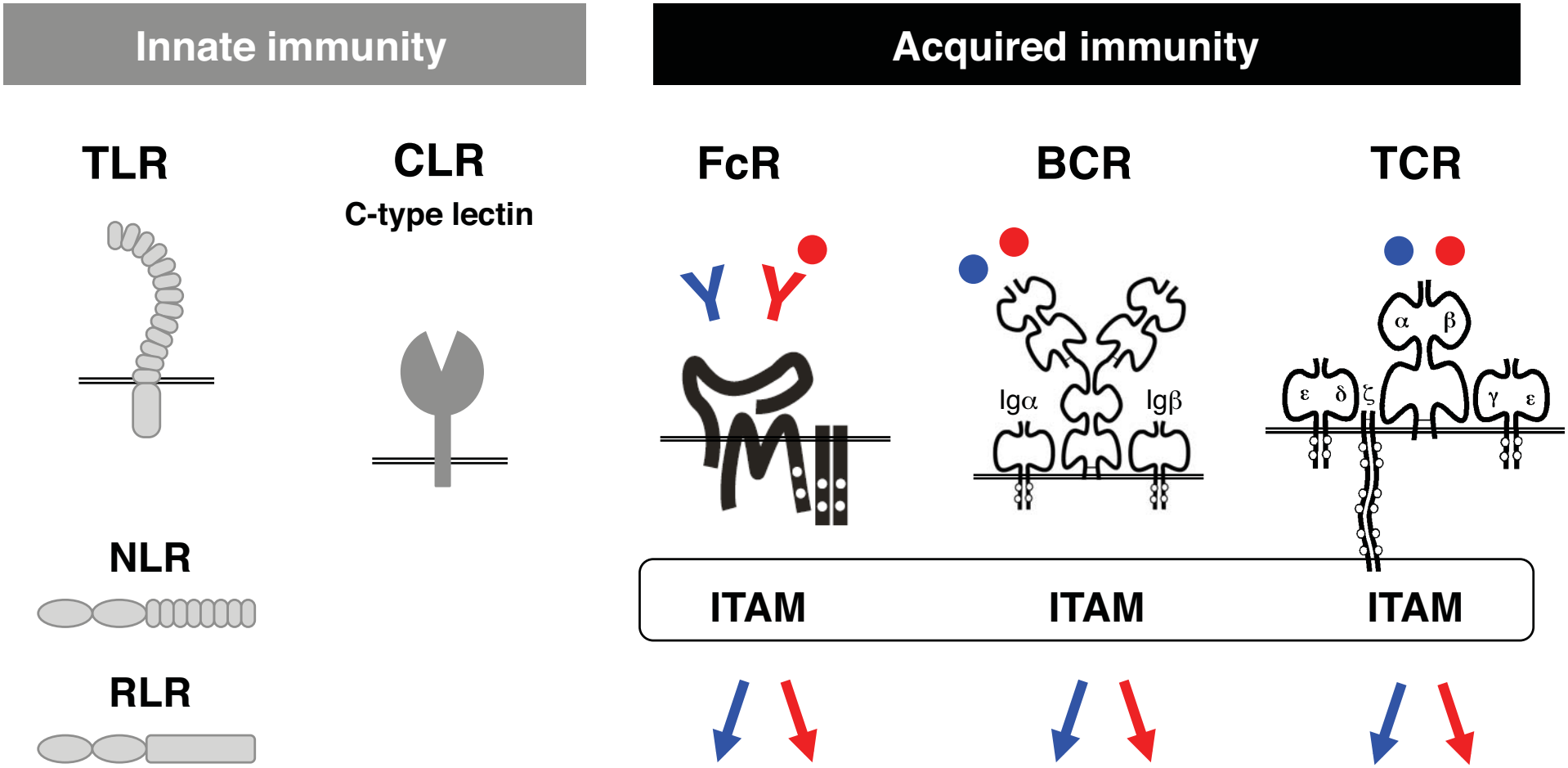
Cタイプレクチンを介する

結核菌アジュバントの作用機序

山崎　晶

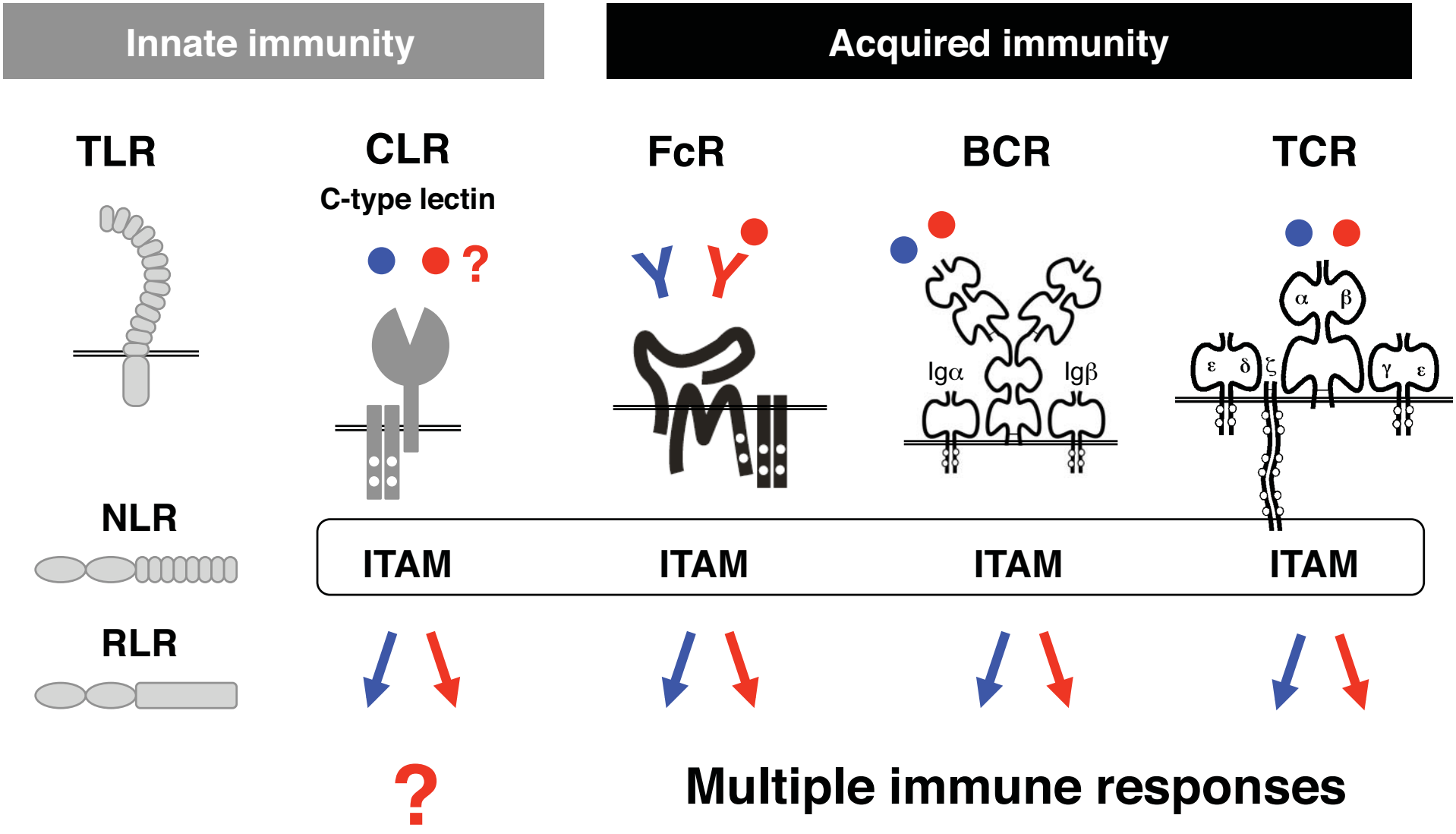
九州大学　生体防御医学研究所　分子免疫学分野

Immune receptors



ITAM: Immunoreceptor Tyrosine-based Activation Motif

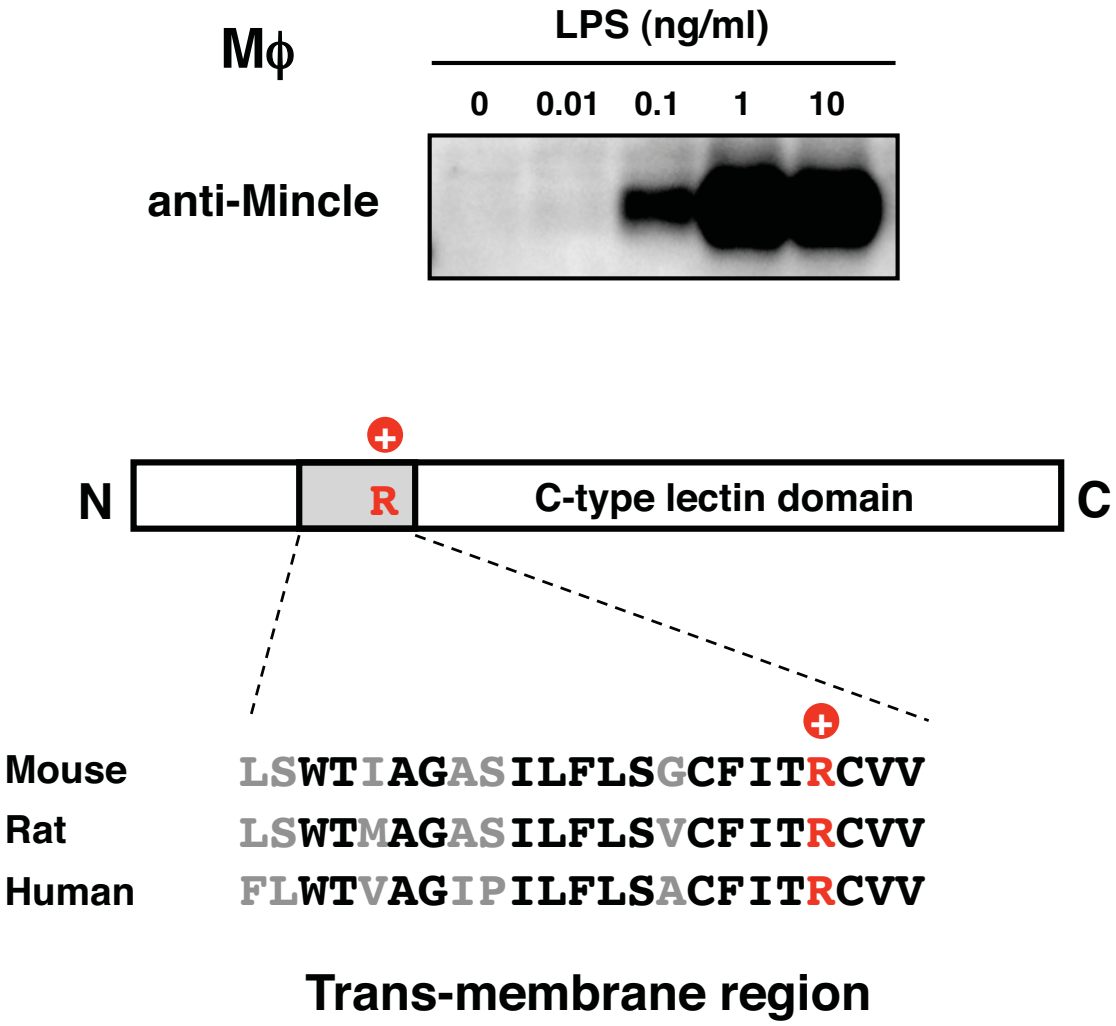
Immune receptors

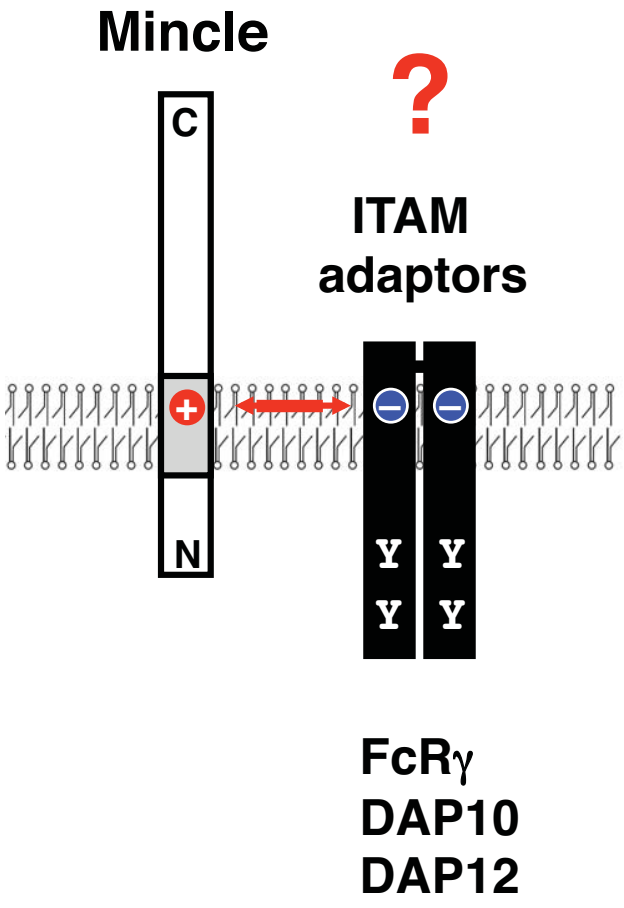


ITAM: Immunoreceptor Tyrosine-based Activation Motif

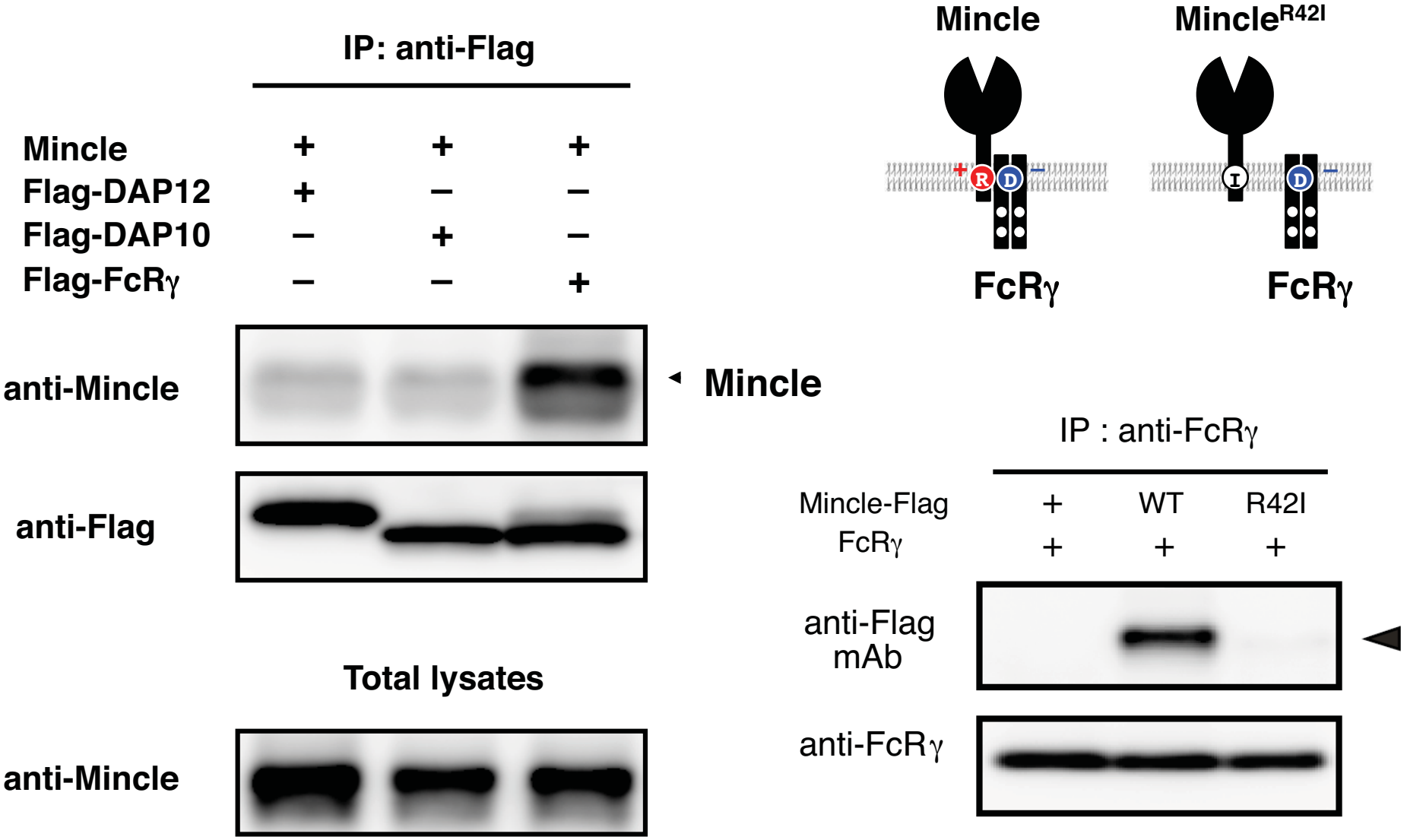
Mincle (Macrophage inducible C-type lectin)

Matsumoto et al. *J. Immunol*. 1999



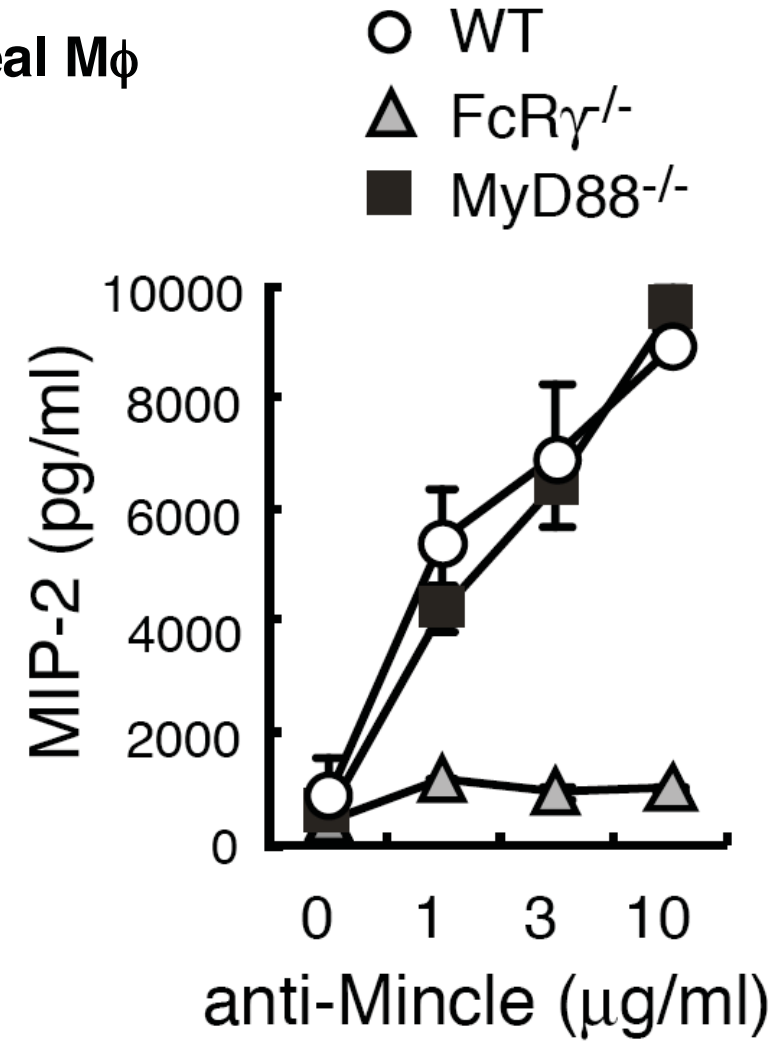


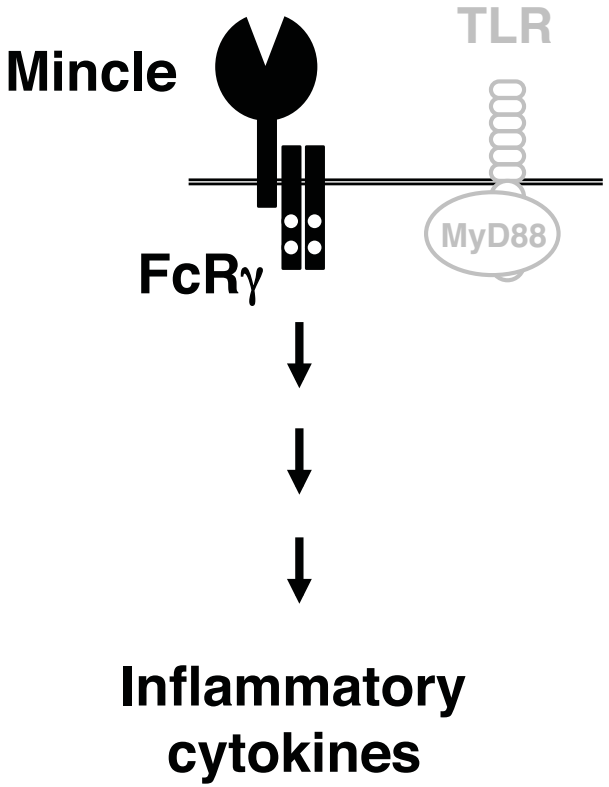
Mincle is associated with FcRγ by charge



