CYTOKINE THERAPY: LESSONS LEARNED

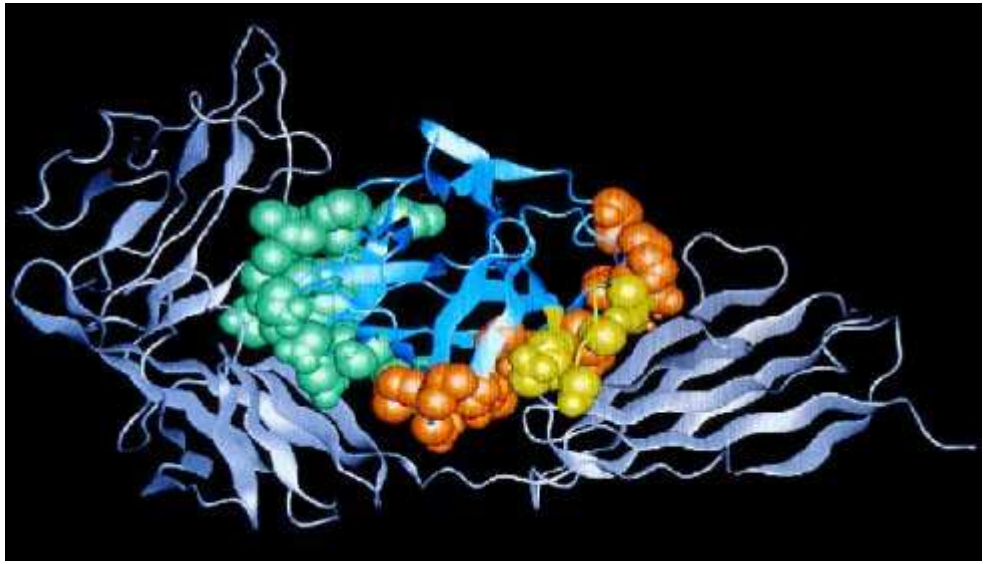
Pierre L. Triozzi, MD

Translational Hematology Oncology Research

Cleveland Clinic

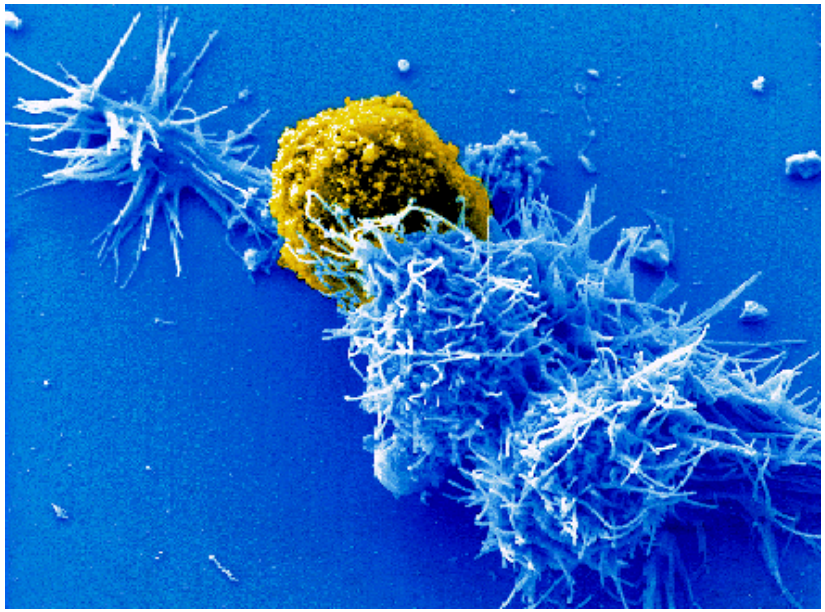
CYTOKINES

- Diverse group of soluble proteins produced by cells
- Affect either the same (autocrine) or another (paracrine) cell
- Interact with specific cell surface receptors



CYTOKINES

- Active at very low concentrations
- Many act as cellular survival factors
  - Prevent apoptosis
- Mediate interactions between cells
- Regulate processes outside cells



CYTOKINES

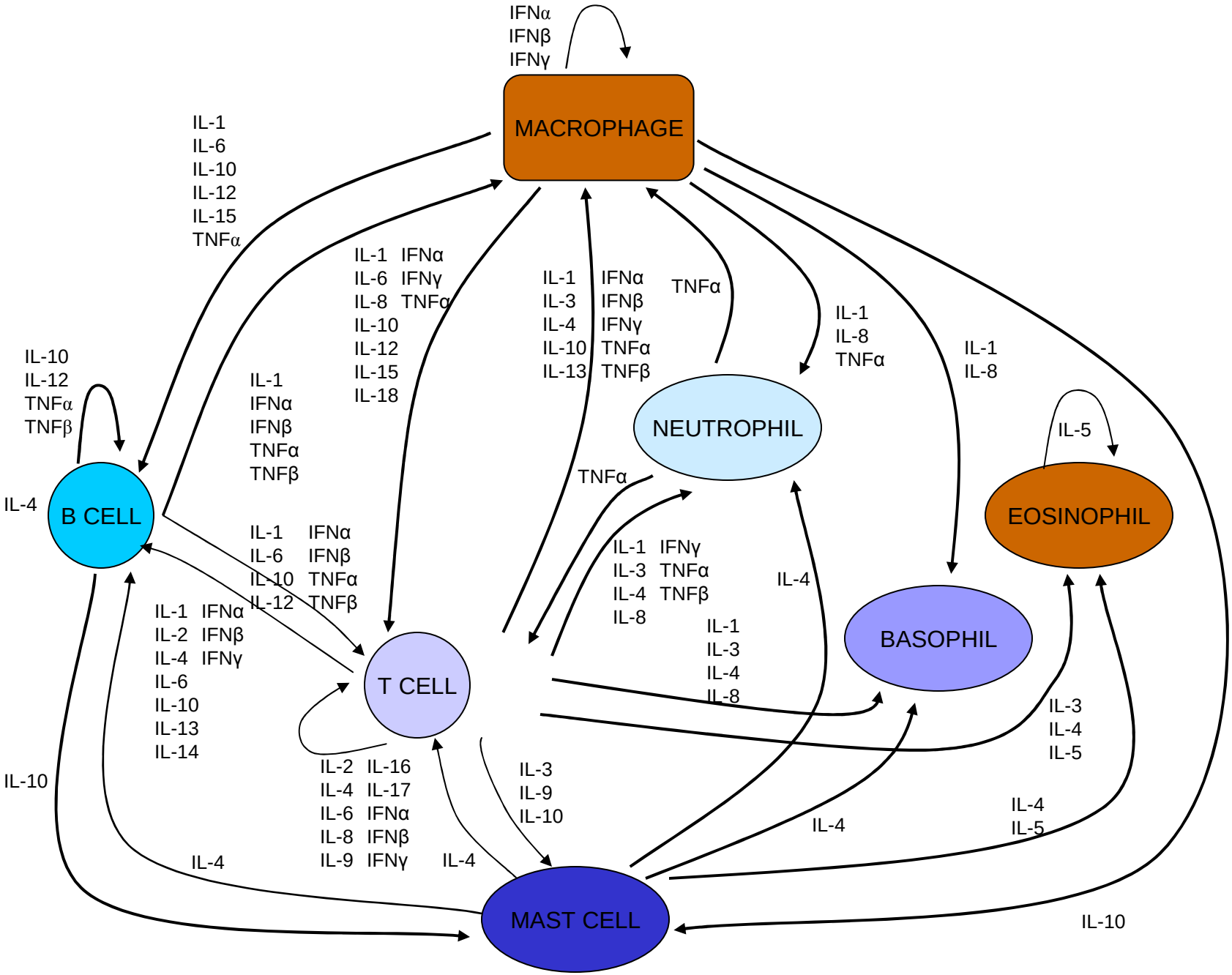
- **Pleiotrophy** — the same cytokine can act on several different cell types and can cause different responses, depending on the cell
- **Redundancy** — several different cytokines acting on a cell can individually cause the same response
- **Synergy** — if two (or more) cytokines are simultaneously present, the sum of the response together is greater than the sum of the individual responses
- **Amplification** — cytokines induce the production of other cytokines
- **Antagonism** — the presence of one cytokine inhibits the action of a different cytokine; one cytokine blocks the effect of the other

CYTOKINES *vs* HORMONES

- Act at a systemic level, participating in processes such as inflammation, septic shock, allergic reactions, and wound healing.

However

- Act on a wider spectrum of target cells than hormones
- Not produced by specific cells organized in specialized glands
  - Produced by cells distributed all over the body
- Sites of expression do not necessarily predict the sites of biological function.


