

The Swedish experience of intravenous immunoglobulin treatment in post-polio

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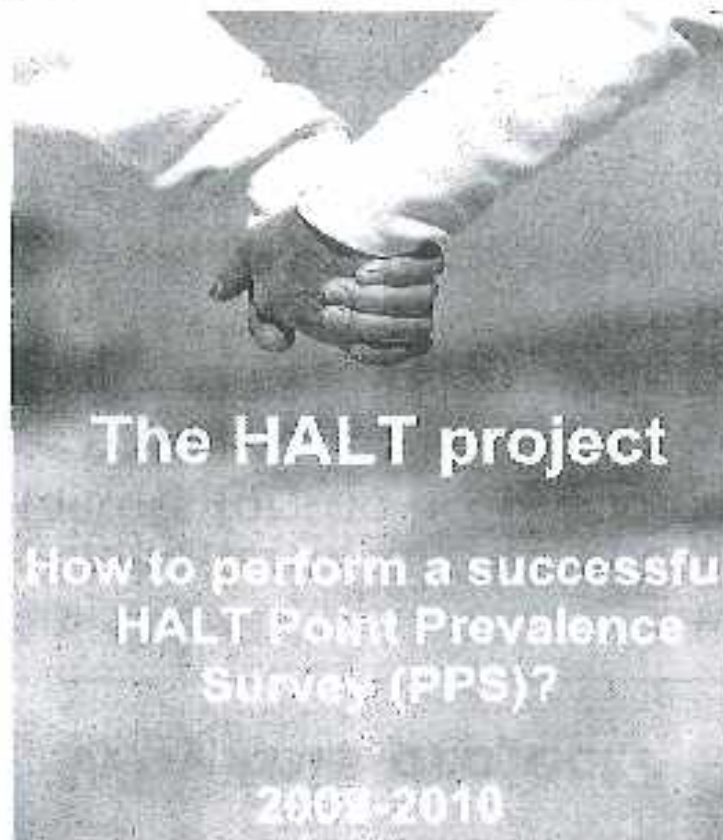




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HAEMATOLOGICAL AND TISSUE
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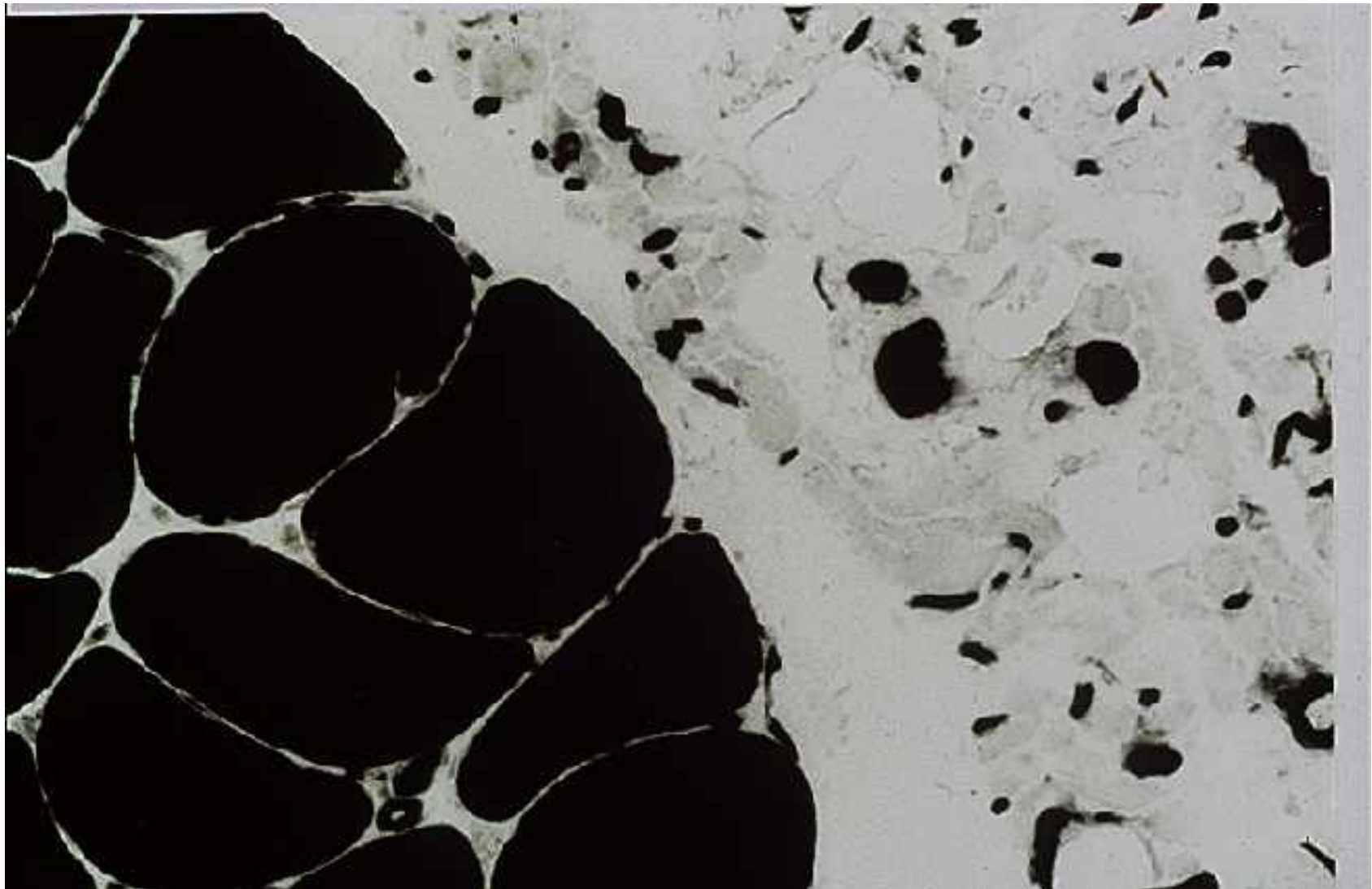
The HALT project

How to perform a successful
HALT Point Prevalence
Survey (PPS)?

2003-2010

Post-polio syndrome – background

- **On-going denervation compensated by reinnervation**
 - **Failing capacity to maintain large motor units ie failing capacity to compensate denervation by reinnervation**
 - **Uncompensated denervation leads to decrease of muscle strength**
-



Pathophysiology denervation-reinnervation

- **Overstress of remaining motor units.**
 - **Overuse of remaining motor units.**
 - **Age.**
 - **Amyotrophic lateral sclerosis (ALS).**
 - **Persistent polio virus infection.**
 - **Immunological factors.**
-

PPS-Inflammation

CNS

Dalakas et al 1984,

Sharief et al 1984, 1991

PPS-Inflammation

Spinal cord

Pezeshkpour and Dalakas 1987

Miller DC 1995

PPS-Inflammation

Muscle

Dalakas et al 1984

Dalakas 1988, 1995

Semino-Mora and Dalakas 1998

PPS-inflammation

Peripheral blood

Ginsberg et al 1989

PPS-inflammation

Peripheral nerve

Brown and Patten 1987

PPS-inflammation

Cytokines

Gonzalez et al 2002

Farbu et al 2007

Fordyce et al 2008



Journal of the Neurological Sciences 205 (2002) 9–13



Journal of the
**Neurological
Sciences**

www.elsevier.com/locate/jns

Prior poliomyelitis-evidence of cytokine production in the central nervous system

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Received 25 October 2001; received in revised form 29 January 2002; accepted 9 April 2002

