Novel approaches to diagnosis and treatment of TTR amyloidosis

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University of Bologna, Italy

Disclosures:
• Research grants from Pfizer
• Speaker and Advisory Board honoraria from Pfizer, GSK, Prothena, Eidos
Agenda

- New pathophysiological insights
- Advances in noninvasive diagnosis
- Broadening the disease phenotype
- New disease-modifying treatments
Apo A

\[ \text{pK}_a \text{ His 6.5} \quad \text{pK}_a \text{ Asp, Glu 4.4} \]

\[
\begin{align*}
\text{pH 7.5} & \quad \text{Native State} & \quad \text{Rearranged} \\
\text{Tetrameric TTR} & \quad \text{Tetrameric TTR} & \quad \text{Monomeric Amyloidogenic Intermediate} \\
& \quad \text{H}^+ & \quad \text{H}^+ & \quad \text{H}^+ \\
& \quad \text{Amyloid Fibrils} & \quad (\text{slightly altered tertiary structure})
\end{align*}
\]

\[
\text{pH 2.0} \quad \text{A-state} \quad \text{H}^+
\]

TTR
Amiloide

Nylon

struttura  microscopio atomico
Pathogenesis of TTR Amyloidosis

Small oligomers

Amyloid fibrils

interaction with microenvironment of target organs GAG, SAP

enzymatic activity proteolysis

Monomer misfolding

Aggregation

Small oligomers

*Tauroursodeoxycholic acid

Folded monomer

Misfolded monomer

Rate-limiting tetramer dissociation

*Tauroursodeoxycholic acid
AMYLOID FIBRIL COMPOSITION

From O.B. Suhr, Journal of Internal Medicine 2017

- *Late-onset Val30Met*
- *m-ATTR non-Val30Met*
- *Wt-ATTR*
- *Early-onset Val30Met*

**Type A fibrils**  →  **Full length + fragments**  →  **Type B fibrils**  →  **Only Full length**

- Proteolytic cleavage at residues 46, 49 and 52
- Misfolded monomers Full-length TTR
- Amyloidogenic N-terminal fragment
- TTR tetramer
- CD loop residues 50-53
Main determinants of phenotypic heterogeneity in ATTR

- Geographic area
- Ethnicity
- Fibril composition (full length vs. mixed full length/fragments)
- Type of aggregation (val30Met):
  - Endemic
  - Non endemic
- Type of mutation
- Age
- Patient gender
- Gender of transmitting parent
55 sites from 18 countries enrolled patients

THAOS REGISTRY
Spectrum of genotypes (%)  
N=2538

- Val30Met: 65.10%
- Thr60Ala: 11.60%
- Phe64Leu: 4.20%
- Ile107Val: 2.00%
- Other mutations: 1.70%
- Val122Ile: 1.50%
- Glu89Gln: 1.30%
- Gly47Ala: 0.90%
- Ser50Arg: 0.90%
- Leu111Met: 0.70%
- Ser77Tyr: 0.70%
- Ile68Leu: 0.70%
- Val20Ile: Other 69 mutations

Data as of 06 January 2015
Frequency of main of phenotypes at presentations N=2064

- Neurologic: 53.8%
- Cardiac: 18.1%
- Mixed: 28.1%

Data as of 06 January 2015
Genotypic-Phenotypic Correlation in ATTR

V30M early onset
V30M late onset
G47A
F64L
E89L
S77Y
V30M
T60A
L111M
I68L
V122I
E89Q
T49A
I107V
WT

"Neurologic"

"Cardiac"

Rapezzi (THAOS database)
Rapezzi EHJ 2013
TTR Cardiac Amyloidosis in Europe: an Insight Through the Transthyretin Amyloidosis Outcome Survey (THAOS)

Thibaud D .... Rapezzi C, EHJ 2018 submitted
Main determinants of phenotypic heterogeneity in ATTR

- Geographic area
- Ethnicity
- Fibril composition (full length vs. mixed full Length/fragments)
- Type of aggregation (val30Met): Endemic, Non endemic
- Type of mutation
- Age
- Patient gender
- Gender of transmitting parent
Gender imbalance in ATTR: a metanalysis of 8563 cases

Val30Met Early Onset (n=2394) 0.52 (0.50, 0.54)
Val30Met Late Onset (n=757) 0.63 (0.60, 0.66)
Cardiogenic mutations (n=1032) 0.76 (0.74, 0.79)
ATTR wild type (n=4380) 0.93 (0.93, 0.94)
Overall (I-squared = 99.8%, p = 0.000) 0.87 (0.86, 0.87)

