Programa Cooperación Farma-Biotech

X encuentro (27 de noviembre de 2013)

Soluble protein AXL as a Heart Failure biomarker

Madrid, 27 de noviembre de 2013

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española

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1. The Institutions

JOINT EFFORT

Group of highly specialized cardiologists in Heart Failure and Heart Transplantation from the Cardiology Department at Hospital Clinic of Barcelona

Basic researcher Montserrat Batlle, Ph.D. in Biomedical Sciences : 1995-2001, Mount Sinai Hospital-NYU, New York

Pablo García de Frutos, PhD: postdoctoral research at Lund University (1992-2001) in plasma proteins. Group leader at IIBB since 2003. Head of Department at IIBB since 2009.

The Product

a) Target Indications

Heart failure (HF) is a syndrome characterized by the following features:

Shortness of breath at rest or during exertion, and/or fatigue
Fluid retention such as pulmonary congestion or ankle swelling
Objective evidence of an abnormality of the structure or function of the heart at rest

Causes: HF can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. HF constitutes the end-stage of many cardiopathies.

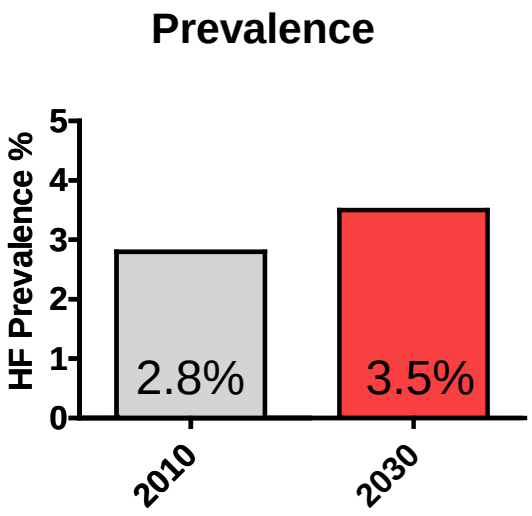
The invention relates to a new method for the prognosis and diagnosis of Heart Failure (HF) based on the determination of soluble AxL protein in serum.

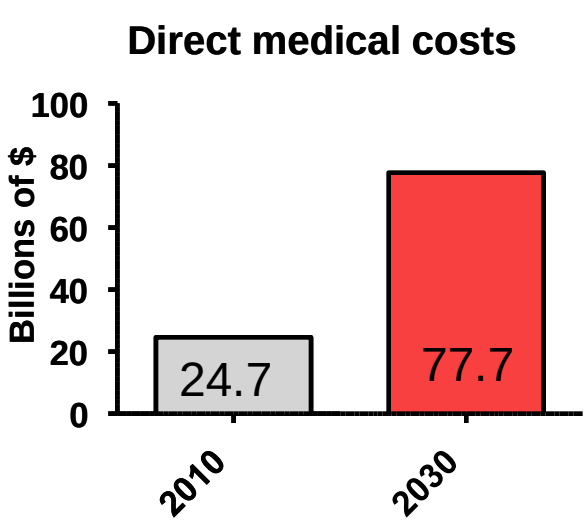
The Product

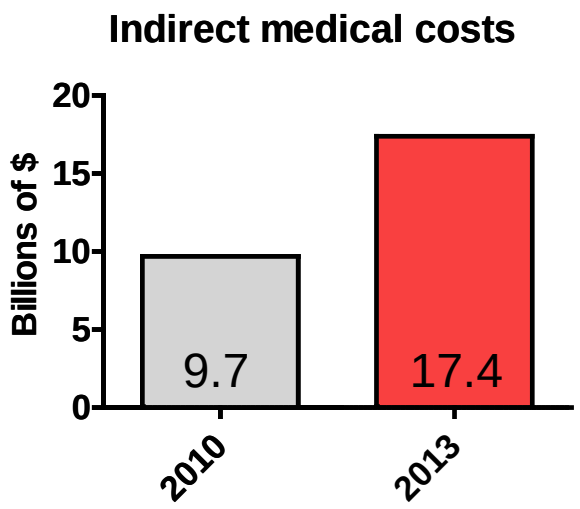
a) Target Indications

- **HF Prevalence :**
  Prevalence is about 2-3% but in 70-80 year old people is between 10-20%(1)

  Projected changes based on the population aging in USA (2)







(1) Eur J Heart Fail 2012 Aug;14(8):803-869
(2) Circulation 2011 Mar 1;123(8):933-944

The Product

a) Target Indications

Data about HF hospitalizations at the HCB, year 2012

Total number of hospitalizations due to HF	425
Total days of hospitalizations due to HF	3.692 mean=8.5days between 1-48 days

