DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

- Research support and/or consultant and/or lecturer for AbbVie, Aflecta, Amgen, Inc., Avillon, Boehringer-Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen Biotech, Inc., LEO Pharma, Menlo, Novartis, OrthoDermatologics, Pfizer, Procter & Gamble, Promius, Regeneron, and Sun Pharmaceuticals

- No stock ownership or Board membership on any Pharmaceutical or Biotechnology company
Fact: Psoriasis is phenotypically a very diverse disease, with 40+ proven gene associations.

Question: Can we target specific therapies to specific psoriatic phenotypes and/or genotypes, i.e. Pharmacogenomics?
Tertiary Care Psoriasis Clinic at Baylor, Dallas Current Patients on Systemic (Biologic and Non-Biologic) Agents as per January 31, 2018 TOTAL 1,940 Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of patients</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Injectable Biologic Agents</td>
<td>1194</td>
<td>65%</td>
</tr>
<tr>
<td>Systemic Oral Agents</td>
<td>746</td>
<td>35%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1,940</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: A number of patients on biologic agents are also receiving concomitant systemic agents, predominantly MTX.
Unmet Needs in the Treatment of Moderate-to-Severe Psoriasis (1)

Questions:

• What are the deficiencies in our current armamentarium that makes the development of new therapies important?
• Has the biologic revolution in psoriasis impacted the patient experience?
• If there is a large unmet need and psoriasis is more common than other immune-mediated inflammatory diseases (e.g. R.A. and Inflammatory Bowel Disease [IBD]), can we ever elevate psoriasis to the status of IBD or R.A.?
Unmet Needs in the Treatment of Moderate-to-Severe Psoriasis (2)

How can we improve these deficiencies?

- Psoriasis Advocacy and Research Associations
  - IFPA, NPF
  - IPC
- Patient and Public Perceptions
- Reimbursement groups – do they still reign supreme?
- Pharmaceutical Industry
- FDA and EMA

…and yes, we as Dermatologists need to be more involved.
Management of psoriasis begins by identifying the extent of cutaneous disease. However, a holistic, contractual approach to treatment is encouraged, with particular reference to psychosocial disability and quality-of-life issues. The use of new treatments should not be a substitute for a detailed evaluation and discussion with patients to ascertain their expectations.
Current Therapies for Psoriasis

Mild disease
- Topicals
- Steroids
- Vitamin D$_3$
- Retinoids
- Tars
- Dithranol

Moderate disease
- Phototherapy, including
  - BB UVB
  - NB UVB
  - Laser directed NB UVB
  - Home units

Severe disease
- PUVA
- Systemic agents (4)
- Biologic agents – all large molecules currently (8)

Combination of all of the above in a significant percentage of patients

So, what is coming down the pipeline?
Clinical Research

Drug Safety
(Phase I)

Is it Safe?

• Using healthy study participants, researchers determine the mode of action, safety and side effects in this phase.
• This phase usually uses 20 to 100 healthy volunteers.
Clinical Research

Drug EFFICACY (Phase II)

Is it effective?

• Researchers use individuals-usually several hundred-who have the disease in question to determine if the drug is effective against that disease or condition.
Is the drug effective and safe in large groups of people?

- Using several hundred to several thousand patients, researchers work to gain a more thorough understanding of the drug’s effectiveness, benefits and the range of possible adverse events.
Clinical Research
FILINA
(Final Phase)

• Researchers file for approval of the research drug.
Drugs in the Psoriatic Therapeutic Pipeline
### Oral Treatments in the Pipeline (1)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo805K1</td>
<td>ApoPharma</td>
<td>Proprietary</td>
<td>II</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Eli Lilly/Incyte</td>
<td>Anti-inflammatory (JAK1 and JAK2 inhibitor)</td>
<td>II</td>
</tr>
<tr>
<td>FP187 (fumaric acid)</td>
<td>Forward-Pharma</td>
<td>Anti-inflammatory</td>
<td>II</td>
</tr>
<tr>
<td>KD025</td>
<td>Kadmon Corporation</td>
<td>Anti-inflammatory (ROCK2 inhibitor)</td>
<td>II</td>
</tr>
</tbody>
</table>
## Oral Treatments in the Pipeline (2)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prurisol</td>
<td>Cellceutix Corporation</td>
<td>Immune modulator (IL-20 and PRINS inhibitor)</td>
<td>II</td>
</tr>
<tr>
<td>VTP-43742</td>
<td>Vitae Pharmaceuticals</td>
<td>Anti-inflammatory (ROR-gamma T inhibitor)</td>
<td>II</td>
</tr>
<tr>
<td>XP23829</td>
<td>Dr. Reddy’s Laboratories and XenoPort</td>
<td>Anti-inflammatory (fumaric acid)</td>
<td>II</td>
</tr>
<tr>
<td>ZPL-389</td>
<td>Ziarco Pharma Ltd.</td>
<td>Anti-inflammatory (histamine H4 receptor antagonist)</td>
<td>II</td>
</tr>
</tbody>
</table>
## Oral Treatments in the Pipeline (3)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAS41008</td>
<td>Almirall</td>
<td>Anti-inflammatory (dimethyl fumarate)</td>
<td>III</td>
</tr>
<tr>
<td>Piclidenoson (CF101)</td>
<td>Can-Fite BioPharma</td>
<td>Anti-inflammatory (adenosine A3 receptor inhibitor)</td>
<td>III</td>
</tr>
<tr>
<td>Xeljanz</td>
<td>Pfizer</td>
<td>Anti-inflammatory (JAK inhibitor)</td>
<td>III</td>
</tr>
</tbody>
</table>
Ponesimod—a future oral therapy for psoriasis?

