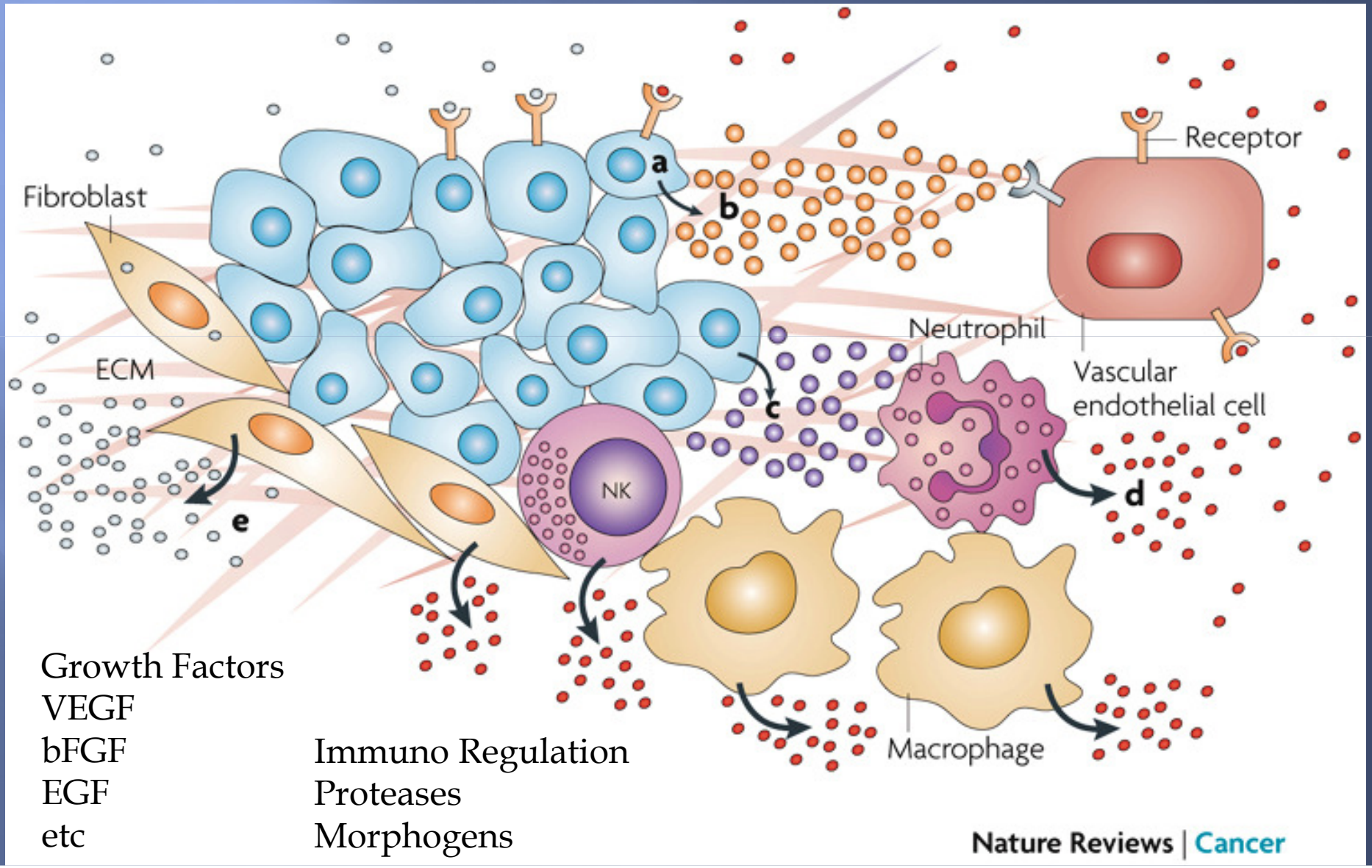
SJTU-School of Pharmacy

Secreted AGR2 Helps Tumor Cells to Establish Its Microenvironment

Dawei Li, Prof.
Center For Cell Engineering And Antibody Medicine
Shanghai Jiao Tong University