Mincle induces inflammatory cytokines

Peritoneal Mϕ





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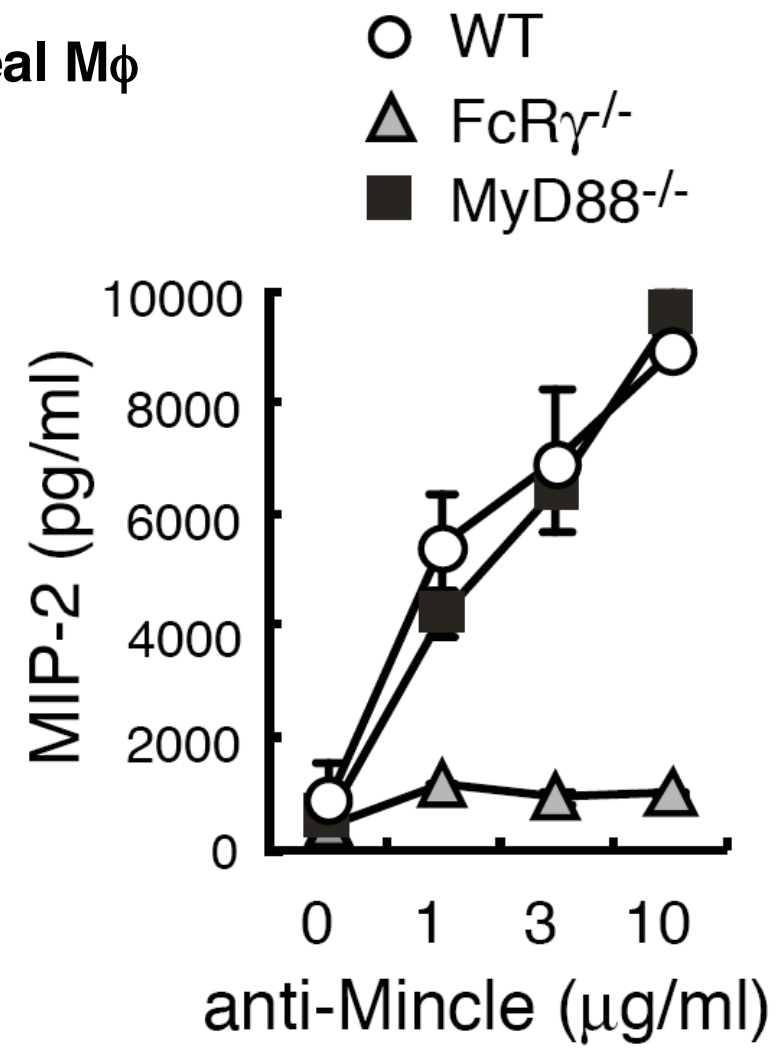
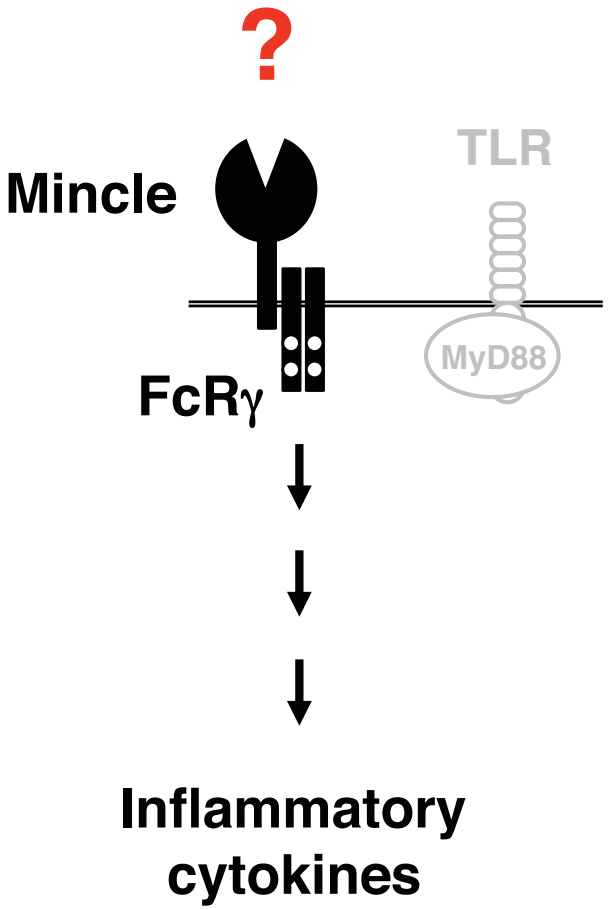
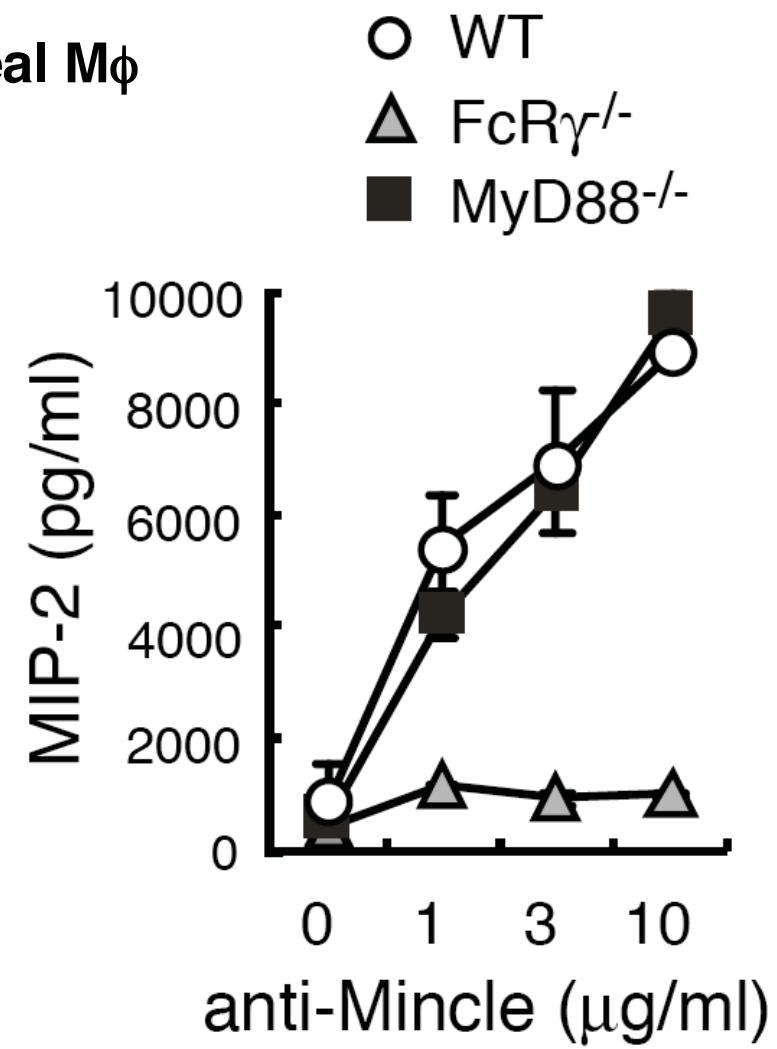
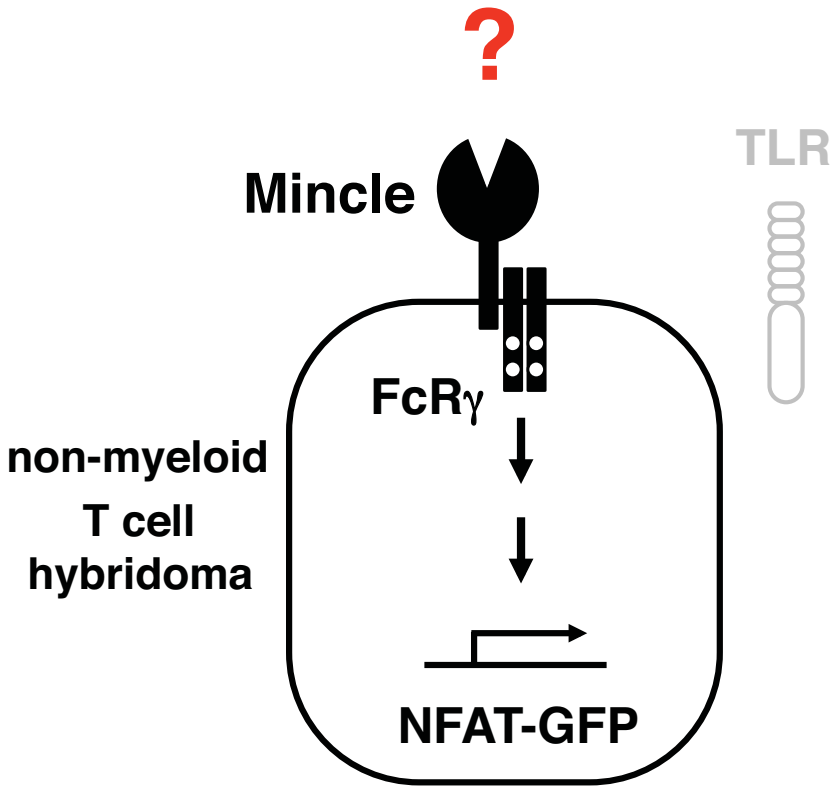


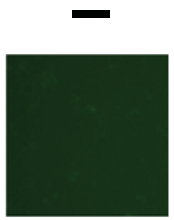


Establishment of indicator cell lines

Peritoneal Mϕ







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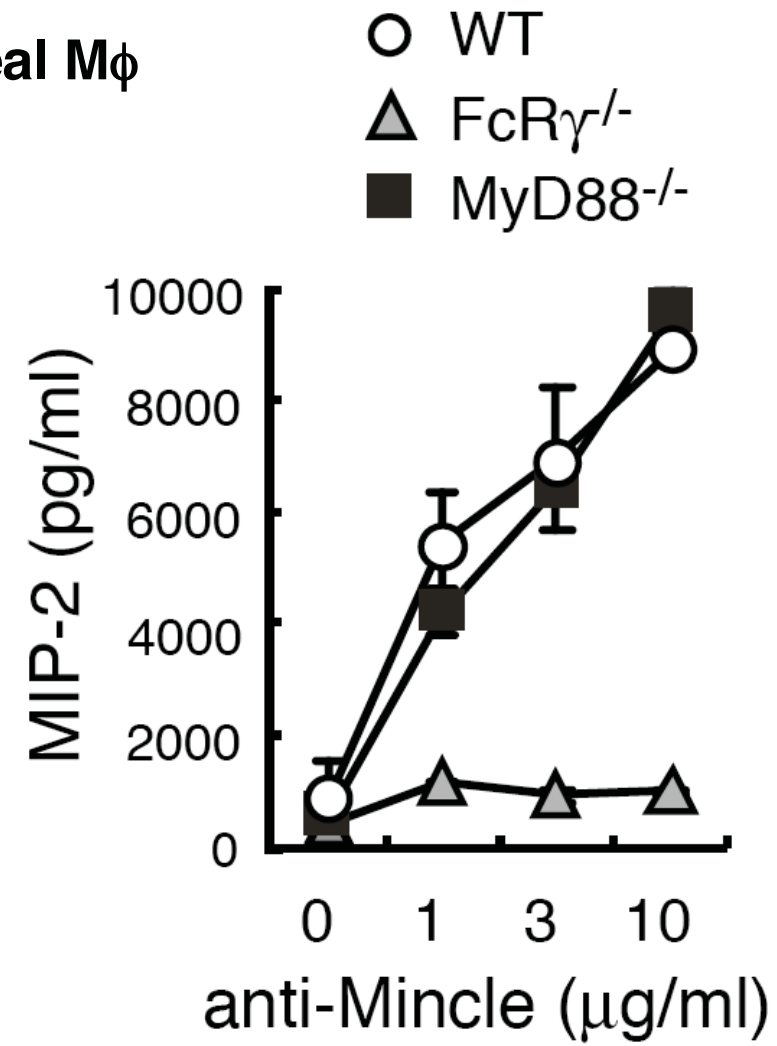
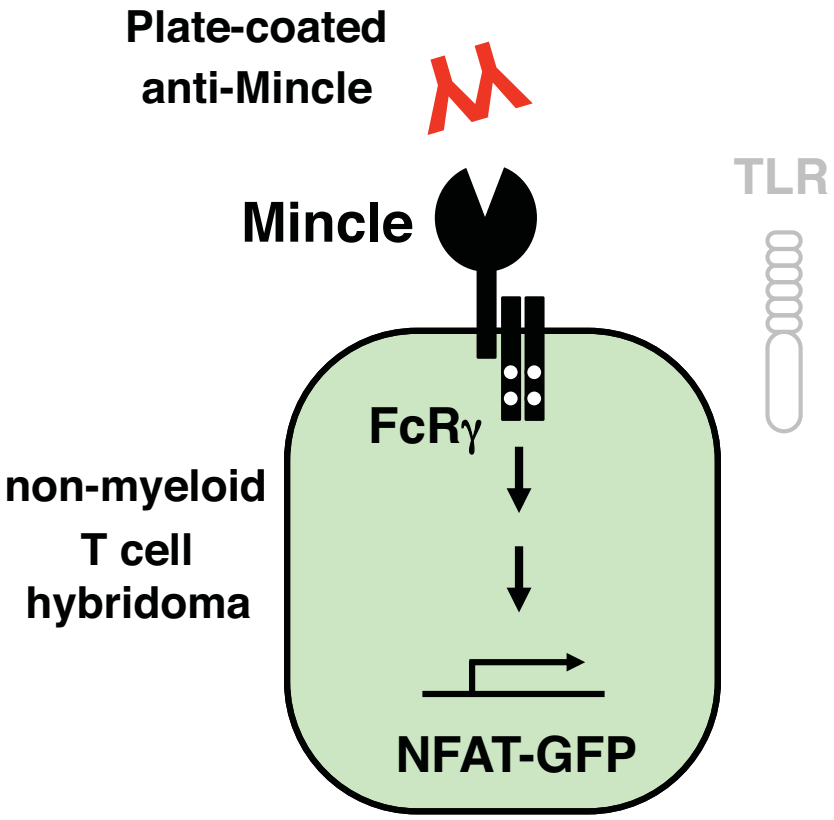
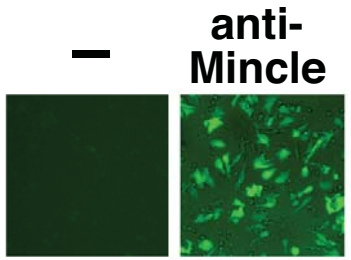
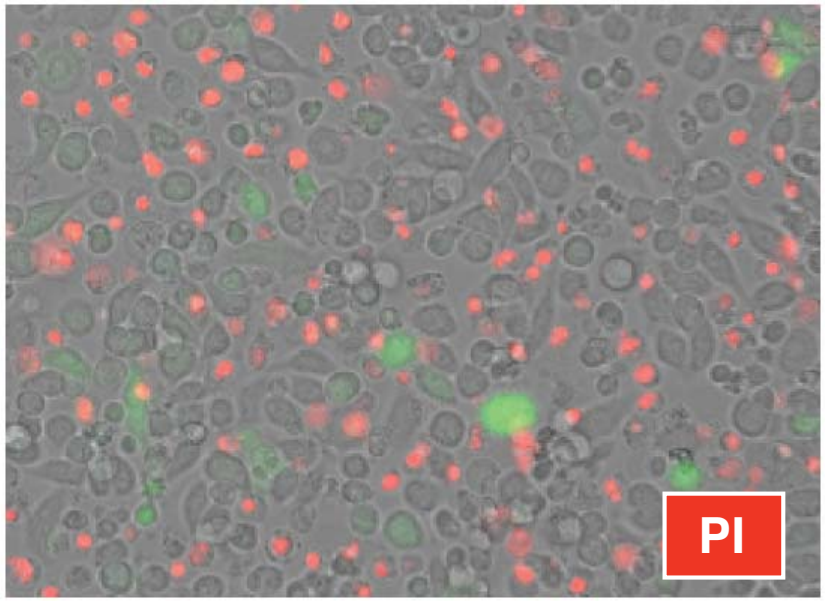






Mincle recognizes

Dead cells

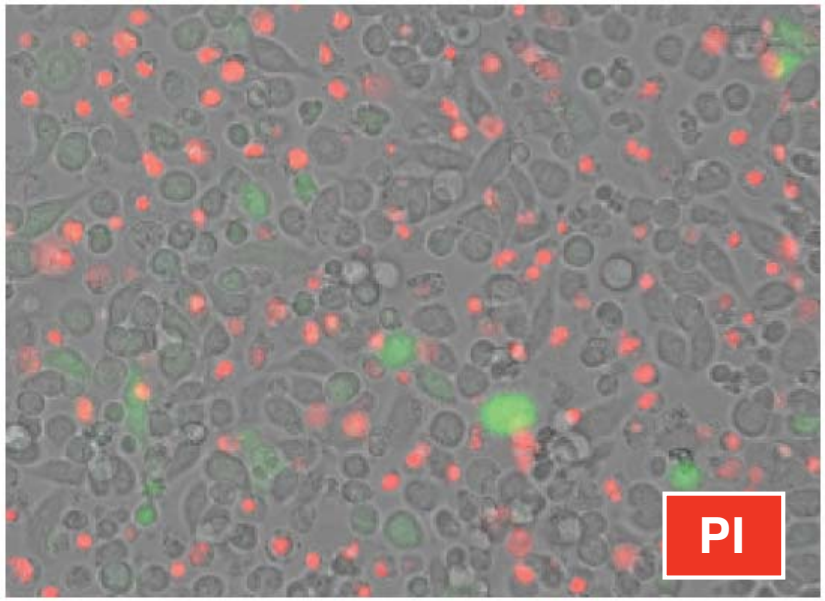


Yamasaki, et al. ***Nat. Immunol.*** 2008

Mincle recognizes

DAMPs

Damage-associated molecular patterns



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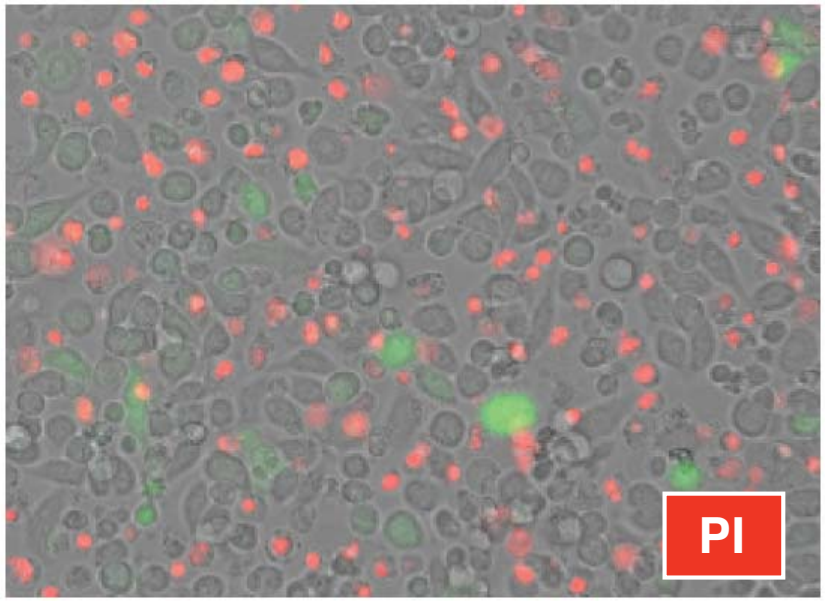


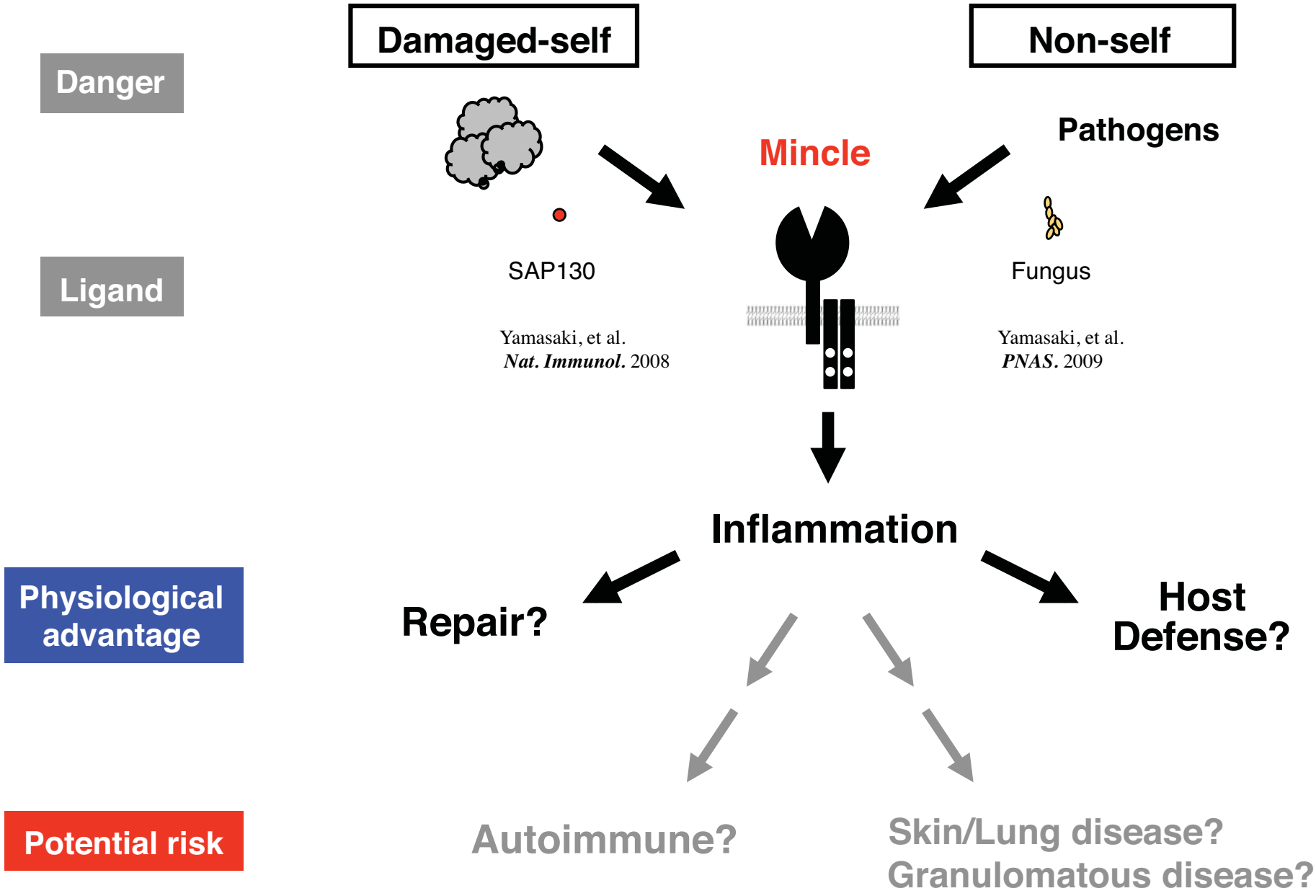
Yamasaki, et al. ***Nat. Immunol.*** 2008

PAMPs

Pathogen-associated molecular patterns

Yamasaki, et al. ***Proc. Natl. Acad. Sci. USA.*** 2009

Mincle may be a dual sensor for the “danger”



