Papel de los anti IL-1 en los síndromes autoinflamatorios

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The new world of the Autoinflammatory diseases

Monogenic inflammatory diseases caused by mutations of genes involved in the innate immune response

First gene identified in 1997

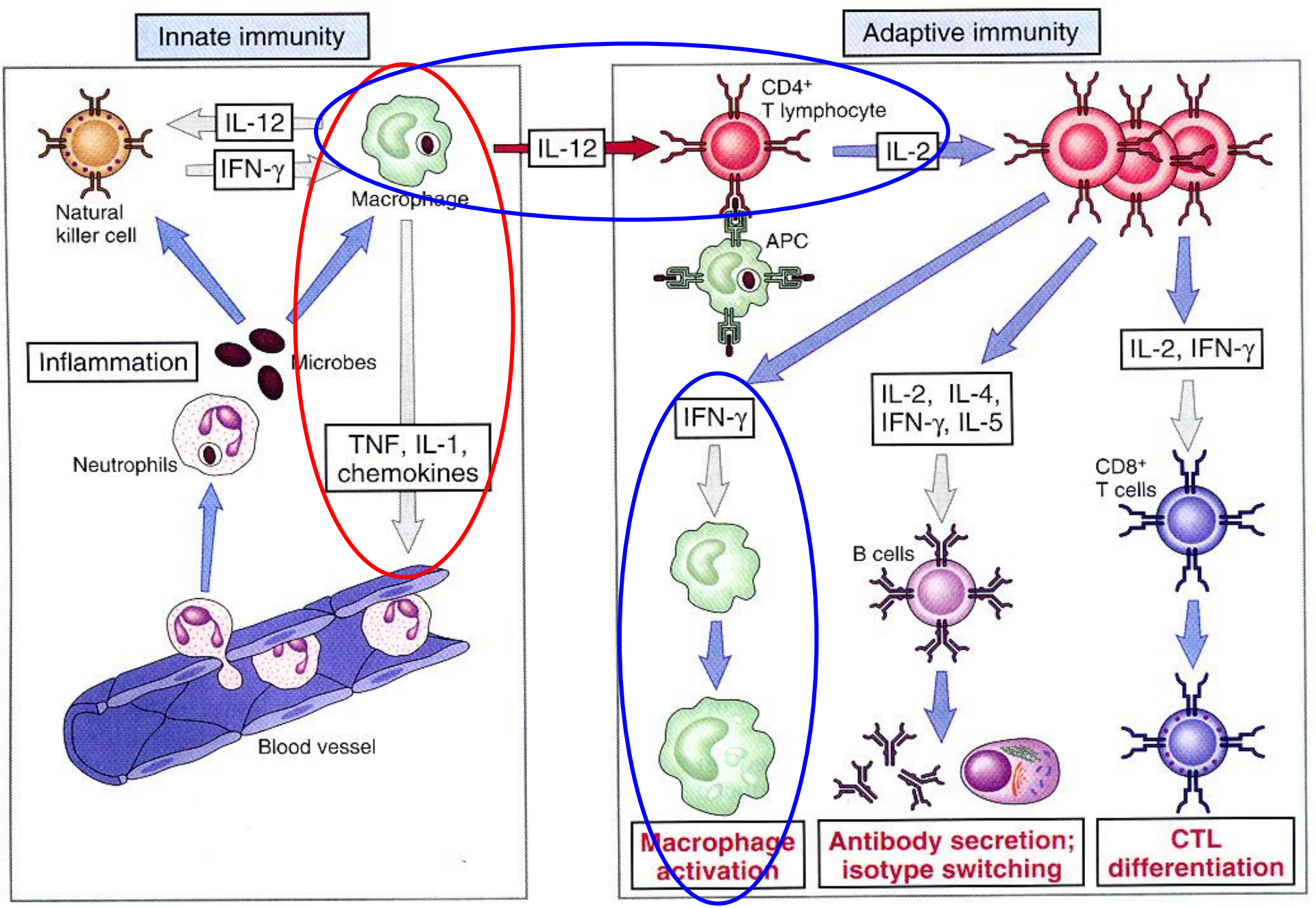
Absence of auto-antibodies and antigen-specific T cells

No class II HLA-association and/or gender disproportion

Responsive to anti-IL1 and -TNF treatments

Autoinflammatory diseases

	Disease (Identification)	Gene Chromosome	Protein	Inheritance	Gene Identification
Periodic Fevers	Familial Mediterranean Fever **(1945)**	*MEVF* 16p13.3	Pyrin	AR	**1997**
	Mevalonate Kinase Deficency **(1984)**	*MVK* 12q24	Mevalonate kinase	AR	**1998**
	TRAPS **(1982)**	*TNFRSF1A* 12p13	p55 TNF receptor	AD	**1999**
NLRPs-related diseases	FCAS, MWS, CINCA **(1940, 1962, 1982)**	*NLRP3/CIAS1* 1q44	Cryopyrin	AD	**2000 2001**
	NLRP12-related periodic fever **(2008)**	*NLRP12* 14p35	NLPR12	AD	**2008**
Granulomatous disorders	Blau's syndrome **(1985)**	*CARD15/NOD2* 16q12	CARD15	AD	**2001**
Pyogenic disorders	PAPA syndrome **(1997)**	*PSTPIP1* 15q24-q25.1	PSTPIP1	AD	**2002**
	Majeed's syndrome **(1989)**	*LPIN2* 18p	LPIN2	AR	**2005**
	DIRA **(2009)**	*IL1RN* 2p22	IL1Ra	AD	**2009**



Autoinflammatory (D. Kastner et al , Cell 1999)

Autoinflammatory diseases

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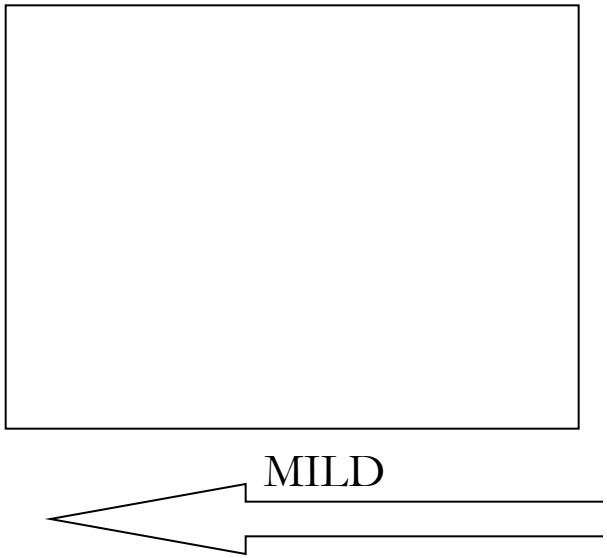
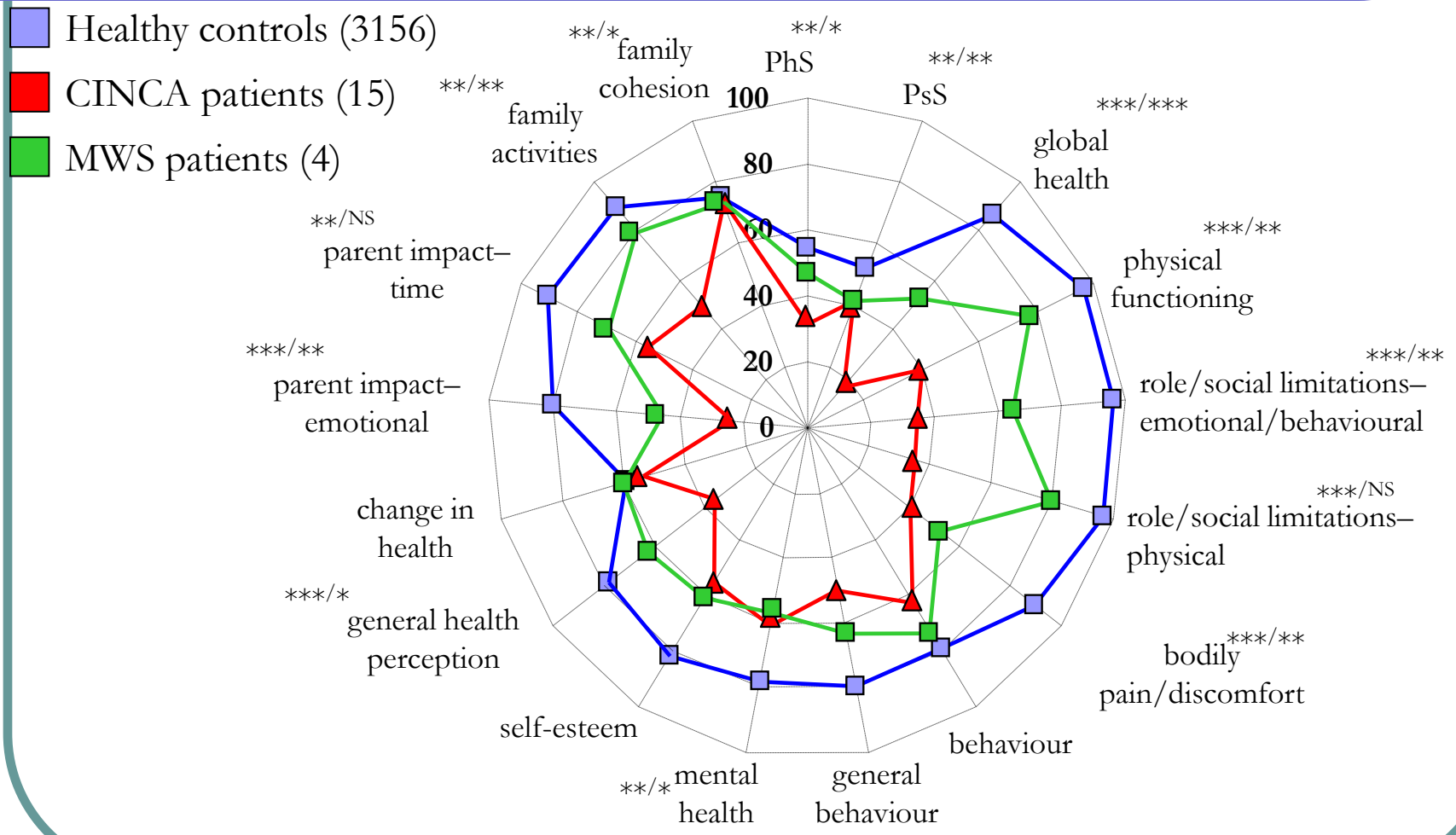
Cyopyrin associated periodic syndrome (CAPS): spectrum of diseases

Familial cold autoinflammatory syndrome (FCAS)

- Autosomal dominant
- Cold-induced
  - Rash
  - Arthralgia
  - Conjunctivitis



Quality of life in CINCA/MWS patients (CHQ-P50)



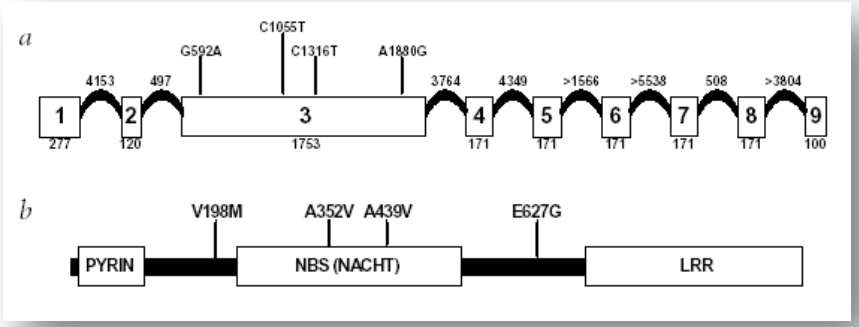
Lepore et al J. Pediatrics 2010

 letter

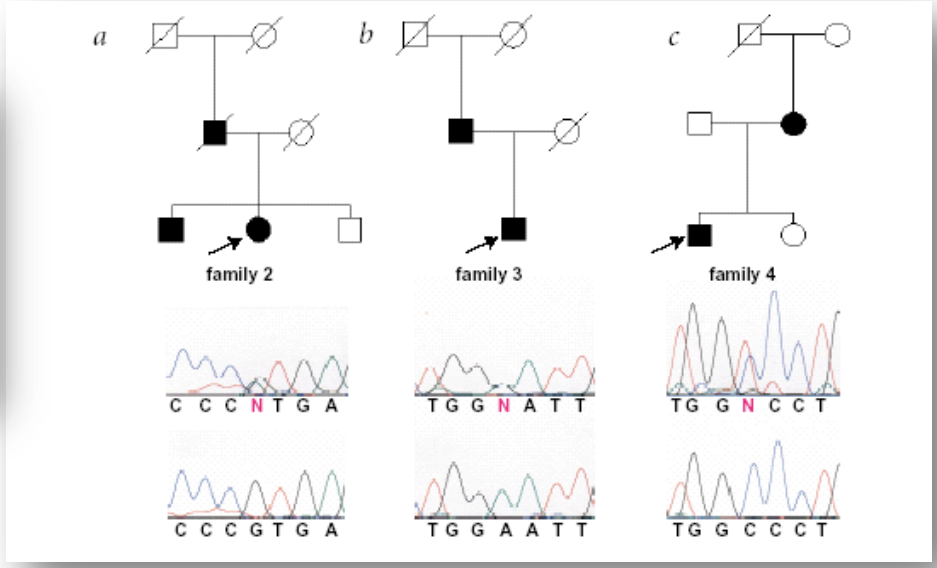
Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome

Hal M. Hoffman[1–3], James L. Mueller[1–4], David H. Broide[2,3], Alan A. Wanderer[5] & Richard D. Kolodner[1,3,4]

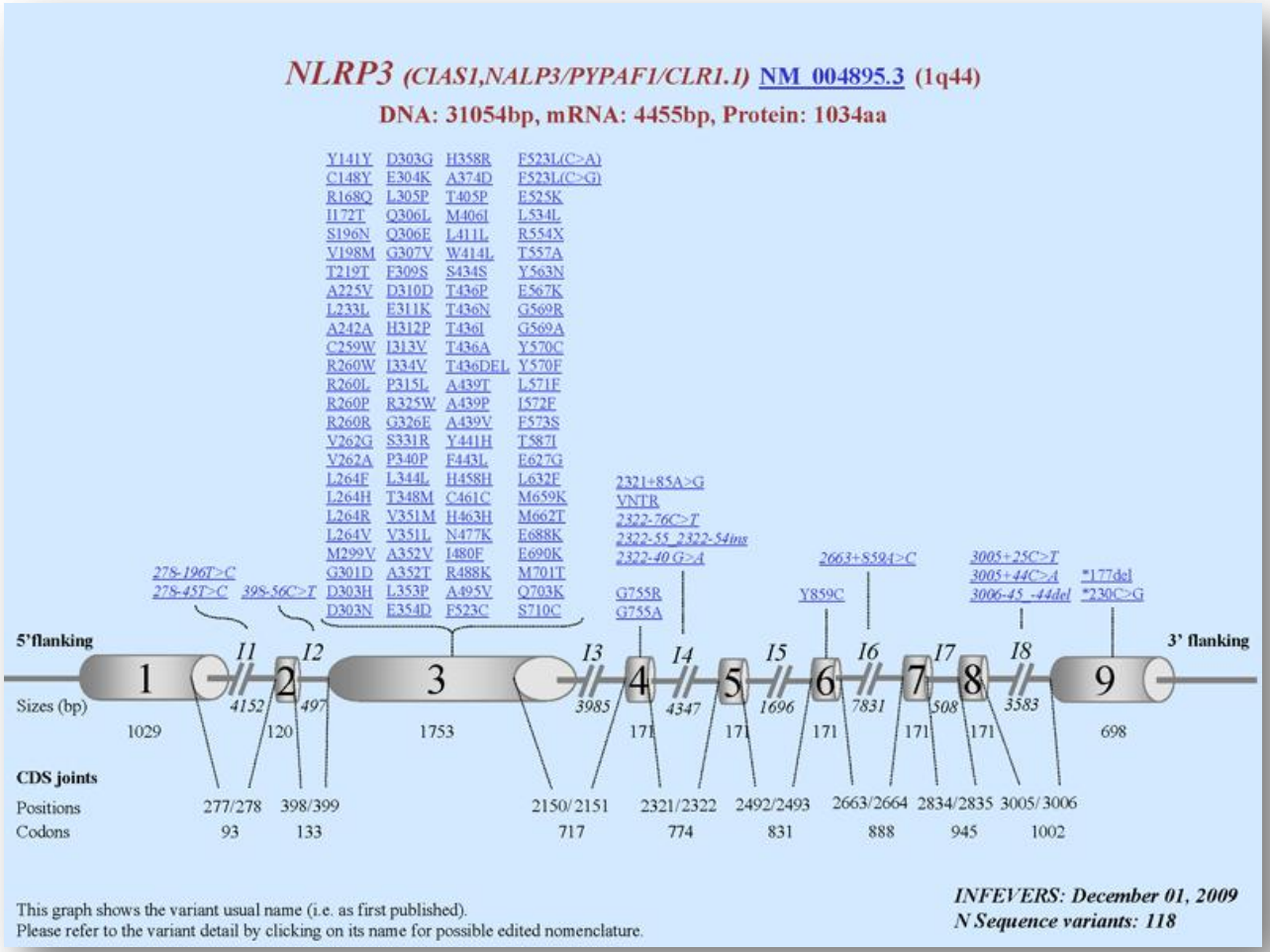
CIAS1/NALP3/NLRP3



Cryopyrin

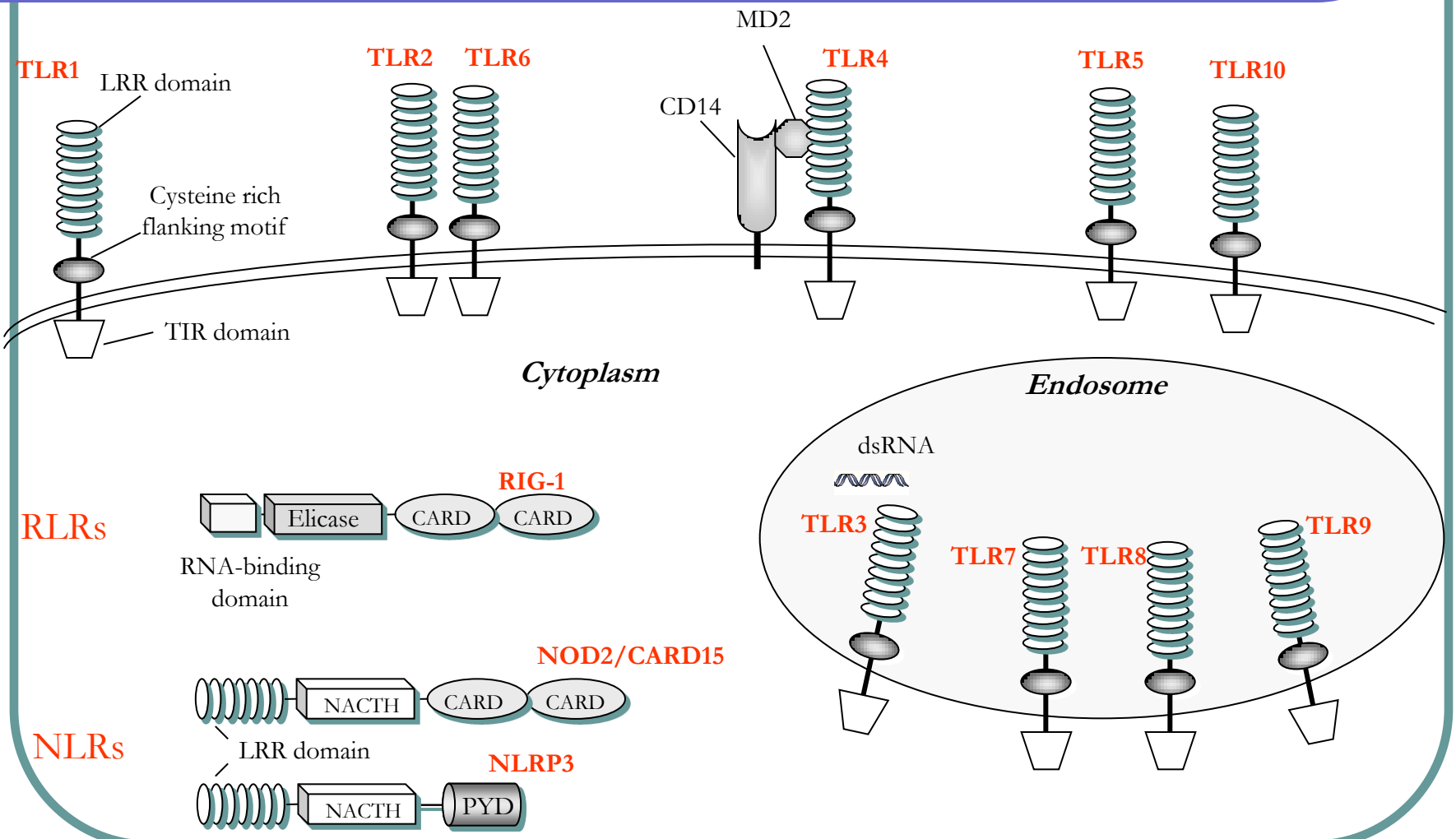


The Infever database (I. Touitou)



