28 de abril de 2021

PA-0661 monoclonal antibody for the treatment of metastatic colorectal cancer

Juan Ignacio Imbaud

Ignacio Casal

Content

1. The Company
2. The Product
    a) Target Indications
    b) Innovative mechanisms of action
    c) Differential features facing the market
    d) Current status of development
    e) IPR protection
    f) Pitfalls & Risks to be considered
3. Partnering Opportunities

The Company: Protein Alternatives, a Spin-off company of CSIC

PROALT: founded in 2006 by researchers from the Spanish National Research Council (CSIC).
Technologies and patents incorporated from CSIC & CNIO.

Key Milestones Achieved

2006-Q2	• ProAlt is established
2006-Q3	• 1st Laboratory set up - **Scientific Park of Madrid**
2008-Q4	• Funding of €0.8M grant/loans
2009-Q4	• **In-license patent-1 CSIC (Diagnostics-Colorectal Ca)**
2010-Q3	• **In-license patent-2 CSIC (Diagnostics-Colorectal Ca)**
2010-Q4	• Own R&D laboratory set up **400 m²**
2010-Q4	• Funding €0.8M grant/loans
2011-Q3	• Funding €1.2M loan
2015-Q3	• Funding €2.3M EU grant
2015-Q3	• **In-license patent-3 CSIC (Therapeutics - mCRC)**
2019-Q3	• Funding €0.7M grant/loans (Therapeutic projects)
2020-Q1	• Funding €0.5M Eurostars grant (Lung Cancer diag.)
2021-Q1	• Funding €0.2M National grant (Therapeutics / CRC)

Tres Cantos, Madrid

Protein Alternatives Activity

The company is structured in three main business areas:

PROALT PROTEIN ALTERNATIVES

PRODUCTS-CRO/CMO

Sales of own manufactured recombinant proteins and antibodies, and the offer of customer tailored services in protein & antibodies design, development and manufacturing.

DIAGNOSTICS

Focused on **biomarkers** discovery, validation and usage for the development of minimally invasive **diagnostic tests for early diagnosis** of colorectal (CRC) and lung cancer (LC).

COLODETECT

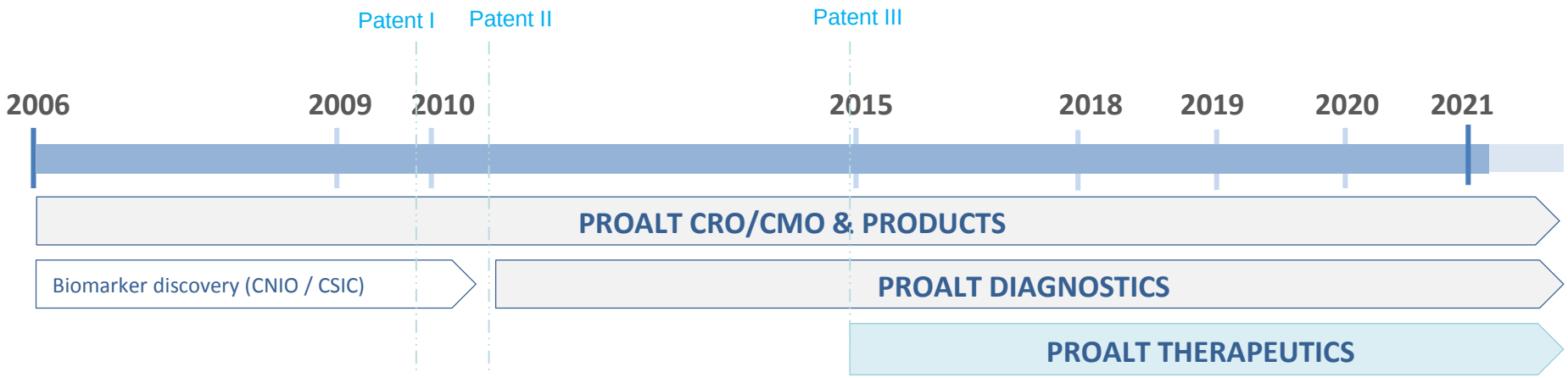
PROFILUX

THERAPEUTICS

Dedicated to the design, development and manufacturing of **therapeutic monoclonal antibodies against novel targets in oncology**, with focus on metastatic tumors.

