Pseudomonas Aeruginosa Hapten For Benign Prostatic Hyperplasia (BPH)

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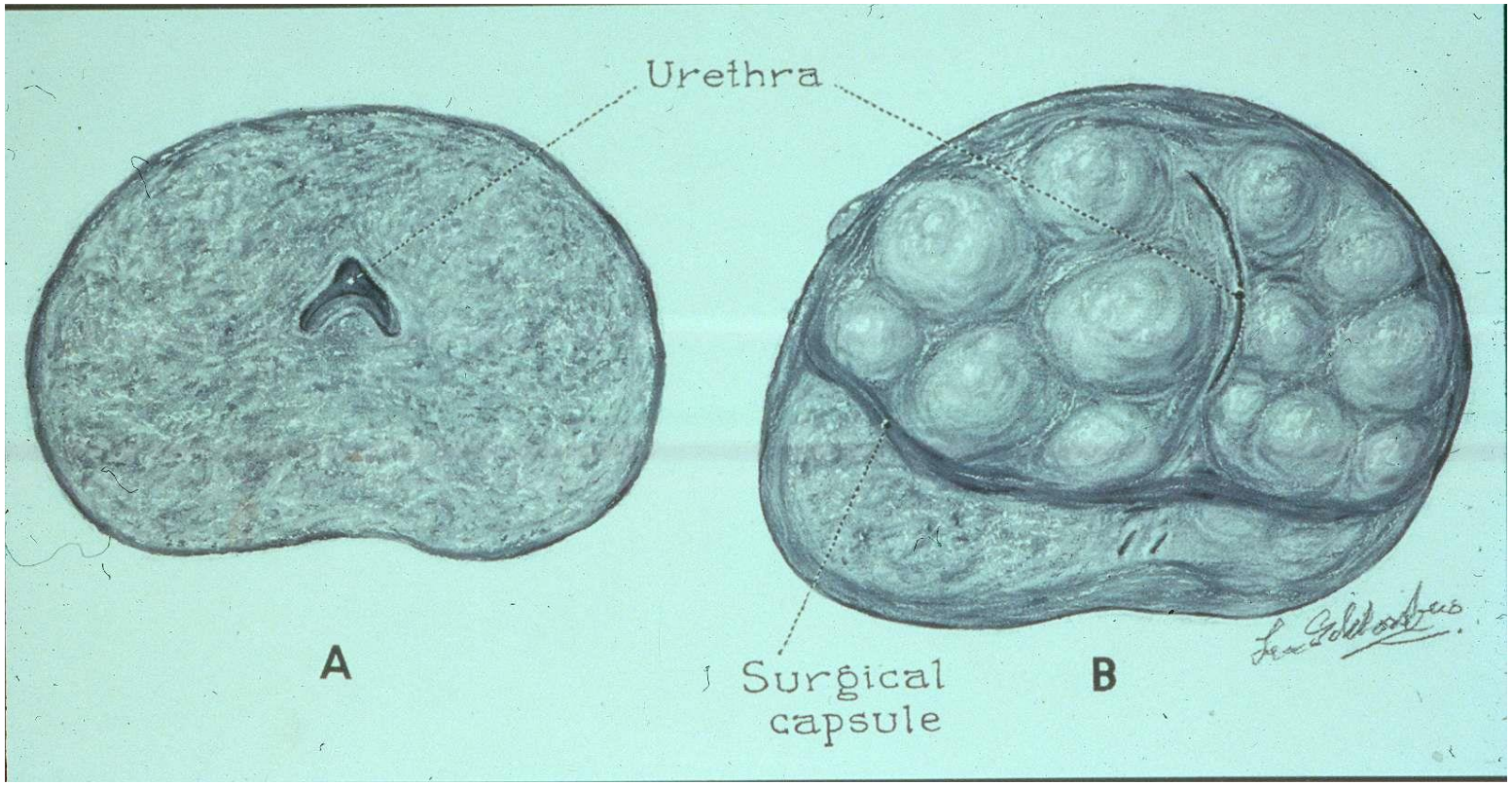
Disclosures J Heesakkers	
• Grants • Consultancy of Spreker	• Astellas, Allergan, Bluewind, Boston Scientific • Astellas, Allergan, Axonics, Pfizer, Urogyn, Boston Scientific

- BPH
- Diagnosis
- Treatment
  - surgical
  - drugs
- Pseudomonas Aeruginosa Hapten
  - development
  - Study
  - Results
- Next Steps

BPH

- Benign prostate growth (cause ?)
- Only men
- Starts from 50 yr on
- 50 yr 50%
- 60 yr 60%
- Causes often complaints
- Lower Urinary Tract Symptoms (LUTS)

