Combination Immune-Antiangiogenic Therapy: Lessons from Ovarian Cancer

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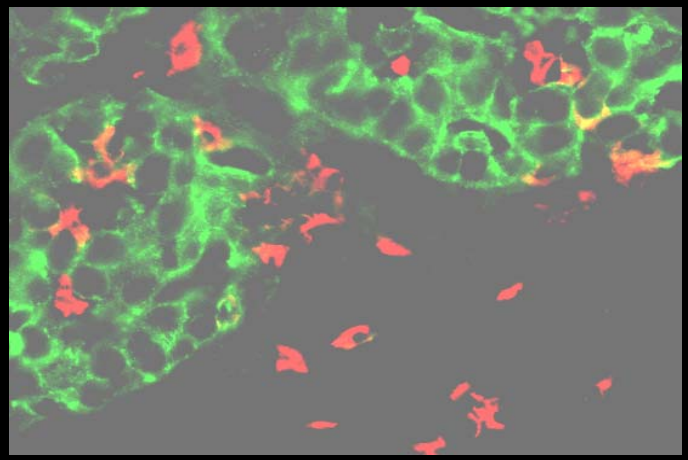
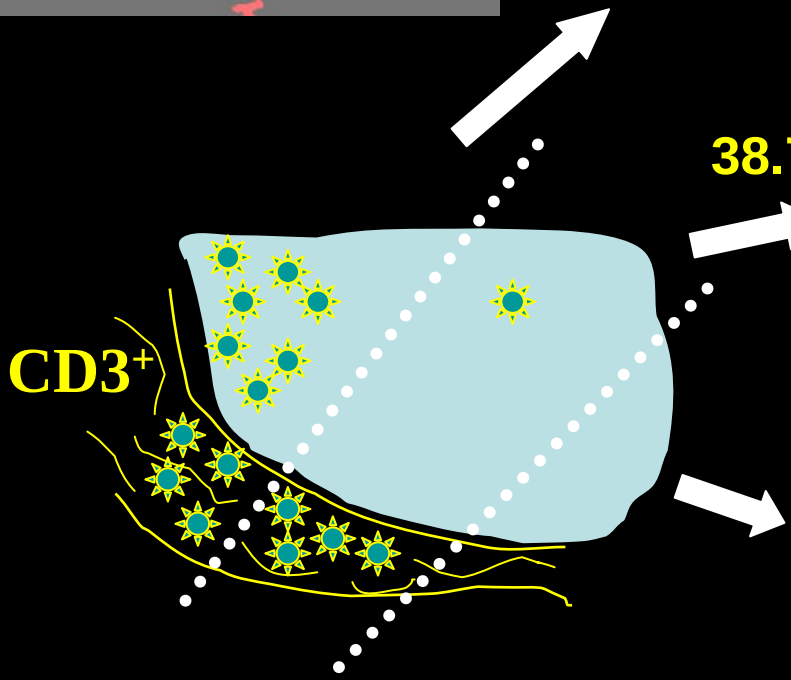
Goals

1) Explain the scientific rationale for the combinations - "Why would it work?“
2) Summarize data on use of the combinations, both preclinical and clinical
3) Summarize potential pitfalls and complications to be aware of - "Why it may not work“
4) Suggest the next steps that should be made

Why would it work?

1) Ovarian cancer is immunogenic tumor
2) Antiangiogenic therapy has produced significant results: Single agent bevacuzimab ~20% RR, higher with metronomic cyclophosphamide
3) VEGF suppresses the maturation of DCs

