DM SEMINAR
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Immunological agents in Pulmonary Medicine

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Classification of Immunological agents in Pulmonary Medicine

1. **Traditional agents**: Corticosteroids
   Cyclophosphamide, Azathioprine, Methotrexate

2. **Newer agents:**

a. Obstructive diseases: Allergic diseases & Asthma/ COPD/ Bronchiolitis/ ABPA

b. Infectious diseases: Tuberculosis/ Fungal/ CAP

c. Carcinoma lung (SCLC/ NSCLC), Mesothelioma.

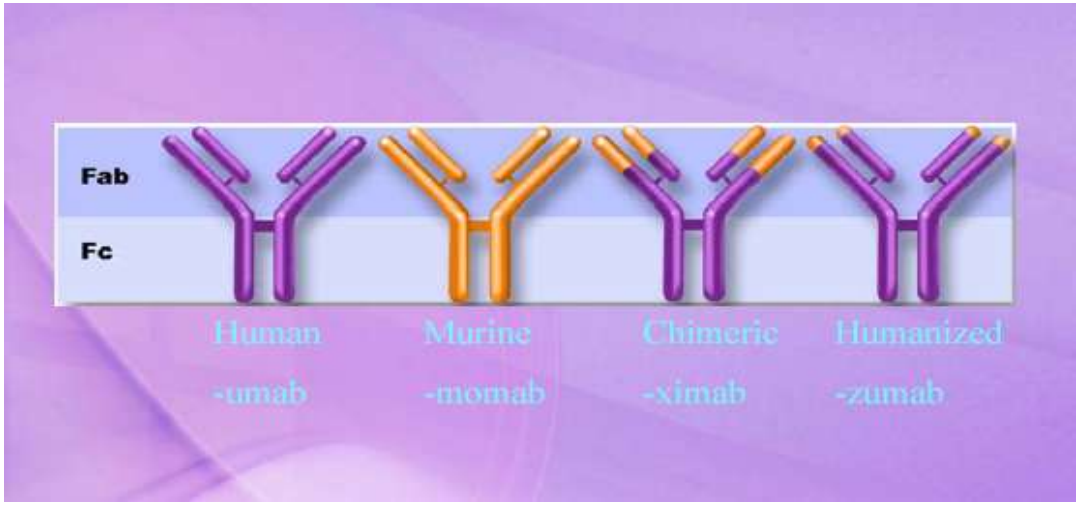
d. Pulmonary vasculitis:

e. DPLD"s: IPF/ CT-ILD/ LAM/ Eosinophilic diseases/ PAP

f. Sarcoidosis

g. Hypersensitivity pneumonitis.

Nomenclature of monoclonal antibodies



The following letters were approved as product source identifiers:

u = human
o = mouse
a = rat
e = hamster
i =primate
xi = chimera

Disease or target class
Viral -vir-
Bacterial -bac-
Immune -lim-
Infectious lesions -les-
Cardiovascular -cir-
Tumors
Colon -col-
Melanoma -mel-
Mammary -mar-
Testis -got-
Ovary -gov-
Prostate -pr(o)-
Miscellaneous -tum-

Newer Immunological agents In Asthma:

1. **Non-traditional multi-step agents**:

   Methotrexate/ Troleandomycin /Gold/ HCQ"S/ Azathioprine/ cyclosporine/ IVIG/ Inhaled heparin/ Inhaled Furosemide/ Dapsone.

2. **Immune down-regulation** (Immunotherapy)

   dust mite rx

   newer tech (peptide based / CpG motifs/ Plasmid DNA vaccine/ anti-inflamm cytokines).

   Probiotics

   Sublingual immunotherapy.

3. **Inhibit Eosinophils**: IL-5 antagonists.

4. **Inhaled Allergen-Eosinophil / Basophil interactions:**

   a. block cell surface adhesion: Cytokines (Th1 agonists/ Th2 antag)/ anti-sense oligonucleotides/ Chalcone derivatives.

   b. block f.n: linear/ cyclic peptides/ polym. Lipid particles/ Glycomimetics.

   c. Low MW Antagonists: VLA-4 antag/ LDV-antag/ N-acetyl phenylalanine based antag.

   d. Monoclonal Ig"s:

5. **Chemokine Antagonists**.

CCR3

CCR4

6. **Activation Pathway inhibition** (FcγR11b)

7. **Down-stream Pathway Inhibition**.

a. MAP Kinases/ P38/ Janus kinases

b. Transcription Factors: GATA3/ STAT 6/ NF-κB

8. **Anti-IgE therapy**:

Omalizumab.

Cytokines in asthma therapy:

Cytokines (Th1 agonists)

- IL-12
- IFNγ
- IL-18

Th2 antagonists

- IL-4 IgG (Pascolizumab)
- soluble IL-4 receptor (Altrakincept)
- IL-5
- IL-13
- IL-9

TNF∞ antagonists.

