ACCcomplishments

THE BODY

HEALTH & WELLNESS

CONDITIONS & DISEASES

PROCEDURES

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IRP researchers have won international recognition and countless awards for research that is truly game-changing—transformational science that advances biomedical knowledge.

The following is a snapshot of some of the IRP’s most outstanding research.
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Blood and Lymphatic System

2015: Creating a blood test to predict recurrence of a common lymphoma

Challenge
Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. Though usually curable, when treatment fails, the long-term prognosis is poor. Relapses of DLBCL often occur because current imaging technology cannot detect residual disease. Researchers set out to find a more precise way to monitor the disease.

Advance
IRP investigators led by Wyndham Wilson, M.D., Ph.D., analyzed serum from 126 patients with DLBCL for the presence of circulating tumor DNA (ctDNA) for years after the patients had completed therapy. By quantifying the levels of tumor DNA pre- and post-treatment, Wilson’s team found that the patients who had detectable levels of ctDNA during surveillance were more than 200 times more likely to experience disease progression.

Impact
Measuring levels of ctDNA enables the detection of DLBCL recurrence earlier than clinical evidence of the disease can be detected. The test also predicts which patients will respond to therapy as early as the second cycle of treatment, a strategy known as interim monitoring, providing doctors and patients with more lead-time to treat the disease.

Publications
2017: How cells combat prions and amyloids

**Challenge**
As immune systems are equipped with multiple anti-viral and anti-bacterial systems, it has been hypothesized that cells must also possess anti-prion and anti-amyloid systems that can remove prions as they arise and before they can cause disease.

**Advance**
IRP researchers, led by Reed Wickner, M.D., and Daniel Masison, Ph.D., found that two proteins, Btn2p and Cur1p, are able to effectively remove most variants of the URE3 amyloid-based prion as they arise in yeast. Both proteins work by bringing prion aggregates together and limiting their propagation in the cell, and are homologous to the human HOOK protein family. In addition to this, researchers found that the Hsp104 chaperone can also cure most variants of the [PSI+] prion as they arise, and that both of these curing systems operate without artificial protein overproduction or deficiency.

**Impact**
The discovery of these anti-prion systems in yeast provides us with the opportunity to search for homologous or analogous systems in humans that are also responsible for removing prions and amyloids. If this research is successful, just as we immunize against viral and bacterial infections, it may also be possible to prime anti-prion systems in the human body to guard against prion and amyloid diseases, such as Alzheimer’s or Parkinson’s disease.

**Publications**


2016: A method of unraveling neural encoding mechanisms

Challenge
A key challenge to understanding how complex behaviors are encoded in the brain is the capability to simultaneously record the activities of large numbers of neurons in deep brain regions with single-neuron resolution in freely behaving animals.

Advance
IRP researchers led by Da-Ting Lin, Ph.D., developed a miniature fluorescent microscope (miniScope) system weighing just 2 grams. Coupled with gradient index (GRIN) lenses, the miniScope allows researchers to record the calcium activities of hundreds of neurons simultaneously in freely behaving mice, with single neuron resolution. They also showed that the recorded neural activities can be used to accurately predict mouse behavior variables, such as locomotion velocities.

Impact
The team’s deep-brain optical imaging method, combined with advanced computational analysis, will help researchers unravel neural encoding mechanisms underlying normal brain functions, as well as in various brain disorders. Further, their techniques may pave the way for identifying novel therapeutic strategies that could lead to the development of effective treatments for psychiatric disorders, such as substance abuse.

Publications

2016: Amygdala is as important as the ventral striatum for reinforcement learning

Challenge
Current models of reinforcement learning—which hold that this process is dependent on the ventral striatum’s ability to process dopaminergic signals in order to associate particular choices with outcomes—fail to take into account that, in Pavlovian conditioned learning, dopamine also goes to the amygdala and that this region of the brain also affects choice behaviors and learning.

Advance
IRP researchers led by Bruno B. Averbeck, Ph.D., used computational modeling and behavioral experiments to confirm the existence of an essential role for the amygdala in reinforcement learning, which is distinct from that of the ventrial striatum. In addition to this, they also defined a novel role for the ventral striatum in affecting trade-offs between accuracy and speed when making decisions.

Impact
By demonstrating that the amygdala is as important as the ventral striatum in reinforcement learning, and that the two areas work together through dopamine signaling, this study has advanced our understanding of how primates learn, and could inform our understanding of how some neurological disorders impact learning and decision-making.
2016: Better techniques for untangling correlations in big fMRI data

Challenge
Functional Magnetic Resonance Imaging (fMRI) has revolutionized our ability to measure and assess brain activity. However, when researchers try to compare fMRI data collected from subjects in naturalistic conditions (such as while watching a movie or listening to music), current methods produce false positive rates so high that the validity of these methods is called into question.

Advance
In part 1 of this two-part study, IRP researchers led by Robert W. Cox, Ph.D., identified ‘subject-wise bootstrapping’ (SWB) as the best nonparametric method for making inter-subject correlation inferences within a single group, while ‘subject-wise permutation’ (SWP) was found to be both more reliable and required far less computation than the cumbersome method traditionally used to define statistics of the inter-subject correlations in two groups. In part 2, researchers identified a parametric approach—linear mixed-effects modeling (LME)—that is more efficient, more adaptable, easier to use, and more robust than traditional nonparametric methods.

Impact
This comprehensive upgrade of modeling and analysis techniques for fMRI data provides both theoretical and practical help to scientists in many different fields who manage big datasets as part of their research. In order to further advance the field, Dr. Cox’s team also offers researchers an open source option in the AFNI (Analysis of Functional NeuroImages) suite, where they can access programs that process, analyze and display fMRI data.

Publications


2016: Discovery of a new protein triaging pathway for neurotoxic proteins

Challenge
In multicellular organisms, the cell-to-cell transmission of misfolded proteins can propagate abnormal polypeptides throughout a tissue, such as the brain. This process is accelerated when transmitted
polypeptides act as a template for further protein misfolding in recipient cells. The accumulation of these misfolded proteins can lead to widespread cell death, which is characteristic of many neurodegenerative diseases. Although the link between protein misfolding and several diseases is well known, it is currently unclear how misfolded proteins can be released from donor cells to initiate further misfolding in recipient cells.

**Advance**
IRP researchers led by Yihong Ye, Ph.D., discovered a novel protein triaging pathway that is dedicated to the removal of misfolded cytosolic proteins. The pathway uses an endoplasmic reticulum-associated enzyme to recruit misfolded cytosolic proteins and package them into vesicles marked for cellular secretion.

**Impact**
Having identified this unconventional protein secretion pathway for misfolded proteins, Dr. Ye’s group is now assessing whether or not this process may contribute to the cell-to-cell propagation of misfolded proteins, which is the underlying cause of the neurodegeneration seen in Alzheimer’s, Parkinson's and Huntington’s disease. If this pathway is shown to play a role in the propagation of misfolded proteins, it could offer a promising target for strategies to combat these serious neurological diseases.

**Publications**

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**2015: Finding molecular signatures of Alzheimer’s disease in blood extracellular vesicles**

**Challenge**
No blood tests currently exist that can detect brain disorders like Alzheimer’s disease (AD) at an early stage or monitor the effectiveness of therapeutic interventions.

**Advance**
IRP researchers led by Dimitrios Kapogiannis, M.D., found that extracellular vesicles, believed to be released from nerve cells, can be isolated from blood samples. The team found that subjects with mild cognitive impairment and AD exhibit major abnormalities in the amounts of several proteins within extracellular vesicles; these proteins were already known to be involved in brain dysfunction and AD. Preliminary studies suggest that these abnormalities may be present up to 10 years before patients are formally diagnosed with the disease.

**Impact**
The findings, if confirmed in larger studies currently underway, suggest that neuron-derived extracellular vesicles circulating in the blood can identify individuals who will develop AD before the onset of symptoms.

**Publications**


2015: Watching deep-brain movement circuits in action

Challenge
Measuring the activity of specific neuronal subtypes in the brain during performance of complex behaviors has proven difficult, as identifying different neurons during electrophysiological recordings is cumbersome, and using microscopes to view neurons constrains the range of behaviors that can be analyzed.

Advance
IRP researchers Guohong Cui, M.D., Ph.D., David M. Lovinger, Ph.D., Steven S. Vogel, Ph.D., and Rui Costa, D.V.M., Ph.D., used a novel optogenetic approach with small fiber-optic implants to measure the activity of two separate neural types in a brain region called the striatum, part of the basal ganglia. They discovered that these different types of neurons are co-active during the initiation of bodily movement sequences, contrary to the long-standing theory that one neuron activates sequences while another terminates them.

Impact
Development of deep-brain fiber-optic photometry is bringing previously inaccessible regions of brain circuitry into view for more detailed experimental observation of behaviors. Finding the co-activity of these two sets of neurons impacts the model of basal ganglia function and may influence the treatment of disorders originating within the brain’s striatum, including Parkinson’s and Huntington’s diseases.

Publications

2013: Alzheimer’s disease: challenging the amyloid dogma

Challenge
The predominant hypothesis for the pathogenesis of Alzheimer’s disease suggests that the deposition of fibrillar amyloid in the brain is its causative trigger. However, the repeated failures of Alzheimer’s disease treatment trials targeting amyloid deposition or clearance have highlighted the need to enhance understanding of alternative disease mechanisms.

Advance
IRP researchers led by Madhav Thambisetty, M.D., Ph.D., discovered that a common genetic risk variant for Alzheimer’s disease in the complement receptor-1 (CR1) gene is associated with lower brain amyloid burden in at-risk older individuals.

Impact
This study is the first demonstration that a genetic risk factor may mediate Alzheimer’s disease pathogenesis by mechanisms distinct from increased deposition of fibrillar amyloid in the brain. The team’s findings have highlighted the importance of seeking alternative mechanisms underlying Alzheimer’s disease and renew hope that identification of such mechanisms may lead to effective treatments.

Publications


2013: Detecting brain changes years before Alzheimer’s disease onset

Challenge
In 2010, it was estimated that as many as 5.2 million people aged 65 and older in the U.S. have Alzheimer’s disease, and that number is expected to more than double by 2050. Developing targeted strategies for the prevention and treatment of Alzheimer’s disease remains a priority, but a major obstacle to early intervention is the identification of early markers of brain changes that occur before the onset of cognitive impairment.

Advance
IRP researchers led by Lori Beason-Held, Ph.D., described for the first time that older adults who later develop cognitive impairment show different patterns of longitudinal change in brain function as measured by cerebral blood flow many years before cognitive decline begins, when compared to individuals who remain cognitively normal throughout life.
**Impact**
This finding demonstrates that changes in brain function are apparent before memory problems arise, and include both longitudinal increases and decreases in brain activity during the preclinical phase of Alzheimer’s disease. Deviation from the expected pattern of longitudinal change in brain function may assist in identifying people at increased risk for Alzheimer’s disease and point to mechanisms associated with memory decline.

**Publications**

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**2013: Finding the key to dendritic spine development**

**Challenge**
Normal brain function requires proper synaptic connections. In schizophrenia, the number of dendritic spines—small protrusions from dendrites that help convey neural signals—is reduced, resulting in impaired neuronal connections and cognition. However, the mechanism behind these changes is unknown.

**Advance**
IRP researchers led by Zheng Li, Ph.D., studied a mouse model of schizophrenia and found an age-dependent role for dopamine D2 receptors (D2R) in dendritic spine development. They showed that, in these mice, D2R over-activation during adolescence led to deficient dendritic spines and impairments in neuronal circuits and working memory.

**Impact**
Dr. Li’s research revealed a previously unknown function for D2R in the development of synaptic connections, suggesting that targeted treatments for aberrant D2R activity during adolescence may prevent cognitive impairment.