Immune-modulatory drugs used in PPS

- Cortison
- Interferon
- Immunosuppressants
- Immunotherapy

In order to down-regulate the inflammatory reaction in CNS, 16 post-polio patients were treated with intravenous immunoglobulin (Xepol)

Prior poliomyelitis—Ivlg treatment reduces proinflammatory cytokine production

Henrik Gonzalez^{a,b,*}, Mohsen Khademi^c, Magnus Andersson^{a,c}, Fredrik Piehl^c,
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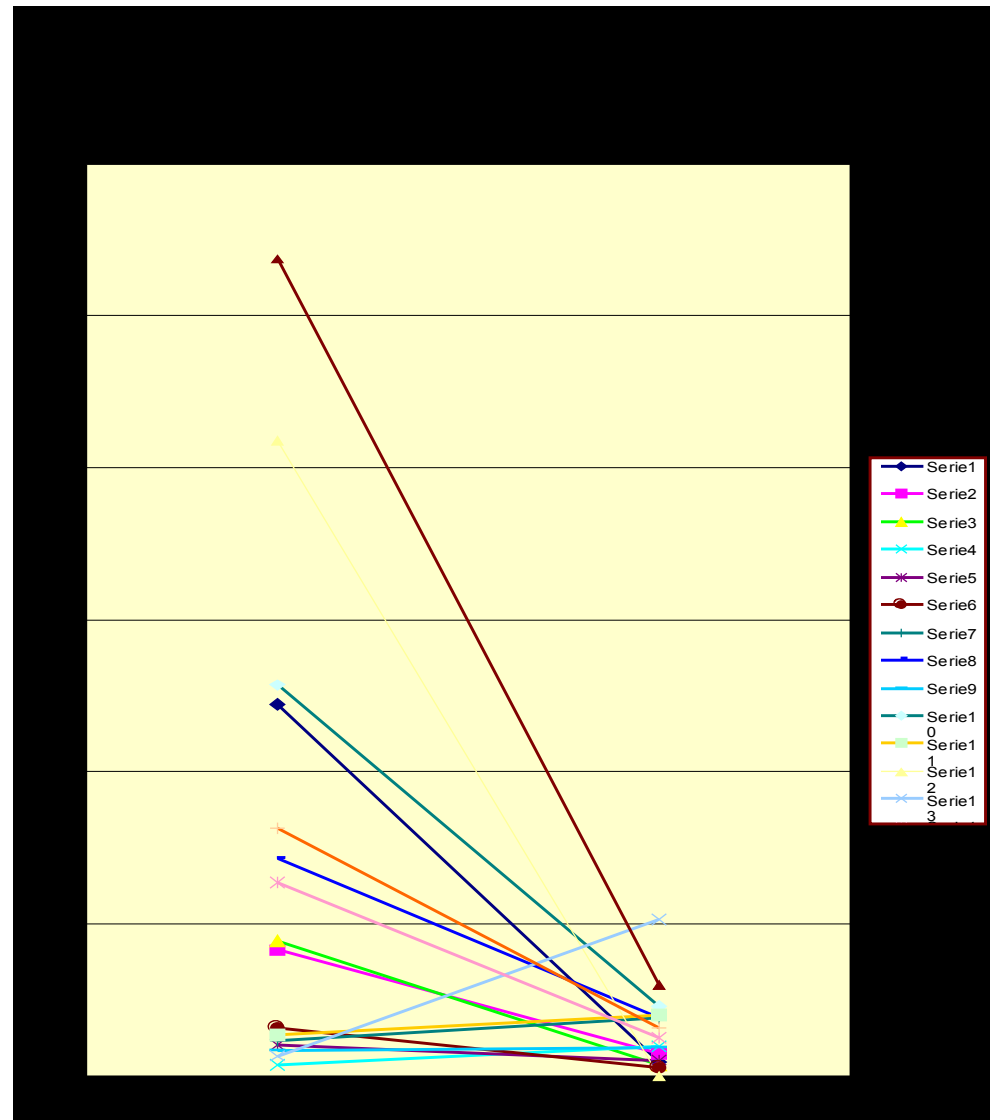
^dDepartment of Rehabilitation Medicine, Huddinge University Hospital, Stockholm, Sweden

Received 27 October 2003; received in revised form 6 January 2004; accepted 7 January 2004

TNF- α

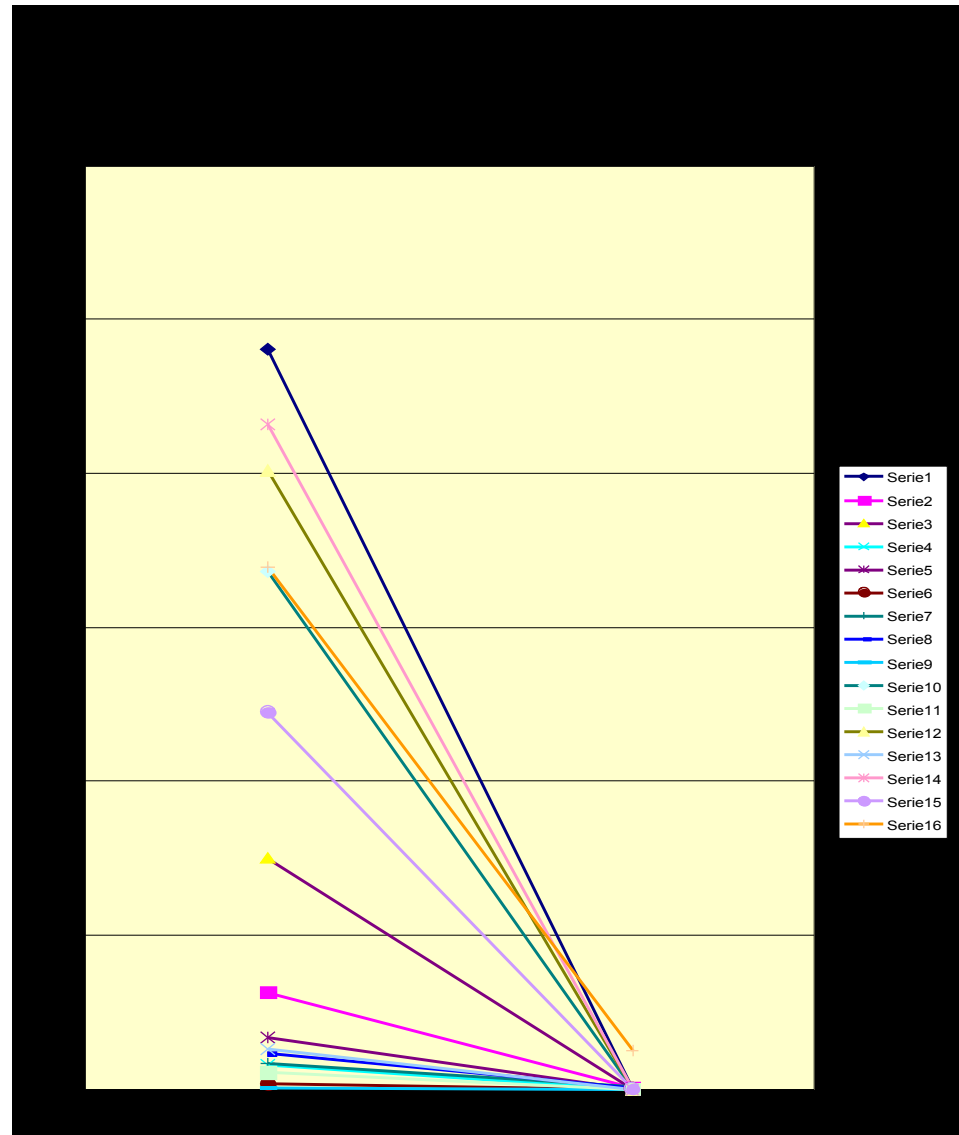
Poliopatients
before and after
Xepol-
treatment

