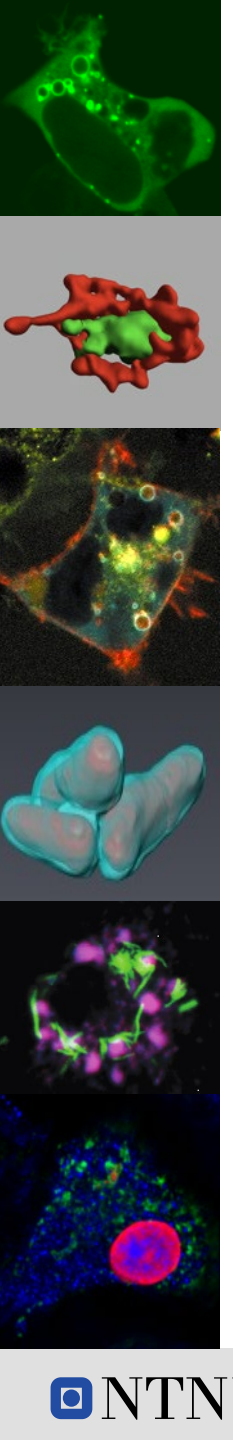


CEMIR

Centre of Molecular Inflammation Research

Norwegian Centre of Excellence

Tuberkulose

- behov for mer effektiv behandling og nye vaksiner
- behov for å forstå vert-mikrobe forholdet bedre
- Persontilpasset behandling: immunterapi + antibiotika

Forskning på tuberkulose – hva skjer?

Fra WHOs globale tuberkuloserapport 2018:

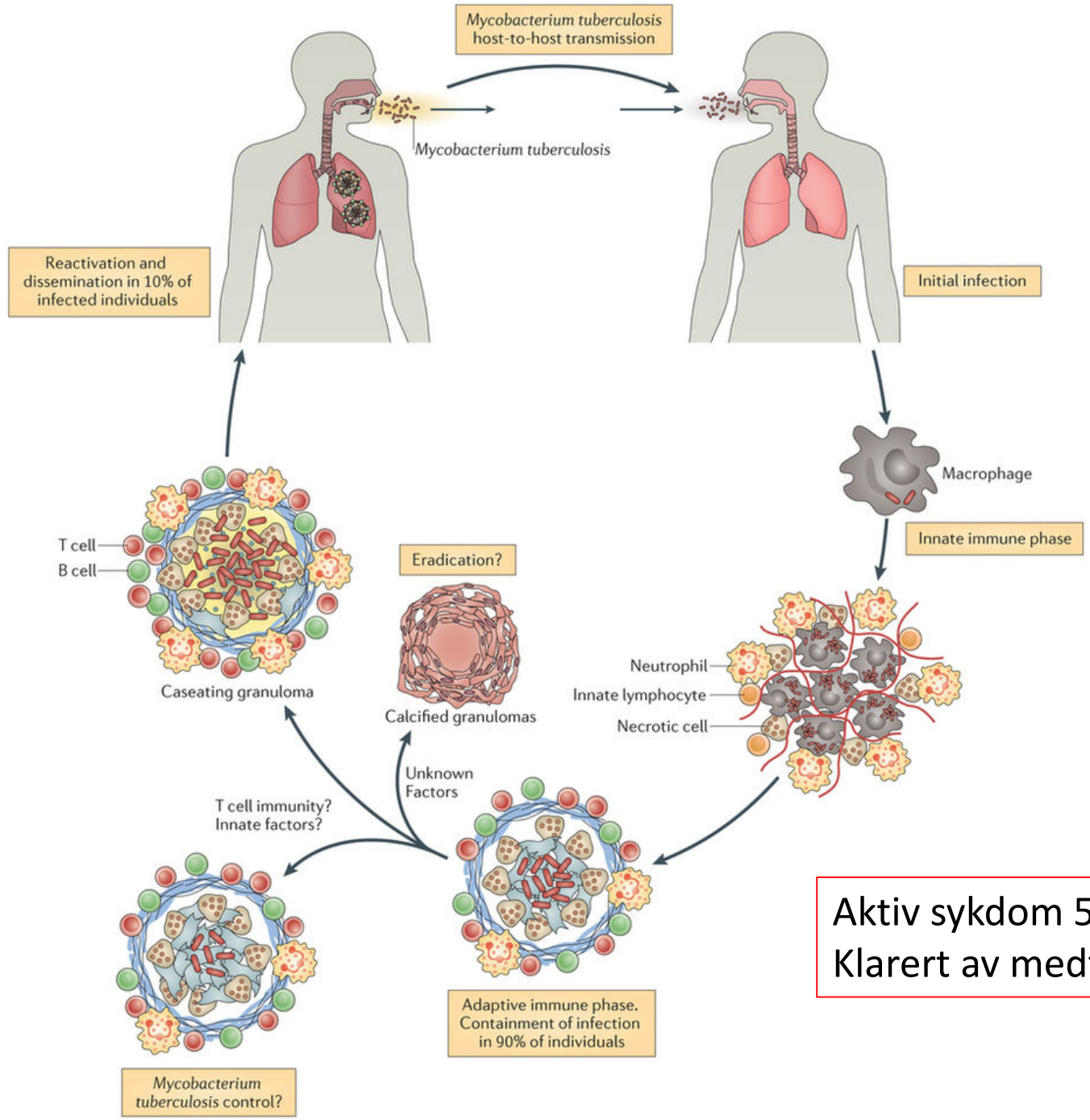
”Tuberculosis research and development is essential to achieve the global TB targets set in the Sustainable Development Goals and the End TB Strategy. A major technological breakthrough is required by 2025, so that the rate at which TB incidence falls can be dramatically accelerated compared with historic levels, to an average of 17% per year between 2025 and 2035.

Priorities for TB research and development include **a vaccine** to lower the risk of infection, a vaccine or new drug treatment to cut the risk of TB disease in the 1.7 billion people already latently infected, **rapid diagnostics** for use at the point of care and **simpler, shorter drug regimens** for treating TB disease.”

Tuberkulose

Reaktivering av sykdom 5-10%

Kontroll Latent sykdom ca. 90%



Aktiv sykdom 5-10%
Klarert av medfødt immunitet ? %

Nature Reviews Microbiology **12**, 2014

Nature Reviews | Microbiology

Tuberkulose – Hva er problemet?

