

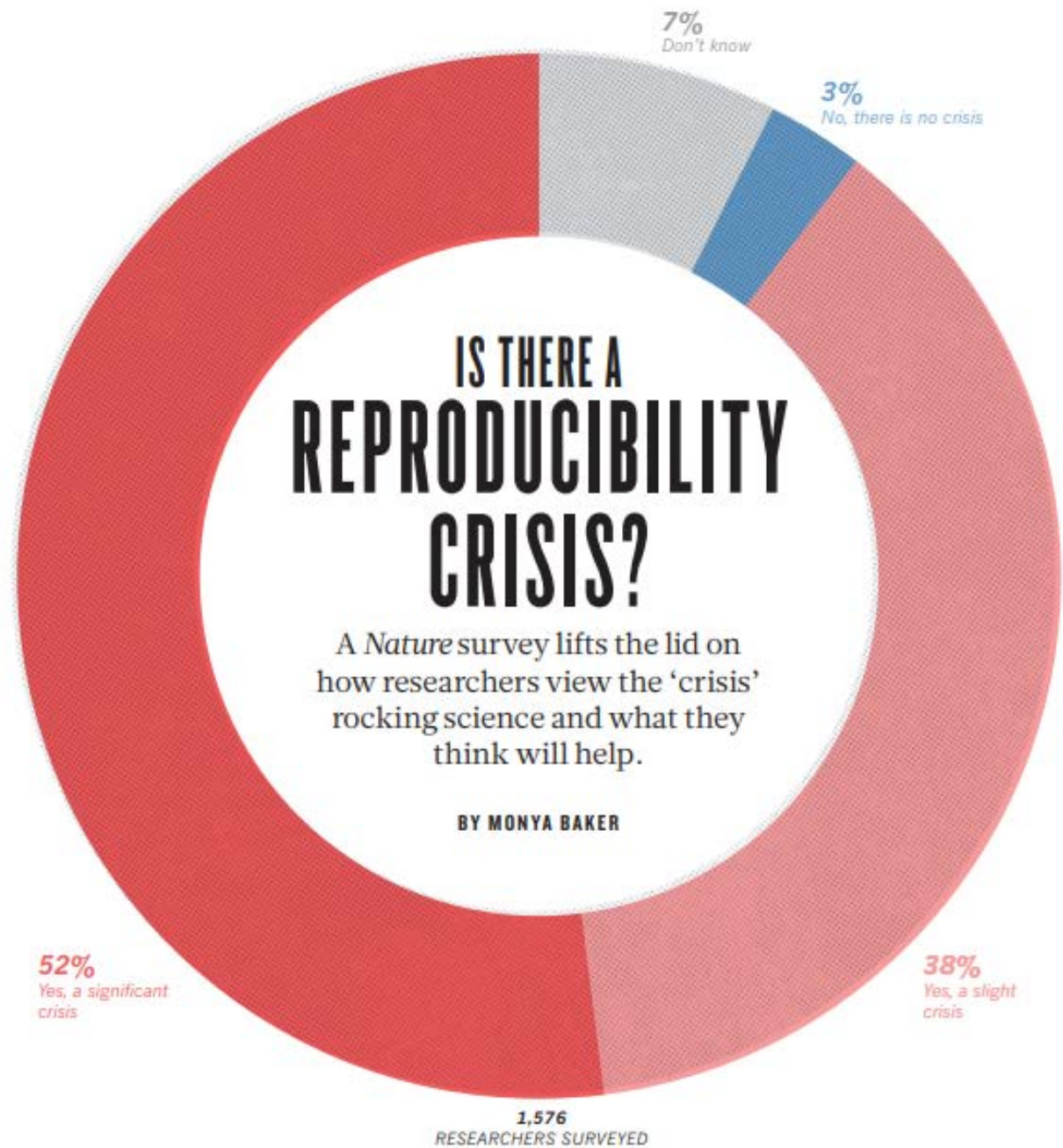


# Что надо понимать под фенотипом в доклинических исследованиях?

?



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ФФМ МГУ имени М.В.Ломоносова  
Rus-LASA



# Causes of poor reproducibility

- **Poor validity of the animal model**
- **Small sample sizes** (lack of statistical power)
- **Analytical flexibility** (p-hacking, HARKing)
- **Risks of bias** (no randomization, no blinding, etc.)



