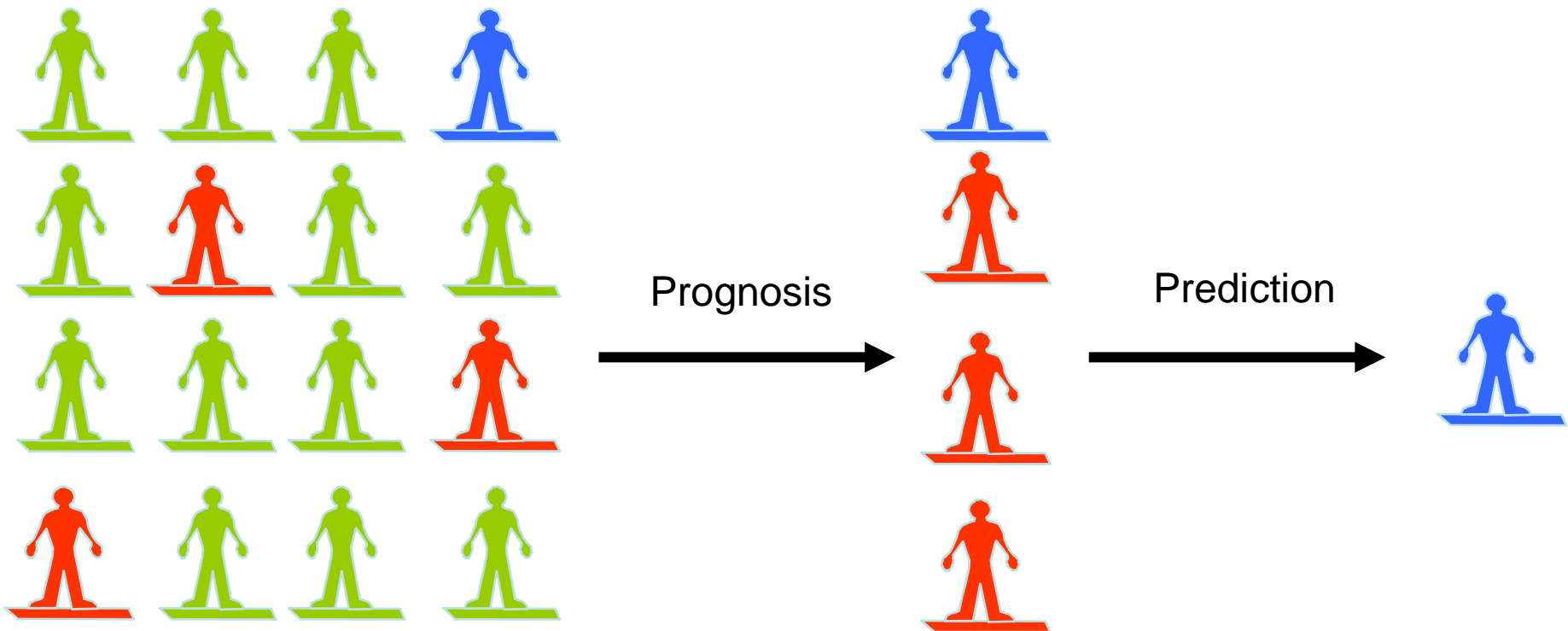




From Biomarker Discovery to the Bedside

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Prognostic biomarker: Indicates the likely course of the disease in an untreated individual.

Predictive biomarker: Identifies subpopulations of patients who are most likely to respond to a given therapy



Example 1

Tissue Inhibitor of Metalloproteinases-1 as a plasma based prognostic marker to be used to select stage II and III colorectal cancer patients for adjuvant chemotherapy.



Medical problem I

Colorectal cancer patients with stage II disease are not offered chemotherapy routinely although it is known that approximately 25% will relapse over 5 years



