NOS1-derived nitric oxide promotes NFκB transcriptional activity through inhibition of Suppressor of Cytokine Signaling-1

Mirza Saqib Baig, PhD

Centre for Biosciences and Biomedical Engineering

Indian Institute of Technology

INTRODUCTION

✓Nitric oxide synthases (nNOS, eNOS & iNOS) are a family of enzymes that catalyze the production of nitric oxide (NO) from L-arginine.

✓NO is an important cellular signaling molecule having essential roles in many biological processes including the control of blood pressure, regulation of neuronal activity and immune responses.

✓eNOS(endothelial NOS or NOS3) and iNOS (inducible NOS or NOS2) have been appreciated as mediators of inflammatory processes. However, considerably less is known about the role of nNOS (neuronal NOS or NOS1) in inflammation.

✓Our study explore the important role played by NOS1 via SOCS1 (Suppressor of Cytokine Signaling-1) in the initiation of inflammatory response and ultimately in lung injury, sepsis and mortality.

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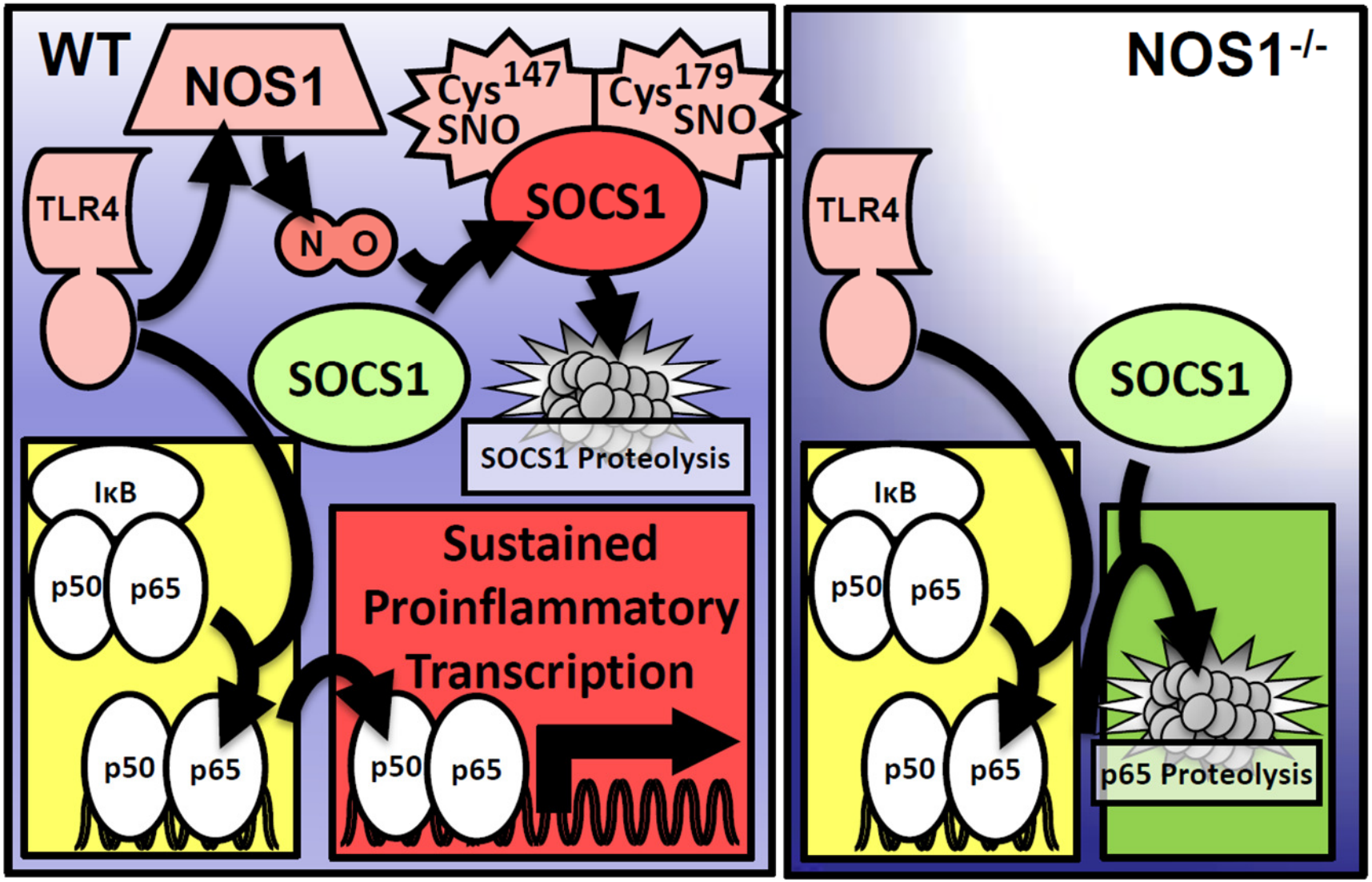
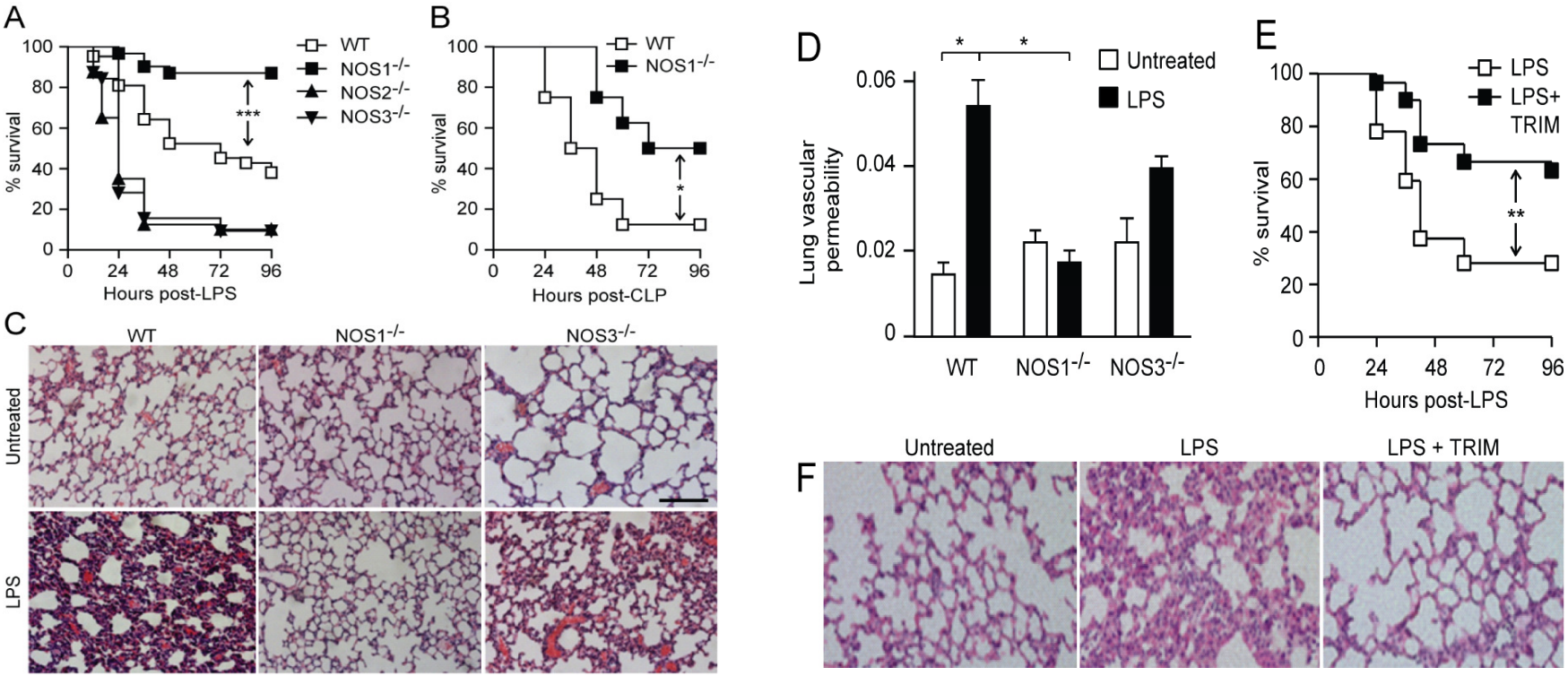
HYPOTHESIS



