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Personalized Medicine course VUMC

Better strategies

- Novel targets
- Combination therapy

**Algorithm based optimization of
angiostatic drug combinations
- towards a personalized approach -**

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The angiogenesis cascade

"Geen bloed waar het niet gaan kan", de Volkskrant

Angiogenesis inhibitors

- Effects still rather limited
- Toxicity
- Resistance

No of patients at risk	0	6	12	18	24	30
IFL + Placebo	411	349	247	77	15	1
IFL + Avastin	402	358	295	105	27	1

Duration of Survival (Months)


5

The angiogenesis cascade

"Geen bloed waar het niet gaan kan", de Volkskrant

Combination therapy

- Selection of drugs for combination based on previous success in monotherapy application (just adding a new drug to a successful strategy)
- Dosing and scheduling based on gut feeling.
- Trial and error.



Problem:
How to find optimal combinations? How many drugs or doses?

e.g. 9 drugs at 5 doses = $5^9 = 1,953,125$ combinations
too big search space; not enough patients

A learning algorithm

To resolve these problems we embarked on a new strategy involving a **learning algorithm** to navigate through the parametric space

Feedback System Control + Differential Evolution
developed by prof. Chieh Ming Ho, UCLA, USA


PROTOCOL

Optimization of drug combinations using Feedback System Control

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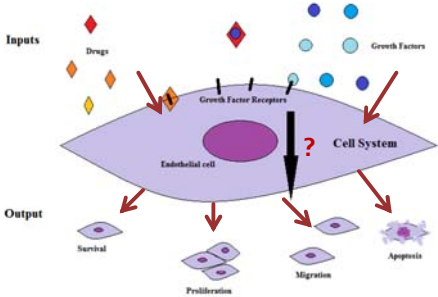
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Wong et al. Proc Natl Acad Sci, 2008

Cell as a black box

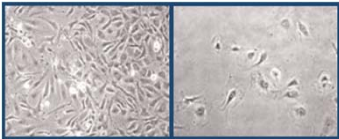


Endothelial cell proliferation



Automated station

Treated ECs

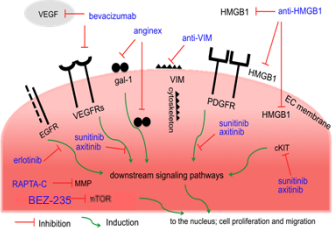


10

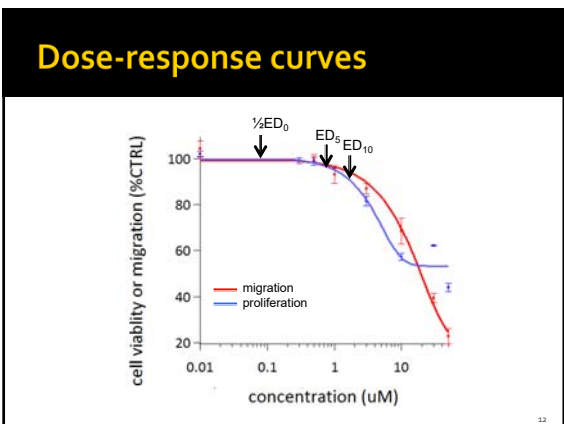
Selection of 9 angiostatic drugs

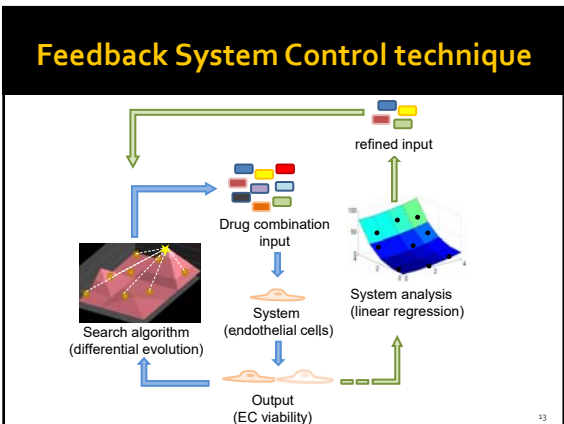
9 drugs were selected

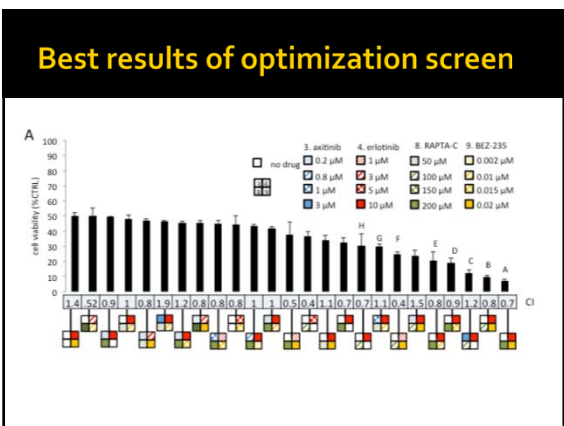
- Sunitinib (VEGFRs PDGFR)
- Axitinib (VEGFRs)
- Bevacizumab (VEGF)
- Erlotinib (EGFR)
- BEZ-235 (mTOR1 and -2)

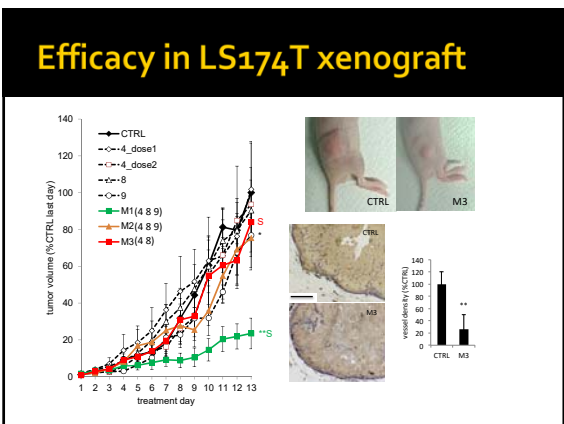


11









Personalization

- The anti-angiogenesis screen proof-of-principle.
- A current screen is being performed on renal cell cancer (RCC) cell lines.
- A wide set of chemotherapeutics and TKIs was used.
- Optimal combinations were cell line dependent, suggesting an open option for personalized therapy.

Conclusions

- FSC technique led to fast identification of a **low dose** three-drug synergistic drug combination identified from an extremely large search space.
- Drug combinations gained endothelial specificity.
- Translation of *in vitro* data to *in vivo* testing succeeded
- Combining drugs allowed the use of appr. 10-fold lower concentrations

17
