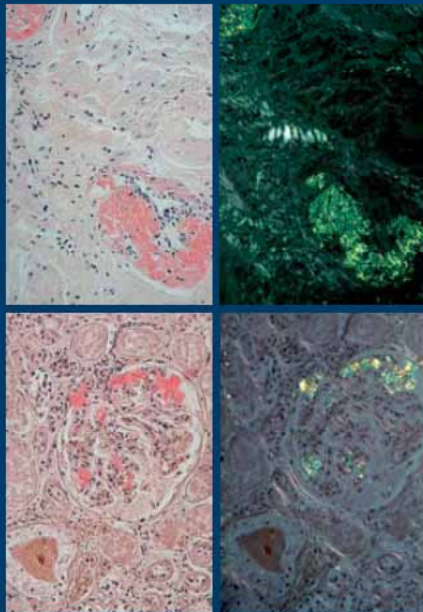




UniversitätsKlinikum Heidelberg



Eröffnungssymposium  
des Amyloidose-Zentrums  
Heidelberg

Samstag, 2. Mai 2009



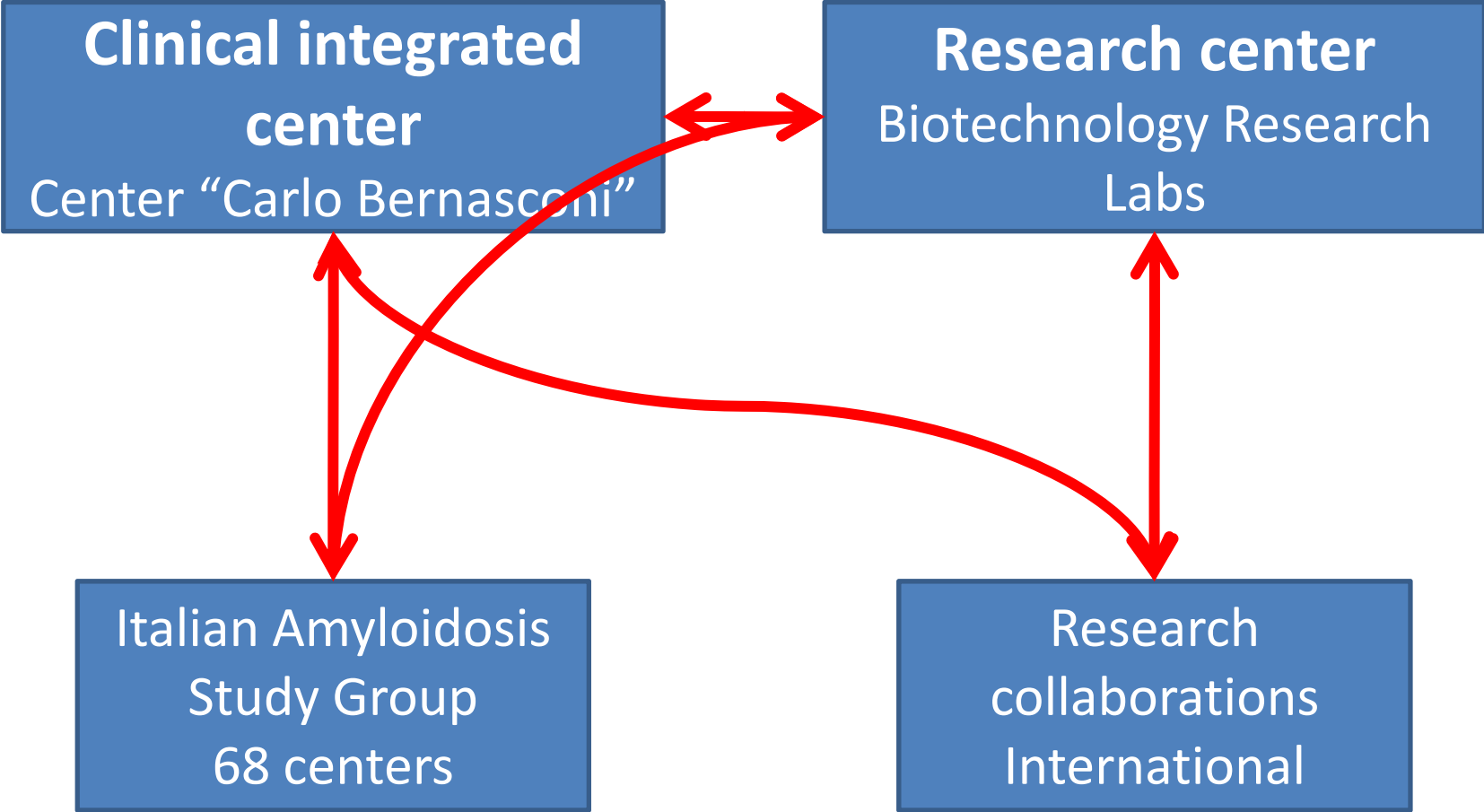
# Amyloid Research and Treatment Center Fondazione IRCCS Policlinico San Matteo University of Pavia, Italy



