Introduction

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

Lectures: Clinical Immunology

Bern, February 22, 2018
Research opportunities for students:
- M.Sc.
- Ph.D.
- M.D./Ph.D.
- Postdoctoral fellowships

www.pki.unibe.ch
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: June 7, 2018, 17:00-18:00 pm
Hörsaal UG 113 im Chemiegebäude
Freiestrasse 3
# Lectures in Clinical Immunology at the phil-nat. faculty

**4540-FS2018-0: Selected topics in Clinical Immunology**

<table>
<thead>
<tr>
<th>Lecturers</th>
<th>Bern Immunology Club (BIC); Coordination: Prof. Dr. S. von Gunten</th>
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<tbody>
<tr>
<td>Type</td>
<td>Lecture, 2h / week, 3 ECTS</td>
</tr>
<tr>
<td>Semester</td>
<td>Master Spring semester, on Thursdays, 4.15 - 6 p.m.</td>
</tr>
<tr>
<td>Place</td>
<td>Institute of Cell Biology, Baltzerstr. 4, lecture room C161</td>
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</tbody>
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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
<table>
<thead>
<tr>
<th>Date</th>
<th>Lecture Title</th>
<th>Overview/Concept</th>
<th>Lecturer(s)</th>
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<tr>
<td>22.2.</td>
<td>Introduction</td>
<td>- Introduction of the course&lt;br&gt;- Why do we need Clinical Immunology?</td>
<td>Stephan von Gunten (16:15) handout</td>
</tr>
<tr>
<td></td>
<td>Glycoimmunology</td>
<td>- Glycan-based vaccines&lt;br&gt;- Tumor glycosylation and immunity</td>
<td>Stephan von Gunten (17:15) handout</td>
</tr>
<tr>
<td>1.3.</td>
<td>Biologics</td>
<td>- Lessons regarding pathogenesis&lt;br&gt;- Cytokines&lt;br&gt;- Cytokine inhibitors/antagonists&lt;br&gt;- Therapeutic antibodies beyond anti-cytokines&lt;br&gt;- Immunoreconstitution</td>
<td>Sabine Adler handout</td>
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<td>8.3.</td>
<td>Tumor Immunology</td>
<td>- Tumor antigens&lt;br&gt;- Immune response to tumors&lt;br&gt;- Why immunity to tumors often does not work</td>
<td>Adrian Ochsenbein handout</td>
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<tr>
<td>15.3.</td>
<td>Allergy</td>
<td>- Classification, pathogenesis and diagnostics of allergic diseases</td>
<td>Anna Gschwend (16.15) handout</td>
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<tr>
<td>22.3</td>
<td>Tolerance</td>
<td>- Tolerance mechanisms&lt;br&gt;- Mucosal immunology&lt;br&gt;- Analyzing tolerance mechanisms in clinical settings</td>
<td>Mirjam Schenk handout</td>
</tr>
<tr>
<td>29.3</td>
<td>Immunological lung diseases</td>
<td>- Hypersensitivity pneumonitis, sarcoidosis&lt;br&gt;- Asthma and respiratory infections</td>
<td>Manuela Funke (16.15) handout&lt;br&gt;Christophe von Garnier (17.15) handout</td>
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<tr>
<td>Topic</td>
<td>Subtopics</td>
<td>Presenter</td>
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</table>
| Autoimmunity | - Autoimmune connective tissue diseases/connectivides
- Vasculitis
- Autoinflammatory diseases | Sabine Adler handout |
| Immunity to microbes | - Immunity to bacteria
- Immunity to fungi
- Immunity to viruses
- Immunity to parasites
- Vaccination | Rami Sommerstein handout |
| Transplantation | - Stem Cells
- Solid Organs | Gabriela Baerlocher (16:15) handout
Daniel Sidler (17:15) handout |
| Immunological skin diseases | - Psoriasis
- Atopic eczema | Christoph Schlapbach (16:15) handout
Dagmar Simon (17:15) handout |
| Immunodeficiencies | - Congenital immunodeficiencies
- Acquired immunodeficiencies | Michaela Fux handout
Andri Rauch handout |
| Immunopharmacology | Drugs affecting the immune system | Stephan von Gunten |
### Possible classification of defective immune systems

<table>
<thead>
<tr>
<th>Immunodeficiency</th>
<th>Hyperreactivity</th>
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<tbody>
<tr>
<td>- congenital</td>
<td>- autoimmunity</td>
</tr>
<tr>
<td>- acquired</td>
<td>- allergy</td>
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<tr>
<td>- innate</td>
<td>- innate</td>
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<tr>
<td>- adaptive</td>
<td>- adaptive</td>
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<tr>
<td>- infectious</td>
<td>- infectious</td>
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<tr>
<td>- non-infectious</td>
<td>- non-infectious</td>
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<tr>
<td>- cellular</td>
<td>- cellular</td>
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<tr>
<td>- humoral</td>
<td>- humoral</td>
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<tr>
<td>- organ-restricted</td>
<td>- organ-restricted</td>
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<tr>
<td>- systemic</td>
<td>- systemic</td>
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<tr>
<td>- iatrogenic</td>
<td>- iatrogenic</td>
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<tr>
<td>- Non-iatrogenic</td>
<td>- Non-iatrogenic</td>
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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

