

Combinazione farmaci  
Angiostatici ed Antinfiammatori  
per la cura della Retinopatia  
diabetica (CAAR)

(F. Semeraro & M. Presta)

## Epidemiologia del diabete

La prevalenza del diabete in Italia è stimata intorno al 3-4% della popolazione ed aumenta con l'età

Proiezioni O.M.S. prevedono il raddoppio dei casi di diabete in Europa entro il 2025

# Epidemiologia della retinopatia diabetica

In Italia 500.000 pazienti affetti da RD

Prevalenza aumentata negli ultimi 40 anni

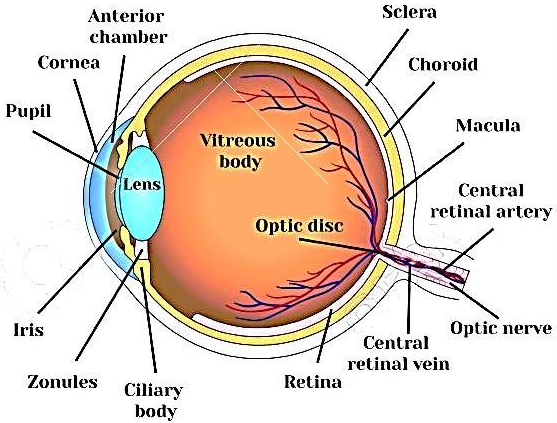
Prevalenza della RD nel DMID 40%

Prevalenza della RD nel DMNID 20%

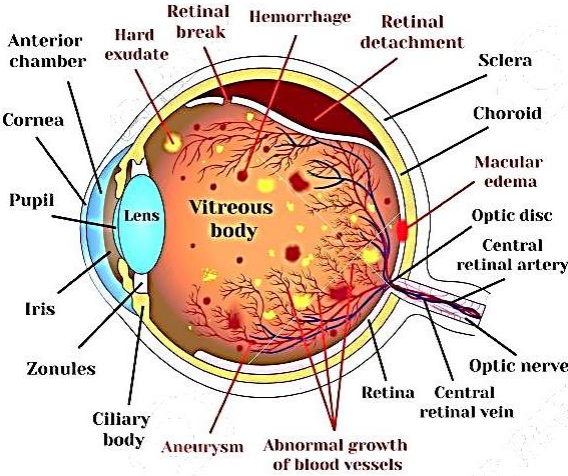
Causa più comune di cecità legale negli  
individui tra 20 e 65 anni (USA)

# Proliferative Diabetic Retinopathy

## Normal vision



## Proliferative diabetic retinopathy



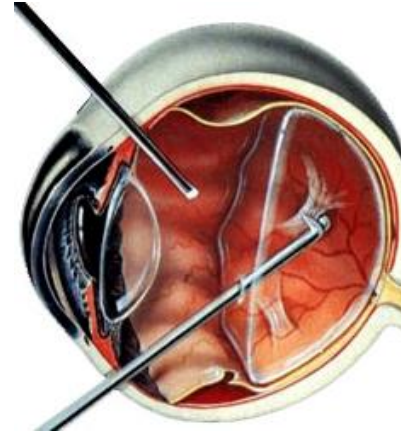
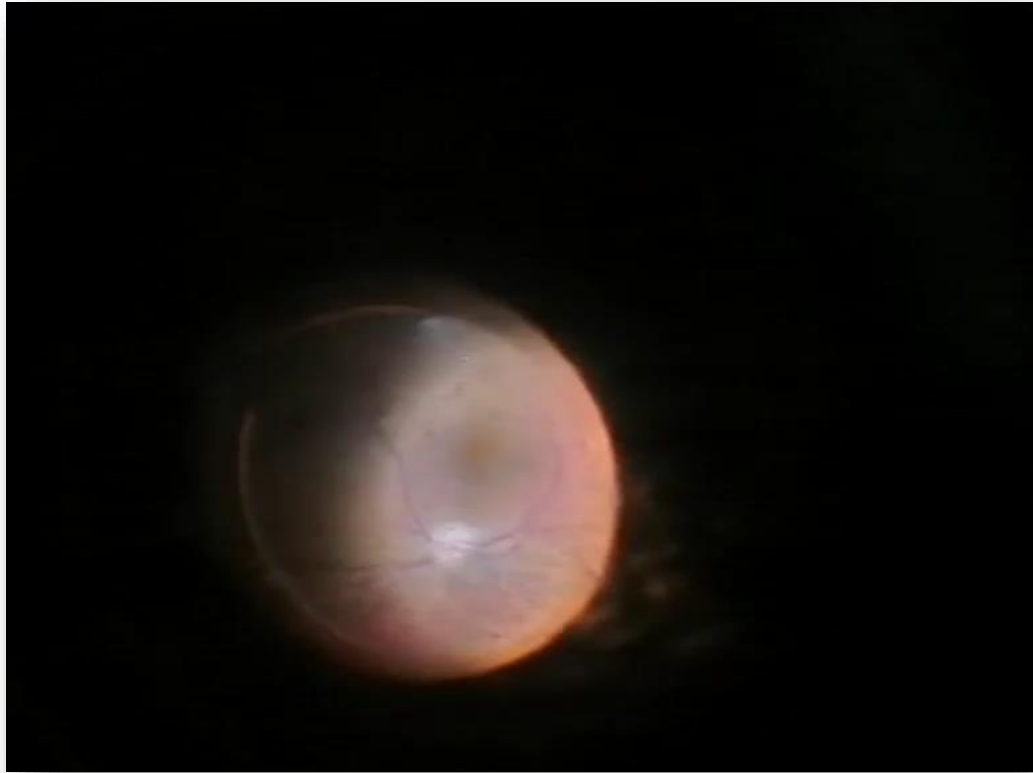
## TREATMENTS

