

# Dissecting Effects of DES -Drugs and Polymers on Inflammation and Thrombosis

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ICI meeting 2009  
Innovations in Cardiovascular Interventions

# Disclosures

I have the following financial relationships to disclose:

Type of relation:

Medtronic CardioVascular

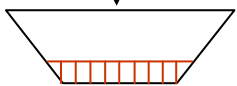
*(Employment; Senior Principal Scientist)*

# Adhesion of Inflammatory Cells is Driven by Polymer Composition

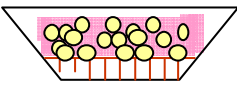
*Increasing the percentage of hydrophilic polymers results in less monocytic adhesion*

Eosinophil & monocytic adhesion to polymer coating

Polymer coated plate

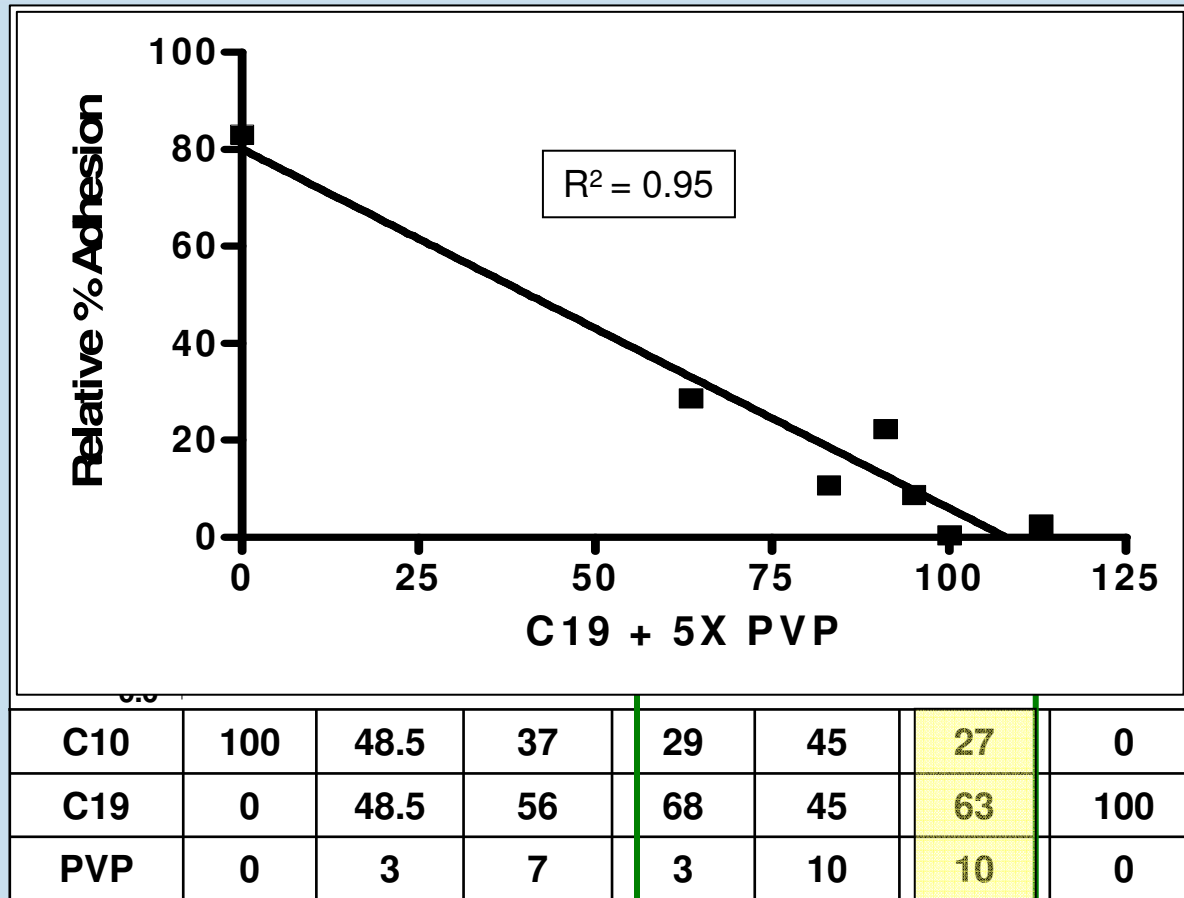


Activated Inflammatory cells on top



Wash and evaluate adhesion

Ratio  
C10:C19:PVP



C10	100	48.5	37	29	45	27	0
C19	0	48.5	56	68	45	63	100
PVP	0	3	7	3	10	10	0

BioLinx (Resolute)

# In-Vitro Biocompatibility of DES-Polymers

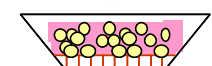
*Inflammatory Adhesion, Thrombosis and Protection from Oxidative Stress*

