UC BERKELEY SUPERFUND RESEARCH PROGRAM
SCIENCE FOR A SAFER WORLD

Long-term effects of early-life exposures on immunity and (infectious) disease risk

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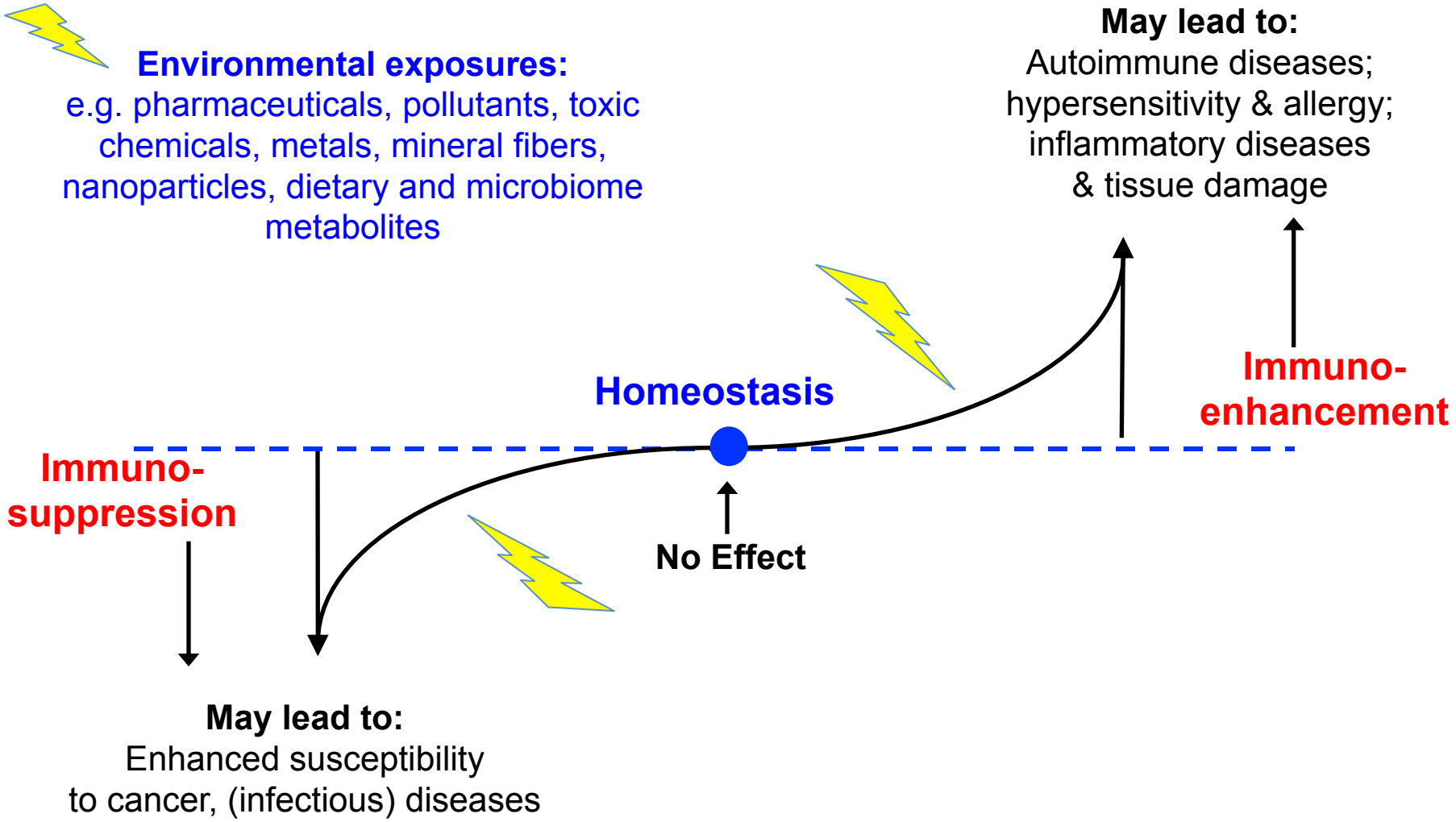
The Interplay Between Environmental Exposures and Infectious Agents, session III: Environmental Chemicals and Immune Response
NIEHS Superfund Research Program
Webinar, 7 November 2016

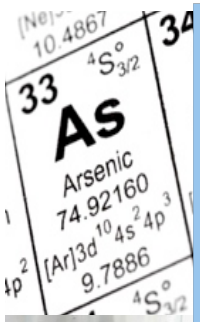
Immunomodulation

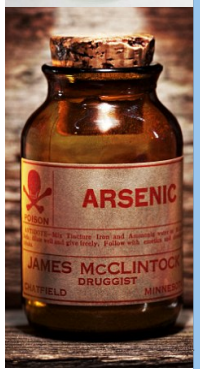


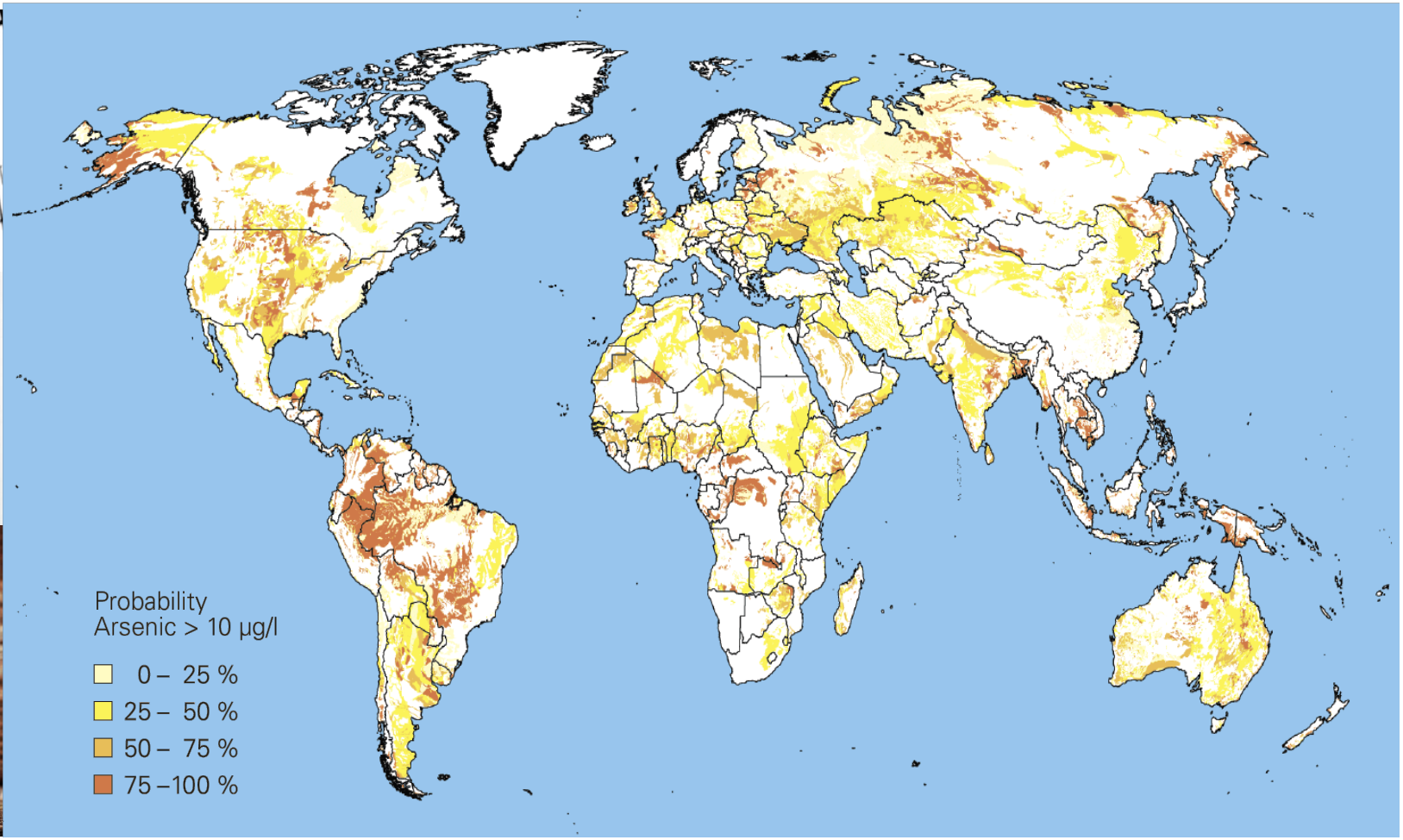
Adapted from: Casarett & Doull's Essentials of Toxicology, 2010. 2nd edition (Klaassen CD, Watkins JB, eds) New York: McGraw-Hill. ISBN – 978-0-07-162240-0

Arsenic, immunity & (infectious) disease risk

Arsenic prevalence







- Modeled global probability of geogenic arsenic in groundwater under reducing and high-pH/oxidizing aquifer conditions
- US EPA & WHO drinking water standard = 10 µg/L .

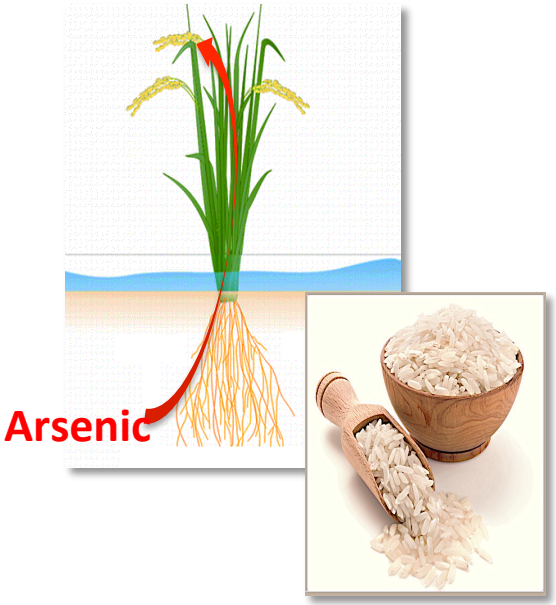
Google Images, Wikimedia Commons

Eawag modeled from Amini M., *et al*. Environ Sci Technol. 2008.

