Clinical Relevance of Immunology & Endotypes in TB

Andrew DiNardo, MD PhD

April 1, 2024

New Directions in TB
April 1 – 2, 2024
Houston, Texas

Andrew DiNardo, MD PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Clinical relevance of immunology & endotypes in TB

April Fools 2024
New Directions in TB Conference

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Clinical relevance Immunology & Endotypes

- TB diagnosis
- TB “in-treatment” outcomes
- Post-TB Cardiovascular Disease (3x ↑risk)
- Post-TB Cancer (~2x ↑risk)
- Post TB lung morbidity (15-80% of TB patients suffer)

So how do we solve the problem?

What is the singular immune modulation we can do to improve long-term TB outcomes?

Summary

- There is no single immune correlate of protection
  →multiple TB endotypes

- Pathology can be driven by:
  1. Pathogen induced pathology
  2. Immune induced pathology (inflammation)
  3. Anergy (immune suppressed) induced pathology

The Virchow- Koch skirmish

1891:
Early HDT failure

NEJM 1891

VIRCHOW ON THE EFFECTS OF KOCH'S METHOD.[1]

At the Berlin Medical Society on January 7th, Professor Virchow exhibited specimens from twenty-one patients treated by Koch's method who died before January 1st. Since then six or seven more necropsies had been made by him and specimens from these were also shown. Of the former series, sixteen were cases of phthisis.

Professor Virchow illustrated the irritating effects of the fluid by the specimen of a brain removed from a child with tuberculous arachnitis, who died after four injections of the lymph amounting in all to two milligrammes. There was intense hyperæmia of the brain and pia mater such as Professor Virchow had never before seen. The vessels of the pia were extremely engorged and the brain-substance internally was of a dusky-red tint. The speaker could not see any signs of retrogressive metamorphosis of the tubercles. Acute hyperæmia and swelling were also seen in the internal organs of other cases. The walls of old cavities in the lungs showed unusual

[1] Medical News, January 17, 1891.

1891 lessons:

1. Tuberculululin induced pathologic IRIS

2. One size doesn't fit all

NEJM 1891

by the injections of the lymph.

The *most important effect observed, however, was an eruption of fresh crops of tubercles after the injections.* This occurs especially in the pleura, pericardium, and peritoneum, and Virchow says that in the case of

Tuberculin: induced IRIS

body by infection with the products of disintegration. Virchow, therefore, urges the greatest caution in the use of the remedy. While admitting that in many cases the lymph does produce the effects claimed for it, he points out that this result is not constant, and he cites cases in which large masses of tubercle

No one-sized fits all approach

out the whole extent of the larynx and trachea.

On January 14th, before the Berlin Medical Association, Professor Virchow resumed his lecture on the subject of cases which have resulted fatally after the inoculations of the Koch remedy. He said that he was not prejudiced against the remedy; he simply wished to give warning regarding its too general application. In the discussion which followed, Professors Frænkel and Baginsky spoke in support of Professor Virchow's contention that tubercular disease

What is the ”right” immune response to TB?

IFN-γ improves in vitro *Mtb* killing

INFECTION AND IMMUNITY, Aug. 1976, p. 337-344

Vol. 14, No. 2
Printed in U.S.A.

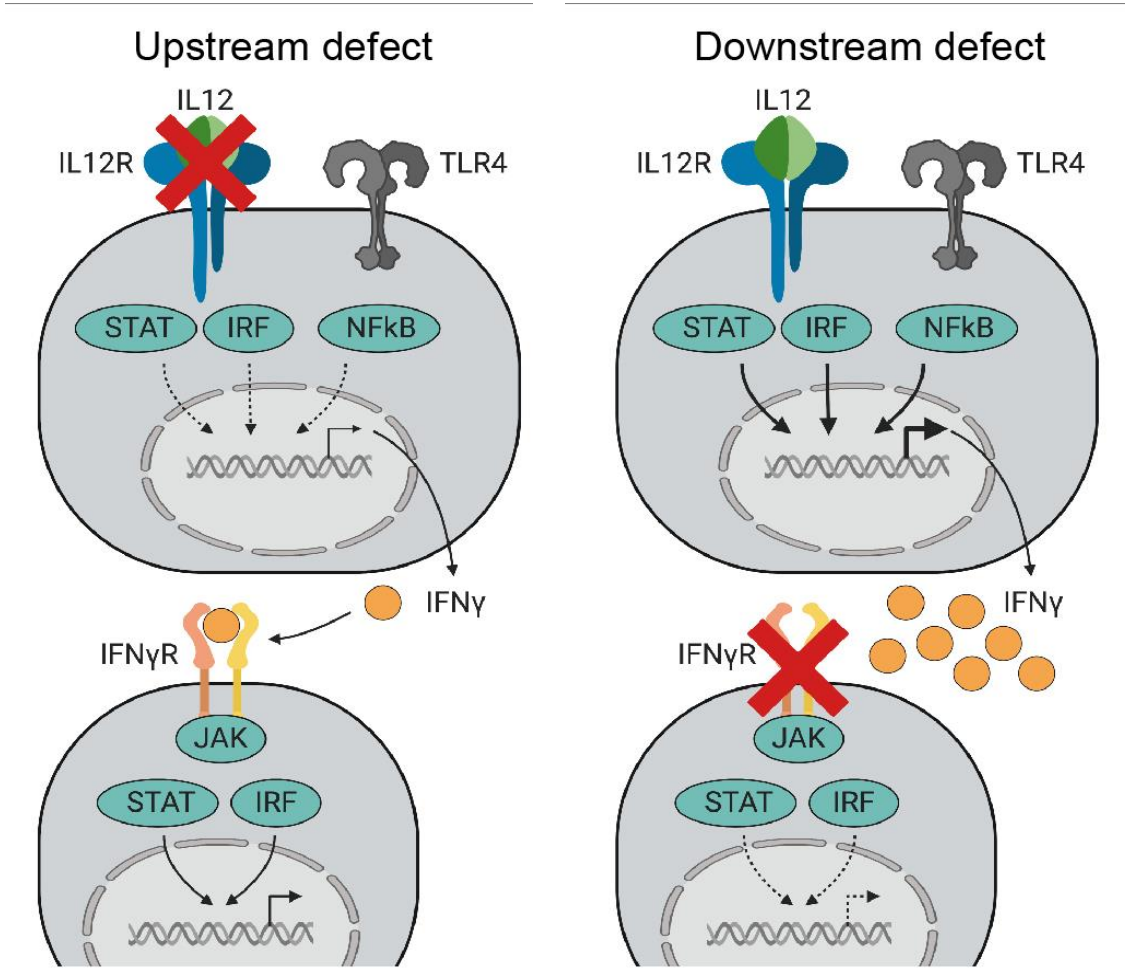
Partial Characterization of a Factor Extracted from Sensitized Lymphocytes That Inhibits the Growth of *Mycobacterium tuberculosis* Within Macrophages In Vitro

R. TURCOTTE,* Y. DES ORMEAUX, AND A. G. BORDUAS

Centre de Recherche en Immunologie, Institut Armand-Frappier, C.P. 100, Laval-des-Rapides, Ville de Laval, Québec, Canada H7N 4Z3

Received for publication 4 March 1976

Immune correlates of Protection
#1: IL12-IFNγ pathway



Upstream MSMDs

- Mutations in *IL12B, IL12RB1, IRF8, NEMO*

- ↓ IFNγ
- ↓ ***killing capacity***

Downstream MSMDs

- Mutations in *IFNGR1, IFNGR2, STAT1, IRF8*

- ↑ IFNγ
- ↓ ***killing capacity***

IFN-γ improves in vitro *Mtb* killing
Recruits additional immune cells

1. ↑P-L maturation
2. Warburg metabolism
3. ROS upregulation
4. Ag processing
5. Chemokine activation

→ IFN-γ mediates killing of intracellular pathogens
and
→ Attracts additional immune cells

IDENTIFICATION OF INTERFERON-γ AS THE LYMPHOKINE THAT ACTIVATES HUMAN MACROPHAGE OXIDATIVE METABOLISM AND ANTIMICROBIAL ACTIVITY*

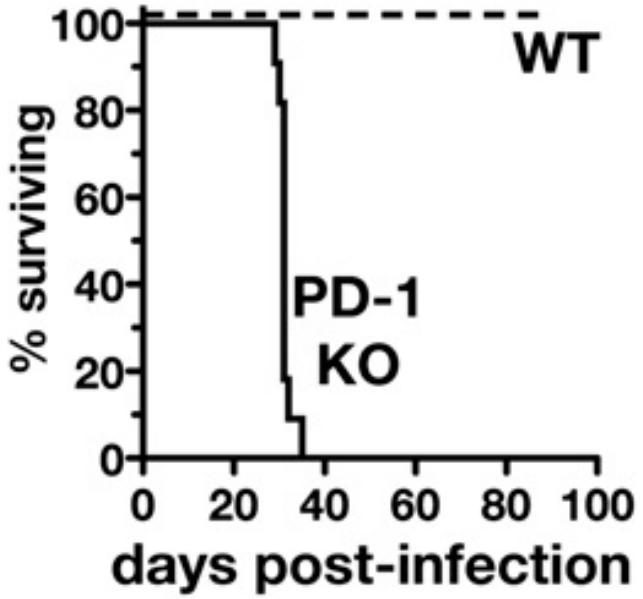
By CARL F. NATHAN,‡ HENRY W. MURRAY,§ MICHAEL E. WIEBE, and BERISH Y. RUBIN

