<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Topic</th>
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<tr>
<td>16:00-17:30</td>
<td>ROUND TABLE</td>
<td>Biologic agents in Internal Medicine</td>
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<td>Chairperson: <strong>Petros P. Sfikakis</strong> (Athens, Greece)</td>
<td>General principles and pathophysiologic background for their implementation</td>
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<td>Biologics in IBD</td>
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<td><strong>Peter Laszlo Lakatos</strong> (Montreal, Canada)</td>
<td>Biologics in rheumatic diseases</td>
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<td><strong>Dimitrios Vassilopoulos</strong> (Athens, Greece)</td>
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Biologic agents in Internal Medicine-2018: Targeted therapies for:

- Chronic inflammatory diseases affecting the skin
- Chronic inflammatory diseases affecting the gut
- Chronic inflammatory diseases affecting the joints
- Systemic autoimmune diseases (SLE, vasculitis, SSc, DM/PM)
- Ocular diseases
- Allergy-Asthma
- Osteoporosis
- Atherosclerosis
- Cancer
- ................
General Principles

A biologic agent (i.e. anti-TNF mAb) neutralizes/REDUCES the EFFECTS of the SPECIFIC TARGET molecule (i.e. TNF) which mediates various mechanisms that are involved in the initiation and perpetuation of the abnormal state (i.e. inflammation)…..

• Target-dependent and/or target-mediated biological processes are negatively affected in patients treated with these drugs

• Pathogenic biological processes operate at different levels in different diseases, as well as in different patients within the same disease spectrum

EFFECTIVE biologic agent: SPECIFIC TARGET molecule should operate as ‘key-player’, ideally as ‘maestro’, in the given disease (patho)physiological background=‘orchestra’
..orchestra’s disharmony (vicious circle=DISEASE)

…..by means of disabling one or more key-players.... the vicious circle becomes disrupted
… .... so that the ‘disharmony’ between physiological mechanisms ends...
AND ‘harmony’ is restored = DISEASE REMISSION!

...
The mechanisms of therapeutic action of any biologic agent are not distinct and may overlap...

- reduction of proinflammatory cytokines, chemokines and acute phase proteins
- downregulation of adhesion molecules expression
- attenuation of vascular permeability and angiogenesis
- deactivation of blood mononuclear cells, and/or epithelial, endothelial and dendritic cells, fibroblasts, myofibroblasts, synovial fibroblasts, osteoclasts
- increases of circulating regulatory T cell numbers
- decreases of pathogenic B cell numbers
- diminished recruitment of inflammatory cells from blood to the inflamed tissue
Transgenic mice expressing human TNF: a predictive genetic model of arthritis
ankle joint

treated with anti-TNF monoclonal antibody

Tg 5453 – IBD model

Tg 197 – RA model
**TNF^ΔARE** mouse model

- Absence of ARE translational silencing of TNF is no longer operative resulting in **spontaneous overproduction** of TNF protein
- **TNF^ΔARE** mice display **chronic inflammatory arthritis** and inflammatory bowel disease

---

**Mesenchymal, Col6a1**

*Mesenchymal TNFR2 promotes the development of polyarthritis and comorbid heart valve stenosis*

Maria Sakkou, Panagiotis Chouvardas, Lydia Ntari, Alejandro Prados, Kristin Moreth, Helmut Fuchs, Valerie Gailus-Durner, Martin Hrabe de Angelis, Maria Denis, Niki Karagianni, George Kollias, JCI Insight, 2018, in press
Comorbidities displayed by TNF$^{\Delta ARE/+}$ mice

- RA
- Aortic valves
- Fibrotic thickening/ myocardium lesions, inflammation
- Lung
- Sublingual Salivary gland
- inflammation of the interstitial lung tissue
- Submandibular Salivary gland
- Maxilla
- Periodontitis

JCI Insight, 2018 in press
The scientific basis for anti-TNF treatment

✓ Human TNF was over-expressed in transgenic mice
✓ These mice developed polyarthritis with synovial inflammation and bone destruction

Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis.
Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kioussis D, Kollias G.

✓ The CAUSAL relationship between TNF and arthritis was in Vivo established
   leading to RCTs and introduction of anti-TNF therapy in clinical practice
Anti-TNF therapies for chronic inflammatory (auto)immune diseases

Rheumatoid arthritis

Psoriasis & Psoriatic arthritis

Juvenile idiopathic arthritis

Ankylosing spondylitis

Uveitis
Sight-threatening panuveitis under p.os Pred+AZA+CsA in Behcet’s disease:
complete suppression by the anti-TNF mAb INFLIXIMAB

Sfikakis et al, Lancet 2001
IV Infliximab and vasculitis of the posterior eye segment

Sfikakis et al, Ann Intern Med 2004
Anti-TNF therapies - The Golden Example

> 5,000,000 patients treated so far !!!!

**Prescription Arthritis Treatments**

Led by biologic response modifiers (BRMs), the market for prescription arthritis treatments is expected to grow at over 8% annually. Abbott’s Humira alone is expected to be the world’s biggest-selling drug by 2016.

