TAT meeting Paris 2011

Universitair Medisch Centrum Utrecht

Can the tumor genome help us to better select patients for antiangiogenic therapy ?

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Modest succes of bevacizumab in common cancers

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Table 1. Randomized Phase III Studies Comparing Chemotherapy With or Without Bevacizumab As First-Line Chemotherapy for Advanced Epithelial Cancers

Tumor Site and Study Name	Primary End Point	Sample Size	Design	PFS			OS			Reported As
				Diff (months)	HR	*P*	Diff (months)	HR	*P*	
Breast										
ECOG E2100[5]	PFS	722	P ± B	+ 5.9	0.60	.0001	+ 1.5	0.88	.16	Positive
AVADO[6]	PFS	736	D ± B7.5	+ 0.8	0.86	.116	− 1.1	1.05	.72	Positive
			D ± B15	+ 1.9	0.77	.006	− 1.7	1.03	.85	
RIBBON-1[7]	PFS	1,237	C ± B	+ 2.9	0.69	.0002	+ 7.8	0.85	.27	Positive
			A/T ± B	+ 1.2	0.64	< .001	+ 1.4	1.03	.83	
Meta-analysis[8]	—	2,447	Ch ± B	+ 2.5	0.64	.0001	+ 0.3	0.97	.56	—
Prostate										
CALGB 90401[10]	OS	1,050	DP ± B	+ 2.4	0.77	.0001	+ 1.1	0.91	.18	Negative
Ovarian										
GOG-0218[11]	OS→PFS	1,873	CT ± B	+ 0.9	0.91	.080	− 0.6	1.04	.36	Positive
			CT + B + mB	+ 3.8	0.72	.0001	+ 0.4	0.92	.25	
Lung										
ECOG E4599[12]	OS	878	CP ± B	+ 1.7	0.66	< .001	+ 2.0	0.79	.003	Positive
AVAiL[13,14]	OS→PFS	1,043	CG ± B7.5	+ 0.6	0.75	.0003	+ 0.5	0.93	.42	Positive
			CG ± B15	+ 0.4	0.85	.046	+ 0.3	1.03	.76	
Pooled analysis*	—	1,921	Ch ± B	+ 1.1	0.73	< .001	+ 1.0	0.91	.22	—
Gastric										
AVAGAST[15]	OS	774	XELP ± B	+ 1.4	0.80	.0037	+2	0.87	.1002	Negative
Pancreas										
CALGB 80303[16]	OS	602	G ± B	+ 0.9	1.00	.07	− 0.1	1.09	.95	Negative
Van Cutsem et al[17]	OS	607	GE ± B	+ 1.0	0.73	.0002	+ 1.1	0.89	.21	Negative
Colorectal										
Hurwitz[18]	OS	813	IFL ± B	+ 4.4	0.54	< .001	+ 4.7	0.66	< .001	Positive
Saltz[19]	PFS	1,401	FOLFOX4 or XELOX ± B	+ 1.4	0.83	.0023	+ 1.4	0.89	.0769	Positive

Ocaña A, et al. J Clin Oncol. 2011;29:254-6

Can we afford to develop drugs the way we used to ?

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How Much Is Life Worth: Cetuximab, Non–Small Cell Lung Cancer, and the $440 Billion Question

Tito Fojo and Christine Grady

J Natl Cancer Inst 2009; 101:1044-1048

Discrepancy between preclinical models and patients

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- In vitro models commonly use cell lines that have been maintained in culture for years
- Investigations focus on knock down of genes by siRNA, but functional consequences of mutations are rarely studied in preclinical models
- In vitro sensitivity to agents does not accurately predict their activity in vivo
- Mouse models employ xenografts of selected cell lines
- Transgenic mouse models have a defined genetic initiator of cancer

- Therefore: huge gap between preclinical models and our patients!!

The patient as readout: Personalized Cancer Treatment

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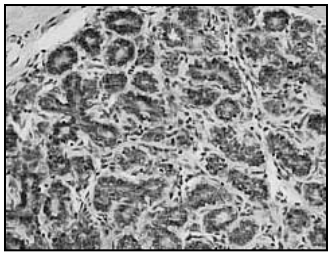
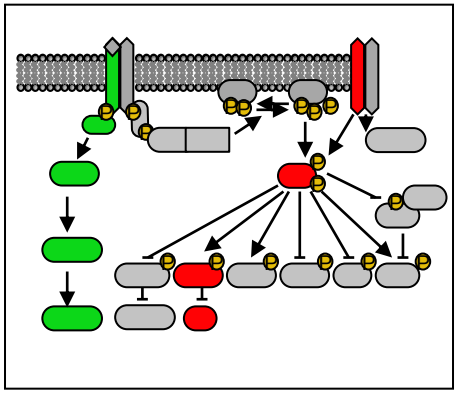
Patient's tissue sample →  →  → Chemotherapy

pathology
grade, size, IHC

Tailored therapy

Patient's tissue sample → Molecular diagnostics →  → Targeted therapy

Which pathways are active?

Proof of concept !

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- After screening tumor samples from approximately **1500** patients with non–small-cell lung cancer for the presence of *ALK* rearrangement, **82** patients with advanced *ALK*-positive disease were identified

- Mean treatment duration of 6.4 months
- Overall response rate : 57% (47 of 82 patients);
- 27 patients (33%) had stable disease.
- The estimated probability of 6-month progression-free survival was 72%, with no median for the study reached.

Kwak EL, et al. N Engl J Med. 2010;363:1693-703.

Proof of concept !

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EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors

- Two secondary mutations within the kinase domain of EML4-ALK in tumor cells isolated from a patient developed during the relapse phase of treatment with an ALK inhibitor.

- Each mutation developed independently in subclones of the tumor and conferred marked resistance to two different ALK inhibitors.

