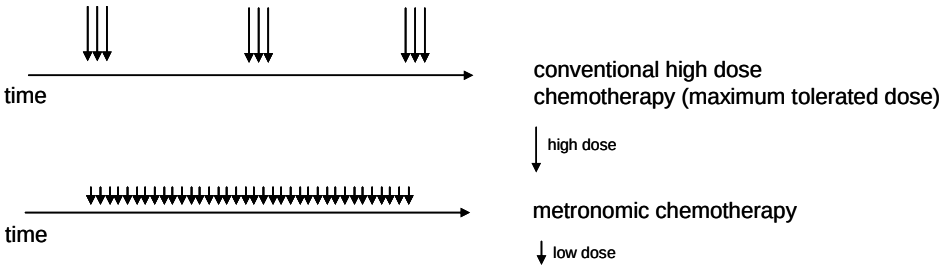
Tumor angiogenesis and drug resistance

Introduction
Despite partial success in cancer therapy in the last decades, treatment of already metastasized or inoperable tumors is still not sufficient. Especially drug resistance is an unsolved problem and has to be overcome to increase the prospect of many patients.

As tumor angiogenesis was recognized to be a limiting factor in tumor progression, several treatment regimes target this process now. Beside specific inhibitors against growth factors as e.g. vascular endothelial growth factor (VEGF) or the corresponding receptors and signaling pathways, metronomic chemotherapy was shown to exhibit antiangiogenic potential.

Different models for studying drug resistance and tumor angiogenesis include *in vivo* xenografts models as well as *in vitro* cell culture models.

Metronomic chemotherapy
In contrast to conventional chemotherapy regimes, metronomic treatment is based on the continuous application of comparatively low dose chemotherapeutics. Several conventional used drugs as e.g. 5-FU, CPA or Doxorubicin have been explored to exhibit antiangiogenic potential when they were given in such treatment regimes.



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Drug resistance
Despite advances in the treatment of progressed cancer via chemotherapeutic regimes, outcome is often unsatisfying. One main obstacle in therapy is the occurrence of resistance against the applied treatment regime. Resistance of tumors towards chemotherapeutic treatment are multifaceted, being primary (intrinsic) or secondary (acquired).
As endothelial cells were proposed to be genetically stable, treatment regimes targeting these cells should be unlikely to induce acquired drug resistance. However, several clinical and experimental studies demonstrate the development of escape mechanisms also against antiangiogenic treatment regimes.

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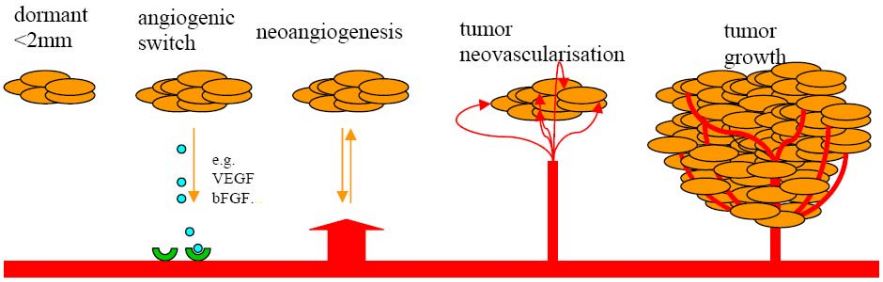
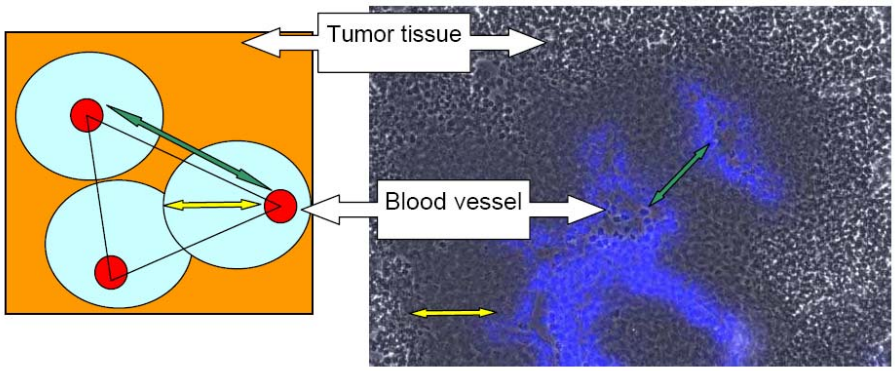
Angiogenesis

Tumor angiogenesis represents a critical step in tumor progression. The dormant, avascular state of solid tumors is characterized by a balance between cell proliferation and cell death. In this stadium the tumor does not grow and remain at a microscopic size. As recently as the tumor switches to an angiogenic phenotype, new formed blood vessels supply the tumor with oxygen and nutrients and tumor growth can occur.



Blood supply in tumor tissue

The microscopic picture (right) displays a functional blood vessel (blue staining: intravenously injected Hoechst33258 dye as a tracer). The distance between functional blood vessels is described as intercapillary distance (green arrow). The area around the blood vessels that is supplied by oxygen is called perivascular cuff (yellow arrow).



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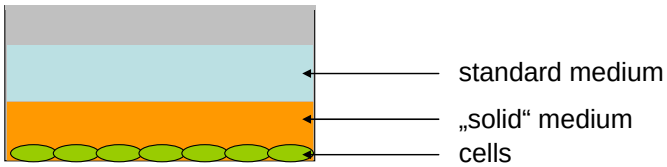
In vitro cell culture

Cell based assays have become an important tool in the development of anticancer drugs. However, they are commonly based on conventional monolayer or suspension cultures and represent a rather different environment compared to the clinical situation. Thus, cellular behaviour against drugs is likely to be artificial. Several approaches have been developed to establish cell culture models that better reflect the microenvironment in cancer in order to decrease the artificial compound of in vitro systems.

Agarose overlay technique

The Agarose overlay technique is based on a monolayer system. Therefore it is suitable for several techniques known from conventional cell culture. However, in contrast to conventional cell culture the system reflects two important aspects of solid tumors:
1: Limited diffusion of metabolites and cytokines
2: Limited diffusion of oxygen and resulting hypoxic environment



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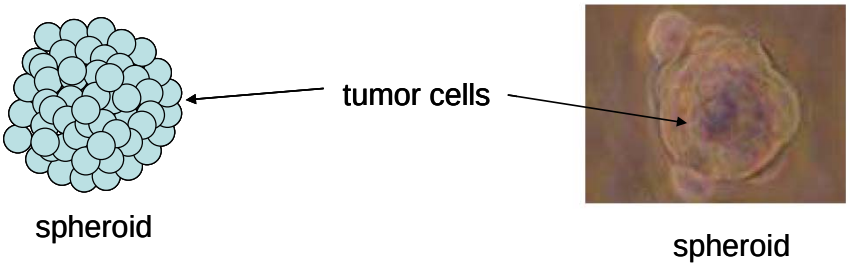
Three-dimensional spheroid cultures

Three-dimensional spheroid cultures reflect several aspects of solid tumors such as hypoxic areas and limited diffusion. Additionally, cells can establish cell-cell contacts among each other and reflect the in vivo microenvironment of tumors much better than conventional monolayer systems.



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Tumor Xenografts

Tumor-Xenotransplantation is the transplantation of living tumor cells from one species (e.g. human) to another (e.g. mouse). In such models, tumor progression, drug activity and development of acquired drug resistance can be studied in an *in vivo* situation.