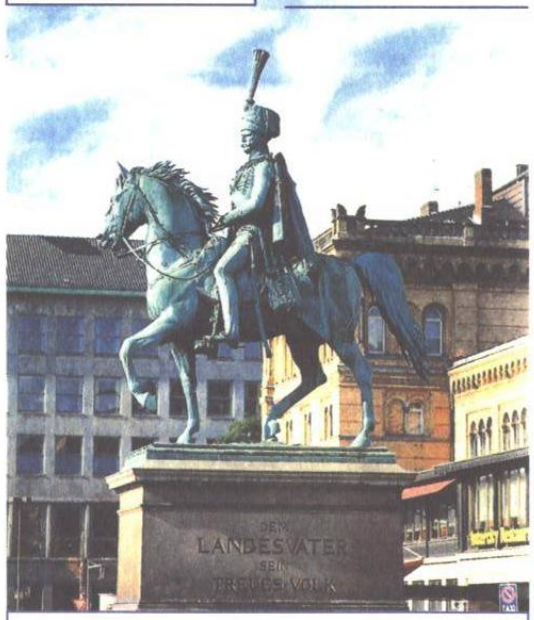
Struensee Haus

PROGRAMM

Hannover-Meeting 2009

NIO NIEDERGELASSENE INTERNISTISCHE ONKOLOGEN Niedersachsen e.V.

State of the Art in Hämatologie und Onkologie



16. / 17. Januar 2009

MARITIM Airport Hotel
Flughafenstraße 5 · 30669 Langenhagen

PROGRAMM

Samstag, 17. Januar 2009

Symposium für Praxis- und Pflegekräfte

Vorsitz: Prof. Dr. U.R. Kleeberg, Hamburg

10.00 Uhr
Ernährung
(Energiestoffwechsel; Wieviel Kalorien benötigt ein Patient?)
E. Gutzmann, Wolfsburg

10.30 Uhr
Neue Substanzen
Wirkung und Nebenwirkung
Prof. U.R. Kleeberg, Hamburg

11.00 Uhr
Palliativversorgung und Hospizarbeit
Dr. R. Charbonnier, Burgdorf

11.30 Uhr
Kaffeepause

11.45 Uhr
Sport und Krebs
Dr. L. Krist, Berlin

12.15 Uhr
Kosmetik und Krebs
C. Rutt, Köln

12.45 Uhr
Verabschiedung
Prof. U.R. Kleeberg, Hamburg

Mittagessen

Veranstalter: NIO Niedersachsen e.V. / APON e.V.

Tagungsort: Maritim Airport Hotel
Flughafenstr. 5, 30669 Hannover-Langenhagen
Telefon (0511) 9 73 70

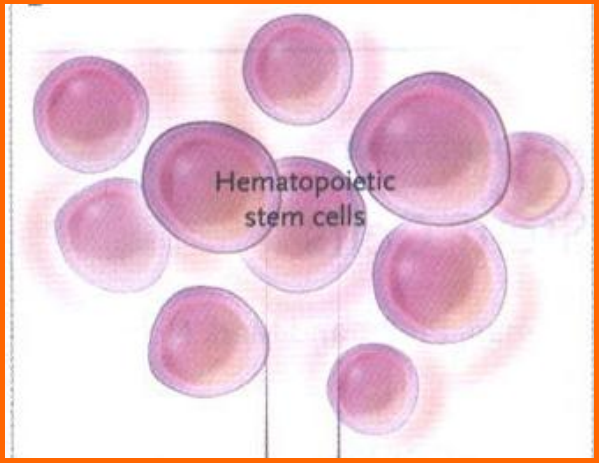
Saal: Langenhagen

Tagungs-organisation: rgb Onkologisches Management GmbH
Paul-Lincke-Straße 14, 31157 Sarstedt
Telefon (05066) 69 20 71, Fax (05066) 69 20 64
e-mail: info@rgb-onkologie.de