CDH17_RGD

IL13Ra2



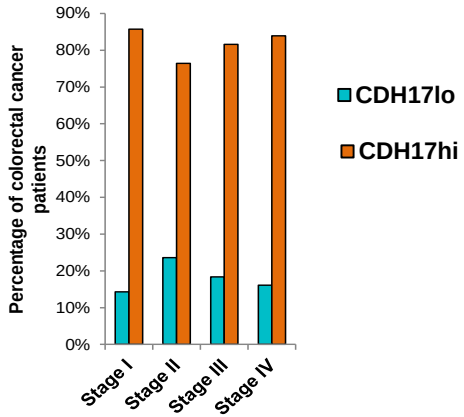
The product: PA-0661 monoclonal antibody targeting CDH17 RGD

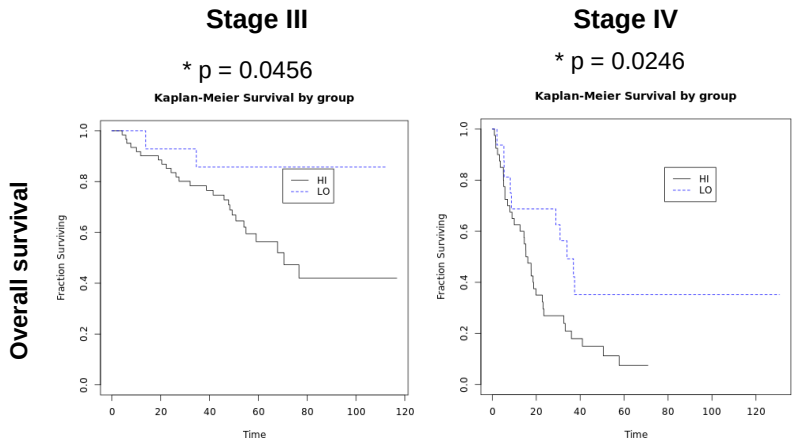
a) Target Indications

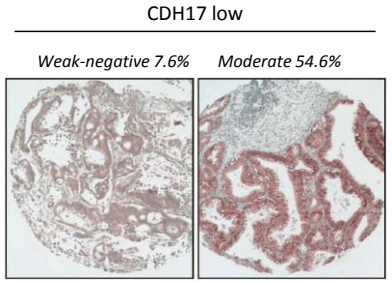
Metastatic colorectal cancer (mCRC) is often **highly aggressive** and has **poor treatment options** at this point. The high incidence of mCRC (>40% of CRC diagnosed cases) and high mortality rates indicate that new druggable targets and therapeutic agents are urgently needed to improve survival prospects of mCRC patients.

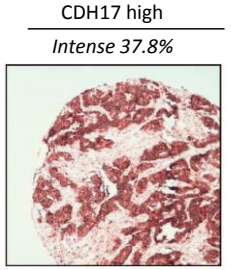
Cadherin 17 (CDH17), also known as LI-Cadherin, which is overexpressed in mCRC cells, has been discovered recently as a novel target. In particular, the **RGD tripeptide motif** (Arg-Gly-Asp) in CDH17 has been identified as a **key factor for α2β1 integrin-mediated metastasis formation** at distal organs.

