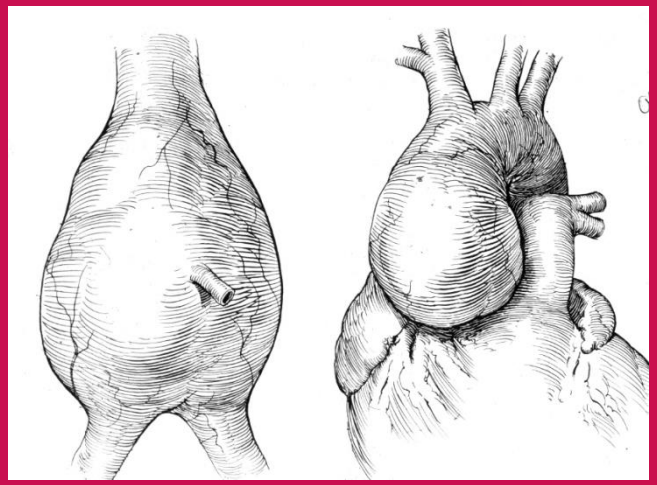
September 15-17
2016
Crowne Plaza Hotel
Liège, Belgium

5th International Meeting on Aortic Diseases

New insights into an old problem CHU Liège, APF

www.chuliege-imaa.be

Medical Treatment of the AAA in Humans: Fiction or Reality?



Gilbert R. Upchurch Jr
Muller Professor of Surgery
University of Virginia, USA

September 15, 2016

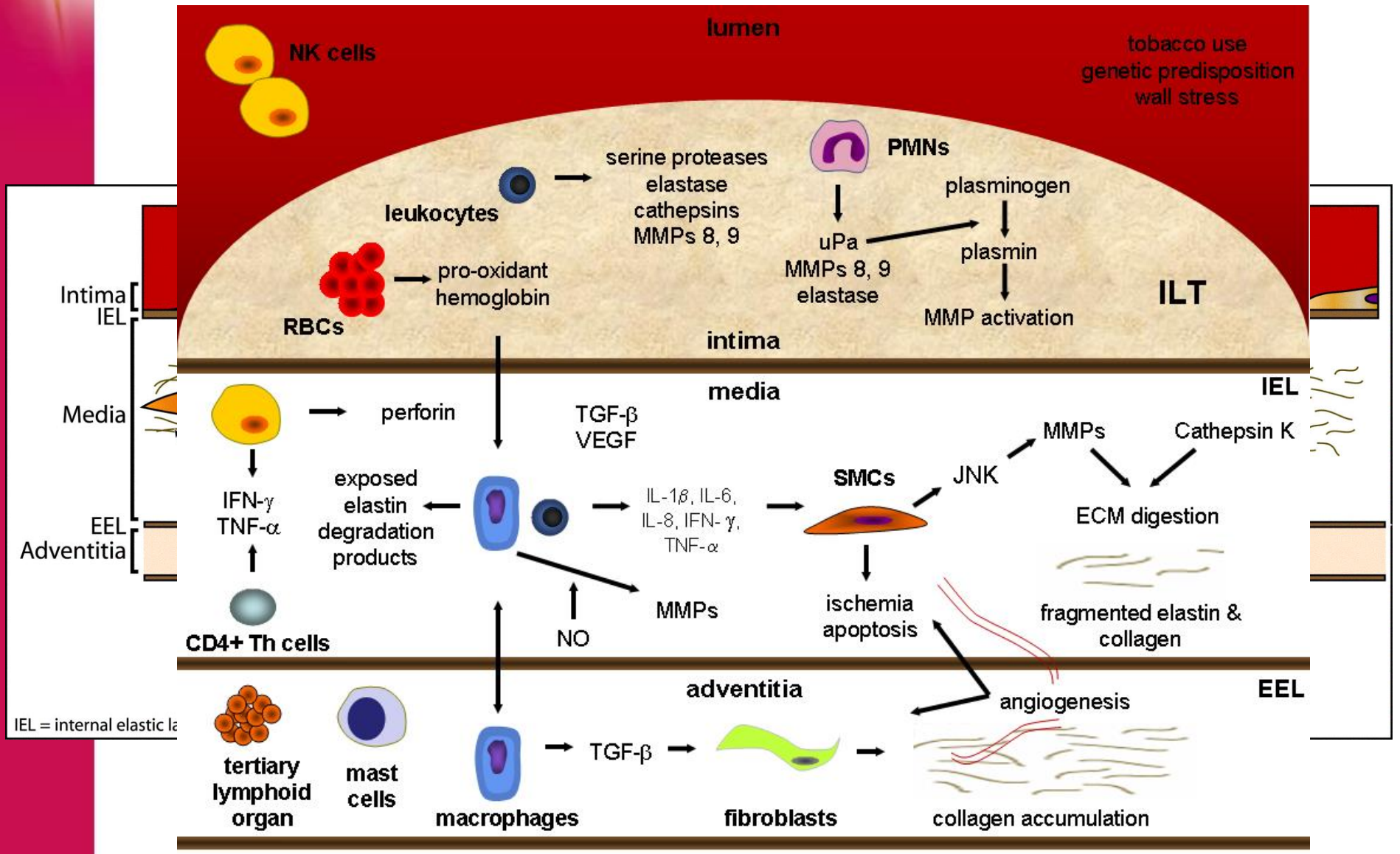
Disclosure of Interest

Gilbert R Upchurch Jr: I have the following potential conflicts of interest to report:

- Part owner in Antyllus Inc., a company aimed at developing a medical therapy for aortic aneurysms

- I do not have any potential conflict of interest

Proposed Mechanisms



English S, Upchurch G, Current Surgical Therapy in Vascular Surgery, 2015

“The fundamental treatment of abdominal aortic aneurysm has changed very little over the past 35 years. This fact is due to our inadequate understanding of the pathogenesis of the disease”