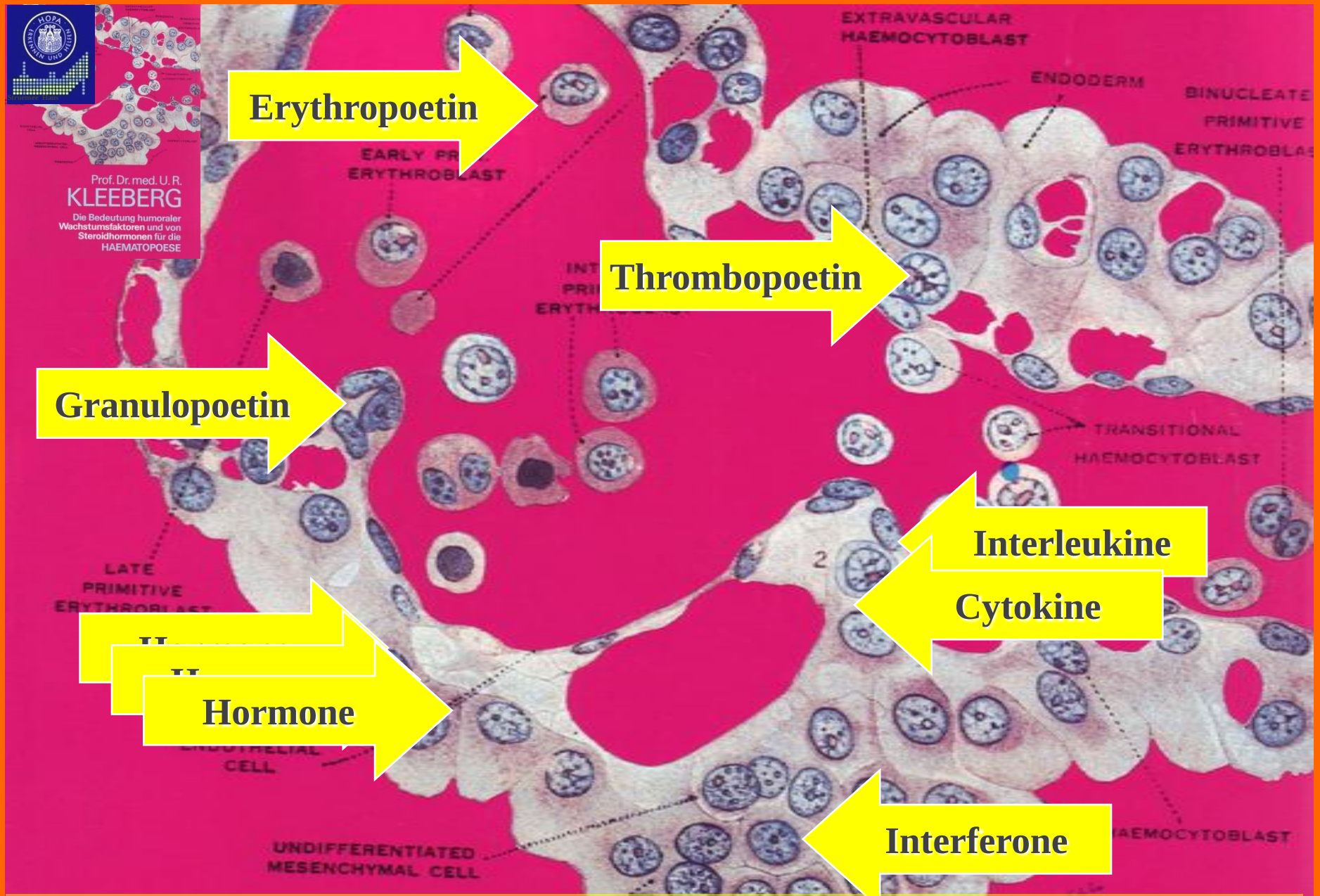
U. R. Kleeberg

Hämatologisch-Onkologische Praxis Altona Tagesklinik Struenseehaus Hamburg

Entdeckung der Stammzelle



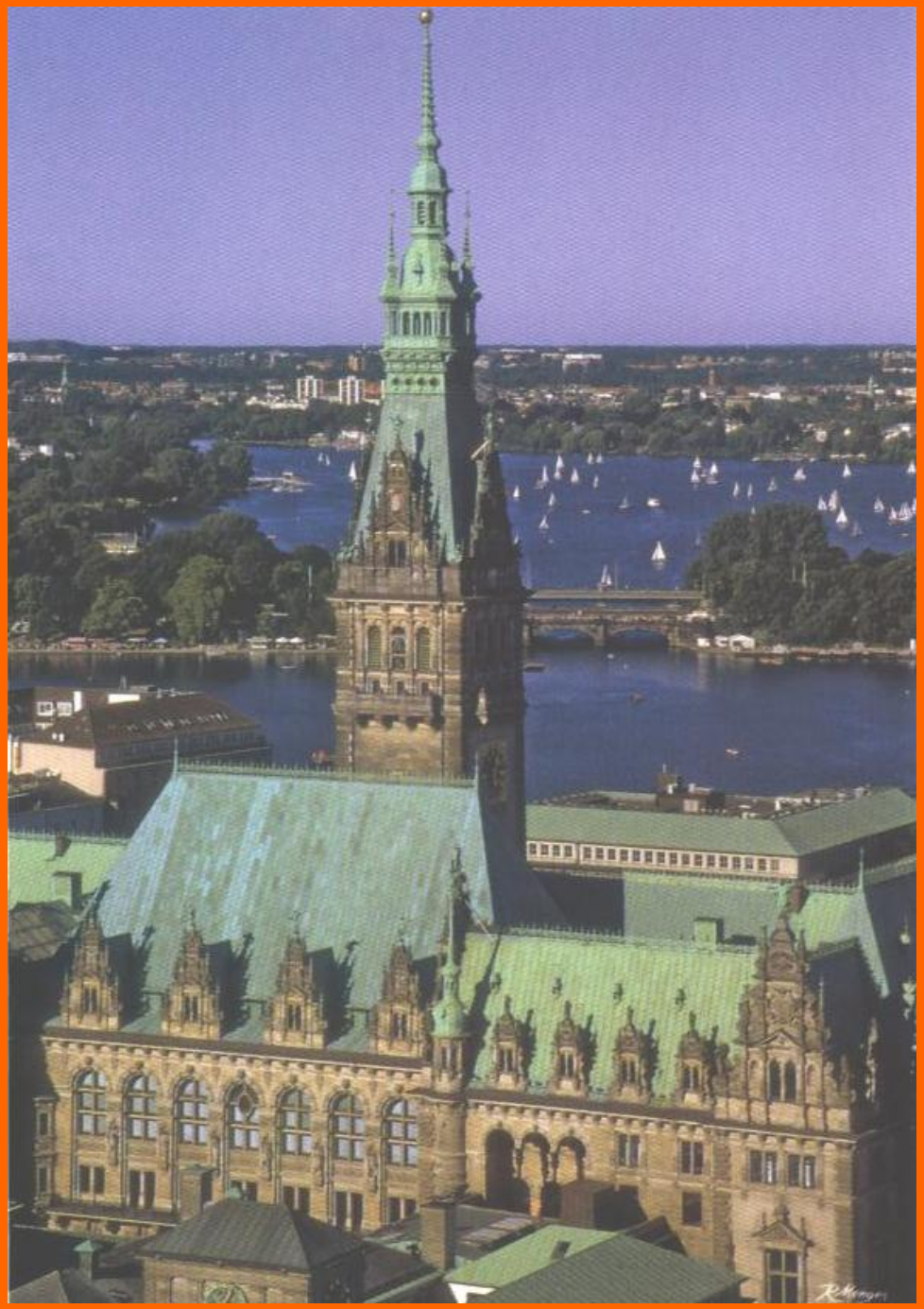
C. T. Jordan: NEJM 2006; 355: 1253-61

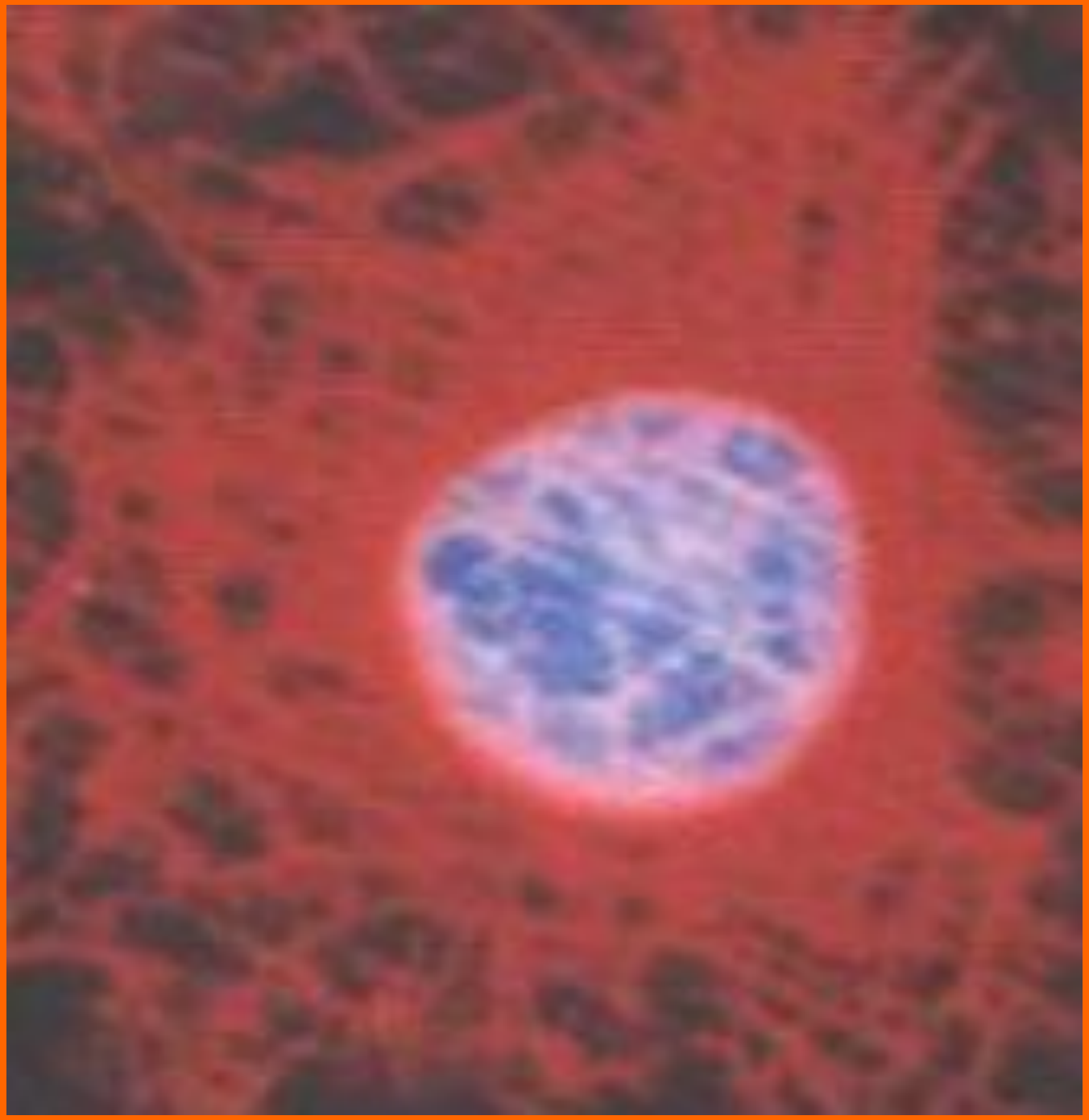


Wachstumsfaktoren ~ Signale

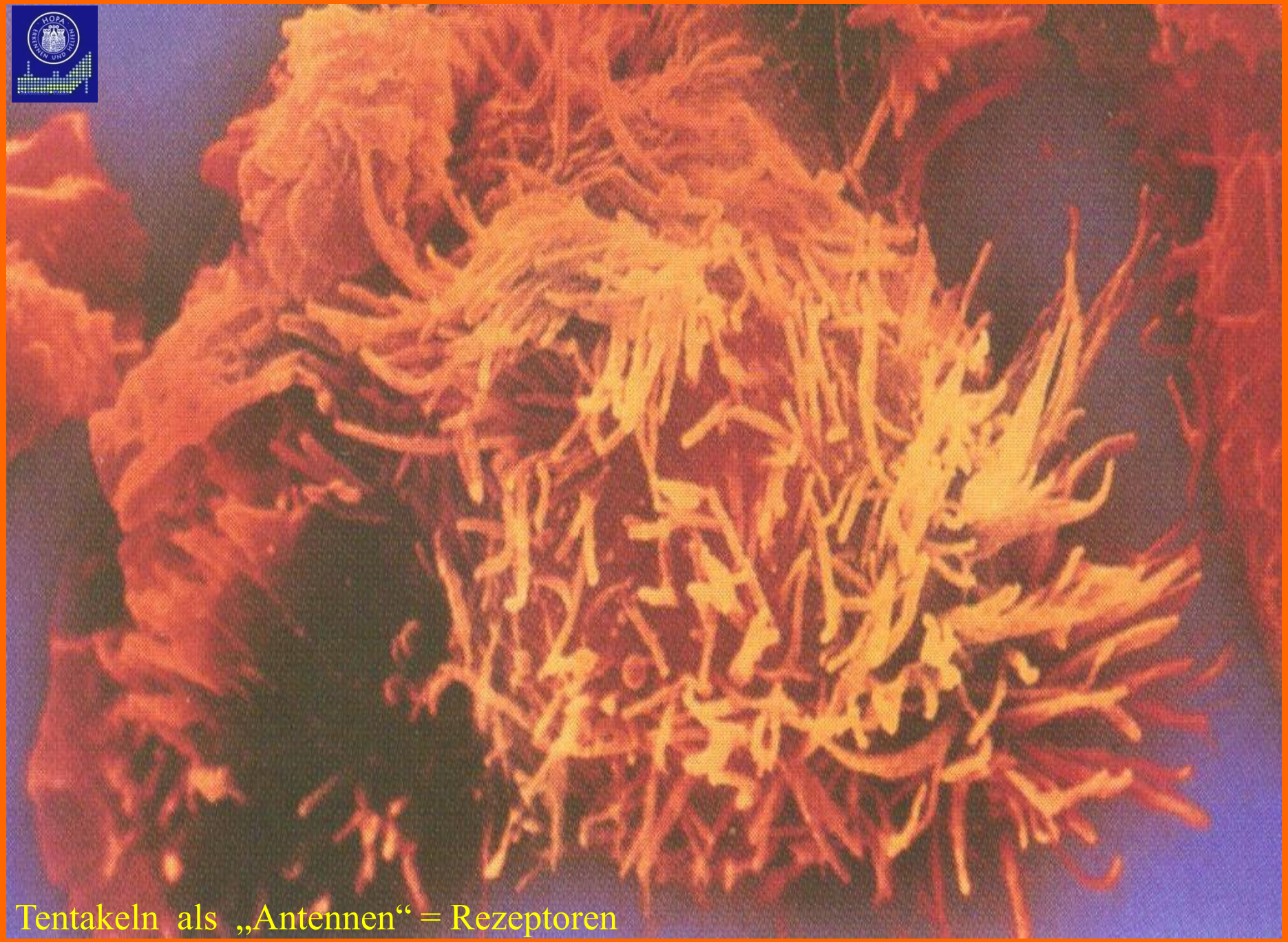
Struensee Haus

Zur Systematik der Signaltransduktion: Der Hamburger Hafen

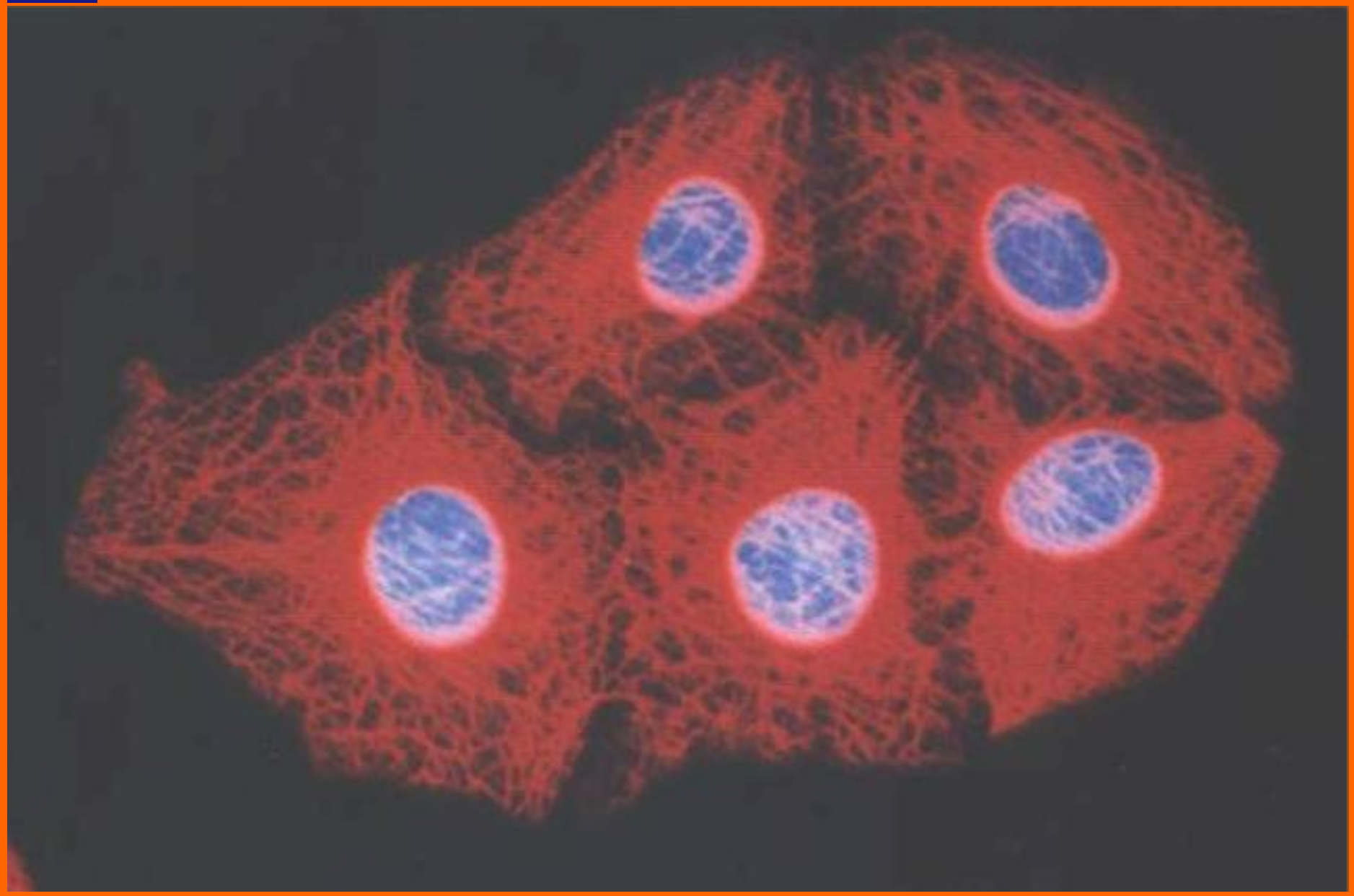




Hämatopoetische Stammzelle

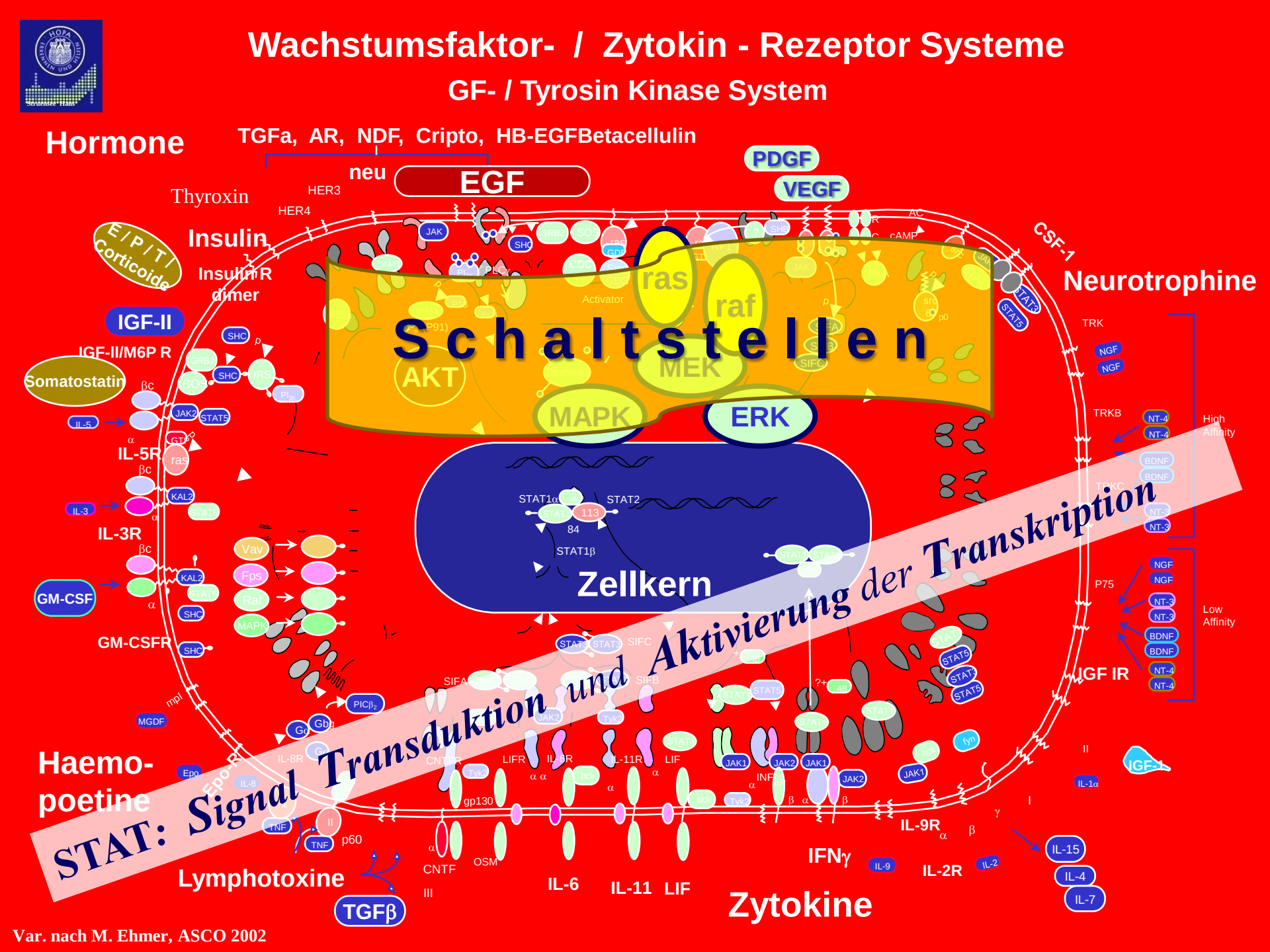


Tentakeln als „Antennen“ = Rezeptoren



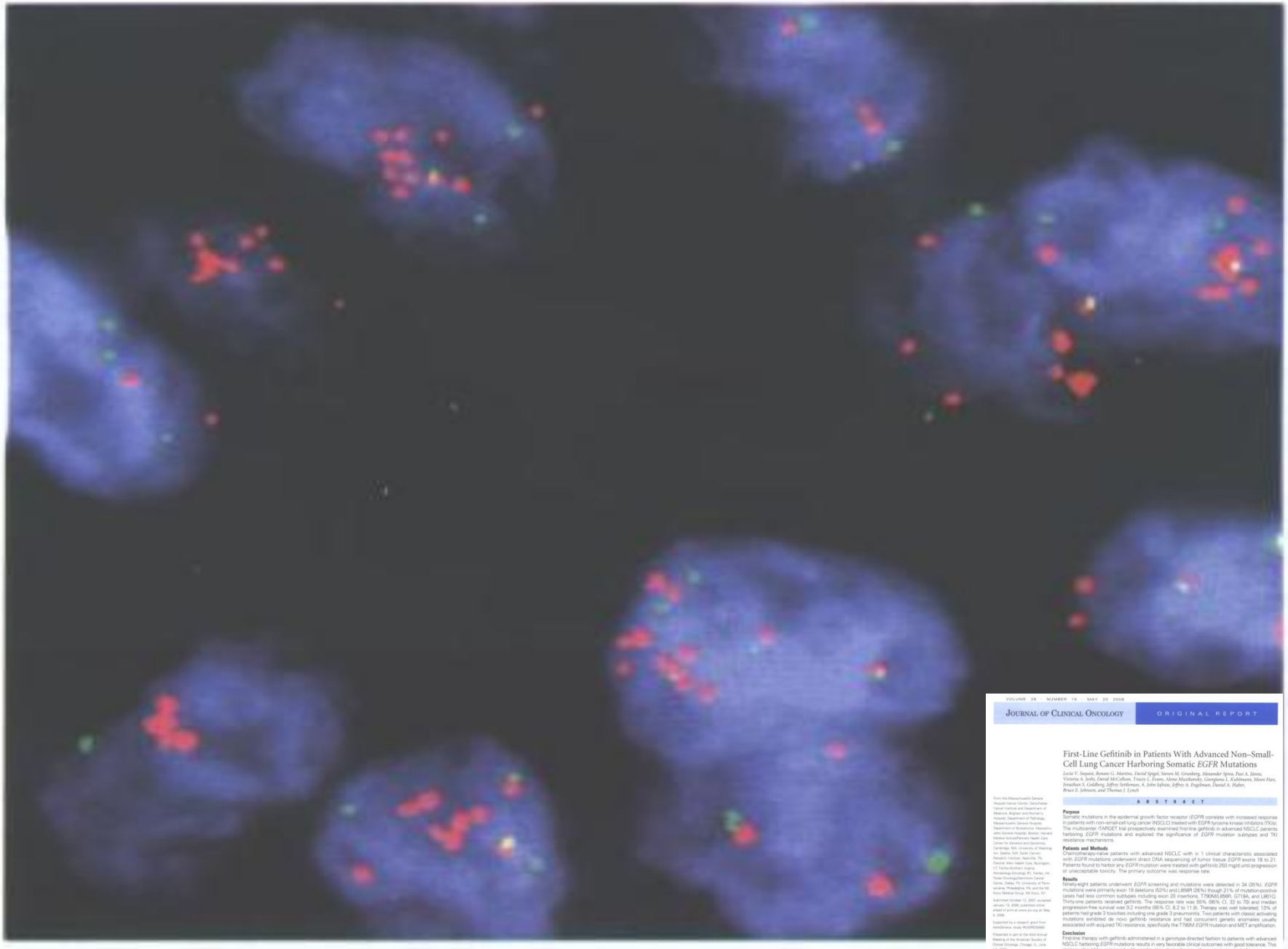
Wachstumsfaktor- / Zytokin - Rezeptor Systeme