M. tuberculosis cellevegg: voksaktig, tåler mye

Antibiotikaresistens
Naturlig toleranse

Tar bolig i makrofager

Aktivt replikerende Mtb: sårbar for antibiotika
Vevsskade, smitte

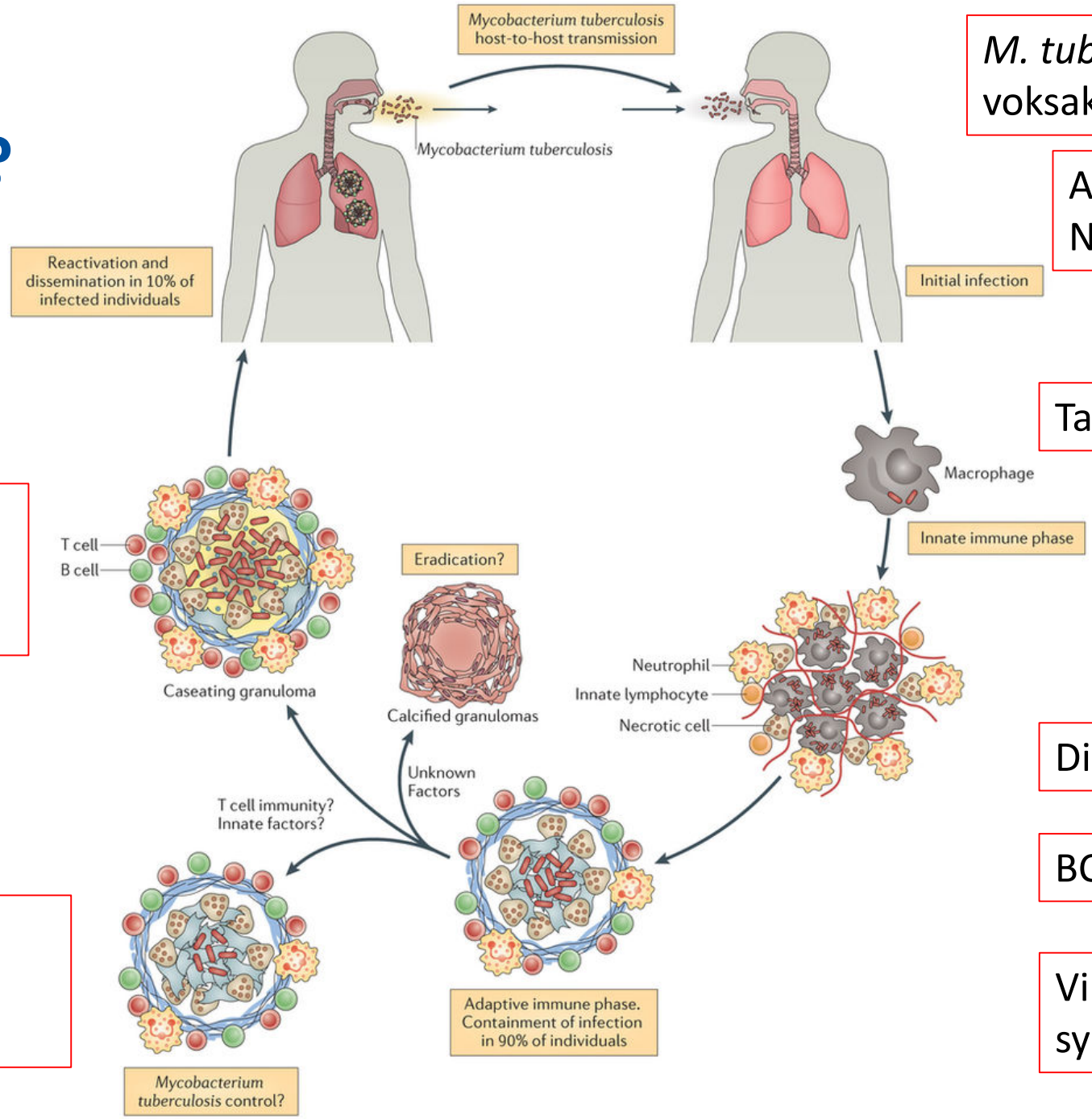
Granulomdynamikk

Latent Mtb: antibiotika mindre effektivt
Fare for reaktivering

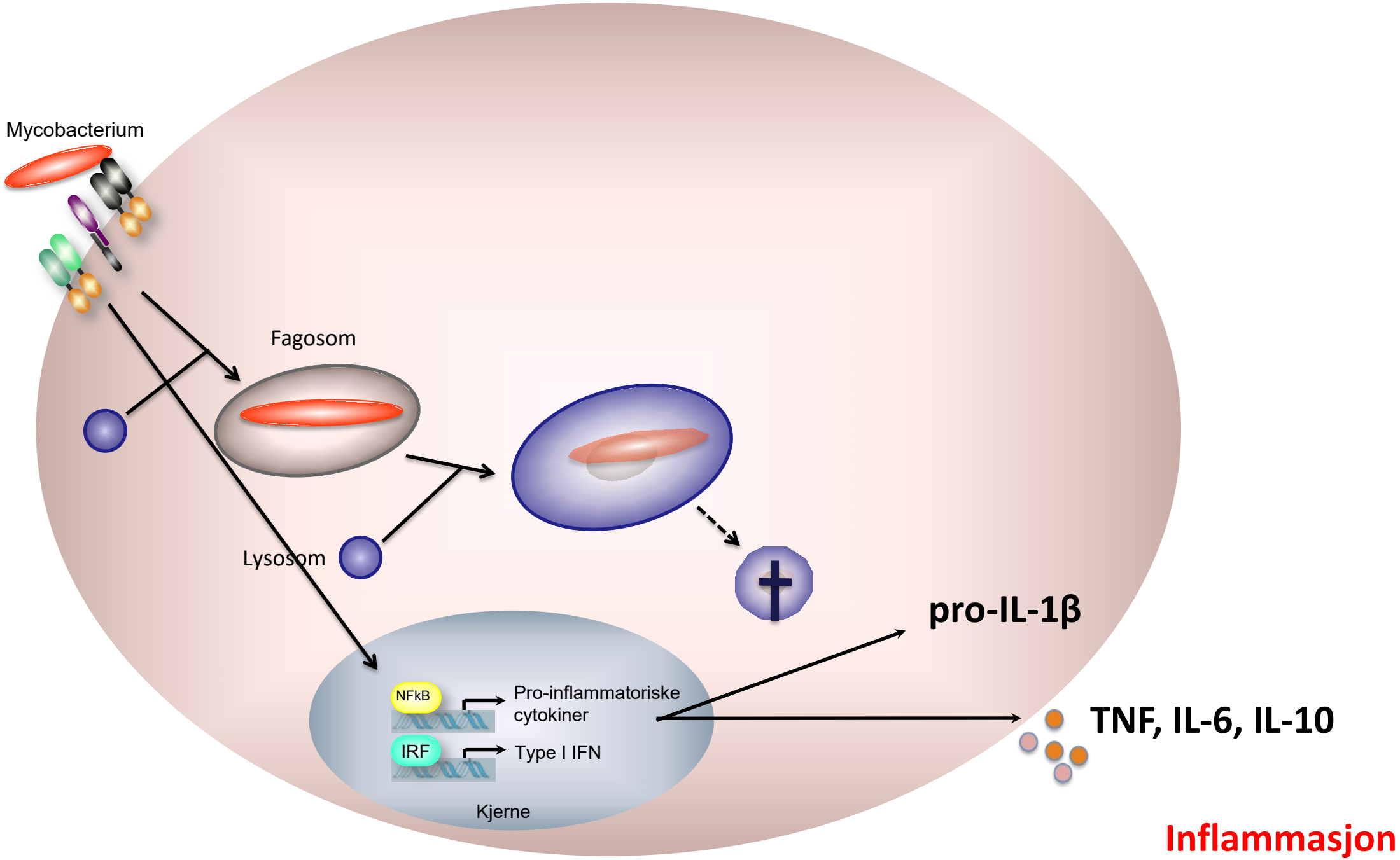
Diagnostikk