**Global Revenues** ($ U.S. Billions)

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales</td>
<td>$23.18</td>
<td>$25.25</td>
<td>$27.50</td>
<td>$29.80</td>
<td>$31.80</td>
</tr>
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**Drug**

<table>
<thead>
<tr>
<th>1998</th>
<th>Infliximab</th>
<th>mAbs</th>
<th>RA, PA, psoriasis, ALS, ulcerative colitis, Crohn disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Etanercept</td>
<td>RD</td>
<td>RA, PA, psoriasis, ALS, juvenile RA</td>
</tr>
<tr>
<td>2008</td>
<td>Adalimumab</td>
<td>mAbs</td>
<td>RA, PA, psoriasis, ALS, juvenile RA, Crohn disease</td>
</tr>
<tr>
<td>2008</td>
<td>Cortolizumab</td>
<td>mAbs</td>
<td>RA, Crohn disease</td>
</tr>
<tr>
<td>2008</td>
<td>Golimumab</td>
<td>mAbs</td>
<td>RA, PA, AS</td>
</tr>
<tr>
<td>2008</td>
<td>TNF-α Kinoid</td>
<td>Vaccine*</td>
<td>RA, Crohn disease</td>
</tr>
<tr>
<td>2008</td>
<td>ESBA105</td>
<td>SC antibody</td>
<td>Anterior uveitis</td>
</tr>
<tr>
<td>2008</td>
<td>ART821</td>
<td>mAbs</td>
<td>RA, psoriasis</td>
</tr>
<tr>
<td>2011</td>
<td>ATN-103</td>
<td>Nanobody</td>
<td>RA</td>
</tr>
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**2010**

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<thead>
<tr>
<th>CEP-37247</th>
<th>Human framework domain antibody</th>
</tr>
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</table>

**2011**

<table>
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<tr>
<th>2011</th>
<th>AVENT</th>
<th>Etanercept Biosimilar</th>
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**2012**

<table>
<thead>
<tr>
<th>2012</th>
<th>ADA-a2H</th>
<th>Bispecific Zybody (Adalimumab+Ang2)</th>
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Example of *vicious circle* leading to disease and implementation of biologic agents:

**Pathophysiological background of Rheumatoid Arthritis (who is the maestro ?)**

The biologic agents currently used in rheumatoid arthritis display similar clinical results – unmet needs for one third of patients...

**Anti-TNF**
- mAbs
  (Infliximab, Adalimumab, Golimumab, certolizumab)
- Soluble TNF-R
  (Etanercept)

**Anti-IL-1**
- IL1R antagonist
  (Anakinra)

**Anti-IL-6**
- Anti-IL6R
  (Tocilizumab)*

*In Phase III trials

**Anti-B cell**
- Anti-CD20 mAb
  (Rituximab)

**Anti-T cell**
- CTLA4 Ig mAb
  (Abatacept)
Cadherin-11 in Synovial Lining Formation and Pathology in Arthritis


Fig. 2. Cadherin-11 in synovial lining formation. The normal synovium consists of lining and sublining layers (left panel). FLS and macrophages compose the lining layer, one to three cells deep. The sublining layer contains blood vessels (brown), adipocytes (white) on the extracellular matrix (ECM) (blue in left panel), as well as sublining fibroblasts and leukocytes (not shown). In contrast to the normal synovium in wildtype (WT) mice, cadherin-11-deficient mice display a hypoplastic synovial lining that lacks the normal numbers of synovial lining cells and does not produce normal amounts of ECM (right panel).
Anti-Cadherin-11 mAb ameliorates inflammatory arthritis induced by arthritogenic K/BxN serum in WT C57BL/6 mice

Lee et al. Science 2007
Cadherin-11 mRNA transcripts are frequently found in rheumatoid arthritis peripheral blood and correlate with established polyarthritis

P.P. Sfikakis\textsuperscript{a,}* , P.F. Christopoulos\textsuperscript{a,\textsuperscript{b}}, A.G. Vaiopoulos\textsuperscript{a,\textsuperscript{b}}, K. Fragiadaki\textsuperscript{a}
Targeting Fibroblast-like Synoviocytes in patients with RA:
by an anti-cadherin-11 mAb!

ClinicalTrials.gov Identifier: NCT03001219  Phase 2
First Posted: December 22, 2016
Last Update Posted: November 28, 2017

A Study of RO7123520 to Evaluate the Safety and Efficacy in Participants With Moderately To Severely Active Rheumatoid Arthritis (RA) Who Are Inadequately Responding to Anti-Tumor Necrosis Factor (TNF)-Alpha Therapy

Primary Outcome Measures:
- Percentage of Participants With Adverse Events [Time Frame: Baseline up to 36 weeks]
- Percentage of Participants Achieving an American College of Rheumatology (ACR) 50 Response at Week 12 [Time Frame: Week 12]
- Percentage of Participants With Anti-Drug Antibodies [Time Frame: Baseline up to 36 weeks]
- Change From Baseline in Bone Mineral Density Lumbar Spine L1-L4 as Assessed by Dual Energy X-ray Absorptiometry (DEXA) Scans [Time Frame: Baseline up to 36 weeks]

Co-administration with anti-TNF:
first time 2 monoclonal antibodies are combined !!!
… to conclude

- The introduction of biologic agents in clinical practice has transformed the lives of many patients refractory to previously available therapies.

- The remarkable efficacy of TNF antagonists in various diseases helped us to better understand that common pathways operate in chronic non-infectious inflammatory diseases.

- Clinical practice guidelines and consensus statements on the criteria of introduction, duration of treatment and cessation of biologic agents, including safety issues, are under constant revision as data from longer periods of patient exposure accumulate.
Future Directions

- More studies on the different outcomes obtained when particular agents are used will help us to better understand pathophysiology.

- Much remains to be learned about:
  - the individualised factors that may enhance the efficacy of biologic agents in the approved indications
  - additional potential indications
  - identifying those patients who will benefit the most from a certain biologic agent
  - predictive biomarkers of response
  - NEW TARGETS

- More efficacious agents that will target only the ‘bad’ biologic effects of the specific targeted molecule without compromising any protective effects are warranted....
The anti-TNF receptor-I (anti-p55) mAb will ideally target the deleterious proinflammatory biologic effects of TNF without compromising its protective role in host defence and (auto)immunity.

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