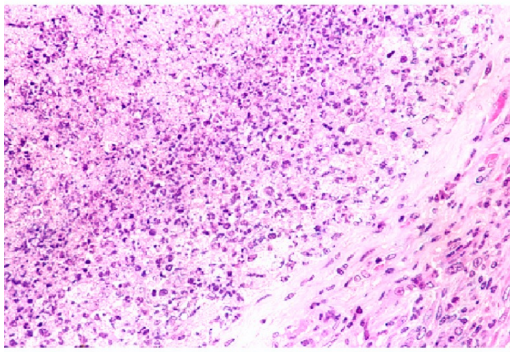
Какую информацию для разработки новых методов лечения и профилактики ТБ у людей можно получить используя лабораторных мышей?

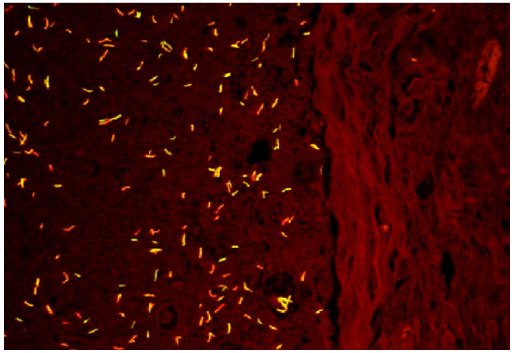
What can we learn about human TB using laboratory mice?

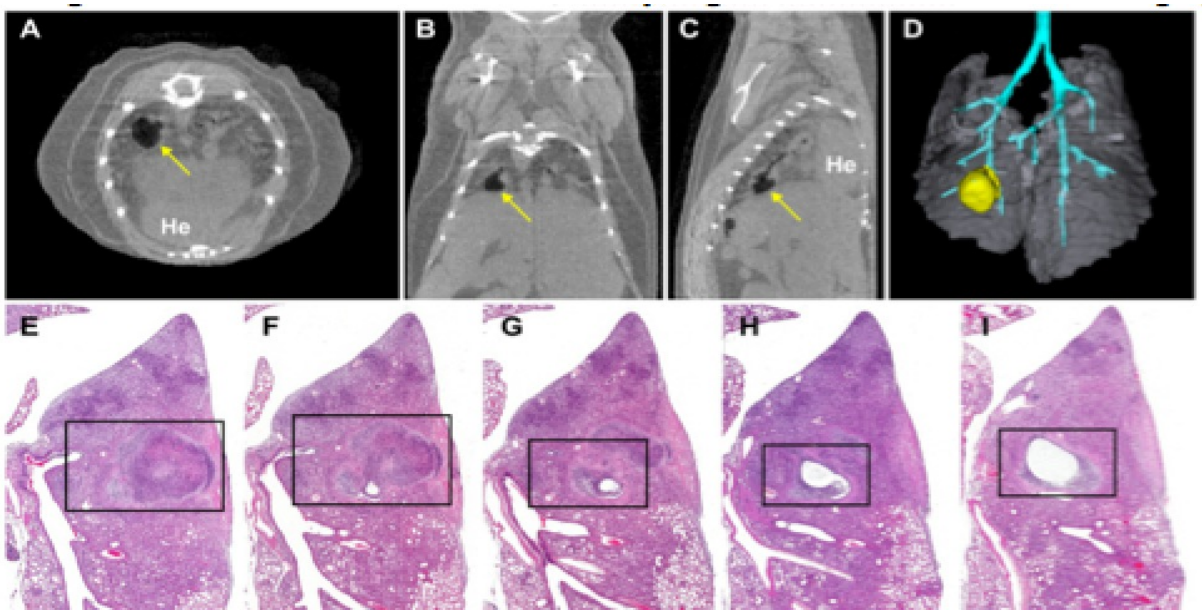
Мыши линии C3HeB/FeJ развивают необычную для мышей патологию

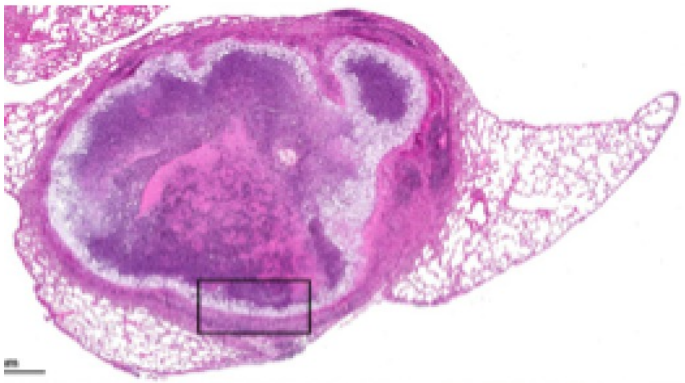
Necrotic TB granulomas and cavities in C3HeB/FeJ mice