# University Hospital “Fondazione IRCCS Policlinico San Matteo” Amyloidosis Research and Treatment Center



Established in 1986

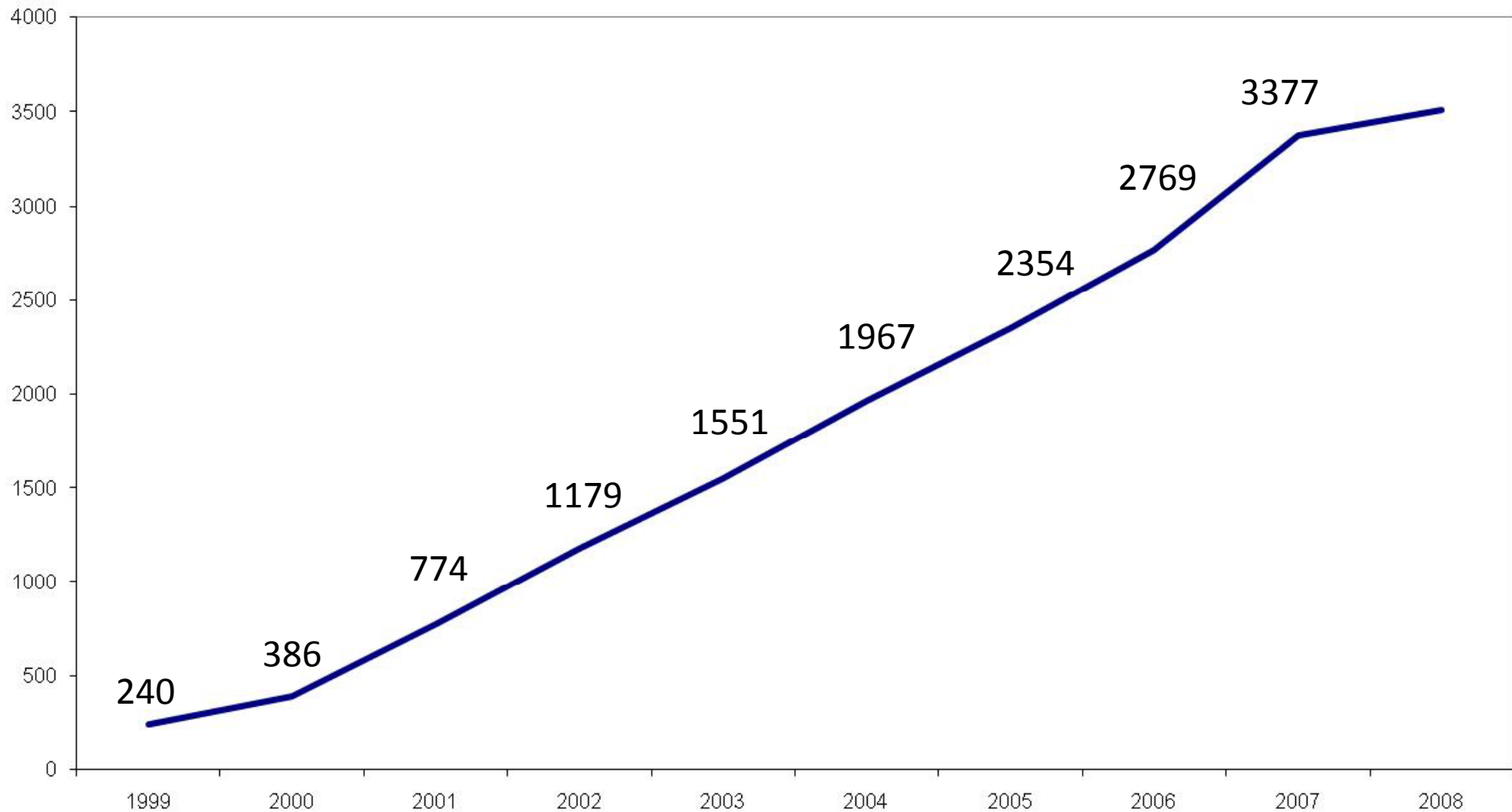




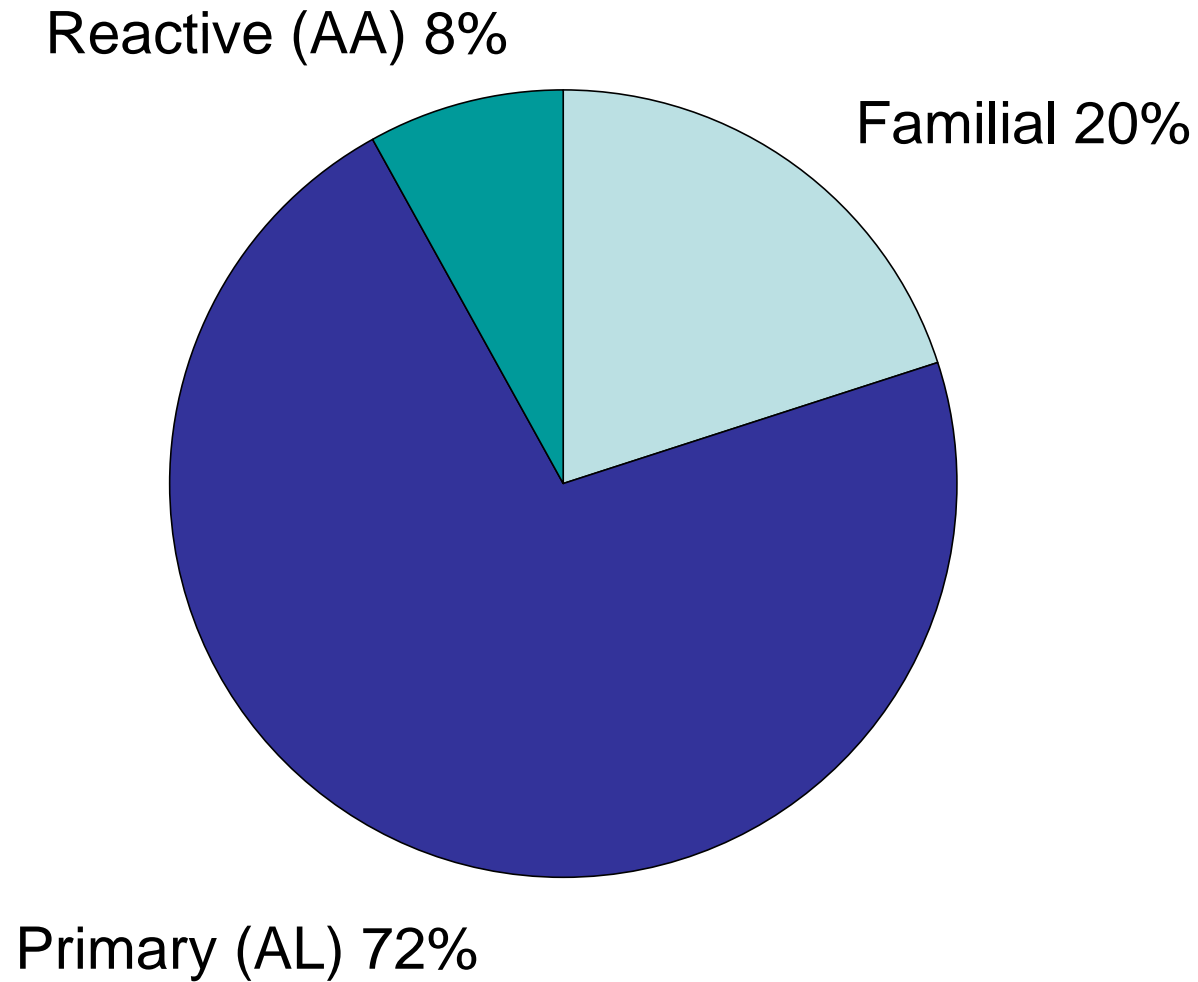
# University Hospital “Fondazione IRCCS Policlinico San Matteo” Amyloidosis Research and Treatment Center



