New treatments against invasive tumors based on Cystatin-C human protein

ONCOMATRIX

Bilbao, 21 de septiembre de 2012

biospain 2012

Content

1. THE COMPANY

ONCOMATRIX pioneering company in personalized cancer medicine

Mission

- *Development of biological products for personalized treatment of invasive stages of cancer:*
  1. *Invasive Diagnostic (biopsies)*
  2. *Non invasive Diagnostic (serum, and urine samples)*
  3. *Personalized Treatment (monoclonal antibodies and other therapeutic proteins)*

Innovation

- *Novel therapeutic approach: Targeting the existing connection between tumor microenvironment and tumor cells. Novel therapy against tumor stroma that facilitates invasiveness and resistance to anticancer treatments.*
- *Application for Multiple tumors: Bladder, Kidney, Pancreas, Breast, Lung, Colon or Head&Neck.*

Business Model

- *Open Innovation Business Model*
- *In house management of external collaborations by a professional team with high knowledge and experience in biopharma industry*
- *Strategic and Market-oriented IP Management*

1. ONCOMATRIX

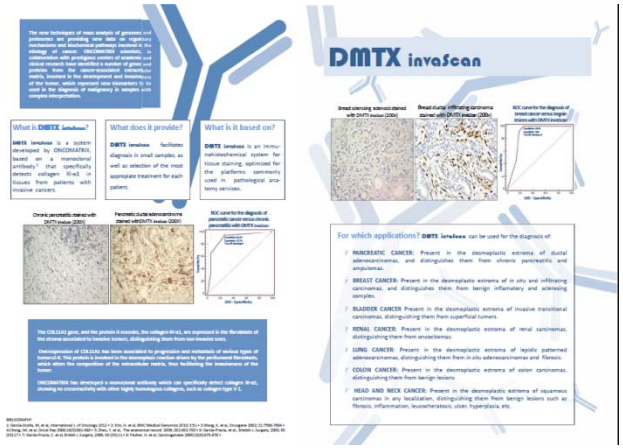
ONCOMATRIX founded in 2009

- **Facilities**: 200 m^2 of laboratories and offices. Technological Park of Bizcaia, Bilbao
- **Managers**:
  - **Dr. Laureano Simón Buela** (CEO) - Founder of successful biotech companies, such as Progenika Biopharma, Proteomika, Brainco or Abyntek
  - **Manuel Sanz Vázquez, MBA** (General Manager) – Managerial positions in international and SME companies as Electrolux, Grupo Ormazabal or QualitySol Group.
  - **Dra. Myriam Fabre** (Senior Project Manager) - R&D manager in Biotech industry. Co-founder and former Executive Vice-president of Alternative Testing Unit in Advancell
  - **Dra. Cristina Ferrer Marsal** (Senior Project Manager) - Research and preclinical development manager in Biotech and International Pharma companies.
  - **Dra. Saioa Dominguez Hormaetxe** (Scientific Project Manager) - Research and management experience in different Biotech companies.
  - **Dr. Simon Santa Cruz** Program Manager and Consultant to Biotechnology Industry

1. ONCOMATRIX Collaborations

1. Oncomatrix Diagnostic Products and Projects

➢ InvaScan - Commercialized



IHC Detection of collagen XI-α1
Differential detection of invasive carcinomas

- Patent application # P7143ES00 (2011)
- ***Int. Journal of Oncol. 2012 40(5):1447-1454***

➢ BladderScan – Clinically validated

IHC detection of bladder cancer
Companion diagnostics for FGFR3-targetted drugs.

- US Patent # 8,124,331 (2007) "**In vitro method to detect bladder transitional cell carcinoma"**
- European Patent # EP1611252B1
- ***Clin Cancer Res 2005 (2);11:459-465***