**Publications**

2013: Itching for an answer

Challenge
Despite the universality of itching, scientists do not have a full understanding of what triggers or maintains the sensation. How do itch sensory neurons transmit signals to the spinal cord? And how is an itch distinguished from other sensory qualities, such as temperature or pain?

Advance
IRP researchers Mark A. Hoon, Ph.D., and Santosh K. Mishra, Ph.D., demonstrated that a single neuropeptide transmitter, Nppb, located in a specific subset of neurons, is the primary mechanism by which itch responses are elicited in mice.

Impact
The team’s discovery opens doors to a wider molecular understanding of how itch sensations originate and are processed, which could lead to more targeted treatments for conditions associated with chronic itching, such as eczema and psoriasis.

Publications

2013: Mapping the adult mouse brain using embryonic gene expression

Challenge
Norepinephrine-producing neurons in the brain comprise a diverse population of cells that differ in their connectivity, function, and response to disease and environmental toxins. These neurons have previously been categorized into several groups on the basis of their location within the adult mouse brain, but the anatomical classification reveals little about the origins of this diversity. Understanding where these neurons originate from would provide insight into how their differentiated expression might be manipulated in therapeutic interventions.

Advance
IRP researchers led by Patricia Jensen, Ph.D., used genetically engineered mice to define subpopulations of norepinephrine neurons based on differences in embryonic gene expression. The team then traced the subpopulations in the adult mouse brain to determine what connections they make with other parts of the nervous system, revealing previously unknown variation among norepinephrine neurons.

Impact
This work uncovered a novel molecular framework for norepinephrine neurons, which may one day enable the functional manipulation of individual circuits in complex behavioral and physiological processes including arousal, attention, mood, memory, appetite, and homeostasis.

Publications
2013: Mind-body practices and yoga may protect against neurodegenerative effects of chronic pain

**Challenge**
Chronic pain debilitates millions of Americans each year. Current drug treatments often fail to relieve chronic pain, and have many side-effects when used long-term. Understanding the relationship between chronic pain and the brain is essential towards developing better treatments and helping patients better manage their pain.

**Advance**
IRP researchers led by M. Catherine Bushnell, Ph.D., showed that chronic pain is associated with reductions in brain gray matter volume, white matter integrity, and alterations in neural circuitry that resemble those seen in neurodegenerative diseases. Conversely, they found that yoga, a mind-body practice, has opposite effects on brain circuitry and structure.

**Impact**
The team’s findings suggest that chronic pain differs significantly from acute pain, and mind-body practices such as yoga may help protect against chronic pain’s effects on the brain. A clinical study is currently underway to examine the effects of yoga on the body’s stress response, pain perception, and the brain’s structure in response to pain.

**Publications**


2013: New views of emotional regulation and decision making

**Challenge**
The orbitofrontal cortex (OFC) was believed to be a central hub in the brain involved in emotional regulation and behavioral flexibility. However, recent research had cast doubt on that theory, and more precise lesion studies were necessary to reassess the role of the OFC in behavior.

**Advance**
In an animal model, Elisabeth Murray, Ph.D., and colleagues found that the OFC is not involved in behavioral flexibility (measured by a learning task) or emotional response (measured by fear of snakes) as previously thought. However, they found that, while the OFC is not involved in emotional regulation, it does help guide decisions based on the value of food rewards.
Impact
The new understanding of the OFC’s function in behavior requires the field of psychiatry to reassess whether psychiatric conditions such as major depression, obsessive-compulsive disorder, and psychopathy are linked to disruption of value representations housed in the OFC, rather than disordered cognitive flexibility as previously thought.

Publications

2012: Fission and fusion to help keep our cells healthy

Challenge
Mitochondria—the subcellular organelles responsible for a cell’s energy production and other metabolic functions—can suffer from defects of normal development, which have been associated with neurodegenerative disorders, such as Parkinson’s disease.

Advance
IRP researchers led by Richard Youle, Ph.D., described two normal mitochondrial processes—fission and fusion—that appear to play an important role in ensuring mitochondrial health via a “cut and paste” mechanism that removes and repairs damage resulting from cellular stress.

Impact
The new knowledge of mitochondrial fission and fusion processes may allow researchers to harness the cells’ natural repair ability to develop new therapies for both mitochondrial and neurodegenerative diseases.

Publications

2009: How voltage ion channels interact with their surroundings

Challenge
Voltage-activated ion channels are important to a variety of physiological processes, including generating nerve impulses, regulating heart contraction, and secreting hormones. Visualizing ion channels in their native environments—for example, within a lipid bilayer—is a technical challenge that if overcome could reshape treatments for many diseases.

Advance
IRP researchers led by Kenton Swartz, Ph.D., used neutron diffraction, solid-state nuclear magnetic resonance (NMR) spectroscopy, and molecular dynamics simulations to gather new information about voltage-activated ion channels, discovering interactions with the surrounding membrane in a way that maintains both the charged nature of the channel and the integrity of the membrane.
Impact
The findings provide perspective for voltage sensors and a new direction for targeted therapeutic
development, since many drugs that affect the nervous system work by modifying the behavior of
voltage-activated ion channels.

Publications

2008: Yeast proteins teach us about Alzheimer’s disease

Challenge
Prions are infectious proteins formed when normal proteins misfold and start clumping together. In
1994, researchers discovered that prions can self-propagate in yeast and thus have properties of a gene.
But what was the mechanism behind that protein self-propagation?

Advance
IRP researchers Rob Tycko, Ph.D., and Reed Wickner, M.D., showed that the infectious amyloid of the
prion domains of several yeast prions (Sup35p, Ure2p and Rnq1p) have a parallel flat sheet architecture.
In this case, and contrary to the long-standing tenet that amino acid sequence determines protein
folding, the overall amino acid composition of a polypeptide (and not the sequence itself) seems to
determine the protein’s ability to become a prion.

Impact
Not only does this research help explain the mechanism behind prion self-propagation, but it has
broad significance in understanding several common human diseases that feature amyloids, including
Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and type 2 diabetes.

Publications
have a parallel in-register beta-sheet structure. Biochemistry 47(13), 4000-4007.

Kryndushkin, D. S., Wickner, R. B. and Tycko, R. (2011). The core of Ure2p prion fibrils is formed by the N-terminal

Lu, J.Z., Qiang, W., Yau, W.M., Schwieters, C.D., Meredith, S.C., and Tycko, R. (2013). Molecular structure of beta-
amyloid fibrils in Alzheimer’s disease brain tissue. Cell 154(6), 1257-68.

2001: Moving toward understanding polyglutamine toxicity

Challenge
Polyglutamine diseases, including Huntington’s disease, arise from multiple repeats of the glutamine
codon—for example CAGCAGCAGCAG—in a variety of genes. Since these diseases likely share similar
mechanisms, a better understanding of how these repeats cause dysfunction could aid in the
development of therapies.
Advance
IRP researchers led by Kenneth Fischbeck, M.D., found that the expanded polyglutamine proteins may act as sticky glue, blocking up their normal clearance process. The excess protein then interferes with a number of nuclear factors important in maintaining genetic stability, causing the cell to enter apoptosis, or programmed cell death. These observations correlate with the neuronal death observed in conditions such as Huntington’s disease.

Impact
The finding that polyglutamine toxicity in cell culture may be due to interference with nuclear factors has potential therapeutic implications, and research is underway to evaluate molecules with potential application as disruptors of that process.

Publications

1970: The first understanding of how brain cells communicate

Challenge
Prior to the 1950s, science knew little about how nerve cells in the brain communicated with each other. Understanding the signal transmission mechanism was a fundamental challenge to meet before researchers could dive deeper into investigations of brain function.

Advance
For more than five decades, Julius Axelrod, Ph.D., studied the underpinnings of nerve communication, culminating in his seminal discovery that neurotransmitters—chemical molecules that nerves use to transmit signals—don’t just degrade upon reaching their destination, but are re-uptaken for reuse in later transmissions.

Impact
Axelrod’s discoveries revolutionized understanding of how nerve cells communicate, laying a foundation upon which development of many targeted medications for depression and anxiety were built. In 1970, he was awarded the Nobel Prize in Physiology or Medicine.

Publications
2014: Mapping Irritable Bowel Syndrome

Challenge
Irritable Bowel Syndrome (IBS) is a common gastrointestinal (GI) disorder that can include debilitating symptoms with significant healthcare and productivity costs. Various GI disorders and conditions, including IBS, are associated with changes in gastrointestinal permeability (GIP). The causes and progression underlying IBS, as well as the clinical implications of increased GIP, are unclear, making accurate diagnoses of gastrointestinal dysfunctions difficult to achieve.

Advance
IRP researchers led by Wendy Henderson, Ph.D., M.S.N., C.R.N.P., adapted, developed, and tested a protocol for examining GI permeability using a single 4-probe solution in patients with and without IBS, showing that colonic permeability was significantly decreased in the IBS patients and demonstrating clinical efficacy of the new diagnostic approach. Dr. Henderson’s group went on to discover that the expression of two microRNAs (miRNAs) with links to pain and inflammatory pathways were up-regulated in patients with IBS.

Impact
The ability to fully characterize an individual’s GI permeability profile along the entire GI tract using a novel 4-probe method for analysis may help clinicians make more informed diagnoses. Furthermore, discovery of the two IBS-correlated miRNAs provides a new path for development of less invasive diagnostic biomarkers and potential therapeutic targets for those who suffer with the symptoms of IBS.

Publications


2010: Creating a new method to measure abdominal pain

Challenge
Chronic abdominal pain of unknown origin affects approximately 20 percent of people in the U.S. and is the most common reason for outpatient medical visits. The short-form McGill Pain Questionnaire is the current standard in assessing pain, but its use is limited in young children who may struggle to understand the questionnaire’s word-based descriptors.

Advance
IRP researcher Wendy Henderson, Ph.D., and her team developed the Gastrointestinal Pain Pointer
(GIPP), a new computerized tool for assessing abdominal pain severity that combines subjective scores with objective heart rate recordings. Patients use an interactive graphical interface to identify the location and intensity of their pain.

**Impact**
The GIPP has proven itself a valid and reliable instrument in both children and adults with abdominal pain, providing clinicians with a more integrated resource for pain assessment that includes location, intensity, and quality, along with physiologic parameters.

**Publications**

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**Ear, Nose, and Throat**

**2014: Guarding against hearing loss from anti-cancer drugs**

**Challenge**
Some widely used therapeutic drugs have an unfortunate side effect of hearing loss. Two major classes of such “ototoxic” drugs are the aminoglycoside antibiotics and the anti-cancer drug cisplatin. These drugs save lives, but can also result in permanent hearing loss. New therapies are needed to protect the inner ear without inhibiting the therapeutic efficacy of the drugs themselves.

**Advance**
IRP researchers led by Lisa L. Cunningham, Ph.D., tested the hypothesis that the inner ear can be ‘conditioned’ by a mild stress that induces an intrinsic protective response, using moderate-level noise exposure. They exposed mice to a “conditioning” sound that was carefully calibrated to stress the inner ear without itself causing damage. The team then treated the mice with the ototoxic drug cisplatin and found that the conditioning noise protected against cisplatin-induced hearing loss.

**Impact**
The use of mild stresses to condition the inner ear holds promise as a therapy to prevent hearing loss in patients receiving ototoxic drugs, while not altering the lifesaving effects of the drugs themselves*.

*The researchers caution that treatment noise levels must be very carefully calibrated in order to avoid resulting in a noise-induced hearing loss, so it is important that patients do not expose themselves to noise in an effort to prevent ototoxic drug-induced hearing loss.

**Publications**
2012: Understanding deafness: the role of auditory nerve mapping

Challenge
A key step in hearing development involves creating synaptic connections between the auditory nerve and sensory cells of the inner ear, yet how this happens is not fully understood. Further knowledge is needed to identify causes of hereditary hearing loss and eventually lead to effective treatments.

