

CLAYTON
BIOTECHNOLOGIES

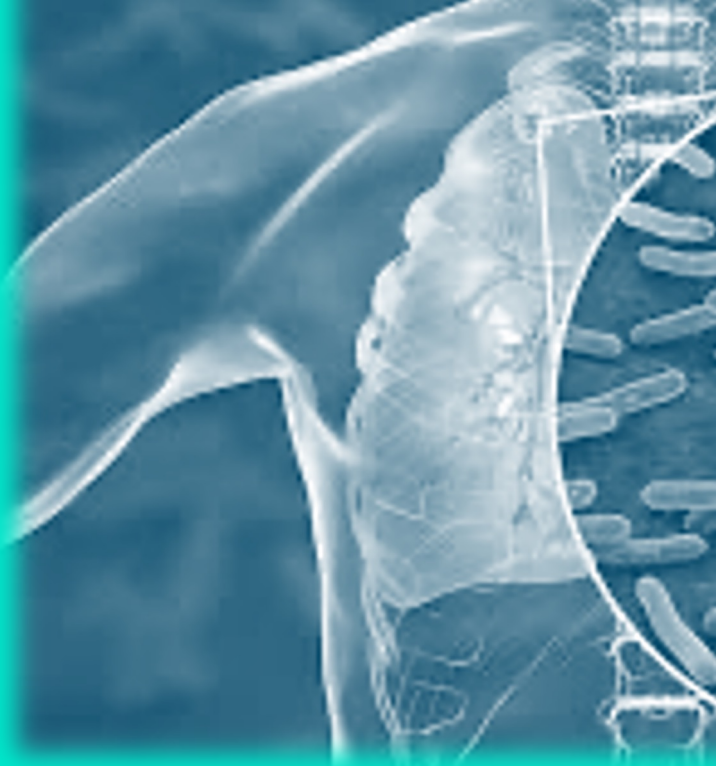


VALPROIC ACID TO TREAT TUBERCULOSIS

Repurposing valproic acid, an HDAC inhibitor for first-line
treatment of tuberculosis (TB)

Tuberculosis

- 11 million cases and 1.6 million deaths, annually.
- In 2022, there were over 8,000 cases of TB in the United States, and TB was the second most infectious killer after COVID-19.
- CDC estimates 13 million people in the United States living with inactive TB.
- 13th leading cause of death worldwide
- Particularly problematic in developing world
- **Current treatments such as antibiotics are not sufficient** due to resistance occurrence, liver toxicity and most importantly, patient adherence due to long timelines for treatment.



TB represents an unmet need

Requirements to develop a new treatment for tuberculosis:

- Cost effective
- Overcome resistance
- Low toxicity profile
- Better patient adherence

Repurposing drugs attractive solution:

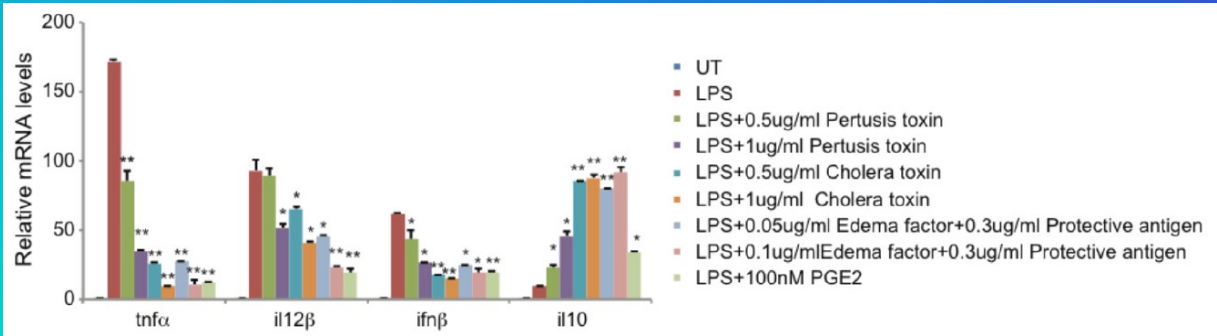
- Clinical development starts with Phase II trials
- Reduced drug development costs
- Quick to market

Orphan drug classification in US and EU
(disproportionately affects less developed countries)



Dr. Montminy at the Salk Institute discovered how some bacteria evade immune destruction and suppress the immune response of their host:

Bacteria produce toxins that stimulate cAMP production in macrophages, which mediate cytokine production in bone marrow macrophages



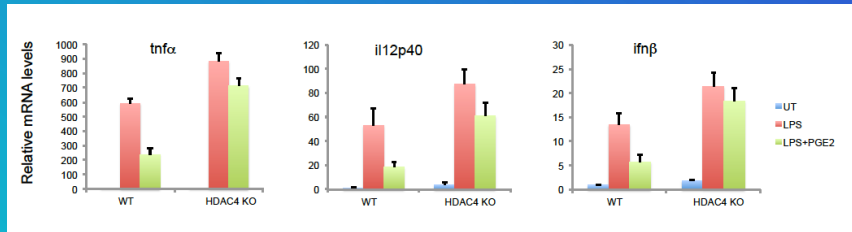
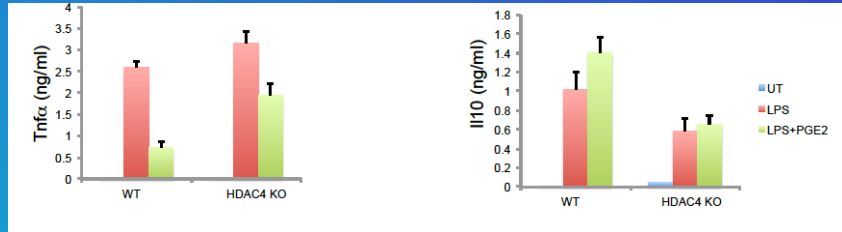
Bacterial toxins mediate effects of cAMP on cytokine production in bone marrow macrophages:

- Decrease in pro-inflammatory cytokines (e.g. TNF α)
- Increase in anti-inflammatory cytokines (e.g. IL-10)

By what mechanism?

Bacterial Toxins induce cAMP, which leads to increased HDAC4 activity

HDAC4 suppresses pro-inflammatory cytokines (e.g. TNF α) and activates anti-inflammatory cytokines (e.g. IL-10)

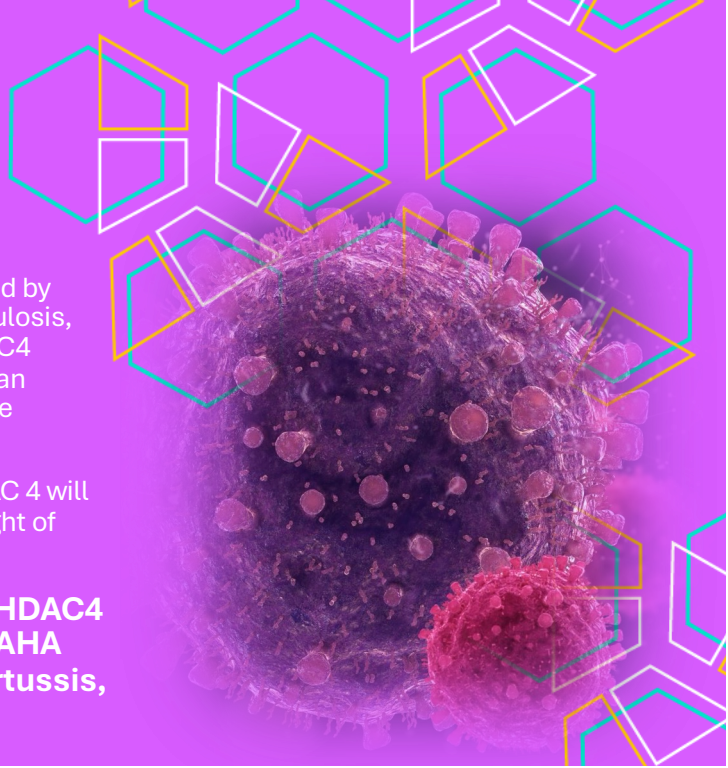


HDAC4 Inhibitors to treat TB - Rationale

We have shown that bacterial toxins produced by bacteria that cause diseases such as tuberculosis, pertussis, cholera and anthrax increase HDAC4 expression in host macrophages resulting in an overall impaired host immune response to the bacterial infection.

