



THE UNIVERSITY OF  
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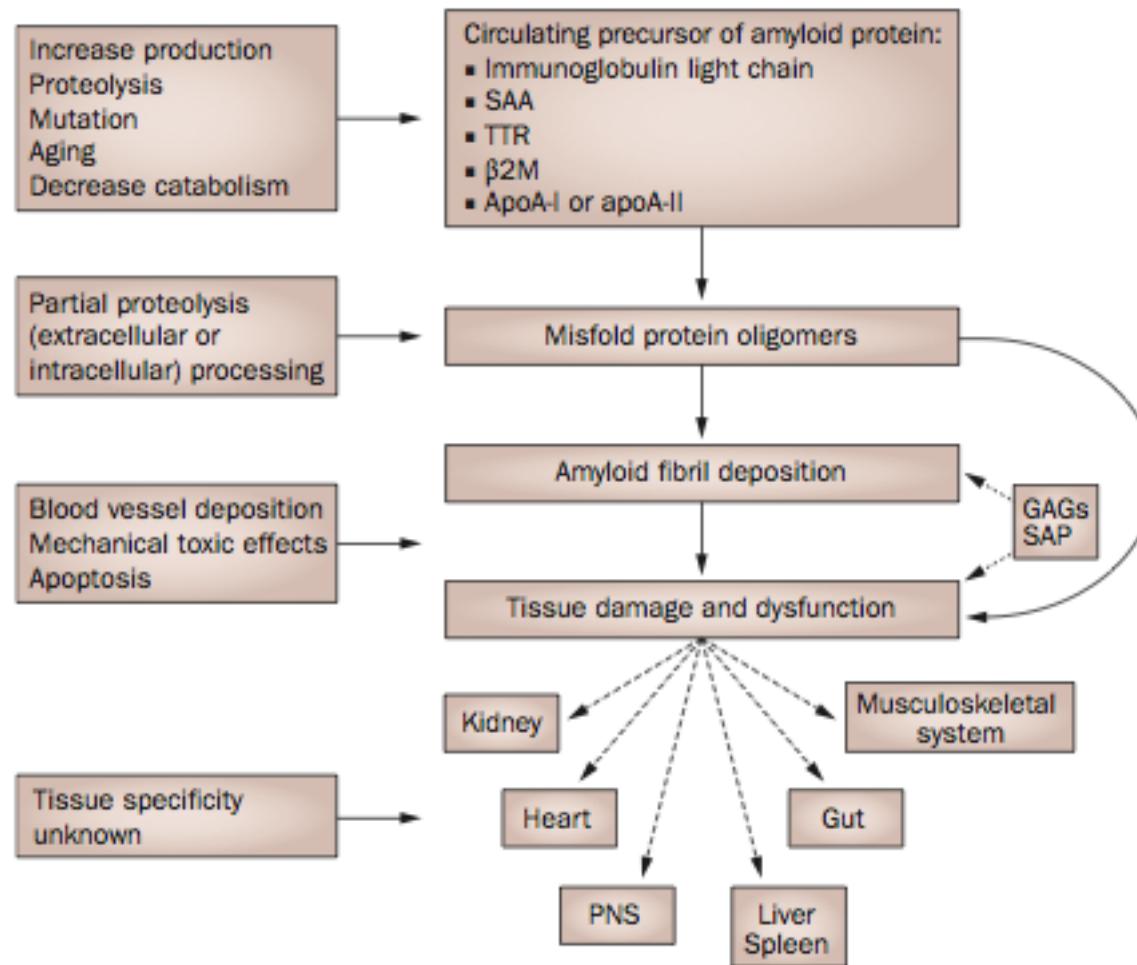


# Current concepts in the management of Amyloid Neuropathy

*Graeme Stewart*  
*Sydney Neurophysiology Workshop*  
*15 November 2014*

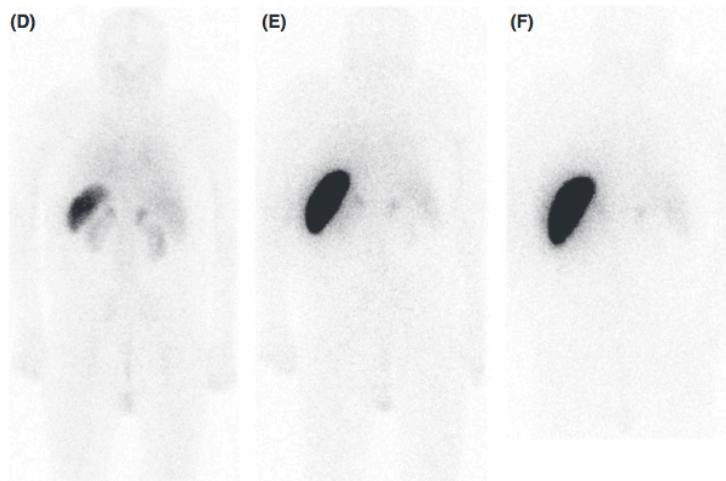
# Amyloid proteins

- About 20 different unrelated proteins can form amyloid fibrils
- Disorders of protein folding
- Normally soluble proteins are deposited as insoluble fibrils
- Disrupt tissue structure and organ function
- Some are natural wild-type proteins, others inherited or acquired variants



# Amyloid deposits : 2 components

- Amyloid fibril with common cross- $\beta$  structure
- Non-fibrillar pentraxin plasma protein :
  - Serum Amyloid P component (SAP)
  - stabilises the fibril and impedes clearance
- Radiolabelled SAP scintigraphy clinically useful



# Amyloidosis is not one disease, it's 20

**Table 1 |** Classification of forms of amyloidosis

Amyloid type	Fibril protein precursor	Systemic (S) or localized (L)	Clinical syndrome
AL	Monoclonal Ig light chains	S or L	Amyloidosis associated with monoclonal plasma cell dyscrasias
AH	Monoclonal Ig heavy chains	S or L	Amyloidosis associated with monoclonal plasma cell dyscrasias
AA	Serum amyloid A protein	S	Reactive systemic amyloidosis associated with chronic inflammatory diseases
A $\beta_2$ M	$\beta_2$ M	S	Amyloidosis associated with long-term hemodialysis
ATTR	Genetically variant TTR Wild type TTR	S S	Familial (autosomal dominant) amyloid polyneuropathy SSA
ACys	Genetically variant cystatin	S	Hereditary cerebral hemorrhage with cerebral and systemic amyloidosis
AGe	Genetically variant gelsolin	S	Familial autosomal dominant systemic amyloidosis Predominant cranial nerve involvement with lattice corneal dystrophy
ALys	Genetically variant lysozyme	S	Familial autosomal dominant systemic amyloidosis Non-neuropathic with prominent visceral involvement
AApoAI	Genetically variant apoA-I	S	Familial autosomal dominant systemic amyloidosis Predominantly non-neuropathic with prominent visceral involvement
AApoAII	Genetically variant apoA-II	S	Familial autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
AFib	Genetically variant fibrinogen A $\alpha$ -chain	S	Familial autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
ALECT2	Leukocyte chemotactic factor 2	L	Acquired renal amyloidosis
AMed	Lactadherin	L	Age-related amyloidosis localized to the aortic media
AANF	Atrial natriuretic factor	L	Amyloidosis localized to the cardiac atria Mainly occurs in patients with atrial fibrillation
Acal	(Pro)calcitonin	L	Occurs in C-cell thyroid tumors
APrP	Prion protein	L	Spongiform encephalopathy
AIAPP	Islet amyloid polypeptide	L	Amyloidosis involving islets of Langerhans
ALac	Lactoferrin	L	Familial amyloidosis involving the cornea
A $\beta$	A $\beta$ PP	L	Amyloidosis associated with Alzheimer disease, aging