P=0.016



INF-gamma

$P=0.00003$



0,00

J Rehabil Med
2006, 1–3, PrEview article

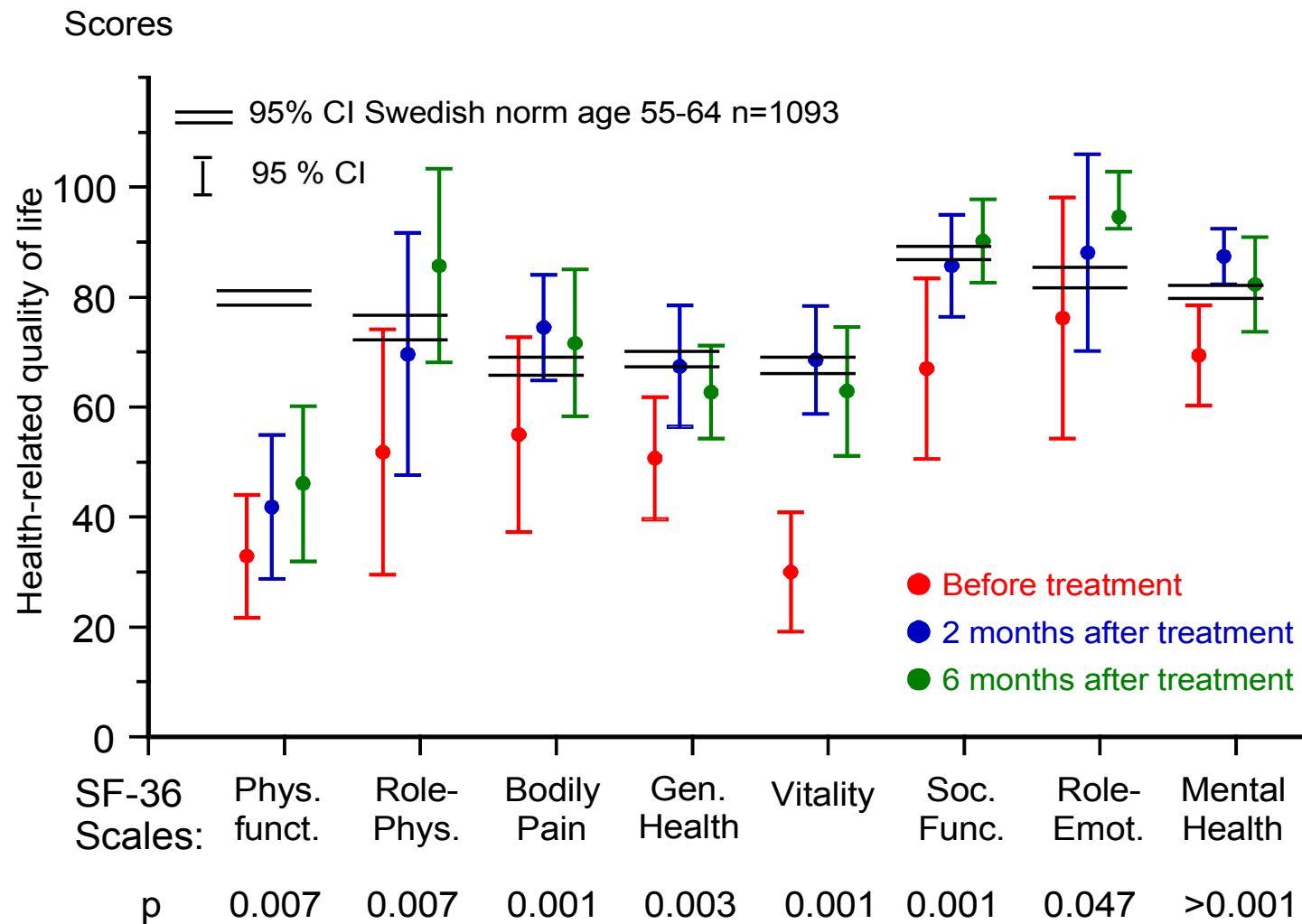


SHORT COMMUNICATION

**EFFECT OF INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH
POST-POLIO SYNDROME – AN UNCONTROLLED PILOT STUDY**

Georgios Kaponides, MD¹, Henrik Gonzalez, MD¹, Tomas Olsson, MD, PhD² and
Kristian Borg, MD, PhD¹

*From the ¹Departments of Public Health Sciences, Division of Rehabilitation Medicine and ²Neuroimmunology Unit,
Center for Molecular Medicine, Karolinska Hospital, Stockholm, Sweden*



Multicenter, placebo-controlled, double-blinded study including 142 post-polio patients

Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial



Henrik Gonzalez, Katharina Stibrant Sunnerhagen, Inger Sjöberg, Georgios Kaponides, Tomas Olsson, Kristian Borg

Summary

Background Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, known as post-polio syndrome. Production of proinflammatory cytokines within the CNS indicates an underlying inflammatory process, accessible for immunomodulatory treatment. We did a multicentre, randomised, double-blind, placebo-controlled study of intravenous immunoglobulin in post-polio syndrome.

Lancet Neurol 2006; 5: 493-501

Published Online

April 25, 2006

DOI:10.1016/S1473-4422(06)