GSE17538-GPL570
232 tumor samples





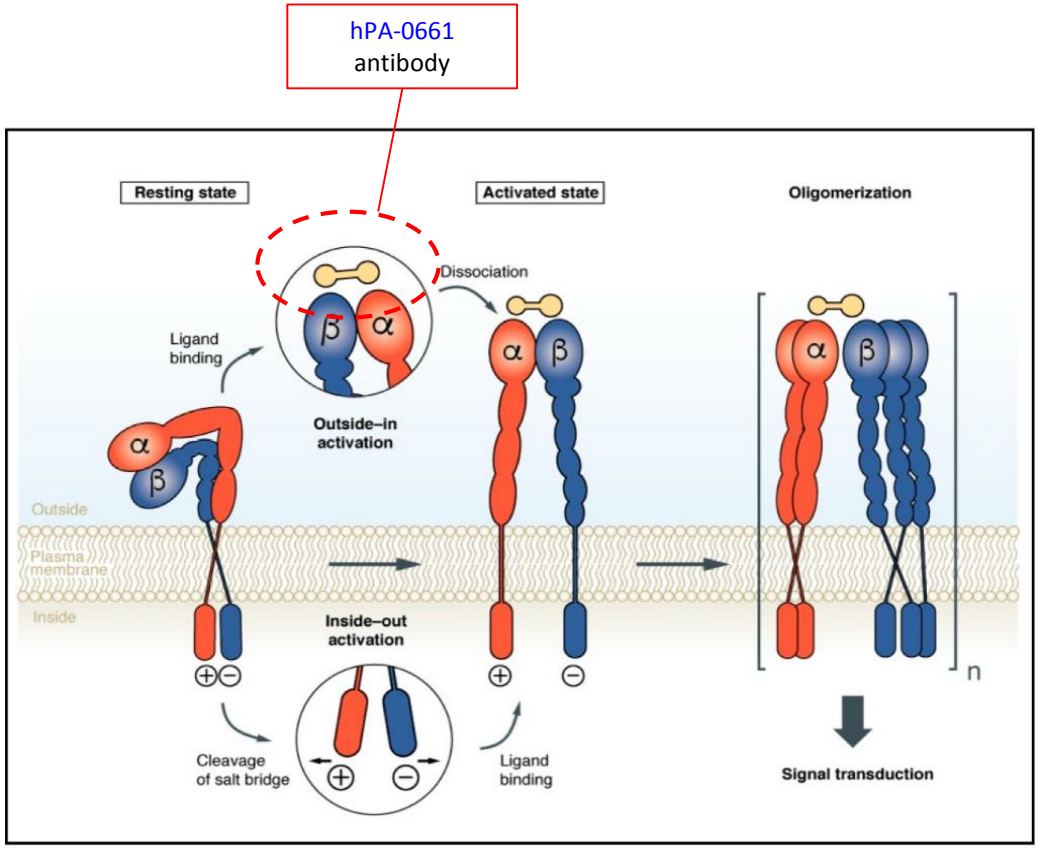




Newly generated **anti-CDH17_RGD specific mAbs** turned out to be very efficacious, improving survival in a challenging **mCRC *in vivo* model** by blocking CDH17/α2β1 integrin interaction.

The product: PA-0661 monoclonal antibody

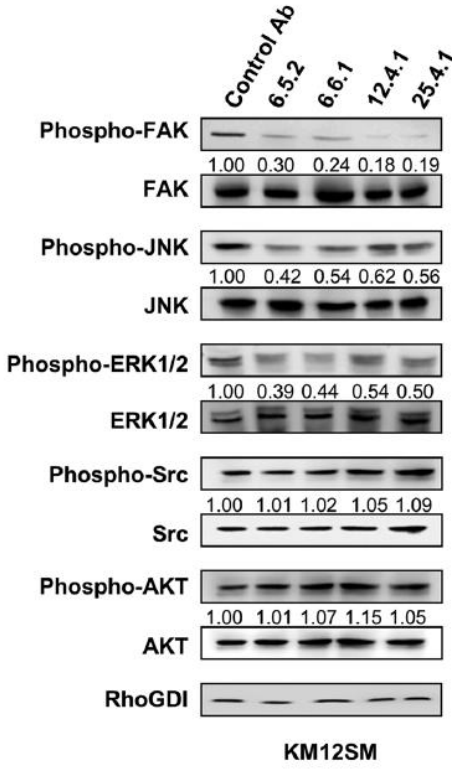
b) Innovative mechanisms of action



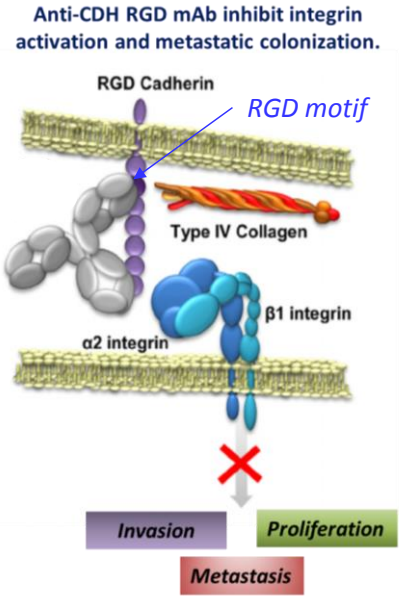
Schematic illustration of integrin activation and the "inside-out" and "outside-in" signaling mechanism [2] **.**

