XIV Encuentro de Cooperación Farma-Biotech

Platform for design and development of universal bacterial vaccines, based on an innovative biotechnological approach

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University Hospital A Coruña

Madrid, 17 de noviembre de 2015

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   b) Innovative mechanisms of action
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1. The Institution and the Group….

O COMPLEXO HOSPITALARIO UNIVERSITARIO A CORUÑA

Hospital Abente y Lago

Hospital Marítimo de Oza

Hospital A Coruña

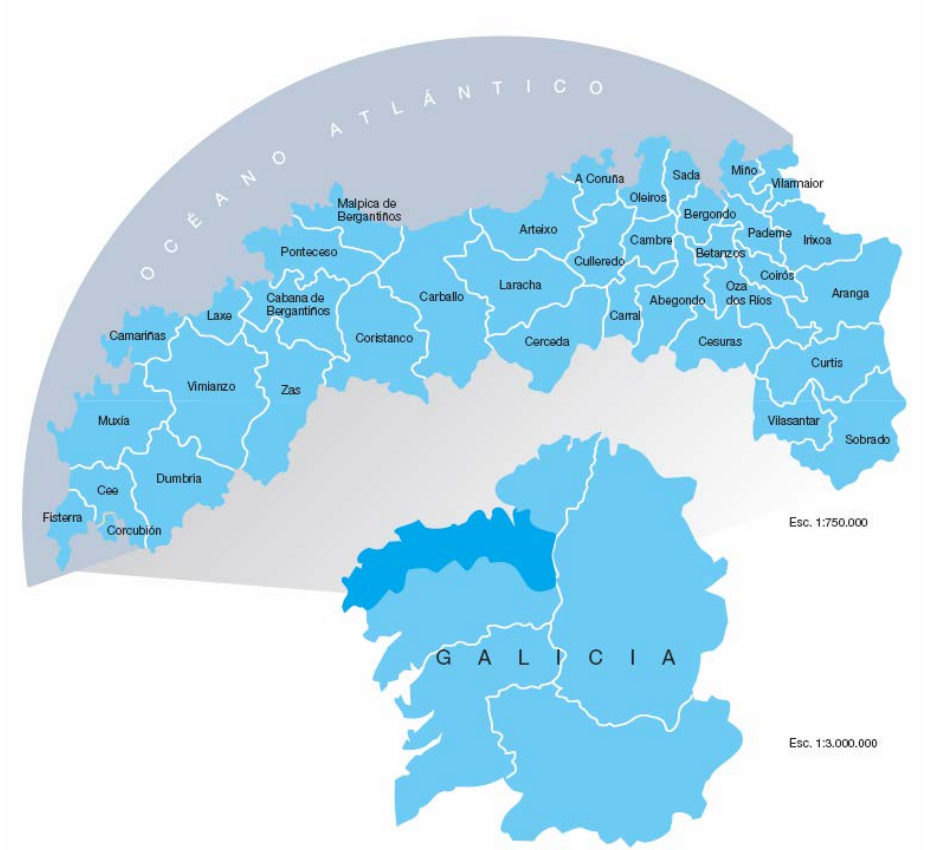
Hospital Materno T. Herrera

CCEE do Ventorrillo

CCEE de Carballo

Lavandería Industrial

CCEE de Betanzos



Recursos

FÍSICOS

Centro	Camas	Quirófanos	Salas de consulta externa
Hospital A Coruña	860	16	55
Hospital Teresa Herrera	302	7	66
Hospital Marítimo de Oza	156		9
Hospital Abente y Lago	116	7	52
Centro de Especialidades do Ventorrillo			57
Centro de Especialidades de Carballo			9
Centro de Especialidades de Betanzos			7
Centro Orientación Familiar Orillamar			3
TOTAL	1.434	30	258

Microbiology Research Group
CHUAC-INIBIC

- **Senior (M. Servet)**
- Maria Tomas
- Alejandro Beceiro
- Margarita Poza
- **Post-doc**
- Astrid Pérez
- Patricia García
- Jose Pérez
- Ana Fernández
- Juan Vallejo
- Carlos Rumbo
- Miriam Moscoso
- Raquel Moure
- Silvia Rodriguez
- **PhD**
- María Merino
- Clara Povoa
- Soraya Rumbo
- Eva Gato
- María López
- Laura Fraga
- Marta Martínez
- **Lab Tech**
- Mª Carmen Fernández

- Head of Microbiology Department (University Hospital A Coruña)

- Director of the Area of Microbiology and Infectious Diseases at Biomedical Research Institute at La Coruña (INIBIC). (www.inibic.org)

- Associate Professor of Medical Microbiology at University of Santiago de Compostela.

- Author or co-author of more than 160 international peer-review manuscripts, including Clin Microb Reviews, J Clin Invest, PNAS, Clin Infect Dis, Antimicrob Agents Chemother, Nature, J Antimicrob Chemother, J Clin Microb, Annals Intern Med, etc.

- In addition Dr. Bou has authored or co-authored 5 patents (1 national, 4 international)

- He already has an H index of 41

- Member of the Editorial Board of the Journal of Clinical Microbiology (2015-2017).

1. The Product

a) Target Indications

- Human and veterinary health;

- Nosocomial and community-acquired infections;

- Prophylaxis and therapeutics;

- Single-species and combination vaccines;

- ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp);

- Acute and chronic infections (CF patients);

