Introduction
Identifying promising targets for anti-melanoma immunotherapeutics requires answering several complex biological questions:
Which proteins are exposed on melanoma cells and can therefore be targeted?
How do melanoma cells suppress the patient’s immune system?
Which factors can re-activate the anti-tumor immune response?
Using Elsevier’s Pathway Studio, researchers can find answers to these complex biological questions rapidly - often in less than 20 minutes.
A deadly disease with increasing rates
Melanoma is the deadliest form of skin cancer, and traditional chemotherapies have shown limited efficacy in treating the disease. This poses a serious health threat to the approximately 232,000 people diagnosed each year worldwide. (1) The disease most commonly occurs in Caucasian populations, and the risk tends to increase at lower latitudes. (1) Melanoma rates are still on the rise and have been increasing sharply over the last 30 years, so extensive efforts to develop effective therapies are of high priority.

Understanding melanoma biology
Many of the drug development efforts are focused on anti-melanoma immunotherapeutics, because due to the unique biology of melanocytes, conventional cytotoxic drugs offer only limited treatment benefit. (2) To effectively protect our skin from UV radiation, melanocytes must be able to survive highly mutagenic environments. As a result, melanoma cells are resistant to chemotherapy induced apoptosis. In addition, melanocyte precursors and primary melanomas have high motility. Combining these characteristics results in a deadly disease that can easily spread throughout the body (figure 1).

Identifying promising targets for anti-melanoma immunotherapeutics requires answering several complex biological questions: Which proteins are exposed on melanoma cells and can therefore be targeted? How do melanoma cells suppress the patient’s immune system? Which factors can re-activate the anti-tumor immune response? Assembling the answers to these questions into functional associations enables us to generate a complete picture of how melanoma cells suppress immune response and stimulate their own proliferation and provides the information we need to identify the best possible drug targets.

“Using Pathway Studio® and CellEffect™ to assess how melanoma cells suppress local immune response can be accomplished by connecting the results of a few simple queries.”

Figure 1. Illustration of Stage 3 Melanoma, noting extension into the vascular system which helps the cancer cells to spread.
The challenge to find all of the relevant information

Accessing all of the necessary information to answer these questions is as big a challenge as understanding and interpreting it. While manually identifying every publication relevant to melanoma might be possible, it is not scalable. As the scope of the research question grows, the knowledge base becomes prohibitively large, and despite even the best efforts, it is inevitable that some important publications will simply be missed.

Gaining access to all of the actual publications adds to the challenge, because many institutions subscribe to a limited subset of journals. Thus, only a portion of the relevant information will be accessible, and this knowledge gap can lead to selection of incorrect or suboptimal drug targets.

Further complicating the search for information is the poor standardization of immune cell nomenclature. As our knowledge of immunology has grown over the years, the naming conventions to describe particular cell attributes have had to evolve, and this has produced significant inconsistencies in the literature. For example, a T regulatory lymphocyte may also be described as a T regulatory cell, a Treg, an immunoregulatory T cell, or a suppressor T cell. That same cell might also be described in the text through its markers, for example: CD3+ CD4+ CD25+ FOXP3+, CD3+ CD25+ CD4+ FOXP3+, CD4+ CD25+, CD25+ FOXP3+, FOXP3+ CD25+, or CD4pos CD25pos. These inconsistencies complicate searches and increase the possibility that we miss publications important to the disease area.

A simple way to gather information in its biological context

Elsevier’s Pathway Studio® enables scientists to explore molecular interactions and cause-and-effect relationships associated with biological processes, by integrating a vast knowledge base of biological relationships with analytical and visualization tools. This biological context lets scientists better understand and interpret experimental observations and literature evidence involving development, disease progression and drug responsiveness. The expertly curated signaling pathway collection makes it possible for researchers to use network and pathways analysis to model the impacts of differential gene or protein expression and protein—protein interactions on disease, and streamlines the process of drug target discovery.

The content is comprehensive, covering over 10,000 journals, 25+ million PubMed abstracts and more than 164,000 clinical trials from which molecular interactions, cell processes and disease-related molecular interactions are extracted. All content is updated weekly, and the growing number of curated pathways (>2000) provides the most current knowledge base available today.