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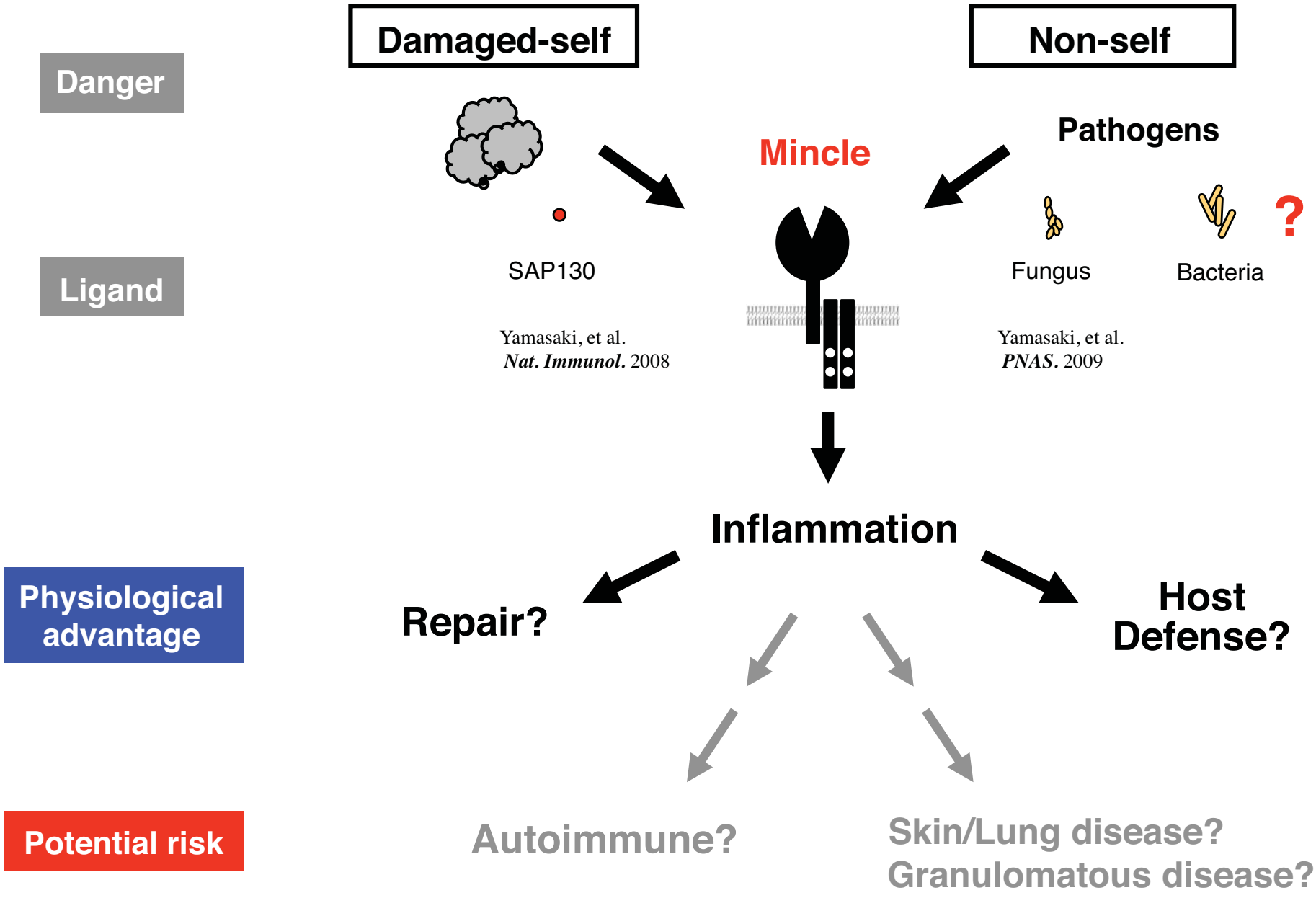
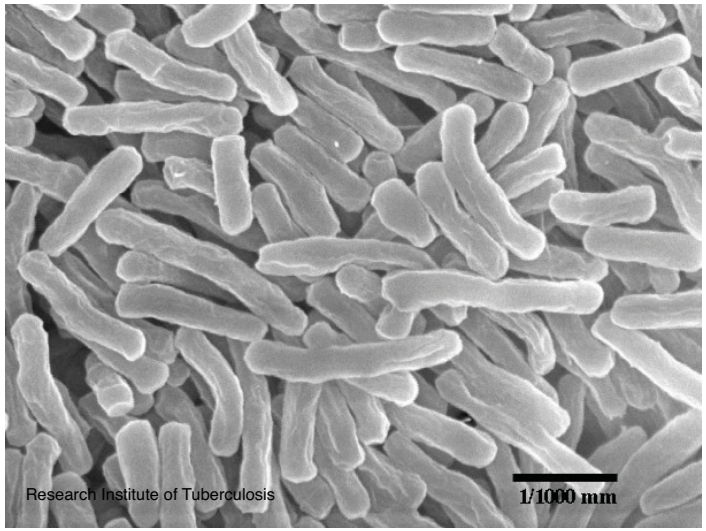


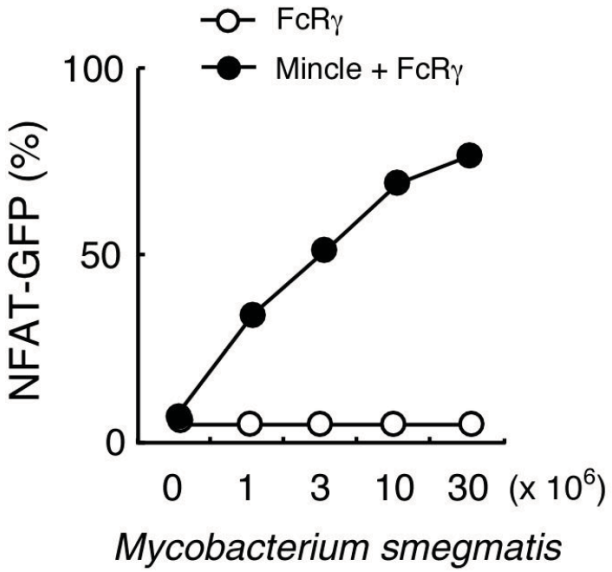
Mycobacterium tuberculosis

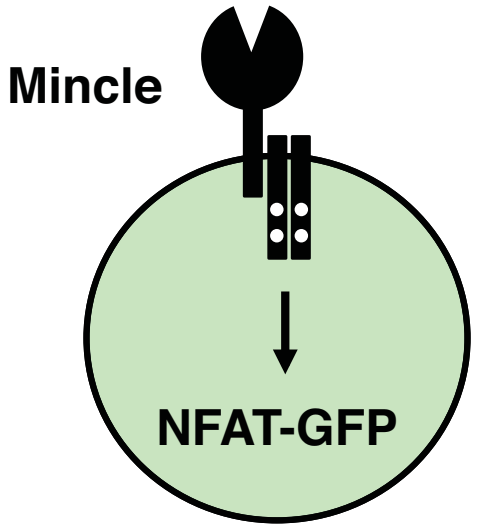


結核菌

Mincle recognizes mycobacteria

Lab strain





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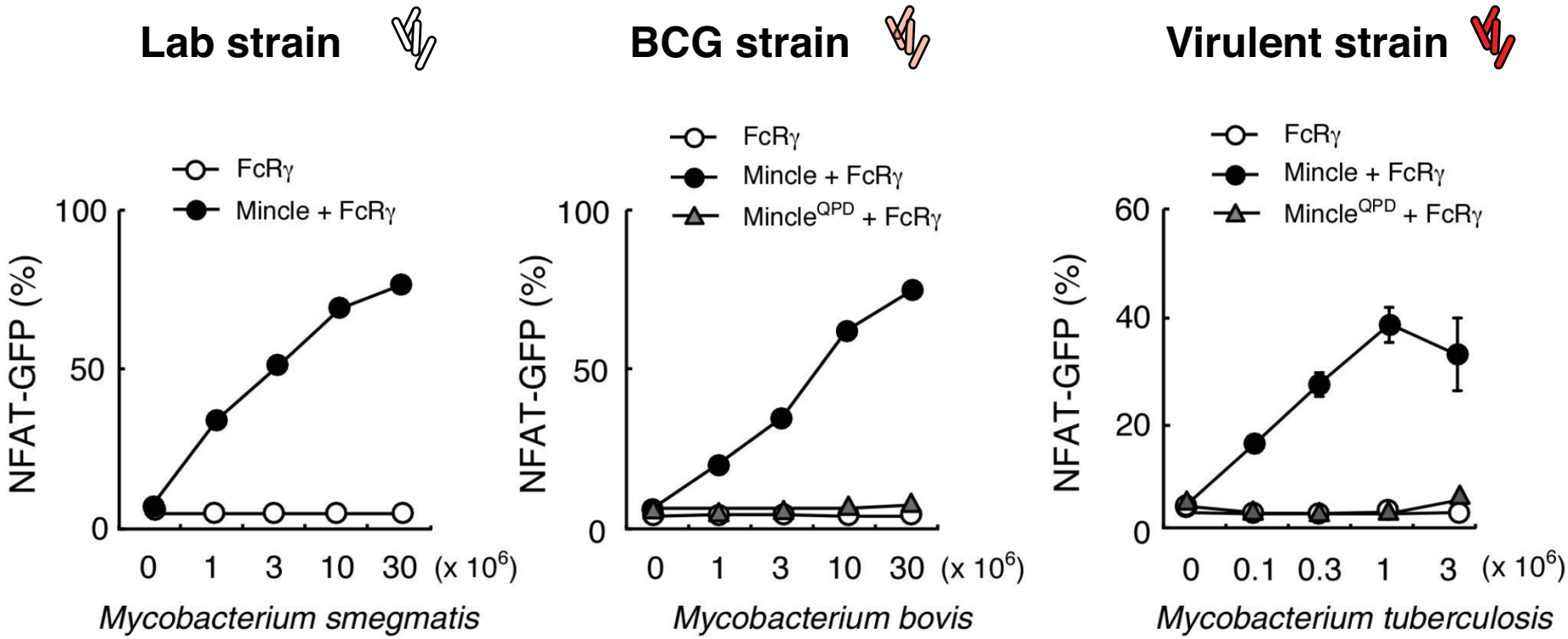
Yasu Morita
Taroh Kinoshita

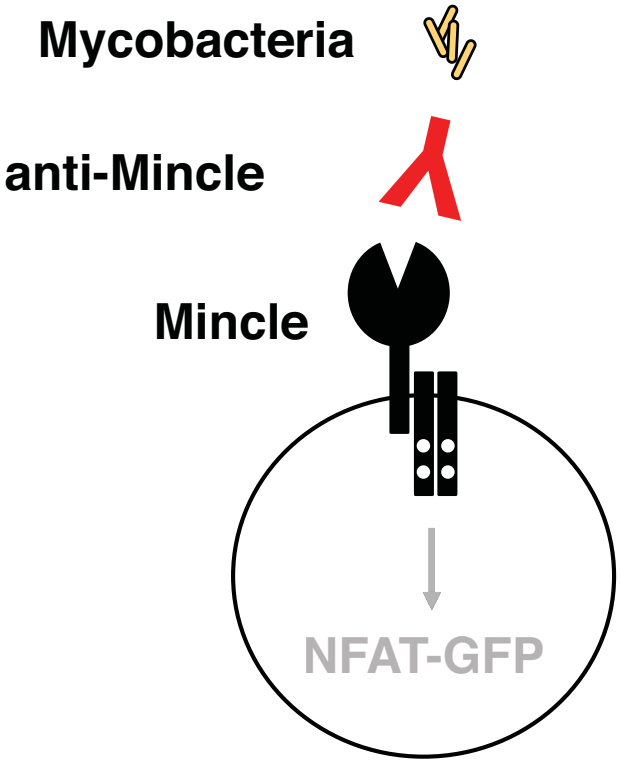
Mincle recognizes mycobacteria

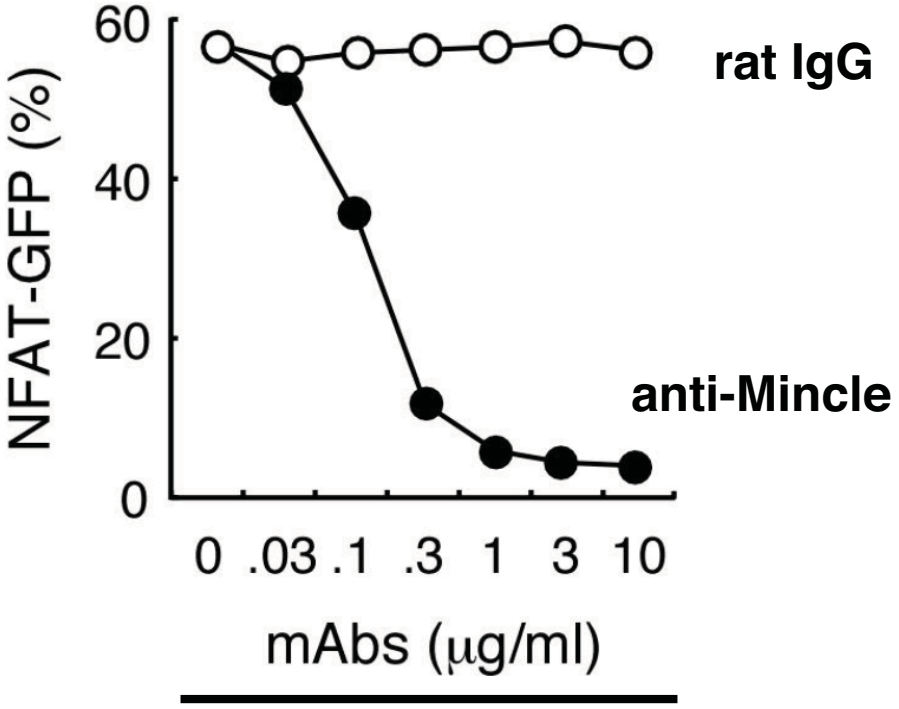


Yasu Morita
Taroh Kinoshita

Hisakata Yamada
Yasunobu Yoshikai

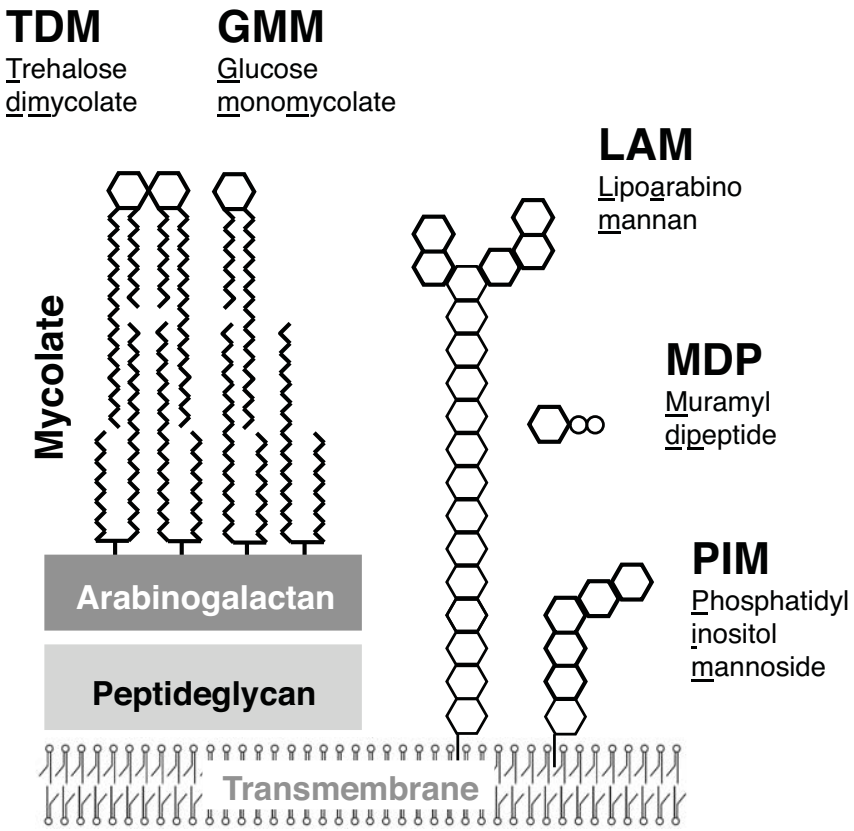
Mincle recognizes mycobacteria





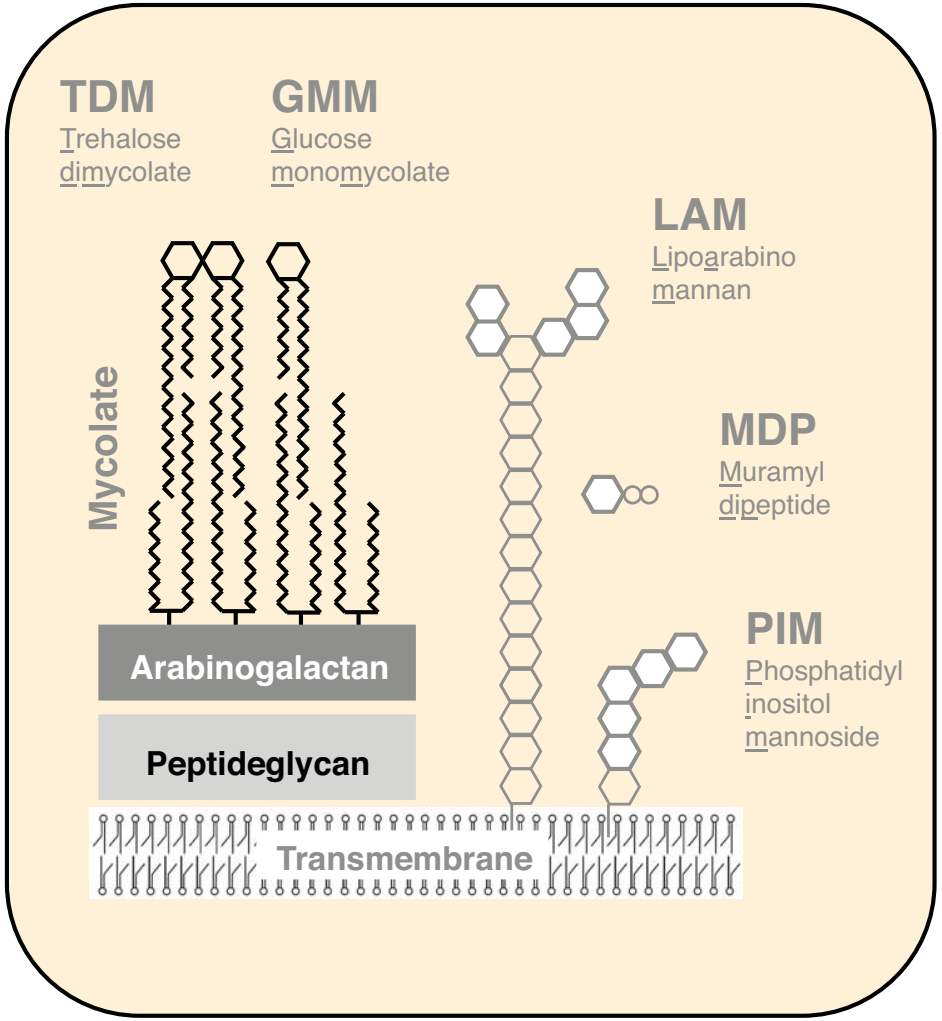
Mycobacterium smegmatis

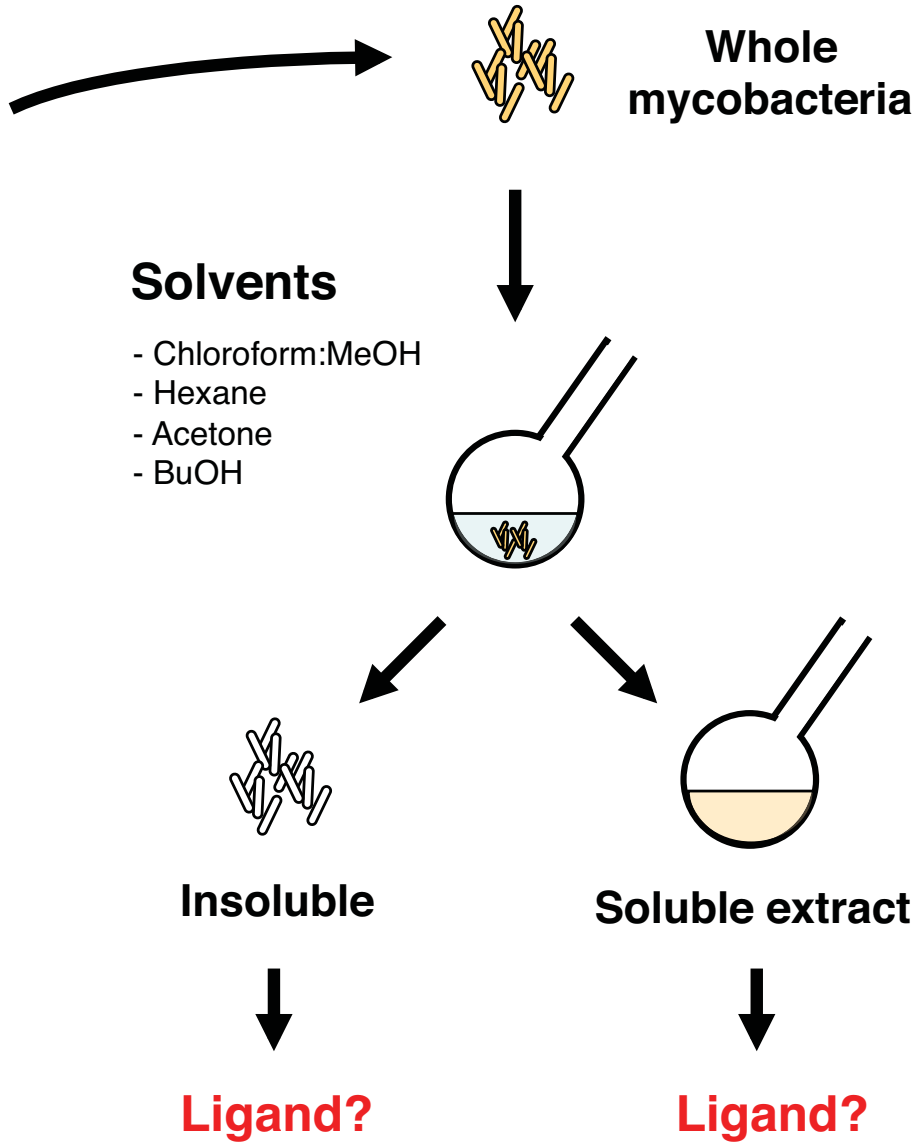
What is the ligand for Mincle?



Mycobacterial cell wall

What is the ligand for Mincle?