Anti-VEGF  
Intravitreal Injection



Laser Photocoagulation

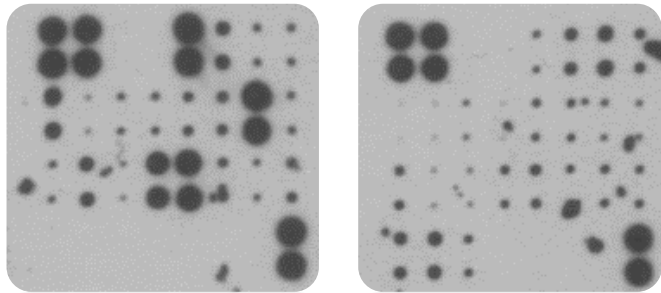
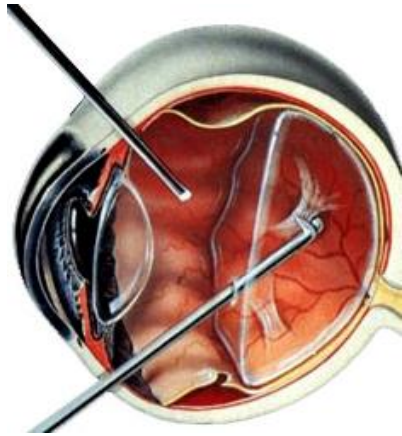




