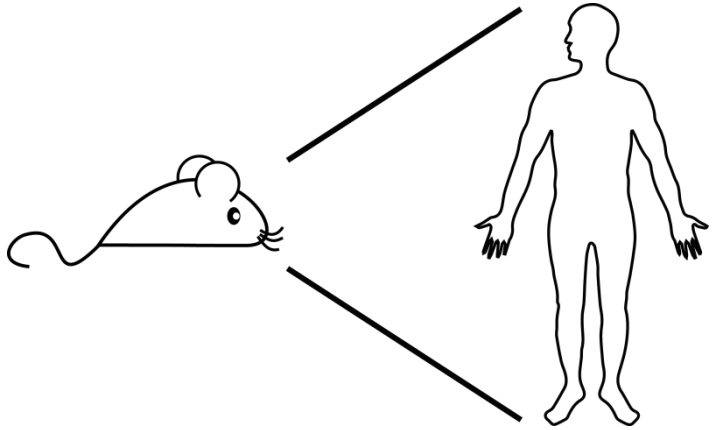
Neue Therapien für Autoimmunerkrankungen: Von der Forschung zur Klinik

DRFZ BERLIN
Deutsches Rheuma-Forschungszentrum
Ein Institut der Leibniz-Gemeinschaft



CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Dr. med. Tobias Alexander
Charité Universitätsmedizin Berlin
Medizinische Klinik m.S. Rheumatologie und Klinische Immunologie

Dr. rer. nat. Andreas Hutloff
Deutsches Rheuma-Forschungszentrum Berlin, ein Leibniz-Institut

