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HYPerforin analogues, zinc and TRPC6 channels – a new antidepressant concept? (HYPZITRP)

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Depression is a widespread illness characterized by low mood, pleasure, motivation and reward. The treatment of major depressive disorders is confounded by high rates of treatment resistance and low rates of lasting remission. These clinical realities, paired with the high economic burden of treating depression necessitate a better understanding of the pathophysiology of depression and the development of alternative therapeutic approaches to treating this disease. Current treatment strategies are based primarily on the monoamine hypothesis of depression. Recent work, however, suggests that the neuropathology of depression is stratified across the reduction of synaptic plasticity. Evidence suggests that the canonical transient receptor potential channel 6 (TRPC6) regulates synaptic plasticity, most likely via the influx of calcium and zinc ions. TRPC6 channels are the molecular target of hyperforin, the active antidepressant constituent of St. John's wort extracts, which have been used since Paracelsus to treat mild to moderate depression. Hyperforin is chemically unstable and is only modestly potent in TRPC6 channels. These qualities limit its use as a lead compound for a new class of antidepressants. The HYPZITRP project will focus on the synthesis and detailed pharmacological and behavioural characterization of new derivatives of hyperforin. It will also examine the interplay of zinc and TRPC6 channels in the pathophysiology of depression.