Introduction

Prof. Dr. Dr. Stephan von Gunten
MD PhD MME

Lecture series: Clinical Immunology
Research opportunities for students:
- M.Sc.
- Ph.D.
- M.D./Ph.D.
- Postdoctoral fellowships

www.pki.unibe.ch
Clinical Pharmacology

Toxicology

Experimental Pharmacology

Immunopharmacology

Patients

Preparing & dispensing drugs

Mechanisms & discovery novel drug targets
Why do we need Clinical Immunology?

Immunologic mechanisms play a key role in the pathogenesis of practically all human diseases.

Clinical Immunology translates progress made in Experimental Immunology into medicine.

The translation concerns pathogenesis, diagnostics, and therapy.

Clinical Immunology represents an interdisciplinary medical discipline, which interacts with and supports multiple other medical disciplines.
Suggested textbook

English:
Abbas AK, Lichtman AH, and Pillai S: Cellular and Molecular Immunology Latest edition SAUNDERS Elsevier
Handouts and exam

Handouts: www.pki.unibe.ch

Exam: www.pki.unibe.ch

June 6, 2019, 17.00-18.00 pm,
Ort: Hörsaal UG113 im Chemiegebäude, Freiestrasse 3
Institute of Pharmacology

Lectures in Clinical Immunology at the phil-nat. faculty

4540-FS2018-0: Selected topics in Clinical Immunology

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<tr>
<th>Lecturers</th>
<th>Bern Immunology Club (BIC); Coordination: Prof. Dr. S. von Gunten</th>
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<tr>
<td>Type</td>
<td>Lecture, 2h / week, 3 ECTS</td>
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<tr>
<td>Semester</td>
<td>Master Spring semester, on Thursdays, 4.15 - 6 p.m.</td>
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<tr>
<td>Place</td>
<td>Institute of Cell Biology, Baltzerstr. 4, lecture room C161</td>
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miscellaneous
The preconditions to visit this lectures are:

- participation in classes Immunology I and II of the Bachelor course or an equivalent education
- an Immunology textbook, we recommend Abbas AK, Lichtman AH und Pillai S: Cellular and Molecular Immunology, 8th Edition
- course preparation according to topic (reading respective chapters, download and study of lecture print-outs)
- knowledge of English language

Exam: June 7, 2018, 17.00-18.00 pm, Ort: Hörsaal UG113 im Chemiegebäude, Freiestrasse 3
Possible classification of defective immune systems

**Immunodeficiency**
- congenital
- acquired
- innate
- adaptive
- infectious
- non-infectious
- cellular
- humoral
- organ-restricted
- systemic
- iatrogenic
- Non-iatrogenic

**Hyperreactivity**
- autoimmunity
- allergy
- innate
- adaptive
- infectious
- non-infectious
- cellular
- humoral
- organ-restricted
- systemic
- iatrogenic
- Non-iatrogenic
Important diagnostic tools of a Clinical Immunologist

Immunoassay (sera, body fluids, cell supernatants)

Immunohistochemistry (biopsies)

Flow cytometry (blood cells)

Additional lab tests (PCR, proliferation, cytotoxicity, etc.)

Functional tests (skin, nose, lung, gut)
Patients

Clinical Pharmacology

Preparsing & dispensing drugs

Pharmacy

Mechanisms & discovery novel drug targets

Experimental Pharmacology

Immunopharmacology

Toxicology
Biologics

„Biologische Substanzen“ (Biologics, Biologika, Biologicals) werden mittels gentechnischer Verfahren (bietechnologisch) hergestellt. Im Gegensatz zu traditionellen systemischen Therapien, die das ganze Immunsystem beeinflussen, wie Methotrexat und Cyclosporin, wirken Biologics sehr gezielt und stellen möglicherweise eine sicherere Behandlungsform dar. Da diese Präparate noch verhältnismäßig neu sind, ist die Sicherheit einschließlich der Langzeitsicherheit noch nicht ausreichend untersucht.


Biologics sind Fusionsproteine, rekombinante Proteine oder monoklonale Antibörper. Da die Herstellung sehr aufwändig ist, sind die Präparate im Vergleich zu herkömmlichen Medikamenten sehr teuer. Sie bleiben daher in der Regel Patienten mit schweren Formen der Psoriasis und Psoriasis-Arthritis vorbehalten, die auf andere systemische Medikamente oder eine PUVA-Therapie nicht ansprechen bzw. wenn diese Therapieformen nicht angewendet werden können.