Arsenic exposure

Industrial & agricultural

Contaminated crops



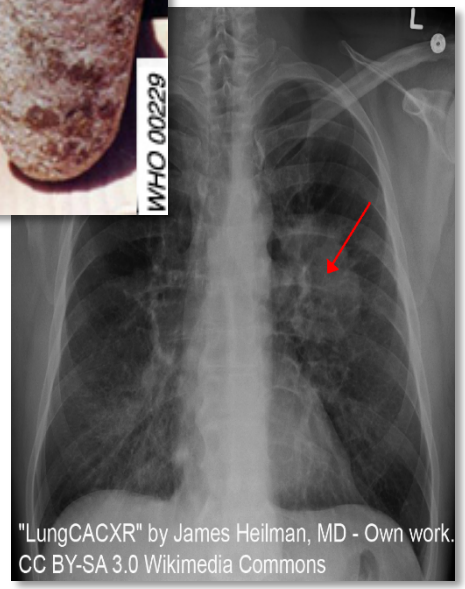
Contaminated drinking water

Coal burning

Google Images, Wikimedia Commons, WHO

Arsenic-related adverse health effects

- Skin lesions
- Cancer (skin, lung, bladder & kidney)
- Cardiovascular diseases
- Reproductive effects
- Diabetes
- Respiratory diseases



World Health Organization

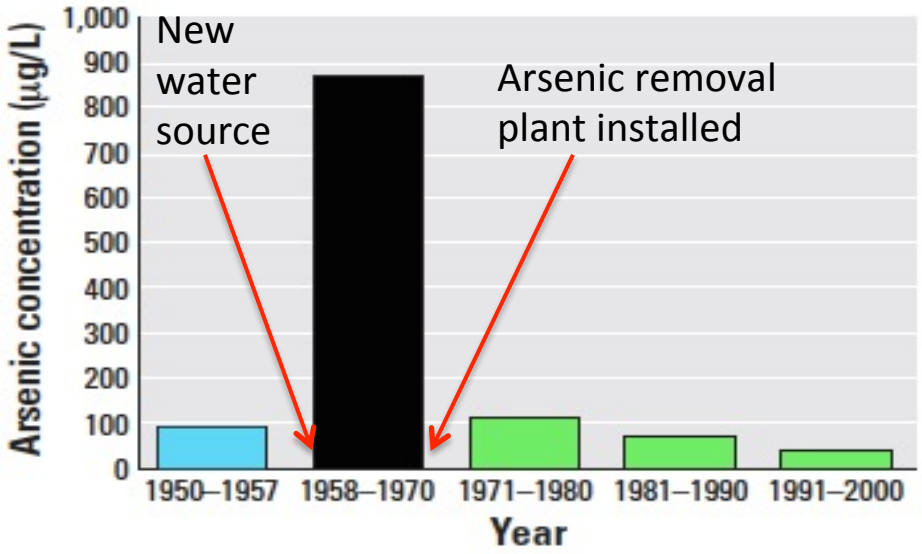
PREVENTING DISEASE THROUGH HEALTHY ENVIRONMENTS

EXPOSURE TO ARSENIC:

A MAJOR PUBLIC HEALTH CONCERN

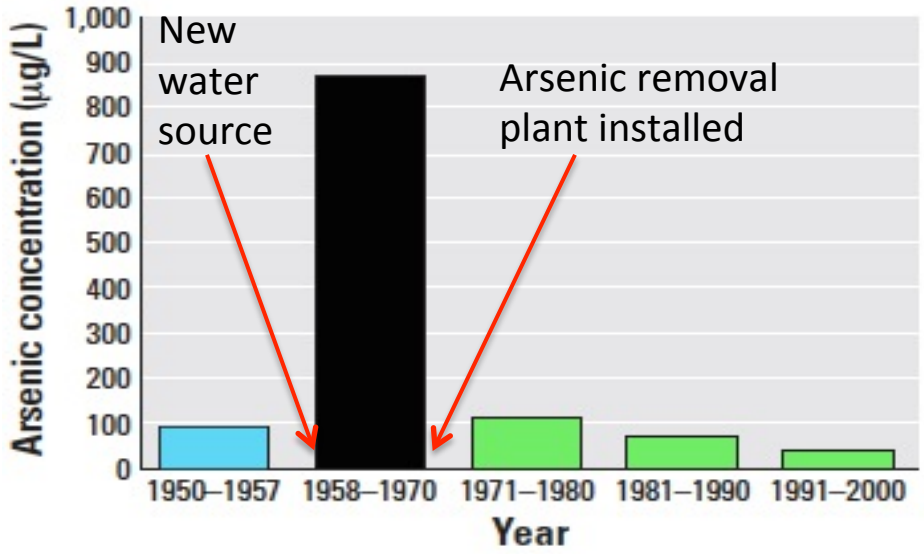
WHO, Wikimedia Commons

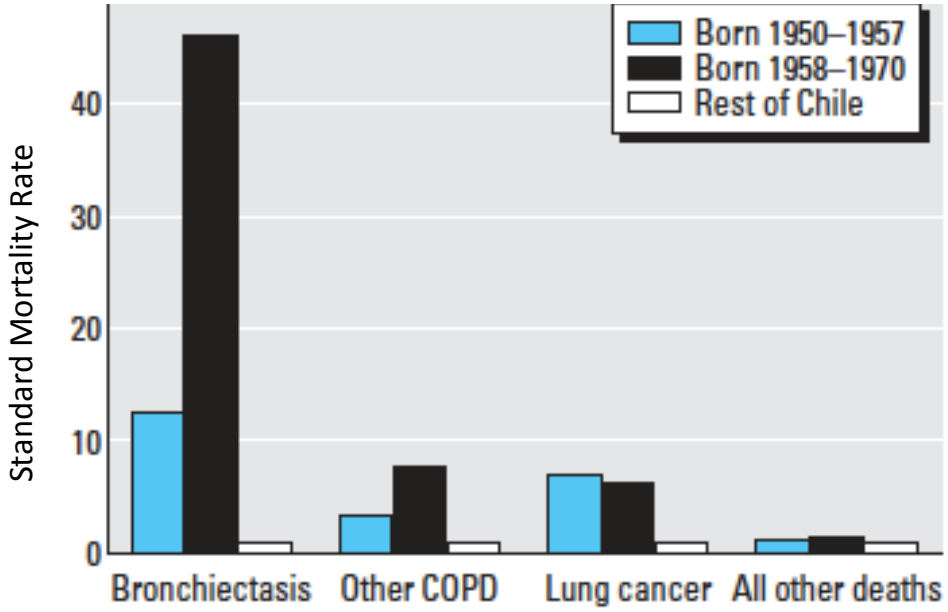
Early-life exposure to arsenic in Chile



Ferreccio, C., *et al.* Epidemiology 2000; Smith, A., *et al.* EHP 2006 ; Yuan, Y., *et al.* Epidemiology 2010; Steinmaus, C., *et al.* CEBP 2013

Early-life exposure to arsenic in Chile



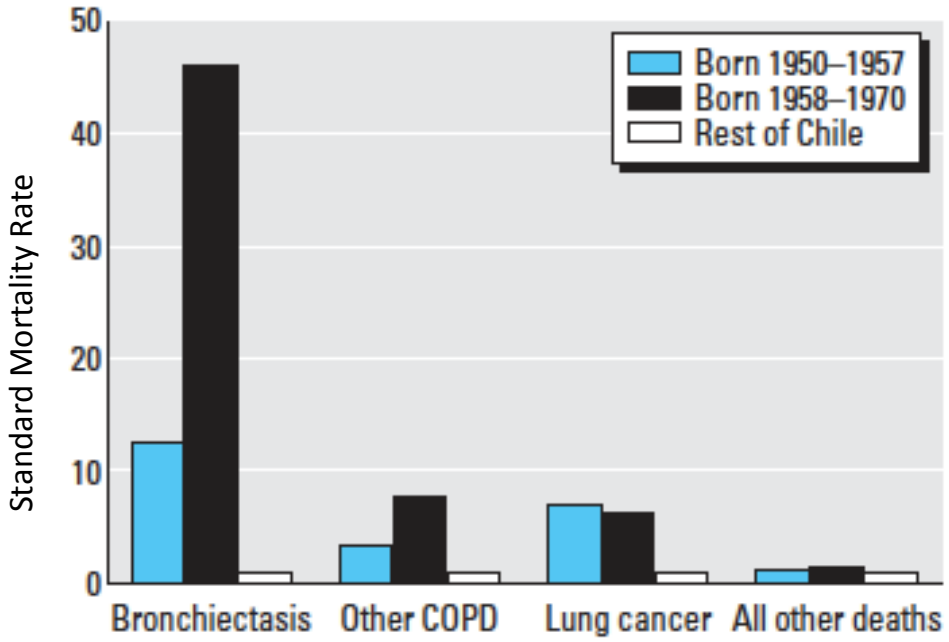


> 40 years later

Smith, A., *et al.* EHP 2006 ; Yuan, Y., *et al.* Am.J.Epi. 2007; Yuan, Y., *et al.* Epidemiology 2010; Steinmaus, C., *et al.* CEBP 2013

Early-life exposure to arsenic in Chile

Rare evidence supporting the "**Developmental Origins of Health and Disease**" hypothesis.