Choi YL. et al. N Engl J Med 2010; 363:1734-1739

Can we achieve the same success for anti-angiogenic therapy ?

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Question that needs to be addressed:

How to determine genetic dependency
or *“angiogene addiction”* ?

"Angiogene addiction"

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- Tumor acquires genetic changes in growth factor pathways early in tumorigenesis that facilitate tumor growth
- Short time between initial mutagenesis and clinical manifestations ?
- Examples: clear cell renal cell cancer; pancreatic NET, PEComa

Mutations in the VHL gene to select patients for anti-angiogenic therapy

kdr-like:egfp

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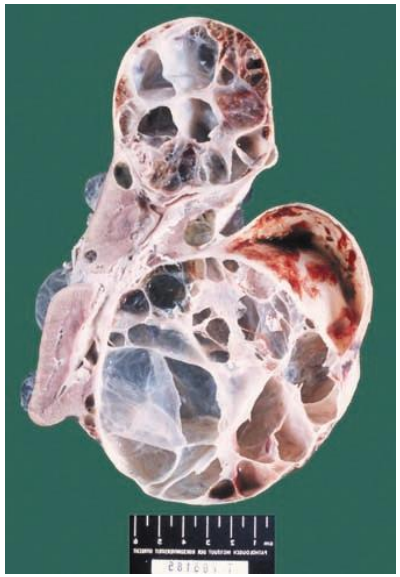

