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Computer-Aided Drug Design on Tuberculosis

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Abstract

Currently, India's Directly Observed Treatment Short Course (DOTS) program is the world's largest and fastest-growing initiative for treating medical patients, second only in terms of population coverage. The main obstacles to TB control in India are inadequate primary healthcare in rural regions of many states, unregulated private treatments resulting in extensive misuse of first- and second-line TB medications, the spread of HIV, a lack of political commitment, and, most importantly, corrupt administration. Tuberculosis (TB) is an airborne disease caused by bacteria from the Mycobacterium tuberculosis complex. tuberculosis is predominantly a lung infection, but it may infect nearly any area of the body. A M. tuberculosis infection can progress from a latent condition, where the bacteria are contained inside granulomas, to a contagious stage, where the patient exhibits symptoms such as fever, chills, coughing, and weight loss. Contagious TB is limited to active pulmonary cases. Drug-resistant tuberculosis (TB) poses a significant challenge in numerous contexts, and TB continues to be a major cause of illness and death in many low- and middle-income countries.

Keywords- Directly Observed Treatment Short Course (DOTS), tuberculosis (TB), drug-resistant TB, first- and second-line TB medications, low- and middle-income nations, active pulmonary TB

INTRODUCTION

Despite advancements in diagnosing and treating tuberculosis, millions still suffer and die from the disease. Tuberculosis remains one of the world's three deadliest infectious diseases, with HIV/AIDS claiming 3 million lives annually, tuberculosis 2 million, and malaria 1 million. Even though the tubercle bacilli were discovered nearly 130 years ago, a complete understanding of the disease's pathogenesis is still lacking.

Tuberculosis can impact people of any age, though individuals with weakened immune systems, such as those with HIV, are more vulnerable. The primary cause of human tuberculosis is Mycobacterium tuberculosis. Other bacteria in the M. tuberculosis complex that can cause tuberculosis include M. bovis, M. microti, and M. africanum. microti does not typically cause tuberculosis in humans and M. africanum infections are rare, M. bovis has a wider range of hosts and is a significant cause of tuberculosis in various animal species. Humans typically acquire M. bovis by consuming milk, dairy products, or meat from infected animals. It is estimated that during the antibiotic era, M. bovis accounted for around 6% of human tuberculosis deaths.

Tuberculosis (TB) is among the oldest known diseases, having co-evolved with humans for thousands or potentially millions of years. The

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earliest molecular evidence of tuberculosis was discovered in a radiocarbon-dated fossil of an extinct bison (Pleistocene bison 17,870 ± 230 years old) and in human remains from a Neolithic settlement in the eastern Mediterranean dating back approximately 9,000 years. Although as early as 1689, Dr. Richard Morton suggested that the lung shape is related ton "tuberculosis," it was due to the diversity of its symptoms that tuberculosis was recognizedas a single disease only in the 1820s, and finally J.L. Schoenlein named it "tuberculosis" in 1839. In 1882, tuberculosis was named. by the bacillus that causes tuberculosis.

Robert Koch discovered Mycobacterium tuberculosis, a breakthrough that earned him the Nobel Prize in Physiology or Medicine in 1905. If left untreated, tuberculosis has a mortality rate exceeding 50%. The information in this review article is derived from the official websites of the World Health Organization (WHO) and the Ministry of Health, Government of India, as well as extensive research using PubMed Central and Google Scholar® search engines.

In recent decades, global efforts to eradicate tuberculosis have shown positive results. Since 2000, the World Health Organization (WHO, 2017) estimated that the global incidence of TB has decreased by 1.5% each year. Furthermore, tuberculosis mortality has been significantly and consistently reduced. The World Health Organization (WHO, 2016) reported that between 2000 and 2015, worldwide death from tuberculosis decreased by 22% [1].

GLOBAL SCENARIO

In Africa, HIV has been the primary factor behind the rise in tuberculosis incidence since 1990.

In 2008, there were 9.37 million new tuberculosis (TB) cases worldwide, with 30% occurring in Africa and 34% in the Southeast Asian region (SEAR). However, the incidence rate in sub-Saharan Africa was nearly twice that of SEAR, exceeding 350 cases per 100,000 people. In the same year, approximately 1.3 million deaths were attributed to TB, with the highest number of fatalities in SEAR and the highest mortality rate per capita in Africa. Global concern over tuberculosis heightened when the WHO declared it a global emergency in 1993. It was projected that by 2004, the world would meet the Millennium Development Goal (MDG) to halt and reverse the incidence, reducing both the frequency and death rates by half compared to the 1990s.

