nPharmakon
The Drug Retargeting Company

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

James Hendrix, Ph.D.
President - Technology

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nPharmakon LLC 44 Stelton Road, Suite 310 Piscataway, NJ 08854 1.732.529.4446 contact@npharmakon.com

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

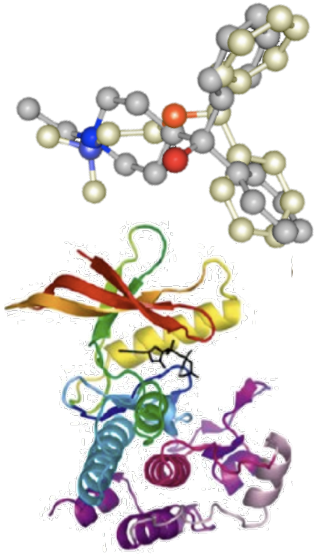
nPharmakon

- 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

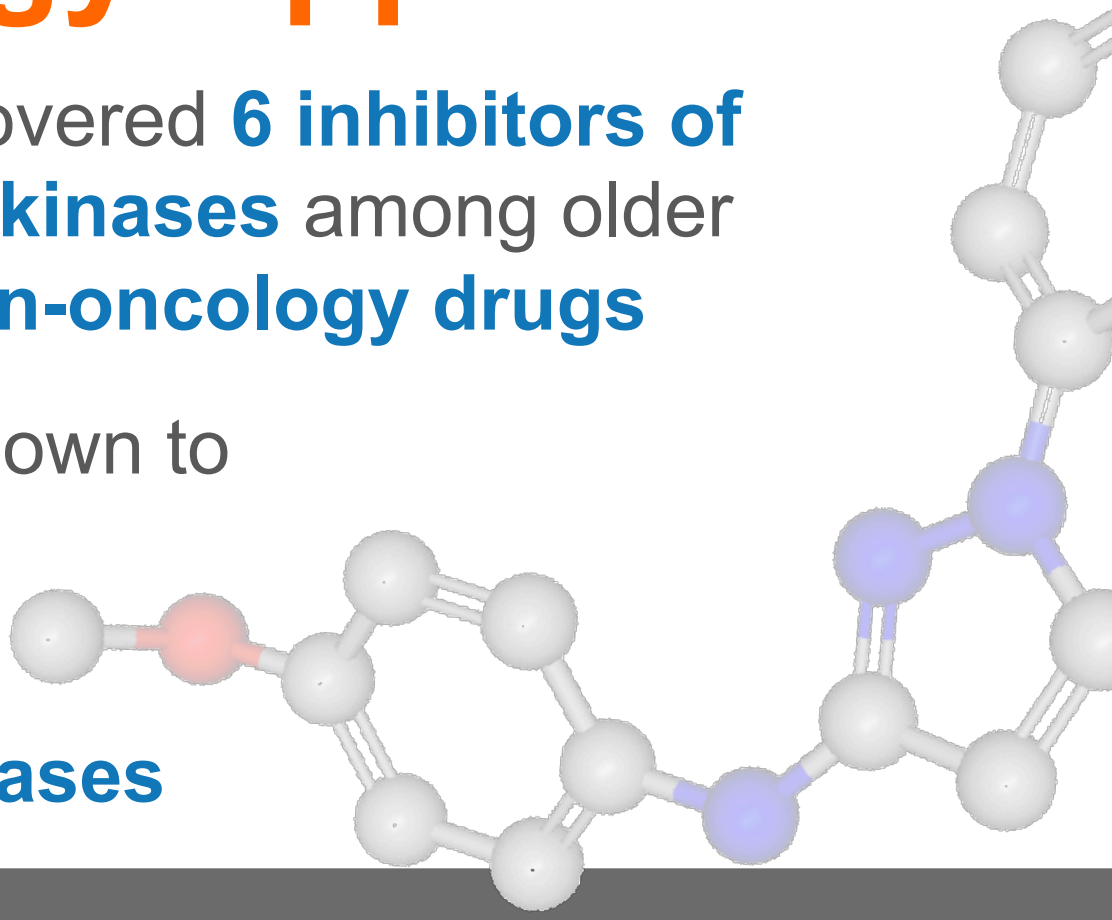