# VITRECTOMIA

# Angiogenic/inflammatory mediators in PDR vitreous fluid

Vitrectomy



Angiogenesis protein array

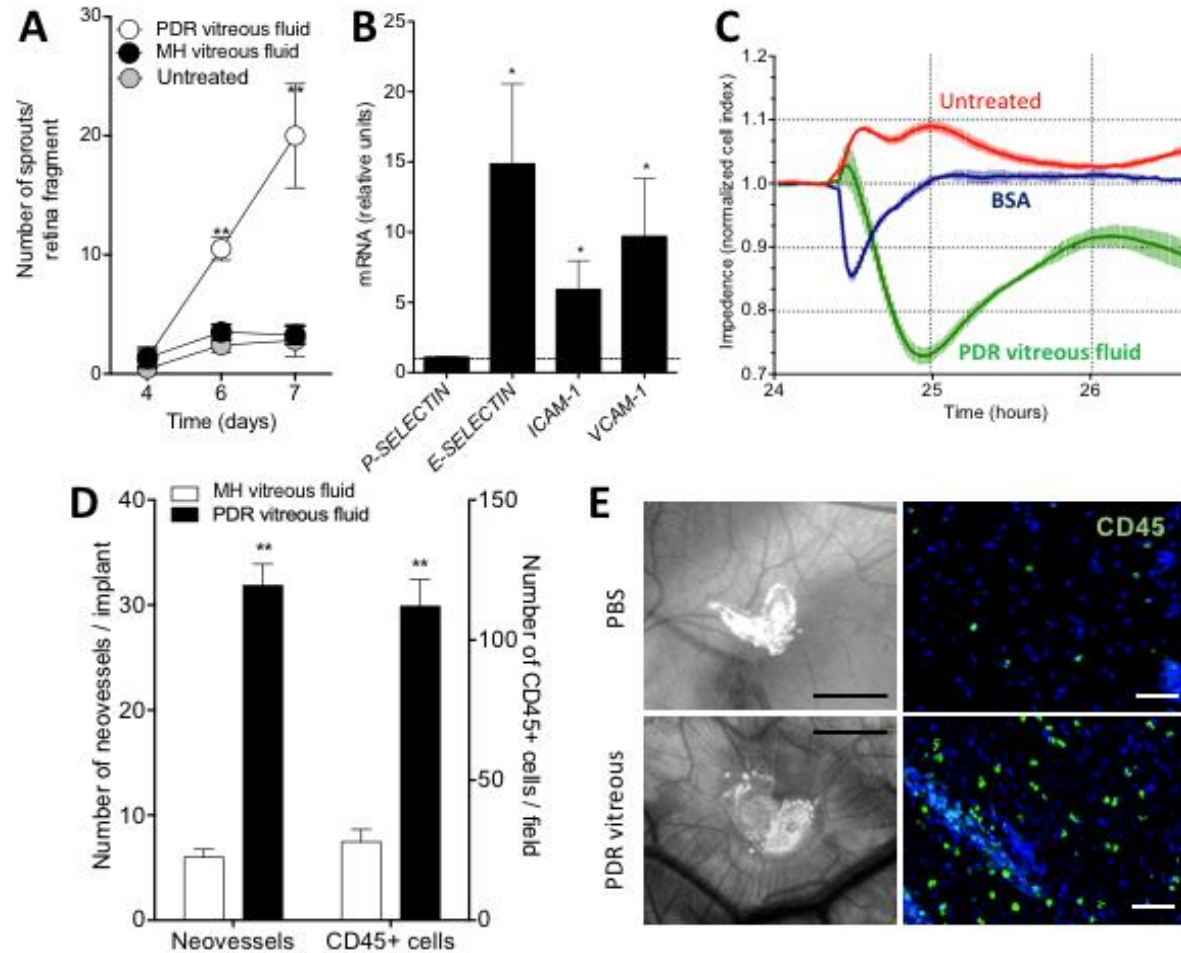


Protein	Relative levels (mean ± SD)	p value
<b>Cytokines</b>		
Tumor necrosis factor α (TNFα)	12 ± 3	*
Interleukin 1-β (IL1β)	11 ± 2	*
Interleukin 1-α (IL1α)	10 ± 1	***
Interleukin 2 (IL2)	7 ± 2	*
Transforming growth factor β (TGFβ)	7 ± 3	*
<b>Chemokines</b>		
Monocyte chemoattractant protein-1 (MCP-1/CCL2)	107 ± 10	**
Growth-regulated protein α (GRO/CXCL1)	39 ± 2	**
RANTES/CCL5	29 ± 2	***
Interleukin 8 (IL8)	21 ± 5	*
Interferon-inducible T-cell α chemoattractant (I-TAC/CXCL11)	18 ± 7	*
Epithelial-derived neutrophil-activating protein 78 (ENA78/CXCL5)	8 ± 4	*
Monocyte chemoattractant protein-4 (MCP-4/CCL13)	5 ± 2	*
I-309/CCL1	5 ± 1	*
<b>Angiogenic factors</b>		
Epidermal growth factor (EGF)	31 ± 7	**
Angiopoietin-2 (Ang-2)	18 ± 4	*
Vascular endothelial growth factor-D (VEGF-D)	14 ± 5	**
Platelet-derived growth factor-B (PDGF-B)	10 ± 5	***
Vascular endothelial growth factor-A (VEGF-A)	10 ± 1	*
Insulin growth factor-1 (IGF-1)	9 ± 2	*
Angiopoietin-1 (Ang-1)	8 ± 2	**
Fibroblast growth factor 2 (FGF2)	8 ± 5	**
Placental growth factor (PlGF)	7 ± 2	*
<b>Other inflammatory/angiogenic mediators</b>		
Angiogenin	108 ± 13	**
Tissue inhibitor of metalloproteinase-2 (TIMP-2)	87 ± 4	**
Tissue inhibitor of metalloproteinase-1 (TIMP-1)	72 ± 4	**
Plasminogen (PLG)	38 ± 4	**
Vascular endothelial growth factor receptor 2 (VEGFR2)	36 ± 8	*
Urokinase-type plasminogen activator receptor (uPAR)	25 ± 2	**
Thrombopoietin (THPO)	20 ± 6	*
Endostatin	18 ± 1	*
Matrix metalloproteinase-9 (MMP-9)	17 ± 1	**
Tyrosine kinase immunoglobulin-like and EGF-like domains 2 (TIE2)	13 ± 3	*
Vascular endothelial growth factor receptor 3 (VEGFR3)	12 ± 2	**
Matrix metalloproteinase-1 (MMP-1)	12 ± 1	**
Platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31)	11 ± 1	*

