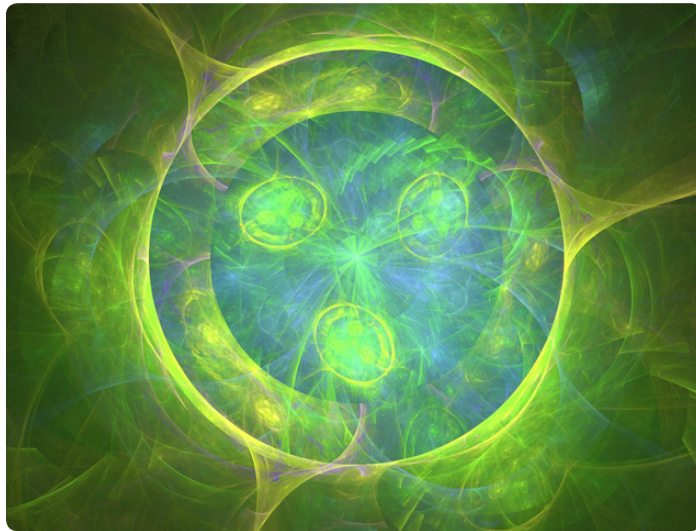




UNLOCKING THE SECRETS OF CELLS

MAYO CLINIC
**BIOMEDICAL
RESEARCH**





FAST-TRACKING RESEARCH FOR PATIENTS

Heart attack, brain tumors, memory loss, and many other conditions result from the breakdown and miscommunication of cells. The goal of biomedical research is to fix broken cells in the body and restore healthy function. Today's medical treatments, life-saving procedures, and disease-prevention approaches are rooted in scientific discoveries that later led to critical innovations in patient care.

Researchers at Mayo Clinic work each day in quest of the next breakthrough in diseases such as cancer and Alzheimer's disease. More than 4,000 world-class physician-scientists, science faculty, and research personnel collaborate in laboratories and at bedsides to solve complex questions in virtually every field of medicine.

But we need even more reinforcements — people who understand and support innovation, opportunity, and entrepreneurship — in our effort to defeat devastating diseases.

At Mayo Clinic, discoveries happen every day. We focus on the needs of the patient, which require that our research model addresses patient-centered, patient-inspired discoveries.





Research can be an arduous process, and modern biomedical investigation often proceeds in an unpredictable fashion when addressing the complexities of deranged tissues and cells, mutant genes, and abnormal proteins. Therapies are years in the making and are the culmination of years of collaboration among scientists, medical investigators, and patients participating in research.

One of the biggest barriers to faster medical breakthroughs is inadequate funding. Traditional funding sources, such as federal grants, cannot cover the cost of cutting-edge discoveries.

Because of our track record of translating discoveries into clinical care, patients around the world expect those advances to come from Mayo Clinic.

Benefactors speed the pace of research, helping us provide the most advanced care to patients who are unable to find answers anywhere else. Gifts to biomedical research at Mayo Clinic make hope and healing possible for those who suffer from the most complex and seemingly incurable diseases.



MAYO CLINIC DISTINCTION

Because of research at Mayo Clinic, we can fix a birth defect like spina bifida (a malformation of the spine that exposes sensitive and delicate nerves to a hostile environment) while the unborn child is still in the womb, preventing paralysis of the legs, bowel, and bladder. We can help patients who suffer from neurological disorders, such as Parkinsonism, through surgically implanted electrodes in the brain to restore normal movement without tremors. And our surgeons can operate on the heart or remove pancreatic cancer through incisions the size of a key hole.

Mayo Clinic's scientists and physician-investigators as well as their supporting professionals from a spectrum of disciplines collaborate and interact to unlock the complex secrets of genes, cells, and molecular pathways to find solutions to an individual's specific medical problems. This close collaboration among our scientists and physicians is one of the unique strengths at Mayo Clinic and serves to develop the outstanding care offered to patients.

Mayo Clinic's multidisciplinary approach to research and its ability to translate biomedical research to patient care set Mayo apart from other medical or research institutions.



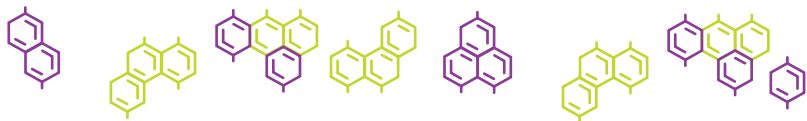
Patients who come to Mayo Clinic typically have three major questions:

- 1 What is my illness and why did I get it?
- 2 What can you do to help me?
- 3 If there are no therapies available for me today, can you give me hope that such treatments will be found in the future?