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- **Rigorous standardization** (poor generalizability)



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META-RESEARCH ARTICLE

## Reproducibility of preclinical animal research improves with heterogeneity of study samples

Bernhard Voelkl, Lucile Vogt, Emily S. Sena, Hanno Würbel 

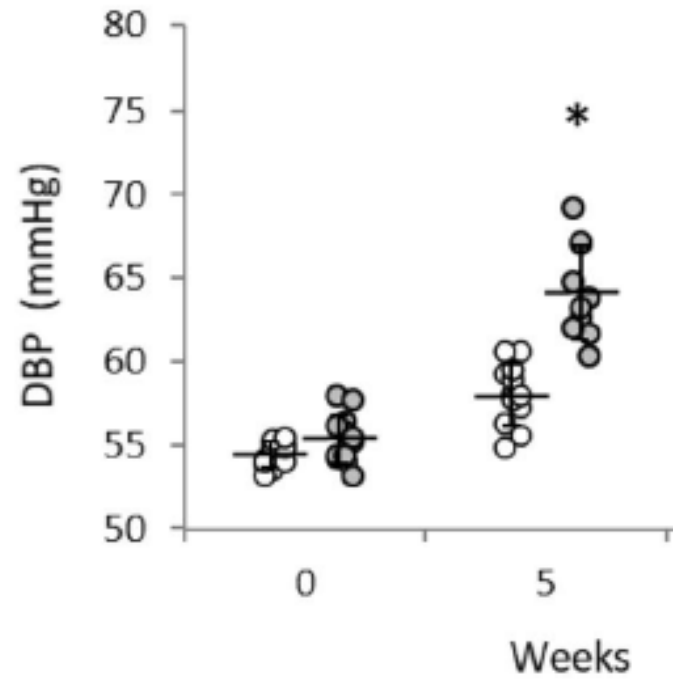
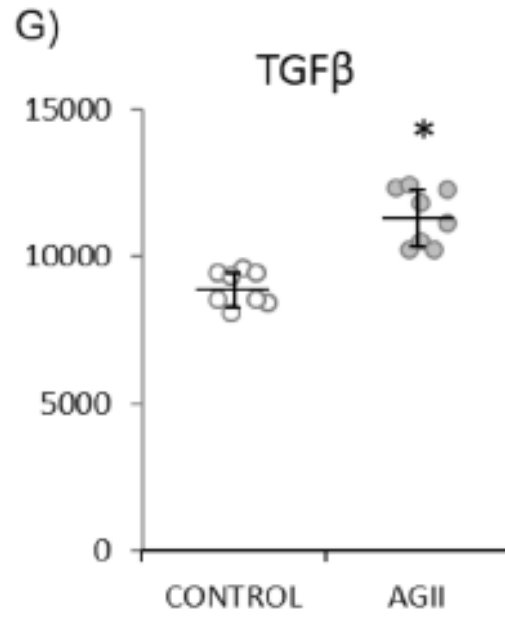
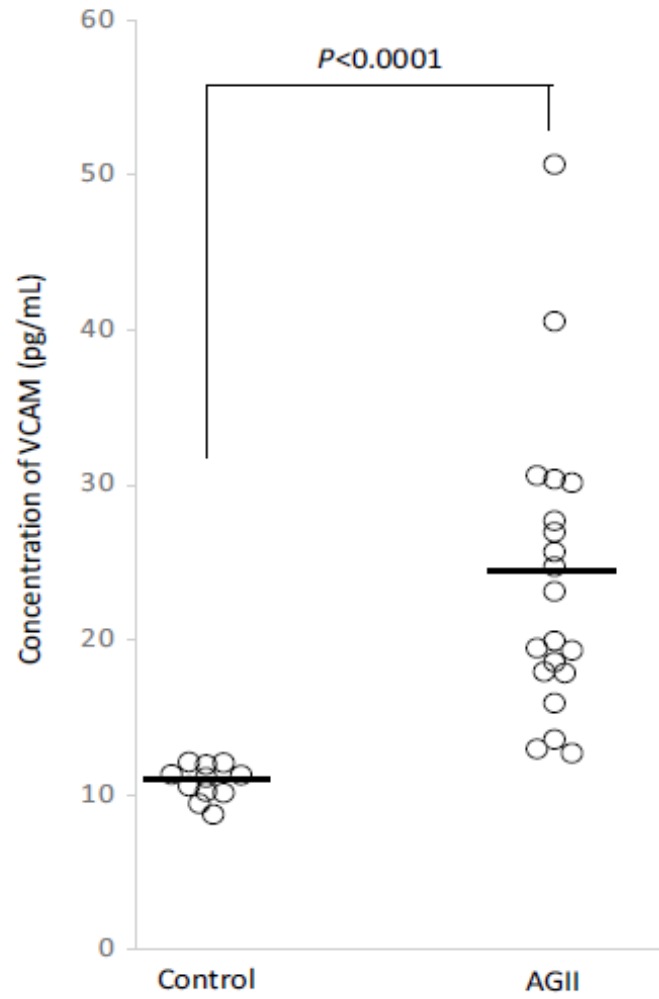
*«Проведение эксперимента хотя бы на двух площадках увеличивает вероятность получения воспроизводимых данных на 42%»*



