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
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
Lectures in Clinical Immunology at the phil-nat. faculty

**4540-F52020-0: Selected topics in Clinical Immunology**

- **Lecturers**: Bern Immunology Club (BIC); Coordination: Prof. Dr. S. von Gunten
- **Type**: Lecture, 2h / week, 3 ECTS
- **Semester**: Master Spring semester, on Thursdays, 4.15 - 6 p.m.
- **Place**: Institute of Cell Biology, Baltzerstr. 4, lecture room C161

**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 4, 2020, 17.00-18.00 pm, Ort: Hörsaal UG113 im Chemiegebäude, Freiestrasse 3
# 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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<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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</table>
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)
**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 Antikörper. 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 TIF-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.
Cytokine storm induced by anti-CD28 antibody

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

Clinical Investigation Unit

Headache, erythema, rigors, myalgia

Hypotension, tachycardia

Fever,

lymphopenia, monocytopenia, thrombocytopenia

Transient improvement

1 4 6
Time (h)

Anti-CD28 First corticosteroid dose

1 4 6 *recurrent in two patients

1 3 5 10 20
Time (d)

Intensive Care Unit (authors)

Multiorgan failure

Lymphocyte recovery

Monocyte recovery

Increased ALT, thrombocytosis

*recurrent in two patients

Phase 1: Cytokine storm

Phase 2: Reactive

Phase 3: Recovery

Phase 4: Steady state

Cytokine storm induced by anti-CD28 antibody

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»
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
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
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


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“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. Rothstein3,4

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...

Potential bias: species differences

IMMUNOBIOLOGY
Characterization of proposed human B-1 cells reveals a pre-plasmablast phenotype
Kris Covens,1,2 Bert Verbinnen,1,3 Nick Geukens,1 Isabelle Meyts,4 Frans Schuit,5 Leentje Van Den Berghe,5 and Xavier Passmu

J Exp Med 2011

Blood 2013
CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULINS (IVIG)

**IVIG pluri potency and the concept of Fc-sialylation: challenges to the scientist.**


PMID: 24762829

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

- Polyarticular rheumatoid arthritis
- Refractory dermatomyositis
- Refractory polymyositis
- Relapsing-remitting multiple sclerosis (RRMS)
- Rheumatoid arthritis
- Severe pemphigus foliaceus
- Severe pemphigus vulgaris
- Polymyositis
- Polyradiculoneuropathy
- Refractory dermatomyositis
- Refractory polymyositis
- Relapsing-remitting multiple sclerosis (RRMS)
- Rheumatoid arthritis
- Severe anemia associated with parvovirus B19
- Severe dermatomyositis
- Severe polymyositis
- Steroid-dependent atopic dermatitis
- Stiff Person syndrome (SPS)
- Systemic lupus erythematosus (SLE)
- Systemic vasculitis
- Toxic epidermal necrolysis (TEN)
- Vasculitis syndrome
**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

Megakaryocyte death

Ineffective megakaryopoiesis


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

Current models of ITP

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

PMID: 24762829

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