Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Interleukin-6
Back to the Future

Prof. Tadamitsu Kishimoto MD, Ph.D.
Graduate School of Frontier Biosciences,
Osaka University

Humanized anti-IL-6R mAb therapy for JIA

Before treatment
HT 107cm, BW 23 kg

18 months after treatment
HT 125.2cm, BW 34 kg

- 5 y.o. Boy, Disease duration 1 years 2 months
- Previous treatment ASA, PSL, mPSL, L6b, CsA, A2P
- Complications:
  - Growth retardation
  - Compression fracture of T-spine due to osteoporosis

REGULATION OF ANTIBODY RESPONSE IN VITRO

VII. Enhancing soluble Factors for IgG and IgA Antibody Response:

TAKAMOTO, KISHIMOTO AND GUMMERE RIGGS

Department of Medicine, The Johns Hopkins University, School of Medicine, in the J. cages. Arthritis 1973.

Accepted for publication May 20, 1993

The screen versions of these slides have full details of copyright and acknowledgements
Interleukin-6

- B cell Stimulatory Factor 2 (BSF-2)
- Interferon β-2 (IFN β-2)
- 26kD protein
- Hybridoma Plasmacytoma Growth Factor (HPGF)
- Hepatocyte Stimulating Factor (HSF)

Em-IL-6 transgenic mouse (Fo 33)

Impaired immune and acute-phase responses in IL-6-deficient mice

The screen versions of these slides have full details of copyright and acknowledgements
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Cytokine receptor systems

1. Dimerization of gp130
2. Activation of JAK-family tyrosine kinases
3. Tyrosine-phosphorylation of gp130 and recruitment of STAT3
4. Tyrosine-phosphorylation of STAT3 and its dimerization
5. Gene activation
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

NF-IL6(C/EBPβ) induces acute phase proteins, cytokines and viruses

Acute phase proteins
Inflammatory cytokines (IL-6, IL-1, IL-8, TNFα, G-CSF, Epo)
Viruses (RSV, HIV-1, FIV, HBV)
Transcriptional activation

NF-IL6 induces HIV-1 replication by inhibiting cytidine deaminase - APOBEC3G

Non-productive HIV-1 infection
Productive HIV-1 infection

Feedback regulation in IL-6 signaling
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Aberrant production of IL-6 in cardiac myxoma cells
Patients suffer from autoimmune inflammatory symptoms

Dramatic increase in the concentration of synovial fluid IL-6 in RA patients

Anti-IL6R antibody blocks IL-6 binding with the receptor as well as neutralizes soluble receptors
**Interleukin-6; Back to the Future**

Prof. Tadamitsu Kishimoto

---

**Recombinant anti-human IL-6R monoclonal antibody**

- Code name actemra, generic name tocilizumab

---

**Anti-human IL-6R antibody (tocilizumab)**

- JIA
- Castleman's disease (skin lesion)
- RA

- Control
- Therapy

---

**Anti-IL-6R antibody therapy of:**

- Castleman's disease
- Rheumatoid Arthritis
- Juvenile Idiopathic Arthritis
Castleman's disease

- Lymphnode swelling with plasmacyte infiltration
- Hyper-g-globulinemia
- Increase in acute phase proteins
- Development into monoclonal gammopathy and multiple myelomas

Detection of KHSV/HHV8 in HIV positive- and negative-
Multicentric Castleman's Disease (MCD)

- The KHSV/HHV8 genome can be detected in most Castleman's disease-affected lymphnodes
- The HHV8 genome includes the viral IL-6 gene
- Viral IL-6 does not bind to the human IL-6R, but can directly bind to human GP130 which stimulates IL-6 production and induces various symptoms
Humanized anti-IL-6 receptor antibody (rhPM-1) therapy for Castleman’s disease

A therapy of Castleman’s disease by humanized anti-IL-6R Ab
The assessment of lymph nodes by Ga scintigraphy

Anti-IL-6R Ab treatment improved laboratory abnormalities
Anti-IL-6R antibody therapy of:

- Castleman’s disease
- Rheumatoid Arthritis
- Juvenile Idiopathic Arthritis

ACR response rate at week 52

<table>
<thead>
<tr>
<th>% Responders</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control DMARDs</td>
<td>35%</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Tocilizumab 8mg/kg</td>
<td>89%</td>
<td>70%</td>
<td>47%</td>
</tr>
</tbody>
</table>

p<0.001

(September 2005)
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Pre and post radiographs

Control

Tocilizumab

Pre
Post
Pre
Post

Inhibition of RANK ligand expression by tocilizumab

IL-6+sIL-6R
IL-6+sIL-6R + actemra

Inhibition of TRAP-positive osteoclast formation by tocilizumab

IL-6+sIL-6R
IL-6+sIL-6R + actemra
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Disappearance of amyloid deposits in the colon by three injections of tocilizumab in a patient with AA amyloidosis

The RADIATE study: Research on Actemra Determining efficacy after Anti-TNF failure
To assess the efficacy and safety of tocilizumab (TCZ) in combination with methotrexate (MTX) vs. placebo with MTX in patients with an inadequate response to anti-TNFs (TNF-IR)

Anti-IL-6R antibody therapy of:
- Castleman’s disease
- Rheumatoid Arthritis
- Juvenile Idiopathic Arthritis

The screen versions of these slides have full details of copyright and acknowledgements
Humanized Anti-IL-6R mAb therapy for JIA

Before treatment
HT 107 cm, BW 23 kg

18 months after treatment
HT 125.2 cm, BW 34 kg

- 5 y.o. Boy, Disease duration 1 years 2 months
- Previous treatment ASA, PSL, mPSL, Ldx, CsA, AZP
- Complications:
  - Growth retardation
  - Compression fracture of T-spine due to osteoporosis

