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DRUG DISCOVERY & DEVELOPMENT

Solution Story: Merging systems biology & chemistry to streamline the quest for natural, active agents

Using Pathway Studio® and Reaxys Medicinal Chemistry®, Scientists at Oriflame found new targets and active natural ingredients much faster than using conventional approaches.

Summary

Scientists from Oriflame's Skin Research Institute, located in Sweden, outline their approach for identifying skin ageing targets and finding active natural ingredients that modulate them using Pathway Studio® and Reaxys Medicinal Chemistry®. By using a targeted, data-driven approach in the early discovery phase, their process yielded several active natural ingredients that were patentable - all within six months, half the usual time for such analytical work.

"After the initial analysis, we went back to Reaxys and searched all the other compounds present in the extracts together with our target molecule. We asked Reaxys Medicinal Chemistry to give us other targets on which those compounds might act. Using that data, we built a network around each extract's main active compound. This enabled us to identify and later to confirm additional benefits of the extract."

- Michele Leonardi, Oriflame Skin Research Institute

Few would argue that multidisciplinary teams are critical to pharma and consumer product R&D success today. But deriving benefit from cross-disciplinary collaborations takes more than just good will. It's critical to have the right tools — tools to crunch and merge data from diverse sources, facilitate communication about terminology, avoid redundancy, and speed discovery. Such tools boost productivity and help ensure that team members are working quickly and cost-effectively, as demonstrated when one company discovered, developed and patented a natural ingredient for skin care.

Oriflame and its Skin Research Institute (SRI), headquartered in Stockholm, Sweden, uses a workflow process that applies equally well to pharma. Substitute "complexity of a disease" for "complexity of skin ageing" and the steps are essentially the same: Identify the right target; discover the right natural ingredient from a sustainable source; demonstrate strong proof of activity in vitro; demonstrate strong proof of clinical efficacy.

Challenge

Skin care — specifically, improving signs of ageing — is a key strategic focus for SRI. As such, Oriflame's skin care technologies, sourced from natural ingredients, are developed for strong activity against their target. In this case, the target is wrinkles, the outward manifestation of a complex, multifaceted process.

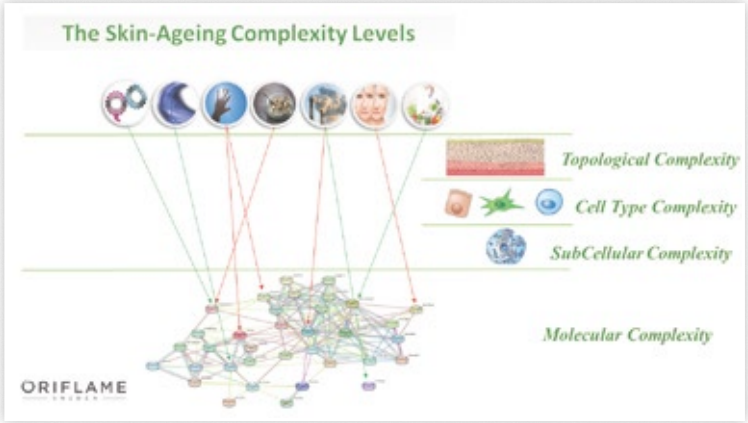

Figure 1. Various factors that influence skin-ageing illustrating the complexity of the process and selection of molecule targets.

"Without Pathway Studio and Reaxys Medicinal Chemistry, it might have taken a year to get to our first phase of testing, instead of just six months. In addition we are reducing cost and minimizing risk by a targeted approach in the early discovery phase."

- Susanne Fabre, Oriflame Skin Research Institute

R&D was charged with identifying and developing a safe, effective product to improve the appearance of age-associated fine lines and wrinkles. To accomplish this, they had to deal rapidly and cost-effectively with a tremendous amount of data from both biology and chemistry, which needed to be explored and honed to uncover appropriate targets and compounds.

To understand the scope of the challenge, the team first identified the various factors that influence how an individual's skin ages. Intrinsic factors include age, gender and genetic propensities; extrinsic factors connected to lifestyle – for example, exposure to smoke, pollution, ultraviolet radiation, food and drink. (Figure 2)

Intrinsic and extrinsic factors take a toll that manifests variously as skin redness, dark spots, irregular tone, dullness, dilated pores, rough texture, sagging and wrinkles – under and on the sides of the eyes, upper lips, forehead and frown lines.

