Angiogenesis at the mold-host interface: a potential key to understanding and treating invasive aspergillosis

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DISSEMINATED ASPERGILLOSIS AND MONILIASIS ASSOCIATED WITH AGRANULOCYTOSIS AND ANTIBIOTIC THERAPY

BY

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(From the Department of Pathology, the Royal Infirmary, Gloucester)

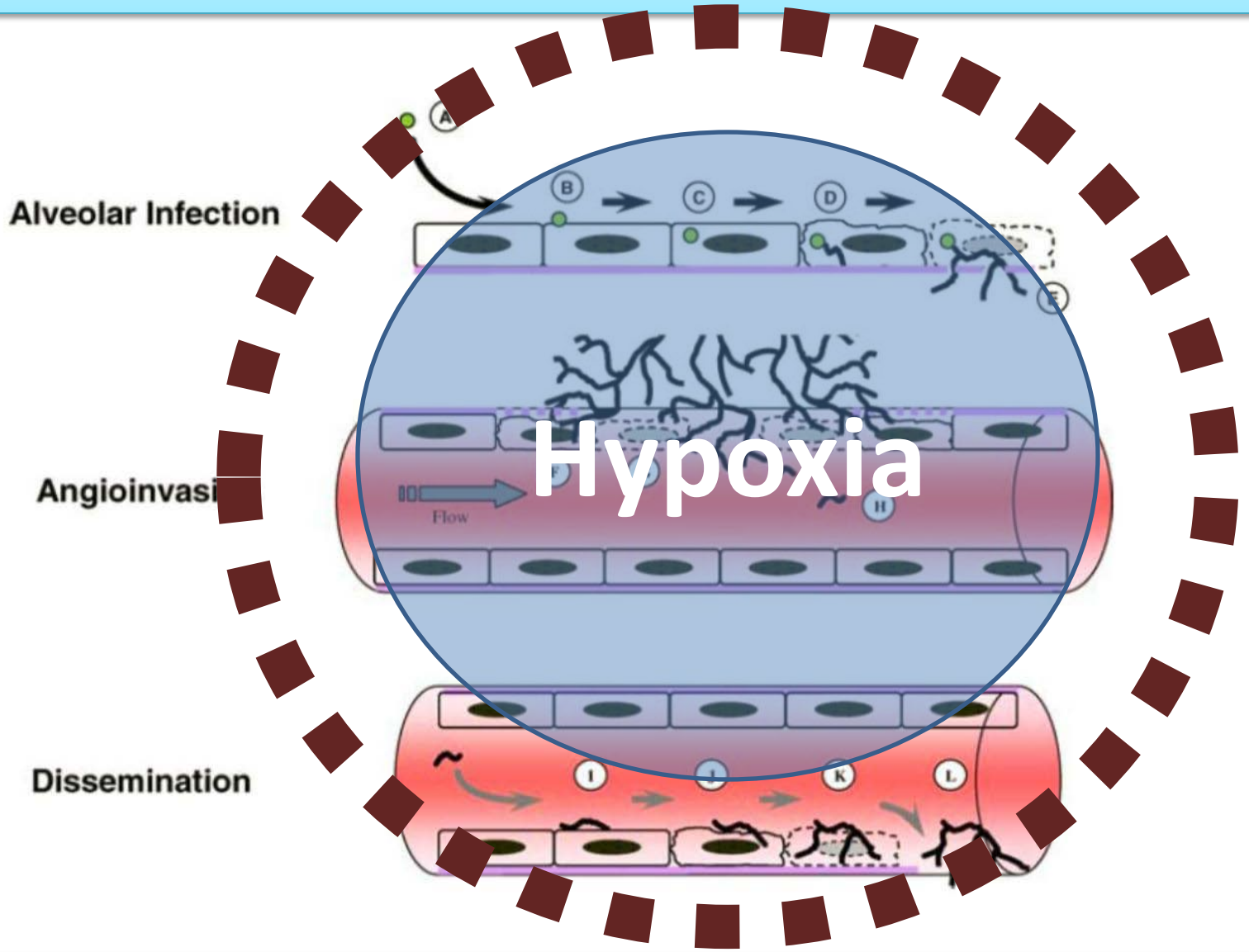
sent on both sides. A large infarct was found in the right upper lobe and a smaller infarct in the middle lobe; the pulmonary arteries to these areas showed thrombosis. In

eosinophils could be seen. Branching mycelium was present throughout the necrotic zone, invading the inflammatory zone and large and small vessels at the edge. The left

"It seemed to have a marked predilection for the blood vessels"