Etanercept
Dieses chimäre Protein hemmt den Tumornekrosefaktor TNF-alpha. Dadurch lassen sich die Entzündungsprozesse stoppen, die zur Entstehung der psoriatischen Hautveränderungen führen.

Etanercept wird zweimal wöchentlich unter die Haut (subkutan) gespritzt und kann auch vom Patienten selbst verabreicht werden. Das Medikament ist sowohl zur Therapie der Schuppenflechte als auch bei Psoriasis-Arthritis sowie bei Morbus Bechterew (eine chronisch entzündliche rheumatische Erkrankung mit Schmerzen und Versteifung von Gelenken) zugelassen.
Anti-CD28 mAb (TGN1412) Trial

The worst affected volunteers were kept alive with mechanical life support and large doses of steroids to reduce inflammation.

Marshall E, Science 2006

Roulette. Six healthy volunteers injected with a test drug had to be rushed into critical care at Northwick Park Hospital; two others injected with a placebo weren’t affected.
March 13, 2006, London, UK:

8 healthy male volunteers participated in a placebo-controlled phase 1 study using an anti-CD28 monoclonal antibody (TGN1412, TeGenero)

6 received verum and developed a severe systemic inflammatory response syndrome

2 received placebo – no effect

Report about clinical and pathological findings during the first 30 days after the infusion

Cytokine storm induced by anti-CD28 antibody

Symptoms
- Headache, erythema, rigors, myalgia
- Hypotension, tachycardia
- Fever, lymphopenia, monocytopenia, thrombocytopenia
- Transient improvement

Clinical Investigation Unit
- First corticosteroid dose
- Anti-CD28

Time (h)
- 1
- 4
- 6
- *recurrent in two patients

Phase 1: Cytokine storm

Intensive Care Unit (authors)
- Multiorgan failure
- Lymphocyte recovery
- Monocyte recovery
- Increased ALT, thrombocytosis

Time (d)
- 1
- 3
- 5
- 10
- 20

Phase 2: Reactive
Phase 3: Recovery
Phase 4: Steady state

Cytokine storm induced by anti-CD28 antibody

Second wave?  T cells first  Counteregulation?

Recurrent fever
Clinical trials in the area of biologics

Biologics are highly efficient drugs, but can be dangerous from the beginning.

Detailed knowledge of the immune system is required.

Early clinical trials are usually supervised by clinical pharmacologists.

Involvement of a clinical immunologist seems to be advisable.

Do we need a clinical immunopharmacologist?
Do we need clinical immunopharmacologists?

«Pharmacologists usually forget that Immunology also deals with receptors, agonists, antagonists, second messenger systems, and genetic variations (for instance, most Pharmacology text books devote 10 times more space to the pharmacology of the autonomic nervous system compared with the immune system»

«Many diseases are caused by abnormalities in the immune system, therefore many new drugs acting on immune cells are used»

«Therefore, this imbalance, although understandable on historical grounds, causes problems and does not prepare clinical pharmacologists for the future»

-«We need clinical pharmacologists to manage the translational interface required for these novel therapeutic interventions»
DRUG TRIALS

Violent Reaction to Monoclonal Antibody Therapy Remains a Mystery

"TGN1412 and analogous antibodies bind to the CD28 receptor on T cells, triggering a powerful expansion of cells dominated by regulatory T cells. Even at “horrific” doses in rats and mice,... regulatory cells dominated, giving credence to the view that these cells’ damping effect would swamp out the more harmful effects of conventional T cells, also activated by TGN1412. The monkey study supported this confidence,.”

Marshall E, Science 2006
When it comes to the immune system, be careful about predicting whether a primate model will predict human responses.” (Ajit Varki)

“The new insights on Siglecs may also help avoid tragedies like the one that recently occurred in a U.K. drug trial.”

