ANGIOGENESIS BLOCKADE
AS A NEW THERAPEUTIC
APPROACH TO EXPERIMENTAL COLITIS

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Background - I

- Neoangiogenesis is defined as the growth of new blood vessels.

- Angiogenesis plays a critical role in the pathogenesis of cancer and several chronic inflammatory disorders, like rheumatoid arthritis, psoriasis, and atherosclerosis.

- In chronic inflammatory disorders neoangiogenesis is called “pathological angiogenesis”, because it is intimately involved in disease mechanisms.
When the endothelium undergoes angiogenesis, it displays a unique pattern of surface molecules not expressed by resting vessels.

Integrin $\alpha V\beta 3$ is a key molecule selectively expressed by angiogenic vessels and absent in resting vessels.

Integrin $\alpha V\beta 3$ is considered the prototypical marker of angiogenic vessels.
Immunohistochemical staining of control and IBD mucosa with antibodies against CD31 and factor VIII

Danese S, Gastroenterology 2006
Increase in $\alpha v\beta 3$-expressing vessels in IBD mucosa

Danese S, Gastroenterology 2006
Given the complex pathogenesis of chronic diseases, multiple cells and pathways may become potential therapeutic targets.

The "disease-feeding" tissue microvasculature has recently emerged as a prime target in both malignant and inflammatory conditions.

Targeting \(\alpha V\beta 3\)-positive neoangiogenic vessels is being explored as a novel therapeutic strategy in inflammatory conditions like rheumatoid arthritis and psoriasis.
Aims

• Investigate whether neoangiogenesis occurs in experimental inflammatory bowel disease (IBD).

• Test the potential therapeutic effect of blocking angiogenesis by targeting integrin $\alpha V\beta 3$ in the IL-10$^{-/-}$ model of colitis.
Methods

• Three week old IL-10-/- mice kept in an ultra barrier facility (UBF) were transferred to conventional housing, where progressively developed colitis over a period of 10 weeks.

• A colitis disease activity index (DAI) was calculated as a total score including diarrhea, bloody stools, and rectal prolapse.

• ATN-161, an anti-angiogenic $\alpha V\beta 3$-blocking peptide, or its scrambled peptide, was given i.p., at 1 mg/kg, 3 times/week.

• Mice were sacrificed after 6 weeks, and inflammation and vascular density were scored in a blinded fashion.

• IL-6 and IL-12 were measured by ELISA in colonic organ cultures.
IL-10^{−/−} STATUS DOES NOT AFFECT MUCOSAL MICROVASCULARIZATION

Danese S, Gut 2007, in press
PROGRESSION OF COLITIS PARALLELS MUCOSAL ANGIOGENESIS

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PROGRESSION OF COLITIS PARALLELS MUCOSAL ANGIOGENESIS

UBF

Conventional housing

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ATN-161 IMPROVES EXPERIMENTAL COLITIS

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ATN-161 DECREASES VASCULAR DENSITY AND IMPROVES COLITIS HISTOLOGICAL SCORE

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ATN-161 DECREASES VASCULAR DENSITY AND IMPROVES COLITIS HISTOLOGICAL SCORE

Danese S, Gut 2007, in press
ATN-161 DECREASES MUCOSAL IL-6 AND IL-12 PRODUCTION

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ATN-161 DOES NOT AFFECT IL-12 PRODUCTION BY LAMINA PROPRIA MONONUCLEAR CELLS

Danese S, Gut 2007, in press
CONCLUSIONS

• Intense neoangiogenesis occurs in the mucosal microvasculature of IL-10−/− colitic mice and parallels progression of inflammation.

• Blockade of \(\alpha V\beta3\) effectively decreases neoangiogenesis and inflammation in this model of IBD.

• Results provide the material and conceptual bases for considering anti-angiogenic strategies in the treatment of human IBD, as currently tested in other chronic inflammatory disorders.
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