Increase of patients evaluated each year at the Amyloidosis Research and Treatment Center



# Distribution of 1689 patients with systemic amyloidosis referred to the Pavia Amyloidosis Research and Treatment Center





# University of Pavia and University Hospital San Matteo



## Amyloid Research and Treatment Center

More than 200 new patients with systemic amyloidosis are evaluated each year. And additional > 3,000 follow-up evaluations are performed every year. The outpatient facility (2,150 square feet) allows for an extensive evaluation of patients within the Center.





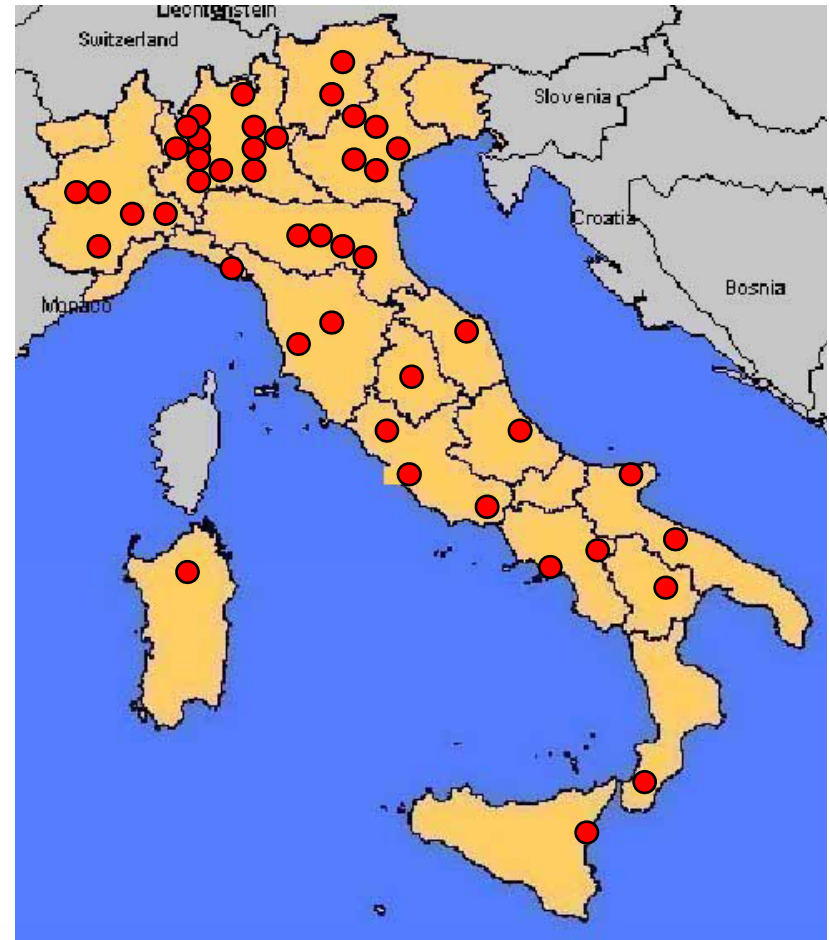
# Fondazione IRCCS Policlinico San Matteo - Univ. di Pavia Amyloid Research and Treatment Center



Italian Amyloidosis Study Group  
**68 medical centers** participate  
in the network

Web site: [www.amiloidosi.it](http://www.amiloidosi.it)

A **common diagnostic and therapeutic protocol** is  
periodically discussed and  
updated:  
last update in Rome May 31 2008  
next update in Turin May 16 2009