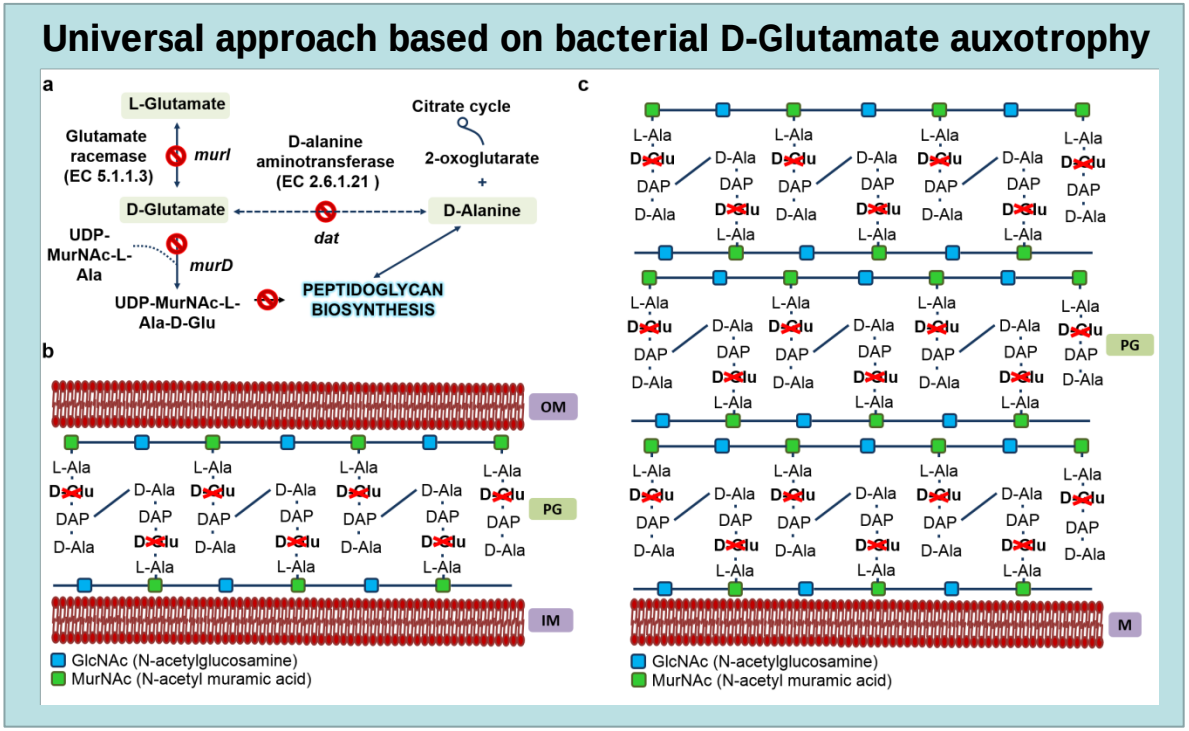
- Bovine mastitis: *Streptococcus agalactiae*, *Staphylococcus aureus*

2. The Product

b) Innovative mechanisms of action

Platform for generating Bacterial Vaccines

Universal approach based on bacterial D-Glutamate auxotrophy



A hallmarked progress in vaccine development

D-Glutamate (D-Glu) is a key component of bacterial peptidoglycan and is found in the cell wall of virtually all bacteria

D-Glu auxotrophy is achieved by inactivation of D-Glu producing enzymes (by unmarked in-frame deletion of coding genes)

This approach overcomes classical difficulties in obtaining virulence attenuation

- **What?**

Universal platform for designing vaccines able to target any microbial pathogen (human or animal) harbouring cell wall by inactivating D-Glu synthesis. As a proof of concept we have developed three different ESKAPE prototypes: *Staphylococcus aureus,* *Pseudomonas aeruginosa,* and *Acinetobacter baumannii*.

- **How it works?**

These strains, auxotrophic for D-Glu show virulence attenuation and self-limited growth *in vivo*. Inmmunization with these whole-cell vaccines elicited high levels of specific and cross-reactive antibodies and stimulated cytokine secretion.

- **Host target?**

Any human or animal (livestock) can be suffering an infection.

- **Where it would apply?**

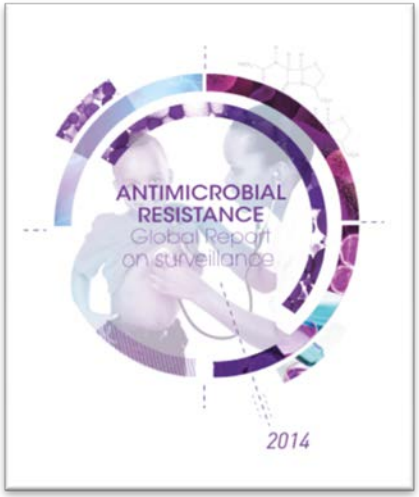
Anywhere.

Platform for generating Bacterial Vaccines

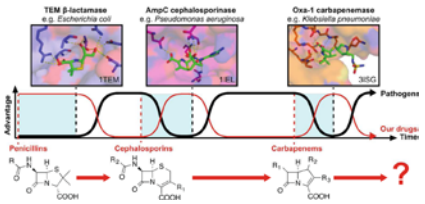
Why?

- Worldwide problem of antibiotic resistance in bacterial pathogens
- A solution is a public health unmet need

World Health Organization



New Antibiotics are Necessary but Not Sufficient



Source: Culyba MJ *et al*. Biochemistry. 2015.54, 3573-82

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

IDSA Report on Development Pipeline • CID 2009:48 (1 January) • 1

ESKAPE

Enterococcus faecium
Staphyloccous aureus
Klebsiella pneumoniae
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacter spp.

No current vaccines for these Bad Bugs!!

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española

inibic instituto de investigación biomédica de a coruña

farmaindustria

XIV Encuentro de Cooperación Farma-Biotech

NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-
RESISTANT
BACTERIA

Vision: *The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic- resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.*

September 2014

THE WHITE HOUSE
WASHINGTON

GOAL 4:
Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines

4.3 Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.