Attività angiogenetica ed infiammatoria  
dell'umor vitreo ottenuto da pazienti con  
retinopatia diabetica



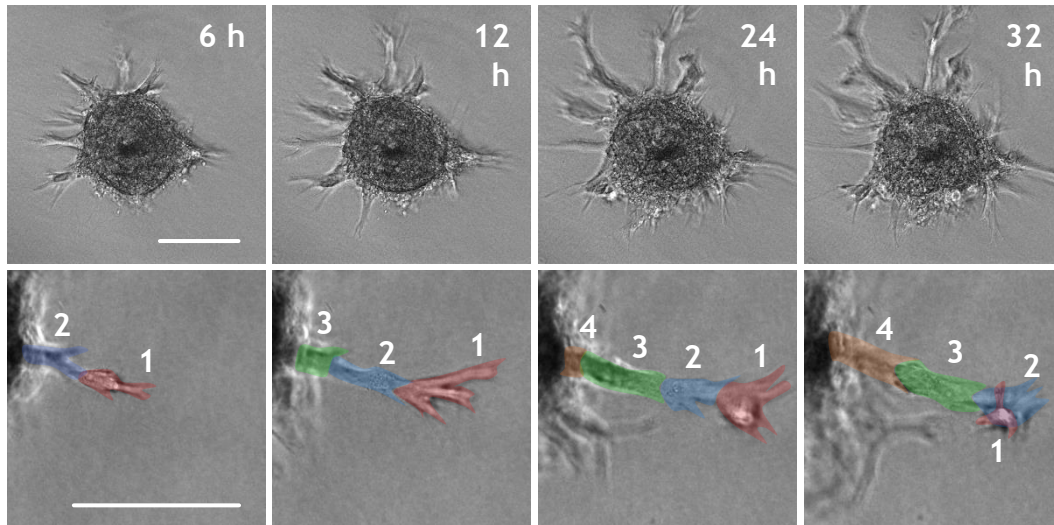
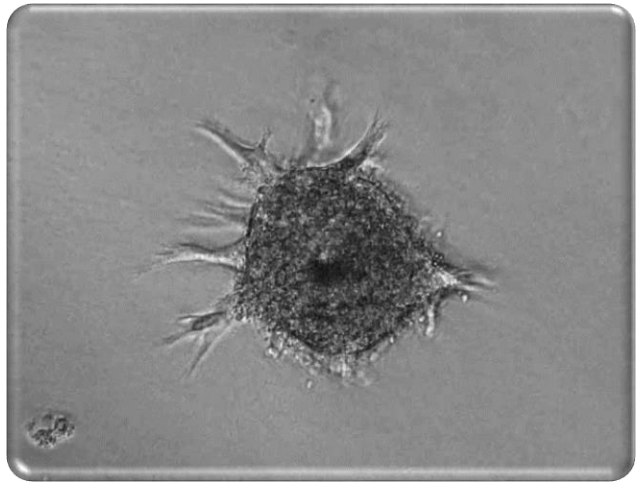
# PDR vitreous fluid induces an **angiogenic/inflammatory response** in endothelial cells