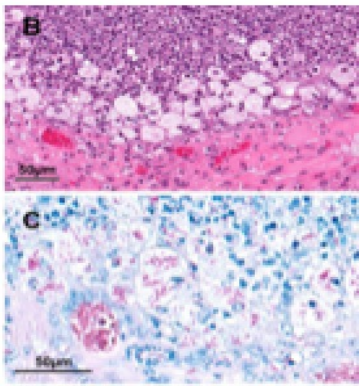










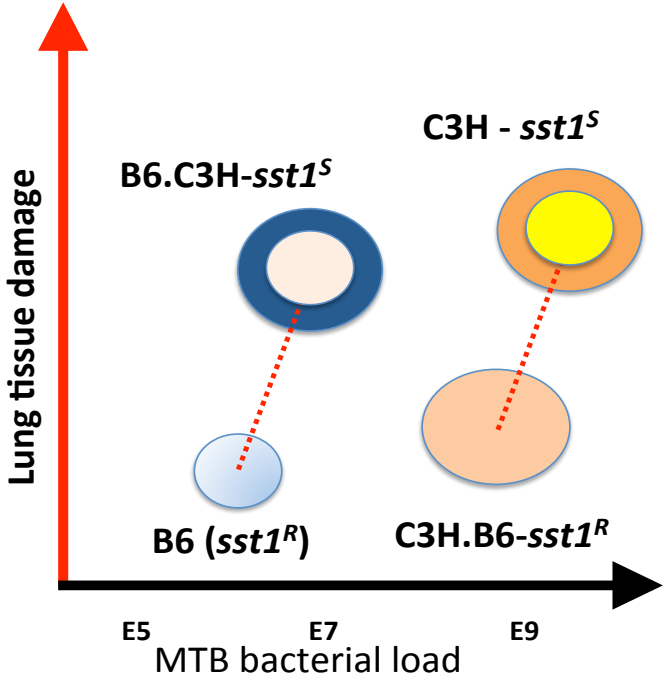


Новый генетический локус контролирует некроз в лёгочных очагах

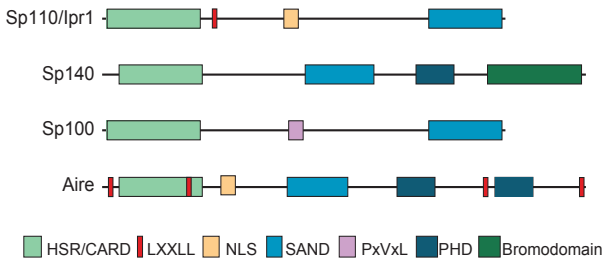
Dominant Role of the *sst1* Locus in Pathogenesis of Necrotizing Lung Granulomas during Chronic Tuberculosis Infection and Reactivation in Genetically Resistant Hosts

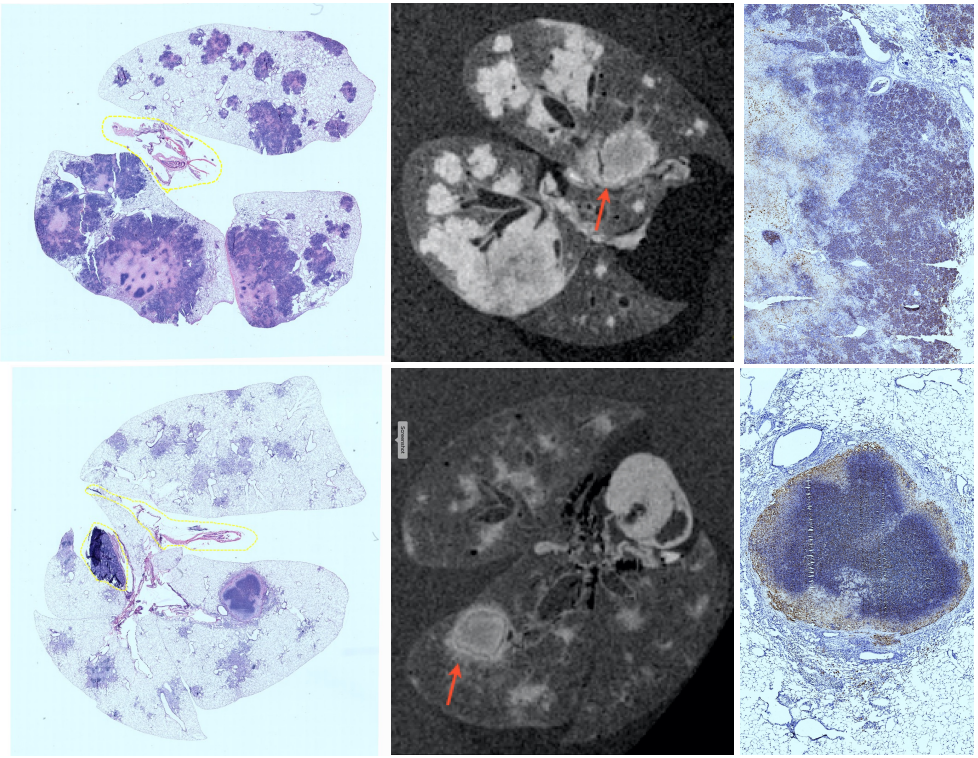
Alexander V. Pichugin,* Bo-Shiun Yan,*
Alex Sloutsky,† Lester Kobzik,‡§ and Igor Kramnik*

From the Departments of Immunology and Infectious Diseases, and Environmental Health,‡ Harvard School of Public Health; the Department of Pathology,§ Brigham and Women's Hospital; and the University of Massachusetts Medical School,† Boston, Massachusetts*



