The Science of Vascular Access
New Frontiers

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Declarations

I have received honoraria and travel sponsorship

- Gore
- Maquet
- VFT
- Cryolife
- Novartis, Astellas, Wyeth, Genzyme, Roche
We have created a disease

- Affects a huge population
- Aggressive, relentless and results in poor quality of life and reduces survival
- There is no effective treatment

Venous Neointimal Hyperplasia
Venous Neointimal Hyperplasia (VNH)
Where?
Why does it happen?
Standard paradigm

Increase flow through a vein

BUT this only occurs in 50 to 80%
Maturation (arterialisation)

50-80%

Failure to mature

50-80%

Excessive maturation (NIH)

20-50%

Disturbed flow

Uraemia

? genetic predisposition

? Direct Trauma

other...
Maturation (arterialisation)

50-80%

Failure to mature

20-50%

Excessive maturation (NIH)

High WSS
- right direction
- non chaotic

Low WSS
- Wrong direction
- Chaotic

Lack of arterial recruitment
fibrosed vein
surgical

Uraemia
? genetic predisposition
? Direct Trauma
other...
So this gives us an interesting re-think

- The vessel is adapting to its environment with a translation of physical changes through molecular signalling to produce a cellular effect
So this gives us an interesting re-think

- The vessel is adapting to its environment with a translation of physical changes through molecular signalling to produce a cellular effect.
NEW FRONTIERS

MOLECULAR

PHYSICAL

CELLULAR
PHYSICAL

Improve the flow and the effect of flow

- uniform
- unidirectional
- above physiological set point
Hypothesis

Increased WSS

Normal WSS

Disturbed WSS

Increase in the Atheroprotective mechanisms

Constitutive expression of Atheroprotective mechanisms

Loss of Atheroprotective mechanisms and expression of pathological mechanisms

"healthy" Remodelling

Maintenance of vessel wall appropriate to "healthy" WSS

Neointimal hyperplasia
**Hypothesis**

- **Increased WSS**
  - Increase in the atheroprotective mechanisms
  - "healthy" remodelling

- **Normal WSS**
  - Constitutive expression of atheroprotective mechanisms

- **Disturbed WSS**
  - Loss of atheroprotective mechanisms and expression of pathological mechanisms
  - Maintenance of vessel wall appropriate to "healthy" WSS

"healthy"** Remodelling*
Hypothesis

Increased WSS

- Increase in the atheroprotective mechanisms
- "healthy" remodelling

Normal WSS

- Cons: tu: ve expression of atheroprotective mechanisms
- Maintenance of vessel wall appropriate to "healthy" WSS

Disturbed WSS

- Loss of atheroprotective mechanisms and expression of pathological mechanisms
- Neointimal hyperplasia
Increased flow - Laminar/“normal”/Pulsatile

INCREASED WSS

CALCIUM/CALMODULIN DEPENDENT PATHWAYS

ERK5
MEK5

HDAC5

MEF2

KLF2

eNOS

RhoA

HO-1

STATINS

anti-oxidant gene expression
reduce MCP-1 and adhesion molecule expression
increased CD59 (complement inhibitory factor)
decreased cell turnover, proliferation and DNA synthesis

NITRIC OXIDE

VASODILATATION
Pathological flow - Oscillating/Zero/Peak WSS

**PATHOLOGICAL WSS**

- PECAM-1
- VE-CADHERIN
- INTEGRINS
- VEGF-R2
- HDAC5
- KLF2
- eNOS
- NO

**HDAC3**

- EGR1
- ERK
- SUPEROXIDE FREE RADICALS
- XBP1

**NFκB**

**MCP1**

**ICAM1/VCAM1/E-SELECTIN**

**RhoA**

**JNK**

**C-JUN**

**ATF-2**

**G0/G1-S TRANSITION**

**NUCLEAR ACTIVATION**

**CATHEPSIN L**

**MMP2**

**MMP9**

**GELATINASES/PROTEASES**

**PROTEOGLYCAN CLEAVAGE PRODUCTS**

**CELL TURNOVER-LEAKY JUNCTION PHENOMENON**
Cells migrate and also phenotypically change

- Media vSMC
- Adventitial fibroblasts
- Myofibroblast
- Circulating EPC
- Macrophages
The New Frontiers
...the journey has already started...

- **Strategy 1: Induce healthy flow and avoid pathological flow**
  - Graft designs
  - Elastase study (PRT-201)
  - Extrinsic nitrates

- **Strategy 2: Switch the EC to atheroprotective phenotype**

- **Strategy 3: Block the cellular response to the signals**
  - Paclitaxel
  - CollR – Sirolimus
  - Vascugel – allogeneic endothelial cells
“The new frontier is not a set of promises – it is a set of challenges”

JFK

Thank you