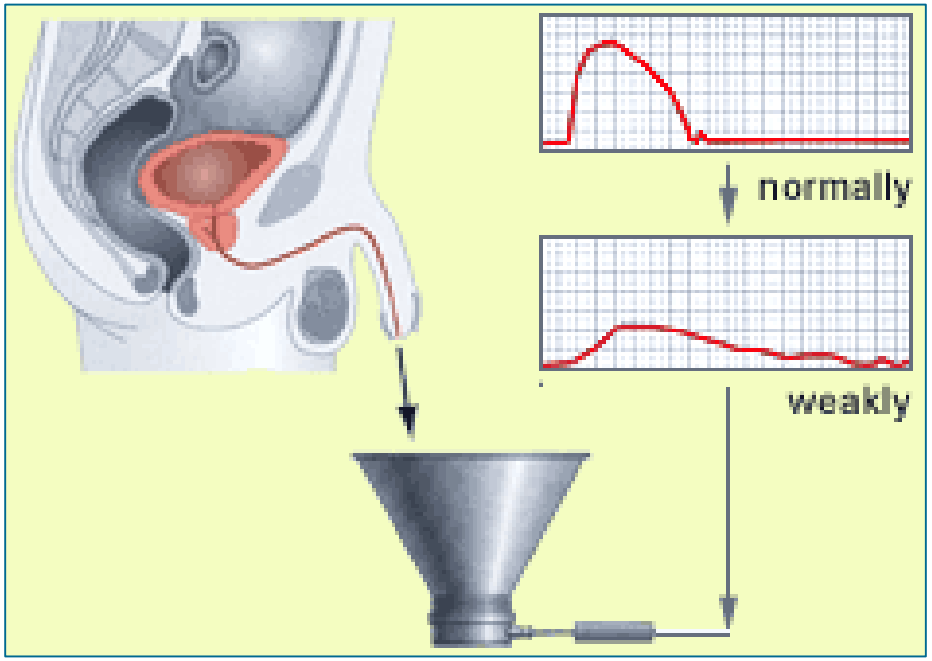
- '***BPH'*** is benign prostate growth
- Often causes obstruction '***BOO'***
- Accompanying complaints '***LUTS'***


Urethra
A
Surgical capsule
B

Diagnosis

- Complaints score (IPSS)
- DRE
- Uroflow: Maximum flow (Qmax)

Uroflowmetry



Treatment BPH

- Surgical
  - TURP, Laser
  - Open surgery
  - Heat treatment
  - Anchors
- Drugs
  - alfa blockers (Xatral, Omnic, Silodyx)
  - 5 alfa reductase inhibitors (Proscar, Avodart)