Background
Systemic-onset Juvenile Idiopathic Arthritis

- Poor QOL (spiking fever, arthritis, etc.)
- Growth retardation
- Osteoporosis
- Disease transition to Macrophage Activation Syndrome, and death (4~6%)
- Limited medications (high-dose corticosteroids)

Decrease in inflammation markers

CRP

ESR

Days

Days
Decrease in fever episodes

Physicians’ assessment of disease activity

Efficacy responses during the double-blind and open-label extension phases

The screen versions of these slides have full details of copyright and acknowledgements
Sustained response to anti-interleukin-6 receptor antibody, tocilizumab in two patients with refractory relapsing polychondritis

Successful treatment of reactive arthritis with anti-interleukin-6 receptor antibody, tocilizumab

Anti-interleukin-6 receptor antibody, tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica

The screen versions of these slides have full details of copyright and acknowledgements
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

The tocilizumab treatment ameliorated skin sclerosis in two patients with systemic sclerosis

Case 1
Case 2

MR16-1, anti-interleukin-6 receptor antibody suppressed dermal thickening and hardness in mouse model of scleroderma

Results

The relationship between ACR response and serum IL-6 concentration with tocilizumab

Japanese phase study MRA009 JP submission DOSSIER
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Suppression of CII-induced arthritis with MR16-1

Suppression of IL-17 production in mice treated with MR16-1
No suppressive effect on Th17 induction with TNFR-Fc

Rat IgG (n=18)  
MR16-1 (n=19)

MR16-1 treatment suppresses the development of Th17 and Th1 cells in lymph node

Rat IgG
MR16-1

The screen versions of these slides have full details of copyright and acknowledgements
**Interleukin-6; Back to the Future**

Prof. Tadamitsu Kishimoto

---

**IL-6 KO mice are resistant to experimental autoimmune uveoretinitis (EAU)**

- EAU Clinical Score
- Histology
- WT
- IL-6 KO

---

**Defective Th17 development in IL-6 KO mice with EAU**

- Day 0
- Day 10
- Day 20
- Gate: CD4 T cells (Draining LN cells)

---

**Both IL-17 KO mice and IFN-γ KO mice develop EAU, but their disease is suppressed by anti-IL-6R Ab treatment**

- EAU Clinical Score
- EAU Clinical Score after therapy

---

The screen versions of these slides have full details of copyright and acknowledgements
Regulatory T cells are important for inhibiting EAU in IL-6 KO mice.

Restored EAU development in IL-6 KO mice after Treg depletion.

EAU Clinical Score after Treg depletion

Gate: IRBP-specific CD4 T cells

TNF-α, IL-1 and IL-23 together with TGF-β do not induce Th17 cells.

TNF-α, IL-1 and IL-23 do not inhibit Foxp3+ Treg cells.
The Aryl hydrocarbon receptor (Ahr) is specifically induced by IL-6 and TGF-β. The receptor is similar to nuclear receptors, also known as dioxin receptor, with exogenous ligands such as dioxin and flavonoids causing diverse toxic effects. Transcriptional activation occurs through protein interactions. The natural ligand of Ahr is not well known, and the receptor is also known as a ligand-dependent E3 ubiquitin ligase. Ahr KO mice exhibit a slower growth rate, normal proportions of lymphocytes in spleen, lymph nodes, and thymus.

Induction of IL-17 by TGF-β plus IL-6 is significantly reduced in Ahr-deficient naïve T cells. The screen versions of these slides have full details of copyright and acknowledgements.
Ahr specifically binds with STAT1 and STAT5, but not STAT3 nor STAT6

Distinct roles of the STAT family in Th17 differentiation

Ahr gene deletion blocks the CIA development
**Interleukin-6; Back to the Future**

Prof. Tadamitsu Kishimoto

---

**T cell-specific deletion of Ahr ameliorates the CIA development**

![Graph showing T cell-specific deletion of Ahr ameliorates the CIA development](image)

- Lck WT
- Lck Ht

Arthritic score vs. Days after immunization

- *P<0.05 #P<0.01

---

**Pro-inflammatory cytokines, RANKL and MMP3 in the sera of Ahr KO mice**

![Bar charts showing pro-inflammatory cytokines, RANKL and MMP3 in the sera of Ahr KO mice](image)

- IL-1β
- IL-6
- RANKL
- MMP3

- WT
- Ahr KO

---

**Cytokine production in the inguinal lymph node cells of Ahr KO mice**

![Graph showing cytokine production in the inguinal lymph node cells of Ahr KO mice](image)

- IL-17
- IL-10
- IFN-γ
- IL-4

- WT
- Ahr KO

---

The screen versions of these slides have full details of copyright and acknowledgements
Interleukin-6; Back to the Future
Prof. Tadamitsu Kishimoto

Collaboration
Laboratory for Immune Signal,
National Institute of Biomedical Innovation

Laboratory of Immune Regulation,
Graduate School of Frontier Biosciences,
Osaka University
- Tetsuji Nakajura
- Minoru Fujimoto
- Satoshi Sarata
- Fumihiko Tanaka

Department of Ophthalmology,
Graduate School of Medicine,
Osaka University
- Nobuyuki Ohguro
- Hiroshi Haruta
- Satoshi Hohki

- Tadamitsu Kishimoto
- Akihiro Kimura
- Taisuke Nakahara
- Ichiro Chinen
- Kazuya Masuda
- Nguyen Nam Trung