➢ BladderScan.uro - Validation phase

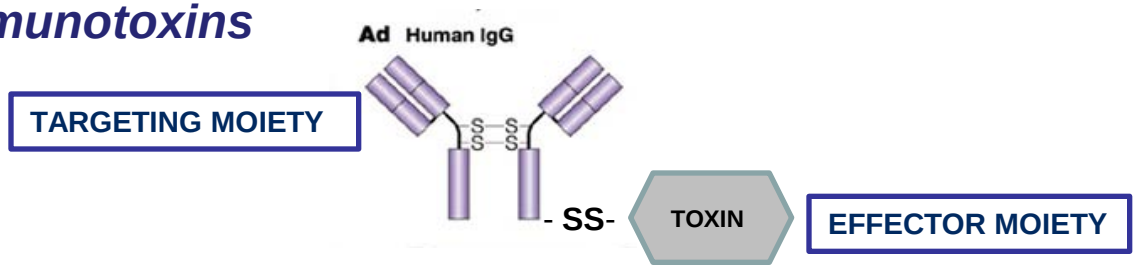
Non invasive detection of bladder cancer in urine samples

1. Oncomatrix Drug Development Projects

- **Human Cystatin- C** protein (Case Comprehensive Cancer Center - CWR University)

- Recombinant therapeutic antibodies and related Immunotoxins or Drug Conjugates, directed against the peritumoral stroma (Stuttgart University)

Immunotoxins



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3. **Partnering Opportunities**

2. Cystatin-C - Therapeutic focus

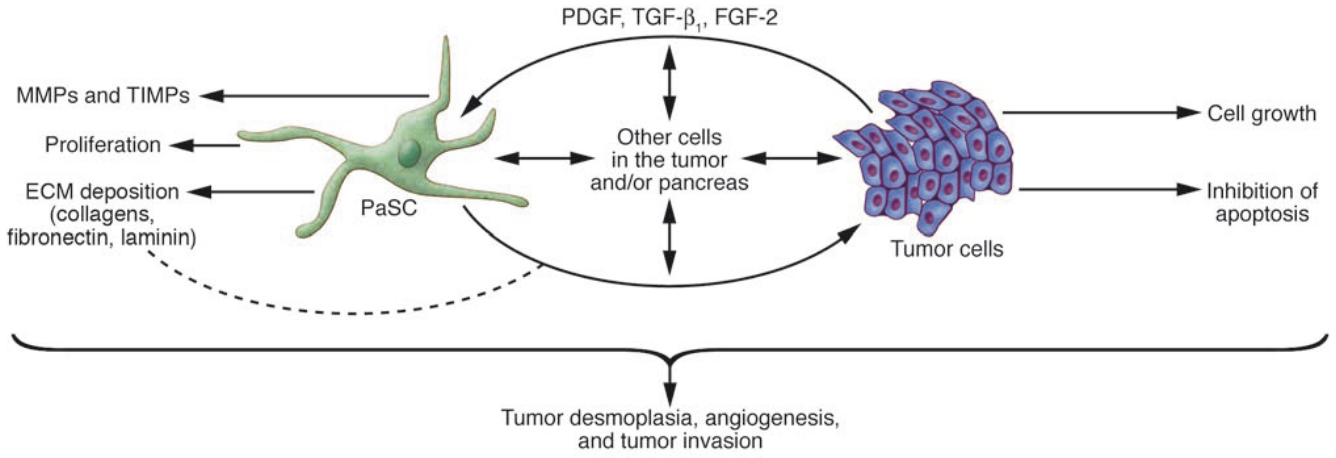
	Incidence and mortality	Indicators
PANCREATIC CANCER	▪ Incidence: 3.9 cases per 100,000 people ▪ Mortality: 96%. Early detected and resected tumors down rate to 75%.	▪ 4th leading cause of cancer death ▪ Highly aggressive and invasive cancers ▪ Difficult to differentiate from pancreatitis ▪ Difficult early diagnosis ▪ High resistance to chemo and radiotherapy
BREAST CANCER	▪ Incidence: 39 cases per 100,000 people (13 M people/year) ▪ Mortality 12,5% (465.000 people/year)	▪ Leading cancer for women ▪ 3rd leading cause of cancer death