Timothy Baxter M.D.
1997

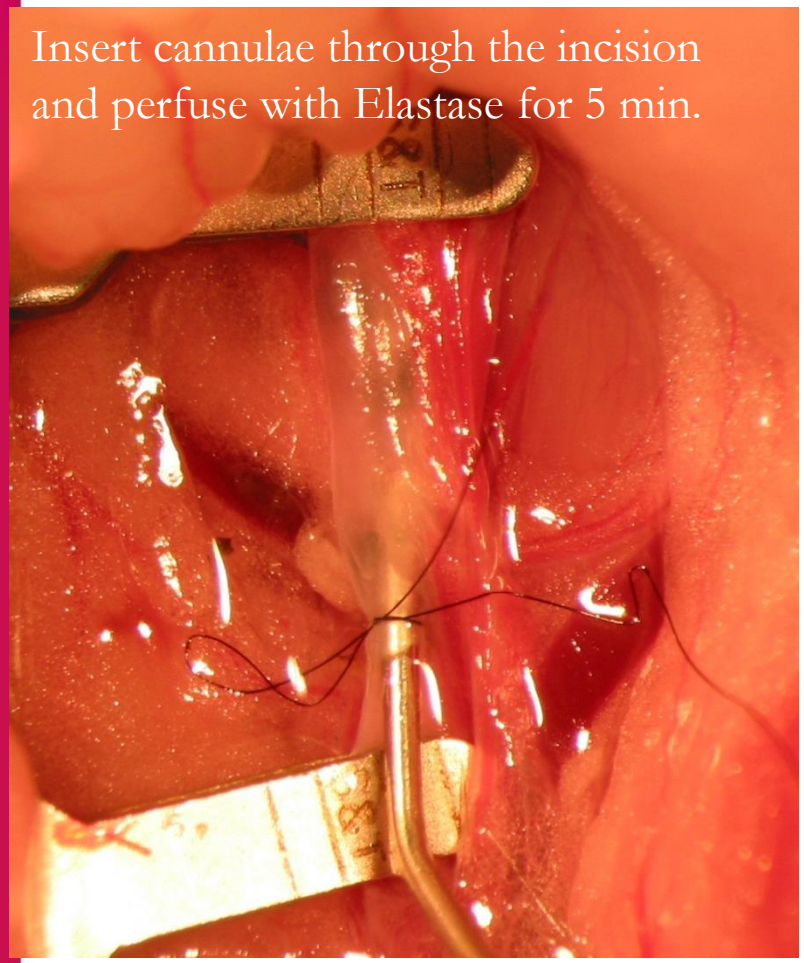
OBJECTIVE

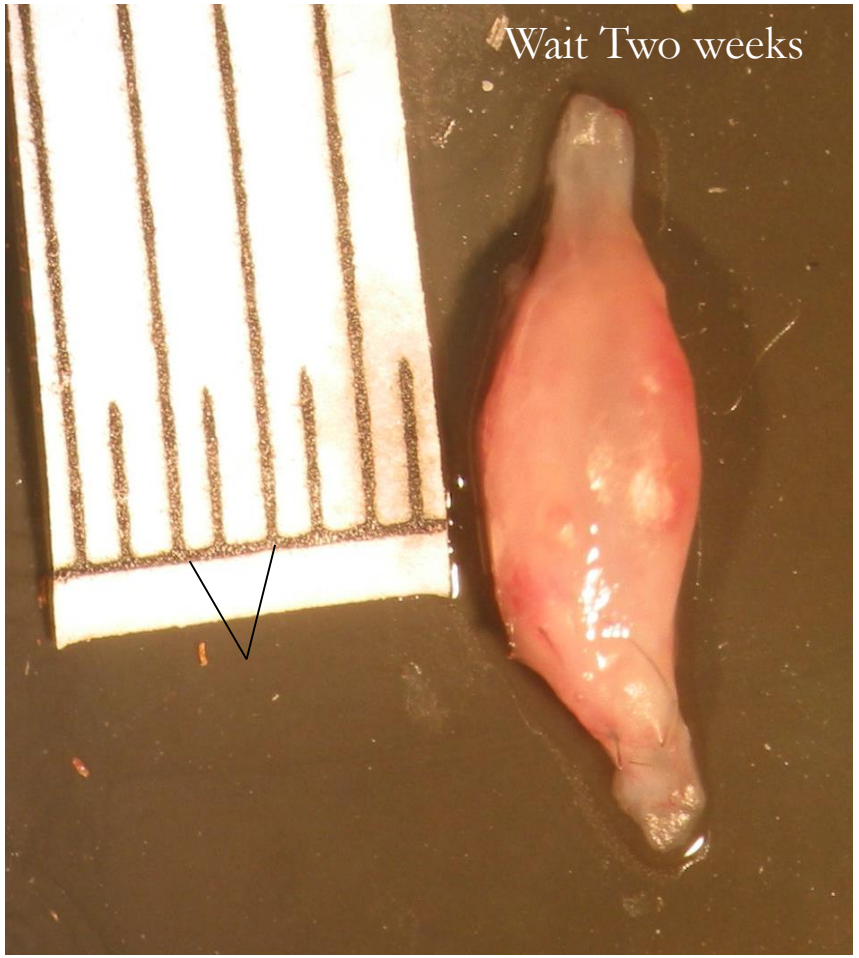
1. **To briefly review data, including that learned from animal models, that might give us a clue as to where to look for a cure for human AAAs**

Aneurysm Models

- Porcine pancreatic elastase perfusion
- $CaCl_2$ periaortic application
- Angiotensin II infusion in Apo E KO
- Angiotensin II infusion in LDL receptor KO
- Lysyl Oxidase KO
- MMP-3 or TIMP-1 KO
- Fibrillin-1 Genetic Mutation (Marfan Mouse)
- Topical elastase

Elastase Perfusion Surgery



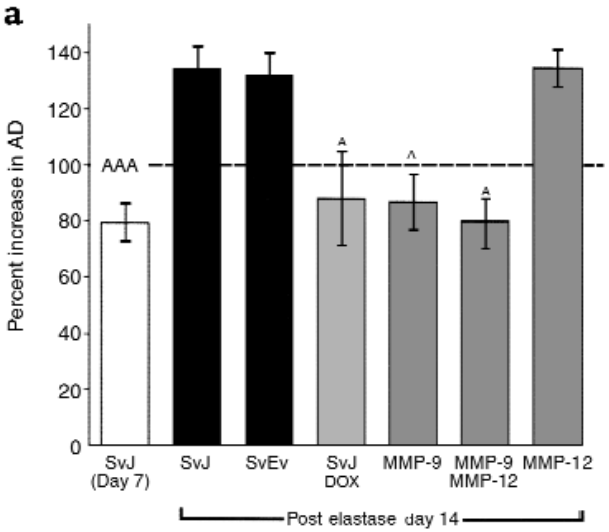


Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms

Robert Pyo,[1] Jason K. Lee,[1] J. Michael Shipley,[2] John A. Curci,[1] Dongli Mao,[1] Scott J. Ziporin,[1] Terri L. Ennis,[1] Steven D. Shapiro,[2,3,4] Robert M. Senior,[2,4] and Robert W. Thompson[1,4,5]

Abdominal aortic aneurysms represent a life-threatening condition characterized by chronic inflammation, destructive remodeling of the extracellular matrix, and increased local expression of matrix metalloproteinases (MMPs). Both 92-kD gelatinase (MMP-9) and macrophage elastase (MMP-12) have been implicated in this disease, but it is not known if either is necessary in aneurysmal degeneration. We show here that transient elastase perfusion of the mouse aorta results in delayed aneurysm development that is temporally associated with transmural mononuclear inflammation, increased local production of several elastolytic MMPs, and progressive destruction of the elastic lamellae. Elastase-induced aneurysmal degeneration was suppressed by treatment with a nonselective MMP inhibitor (doxycycline) and by targeted gene disruption of MMP-9, but not by isolated deficiency of MMP-12. Bone marrow transplantation from wild-type mice prevented the aneurysm-resistant phenotype in MMP-9–deficient animals, and wild-type mice acquired aneurysm resistance after transplantation from MMP-9–deficient donors. These results demonstrate that inflammatory cell expression of MMP-9 plays a critical role in an experimental model of aortic aneurysm disease, suggesting that therapeutic strategies targeting MMP-9 may limit the growth of small abdominal aortic aneurysms.