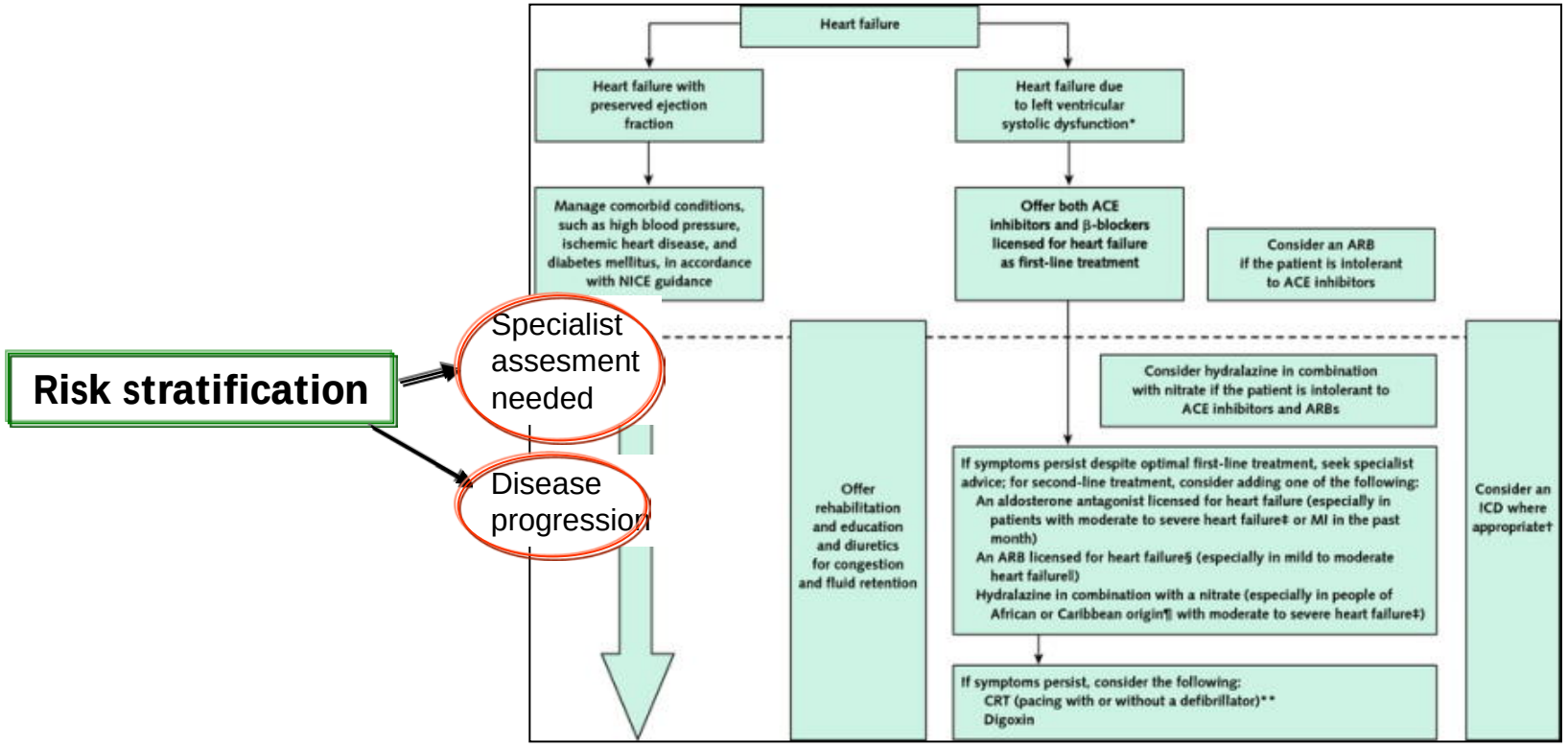
3.692 days= 10.3% total capacity Cardiology Department
3.692 days= 1.5% total capacity HCB

Total Cost of hospitalizations	**1.203.929€**
Mean cost/hospitalization	**2.833€**

The Product

a) Target Indications

Management of Chronic Heart Failure in Adults: Synopsis of the National Institute for Health and Clinical Excellence Guideline.



(Annals of Internal Medicine. 155(4):252-259, 2011)