Abbreviations: A $\beta$ PP, A $\beta$  protein precursor; apoA-I, apolipoprotein A-I; apoA-II, apolipoprotein A-II;  $\beta_2$ M,  $\beta_2$ -microglobulin; Ig, immunoglobulin; SSA, senile systemic amyloidosis; TTR, transthyretin.

# 3 proteins make up almost all patients

- Amyloid A (AL)
  - Ig light chain
  - plasma cell dysplasia (myeloma, MGUS etc)
- Amyloid A (AA)
  - chronic inflammation (high SAA)
- Amyloid transthyretin (ATTR)
  - familial amyloid polyneuropathy (mutant TTR)
  - senile systemic amyloidosis, SSA (wild-type TTR)



# WESTMEAD AMYLOIDOSIS CLINIC

## *clinical phenotype*

	AL	AA	ATTR	SSA
Kidney <sup>1</sup>	+++	+++	+	-
Heart <sup>1</sup>	+++	+	+++	+++
Peripheral nervous system	++	-	+++	+ <sup>1</sup>
Autonomic nervous system	++	++	+++	-
Liver	++	++	-	-
Spleen	+	++	-	-
Skin	(+)	-	-	-
Gastrointestinal tract	++	+	-	-
Musculoskeletal system	++	-	(+)*	-
Thyroid	+	+	-	-
Adrenal glands	+	+	-	-
Eyes	-	-	++	-
Testis	(+)	-	-	-
Tongue	+++	(+)	-	-
Factor X deficiency	+	-	-	-



# UK NATIONAL AMYLOIDOSIS CENTRE

## *5,100 patient experience 1987-2012*

Amyloid L	3468 (67%)
- systemic AL	2869 (56%)
- localised AL	599 (12%)
Amyloid A	633 (12%)
Amyloid TTR	507 (10%)
- TTR mutation	339 (7%)
- Wild Type (senile)	168 (3.4%)
Other inherited Amyloidoses	269 (6%)
Not definitively typed	208 (4%)



# WESTMEAD AMYLOIDOSIS CLINIC

## *first 150 patients*

	WAC	UK NAC
Systemic AL	46%	56%
Localised AL	14%	12%
Amyloid A	10%	12%
ATTR Familial	11%	10%
ATTR WT (Senile)	12%	6%
Other inherited	1%	6%
Not definitive	6%	4%



# UK NATIONAL AMYLOIDOSIS CENTRE

## *5,100 patient experience 1987-2012*

10 year survival

Systemic AL	20%
Localised AL	73%
AA	40%
ATTR mutation (familial)	54%
ATTR WT (senile systemic)	31%
AFib	59%
AApoA1	64%

# When and how should a Neurologist pursue a diagnosis of amyloidosis?

## WHEN ?

- Can't exclude it clinically
- Nerve Conduction Studies don't exclude it

## HOW ?

- EPG/IEPG, serum free light chains (AL)
- CRP, SAA (AA)
- Cardiac ECHO, pro-BNP
- Tissue biopsy
  - Abdominal fat
  - rectal, gastric, renal, skin, cardiac
  - endoscopic GIT Bx 85% sensitivity
  - sural nerve Bx much less sensitive



## WESTMEAD AMYLOIDOSIS CLINIC

- Started 2008 as a Sydney-wide resource
- All disciplines represented
- Adam Gardiner Foundation grant of \$100k funded
  - full genetic testing under David Booth
  - immunohistochemistry
- Relationship with UK National Amyloidosis Centre (Phil Hawkins)
  - back up immunohistochemistry



Westmead Hospital



University of Sydney

Haematologists  
Prof David Gottlieb  
Dr John Taper  
Dr Peter Mollee (QLD)