2. Cystatin-C – Innovative Mechanism of action

Peritumoral stroma as strategic target for tumor treatment

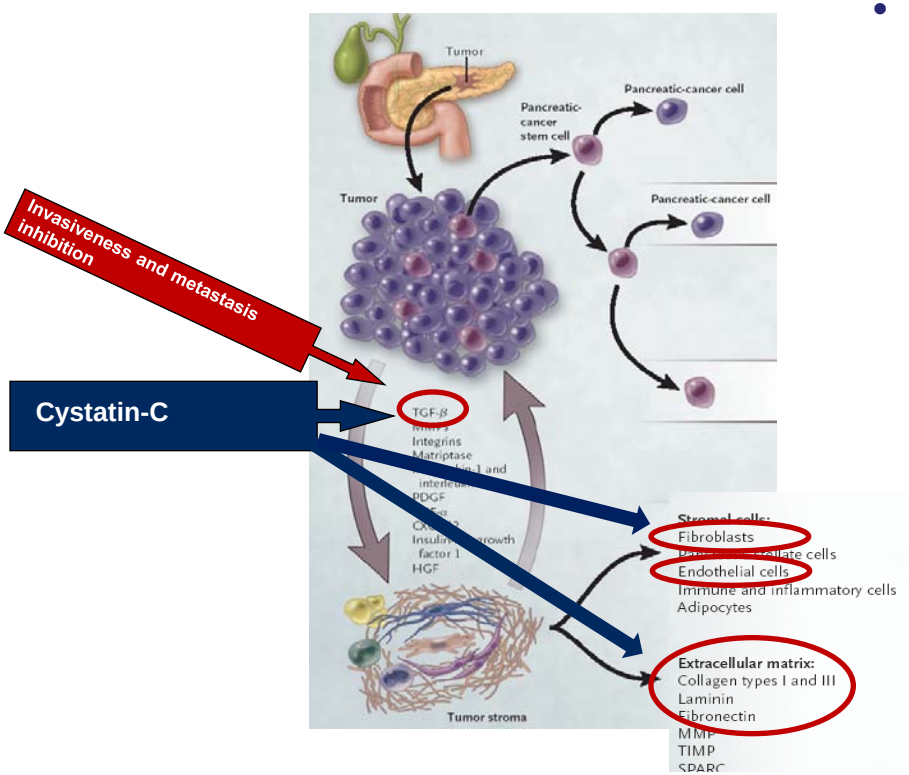
- Peritumoral stroma: one of the main promoters of tumor invasiveness, as well as resistance against current anti-cancer therapies (*).

- Therapeutic approach based on the development of new biological and personalized drugs targeting proteins located in the stroma (Fibroblasts and/or ECM): new and innovative cancer treatment directed not against tumor cells but the cells that promote their invasiveness and/or drug resistance.



(*) Olive, K.P. et al. (2009)Science 324(5933):1457-61

2. Cystatin-C – Innovative Mechanism of action



- **Cystatin-C** is a natural secreted protein that regulates bone resorption, inflammatory response or neutrophil chemotaxis.
- Related to cancer, **Cyst-C** has an antitumor function with different activities within the tumor microenvironment:
  - **Cyst-C** is already well-known cathepsin-B inhibitor. By inhibiting cathepsin-B Cyst-C blocks degradation of the extracellular matrix that facilitates cell migration and invasiveness.
  - **Cyst-C** also inhibits TGF-β by binding to TGβRII (Oncomatrix industrial property). Cyst-C blocks TGFβ signaling in endothelial cells, antagonizing angiogenesis, as well as in breast tumor cells inhibiting tumor growth and metastasis.

2. Cystatin-C – Differential features facing the market

Target	Product	Company	Phase
LOXL2	**GS6624 (AB0024)** Humanized monoclonal antibody (mAb) against Lysyl oxidase-like 2	**Gilead Sciences Inc** (**Arresto Biosciences, Inc**.)	Phase II started (02/2012)
CD-105	**TRC105** Chimeric monoclonal antibody against endoglin	**TRACON Pharmaceuticals**	Phase I/Phase II (20011/2012) different indications

BioCentury data

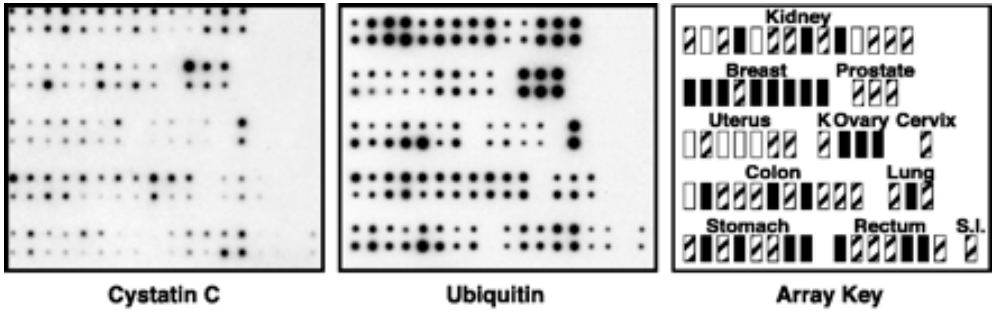
2. Cystatin-C – Differential features facing the market

