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Red de Terapia Celular

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Centro de Investigación Biomédica en Red de
Diabetes y Enfermedades Metabólicas Asociadas

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CENTRO ANDALUZ DE BIOLOGÍA MOLECULAR
& MEDICINA REGENERATIVA

“ON THE VALUE OF KNOWLEDGE”

Bernat Soria MD, PhD, FRCP
bernat.soria@cabimer.es



TOILET'S CHAT (10 min ago)

- *What is the Opening Lecture about ?*
- *Something on the knowledge...*
- *Oh Nooo ! Another tedious and boring scientific lecture!*





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“ON THE VALUE OF KNOWLEDGE”

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Invited Star: Marshall Dozier



ON THE VALUE OF KNOWLEDGE

Value ≠ Price

Value ≠ Cost



Les demoiselles d'Avignon,
(Pablo Ruiz Picasso, 1907)



Zonnebloemen,
(Vincent Willem Van Gogh, 1889)

- Frame (wood) = 25 €
- Oils + paintings = 15 €
- Canvas = 25 €

TOTAL = 65 €

+ Talent / Knowledge

20-30 Million €

Which is the Value of Marshall?

Weight = 60 kg (estimated)



THE "BIOCHEMIST" METHOD

- Proteins 12 Kg (x 15 €/kg) = 180 €
- Water (Evian) 42 l (x 2 €/l) = 84€
- Fat
 - Total: 6 kg (4 €/kg) = 24 €
 - Subcutaneous = 0
 - Cell membranes = 6 kg
- Glucose 4-5 g (Sigma catalog) = 2 €
- Bone
 - Calcium Phosphate (Sigma catalog) = 10 €

TOTAL = 300 €

OBVIOUSLY WRONG,

- *How can we estimate the value of Marshall ?*
- *Let's consider another method, we will call this "the Savings-Mortgage Bank Method"*

THE SAVINGS-MORTGAGE BANK METHOD



THE SAVING-MORTGAGE BANK METHOD (Dialog)

- **Marshall: *I need some cash to buy a cottage near Edinburgh***
- **The Banker : *A cottage? It is a good idea. Yes a cottage near Edinburgh.. (in the meanwhile he is making an idea of Marshall: young, seems to be a professional, quite nice...) and.. What you do...? Your occupation?***
- **Marshall: *Well, I am the Director of the Library of the School of Medicine...***
- **The Banker. *The School of Medicine... You know Prof Garden, Jim Garden ? I met so many people... and Prof Sthephen Wigmore, you know them?***
- **Marshall: *Yes, Yes, ... they are my customers..., for the last 10 years***

THE SAVING-MORTGAGE BANK METHOD (Dialog)

- The Banker: *Yes, .. Very nice people, 10 years? You look so young!!!
(thinking, so 10 years.. She has a permanent position...)
Well we have to fill some stuff...Age ?*
- **Marshall: 35 y**
- The Banker: *Gross salary, per annum?*
- **Marshall: 50.000 British pounds**

*(The Banker: Thinking good, good, 50.000, good ...)
Etc*

*The Banker begins to make comments on the weather, last holidays in Spain... He
wants to know more about Marshall, **BUT HE IS MAKING ESTIMATIONS...***

50.000 pounds/year

- *minus taxes...makes: 30.000*
- *30% to pay the mortgage makes 10.000 per year*
- *10.000 = fee + annual rate of 5%*
- *she is 35 and looks quite healthy, 30 more years to pay makes 300.000 £*
- *minus Life Insurance = 250 pounds / month*
- *minus House Insurance = 100 pounds / month*
- *the mortgage could be 200.000 £ & we will make...*

TOTAL AMOUNT PAID AFTER 30 years = 300.000 £

The Banker:



= 300.000 £

(1000-fold more than the Biochemist)



The Whole Story Behind David Bowie's \$55 Million Wall Street Trailblaze 1/13/2016 by [Ed Christman](#)

1947-2016

Bowie Bonds:

- A catalog-tied financial instrument of Wall Street
- D Bowie, in addition of a great artist, was a clever businessman. He devised a financial instrument
- a. From the very beginning, as a young artist, he negotiated to keep the master records back when dealing with big companies
 - b. In 1997, he began with 1000\$-denominated bonds rated by the 3 credit agencies (Moody's, Standards & Poors and Fitch) of a stock of 55 million \$
 - c. Before, D Bowie licensed his catalog to EMI for 15 years bringing him 30 millions \$ (credit enhancement)

- **Marshall: 300.000 £**
- **David Bowie (estimated) = 300 million \$**
- and Bernat Soria? Using the Bowie's system...

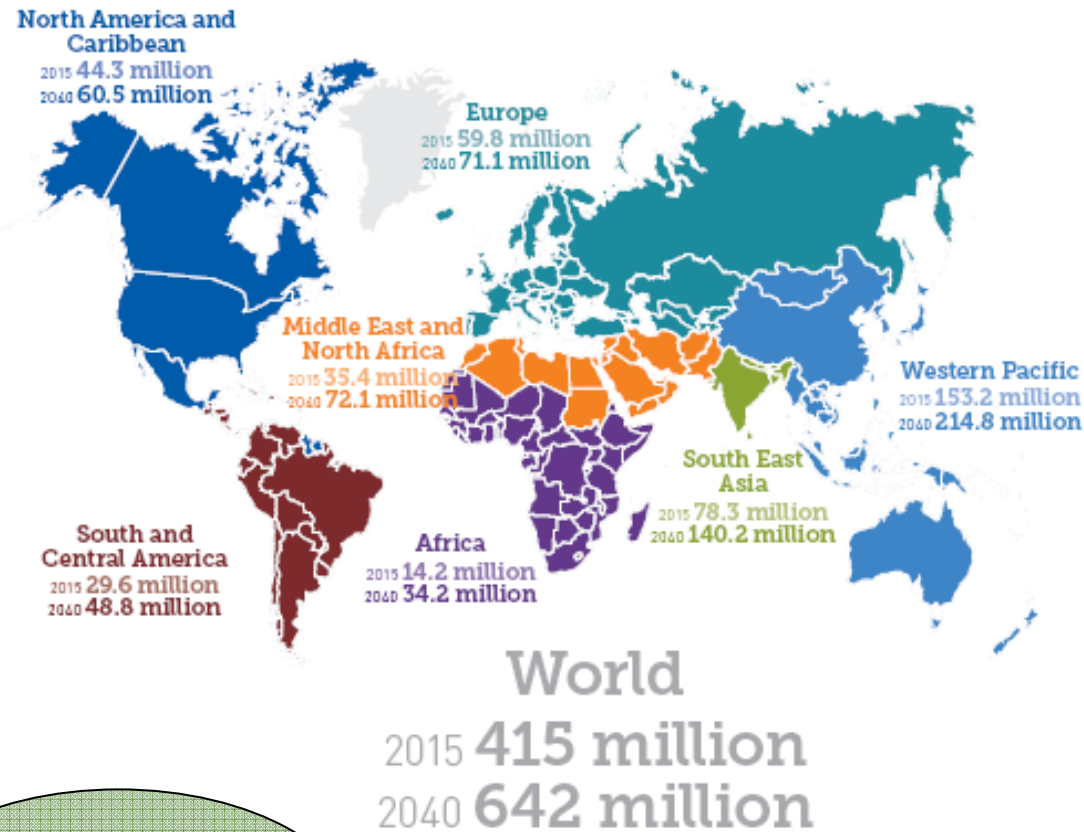
The Banker & Bernat Soria (Dialog)
- The Banker: Marshall
- Bernat: Bernat

Bernat (To the banker):

*I am a great scientist, with many honors and medals, former Minister, etc..
I had the opportunity to address United Nations Assembly ...*



Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



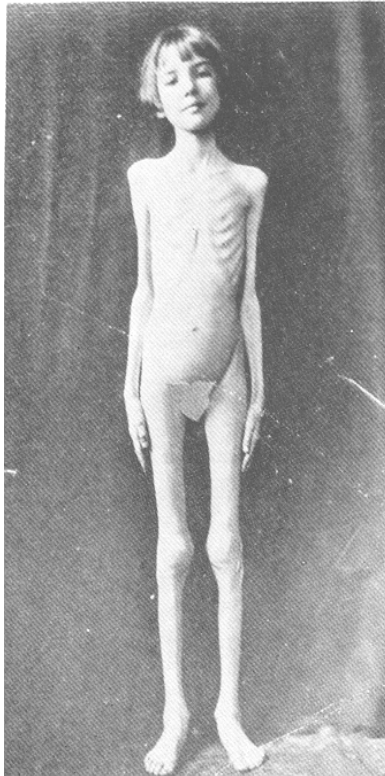
**LET'S TALK
ABOUT
DIABETES**

**Cost:
> 600 billion €**

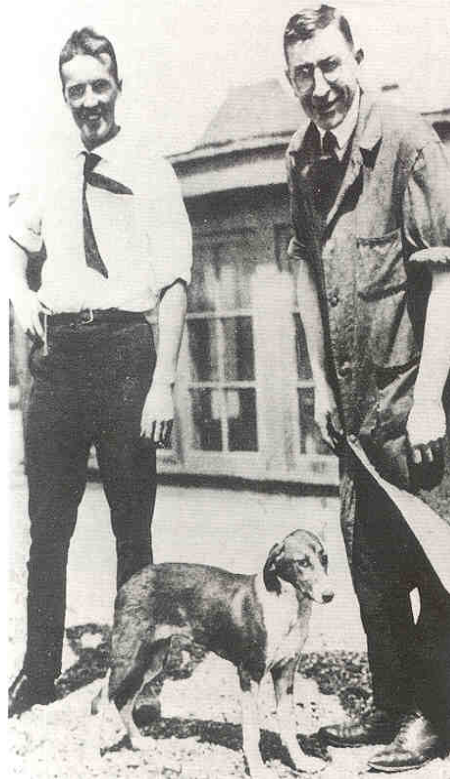
SPAIN:

- 13,5 % (18-75 a) approx **3,5 million people**
(Estudio di@bet.es, Diabetologia)
- Direct Costs: **6000 million € /year**
(Crespo et al, 2014 Av Diabetologia)

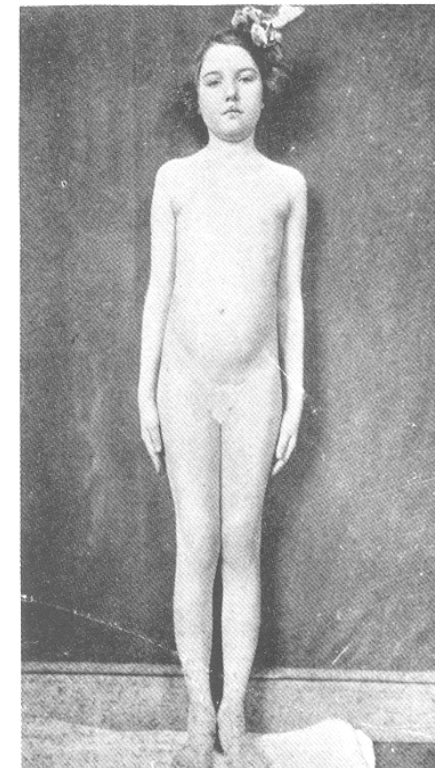
INSULIN SAVED MILLIONS OF LIVES...



**Before
Insulin**

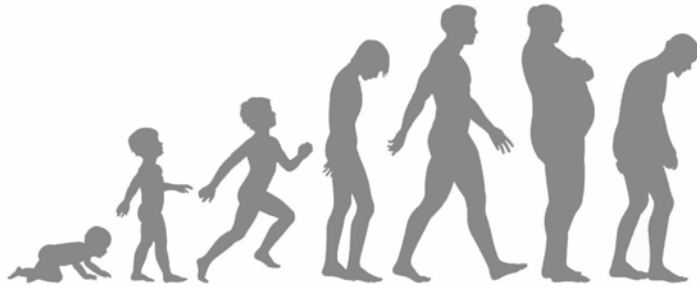


**Banting & Best
1922**



**After
Insulin**

... BUT DID NOT SOLVE COMPLICATIONS !!!



COMPLICATIONS

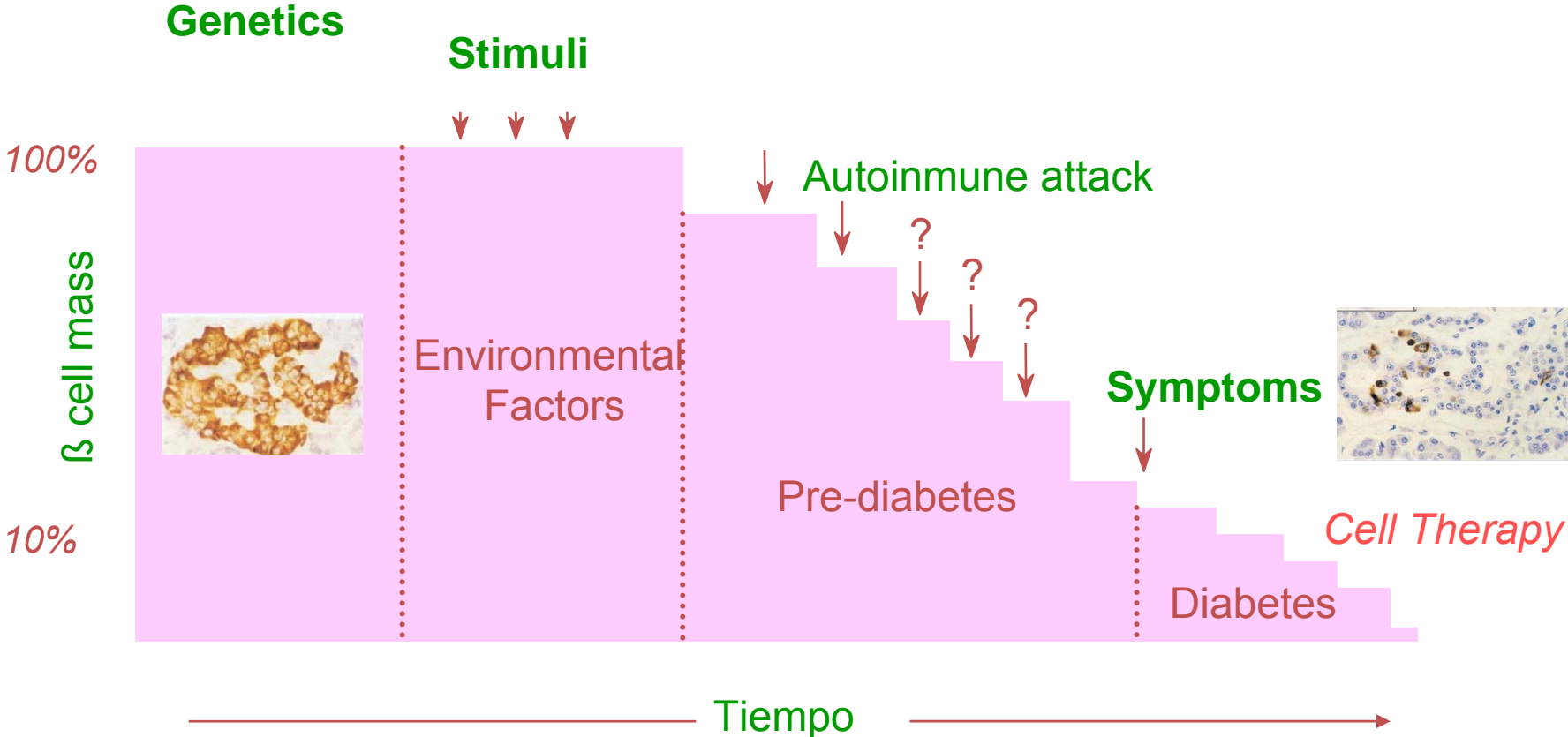
- Atherosclerosis
- Myocardial Infarction
- Stroke
- Diabetic foot
- Rethinopathy
- Kidney failure