The Product

a) Target Indications

Management of Chronic Heart Failure

HF patient

Risk stratification

Good-prognosis patient

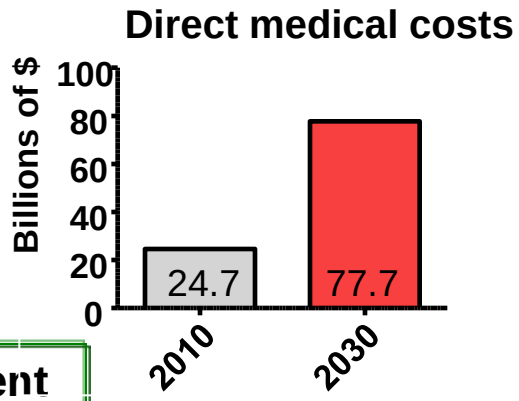
Bad-prognosis patient

Follow-up at primary care

Follow-up at tertiary care

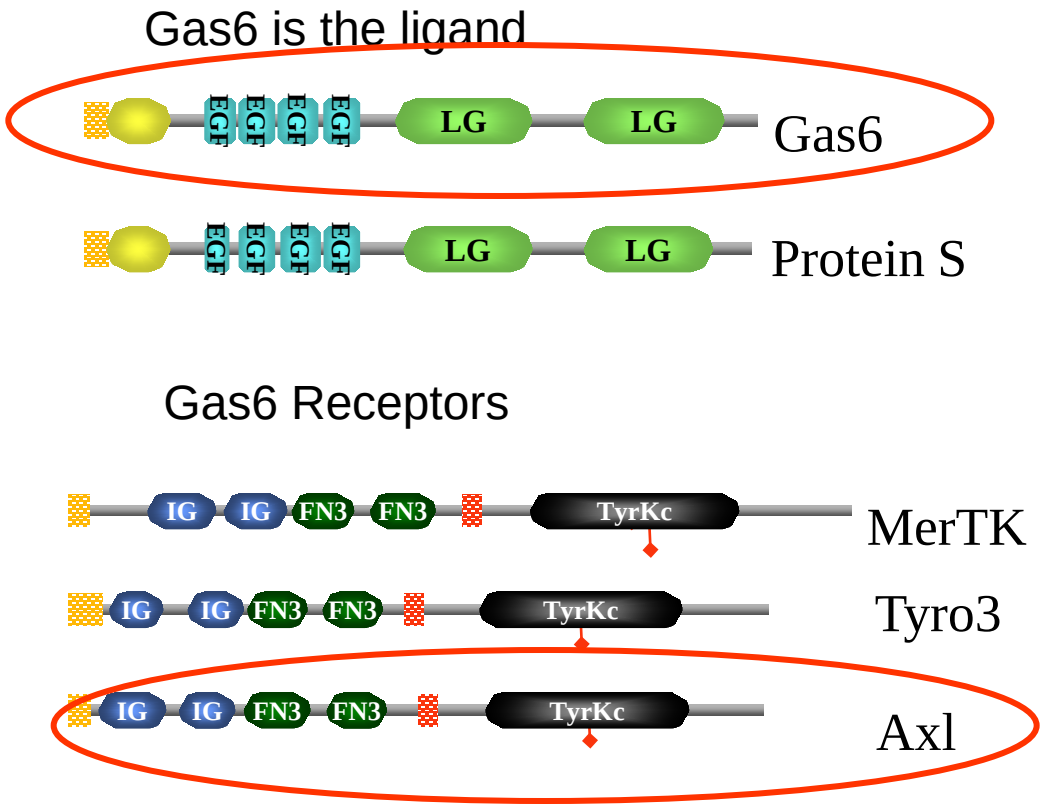
Optimization of health costs

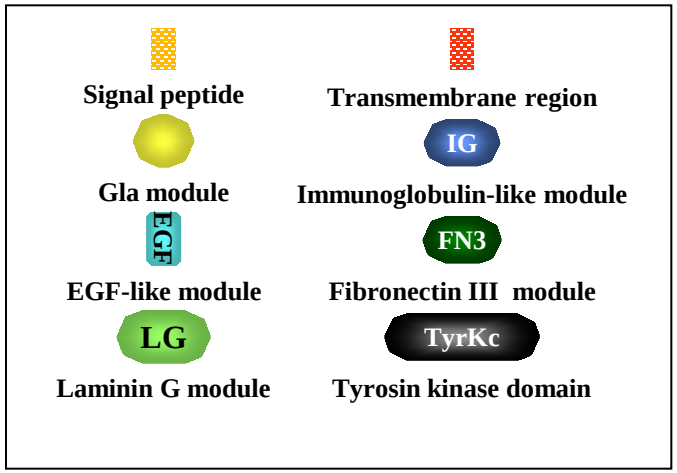
Reduction of HF Hospitalizations



The Product

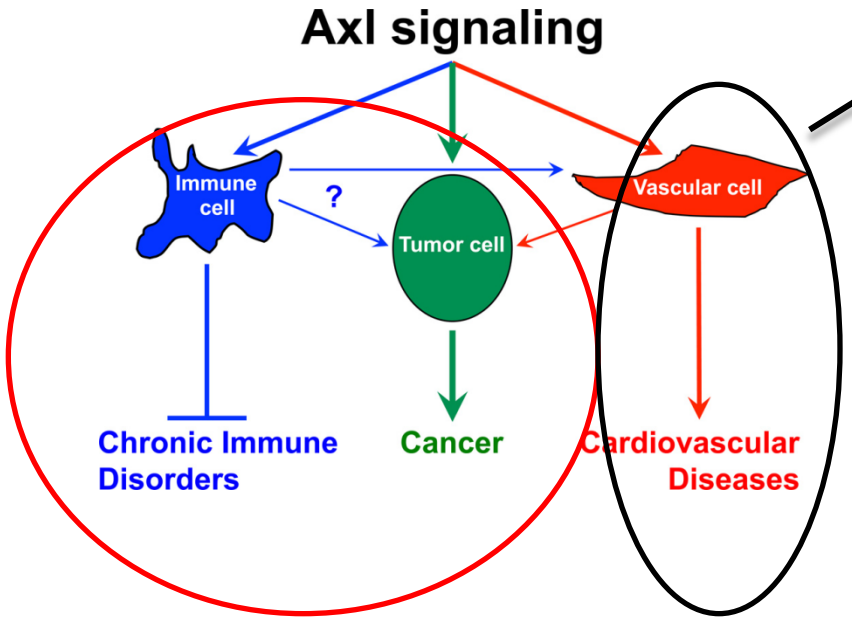
b) Innovative mechanisms of action





The Product

b) Innovative mechanisms of action



Clin Sci 2012; 122(8): 361–368.

AXL roles related to cardiovascular diseases?

