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# THE PROTEASOME AS A TARGET FOR CANCER THERAPY

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, den 13 juni 2023, kl. 9.00

av Peter Larsson

Fakultetsopponent:

Professor Sven Nelander,

Uppsala universitet, Sverige

**Avhandlingen baseras på följande delarbeten**

I. **Larsson P**, Pettersson D, Engqvist H, Werner Rönnerman E, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, and Parris TZ, Pan-cancer analysis of genomic and transcriptomic data reveals the prognostic relevance of human proteasome genes in different cancer types. *BMC Cancer* 22, 993 (2022)

II. **Larsson P**, Olsson M, Fäldt Beding A, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, and Parris TZ, Multi-omics analysis identifies repurposing bortezomib in the treatment of kidney-, nervous system-, and hematological cancers. Submitted (2022)

III. **Larsson P**, Engqvist H, Biermann J, Werner Rönnerman E, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, and Parris TZ, Optimization of cell viability assays to improve replicability and reproducibility of cancer drug sensitivity screens. *Sci Rep* 10, 5798 (2020)

IV. **Larsson P**, De Rosa MC, Righino B, Olsson M, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, and Parris TZ, Integrated transcriptomics- and structure-based drug repositioning identifies putative proteasome inhibitor-like compounds. Submitted (2022)

V. **Larsson P**, Pettersson D, Olsson M, Ittner E, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, and Parris TZ, Repurposing proteasome inhibitors for improved treatment of triple-negative breast cancer. Submitted (2023)

**SAHLGRENSKA AKADEMIN**
**INSTITUTIONEN FÖR KLINISKA VETENSKAPER**

GÖTEBORGS UNIVERSITET

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# THE PROTEASOME AS A TARGET FOR CANCER THERAPY

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## Abstract

The main objective of this PhD thesis was to evaluate the significance of proteasome genes as prognostic markers for different cancer types and identify specific cancer forms that respond to proteasome inhibition. The proteasome (PSM) plays an important role in maintaining cellular proteostasis and degrades the majority of proteins that require breakdown in the cell. Elevated PSM activity has been detected in most cancer types, making it an interesting target for cancer treatment. PSM inhibitors interfere with protein degradation, leading to a decrease in free amino acids, increased accumulation of proteins, and apoptosis. This doctoral thesis is based on five studies focusing on the proteasome and cancer.

In Study I, pan-cancer data from The Cancer Genome Atlas (TCGA) was used to study the relationship between PSM gene expression patterns and genetic changes, as well as expression and patient survival. Several PSM genes (e.g., PSMB4-5, PSMD2) were identified and shown to affect patient survival. In Study II, comprehensive bortezomib sensitivity, genomic and transcriptomic data from >800 cell lines were used to investigate the effect of PSM inhibition on e.g. cancer cell survival. We identified 33 genes involved in bortezomib resistance and cancer types that were sensitive to bortezomib. In Study III, we developed a strategy to identify and minimize the influence of environmental and experimental factors to improve the replicability and reproducibility of cell viability analysis. Several confounding factors (e.g., number of solvent controls, drug storage, plate construction) were shown to have an impact on the replicability and reproducibility of the resazurin-based cell viability assay. In Study IV, extensive data from e.g. CMap were used to study the transcriptomic signature of compounds to identify putative proteasome inhibitors similar to known proteasome inhibitors (bortezomib, MG-132, and MLN-2238). Six possible proteasome inhibitors were identified with a high affinity for the chymotrypsin-like catalytic domain (β5) of the proteasome. In Study V, a high-throughput drug screen was performed to identify chemotherapeutic agents (conventional breast cancer chemotherapy and proteasome inhibitors) used as single agents or in combination that can potentially improve the treatment of triple-negative breast cancer (TNBC). We identified potent drugs e.g., bortezomib and cisplatin (as single) or e.g., bortezomib+nedaplatin (in combination) that had an adverse impact on the survival of TNBC cells.

In summary, several cancer types demonstrated an association between PSM gene expression and clinical outcome, as well as sensitivity to proteasome inhibitors. Therefore, the proteasome is an attractive target for cancer treatment.

**Keywords:** Cancer, cell viability assay, chemotherapy, drug repurposing, genomic and transcriptomic signatures, prognostic biomarkers, proteasome, proteasome genes, proteasome inhibitors, drug sensitivity biomarkers, synergistic effect, triple-negative breast cancer

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