

**VIP (Vasoactive Intestinal Peptide) serum levels as  
prognostic biomarker in patients with rheumatoid arthritis  
and other autoimmune disorders**



Madrid, 27 de noviembre de 2013



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# The Institutions



Cellular Biology Departments.  
Biology and Medicine Schools.



Servicio de Reumatología. IIS-IP

- **Scope:**

- Role of VIP and its receptors in the Immune system

- **Main achievements:**

- 90's: VIP expression on immune system
- 2000-2005: Immunoregulatory role of VIP on murine models
- 2005 – : Immunoregulatory role of VIP on human.
  - VIP expression on human cells (synoviocytes, lymphocytes).
  - “In vitro” models

- **Scope:**

- Pathogenesis, biomarkers, biologic therapies in autoimmune disorders

- **Main achievements:**

- Basic research on inflammation since 80's: CD69, IL15,...
- Traslational research:
  - Early arthritis register: 2000 –
  - Biological Therapy Unit
  - Early spondyloarthritis register: 2005 –
- Epidemiological research (SER):
  - BIOBADASER, emAR, EMECAR, RELESSER

## Role of VIP in human rheumatic disorders



# The Institutions

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## RIER: Red de Inflamación y Enfermedades Reumáticas (Inflammation and Rheumatic Disorders Network)

- ✓ Funded by ISCIII: RD08/0075, RD12/0017
  - ✓ Measurement of VIP serum levels in patients with early arthritis, ankylosing spondylitis and SLE
  - ✓ Genetic expression of VIP, VPAC1 & VPAC2 in PBL from EA.
  - ✓ Genetic variability of VIP in rheumatic disorders.
  - ✓ Study of synovial fibroblasts



# Immune-modulatory properties of VIP



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## Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease

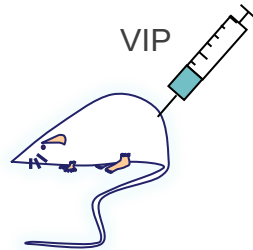
MARIO DELGADO, CATALINA ABAD, CARMEN MARTINEZ, JAVIER LECETA & ROSA P. GOMARIZ

Department Cell Biology, Faculty of Biology, Complutense University, Madrid, Spain  
Correspondence should be addressed to M.D.; email: mariodm@eucmos.sim.ucm.es

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease of unknown etiology, characterized by chronic inflammation in the joints and subsequent destruction of the cartilage and bone. We describe here a new strategy for the treatment of arthritis: administration of the neuropeptide vasoactive intestinal peptide (VIP). Treatment with VIP significantly reduced incidence and severity of arthritis in an experimental model, completely abrogating joint swelling and destruction of cartilage and bone. The therapeutic effect of VIP was associated with downregulation of both inflammatory and autoimmune components of the disease. Our data indicate VIP as a viable candidate for the development of treatments for RA.

Crohn disease  
Sepsis

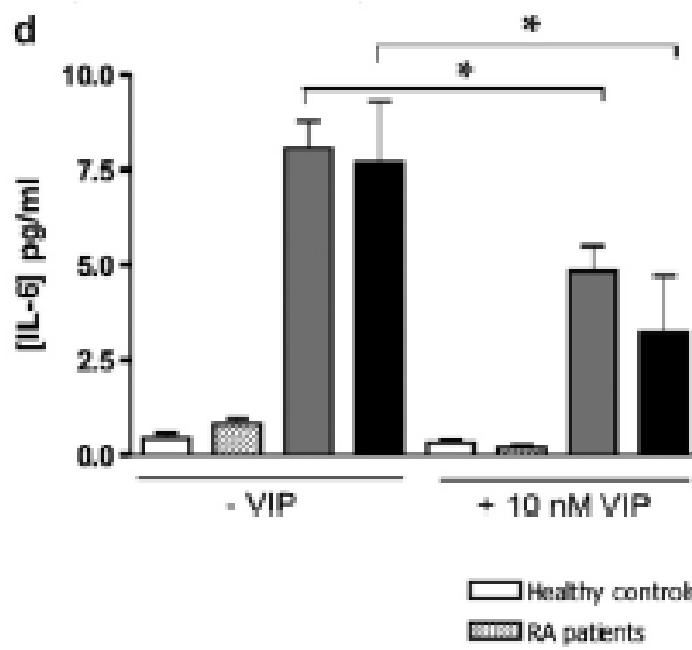
## ✓ VIP ameliorates murine CIA



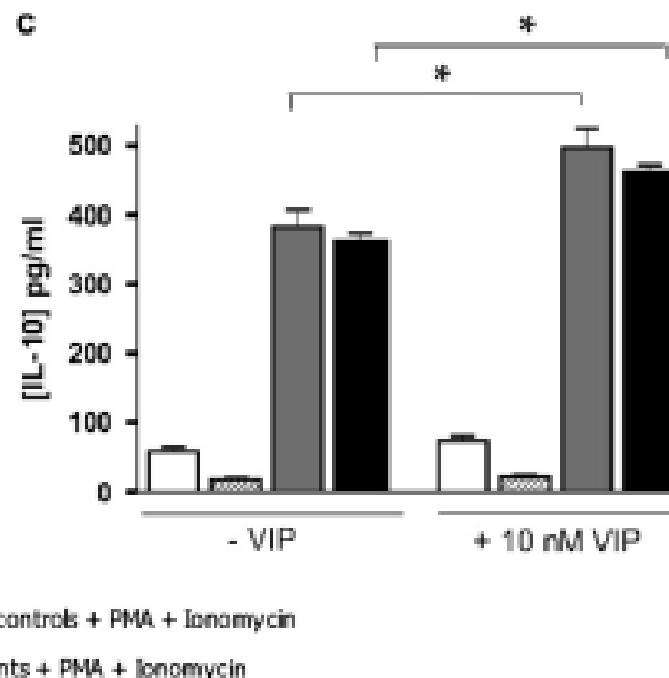
- Decreases incidence
- Decreases severity
- Regulates Th1 / Th2 balance
- Inhibits joint damage