Eosinophil & monocytic adhesion to polymer coating

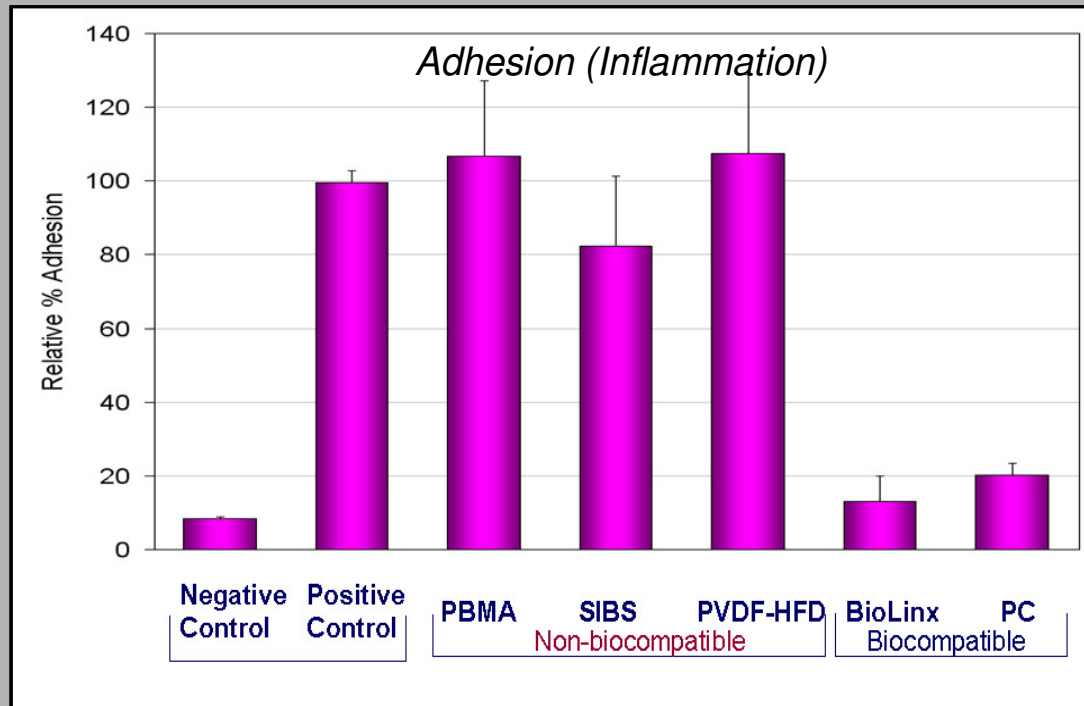
Polymer coated plate



Activated Inflammatory cells on top



Wash and evaluate adhesion



S... Polymer C10 (Xience)

# In-Vivo; Disease-Relevant Pre-clinical Model

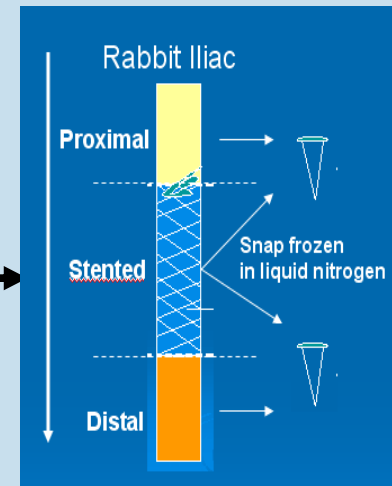
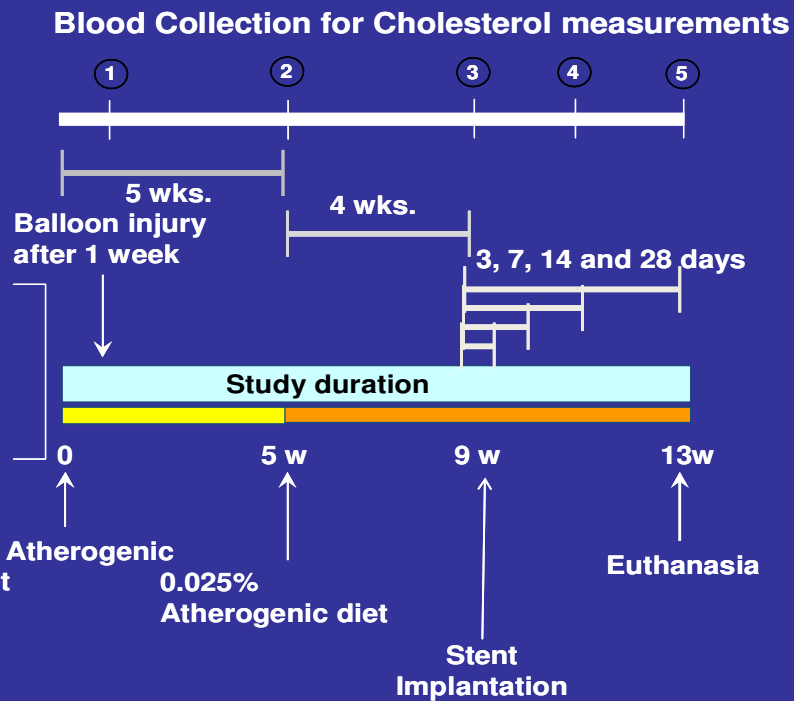
*Effects of DES; Histology and Gene Profiling*