Proportion of males

Rapezzi C et al, submitted
Gender imbalance in ATTR: a metanalysis of 8563 cases

Rapezzi C et al, submitted
Multivariate Regression Analysis *  
(parameter estimate and p values)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Cardiac mutations</th>
<th>V30M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.0082 (p=0.023)</td>
<td>0.0042 (p=0.65)</td>
<td>0.0044 (p=0.187)</td>
</tr>
<tr>
<td>Age at ECHO</td>
<td>0.0087 (p&lt;0.0001)</td>
<td>0.0141 (p=0.0011)</td>
<td>0.0064 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

*data from 227 pts with complete echocardiographic evaluation

male gender and age = positive independent predictors of increasing mean parietal LV thickness in the overall population

Rapezzi C et al, submitted
Agenda

- New pathophysiologic insights
- Advances in noninvasive diagnosis
- Broadening the disease phenotype
- New disease-modifying treatments
General Profile of TTR-CM patients with Exclusively Cardiac Phenotype

- **Male** gender
- Average age ~ 75 yrs
- **No apparent family history** of ATTR
- Heart failure symptoms
- Frequent history of CTS
- Symmetric “LV hypertrophy”
- Absent or mild LV dilatation
- Mild LV systolic **dysfunction**
Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths

**ATTRwt's clinical spectrum**

- Mode of presentation:
  - HF (67.6%)
  - AV block (7.4%)
  - Stroke
  - HCM or RCM (13.9%)
  - Degenerative AS
  - Incidental (11.1%)

**Age, gender and comorbidities**
- Males (81.5%)
- Females (18.5%)
- Late 70s symptoms onset
- HTN (54.6%)

**ECG**
- AF (55.6%)
- Pseudoinfarct pattern (63.2%)
- Low voltage (22%)
- LVH (10.5%)
- L/RBBB (17-15%)

**Echocardo**
- Symmetric LVH (75.7%)
- Asymmetric LVH (23.4%)
- LVEF<50% (35.8%)
- Restrictive diastolic pattern (35%)
- Pericardial effusion (42.1%)

**Survival**
Overall survival at 12, 24 and 36 months: 93, 89 and 74%, respectively
Towards the definite diagnosis of AC

Histology +/- proteomic +/- DNA +/- immunohistochemistry

«bone tracers» scintigraphy

CMR

Clinical evaluation, Lab exam, ECG, Echocardiogram
Towards the definite diagnosis of AC

- Histology +/- proteomic +/- DNA +/- immunohistochemistry
- CMR
- Clinical evaluation, ECG, Echocardiogram Biomarkers
- Bone scintigraphy
- Tracers
Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis

Candida Cristina Quarta¹,², Esther Gonzalez-Lopez³, Janet A. Gilbertson¹, Nichola Botcher¹, Dorota Rowczenio¹, Aviva Petrie⁴, Tamer Rezk¹, Taryn Youngstein¹, Shameem Mahmood¹, Sajitha Sachchithanantham¹, Helen J. Lachmann¹, Marianna Fontana¹, Carol J. Whelan¹, Ashutosh D. Wechalekar⁴, Philip N. Hawkins¹, and Julian D. Gillmore¹⁶

Table I  Diagnostic sensitivity of fat pad fine needle aspiration in different cardiac amyloidoses

<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>n</th>
<th>Number positive by Congo red staining</th>
<th>Diagnostic sensitivity (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic AL amyloidosis</td>
<td>216</td>
<td>181</td>
<td>84% (78–88%)</td>
</tr>
<tr>
<td>ATTRm</td>
<td>113</td>
<td>51</td>
<td>45% (36–54%)</td>
</tr>
<tr>
<td>Val122Ile</td>
<td>69</td>
<td>23</td>
<td>33%</td>
</tr>
<tr>
<td>Thr60Ala</td>
<td>21</td>
<td>14</td>
<td>67%</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>271</td>
<td>42</td>
<td>15% (11–20%)</td>
</tr>
</tbody>
</table>
TcDPD Scintigraphy

Perugini et al, J Am Coll Cardiol 2005
Paradox!