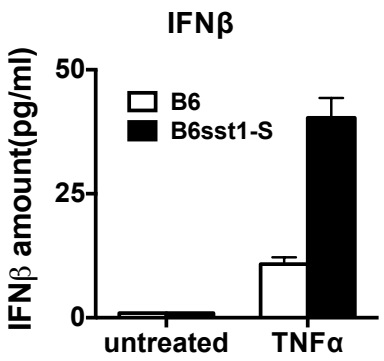
The Sp100 protein family

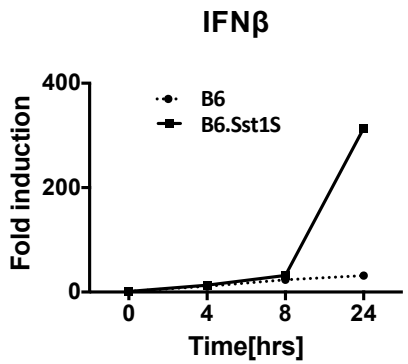


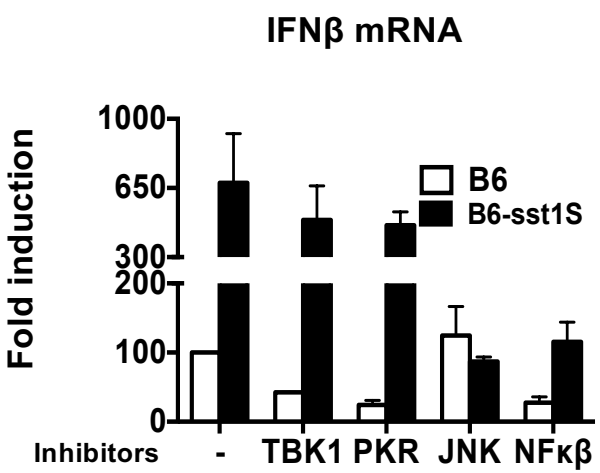


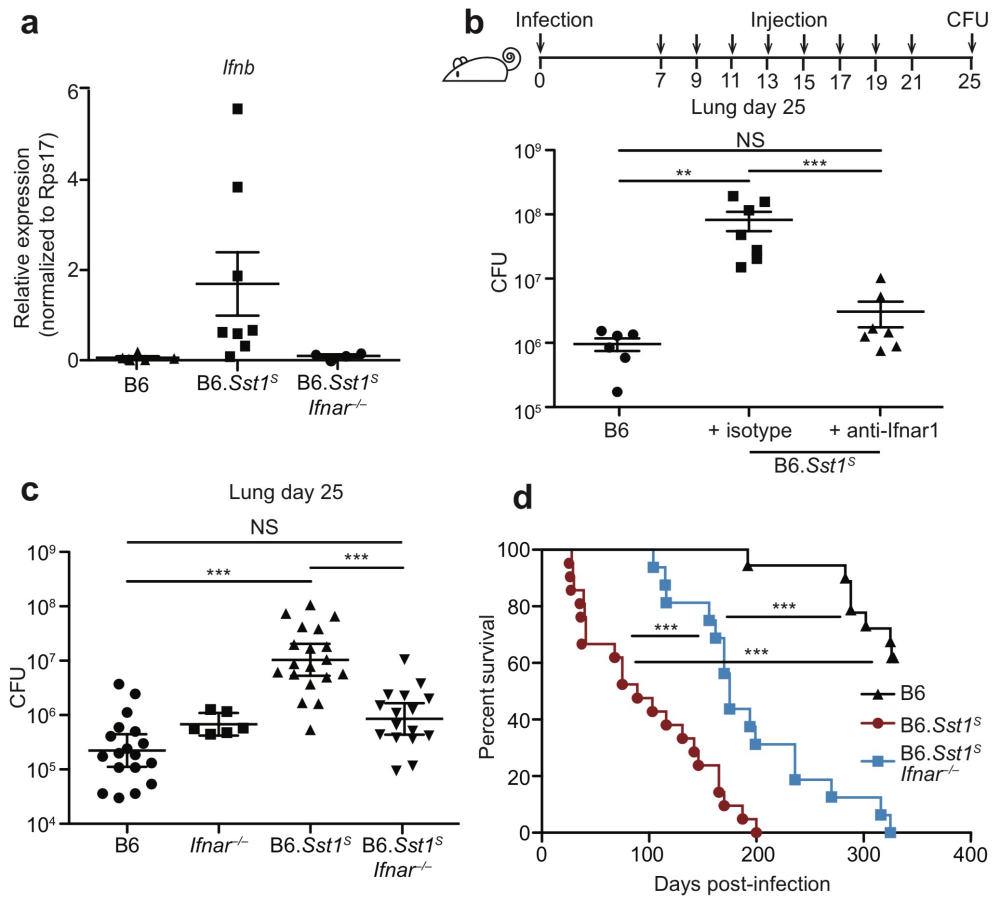
Бета-интерферон играет важную роль в чувствительности к туберкулезу

IFNb drives the sst1-mediated susceptibility





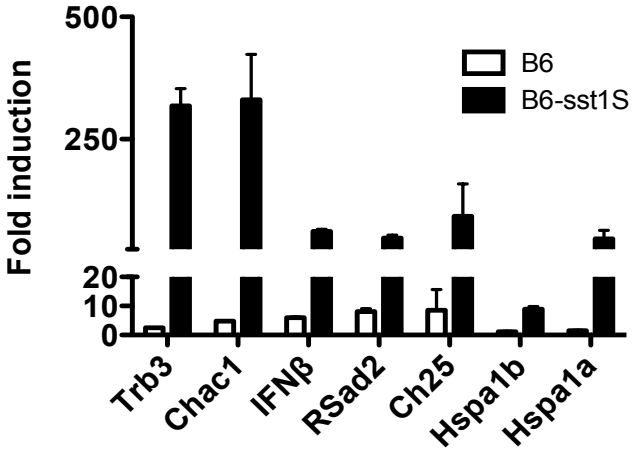


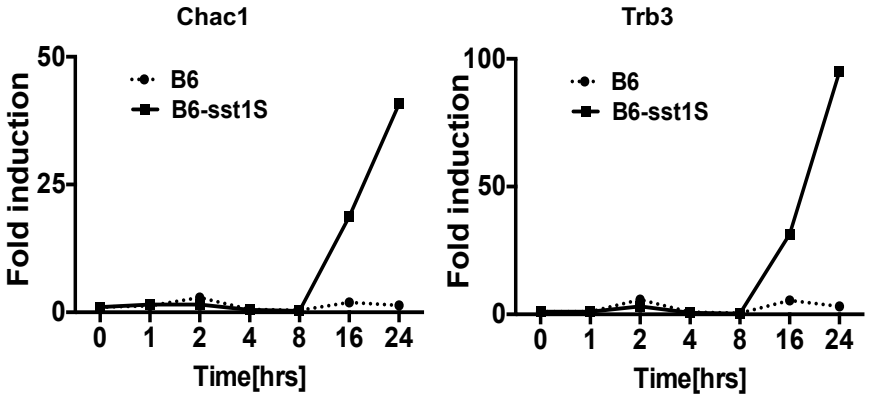


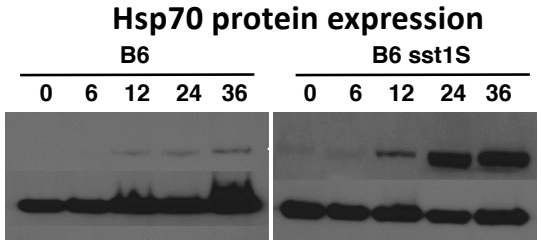
Interleukin-1 receptor antagonist mediates type I interferon-driven susceptibility to Mycobacterium tuberculosis. Daisy X. Ji, … Igor Kramnik, K. Heran Darwin, Russell E. Vance. Nature Microbiology, 2019