IFNα
IFNβ
IFNγ
MACROPHAGE
IL-1
IL-6
IL-10
IL-12
IL-15
TNFα
IL-1 IFNα
IL-6 IFNγ
IL-8 TNFα
IL-10
IL-12
IL-15
IL-18
IL-1 IFNα
IL-3 IFNβ
IL-4 IFNγ
IL-10 TNFα
IL-13 TNFβ
TNFα
IL-1
IL-8
TNFα
IL-1
IL-8
IL-10
IL-12
TNFα
TNFβ
IL-4
B CELL
IL-1
IFNα
IFNβ
TNFα
TNFβ
NEUTROPHIL
IL-5
EOSINOPHIL
TNFα
IL-1 IFNα
IL-6 IFNβ
IL-10 TNFα
IL-12 TNFβ
IL-1 IFNγ
IL-3 TNFα
IL-4 TNFβ
IL-8
IL-4
IL-1 IFNα
IL-2 IFNβ
IL-4 IFNγ
IL-6
IL-10
IL-13
IL-14
T CELL
IL-1
IL-3
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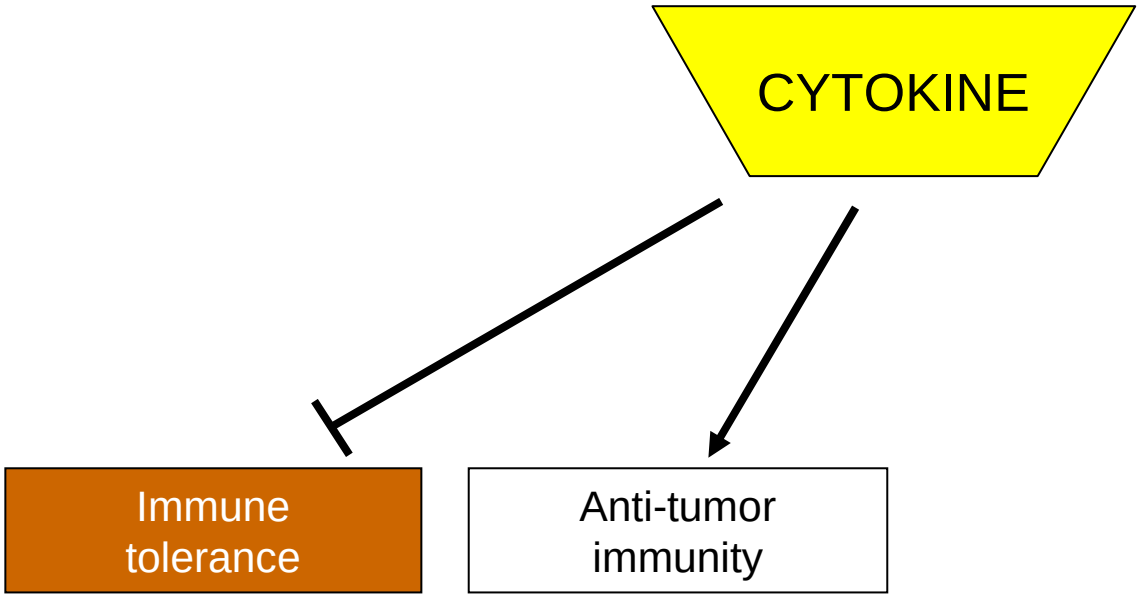
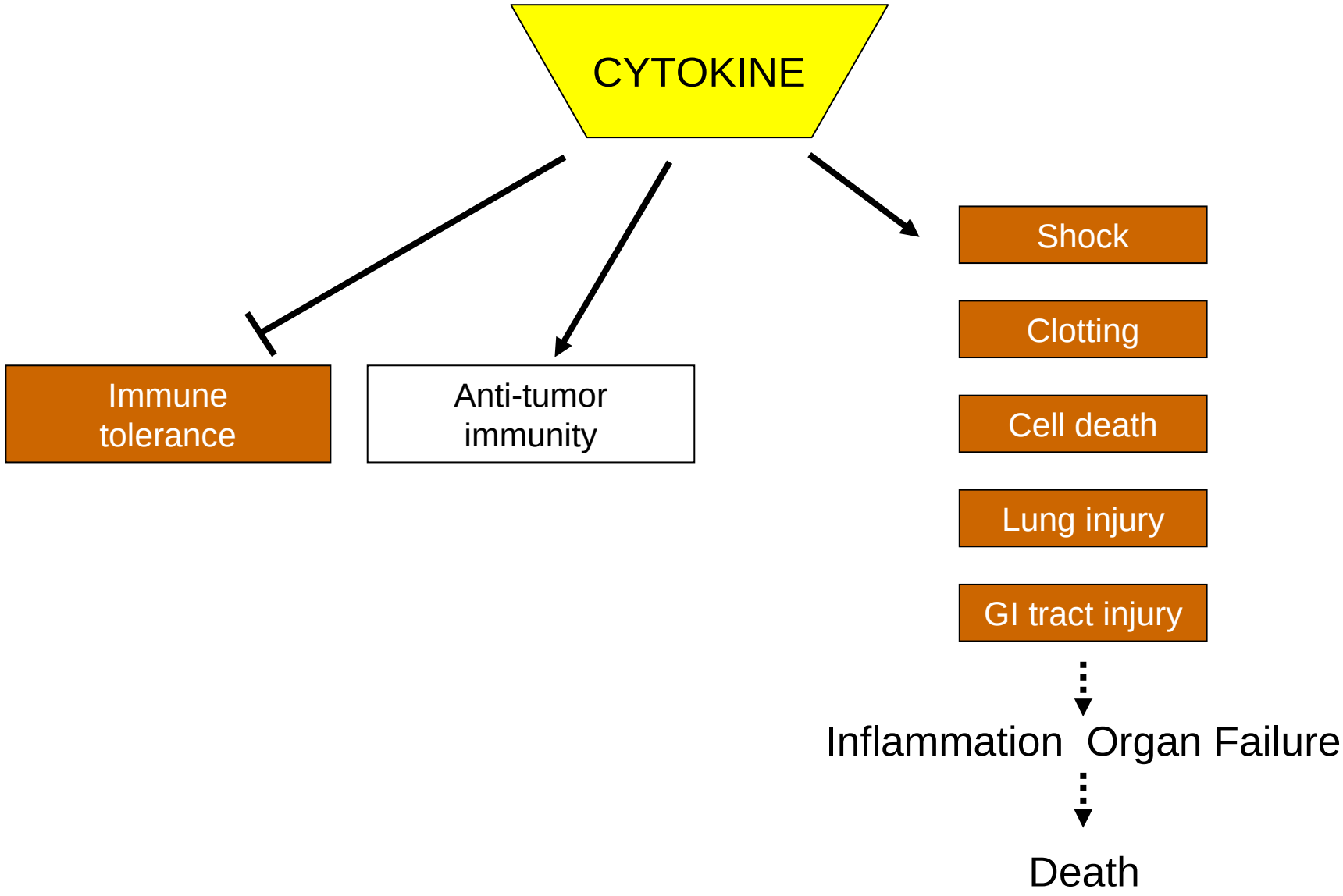
IL-8
BASOPHIL
IL-3
IL-4
IL-5
IL-10
IL-2 IL-16
IL-4 IL-17
IL-6 IFNα
IL-8 IFNβ
IL-9 IFNγ
IL-4
IL-3
IL-9
IL-10
IL-4
IL-4
IL-5
IL-4
MAST CELL
IL-10


CYTOKINE
Immune tolerance
Anti-tumor immunity


CYTOKINE
Immune tolerance
Anti-tumor immunity
Shock
Clotting
Cell death
Lung injury
GI tract injury
Inflammation
Organ Failure
Death

CYTOKINE THERAPY
Pharmacology

- Multiplicity of biologic effects
- Effects dependent on dose, route, and schedule
- PK of agent *vs* PK of biologic effects
  - Blood levels do not necessarily correlate with clinical activity
- Recombinant proteins, differ from the natural substance
  - All are immunogenic, impacts PK (toxicity/efficacy)

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Considerable inter-individual variability

CYTOKINES
FDA Approved

Cytokine	*Indications*	*Year First Approved*
IFN-α	Hairy-cell leukemia, CML, melanoma, Kaposi sarcoma, NHL, condyloma accuminata, hepatitis B and C	1986
G-CSF	Neutropenia, nonmyeloid malignancy	1991
GM-CSF	Bone marrow transplantation	1991
IL-2	Renal cell carcinoma, melanoma	1992
IFN-β	Multiple sclerosis	1993
IL-11	Thrombocytopenia	1997
IFN-γ	Chronic granulomatous disease, osteopetrosis	1999

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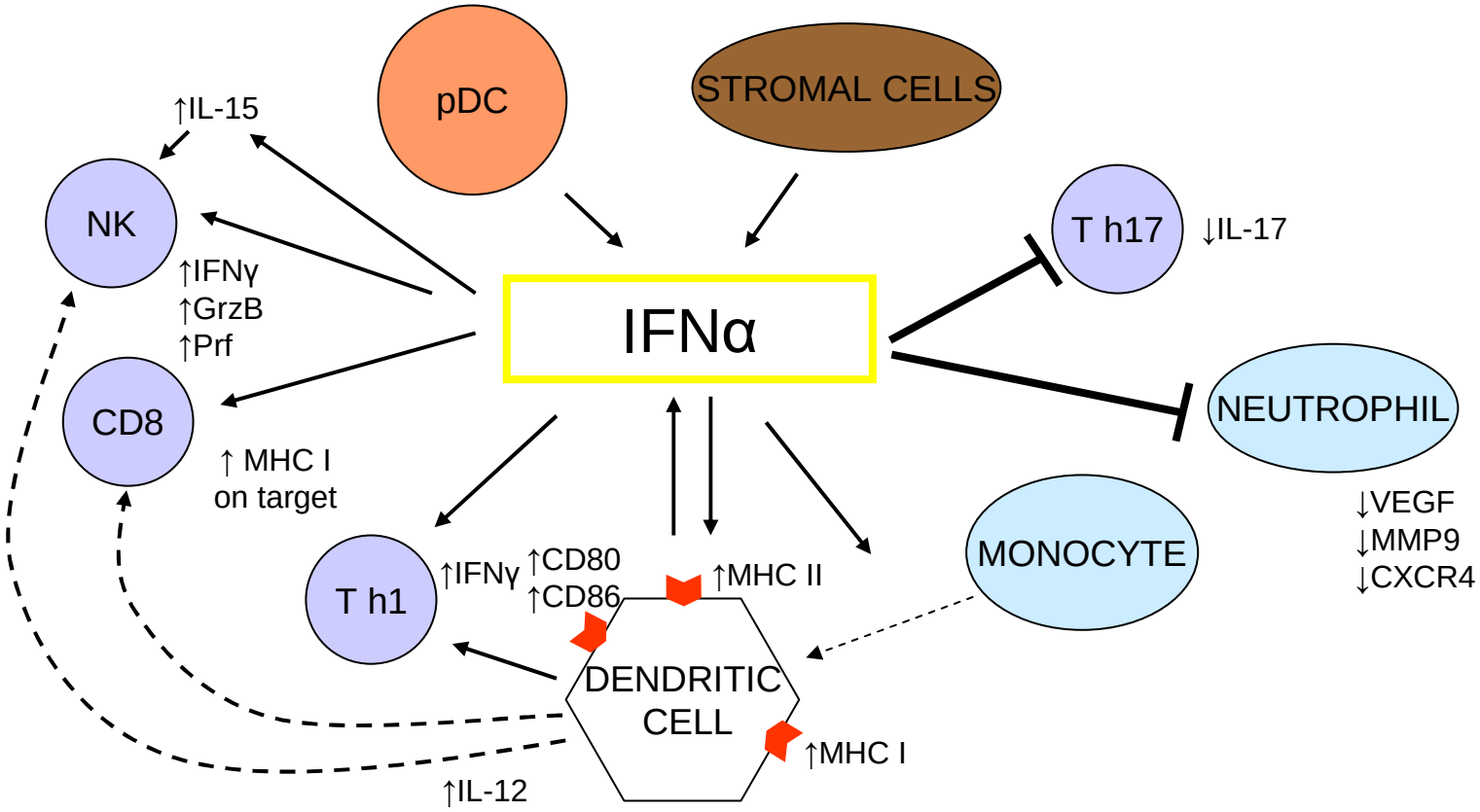
IFN-α

- Immunologic effects



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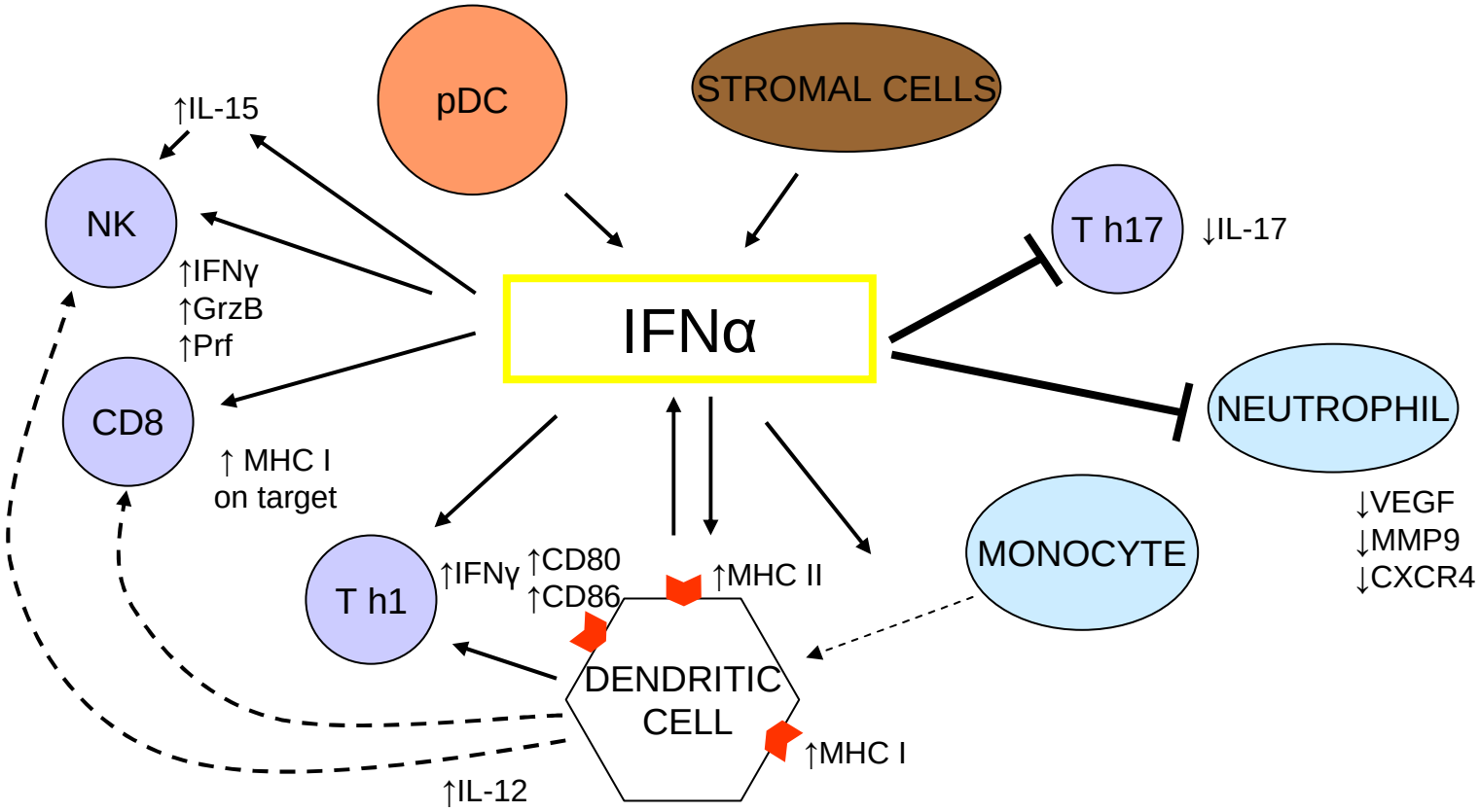
IFN-α

