28AB-ISMS29 **Novel CDK8 Inhibitors with Long Residence Time: New Opportunities for Cancer Treatment**

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Frequent up-regulation of CDK8 has recently been described for colon-, gastric- and breast cancer as well as melanoma, rendering CDK8 as an attractive target for the development of selective and efficacious inhibitors. This notion is strongly supported by the observation that inhibition of CDK8 by RNA-interference results in profound inhibition of in vivo tumor growth.

Based on the recent findings that in contrast to all other CDK family members, CDK8 is amenable to a type II inhibition mode, we set out to design selective CDK8 inhibitors pursuing a privileged structure-based target family-centric library approach. The employed privileged structures are tailor-made for disrupting the hydrophobic R spine within the N-terminal lobe of a kinase, thereby leading to an induced-fit mechanism of derived inhibitors that will exhibit a pre-engineered binding kinetic signature. This “Retro-Design” approach allows keeping the molecular complexity of emerging inhibitors at a minimum level since the seed scaffold is targeted towards the deep pocket of the conformationally rearranged binding site of the enzyme.

Here we report on the discovery and optimization of a new class of CDK8 inhibitors based on an IP-free scaffold. Screening of 80 pre-designed scaffold fragments eventually resulted in fully elaborated inhibitor MC085. MC085 shows superior selectivity over a huge panel of kinases when compared to market approved drugs such as Sorafenib or Lapatinib. This selectivity is attributed to the distinct inhibition mechanism which is corroborated by detailed binding kinetic studies which reveal residence times for MC085 in the range of several hours.