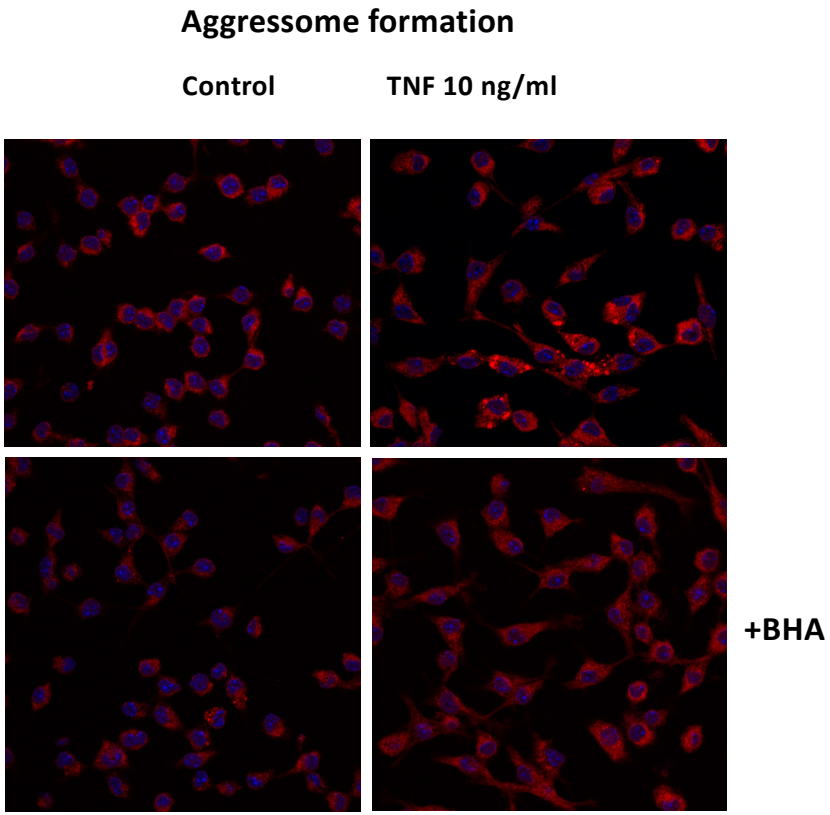
ТНФ индуцирует хронический стресс и образование белковых агрегатов

TNF induces unresolving oxidative and proteotoxic stress and in B6.Sst1S Mphs



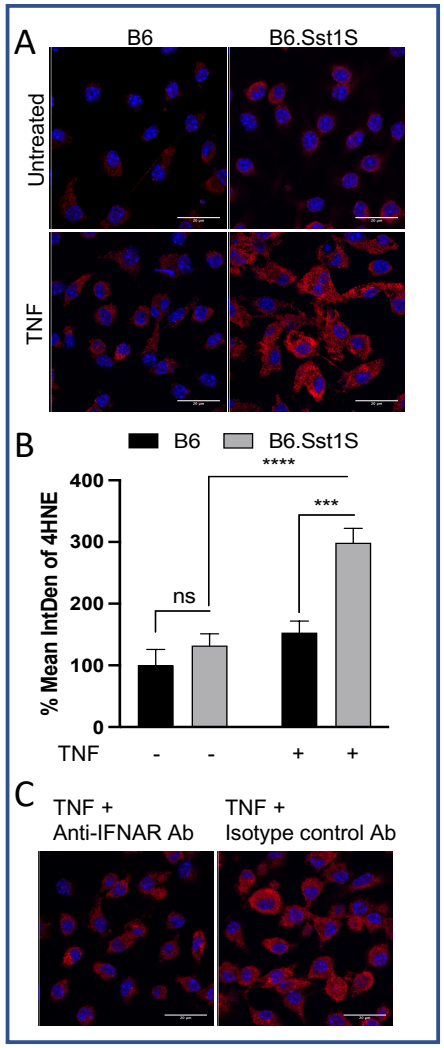


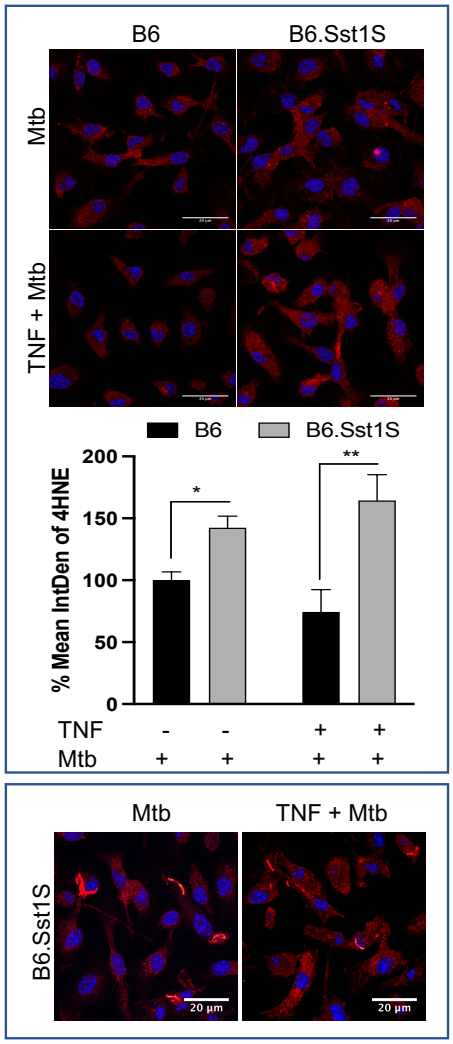


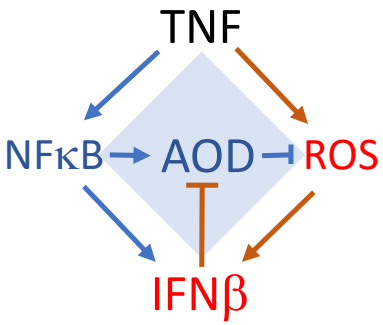


Накопление продуктов окисления жиров в чувствительных макрофагах стимулированных ТНФ или зараженных МТБ

Accumulation of lipid peroxidation products in TNF-stimulated or Mtb-infected macrophages







