Statins as adjunctive host-directed therapy for TB

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Acknowledgments

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Michael Pinn
Dalin Rifat, Ph.D.
Lee Klinkenberg, Ph.D.
Yu-Min Chuang, M.D., Ph.D.
Edith Torres-Chavolla, Ph.D.
Alpaslan Alp, M.D.
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Hee-Sun Choi

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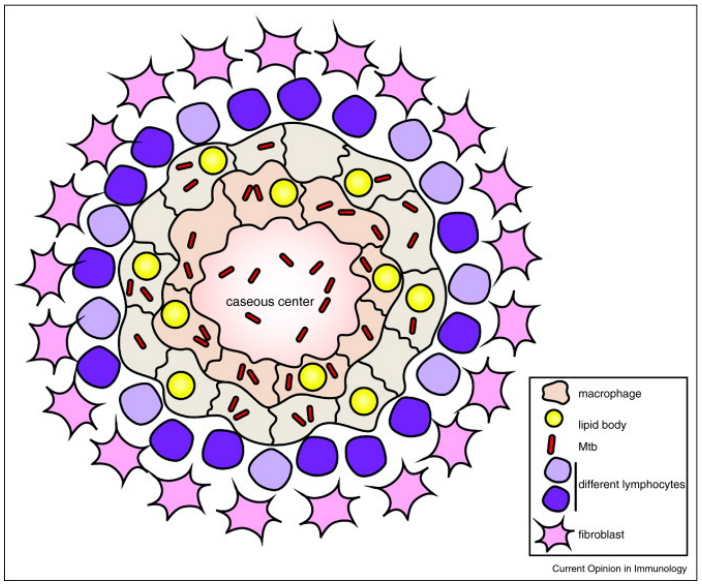
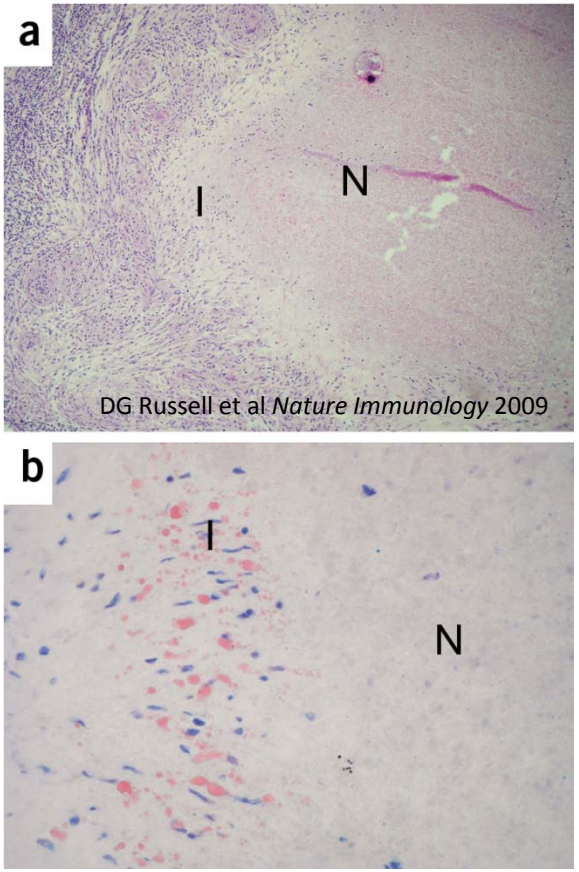
Lanbo Shi, Ph.D.
Pratik Datta, Ph.D.
Arnold Barton, Ph.D.
Pooja Vir, Ph.D.
Riccardo Arrigucci, Ph.D.

Funding:
R01AI083125
R01HL106786
R01HL106788

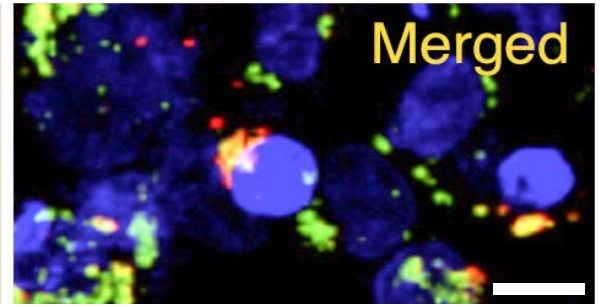
Rutgers U.
Richard Pine, Ph.D.
Veronique Dartois, Ph.D.

Lipid-laden macrophages in tuberculosis





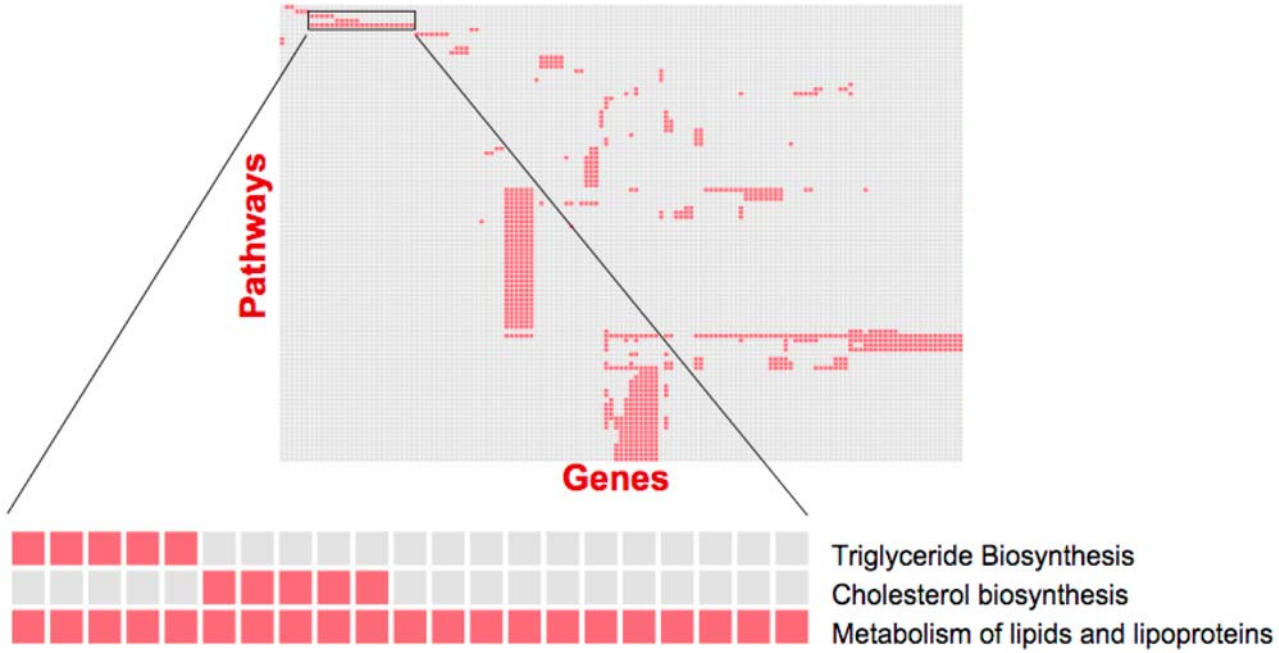
Lipid droplets in *M. tuberculosis*-infected macrophages *in vitro*