ATTR

AL

LV

RV

99mTc-DPD
Early Diagnosis of TTR-Related Cardiac Amyloidosis in asymptomatic carriers

Rapezzi et al, JACC Imaging 2011
$^{99m}$Tc-PYP in Cardiac Amyloidosis

**Visual Cardiac Score**
- 0 Absent Myocardial Uptake
- 1 Myocardial Uptake $<$ Bone
- 2 Myocardial Uptake $=$ Bone
- 3 Myocardial Uptake $>$ Bone

**Heart-to-Contralateral Ratio**
\[
\text{H/CL Ratio} = \frac{\text{Heart ROI Mean Counts Per Pixel}}{\text{Contralateral ROI Mean Counts Per Pixel}}
\]
Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Rodney H. Falk, MD; Giampaolo Merli, MD; Thibaud Damy, MD; Angela Dispenzieri, MD; Ashutosh D. Wechalekar, MD, DM; John L. Berk, MD; Candida C. Quarta, MD, PhD; Martha Grogan, MD; Helen J. Lachmann, MD; Sabahat Bokhari, MD; Adam Castano, MD; Sharmila Dorbala, MD, MPH; Geoff B. Johnson, MD, PhD; Andor W.J.M. Glaudemans, MD, PhD; Tamer Rezk, BSc; Marianna Fontana, MD; Giovanni Palladini, MD, PhD; Paolo Milani, MD; Pierluigi L. Guidalotti, MD; Katarina Flatman; Thirusha Lane, MSc; Frederick W. Vonberg, MBBS; Carol J. Whelan, MD; James C. Moon, MD; Frederick L. Ruberg, MD; Edward J. Miller, MD, PhD; David F. Hutt, BApSc; Bouke P. Hazenberg, MD, PhD; Claudio Ravezzi, MD; Philip N. Hawkins, PhD, FMedSci

Circulation. 2016;133:2404-2412.
Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloidosis

Bone scintigraphy with $^{99m}$Tc-DPD/HMDP/PYP

- **Grade 0**
  - Cardiac AL/ATTR amyloidosis unlikely

- **Grade 1**
  - Need specialized assessment for Diagnosis: Histological confirmation and typing of amyloid
    - Review/request CMR

- **Grade 2 to 3**
  - Cardiac ATTR amyloidosis
  - TTR genotyping

Serum immunofixation + Urine Immunofixation + serum free light chain assay (Freelite)
Monoclonal protein present?

- **No**
  - Cardiac amyloidosis (AL/APOAI/ATTR/other)

- **Yes**
  - **Yes**
    - Variant ATTR amyloidosis
  
  - **No**
    - Wild-Type ATTR amyloidosis
Broadening the DIAGNOSTIC HORIZON of ATTR

- Unexpected myocardial uptake during «bone» scintigrapghies
- Carpal tunnel syndrome
- HFpEF
- Paradoxical «low flow low gradient» AO stenosis in the elderly
- Diagnosis of «HCM» in the adult or in ATTR endemic areas
Prevalence of incidental myocardial uptake of 99 mTc-DPD (n=12,300)
Standardized incidence ratios of carpal tunnel syndrome reported by years before the diagnosis of amyloidosis.

Bologna, n= 435

Rapezzi C et al, submitted
ATTRwt Cardiac Amyloid: Common in HFpEF

Distribution of Ejection Fraction in Subjects Hospitalized with Heart Failure

- HFrEF
- HFpEF
- HFnEF

? Prevalence of ATTR Cardiac Amyloid

13% of HFnEF have ATTR Cardiac Amyloid

Technetium 99m bone tracers (DPD, PYP, HDP) have ~90% sensitivity/specificity for identifying ATTR cardiac amyloid

Gonzalez-Lopez E, Eur Heart J. 2015;36:2585-94
Castano A et al, Eur Heart J. 2015;36:2595-7
5/43 pts (12\%)
Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement

Adam Castaño\textsuperscript{1,2,*}, David L. Narotsky\textsuperscript{1}, Nadira Hamid\textsuperscript{3}, Omar K. Khalique\textsuperscript{3}, Rachelle Morgenstern\textsuperscript{2}, Albert DeLuca\textsuperscript{2}, Jonah Rubin\textsuperscript{1}, Codruta Chiuzan\textsuperscript{4}, Tamim Nazif\textsuperscript{3}, Torsten Vahl\textsuperscript{3}, Isaac George\textsuperscript{3}, Susheel Kodali\textsuperscript{3}, Martin B. Leon\textsuperscript{3}, Rebecca Hahn\textsuperscript{3}, Sabahat Bokhari\textsuperscript{2}, and Mathew S. Maurer\textsuperscript{1}

European Heart Journal (2017) 38, 2879–2887

TcPYP Screening in 151 pts with AS

![Pie charts showing prevalence of ATTR-CA in females and males.](image-url)
• 298 consecutive patients diagnosed with increased LVWT
• Median age 62, 74% men, 23% of African origin; median LVWT 18 mm

