

TNF inhibition and Cancer

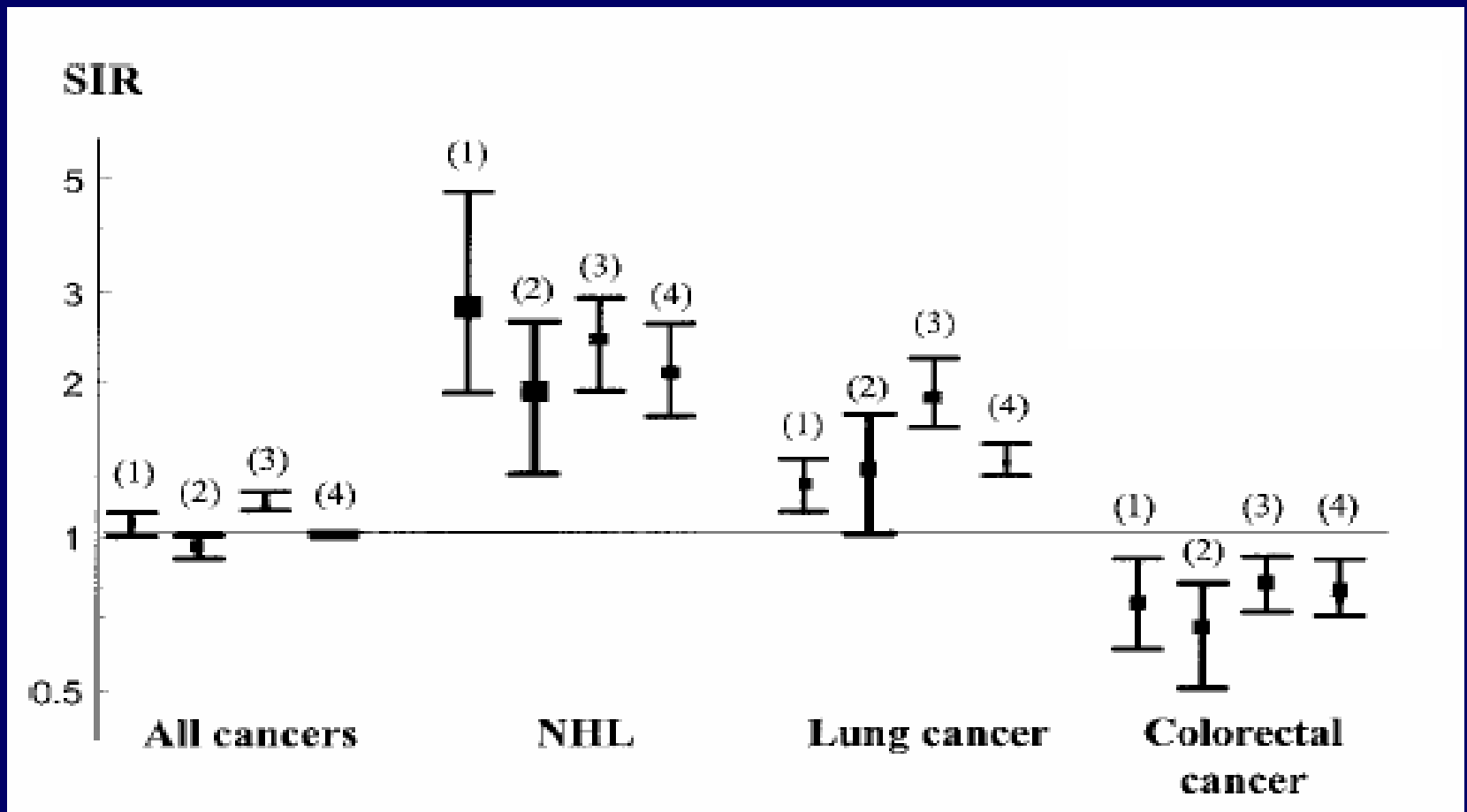
Robert Rottapel MD

**St. Michaels Hospital
Ontario Cancer Institute
University of Toronto**

Striking a Balance

- Can you treat the RA patient who has a history of malignancy with TNF inhibitors?
- Should you continue to treat an RA patient with TNF inhibitors who is recently diagnosed with cancer?

