Nonhuman primate models for translational research in endometriosis

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- Coordinator Leuven Univ Fertil Ctr (B),
- Chair, Int’l Advisory Board, Institute of Primate Research (WHO Collab Ctr), Nairobi, Kenya

Learning Objectives: NHPmodels for translational research in endometriosis

1. Introduction
2. Endometriosis cost
3. NHPrimate >> rodent models
4. Development baboon model endo
5. Unicity/validation baboon model endo:
   20 relevant points
6. Endo research baboon model:
   5 relevant observations
Disclosure

• Full Professor and Merck Serono Chair (2005-09) Reproductive Medicine (Leuven University)
• Clinical Head Leuven University Fertility Center
• Chair ESHRE Special Interest Group for Endometriosis
• PI ENDOCOST study

Disclosure

• Board member, WERF
• Editor-in-Chief Gynecologic and Obstetric Investigation
• Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya
• Fundamental Clinical Investigator for endometriosis, Belgian Research Foundation
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Endometriosis

- EM (glands/stroma) outside the uterus + chronic inflammation
- Retrograde menstruation (Sampson 1927)
- Variable phenotype, localization and extent
- Subfertility, pelvic pain, reduced QOL
- Prevalence
  - 7-15% of reproductive age women
  - up to 50% patients with pelvic pain/infertility
- Estrogen dependent
  - rare before menarche or after menopause
- Progressive:
  - >50% women/baboons after 1-2 years

Endometriosis treatments

- Pain killers
- Oral contraceptives
- Progestins
- GnRH-agonists
- Surgery
- Assisted reproductive therapies
- Hysterectomy
- Yet little investment in causal research

- Often more than one
- Hit and miss
- All have side effects
- No cure
Learning Objectives: NHP models for translational research in endometriosis

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3. NHP primate > rodent models
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The cost of endometriosis

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DIAGNOSTICS</th>
<th>SURGERY</th>
<th>HEALTH CARE</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs, Progestagens, OCP</td>
<td>Ultrasound scan, Hernial scan, MRI</td>
<td>Laparoscopy, Laparotomy, Hysteroscopy, Hysterectomy</td>
<td>Gynaecologist, Nurse, Urologist, Gastro-enterologist, Radiologist</td>
<td>ART, A&amp;E visits, Transportation, Child care, Work absence, productivity, education, activities</td>
</tr>
<tr>
<td>Danazol, Gestrinone, GrfH-a, Add-back HRT</td>
<td>Blood tests, Barium enema, Sigmoidoscopy</td>
<td>Endoscopic ablation, Theatra costs</td>
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<tr>
<td>Mirena, Antibiotics, Anti-depressants</td>
<td>X-rays</td>
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</table>

Comparative cost: Endometriosis versus other chronic diseases

- Review of endo-related cost estimates in USA (Simoens et al, 2007)

1. annual (2002) healthcare costs + costs of productivity loss: about $ 4000 per patient per year
2. USA cost per year for endo (2002) $22 billion per year (at 10% prevalence of endo among women of reproductive age)
3. Endo cost considerably higher than cost related to Crohn’s disease or to migraine in the USA for 2002
COMPARATIVE COST: ENDOMETRIOSIS versus OTHER CHRONIC DISEASES

- Retrospective review of administrative data for commercial payers of a US insurance company (Mirkin et al, 2007):

  Extrapolated cost per patient per month (PPPM):
  
  $ 791: endo
  $ 500: hypertension
  $ 916: diabetes
  $ 1,121: rheumatoid arthritis

  explained by high hospital admission rate/ surgical procedures.

Women with endometriosis: total direct medical costs: 63% higher than average women

Explained by added cost due to comorbid conditions:
- interstitial cystitis,
- depression,
- migraine,
- irritable bowel syndrome,
- chronic fatigue syndrome,
- abdominal pain and infertility,...