GF- / Tyrosin Kinase System



Var. nach M. Ehmer, ASCO 2002

1734
1734



VOLUME 26 · NUMBER 15 · MAY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

First-Line Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer Harboring Somatic *EGFR* Mutations

Lecia V. Sequist, Renate G. Martins, David Spigel, Steven M. Grunberg, Alexander Spira, Pasi A. Jänne, Victoria A. Joshi, David McCollum, Tracey L. Evans, Alona Muzikansky, Georgeana L. Kuhlmann, Moon Hee, Jonathan S. Goldberg, Jeffrey Settleman, A. John Iafrate, Jeffrey A. Engelman, Daniel A. Haber, Bruce E. Johnson, and Thomas J. Lynch

From the Massachusetts General Hospital Cancer Center, Dana-Farber Cancer Institute and Department of Medicine, Brigham and Women's Hospital, Department of Pathology, Massachusetts General Hospital, Department of Biostatistics, Massachusetts General Hospital, Boston, Harvard Medical School/Partners Health Care Center for Genetics and Genomics, Cambridge, MA; University of Washington, Seattle, WA; Sarah Cannon Research Institute, Nashville, TN; Fletcher Allen Health Care, Burlington, VT; Fairfax/Northern Virginia Hematology-Oncology PC, Fairfax, VA; Texas Oncology/Sammons Cancer Center, Dallas, TX; University of Pennsylvania, Philadelphia, PA; and the Toronto Medical Group, Toronto, ON.

Submitted October 12, 2007; accepted January 15, 2008; published online ahead of print at www.jco.org on May 5, 2008.

Supported by a research grant from AstraZeneca, study IRUSFIRS3880.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007.

Terms in italic are defined in the glossary, found at the end of this article and online at www.jco.org.

A B S T R A C T

Purpose

Somatic mutations in the epidermal growth factor receptor (*EGFR*) correlate with increased response in patients with non–small-cell lung cancer (NSCLC) treated with *EGFR* tyrosine kinase inhibitors (TKIs). The multicenter iTARGET trial prospectively examined first-line gefitinib in advanced NSCLC patients harboring *EGFR* mutations and explored the significance of *EGFR* mutation subtypes and TKI resistance mechanisms.

Patients and Methods

Chemotherapy-naïve patients with advanced NSCLC with ≥ 1 clinical characteristic associated with *EGFR* mutations underwent direct DNA sequencing of tumor tissue *EGFR* exons 18 to 21. Patients found to harbor any *EGFR* mutation were treated with gefitinib 250 mg/d until progression or unacceptable toxicity. The primary outcome was response rate.

Results

Ninety-eight patients underwent *EGFR* screening and mutations were detected in 34 (35%). *EGFR* mutations were primarily exon 19 deletions (53%) and L858R (26%) though 21% of mutation-positive cases had less common subtypes including exon 20 insertions, T790M/L858R, G719A, and L861Q. Thirty-one patients received gefitinib. The response rate was 55% (95% CI, 33 to 70) and median progression-free survival was 9.2 months (95% CI, 6.2 to 11.8). Therapy was well tolerated; 13% of patients had grade 3 toxicities including one grade 3 pneumonitis. Two patients with classic activating mutations exhibited de novo gefitinib resistance and had concurrent genetic anomalies usually associated with acquired TKI resistance, specifically the T790M *EGFR* mutation and MET amplification.

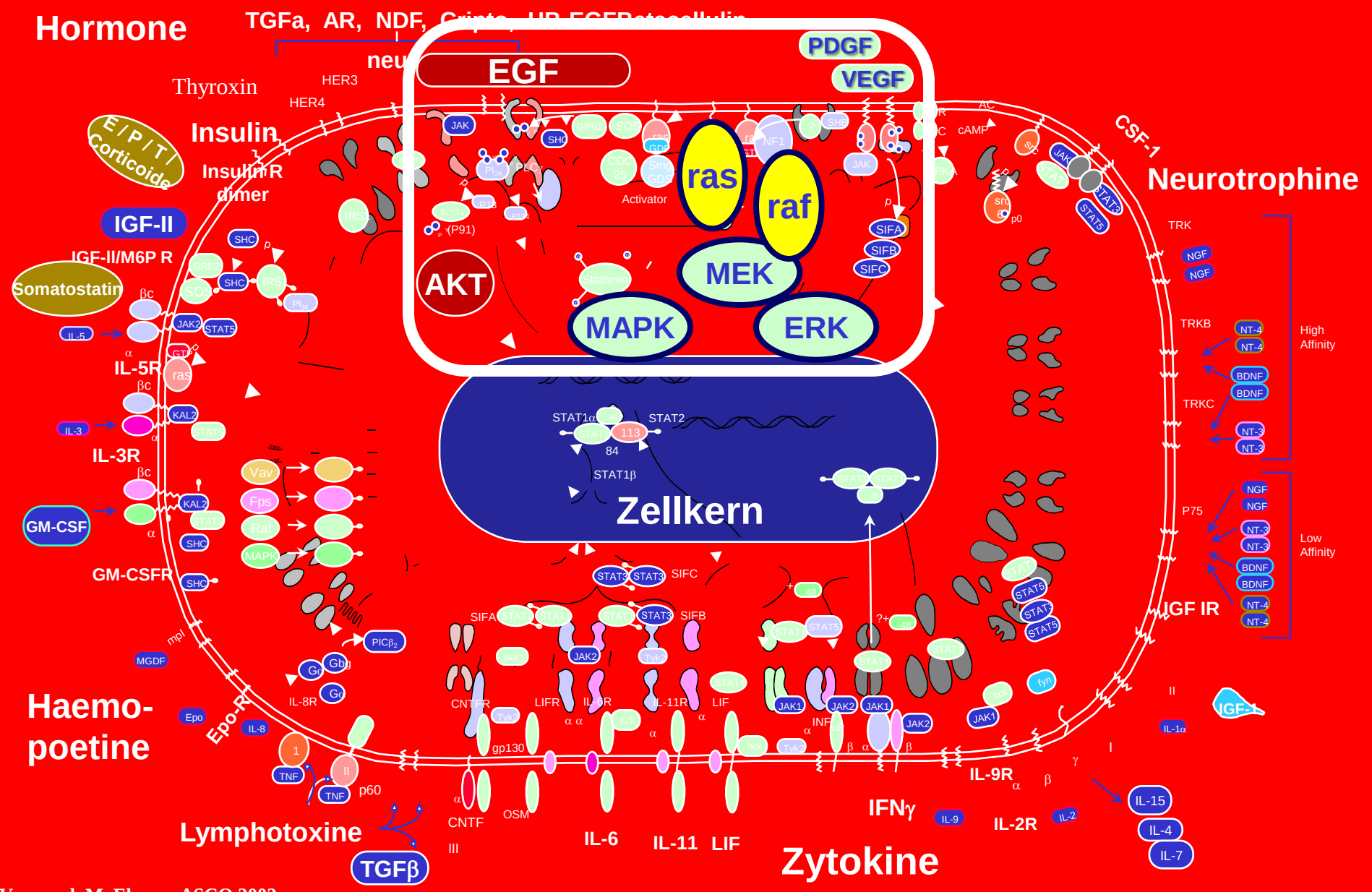
Conclusion

First-line therapy with gefitinib administered in a genotype-directed fashion to patients with advanced NSCLC harboring *EGFR* mutations results in very favorable clinical outcomes with good tolerance. This strategy should be compared with combination chemotherapy, the current standard of care.

J Clin Oncol 26:2442-2449. *© 2008 by American Society of Clinical Oncology*

Wachstumsfaktor- / Zytokin - Rezeptor Systeme

GF- / Tyrosin Kinase System



Var. nach M. Ehmer, ASCO 2002

T. Pawson / European Journal of Cancer Vol. 38 Suppl. 5 (2002) S3–S10

RTK

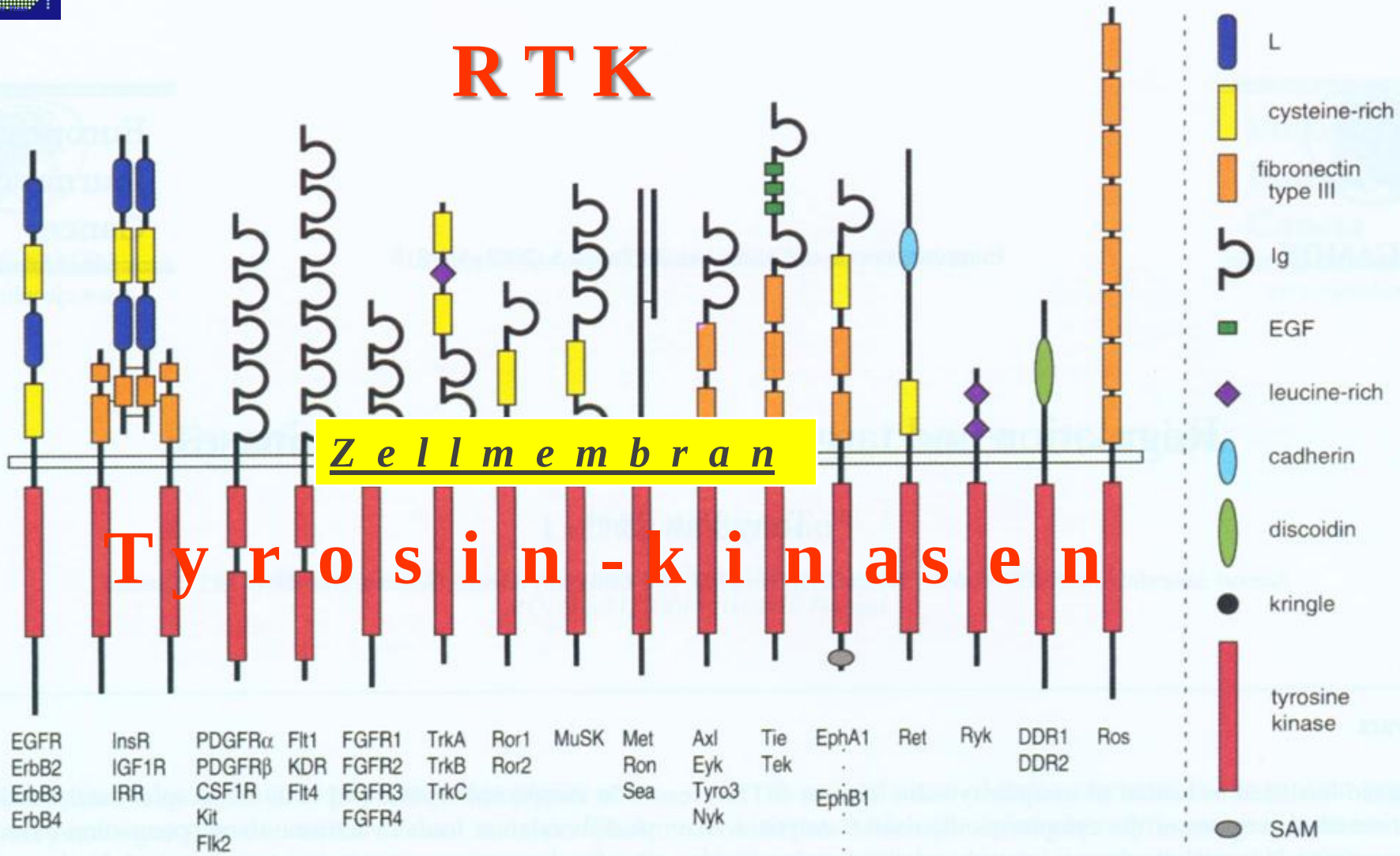


Fig. 1. Schematic representation of structural components of receptor tyrosine kinase (RTK) subfamilies.

Status of Epidermal Growth Factor Receptor Antagonists in the Biology and Treatment of Cancer