> 40 years later

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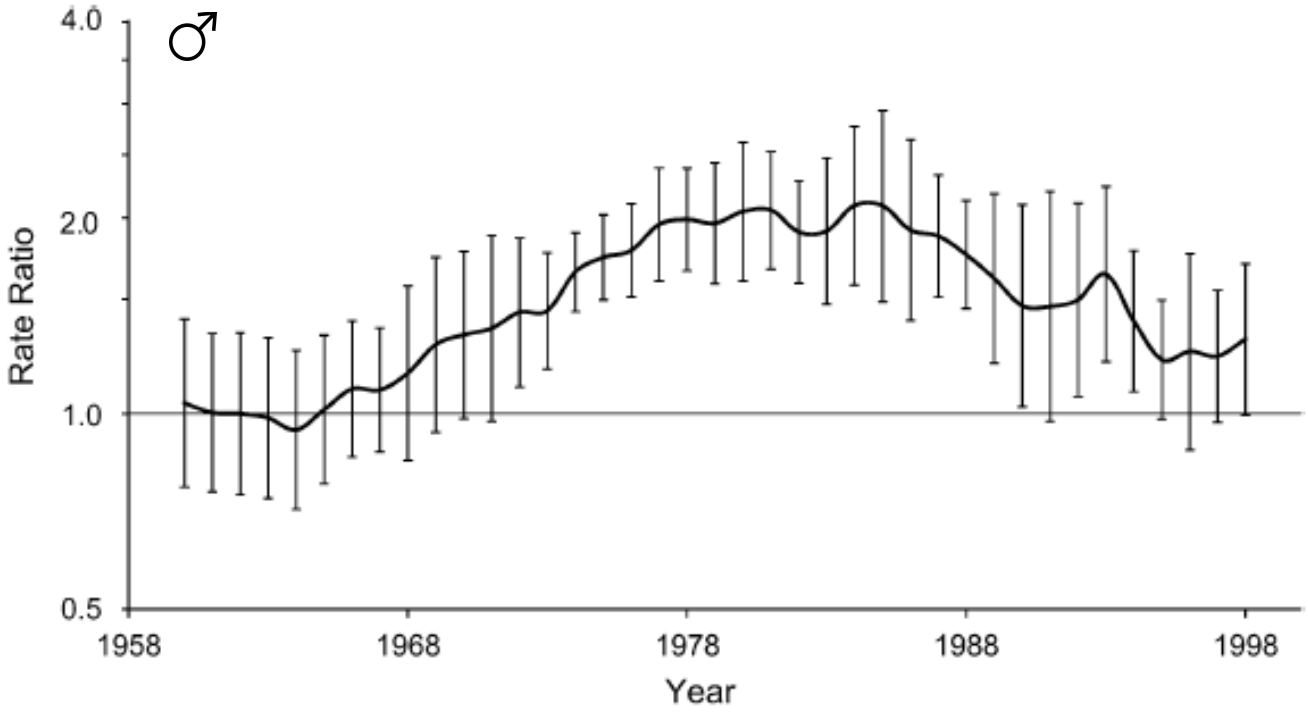
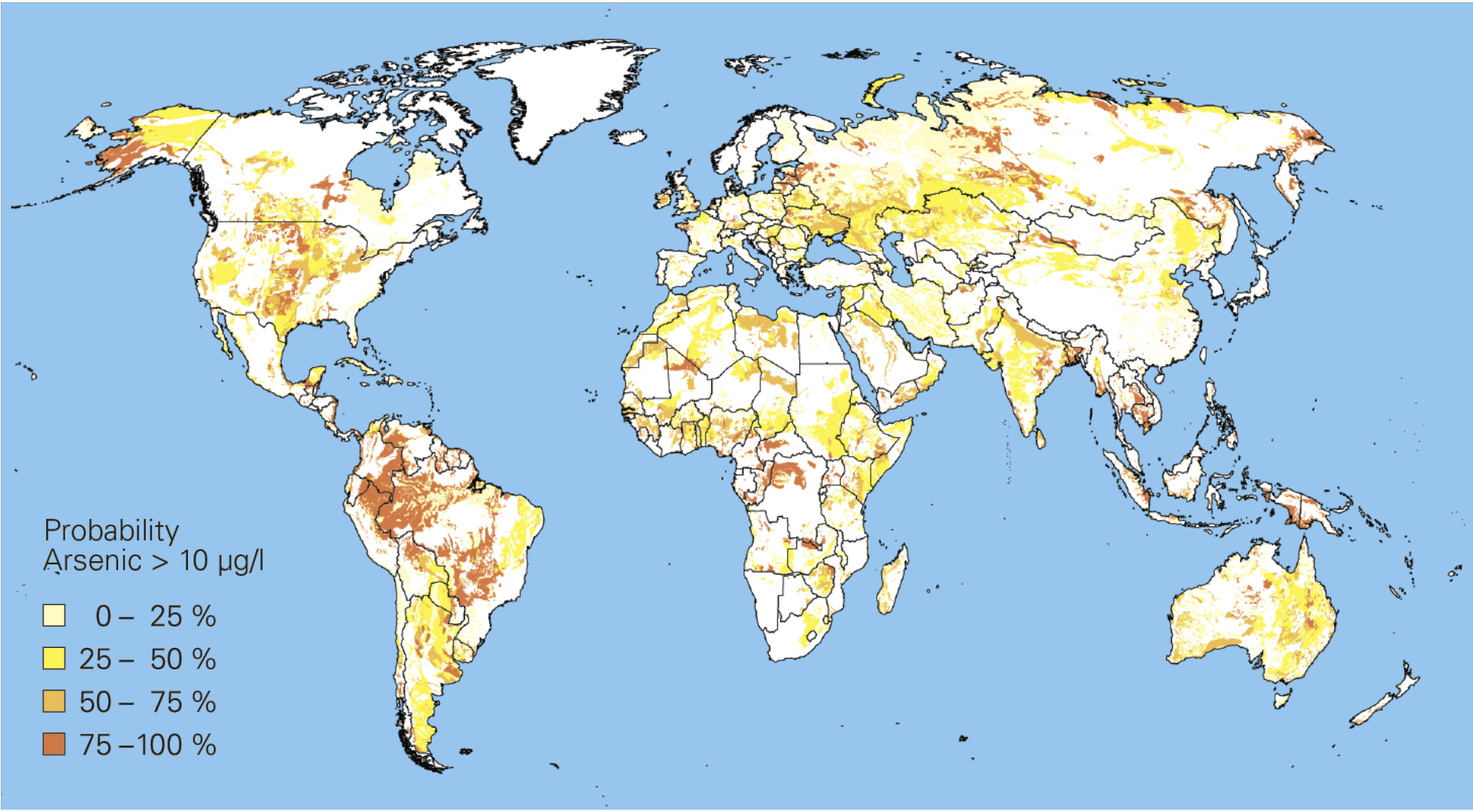
Early-life exposure to arsenic in Chile

Tuberculosis mortality



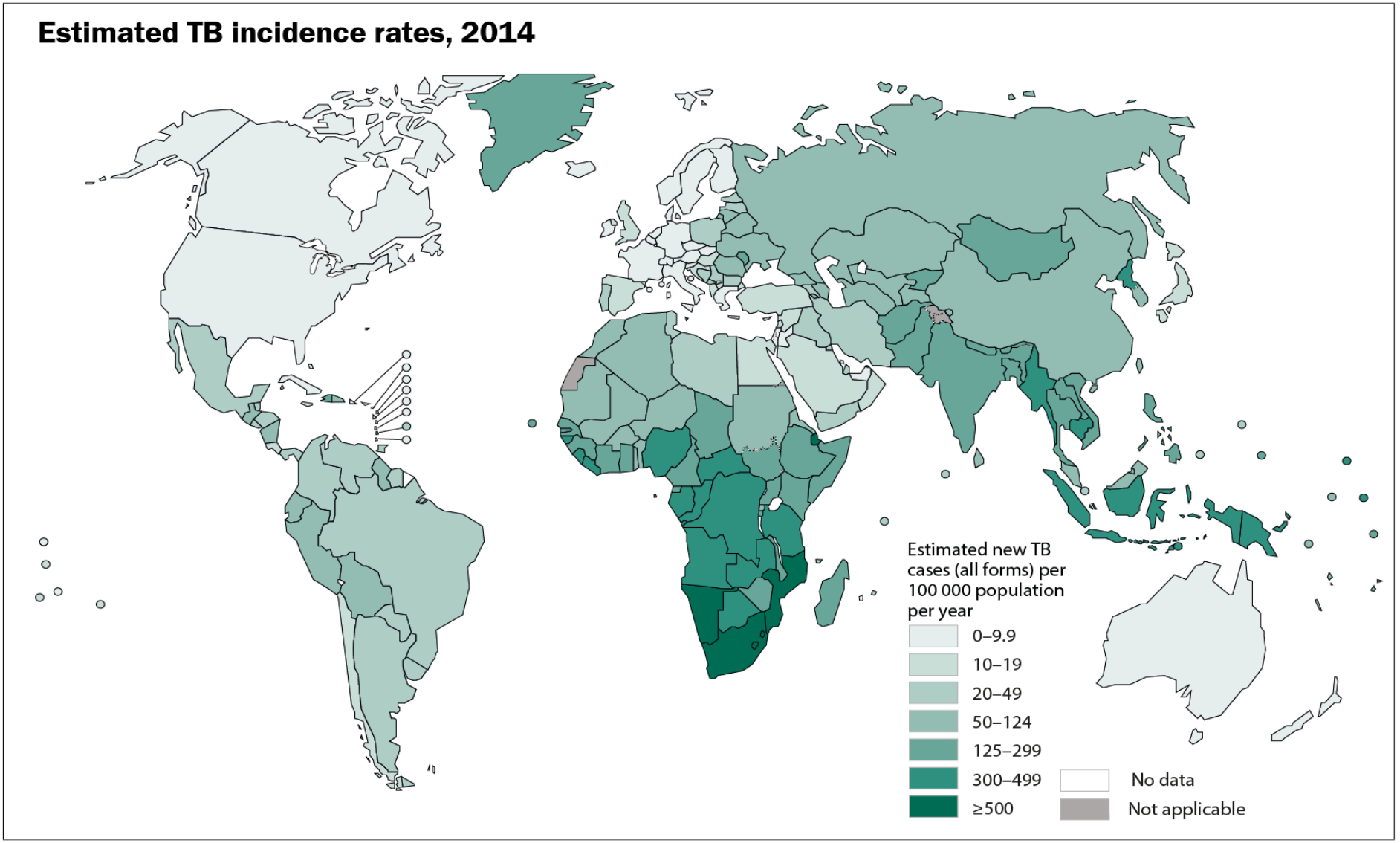
Smith, A., *et al.* EHP 2006; Smith, A. *et al.* Am. J. Epi. 2011

Arsenic prevalence



Eawag modeled from Amini M., *et al*. Environ Sci Technol. 2008.

Tuberculosis incidence

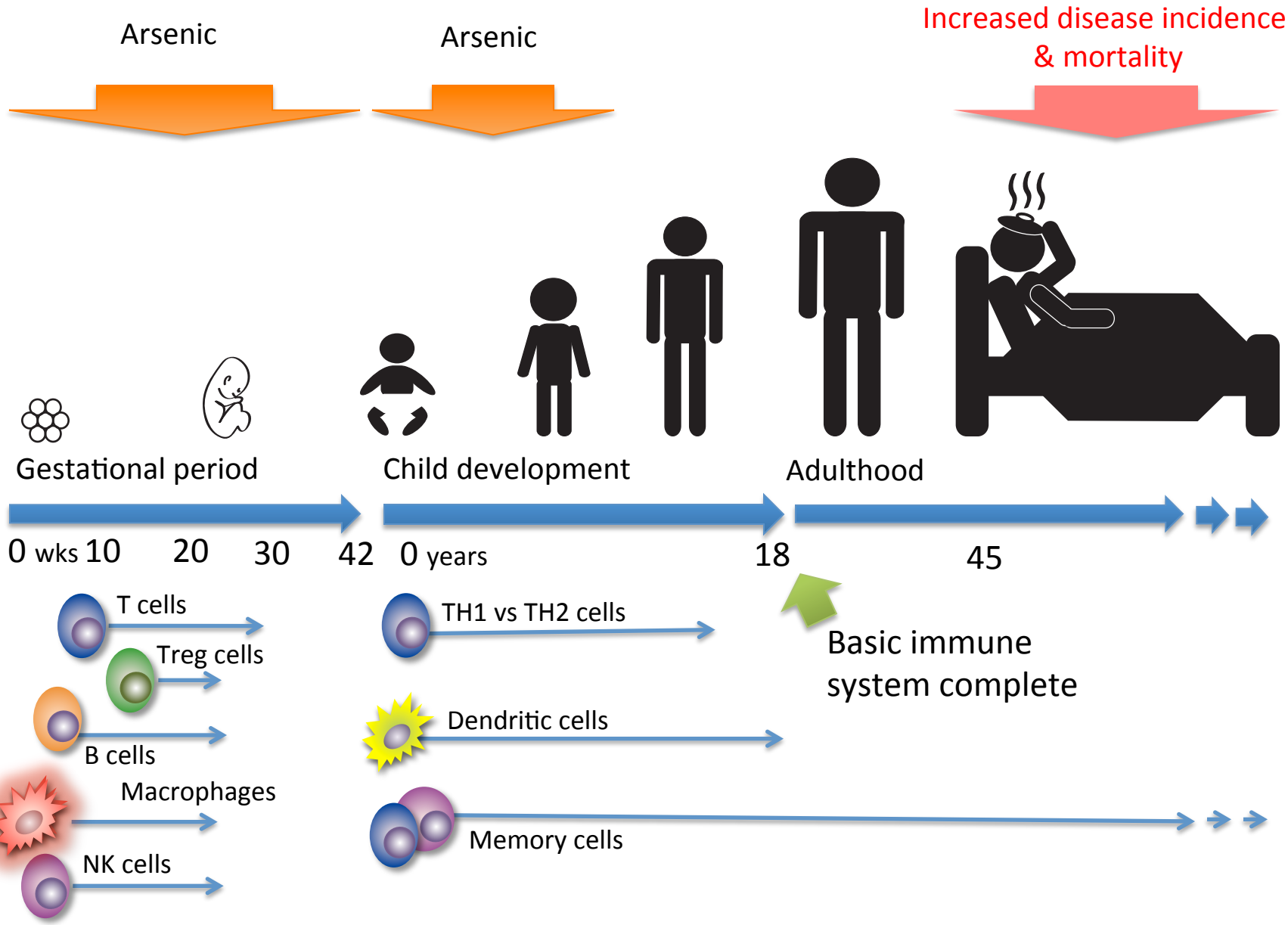


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Early-life exposure to arsenic



General hypothesis:

Exposure-induced immune developmental changes contribute to the persistent global burden of infectious and chronic diseases.