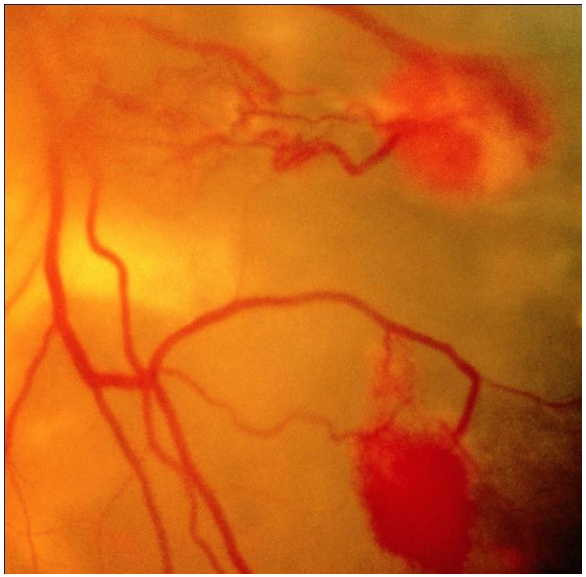

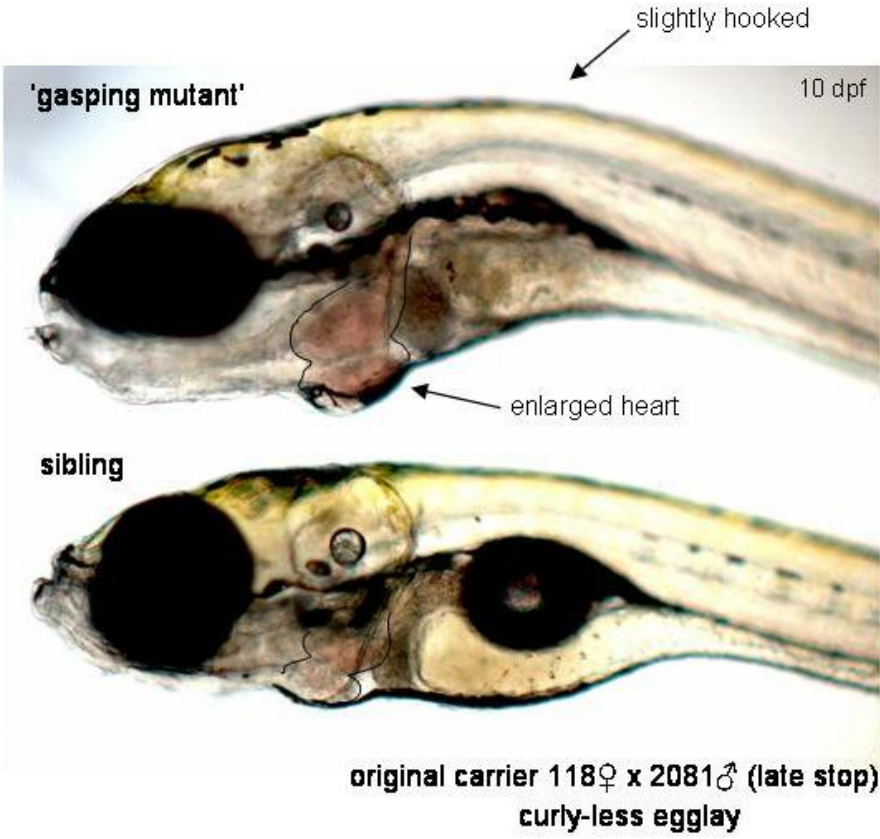

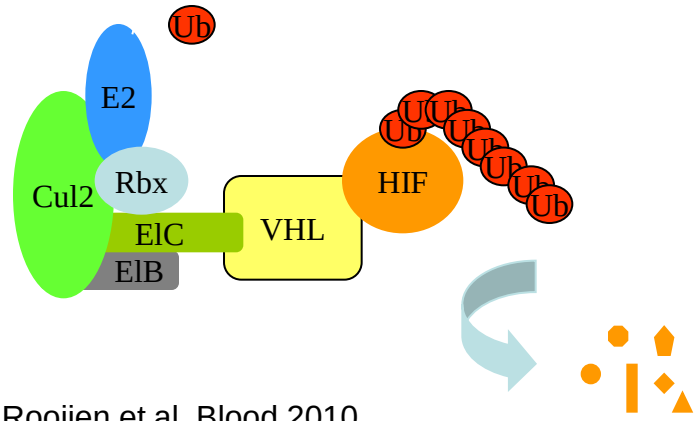

Rooijen et al. Blood 2010

Nordstrom-O'Brien et al., Human Mutations 2010

Rooijen et al., Dis Models Mech 2010