By John Mendelsohn and Jose Baselga

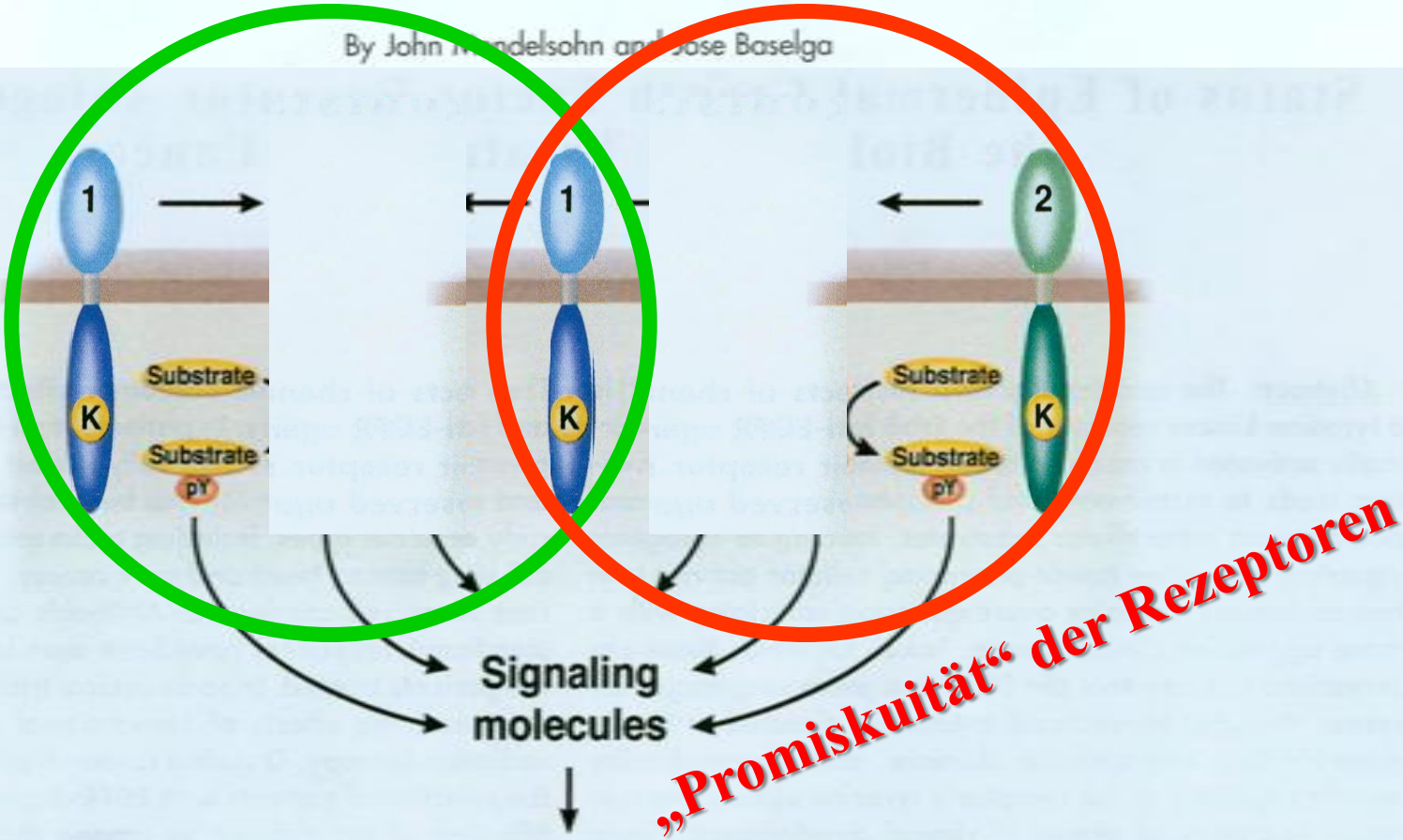
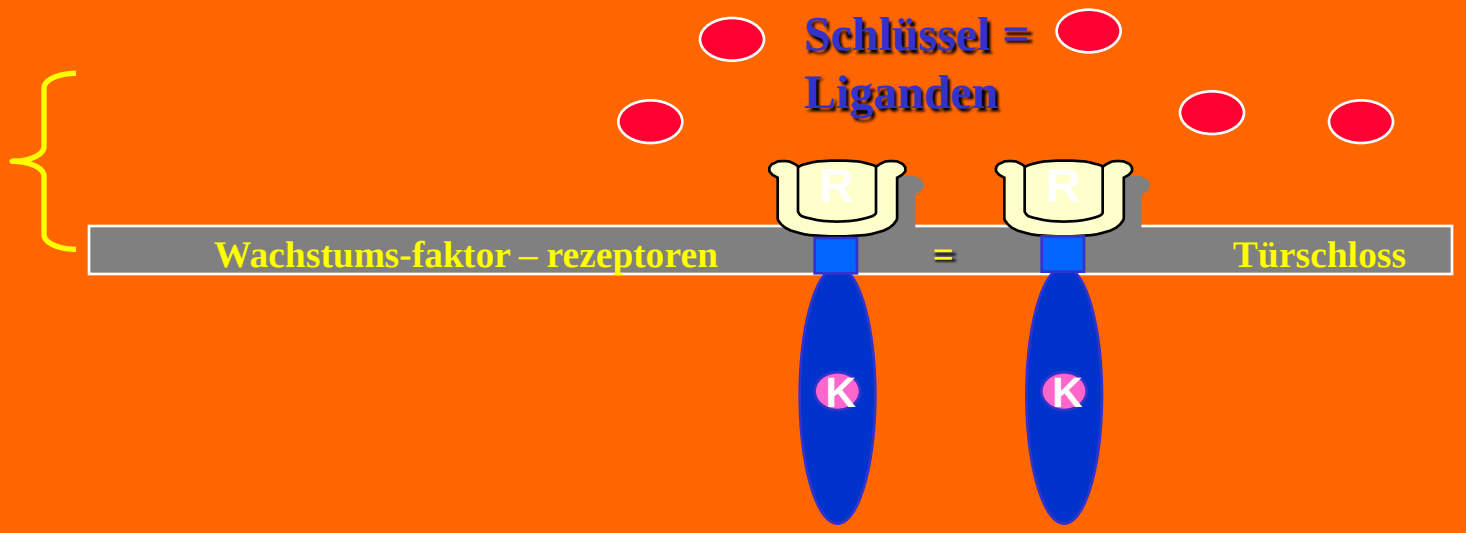


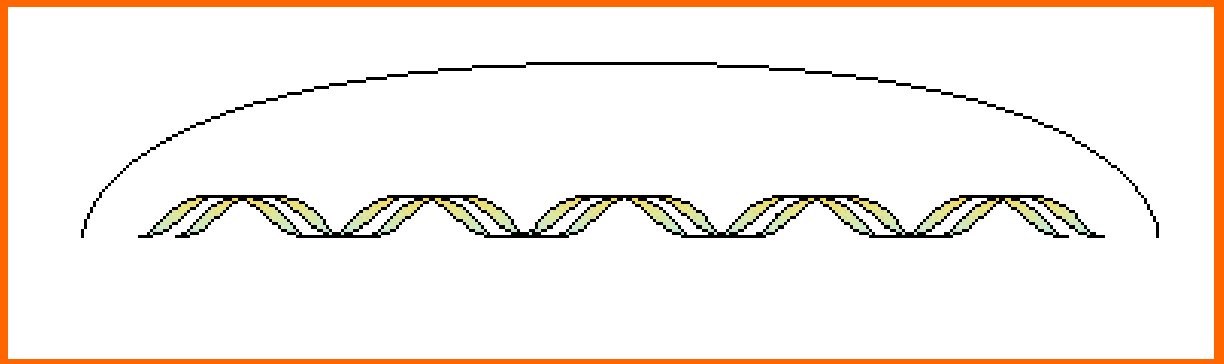
Fig 1. Mechanisms of receptor activation. Epidermal growth factor receptors and members of the receptor family (HER2/3/4) become activated by dimerization. The mechanisms that promote the formation of receptor dimers include ligand binding, receptor overexpression, and transactivation (heterodimerization). After receptor dimerization, activation of the intrinsic protein tyrosine kinase activity occurs, resulting in tyrosine autophosphorylation. These events result in the recruitment and phosphorylation of several intracellular substrates, leading to mitogenic signaling and other cellular activities.