J. Clin. Invest. **105**:1641–1649 (2000).



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Experimental Abdominal Aortic Aneurysm Formation Is Mediated by IL-17 and Attenuated by Mesenchymal Stem Cell Treatment

Ashish K. Sharma, Guanyi Lu, Andrea Jester, William F. Johnston, Yunge Zhao, Vanessa A. Hajzus, M. Reza Saadatzadeh, Gang Su, Castigliano M. Bhamidipati, Gaurav S. Mehta, Irving L. Kron, Victor E. Laubach, Michael P. Murphy, Gorav Ailawadi and Gilbert R. Upchurch, Jr

Circulation. 2012;126:S38-S45
doi: 10.1161/CIRCULATIONAHA.111.083451
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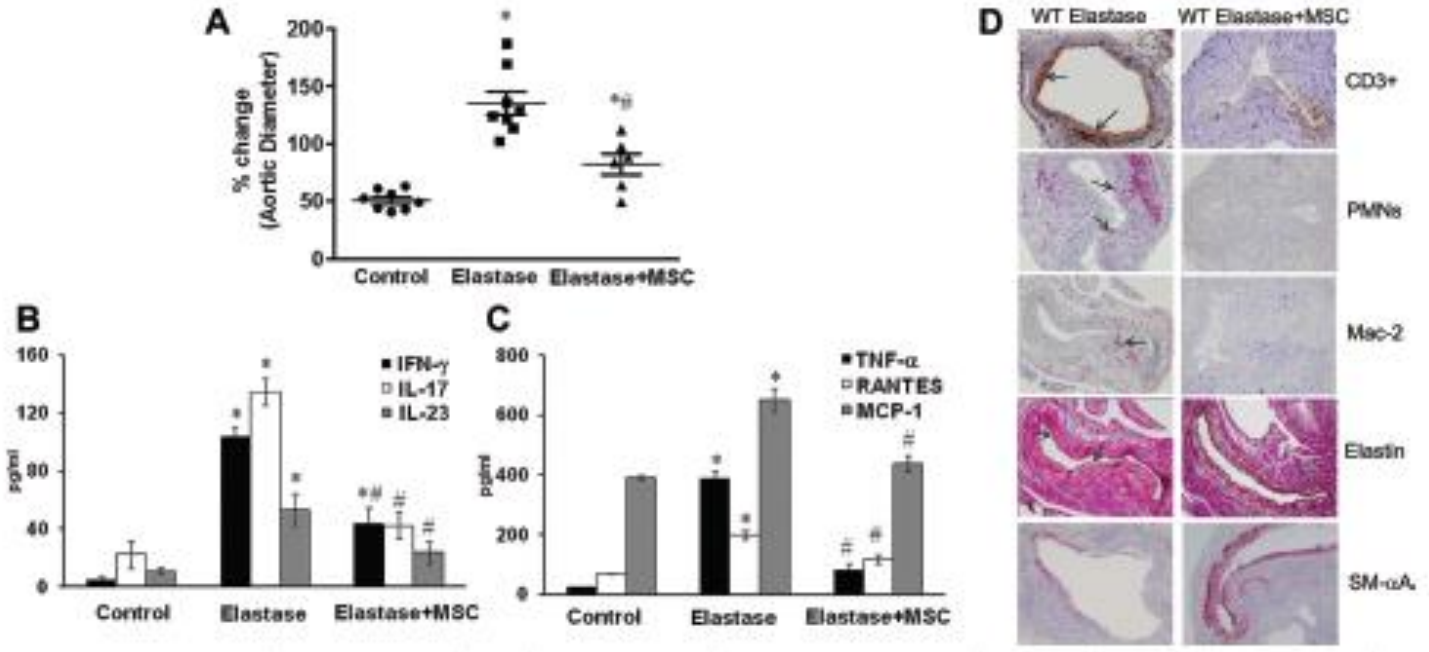

The FASEB Journal article fj.201600144RR. Published online September 12, 2016.
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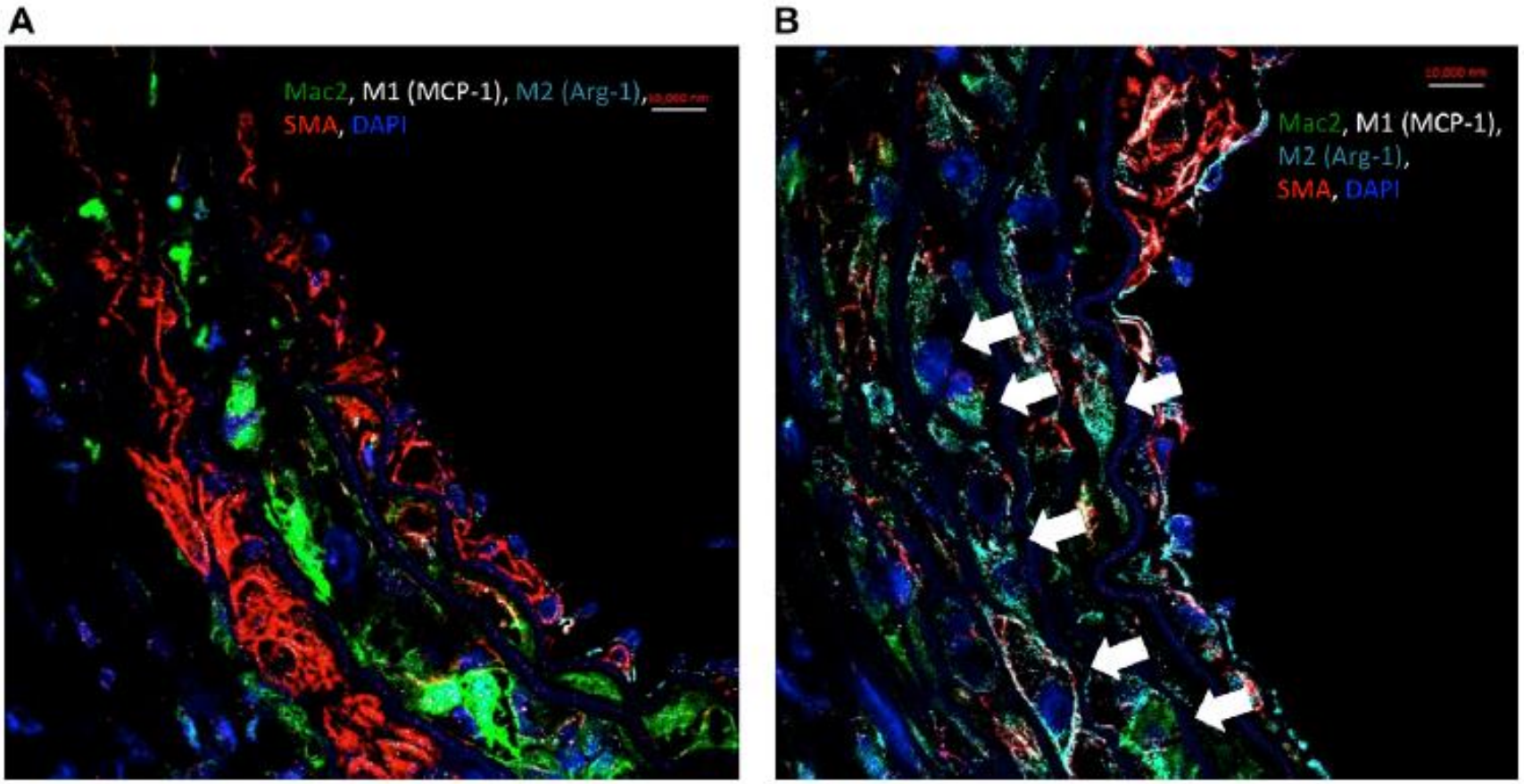


RESOLUTION, RATHER THAN CREATION, OF INFLAMMATION MAY BE IMPORTANT

SUMMARY (1)

- **Using models and human tissue/ serum, we have identified a number of targets for directed medical therapy for a cure**

OBJECTIVE

2. To summarize ongoing trials in humans of potential medical therapies to inhibit AAA growth.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Medical Management of Small Abdominal Aortic Aneurysms

B. Timothy Baxter, Michael C. Terrin and Ronald L. Dalman

Circulation. 2008;117:1883-1889
doi: 10.1161/CIRCULATIONAHA.107.735274
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Table. Results of Interventions on AAA Growth

Intervention	Reference(s)	Effect on AAA Growth	Level of Evidence	Class of Recommendation
Propranolol	46, 69	No inhibition	A	III
Macrolides	60	Inhibition	B	IIa
Tetracycline*	67	Inhibition	B	IIa
Statins	38, 39	Inhibition	B	IIb
ACE inhibitors	27, 39, 52, 53	No inhibition	B and C	IIb
AR blockers	46, 50	Animal data	C	IIb

*Inhibition at 6 and 12 months after 3 months of treatment.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Medical Therapy of Thoracic Aortic Aneurysms : Are We There Yet?