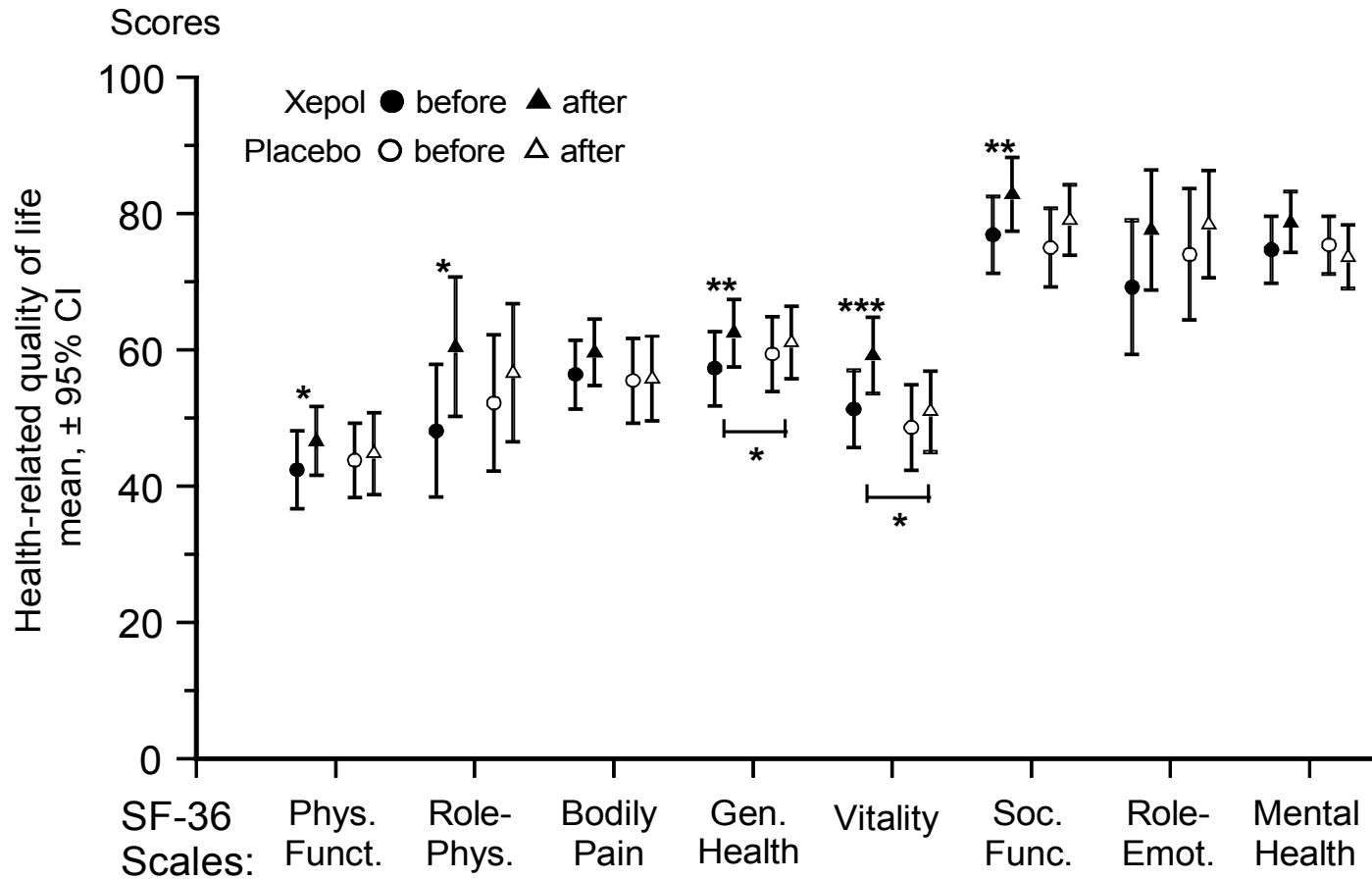
20447-1

Increase of muscle strength

Treated + 4.3%

$P < 0.05$

Placebo - 5.7%



One year follow-up study

Gonzalez et al 2010

subm for publ

- Still significant decrease of cytokines
 - Still significantly better quality of life for physical domains
-

*One
year
follo
w up*

SF-36 score	IVIG (n=20)			Placebo (n=21)			Between
	Before mean (SD)	1 year mean (SD)	p	Before mean (SD)	1 year mean (SD)	p	group diff. p
PF	33.2 (17.9)	39.8 (19.2)	0.014	40.7 (22.7)	41.0 (22.0)	0.761	<u>0.028</u>
RP	30.0 (28.8)	42.5 (39.8)	0.240	50.0 (40.3)	48.0 (40.0)	0.757	0.278
BP	50.8 (18.1)	55.5 (21.6)	0.189	55.4 (24.5)	50.7 (27.3)	0.224	0.075
GH	53.1 (22.4)	61.3 (24.2)	0.058	58.1 (22.5)	61.8 (24.2)	0.190	0.290
VT	43.0 (22.6)	49.3 (27.3)	0.267	46.4 (23.8)	47.3 (22.2)	0.948	0.300
SF	66.9 (24.1)	73.8 (26.6)	0.094	70.8 (26.3)	71.4 (23.8)	0.897	0.191
RE	61.7 (43.6)	66.7 (40.5)	0.665	63.5 (43.3)	73.0 (38.9)	0.261	0.736
MH	74.4 (17.9)	76.0 (19.3)	0.652	72.6 (17.2)	72.5 (17.6)	0.881	0.844
PCS	28.9 (6.1)	32.8 (8.2)	0.021	34.0 (10.0)	33.1 (11.3)	0.394	<u>0.020</u>
MCS	48.7 (13.2)	50.0 (12.5)	0.681	47.6 (12.4)	49.3 (11.9)	0.192	0.531

One year follow-up

6MWT, m

XEPOL	351 (110) n=19	400 (112) n=19	p<0.001
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Placebo	306 (111) n=20	325 (125) n=20	0.145
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Between groups	0.415
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One year follow-up

Cytokines

PPS (n=37)

OND (n=30)

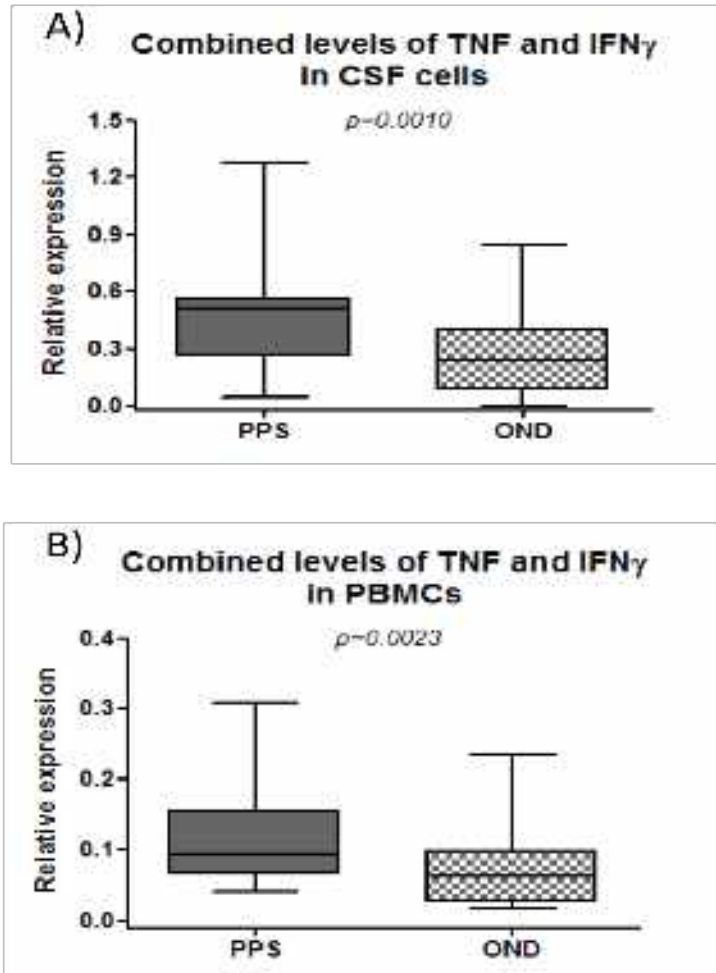
(Mean \pm SEM)

	PPS (n=37)		OND (n=30)	
	CSF cells	PBMCs	CSF cells	PBMCs
TNF*	0.204 \pm0.0340	0.058 \pm0.0071	0.112 \pm0.0198	0.034 \pm0.0060
IFN-γ*	0.281 \pm0.0380	0.063 \pm0.0072	0.158 \pm0.0292	0.040 \pm0.0082
TGF- β	0.391 \pm 0.0234	0.477 \pm 0.0275	0.398 \pm 0.0428	0.403 \pm 0.0440
IL-10	0.148 \pm 0.0283	0.009 \pm 0.0019	0.129 \pm 0.0367	0.011 \pm 0.0030
IL-13	0.336 \pm 0.0307	0.117 \pm 0.0087	0.426 \pm 0.0448	0.123 \pm 0.0092
IL-23	0.238 \pm 0.0446	0.103 \pm 0.0177	0.274 \pm 0.0333	0.125 \pm 0.0213

***The levels of TNF and IFN- γ were increased in both CSF cells ($P=0.036$ and $p=0,02$ respectively) and PBMCs ($p=0,0164$ and $p=0,0358$ respectively) in PPS group compared to OND.**

