General Session:
The Art and Science of Endometriosis Research
(Didactic)

CHAIR
Victor Gomel, MD

Asgi T. Fazleabas, PhD    Robert N. Taylor, MD    Linda G. Griffith, PhD
Professional Education Information

**Target Audience**
This educational activity is developed to meet the needs of residents, fellows and new minimally invasive specialists in the field of gynecology.

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Table of Contents

Course Description........................................................................................................................................ 1

Disclosure...................................................................................................................................................... 3

Endometriosis in the Baboon – A Model to Understand This Enigmatic Disease
A.T. Fazleabas................................................................................................................................................ 4

Endometriosis Lesions Are Reported to Be “Estrogen Sensitive and Progesterone Resistant”
What Does This Mean for Our Clinical Management?
R.N. Taylor.................................................................................................................................................... 9

Systems Biology Approaches to Endometriosis
L.G. Griffith.................................................................................................................................................. 14

Cultural and Linguistics Competency ......................................................................................................... 21
General Session: The Art and Science of Endometriosis Research

Endometriosis in the Baboon – A Model to Understand This Enigmatic Disease

Asgi T. Fazleabas

Endometriosis results in chronic pelvic pain and infertility and affects 10% of women of reproductive age. The initiation of endometriosis is difficult to evaluate because at the time of clinical diagnosis the disease has been prevalent for 8-11 years in women. Therefore, identification of molecules involved with the early pathogenesis of endometriosis, non-invasive diagnosis and strategic therapies for treatment is critical. Using a baboon model endometriosis is induced via laparoscopic inoculation of menstrual tissue into the peritoneal cavity. Peritoneal endometriosis develops within one month and in turn markedly alters the gene signature of the eutopic endometrium during the window of uterine receptivity. During disease progression there is a transitory dominance of an estrogenic phenotype which eventually results in a more permanent progesterone resistant phenotype. Accompanying changes in miRNA’s also regulate target genes that contribute to increased proliferation, decreased apoptosis and inhibition of progesterone signaling.

Learning Objectives: At the conclusion of this course, the participant will be able to: 1) Recognize the importance of developing appropriate animal models to study human disease and evaluate the potential consequences of endometriosis on fertility.

Endometriosis Lesions Are Reported to Be “Estrogen Sensitive and Progesterone Resistant” What Does This Mean for Our Clinical Management?

Robert N. Taylor

This talk will provide the practicing physician and educator with a comprehensive review of evolving concepts about the derivation, pathogenesis and hormone responsiveness of endometriosis lesions. Abnormalities within the eutopic endometrium of women with endometriosis also will be defined, particularly emphasizing their impact on infertility and pelvic pain. Surgery continues to be the mainstay of endometriosis therapy, but ongoing research promises to offer new adjuvant approaches to enhance efficacy, improve compliance, or reduce side-effects of medical treatments. The rationale and potential advantages of these emerging strategies will be illustrated.

Learning Objectives: At the conclusion of this course, the participant will be able to: 1) Recognize the endocrine responsiveness of endometriosis lesions; and 2) interpret the rationale of emerging adjuvant medical therapies for symptomatic endometriosis.

Systems Biology Approaches to Endometriosis

Linda G. Griffith

This talk provides a basic introduction to how approaches from systems biology and tissue engineering are being applied to understand the etiology and pathophysiology of endometriosis, with the aim of aiding development new ways to diagnose and treat the disease. Computational systems biology
approaches integrate multiple kinds of data from various –omics measurements made on samples relatively easily obtained in surgical practice (e.g., peritoneal fluid) to provide insight on cellular crosstalk and possible points of intervention in inflammatory networks. Tissue engineering approaches allow cells from patients to be cultured in a physiological environment for analysis of disease processes and responses to potential therapeutics.