T Regulatory cells

Site/mode of action	Target	Therapy/proposed therapy	Clinical status
B-cell / IgE blockade	IgE	Anti-IgE (omalizumab)	Food and Drug Administration-approved; available
T-cell manipulation			
Th2 cytokine blockade	IL-5	Mepolizumab, SCH55700	Clinical trials underway
	IL-4	Soluble IL-4 receptor (altrakincept)	Inefficacious in phase III trials
		Anti-IL-4R antibody	Preclinical development
		IL-4 double mutein	Clinical trials underway
		Anti-IL-4 mAb (pascolizumab)	Inefficacious in phase III trials
	IL-13	Soluble IL-13Rα2	Preclinical development
Th1 cytokine enhancement	IFNγ	Recombinant IFNγ	Phase I study done; no father development
	IL-10	Recombinant IL-10	Approved for psoriasis and Crohn's disease; no human asthma studies to date
	IL-12	Recombinant IL-12	Small clinical trials showed adverse side effect profile and lack of efficacy
	IL-18	Recombinant IL-18	Theoretical
T-regulatory cell manipulation	CD25+ Treg	TGFb-mediated	Theoretical
	NK T cell	induction of foxp3	
	IL-10 Treg	Glucocorticoids + vitamin D3	Theoretically available
T-cell inflammatory cytokine blockade	TNFα	Infliximab, adalimumab, etanercept	Clinical trials underway (available for rheumatoid arthritis and other indications)
Modulation of cell trafficking			
Chemokine blockade	Eotaxin / CCL11	Anti-eotaxin antibody	Preclinical studies only
Chemokine receptor blockade	CCR3		
Adhesion molecule blockade	LFA-1	Efalizumab	Approved for psoriasis; asthma clinical trials underway
	ICAM-1		Preclinical studies done
Intracellular targets			
Transcription factors	NFκB, GATA-3, T-bet, STAT-6	ODN decoys	Theoretical
Protein kinases	P38 MAP kinase	CSAIDs	Preclinical development
	JNK	Blocking peptide	Theoretical
	Lyn	Blocking peptide	Preclinical development

Omalizumab: Humanized monoclonal antibody that binds human IgE and prevents it from attaching to mast cells and basophils

Indications: Moderate or severe persistent asthma that has not responded well to inhaled corticosteroids and long-acting beta agonists

Side effects: Urticaria in 2%–3% of patients; anaphylaxis in 0.01%–0.1%

Route and frequency: Subcutaneous, monthly or every 2 weeks depending on the dose

Dose: 0.016 mg *body weight (kg)*IgE level (IU/mL)

Cost: Varies on the basis of dose needed, but will average about $12,000/yr

Who are Candidates For Omalizumab?

- Moderate or severe persistent allergic asthma
- Age greater than 12 years
- Symptoms despite inhaled corticosteroid therapy
- A serum total IgE level between 30 and 700 IU/mL

. A positive result on skin-prick testing or RAST testing with at least one perennial (ie, always-present) allergen.

The recommended dose is 0.016 mg/ kg unit of IgE every four weeks, administered sc at either four-week or two-week intervals
for adults and adolescents (persons 12 years of age and older) with allergic asthma.

Omalizumab doses larger than 300 mg per month must be given in divided doses every 2 weeks.

Omalizumab is concentrated to 150 mg/1.2 mL

Dosage is given as per normogram or calculated every patient.

Cost-effectiveness of Omalizumab.

Hospitalizations account for a large part of the expense of asthma care.

One emergency department visit with subsequent hospitalization for asthma was estimated to cost $3,102

Omalizumab has been shown, in a pooled analysis of three multi-center trials, to prevent 92% of hospitalizations when compared with placebo.

most cost-effective if given to patients who are hospitalized two or more times a year despite multi-drug asthma therapy.

Multiple studies have shown Omalizumab to also be effective in IgE-mediated allergic rhinitis

ADELROTH et al
NAYAK et al

Side effects of Omalizumab.

Urticaria. In the trial by Milgrom et al,17 urticaria developed in 8 (7.5%) of 106 patients in the high-dose group, 6 (5.7%) of106 patients in the low-dose group, and 3(2.9%) of 105 patients in the placebo group.

Urticaria tends to be mild and happens only with the first infusion, suggesting that it is not IgE mediated.

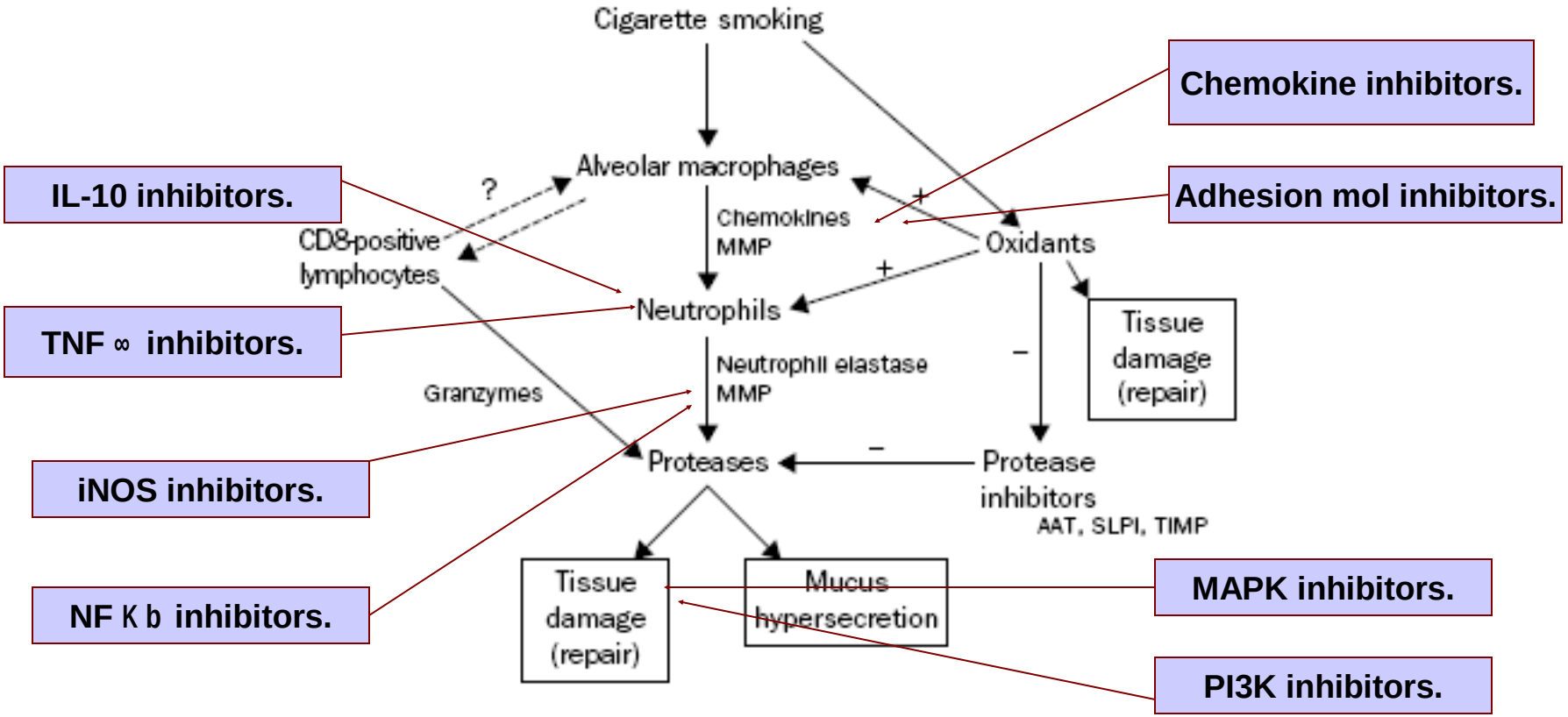
Anaphylaxis. Three patients in whom no other allergic trigger could be found have experienced anaphylaxis during treatment with Omalizumab. This incidence represents less than 0.1% of patients treated.