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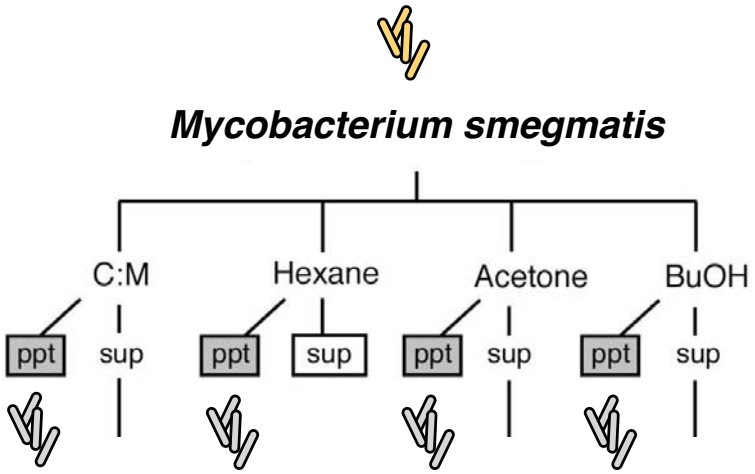
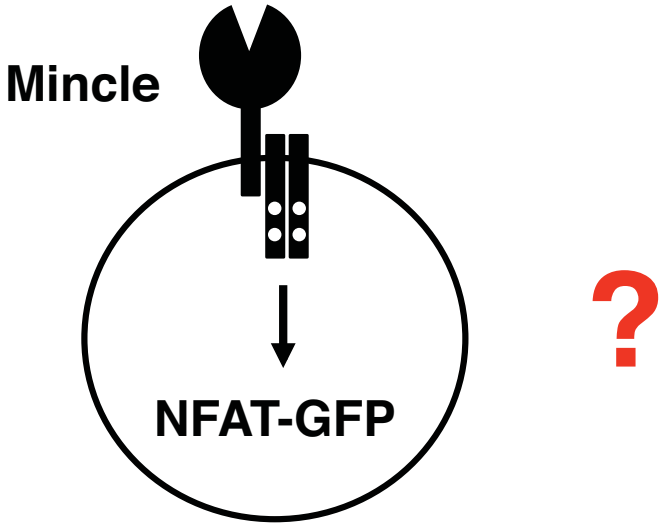


Insoluble fractions



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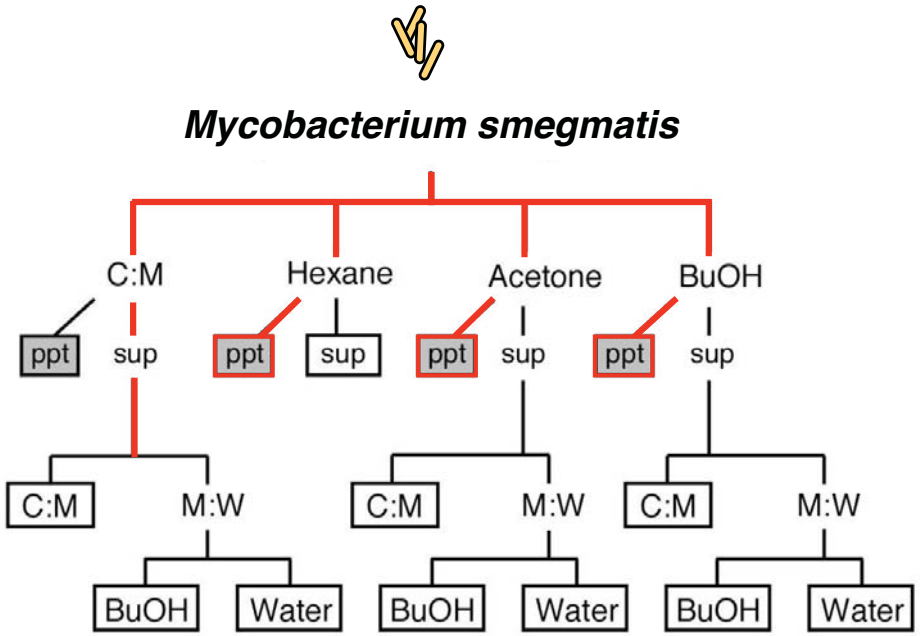
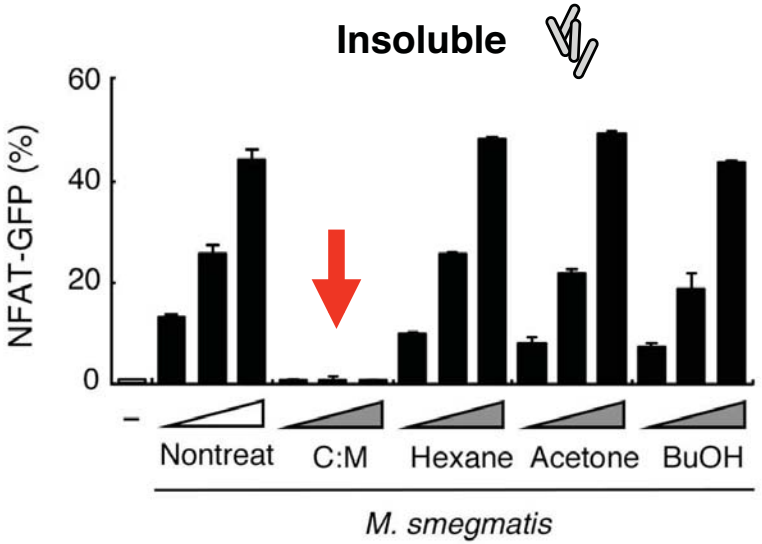
What is the ligand for Mincle?





C:M ; Chloroform:MeOH = 9:1

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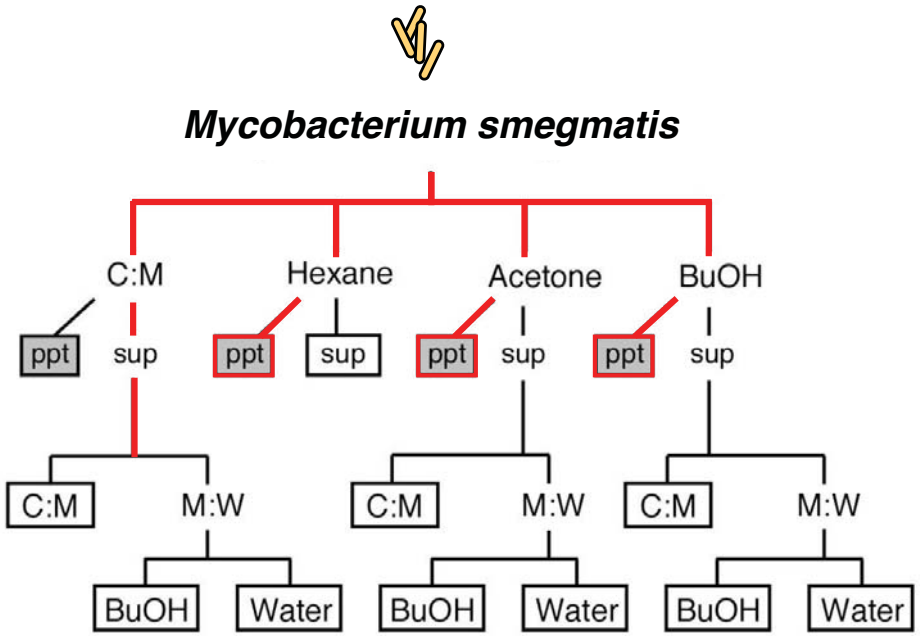

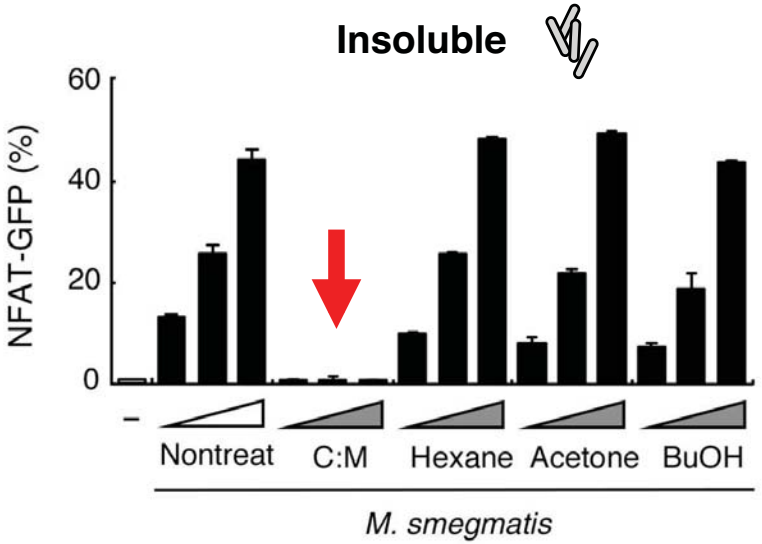

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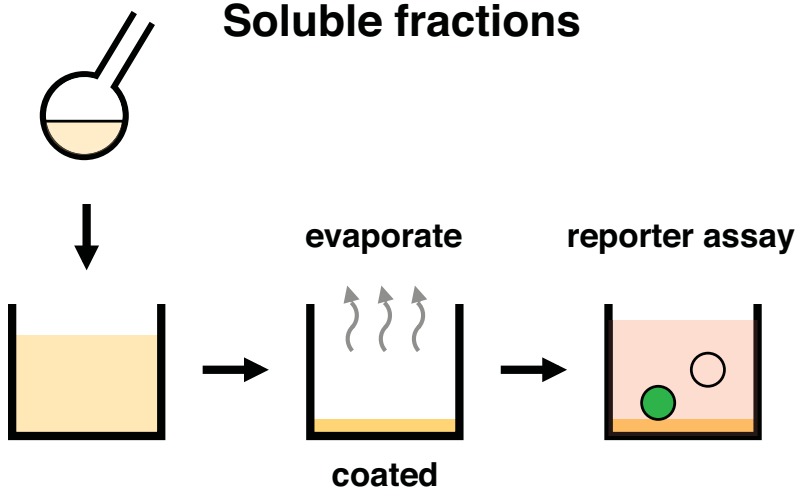
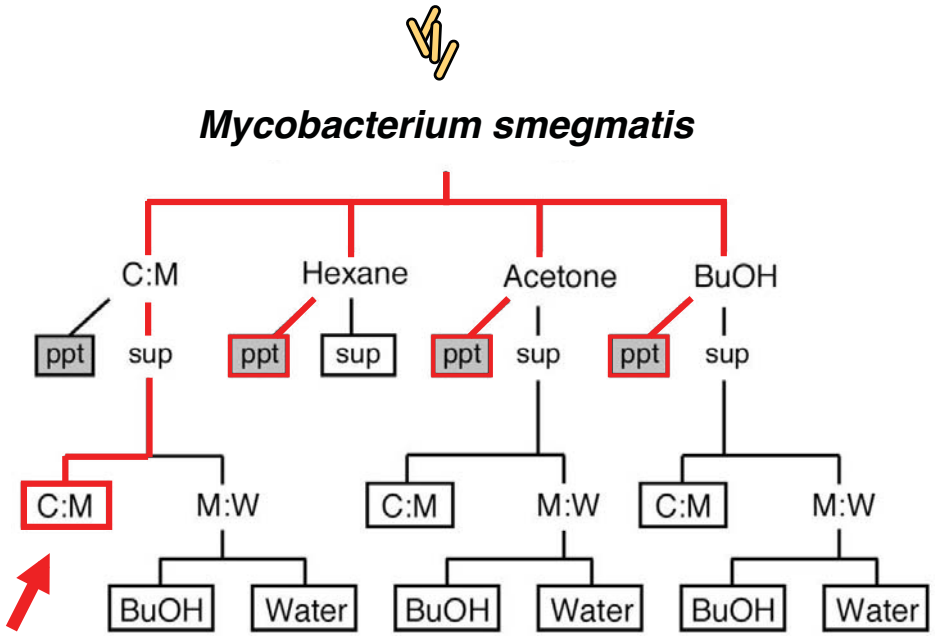
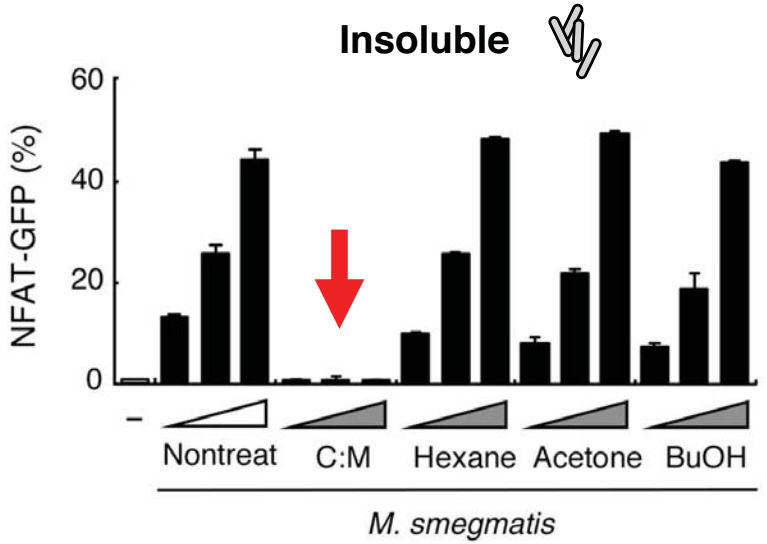
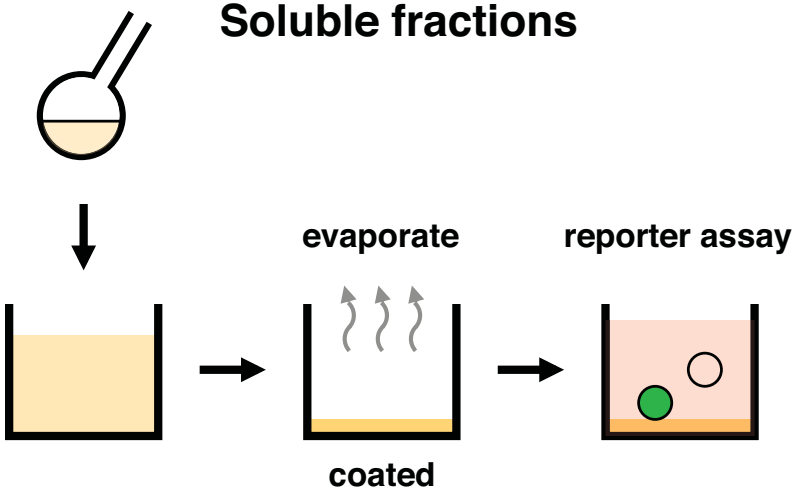
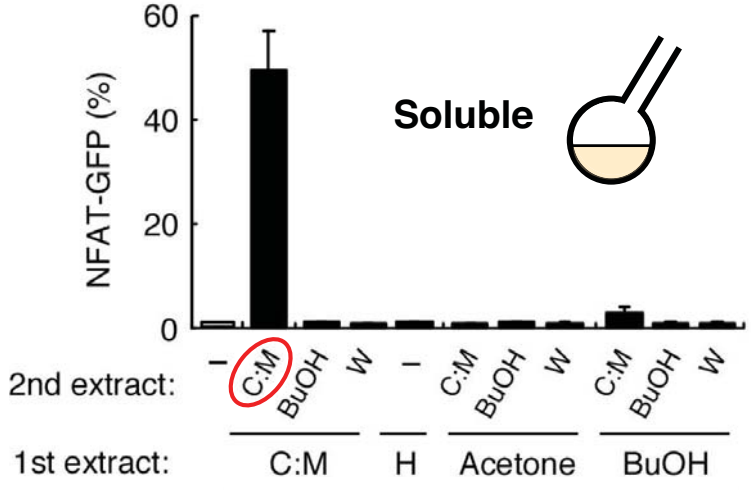


Ligand was extracted into “lipophilic” fraction









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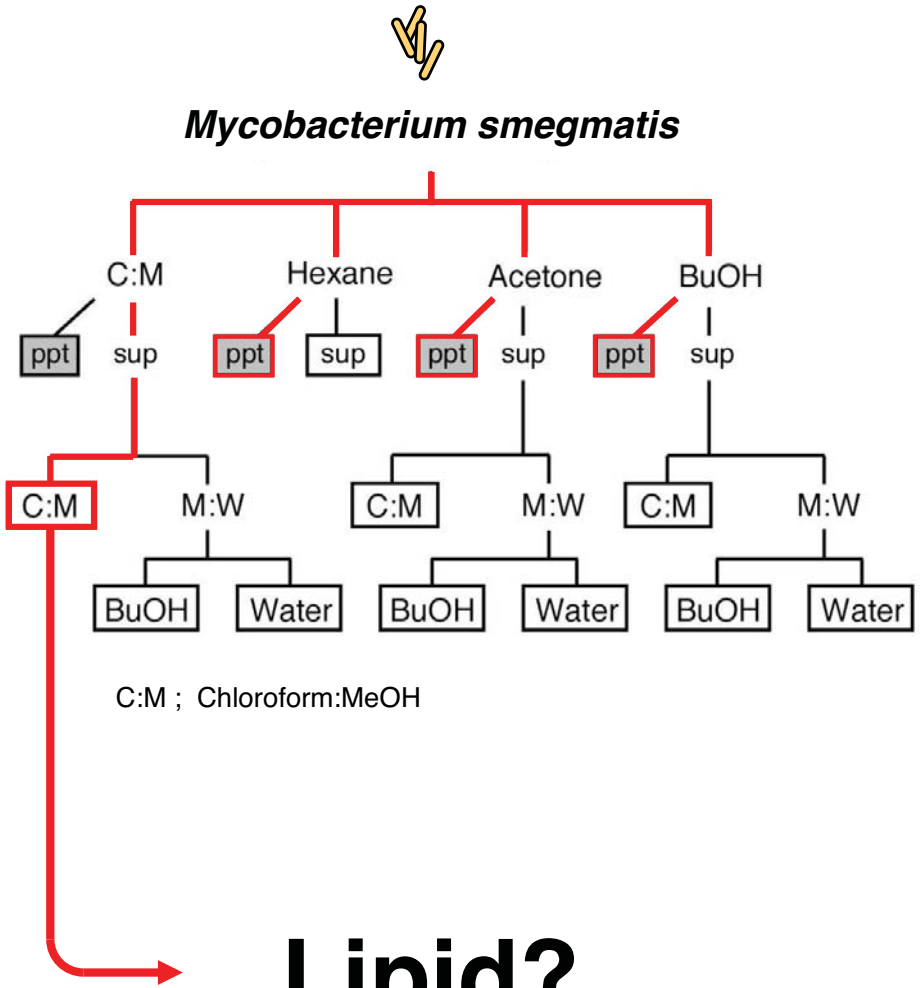
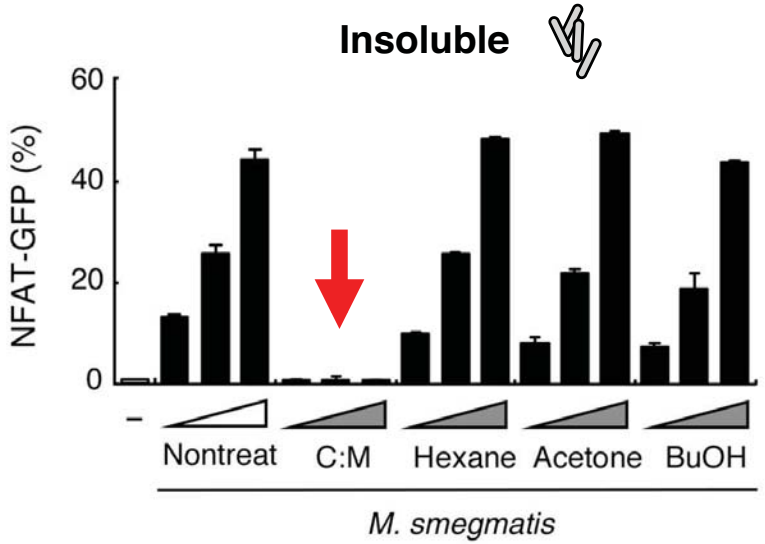
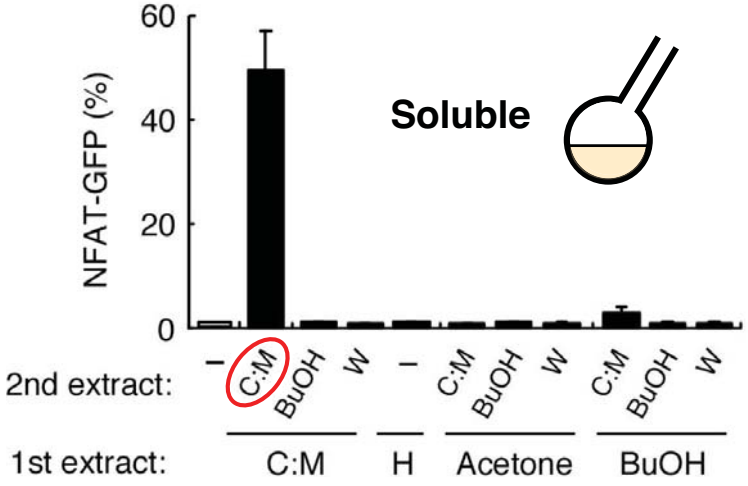
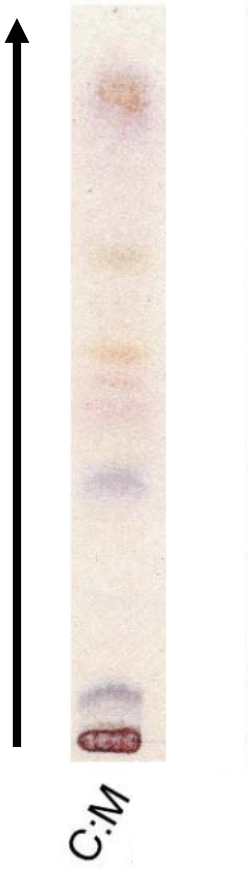






TLC (Thin Layer Chromatography)