Advance
IRP researchers led by Matthew Kelley, Ph.D., demonstrated that expression of Pou3f4—a protein that helps transcribe DNA into RNA—interferes with auditory nerve axon growth by forcing the axons to grow along specific tracks toward inner ear sensory cells.

Impact
The finding helps explain why mutations in the Pou3f4 gene cause hearing loss. It may also lead to improvements in the function of cochlear implants, which must connect with the auditory nerve to alleviate deafness.

Publications

Endocrine System (Hormones)

2016: Hormones boost gene activity through super enhancers

Challenge
It is well established that pregnancy hormones activate genetic programs that control the development of mammary tissue and the production of milk to nourish the young. However, the molecular mechanisms that activate genes during pregnancy by up to 1,000-fold were unknown.

Advance
IRP researchers, led by Lothar Hennighausen, Ph.D., discovered mammary-specific super enhancers that responded to pregnancy hormones by activating specific gene sets. By using CRISPR/Cas9 gene editing technology they dissected, for the first time, a complex super-enhancer and discovered a functional hierarchy among its individual constituent components.

Impact
Super enhancers, or stretch enhancers, have previously been defined by their structure but evidence of their functional significance within a living organism has been lacking. For the first time ever, this study used genome editing in a mouse model to define the biological role of super-enhancers, and the discovery of hierarchies within these enhancers points to a higher level of complexity than had originally been anticipated.
2012: Taking a closer look at our on/off relationship with insulin

**Challenge**
Diabetes now affects more than 25 million people of all ages yet the molecular underpinnings of the disease remain unclear. Although the overall pathways that drive the production of insulin are known, the molecular mechanisms that control rapid changes in insulin synthesis—for example following a meal—are not.

**Advance**
IRP investigators led by Eun Kyung Lee, Ph.D., identified a previously unknown component of the pathway—an RNA-binding protein named HuD, expressed in pancreatic β cells—that can bind insulin mRNA and inhibit its translation into protein, essentially blocking its production. The researchers also showed that, in response to increased glucose levels, HuD releases insulin mRNA, allowing the production of insulin protein.

**Impact**
The discovery that an RNA-binding protein can repress insulin translation in a rapidly reversible manner suggests that deficiencies in this protein could underlie some cases of diabetes. Work is underway to systematically compare HuD in the pancreatic β cells of diabetic and non-diabetic subjects, with the aim of determining if HuD could be a new therapeutic target.

**Publications**

2011: Tracking the devastating effects of diethylstilbestrol (DES), a trans-placental carcinogen

**Challenge**
Between 1940 and the early 1970s, millions of pregnant women were given diethylstilbestrol (DES), the first synthetic estrogen, to prevent pregnancy complications. DES was later found to be a carcinogen that could cross the placenta and cause a range of health-related issues in women, including developmental defects and cancers. Rigorous follow-up reporting and analysis would be required to fully understand the devastating effects of DES on the women who were exposed in utero years before.

**Publications**

**Advance**
IRP investigators led by Robert Hoover, M.D., Sc.D., re-contacted more than 4,600 women who had participated in an initial landmark study, which described a rare vaginal cancer typically seen only in older women. These women were then followed long-term, and researchers were able to identify and track a number of adverse health outcomes linked to DES exposure, including pre-term delivery, ectopic pregnancy, and cancers of the cervix.

**Impact**
Without long-term follow-up studies, many outcomes of DES exposure might have gone unreported. This investigation, and others like it, serves as a model for an entire area of research focused on the role of endocrine disruption in early life and subsequent health effects.

**Publications**


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**Eyes and Vision**

**2011: Unraveling a complex world of neuronal connections**

**Challenge**
Neurons have always appeared to be somewhat haphazardly wired together, yet their complex connectivity forms the basis of all neural circuits, whether in the brain, auditory tissues, or the retina of the eye, suggesting the process must have some degree of specificity.

**Advance**
IRP researchers led by Kevin Briggman, Ph.D., used new technologies, such as two-photon calcium imaging and serial block-face electron microscopy, to thoroughly visualize the neuronal circuitry used by the eye to detect motion.

**Impact**
The group’s findings demonstrate that neuronal wiring in the retina is far more structured than initially thought, providing a basis for new neuronal models of development and disease, which could eventually lead to techniques for repairing damaged neuronal networks.

**Publications**

Immune System

2016: Insights into influenza through human challenge

Challenge
Influenza continues to kill thousands of Americans each year. Although flu vaccines are available, the protection they provide can be incomplete and the vaccine must be re-developed each year to defend against current circulating strains. In the absence of human challenge studies, the induced immune response (antihemagglutinin (HA) antibody) used to evaluate seasonal vaccines has not been examined since the 1970s.

Advance
IRP researchers led by Matthew Memoli, M.D., M.S., successfully developed and implemented the first influenza challenge study in healthy volunteers in the U.S. in over a decade. In this study, doctors exposed individuals to a flu virus and then studied their immune responses to better understand how flu makes us sick, how we best recover, and how to develop better therapies and broadly protective vaccines. Through this approach, researchers demonstrated for the first time that antineuraminidase (NA) antibody titer is more accurately and independently predictive of flu protection and reduced disease than the previous gold standard of HA antibodies.

Impact
With antineuraminidase (NA) antibody titer as a more accurate indication of flu protection, we may soon be able to develop more effective annual flu vaccines. Development of the influenza challenge model greatly facilitates testing of novel universal broadly protective vaccine candidates, therapeutic approaches, and diagnostic techniques that could have a significant impact in reducing influenza morbidity and mortality. Moreover, the model generated considerable data on components of human flu response that may lead to the development of a universal influenza vaccine.

Publications

2015: Dissecting the Immune Response

Challenge
The RAG1 and RAG2 proteins work together to initiate the complex cut-and-paste process of coding DNA that allows the immune system to fight off a large variety of infections. Mutations of these proteins are known to cause a sizable fraction of immune deficiencies in children, but the complex interaction of the RAG proteins was not well understood.
**Advance**
IRP researchers led by Wei Yang, Ph.D., and Martin Gellert, Ph.D., captured a detailed three-dimensional crystal structure of the RAG1-RAG2 protein complex, allowing them to characterize more than 60 mutations known to result in immunodeficiency. The close relationship of the RAG1-RAG2 complex to other species’ DNA rearranging proteins demonstrates that these proteins have been highly conserved.

**Impact**
Visualizing the RAG1-RAG2 structure not only helps to explain the functional defects of known disease mutations, but can now help researchers understand the many immunodeficiencies that do not yet have a known underlying mutation.

**Publications**

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**2014: Learning that cells can use their nuclei like pistons to move**

**Challenge**
The controlled movement of cells through complex, three-dimensional tissues is essential for human health. A moving cell can undergo dramatic changes in size and shape, suggesting that cells may use more than one molecular mechanism to migrate in the body, but understanding of how healthy and diseased cells move was limited.

**Advance**
IRP researchers led by Kenneth M. Yamada, M.D., Ph.D., pioneered the measurement of pressure inside single human cells and discovered a new mechanism of cell movement. The team found that normal human cells such as fibroblasts can use their nucleus like a piston to pressurize the cell and subsequently produce a force that is strong enough to push the cell through three-dimensional environments.

**Impact**
Characterizing types of cell migration in normal tissue remodeling, wound repair, and cancer invasion, including the new nuclear piston mechanism, will likely help identify new therapeutic targets for a large number of cell movement-related diseases.

**Publications**
2014: Programmed cell death drives generation of immune system’s regulatory T cells

**Challenge**
Without regulatory T cells (Tregs)—a type of immune cell that can be generated in the thymus—an individual would have uncontrolled, lethal inflammation. Despite the importance of Tregs, the cellular and molecular mechanisms controlling their development were a mystery.

**Advance**
IRP researchers led by WanJun Chen, M.D., discovered that the vital ingredient for making Tregs in the thymus is a molecule called transforming growth factor-beta (TGFβ). They also showed that thymic apoptosis (programmed cell death) plays an important role in helping to develop regulatory T cell generation, also through the production of TGFβ.

**Impact**
The discovery opens new doors to a complete understanding of how Tregs develop in the thymus. Such findings of the pathways and molecular players involved in Treg cell development and function may enable the identification of molecular targets for developing therapies for people with autoimmune diseases, chronic inflammation, and cancer.

**Publications**

2012: Discovering monogenic forms of common variable immunogenicity

**Challenge**
Common variable immunodeficiency (CVID) is one of the most common primary immunodeficiency diagnoses. Early diagnosis of CVID is essential to ensuring reduced severity of infections via intravenous immunoglobulin (IVIG) treatment.

**Advance**
IRP researchers E. Michael Gertz, Ph.D., Alejandro A. Schäffer, Ph.D., and colleagues used genetic linkage analysis in families to identify homozygous mutations in the lipopolysaccharide responsive beige-like anchor gene (LRBA) as a frequent cause of CVID in patients who have early onset and autoimmune manifestations.

**Impact**
LRBA-deficient patients can now receive a prompt diagnosis via genetic analysis and start IVIG treatment sooner, which helps reduce the severity of recurrent infections and improves overall outcomes.

**Publications**

**2011: Reclassification of diseases improves understanding and outcomes**

**Challenge**
Little is known about the causes or how to treat a group of rare heterogeneous autoimmune muscle diseases called idiopathic inflammatory myopathies, including Dermatomyositis, Polymyositis, and Inclusion Body Myositis. For unknown reasons, these diseases are increasing in prevalence in both children and adults, and a better understanding of their pathogenesis, underlying genetics, and molecular basis is urgently needed.

**Advance**
IRP researchers led by Frederick W. Miller, M.D., Ph.D., took a novel approach to understanding these heterogeneous syndromes and showed that the genetic and environmental risk factors, symptoms, and responses to therapy and prognosis can be predicted by categorizing the syndromes into mutually exclusive and stable phenotypes based on clinical and immune response features.

**Impact**
Redefining autoimmune muscle diseases into novel phenotypes has advanced the understanding of their unique pathogenesis and helped clinicians to recognize and manage these debilitating disorders.

**Publications**


**1976: Discovery of interleukin-2 (IL-2)**

**Challenge**
In the 1970s, researchers sought to define whether retroviruses are causative agents of human diseases, including cancers. In order to discover and study human retroviruses, researchers first needed to identify a way to grow and maintain T lymphocytes, or T-cells, long-term in the lab.

**Advance**
IRP researchers led by Robert Gallo, M.D., found a way to successfully grow T-cells in culture for more than nine months. They accomplished the feat by first stimulating lymphocytes with phytohemagglutinin, a protein found in plants, and then examining for the production of potential growth factors in the culture fluid. The team identified T-cell growth factor (TCFG), now known as interleukin-2 (IL-2).
**Impact**
The discovery and purification of IL-2 allowed researchers to grow T-cells and study their immunology, which led to the discovery of human T-cell leukemia virus (HTLV), the first retrovirus identified in humans.

**Publications**


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**Kidney and Urinary System**

**2010: Understanding health disparities in kidney disease**

**Challenge**
African Americans experience higher rates of kidney disease than do European-Americans, yet the increased prevalence of chronic kidney and end-stage kidney diseases in populations of African ancestry remains largely unexplained.

**Advance**
IRP researchers Jeffrey Kopp, M.D., and Cheryl Winkler, Ph.D., led a team that identified a genetic region on chromosome 22 within a specific gene—MYH9, a key component of the actin cytoskeleton—that genetically predisposes individuals to chronic kidney disease. Genetic variation in this region substantially explains the major health disparity between African Americans and those of non-African descent.

**Impact**
The finding inspired subsequent work on this locus, led by Dr. Martin Pollak, that identified the main contributor as genetic variants in APOL1, encoding apolipoprotein L1. APOL1 is a component of the innate immune system, and work defining how the variants disrupt cell function may offer new pharmacologic approaches to treating kidney disease.