Mutations in the VHL gene to select patients for anti-angiogenic therapy

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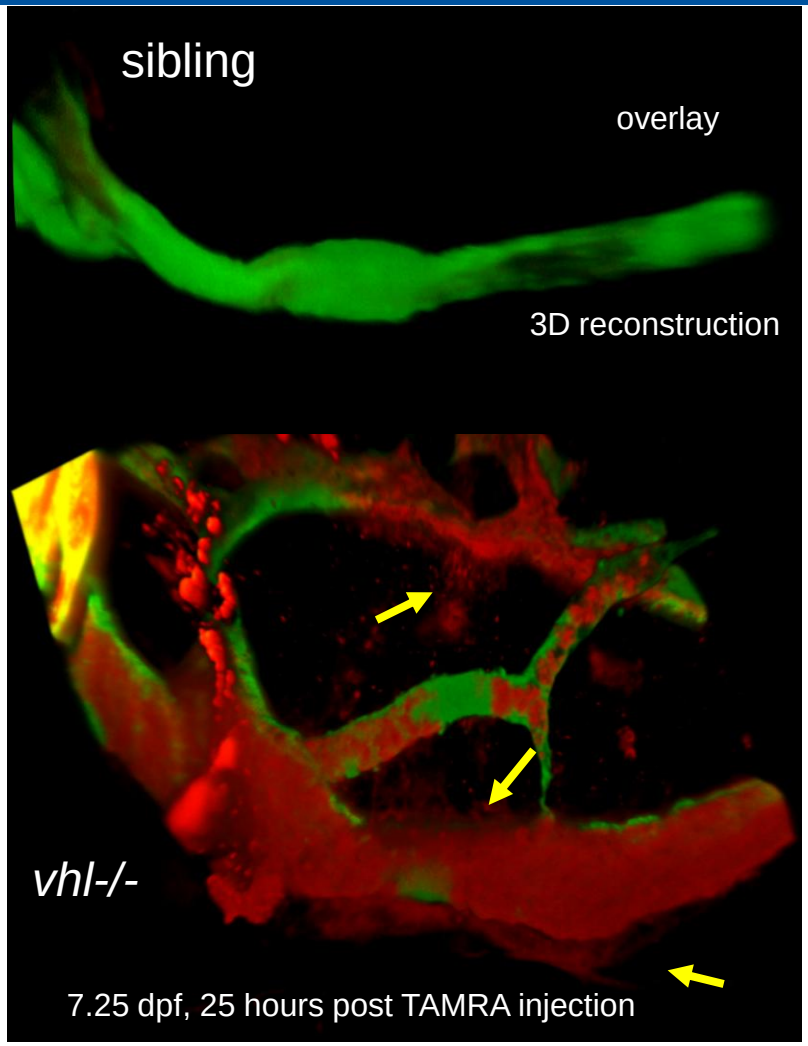
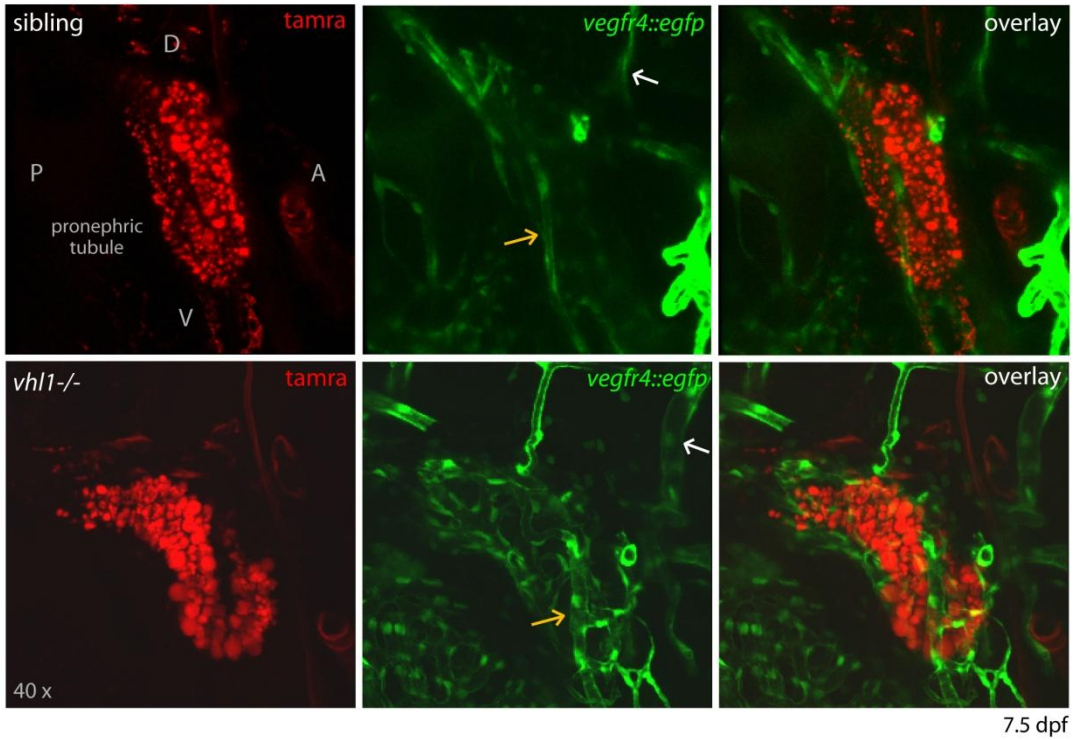
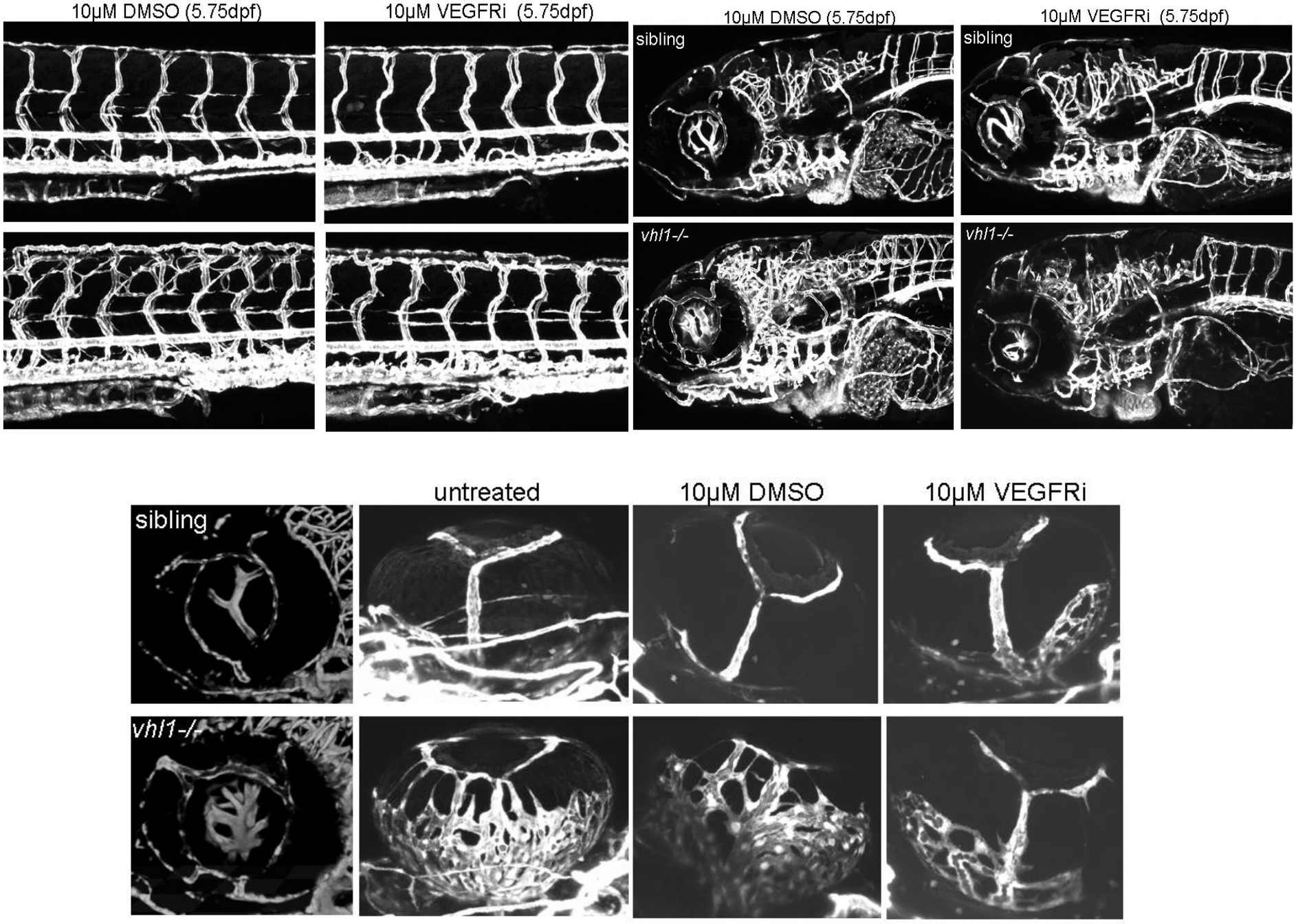