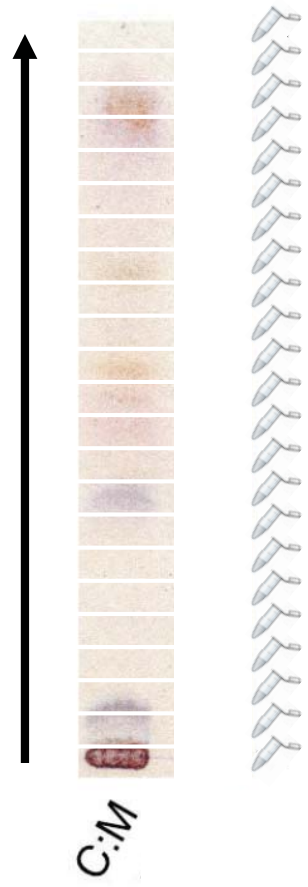


Solvent front

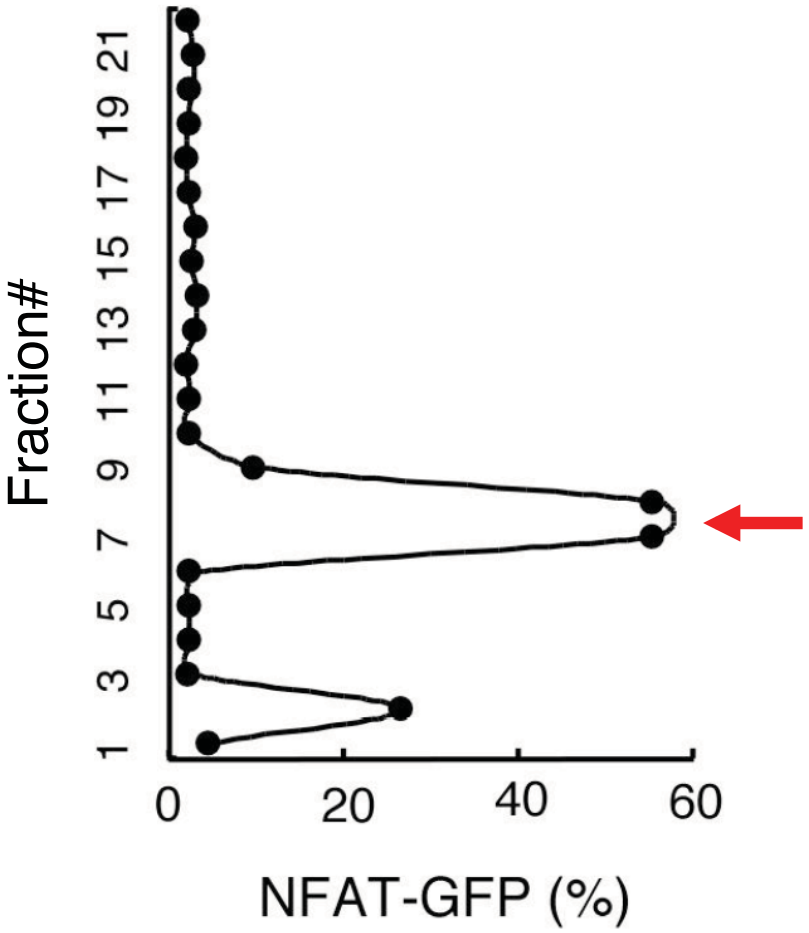
Sample spot

C:M = 9:1

TLC (Thin Layer Chromatography)



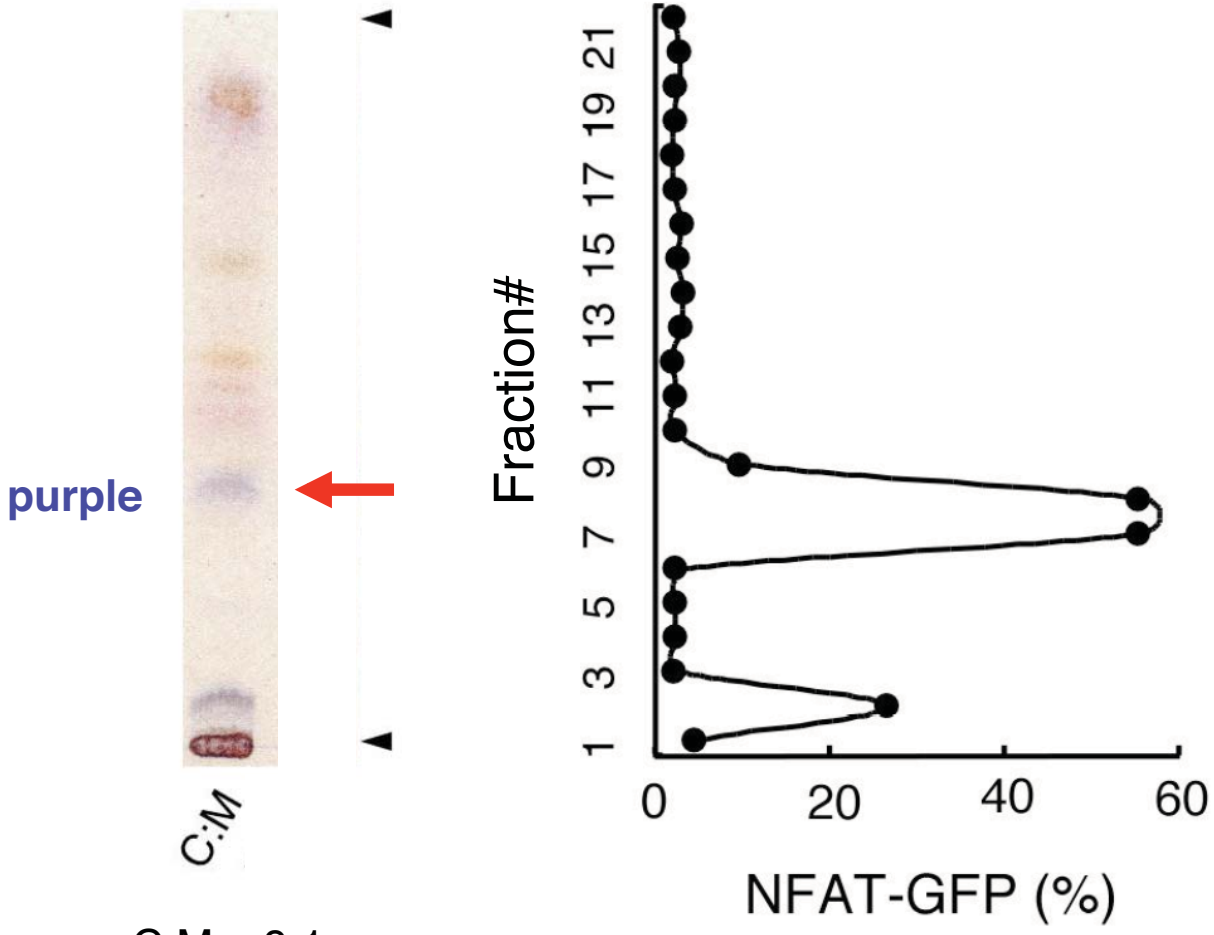
C:M = 9:1



Yasu Morita
Tetsuaki Ishikawa

Active fraction contains sugar and lipid moiety

Orcinol stain



C:M = 9:1

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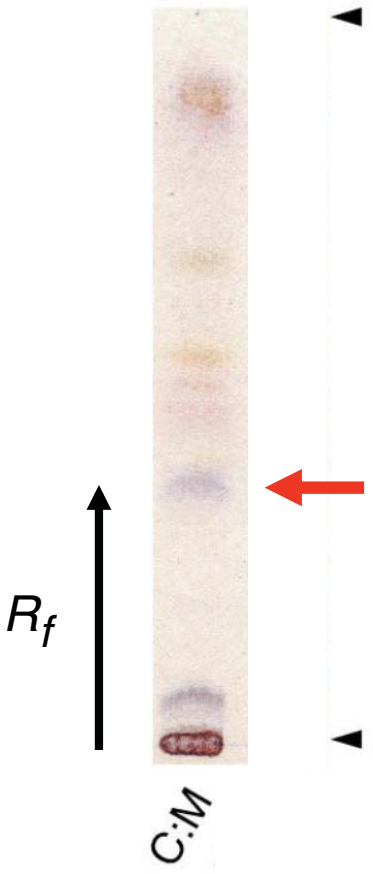
Tetsuaki Ishikawa

Active fraction contains sugar and lipid moiety

Glycolipid

Orcinol stain



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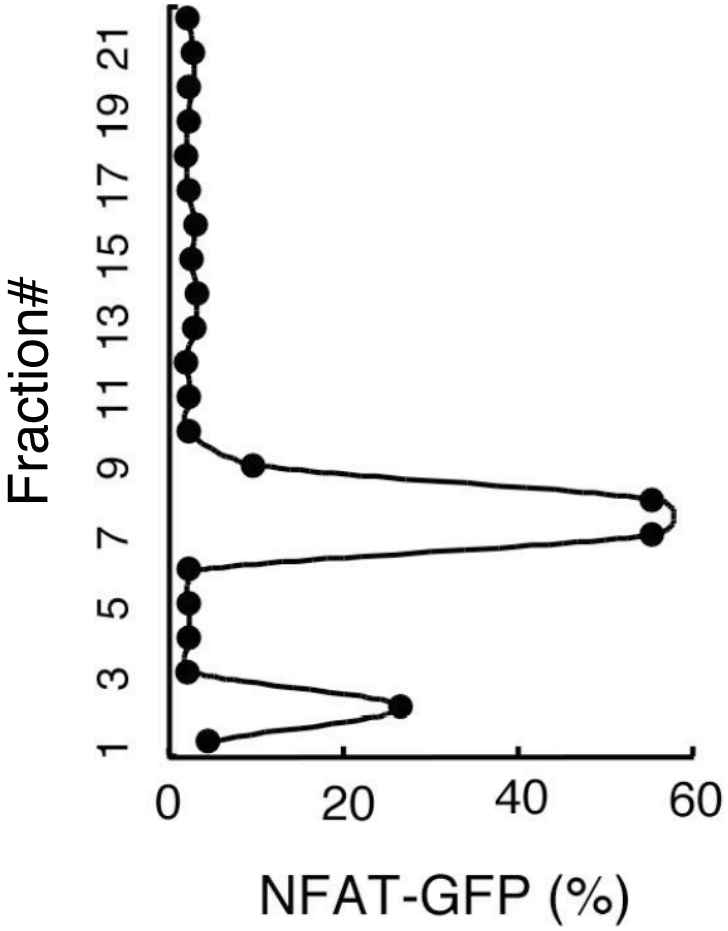

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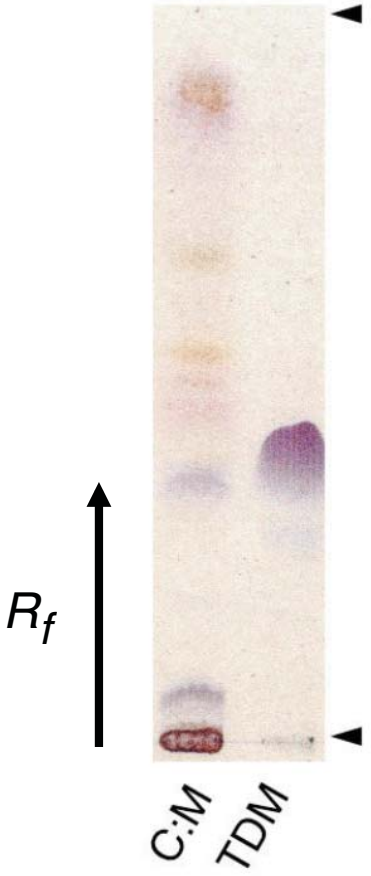

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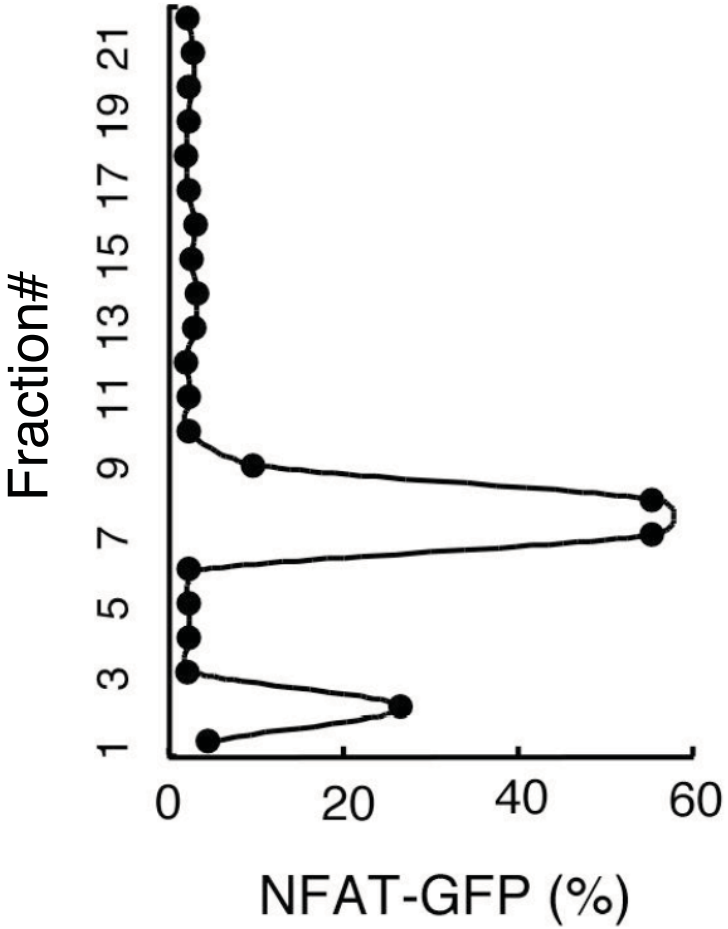
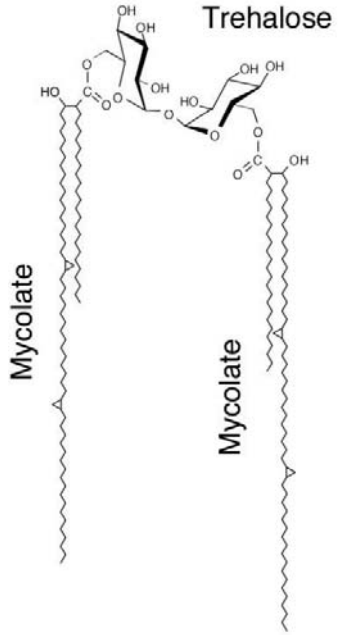
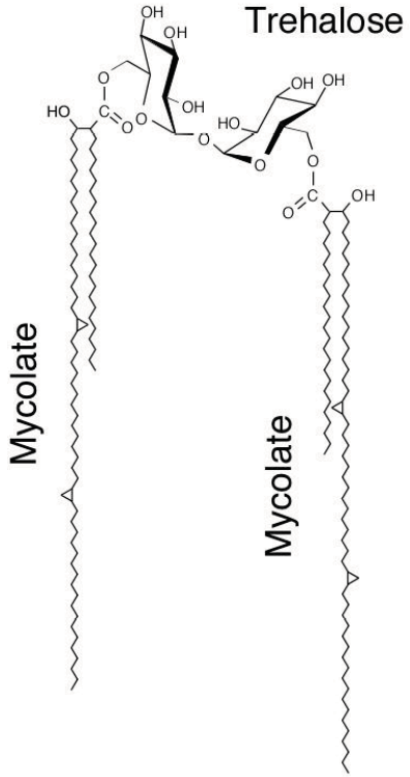


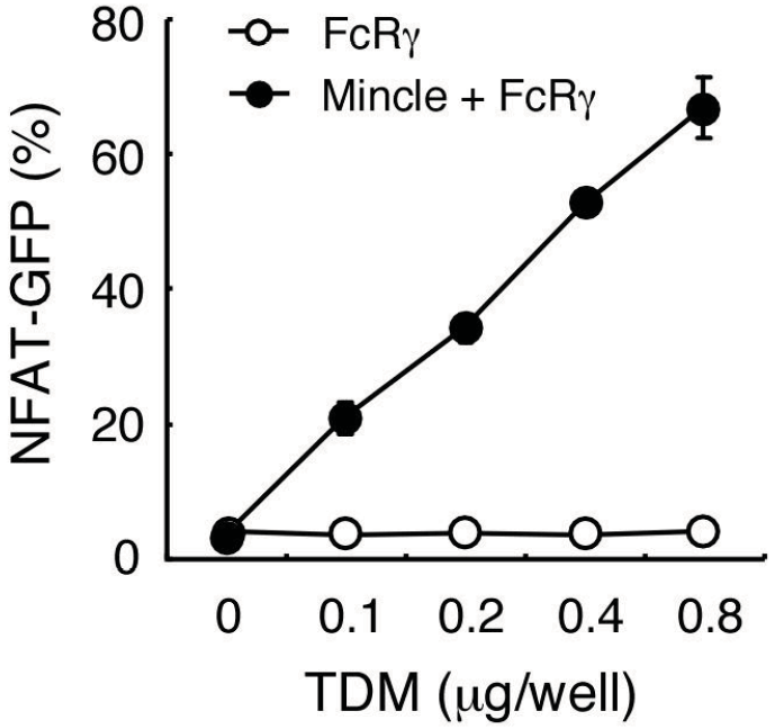
TDM

Trehalose dimycolate



TDM (trehalose 6,6’ dimycolate)





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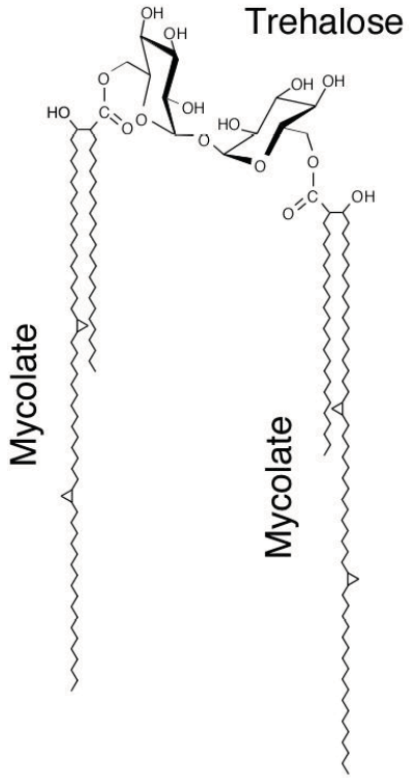
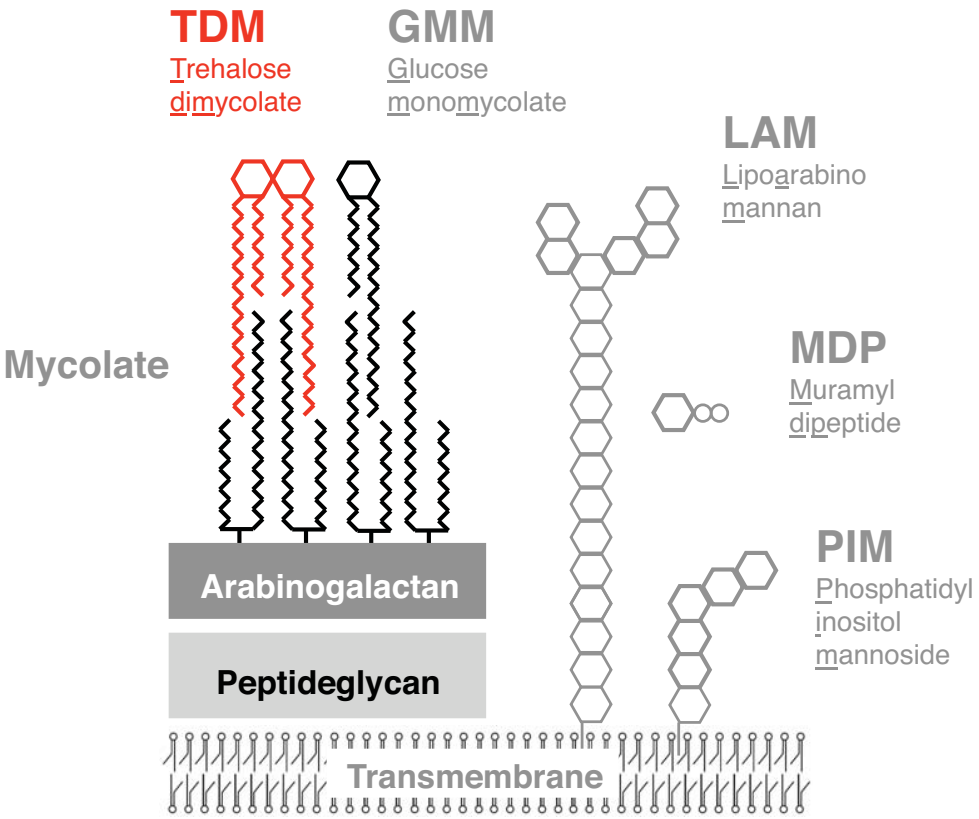
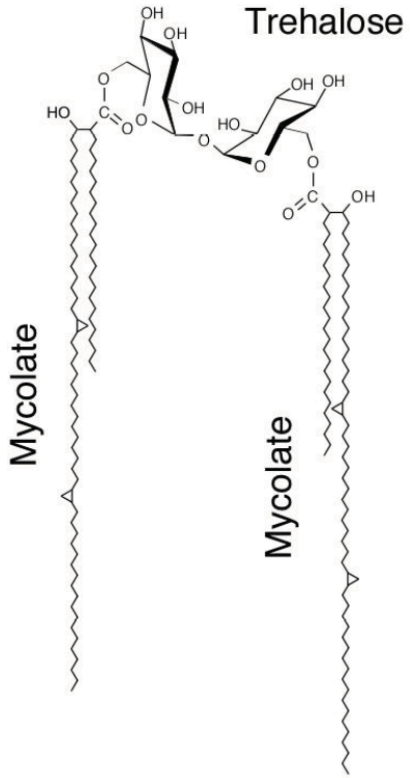


- unique mycobacterial glycolipid



Mycobacteria

TDM (trehalose 6,6’ dimycolate)



- unique mycobacterial glycolipid

- immunostimulant called “cord factor”

Kekkaku 9:521-4., 1955

家兎肺臓における実験的結核性空洞の形成

その 4　流動パラフィン抽出液による空洞形成

国立療養所刀根山病院　(院長　渡辺三郎博士)

山口　正民・小川　弥栄・遠藤　一男・竹内　弘之

矢坂　茂・中村　滋・山村　雄一

(本論文要旨は昭和 29 年 11 月第3回日本アレルギー学会総会において発表した。)

(受付　昭和 30 年4月8日)

第 1 表　Oil-extract の抽出法

加熱死菌の乾燥菌体 (BCG 100 g)

9 倍量の流動パラフィン添加
60°C 4 時間，攪拌

沈澱　3,000 rpm 1 時間遠沈　上清

沈澱：3 倍量の流動パラフィン添加，攪拌

沈澱　上清 → 粗抽出液

沈澱　20,000 rpm 1 時間遠沈　上清

9 倍容量のエーテル添加

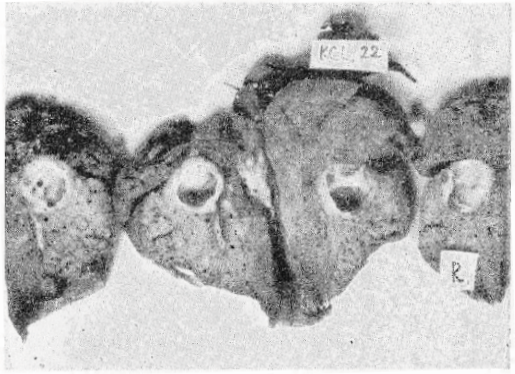
Chamberland L_3 沪過器にて沪過

エーテル除去

Oil-extract

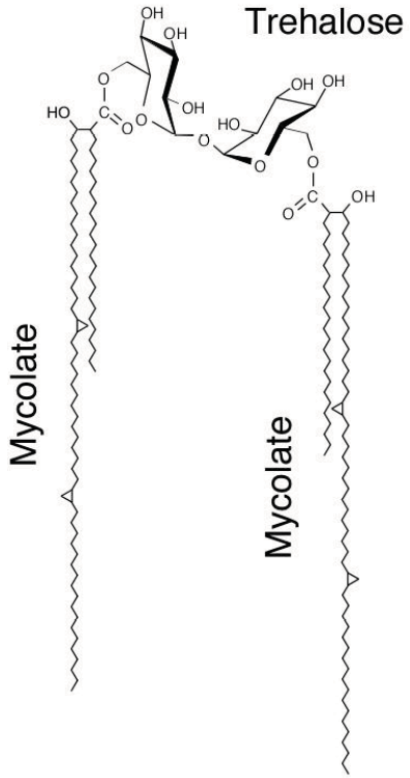
Cord factor
(= TDM)

Lung cavity



注；原液注射 30日後の空洞（非感作家兎）

TDM (trehalose 6,6’ dimycolate)



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- major adjuvant component of CFA

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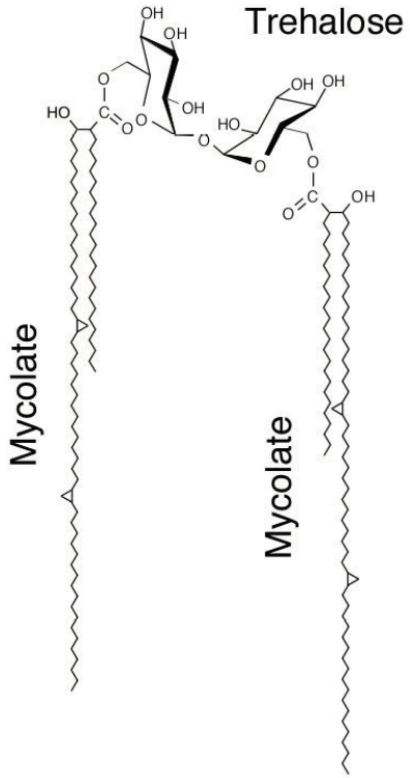

- unique mycobacterial glycolipid
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- major adjuvant component of CFA
- specific receptor??