Nieberler et al., Cancers 2017, 9, 11
Mas-Moruno et al., Angew. Chem. Int. Ed. 2016, 55, 7048–7067. [2]

In **KM12SM colon cancer cells**, the anti cadherin-RGD monoclonal antibodies diminished the activation of FAK, JNK, and ERK kinases, which correlate with a **decrease in cell adhesion and proliferation**, but they did not affect Src or AKT activation.



hPA-0661
a-CDH17 RGD

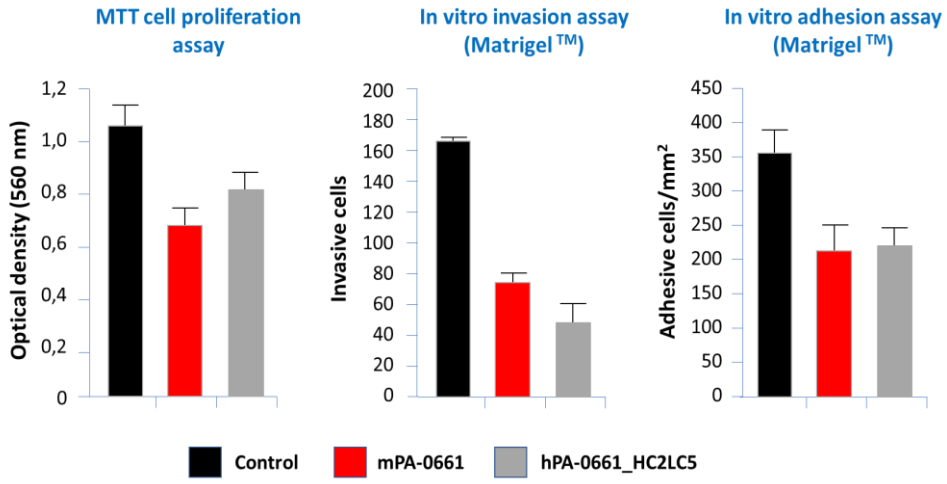


Bartolomé et al., (2018). Clinical Cancer Research, 24(2), 433-444.
Casal and Bartolomé (2018). BBA-Reviews on Cancer, 1869(2), 321-332.

The product: PA-0661 monoclonal antibody

In vitro Data

The humanized antibody hPA-0661 reproduced the excellent activity of its murine counterpart mPA-0661 in *in vitro* cell adhesion, invasion and proliferation assays.

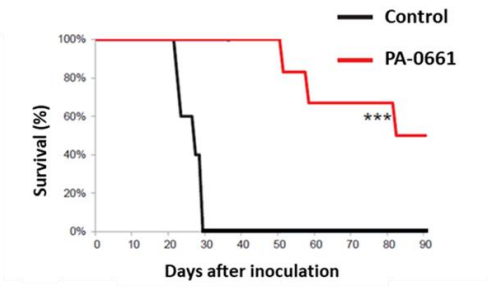


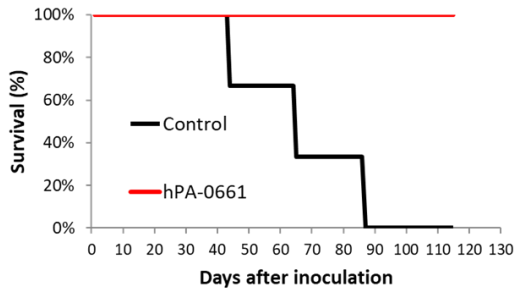
In vivo Data

mCRC orthotopic intra-splenic injection model

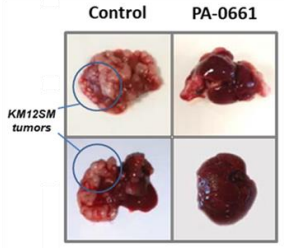
PA-0661 (murine & humanized) significantly improved survival rates of all treated animals and avoided metastasis formation in 50% of the treated individuals in the metastatic CRC tumor model