nPharmakon Collection

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

nPharmakon Pipeline

NPH29 skin pigmentation; clinical

NPH12 atopic dermatitis; preclinical

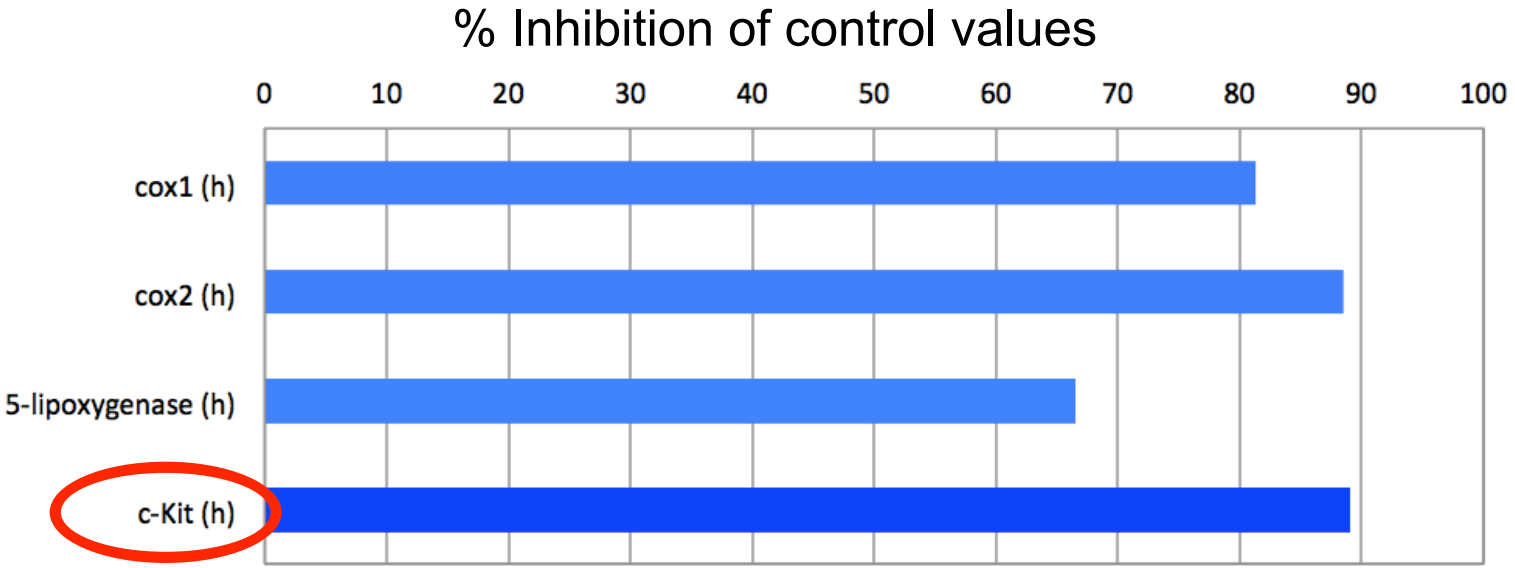
Pipeline, Continued

NPH09 fibrosis; exploratory

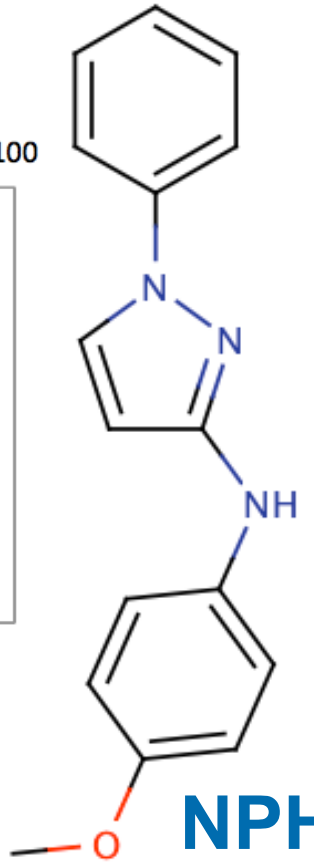
NPH39 p53-negative cancer; exploratory

NPH40 liver cancer; exploratory

NPH29 (FPL-62064) is a Topical Anti-inflammatory with Previously Unknown Activity against c-Kit