CellEffect™ is a new data resource created for Pathway Studio that helps scientists explore complex molecular interactions within and between cells under normal conditions, so they can understand how these interactions change in disease states. CellEffect supports in-house target and biomarker discovery programs and pathway analysis of clinical and experimental data by providing access to data extracted from peer-reviewed research, including changes in protein activity, gene expression, metabolite concentrations, epigenetic methylation, along with information on gene mutations and deletions. In addition, the data mining algorithm can parse the complex nomenclature of immune cells and understand cell names based on cellular epitopes and can even interpret variations in the names.
Using Pathway Studio and CellEffect to assess how melanoma cells suppress local immune response

By deconstructing the question, “How do melanoma cells suppress the local immune response?” researchers can easily connect the results of a few simple queries using Pathway Studio and the CellEffect database to assess the mechanism of melanoma progression as mediated through local immune suppression. The first question is to find out which proteins are secreted by the melanoma cells, because these can affect neighboring immune cells and influence their biological function. The next question is to determine which immune cells are negatively regulated by the secreted proteins. And the last question is to explore what effects these immune cells have on the melanoma cells.

Together, the answers to these three questions can show how melanoma modulates patient immune response by repressing the anti-tumor immune cells. Using Pathway Studio with the CellEffect database, a scientist can easily complete the entire workflow for this query in less than 20 minutes. This strategy saves countless hours and ensures completeness. Attempting to gather the same information and construct a similar picture using manual methods would be overly pain-staking and time consuming. Plus, the likelihood of missing important information using manual methods is too large, and the resulting incomplete picture can increase the risk of selecting sub-optimal targets and drug failure later in development.

The analysis workflow using Pathway Studio and CellEffect (illustrated in figures 2–5) is simple and involves applying different filters that ensure each query returns relevant and specific results. The first query examines the types of proteins that are secreted specifically by the cancer cells and not by healthy cells. These melanoma-specific proteins can have inhibitory effects on other cell types, such as immune cells. Thus, the next query uses a regulation filter to examine which cell types are connected to the secreted proteins via inhibition mechanisms. And the final analysis examines which cell types negatively regulate the melanoma cells through inhibition.

Data-driven selection of anti-melanoma drug targets

After identifying all of the critical associations between melanoma disease and immune system regulation, the researcher can begin to explore key proteins and cell types as potential drug targets. Overlaying experimental data from known drugs onto these literature findings using Pathway Studio helps the researcher assess how various drugs may affect particular targets and better postulate downstream toxicity or side effects. The ability to quickly and easily understand all of these details in their complete biological context informs drug target selection and supports eliminating poor targets from further development, increasing the chance of developing a successful drug.
Workflow in Pathway Studio that addresses the question “How do melanoma cells suppress local immune response?”

**Step 1**
Find proteins that are secreted from melanoma cells.
Disease ➔ Secreted ➔ Proteins

**Step 2**
Find cells that are inhibited by these secreted proteins.
Protein ➔ Regulations ➔ Cells

**Figure 2.** The first query assesses which proteins are secreted specifically by the melanoma cells.

**Figure 3.** The second query examines which cell types are negatively regulated by the secreted melanoma proteins.
**Step 3**

Find cells that inhibit melanoma.

Cell ➔ Regulation ➔ Disease

*Figure 4.* The third query examines which cell types inhibit the melanoma cells. These inhibitory cells are shown as blue ovals.

**Step 4**

Remove proteins not connected to cells that inhibit melanoma and cells connected only to proteins.

*Figure 5.* Now only cells that have direct regulation on melanoma are shown along with the secreted proteins from melanoma. This set of secreted proteins could be potential drug targets which, if blocked, could allow immune cell(s) to work against melanoma.
References


Pathway Studio for Drug Discovery & Development

Pathway Studio helps customers streamline target and biomarker identification and drug repurposing by providing biological researchers with greater insight into the mechanisms of disease and facilitating the interpretation of experimental data.

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