***... and we are developing treatments for both
diabetes and their complications !!!***



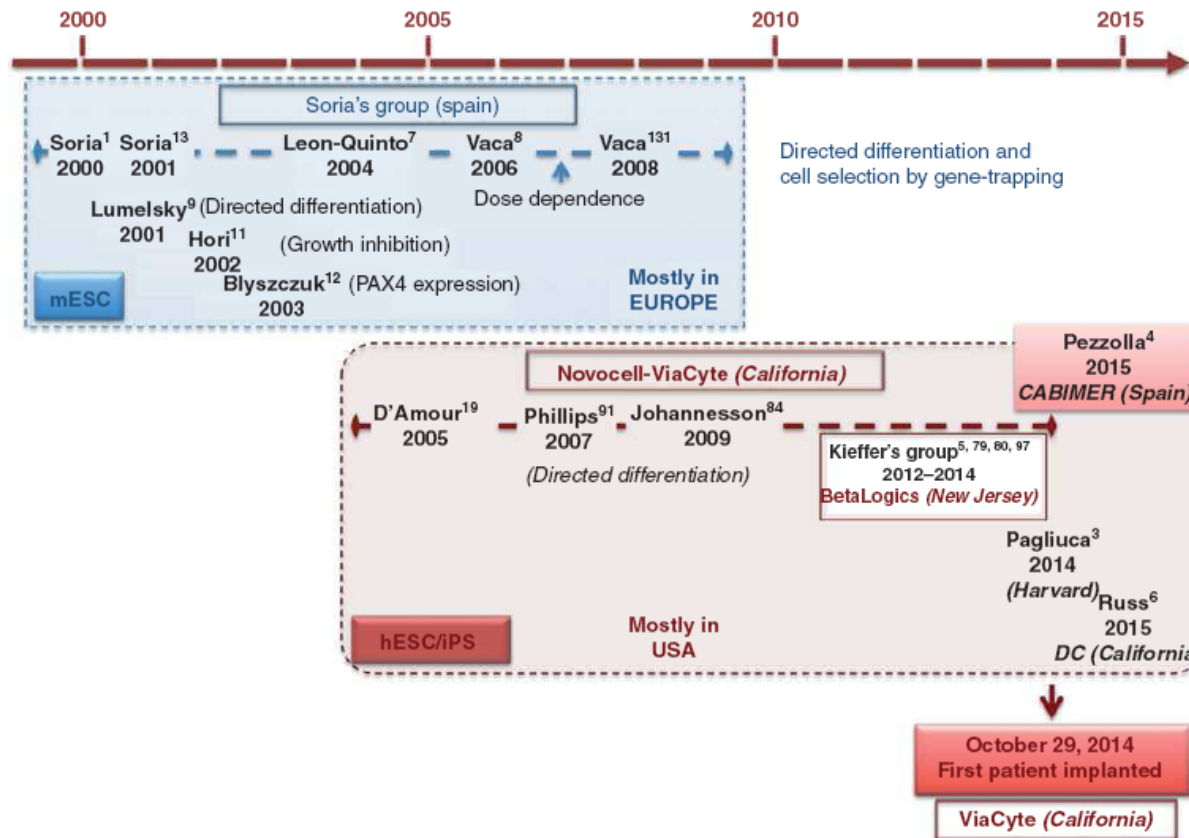
Diabetes

β cell mass decrease



***Making Insulin producing cells from
Embryonic Stem Cells***

Using stem cells to produce insulin

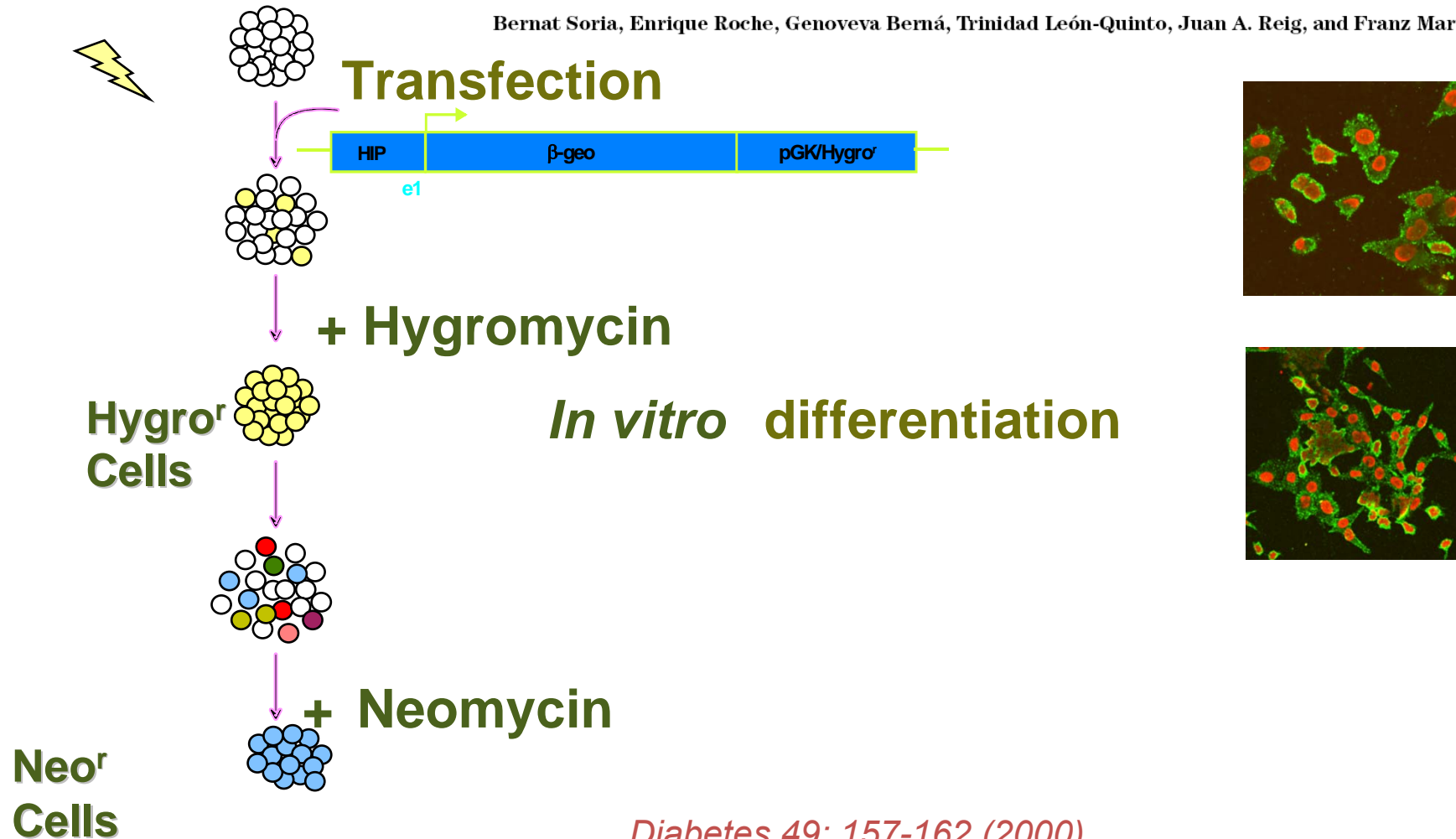


Expert Opinion in Biol Ther, 2015

21-10-14 hESC derived cardiomyocytes implanted in man (Paris)
29-10-14 hESC derived insulin producing cells implanted in man
(USA, Janssen Pharmaceuticals)