Link Between RA and Malignancy Prospective Cohort Studies⁵



¹Isomaki HA et al, J Chronic Dis 1978; 31:691-6, ²Gridley G et al, J Natl Cancer Inst 1993; 85:307-11,
³Mellemkjaer L, et al, Eur J Cancer 1996; 32A:1753-7, ⁴Thomas E et al, Int J Cancer 2000; 88:497-502,
⁵Symmons DP, Silman AJ, Arthritis and Rheumatism 2004; 50:1703-1706

RA and Cancer

- Overall rates for all cancers in RA are marginally increased
- Rates for lymphoma and lung are increased
- Rates for colon are lower (NSAID effect?)
- Cancer risk in RA related to:
 1. severity of disease
 2. duration of disease
 3. exposure to cytotoxic drugs

Anti-TNF Therapy and Cancer: The clinical experience to date

FDA Concerns Over Incidence of Lymphoproliferative Disorders

	Etanercept	Infliximab	Adalimumab
Treated/exposure			
patient numbers	3389	1298	8729
patient years	8336	2458	7885
Total number of lymphomas	9	4	13
Hodgkin's	3	1	1
non-Hodgkin's	6	3	12
mean time to onset	21 months	10-19 months	21 months
Standardized incidence ratio compared with general population	3.47	6.4	4.35

Table II

*Lymphoma clinical trial experience*⁵

Lymphoma in RA: Wolfe NDB Study¹

	N	SIR
All Patients	18,572	1.9 (CI 1.3-2.7)
MTX (Only)	6,396	1.7 (CI 0.8-2.7) ¹
All biologics	8,614	2.9 (CI 1.7-4.9)
Infliximab or Infliximab & etanercept	6,465	2.6 (CI 1.4-4.5)
Etanercept or etanercept & infliximab	3,381	3.8 (CI 1.9-7.5)

¹Wolfe F, et al, *Arthritis and Rheum* 2004;50:1740-1751

Wolfe NDB Study: Limitations

Absolute number of lymphomas were small: 29

Infliximab: 9

Etanercept: 8

MTX: 10

Not treated: 5

Channeling Bias: Those treated with anti-TNF inhibitors typically had severe disease for the longest period of time

Difficulty in quantifying and modeling the effect of exposure to other drugs prior to TNF inhibitors

Even though this was SIRs were elevated in the treated groups, the confidence intervals did not distinguish between each group statistically

The South Swedish Arthritis Treatment Group Registry (SSATG)

- Captures 90% of anti-TNF treated patients in the area
- Included 757 patients treated with etanercept (30%) or infliximab (70%) from Feb 1 1999 to Dec 31, 2002
- Comparison cohort 800 patients with conventional DMARD therapy in a community based practice
- All patients with previous malignancy were excluded

The South Swedish Arthritis Treatment Group Registry (SSATG)

- Control group had 69 tumors, 2 lymphomas
- Anti-TNF group had 16 tumors, 5 lymphomas
- Overall tumor risk not elevated in the treated group
- SIR for all tumors:
 - Control group 1.4 (CI 1.1-1.8)
 - Anti-TNF group 1.1 (CI 0.6-1.1)
- SIR for lymphomas:
 - Control group 1.3 (CI 0.2-4.5)
 - Anti-TNF group 11.5 (CI 3.7-26.9)
- All other cancers similar or lower in anti-TNF group

WGET Trial (Etanercept in Wegener's)

- Determine the effect of Etanercept in maintaining remission in a cohort of 180 Wegener patients followed over 27 months.
- Six cancers were identified during the trial and all occurred in the etanercept group
- When compared against the SEER database, on the basis of age- and sex-specific incidences rates, 1.92 solid cancers were expected in the etanercept group (SIR 312 percent; P=0.004)
- the combination of TNF- α inhibition and cyclophosphamide may heighten the risk of cancer beyond that observed with cyclophosphamide alone.

The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group, Etanercept plus standard therapy for Wegener's Granulomatosis, N Engl J Med 2005; 352:351-61

Anti-TNF Therapy and Cancer

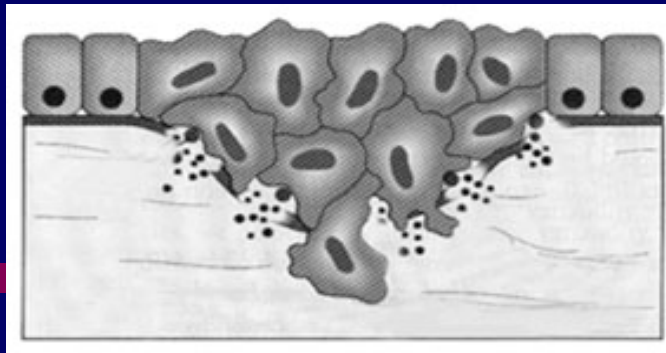
- Observed rates and incidence of most cancers are similar to those expected in the general population
- The rate of lymphoma is marginally elevated but obscured by selection bias of patients treated with severe or chronic RA, those known to have elevated risk
- The risk of solid tumors in Wegener's patients previously treated with cytotoxic drugs and exposed to Etanercept may be elevated