Solution

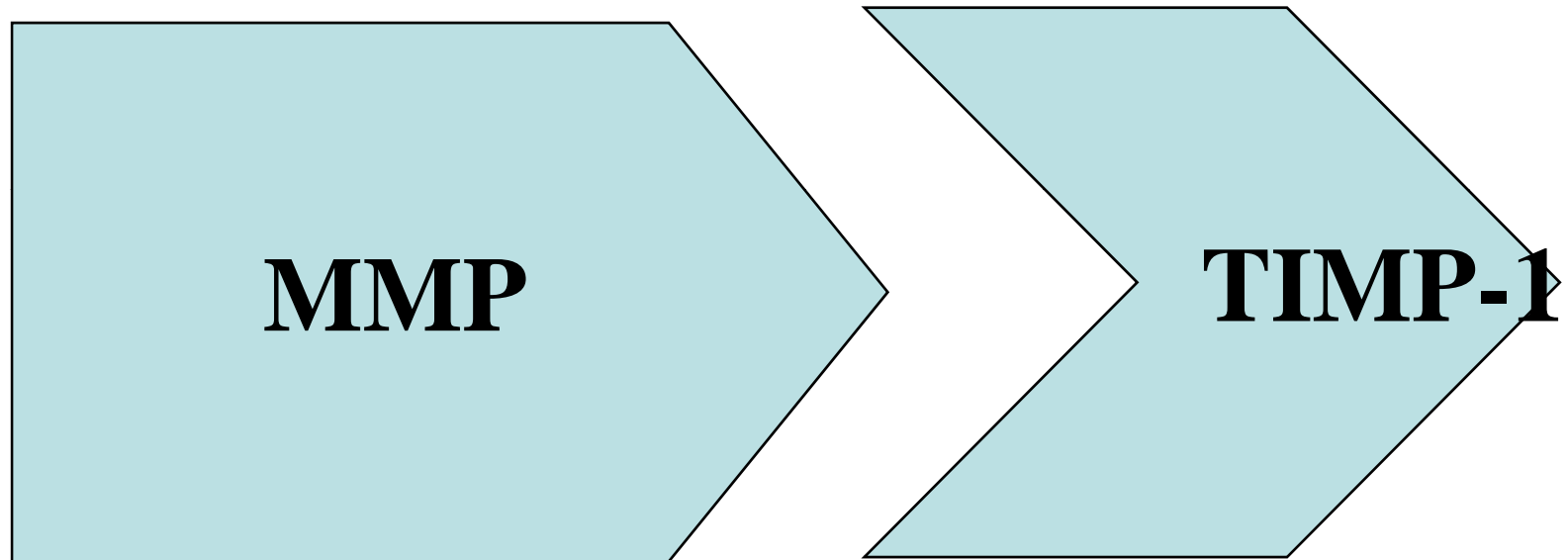
Search for biomarkers that can be used to identify stage II patients with a poor prognosis and stage III patients with a good prognosis.



Tissue Inhibitor of Metalloproteinases 1



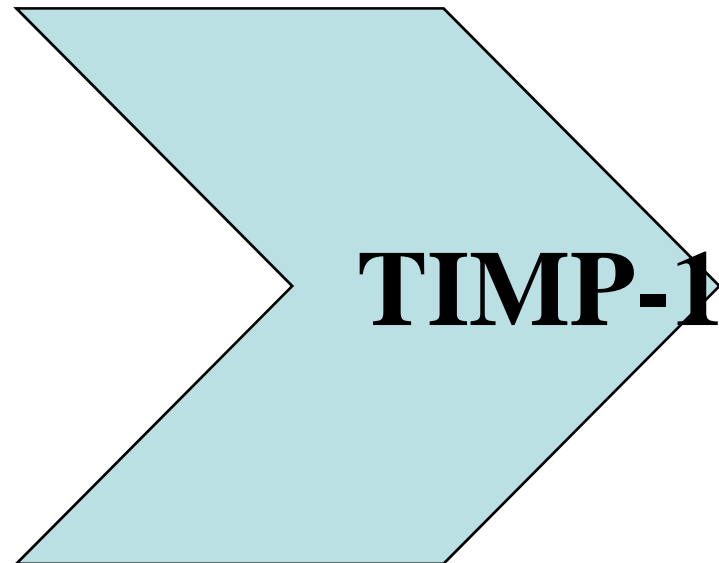
TISSUE INHIBITOR OF METALLOPROTEINASES-1



**TIMP-1 inhibits MMP-mediated tissue remodelling
and tissue destruction**



MMP independent functions of TIMP-1



TIMP-1 is involved in cancer progression



Potential molecular mechanisms of action of TIMP-1

- Inhibition of protein degradation or modification
- Modulation of angiogenesis
- Inhibition of apoptosis
- Promotion of cell proliferation



Hypothesis:

Since TIMP-1 stimulates cell proliferation and inhibits apoptosis:

High TIMP-1 levels in the tumor might result in a poor patient outcome

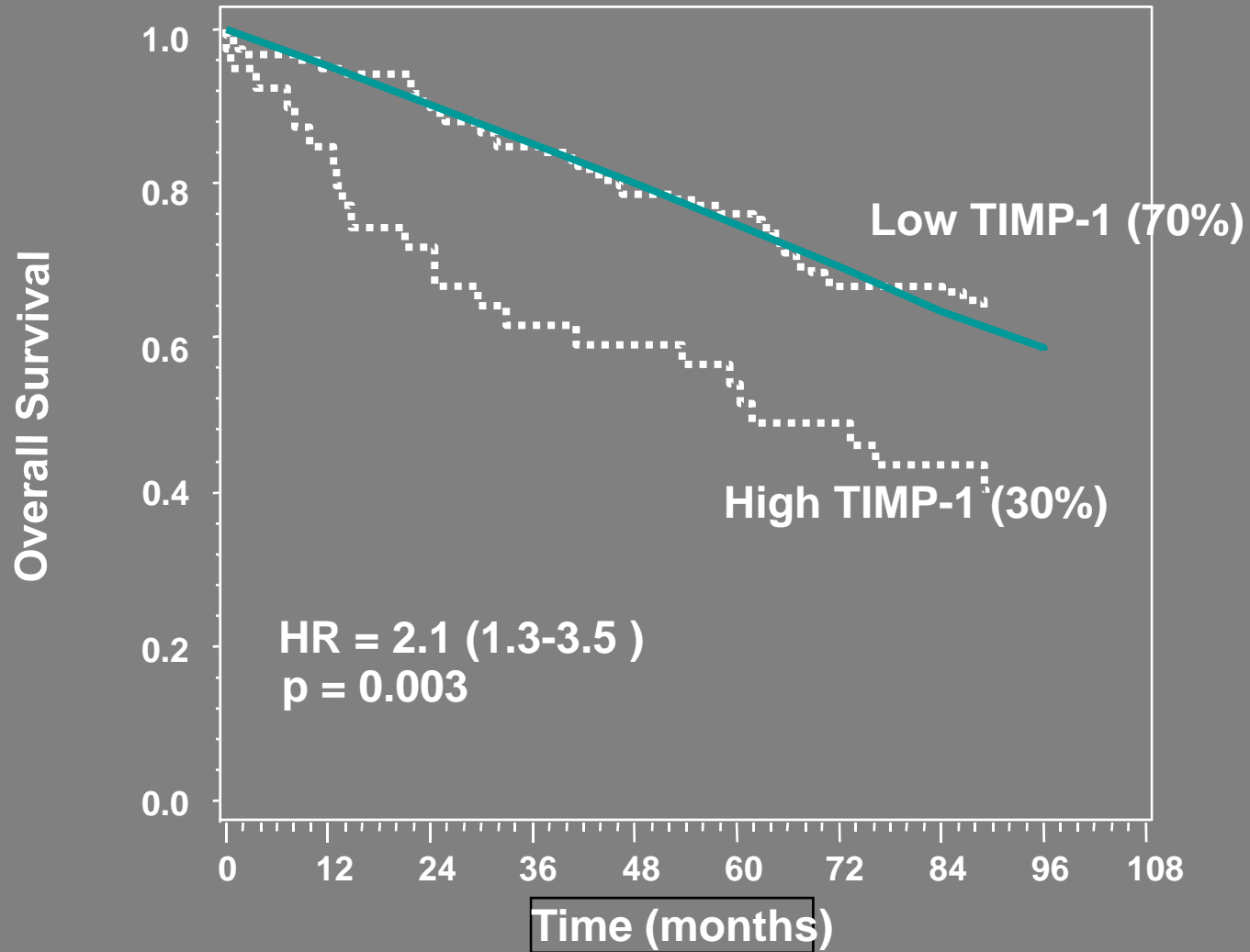


Prognostic value of TIMP-1 in CRC

- **588 colorectal cancer patients (RANX05 study group)**
- **Dukes' stages: 58 A, 218 B, 175 C, 137 D**
- **Observation time: median 6.8 years (5.7 – 7.9)**
- **236 females and 352 males**
- **Pre-operative EDTA plasma samples from all patients**
- **TIMP-1 plasma levels determined by ELISA**
- **Clinical parameters included**
- **Statistical survival analysis**

