From theory to practice: MUC-1 – a new target for anticancer therapy

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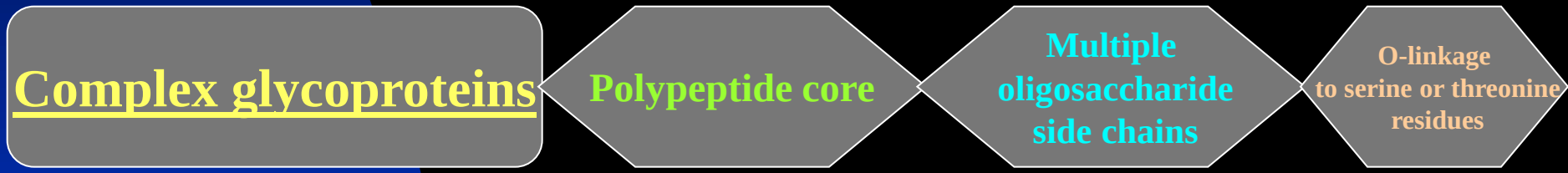
Targeted therapy is the XXI-th century therapy

Mucins are the big family of human tumor-associated antigens

The MUC-1 Mucin (CD227)



The MUC-1 Mucin (CD227)

- The mature molecule is anchored within the cell surface by a characteristic transmembrane domain
- Most of the mucin is expressed extracellularly in an elongated form extending far beyond most other cell surface expressed macromolecules
- A large region of the protein core of the MUC1 mucin consists of variable numbers of a highly conserved 20-amino acid repeat unit

MUC-1 картинка

Anti-MUC-1 MABs

The majority of MABs reacts with a dominant peptide region

Others MABs react with carbohydrate moieties on the mucin (MABs ICO-25, LU-BCRU-G7)

The MUC-1 Mucin (CD227)

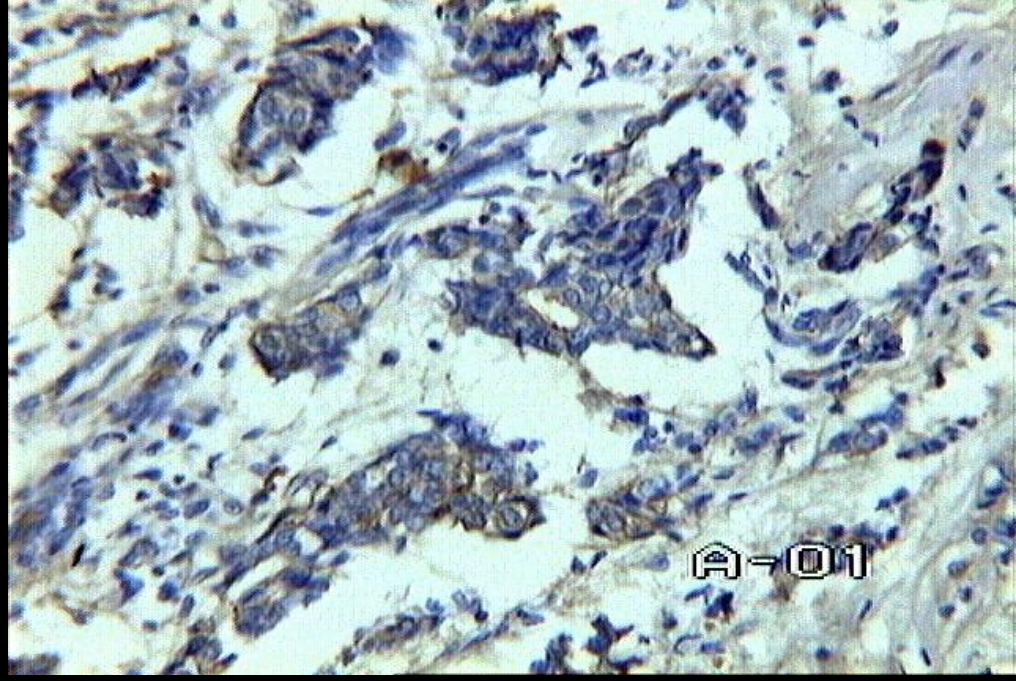
- Considerable impact as markers of many human carcinomas
- In malignant cells:
  - The expression is elevated
  - The orientation is no longer polarized at apical surfaces
  - The glycosylation is frequently altered (incomplete or aberrant)
  - MUC1 mucins released from their surface location may therefore have access to the circulation (CA15.3)