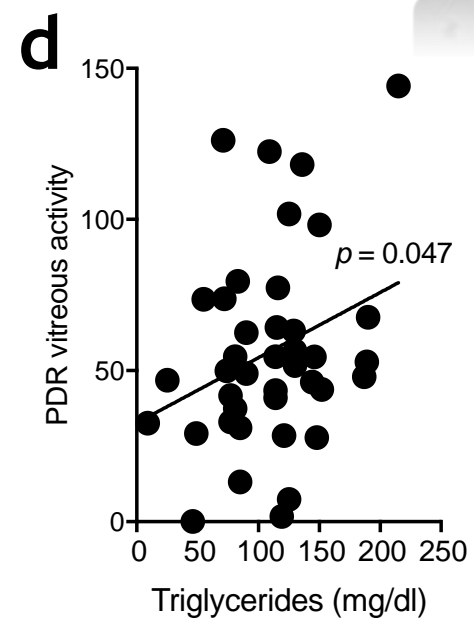
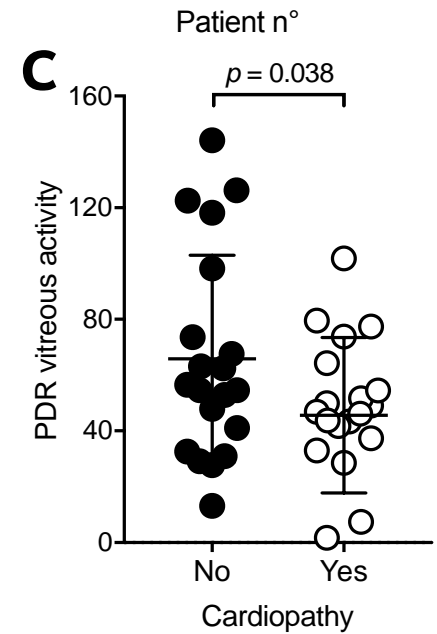
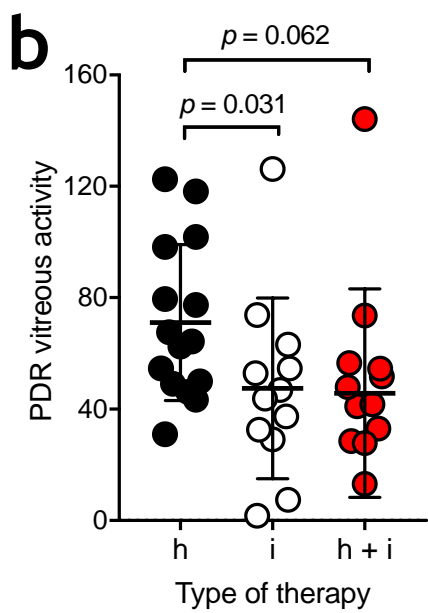
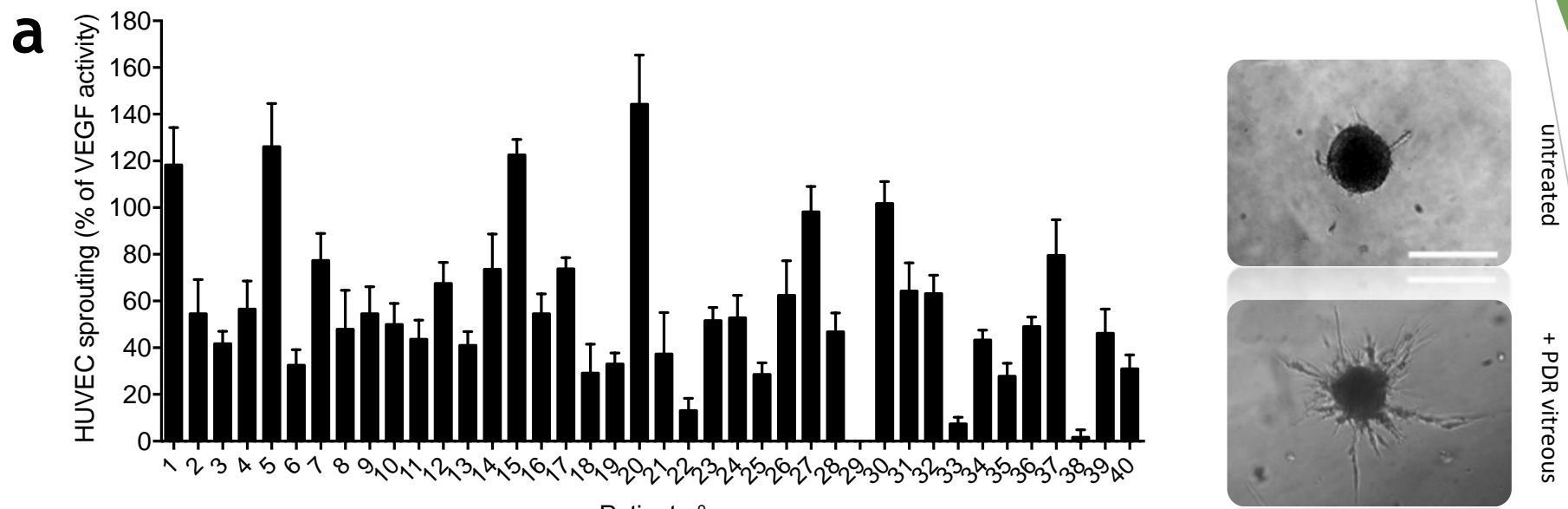
**Figure 1. Proangiogenic/proinflammatory effect of PDR vitreous fluid on ECs and neovascularization.** **A)** Murine retina fragment EC sprouting induced by PDR or MH vitreous samples. **B)** qRT-PCR analysis of gene expression levels after EC treatment with PDR vitreous. **C)** Trans-endothelial electrical resistance in BSA-treated or PDR vitreous-treated EC monolayers. **D)** Number of neovessels/implant and of CD45+ cells/microscopic field infiltrating the CAM mesenchyme. **E)** Neovessels and CD45+ infiltrate in PBS and PDR vitreous-treated CAMs; nuclei were stained with DAPI (blue).