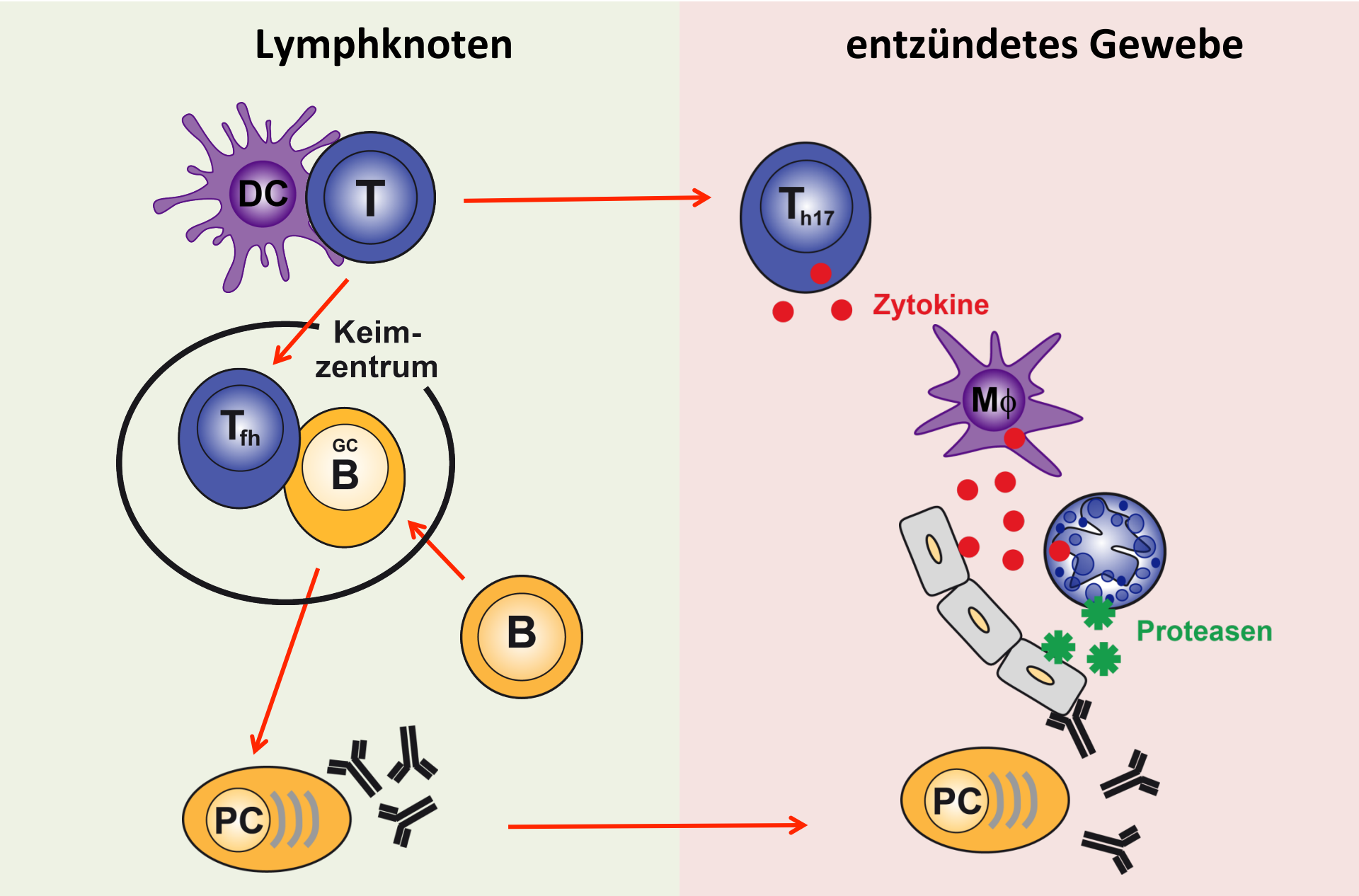
Rheumatoide Arthritis

[1] New Engl J Med 2011
[2] DGRh 2017
[3] National RA Foundation 2017

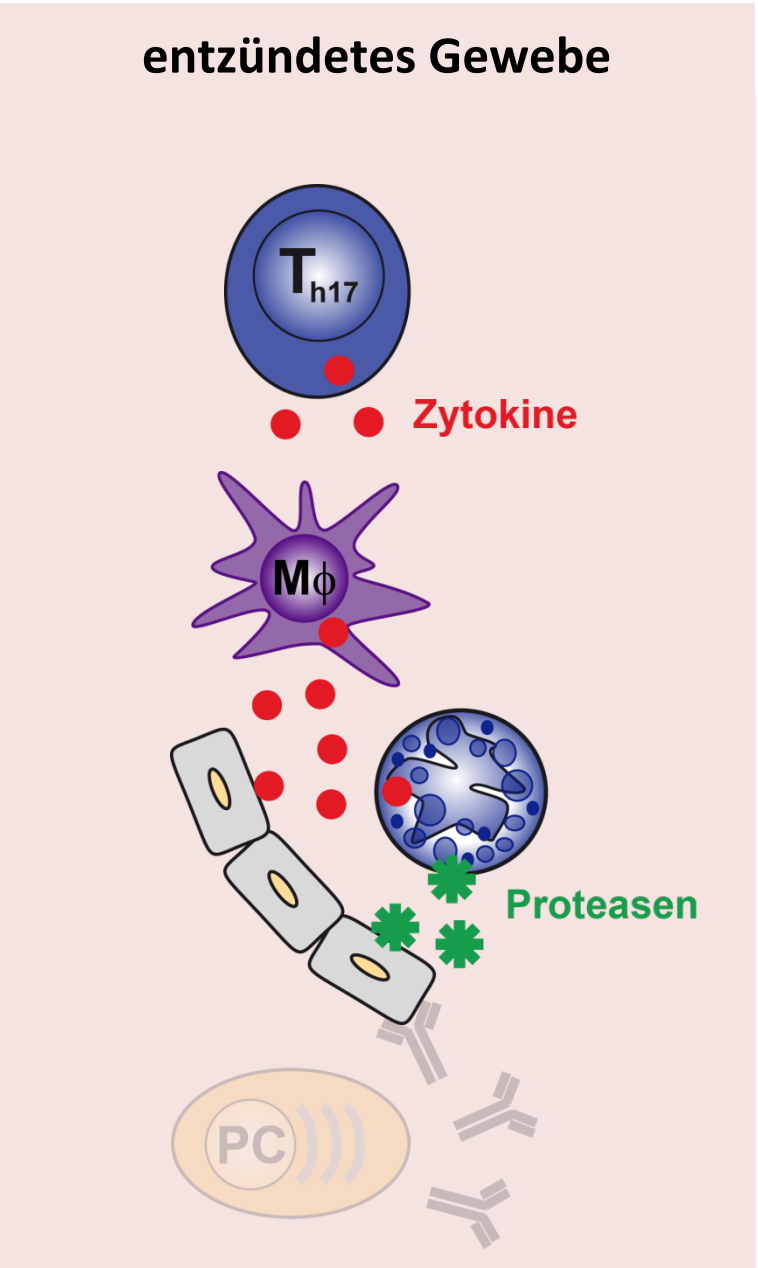
Rheumatoide Arthritis

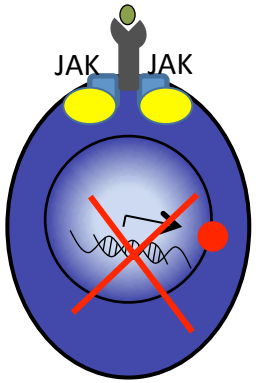
[4] New Engl J Med 2011
[5] Arthritis Res Therapy 2010
[6] Rheumatology 2015
[7] R Occop Med 2006

Immunologische Ursachen von rheumatoider Arthritis

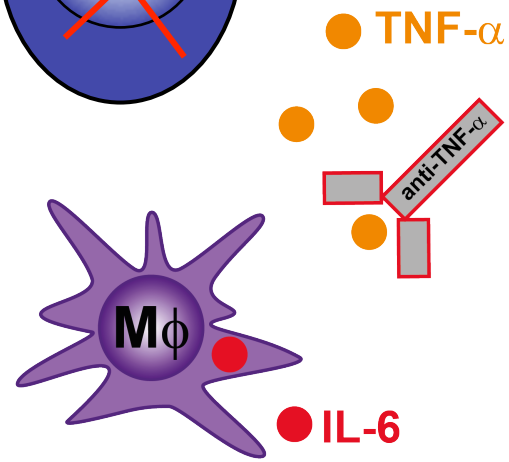


Etablierte Therapien bei rheumatoider Arthritis





JAK-Inhibioren
Tofacitinib (neu 2017)
Baricitinib (neu 2017)

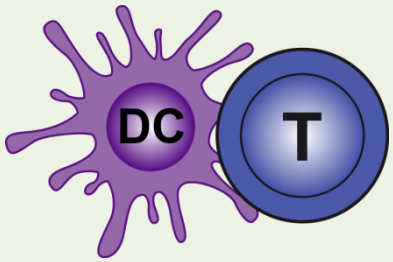


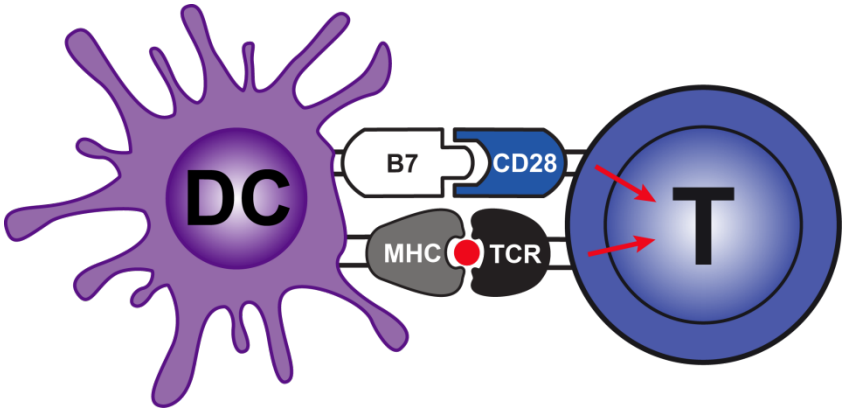
TNFα-Blocker
Infliximab
Adalimumab
Etanercept
Certoliumab
Golimumab

IL-6 Rezeptor Blocker
Tocilizumab
Sarilumab (neu 2017)