## Study design for Atherosclerosis



New Zealand White Rabbits

Groups:  
Driver  
Xience V  
Resolute

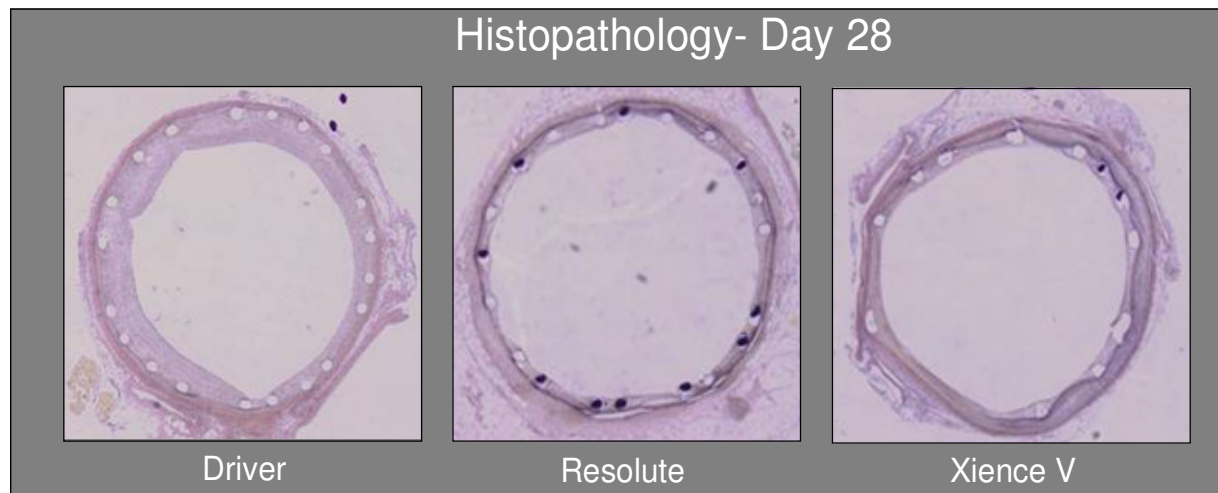


*Histology*  
*Gay14, day 28*

*Gene Profiling*  
*Day 3, 7, 14 and 28*

# Histopathology- Day 28

*Effects of DES; Comparable Efficacy*



**Driver**

**Resolute**

**Xience**

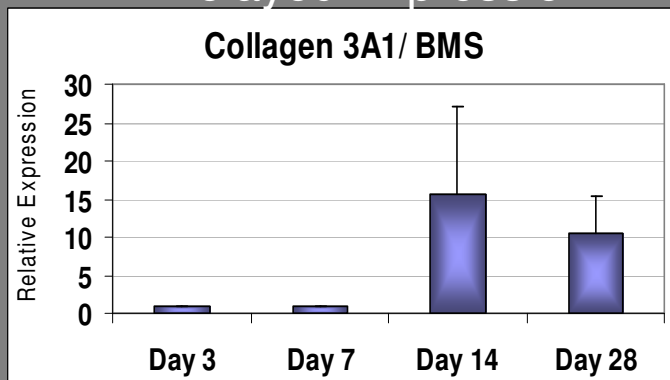
# Study Design

- To evaluate temporal expression of inflammatory biomarkers;
  - Atherosclerotic rabbit disease model, over days 3, 7, 14 and 28 post-stenting

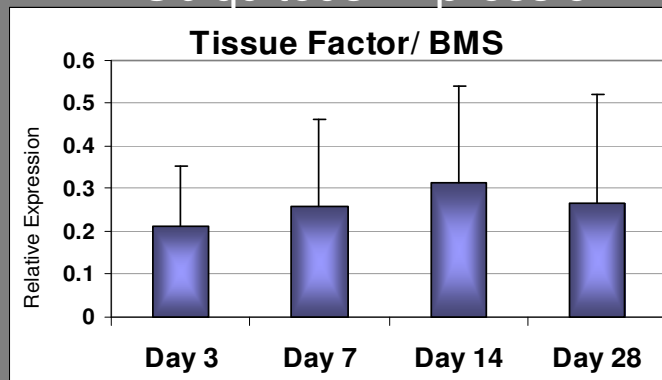
# Distribution of Gene Expression

*Variable kinetics of expression; Early, ubiquitous or delayed*

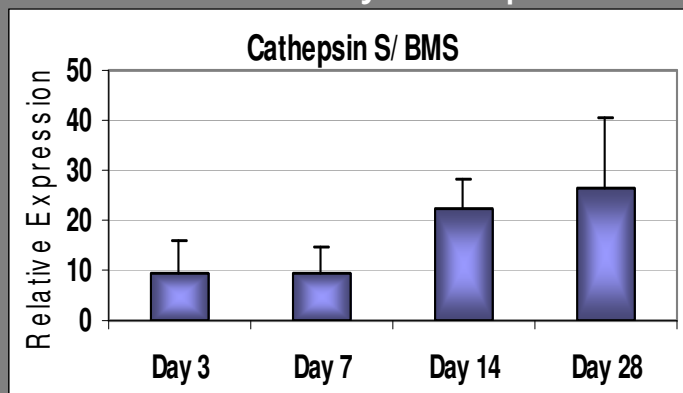
## Delayed Expression



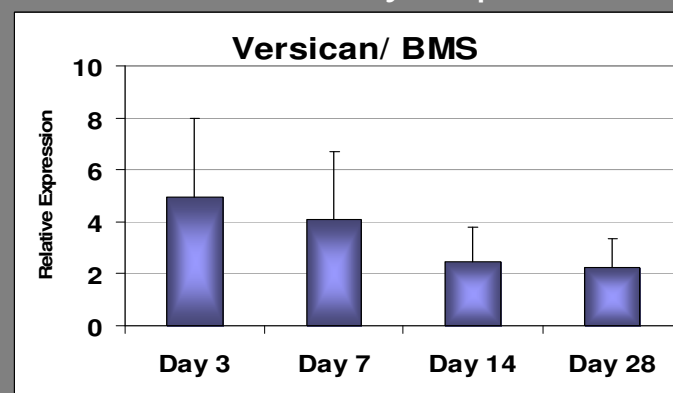
## Ubiquitous Expression



## Enhanced /Delayed Expression



## Enhanced / Early Expression



# Study Design

## *Gene expression*

- To compare expression of respective biomarkers
  - BMS vs. DES;
  - DES; Resolute vs. Xience