J. Exp. Med. © The Rockefeller University Press · 0022-1007/83/09/0670/20 $1.00
Volume 158 September 1983 670–689

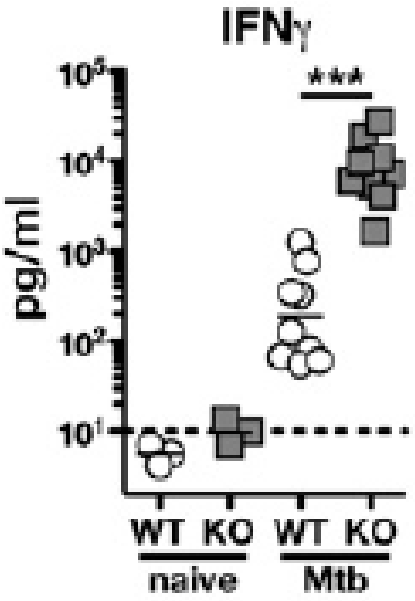
IFN-γ : fatal immune pathology

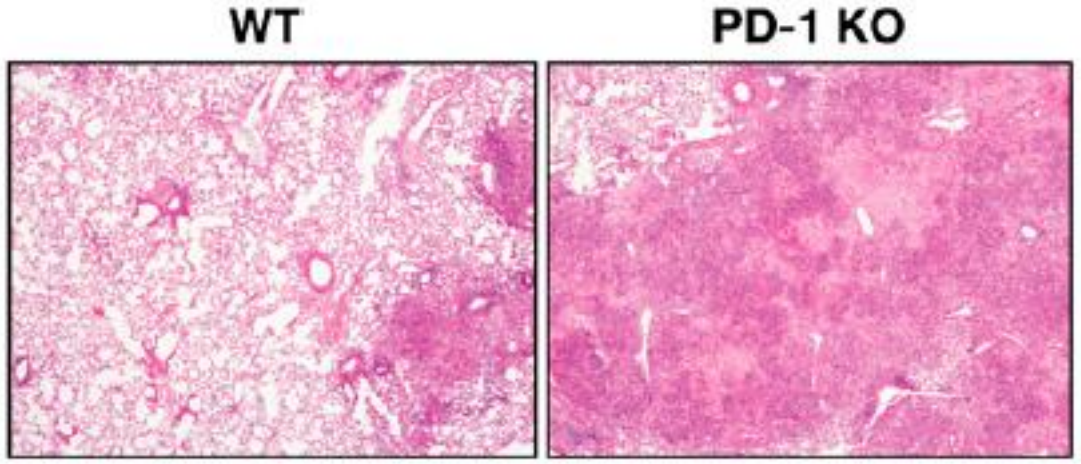
CD4 T Cells Promote Rather than Control Tuberculosis in the Absence of PD-1–Mediated Inhibition

Daniel L. Barber, Katrin D. Mayer-Barber, Carl G. Feng, Arlene H. Sharpe and Alan Sher



Inhibit PD1→↑IFNγ





TNF improves in vitro *Mtb* killing
Recruits additional immune cells

Proc. Nat. Acad. Sci. USA
Vol. 72, No. 9, pp. 3666–3670, September 1975
Immunology

An endotoxin-induced serum factor that causes necrosis of tumors

(activated macrophage)

E. A. CARSWELL, L. J. OLD, R. L. KASSEL, S. GREEN, N. FIORE, AND B. WILLIAMSON

Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021

Communicated by Lewis Thomas, June 23, 1975

572, June, 1995,

Tumor Necrosis Factor-α Is Required in the Protective Immune Response Against Mycobacterium tuberculosis in Mice

JoAnne L. Flynn,[1] Marsha M. Goldstein,[2]
John Chan,[3] Karla J. Triebold,[4]
Klaus Pfeffer[5,6], Charles J. Lowenstein,[7]
Robert Schreiber,[8] Tak W. Mak,[5]
and Barry R. Bloom[4]

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Immunity, Vol. 2, 561–572, June, 1995, Copyright © 1995 by Cell Press

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1. Granuloma formation
2. Reactive nitrogen production
3. Nitric oxide production
4. Chemokine production
5. Apoptosis / autophagy / necroptosis

→ ↑ killing of intracellular pathogens
and
→ Attracts additional immune cells

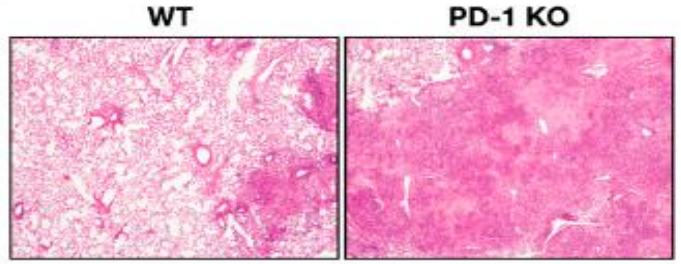
More is better?

More IFNγ or TNFα prevents TB?

Immune induced pathology & death

CD4 T Cells Promote Rather than Control Tuberculosis in the Absence of PD-1–Mediated Inhibition

Daniel L. Barber,* Katrin D. Mayer-Barber,* Carl G. Feng,* Arlene H. Sharpe,† and Alan Sher*

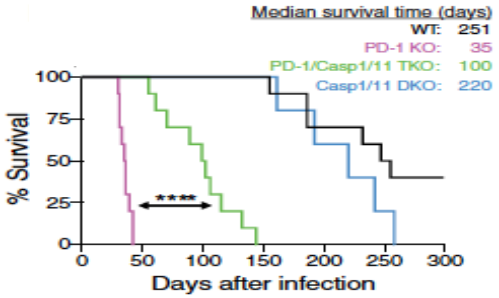


SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

IMMUNOTHERAPY

PD-1 blockade exacerbates *Mycobacterium tuberculosis* infection in rhesus macaques

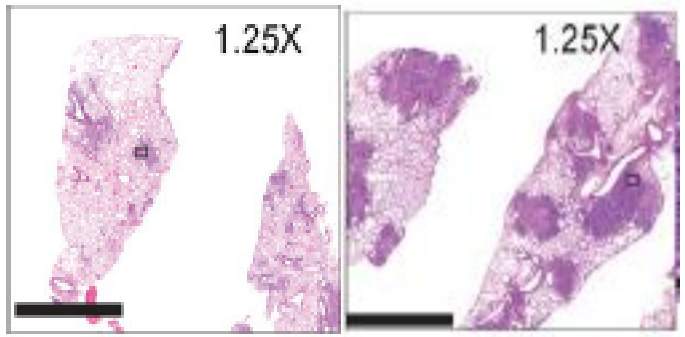
Keith D. Kauffman[1], Shunsuke Sakai[1], Nickiana E. Lora[1], Sivaranjani Namasivayam[2], Paul J. Baker[3], Olena Kamenyeva[4], Taylor W. Foreman[1], Christine E. Nelson[1], Deivide Oliveira-de-Souza[5], Caian L. Vinhaes[5], Ziv Yaniv[6], Cecilia S. Lindestam Arleham[7], Alessandro Sette[7,8], Gordon J. Freeman[9], Rashida Moore[10], NIAID/DIR Tuberculosis Imaging Program*, Alan Sher[2], Katrin D. Mayer-Barber[3], Bruno B. Andrade[5], Juraj Kabat[4], Laura E. Via[11]*, Daniel L. Barber[1†]



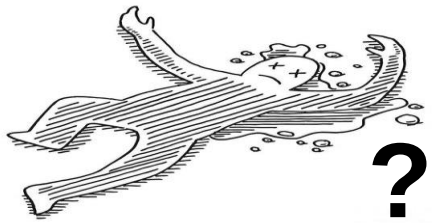
BRIEF DEFINITIVE REPORT

Irg1 expression in myeloid cells prevents immunopathology during _M. tuberculosis_ infection

Sharmila Nair[1]*, Jeremy P. Huynh[2]*, Vicky Lampropoulou[3], Ekaterina Loginicheva[3], Ekaterina Esaulova[3,4], Anshu P. Gounder[2], Adrianus C.M. Boon[1,2,3], Elizabeth A. Schwarzkopf[3], Tara R. Bradstreet[3], Brian T. Edelson[3], Maxim N. Artyomov[3], Christina L. Stallings[2], and Michael S. Diamond[1,2,3,5]