- Cystatin C is a natural protein from human origin
- It has a natural inhibitory function of tumor growth and invasiveness (inhibitor of cathepsin-B and TGFβ functions)
- It has an antiangiogenic activity acting on endothelial cells and inhibits epithelial-mesenchymal transition (EMT) in cancer cells
- It has the potential to increase the antitumoral activity of existing anticancer drugs, acting in the tumor-associate stroma
- Its expression is down-regulated in different aggressive and metastatic tumors

2. Cystatin-C – Differential features facing the market

Cystatin expression is downregulated in 44% of human cancers patients analyzed

Cyst C expression was altered in 49% of human malignancies analyzed (91% of the alterations were downregulation of CystC expression)



Cystatin C Expression in Human Tumors:

Altered	Downregulated	Upregulated
49% (33/68 cases)	91% (30/33 cases)	9% (3/33 cases)

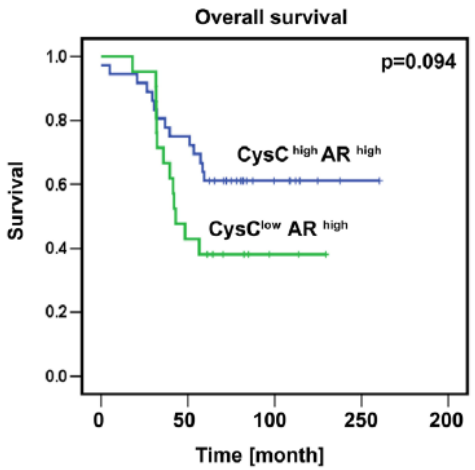
Tumorigenesis alters CystC expression in human tissues. Radiolabeled cDNA probes corresponding to either human CystC (left panel) or ubiquitin (middle panel) were hybridized to match human normal/tumor cDNA array. Shown are the resulting autoradiographs depicting CystC and ubiquitin expression in paired normal (upper spot) and malignant (bottom spot) tissues. CystC expression was normalized to that of ubiquitin and tumor:normal tissue CystC expression ratios were determined. Ratios ≥2 or ≤0.5 were considered significant. Tumor type and metastasis status are indicated by: (a) open boxes, no information; (b) filled boxes, metastasis observed; and (c) stripped boxes, metastasis not observed (right panel). K, kidney; S.I., small intestine.

J.Sokol & W. Schiemann (2004) Mol.Can.Res. 2(3):183-195

2. Cystatin-C – Differential features facing the market

- Prostate cancer patients with low expression of Cyst C and high expression of androgen receptor (AR) have worse overall survival than patients with high expression of Cyst C and AR.

The study was performed in tissue specimens from 448 patients with prostate cancer. Cyst C expression was significantly lower in cancer specimens than in benign tissues



Kaplan-Meier survival analysis in 99 patients with advanced prostate cancer. Overall survival in a group of 99 patients with the most advanced prostate cancer (Gleason grade 4–5) which were characterized by high expression of AR and were separated to different groups based on Cystatin C levels (low- intensity score 0–1.5 and high-intensity score 2–3).

B.Wegiel et al. (2009) PlosOne 4(11): e7953

2. Cystatin-C – Differential features facing the market

- There is a significant depressed expression of Cyst C in glioblastomas compared with low-grade astrocytomas suggesting that there is a low level of Cyst-C expression in gliomas of patients with unfavorable clinical outcome.

The study was performed in tissue samples from 40 male and 17 female patients. There was a clear correlation between Cyst-C and cathepsin-B expression

Table 1 Scores of cystatin C and cathepsin B protein expressions in gliomas

WHO grade	Cystatin C			Cathepsin B		
	1	2	3	1	2	3
II	0	9	12	13	8	0
III	8	6	3	2	4	11
IV	17	2	0	0	2	17

NOTE. Score 1, LI ≤5%; score 2, LI >5% to 30%; and score 3, LI >30%.