OPEN

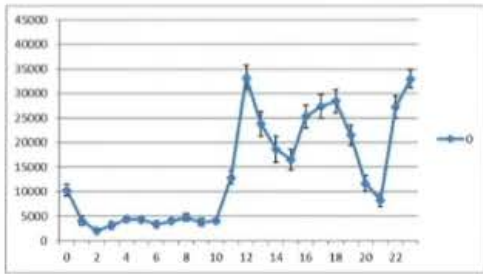
## Characterization of a murine model of endothelial dysfunction induced by chronic intraperitoneal administration of angiotensin II

Celeste Trejo-Moreno<sup>1,9</sup>, Enrique Jiménez-Ferrer<sup>2✉</sup>, Gabriela Castro-Martínez<sup>1</sup>, Marisol Méndez-Martínez<sup>1,3</sup>, María Angélica Santana<sup>4</sup>, Gerardo Arrellín-Rosas<sup>1,5</sup>, José Pedraza-Chaverri<sup>6</sup>, Omar Noel Medina-Campos<sup>6</sup>, Beatriz Hernández-Téllez<sup>7</sup>, Oscar Ramírez-Pliego<sup>4</sup>, Maribel Herrera-Ruiz<sup>2</sup>, Jacquelynne Cervantes-Torres<sup>8</sup>, Zimri Aziel Alvarado-Ojeda<sup>1</sup>, Alejandro Costet-Mejía<sup>1</sup>, Gladis Fragoso<sup>8</sup> & Gabriela Rosas-Salgado<sup>1✉</sup>

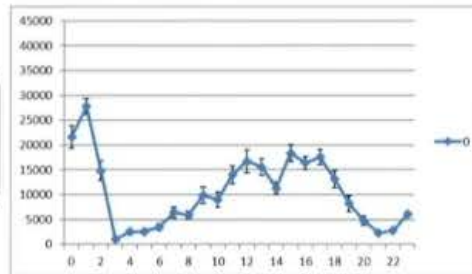


# Cage make up matters

## C57BL/6J



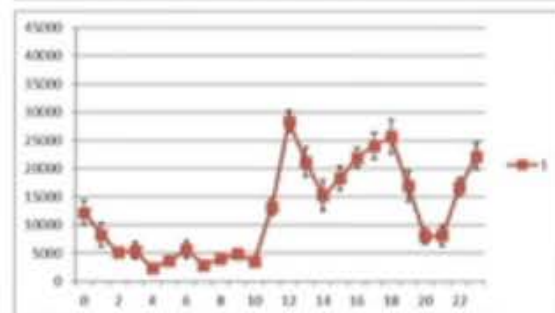
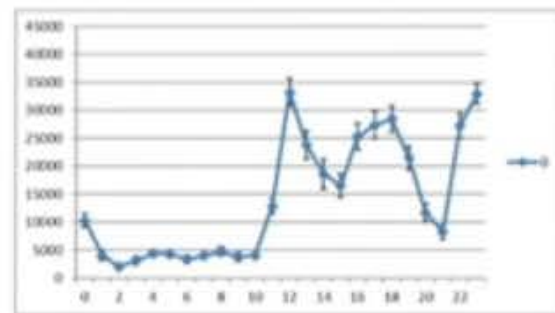
## FVB/NCrIBRH