Test concentration: 10 μM

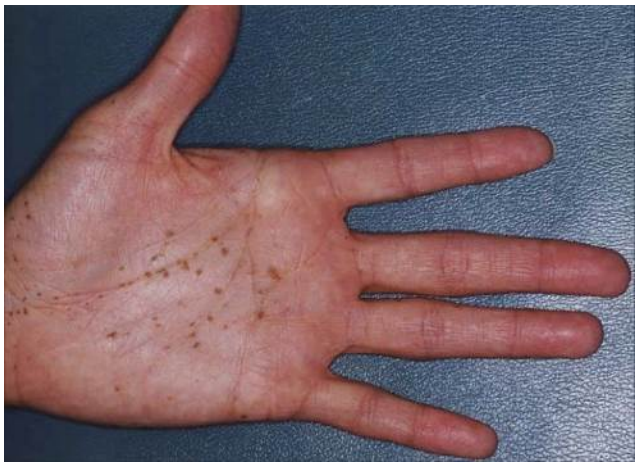


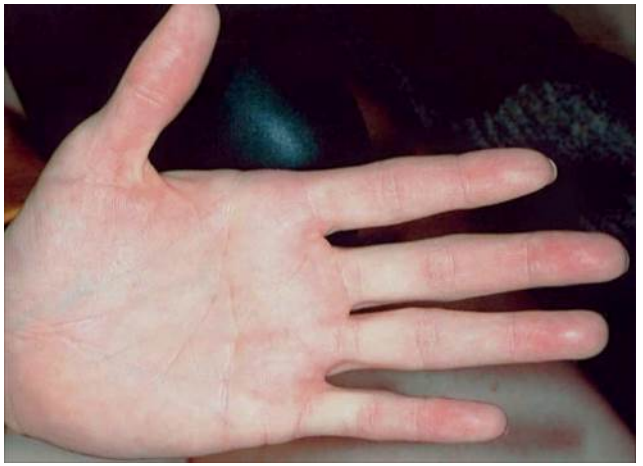
NPH29

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





Arch Dermatol (2009) **145**:1313

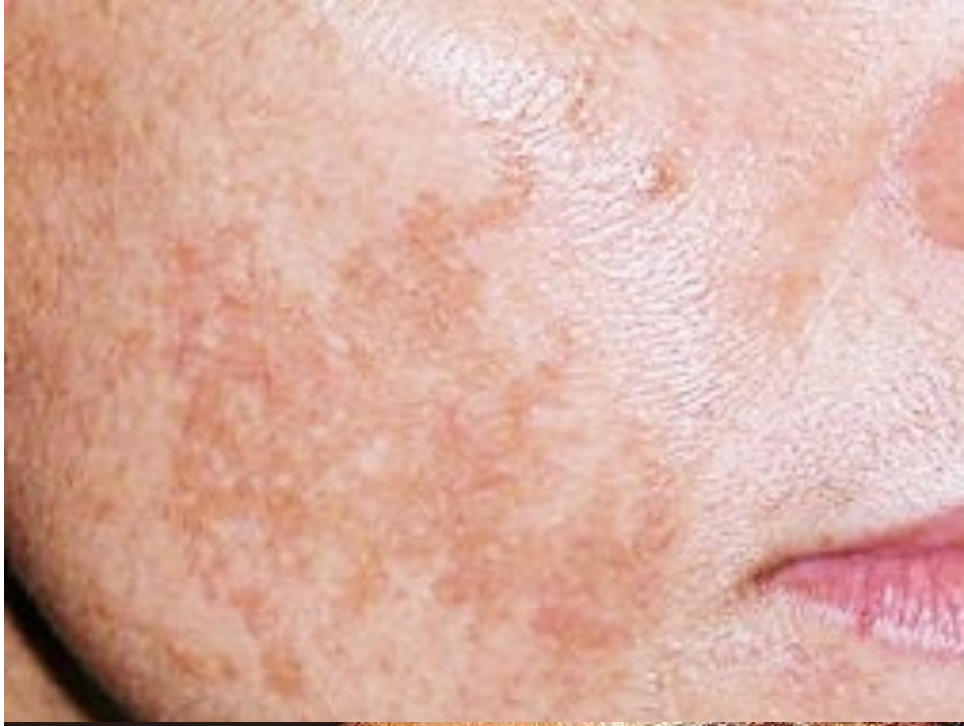
- Depigmentation is reported in **~70%** of cancer patients taking systemic Kit inhibitor drugs
- **No topical Kit inhibitor is currently available**