MUC-1 (CD227)
is over-expressed in many malignancies:

- Breast cancer
- Ovarian cancer
- Gastric cancer
- Colon cancer
- NSCLC

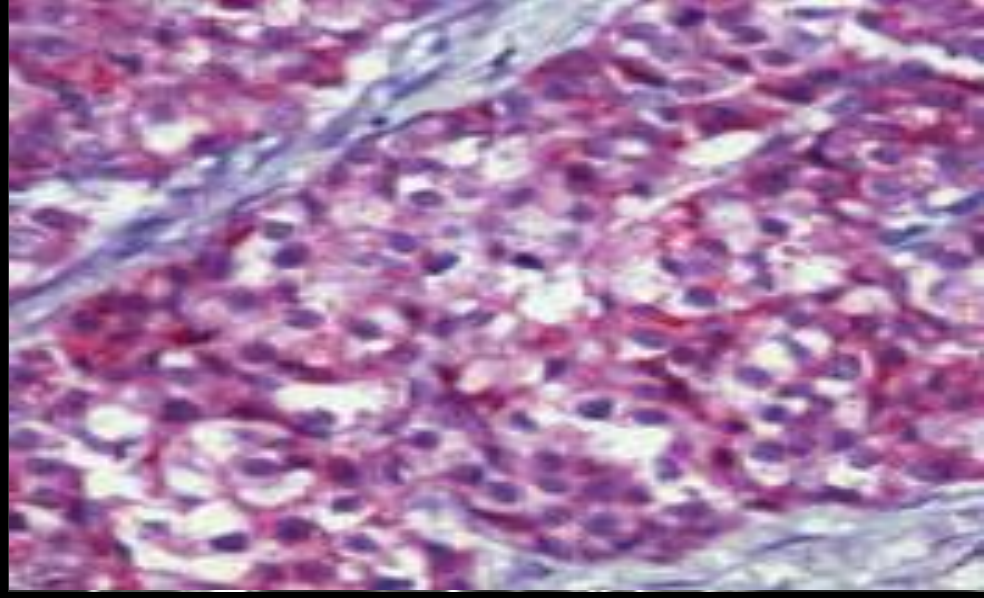
Breast cancer (MABs ICO-25)