Lately, there has been an association between the use of monoclonal antibodies that target the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) and an elevated risk of tuberculosis. These antibodies are biologic treatments for inflammatory conditions and include medications such as infliximab, adalimumab, etanercept, and golimumab. Patients on these medications should be screened for tuberculosis before and during treatment. The World Health Organization (WHO) states that tuberculosis remains a global health crisis. 13 of the 15 countries with the highest incidence of TB arein Africa, while half of the new cases occur in six Asian countries, namely Bangladesh, China, India, Indonesia, Pakistan and the Philippines. A fact sheet on tuberculosis published by the World Health Organization in March 2010 stated that a total of one third of the world's population (more than 2 billion people) is currently infected with the tuberculosis bacillus. According to it,one in two people in the world has recently been infected by tuberculosis bacillus, and onein ten newly infected people will become ill or become infected later in life. With 25% of the world's population and 30% of the world's poor, the region struggles with both infectious and non-infectious diseases amidst relatively inadequate health infrastructure.

Progress in global health relies not only on theoretical advancements but also on tangible improvements in healthcare delivery on the ground. This includes comprehensive management of public health systems, encompassing political commitment, accurate case detection using high-quality bacteriology, effective short-course chemotherapy, patient adherence to treatment, equitable access to medications, and robust reporting and record-keeping systems. From 1995 to 2008, DOTS programs successfully treated 36 million TB patients worldwide and prevented up to 6 million deaths. In the

Southeast Asian Region (SEAR), an estimated 3.6 million individuals are living with HIV/AIDS, highlighting a complex and diverse epidemic that varies within countries and across the region.

The Directly Observed Case Study (DOC) is an internationally recognized strategy for providing evidence on TB case finding and treatment. In 2007, the global success rate for DOTS cohorts, which reached approximately 86%, surpassed the global target of 85% for the first time. The use of immunosuppressive agents, such as prolonged corticosteroid therapy, has also been linked to an increased risk. Most people who get TB live in low- and middle-income countries, but TB occurs all over the world. Eight countries—Bangladesh, China, India, Indonesia, Nigeria, Pakistan, the Philippines, and South Africa—account for half of all tuberculosis cases. Individuals infected with tuberculosis bacteria have a 5-10% lifetime risk of developing the disease. People with compromised immune systems, such as HIV infection, malnourished or diabetics or tobacco usersare at greater risk of developing the disease [2].

Tuberculosis (TB) is a human disease caused by the bacterium Mycobacterium tuberculosis, mainly affecting the lungs, with pulmonary tuberculosis being the most common form. However, it can also impact other organs and systems, including the respiratory, gastrointestinal (GI), lymphatic, skin, central nervous, musculoskeletal, reproductive systems, and liver.

In recent decades, there has been a focused global initiative to eliminate tuberculosis. Although control measures have increased and the number of new cases and mortality rates have declined, tuberculosis remains a significant global health challenge. This review discusses the evaluation and treatment of tuberculosis, highlighting the importance of collaborative efforts among healthcare professionals to provide coordinated care and improve patient outcomes.

In four southern Indian states, HIV prevalence appears to be slowly declining. In Indonesia, where overall HIV prevalence is low, three provinces are reported to have much higher HIV prevalence.

Post-Independence Initial Nationwide TB Control Programs

District TB program

In 1961, the Indian government initiated a District Tuberculosis Program, designating Anantapur district in Andhra Pradesh as the inaugural Model District Tuberculosis Center (DTC). The program aimed to merge tuberculosis monitoring systems with established public health services, striving to economically address tuberculosis issues within the community. Soon after the Anantapur DTC was confirmed, it became clear that although cases could be detected anywhere without difficulty, the biggest problem in TB control was keeping patients on continuous treatment until recovery. achieved. Using this district tuberculosis center model.

