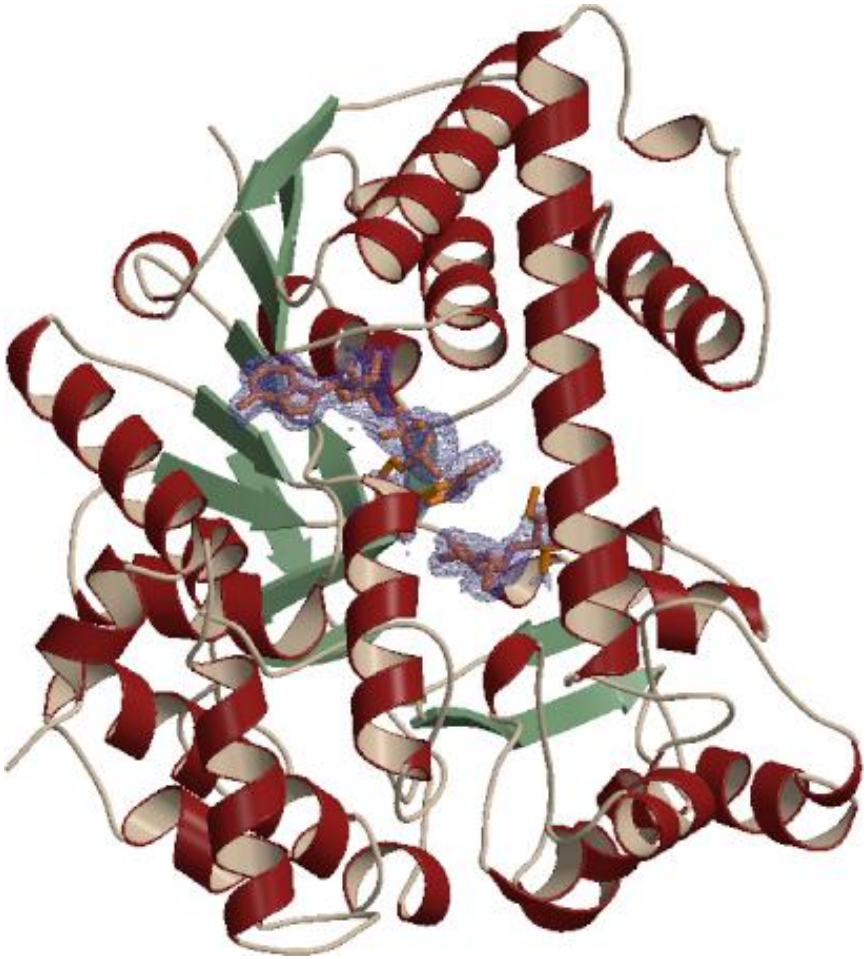
# Clinical aspects of Pompe



# Contents

1)History

2) Pathology

3)Clinical presentation

4) Treatment

5) Future

# Pompe disease:

**History**

- JC Pompe  described original clinical phenotype in 1932
- Classified as Glycogen storage disorder By Cori in 1954
- Discovered by Hers in 1963 to be due to a deficiency in acid α glucosidase (  acid maltase)
- Encoded by GAA on C17q25
- Currently>80 deleterious mutations described

# Pathology

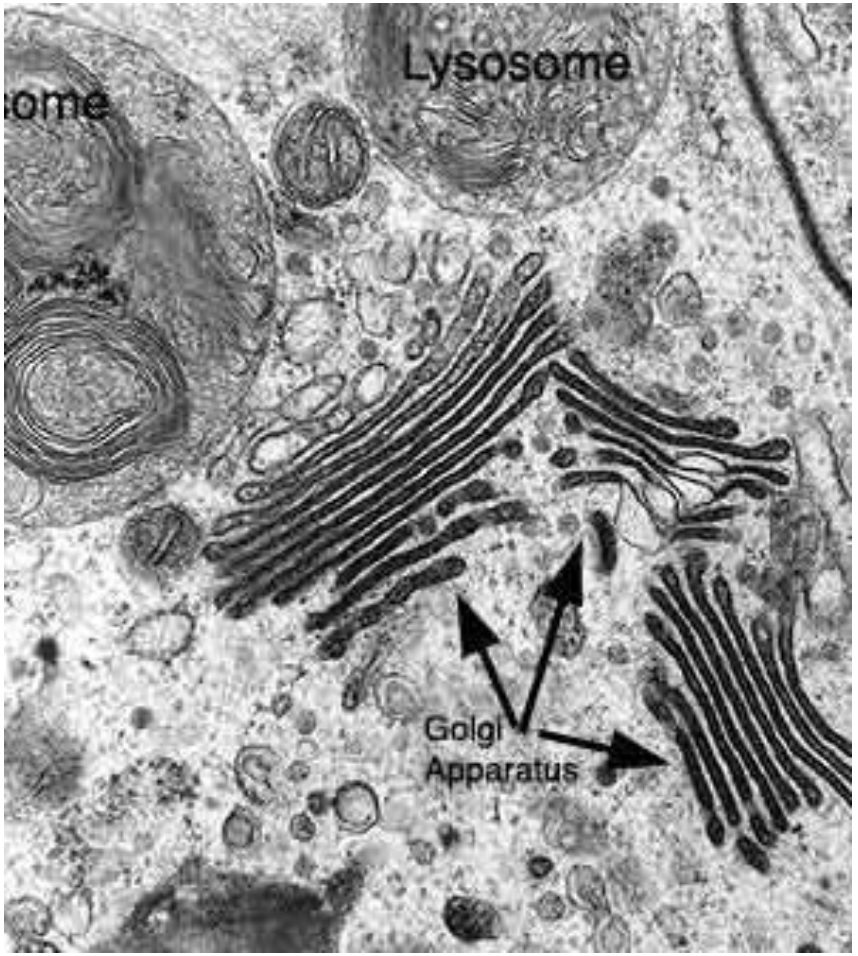
- Acid α glucosidase is a lysosomal enzyme

- Action: cleaves glycogen 1,4 and 1,6 alpha-glycosidic linkages producing glucose→ cytoplasm