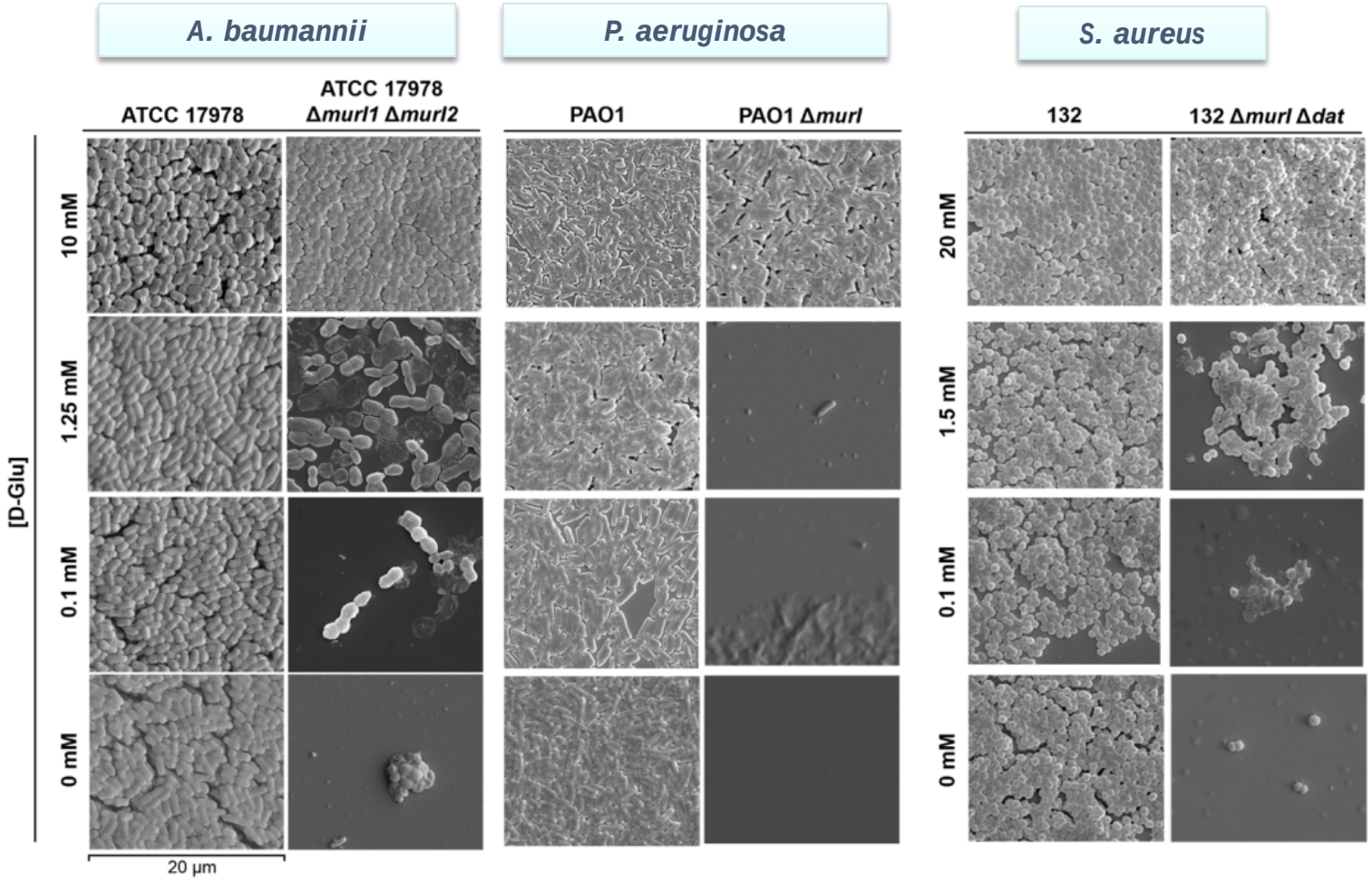
GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Plataforma Tecnológica Española

instituto de investigación biomédica de a coruña

farmaindustria

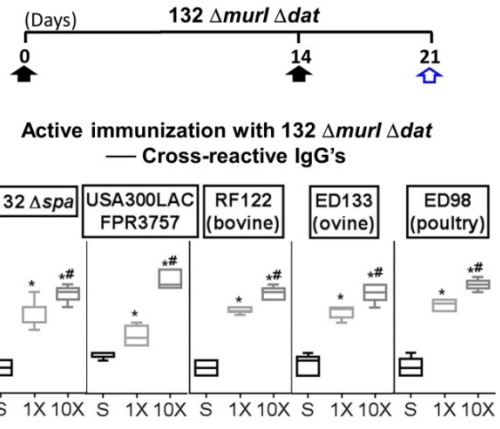
Auxotrophic vaccines strains show impaired growth in D-Glutamate deprivation



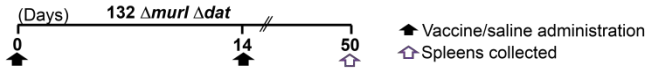
In vivo immunogenicity : Humoral and Celullar responses after vaccination with auxotrophic strains

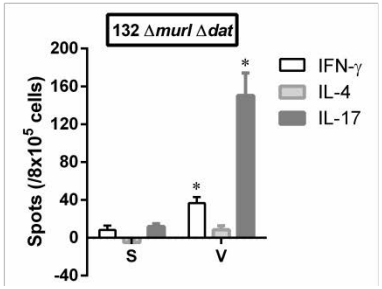
S. aureus

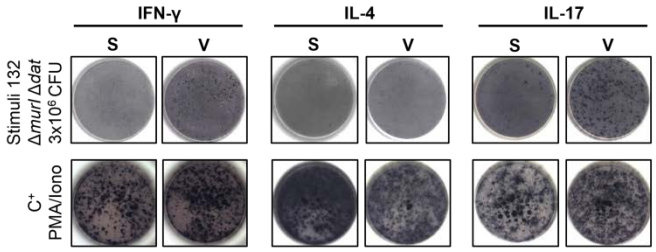
High level of specific and cross-reactive IgG antibodies