In 1962 Utilizing this District Tuberculosis Center model, the Government of India launched the National Tuberculosis Control Program (ncr1) in 1962. Keep in mind that the Mantoux test shows exposure to or latent tuberculosis. However, it lacks specificity, requiring patients to return for follow-up visits to interpret results and confirm findings with chest X-rays. While the Mantoux test is fairly sensitive, it lacks specificity and can yield false positive results in individuals who have received the BCG vaccine [3].

Interferon Release Assays (IGRA, QuantiFERON Assays)

The advantages of antigen-specific stimulation of IFN-γ release, especially in those previously vaccinated with the BCG vaccine, include a test that requires single blood sample, eliminating the need for repeated visits to interpret results. Additionally, additional tests such as HIV screening can be performed with the same blood sample (with the patient's consent).

This screening test for tuberculosis measures the level of a specific inflammatory cytokine, gamma interferon, and is considered to be more accurate and equally sensitive compared to the Mantoux test. Similarly to the Mantoux test, it can also produce incorrect positive results in individuals who have been vaccinated with BCG.

Screening in Immunocompromised Patients

Immunocompromised patients may have a lower reaction to PPD or a false-negative Mantoux because of skin anergy.

Consider a high level of suspicion when interpreting negative TB screening tests in people who are HIV-positive [4].

Screening Questionnaires for Resource-Poor Settings

Multiple validated screening questionnaires are available for identifying tuberculosis among healthcare workers in underserved and remote areas.

These questionnaires use an algorithm that combines different clinical signs and symptoms of tuberculosis. Some of the most frequently used symptoms include:

- Chronic cough
- Weight loss
- Fewer and night sweats
- History of contact
- HIV status
- Blood in sputum

Several studies have confirmed the benefit of using multiple criteria rather than focusing only on chronic cough or weight loss.

Confirmatory and Diagnostic Tests

- Chest X-ray is intended to exclude or exclude the presence of active disease all positive screening tests.
- Acid Fast Staining-Ziehl-Nelsen
- Culture

This tuberculosis screening test is as sensitive as the Mantoux test but more specific. It measures the level of the inflammatory cytokine interferon-gamma.

The advantage of antigen-specific stimulation of IFN-γ release, especiallyin those previously vaccinated with BCG vaccine, is that the test requires single blood sample, eliminating the need for repeated visits to interpret results. In addition, with the same blood test (with the patient's consent), additional tests, such as HIV screening, can be performed.

Drawbacks of QuantiFERON include its cost and the technical expertise needed to conduct the test.

New molecular techniques are faster and allow rapid diagnosis with high accuracy. Confirming tuberculosis can occur within hours, instead of the days or weeks typically required for a conventional culture, which is crucial, particularly in immunocompromised individuals who often experience high rates of false negatives. Certain molecular tests are capable of identifying multidrug-resistant tuberculosis as well [5].

Treatment and Management

Latent Tuberculosis

The 2020 LTBI treatment guidelines endorsed by the NTCA and CDC include three recommended rifamycin-based regimens and two alternative monotherapy regimens using daily isoniazid. These treatments are specifically recommended for individuals infected with Mycobacterium tuberculosis believed to be susceptible to isoniazid or rifampin. A highly recommended regimen involves a 3-month course of once-weekly isoniazid and rifapentine for children over 2 years old and adults. Another option is four months of daily rifampicin for HIV-negative individuals of all ages. For adults, children of all ages, and individuals with HIV infection, a temporary first-line treatment of three months of daily isoniazid and rifampicin is also recommended. Alternatively, 6 or 9 months of daily isoniazid are recommended [6].

Treatment of Active Infection

The treatment for active tuberculosis always involves a combination of medications. Monotherapy should never be used for treating tuberculosis. Common medications used for TB treatment include the following TB drugs:

First-Line Medications, Group 1

- Isoniazid
- Rifampicin
- Rifabutin
- Rifapentine
- Pyrazinamide
- Ethambutol

Second-Line Anti-tuberculosis Drugs, Group 2

Injectable aminoglycosides and injectable polypeptides
Injectable aminoglycosides

- Amikacin
- Kanamycin
- Streptomycin

Second-Line Anti-Tuberculosis Drugs, Group 3, Oral and Injectable Fluoroquinolones

- Levofloxacin
- Moxifloxacin
- Ofloxacin
- Gatifloxacin

Injectable polypeptides

- Capreomycin
- Viomycin

Second-Line Anti-tuberculosis Drugs, Group 4

- Para-amino salicylic acid
- Cycloserine
- Terizidone
- Ethionamide
- Prothionamide
- Thioacetazone
- Linezolid

Third-Line Anti-Tuberculosis Drugs, Group 5

These are anti-tuberculosis drugs with varying effectiveness that are considered as a final option for treating extensively drug-resistant tuberculosis.