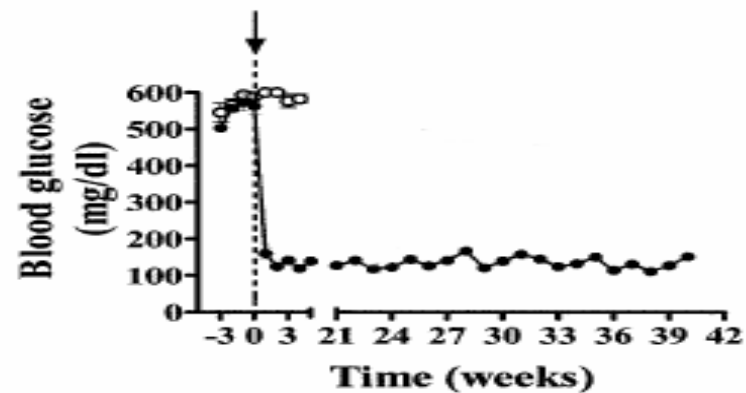
Insulin-Secreting Cells Derived From Embryonic Stem Cells Normalize Glycemia in Streptozotocin-Induced Diabetic Mice

Bernat Soria, Enrique Roche, Genoveva Berná, Trinidad León-Quinto, Juan A. Reig, and Franz Martín



Diabetes 49: 157-162 (2000)
Diabetologia 47: 1442-1451 (2004)
Stem Cells 24(2): 258-265 (2006)
Exp Cell Res 314: 969-974 (2008)

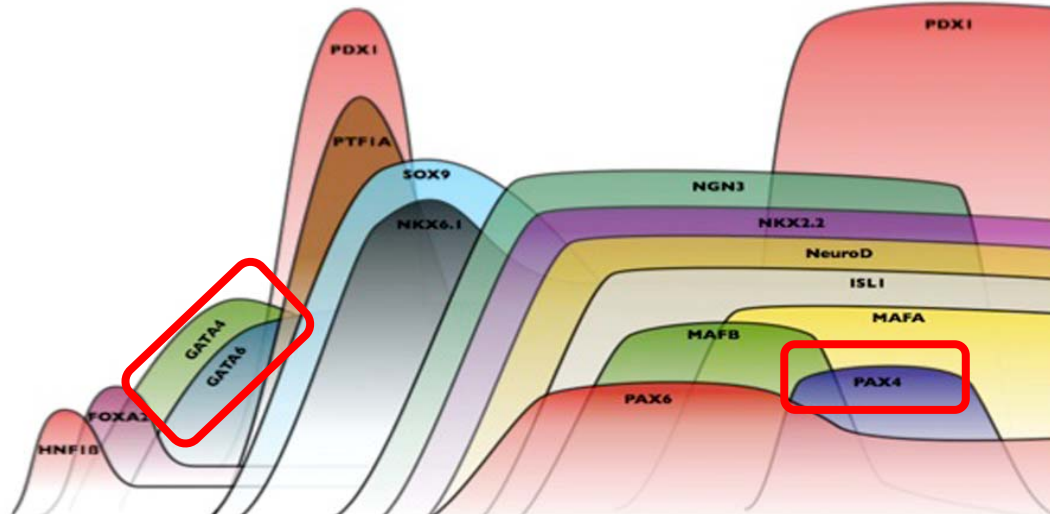
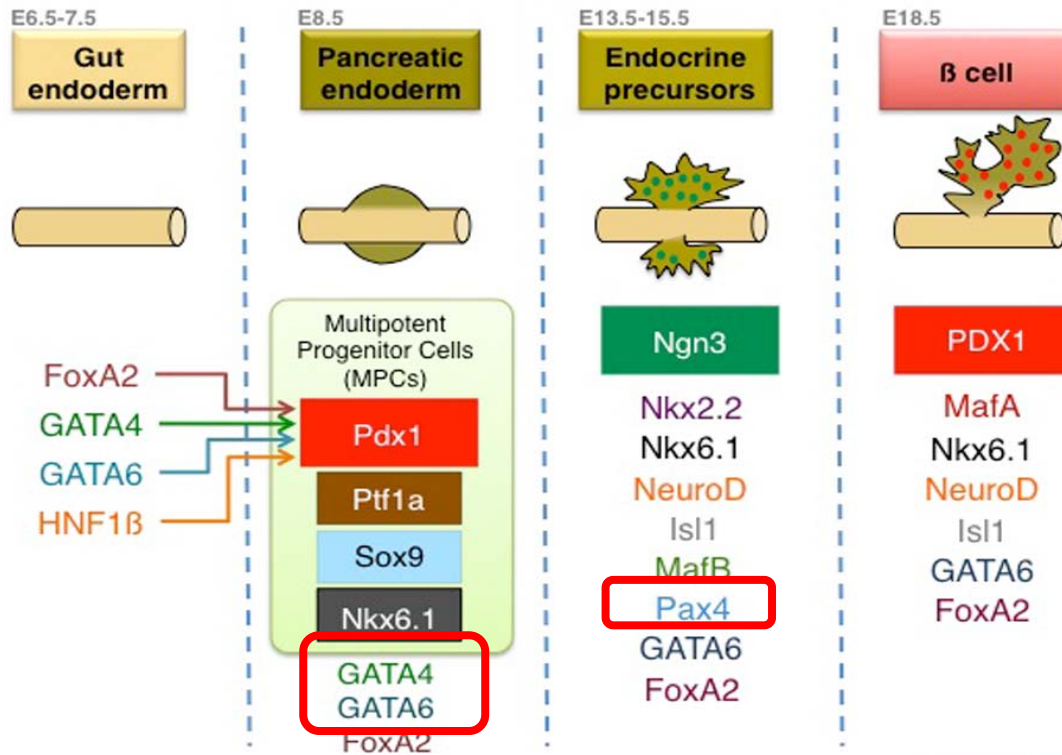
Insulin-producing cells normalize glycaemia in STZ-diabetic mice



Diabetes 49: 157-162 (2000)
Diabetologia 47: 1442-1451 (2004)
Stem Cells 24(2): 258-265 (2006)
Exp Cell Res 314: 969-974 (2008)

Insulin secreting cells from human ESC and iPSC

1. Developmental Approach



SCIENTIFIC REPORTS

OPEN PAX4 Defines an Expandable β -Cell Subpopulation in the Adult Pancreatic Islet

Received: 22 June 2015
Accepted: 05 October 2015
Published: 27 October 2015

Petra I. Lorenzo¹, Esther Fuente-Martín, Thierry Brun², Nadia Cobo-Vuilleumier¹, Carmen María Jiménez-Moreno¹, Irene G. Herrera Gomez¹, Livia López-Noriega¹, José Manuel Mellado-Gil¹, Alejandro Martín-Montalvo¹, Bernat Soria^{1,2*} & Benoit R. Gauthier²

Research article Related Commentaries, page 2469

GATA4 and GATA6 control mouse pancreas organogenesis

Manuel Carrasco, Irene Dolgado, Bernat Soria, Francisco Martín, and Anabel Rojas
Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Sevilla, Spain.
Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain.



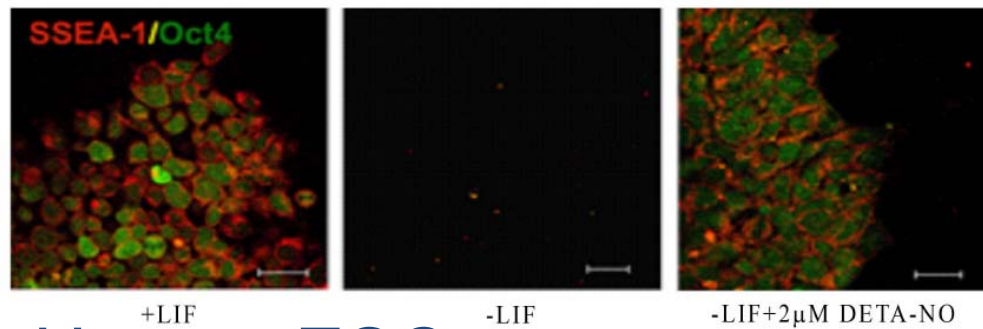
2. “Small Molecule” Approach

- a. Nitric oxide*
- b. Sirt-1*
- c. Resveratrol*

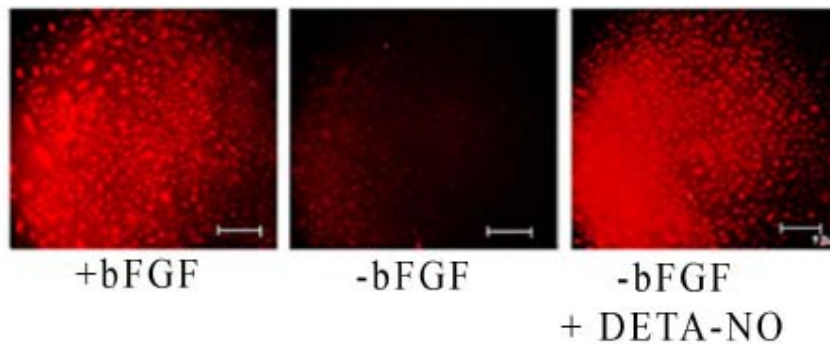
Low concentrations of nitric oxide delay the differentiation of embryonic stem cells and promote their survival