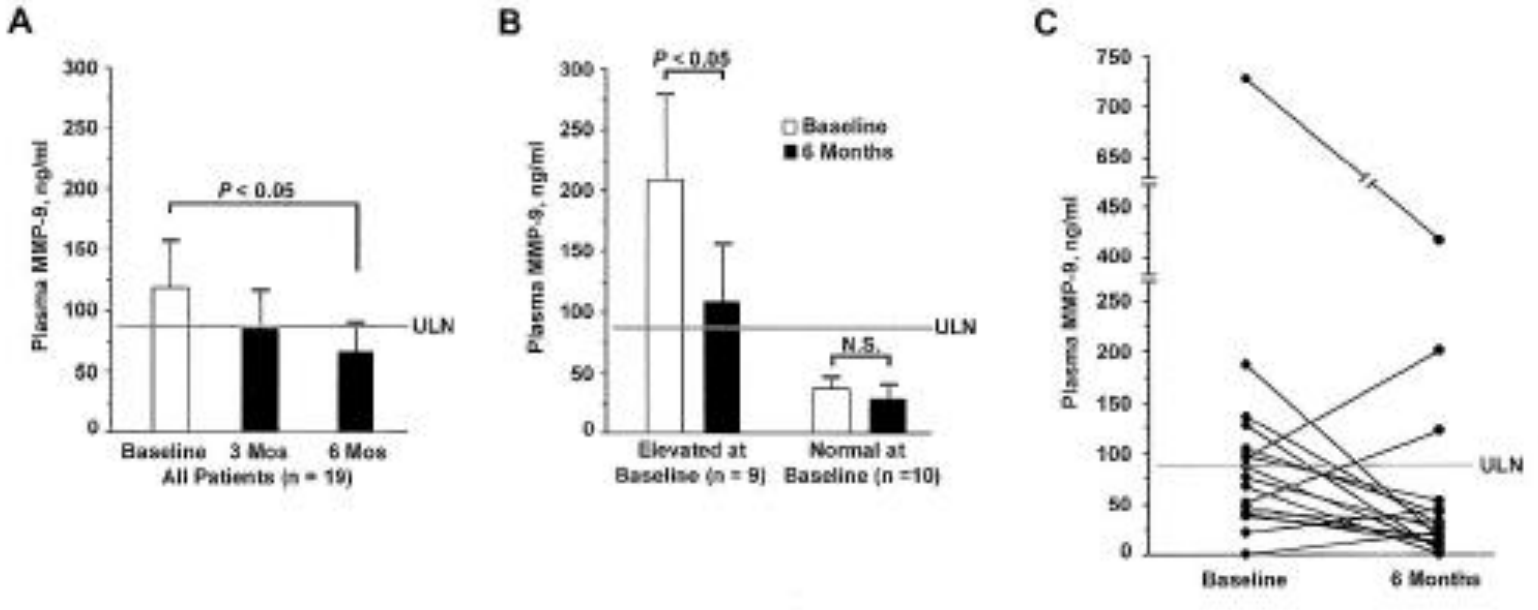
Table. Clinical Studies of Medical Therapy for Aortic Aneurysms

Authors	Study Design	Intervention	Patients, n	Findings
Shores et al[59]	Marfan syndrome; randomized, prospective study; ≈10-y mean follow-up	Propranolol	32 Treated, 38 control subjects	Propranolol caused significantly reduced aortic root dilatation
Gadowski et al[57]	Infrarenal AAA; observational, prospective study; 43-mo mean follow-up	β-blocker	38 Treated, 83 control subjects	Patients with large aneurysms on β-blockers had significantly lower AAA expansion rate
Leach et al[58]	AAA; observational, retrospective study; 34-mo mean follow-up	β-blocker	12 on β-blocker, 15 not on β-blocker	Patients on β-blocker had significantly lower AAA expansion rate
Propranolol Aneurysm Trial Investigators[61]	AAA; prospective, randomized, double-blind study; 2.5-y mean follow-up	Propranolol	276 on propranolol, 272 on placebo	Propranolol did not significantly affect small AAA growth; high discontinuation rate of propranolol
Lindholt et al[60]	AAA; randomized, controlled study; 2-y follow-up	Propranolol	54 Asymptomatic patients	Increased mortality in propranolol group; only 22% could be treated
Baxter et al[66]	AAA; prospective, observational study; 6-mo phase II study	Doxycycline	36 Patients	Doxycycline was safe and caused MMP-9 level decrease
Mosorin et al[67]	AAA; randomized, placebo controlled, double-blind study; 18-mo follow-up	Doxycycline	17 on doxycycline, 15 on placebo	Aneurysm expansion rate was significantly lower in the doxycycline group
Vammen et al[68]	AAA; randomized, double-blind study; 1.5-y mean follow-up	Roxithromycin	43 on roxithromycin, 49 on placebo	4 wk of therapy reduced AAA expansion rate
Sweeting et al[75]	AAA; prospective, observational study; 1.9-y mean follow-up	ACEI	169 on ACEI, 1532 not on ACEI	Patients on ACEI had a faster AAA growth rate than patients not on ACEI
Ferguson et al[70]	AAA; observational, prospective study; 5-y median follow-up	Statins	394 on statins, 258 not on statins	Statins were not associated with reduced AAA growth rate
Gambarin[62]	Marfan syndrome; open-label phase III study	Losartan, nebivolol	291 patients	Ongoing

AAA indicates abdominal aortic aneurysm; MMP, matrix metalloproteinase; and ACEI, angiotensin-converting enzyme inhibitor.

Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: Report of a prospective (Phase II) multicenter study

B. Timothy Baxter, MD,[a] William H. Pearce, MD,[c] Eugene A. Waltke, MD,[b] Fred N. Littooy, MD,[d] John W. Hallett, Jr, MD,[e] K. Craig Kent, MD,[f] Gilbert R. Upchurch, Jr, MD,[g] Elliot L. Chaikof, MD, PhD,[h] Joseph L. Mills, MD,[i] Beverly Fleckten, BS, CCRC,[a] G. Matt Longo, MD,[a] Jason K. Lee, MD,[j] and Robert W. Thompson, MD,[j] *Omaha, Neb; Chicago and Maywood, Ill; Rochester, Minn; New York, NY; Ann Arbor, Mich; Atlanta, Ga; Tuscon, Ariz; and St Louis, Mo*



(J Vasc Surg 2002;36:1-12.)

Medical treatment for small abdominal aortic aneurysms (Review)

Rughani G, Robertson L, Clarke M

THE COCHRANE COLLABORATION®

"In general, there is suprisingly little high quality evidence on medical treatment for small AAAs."