CALCULATION OF ENDOMETRIOSIS COST IN EU IS NEEDED FOR
INCREASED AWARENESS OF ENDOMETRIOSIS IN POLITICS DETERMINING HEALTH POLICY + RESEARCH FUNDING
Role of ESHRE Special Interest Group for Endometriosis (SIGEE)

- Education and training
- ESHRE Guidelines for endometriosis: Annual update via Working Group
- ESHRE endometriosis cost working group: 2007-10

ESHRE Endometriosis Cost Working Group

- Initiative for ENDOCOST study
- 8 countries, 10 centers: Germany, Hungary, UK, Italy, Denmark, France, Netherlands, Belgium, Switzerland, USA (2)
- Retrospective/Prospective study (2009)
- Team per center: 1 gynecologist + 1 health economist
- Travel/lodging supported by ESHRE
- Collaboration with ASRM SIG Endometriosis
- Sponsored by World Endometriosis Research Foundation
European Network on Endometriosis

First ever EU research grant for endometriosis
1. Pan European epidemiological study
2. Internet based endometriosis gateway
3. Consolidate and formalise the European Alliance
   • 8 Associate partners and 4 Collaborating partners
     - Endometriosis UK lead partner
     - Belgium, Denmark, Italy, UK
   • Application scored very highly – 87/100 and received funding 300,000 Euro (2007-9)

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LACK OF PROGRESS IN ENDOMETRIOSIS RESEARCH

1. Unknown duration of endo at diagnosis
2. Inadequate study design: nl controls needed
   • pelvic condition (endo, nl pelvis, other)
   • symptoms (none, infertility, pain, other)
4. Need for good animal models.
### NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

**Rodents:**

- **Advantages:**
  1. Low cost
  2. Easy handling
  3. Genetic manipulation possible (cost!):
     - KO mice, K-ras transgenic mice
       (Dinulescu et al, 2006)

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Rodents</th>
<th>NHPs</th>
<th>Humans</th>
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</thead>
<tbody>
<tr>
<td>Genetic ally close to humans</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Repro anatomy close to humans</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Estrus behavior</td>
<td>*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Repro cycle</td>
<td>5 days</td>
<td>28-33 days</td>
<td>28-30 days</td>
</tr>
<tr>
<td>Embryonic aneuploidy</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Optional diapause</td>
<td>*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Multiple implantations</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Embryonic control of endometrium</td>
<td>*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Invasive implantation</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Menstruation</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Spont Endo</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Spont PF</td>
<td>-</td>
<td>+</td>
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</tr>
</tbody>
</table>

**Disadvantages:**

1. wide phylogenetic gap with humans
2. different reproductive endocrinology and anatomy,
3. no menstruation
4. no peritoneal fluid
5. no spontaneous endometriosis,
NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

Rodents:
6. Induced endo: unphysiological induction by uterine square autotransplantation (adhesion formation)
7. Induced endo: unphysiological "endometriotic lesions" with limited phenotypes
8. Human EM-murine peritoneal interaction in nude/SCID: extrapolation possible to human endometriosis?
9. Preclinical model for studies testing new drugs: extrapolation not always possible to human endometriosis (Interferon alpha 2b: + in mice, - in women)

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

NHPs:
• Disadvantage:
1. High cost (affordable outside EU and US)
2. Handling requires special expertise/infrastructure
3. Ethically sensitive research

NEED FOR NHP MODELS FOR THE STUDY OF ENDOMETRIOSIS

NHPs:
• Advantages when compared to humans:
1. Very narrow phylogenetic gap
2. Comparable reproductive endocrinology/anatomy
3. Menstruation (baboon, rhesus, not all other NHPs)
4. Spontaneous endometriosis,
5. Induced endometriosis by autologous seeding or injection of eutopic EM in pelvis (baboons, rhesus, cynomolgus)
6. Both spontaneous and induced endometriosis: similar phenotype as human endometriosis
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Baboon model endo
Institute of Primate Research
Nairobi, Kenya