Significative IFN-γ and IL-17-producing cells



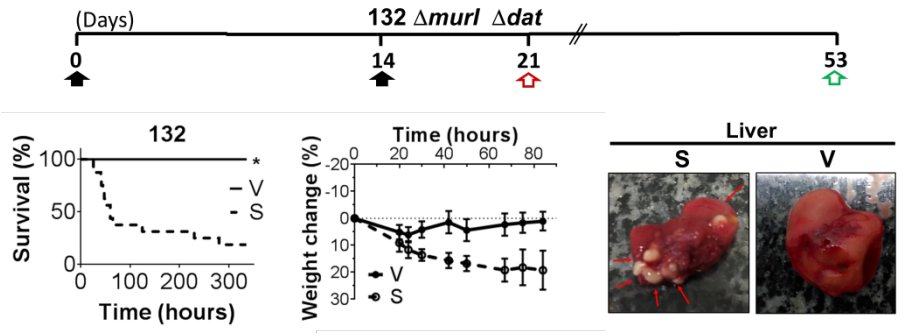




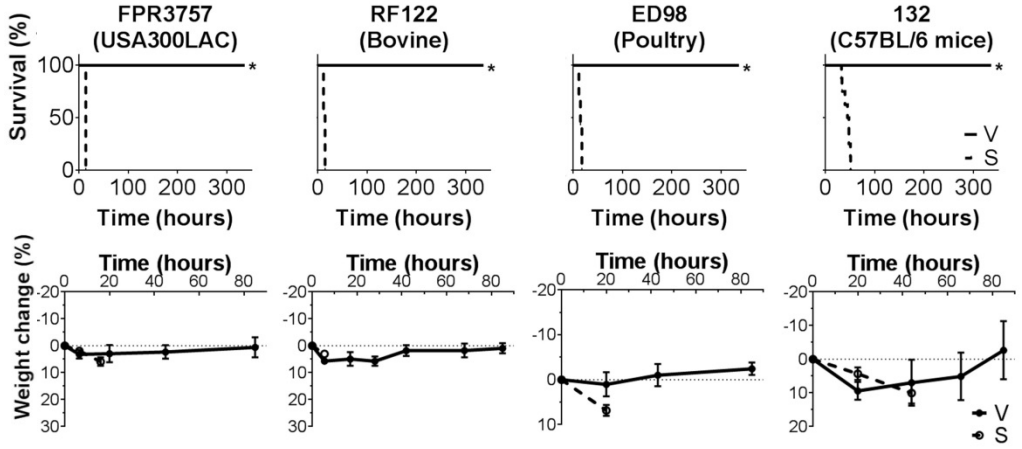
In vivo protection of mice against acute systemic infection after vaccination with auxotrophic strains

100% vaccine efficacy against wild-type strain

S. aureus

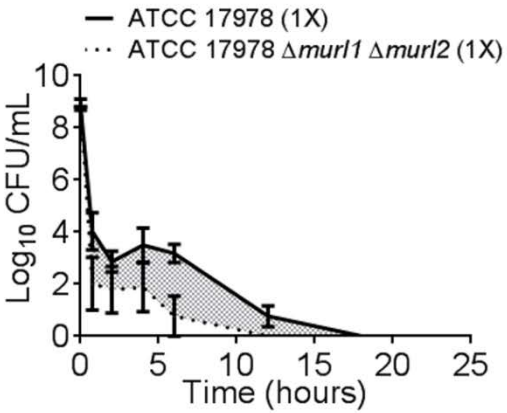


100% vaccine efficacy against Comunity-acquired USA300LAC high-risk clone and heterologous strains of animal origin

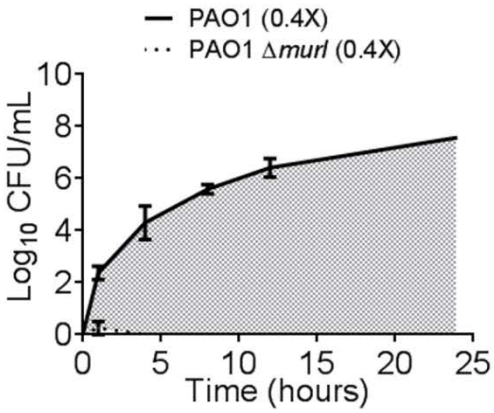


- ***In vivo* safety: rapid blood clearance of auxotrophic strains**
- **Environmental safety: no phenotype reversion**
- **Environmental safety: lower persistence in non-optimal conditions (*vs* wild-type strain)**

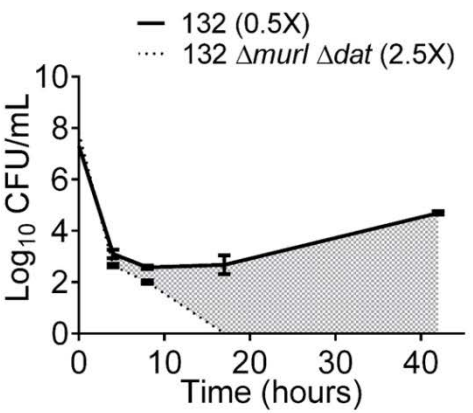
A. baumannii



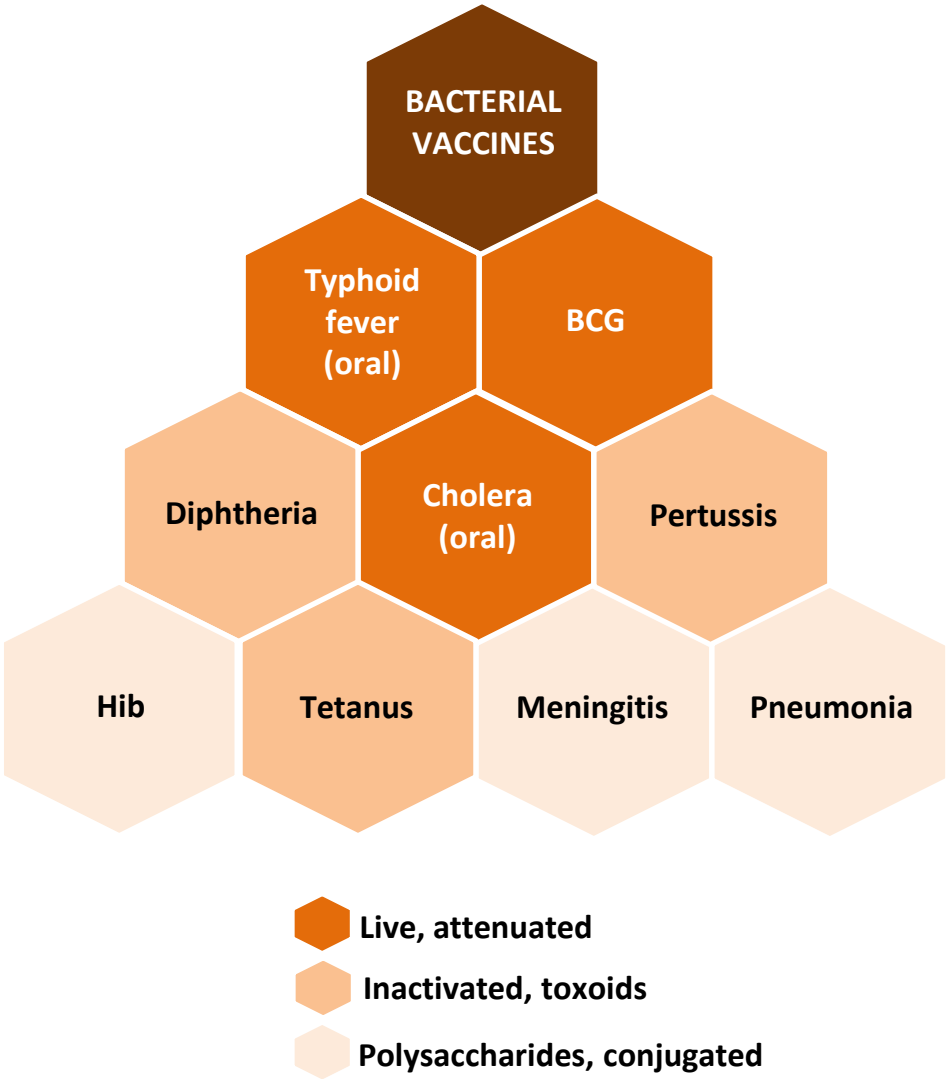
P. aeruginosa



S. aureus



The background for the generation of live attenuated bacterial vaccines auxotrophic for D-glutamate - why the effort?