Efficacy

Medication

- IPSS decreases from 20 to 14
- Qmax from 10 ml/s to 13ml/s

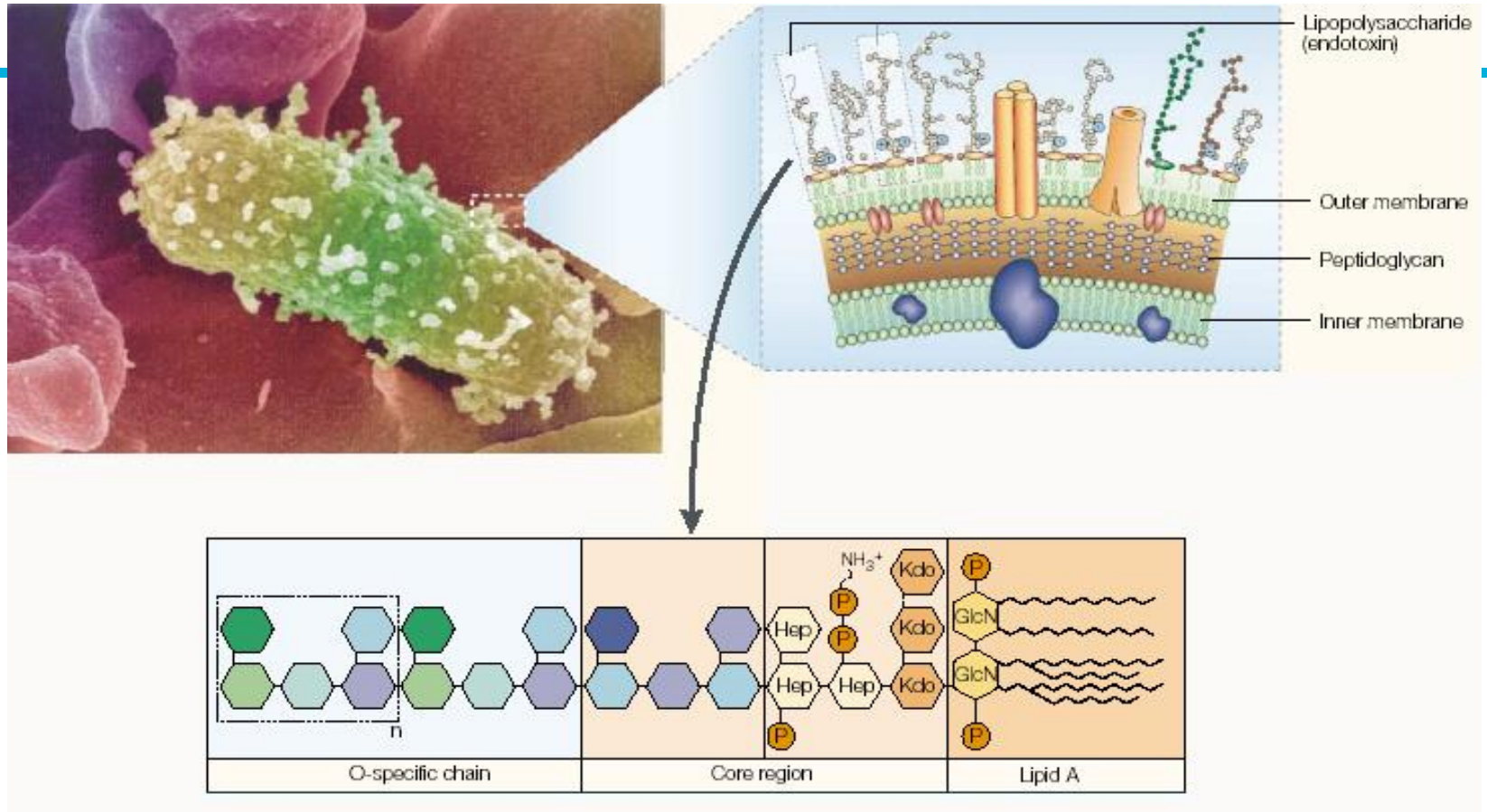
Surgery

- IPSS decreases from 22- to 7
- Qmax from 10 ml/s to 18-20 ml/s

N'Dow BJUint 2013

Pseudomonas Aeruginosa Hapten

- Hapten is incomplete antigen
- In combination with antibodies immune response is evoked
- Haptens are polysaccharids, made from parts of bacteria
- Toxic effect is gone, immune response remains
- Presumed working mechanism is fibrinolysis



- Pseudomonas Aeruginosa
- Hapten/ incomplete antibody/ lipid A
- Polysaccharide O+C/ nucleic acids remains/ carrier

Cheloids → BPH

common features..

- Hyperplastic nodules with fibroblast proliferation
- Collagen accumulation
- Lymphoid infiltration

Benign Prostatic Hyperplasia

- Growth of glands of prostate
- Growth of muscle tissue of prostate
- Growth of fibrotic tissue of prostate
- Cause unknown, however inflammation present

  Gandaglia G et al BJU Int. 2013 Aug;112(4):432-41

- BPH can be triggered by immune system

Pseudomonas Aeruginosa Hapteen

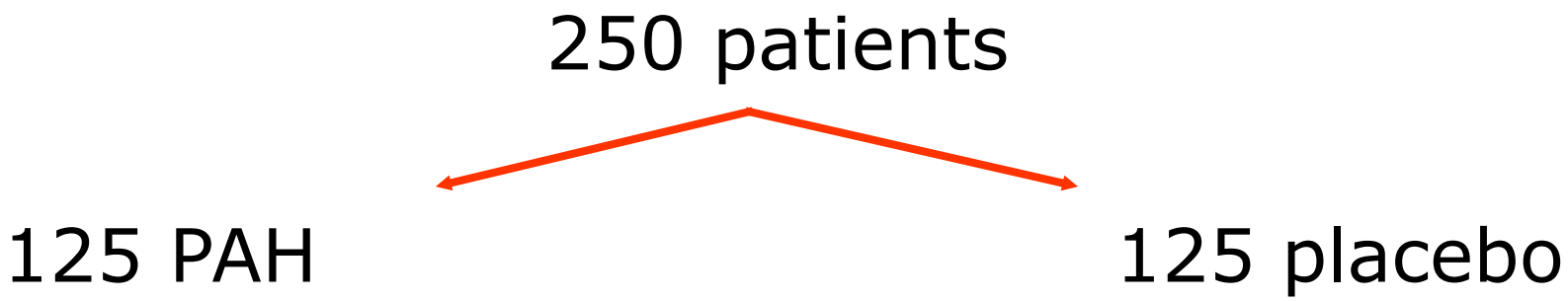
- Developed by Dr Hipoli
1984 onwards

- Admitted in scar tissue

- Tested in patients at Fu
Buenos Aires, Argentina

Study

- men with LUTS by BPH



Study

- Blinded
- Approval from MEC
- Randomised between PAH & placebo
- Subcutaneous injections
- Every day an injection during 120 days

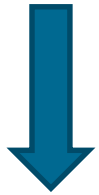
Study

Outcome

- Uroflow (Qmax, residual urine)
- Consistence of prostate
- Size of prostate
- IPSS score (Boyarski)
- PSA