Caitriona Ryan, Alan Menter, Department of Dermatology, Baylor University Medical Center and Texas A&M Health Science Center, Dallas, TX 75246, USA

17 August 2014

A potentially potent new oral treatment
Ponesimod-a future oral therapy for psoriasis?

• Sphingosine-1- phosphate is a lysosphospholipid whose activity is mediated through five G-protein coupled S1P receptors.

• Ponesimod is the first oral selective modulator of the S1P receptor-1 (S1P₁) for the treatment of psoriasis.

• Posenimod and fingolimod, another functional antagonist of S1P, have been used successfully in the treatment of multiple sclerosis, another Th17-mediated inflammatory disease.
Ponesimod-a future oral therapy for psoriasis?

Study:
- 326 patients
- 20 mgs and 40mgs daily for up to 28 weeks vs. placebo

Results: (PASI 75)
- Week 16: 20 mgs - 46%  
  Placebo 13.4%
  40 mgs - 48.1%
- Week 28: 20 mgs - 71.4%  
  40 mgs - 77.4%

Side effects: Second degree heart block in 4 patients leading to withdrawal  
  • also seen in MS studies
Our Current Understanding of the Methotrexate Metabolic Pathway

Can we improve our current MTX therapy, which is still the gold standard worldwide – approved in 1972?

- 3,969,000 MTX prescriptions in 2006
- MTX fails in numerous patients potentially because of:
  - Bioavailability and incomplete PG formation
  - Adverse events, e.g.
    - Hepatotoxicity
    - Bone marrow suppression
    - Drug interactions

- Original psoriasis drug: Aminopterin

**New Oral Drugs in Pipeline for Psoriasis**

Enzymes of folate / purine / pyrimidine pathways

FPGH → FPGS

MTX polyglutamates

Adenosine
Intestinal Transport of Aminopterin Enantiomers in Dogs and Humans with Psoriasis is Stereoselective: Evidence for a Mechanism Involving the Proton-Coupled Folate Transporter

Intestinal Transport of Aminopterin Enantiomers in Dogs and Humans with Psoriasis is Stereoselective: Evidence for a Mechanism Involving the Proton-Coupled Folate Transporter

**Study:**

- L/D-AMT is the result of a novel synthetic route developed for commercial-scale production of the L-enantiomer
- L/D-AMT entered Phase I clinical development based on pre-clinical and clinical studies that suggested the L-enantiomer may offer improved efficacy and/or safety compared with MTX
- This is the first report of L/D-AMT administered to human subjects (22 patients in our study)
- Phase III study imminent
## Biologic Drugs for Psoriasis in Pipeline
(Partial List)

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-122</td>
<td>IL-17 and TNF-α inhibitor</td>
<td>AbbVie</td>
<td>II</td>
</tr>
<tr>
<td>Namilumab</td>
<td>Anti-inflammatory (granulocyte macrophage colony stimulating factor antagonist)</td>
<td>Takeda</td>
<td>II</td>
</tr>
<tr>
<td>Risankizumab (BI 655066)</td>
<td>IL-23 inhibitor</td>
<td>Boehringer-Ingelheim and AbbVie</td>
<td>III</td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>IL-23 inhibitor</td>
<td>Merck and Sun Pharma</td>
<td>III</td>
</tr>
<tr>
<td>Cimzia (certolizumab pegol)</td>
<td>TNF-α inhibitor</td>
<td>UCB/Dermira</td>
<td>III</td>
</tr>
</tbody>
</table>
**Tildrakizumab**

- *Tildrakizumab (MK-3222, Merck & Co., Kenilworth, NJ, USA)* is a humanized IgG1κ monoclonal antibody that targets the unique p19 subunit of IL-23.

**CLINICAL TRIALS:**

- A randomized, double-blind, phase IIb clinical trial revealed that Tildrakizumab was effective in treating moderate-to-severe plaque psoriasis.
- At week 16, the proportion of subjects achieving PASI 75 was significantly higher at all doses when compared to placebo: 33.3% on 5 mg, 64.4% on 25 mg, 66.3% on 100 mg, and 74.4% on 200 mg, compared to 4.4% on placebo.
- The final drug dose was given on week 40, and the participants were followed until Week 72.
- Tildrakizumab demonstrated a low rate of relapse after cessation of therapy, with only 3.6% of the participants who achieved PASI 75 at week 52 on any dose of Tildrakizumab relapsing before week 72.
- Phase III studies are in progress.
Risankizumab

Risankizumab (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a high affinity monoclonal antibody targeting the p19 subunit of IL-23 and is currently in development for moderate-to-severe psoriasis and Crohn’s disease.