# Immune-modulatory properties of VIP

VIP decreases pro-inflammatory cytokine production

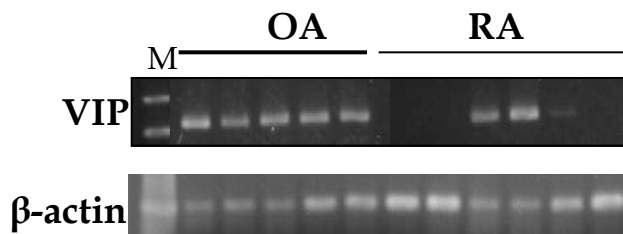


VIP increases anti-inflammatory cytokine production

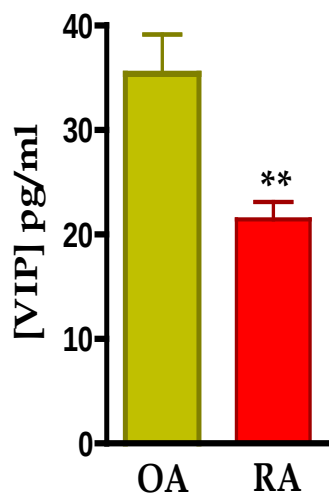
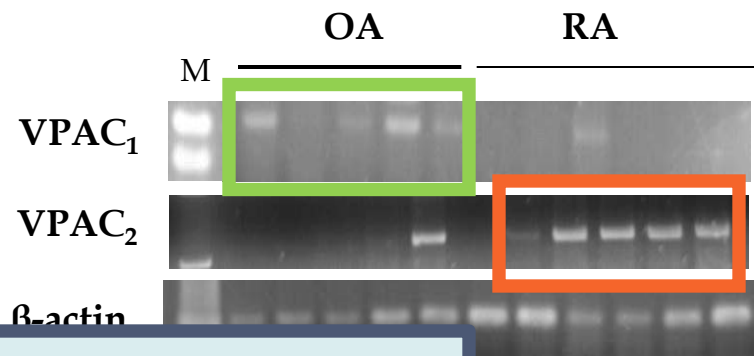


# Immune-modulatory properties of VIP

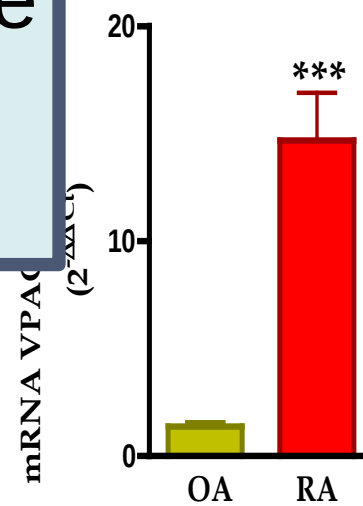
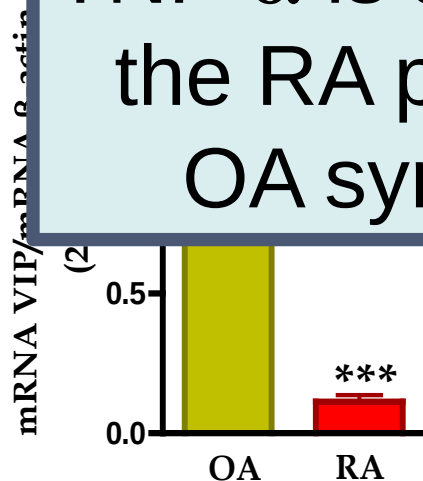
VIP expression on human synoviocytes