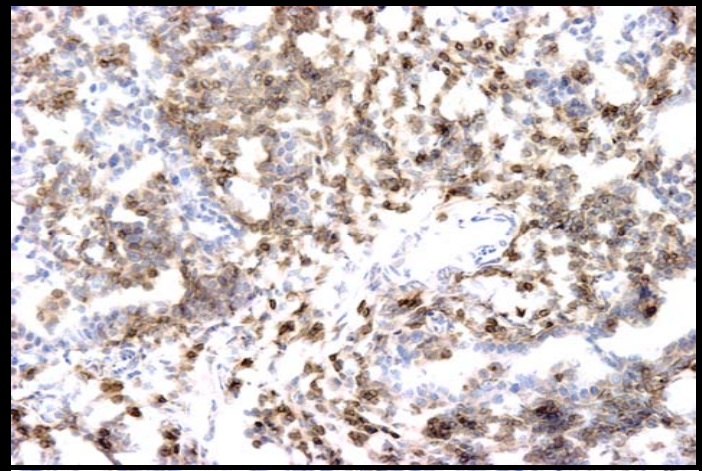


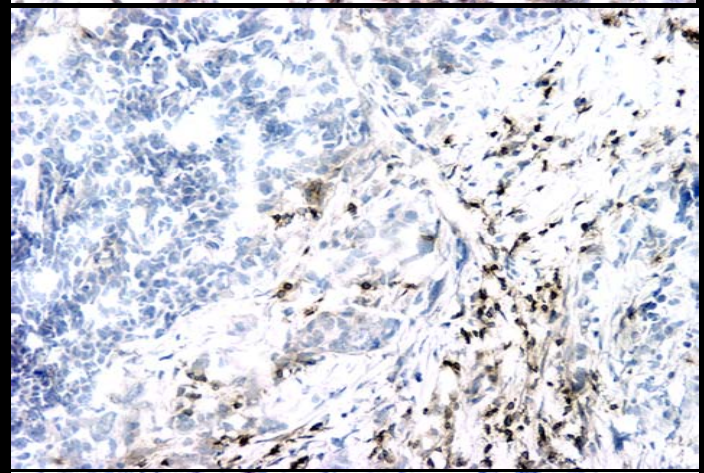


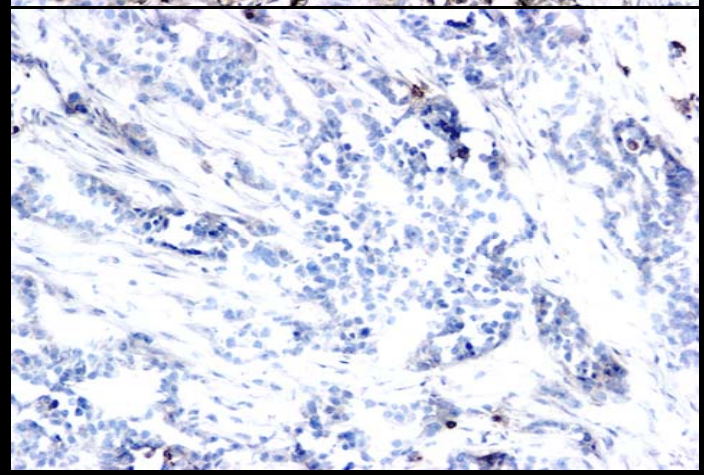
54.8%

38.7%

6.5%







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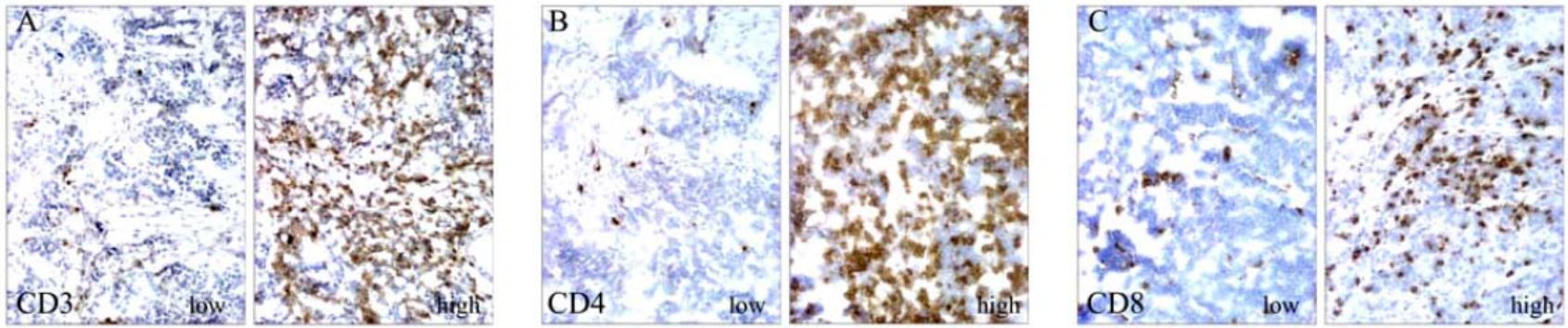
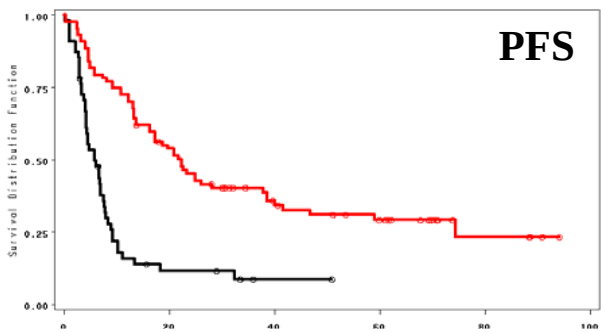
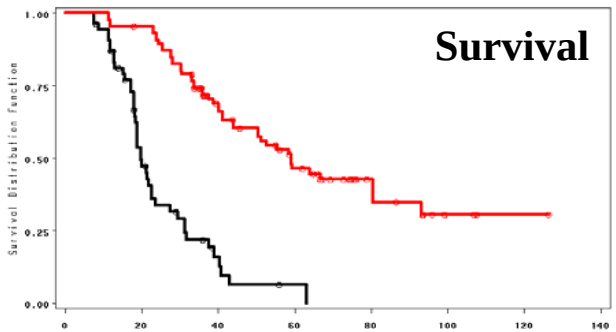
Zhang et al., *NEJM* 2003

