Congratulations to IMCB's latest PhD graduate – Mert Burak OZTURK

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Thesis Title: Identification of Novel Transcriptional Modulators on Oncogenesis

Oncogenesis is the process by which cells undergo a series of genetic and cellular changes and enable unlimited proliferation. Healthy cells have developed various mechanisms to prevent oncogenesis. One of them is controlling the regulation of telomere lengths. Telomeres shorten after each cell division and if they reach a critically short length, cells enter senescence followed by crisis, and eventually, they undergo death. However, some cells can bypass phases like senescence and crisis by elongating telomeres through telomerase reactivation and become malignant. Telomerase is a holoenzyme consisting of multiple subunits. Human telomerase reverse transcriptase (hTERT) is the catalytic subunit of telomerase and carries reverse transcription activity to elongate telomeres. There is also an established noncanonical function of hTERT, it can contribute to cancer development by regulating cell proliferation-related genes. Hence, hTERT has been an attractive therapeutic target. However, not only cancer cells but also stem cells also require hTERT expression and telomerase activity for their self-renewal.

Thus, targeting hTERT expression and telomerase activity could also cause some adverse effects on stem cells. In order to overcome this problem, finding a strategy to target hTERT expression and telomerase activity in a cancerspecific way would be more promising.

In my studies, I performed a high-throughput small molecule screen (HTS) using hTERT promoter-specific reporter cells in order to develop a cancer-specific inhibitor. I generated hTERT-specific reporter cells by using the most advanced genome editing tool, clustered regularly interspaced short palindromic repeats (CRISPR). Small molecule screening for epigenetic modulators identified that SP2509, a lysine-specific histone demethylase 1 (LSD1) inhibitor, significantly decreased hTERT expression as well as telomerase activity, unlike other LSD1 inhibitors. Intriguingly, the effect of SP2509 on hTERT expression and telomerase activity was specific to colorectal cancer. The compound did not affect hTERT expression and telomerase activity in other cancer types such as glioblastoma, melanoma and cervical cancers. Moreover, SP2509 did not affect hTERT expression and telomerase activity in human stem cells. Although SP2509 is very well known as an LSD1 inhibitor, the inhibitory mechanism regulating hTERT expression by SP2509 was not LSD1 mediated. Drug target engagement showed that pirin, a transcription co-regulator, was a target of SP2509. Silencing of pirin using RNA interference mechanisms or inhibition of pirin using known small molecules decreased hTERT expression and telomerase activity. In conclusion, this study identified that hTERT expression could be regulated by a pirin-mediated complex and disruption of this complex by SP2509 could be a promising therapeutical strategy specifically in colorectal cancer.

Main Supervisor: Vinay Tergaonkar
Co-Supervisor: Ramanuj Dasgupta

Figure

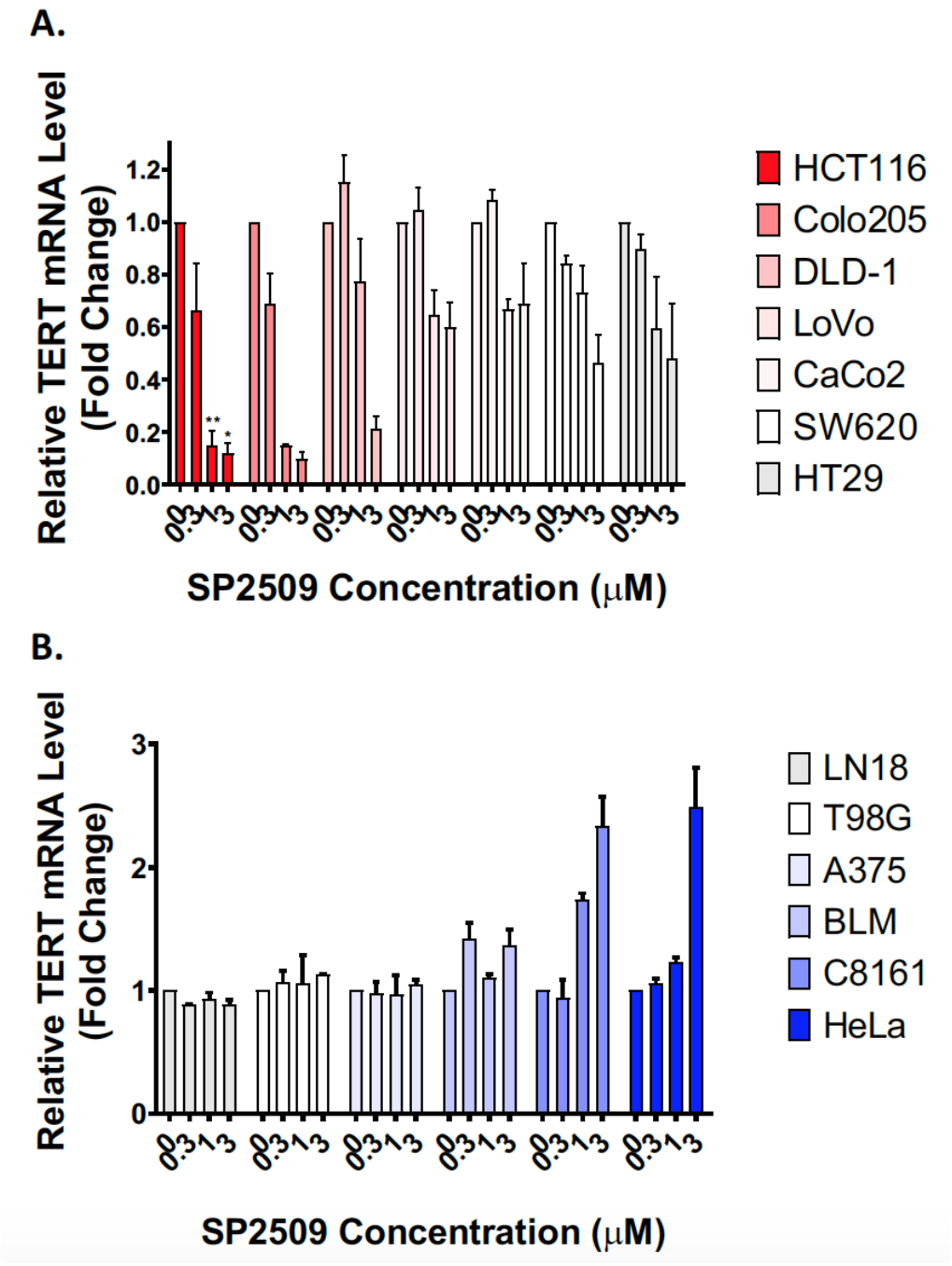

Figure Legend: SP2509 reduced hTERT expression in colorectal cancer (CRC)-specific manner. A) hTERT mRNA level reduced in CRC cell lines upon 2-day SP2509 treatment. B) SP2509 did not decrease hTERT mRNA level in different cancer types such as glioblastoma (LN18, T98G), melanoma (A375, BLM, C8161), cervical (HeLa). Data were normalized to β-Actin. Error bars indicate the mean ± SD of the two independent experiments.