Switched to active treatment

Results after 120 days

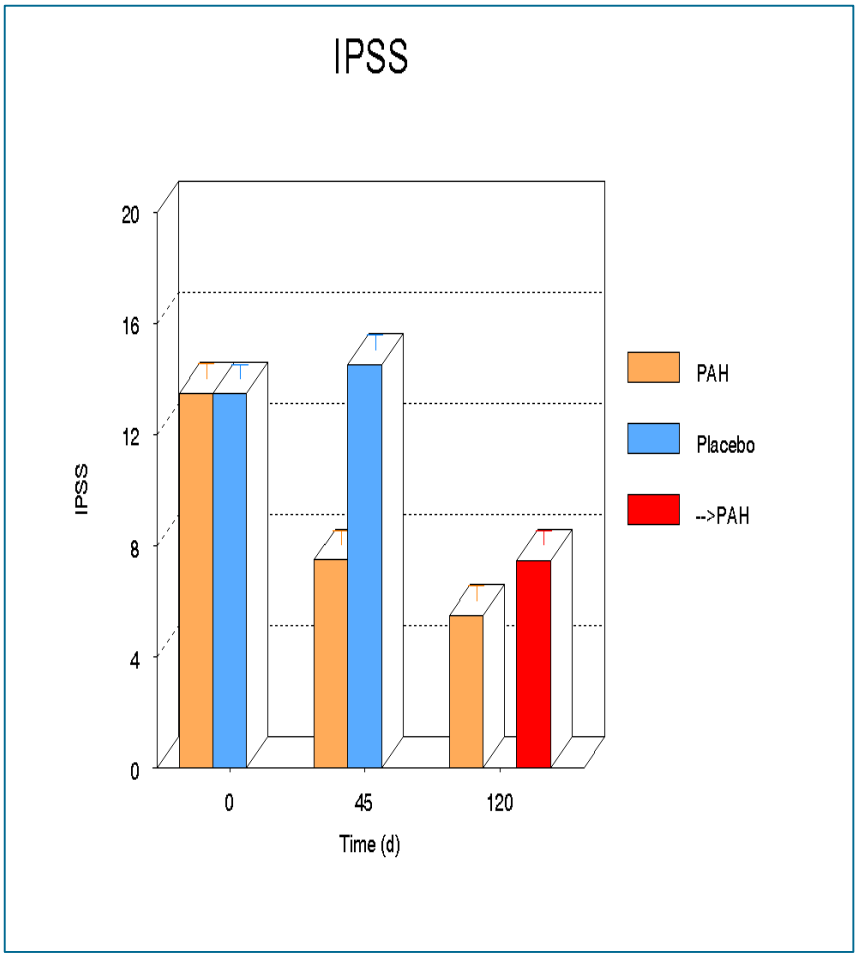


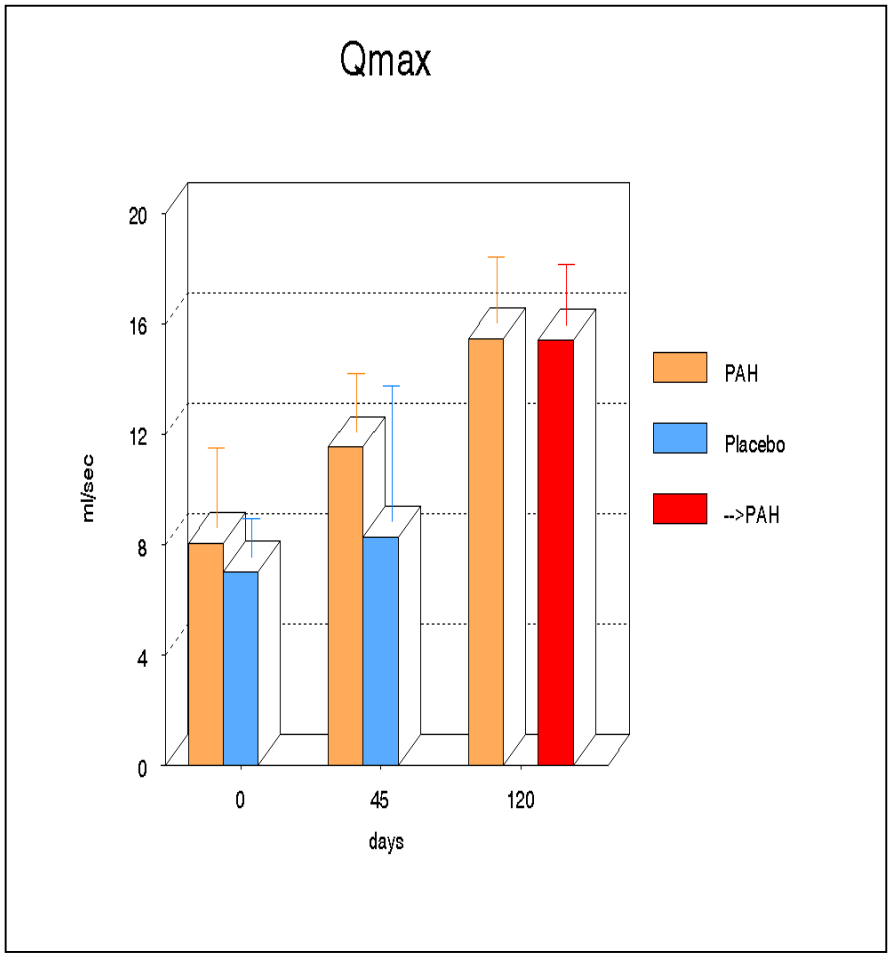
	PAH (n=119)			Placebo (n=115)		
	day 0	day 45	day 120	day 0	day 45	day 120
Age (years)	65 ± 8			65 ± 9		
Qmax (ml/s)	8.1 ± 2.9	11.5 ± 2.1	15.5 ± 2.4	7.0 ± 1.4	8.3 ± 4.9	15.4 ± 2.2
residual urine (ml)	188 ± 56	89 ± 24.2	47 ± 14	151 ± 45	148 ± 58.1	45 ± 15
DRE score (0-4)	3.1 ± 0.9	2.3 ± 0.9	1.5 ± 0.6	3.4 ± 0.8	3.4 ± 0.8	1.5 ± 0.5
prostate size (ml)	73 ± 24	65 ± 21	58 ± 18	73 ± 24	76 ± 23.1	63 ± 18.3
PSA (ng/l)	6.1 ± 2.9	4.9 ± 2.4	3.3 ± 2.0	6.4 ± 1.0	6.1 ± 1.1	2.5 ± 1.2