183 tumors were studied



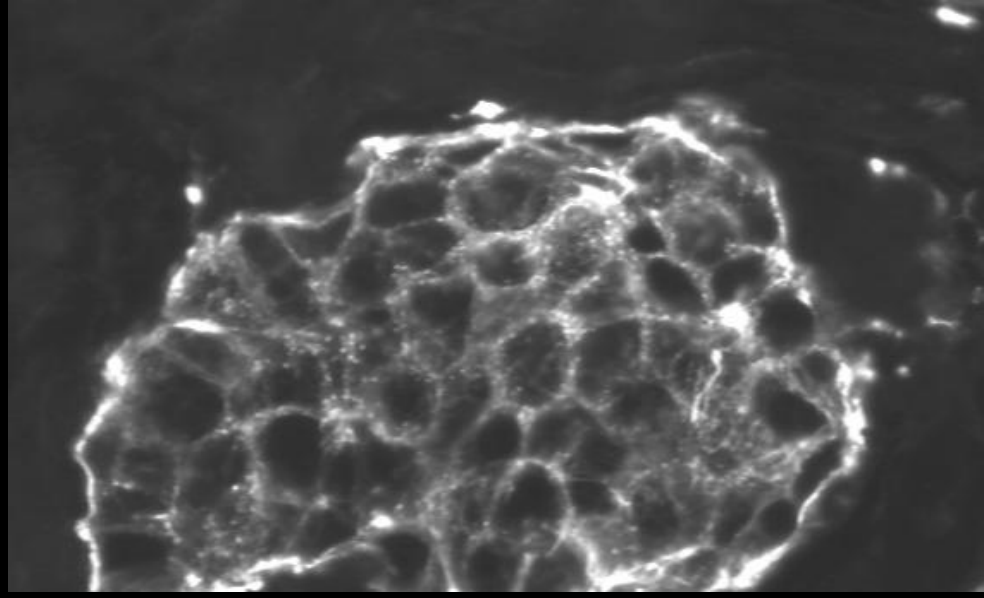
Antigen	Type of reaction: monomorphic	mosaic	negative
MUC-1 (ICO-25)	56,3% (103/183)	37,7% (69/183)	6,0% (11/183)

Breast cancer (MABs ICO-25)



- ICO-25 epitope was found on the breast cancer cells in 94% of all cases
- Antigen is localized on the membrane and in the cytoplasm of the malignant cells
- Neoadjuvant chemotherapy and radiation therapy did not diminished the expression of MUC-1

Metastases in lymph nodes



- The usual histological study 45,8% (33/72)
- Immunohistochemical study (MABs ICO-25) 55,6% (40/72)

+9,8%

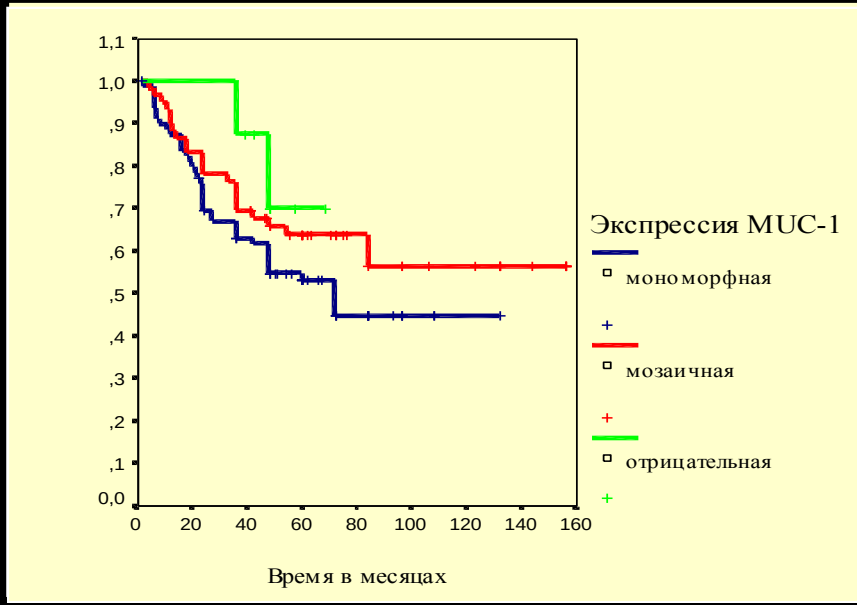
Breast cancer

MUC1 (ICO-25) expression correlated with CEA (p=0,007) and did not correlate with levels of lymphocyte or macrophage infiltration and stage of breast cancer

Survival of breast cancer patients

Expression of MUC1	5-year survival	
	Overall	Desease-free
Negative	75,0±21,7%	70,0±18,2%
Mosaic	74,8±5,9%	63,5±6,3%
Monomorphic	67,1±5,4%	51,1±5,8%
Log-Ranc	0,1905	0,0905

Desease-free survival



MUC1: Galß1-3GlcNAc (Le^c) – determinant of MABs LU-BCRU-G7 on the breast cancer cells