1. **There is limited evidence that antibiotics might have a slight protective effect in retarding expansion rates of small AAAs**
2. **Propanolol poorly tolerated and demonstrated only minimal and non-significant effects.**

Statin Therapy

Eur J Vasc Endovasc Surg (2011) xx, 1–5

Table 1 Cohort studies on pharmacological interventions.

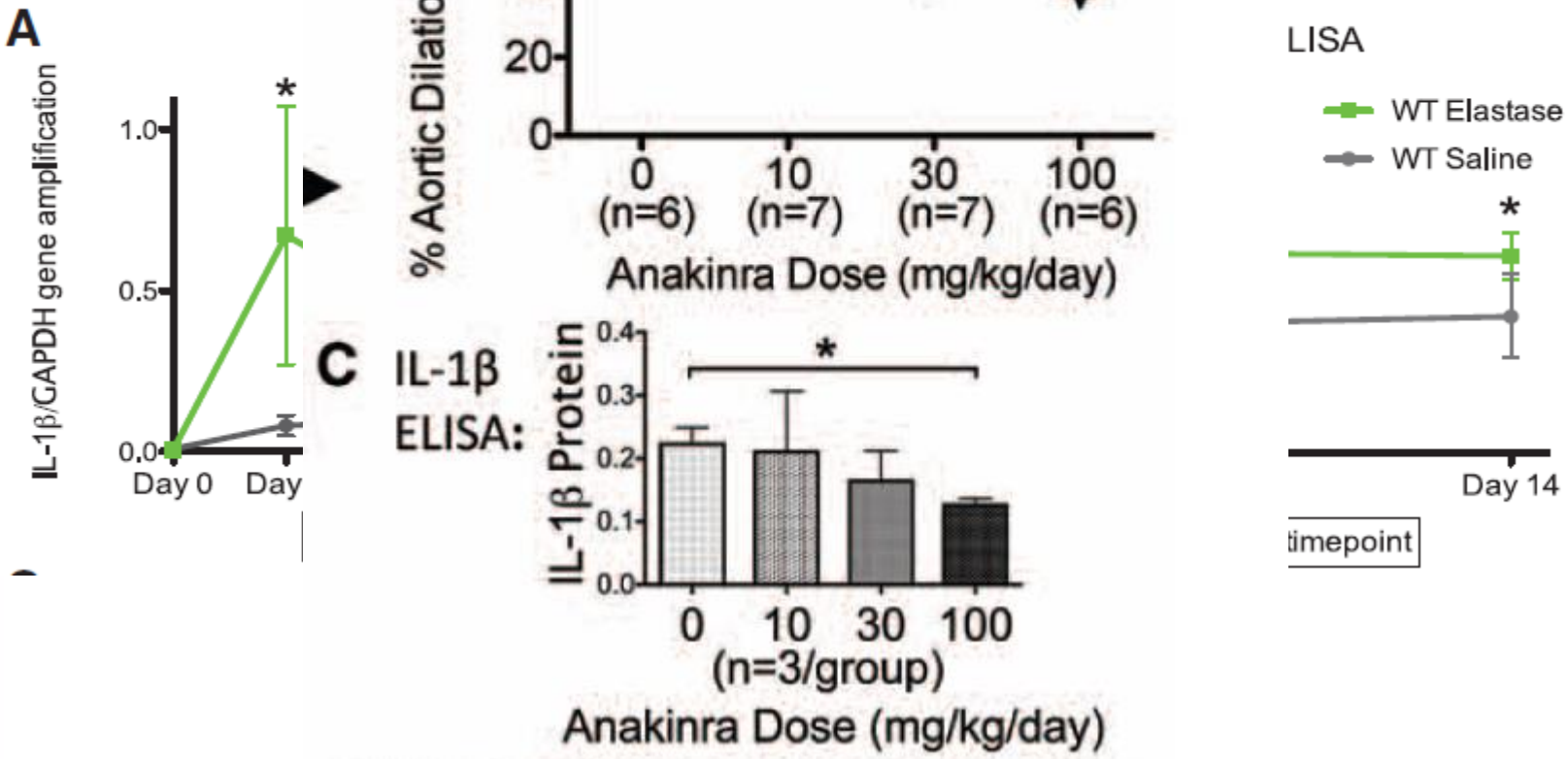
Author		No	Substances studied	Expansion rate, mm/y	*P*-value
Biancari[19]	2002	41	ß-block vs control	1.5 vs 2.2	NS
Brady[6]	2004	1743	Antihypertensives vs no	2.6 vs 2.7	NS
Ferguson[20]	2010	652	Statin vs no statin	OR 1.04	NS
Gadowski[21]	1994	121	ß-block vs control	3.0 vs 4.4	0.07
Leach[22]	1988	27	ß-block vs control	1.7 vs 4.4	NS
Lindholt[23]	2001	137	ß-block vs control	1.6 vs 2.5	0.01
Lindholt[24]	2008	148	ASA vs no ASA	2.5 vs 2.2	NS
Mosorin[25]	2008	121	Statin vs no statin	1.9 vs 2.6	NS
Schlösser[26]	2008	230	Lipid lowering vs no	Diff. 1.21	<0.02
Schouten[27]	2006	150	Statin vs no statin	2.0 vs 3.6	<0.001
Sukhija[28]	2006	130	Statin vs control	0 vs 0.4	<0.001
Sweeting[13]	2010	1701	ACEI vs no	3.33 vs 2.77	0.009
Thompson[29]	2010	1231	ACE vs no	Diff 0.28	NS
			Statin vs no	Diff 0.29	NS
Walton[30]	1999	78	NSAID vs control	1.5 vs 3.2	<0.01
Wilminck[31]	2002	5811	Antihypertensives vs no	0.5 vs 0.8	NS

Mechanism: Likely not cholesterol lowering

(*Arterioscler Thromb Vasc Biol*. 2013;33:294-304.)

Genetic ar … terleukin-1β
Signaling In … sm Formation

… Lu,
Matthew J. St … Goray Ajlawadi



DID NOT TRANSLATE IN HUMANS!:
NEED TO PUBLISH NEGATIVE CLINICAL TRIALS

SUMMARY (2)