WHO Collaborating Center
Research areas:
Reproduction
Infectious Diseases
Ecology and Conservation

20 yrs research collaboration
Leuven-Nairobi

- 1990-1993 Baboon model for Endometriosis, Institute Primate Research, Nairobi, Kenya
- 1993-1995 Fellowship Reproductive Immunology, Brigham and Women’s Hospital, Harvard Medical School, Boston, (JA Hill/ DJ Anderson)
  Endometriosis in baboons and women
- PhD Leuven 1994 (Promotors: PR Koninckx, CS Sambra) Baboon as model for endometriosis
- 1996-present: coordinator Center Reproductive Medicine, Leuven University Hospital, Belgium (ISO 9001-2000 certified 11/04)
20 yrs research collaboration
Leuven-Nairobi
1998-2008: 50% fundamental clinical investigator (Flemish fund scientific research)

Clinical Leuven: biobank frozen tissue and DNA + clinical database since 1998

Preclinical IPR Nairobi:
Baboon model: pathogenesis and testing of new drugs (prevention/treatment of endometriosis)

IPR International Advisory Board

- Established 2007
- Initiative by NMK/IPR + supported by WHO (P. Van Look)
- Aim:
  - advise Kenyan leaders about long term development of IPR into African Center of Excellence
  - increase international research collaboration

12 experts in areas of reproduction, infectious diseases, ecology and conservation
Chair T. D’Hooghe
Annual meetings, (August + December 07, February 09)
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UNICITY OF BABOON MODEL

1. Cost affordable outside EU or USA
2. Ethical issues

Institute of Primate Research, Nairobi, Kenya

Cost per baboon
Purchase: $450
Per diem: $3
Surgery: $60/hour

Proof of concept RCT
15-20 baboons, 6/12: $100,000 USD
2. Ethics of endometriosis research in baboons at IPR

2.1. Baboons are not an endangered species but represent a threat to agriculture in Africa
2.2. Baboons live in their natural habitat at IPR
2.3. Lack of other clinically relevant preclinical animal models to study cause-effect relationships: Only NHPs do have spontaneous/induced endo similar to the disease in women
2.4. Ethical need to show safety + efficiency of new drugs before application in women

2.5. For each project: double approval by ethical committees from both IPR and from Leuven University
2.6. Global level: capacity building of Primate Research Center in poor resource country could/should be seen as relevant effort in the context of North-South collaboration

UNICITY OF BABOON MODEL

3. Noninvasive monitoring of menstrual cycle:
   - Perineal inflation = Foll. Phase
   - Perineal deflation = Luteal phase
   - Ovulation = perineal deflation minus 2 days
UNICITY OF BABOON MODEL

4. Continuous breeding in captivity
   (> rhesus)
5. Size (12-15kg) and Strength
   (> rhesus > cynomolgus)
   - repetitive blood sampling
     (hourly during 24 hr in chair; daily)
   - repetitive surgery
     (every 2-3 days; D’Hooghe et al, 1996)

6. Spontaneous peritoneal fluid (PF)
   about 2 mL after ovulation (> rhesus)
   (D’Hooghe et al, 1991)

7. Vaginal transcervical uterine access.
   - endometrial biopsy (D’Hooghe et al, 1991)
   - embryo transfer
   - preimplantation embryo flushing
     - hysteroscopy
     (D’Hooghe et al, 1991; 1996; 2004; Nyachieo et al, 2007; Chai et al., 2007).