## 3D-endothelial cell spheroid/human vitreous assay



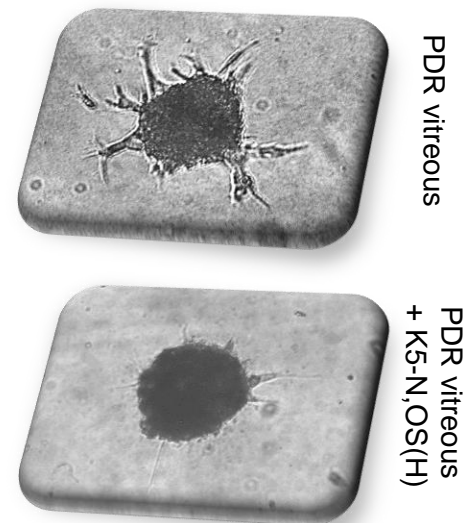
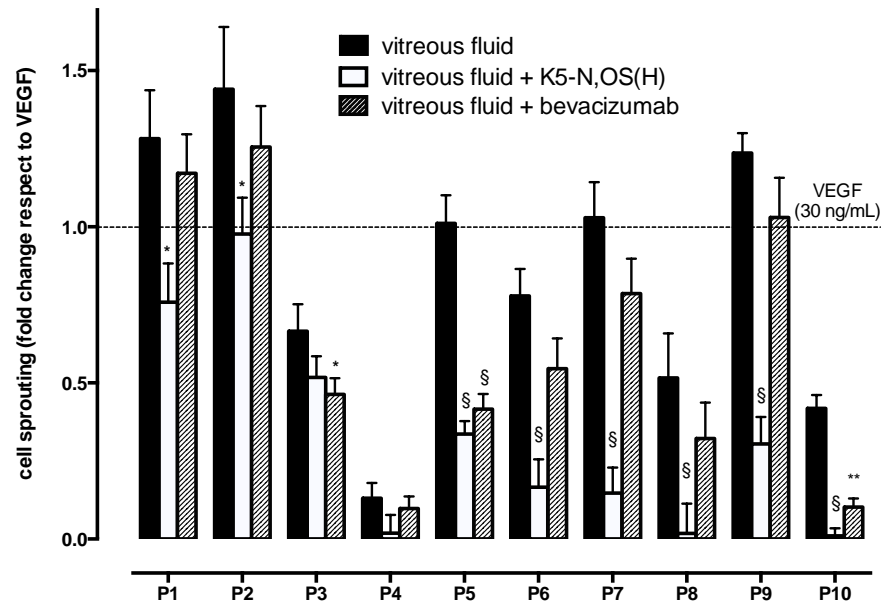
Individual vitreous samples from PDR patients show a **different** angiogenic potential



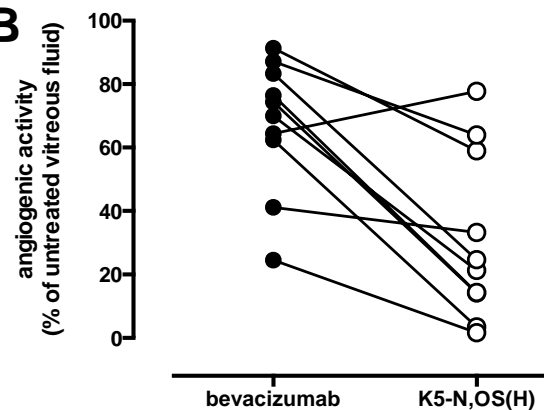
# Individual response to anti-angiogenic molecules