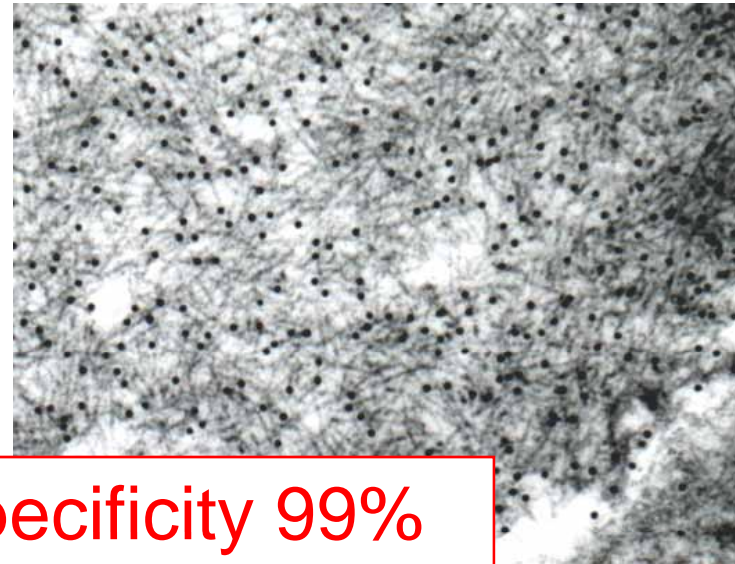
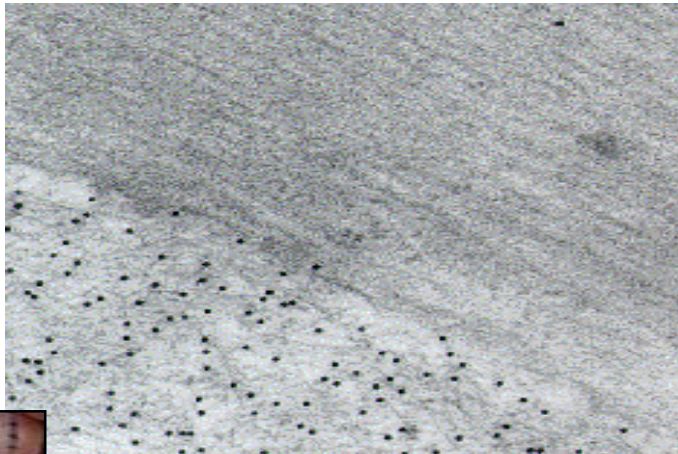


**ISA**

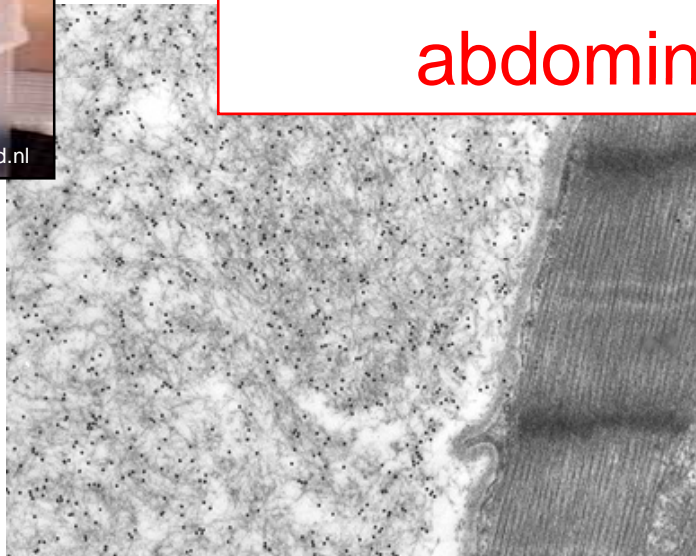
INTERNATIONAL SOCIETY OF AMYLOIDOSIS

# Typing of amyloid deposits

Ultrastructural (EM) immunohistochemistry with gold-labelled Ab



sensitivity 93%, specificity 99%  
based on 598 tests performed on  
abdominal fat aspirates

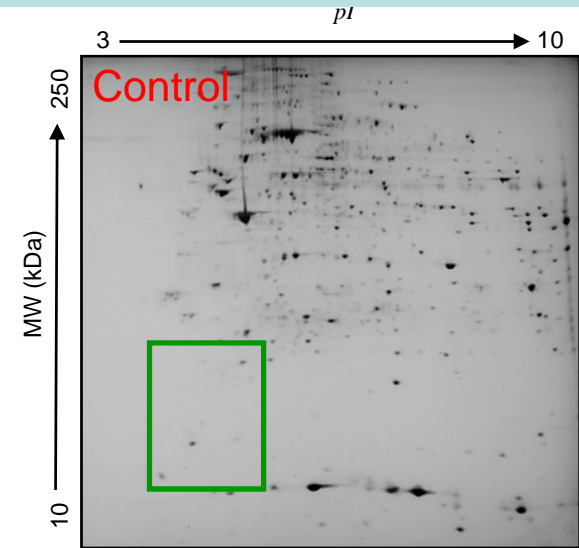
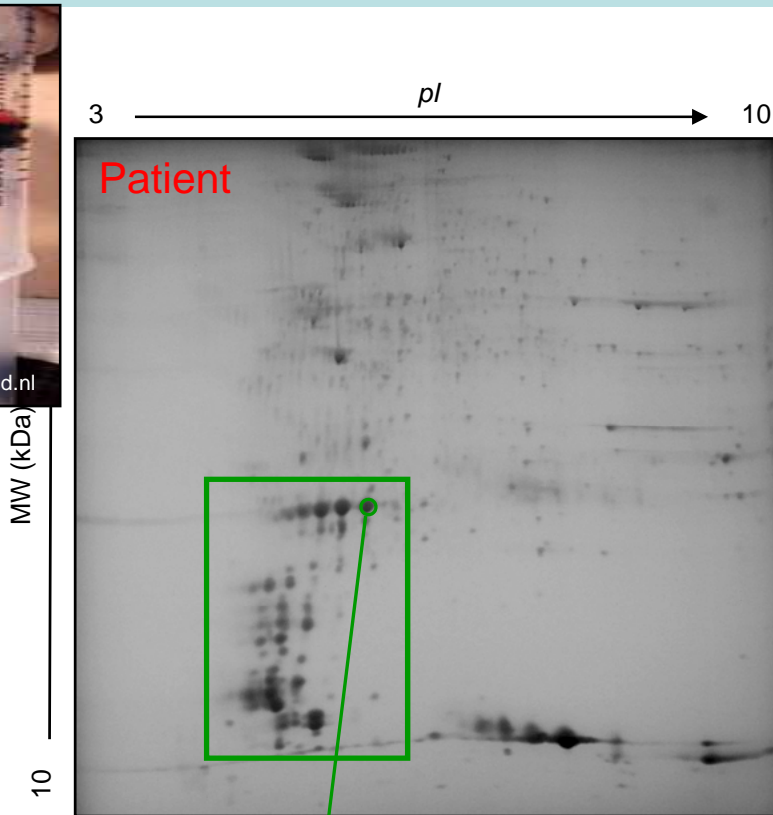


