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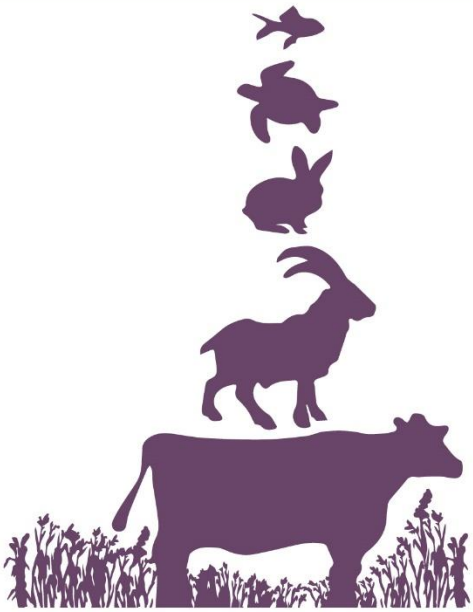

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Intraphagosomal acidification blockage is not a conserved feature of all members of the *Mycobacterium tuberculosis* complex

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The *Mycobacterium tuberculosis* complex (MTBC) comprises bacteria responsible for causing tuberculosis in humans and animals. Although all MTBC species can lead to disease, apart from *M. tuberculosis*, the survival mechanisms of other MTBC species inside the phagosome have not received much attention. This study aims to compare the phagossome maturation of human macrophages when infected with *M. tuberculosis, M. bovis, M. africanum* and *M. caprae* and, as an evolutionary reference, *M. canettii.* CF-SE marked MTBC bacteria was evaluated by an adapted assay in a spectrofluorometer to evaluate real-time phagosome's maturation of the macrophages infected by the MTBC bacteria, using pH measurements as proxy. While *M. tuberculosis* was able to halt phagosome acidification for three hours, phagosomes containing *M. canettii* and *M. bovis* presented a stage of "transient acidification" (pH 6.5 - 6.1) and phagosomes containing M. africanum L5 and *M. caprae* progressed to a profile of late phagosome maturation (pH 6.1 - 5.9 and pH 5.5 - 4.5, respectively), with *M. caprae* presenting severe inability to halt the acidification of the phagosome. These results suggest that acidification blockage is not a conserved characteristic of all MTBC species.

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Impact of diabetes on the expression of variants related with resistance to isoniazid and rifampicin in *M. tuberculosis*

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Drug resistance in tuberculosis has become a global public health crisis. It has been found that patients with comorbidity with tuberculosis-type 2 diabetes mellitus (TB-T2DM) show higher risk of treatment failure and development of drug-resistance. The present study uses whole genome sequences of *M. tuberculosis* to analyze variants that cause resistance against rifampicin and isoniazid and to identify whether the presence of T2DM influences its expression. For this purpose, 36 genome sequences from multidrug resistant tuberculosis isolates were analyzed, 29 were from individuals with T2DM and seven from individuals with TB-MDR only. The sequences were analyzed by PhyResSE, as preliminary results, 12 different variants associated with resistance were identified. The low fitness variants katGS315T and rpoBS450L were prevalent in both groups. The analysis of the frequencies of the variants shows that the proportions were similar in both groups. Nevertheless, the number of variants associated with resistance was higher in the T2DM group (5 for isoniazid and 7 for rifampicin) than that found in the TB-MDR (2 and 3 variants respectively). Recent reports have shown that the host environment can influence mutational events in mycobacteria. The production of reactive oxygen species and the alteration in the pharmacokinetics of drugs, secondary to hyperglycemia, could explain the increase in the number of drug-resistance variants in individuals with TB-T2DM. Additional studies need to be performed to confirm this hypothesis. Project financed by CONACYT-Basic Science fund: Influencia de la diabetes mellitus tipo 2 en el desarrollo de mutaciones asociadas con multidrogorresistencia en Tuberculosis, A1-S-22956.

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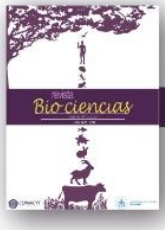
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Utilization of human vitreous humor for an in vitro granuloma system to study *Mycobacterium tuberculosis* infection

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Granuloma formation is the hallmark of tuberculosis. Generated in an immune microenvironment that responds to *Mycobacterium tuberculosis* (Mtb) infection, provides a niche were mycobacteria can survive. More detailed studies of Mtb-infectivity are essential to understand the complexity and chronic-nature of the disease. In vitro models for studying granuloma formation have been insufficient in recreating the microenvironment of an infected human host. An extracelular-matrix (ECM), thought to play a major role in macrophage activation, establishes the environment necessary to generate an immune response to infection. Current commercially available ECMs are limited to collagen and synthetic matrices, and although these substances facilitate granuloma formation, they do not reflect the complexity of the human tissue. This study utilized human vitreous humor (hVH) to assess the interaction between human ECM and macrophages in granuloma formation. THP-1 human monocytic cells, were seeded on hVH obtained from human cadavers and then cultured under three different conditions: hVH only, hVH+vitamin D, and hVH+PMA for 3 days. The system was evaluated for granuloma formation with and without the inoculation of Mtb for 10 days. We observed that Mtb-exposed THP-1 monocytes can form granulomas in hVH as early as day 7. Treatment with Vit D led to a faster granuloma formation (day 6) of a larger area. Granuloma formation in PMA-transformed cells or in Mtb-unexposed cells under any treatment was unremarkable. Our data suggests that hVH serves as a viable ECM able to activate macrophages upon exposure to Mtb, providing a more physiologically comparable model to study TB pathogenesis.

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MIRU-VNTR molecular typing of *Mycobacterium tuberculosis* isolates from Caldas, Colombia

Tovar Aguirre OL[1], **Bohada Lizarazo DP[2*],** Siller-López F[1], Guerrero MI[2]

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Introduction: Tuberculosis is a main cause of adult's death from a single infectious agent killing ~2 million people/year. In Caldas-Colombia, about 25 new cases by million inhabitants occur monthly, constituting a serious public health problem. Source identifying of infection transmission is necessary to decrease tuberculosis. In this study we used VNTR to MIRU and ETR to determining the tuberculosis transmission dynamic during 2016 to 2017. Methods: Fifty isolates from 11 municipalities were collected. MIRU-VNTR was performed to 37 out of 50, for 24 specific targets: 12 MIRU-VNTR loci, 5 ETR locus, 3 QUB locus and 4 Mtb locus. All was carried out by primers specific for as well by polymerase chain reaction. Genetic relationship analyses were performed by MVSP software and MIRU-VNTRplus website. Results: 30 distinct patterns were identified including 5 clustered patterns and 25 unique patterns. Combined analysis from VNTR data from MIRU, QUB, Mtb and ETR, we increased the discriminatory power of typing methods. Loci 26, 24 in MIRU, 11b, 26 in QUB and 21, 29 in Mtb were highly discriminatory. Distribution of lineages in our study according to similarity from tentative data in MIRU-VNTRplus database was multimatches. The minimum estimate for tuberculosis proportion due to ongoing transmission was 29.1%. Conclusion: Tuberculosis status due to minimum estimate of tuberculosis transmission was 29%, the reactivation of tuberculosis was responsible for more than 70% of new tuberculosis. According to the results we strongly recommend to use 15-MIRU-VNTR analyzed by MIRU-VNTRplus as an easy, reliable, reproducible, and highly discriminatory power method.

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Prevalence, drug resistance and genotypic diversity of RDRio sublineage of *Mycobacterium tuberculosis* in Ecuador

Castro B[1*], Franco-Sotomayor G[2], Garcia-Bereguiain MA[1]

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Tuberculosis (TB) is a significant public health problem in Ecuador with an incidence of 43 per 100,000 inhabitants and an estimated multidrug-resistant-TB prevalence in all TB cases of 9%. The Latin American & Mediterranean (LAM) spoligotype family is one of the most successful genotype of *Mycobacterium tuberculosis* worldwide and particularly prevalent in south american countries like Ecuador. Within this family, a sublineage named Region of Difference Rio (RDRio) was reported initially in Brazil and is characterized by a genomic deletion of about 26.3 kb. This lineage seems to show a specific adaptation to the Euro-Latin American population, spreading to countries like Venezuela, Argentina and Paraguay, and in this context we sought to evaluate the presence of the RDRio genotype in Ecuador. We screened a country wide 814 MTB strain collection from years 2014-2016 for presence of the regions of difference RDRio and found 35 (4,3%) positive RDRio MTB strains. Drug susceptibility information was avalaible for 30 of these strains, 15 (50%) were resistant to isoniazide; 13 (43,3%) of those were MDR TB strains. Spoligotyping and 24 loci MIRU-VNTR genotypic analysis is ongoing for further characterization of RDRio in Ecuador and phylogenetical comparasion with RDRio from other south american countries. In conclusion, RDRio sublineage is present in Ecuador and it is strongly associated to drug resistance.