**Publications**

Mental Health and Behavior

2016: Ketamine for the treatment of depression and other anxiety-related disorders

Challenge
Ketamine and its analogs have been found to provide rapid anti-depressive relief in depression and other anxiety-related disorders. Despite legitimate medical uses, ketamine also has dissociative, euphoric, and addictive properties, making it a potential drug of abuse and limiting its usefulness. This has prompted a search for metabolites that retain antidepressant properties, but lack the undesirable side effects of ketamine.

Advance
IRP researchers led by Carlos Zarate, M.D., and collaborators found that the (2R,6R)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone ((2R,6R)-hydroxynorketamine (HNK)) metabolite reverses depression-like behaviors in mice without triggering the undesirable side effects. In contrast to the prevailing view that ketamine produces its antidepressant effects by blocking glutamatergic N-methyl-D-aspartate (NMDA) receptors, the team found that the rapid antidepressant-like effects required activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Impact
A stereospecific bioactive ketamine metabolite (2R, 6R-HNK) was identified that exerts rapid-acting antidepressant effects and is devoid of addictive properties. This metabolite and associated methods of treatment are available for collaboration and licensing. Further, by elucidating the molecular target, the results of this study open new avenues for further antidepressant drug discovery and development.

Publications
2014: Identifying a key neurological regulator of social memory and aggression

**Challenge**
Aggressive behavior in humans—particularly when it is socially inappropriate or violent—can be a symptom of mental illness. Brain activity during inappropriate aggression is not fully understood, making prevention and treatment difficult for patients, families, and healthcare providers. Research indicates that social behavior in mammals is regulated by the neuropeptides oxytocin and vasopressin.

**Advance**
IRP researchers led by W. Scott Young, M.D., Ph.D., and Serena Dudek, Ph.D., led a study that identified a single vasopressin receptor, Avpr1b, located primarily in the brain’s hippocampal region, as a key regulator of social memory and social aggression.

**Impact**
A number of psychiatric diseases with social components appear to involve the hippocampus or the Avpr1b receptor, such as childhood aggression, autistic traits, and schizophrenia. With this information, researchers can now pursue the development of targeted therapies that can help correct misperceptions of potential threat and reduce inappropriately aggressive behavior and violence.

**Publications**

2014: Understanding sensory symptoms in autism: seeing the trees, but not the forest

**Challenge**
People with autism report exceptionally quick and accurate perception of small visual details, but often have difficulty integrating the details into their overall view of the world—prompting the colloquial symptomatic description of “seeing the trees, but not the forest.” The neurobiological roots of autistic sensory symptoms were unknown.

**Advance**
IRP researchers led by Chris I. Baker, Ph.D., discovered reduced activity in visual brain areas of individuals with autism when they were “seeing the trees, but not the forest.” However, by simply giving individuals more time to process visual information, Baker and his team showed full restoration of “global perception” in autistic individuals, as well increased activity in visual areas of the brain.

**Impact**
Dr. Baker’s research sheds light on the neurobiological basis of a common symptom of autism and suggests that the sensory symptoms associated with the condition may reflect a fundamental perturbation in neural circuitry. Understanding that autistic perception deficits are due to atypical processing of information in the visual parts of the brain provides researchers with target areas for the development of future therapies.
2013: Exploring racial differences in antidepressant response

Challenge
It has long been recognized that antidepressants are less effective for African-Americans with major depression than for individuals of other races\(^3\). The difference has generally been attributed to factors such as greater treatment drop-out rates and socioeconomic adversity. A better understanding of possible genetic causes could help reduce the existing health disparities.

Advance
IRP researchers led by Francis McMahon, M.D., used genome-wide single-nucleotide polymorphism (SNP) data to show that genetic ancestry, rather than self-reported race, helps drive racial differences in response to treatment with the antidepressant citalopram.

Impact
This was the first demonstration of genetic effects on antidepressant response independent of race in African-Americans with major depression. The study highlights the importance of including more African-American patients in drug development and treatment trials to ensure new therapies are effective in this population.

Publications
2013: Identifying an Alzheimer’s disease risk gene

Challenge
Alzheimer’s disease is a devastating, progressive brain disease that affects as many as 5.1 million Americans, and is the most common cause of dementia among older people. How the disease process begins remains unknown, creating an urgent need to better understand Alzheimer’s disease risks.

Advance
Two international teams of researchers, including IRP researchers led by Andrew Singleton, Ph.D., identified a unique variant in the TREM2 gene—a gene involved in inflammation and the immune response—as a significant risk factor for the development of late-onset Alzheimer’s disease.

Impact
For many years the only genetic variant consistently associated with late onset Alzheimer’s disease was in the ApoE4 gene. These are the first studies to identify the involvement of TREM2 in the Alzheimer’s disease process. TREM2 plays a very specific role within the immune system, which suggests that perturbation of this system in some way may lead to the development of the disease. Discovering that pathway now provides targets for potential therapies.

Publications

2012: Spur of the moment purchase? Blame your orbitofrontal cortex

Challenge
Scientists have long assumed that an area of the brain called the orbitofrontal cortex plays a role in decision-making. While the idea gained widespread acceptance in the scientific community, it was based on correlative evidence. New research was needed to determine exactly what role the region plays, and how that may affect our understanding of certain diseases, for example addiction disorders.

Advance
IRP researchers led by Geoffrey Schoenbaum, M.D., Ph.D., designed a series of experiments and discovered that the orbitofrontal cortex in fact does play a role in decision-making, but only in spur-of-the-moment, quick decisions and not decisions made previously or through habit. This finding was true for both decision-making and learning—in other words, if a decision is assumed and doesn’t occur, that knowledge can be used to drive the process of learning.
Impact
This research fundamentally changed scientific understanding of the orbitofrontal cortex's role in normal behavior and how its alteration may contribute to behaviors seen in addiction disorders. Future work will characterize how drugs such as cocaine adversely affect this region of the brain, as well as identify pre-clinical approaches to restore function to damaged regions.

Publications

2011: Stimulating new ideas on caffeine action in the brain

Challenge
Caffeine is one of the oldest and most widely consumed cognitive stimulants on earth. Although it has pharmacological effects on many brain areas, its primary physiological site of action has not been established. Understanding how caffeine functions may provide clues to understanding sleep disorders, depression, and a range of conditions involving altered cognitive functioning.

Advance
IRP researchers led by Serena Dudek, Ph.D., discovered that caffeine, at levels similar to that consumed by humans, along with similar, more selective A1 adenosine receptor blockers, strongly enhanced synaptic responses in an area of the brain known as "hippocampal area CA2." The hippocampus is known for its role in learning and memory.

Impact
By discovering that this small region of the brain is the primary site of caffeine action, these studies highlight the CA2 region as a potential target for drug development to combat symptoms of fatigue due to sleep deprivation and depression, as well as sleep disturbances in neurodevelopmental disorders such as autism.

Publications

2010: The need for speed: A new approach to treating depressive disorders

Challenge
Current therapies for depressive disorders take many weeks to work, during which time the symptoms of depression, including suicidal thinking, persist and can be fatal. Patients need better treatments that begin relieving symptoms immediately.
**Advance**
IRP researchers led by Carlos A. Zarate, M.D., took a novel approach to the problem and discovered that a single infusion of ketamine provides a fast, robust, and sustained antidepressant effect, including reduction of suicidal thoughts within minutes.

**Impact**
Having demonstrated unprecedented speed of symptom relief, ketamine and its analogs are now being tested in clinical trials around the world and, if approved for use, could become a new standard of care for treating people with depressive disorders.

**Publications**

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**2008: Could you become addicted to something? Your genes reveal all**

**Challenge**
Genetic influences on quitting smoking and beginning use of common addictive substances are well documented in the scientific literature. Doctors recommend prevention interventions for individuals who may be at risk of substance abuse. However, a test is needed to indicate the most urgent candidates for prevention intervention.

**Advance**
IRP researchers at the National Institute on Drug Abuse (NIDA) developed the first genetic test for smoking cessation and discovered that the test’s score is able to robustly separate individuals who rapidly accelerate use of addictive substances from those who do not.

**Impact**
This is the first test to identify individuals at risk for addiction, who might benefit most from prevention efforts since they are more likely to escalate use if they start and have more difficulty quitting if they develop regular use, abuse, and dependence.

**Publications**

**1994: First successful treatment of childhood schizophrenia**

**Challenge**
Although schizophrenia is rare in children and adolescents (roughly 1 in 40,000), symptoms such as psychosis must be treated quickly and effectively to ensure the least amount of disruption to school and social activities. Treatment includes education and support, psychosocial counseling, and psychiatric medication. Medications for the pediatric population require additional levels of scrutiny and review, and pharmaceutical options were seriously lacking in this area of mental health.

**Advance**
Judith Rapoport, M.D., and colleagues enrolled 11 children meeting the criteria for schizophrenia in a six-week open trial of clozapine. At six weeks, behavior was rated on a number of pediatric scales, including the Brief Psychiatric Rating Scale and Children’s Global Assessment Scale. More than half the children showed marked improvement in behavior after six weeks of clozapine therapy compared to their previous medication.

**Impact**
The team’s research was the first time that clozapine was found to be a promising treatment for children and adolescents with schizophrenia who were not responding well to typical neuroleptics.

**Publications**

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**1985: First successful treatment of childhood OCD**

**Challenge**
Childhood-onset obsessive-compulsive disorder (OCD) affects 1–2% of children and adolescents. Characterized by recurrent obsessions and compulsions, the illness can create severe distress as it interferes with daily life. A treatment was needed to effectively control symptoms in the pediatric population without concomitant adverse events.

**Advance**
Judith Rapoport, M.D., and colleagues evaluated 19 children with severe primary OCD as they completed a 10-week, double-blind, controlled clinical trial of the tricyclic antidepressant clomipramine hydrochloride or placebo, each of which was administered for five weeks. Half of the subjects had not responded to previous treatment with other tricyclic antidepressants. The study demonstrated significant improvements in observed and self-reported obsessions and compulsions and was well-tolerated, a first for a medication in pediatric OCD.

**Impact**
The team’s research was the first to demonstrate a drug’s effectiveness in treating children with obsessive-compulsive disorder, which led the way for an eventual FDA approval of clomipramine in 1998 to help improve pediatric patients’ lives.
1970: A sense of calm in bipolar disorder: The clinical trials of lithium

Challenge
In 1949, the Australian physician John Cade published a paper on using lithium salts to treat psychotic mania, noting that the drug produced a “pronounced calming effect”. The publication piqued great interest among the psychiatry community, but large multicenter clinical studies were needed to confirm lithium’s role as a potential new tool in the treatment of mania associated with bipolar disorder.

Advance
In the decades following Cade’s publication, the National Institute of Mental Health (NIMH) and several university centers established large, rigorously controlled, multicenter clinical trials that clearly demonstrated the antimanic effects of lithium. The ability to convene, lead, and analyze data from these trials contributed to the FDA’s 1970 approval of lithium to treat acute mania.

Impact
More than 60 years after its discovery, lithium is still the first-line therapy for treatment of bipolar disorder. In addition to being tremendously successful in treating the illness, lithium provides enormous financial savings by reducing the lost productivity of affected earners, homemakers, caregivers, and other individuals by billions of dollars annually.

Publications

Reproduction and Sexual Health

2017: Quantitative control mechanisms ensure the fidelity of cell division

Challenge
Centrioles are essential organelles that play critical roles in cell division, cell signaling, and cell motility. The number of centrioles in a cell must be strictly maintained, as some human cancers and primary microcephaly can arise when centriole numbers deviate from the norm. How centriole numbers are precisely controlled in healthy cells and what malfunctions lead to unbalanced numbers are not well understood.
**Advance**
IRP researchers led by Kevin O’Connell, Ph.D., found two protein phosphatases functioning in opposing ways to ensure that numbers of centrioles remain constant from one cell generation to the next. Protein phosphatase 2A promotes expression of the kinase ZYG-1, a master regulator of centriole biogenesis. Loss of protein phosphatase 2A results in the underproduction of centrioles and cell division failure. Conversely, protein phosphatase 1 inhibits the expression of ZYG-1, and the loss of protein phosphatase 1 results in the overproduction of centrioles and abnormal cell division.