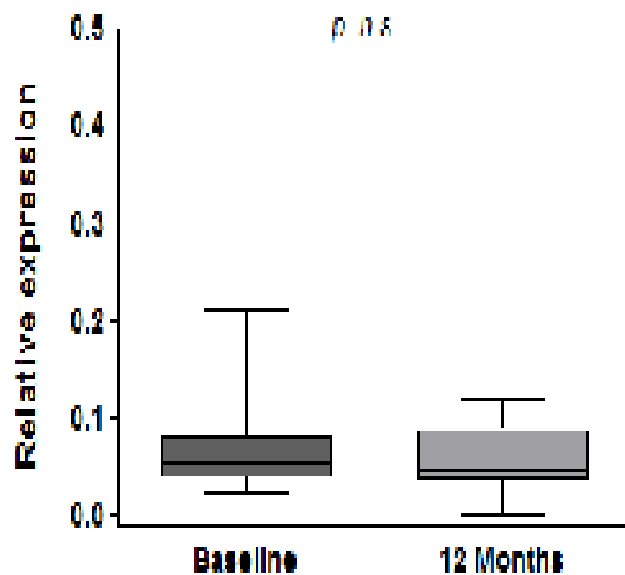
One year follow-up

Figure 2

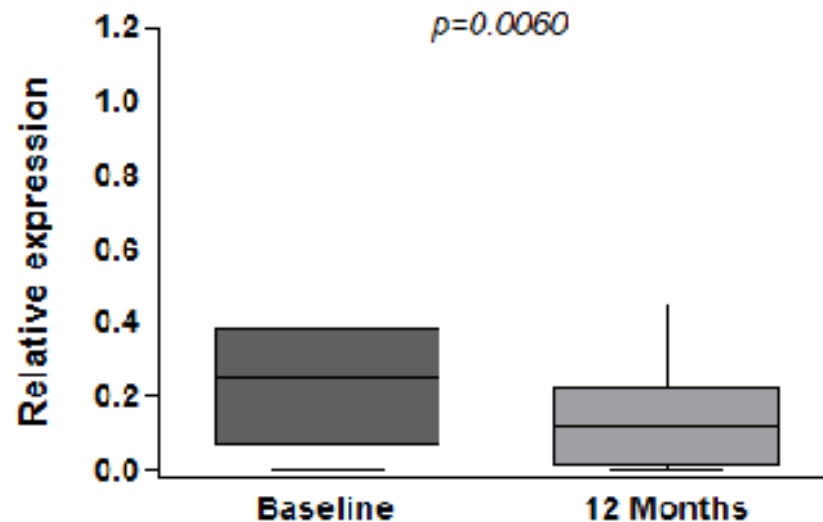


One year follow-up

TNF in CSF cells; effect of IVIG

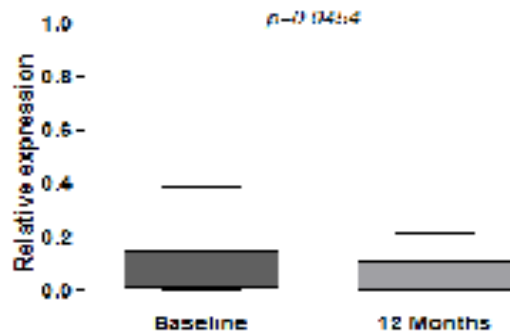


IFN γ in CSF cells; effect of IVIG

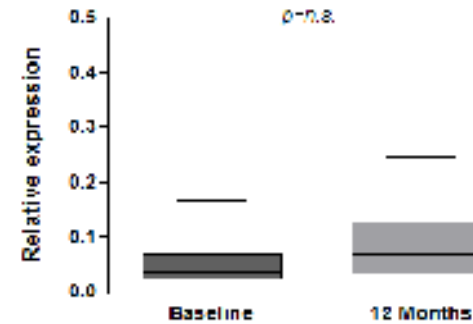


One year follow-up

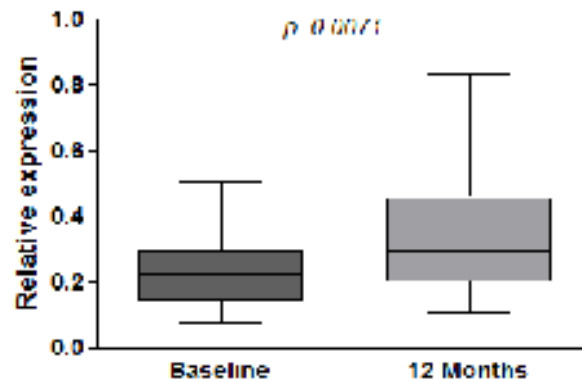
IL-23 in CSF cells; effect of IVIG



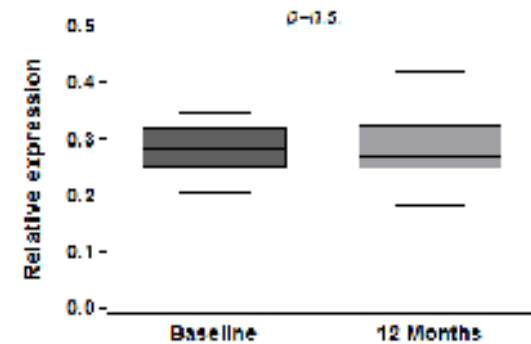
IL-10 in CSF cells; effect of IVIG



IL-13 in CSF cells; effect of IVIG



TGFb In CSF cells; effect of IVIG



2.5 year follow-up study

Gonzalez et al 2010 in preparation

- Cytokine levels ?
- Clinical parameters back to base-line

Werhagen and Borg 2010

Submitted for publication

- 64 PPS patient treated
 - 90 gram IVIG
-

Werhagen and Borg 2010

- Significant effect of IVIG
 - 2/3 of patients had a decrease of pain (more than 10 units on VAS-scale)
 - 2/3 of patients had a decrease of fatigue
-

Werhagen and Borg 2010

- Effect correlated to age and paresis
- Better effect if the patients was < 10 years of age at the acute polio

Östlund et al 2010

In manuscript

- 140 patients
 - 90 g IVIG
 - Open study
 - Evaluation after 6 and 12 month
-

Östlund et al 2010

Table 1a. Descriptive for all participants before treatment and 6-month follow-up.

	n	Treatment median (q1-q3)	6 month median (q1-q3)	p-value
SF-36				
PF	109	40 (20-50)	40 (25-55)	0.069
RP	107	25 (0-50)	25 (0-75)	0.145
BP	112	41 (32-62)	51 (41-72)	0.002
GH	105	52 (30-67)	47 (32-62)	0.805
VT	110	40 (20-55)	50 (25-65)	0.006
SF	111	75 (50-88)	75 (50-100)	0.020
RE	102	67 (0-100)	100 (33-100)	0.017
MH	110	72 (56-84)	76 (60-84)	0.140
PCS	93	30 (23-36)	31 (24-37)	0.729
MCS	93	47 (36-55)	50 (42-58)	0.006
PASE	81	76 (52-116)	76 (52-114)	0.853
VAS pain	108	26 (12-46)	21 (7-44)	0.145

Östlund et al 2010

Table 1b. Descriptive for all participants at treatment and 12-month follow-up

	n	Treatment median (q1-q3)	12 month median (q1-q3)	p-value
SP-36				
PF	93	35 (15-55)	35 (15-55)	0.264
RP	91	25 (0-50)	25 (0-75)	0.138
BP	94	41 (31-61)	51 (41-62)	0.029
GH	90	47 (30-72)	47 (25-62)	0.045
VT	92	40 (20-55)	40 (20-60)	0.150
SF	94	75 (38-88)	75 (50-100)	0.197
RE	90	67 (0-100)	100 (33-100)	0.014
MH	92	70 (52-84)	74 (56-90)	0.262
PCS	85	29 (23-36)	29 (23-34)	0.507
MCS	85	47 (35-55)	51 (38-58)	0.071
PASE	68	84 (55-138)	73 (42-105)	0.066
VAS pain	92	25 (12-50)	30 (9-50)	0.824

Östlund et al 2010

Table 2b. Vitality as outcome. Between groups comparison at 6-month follow-up.