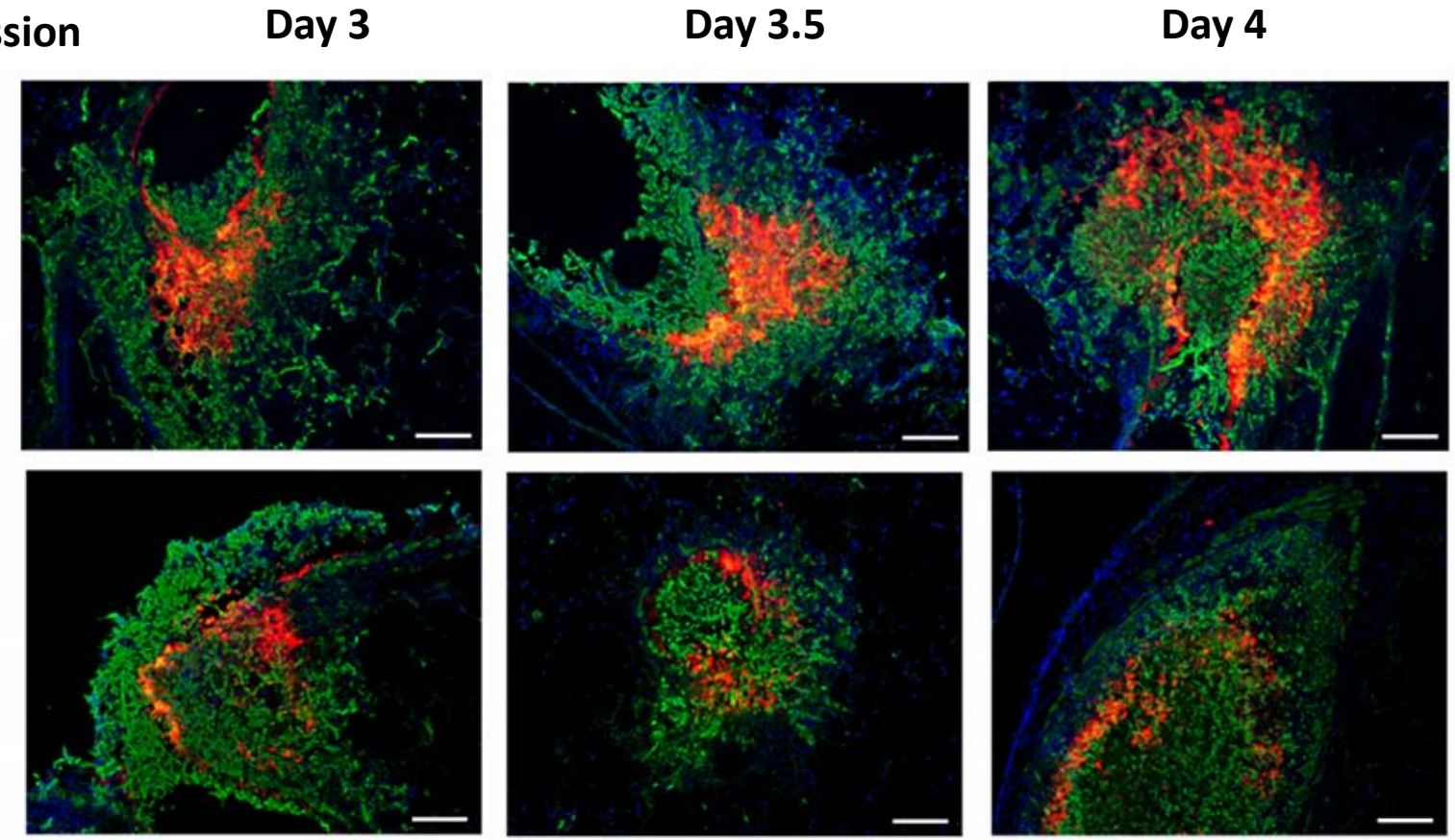
Rankin et al, BMJ 1953

The microenvironment in invasive aspergillosis: angioinvasion, inflammation, and tissue hypoxia



Kamai, Cell Microbiol 2009; Lopes Bezerra, Blood 2004; Filler, PLoS pathog 2006

The site of invasive aspergillosis is an hypoxic environment



Hypoxyprobe = orange

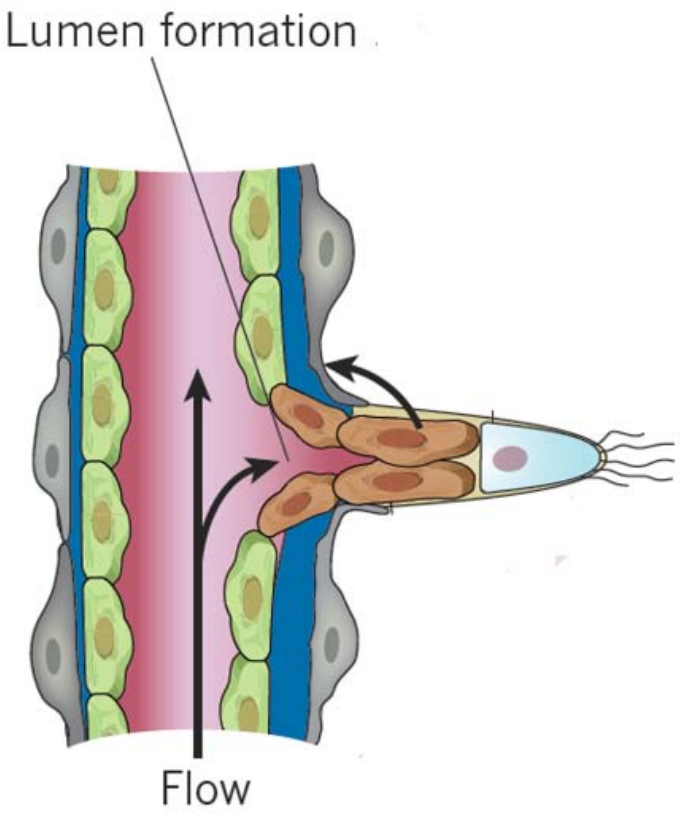
Grahl et al. PLoS Pathog 2011

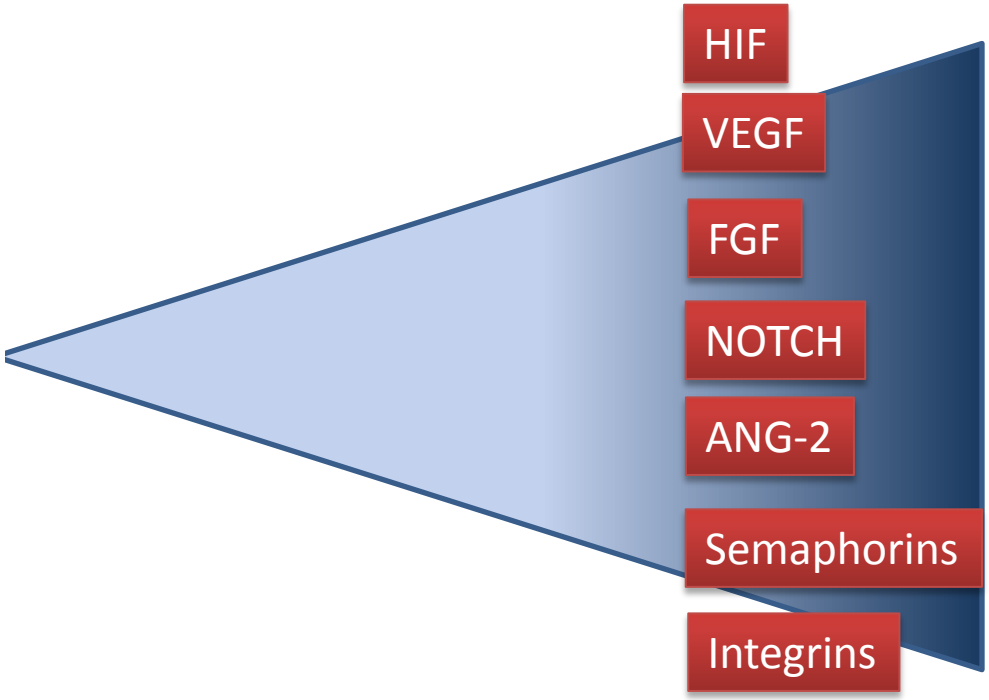
Aspergillus: adaptation to hypoxia requires a sterol regulatory element binding protein

- Sterol regulatory element-binding protein (SrbA) is required for growth in hypoxic conditions
- *ΔSrbA* essentially avirulent in neutropenic mice
- SrbAp also affects azole resistance and hyphal morphology
- Adaptation to hypoxia is a virulence requirement