kdr-like:egfp



Rooijen et al. Blood 2010
Nordstrom-O'Brien et al., Human Mutations 2010
Rooijen et al., Dis Models Mech 2010


10µM DMSO (5.75dpf)
10µM VEGFRi (5.75dpf)
10µM DMSO (5.75dpf)
10µM VEGFRi (5.75dpf)
sibling
sibling
vhl1-/-
vhl1-/-
untreated
10µM DMSO
10µM VEGFRi
sibling
vhl1-/-
5.75 dpf, kdra::egfp

von Hippel-Lindau gene status and response to VEGF targeted therapy for metastatic ccRCC

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- 700 different types of mutations, derived from this protein of only 213 amino acids.

- Retrospective analysis in 123 ccRCC patients. Patients with VHL inactivation had a response rate of 41% vs 31% for those with wild-type VHL (p = 0.34). Patients with loss of function mutations had a 52% response rate vs 31% with wild-type VHL (p = 0.04).

- On multivariate analysis the presence of a loss of function mutation remained an independent prognostic factor associated with improved response.

- In VHL disease, clear evidence supports strong genotype-phenotype correlations, but the situation in sporadic ccRCC is less clear.

Choueiri TK et al, J Urol 2008, Gossage L, Eisen T. Nat Rev Clin Oncol. 2010, Nordstrom-O'Brien, et al. Human Mutations 2010

An other example of "*angiogene addiction*" ?
Comparative Genomic Hybridization of PEComa's

Pan et al, Human Pathology 2006

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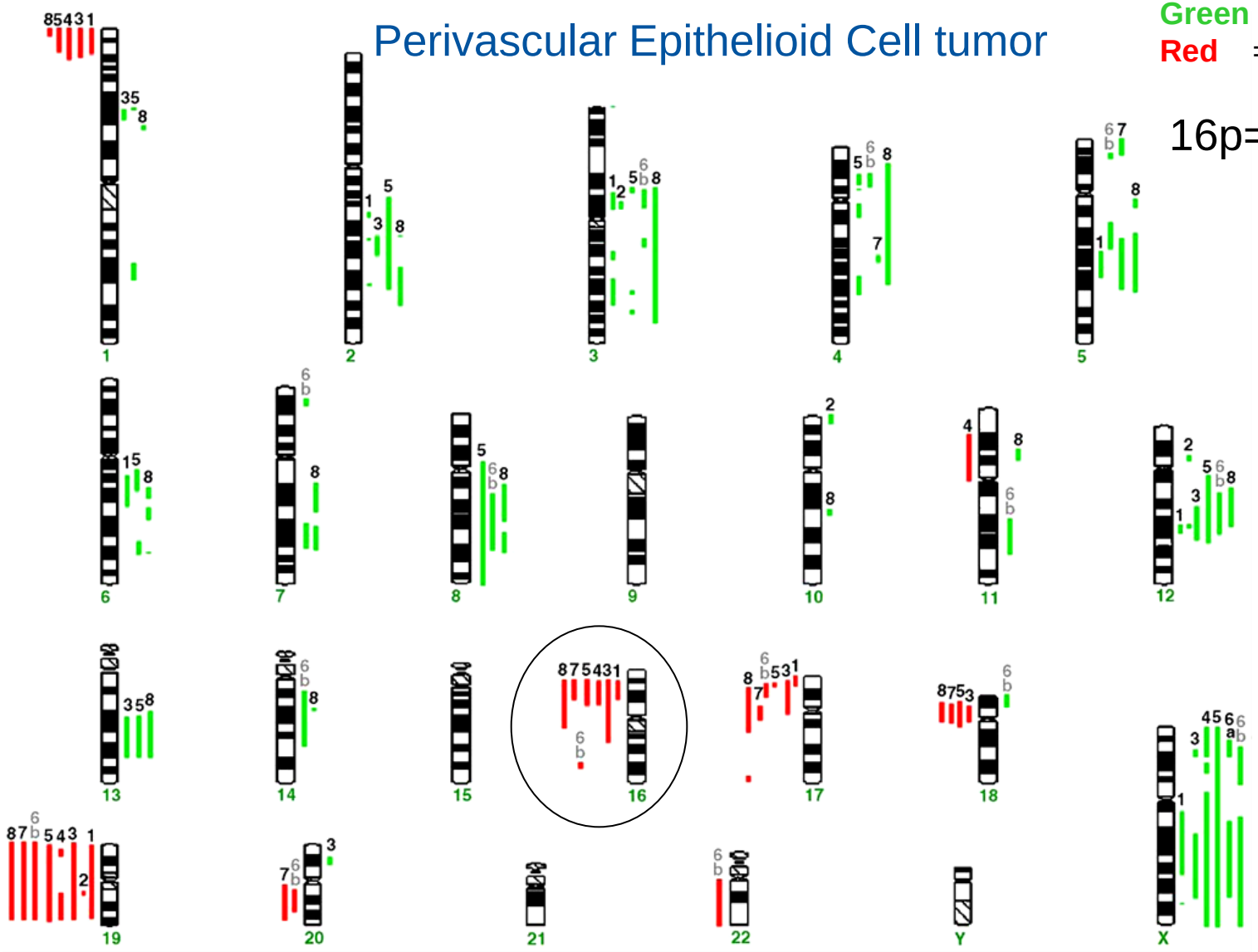
Perivascular Epithelioid Cell tumor

Green = chromosomal gain
Red = chromosomal loss

16p=TSC2 locus



Proof of concept…

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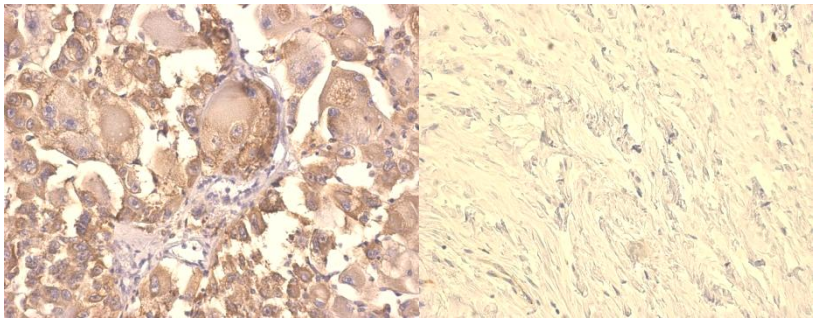
- Clinical Activity of mTOR Inhibition With Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors. Wagner et al. J Clin Oncol Feb 2010