	Positive		Non		Negative		p-value
	n	median (q1-q3)	n	median (q1-q3)	n	median (q1-q3)	
SF-36							
PF	41	45 (30-65)	47	44 (25-50)	20	28 (19-58)	0.122
RP	42	50 (25-100)	46	25 (0-50)	20	13 (0-69)	0.021
BP	42	57 (41-74)	48	42 (41-70)	20	51 (41-72)	0.469
GH	42	56 (44-68)	46	44 (30-63)	18	42 (20-56)	0.034
VT	42	65 (55-80)	48	40 (20-55)	20	28 (11-40)	<0.001
SF	42	88 (63-100)	48	75 (50-100)	19	63 (38-75)	0.039
RE	42	100 (33-100)	46	67 (25-100)	17	100 (33-100)	0.359
MHI	42	82 (71-92)	48	68 (56-80)	20	76 (50-84)	0.008
PCS	41	33 (26-39)	44	30 (25-37)	16	24 (18-32)	0.016
MCS	41	54 (46-63)	44	45 (39-56)	16	49 (40-54)	0.036
PASR	36	95 (62-132)	40	65 (50-118)	15	76 (47-95)	0.816
VAS pain	39	18 (10-41)	47	22 (7-44)	20	18 (2-40)	0.215

Östlund et al 2010

Table 2c. Vitality as outcome. Between group comparison at 12-month follow-up.

	Positive		Non		Negative		p-value
	n	median (q1-q3)	n	median (q1-q3)	n	median (q1-q3)	
SF-36							
PF	29	40(11-70)	27	30(15-55)	12	35(20-51)	0.849
RP	29	33(0-100)	27	25(0-50)	12	38(0-100)	0.321
BP	29	41(37-71)	27	51(41-62)	13	51(36-73)	0.908
GH	29	47(35-65)	27	47(20-62)	13	50(33-60)	0.704
VT	29	50(20-60)	27	35(10-55)	12	45(27-64)	0.170
SF	29	75(50-94)	27	63(50-88)	13	88(50-100)	0.429
RE	29	100(0-100)	27	67(33-100)	13	100(83-100)	0.092
MH	29	80(58-96)	27	68(56-84)	12	72(56-92)	0.308
PCS	29	29(23-36)	27	29(22-32)	12	37(23-36)	0.762
MCS	29	53(39-60)	27	49(38-58)	12	54(41-62)	0.402
PASE	24	80(46-143)	24	63(52-92)	8	41(30-118)	0.454
VAS pain	29	31(7-50)	26	31(12-50)	12	24(4-61)	0.871

Östlund et al 2010

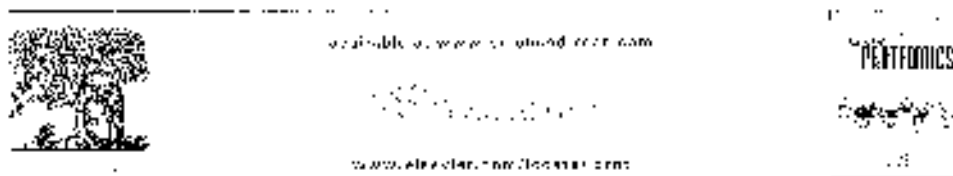
In manuscript

- Statistically significant effect on Quality-of-life (SF-36) at 6 month
 - Low vitality - effect
 - High vitality - no effect
-

Other studies

- Farbu et al 2007.
TNF-alfa increase, effect on pain after 3 months.
 - Fordyce et al 2008
TNF-alfa increase correlated to pain, no intervention
-

PPS - BIOMARKER



Identification of novel candidate protein biomarkers for the post-polio syndrome — Implications for diagnosis, neurodegeneration and neuroinflammation

Hérvik González^{1,2,3}, Jan Ottavald^{4,5,6,7}, Kerstin C. Nilsson⁸, Niclas Sjögren⁹, Tasso Miličević¹⁰, Helena Von Borstel¹¹, Mahan Khademi¹², Bodil Ericsson¹³, Sven Kjellström¹⁴, Alaa Vegvari¹⁵, Robert Harris¹⁶, György Marko-Varga¹⁷, Kristian Borg¹⁸, Johan Nilsson¹⁹, Thomas Laurell²⁰, Tomas Olsson^{21,22}, Bo Frenzen^{14,23}

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ABSTRACT

Identification of putative biomarkers for post-polio syndrome (PPS) was performed using a combination of random proteomic post-polio analysis (PPA) and a data-driven “bottom-up” proteomic post-polio analysis (PPA) of the analysis. A total of 1,147 proteins were identified in the PPA. The underlying pathways were analyzed using network and network analysis to identify the most enriched biological processes. The results of the PPA analysis were compared to the results of the PPA analysis.

The 1,147 proteins with the highest PPA were analyzed using protein annotation analysis. The results were compared to the results of the PPA analysis. The results of the PPA analysis were compared to the results of the PPA analysis. The results of the PPA analysis were compared to the results of the PPA analysis.

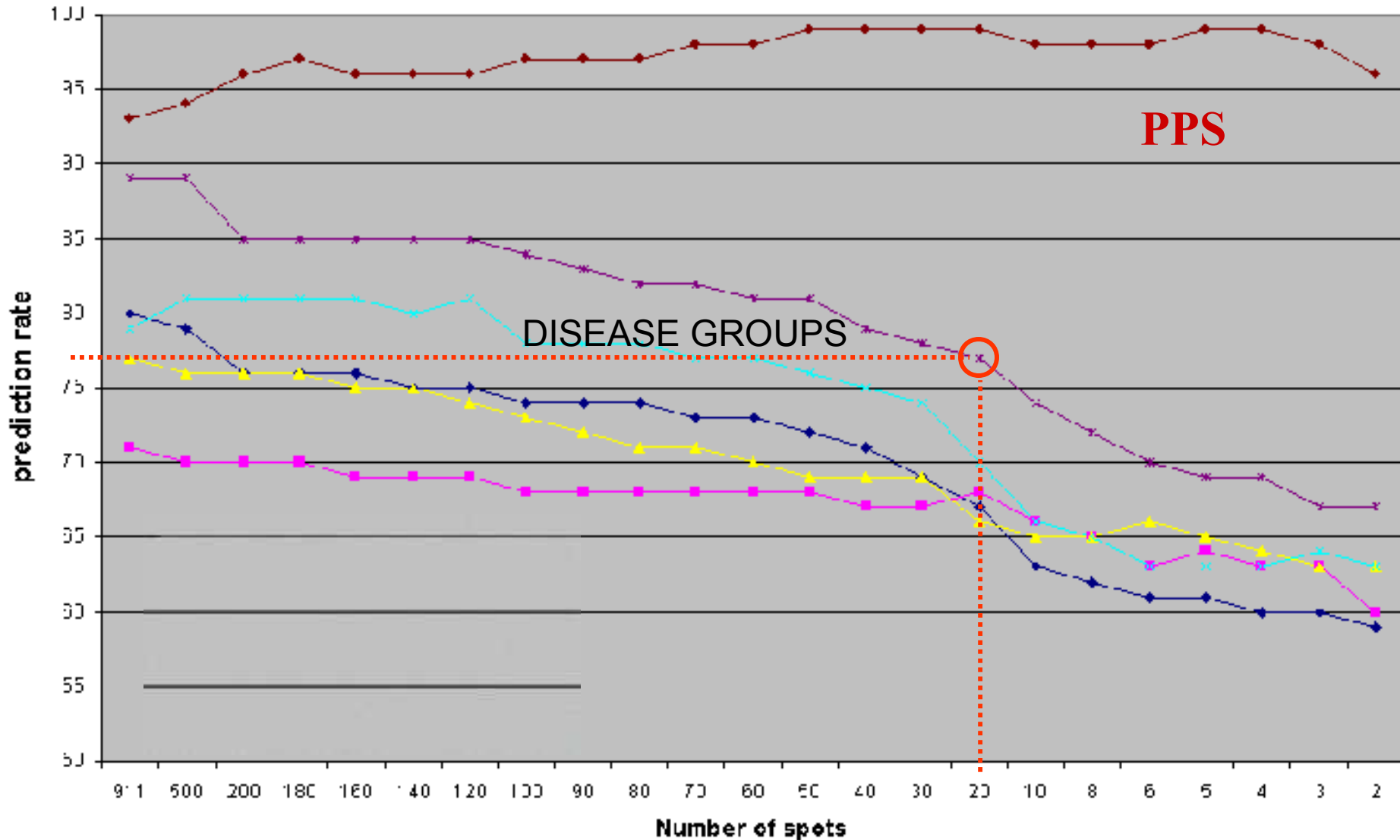
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Gonzales et al 2009 - a proteomic study of CSF