Cohen J, Science 2006
ANIMAL MODELS

BENEFITS/ACHIEVEMENTS:
- *In vivo* (physiological setting)
- History of revolutionary findings
- Disease pathogenesis
- Drug safety
- Advantage publication/funding

CHALLENGES:
- Non-human
- Traditions, glorification
- Artificial, partial aspects of disease
- Accidents (over-/misinterpretations)
- Labor-intensive experimentation
- High costs
- Ethical concerns
- Intellectual challenges (species, model)

NEED FOR A SCIENTIFIC AND PUBLIC DISCOURSE
ANIMAL MODELS: SKILLS

- Study design (science, ethics, costs)
- Confounding variables (species differences, model, strains)
- Update methodological approach
- Identification of model weaknesses and development of alternatives
- Avoidance of mis- or overinterpretations in translation to humans (drug safety, textbooks)
- Attitude (objective/critical, avoid glorification [in vivo but non-human])
- Communication with peers and public
DISEASE MODELS

Evolutionary relationship

Max. Individual patient

Patient cohorts (clinical studies)

Primates

Dogs

Cats

Rodents

Fishes

Drosophila

Ethical concerns

Max.

Humanized mice
IN Vivo Experiments Using Mice With a Human NK Cell Compartment

Reconstitution of human immune system components was checked: human Siglec-7, BUT NOT Siglec-9 on NK cells

Genomic responses in mouse models poorly mimic human inflammatory diseases


Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305; Departments of Pediatrics and Medicine, Anesthesiology and Critical Care Medicine, and Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; Ingenuity Inc., Redwood City, CA 94063; Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; Department of Surgery, Harborview Medical Center, Seattle, WA 98195; Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80248; Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; Department of Surgery, University of Rochester School of Medicine, Rochester, NY 14642; Department of Surgery, University of Pittsburgh Medical Center Presbyterian University Hospital, University of Pittsburgh, PA 15213; Department of Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8; Department of Surgery, San Francisco General Hospital, University of California, San Francisco, CA 94143; Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada M4N 3M5; Department of Surgery, Stritch School of Medicine, Loyola University, Chicago, IL 60153; Department of Anesthesiology, Washington University, School of Medicine, St. Louis, MO 63110; and Department of Surgery, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ 08903

“Responses to several TI-2 antigens are made prominently by B-1 cells (also known as CD5 B cells), which comprise an autonomously replicating subpopulation of nonconventional B cells”

“... controversy regarding whether B1 cells exist at all in *Homo sapiens*,....”

Griffin DO, J Exp Med 2011

“To B1... or not to B1: that really is still the question!”

Tangye SG, Blood 2013
Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20^+CD27^+CD43^+CD70^-

Daniel O. Griffin,^1,2^ Nichol E. Holodick,^2^ and Thomas L. Rothstein^3,^4^

^1^Elmezzi Graduate School of Molecular Medicine and ^2^Center and for Oncology and Cell Biology, the Feinstein Institute for Medical Research, Manhasset, NY 11030
^3^Department of Medicine and ^4^Department of Molecular Medicine, Hofstra North Shore–LI School of Medicine, Manhasset, NY 11030

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A human equivalent of mouse B-1 cells?

Descatoire M, Weill JC, Reynaud CA, Weller S.


The nature of circulating CD27^+CD43^+ B cells.

Perez-Andres M, Grosserichter-Wagener C, Teodosio C, van Dongen J.

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**IMMUNOBIOLOGY**

Characterization of proposed human B-1 cells reveals a pre-plasmablast phenotype

Kris Covens,^1,3^ Bert Verbinnen,^1,3^ Nick Geukens,^1^ Isabelle Meyts,^4^ Frans Schuit,^5^ Leentje Van den Berghe,^1^ and Xavier Bossuyt^1,3^

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**Blood** 2013

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J Exp Med 2011

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Blood 2013
### CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULINS (IVIG)