**Learning Objectives:** *At the conclusion of this course, the participant will be able to:* 1) Explain how computational systems biology approaches are being used to classify disease processes in endometriosis patients; and 2) identify opportunities to improve communication between surgeons and scientists about how to describe endometriosis disease processes.
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop and have no conflict of interest to disclose (in alphabetical order by last name).
Art Arellano, Professional Education Manager, AAGL*
Viviane F. Connor
Consultant: Conceptus Incorporated
Kimberly A. Kho*
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FACULTY DISCLOSURE
The following have agreed to provide verbal disclosure of their relationships prior to their presentations. They have also agreed to support their presentations and clinical recommendations with the “best available evidence” from medical literature (in alphabetical order by last name).
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Victor Gomel*
Linda G. Griffith*
Robert N. Taylor
Consultant: AbbVie, Allere

Asterisk (*) denotes no financial relationships to disclose.
ENDOMETRIOSIS IN THE BABOON: A MODEL TO UNDERSTAND THIS ENIGMATIC DISEASE

Asgi T. Fazleabas
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Mechanisms of Hormone Resistance & 42nd Global Congress on Minimally Invasive Gynecology
November 13th, 2013

DISCLOSURE

I have no financial relationships to disclose.

OBJECTIVES

Learning Objectives:
1) Recognize the importance of developing appropriate animal models to study human disease.
2) Evaluate the potential consequences of endometriosis on fertility.

LIMITATIONS IN OUR UNDERSTANDING OF ENDOMETRIOSIS

Endometriosis was first described in 1690 by Daniel Shroen. In 1927, Sampson first proposed his theory of retrograde menstruation. However, we still do not understand the underlying mechanisms associated with:
- The spontaneous evolution of endometriosis AND whether an inherently defective endometrium contributes to the growth of endometriotic lesions?
- Does the presence of endometriotic lesions affect the uterine endometrium?
- What is the pathophysiology of endometriosis-associated infertility?

ADVANTAGES OF THE USE OF PRIMATES AS A MODEL FOR ENDOMETRIOSIS

- Reproductive anatomy and physiology are similar to humans.
- Non-human primates develop endometriosis spontaneously and the disease can also be induced which is histologically similar to the human disease - absent in non primate models.
- Ability to induce the disease permits the study of its etiology and progression from the time of initiation of the disease.
- Long term and invasive studies and multiple surgical procedures are possible under experimentally controlled conditions.
- Close phylogenetic relationship permits the use of human molecular probes and antibodies.
- Evaluation of treatment modalities for the human disease can be tested for treatment and long term safety.
**EXPERIMENTAL DESIGN**

**INDUCTION OF ENDOMETRIOSIS**

- **Menses**
  - Laparoscopy & Innoculation with Menstrual Tissue
  - Induced disease in the baboon
  - Spontaneous bubble in women

**CHANGES IN ENDOMETRIAL GENE EXPRESSION DURING THE WINDOW OF UTERINE RECEPTIVITY**

- **Innoculation**
- **Early Responses**
  - FOS
  - CYR61
  - EMMRIN
- **Late Responses**
  - PROGESTERONE RESISTANCE
  - Pgr
  - PPAR
  - Calcitonin
  - HOXA10

**TIME COURSE OF GENE DYSREGULATION EUTOPIC**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Genes differentially expressed</th>
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<tr>
<td>1</td>
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<td>1,613 genes</td>
</tr>
<tr>
<td>12</td>
<td>2,170 genes</td>
</tr>
</tbody>
</table>

**CHANGES IN GENETIC EXPRESSION DURING THE WINDOW OF UTERINE RECEPTIVITY**

- **Early Responses**
  - FOS
  - CYR61
  - EMMRIN
- **Late Responses**
  - PROGESTERONE RESISTANCE
  - Pgr
  - PPAR
  - Calcitonin
  - HOXA10

**MIR-29c EXPRESSION PATTERN**

- **miR-29c expression in Baboon Endometrium**
  - Fold Change: D, C
  - P-values: 0.0012, 0.0335

**WHAT ARE THE TARGETS OF MIR-29c?**

- Target prediction for miR-29c.
- Predicted interaction between miR-29c and various targets.
- Seed sequence of miR-29c: AUUGGUGAAGUUUCCAGCUU.