A) role in the vascular response to different injuries:

mechanical damage and hypertension-associated vascular remodeling. *Am J Pathol*. 2012;180:2134. *Hypertension*. 2007;50:1057. *J Biol Chem*. 2004;279:28766.

vascular calcification *Circ Res*. 2003; 92:1123. *Circ Res*. 2007; 100:502. *Circ Res*. 2006;98:1024

B) GAS6 facilitates the interactions between endothelial cells, platelets, and leukocytes *Blood*. 2008;111:4096, *Circ Res*. 2006; 98: 1446

The Product

c) Differential features facing the market

A) sAXL is very stable in serum	→	Lower manipulation cost and easier technology
B) sAXL levels in controls do not correlate with age	→	No need of different cut-offs
C) Patients from Chronic Obstructive Pulmonary Disease (COPD) do not have high sAXL levels	→	Discrimination between dyspnea due to HF or COPD
D) There is no increase of sALX in patients with Atrial Fibrillation or post-Acute Myocardial Infarction	→	Discrimination between HF and other Cardiovascular Diseases

The Product

c) Differential features facing the market

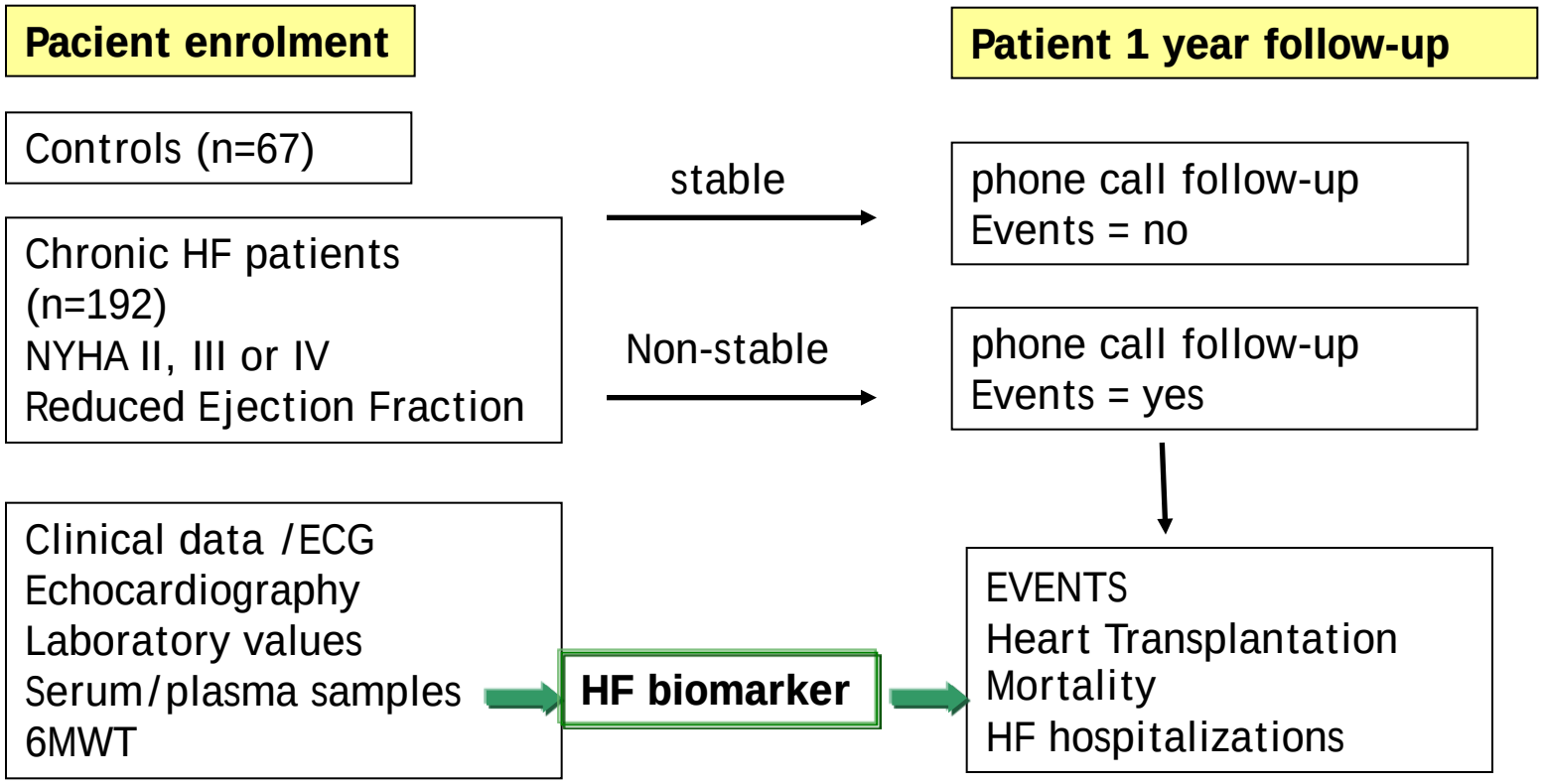
D) Measures of the HF biomarkers BNP and NT-proBNP have a high cost → ≥ Cost of sAXL measure

E1) sAXL serum levels DO NOT correlate with echocardiographic parameters: LVESD, LVEDD, LVEF, LAD, IVST, LVPWT → sAXL levels are not dependant on myocyte stretch

E2) Linear regression analysis indicates that serum BNP levels were not predictive of sAXL levels → Different behavior from BNP and NT-proBNP