Trondheim
im Mai 2008

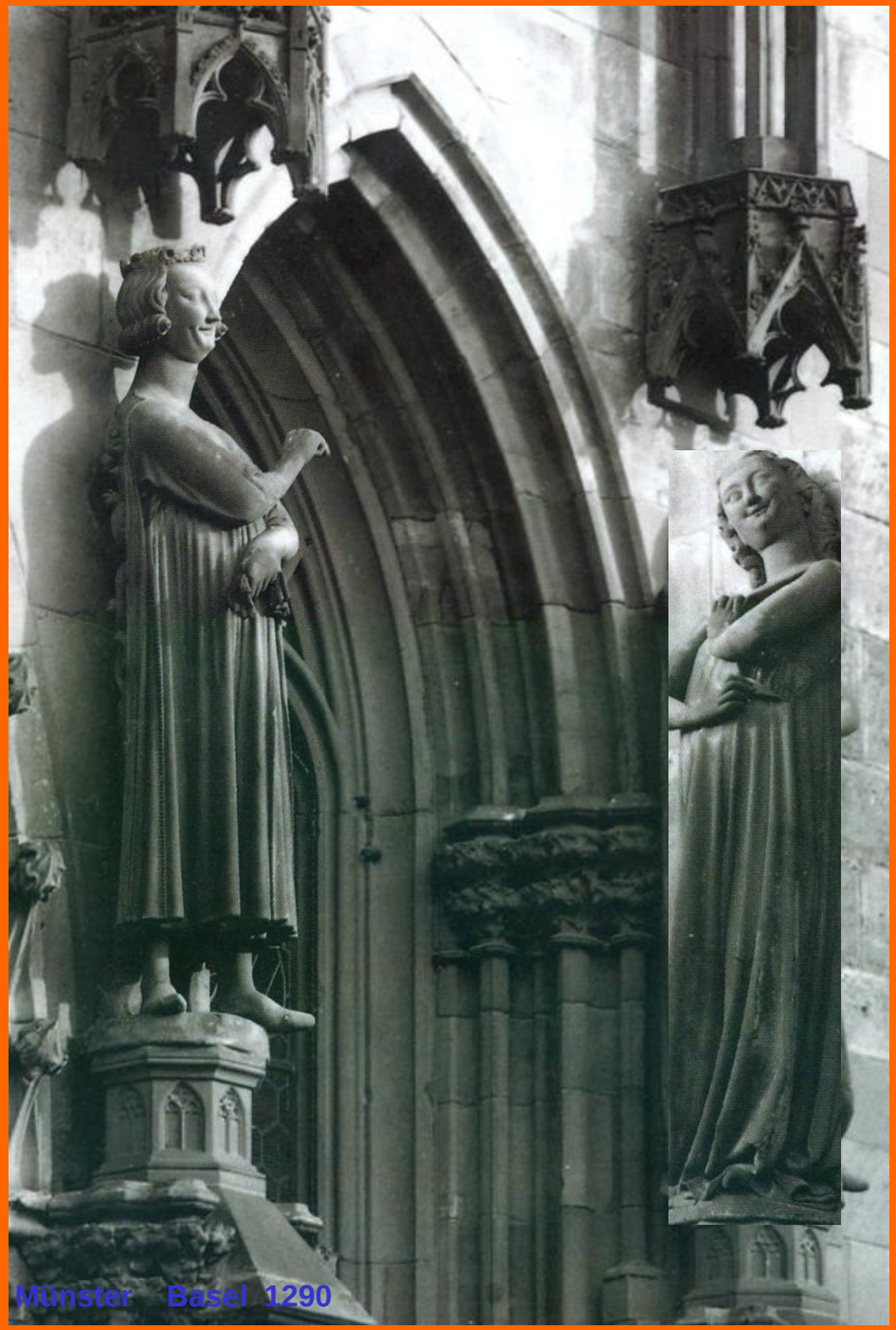
Zell – oberfläche



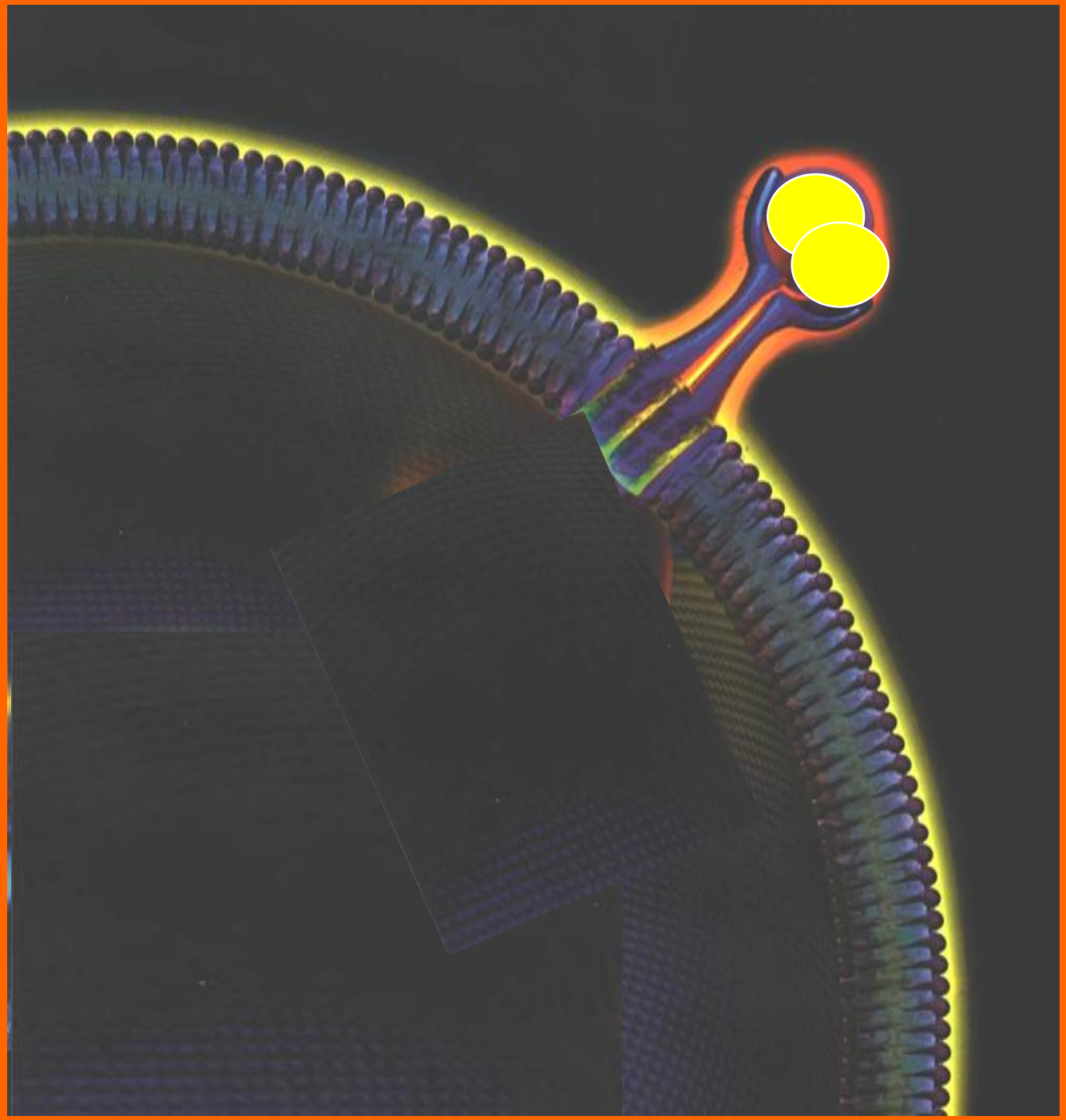
Zellkern



Var. nach Josep Tabenero, Vall d'Hebron Universitätskliniken, Barcelona, Spanien



Verführer und törichte Jungfrau Münster Basel 1290

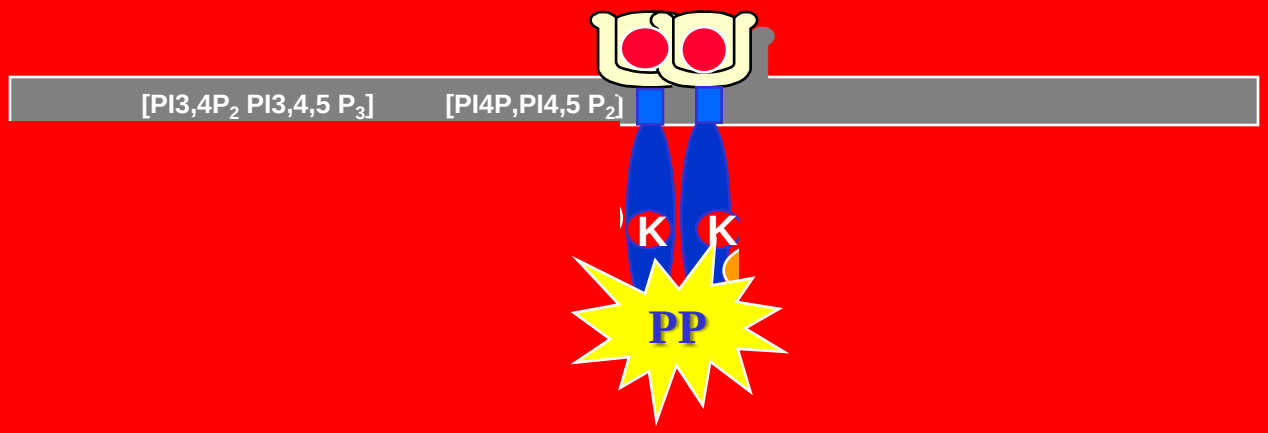


Signal

The journal of EGFR-targeted cancer therapy

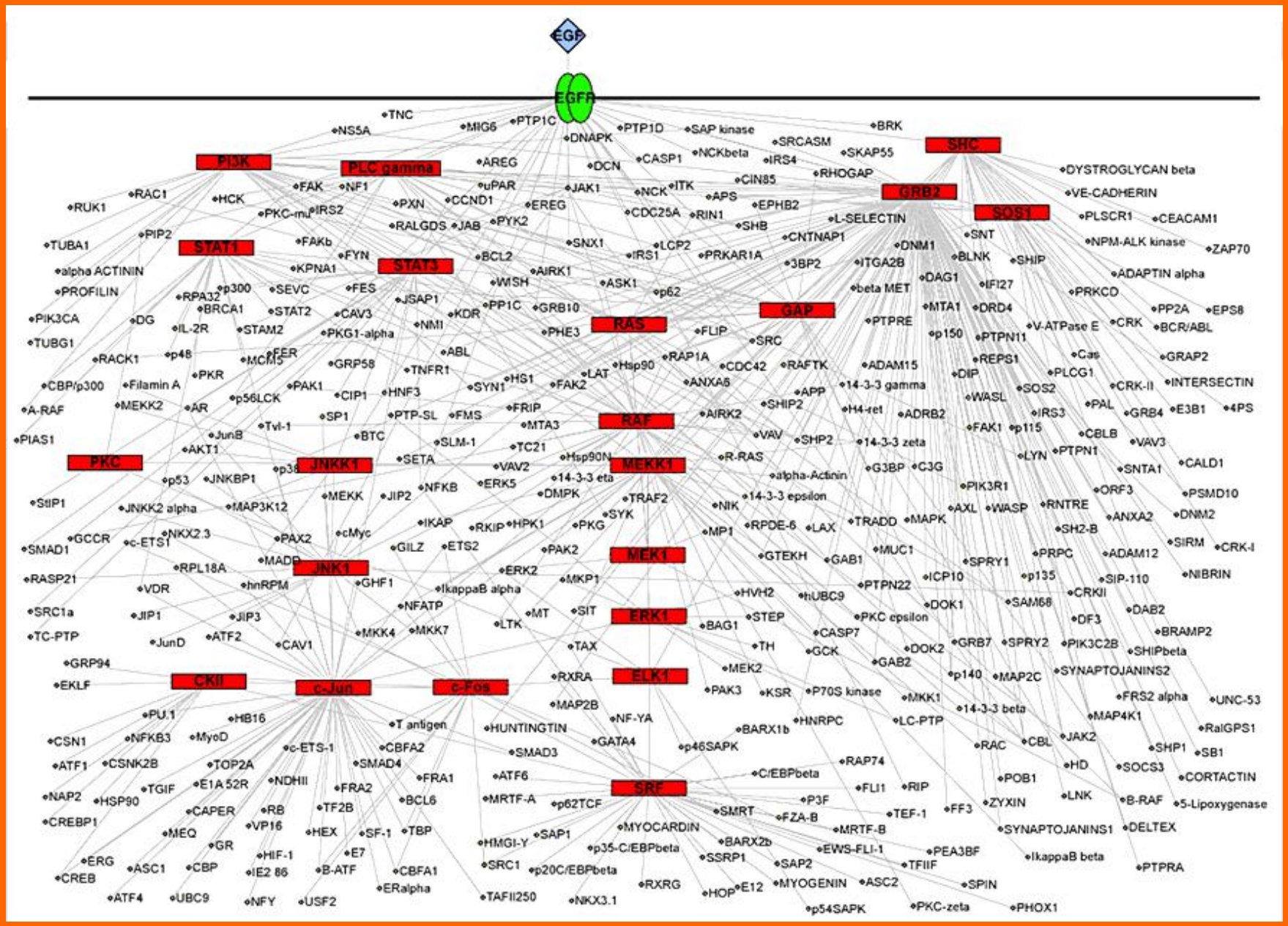
Var. nach Josep Tabenero, Vall d‘Hebron Universitätskliniken, Barcelona, Spanien