# Dissecting Effect of DES Drug from Polymer *Gene Expression\**

**Prominent  
Polymer Effect**

**EES or ZES  
with different polymers  
(Fluoropolymer vs BioLinx)**

**Prominent Limus Drug Effect**

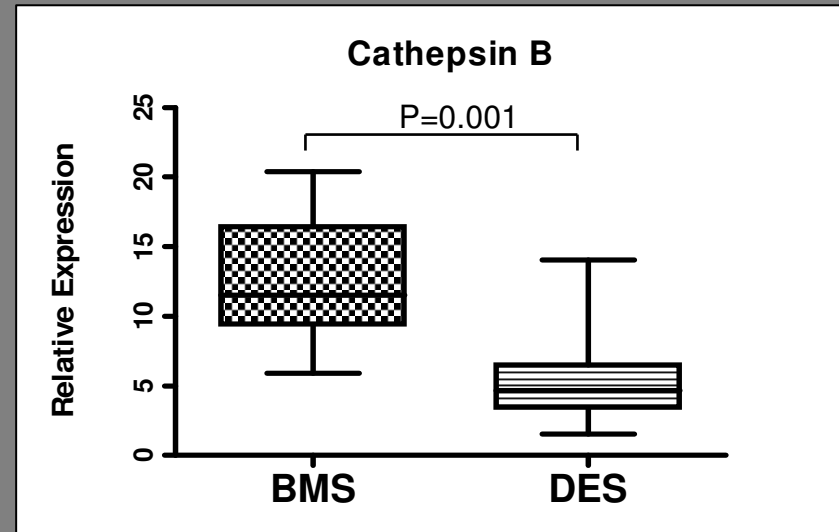
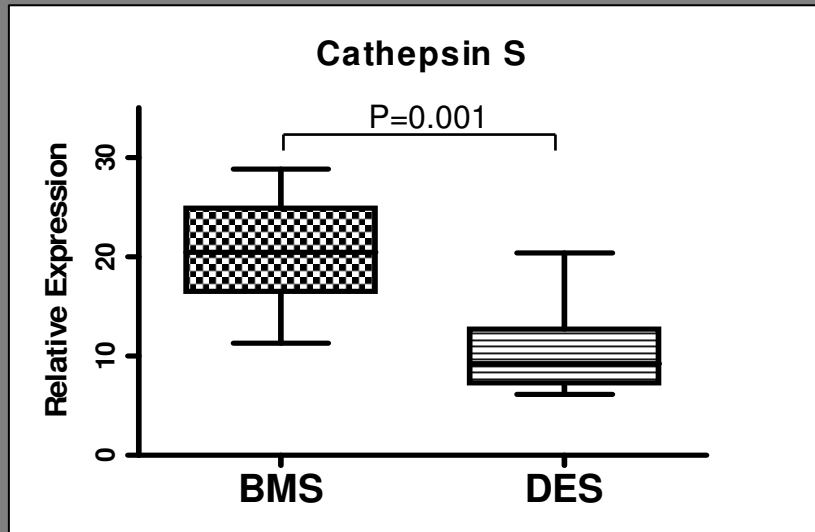
DES vs. Driver

