New Therapy in Pulmonary Fibrosis

CCR6 Mediates CCL18 Induced Fibrosis and EMT

Technology

CCL18 is a chemokine released by alternatively activated macrophages. We have recently documented that serum CCL18 concentrations correlate with the course of pulmonary function and reflect pulmonary fibrotic activity in patients with IIPs and SSc.
The value of CCL18 as a biomarker is based on the fact that CCL18 induces collagen and αSMA expression in Fibroblasts. This induction is based on the interaction of CCL18 with its newly described receptor CCR6. Blockade of CCR6 with antibodies or an inhibitory peptide abrogates or diminishes collagen and αSMA expression in fibroblasts. In addition, we could demonstrate that CCL18 induces EMT in adenocarcinoma cells, a prerequisite of tumour metastasis.

Innovation

- Therapy based on the pathophysiology of idiopathic pulmonary fibrosis (UIP)
- Replaces or adds to harmful and often insufficient standard therapies

Application

- Treatment of Usual Interstitial Pneumonia (UIP)
- Treatment of Non-Specific Interstitial Pneumonia (NSIP)
- Treatment of lung involvement in Systemic Sclerosis
- Prevention of tumour metastasis.

Market Potential

- The prevalence of UIP in Germany is estimated to be 30 per 100,000 for man and 15 per 100,000 for women. Same rates may be assumed for the European Community
- In the US the prevalence is even higher (43/100,000)
- The prevalence rate in patients at the age of 70 and higher the prevalence of IPF is 250/100,000
- The Incidence rate is increasing in all investigated countries
- In Germany bronchial carcinoma represent the third most frequent tumor in man. Approximately one third are adenocarcinomas

Responsible Scientist

Prof. Dr. Gernot Zissel

University Medical Center Freiburg
Dept. of Internal Medicine, Division of Pneumology

Branch

Pneumology, Oncology

Patent Status

Granted Patents:
EP 2399598 B1 with HK,
EP 2585089 B1 (div.) with HK
JP 5864564, JP 5946937 (div.)
Patent Applications pending in
RU, US, US (div.) and CN,
WO 2012 000 906 A1

Filed (PRD) June 28th 2010

Reference Number

ZEE20090302

Status: Sept-16

CTF – The R & D Company of the Freiburg University and the Freiburg University Medical Center

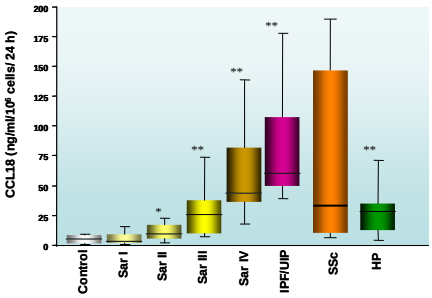
Contact
Dr. Claudia Skamel
Campus Technologies Freiburg GmbH
Stefan-Meier-Str. 8 | D-79104 Freiburg
Email: Claudia.Skamel@campus-technologies.de
Tel: +49 (0)761 203-4987
Fax:+49 (0)761 203-5021

CCR6 is a CCL18 Receptor
Effects on Lung Fibroblasts

CC-Chemokine Ligand-18 (CCL18)

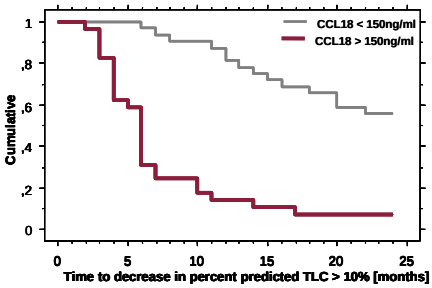
- 89 amino acids (~8kD)
- PARC, MIP-4, AMAC-1, DC-CK1
- Released by alternatively activated Macrophages
- Chromosome 17q11.2. (close to MIP-1a)
- 61% identity with MIP-1a
- probably a fusion gene: two MIP-1a-like genes/
- deletion AND selective usage of specific exons
- late in the Evolution \ CCL18 only in primates

CCL18 in Interstitial Lung Diseases



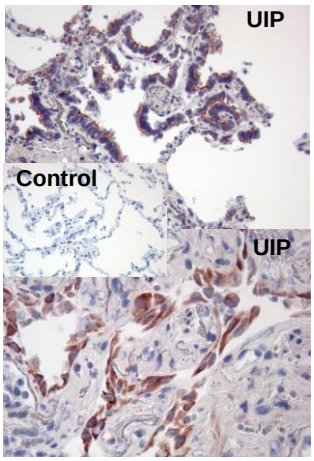
CCL18 Release is significantly increased in interstitial lung diseases associated with pulmonary fibrosis