More than one million patients come to Mayo Clinic each year to receive trusted answers to these questions because of our model of care and legacy of innovation and discovery.



Disease is the breakdown of the “checks and balances” within and between cells. Biomedical researchers investigate the reasons underpinning specific breakdowns and discover ways to repair or reverse the disease with new treatments, often based on interventions at the level of the cell, molecule, or gene. Research conducted at Mayo Clinic is a primary source of groundbreaking treatments and procedures practiced by physicians around the globe.



The activities in biomedical research are broad and encompassing. The following are particular categories that explain how critical advancing research is to patients:



> **DRUG TARGETING**

Mayo Clinic participates in the pharmaceutical discovery process at every stage, beginning with basic research into the molecular mechanisms of a disease. Researchers examine the effects of promising drugs on cells, and when warranted, in small phase I human trials, followed by larger phase II and then comprehensive phase III trials.

Targeted small molecule discovery keeps Mayo Clinic at the cutting edge of pharmaceutical progress and guarantees that we have access to the most promising, newly developed drugs for our patients.



> **METABOLOMICS**

Cellular metabolism is a dynamic process in which molecules (“metabolites”) are synthesized or degraded. These metabolites are essential for normal cell function and communication. Metabolomics is a discipline that studies metabolites and their fate, the latter, to a large part, determined by their relevant chemical pathways. Using cutting-edge technologies that can identify and follow the fate of these metabolites, investigators at Mayo Clinic have uncovered fundamental insights in diabetes mellitus, obesity, cancer, and aging.

Research at Mayo will continue to disclose how metabolic pathways falter in diseases and how novel insights can delineate new therapeutic strategies to repair these abnormalities.



IMAGE GUIDANCE

> Imaging technologies are advancing at breakneck pace, transforming the practice of medicine and the face of biomedical research. Real-time imaging allows us to insert needles or thread catheters to any location in the body, and guide an ever-expanding array of “interventional radiology” procedures — tissue biopsy, blood vessel stenting, tumor excision, electrical stimulation, and others.

Today’s high-resolution technologies — from X-rays, to radioactive isotopes, and PET, to magnetic resonance — allow us to see smaller and smaller structures, for earlier and more accurate disease detection.





EVIDENCE OF SUCCESS

Patients at Mayo Clinic have received trusted answers in virtually every medical specialty. Our discoveries have given rise to new and improved diagnostic tools, medications, and treatment protocols. Below we showcase three notable advances in detecting breast cancer, understanding Alzheimer's disease, and stopping myelofibrosis. These examples are just a sampling of the varied and copious biomedical research conducted at Mayo Clinic.

> FINDING CANCER FASTER: The Many Advantages of Molecular Breast Imaging

Early detection of breast cancer is the goal of mammography. However, if a woman has dense breast tissue, mammography may not find these destructive cells.

Having high breast density reduces the sensitivity of mammography by about half and increases the risk of developing breast cancer three- to four-fold. Approximately half of women aged 40 years and older have dense breast tissue.

Mayo Clinic developed Molecular Breast Imaging (MBI) to improve detection of cancer in women with dense breasts. The imaging harnesses differences in the molecular behavior of tumor cells compared to normal cells in order to detect cancer. This is unlike mammography, which depends on differences in the appearance of tumor cells, which can be obscured in the dense breast.

The MBI system uses a gamma camera, which detects the ability of breast cancer cells to take up an injected radiotracer that is commonly used in heart stress tests. The radiotracer is absorbed preferentially by tumor cells,

and the degree of uptake is not impacted by the density of the surrounding tissue. Thus, tumors stand out clearly even amidst a background of dense tissue.