2. The Product

c) Differential features facing the market

- **Originality**: Auxotrophic vaccines combine the advantages of both attenuated and inactivated vaccines without displaying its disadvantages
- **Universality**: common target (D-Glu synthesis) among bacterial pathogens
- **Easy industrial development**: only requirement is to add D-Glu for bacterial growth
- **Safety**: Self-destroy in a few hours after removing D-Glu and no reversion to wt phenotype
- **Lack of toxicity** in acute infection mice model. Data has been confirmed by external regulatory company

Nª of dosis			
Need for booste			
Reactogenicity			
Growth of bacte			
Risk of disease			
Risk of transmis			
Possibility of re			
Humoral inmune			
Cellular inmune response	Yes	Scarce	**Yes**

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2. The Product

d) Current status of development

P. aeruginosa

BIOFABRI, S. L. Early stages of industrial development of an anti-*P. aeruginosa* D-Glu auxotrophic vaccine in GMP conditions: lyophilization, choice of the stabilizers and stability tests

Preliminary safety assays in animals with regulatory validity

A. baumannii | *P. aeruginosa* | *S. aureus*

PRECLINICAL STUDIES with intranasal vaccine administration, testing vaccine efficacy against acute pneumonia

2. The Product

e) IPR protection

11th October 2013, OEPM

MINISTERIO DE INDUSTRIA, TURISMO Y COMERCIO

Oficina Española de Patentes y Marcas

Justificante de presentación electrónica de solicitud de patente

Este documento es un justificante de que se ha recibido una solicitud española de patente por vía electrónica, utilizando la conexión segura de la O.E.P.M. Asimismo, se le ha asignado de forma automática un número de solicitud y una fecha de recepción, conforme al artículo 14.3 del Reglamento para la ejecución de la Ley 11/1986, de 20 de marzo, de Patentes. La fecha de presentación de la solicitud de acuerdo con el art. 22 de la Ley de Patentes, le será comunicada posteriormente.

Número de solicitud:	P201331504
Fecha de recepción:	11 octubre 2013, 17:52 (CEST)
Oficina receptora:	OEPM Madrid
Su referencia:	900 142
Solicitante:	Servicio Galego de Saúde (SERGAS)
Número de solicitantes:	2
País:	ES
Título:	Vacunas bacterianas vivas atenuadas auxótrofas para D-glutamato

2. The Product

e) IPR protection

PCT, 13th October 2014, EPO

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of your request for the processing of an international application according to the Patent Cooperation Treaty as follows:

Submission number	3057271
PCT application number	PCT/EP2014/071926
Date of receipt	13 October 2014
Receiving Office	European Patent Office, The Hague
Your reference	176949aa/npo
Applicant	SERVIZIO GALEGO DE SAÚDE (SERGAS)
Number of applicants	2
Country	ES
Title	LIVE ATTENUATED VACCINES

2. The Product

e) IPR protection

15th April 2015, OEPM

MINISTERIO DE INDUSTRIA, ENERGÍA Y TURISMO

Oficina Española de Patentes y Marcas

Justificante de presentación electrónica de solicitud de patente

Este documento es un justificante de que se ha recibido una solicitud española de patente por vía electrónica, utilizando la conexión segura de la O.E.P.M. Asimismo, se le ha asignado de forma automática un número de solicitud y una fecha de recepción, conforme al artículo 14.3 del Reglamento para la ejecución de la Ley 11/1986, de 20 de marzo, de Patentes. La fecha de presentación de la solicitud de acuerdo con el art. 22 de la Ley de Patentes, le será comunicada posteriormente.

Número de solicitud:	P201530508	
Fecha de recepción:	15 abril 2015, 18:27 (CEST)	
Oficina receptora:	OEPM Madrid	
Su referencia:	900748	
Solicitante:	Fundación Profesor Novoa Santos	
Número de solicitantes:	2	
País:	ES	
Título:	VACUNAS VIVAS ATENUADAS DE STAPHYLOCOCCUS AUREUS	
Documentos enviados:	Descripcion.pdf (40 p.) Reivindicaciones.pdf (3 p.)	package-data.xml es-request.xml

