Structure Based Drug Design of Clinical Compound MK-8353, a Novel inhibitor of ERK

Alan Hruza [a], Sobhana Babu Boga[a], Abdul-Basit Alhassan[a], Alan B. Cooper [a], Ronald Doll [a], Neng-Yang Shih [a], Gerald Shipps [b],Yongqi Deng [b], Hugh Zhu [a], Yang Nan [b], Robert Sun [a], Liang Zhu [b], Jagdish Desai [a], Mehul Patel [b], Kiran Muppalla [b], Xiaolei Gao [a], James Wang [a], Joseph Kelly [a], Subrahmanyam Gudipati [a], Sunil Paliwal [a], Hon-Chung Tsui [a], Tong Wang[b], Bradley Sherborne [a] Li Xiao [a], Alexei Buevich [a], David Hesk [a], Ahmed A. Samatar [a], Donna Carr [a], Brian Long [a], Stuart Black [a], Priya Dayananth [a], William Windsor [a], Paul Kirschmeier [a], Robert Bishop [a]

[a] *Discovery Chemistry, Merck & Co., Inc.,2015 Galloping Hill Rd, Kenilworth, NJ 07033, United States*
[b]*Discovery Chemistry, Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115, United States*

The Ras/MAPK (RAF/MEK/ERK) pathway plays a central role in regulating mammalian cell growth, differentiation, and survival by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors, making it an excellent target for treatment for cancers with activation of this pathway. This poster presents the identification of the initial hit from ALIS (Automated Ligand Identification System) and the optimization of the hit towards MK-8353. The modifications were required to improve activity, pharmacokinetics, and off target activity (HERG and CYP), while maintaining the novel movements of the glycine rich loop which opens up a new cavity for interaction with the inhibitor and ERK, allowing for better selectivity against other Kinases. MK-8353 was found to have an overall response rate of 20% (evaluable patients) during its Phase 1a/2b MK-8353-001 clinical trial.