The Product

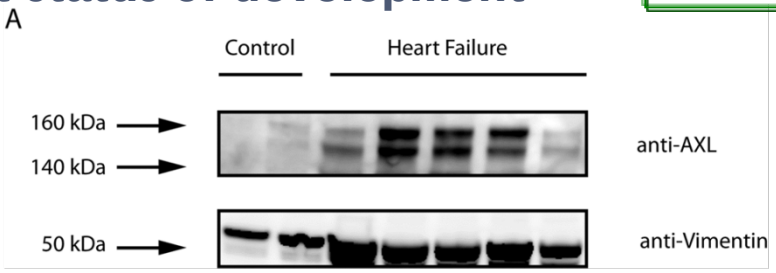
d) Current status of development

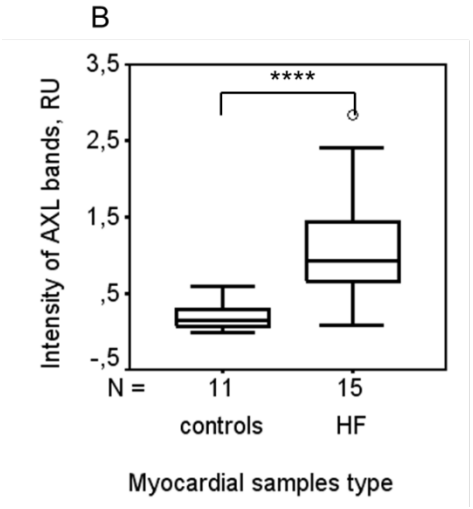


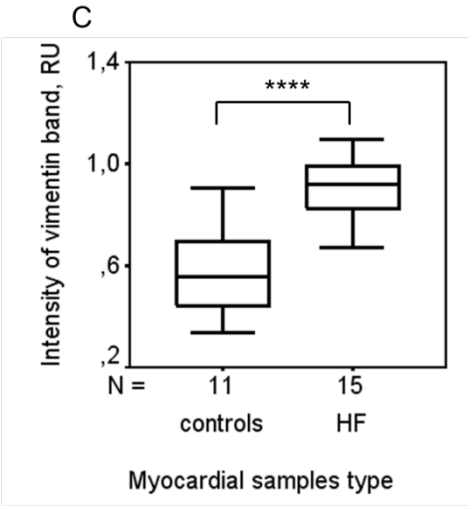
The Product

d) Current status of development

Increase in HF cardiac tissue







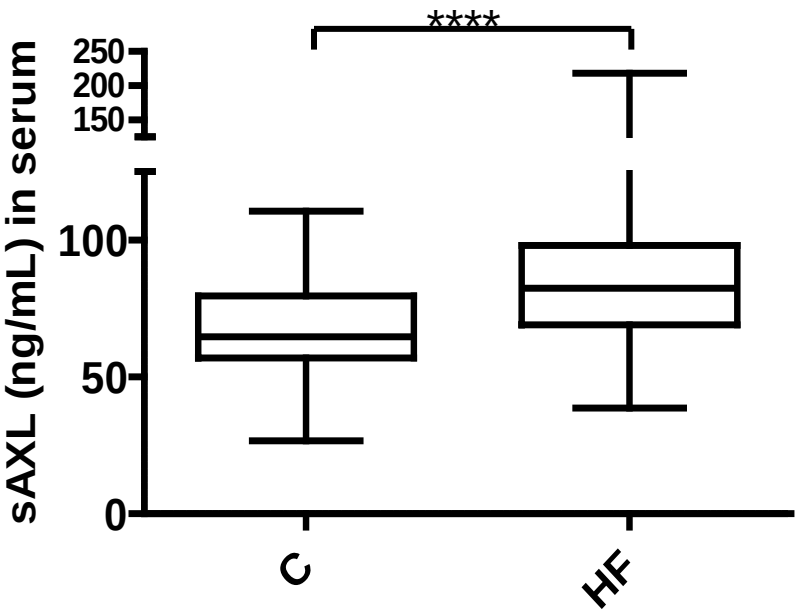
****P<0.0001

AXL protein is higher in myocardial samples from end-stage HF patients than in controls

The Product

d) Current status of development

Increase in HF serum



Group	Controls (C)	Heart Failure (HF)
n	67	192
sAXL ng/mL	67.8±2.0	86.3±2.0

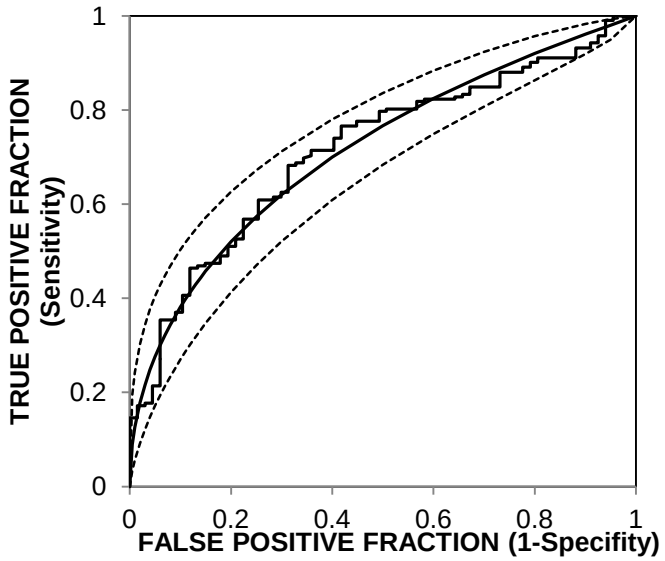
****P<0.0001

Soluble AXL protein is higher in serum samples from HF patients than in controls

The Product

d) Current status of development

Discrimination



ROC curve
AUC=0.72
[95% IC= 0.649-0.782]