Willger et al., PLoS pathog 2008

The host: angiogenesis is an adaptive response to hypoxia and inflammation

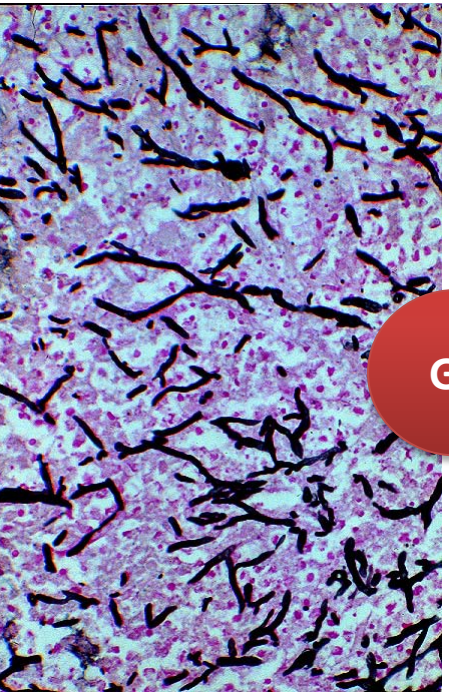




Carmeliet et al. Nature 2011

Oxygen sensing in host cells: HIF/NFkB pathway essential for neutrophil survival and angiogenesis

?