Аутокаталитическое воспаление

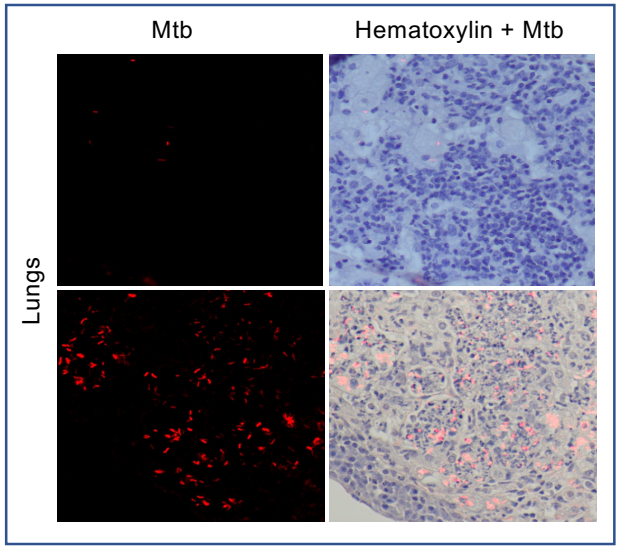
Усиленное рекрутирование моноцитов и нейтрофилов

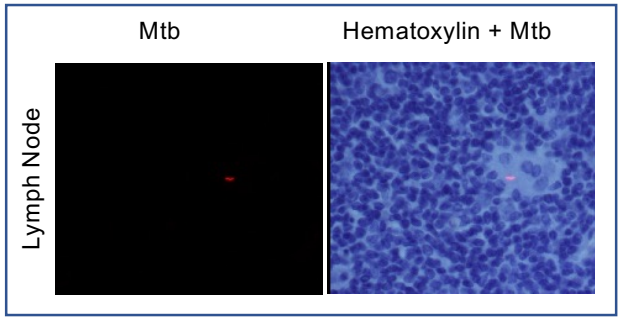
Увеличение продукции протеаз деградирующих матрикс

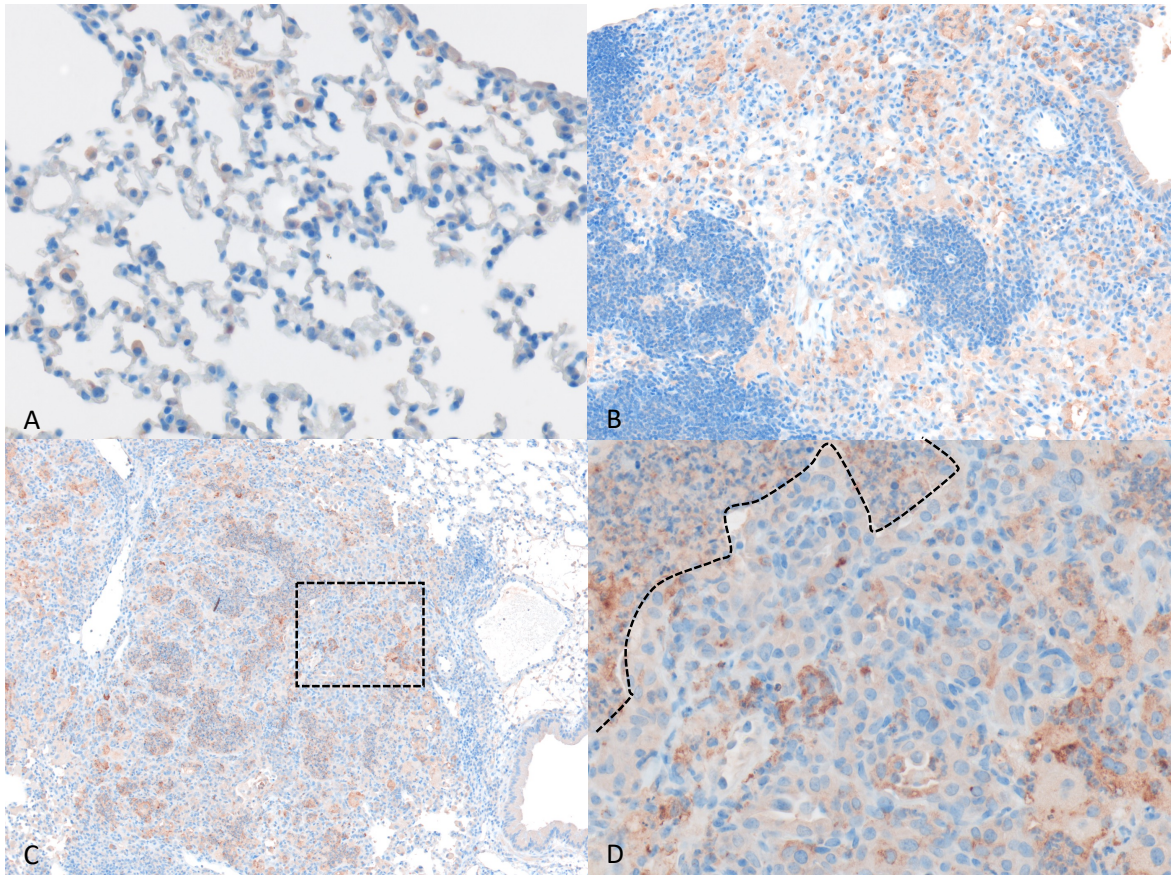
Продукция медиаторов апоптоза и иммуносупрессии