BCG vaksine ineffektiv

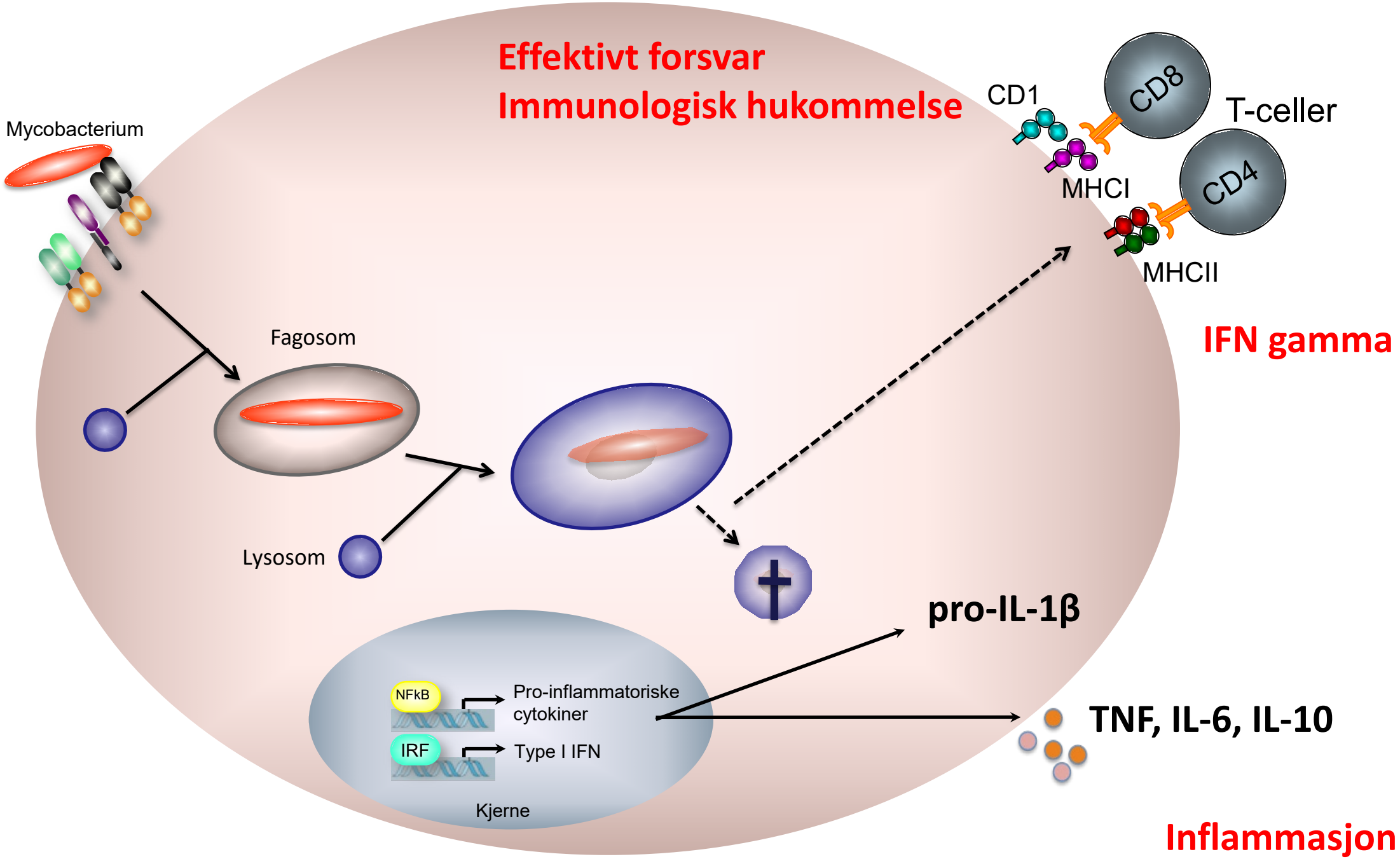
Vi forstår ikke sykdommen godt nok



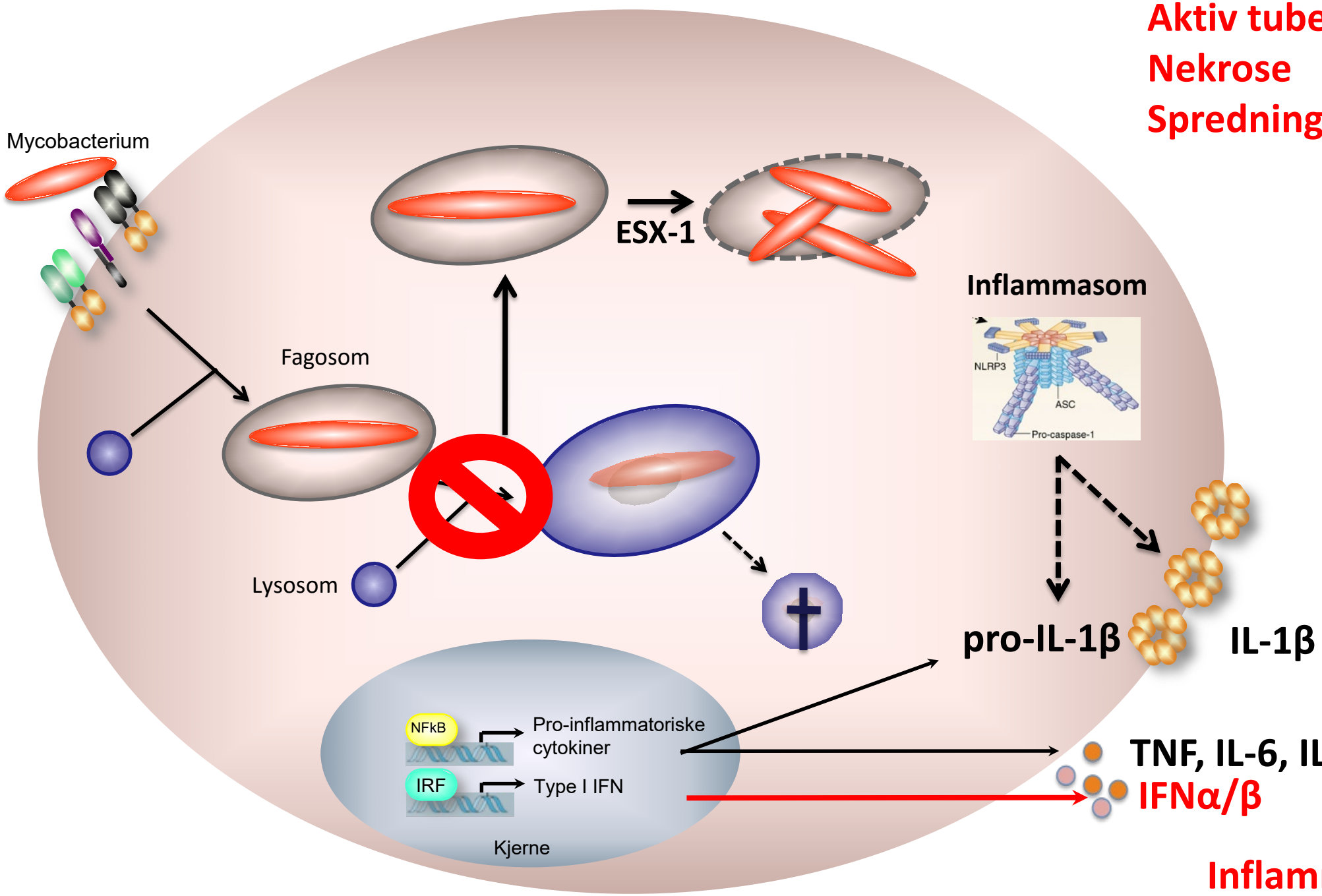
Nature Reviews | Microbiology
Nature Reviews Microbiology **12**, 2014



Inflammasjon


Effektivt forsvar
Immunologisk hukommelse
Mycobacterium
Fagosom
Lysosom
CD1
CD8
T-celler
CD4
MHCI
MHCII
IFN gamma
pro-IL-1β