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Molecular epidemiology of *Mycobacterium tuberculosis* on the Ecuadorian province of El Oro at the border Ecuador-Peru

Castro B[1*], León K[1], Garzon-Chavez D[2], Franco-Sotomayor G[3], Garcia-Bereguiain MA[1]

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Tuberculosis (TB) is a significant public health problem in Ecuador with an incidence of 43 per 100,000 inhabitants and an estimated multidrug-resistant-TB prevalence in all TB cases of 9%. Genotyping of *Mycobacterium tuberculosis* (MTBC) is important to understand regional transmission dynamics. The aim of this study is to describe the main MTBC lineages and sublineages circulating in the province of El Oro at the border Ecuador-Peru. A representative sample of 71 MTBC strains with data comprising drug susceptibility, were genotyped using 24 loci-MIRU-VNTR and spoligotyping. We show that lineage 4 is predominant (83.1%) and only 1 strains belongs to lineages 2-sublineage Beijing (1.4%). Lineage 4 strains included sublineages LAM (35.2 %), Haarlem (16.9 %), S (4.2 %) and X (11.3 %). 8 strains have new spoligotypes and 31 strains (43,7%) have spoligotypes previously reported on Peru. However, neither clusters nor clonal complexes were found involving MTB strains from our study and reported MTB strains from Peru based on MIRU-VNTR analysis. No active or recent transmission of tuberculosis between Ecuador and Peru was found in our study.

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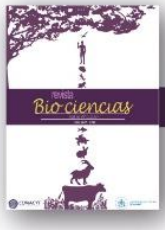

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General description of gene expression for the Host-pathogen interaction during *M. tuberculosis* in-vivo infection with Beijing-like strain, using a mouse model

Cerezo-Cortés MI[1*], Rodríguez-Castillo JG[1], Mata-Espinosa D[2], Bini EI[2], Marquina-Castillo BN[2], Barrios-Payan[2] J, Bobadilla del Valle M[3], Ochoa-Leyva A[4], López G[4], Cornejo F[4], Del Portillo P[5], Anzola JM[5], Murcia MI[1], Hernández-Pando R[2]

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Mycobacterium tuberculosis Beijing genotype is one of the most spread worldwide, these strains are characterized for its high virulence and highly drug resistance. In Colombia Beijing genotype is present since 1997 and circulate in the pacific coast. Using molecular epidemiology and NGS tools, we´ve determined that the most predominant strains belong to Beijing-Like SIT 190 and all the strains have any profile of antibiotic resistance. To study the virulence, we used a Beijing-Like SIT 190 strain 323 to infect BalB/c mice and observed the survival, pulmonary bacillary loads, histopathology and host and pathogen gene expression using massive RNA-seq sequencing. The clinical outcome of the animals was fatal as early as day 35 post-infection, characterized for high pulmonary bacillary load, extensive pneumonia by day 28 post-infection. Based on the pulmonary histological issues, the lungs of day 3, 14, and 28 post-infection were collected for RNAseq of the mice and the bacteria. Transcriptional analysis of mice showed a proinflammatory response at day 3 and 28, but at day 14 showed an anti-inflammatory response, conducted by the genes Nkiras, Dleu2 and TGFβ. This immune response at day 14, is possibly induced by the bacillus, rising the bacterial load producing the phenotype observed. At the pathogen level a preliminary analysis showed and interesting expression profile of virulence genes associated to immune response evasion modulated by the ESX genes, and overexpression of cell wall synthesis genes as RNAse and Poliketide synthase, this expression profile could be the responsible of the immune phenotype of the animal.

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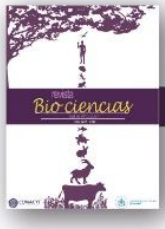
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Metformin regulates the inflammatory response of human macrophages to *Mycobacterium tuberculosis* through a reduction of M1 polarization

Cervantes JL[1*], Sanca A[3], Barragan J[1], Kositangool P[1], Vargas-Medrano J[2], Diaz-Pacheco V[2], Campbell A[2], Gadad BS[2]

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Besides its ability to control hyperglycemia, Metformin (MTF) has effects on macrophage and lymphocyte functions, improving control of *Mycobacterium tuberculosis* (Mtb) infection and decreasing disease severity. We aimed to better understand the effects of MTF on human macrophages' response to Mtb. PMA-differentiated THP-1 cells were treated with 2mM of MTF for 4 hours, and then inoculated with Mtb from various lineages. Since MTF can also directly inhibit key metabolic processes of Mtb, we utilized gamma-irradiated mycobacteria. Phagocytosis was assessed by immunofluorescent assay. Supernatants were tested with a multiplex ELISA system. Phagocytosis of all Mtb strains was increased in MTF-treated macrophages. A diminished NF-κB activation after Mtb stimulation was observed in MTF-treated macrophages. There was no effect on IRF activation by MTF pretreatment. Results from the multiplex ELISA showed a modulatory effect by MTF on the secretion of various pro-inflammatory cytokines, with no effect on anti-inflammatory cytokines. Reduction in the expression of M1 polarization markers was observed in MTF-treated cells upon Mtb stimulation. Our results indicate that MTF improves phagocytosis of Mtb by macrophages, while at the same time modulating their inflammatory response. This occurs through a downshift of M1 polarization. Excessive inflammation is a phenomenon associated with active tuberculosis (TB) and with disruption of the granuloma architecture. MTF treatment could allow for an improved response of macrophages to Mtb infection. These results support the effects of MTF in key steps of Mtb infection control, and support its use as an additional treatment for TB.

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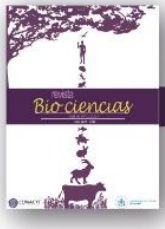
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Infection capacity of Mycobacterium leprae's Colombian strains associated to recurrent leprosy events

Chavarro-Portillo B[1,2*], Soto CY[2], Guerrero MI[1]

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The peripheral nervous system is the preferred residence to oldest bacterial pathogen known to humanity, Mycobacterium leprae. It has a remarkable ability to invade the Schwann cells. These cells provide the safer niche to *M. leprae's* during initial colonization, its survival and propagation. We studied the infection capacity of *M. leprae* strains associated and not associated with possible relapses into in vitro model of Schwann Cells to determine differences between strains of *M. leprae* causing leprosy recurrences, versus strains obtained from new cases. The *M. leprae* strains obtained and purified from new patients, and patients with suspected disease relapse were used to infect human Schwann cells. *M. leprae* multiplied exponentially during the cultivation time 1-12 days. The experimental conditions set out in this study showed that 33°C and 5% CO2 are optimal for infection of Schwann cells with M. leprae, to allow the culture to be maintained up to 12 days after infection. A variation in the infective capacity of strains was found at initial infection time oscillating between 6.5% and 27% infection rates, which reached maximum between 16.5% and 54% oscillating infection percentages. These results represent the differences in the infective capacity of each strain. Our study provides evidence that the entry of *M. leprae* not only depend on the bacterial load but also the PGL-I cell envelope glycolipid through which the SC is recognized, and its phenotype is modulated, favoring the intracellular persistence. The changes in cellular properties may be associated with the genotype of *M. leprae.*

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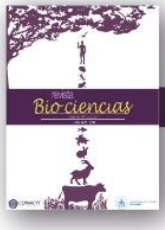

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Diagnosis of tuberculosis by multiplex amplification of markers IS6110, Rv2341, Pks15/1 by endpoint PCR in sputum samples

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Late diagnosis of TB is a major problem because it causes increased morbidity and mortality of patients and promotes the spread of TB. Therefore, the aim of the present work is to develop a molecular diagnostic test for TB using the endpoint PCR technique, simultaneously amplifying three markers; IS6110, Rv2341 and pks15/1 using sputum samples directly. This test will allow the simultaneous diagnosis of TB and the presence of L1 or L4 lineage. Initial standardization was performed using DNA from clinical TB cultures in which the presence of three bands was confirmed: 262 bp of the IS6110 gene, 302 bp of the Rv2341 gene and 405 bp of the pks15/1 gene. Performance of the assay using DNA from 12 sputum samples with positive and 12 samples with negative sputum showed the presence of three bands in all positive samples and the absence of these bands in the negative sputum samples. This would confirm the excellent correlation of the test. The influence of sample conditions and sample collection time was also evaluated. Although these are preliminary data, the results obtained would confirm the sensitivity and specificity of the test; however, additional tests are required to determine the detection capacity of the test. Project financed with resources from the CONACYT-Basic Science Fund: Influence of type 2 diabetes mellitus in the development of mutations associated with multi-drug resistance in Tuberculosis, A1-S-22956.