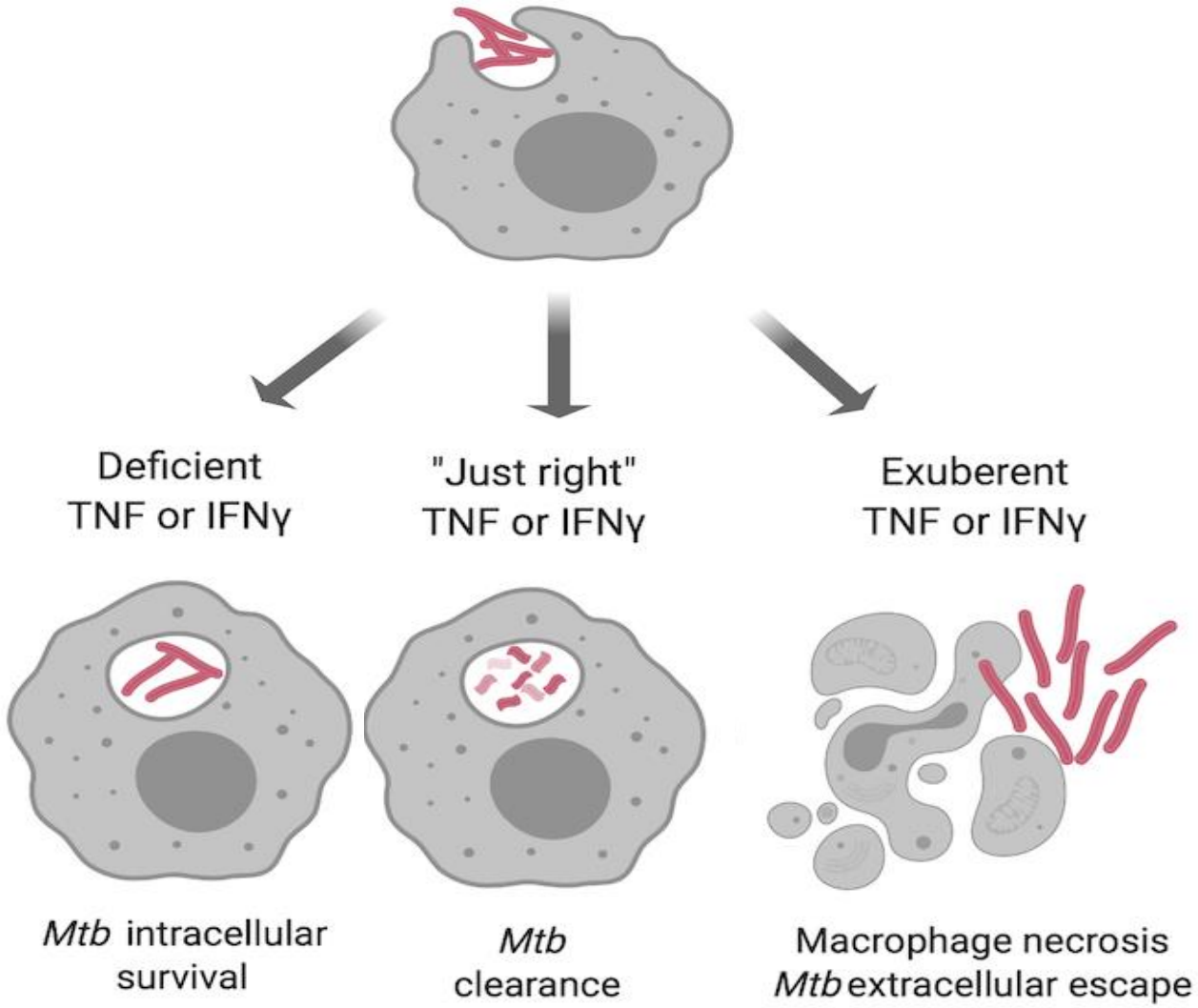


Clinical trial of aerosolized IFN-γ in MDR TB halted early due to increased death (10 vs 5 deaths)



Dawson R, Condos R, Tse D, et al. Immunomodulation with recombinant IFN-γ in pulmonary tuberculosis. PLoS One 2009; 4:e6984.

Narrow therapeutic immune window

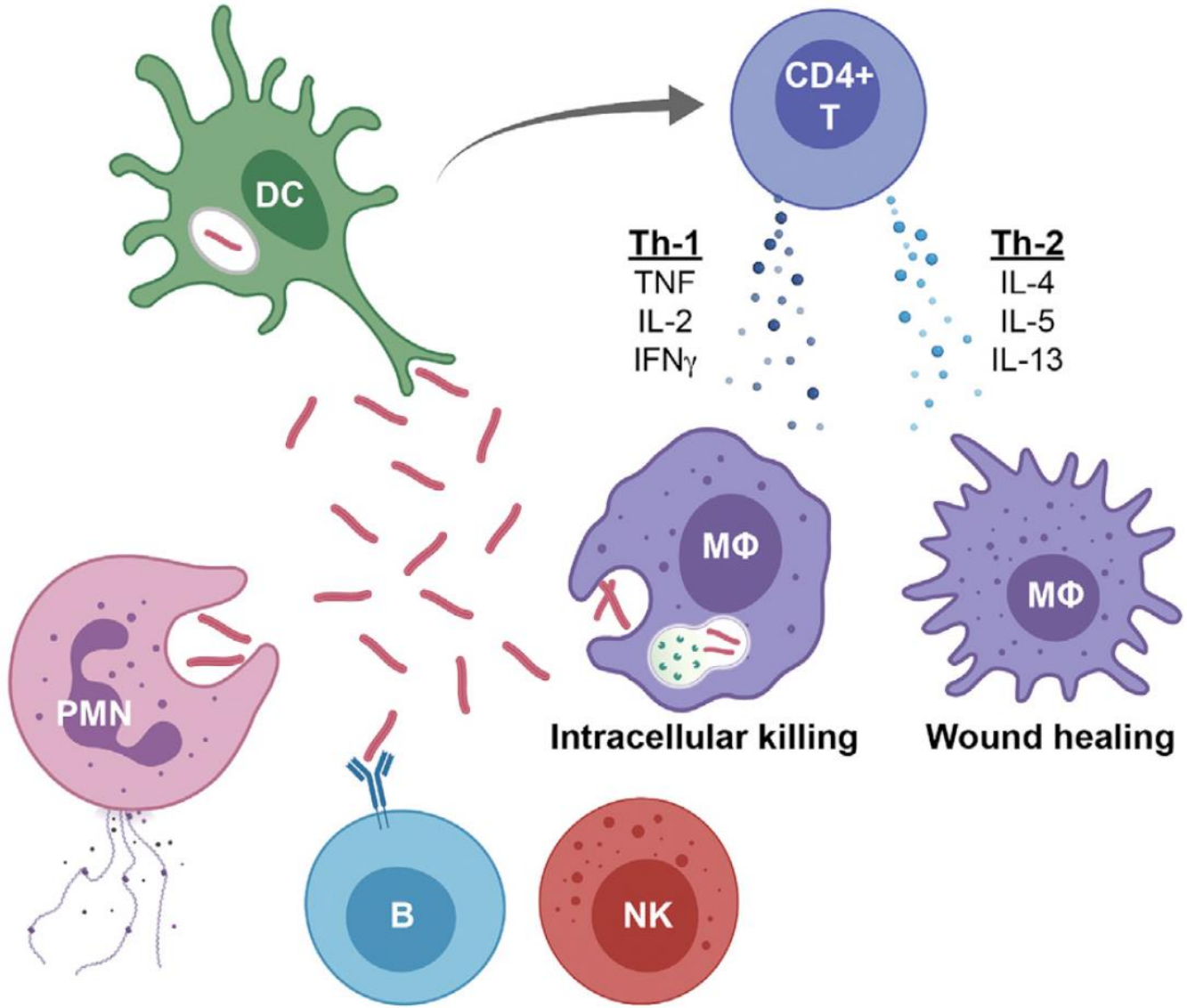


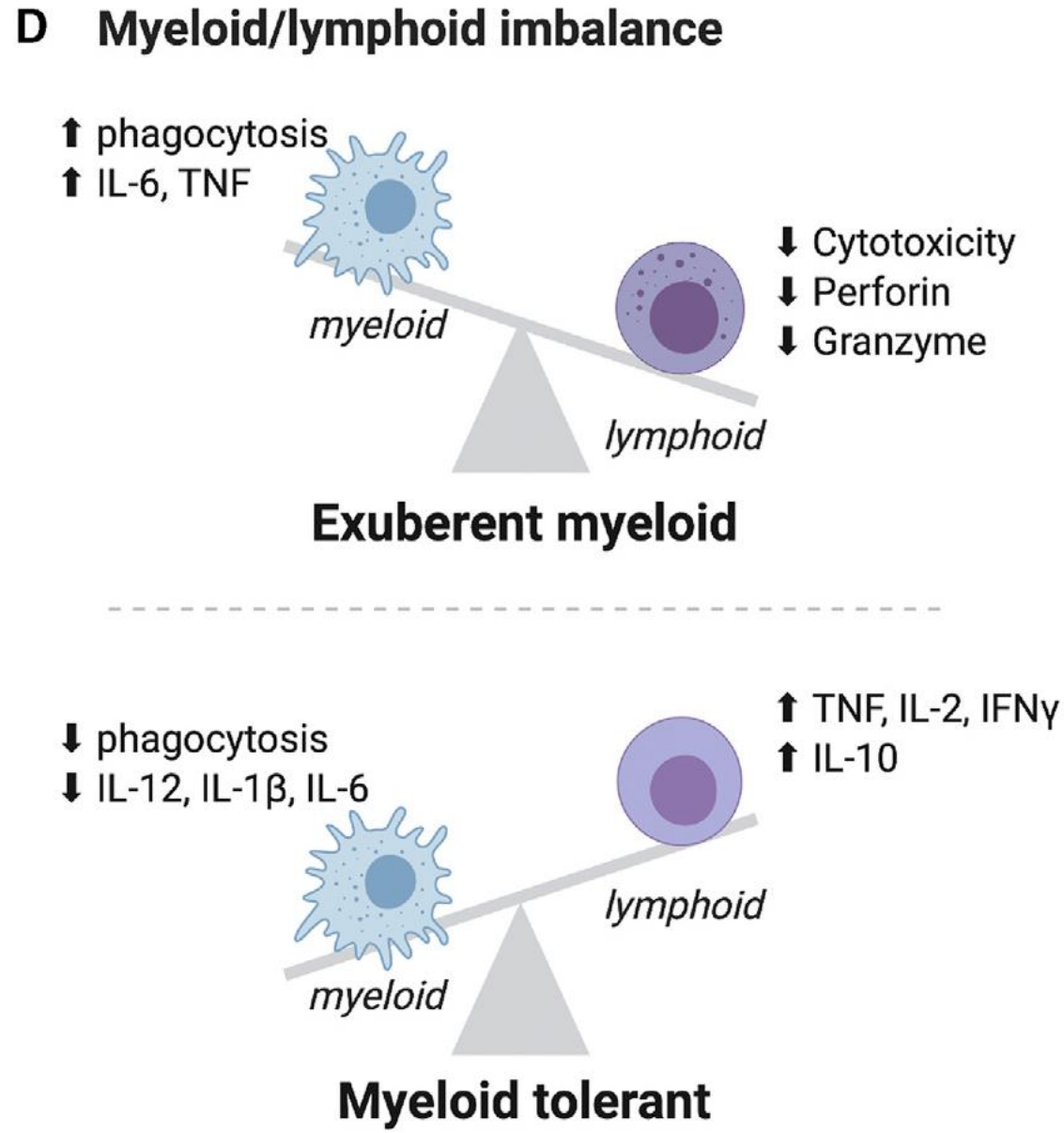
How do we make this clinically applicable?