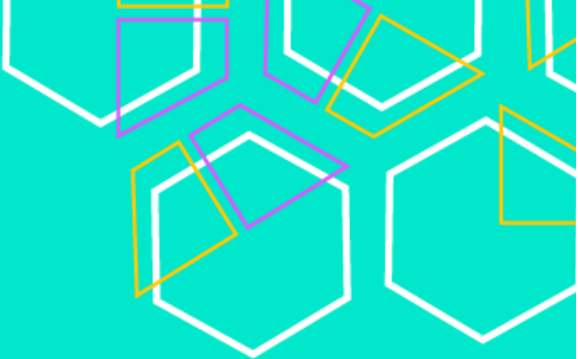
We propose that using drugs that inhibit HDAC 4 will reactive the patient's immune response to fight of bacterial infection.

We propose to **repurpose approved HDAC4 inhibitors** such as **Valproic acid** or **SAHA** (viconostat) to treat **tuberculosis, pertussis, cholera and anthrax**



Our results validated by independent research at the Pasteur Institute

- HDACs play important roles in immune response and can be targeted by pathogens, and inhibition of HDACs may reduce infection
- SAHA and Trichostatin A can target various bacteria



OXFORD **EAM** **FEMS**
European Academy of Microbiology

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<https://doi.org/10.1093/femsmi/uqab013>
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Short Review

SHORT REVIEW

Patho-epigenetics: histone deacetylases as targets of pathogens and therapeutics

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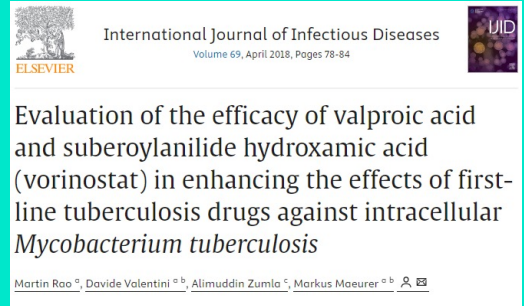
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One sentence summary: HDACs play important roles in gene regulation and the immune response, thus they are targeted by pathogens to manipulate the host cell and their inhibition may allow to fight infections.

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Valproic Acid and SAHA excellent candidates for adjunct to standard TB therapy

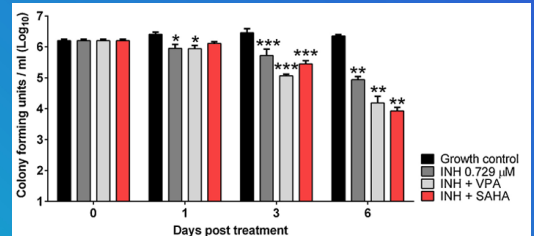
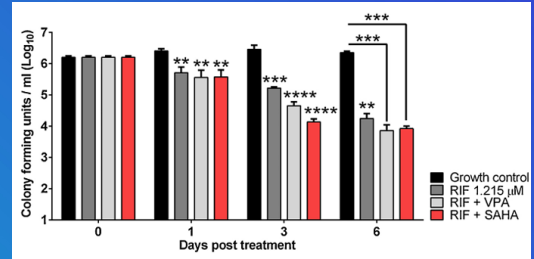
- **Valproic acid (VPA)** and **SAHA** are histone deacetylase inhibitors with excellent repurposing value.
- Authors conclude, “**Clinical evaluation of VPA and SAHA as adjuncts to standard therapy to reduce treatment duration and improve outcomes in TB is warranted.**”



The efficacy of VPA and SAHA improves killing of intracellular *M. tuberculosis* in infected macrophages

- The efficacy of VPA and SAHA against intracellular *M. tuberculosis* with and without other drug (isoniazid or rifampicin) was tested by treating infected macrophages
- Improved in killing of *M. tuberculosis* with standard treatment was observed (3 days instead of 6 days *in vitro*)

Rao et al. (2018)



Valproic acid improves *M. tuberculosis* killing in macrophages

> Tuberculosis (Edinb). 2019 Jan;114:123-126. doi: 10.1016/j.tube.2018.12.007. Epub 2019 Jan 2.