**Desirable  
Drug Effect**

**Undesirable  
Drug Effect**

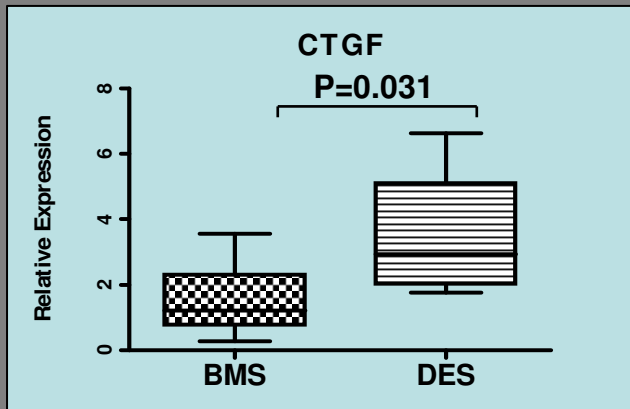
# DES Desirable Drug Effects

Inflammatory activation/ Leukocytic extravasation

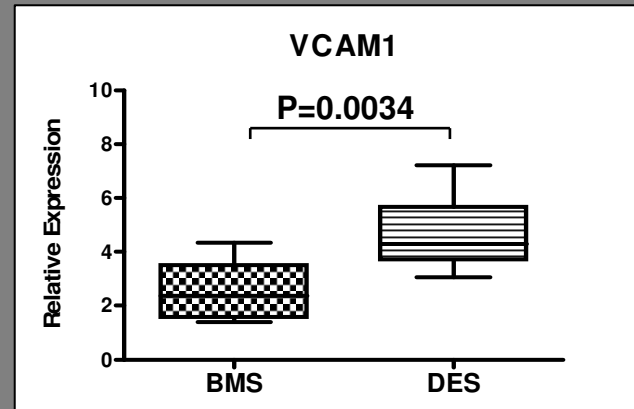


# DES Undesirable Drug Effects

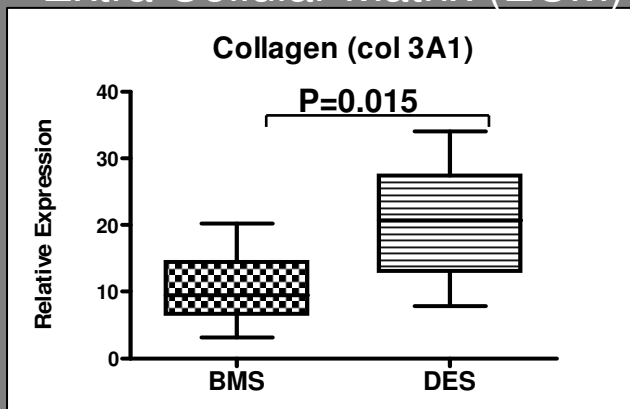
## Production of ECM



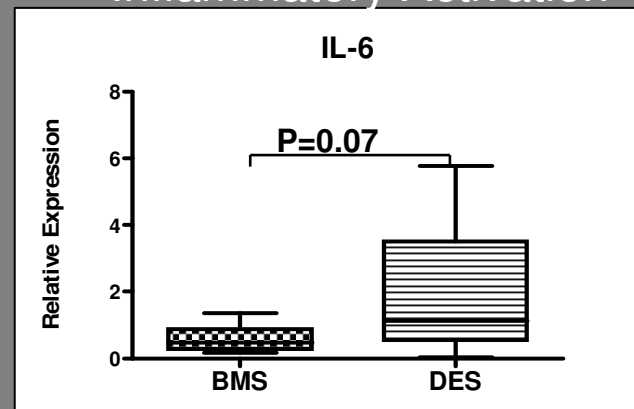
## Inflammatory Adhesion



## Extra Cellular Matrix (ECM)

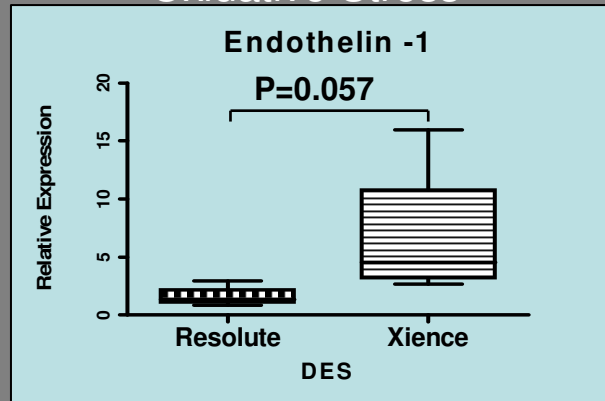


## Inflammatory Activation

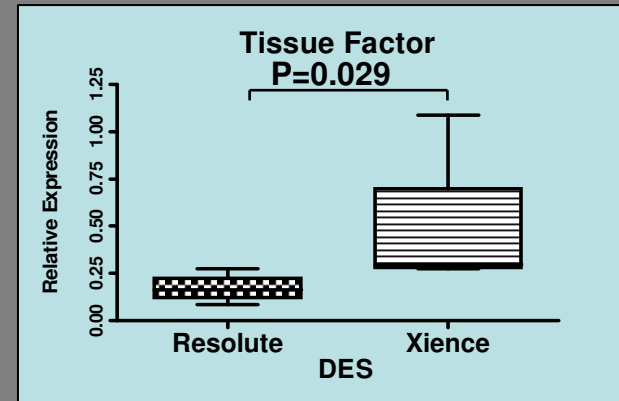


# DES prominent polymer effect

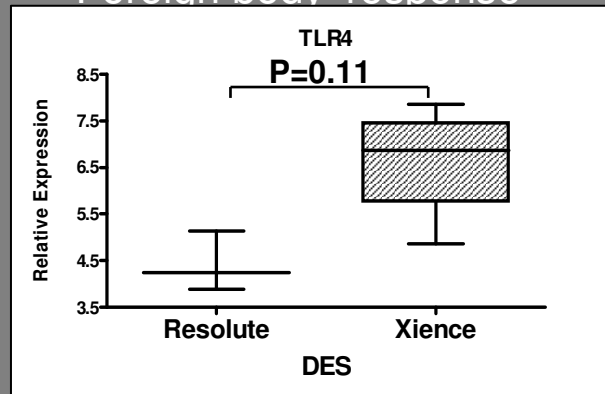
## Oxidative Stress



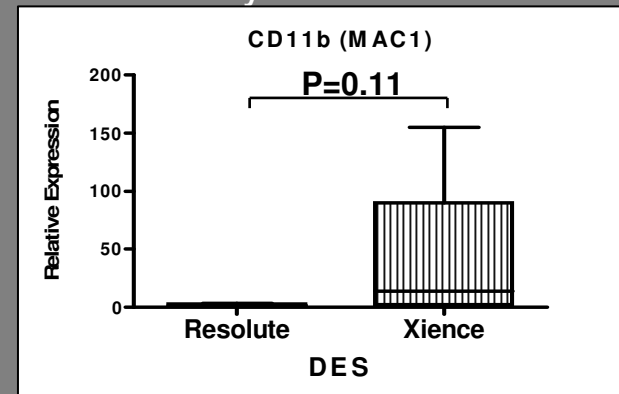
## Thrombotic activation



## 'Foreign body' response

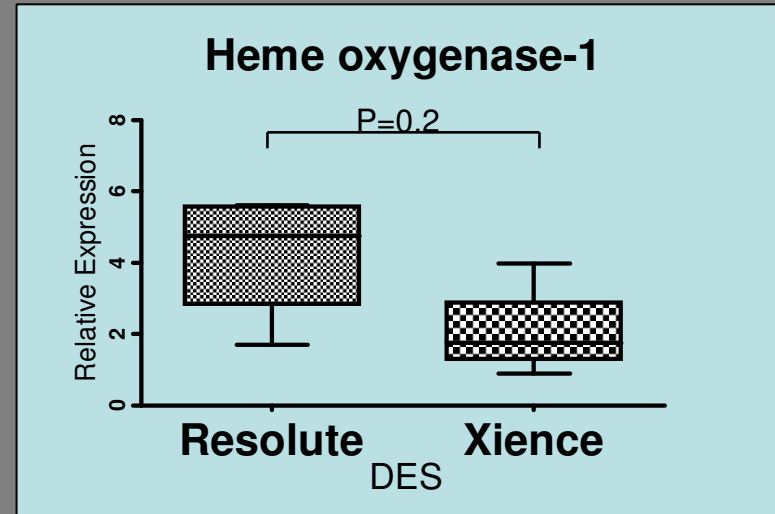