- Disease specific differential expression of 3 proteins
- Involved in neuroinflammation and/or apoptosis

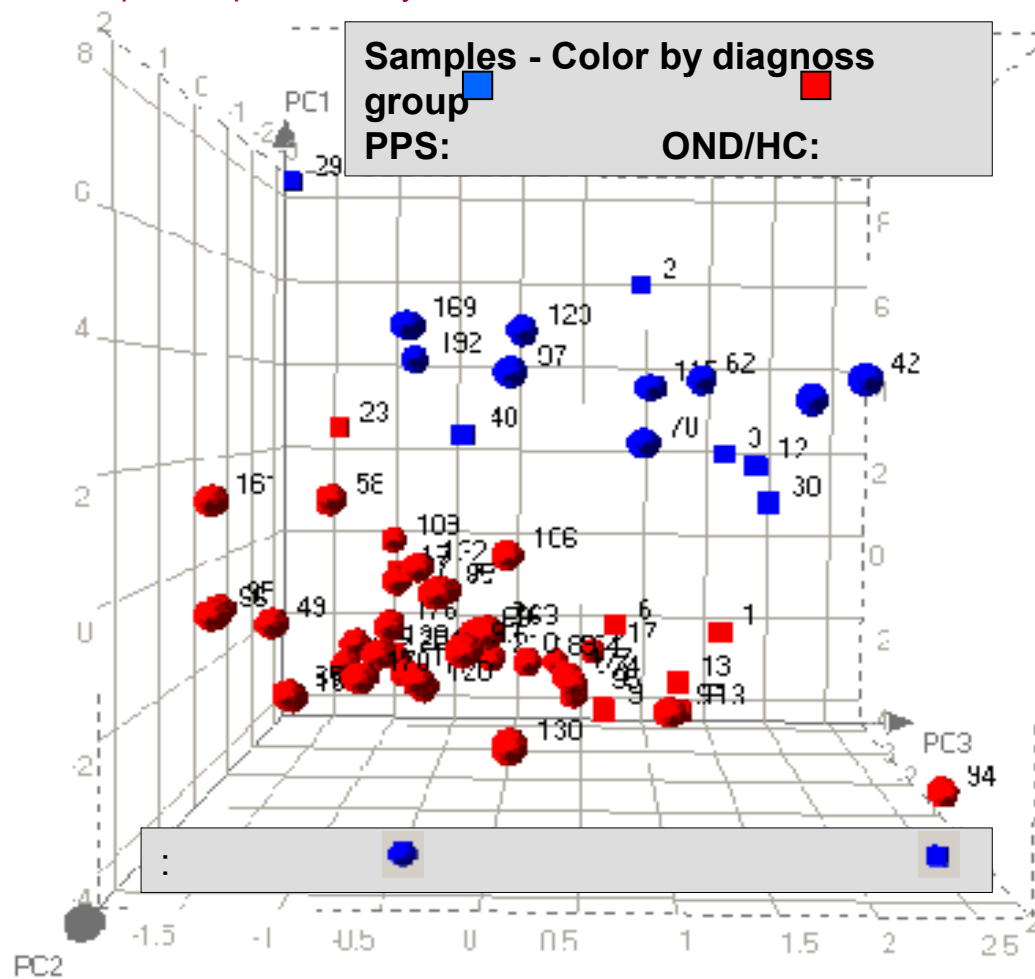
Results

Prediction of disease groups (vs controls)

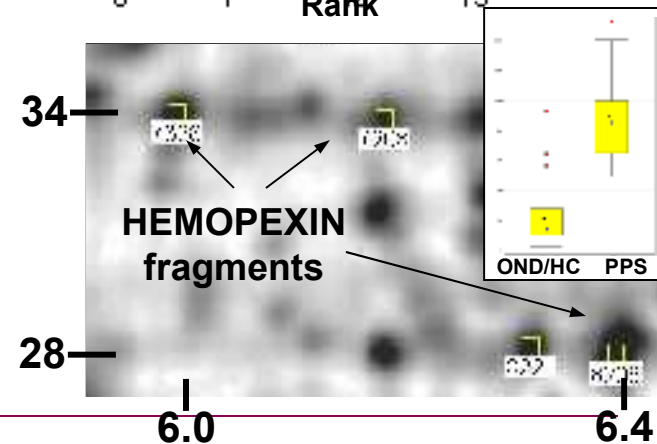
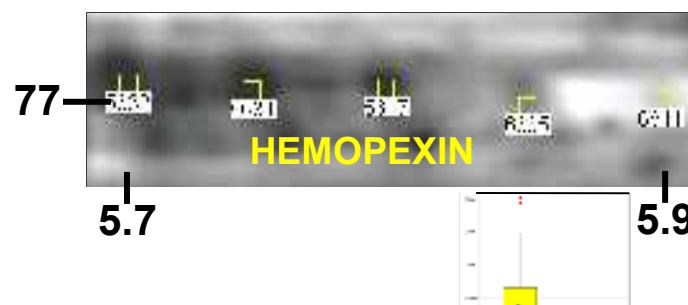
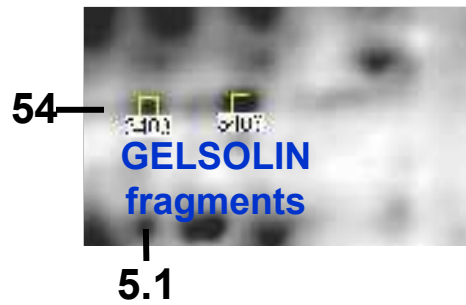
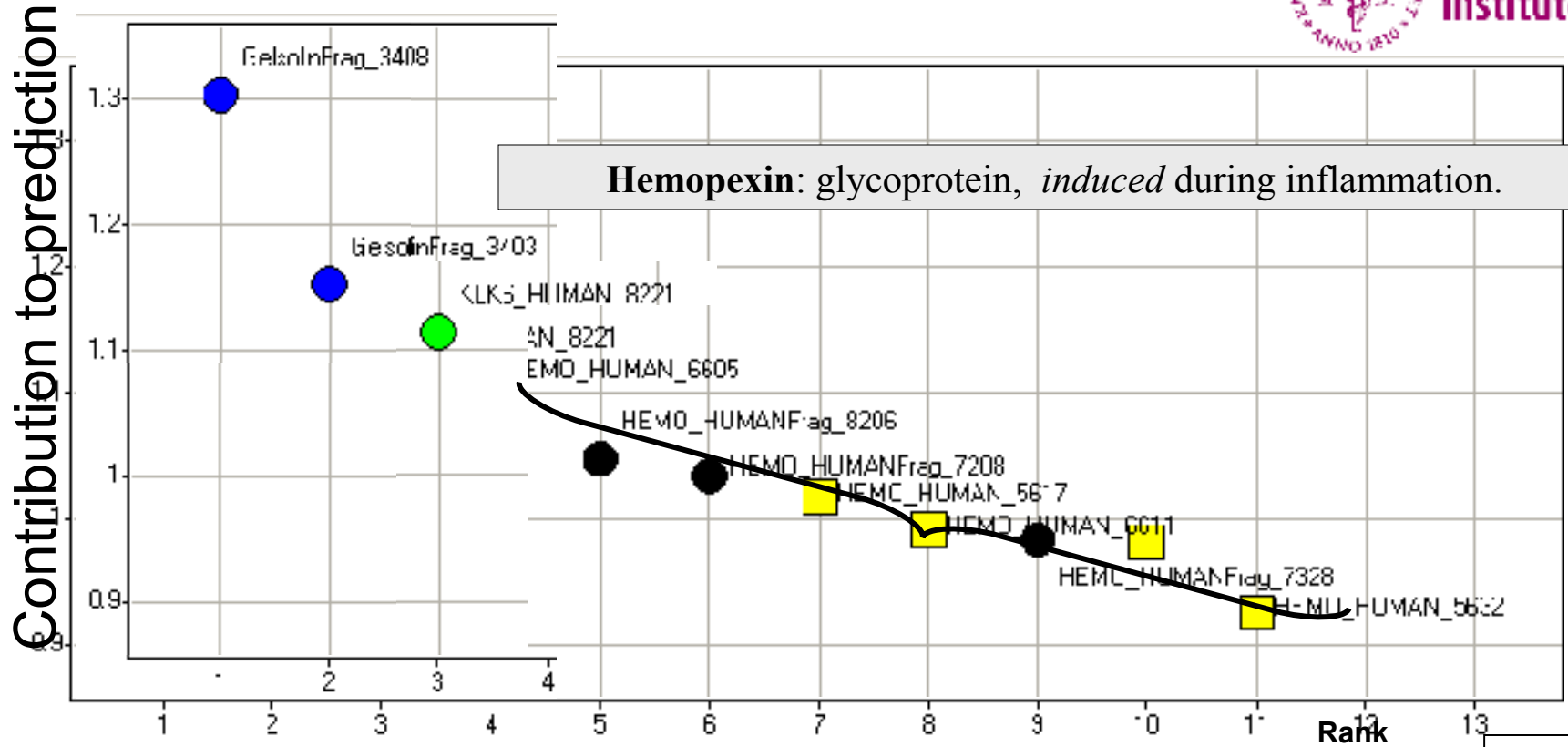