Накопление продуктов окисления жиров в лёгочных очагах воспаления

Accumulation of lipid peroxidation products in pulmonary TB lesions

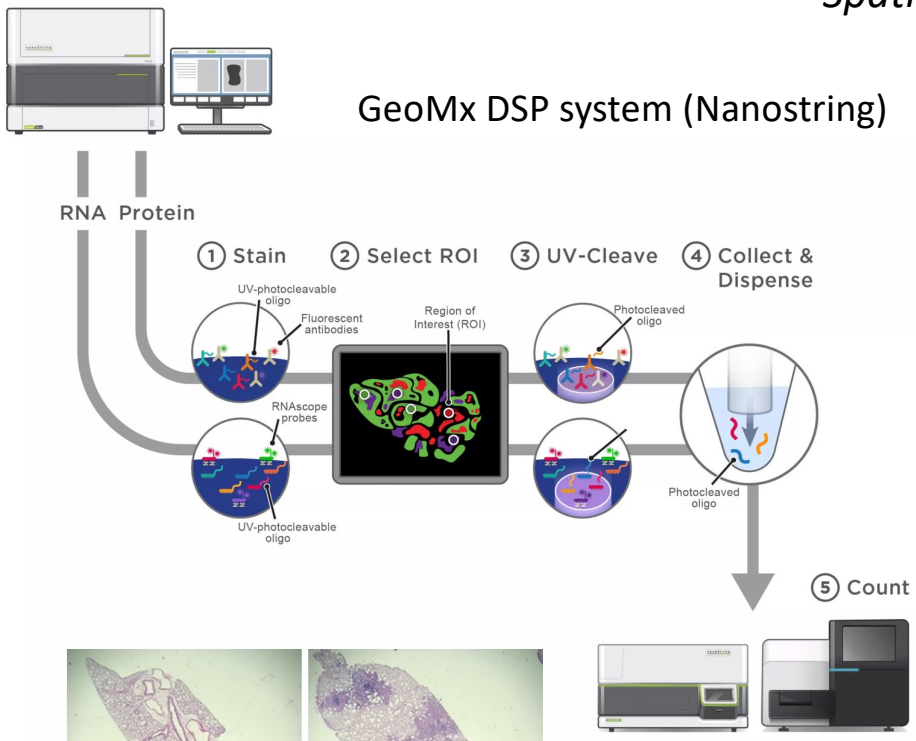


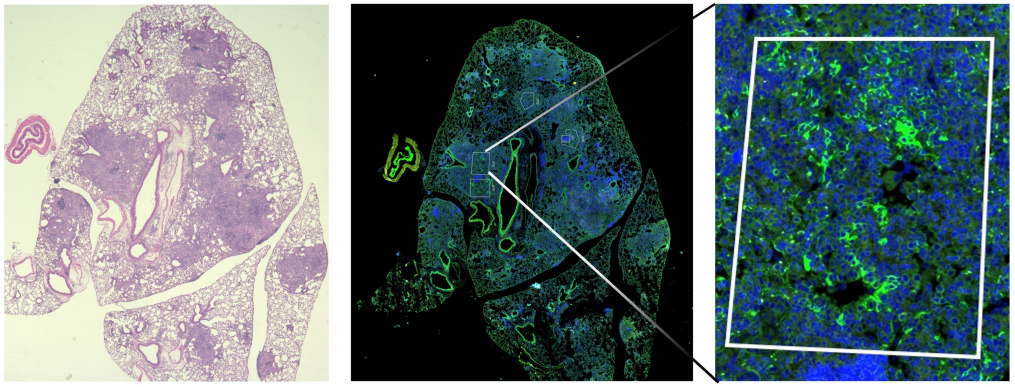


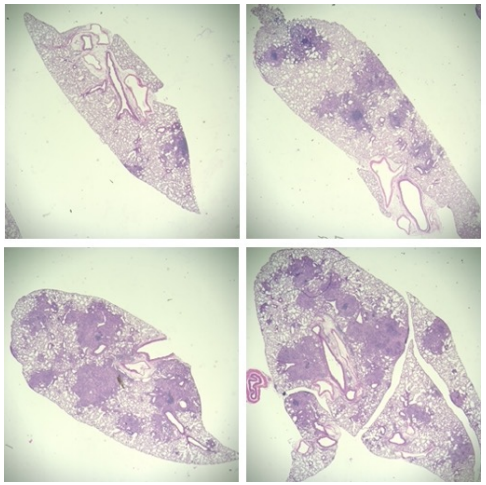


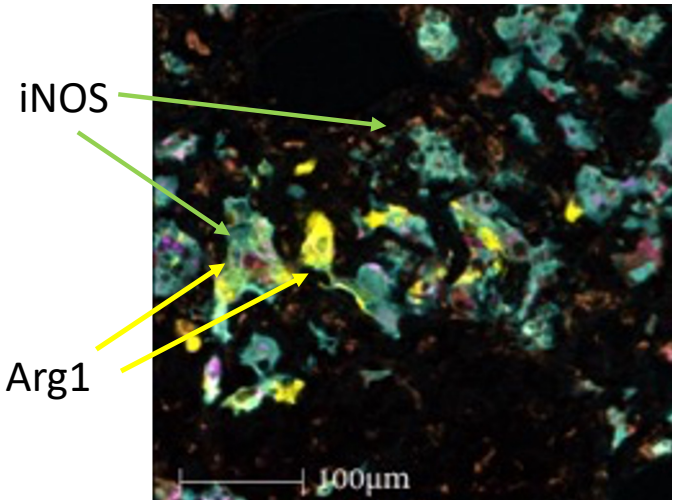
Анализ экспрессии генов в легочных очагах