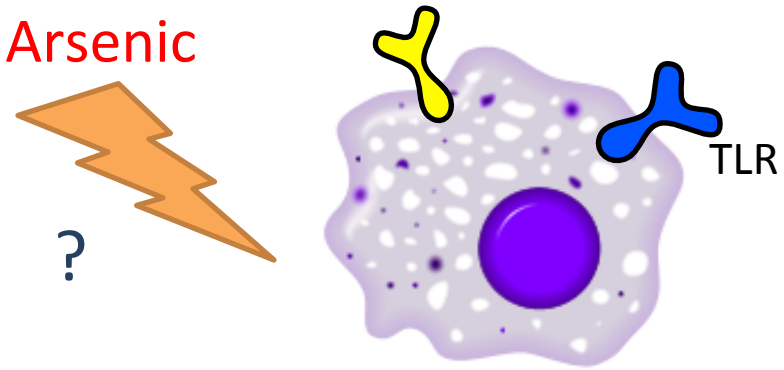
Study models: Arsenic & TB

Google Images, Wikimedia Commons

Arsenic & macrophages

Specific hypothesis:

Early-life exposure to arsenic alters macrophage development & function causing increased disease later in life.



Cytokines/chemokines

Nitric Oxide

Signaling lipids

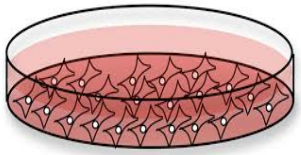
M1:
Pro-inflammatory, Bactericidal activity, Tumor suppression

M2:
Scavenging, Tissue repair, Angiogenesis, Tumor promotion

Wikimedia Commons

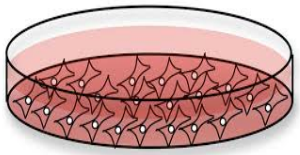
How does arsenic alter macrophages?

Homeostasis



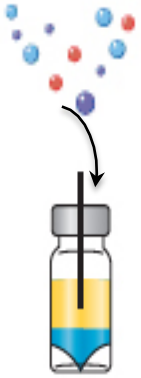
Macrophages

Mouse bone marrow



Arsenic-treated macrophages

Metabolite analysis



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Arsenic alters signaling lipids expression

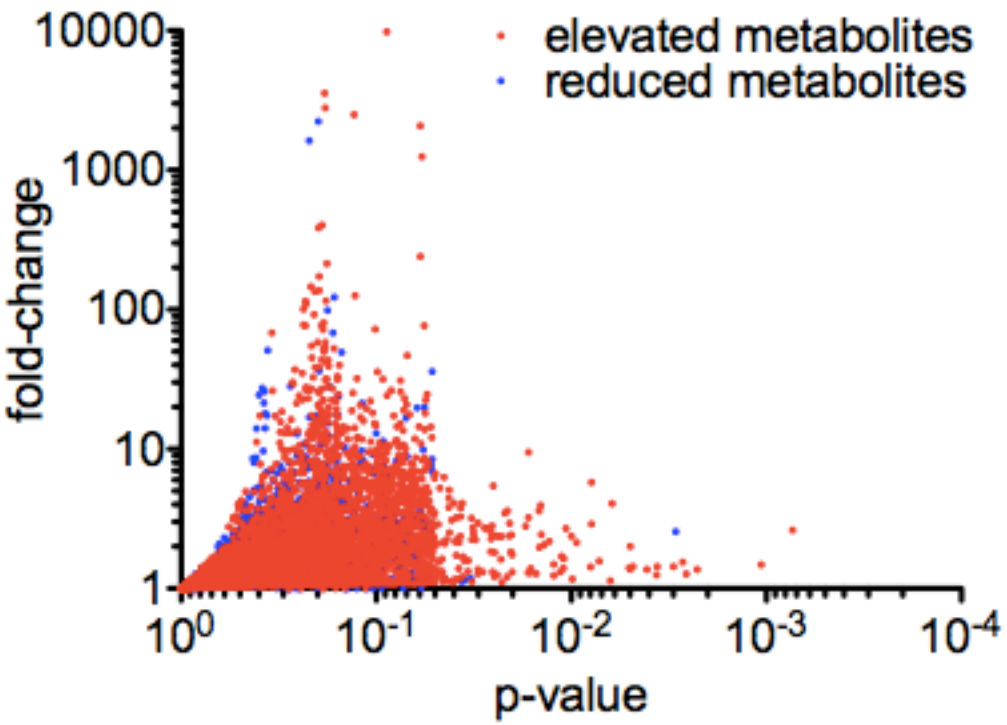
Homeostasis

Macrophages

Mouse bone marrow

Arsenic-treated macrophages

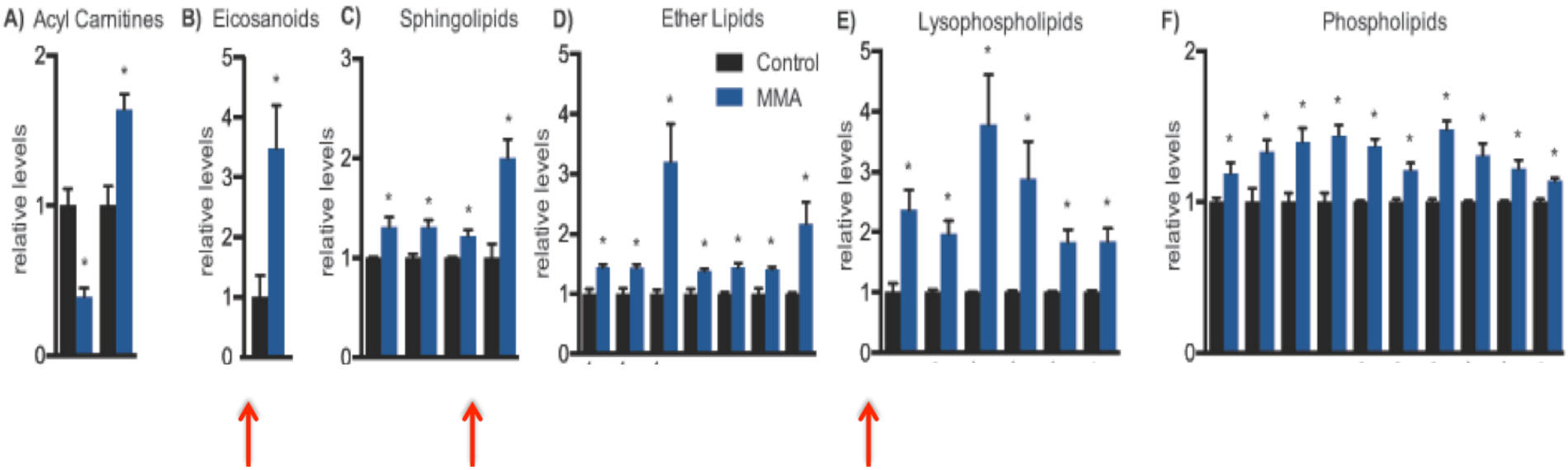
Metabolite analysis



Sillé *et al*, unpublished

Arsenic alters signaling lipids expression

Homeostasis



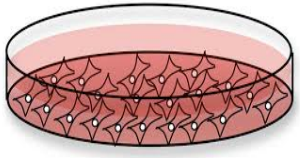
Pro-inflammatory and pro-tumorigenic signaling lipids

Sillé *et al*, unpublished

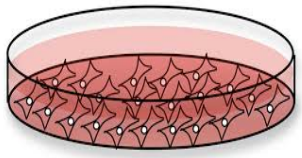
How does arsenic alter macrophages?

Homeostasis

Mouse bone marrow

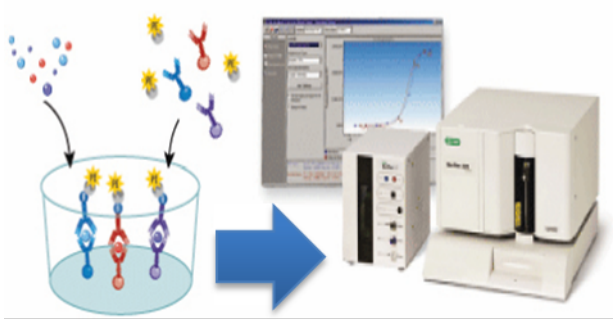


Macrophages



Arsenic-treated macrophages

Signaling protein analysis

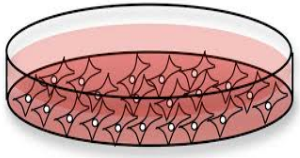


Google Images, Wikimedia Commons

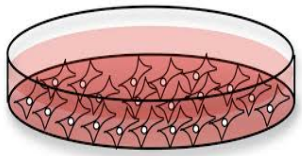
Arsenic alters cytokine/chemokine expression