anti-TTR antibody

anti-apolipoprotein A-I antibody

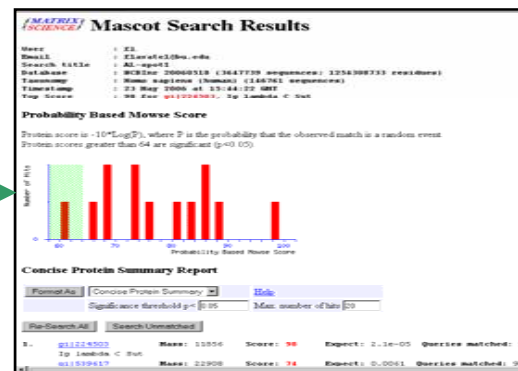
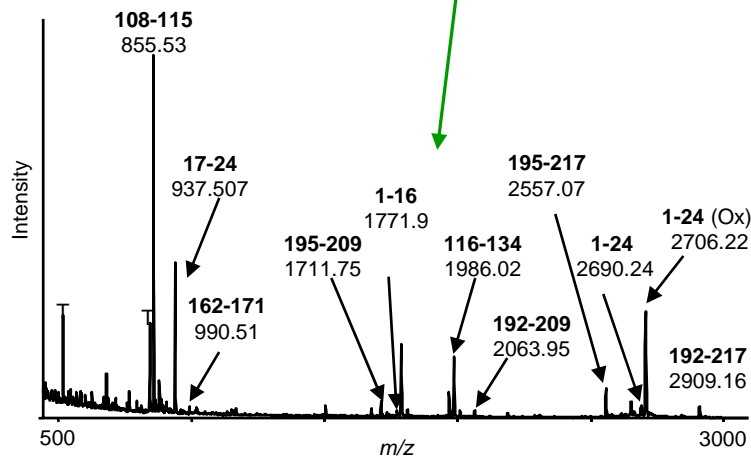
# TYPING AMYLOIDOSIS: PROTEOMICS ON ABDOMINAL FAT ASPIRATE

Lavatelli et al, Mol Cell Proteomics. 2008;7:1570-83.



LC sequence (from bone marrow) and coverage (underlined)

DFMLIQPHSV SESPGKTVTI SCTRSSGNIA SNYVQWYQQR PGSSPTTVIY  
 EDNQRPSGVP DRFSGSIDSS SNSASLTISG LKTEDEADYY QSDDESSVHW  
 VFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT  
 VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCVQ  
 THEGSTVEKT VAPTECS



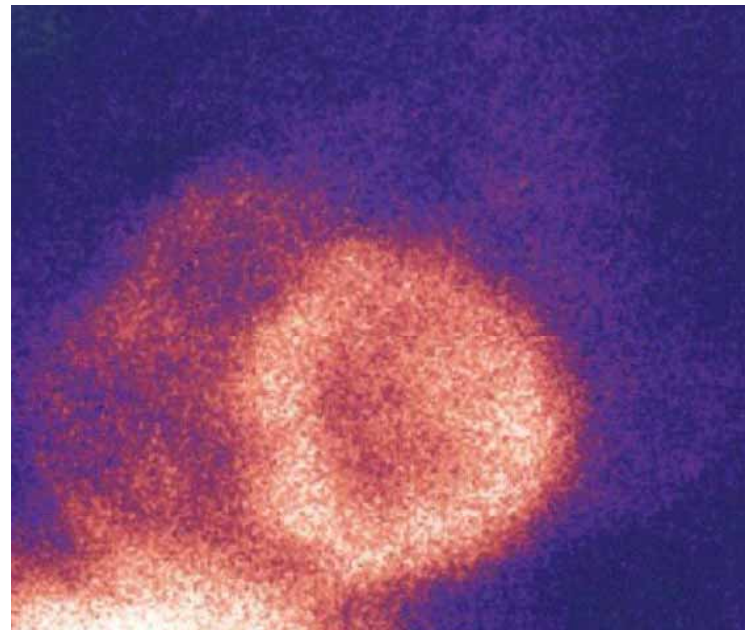
Lambda 6 light chain



# CARDIAC AMYLOID IMAGING

## ACCURACY OF $^{99m}\text{Tc}$ -APROTININ SCINTIGRAPHY FOR THE DETECTION OF MYOCARDIAL AMYLOIDOSIS: LONG-TERM FOLLOW-UP OF 108 PATIENTS

- SENSITIVITY 0.95
- SPECIFICITY 0.97
- ACCURACY 0.96



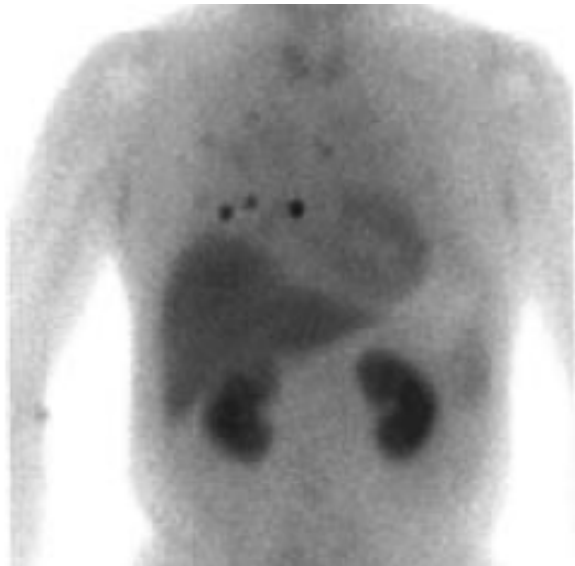
*Aprile et al, Eur J Nucl Med. 1995;22:1393-401*

# AMYLOID IMAGING

## <sup>99m</sup>Tc-Aprotinin Scintigraphy in Amyloidosis

*Schaadt et al, J Nucl Med. 2003;44:177-83*

Focal accumulations of <sup>99m</sup>Tc aprotinin were seen in different organs of 22 patients with a total of 90 lesions, of which 20 were confirmed by biopsy or autopsy. Scintigraphy revealed “silent” amyloid deposits in at least 5 patients who later developed clinical symptoms.



