Bristol-Myers Squibb is actively conducting translational medicine research to further our understanding of cancer biology and to identify which patient populations may be more likely to derive benefit from Immuno-Oncology (I-O) agents.
Our vision is for tumor biology to inform treatment selection for each patient at each stage of therapy.
Areas of Focus in Biomarker Research

**Inflamed Tumor Microenvironment:** Biomarkers within the tumor, T cells or microenvironment that may predict response

**Tumor Immune Suppression:** Biomarkers related to mechanisms of resistance via specific immune pathways that may be addressed with I-O treatment

**Tumor Antigens:** Biomarkers to identify hypermutation and neo-antigens that may predict response to I-O

**Host Environment:** Biomarkers to characterize the host environment, beyond the tumor microenvironment, which may reveal immune-related mechanisms predictive of response

**Pharmacodiagnostics (PDx):** Diagnostic tests for biomarker expression that may predict patient response prior to treatment
Areas of Focus in Biomarker Research

Inflamed Tumor Microenvironment: Biomarkers within the tumor, T cells or microenvironment that may predict response

For example, PD-L1 is expressed in a variety of healthy cell types and tumor cells. PD-L1 binds to the PD-1 receptor on T cells, inhibiting T cell activation. PD-L1 may be expressed only on a portion of the tumor cell and expression levels may change over time.

Tumor Antigens: Biomarkers to identify hypermutation and neo-antigens that may predict response to I-O

Tumor Immune Suppression: Biomarkers related to mechanisms of resistance via specific immune pathways that may be addressed with I-O treatment

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Areas of Focus in Biomarker Research

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Host Environment: Biomarkers to characterize the host environment, beyond the tumor microenvironment, which may reveal immune-related mechanisms predictive of response.

For example, CSF1R is a receptor on the surface of macrophages and other cells of the myeloid lineage. High levels of CSF1, the ligand for CSF1R, may indicate that tumors are using CSF1R pathway to drive immunosuppression.

Pharmacodiagnostics (PDx): Biomarkers that predict patient response prior to treatment.
Areas of Focus in Biomarker Research

Inflamed Tumor Microenvironment: Biomarkers within the tumor, T cells or microenvironment that may predict response

Tumor Immune Suppression: Biomarkers related to mechanisms of resistance via specific immune pathways that may be addressed with I-O treatment

Tumor Antigens: Biomarkers to identify hypermutation and neo-antigens that may predict response to I-O therapies.

For example, a growing body of research suggests that assessing the quantity of mutations carried by a tumor—the tumor mutation burden—may predict the likelihood that a patient could benefit from certain I-O therapies.¹⁻³

Host Environment: Biomarkers to characterize the host environment, beyond the tumor microenvironment, which may reveal immune-related mechanisms predictive of response

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For example, markers in microorganisms (i.e., microbiome) may play a role in developing resistance to I-O treatment

Pharmacodiagnostics (PDx): Diagnostic tests for biomarker expression that may predict patient response prior to treatment
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Diagnostic tests for biomarker expression that may predict patient response prior to treatment. PD-L1 assays are in vitro diagnostic tests used to detect PD-L1 in certain types of cancer. This test can help determine appropriate treatment.
Imaging and Technologies

State-of-the-art technology and complex analytical platforms help us answer basic research questions.

Biomarkers and Pharmacodiagnostics (PDx)

Clinical Pharmacology and Pharmacometrics

Exploratory Translational Research

Bioinformatics and Integrated Sciences

Collaboration
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<tr>
<th>Section</th>
<th>Description</th>
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<tr>
<td>IMAGING</td>
<td>Molecular imaging allows researchers to study specific targets and guide treatment decisions without invasive procedures</td>
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<tr>
<td>GENOMICS &amp; GENETICS</td>
<td>Mapping, characterizing and quantifying gene expression and mutations to allow for a deeper understanding of disease biology and mechanisms of drug response</td>
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<tr>
<td>FLOW CYTOMETRY &amp; FUNCTIONAL BIOLOGY</td>
<td>Method of single-cell analysis that allows for cell sorting, detection of disease biomarkers and a better understanding of cell biology</td>
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<tr>
<td>SAMPLE MANAGEMENT</td>
<td>System for storing and organizing samples for efficient future use</td>
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Applying cutting-edge methods for integrative analysis of large-scale, complex biological data and developing actionable insights to drive development of Biomarkers and Pharmacodiagnostics (PDx).
Gene expression network derived from analysis of TCGA RNA sequencing data

Loss of CDKN2A is associated with reduced estimates of T cells in the tumor microenvironment in some cancers

Our Translational Bioinformatics team uses cutting-edge methods to perform integrative data analysis. We study the interplay of tumor genomes, their regulation and the tumor microenvironment to further our understanding of response to I-O agents.