Good Medical Therapy in Humans

- Beta blocker
- Statin
- ACE inhibitor

ALL GOOD MEDICAL THERAPY REGARDLESS OF AAA REGRESSION

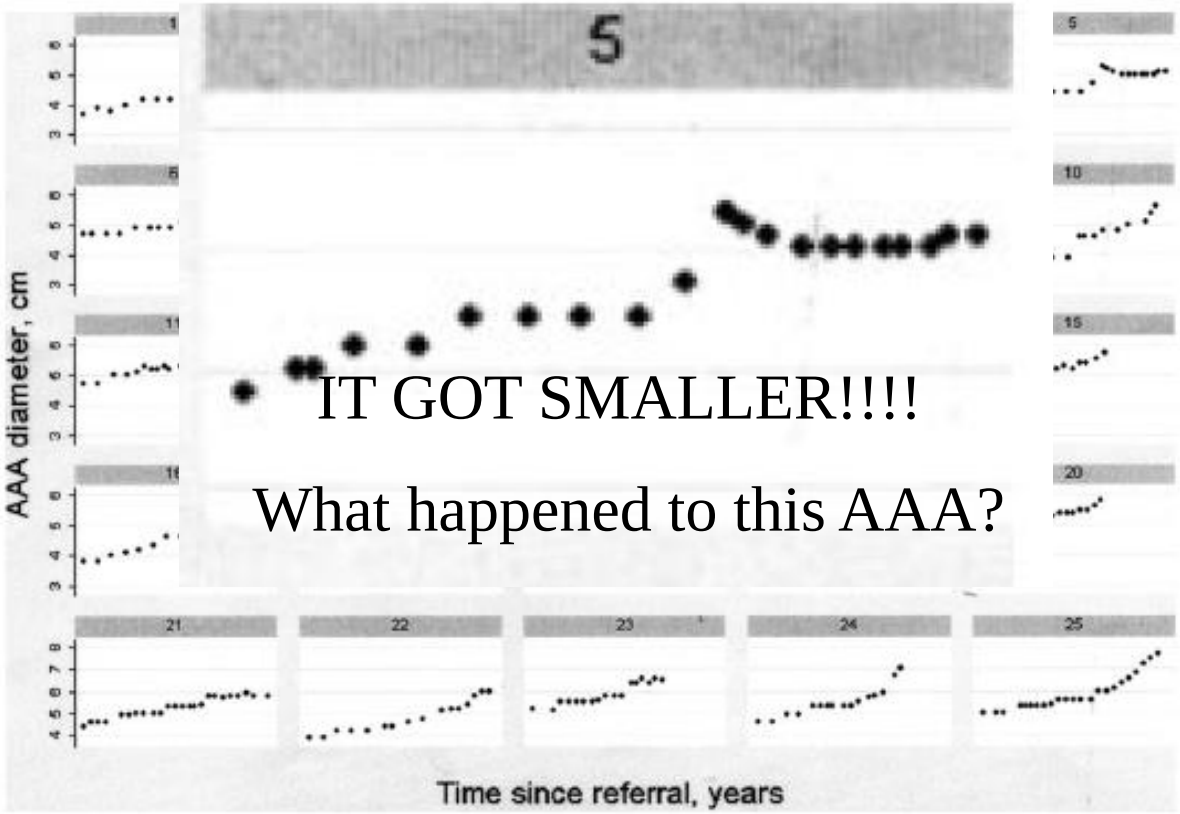
OBJECTIVE

3. To consider why we have not found a cure for AAAs yet! (**Is there hope?**).

Abdominal Aortic Aneurysm Expansion

Risk Factors and Time Intervals for Surveillance

Anthony R. Brady, MSc; Simon G. Thompson, DSc; F. Gerald R. Fowkes, FRCPE;
Roger M. Greenhalgh, MD; Janet T. Powell, MD;
on behalf of the UK Small Aneurysm Trial Participants



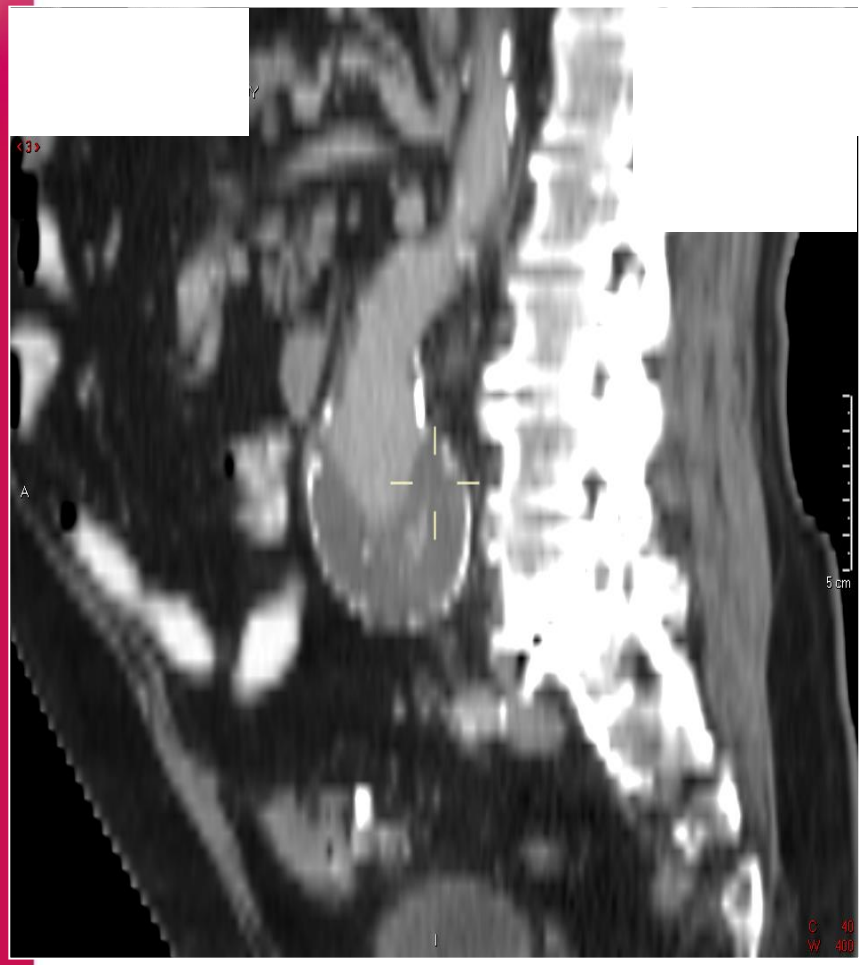
IT GOT SMALLER!!!!

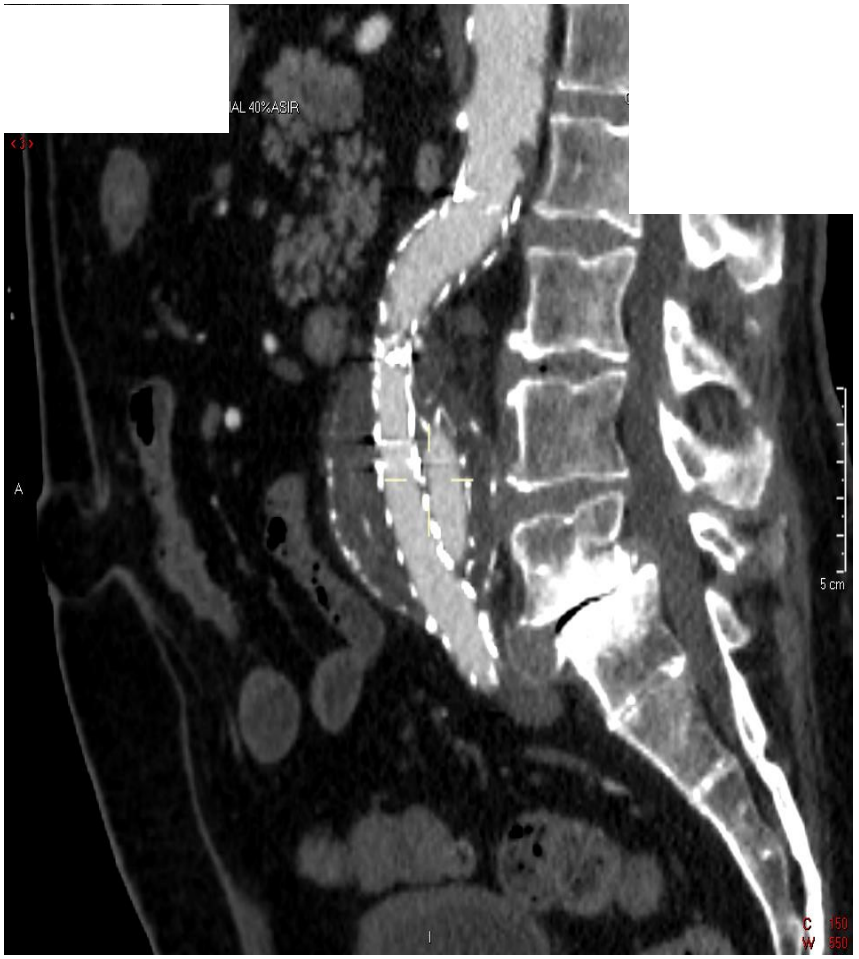
What happened to this AAA?