¹Smith K, Skelton H, J Am Acad Dermatol (2001) 45: 953-6, ²Bakland G, Nossent H, Rheumatology (2003) 42: 900-1, ³Alcain G et al, AM J Gastroenterol (2003) 98: 2577

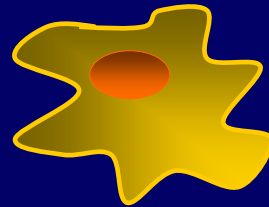
⁴Esser AC et al, J Am Acad Dermatol (2004) 50:S75-7

Invasion in Rheumatoid Arthritis and Cancer





Synovial macrophage



Tumor cell

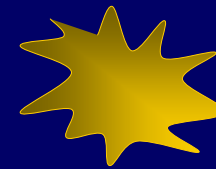
TNF α



fibroblast



Endothelial cell



osteoclast

Remodelling or the Extracellular
Matrix/Stroma

Neoangiogenesis

Boney invasion

Inflammation and Cancer

- 1898-Coley identifies a bacterial toxin that can induce tumor necrosis in sarcomas
- 1975-TNF discovered by Carswell. Elaborated by host macrophages
- 1984-TNF is cloned by Aggarwal at Genentech
- 1985-Cachectin shown to be identical to TNF

The Paradoxical role of TNF and Cancer Progression

- TNF controls Tumor Immune Surveillance
 - > TNF inhibition may promote cancer
- TNF is an important cytokine required for tumor progression
 - > TNF inhibition may treat tumor progression or paraneoplastic symptoms

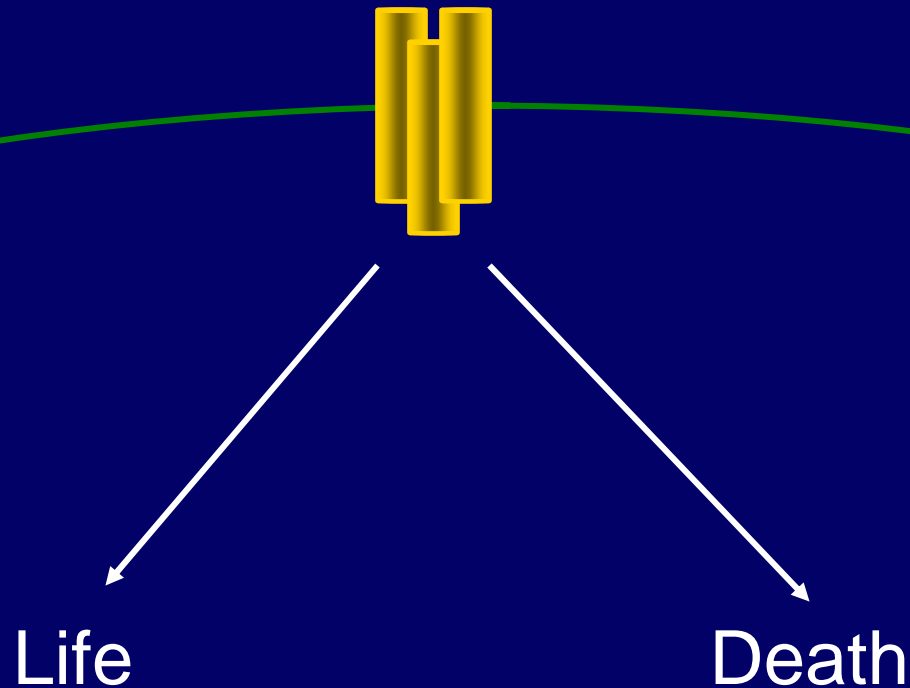
Anti-tumor activity of TNF

- High concentrations can induce thrombosis, vascular collapse and necrosis
- TNF can directly induce apoptosis
- TNF-mediated immune surveillance results from:
 - T cell differentiation factor
 - Induction of superoxide dismutase (H_2O_2 production)
 - Induction of iNOS
 - Promotion of granuloma-delayed type hypersensitivity