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Field evaluation of the protective efficacy of *Mycobacterium bovis* BCG vaccine against bovine tuberculosis in a dairy herd

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Bovine-tuberculosis (TBb) prevalence in some dairy herds ranges from 16%-70% in Mexico, the control strategy based on segregation or elimination of reactor cattle in high-prevalence herds is not affordable when disease rates are high, so vaccination is considered a better option in these circumstances. In cattle, different BCG strains, administered parenterally at a dose of 104-106 CFU or orally at a high dose of 108 CFU, have been tested, observing a significant level of protection against TBb experimentally. Therefore, the objective of this work was to assess the protective efficacy of BCG Phipps vaccine against natural *M. bovis* infection in calves establishing a program of continuous vaccination of newborn calves with BCG Phipps at a dose of 1x105 CFU subcutaneously. Initially, the prevalence of TBb in calves younger than 6 months was of 5.6%; while in a heifers population was of 17%. On the other hand, safety measures were implemented such as feeding the calves with colostrum or milk obtained from non-reacting mothers, vaccinating all births, and segregation of those reactors animals to the tuberculin skin test (TST), this test was applied to the entire herd periodically. Currently, almost 1200 calves have vaccinated and an evident decrease in prevalence it has been registered after a year and a half of establishing the program, 10% in calves older than 6 months and 2.5% in calves younger than 6 months. The BCG Phipps vaccine, together with safety measures, has shown that it is useful in the control of TBb in this herd.

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Assessment of protein fractions culture supernatant of *Mycobacterium bovis* in interferon gamma release assays by ELIspot

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Interferon-gamma (IFN-ã) is one of the most critical effector molecules to the establishment of a cell-mediated immune response required for control of *Mycobacterium bovis* infection, so its evaluation have been considered a biomarker of disease. The ELIspot assay has been used as a research tool to detect cell populations that releasing IFN-ã following exposure to mycobacterial antigens. The aim of this study was to evaluate the ability of inducing IFN-ã fractions of the protein extract from the culture filtrate of *M. bovis* separated by isoelectrofocusing in ELIspot assays. For which, were separated PBMC from 24 cows tuberculin reactors and 22 non-reactors. The cells culture were also stimulated with the different fractions obtained by the isoelectrofocusing, as well as, bovine PPD and avian PPD, ESAT-6 and CFP-10 antigens, pokeweed mitogen and the no-antigen control. The quantification of reaction points was performed using an automatic counter ImmunoSpot 3.2. IFN-ã produced with different antigens in whole blood cultures were also evaluated by ELISA. A Kruskal-Wallis test was applied to analyze the results obtained between groups, and the Mann-Whitney test to compare the different antigens. The analysis indicated difference among bovine PPD, the CFP-10, ESAT-6 and some fractions. Greater specificity was determined to bovine PPD itself, ESAT-6, and fractions 1, 2, 3, 4, 17 and 19 for the group of reactors cows by which are suitable for the purpose searched of disease diagnosis. There was a high concordance between the production of IFN-ã evaluated by ELISA and the ELIspot assays with the antigens evaluated.

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PII proteins in mycobacteria

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The PII proteins are a family of signal transduction protein widely distributed within prokaryotes. Remarkably, PII proteins are able to sense signals from the carbon, nitrogen and energy status, changing their conformational state. These two conformation states define a differential interaction with diverse target proteins, mainly of which are involved in nitrogen assimilatory pathway. In some bacteria, PII proteins are also involved in carbon metabolism by modulating the activity of acyl-CoA carboxylases. The function of PII proteins in mycobacteria, including the pathogen *Mycobacterium tuberculosis*, has not be addressed.

In order to elucidate its role in mycobacteria, we constructed an in-frame deletion mutant of PII gene in *Mycobacterium smegmatis* by homologous recombination. This mutant showed no growth defect in media containing ammonia or nitrate as sole nitrogen source. On the other hand, when this strain was grown in nitrite the mutant presented a prolonged lag phase compared to de wild type strain and reached lower optical densities. This effect was exacerbated when the nitrite concentration was increased. Regarding the modulation of acyl-CoA activity, we analyzed the acetyl-CoA and propionil-CoA activity in protein extracts of *M. smegmatis* grown in an ammonia limiting condition, and after an ammonia shock. However, no change in acyl-CoA activity was observed.

In conclusion, we showed that PII is a non-essential protein for *M. smegmatis* and nor participate in ACCase activity modulation. However, it seems to be involved in nitrite assimilation and/or detoxification. Further experiments are being carried out to clarify PII role in this organisms.

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Genetic diversity of *Mycobacterium tuberculosis* clinical isolates from Hospital Universitario Dr José Eleuterio González, UANL

Flores-Arechiga A[1]*, Tamez-Guerra R[2], Rivera-Morales LG[2], Vázquez-Cortes CG[1], Castro-Garza J[2,3], Rendón-Perez, LA[1], Vázquez-Guillén JM[2], Rodríguez-Padilla C[2].

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Tuberculosis (TB) is a re-emerging disease considered a public health problem. Is present worldwide and its prevalence has been associated to comorbidities (HIV/AIDS and diabetic people) and to the emerging of *Mycobacterium tuberculosis* (Mtb) genetic variants generating drug resistance strains. The aim of this study was to analyze the genetic diversity of Mtb strains isolated from pulmonary TB patients with comorbidities to determine their drug resistance. Isolates of Mtb (n= 190) were obtained from patients with pulmonary tuberculosis from the Hospital Universitario Dr Jose Eleuterio Gonzalez, UANL. The spoligotype of all strains were uploaded into the SITVIT2 database. Drug susceptibility was performed by Seegene following manufacturer instructions. Spoligotypes found were 35 SIT119 (18.4%); 26 SIT53 (13.6%); 20 orphans (10.5%) and 11 SIT1 (Beijing) (5.8%); 7 SIT50 (3.7%); 6 SIT200 (3.1%) and others in low percentage. Drug resistance results were: 7 to rifampicin and isoniazid; 5 to isoniazid alone; 3 to fluoroquinolones (2.7%); 1 to rifampicin; and 1 multi resistant to rifampicin, isoniazid and fluoroquinolone. Regarding the patients: 124 were men (65.3%), 59 women (31%) and we did not get the data of 7 (3.7%). Comorbidities: 26 (13.7%) were VIH+, 121 (63.7%) were VIH- and 43 (22.6%) did not reported VIH status, while 74 (39%) patients were diabetics. Comorbidities have been associated with a higher risk to develop TB, also certain spoligotypes have been related with drug-resistance. The results of this work show the need to find the relationship between these factors and monitor patients with comorbidities and the infecting strains.

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Infection of placental tissues with *Mycobacterium tuberculosis*

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Few cases of congenital tuberculosis (TB) have been reported around the world. However, this health problem is under-estimated, since clinical manifestations of neonates are variable and pregnant women often do not present clinical TB background or symptoms; therefore, most cases are not diagnosed and lead to neonatal death. How mycobacteria get to infect the maternal-fetal interface is unknown. The aim of this study was to demonstrate if placental explants of healthy pregnant women are susceptible to the *Mycobacterium tuberculosis* infection. We standardized an ex-vivo infection model in placental explants using adapted to cholesterol *M. tuberculosis* H37Rv obtained from three phases: 1) exponential-phase, 2) Non-replicative-persistence phase (NRP) 1 reactivated from a hypoxic dormancy model; and 3) NRP2 reactivated growth. Infection kinetics were assessed at 4, 24, 48 and 72 hours post infection (hpi) with three doses of infection (1x105, 1x106 and 1x107 UFC) in placental explants of 0.1 g. Controls without infection were included, experiments were triplicated. Surviving mycobacteria were measured by colony counting and placental tissues were evaluated through KinYoun staining. Our results showed that *M. tuberculosis* H37Rv is able to successfully infect placental tissue. We observed infected tissues with 1X105 UFC obtained from exponential-phase since 24 hpi, while at higher doses from the same phase, bacteria were observed since 4 hpi. Reactivated bacteria from NRP1 showed a similar behaviour as exponential-phase and reactivated bacteria from NRP2 showed a less aggressive infection. Our observations suggest that vertical transmission of TB is possible to occur by maternal blood throughout placenta.