- Clofazimine
- Linezolid
- Amoxicillin/clavulanic acid
- Imipenem/cystatin

Era of Short-Course Chemotherapy

Tuberculosis treatment underwent significant advancements in the 1970s when two drugs, rifampicin and pyrazinamide, became available. These medications were well-tolerated and highly effective, enabling the development of short-course chemotherapy and simplifying treatment regimens. Rifampicin, discovered in 1967, is regarded as a major breakthrough in tuberculosis drug development history. Since its discovery, no newly developed drug has equaled rifampicin's effectiveness against tuberculosis [7].

In the mid-20th century, coinciding with India's independence in 1947, effective tuberculosis drugs became accessible (streptomycin: 1944, PAS: 1946, thioacetazone: 1950, isoniazid: 1952, and rifampicin). In 1956, the Government of India established the Tuberculosis Research Center (TRC) in Chennai, collaborating with the Indian Council of Medical Research (ICMR), the World Health Organization (WHO), and the British Medical Research Council (BMRC). This center played a key role in disseminating information on comprehensive outpatient chemotherapy for treating pulmonary tuberculosis. In 1959, the National Tuberculosis Institute (NTI) was established in Bangalore to use research to develop a practical tuberculosis program that could be implemented in all parts of the country by training doctors and paramedics in the effective implementation of proven tuberculosis. methods. rural and urban areas [8].

Current WHO-Assisted Ongoing TB Control Program

In 1992, the Indian government partnered with the WHO and the Swedish International Development Agency (SIDA) to assess the national program. They identified administrative deficiencies, funding adequacy concerns, excessive X-ray exposure, unconventional treatment plans, low compliance and discontinuation rates, and a lack of organized data on treatment results. Around the same period, in 1993, the WHO declared tuberculosis a worldwide emergency and introduced the DOTS strategy, urging all nations to implement it. This strategy was founded on five core elements: political commitment and sustained funding for TB control programs, sputum diagnosis through smear tests, consistent supply of high-quality TB medications, direct observation of drug intake, and accurate reporting and registration of all cases. data cases.

The World Bank agreed that the DOTS strategy was the most cost-effective health intervention and agreed to provide credit assistance to the NTCP, which initially covered 271 million people, later revised to 730 million people. Other international organizations currently participating include the Danish Agency for International Development (DANIDA), Department for International Development (DFID), United States Agency for International Development (USAID), Global Fund to Fight HIV/AIDS, Tuberculosis, and Malaria (GFATM), Global Drug Facility (GDF), and WHO, all of which play a vital role in supporting the program. The primary global funding source for tuberculosis control efforts is the Global Fund to Fight HIV/AIDS, Tuberculosis, and Malaria.

In 1997, the Revised National Tuberculosis Control Program (RNTCP) was introduced to enhance and reinforce the NTCP with support from these global entities. It implemented the internationally endorsed DOTS strategy as the most structured and efficient method to rejuvenate tuberculosis control initiatives in India. Key priorities included political and administrative commitment to delivering

organized and comprehensive TB services, reliable early diagnosis through sputum microscopy, consistent supply of high-quality TB medications, effective treatment with short-course chemotherapy under direct observation, and robust accountability through accurate reporting, record-keeping, and effective supervision.

Currently, India's DOTS program is the largest and most rapidly growing initiative globally in terms of patients starting treatment, and it ranks second in terms of population coverage. The WHO remains a crucial supporter of the program, offering invaluable assistance [9].

HIV AND TB

In countries where both HIV and TB are prevalent, individuals with HIV are much more prone to developing active TB compared to those without HIV. Tuberculosis is the primary cause of death among people with HIV, accounting for over a quarter of the 2 million AIDS-related deaths in 2008. It is the most widespread opportunistic disease related to HIV globally, hastening HIV disease progression, increasing transmission rates, and diminishing the efficacy of HIV treatment.