http//fmf.igh.cnrs.fr/infevers/

Pattern-recognition receptors



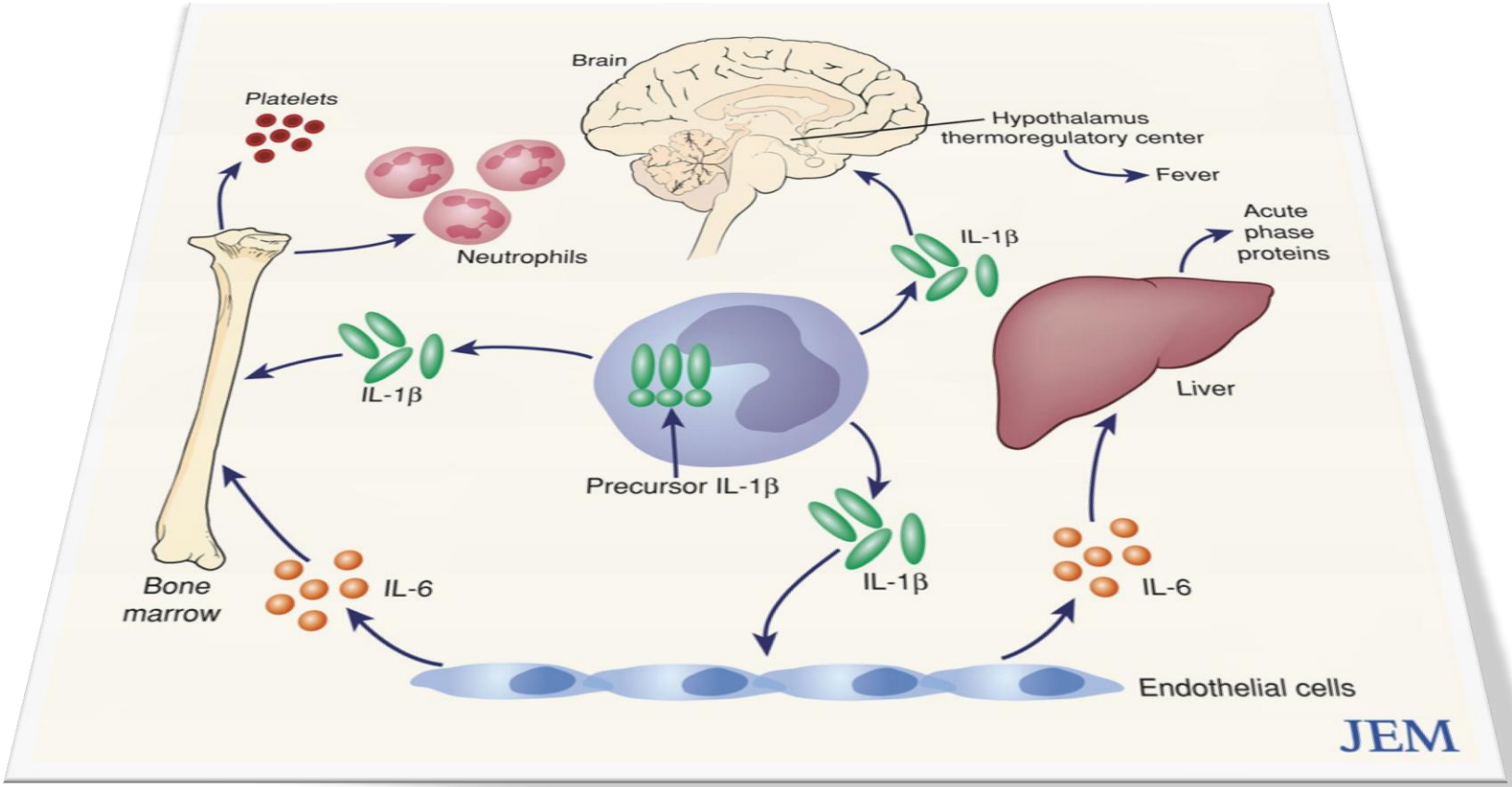
Pathogens associated molecular patterns (PAMPs)

Damage associated molecular patterns (DAMPs)

The Inflammasome

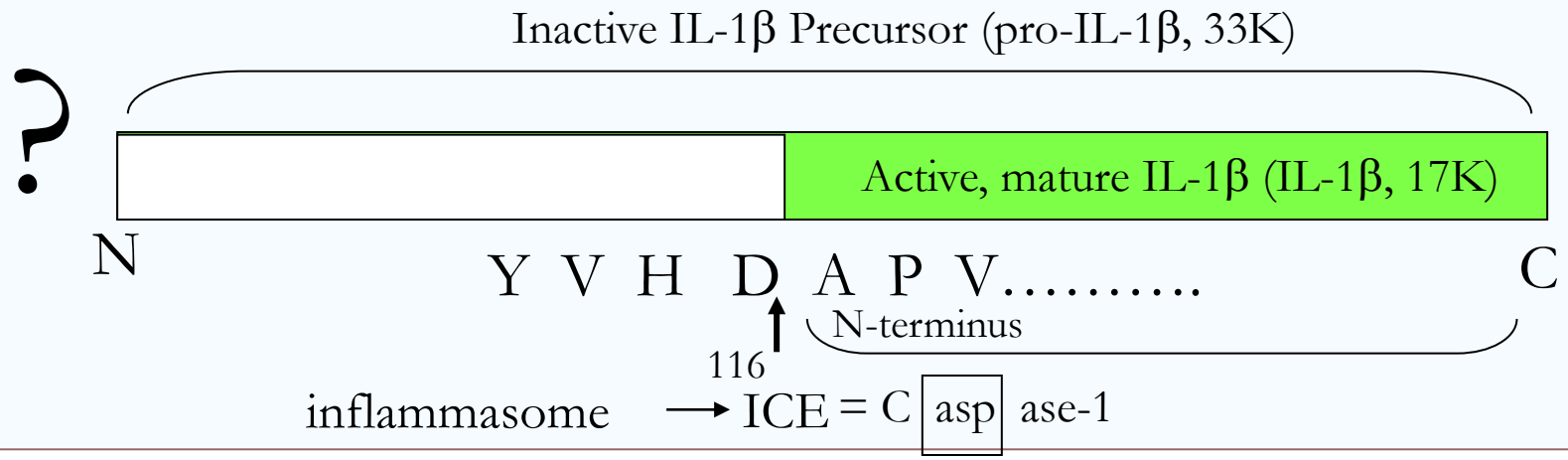
NLPR3/Cryopyrin is a pivotal protein for the Caspase-1 activation pathway and IL-1 secretion

IL-1β is a major pro-inflammatory cytokine



Charles Dinarello 1982-2011

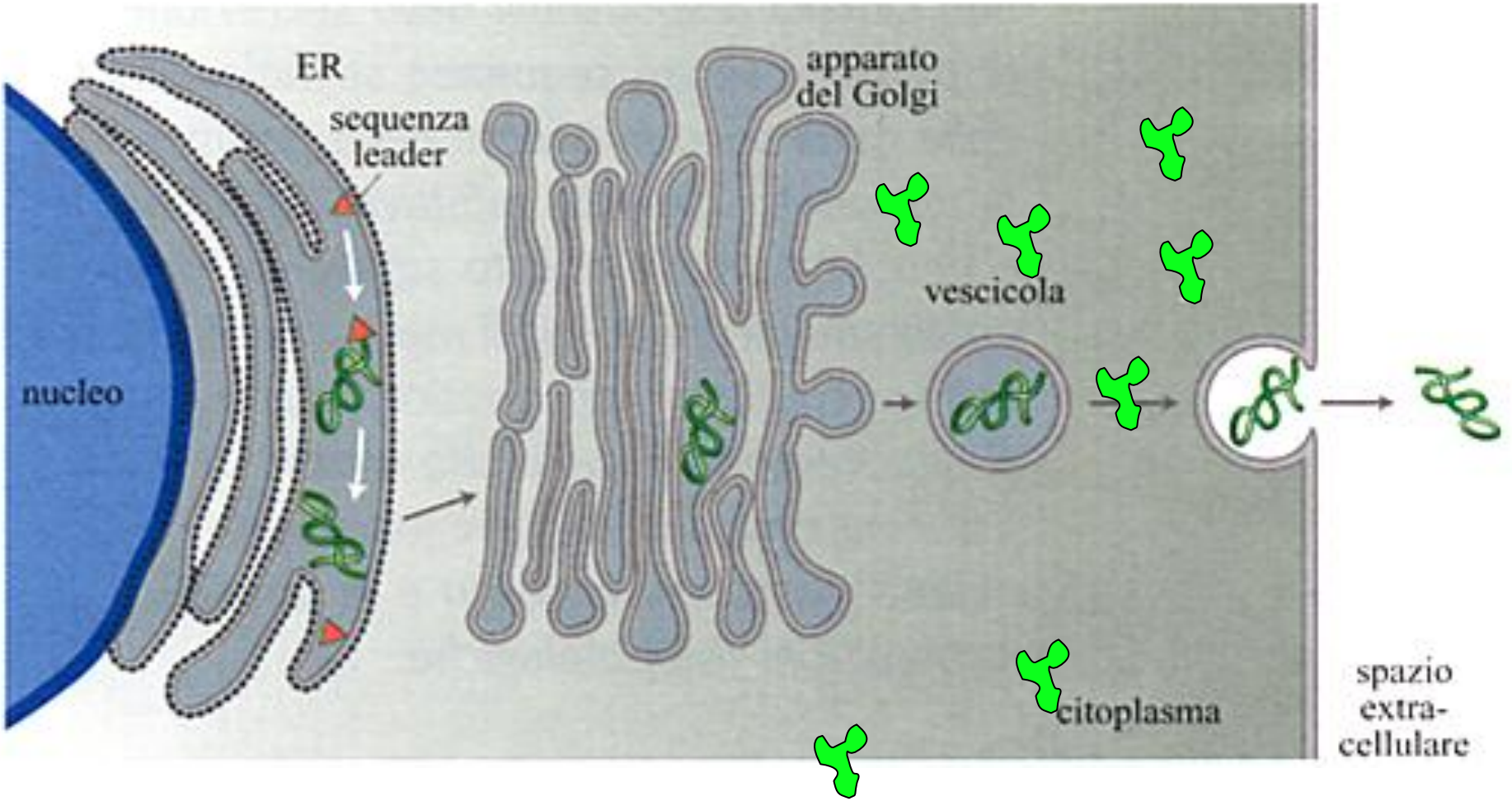
Interleukin-1



- IL-1β secretion occurs via a non classical pathway *(Rubartelli et al, 1990)*

- IL-1β activity is controlled mostly at post-translational level (processing, secretion, production of IL-1ra)

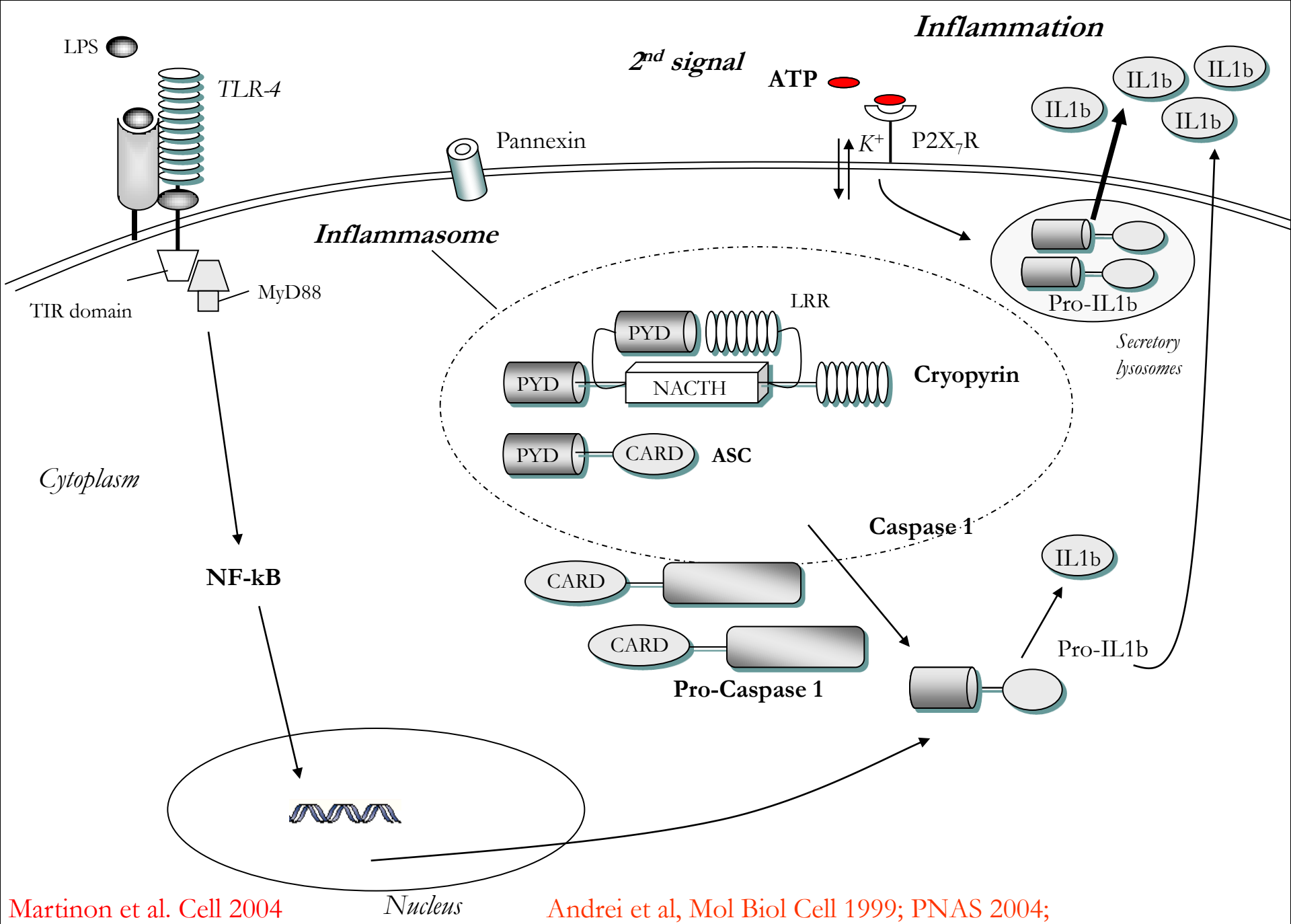
How can a leaderless secretory protein be externalized?



"classical" secretory protein

"Leaderless" secretory protein

Leader sequence



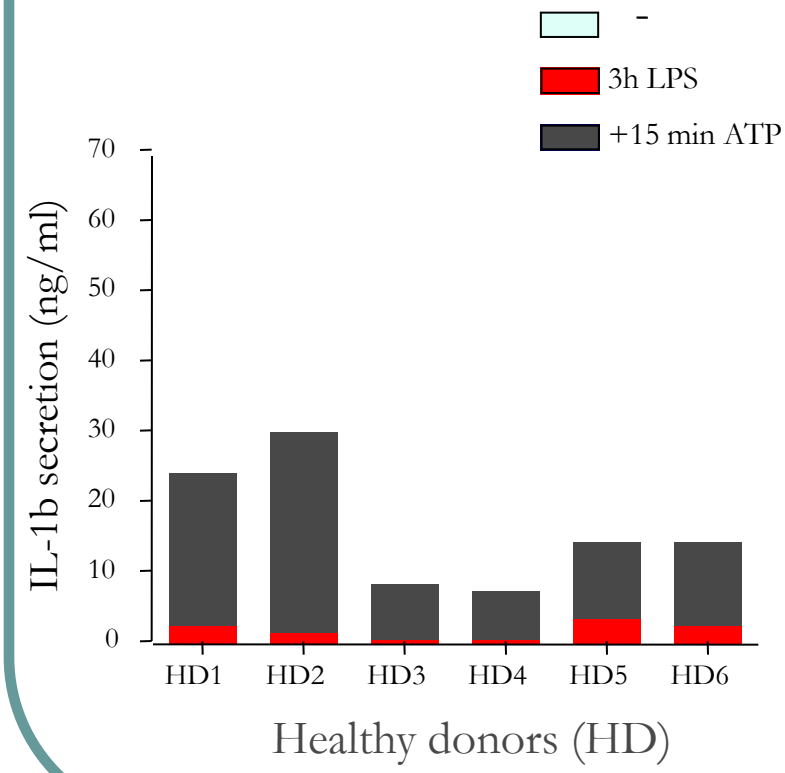
Martinon et al. Cell 2004
Agostini et al, Immunity, 2004

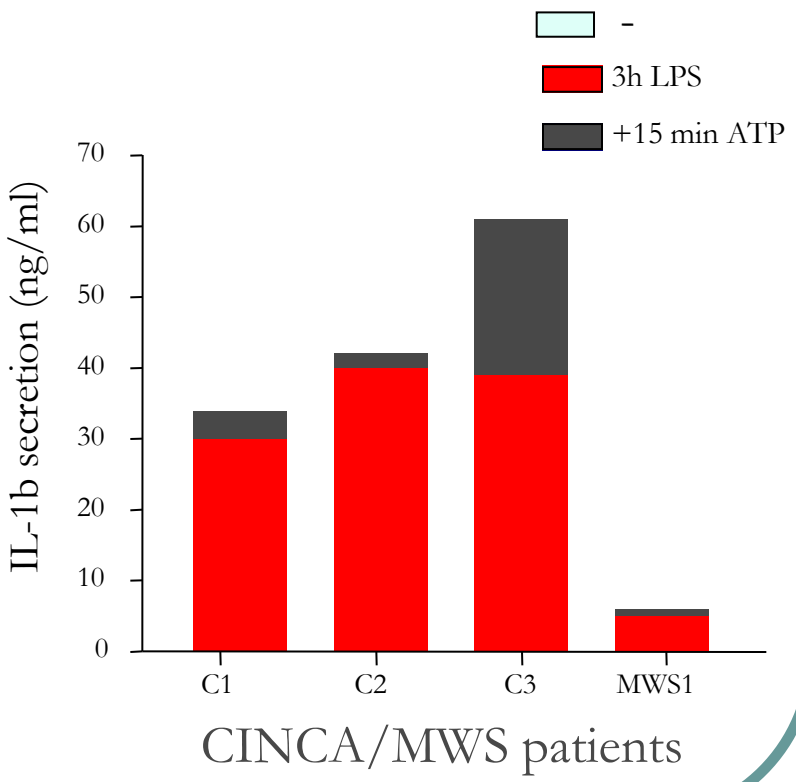
Andrei et al, Mol Biol Cell 1999; PNAS 2004;
Mariathasan, Science 2006

CIAS-1 mutated monocytes over-secrete IL-1ß upon 1st stimulation (LPS) without the need of a 2nd signal (ATP)

supernatants

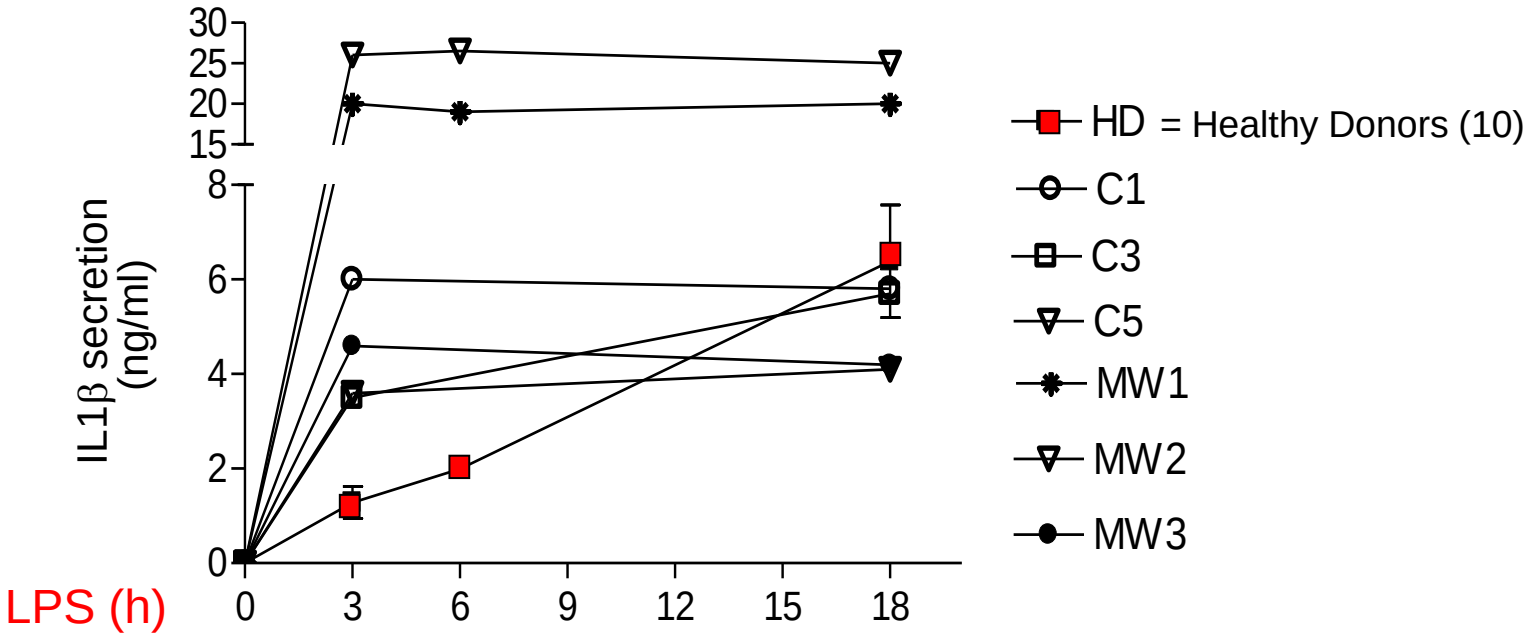
0.5 to 5 ng/10^6 cells in 3h LPS stimulation and from 4 to 40 ng/10^6 cells in response to ATP (15min)