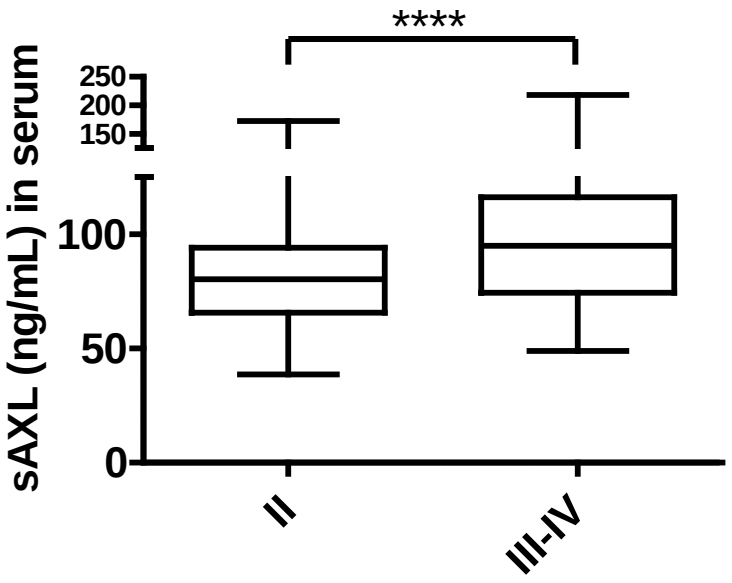
******P<0.0001**

Soluble AXL protein levels discriminate between HF patients and controls

The Product

d) Current status of development

Differences in Functional Class



Group	HF class II	HF class III-IV
n	138	54
sAXL ng/mL	80.9±2	100.2±5.0

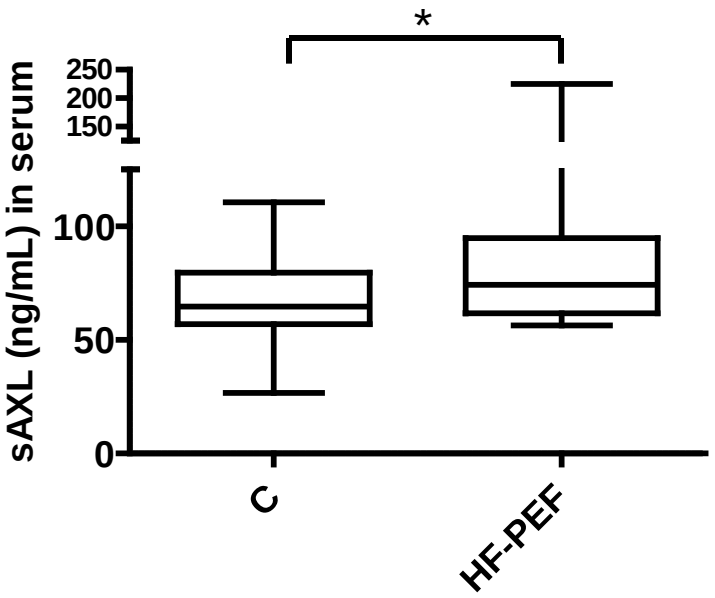
****P<0.0001

Soluble AXL protein is higher in serum samples from HF patients in NYHA functional class III-IV than HF patients in class II

The Product

d) Current status of development

Increase in HF patients with Preserved Ejection Fraction (HF-PEF) serum



Group	Controls (C)	Heart Failure (HF-PEF)
n	67	25
sAXL ng/mL	67.8±2.0	85.4±7.3

***P<0.05**

Soluble AXL protein is higher in serum samples from HF patients with preserved ejection fraction than in controls

The Product

d) Current status of development

Correlation of sAXL levels with other parameters

sAXL serum levels directly correlated with:

- BNP levels
- serum creatinine levels
- C reactive protein
- uric acid

Worse HF prognosis

sAXL serum levels inversely correlated with:

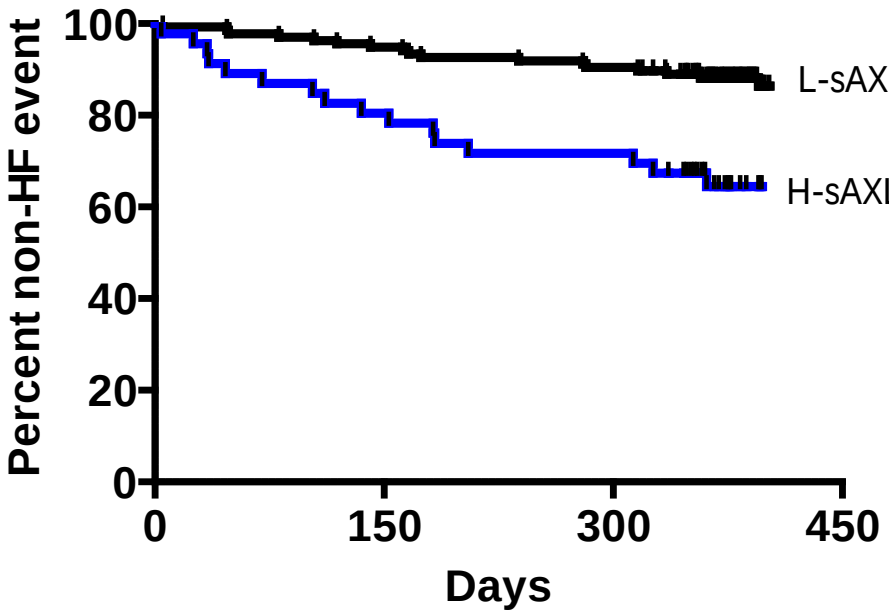
- systolic blood pressure
- diastolic blood pressure
- 6-minutes walk distance
- glomerular filtration rate
- hemoglobin
- hematocrit
- hematies count