Kaplan – Meier Survival Results

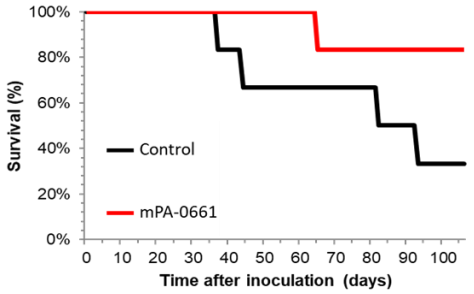




Representative pictures of livers after necropsy



Established tumor model (Delayed treatment)



Bartolomé et al., (2018). Clinical Cancer Research, 24(2), 433-444.

The product: PA-0661 monoclonal antibody

c) Differential features facing the market

Main competitors *Avastin®, Erbitux®* and *Vectibix®,* currently used for metastatic colorectal cancer treatment, had global sales of 7,936M € in 2018.

Vectibix®/Panitumumab (Amgen)

Avastin®/Bevacizumab (Roche)

Erbitux®/Cetuximab (MSD/Lilly)

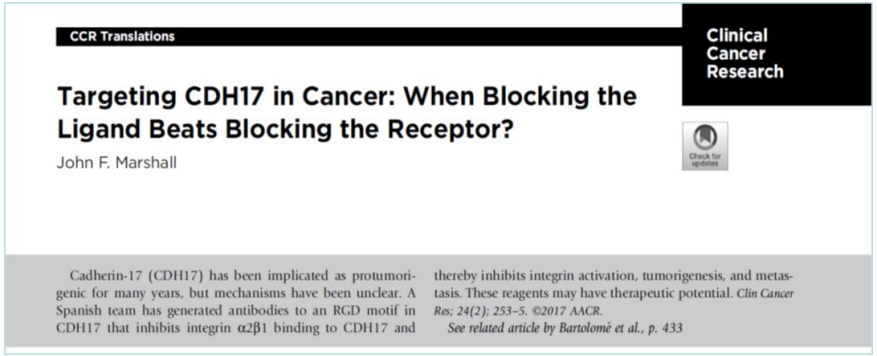
- **First-in-class**

The discovery of RGD motifs in cadherins (novel target) and their critical role in the **activation of integrins** (different MOA) that promotes **cell migration, adhesion, proliferation** and **metastasis formation** represent an original and promising therapeutic approach.

Avoiding the activation of an integrin-mediated cell signaling pathway through anti cadherin-RGD specific antibodies, represents a new and unique mechanism of action for the treatment a metastatic tumours, different from the mode of action of therapeutic monoclonal antibodies currently on the market (anti-VEGF, anti angiogenic; anti-EGFR, cell growth and division).

Unique mode of action: Binding the Ligand-Receptor structure.

The strategy of blocking the ligand instead of blocking the receptor was rightfully recognized in an editorial article of *Clinical Cancer Research* journal, where the author referred to the latest publication of Dr Casal about anti CDH17-RGD antibodies.



CCR Translations

Clinical Cancer Research

Targeting CDH17 in Cancer: When Blocking the Ligand Beats Blocking the Receptor?

John F. Marshall

Cadherin-17 (CDH17) has been implicated as protumorigenic for many years, but mechanisms have been unclear. A Spanish team has generated antibodies to an RGD motif in CDH17 that inhibits integrin α2β1 binding to CDH17 and thereby inhibits integrin activation, tumorigenesis, and metastasis. These reagents may have therapeutic potential. *Clin Cancer Res; 24(2): 253–5. ©2017 AACR.*

See related article by Bartolomé et al., p. 433

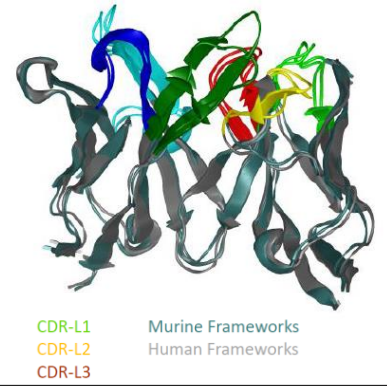
The product: PA-0661 monoclonal antibody

d) Current status of development

The **humanized version of the monoclonal antibody** has been generated (hPA-0661_HC2LC5), which showed a similar or improved potency in all *in vitro* assays compared to the murine counterpart and an excellent activity in the mCRC animal model.