Homeostasis

Mouse bone marrow



Macrophages



Arsenic-treated macrophages

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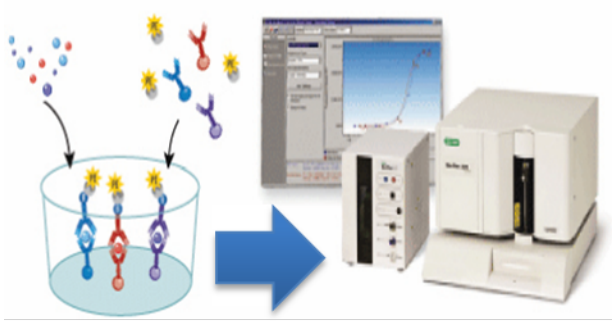
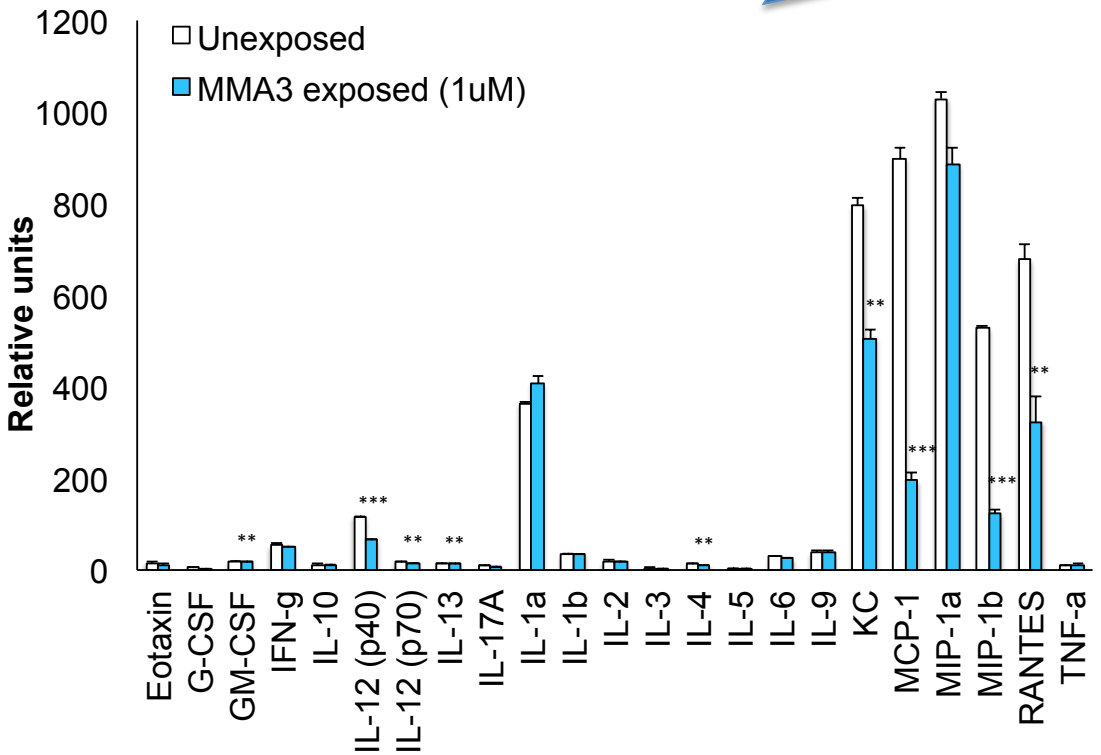
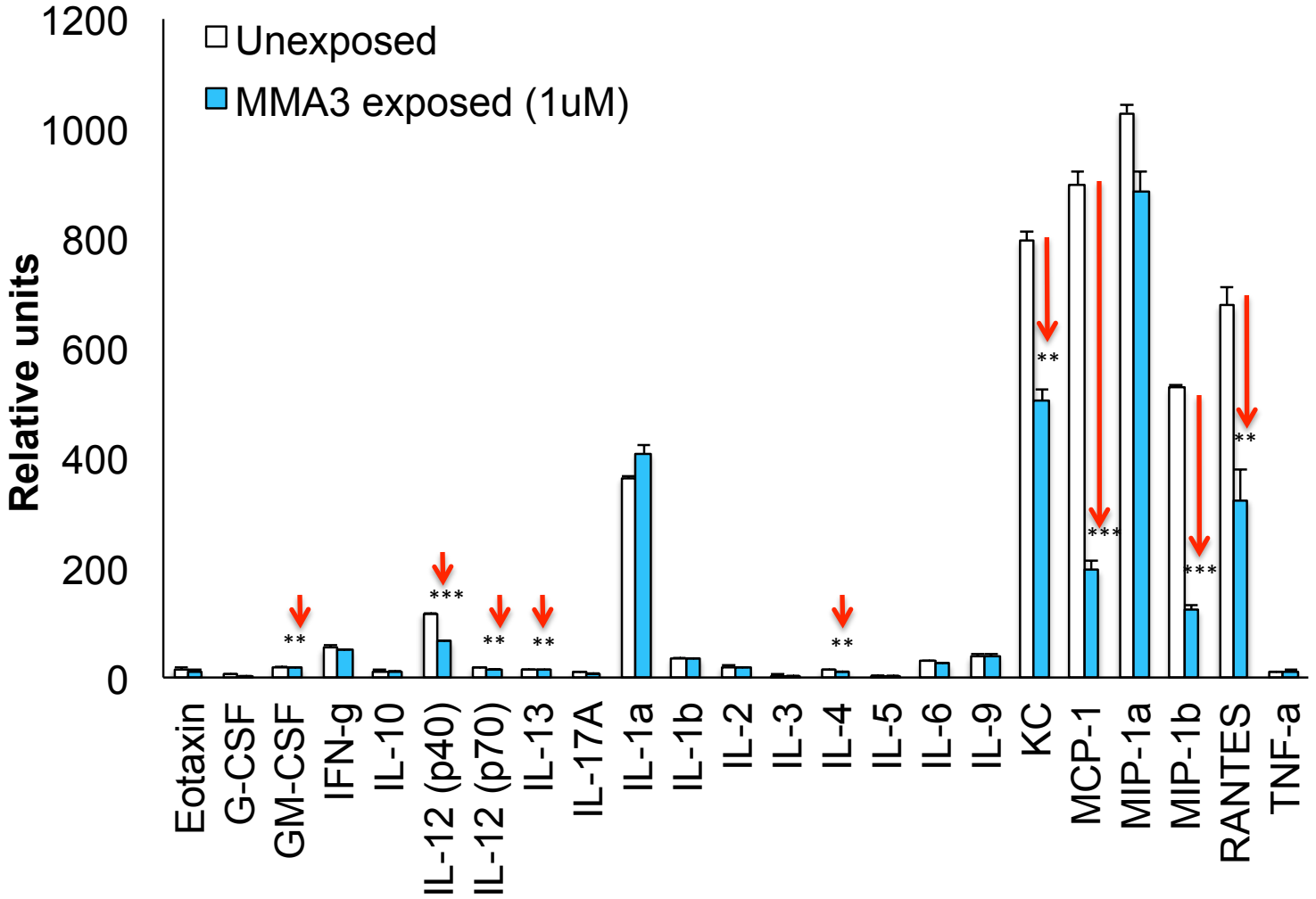




Sillé *et al*, unpublished

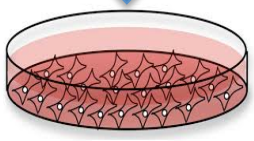
Arsenic alters cytokine/chemokine expression

Homeostasis



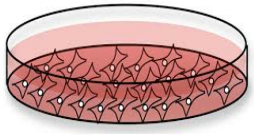
Sillé *et al*, unpublished

Does arsenic alter macrophage activation?