Toxicology

Preparation & dispensing drugs

Pharmacy

Mechanisms & discovery novel drug targets

Experimental Pharmacology

Immunopharmacology
Violent Reaction to Monoclonal Antibody Therapy Remains a Mystery

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
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
- Anti-CD28
- First corticosteroid dose

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

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

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

Phase 1: Cytokine storm
Phase 2: Reactive
Phase 3: Recovery
Phase 4: Steady state

Cytokine storm induced by anti-CD28 antibody

- Second wave?
- T cells first
- Recurrent fever
- Counteregulation?
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?
"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"
When it comes to the immune system, be careful about predicting whether a primate model will predict human responses. (Ajit Varki)

Marshall E, Science 2006

“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

Potential bias: species differences
IMMUNOLOGY

Differences in Immune Cell “Brakes” May Explain Chimp-Human Split on AIDS

“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
Differences in Immune Cell “Brakes” May Explain Chimp-Human Split on AIDS

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

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Cohen J, Science 2006
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

Human CD34+

NSG (NOD/LtSz-SCID IL-2Rγnull) mice

6h → 12 weeks

Genomic responses in mouse models poorly mimic human inflammatory diseases


2013
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. Rothstein²,³,⁴

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

Potential bias: species differences

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

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 Doorslaer and Xavier Bossuyt¹,³

CD20⁺CD27⁺CD43⁺ CD70⁻ cells

A
IgA
IgG
IgM

Memory B cells

B

Plasmablasts

C

J Exp Med 2011

D

Blood 2013
IVIG pluripotency and the concept of Fc-sialylation: challenges to the scientist.

PMID: 24762829

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<thead>
<tr>
<th>Replacement Therapy</th>
<th>Immunomodulatory Therapy</th>
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<tr>
<td><strong>FDA-Accredited</strong></td>
<td><strong>FDA-Accredited</strong></td>
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<tr>
<td>Primary immunodeficiencies (PID):</td>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)</td>
</tr>
<tr>
<td>Common variable immunodeficiency disorders</td>
<td>Immune thrombocytopenic purpura (ITP)</td>
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<tr>
<td>Congenital agammaglobulinemia and hypogammaglobulinemia</td>
<td>Kawasaki disease</td>
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<tr>
<td>Severe combined immunodeficiencies (SCID)</td>
<td>Multifocal motor neuropathy (MMN)</td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>Guillain-Barre syndrome (GBS)</td>
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<td>Secondary immunodeficiencies (SID):</td>
<td><strong>Off-Label Uses</strong></td>
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<tr>
<td>After immunosuppression in solid organ transplantation</td>
<td>Anti-Factor VIII autoimmune disease</td>
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<tr>
<td>Allogeneic bone marrow transplantation</td>
<td>Anti-phospholipid syndrome</td>
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<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>Autoimmune blistering disease</td>
</tr>
<tr>
<td>Congenital / Pediatric HIV infection</td>
<td>Autoimmune hemolytic anemia</td>
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<th>Off-Label Uses</th>
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<tr>
<td>Secondary immunodeficiencies (SID), associated with:</td>
<td>Anti-Factor VIII autoimmune disease</td>
</tr>
<tr>
<td>Anti-CD20 therapy</td>
<td>Anti-phospholipid syndrome</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Autoimmune blistering disease</td>
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<tr>
<td>Hemolytic anemia</td>
<td>Autoimmune hemolytic anemia</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Autoimmune neutropenia</td>
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<tr>
<td>Sjögren’s syndrome</td>
<td>Birdshot retinoopathy</td>
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<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Cytomegalovirus infection</td>
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<tr>
<td>Low-grade non-Hodgkin’s lymphoma</td>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Epidermolysis bullosa acquista</td>
</tr>
</tbody>
</table>

**CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULINS (IVIG)**
SPECIES DIFFERENCES!

Experimental autoimmune encephalomyelitis (EAE): B6 mice immunized with MOG_{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

Healthy donor

ITP: apoptosis

ITP: para-apoptosis

Ineffective megakaryopoiesis


Houwerzijl EJ, Blood. 2004

Morision IM, Nat Genet. 2008
Immune thrombocytopenia (ITP): mechanisms

Current models of ITP

von Gunten S, Semin Hematol modified
IVIG pluripotency and the concept of Fc-sialylation: challenges to the scientist.

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Healthy human sera:
IgG1: 5 - 9.5 mg/ml

After high-dose IVIG:
20 mg/ml