Role-

1)Removal of autophaogytosed glycogen

2) ? Physiological role



REVIEW

# Glycogen autophagy in glucose homeostasis

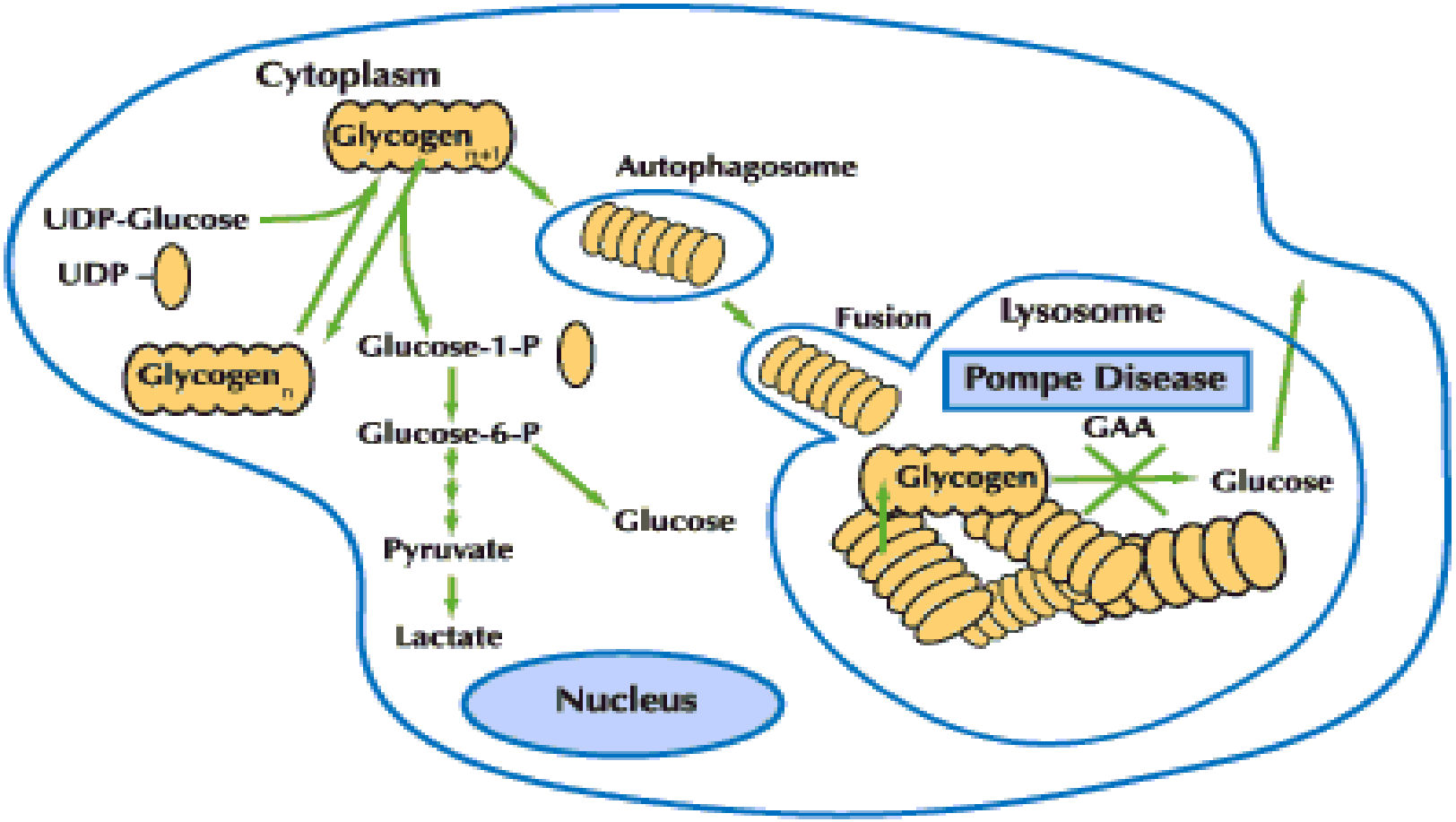
O.B. Kotoulas*, S.A. Kalamidas, D.J. Kondomerkos

- Liver and heart lysosomal α glucosidase activity is low at birth, but increases at 3–4 h and then decreases progressively

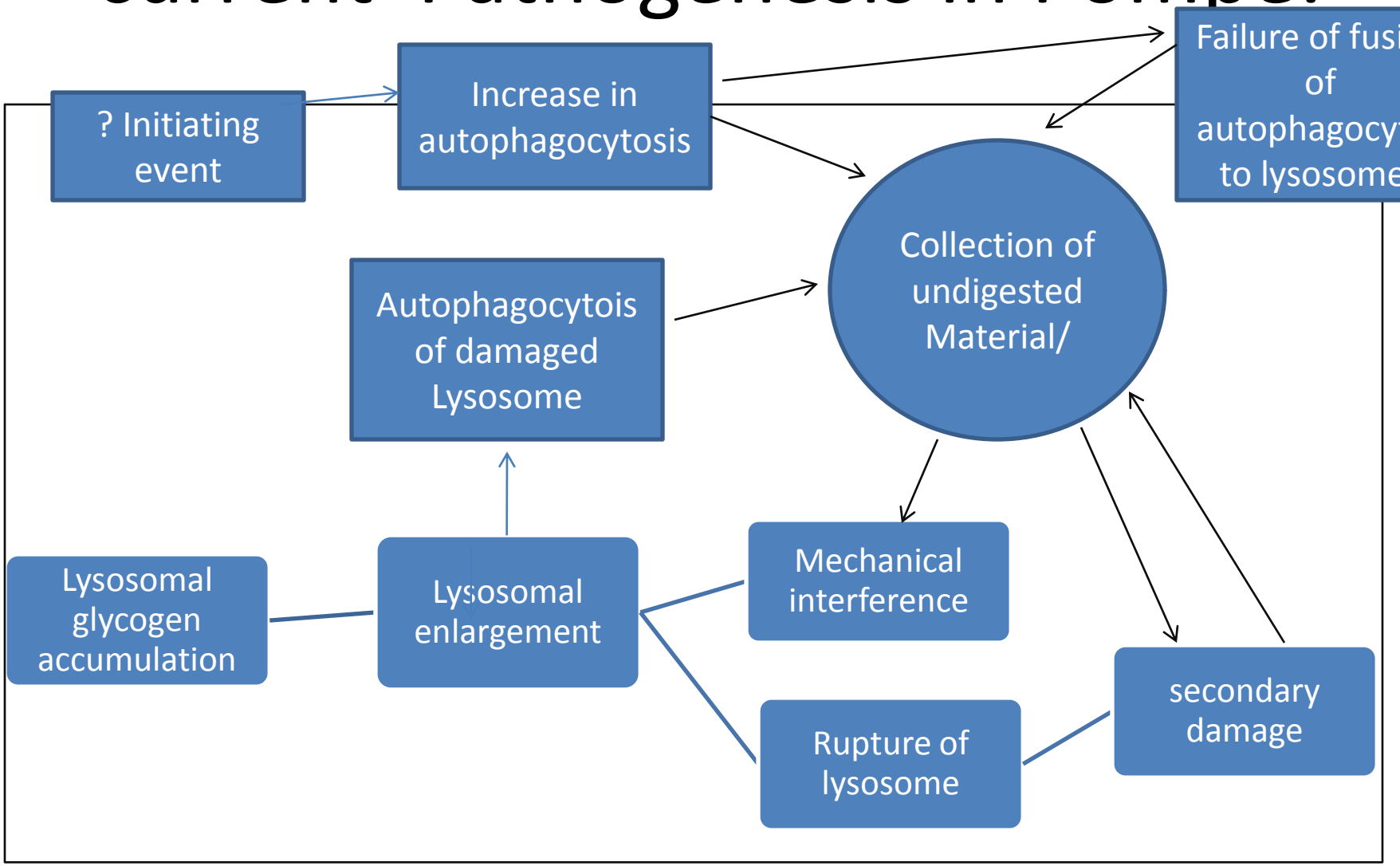
- Autophagic vacuoles are not distributed randomly throughout the cytoplasm, but are deployed predominantly at the junction of cytoplasmic glycogen areas with glycogen free areas

