Targeting TONSL for cancer therapy

Structure-based design of novel small molecule inhibitors

Biotech and Health Care

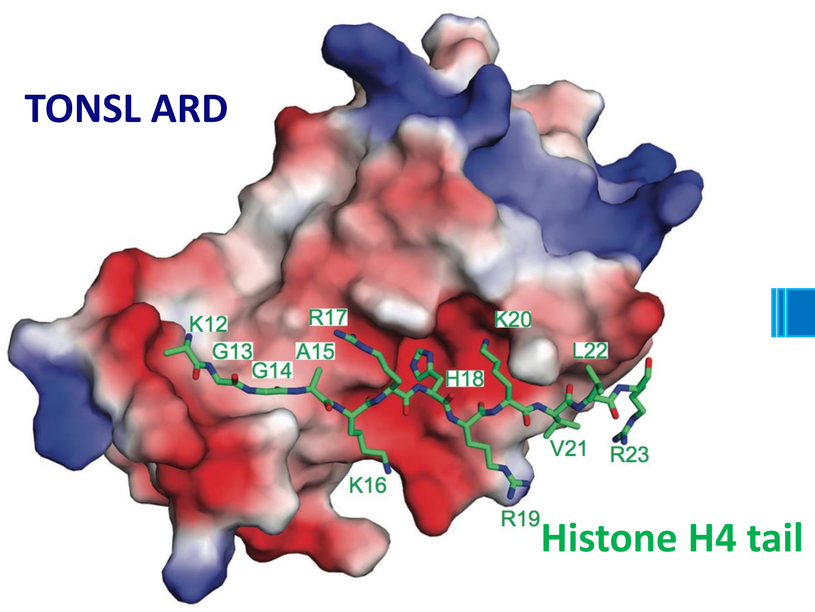
BACKGROUND & THERAPEUTIC CONCEPTS

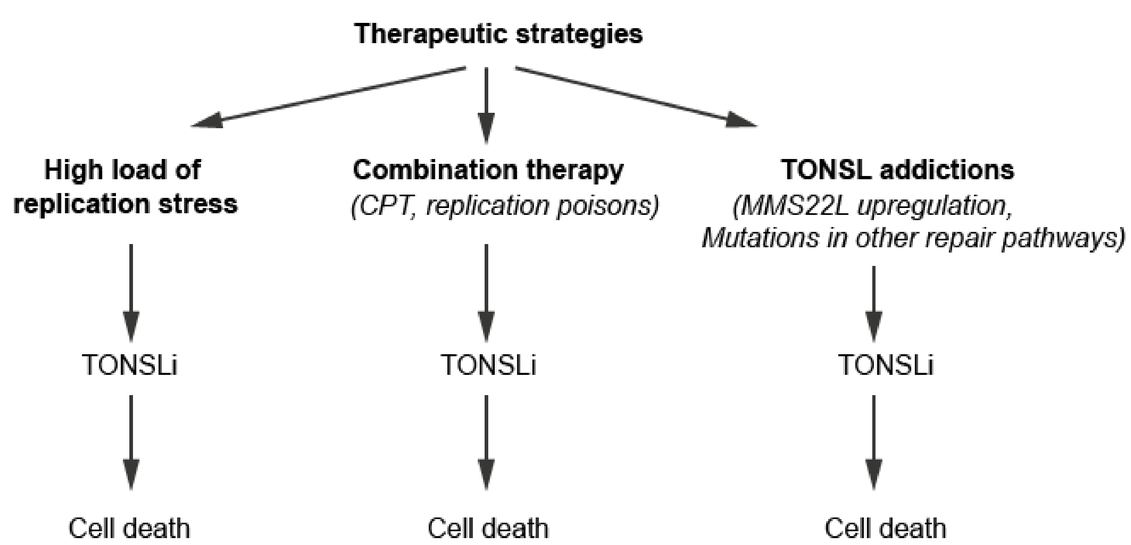
The TONSL protein is required for maintenance of genome stability in dividing cells. TONSL is involved in repair of replication associated DNA damage and DNA double-strand breaks (DSBs) through a mechanism called homologous recombination (HR). We have recently identified the mechanism that recruits TONSL to DNA repair sites and enables its function. If TONSL function is inhibited or destroyed, dividing cells accumulate DNA damage and will die.

Cancer cells experience high loads of replication stress, creating addiction to HR in order to sustain proliferation. Also, many chemotherapeutics act by disrupting DNA replication, making HR an important mechanism for the cancer cells to escape treatment. Inhibition of TONSL and thereby HR is therefore a promising novel target for cancer therapy.