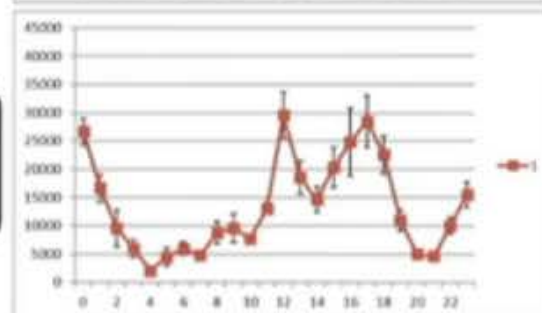
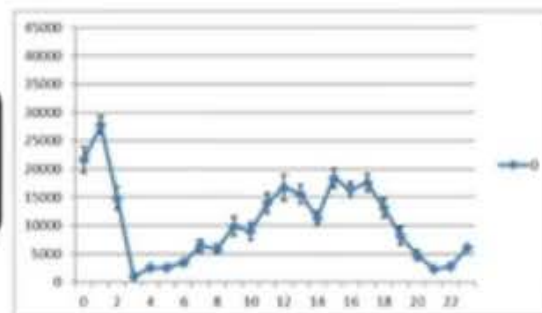


# Cage make up matters

C57BL/6J

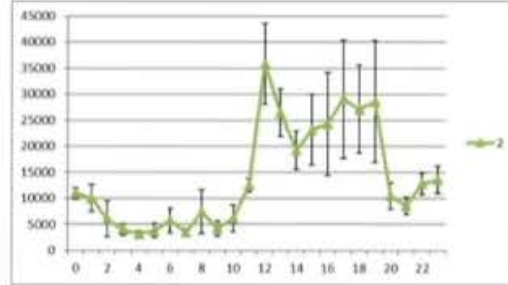
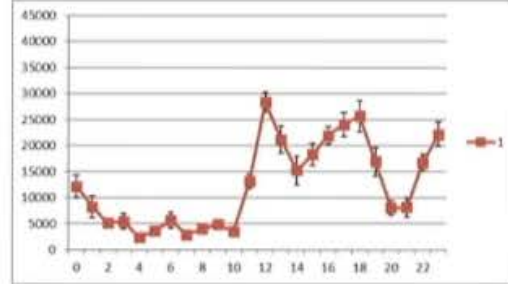
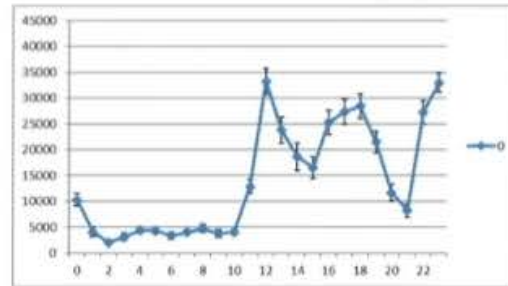


FVB/NCrIBRH

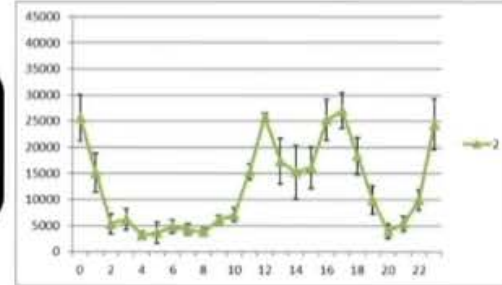
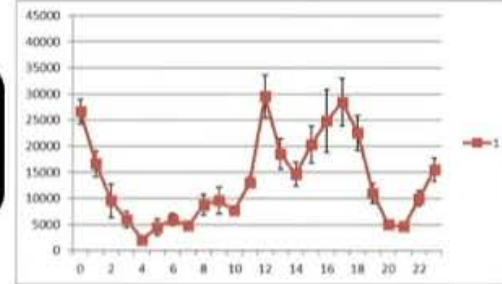
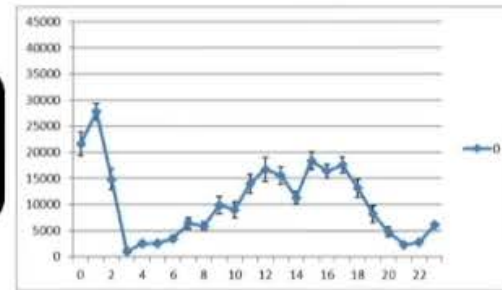


# Cage make up matters

## C57BL/6J



## FVB/NCrIBRH



(Unpublished data)



# Внеклеточные и внутриклеточные эффекты урокиназы и рецептора урокиназы

*Arch Biochem Biophys.* 1956 Jun;62(2):500-1.