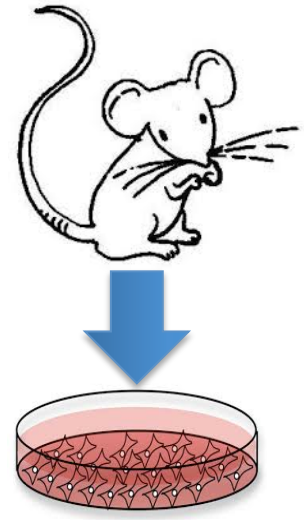
Macrophages

TLR2 activation: PamCys3



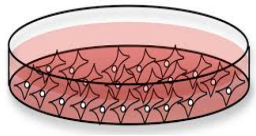
Arsenic-treated macrophages

Arsenic alters cytokine/chemokine expression in activated macrophages

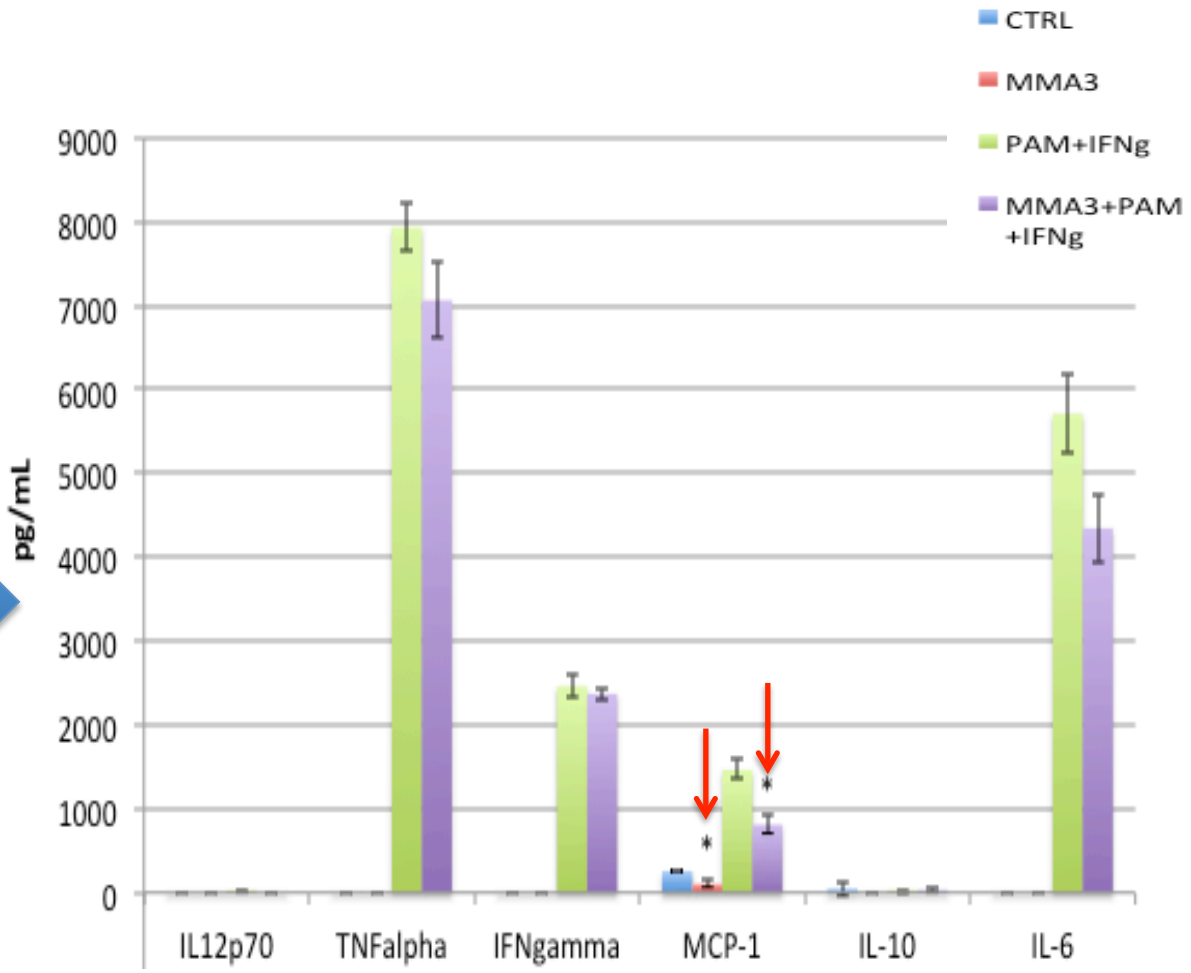


Macrophages

TLR2 activation: PamCys3

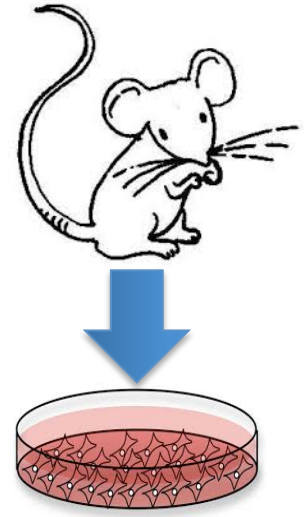


Arsenic-treated macrophages



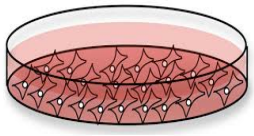
Sillé *et al*, unpublished

Arsenic alters nitric oxide production in activated macrophages

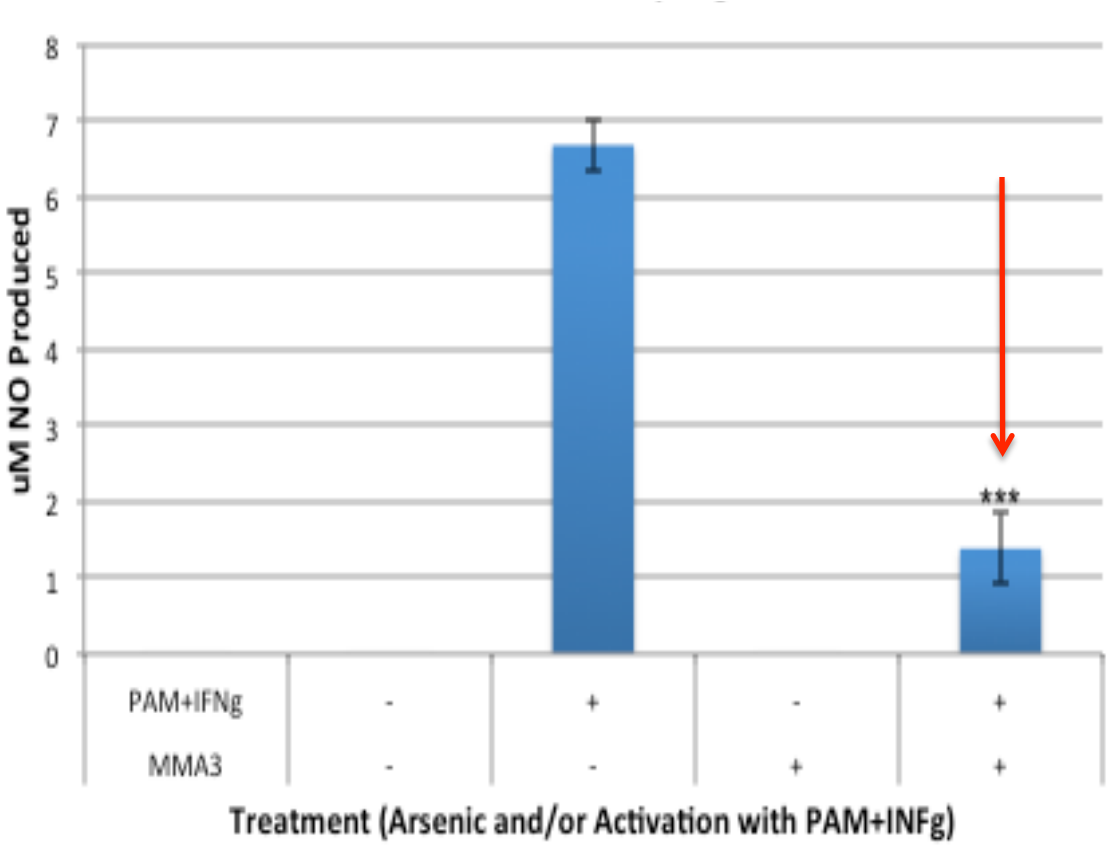


Macrophages

TLR2 activation: PamCys3

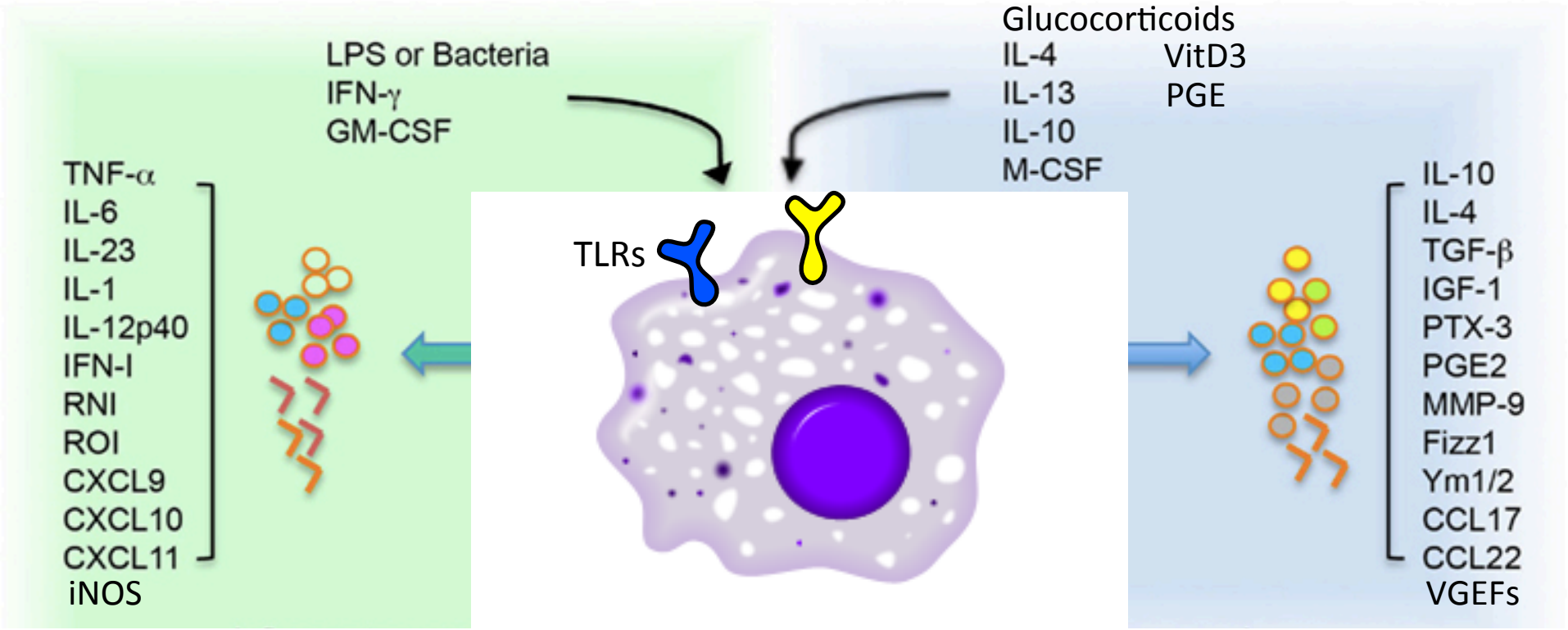


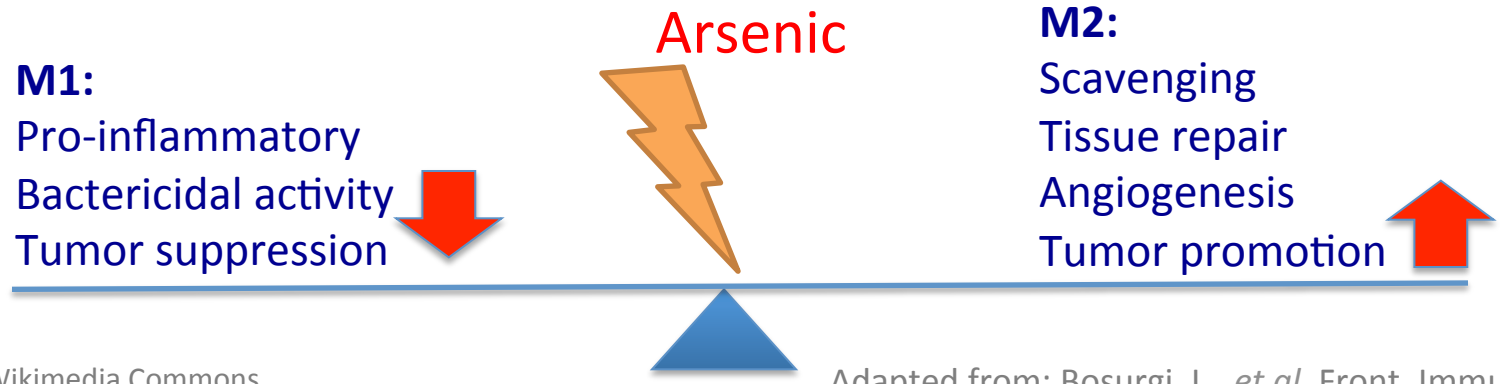
Arsenic-treated macrophages



Sillé *et al*, unpublished

Arsenic & macrophages

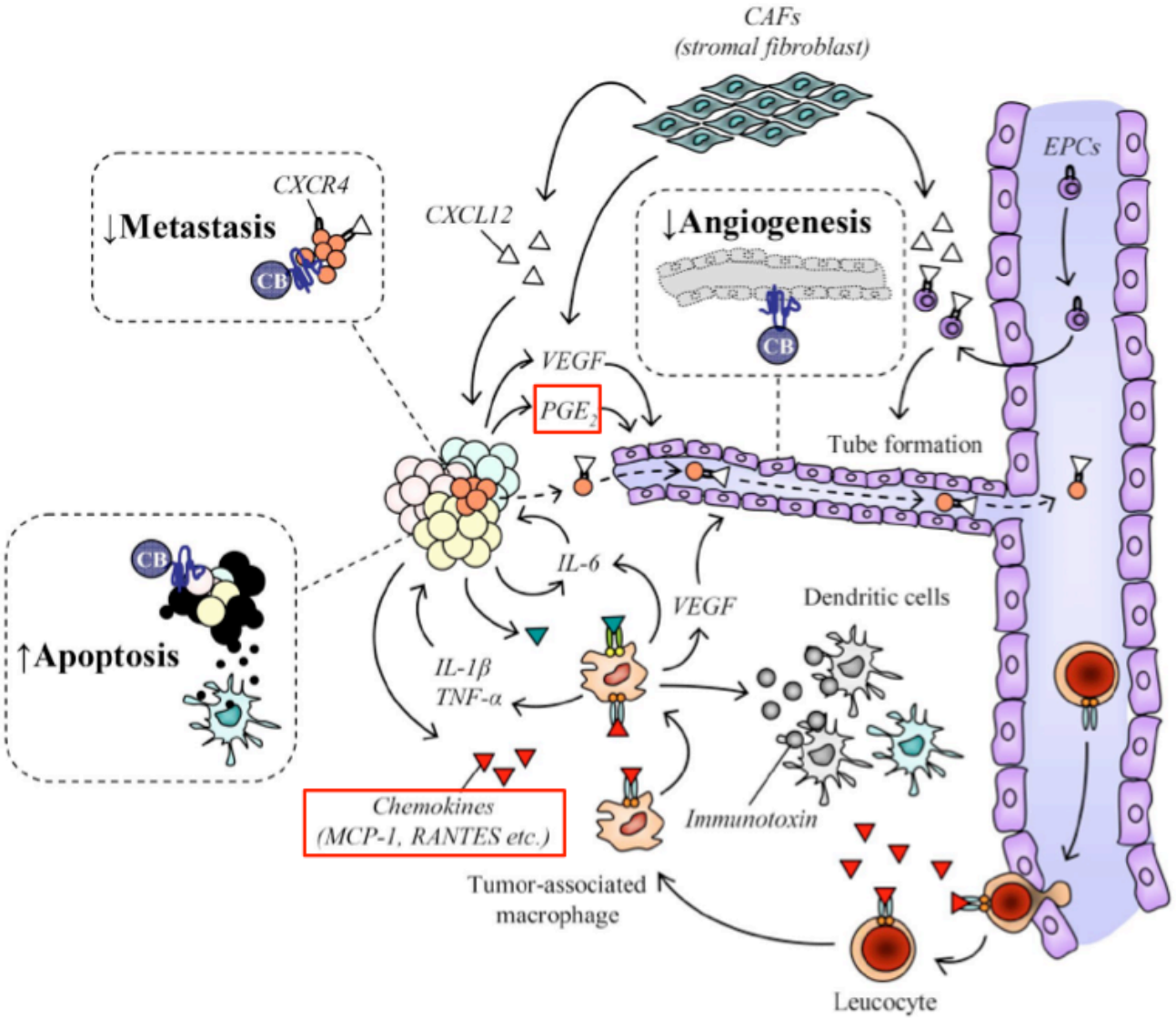