## HUVEC spheroid assay

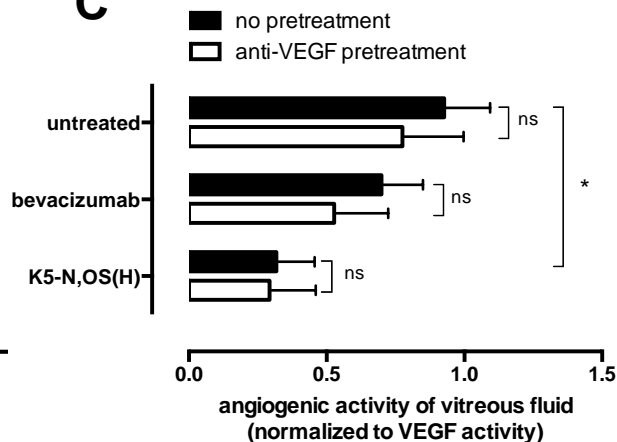
**A**



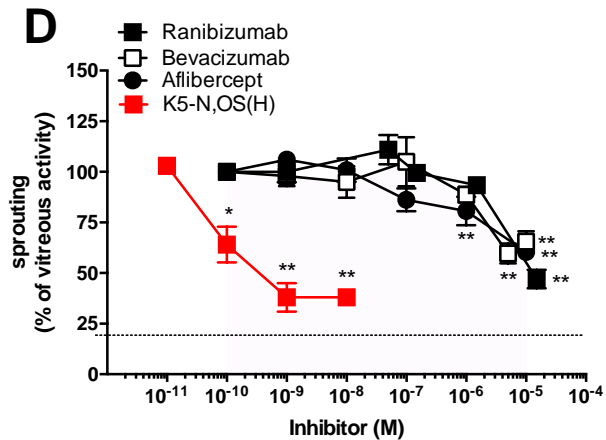
**B**



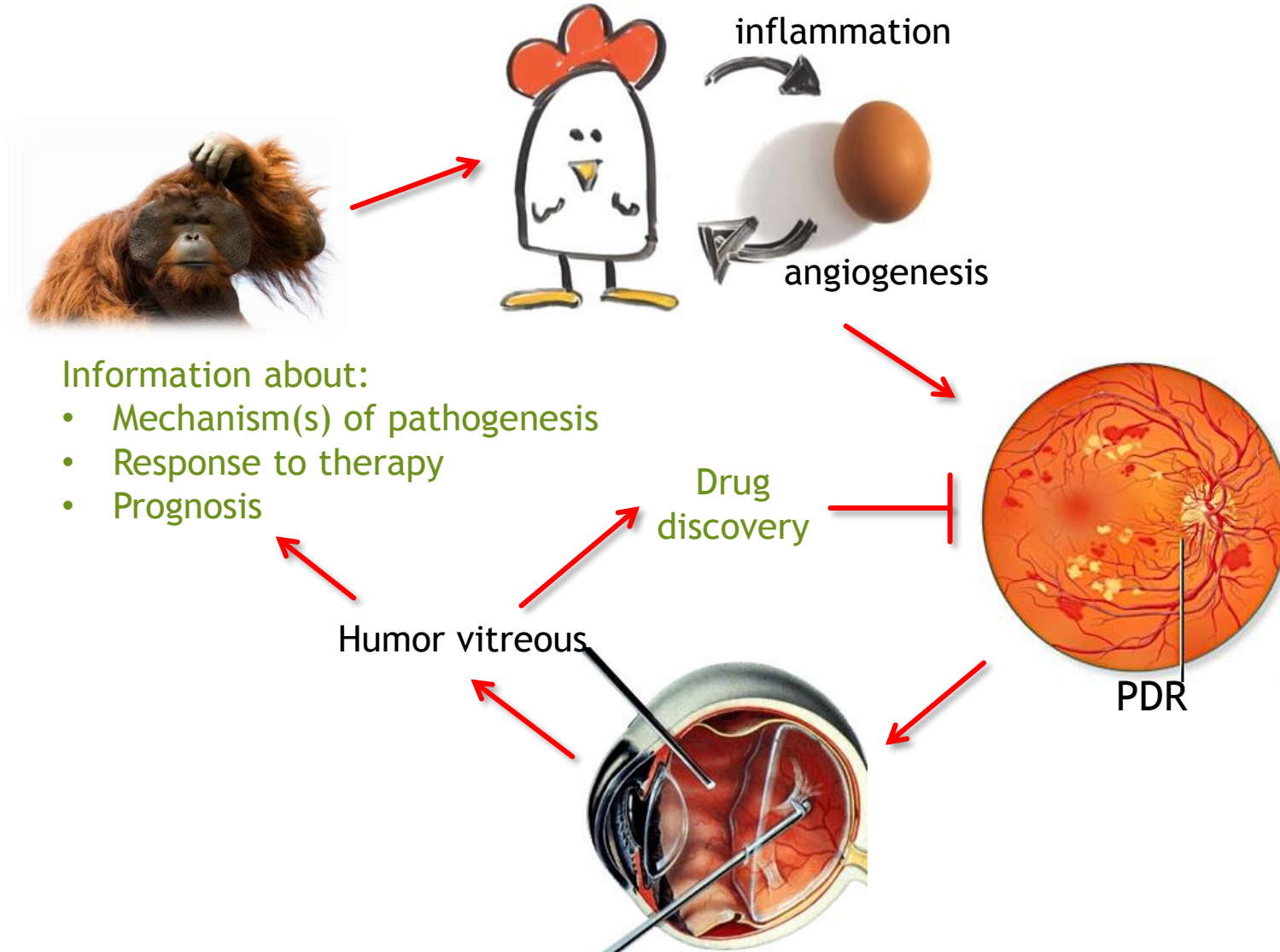
**C**



**D**



# Conclusions



## **Produzione scientifica**

- Pubblicazioni peer reviewed: 14 (+ 1 under revision)
- Totale citazioni: 421
- Citazioni medie: 30.1
- Totale IF: 98.9
- IF medio: 7.1
- Articoli divulgativi: 2

## **Presentazione dati a congressi:**

- ARVO Meeting, on line meeting, Maggio 2021 (AMKC)
- ARVO Meeting, on line meeting, Aprile 2020 (SR)
- XXVIII Congresso Nazionale SID, on line meeting, Dicembre 2020 (SR)
- XXVII Congresso AMD-SID, on line meeting, Ottobre 2020 (SR)
- XXII Parma Diabete, Parma, Gennaio 2020 (SR)
- XXVI Congresso AMD-SID, Coccaglio (BS), Ottobre 2019 (SR)
- Retina in Progress, Milano, Maggio 2019 (SR)
- ARVO Meeting, Vancouver, Aprile 2019 (SR)
- XXVI Congresso Nazionale SID, Rimini, Dicembre 2018 (MP)
- ARVO Meeting, Baltimore, Maggio 2018 (MIN)
- XIII AOPT meeting, Firenze, Febbraio 2017 (MP)