Expression of VIP receptors on human synoviocytes



TNF- $\alpha$  is able to induce the RA phenotype in OA synoviocytes



$\beta$ -actin: charge control

# The Product



# The Product

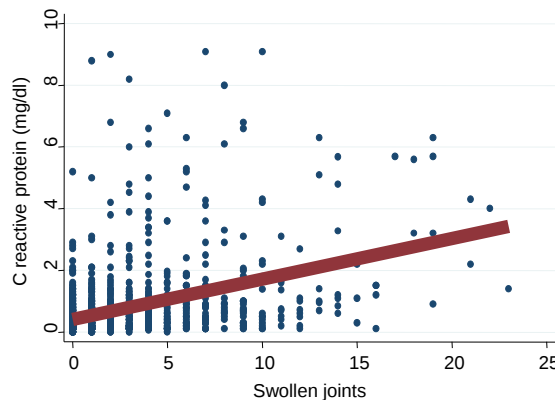
## DIAGNOSIS BIOMARKER



RF, ACPA



## PROGNOSIS BIOMARKER



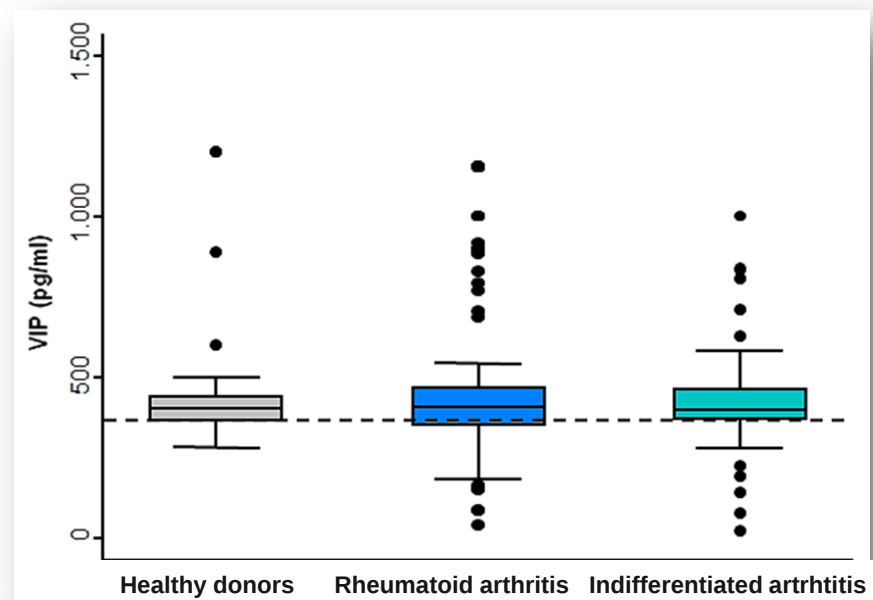
## DISEASE ACTIVITY BIOMARKER

# The Product: Innovative MoA

VIP is not a  
DIAGNOSIS BIOMARKER

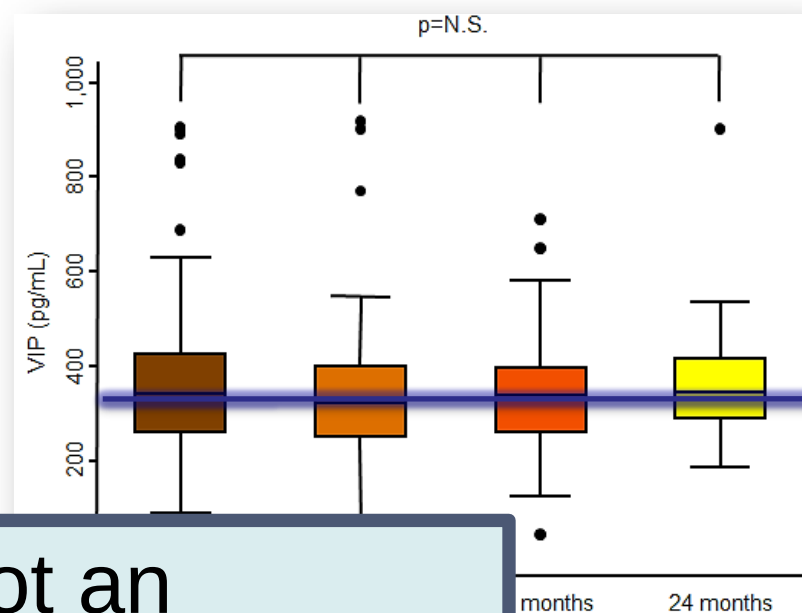
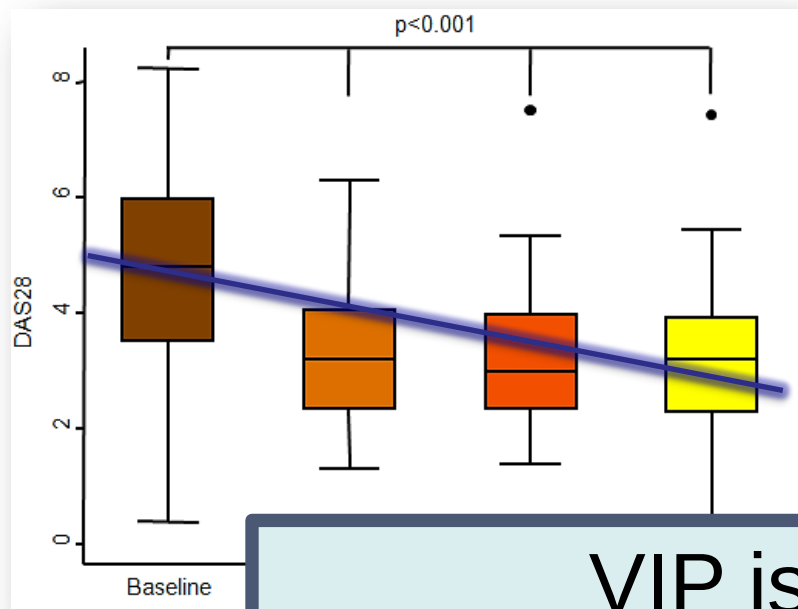
## Population

- ✓ 100 healthy blood donors
- ✓ 91 patients with early arthritis:



# The Product: Innovative MoA

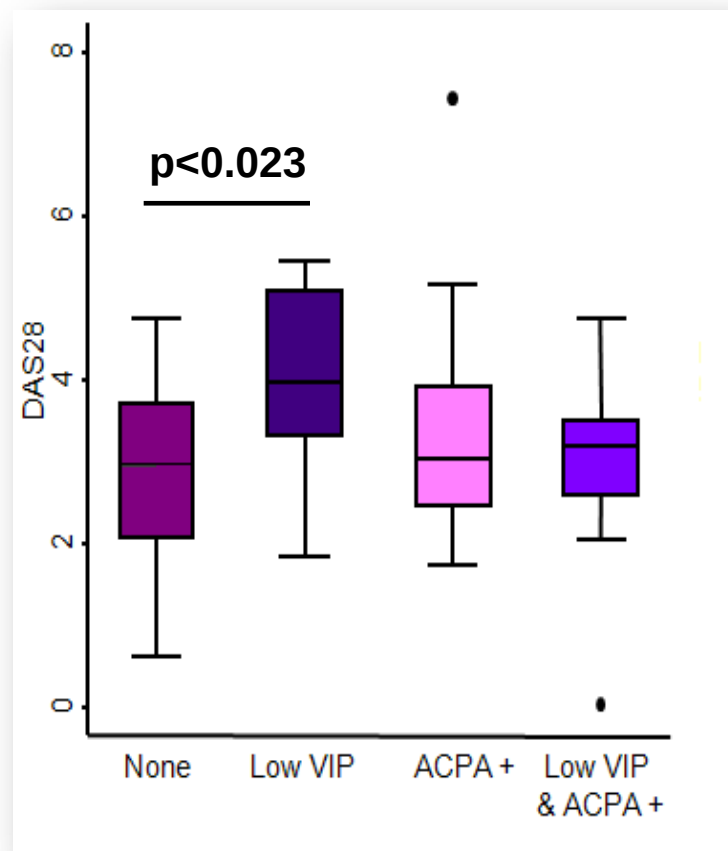
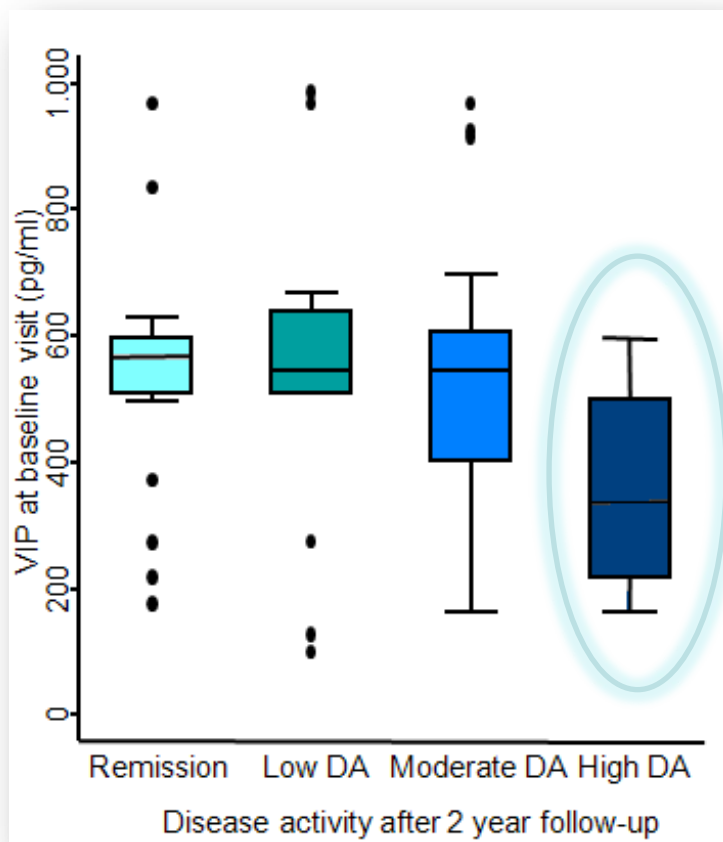
Unlike disease activity, VIP serum levels did not decrease over the follow-up