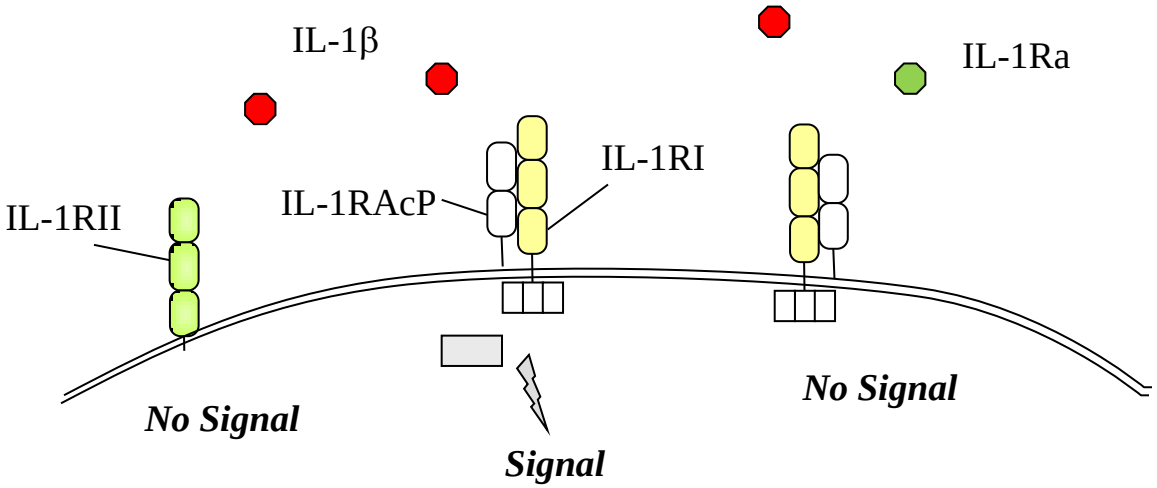
(Gattorno et al, A&R 2007 56(9):3138-8)

PAMP-induced IL-1β secretion by CAPS monocytes is faster than by normal monocytes



Tassi et al PNAS 2010

Strategies for IL-1 down-modulation



Recombinant IL-1 receptor antagonist (Anakinra)

IL-1 blockade in CAPS patients

ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 607–612
DOI 10.1002/art.20033

Spectrum of Clinical Features in Muckle-Wells Syndrome and Response to Anakinra

Philip N. Hawkins,[1] Helen J. Lachmann,[1] Ebun Aganna,[2] and Michael F. McDermott[2]

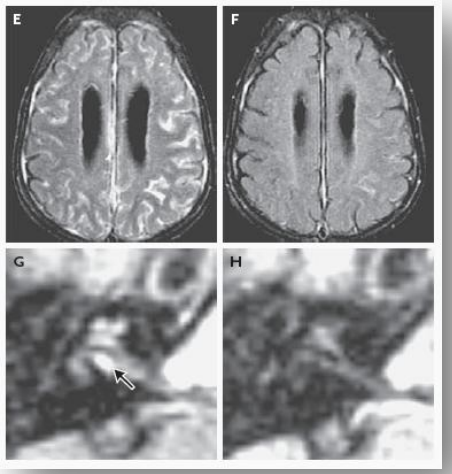
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1β Inhibition

Raphaela Goldbach-Mansky, M.D., Natalie J. Dailey, M.D., Scott W. Canna, M.D., Ana Gelabert, M.S.N., Janet Jones, B.S.N., Benjamin I. Rubin, M.D.,

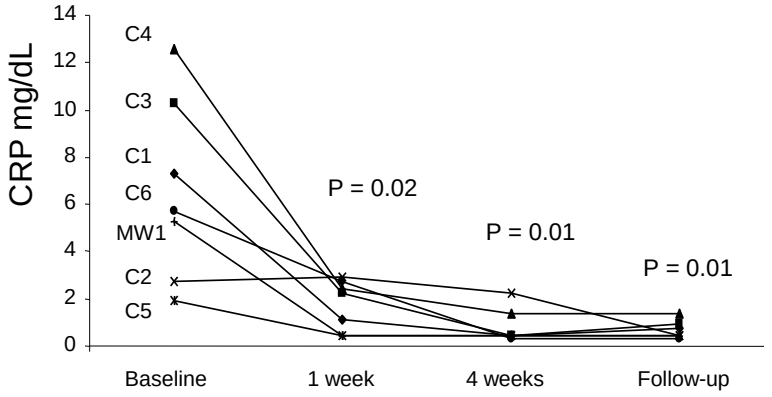
N ENGL J MED 355;6 WWW.NEJM.ORG AUGUST 10, 2006



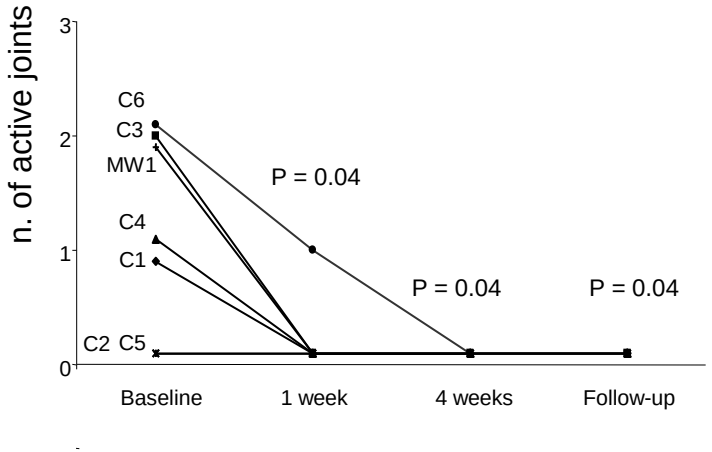
CINCA/MWS patients treated with Anakinra

Follow-up 4,2 years (range 1,2-4,9)

11/4/05



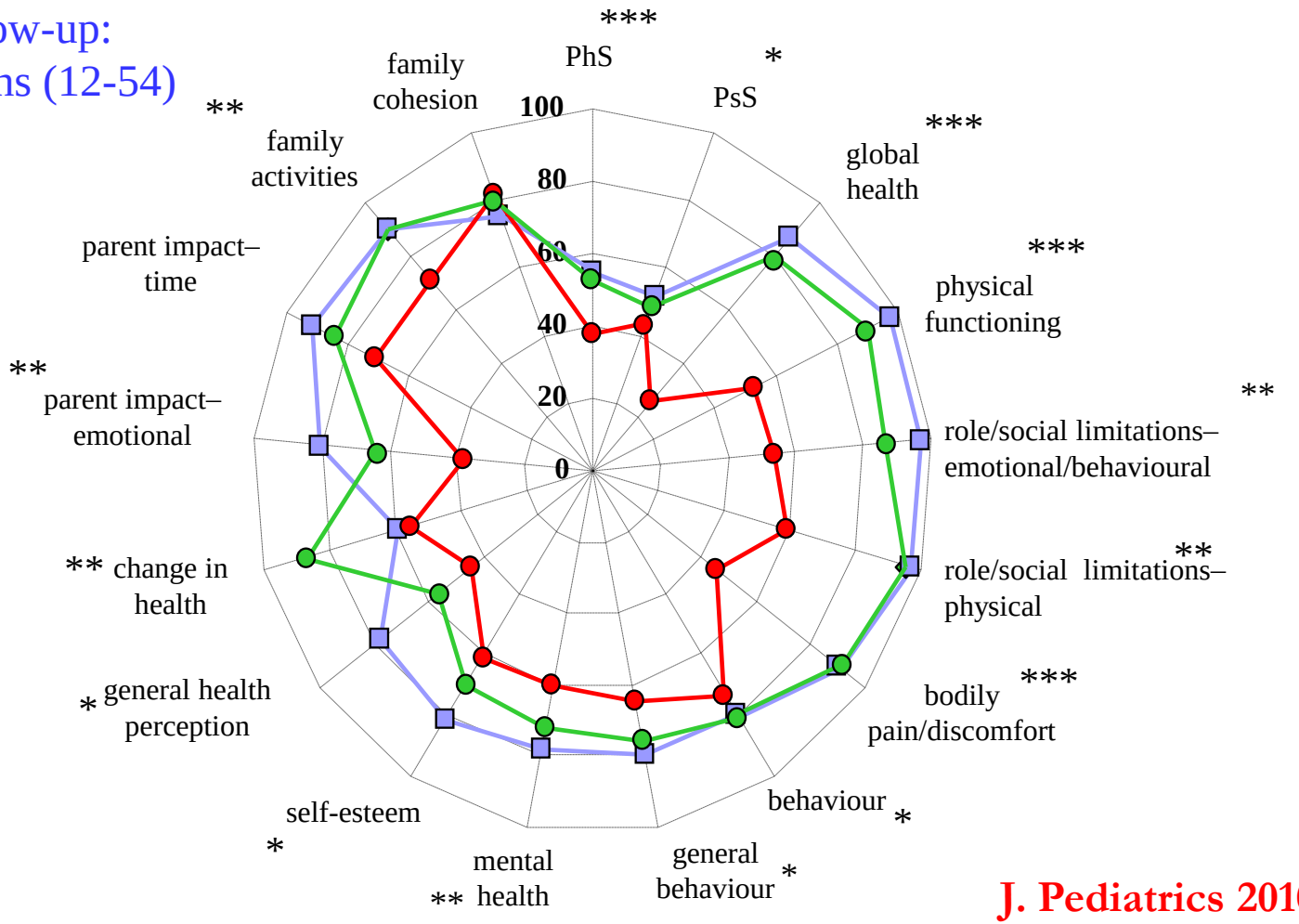
12/4/05



Gattorno et al. Arthritis & Rheumatisms 2007 56(9):3138

Long term improvement of quality of life in CAPS patients treated with Anakinra (Italian Registry)

Mean follow-up:
35,7 months (12-54)



J. Pediatrics 2010

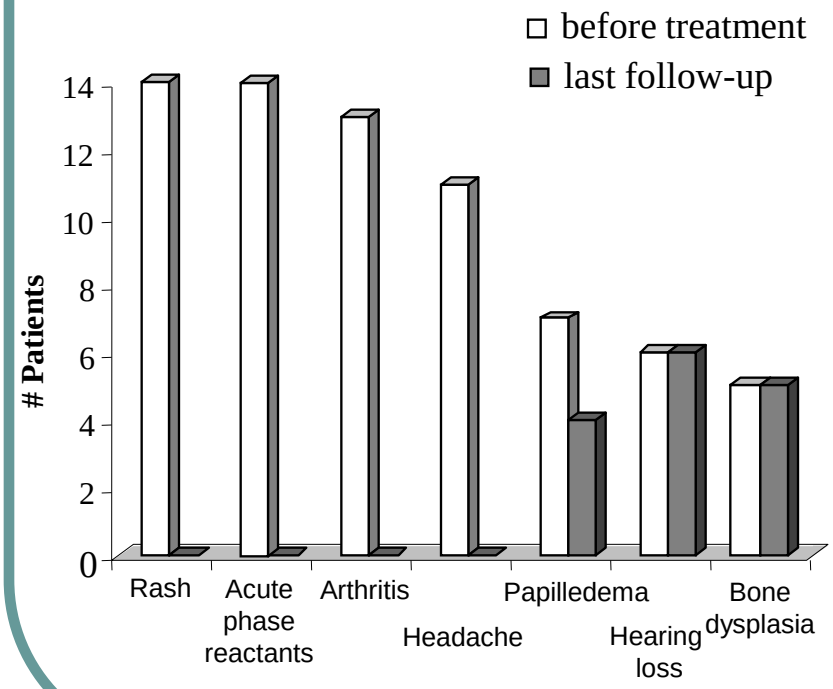
Healthy controls

CINCA/MWS pts before treatement (14)

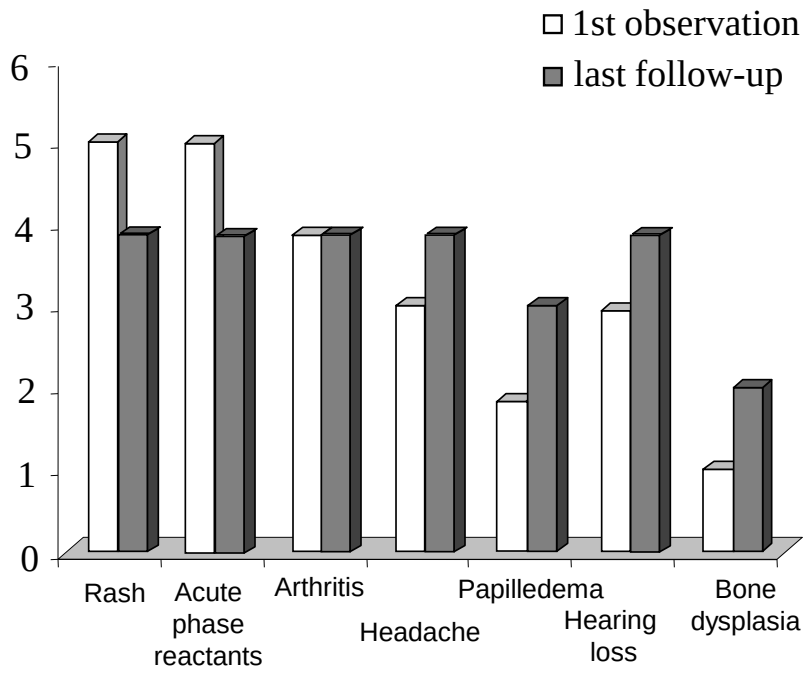
CINCA/MWS after treatement (14)

High rate of refusal to treatment with Anakinra

Treated patients (14)



Untreated patients (5)



Lepore et al. J. Pediatrics 2010

New IL-1 blockers

Rilonacept: a dimeric fusion protein (251 kDa)

Specific blocker of IL-1-incorporating components required for IL-1 signalling

- IL-1RI(IL-1 receptor sub-type 1)
- IL-1RAcP (IL-1 receptor accessory protein)

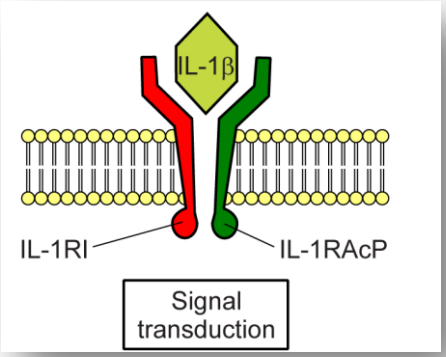
Prolonged circulation

Half-life in-vivo (8.6 days) *(H. Hoffman, A&R 2008)*

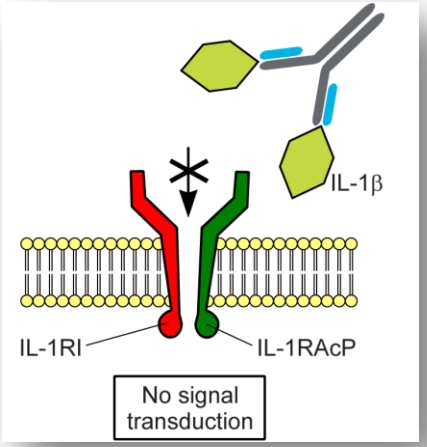
Canakinumab

- A fully human IgG1 anti-IL-1β monoclonal antibody[1]
  - Does not cross-react with IL-1α or IL-1Ra
- Binds to human IL-1β with high affinity, thus prevents IL-1β from binding to its receptor, IL-1RI
- Long plasma half-life: 21–28 days,[1,2] effective in the picomolar range
  - Administered by subcutaneous injection once every 8 weeks, 150 mg/injection in adults[3]
- Inhibits IL-1-induced joint inflammation in mouse models of arthritis[1]

Normal IL-1β signalling



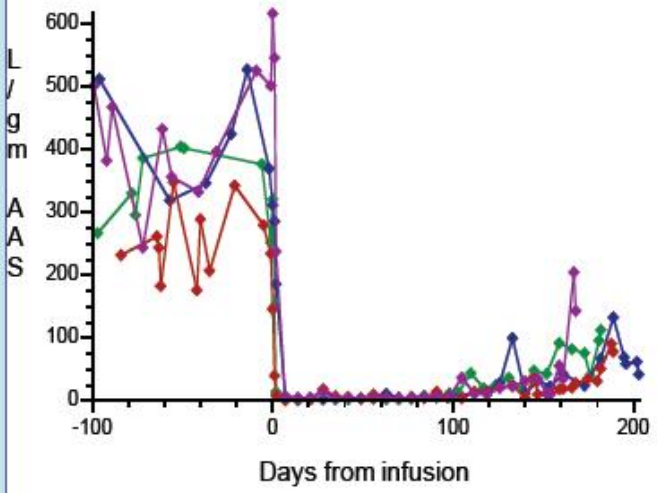
Canakinumab: binds to IL-1β



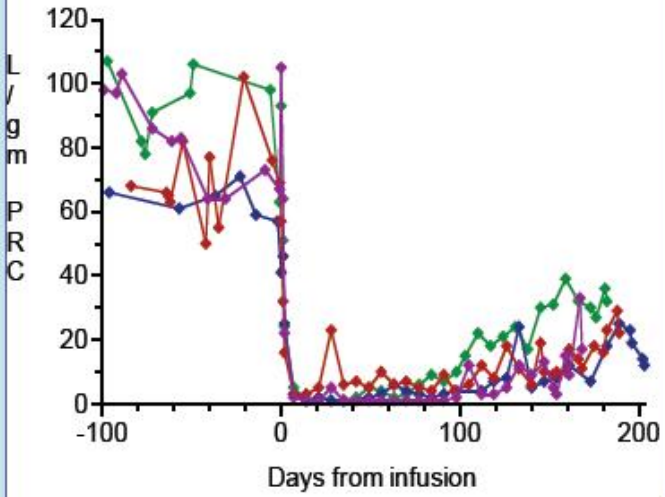
IL-1R1, IL-1 receptor;
IL-1RAcP, IL-1 receptor accessory protein

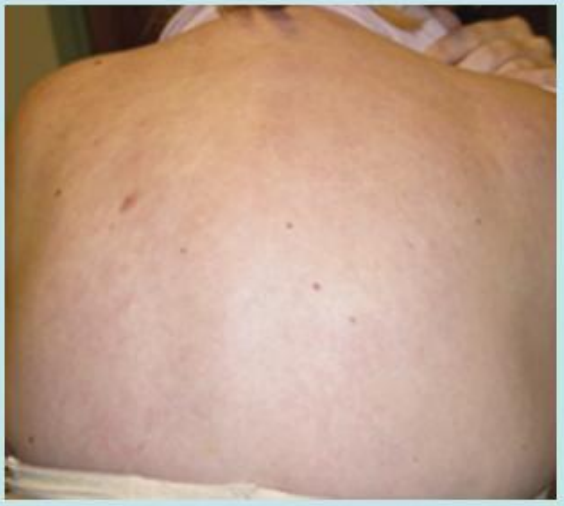
[1]Alten R *et al.* 2008; [2]Lachmann HJ *et al.* 2008; [3]Lachmann HJ *et al.* 2009