When does TB therapy need an immune boost?

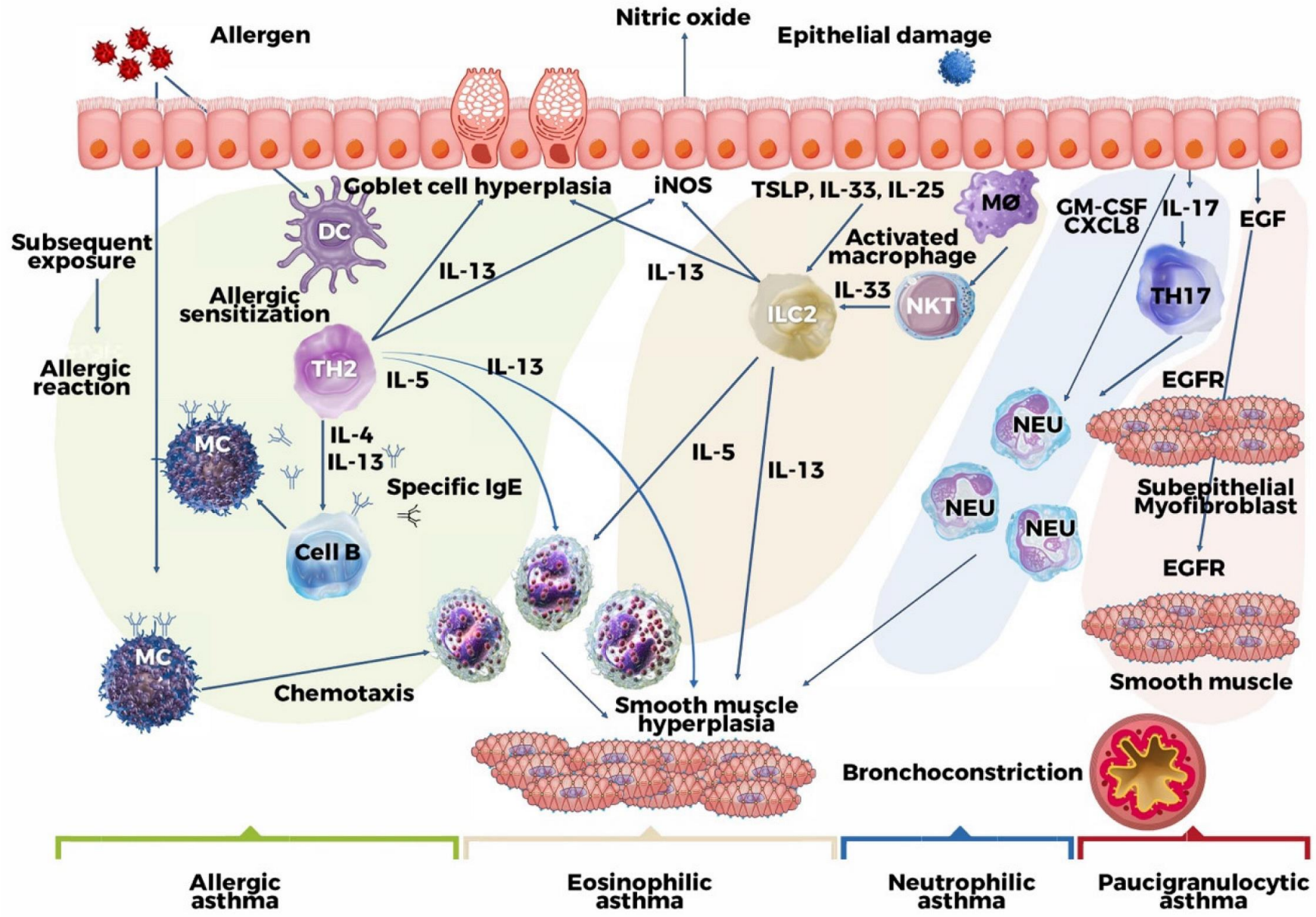
When does pathologic inflammation need to be suppressed?

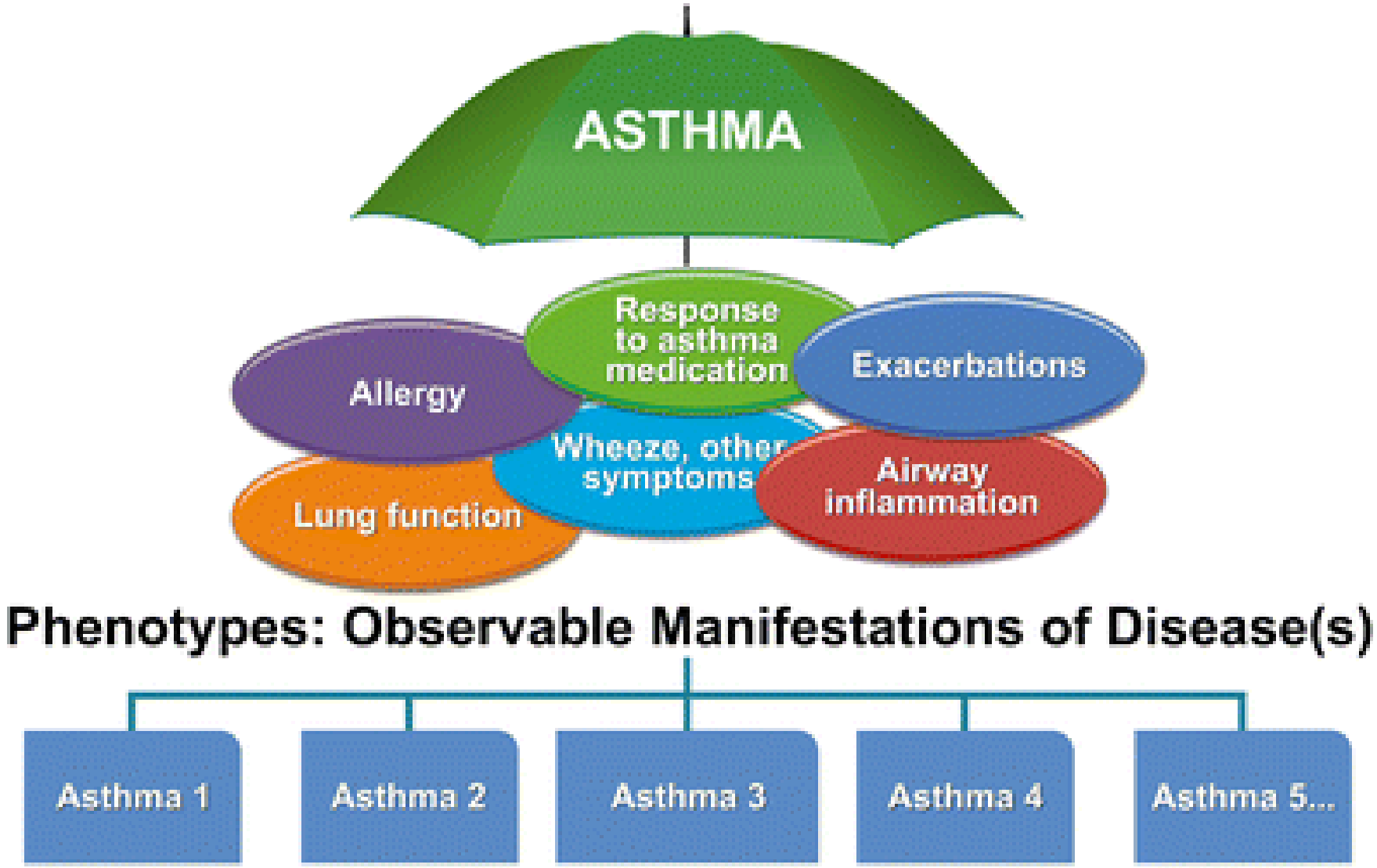
Even more complicated…





An existing examples




ASTHMA
Response to asthma medication
Allergy
Exacerbations
Wheeze, other symptoms
Airway inflammation
Lung function
Phenotypes: Observable Manifestations of Disease(s)
Asthma 1
Asthma 2
Asthma 3
Asthma 4
Asthma 5...
Endotypes: Different Diseases With Different Causes