- Immunologic effects



- Anti-proliferative effects
- Antiviral effects
- Anti-angiogenic effects

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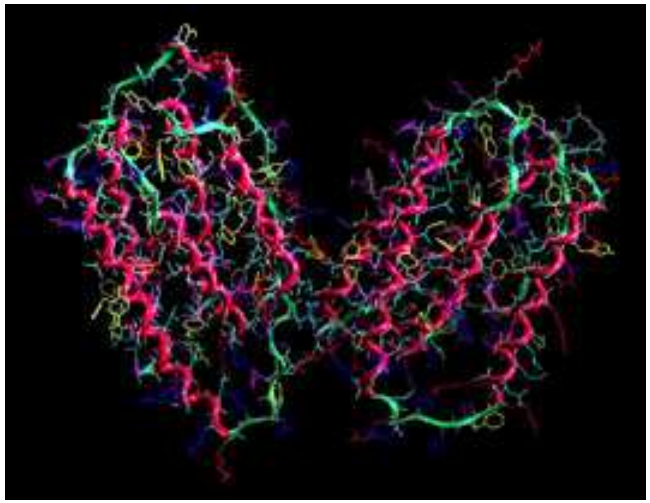
IFN-α
(Interferon alfa-2b; Intron A®)

- Position 23 Arg instead of Gly of natural sequence
- Administered SC or IV
- Dosing
  - High (>10 MIU)
  - Intermediate (5-10 MIU)
  - Low (<3 MIU)
- Schedule: either qd or tiw
- t½ = 4 hours



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IFN-α
Hematologic Malignancies

Malignancy	*Dose schedule*	*RR (%) (mean)*
Hairy cell leukemia	3 MIU/m^2/d	70-90 (80)
CML	5 MIU/m^2/d	45-85 (58)
NHL (follicular)	3-50 MIU/m^2/d or tiw	9-67 (47)
CTCL	3-50 MIU/m^2/d or tiw	27-85 (48)
Myeloma	5-12 MIU/m^2/d or tiw	3-18 (15)

IFN-α
Solid Tumors

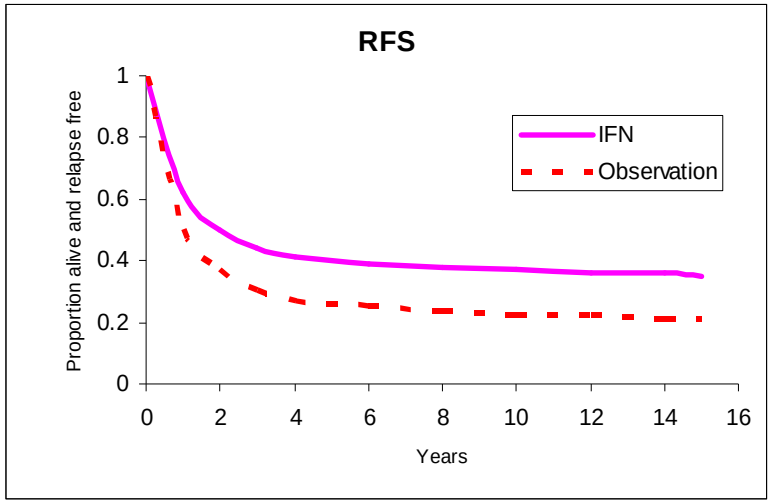
Tumor	*Dose schedule*	*RR (%) (mean)*
Melanoma	5-20 MIU/m^2/d or tiw	7-19 (18)
Kaposi's sarcoma	3-20 MIU/m^2/d or tiw	3-67 (30)
Renal cell	5-50 MIU/m^2/d or tiw	8-23 (15)
Endocrine pancreatic	3-5 MIU/m^2/d or tiw	33-77 (50)
Carcinoid	12-24 MIU/m^2/d or tiw	20-40 (20)

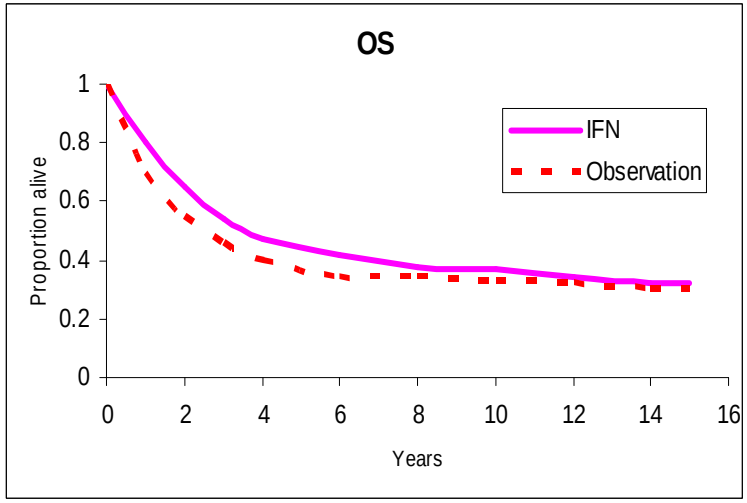
IFN-α
Melanoma

INDICATIONS AND USAGE

Malignant Melanoma

Indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery.





20 MIU/m2 IV qd for 5 days weekly X 4 weeks (high dose induction)
THEN
10 MIU/m2 tiw SC for 48 weeks (moderate dose maintenance)

Kirkwood et al. J Clin Oncol 1996

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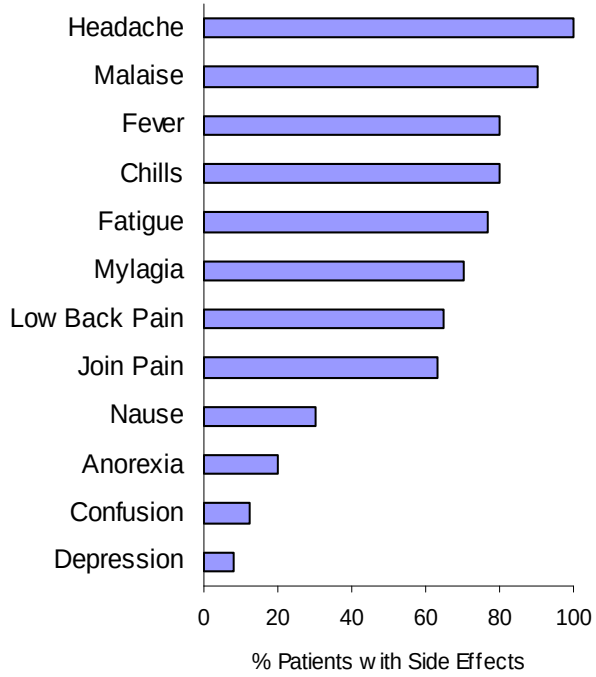
IFN-α
Toxicity

- Severity is dose- and time-related
- Acute: flu-like
  - Fever, chills, myalgia, arthralgia, headaches
  - Subsides with continued treatment
- Cumulative: constitutional
  - Anorexia, depression, and fatigue
  - Progressive and often dose-limiting



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Important Safety Information

WARNING

Alpha interferons, including INTRON® A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping INTRON A therapy.

All patients receiving INTRON A therapy experienced mild-to-moderate side effects. Some patients experienced more severe side effects, including neutropenia, fatigue, myalgia, headache, fever, chills, and increased SGOT. Other frequently occurring side effects were nausea, vomiting, depression, alopecia, diarrhea, and thrombocytopenia. DEPRESSION AND SUICIDAL BEHAVIOR, INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES, HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALFA INTERFERONS, INCLUDING INTRON A THERAPY.

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IFN-α
Antibody Induction

- Antibodies to recombinant IFN-α in 67%
- Neutralizing antibodies in 33%.
  - Often accompanied by a decrease in adverse effects
  - Impact on efficacy?

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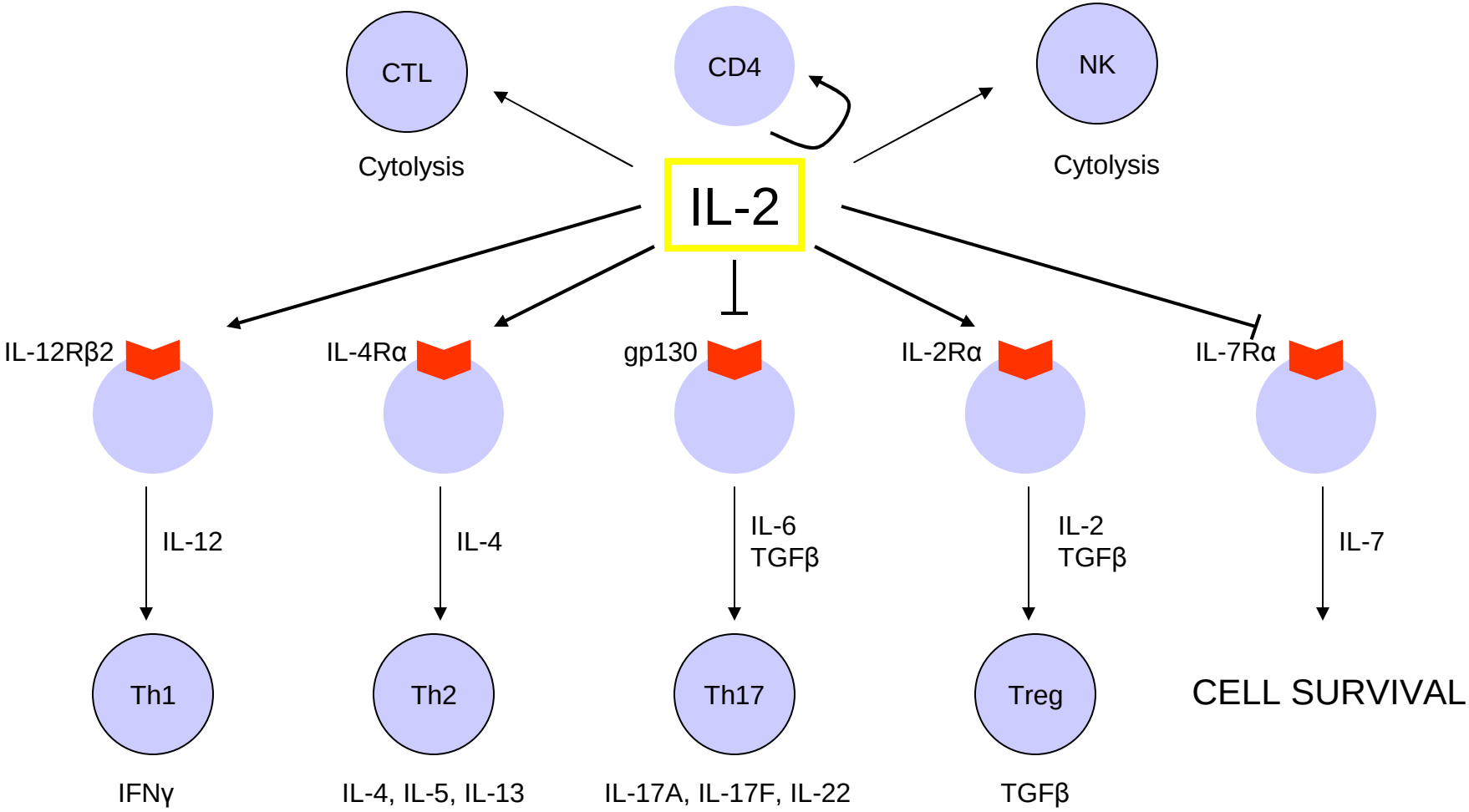