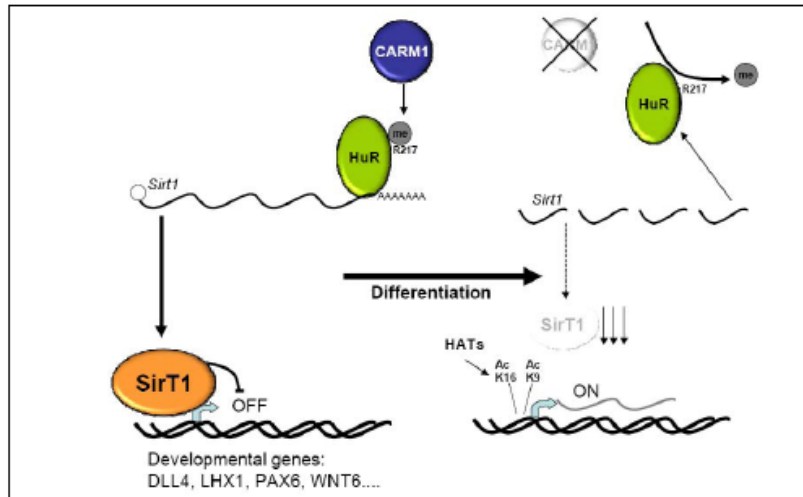
JR Tejedo^{*1}, R Tapia-Limonchi², S Mora-Castilla¹, GM Cahuana¹, A Hmadcha², F Martin¹, FJ Bedoya¹ and B Soria²

Mouse ESC



Human ESC



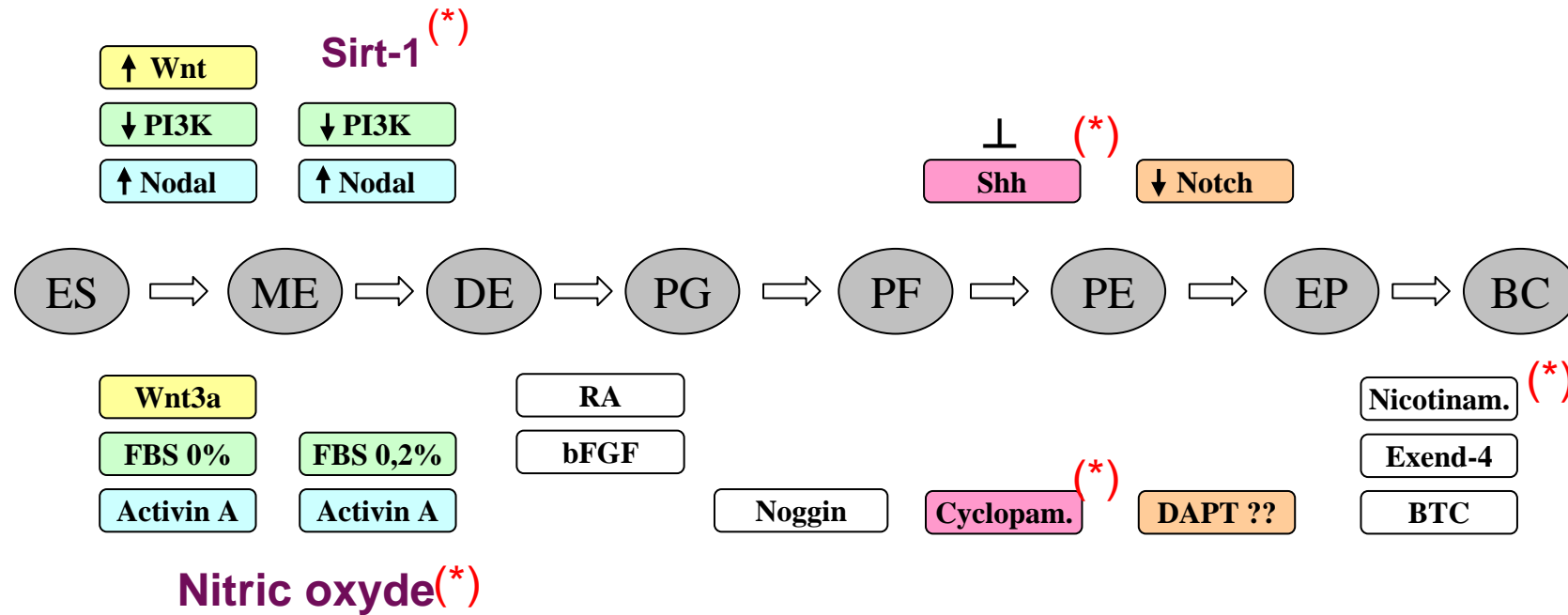


Model for SirT1 action on developmental genes promoter during hESC differentiation. In pluripotent hESCs, CARM1 methylation of HUR increases HuR/SirT1 binding and, consequently, the SirT1 mRNA stability and SirT1 protein level. Under these conditions, SirT1 binds to the promoter and epigenetically represses specific developmental genes such as DLL4, LHX1, PAX6 and WNT6. In EBs, the decrease of CARM1 is associated with a decrease of HuR methylation and, consequently, of HuR/SirT1 binding, which results in less SirT1 mRNA and protein and the epigenetic reactivation of its target developmental genes.