Conclusions: 5% of patients diagnosed with hypertrophic cardiomyopathy have mTTR-FAC (V142I = 8, V50M = 2, and I127V = 2). Mutated transthyretin genetic screening is warranted in elderly subjects with increased LVWT, particularly, those of African descent with neuropathy, carpal tunnel syndrome, ECG low voltage, or LGE.
Ile68Leu in Italy (50 families)

Gagliardi C. et al, submitted
Agenda

- New pathophysiologic insights
- Advances in noninvasive diagnosis
- Broadening the disease phenotype
- New disease-modifying treatments
TTR Amyloidosis: Therapeutic opportunities

Suppression of TTR synthesis
- Liver transplantation

*Tauroursodeoxycholic acid

Small oligomers
Amyloid fibrils

Folded monomer
Misfolded monomer
Monomer misfolding
Aggregation
Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

Bo-Göran Ericzon,1 Henryk E. Wilczek,1 Marie Larsson,1 Priyantha Wijayatunga,2 Arie Stangou,3 João Rodrigues Pena,4 Emanuel Furtado,5 Eduardo Barroso,4 Jorge Daniel,6 Didier Samuel,7 Rene Adam,7 Vincent Karam,7 John Poterucha,8 David Lewis,9 Ben-Hur Ferraz-Neto,10 Márcia Waddington Cruz,11 Miguel Munar-Ques,12 Juan Fabregat,13 Shu-ichi Ikeda,14 Yukio Ando,15 Nigel Heaton,16 Gerd Otto,17 and Ole Suhr18
Suppression of TTR synthesis
- Liver transplantation
- Gene silencing:
  - siRNA: PATISIRAN
  - ASO: INOTERSEN

TTR Amyloidosis: Therapeutic opportunities

Suppression of TTR synthesis
- Liver transplantation
- Gene silencing:
  - siRNA: PATISIRAN
  - ASO: INOTERSEN

Please note that molecules and treatments mentioned in this slide may not be approved in all countries and may have specific and restricted indications – refer to their local SmPCs for further information.
Patisiran Phase 3 APOLLO Study Design

Patient Population
- hATTR amyloidosis: any TTR mutation, FAP Stage 1 or 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01963348

Primary Endpoint
- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
- Norfolk QOL-DN
- NIS-weakness
- R-ODS
- 10-meter walk
- mBMI
- COMPASS-31

Select Exploratory Endpoints
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Skin biopsies for nerve fiber density and amyloid

Patients who completed study may be eligible for patisiran treatment on Global OLE Study

*Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use.

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).
Patisiran Phase 3 APOLLO Study Results

Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months

<table>
<thead>
<tr>
<th>TTR Change</th>
<th>Change from baseline at 9 months</th>
<th>Change from baseline at 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td>Mean (SEM) Serum TTR Knockdown</td>
<td>1.5% (4.47)</td>
<td>82.6% (1.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=77)</td>
<td>Patisiran (N=148)</td>
</tr>
<tr>
<td></td>
<td>4.8% (3.38)</td>
<td>84.3% (1.48)</td>
</tr>
</tbody>
</table>
Patisiran Phase 3 APOLLO Study Results

- **mNIS+7: Change from Baseline**

  - **Better**
    - LS mean (SEM) change in mNIS+7 from baseline at 18 mos: -33.99 (9.26 × 10^{-24})
  - **Worse**
    - Placebo: 27.96 (2.60)
    - Patisiran: 13.95 (2.10)

  - Difference at 18 mos (Pati – PBO): -6.03 (1.74)
  - p-value: 9.26 × 10^{-24}
Patisiran Phase 3 APOLLO Study Results

- **Norfolk QOL-DN: Change from Baseline**

![Graph showing change in Norfolk QOL-DN from baseline]

- **Difference at 18mos**
  - (Pati – PBO): -21.1
  - p-value: $1.10 \times 10^{-10}$

LS mean (SEM) change in Norfolk QOL-DN from baseline:
- **Placebo**
  - Baseline: 55.5 (8, 111)
  - 9 Months: 7.5 (2.15)
  - 18 Months: 14.4 (2.73)
- **Patisiran**
  - Baseline: 59.6 (5, 119)
  - 9 Months: -7.5 (1.52)
  - 18 Months: -6.7 (1.77)

**Legend**
- Worse
- Better

**Notes**
- MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
- Norfolk QOL-DN reference range: -4 to 136
Inotersen Phase 3 NEURO-TTR

mNIS+7 Primary Endpoint

Statistically significant difference was observed at both 8 months and 15 months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Inotersen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (absolute value)</td>
<td>74.12</td>
<td>79.35</td>
</tr>
<tr>
<td>Change from baseline to month 15</td>
<td>25.53</td>
<td>5.80</td>
</tr>
</tbody>
</table>
TTR Amyloidosis: Therapeutic opportunities