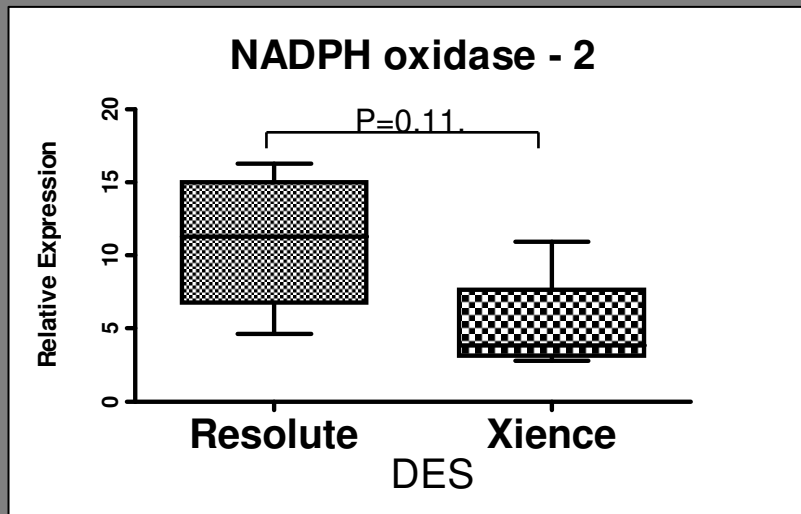


## Monocytic adherence



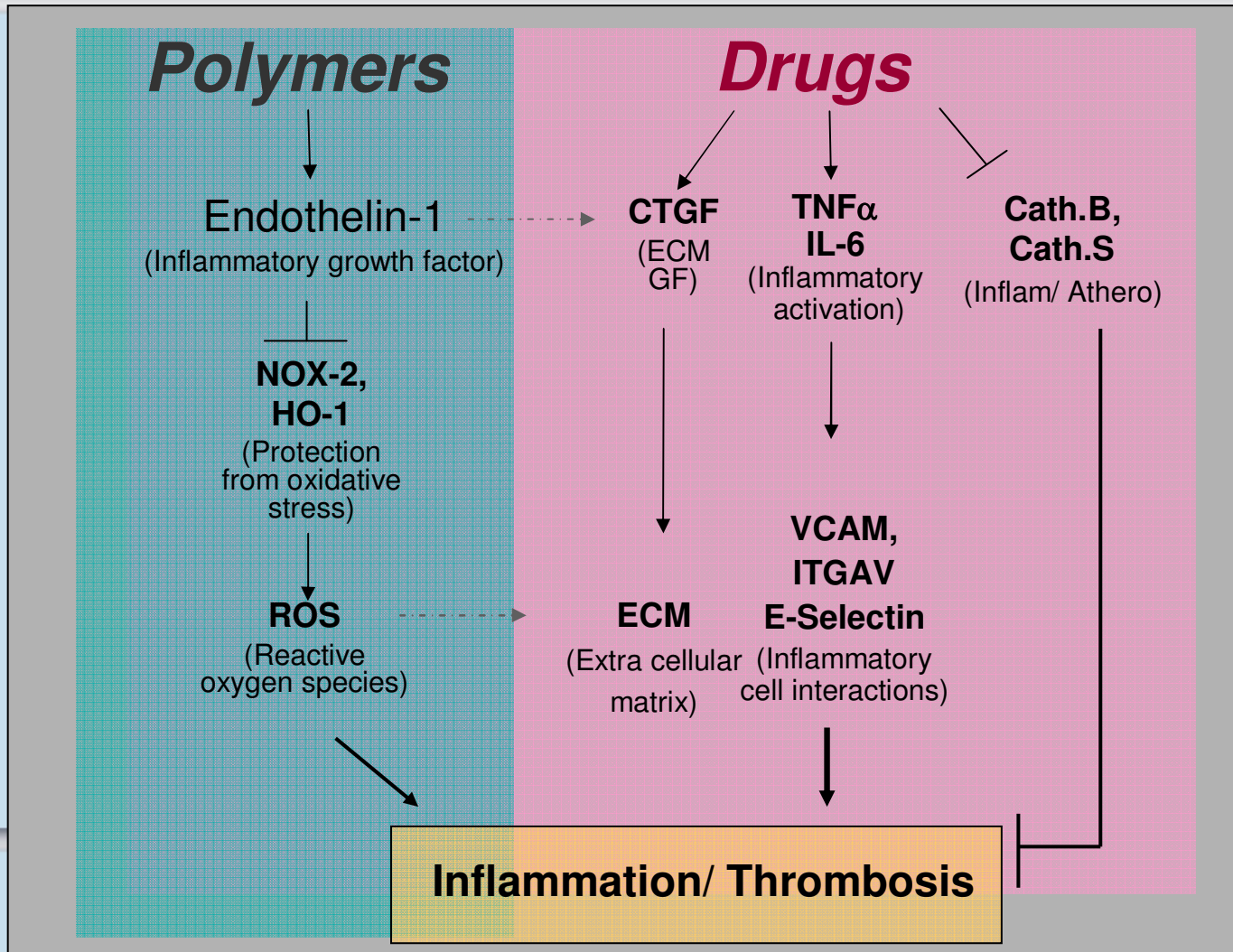
# DES prominent polymer effect

## Protection from Oxidative Stress



# Pathways for Additional Effects

*by DES Drugs and Polymers*



# What Did We Learn?

## *Dissecting Effects of DES -Drugs and Polymers*

- **DES (Resolute vs. Xience) performance in atherosclerotic rabbit model**
  - Confirmed efficacy
  - Temporary gene expression (Inflammation/ Thrombosis)
- **DES drugs and polymers have distinct biological effects**
  - Less biocompatible polymers can trigger oxidative stress and TF activation
  - Confirmed the non-inflammatory design for BioLinx (Resolute)