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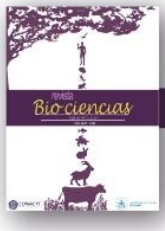
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The MapH (Rv2577) phosphatase activity against 3-phosphoglycerate could implicate a connection with carbohydrates metabolism

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Mycobacterium tuberculosis (Mtb) establishes an active/chronic infection in the host as a consequence of an immune system modulation based on its multiple virulence factors. Mycobacterial phosphatases and phosphodiesterases are key in this process. We have recently shown that Rv2577 (MapH) is a new Mtb virulence factor with dual phosphatase/phosphodiesterase activities. MapH exhibits a βαβαβ three-dimension and active site typical of metallophosphoesterase superfamily (MPE). Our aim was to decipher the MapH activity and its relevance in mycobacteria´s physiology. For this, we investigated the MapH activity against different phospho(Pi)-substrates and performed a proteomic study, by nano-HPLC-MS/MS, of *M. smegmatis* (Ms) overexpressing MapH or its inactive Y220A variant, to understand its hydrolytic activity relevance. MapH catalyzed the 3-phosphoglycerate (3Pi-G) hydrolysis among other Pi-substrates such as AMP and cAMP. Interestingly, the proteome of Ms overexpressing MapH showed a decreased expression of Quinolinate and Glucosyl-3-phosphoglycerate(3Pi-G) synthases involved in the biosynthesis of quinolinate and 6-O-methylglucose lipopolysaccharide from dyhydroxyacetone-phosphate (DHA-Pi) and 3Pi-G, respectively. The reduced expression of these enzymes could be, in part, a consequence of MapH activity against 3Pi-G demonstrated by in vitro assay. In addition, the proteome showed a reduced expression of the glyoxylate cycle´s enzyme, isocitrate lyase. Complementary, we observed a high expression of topoisomerases, DNA repair enzymes and transcription factors suggesting an MapH activity against nucleic acids, as described for some MPE members. Nevertheless, any helicase/nuclease activity were detected in vitro against circular or linear plasmid DNA. Additional studies are needed to deepen the putative role of MapH in the carbohydrate's metabolism.

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Effect of the site of inoculation of the tuberculin test on the caudal folds in cattle with tuberculosis

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The official diagnosis of bovine tuberculosis is through the tuberculin skin test. In Argentina (Res. SENASA N° 128/2012), screening diagnosis is performed through inoculations of 0.1 mL a purified protein derivative (PPD) of *M. bovis* in internal caudal fold test (iCFT). In other countries the diagnosis it is external caudal fold test (eCFT). Our objective was to compare the positive proportion in iCFT and eCFT in naturally infected cattle. In total, 148 bovines in the same dairy herd were inoculated with PPD at the same time in iCFT and eCFT. The skin thickness increase was measurement with a caliper. Two cut-off were used to interpret the positive results: standard interpretation (≥ 5mm) and severe interpretation (≥ 3mm). Pearson correlation and mixed logistic regression model (cattle as a random effect) adjusting for covariates was fit to evaluate the effect of the inoculation site on the results. The median (minimum and maximum) of the skin thickness at 72 hs in iCFT and eCFT was 8 (2 to 27) and 17 (5 to 30) mm, respectively. Correlation was significant ($r=0.7$; $p<0.01$). For severe interpretation, 86% and 89% of cattle were positive for iCFT and eCFT ($p=0.83$). For standard interpretation, 68% and 77% of the cattle were positive for iCFT and eCFT, respectively ($p=0.02$). Our results suggest that, for severe interpretation both sites of inoculation they had similar positive proportion although for the standard interpretation, the eCFT is more sensitivity as screening diagnosis for detection of infected animals.

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Strategy for planning basic care as a tuberculosis control tool in the prison system: pilot project

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Tuberculosis control in prisons represents a major global challenge. Brazil has a National Policy for Comprehensive Health Care for Persons Deprived of Liberty in the Prison System (PNAISP) and Prison Primary Care Teams (EABp). Health Care Planning is a proposal by the National Council of Health Secretaries with the support of the Pan American Health Organization. Objective: To describe the experience of implementing health care planning in the prison system in Rio Grande do Sul. Methods: Experience report of the pilot project for the reorganization of primary care developed with an EABp in a medium-sized prison, with content adapted from the Primary Care Planning Project developed in the state. The activities took place in six thematic workshops, from June to September 2019, on the premises of the prison, with the participation of health and safety workers. The project was approved by CEP / UNISC under Opinion 3.044.200. Results: Ten workers participated in the workshops that led to problematization of the practices experienced, reflections on their attributions in the penal institution and the role of the worker as the protagonist of the change. Regarding tuberculosis control, it was possible to enhance knowledge actions and readjust the physical space, identification of cases and communicants, active search for respiratory symptoms with support from security professionals, referral protocols, records and notifications, monitoring and evaluation of control indicators of the disease. Conclusion: Prison Health Care Planning is a pioneering project and can enhance tuberculosis control actions in penal institutions.

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Detection of *Mycobacterium bovis* in whey, by multiplex polymerase chain reaction (PCR) and bacteriological culture

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To detect *Mycobacterium bovis* in whey, 233 cow milk samples were analyzed together with 26 tank milk samples from dairy herds of several states of Mexico (Querétaro, San Luis Potosí, Guanajuato, Hidalgo, Coahuila). DNA was obtained from whey and used for polymerase chain reaction-multiplex (PCR-M). Tuberculosis complex was first identified through the detection of gene RD1. Positive samples were subjected to a second PCR-M for gene RD9 to identify *M. bovis.* Samples were bacteriologically cultured using conventional techniques. Cohen's Kappa test (k) and Pearson's Chi2 were carried out for statistical analysis. A 150 bp amplification product of the RD1 region was obtained, which corresponds to the tuberculosis complex, in 34/233 (14.59%) of the individual milk samples and in 4/26 (15.38%) of the tank milk samples. PCR-M with primer RD9, of the 34 individual samples and the 4 tank milk samples, gave an amplification product of 200 pb, which is the expected product for *M. bovis*. By bacteriological culture, six isolates were obtained; four in individual whey samples and two from tank milk samples, which were then classified by biochemical tests as *M. bovis*. The concordance between RD1, RD9 PCR-M and bacteriological culture was low, but there was a significant difference between diagnostic techniques with a P = 0.000. The results showed the potential of the PCR-M as a confirmatory test for the diagnosis of tuberculosis in cattle, as well as the advantage of using whey samples, that may be a possible source of infection for the herd and/or humans.

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Neuroinflammation during experimental pulmonary tuberculosis

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During the development of chronic inflammation, there is neuronal activation and changes in the synthesis and production of neurotransmitters and cytokines, that affect functions such as learning, memory and mood. Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (M. tb) that induces chronic inflammation. Patients with TB develop various mental disturbances like depression and anxiety. Thus, we investigated the effect of lung infection with M. tb on the immune response in the central nervous system (CNS) and its relationship with behavioural changes in the absence of culturable mycobacteria in the brain in a murine model of pulmonary TB. The results showed an increase in TNF□, IFN□, IL-12, IL-4 and TGF-β, as well as the enzymes IDO and iNOS in the hypothalamus, hippocampus and cerebellum. There were significant changes in the production of the neurotransmitter's noradrenaline, adrenaline, dopamine and serotonin. Neuronal damage occurred in the hippocampus and cortex at an early stage of the disease, and it led to neuronal death in the progressive phase of the disease, with an increase of p38 and JNK. BDNF levels decreased, and an increase of blood-brain barrier permeability. All these changes coexisted with depressive-like behaviour, sickness behaviour, anxiety-like behaviour, neurological damage and impairment of short and long-term memory.
These results show for the first time that chronic inflammation during pulmonary tuberculosis causes neuroinflammation and behavioural abnormalities in the absence of brain infection.

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Use of BCG vaccine in the immunodiagnosis of *Mycobacterium bovis* in naturally infected cattle

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The gamma interferon (IFN-γ) is one of the most critical effector molecules for the control of mycobacterial infection; therefore, its evaluation as a mediator of the cellular immune response has been considered for the diagnosis of tuberculosis. Mostly, in advanced stages of the disease there is a change in the cellular-type immune response to a humoral immune response. Consequently advisable to apply diagnostic tests in tandem, to evaluate both cellular and humoral immunity, thus providing a greater opportunity to identify cattle in different states of infection. The aim of the study was to evaluate and compare the diagnostic usefulness of a sonicated extract of BCG (SBCG) vaccine from *Mycobacterium bovis* in gamma-interferon release and ELISA assays. For this purpose, blood samples from 42 Holstein-Friesian cows with a history of reactivity to intradermal tuberculin test (ITT) were used to evaluate the above tests, jointly with other established laboratory tests (BOVIGAM and comparative ELISA). The results obtained were analyzed by the Mann-Whitney and Kruskal-Wallis tests and determined the agreement between tests by Cohen's kappa coefficients. The seropositivity results obtained in the SBCG-ELISA showed a good concordance (value of k=0.81) between this test and the ITT; not so with the comparative ELISA, whose concordance was moderate. The use of this antigen (SBCG) in IFN release assays had a better correlation with the tuberculin test, so its usefulness in immunodiagnostic methods of the disease is recommended, both for the serological determination of antibodies, as in methods based on cell type immunity.

