Precision Medicine and Biomarkers

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Potential conflict of interest:

WntResearch AB
Oncology Venture A/S
2cureX A/S
Scandion Oncology A/S
Personalized/precision cancer medicine

The right treatment, at the right time, at the right dose and to the right patient

The goal is to provide better healthcare to cancer patients
TUMOUR MARKERS - A GENERAL VIEW

"A molecule, a substance, or a process, which is altered quantitatively or qualitatively in pre-malignant or malignant conditions, the alteration being measurable by an assay"


- Risk stratification
- Detection and/or diagnosis
- Prognostic information
- Monitoring
- Prediction of response to treatment
RISK STRATIFICATION

Pre-malignant diseases to select patients for personalized preventive cancer medicine ex “high risk” adenomas.

Malignant diseases to select patients for adjuvant treatment (prognostic stratification)
Prognostic biomarker: Indicates the likely course of the disease in an untreated individual. The blue and red patients are those who will relapse.

Predictive biomarker: Identifies subpopulations of patients who are most likely to respond to a given therapy.
Dukes’ A+B Colon Cancer only

HR = 2.1 (1.3-3.5)

p = 0.003
Post-op TIMP-1 (minimal residual disease?)

Holten-Andersen et al., 2006
Monitoring of disease

Circulating cell free tumor DNA
Circulating tumor DNA (ctDNA)

Key application areas

- Stratification
- Companion Dx

- Response and efficacy
- Biomarkers for sensitivity

Wan et al, Nature Reviews Cancer 2017
Prediction of response to treatment

Prediction of ex vivo sensitivity/resistance to therapy
IndiTreat®

IndiTreat™ - measures tumor growth and treatment efficacy

Day 0  Day 4  Day 7  Day 11

Control

No treatment

Drug addition

Treatment A

Tumor is sensitive

Cancer therapy optimized for each patient
Prediction of response to treatment

Prediction of adjuvant FOLFIRI treatment in CRC
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
Based on results from the DEN50-R research platform (isogenic pairs of drug sensitive and drug resistant cancer cell lines) we raised the hypothesis that high ABCG2 and low TOP-1 expression will define patients with irinotecan resistant cancers.
Biomarkers for drug resistance

The PETACC-3 study

Using ABCG2 and TOP1 mRNA expression in the tumors from PETACC-3 to dichotomize the patients, a significant 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).
These data transformed into a 15.3% (57 versus 65.7) relative gain in 5 year RFS between the two FOLFIRI treated groups and an 8.1% (60.8 versus 65.7) relative gain in 5 year RFS between FOLFIRI “sensitive” patients and the group of patients receiving 5FU/LV alone.
Next steps

1. Validate the data in an independent cohort
2. Transform the assay to a more easy method
3. Perform a prospective randomized trial:
   ABCG2 low and TOP-1 high

FOLFIRI  FOLFOX
Drug resistance is a major clinical problem in Oncology

What is drug resistance and how do we define it in the clinic?

Can targeting drug resistance be turned into Precision medicine?

Primary resistance
Acquired resistance
Cross resistance
Do we have any means to target drug resistance today?

New drugs? Biomarkers? Trial design?
Working hypotheses:

With established isogenic pairs of drug sensitive and drug resistant cancer cell lines it will be possible by “omics” analyses to identify molecular mechanisms involved in drug resistance and thereby disclose new potential targets for anti-cancer therapy.

These cell lines will also serve as screening platform for drugs that bypass or inhibit drug resistance mechanisms.

Genes or their products being involved in drug resistance might also serve as predictive biomarkers allowing a precision medicine approach.
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

Drug RESISTANT clones

Drug RESISTANT pool
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
- Omics
- Mechanisms of action
- Biomarker research

Clinical trials
Example of a novel drug that interferes with drug resistance

This drug was identified using the DEN50-R screening platform
**Anti-tumor effect**

- SCO-101 reduces tumor volume to 83% of vehicle.
- Paclitaxel reduces tumor volume to 66% of vehicle.
- **Combination of paclitaxel and SCO-101 reduces tumor volume to 37% of vehicle.**

This clearly demonstrates a combinatorial anti-tumor effect of paclitaxel and SCO-101 in vivo.
Significant results in colorectal cancer

Mechanisms of action studies have revealed that SCO-101 interferes with ABCG2 and with specific kinases.

- **Improvement Effect**: The viability of irinotecan/SN38 resistant colon cancer cells is reduced by 65% by combining SCO-101 and SN38 in comparison to SN38 alone.
Conclusions

1. It is possible to develop and validate biomarkers that can be used to introduce precision medicine in cancer patients

2. Using our DEN50-R screening platform we can identify novel drugs that interfere with common drug resistance mechanisms

Thank you for your attention