Immediately pre first treatment



ACZ885 induced a complete clinical and biochemical response in all cases

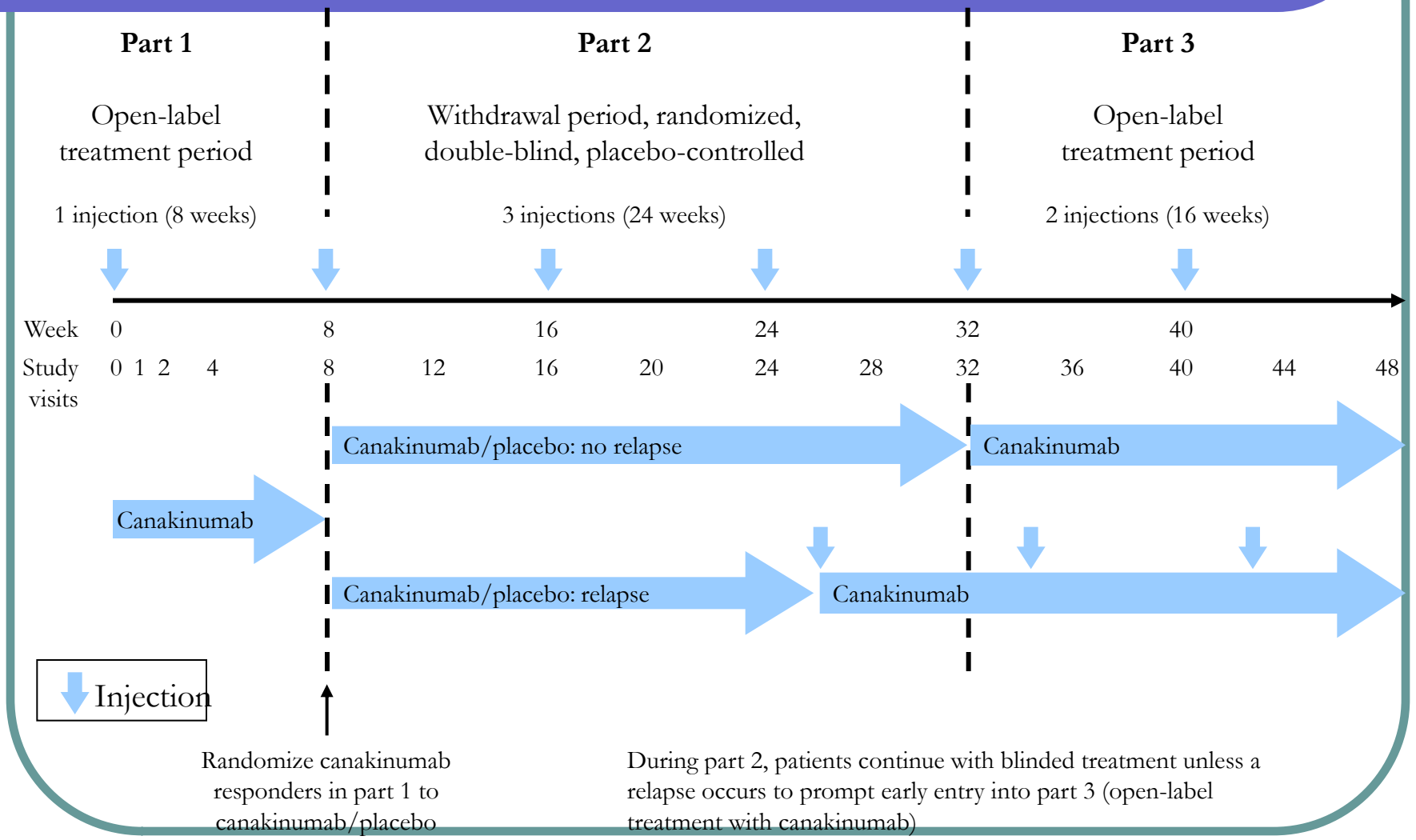




24 hours post treatment

Lachmann HJ *et al.* Personal communication, Rome 2008

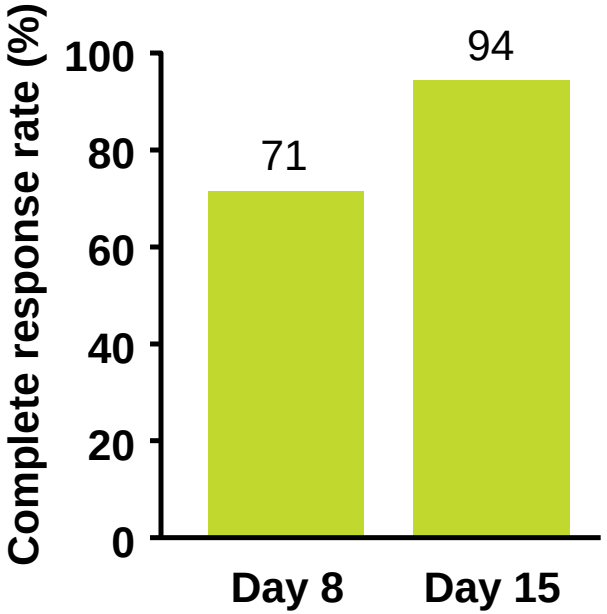
Multicentre, Randomized, Double-blind, Phase III Study



Adapted from Lachmann HJ *et al.* NEJM 2009

Complete responses following a single dose of canakinumab were achieved in 97% of patients in part 1

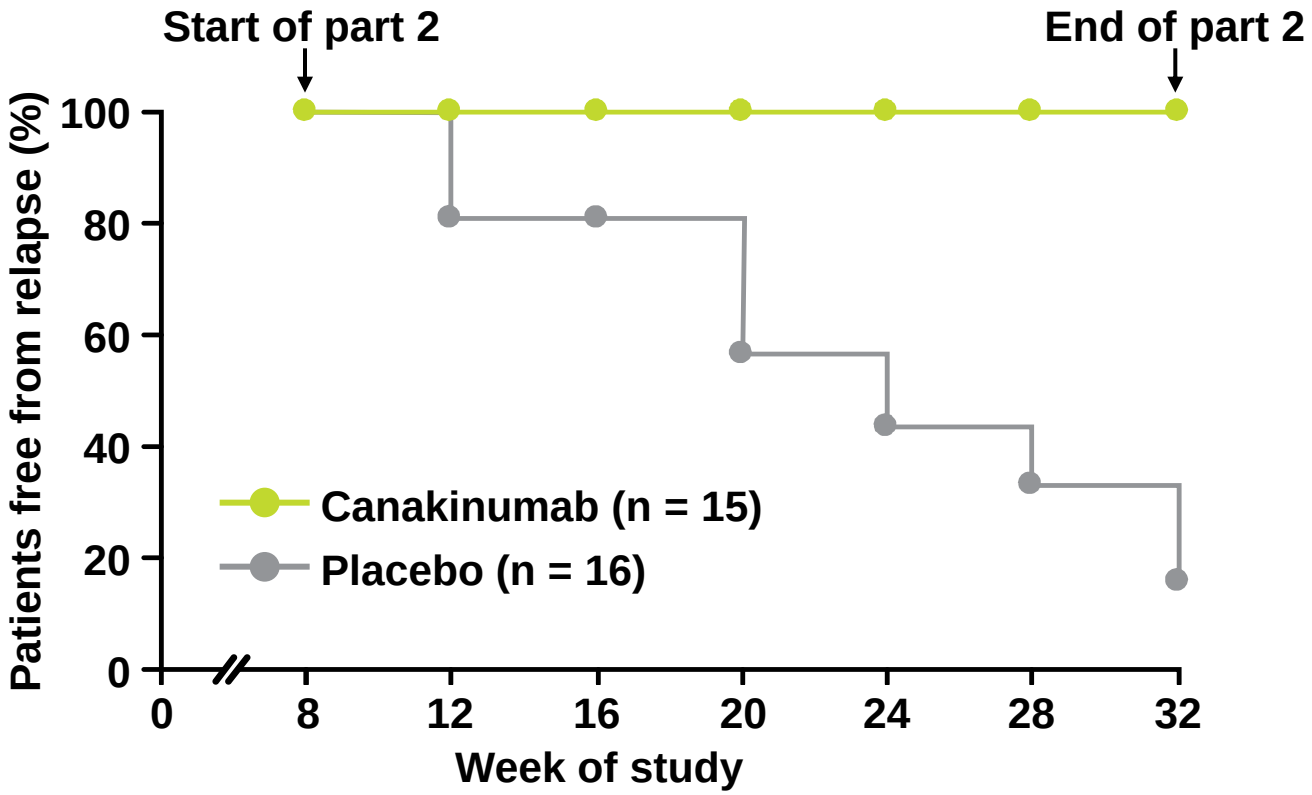
- 35 patients enrolled
- Complete responses were achieved in 34 (97%) patients
  - One patient who self-injected study medication did not achieve a complete response and had not received the full dose
- 3 patients with a complete response did not proceed to part 2



Before injection 24 h after injection

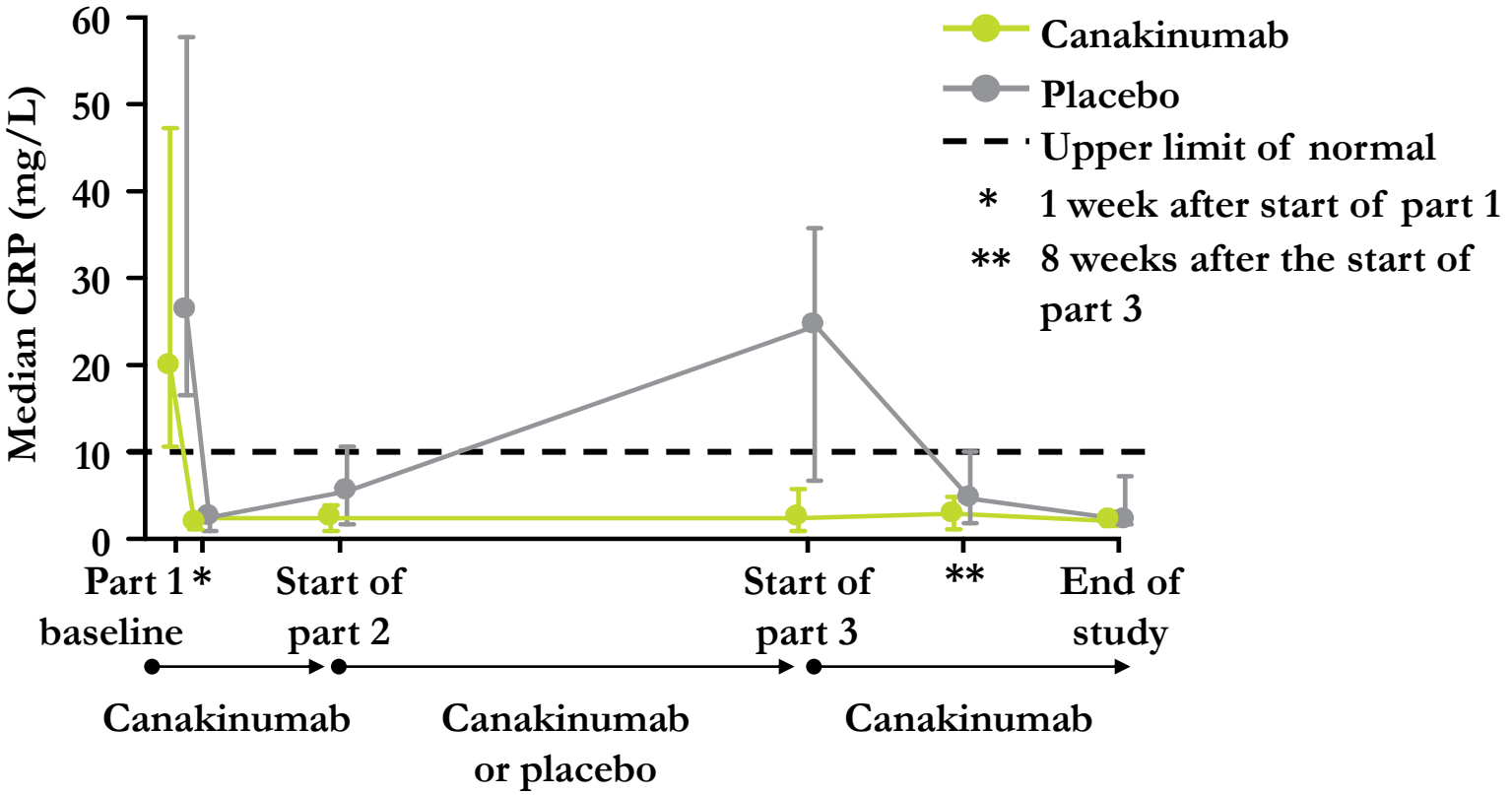
Lachmann HJ *et al.* NEJM 2009

All patients randomized to canakinumab remained in remission in part 2



Adapted from Lachmann HJ *et al.* NEJM 2009

Most patients remained in remission at the end of part 3



Adapted from Lachmann HJ *et al.* NEJM 2009

Canakinumab – safety data

Adverse events (AEs), n (%)	Part 1 (N = 35)	Part 2		Part 3 (N = 31)
		Canakinumab (N = 15) Mean duration of treatment, 169 days	Placebo (N = 16) Mean duration of treatment, 118 days	
Serious AEs	0	0	0	2 (6)*
Discontinuation due to an AE	0	0	0	1 (3)
Any AE	29 (83)	15 (100)	14 (88)	24 (77)
Severe AE	4 (11)	1 (7)	0	4 (13)
Any infectious event ‡	12 (34)	12 (80)	9 (56)	10 (32)
Suspected infectious AE	7 (20)	10 (67)†	4 (25)	5 (16)

*Two serious AEs reported in part 3 were recurrent antibiotic-resistant lower urinary tract infection and sepsis in 1 patient and vertigo and increased intraocular pressure, acute glaucoma and unilateral blindness in a second patient.

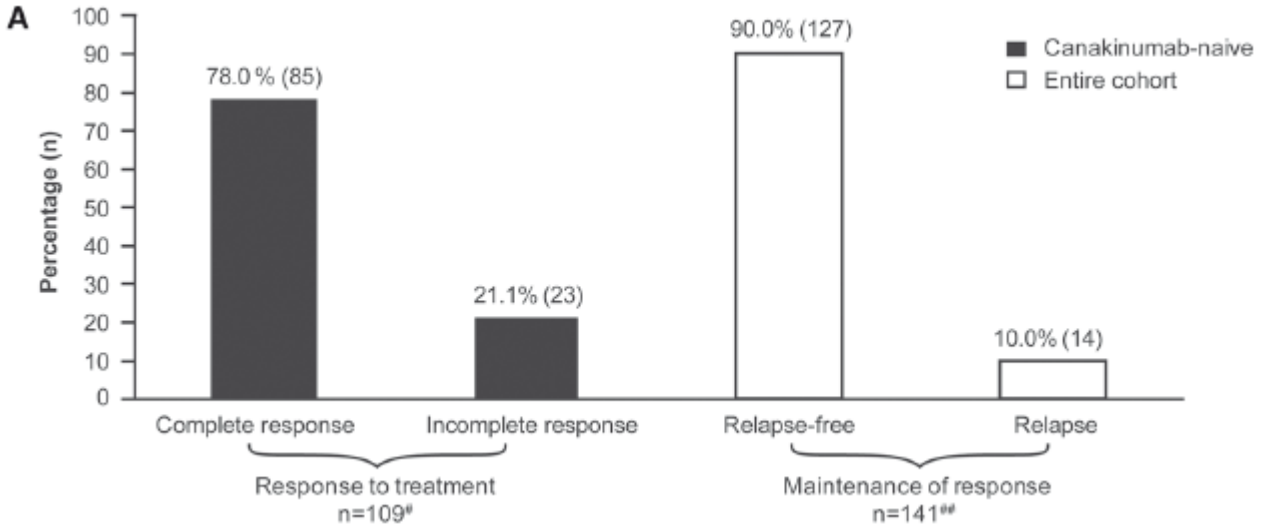
†$p = 0.03$ vs placebo in part 2.

‡As defined by MedDra® (Medical Dictionary for Regulatory Activities)

Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with CAPS across different severity phenotypes.

166 (47 pediatric) pts (30 FCAS; 103 MWS; 32 MWS/NOMID [14 NOMID]

A **complete response** (CR) was achieved in 85/109 **(78%)** canakinumab-naïve patients (80 patients achieved CR within 8 days, the others achieved CR within 21 days).



J. Kuemmerle-Deschner et al. ARD, 2011

Dose adjustments

Table 4 Increase in dose or dosing frequency by age-group and phenotype

Adjustments	Total n=166	Adult n=119	Paediatric n=47	FCAS n=30	MWS n=103	NOMID/CINCA n=32
Dose or frequency adjustments	40 (24.1)	23 (19.3)	17 (36.2)	5 (16.6)	20 (19.4)	15 (46.9)
Dose adjustments	36 (21.7)	20 (16.8)	16 (34.0)	5 (16.6)	17 (16.5)	14 (43.8)
Frequency adjustments	19† (11.4)	8 (6.7)	11 (23.4)	0	11 (10.7)	8 (25.0)

Table 3 Dose by phenotype and weight groups

Phenotype (>40 kg/≤40 kg)	Weight groups	
	>40 kg Mean dose, mg	≤40 kg* Mean dose, mg/kg
FCAS (27/3)	188.9	2.7
MWS (90/13)	199.8	5.5
NOMID/CINCA (19/13)	228.9	5.8

J. Kuemmerle-Deschner et al. ARD, 2011

Autoinflammatory diseases

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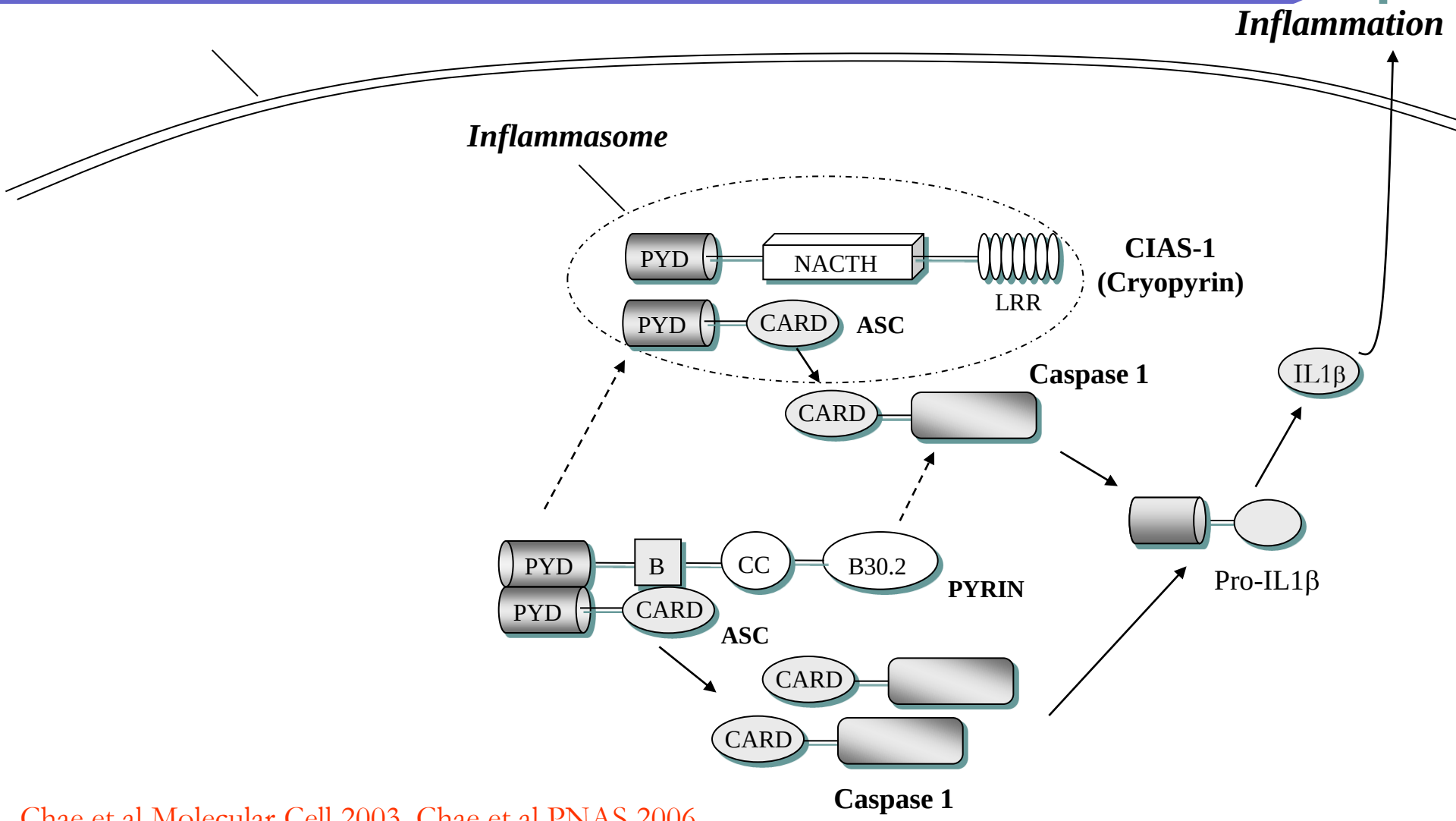
Familial Mediterranean Fever



Chae et al Molecular Cell 2003, Chae et al PNAS 2006
Fernandes-Alnemri et al Cell Death Diff 2007, Chae et al Immunity, 2011

Treatment for FMF

Colchicine:

Dose adult patients: 1.2-1.8 mg/die

Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med 1972; 287(25):1302.

Pediatric age:

< 5 years: ≤ 0.5 mg/die

6-10 years: 1 mg/die

> 10 years: 1.5 mg/die

Increase the dose of 0.25 up to the max of 2 mg

Kallinich et al Pediatrics 2007 (Consensus)

N.B. (!) Interaction with: macrolides, cimetidine, simvastatine (hepatic enzymatic system CYP3A4)

Anti-IL-1 treatment in FMF

Chae JJ et al

The B30.2 domain of pyrin, the familial

Mediterrean Fever

PNAS 2006, 27;103(26):9982-7

Roldan R et al Joint Bone Spine. 2008 Jul;75(4):504-5.

Calligaris L et al. Eur J Pediatr. 2008 Jun;167(6):695-6.