By the conclusion of 2007, India had 2.5 million individuals living with HIV and AIDS (PLHIV), and around 1.8 million new cases of tuberculosis were reported each year. The relationship between HIV and TB in individuals co-infected with both diseases is mutually reinforcing and synergistic. The level of immunosuppression determines the resulting clinical picture of the disease. Pulmonary involvement occurs in approximately 75%of all patients infected with HIV/TB.

In HIV-positive individuals, tuberculosis affecting lymph nodes, particularly in the cervical region, is the most frequently observed form of extrapulmonary tuberculosis. Co-infection of HIV and tuberculosis also causes MDR-TB to develop more rapidly [10].

The National AIDS Control Organization and the Central TB Division have established a national policy to align collaborative efforts in combating HIV/AIDS and tuberculosis. TB and TB/HIV interventions are integrated into the national policies of both programs.

Of the 1.5 million TB cases reported under the national program in 2008, around 73,720 cases were found to be HIV-positive. The updated "national framework for collaborative TB/HIV activities" was initiated in early 2008 and now spans the entire country. An enhanced TB/HIV package introduced in 2008 is currently operational in 11 states and districts with high HIV prevalence, encompassing a population of over 400 million people. The Indian government aims to extend the intensified package nationwide by 2012.

Current guidelines (National Organization for AIDS Control, 2007) recommend that tuberculosis treatment, regardless of HIV status, typically lasts for 6 months. It involves a four-drug regimen (including rifampicin) during the intensive phase for 2 months, followed by isoniazid and rifampicin for an additional 4 months, given daily or intermittently. The guidelines also classify available antiretroviral medications as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, chemokine receptor antagonists, and entry inhibitors. Patients on HAART (highly active antiretroviral therapy) (treated with a combination of at least three ART drugs) were found to have an 80% reduction in HIV infection in Brazil compared to ART-naïve patients. In India, a combination of two NRTIs and efavirenz or, less commonly, nevirapine is recommended for HIV/TB patients.

Common combinations of nucleoside reverse transcriptase inhibitors (NRTIs) include zidovudine with lamivudine, stavudine with lamivudine, tenofovir with lamivudine, and sometimes abacavir with lamivudine or diagnosing with lamivudine.

A frequent side effect of highly active antiretroviral therapy (HAART) is immune reconstitution inflammatory syndrome (IRIS), which involves a temporary exacerbation of existing symptoms, signs, or radiographic findings, or the onset of new, transient symptoms, signs, or radiographic findings after beginning HAART. Tuberculosis is the primary cause of IRIS, with lymph node enlargement being its most frequent manifestation. According to research, IRIS incidence was 2% in TB patients alone, rising to 7% in individuals co-infected with HIV, and further increasing to 36% among those starting HAART.

Monitoring of HIV infection in TB patients was previously done in special studies and is now based on routine reporting of HIV status among TB patients.

National policy databases contained information about a decentralized trial of cotrimoxazole preventive therapy (CPT) for HIV-positive TB patients in three high-HIV districts of Andhra Pradesh. PLHIV patients receive free HIV treatment in a network of antiretroviral treatment centers (ART). These facilities are situated within medical institutions, primarily operated and overseen by National AIDS Control Societies, with some also situated in private or NGO-affiliated institutions. As of September 2009, the country hosted 217 ART centers along with 10 regional centers of excellence offering specialized services to individuals living with HIV [11].

MULTIDRUG-RESISTANT TUBERCULOSIS

Multidrug-resistant tuberculosis (MDR-TB) is caused by strains of M. tuberculosis that are resistant to both isoniazid and rifampicin, which are the most potent anti-tuberculosis medications. Extensively drug-resistant tuberculosis (XDR-TB) is a type of tuberculosis caused by bacteria resistant not only to isoniazid and rifampicin (MDR-TB) but also to any fluoroquinolone and at least one of three injectable anti-tuberculosis drugs (amikacin, kanamycin, or capreomycin).

These types of tuberculosis do not improve with the standard six-month treatment using initial TB medications and typically necessitate treatment for over two years with less effective, more toxic, and considerably more expensive drugs. Both MDR-TB and XDR-TB pose growing challenges to the effectiveness of tuberculosis control programs.