Tumor Microenvironment:
Multiple Cell Types , Factors, Receptors

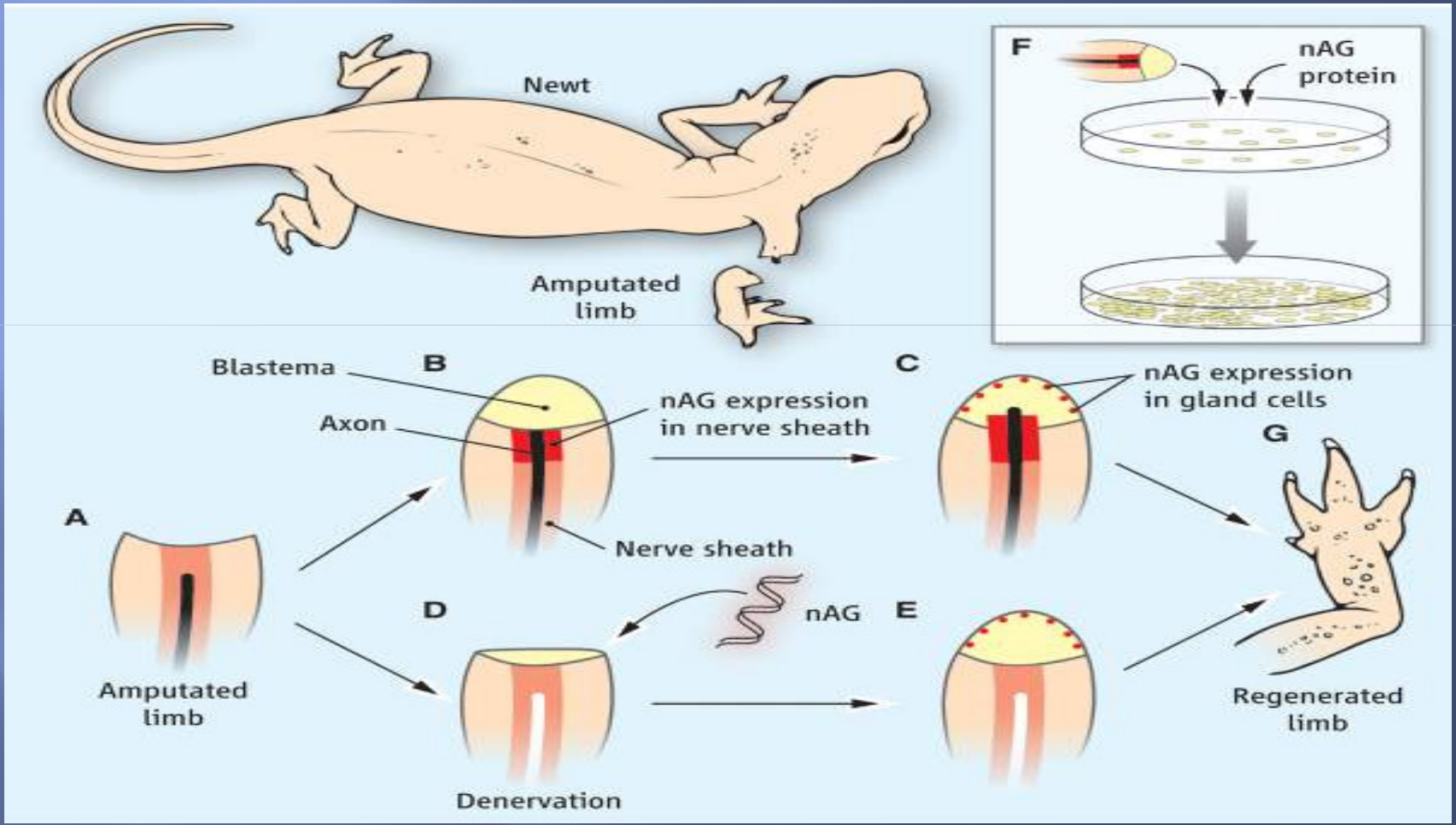


Growth Factors
VEGF
bFGF
EGF
etc

Immuno Regulation
Proteases
Morphogens

AGR2 Is a Key Factor in Tissue Remodeling

- AGR2 is critical in regeneration and promotes cancer formation



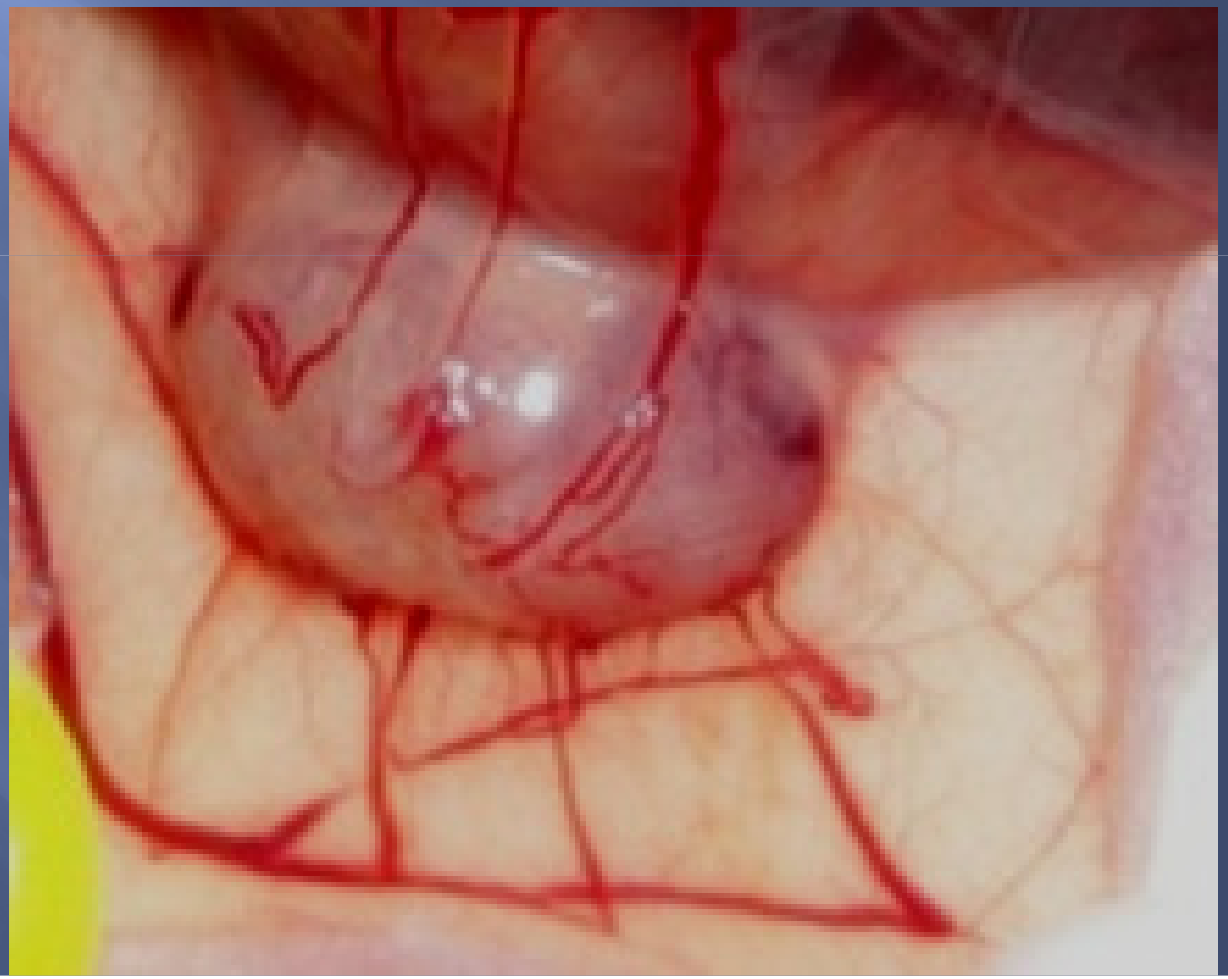
Science (2007) Kumar et al

Targeting Cancer Microenvironment: Beyond Angiogenesis ?

Tumor Remodels Its Microenvironment With Multiple Secreted Factors

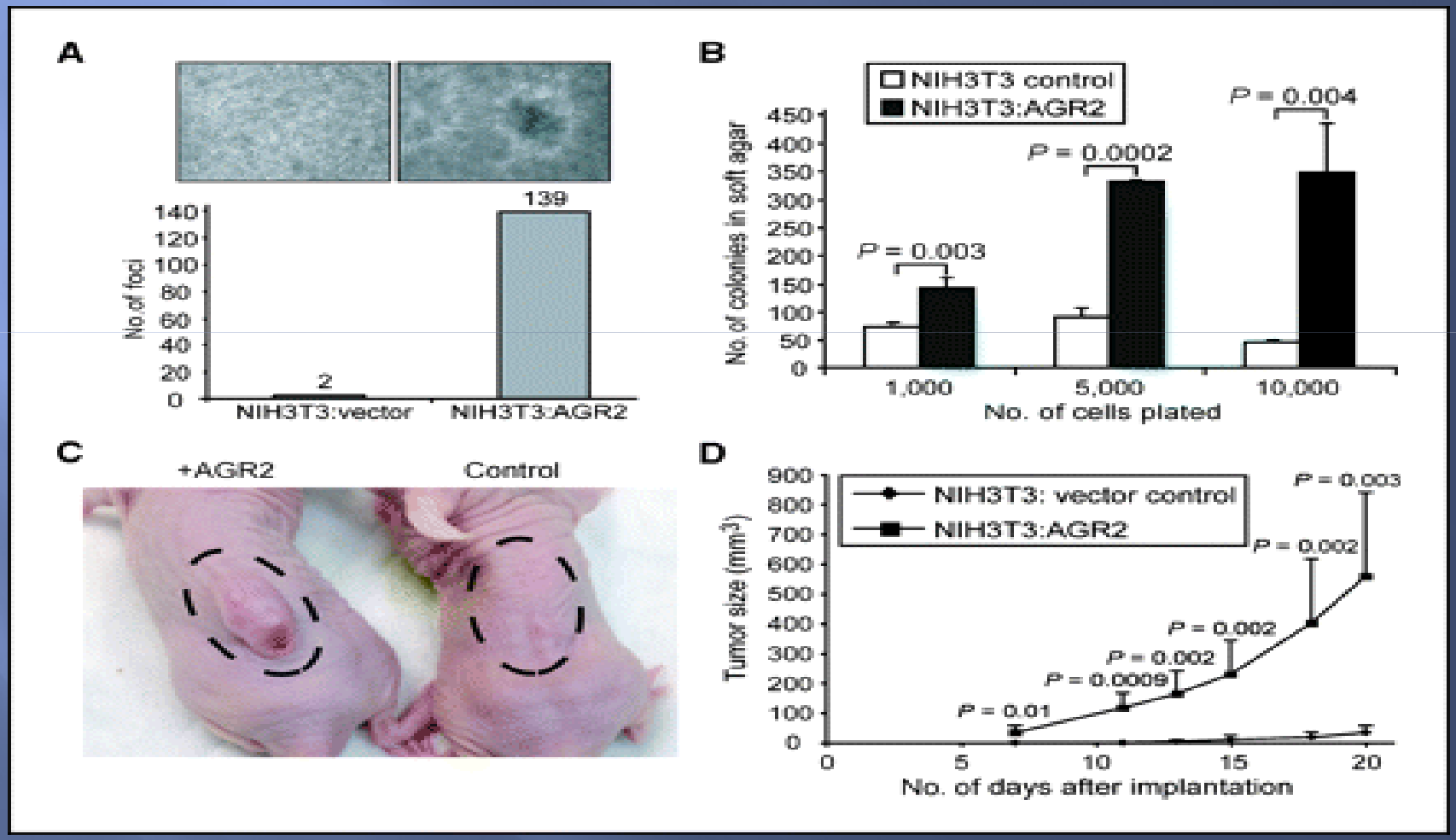
Non-tumor Cells:

