Translational Research in Endometriosis

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ESHRE Campus Course, Leuven 2009
Key global R&D facts, 1995-2004
Success rates from first-in-man to registration

(Kola I., 2004 Nat Rev Drug Discovery)
Reasons for attrition in the clinic

(Kola I., 2004 Nat Rev Drug Discovery)
What is slowing down drug development in endometriosis

- No validated, predictive therapeutic models
- No therapeutic models for endometriosis-related pain
- No diagnostic tools
- Clinical studies complicated: no biomarkers for patient stratification or early proof-of-concept
- No biomarkers/surrogate endpoints to monitor therapeutic efficacy endpoint, pain
- Lack of novel, innovative targets
### Overview of the endometriosis pipeline, 2007

<table>
<thead>
<tr>
<th>Brand/Research code</th>
<th>Generic</th>
<th>Formulation</th>
<th>MoA</th>
<th>Originator</th>
<th>Licensee</th>
<th>Status</th>
<th>Country</th>
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</thead>
<tbody>
<tr>
<td>Visanne</td>
<td>dienogest</td>
<td>Oral</td>
<td>Progesterone agonist</td>
<td>Jenapharm GmbH &amp; Co KG</td>
<td>Mochida, Bayer/Schering</td>
<td>Pre-registration (Japan), Phase III (W.EU)</td>
<td>Japan, W.EU</td>
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<tr>
<td>Libra</td>
<td>deslorelin, estradiol, testosterone</td>
<td>nasal spray</td>
<td>GnRH agonist; estradiol agonist; Androgen</td>
<td>Balance Pharma</td>
<td>n/a</td>
<td>Phase III</td>
<td>US</td>
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<tr>
<td>FP-1096</td>
<td>n/k</td>
<td>vaginal/intrauterine oral capsule</td>
<td>receptor agonist possible androgen</td>
<td>FemmePharma</td>
<td>KV Pharma</td>
<td>Phase III</td>
<td>US</td>
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<tr>
<td>Proellex/Progenta (CDB-4124)</td>
<td>n/k</td>
<td>n/k</td>
<td>Selective progesterone modulator aromatase inhibitor estrogen receptor beta agonist</td>
<td>National Institutes of Health</td>
<td>Repros Therapeutics</td>
<td>Phase II</td>
<td>EU &amp; US</td>
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<tr>
<td>Femathina (MPI-674)</td>
<td>n/k</td>
<td>oral tablet</td>
<td>GnRH antagonist</td>
<td>Meditrina Pharma Pfizer¹</td>
<td>Wyeth Research</td>
<td>Phase II</td>
<td>US</td>
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<td>ERB-041, WAY-202041</td>
<td>n/k</td>
<td>Oral</td>
<td>beta 2 adrenoreceptor</td>
<td>Neurocrine Biosciences Columbia Laboratories and</td>
<td>n/a</td>
<td>Phase II</td>
<td>US</td>
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<tr>
<td>NBI-56418</td>
<td>terbutaline</td>
<td>vaginal gel</td>
<td>beta 2 adrenoreceptor</td>
<td>n/a</td>
<td>Phase II</td>
<td>US</td>
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<tr>
<td>A-ENDO</td>
<td>n/k</td>
<td>Oral</td>
<td>agonist; Androgen modulator; estrogen &amp; progesterone receptor agonist</td>
<td>Ardana Pantarhei Bioscience</td>
<td>n/a</td>
<td>Phase II</td>
<td>Netherlands</td>
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<td>SH-T-04268-H</td>
<td>n/k</td>
<td>Oral</td>
<td>Chemokine receptor antagonist GnRH antagonist</td>
<td>Bayer Schering Pharma AG</td>
<td>n/a</td>
<td>Phase II</td>
<td>EU</td>
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<td>Antarelix</td>
<td>teverelix extended release subcutaneous injection n/k</td>
<td>steroid sulfatase inhibitor sodium channel inhibitor Progesterone receptor agonist</td>
<td>PregLem Metris Therapeutics Population Council</td>
<td>Zentaris GmbH Arcana</td>
<td>n/a</td>
<td>Phase I</td>
<td>UK</td>
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<tr>
<td>PSD-509 (M-5004)</td>
<td>n/k</td>
<td>vaginal/intruterine subdermal implant</td>
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<td>Metris Therapeutics Population Council</td>
<td>n/a</td>
<td>Phase I</td>
<td>UK</td>
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<tr>
<td>Nestorone (ST-1435)</td>
<td>synthetic progestin</td>
<td></td>
<td></td>
<td>Plethora Solutions Preclinical</td>
<td>n/a</td>
<td>Preclinical</td>
<td>US</td>
</tr>
</tbody>
</table>

1. Contract manufacturing and supply agreement with Pfizer
GnRH = gonadotrophin, MoA = mechanism of action, n/a = not applicable, n/k = not known

Target discovery

Target identification
- Internal Research
- Literature Research - Collaborations
- Bioinformatics (external databases)
- Research on physiology / disease (models)

In vivo validation
- Tissue distribution
- Transgenic animals
- Knockout animals
- Human genetics