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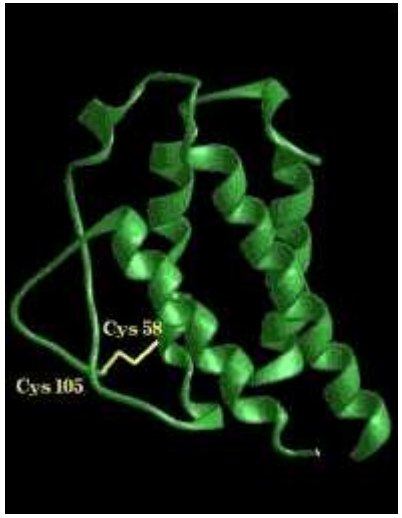
IL-2
(Aldesleukin; Proleukin®)

- Mutation of free-cysteine to reduce aggregation
- Administered IV or SC
- Dosing
  - High (>100 MIU)
  - Moderate (5-20 MIU)
  - Low (1-5 MIU)
  - Ultra-low (<1 MIU)
- Schedule: qd X 5-7 days (with rest)
- t½ = 1.5 hours



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IL-2
Dosing

- Standard high-dose regimen:
  - 600,000-720,000 IU/kg q 8h over 5 days followed by 7-10 days of rest and then a repeat 5-day course.
  - Responders are retreated following 2 months of rest
- Moderate- and low-dose outpatient regimens
  - Better tolerated
  - Efficacy?

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No consensus regarding the best way to deliver IL-2 from a risk-to-benefit standpoint

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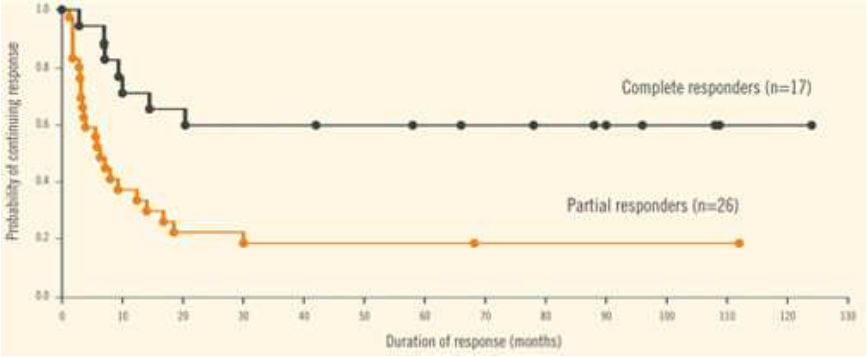
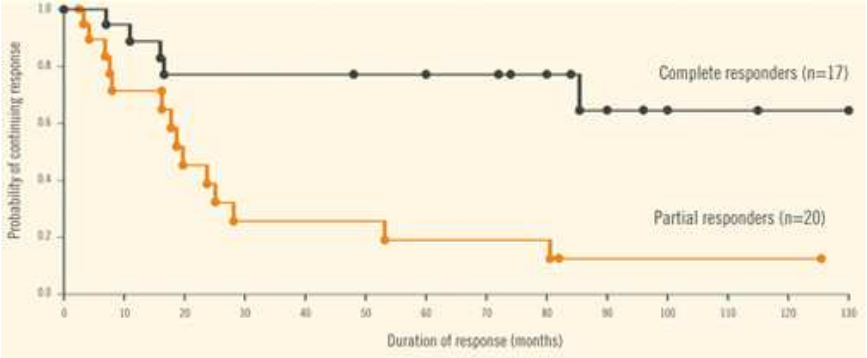
IL-2
Efficacy

Melanoma	Renal Cell Carcinoma
RR (high-dose bolus) = 16% (CR 6%)	RR (high-dose bolus) = 15% (CR 7%)
Clinical Response Duration	Clinical Response Duration
	

http://www.proleukin.com/

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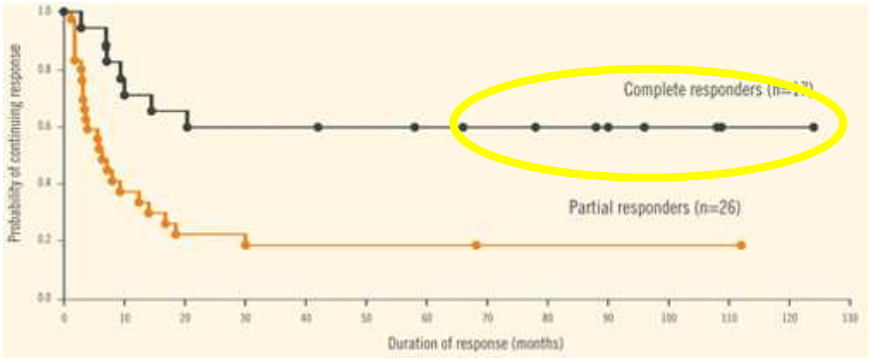	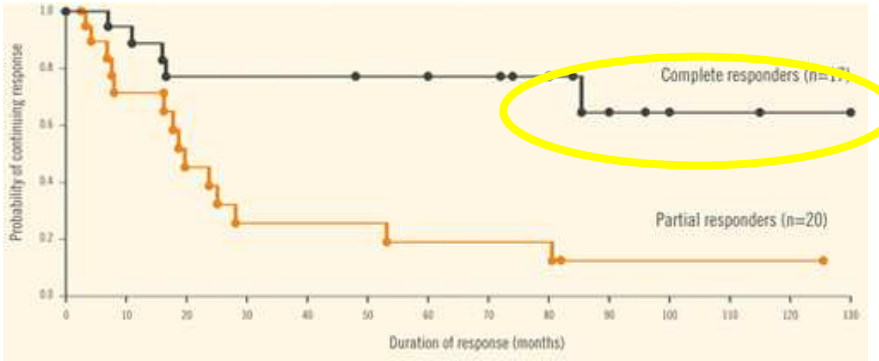

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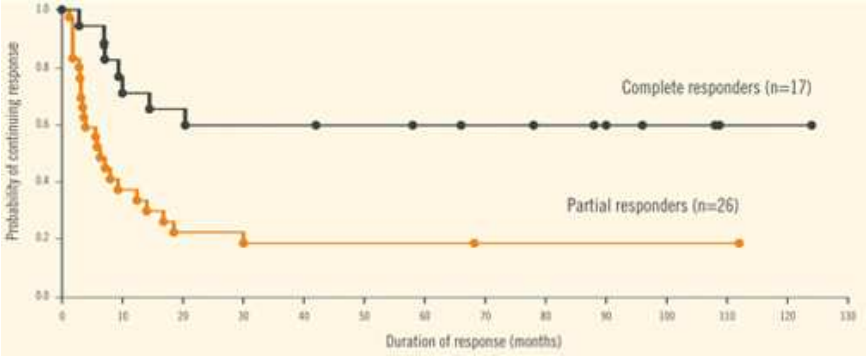	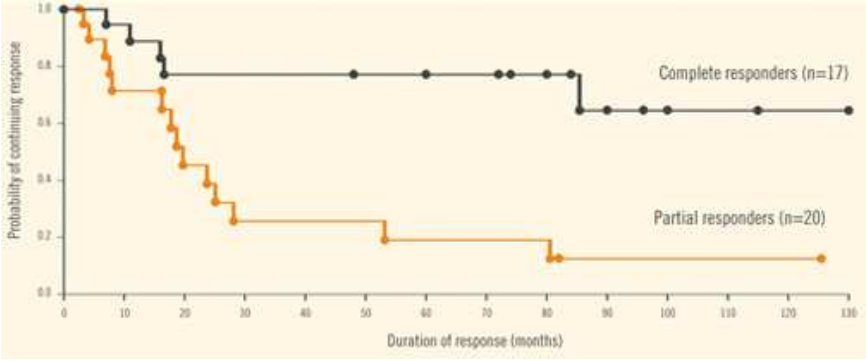

Effect on overall survival?

http://www.proleukin.com/

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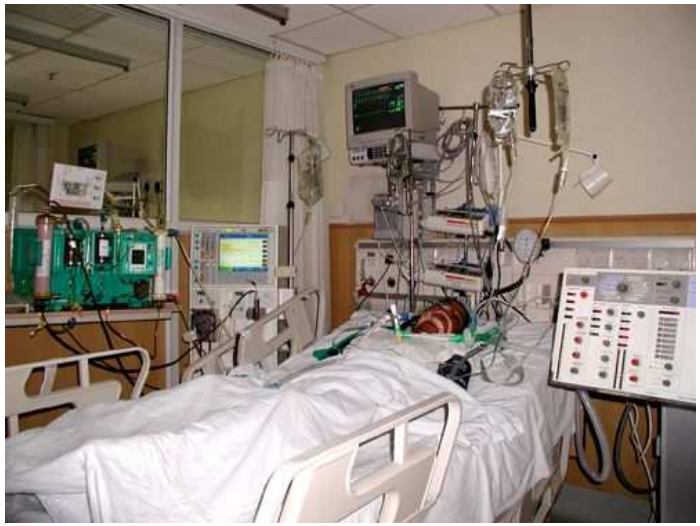
IL-2
Toxicity

- ↑ vascular permeability → interstitial edema
- ↑ other cytokines, e.g. TNF
- Lymphoid infiltration into organs



Organ system	*Toxicity*	*Incidence (%)*
General	Chills, fever Edema	97 55
Hematologic	Anemia Thrombocytopenia	99 83
Gastrointestinal	N/V Diarrhea	89 81
Hepatic	↑ transaminase ↑ bilirubin	75 85
Renal	Oliguria ↑ creatinine	81 81
Pulmonary	Dyspnea ARDS	57 1
Cardiovascular	Hypotension Arrhythmia MI	96 14 2
Neurologic	Altered MS Seizures	82 2
Skin	Rash Pruritus Exfoliative dermatitis	42 24 18

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WARNINGS

Therapy with PROLEUKIN® (aldesleukin) for injection should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.

PROLEUKIN therapy should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

PROLEUKIN therapy administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema and mental status changes.

PROLEUKIN treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection including sepsis and bacterial endocarditis. Consequently preexisting bacterial infections should be adequately treated prior to initiation of PROLEUKIN therapy. Patients with indwelling central lines and particularly at risk of infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillian, nafcillin, ciprofloxacin or vancomycin has been associated with a reduced incidence of staphylococcal infections.

PROLEUKIN therapy administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may results in coma.

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ALDESLEUKIN
Antibody

- Low titers anti-aldesleukin antibodies in 66-74%
- Neutralizing antibody in <10%
  - Impact on adverse effects?
  - Impact on efficacy?