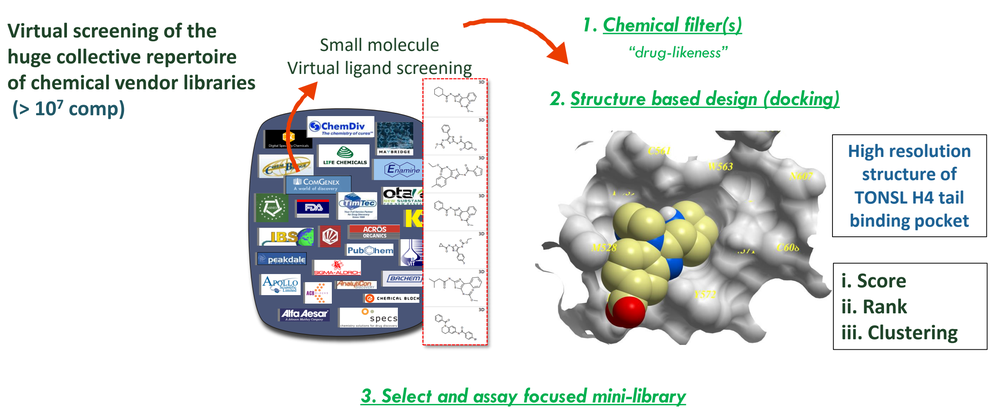
TONSL exists in a complex with another protein called MMS22L, which facilitates loading of the key HR factor Rad51. So far there was no opportunity to target the TONSL-MMS22L function. However, we have now discovered that TONSL is recruited to chromatin and DNA repair sites via binding to the tail of histone H4. In collaboration with professor Dinshaw Patel and his co-worker Dr. Hongda Huang from Memorial Sloan-Kettering Cancer Center we have solved the structure of TONSL in complex with the H4 substrate and demonstrated that this interaction is required for TONSL function in genome maintenance.

We are currently using the obtained high-resolution X-ray structure to develop small molecules to inhibit TONSL recruitment to DNA lesions and its function in HR. This constitutes a novel and potentially broadly applicable approach in cancer therapy that complements other efforts to interfere with DNA repair mechanisms.





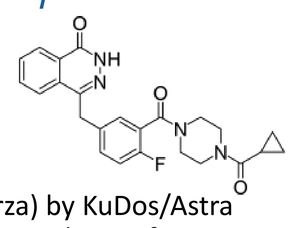
DEVELOPMENT OF TONSL INHIBITORS



CLINICAL/COMMERCIAL POTENTIAL

Benchmark:

PARP inhibitor



Olaparib (lynparza) by KuDos/Astra Zeneca FDA approved 2014 for treatment of ovarian cancer (BRCA-mutated = Exploit synthetic lethality)

Sales forecast: $ 2 billion

> 300 Clinical trials in DNA repair

Target/drug	Phase	Approach
Chk 1 (kinase)	II,III (many indications)	Mono & combination
Niraparib (PARP1 and PARP2 inhibitor)	Approved (2017) for ovarian cancer	Mono/combo (PD1 inhibitors – breast cancer)
ATR (kinase)	I/II (solid, lung)	Mono/ topetecan

Value proposition/USP

Small molecule inhibitors of the TONSL protein represent a novel concept for treatment of cancer. TONSL is involved in repair of replication associated DNA damage through homologous recombination. Cancer cells experience high loads of replication stress and are highly dependent on homologous recombination repair for survival. Inhibiting TONSL's function will lead to accumulation of DNA damage in and death of cancer cells.

Business Opportunity/Objectives

The need for novel anti-cancer treatments remains high and the market opportunities significant. A benchmark compound Olaparib, inhibiting the DNA repair enzyme PARP, was approved 2014 for treatment of ovarian cancer and is forecasted to sell for $ 2 billion. We are aiming at establishing a spinout company/entering collaboration with established pharma companies.

Technology description

TONSL is recruited to chromatin and DNA repair sites via **binding to the tail of histone H4**. The structure of TONSL in complex with the H4 substrate has been solved as a high-resolution X-ray structure and is used to design novel small molecule inhibitors by in-silico screening.

Development phase

Under a pre-seed grant from the Novo Nordisk Foundation we are working with external partners in USA, Canada and France on designing and syntesizing novel small molecule inhibitors. In parallel, we are aiming at validating TONSL as a clinically relevant cancer target through a number of in-vitro and in-vivo screens of cells and animal models. The focus is to determine what type of cancers could benefit most from treatment with TONSL inhibitors.

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