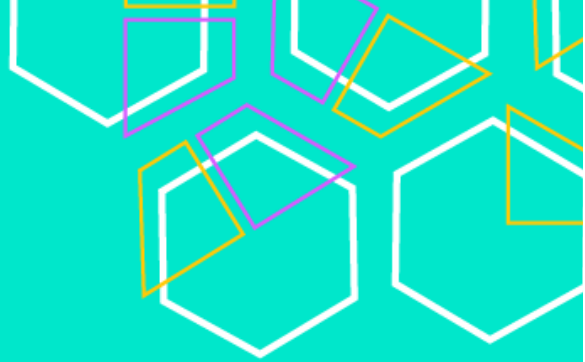
Valproic acid promotes a decrease in mycobacterial survival by enhancing nitric oxide production in macrophages stimulated with IFN- γ

Erik Nieto-Patlán ¹, Jeanet Serafín-López ², Isabel Wong-Baeza ², Sonia M Pérez-Tapia ³, Laura Cobos-Marín ⁴, Sergio Estrada-Parra ², Iris Estrada-García ², Alma D Chávez-Blanco ⁵, Rommel Chacón-Salinas ⁶

Affiliations + expand

PMID: 30711151 DOI: 10.1016/j.tube.2018.12.007

- **Valproic Acid** improved ***M. tuberculosis* killing** in macrophages
- Macrophages infected with *M. tuberculosis* and treated with Valproic acid and IFN- γ showed a significant reduction in intracellular bacteria.



HDAC inhibitors such as Valproic acid are effective in controlling tuberculosis infection and help overcome resistance to rifampicin

RESEARCH ARTICLE

Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 118: e230143, 2023 1 | 11

Histone deacetylase (HDAC) inhibitors- based drugs are effective to control *Mycobacterium tuberculosis* infection and promote the sensibility for rifampicin in MDR strain

Adrián Rodríguez-Carlos¹, Yolanda Jacobo-Delgado¹, Alan Orlando Santos-Mena¹, Mariana H García-Hernández¹, Luis Adrian De Jesus-Gonzalez¹, Edgar E Lara-Ramirez², Bruno Rivas-Santiago^{1/+}

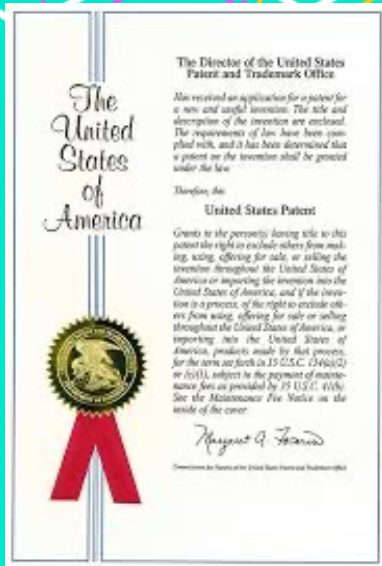
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Intellectual Property

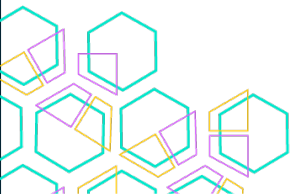
US patent 9693994

- Claims on methods of treating bacterial infections with a variety of HDAC4 inhibitors
- HDAC4 inhibitors include:
 - **Valproic Acid** (also called valproate)
 - SAHA (suberoylanilide hydroxamic acid, also called vorinostat)
 - Trichostatin A (TSA)
 - Other compounds (LMK235, MC1568)
- Variety of bacterial diseases covered
 - **Tuberculosis**
 - Pertussis (Whooping cough)
 - Bacteria use toxin to increase cAMP expression in order to evade immune system
- **Granted Patent (expires in June 2035)**



FDA Approved Drugs

- **Valproic Acid** (also called valproate)
 - FDA approved (since 1978)
 - Brand names: Belvo, Depakote, Dyzantil, Convulex, Syonell
 - used to treat seizures or prevent migraines
- **SAHA** (suberoylanilide hydroxamic acid, also called vorinostat)
 - FDA approved (in 2006)
 - Brand name: Zolinza™
 - used to treat cutaneous T-cell lymphoma



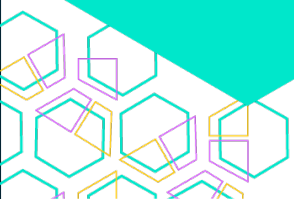
VALPROIC ACID TO TREAT TUBERCULOSIS

Valproic acid is an FDA approved drug that can be repurposed for treatment of tuberculosis
Extensive clinical data on Valproic acid

Because Valproic acid re-activates the immune system, following hijacking by bacterial toxins, treatment duration should be shorter compared to current standard of care

Approach based on research carried out by Dr. Montminy and his team at the Salk Institute showing how bacterial toxins activate HDAC4 to dampen the host immune system

Independent validation





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VALPROIC ACID TO TREAT TUBERCULOSIS

Repurposing valproic acid, an HDAC inhibitor for first-line
treatment of tuberculosis (TB)

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