Sirtuin 1 regulation of developmental genes during differentiation of stem cells

Calvanese et al (2010) Proc Natl Acad Sci USA 107:13736-13741

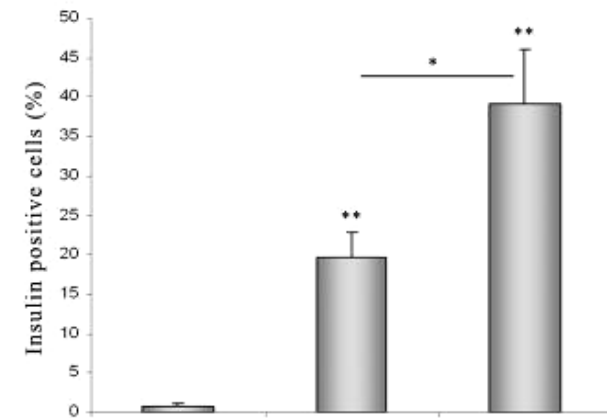
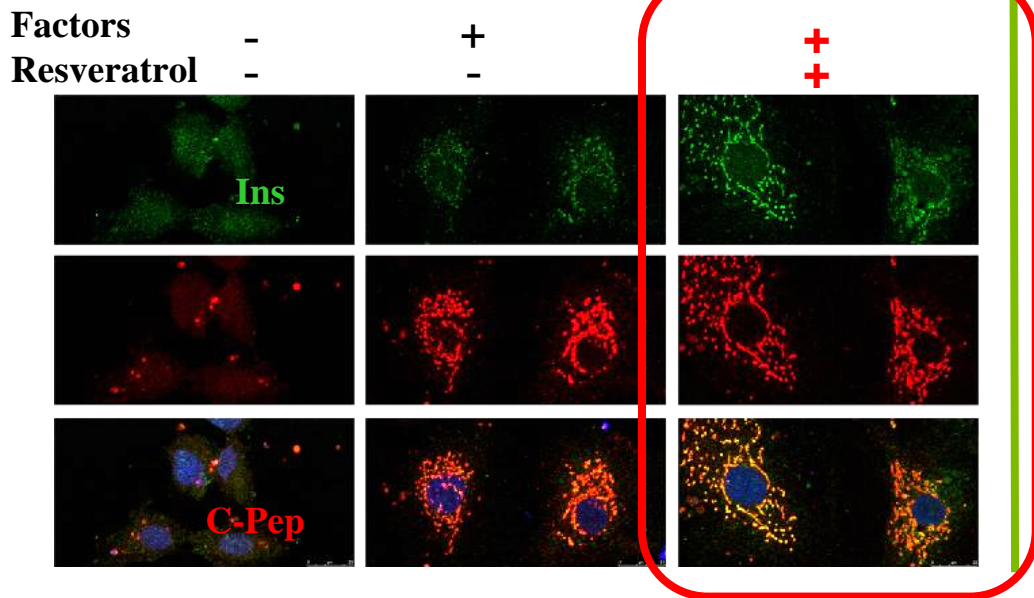
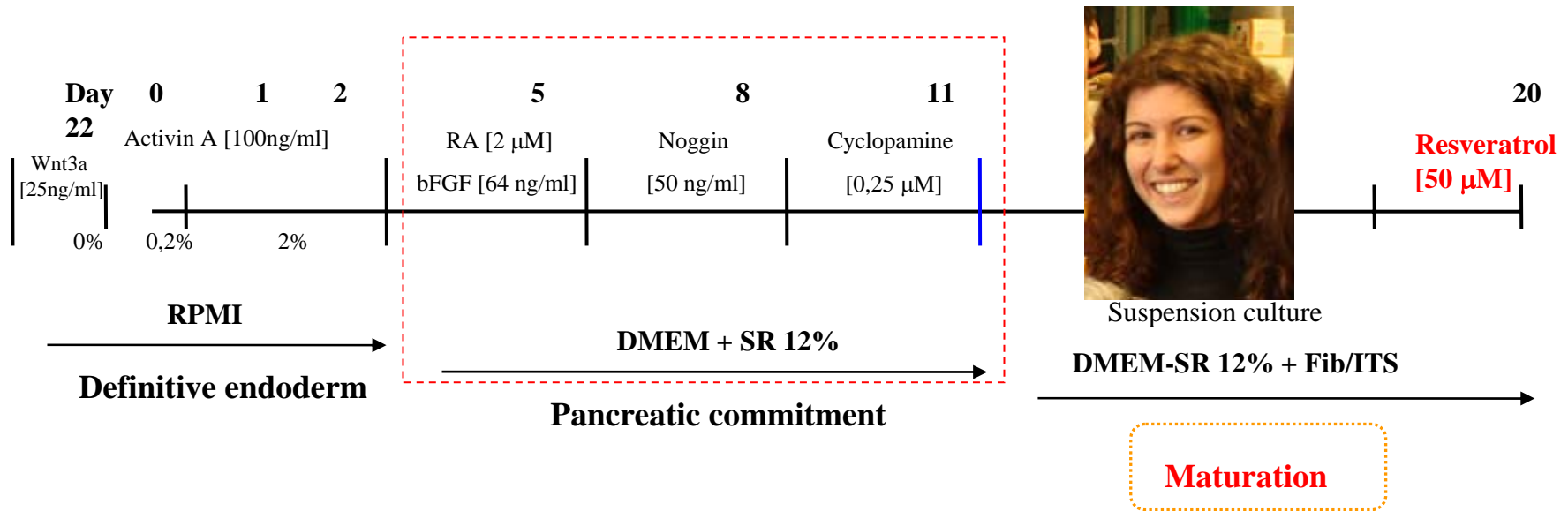
Design of new differentiation protocols



ES: embryonic stem cells; **ME:** mesendoderm; **DE:** definitive endoderm; **PG:** primitive gut; **PF:** posterior foregut;

PE: pancreatic endoderm; **EP:** endocrine precursors; **BC:** beta cells;

DAPT: N-[N-(3,5-difluorophenacetyl)-L-alanyl-S-phenylglycine t-butyl ester]; **BTC:** betacelulin.



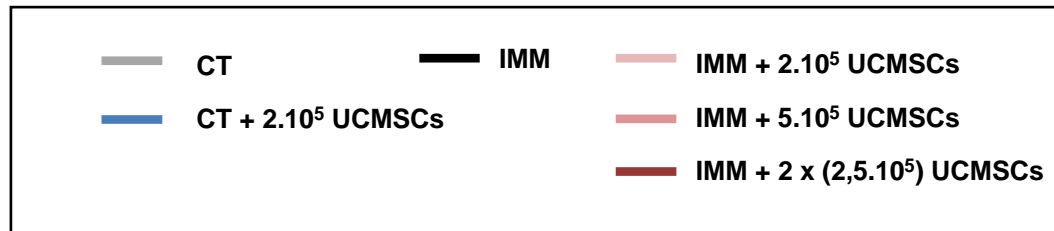
Factors	-	+	+
Resveratrol	-	-	+



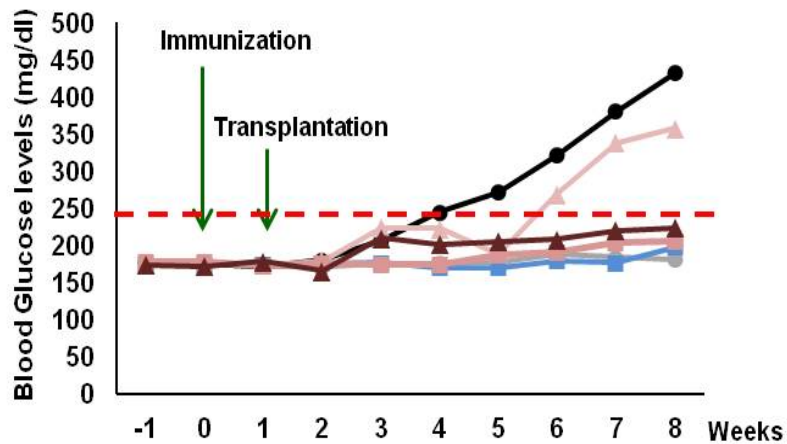
Towards a cure for Diabetes Effect on Insulitis and Glycaemia



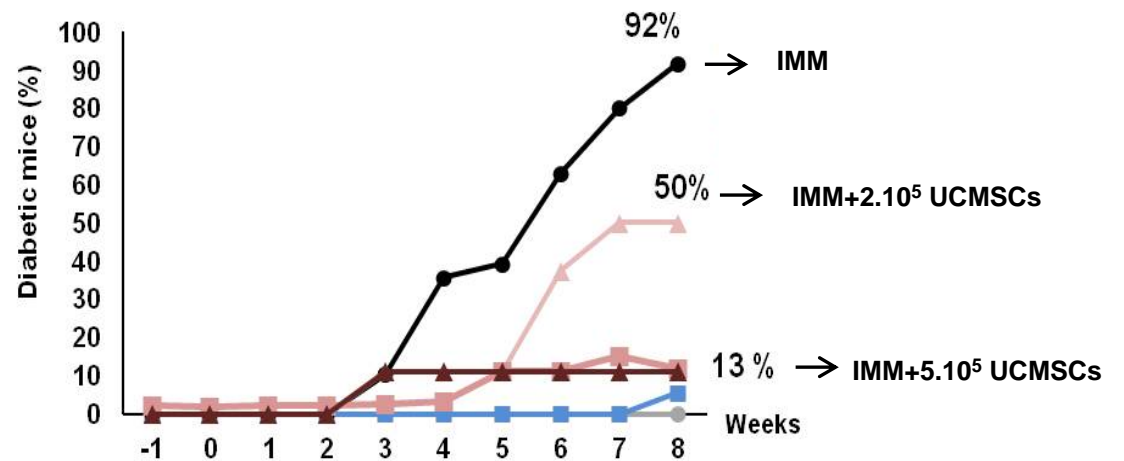
UCMSCs transplantation delayed or blocked the development of hyperglycemia in immunized RIP-B7.1 mice



Glycemia RIP-B7.1 mice



**Percentage of diabetic mice
(≥250 mg/ml)**



- Bernat: *We think we have a solution for diabetes.*

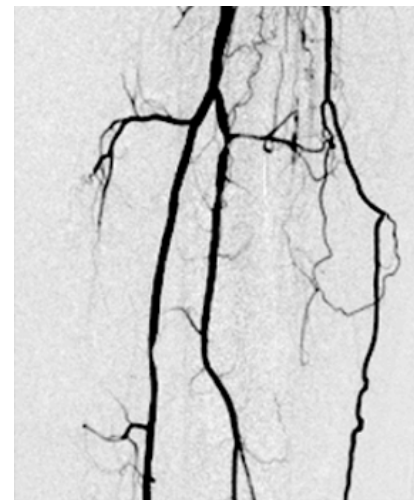
Even more we have cells that DO STOP AMPUTATION.. Look at this...