Dukes' A+B Colon Cancer only

Plasma TIMP-1



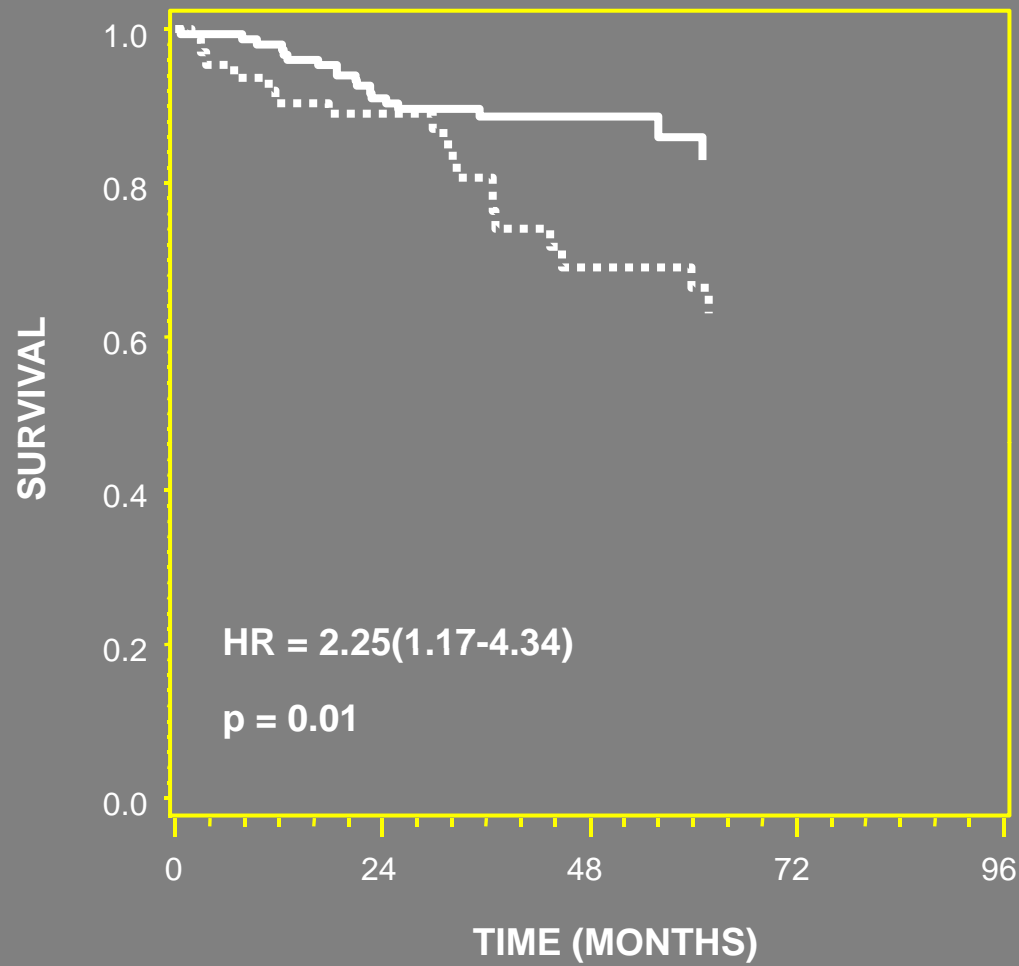
Holten-Andersen et al., 2000



1. Validation study "The Lund Cohort"

- **316 preoperative plasma samples from patients with rectal cancer**
- **Total TIMP-1 assay**
- **Univariate survival analysis**