Etablierte Therapien bei rheumatoider Arthritis

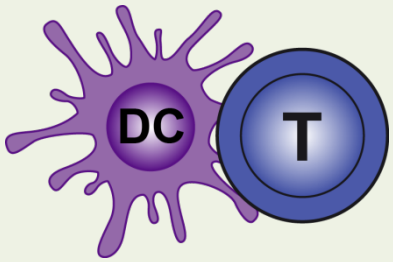
Lymphknoten



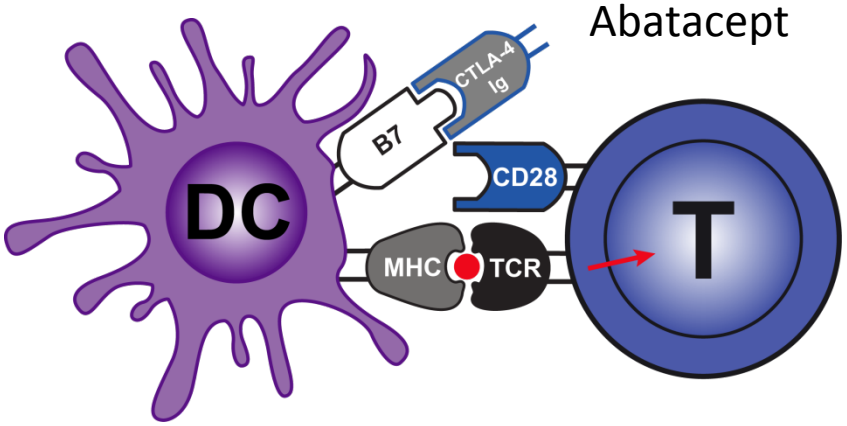


Etablierte Therapien bei rheumatoider Arthritis

Lymphknoten

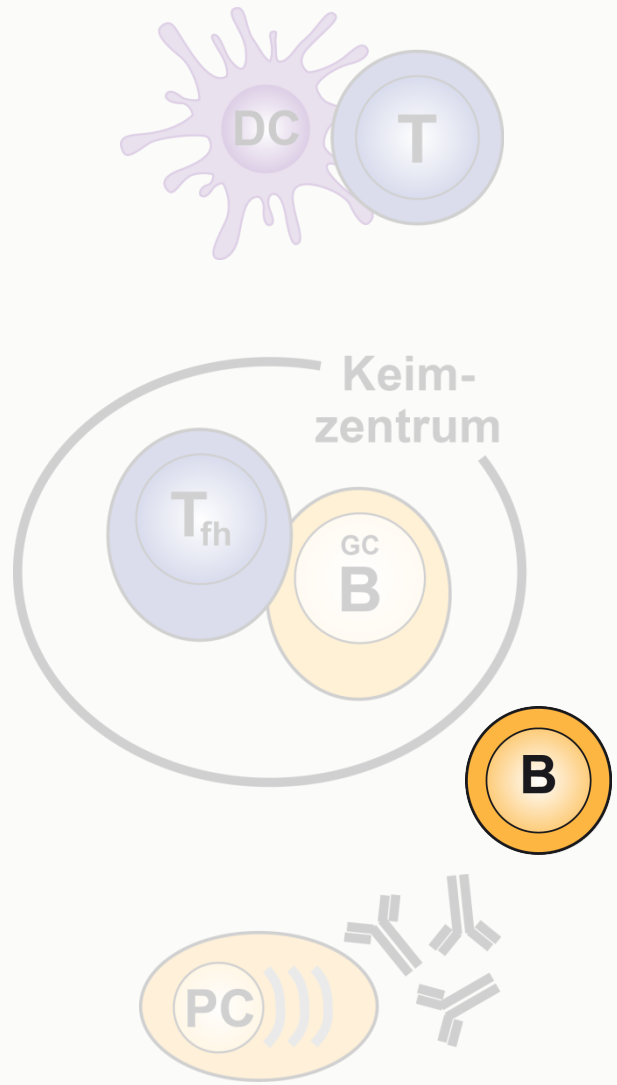


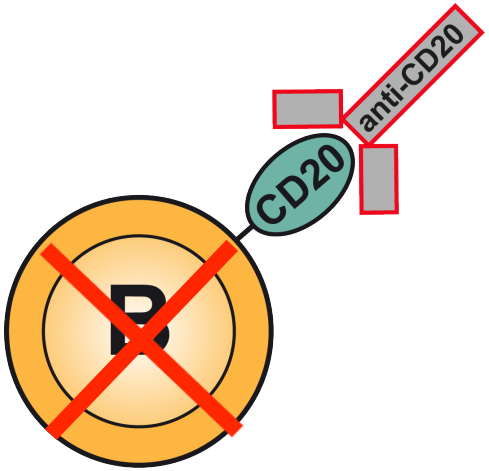
CTLA4-Ig
Abatacept



Etablierte Therapien bei rheumatoider Arthritis

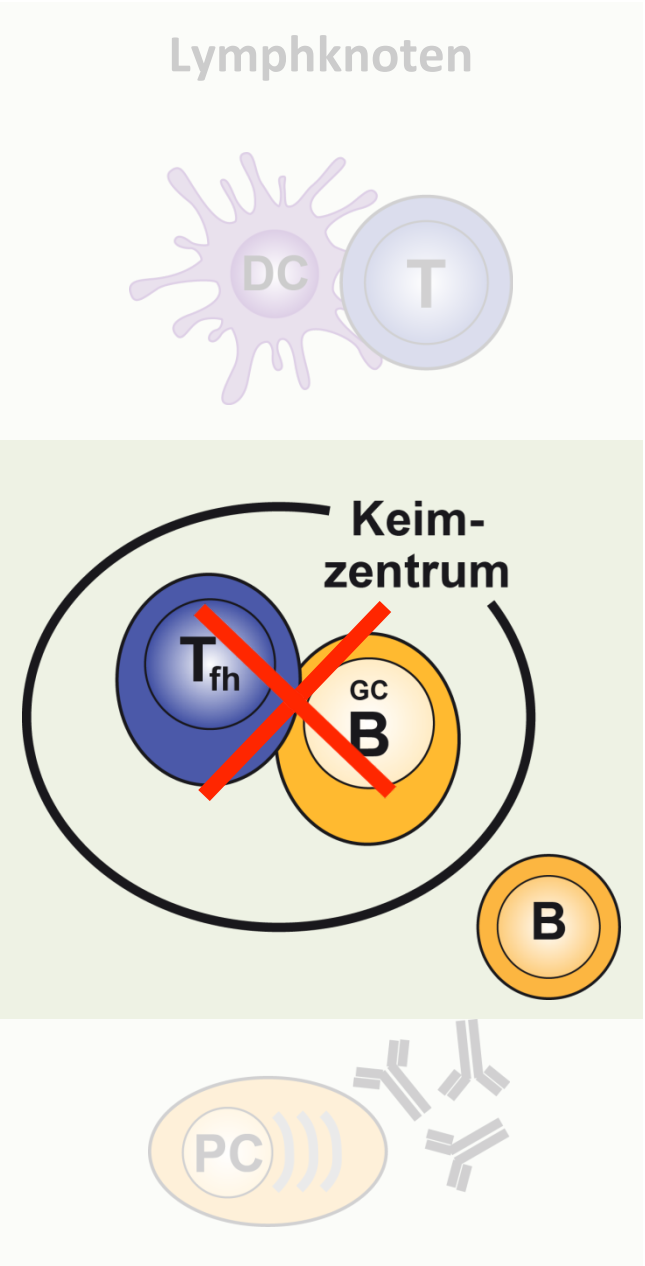
Lymphknoten





Anti-CD20
Rituximab

Auf dem Weg zu neuen Therapien bei rheumatoider Arthritis



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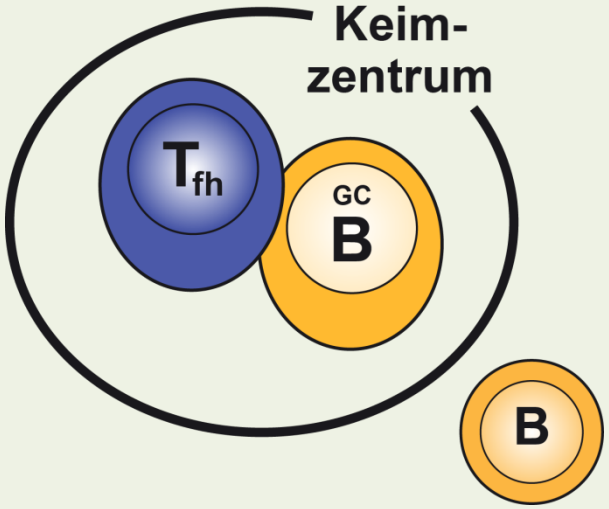
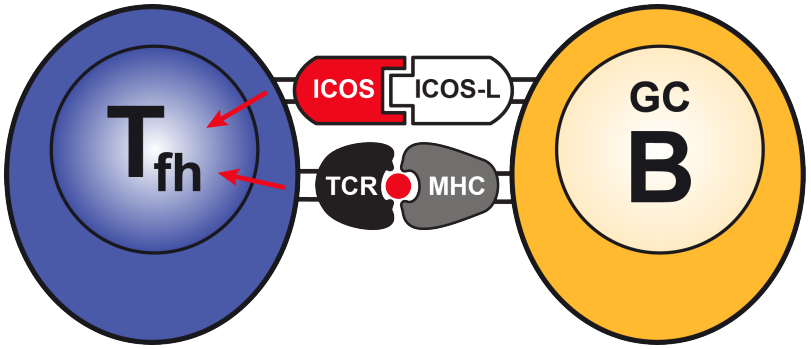
Auf dem Weg zu neuen Therapien bei rheumatoider Arthritis