- Four hours after birth, autophagic activity is found to be increased→↑ number, size and total volume of autophagic vacuoles

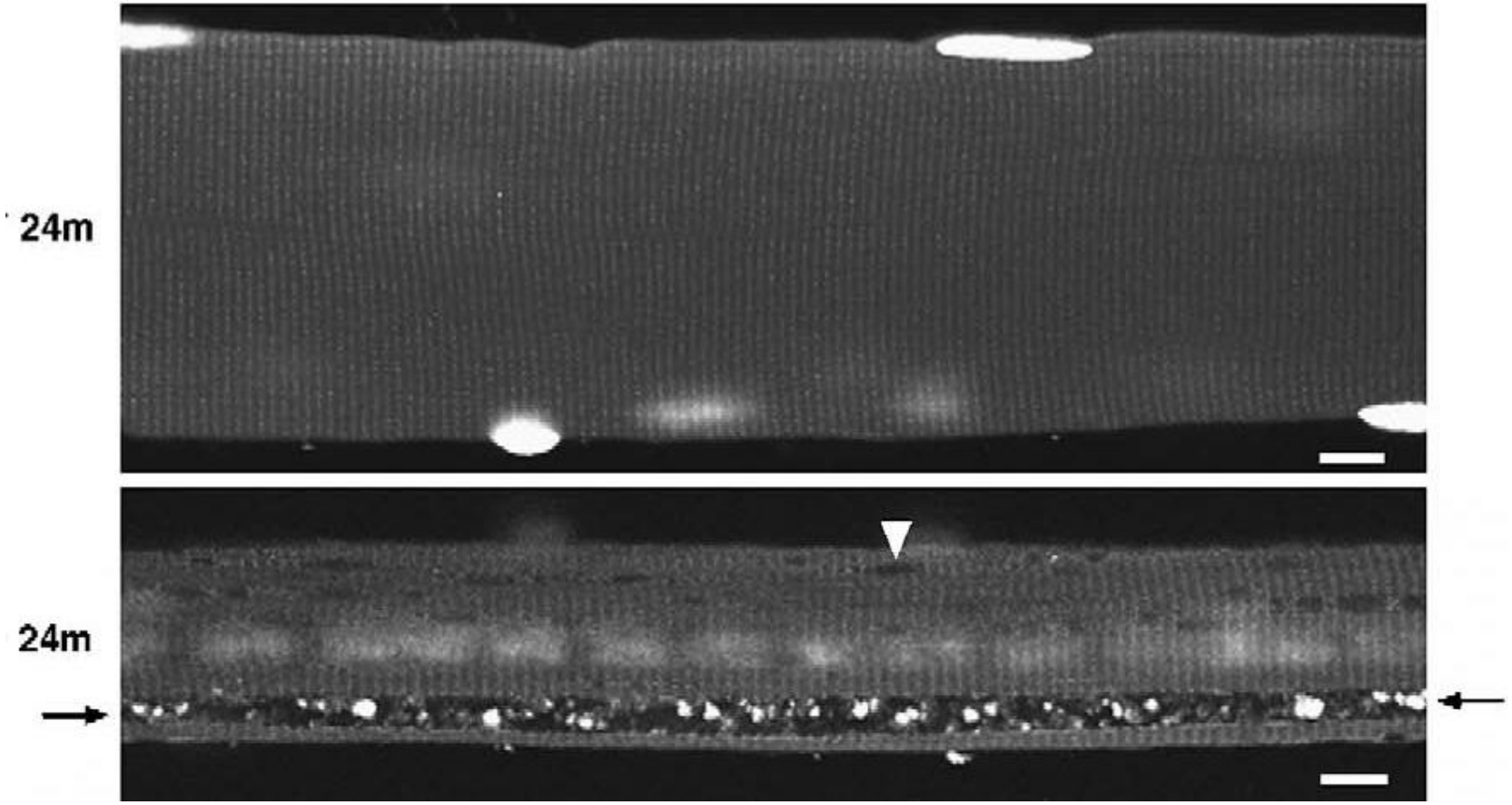
- This process is interrupted by parenteral glucose/ insulin infusion


Cytoplasm
Glycogen n+1
Autophagosome
UDP-Glucose
UDP
Glycogen n
Glucose-1-P
Glucose-6-P
Glucose
Pyruvate
Lactate
Nucleus
Fusion
Lysosome
Pompe Disease
GAA
Glycogen
Glucose

# current Pathogenesis in Pompe:



# WT fibre v Pompe KO fibre in adult mouse (Fukuda T et al MOLECULAR THERAPY Vol. 14, No. 6, December 2006)



# clinical

- Overall Incidence 1 in 40,000 though racial variations
- Incidence of Infantile Pompe 1 in 138,000
- Glycogen accumulates in all organs but major affected heart and skeletal muscle

# The Natural Course of Infantile Pompe's Disease: 20 Original Cases Compared With 133 Cases From the Literature

Hannerieke M. P. van den Hout*; Wim Hop¶; Otto P. van Diggelen§; Jan A. M. Smeitink‖; G. Peter A. Smit#; Bwee-Tien T. Poll-The**; Henk D. Bakker‡‡; M. Christa B. Loonen‡; Johannis B. C. de Klerk*; Arnold J. J. Reuser§; and Ans T. van der Ploeg*

Median age of presentation 2-3 months

Median age of hospitalization 4months

Median age of death 7.5 months

Motor: 40 %

Resp: 25%

Cardiac: 25%

Poor weight gain/ other 5%

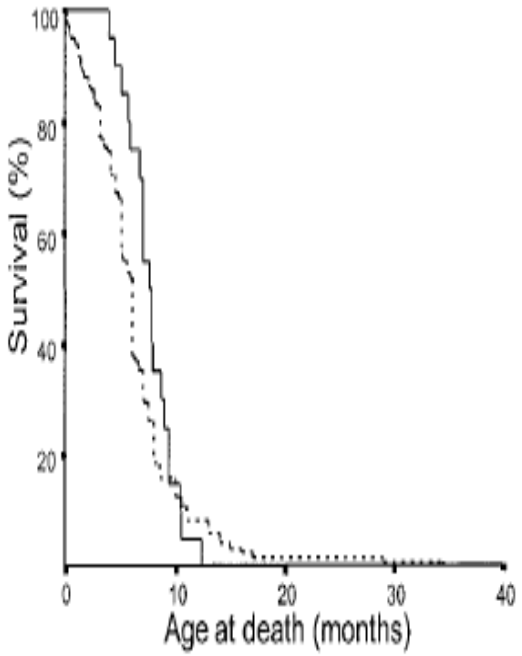



Fig 1. Survival curve of patients with infantile Pompe's disease. The Dutch patient population (solid line) and the literature cases (dashed line) are illustrated separately.