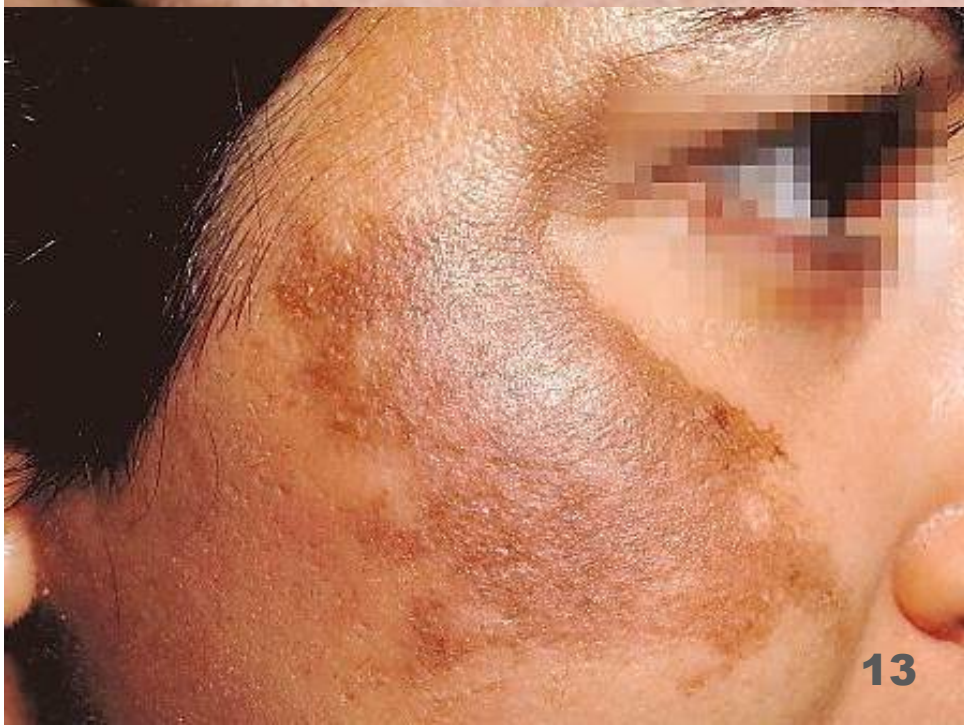
Melasma:

US **7M**, Japan **3M**

persons affected

- Highly distressing, frequently life-altering condition
- Existing therapies are unsatisfactory