CLINICAL TRIALS:
• A phase I, proof-of-concept study of BI-655066 demonstrated a similar frequency of side effects with varying doses of BI-655066 compared to placebo.
• The most common side effects were mild-to-moderate upper respiratory infections, mild nasopharyngitis, and mild-to-moderate headache.
• After a single intravenous or subcutaneous dose, PASI 75 was achieved in 87% of subjects, PASI 90 in 58% of subjects, and PASI 100 in 16% of subjects.
• Phase II trials have been completed, and publication of results is pending.
• Additional trials are ongoing.
## Biosimilar Drugs

(1)

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biosimilars for Remicade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABP 710</td>
<td>TNF-α inhibitor</td>
<td>Amgen</td>
</tr>
<tr>
<td>PF-06438179</td>
<td>TNF-α inhibitor</td>
<td>Pfizer</td>
</tr>
<tr>
<td>SB2</td>
<td>TNF-α inhibitor</td>
<td>Samsung Bioepis</td>
</tr>
<tr>
<td><strong>Biosimilars for Humira</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCD-057</td>
<td>TNF-α inhibitor</td>
<td>BIOCAD</td>
</tr>
<tr>
<td>CHS-1420</td>
<td>TNF-α inhibitor</td>
<td>Coherus Biosciences</td>
</tr>
<tr>
<td>GP2017</td>
<td>TNF-α inhibitor</td>
<td>Sandoz</td>
</tr>
<tr>
<td>M923</td>
<td>TNF-α inhibitor</td>
<td>Momenta</td>
</tr>
<tr>
<td>Cyltezo</td>
<td>TNF-α inhibitor</td>
<td>Boehringer Ingleheim</td>
</tr>
</tbody>
</table>
## Biosimilar Drugs (2)

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biosimilars for Humira (cont)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSB11022</td>
<td>TNF-α inhibitor</td>
<td>EMD Serono</td>
</tr>
<tr>
<td>PF-06410293</td>
<td>TNF-α inhibitor</td>
<td>Pfizer</td>
</tr>
<tr>
<td>SB5</td>
<td>TNF-α inhibitor</td>
<td>Samsung Bioepis</td>
</tr>
<tr>
<td><strong>Biosimilars for Enbrel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD203</td>
<td>TNF-α inhibitor</td>
<td>Hanwha Chemical</td>
</tr>
<tr>
<td>SB4</td>
<td>TNF-α inhibitor</td>
<td>Samsung Bioepis</td>
</tr>
<tr>
<td>GP2017</td>
<td>TNF-α inhibitor</td>
<td>Sandoz</td>
</tr>
</tbody>
</table>
Biopharmaceuticals and Biosimilars in Psoriasis: What the Dermatologist Needs to Know

Biosimilars in Psoriasis Regulatory Status (1)

US FDA
- The FDA has established criteria to approve biosimilars in the US
- The FDA has recognized that new marketing applications would be required for biosimilars, based on the inherent variation in structure and potential contaminants compared with the original biologic
- Important factors to be considered include: integrity and consistency of the manufacturing process, consistency of product characteristics with appropriate standards or comparators (including pharmacokinetic and pharmacodynamic data), and existing clinical evidence
Biosimilars in Psoriasis Regulatory Status (2)

**EMA (European Medicines Agency)**

- Have concluded that biosimilars can only be similar, and not identical to, the original biologic
- Recent EU pharmacological legislation has established a new legal pathway for approval of biosimilars with scientific guidelines on the quality, non-clinical standards and clinical standards
- Approval of biosimilars may be based on demonstrating bioequivalence to the original biologics
- The manufacturer of a biosimilar must therefore conduct non-clinical and clinical studies to support biosimilarity and not necessarily efficacy and safety
- In general, pharmacokinetic, pharmacodynamic and immunogenicity studies must be performed
The Future of Immunotherapy for Psoriasis

The Use of Pharmacogenomics in Psoriasis

C Ryan, A Bowcock, A Menter

Clinical Investigation, March 2011, Vol 1, 3: 399-411
Conclusions:

• Use of the results of recent genome-wide association scans and accumulating data from RNA microarrays in the skin and serum of psoriasis patients to genetically profile these patients is likely to produce important results in an adequately powered patient population.

• The characterization of psoriasis patients according to common molecular mechanisms rather than by clinical phenotype may also allow targeting of more selective therapeutic agents to genetically distinct groups of patients.
Goals for 2020 at our Baylor Immunology Research Center, Dallas, Texas

Psoriasis patient

Translational profiling

Most Appropriate Therapy

i.e. TRUE Translational Research
Thank you for your attention!