GT

TNF α

NF kB

HIF 1 α transcription factor

-OH

Ub

PHD

DNA

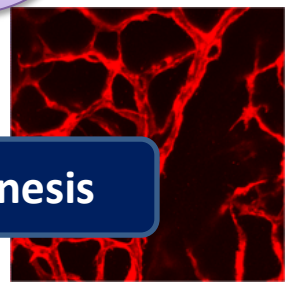
FLT1

bFGF

VEGF

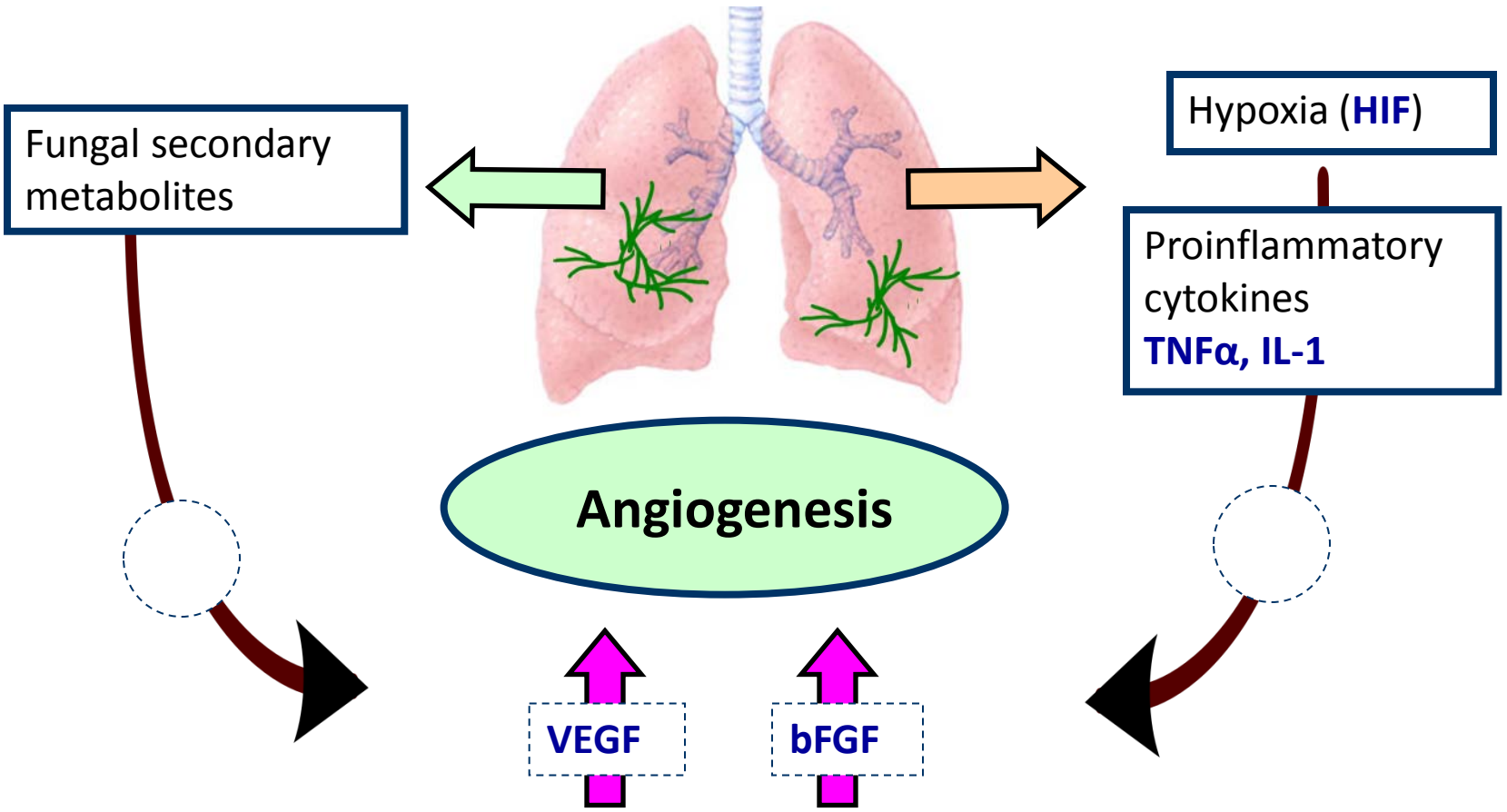
Neutrophil survival

Angiogenesis

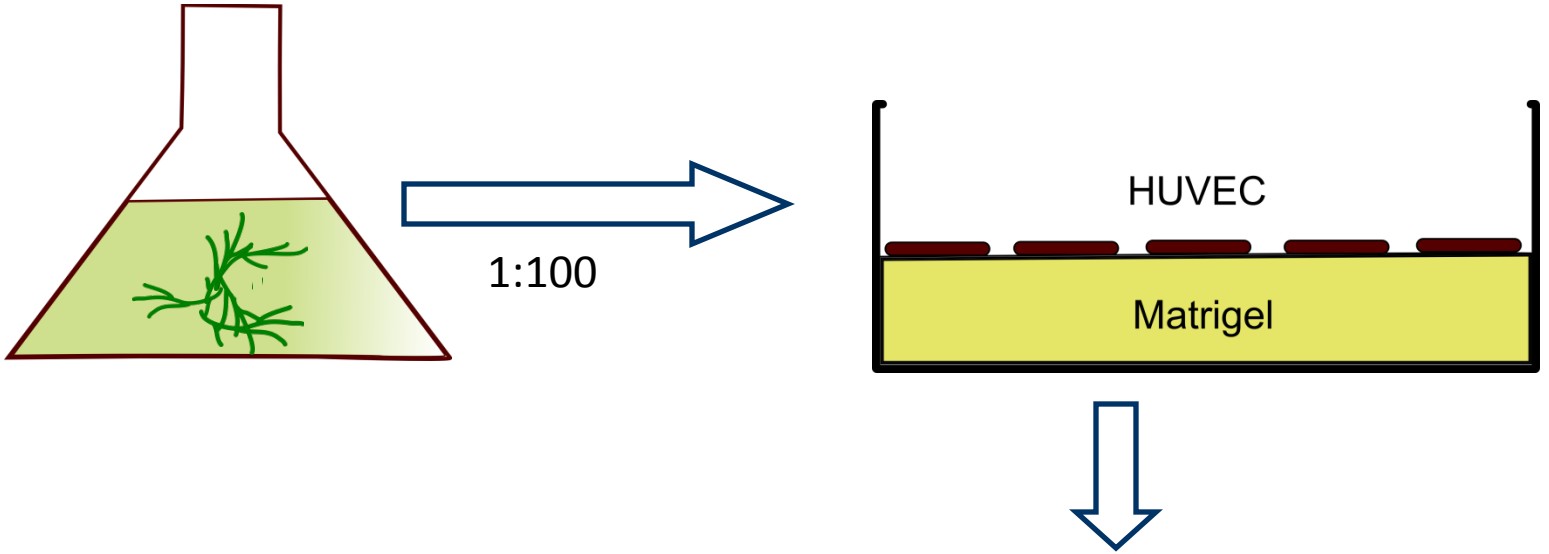


Walmsley et al., JEM 2005

The angiogenesis tipping point: equilibrium between pro- and anti-angiogenic signals?