VIP is not an  
DISEASE ACTIVITY  
BIOMARKER

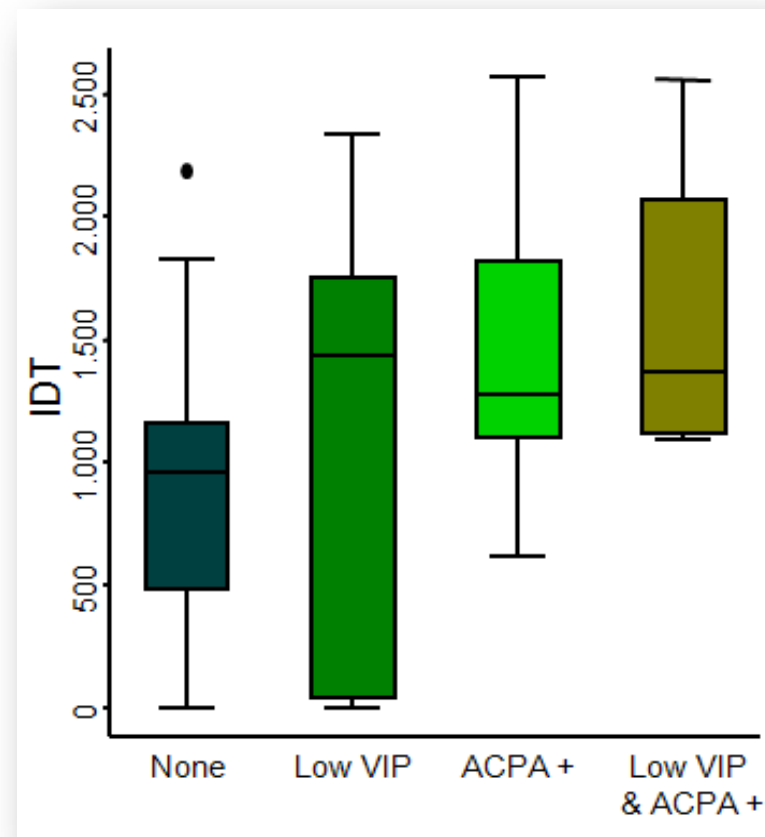
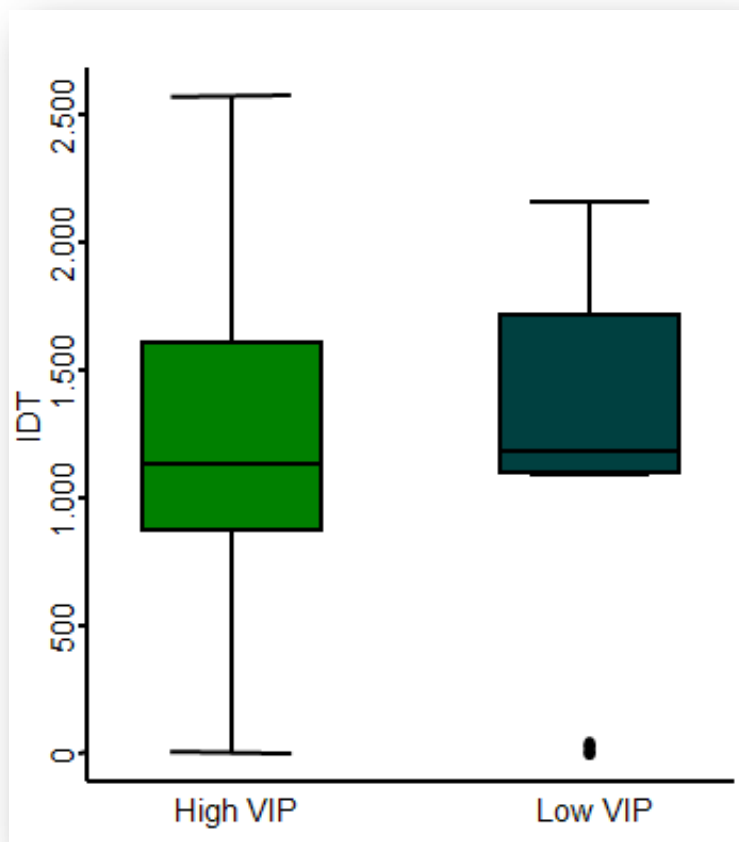
# The Product: Innovative MoA

Low baseline VIP levels negatively correlated with disease activity.  
Interaction with ACPA positivity