**ivon Gunten S, Shoenfeld Y, Blank M, Branch DR, Vassilev T, Käsermann F, Bayry J, Kaveri S, Simon HU.**


PMID: 24762829

<table>
<thead>
<tr>
<th>Replacement Therapy</th>
<th>Immunomodulatory Therapy</th>
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<tr>
<td><strong>FDA-Approved</strong></td>
<td><strong>Anti-Factor VIII autoimmune disease</strong></td>
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<td>Primary immunodeficiencies (PID):</td>
<td><strong>Anti-phospholipid syndrome</strong></td>
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<tr>
<td>Common variable immunodeficiency disorders</td>
<td><strong>Autoimmune blistering disease</strong></td>
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<td>Congenital agammaglobulinemia and hypogammaglobulinemia</td>
<td><strong>Autoimmune hemolytic anemia</strong></td>
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<td>Severe combined immunodeficiencies (SCID)</td>
<td><strong>Autoimmune neutropenia</strong></td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
<td><strong>Birdshot retinoathy</strong></td>
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<tr>
<td>Secondary immunodeficiencies (SID):</td>
<td><strong>Cytomegalovirus infection</strong></td>
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<td>After immunosuppression in solid organ transplantation</td>
<td><strong>Dermatomyositis</strong></td>
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<td>Allogeneic bone marrow transplantation</td>
<td><strong>Epidermolysis bullosa acquisita</strong></td>
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<td>Chronic lymphocytic leukemia (CLL)</td>
<td><strong>Fetal hemolytic disease</strong></td>
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<tr>
<td>Congenital / Pediatric HIV infection</td>
<td><strong>Fetal neonatal alloimmune thrombocytopenia (FNAIT)</strong></td>
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<td><strong>Off-Label Uses</strong></td>
<td><strong>Graft-versus-host disease</strong></td>
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<td>Secondary immunodeficiencies (SID), associated with:</td>
<td><strong>HIV-associated thrombocytopenia</strong></td>
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<td>Anti-CD20 therapy</td>
<td><strong>Inclusion body myositis</strong></td>
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<td>Chemotherapy</td>
<td><strong>Lambert-Eaton myasthenic syndrome</strong></td>
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<td>Hemolytic anemia</td>
<td><strong>Mucous membrane (cicatricial) pemphigoid</strong></td>
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<td>Rheumatoid arthritis</td>
<td><strong>Multiple sclerosis</strong></td>
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<td>Sjögren's syndrome</td>
<td><strong>Myasthenia gravis (MG)</strong></td>
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<td>Systemic lupus erythematosus (SLE)</td>
<td><strong>Necrotizing fasciitis</strong></td>
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<tr>
<td>Low-grade non-Hodgkin's lymphoma</td>
<td><strong>Neonatal alloimmune thrombocytopenia</strong></td>
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<tr>
<td>Multiple myeloma</td>
<td><strong>Opsonolus myocutaneous syndrome (OMS)</strong></td>
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<td><strong>Pemphigus foliaceus</strong></td>
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<td><strong>Pemphigus vulgaris</strong></td>
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<td><strong>Polymyositis</strong></td>
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<td><strong>Polyarthritis rheumatoid</strong></td>
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<td><strong>Refractory dermatomyositis</strong></td>
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<td><strong>Refractory polymyositis</strong></td>
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<td><strong>Relapsing-remitting multiple sclerosis (RRMS)</strong></td>
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<td><strong>Rheumatoid arthritis</strong></td>
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<td><strong>Sepsis syndrome</strong></td>
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<td><strong>Severe anemia associated with parvovirus B19</strong></td>
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<td><strong>Severe dermatomyositis</strong></td>
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<td><strong>Severe polymyositis</strong></td>
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<td><strong>Steroid-dependent atopic dermatitis</strong></td>
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<td><strong>Stiff Person syndrome (SPS)</strong></td>
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<td><strong>Systemic lupus erythematosus (SLE)</strong></td>
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<td><strong>Systemic vasculitis</strong></td>
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<td><strong>Toxic epidermal necrolysis (TEN)</strong></td>
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<td></td>
<td><strong>Vasculitis syndrome</strong></td>
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SPECIES DIFFERENCES!

Experimental autoimmune encephalomyelitis (EAE): B6 mice immunized with MOG\textsubscript{35-55} peptide emulsified in complete Freund’s adjuvant (CFA)


Quast I et al. J Neuroinflammation 2016
Immune thrombocytopenia (ITP): mechanisms

1950: Self-experiment Dr. W. Harrington

Kinetic experiments
-> platelet generation problem

Megakaryocyte death

A
Healthy donor

B
ITP: apoptosis

C
ITP: para-apoptosis

Ineffective megakaryopoiesis

b

Morision IM, Nat Genet. 2008


Houwerzijl EJ, Blood. 2004
Immune thrombocytopenia (ITP): mechanisms

Current models of ITP

von Gunten S, Semin Hematol modified