**MICRO RNA’S – A SIGNIFICANT ROLE IN ENDOMETRIOSIS?**

miRNA’s play a significant role in normal physiological development and pathologic conditions. Biologically plausible miRNA targets have the clinical utility of being selected for the development of agonists or antagonists.
Studies in the rodents have established that progesterone receptor mediated uterine receptivity is controlled by FKBP4. FKBP4 knockout mice have an implantation failure phenotype. Absence of FKBP4 may be associated with progesterone resistance observed in endometriosis.

**WHY FKBP4?**

FKBP4 gene codes for the FKBP52 protein. FKBP4 is a co-chaperone associated with the steroid hormone receptor complex. Studies in the rodents have established that progesterone receptor mediated uterine receptivity is controlled by FKBP4. FKBP4 knockout mice have an implantation failure phenotype. Absence of FKBP4 may be associated with progesterone resistance observed in endometriosis.

**WESTERN BLOT SHOWING FKBP52 PROTEIN EXPRESSION IN MID-SECRETORY PHASE IN EUTOPIC ENDOMETRIUM OF BABOON AND HUMAN**

**DECIDUALIZATION AND OPTIMAL PREGNANCY OUTCOME**

- Decidualization is compromised as a consequence of endometriosis.
  - Impaired decidualization is associated with implantation failure.
  - Defective decidualization leads to recurrent pregnancy loss.
  - Absent or deficient decidualization is associated with potentially catastrophic hemorrhage seen in patients with ectopic pregnancy or placenta accreta (abnormal deep placental invasion).
  - Decidual senescence contributes to pre-term labor and premature fetal delivery.

**CORRELATION OF FKBP4 EXPRESSION AND IMPAIRED DECIDUALIZATION IN ENDOMETRIOSIS**

**POSTULATED MECHANISM OF miR 29c AND FKBP52 INTERACTION IN THE PATHOGENESIS OF ENDOMETRIOSIS**

- Impaired decidualization is associated with implantation failure.
- Defective decidualization leads to recurrent pregnancy loss.
- Absent or deficient decidualization is associated with potentially catastrophic hemorrhage seen in patients with ectopic pregnancy or placenta accreta (abnormal deep placental invasion).
- Decidual senescence contributes to pre-term labor and premature fetal delivery.
Cytoskeletal reorganization and Notch 1 expression are coupled with decidualization

- Notch1 transcriptionally regulates the expression of αSMA, which is essential for decidualization.
- Notch 1 expression in stromal cells is critical for the initiation of decidualization.
  Afshar et al. Endo 2012
- αSMA expression is blunted in the endometrium of baboons with endometriosis.
  Sherwin et al., Endo, 2010
- Inhibition of Notch1 in stromal cells prevents cells from undergoing decidualization.

Working Hypothesis
- Notch is an evolutionary conserved arbiter of cell fate and regulates diverse cellular functions, including survival, proliferation, and differentiation.

αSMA, FOXO1 & FOXO3a
IL11, COX-2
Inhibit Apoptosis & Initiate Differentiation

αSMA
Progesterone INHIBITION OF NOTCH SIGNALING AT THE INITIATION
Notch 1
of DECIDUALIZATION INHIBITS STROMAL CELL DIFFERENTIATION

Altered expression of the Notch signal transduction cascade in endometriosis

Human Endometrium - Spontaneous Disease

Altered expression of the Notch signal transduction cascade during in vitro decidualization

Inhibition of Notch signaling at the initiation of decidualization inhibits stromal cell differentiation

Working Model: Notch 1 as an Initiator of Decidualization
CONCEPTUS MEDIATED TRANSFORMATION OF THE STROMAL FIBROBLASTS

ENDOMETRIOSIS

Progesterone Resistance

Inhibition of Decidualization Cascade

Decidual cell

CG

& Progesterone

CONCEPTUS MEDIATED TRANSFORMATION OF THE STROMAL FIBROBLASTS

Conceptus

IL-1

α

SMA & Notch-1

IGFBP-1 & Prl

REFERENCES


Endometriosis Lesions are Reported to be ‘Estrogen Sensitive and Progesterone Resistant’: What Does this Mean for Our Clinical Management?