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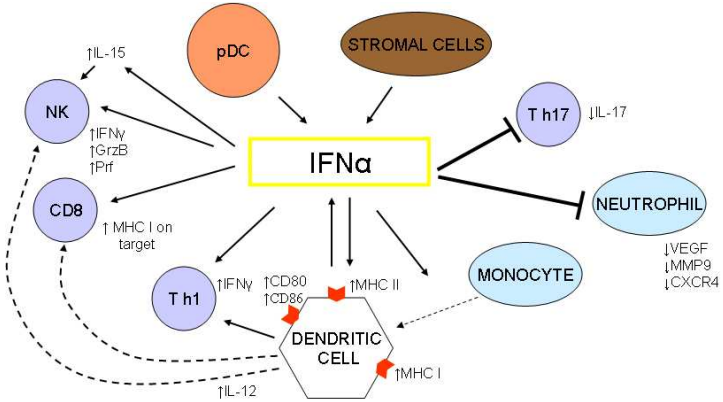
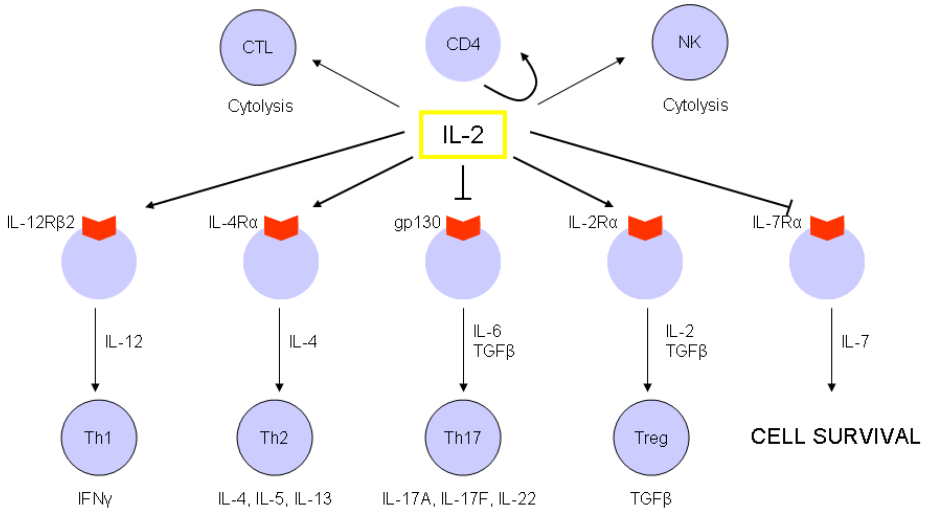
Mechanism of action?





- The molecular targets that influence the clinical response to cytokine therapy have not been defined
- The genetic or other host factors that differentiate responders and treatment failures are unknown.

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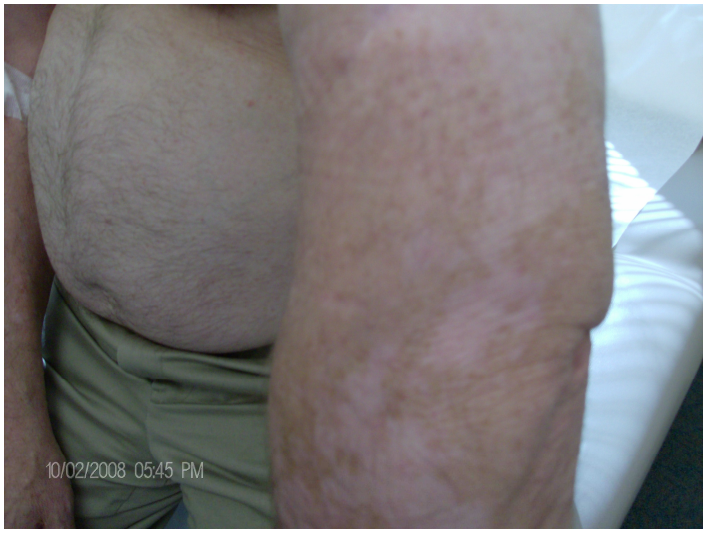
CYTOKINE THERAPY
Autoimmunity



Vitiligo

Autoimmune sequelae are more prominent in patients that respond to cytokine immunotherapy?

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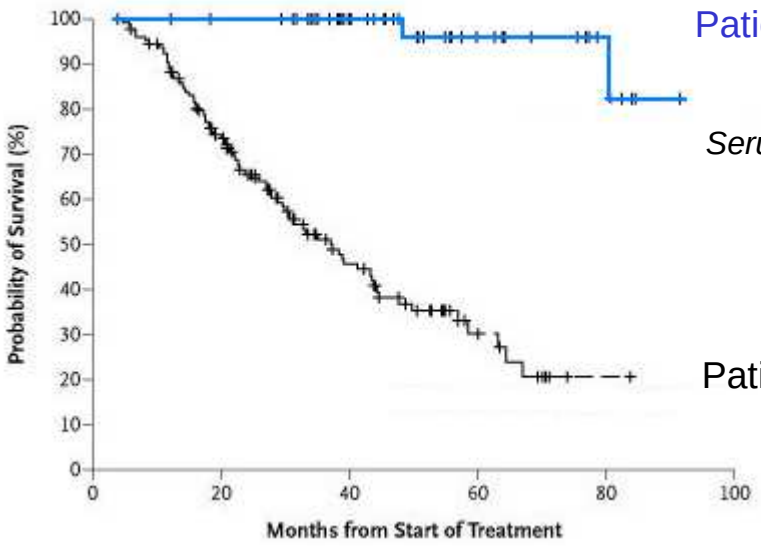
ADJUVANT IFN-α2b
Autoimmunity and Response



Patients with autoimmunity (n=52)

Vitiligo

Serum anti-thyroid, nuclear, DNA, and cardiolipin antibodies

Patients without autoimmunity (n=148)

Gogas et al. NEJM 2006

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IL-2
Autoimmunity and Response

	Responders	***Non-responders***	***P***
Vitiligo	28/58 (48%)	56/316 (18%)	P=0.000001
Thyroiditis (abnormal TSH)	43/58 (74%)	176/314 (57%)	P=0.01

Phan et al. J Clin Oncol 2001

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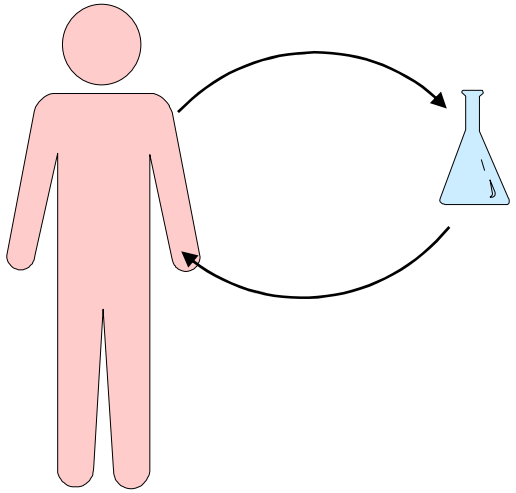
CYTOKINES
Clinical Trials

IL-1β	Ineffective Toxic (Did mitigate IL-2 toxicity)
IL-4	Minimal activity Toxic (growth factor for myeloma)
IL-6	Minimal activity Toxic
IL-12	Minimal activity Toxic
TNF	Ineffective Toxic (hypotension)
GM-CSF	Inconsistent single agent activity Well tolerated

MELANOMA
Adoptive Cellular Therapy



Generate TIL *Excise tumor* *Culture with IL-2* *Assay specificity* *Select/expand* *(10^{10} cells)*	*Non-myeloablative* FuCy		Infuse TIL	IL-2	RR = 51% (n=35)
	Myeloablative Collect PBSC (G-CSF)	FuCy TBI (2 v 12 Gy)		PBSC IL-2	RR 52% (2 Gy, n=25) RR 72% (12 Gy, n=25)

Rosenberg et al. Science 2006; Dudley et al. JCO 2008

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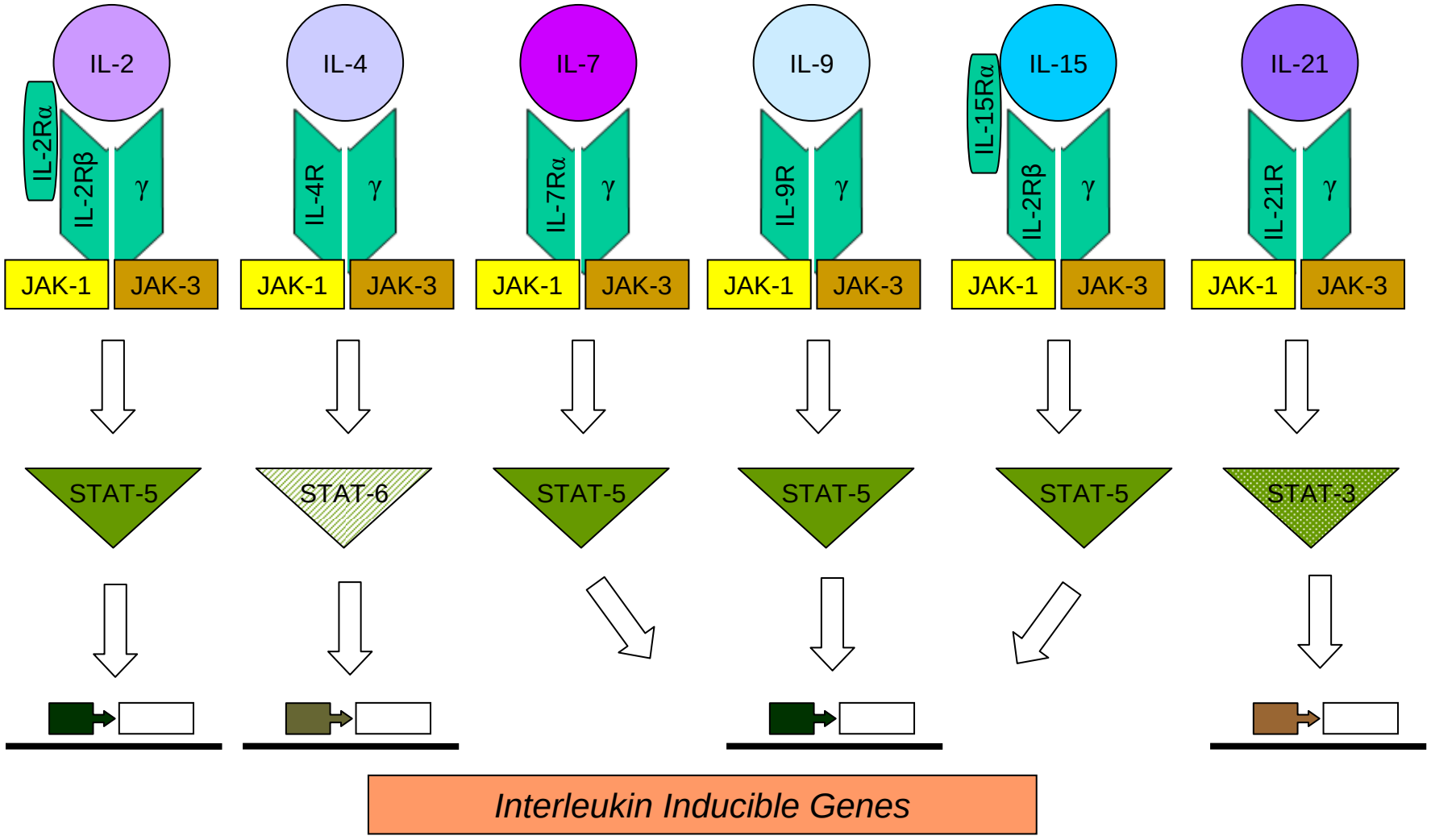
γ CHAIN CYTOKINES



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γ CHAIN CYTOKINES
Clinical Trials