According to Sir John Crofton, whose innovative use of combination therapies in tuberculosis treatment saved many lives, the most serious consequence for a tuberculosis patient is developing resistance to one or more of the standard drugs. The emergence of drug resistance can be a tragedy not just for the patient, but also for others, as they can spread their drug-resistant bacteria to others.

Drug resistance is typically categorized as either primary or acquired. Primary resistance refers to resistance in a patient who has never been treated with TB drugs before. Acquired resistance refers to resistance that develops due to previous treatment. The WHO now uses the term "drug resistance among new cases" instead of "primary resistance," and "drug resistance in previous" instead of "acquired resistance [12].

Poorly treated cases. The development of drug resistance in tuberculosis patients is largely due to \insufficient or deteriorating tuberculosis programs. Factors associated with the development of drug resistance include: inadequate or ineffective delivery of effective therapy; bad case; use of low quality drugs; insufficient or irregular supply of medicines; lack of knowledge of health workers about the treatment and control of tuberculosis; discontinuation of chemotherapy due to side effects; non-compliance with treatment regimens prescribed by the patient; over-the-counter anti-tuberculosis drugs; illiteracy; low socioeconomic status of patients; high bacterial load;laboratory delays in M detection and susceptibility testing. Tuberculosis samples and absence of consistent laboratory protocols and quality assurance measures.

According to WHO guidelines the current treatment plan for MDR-TB recommends a standardized regimen for empiric treatment patients who previously received only first-line TB drugs. The standardized regimen includes a combination of necessary medications: streptomycin, pyrazinamide, ethambutol, and thioacetazone; and additional medications such as aminoglycosides (kanamycin, amikacin, capreomycin), thioamides (ethionamide, protionamide), fluoroquinolones (ofloxacin, ciprofloxacin), cycloserine/terizidone, and para-aminosalicylic acid.

Surgery may be an option for patients whose TB bacteria are resistant or likely resistant to all but a few less effective drugs. However, many of these patients have extensive disease or poor lung function, making surgery impractical. For patients with a large, localized cavity, minimal additional disease, reasonable lung function, and limited availability of effective medications, surgery should be carefully considered.

Because current information on drug resistance affects the planning of treatment programs and practices, reliable information on drug resistance at the national level is needed both urgently and regularly. In 2005, MDR-TB cases diagnosed and reported in India amounted to 0.04%, a figure that rose to 0.15% in 2007, marking a four-fold increase. Currently, designated sites in six states offer MDR-TB treatment services, and state-level laboratories in five states provide culture and drug susceptibility testing (DST) facilities. Limited laboratory capacity significantly hinders the expansion of MDR-TB services. Collaboration in TB/HIV activities has many opportunities for expansion. The government should ensure and promote the rational use of TB drugs outside the revised national TB control program [13].

CONCLUSIONS

As mentioned earlier, substantial strides have been made in fighting this lethal disease. However, echoing the sentiment of the famous poet Robert Frost, who noted that there is still much ground to cover before we can rest, we continue to face a considerable journey in eradicating tuberculosis from the planet.

The WHO's "STOP TB" strategy aims to achieve the worldwide eradication of tuberculosis as a public health concern by 2050. Enhancing our surveillance programs is crucial to accurately assessing the burden of all types of TB—childhood TB, HIV/TB, and MDR-TB. It is crucial to implement strict controls on the appropriate use of both primary and secondary tuberculosis medications, preventing their unrestricted sale without prescription. In India and other developing nations, local governments should invest in and promote efforts for local production of TB drugs, which would improve control over production and uphold quality standards. Quality control measures should include identifying products damaged by poor manufacturing, degraded due to inadequate distribution and storage, or falsified for illicit profit. Numerous studies have highlighted the prevalence of counterfeit and substandard drugs, particularly antimalarials, in developing regions. If fake drugs in this category are circulating on the market, it is reasonable to expect that counterfeit TB drugs aren also available on that market. Computer-aided drug design (CADD) has emerged as a powerful tool in the fight against tuberculosis (TB), providing innovative solutions to accelerate the development of new drugs. Using computer simulations and algorithms, CADD enables researchers to predict the behavior of molecules, screen large chemical libraries and optimize drug candidates more accurately and efficiently than traditional methods.

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