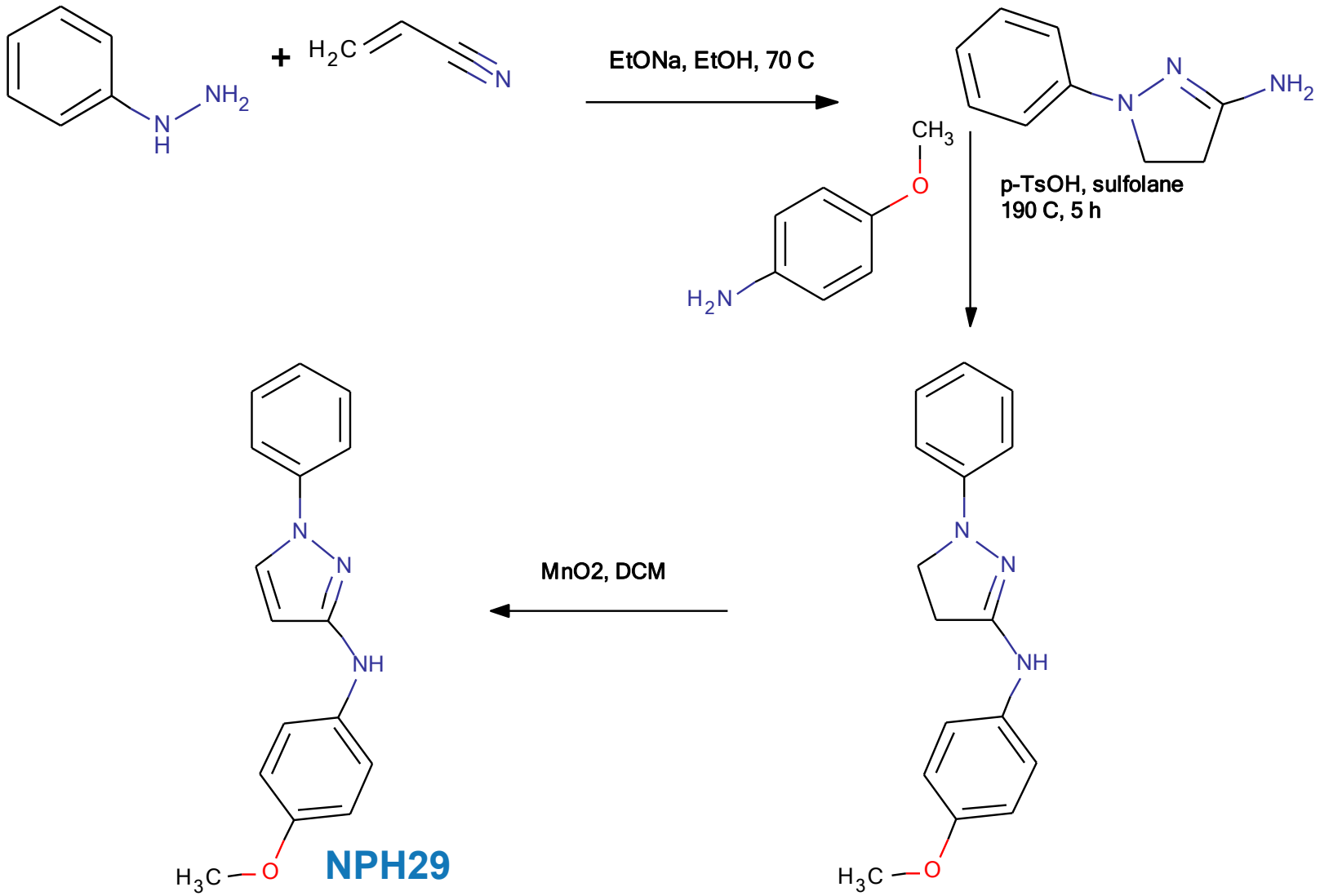




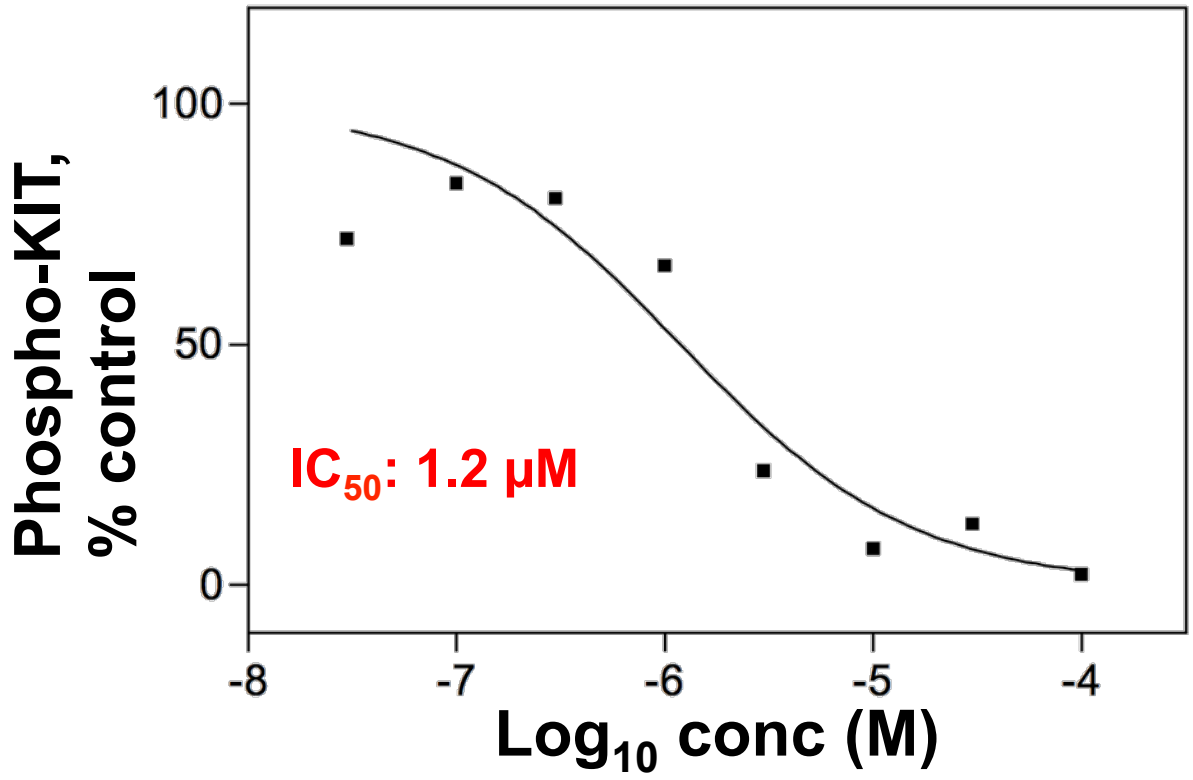
NPH29: Summary of Historical Data

- **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

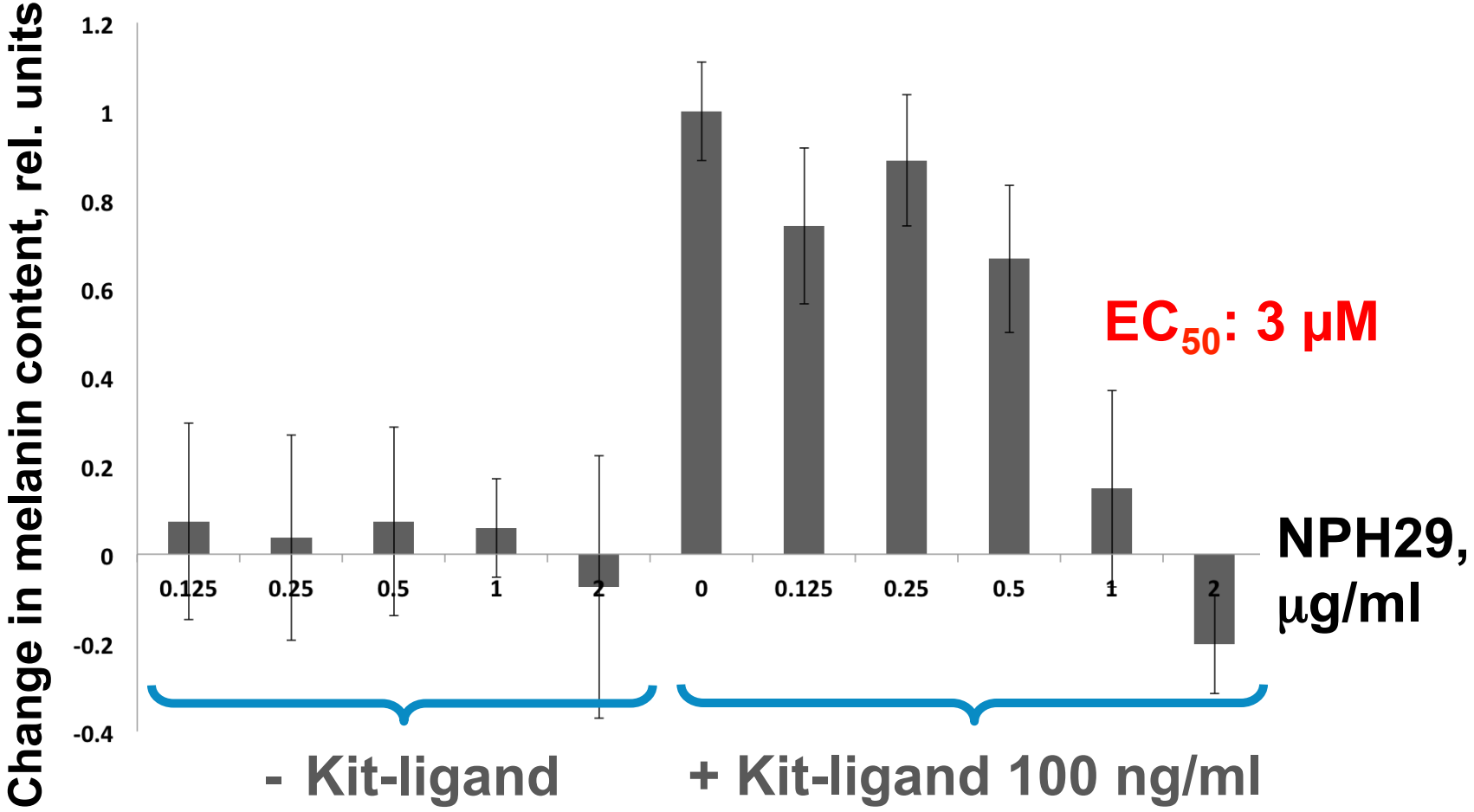


NPH29 Inhibits Kit Kinase Activity in Cells