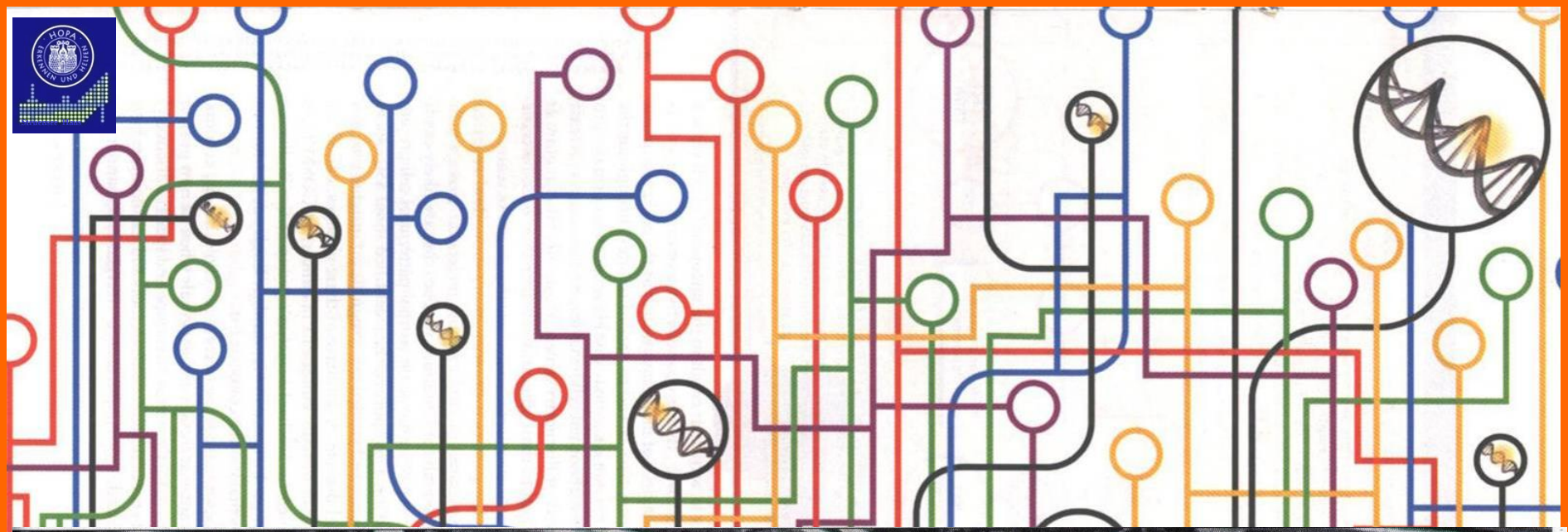
Zell – oberfläche

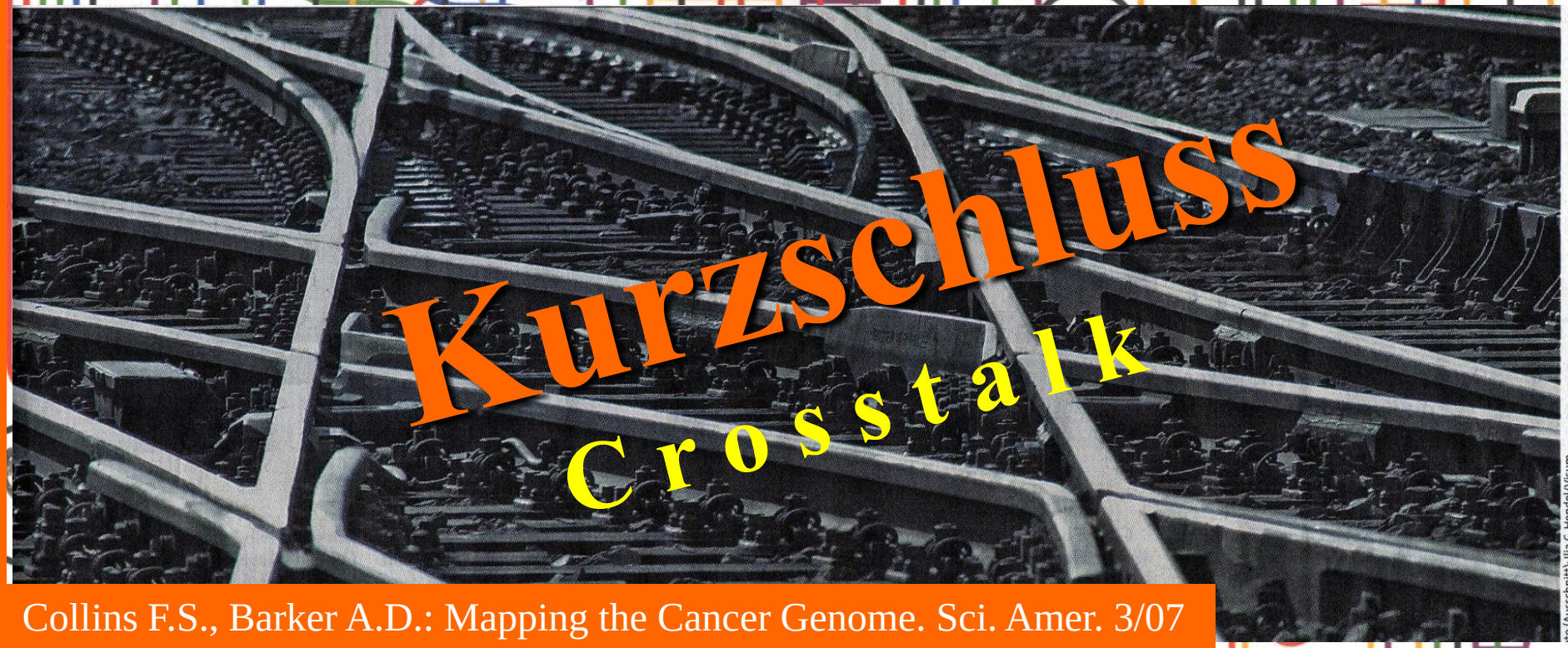


Hochkomplexe Signalnetzwerke

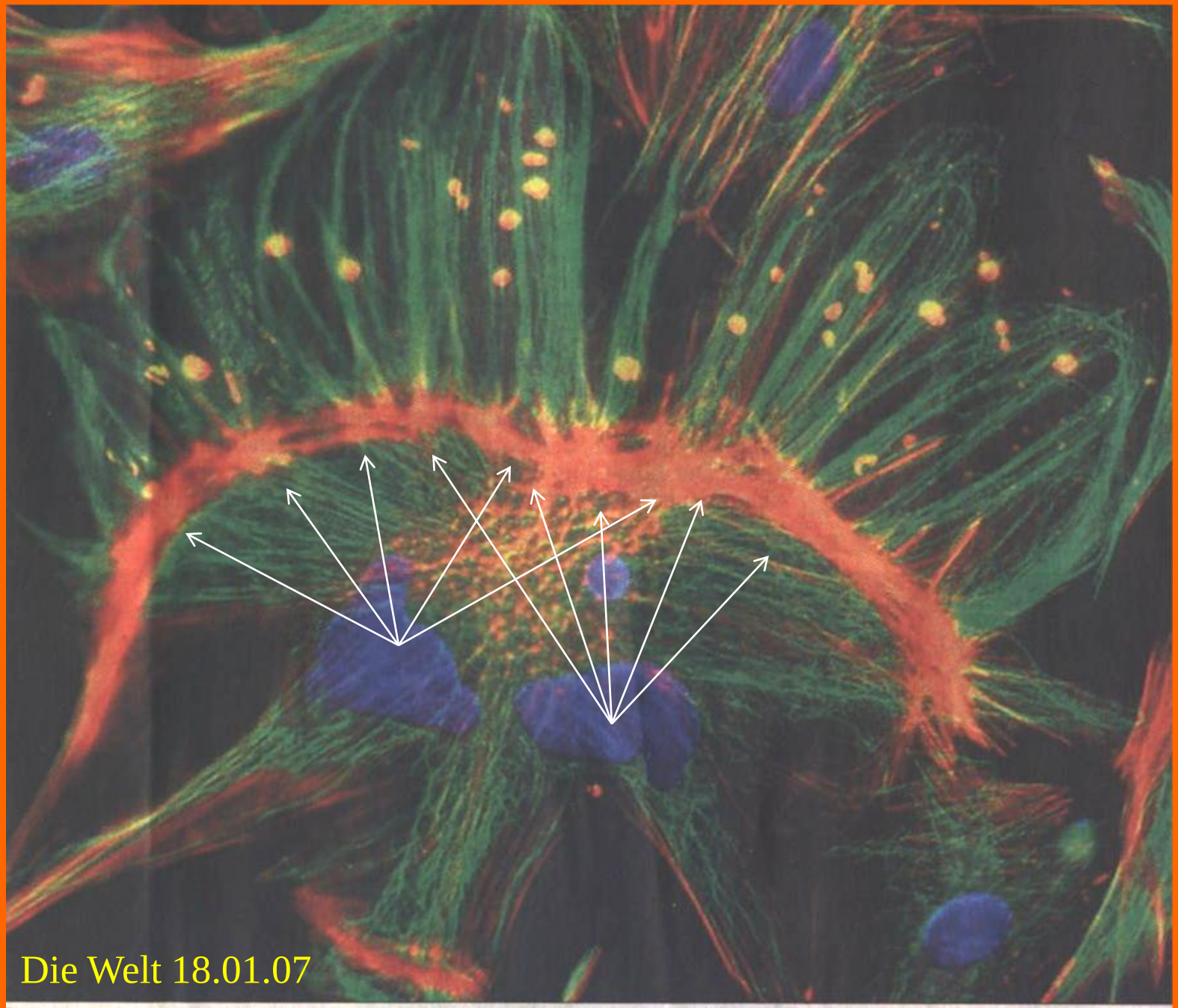
Universitätsklinikum Hamburg-Eppendorf





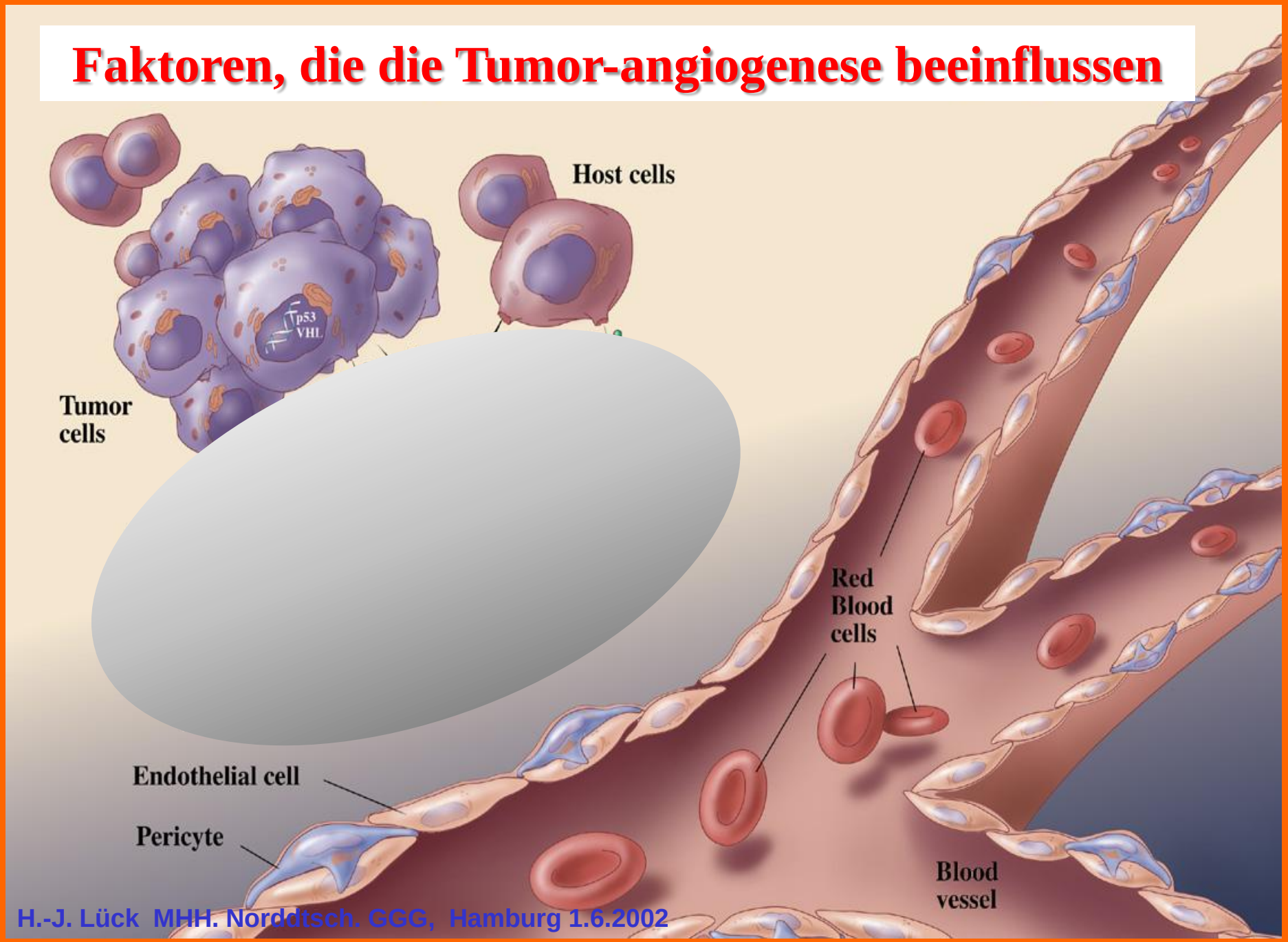


Collins F.S., Barker A.D.: Mapping the Cancer Genome. Sci. Amer. 3/07

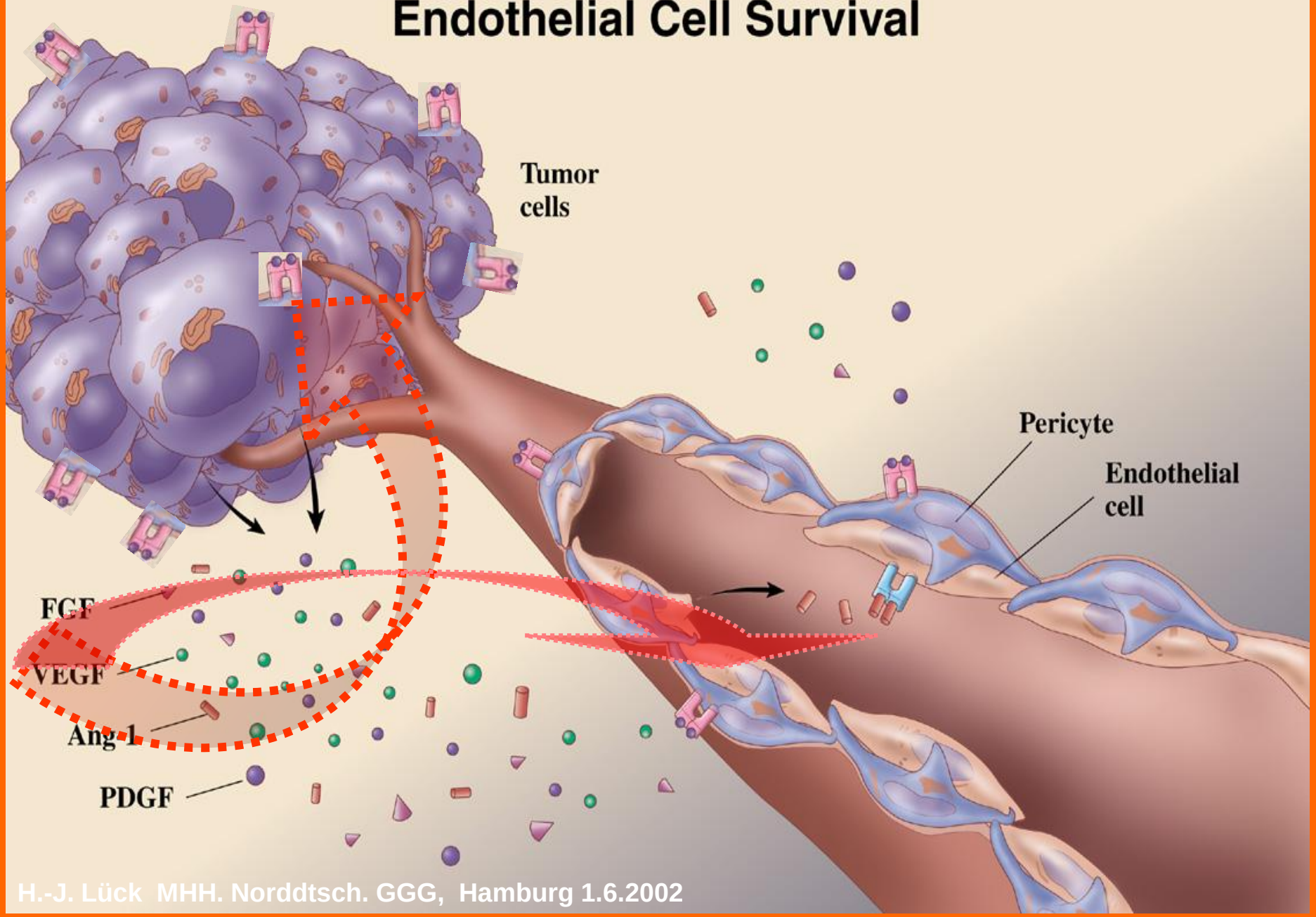


Ästhetik der Unsicherheit: Krebszellen unter dem Fluoreszenzmikroskop (Zellkerne: blau) FOTO: MAURITIUS

Faktoren, die die Tumor-angiogenese beeinflussen



Endothelial Cell Survival

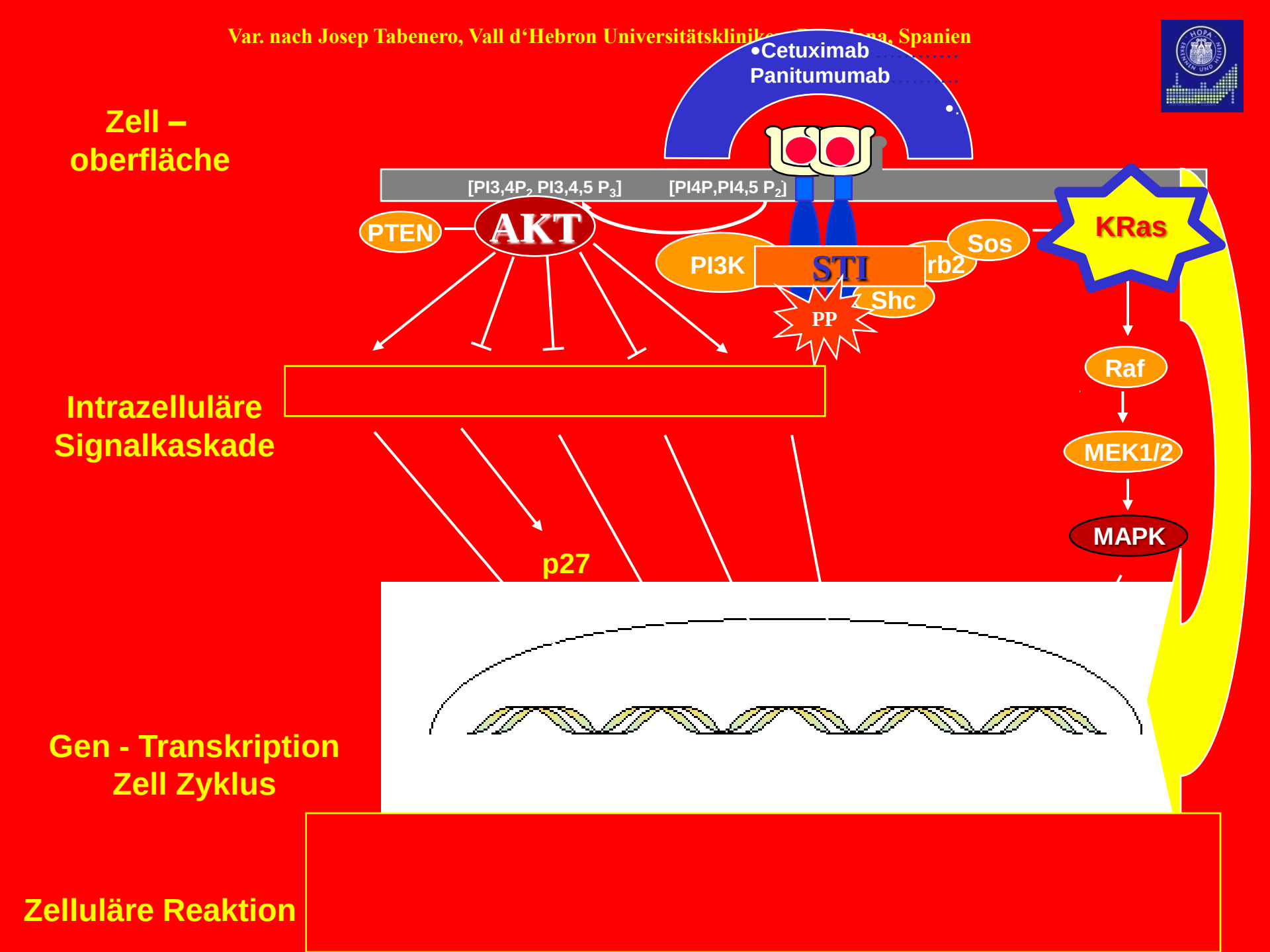


Zellbiologie Universität Heidelberg

Signal

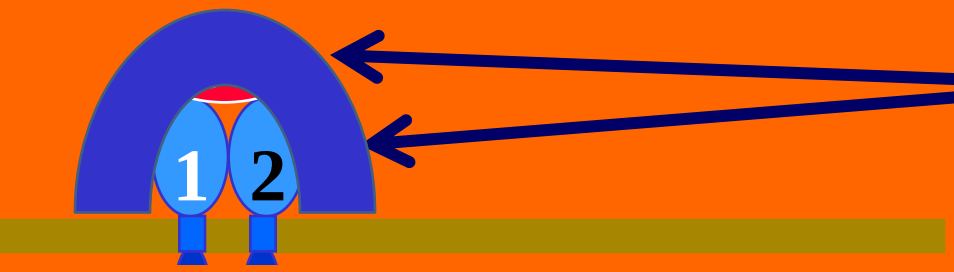
The journal of EGFR-targeted cancer therapy