# Chest x- ray and ECG

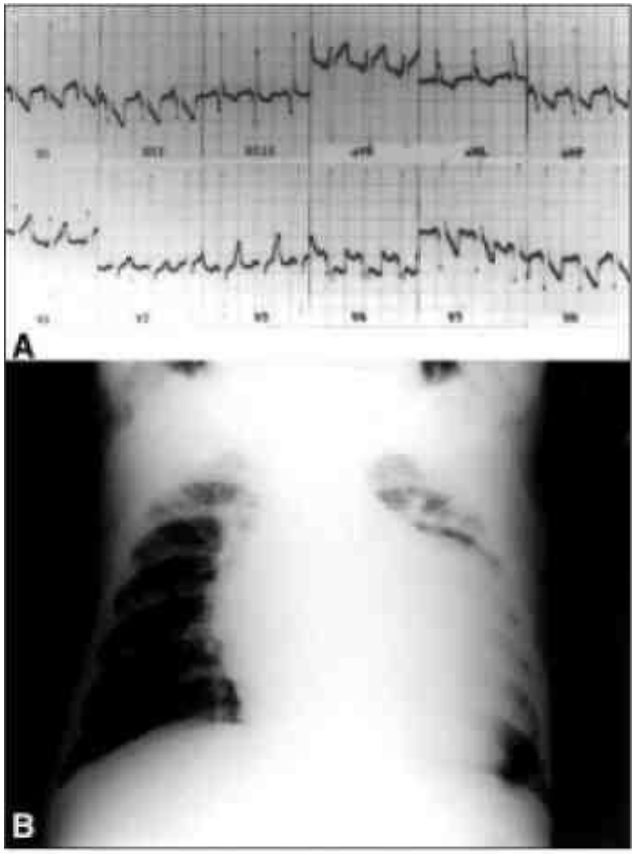



Fig. 1 – A) The electrocardiogram shows sinus rhythm with a short PR interval with left ventricular hypertrophy. Note the deep Q waves in the inferior and lateral walls; B) the chest film demonstrates severe cardiomegaly and pulmonary congestion with increased perfusion of the left lung apex.

## Routine biochemistry:

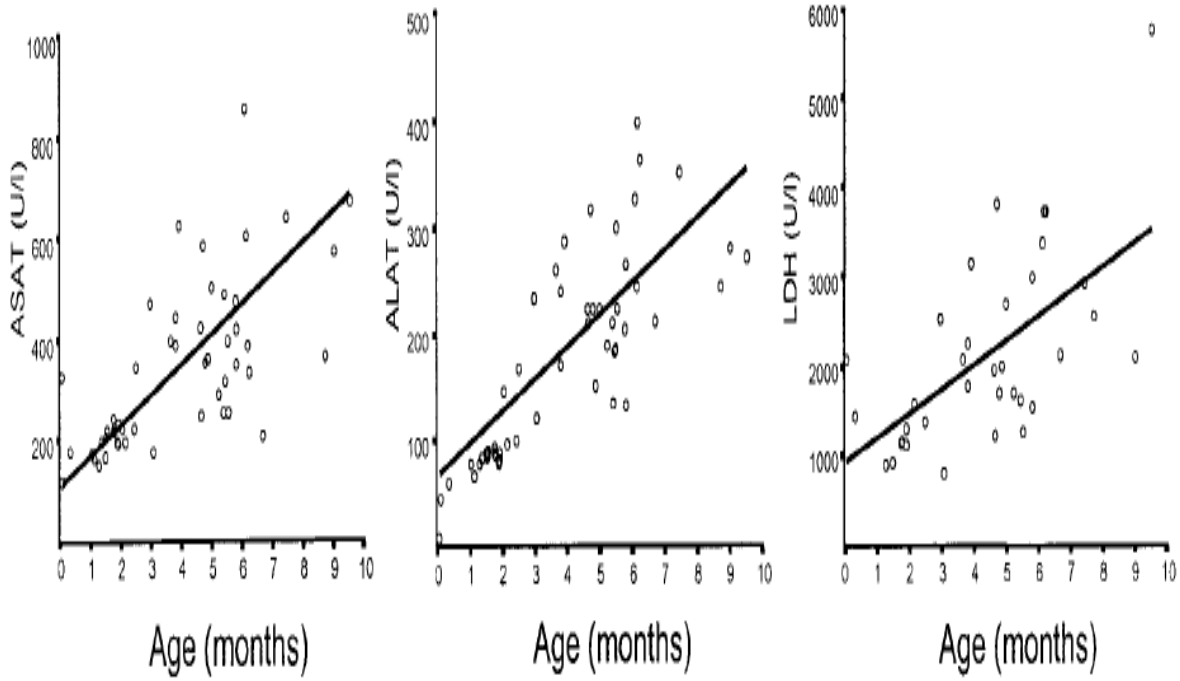
Routine biochemistry:

Levels of CK, CK-MB, LDH, AST, and ALT generally appeared to be increased

AST/ ALT/LDH increase with age

CK median value = 690 IU NB can be normal 12.5 % of cases of infantile presentation

No cases had normal levels of all the combined enzyme assays at the same time.



Genet Med. 2009 Jul;11(7):536-41

**Long-term monitoring of patients with infantile-onset Pompe disease on enzyme replacement therapy using a urinary glucose tetrasaccharide biomarker.**

Young SP, Zhang H, Corzo D, Thurberg BL, Bali D, Kishnani PS, Millington DS.

Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina, USA. young116@mc.duke.edu