**Suppression of TTR synthesis**
- Liver transplantation
- Gene silencing:
  - siRNA: **PATISIRAN**
  - ASO: **INOTERSEN**

**TTR stabilizers**
- Non-selective: **DIFLUNISAL**
- Selective:
  - **TAFAMIDIS**
  - **TOLCAPONE**
  - AG10
  - (curcumin)
  - green tea (EGCG)

*Please note that molecules and treatments mentioned in this slide may not be approved in all countries and may have specific and restricted indications – refer to their local SmPCs for further information*
Tafamidis for TTR Cardiomyopathy: Phase 3 Randomized ATTR-ACT Trial

**Patient population**
- History of HF (≥1 prior hospitalization for HF or clinical evidence of HF)
- TTR amyloid cardiomyopathy
  - Mutant of WT TTR
- IVS wall >12 mm
- 6-min WT >100 m
- NYHA class <IV

**Primary endpoint measures**
- All-cause mortality and frequency of CV-related hospitalizations to Month 30

**Other endpoints**
- 6-min WT, KCCQ
Pfizer Announces Positive Topline Results from Phase 3 ATTR-ACT Study of Tafamidis in Patients with Transthyretin Cardiomyopathy

—Tafamidis demonstrated a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalizations in global trial—

—Currently, there are no approved pharmacological medications specifically indicated for treating transthyretin cardiomyopathy—
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TTR stabilizers
- Non-selective: DIFLUNISAL
- Selective:
  - TAFAMIDIS
  - TOLCAPONE
  - AG10
  - (curcumin)
  - green tea (EGCG)

Amyloid fibril degradation ± macrophage activation
- Doxycycline + TUDCA
- (green tea (EGCG))
- (curcumin)
- Antibodies anti SAP
- Antibodies anti TTR

*Note: Molecules and treatments mentioned in this slide may not be approved in all countries and may have specific and restricted indications – refer to their local SmPCs for further information.
Doxycline/TUDCA- preclinic studies

Synergy of combined Doxycycline/TUDCA treatment in lowering Transthyretin deposition and associated biomarkers: studies in FAP mouse models

Isabel Cardoso¹,², Diana Martins¹, Tania Ribeiro¹, Giampaolo Merlín³, Maria João Saraiva¹ ⁴

Doxycycline+TUDCA administration to mice with amyloid deposition, using two different concentrations of both drugs, was more effective than either individual doxycycline or TUDCA, in significantly lowering TTR deposition and associated tissue markers.
Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component


This article was published on July 15, 2015, at NEJM.org.
SAP & amyloidogenesis

- SAP is universal in amyloid deposits
- SAP in amyloid deposits is not degraded
- SAP binding stabilises amyloid fibrils in vitro
- SAP promotes fibrillogenesis in vitro

Tennent et al, PNAS 1995;92:4299-4303
Development of CPHPC

K_d 10 nM

A novel therapeutic strategy

- CPHPC clears SAP from plasma but leaves some SAP in amyloid
- Antibodies to SAP can reach the amyloid
Anti-SAP Day 1 post antibody (in mice)

Congo red (global marker)

F4/80 (macrophage marker)

Courtesy of NAC, London
Monoclonal antibody therapies for systemic amyloidosis

Targeting the amyloid deposits

Chimeric fibril-reactive antibody 11-1F4 in AL

Prothena NEOD001 for AL Amyloidosis targeting ‘misfolded light chain proteins’
Phase III

GSK/NAC CPHPC + anti-SAP mAb targeting the amyloid bound SAP present in all amyloid deposits Phase II
TTR Disease Modifying Opportunities

A. Suppression of TTR Synthesis
- Liver transplantation
- Gene silencing (siRNA):
  - IONIS TTR-Rx
  - ALN-TTRsc

B. TTR Stabilization
- Diflunisal (non-selective)
- Tafamidis (selective)
- Doxycycline
- EGCG (Green Tea)
- AG-10
- Tolcapone

C. Fibril Degradation & Reabsorption
- Doxycycline + TUDCA
- CPHPC + SAP Antibodies
- PRX004

Liver → TTR Tetramer → Monomer → Monomer Misfolding → Amyloid Fibrils
TTR-CM: the great pretender

- Challenging
- Facinating
- Mysterious
- Not as rare as supposed
- Relatively easy to detect (when suspected !)
- Treatable