The team then teased out the levels of biological complexity involved in skin-ageing, which emerge from numerous protein–protein, protein–gene and metabolic interactions inside complex molecular networks. In addition to molecular complexity, differences in cell types, topological localization (layers of the skin) and function are among the components that affect skin homeostasis and phenotypes. (Figure 2)

With this understanding, and with state-of-the-art tools for data analysis in place, they embarked on a discovery process remarkably similar to that of pharma.

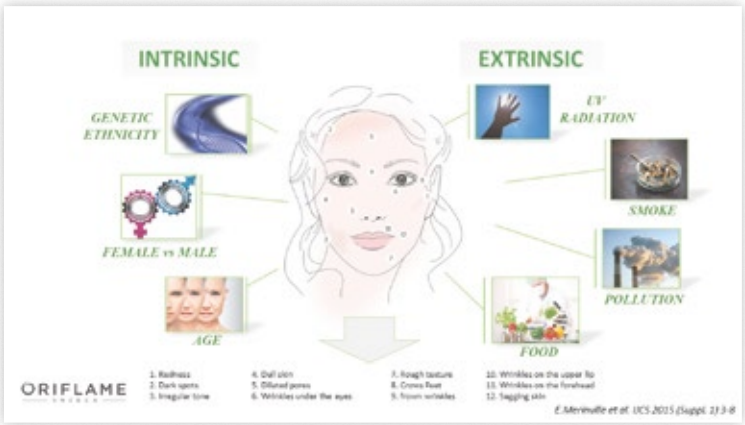

Figure 2. Both intrinsic and extrinsic factors play a role in skin ageing and affect skin homeostasis and phenotype expression.

"Network Pharmacognosy™" workflow summary

Network Pharmacognosy is an approach developed by Oriflame's Skin Research Institute to serve as a blueprint and vision for discovering novel active compounds. Simply put, the model merges the protein–protein "skin-ageing" network identified primarily through Elsevier's Pathway Studio (left side of Figure 3), with the activity-based extract network, driven mainly by medicinal chemistry input from Reaxys (right side of Figure 3).

By matching the two networks, researchers can more accurately define the targets on which the extract works. In addition to the primary target, secondary targets are also identified, as are potential synergies. The model also allows for screening and evaluation of known extracts that also may have activity against the primary target.

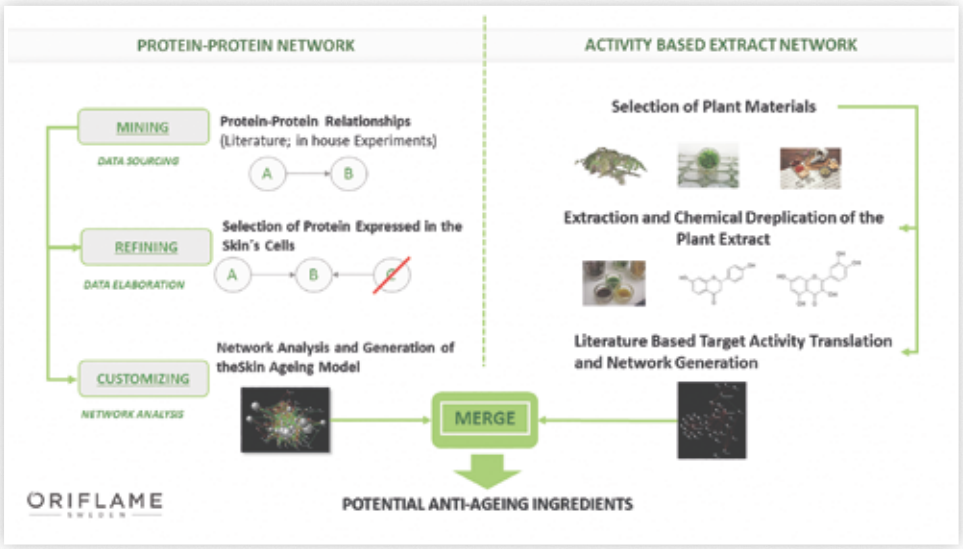

Figure 3. An overview of the "Network Pharmacognosy™" workflow defined by Oriflame and used to find both patentable active natural ingredients and their targets.