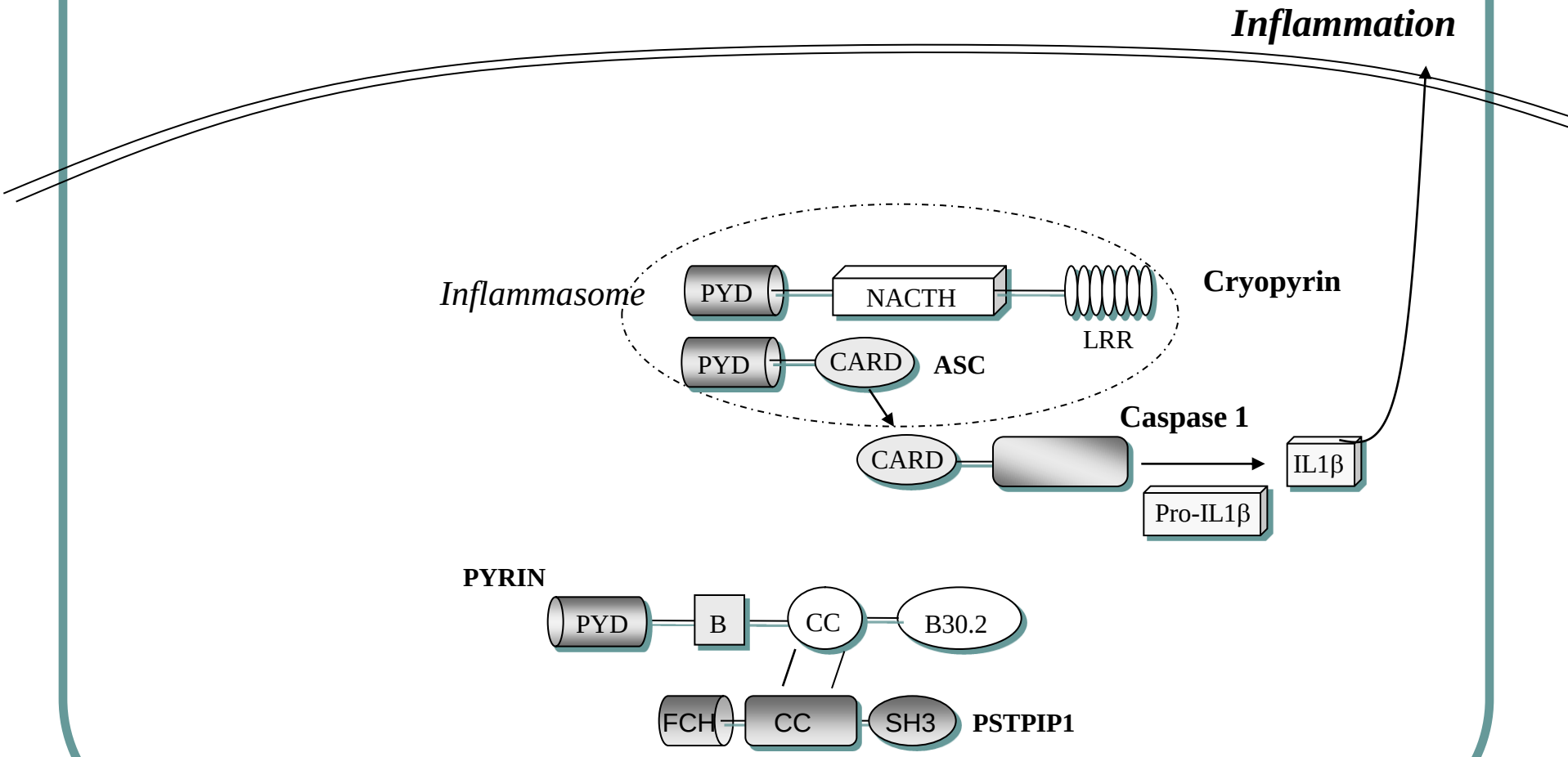
Ulrich Meinzer et al

Interleukin-1 Targeting Drugs in Familial Mediterranean Fever: A Case Series and a Review of the Literature

Semin Arthritis Rheum. 2011 Jan 28.

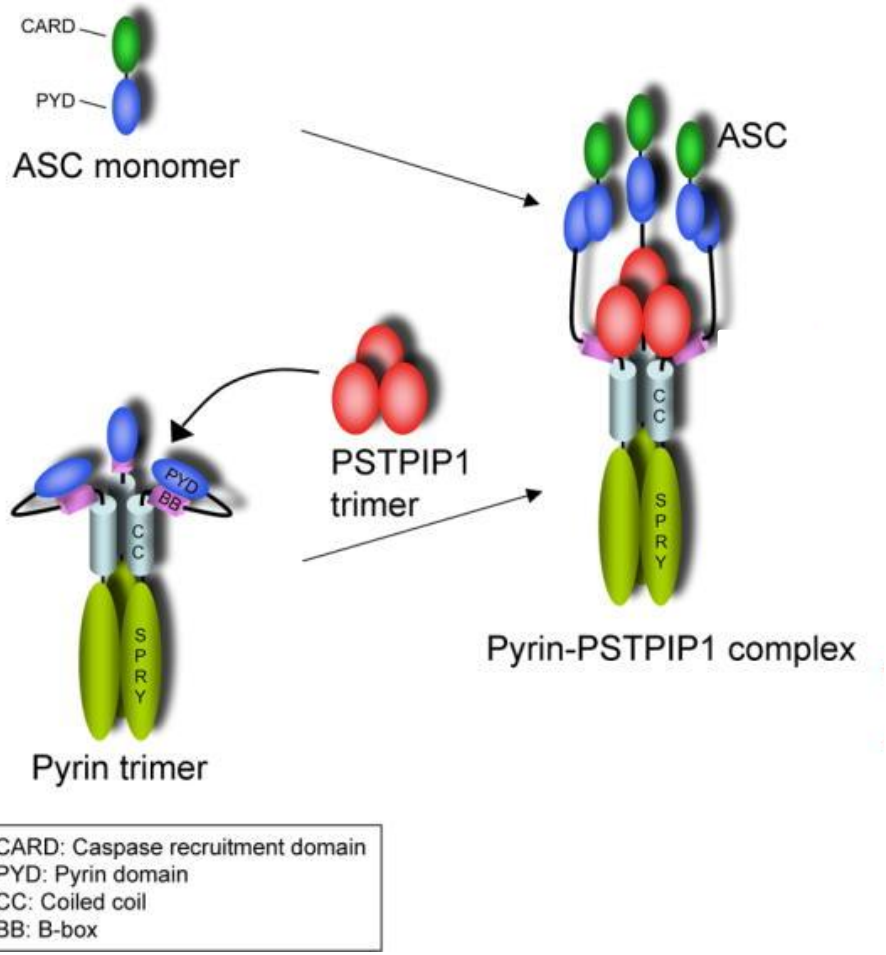
PAPA syndrome (OMIM 604416)

(Pyogenic sterile arthritis, pyoderma gangrenosum, acne)



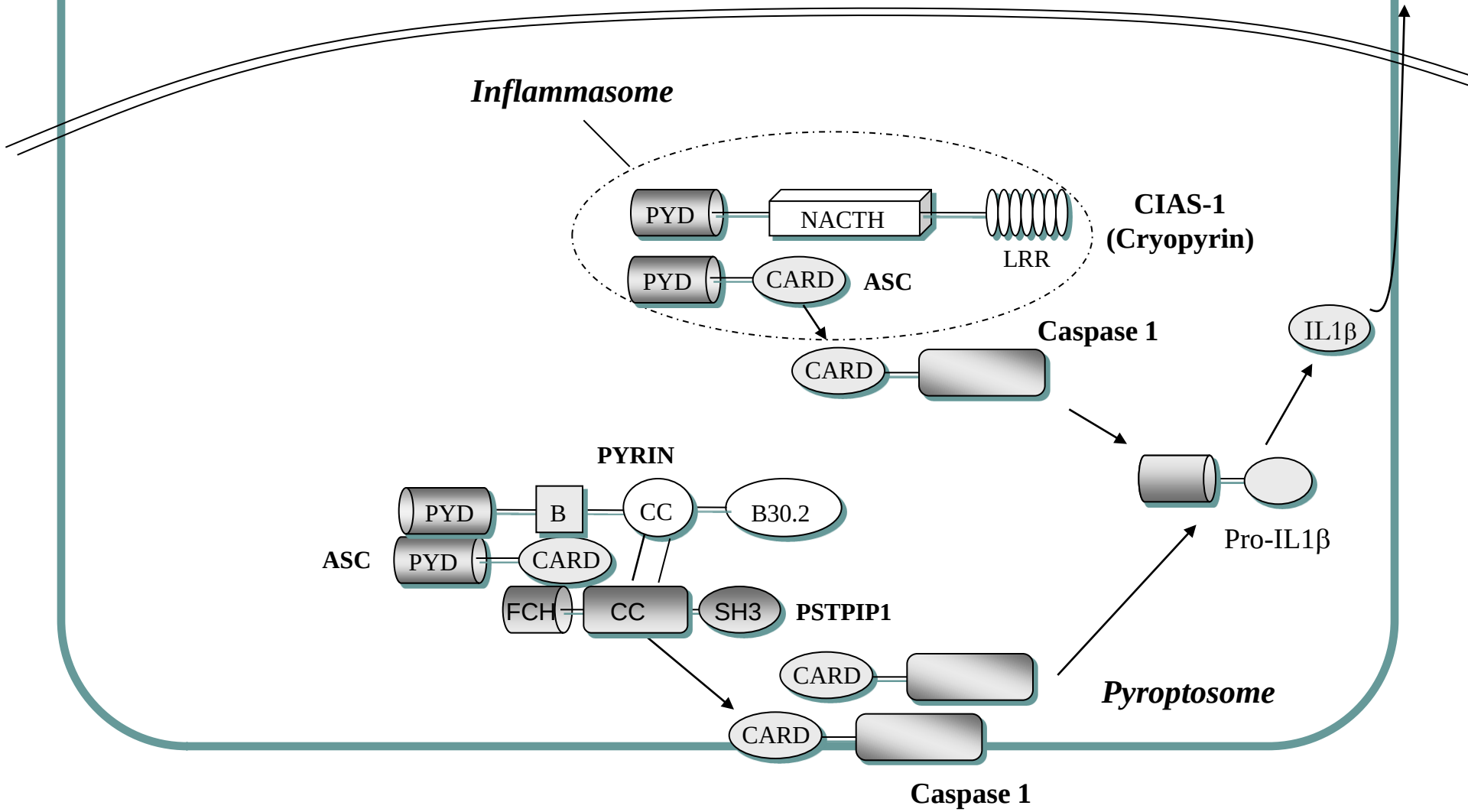
Shoham NG et al PNAS 2006

Pyrin and PSTPIP1 interact with ASC



Shoham NG et al PNAS 2006
Yu et al Mol Cell 2007

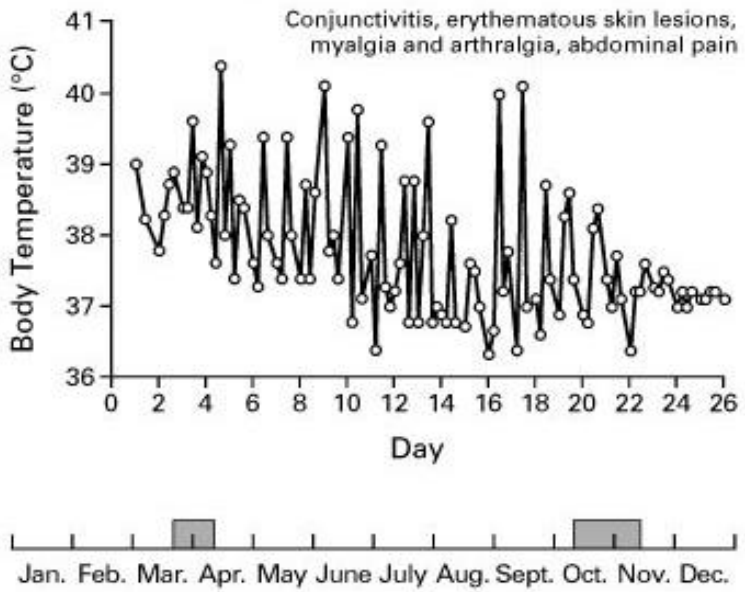
The pyroptosome



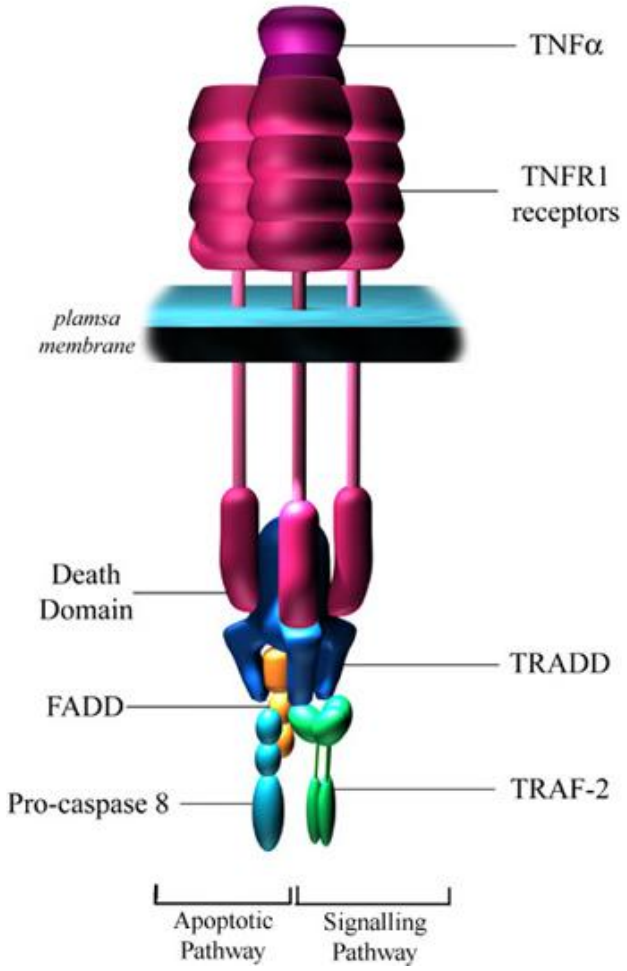
Autoinflammatory diseases

	Disease (Identification)	Gene Chromosome	Protein	Inheritance	Gene Identification
Periodic Fevers	Familial Mediterranean Fever **(1945)**	*MEVF* 16p13.3	Pyrin	AR	**1997**
	Mevalonate Kinase Deficency **(1984)**	*MVK* 12q24	Mevalonate kinase	AR	**1998**
	TRAPS **(1982)**	*TNFRSF1A* 12p13	p55 TNF receptor	AD	**1999**
NLRPs-related diseases	FCAS, MWS, CINCA **(1940, 1962, 1982)**	*NLRP3/CIAS1* 1q44	Cryopyrin	AD	**2000 2001**
	NLRP12-related periodic fever **(2008)**	*NLRP12* 14p35	NLPR12	AD	**2008**
Granulomatous disorders	Blau's syndrome **(1985)**	*CARD15/NOD2* 16q12	CARD15	AD	**2001**
Pyogenic disorders	PAPA syndrome **(1997)**	*PSTPIP1* 15q24-q25.1	PSTPIP1	AD	**2002**
	Majeed's syndrome **(1989)**	*LPIN2* 18p	LPIN2	AR	**2005**
	DIRA **(2009)**	*IL1RN* 2p22	IL1Ra	AD	**2009**

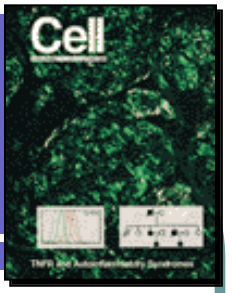
TNF receptor associated periodic syndrome (TRAPS)

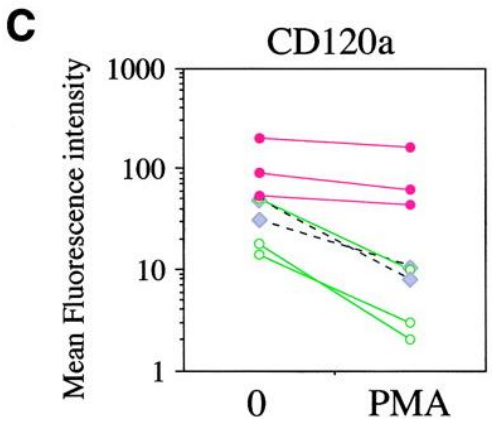


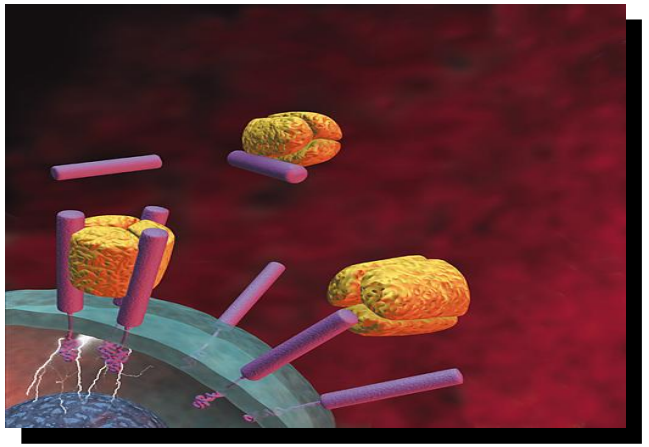
Type I TNF-receptor

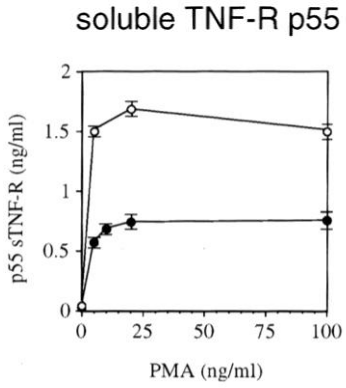


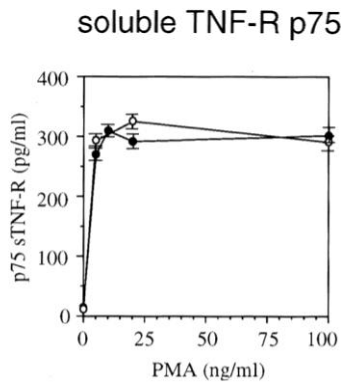
1) Defective shedding of TNF-R1







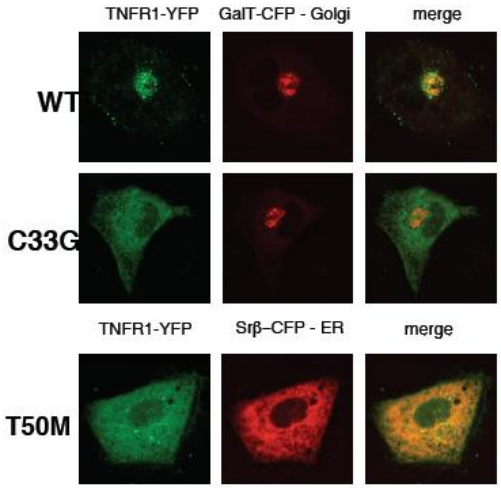




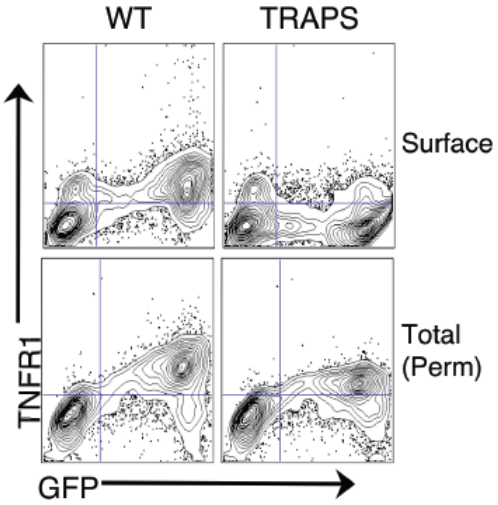
Mc Dermott, Cell, 1999

Mutated TNFR1 shows trafficking abnormalities

Transfected cells

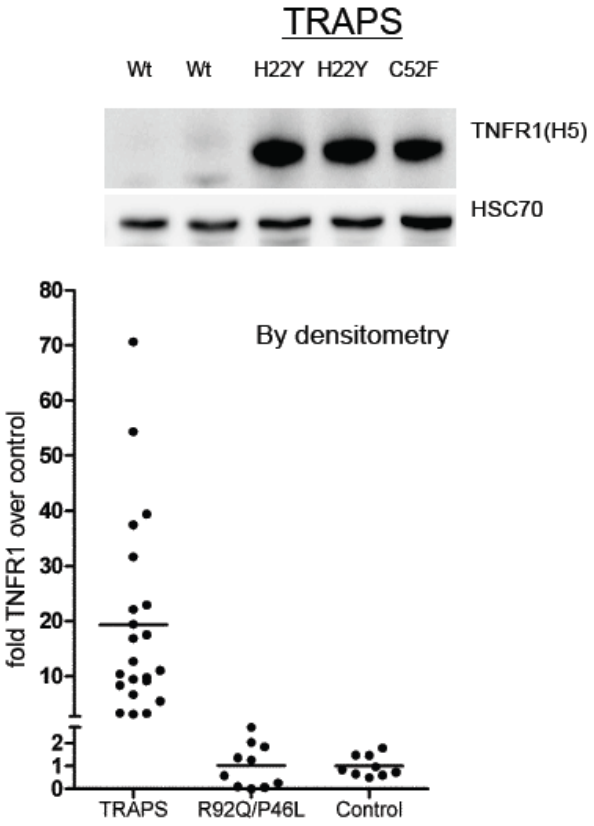


Lobito et al Blood 2006



Todd et al, Immunology 2004
Siebert et al FEBS Letters 2005

Patients



(Simon et al PNAS 2010)