Immunologists  
Prof Graeme Stewart  
Dr Ming-Wei Lin

Cardiologists  
A.Prof David Richards  
A.Prof Liza Thomas

Neurologists  
A.Prof Robert Heard  
Dr Steve Vucic

Renal Physicians  
Dr Richard Phoon  
Prof Jeremy Chapman

Molecular Geneticist  
Dr David Booth

Nuclear Medicine &  
PET Physicians  
Dr Simon Gruenewald  
Dr Kate Saunders

Radiopharmacist  
Dr Vijay Kumar

Histopathologist  
Dr Raghu Sharma

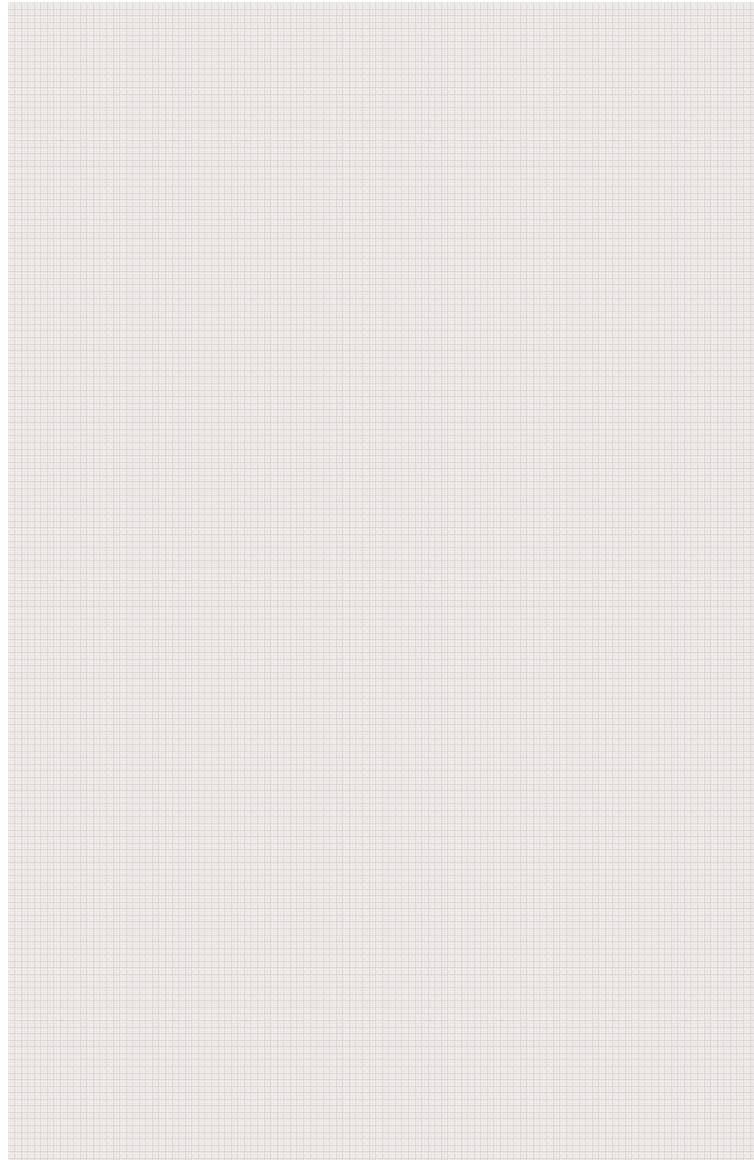
International Affiliates  
Prof Philip Hawkins  
(UK)  
Dr Hugh Goodman  
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Clinical Co-ordinator  
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Proudly supported by the

Adam  
Gardiner  
Foundation

## WESTMEAD AMYLOIDOSIS CLINIC



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# WESTMEAD AMYLOIDOSIS CLINIC

## *clinical purpose*

- Definitive identification of the pathogenic amyloid protein
- Assessment of target organ damage
- Advice on specific management



# WESTMEAD AMYLOIDOSIS CLINIC

*definitive identification of amyloid protein*

- clinical phenotype
- specialised immunohistochemistry
  - light chain, AA, TTR (Westmead, UK NAC)
- genotyping for inherited disease
  - Westmead Millennium Institute (David Booth)
- mass spectroscopy (Mayo Clinic, Brisbane)



# WESTMEAD AMYLOIDOSIS CLINIC

## *Advice on specific management*

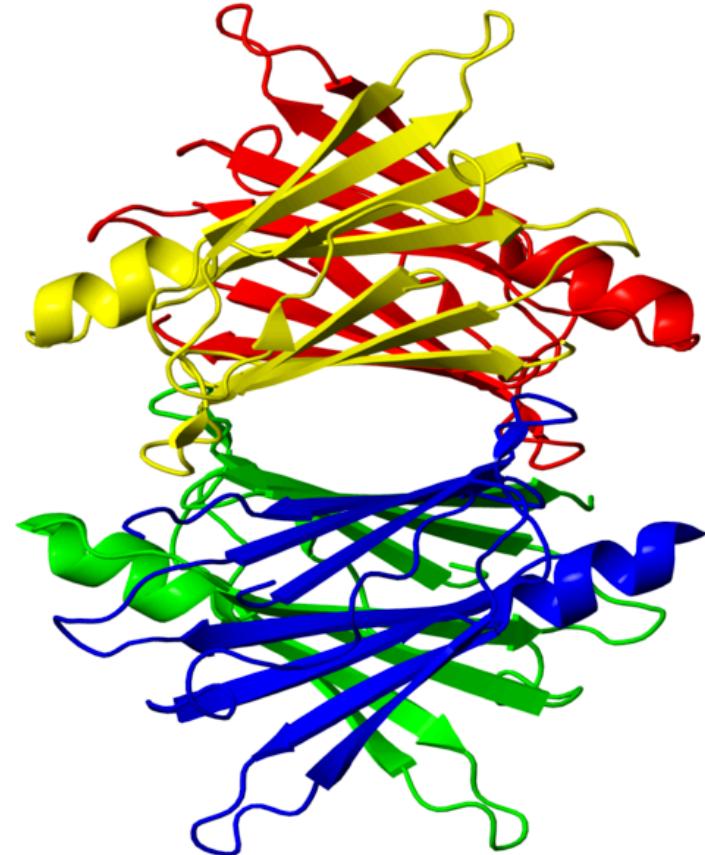
- Varies greatly with causative amyloid protein
  - AL (systemic) : chemoRx, Stem Cell Tx
  - AA : Rx underlying disease, anakinra (anti-IL1)
  - ATTR (senile systemic) : TTR stabilisers
  - ATTR (mutation) : TTR stabilisers, liver Tx
  - Other familial Amyloid : liver Tx
- Treatment options are rapidly improving
- Early diagnosis makes a big difference