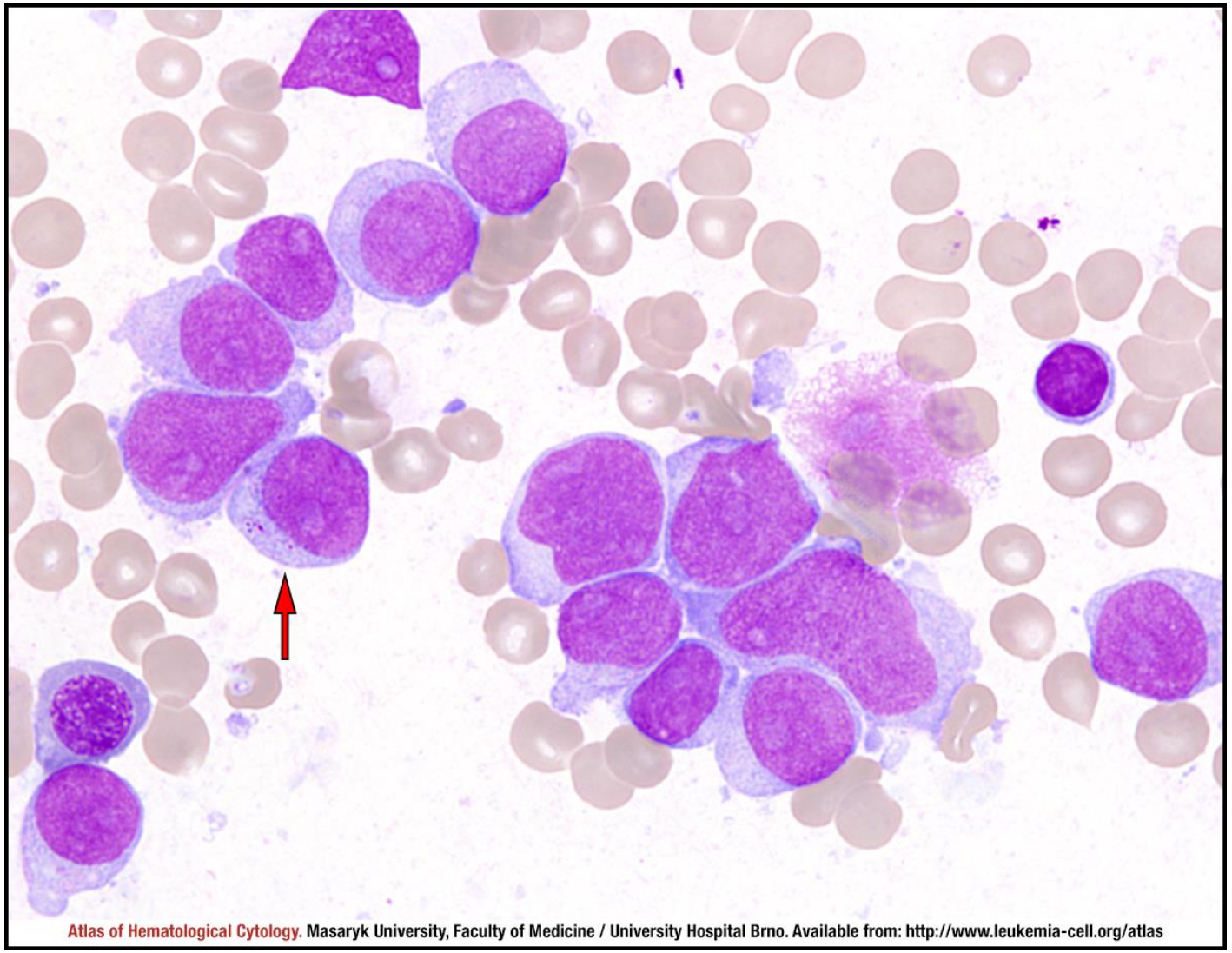
Another example:

33 yr presents with 3 weeks of fatigue and cough.

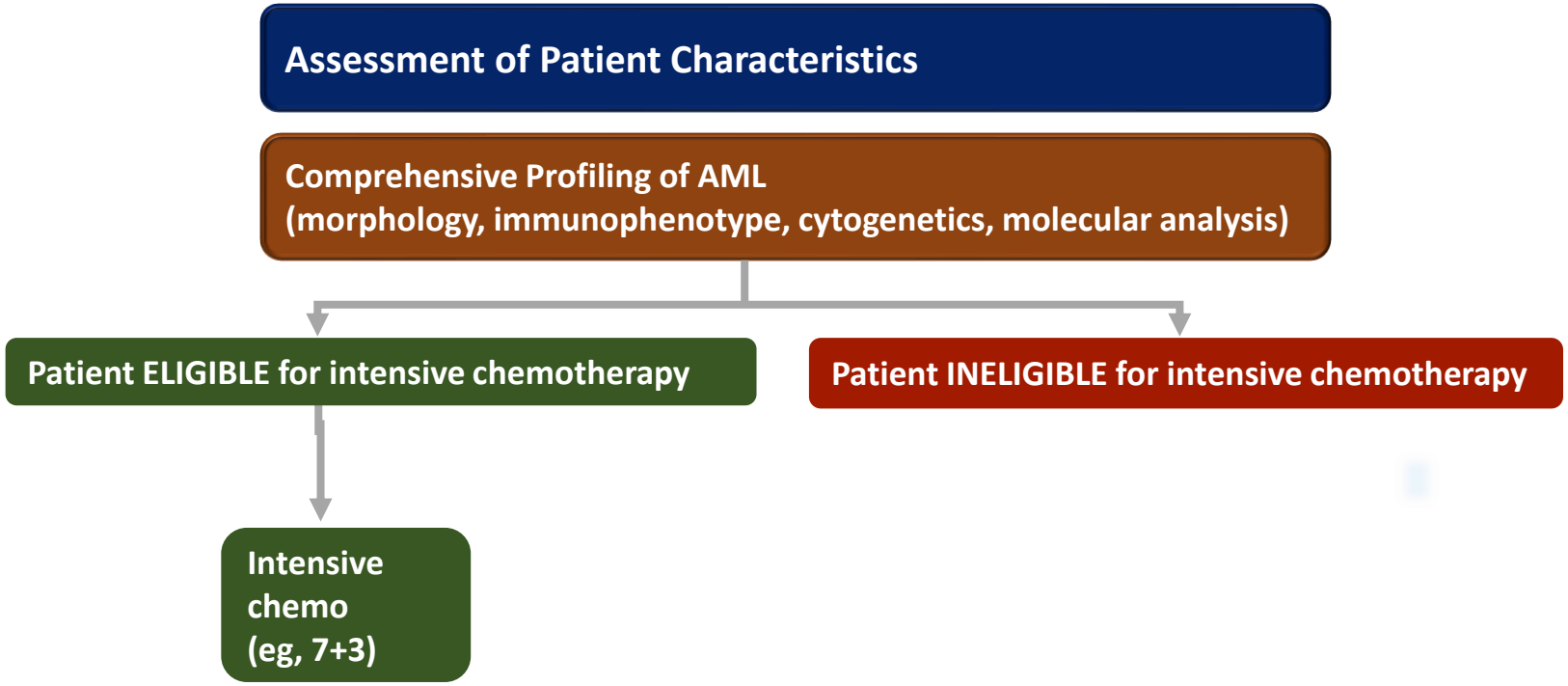
Found to have Hg of 8, PLT 30, and WBC 110

Acute myelogenous leukemia seen on cytology.

What is the treatment?



Pre- endotype identification Leukemia Rx (2017)



AML-MRC, AML with myelodysplasia-related changes;

t-AML, therapy-related AML, GO, gemtuzumab ozogamicin.

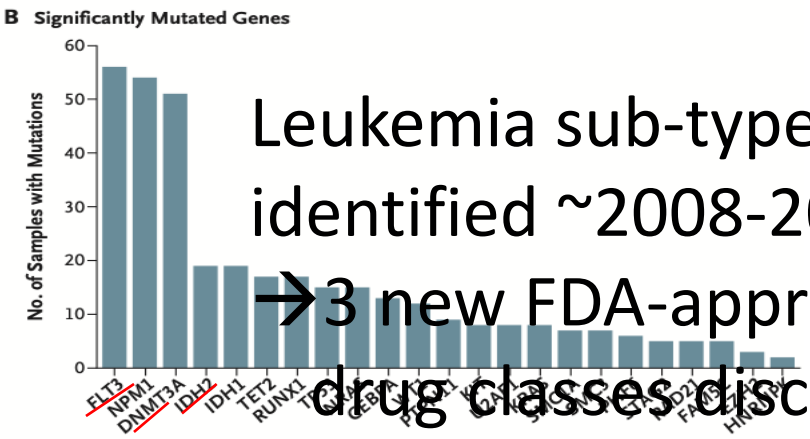
Richard-Carpentier G, DiNardo CD. Hematology *Am Soc Hematol Educ Program*. 2019;2019:548-556.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2013 VOL. 368 NO. 22

Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia

The Cancer Genome Atlas Research Network



Leukemia sub-types identified ~2008-2013;

→3 new FDA-approved drug classes discovered

→New standard of care therapy

→ ↑ survival!

