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

Cellular Biology Departments. Biology and Medicine Schools.

- **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
    - VIP expression on human cells (synoviocytes, lymphocytes).
    - “In vitro” models

Servicio de Reumatología. IIS-IP

- **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
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

VIP ameliorates murine CIA

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

Crohn disease
Sepsis
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-α is able to induce the RA phenotype in OA synoviocytes
The Product
The Product

**DIAGNOSIS BIOMARKER**

- RF, ACPA

**PROGNOSIS BIOMARKER**

**DISEASE ACTIVITY BIOMARKER**

C reactive protein (mg/dl)

Swollen joints
The Product: Innovative MoA

VIP is not a DIAGNOSIS BIOMARKER

Population

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

p < 0.023
Low baseline VIP levels is associated with a higher intensity of DMARD treatment (IDT). Interaction with ACPA positivity
The Product: Innovative MoA

VIP is a PROGNOSIS BIOMARKER
The Product: Target Indications

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

✓ Early Spondyloarthritis Register

![Graphs showing the relationship between BASFI and VIP levels with different patient groups.](image)
The Product: Features facing the markets

- **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
Treatment with TNF-blockers increases VIP serum levels

Rheumatoid arthritis

Ankylosing spondylitis

VIP (pg/ml)

Pre-TNF blocker  Post-TNF blocker

VIP (log[pg/ml])

Pre-TNF blocker  Post-TNF blocker
The Product: Features facing the markets

- 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

- **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
The Product: IPR protection

The protection refers to the definition of low VIP levels. All cut-offs below the 50th percentile of a healthy population has been protected. Irrespective of the assessment assay.
The Product: Pitfalls & Risks

- 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

- 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!