RESULTS

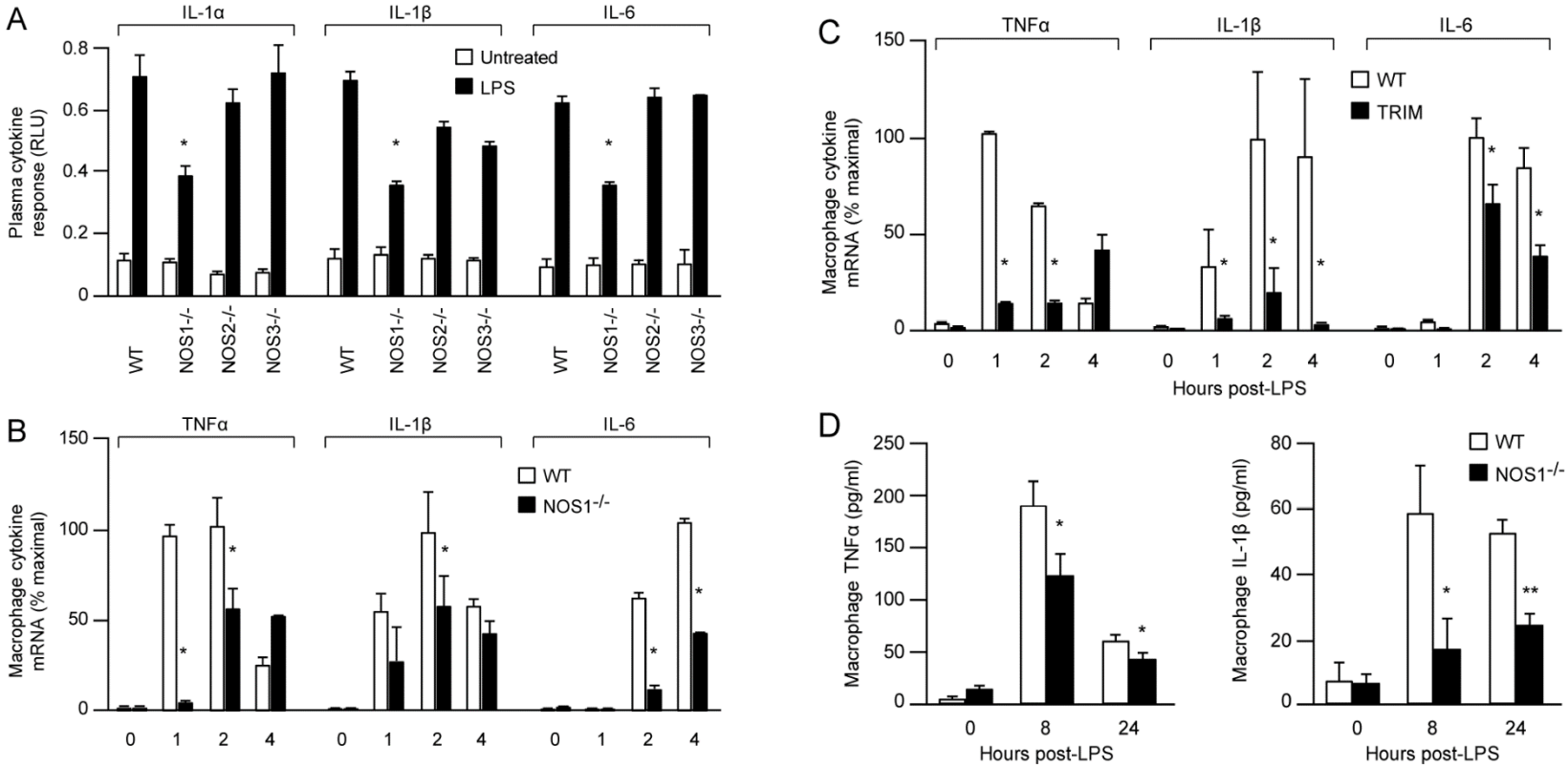
NOS1 deficiency protects against model of septic injury