Cytokine	Main Function	Cancer Indications	Clinical Trial
IL-2	T cell generation and function, NK activation	Melanoma, renal	FDA approved
IL-4	Th2 polarization, T proliferation, B cell activation	None	None

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IL-7	Pre-B and pre T cell development	Solid tumors (HIV and HSCT)	Phase II
IL-15	Stimulates T and NK cells	Melanoma, renal, solid tumors	Phase I, I/II
IL-21	Induction of B, T, and NK cells	Melanoma, renal ovarian, solid tumors	Phase II

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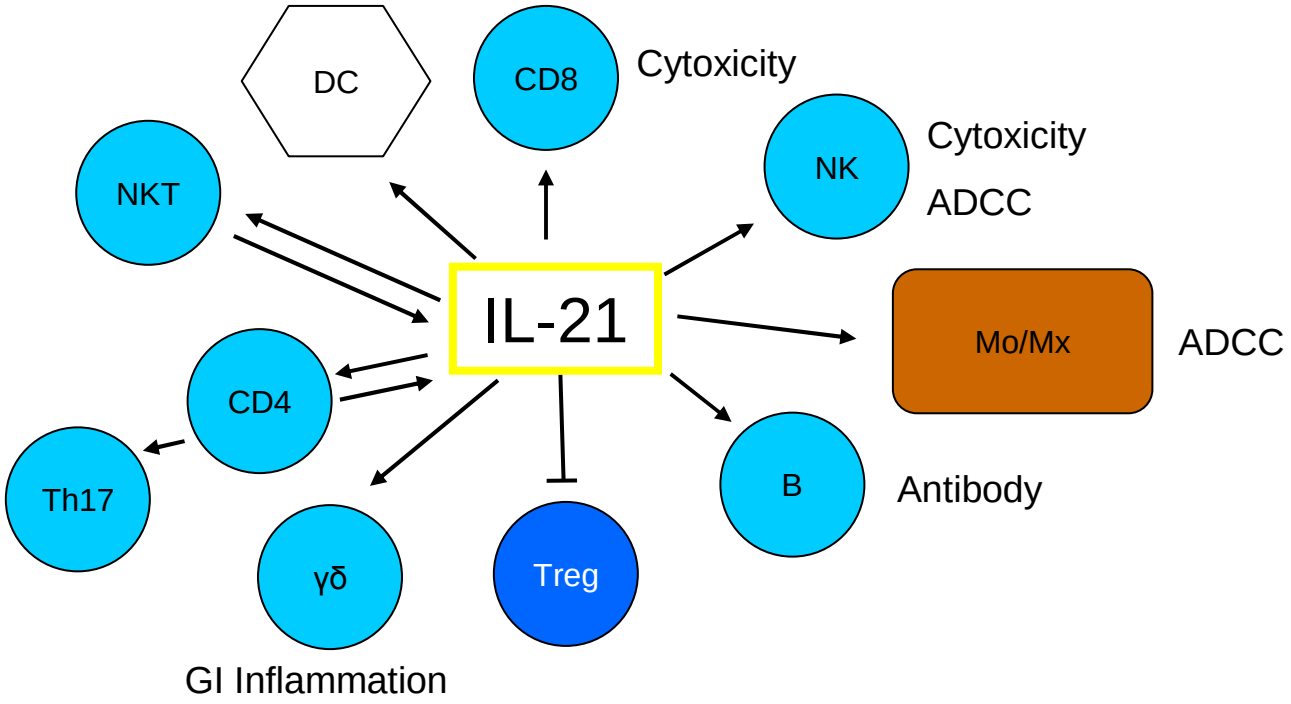

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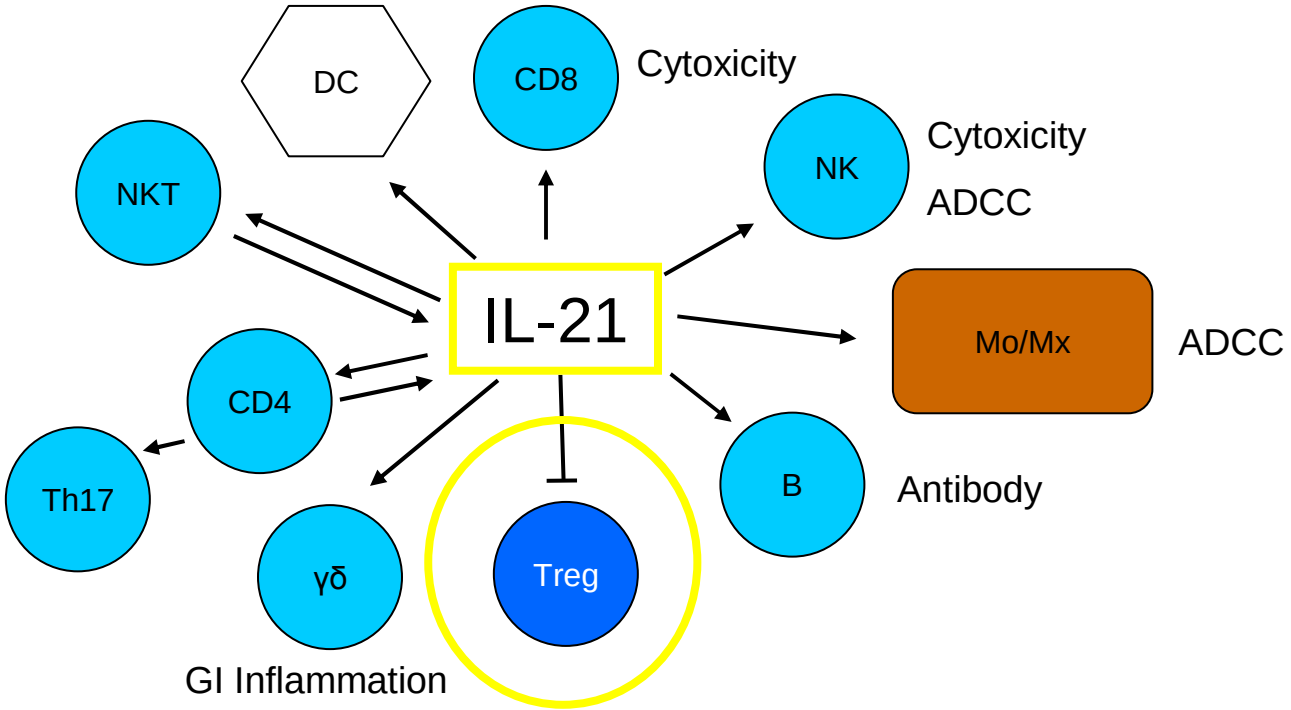

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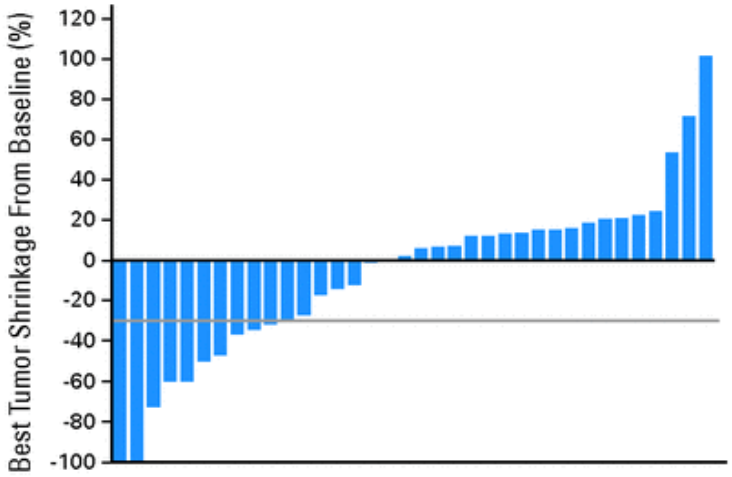
IL-21

- Phase II study of three dosing regimens
- Metastatic melanoma (N=40)
- RR = 22.5% (9/40 PR)
  - RR not depended on IL-21 receptor expression or *BRAF* mutation status.
- OS = 12.4 months; PFS = 4.3 months
- Common adverse events were fatigue, rash, diarrhea, nausea, and myalgia.
  - 6 patients had dose-limiting toxicities



Petrella et al. J Clin Oncol 2012

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IL-1 FAMILY

	Receptor/co-receptor	Property
IL-1α	IL-1RI/IL-1RacP	Proinflammatory
IL-1β	IL-1RI/IL-1RacP	Proinflammatory
IL-1Ra	IL-1RI	Antagonist for IL-1α, β
IL-18	IL-18Rα/IL-18Rβ	Proinflammatory
IL-36Ra	IL-1Rrp2	Antagonist for IL-36
IL-36α	IL-1Rrp2/IL-1 RAcp	Proinflammatory
IL-37	IL-18Rα, IL-18BP	Anti-inflammatory
IL-36β	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-36γ	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-38	IL-1Rrp2	? Antagonist
IL-33	ST2/IL-1RAcP	Proinflammatory

IL-1 FAMILY

	Receptor/co-receptor	Property
IL-1α	IL-1RI/IL-1RacP	Proinflammatory
IL-1β	IL-1RI/IL-1RacP	Proinflammatory
IL-1Ra	IL-1RI	Antagonist for IL-1α, β
IL-18	IL-18Rα/IL-18Rβ	Proinflammatory
IL-36Ra	IL-1Rrp2	Antagonist for IL-36
IL-36α	IL-1Rrp2/IL-1 RAcp	Proinflammatory
IL-37	IL-18Rα, IL-18BP	Anti-inflammatory
IL-36β	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-36γ	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-38	IL-1Rrp2	? Antagonist
IL-33	ST2/IL-1RAcP	Proinflammatory

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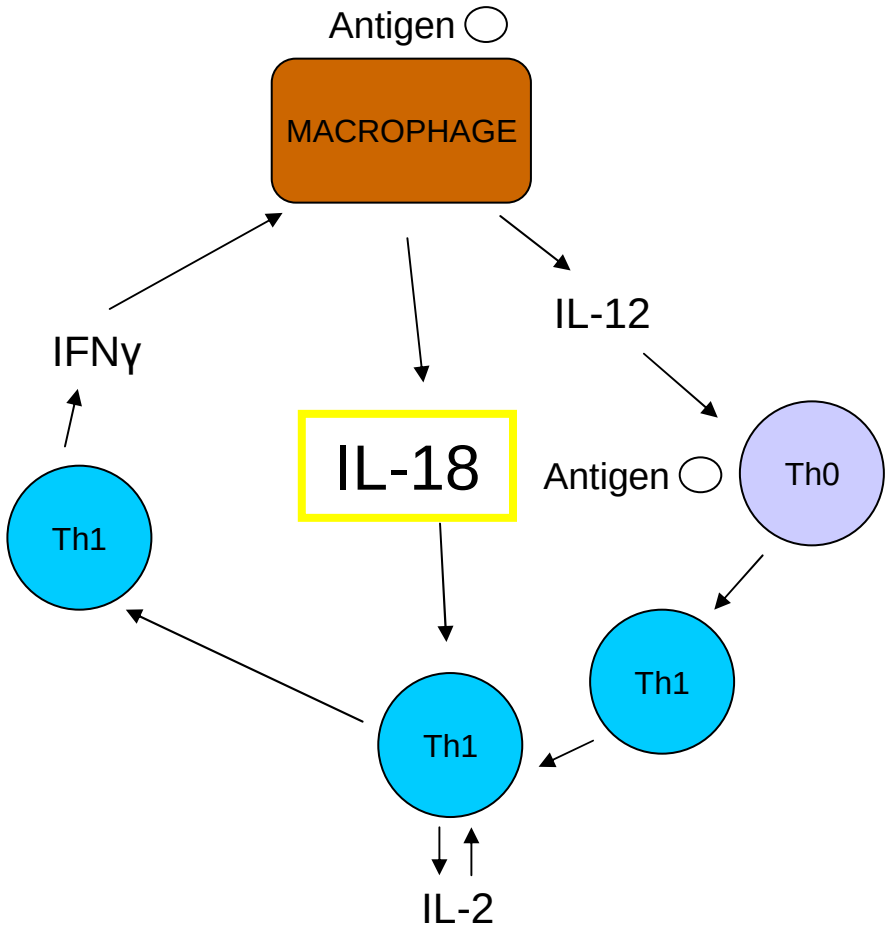