- Migration
- Cell Cycle
- Vascularization



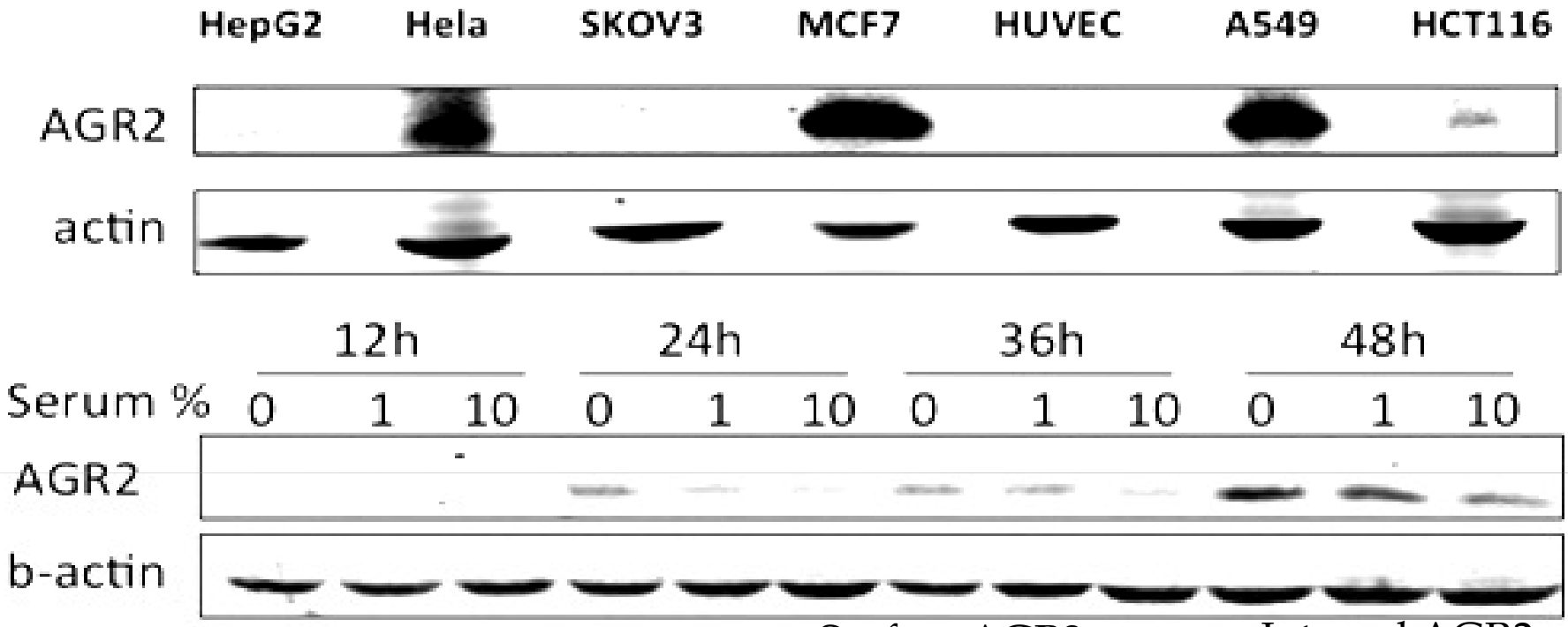
AGR2 Is a Drug Target Against Cancer

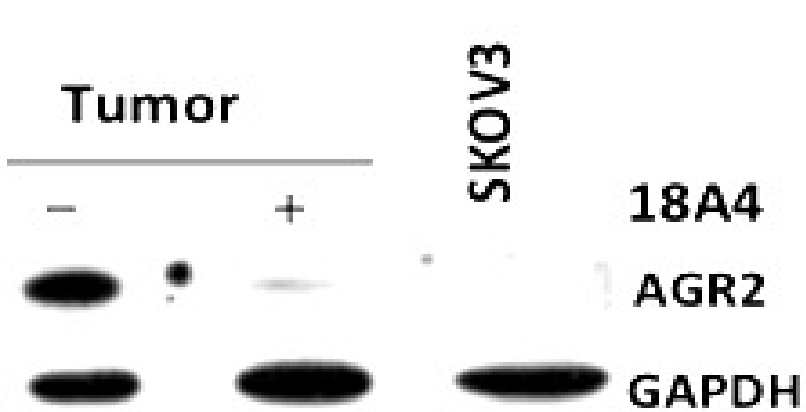
- AGR2 Overexpression increases tumorigenic potential