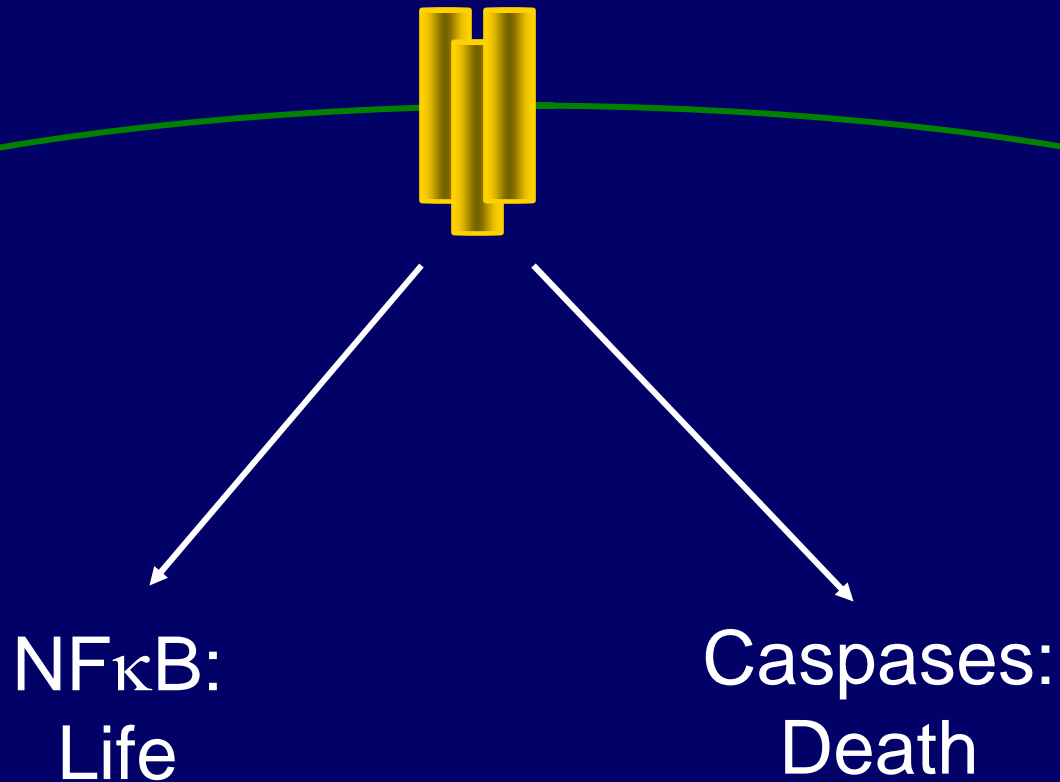
Tumor Promoting activity of TNF TPF?

- TNF is a survival factor
- Tissue remodeling required for metastasis-induction of metalloproteinases
- Abundantly expressed in the stroma surrounding solid tumors, tumor microenvironment
- Increased cell motility (downregulation of Cadherins)
- Induction of angiogenesis -VEGF
- Induction of myc, ras and β -catenin proto-oncogenes

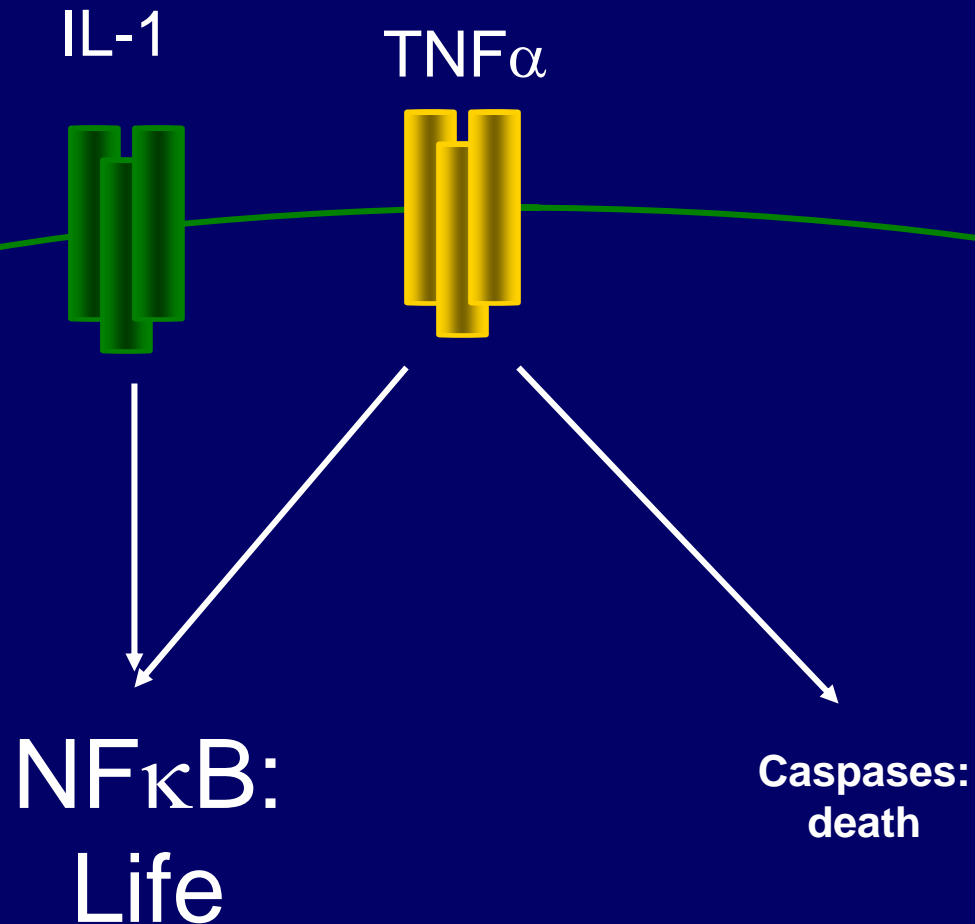
What is the molecular basis of the Paradox?