Survival of Dukes' stage A+B rectal cancer patients



EVENTS

18

18

PATIENTS AT RISK

145

62

122

51

45

26

17

13

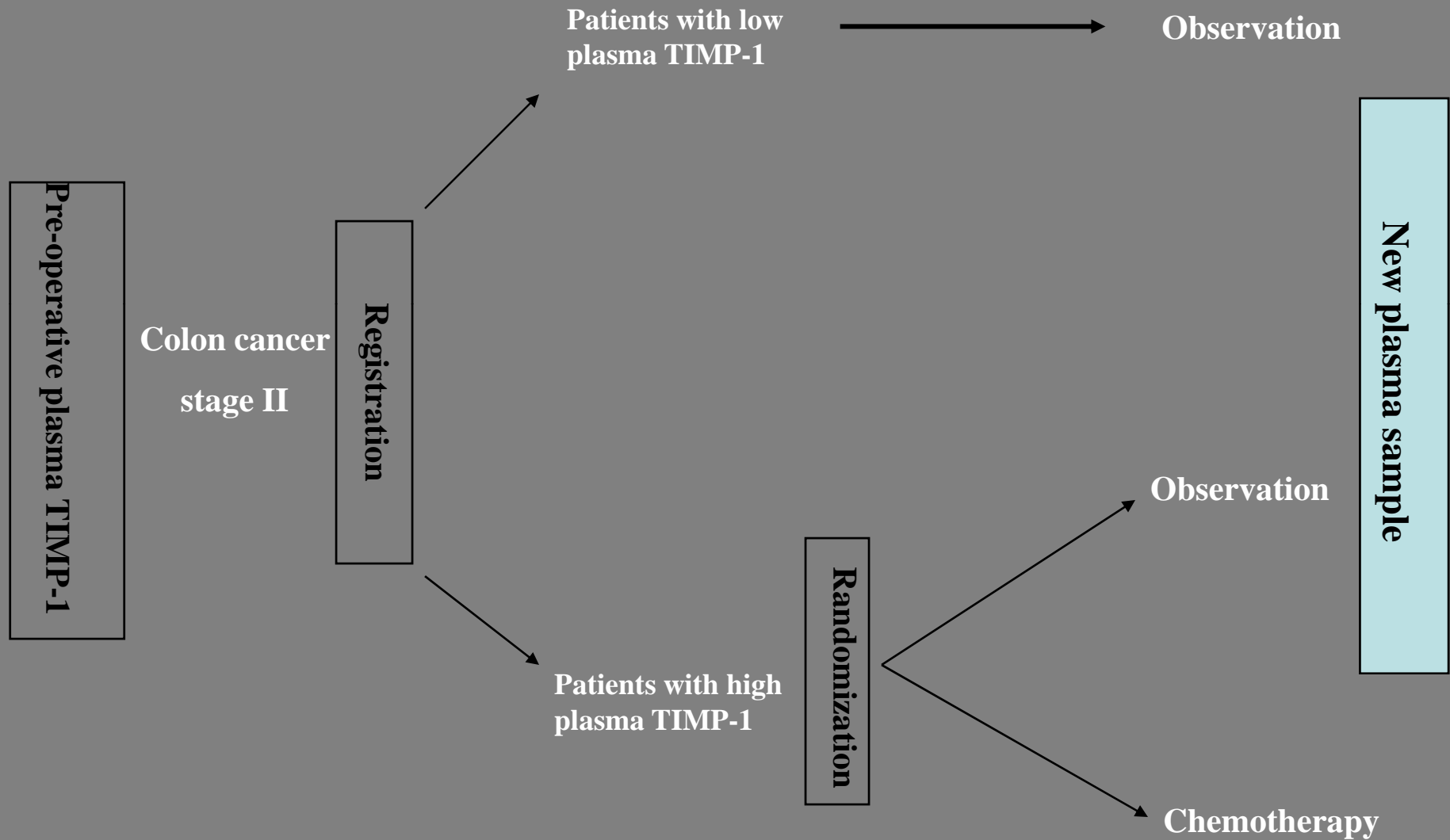
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Low TIMP-1

High TIMP-1

Example of a study design that could be used in the final analyses of the association between plasma TIMP-1 and stage II CC patient outcome





ACKNOWLEDGEMENT

- **The Danish Colorectal Cancer Group**
- **RANX05**
- **The Lund team**
- **The Vesterås/Uppsala team**