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Seroprevalence and risk factors associated to bovine tuberculosis in dairy herds under different production systems

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The objective of this work was to carry out a serological study of bovine tuberculosis and to determine the risk factors associated with the disease in dairy herds under different production system in states of the Mexican Republic. 4580 serum samples were collected from of Aguascalientes, Chiapas, Chihuahua, Coahuila, Durango, Guanajuato, Hidalgo, Jalisco, Querétaro, Sinaloa and Veracruz. Sera were analyzed by a comparative ELISA, using protein extracts from of *Mycobacterium bovis* and *M. avium.* The overall seroprevalence of the disease was 13.67 %. It was identified, there is variability in the index of seroprevalence in relation to the production system, in such a way that the intensive system reported two units higher than the general prevalence (16.4%); while, for the dual purpose system the index was 11% and for the familiar one 10%. The multivariate analysis showed that there a higher probability of the disease occurring in intensive and dual-purpose production systems. The presence of paratuberculosis increases the risk of tuberculosis in herds. A high seroprevalence recorded for the States of Sinaloa and Chihuahua, which according to data from the Campaign against the disease, are States in the eradication phase. The difference can be explained, taking into account that the data provided were obtained mainly from dairy herds, while the campaign data are generally obtained from herds destined for meat production. Highly seroreactive animals are potential sources of infection, as the official test does not normally identify them, hence the importance of considering serological tests as part of the diagnosis.

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3D architecture and structural flexibility revealed in the subfamily of large glutamate dehydrogenases by a mycobacterial enzyme

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Glutamate dehydrogenases (GDHs) are widespread metabolic enzymes that play key roles in nitrogen homeostasis. Large glutamate dehydrogenases (L-GDHs) composed of 180 kDa subunits (L-GDHs180) contain long N- and C-terminal segments flanking the catalytic core. Despite the relevance of L-GDHs180 in the physiology of environmental and pathogenic bacteria, the lack of structural data for these enzymes has limited the progress of functional studies. We report the 3D structure of the mycobacterial L-GDH180 isoform from *Mycobacterium smegmatis* (mL-GDH180), obtained through an integrative approach that combined single-particle cryo-EM and X-ray protein crystallography. mL-GDH180 adopts a quaternary structure that is radically different from that of related low molecular weight enzymes. Intersubunit contacts in mL-GDH180 involve a C-terminal domain that we propose as a new fold and a flexible N-terminal segment comprising ACT-like and PAS-type domains that could act as metabolic sensors. These findings reveal unique characteristics of domain organization and oligomeric assembly in the subfamily of L-GDHs, thus allowing to update the annotation of the Pfam family PF05088 that includes the L-GDHs180. Furthermore, our cryo-EM data evidenced fluctuations in the quaternary structure of mL-GDH180 that are possibly relevant for the allosteric regulation of the enzyme activity, uncovering unique aspects of the structure-function relationship in the L-GDHs subfamily.

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Genotyping of *Mycobacterium tuberculosis* circulating in jurisdiction V, Xalapa, Veracruz, Mexico using MIRU-VNTR 15 loci

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Despite that the jurisdiction V from, Veracruz, México, has an important prevalence of Tuberculosis (TB), the genotypic characteristics of tuberculosis circulating in the population is unknown. Therefore, the objective of this work was to characterize the circulating TB lineages in jurisdiction V, using MIRU-VNTR 15 loci.

Of the 49 individuals included in the study 61% were male. The age predominant age was 35 years old and 16% had Type 2 diabetes mellitus (T2DM). Resistance patterns for the same number of isolates show that 37% had resistance to isoniazid, 33% to rifampicin and 31% were MDR-TB. All isolates were included within lineage L4 (Euro-American). The predominant sublineages were: H (27%), T (27%), X (20%) and LAM (14.3%). Infection by lineage X was a risk factor for resistance to isoniazid (OR = 5.93, [1,297-27,203]), Rifampicin (OR = 4,350 [1,015-18,639]), and to T2DM (OR = 6.66 [1.05-42.065]).

The high frequency of L4, and H sublineage differs from that observed in other regions of the state and México. The association of lineage X with MDR-TB shows the need for more studies to understand why this lineage is more prevalence in Jurisdiction V and confirm the possible dispersion of isolates with lineage X carrying MDR-TB.

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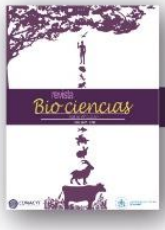
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Deletion of the heavy metal transporter CtpA in *Mycobacterium tuberculosis* and its response to stress conditions

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Tuberculosis (TB) continues be the top infection killer in the world, which caused 1.4 million deaths in 2019. At present, the identification of *Mycobacterium tuberculosis* (Mtb) attenuation targets associated to viability and virulence is a priority for designing live attenuated whole-cell anti-TB vaccines (WCV). Given that, P-type ATPases respond to different hostile conditions faced by the bacillus within the phagosome. The importance of heavy metal transport mediated by P-type ATPases in the viability of the bacillus is well known, as well as, the role on the plasma membrane homeostasis, and the Mtb virulence.

In the present work, MtbH37Rv strain defective in the ctpA gene was constructed by recombineering, and confirmed by genotypic analysis. Using neutral red (RN) test of virulence, it was found the deletion of ctpA could be related to the Mtb virulence. Besides, the defective strain tolerance and compensatory P1B-type ATPase activity to high concentrations of copper, as well as oxidative and nitrosative stress condition have been evaluated. This work is part of a project aimed to evaluate by in vitro and in vivo experimental models, if P-type ATPases could be potential Mtb attenuating targets on the construction of live anti-TB vaccines against TB.

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Comparative study of the protective effect of BCG vaccine and *Mycobacterium bovis* culture filtrate proteins in calves under field conditions

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Bovine tuberculosis (TBb) causes significant economic losses worldwide. Currently no registered vaccines against TBb; however, interest has grown for the use of vaccines such as *Mycobacterium bovis* bacillus from Calmette-Guérin (BCG), proteins filtrate culture (CFP), recombinant proteins, and attenuated strains of *M. bovis* for the control of the disease. Much of the research on this topic has been done under controlled conditions and few studies have been done under field conditions, so the objective of the work was to assess the protective effect of BCG Phipps strain and CFP, against natural infection by *M. bovis*. For this purpose, fifty calves belonging to a farm with a high prevalence of TBb located in the state of Hidalgo were used, which were randomly formed 5 groups of 10 calves. Each group received a different vaccine (CFP 300 µg, CFP 600 µg, BCG 1x104 CFU, BCG 1x106 CFU or PBS). The animals were clinically monitored for 16 months and evaluated by the tuberculin skin test (TST), interferon gamma release assay (IGRA) and PCR. In the group vaccinated with CFP 600 µg an infected animal was identified; while in the control group, two animals were infected according to the criteria of positivity to IGRA, TST and PCR. On the other hand, one animal from each of the other groups tested were positive for IGRA but not for TST and PCR. The BCG and the CFP tested in this study had a protective effect on vaccinated calves, so that they could be good vaccine candidates.

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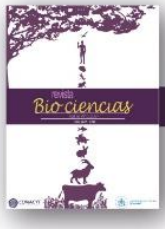
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Study of T cell subsets in cattle vaccinated with BCG Phipps or Mycobacterium bovis culture filtrate proteins (CFP)

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Control of bovine tuberculosis (bTB), caused by *Mycobacterium bovis* (*M.bovis*) is needed on a global scale. Vaccination of cattle may supplement existing control programs; however, is important to understand immune response induced by vaccination. The aim of this study was to compare T cell subsets in response to parenteral vaccination with BCG and *M. bovis* culture filtrate proteins (CFP) in cattle. Fifty Holstein calves aged 2-4 months were randomly grouped into five groups and subcutaneously immunized with either *M. bovis* BCG (Phipps) ($1x10^4$ or $1x10^6$ CFU), CFP (300 µg or 600 µg) or PBS (control). Blood samples from calves were obtained periodically in order to evaluate the surface marker expression and interferon gamma (IFN-γ) production after *in vitro* antigenic stimulation of cultures peripheral blood mononuclear cells (PBMC) with PPD bovis. The results indicate that the different doses of BCG and CFP used were able to induce a proliferative response of $CD4^+$ and $CD8^+$ lymphocytes, exhibiting a higher degree of activation as a function of time for the cytotoxic population as opposed to the $CD4^+$ population, particularly in the CFE vaccinated groups. It indicates a regulation of immune response in which other cell types and soluble mediators could be participating. IFN-γ production was moderately increase in the different groups according to time. The evaluation of the degree of protection offered by these vaccines in the long term and the assessment of immunological memory markers continue, this will make possible to define which of them is suitable for disease control.