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IL-18

- Phase 2, randomized dosing study
- Metastatic melanoma (N=64)
- RR: 2% (1/64 PR)

TOXICITY

	Dose Group, mg/kg/d								
	0.01 n=21		0.1 n=21			1.0 n=22		Total N=64	
	No. of Subjects (%)								
Adverse Event	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3-5**
Fatigue	2 (10)	—	—	—	—	2 (9)	—	—	4 (6)
Abdominal pain	1 (5)	—	1 (5)	—	—	—	—	1 (5)	3 (5)
Back pain	1 (5)	—	1 (5)	—	—	—	—	—	2 (3)
Dyspnea	1 (5)	—	2 (10)	—	1 (5)	2 (9)	—	—	5 (8)
Ascites	—	—	1 (5)	—	—	—	1 (5)	—	2 (3)
Pleural effusion	—	1 (5)	—	—	—	2 (9)	—	—	3 (5)
Polyarthritis	1 (5)	—	—	—	—	—	—	—	1 (2)
Deep vein thrombosis	1 (5)	—	—	—	—	—	—	—	1 (2)
Pulmonary embolism	1 (5)	—	—	—	—	—	—	—	1 (2)
Cognitive disorder	—	—	1 (5)	—	—	—	—	—	1 (2)
Lipase increased	—	—	—	1 (5)	—	—	—	—	1 (2)

Tarhini et al. Cancer 2009

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CYTOKINE THERAPY

- Reponses are infrequent (but durable)
- Toxicity is limiting
- Treatments are cumbersome
  - Multiple injections/infusion
  - Immunogenic

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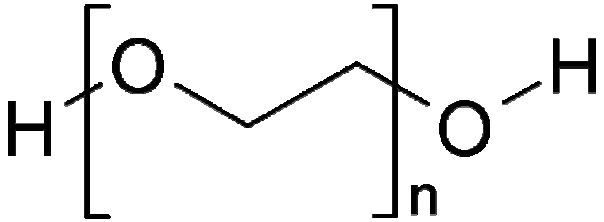
CYTOKINE THERAPY

- Improve cytokine delivery
  - PEGylation
  - Cytokine-antibody fusion molecules
  - Recombinant virus delivery systems
- Combination therapy
  - Cytokine + vaccine

PEGYLATION

covalent attachment of polyethylene glycol (PEG) polymer chains to drug



- ↑ drug solubility
- ↑ circulating life
- ↑ Increased drug stability
  - ↑ protection from proteolytic degradation
- ↓ immunogenicity and antigenicity
- ↓ dosage frequency
  - Without diminished efficacy
  - Potentially reduced toxicity

Improve PK

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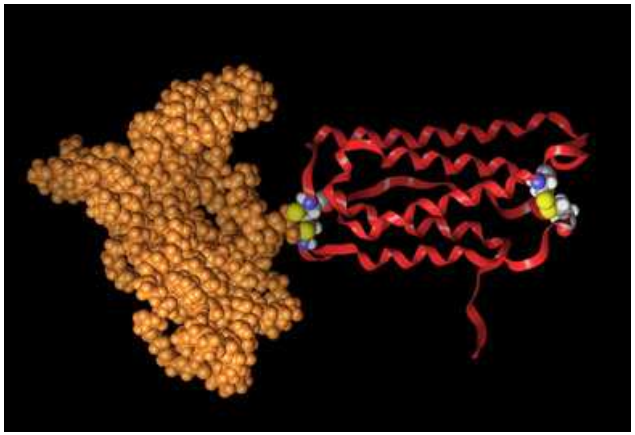
CYTOKINE PEGYLATION

Drug	Composition	Indication	FDA Approval
Pegineterferon alfa-2b (PegIntron; Sylatron)	PEGylated interferon alpha	chronic hepatitis C and hepatitis B; melanoma	2000 (2011 melanoma)
Peginterferon alfa-2a (Pegasys)	PEGylated interferton	chronic hepatitic C and hepatitis B	2001
Pegilgrastim (Neulasta)	PEGylated recombinant methionyl human granulocyte colony-stimulating factor	chemotherapy-induced neutropenia	2002



Pegylated Interferon alfa-2b

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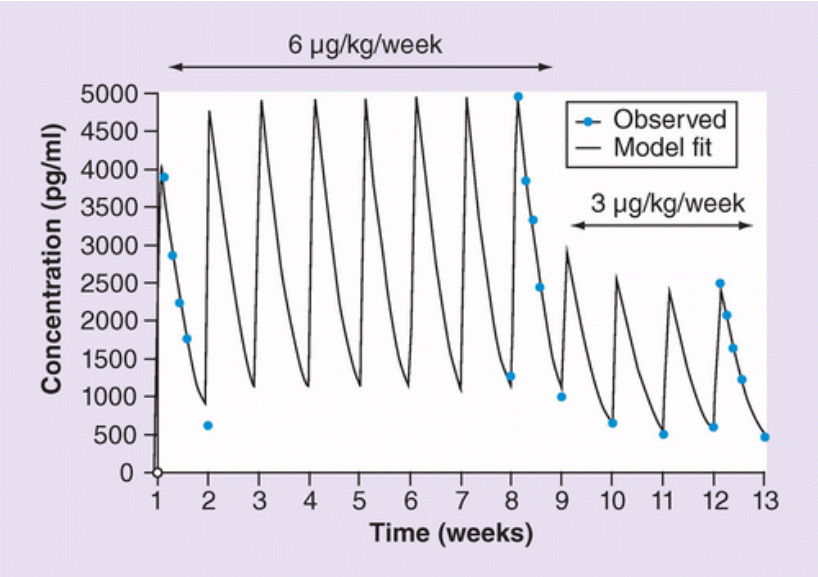
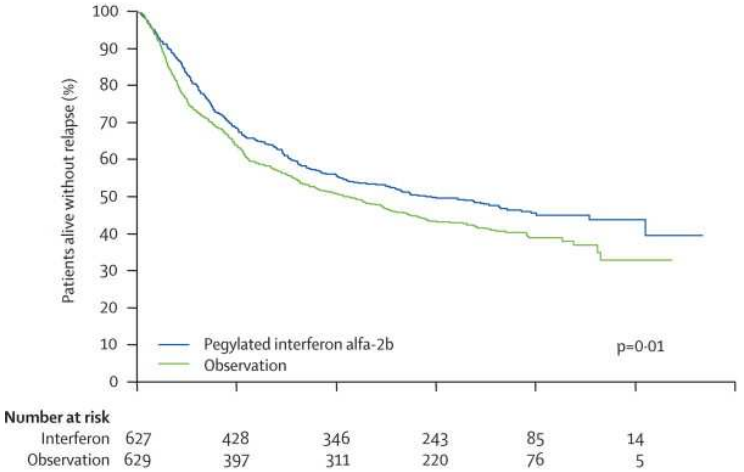
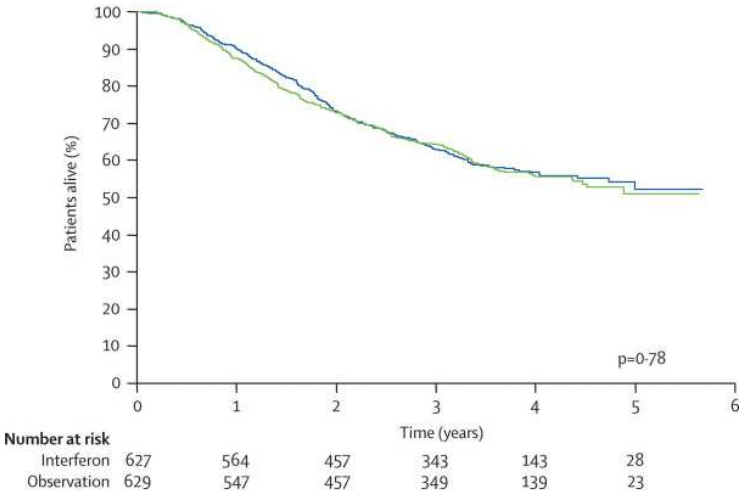
ADJUVANT INTERFERON
Pegylated Interferon alfa-2b

6 mcg/kg/week SC for 8 doses
THEN
3 mcg/kg/week SC for up to 5 yr







Eggermont et al. Lancet 2008

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ADJUVANT INTERFERON
Pegylated Interferon alfa-2b

	HD IFN	PEG-IFNa2b
Cytopenia	+	
Flu like symptoms	+	
Hepatotoxicity	+	
Neurotoxicity	+	
Fatigue	+	+
Anorexia	+	+
Depression	+	+

More favorable safety profile

+

Greater convenience (less frequent dosing)

FDA approval adjuvant treatment for stage III melanoma.

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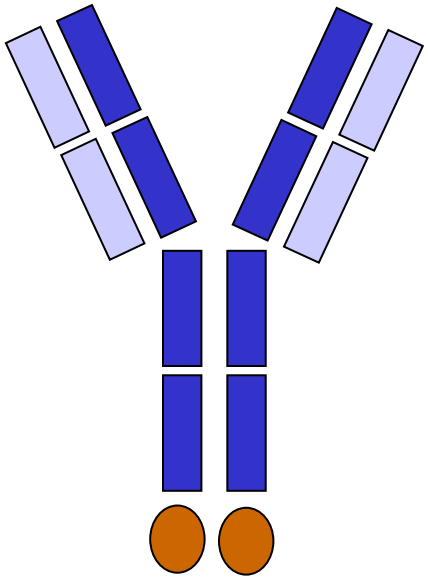
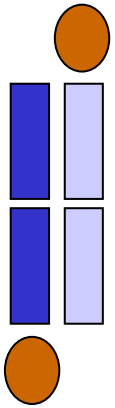
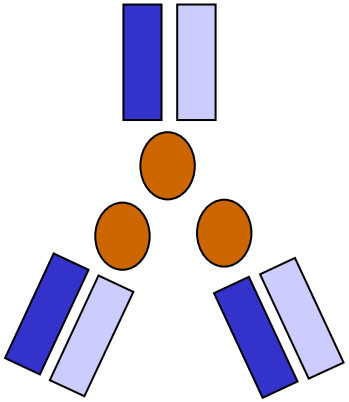
IMMUNOCYTOKINES



IgG-Cytokine



Diabody-Cytokine



scFv-Cytokine

Combine the specificity of antibody with the activity of cytokines

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IMMUNOCYTOKINES
Clinical Development

Immunocytokine	Format	Antigen	Indication	Clinical Trial
F16-IL2	Diabody	Tenascin C A1 domain	Breast, lung	Phase Ib/II
Hu14.18-IL2	IgG	GD2	Melanoma, neuroblastoma	Phase II
L19-IL2	Diabody	Fibronectin EDB	Melanoma, pancreas, renal	Phase IIb
NHS-IL2LT	IgG	DNA	Lung, NHL	Phase I/II
BI-IL12	IgG	Fibronectin domain VII	Melanoma	Phase I/II
NHS-IL12	IgG	DNA/histone	Solid tumors	Phase I
L19-TNF	scFv	Fibronectin EDB	Melanoma	Phase I/II

L19-IL2
(Darleukin)

- Immunocytokine composed of a diabody specific to the EDB domain of fibronectin, a tumor angiogenesis marker, and of human interleukin-2 (IL2).
- Delivers IL2 to the tumor site exploiting the selective expression of EDB on newly formed blood vessels.