ORIGINAL ARTICLE

JUNE 21, 2018

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

ORIGINAL ARTICLE

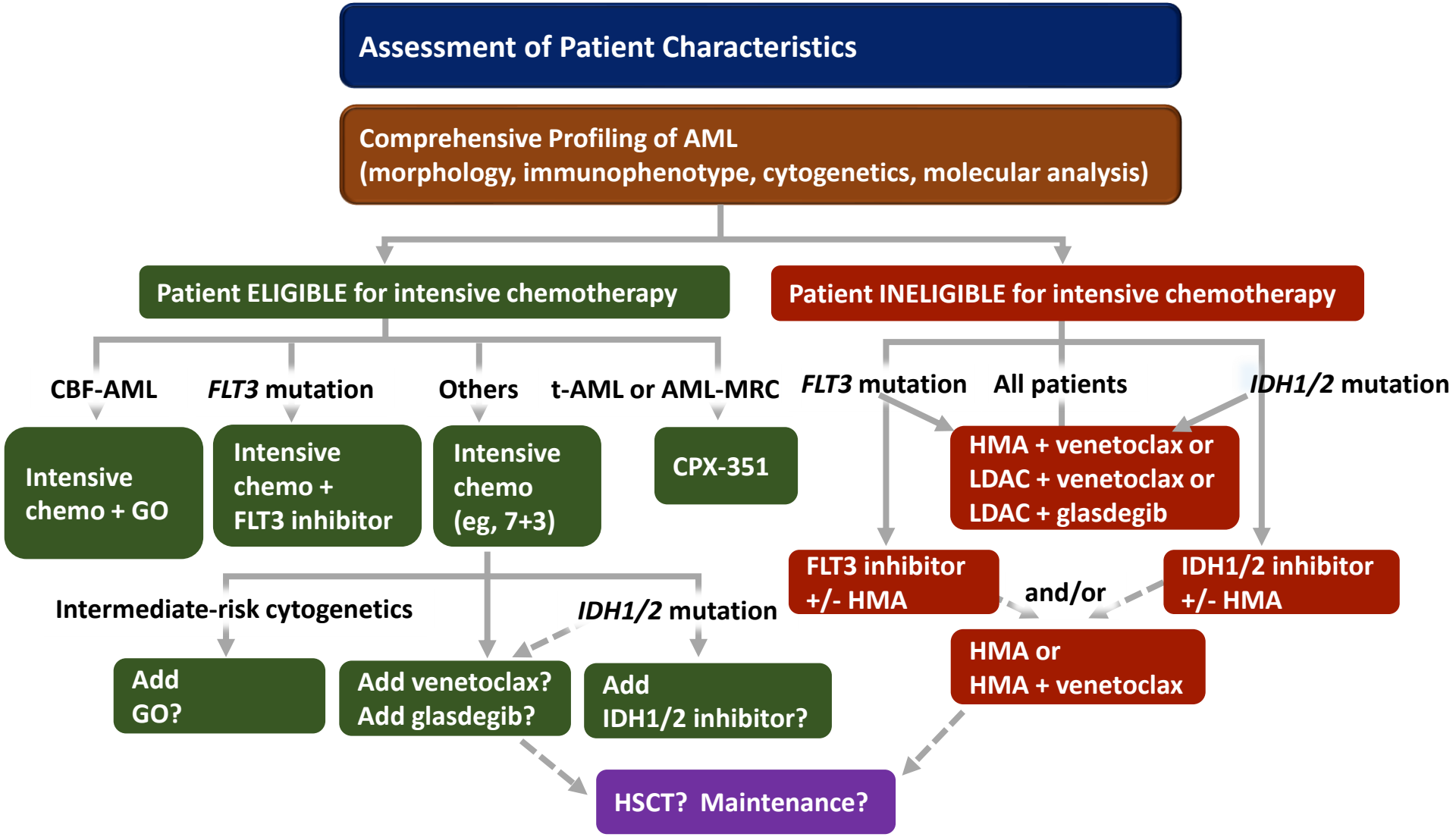
OCTOBER 31, 2019

Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

Post endotype identification Leukemia Rx (2020)



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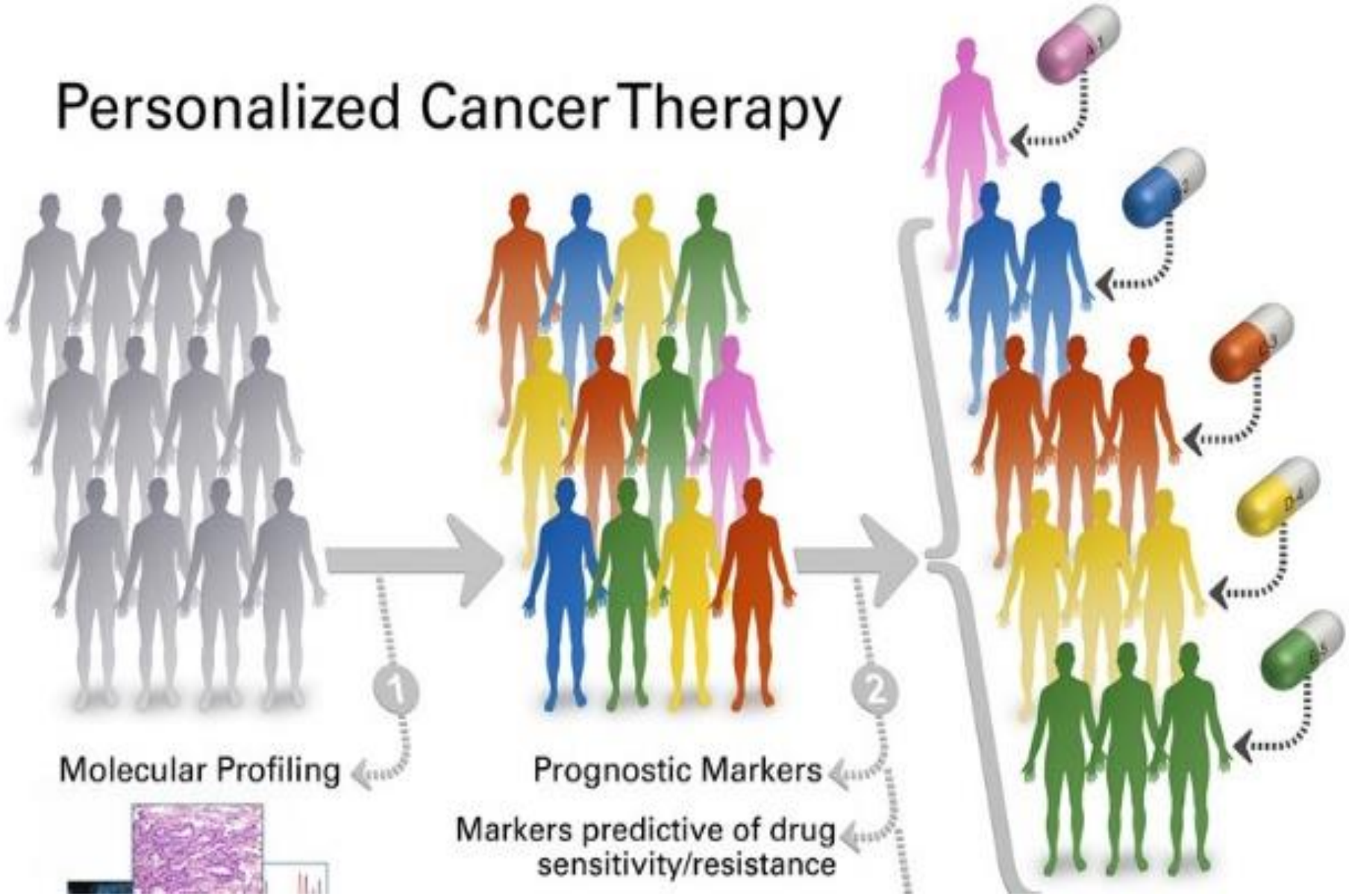
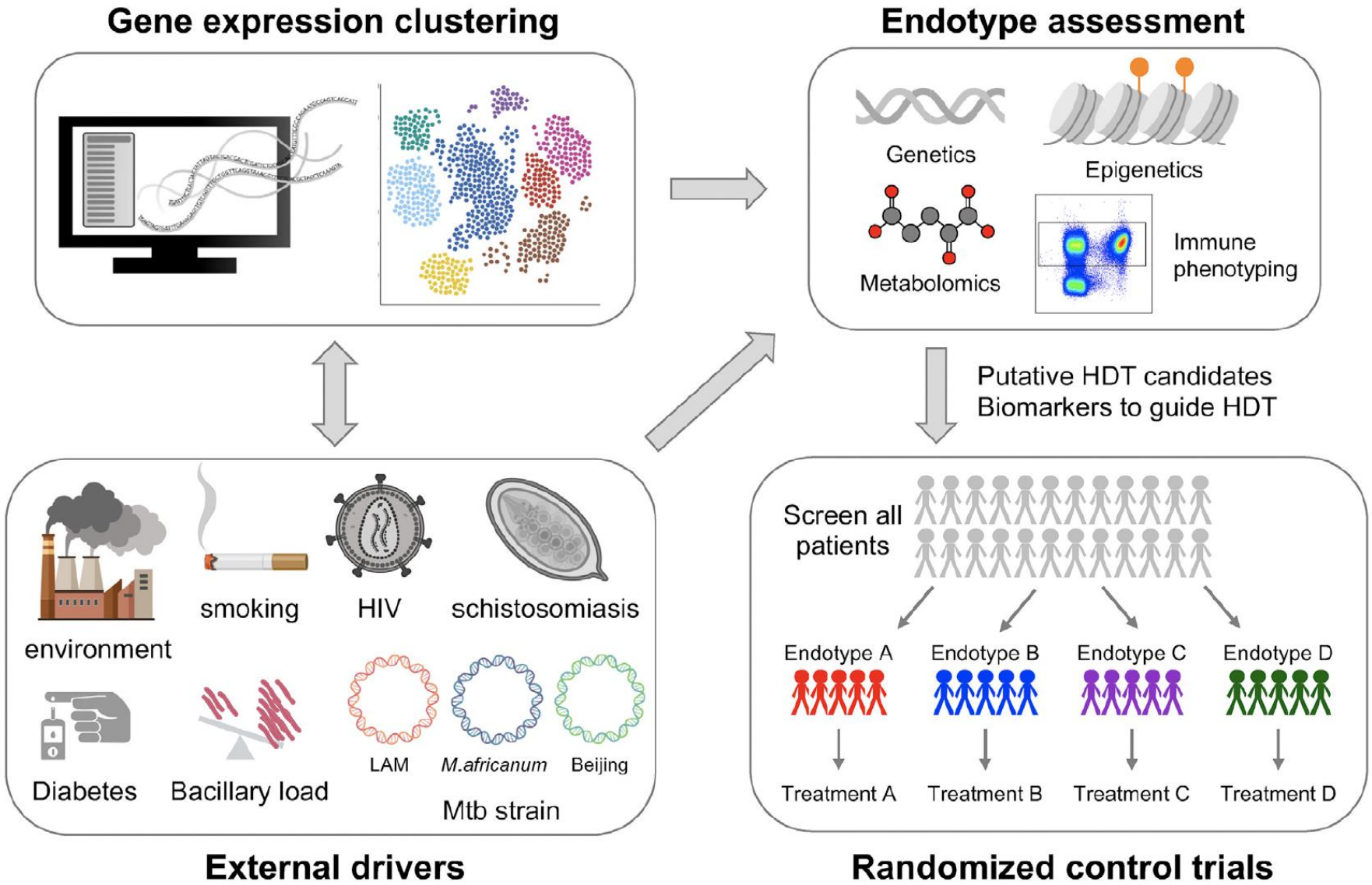
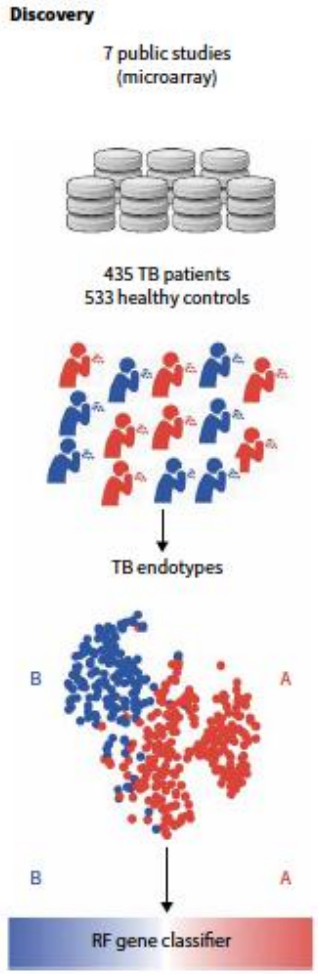
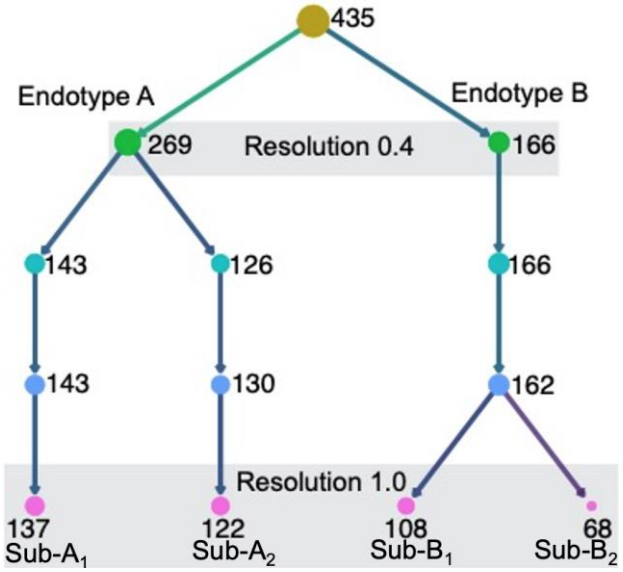