Spatial gene expression profiling in TB lesions









Анализ экспрессии генов в легочных очагах

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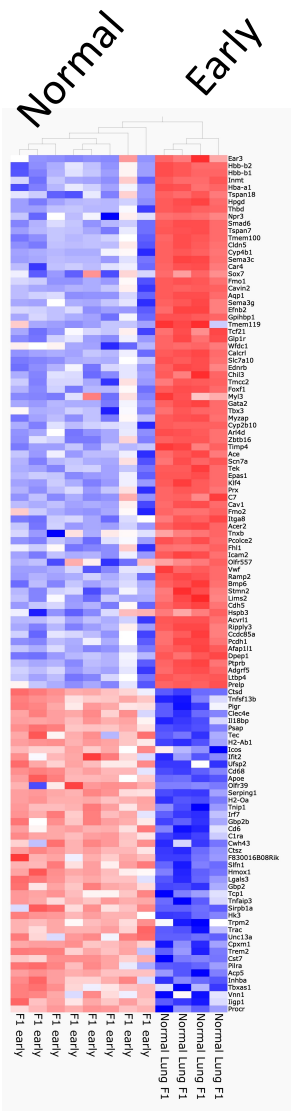
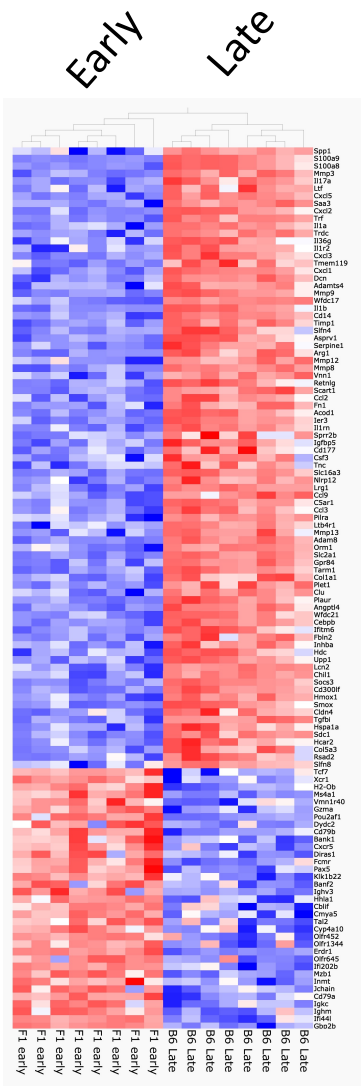




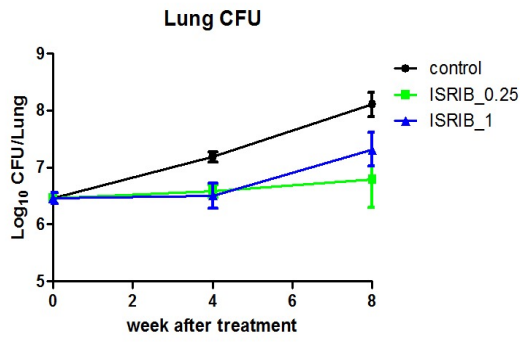
MSigDB Hallmark 2020 Bar Graph **Table** Clustergram Appyter

Hover each row to see the overlapping genes.

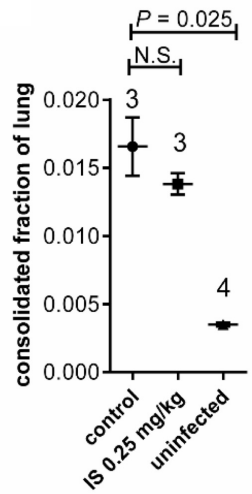
10 entries per page Search:

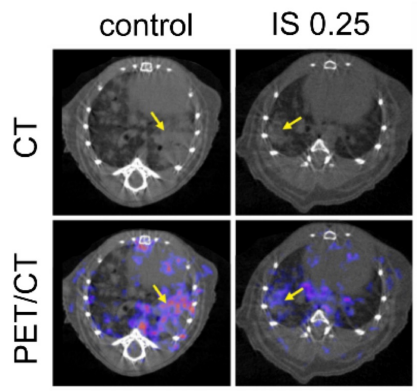
Index	Name	P-value	Adjusted p-value	Odds Ratio	Combined score
1	TNF-alpha Signaling via NF-kB	2.480e-48	1.116e-46	20.49	2245.92
2	Epithelial Mesenchymal Transition	9.977e-46	2.245e-44	19.41	2010.77
3	Inflammatory Response	2.001e-39	3.002e-38	16.86	1502.23
4	Hypoxia	1.318e-34	1.483e-33	14.98	1168.23
5	IL-6/JAK/STAT3 Signaling	2.992e-21	2.693e-20	18.71	884.41
6	Coagulation	2.791e-20	2.093e-19	12.44	559.97
7	Complement	1.798e-19	1.156e-18	9.30	401.36
8	IL-2/STAT5 Signaling	1.102e-16	6.202e-16	8.29	304.69
9	KRAS Signaling Up	1.271e-16	6.354e-16	8.24	301.71
10	Apoptosis	2.463e-16	1.108e-15	9.36	336.46

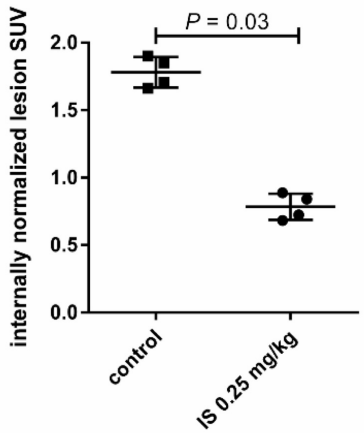
Inhibition of the Integrated Stress Response pathway reduces lung damage and increases resistance to Mtb of the *sst1*-susceptible B6.Sst1S mice