What is the molecular basis of the Paradox?



What is the molecular basis of the Paradox? Cellular Context



Genetics of TNF and Cancer Susceptibility

Increased TNF levels correlate with poor survival and chemoresistance

- TNF knockout mice have 10x fewer skin tumors than normal mice
- TNFR1 knockout mice develop fewer hepatic metastasis
- Lpr mice develop attenuated lymphoma in TNFR1 knockout background

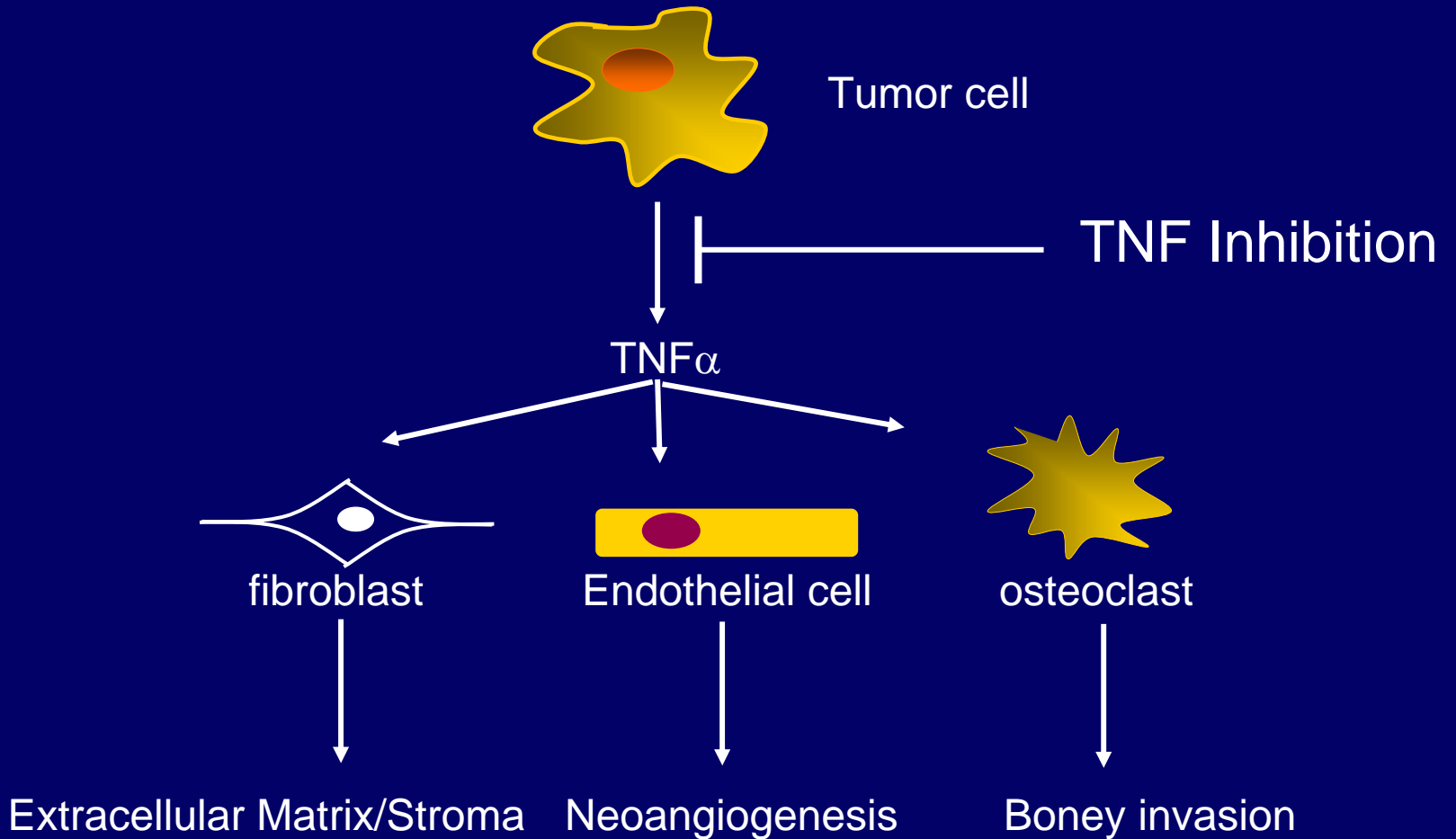
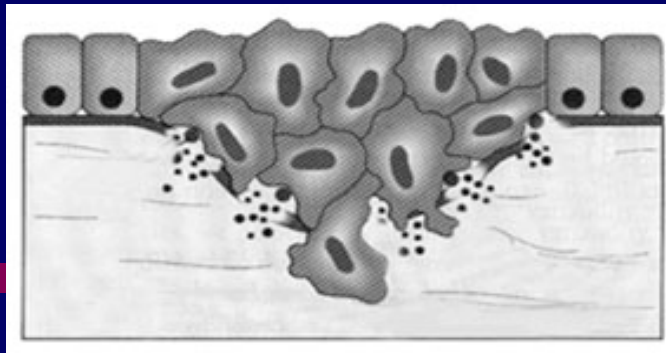
Genetics of TNF and Cancer Susceptibility