Robert N. Taylor, MD PhD
Department of Obstetrics and Gynecology
Wake Forest School of Medicine

Learning Objectives

At the conclusion of this course, the participant will be able to:

1) recognize the endocrine responsiveness of endometriosis lesions; and
2) interpret the rationale of emerging adjuvant medical therapies for symptomatic endometriosis.

Classical Hormone Induced Changes in Endometrial Morphology

Noyes et al, 1950
Markee, 1978

Effects of Steroid Hormones on Endometrial and Endometriosis Cells

Estrogen: activation of the cell cycle epithelial & stromal mitogenesis angiogenesis

Progesterone: epithelial secretion receptivity biomarker induction stromal edema & decidualization preparation for apoptosis
Estrogen Receptor Action, 2013

Estrogen Receptor β is Over-expressed in Endometriosis Cells

ERβ increased 3x in endometriosis vs. normal endometrial stromal cells (Brandenberger et al, 1999)

ERβ/ERα increased >30x in endometriosis vs. normal endometrial tissues (Xue et al, 2007)

Cell Cycle Regulation

Estradiol Stimulates PCNA in Endometriosis Stromal Cells

Proliferating Cell Nuclear Antigen: an 36 kDa homotrimeric DNA binding protein increases the processivity of DNA polymerase δ and leading strand synthesis during DNA replication

G1 / S checkpoint

10 nM E2

0h 8h 24h

PCNA (36 kDa)

β-actin (42 kDa)

Medical Treatments Reduce PCNA And Cell Proliferation in Lesions

PCNA Expression in Murine Endometriosis is ER and PR Dependent

Gomes et al, 2009

Fang et al, 2004
Return of Postoperative Pain in Endometriosis

Stratton et al, 2008

Progesterone Receptor Mechanism of Action

RNA pol II transcription complex

PR-A PR-B

Stromal Cells from Eutopic Endometrium of Endometriosis Patients show Impaired Decidualization

Yu et al, under review

Progesterone Receptor, ergo Response, is Reduced in Endometriosis Cells

Attia et al, 2000

Endometriosis Normal

proliferative secretory

endometriosis normal

Dmowski et al, 2001

Apoptosis: “The ‘Dropping Off’ of Leaves from Trees”

“programmed cell death”

Endometrial Apoptosis: Reduced TUNEL in Eutopic Endometrium

Dmowski et al, 2001
“Reflux Redux”: Disposition of Shed Menstrual Endometrium in Women

Norethindrone Acetate (2.5 mg/d) is Partly Effective in Relief of Pelvic Pain

Vercellini et al, 2012

Natural Herbal Chemotherapeutics?

Curcumin has Multiple Relevant Cellular Targets in Endometriosis

Curcumin and EF-24 Induce Apoptosis In Endometriosis Cells

Novel Curcumin Analogs have Improved Potency and Bioavailability
Summary

- Endometriosis cells are estrogen sensitive and show time- and dose-dependent PCNA induction; P₄ resistance may render these cells less prone to cell cycle blockade
- Selective estrogen receptor modulators, to date, have not demonstrated much clinical efficacy for pain relief
- Programmed cell death in endometrial stromal cells is progesterone dependent and dysregulated in endometriosis
- While moderately effective, P₄ resistance due to low PR expression may limit the clinical utility of progestins for endometriosis pain
- Natural herbal compounds, including curcumin, can induce stromal cell apoptosis via NF-κB, relatively independent of PR
- Synthetic curcuminoids (eg, EF-24) have good bioavailability, high potency and are promising new agents for non-hormonal therapies of endometriosis symptoms

References


Endometriosis Study Collaborators

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Why are endometriosis patients different from other women - and different from each other in how they respond to therapies?