The Product

d) Current status of development

1 year follow-up

cut-off point= sAXL 3rd quartile



HF events:
Heart transplantation
All-cause mortality
HF-hospitalizations

***** P<0.001**
Hazard ratio = 3.3

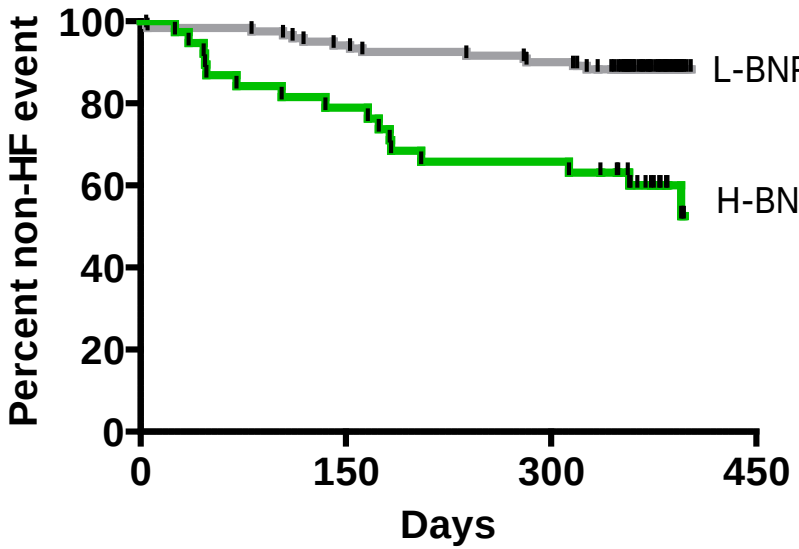
→ **sAXL levels in serum are predictive of HF events at short-term follow-up**

The Product

d) Current status of development

1 year follow-up

cut-off point= BNP 3rd quartile



HF events:
Heart transplantation
All-cause mortality
HF-hospitalizations

****** P<0.0001**
Hazard ratio = 4.4

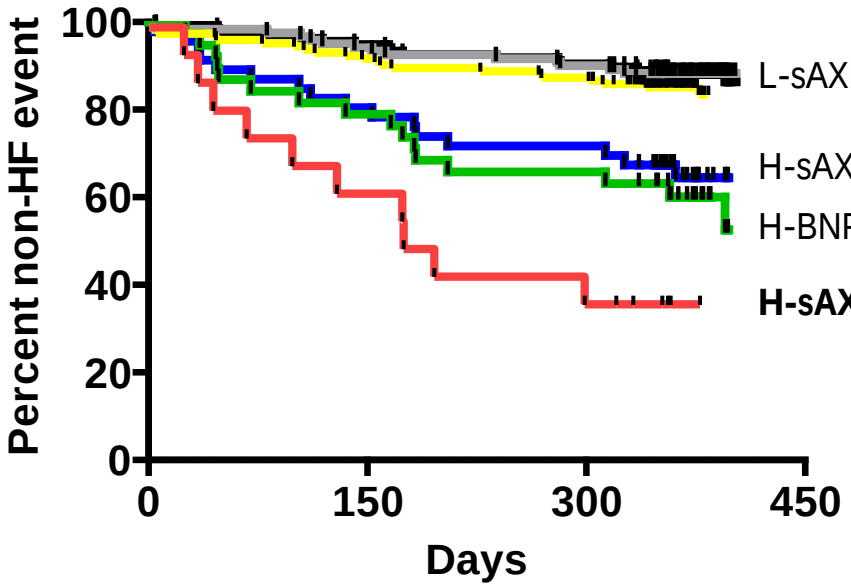
→ **BNP levels in serum are predictive of HF events at short-term follow-up**

