UNIVERSITÄT BERN

Institute of Pharmacology
www.pki.unibe.ch

PKI

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**

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Patients

Clinical Pharmacology

Preparing & dispensing drugs

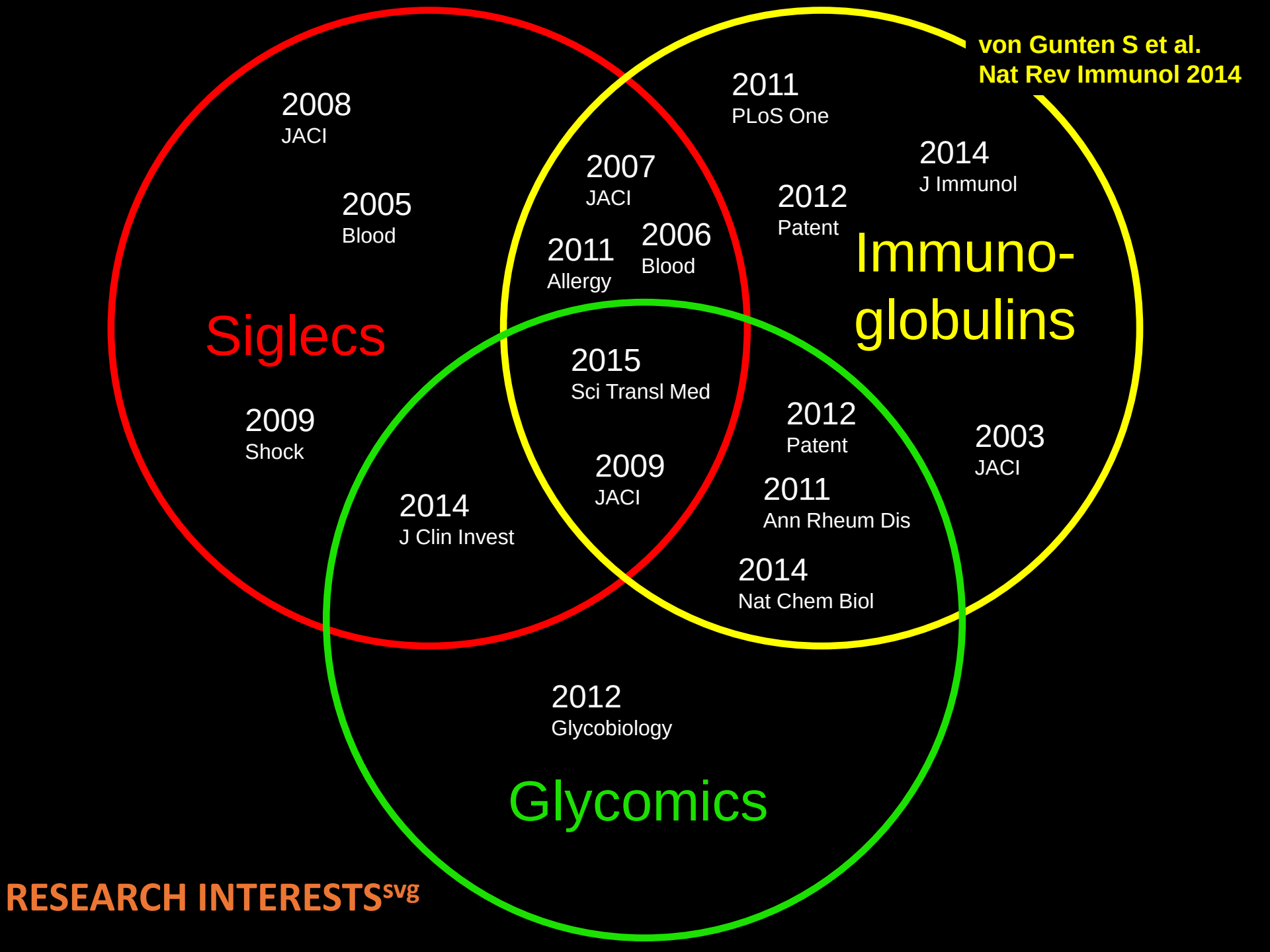
Pharmacy

Mechanisms & discovery novel drug targets

Toxicology

Experimental Pharmacology

Immunopharmacology


von Gunten S et al.
Nat Rev Immunol 2014
2008
JACI
2005
Blood
2007
JACI
2011
Allergy
2006
Blood
2011
PLoS One
2014
J Immunol
2012
Patent
Siglecs
Immuno-
globulins
2015
Sci Transl Med
2009
Shock
2009
JACI
2014
J Clin Invest
2012
Patent
2003
JACI
2011
Ann Rheum Dis
2014
Nat Chem Biol
2012
Glycobiology
Glycomics
RESEARCH INTERESTS.svg

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

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 7, 2018, 17.00-18.00 pm, Ort: Hörsaal UG113 im Chemiegebäude, Freiestrasse 3

Possible classification of defective immune systems

Immunodeficieny

- congenital
- aquired

- 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

Preparing & dispensing drugs

Pharmacy

Mechanisms & discovery novel drug targets

Toxicology

Experimental Pharmacology

Immunopharmacology

gut leben mit Psoriasis

Biologics

„Biologische Substanzen" (Biologics, Biologika, Biologicals) werden mittels gentechnischer Verfahren (biotechnologisch) 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 wirken auf T-Lymphozyten, die hauptsächlich für die Entzündung bei der Psoriasis verantwortlich sind. Einige Biologics hemmen die Aktivierung der T-Lymphozyten. Andere verhindern die Produktion der Substanzen, die von ihnen freigegeben werden. Eine weitere Gruppe verringert die Zahl T-Lymphozyten.

Die Behandlung wird gewöhnlich gut vertragen. Je nach Wirkungsweise und Art der Anwendung (Injektionen, Infusionen) kann es zu unterschiedlichen Nebenwirkungen kommen, wie allergische Reaktionen oder örtliche Reaktionen an der Einstichstelle (Blutungen, Blutergüsse, Rötung, Juckreiz, Schmerzen oder Schwellungen). Da durch die Biologics bestimmte Reaktionen des Immunsystems unterdrückt werden, ist auch das Infektionsrisiko erhöht. Wenn Sie mit einem solchen Medikament behandelt werden, ist es daher wichtig, dass Sie auf mögliche Anzeichen einer Infektion, wie Fieber, Husten oder andere grippeähnliche Beschwerden achten und Ihren Arzt darüber informieren.

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 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.

Biotechnology

Targeted therapy

Safe (?)

T cells (?)

DRUG TRIALS

Violent Reaction to Monoclonal Antibody Therapy Remains a Mystery

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.