88 cases of breast cancer $T_{1-2}N_0M_0$ were studied

Antigen	Type of reaction:		
	monomorphic	mosaic	negative
MUC-1 (LU-BCRU-G7)	21,6% (19/88)	35,2% (31/88)	43,2% (38/88)

positive 56,8% (50/88)

MUC1: Galß1-3GlcNAc (Le^c) – determinant of MABs LU-BCRU-G7 on the breast cancer cells

88 cases of breast cancer T1-2N0M0 were studied

MUC1 (LU-BCRU-G7) expression

- Is not correlated with histology type of tumors and levels of lymphocyte or macrophage infiltration
- Is correlated with CD71 expression (p=0,007) and tumor size (p=0,004):

	MUC1 (LU-BCRU-G7) expression	
tumor size > 3 sm	85,0% (17/20)	
tumor size < 3 sm	48,4% (33/68)	p=0,004

MUC1: Galß1-3GlcNAc (Lé) – determinant of MABs LU-BCRU-G7 on the breast cancer cells

88 cases of breast cancer T1-2N0M0 were studied

Survival of breast cancer patients (p>0,05)

Expression of Galß1-3GlcNAc	Disease-free survival		Overall survival	
	5-year %±m	mediana	5-year %±m	mediana
Negative	79,0±6,0	-	81,1±6,4	-
Positive	65,7±6,8	-	79,6±5,8	-

MUC1: Galß1-3GlcNAc (Lê) – determinant of MABs LU-BCRU-G7 on the breast cancer cells

P=0,047

Metastases in lung	Expression of Galß1-3GlcNAc
YES	7/8 – 87,5%
NO	41/77 – 53,2%

Biotherapy is new perspective direction of treatment of cancer

The most impotent road of biotherapy is the application of MABs to different tumor-associated antigens.

- MABs can efficiently kill the targeted cells through either complement-mediated or antibody-dependent cellular cytotoxic (ADCC) mechanism.

MABs ICO-25 (Ig G1)

- High specificity
- Negative reaction with non-epithelial cells
- Low level of expression of MUC1 in normal tissues
- High content of antigen in cancer cells
- Antitumor activity *in vivo*

Based on MABs ICO-25 the medicine IMUTERAN was created

IMUTERAN (MABs ICO-25)

- is the original russian medicine;
- is created by Russian Cancer Research Center n.a. N.N.Blokhin in common with Moscow Oncological Institute n.a. P.A.Gertzen.

IMUTERAN

- The sterile solution of mouse MABs ICO-25
- The concentration is 5 mg/ml
- One vial contains 5 ml (25 mg) of MABs ICO-25

Phase I study of IMUTERAN

10 subjects with advanced solid tumors

Tumor Type	Number of patients
Breast cancer	6
Metastases from Метастазы из НПО	2
Ovarian cancer	1
Uterine carcinoma	1
Total	10

Objectives:

- Dose-escalation study
- Determination of maximum endurable dose
- Determination of dose-limiting toxicity

Regimen of treatment

- Start dose – 5 mg
- To dilute in 250 ml saline
- Intravenous infusion (5 ml/min)
- On day 1, 8, 15 and 22 of 4 weeks cycle

Phase I study of IMUTERAN

A total of 10 patients were treated.
10 courses of treatment were carried out (a total 34 infusion)

- **The planned research for 8 patients was fully carried out**
- **The treatment of 2 patients after the first infusion of Imuteran (dose 925 % of starting) was canceled because of toxicity**

% of starting dose	Single dose mg	Number of infusion	Course dose mg	Number of patients
100	5	4	20	1
350	17,5	4	70	2
525	26,25	4	105	1
700	35,00	4	140	3
925	46,25	4 1	185 46,25	1 2