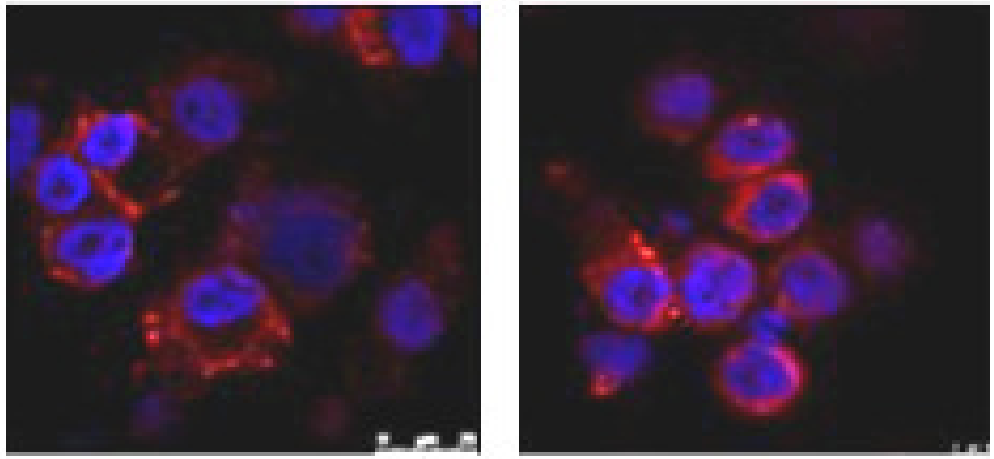
Cancer Research (2008) Wang Zheng et al

AGR2 Is Expressed Through Low Serum Induction



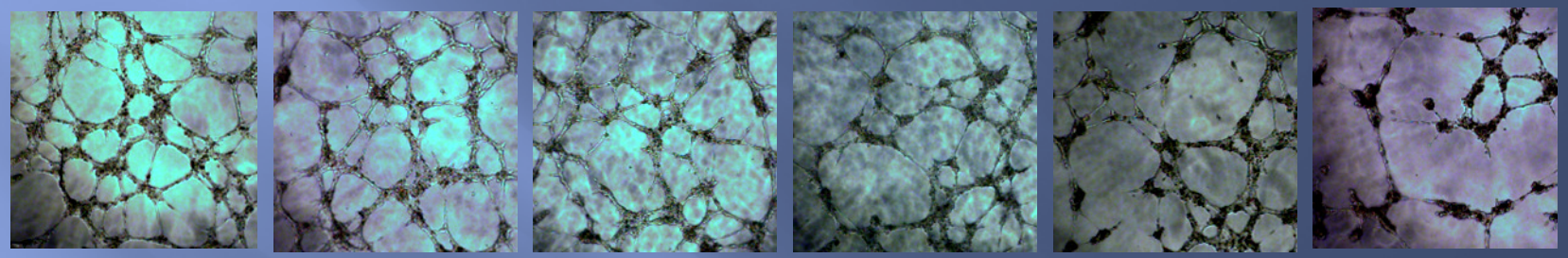


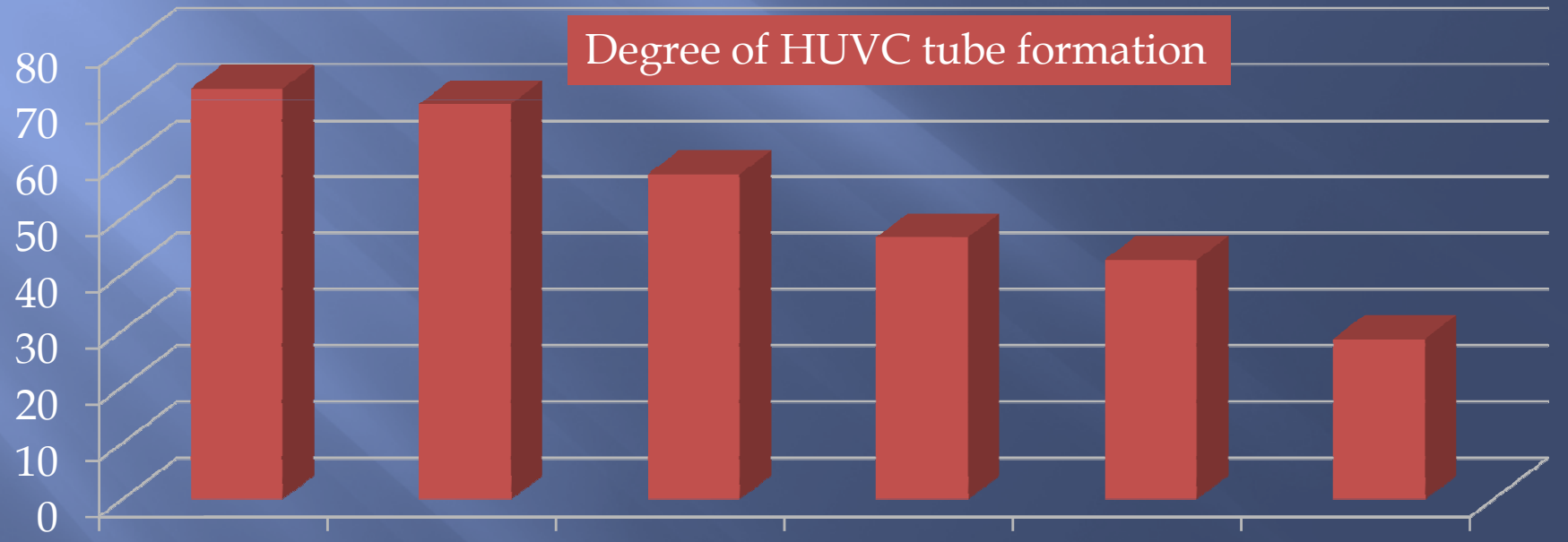
Surface AGR2 Internal AGR2



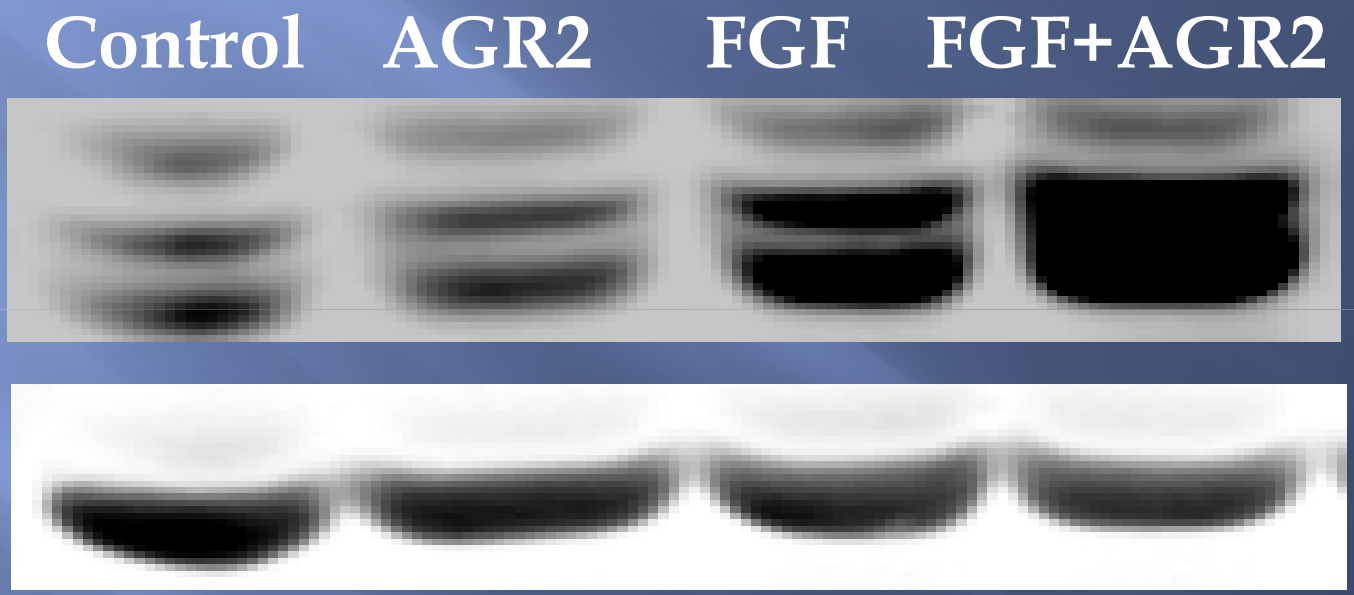
Angiostatic Effect of 18A4