Expressions of Cystatin-C and cathepsin-B proteins are summarized in the Table. High-grade (WHO grades III and IV) gliomas tended to have low Cyst-C and high cathepsin-B protein.

H.Nakabayashi et al. (2005) Human Pathol. 36 (9):1008-1015

2. Cystatin-C – Current status of development

CystC activity has been assayed in vitro in highly tumorigenic and invasive cell lines

Fig A

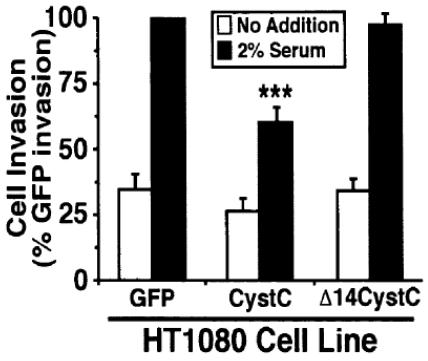


Fig B

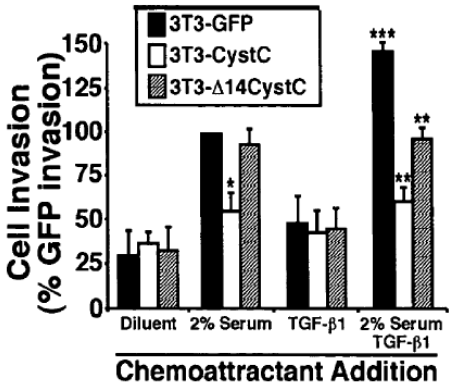
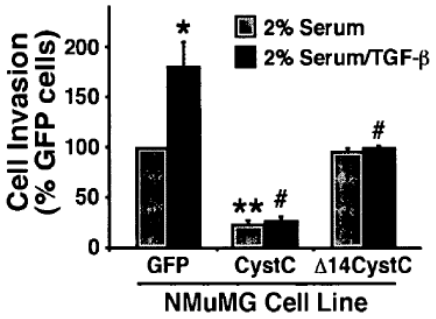


Fig C

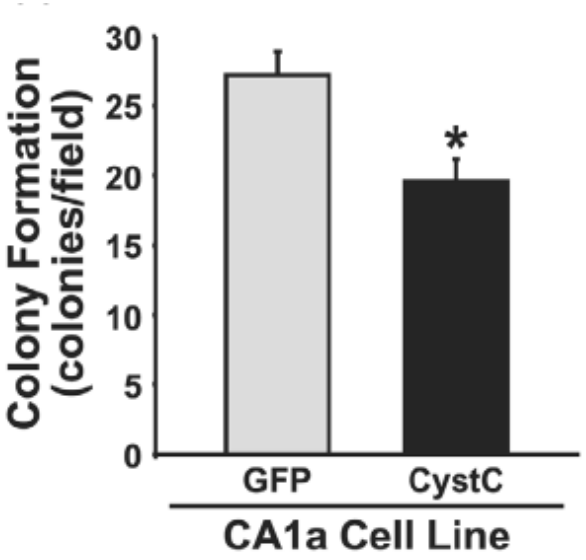


CystC expression in HT 1080 fibrosarcoma cells (Fig A) in 3T3-L1 pre-adipocyte cell line (Fig B) and in NMuMG mouse mammary epithelial cell line (Fig C) significantly inhibited cell invasion in Matrigel matrices assays in comparison to negative control (GFP) or a deleted CystC derivative (Δ14CystC)

J.Sokol & W. Schiemann (2004) Mol.Can.Res. 2(3):183-195
J.Sokol et al. (2005) Breast Can. Res. 7(5):R844-R853