Impact of Inratumoral T cells on Outcome in Ovarian Cancer Stage III/IV patients







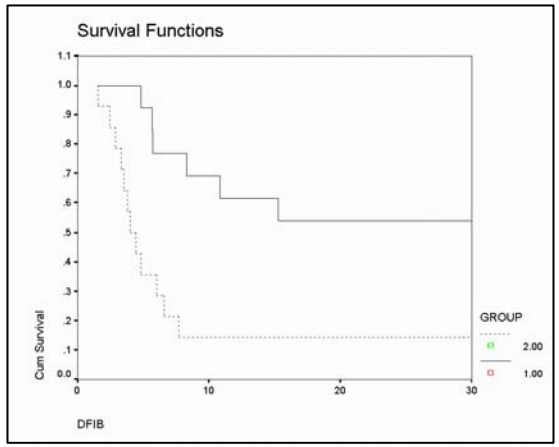
+ TILs

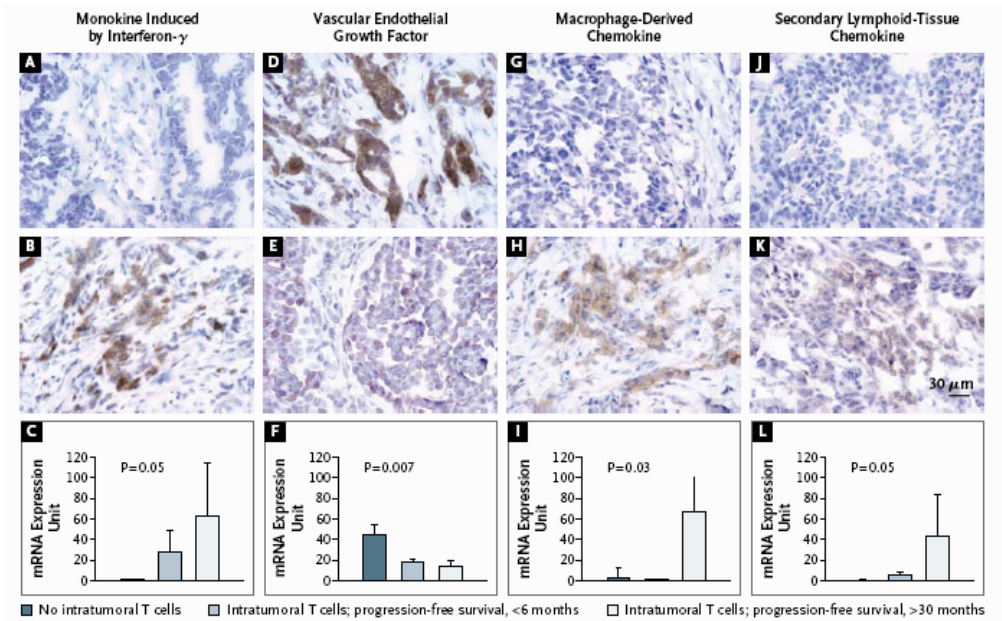
- TILs

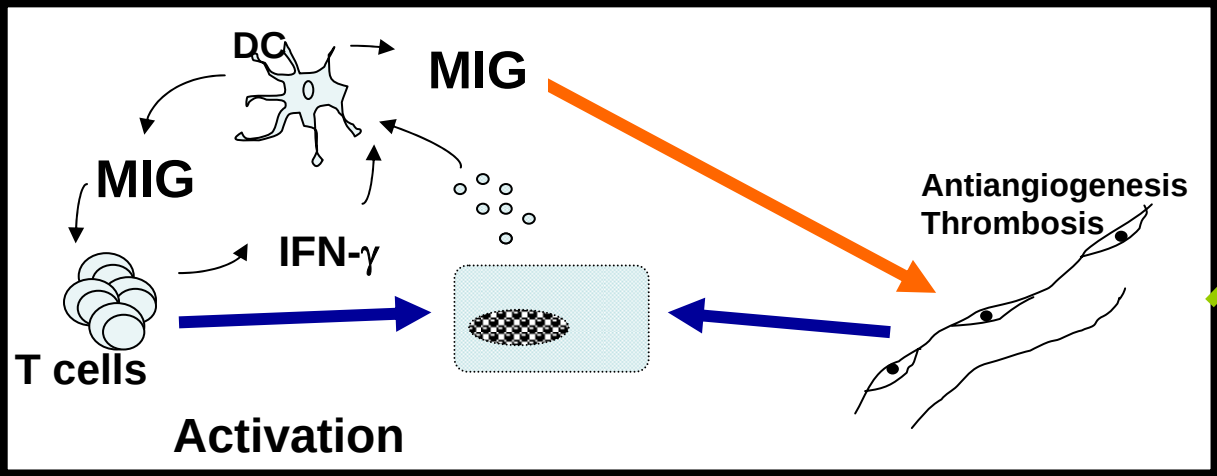