Digital subtraction angiography



Basal



6 months



12 months

The Banker & Bernat Soria (Dialog)

- ***The Banker: Marshall***

- ***Bernat: Bernat***

- The Banker: *Mr Soria... Please explain me that again ...*

- *You have worked for 20 years and transferred the rights to a Publishing Company?*

- ***Bernat: Yes, I even pay to give “open access” to everyone***

- The Banker: **“Open access?” *Who was the idiot who invented this system? Open access... ?***

- ***Bernat (offended): Not idiot at all, hundreds of people, the most clever people in the world... Nobel laureates do agree... Best in class students do the same! Even... the European Union promoted Open Access with the “Berlin Declaration”...***

The Banker & Bernat Soria (Dialog)

- The Banker: Marshall

- Bernat: Bernat

-The Banker: Yes, yes, ... Open Access... for free ... to everyone...

- Bernat (in off) (at this moment Marshall appears at the door)

- The Banker: *Oh Miss/Mrs Marshall YOUR MORTGAGE HAS BEEN APROUVED!!!*

- Bernat: and ... mine?

-The Banker: *Well.. We have to thing about, it seems quite relevant your work... diabetes, a big problem... I know... my grand parent suffered diabetes... a pity he died some years ago... I will call you. Yes, I will call you... Give us... 3 or 6 months,.. Yes ... we will call you...*

SUMMARY (so far): “On the value of...what?”

1. Marshall: 300.000 £

2. David Bowie (estimated) = 300 million \$

3. Bernat Soria = ?



SUMMARY (so far): “On the value of...what?”

1. Marshall: 300.000 £

2. David Bowie (estimated) = 300 million \$

3. Bernat Soria = 0 €

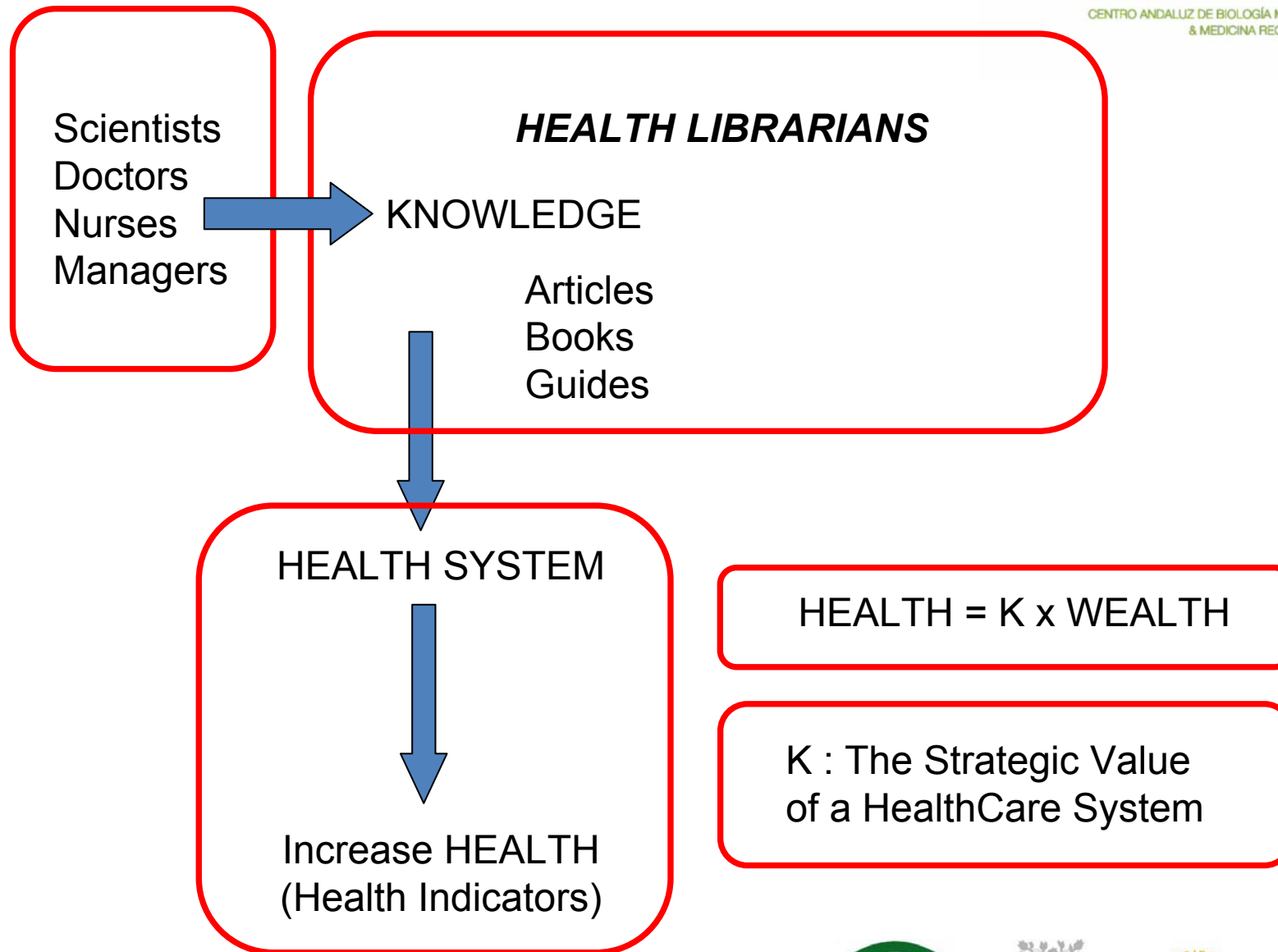


Where is the value?



Where is the value?

HEALTH LIBRARIANS in the Core of the Value of Knowledge



The Bernat & Marshall's equation:

$$\text{HEALTH} = \kappa \times \text{WEALTH}$$

κ = The Strategic Value
of a HealthCare System

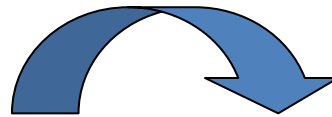
$$\text{Productivity} = \frac{\text{Aggregated Value of Products}}{\text{Costs}}$$