Overexpression
- Transfection
- Transduction

Functional interference
- siRNA
- Blocking antibodies
- Antisense
- Induce mutations
Research focusses of academia and industry: an understandable mismatch

**University (Medical Center)**
- Hypothesis driven
- Funding guided
- Publication oriented

**Pharma**
- Target/compound driven
- Patent/market oriented

**How to create synergy**
- Understand biology
- Improve diagnosis/therapy
- Identification of NCEs
- Proof-of-mechanism
- Structure-activity relation
- Develop novel, better, safer drugs
What makes a target

- A biological entity that is linked to a disease
- Inhibition (or activation) of this biological entity should reverse the development or inhibit progression of the disease
- Must be assayable in order to develop HTS assays
- Must be drugable
Currently Identified Drug Targets: ~ 500

- Receptors (52%)
- Enzymes (22%)
- Growth factors (13%)
- Miscellaneous (7%)
- Unknown (6%)

Source: J. Drews, Hoffman - La Roche, Nature Biotechnology, November 1996
General R&D process

Lead Finding
- Target
- Lead
- Lead Optimization
- Selection phase

Lead Optimization
- Discovery
- Early clinical development
- Full Development and Launch

Research
- Prioritization over projects

Development

Prioritization over projects
Success rates by phase of development

Failure rate of Proof-of-concept (Phase II) and efficacy studies (Phase III) is 80%
General R&D process

Lead Finding
- Target
- Lead
- Lead Optimization
- Selection phase

Lead Optimization
- Phase I Safety/tolerability
- Phase II Proof-of-concept
- Phase III Efficacy

Discovery
- Early clinical development
- Prioritization over projects

Research

Development
- Full Development and Launch
Translational Research/Medicine

Translational medicine is the integrated application of:

- innovative pharmacology tools
- biomarkers
- clinical methods and technologies
- study designs to improve confidence in drug targets
- increase confidence in drug candidates
- understand the therapeutic index in humans
- enhance cost effective decision making

in exploratory development and increase phase II success leading to a sustainable pipeline of new products

Bruce H. Littman MD
VP translational medicine Pfizer, quote 2006
Implementation

- Predictive therapeutic models
- ID and validate biomarkers prior to FIH
- Develop clinical assays/technologies, i.e. MRI, serum/urine-based assays biomarkers/surrogate endpoints
- PK/PD
- Ask the right questions to get the right answers, to make the right decisions
- Early feedback from clinical studies
Ask the right questions to get the right answers, to make the right decisions

- Compound selection

- Traditionally we only ask: does the drug work and is it safe?

- We need to ask other questions as well: why does it (not) work and why is it (not) safe?
Question based approach

- Does the compound get to the site of action?
- Does the compound modulate the target?
- Does the compound cause its intended pharmacological/functional effects?
- Does the compound have beneficial effects on disease or clinical pathophysiology?
- Does the compound modulate non-registration endpoints that predict efficacy?
- What are the key toxicity issues related to the therapeutic target/compound that determine the efficacy/safety ratio?
- What is the therapeutic window (how safe is the drug)?
- How do sources of variability in drug response in target population affect efficacy and safety?

BIOMARKERS
PK-PD models transform biomarkers into a quantitative decision making tool

• In many cases, biomarkers are the PD in PK-PD
• Optimal use of a biomarker requires that we relate the biomarker response to the PK data in order to understand the determinants of the response
• Mechanistic PK-PD models describing exposure-response and time course of response of biomarkers can:
  – increase our confidence in the mechanism of action
  – help predict the anticipated human dose and assess therapeutic window
Important assets of PK-PD M&S in relation to biomarker data

- PK-PD models can do more than describing concentration response relationships:
  - Can describe **time dependencies** in response to treatment
  - Can range from **empirical** to **mechanistic**
  - Allow **pooling of data** from different trials and different sources (e.g. literature)
  - **Translate** biomarker data across species
  - Models enable **predictions** of drug effects in situations that have not yet been tested
Preclinical *vitro/vivo* disease models

- Cultures (immortalised) cells from endometrium/endometriotic tissue
- Tissue recombination under renal capsule immortalized human endometriotic cell lines
- Mouse primary xenografts (human endometrium/endometriosis tissue from patients)
- Non-human primate models for endometriosis (Rhesus maqaque, baboon)
**General R&D process**

**Research**
- Target
- Lead
- Lead Optimization
- Selection phase

**Discovery**
- Early clinical feedback essential
- Target validation
- Develop in vitro/vivo disease model/assays

**Development**
- Phase I
  - Safety/tolerability
- Phase II
  - Proof-of-concept
- Phase III
  - Efficacy
- Registration
- Marketing
- Full Development and Launch

**PK/PD**
- Biomarker discovery, assay development and validation
Translational research in endometriosis

• Rigorous validation of targets and disease models is needed in order to confidently select the best compounds as early as possible

• Biomarkers/surrogate endpoints (and validated assays to measure them, are essential to be able to receive clinical feedback in a much earlier stage in order to realise earlier deselection/selection of clinically active compounds