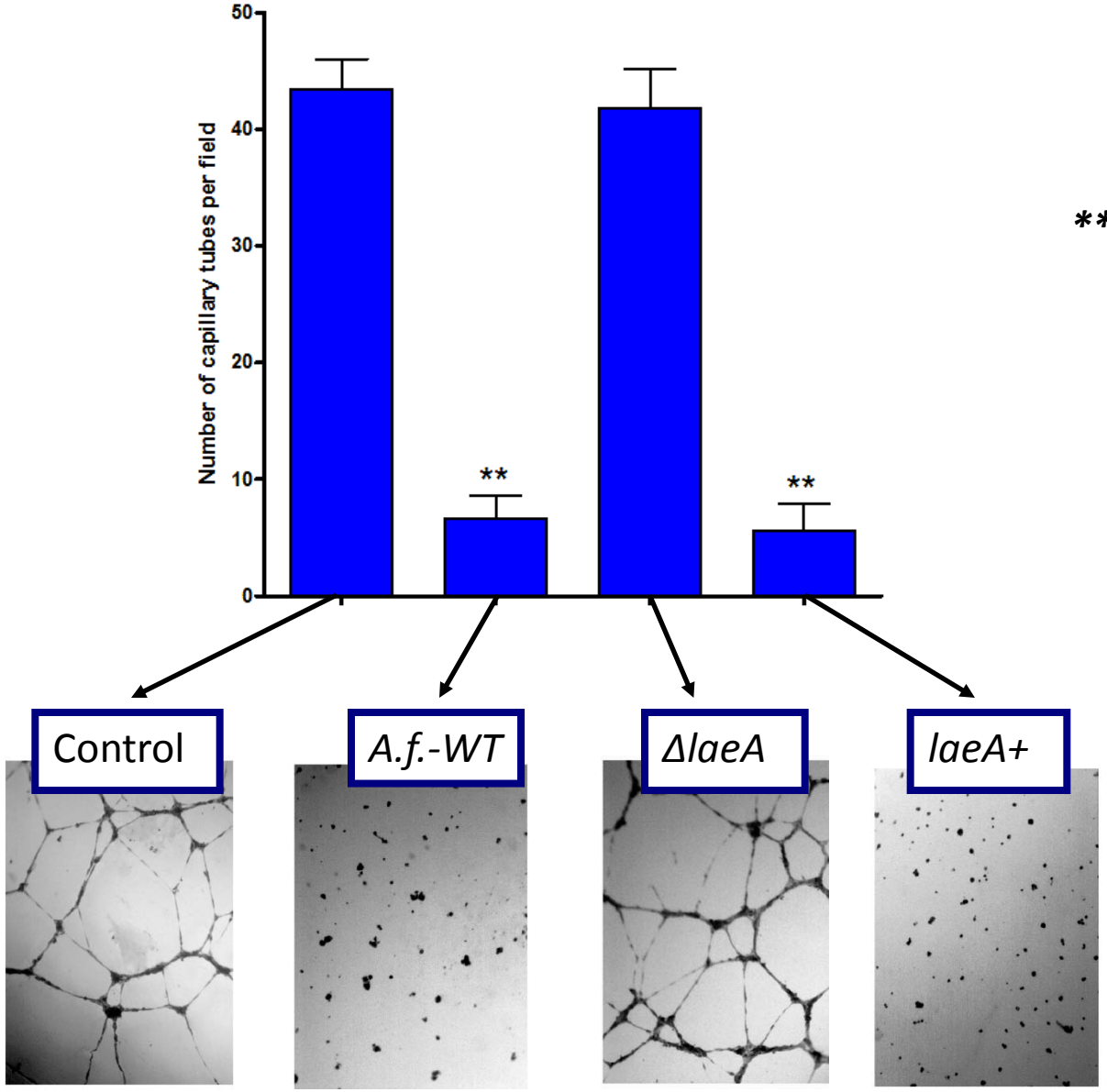


Aspergillus fumigatus culture filtrates inhibit angiogenesis in vitro



Ben-Ami et al. Blood 2009

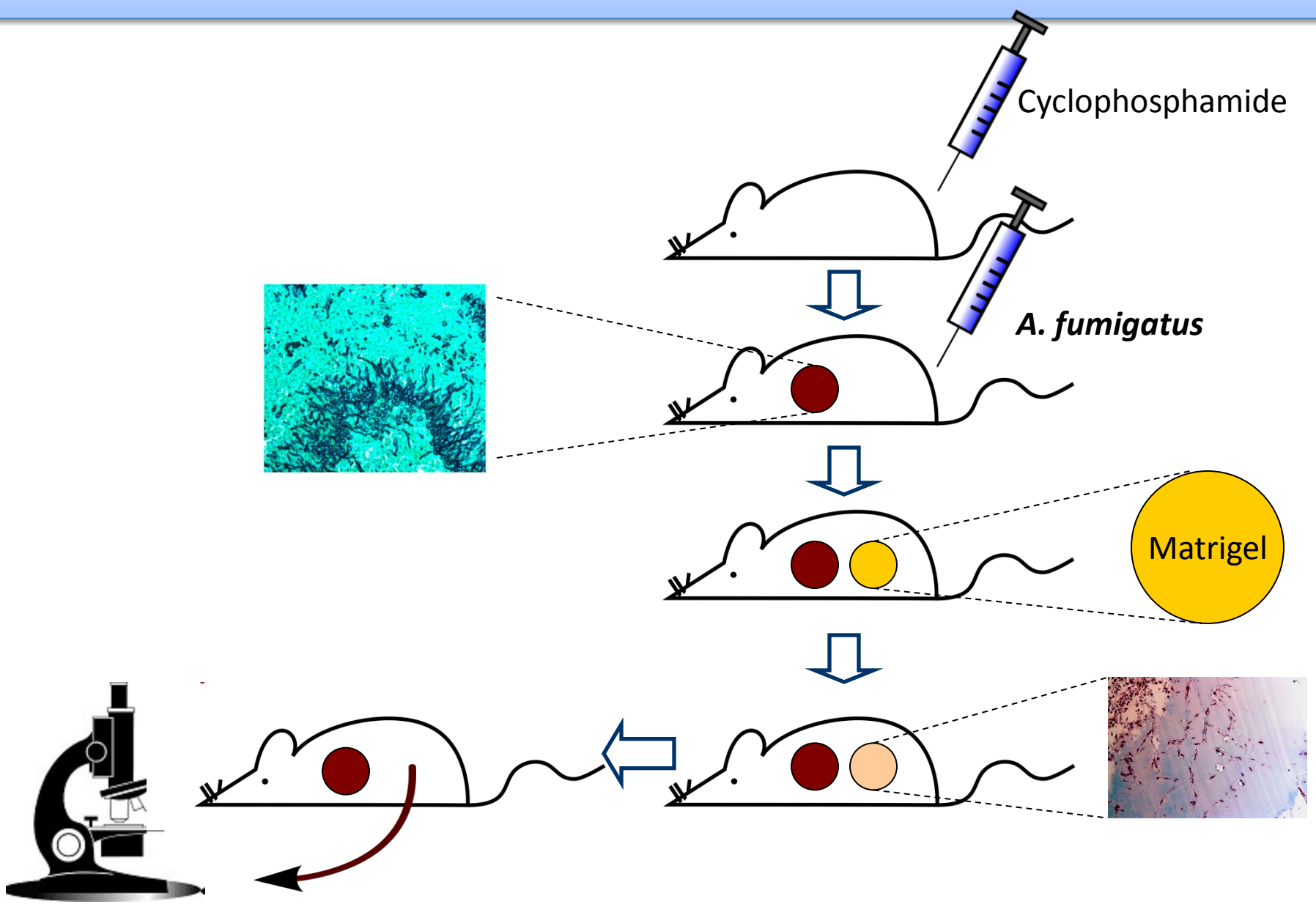
Suppression of angiogenesis is dependent on secondary metabolism



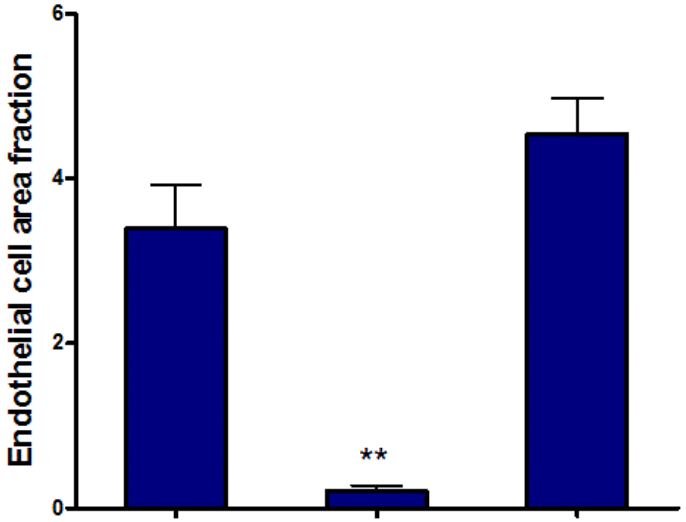
***P*<0.001

Ben-Ami et al. Blood 2009

Cutaneous murine aspergillosis as a model to monitor angiogenesis at the site of infection



Angiogenesis is suppressed in animal model of cutaneous aspergillosis



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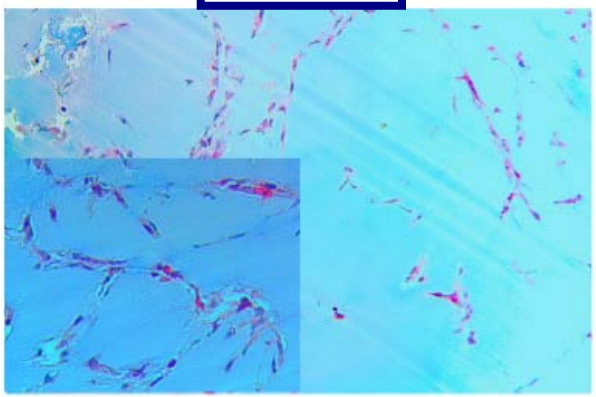
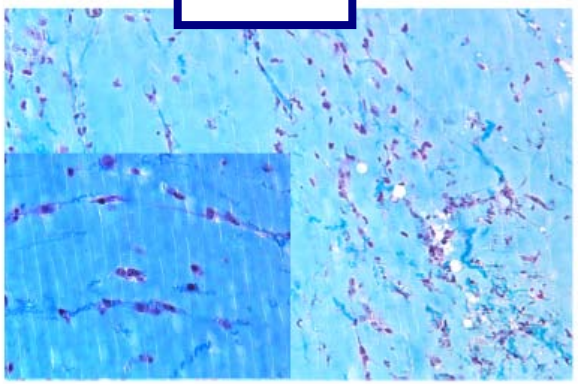
Control