Mutated TNFR1s create intracellular aggregates (aggresomes)

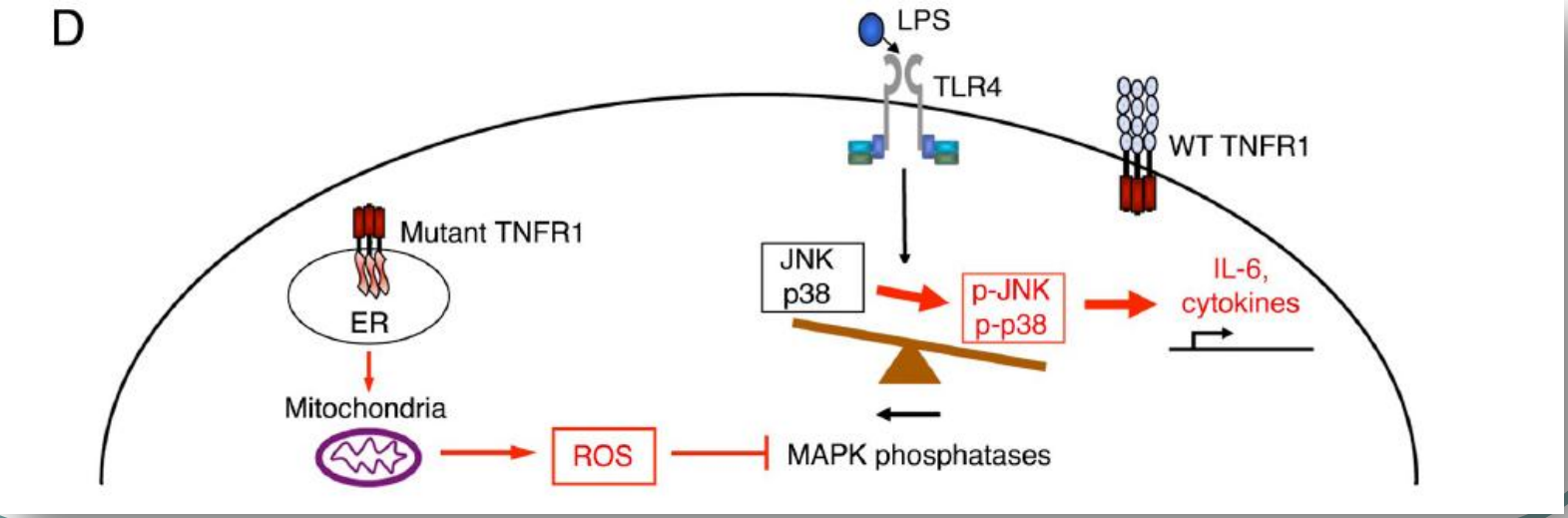
293T cells

(Bacchetti et al., in preparation)

Huggins et al. Arthritis Rheum. 2004
Todd I et al. Immunology 2004

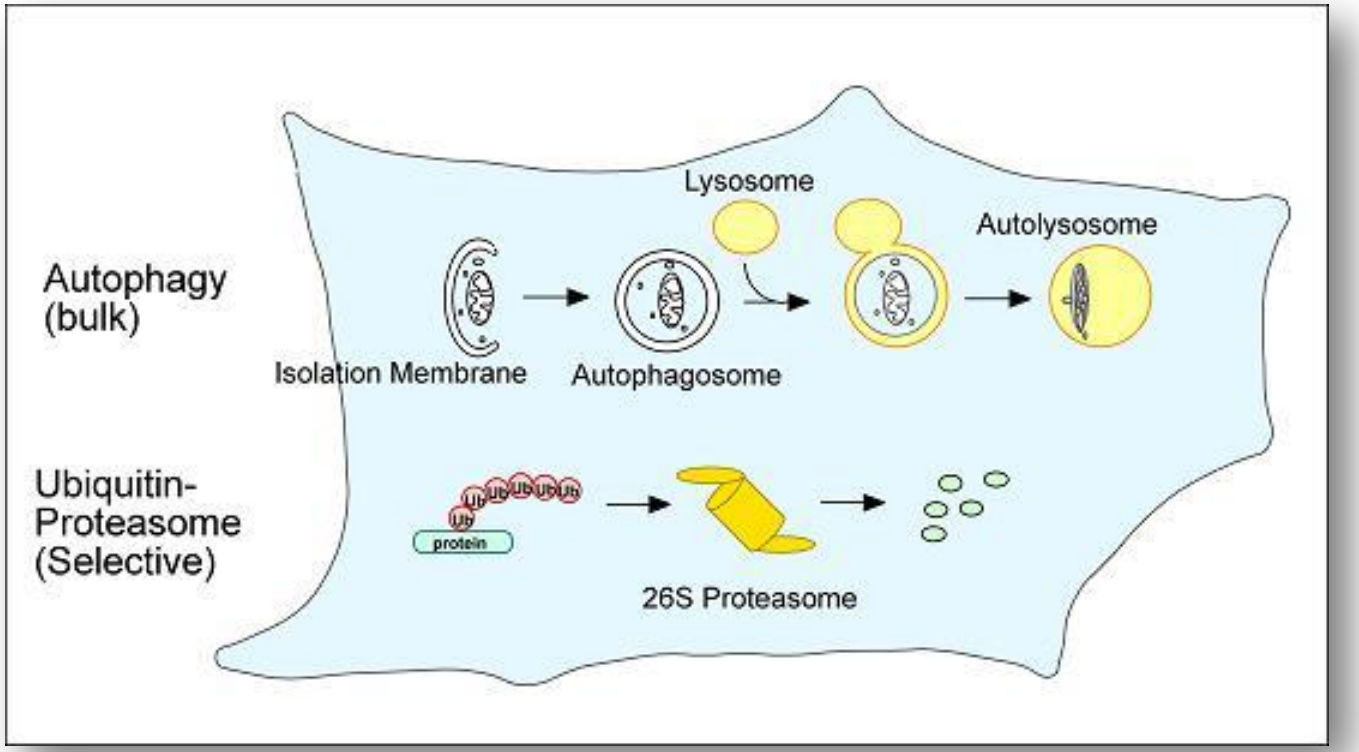
Consequences of intracellular protein misfolding?

- Increased MAPK activation by mithocondrial ROS (Simon PNAS 2010, Bulua JEM 2011).
- This activation may prime TRAPS cells to become more susceptible to low doses of inflammatory stimuli such as LPS



Bulua et al, JEM 2011

Two cellular mechanisms are related to the elimination of misfolded proteins: **the ubiquitin proteasome system** (UPS) and **autophagy**



nature Vol 456 | 13 November 2008 | doi:10.1038/nature07383

LETTERS

Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1β production

Tatsuya Saitoh[1,3]*, Naonobu Fujita[4]*, Myoung Ho Jang[2], Satoshi Uematsu[1,3], Bo-Gie Yang[1,3], Takashi Satoh[1,3], Hiroko Omori[4], Takeshi Noda[4], Naoki Yamamoto[5], Masaaki Komatsu[6,7,8], Keiji Tanaka[6], Taro Kawai[1,3], Tohru Tsujimura[9], Osamu Takeuchi[1,3], Tamotsu Yoshimori[4,10] & Shizuo Akira[1,3]

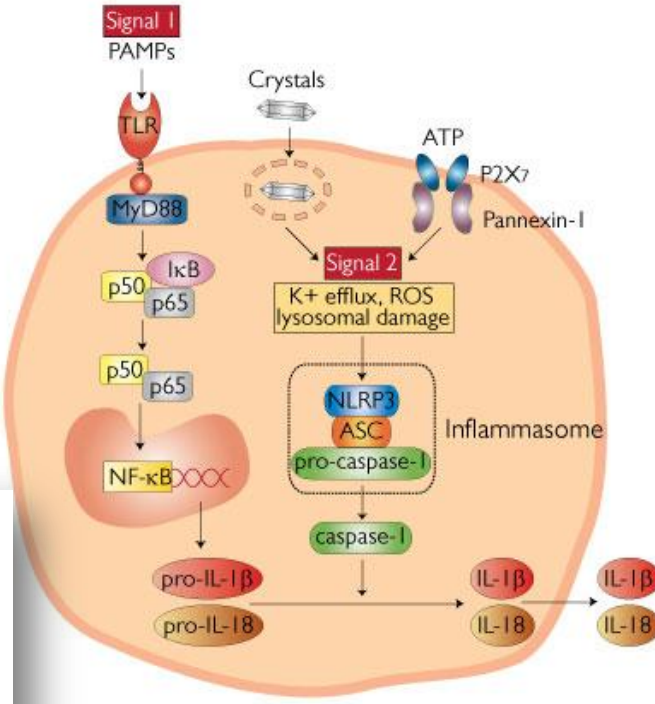
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 286, NO. 11, pp. 9587–9597, March 18, 2011

Autophagy Controls IL-1β Secretion by Targeting Pro-IL-1β for Degradation

Received for publication, November 15, 2010, and in revised form, January 5, 2011 Published, JBC Papers in Press, January 12, 2011, DOI 10.1074/jbc.M110.202911

James Harris[‡§1], Michelle Hartman[¶2], Caitrionna Roche[‡], Shijuan G. Zeng[‡], Amy O'Shea[‡], Fiona A. Sharp[‡3], Eimear M. Lambe[‡], Emma M. Creagh[‖], Douglas T. Golenbock[¶], Jurg Tschopp[**], Hardy Kornfeld[¶], Katherine A. Fitzgerald[¶], and Ed C. Lavelle[‡§4]

*From the ‡Adjuvant Research Group, §Immunology Research Centre, ‖Cytokine Research Group, School of Biochemistry and Immunology, Trinity College Dublin, College Green, Dublin 2, Ireland, the ¶Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01655, and the **Department of Biochemistry, University of Lausanne, 1066 Epalinges, Switzerland*



nature immunology

Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome

Kiichi Nakahira[1], Jeffrey Adam Haspel[1,2], Vijay A K Rathinam[3], Seon-Jin Lee[1], Tamas Dolinay[1], Hilaire C Lam[1], Joshua A Englert[1], Marlene Rabinovitch[4], Manuela Cernadas[1], Hong Pyo Kim[1,5], Katherine A Fitzgerald[3], Stefan W Ryter[1] & Augustine M K Choi[1]

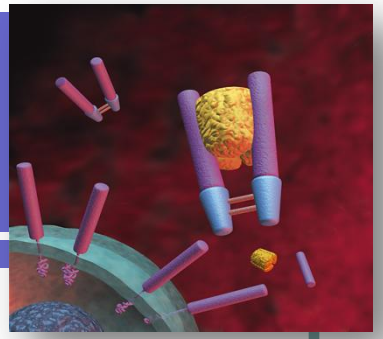
Treatment (literature)

- Efficacy of oral steroid during fever episodes
- Dose and duration?
- 1 mg/kg for 3-5 days and slow *tapering*

- Second line treatment?
- Anti-TNFR1 fusion protein: failure (Drewe et al, Rheumatol 2003)
- Lack of efficacy of colchicine and immunosuppressant (azathioprine, cyclosporine, thalidomide and cyclophosphamide)

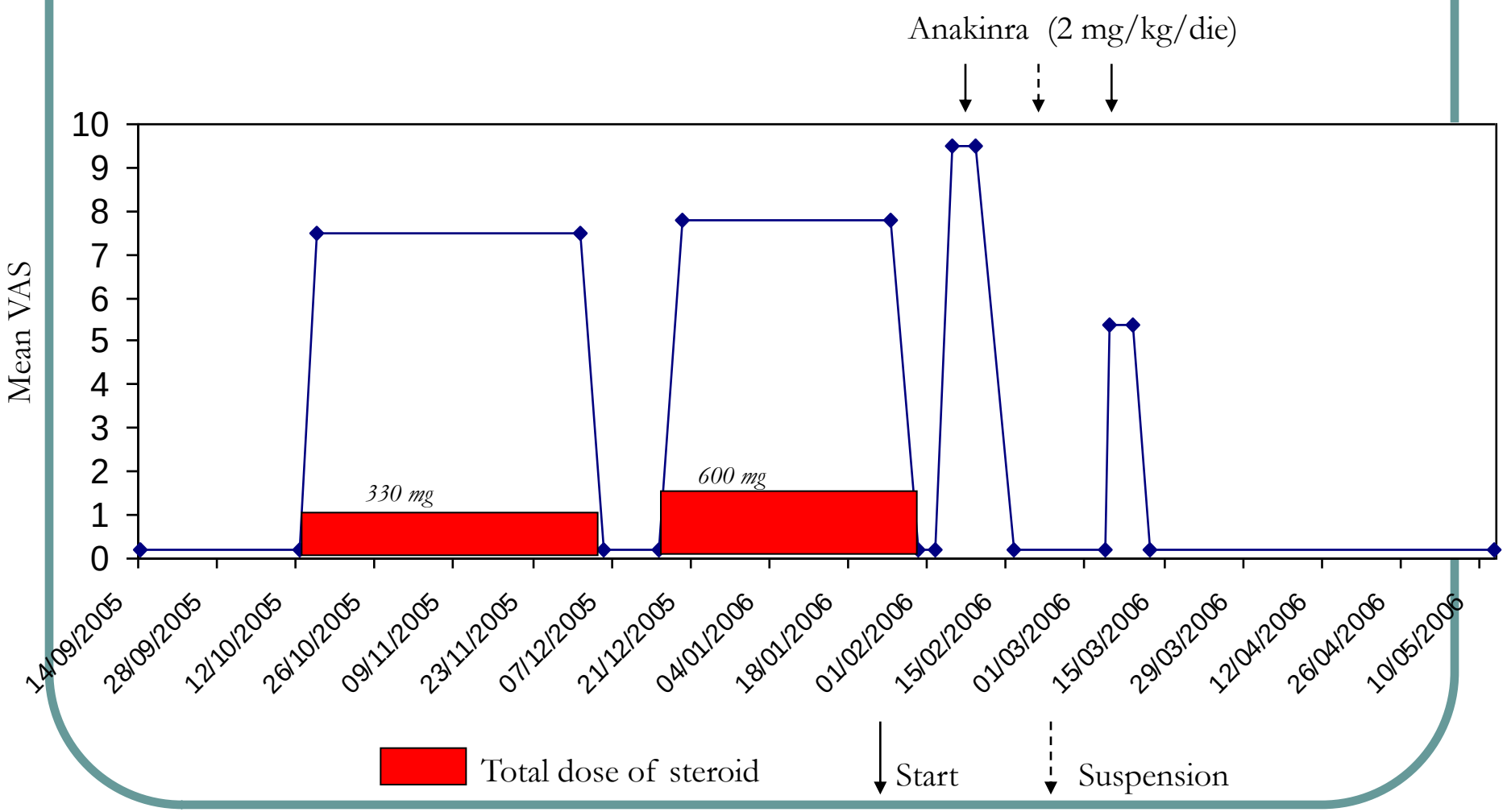
Hull KM et al. Medicine, 2002

Etanercept

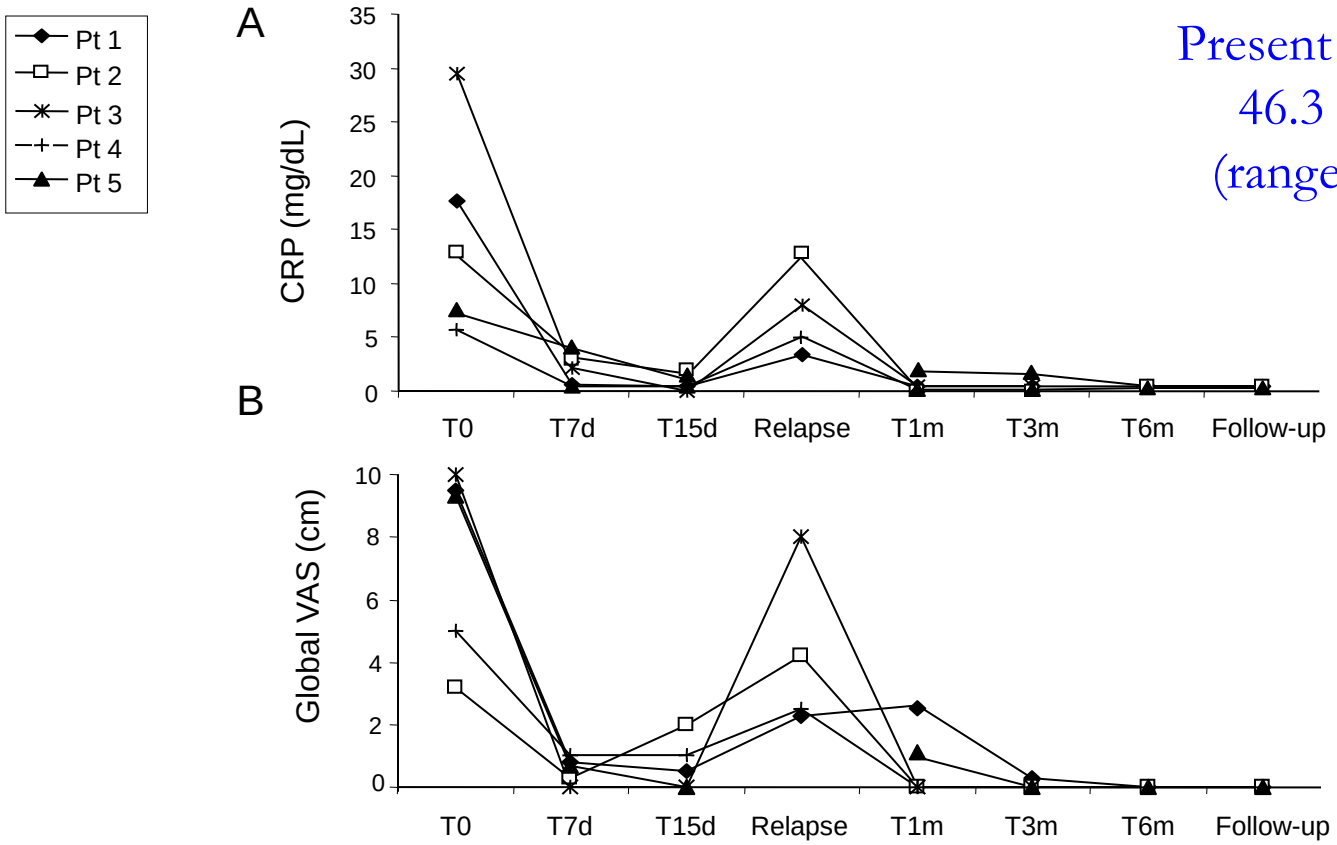


- Anecdotal reports
- Good response (duration and severity of associated symptoms)
  Simon et al, Arch Int Med, 2001
  Hull et al, Medicine, 2002
  Drewe et al. Rheumatology, 2004
- Poor or transient response
  Galon J et al, Curr Opin Immunol 2000
  Kastner D (personal communication)
  Gattorno et al A&R 2008
  Nedjai et al A&R 2009
- Worsening (infliximab)
  Jacobelli et al, Rheumatology 2005 (C306, R92Q)
  Drewe et al. Rheumatology, 2007
  Siebert et al. Rheumatology, 2008

Treatment with Anakinra in Giovanni (C55Y)



Dramatic and persistent efficacy of anti-IL1 treatment (Anakinra) in 5 TRAPS patients