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

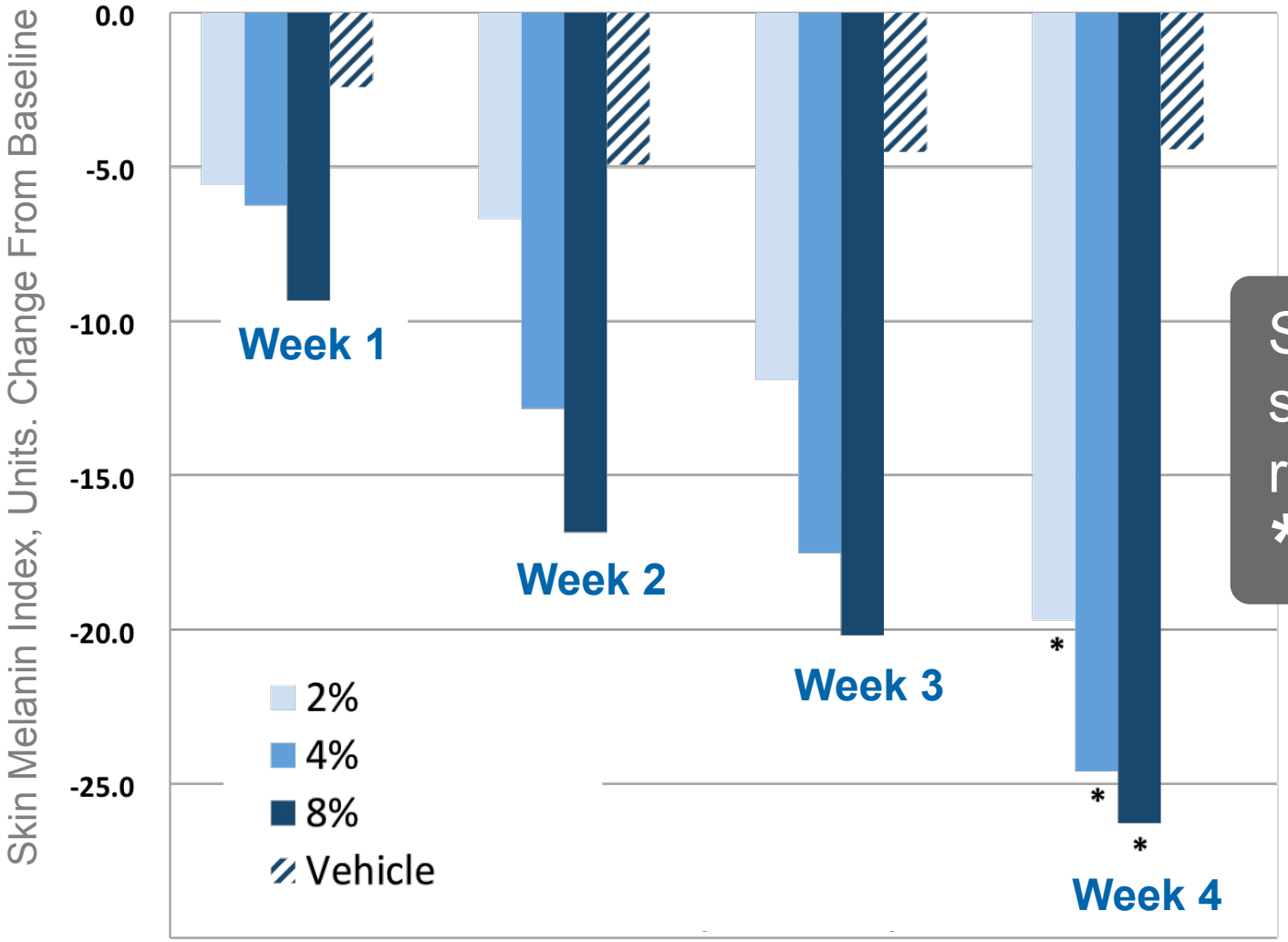
NPH29 Suppresses Kit-ligand -induced Melanin Production In Vitro



Melan-a mouse melanocyte cells

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

Informatics. Co-inventor of nPharmakon's technology. Fmr. Head, Informatics, Sanofi-Aventis

Felix Sheinerman PhD
Chief Scientific Officer

Drug design. Co-inventor of nPharmakon's technology. Fmr. Head, Chemogenomics, Sanofi-Aventis.

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