#1722

Diphencyprone for the treatment of dermatological disorders with an immunological component

1William Levis MD, 2Karen Bulock PhD, 2James Cardia PhD, 2Pamela Pavco PhD, 2Geert Cauwenbergh, Dr. Med. Sc.

1 NYU/Rockefeller University/Hapten Pharmaceuticals, LLC New York, NY
2 RXi Pharmaceuticals Corp., Marlborough MA

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Diphencyprone (DPCP)

- DPCP is a topical immunomodulator
- Topical treatment for warts, alopecia areata and cutaneous metastasis of melanoma
  - Efficacy in the three target indications reported in peer-reviewed journals
- Despite extensive safe and effective use, DPCP is not an FDA approved drug
  - No standardized treatment regimen or formulation
  - 2.0 % DPCP sensitization dose may lead to hyper-sensitization of patients to challenge doses
  - DPCP is negative in Ames test
- Samcyprone™
  - Proprietary topical formulation of DPCP
  - Provides standardized treatment regimen and formulation
  - Allows for use of a lower sensitization dose (0.4 % DPCP)
## Treatment with Diphencyprone (DPCP)

<table>
<thead>
<tr>
<th>Alopecia Areata</th>
<th>Warts (refractory, plantar &amp; periungual)</th>
<th>Cutaneous Metastases of Melanoma (refractory)</th>
</tr>
</thead>
</table>
| • >200 patients treated for several months  
• Response rates of 67-78%  
Cotellessa, C et al. JAAD 2001;44:73-6 | ● >350 patients treated for 12 – 24 weeks  
• Response rates of 80 - 85%  
• 46% complete clearance and 38% partial clearance  

![Alopecia Areata](image1)  
![Warts](image2)  
![Cutaneous Metastases](image3)
Samcyprone™
Current Indications Being Pursued

• Alopecia areata (Phase 2a)
  – Common autoimmune disease resulting in loss of hair on the scalp and elsewhere
  – Estimated 4.6\(^1\) – 6.5\(^2\) million cases in the US

• Recalcitrant Warts (Phase 2a)
  – Caused by human papilloma virus (HPV)
  – Estimated prevalence rates of 1-13\(^3\) with higher rates in children

• Cutaneous metastases of melanoma (Phase 2a)
  – Adjuvant treatment to improve locoregional control
  – Potential orphan indication

**Samcyprone™**

*Additional Potential Indications*

*Successes in literature noted using topical sensitizer therapy for:*

- Various skin cancers
  - Basal cell carcinoma (BCC)
  - Squamous cell carcinoma (SCC)
  - Bowen’s disease (pre-invasive SCC)
  - Actinic Keratosis (pre-cancerous skin lesions)
  - Metastatic Merkel cell carcinoma
  - Cutaneous T-cell lymphoma
DPCP Mechanism of Action

• Unknown

• Various hypotheses since inducing inflammation is counter intuitive for treating an autoimmune disorder

• To investigate this; Gulati, N et al, have studied with microarray and microRNA profiling DPCP (DTH) reactions in normal volunteers at various time points
Visualization of Inflammatory Reactions Induced by DPCP

| a Placebo | b DPCP day 3 | c DPCP day 7 | d DPCP day 14 |

Subjects were sensitized with 0.4% DPCP and challenged with 0.04% DPCP. Biopsies collected 3, 7 or 14 days after challenge. (Gulati et al. JID April, 2014)
Reactions to DPCP Include Immune Activation Markers that are Present at Day 3 but Diminish Over Time

(Placebo)                        (DPCP day 3)                        (DPCP day 14)                        (DPCP late)

(Gulati et al. JID April, 2014)
Samcyprone™ Next Steps

• Continue and complete Phase 2a trials

• Initiate Phase 2b trials

• Evaluate other indications for potential new trial(s) using Samcyprone

• Potential to develop new targets using sd-rxRNA technology
  – The mechanism of action of Samcyprone™ is linked to DPCP's ability to alter the expression of multiple genes and miRNAs involved in the immune response
  – Specific targets for potential treatment of immunological disorders that are relevant to the skin as well as various systemic diseases
RNAi Mechanism Leads to Selective Gene Silencing

1. RNAi compound administered to tissue
2. RNAi compound enters cells
3. RNAi compound loads into RNA induced silencing complex (RISC)
4. Target mRNA is cut & destroyed, blocking protein expression

Property of RXi Pharmaceuticals
sd-rxRNA: Robust Cellular Uptake

*in vitro and in vivo*

The RXi Platform

Delivery and silencing demonstrated in many different cell types
Human, Primate, Rat, Mouse, Adherent, Non-adherent, Primary, Transformed

Efficient delivery of sd-rxRNA to multiple tissues *in vivo* upon local and systemic administration

Skin, Eye, Spinal cord, Alveolar macrophages, Liver

Property of RXi Pharmaceuticals
**Microarray Data: Top 5 down-regulated genes**

DPCP day 3 and DPCP day 14 versus placebo samples

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Fold decrease vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL37 Interleukin 37</td>
<td>-46.0</td>
</tr>
<tr>
<td>ATP1A2 ATPase, Na⁺/K⁺ transporting, a2 polypeptide</td>
<td>-38.3</td>
</tr>
<tr>
<td>GDF10 Growth differentiation factor 10</td>
<td>-36.4</td>
</tr>
<tr>
<td>SGCG Sarcoglycan, g (35 kDa dystrophin-associated glycoprotein)</td>
<td>-29.8</td>
</tr>
<tr>
<td>MYOC Myocilin, trabecular meshwork inducible glucocorticoid response</td>
<td>-29.2</td>
</tr>
</tbody>
</table>

(Gulati et al. JID April, 2014)
Conclusions

- DPCP is useful for treating Melanoma, Alopecia Areata and Recalcitrant Warts
- Samcyprone provides the following benefits compared to current DPCP treatment:
  - Standardized treatment regimen and formulation
  - Allows for use of a lower sensitization dose, 0.4 % DPCP
- Gene expression analysis of biopsies from subjects treated with DPCP allows for the identification of potential targets for the treatment of Melanoma and Alopecia Areata.
- siRNA approach may be a novel way to improve the response to DPCP or alternatively may lead to more targeted approach to treating these indications