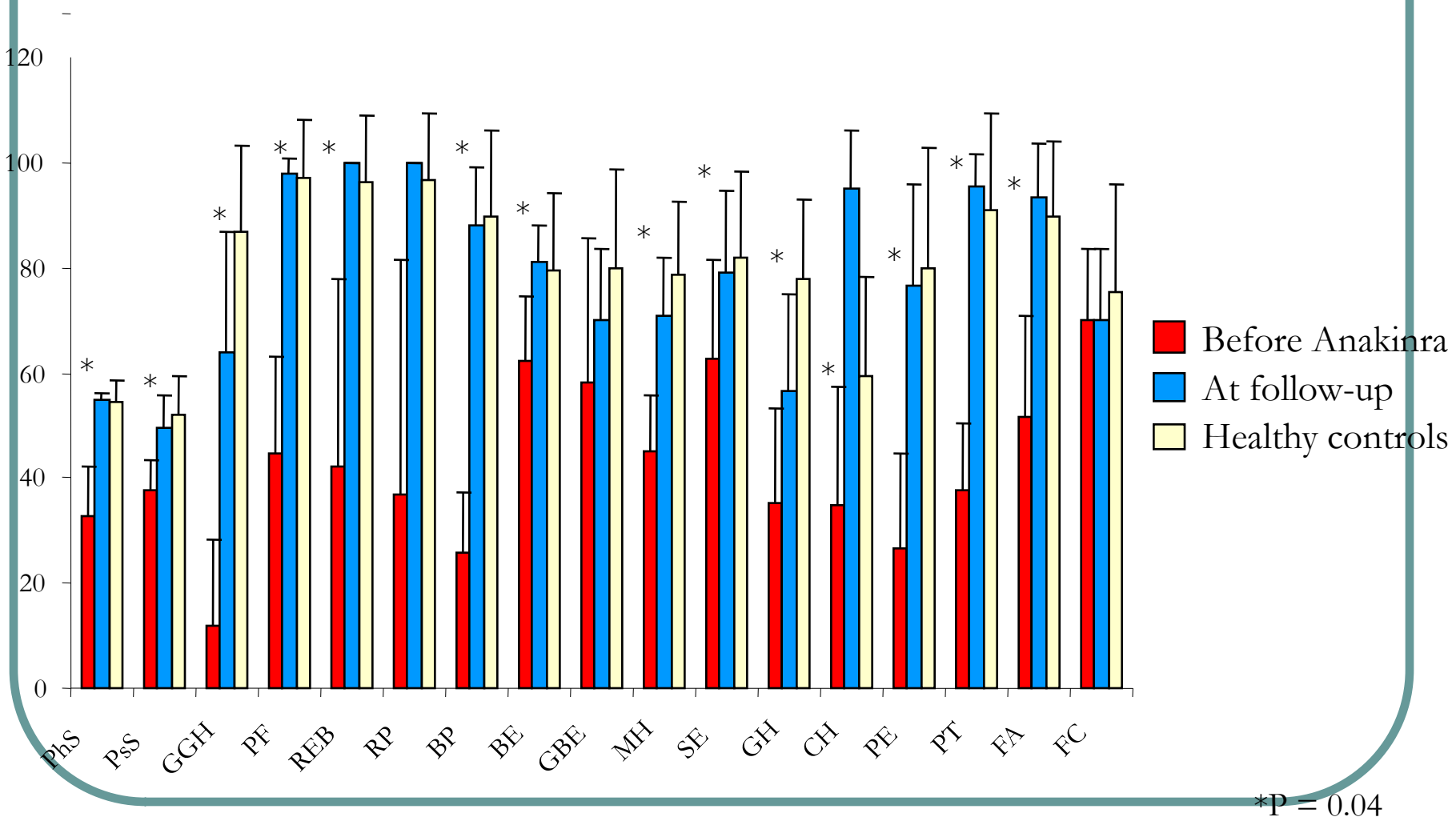


Present follow-up:
46.3 months
(range 25 – 52)

M. Gattorno et al A&R 2008

A trial with Canakinumab is ongoing

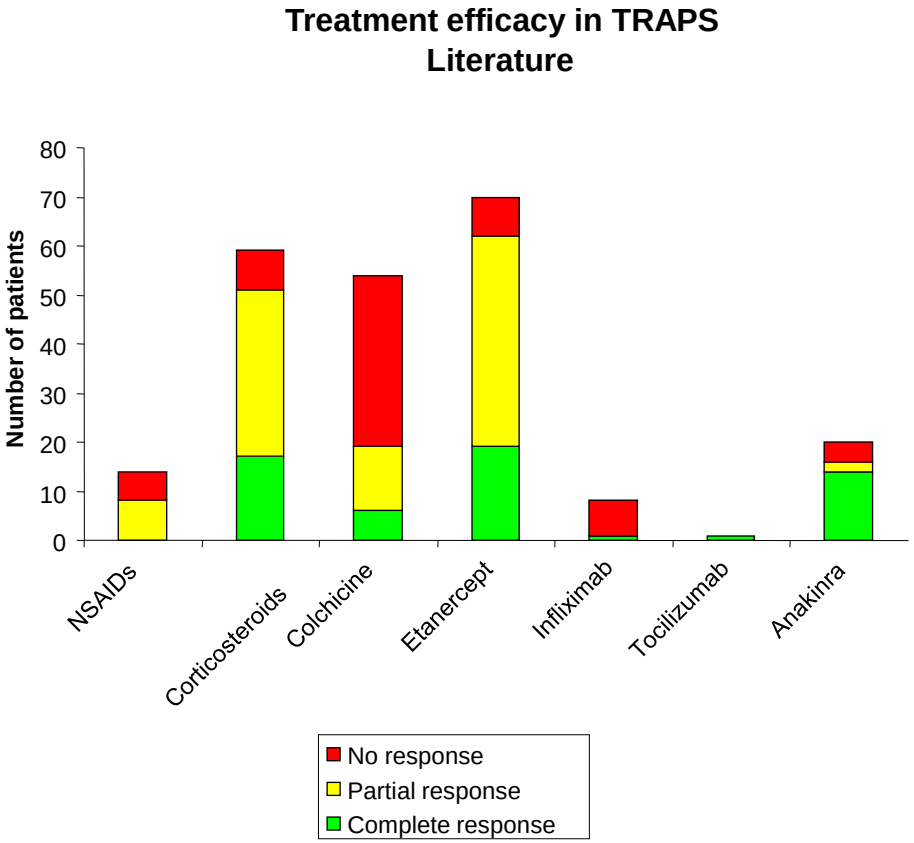
Long-term effect of Anakinra on the quality of life

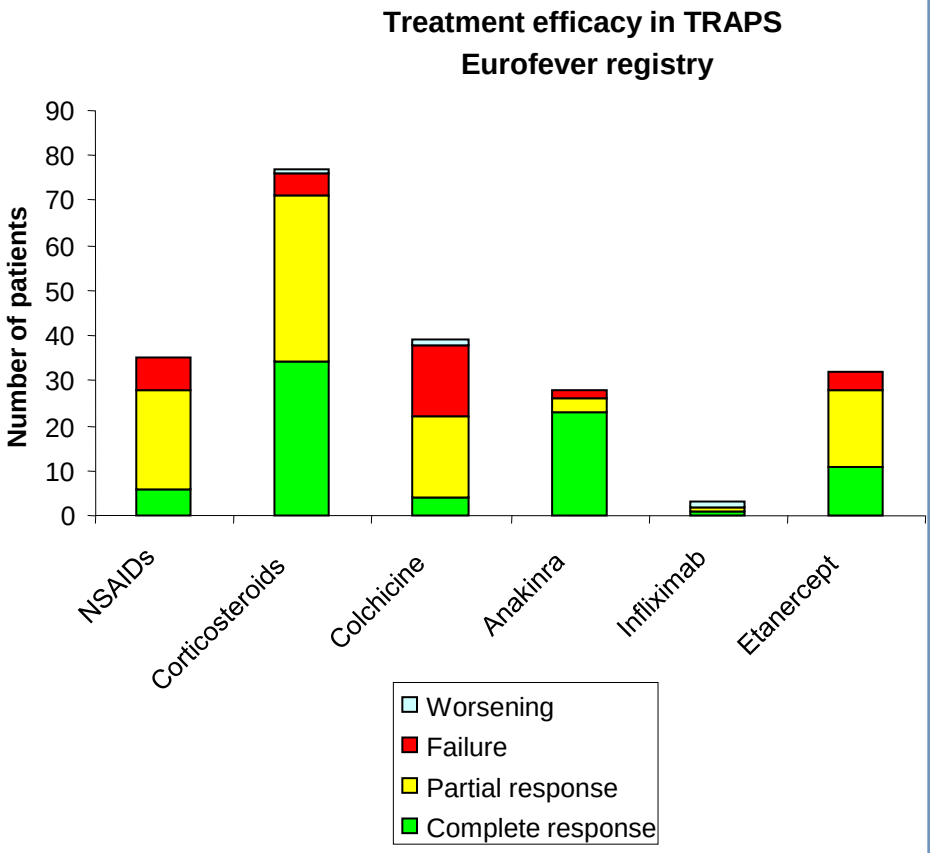


*P = 0.04

Comparison of baseline vs follow-up data by Wilcoxon test

Data from Eurofever registry





N. ter Haar, in preparation

Canakinumab trial in TRAPS (Italy, Ireland, UK)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Study 1 of 1 for search of: traps, canakinumab
Previous Study Return to Search Results Next Study

Full Text View | Tabular View | No Study Results Posted | Related Studies

Efficacy and Safety Study of ACZ885 in Patients With Active Recurrent or Chronic TNF-receptor Associated Periodic Syndrome (TRAPS)

This study is currently recruiting participants.
Verified on January 2011 by Novartis

First Received on November 16, 2010. Last Updated on June 15, 2011 History of Changes

Sponsor:	Novartis Pharmaceuticals
Information provided by:	Novartis
ClinicalTrials.gov Identifier:	NCT01242813

Purpose

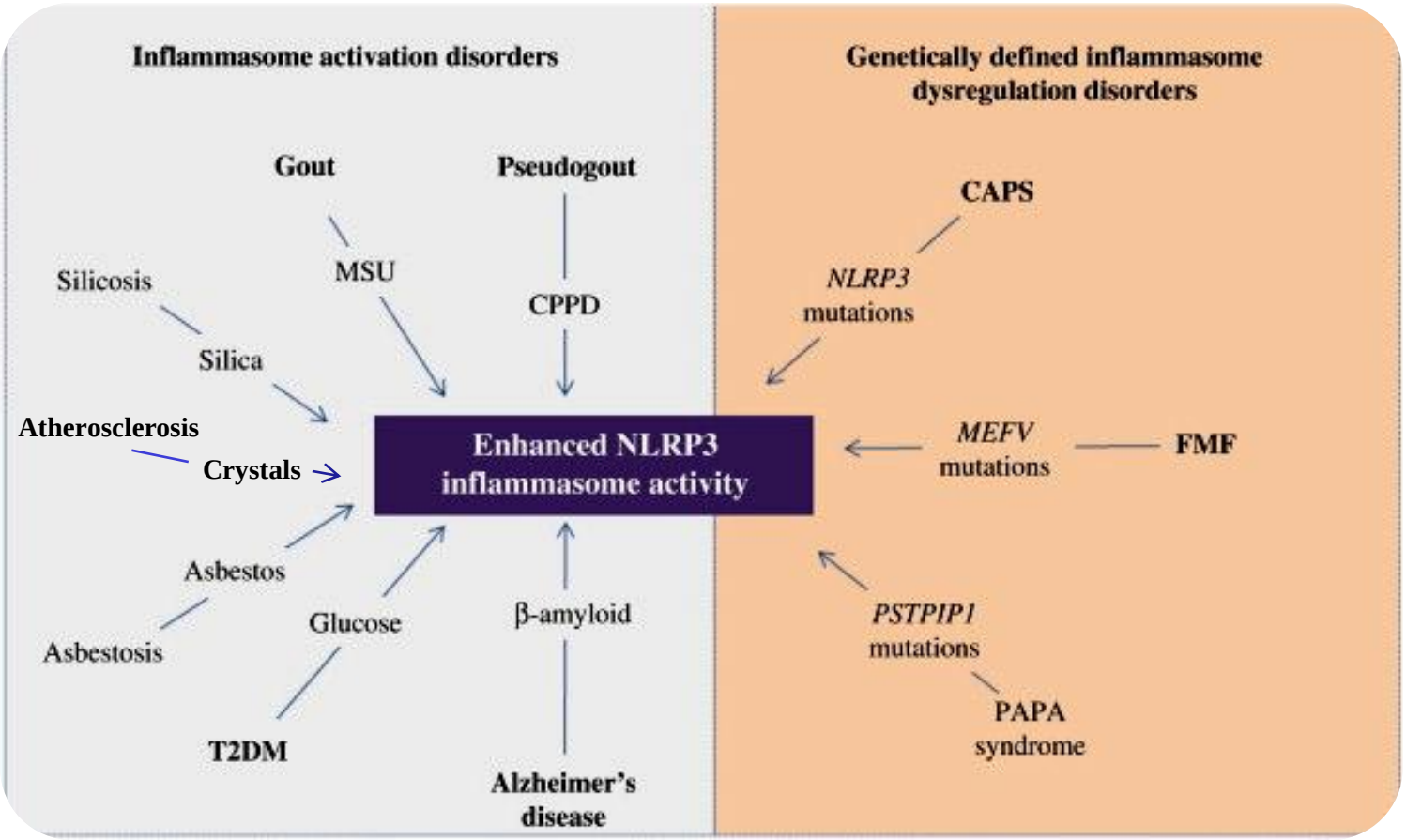
This trial will assess the safety and efficacy of **ACZ885** in patients with active recurrent or chronic **TNF-receptor associated periodic syndrome** (**TRAPS**).

Condition	Intervention	Phase
TNF-receptor Associated Periodic Syndromes (**TRAPS**)	Biological: **ACZ885**	Phase II

Study Type: Interventional
Study Design: Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-label, Multicenter, Efficacy and Safety Study of 4-month **Canakinumab** Treatment With 6-month Follow-up in Patients With Active Recurrent or Chronic **TNF-receptor Associated Periodic Syndrome** (**TRAPS**)

The Inflammasome-revolution!



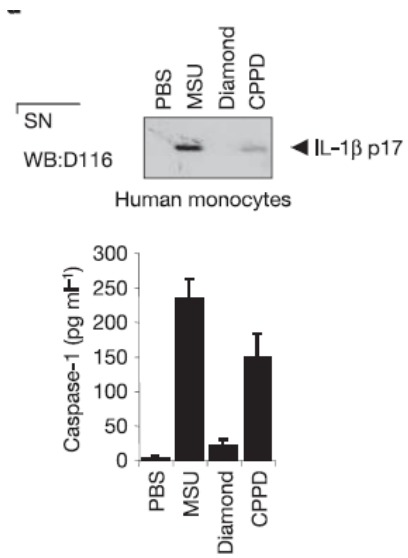
Gout

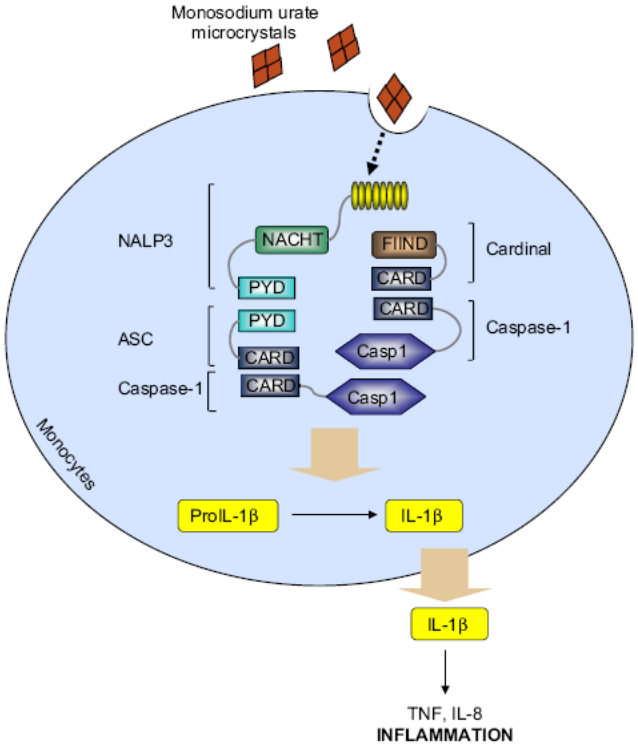
Vol 440|9 March 2006|doi:10.1038/nature04516 nature

LETTERS

Gout-associated uric acid crystals activate the NALP3 inflammasome

Fabio Martinon[1], Virginie Pétrilli[1], Annick Mayor[1], Aubry Tardivel[1] & Jürg Tschopp[1]





From Petrilli & Martinon, 2007

Canakinumab is effective (A. So et al, A&R 62: 3064-76, 2010)

Anti IL-1 responding diseases

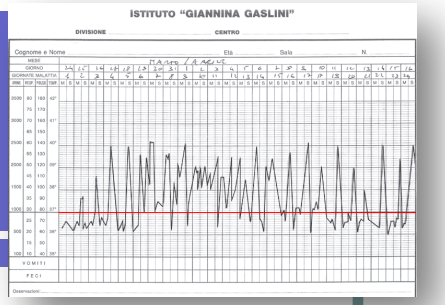
Multifactorial

- Rheumatoid Arthritis
- Systemic-onset JIA
- Adult-onset Still's disease
- Schnitzler's syndrome
- Gout
- Sweet syndrome
- Recurrent Pericarditis

Monogenic autoinflammatory diseases

- FCAS, Muckle-Wells, CINCA (*NALP3*)
- FMF (*MEFV*)
- HyperIgD (*MVK*)
- Blau's syndrome (*NOD2/CARD15*)
- TRAPS (*TNFRSF1A*)
- PAPA syndrome (*PSTPIP1*)
- *Deficency of IL-1 receptor antagonist* DIRA (*ILR1N*)
- NALP12-mediated periodic syndrome

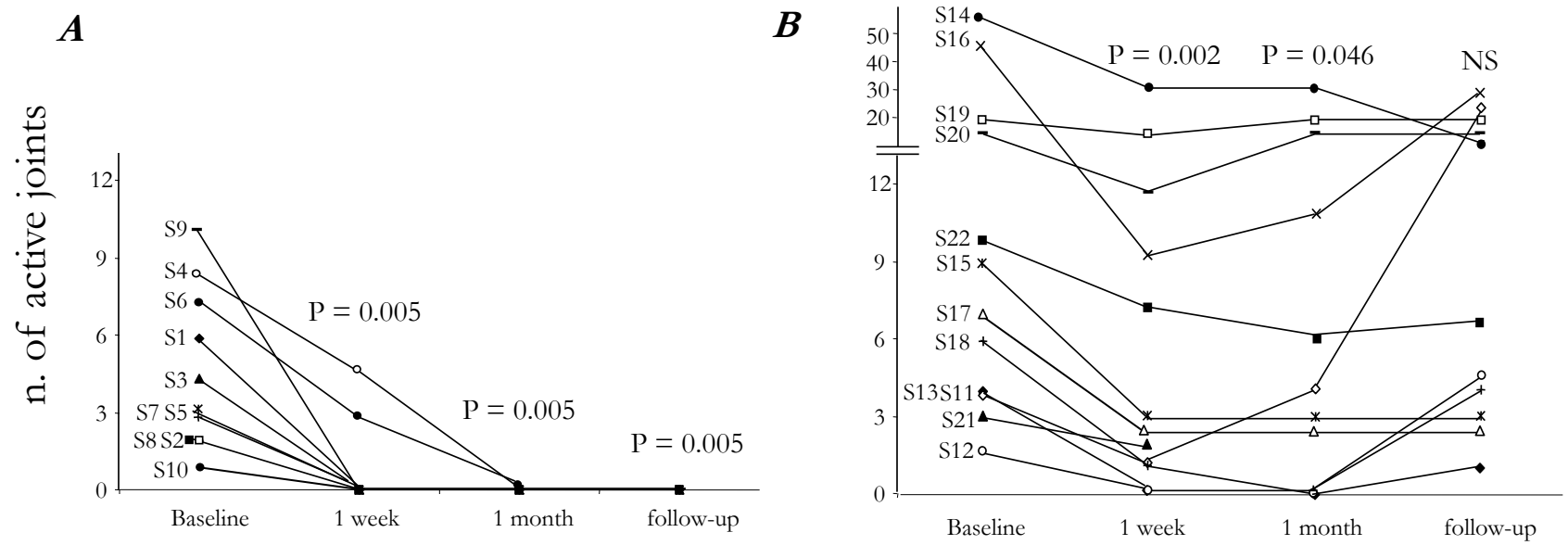
Systemic onset JIA



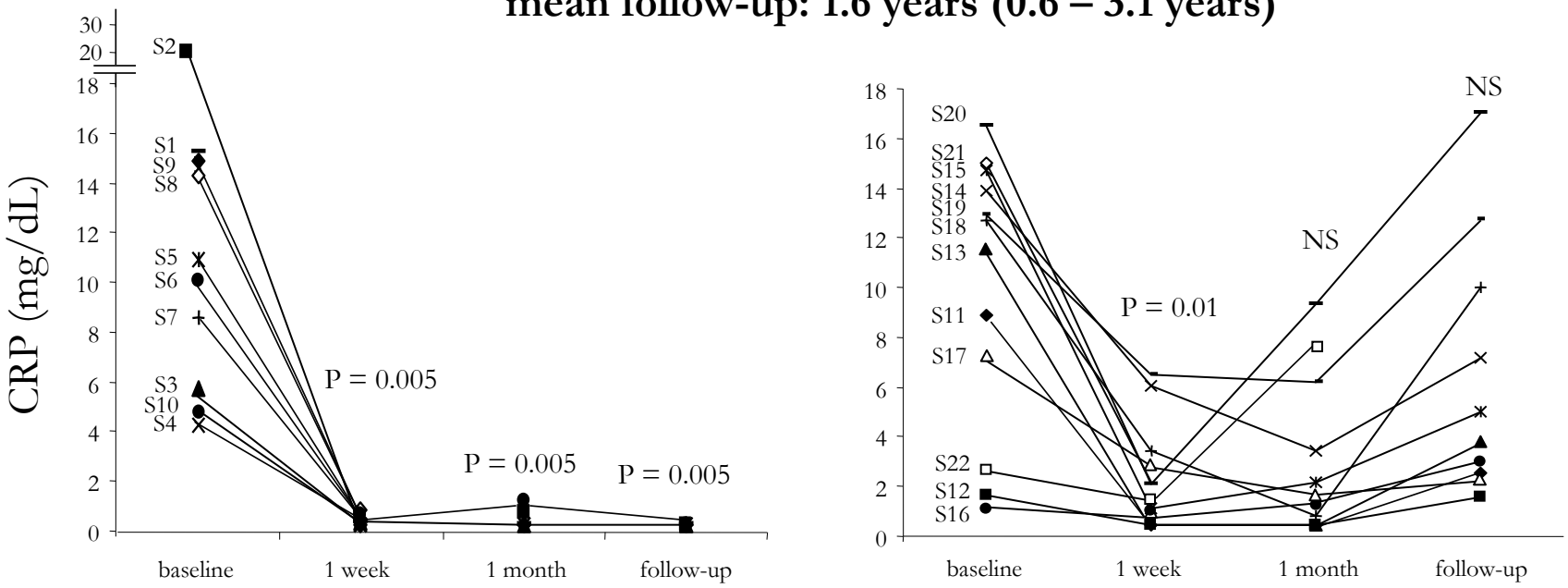
- Intermittent fever
- Rash during fever's spikes
- Hepato-splenomegaly
- Arthritis