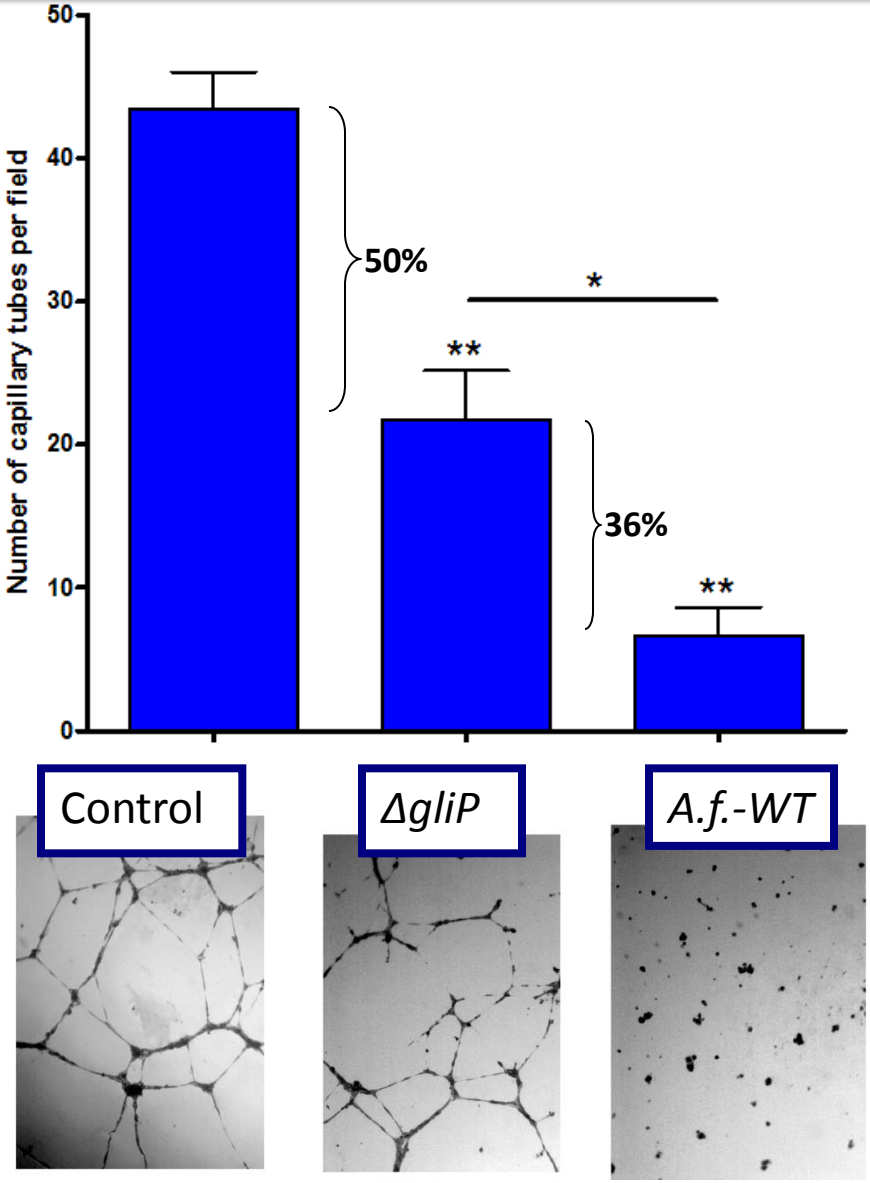
A.f.-WT

ΔlaeA



Ben-Ami et al. Blood 2009

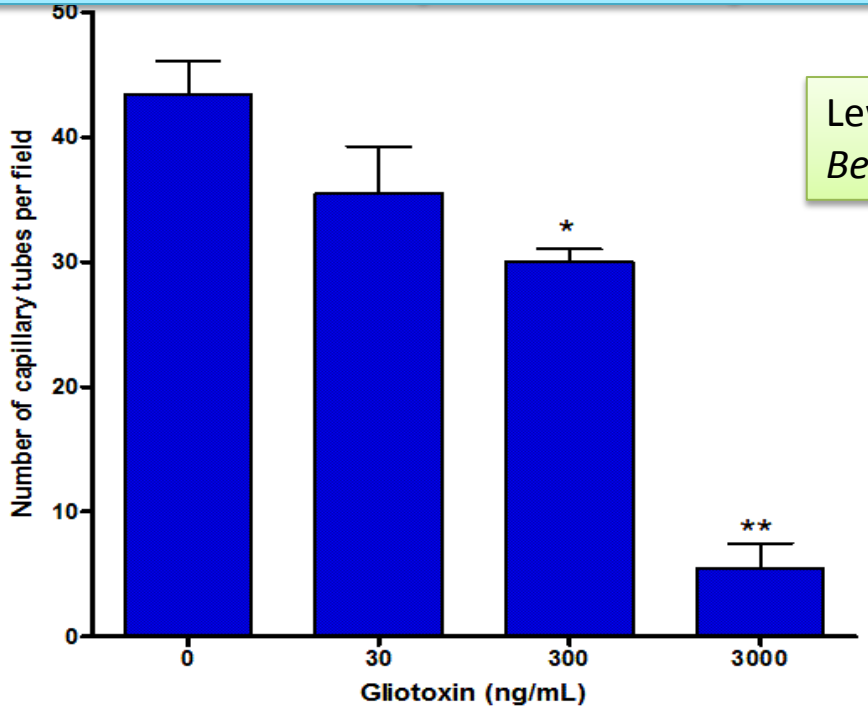
Gliotoxin is responsible for part of culture filtrate-induced angiogenesis inhibition



*P<0.01
**P<0.001

Ben-Ami et al. Blood 2009

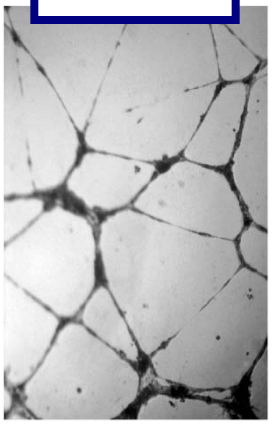
Gliotoxin suppresses angiogenesis at concentrations measured in pulmonary tissue



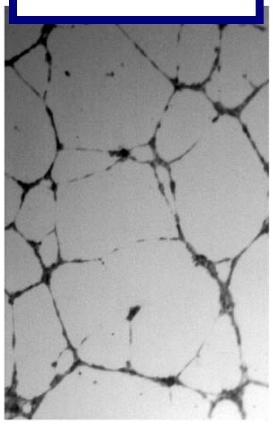
Lewis et al. *Infect Immun* 2005
Ben-Ami et al. Blood 2009