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

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

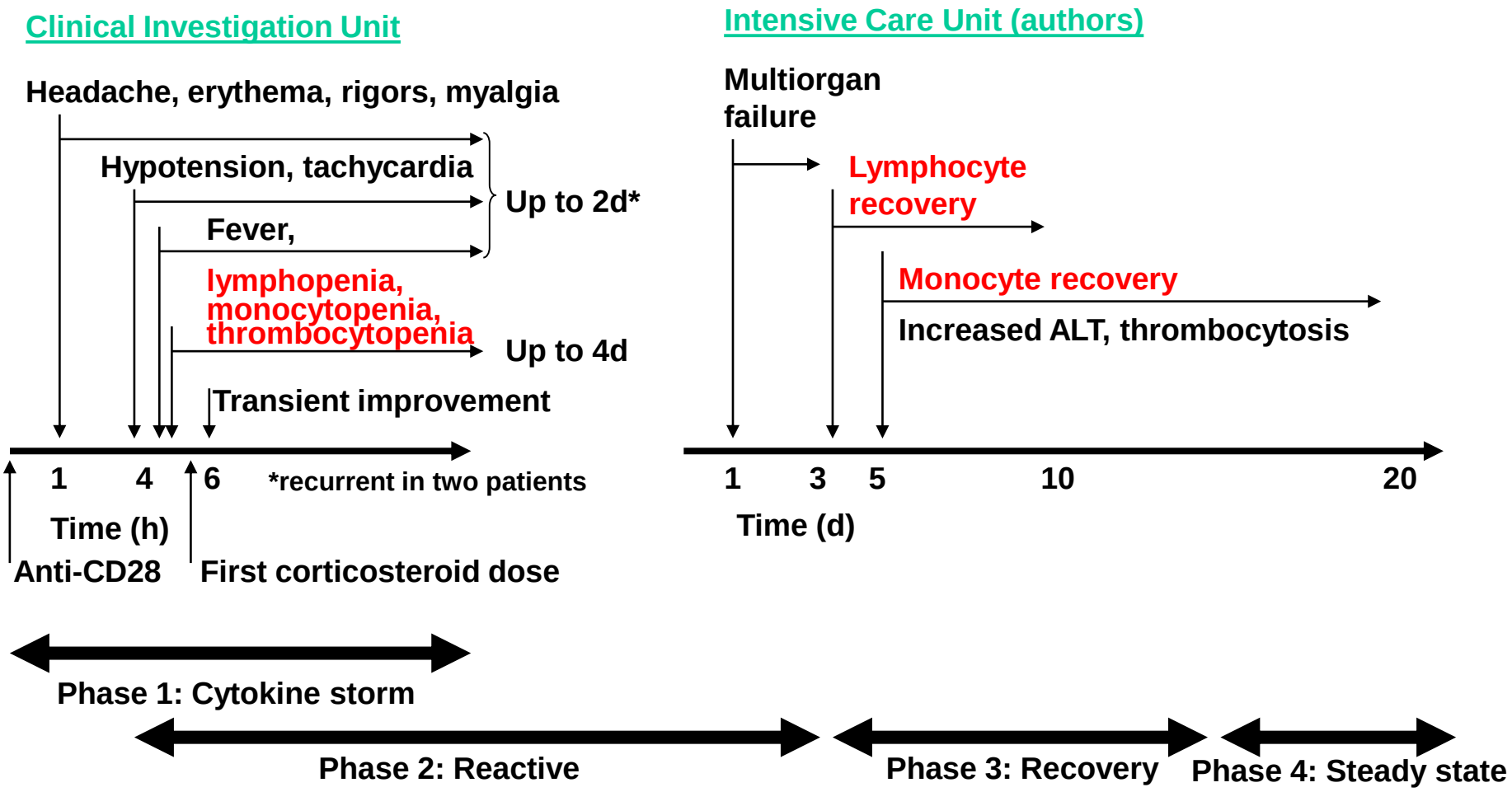
2 received placebo – no effect

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

Suntharalingam G et al., N Engl J Med 355 (2006), 1018-1028

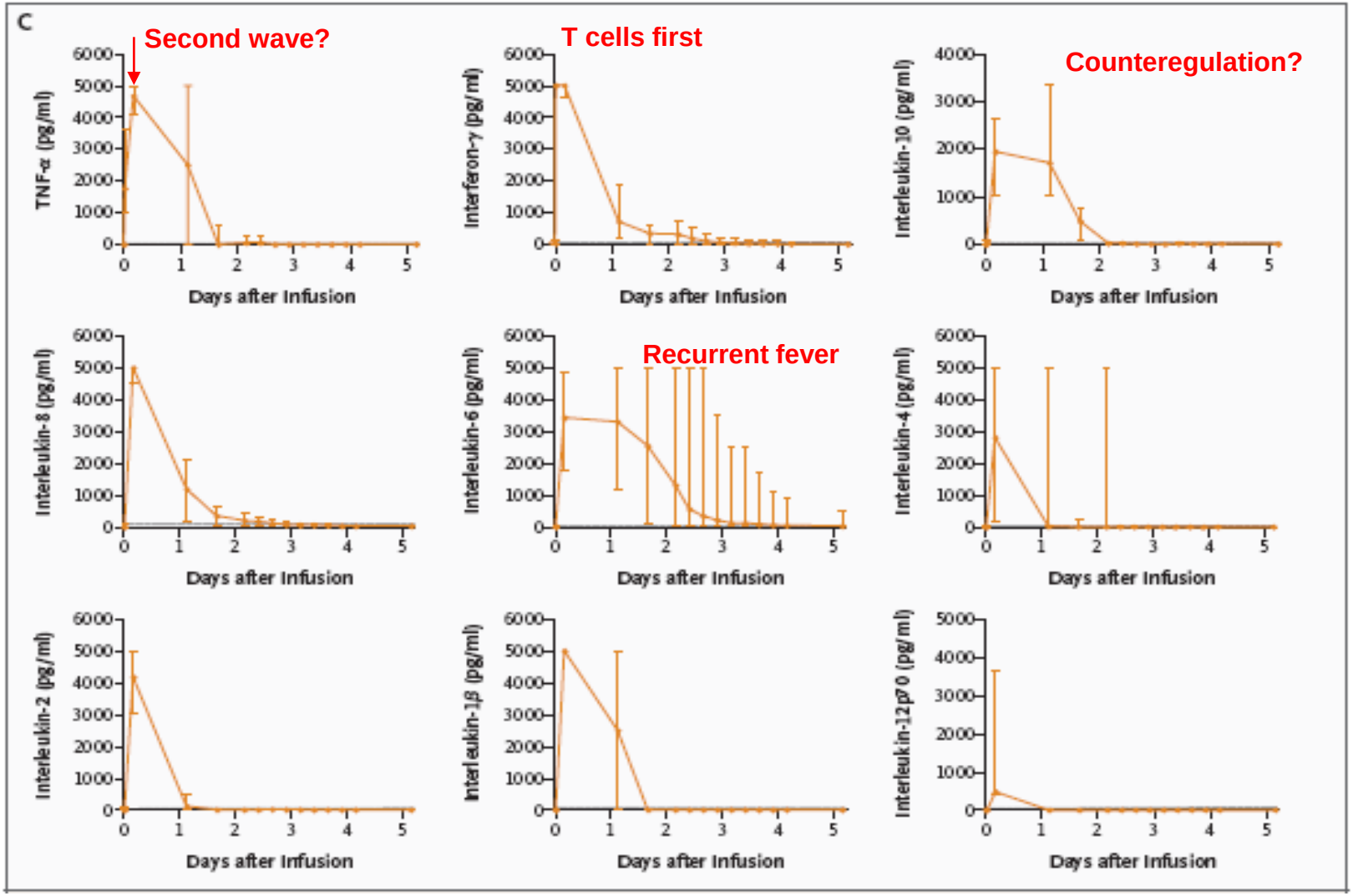
Symptoms

Cytokine storm induced by anti-CD28 antibody



Suntharalingam G et al., N Engl J Med 355 (2006), 1018-1028

Cytokine storm induced by anti-CD28 antibody



Suntharalingam G et al., N Engl J Med 355 (2006), 1018-1028

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

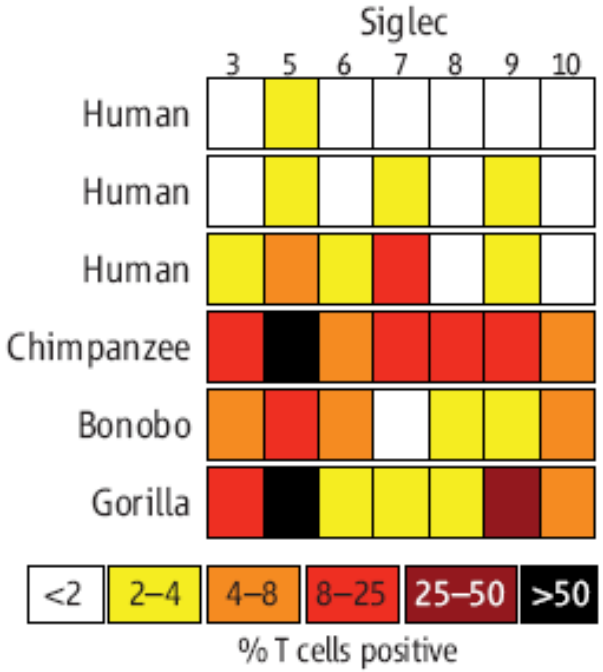
"TGN1412 and analogous antibodies bind to the CD28 receptor on T cells, triggering a powerful expansion of cells dominated by regulatory T cells.