Var. nach Josep Tabenero, Vall d'Hebron Universitätsklinik[illegible]na, Spanien



Bussalpe, Grindelwald 8/05

Kleine Moleküle: Therapeutische Zielstrukturen



Anti-EGFR / HER MAK

Anti-HER1, HER2, HER4 Tyrosinkinase-Inhibitoren

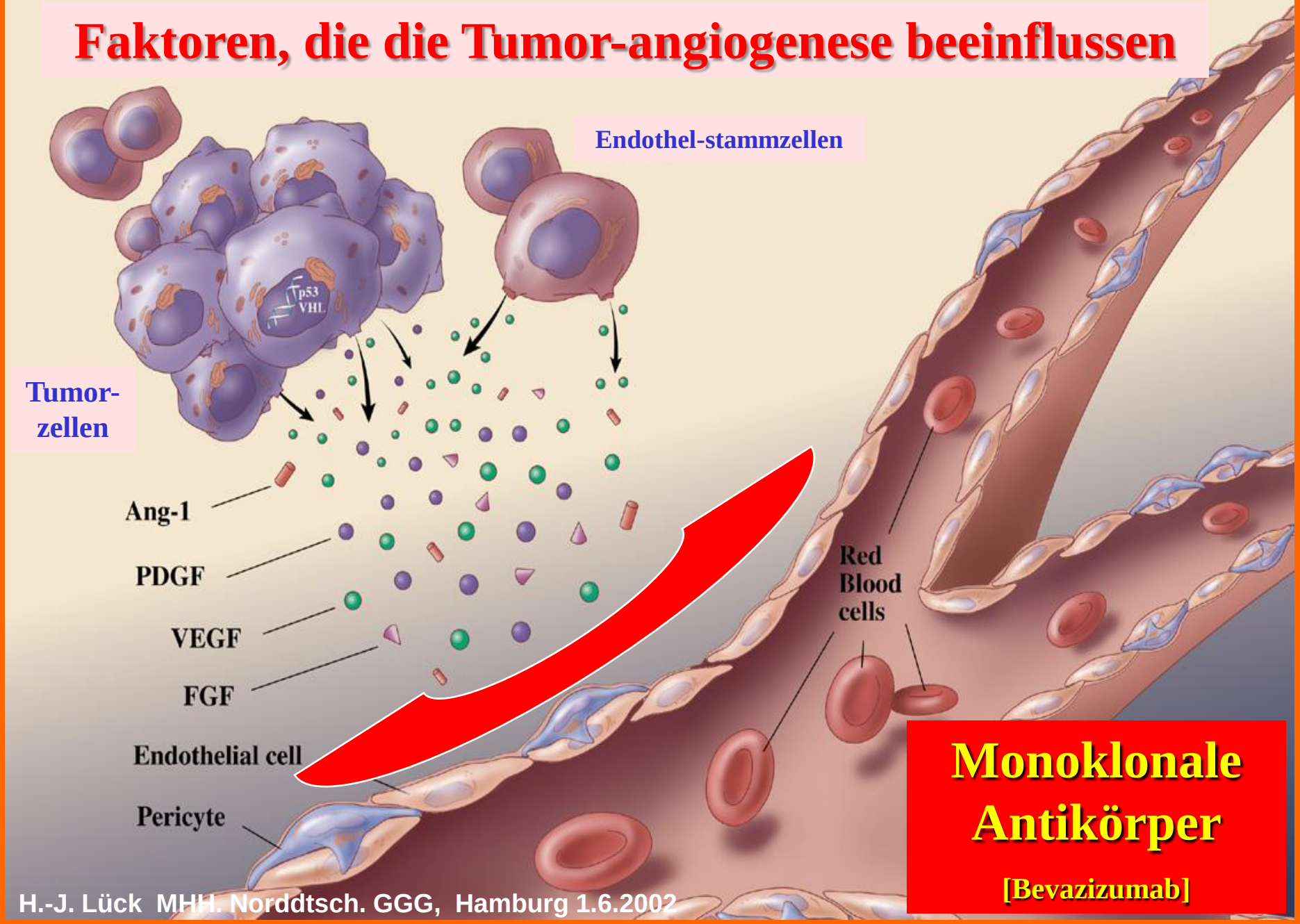
RAS-Farnesyltransferase-Inhibitoren

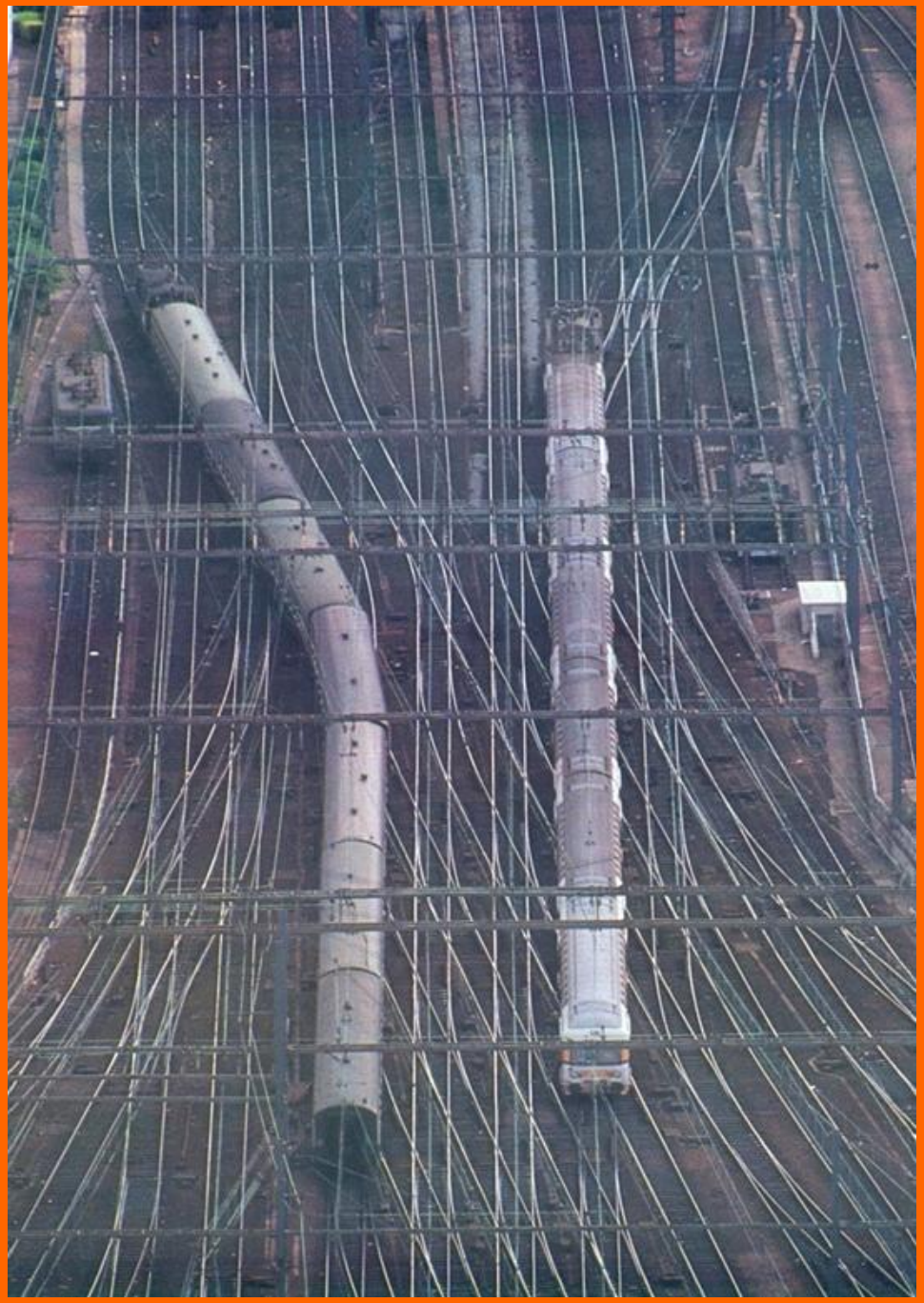
RAF- Inhibitoren

MEK- Inhibitoren

mTOR- Inhibitoren

Faktoren, die die Tumor-angiogenese beeinflussen

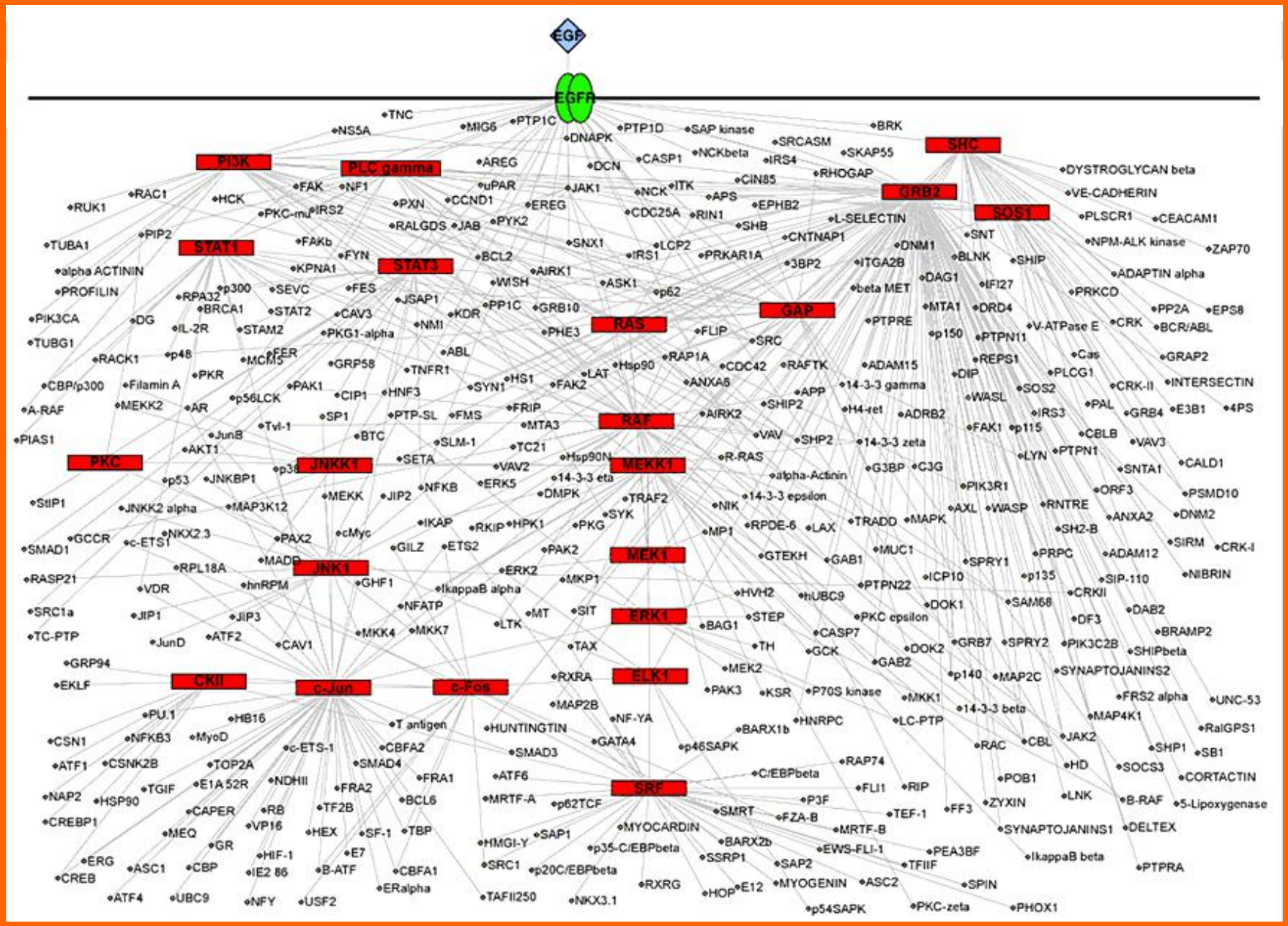




D.C. Lustig 1990
Eisenbahnen der Welt

Hochkomplexe Signalnetzwerke

Universitätsklinikum Hamburg-Eppendorf



Stellwerk Maschen

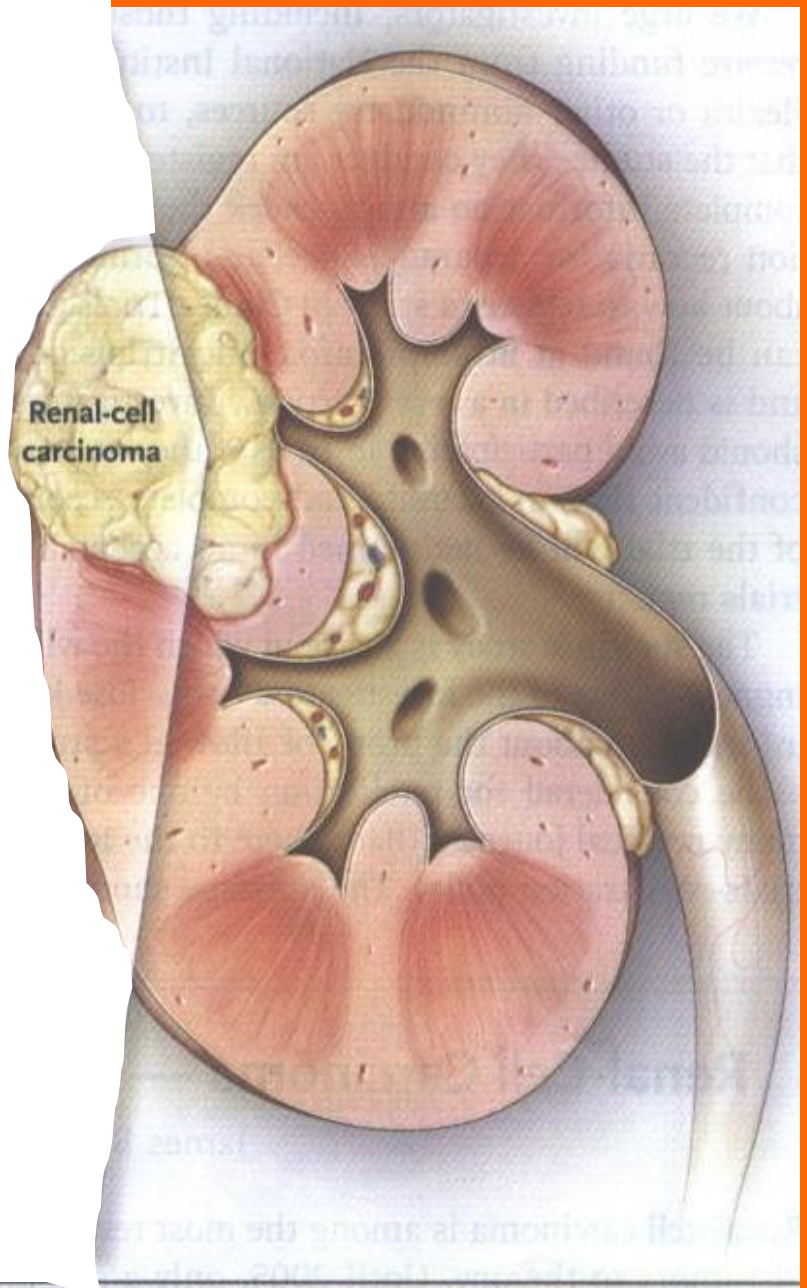


Figure 1. Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma.

Das Nebenwirkungsprofil von Nexavar

Mehrheit der Nebenwirkungen waren Grad 1 und 2

Häufig:	**Hauttoxizität**	**66%**
	Hand-Fuß-Reaktion	**62%**
	Fatigue	**73%**
	Schmerzen	**58%**
	Diarrhoe	**58%**
Bluthochdruck Grad 3		**31%**

Inzidenz (%) nicht-hämatologischer UE, die bei ≥10% der Patienten auftraten

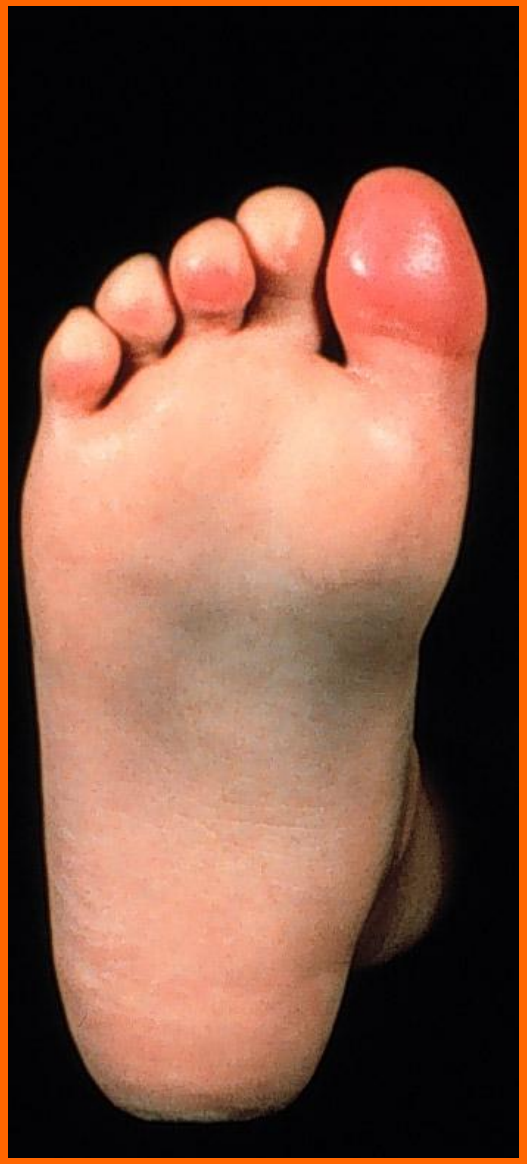
Unerwünschtes Ereignis	Sunitinib (N = 63)	
	Grad 1-2	Grad 3/4
Müdigkeit/Asthenie	43	22 / 5
Schmerzen/Myalgie	43	14 / 3
Übelkeit/Erbrechen	43	10 / 0
Stomatitis/Mukositis	41	3 / 0
Dyspnoe	21	13 / 0
Appetitlosigkeit, Gewichtsabnahme	30	5 / 0
Diarrhoe	27	3 / 0
Geschmacksstörungen	25	0 / 0
Kopfschmerzen	19	5 / 0
Husten	21	2 / 0

Inzidenz (%) nichthämatologischer UE, die bei ≥10% der Patienten auftraten (Forts.)