- "Nuovi farmaci biotecnologici" meeting, Catania, Ottobre 2015 (MP)
- V Workshop SIICA-SIC "Angiogenesi", Pontignano (SI), Maggio 2015 (SR)
- V meeting on Angiogenesis, Amsterdam, Marzo 2014 (SR)
- V Tumor-host interaction and angiogenesis meeting, Ascona, Giugno 2013 (SR)
- IV Workshop SIICA-SIC "Angiogenesi", Pontignano (SI), Maggio 2013 (SR)

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- Contratto NOVARTIS 75.000 €
- Contratto SOOFT 25.000 €
- Contratto SOOFT 36.000 €

### **Premi per la produzione scientifica:**

- Premio SID giovani ricercatori per la miglior pubblicazione in diabetologia  
Premio Parma Diabete per giovani ricercatori
- Travel Grant Fondazione Bietti per partecipare all'ARVO meeting (USA)
- Travel Grant CIB per partecipare V Workshop SIICA-SIC "Angiogenesi"

### **Attività di Formazione**

- Tesi di Laurea (Medicina e Chirurgia): 2
- Tesi di Laurea (Biotecnologie/Biotecnologie Mediche): 3
- Studenti di Dottorato/Scuola di Specialità: 7
- Tesi di Dottorato: 5
- Tesi di Specialità: 1

Grazie per l'attenzione