Novel Drug Candidates

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Technology description

Summary

Pneumonia caused by Pneumocystis carinii (PcP) remains a major opportunistic infection associated with AIDS patients, even in the era of Highly Active Anti-Retroviral Therapy (HAART). In the previous 2 decades, patients with AIDS have been a primary target of PcP, the population in which it remains a leading opportunistic infection. Limited therapeutic choices and adverse reactions to the two standard treatments, trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine (Mei, Gurunathan et al., 1998), cause the clinical management of this infection to remain problematic. Moreover, side effects in almost half of AIDs patients required switching to a less effective therapy.

Despite the efforts of several in vitro and in vivo screening projects, no better treatment than TMP-SMX for PcP has been identified. Strategies to exploit the effective combination of dihydrofolate reductase inhibitor and DHPS inhibitor of the TMP-SMX combination, by substitution of each component (e.g. TMP-dapsone) have not resulted in any therapies with increased efficacy. More recently, mutations in Pneumocystis genes which are the targets of TMP-SMX, atovaquone and dapsone were similar to those conferring resistance in other organisms such as Plasmodium falciparum. Previous therapy with these agents had a strong correlation to presence of the mutation, suggesting a selective mechanism was operational. Moreover, a Pc genotype with double mutations in the DHPS gene replaced the wild type genotype (no mutations) as the predominant type in certain regions of the country (e.g. San Francisco) implying that again, a dominant selection was occurring and these organisms were being transmitted throughout the human population in these regions.

The limited repertoire, problems in tolerance, and potential emerging resistance make it necessary to identify new efficacious treatments for PcP. Drug screening and development for anti-PcP agents has taken advantage of available rodent models of PcP and short term in vitro systems. Recombinant proteins have been used in some biochemical assays when the Pc gene was cloned as in the case of dihydrofolate reductase, but this application has been rarely used due to the paucity of Pc gene sequences previously available. Researchers at UC and Xavier University of Louisiana have developed a series of novel compounds which may be useful for the treatment of viral infections, such as pneumonia and for instance, pneumonia caused by Pneumocystis carinii. In vitro evaluation of these compounds using a P. carinii ATP detection assay indicated that the bisbenzamidines of the present invention functioned as anti-P. carinii agents.

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