2. Cystatin-C – Current status of development

CystC inhibits in vitro the anchorage-independent growth of breast cancer cells

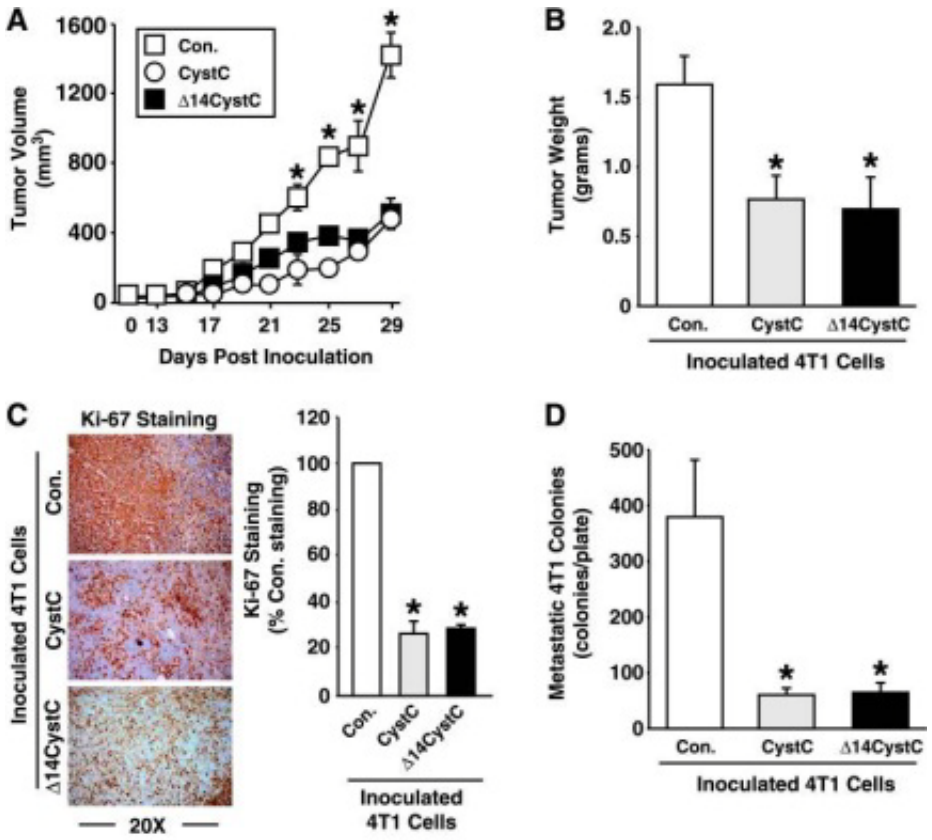


Control and CystC-expressing MCF10A-CA1a cells were cultured in soft agar for 14 days, whereupon MCF10A-CA1a colony formation was quantified by light microscopy. Values are colony formation per microscope field (means ± SEM) observed in two independent experiments. CystC expression significantly reduced anchorage-independent growth of MCF10A-CA1a cells (*P < 0.05; Student's t-test).