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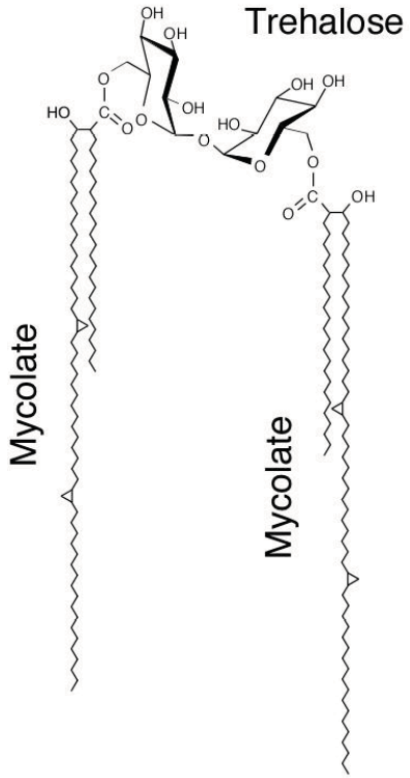

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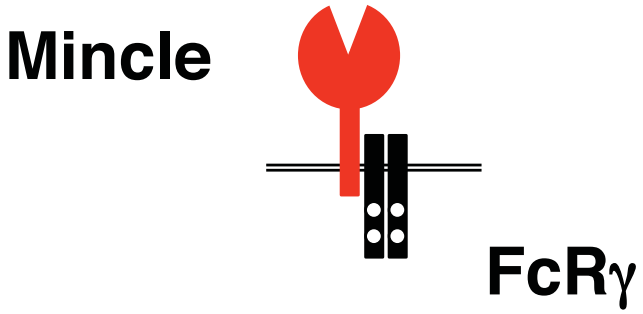
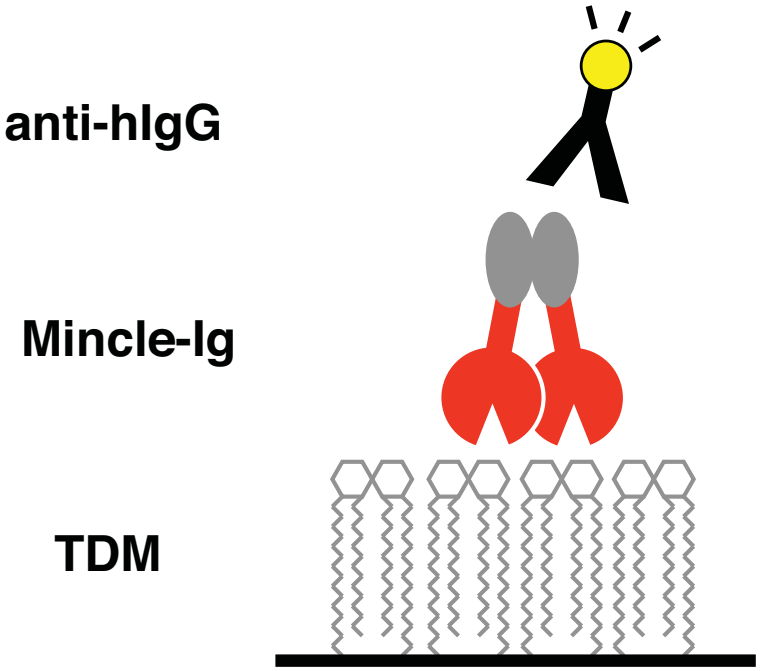
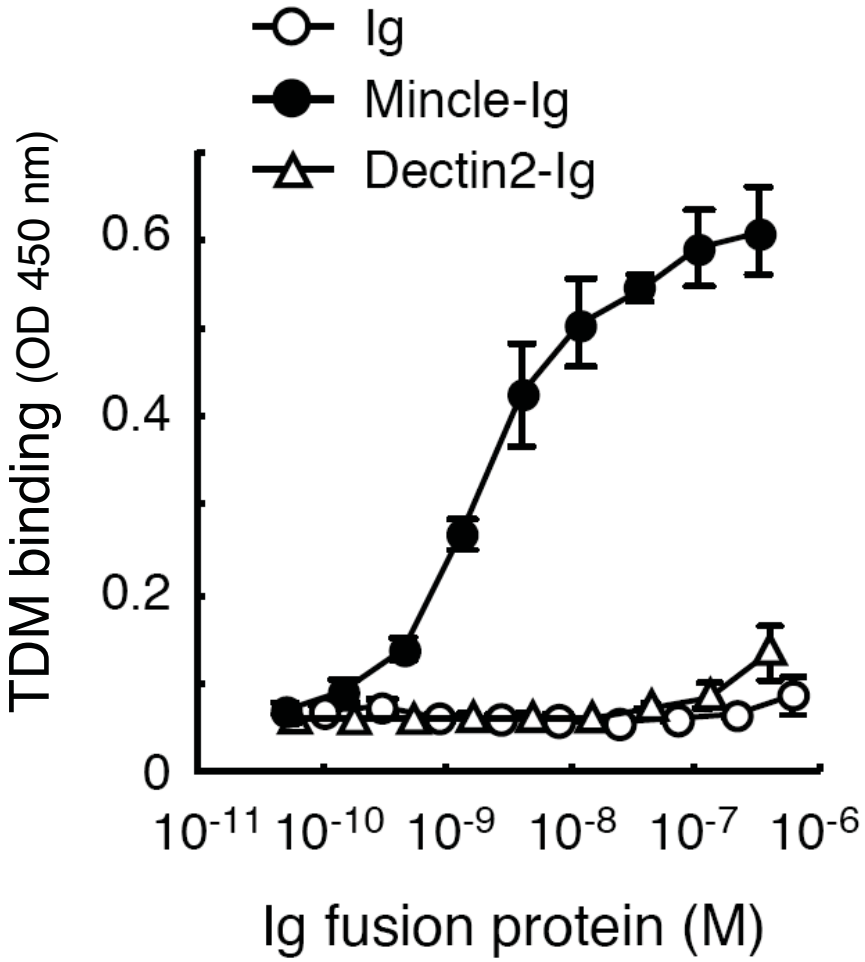


Direct receptor?

Mincle is a direct receptor for TDM





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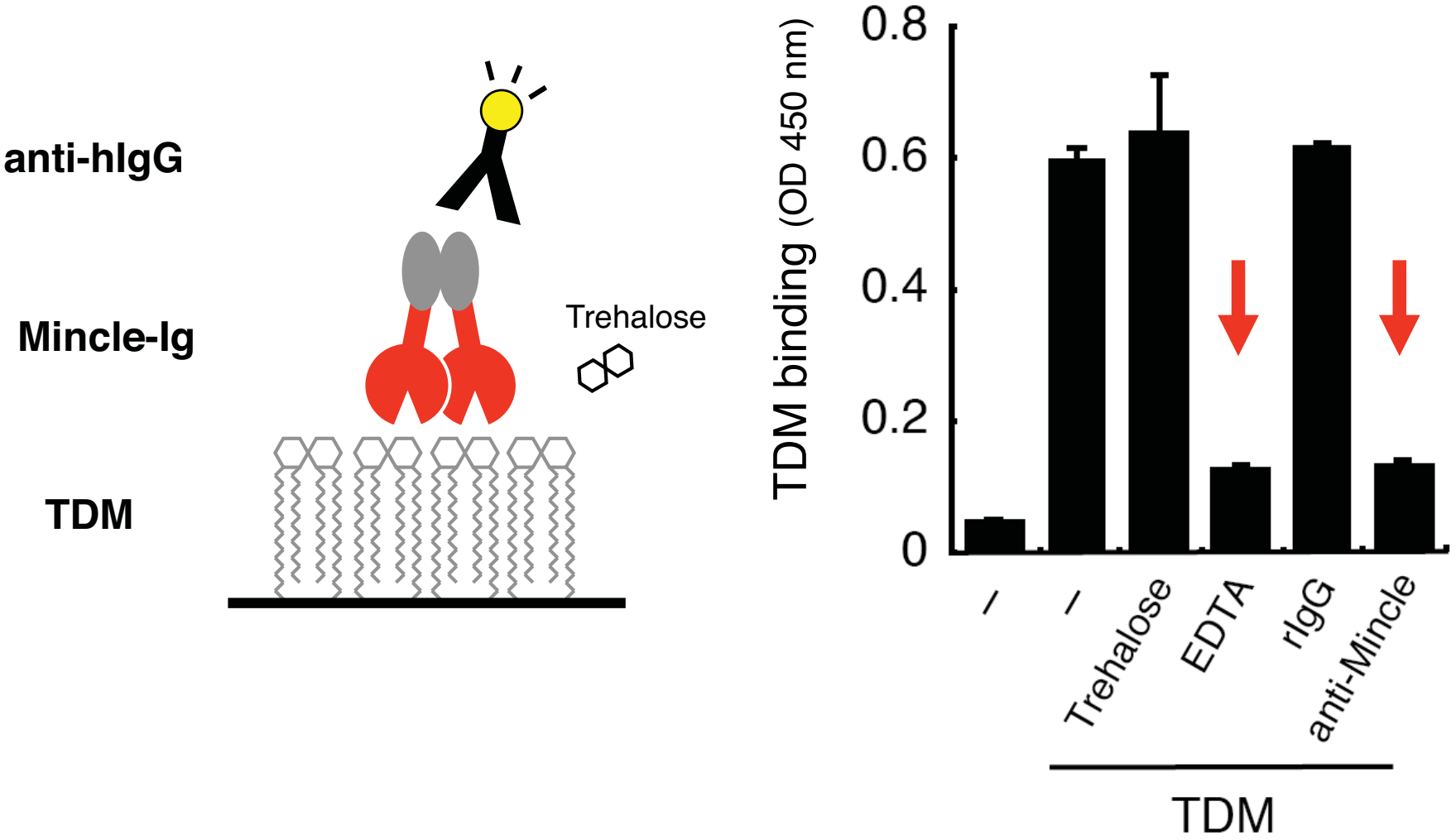
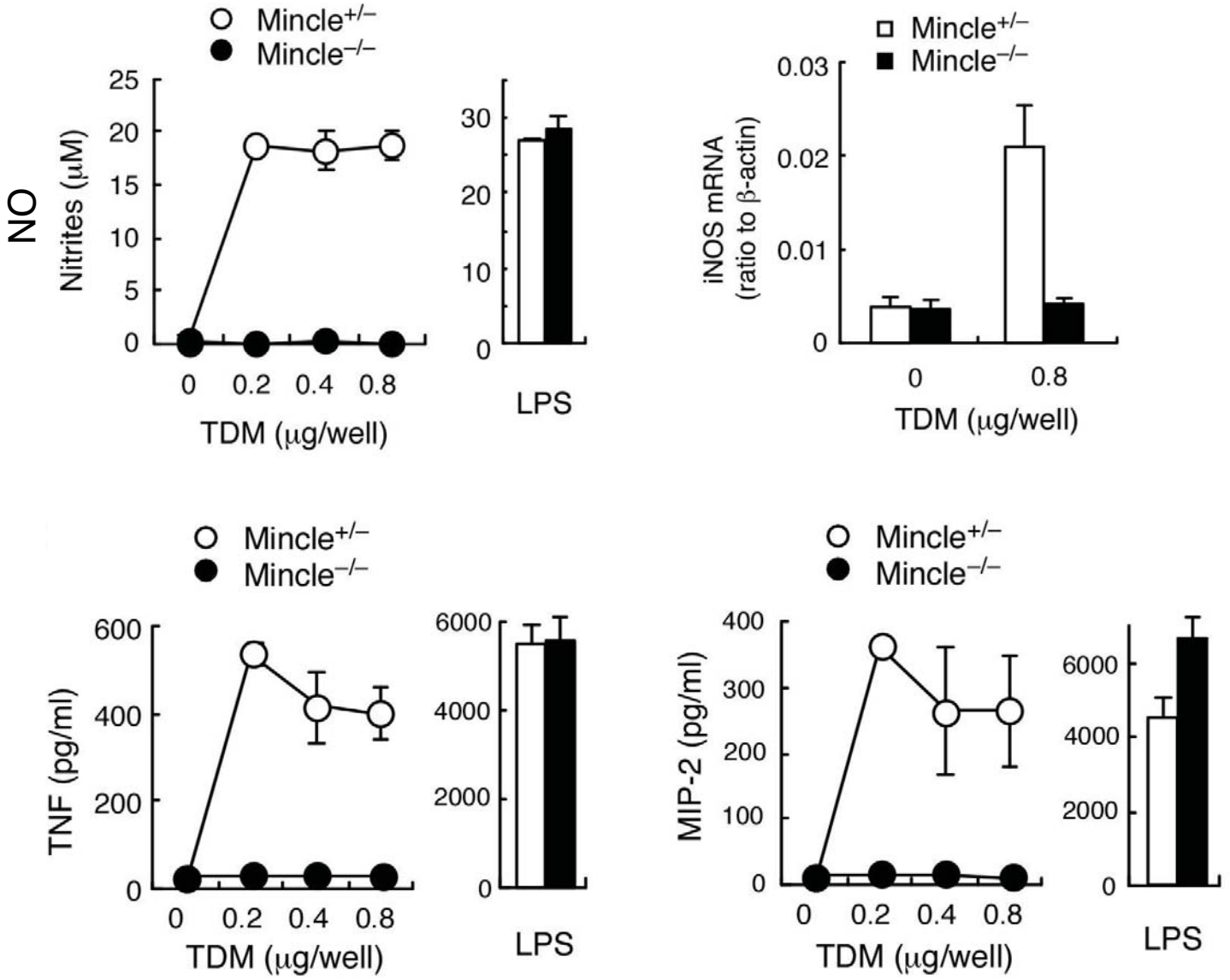


Mincle-deficient mice?

Mincle is essential for TDM-induced Mϕ activation

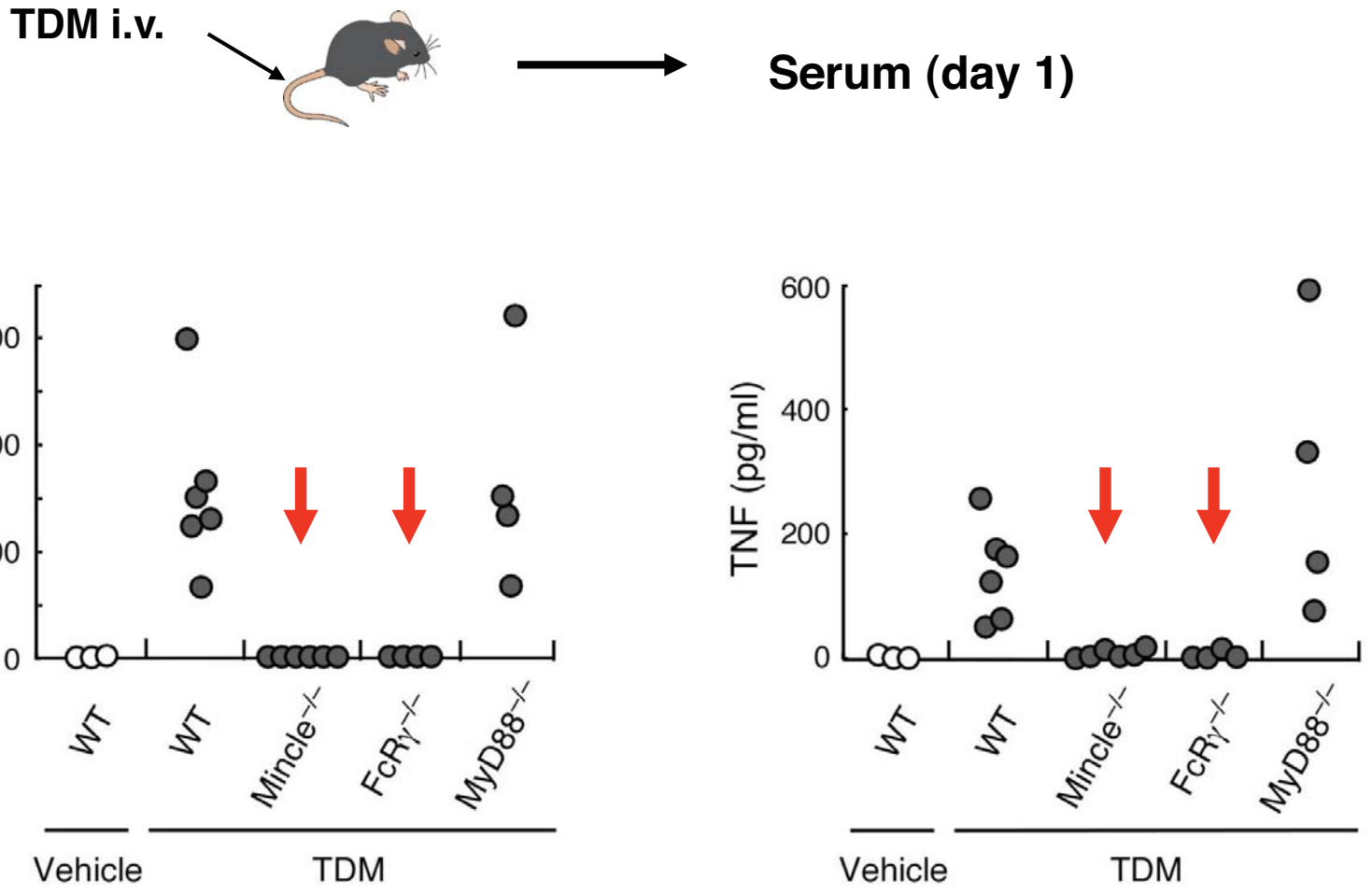
BMMϕ



Shizuo Akira

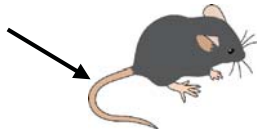
In vivo response?

TDM-induced systemic inflammation



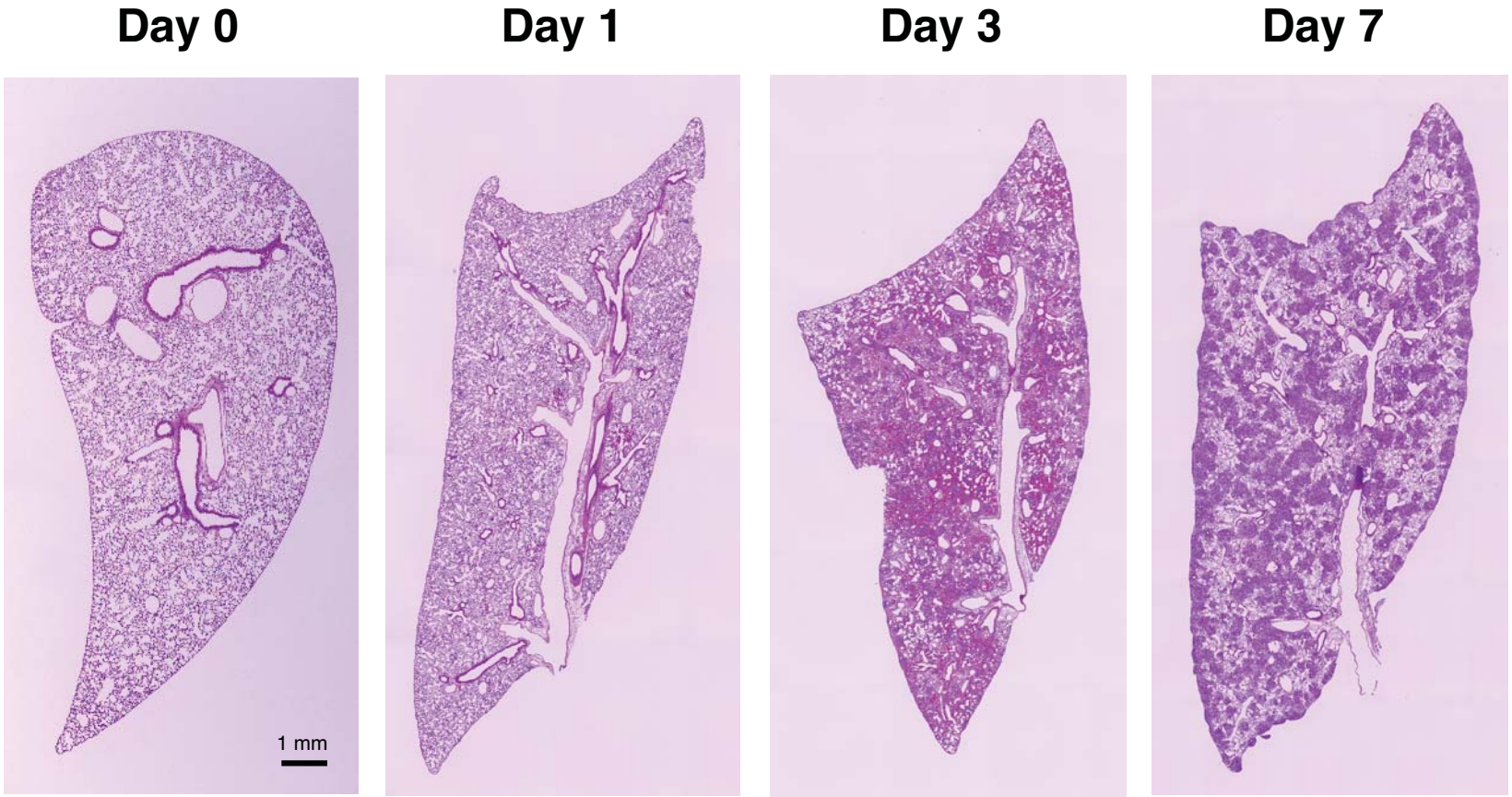
TDM-induced lung inflammation

TDM i.v.