**Impact**
The team’s identification of a novel mechanism that maintains centriole numbers and contributes to the fidelity of cell division, a fundamental biological process that is essential for human health, may lead to new ways of treating diseases that arise due to aberrant centriole numbers.

**Publications**


**Skin, Hair, and Nails**

2014: Learning about human skin’s microbiota

**Challenge**
Healthy skin is the natural home to myriad bacteria, fungi, and viruses. Many of these microbes are difficult to culture and thus have not been identified as part of the skin-associated community. Using DNA sequencing to catalog the microbial communities in healthy volunteers would provide insight into human health and empower clinical studies that explore how shifts in microbial communities contribute to skin diseases.

**Advance**
Dermatologist Heidi Kong, M.D., M.H.Sc., geneticist Julie Segre, Ph.D., and colleagues performed large-scale DNA sequencing on skin swabs from 18 distinct areas, including the chest, forehead, toe web, and inner elbow, from 15 healthy volunteers. Their analysis showed that the skin demonstrated a surprising diversity, dependent on the specific location and individual.

**Impact**
Having pioneered these investigations in healthy volunteers, IRP researchers are now exploring changes in skin microbial communities associated with common skin disorders—such as childhood eczema—and rare disorders, such as those associated with primary immune deficiencies.
2012: Only skin deep? New insights on retinoic acid in skin development

Challenge
Skin protects us from foreign organisms and allergens, but how it develops into a protective barrier is still unknown. Molecular-level understanding of the process could lead to treatments for skin conditions and diseases.

Advance
IRP scientists led by Maria Morasso, Ph.D., discovered that high levels of retinoic acid—a popular skin cream ingredient—during embryonic development in mouse models resulted in abnormalities of the epidermis, the outermost skin layer, and interfered with the skin’s normal barrier function.

Impact
The new insights into abnormal skin development open a door that may lead to treatments for aberrant skin growth and barrier dysfunction associated with conditions ranging from hypothermia and prenatal dehydration to atopic dermatitis.

Publications
Environmental Health

2012: Linking heavy exposure to diesel exhaust to lung cancer deaths in miners

Challenge
Despite numerous studies investigating the relationship between diesel engine exhaust exposure and risk of death from lung cancer, the lack of quantitative exposure data and large sample sizes restricted our ability to accurately evaluate this risk. Accurate evaluation of the exposure-response for diesel exhaust and lung cancer is critical for the millions of people around the world who are occupationally exposed to potentially fatal carcinogens.

Advance
In 1992, IRP researchers led by Debra T. Silverman, Sc.D., and colleagues at the National Institute for Occupational Safety and Health (NIOSH) embarked on a 20-year study of more than 12,000 miners, which became the first to show a statistically significant association between heavy exposure to diesel exhaust and lung cancer death.

Impact
These findings are important for public health, with implications for not only the 1.4 million American workers who are exposed to diesel exhaust in the workplace7, but also the many millions of urban populations in the U.S. and around the world who may be exposed to diesel exhaust.

Publications

**1957: Fluoridation: A public health milestone to make us all smile**

**Challenge**
More than half a century ago, tooth loss and decay was a serious public health issue afflicting most people, often at a young age. Periodontal diseases and dental caries left 17 million Americans age 45 and older (about three in 10) with none of their natural teeth. Tooth Decay. If researchers could discover a way to prevent tooth decay, everyone would benefit.

**Advance**
IRP investigators at the National Institute of Dental Research (now the National Institute of Dental and Craniofacial Research (NIDCR)) spearheaded studies in the 1940s and 1950s that showed the rate of tooth decay in children who drank fluoridated water fell more than 60 percent.

**Impact**
Water fluoridation stands out as one of the most significant and cost-effective public health milestones of the last century.

**Publications**


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**1951: Understanding and Treating Fungal Infections**

**Challenge**
Fungal infections emerged as a growing health threat, especially in people whose immune systems are weakened by HIV or other causes. Cryptococcosis, caused by the ubiquitous fungus *Cryptococcus neoformans*, rarely affects people with healthy immune systems, but it is the most common fungal brain disease in AIDS patients. If left untreated, cryptococcosis is invariably fatal.

**Advance**
- During the 1950s, IRP researcher Chester Emmons, Ph.D., discovered the environmental source of *C. neoformans*: soil contaminated with pigeon excrement.
- While only the asexual, yeast-like form of the fungus has been found in infected humans, *C. neoformans* can also reproduce sexually. Sexual reproduction of *C. neoformans*, which was first described by IRP scientist Kyung J. Kwon-Chung, Ph.D., during the 1970s, forms infectious spores.
- Discovery of sexual reproduction enabled genetic determination of virulence factors of *C. neoformans*.
- In addition to advancing knowledge of *C. neoformans* biology, IRP scientists have focused on developing treatments for fungal infections, and much of the pioneering work on the antifungal drug amphotericin B and flucytosine was performed at the IRP.

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**Impact**

Nearly two decades after the IRP’s basic findings, NIH-funded scientists reported that amphotericin B plus flucytosine, followed by the antifungal drug fluconazole, substantially decreases the risk of dying from cryptococcosis in patients with AIDS or other immunodeficiencies.

**Publications**


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**Food, Nutrition, and Metabolism**

**2016: Folic acid levels and the impact on the newborn epigenome and childhood asthma risk**

**Challenge**

Folic acid supplementation in pregnancy is recommended worldwide to prevent neural tube defects, despite the fact that the mechanism underlying this protection is largely unknown. Recently, concerns have been raised about the possible adverse effects of increasing folate levels across the population as whole, including impacts on the developing epigenome of newborns, and a possible increase in asthma risk.

**Advance**

IRP researchers led by Stephanie J. London, M.D., Dr.P.H., and collaborators in Norway, set out to validate their initial findings that showed that an increased risk of early childhood respiratory illness and asthma is associated with higher maternal folate levels during pregnancy. By conducting a study across a large prospective population-based cohort, the team found that pregnant women taking supplemental folic acid at or above the recommended dose, combined with a diet rich in folate, reached a total folate level associated with a slightly elevated risk of their children developing asthma. By examining possible epigenetic impacts, these researchers, along with colleagues in the Netherlands also found that maternal folate, measured in plasma, had widespread impacts on methylation across the genome of a fetus.

**Impact**

The discovery that maternal folate levels can impact the genome-wide methylation of a fetus, may shed light on the mechanisms by which this essential vitamin acts to prevent the development of neural tube defects. While the discovery that children of mothers with very high levels of folate intake have
a slightly higher risk of developing asthma is important, this association does not negate the public health recommendation for the use of folic acid supplementation for the prevention of neural tube defects. However, in the future this information may prove useful to countries looking to adjust the fortification of their food supply.

### Publications


### 2014: Identifying genetic risk for type 2 diabetes and obesity

**Challenge**

Type 2 diabetes and obesity disproportionally affect minority populations, in particular American Indians, who are more than twice as likely as white Americans to have diabetes [link](#). Identifying genetic variations that increase American Indians’ risk for type 2 diabetes and obesity could help researchers develop better prevention strategies for both this group and among the broader population.

**Advance**

IRP researchers led by Robert Hanson, M.D., M.P.H., and Leslie J. Baier, Ph.D., identified several genes that affect type 2 diabetes and obesity risk by studying Pima Indians, a group particularly prone to these issues. By applying molecular-genetic approaches to biological samples and examining family histories collected over decades of research with the Pima Indian population, the researchers found that one gene variant, if inherited from the mother, nearly doubles the risk for type 2 diabetes. Another gene variant discovered via this research causes children to become overweight and obese at very young ages.

**Impact**

Genetic testing for high-risk variants can help identify people who would benefit from early intervention, potentially reducing the prevalence of diabetes and obesity among the Pima Indian population. These studies could also help identify novel therapeutic targets that might lead to improved treatments.

### Publications


2014: Extreme obesity may shorten life expectancy by up to 14 years

**Challenge**
The prevalence of extreme obesity is on the rise, with six percent of U.S. adults now classified as extremely obese (class III obesity, with a body mass index (BMI) of 40 kg/m2 or above). Little information exists on the rates of total or cause-specific deaths associated with extreme obesity.

**Advance**
IRP researcher Cari Kitahara, Ph.D., and colleagues used data from 20 prospective cohort studies to show that risk of dying is substantially higher for individuals with class III obesity, and the risk continues increasing as BMI goes up. A person with BMI between 40 and 59 kg/m2 experienced an estimated 6.5 to 13.7 years of life loss, compared to a normal weight person with similar characteristics. The loss in life expectancy attributable to extreme obesity was similar to the difference in life expectancy between current and never cigarette smokers.

**Impact**
The team’s findings suggest that class III obesity is associated with a substantially increased rate of death and may soon emerge as a major cause of death in this and other countries worldwide.

**Publications**

2014: Identifying genetic risk for type 2 diabetes and obesity

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Impact
Genetic testing for high-risk variants can help identify people who would benefit from early intervention, potentially reducing the prevalence of diabetes and obesity among the Pima Indian population. These studies could also help identify novel therapeutic targets that might lead to improved treatments.

Publications


2013: The calculus of calories: mathematical models to quantify obesity and its treatment

Challenge
Obesity presents a major public health challenge. Many obesity interventions have been proposed to help both individuals and populations, but previous methods for predicting weight loss did not account for dynamic changes in metabolism and body composition as people gain and lose weight.

Advance
IRP researchers led by Kevin D. Hall, Ph.D., and Carson C. Chow, Ph.D., created and validated novel mathematical models of human metabolism and body weight dynamics to provide accurate
predictions about the development of obesity and its treatment in adults and children.

**Impact**
Award-winning Web and smartphone applications for predicting human weight dynamics based on the new algorithms have been used by more than one million people so far. The models quantify the calorie imbalance underlying the obesity epidemic and predict how interventions will impact body weight in individuals, as well as in entire populations.

**Publications**


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**2012: Peripheral CB1 cannabinoid receptors as therapeutic targets in obesity and diabetes**

**Challenge**
Endogenous cannabinoids are lipid messengers that activate CB1 receptors in the brain to stimulate food intake. They are known to play a role in pathogenesis, including dyslipidemia and insulin resistance, and increased activity of the endocannabinoid system is associated with obesity. Molecules that disrupt the CB1 receptor (CB1 antagonists) are effective not only in reducing body weight, but also in alleviating metabolic complications. However, therapeutic development of this class of compounds was halted due to unwanted neuropsychiatric side effects from CB1 blockade in the brain.

**Advance**
IRP researchers led by George Kunos, M.D., Ph.D., hypothesized that CB1 antagonists with limited brain penetrance may retain their metabolic efficacy without the unwanted neuropsychiatric effect. The team provided the first proof of this concept using a novel peripheral CB1 antagonist in an animal model of diet-induced obesity and type 2 diabetes.

**Impact**
The team’s research shows that peripheral CB1 antagonists have potential for treating metabolic syndrome and type 2 diabetes without causing unwanted neuropsychiatric side effects. Their prototype compound is currently undergoing toxicology screening in preparation for testing in clinical trials.
Substance Abuse

2017: Potential compounds for prevention and treatment of prescription opioid abuse

Challenge
The dramatic increase in use of prescription opioid analgesics, such as oxycodone, parallels escalated opioid dependence and drug-related deaths worldwide. Despite decades of research, a non-addictive opioid analgesic has yet to advance to the clinic. Compelling preclinical evidence suggests a crucial involvement of brain dopamine D3 receptors (D3R) in drug reward and addiction, providing a potential target for reducing opioid abuse liability without diminishing pain relief.