Lymphknoten

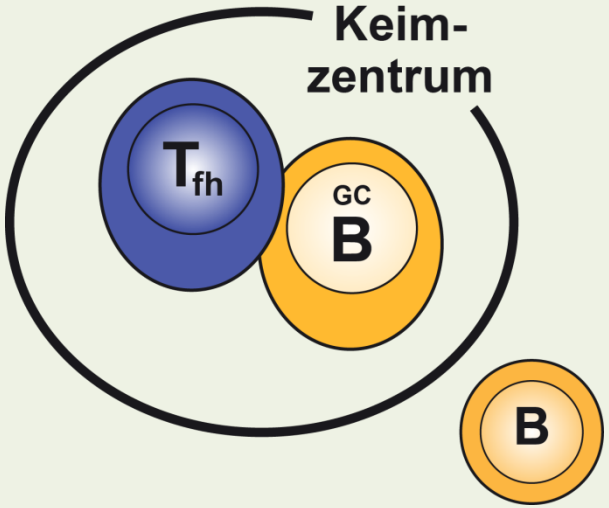


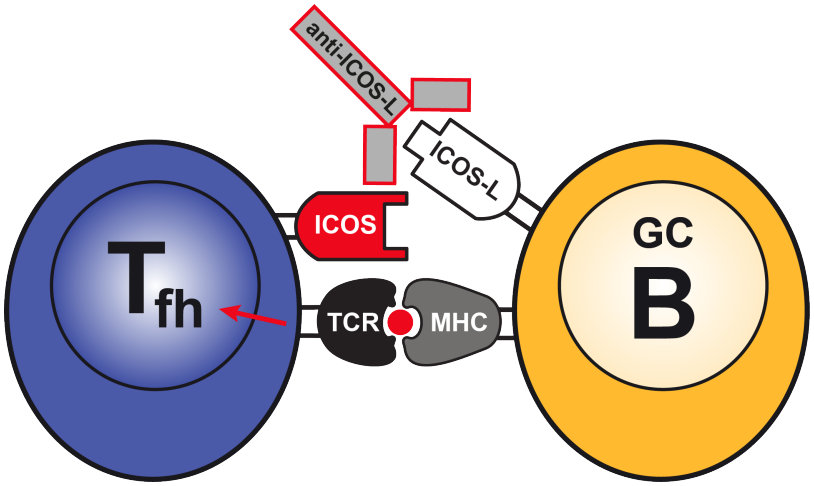


ICOS ist wichtig für die
Interaktion von T- und B-Zellen

Auf dem Weg zu neuen Therapien bei rheumatoider Arthritis

Lymphknoten





Ein Antikörper gegen ICOS
blockiert die Interaktion

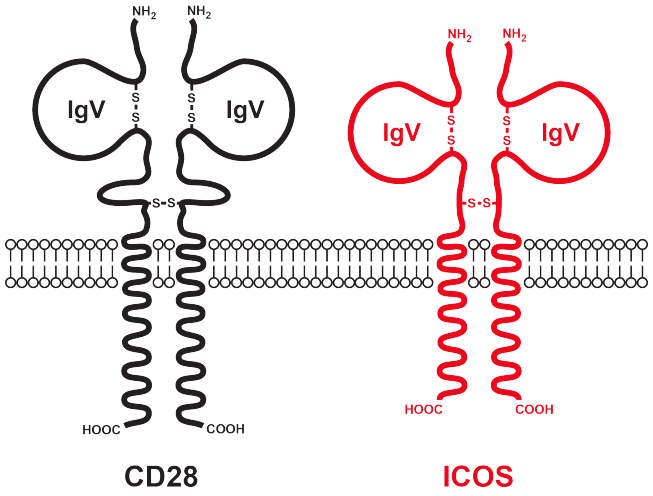
Identifizierung und Klonierung von ICOS

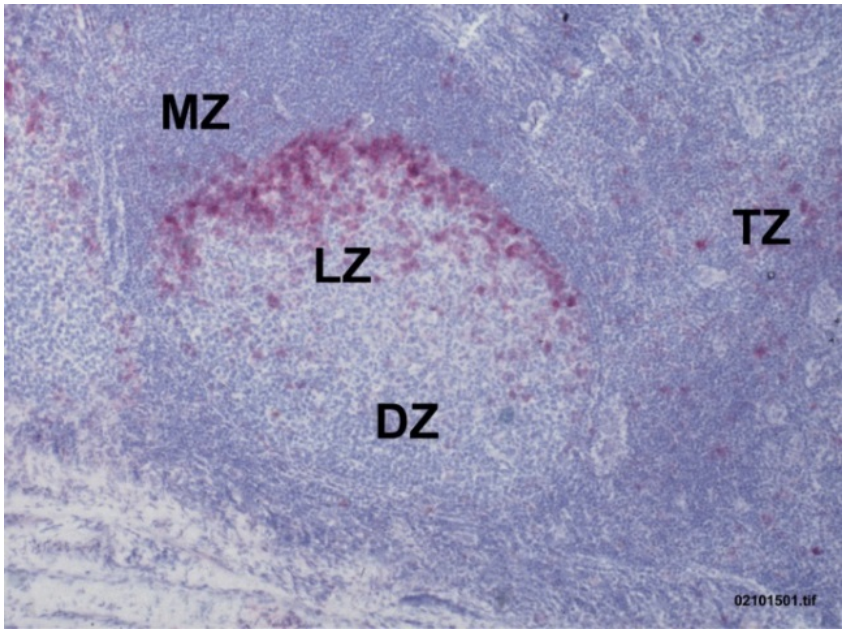
NATURE | VOL 397 | 21 JANUARY 1999

ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28

Andreas Hutloff*, Anna M. Dittrich*†, Katja C. Beier*†, Barbara Eljaschewitsch*, Regine Kraft‡, Ionnis Anagnostopoulos§ & Richard A. Kroczek*

** Molecular Immunology, Robert Koch-Institut, Nordufer 20, 13353 Berlin, Germany*
‡ Department of Protein Chemistry, Max-Delbrück-Centrum, Robert-Rössle-Str. 10, 13122 Berlin, Germany
§ Institute of Pathology, Klinikum Benjamin Franklin, Freie Universität Berlin, Hindenburgdamm 30, 12200 Berlin, Germany

