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**A New Family Of Phosphodiesterase Inhibitors Discovered By Co-Crystallography And Scaffold-Based Drug Design.** Kam Y.J. Zhang, Graeme L. Card, Landy Blasdel, Bruce P. England, Chao Zhang, Yoshihisa Suzuki, Sam Gillette, Daniel Fong, Prabha N. Ibrahim, Dean R. Artis, Gideon Bollag, Michael V. Milburn, Sung-Hou Kim<sup>¶</sup>, Joseph Schlessinger<sup>§</sup>, Plexxikon Inc., Berkeley, CA94710; <sup>¶</sup>Dept. of Chemistry, UC, Berkeley, CA 94720; <sup>§</sup>Dept. of Pharmacology, Yale U., New Haven, CT 06520

Cyclic nucleotide phosphodiesterases (PDEs) regulate a variety of cellular processes and are targets of many drugs. We describe a new class of PDE4 inhibitors discovered using scaffold-based drug design. This method starts with low affinity screening of a low molecular weight compound library followed by high throughput co-crystallography of the screening hits to select compounds that exhibit a dominant binding mode and have appropriate sites for substitution. These scaffold compounds serve as the starting point for lead development. We report the discovery of a novel inhibitor scaffold (3,5-dimethyl-1H-pyrazole-4-carboxylic acid ethyl ester) for PDE4 using co-crystallography, and validation of the scaffold and synthesis of a chemical series that contains pyrazole derivative with 20-60nM potency. The 4000-fold potency improvement achieved within two rounds of chemical synthesis demonstrated the robustness of this scaffold-based approach in the identification of new inhibitors for drug development.