N=174

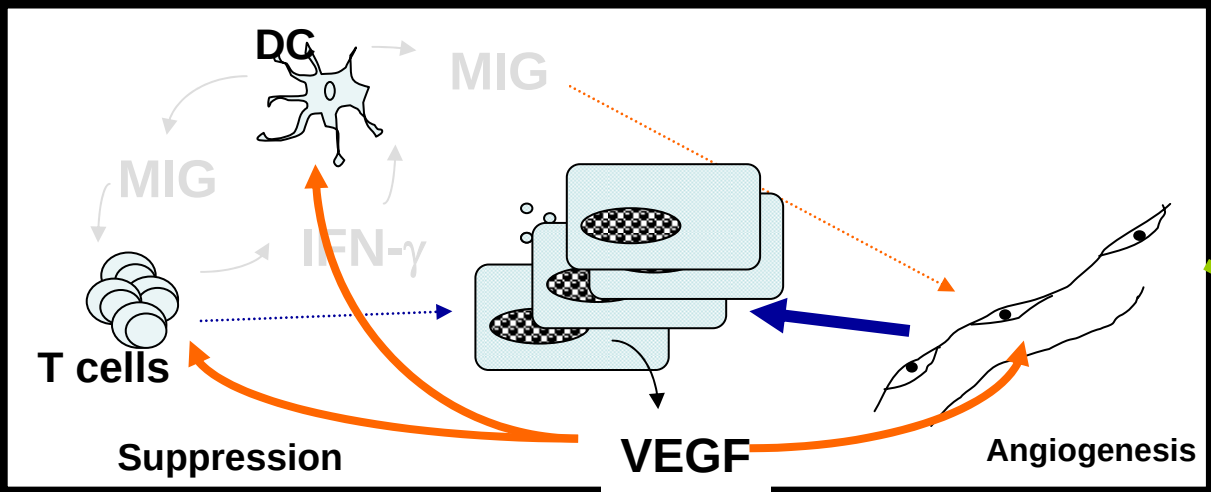
Zhang et al., *NEJM* 2003

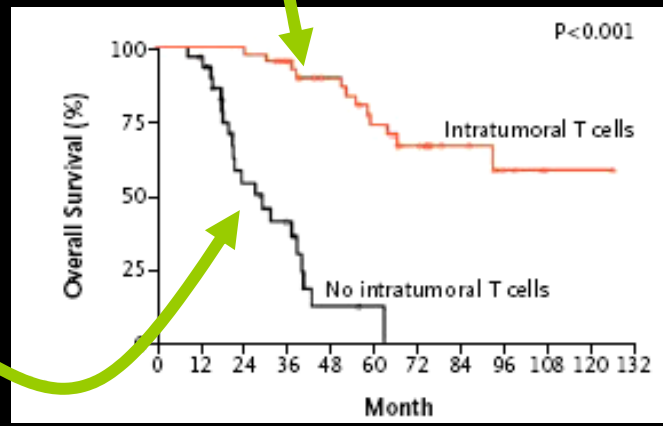
VEGF associates with poor outcome and absence of intratumoral T cells