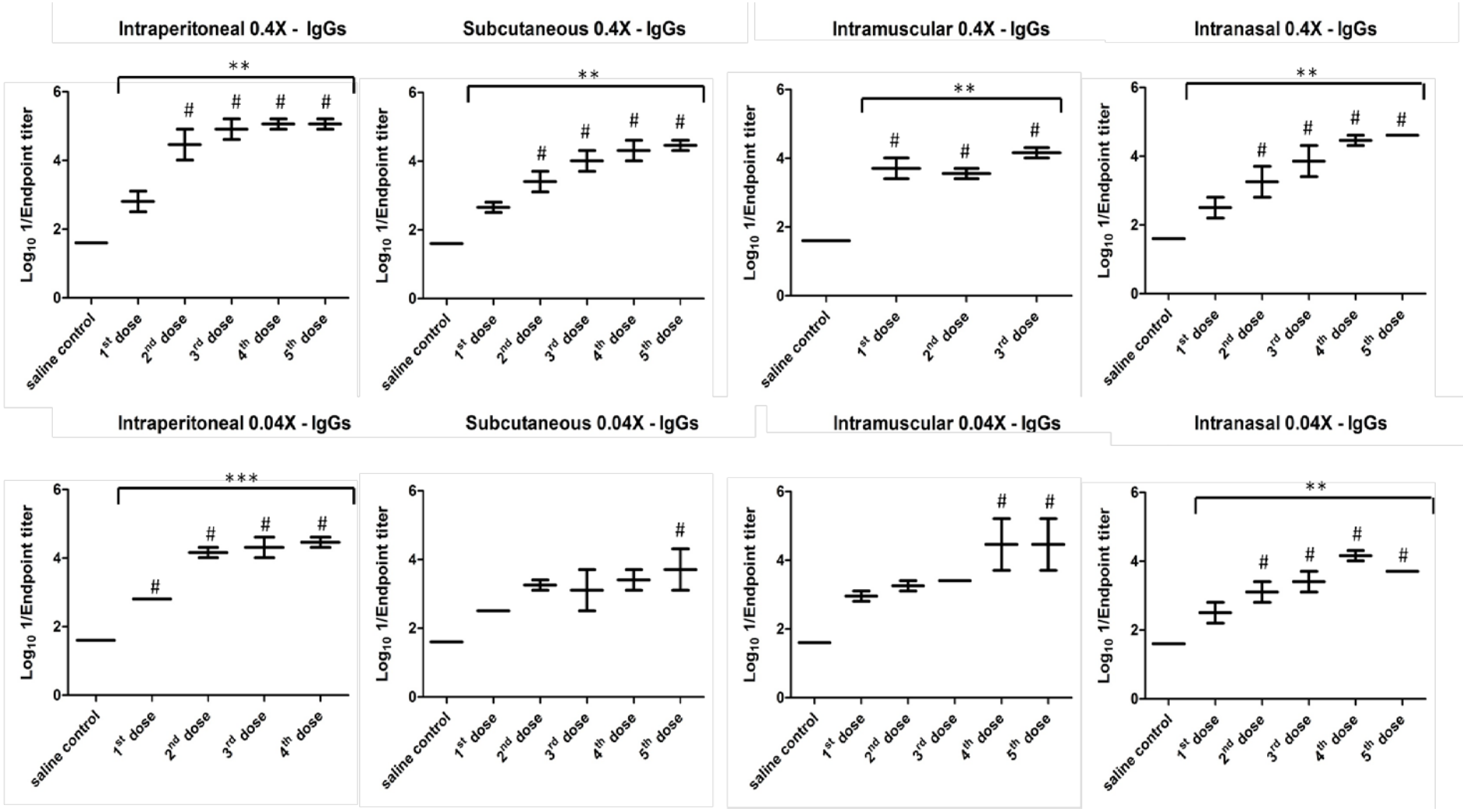
2. The Product

f) Pitfalls & Risks to be considered:

- Reactogenicity: preclinical studies in mice model did not show toxicity, local or systemic.

➡ **We are studying other routes of administration to minimize toxicity, improvement of dosage etc**

Evaluation of antibody-mediated inmune response (IgG) by indirect ELISA, other routes of vaccine administration



2. The Product

f) Pitfalls & Risks to be considered:

- Lack of efficacy: preclinical studies in mice model: either immunological or challenge with clinical bacterial isolates always showed inmmune response and protection towards lethal dose of infection with the three studied pathogens in intraperitoneal (sepsis) models.

→ **We need to evaluate this efficay in other routes of administration. For example: intranasal, intramuscular…..**

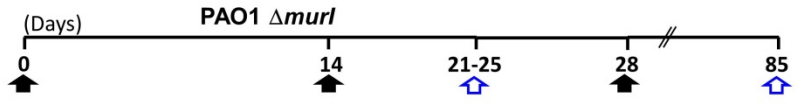
- Reduced coverage: The three prototypes recognizes heterologous clinical bacterial isolates.

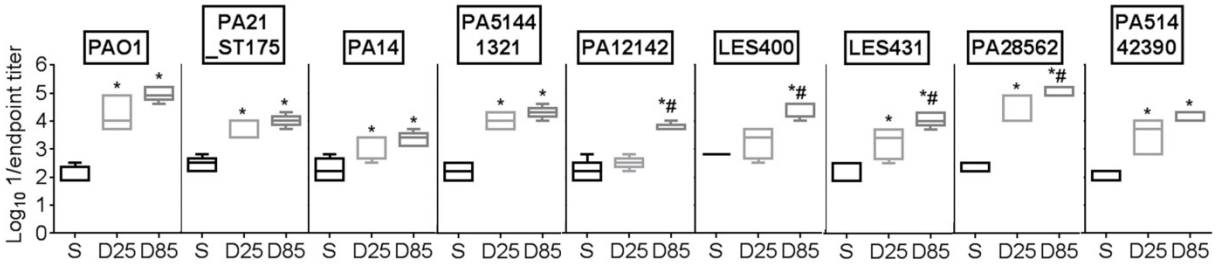
→ **We need to evaluate this efficay in worldwide representative bacterial strains, and if necessary incorporate other strains in the final vaccine**

- Final formulation: models lyophilization, choice of the stabilizers and stability tests