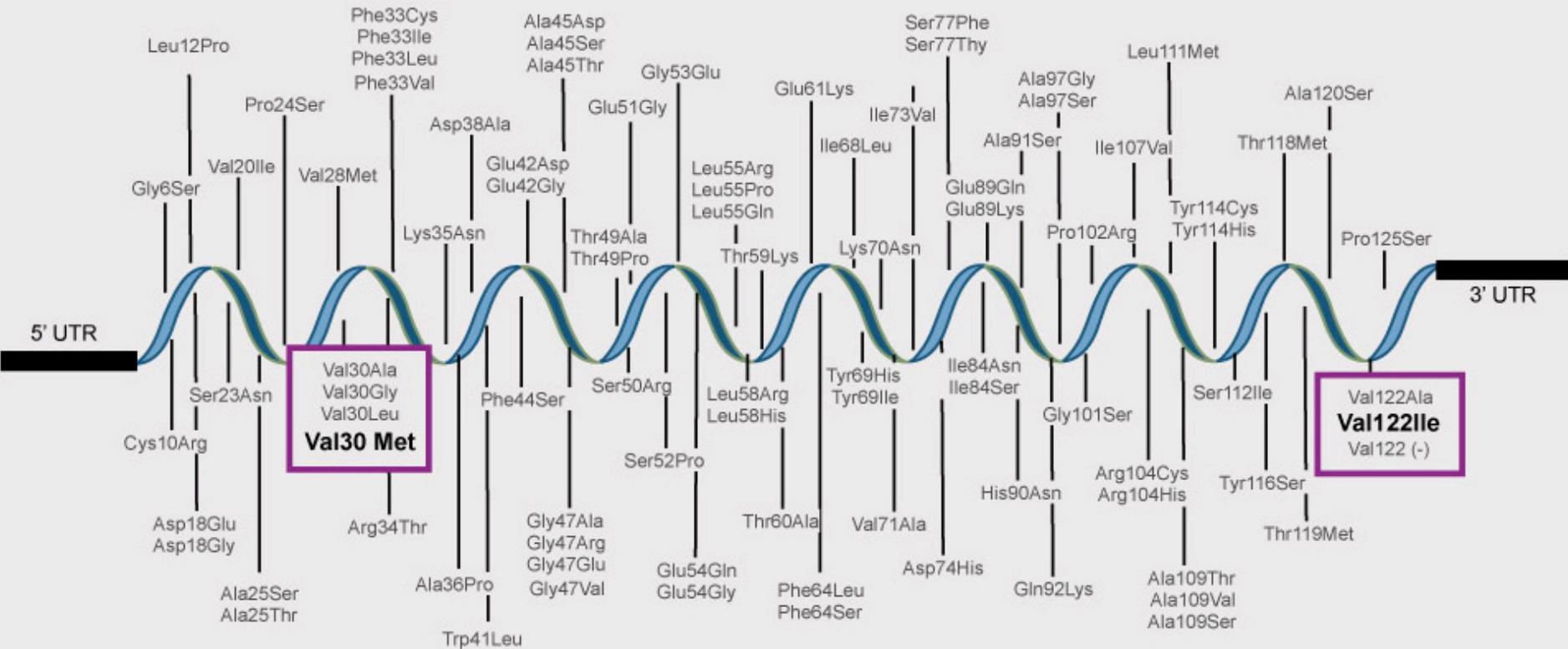


# WESTMEAD AMYLOIDOSIS CLINIC

## *TTR Familial Amyloidosis*

- Transthyretin transports thyroxin in blood and CSF
- Produced in liver (+ eye)
- Circulates as a tetramer
- Disaggregation into monomers can lead to tissue deposition as amyloid
- Mutations enhance monomer formation
- Wild type causes senile systemic amyloidosis

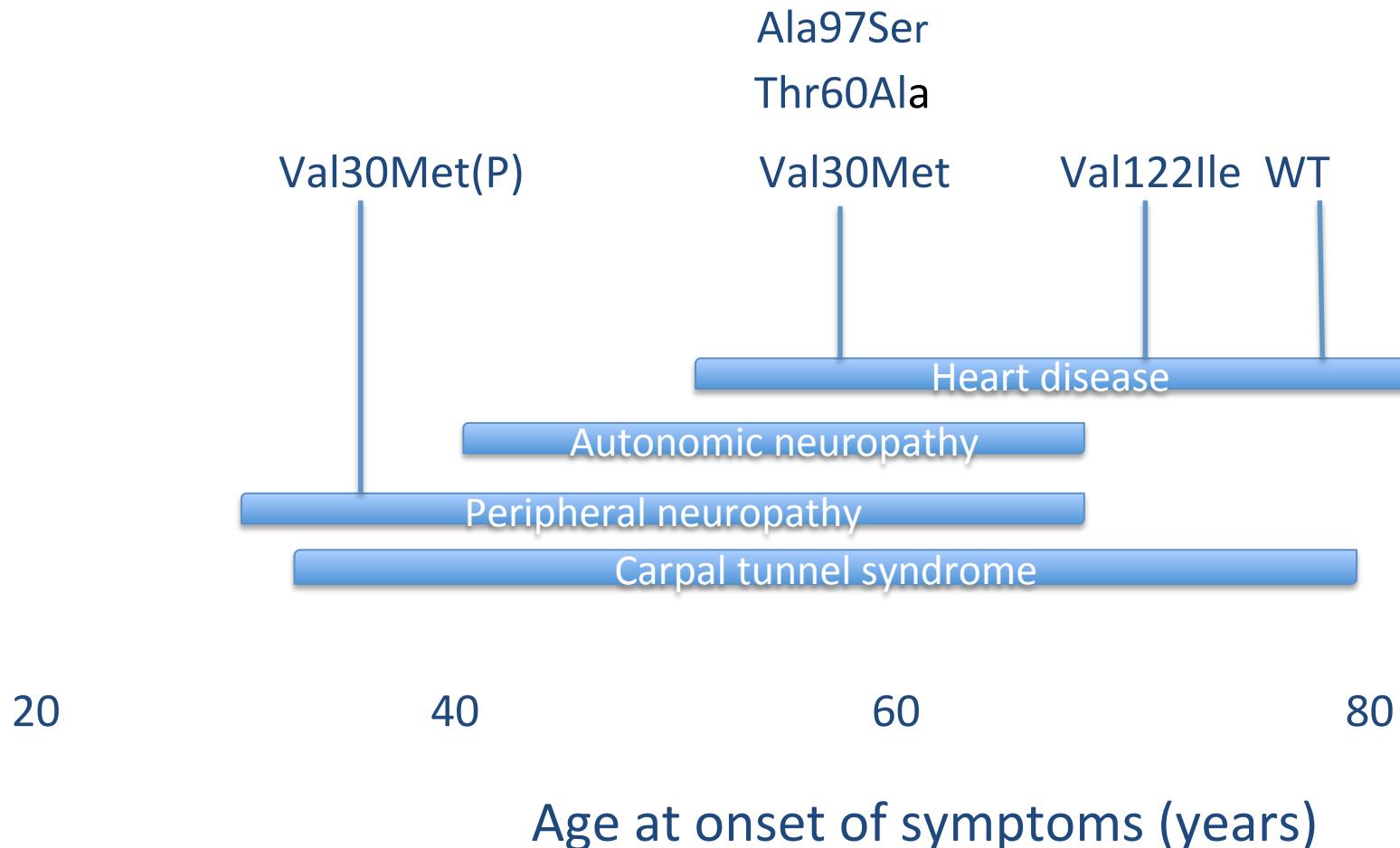






# TTR GENOTYPE EFFECT ON PHENOTYPE

## *familial amyloidosis*



# When should a Neurologist suspect TTR FAP?

- Family history of known or possible amyloidosis
- Progressive, length-dependent axonal polyneuropathy predominantly affecting temperature and pain
- Associated multi-system disease
  - autonomic neuropathy
  - cardiac disease (arrhythmia, heart failure, thick IVS on TTE)
  - carpal tunnel syndrome (can precede neuropathy by >10 yrs)
  - vitreous deposits (cotton wool)

# When should a Neurologist suspect TTR FAP?

- F/H of neuropathy, especially associated with heart failure
- Neuropathic pain or progressive sensory disturbances
- Carpal tunnel syndrome, particularly bilateral
- GI motility disturbances, erectile dysfunction, orthostatic hypotension, neurogenic bladder
- Cardiac disease characterized by thickened ventricular walls in the absence of hypertension
- Advanced atrio-ventricular block of unknown origin, particularly when accompanied by a thickened heart
- Vitreous body inclusions of the cotton-wool type

# Vitreal amyloid deposits in a 46 year old man with the Val71Ala transthyretin mutation

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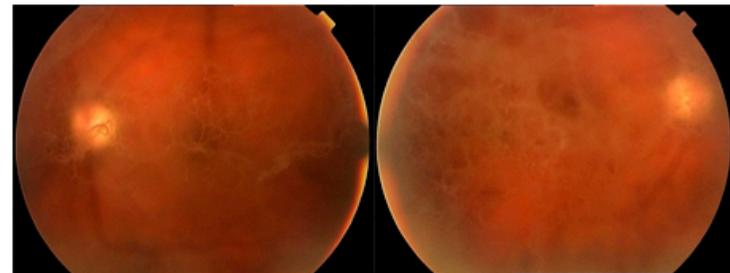


Figure 1. Bilateral vitreal opacities.

