Discovery of a First-In-Class Topically Bioavailable Kit Inhibitor With Clinical Activity Using Computational Chemogenomics Technology

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Introduction

- Standard Approach to Drug Discovery
  
  Pick a disease ➔ Pick a Target ➔ Screen for Compounds

- nPharmakon: Indication-Agnostic Approach
  
  Safe Drug ➔ Find New Target ➔ New Disease

- To Discover A Drug – Start with a Drug
Repurposing vs. Retargeting

- Repurposing
  - Popular approach, efforts by many
  - Take an approved drug with an established MOA and find a new indication for **the same MOA**

- Retargeting
  - Emerging approach
  - Take a safe drug or drug candidate and find a **new MOA (target)** which will lead to a new indication
nPharmakon

- Founded 2008, privately funded
- Team: ex-pharmaceutical industry
- **Drug retargeting:**
  matching safe drugs with new indications

Proprietary computational technology
nPharmakon Technology

Uncovering Previously Unrecognized Targets of Drugs

Ligand analogy
Analyzing Small Molecules: Drugs, Tool Compounds

Target analogy
Analyzing Proteins

Enterprise-grade computing, outsourced experiments
nPharmakon Collection

Rich source of clinically safe leads, development candidates

- **7,000** small molecules past Phase I
- Many previously used in clinic **around the world** (Europe, Russia, Japan, etc.)
- MW < 500 Da only; no proteins, peptides, complex natural products, lipids, or inorganics
Technology Application

- nPharmakon discovered 6 inhibitors of protein and lipid kinases among older clinically safe non-oncology drugs.
- Drugs were not known to inhibit any kinase.
- Technology is not limited to kinases.

Modulators of critical pathways found among out-of-patent drugs.
nPharmakonon Pipeline

**NPH29**  
skin pigmentation;  
clinical

**NPH12**  
atopic dermatitis;  
preclinical
Pipeline, Continued

NPH09 fibrosis; exploratory

NPH39 p53-negative cancer; exploratory

NPH40 liver cancer; exploratory
NPH29 (FPL-62064) is a Topical Anti-inflammatory with Previously Unknown Activity against c-Kit

% Inhibition of control values

<table>
<thead>
<tr>
<th></th>
<th>% Inhibition</th>
</tr>
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<tbody>
<tr>
<td>cox1 (h)</td>
<td>80</td>
</tr>
<tr>
<td>cox2 (h)</td>
<td>90</td>
</tr>
<tr>
<td>5-lipoxygenase (h)</td>
<td>70</td>
</tr>
<tr>
<td>c-Kit (h)</td>
<td>85</td>
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</tbody>
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Test concentration: 10 µM
Kit Inhibition is a Highly Validated Therapeutic Strategy for Depigmentation

- **Kit receptor tyrosine kinase** is expressed in skin and hair follicle melanocytes; controls expression of enzymes that make skin pigment *melanin*; activated by **Kit ligand**.

- **Up-Regulation** of Kit signaling (e.g., injection of Kit ligand, Kit ligand gain-of-function genetic mutation) increases pigmentation.

- **Down-Regulation** of Kit signaling (e.g., Kit loss-of-function genetic mutation, injection of anti-Kit antibody) reduces pigmentation.

- Kit and Kit ligand are overexpressed in *melasma*, a prevalent pigmentation disorder of the skin.
Kit Inhibitor Oncology Drugs Cause Skin Depigmentation

- Depigmentation is reported in ~70% of cancer patients taking systemic Kit inhibitor drugs
- No topical Kit inhibitor is currently available
Melasma:
US 7M, Japan 3M persons affected

- Highly distressing, frequently life-altering condition
- Existing therapies are unsatisfactory
NPH29: Summary of Historical Data

- **NPH29 (FPL-62064)** was developed by Fisons plc. (Loughborough, Leics., UK), currently part of AstraZeneca; US patent issued in 1989

- **Anti-inflammatory agent:** Inhibits arachidonic acid metabolism via dual inhibition of 5-lipoxygenase and prostaglandin synthase (COX)

- **Active in animals:** Inhibits UV induced erythema and edema in guinea pig, mouse, rat, rabbit

- **Rapid systemic clearance:** Reported rapidly and extensively metabolized upon intravenous administration; inactive by the oral route at doses up to 200 mg/kg (in rat)

- **Topically bioavailable:** 2% topical formulation of FPL-62064 has been developed as a treatment for psoriasis

- **Safety in humans:** topical application of the drug reported safe and well tolerated in human patients; drug advanced to Phase III
NPH29: Synthesis

\[
\begin{align*}
\text{NH}_2 \quad \text{EtONa, EtOH, 70 C} & \quad \text{NH}_2 \\
\text{C} & \\
\text{NH} & \quad \text{EtONa, EtOH, 70 C} \\
\text{N} & \\
\text{EtONa, EtOH, 70 C} & \quad \text{CH}_3 \\
\text{p-TsOH, sulfolane} & \quad 190 \text{ C, 5 h} \\
\text{CH}_3 & \\
\text{MnO}_2, \text{DCM} & \quad \text{MnO}_2, \text{DCM} \\
\text{H}_3\text{C} & \\
\text{NPH29} & \\
\text{H}_3\text{C} & \\
\end{align*}
\]
NPH29 Inhibits Kit Kinase Activity in Cells

Inhibition of Kit kinase autophosphorylation in human leukemia cell line M07e after Kit-ligand stimulation, determined using substrate specific sandwich ELISA.

IC$_{50}$: 1.2 µM
NPH29 Suppresses Kit-ligand -induced Melanin Production In Vitro

Melan-a mouse melanocyte cells

EC_{50}: 3 \mu M
Clinical Proof-of-Concept

NPH29 Topical Gel Reduces Skin Pigment

Statistical significance reached

* p < 0.05
Conclusions

- **Novel** safe topically bioavailable **Kit inhibitor** is identified
- Clinical proof of concept achieved in **18 months** from discovery
- Previously unknown molecular activity of NPH29 is shown to be **clinically relevant**

nPharmakon’s systematic computational analysis reveals unknown yet therapeutically important targets of drugs, suggests new uses
Executive Team

Combined drug discovery experience: 80 years

Dmitri Rebatchouk PhD
CEO

Felix Sheinerman PhD
Chief Scientific Officer

James Hendrix PhD
Pres., Technology
Medicinal chemistry. Fmr. CNS Chem. Site Head, Sanofi-Aventis

Donald Picker PhD
VP Drug Development
Drug development. Fmr. EVP R&D, Genta. Led >30 drug development projects