Role of Basic Science in Medical Research

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Mortality for CV Disease in Europe from 1965-2010

All vascular mortality at ages 35–69

All cancer mortality at ages 35–69

Courtesy of Prof Sir Richard Peto
Atrial fibrillation

Sinus Rhythm

Atrial Fibrillation

Current management of atrial fibrillation

• With the exception of anticoagulants, no treatment has beneficial effects on death, stroke or heart failure.

• Mostly directed to symptoms (e.g., ablation)

• Potentially unsafe (pro-arrhythmic/invasive)
Identification and testing of a new therapeutic target in AF

Atrial NOX2 oxidase

2005

NOX2 is the main source of ROS in the human atrial myocardium (*Circ Res* 2005)

Atrial NOX2 activity is increased in human and experimental AF (*Circ Res* 2005)

Antiarrhythmic and cardioprotective effects of statins are currently tested in a large clinical trial (*STICS*)

2014

NOX2 activity is inhibited by short-term statin therapy (*Circulation* 2011, *JACC* 2012)

Atrial NOX2 overexpression is sufficient to promote AF in the mouse

Predicts new onset of AF after cardiac surgery (*JACC* 2007, 2012)

Atrial NOX2 activity is increased in human and experimental AF (*Circ Res* 2005)

NOX2 activity is inhibited by short-term statin therapy (*Circulation* 2011, *JACC* 2012)

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Peripartum Cardiomyopathy
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Peripartum cardiomyopathy is a disorder of unknown etiology that leads to heart failure between the last month of pregnancy and the first 6 months after delivery.

Incidence

Africa: 1:600
Haiti: 1:300
Europe: 1:1700


Prof Denise Hilfiker-Kleiner
Hanover, Germany
Unbalanced oxidative stress via cleavage of the nursing hormone prolactin mediates PPCM. Destruction of blood vessels by a 16kDa prolactin fragment is the driving factor. *Cell* 2007

Blocking prolactin with the established medication bromocriptine was successful in preventing PPCM in mice. *Cell* 2007; *Nature* 2012.

A proof-of-concept pilot study in Africa and data from the German PPCM registry suggest that bromocriptine is beneficial in patients with PPCM. *Circulation* 2010; *BRC* 2013.
Brugada Syndrome: a more complex inheritance model

- Loss of function mutation of SCN5A has low penetrance and variable disease expression

- **Common genetic variations** can have a strong impact on the predisposition of sudden cardiac death *Nat Genetics 2013*

- Genetic variations regulate the expression and patterning of SCN5A in the myocardium *Nat Genetics 2013*
Relevance of Basic Science to Cardiovascular Health in Europe

• There has been huge progress in the management of cardiovascular disease but there is more to do.

• Basic science generates novel insights that can be rapidly translated into improved health outcomes.

• How to make it even more effective?
  — Use human material to generate/validate hypotheses
  — Use better animal models of human disease
  — Use better experimental practice
No basic science =

- No mechanisms
- No new targets
- No pipeline
- No progress