A 64-y-old man (patient 5) with renal AL amyloidosis.

Whole-body scintigram shows pathologic uptake in heart, liver, and right lung or pleura (anterior view).

Patient had no symptoms from heart at time of scintigraphy but died of heart failure 8 mo later.

# The iodinated anthracycline 4'-iodo-4'-deoxydoxorubicin binds specifically and with very high affinity to amyloid fibrils

*PNAS 1995;92:2959*

*Am J Pathol 2000;156:1919*

## Promotes fibril disaggregation in vitro

*Am J Pathol 2000;156:1919*

*Biochem J 2000;351:273*

*FASEB J 2003;17:803*

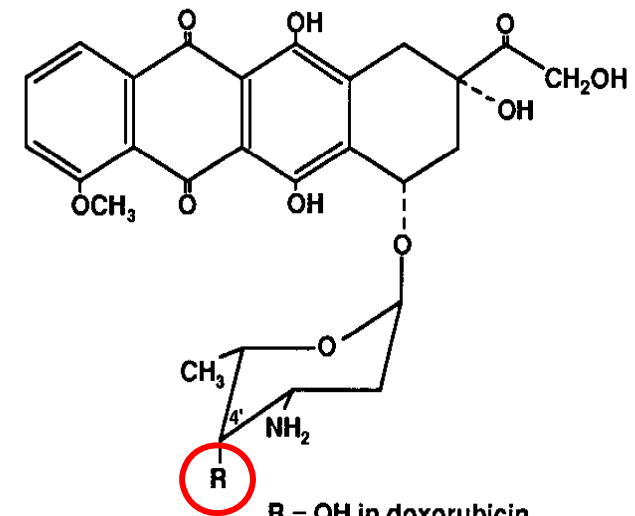
## Induces 15% (15 mg/m<sup>2</sup>)-40%

(80-30 mg/m<sup>2</sup>) of responses in AL patients

*Blood 1995;86:855*

*Blood 1999;93:1112*

*Amyloid 2002;9:24*



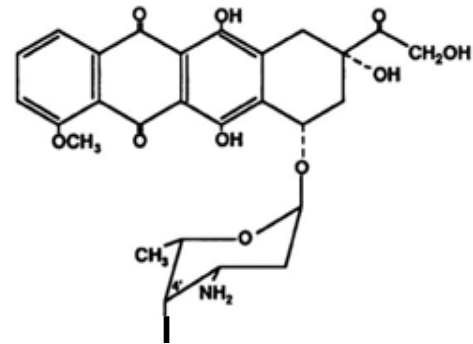
R = OH in doxorubicin

R = I in 4'-iodo-4'-deoxydoxorubicin

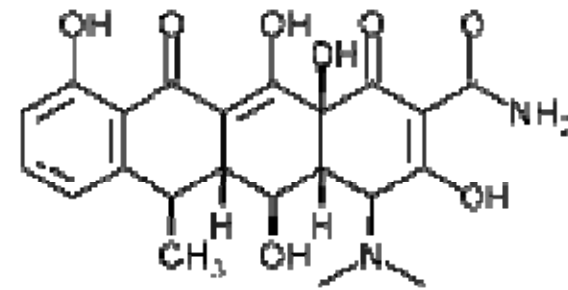
**best use in conjunction with chemotherapy**

4'-iodo-4'-Deoxydoxorubicin and tetracyclines disrupt transthyretin amyloid fibrils in vitro producing noncytotoxic species: screening for TTR fibril disrupters

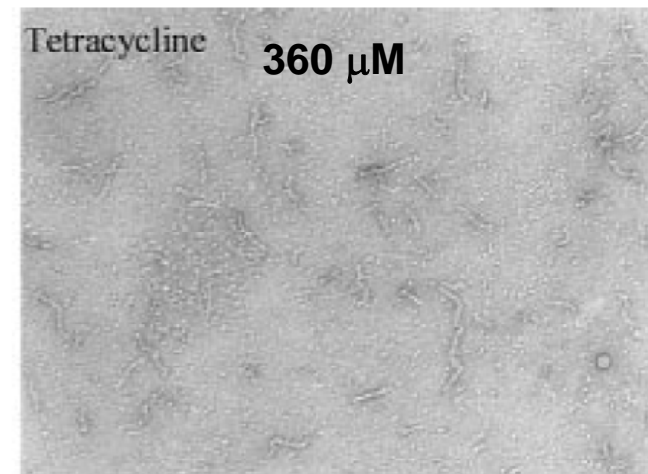
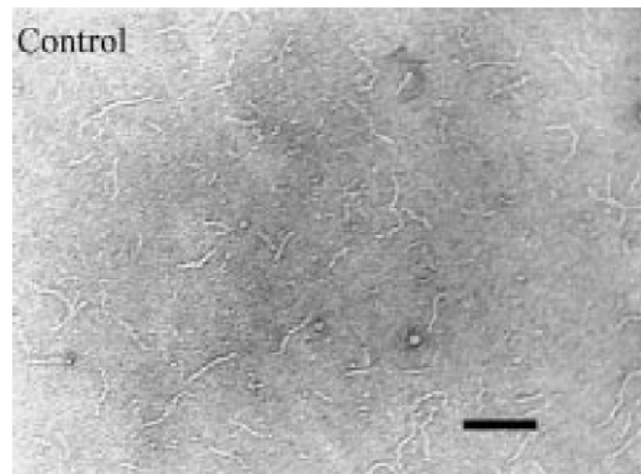
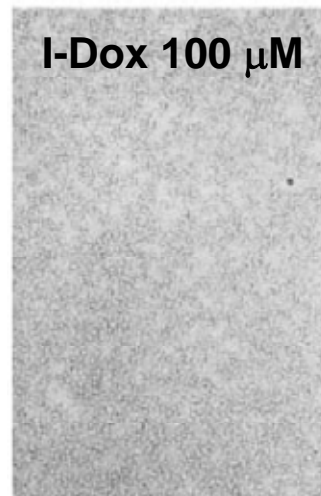
Cardoso I, Merlini G, Saraiva M, *FASEB J.* 2003; 17:803–809