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

IMMUNOLOGY

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



Disease dodger? Higher levels of Siglecs expressed by ape T cells may explain why they do not suffer many common ailments that plague humans.

"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* (physiologial setting) ⟷
- History of revolutionary findings ⟷
- Disease pathogenesis ⟷
- Drug safety ⟷
- Advantage publication/funding

CHALLENGES:

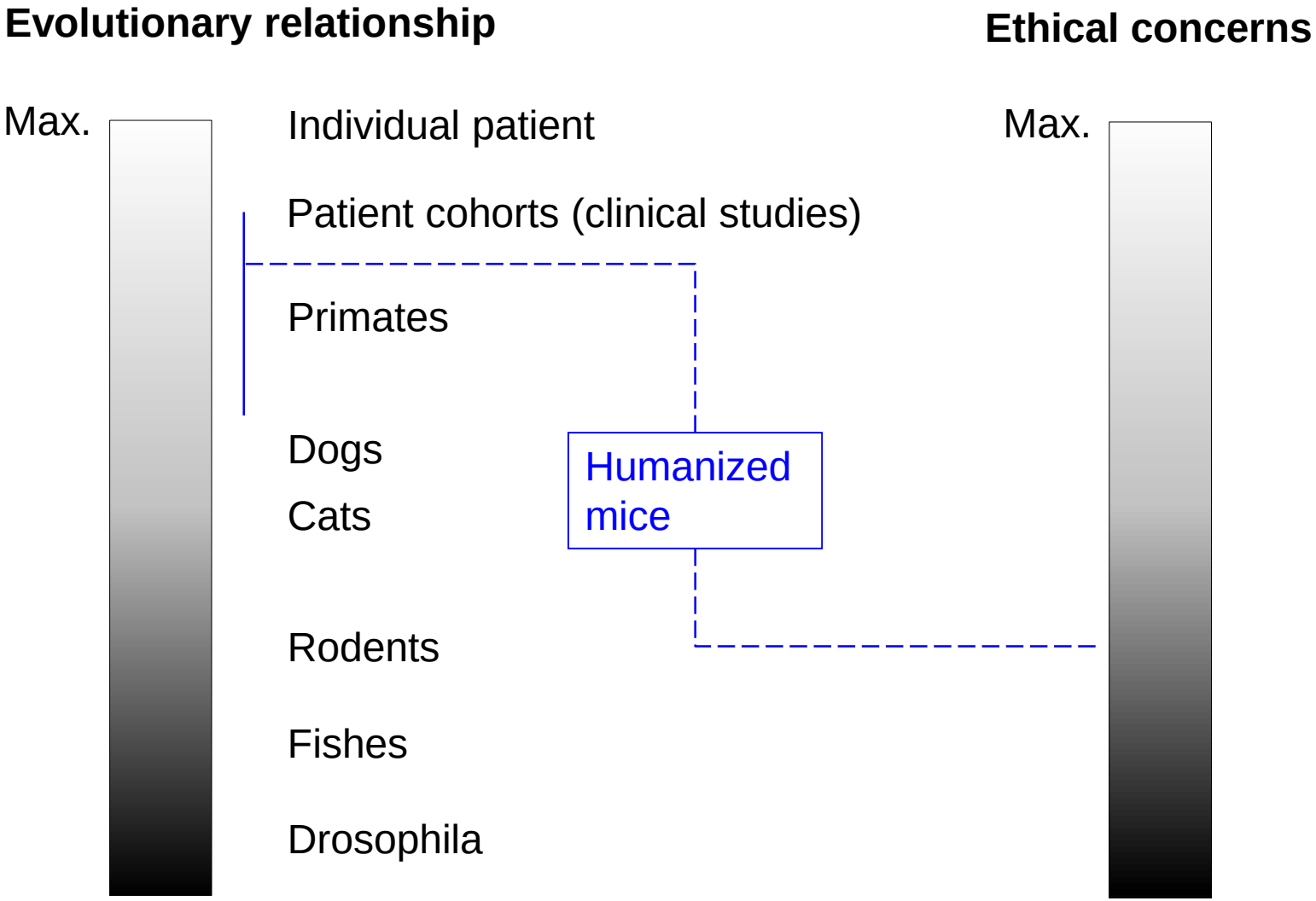
- Non-human
- Traditions, glorification
- Artificial, partial aspects of disease
- Accidents (over-/misinterpretations)
- Labor-intensive experimentation
- High costs
- Ethical concerns
- Intellectual challenges (species, model)