Léon P. F. Winkel
Marloes L. C. Hagemans
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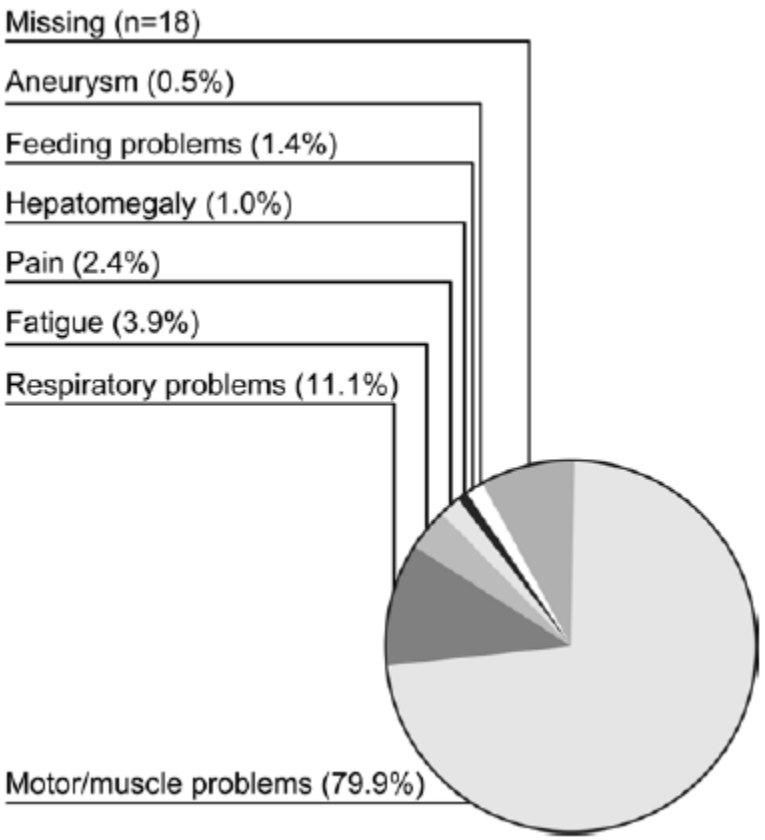
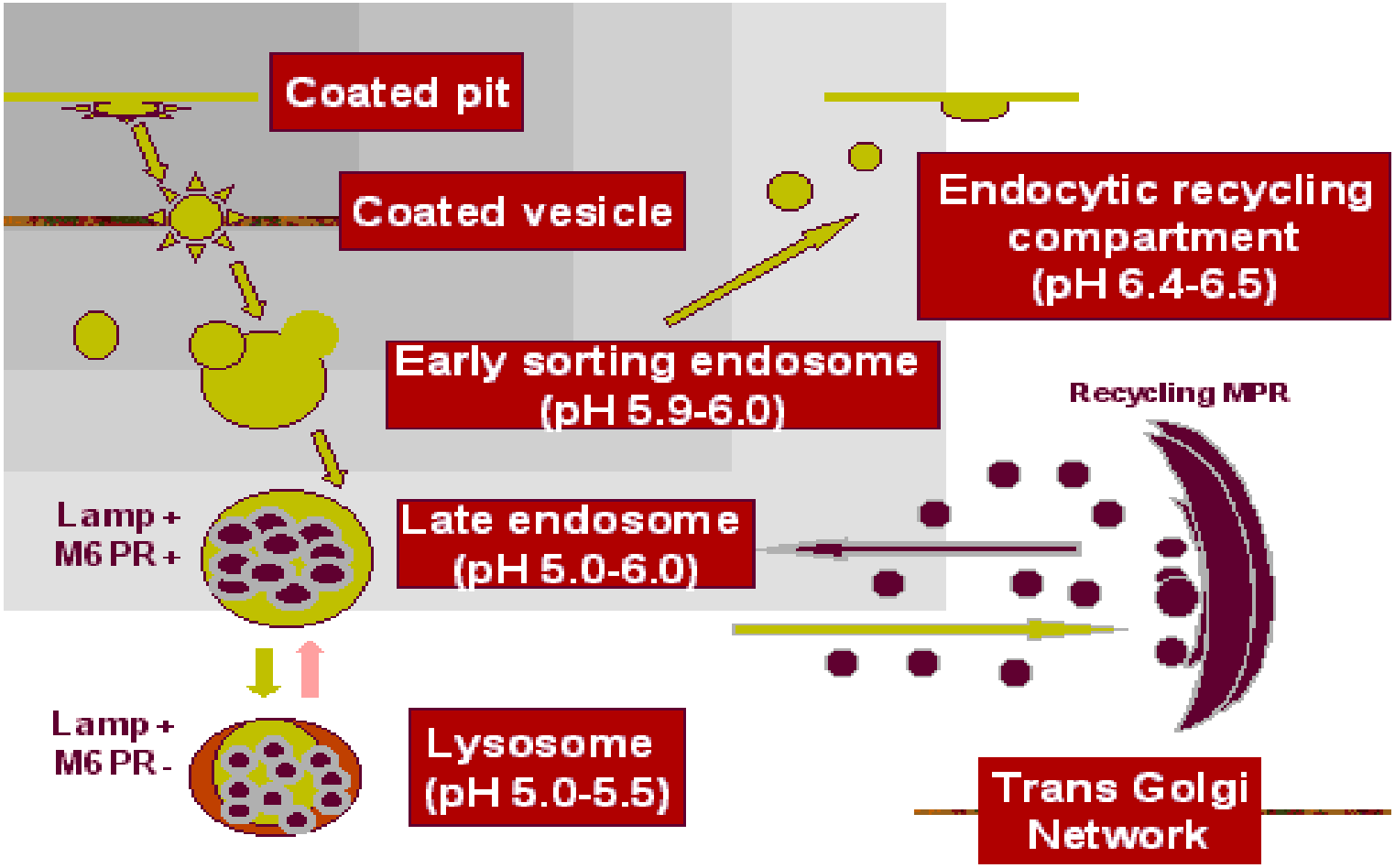
Wim J. C. Hop
Arnold J. J. Reuser
Ans T. van der Ploeg