Mutations in the TNF promoter is associated with poor outcome

- SNP TNF308 is associated with high plasma TNF levels and poor prognosis in lymphoma, MGUS, myeloma, renal cell carcinoma patients
- SNP TNF238 carry 6.5x increased RR for renal cell carcinoma
- SNPTNF488 carry 17x increased RR for prostate cancer

**Is there a role for anti-TNF
therapy in Cancer Treatment?**





Cachexia and TNF

- Cachexia is a major morbidity factor in cancer
- Cachexia is caused by increased levels of TNF, IL-1 and IL-6
- Phase II trials underway for tumor-induced cachexia with variable response

Role for Anti-TNF Therapy in Cancer Supportive Care

- Metastatic Bone Pain
- Fatigue
- Depression
- Side effects of radiotherapy
- Graft vs. host disease

Summary: Anti-TNF agents in RA and Cancer predisposition

- Does not appear to be a link between anti-TNF therapy and most malignancies
- Elevated concern with respect to lymphoma
- Synergy between TNF inhibition and prior exposure to cytotoxic drugs

Summary: Anti-TNF agents to treat Cancer

The pathogenic role of $\text{TNF}\alpha$ in inflammatory disorders such as RA is well established

The pathogenic role of $\text{TNF}\alpha$ as an anti-cancer agent or cancer promoting agent remains unclear.

High pharmacologic doses of $\text{TNF}\alpha$ combined with chemotherapy can regress intractable tumors and would argue against the use of TNF inhibitors in the cancer patient.

However, metastasis and cachexia may be treatable by $\text{TNF}\alpha$ inhibitors

We have more to learn!

Future Questions

Patients currently being treated for cancer?

Patients with prior history of cancer?

BRCA, APC etc positive patients?

Risk versus the duration of TNF α treatment?

Risk of prior exposure to cytotoxic drugs?

Risk for patients with chronic active RA?

Future questions

- Does anti-TNF initiate or unmask pre-existing tumors?
- Might anti-TNF therapy reduce cancer risk in RA patients due to reduced disease activity and possible tumor promoting activity of TNF?

Future questions

- Median time interval of exposure in the first 26 lymphomas observed in RA patients treated with etanercept or infliximab was 8 weeks
- Type of anti-TNF agent, bioavailability, pharmacokinetics