Malignancies: Malignancies occurred in 0.5% of patients on active treatment and 0.2% of patients on placebo in the studies that were submitted to obtain FDA approval. Unlikely to be therapy related.

QUESTIONS FOR RESEARCH

- *What are it's long-term effects?*
- *Will it prevent airway remodeling?*
- *Will it facilitate immunotherapy?*
- *Will it be beneficial in severe asthma?*
- *Can it be used in other allergic diseases?*

Summary of immunotherapy in COPD

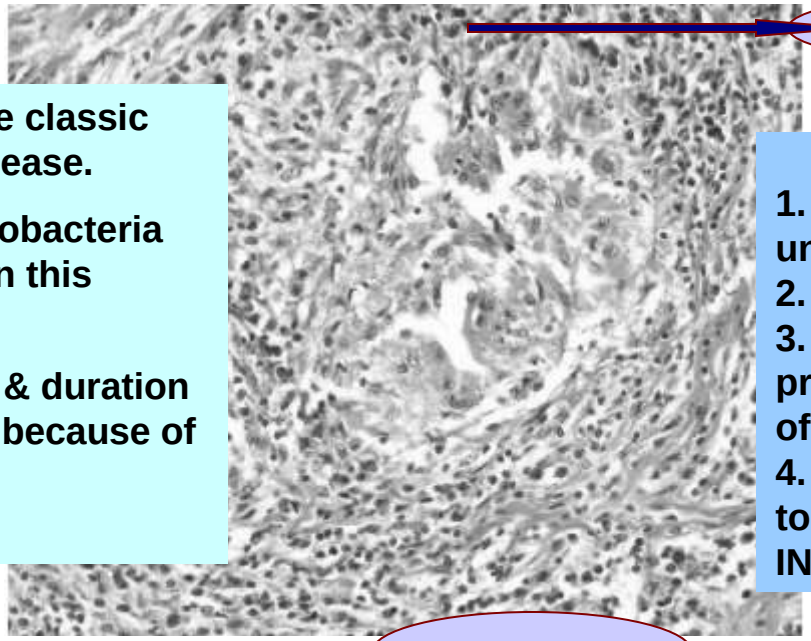


Immunotherapy of tuberculosis:

1. Granulomas are the classic way of containing disease.

2. Paradoxically, Mycobacteria survive persistently in this milieu.

3. The risk of relapse & duration of current regimes is because of this phenomenon.



MYCOBACTERIAL RESPONSE

1. stationary colony-forming unit (CFU)
2. decreased metabolism,
3. Altered gene-expression profiles (including activation of Rv3133c/DosR)
4. Decreased susceptibility to the bactericidal effects of INH.

6 month schedule

Long treatment schedule limits trials.

Most studies are hence in
1. MDR patients (sputum positive) or
2. Use surrogate end points

Clinical trials of adjunctive IFNγ for treatment of multi drug-resistant pulmonary tuberculosis.

IFN-γ increases the Mycobactericidal capacity of macrophages by promoting the production of reactive nitrogen intermediates, such as nitric oxide

Condos et al. [18]	5	500 μg of IFN-γ 3 times per week by aerosol for 1 month
Giosuè et al. [19]	7	3 MU of IFN-α 3 times per week by aerosol for 2 months
Suarez-Mendez et al. [20]	5	1 MU of IFN-γ daily, then 3 times per week im for 6 months
Koh et al. [21]	6	2 MU of IFN-γ 3 times per week by aerosol for 6 months

CFU"S decreased and sputum became negative

No utility!!

Placebo controlled RCT in MDR TB by Intermune investigators in 2000

NO UTILITY IN PRELIM ANALYSIS.

IFN–induced genes, such as *IP-10* and *iNOS,* are already up-regulated in the lung in patients with tuberculosis and that therapeutic aerosol IFN has relatively little additional effect

Clinical trials of adjunctive IL-2 for treatment of tuberculosis

IL-2 promotes T cell replication and is essential for cellular immune function and granuloma formation.