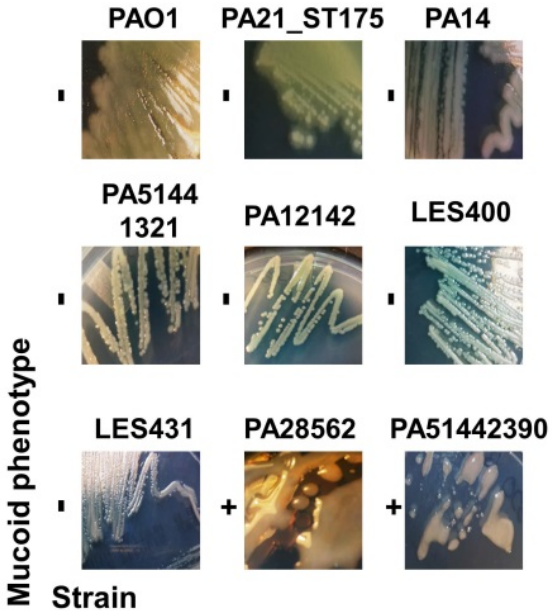
→ **Biofabri**

P. aeruginosa

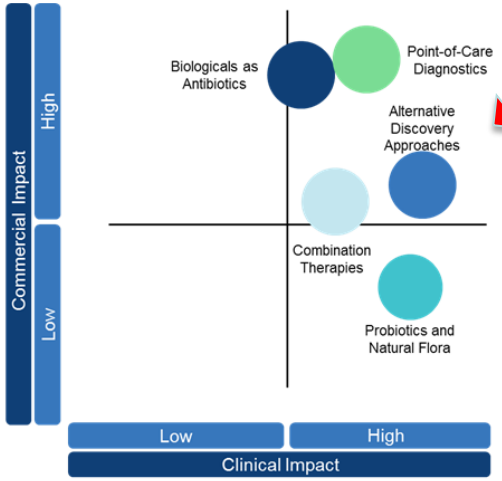




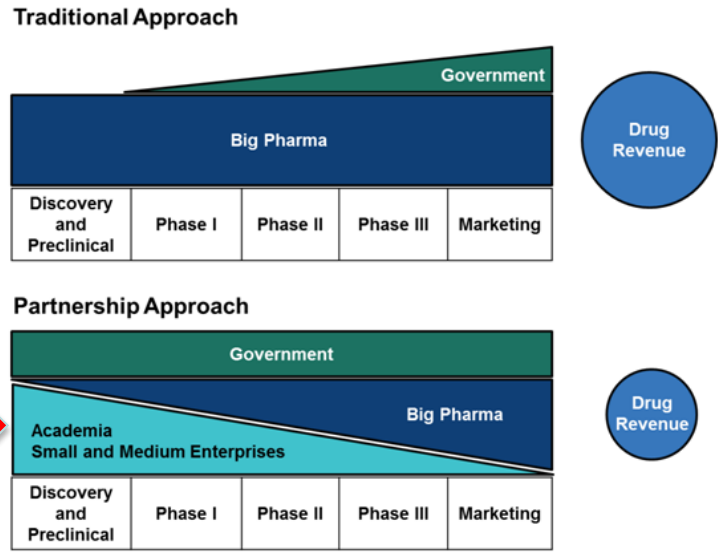
Different *P. aeruginosa* strain analyzed



3. Partnering Opportunities



Auxotrophic vaccines are probably here



Business Opportunity

Impact of Nosocomial Infections

Table 2. Estimated yearly human burden of infections due to the selected antibiotic-resistant bacteria and percentage of this burden due to bloodstream infections, EU Member States, Iceland and Norway, 2007.

Antibiotic-resistant bacteria[a]	No. cases of infection (four main types)[b] (% bloodstream infections)	No. extra deaths (% from bloodstream infections)	No. extra hospital days (% from bloodstream infections)
Antibiotic-resistant Gram-positive bacteria			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	171 200 (12%)	5 400 (37%)	1 050 000 (16%)
Vancomycin-resistant *Enterococcus faecium*	18 100 (9%)	1 500 (28%)	111 000 (22%)
Penicillin-resistant *Streptococcus pneumoniae*[c]	3 500 (27%)	–[f]	–
Sub-total	*192 800 (12%)*	*6 900 (35%)*	*1 161 000 (16%)*
Antibiotic-resistant Gram-negative bacteria			
Third-generation cephalosporin-resistant *Escherichia coli*[d]	32 500 (27%)	5 100 (52%)	358 000 (27%)
Third-generation cephalosporin-resistant *Klebsiella pneumoniae*	18 900 (27%)	2 900 (52%)	208 000 (27%)
Carbapenem-resistant *Pseudomonas aeruginosa*[e]	141 900 (3%)	10 200 (7%)	809 000 (3%)
Sub-total	*193 300 (9%)*	*18 200 (27%)*	*1 375 000 (13%)*
Total	386 100 (11%)	25 100 (29%)	2 536 000 (14%)

[a] *Data on antimicrobial resistance for* Klebsiella sp. *other than* K. pneumoniae, Enterobacter spp. *and* Acinetobacter spp. *were not available from EARSS. Although coagulase-negative staphylococci as well as beta-haemolytic and viridans streptococci are among the 10 most common bacteria isolated from blood cultures [20], they were excluded from the study because reliable resistance data are not available for these bacteria.*

[b] *Bloodstream infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.*

[c] *Most fully penicillin-resistant* Streptococcus pneumoniae *isolates are resistant to both penicillin and macrolides.*

[d] *Resistant to cefotaxime or ceftriaxone or ceftazidime.*

[e] *Resistant to imipenem or meropenem.*

[f] *–, could not be calculated*

These infections cause a substantial increase in healthcare expenditure as well as unnecessary deaths

They increase hospital burden considerably

Source: The Bacterial Challange; time to react (2009) European Centre for Disease Prevention and Control,

Impact of Nosocomial Infections

Table 3. Estimated yearly economic burden of infections (four main types[a]) due to the selected antibiotic-resistant bacteria, EU Member States, Iceland and Norway, 2007.

Antibiotic-resistant bacteria[b]	Extra in-hospital costs (EUR)	Extra outpatient costs[c] (EUR)	Productivity losses due to absence from work (EUR)	Productivity losses due to patients who died from their infection (EUR)	Overall costs (EUR)
Antibiotic-resistant Gram-positive bacteria	*424 700 000*	*5 500 000*	*91 100 000*	*145 600 000*	*666 900 000*
Antibiotic-resistant Gram-negative bacteria	*503 100 000*	*4 500 000*	*59 300 000*	*300 300 000*	*867 200 000*
Total	927 800 000	10 000 000	150 400 000	445 900 000	1 534 100 000

[a] Bloodstream infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.

[b] Gram-positive bacteria: methicillin-resistant Staphylococcus aureus *(MRSA), vancomycin-resistant* Enterococcus faecium. *Data for penicillin-resistant* Streptococcus pneumoniae *were not available. Gram-negative bacteria: third-generation cephalosporin-resistant* Escherichia coli *and* Klebsiella pneumoniae *(i.e., resistant to cefotaxime or ceftriaxone or ceftazidime) and carbapenem-resistant* Pseudomonas aeruginosa *(i.e., resistant to imipenem or meropenem).*
Data on antimicrobial resistance for Klebsiella sp. *other than* K. pneumoniae, Enterobacter spp. *and* Acinetobacter spp. *were not available from EARSS. Although coagulase-negative staphylococci as well as beta-haemolytic and viridans streptococci are among the 10 most common bacteria isolated from blood cultures [20], they were excluded from the study because reliable resistance data are not available for these bacteria.*

[c] Visit to general practitioner.