# The natural course of non-classic Pompe's disease; a review of 225 published cases

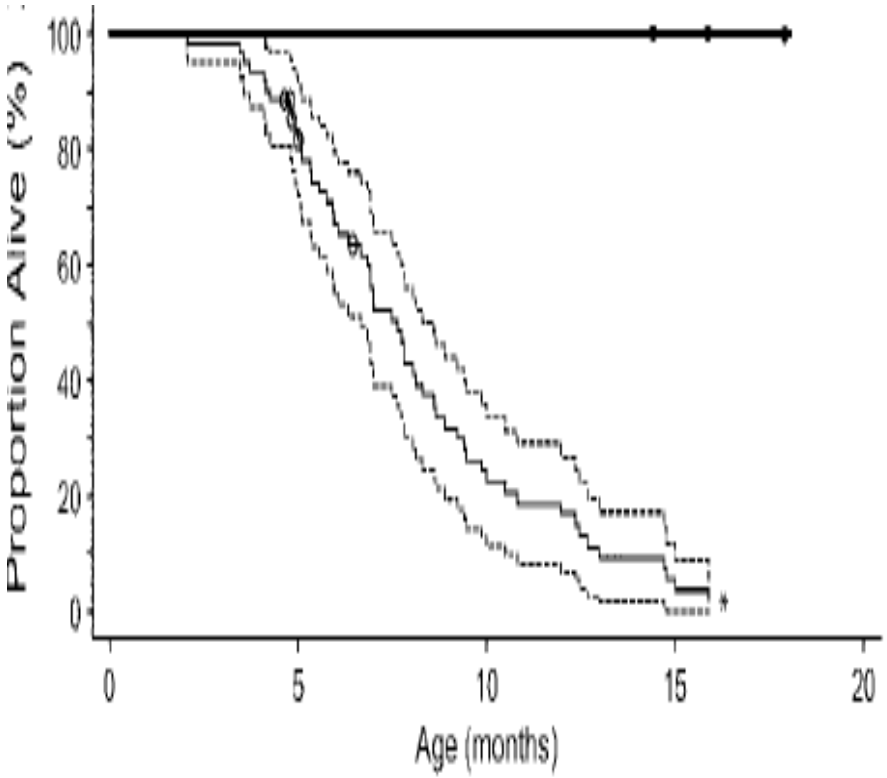


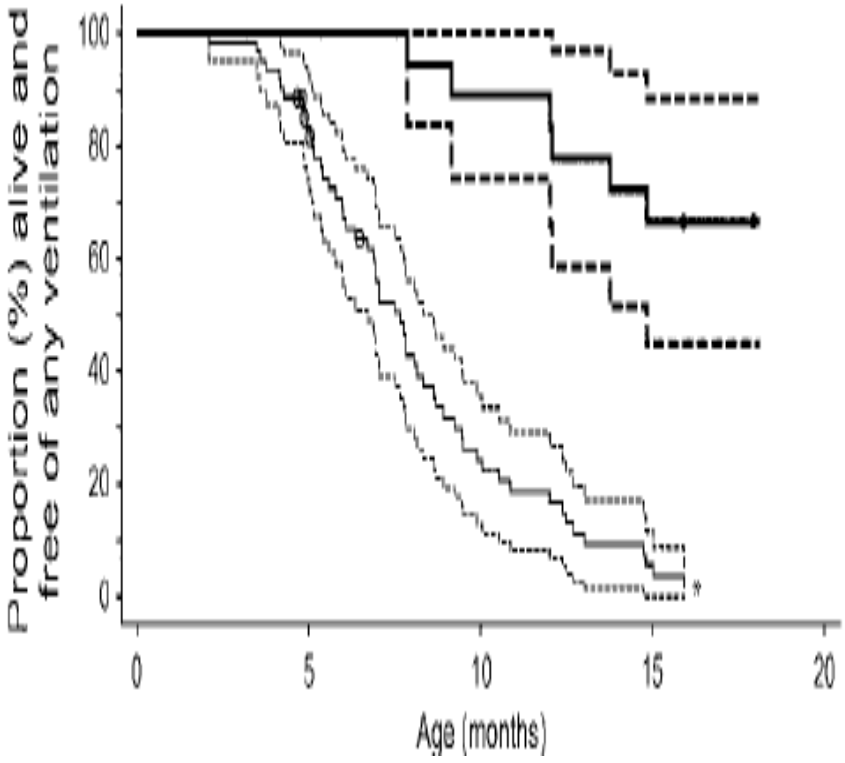

| | Age at onset | | | | |
|---|---|---|---|---|---|
| | Whole Group n = 225 | 0–1 years n = 32 | 1–6 years n = 24 | 6–18 years n = 30 | 18 years and older n = 139 |
| Muscular symptoms | | | | | |
| Muscle weakness | 213 (95) | 31 (97) | 23 (96) | 26 (87) | 133 (96) |
| Walking problems | 106 (47) | 23 (72) | 20 (83) | 10 (33) | 53 (38) |
| Problems rising | 59 (26) | 20 (63) | 8 (33) | 5 (17) | 26 (19) |
| Problems climbing stairs | 58 (26) | 18 (56) | 9 (38) | 5 (17) | 26 (19) |
| Problems sporting/running | 40 (18) | 7 (22) | 9 (38) | 5 (17) | 19 (14) |
| Delayed motor milestones | 31 (14) | 26 (81) | 5 (21) | 0 | 0 |
| Use of wheelchair | 18 (8) | 4 (1) | 2 (8) | 3 (10) | 9 (6) |
| Difficulty lifting objects | 5 (2) | 0 | 0 | 0 | 5 (4) |
| Difficulty combing hair | 3 (1) | 0 | 0 | 0 | 3 (2) |
| Respiratory symptoms | | | | | |
| Respiratory symptoms | 99 (44) | 17 (53) | 6 (25) | 12 (40) | 64 (46) |
| Artificial ventilation | 62 (28) | 13 (41) | 3 (13) | 5 (17) | 41 (30) |
| Skeletal symptoms/deformities | | | | | |
| Lordosis/kyphosis/scoliosis | 45 (20) | 3 (9) | 6 (25) | 7 (23) | 29 (21) |
| Scapula alata | 5 (2) | 1 (3) | 3 (13) | 1 (3) | 0 |
| Foot abnormalities | 5 (2) | 1 (3) | 1 (4) | 2 (7) | 1 (1) |
| Cardiac symptoms | | | | | |
| Hypertrophic cardiomyopathy | 12 (5) | 12 (38) | 0 | 0 | 0 |
| Cor Pulmonale | 4 (2) | 0 | 0 | 1 (3) | 3 (2) |
| Other heart abnormalities | 9 (4) | 4 (1) | 2 (8) | 0 | 3 (2) |
| Neurological symptoms | | | | | |
| Low/absent reflexes | 37 (16) | 6 (19) | 5 (21) | 3 (10) | 23 (17) |
| Hypotonia | 25 (11) | 17 (53) | 2 (8) | 2 (7) | 4 (3) |
| Pain | 13 (6) | 0 | 1 (4) | 1 (3) | 11 (8) |
| Aneurysmata | 6 (3) | 1 (3) | 1 (4) | 2 (7) | 2 (1) |
| Epilepsy | 2 (1) | 0 | 0 | 0 | 2 (1) |
| Other symptoms | | | | | |
| Fatigue | 23 (10) | 2 (6) | 2 (8) | 3 (10) | 16 (12) |
| Large tongue | 20 (9) | 13 (41) | 1 (4) | 1 (3) | 5 (4) |
| Feeding problems | 14 (6) | 12 (38) | 1 (4) | 0 | 1 (1) |
| Underweight | 9 (4) | 1 (3) | 3 (13) | 1 (3) | 4 (3) |
| Abnormal speech | 9 (4) | 2 (6) | 1 (4) | 0 | 6 (4) |
| Hepato(spleno)megaly | 8 (4) | 5 (16) | 3 (13) | 0 | 0 |
| Abnormal mental development | 3 (1) | 1 (3) | 1 (4) | 0 | 1 (1) |
| Hyperparathyreoidism | 1 (0.5) | 0 | 0 | 1 (3) | 0 |

# Principles of ERT in LSDs



# Recombinant human acid -glucosidase
# Major clinical benefits

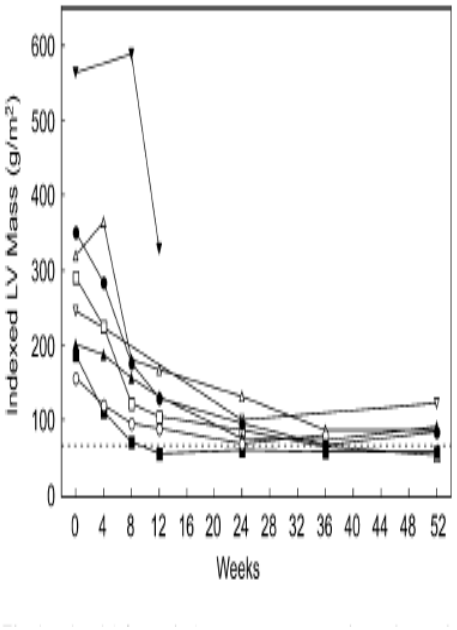


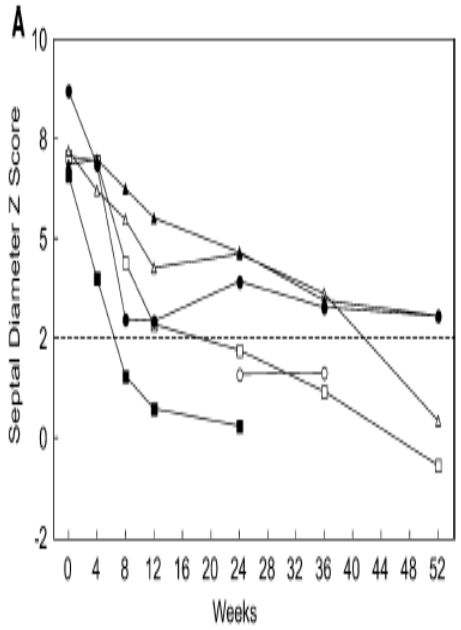




P.S. Kishnani et al neurology 2007

# Cardiac Remodeling After Enzyme Replacement Therapy with Acid α-Glucosidase for Infants with Pompe Disease

Jami C. Levine · Priya S. Kishnani · Y. T. Chen · J. Rene Herlong · Jennifer S. Li