3-dimensional result of three proteins

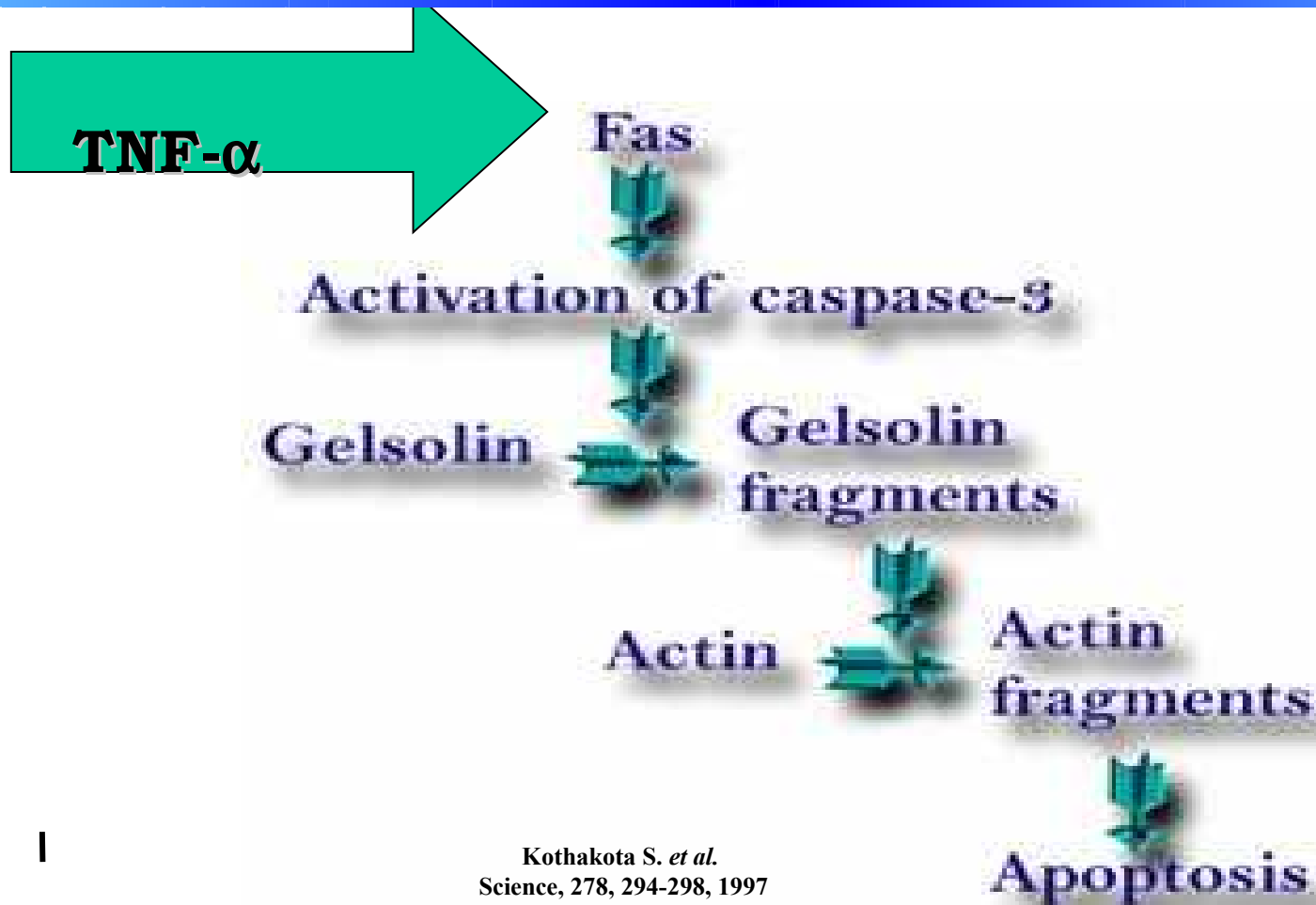
Principal component analysis of PPS & controls



Identification of predictive proteins



Inflammatory cascade - Gelsolin - cell death



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Kothakota S. *et al.*
Science, 278, 294-298, 1997

Summary

- **Post-polio patients have an increase of cytokines in the CSF indicating an inflammation in the CNS**
 - **The inflammation is down-modulated by means of treatment with intravenous gammaglobulin**
 - **Clinically, the down-modulated inflammation leads to an increased muscle strength and a better quality of life, mainly for the general health and vitality domains, as well as for pain and fatigue**
 - **The effect remains for between 1 and 2.5 years after treatment**
-

Summary

- **The effect of IVIG is correlated to muscle power and the age of the patient**
 - **Low vitality seems to be the most important treatment criteria**
 - **Patients with high vitality should not be treated**
 - **Recent studies suggest that there are specific biomarkers for PPS in CSF and blood**
-







GRIFOLS

PHARMALINK

ASTRA-ZENECA

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