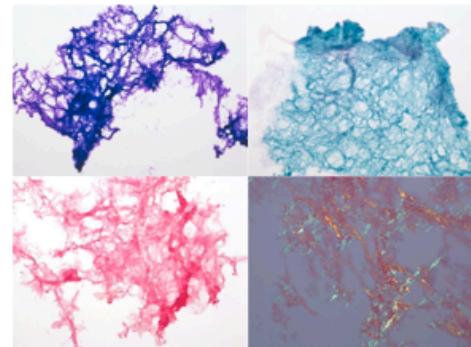


Figure 2. Cytological diagnosis of vitreal amyloidosis. Amyloid deposits stained purple with *giemsa* (A) and turquoise with *papanicolaou* (B). With Congo red staining, deposits were brick red in normal light (C), demonstrating apple-green birefringence in polarised light (D).



# WESTMEAD AMYLOIDOSIS CLINIC

## *Familial Amyloidosis: 36 patients, 19 families*

Gene	Mutation	Patients	Families
TTR	Ser77Tyr	4	2
	Val122Ile	8	3
	Val30Met	6	3
	Thr60Ala	7	2
	Gly47Val	1	1
	Ala97Ser	2	1
	Ala109Ser	1	1
	Val71Ala	1	1
Lysozyme	Lys67His	2	1
aFib		3	3
Apo	Gly26Arg	1	1



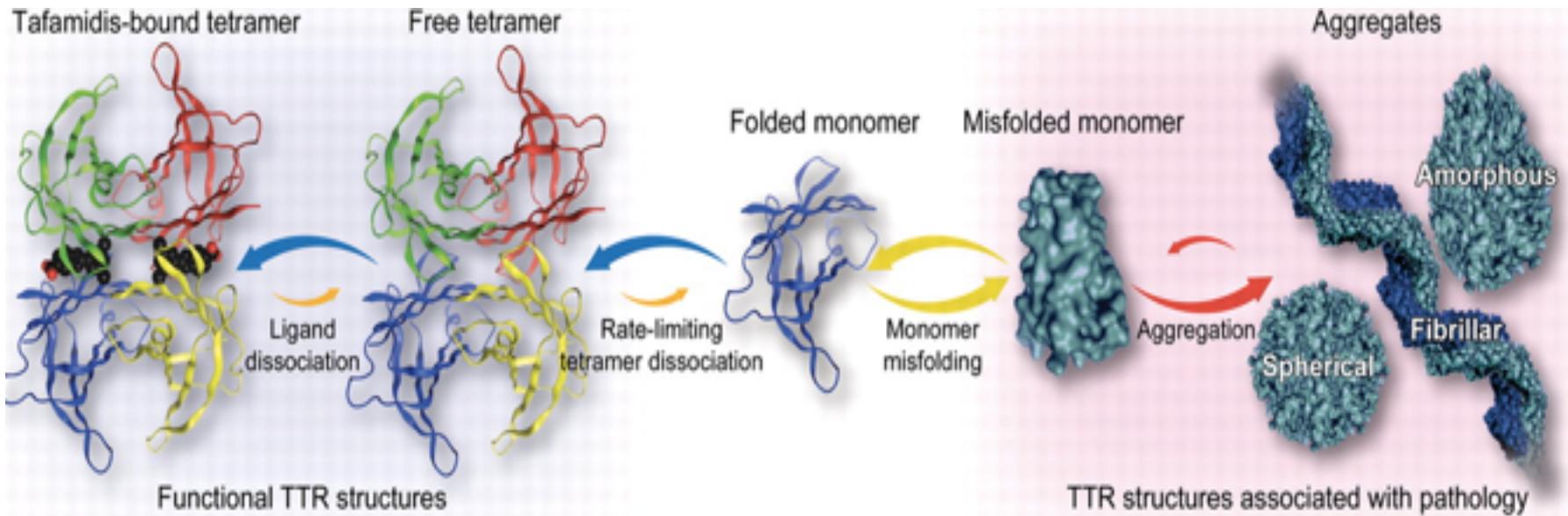
# MANAGEMENT AND COUNSELLING

## *TTR familial amyloidosis*

- TTR stabilisers
  - Diflunisal (NSAID, proven, available)
  - Doxycycline-TUDCA (proven, available)
  - Tefamidis (proven, not available in Australia)
- TTR synthesis suppression (in progress)
- Liver transplantation
- The Horizon : CPHPC + Anti-SAP monoclonal
  - removes amyloid deposits

# TTR TERAMER STABILISER : Tafamidis

- Approved, European Union July 2012 for TTR neuropathy, cost Euro 100k per year
- Knocked back by FDA 2013
- Australian approval unlikely without further trial data



## ORIGINAL ARTICLE

# Safety and Efficacy of RNAi Therapy for Transthyretin Amyloidosis

Teresa Coelho, M.D., David Adams, M.D., Ph.D., Ana Silva, M.D., Pierre Lozeron, M.D., Philip N. Hawkins, Ph.D., F.Med.Sci., Timothy Mant, M.B., Javier Perez, M.D., Joseph Chiesa, M.D., Steve Warrington, M.D., Elizabeth Tranter, M.B., Malathy Munisamy, M.D., Rick Falzone, M.P.H., Jamie Harrop, B.A., Jeffrey Cehelsky, M.B.A., Brian R. Bettencourt, Ph.D., Mary Geissler, M.P.H., James S. Butler, Ph.D., Alfica Sehgal, Ph.D., Rachel E. Meyers, Ph.D., Qingmin Chen, Ph.D., Todd Borland, B.S., Renta M. Hutabarat, Ph.D., Valerie A. Clausen, Ph.D., Rene Alvarez, Ph.D., Kevin Fitzgerald, Ph.D., Christina Gamba-Vitalo, Ph.D., Saraswathy V. Nochur, Ph.D., Akshay K. Vaishnaw, M.D., Ph.D., Dinah W.Y. Sah, Ph.D., Jared A. Gollob, M.D., and Ole B. Suhr, M.D.

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## ABSTRACT

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### BACKGROUND

Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart. A therapeutic approach mediated by RNA interference (RNAi) could reduce the production of transthyretin.