NEED FOR A SCIENTIFIC AND PUBLIC DISCOURSE

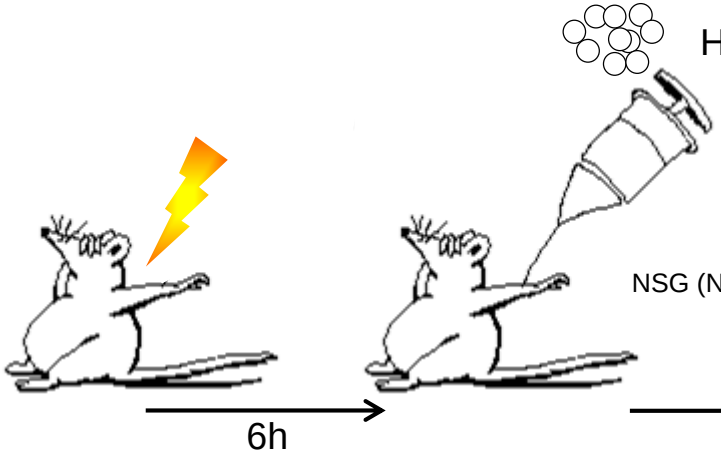
ANIMAL MODELS: SKILLS

- 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

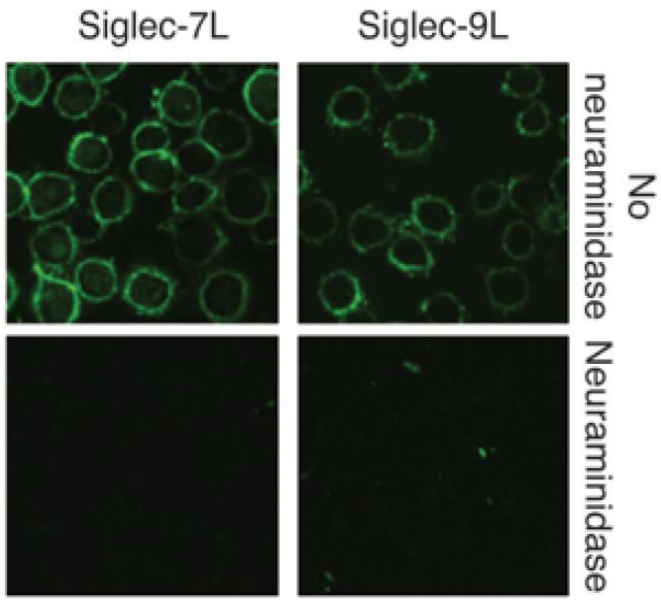
DISEASE MODELS

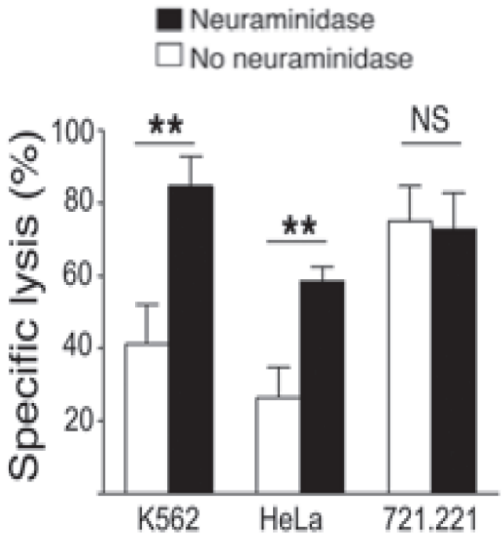


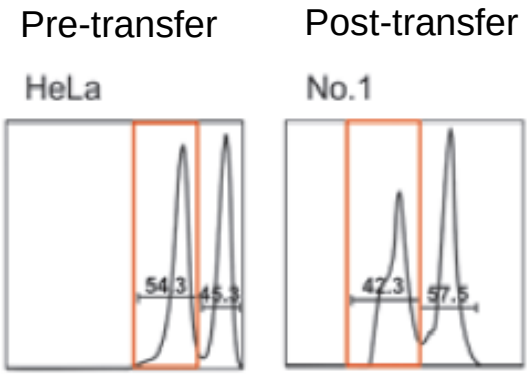
IN VIVO EXPERIMENTS USING MICE WITH A HUMAN NK CELL COMPARTMENT



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







Jandus C & Boligan KF et al. J Clin Invest. 2014

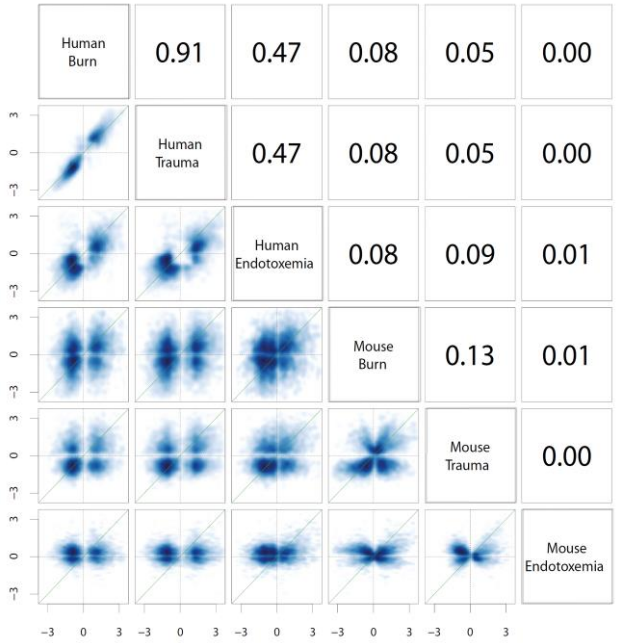
2013

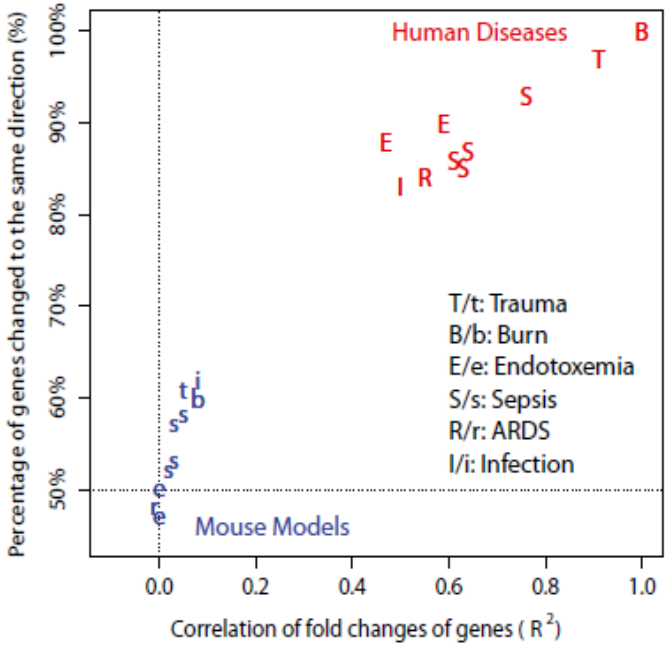
PNAS

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

[a]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305; Departments of [b]Pediatrics and Medicine, [s]Anesthesiology and Critical Care Medicine, and [t]Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; [c]Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; [d]Ingenuity Inc., Redwood City, CA 94063; [e]Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; [f]Department of Surgery, Harborview Medical Center, Seattle, WA 98195; [g]Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; [h]Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045; [i]Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; [j]Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; [k]Department of Surgery, University of Rochester School of Medicine, Rochester, NY 14642; [l]Department