The workflow process

To "solve" the problem of skin wrinkling, the team followed a three-pronged roadmap:

1. Construct a skin-ageing molecular network by investigating critical components — e.g., collagen, elastin and fibrillin — to understand the cellular interactions involved in their regulation;
2. Screen to identify a novel, patentable anti-ageing extract by constructing an activity-based extract network; and
3. Validate the safety and efficacy of the extract in a series of in vitro and ex vivo studies.

Constructing the molecular network

Various steps and tools were involved in constructing the molecular network to guide discovery.

- Data mining. Using Elsevier's Pathway Studio, the team mined big data to obtain a list of proteins that correlated with skin ageing, and found that most of them targeted collagen. From there, they zoomed in on collagen I (COL1A1) and collagen IV (COL4A1). (Figure 4)
- Data extraction/refinement. The team then used Pathway Studio, adding data on gene expression derived from the publicly available Human Protein Atlas, to select only collagen-targeting proteins that are expressed in skin cells. The refinement process yielded 159 proteins with 2,458 relationships to collagen.
- Data customization. To generate a skin ageing model, the team used the refined data and open-source network analysis software to generate a directed network containing all the information relative to the relationships (expression, binding, regulation) and suitable for final customization in Pathway Studio. They found about 15,000 articles in the literature that supported the model, giving them confidence that the product that evolved from the process would be effective. (Figures 4 & 5)
- Candidate target selection. Using various open-source programs and proprietary algorithms, the team selected candidates and reviewed them in dynamic models for drug-ability and assay feasibility. To increase the success rate, they evaluated multiple candidate targets in parallel and also investigated combinations of active ingredients and different product formulations that might enhance outcomes. (Figure 4)

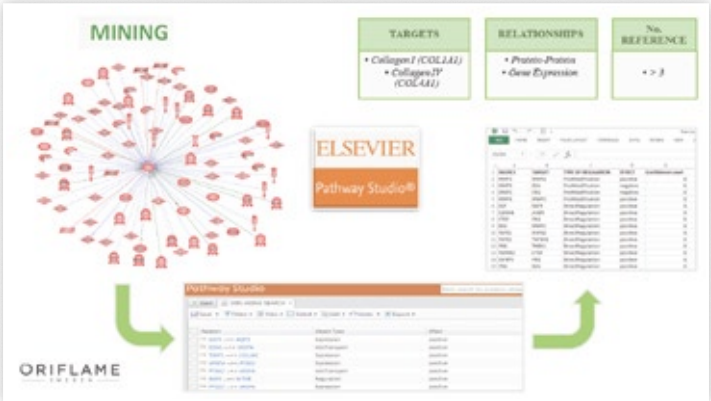

Figure 4. Identifcation of biologically important collagen targets using data from Pathway Studio.

Figure 5. Final model refinement using Pathway Studio.

Screening to identify novel extracts

In this stage, the team focused first on selecting natural agonists for the selected target and then on selecting plant sources that contain the target compound(s). Reaxys was an important tool for both phases.

In silico selection of natural agonists led to five hits, based on Ki and IC50 values reported in the literature, as determined by Reaxys. The first in vitro study confirmed bioactivity in all five selected agonists, with increases in pro-collagen 1 of up to 50%. After ranking the compounds based on activity, the researchers selected the ones that were most active. (Figure 6)