J.Sokol et al. (2005) Breast Can. Res. 7(5):R844-R853

2. Cystatin-C – Current status of development

CystC inhibits tumor growth and metastasis in vivo in 4T1 induced tumor mice

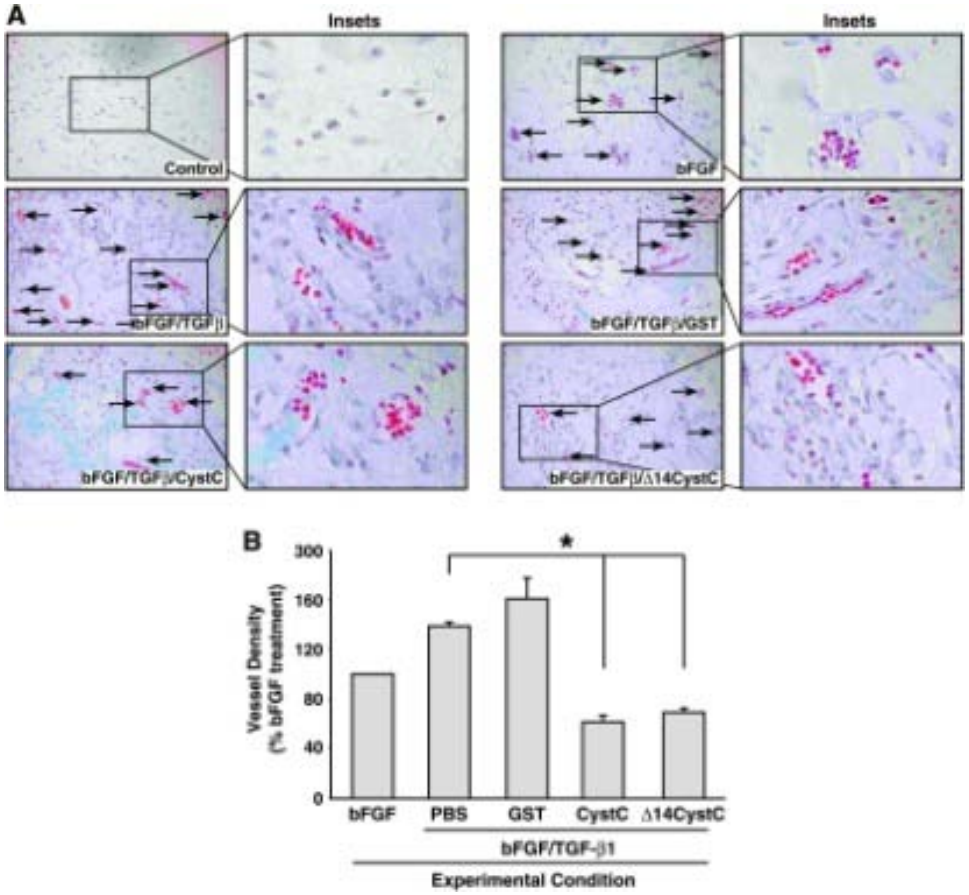


CystC inhibits 4T1 tumor growth and pulmonary metastasis. (A and B) Control (Con.)-, CystC-, or Δ14CystC-expressing 4T1 cells were injected orthotopically into the mammary fat pads of Balb/C mice. Ten days after injection, tumor volumes were measured every second day until they were killed on day 30. Data are mean (±SE) tumor volumes (A) or wet weights (B) observed in three independent experiments. (C) Tumor sections were stained with antibodies against Ki-67. Accompanying data are the mean (±SE) proliferating tumor cells (brown) relative to those present in sections of control 4T1 tumors. (D) Lung single-cell suspensions were cultured onto 10-cm plates supplemented with 6-thioguanine (60 µM). After 14 days, the surviving metastatic colonies were fixed, stained with crystal violet, and counted. Data are mean (±SE) surviving colonies per plate observed in three independent experiments. *P < .05, Student's t test.

M.Tian & W.Schiemann (2009) Trans. Oncol. 2(3):174-183

2. Cystatin-C – Current status of development

CystC shows anti-angiogenic activity in vivo in Matrigel plug implantation studies in mice



CystC inhibits TGF-β-stimulated angiogenesis and vessel development in genetically normal mice. C57BL/6 female mice were injected subcutaneously with Matrigel supplemented with diluent (i.e., PBS), bFGF (300 ng/ml), or bFGF (300 ng/ml) in combination with TGF-β1 (5 ng/ml) in the presence of recombinant (20 μg/ml) of GST, GST-CystC, or GST-Δ14CystC as indicated. Mice were killed on day 10, and the resulting plugs were harvested, fixed, sectioned, and stained with Masson's trichrome to visualize infiltrating blood vessels [denoted by arrow heads (A)], which were subsequently quantified by counting 10 independent fields per slide under a light microscope (B). Data are the mean (±SE) vessel densities relative to bFGF treatment observed in three independent experiments. *P < .05, Student's t test.

M.Tian & W.Schiemann (2009) Trans. Oncol. 2(3):174-183

2. Cystatin-C – IPR protection

Cystatin -C Oncomatrix IP

- *US Patent # 7,282,477 (Issued) (2007)* ***"Cystatin-C as an antagonist of TGF-β and methods related thereto"***
- *US Patent # 7,749,958*
- *US Patent # 8,058,396*
- *Australian Patent # AU-B-2004281152*
- *Patents pending:*
  - *US # 13/248,539*
  - *Australian # 2012200038*
  - *European # 04795359.1*
  - *Canadian # 2,546,623*

Patent protection until 2024

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3. **Partnering Opportunities**

3. Availability for cooperation

Oncomatrix aims to partner with BioPharmaceutical Companies in the co-development of Cystatin-C biological drugs

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THANK YOU FOR YOUR ATTENTION!

Bilbao, 21 de septiembre de 2012

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