In 1997,a small, unblinded study of 2 low-dose IL-2 regimens (daily or in 5-day “pulses”) in patients with MDR tuberculosis found that the daily regimen appeared to decrease sputum acid-fast bacilli counts

RCT, placebo-controlled trial of the effect of IL-2 on conversion of sputum culture results conducted by the Case Western Reserve University Tuberculosis Research Unit with 110 Ugandan, HIV-uninfected patients with drug-susceptible tuberculosis

IL-2 or placebo was administered twice daily for the first month of standard therapy.

Significant delays in clearance of viable *M. tuberculosis* CFU and conversion of sputum culture results in the IL-2 treatment arm.

Clinical trials of adjunctive TNF-∞ for treatment of tuberculosis

TNF ∞ plays a central role in the host response to *M. tuberculosis.*

Monocytes express TNF ∞ after phagocytosis of Mycobacteria or after stimulation by mycobacterial proteins or glycolipids

TNF essential for the formation and maintenance of granulomas.

TNF- antagonists associated with significant side effects. In a recent meta-analysis, the pooled odds ratio for malignancy was 3.3 and for serious infection was 2.0 Malignancies significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. The NNH was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, it was 59 (95% CI, 39-125) within 3 to 12 months.

TNF ∞ not studied in tuberculosis immunotherapy but antagonists have been evaluated

Clinical trials of adjunctive TNF-∞ inhibitors for treatment of tuberculosis

Two trials for the effects of potent immunosuppressive and/or anti-TNF therapies on microbiologic outcomes in tuberculosis in HIV-1–infected patients with preserved tuberculosis immune responses

Etanercept(25 mg sc twice weekly for 8 doses) given to 16 subjects, starting on day 4 of tuberculosis treatment.

Well tolerated. No serious opportunistic infections.

CD4 cell counts increased by 96 cells/μL.

Trends toward

- superior resolution of lung infiltrates,
- Closure of lung cavities,
- improvement in performance
- score, and
- weight gain

Clinical trials of adjunctive high dose methyl prednisolone for treatment of tuberculosis

189 subjects who were treated with prednisolone(2.75 mg/kg/day) or placebo during the first month of standard ATT.

The daily dose was tapered to 0 mg/kg during the second month; a cumulative dose of 16500 mg.

50% prednisolone-treated subjects had conversion of sputum culture results to negative after 1 month of treatment, compared with 10% of subjects in the placebo

In several studies of HIV-TB, sputum conversion is better in the HIV group.

Granuloma disruption is likely to be an effective adjunct in tubercular therapy.

Benefit % overshadows Rifampin!!
Toxicity unlikely to be acceptable

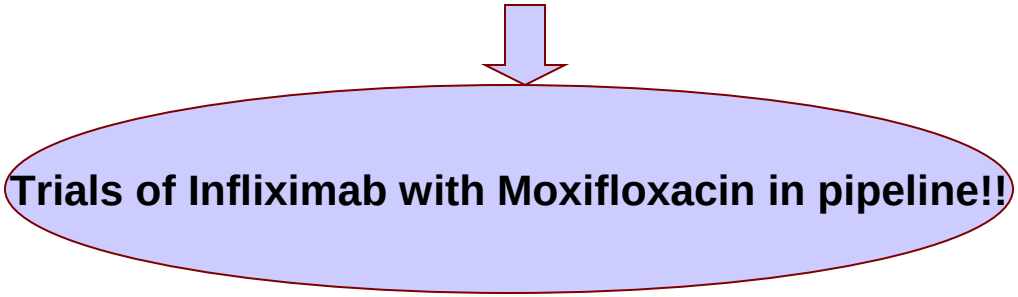
Emerging paradigm that granulomas while necessary for containing disease in the natural state interfere with sterilization.

- trials of immunotherapy mentioned above.
- Vaccination with BCG ↓ the bactericidal activity of INH in the guinea pig
- Although the total rates of TB recurrence in HIV is more, most are re-infections. Relapses were only 50% as common.
- Sputum conversion at 2 months greater in HIV infected
- HIV with IRIS have high rates of relapse (6 fold).

Chemotherapy is hence at loggerheads with body"s response.

Differential role of Infliximab & Etanercept in TB recurrences.

Immunotherapy to re-synchronize this might lead to better outcomes & faster cures.



Other Agents being tried in the Treatment of MDR-TB:

1. Thalidomide
2. Pentoxifylline
3. Levamisole
4. Transfer factor
5. Inhibitors of transforming growth factor-
6. Interleukin-12
7. Interferon-∞
8. Imiquimod (an oral agent that stimulates the production of interferon-∞)

Immunotherapy of invasive fungal infections:

Risk factors IFI in patients:

Therapy related

Neutropenia

defects in lymphocyte number & function

mucositis

invasive vascular devices.