TNF, IL-6, IL-10
NFkB
Pro-inflammatoriske cytokiner
IRF
Type I IFN
Kjerne
Inflammasjon

Aktiv tuberkulose
Nekrose
Spredning



Inflammasjon

Mtb

Kjernen

Inflammasom

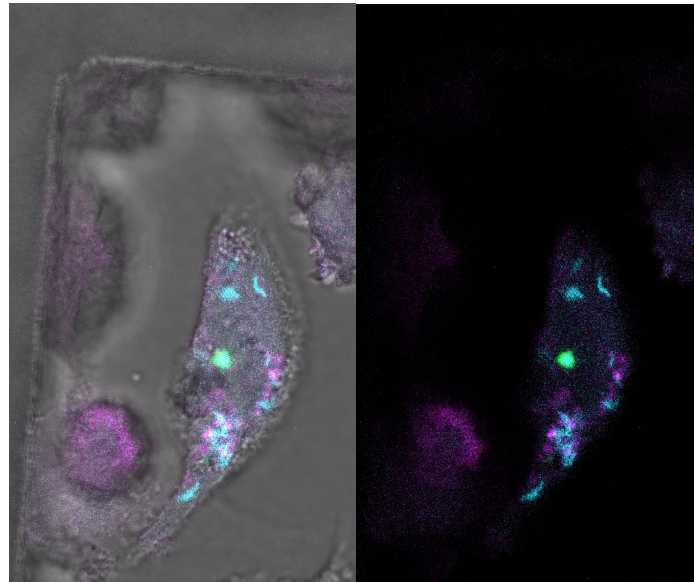
PM

Mtb

Mitokondrier

Golgi

ER



Marianne Beckwith

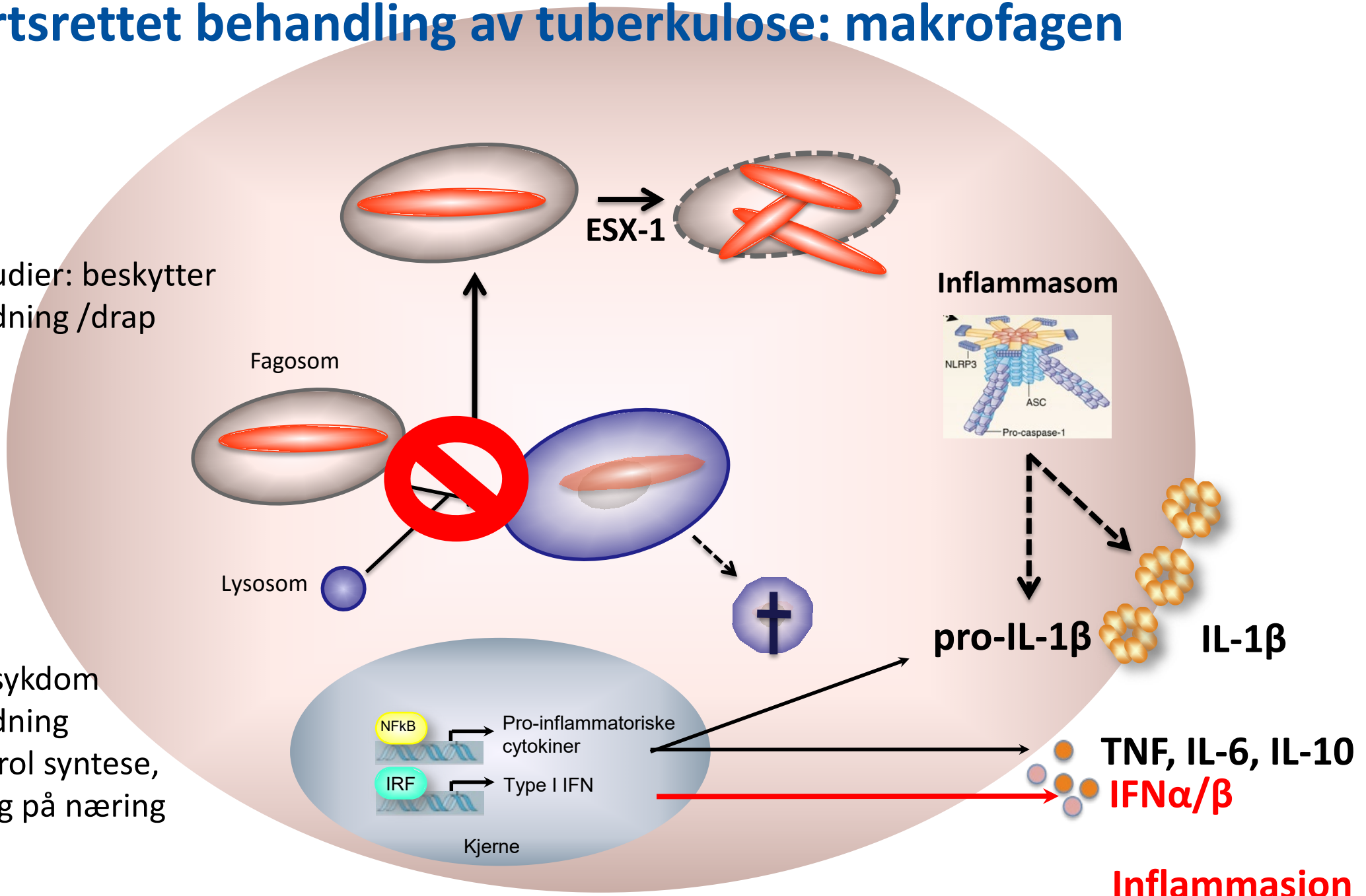
Vertsrettet behandling av tuberkulose: makrofagen