Eigentler et al. Clin Cancer Res 2011

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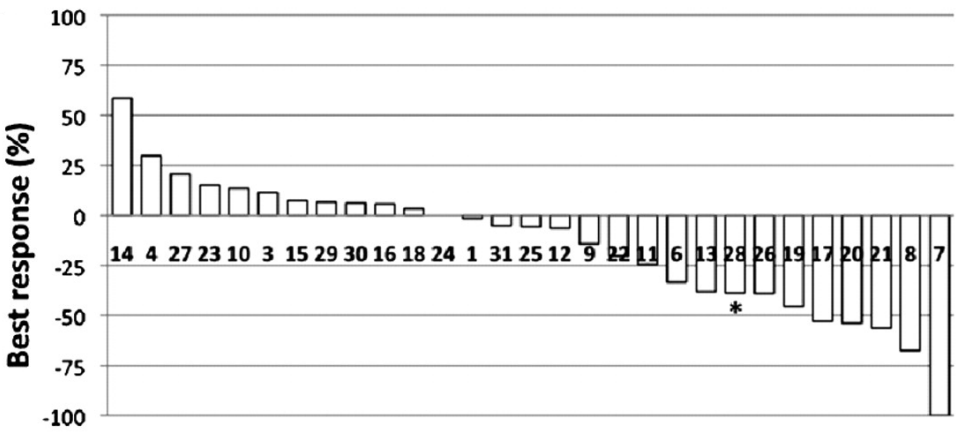
L19-IL2
Clinical Trial

- Metastatic melanoma (N=32)
- RR: 8/29 (28%); 1 CR
- Median overall survival 14.1 months
  - 12-month survival rate 61.5%
- Most frequent adverse events included chills, fatigue, and fever
  - Dose related
  - Mild or moderate in severity



Eigentler et al. Clin Cancer Res 2011

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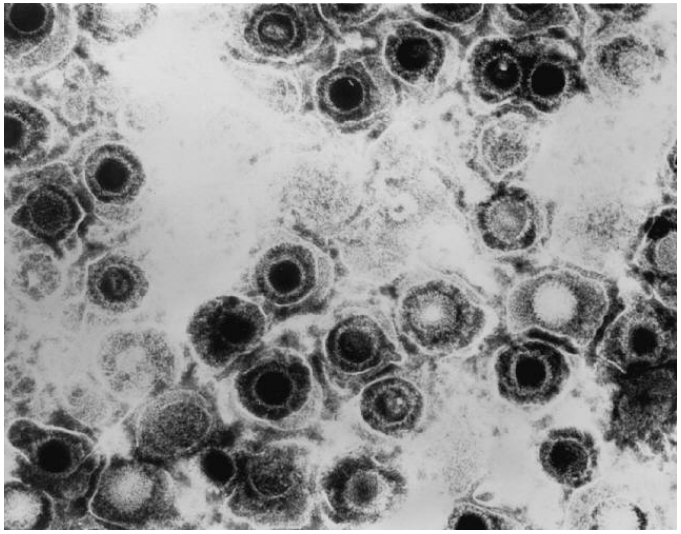
T-VEC
(Talimogene Laherparepvec; OncoVEX$^{GM\text{-}CSF}$)

- Attenuated herpes virus
- Expresses GM-CSF



Recombinant virus delivery systems

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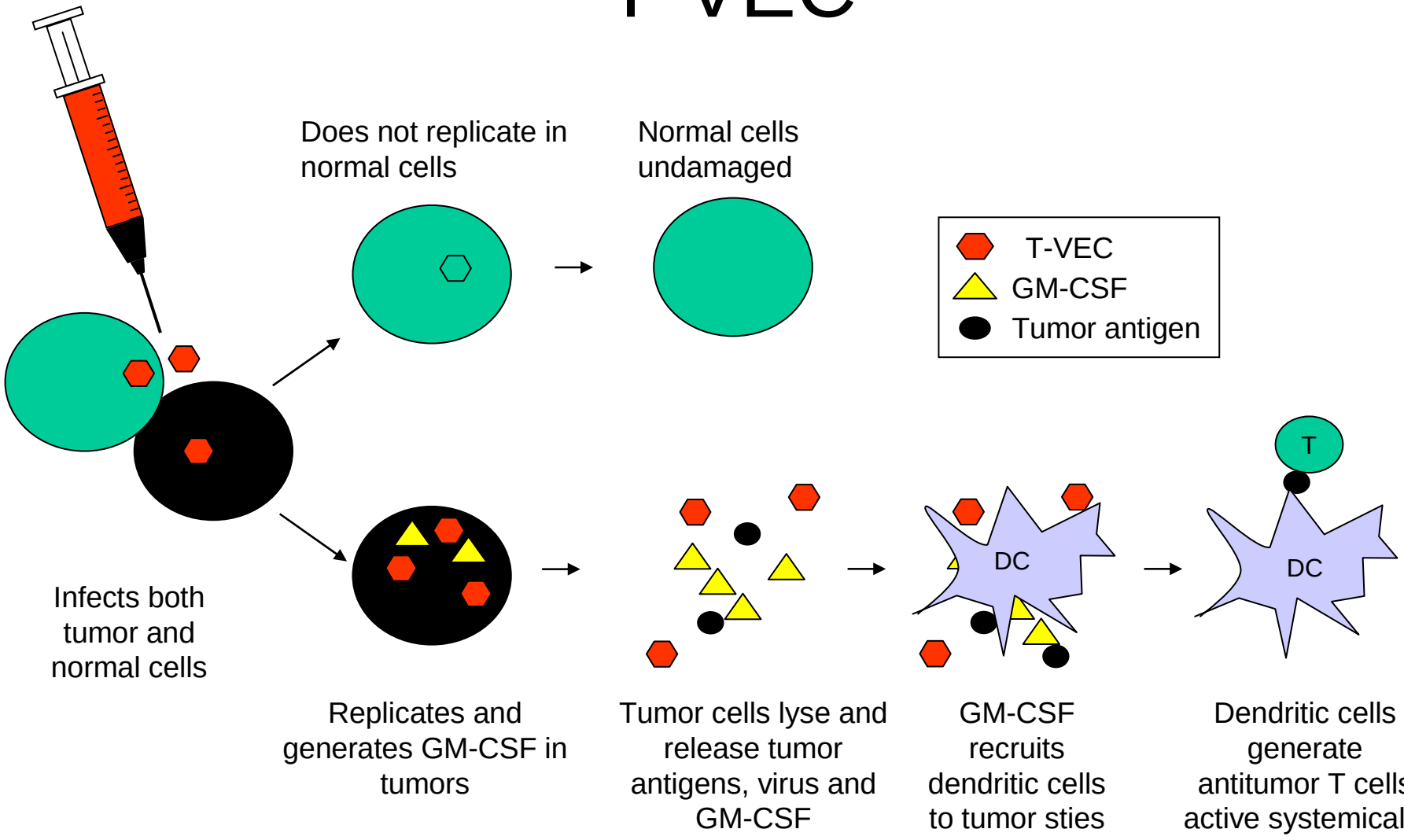
T-VEC



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T-VEC
Clinical Trial

Unresectable melanoma
Stage IIIB/C or IV
Injectable cutaneous, SC, or nodal lesions

↙ ↘

	T-VEC Intralesional N=295	GM-CSF SC N=141	
Durable RR (≥6mo)	16%	2%	P<.0001
ORR	26%	6%	P<.0001
CR	11%	1%	P<.0001
OS	23.3 mo	19.0 mo	P=.07

- Well tolerated
  - Mild fatigue, chills, or fever
  - Most common serious adverse event was cellulitis (2%)

Andtbacka et al. ASCO 2013 (abstr)

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CYTOKINE THERAPY
Combinations

- Despite yielding higher response rates, regimens that combine IFN with IL-2 (and/or chemotherapy) have not produced better survival

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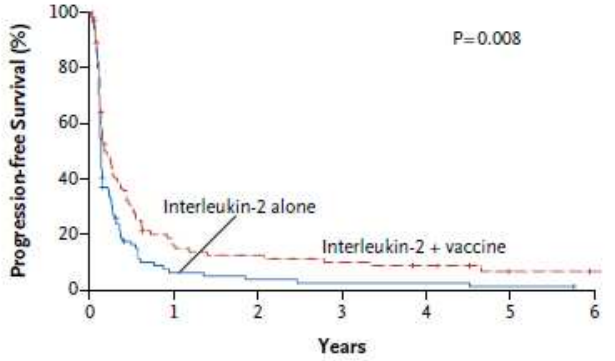
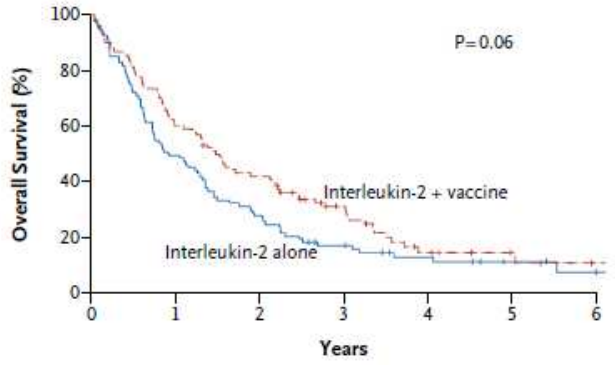
MELANOMA VACCINE

HD IL-2 ± Immunization

	gp100:209-217(210M) peptide vaccine followed by HD IL-2	HD IL-2	P
N	91	94	
RR	16%	6%	.03
PFS	2.2 mo	1.6 mo	.008
OS	17.8 mo	11.1 mo	.06





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Schwartzentruber et al. NEJM 2011

CYTOKINE THERAPY

- One of the few approaches that can induce complete and durable tumor responses
- Single agent response rates have been low
- Dosing and scheduling have been empiric
- Limited by frequent and often severe toxicity
- Mechanism of responses are not known

CYTOKINE THERAPY
Future Directions

- Improve PK/PD
- Combinations

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CYTOKINE THERAPY
PK/PD

- Prolong half-life
  - PEGylation
- Enhanced specificity
  - Cytokine-antibody fusion molecules
  - Recombinant virus delivery systems

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CYTOKINE
Combinations

- Cytokines + chemotherapy/targeted therapy
- Cytokines + other immune-stimulating agents
  - Vaccines
  - Adoptive cellular therapy
- Cytokine + agents that target immunosuppression
  - Checkpoint inhibitors (anti-CTLA-4, anti-PD1)
  - Myeloid-derived suppressor cells (e.g. sunitinib).

CYTOKINE
Combinations

- Combination approaches will be challenging
  - Attributing toxicity
  - Attributing response.
- Some cytokines (e.g. IL-2) are thought to be most effective at high doses

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CYTOKINE THERAPY
Biomarkers

- PD/immune monitoring
  - Cumbersome
  - Reproducibility
- Identify factors that predict response
  - Spare ‘non-responders’ unnecessary treatment and toxicity

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Final Rankings of Agents with High Potential for Use in Treating Cancer

Rank	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-PD1 and/or B7-H1	T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell Stimulator
5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti-4-1BB)	T-Cell Stimulator
9	Anti-TGF-beta	Signaling Inhibitor
10	Anti-IL-10 Receptor or Anti-IL-10	Suppression Inhibitor
11	Flt3L	Dendritic Cell Growth Factor
12	Anti-GITR	T-Cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A	Vaccine Adjuvant
15	Poly I:C and/or Poly ICLC	Vaccine Adjuvant
16	Anti-OX40	T-Cell Stimulator
17	Anti-B7-H4	T-Cell Checkpoint Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti LAG-3	T-Cell Checkpoint Blockade Inhibitor