Genetic polymorphisms

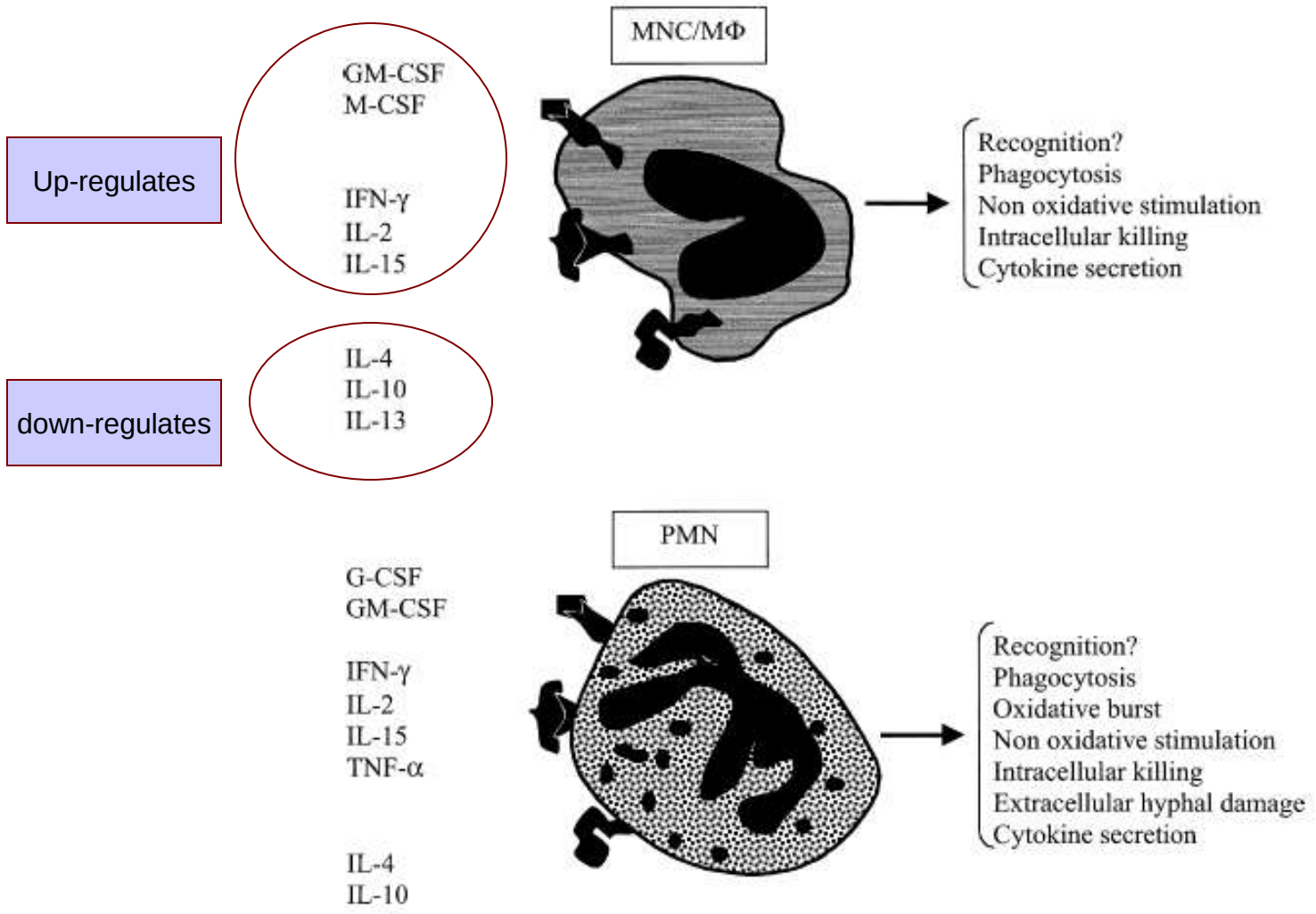
HLA polymorphisms

microbicidal pathways.

Current challenges:

1. to dissect the risk factors for IFI s and develop a more refined algorithm
2. Modulation of host defenses as another approach of management of IFI s

Immunotherapy of invasive fungal infections:



Summary:

- ACON recommends that high-risk patients (more than 40% risk of febrile neutropenia) receive G-CSF or GM-CSF prophylactically.
- During the onset of febrile neutropenia in patients not receiving a HGF, only when the duration of neutropenia is predicted to be long, G-CSF or GM-CSF is suggested.
- Although no data exist, patients who have had an episode of IFI in the past and become neutropenic again should be treated with a HGF.
- With regard to documented IFI s in neutropenic patients, the 1997 IDSA guidelines state that these factors „may be indicated"
- Prophylactic use of IFN-γ in patients with CGD. In this setting, human IFN- γ should be administered at a dose of 50 µg/m2 3/week sc. Doses up to 100 µg/m2 have been used.

Macrolides As Immunotherapy

Macrolides have been found to have significant ant-inflammatory activity and this has been used in a variety of non-infectious inflammatory states.

These include

1. Asthma
2. Chronic sinusitis
3. Bronchiectasis
4. ??cystic fibrosis
5. Sino-bronchial syndrome.
6. COPD
7. DPB
8. Community acquired pneumonia (pneumococcal bacteremia)

Mechanisms of Macrolides As Immunotherapy

Macrolides modulate inflammatory activity in airway epithelial cells by inhibiting NF-κB activation

Cause reduced IL-8 production and enhanced neutrophil accumulation.

Macrolides inhibit the expression of ICAM, thereby also modulating the recruitment of neutrophils to inflamed sites.

The extra-ribosomal effects of Macrolides reduce the number of neutrophils in the BAL fluid from patients with neutrophilic, inflammatory airway diseases

Macrolides also may attenuate mucus hyper secretion by goblet cells as an indirect consequence of inhibiting neutrophil migration, activation, and accumulation

In chronic colonization by virulent organisms, non-ribosomal actions like inhibition of twitching motility, alginate production and biofilms (eg Ps.aeruginosa) are also important

Failed Therapies In Sepsis:

1. p80 soluble receptor to TNF
2. NO synthase inhibition(1-n-methyl arginine)
3. Anti-endotoxin trial of human monoclonal antibody (MAb) HA-1A10
4. Ibuprofen
5. Bactericidal permeability increasing protein
6. Corticosteroids
7. Granulocyte colony-stimulating factor
8. Hemoglobin solutions (*eg,* NO scavengers)
9. Hemoperfusion with polymixin B
10. High-density lipoproteins
11. Immunonutrition (fish oil)
12. Lipopolysaccharide analogues
13. Recombinant PAF inhibitor
14. TNF receptor p55
15. IL-1rA trials
16. tPAI
17. AT III

What is wrong with trials in sepsis immunotherapy?

