Novel High Affinity Inhibitors Of The K-Ras Trafficking Chaperone PDE6D

Pelin Kaya, Elisabeth Schaffner-Reckinger, Ganesh babu Manoharan, Bastien Salay and Daniel Abankwa

Cancer Cell Biology and Drug Discovery Group, Department of Life Sciences and Medicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg

K-Ras is a major cancer drug target that is established for several decades. Since direct targeting of K-Ras is extremely difficult, the GDI-like protein PDE6D has been nominated as a surrogate drug target. PDE6D is a trafficking chaperone of several prenylated proteins, including K-Ras. Several high-affinity PDE6D inhibitors have been developed previously, which all target its prenyl-binding hydrophobic pocket. However, these compounds have several drawbacks including off-target effects, metabolic instability and water insolubility. Here, we present data of the next generation of our PDE6D inhibitors, called Deltaflexins.

As compared to previous generations, our top novel Deltaflexins have sub- or low-nanomolar affinity for PDE6D, which correlates with their higher target engagement in cells as demonstrated using BRET biosensors. However, increasing the affinity also increased the off-target activity of PDE6D inhibitors against the PDE6D-related chaperone protein UNC119A and reduced their solubility. Additionally, compounds with a higher affinity showed a lower K-Ras- vs. H-Ras-selectivity in cellular BRET assays. This was also reflected in 2D proliferation data, where compounds with affinities below 2 nM showed overall higher potency, but less selectivity for PDE6D-dependent and KRAS-mutant cancer cell lines. Of note, as compared to previously established PDE6D inhibitors, Deltaflexins showed improved reduction of pERK- and pS6-levels. Moreover, they significantly inhibited micro-tumor growth in the chicken egg CAM-model.

These data suggest that improving PDE6D inhibitors for affinity, may be detrimental for their pharmacological- and solubility-properties. Instead, we propose to combine PDE6D inhibitors with potencies around 5 nM with other compounds that reduce the affinity of K-Ras to PDE6D in order to achieve a focused inhibition of K-Ras in cancerous cells.