of Surgery, University of Pittsburgh Medical Center Presbyterian University Hospital, University of Pittsburgh, PA 15213; [m]Department of Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8; [n]Department of Surgery, San Francisco General Hospital, University of California, San Francisco, CA 94143; [o]Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada M4N 3M5; [p]Department of Surgery, Stritch School of Medicine, Loyola University, Chicago, IL 60153; [q]Department of Anesthesiology, Washington University, School of Medicine, St. Louis, MO 63110; and [r]Department of Surgery, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ 08903





Murphy K, Travers P, Walport M, Janeway C. 2012. *Janeway's Immunobiology.* New York: Garland Science:

"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!"

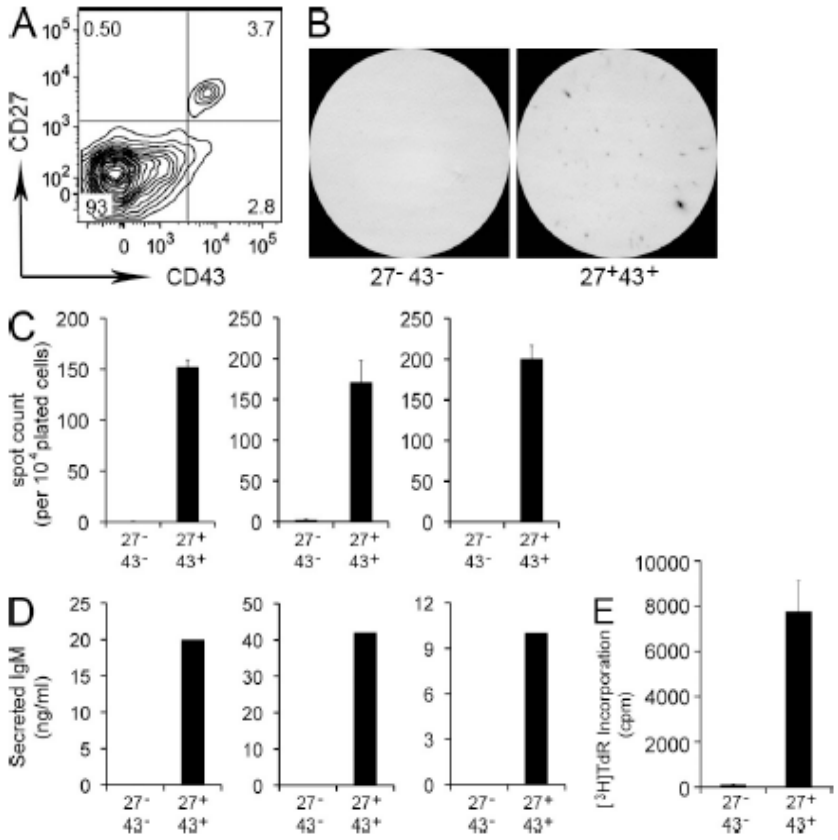
Tangye SG, Blood 2013

Potential bias: species differences

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[2,3,4]

[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-LIJ School of Medicine, Manhasset, NY 11030



J Exp Med 2011

J Exp Med. 2011 Dec 19;208(13):2563-4. doi: 10.1084/jem.20112232.

A human equivalent of mouse B-1 cells?

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

J Exp Med. 2011 Dec 19;208(13):2565-6. doi: 10.1084/jem.20112203.

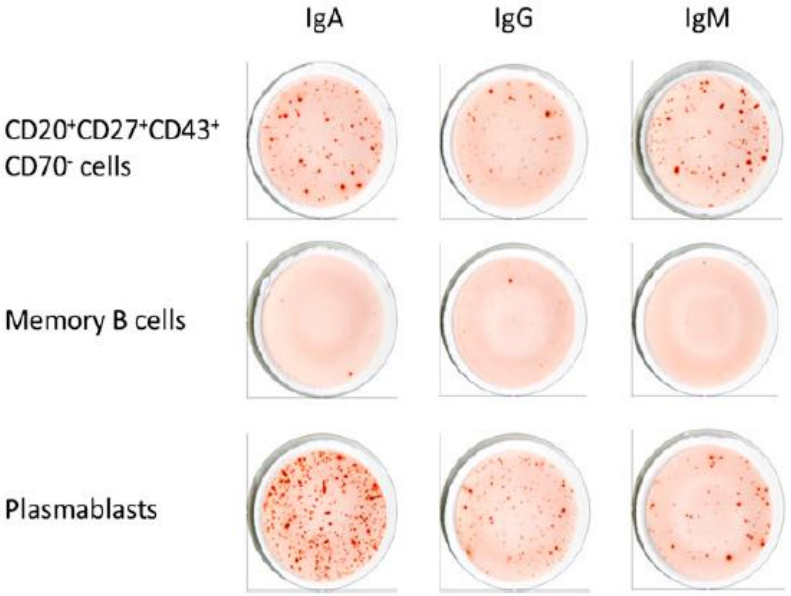
The nature of circulating CD27+CD43+ B cells.