- Genes?
- Exposure to environmental chemicals?
- Infections?
- Parental/Grandparental Exposure to (environmental) chemicals/radiation?
- Nutrition (gut microbiota)?
- Infections?

**Endometriosis**

Is not a benign disease

- Incidental finding during surgery for something else
- Symptomatic (minimum/mild)
- Symptomatic (moderate/severe/deep infiltrating)
- Malignant (cancer)

1. How to stratify patients for treatment?
   - Pre-surgery – imaging, response to OCP (biomarkers)
   - Post-surgery – geographic & morphological appearance of lesions (molecular biomarkers?)
2. Molecular mechanisms of disease progression – new drugs
3. Disease Etiology and prevention

**Consensus Molecular Markers for Stratification of Breast Cancer Patients**

- **ER**
  - Surgery
  - Surgery + radiation
- **PR**
  - Surgery + standard chemotherapy (e.g., AC/T) + radiation
  - Surgery + standard chemotherapy + herceptin + radiation
- **HER2**
  - Surgery + dose-dense chemotherapy + radiation

Most breast cancers are spontaneous – genetic markers like BRCA1 may guide facets of treatment, but for only a small fraction of patients.

**Similar Markers for Endometriosis?**

- ER
- PR
- HER2

**Human Genome**

- Over 3 billion base pairs
- Only 2% of total codes for proteins (~25,000 genes)
- Cost to sequence a complete human genome
  - >30,000 individuals completely sequenced to date
- Maps of regions that vary most enable clinical researchers to use lower-cost (~$300) partial sequencing methods to compare patients

**Disclosure**

I have no financial relationships to disclose.
Are genetic tests on the horizon?

Genome-Wide Association Studies ("GWAS")
Identify candidate genetic loci associated with disease risk
- Complex traits require very large populations with careful phenotyping
  - GWAS results have identified 3 possible loci but explain very little of the heritability
    - Separating studies in Japanese and European populations yielded different top candidates
    - Relatively small population sizes and crude phenotype (i.e., endometriosis vs not) limits analytical power
    - Need much better symptomatic/clinical stratification of patients to improve resolution

Endometriosis GWAS results have identified 3 possible loci but explain very little of the heritability
- Separate studies in Japanese and European populations yielded different top candidates
- Relatively small population sizes and crude phenotype (i.e., endometriosis vs not) limits analytical power
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Statistical Comparisons
- Replication


Epigenetic Modification in Endometriosis
- DNA & histone modification alter gene transcription
- Drugs modifying the enzymes in these processes are being studied for cancer & several inflammatory diseases, including endometriosis – but they are relatively non-specific
- Histone de-acetylase inhibitors (HDAcs)
  - Valproic acid
  - Romidepsin
  - suberoylanilide hydroxamic acid
- DNA methylation reversal
  - 5-Aza-2’-deoxycytidine
- DNA & histone modification

Insights are only the tip of the iceberg

Genomic Insights are only the tip of the iceberg
- Need epigenomics to understand the whole picture – inherently an inflammatory process involving multiple processes

Caution: targeted drug discovery should not be disconnected from mechanistic understanding of dynamic signaling networks
“Systems Biology” integrates information flow over multiple hierarchies

DNA → RNA → Protein → Metabolites

- Genomics
  - GWAS/SNP
  - ChIP-Seq
  - Deep sequencing
  - Methylation
- Transcriptomics
  - mRNA expression
  - miRNA expression
- Proteomics
  - Phospho-proteomics
  - Protein mass spectrometry
- Metabolomics
  - Lipidomics
  - Glycoproteomics