Figure 1. AAA diameter measurements for 25 patients with longest follow-up (the bottom row has a different vertical scale).

(*Circulation*. 2004;110:16-21.)

EVAR DOCUMENTED NEGATIVE REMODELING IS REAL





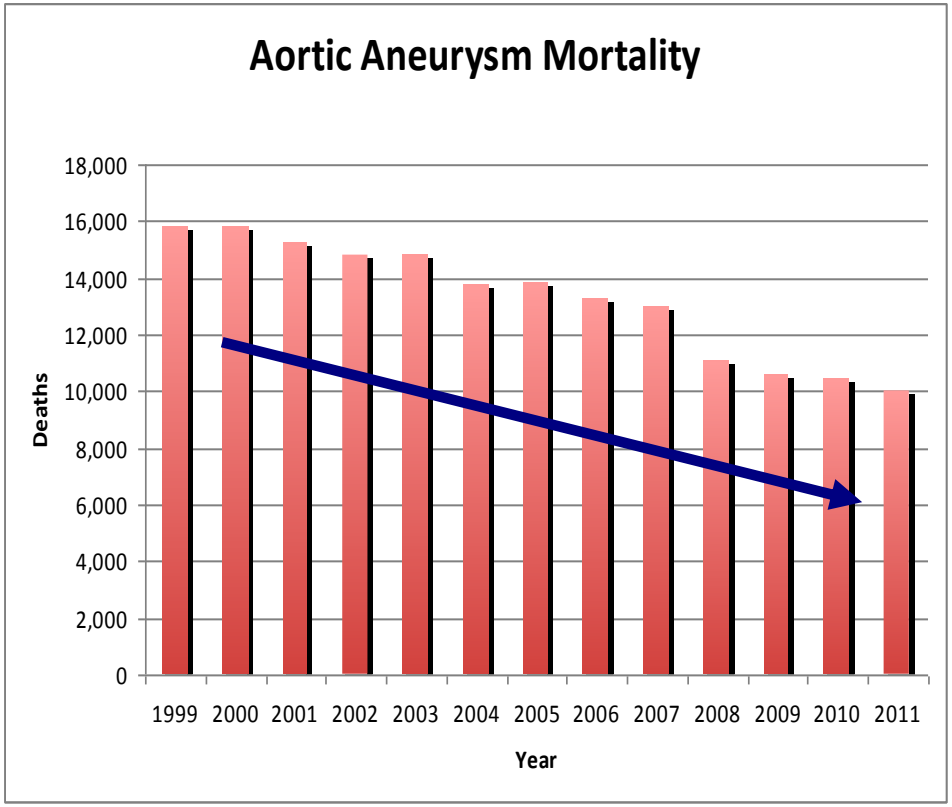
6.2 cm

5.6 cm

DECREASED 0.6 CM IN 1 MOS

SUMMARY (3)

WE ARE MAKING PROGRESS!!!



Deaths secondary to

AAA are decreasing!

CDC, National Vital Stats

BIG QUESTION!

Why have observations not been translated into aneurysm-specific therapy in humans?

1.Bad Models

2. Too costly to develop clinical trial

(not fiscally worth investing in by companies)

3. Problem not costly enough in lives per year

4. Targeting events that only occur early

5. Need to publish our negative results

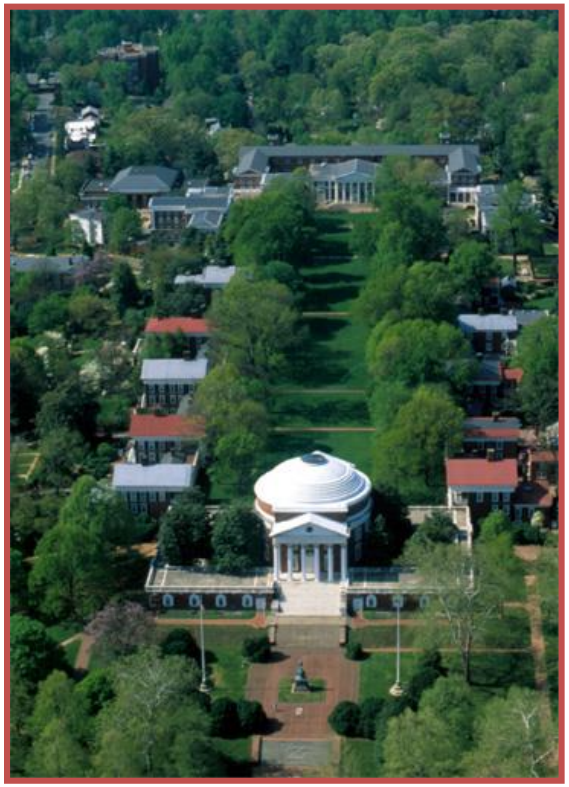
Potential Approaches to Developing Targets

1. Promote Extracellular Matrix Regeneration
   - Regenerative Therapies

2. Decrease Inflammation/ ECM Destruction
   - Need to examine late events

3. Improve Delivery of Drugs to Aorta

ALL NOBLE OBJECTIVES FOR FUTURE!



"I was bold in the pursuit of knowledge, never fearing to follow truth and reason to whatever results they led, and bearding every authority which stood in their way."

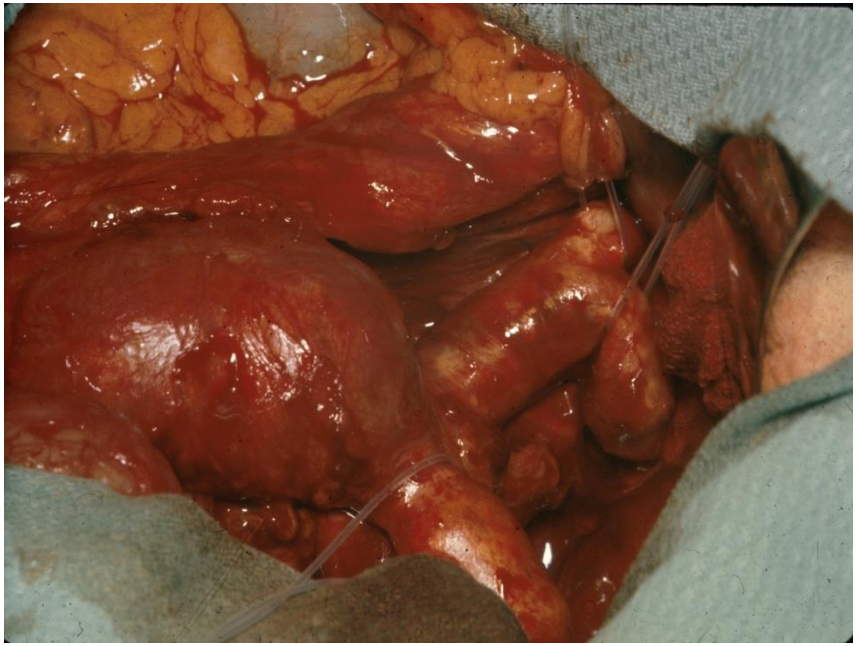
Thomas Jefferson Must Have Been taking care of Aortic Disease