Personalized Cancer Therapy
1
2
Molecular Profiling
Prognostic Markers
Markers predictive of drug sensitivity/resistance


Gene expression clustering
Endotype assessment
Genetics
Epigenetics
Metabolomics
Immune phenotyping
Putative HDT candidates
Biomarkers to guide HDT
environment
smoking
HIV
schistosomiasis
Diabetes
Bacillary load
LAM
M.africanum
Beijing
Mtb strain
Screen all patients
Endotype A
Endotype B
Endotype C
Endotype D
Treatment A
Treatment B
Treatment C
Treatment D
External drivers
Randomized control trials

Evidence for TB endotypes:

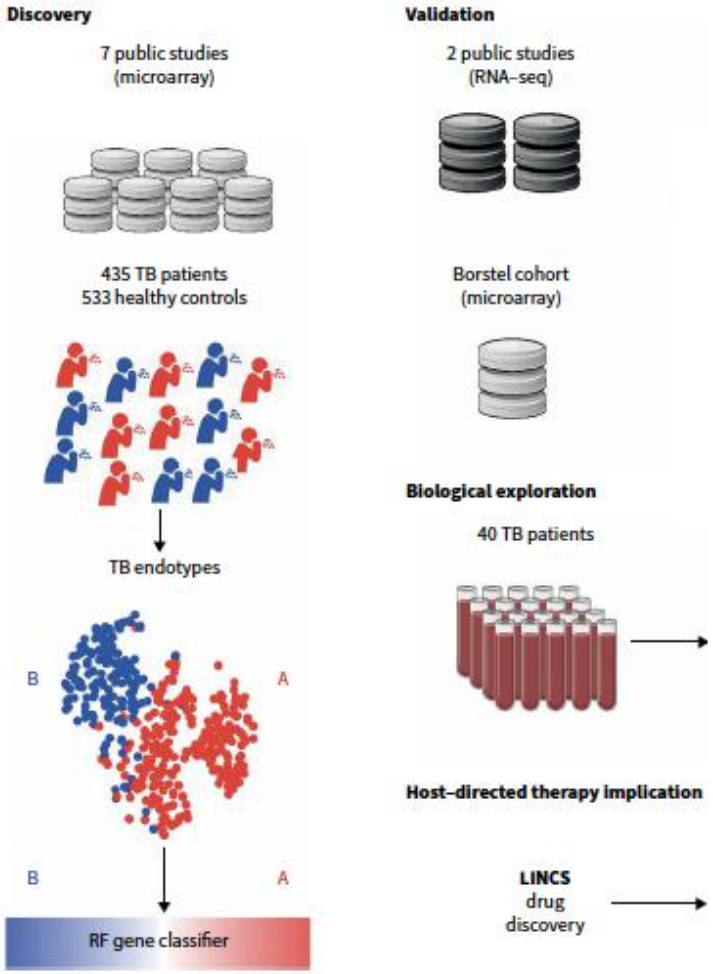


- Data mined 9 TB studies from 7 different countries
- 435 TB cases & 533 healthy controls
- Unbiased Seurat clustering
- 2-4 different TB endotypes identified



ERJ 2022

Evidence for TB endotypes:



- Validated w 2 unique RNAseq datasets
- Validated with German/ Romanian cohort
- Validated with Eswatini immunology cohort
- Linked to data base of HDT drugs

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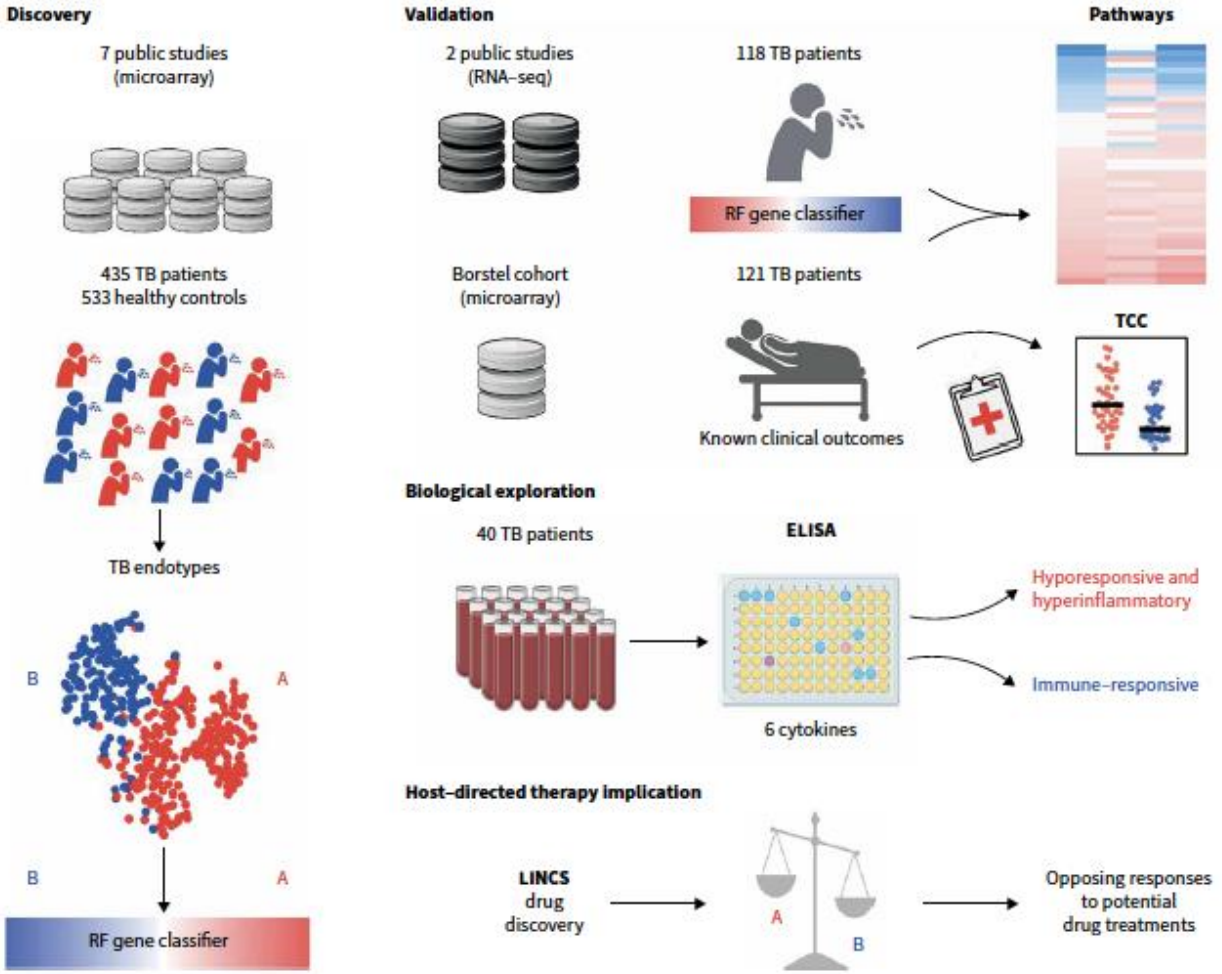
TB endotypes: different molecular pathologies that can lead to similar disease phenotypes