Perez-Andres M, Grosserichter-Wagener C, Teodosio C, van Dongen JJ

IMMUNOBIOLOGY

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

Kris Covens,[1,2] Bert Verbinnen,[1,3] Nick Geukens,[1] Isabelle Meyts,[4] Frans Schuit,[5] Leentje Van and Xavier Bossuyt[1,3]



Blood 2013

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

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

Nat Rev Immunol. 2014 May;14(5):349. doi: 10.1038/nri3401-c1.

PMID: 24762829

Replacement Therapy

FDA-Approved

Primary immunodeficiencies (PID):

Common variable immunodeficiency disorders
Congenital agammaglobulinemia and hypoglobulinemia
Severe combined immunodeficiencies (SCID)
Wiskott-Aldrich syndrome

Secondary immunodeficiencies (SID):

After immunosuppression in solid organ transplantation
Allogeneic bone marrow transplantation
Chronic lymphocytic leukemia (CLL)
Congenital / Pediatric HIV infection

Off-Label Uses

Secondary immnunodeficiencies (SID), associated with:

Anti-CD20 therapy
Chemotherapy
Hemolytic anemia
Rheumatoid arthritis
Sjörgren's syndrome
Systemic lupus eryteomatosus (SLE)
Low-grade non-Hodgkin's lymphoma
Multiple myeloma

Immunomodulatory Therapy

FDA-Approved

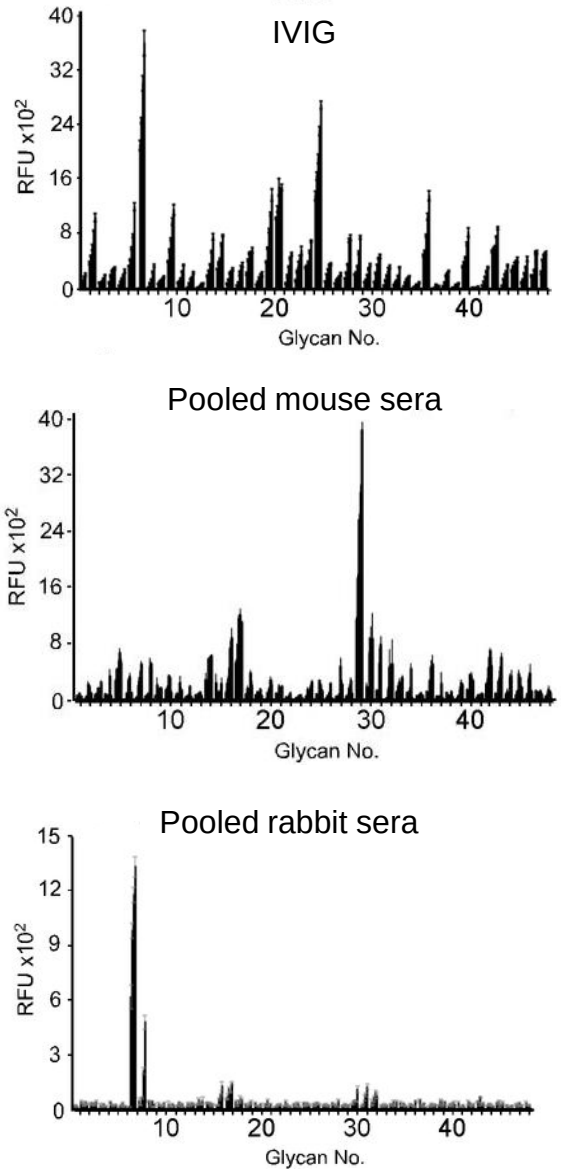
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Immune thrombocytopenic purpura (ITP)
Kawasaki disease
Multifocal motor neuropathy (MMN)
Guillain-Barré syndrome (GBS)

Off-Label Uses

Anti-Factor VIII autoimmune disease
Anti-phospholipid syndrome
Autoimmune blistering disease
Autoimmune hemolytic anemia
Autoimmune neutropenia
Birdshot retinopathy
Cytomegalovirus infection
Dermatomyositis
Epidermolysis bullosa acquisita
Fetal hemolytic disease
Fetal neonatal alloimmune thrombocytopenia (FNAIT)
Graft-versus-host disease
HIV-associated thrombocytopenia
Inclusion body myositis
Lambert-Eaton myasthenic syndrome
Mucous membrane (cicatricial) pemphigoid
Multiple sclerosis
Myasthenia gravis (MG)
Necrotizing fasciitis
Neonatal alloimmune thrombocytopenia
Opsoclonus myoclonus syndrome (OMS)
Pemphigus foliaceus
Pemphigus vulgaris
Polymyositis
Polyradiculoneuropathy
Refractory dermatomyositis
Refractory polymyositis
Relapsing-remitting multiple sclerosis (RRMS)
Rheumatoid arthritis
Sepsis syndrome
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

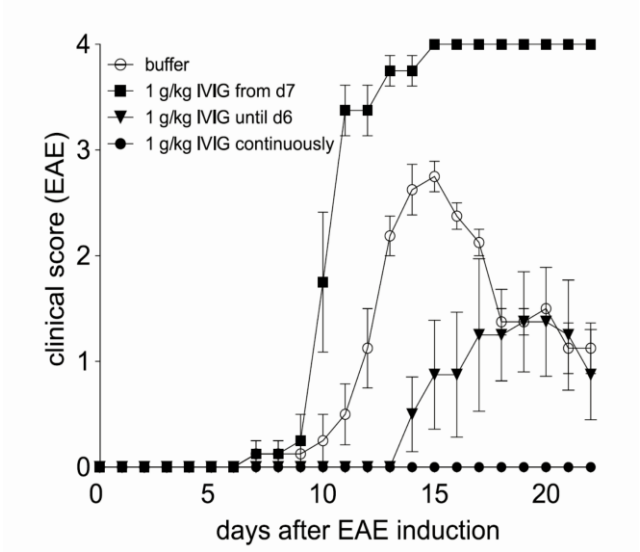
CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULINS (IVIG)

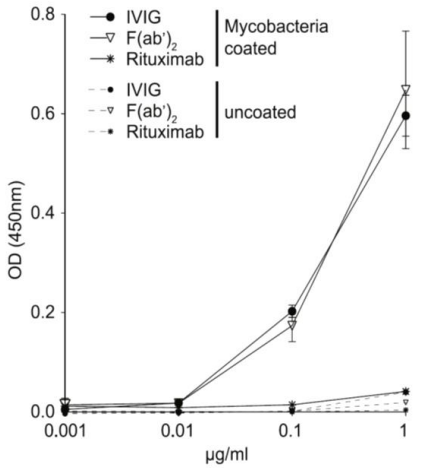
SPECIES DIFFERENCES!