(Baig et al, JEM, 2015)

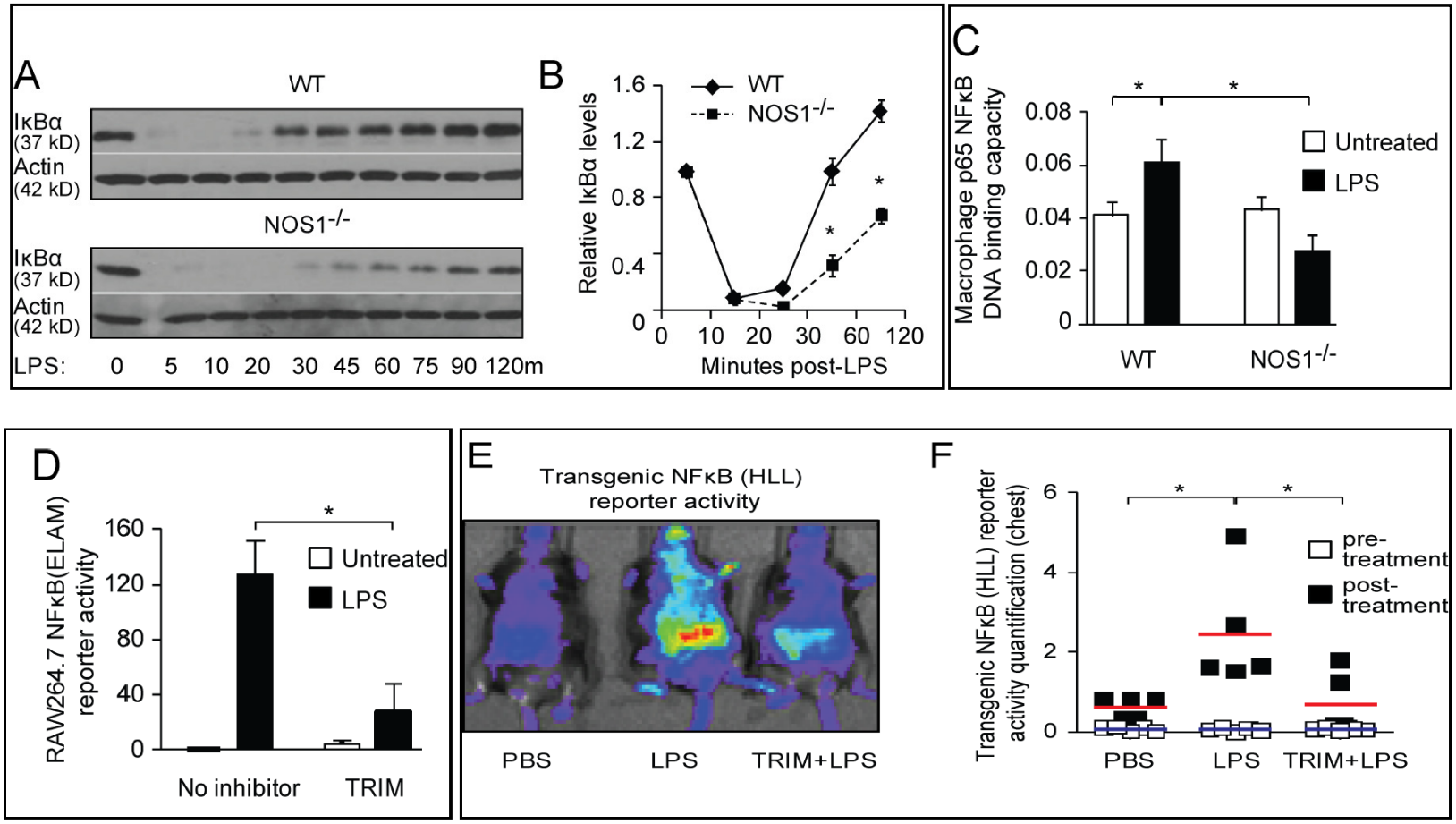
TRIM: 1-(2-trifluoromethylphenyl) imidazole

Proinflammatory cytokine responses to LPS are diminished in *NOS1-/- animals* and cultured macrophages