Metformin

- type II diabetes
- retrospektive studier: beskytter
- økt fagosommodning /drap

Statiner

- kardiovaskulær sykdom
- økt fagosommodning
  hemmer kolesterol syntese,
  begrenser tilgang på næring



Vertsrettet behandling av tuberkulose: immunterapi

Granulom-dynamikk:

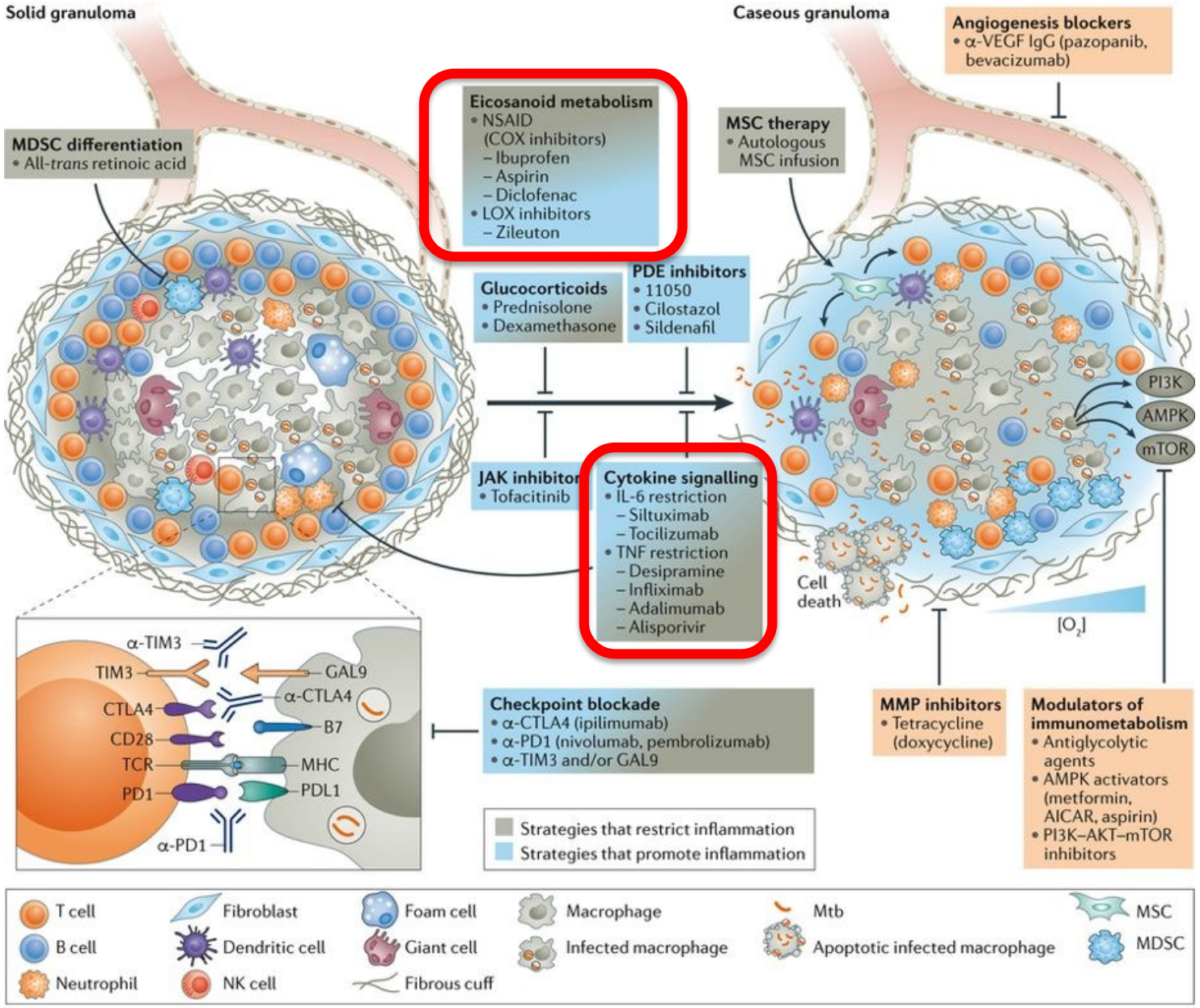
En og samme pasient kan ha godt kontrollerte granulomer og granulomer med aktivt replikerende *M. tuberculosis*

Valg av immunterapi er avhengig av formålet /pasienten:

- Begrense vevsskade (resultat av overdreven immun-aktivitet og vevsnekrose)
- Adjunkt behandling for å fremme inflammasjon og fasilitere antibiotika-mediert drap av aktivt replikerende *M. tuberculosis* («kick and kill»)