BABOON MODEL for non-endometriosis

REPRODUCTIVE RESEARCH

- HCG exposure – EM implantation model
  (oviductal minipump HCG) – Fazleabas
- Embryo- EM implantation model
  (hysteroscopic interventions) – Leuven/IPR
- Reproducible IVF system in baboons
  (Embryonic stem cell development) – Leuven/IPR
- Prevention heterosexual transmission SHIV
  (vaginal immunology) – Leuven/IPR/BU
UNICITY OF BABOON MODEL

8. Spontaneous endo similar to human endo:
   laparoscopic appearance, pelvic localization, microscopic aspects
   [D’Hooghe, 1997]

9. AFS/ASRM endo classification system adapted for baboon (D’Hooghe et al, 1995)

10. Full spectrum of spontaneous endo:
    minimal endo (prev 25%, D’Hooghe et al, 1991)
    to severe endo ➔ bowel obstruction/death

11. Induced endo similar to human endo:
    laparoscopic appearances, pelvic localization, microscopic aspects
    [D’Hooghe et al, 1995]
12. In vivo culture model for study of early endometrial-peritoneal interaction (after induction)

- EM pellet versus EM supernatant
- Early establishment of endo:
  D1-3-6-10-15-25

13. Preclinical model for study of cause-effect relationships in endometriosis (after induction)

Design:
- Longitudinal observation in same baboon
- Before, during and after induction
- Interventions at well defined times of the cycle
- Assess local effects: EM, PF, nl peritoneum, endo lesions
- Assess systemic effects: PB

IDEAL ANTI-ENDOMETRIOSIS DRUG

1. Prevent the development of endometriosis
2. Cures existing endometriosis, also after cessation of treatment
3. No interference with menstrual cycle
4. No side effects
5. Safe for women who wish to become pregnant
14. Evaluate new drugs for prevention of endometriosis

Aim: prevent endometrial-peritoneal attachment after IP injection of menstrual EM

3 groups, n=5 each,
test drug, - control, + control

a. Pretreatment of baboons N days before induction
b. Pretreatment of EM at time of induction
c. Combination of a+b

(TNF-alpha inhibitors, D’Hooghe et al, 2006)

15. Evaluate new drugs for treatment of endometriosis

Aim: reduction of existing endometriotic lesions (after induction using IP injection of menstrual EM)

3 groups, n=5 each,
test drug, - control, + control

1. Induction laparoscopy (D1-2)
2. Staging laparoscopy pre-treatment (D25)
3. RCT 3 groups and treat during 1-3 months
4. Staging laparoscopy post-treatment

(TNF-alpha inhibitors, Falconer et al, 2006; ROSI, Lebovic et al, 2007)

16. Endometriosis outcome variables in prevention or treatment trials

(D’Hooghe et al, 2006; Falconer et al, 2006; Lebovic et al, 2007)

1. Endometriosis Lesions: N, surface area, depth, volume
2. Phenotype of endo lesions: black, red, white,....
3. Adhesions: N and surface area
   - endo-related versus non endo-related
   - integrated in >X independent from ASRM staging
4. Adapted ASRM classification: score and stage
17. General and reproductive safety in prevention or treatment trials (D’Hooghe et al, 2006; Falconer et al, 2006; Lebovic et al, 2007)

1. General: side effects
2. Cyclicity
   - cycle length, length follicular phase/luteal phase
   - E2/P assays
3. Fertility and miscarriage
4. Offspring: congenital abnormalities


1. Normal MFR in baboons with minimal endo
2. Reduced MFR in baboons with mild, moderate or severe endo (spontaneous and induced), related to an increased incidence and recurrence of the Luteinized Ruptured Follicle Syndrome
   - also in the absence of ovarian endometriotic cysts (D’Hooghe, 1997; D’Hooghe et al, 1996 several studies).
   - ? Causal role of EM changes (Fazleabas)
   - ? Temporal relationship between time of induction and onset of subfertility

19. Model for Treatment of endometriosis-associated subfertility (Falconer et al, 2007)

with standardization for:
1. Degree of endometriosis (amount EM for Ipseeding)
2. Ovulation (perineal cycle),
3. Male factors (proven fertility, nl sperm)
4. Sexual intercourse
   - timing
   - behavioral observation
   - postcoital test
UNICITY OF BABOON MODEL