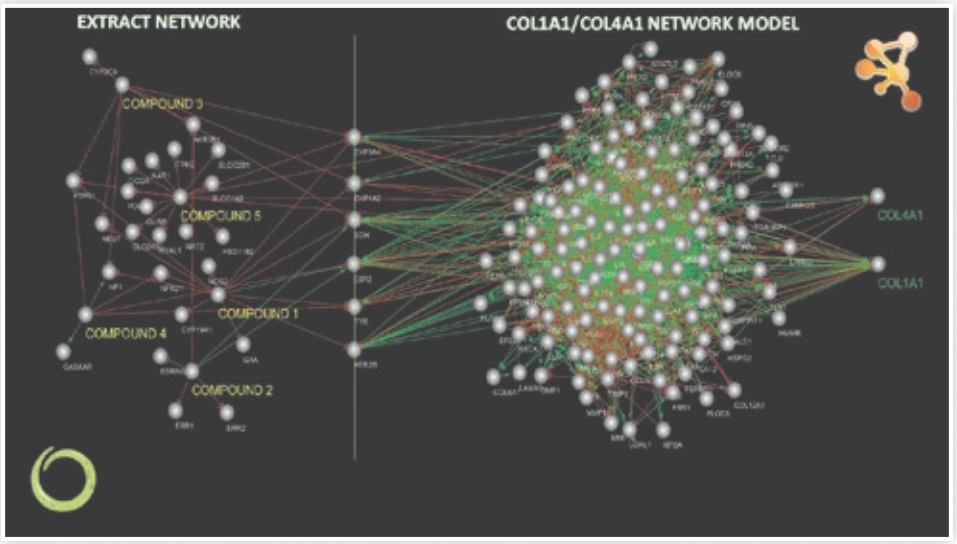

Figure 6. *In silico* selection of natural agnostic for a selected target using Reaxys. Once the compounds were identified, they were analyzed using Cytoscape to verify that the selected targets were modulated.

Next, Reaxys was used to determine the corresponding patentable plant sources containing the target compounds.

Fifteen extracts ultimately were obtained, and underwent chemical dereplication and in vitro and ex vivo studies, to confirm activity and potential synergism.

Validating safety and efficacy

Much like how pharma tests drug candidates in the earliest preclinical stage, the SRI team validated the selected extract and tested it on fibroblasts to confirm that the full extract had the same activity as the pure compound, and actually would increase the amount of collagen released from cells.

The result

The process yielded a novel, patentable plant extract that acts safely and effectively on multiple skin-ageing targets, and is supported by data from the literature, in vitro experiments and in silico modeling. The final full extract had a synergistic effect, yielding 100% increase in the release of pro collagen I and 280% increase of collagen IV.

Additional results, based on network analysis prediction, suggest the extract can also protect against UV-induced and diesel particulate matter-induced skin-ageing activity.

The impact

Using the appropriate tools at each stage enabled the team to:

- Reduce risk in the early stages, impacting:
  - Assay screening and development: With information on relevant biomarkers for efficacy testing, the team was able to minimize the risk of assay development failure.
  - Plant source selection: Using Reaxys, the team quickly identified sources of relevant natural compounds.
  - Toxicity testing: Rapid access to relevant data allowed the team to predict negative side effects early on.
- Reduce development time. Using Pathway Studio and Reaxys enabled SRI to save time both during the data mining/target-identification stage and in the feasibility evaluation of selected candidate targets, effectively reducing development time to about six months.
- Reduce costs. Cost reductions occurred as a result of reduced development time and minimizing failure due to lack of efficacy. The provision of multiple potential sources enabled the team to select the most cost-effective option.
- Improve the success rate for treatment efficacy. The team was able to rapidly identify a target with multiple positive effects on skin ageing. This is informing the full development of the new active ingredient; if, as anticipated, it works synergistically with other active ingredients to impact multiple targets within the same relevant pathway, for example, this could facilitate dosing, solubility and bioavailability.

Looking ahead

More advanced testing will involve the use of 3D-reconstructed skin models and ex-vivo skin from surgical procedures. Researchers will apply the extract topically, then check for deeper effects — e.g., on collagen levels in the dermis. Those studies will be followed by in-house clinical testing to look at the final effects on wrinkles, skin elasticity and other markers of skin ageing.

Conclusion

Using a proven, cross-disciplinary approach and robust technological tools, researchers were able to unlock the power of massive amounts of data from biology and chemistry to rapidly discover a novel natural compound that met their requirements; determine the best natural sources of that compound; establish potential synergies with related active substances; translate the findings into a topical application; and ensure safety and efficacy through multiple rounds of testing.