PhosphoS6 staining



A clinical example of a successful DNA guided anti-angiogenic treatment

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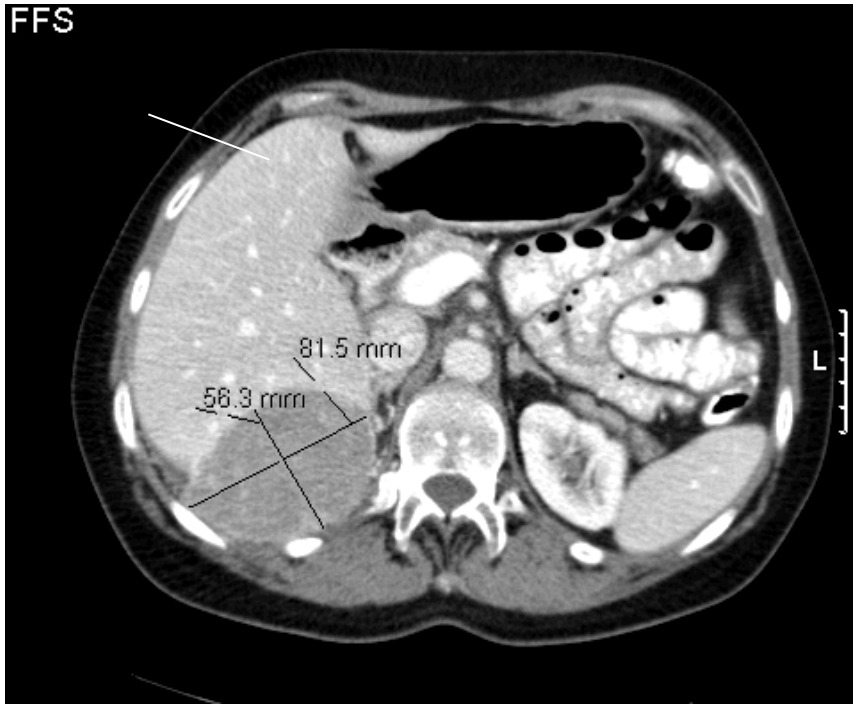
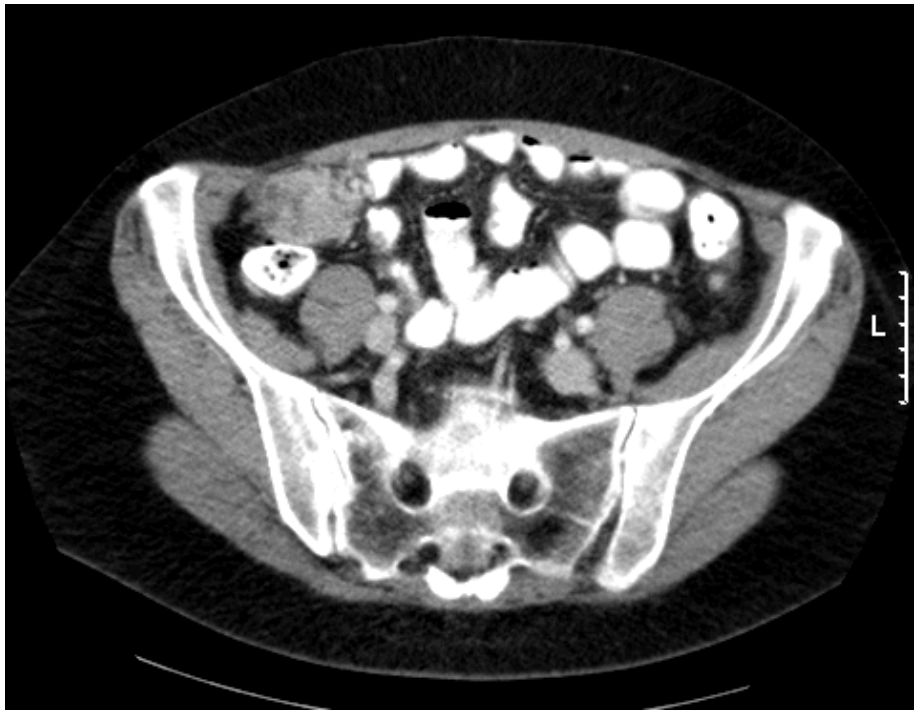
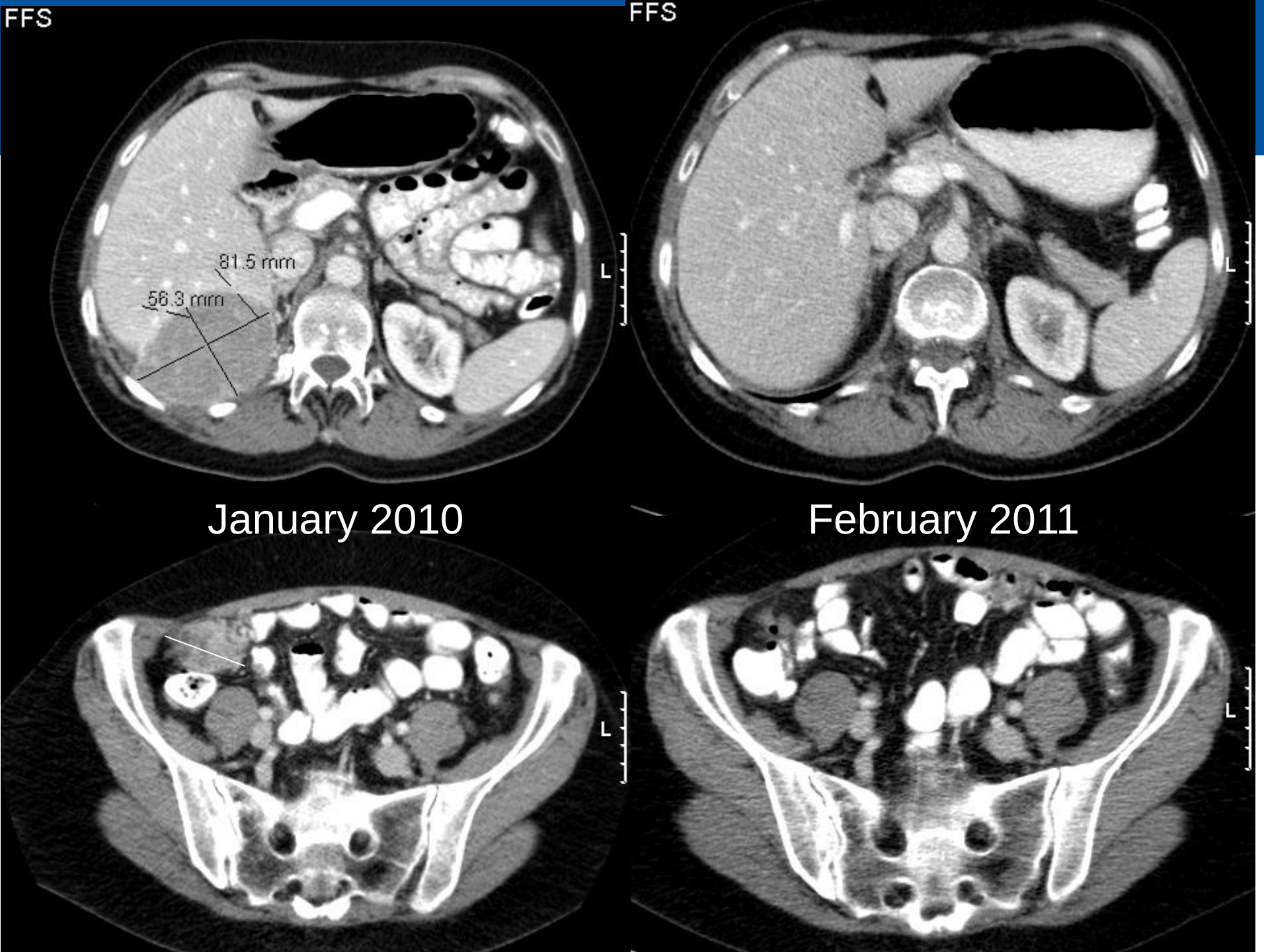
- Patient with a perivascular epitheloid cell tumor (PEComa) with liver and intraperitoneal metastases