Advance
IRP researchers led by Amy Newman, Ph.D., used a structure-based approach to discover highly D3R-selective antagonist/partial agonist compounds that, in animal models, reduce oxycodone self-administration, naloxone precipitated withdrawal, and reinstatement of drug seeking behaviors, without affecting analgesia.

Impact
The team’s data suggest that selective D3R blockade may reduce the development of opioid dependence without diminishing the effectiveness of prescription pain killers. In addition, the lead molecules identified may offer a potential stand-alone or adjunctive treatment to existing medications for the treatment of opioid use disorders. Recent licensing of this NIH technology by pharmaceutical industry partners has initiated further development of these promising molecules to combat the opioid epidemic through prevention and treatment.

Publications
2016: High prevalence of electronic cigarette use among rural youth with asthma

Challenge
Mirroring the decline of cigarette smoking in recent years, electronic cigarettes have become the most commonly used tobacco product among U.S. youth link. Given the sensitive airways among young people with asthma, it is important to know if that group is disproportionately more likely than youth without asthma to use e-cigarettes.

Advance
IRP researchers led by Kelvin Choi, Ph.D., and collaborators examined data from the 2012 Florida Youth Tobacco Survey and found that youth with asthma are significantly more likely than youth without asthma to use e-cigarettes. The behavior is particularly common among asthmatic youth residing in non-metropolitan/rural areas. The study also showed that e-cigarette use is associated with past-year acute asthma exacerbation.

Impact
The team’s findings alerted the public health community to the prevalence of e-cigarette use among young people with asthma, a population that is already highly vulnerable to respiratory problems. Their research highlighted the need to further investigate the underlying reasons for e-cigarette use among asthmatic youth and develop interventions to prevent e-cigarette use in this population, and both efforts are currently underway.

Publications

2015: Exploring the role of dopamine in cocaine abuse

Challenge
It is almost impossible to determine which individuals have a higher biological risk for addiction to cocaine and other stimulants. But, in some individuals, cravings correlate with high levels of dopamine, and those levels can be increased even further simply by visualizing drug-associated cues. Similarly, low levels of available dopamine D2 receptors are often seen in cocaine-users, but whether low receptor levels are a cause or consequence of stimulant dependence was unclear.

Advance
IRP researchers led by Veronica A. Alvarez, Ph.D., addressed the challenge using a newly available transgenic mouse model with selective deletion of dopamine D2 receptors in the same neurons that release dopamine into the forebrain—autoreceptors that provide negative feedback regulation over dopamine release. They discovered that a reduction in D2 autoreceptors enhanced the likelihood that mice would engage in cocaine use, which also made them more vulnerable to cocaine in an animal model of relapse.

Impact
Identifying a low level of dopamine D2 receptors as a potential vulnerability factor in the development
of addictive behaviors is an important step towards the implementation of drug abuse prevention strategies. Additionally, this work contributes to a body of research that is demonstrating the value of animal models in behavioral science.

**Publications**

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**2015: Interleukin-22 therapy: Providing new hope for alcoholic hepatitis**

**Challenge**
Alcoholic hepatitis is a severe form of alcoholic liver disease, and how the condition progresses is largely unknown. No FDA-approved therapies exist at this time.

**Advance**
IRP researchers led by Bin Gao, M.D., Ph.D., established a new animal model (chronic-plus-binge ethanol feeding) that better mimics human patterns of alcohol abuse than previous models, reproducing some features of liver damage and inflammation in patients with alcoholic hepatitis. Dr. Gao’s group discovered that interleukin-22 is a protein with the ability to protect the liver from damage and promote liver regeneration.

**Impact**
Interleukin-22 is currently the subject of clinical trials for the treatment of alcoholic hepatitis. The chronic-plus-binge model is now widely used for studying the development and progression of early alcoholic hepatitis.

**Publications**


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**2014: Approaching a treatment for marijuana addiction**

**Challenge**
The number of past-month marijuana users in the U.S. in 2012 was approximately 18 million, compared to 1.6 million cocaine and 0.3 million heroin users. Although estimates from research show that dependence rates for marijuana are lower than for cocaine or heroin (9 percent versus 17 and 23 percent, respectively), higher marijuana usage means that marijuana dependence is more prevalent.
than dependence on cocaine or heroin\textsuperscript{10}. Despite a clear need, there are currently no FDA-approved medications to treat marijuana addiction.

**Advance**

IRP researchers led by Zuzana Justinova, M.D., Ph.D., and Steven R. Goldberg, Ph.D., discovered that enhancing levels of kynurenic acid in two reward-related brain areas, the nucleus accumbens (NAc) and the ventral tegmental area (VTA), of an animal model significantly reduced the neurochemical and behavioral effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis.

**Impact**
The team’s finding suggests that modulation of kynurenic acid levels could be a pharmacological strategy for achieving abstinence from cannabis and preventing relapse.

**Publications**

**2014: Discovering how amphetamine works in the brain**

**Challenge**
Amphetamines have long been known to increase dopamine levels and regulate the activity of glutamate—two important neurotransmitters. However, doctors still did not understand exactly what happens in the brain to cause amphetamines’ stimulating effects.

**Advance**
Working with cultured mouse neurons, a team led by Susan Amara, Ph.D., identified a series of chemical events that underlie amphetamines’ stimulating effects. They showed that amphetamine enters dopamine neurons through specific entry proteins on the cell surface. Once inside the cells, the drug triggers the internalization of a glutamate transporter from the cell surface, which enhances the excitatory actions of amphetamine.

**Impact**
With knowledge of the specific chain of events amphetamines set in motion in the brain, it is now possible to target the cascade of molecules—from outside the cell, to cell membrane, to inside the cell—in the development of better drug therapies in, for example, ADHD.

**Publications**

2014: Treating cocaine addiction with transcranial magnetic stimulation

Challenge
There are very few successful strategies for treating cocaine addiction. Patients urgently need ways to relieve symptoms of cocaine craving to overcome the disease.

Advance
IRP researchers led by Antonello Bonci, M.D., took a novel approach to the problem of cocaine addiction and discovered that, while chronic cocaine exposure significantly reduces brain activity in regions of the prefrontal cortex, optogenetic stimulation of those same brain areas in rodents reduced their cocaine consumption. In clinical studies, repeated transcranial magnetic stimulation (rTMS) was administered to treatment-seeking patients diagnosed with cocaine addiction. The majority of patients in those trials stopped cocaine consumption after 4 weeks of rTMS treatments.

Impact
The team’s very preliminary findings demonstrated that rTMS holds very strong promise as a therapy for cocaine craving in treatment-seeking patients.

Publications


2013: Linking a genetic variant to alcoholism

Challenge
Alcoholism has a moderate to high heritability, but genetic variations that contribute to alcoholism have been difficult to identify, partly because many are uncommon.

Advance
IRP researchers led by David Goldman, M.D., and Markus Heilig, M.D., Ph.D., found that a specific glutamate receptor plays a role in alcohol-seeking in rats. They showed that animals with a naturally occurring truncated version of that receptor gene preferred alcohol more than wild-type, outbred animals. Experiments to pharmacologically block the receptor in wild-type animals led to an increase in alcohol consumption, as did experiments to completely knock out the gene, suggesting that this receptor plays a pivotal role in alcohol preference.

Impact
The discovery of this genetic variant within an alcohol-preferring rat strain—the standard animal model of alcoholism—clearly illuminates one mechanism involved in alcohol abuse and provides an important step in the scientific path to understanding causation of alcoholism.
2013: Stimulating brain cells prevents compulsive cocaine seeking

**Challenge**
Loss of control is one of the most intractable aspects of addiction, as substance abusers continue to pursue drugs despite incurring significant negative consequences. Human studies have suggested that deficient brain function in the prefrontal cortex leading to loss of inhibition could be promoting compulsive drug use. However, it remained unknown whether chronic drug use compromises cortical activity and if such a deficit leads to compulsive cocaine seeking.

**Advance**
IRP researchers led by Antonello Bonci, M.D., explored the relationship between drug use and cortical activity with a rat model of compulsive drug seeking, in which cocaine seeking persists despite the delivery of foot shocks. They showed that prolonged self-administration of cocaine decreases the excitability of neurons deep within the prelimbic cortex, an effect even more pronounced in compulsive drug-seeking animals. When the researchers stimulated those neurons with optogenetics, they observed a decrease in compulsive cocaine seeking, whereas inhibition of the neurons significantly increased compulsive cocaine seeking.

**Impact**
The team’s results provide a basis for transcranial magnetic stimulation (TMS) clinical studies in humans, which would aim to stimulate the prelimbic cortex as a potential novel therapy for treating compulsive drug use.

**Publications**

2012: A non-addictive form of cocaine? A potential therapy awaits

**Challenge**
Cocaine addiction is a chronic and relapsing disorder that affects millions worldwide, exerting a toll in lives lost, families torn, and communities destroyed. No medications are currently available to treat cocaine addiction.

**Advance**
IRP and international researchers led by Amy Hauck Newman, Ph.D., discovered that R-modafinil, like cocaine, inhibits dopamine uptake, but binds to the dopamine transporter in a unique fashion that may not result in the same addictive response as cocaine.

**Impact**
Molecular and preclinical pharmacological findings support translation of R-modafinil studies to clinical trials in the cocaine-abusing population as a potential treatment.

**Publications**

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**2012: Chronic drinking may alter the brain and increase PTSD risk**

**Challenge**
While alcoholism and anxiety disorders like post-traumatic stress disorder (PTSD) are often seen together, few studies have explored how chronic alcohol exposure can affect recovery from a traumatic experience.

**Advance**
IRP researcher Andrew Holmes, Ph.D., and colleagues used an animal model to determine that chronic alcohol exposure remolds the brain’s neuronal wiring, impairing the ability to suppress fear and recover normally from a traumatic experience.

**Impact**
The results show that chronic drinking rewrites brain circuitry, which may increase susceptibility for anxiety disorders like PTSD. These findings provide a basis for the development of neurochemical therapies that target these specific areas of the brain with an aim to restoring normal functions.

**Publications**

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**Wellness and Lifestyle**

**2016: Increased physical activity is associated with lower risk of 13 types of cancer**

**Challenge**
Previous studies that had examined associations between physical activity and cancer risk showed that people who engage in more physical activity have reduced risks of developing colon, breast, and endometrial cancers. However, research results were inconclusive for other cancer types due to small numbers of participants in the studies.
Advance
IRP researchers led by Steven Moore, Ph.D., M.P.H., pooled data on 144 million people from 12 prospective U.S. and European cohorts and found that increased leisure-time physical activity is associated with lower risks for 13 cancer types (esophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, head and neck, rectal, bladder, and breast). Most of the associations were evident regardless of body mass index or smoking history.

Impact
The team’s findings confirm and provide specific evidence that physical activity has significant positive effects on cancer risk and should play a key role in population-wide cancer prevention and control efforts.

Publications

2016: Low-intensity smokers are at increased risk of earlier death

Challenge
Cigarette smoking causes more than 20 types of cancer, as well as other diseases, but the effects of low-intensity smoking (10 or fewer cigarettes per day) have not been well studied. If doctors and patients knew the effects of low-intensity smoking on human health, they could make more informed lifestyle decisions.

Advance
IRP researchers led by Maki Inoue-Choi, Ph.D., M.S., R.D., and Neal Freedman, Ph.D., M.P.H., found that among 290,215 adults in the NIH-AARP Diet and Health Study, current smokers who had smoked less than 1 cigarette per day over their lifetimes had a 64% higher all-cause mortality risk, and smokers who had smoked 1 to 10 cigarettes per day had a 87% times higher risk than people who never smoked. Former smokers has a lower mortality risk compared to those who continued to smoke, and risks fell with earlier ages at quitting.

Impact
The team’s results provide further evidence to demonstrate that there is no safe level of exposure to tobacco smoke, and even low-intensity smokers do benefit from quitting.