Lipid droplets
M. tuberculosis
Nuclei

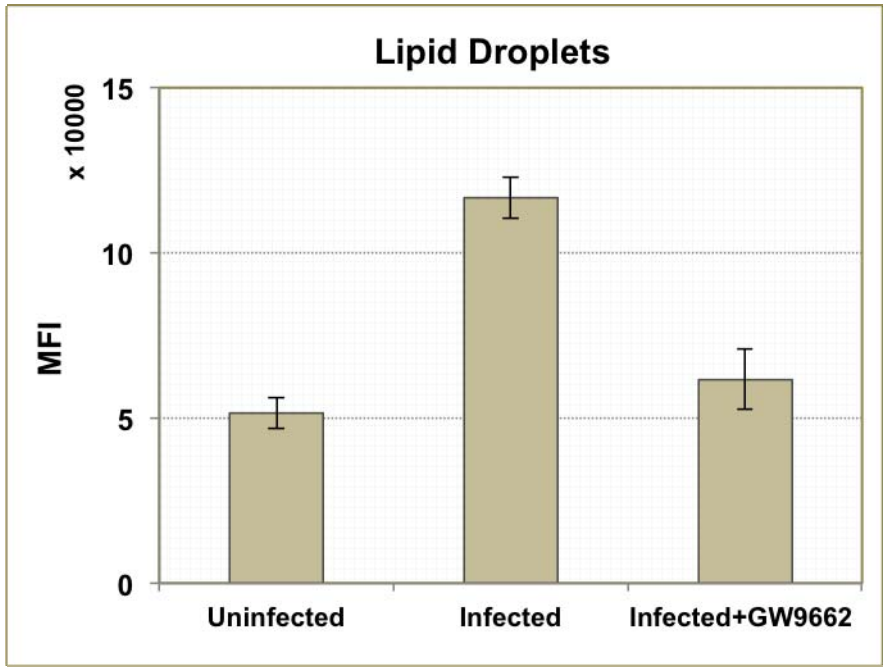
Lipid-laden macrophages in tuberculosis

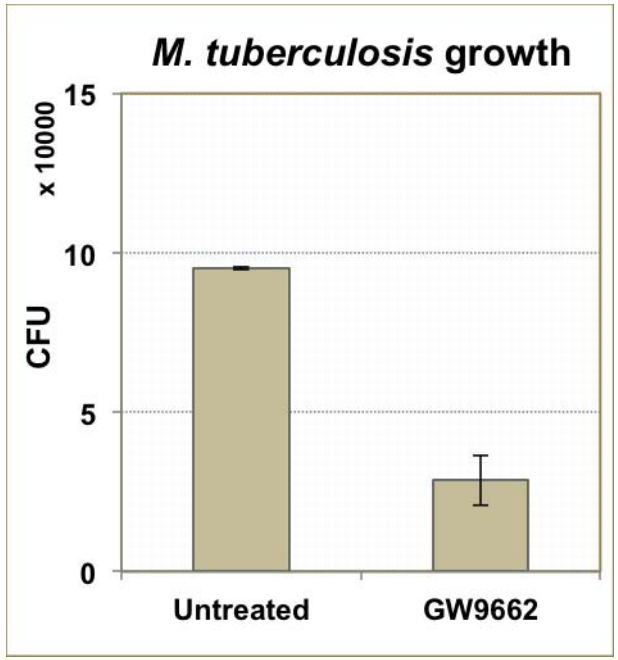
Metabolism of lipids and lipoproteins in pathway analysis of gene expression in *M. tuberculosis*-infected THP1 cells