1. **Testing for the wrong hypothesis (TNF∞ trials)**
2. **errant study design (**IL-1rA trials)
3. **using the wrong agent (**P-80 TNF receptor),
4. **focusing on an inappropriate target group (**E5 anti-endotoxin)
5. **excessive expectations (anti-TNF trials)**
6. **uncontrolled variables(**1-n-methyl arginine)

Few successes also….

Variables	Relative Risk of Death (95% CI)*	p Value	Absolute % Reduction in Risk
Anti-TNF	0.90	0.049	3.6
Activated protein-C	0.81 (0.69–0.94)	0.005	6.1
Hydrocortisone	0.84†	0.02	10

Adjunctive immunotherapy in AASVV:

1.Mycophenolate mofetil

Preliminary data promising.

1.**Nowack et al JASN 99; 1965-71**

open-label, prospective standardized study OF I G MMF twice per day 11 AASV following remission induction with daily CYC. Of the 11 patients, one WG patient (9%) relapsed in the 14th month of maintenance therapy. Well tolerated

2.Nachmann (n=12) JASN 2K(33% relapse)

3. Stegman. Used as a induction.

The IMPROVE trial of the EUVAS is testing MMF as a remission maintenance therapy

2. IVIG

Jayne 93 Lancet 1137.

3 Open label trials and 1 rct

Found no utility of IVIG in WG of varying stages beyond 3 months

3.Leuflonamide:

Interesting new option drawn from R.A therapy.

Metzler Arth Rheum 99: 5315.n=20

1 yr 75% remission.

4. Cyclosporine.

2 trials of 5 & 7 patients available.

1.2/5 relapse on reducing dose

2. Haubitz. NO ROLE.

5. Deoxyspergualin

Synthetic analog of spergualin, a product of *Bacillus laterosporus*
In a prospective open-label study by Birck et al,N=20 patients with AASV who had resistance or contraindications to standard therapy
Leukopenia. Mild to moderate infections were observed, not associated with mortality or sepsis.
Disease improvement was said to occur in 70% of cases, although
outcome measures were not clearly defined.

TNF-α inhibitors:

Anti-TNF- therapy ,has proved extremely successful and is now widely used to treat these patients for R.A and IBD

At present most reports of TNF- blockade in vasculitis relate to case series or small uncontrolled trials.

The WGET placebo-controlled trial of etanercept in Wegener"s granulomatosis reported that in 180 patients etanercept was not effective at either induction or maintenance of disease remission when used in addition to conventional therapy

NEJM 352;27, 2005

Rituximab.

Data as case reports or as small series < 10 only.

Promising drug in refractory disease for remission induction.

Karina A. Keogh AJRCC **173. pp 180–187, 2006**

Newer Immunological agents In Ca lung:

2-year survival rate for NSCLC patients with the most favorable prognostic factors is only approximately 15%

The results of large RCT"S suggest that a survival plateau has been reached using currently available chemotherapy doublets

Unlikely that rearranging drug combinations or changing drug doses and schedules will result in significant progress.

Therapies directed at targets that provide growth and survival advantages for malignant cells might be a more effective way of treating neoplasms.

Six „Hallmarks Of Cancer"

1. Self-sufficiency In Growth Signals,
2. Insensitivity To Antigrowth Signals,
3. The Ability To Invade & Metastasize,
4. Limitless Replicative Potential,
5. Stimulation Of Angiogenesis, and
6. Evasion Of Apoptosis.

Classification of newer Immunological agents In Ca lung:

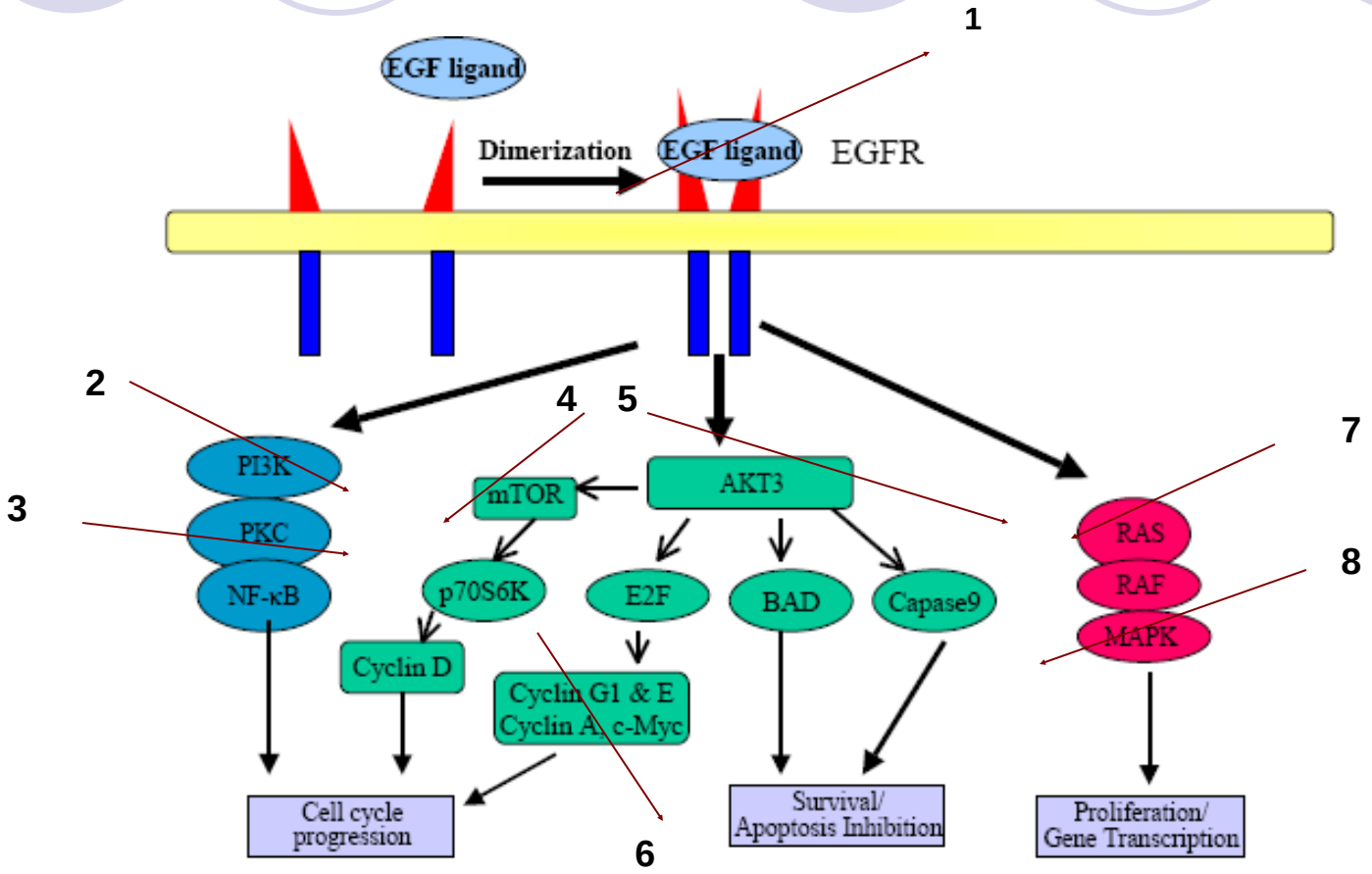
Novel therapies:

protein kinase inhibitors	receptor assoc:	EGFR
		HER2/neu
		c-kit/ c-met
	non-receptor:	mTOR
		VEGF
mitogen assoc kinases		farnesyl kinase inhibitors
		protein kinase C inhibition
Apoptotic pathways		p53 pathway/ HDAC inhibitors
cell survival pathways		cell cycle inhibitors specific/ retinoids
		Bcl-2 Inhibitors
		proteosome inhibitors
others		matrix metalloproteinase inhibitors
		COX-2 inhibitors/ HSP inhibitors

Tumor associated antigens NCAM/ GRP/ GD3

Tumor vaccines

1. Anti-EGFR IgG:



Potential steps in the inhibition of EGFR and downstream pathways:

The Erb B family is made up of EGFR (HER1), HER2, HER3, and HER4; also described as erbB-1, erbB-2, erbB-3, and erbB-4.

EGFR is over-expressed in 40% to 80% of NSCLC

Over-expression is associated with a poor prognosis

EGFR over-expression is rare in SCLC

EGFR inhibition leads to

- decreased cell proliferation,
- increased apoptosis,
- and reduced angiogenesis

Several strategies exist for EGFR inhibition:

- inhibition of the RTK domain,
- monoclonal antibodies against the extra-cellular domain, and
- Anti-sense oligonucleotides.

EGFR inhibition:

Cetuximab (erbitux) C225
- females
- non-smokers
- adenocarcinomas
- ?specific mutations

ABX-EGF (Panitumumab)

Others: Geftinib
- Erlotinib
- EKB 569
- OSI-774 (Tarceva)

Dual (erb B1 & B2 inhibition)
- CI 1033
- GW 572,016
- PKI 166

Antibodies have no established place yet!!
In phase 2 trials with chemotherapy
Dual antibody & small mol inhibition novel idea!!!

HER2/neu (trastuzumab)

established in Ca breast

unlikely to be useful in NSCLC (in ph 2 trials)

C-kit (in SCLC)

receptor of SCF

Inhibits apoptosis, growth and affects motility.

Imatinib: NOT USEFUL

C-met:

in cellular proliferation and motility.

72% of NSCLC adenocarcinomas and 38.5% of NSCLC squamous carcinomas

Poor prognosis

Inhibitors available

- SU11274 and
- PHA665752

Non-receptor tyrosine kinases

1. Phosphatidylinositol-3V-kinase/Akt/mammalian target of rapamycin

The PI3K family is involved in regulating motility, migration, adhesion and proliferation of cells

PI3K plays an important role in cell growth and apoptosis inhibition

Inhibitors being developed

- RAD001
- CCI-779 and
- AP23573

2. Angiogenesis

essential mechanism for tumor growth and metastasis

inhibition is an attractive target for investigators

VEGF and its tyrosine kinase receptor (VEGFR) are the principal molecules that are involved in endothelial cell proliferation, formation of new blood vessels, and vascular permeability

Strong VEGF expression has been demonstrated in 40% to 50% of lung, colon, and breast cancers

Increased levels of VEGF are associated with a worse prognosis in many cancers, including NSCLC

Bevacizumab(Avastin)

in phase 2 trials with standard chemotherapy.

problems in use are

- Hemoptysis(esp in central squamous carcinomas)
- major bleed
- increase in thrombosis

Other VEGF inhibitors

- valanatib
- ZD 6474
- Angistatin
- endostatin
- neovastat

Mitogen associated protein kinase inhibition:

Farnesyl transferase inhibitors

30% of human cancers including NSCLC contain Ras mutations

Important transforming factor

One approach to inhibiting Ras involved inhibiting of farnesyl transferase activity

In ph 1 trials only. farnesyl transferase inhibitors being evaluated are

R115777

SCH66336

BMS 214,662.