| Parameter | Baseline ($n = 8$) Range | 52 weeks ($n = 6$) Range | $p$ value |
|---|---|---|---|
| LV mass by 2D echo (g/m$^2$) | 191 (157–565) | 87 (53–124) | <0.001 |
| PR interval on ECG (ms) | 90 (80–100) | 120 (100–140) | <0.001 |
| Sv1 + RV6 on ECG (mV) | 54 (40–71) | 36 (18–60) | 0.02 |
| Cardiothoracic ratio on CXR | 0.70 (0.60–0.73) | 0.57 (0.55–0.60) | 0.06 |

# Problems with ERT

- Technical/dangerous
- Intrusive
- Expensive

?effective

# Efficacy with ERT :

Timing of onset of ERT is crucial

- Raben 2002

- Used a tetracycline-regulated transactivator responsive promoter linked to GAA to turn production on and off
- 20-30% would completely clear glycogen← cardiac tissue at one month
- only partial clearance was achieved 6 months of age when the enzyme >150%
- Clinically hamden et al 2008

# skeletal

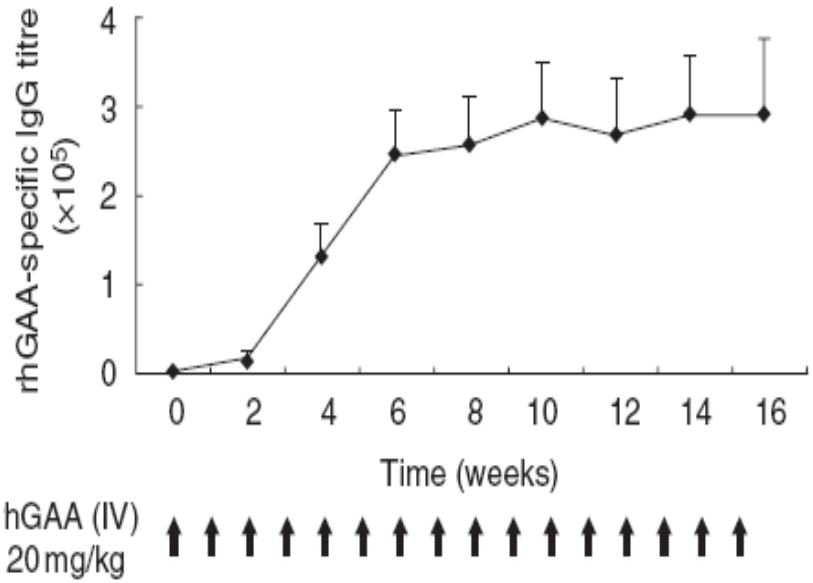
Poor skeletal muscle response:

- low abundance of the CI-MPR in skeletal muscle→ increase dose 20 times that of other ERT