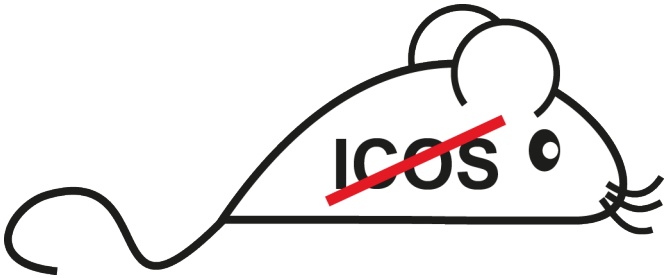




Spezifische Expression von ICOS im Keimzentrum

1999 | 2001 | 2003 | 2004 | 2008 | 2015

Generierung von ICOS knock-out Mäusen



ICOS knock-out Mäuse haben eine schwere Störung der T-Zell-abhängigen B-Zellantwort

NATURE | VOL 409 | 4 JANUARY 2001

ICOS co-stimulatory receptor is essential for T-cell activation and function

Chen Dong*†¶, Amy E. Juedes‡§, Ulla-Angela Temann*§¶, Sujan Shresta‖, James P. Allison‖, Nancy H. Ruddle‡ & Richard A. Flavell*¶

* Howard Hughes Medical Institute, Section of Immunobiology, and ¶ Yale University School of Medicine, New Haven, Connecticut 06520, USA

ICOS is critical for CD40-mediated antibody class switching

Alexander J. McAdam*, Rebecca J. Greenwald*, Michele A. Levin*, Tatyana Chernova†, Nelly Malenkovich†, Vincent Ling‡, Gordon J. Freeman†§ & Arlene H. Sharpe*§

* Departments of Pathology, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, Massachusetts 02115, USA

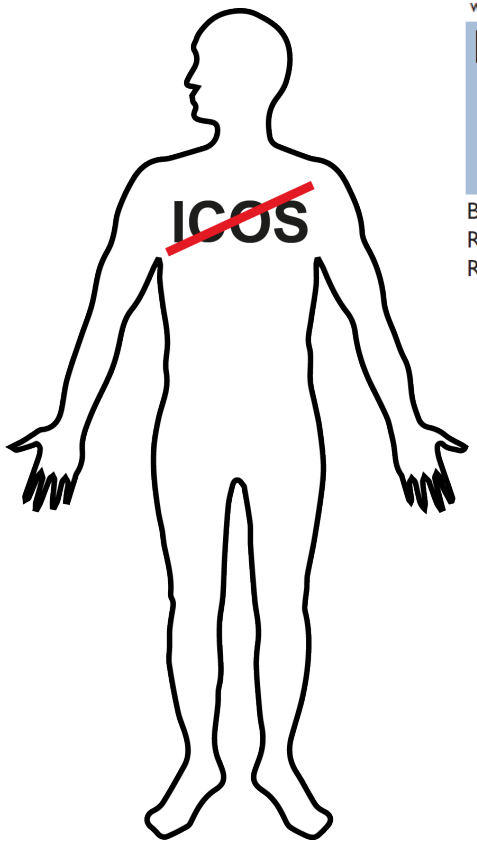
ICOS is essential for effective T-helper-cell responses

Anna Tafuri*†‡, Arda Shahinian*†‡, Friedhelm Bladt*§, Steve K. Yoshinaga‖, Manel Jordana¶, Andrew Wakeham†‡, Louis-Martin Boucher†‡, Denis Bouchard†‡, Vera S. F. Chan‡, Gordon Duncan†‡, Bernhard Odermatt*, Alexandra Ho†‡, Annick Itie†‡, Tom Horan‖, John S. Whoriskey‖, Tony Pawson§, Josef M. Penninger†‡, Pamela S. Ohashi‡ & Tak W. Mak†‡

† Amgen Institute, 620 University Avenue, Toronto, Ontario M5G 2C1, Canada

1999 | 2001 | 2003 | 2004 | 2008 | 2015

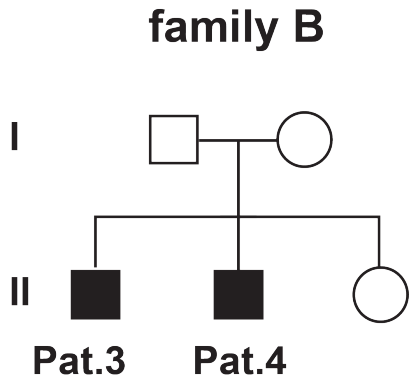
Identifizierung von ICOS-defizienten Patienten

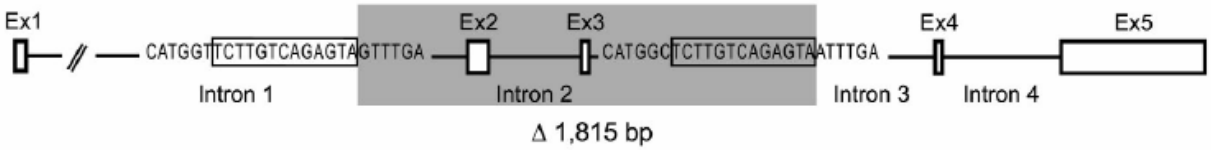


www.nature.com/natureimmunology • march 2003 • volume 4 no 3

Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency

Bodo Grimbacher[1]*, Andreas Hutloff[2]*, Michael Schlesier[1], Erik Glocker[1], Klaus Warnatz[1], Ruth Dräger[1], Hermann Eibel[3], Beate Fischer[3], Alejandro A. Schäffer[4], Hans W. Mages[2], Richard A. Kroczek[2]* and Hans H. Peter[1]*