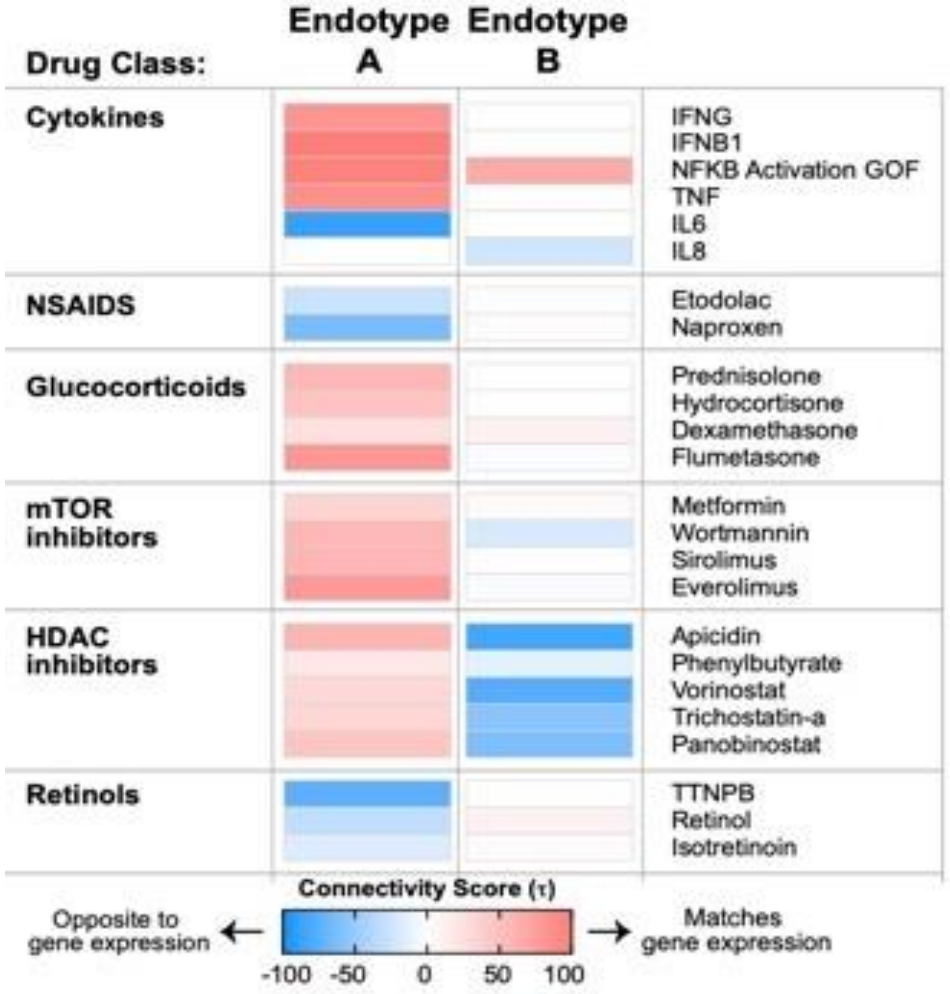


- Lowest resolution: 2 endotypes
- Endotype A: hyper-inflammatory & hypo-responsive; slower time to culture conversion

ERJ 2022

TB endotypes: different molecular pathologies that can lead to similar disease phenotypes

HDT predicted to be beneficial for one endotype either inconsequential or detrimental for other endotype



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Next steps for improving endotype-specific TB care

Long term good outcomes likely require:

1. Eradicating *Mtb* organisms

2. Reducing pathologic inflammation

3. Restoring immune responsiveness

TCGA: The Cancer Genome Atlas

- NIH run database including:
  - RNA-seq
  - Proteomics
  - Epigenomics
  - Metabolomics
  - All linked to long-term clinical outcomes
  - All data publicly available with rich meta-data
- >11,000 Cancer patients
- >15,000 publications
- Hundreds of new therapies→ improved clinical outcomes!

A Texas TB-equivalent to the TCGA?

- Linking long-term clinical outcomes (M&M)
  - Mortality
  - Lung function
  - Cardiovascular disease
  - Microbiology
  - Banked samples

A Texas solution that can transform TB clinical care in the next decade?

Thank you…

TB endotypes in 5 minutes…

Keystone 2024

Take home from previous Keystones

1. There is no single immune correlate of protection
   → Multiple TB endotypes

2. Poor outcomes are driven by at least 3 different pathologies
   → Pathogen induced pathology
   → Immune induced pathology
   → Anergy

Summary

- TB endotypes
- Different molecular pathologies can result in similar clinical TB phenotype
  - Therefore
    - Sometimes HDT will need to temper exuberant immunity
    - Other times, HDT will need to rejuvenate persistent exhauster/ anergic immunity

How does the field accelerate identification of endotype-specific HDT?

Extra slides

During TB

- 10-90% of patients have immune induced pathology

After microbial cure for TB

- Only ~50% of patients normalize inflammation
- Only ~60% normalize immune responsiveness

Estimated long-term outcomes for 10^7 TB patients

~10,000,000
TB Cases a year

5-year Post-TB Outcomes

Pre/ In-Rx Death	**10-15% CFR**	**1.5 million deaths/ yr.**
Relapse	**~2%**	**200,000 relapses/ yr.**
Post-Rx death	**2-6 deaths/ 100 PYs**	**105-300,000 deaths**
Post-Rx CVD	**1.7 CVD deaths/ 100 PYs**	**88,000 CVD deaths**
Post-Rx cancer (Ca)	**1.2 Ca deaths/ 100 PYs**	**60,000 Ca deaths**
Lung Dysfunction	**15% w severe disease**	**1.5 million w severe PTLD**

References & Notes
1: 2021 WHO Report; * TB mortality dramatically reduces once antimicrobial therapy is started.
2: Vega et al 2021, BMJ Thorax, PMID: 33547088; alternative reference PMID: 20074418
3: Romanowski & Lee-Rodriguez;
4: Blondal: 81 post-TB CVD deaths; * only represents CVD deaths, not all CVD.
5: Christensen; 22% Post-TB mortality due to Cancer; only represents Cancer deaths, not all cancers
6: Ravimohan 2018; 2020; Pasipanodya 2007

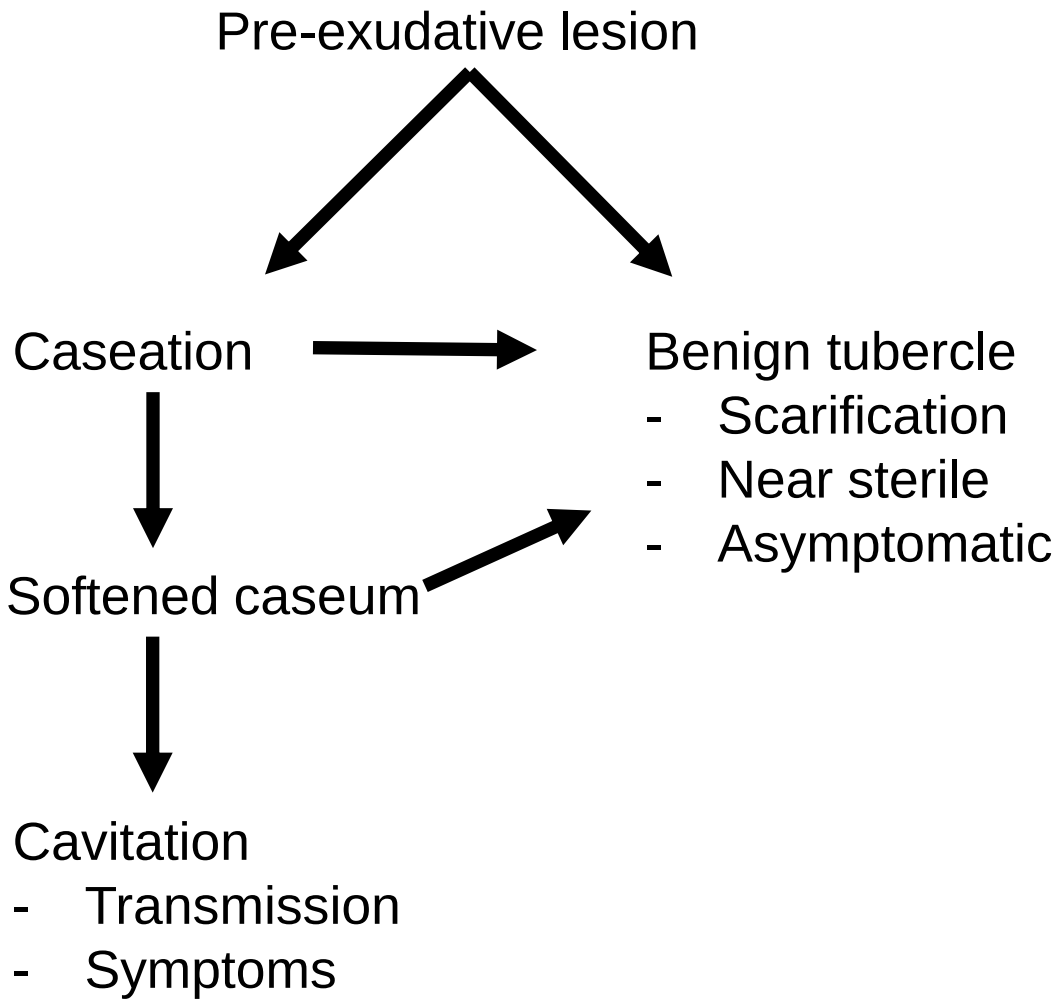
THE TUBERCLE BACILLUS

IN THE PULMONARY LESION OF MAN

Histobacteriology and its Bearing on the Therapy of Pulmonary Tuberculosis

By GEORGES CANETTI, M.D.
Director of Laboratory, Pasteur Institute, Paris

Foreword by RENE J. DUBOS
and WALSH McDERMOTT



Autopsy report of >1500 TB patients from the pre-Abx era

Canetti 1955

THE TUBERCLE BACILLUS

IN THE PULMONARY LESION OF MAN

Histobacteriology and its Bearing on the Therapy of Pulmonary Tuberculosis

By GEORGES CANETTI, M.D.
Director of Laboratory, Pasteur Institute, Paris

Foreword by RENE J. DUBOS
and WALSH McDERMOTT

Autopsy report of >1500 TB patients from the pre-Abx era

3 morphologies of soft caseum

1. Fibrino-macrophage alveolitis
   - ~581 bacilli/ 100 HPF
   - Predominant macrophages
   - Evolves rapidly to caseation w 2400 bacilli/HPF

2. Pure fibrinous alveolitis
   - ~13 bacilli/ 100 HPF
   - Rare immune cells; +fibrin
   - He hypothesized this led to solid caseation

3. Polymorphonuclear alveolitis
   - ~1670 bacilli/ 100 HPF
   - Predominant PMNs
   - He hypothesized this led directly to necrosis

Canetti 1955