### METHODS

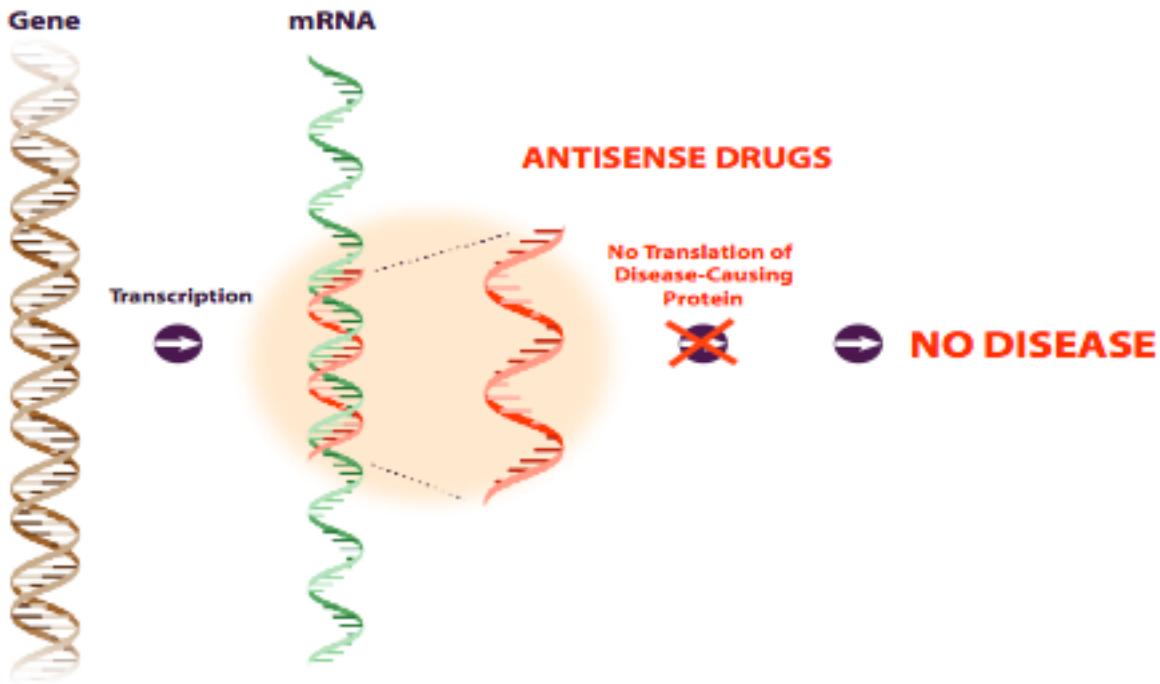
We identified a potent antitransthyretin small interfering RNA, which was encapsulated in two distinct first- and second-generation formulations of lipid nanoparticles, generating ALN-TTR01 and ALN-TTR02, respectively. Each formulation was studied in a single-dose, placebo-controlled phase 1 trial to assess safety and effect on transthyretin levels. We first evaluated ALN-TTR01 (at doses of 0.01 to 1.0 mg per kilogram of body weight) in 32 patients with transthyretin amyloidosis and then evaluated ALN-TTR02 (at doses of 0.01 to 0.5 mg per kilogram) in 17 healthy volunteers.

### RESULTS

Rapid, dose-dependent, and durable lowering of transthyretin levels was observed in the two trials. At a dose of 1.0 mg per kilogram, ALN-TTR01 suppressed transthyretin, with a mean reduction at day 7 of 38%, as compared with placebo ( $P=0.01$ ); levels of mutant and nonmutant forms of transthyretin were lowered to a similar extent. For ALN-TTR02, the mean reductions in transthyretin levels at doses of 0.15 to 0.3 mg per kilogram ranged from 82.3 to 86.8%, with reductions of 56.6 to 67.1% at 28 days ( $P<0.001$  for all comparisons). These reductions were shown to be RNAi-mediated. Mild-to-moderate infusion-related reactions occurred in 20.8% and 7.7% of participants receiving ALN-TTR01 and ALN-TTR02, respectively.

### CONCLUSIONS

ALN-TTR01 and ALN-TTR02 suppressed the production of both mutant and nonmutant forms of transthyretin, establishing proof of concept for RNAi therapy targeting messenger RNA transcribed from a disease-causing gene. (Funded by Alnylam Pharmaceuticals; ClinicalTrials.gov numbers, NCT01148953 and NCT01559077.)



# Antibodies to human serum amyloid P component eliminate visceral amyloid deposits

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**Accumulation of amyloid fibrils in the viscera and connective tissues causes systemic amyloidosis, which is responsible for about one in a thousand deaths in developed countries<sup>1</sup>. Localized amyloid can also have serious consequences; for example, cerebral amyloid angiopathy is an important cause of haemorrhagic stroke. The clinical presentations of amyloidosis are extremely diverse and the diagnosis is rarely made before significant organ damage is present<sup>1</sup>. There is therefore a major unmet need for therapy that safely promotes the clearance of established amyloid deposits. Over 20 different amyloid fibril proteins are responsible for different forms of clinically significant amyloidosis and treatments that substantially reduce the abundance of the respective amyloid fibril precursor proteins can arrest amyloid accumulation<sup>1</sup>. Unfortunately, control of fibril-protein production is not possible in some forms of amyloidosis and in others it is often slow and hazardous<sup>1</sup>. There is no therapy that directly targets amyloid deposits for enhanced clearance. However, all amyloid deposits contain the normal, non-fibrillar plasma glycoprotein, serum amyloid P component (SAP)<sup>2,3</sup>. Here we show that administration of anti-human-SAP antibodies to mice with amyloid deposits containing human SAP triggers a potent, complement-dependent, macrophage-derived giant cell reaction that swiftly removes massive visceral amyloid deposits without adverse effects. Anti-SAP antibody treatment is clinically feasible because circulating human SAP can be depleted in patients by the bis-D-proline compound CPHPC<sup>4</sup>, thereby enabling injected anti-SAP antibodies to reach residual SAP in the amyloid deposits. The unprecedented capacity of this novel combined therapy to eliminate amyloid deposits should be applicable to all forms of systemic and local amyloidosis.**

in normal extracellular matrix<sup>8,9</sup> (Supplementary Information, section 2) and in the amyloid deposits (Supplementary Information, section 3), just as in humans. Amyloid was quantified in each mouse by whole-body retention of  $^{125}\text{I}$ -SAP (ref. 10) and the mice were allocated to three groups closely matched for age, sex and amyloid load. The model closely reflects clinical amyloidosis because human SAP binds much more avidly to amyloid than does mouse SAP<sup>10</sup>, and CPHPC depletes circulating human but not mouse SAP *in vivo*<sup>4</sup>. Two groups of mice then received CPHPC at 1 mg ml<sup>-1</sup> in their drinking water for the rest of the experiment. Circulating human SAP was depleted but, as in humans treated with CPHPC, significant amounts of SAP remained in the amyloid deposits (Supplementary Information, section 4). Five days after starting on CPHPC, one group received a single intraperitoneal injection of 50 mg of the IgG fraction of monospecific polyclonal sheep anti-human-SAP antiserum, containing 7 mg of anti-SAP antibody. A control group received 50 mg of unrelated sheep IgG (Supplementary Information, section 4). The third group received no treatment and thus controlled for spontaneous regression of AA amyloid<sup>11</sup>. Twenty-eight days after the antibody or control IgG injection, the visceral amyloid load was scored histologically and human SAP was quantified in the individual sera and organs (Supplementary Information, section 4).