**P*<0.01
***P*<0.001

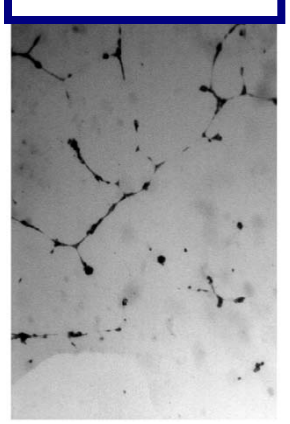
Control



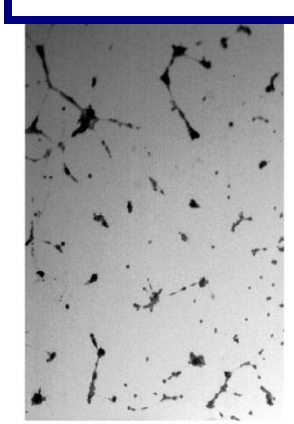
30 ng/mL



300 ng/mL

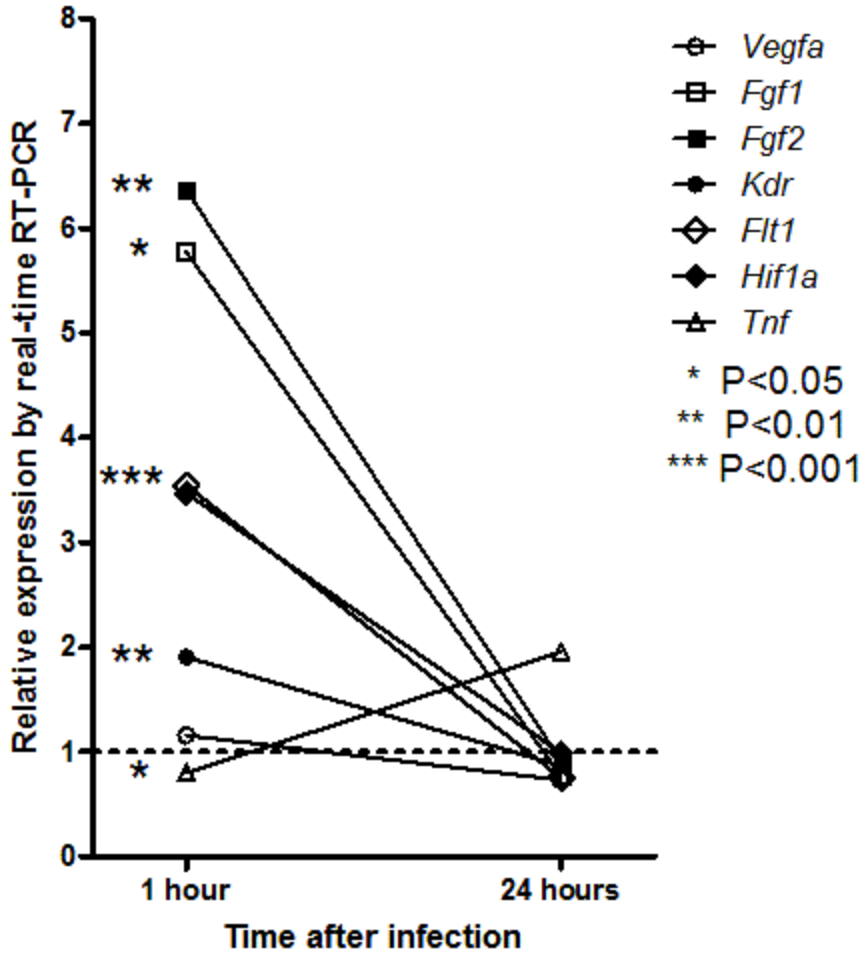


3000 ng/mL

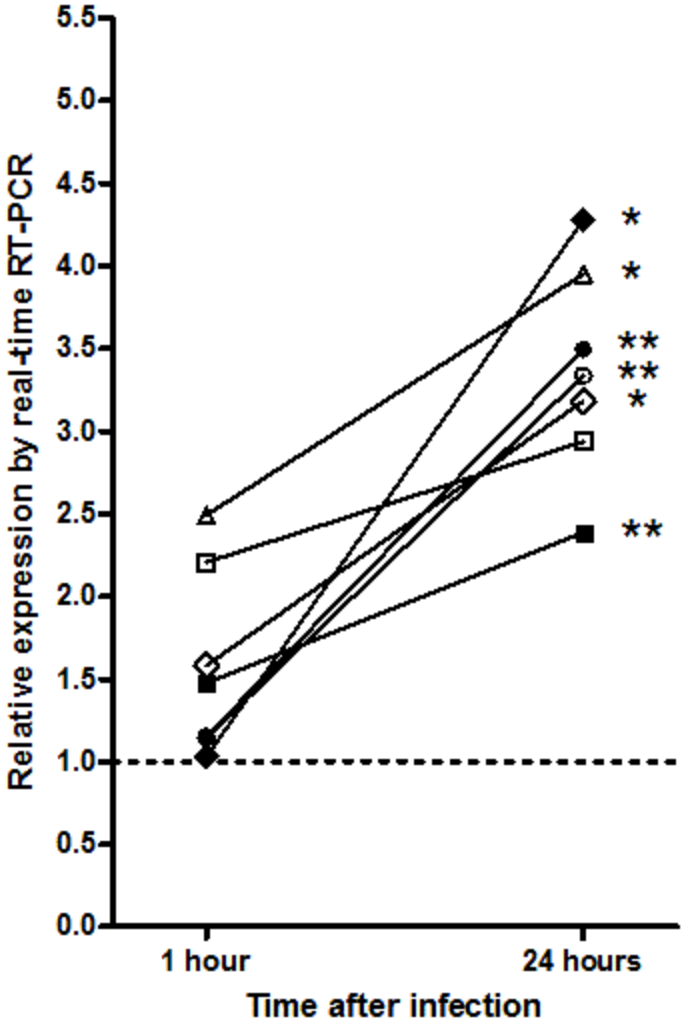


Expression of angiogenesis-relevant genes during the initial 24 h of IPA depends on method of immunosuppression