Google Images, Wikimedia Commons

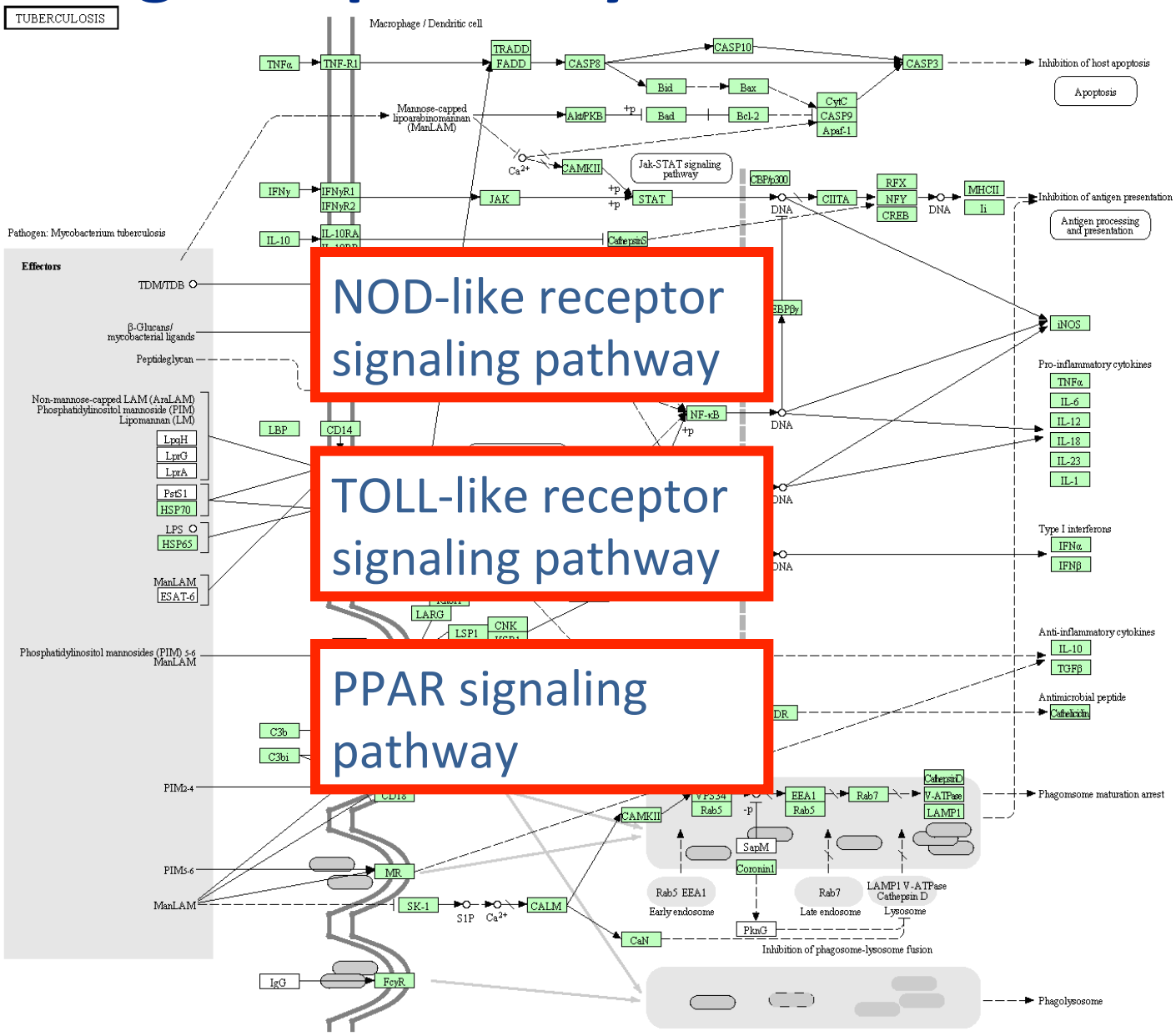
Adapted from: Bosurgi, L., *et al*. Front. Immunol. 2011

Arsenic-targeted pathways that favor tumor progression



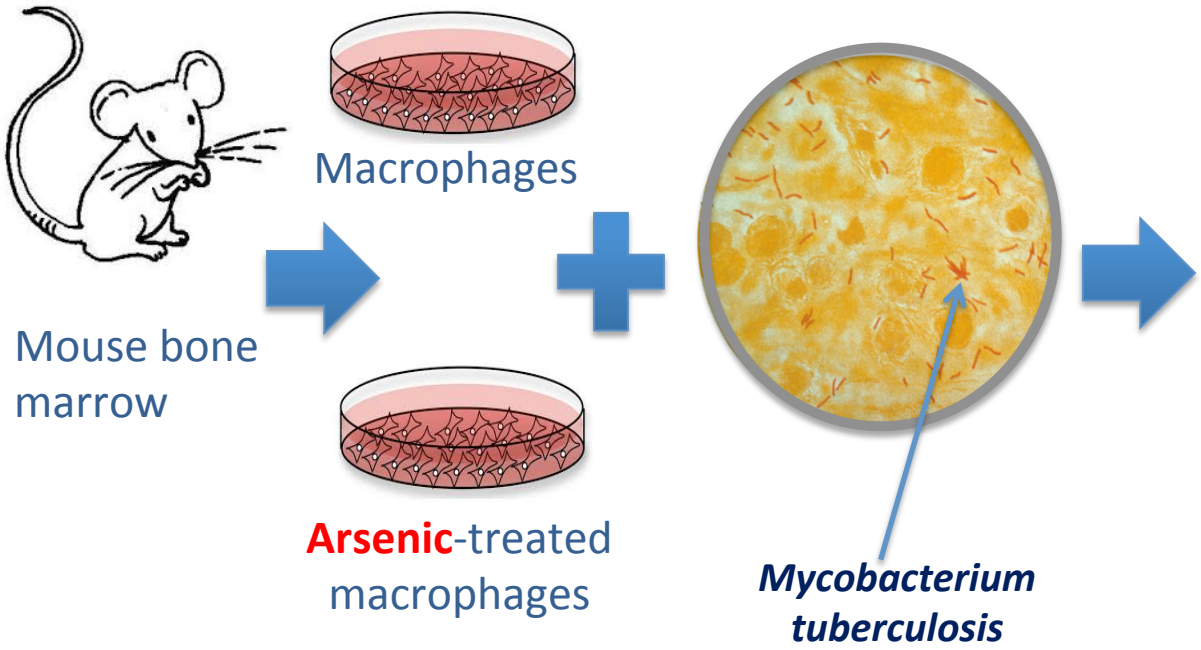
Stefano Fogli, et al. (2008) The molecular bases of cannabinoid action in cancer. Cancer Therapy Vol 6, 103-116, 2008.

Arsenic-targeted pathways relevant to TB



Kanehisa M, et al. (2000) Kegg: Kyoto encyclopedia of genes and genomes. Nucleic acids research. (28):27-30. PMCID: 102409.

Does arsenic alter tuberculosis outcome?



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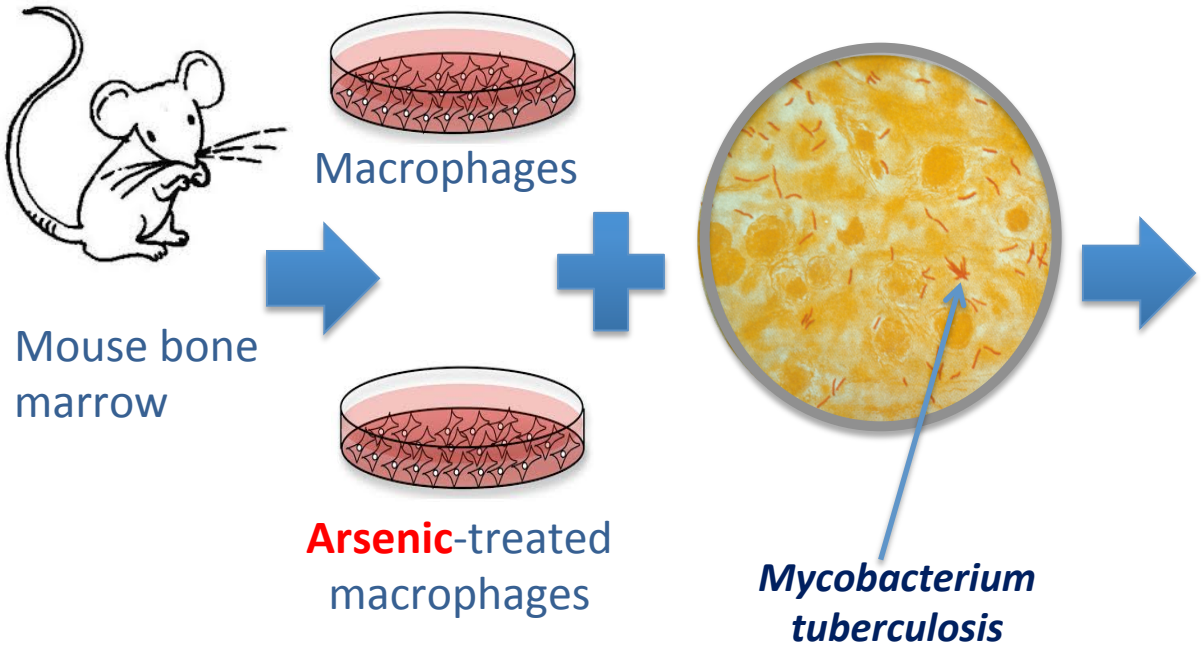
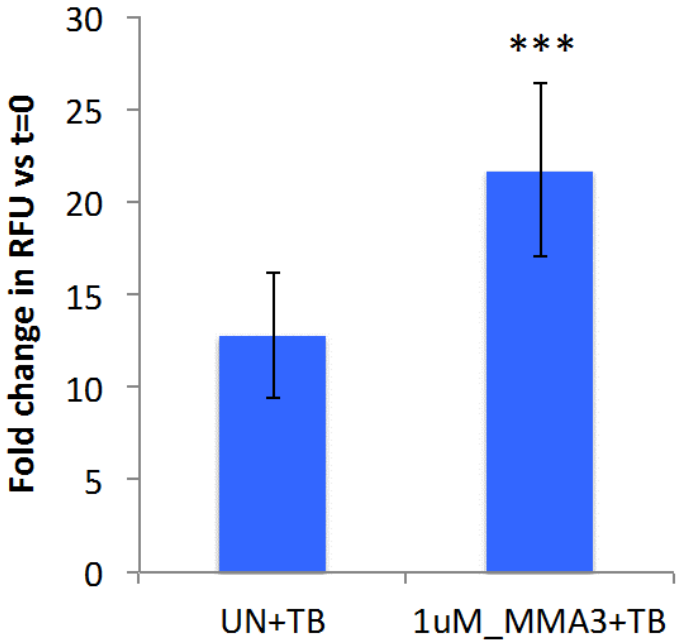
Arsenic during differentiation alters *M. tuberculosis* infections