Vertsrettet behandling av tuberkulose: immunterapi

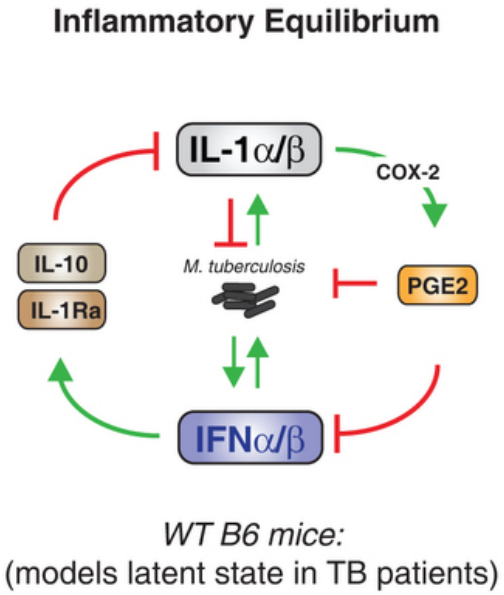
Inaktiv latent Mtb
Kontroll



Aktivt replikerende Mtb
Spredning
Vevsskade

Kaufmann et al,
Nat Rev Drugs Discovery 2018

Verts-rettet adjuvant behandling av tuberkulose



IL-1 viktig i tuberkuloseforsvar. Aktiverer COX -> **PGE2**

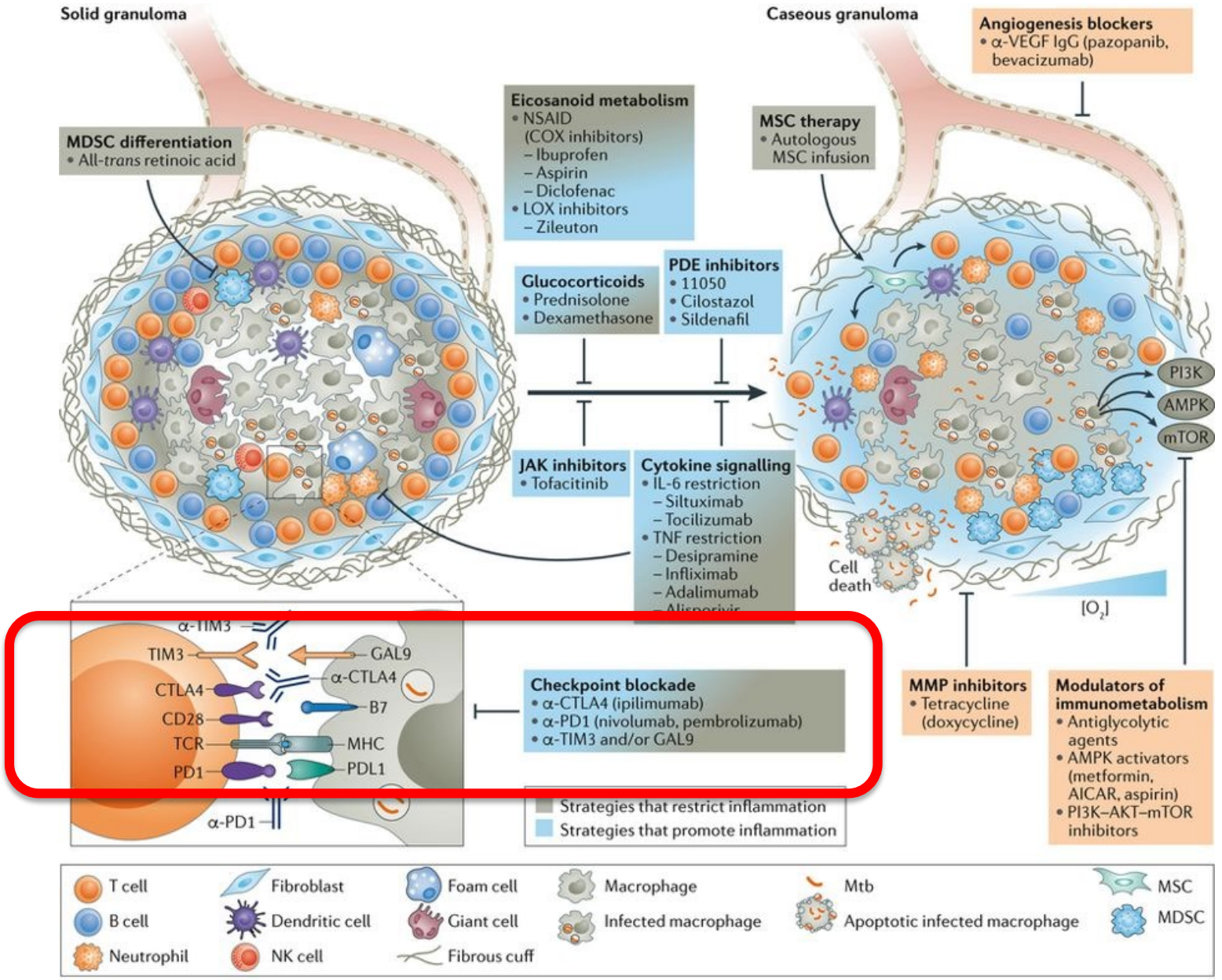
PGE2 hemmer Mtb replikasjon, påvirker T-celler, hindrer **nekrose**

Type I IFN øker patologi. **IL-10** (anti-inflammatorisk), hemmer IL-1 (og IFNg, IL-12)

Zileuton hemmer 5-lipoxygenase → leukotriener som virker motsatt av PGE2

K. Mayer-Barber, Alan Sher *Nature* **511**, 99–103 (03 July 2014)

Vertsrettet behandling av tuberkulose: sjekkpunkt hemmere



Kaufmann et al,
Nat Rev Drugs Discovery 2018

Vertsrettet behandling av tuberkulose: sjekkpunkt hemmere

SCIENCE TRANSLATIONAL MEDICINE | REPORT

IMMUNOTHERAPY

Tuberculosis following PD-1 blockade for cancer immunotherapy

Daniel L. Barber[1]*, Shunsuke Sakai[1], Ragini R. Kudchadkar[2], Steven P. Fling[3,4], Tracey A. Day[5], Julie A. Vergara[5], David Ashkin[6], Jonathan H. Cheng[7], Lisa M. Lundgren[4], Vanessa N. Raabe[8], Colleen S. Kraft[9], Jorge J. Nieva[7], Martin A. Cheever[3,4], Paul T. Nghiem[10], Elad Sharon[11]*