The **preclinical and clinical development of hPA-0661** will be a relevant contribution for the improvement of the present existing therapies for mCRC. Alone or in synergy with the current treatment regimens, it could contribute significantly to reduce mortality rates of patients.

PA-0661 antibody: structural comparisons of the humanized to the murine variable domain structure



PRECLINICAL DEVELOPMENT STAGE REQUIRES UP TO 6 M€ OF INVESTMENT:

ACTIVITY	YEAR 1	YEAR 2	Investment (€)
1. Cell Line Development and Complementary studies in animals			600.000
Milestone: manufacturing cell bank; bioimaging animal models; combined treatments; preliminary Tox			
2. GMP development Part-I			2.900.000
Milestone: release of the Tox/Safety pre-GMP batch			
3. Preclinical PK / PD / Tox studies			1.000.000
Milestone: studies in monkeys (or minipigs) completed			
4. GMP development Part-II			1.500.000
Milestone: GMP batch released (to be used in Phase I/II clinical trial); CTA / IND filed			
		TOTAL INVESTMENT	**6.000.000**

The product: PA-0661 monoclonal antibody

e) IPR protection

APPLICANT / INVENTORS

CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

CASAL ÁLVAREZ, José Ignacio – Centro de Investigaciones Biológicas (CIB)

TITLE

AGENTS BINDING SPECIFICALLY TO HUMAN CADHERIN-17 AND/OR CADHERIN 5, 6, 20, AND METHODS AND USES THEREOF

SUMMARY

The invention relates to agents binding specifically to human cadherin 17 (CDH17), and/or CDH5, and/or CDH6, and/or CDH20 and relates to the use of these agents in therapy and pharmaceutical compositions comprising said agents.

STATUS

- International Application No. **PCT/EP2015/058527** (Filed 22 April 2015 and published in October 2016); extended to US, CA, AU and JP.
- Granted in Europe and EEUU.
- Filed in Australia and Canada.
- Abandoned in Japan (new patent application with the humanized sequence to be prepared)

THERAPEUTICS PATENT FAMILY
(Priority 2015)

Reference	Country	Status
EP3286218	Europe	Granted
2,980,495	Canada	Filed
2015392603	Australia	Filed
15/565,937	EEUU	Granted

Patent agents:

Spain

Canada

EEUU

Australia

The product: PA-0661 monoclonal antibody

f) Pitfalls & Risks to be considered

Urgent medical need: mCRC has still a critical prognosis with a 5-year survival rate of <15%.

RISK	PROBABILITY	BACKGROUND INFORMATION
Production	Low	Formulation; Stability & Aggregation studies. **>50 monoclonal antibody products already approved** in US and Europe for several diseases.
Target & MOA validation	Low	**Exhaustive pre-clinical target validation.** Use of *in vitro* cell-based models, patient-derived xenograft and metastasis specific murine models validated the target and provided solid information about the MOA.
Safety	Low	Unwanted side effects not expected due to organ specific presence of target (CDH17/α2β1). **No signs of side effects observed in studies conducted in animals. Monos y cerdos**
Competitors	Low	Proven interest of big pharma companies in cadherin targets but no advanced competition at this point (CDH3 and CDH6 therapeutic mAbs developed by Pfizer, Novartis and Fujifilm are in Phase I). **No Cadherin RGD specific drugs under development.**

Partnering Opportunities

PROALT is looking for financing (Private Investors, 6 M€) or co-development partners to conduct the preclinical development of hPA-0661 and to move forward its pipeline projects related to other RGD cadherins (CDH5, CDH6 and CDH16) associated to different metastatic tumors (ovary, renal, melanoma…).

Contact Information

www.proteinalternatives.com

Juan Ignacio Imbaud, PhD
Chief Operating Officer

✉ jimbaud@proteinalternatives.com

☎ +34 91 804 73 22

www.cib.csic.es

Ignacio Casal
Company Founder

✉ icasal@cib.csic.es

☎ +34 91 837 3112 Ext: 4363