Boyarski score (0-27)	13.5 ± 0.5	7.5 ± 0.5	5.5 ± 0.5	13.5 ± 0.5	14.5 ± 0.5	7.5 ± 0.5

Results after 5 years

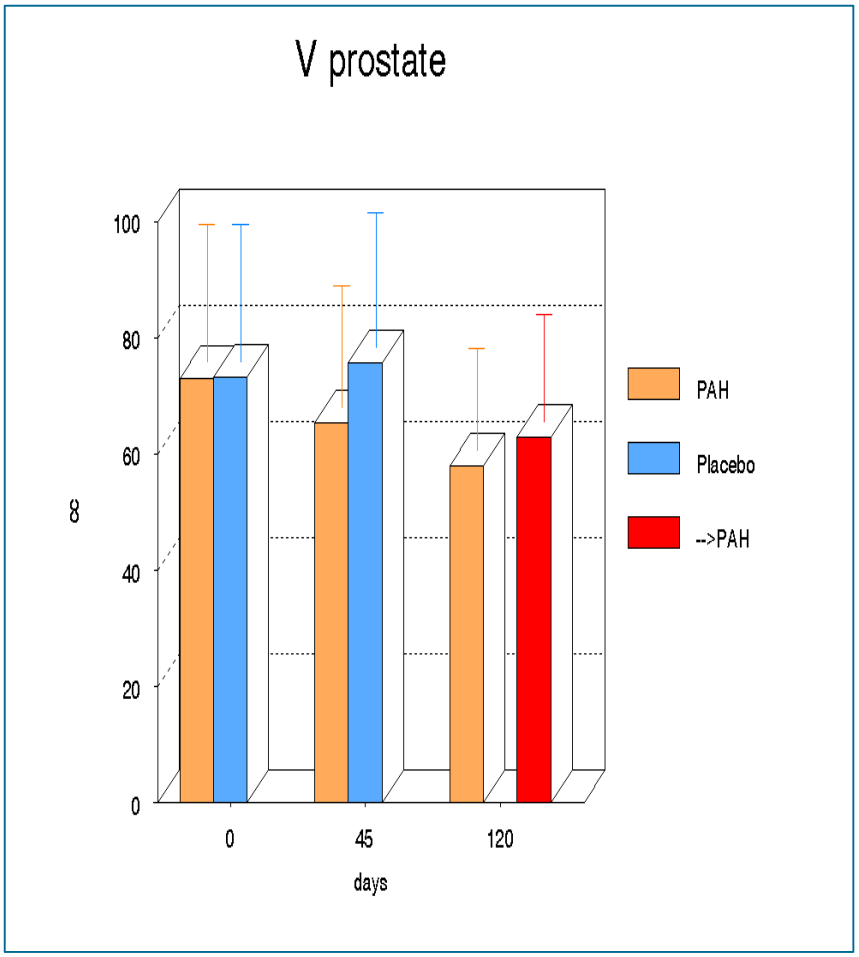
	day 0	1 year	2 years	3 years	4 years	5 years
	n=234	n=209	n=190	n=164	n=148	n=83
Qmax (ml/s)	7.5 ± 1.9	16.6 ± 3.1	17.7 ± 3.6	18.9 ± 3.5	21.3 ±3.5	21.0 ± 3.7
residual urine (ml)	169 ± 50	47 ± 11	44 ± 11	41 ± 9	36 ± 8	34 ± 6
DRE score (0-4)	3.2 ± 0.9	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.3 ± 0.5
prostate size (ml)	73 ± 24	61 ± 18	62 ± 19	62 ± 16	60 ± 16	64 ± 12
PSA (ng/l)	6.3 ± 1.8	2.9 ± 1.4	2.8 ± 1.2	2.7 ± 1.1	2.2 ± 1.1	2.0 ± 1.0
Boyarski score (0-27)	13.5 ± 0.5	6.7 ± 0.9	8.1 ± 1.2	8.3 ± 1.4	8.2 ± 0.8	9.8 ± 0.6