4'-iodo-4'-deoxydoxorubicin



Doxycycline





University of Pavia and University Hospital San Matteo



Amyloid Research and Treatment Center

## Clinical research

- new diagnostic approaches (proteomics)
- new imaging techniques
- development of novel drugs (phase I-II and III trials)
  - Phase I-II:       bortezomib in AL amyloidosis  
                      Fx-1006 in ATTR amyloidosis
  - Phase II:         CLD in AL amyloidosis  
                      Diflunisal in ATTR amyloidosis  
                      Doxycyclin in ATTR amyloidosis
  - Phase III:        MDex vs BMDex



University of Pavia and University Hospital San Matteo



## Amyloid Research and Treatment Center

The Amyloid Center and the **Biotechnology Research Laboratories** (BRL) are a single unit within the University Hospital, combining clinical and basic research.

The BRL laboratory space is approximately 4,300 square feet.

The BRL comprises a serum/tissue bank of more than 1000 amyloid patients.

The BRL instruments allow all the proteomic and genetic studies that are part of the project.

The BRL facilities include state-of-the-art equipment, for protein purification and analysis and for proteomics studies including mass spectrometers (MALDI-TOF, Q-TOF) operated by expert personnel of the BRL.



# University of Pavia and University Hospital San Matteo



## Amyloid Research and Treatment Center



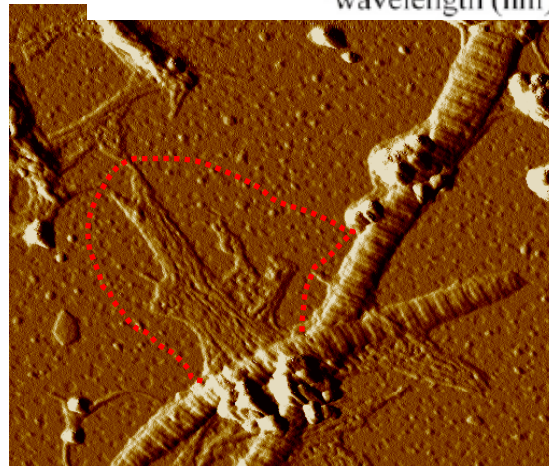
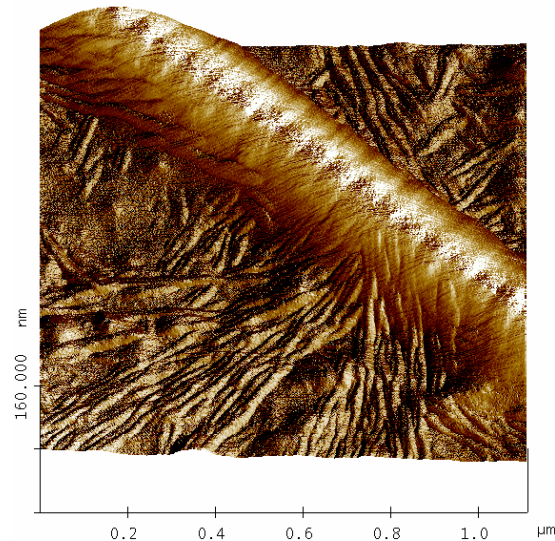
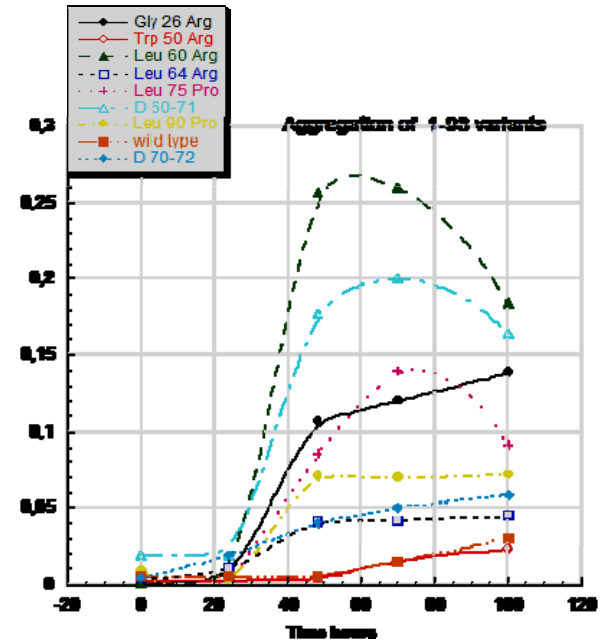
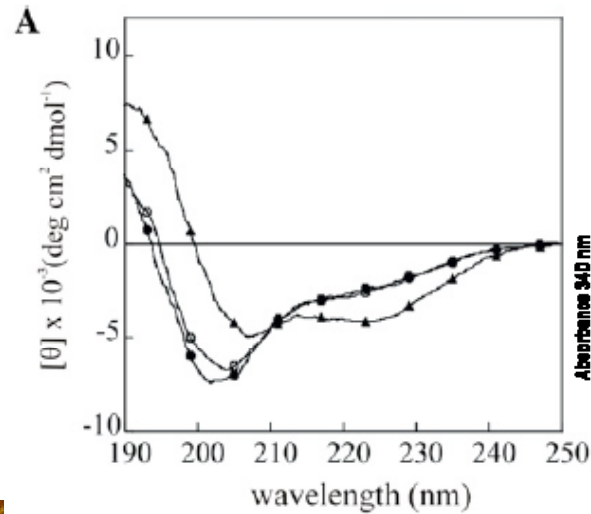