## Isolation of a plasminogen activator (urokinase) from urine.

*PLOUG J, KJELDGAARD NO.*

PMID: 13328139

*Cancer Res.* 1985 Feb;45(2):630-6.

## Receptors for plasminogen activator, urokinase, in normal and Rous sarcoma virus-transformed mouse fibroblasts.

*Del Rosso M, Dini G, Fibbi G.*

### Abstract

We have prepared a conjugate of the plasminogen activator urokinase (UK) and ferritin, which maintains fibrinolytic activity. Monolayers of BALB/c-3T3 cells and of Rous sarcoma virus-transformed highly malignant line AA12-3T3, subcultured in plasminogen-free serum, were incubated with UK-ferritin at 0 degree and processed for transmission electron microscopy. Under these conditions, both of the lines showed specific receptors on the cell surface that were distributed in singlets, in small or large clusters. In the presence of excess native UK, the binding of ferritin was reduced by 99%, indicating the interaction of UK:ferritin with a specific receptor. The ligand-receptor interaction involves the catalytic site of UK, since the binding was completely impaired by preincubation of UK:ferritin with p-aminobenzamide, a competitive inhibitor of the catalytic site of UK. The number and density of receptors decreased about one order of magnitude on the membrane of AA12 cells when compared with normal 3T3 cells. Saturation kinetics, using 125I-labeled UK, indicate the presence of  $4 \times 10^4$  and  $2.5 \times 10^3$  receptors on the membrane of 3T3 and AA12 cells, respectively. At 37 degrees, UK:ferritin redistributed on the plane of the membrane, in a process which was faster in malignant than in normal cells. Ferritin particles clustered in large groups on coated areas of the surface and were internalized by adsorptive pinocytosis. After 10 min at 37 degrees, the vesicles showed a progressively deeper internalization and a fusion with lysosomes, and some were observed in the Golgi complex area. Since the experiments were planned in order to exclude the presence of protease-nexin in the incubation medium, these data suggest the existence of a plasminogen-independent novel receptor for plasminogen activators, the number on the cell surface of which decreases in Rous sarcoma virus-transformed mouse

PMID: 2981611

*Clin Exp Metastasis.* 1998 Jan;16(1):9-20.

## Inhibition of establishment of primary and micrometastatic tumors by a urokinase plasminogen activator receptor antagonist.

*Iqanar DM<sup>1</sup>, Andrews JL, Witherspoon SM, Leray JD, Clay WC, Kilpatrick K, Onori J, Kost T, Emerson DL.*

*Cancer Metastasis Rev.* 1990 Dec;9(4):353-67.