Hugh Salamon

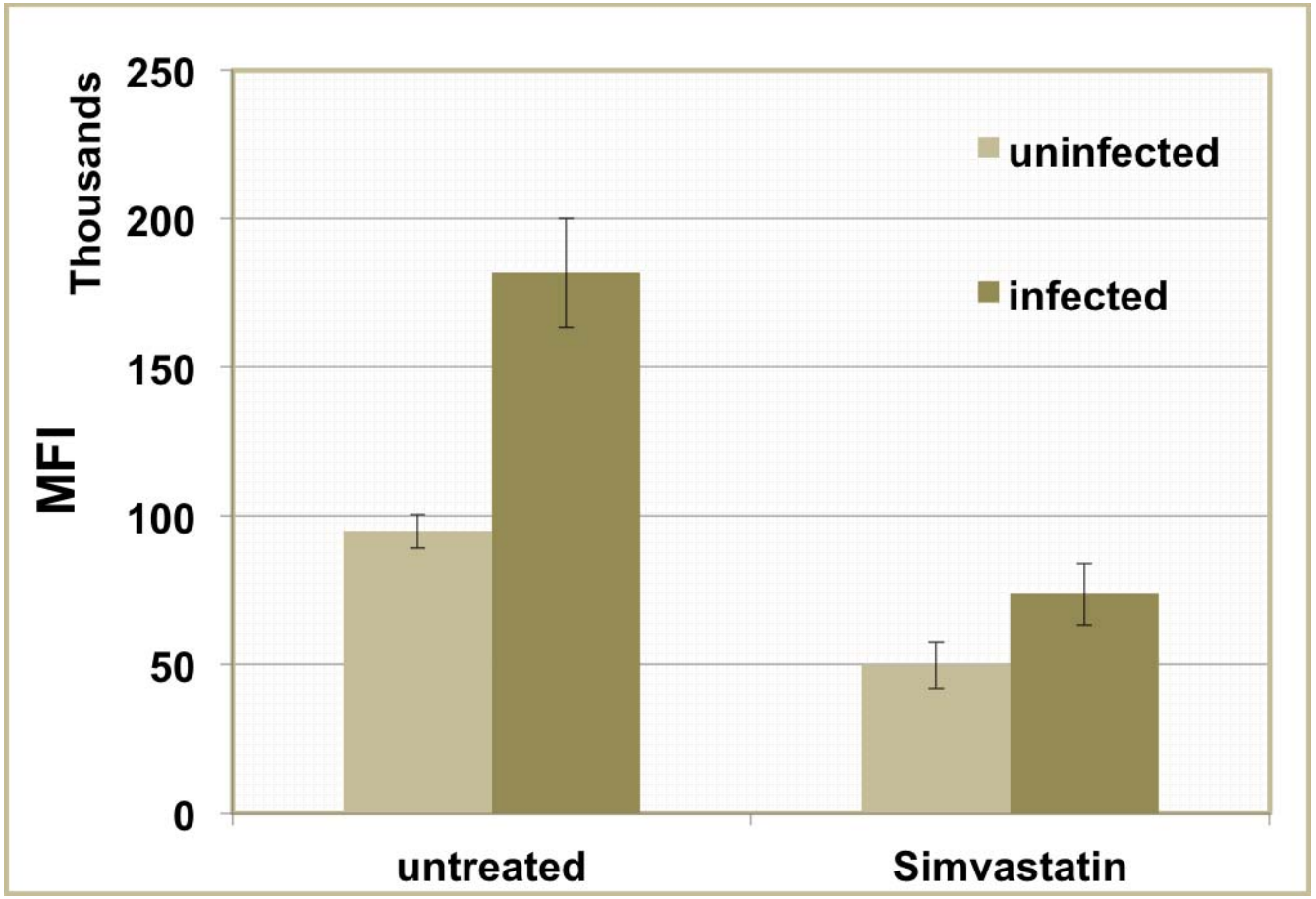
Agents that block lipid droplet formation usually inhibit intracellular growth of *M. tuberculosis* – an example is a PPARγ antagonist





Natalie Bruiners

Simvastatin blocks lipid droplet formation in infected macrophages



Karim Lakehal

Statins: Common clinical use

- Statins are among the best-selling drugs worldwide and used extensively to reduce morbidity and mortality in patients with coronary disorders and hypercholesterolemia.

Ray KK, et al. *Arch Intern Med*. 2010;170:1024-31.
Endo A. *J Lipid Res.* 1992;33:1569-82.

Statins: Host-modulating properties

- Statins have pleiotropic effects, including broad-range immunomodulatory and anti-inflammatory properties.

- Statin use reduced mortality in patients with bacteremia[1] and multiple organ dysfunction syndrome.[2]

[1]Tleyjeh IM, et al. *Arch Intern Med*. 2009;169:1658-67.
[2]Schmidt H, et al. *Intensive Care Med.* 2006;32:1248-51.

Statins: Protective effect against intracellular pathogens

- Lovastatin and atorvastatin reduced *Salmonella enterica* growth in a murine macrophage cell line and in mouse spleens/livers, respectively.

- Mice treated with simvastatin had reduced growth of *Chlamydia pneumoniae* in the lungs.