18A4 Reduce HUVE Cell Tube Formation

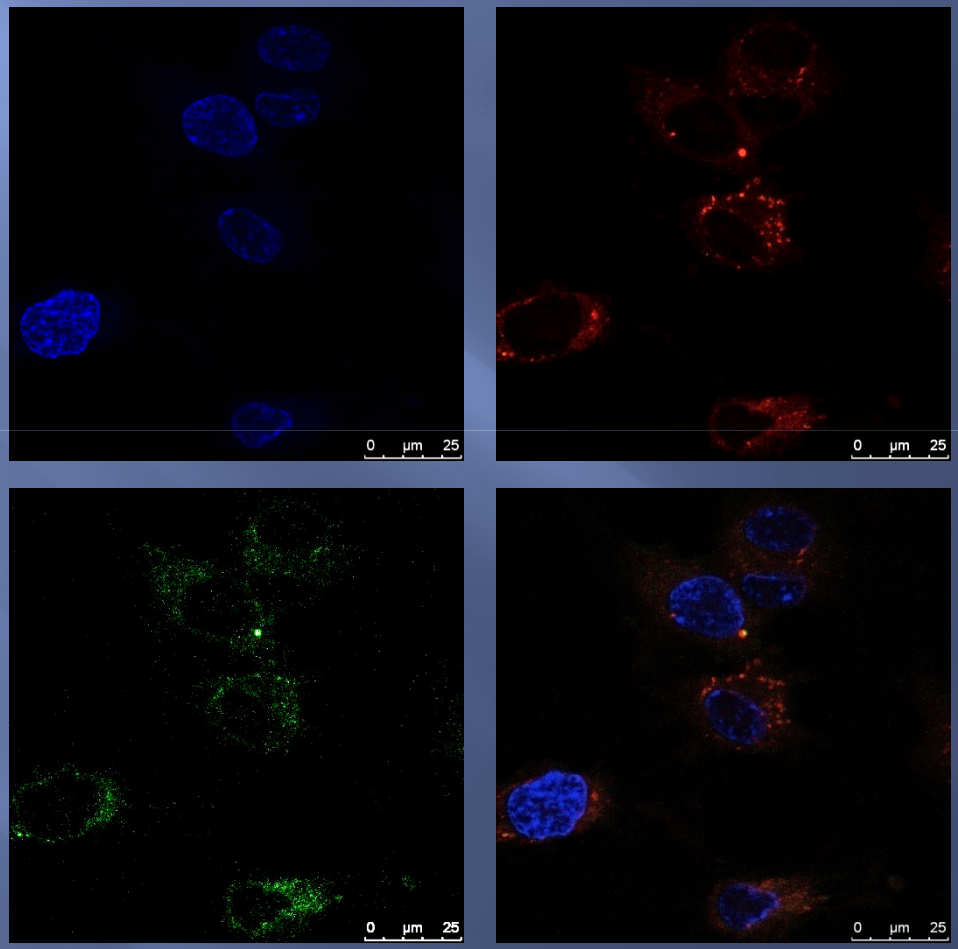




AGR2 Is A Multi-Functional Proliferation Enhancer

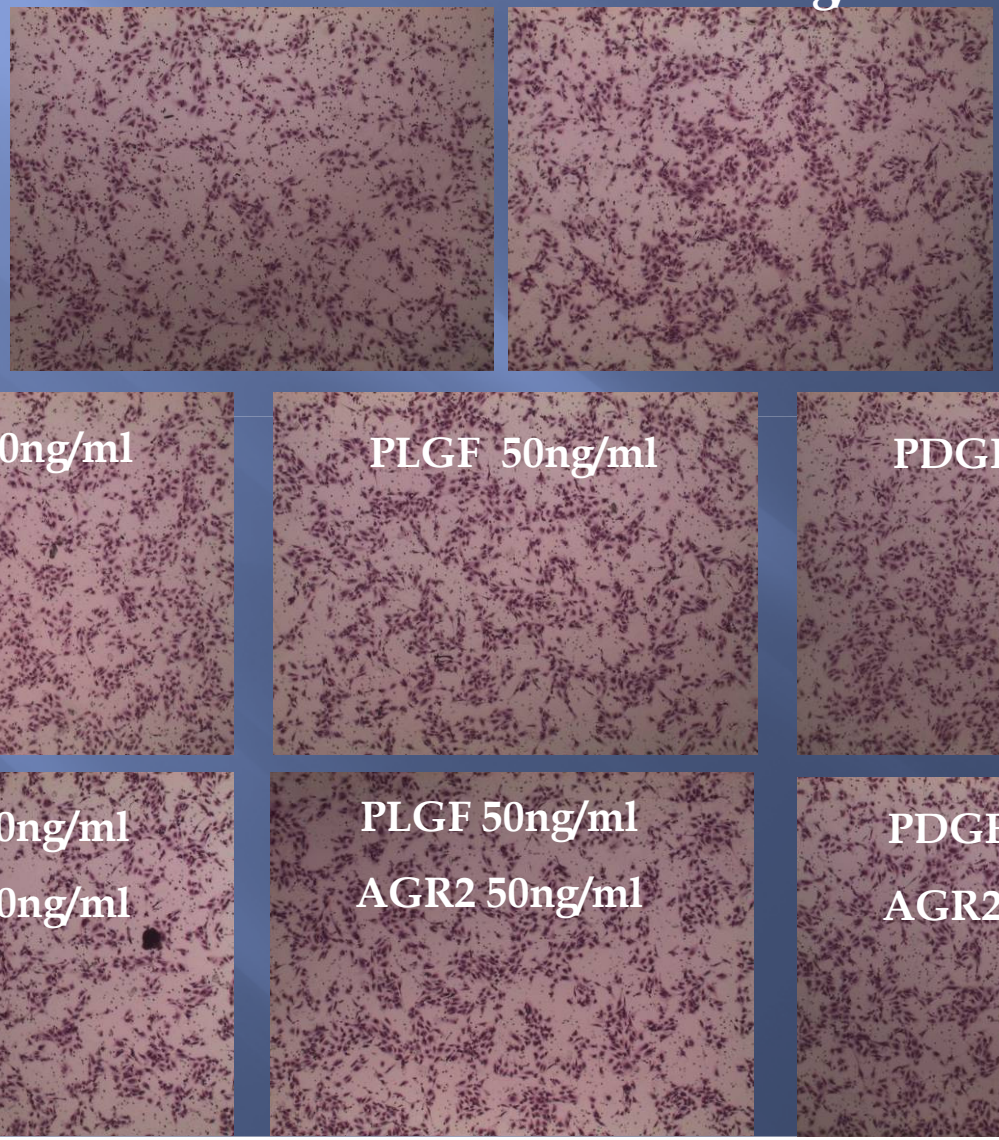


荧光Confocal共定位-AGR2和bFGF相互作用



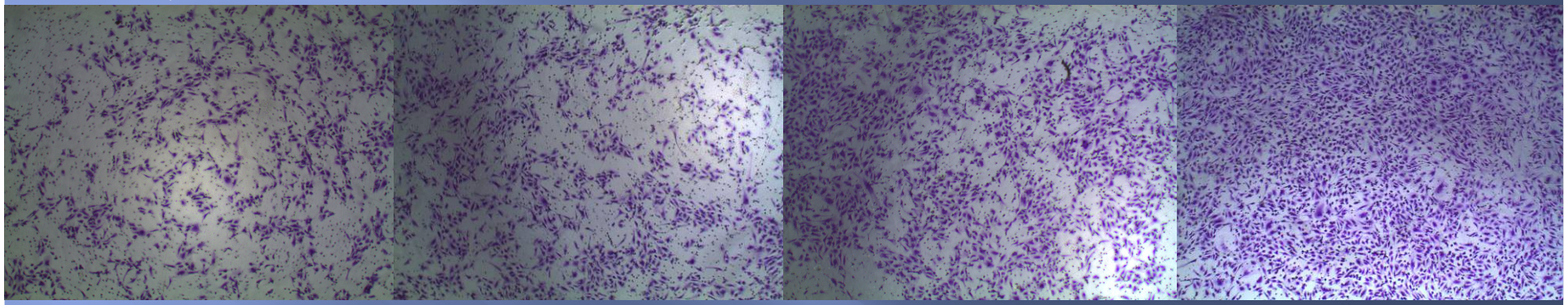
Binding with bFGF, then binding to the membrane of HUVEC.