There was markedly less amyloid after treatment with CPHPC plus anti-SAP antibody than in the other two groups but there was no difference between CPHPC alone and no treatment (Fig. 1 and Supplementary Information, section 4). Apart from the amyloid deposits there were no other significant histological abnormalities in any animal. Anti-SAP antibody thus produced remarkable regression of amyloid with no disruption to the normal parenchymal or connective-tissue structure of the liver, spleen or other organs. Furthermore, there were no clinical signs in any of the animals receiving anti-SAP antibody, indicating that the antibody is well tolerated.

# Sustained pharmacological depletion of serum amyloid P component in patients with systemic amyloidosis

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## Summary

Serum amyloid P component (SAP) is a universal constituent of amyloid deposits and contributes to their formation and/or persistence. We therefore developed CPHPC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2 carboxylic acid), a novel bis(D-proline) drug, to specifically target SAP and report here a first, exploratory, open label proof of principle study in systemic amyloidosis. CPHPC produced sustained, >95% depletion of circulating SAP in all patients and c. 90% reduction in the SAP content of the two amyloidotic organs that became available. There were no significant adverse effects of either SAP depletion or CPHPC itself. No accumulation of amyloid was demonstrable by SAP scintigraphy in any patient on the drug. In hereditary fibrinogen amyloidosis, which is inexorably progressive, proteinuria was reduced in four of five patients receiving CPHPC and renal survival was prolonged compared to a historical control group. These promising clinical observations merit further study.

Keywords: amyloid, amyloidosis, CPHPC, depletion, P component.



# MANAGEMENT AND COUNSELLING

## *familial amyloidosis*

### FAMILY COUNSELLING – PREDICTIVE TESTING

- Penetrance
- Likely age at onset (incl anticipation)
- Preventive treatment (TTR stabilisers)
- Reproductive options : pre-natal, pre-implantation GT



## CONCLUSIONS

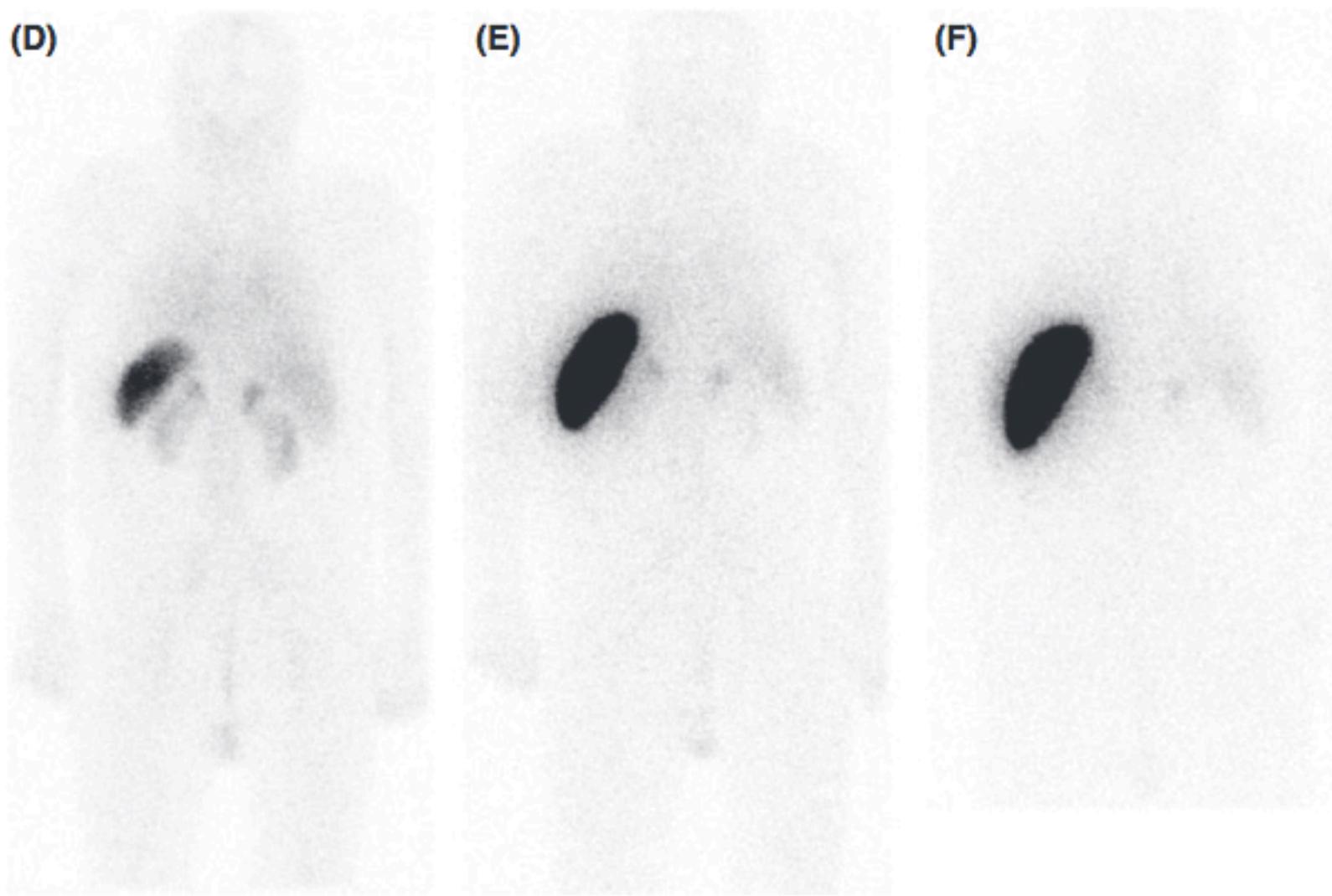
### *treatment of amyloid neuropathy*

- Early diagnosis matters
- Essential to identify causative protein
- Specific treatment for AL and AA
- Liver transplantation for ATTR
- Evolving medical therapy for ATTR
- Potential soon for definitive therapy (CPHPC + anti-SAP)
- Possible early access through clinical trial

(D)

(E)

(F)



ORIGINAL ARTICLE

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Jared A. Gollob, M.D., and Ole B. Suhr, M.D.