Our comprehensive analysis of The Cancer Genome Atlas (TCGA) identified networks of co-expressed genes that can be used to identify specific types of immune cells in the tumor microenvironment. In some tumors, certain genetic mutations correlate with the abundance of such cells.
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The mandate of integrated sciences is to integrate, analyze and synthesize data derived from both external and internal studies addressing fundamental translational questions in I-O to develop actionable insights and hypotheses that help drive discovery and clinical development.
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Our combined CP&P team is fully integrated across all phases of development to validate MOA of novel targets using mechanistic modeling, predict how assets may work together in combination in humans and identify the optimal safe and effective dose in patients through modeling and simulation.
Mechanistic Modeling (QSP) Fuels New Questions and Continued Exploration in Immuno-Oncology

Hypothesis Testing

Prior Knowledge

Model Application

Model Development

Hypothesis Generation

\[
\begin{align*}
\frac{dx_1}{dt} &= f_1(x_1, x_2, \ldots, x_n) \\
\frac{dx_2}{dt} &= f_2(x_1, x_2, \ldots, x_n) \\
&\quad \vdots \\
\frac{dx_n}{dt} &= f_n(x_1, x_2, \ldots, x_n)
\end{align*}
\]
Mechanistic Modeling (QSP) Fuels New Questions and Continued Exploration in Immuno-Oncology

Hypothesis Testing

The hypotheses simulated from the QSP model can be tested in clinical studies.

Prior Knowledge

Prior knowledge can be integrated into a theoretical model of the cancer-immunity cycle.

Model Application

The QSP model can then be used to generate hypotheses through simulation of potential clinical biomarker/tumor responses.

Model Development

The theoretical model of the cancer-immunity cycle can be converted into a mathematical QSP model.
Mechanistic Modeling (QSP) Fuels New Questions and Continued Exploration in Immunology

Hypothesis Testing

Hypothesis Generation

Prior Knowledge

Model Development

dx_1 \, dt = f_1(x_1, x_2, \ldots, x_n( ))

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\ldots

dx_n \, dt = f_n(x_1, x_2, \ldots, x_n( ))

The theoretical model of the cancer-immunity cycle can be converted into a mathematical QSP model. The QSP model can then be used to generate hypotheses through simulation of potential clinical biomarker/tumor responses. The hypotheses simulated from the QSP model can be tested in clinical studies. Prior knowledge can be integrated into a theoretical model of the cancer-immunity cycle.
Exploratory Translational Research generates internal data to enable scientific discovery.

Biomarkers and Pharmacodiagnosics (PDx)

Imaging and Technologies

Bioinformatics and Integrated Sciences

Clinical Pharmacology and Pharmacometrics

Exploratory Translational Research

Collaboration
Insights gained from this research can quickly be implemented in prospective clinical trials to enhance and accelerate our pipeline.

Experimentation provides the knowledge and data to form hypotheses that can be tested in the clinic.

We leverage existing and advanced clinical assays to explore and test new hypotheses using biologic samples.
SINGLE CELL GENOMICS: Leveraging next generation technologies to examine sequence information from individual cells.

PROTEOMICS: Study of proteins and how they interact within tumor microenvironment.

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Conducting Research to Understand the Immune System in Patients with Cancer

Gene expression: mRNA and miRNA

Cell isolation for functional assays

Plasma analytes

Plasma

PAXgene

Gene expression: mRNA and miRNA

Functional assays: signaling, cytokine induction

Comprehensive phenotyping

Whole Blood

PBMC

Fresh tissue

Frozen tissue

FFPE

IHC/Proteomics

Mass Spectrometry

Genetics/genomics experiments to tissue samples

BLOOD

TISSUE
Conducting Research to Understand the Immune System in Patients with Cancer

Gene expression: mRNA and miRNA

Cell isolation for functional assays

Plasma analytes

Whole Blood

PBMC

Plasma

Functional assays: signaling, cytokine induction

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BIOLOGY

TISSUE

GENETICS/GENOMICS

experiments to tissue samples

Biomarkers and Pharmacodiagnostics (PDx)

Imaging and Technologies

Bioinformatics and Integrated Sciences

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Exploratory Translational Research

Collaboration
Collaboration

Bristol-Myers Squibb has long believed the future of cancer research is dependent on investments in science and partnerships. Collaboration is integrated into our organizational framework across translational medicine and R&D.

- Biomarkers and Pharmacodiagnostic (PDx)
- Imaging and Technologies
- Bioinformatics and Integrated Sciences
- Clinical Pharmacology and Pharmacometrics
- Exploratory Translational Research

Collaboration
Our scientific collaborations with academic centers around the globe expand our research capabilities and accelerate our collective ability to advance the science.

We seek to partner with other I-O experts to expand our translational medicine capabilities.
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A global peer-to-peer collaboration between Bristol-Myers Squibb and academia that aims to advance I-O science and translational medicine to benefit patients.

Research collaborations with select European research institutions to appropriately accelerate, expand and more effectively advance I-O research.

Working with partners like Foundation Medicine and GRAIL helps to drive the identification, validation and application of predictive biomarkers.
Our robust translational medicine program informs key areas of research, including:

- Disease targeting and responsive patient segmentation
- Ideal treatment strategies, including combinations, for each patient
- Optimal dosing, schedule and clear understanding of MOA