CAGR2 Has No Effect on Ang-1/PLGF/PDGF Induced Migration

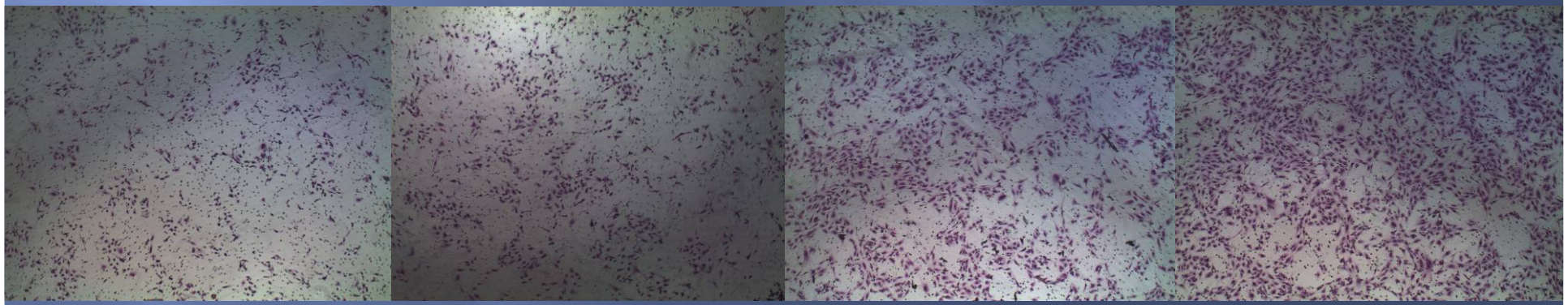


AGR2 增强 bFGF / VEGF在细胞转移实验中的作用

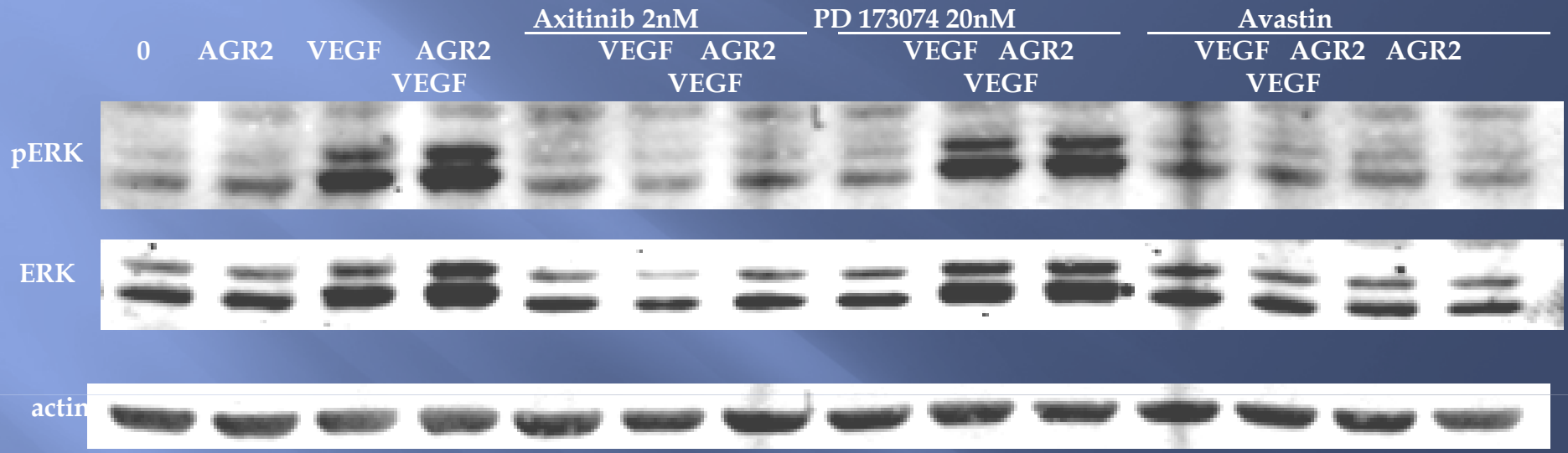
对照 AGR2 VEGF VEGF+AGR2

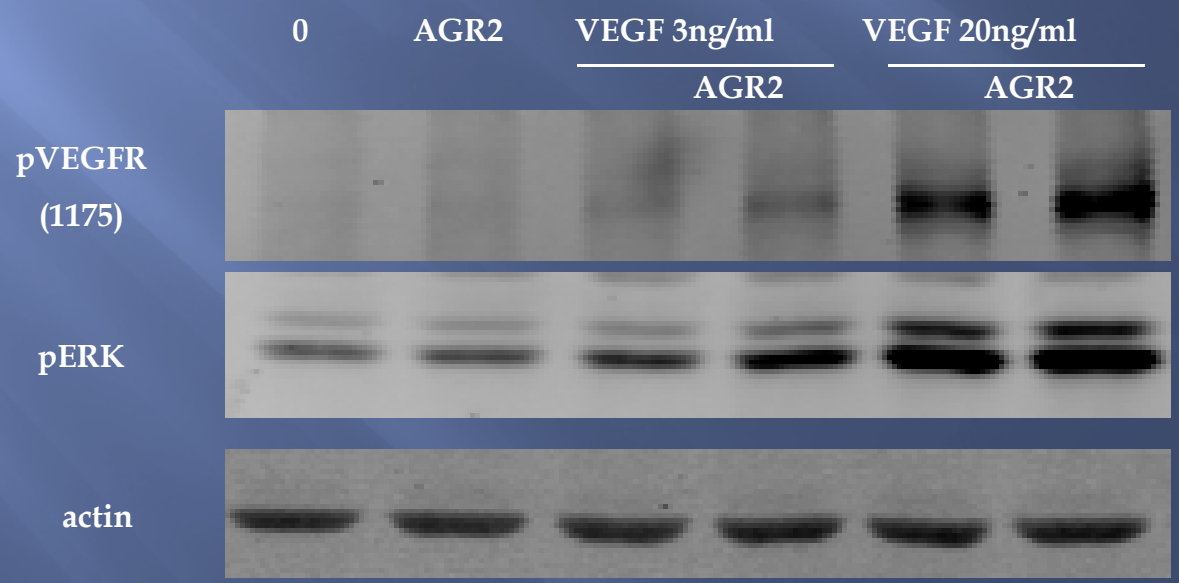


对照 AGR2 bFGF AGR2+bFGF

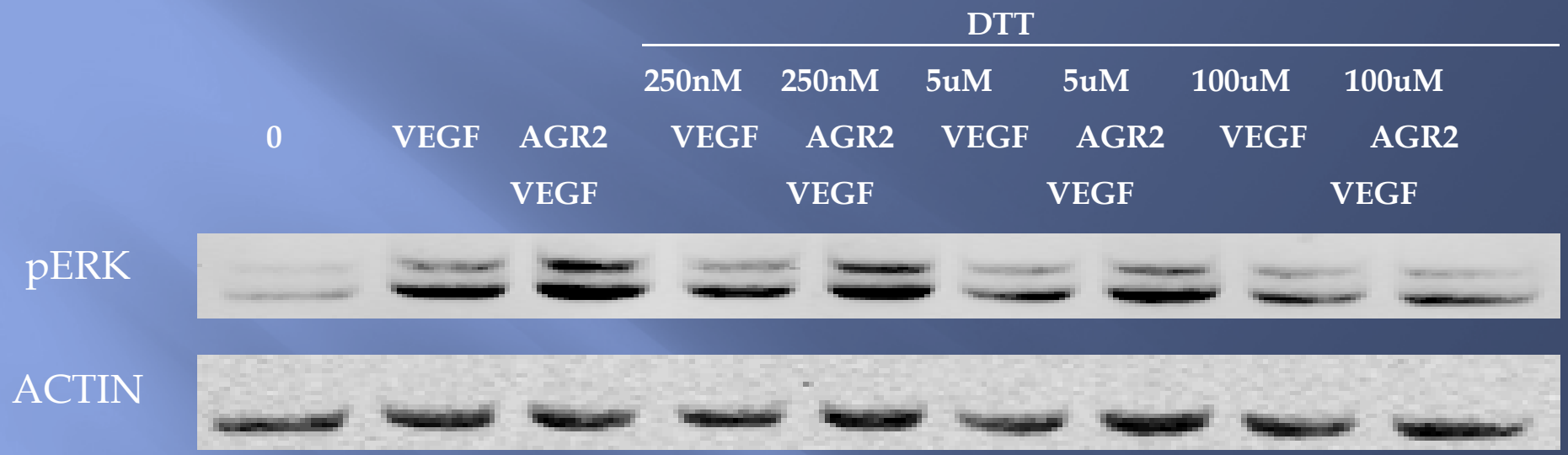


AGR2 can enhance the phosphorylation of ERK and VEGFR caused by VEGF and this effection can be disturbed by VEGFR inhibitor or VEGF antibody

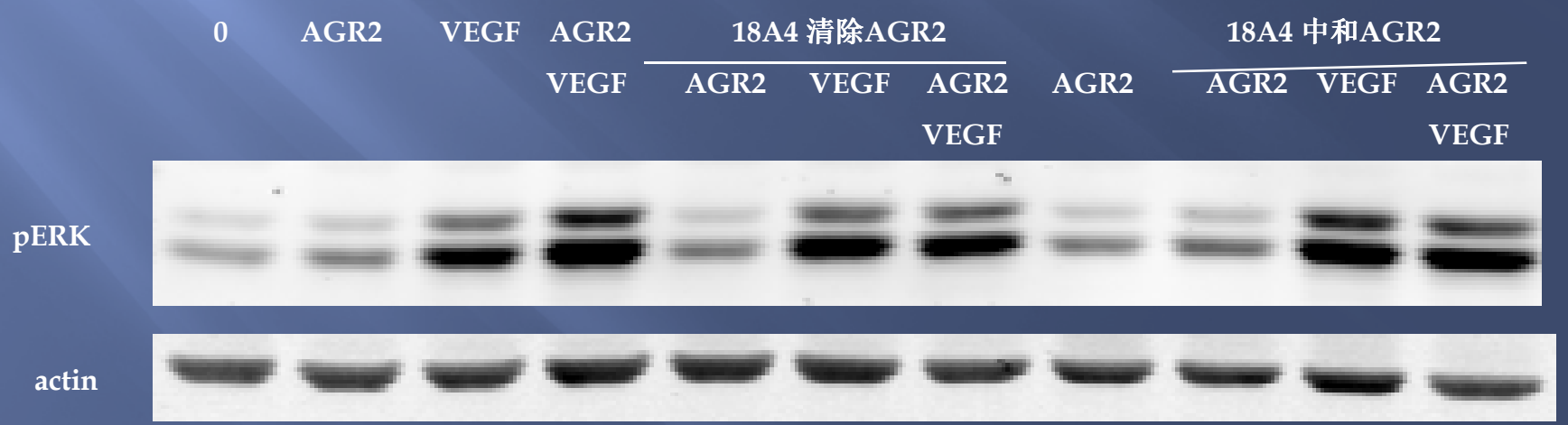




DTT can disturb the AGR2 signaling activities



AGR2抗体阻断VEGF对ERK1/2的促进作用



Generation of Agtuzumab Against AGR2

18A4 Hybridoma: Patent #ZL200910045963.2

18A4 Sequence and Target: Patent Pending 201110186469.5

Agtuzumab: International Patent -PCT and Countries

- AGR2 is an early marker for ovarian cancer
- Agtuzumab from A18A4 specifically binds AGR2 in its denatured or native form
- Agtuzumab specifically inhibits AGR2's growth enhancing function