## Amyloid Research and Treatment Center

### Basic research

- Mechanism of amyloid formation in  $\beta 2m$  and apoA1 amyloidosis

- Amyloid tissue targeting



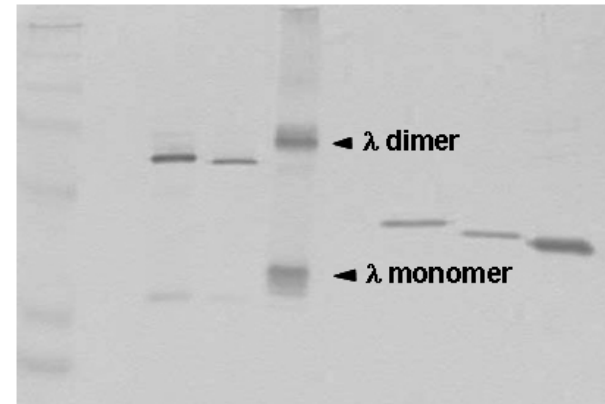
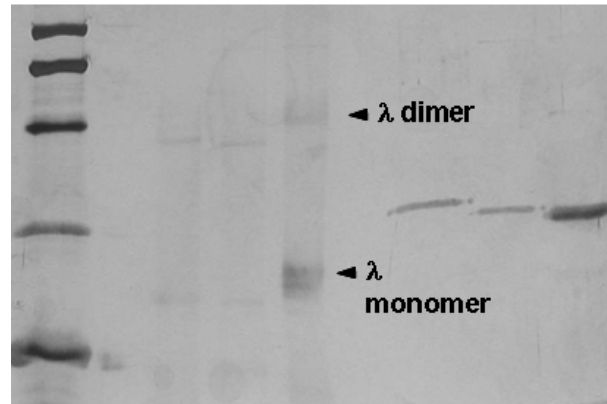




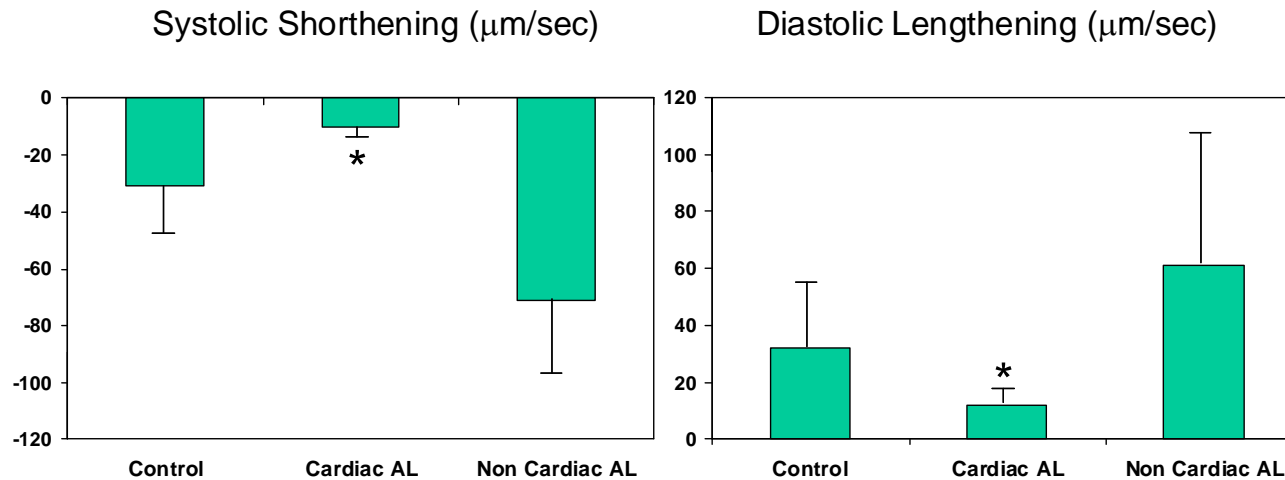
## Amyloid Research and Treatment Center

### Basic research

- Amyloid **tissue damage**: investigating amyloid cardiotoxicity
  - production of recombinant complete light chains



- testing the toxicity on cardiomyocytes





University of Pavia and University Hospital San Matteo



## Amyloid Research and Treatment Center

### Collaborations

EURAMY Group (Uppsala, Umea, Groningen, Berlin, Limoges, Porto)

National Amyloid Centre, London (Prof. M. Pepys, Prof. P. Hawkins)  
biomarkers – new drugs

Instituto de Biologia Molecular e Celular, Porto, Portugal (Prof. Maria J. Saraiva)  
new drugs

Institute of Neuropathology, University Hospital of Zürich (Prof. A. Aguzzi)  
animal models

Boston University Amyloid Program (Dr. D. Seldin, Dr. C. Costello)  
proteomics, clinical trials

Mayo Clinic, Monoclonal Gammopathy Centre (Dr. M. Gertz, Dr. Dispenzieri)  
clinical trials



# University of Pavia and University Hospital San Matteo



## Amyloid Research and Treatment Center

*Vittorio Bellotti  
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 Francesca Lavatelli  
 Paola Russo  
 Mario Nuvolone  
 Laura Verga  
 Monica Stoppini  
 Irene Zorzoli  
 Palma Mangione  
 Sofia Giorgetti  
 Simona Casarini  
 Simona Donadei  
 Valentina Navazza  
 Silvia Gabba  
 Sara Marini  
 Alberto Bovera  
 Chiara Crosignani*



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