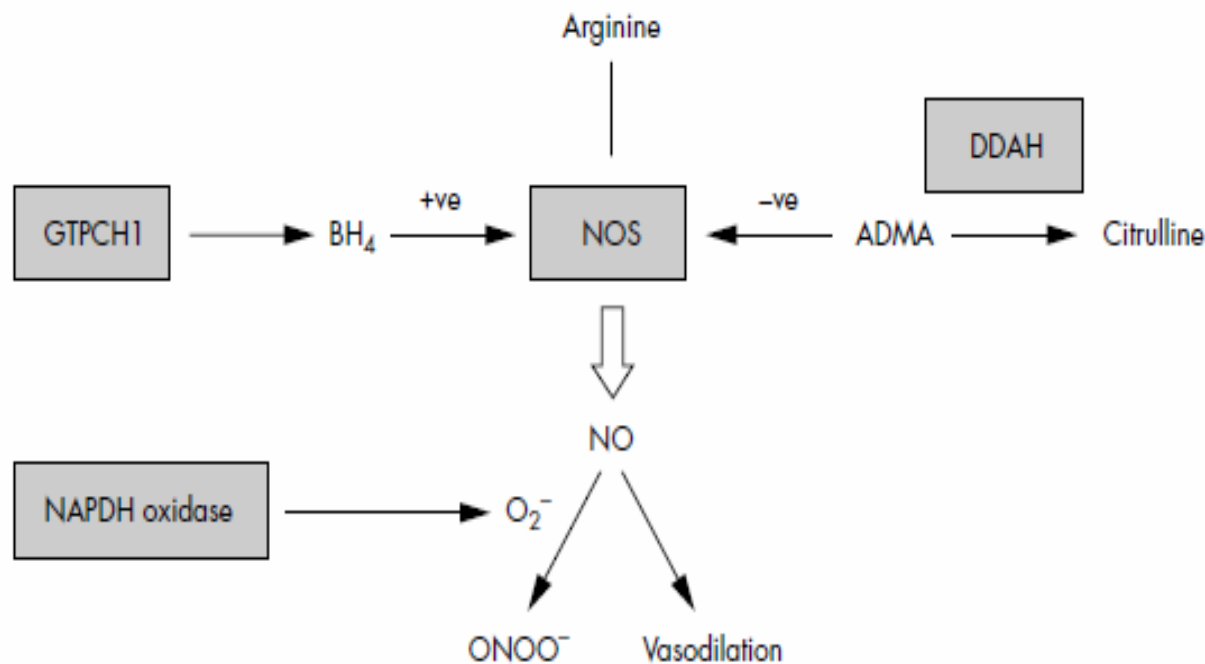
# ICI 09 Thanks!

- Ayala [Hezi-Yamit@medtronic.com](mailto:Hezi-Yamit@medtronic.com)
- Poster # 40

‘Dissecting Effects of DES -Drugs and Polymers on Inflammation and Thrombosis’