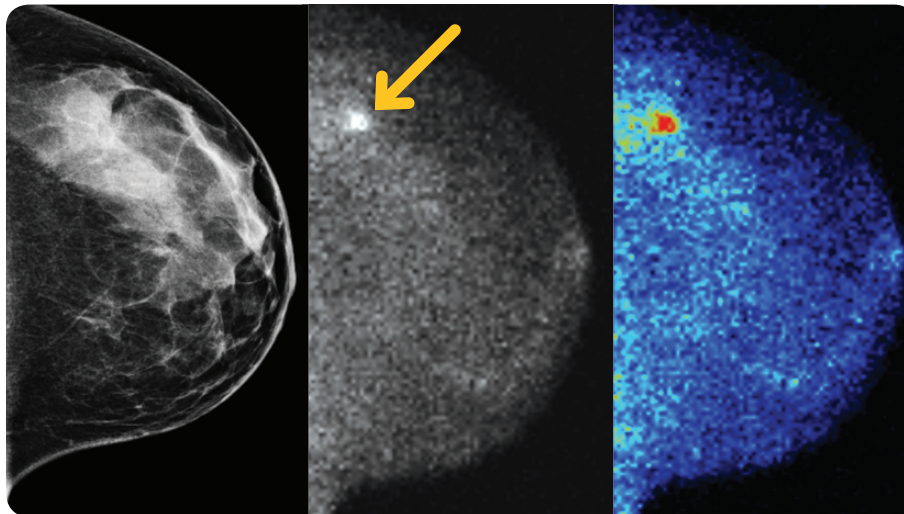
In screening studies at Mayo Clinic conducted in over 3000 women with dense breasts, mammography alone finds only 2 or 3 in 10 cancers in the dense breast, while the combination of mammography and MBI finds 9 in 10 cancers. Because of this greater accuracy, the number of additional biopsies needed to make a definite diagnosis is much lower than with other types of breast imaging, such as ultrasound or magnetic resonance imaging (MRI).

MBI is very useful in defining the extent of breast cancer (such as tumor size and additional tumors). This can be critical in surgical decision-making. MBI is also effective in assessing response to chemotherapy in women with advanced tumors who receive chemotherapy prior to surgery. Because MBI can show whether the tumor is shrinking within weeks of starting chemotherapy, MBI may help tailor the chemotherapy regimen to the individual patient response.





Molecular Breast Imaging: Pinpointing Breast Cancer



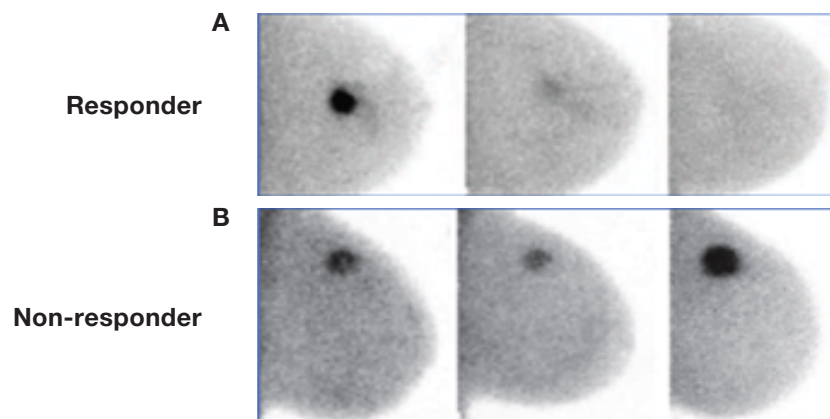
Digital Mammogram

MBI

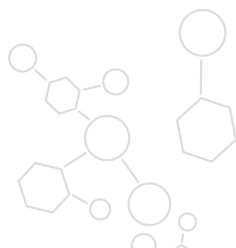
MBI – Color Image

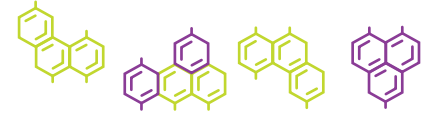
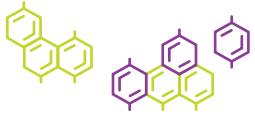
Hruska et al Am J Surg. 2008;196:470-6
Am J Roentgenol. 2008; 191:1805-15

Molecular Breast Imaging to Assess Tumor Response (at 3-5 Weeks of Therapy) to Neoadjuvant Chemotherapy in Women with Locally Advanced Breast Cancer



Mitchell, Hruska et al: Clin Nucl Med. 2013; 38: 949-56





> **THE TAU OF ALZHEIMER'S DISEASE:
Imaging for Earlier and More Accurate Disease Detection**

Alzheimer's disease (AD) is reaching epidemic proportions, and no cure exists. The effects of this disease are devastating to the patients and their family and friends. But we believe research in Alzheimer's disease sits on a tipping point for breakthroughs.

In Alzheimer's disease, the connections within as well as between brain cells degenerate and die, causing a steady decline in memory and mental function.