- Initial response on doxorubicin but progressive disease within 6 months, no other treatment options






FFS
81.5 mm
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January 2010
February 2011
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"*Angiogene addiction*" in common cancer?

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- Potential examples of "*angiogene addiction*" : ccRCC, GIST, PEComa, pancreatic NET
- Better selection of patients with common cancers is essential
- Can tumor DNA provide answers ?

Can we achieve the same success in common cancers ?

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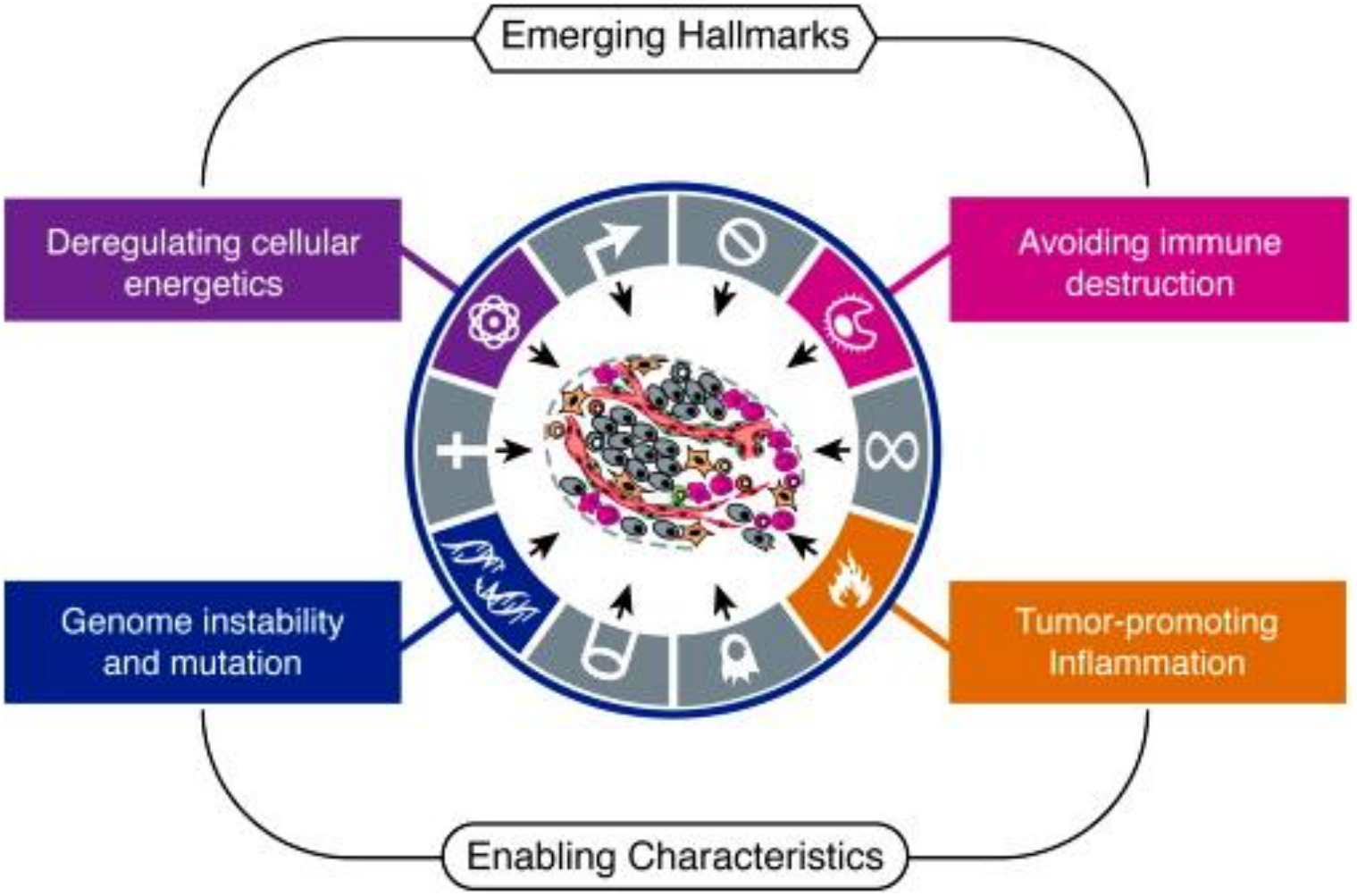