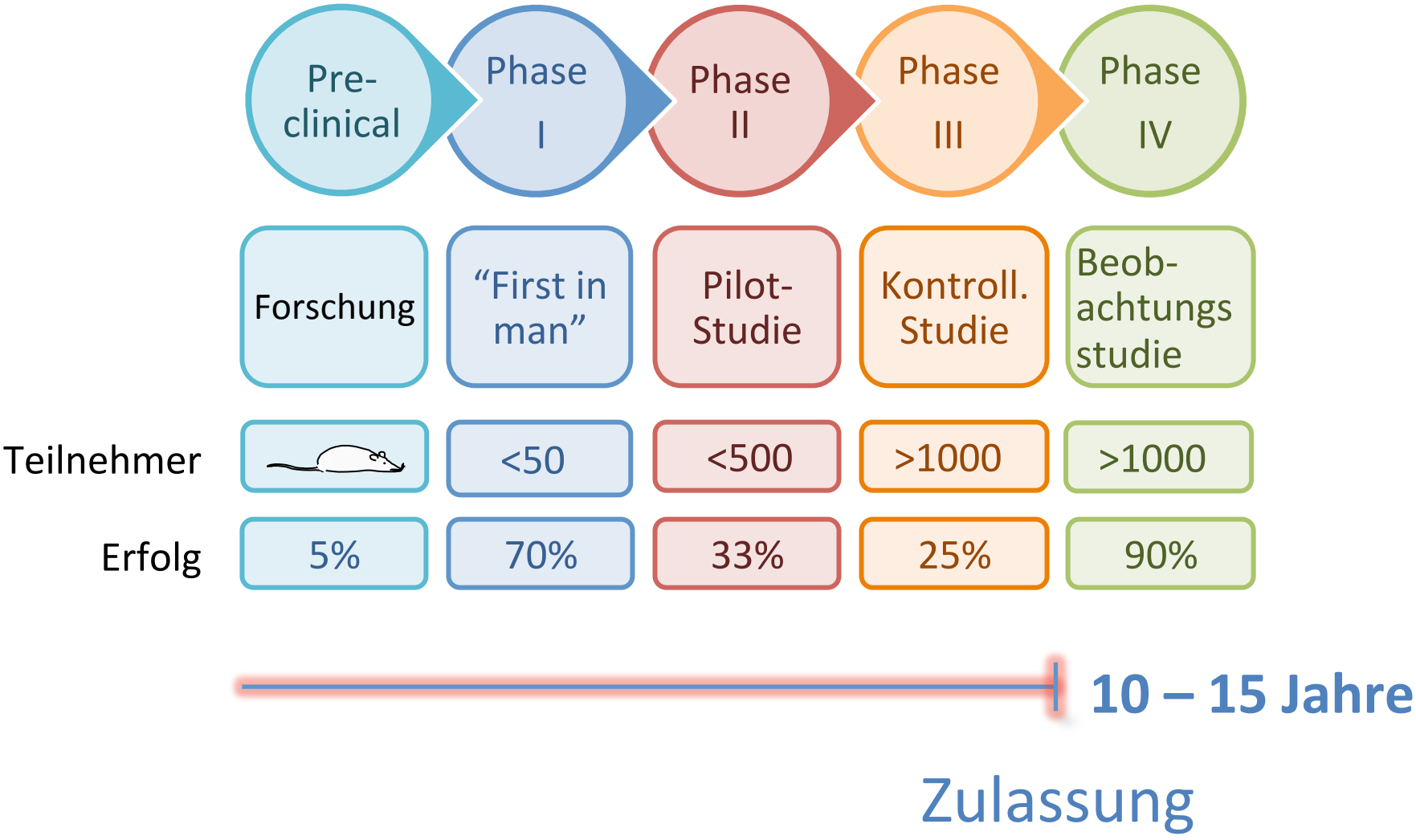




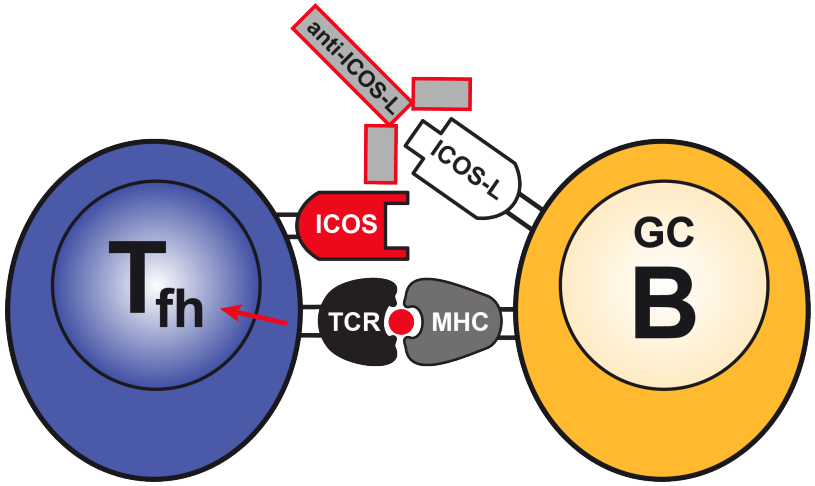
ICOS-defiziente Patienten haben eine schwere Störung Antikörper-vermittelter Immunreaktionen

1999 | 2001 | **2003** | 2004 | 2008 | 2015

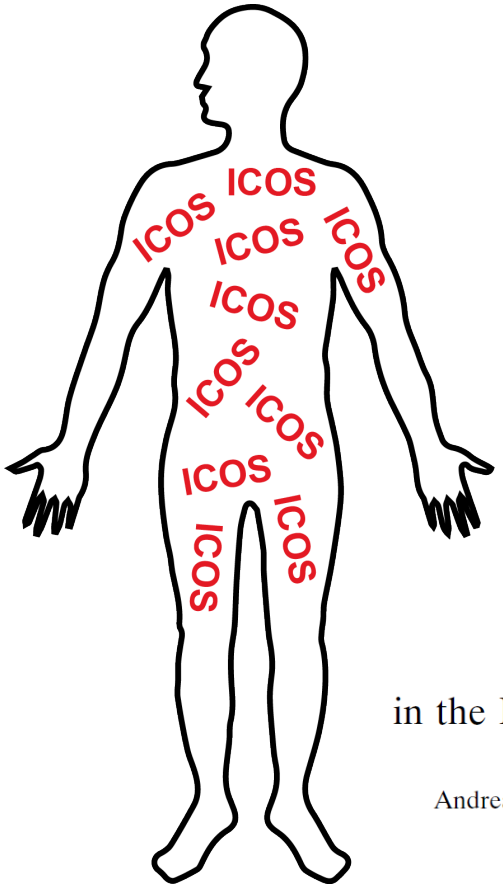
Phasen der klinischen Studien

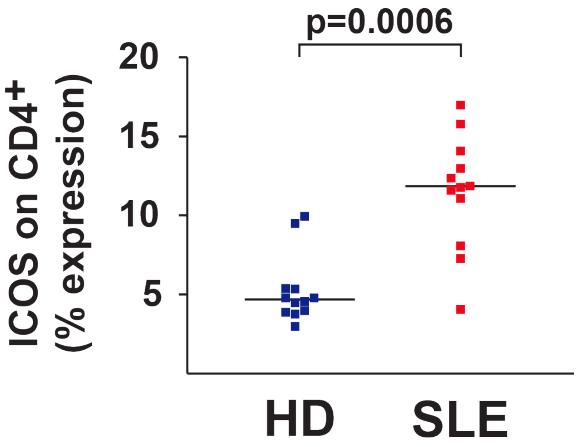


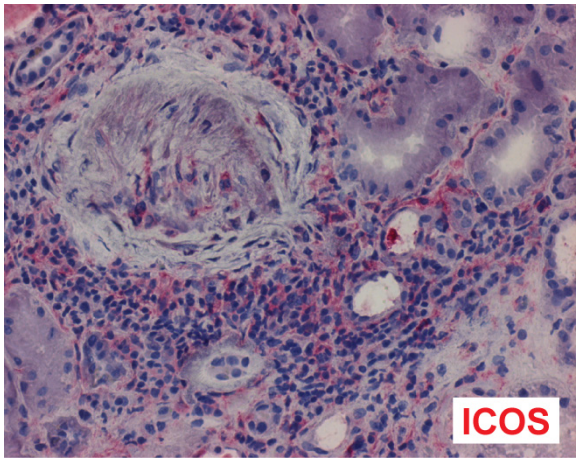
Entwicklung eines neuen Rheuma-Medikamentes am Beispiel des ICOS-Ligand Antiköpers