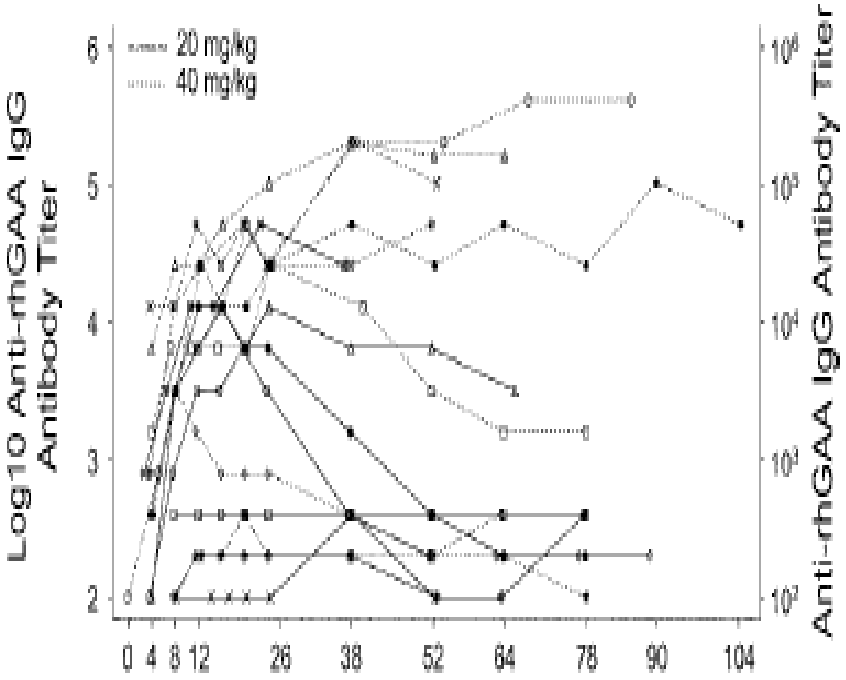
→ antibodies

# Antibody response to rhGAA

**A Joseph et al Ex Immun 2008**



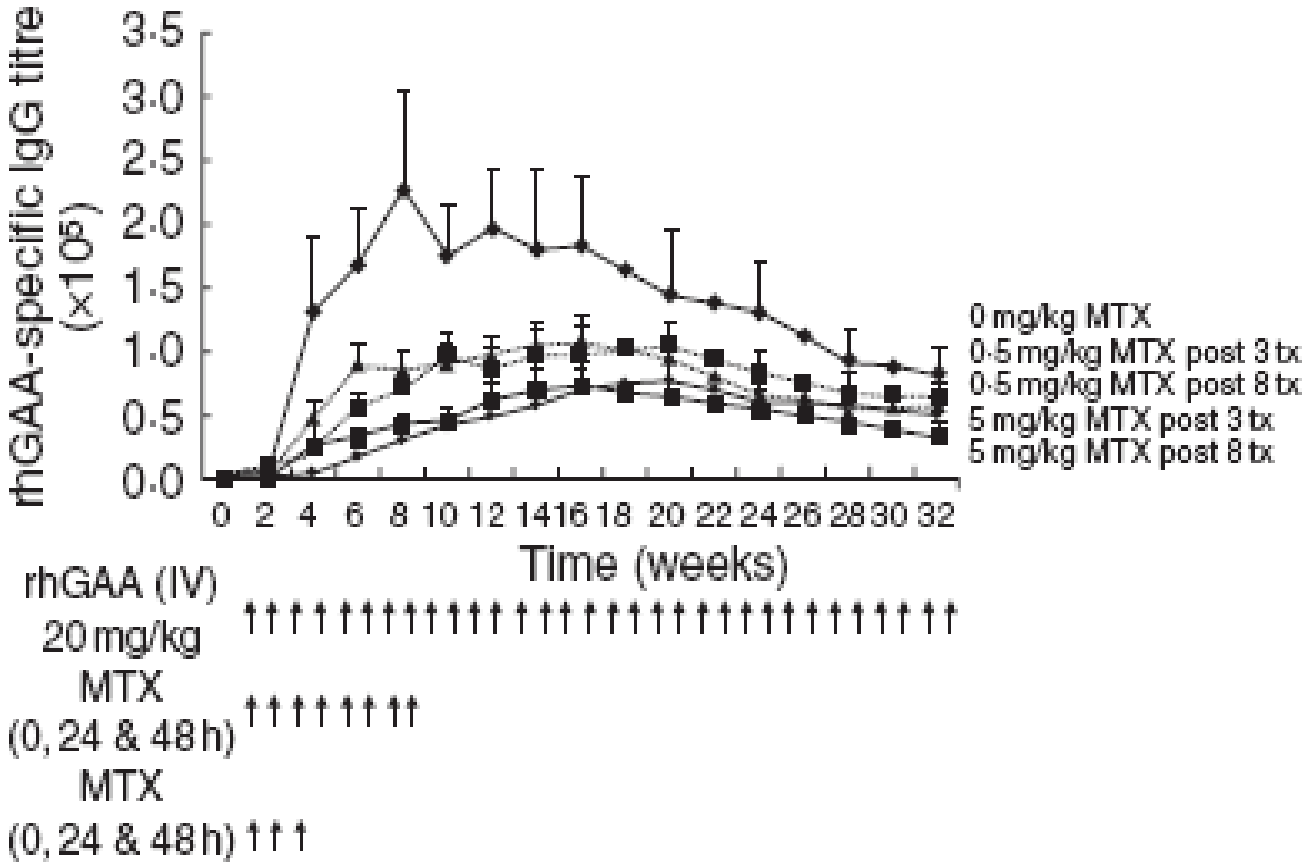

**P.S. Kishnani et al neurology 2007**



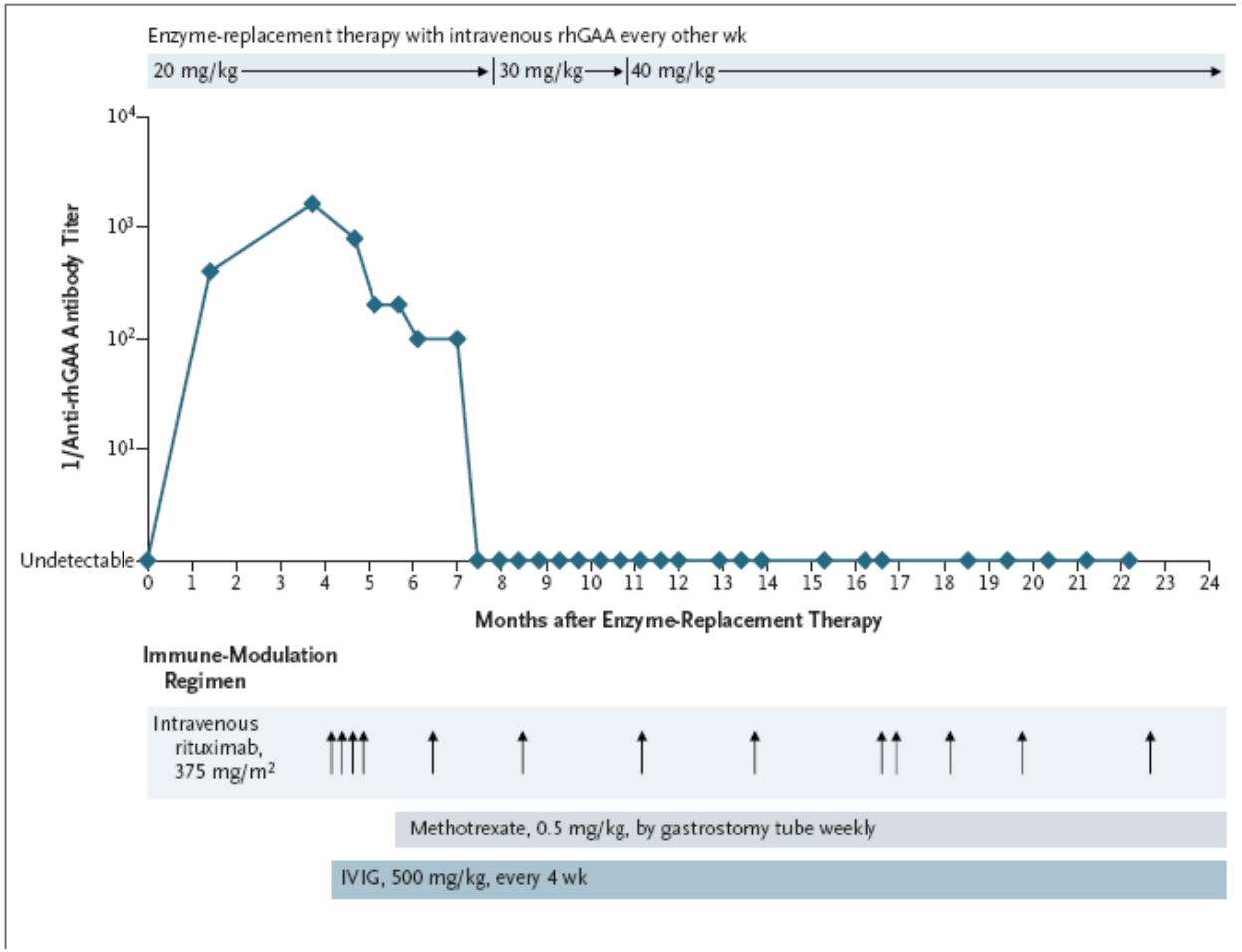
# Importance of CRIM status

- In Pompe up to 30% of patients may be CRIM negative
- No difference in the clinical or biochemical characteristics of the CRIM-negative patients when compared to the CRIM-positive patients.
- However outcome of CRIM –ve patients currently v poor

# Antibody levels modifyed by the addition of methotrexate



# Elimination of Antibodies to Recombinant Enzyme in Pompe's Disease



# Development of new phenotypes on treatment

## Acute Progression of Neuromuscular Findings in Infantile Pompe Disease

T. Andrew Burrow, MD*,
Laurie A. Bailey, MS*,
Douglas G. Kinnett, MD†, and
Robert J. Hopkin, MD*

# The future

*Human Molecular Genetics, 2010, Vol. 19, No. 4* **684–696**
*doi:10.1093/hmg/ddp535*
*Advance Access published on December 3, 2009*

## Restoration of muscle functionality by genetic suppression of glycogen synthesis in a murine model of Pompe disease

Gaelle Douillard-Guilloux[1,2†], Nina Raben[3], Shoichi Takikita[3], Arnaud Ferry[4,5,6], Alban Vignaud[4,5], Isabelle Guillet-Deniau[1,2], Maryline Favier[1,2], Beth L. Thurberg[7], Peter J. Roach[8], Catherine Caillaud[1,2,*] and Emmanuel Richard[1,2‡]