Inhibition of protein kinase C

NOT USEFUL!!

Protein kinase C is a complex family of isoenzymes that affect signal transduction

Cause modulation of proliferation, apoptosis, and cellular differentiation

Protein kinase C activity can be inhibited by

staurosporine,

bryostatin, or

antisense oligonucleotides

Anti-apoptotic pathway inhibition:

p53 gene therapy

The p53 gene and its associated protein have been referred to as a cellular gatekeeper for growth and division

trials using viral vectors to incorporate wild-type p53 into malignant tumors simultaneously with chemotherapy as first- line therapy for advanced NSCLC patients

Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors induce apoptosis, growth arrest, or differentiation in malignant cells.
Alterations in histone acetylation cause structural changes and dysregulation of genes that control cell cycle progression and apoptosis.
Alterations of HDAC activity can be associated with malignant transformation

Inhibitors being tried are:

hydroxamic acid,

CI-994,

Pivanex.

Proteasome inhibitors

Proteasomes are considered „cellular housekeepers" because they degrade cellular proteins.

This function serves to regulate the cell cycle, apoptosis, and angiogenesis.

Several proteins, such as cyclins, cyclin-dependent kinases, and nuclear factor kB (NFkB) are degraded in this manner.

Bortezomib (PS 341,Velcade) is established therapy in Multiple myeloma.

In phase 1 & 2 trials for NSCLC.

B-cell leukemia 2 and antisense therapy

The bcl-2 protein inhibits apoptosis
confers resistance to cytotoxic chemotherapy, radiation, and monoclonal antibodies
Overexpression of bcl-2 occurs in 70% to 93% of SCLCs and 16% of NSCLCs
Oblimersen (G3139, Genasense) is an antisense oligonucleotide that is designed to bind the first six codons of human bcl-2 mRNA.

Being evaluated in phase 2 trials for NSCLC.

HSP inhibitors:

Molecular chaperones.

inhibition results in effects similar to proteosome inhibition.

Inhibitors include

17-allyloaminogeldanamycin (inhibits HSP90)

STA4783

Matrix metalloproteinase inhibition:

involved in matrix destruction

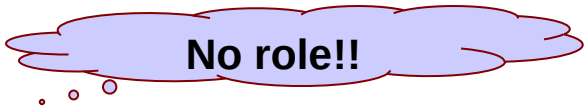
inhibitors may decrease invasion and secondaries

agents being studied

Prinomostat

BAY 1-9566

Marimastat.



Cyclooxygenase-2 inhibitors

Up regulation of COX-2 expression is seen in 70% of invasive adenocarcinomas of the lung

In early-stage NSCLC, COX-2 over-expression has been correlated with poor survival

In vitro studies have demonstrated that COX-2 inhibitors have additive or synergistic activity with chemotherapeutic agents

Paclitaxel up regulates prostaglandin E2 levels and COX-2 expression in human cell lines in vitro

Therefore, the addition of COX-2 inhibitors to paclitaxel in vivo might result in increased efficacy.

Several clinical studies using COX-2 inhibitors in the treatment of NSCLC are accruing patients.

Tumor antigens:

Potential immunotherapeutic targets for antibody therapy and vaccine trials.

These include

- neural cell adhesion molecule (NCAM)
- gastrin-releasing peptide (GRP),
- ganglioside GD3.
- N901- blocked ricin (capillary leak syndrome)

Tumor vaccines:

- GM-CSF
- CTLA-4
- SRL 177 (killed M vaccae vaccine)
- GD3 (BE2) BE2+ M vaccae
- cocktail vaccines: GM2/ Globo H/ fucosyl GM1 with limpet hemocyanin/ polysialic acid

Summary of immunological agents in Ca lung:

Multiple pathways with common downstream effects exist

No agent has been found to be definitely useful.

The best combination with existing therapies is a matter of conjecture

Unexpected toxicities may occur. These may not be suspected in ph 2& 3 Trials.

Single agent unlikely to revolutionize therapy.

Immunotherapy of Mesothelioma:

1. Mesothelioma has a dismal median survival time of 12 months only.
2. It is typically poorly responsive to conventional chemotherapy and radiotherapy.
3. Newer agents that have been used show poor promise (Pemetrexed)
4. Ease of delivery of immuno-active agents into pleural agents.
5. Local control is more important as it causes morbidity & mortality.
6. Conventional advantages of immunotherapy.

Anti-angiogenesis pathway & mesothelioma:

1. VEGF, HGF, PDGF & FGF secreted in large amounts
2. VEGF Receptors flk-1 & fl-1 expressed in good intensity.
3. Strong VEGF immuno-reactivity.
4. Levels are independent poor prognostic marker.
5. SV40 linked VEGF expr. By TAG gene product and P53 inactivation.

Anti-angiogenesis pathway inhibitors in mesothelioma

Antibody inhibitors:

1. SU 5416(Semaxinib): inhibits flk-1. not being licensed.

2. Bevacizumab: Ig inhibiting VEGF to receptor.
   n=106, PFS 6.4, OS 15.7 mo, 1 yr 60%
   being randomized to erlotinib arm.

Others:

1. Thalidomide
2. PTK 787: oral VEGF/ PDGF inhibitors.
3. BAY 43-9006 (VEGF R-2, PDGF-ß & raf kinase.)
4. AZD 2171 VEGF KDR & flt-1
5. Imatinib mesylate
6. terathiomolybdate

Other specific mesothelioma pathways

the HDAC Inhibitor superoylanilide hydroxamic acid.

Proteosome inhibitors.

Anti-mesothelin monoclonal antibodies labeled with toxins are also being investigated for the treatment of malignant mesothelioma