Publications
Cancers

**2017: Fostering the first FDA-approved drug for Merkel cell carcinoma**

**Challenge**
Merkel cell carcinoma is a very rare disease in which cancer cells form in the skin. Merkel cell carcinoma tends to grow quickly and metastasize at an early stage. Prior to 2017, no FDA-approved treatment existed for this disease.

**Advance**
IRP investigators, in collaboration with EMD Serono, Inc., developed and tested avelumab, an immunotherapy drug that targets the protein programmed death-ligand 1 (PD-L1), as a treatment for Merkel cell carcinoma. The team’s preclinical research demonstrated that avelumab allows T cells to efficiently kill a variety of tumor cells. Based on these findings, the team launched the first-in-human trials of avelumab that established safety and pharmacokinetic data on the drug. Based on these results, a multicenter clinical trial was initiated, which included the IRP, and successfully demonstrated the use of avelumab in metastatic Merkel cell carcinoma patients.

**Impact**
In 2017, the U.S. Food and Drug Administration approved avelumab for adults and patients 12 years of age and older with metastatic Merkel cell carcinoma.

**Publications**


2016: Stimulating interferon genes to interfere with cancer

Challenge
There are currently very few treatment options for patients with recurrent or metastatic head and neck cancer. Only 20% of patients with head and neck squamous cell carcinoma respond to immunotherapy, despite many displaying a T cell-inflamed phenotype, which highlights the serious need to develop new therapies for this disease.

Advance
IRP researchers led by Clint Allen, M.D., discovered that the stimulation of interferon genes induces a robust anti-tumor immune response in a mouse model of T cell-inflamed head and neck cancer, controlling the growth of primary tumors and rejecting those tumors that were already established.

Impact
The team’s research indicates that it may be possible to control the growth of head and neck cancer through the activation of interferon genes. As a result of the initial animal studies, a Phase I clinical trial is now underway, and, if shown to be clinically safe and effective, this therapeutic approach has the potential to transform treatment options for patients with head and neck cancer.

Publications

2016: Engineering immunity to tumor elements

Challenge
The immune system effectively recognizes tumors as foreign elements and fights them. Cancer cells, however, find ways to avoid being attacked by the immune system. To enable the body to effectively remove cancerous cells, the immune system must get past cancer cells’ defense mechanisms.

Advance
IRP researchers led by Nicholas Restifo, M.D., have demonstrated how two elements that are common in the body, oxygen and potassium, suppress immune activity and create opportunities for tumors to grow. In animal studies, Restifo and his colleagues have shown that it is possible to engineer antitumor immune cells to be less sensitive to the effects of potassium or oxygen, which makes them more effective in places where cancer cells might otherwise grow unopposed.
Impact
These findings hold promise for designing more effective cancer immunotherapies. It may be possible to empower patients’ immune cells using drugs or genetic manipulation targeting these elemental processes.

Publications


2016: Enhanced risk-based lung cancer screening may prevent more deaths

Challenge
The U.S. Preventive Services Task Force (USPSTF) recommends annual computed tomography (CT) screening for individuals between 55 and 80 years old with a history of heavy smoking (at least one pack of cigarettes per day for 30 years or more) and who currently smoke or have quit within the past 15 years. However, selecting ever-smokers for screening using individualized lung cancer risk calculations may be more effective and efficient at preventing deaths than current USPSTF recommendations.

Advance
IRP researchers led by Hormuzd Katki, Ph.D., Anil Chaturvedi, Ph.D., and colleagues used data from two lung cancer screening studies and a U.S. health survey to develop and validate risk models for selecting smokers and former smokers who may be candidates for lung cancer screening with low-dose CT, and estimated the performance of risk-based selection into lung screening programs.

Impact
Because the researchers estimated that risk-based selection for screening might prevent more lung-cancer deaths, with greater effectiveness and efficiency, than would current screening recommendations, they have created an online lung-cancer screening risk-tool to provide individualized risk information for patients considering entering lung screening.

Publications

Online lung cancer screening risk tool: https://analysistools.nci.nih.gov/lungCancerScreening/
**2015: Harnessing the immune system to fight epithelial cancers**

**Challenge**
Immunotherapy harnesses a person’s own immune system to fight cancer and has been heralded as the most promising cancer treatment strategy of the modern day. However, while immunotherapy has been incredibly successful for some cancer types, such as lung cancer, melanoma, and head and neck cancers, its usefulness in battling common epithelial cancers, including gastrointestinal cancers, had not been established.

**Advance**
IRP researchers led by Steven Rosenberg, M.D., Ph.D., used next-generation sequencing to demonstrate that most patients with metastatic gastrointestinal cancers have tumor-specific mutations in genes such as KRAS, which can be identified by T lymphocytes (cell-killing white blood cells). They then showed that when a patient with metastatic bile duct cancer was treated with a population of T cells that had reacted to tumor-specific antigens, the patient experienced tumor regression.

**Impact**
The team’s findings are important because the most common form of immunotherapy—checkpoint inhibition—has not shown efficacy against most gastrointestinal cancers to date. Their study identified a new strategy for developing highly personalized immunotherapies that have the potential to be very effective at treating metastatic epithelial cancers, and possibly many other cancers.

**Publications**


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**2014: HPV test better predicts cervical cancer risk than Pap test**

**Challenge**
Human papillomavirus (HPV) is the cause of nearly all cervical cancers. Newer approaches to cervical cancer screening test for HPV DNA (or RNA) at the cervix, whereas traditional Pap tests detect abnormal cell changes associated with the development of cancer. Co-testing is now recommended for most women, but clinicians remained unsure of the value of concurrent HPV testing.

**Advance**
Based on a study that included more than one million women, IRP researcher Julia C. Gage, Ph.D., M.P.H., and colleagues determined that a negative test for HPV infection provides greater safety, or assurance, against future risk of cervical cancer, compared to a negative result from a Pap test.
Impact
The team’s findings provide evidence to support the currently recommended co-testing strategy with HPV and Pap, as well as the possibility of primary HPV testing as another alternative for cervical screening.

Publications

2014: Time between morning wake-up and smoking a cigarette associated with rate of lung cancer risk

Challenge
Lung cancer is the second most common cancer in humans and the primary cause of cancer-related death in both men and women in the U.S. link. Public health experts continue seeking efficient ways to identify smokers at highest risk for lung cancer.

Advance
IRP researchers led by Fangyi Gu, M.Med., Sc.D., and Neil Caporaso, M.D., found that people who smoke their first cigarette within five minutes of waking up have more than three times the risk of lung cancer compared with those who wait longer than an hour before their first cigarette of the day. The increased risks were observed for both heavy and light smokers, and the lung cancer rate per “pack-years” of smoking increased faster among smokers who had a shorter time to first cigarette.

Impact
Assessing time to a first cigarette may help clinicians quickly assess lung cancer risk. The findings suggest the need for even light smokers to quit, because even light smokers who take their first morning cigarette within 5 minutes can be at substantial risk for developing lung cancer.

Publications

2010: Deciphering how chromosomal mix-ups lead to tumors

Challenge
Scientists do not fully understand the underlying genetic causes of lymphoma and leukemia. If they can identify the location and cause of errors in the genome, that knowledge could provide new therapeutic targets for treatment of disease.
**Advance**
IRP scientists led by Rafael Casellas, Ph.D., discovered that recurrent chromosomal rearrangements, or translocations, occur when broken strands of DNA from one chromosome are mistakenly joined with those of another, which can lead to uncontrolled cell growth or cancer. The researchers found that an enzyme called Activation Induced Deaminase (AID) plays a key role in promoting translocations.

**Impact**
The new findings helped clarify the origin of cancer-inducing translocations and identified AID as a potential therapeutic target to prevent the development of many human cancers.

**Publications**

**2001: The HPV vaccine: Two decades of research pays off**

**Challenge**
Human papillomavirus (HPV) is the most common sexually-transmitted infection around the world. With more than 40 variations and clear linkages to cervical cancer and a range of genital cancers, the challenge to develop a broadly protective vaccine was unparalleled.

**Advance**
Douglas R. Lowy, M.D., and John T. Schiller, Ph.D., spent more than two decades investigating how to prevent HPV infection, culminating in the discovery and production of virus-like particles (VLPs), which block certain mechanisms essential to HPV infection. Their work led to the production of the first commercially available vaccine against the two deadliest forms of the virus, HPV16 and HPV18, in 2006.

**Impact**
The HPV vaccine has been shown to be 100 percent effective, and governments across the globe now recommend routine vaccination of all girls (and in some countries, boys) aged 11 or 12 years. The hope is that widespread vaccination could reduce HPV-associated cancer deaths by up to two-thirds.

**Publications**

FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus – Rapid Approval Marks Major Advancement in Public Health.

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2001: There’s no “magic bullet” for cancer. Or is there?

Challenge
In the U.S., it is expected that approximately 1.5 million people will be diagnosed with cancer each year, and one third of those will die of the disease. To combat such a complex and multifactorial disease\(^\text{15}\), doctors need more efficient and targeted treatments to destroy cancers cells without harming healthy tissues.

Advance
IRP researcher Ira Pastan, M.D., and colleagues created recombinant immunotoxins that specifically target cancer cells. The “magic bullets” are made by genetically engineering a potent bacterial toxin, *Pseudomonas* exotoxin A, with an antibody fragment that selectively binds to receptors on the cancer cell surface.

Impact
Delivering a toxic payload to the inside of a cancer cell while leaving healthy tissue unscathed is a major step forward in the battle against cancer. Research continues to determine which tumors might respond best to this type of targeted approach, but clinical trials are already underway, with some immunotoxins producing partial or complete remissions.

Publications


2000: Finding one disease is actually many: Diffuse large B-cell lymphomas

Challenge
Some patients with diffuse large B-cell lymphomas (DLBCL) live longer and respond better to therapy than others, highlighting an urgent need to better understand the disease’s underlying biology and inform more effective treatment approaches.

Advance
IRP researchers led by Louis Staudt, M.D., Ph.D., profiled the genes expressed in patients with DLBCL and found important differences, leading to the identification of three new molecularly and clinically distinct subclasses of the disease: germinal center B-cell-like, activated B-cell-like (ABC), and primary mediastinal B-cell lymphoma (PMBL).

Impact
These discoveries revealed new molecular targets based on each subclass and informed the development of new therapies. For example, the discovery that one subgroup of DLBCL relies on the NF-κB signaling pathway allowed physicians to target that pathway directly, leading to complete remission in a number of cases.

**Publications**


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**1995: Lifting the lid on kidney cancer: Exposing the underlying genetics**

**Challenge**

In the early 1980s, little was known about the genetic basis of kidney cancer, and patients continued to succumb to the disease despite chemotherapy treatment. Today, more than 13,000 renal carcinoma patients in the U.S. still die every year\(^6\), demonstrating a continuing need for better approaches to battling this disease.

**Advance**

During the past two decades, IRP researcher **W. Marston Linehan, M.D.**, and colleagues made seminal discoveries about the genetic basis of kidney cancer, including identification of the von Hippel-Lindau (*VHL*) gene (the 6th human cancer gene identified) and the hereditary papillary renal cell carcinoma (*HPRC*), hereditary leiomyomatosis, and renal cell cancer (*HLRCC*) genes: *c-Met*, *BHD*, and fumarate hydratase.

**Impact**

These discoveries have led to new approaches for molecular-based therapies against renal carcinoma, and clinical trials are now ongoing with a number of promising treatments.

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**Publications**


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1989: Discovering a growth factor and its incredible healing powers

Challenge
For decades, nothing was available to prevent or reduce the severity of oral mucositis (ulcerative lesions of the mouth), a common side effect of high doses of chemotherapy and radiation, which increases the risk of infection in cancer patients. A therapy was needed to reduce the incidence of this painful and life-threatening side-effect of many cancer therapies.