Integrative Analysis

Biological Insight

Clinical Management

Wish list (quantitative annotated data base of surgical findings, symptoms)

**Can we learn how to intervene, in predictive manner, in complex multi-cellular, multi-cytokine/chemokine, multi-pathway system?**

- e.g., for therapeutic targets (likely combinatorial)
- small molecule pathway inhibitors
- cytokines/chemokines or blocking antibodies
- cell additions or depletions

**Can we learn how to intervene, in predictive manner, in complex multi-cellular, multi-cytokine/chemokine, multi-pathway system?**

Notion: a multitude of molecular and cellular constituents are all important; the problem is not presuming to ascertain which is “singularly important” (i.e., the ‘magic bullet’ target), but rather what happens when any/some of these in particular are perturbed

**Multiplex Molecular Profiling of Inflammatory Cytokines**

**Unsupervised Molecular Classification of Endometriosis Patients using Highly Multiplexed Molecular Profiling of Peritoneal Cytokines**
### Hematopoietic Expression Profile Databases

<table>
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<th># Populations</th>
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<td>Immunological Genome Project</td>
<td>Mouse</td>
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<td>221</td>
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</table>

### Predicted Immunologic Network

![Diagram of Predicted Immunologic Network]

### In vitro Evidence for Peritoneal Macrophage Activation

- Controls
- Endometriosis
- Insights into new therapies targeting activation pathways

### EPHect Project:

**Endometriosis Phenome and Biobanking Harmonisation Project**

- Facilitate large-scale, cross-centre, longitudinal, epidemiologically robust, biomarker and treatment target discovery research in endometriosis
- Consensus format for detailed clinical phenotyping (phenome) data to be collected from women with endometriosis and controls to allow collaborative sub-phenotype discovery and validation analyses;
- Consensus Standard Operating Procedures (SOPs) for banking of biological samples from women with endometriosis and controls

**Essential connection between the clinical and basic research communities**

**Building an Endometriosis “APP” for patient management and research data collection (beyond RedCap)**

- Open source
- Data encryption via Mylar
- Web-based platform for mobile or other formats
- Future Bluetooth device integration
http://endogentest.meteor.com

- (will log on to APP web site here to demo)

Quiz

- Genome-wide association studies of endometriosis patients have resulted in a genetic test for endometriosis susceptibility in European women (yes/no)
  Answer = No

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NIH Transformative R01 – NBIB
Anonymous Foundation

Three Facets of System Integration Needed

“Horizontal” – greater number of molecular components considered together
“Vertical” – greater number of space and time scales considered together
“Operational” – greater number of properties considered together

[D. Lauffenburger, Integrative Biology (2012)]

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[D. Lauffenburger, Integrative Biology (2012)]

MIT BE
Cultural and Linguistic Competency

Governor Arnold Schwarzenegger signed into law AB 1195 (eff. 7/1/06) requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California’s physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP).

California Business & Professions Code §2190.1(c)(3) requires a review and explanation of the laws identified above so as to fulfill AAGL’s obligations pursuant to California law. Additional guidance is provided by the Institute for Medical Quality at http://www.imq.org

Title VI of the Civil Rights Act of 1964 prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 http://www.usdoj.gov/crt/cor/pubs.htm.

Executive Order 13166, “Improving Access to Services for Persons with Limited English Proficiency”, signed by the President on August 11, 2000 http://www.usdoj.gov/crt/cor/13166.htm was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

Dymally-Alatorre Bilingual Services Act (California Government Code §7290 et seq.) requires every California state agency which either provides information to, or has contact with, the public to provide bilingual interpreters as well as translated materials explaining those services whenever the local agency serves LEP members of a group whose numbers exceed 5% of the general population.

If you add staff to assist with LEP patients, confirm their translation skills, not just their language skills. A 2007 Northern California study from Sutter Health confirmed that being bilingual does not guarantee competence as a medical interpreter. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2078538.