- Options:
1. *Decrease Costs*
 2. *Increase Value = Innovation*

However, Innovation Is Not Enough

RESEARCH IN HEALTH: GUARANTEES WELFARE

Increase in R+D+i



Improvement of welfare

Concepts **NOT** always linked

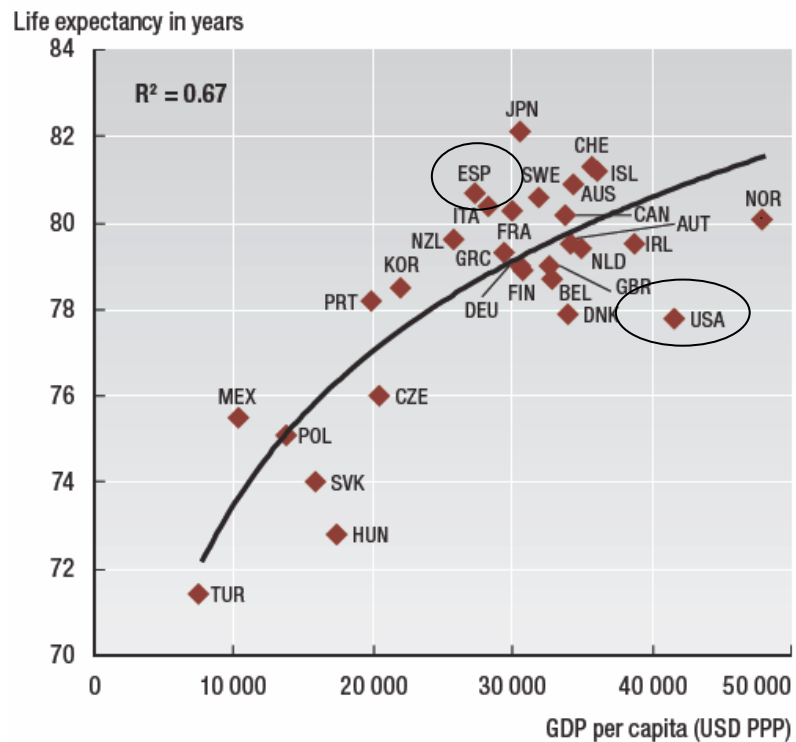
Health Indicators

	USA		SPAIN	
	1986	2005	1986	2005
<i>Life expectancy Females</i>	78,2	80,4	79,9	83,7
<i>Males</i>	71.2	75.2	73.4	77.0
<i>Infant mortality Deaths/1.000 live births</i>	10,4	6,9	9,2	3,8
<i>Potential years of life lost All causes <year/100.000</i>	6.471	4.965	4.968	3.201
<i>Causes of mortality (ischaemic heart diseases males deaths/100.000)</i>	261,1	144,6	104,9	77,9

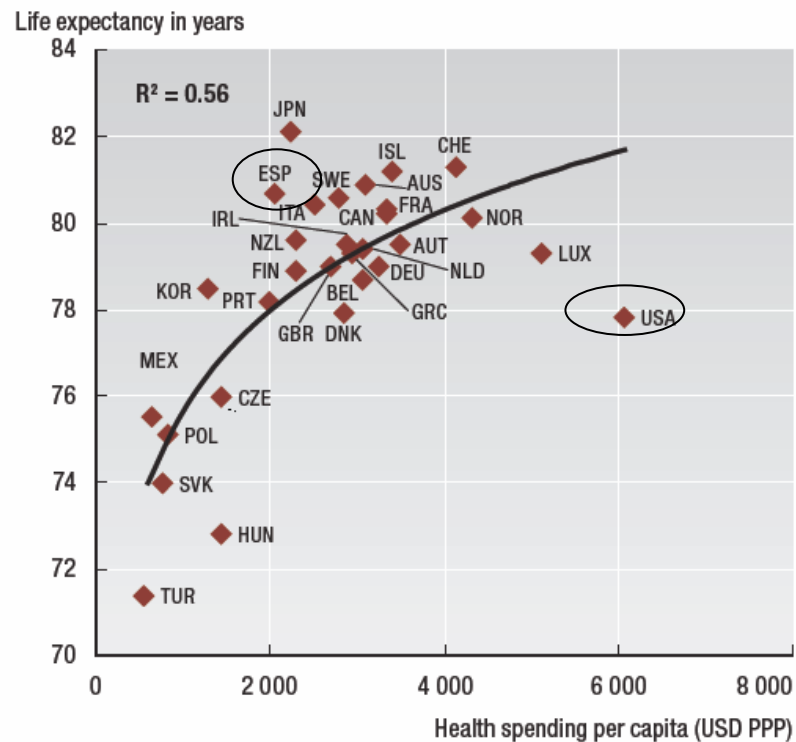
HEALTH STATUS

LIFE EXPECTANCY AT BIRTH

Life expectancy at birth and GDP per capita, 2005



Life expectancy at birth and health spending per capita, 2005



SPAIN NHS: AN EFFICIENT SYSTEM

	Expenditure (aprox)/ inhabitant per year:	Perinatal Mortality
SPAIN	2.000 \$ (1.300 €)	3,9 x 1000
USA	6.000 \$ (4.500 €)	6,9 x 1000

OECD Health Data 2008.

RESEARCH IN HEALTH: GUARANTEES WELFARE

Increase in R+D+i

Improvement of welfare

Concepts **NOT** always linked

USA
World N. 1 in R+D+i
↓
Lacks a good health system
↓
Bad health indicators

NEEDS HEALTH STRUCTURE
WHICH TRANSFORMS
KNOWLEDGE → WELFARE
↓
THE NATIONAL HEALTH SYSTEM

A HEALTH SYSTEM GIVES VALUE TO INNOVATION

Strategic Value of the National Health System

SPANISH NATIONAL HEALTH SYSTEM

Among the best in the world

- Ranked **4th** among the 19 most developed countries

Health Affairs (Health Affairs. 2008, 27: 58-71)

- Ranked **6th** among 191 countries

British Medical Journal (Evans DB & cols. Comparative efficiency of national health systems: cross national econometric analysis. BMJ. 2001 Aug 11;323(7308):307-10)

- Ranked **7th** among 191 countries

WHO (World Health Report 2000. Health Systems. Improving performance)

STRATEGIC VALUE of HealthCare System



1. Warrants the state of health of the country's workforce
2. Since healthcare is covered, citizens may take on other economical risks (buying houses, etc.)
3. Provides of direct high-quality employment that cannot be delocalised

Spain - Labour Force Survey: 5.85 % of total employment (1,119,200 employees, women > men)

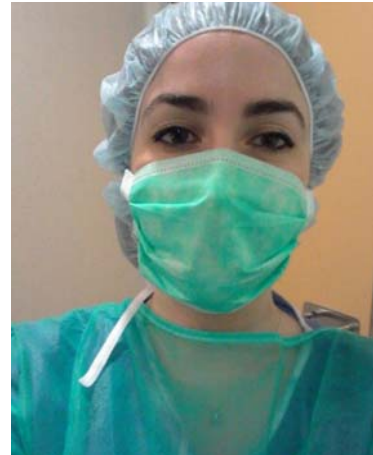
4. Direct source of wealth generation with a Return on Investment Factor (Drag Factor) = 40%

2006 Expenditure €82,064 million → Return €32,825 million

5. Niche for the traditional business diversification :
Biotechnology, Pharmacy Industry, Services and Tourist Industry (our first industry: 60 million visitors/year)

A TRIBUTE TO MY FAMILY





EL FUTURO
DEL LIBRO SE
JUEGA AQUÍ

No future without LIBRARIANS

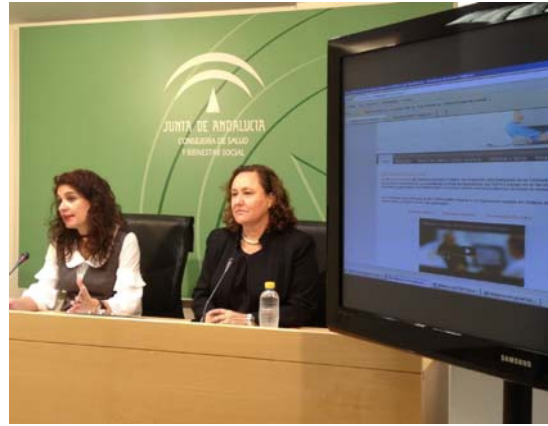
A TRIBUTE TO HEALTH LIBRARIANS





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CENTRO ANDALUZ DE BIOLOGÍA MOLECULAR
& MEDICINA REGENERATIVA





WHERE IS THE VALUE ?



Rome, 2014



WHERE IS THE VALUE ?



Seville, 2016





YOU ARE THE VALUE

No future without LIBRARIANS

by Bernat Soria and Marshall Dozier (invited star)