## The role of urokinase-type plasminogen activator in aggressive tumor cell behavior.

*Testa JE<sup>1</sup>, Quigley JP.*

Author information

### Abstract

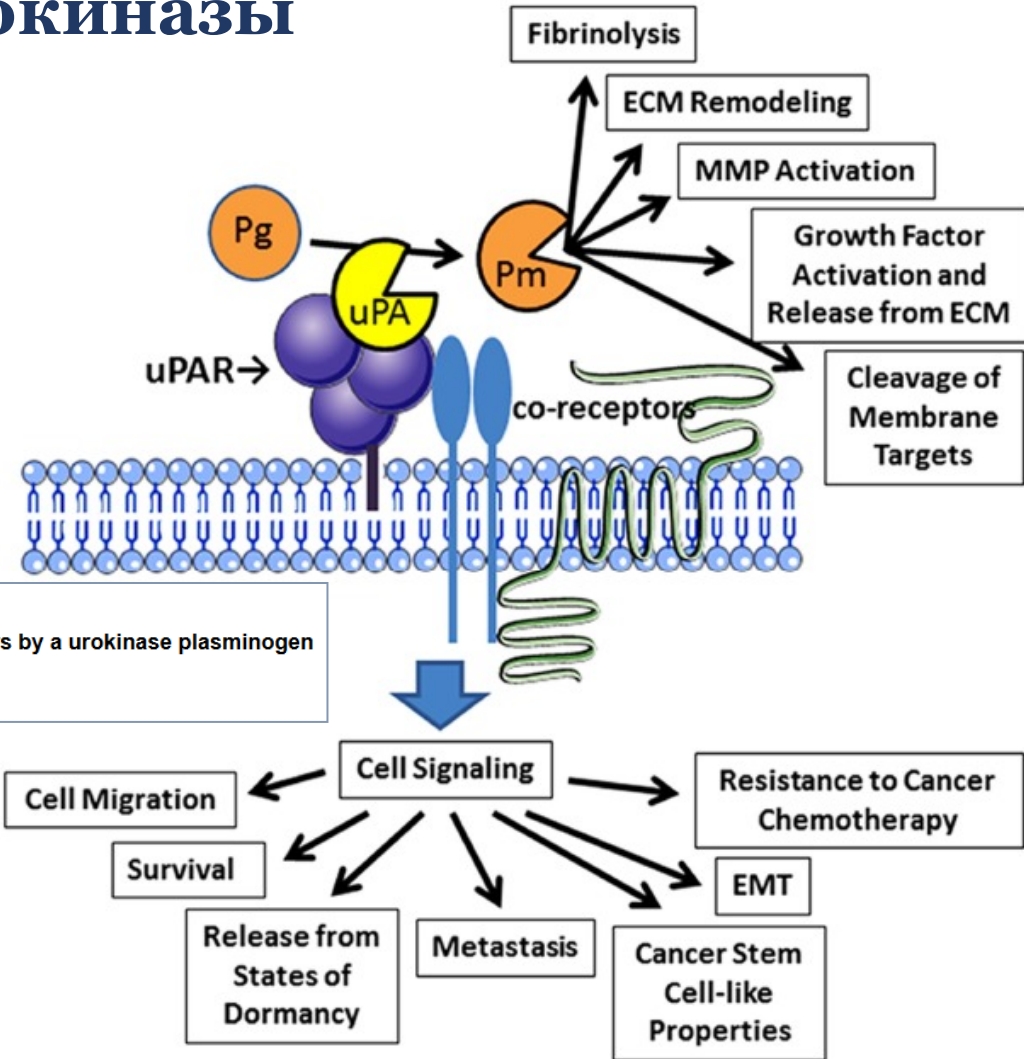
The correlation between urokinase-type plasminogen activator (uPA) expression and tumor cell invasion and metastasis has been well documented. Urokinase converts the zymogen plasminogen to plasmin, a trypsin-like enzyme with broad substrate specificities. Net uPA activity is determined not only by the amount of the enzyme itself, but also by its state of activation and the amount of specific plasminogen activator inhibitors (PAIs) present. Both uPA and its substrate, plasminogen, can bind to cells via specific membrane-associated receptors. Expression of uPA, uPA receptor (uPAR), and PAIs is regulated by growth factors, oncogenes, and other effector molecules. In the present review we discuss the interactions of uPA with its receptor, inhibitors, and substrate and how these interactions influence malignant behavior. We also review recent reports in which investigators have used anti-catalytic antibodies and/or gene transfection to demonstrate that uPA is directly involved in tumor cell invasion and metastasis.

*Proc. Natl. Acad. Sci. USA*  
Vol. 90, pp. 5021-5025, June 1993  
Cell Biology

## Prevention of metastasis by inhibition of the urokinase receptor

*CRAIG W. CROWLEY\*, ROBERT L. COHEN†‡, BRIAN K. LUCAS\*, GUOHUI LIU†, MARC A. SHUMAN†, AND ARTHUR D. LEVINSON\**

\*Department of Cell Genetics, Genentech, Inc., South San Francisco, CA 94080; and †Cancer Research Institute, University of California, San Francisco, CA 94143



Urokinase receptor and resistance to targeted anticancer agents.  
Gonias and Hu. *Front Pharmacol.* 2015

Спасибо за внимание к фенотипу!