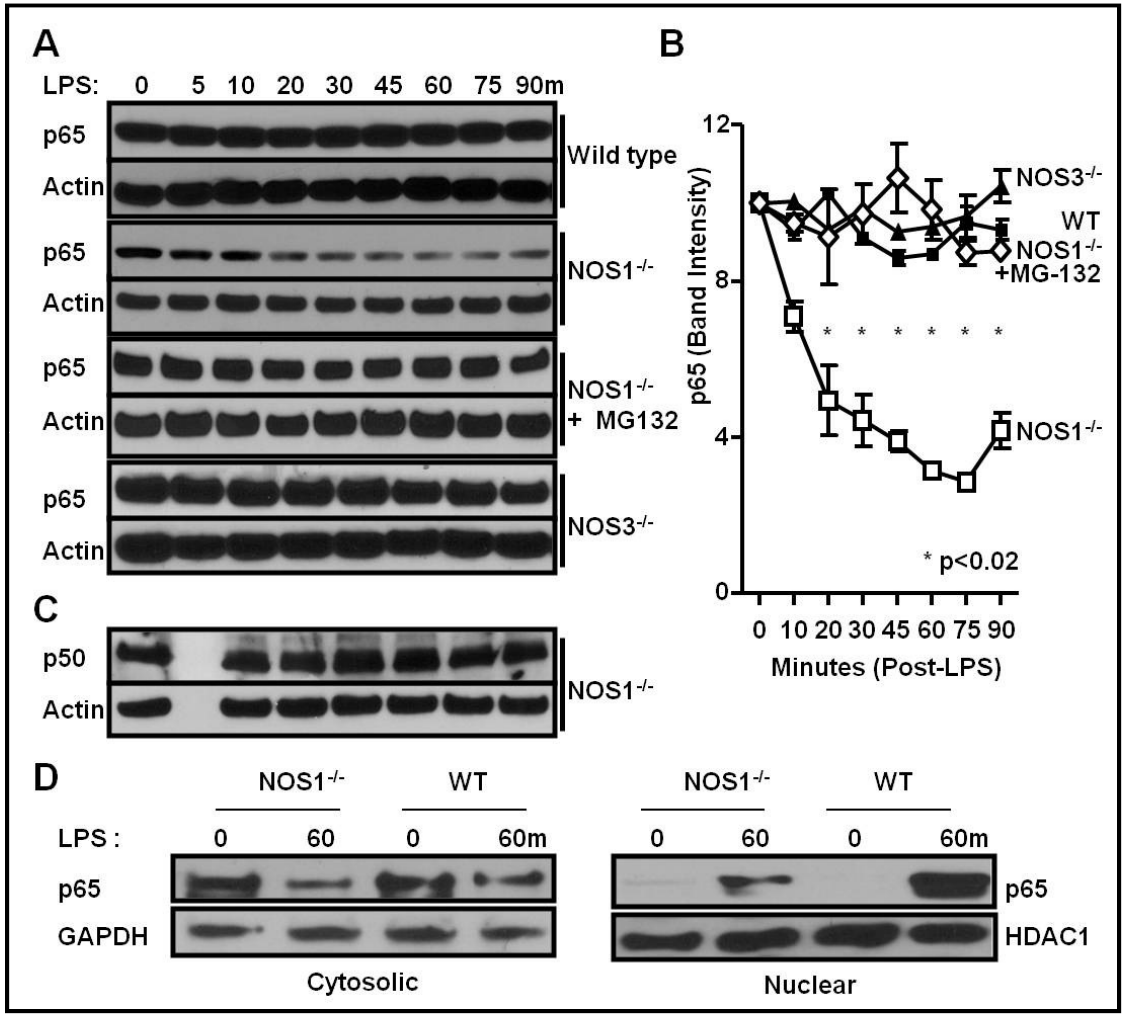
(Baig et al, JEM, 2015)