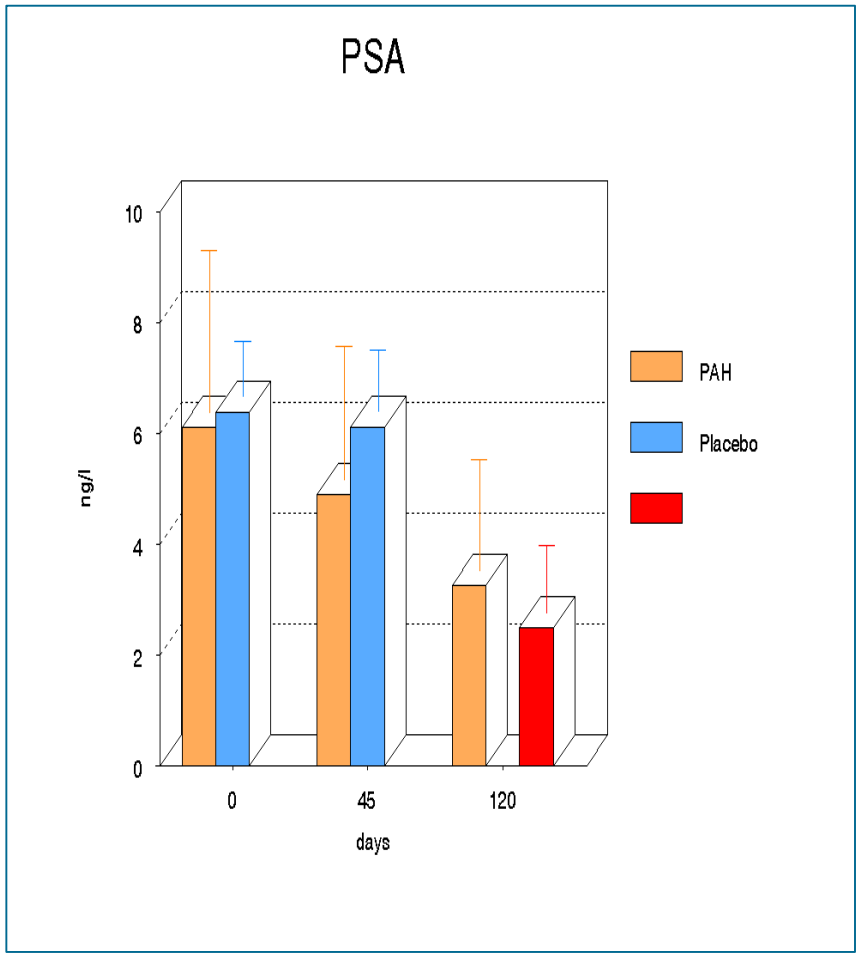
Results I


IPSS
20
16
12
8
4
0
IPSS
0
45
120
Time (d)
PAH
Placebo
-->PAH


Qmax
20
16
12
8
4
0
ml/sec
0
45
120
days
PAH
Placebo
-->PAH

Results III


V prostate
100
80
60
40
20
0
8
0
45
120
days
PAH
Placebo
-->PAH


PSA
10
8
6
4
2
0
ng/l
0
45
120
days
PAH
Placebo

Conclusions

- Effective
- Safe (?)
- Better than other treatments (?)
- Scientific proof

PAH and PC3

IL-6 and IL-8 blocking?