Example 2

**TIMP-1 as a predictive
biomarker in breast cancer.**



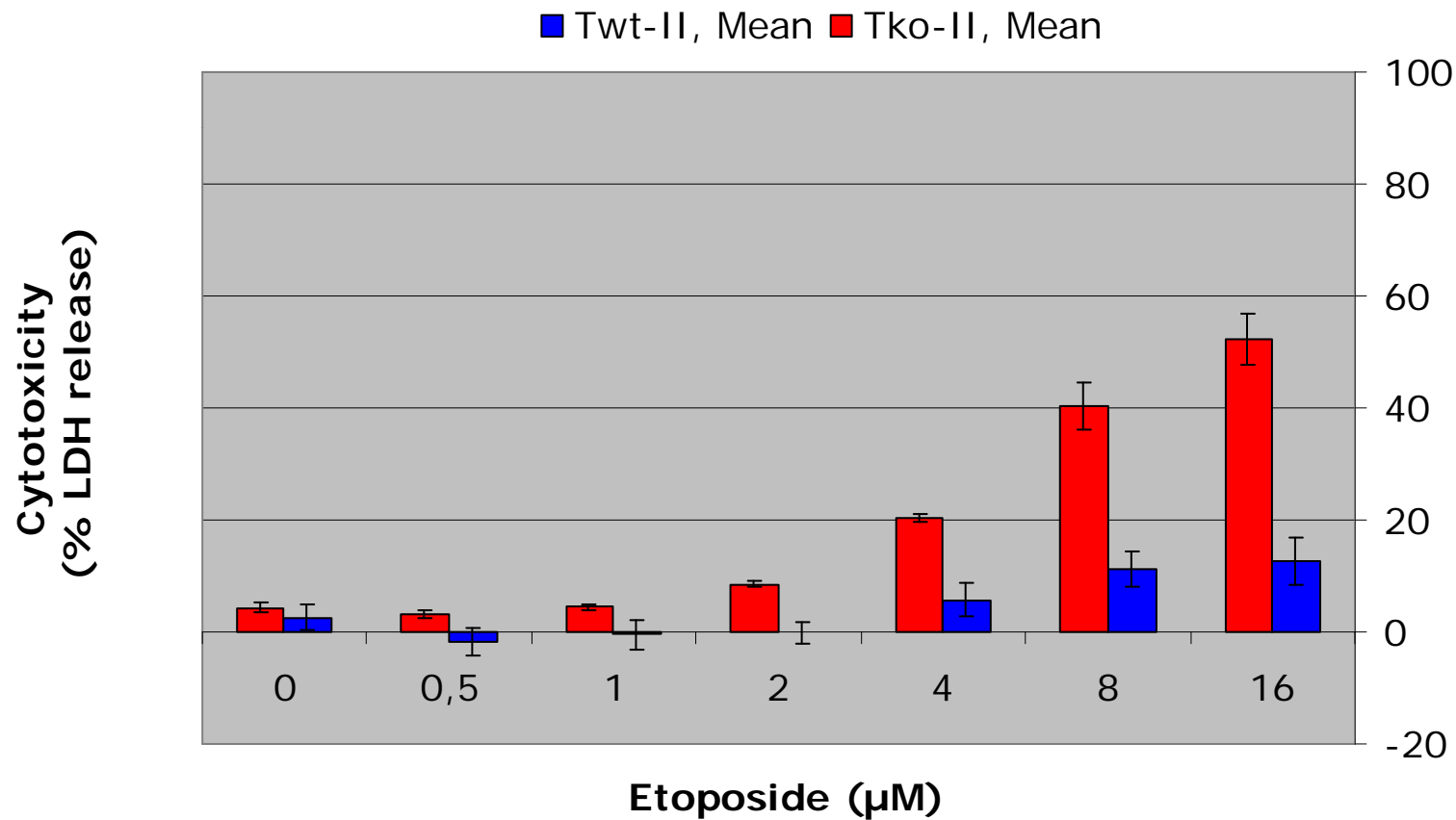
Hypothesis:

Since most types of chemotherapy induce apoptosis in the cancer cells and since TIMP-1 protects against apoptosis:

High TIMP-1 levels in the tumor might protect against chemotherapy-induced apoptosis

PREDICTING RESPONSE TO CHEMOTHERAPY

NR108 Twt-II and Tko-II exposed to Etoposide for 48 hrs.





Breast cancer study

- **173 patients with metastatic breast cancer**
- **TIMP-1 determined by ELISA in primary tumor extracts**
- **TIMP-1 values correlated with objective response to chemotherapy.**



PREDICTING RESPONSE TO CHEMOTHERAPY IN BREAST CANCER

TIMP-1	High (N=18)	Low (N=156)
Complete/ partial response	0%	41%
No change/ progressive disease	100%	59%

N=174

Objective response rates according to tumour tissue TIMP-1 levels.

Chemotherapy CMF or CAF.



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