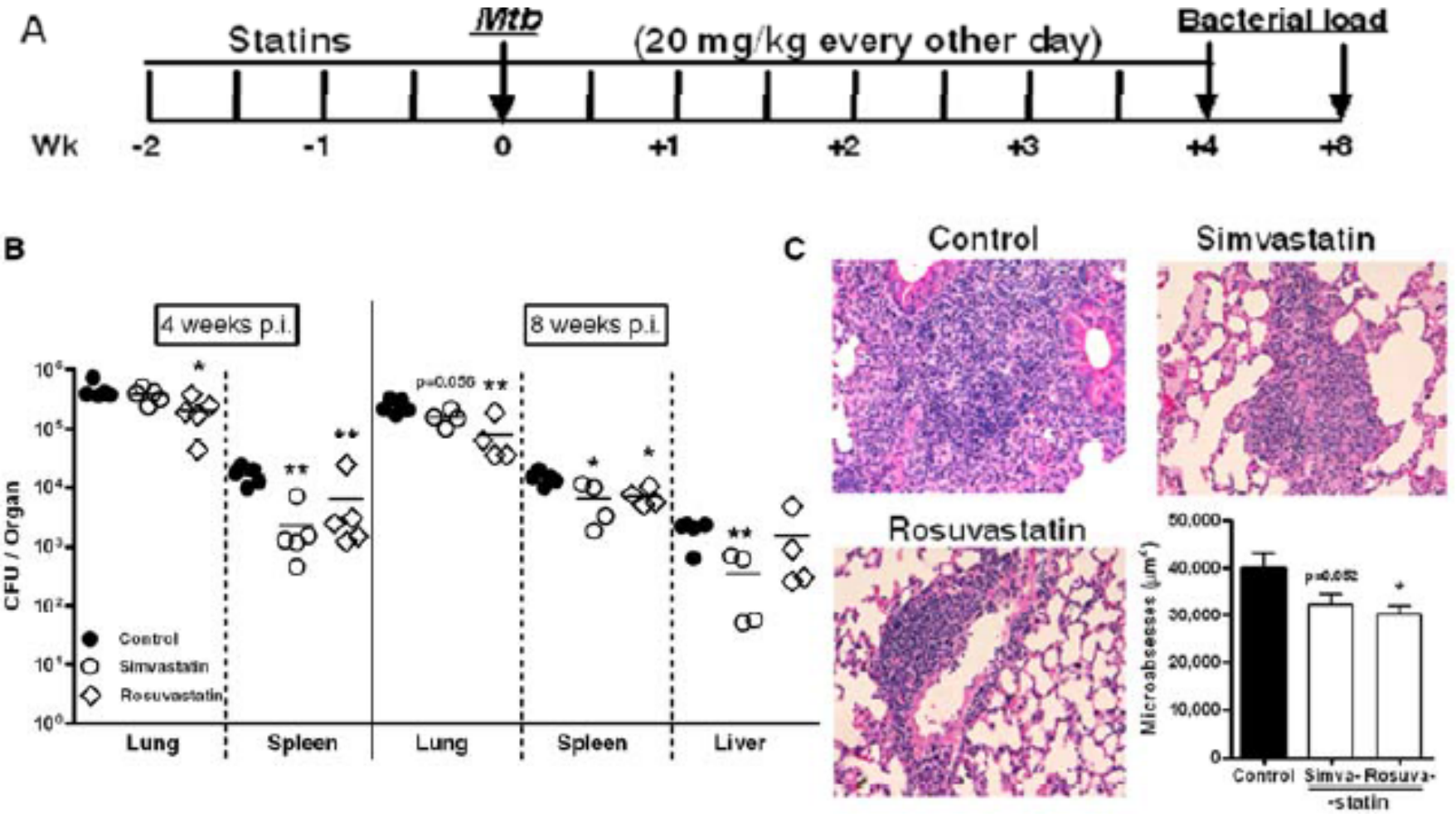
Catron DM, et al. *Infect Immun*. 2004;72:1036-42.
Erkkila L, et al. *Antimicrob Agents Chemother.* 2005;49:3959-62.

Anti-TB effect of statins

- PBMCs and MDMs from statin-treated FH patients were more resistant to Mtb infection compared to those of healthy donors.
- Statin treatment of Mtb-infected mice increased host protection with reduced lung burden and improved histopathology.
- The effect of statins appears to be mediated by reduction of membrane cholesterol, which promotes phagosomal maturation and autophagy.

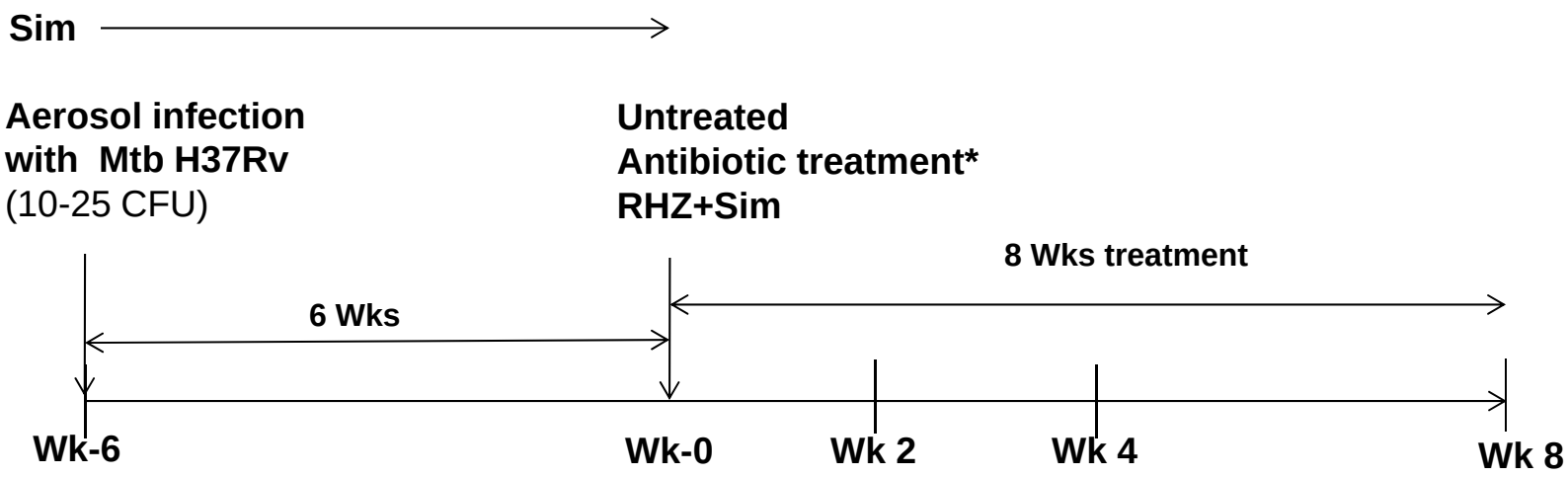
Parihar S, et al. *J Infect Dis*. 2014;209:754-63

Statins mediate increased host protection against Mtb infection in mice



Parihar S, et al. *J Infect Dis*. 2014;209:754-63

Statins as adjunctive therapy in combination with the standard first-line regimen