Toxicity

- Chill – 6 (60%) patients — 32,4% of infusion
- Nausea and vomiting – 2 (20%) patients — 5,9% of infusion
- Urticaria, angioneurotic (Quinke's) edema –1 (10%) patient
- Bones pain – 1 (10%) patient (in combination with chill, high blood pressure, nausea and vomiting)

  } First infusion – treatment was stopped

- Low blood pressure, orthostatic collapse – 2 (20%) patients — 11,8% of infusion
- High blood pressure – 2 (20%) patients — 8,8% of infusion

The treatment of 2/10 (20%) patients after the first infusion of Imuteran (dose 925% of starting) was stopped because of toxicity

Results of phase I

- The program of dose-escalation is fully complete.
- The treatment of 2 patients after the first infusion of Imuteran was canceled because of toxicity: during the infusion of Imuteran 2/3 patients with the single dose 46,25 mg (925% of starting dose) had serious *adverse events* – the treatment was stopped.
- The major toxicities were allergic reactions (chill, collapse, urticaria, angioneurotic (Quinke's) edema).
- Imuteran treatment did not cause neither myelosuppression nor changes in biochemistry.

Phase II study of IMUTERAN

- *Regimen:*

  Imuteran – 35 mg (700% of starting dose) intravenous infusion

7 patients: on day 1, 8, 15 and 22 of 4 weeks cycle, the break 2 weeks;

13 patients: weekly infusion without the break

- *Premedication:*

Dimedrolum

1% - 3,0 ml i.v.

+/- Dexamethazonum

8 mg i.v.