20. Endometriosis-associated pain
- Under investigation at IPR
- Pilot study in 5 baboons with 24 hour camera surveillance before-after induction
- Collaboration Dr Coleman (Oregon Primate Center, USA)

VALIDATION OF BABOON ENDOMETRIOSIS MODEL

- Pub Med (updated 28th Jan 2009):
  - Baboon AND Endometriosis N=62
    - 34 Leuven-IPR Nairobi group (T. D’Hooghe)
    - 14 Chicago group (A. Fazleabas)
    - 6 San Antonio Group (B. Barrier)
    - 8 others

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5 observations

BABOON ENDOMETRIOSIS MODEL

- Uninterrupted retrograde menstruation causes endometriosis
- Endometriosis causes pelvic inflammation + systemic immunomodulation
- Endometriosis causes secondary endometrial changes
- General immunosuppression does not cause or cure endometriosis
- Specific immunomodulation may prevent and/or cure endometriosis

UNINTERRUPTED RETROGRADE MENSTRUATION CAUSES ENDOMETRIOSIS

1. Prevalence of spontaneous endometriosis increases with duration of captivity (D’Hooghe et al., 1996a).
2. Spontaneous endometriosis is progressive when followed during 2 years (D’Hooghe et al., 1996b).
3. Baboons with an initially normal pelvis develop in 64% histologically proven minimal endometriosis after 32 months (D’Hooghe et al., 1996c).
4. Positive correlation between weight of EM tissue used for intrapelvic seeding and extent of endometriosis in baboons (D’Hooghe et al., 1995).

UNINTERRUPTED RETROGRADE MENSTRUATION CAUSES ENDOMETRIOSIS

5. Iatrogenic obstruction of the cervix (supracervical ligation) leads to diminished antegrade menstruation + pelvic endometriosis within 3 months (D’Hooghe et al., 1994).
6. Menstrual EM: higher capacity than secretory EM in endo induction (D’Hooghe et al., 1995).
ENDOMETRIOSIS CAUSES
PELVIC INFLAMMATION + SYSTEMIC IMMUNOMODULATION
(D’Hooghe et al., 2001, Kyama et al., 2003)

1. PF: Increased volume, WBC conc, inflamm cytokines:
   - during spontaneous retrograde menstruation
   - following intrapelvic injection of endometrium (within 1/12)
   [D’Hooghe et al., 1999, D’Hooghe et al., 2001].

2. PF: Increased WBC concentration, increased % of macrophages and cytotoxic T cells:
   - in PF of baboons with spontaneous endometriosis
   [D’Hooghe et al 1996a, D’Hooghe et al 1997a].

3. PB:
   increased % of CD4+ and IL2R+ cells in baboons with stage II-IV endo
   (both spontaneous long term endo and induced endo)
   < recent spontaneous endometriosis (Stage I) or nl pelvis.

Endometriosis causes secondary EM changes

• Research Group A. Fazleabas (Chicago)
• Clinical relevance to endometriosis-associated subfertility
General immunosuppression does not cause or cure endometriosis

3/12 high dose immunosuppression with azathioprin and methylprednisolone

1. No effect on:
   - the incidence of spontaneous endometriosis
   - the extent of induced endometriosis,

2. Only marginal stimulatory effect on:
   progression of spontaneous endo

[D’Hooghe et al., 1995c]

Specific immunomodulation may prevent and/or cure endometriosis

- PPAR-gamma activators reduce and prevent induced endometriosis (Lebovic et al, 2007; 2009)
- TNF alpha antagonists prevent and reduce spontaneous or induced endometriosis, mainly via an effect on active red peritoneal lesions (3 independent studies Barrier et al, 2004; D’Hooghe et al, 2006; Falconer et al, 2006)

MAJOR CONCERN: GENERAL AND REPRODUCTIVE SAFETY

Overall conclusions

- NHPs = most relevant preclinical models for endo research
- Among NHPs, baboons represent
  - the most relevant and
  - the best validated model for endo research
Overall conclusions