Lung (day 0, 1, 3, 7)

H&E staining



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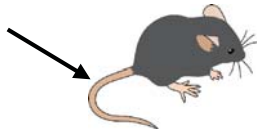
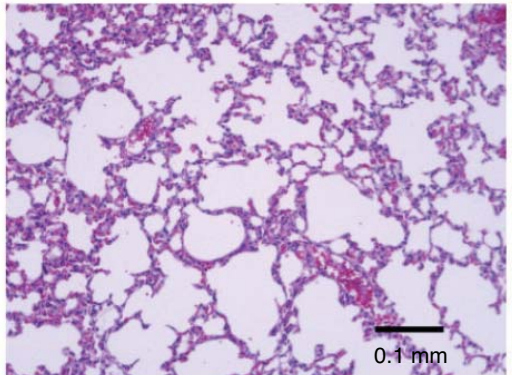
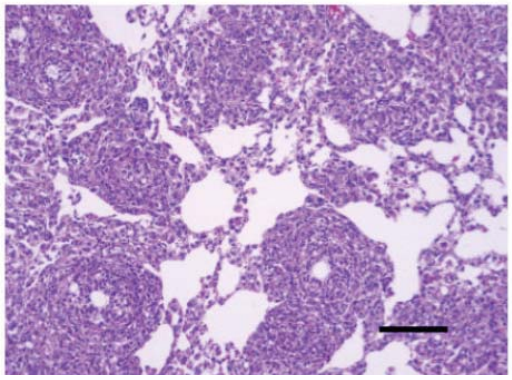
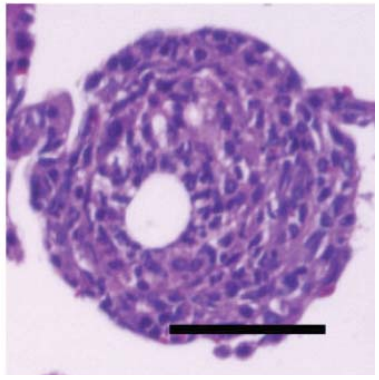


Lung (day 7)

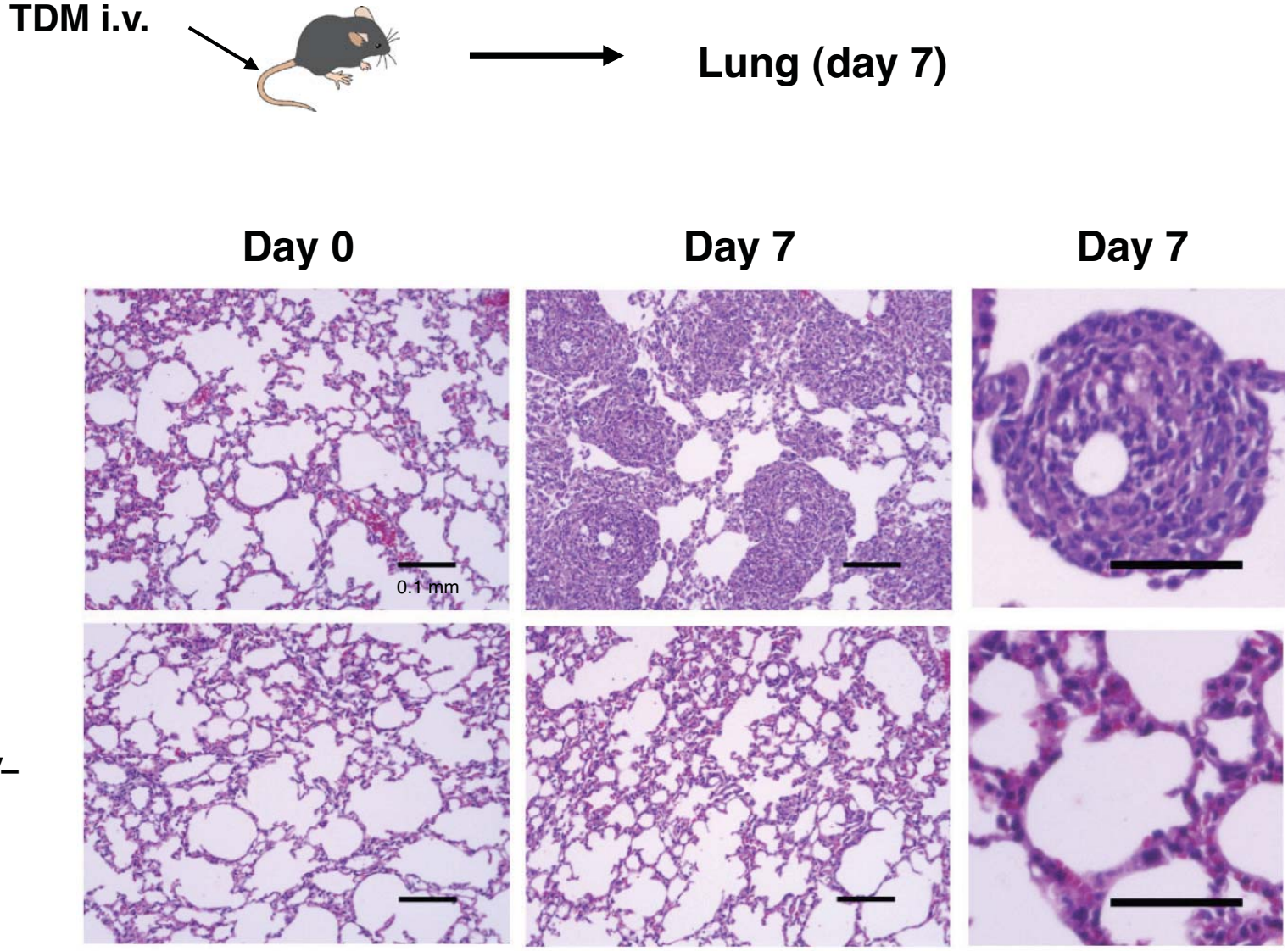
	Day 0	Day 7	Day 7
WT			

Granuloma

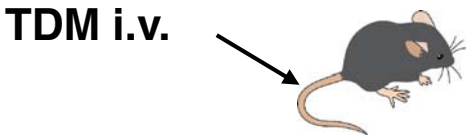
肉芽腫

H&E staining / lung

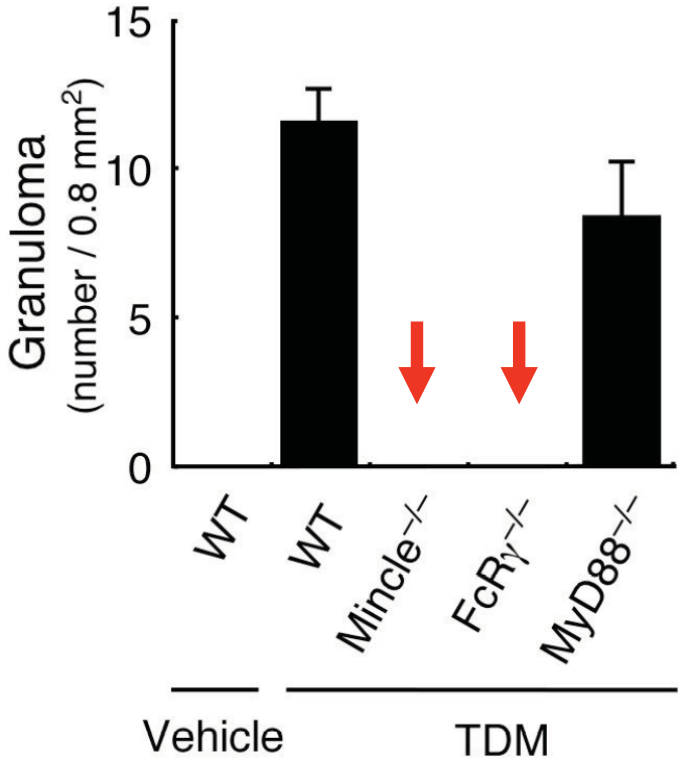
TDM-induced lung inflammation

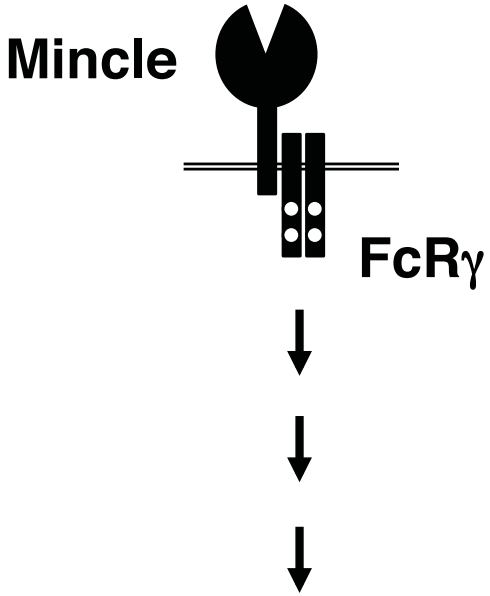


Mincle mediates granuloma-forming signal *in vivo*



Lung (day 7)

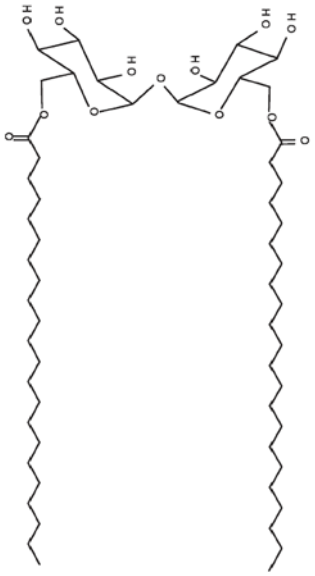




Granuloma

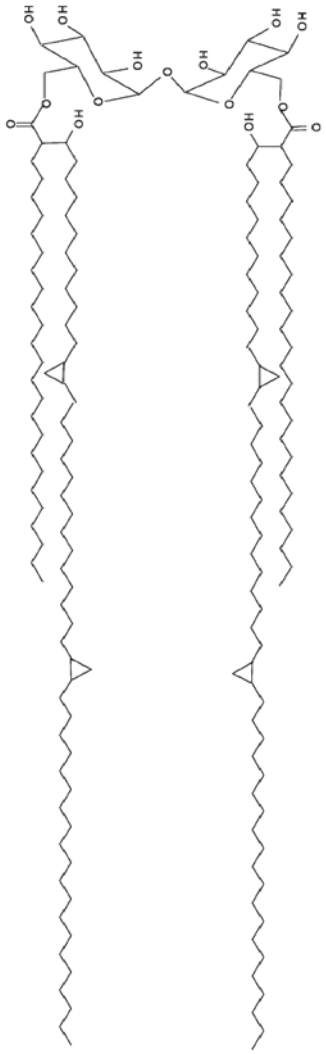
肉芽腫

Synthetic adjuvant, TDB



TDB

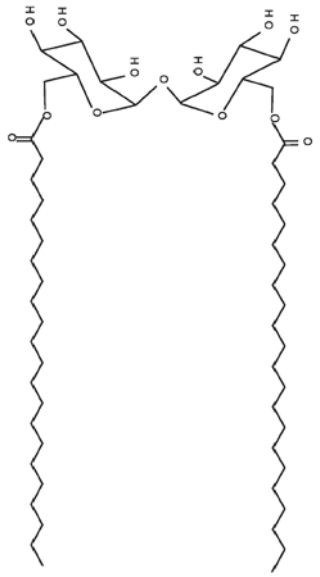
Trehalose dibehenate



TDM

Trehalose dimycolate

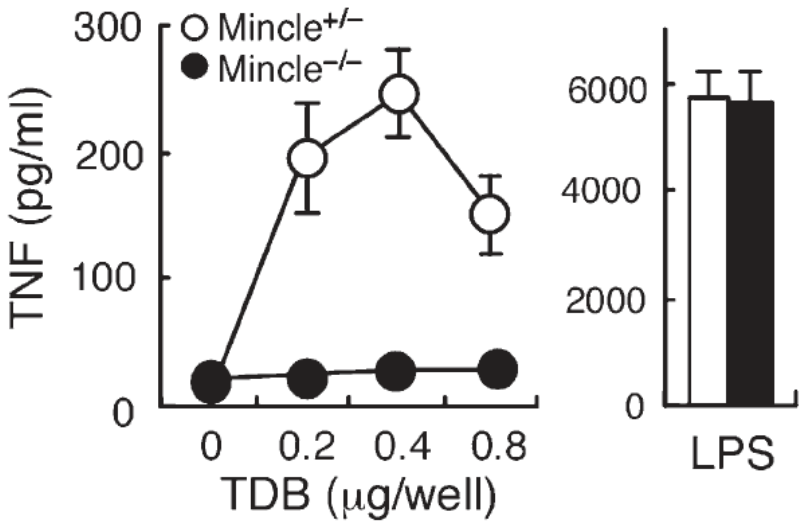
TDB acts through Mincle

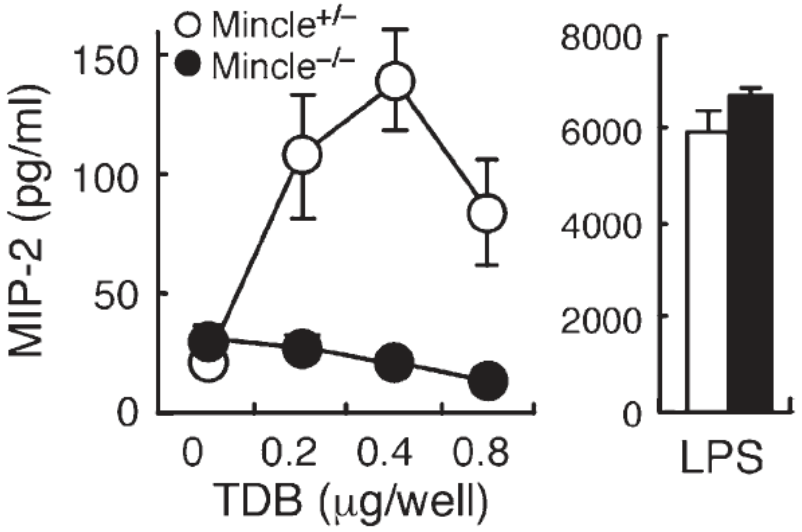


TDB

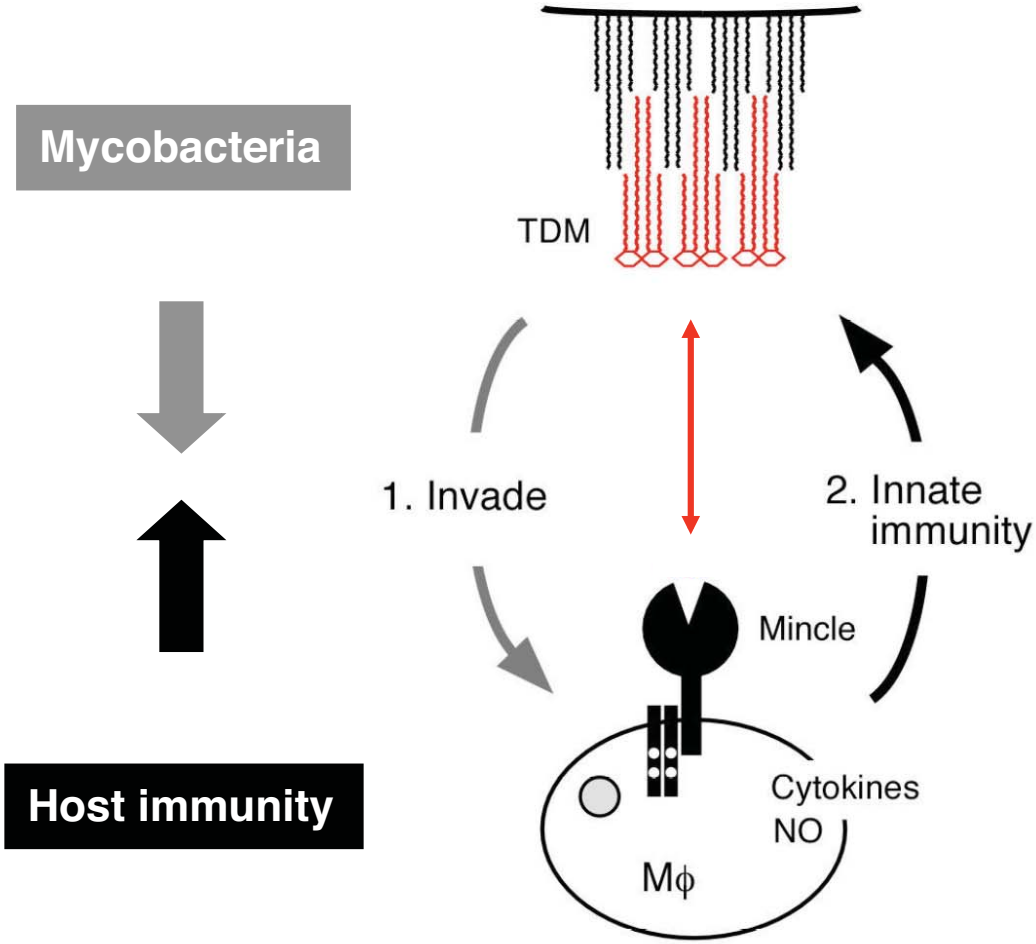
Trehalose dibehenate

BMMϕ





Evolutional struggle between host and mycobacteria?



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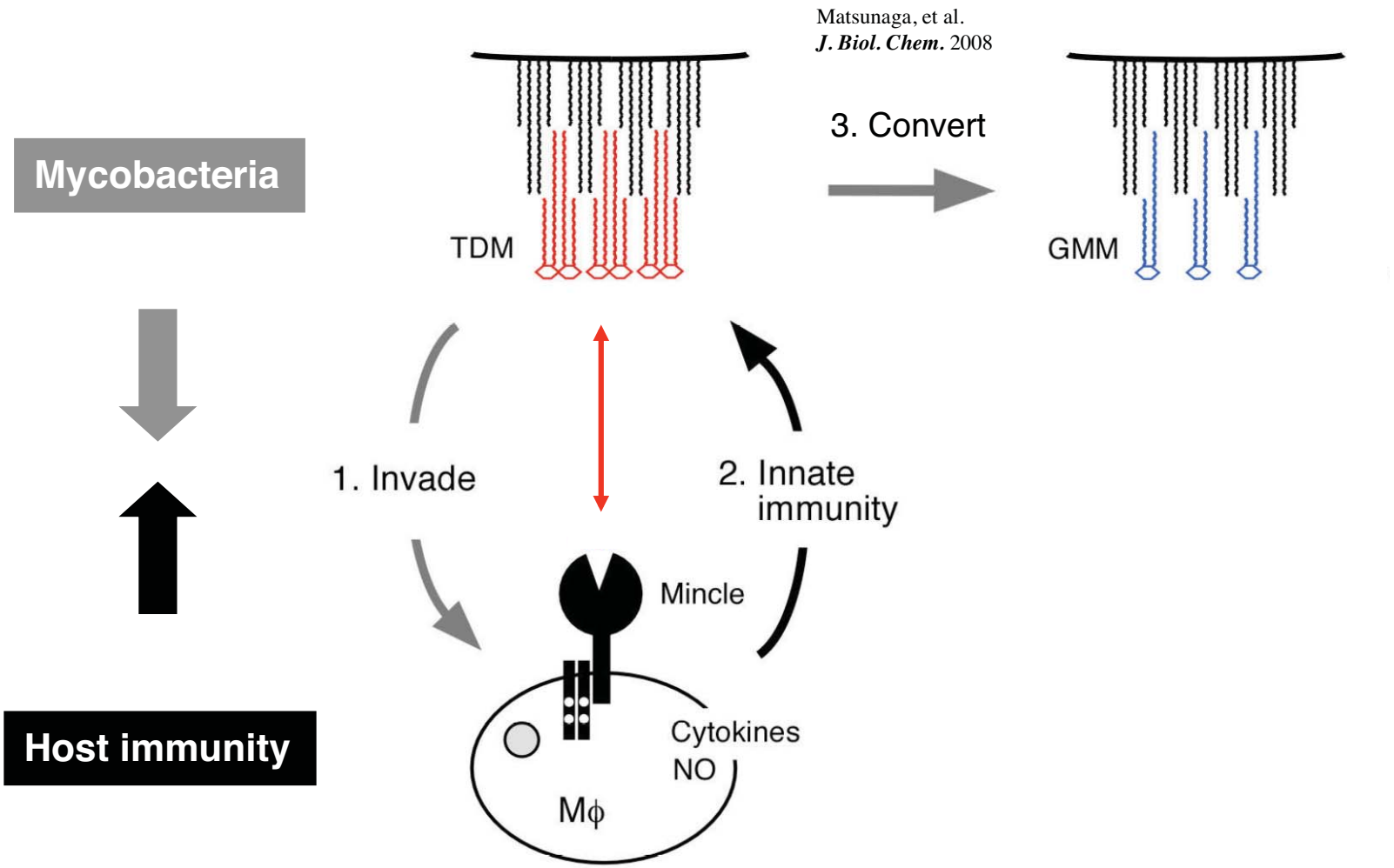