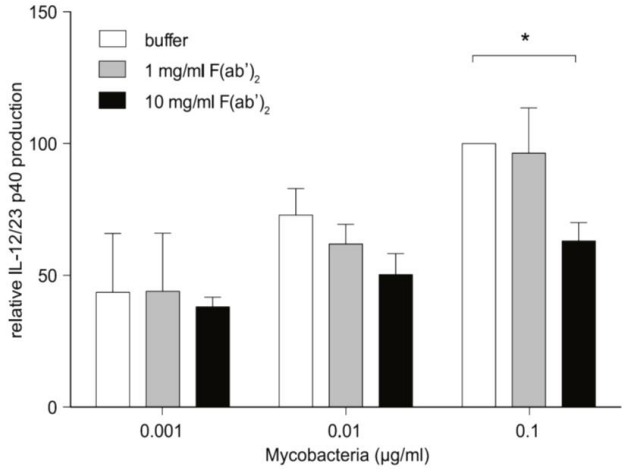


Stowell SR et al. Nat Chem Biol, 2014

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



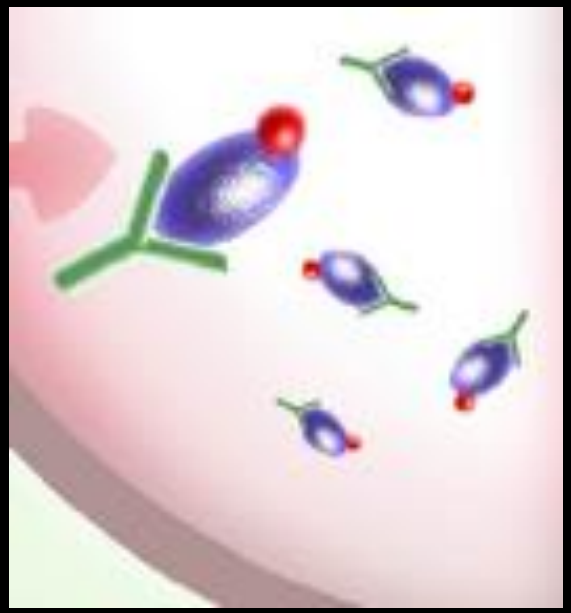




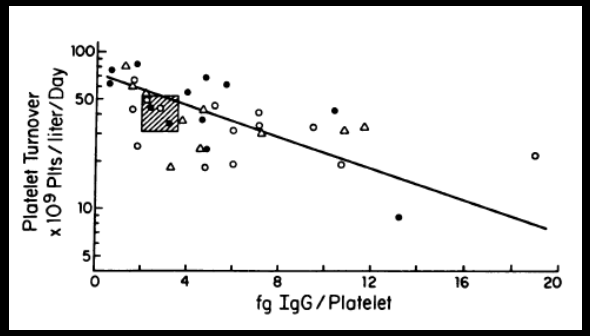
Quast I et al. J Neuroinflammation 2016

Immune thrombocytopenia (ITP): mechanisms

1950: Self-experiment Dr. W. Harrington

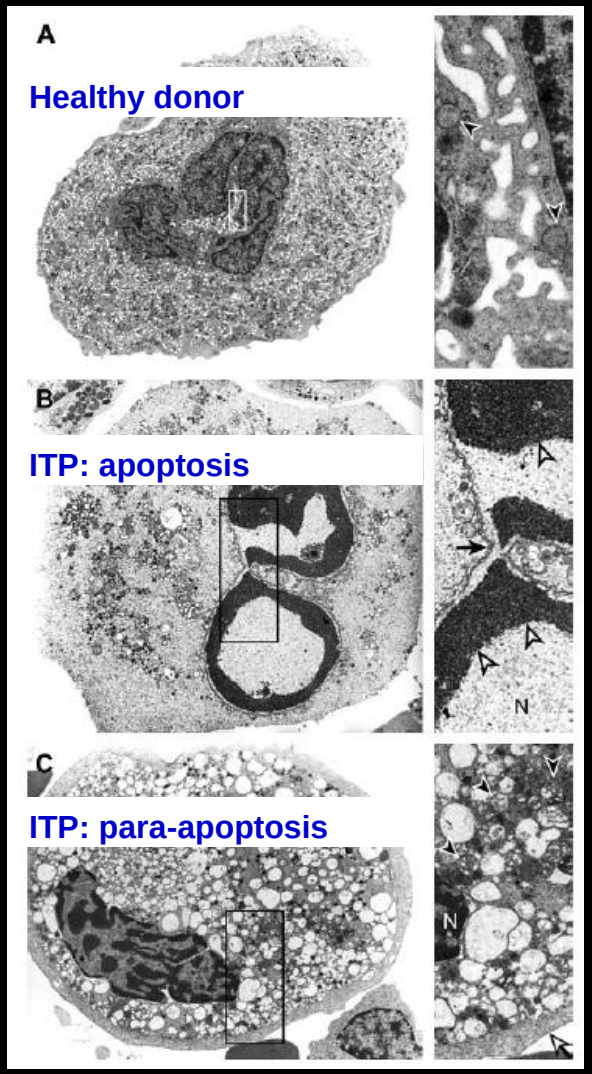


Kinetic experiments
-> platelet generation problem



