Whitehead Institute Symposium XIV - CANCER Kresge Auditorium.
Tuesday October 22, 1996. 2:00 to 5:30 pm

Therapy and Diagnostics

~~Thank you Dr. Fink.~~ This session is on new directions in "Therapy and Diagnostics," by 4 distinguished speakers. ~~After each talk of about 30 minutes, there will be 10 minutes for questions and discussion.~~

I would like to make some brief introductory remarks about the theme of this session.

As you listen to the speakers, it may be helpful to keep in mind, that by the time a tumor is detected, it usually has already induced an extensive network of vascular endothelial cells, from which it receives **paracrine** support.

For example, a cubic centimeter of tumor that contains approximately 100 million to 1 billion tumor cells, also contains at least 20 million endothelial cells (by FACS analysis).

Data emerging from many laboratories argues that therapeutic control of this expanding endothelial population may be an important **platform** for increasing the efficacy of any therapy which is directed against the tumor cell population, ...regardless of whether the tumor cell compartment is treated with conventional cytotoxic drugs, or by newer approaches which we will hear about this afternoon from **Allen Oliff**, **Frank McCormick** and **Tom Waldmann**.

Slide 13: Human **prostate** in SCID mice. 28 days. (PC-3)

T/C = 0.05 = again > **95%** inhibition. **(Human angiostatin purified from plasminogen).**

Slide 14: **Magnify** the vertical scale by factor of 10, so can see down to 100 instead of 1000 $mm.^3$

-Saline control goes off scale out of site.

-1 mm^3 = approximately 1 milligram

- Rather abrupt inhibition of tumor followed by REGRESSION (in contrast to TNP-470, never regressed tumor, only slowed its growth.

Slide 15: Dormant tumor under skin.

Slide 16: **Colon**

Slide 17: Colon (mice)

Interesting development among post-docs in the lab who are treating the mice. *They no longer care what the tumor type is!* They just increase the dose to match the angiogenic output of the tumor.

Slide 18: (Endostatin)

-**Endostatin** isolated from a hemangioendothelioma.

• **20** kD specific inhibitor of endothelial cell proliferation was isolated and from hemangioendothelioma tumor cells in

serum- free medium, instead of urine).

- N-terminal of endostatin is identical to the carboxy-terminal of **collagen 18** (187 amino acid stretch beginning with histidine).
- Collagen 18 was reported in PNAS in 1994 in same issue by Bjorn Olson at Harvard and Rehn and Pih-la-jan-iemi in Oolu University, Finland.

-Collagen 18 is EXPRESSED mainly in the walls of blood vessels or around them (and in the placenta, only in maternal vessels).

Slide 19: **Recombinant ENDOSTATIN** from E. Coli . Potent anti-tumor activity. Not toxic. **20** mgm/kg/day. No direct effect on tumor cells. **>99% inhibition.**

Slide 20: **Magnified scale:** 5 days tumor growth before treatment.
Slide 21: Rows of mice **day 20.**
Slide 22: On closer inspection, can see residual tumor (mainly scar).
Slide 24: Beneath the skin, can barely see **dormant** tumor.

SLIDE 25: (cycled dormancy therapy).

To demonstrate the power of this new generation of angiogenesis inhibitors and that tumors do **not** develop **drug resistance**, here is a long-term experiment currently underway in the lab. Key points are:

4 animals per group, because we have to make batch of recombinant endostatin for an experiment that may go