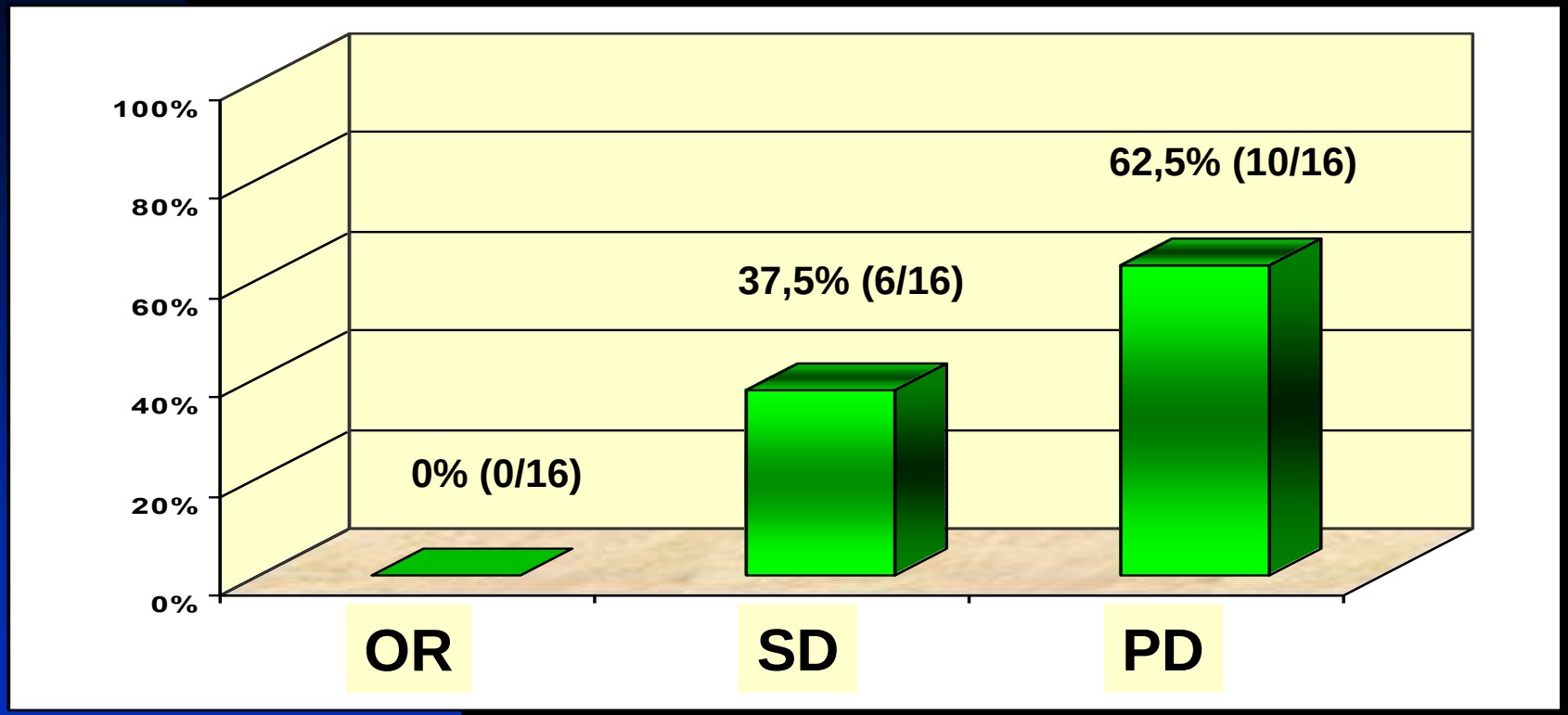
30 min before infusion

Phase II study of IMUTERAN

Diagnosis	Number of patients (examined)	Number of courses (complete)	Response (examined 16 patients)
Breast cancer	6 (4)	7 (5)	2/4 – SD 15 w. и 9 w. 2/4 – PD 2 – not examined (allergic reactions – the treatment was stopped)
Colorectal cancer	5 (5)	6 (6)	2/5 – SD 8 w. и 9 w. 3/5 – PD
Ovarian cancer	6 (5)	6 (5)	5/5 – PD 1 –not examined (enteroparesis – the treatment was stopped)
Зл. герминогенная опухоль яичников	1 (0)	1 (1)	Excluded
Cancer of fallopian tube	2 (2)	6 (6)	2/2 – SD 19 w и 11 w.
TOTAL	20 (16)	26 (23)	6/16 (37,5%) – SD 11,8±4,3 w. (mediana 10 w.) 10/16 (62,5%) – PD

Phase II study of IMUTERAN

16/20 patients were examined



- **Duration of stabilization** – 8 w., 9 w., 9 w., 11 w., 15 w. и 19 w. (11,8±4,3 w., mediana 10 w.)

The analysis of patients with the stable disease

Diagnosis	N	Previous treatment	Mts location	Dur. of st.
Breast cancer	2	1 – adjuvant ChT, 3 lines of ChT (docetaxel + doxorubicin, capecitabine, gemcitabine + vinorelbine), 3 lines of hormonotherapy (ovarian function suppression, tamoxifen, letrozole) 1 –ChT CAF, RT (70 Гр)	Hepar, bones Soft tissues, lymph nodes	15 w. 9 w.
Colorectal cancer	2	1 – 4 lines of ChT (5-FU+FA, raltitrexed, CAMPTO, Capecitabine) 1 – 2 lines of ChT (5-FU+LV, raltitrexed), IL-2/LAK immunotherapy	Pelvis minor Hepar	9 w. 8 w.
Cancer of fallopian tube	2	1 – 3 lines of ChT (CP, paclitaxel+CBDCA, doxorubicin +VP-16), RT 1 – adjuvant ChT , 2 lines of ChT (CAP, 5-FU+LV+VP-16)	Lymph nodes, brain Greater omentum	19 w. 11 w.

Phase II study of IMUTERAN

- **Serious adverse events** (after premedication):

3/20 (15%) patients:

1 – enteroparesis

2 – allergic reactions

- **Imuteran treatment did not cause myelosuppression and changes in biochemistry.**

PERSPECTIVES:

CREATION OF CHIMERIC OR HUMANIZED MABs ICO-25