

## Hot News

### Ingenol Derivates Promising for HIV Eradication

The eradication of HIV is at this moment one of the greatest challenges in the fight against HIV/AIDS. Despite the prolonged effectiveness of current anti-HIV therapies, capable of keeping patients with undetectable viremia for long periods of time, HIV-infected patients cannot be cured due to the establishment of HIV latent reservoirs. Therefore, several therapeutic strategies are being evaluated to eliminate these viral reservoirs. One of these strategies, termed “shock and kill”, aims to attack the latent reservoir by simultaneous treatment with HIV-activating agents to stimulate viral replication in latently infected cells and antiretroviral therapy to block new infections. A number of compounds have been suggested for the shock and kill strategy including histone deacetylase inhibitors (HDACI), histone methyltransferases (HMT), DNA methyltransferase inhibitors (DNMTI), and protein kinase C (PKC) activators.

The PKC activation followed by nuclear factor kappa B (NF- $\kappa$ B) nuclear translocation is an important step required for reactivation of latent HIV. Various natural and synthetic compounds are able to activate PKC by binding to its regulatory domain, mimicking the physiologic ligand diacylglycerol (DAG). A novel semi-synthetic PKC activator, ingenol-B (Ing-B), derived from ingenol diterpenes isolated from the Brazilian plant *Euphorbia tirucalli*, has been recently identified as a promising compound to reactivate latent HIV (Jiang, et al. AIDS. 2014;28:1555-66; Abreu, et al. Plos One. 2014;9:e97257; Pandeló, et al. Virology. 2014;462-463;328-39).

Ingenol-B has a dual role on HIV replication: it efficiently upregulates HIV LTR-dependent transcription in reporter cell lines and CD4<sup>+</sup> T-cells isolated from virally suppressed patients, and also down-regulates CD4, CXCR4, and CCR5 surface proteins that are essential for HIV replication. Moreover, the ability of Ing-B to reactivate HIV latency has also been proven in a study with Rhesus macaque models (Gama, et al. 6<sup>th</sup> International Workshop on HIV persistence during therapy 2013. Abstract 66). Ingenol-B was orally administered to SIVmac251-infected macaques in escalating doses (1, 2.5, 5 mg BID) for one week each, alternated with off-treatment weeks. The SIV-infected macaques had a significant increase in reactivated latent cells and viral RNA transcription with no apparent side effects.

Overall, Ing-B appears to be less cytotoxic than other diterpenes and has presented a low toxicity

profile in mice, rats, dogs, and monkeys determined by oral dosing. Indeed, another ingenol derivate, ingenol mebutate, has been recently approved by the FDA and EMA for the treatment of actinic keratosis, one of the most common dermatological pathologies considered a biomarker for the risk of skin cancer.

In summary, Ing-B is highly effective in reactivating HIV, being less toxic than other PKC activators. These properties support this molecule as a promising candidate for future clinical trials as an anti-HIV latency drug in combination with suppressive antiretroviral therapy. Consequently, ingenol derivatives may provide novel opportunities for HIV reactivation from latent viral reservoirs joining efforts towards HIV eradication.

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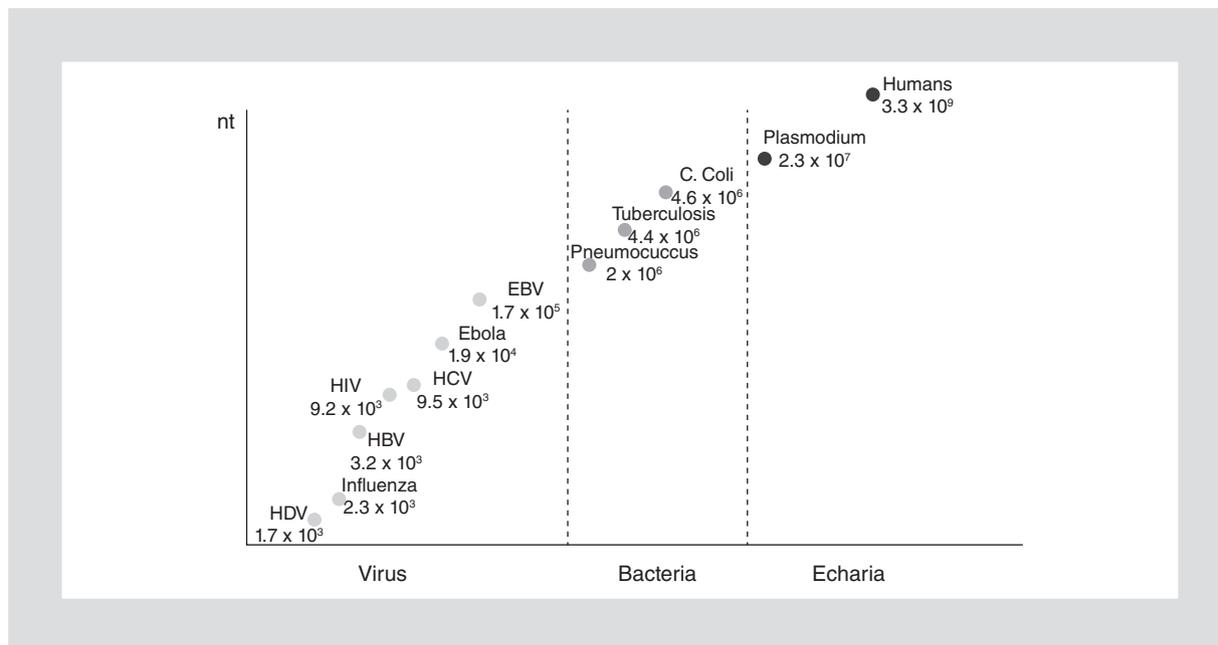
### RNA Viruses at the Forefront of Human Infections – HIV, Hepatitis C, and Now Ebola