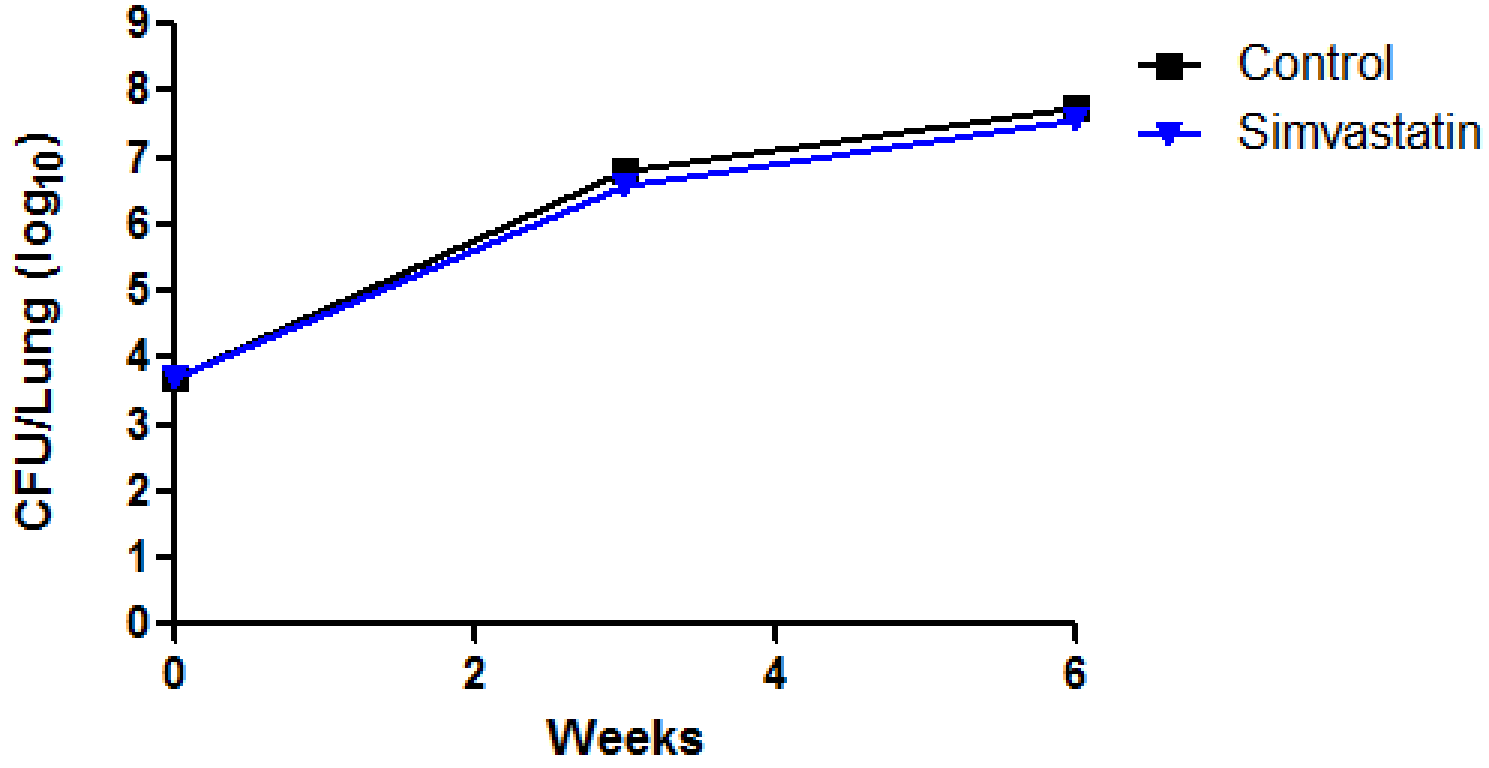


*Antibiotic treatment, H= isoniazid 10mg/kg
R= rifampin 10 mg/kg
Z= pyrazinamide 150 mg/kg
Sim= simvastatin 25 mg/kg[†]

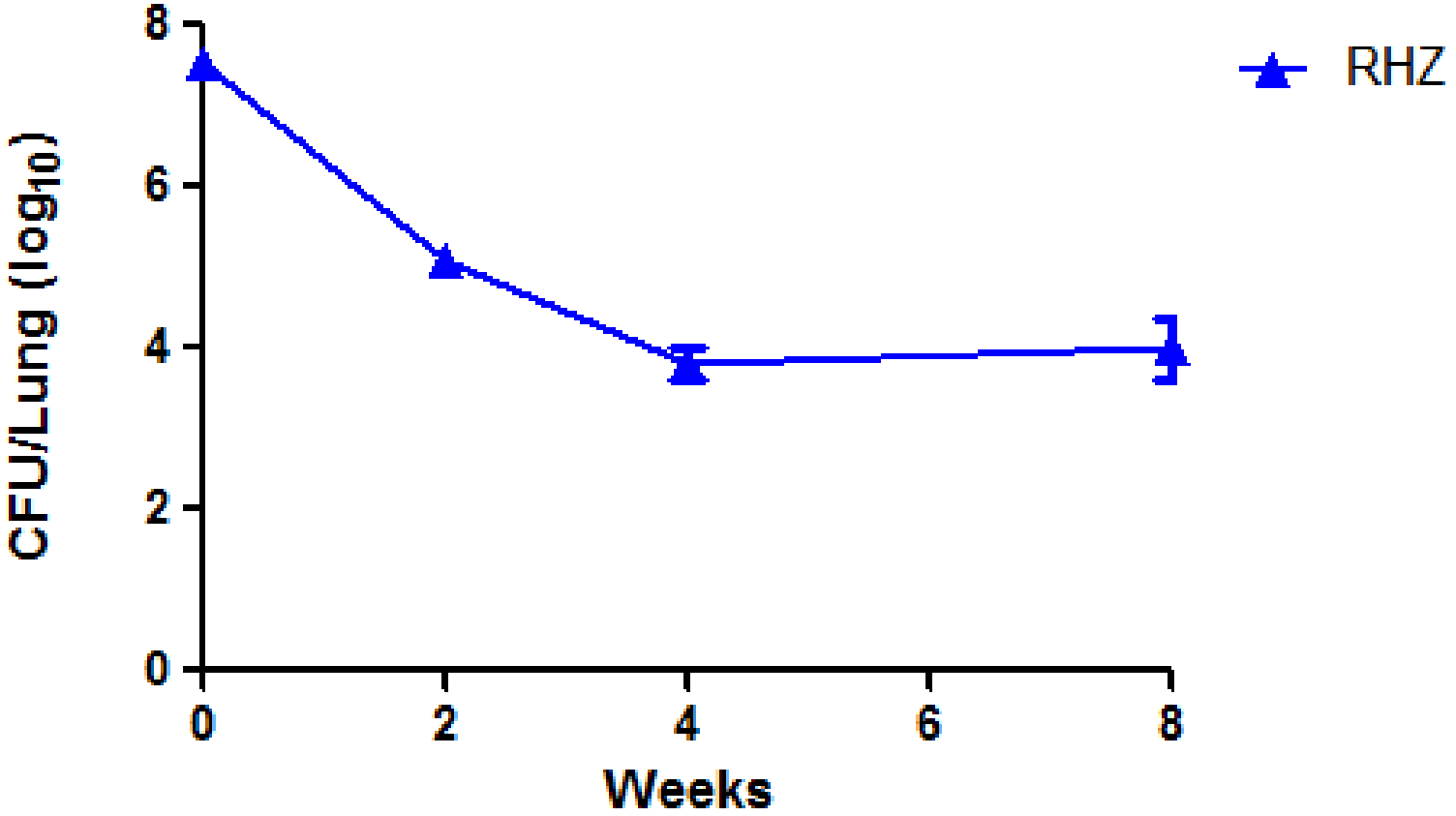
All antibiotics were given 5 times/week by oral gavage