Cyclophosphamide/cortisone



Cortisone only



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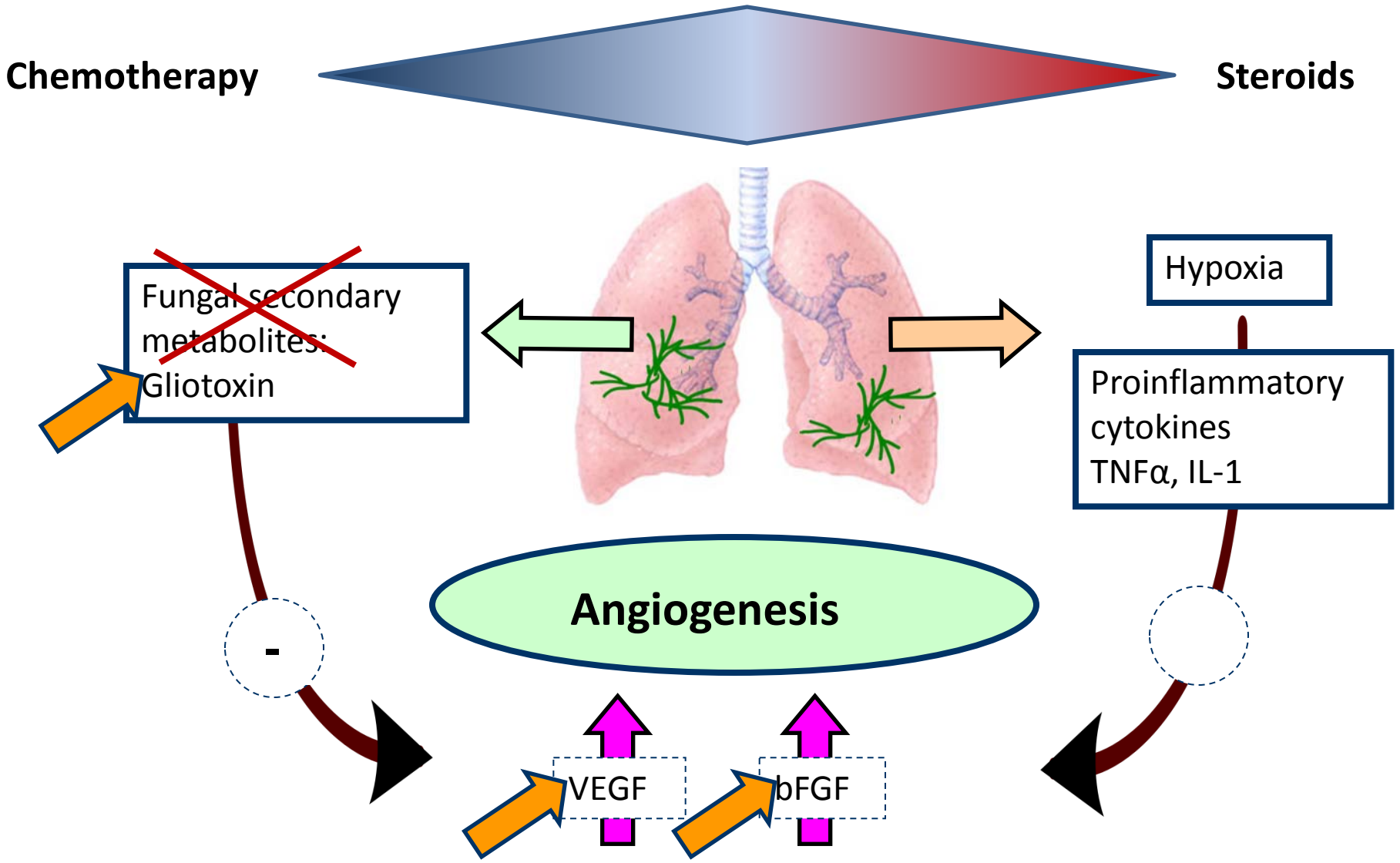
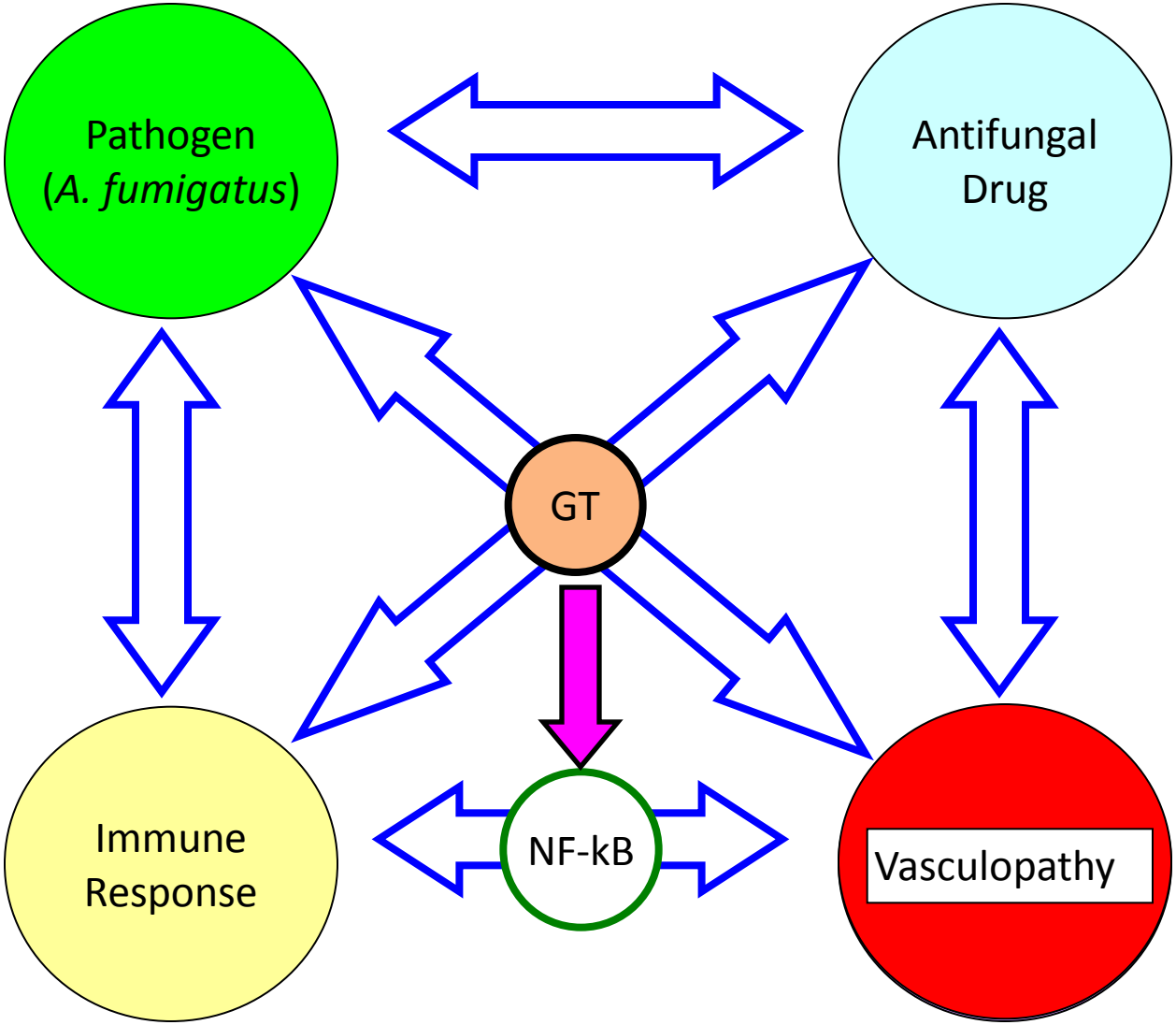
The pro/anti angiogenic equilibrium: a potential therapeutic target?



Invasive pulmonary aspergillosis



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