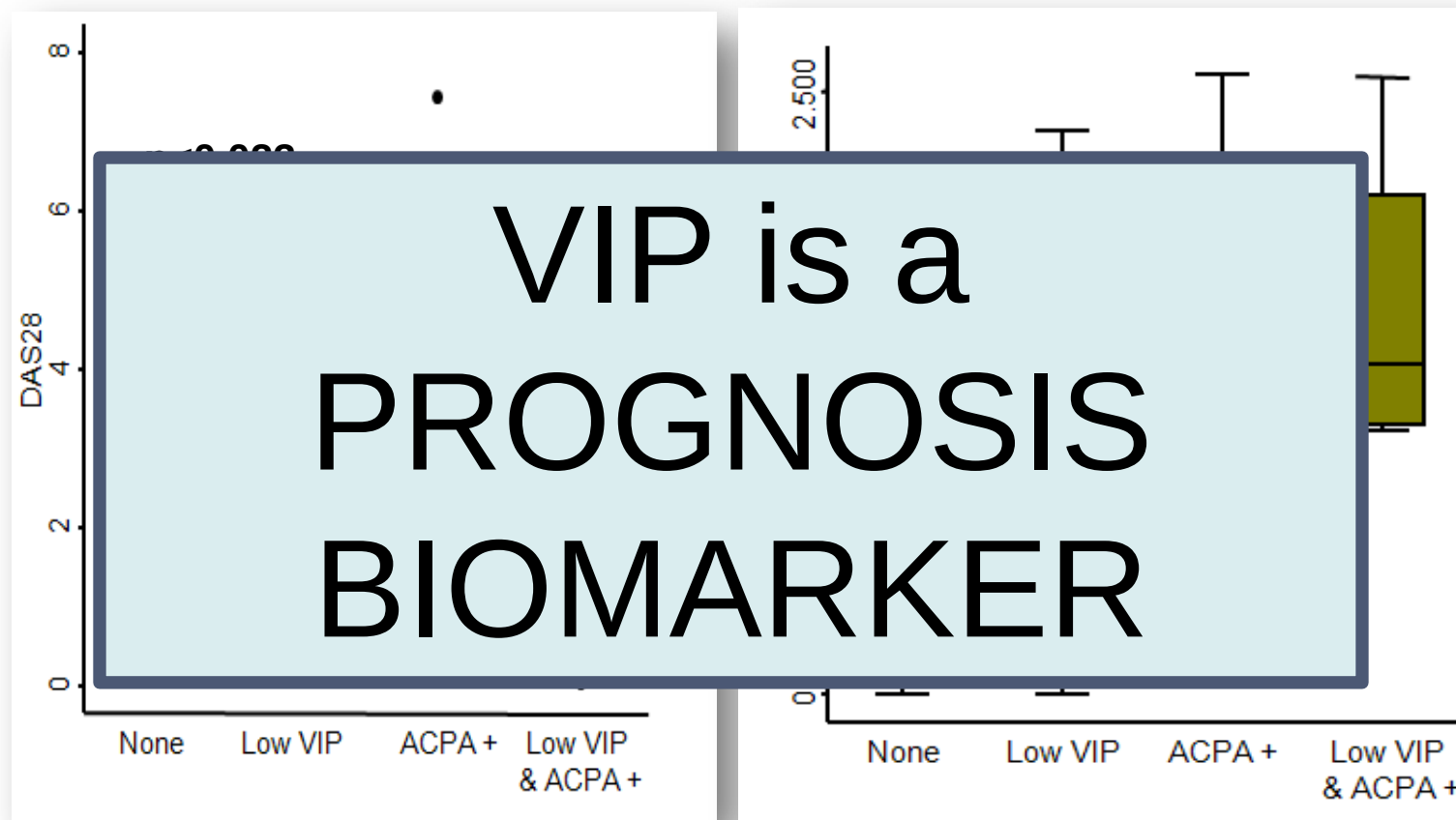


# The Product: Innovative MoA

Low baseline VIP levels is associated with a higher intensity of DMARD treatment (IDT).  
Interaction with ACPA positivity



# The Product: Innovative MoA



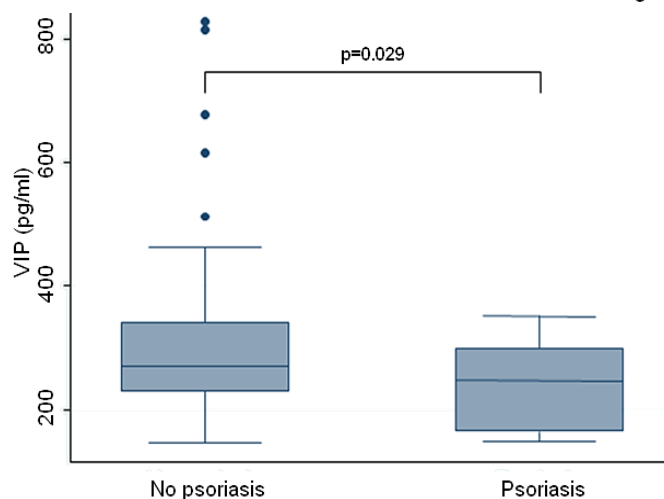
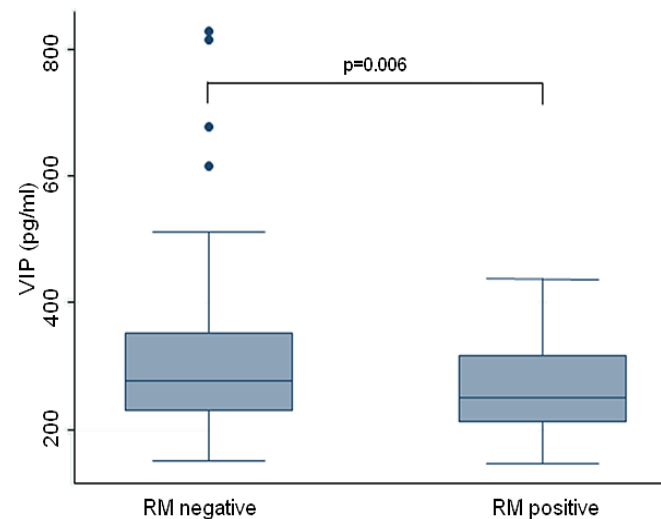
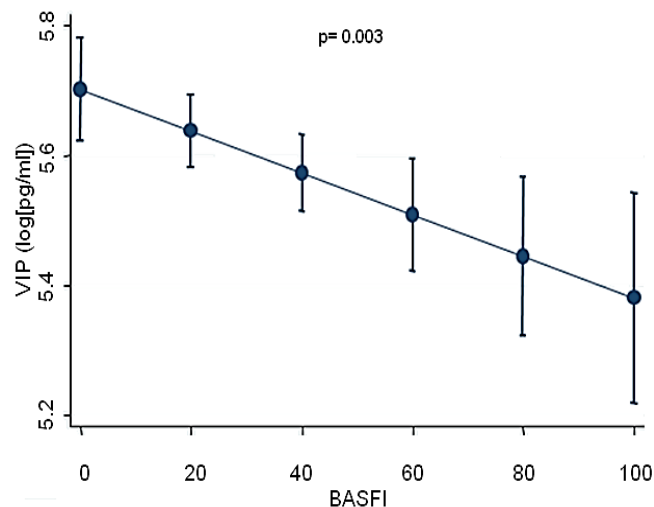
# The Product: Target Indications

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- ✓ Immune-mediated inflammatory disorders (IMID)
  - ✓ Rheumatoid Arthritis
  - ✓ Ankylosing Spondylitis
  - ✓ Psoriasis
  - ✓ Systemic lupus erythematosus?
  - ✓ Inflammatory bowel disease?