Kuijpers, Schalken, Heesakkers
URL Radboud UMC NL 2006

Introduction

- BPH is histologically associated with chronic inflammation

Gandaglia G et al BJU Int. 2013 Aug;112(4):432-41

- Toll-like receptors are expressed in BPH and PCa tissue

Konig J, The Prostate 58 2004: 121-129

- Toll-like receptors (TLR) play important role in inflammatory host cell response towards bacteria and bacterial products

Hypothesis

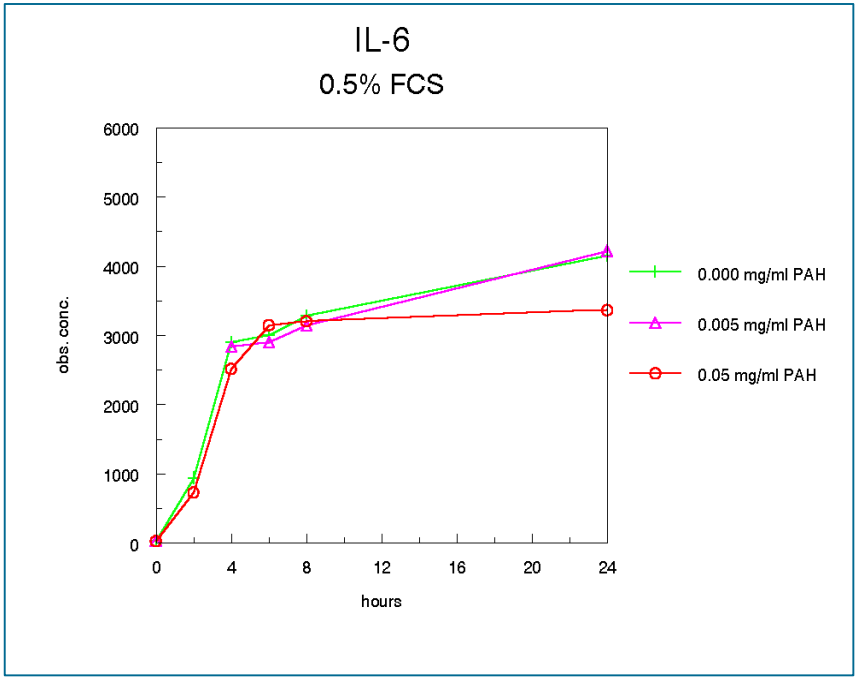
- In inflammatory network of tissue from BPH, PCa & PC3 cell lines, microbial & immunological stimuli lead to changes in inflammatory cascades

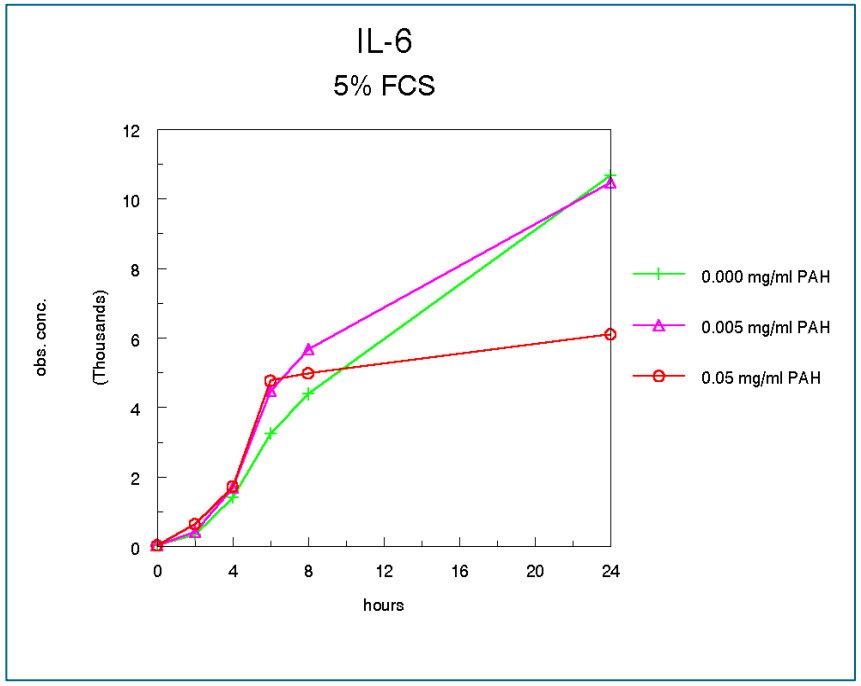
- Assessed by release of cytokines, expression of chemokine receptors and Toll-like receptors