UVA Aneurysm Team

ANEURYSM PATHOLOGY

Findings include:

- Inflammatory infiltrate
- Medial elastin & collagen fragmentation
- SMC apoptosis
- Cytokine up-regulation



SURGEONS HAVE PLAYED A CRITICAL ROLE IN UNDERSTANDING PATHOGENESIS

Pearce

Tilson

Thompson

Dalman

Baxter

Aneurysm Models

- Porcine pancreatic elastase perfusion
- $CaCl_2$ periaortic application
- Angiotensin II infusion in Apo E KO
- Angiotensin II infusion in LDL receptor KO
- Lysyl Oxidase KO
- MMP-3 or TIMP-1 KO
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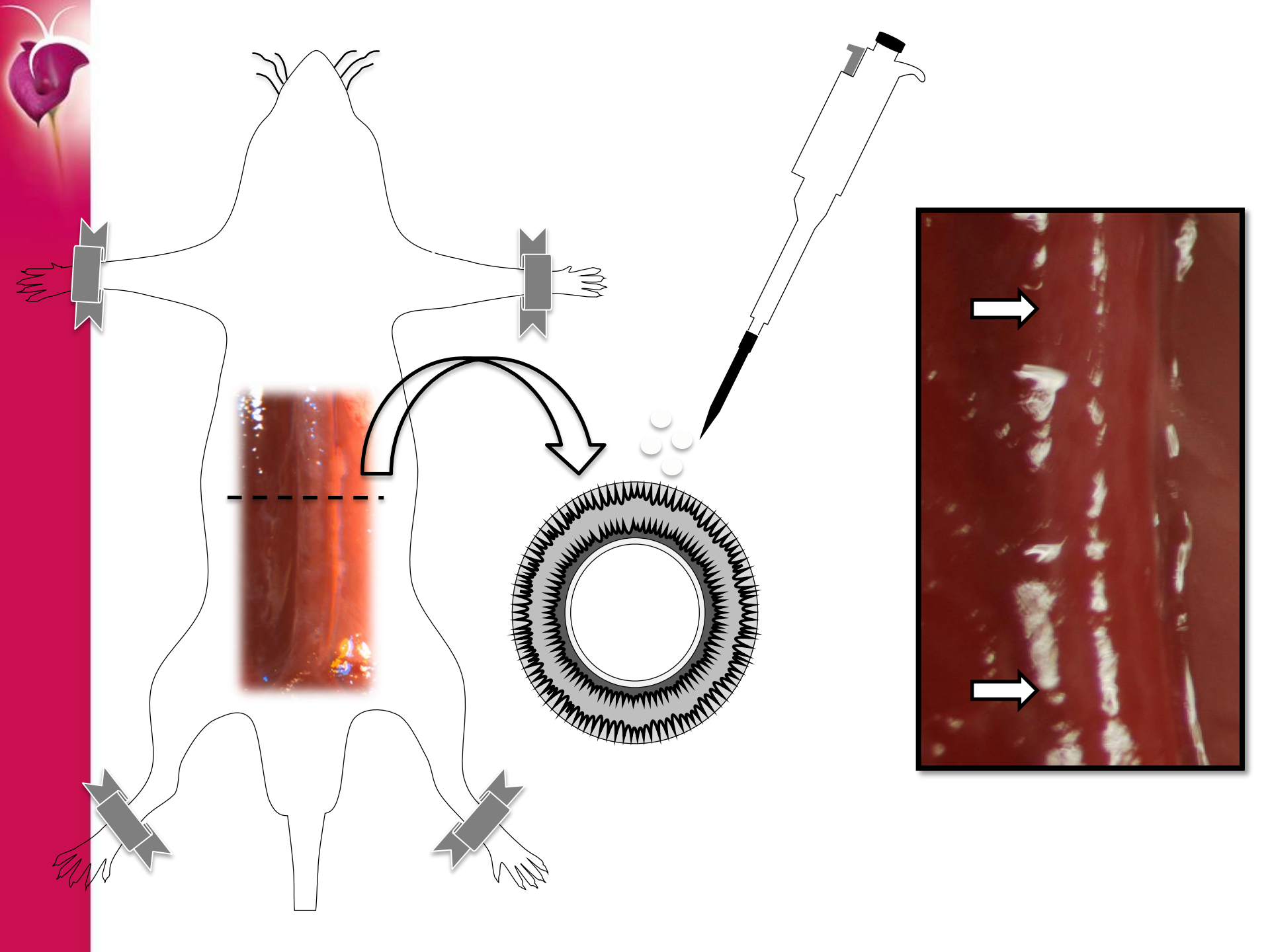

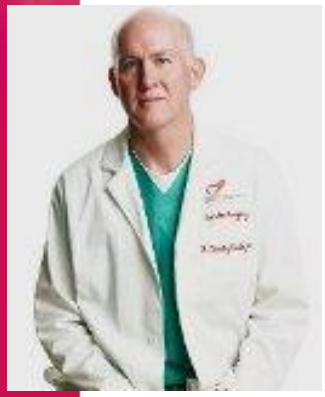

MMP-12 has a role in abdominal aortic aneurysms in mice

G. Matthew Longo, MD,[a] Steven J. Buda, MD,[a] Nicola Fiotta, MD,[a] Wanfen Xiong, PhD,[a] Timothy Griener, MD,[b] Steven Shapiro, MD,[c] *and* B. Timothy Baxter, MD,[a,c,d] *Omaha, Neb, and Boston, Mass*

Background. *Matrix metalloproteinase (MMP)-12 levels are increased in the abdominal aortic aneurysm (AAA), implicating this protease in AAA pathogenesis. The purpose of this study was to assess the role of MMP-12 in aneurysm formation.*

Methods. *A murine aneurysm model was generated by periaortic application of 0.25 mol/L calcium chloride ($CaCl_2$) for 15 minutes. Aortic diameters were measured and compared before and 10 weeks after aneurysm induction. Aortic diameter changes for wild type (WT) and MMP-12 knockout (MMP-$12^{-/-}$) mice were determined. MMP-12 production in mouse aorta was analyzed by casein zymography. MMP-2 and MMP-9 expressions were examined by gelatin zymography. Immunohistochemical study was used to measure macrophage infiltration into the aorta.*

Results. *There is an increase of 63 ± 5 % (mean ± SEM) in aortic diameters of WT mice after $CaCl_2$ inductions, while MMP-$12^{-/-}$ mice increased only 26 ± 14%. Connective tissue staining of aortic sections from WT mice showed disruption and fragmentation of medial elastic fibers, while MMP-$12^{-/-}$ mice showed only focal elastic lamellae breakdown. MMP-12 levels in WT mice were significantly increased after $CaCl_2$ treatment, whereas no MMP-12 was detected in MMP-$12^{-/-}$ mice. There was no difference in the MMP-2 and MMP-9 productions between WT and MMP-$12^{-/-}$ mice. Immunohistochemical analysis demonstrated that infiltrating macrophages in the aorta of MMP-$12^{-/-}$ mice were significantly less than WT controls.*

Conclusions. *MMP-12 deficiency attenuates aneurysm growth, possibly by decreasing macrophage recruitment. (Surgery 2005;137:457-62.)*