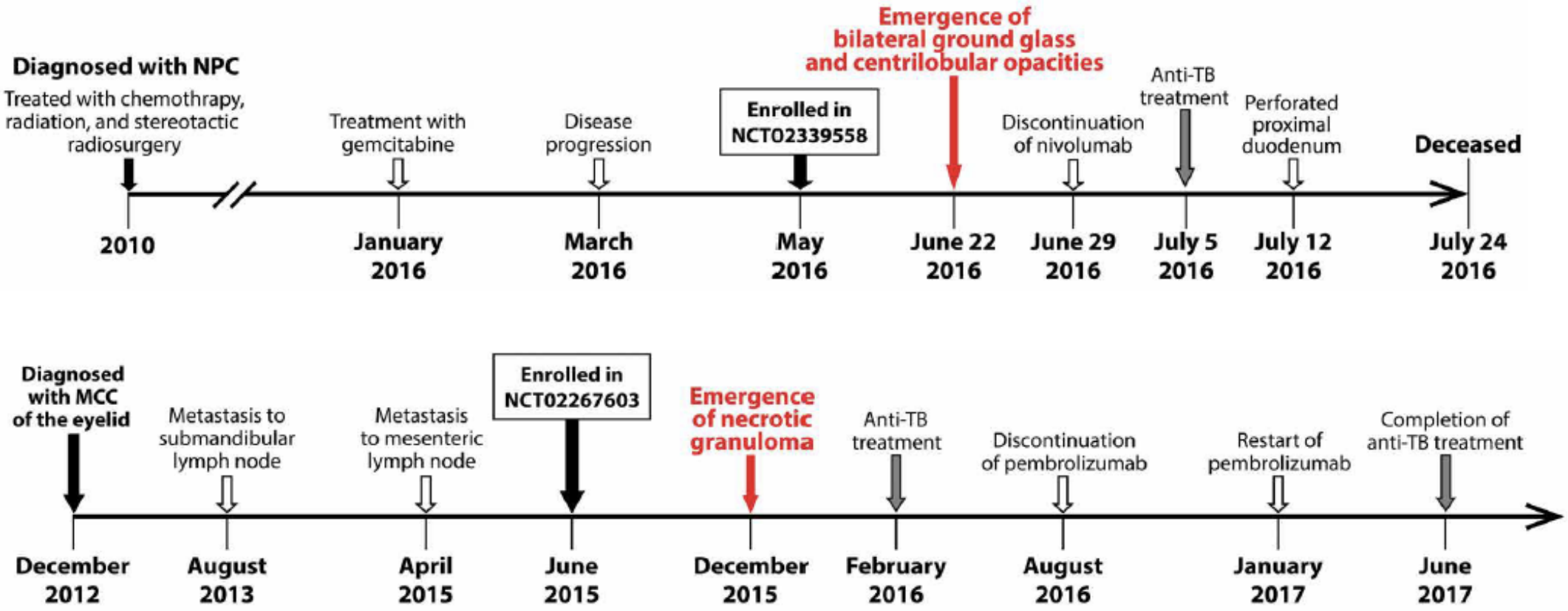
Because of the well-established therapeutic benefit of boosting antitumor responses through blockade of the T cell inhibitory receptor PD-1, it has been proposed that PD-1 blockade could also be useful in infectious disease settings, including *Mycobacterium tuberculosis* (Mtb) infection. However, in preclinical models, Mtb-infected PD-$1^{-/-}$ mice mount exaggerated T_H1 responses that drive lethal immunopathology. Multiple cases of tuberculosis during PD-1 blockade have been observed in patients with cancer, but in humans little is understood about Mtb-specific immune responses during checkpoint blockade–associated tuberculosis. Here, we report two more cases. We describe a patient who succumbed to disseminated tuberculosis after PD-1 blockade for treatment of nasopharyngeal carcinoma, and we examine Mtb-specific immune responses in a patient with Merkel cell carcinoma who developed checkpoint blockade–associated tuberculosis and was successfully treated for the infection. After anti–PD-1 administration, interferon-γ–producing Mtb-specific CD4 T cells became more prevalent in the blood, and a tuberculoma developed a few months thereafter. Mtb-specific T_H17 cells, CD8 T cells, regulatory T cells, and antibody abundance did not change before the appearance of the granuloma. These results are consistent with the murine model data and suggest that boosting T_H1 function with PD-1 blockade may increase the risk or severity of tuberculosis in humans.