# Determination of the causative amyloid protein

- Clinical phenotype
- Congo red positive biopsy
- Immunohistochemistry
- Molecular genotyping – TTR, others (Westmead)
- Last resort : Laser dissection mass spectroscopy (Brisbane, Mayo)



# WESTMEAD AMYLOIDOSIS CLINIC

## *clinical phenotype*

**Table 2** Clinical manifestations of some systemic amyloidoses according to the major site of involvement\*



# The NEW ENGLAND JOURNAL of MEDICINE

## Misdiagnosis of hereditary amyloidosis as AI (primary) amyloidosis

Lachmann, Helen J ; Booth, David R ; Booth, Susanne E; Bybee, Alison ; Gilbertson, Janet A; et al. **The New England Journal of Medicine** 346.23 (Jun 6, 2002): 1786-91.

Amyloidogenic mutations were present in 34 of the 350 patients (9.7 percent), most often in the genes encoding fibrinogen A  $\alpha$ -chain (18 patients) and transthyretin (13 patients). In all 34 of these patients, the diagnosis of hereditary amyloidosis was confirmed by additional investigations. A low-grade monoclonal gammopathy was detected in 8 of the 34 patients (24 percent).



# WESTMEAD AMYLOIDOSIS CLINIC

*definitive identification of amyloid protein*

- clinical phenotype
- genotyping for inherited disease
- specialised immunohistochemistry
  - light chain, AA, TTR (W'mead, UK NAC)
- mass spectroscopy (Mayo Clinic, Brisbane)



# WESTMEAD AMYLOIDOSIS CLINIC

## *clinical purpose*

- Assessment of target organ damage
  - cardiac ECHO (Liza Thomas) +/- Bx
  - nerve conduction studies (Steve Vucic)
  - autonomic neuropathy



# UK NATIONAL AMYLOIDOSIS CENTRE

## *5,100 patient experience 1987-2012*

1987-1999      1999-2012

Amyloid L (AL)	55%	55%
Amyloid A (AA)	32%	7.0%
Senile Systemic (TTR WT)	0.2%	6.4%



# WESTMEAD AMYLOIDOSIS CLINIC

## *familial amyloidosis*

	WAC n=18	UK NAC n=608
ATTR* (Transthyretin)	16 (89%)	339 (56%)
AFib*		87 (14%)
AB2M		93 (15%)
ApoA1*		40 (7%)
AGel		9 (1%)
ALECT2		16 (3%)
ALys* (Lysozyme)	2 (11%)	17 (3%)
ACysC		4 (1%)
AlnS		3 (1%)



# MANAGEMENT AND COUNSELLING

## *TTR familial amyloidosis*

### MANAGEMENT

- Symptomatic
- TTR stabilisers : Diflunisal, Tefamidis
- Liver transplantation
- Prognosis
- Providing hope (eg Anti-SAP monoclonal Rx)

### FAMILY COUNSELLING – PREDICTIVE TESTING

## Vitreal deposits in Val71Ala transthyretin amyloidosis

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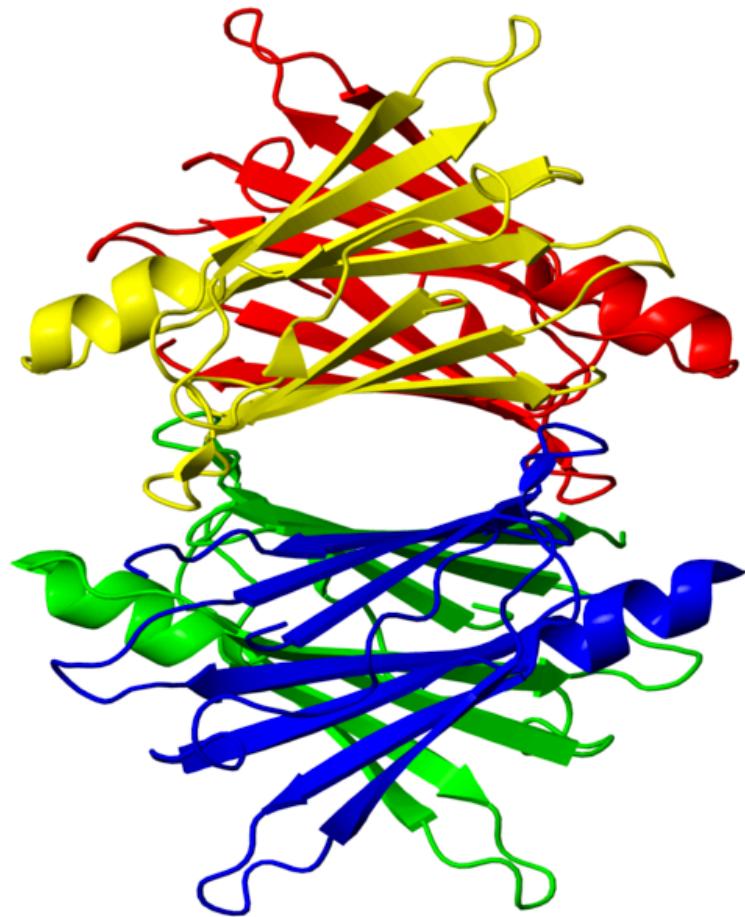




# WESTMEAD AMYLOIDOSIS CLINIC CONCLUSIONS

- Useful addition to Australian medicine as a “centre of excellence” for a group of rare diseases
- Could support a national network
- Genetic testing is a major attraction for referrals
- Wouldn’t work without multidisciplinary commitment or a funded co-ordinator
- Leadership from Clinical immunologists appropriate
- Still on a steep learning curve assisted by the UK NAC experience
- For teaching and training, there are many lessons apart from the specific knowledge of rare diseases.

# TRANSTHYRETIN TETRAMER





# WESTMEAD AMYLOIDOSIS CLINIC

Result Date:

Sample Received:

## *Amyloid Gene Testing*

**Patient Name :**

**Referring Doctor :**

### **Tests Done**

Transthyretin: sequenced all coding exons

Lysozyme: sequenced exon 2 (where known lysozyme mutations are encoded)

$\alpha$  fibrinogen: sequenced exon 5 (where known  $\alpha$  fibrinogen mutations are encoded)

Apolipoprotein A1: sequenced exon 3, exon 4

### **Result**

No mutations detected.

A/Prof David Booth  
Principal Research Scientist  
Ph 02 98458498

Prof Graeme Stewart  
Supervising Pathologist

Test performed in a Research Laboratory