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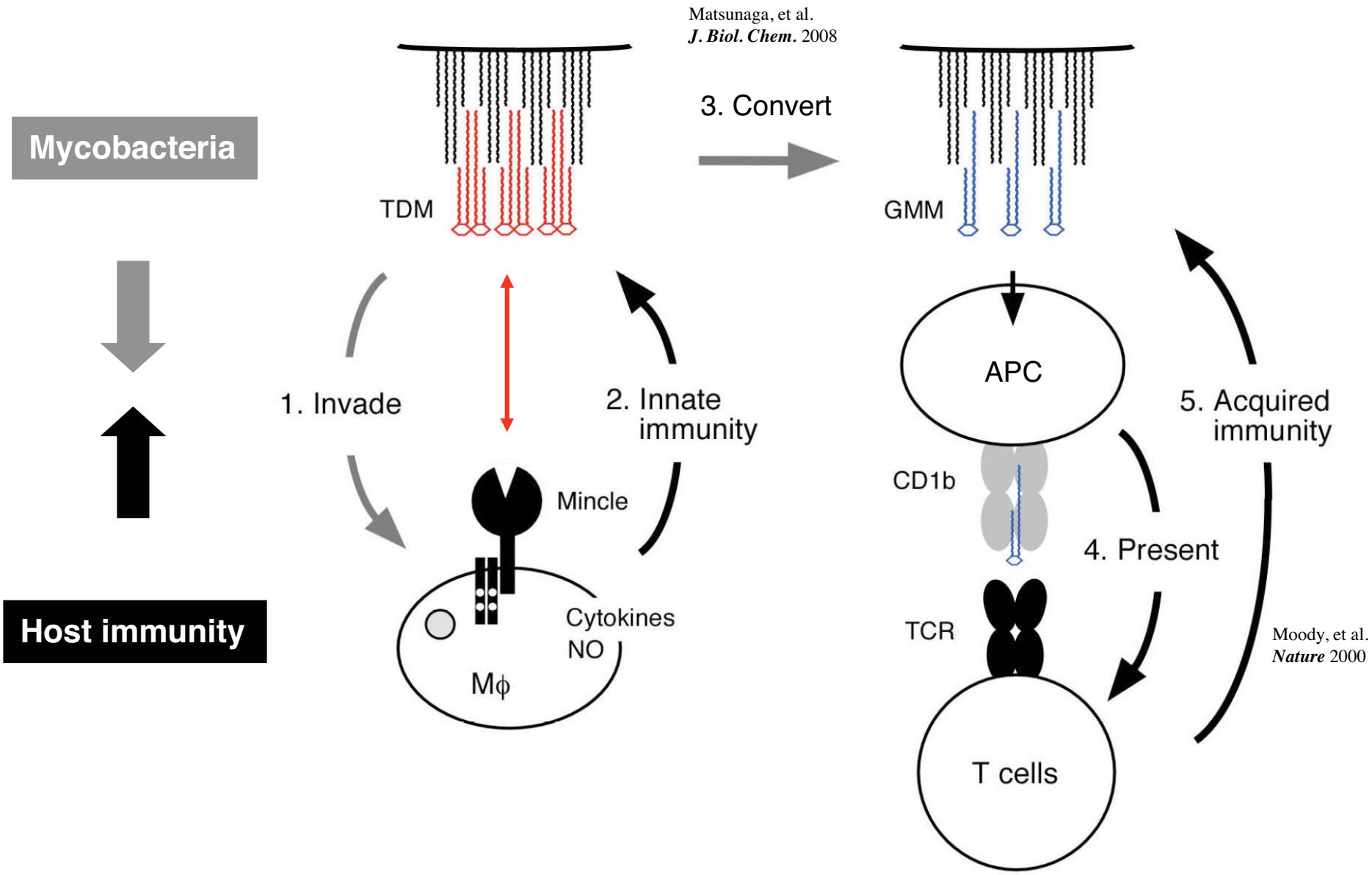

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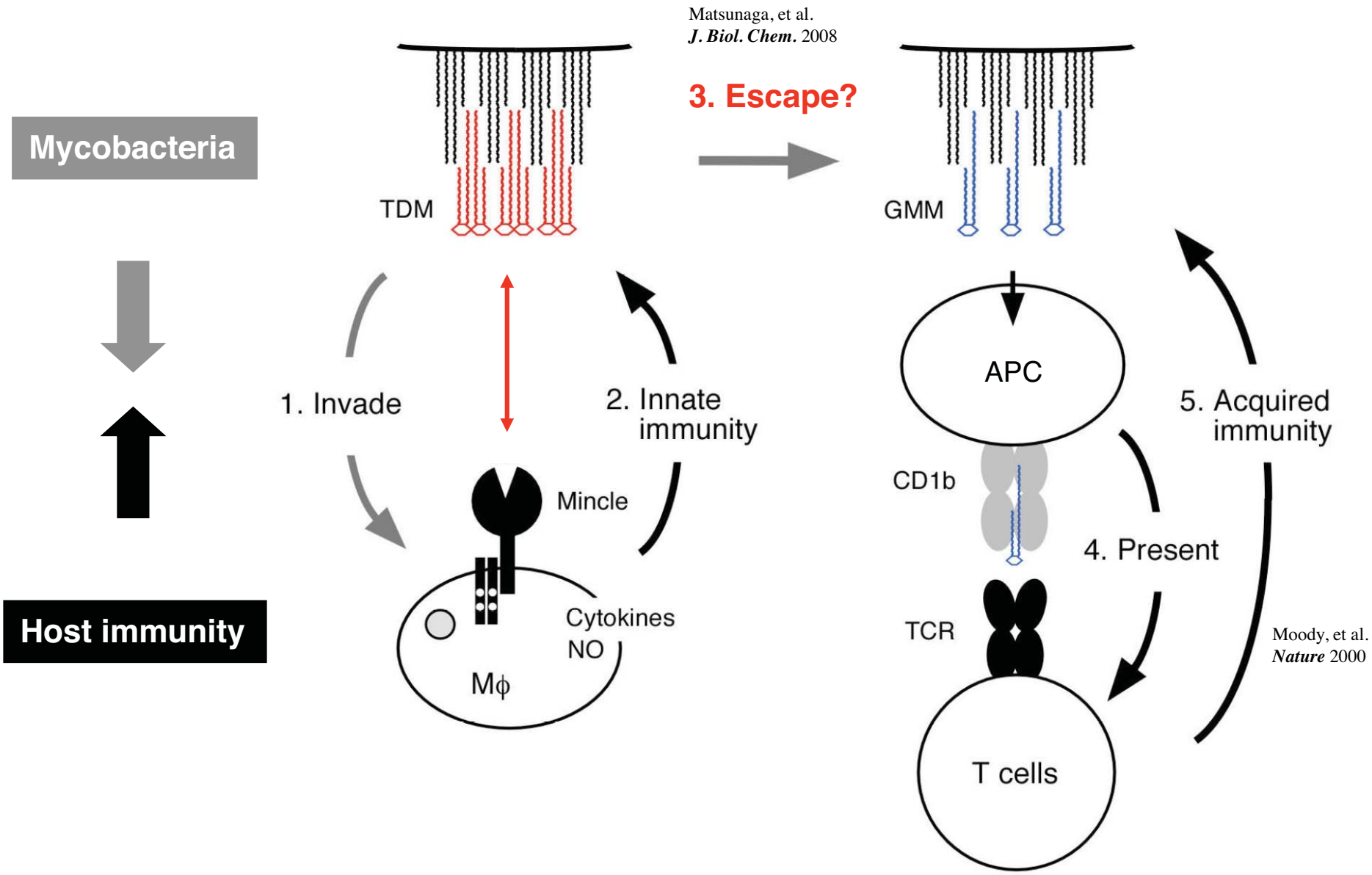


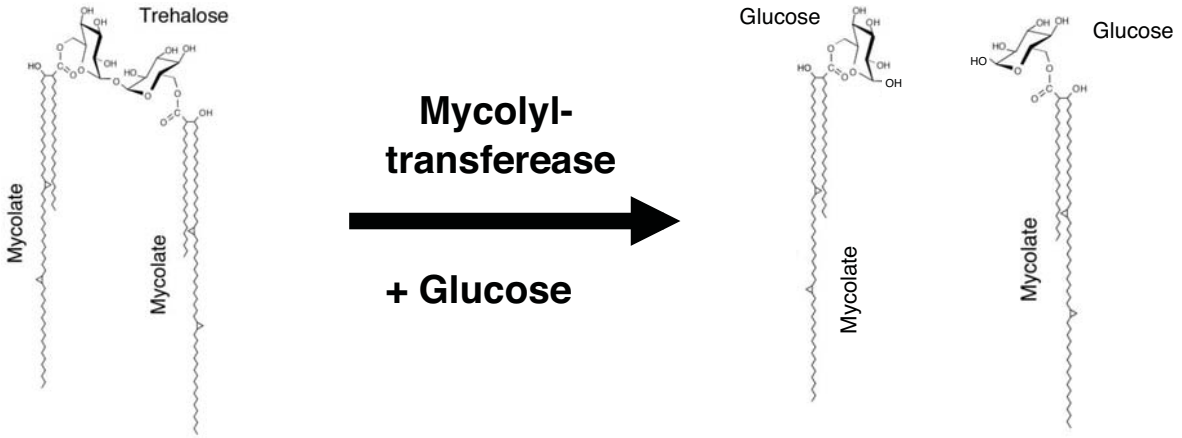
In vitro mimic of bacterial conversion

TDM
Trehalose dimycolate

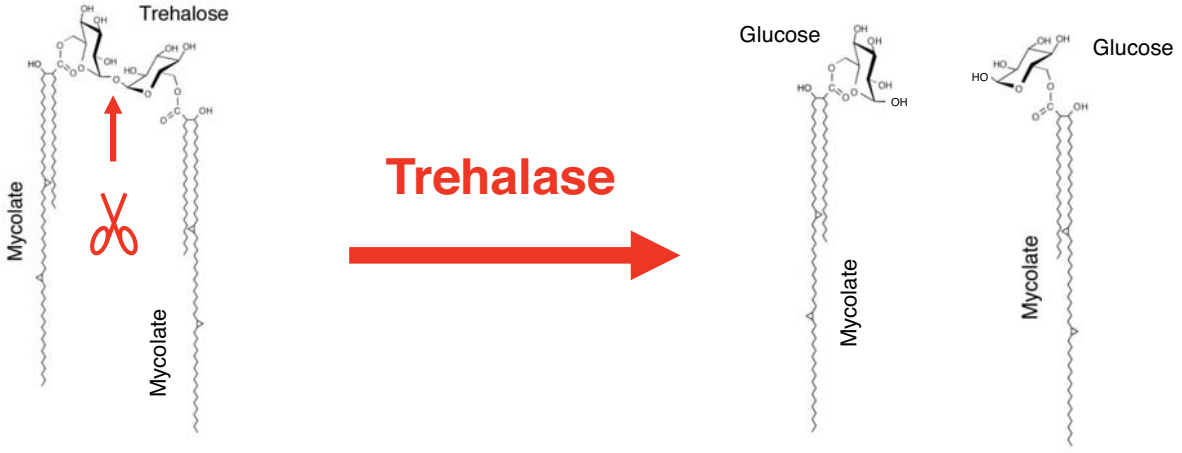
Conversion

GMM
Glucose monomycolate

Mycobacteria



***In vitro* mimic**



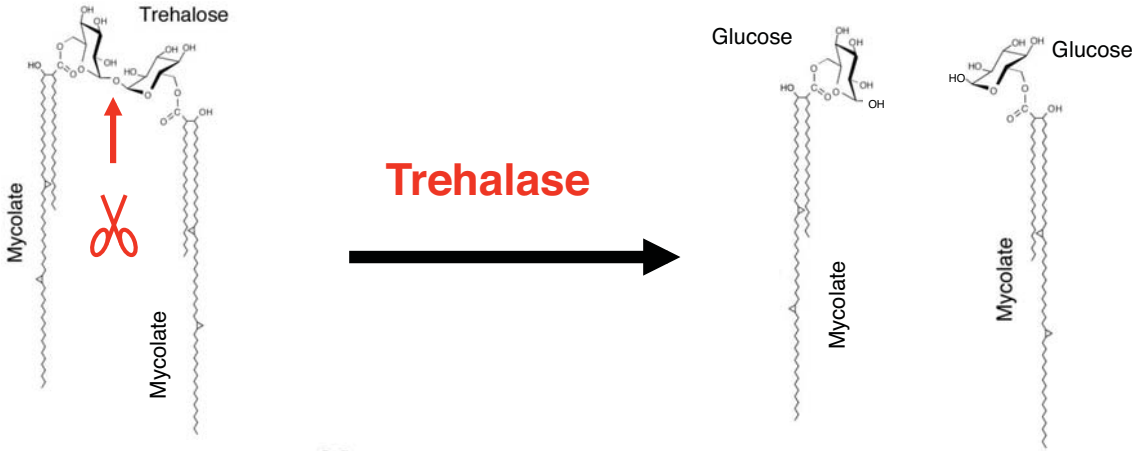
GMM conversion may be an escape strategy

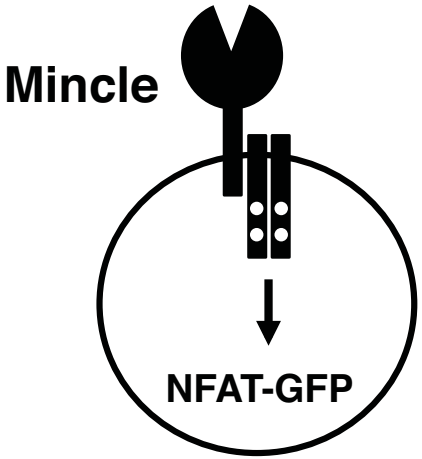
TDM
Trehalose dimycolate

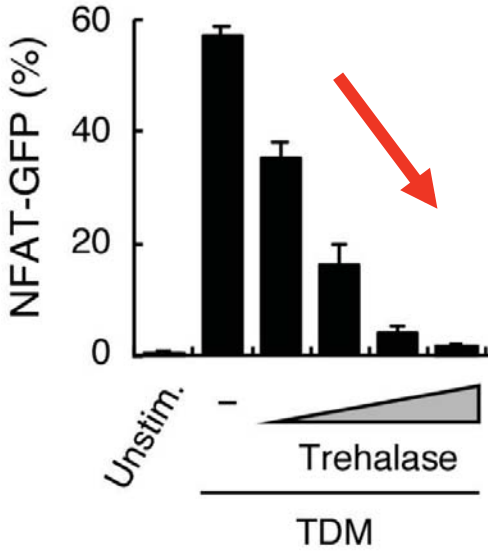
Conversion

GMM
Glucose monomycolate

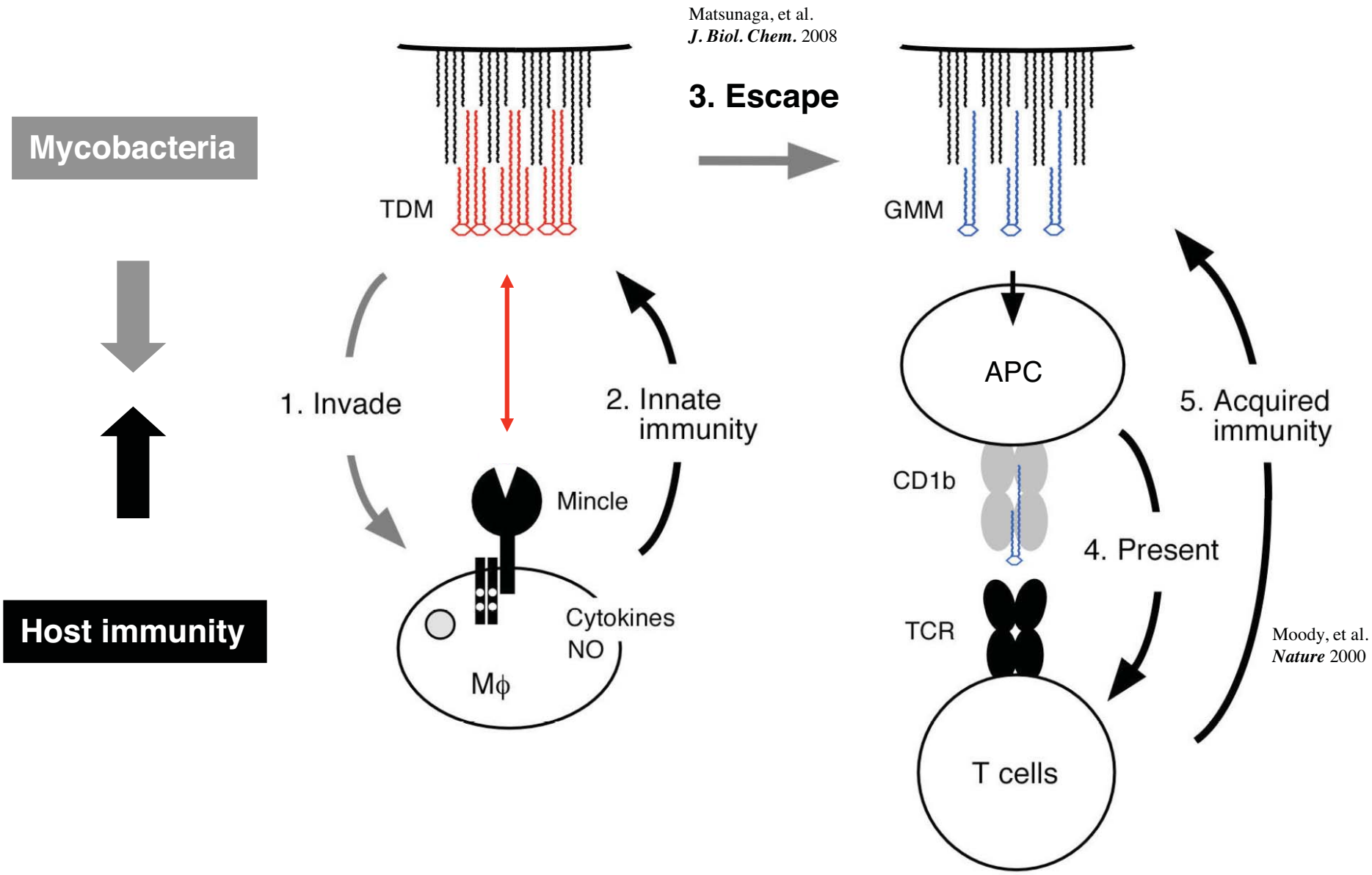
***In vitro* mimic**







Evolutional struggle between host and mycobacteria?



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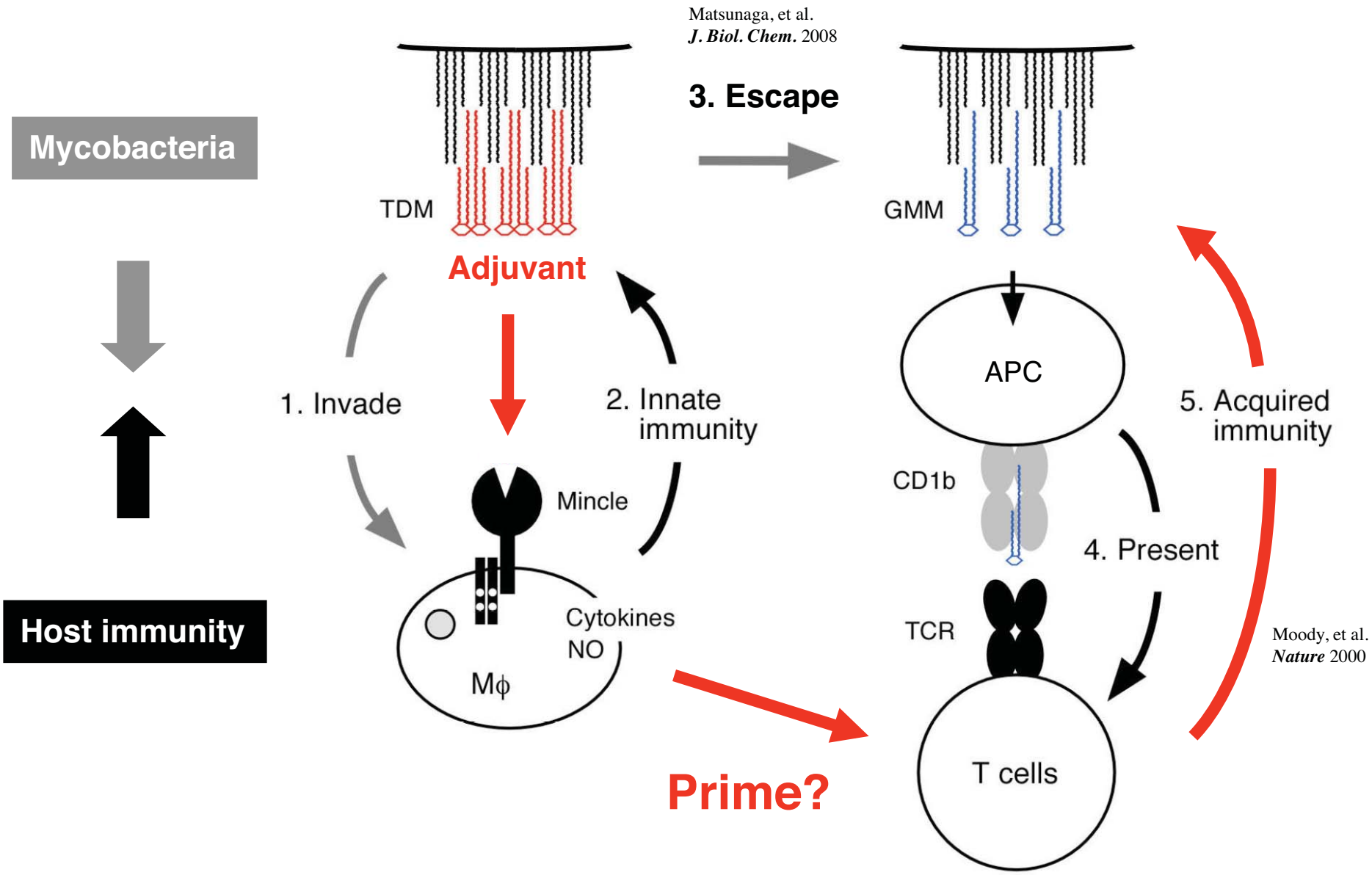

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