SLE-Patienten haben eine stark erhöhte ICOS Expression







ARTHRITIS & RHEUMATISM
Vol. 50, No. 10, October 2004, pp 3211–3220

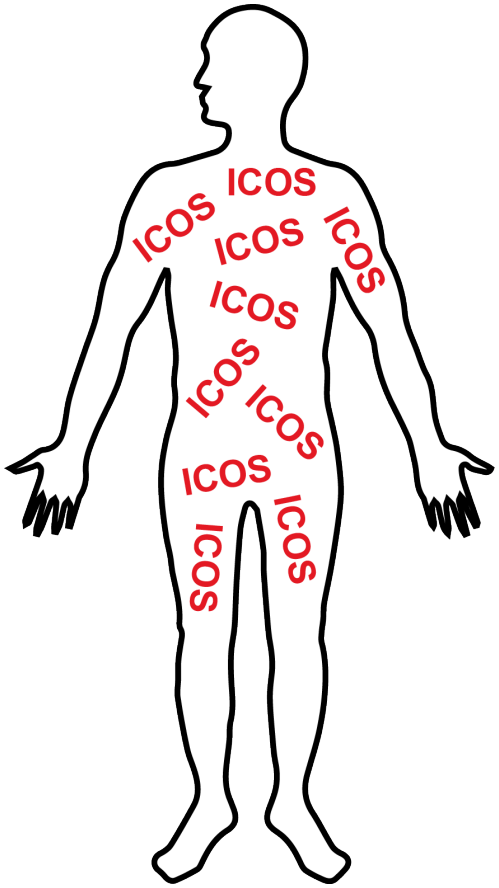
Involvement of Inducible Costimulator in the Exaggerated Memory B Cell and Plasma Cell Generation in Systemic Lupus Erythematosus

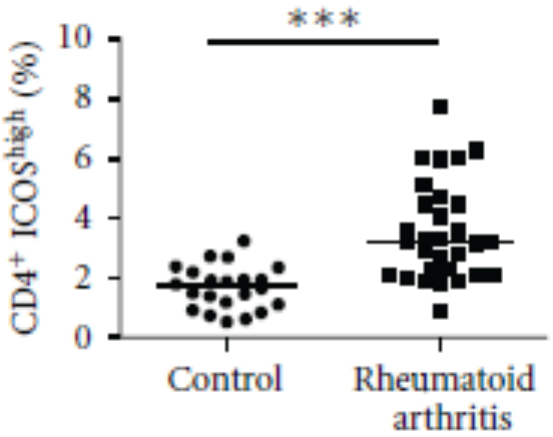
Andreas Hutloff,[1] Kerstin Büchner,[1] Karin Reiter,[2] Hans J. Baelde,[3] Marcus Odendahl,[2] Annett Jacobi,[2] Thomas Dörner,[2] and Richard A. Kroczek[1]

Pre-clinical

1999 | 2001 | 2003 | 2004 | 2008 | 2015

Erhöhte ICOS-Expression auch in RA Patienten





Clinical and Developmental Immunology
Volume 2012, Article ID 827480, 7 pages
doi:10.1155/2012/827480

Clinical Study

Increased Frequency of Circulating Follicular Helper T Cells in Patients with Rheumatoid Arthritis

Jie Ma,[1] Chenlu Zhu,[1] Bin Ma,[1] Jie Tian,[1] Samuel Essien Baidoo,[1] Chaoming Mao,[2] Wei Wu,[2] Jianguo Chen,[1] Jia Tong,[1] Min Yang,[3] Zhijun Jiao,[4] Huaxi Xu,[1] Liwei Lu,[3] and Shengjun Wang[1]

Immunity *39*, 770–781, October 17, 2013

Circulating Precursor CCR7^{lo}PD-1^{hi} CXCR5^{+} CD4^{+} T Cells Indicate Tfh Cell Activity and Promote Antibody Responses upon Antigen Reexposure

Jing He,[1,17] Louis M. Tsai,[2,17] Yew Ann Leong,[2] Xin Hu,[2,3] Cindy S. Ma,[4,5] Nina Chevalier,[4,6] Xiaolin Sun,[1] Kirsten Vandenberg,[7] Steve Rockman,[7] Yan Ding,[1] Lei Zhu,[1] Wei Wei,[8] Changqi Wang,[9] Alexander Karnowski,[10] Gabrielle T. Belz,[10] Joanna R. Ghali,[11] Matthew C. Cook,[3,12] D. Sean Riminton,[13] André Veillette,[14] Pamela L. Schwartzberg,[15] Fabienne Mackay,[16] Robert Brink,[4,5] Stuart G. Tangye,[4,5] Carola G. Vinuesa,[3] Charles R. Mackay,[2] Zhanguo Li,[1,*] and Di Yu[2,*]

Pre-clinical

Aufklärung des molekularen Mechanismus

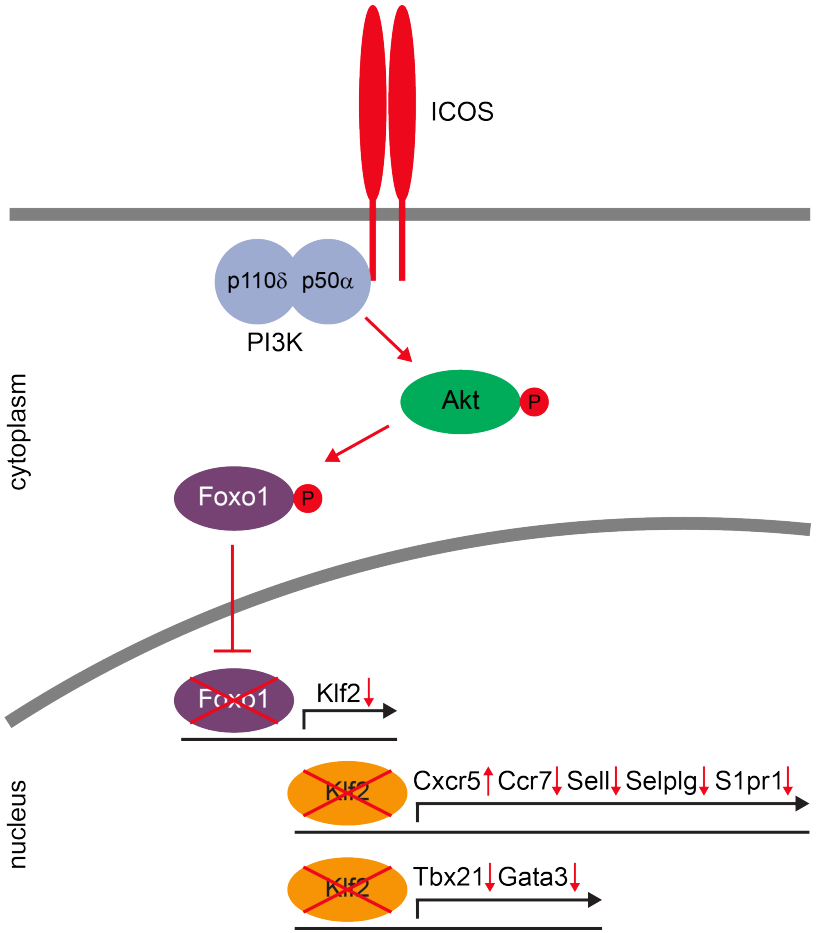
J. Exp. Med. 2015 Vol. 212 No. 2 217–233