DC
MIG
MIG
IFN-γ
T cells
Activation
Antiangiogenesis
Thrombosis

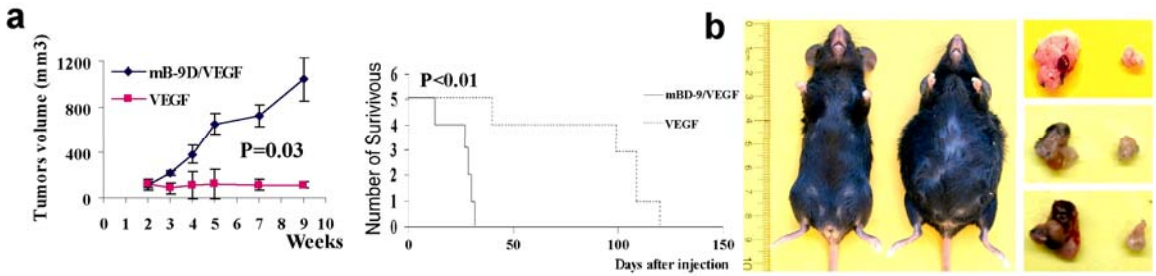

DC
MIG
MIG
IFN-γ
T cells
Suppression
VEGF
Angiogenesis

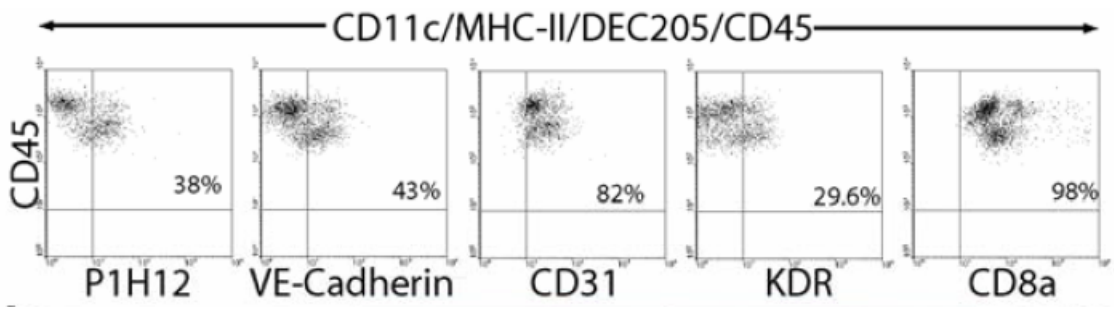

P<0.001
Overall Survival (%)
100
75
50
25
Intratumoral T cells
No intratumoral T cells
0 12 24 36 48 60 72 84 96 108 120 132
Month

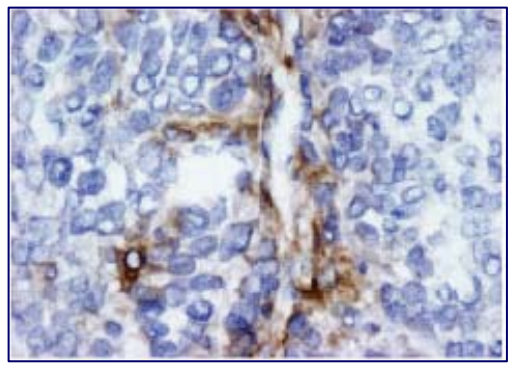
nature medicine

Tumor-infiltrating dendritic cell precursors recruited by a β-defensin contribute to vasculogenesis under the influence of Vegf-A