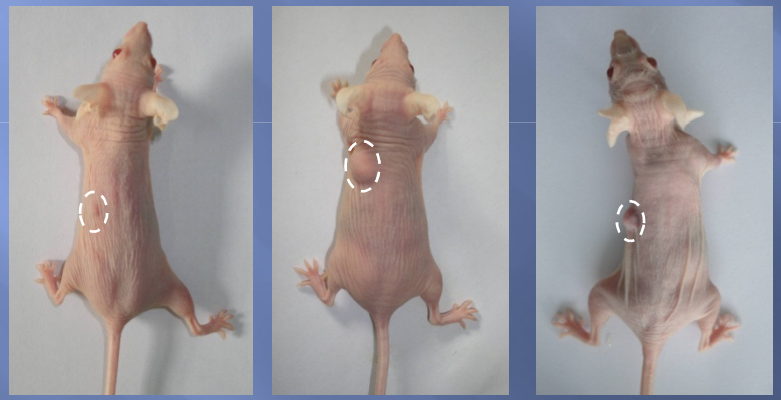
AGR2 mAb Inhibits Cancer Cell Growth

A

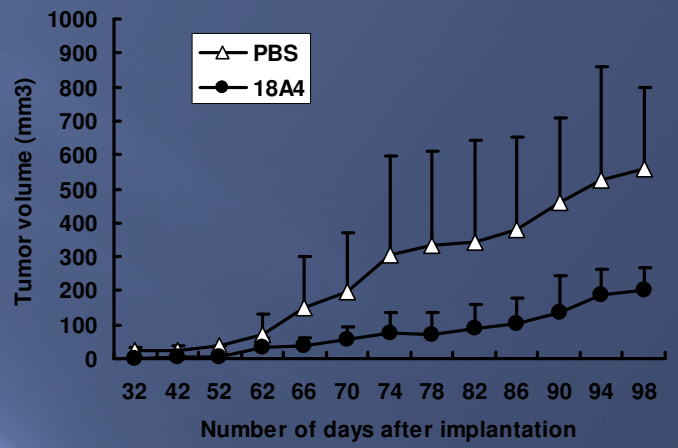
PBS



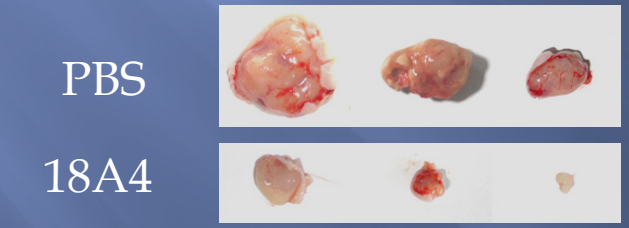
18A4



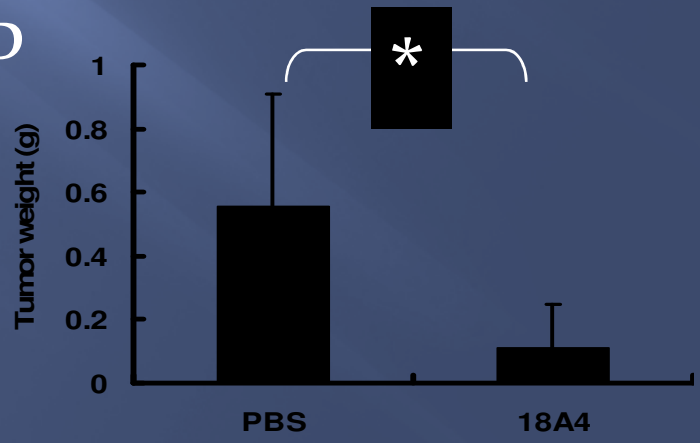
B



C



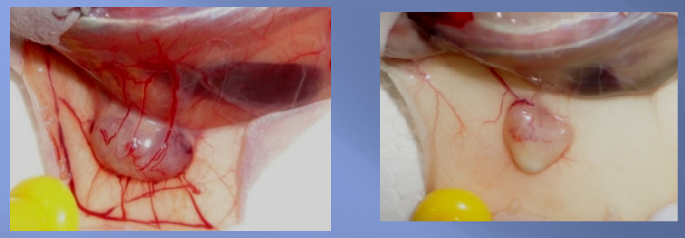
D



A. mAb 18A4 inhibit the growth of SKOV3 Xenograft model of nude mice. Comparison of tumor size between control group and 18A4 treatment group. **B.** Growth curve of the SKOV3 allograft tumors of nude mice. **C and D,** Comparison of tumor size and weight.

The Angiostatic Effect 8A4 Inhibits cancer cell growth in vivo

A



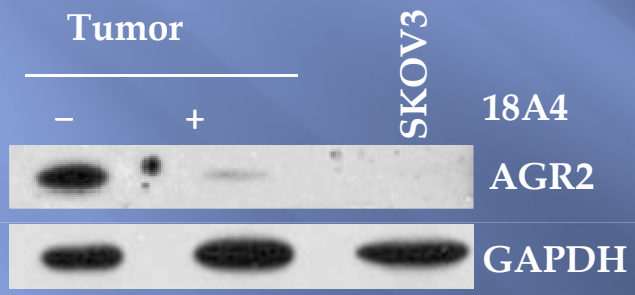
Control 18A4

B



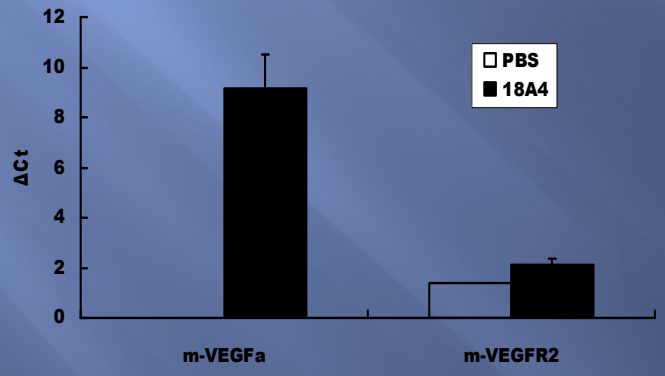
Detection of AGR2 expression by semi-quantitative RT-PCR