ICOS maintains the T follicular helper cell phenotype by down-regulating Krüppel-like factor 2

Jan P. Weber,[1,4*] Franziska Fuhrmann,[1,4*] Randi K. Feist,[1,4*] Annette Lahmann,[1,4*] Maysun S. Al Baz,[1,4] Lea-Jean Gentz,[1,4] Dana Vu Van,[1,4] Hans W. Mages,[4] Claudia Haftmann,[2] René Riedel,[2] Joachim R. Grün,[3] Wolfgang Schuh,[5] Richard A. Kroczek,[4] Andreas Radbruch,[2] Mir-Farzin Mashreghi,[2] and Andreas Hutloff[1,4]

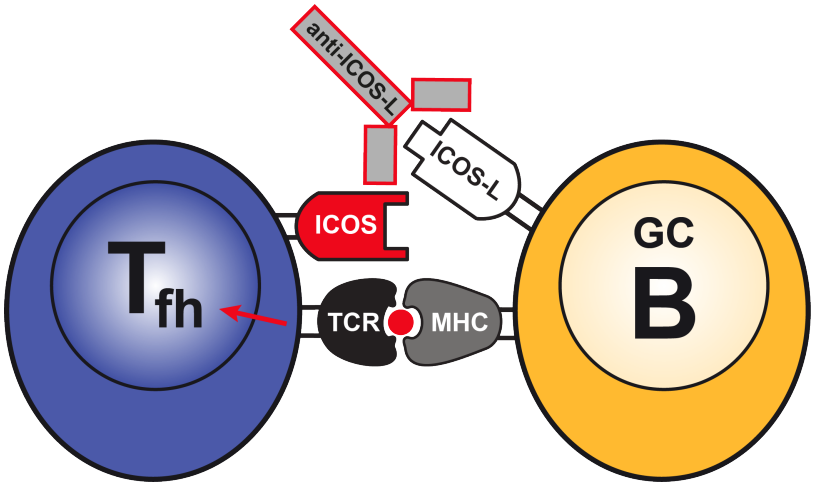
[1]Chronic Immune Reactions, [2]Cell Biology, and [3]Bioinformatics, German Rheumatism Research Centre, a Leibniz Institute, 10117 Berlin, Germany

Pre-clinical



1999 | 2001 | 2003 | 2004 | 2008 | 2015

Klinische Testung eines ICOS-Ligand Antikörpers



AMG557 / MEDI5872

AMGEN

MedImmune

Phase I

Lupus Science & Medicine 2016;**3**:e000146.

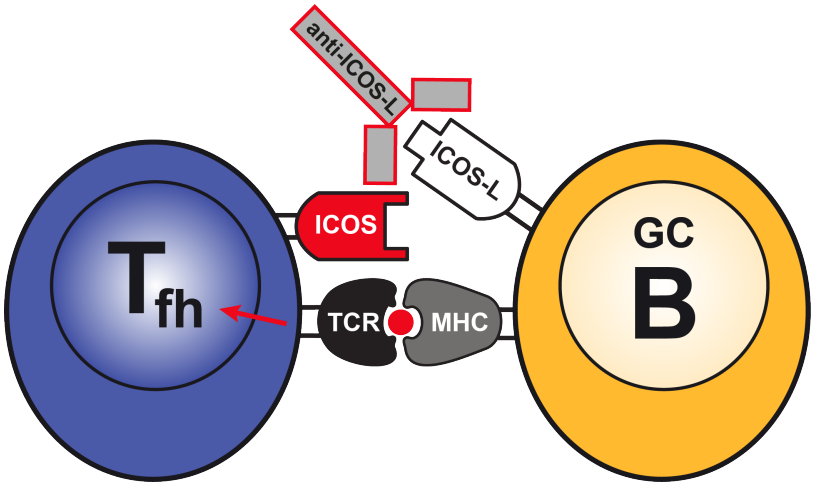
LUPUS SCIENCE & MEDICINE

Inducible T-cell co-stimulator ligand (ICOSL) blockade leads to selective inhibition of anti-KLH IgG responses in subjects with systemic lupus erythematosus

B A Sullivan,[1] W Tsuji,[1] A Kivitz,[2] J Peng,[1] G E Arnold,[1] M J Boedigheimer,[1] K Chiu,[1] C L Green,[1] A Kaliyaperumal,[1] C Wang,[1] J Ferbas,[1] J B Chung[1]

1999 | 2001 | 2003 | 2004 | 2008 | 2015

Klinische Testung eines ICOS-Ligand Antikörpers



AMG557 / MEDI5872

AMGEN

MedImmune

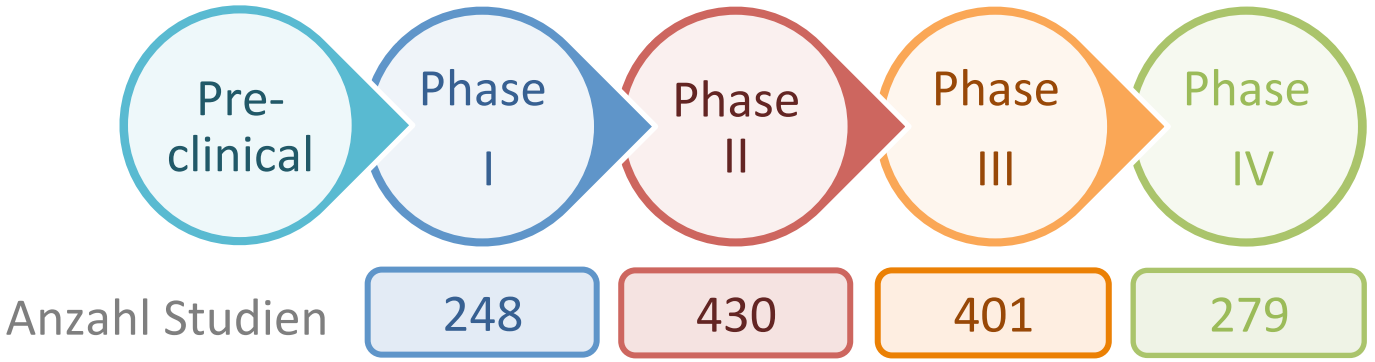
Phase II

A Phase 2a, Randomized, Placebo Controlled, Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Primary Sjögren's Syndrome

Therapie: AMG 557/MEDI5872 subkutan wöchentlich
Studiendauer: 2015-2018

1999 **2001** **2003** **2004** **2008** **2015**

Was ist noch in der Pipeline für Rheumatoide Arthritis?



NIH U.S. National Library of Medicine

ClinicalTrials.gov

12.10.2017

Licht am Ende des Tunnels