Hanahan and Weinberg, Cell, april 2011

Cell PRESS

The Adenoma-Carcinoma Sequence in Colorectal Cancer: tumor initiation, progression, and metastasis

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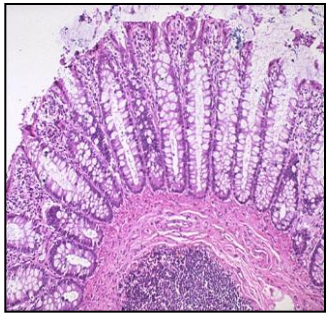
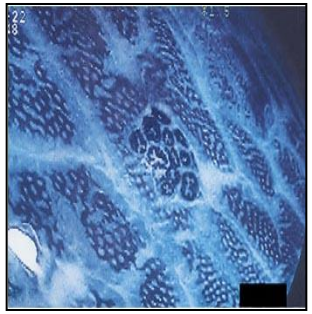
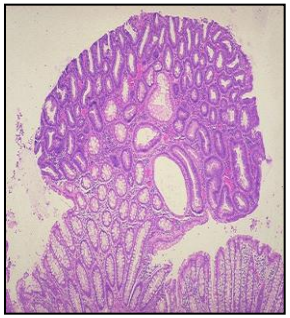
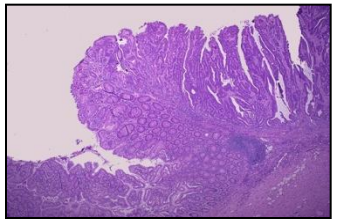
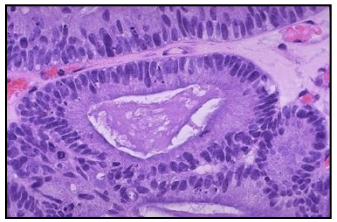
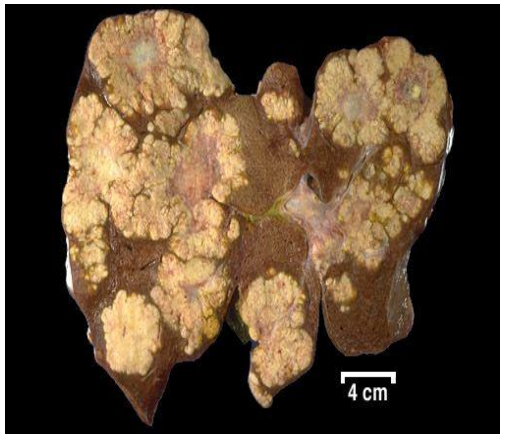

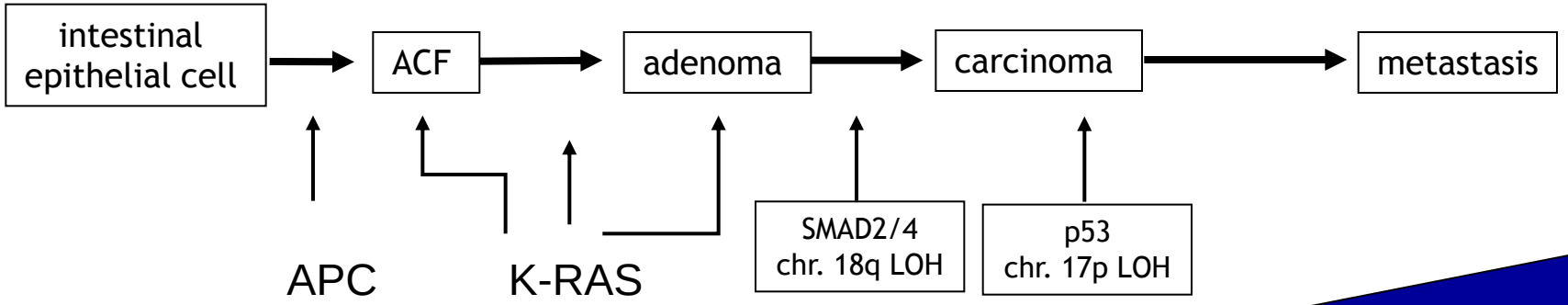

Genetic alterations

Are we sure that the target is present in metastatic disease ? Primary tumors are not the same as metastases

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- Paired colorectal tumors and metastasis of 21 patients were selected (42 tumor samples)
- Tumor DNA was isolated by microdissection and sequenced for 1263 genes covering all major pathways and kinases
- Looking for function altering genetic changes
- Very stringent SNP calling

- **On average a metastasis gains 89 relevant mutations and loses 70 mutations present in the primary**

Conclusions

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- Molecular diagnostics (sequencing, molecular imaging) will improve patient selection for targeted therapy
- Single agent activity of anti-angiogenics is most likely seen in tumors addicted to mutations in growth factor pathways
- Mutations, copy number variations, structural variance all contribute
- Next generation sequencing data within clinical trials need to be connected through data sharing (open source !!!)
- Biopsies of tumor at start of and at progression under treatment are essential

Acknowledgements

- Marco Koudijs
- Sander Schouten
- Joost Vermaat
- Martijn Lolkema
- Wijnand Roessingh
- Nicolle Besselink
- Ilse van Oosterom
- Oscar Paling
- Laura Daenen
- Julia Houthuijzen
- Jeanine Roodhart
- Marlous Hoogstraat
- Stef van Lieshout
- Geert Cirkel
- Christa Hooijdonk

CPCT
Center for Personalized Cancer Treatment

Amsterdam: Jan Schellens, Rene Bernards

Rotterdam: Stefan Sleijfer, John Martens

Utrecht: Edwin Cuppen, Emile Voest

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