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Genotyping and identification of mutations associated to drug resistance in *Mycobaterium tuberculosis* complex isolates in Oaxaca, Mexico

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Worldwide, Tuberculosis (TB) is the first cause of death due to an infectious agent. *Mycobacterium tuberculosis* complex (MTBc) drug resistant strains are partly responsible for the increasing number of TB cases. Studies around the world have reported recurrent mutations in genes which encode target proteins of the antibiotics included in TB treatment. There is not a report about the relationship between the different MTBc sub-linages identified in Mexico and mutations related to drug resistance in target genes. Therefore, we studied this relationship in 35 MTBc isolates from Oaxaca state patients. Sub-linages identified by 24 loci MIRU-VNTR, spoligotyping and long sequence polymorphism (LPS) were: Haarlem, EAI, H37Rv-like, LAM, S, Ghana, X, *M. bovis* and Uganda I. Molecular analysis by PCR and sequencing of rpoB, embB, rrs, rpsL and pncA genes led to the identification and characterization of mutations related to drug resistance. Isolates containing mutations in rpoB and resistant to rifampin by indirect proportion method, belonged to EAI and S sub-lineages. Mutations in codon 306 in embB were characterized in S sub-lineage ethambutol resistant isolates. Resistance to streptomycin was found in isolates belonging to LAM, Haarlem, EAI and S sub-lineages which also held mutations in rrs and/or rpsL. No pyrazinamide resistant isolates were identified, however mutations in pncA were characterized in an H37Rv-like isolate. Among Ghana, X, Uganda I and Bovis sub-lineages no mutations were characterized in the studied genes. This analysis showed that most of the main mutations associated to drug resistance are present in EAI and S sub-lineages.

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Phylogeography of Mycobacterium tuberculosis clinical samples in Mexico and their antibiotic resistance profiles

Mejía-Ponce PM[1*], Lara-Ramírez EE[2], Ramos-García AA[1], Zenteno-Cuevas R[3], Valdez-Salazar F[2], Soriano-Herrera AR[2], Castro-Garay CY[2], Núñez-Contreras J[2], De Donato-Capote M[1], Sharma A[1], Ramos-González EJ[2], Espinoza-Ayala G[5], Montoya-Fuentes H[6], Castañeda-Delgado JE[4], Enciso-Moreno JA[2], Licona-Cassani C[1]

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Mycobacterium tuberculosis (Mtb) is the principal causative agent of human tuberculosis (TB) which remains one of the deadliest infectious diseases worldwide. Mexico, where ~24,000 TB cases were reported in 2018, routinely uses gold standard methods to diagnose TB, which preclude contact tracing, lineage identification or to obtain a complete antibiotic resistance profile (ARp). Here, we present a phylogeographic analysis and a complete ARp based on whole genome variant analysis of 133 clinical samples of Mtb from 17 states of Mexico. A 11,166 SNPs-based phylogenetic tree was reconstructed and annotated according MTBseq lineage identification. We found 128 of our samples belong to the Lineage 4 (Euro-American) and the other five to the Lineage 2 (EAI Manila and Beijing). Main sublineages represented were: X-type (33.08%), LAM (22.56%) and Haarlem (21.05%). Complete ARp was predicted using TB-profiler, which showed 45.1% samples as Sensitive, 17.3% as Pre-MDR, 27.8% as MDR, 3.8% as Pre-XDR, 1.5% as XDR and 4.5% as Other. Comparison of Drug Sensitivity Test (MGIT 960) and TB-profiler ARp prediction indicated that 33.83% of samples differed. After a deep variant analysis of Pre-MDR and MDR samples, we found interesting signatures that may be unique for resistant Mtb Mexican lineages. From this observation, we encourage to invest in WGS projects of Mtb clinical samples in Mexico for better determine complete ARp and also, to efficiently detect transmission groups and spread of antibiotic resistant strains that will serve as a solid base for the timely decision-making and public policy in the country.

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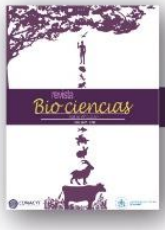

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In vitro and in vivo antimicrobial effect of 1,4-benzoquinone (Blue Compound) obtained from scorpion venom against susceptible and multi-drug resistant *M. tuberculosis*

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Tuberculosis is a lung disease caused by *Mycobacterium tuberculosis* (Mtb) and according to WHO, the leading cause of death worldwide from a single infectious agent. The emergence of multidrug-resistant (MDR) strains has created the need to find new chemotherapeutic molecules and the venoms of dangerous animals (snakes, spiders, scorpions) have proven to be a good source. A new compound isolated from the venom of Diplocentrus melici scorpion, the “Blue Compound” (5-methoxy-2,3-bis(methylthio)cyclohexa-2,5-diene- 1,4-dione or BC), has demonstrated antibacterial activity against Mtb (MIC = 8 µg/mL) comparable to currently used antibiotics; promoting disruption of the cell wall and a significant decrease in intracellular bacillary load in infected MH-S cells (>5 µg/mL). To assess its therapeutic activity in vivo, BC was used as a therapy in an experimental model of progressive pulmonary tuberculosis with mice infected with a H37Rv or a MDR strain. Mice treated with 8 µg for two months had a significant decrease in lung bacillary load and lung tissue damage without adverse effects. Moreover, the combination of BC with either isoniazid or moxifloxacin showed an increase of the bactericidal effect in vitro of both drugs. Despite this, when testing the combination of BC and first-line antibiotics in the mouse model the previously described effect was not seen. Finally, the mechanism of action of this molecule was established, showing that generates an increase in the production of ROS in an Mtb culture leading to cell death. According to the results, BC can be a new alternative in the treatment for Tuberculosis.

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Genomic characterization of clinical isolate of *Mycobacterium tuberculosis* drug-resistant from Ecuador

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Introduction: Tuberculosis is considered a re-emerging disease due to increased multidrug-resistance (MDR) and extreme drug resistance (XDR), which remains the challenge for tuberculosis control. *Mycobacterium tuberculosis* has different mutations associated with resistance. In Ecuador, genetic studies related to the resistance of *Mycobacterium tuberculosis* are limited. This study assesses the characterization of resistance of clinical isolates of *Mycobacterium tuberculosis* through whole-genome sequencing (WGS). Methods: Subsequently to resistance microbial characterization, DNA was extracted using CTAB method and genomes were sequenced on the MiniSeq platform with High Output Reagent Kit (2 x 150 bp) following tagmentation-based library according to the manufacturer's instructions. The sequencing reads were mapped to the *M. tuberculosis* H37Rv reference genome. Associated resistance mutations were identified by both PhyResSE and TB-Profiler. Results: Genome sequence from twenty-four isolates were classified in 2 pre-MDR, 16 MDR, 4 pre-XDR, and 2 XDR; 105 associated mutations were identified in genetic regions: embA, embB, ethA, ethR, fabG1, gid, gyrA, katG, pncA, rpoB, rpsL and rrs being the more frequent the missense mutation (82.86%) in gene rpoB (23.81%), katG (18.10%), embB (14.29%), and pncA (12.38%) associated with resistance to rifampicin, isoniazid, ethambutol, and pyrazinamide, respectively. Also, 6.67% mutations affect the frameshift in gene ethA, gid and pncA, of which, 57.14% are deletions. Conclusion: This study shows the presence of different mutations associated with first-line antibiotic resistance genes in tuberculosis patients. This highlights the necessity to apply WGS to characterize mutations that can cause serious problems generating MDR and XDR strains, as a part of surveillance programs.