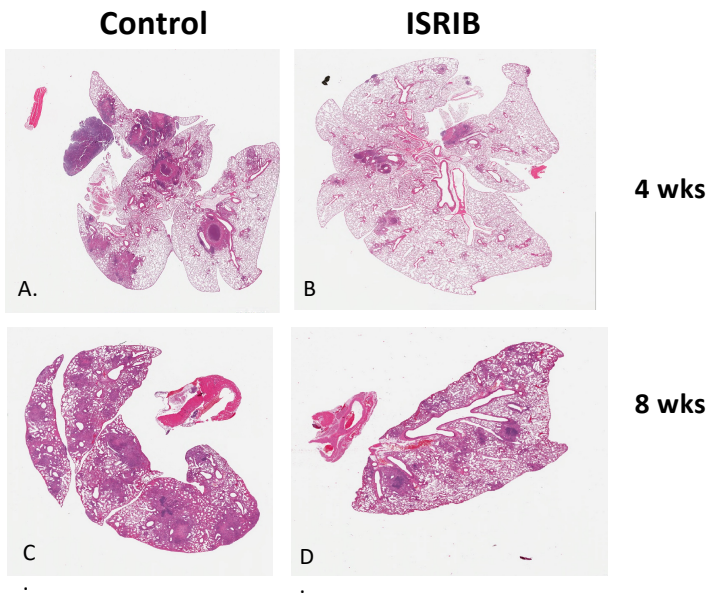


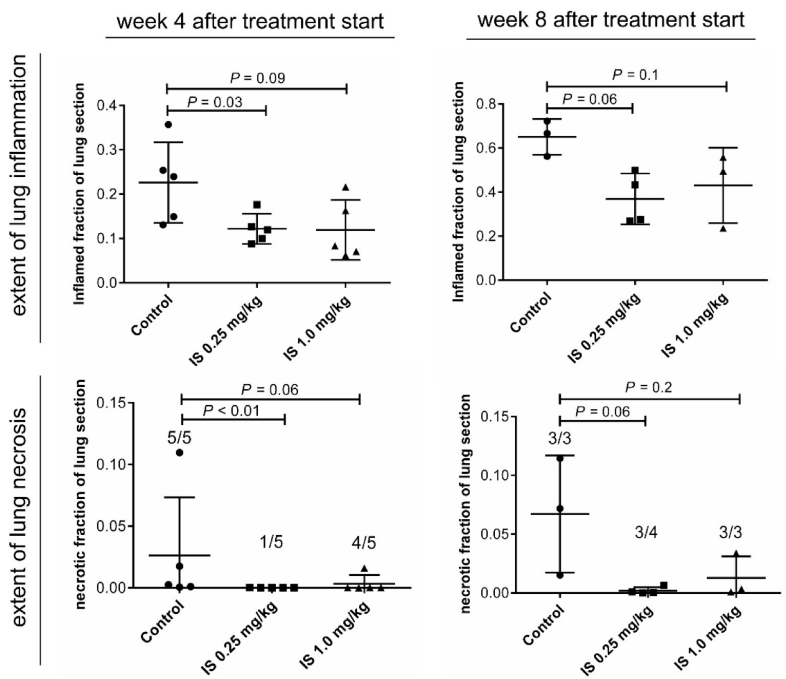
Treatment started 4 weeks after infection











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Article

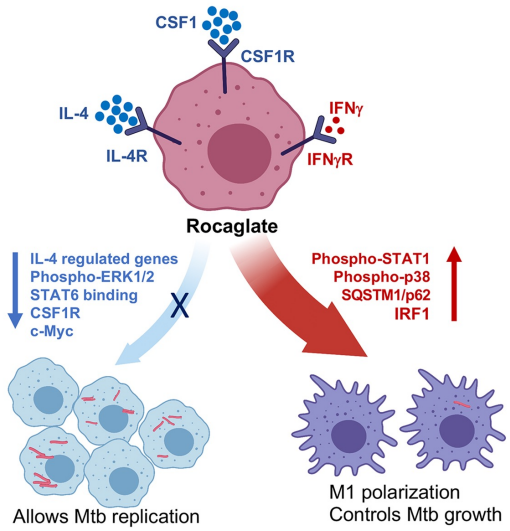
Channeling macrophage polarization by rocaglates increases macrophage resistance to *Mycobacterium tuberculosis*

Sujoy Chatterjee,[1,7] Shivraj M. Yabaji,[1,7] Oleksii S. Rukhlenko,[2] Bidisha Bhattacharya,[1] Emily Waligurski,[1] Nandini Vallavoju,[3] Somak Ray,[4] Boris N. Kholodenko,[2,5] Lauren E. Brown,[3] Aaron B. Beeler,[3] Alexander R. Ivanov,[4] Lester Kobzik,[6] John A. Porco, Jr.,[3] and Igor Kramnik[1,8,*]

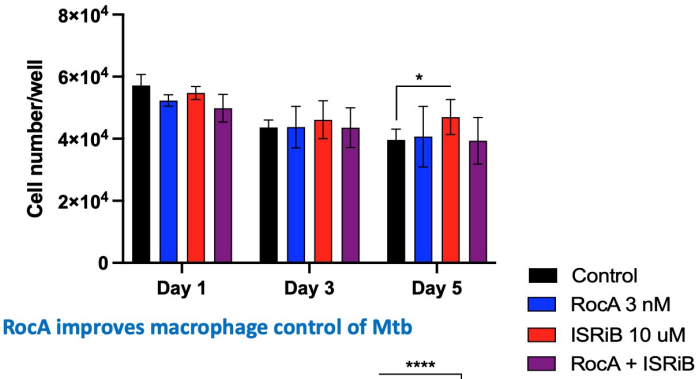
SUMMARY

Macrophages contribute to host immunity and tissue homeostasis via alternative activation programs. M1-like macrophages control intracellular bacterial pathogens and tumor progression. In contrast, M2-like macrophages shape reparative microenvironments that can be conducive for pathogen survival or tumor growth. An imbalance of these macrophages phenotypes may perpetuate sites of chronic unresolved inflammation, such as infectious granulomas and solid tumors. We have found that plant-derived and synthetic rocaglates sensitize macrophages to low concentrations of the M1-inducing cytokine IFN-gamma and inhibit their responsiveness to IL-4, a prototypical activator of the M2-like phenotype. Treatment of primary macrophages with rocaglates enhanced phagosome-lysosome fusion and control of intracellular mycobacteria. Thus, rocaglates represent a novel class of immunomodulators that can direct macrophage polarization toward the M1-like phenotype in complex microenvironments associated with hypofunction of type 1 and/or hyperactivation of type 2 immunity, e.g., chronic bacterial infections, allergies, and, possibly, certain tumors.

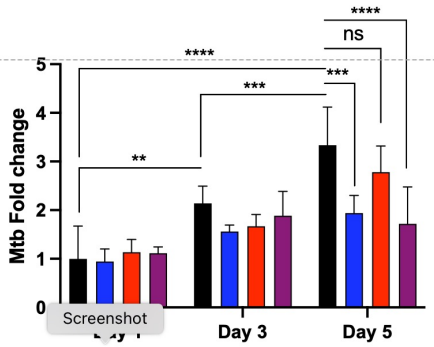
[1]Pulmonary Center, Department of Medicine, Boston University School of Medicine, National Emerging Infectious Diseases Laboratories (NEIDL), Boston University, Boston, MA 02118,



ISRIB improves the survival of Mtb-infected macrophages



RocA improves macrophage control of Mtb



Mtb acid fast staining in the treated macrophage monolayers