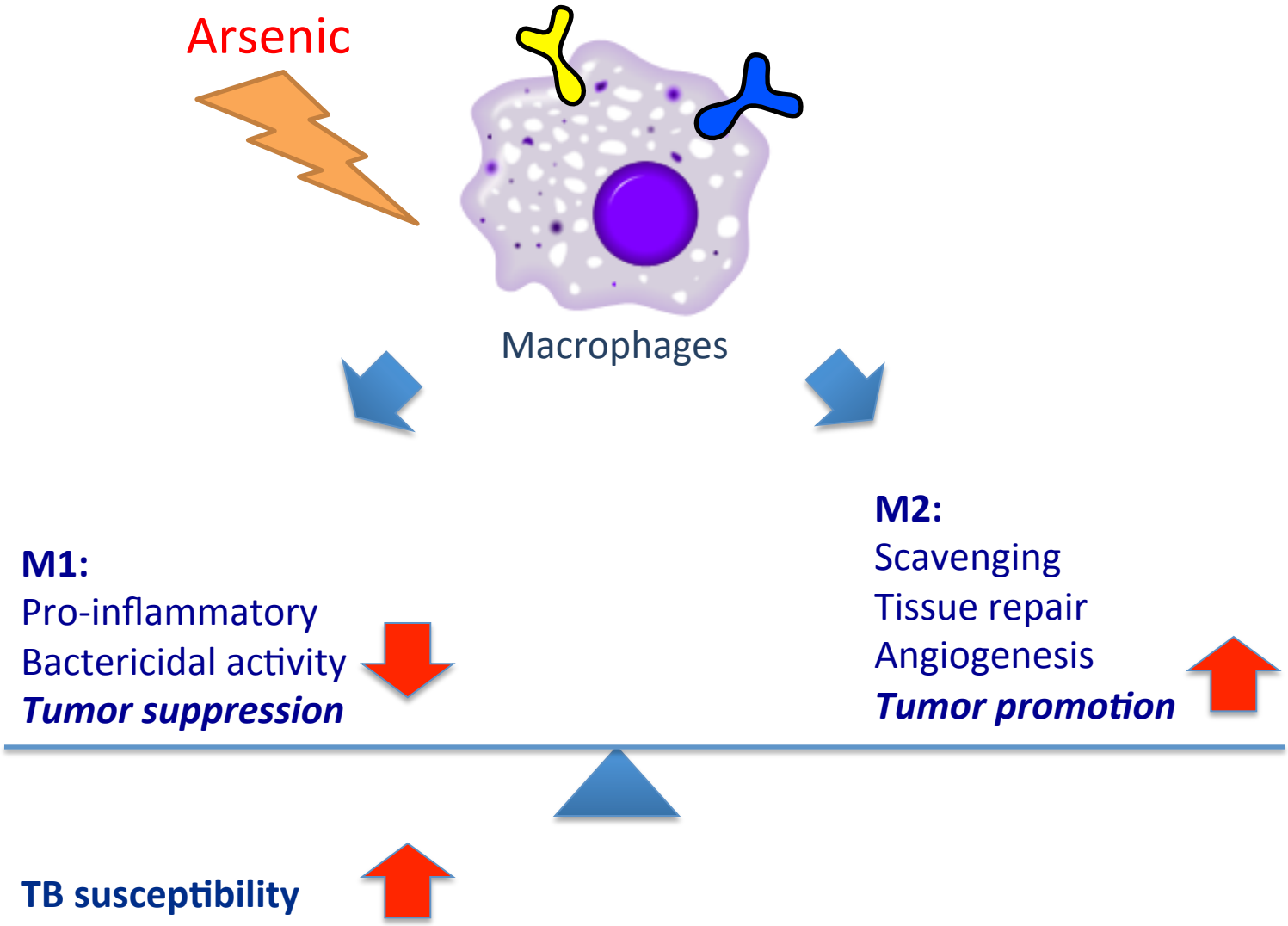
6hrs MMA3 + 24hrs *M. tuberculosis*





Sillé *et al*, unpublished

Arsenic alters innate immunity & disease risk



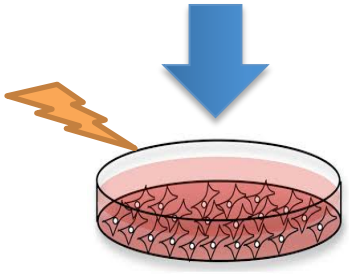
Google Images, Wikimedia Commons

Next steps:

Aim 1

In vitro

Differentiation



Arsenic-treated macrophages

Aim 2

In vivo

Early-life arsenic-exposed mouse studies

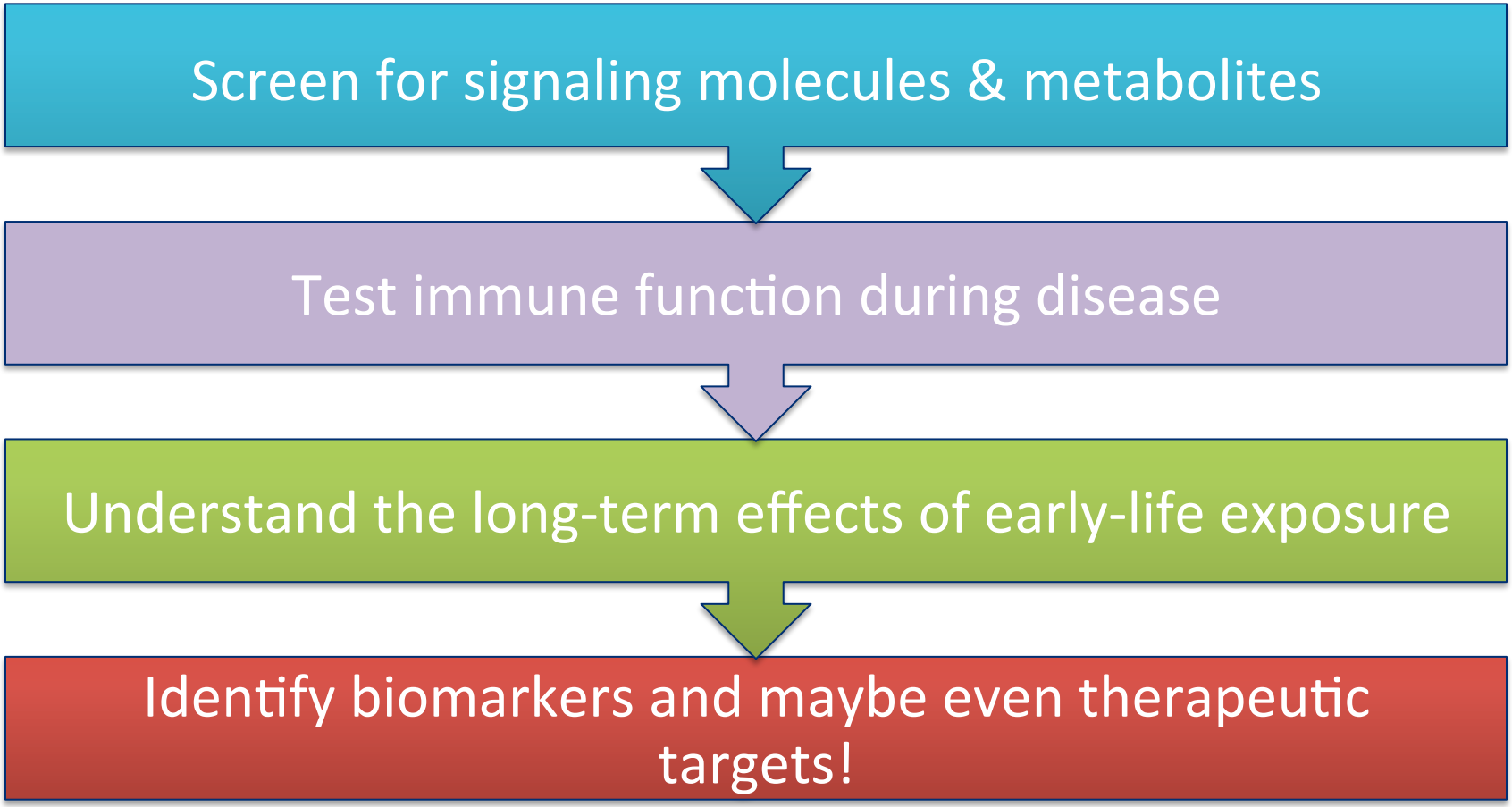
Aim 3

Ex vivo

Early-life arsenic exposed human population study

Google Images, Wikimedia Commons

Next steps:


Screen for signaling molecules & metabolites
Test immune function during disease
Understand the long-term effects of early-life exposure
Identify biomarkers and maybe even therapeutic targets!

UC BERKELEY SUPERFUND RESEARCH PROGRAM
SCIENCE FOR A SAFER WORLD

Thank you!

Berkeley
UNIVERSITY OF CALIFORNIA

COLLEAGUES:

- PI: Martyn Smith, PhD (UC Berkeley)
  - Sylvia Sanchez (UC Berkeley)
  - Felicia Castriota (UC Berkeley)
  - Smith lab members
- PI: Daniel Nomura, PhD (UC Berkeley)
  - Daniel Medina-Cleghorn (UC Berkeley)
  - Breanna Ford (UC Berkeley)

COLLABORATORS:

- Craig Steinmaus, MD, MPH (UC Berkeley)
- Catterina Ferreccio, MD, MPH (Pontificia Universidad Católica de Chile)
- Allan Smith, PhD (UC Berkeley)
- Lee Riley, MD, PhD (UC Berkeley)
- Sarah Stanley, PhD (UC Berkeley)

FUNDING:

- NIEHS SuperFund Grant # P42ES004705
- NIEHS K99 Grant# K99ES024808

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