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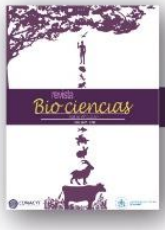

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Inhibitory effect of Precatorin A flavonoid on *Mycobacterium bovis* BCG biofilm

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One third of the world population is infected with the tubercle bacilli, potentially leading to the development of the active tuberculosis form. Studies suggest that *Mycobacterium tuberculosis* (MTB) and non-tuberculous mycobacteria (NTM) can develop biofilm microcolonies in animal and human tissues. These microbial matrices provide resistance to drugs, possibly hampering the elimination of latent infection in healthy household contacts and patients. Therefore the development of new inhibitors or disruptors of biofilms is considered as an alternative to increase the efficiency of current drugs, as well to reduce the period of treatment and consequentially its toxicity. We evaluated the effect of flavonoids from Rhynchosia precatoria on biofilm growing bacteria. *M. bovis* BCG Pasteur was used as a model for MTB since rifampicin, isoniazid, ethambutol and bioactive compounds showed similar minimal inhibitory concentrations (MIC) according to the Fluorescence Resazurin Microtiter Assay (fREMA). Biofilm formation evaluated by Crystal Violet Staining exhibited the mycobacteria's ability to proliferate and develop biofilm in presence of inhibitory drug concentrations. The flavonoid Precatorin A had a major effect on delating the biofilm development with a low viable cell number, similar to rifampicin, however an effect on pre-formed biofilms was detected only with super inhibitory drug concentrations. Biofilm analysis by Confocal Microscopy displayed morphologic differences on cell distribution, meanwhile roughness changes detected by Atomic Force Microscopy suggests the flavonoid affects the mycobacteria's cell wall. Altogether, these findings indicate a potential inhibitory effect of Precatorin A, further molecular analysis will contribute to decipher its action mechanism.

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Immunomodulatory effect of Lepidium meyenii in the inflammatory response of human macrophages to BCG

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Lepidium meyenii (L.m.), also known as maca, is an Andean crop used medicinally for multiple purposes. Studies have shown an immunomodulatory anti-inflammatory effect in murine macrophages. Bacillus Calmette–Guérin (BCG) is the vaccine used to prevent forms of tuberculosis other than pulmonary. We aimed to assess the effect of L.m. on the inflammatory response of human macrophages to mycobacteria. Human monocytic THP-1 cells bearing two plasmid reporter systems for NF-kB and IRF activation, were differentiated into macrophages and then treated with Lm at concentrations of 1ug/ml, 5ug/ml and 10 ug/ml for 48 hours. Cells were then infected with *Mycobacterium tuberculosis* (Mtb), *Mycobacterium smegmatis,* and BCG for 24 hours. L.m.-treated cells showed a dose response increase in the activation of NF-kB. After infection with BCG we observe a reduction of the NF-kB activation in cells treated with 1 and 5 ug/mL of L.m. Cells treated with 10 ug/mL showed a reverse to values similar to untreated cells. No effect was observed in IRF activation, or in the phagocytosis of mycobacteria upon L.m. treatment. A decrease in the number of internalized BCG was observed in L.m.-treated cells. Our results indicate that LM exerts an immunomodulatory effect on the NF-kB activation of human macrophages upon mycobacteria challenge. This is in line with a previous report on the anti-inflammatory effect of L.m. on an acute hepatitis murine model. Our findings could potentially translate into a beneficial effect in the exacerbated inflammatory response associated with BCG or even active TB.

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Sera from tuberculous cows induce changes in the nuclear morphology of human neutrophils

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Introduction: Bovine TB is an infectious-contagious disease caused by *Mycobacterium bovis*. The primary cells involved in the infection control are resident macrophages, dendritic cells and neutrophils. In a previous study we found that the sera of people with tuberculosis, but not the sera of healthy people, induced nuclear changes in neutrophils and NETs formation. This finding made us think that something similar could happen in bovine tuberculosis. The objective of this study was to assess whether the sera of tuberculous cows were also able to induce changes in neutrophils of healthy people. Methodology: Neutrophils were obtained by centrifugation on Polymorphrep, and incubated in vitro for 3 or 6 hours with healthy or diseased (PPD+) cow sera. The cell monolayers were treated with the Hoechst 33342 dye for fluorescence microscopy and analysis with ImageJ software. Results: 10 sera were studied per study group. The percentage of neutrophils with cell alterations, and the nuclear area of cells was quantified. A significant statistical difference was found between the groups ($p < 0.001$, Student T test). Conclusion: Healthy cow sera did not induce significant changes in neutrophils while sera of sick cows induced changes comprising pyknosis, chromatin decompaction and cell aggregation, suggestive of early apoptosis. Along with the PPD test, our test can help distinguish with certainty between healthy cows and sick cows, facilitating the veterinarian's decision on the fate of sick cows. Study supported by the IPN (SIP, COFAA, EDI) and CONACYT, Mexico.

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The dendritic cell pulsed with peptides: master of the regulation in immunology protective response against *Mycobacterium tuberculosis*

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Mycobacterium tuberculosis (Mtb) is one of the most successful pathogens of humanity, being the main cause of tuberculosis, responsible for the highest number of deaths worldwide by an infectious agent that estimates a third of the world's population is a carrier of the bacillus. The evolutionary adaptation of this pathogen is mainly due to its ability to evade the host's immune system, preventing it from displaying an effective immune response in cases where active tuberculosis develops. This is how it is necessary to improve the recognition of the pathogen by actors of the immune system for which dendritic cells (DC) can be contained. The DCs derived by standard methods with 1,25 ng/mL IL-4 and 2,5 ng/mL GM-CSF were pulsed with synthetic peptides (n=114) from proteins (n=16) involved in the mycobacterial-host interaction, which have been modified in the amino acid sequence; the strategic changes allow greater interaction with the host MHC-II and thus make the peptides more immunogenic than the native sequences. This interaction allows contact with TCD4+ lymphocytes, which is evaluated by clonal expansion of memory cells and differentiation of Th1/Th2/Th17 profiles mediated production of cytokines. This work thus contributes to the fact that using peptides modified specifically as vaccine candidates against tuberculosis and pulsed by CD, can increase the individual's immune response and contribute to the control of Mtb infection by antigenic presentation to TCD4+ lymphocytes known as major effectors in immunity against tuberculosis.

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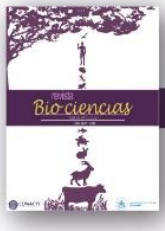

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Therapeutic drug monitoring of rifampicin and isoniazid as predictors of short and long-term clinical outcomes in patients with tuberculosis

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The directly observed treatment short-course (DOTS) for tuberculosis (TB) disease is based on a fixed-drug combination formulation but disposition may be affected by several factors including interactions, genetic variants, body weight and comorbidities that may lead to the development of drug resistance. A prospective study was approved by the Research Ethics Committee from Hospital Central Dr.Ignacio Morones Prieto (San Luis Potosi, Mexico) and conducted through the consecutive inclusion of TB patients under DOTS scheme from 2013 to 2019. Clinical information was retrieved from medical records. Rifampicin (RMP) and isoniazid (INH) plasma concentrations were quantified at 2 and 4-hours after last dose by liquid chromatography coupled to mass spectrometry. Forty-nine TB patients (18-79 years) with a success rate of 85% to anti-TB treatment were included. The most frequent was pulmonary infection (40%) and 25% of patients had type 2 diabetes mellitus. The main variables related to adverse clinical outcome, reported as time to sputum conversion or symptoms resolution, as well as long-term outcomes after discharge, were lower INH and RMP plasma concentrations at 2-hour after last dose compared to those patients with clinical success [1.9 vs 3.7 mg/L and 16.9 vs 10.0 mg/L ($p<0.05$), respectively]. A considerable proportion of patients showed subtherapeutic concentrations of RMP and INH which is associated with overall therapeutic failure. Dose adjustment can be performed during the first week according to a 2-hour sample to avoid adverse clinical outcome; however, to interpret the results correctly and simulate a future regimen, a 4-hour sample should be included.

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How mycobacteria initiate mycolic acid biosynthesis in the fatty acid synthase II system?

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The biosynthesis of fatty acids (FA) in mycobacteria involves two different systems of fatty acid synthases (FAS), FAS I and FAS II. Both synthases are involved in the biosynthesis of membrane FA and several lipid components of the cell wall. For example, for the biosynthesis of mycolic acid (MA), essential for viability and pathogenesis, FAS I and FAS II have to work in a coordinate way to maintain lipid homeostasis. These two systems are linked by a beta-ketoacyl-acyl carrier protein synthase III (KASIII), named FabH, that catalyzes the first reaction of FAS-II using FAS-I products as substrate. Although *Mycobacterium tuberculosis* FabH has been studied at the biochemical level, there are no genetic analysis that unequivocally establishes the physiological role of this enzyme. In this work, we constructed a mutant strain in the putative gene coding for FabH in *Mycobacterium smegmatis* and carried out a physiological characterization and lipid analysis. Our results show that the fabH gene it is not essential in the studied conditions and the resulting mutant strain is able to synthesize MA. However, we observed different growth behavior under different stress conditions, including altered response to isoniazid. We believe there must be other gene/s, distantly related to well known KASIII, implicated in MA biosynthesis in *M. smegmatis*. The characterization of key enzymes participating in MA biosynthesis not only allows better understanding of their role in the physiology of mycobacteria, but also might lead to the identification of new drug targets for the development of new antimycobacterial compounds.