# The Product: Target Indications

## ✓ Early Spondyloarthritis Register



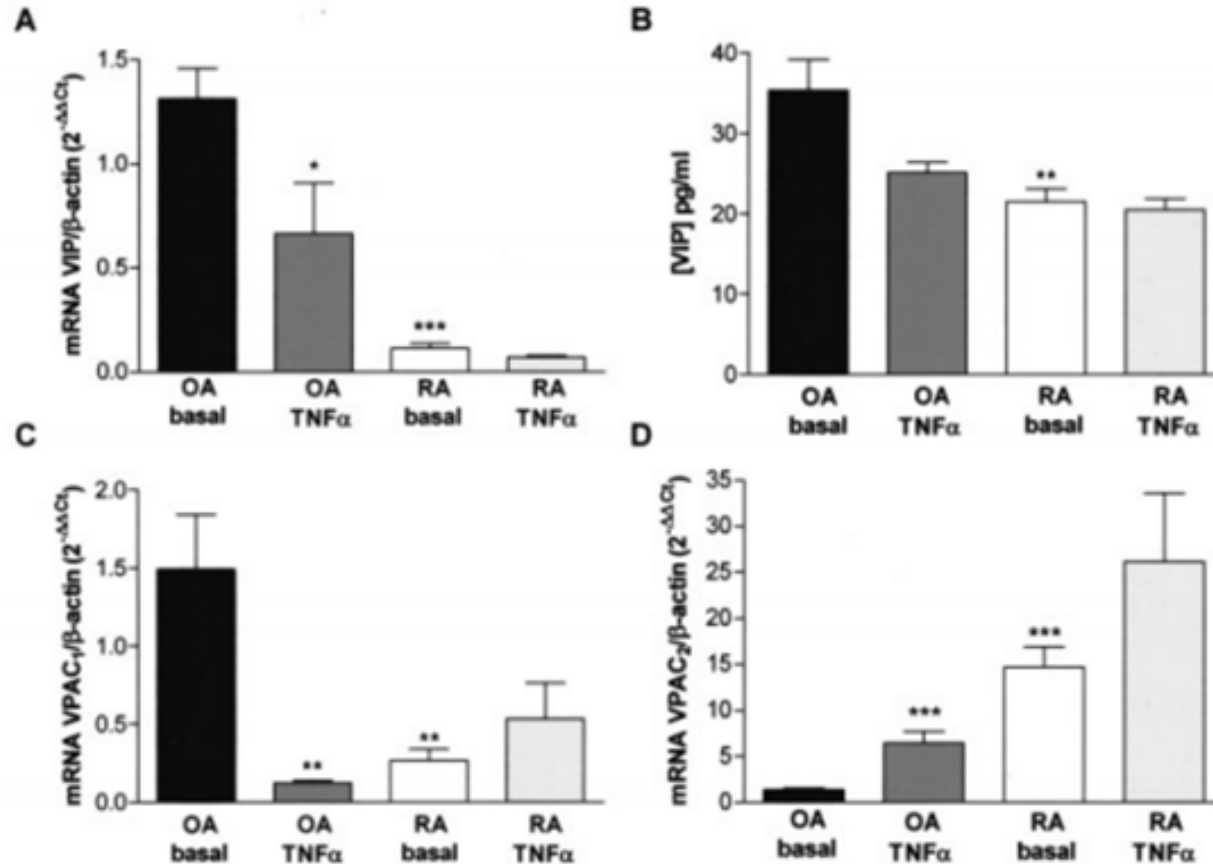
# The Product: Features facing the markets

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- ✓ **IMID severity biomarker** (broader target population)
  - ✓ Rheumatoid arthritis
    - ✓ VIP improves the prognostic value of ACPA
    - ✓ Selection of candidates for more intense treatment
      - ✓ Early biologic therapy indication:
        - ✓ Marker for **TNF-blocker** prescription
  - ✓ Ankylosing spondylitis
    - ✓ No prognostic biomarkers already defined
    - ✓ Selection of candidates for **TNF-blockers**

# The Product: Features facing the markets

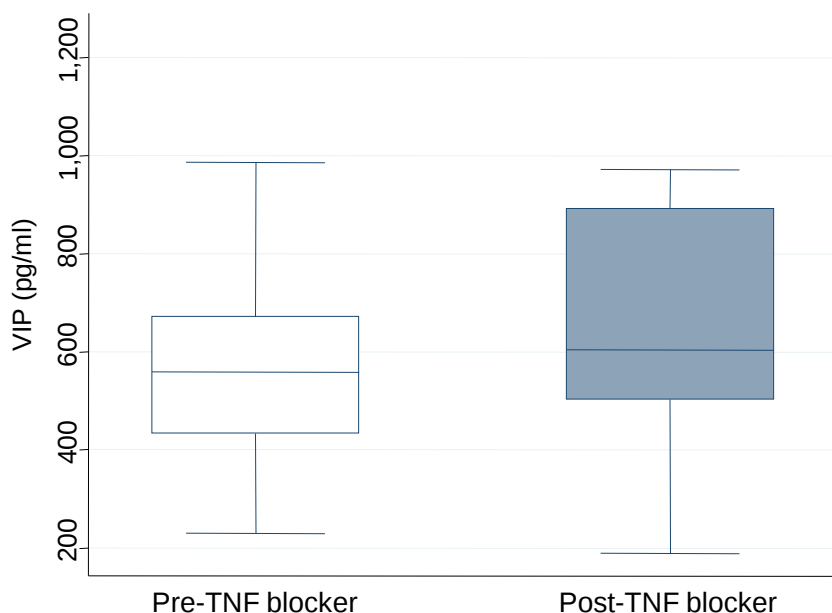
TNF- $\alpha$  is able to induce the RA phenotype in OA synoviocytes