Most important areas of endometriosis research in baboons:
1. Early pathogenesis
2. Cause-effect relationship studies
   may lead to discovery of new biomarkers
   and therapeutic targets
3. Test new drugs in prevention or treatment of endometriosis and
   endometriosis-associated subfertility
4. Test new endometriosis drugs with respect to general and
   reproductive safety
5. Validation baboon model for pelvic pain

Overall conclusions

Long term support for IPR, Nairobi, Kenya
1. Increasing international collaboration
2. Role of IPR International Advisory Board,
   Kenya Government and WHO

GLOBAL RESEARCH EFFORT TO STUDY
CAUSE-EFFECT RELATIONSHIPS OF ENDOMETRIOSIS
IN BABOON MODEL AT IPR
1. Sufficient N baboons with long term follow-up (+ pain)
2. Paired comparisons before+after induction (+ pain)

Building biobank for international collaborative research

Acknowledgments of mentors

- Institute Primate Research, Nairobi, Kenya: CS Bambra, PhD
- Harvard Medical School, Boston, USA
  (93-95) JA Hill, MD; DJ Anderson, PhD
Leuven-Nairobi Endometriosis Research Group

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A. Sharkey (Cantbride, UK)
F. Véghes (Budapest, HUN)

K. Coleman (Oregon Primate Center, USA)

EU Network for Endometriosis (ENE)

PhD Students Leuven – int’l
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H. Falconer (Karolinska)

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Ph Aalberg
V Vloeberghs

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F. Enssie
U. Vansteendbrrok
M Vermeers

Center for Medical Genetics
JF Fryes
E Engel
T de Rond de l’Argenber
Andrology
D Vanendscharens
Ph Mees

Urology
D Dételéer
D Bugaert

Parental staff
E Rotbroeke
H De Bie
K Ghoutt
J Gerserins
V Giglens
S Kompfner
K Lerauer
L Mafia
L Bijnen
S Schillenderen
H Verbeet
S Vliechenderen
A Verlinden
C Crayen
W Louis
G Roels

Fertility Lab
S Debrock
G Barts
D Willers
H Deve
e
A. Aerts
D De Waele
L Hollanders
A Versluis
F Vynckers
P Bils
B Vergoossen
A Buiters
D Quirinnes

Urology
D Kröger
D De Vlaeminck

Europian Network on Endometriosis

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- 8 Associate partners and 4 Collaborating partners
  - Endometriosis UK lead partner
  - Belgium, Denmark, Italy, UK

- Application scored very highly – 87/100 and received funding 300,000 Euro (2007-9)
International Collaboration

- Institute of Primate Research, Nairobi, Kenya, WHO Collaborating Center
- WHO
- University of Milwaukee, WI, USA (D. Lebovic)
- Oxford and Cambridge Universities, UK
- European Network Endometriosis
- Karolinska University, Stockholm, Sweden (H. Falconer)
- Semmelweis University, Budapest, Hungary (A. Bokor)
- Endometriosis Association, Milwaukee, USA
- World Endometriosis Research Foundation, London, UK

Funding since 1998

- Leuven University Research Council
- Leuven IRO (International Council for Development Collaboration)
- Leuven University Hospital Clinical Research Foundation
- Belgian Fund for Scientific Research (FWO)
- Belgian Institute for Science/Technology (IWT)
- Flemish Government (endocrine disrupters)
- Endometriosis Association USA
- University Michigan Ann Arbor, University Milwaukee, WI, USA
- World Endometriosis Research Foundation
- EU Public Health Grant
- Merck Serono Pharmaceuticals
  Serono Chair Reproductive Medicine 2005-2010

System biology tools and preclinical models for translational research in endometriosis and adhesion formation: lessons from cancer and inflammation biology.

ESHRE Campus 2009
Leuven Belgium, 4-5 September 2009