NOS1 is required for NFκB transcriptional activation but not upstream signaling

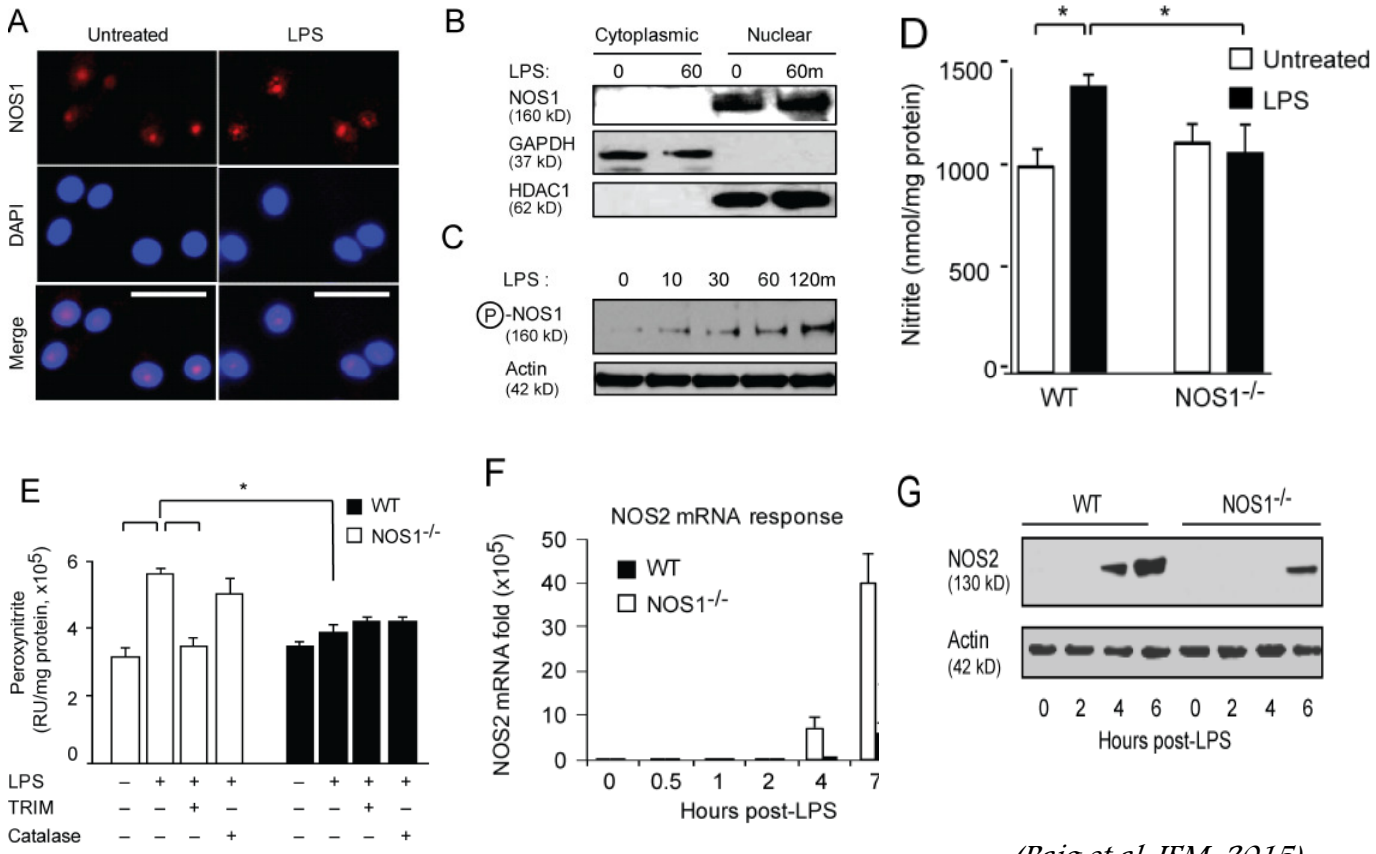


(Baig et al, JEM, 2015)