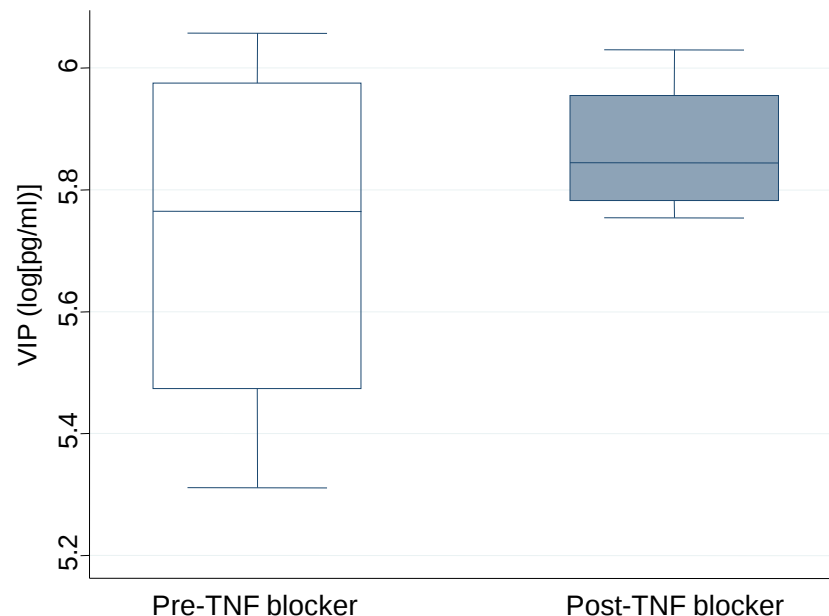
# The Product: Features facing the markets

Treatment with TNF-blockers increases VIP serum levels

Rheumatoid arthritis



Ankylosing spondylitis



# The Product: Features facing the markets

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- ✓ **IMID severity biomarker** (broader target population)
- ✓ IMID's prevalence is about 15% of population:
  - ✓ Thyroid autoimmune disorders, Psoriasis, RA, IBD, AS,...
- ✓ Biologic therapy in IMID
  - ✓ RA and AS about 20-30% of cases.
  - ✓ Psoriasis & IBD slightly lower.
  - ✓ SLE & Thyroid autoimmune disorders starting
- ✓ VIP measurement: several kits already available.
- ✓ Validation clinical data in all IMID: 2-3 years.

# The Product: Current status of development

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- Rheumatoid arthritis
  - ✓ Disease activity and needs for aggressive treatment
    - Validation in other cohorts: RIER
  - Radiological damage: RIER, Leyden cohort
  - Mortality
- Ankylosing spondylitis
  - Disease activity and needs for aggressive treatment
  - Radiological damage
- Other IMID: **SLE**, Psoriasis, IBD.

# The Product: IPR protection



MINISTERIO  
DE INDUSTRIA, TURISMO  
Y COMERCIO



Oficina Española  
de Patentes y Marcas

## TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES NOTIFICACIÓN DE LA RECEPCIÓN DE LOS DOCUMENTOS QUE CONSTITUYEN SUPUESTAMENTE UNA SOLICITUD INTERNACIONAL PRESENTADA DE FORMA ELECTRÓNICA.

### (Instrucciones Administrativas del PCT, Parte Séptima)

- 1.-Se notifica al solicitante que la Oficina Receptora ha recibido en la fecha de recepción indicada más abajo, los documentos que supuestamente constituyen una solicitud internacional.
- 2.-Se llama la atención del solicitante sobre el hecho de que la Oficina Receptora no ha comprobado aún si estos documentos satisfacen las condiciones del art. 11.1, es decir, si cumple los requisitos para que le sea atribuida una fecha de presentación internacional. En cuanto la Oficina Receptora haya comprobado los documentos, avisará al solicitante.
- 3.-El número de la supuesta solicitud internacional indicado más abajo ha sido otorgado automáticamente a estos documentos. Se invita al solicitante a mencionar este número en toda la correspondencia con la Oficina Receptora.

|                                                        |                                                                                   |
|--------------------------------------------------------|-----------------------------------------------------------------------------------|
| Número de presentación                                 | 300092919                                                                         |
| Solicitud Número PCT                                   | PCT/ES2013/070347                                                                 |
| Fecha de recepción                                     | 30 mayo 2013                                                                      |
| Oficina Receptora                                      | Oficina Española de Patentes y Marcas, Madrid                                     |
| Referencia del expediente del solicitante o mandatario | PCT1595.41                                                                        |
| Solicitante                                            | FUNDACIÓN DE INVESTIGACIÓN BIOMÉDICA DEL HOSPITAL UNIVERSITARIO LA PRINCESA (51%) |
| Número de solicitantes                                 | 2                                                                                 |
| País                                                   | ES                                                                                |
| Título de la invención                                 | USO DE VIP COMO MARCADOR PRONÓSTICO DE ENFERMEDADES AUTOINMUNES                   |

