Identification and clinical validation of biomarkers for drug resistance.

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Medical problem:

Drug resistance being pre-existing or acquired is considered the most important obstacle to successful medical cancer treatment.

This means that approximately half of all cancer drugs being given to patients have no beneficial effects but the patients will suffer from drug-induced side effects.
The solution:

Introduce biomarkers that can be used to introduced a personalized treatment approach, where only patients with a high likelihood of treatment benefit will receive the treatment
How can we at the University contribute to the introduction of predictive biomarkers?
DEN50-R drug screening and biomarker identification research platform

In analogy with the NCI60 cell line repository, we have established the DE
N50-R being a cell line repository that in contrast to the NCI60 constitutes isogenic pairs of parental drug sensitive and derived drug resistant cell lines (Jensen et al., Mol Oncology 2015).

All cell lines are subjected to thorough “omics” analyses followed by bioinformatics and systems biology analyses in order to reveal genes and pathways being involved in drug resistance.

All data generated with the DEN50-R platform will be placed in the new National Danish Life Science Supercomputer with secure, regulated access, thus providing a unique and innovative integrative analysis resource for academic, clinical and industrial researchers involved in anti-cancer drug development and cancer diagnostics at both pre-clinical and clinical levels.
DEN50-R research and drug screening platform

Ten pairs of isogenic wild-type (sensitive) and drug resistant sublines from each of these five cancer forms
DEN50-R research and drug screening platform

Drug screenings

Algorithms

RNAi screens

Oomics

Mechanisms of action

Biomarker research

Clinical trials
Establishing drug resistant cancer cell lines

Parental cell lines (drug sensitive)

Step-wise increase in drug concentrations

One initial high drug concentration

Cycles of drug exposure

Drug RESISTANT pool
Biomarkers for drug resistance

Example on predictive biomarkers for irinotecan resistance

From SN38 (the active metabolite of irinotecan) resistant colorectal cancer cell lines we identified the xenobiotic drug efflux pump ABCG2 to be the most upregulated gene. Subsequent functional analyses demonstrated that inhibition of ABCG2 resulted in reversal to a SN38 sensitive phenotype. Moreover, the target for SN38, TOP1, was down-regulated in the resistant cells.

In collaboration with the PETACC-3 study group we analysed the association between ABCG2 and TOP1 gene expression in the PETACC-3 prospective randomized adjuvant trial (van Cutsem et al., JCO, 2009).
Biomarkers for drug resistance

The PETAAC-3 study

Patients with stage III colon cancer were randomized to receive adjuvant 5FU + leucovorin +/- irinotecan.

The addition of irinotecan did not significantly improve recurrence free survival or overall survival.
Kaplan-Meier plots according to random allocation group for (A) disease-free survival, (B) relapse-free survival, and (C) overall survival for patients with stage III disease treated with the leucovorin/fluorouracil (LV5FU2) regimen with or without irinotecan

Similar results were obtained in the CALGB 89803 study

Eric Van Cutsem et al. JCO 2009;27:3117-3125
Biomarkers for drug resistance

The PETACC-3 study

Using ABCG2 and TOP1 mRNA expression in the tumors to dichotomize the patients, a pronounced effect on recurrence free survival and overall survival was seen in FOLFIRI treated patients.

No differences were seen in 5FU + leucovorin only treated patients.

The next slide will show the Kaplan Meier survival curves (RFS) for patients with low ABCG2 and high TOP1 (sensitive patients) compared to patients with high ABCG2 and low TOP1 (resistant patients).
Biomarkers for drug resistance

RFS in stage 3 CRC, 5FU/LV treatment

HR = 1.05 (95% CI: 0.57 - 1.91)

RFS in stage 3 CRC, FOLFIRI treatment

HR = 0.56 (95% CI: 0.25 - 1.05)
In conclusion:

We have demonstrated Proof of Concept of our DEN50-R research platform in relation to identification and subsequent clinical validation of biomarkers for drug resistance.

We are currently using the DEN50-R platform to identify drugs that interfere with drug resistance.