[†] Wise LD et al. *Yakuri to Chiryo* 1990;39:143–58.

Simvastatin does not enhance immune-based killing during acute TB infection in mice



Simvastatin accelerates bacterial clearance in combination with RHZ



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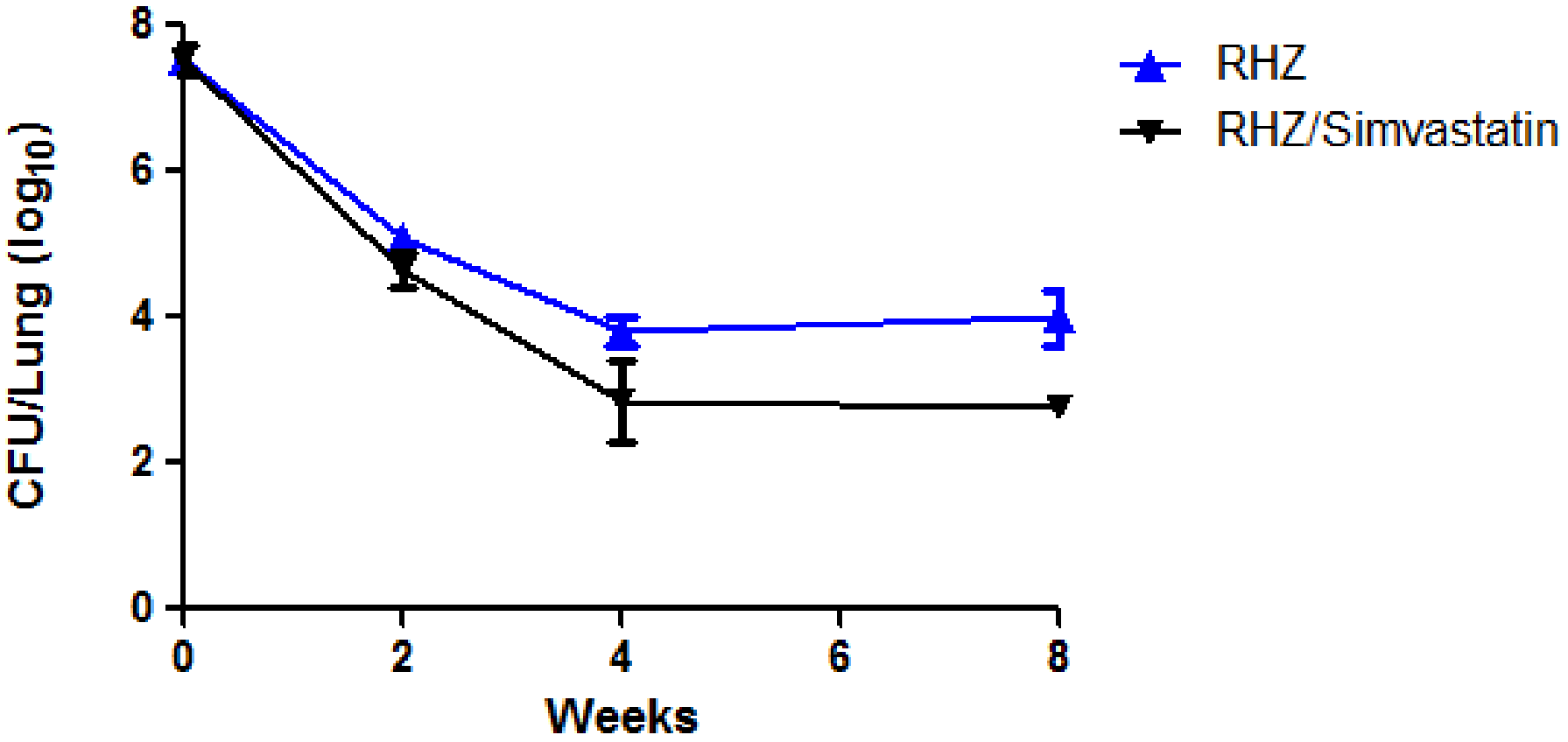


