In silico Identification of Potential TRPM7 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma

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Pancreatic cancer is projected to become the second leading cause of cancer-related mortality by 2030.[1] Approximately 90% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDAC), which affect the exocrine part of the pancreas. The mortality rate associated with PDAC is very high because it is often diagnosed at an advanced stage. The only treatment that can improve the 5-year survival rate of patients to 20% is surgery, but this option is available for less than 15% of patients.[2] Therefore, PDAC is a significant public health issue, making it crucial to better understand its development.

Our collaborators' research has highlighted the overexpression of the cation channel TRPM7 (Transient Receptor Potential Cation Channel Subfamily M Member 7) in PDAC, which is associated with poor survival.[3] TRPM7 is a non-selective cation channel essential for the intestinal absorption of divalent cations[4] and for maintaining cellular magnesium (Mg^{2+}) homeostasis.[5] The TRPM7 protein contains a functional kinase domain at the C-terminal, which belongs to the class of α-kinases.[6] Our collaborators have observed that TRPM7 regulates the migration and invasion of pancreatic cancer cells.[7]

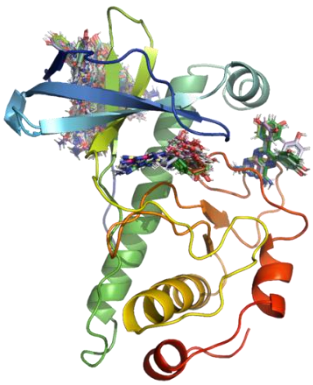

Figure 1. Blind docking of the reference compound TG100-115.

Currently, there are no specific blockers for the kinase function of TRPM7. Therefore, we have implemented a 'docking' screening of the CERMN chemical library. From this screening, we selected about ten compounds that were evaluated in vitro. The tests revealed two candidate molecules capable of inhibiting the kinase domain of TRPM7.

Keywords: Screening, Docking, TPRM7 channel, Pancreatic cancer.

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