Total p65 level in bone marrow derived macrophages exposed to LPS



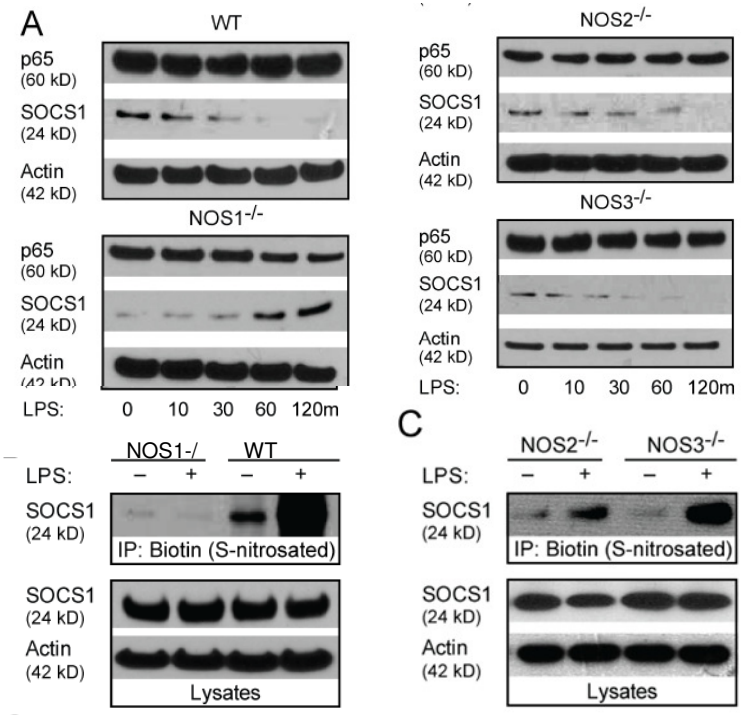
NOS1 localizes to the nuclei of macrophages and is required for rapid NO production after LPS treatment

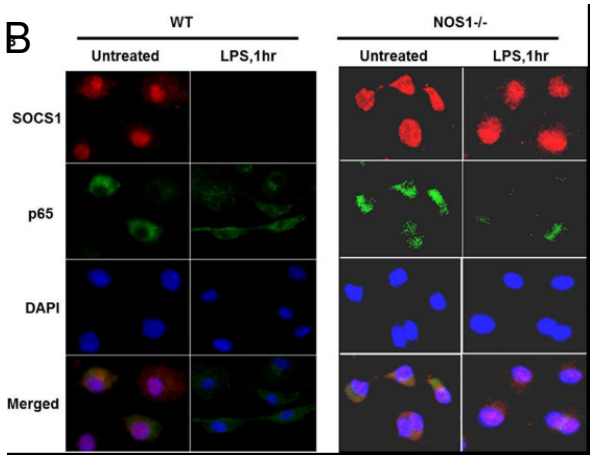


(Cumarin-7-boronic acid)

(Baig et al, JEM, 2015)

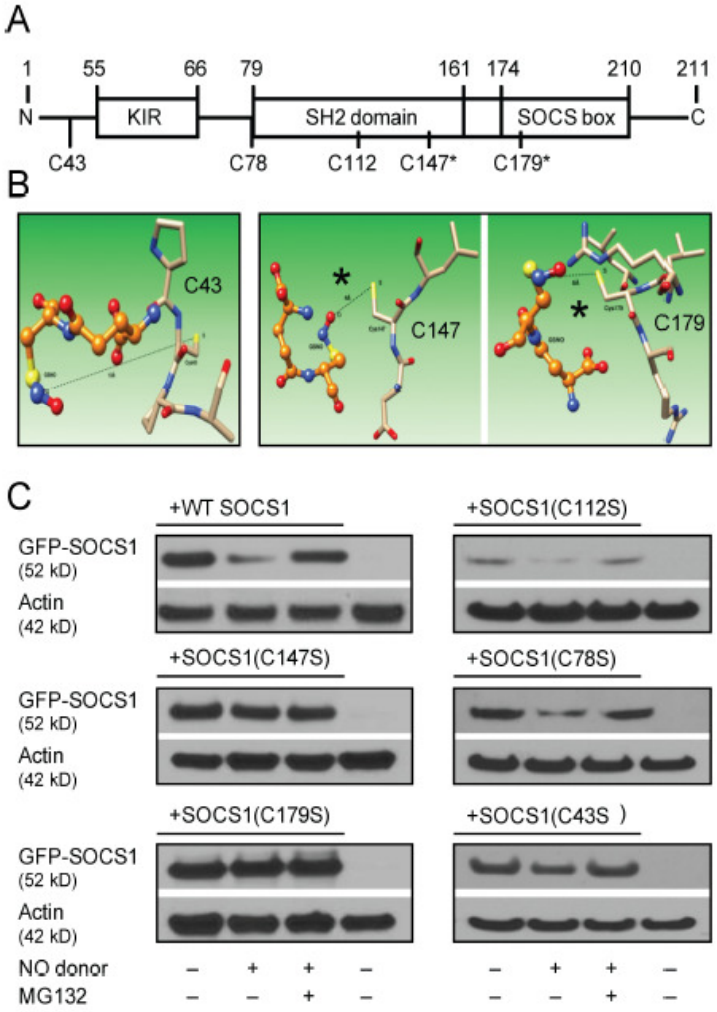
NOS1-derived NO mediates S-Nitrosation of SOCS1 and prevents SOCS1- mediated proteasomal degradation of p65