AIDS emerged in 1981, breaking a period of proud medical progresses in controlling infectious diseases with antimicrobials and vaccines. In an unprecedented way, HIV has attracted much attention for three decades, driving the discovery of new extraordinary molecular diagnostic tools and antiviral drugs. As a result, advances in antiretroviral therapy have made it possible to change HIV infection into a chronic illness. However, the prospects for HIV eradication in the short term are not envisioned for the more than 35 million people worldwide estimated to be living with HIV.

In 1989 another RNA virus, HCV, was identified as the major agent for non-A, non-B chronic hepatitis. Hepatitis C is the most frequent cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. Around 150 million people are chronic HCV carriers.

**Table 1. Recent pandemic viral outbreaks**

- WNV (1999)
- SARS (2003)
- Avian Influenza H5N1 (2005)
- Swine Influenza H1N1 (2009)
- MERS (2012)
- Chikungunya (2013)
- Ebola (2014)



**Figure 1.** Genome size of living organisms.

Fortunately, during the last couple of years, a group of potent, direct-acting, oral antivirals have been developed. No doubt their wider use will transform the HCV landscape, since 8-12 weeks of combination therapy cures more than 90% of patients. Besides, regression of liver damage follows HCV eradication in most treated and cured individuals.

While enthusiasm continued unabated, epidemic outbreaks produced by other RNA viruses including influenza or corona viruses have occurred during the last decade, as shown in the Table. Interestingly, many of these infectious crises are zoonosis and follow the jumping of viruses from distinct animal reservoirs to humans, propitiated by climate changes and ecosystem disturbances. Like David and Goliath, it is intriguing that the smallest living organisms are becoming the major enemies for our sophisticated human organism (Fig. 1).

There is no doubt that the ongoing 2014 Ebola outbreak in West Africa has become one of the most worrisome of all human infection illnesses caused by RNA viruses. Since the first cases were reported in December 2013 and up to October 2014, more than 10,000 cases and 4,000 deaths have occurred. The African countries affected are amongst the poorest in the world, where Ebola is producing a devastating social and economic collapse beyond the medical crisis. Alarms and fears have been further triggered following the recent diagnosis of Ebola in Europe and North America among travelers to West Africa and healthcare workers caring for repatriated patients.

The Ebola virus is an enveloped, non-segmented, negative, single-stranded RNA agent of 19,000 nt genomic length. The virus generally presents with a characteristic filamentous morphology. Fruit bats are the major animal reservoir. The virus is mainly transmitted through direct contact of skin or mucosa with contaminated body fluids or secretions. There is no efficient airborne transmission such as in flu or tuberculosis. The incubation period from exposure to development of symptoms varies from two to 21 days. Symptoms progress from fever, chills, rash, vomiting, and diarrhea to hemorrhage and eventually hemodynamic shock. On average the mortality rate is around 40%. Interestingly, patients who recover develop protective immunity. Based on this observation, several promising vaccines are being tested for primary prophylaxis.

Like HCV and in contrast to HIV, the Ebola virus does not integrate into infected cells. Once elicited, host immunity precludes the establishment of chronic filoviral infection. Several RNA polymerase inhibitors (e.g. favipiravir) are being investigated as antivirals for preventing and/or treating Ebola virus disease. Altogether, the battle against Ebola in the near future seems promising with the advent of effective antivirals and vaccines. Unfortunately, the human tragedy suffered in West Africa has been the high cost paid to awaken everyone.

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