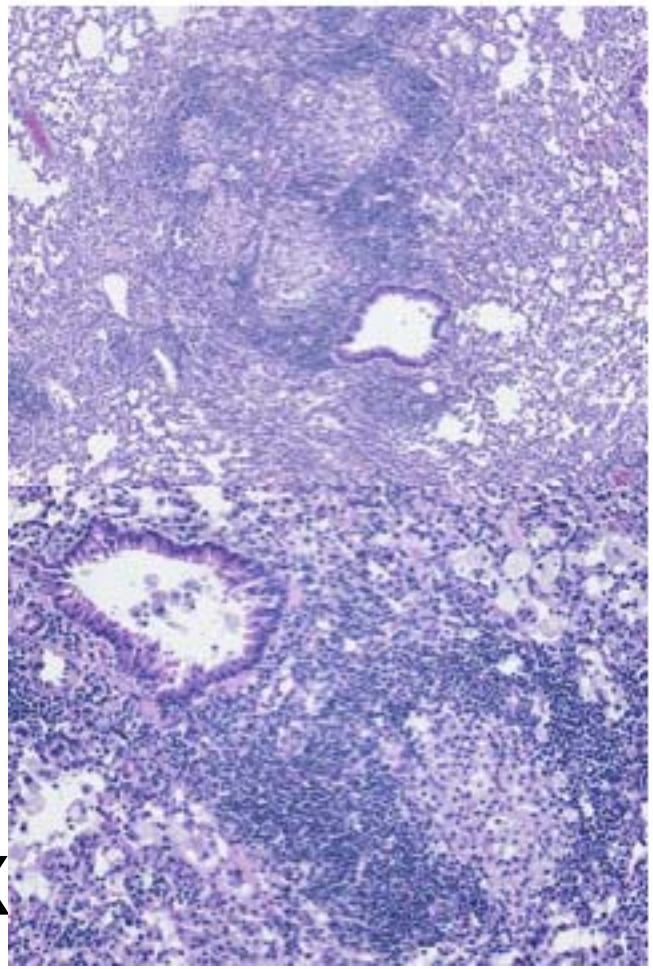
Histopathology: 4 weeks after treatment

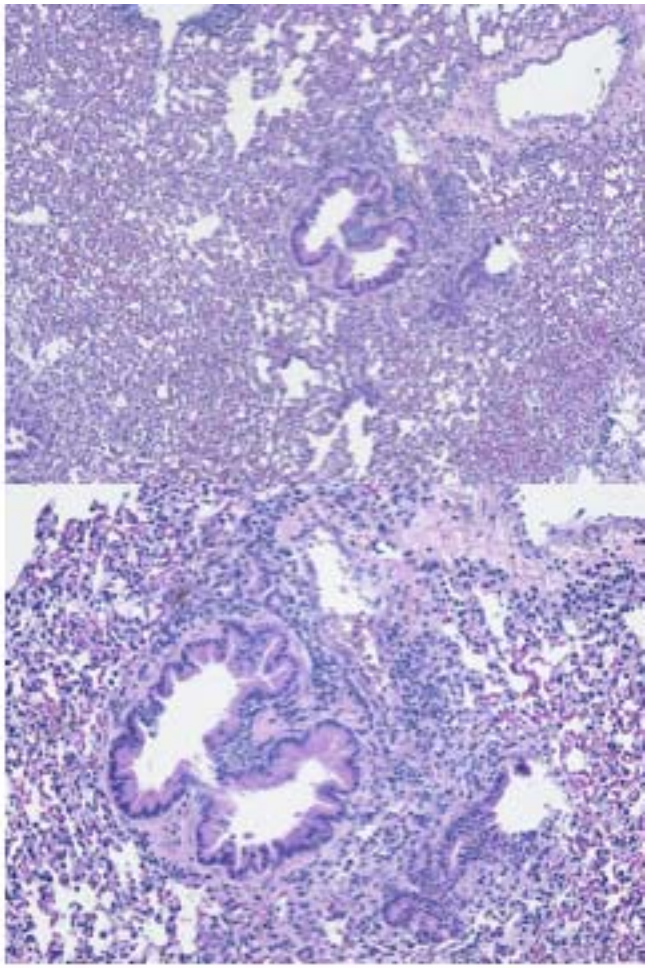
RHZ

RHZ + Sim

100X

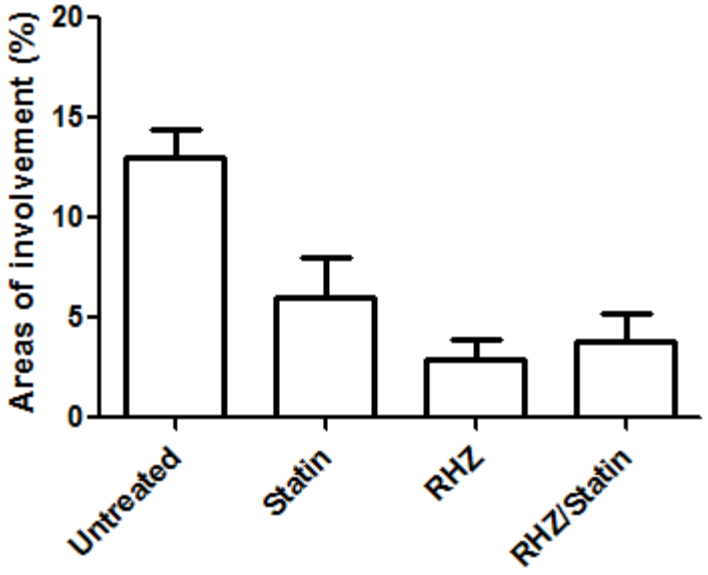
200X



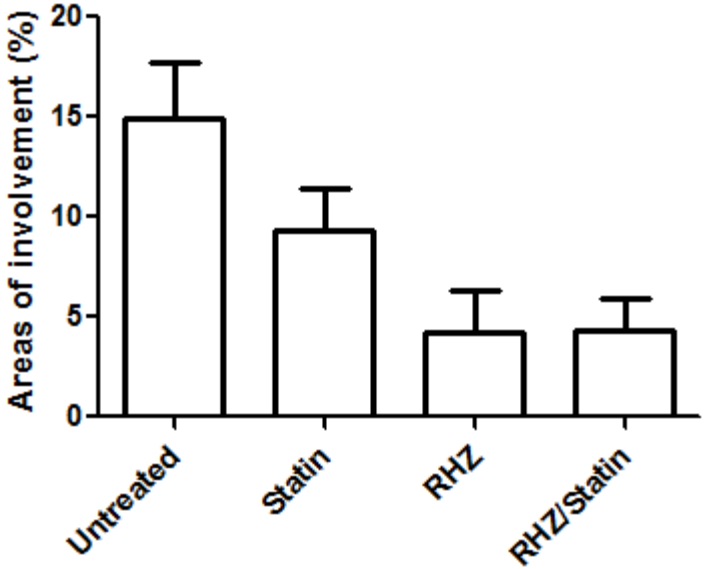


Lung histology: Morphometry analysis

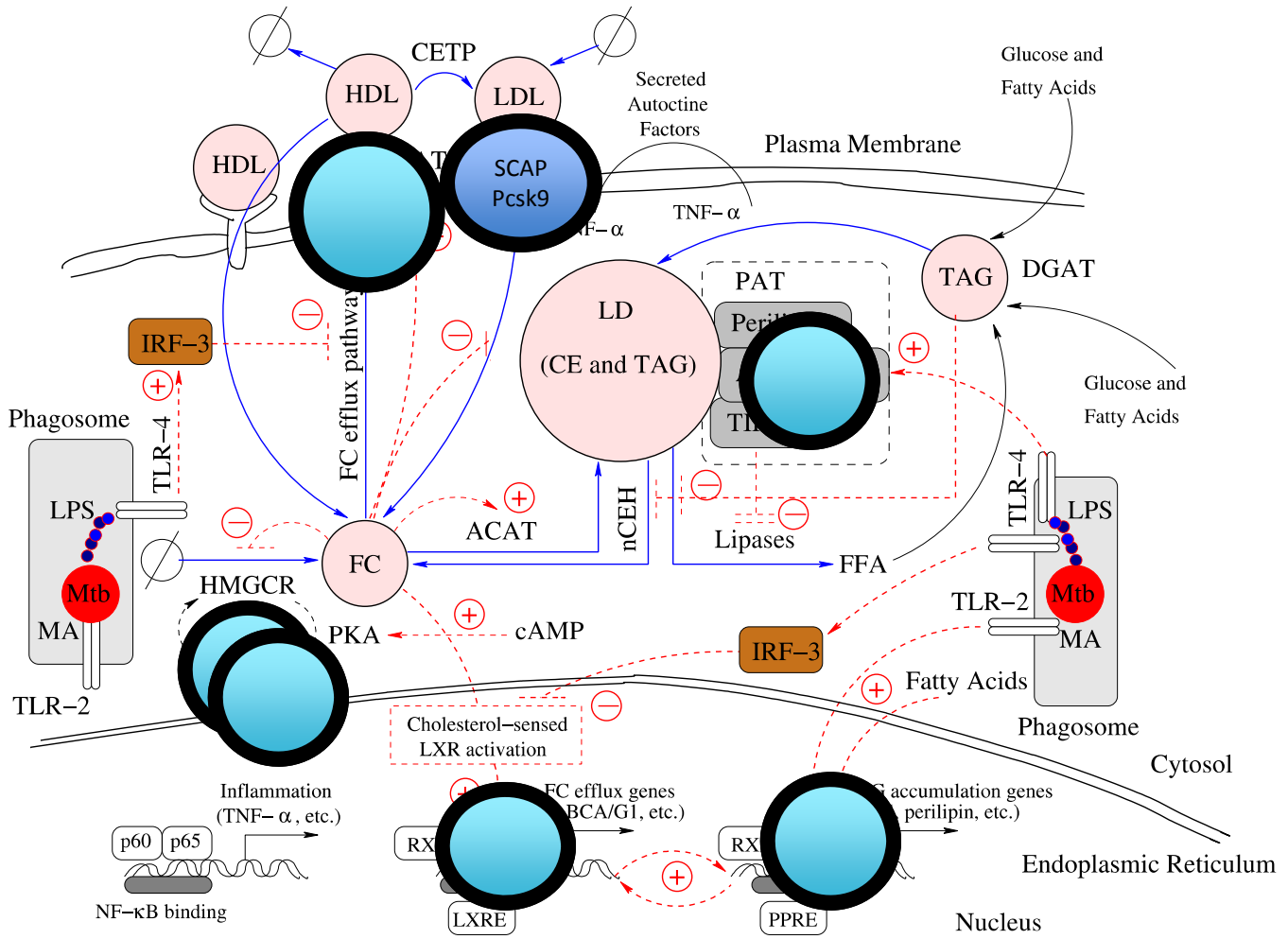
Week 4



Week 8



A panoply of drugs



Zhenya Nikolaev

Conclusions

- Statins are among the most commonly prescribed drugs and have a very favorable toxicity profile.
- This class of drugs appears to have host-protective properties against various intracellular pathogens.
- Readouts such as lipid droplet formation, intracellular growth of *M. tuberculosis*, and macrophage cytotoxicity can be used to investigate the basis of the antibacterial mechanisms of statins.
- Simvastatin, when added to RHZ, increased *M. tuberculosis* killing in murine lungs.

Unanswered questions

- Does adjunctive use of statins reduce the time required to achieve stable cure (relapse-free state) in mice?
- What is the optimal statin to use for adjunctive anti-TB therapy?
- What is the optimal dosing?
- Are statins as effective in the immunodeficient host?
- Are statins active against MDR-TB?
- Are there additional lipid-lowering drugs that can be evaluated as HDT for TB?