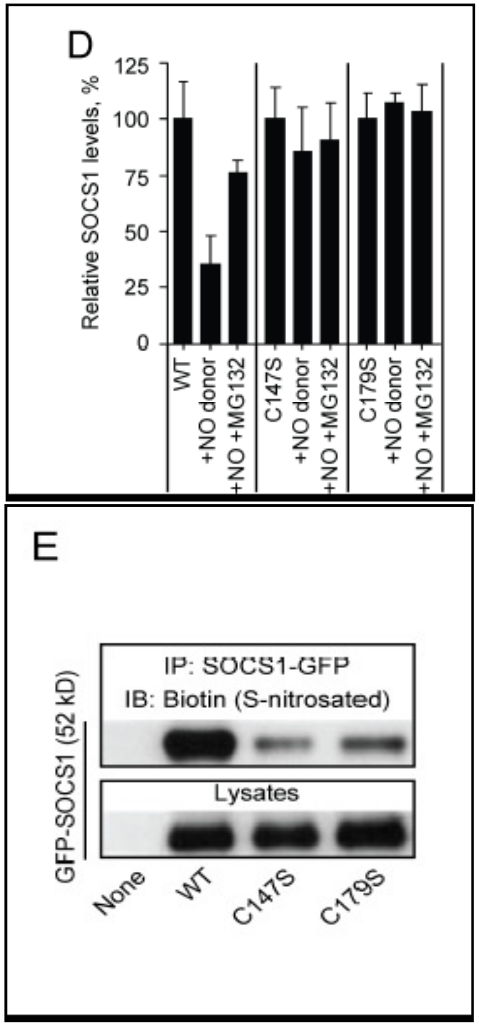




(Baig et al, JEM, 2015)

Molecular modeling and functional testing demonstrate that Cys147 and Cys179 of SOCS1 are the targets for S-Nitrosation





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SUMMARY

- NO specifically derived from NOS1 acts early in the downstream signaling of TLR4 and thus has implications for inflammatory tissue injury.

- SOCS-1 levels increase dramatically in the absence of NOS1, whereas decreases in control macrophages. This increase in SOCS1 protein correlates with a potent increase in binding of SOCS1 and p65. This binding event has been shown to determine the fate of p65 by targeting it to proteasomal degradation.

- The specific regulation of NF-κB by NOS1-derived NO represents an important advance in the understanding of NF-κB biology, a pathway that is relevant to a very broad spectrum of clinically relevant disorders from infectious disease to cancer and autoimmunity.

- This study provides more evidence that NOS1 has critical functions outside of the nervous system. A greater understanding of the detailed mechanisms by which NOS1 can regulate inflammation may yield opportunities to therapeutically modulate inflammation

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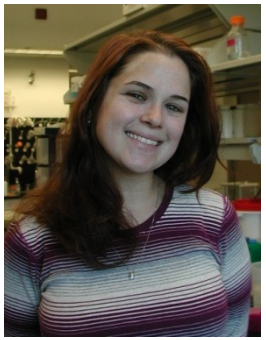

Dr. Kristine Ansenberger
Senior Scientist
Abbott Laboratories, IL

Dr. Sofia V. Zaichick, PhD

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THANK YOU