The Product

d) Current status of development

1 year follow-up

cut-off point= sAXL + BNP 3rd quartile

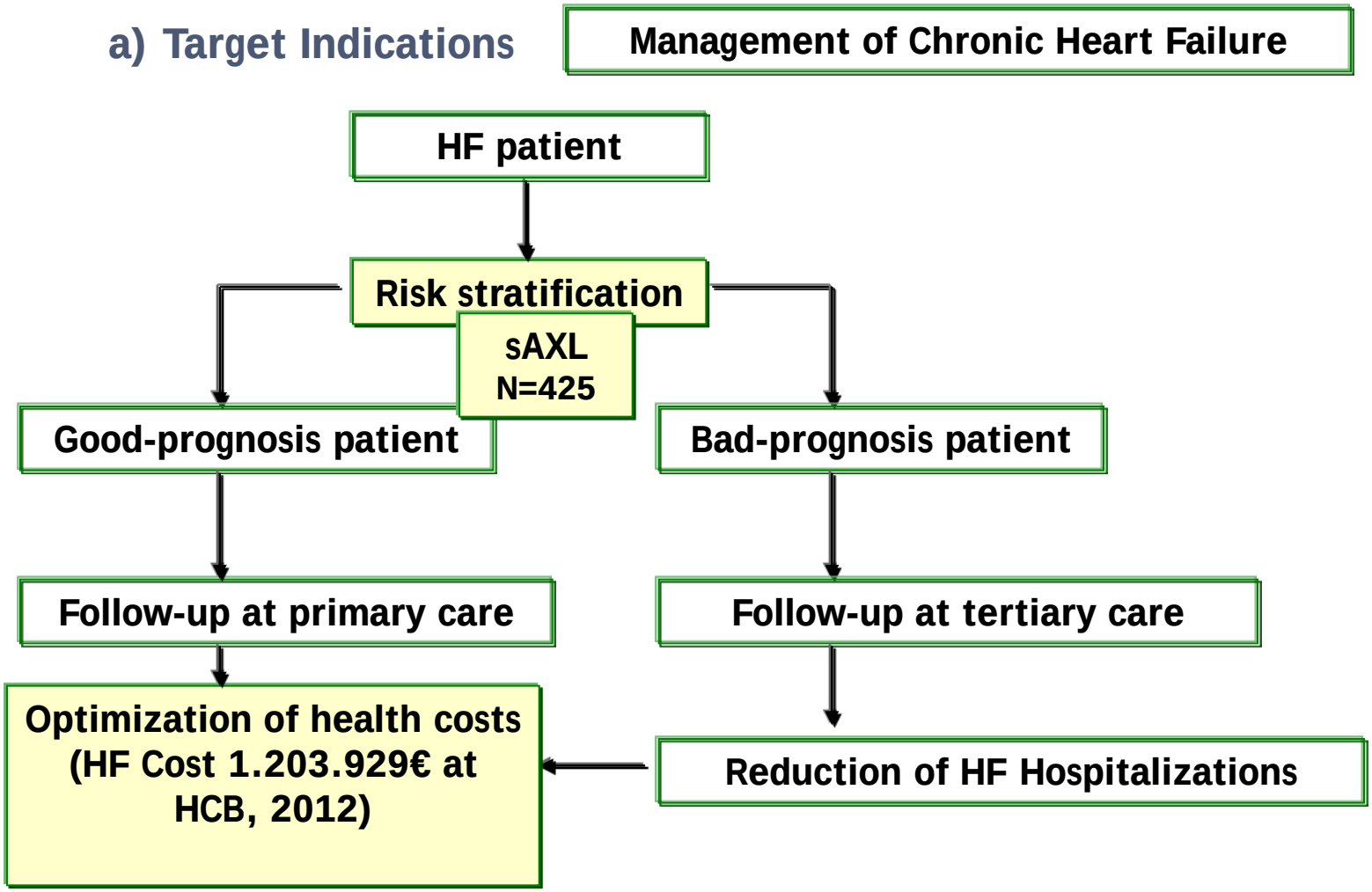


L_sAXL and/or L_BNP vs
H_sAXL and H_BNP
****** P<0.0001**
Hazard ratio = 6.8

Use of sAXL adds predictive value to BNP

The Product

a) Target Indications



The Product

c) Differential features facing the market

Prognosis

2013 ACCF/AHA Guidelines for the Management of Heart Failure

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF

Measurement of **other** clinically available tests such as **biomarkers** of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF, besides BNP or NT-proBNP

AXL

The Product

e) IPR protection

A European patent application filed on February 2012: **EP12382048**

PCT application filed on August 2013: **PCT/EP2013/052743**

- INVENTORS: Dra. Montserrat Batlle and Dr. Pablo García de Frutos
- APPLICANTS: IDIBAPS and CSIC
- TITLE: *Use of the soluble form of AXL in the diagnosis and/or prognosis of Heart Failure Syndrome*

The Extended European Search Report (EESR) considered that the patent complied with the conditions of novelty and industrial application

For more information: https://register.epo.org/application?number=EP12382048

The Product

f) Pitfalls & Risks to be considered

- The natriuretic peptides (BNP, NT-proBNP) are well established in the HF field

Biomarker	Study Population	NYHA FC	n	Events	Years follow-up	Outcome	Reference
sAXL	**Chronic HF**	**II-IV**	**192**	M, HT, HF-hosp	1	Predictor of major HF events	
Troponina-I	**Advanced, Chronic HF**	**III-IV**	**238**	M, urgent HT	1.5	Predictor of mortality + urgent HT	Circ 2003;108:833
Galectin-3	**Chronic HF**	**I-IV**	133	M, HT, HF-hosp	**5**	Predictor of mortality	Am J Cardiol 2011;108:385–390
sST2	**Acute, destabilized HF**	**III-IV**	137	M	1	Predictor of mortality	Clin Chem. 2008;54 (4):752-6

M all-cause mortality, HT heart transplantation, HF-hosp heart failure hospitalizations

Partnering Opportunities

We are looking for companies interested to further develop this technology via:

- Collaboration (Option Agreement)
- Licensing out the patent (License Agreement)

FURTHER DEVELOPMENT and VALIDATION:

- Further analyze sAXL levels in a broader HF cohort and with a longer follow-up period
- Further analyze sAXL as a biomarker for HF patients with preserved ejection fraction
- Further analyze sAXL application to discriminate HF from other pathologies
- Improvement of ELISA assay: obtaining new Antibodies based on our own recombinant material and using state of the art techniques for sAXL quantification in serum

Programa Cooperación Farma-Biotech

X encuentro (27 de noviembre de 2013)

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IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

CSIC

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