The economic impact of the hospital burden has been quantified

Overall the cost is approximately 1,500 million Euros

Source: The Bacterial Challange; time to react (2009) European Centre for Disease Prevention and Control,

Impact of Bovine Mastitis

- **Mastitis:**

  The main cause of economic loss in milk production worldwide

  The disease is caused by

  – Mechanical damage; Automatic milking causes mechanical damage to the mammary gland causing its inflammation.

  – **Infection b**

  From a pub ***ylococcus aureus*** are highly ge body of legislation '853/2004.

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World's Top 10 Cow's Milk Producing Countries in 2012 (Tonnes)			
	2010	2011	2012
United States of America	87,474,381	89,015,235	90,865,000
India	54,903,000	53,500,000	54,000,000
China	36,036,043	36,928,896	37,767,991
Brazil	30,715,460	32,096,214	32,304,421
Russian Federation	31,585,230	31,385,732	31,576,047
Germany	29,616,284	30,323,465	30,506,929
France	23,331,837	24,361,095	23,983,197
New Zealand	17,010,456	17,893,848	20,053,000
Turkey	12,418,544	13,802,428	15,977,837
United Kingdom	14,071,000	13,849,000	13,884,000
World	**597,071,398**	**607,391,767**	**620,361,802**

Source: http://www.dairyco.org.uk/market-information/supply-production/milk-production/world-milk-production/#.U8ulnbmKDKJ; United States Department of Agriculture (July 2014) Dairy World Markets and Trade

Source: Gasque Gómez, R. (2008) Enciclopedia Bovina, Capítulo IV, 176-181, Universidad Nacional Autónoma de México, facultad de Medicina Veterinaria y Zoología; Wolter *et al.*, La mastitis bovina. http://www.infolactea.com/descargas/biblioteca/608.pdf

Sales Forecasts based on external consulting business

Realistic Scenario in Nosocomial Diseases

	2025	2026	2027	2028	2029	2030	2031	2032	2033
USA	7.909.405 €	26.590.395 €	40.227.056 €	54.095.257 €	54.558.371 €	55.025.449 €	55.496.526 €	55.971.636 €	56.450.814 €
France	2.096.829 €	7.011.296 €	10.549.846 €	14.110.467 €	14.154.611 €	14.198.893 €	14.243.313 €	14.287.873 €	14.332.571 €
Germany	3.482.658 €	11.583.380 €	17.336.933 €	23.065.174 €	23.014.549 €	22.964.035 €	22.913.631 €	22.863.338 €	22.813.156 €
UK	1.647.808 €	5.518.184 €	8.315.691 €	11.139.045 €	11.190.740 €	11.242.676 €	11.294.852 €	11.347.271 €	11.399.933 €
Spain	964.517 €	3.233.956 €	4.879.448 €	6.544.172 €	6.582.639 €	6.621.332 €	6.660.252 €	6.699.400 €	6.738.779 €
Italy	1.454.372 €	4.851.368 €	7.282.247 €	9.716.594 €	9.723.531 €	9.730.473 €	9.737.420 €	9.744.372 €	9.751.328 €
Total	**17.555.590 €**	**58.788.579 €**	**88.591.220 €**	**118.670.710 €**	**119.224.441 €**	**119.782.857 €**	**120.345.994 €**	**120.913.890 €**	**121.486.582 €**

The peak sales are approximately $120 million

Optimistic Scenario in Nosocomial Diseases; Sales Forecasts

	2025	2026	2027	2028	2029	2030	2031	2032	2033
USA	21.091.748 €	70.907.720 €	107.272.149 €	165.892.122 €	181.861.236 €	183.418.164 €	184.988.420 €	186.572.120 €	188.169.378 €
France	5.591.544 €	18.696.789 €	28.132.922 €	43.272.099 €	47.182.036 €	47.329.642 €	47.477.711 €	47.626.242 €	47.775.238 €
Germany	9.287.088 €	30.889.013 €	46.231.822 €	70.733.201 €	76.715.163 €	76.546.782 €	76.378.771 €	76.211.128 €	76.043.853 €
UK	4.394.155 €	14.715.158 €	22.175.176 €	34.159.737 €	37.302.468 €	37.475.586 €	37.649.508 €	37.824.236 €	37.999.776 €
Spain	2.572.047 €	8.623.883 €	13.011.861 €	20.068.795 €	21.942.130 €	22.071.105 €	22.200.839 €	22.331.335 €	22.462.598 €
Italy	3.878.325 €	12.936.980 €	19.419.324 €	29.797.556 €	32.411.770 €	32.434.910 €	32.458.066 €	32.481.239 €	32.504.428 €
Total	**46.814.906 €**	**156.769.543 €**	**236.243.255 €**	**363.923.510 €**	**397.414.802 €**	**399.276.189 €**	**401.153.314 €**	**403.046.300 €**	**404.955.272 €**

The product has potential peak sales of approximately $400 million

Estimates Sales in Mastitis

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033
USA	166.282 €	556.618 €	838.458 €	1.291.073 €	1.691.131 €	1.698.283 €	1.705.466 €	1.712.679 €	1.719.923 €	1.727.197 €	1.734.503 €	1.741.839 €	1.749.206 €	1.756.604 €
Total EU	305.606 €	1.032.389 €	1.569.416 €	2.438.810 €	3.223.850 €	3.267.218 €	3.311.170 €	3.355.713 €	3.400.855 €	3.446.604 €	3.492.969 €	3.539.958 €	3.587.578 €	3.635.840 €
Total	**471.888 €**	**1.589.007 €**	**2.407.874 €**	**3.729.883 €**	**4.914.980 €**	**4.965.501 €**	**5.016.636 €**	**5.068.392 €**	**5.120.778 €**	**5.173.802 €**	**5.227.472 €**	**5.281.796 €**	**5.336.784 €**	**5.392.444 €**

The product has potential peak sales of approximately $5,2 million

Source: Bogdan & Villiger (2007) Valuation in Life Sciences: A Practical Guide, Springer

WORKING PATH or WORK PLAN:

Co-development agreement with an industrial partner

- Spin-off (in progress)
- Investor contacts start: Big Pharma. **Walking hand in hand from now. Negotiate with Pharma a workplan for mutual benefit. To design a working path with milestones and deliverables. Investments according to the delivery of the deliverables. To decide final clinical indications in each prototype**
- Complete preclinical phase according to clinical indications
- Move towards clinical phase with specific indications.

Source: Yan W. Nature Medicine. 2015. 21: 968-971

Thank you!