Unerwünschtes Ereignis	Sunitinib (N = 63)	
	Grad 1-2	Grad 3/4
Obstipation	21	0 / 0
Periphere Ödeme	14	2 / 0
Benommenheit	14	0 / 0
Dyspepsie	14	0 / 0
Mundtrockenheit	13	0 / 0
Depression	10	2 / 0
Hauttrockenheit	11	0 / 0
Hypertonie	6	5 / 0
Hautausschlag	11	0 / 0
Hautverfärbung	11	0 / 0

Socinski et al. ASCO 2006; Abstract 7001.

Hand–Fuß-Hautreaktion



1 Robert C, Soria J-C, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet 2005;6:491–500.
2. Sorafenib prescribing information 2005, available at www.nexavar.com

Hand – Fuß – Syndrom Grad III

Hautverfärbung

1 Robert C, Soria J-C, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet 2005;6:491–500.

2. Sorafenib prescribing information 2005, available at www.nexavar.com

Hautveränderungen

Kutane Nebenwirkungen
Behandlungsvorschläge

Feuchtigkeitscreme	**morgens**		**-----**
Sonnenschutzcreme	**morgens**		**-----**
Topische Corticosteroide	**-----**		**abends**
Doxycyclin 100 mg	**morgens**	**und**	**abends**

Mitchell E. et al:
WCGIC 2008
Abstract O-021

Hämatotoxizität

N= 33	% Grad I	% Grad II	% Grad III
Neutropenie	24 %	21 %	21 %
Anämie	27 %	6 %	0 %
Thrombopenie	44 %	9 %	6 %

VOLUME 25 · NUMBER 21 · JULY 20 2007

Journal of Clinical Oncology, Vol 25, No 21 (July 20), 2007: pp 2993-2995
DOI: 10.1200/JCO.2007.11.5113

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Hypertension, Proteinuria, and Antagonism of Vascular Endothelial Growth Factor Signaling: Clinical Toxicity, Therapeutic Target, or Novel Biomarker?

>>> Ekzem >>> Hypertonie

Willem J. van Heeckeren, *Division of Hematology/Oncology, Department of Medicine, Case Western Reserve University (CASE), School of Medicine, Cleveland, OH*
Jose Ortiz, *Division of Cardiology, Department of Medicine, CASE School of Medicine, Cleveland, OH*
Matthew M. Cooney and Scot C. Remick, *Division of Hematology/Oncology, Department of Medicine, CASE School of Medicine; and Developmental Therapeutics Program, CASE Comprehensive Cancer Center, University Hospitals CASE Medical Center, Cleveland, OH*

Dauer der Studientherapie

	Sunitinib (N = 63)
Anzahl der begonnenen Zyklen, Median (Bereich)	2 (1–7)
Therapieunterbrechung* (%)	27
Unerwünschtes Ereignis	24
Sonstige Gründe	3
Dosisreduktion** (%)	21
Unerwünschtes Ereignis	10
Sonstige Gründe	11
Abbruch wegen UE (%)	38

* Therapieunterbrechung: Verzögerte Gabe innerhalb eines Zyklus
** Dosisreduktion: 16% reduziert auf 37,5 mg, 5% auf 25 mg

Socinski et al. ASCO 2006; Abstract 7001.

Hemmung diverser Rezeptoren / Enzymkinasen durch Tyrosinkinase-inhibitoren (TKI)

TKI / REZEPTOREN (R)	erbB2 . /. FGF R	c-KIT / Abl	PDGF R	VEGF R	EGF R	EPHA R		*SRC Kinase*	*RAF Kinase*

EPHA Ephrin A Rezeptor / SRC – Kinase

Socinski et al. ASCO 2006; Abstract 7001.

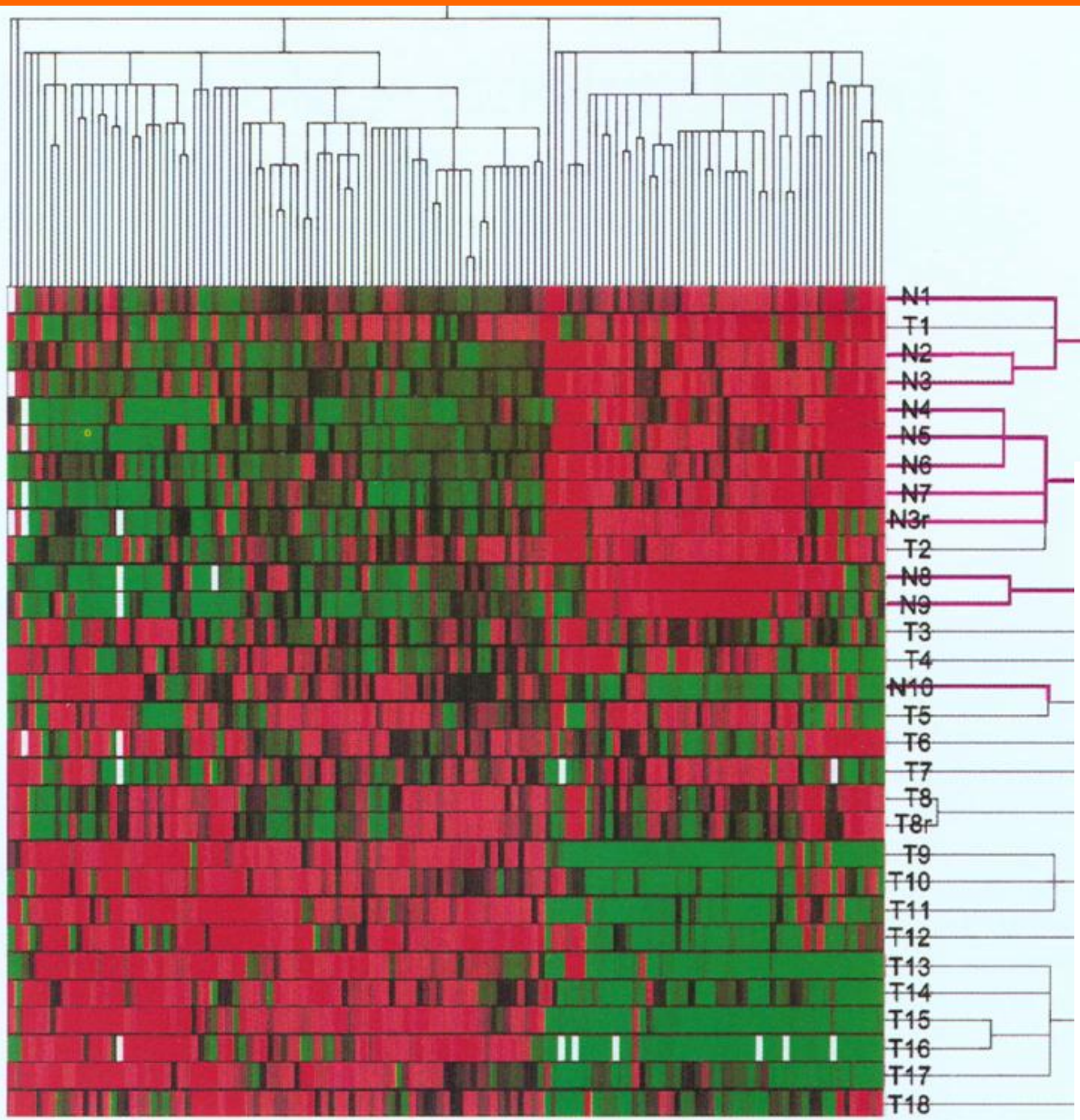
THE MAGIC OF MICROARRAYS

Research tools known as DNA microarrays are already clarifying the molecular roots of health and disease and speeding drug discovery. They could also hasten the day when custom-tailored treatment plans replace a one-size-fits-all approach to health care

BY STEPHEN H. FRIEND AND ROLAND B. STOUGHTON

DOT PATTERNS EMERGE when DNA microarrays analyze tissue samples. Individual differences in those patterns could one day help doctors match treatments to the unique needs of each patient.

Socinski et al. ASCO 2006; Abstract 7001.



Rot:
Aktive Gene

Grün:
Gene niederer Aktivität

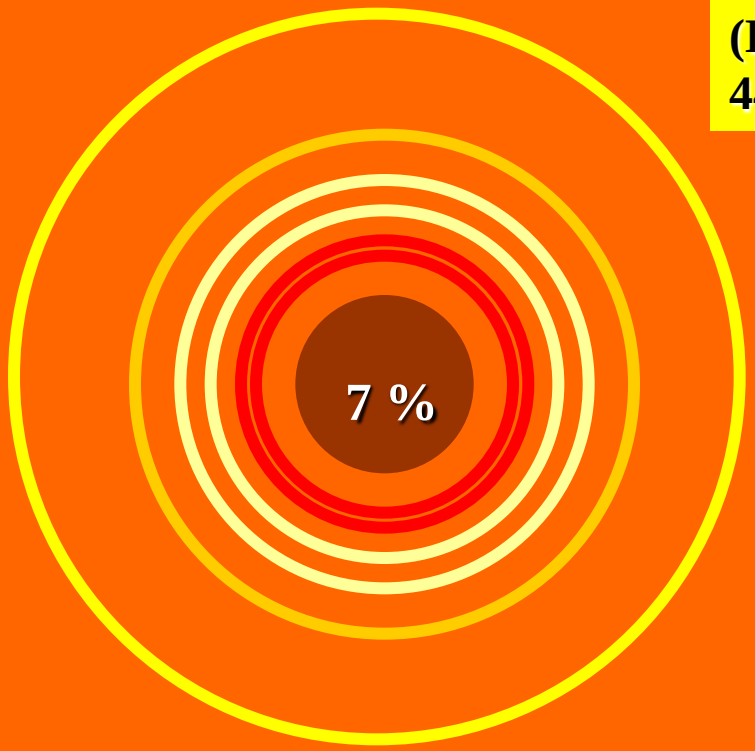
T:
Tumorgewebe

Socinski et al. ASCO 2006; Abstract 7001.

Molekulare Prädiktoren eines STI - Effektes

Hohe Expression des HER (EGFR) - Genprodukts
44 %

Amplifikation von HER1 (EGFR) Gen Kopien 5 %



Amplifikation von HER (EGFR) Gen Kopien und Expression des EGFR-Genprodukts
20 %

Isolierte HER (EGFR) Gen Mutation
1 %

Amplifikation von HER (EGFR) Gen Kopien & HER-Mutation
1 %

Amplifikation von EGFR Gen Kopien mit hoher Expression des HER (EGFR)-Genprodukts & EGFR-Mutation 7%

Hohe Expression des HER (EGFR) - Genprodukts & EGFR Mutation
3 %

The biology of anti-hormone failure in breast cancer in pre-clinical models

Rob Nicholson
Tenovus Centre for Cancer Research,
Welsh School of Pharmacy, Cardiff University, UK

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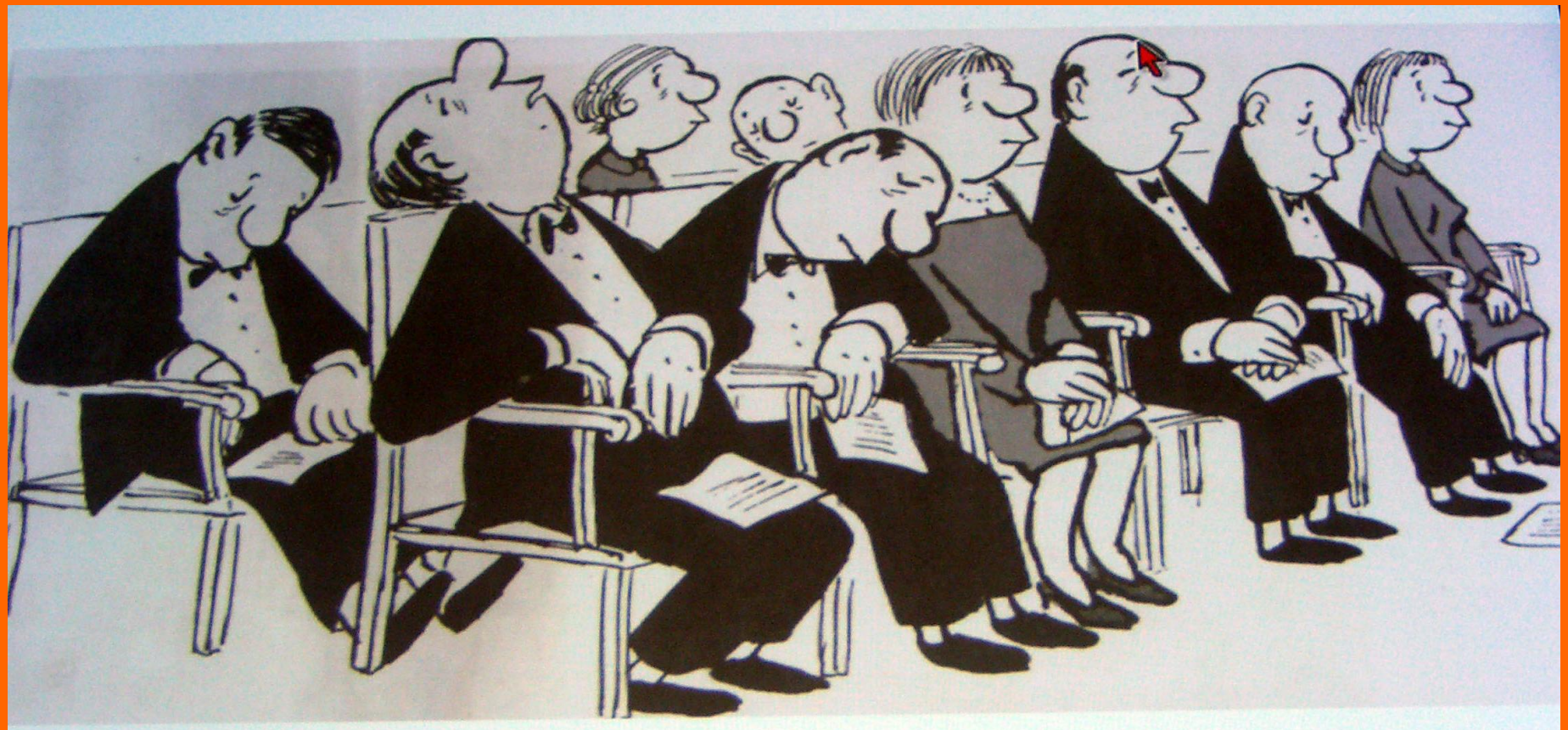

Gibt es Fragen?