C

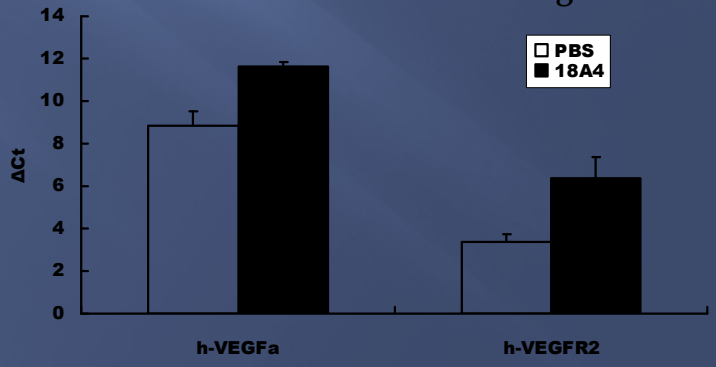




D



E

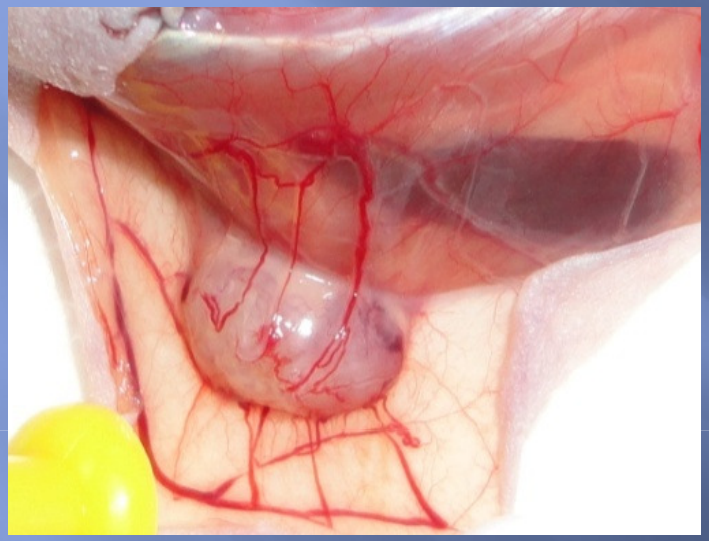


A. B, PCR of the cDNA of 0.5ml tumor tissue with 25 cycles shows that human AGR2 is expressed in tumors, but SKOV3 doesn't express AGR2. AGR2 decrease in tumor tissue of treatment group. C, expression of AGR2 in SKOV3 cell and SKOV3 xenograft tumor. D E, Figure 6. Comparison of the expression of mouse and humon growth factors in tumor by realtime PCR.

Angiostatic Effect

Reduced Angiogenesis in Tumor Tissue After 18A4 Treatment

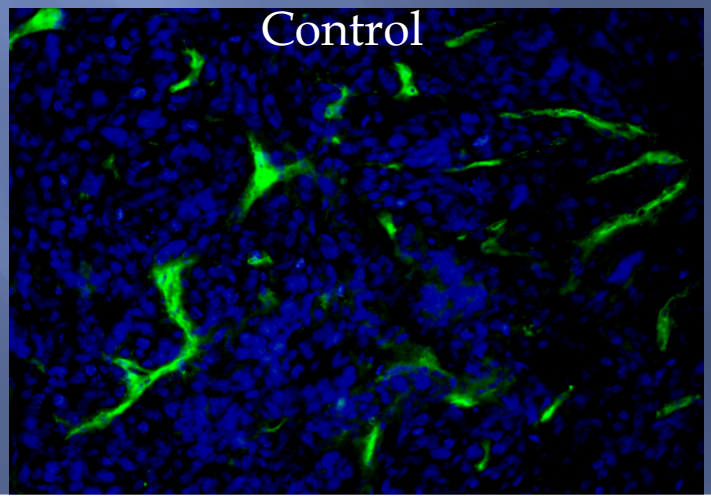
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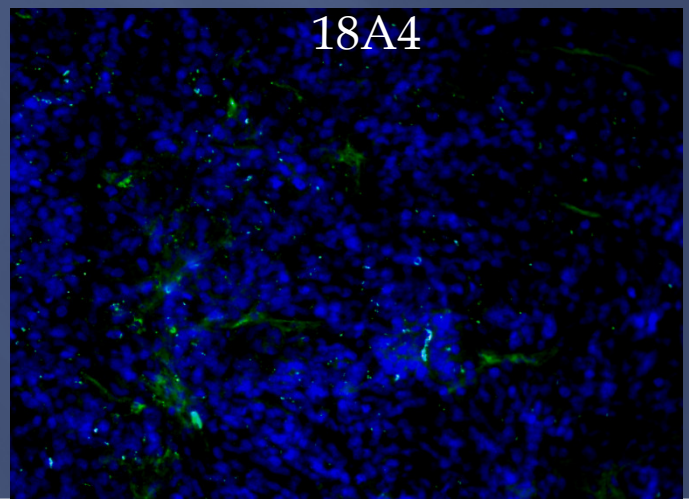


18A4

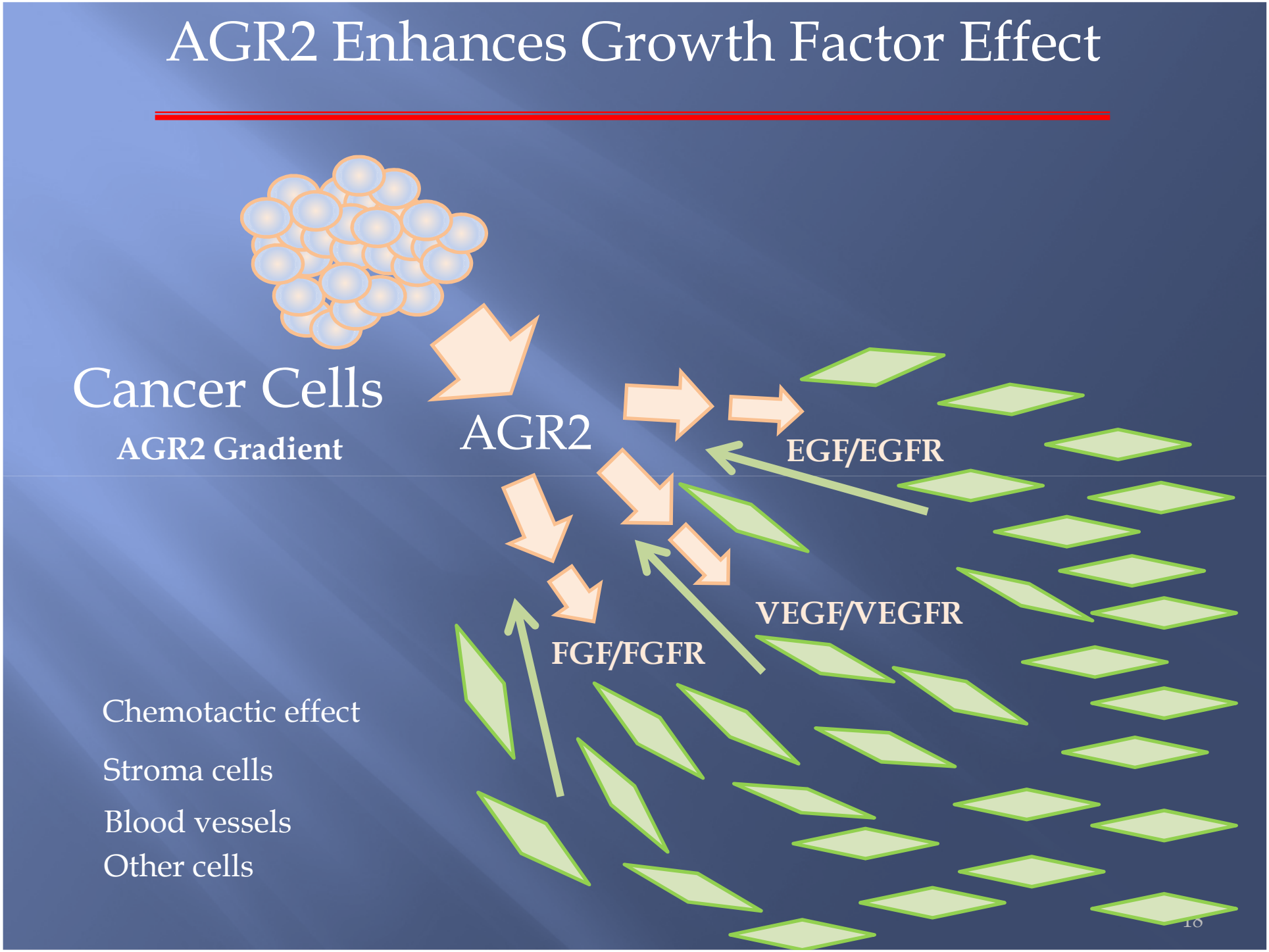


Tumor Section Stained with CD31, a Blood vessel marker





AGR2 Enhances Growth Factor Effect



ACKNOWLEDGEMENT

Lab members:

Zhenghua Wu

Weiguo Xu

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Hao Guo

Dhairi Mashuasi

Hao Chen

Haochuan Lou





Collaborators

Dr. Chuanhua He (Yale/Int. Med)

Dr. Ronny Drapkin (Harvard/DFCI)

Dr. Steven Skates (Harvard/MGH)