Elsevier's Pathway Studio suite and the Reaxys Medicinal Chemistry database were indispensable tools throughout the process — speeding discovery, helping to ensure safety and efficacy, and facilitating validation studies. They will also be useful as the research team moves forward through product development and commercialization.

Acknowledgments

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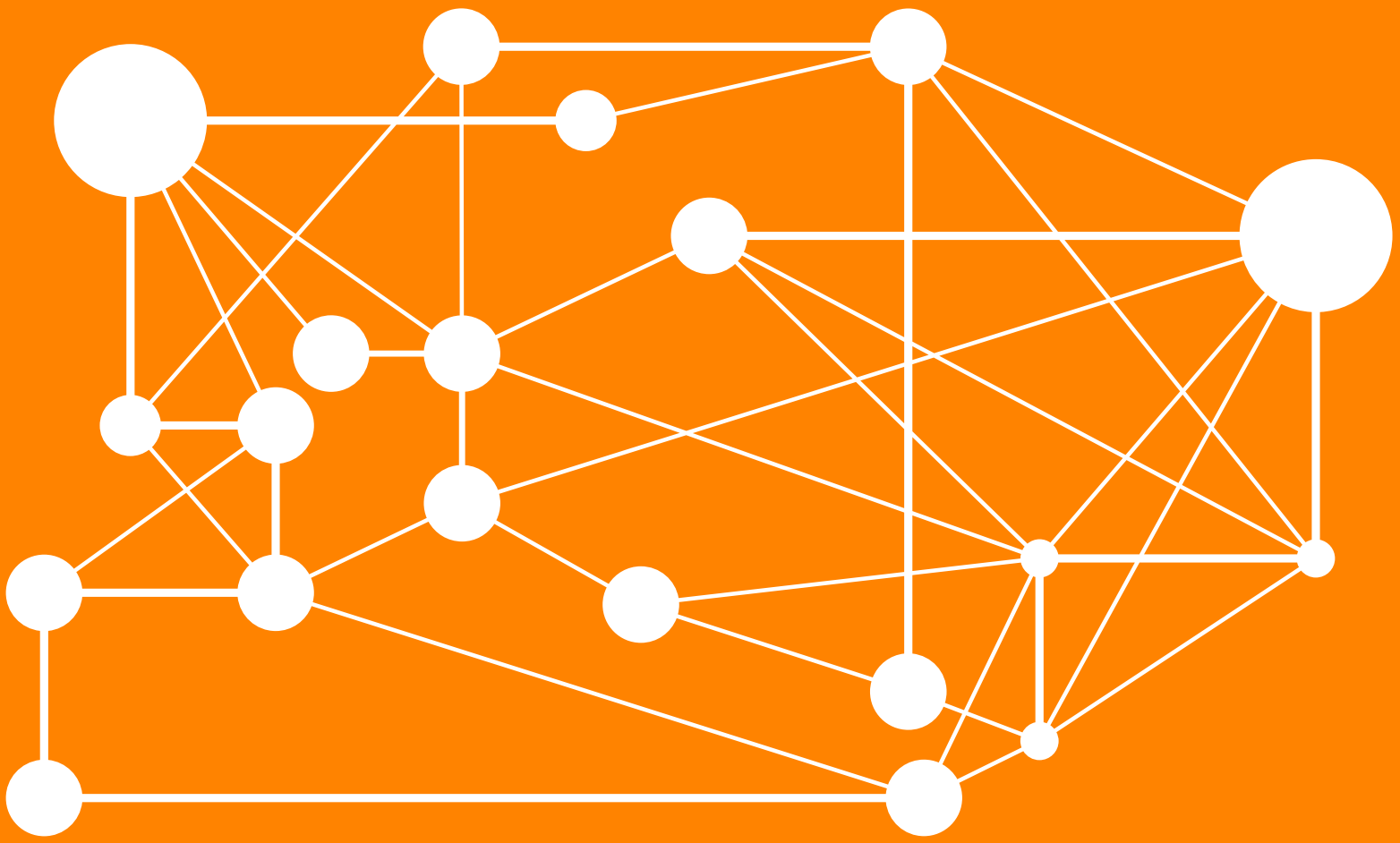

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