Vertsrettet behandling av tuberkulose: sjekkpunkt hemmere

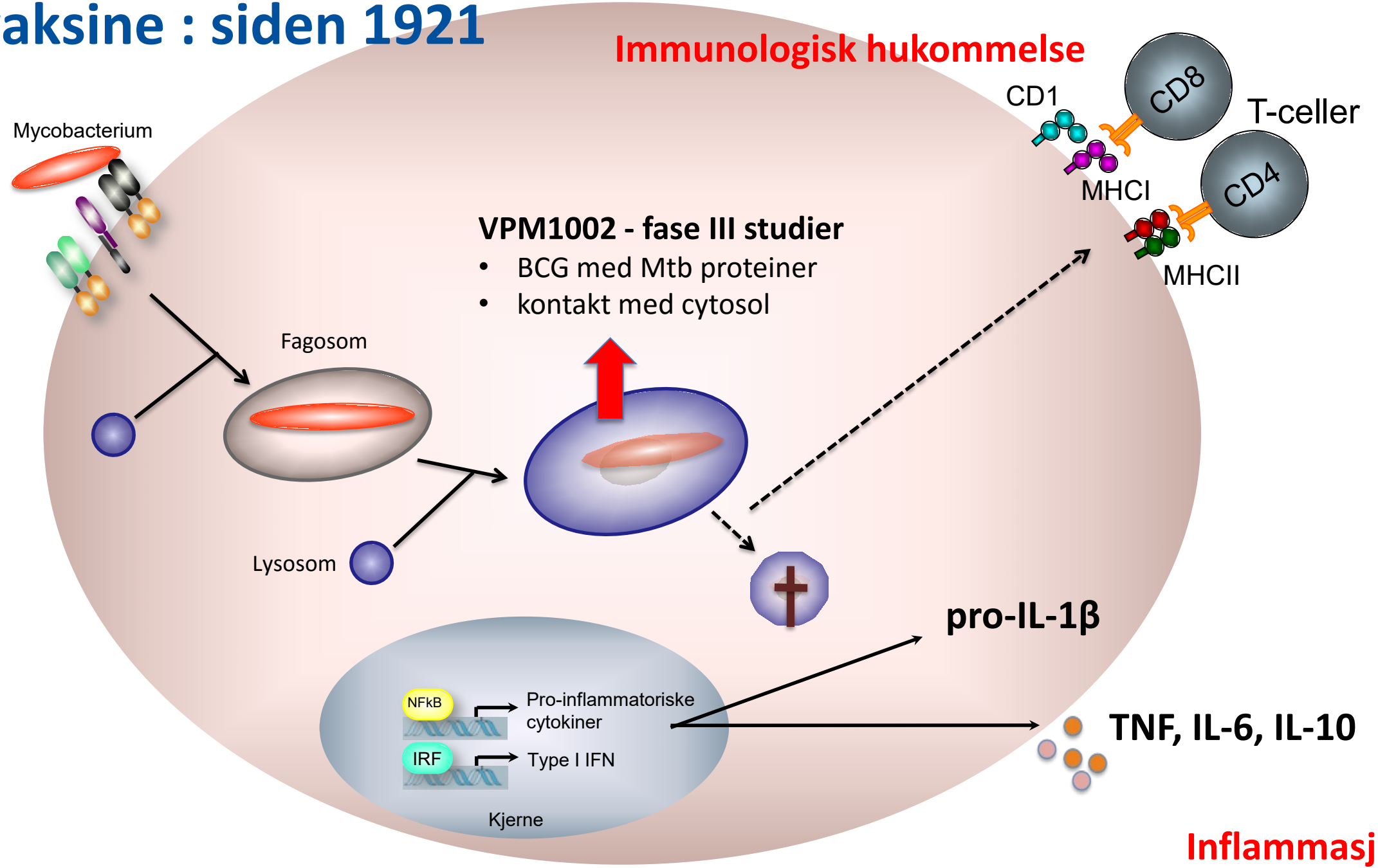
SCIENCE TRANSLATIONAL MEDICINE | REPORT

IMMUNOTHERAPY

Tuberculosis following PD-1 blockade for cancer immunotherapy



BCG vaksine : siden 1921



BCG vaksine : siden 1921

Cell

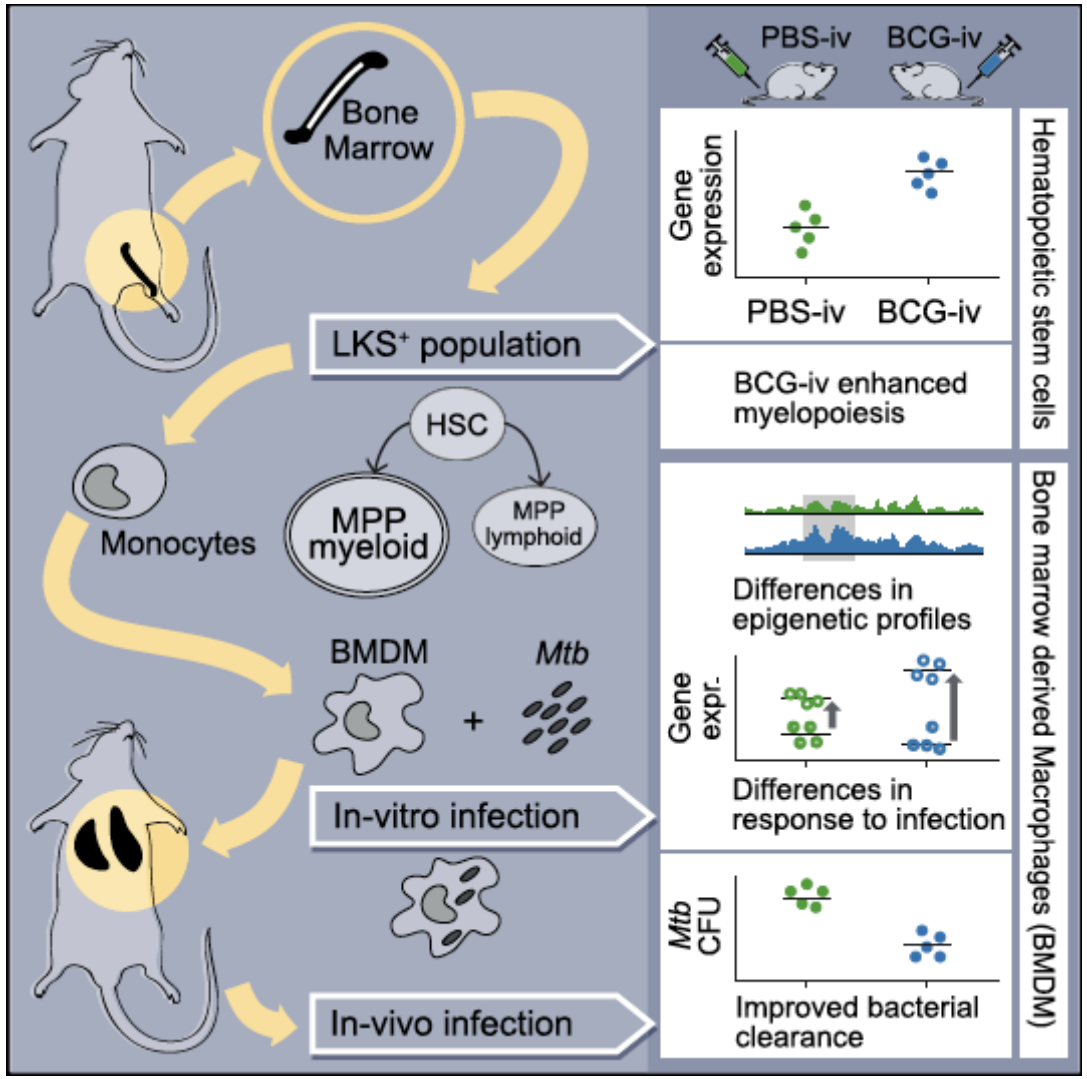
Article

BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis

Eva Kaufmann,[1,7] Joaquin Sanz,[2,3,7] Jonathan L. Dunn,[1,7] Nargis Khan,[1] Laura E. Mendonça,[1] Alain Pacis,[2,3] Fanny Tzelepis,[1] Erwan Pernet,[1] Anne Dumaine,[3] Jean-Christophe Grenier,[3] Florence Mailhot-Léonard,[3] Eisha Ahmed,[1] Jad Belle,[4] Rickvinder Besla,[5] Bruce Mazer,[1] Irah L. King,[1] Anastasia Nijnik,[4] Clinton S. Robbins,[5] Luis B. Barreiro,[3,6,*] and Maziar Divangahi[1,8,*]

BCG vaksine gitt intravenøst når beinmargen og reprogrammerer stamceller

- Økt ekspansjon av «trente» myeloide celler
- Økt beskyttelse mot tuberkulose
- Mus...



Oppsummert

- Tuberkulose er et globalt helseproblem og antibiotikaresistens øker
- Ingen stor framgang i utvikling av vaksine : vet ikke hvordan vi oppnår immunitet
- Effektivisering av behandling effektivt : nye medikamenter, kortere behandlingstid, kombinasjon med adjuvant verts-rettet behandling
- Inflammasjon er tveegget
- Immunterapi i tuberkulosebehandling må være persontilpasset

Edward Munch, 1896