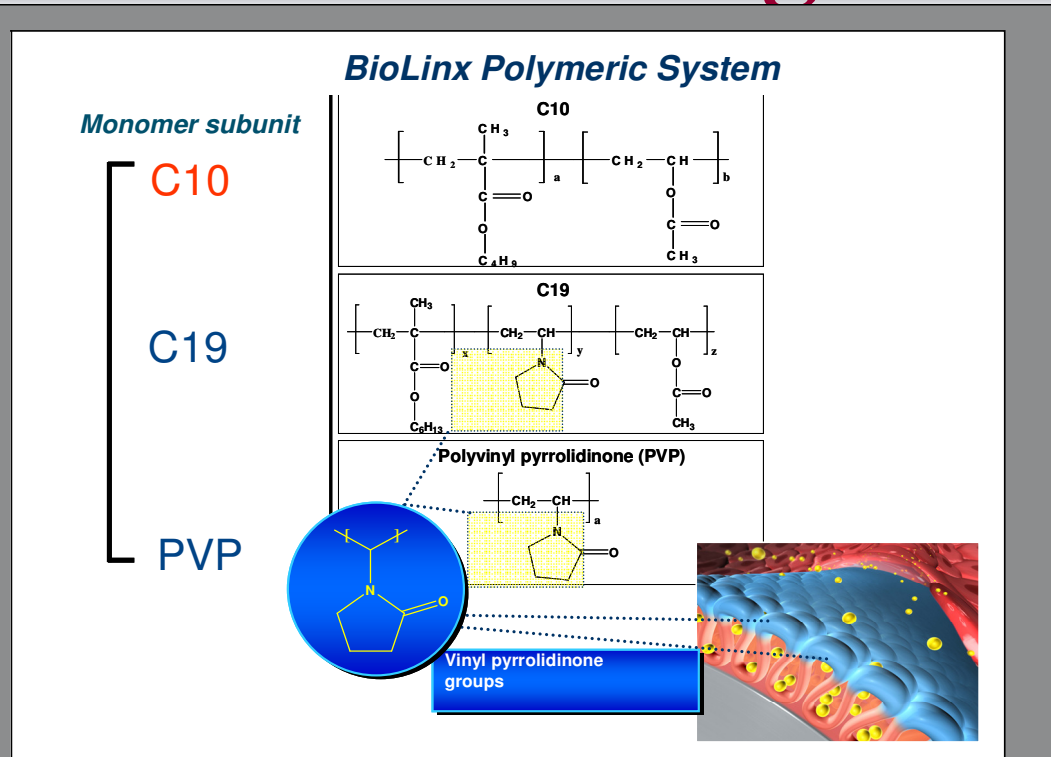
# Backup

# Regulation of Nitric oxide (NO) in the Vascular endothelium



**Figure 1** Regulation of nitric oxide (NO) synthesis in the vascular endothelium. NO is synthesised by the enzyme endothelial oxide synthase (NOS) which requires tetrahydrobiopterin (BH<sub>4</sub>) as a cofactor. The first and rate limiting enzyme in the synthesis of BH<sub>4</sub> is GTPcyclohydrolase 1 (GTPCH1). NOS is inhibited by asymmetric dimethylarginine (ADMA) which in turn is metabolised by dimethylarginine dimethylaminohydrolase (DDAH). NO has vasodilator and antiatherogenic properties but can be inactivated by reaction with O<sub>2</sub><sup>-</sup> to ONOO<sup>-</sup>. One important vascular source of O<sub>2</sub><sup>-</sup> is the NADPH oxidase enzyme.

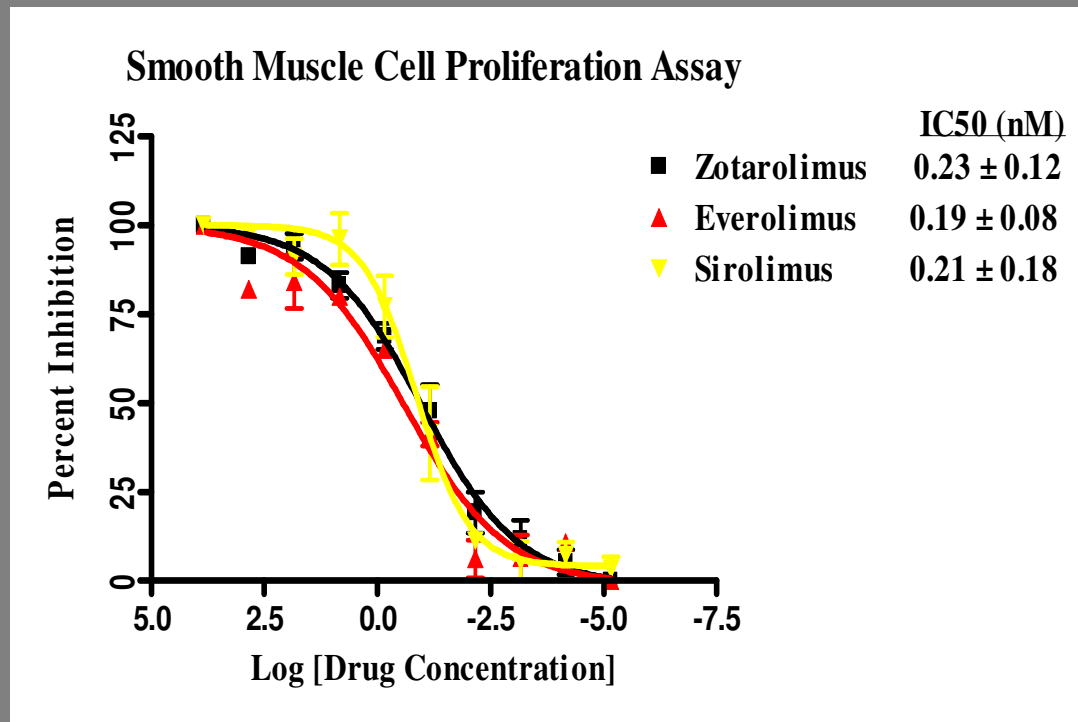
# BioLinx Design



Endeavor Resolute polymeric composition -designed to slow drug release while maintaining a surface hydrophilicity

# Limus Drugs Potency

*Comparable Inhibition of Smooth Muscle Cell Proliferation*



# Dissecting Effect of DES Drug from Polymer Gene Expression

<b>Prominent Polymer Effect</b> <b>BioLinx vs. Fluoropolymer</b> <p><math>p &lt; 0.05</math> (or trend)</p>	<b>Prominent Limus Drug Effects</b> <b>DES vs. BMS <math>p &lt; 0.05</math></b>	
	<b>Desirable Drug Effect</b>	<b>Undesirable Drug Effect</b>
<b>Inflammation /Thrombosis</b> TLR-4 TF (Tissue Factor) ET-1 (Endothelin 1) ITGAV (Vitronectin Receptor)	<b>Inflammation</b> Cathepsin B Cathepsin S  <b>Inhibition of proliferation</b> CDKN1B (p27)	<b>Inflammation</b> TNF            IL-6 VCAM        ECE-1 MMP2        MMP-9 ITGAV        PAI-1 E-selectin
<b>Oxidative Stress (Protection)</b> NADPH (Nox 2/CYBB) HO1 (Hemeoxygenase-1) Thrombomodulin	<b>Oxidative Stress (Protection)</b> DDAH2	<b>ECM</b> CTGF Collagen (Col3A1) Biglycan Versican Decorin
7 genes of interest	4 genes of interest	14 genes of interest

(unsorted) lists and normalized to endogenous gene (Ct1) (1)