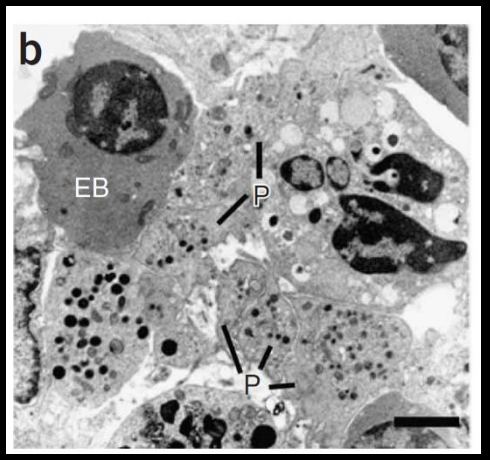
Ballem PJ et al. J Clin Invest. 1987

Megakaryocyte death



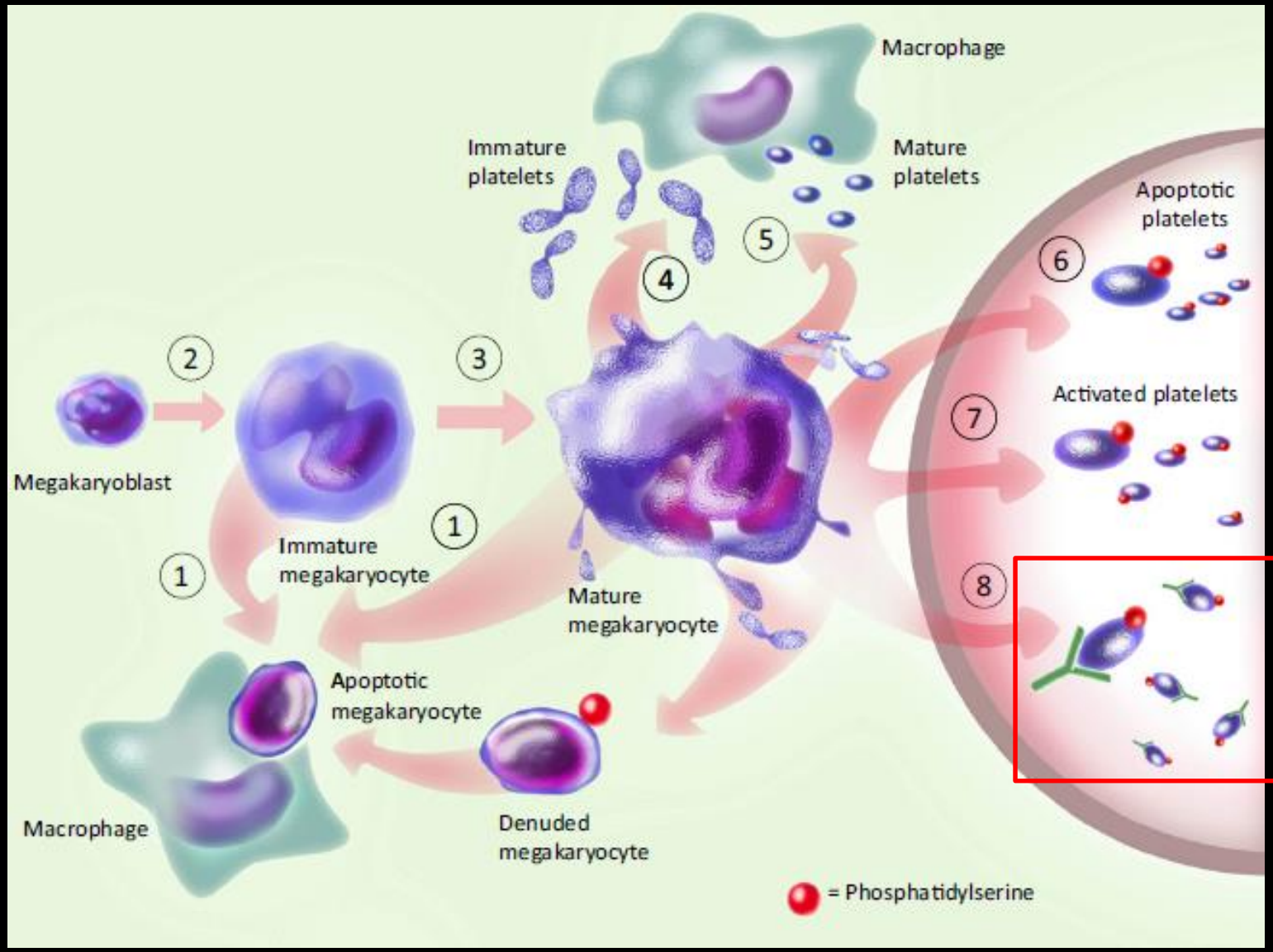
Houwerzijl EJ, Blood. 2004

Ineffective megakaryopoiesis



Morision IM, Nat Genet. 2008

Immune thrombocytopenia (ITP): mechanisms



Current models of ITP

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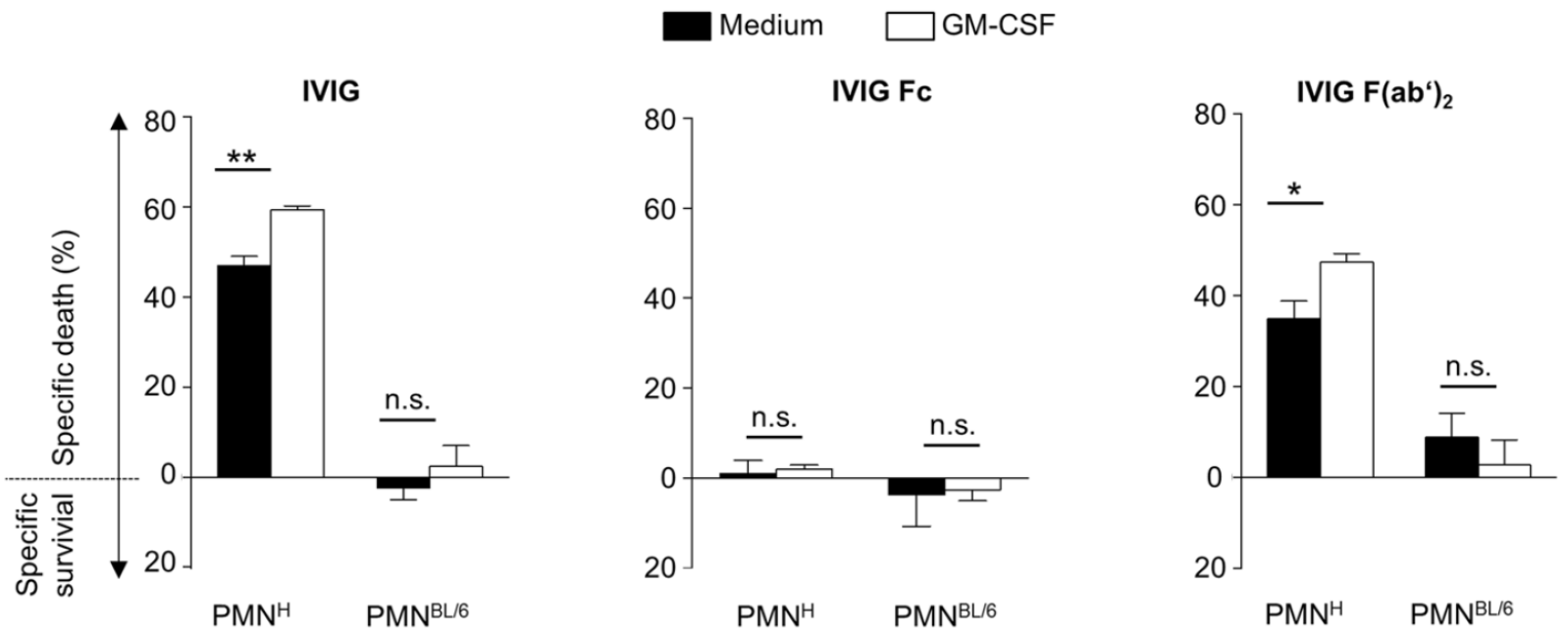

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