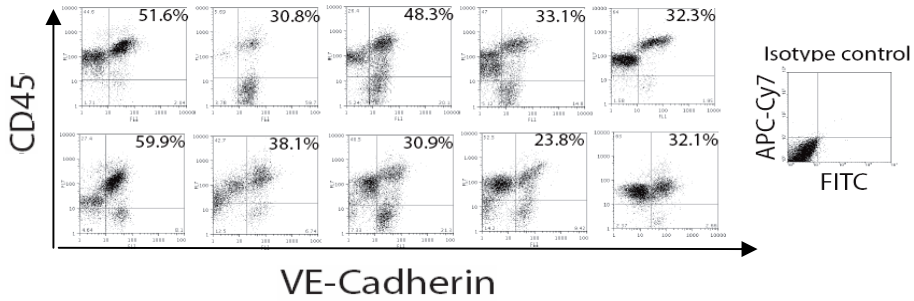
Jose R Conejo-Garcia[1,5], Fabian Benencia[1,5], Maria-Cecilia Courreges[1], Eugene Kang[1], Alisha Mohamed-Hadley[1], Ronald J Buckanovich[1], David O Holtz[1], Ann Jenkins[1], Hana Na[1], Lin Zhang[1,2], Daniel S Wagner[3], Dionyssios Katsaros[4], Richard Caroll[2] & George Coukos[1,2]

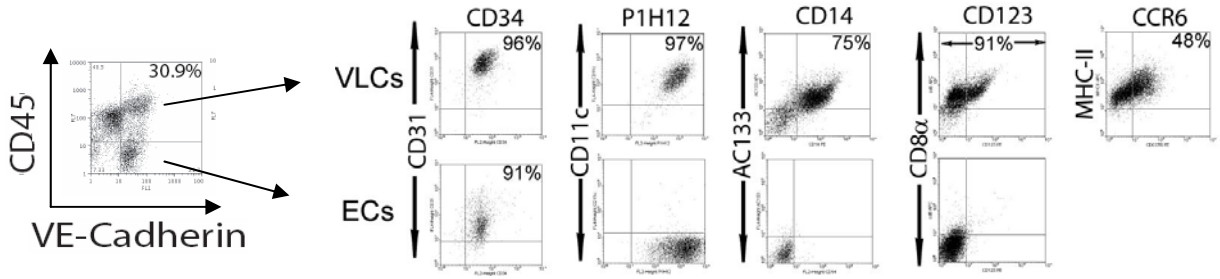


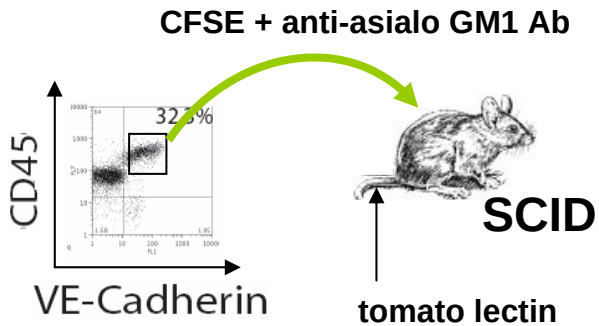


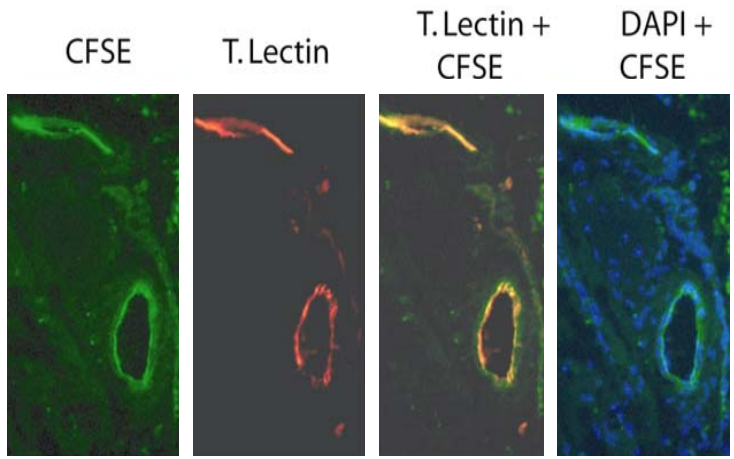


Discovery of Human Vascular DCs









Conejo-Garcia et al., *Blood*. 2005

Why would it NOT work?

1) Non immunogenic tumors – Immune mechanisms have little impact

2) Antiangiogenic therapy has not produced significant results as single agent – Angiogenesis more complex than anticipated, angiogenesis targets less obvious

Future Directions

1) Clinical testing in immunogenic tumors where antiangiogenic therapy has produced significant results as single agent – ovarian cancer

2) Preclinical investigation to identify angiogenesis targets in other tumors and test combination approaches