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Better strategies

- Novel targets
- Combination therapy

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

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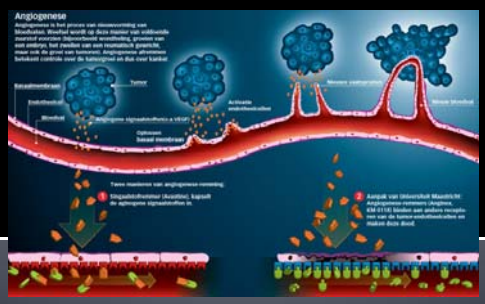
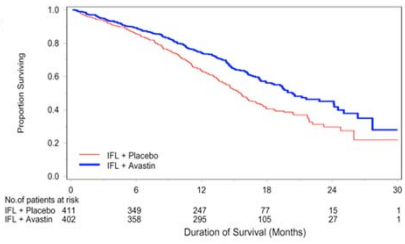
The angiogenesis cascade



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

Angiogenesis inhibitors

- Effects still rather limited
- Toxicity
- Resistance



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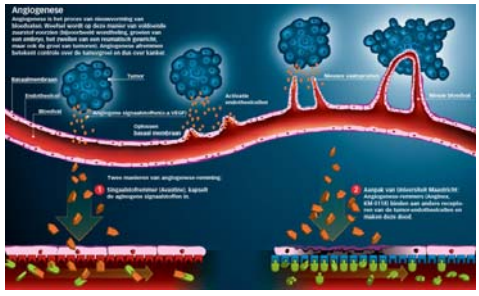
The angiogenesis cascade



'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

Wong et al. Proc Natl Acad Sci, 2008

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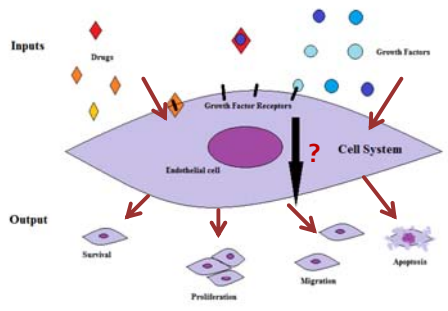
Cell as a black box



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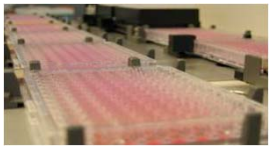
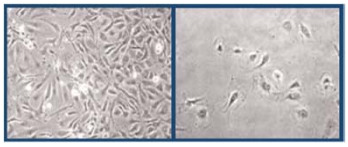
Endothelial cell proliferation



Automated station



Treated ECs

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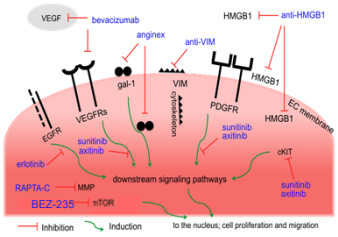
Selection of 9 angiostatic drugs

9 drugs were selected

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



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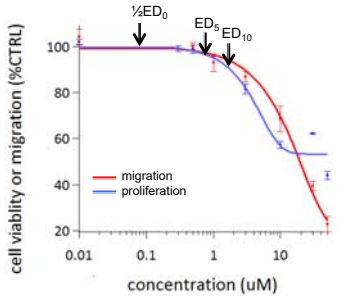
Dose-response curves



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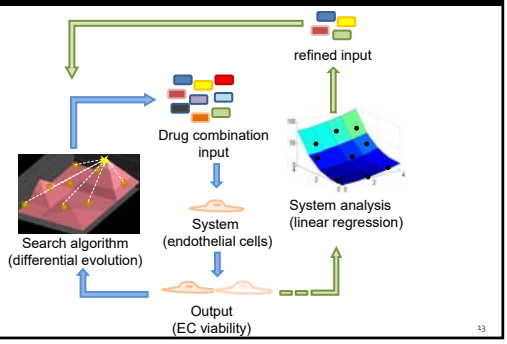
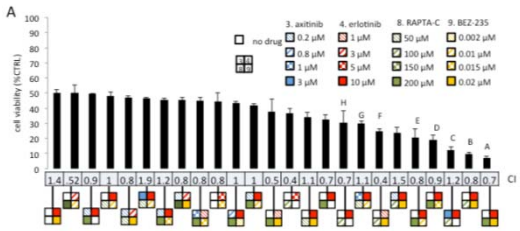
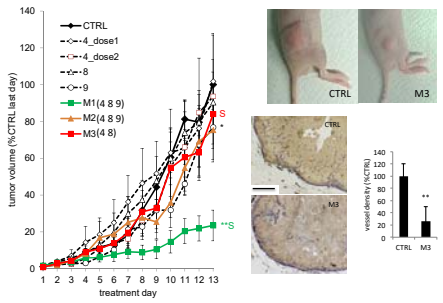
Feedback System Control technique



Best results of optimization screen



Efficacy in LS174T xenograft



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

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