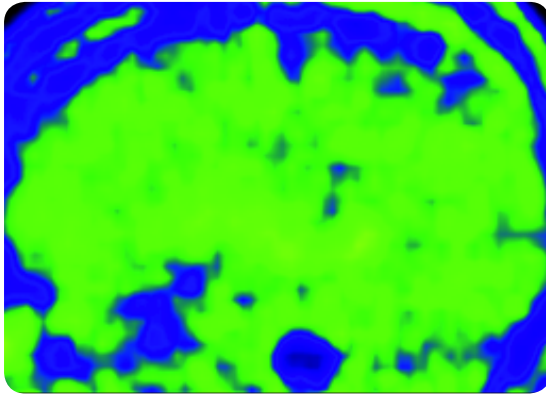
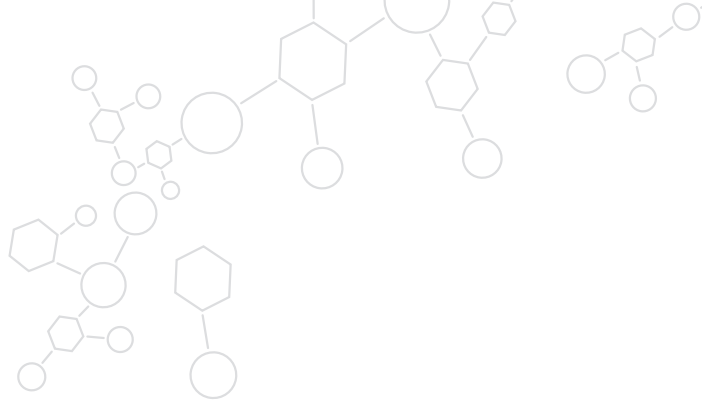
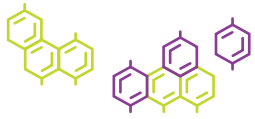


At Mayo Clinic, we have the largest study of patients with Alzheimer's disease in the world. The Centers for Medicare and Medicaid Services (CMS) have stated that the work of Mayo is crucial to understanding and managing Alzheimer's disease in the future.

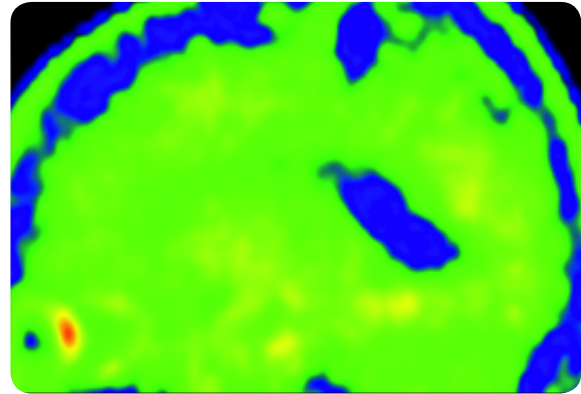
Currently, we are using Positron Emission Tomography (PET) to investigate how much amyloid plaque (a possible cause of Alzheimer's disease) has formed in the brains of living, aging people. We are extending this research to a new level with PET by imaging another protein, called tau, and how it can accumulate abnormally in the brain.

Opposite are images of PET scans of tau protein in people with no disease (Healthy Control), mild memory loss (MCI, MMSE 26), early Alzheimer's disease (MMSE 21), and late Alzheimer's disease (MMSE 7). The images show more tau protein accumulation (yellow progressing to red color) in worsening stages of Alzheimer's disease. Imaging tau will add another piece to the puzzle in understanding how and when damage occurs in brain disease such as Alzheimer's disease. The results potentially bring new opportunities for early diagnosis, treatment, and possibly a cure in the future.