Complete responders (n =10)

Incomplete or non-responders (N = 12)



mean follow-up: 1.6 years (0.6 – 3.1 years)



M Gattorno Arthritis Rheum. 2008;58(5):1505

SoJIA Canakinumab study (N=23)

Variables	All patients (Mean SD)
Age (years)	9.5 4.2
Gender	12 males, 11 females
MD DA global (mm) (n=22)	70.6 21.6
No. Active joints (n=22)	20.9 15.4
No. joints with LOM (n=22)	24.6 16.0
Patient DA global (mm) (n=22)	68.9 20.5
CHAQ	2.1 0.7
CRP mg/L (n=22)	133 69
Fever	Yes
Prednisolone Equivalent dose (mg/kg) (n=18)	0.34 0.18

Ruperto et al ACR Meeting 2010

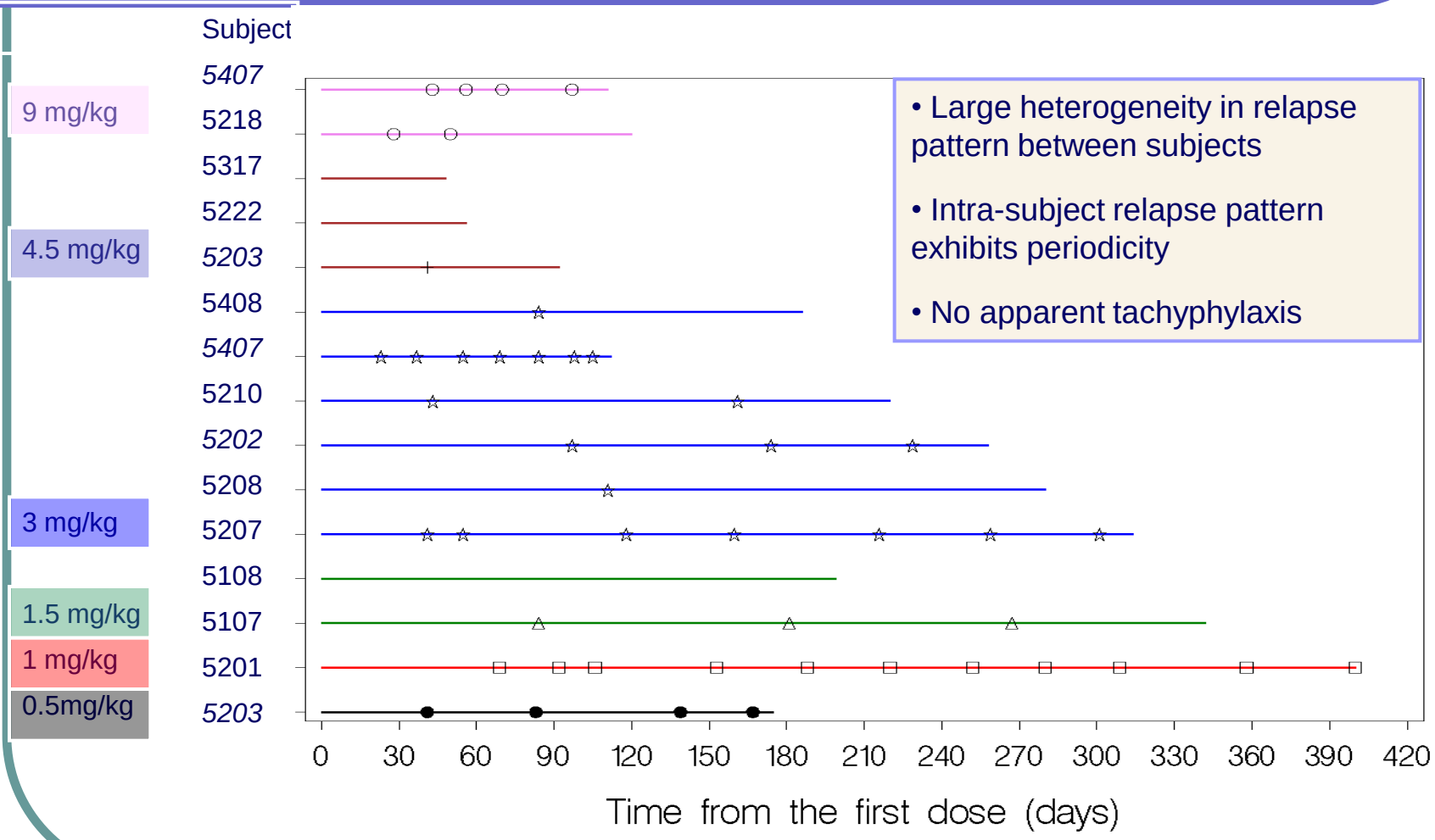
Efficacy results for responders

- **13/22* (59%)** patients showed a substantial clinical benefit at Day 15 (ACR50)
  - **4/22 (18%)** responder patients achieved inactive disease status at Day 15
- 9/22 (41%) did not respond

*One patient was excluded from the efficacy analysis (received bolus steroid for adverse events, jeopardizing response assessment)

Ruperto et al ACR Meeting 2010

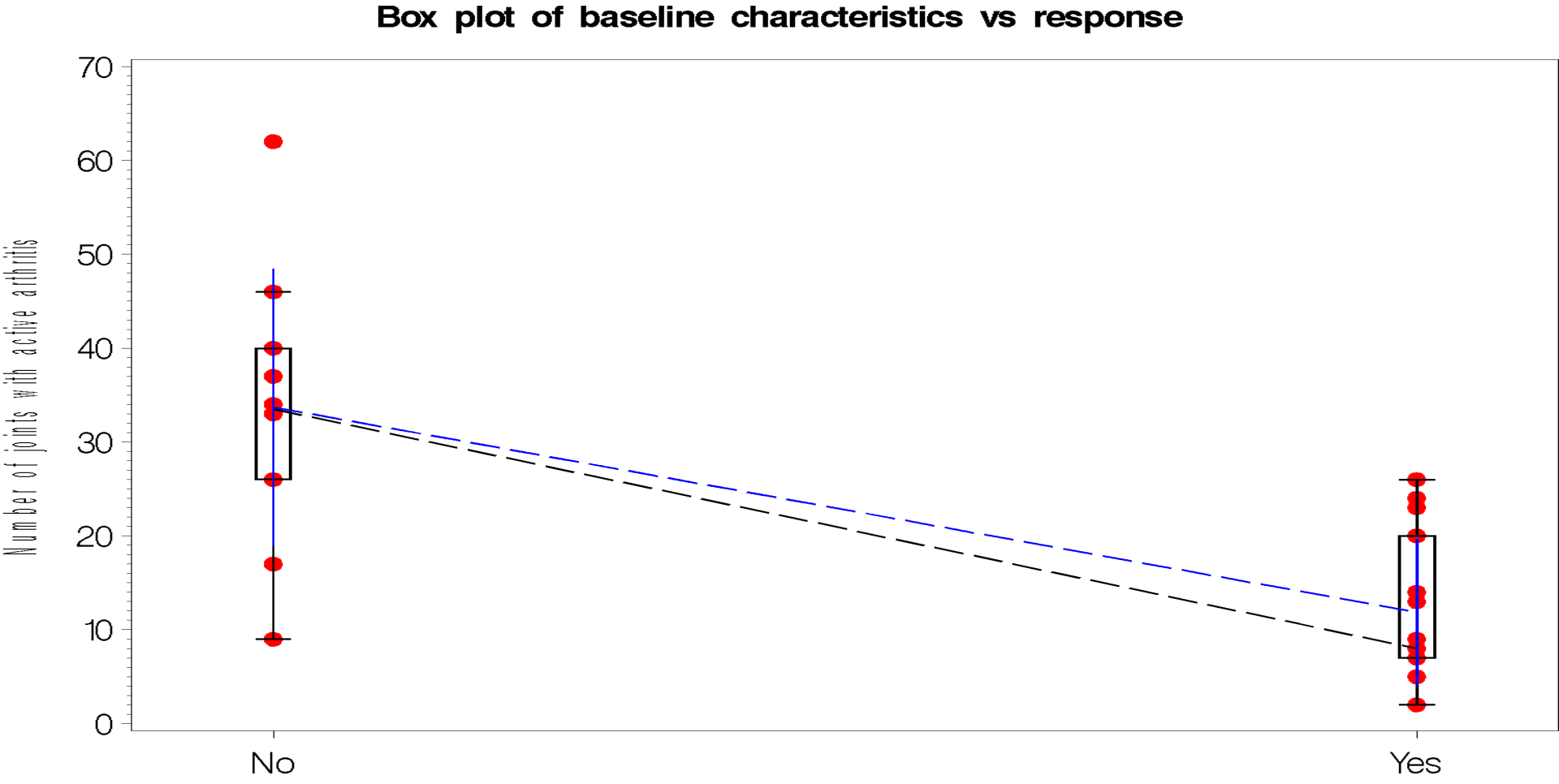
Canakinumab time to flare in SoJIA



- Large heterogeneity in relapse pattern between subjects
- Intra-subject relapse pattern exhibits periodicity
- No apparent tachyphylaxis

Ruperto et al ACR Meeting 2010

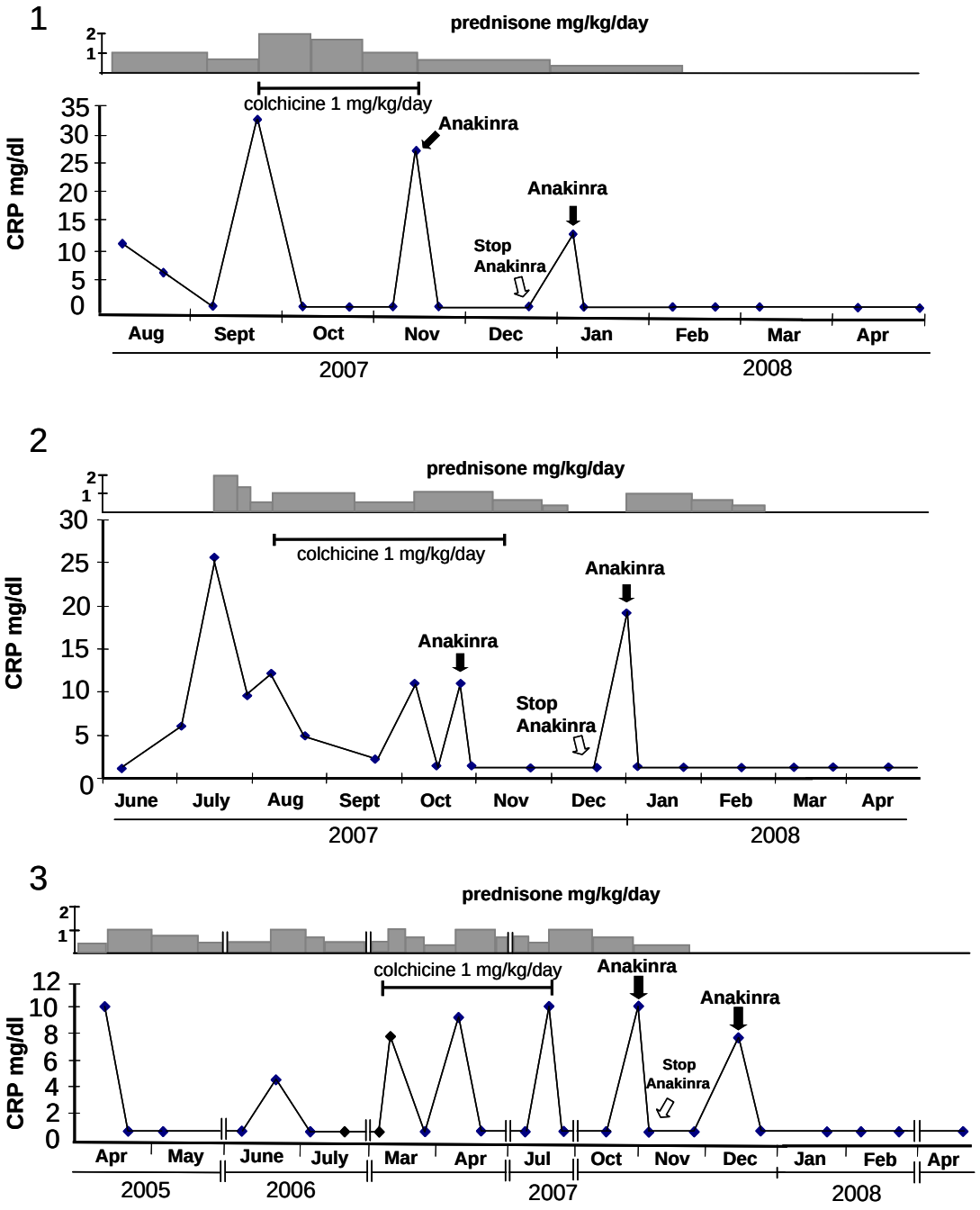
Number of active joints: best predictor of response



Recurrent pericarditis

3 patients
Colchicine-resistant
Steroid-dependent

Anakinra (1.5 mg/kg)



P. Picco et al, A&R 2009

Conclusions

- IL-1 blockade is the treatment of choice for CAPS
- Autoinflammatory diseases as experiments in nature to analyze some key points in the regulation of IL-1β in the inflammatory response
- Growing number of multifactorial diseases responding to anti-IL-1 treatment
- Few information on other Autoinflammatory diseases (need for a large network)

Open questions

- Early recognition still to improve
- Availability of the IL-1 blockers (high cost!)
- Effects on hearing loss and neurological involvement
- No effect on bone dysplasia
- Efficacy and safety on the long run
- Cost effectiveness (health economics)

Thank you…!

The Eurofever Project

pediatric
rheumatology
european
society

Autoinflammatory Diseases' Working Party

Executive Agency for Health and Consumers

EURO FEVER

The PRES network for Autoinflammatory diseases in childhood "EuroFever"

(Grant. N. 2007332 Public Health Program 2007)

www.printo.it/eurofever

The Eurofever Registry

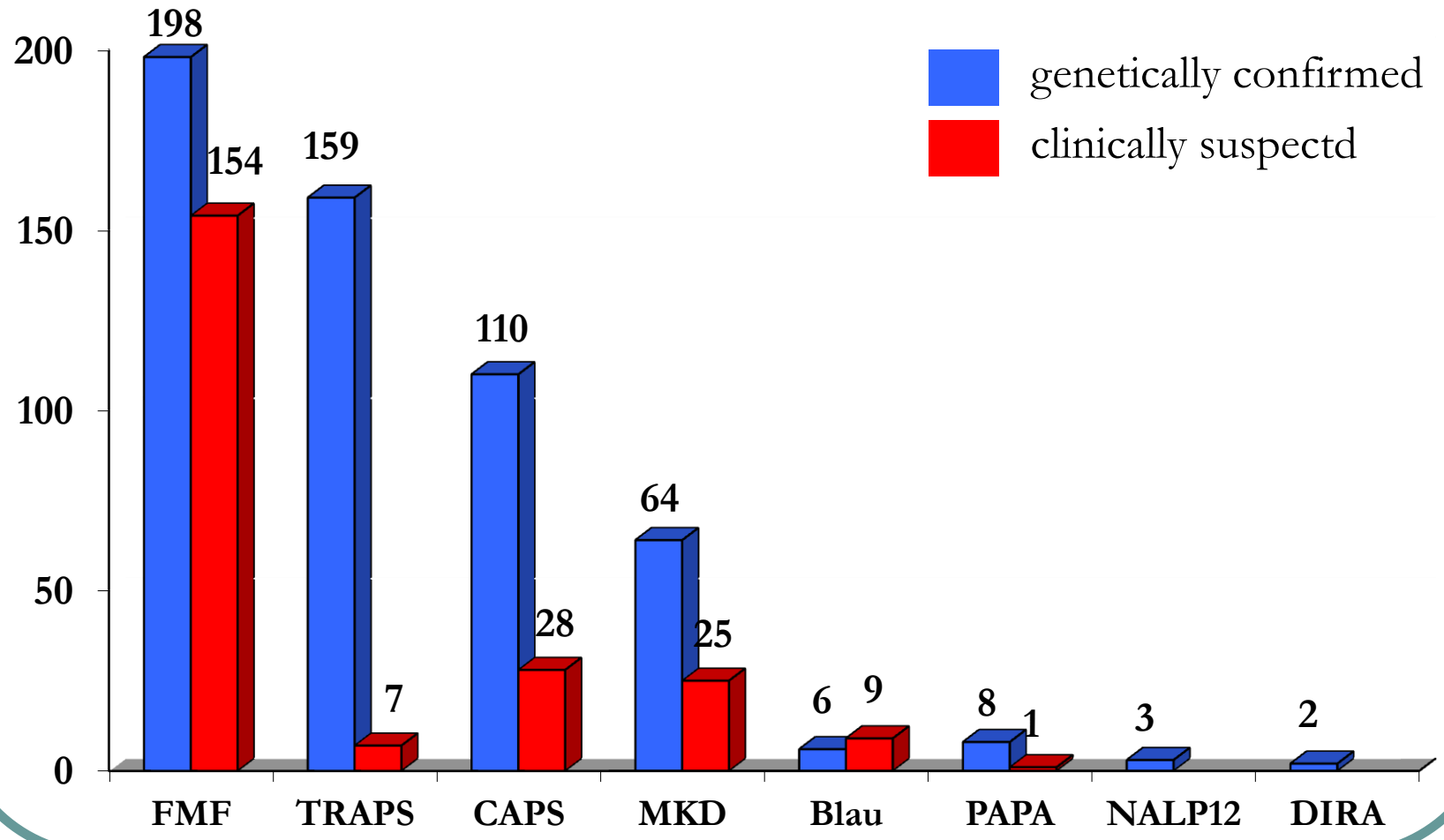
Primary endpoint:
Collect information on the clinical presentation, outcome and response to treatment of patients affected by the major Autoinflammatory diseases.

Enrollemnet (March 10th 2011)

62 Centers from 40 countries

1422 pts

Patients enrolled



EUROFEVER PROJECT

Pædiatric Rheumatology InterNational Trials Organisation

paediatric rheumatology european society

Executive Agency for Health and Consumers

Welcome to the web site of the Eurofever Project.

This Project was promoted by the Autoinflammatory Diseases' Working Group of the Paediatric Rheumatology European Society (PRES) and is supported by the Executive Agency for Health and Consumers (EAHC, Project No2007332, http://ec.europa.eu/eahc/projects/database.html)

The general aims of the Eurofever project are to:

- sensitize pediatricians and pediatric rheumatologists to the prompt recognition of Autoinflammatory Diseases;
- provide proper information to families affected by these conditions
- increase the knowledge on the clinical presentation, response to treatment and complications of theses rare disorders.

The Eurofever project includes the following actions:

- a survey on the prevalence of diagnosed or suspected autoinflammatory diseases among all European Paediatric Rheumatology Centers
- an international Registry for Autoinflammatory diseases
- a survey on the efficacy of treatment in these disorders
- elaboration of outcome measures for possible future therapeutic trials
- informative webpages for patients and physicians on each disorder

The following conditions are considered by the Project:

- Behçet disease
- Blau's syndrome/Early onset sarcoidosis
- Cryopyrin associated periodic syndrome
- Chronic recurrent multifocal osteomyelitis
- Deficiency of IL-1 receptor antagonist
- Familial Mediterrean Fever
- Mevalonate kinase deficency (Hyper IgD syndrome)
- NLRP12 -associated periodic syndrome
- Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome

www.printo.it/eurofever

Genetically negative patients

- 30-40% of clinically diagnosed CINCA patients show no heterozygous germline NLRP3 mutation

- Somatic NLRP3 mosaicism was identified in 18 of 26 genetically-negative patients (69.2%).
- Level of mosaicism ranged from 4.2% to 35.8%
- Mosaicism was not detected in any of the 19 healthy relatives

N. Tanaka et al A&R 2011