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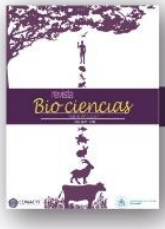

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Angiogenesis is not influenced by Type 2 Diabetes Mellitus in *Mycobacterium tuberculosis*-infected macrophages

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Introduction. Monocyte-derived macrophages (MDM) infected by *Mycobacterium tuberculosis* (Mtb) produce angiogenic factors, a mechanism proposed as a way to facilitate bacilli migration causing extrapulmonary tuberculosis (TB). The influence of Type 2 diabetes mellitus (T2DM) in this phenomenon has not been studied. Methods. MDM from T2DM patients and a control group were infected with Mtb and the relative expression of nine molecules associated with angiogenesis was evaluated by RT-qPCR. Results. The mRNA levels of angiogenic markers were similar between patients and controls at both, the basal condition (driven by T2DM itself) and after Mtb-infection. Conclusions. In MDM no exacerbation due to T2DM in the production of angiogenic transcripts was seen, neither such mRNA expression was modified in T2DM by Mtb-infection, consistent with the literature reporting epidemiologically no higher extrapulmonary TB in T2DM patients.

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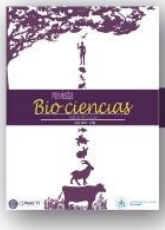
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Identification of *Mycobacterium bovis* and *Brucella abortus* by molecular methods in milk samples from the Sumapaz region, Cundinamarca, Colombia

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One of the main challenges in livestock productivity is the spread of zoonotic diseases such as bovine tuberculosis (BTB) and brucellosis which represent a risk for both livestock farmers and consumers of dairy products. Diagnosis is performed by caudal fold test and serological tests which are not specific and unavailable to small and medium farmers. Our aim was to set up a molecular method for specific identification of *M. bovis* and *B. abortus* in milk samples. Mapping of BTB and brucellosis cases was performed according to the weekly epidemiological bulletin from the Epidemiological Surveillance from The Colombian Agricultural Institute. A protocol for bacterial DNA extraction and amplification was standardized for the identification of *M. bovis* within the Mtb complex and *B. abortus* serotypes by multiplex PCR in field isolates. Conditions for PCR techniques were tested successfully with an *M. bovis* reference strain, and the reference strains of *B. abortus*, S19 and RB51. We have no bacterial detection in 20 milk samples analyzed from livestock farms from the Sumapaz region. However, 26 cases of brucellosis (12.3%) were reported in Cundinamarca out of the 211 cases in Colombia and 30 cases (66.6%) of BTB in Cundinamarca out of the 45 reported nationwide. Here we proposed a new screening flowchart to establish a new diagnostic protocol for zoonotic pathogens. Our results might be very useful for animal health control authorities and for a possible design of preventive policies in the control of brucellosis and bovine TB in the Sumapaz region from Colombia.

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Deletion of the ctpF gene encoding a calcium P-type ATPase of the plasma membrane impairs the *Mycobacterium tuberculosis* virulence

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Tuberculosis (TB) is the main cause of death triggered by an infectious agent worldwide. It is considered a threat to public health due to its high incidence, emergence of multidrug and extensively resistant strains, TB-HIV coinfection and limited efficacy of the BCG vaccine. Therefore, the identification of alternative attenuation targets of Mtb is pivotal for designing live attenuated vaccines. Previous studies have suggested the relevance of membrane proteins in the mycobacterial physiology and host-pathogen interaction, such as CtpF, a pump involved in calcium detoxification, which is activated in response to redox stress similar to the observed in the phagosomal environment.In the present work, the ctpF gene was deleted in the MtbH37Rv strain (MtbΔctpF), and the virulence of the mutant strain was evaluated in vitro on murine alveolar macrophages (MH-S). During the 7 days post-infection (T0 vs T7), the CFU increased 100-fold in macrophages infected with MtbH37Rv; in contrast, the CFU increased only 5-fold in macrophages infected with MtbΔctpF. Furthermore, in vivo assays in BALB/c mice showed median survival times of 59 and 84 days in animals infected with the MtbH37Rv and MtbΔctpF strains, respectively. These results demonstrate that CtpF is relevant during the process of infection; apparently the ctpF deletion alters relevant physiological mechanisms for the Mtb survival and proliferation in macrophages. Therefore, the ctpF deletion impars the Mtb virulence in a mouse model with progressive pulmonary tuberculosis.

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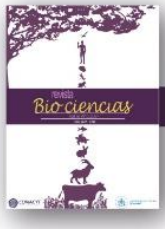

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Unmarked *Mycobacterium tuberculosis* strains defective in P-type ATPases as potential live attenuated vaccines

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Tuberculosis (TB) is an infection disease caused by *Mycobacterium tuberculosis* (Mtb), an intracellular pathogen that caused 1.3 million deaths worldwide in 2018 (WHO, 2019). Therefore, the search for new strategies for TB control, including the development of attenuated strains, is a priority. The present work describes the construction of unmarked mutants (free of antibiotic resistance markers) of Mtb defective in the ctpF and ctpH genes that encode for P-type ATPases associated with detoxification against high concentrations of Ca2+ and Na+/K+ respectively. These P-type ATPases transporters are known to be related to the virulence and survival of Mtb in macrophages. For obtaining the mutants by recombinering, allelic exchange substrates (AES) were constructed in the pYU854 vector, where the genes of interest were interrupted by a hygromycin resistance cassette, in turn flanked by resolvase sites. These recombinant plasmids are transformed into Mtb strains previously mutated into ctpH and ctpF genes. The hygromycin cassette deletion occurs by transformation of the mutant strain with plasmids containing the gene for the δγ resolvase transposon (tnpR). Excision of the hygromycin cassette is performed by culture on a selective medium and testing by PCR.

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New potential inhibitors of the membrane transporter CtpF of *Mycobacterium tuberculosis* by pharmacophore-based virtual screening

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Tuberculosis (TB) caused 1.2 million deaths in 2019. The global health outlook is bleaker when considering the emergence of multidrug resistant (MDR) and Extended-drug resistant (XDR) *Mycobacterium tuberculosis* (Mtb) strains, latent infection and co-infection with HIV/AIDS. This situation forces the search for alternative therapeutic targets and methodologies for the rational design of new and more effective drugs. The P-type ATPases are membrane proteins interesting as therapeutic targets considering their importance in ionic homeostasis and their role in the survival of (Mtb) during infection. The ctpF gene encodes a Mtb Ca2+-ATPasa protein, which has been activated under conditions of oxidative stress, hypoxia, and infection, suggesting that the plasma membrane transporter CtpF may be part of the strategies used by Mtb to evade the immune response by pumping calcium. Recognizing the importance of CtpF in the viability of Mtb and based on previous results we proposed a strategy to obtain new compounds with potential activity against CtpF. The insilico analysis of the poses and the interactions with the functionally active residues between CtpF and cyclopiazonic acid (CPA), and other CtpF inhibitors previously identified in our group was taken as reference. The strategy was based on different chemoinformatic methods such as: molecular dynamics, pharmacophore and docking-based virtual screening, protein ligand interaction fingerprints and ligand-protein interaction energy calculations. This strategy allowed the identification of 11 compounds with potential activity against CtpF. These compounds will be subjected to in vitro tests to evaluate and confirm their biological activity.

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Presence of SNPs in genes related to base excision repair (BER) in *M. tuberculosis* isolated from patients with / without type 2 diabetes mellitus: preliminary study

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The base excision repair (BER) pathway plays a key role in maintaining the integrity and diversification of DNA, and thus in drug resistance. Through the analysis of 90 genomes of *M. tuberculosis* of the Euro-American lineage of patients with / without type 2 diabetes mellitus, the presence of SNPs in the genes that eliminate damaged bases was analyzed: BER-oxidation (MutM, MutY, Fpg2, Nei1, Nei2 and Nth), alkylation / methylation of BER (TagA, AlkA, OgT and Mpg) and BER-uracil (Ung and UdgB). SNPs detection was performed using the PhyResS® platform. Differences in the presence of SNPs in the Fpq2, Nei1, Nei2 and UdgB genes were identified between patients with and without type 2 diabetes mellitus ($p < 0.05$); as well as in MutM and Nei1 between the sensitive and resistant strains ($p < 0.05$). Low negative correlations were observed between drug resistance, the presence of SNPs in the BER-oxidation genes (MutM and Nei1), and the total number of SNPs in the BER genes ($p < 0.05$). As well as negative correlations between the number of SNPs in BER-Oxidation and the SNPs in BER-alkylation/methylation and BER-uracil ($p < 0.05$). Although this is preliminary work, there are differences in the SNPs present in the genes analyzed between the study groups that require detailed evaluation.

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