Material and methods

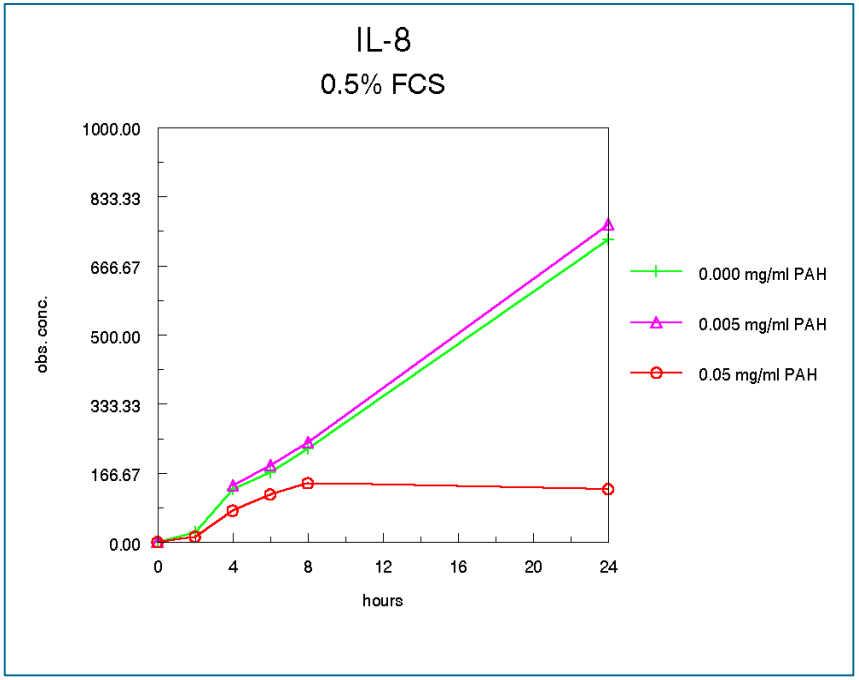
- $2.5x10^5$ cells/ml with or without various PAH concentrations were cultured for 24 hours
- Culture supernatants collected and stored at -20^oC
- IL-6 and IL-8 concentrations measured with ELISA-like Bio-plex assay
- Cell viability using Trypane blue

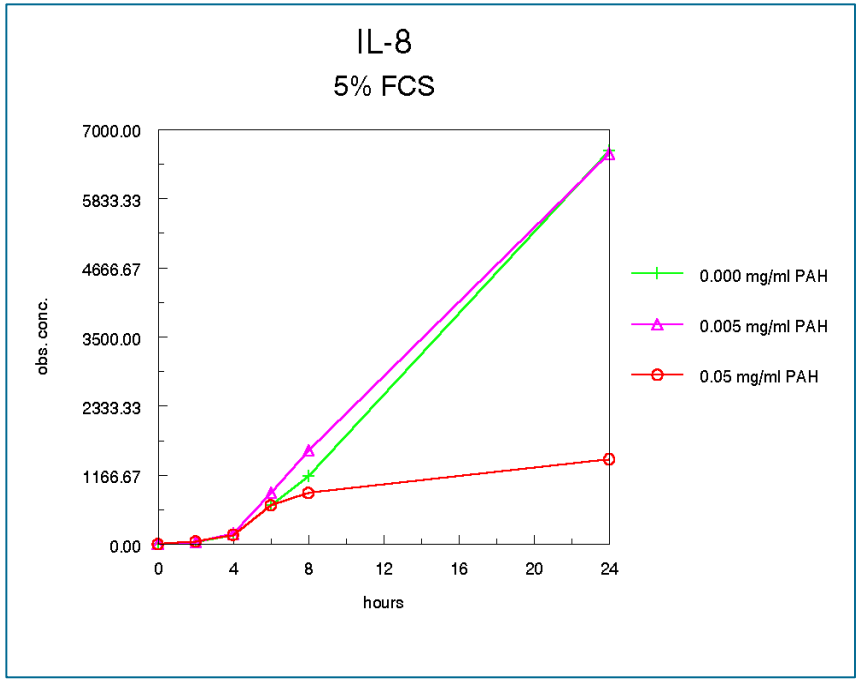
IL-6


IL-6
0.5% FCS
obs. conc.
6000
5000
4000
3000
2000
1000
0
0
4
8
12
16
20
24
hours
0.000 mg/ml PAH
0.005 mg/ml PAH
0.05 mg/ml PAH


IL-6
5% FCS
obs. conc.
(Thousands)
12
10
8
6
4
2
0
0
4
8
12
16
20
24
hours
0.000 mg/ml PAH
0.005 mg/ml PAH
0.05 mg/ml PAH

IL-8


IL-8
0.5% FCS
1000.00
833.33
666.67
500.00
333.33
166.67
0.00
obs. conc.
0
4
8
12
16
20
24
hours
0.000 mg/ml PAH
0.005 mg/ml PAH
0.05 mg/ml PAH


IL-8
5% FCS
7000.00
5833.33
4666.67
3500.00
2333.33
1166.67
0.00
obs. conc.
0
4
8
12
16
20
24
hours
0.000 mg/ml PAH
0.005 mg/ml PAH
0.05 mg/ml PAH

Conclusions

- PAH may inhibit IL-8 and IL-6 production in PC3 via Toll-like receptor
- Rationale for PAH treatment for BPH may exist

Issues & Next Steps

- Studies Sound?
- Product made according to GLP?
- Valid in Europe & US?
- IP issues?
- Introduction from scratch on?