PCT1595.41

1/5

### PETITORIO PCT

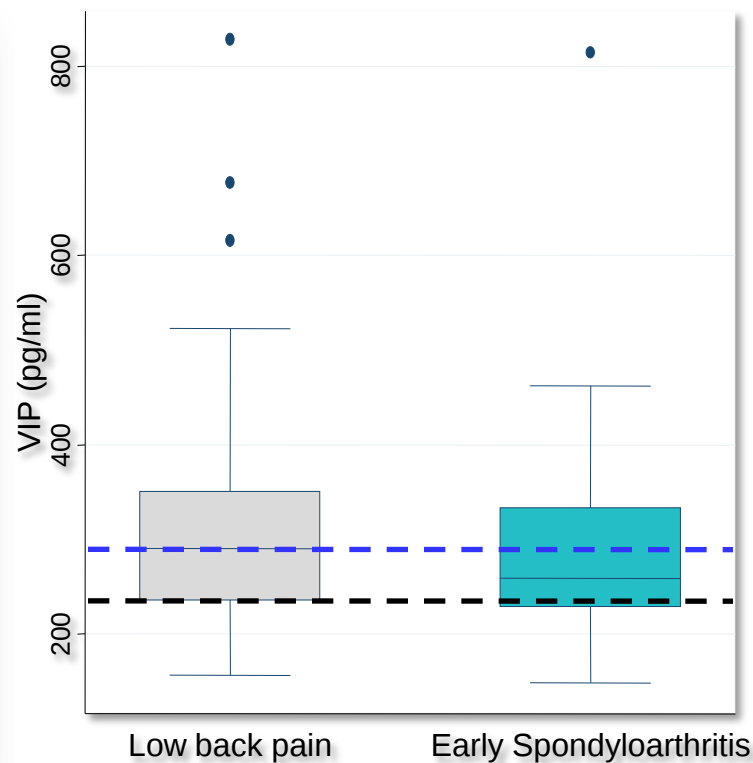
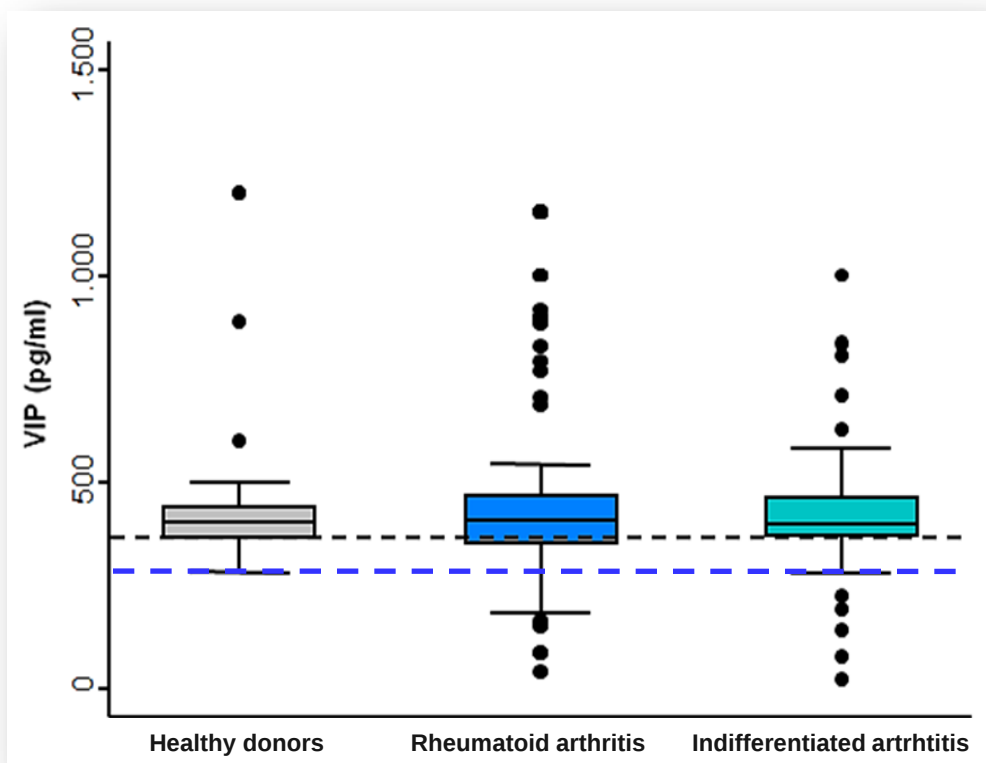
Impresión (original en formato electrónico)

|         |                                                                |                                                                                                                                           |
|---------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 0       | Para uso de la oficina receptora únicamente                    |                                                                                                                                           |
| 0-1     | Solicitud internacional No.                                    |                                                                                                                                           |
| 0-2     | Fecha de presentación internacional                            |                                                                                                                                           |
| 0-3     | Nombre de la Oficina receptora y "Solicitud Internacional PCT" |                                                                                                                                           |
| 0-4     | Formulario PCT/RO/101 Petitorio PCT                            |                                                                                                                                           |
| 0-4-1   | Preparado usando                                               | PCT Online Filing<br>Version 3.5.000.232 MT/FOP<br>20020701/0.20.5.20                                                                     |
| 0-5     | Petición                                                       | El abajo firmante pide que la presente solicitud internacional sea tramitada con arreglo al Tratado de Cooperación en materia de Patentes |
| 0-6     | Oficina receptora (indicada por el solicitante)                | Oficina Española de Patentes y Marcas (RO/ES)                                                                                             |
| 0-7     | Referencia al expediente del solicitante o del mandatario      | PCT1595.41                                                                                                                                |
| I       | Título de la invención                                         | USO DE VIP COMO MARCADOR PRONÓSTICO DE ENFERMEDADES AUTOINMUNES                                                                           |
| II      | Solicitante                                                    |                                                                                                                                           |
| II-1    | Esta persona es:                                               | Solicitante únicamente                                                                                                                    |
| II-2    | Solicitante para                                               | Todos los Estados designados                                                                                                              |
| II-4    | Nombre                                                         | FUNDACIÓN DE INVESTIGACIÓN BIOMÉDICA DEL HOSPITAL UNIVERSITARIO LA PRINCESA (51%)                                                         |
| II-5    | Dirección                                                      | C/ Diego de León, 62<br>28006 MADRID<br>España                                                                                            |
| II-6    | Estado de nacionalidad                                         | ES                                                                                                                                        |
| II-7    | Estado de domicilio                                            | ES                                                                                                                                        |
| III-1   | Solicitante y/o inventor                                       |                                                                                                                                           |
| III-1-1 | Esta persona es:                                               | Solicitante únicamente                                                                                                                    |
| III-1-2 | Solicitante para                                               | Todos los Estados designados                                                                                                              |
| III-1-4 | Nombre                                                         | UNIVERSIDAD COMPLUTENSE DE MADRID (49%)                                                                                                   |
| III-1-5 | Dirección                                                      | C/ Donoso Cortés, 65, 1º<br>28015 MADRID<br>España                                                                                        |
| III-1-6 | Estado de nacionalidad                                         | ES                                                                                                                                        |
| III-1-7 | Estado de domicilio                                            | ES                                                                                                                                        |



# The Product: IPR protection

The protection refers to the definition of low VIP levels.  
All cut-offs below the 50<sup>th</sup> percentile of a healthy population has been protected.  
Irrespective of the assessment assay.



# The Product: Pitfalls & Risks

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- ✓ High inter-assay variability. High serum volumes required.
  - ✓ Adapting the kits to human diagnosis requirements
- ✓ Validation in other early arthritis cohorts
  - ✓ The necessity to find similar cohorts
- ✓ Ankylosing spondylitis
  - ✓ Few prospective early AS cohorts
  - ✓ RMN studies are expensive
- ✓ Possible failure to reproduce results in other IMIDs

# Partnering Opportunities

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- ✓ Companies with diagnosis department
  - ✓ Specially with ACPA test
- ✓ Companies with biological therapy in their portfolio
  - ✓ Specially TNF-Blockers
- ✓ Validation of clinical data
  - ✓ Pharmaceutical companies have greater influence to involve colleagues
    - ✓ Large cohorts
    - ✓ International diffusion

Thank you for attention!