Kaplan-Meier Analysis: Time to progress

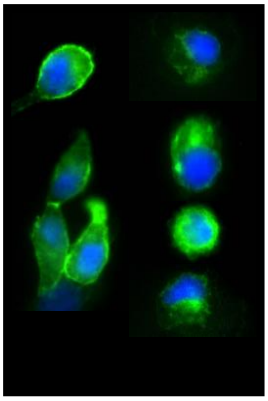


CCL18 serum levels predict the time to progress in patients with IPF

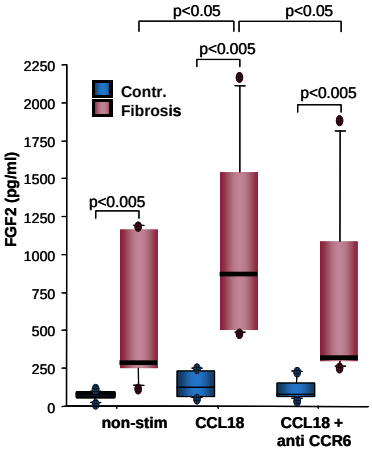
CCR6 / CCL18 Interactions in IPF



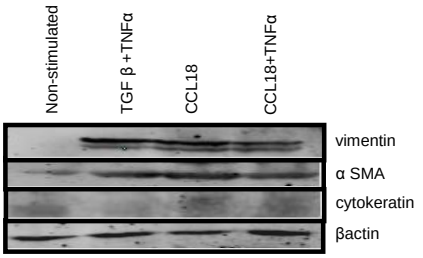
CCR6 is expressed in alveolar epithelial cells type II and in fibroblasts in lungs from patients with IPF but not in control lungs (insert).



CCL18 induces receptor internalization in CCR6*GFP transfected rat lung epithelial cells (RLE-6TN)

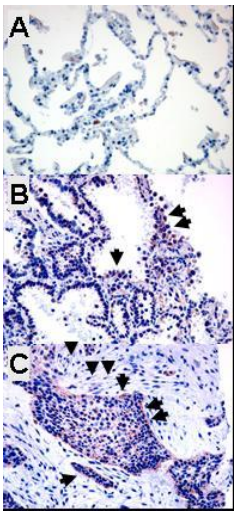


CC18 induces an up-regulation of FGF2 release in lung fibroblasts from IPF patients but not in cells from controls. This up-regulation is inhibited by an anti-CCR6 antibody.

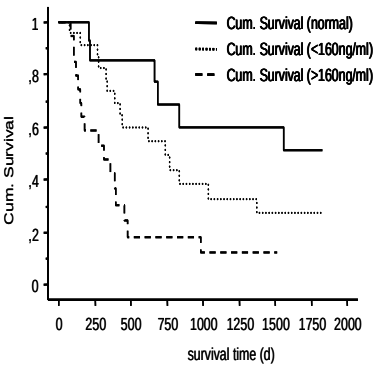


CCL18 induces EMT in uman primary AECII

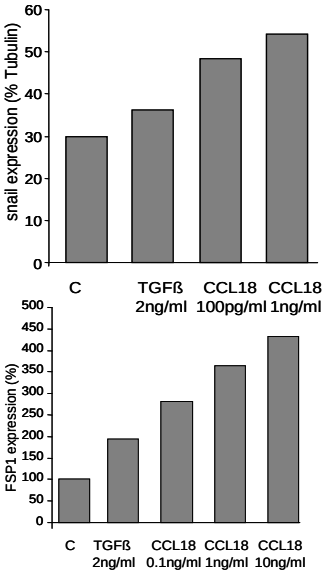
CCR6 / CCL18 Interactions in Adenocarcinoma



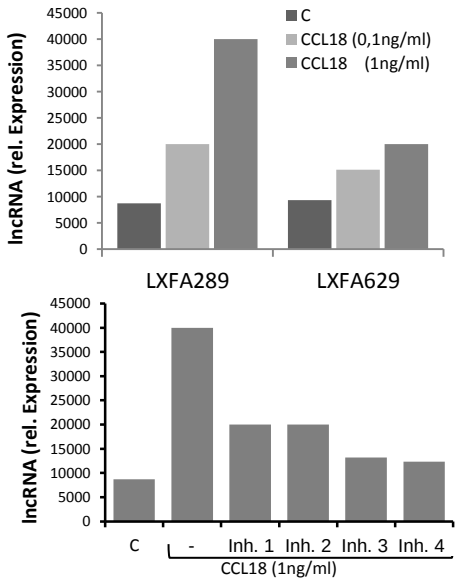
CCR6 is expressed in tumour cells and adjacent fibroblasts in lungs from patients with adenocarcinoma (B, C) but not in control lungs (A).



CCL18 levels in serum predict survival time of adenocarcinoma patients as demonstrated by Kaplan-Meier-Analysis.



CCL18 induces EMT in adenocarcinoma cells as demonstrated by increased expression of snail (upper panel) or FSP1 (lower panel).



CCL18 induces the Expression of a long-non-coding RNA in adenocarcinoma cells (upper panel). Peptides blocking the receptor abrogate this induction (lower panel).