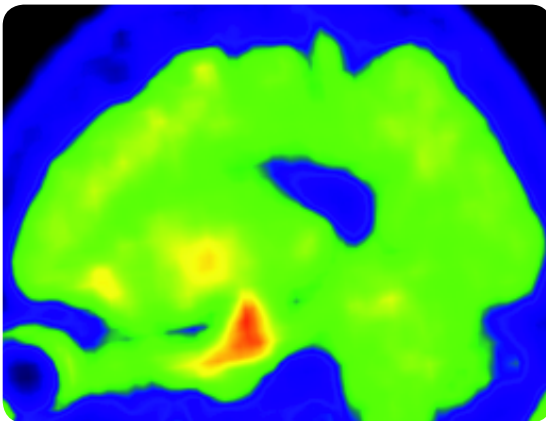




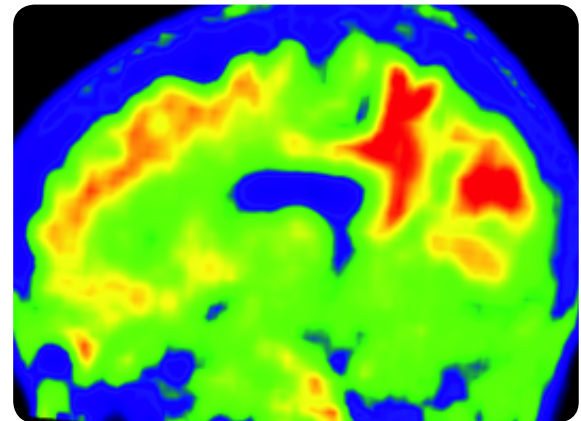
Healthy Control



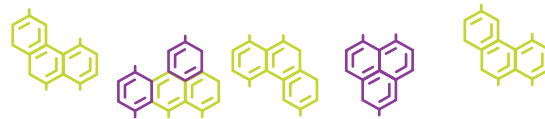
MCI (MMSE 26)



AD (MMSE 21)



AD (MMSE 7)



STOPPING HEMATOLOGICAL CANCER: New Drug Induces Remissions in Myelofibrosis

The results of a Mayo Clinic study demonstrate that a drug named imetelstat induces remissions in some patients with myelofibrosis. This is a form of chronic leukemia that affects the patient's bone marrow that is replaced by fibrosis (scar tissue) instead of blood-producing cells.

Scientists do not yet know the exact mechanism of action for imetelstat, but believe it interferes with the survival and proliferation of cancer cells by inhibiting a critical enzyme called telomerase. One of the functions of telomerase is to repair the ends of chromosomes called telomeres, and because cancer cells have shorter than normal telomere size, they are particularly susceptible to the drug.

The study results are promising. Some patients participating in the clinical trial taking imetelstat obtained dramatic responses, and we have seen some complete responses (tantamount to a cure), which is almost unheard of in this disease.

Although patients may experience relief in response to other treatments, their bone marrow does not usually return to normal. But in the case of this new therapy, some of the patients participating in the trial developed normal bone marrow.

Researchers studied imetelstat in 33 patients at Mayo Clinic and have now followed the first 22 patients for more than six months. Among these 22 patients, two achieved complete remissions and three partial remission, including reversal of bone marrow fibrosis in four of the five patients.



THE NEED TO DISCOVER, IMPROVE, AND ADVANCE

Research is the fundamental reason that people across the globe are living longer, healthier lives.

Mayo Clinic applies basic science to unlock the destructive secrets of cells and discover how to repair or reverse the damage. We then translate that knowledge into first-time cures and treatments for a wide range of life-threatening diseases and chronic conditions.

Patients receive research-driven care at Mayo Clinic, which possesses a long legacy of providing a team-based approach to integrating patient care, research, and education.

But more breakthroughs are necessary for our patients. We need to better understand and more effectively treat diseases ranging from the most prevalent like cancer to the rarest disorders. In such spectrum of diseases, we need to know why communication between cells breaks down.

Generous donors enable Mayo Clinic to spearhead the most advanced research and offer hope to patients around the globe in the form of new treatments and technologies. By investing in Mayo's research programs, benefactors contribute to developing faster treatments and cures for patients who need them now.



Gregory J. Gores, M.D.

Ronald F. Kinney Executive Dean
for Research at Mayo Clinic

BIOMEDICAL RESEARCH LEADER

Gregory J. Gores, M.D., is the Ronald F. Kinney executive dean for research at Mayo Clinic and leads and manages all of Mayo’s research activities. He also is a member of the Division of Gastroenterology and Hepatology and holds the academic rank of professor of physiology and medicine. Mayo Clinic recognizes Dr. Gores with the distinction of a named professorship, the Reuben R. Eisenberg Professorship.

Dr. Gores’ clinical and research contributions include advances in the understanding of hepatobiliary malignancies, liver transplantation, and mechanisms of liver cell injury. He has published more than 500 articles that include peer-reviewed papers, editorials, and book chapters.

Mayo Clinic honored Dr. Gores with the Research Career Achievement and Distinguished Investigator Award.





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