Advance
In the late 1980s, IRP scientists Jeffrey Rubin, M.D., Ph.D., Paul Finch, Ph.D., and Stuart A. Aaronson, M.D., discovered and purified keratinocyte growth factor (KGF). Several studies later demonstrated that KGF occurs naturally and stimulates the growth of surface layer cells in the mouth, which speeds healing of ulcers, reducing infection risks. The NIH partnered with Amgen in 1992 to develop Kepivance, a therapeutic treatment based on KGF.

Impact
Clinical trial results showed that Kepivance decreased the incidence and duration of severe oral mucositis in cancer patients who were given intensive chemotherapy and radiation prior to bone marrow/blood cell transplants. FDA approved in 2004, Kepivance now benefits about 11,000 American adults who undergo bone marrow transplants each year.

Publications


Genetics and Birth Defects

2016: Gene therapy to restore the architecture of the inner ear

Challenge
Deafness is the most common inherited sensory impairment, with the majority of cases associated with no other signs or symptoms. For many people, deafness is caused by defects in the actin-rich stereocilia bundles on the surfaces of sensory hair cells—defects which could not be corrected. While hearing aids and cochlear implants are possible treatment options, they do not work for all patients and do not offer a biological cure.
Advance

IRP researchers led by Lisa Cunningham, Ph.D., and Wade Chien, M.D., investigated the potential for gene therapy to restore the morphology of defective stereocilia bundles. They discovered that when sensory hair cells received gene therapy delivered through a virus injected into the inner ears of mice, defective bundles were restored to normal length and morphology.

Impact

In finding a viable option for reviving normal stereocilia architecture, the team’s research has demonstrated the feasibility of gene therapy for restoring structural defects in the inner ear. It also suggests that gene therapy holds promise for correcting hereditary deafness caused by structural flaws, should it be shown to be safe and effective in human patients.

Publications


2014: Linking genetics to recurrent strokes in children with DADA2

Challenge

Sometimes, the clinical presentation of a disease and its underlying genetics are difficult to link, which can make successful treatment extremely challenging. Such was the case with Deficiency of ADA2 (DADA2), where the connection between its genetic variant and childhood symptoms of recurrent strokes remained a mystery.

Advance

IRP teams led by Manfred Boehm, M.D., and Daniel Kastner, M.D., Ph.D., developed in vitro disease modeling studies that identified the ADA2 gene as a key regulator in monocyte/macrophage differentiation, which leads to endothelial cell activation and damage that is a likely disease mechanism for the recurrent strokes in children with DADA2.

Impact

The finding provides new insights into the causes of strokes in children and the role of ADA2 in inflammatory vasculopathies. As a result, children with DADA2 were not treated with standard blood thinners, but were treated with TNF inhibition, which greatly improved the lives of both the affected children and their families.

Publications

2014: Studying childhood stroke to better understand inflammatory diseases

**Challenge**
The immune system plays a very important function, protecting us against viruses, bacteria, and other disease-causing pathogens. Autoinflammatory diseases cause the immune system to malfunction, resulting in unprovoked inflammation that can lead to fevers and other dangerous symptoms. Researchers do not yet have a full understanding of these diseases’ underlying genetic mechanisms.

**Advance**
IRP scientists led by Massimo Gadina, Ph.D., Qing Zhou, Ph.D., Dan Yang, M.D., Manfred Boehm, M.D., Daniel L. Kastner, M.D., Ph.D., and Ivona Aksentijevich, M.D., studied the occurrence of stroke in young children and showed that a genetic mutation leading to the absence of a white blood cell protein, ADA2, in blood plasma results in inflammation and vascular anomalies.

**Impact**
The team’s finding advances understanding of how white blood cells regulate immune response to pathogens and keep inflammation under control. Their results also help scientists understand the genetic basis of inflammatory and vascular diseases, aiding in the development of targeted treatment strategies.

**Publications**

2014: They might be giants: Understanding a childhood genetic defect

**Challenge**
A small number of genes have been identified as being involved in early childhood overgrowth, also known as gigantism, but the molecular explanation for the genetic condition remained unclear, and treatments aimed at alleviating the disorder were often ineffective.

**Advance**
IRP researchers led by Constantine A. Stratakis, M.D., D.(med)Sci., took a new approach to the problem and looked at copy-number variants in the genome of patients with gigantism, rather than sequencing individual genes. The group discovered that a single defect on the X-chromosome was responsible for most cases of gigantism in early childhood, through the subsequent over-expression of growth hormone.

**Impact**
Having demonstrated that an identifiable genetic defect on the X-chromosome is responsible for the majority of cases of early-onset gigantism, clinicians can now use the test for more accurate
identification and treatment. One of the genes responsible for overgrowth, GPR101, is a new target for understanding growth hormone secretion and its effects on growth. Its discovery may lead to new treatments for gigantism and new research on the regulation of growth in young children.

**Publications**


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**2013: Power in numbers: identifying new genes associated with ankylosing spondylitis**

**Challenge**

Ankylosing spondylitis is an incurable inflammatory arthritis of the spine that most often begins in young adulthood and can lead to life-long inflexibility, posture changes, and pain. Researchers have explored the disease’s genetic risk factors for decades, but further knowledge is necessary to understand what causes the inflammation and how to treat it.

**Advance**

IRP researchers led by Michael M. Ward, M.D., partnered with the International Genetics of Ankylosing Spondylitis Consortium to compare genes from thousands of people with ankylosing spondylitis to those from people without the disease. The team discovered 13 new genetic markers associated with ankylosing spondylitis and confirmed the importance of 12 previously identified biomarkers.

**Impact**

Results from this study help researchers pinpoint therapeutic targets—such as the interleukin-23 inflammation pathway and the immune system protein HLA-B27—that may lead to effective treatments for controlling ankylosing spondylitis.

**Publications**

**2013:** Tackling the mysteries of osteosarcoma in children by uncovering gene variants associated with risk

**Challenge**
Osteosarcoma is the most common malignant bone tumor in children and adolescents. However, researchers know very little about its common genetic risk factors, partly due to the tumor’s rarity in the general population: there are approximately 800 new cases in the United States each year.

**Advance**
IRP investigators lead by Sharon Savage, M.D., completed the first genome-wide association study of genetic risk variants for osteosarcoma. The researchers discovered that osteosarcoma patients with specific variants in different genetic loci—within the glutamate receptor metabotropic 4 (GRM4) gene and on chromosome 2p25.2—were at significantly increased risk of osteosarcoma.

**Impact**
If validated in other populations, the identified genetic markers could serve as a tool that helps researchers find new mechanisms of osteosarcoma development and possibly help clinicians diagnose individuals at risk of osteosarcoma. In addition, IRP researchers are leading analyses to uncover genetic factors associated with osteosarcoma clinical outcomes, such as metastasis or response to therapy.

**Publications**

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**2012:** A new approach to treating organ damage in inflammatory diseases

**Challenge**
The rare and debilitating genetic disorder known as neonatal-onset multisystem inflammatory disease (NOMID) causes persistent inflammation and ongoing tissue damage, often beginning within the first weeks of life. Because NOMID affects numerous organs and body systems, early diagnosis and treatment are important for preventing long-term organ damage.

**Advance**
IRP researchers led by Raphaela Goldbach-Mansky, M.D., M.H.S., discovered that blocking interleukin-1 (IL-1)—an inflammatory protein made by immune system cells—with increasing doses of the FDA-approved rheumatoid arthritis treatment, anakinra, could preserve organ function in most patients.
Impact
Although overproduction of IL-1 can lead to damaging inflammation, the immune system still requires certain levels of IL-1 to help fight infections. The results alleviate concern that treating NOMID by blocking IL-1 may leave the body vulnerable to infection by showing that anakinra is effective and well-tolerated in the treatment of NOMID.

Publications

2012: DNA and damage control: A complex web of players

Challenge
Fanconi anemia (FA) is a genetic disease characterized by congenital defects, bone marrow failure, and cancer susceptibility. At least 15 genes are known to be involved in the disease, whose gene products normally constitute a DNA damage response network that is essential for repair of DNA strand damage. Understanding how FA proteins are recruited to the DNA damage sites could uncover new drug targets.

Advance
IRP investigators led by Zhijiang Yan, Ph.D., showed for the first time that the FA network is controlled by a novel ubiquitin signaling cascade initiated by the RNF8 ubiquitin ligase and its partner, UBC13, and mediated by FAAP20, a newly described component of the FA core complex.

Impact
Transmission of DNA damage signals is vital in setting the rate and extent of DNA repair during aging and the development of cancer. The newly discovered cascade is now a potential target for drug intervention: agonists that promote repair could aid in the function of aging cells, whereas antagonists that inhibit the cascade could disrupt DNA repair in cancer cells to make them more susceptible to chemotherapy.

Publications
**2012: Using genetics to understand stuttering**

**Challenge**
Stuttering is a common but poorly understood speech disorder. Current therapy options show only limited long-term success for individuals who stutter beyond childhood.

**Advance**
Recognizing that stuttering often runs in families, IRP researchers led by Dennis Drayna, Ph.D., sought to understand the disorder’s hereditary basis. The team identified a number of mutations in three genes that control the production of enzymes involved in cellular waste disposal via the lysosome. When these enzymes are disrupted, bone, connective tissue, and neurologic symptoms typically follow.

**Impact**
The discovery that stuttering may have a genetic component related to the lysosome has spurred further research towards understanding how dysregulation of this biochemical pathway could give rise to stuttering and what pharmacotherapeutic options may be effective in treatment.

**Publications**


**2011: Team science unravels the link between ALS and FTD**

**Challenge**
Amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease) is a fatal neurodegenerative disorder that leads to progressive paralysis and respiratory failure.19 Frontotemporal dementia (FTD) is the most common form of dementia in the under-65 population.20 Researchers have long suspected an overlap between the two diseases, but the molecular and genetic basis of this intersection was unknown.

**Advance**
IRP researcher Bryan J. Traynor, M.D., Ph.D., brought historically competitive research groups together to focus their efforts on identifying the underlying genetic cause of ALS and FTD. The new international consortium discovered that an insertion mutation disrupting the C9ORF72 gene is the most common genetic cause of both ALS and FTD identified to date, accounting for 40 percent of all familial cases of ALS and FTD in European and North American populations.

Impact

Discovery of this mutation changed scientific understanding of neurodegenerative diseases, influencing the diagnosis and investigation of ALS and FTD and, for the first time, mechanistically linking the two disorders. It also suggested a therapeutic target for gene therapy, with further research ongoing.

Publications

1997: Breaking down complex autoinflammatory diseases, and building up new hope

Challenge

In some individuals, the immune system attacks the body’s own tissues, causing inflammation. The recent discovery that a subset of autoinflammatory diseases has genetic components complicates diagnosis, making development of therapeutics a challenge.

Advance

IRP researcher Daniel L. Kastner, M.D., Ph.D., and colleagues identified, classified, and characterized more than 10 new hereditary autoinflammatory disease pathways, including FMF, TRAPS, NOMID, and DIRA. IRP scientists develop and test new therapies aimed at reducing inflammation in these diseases, in some cases completely reversing them.

Impact

Patients with complex genetic autoinflammatory disorders may soon no longer need to experience trial and error prescribing in an effort to control their debilitating symptoms. For some diseases, genetic analyses combined with molecular studies of the affected pathways can inform the selection of targeted therapeutics and provide immediate and sustained relief.

Publications


**1991: Therapy for inherited enzyme deficiencies**

**Challenge**
Gaucher disease stems from deficiency of the enzyme glucocerebrosidase, leading to accumulated lipids that cause symptoms ranging from mild pigmentation to life-threatening seizures and brain damage. Although the concept of enzyme replacement had been proposed many years ago, a targeted approach is needed to ensure delivery of the enzyme to the correct cell type.

**Advance**
IRP researchers led by Roscoe Brady, M.D., developed a macrophage-targeted glucocerebrosidase, designed to deliver the missing enzyme directly into the macrophages of patients with Gaucher disease. The team conducted the first clinical trial with the new therapy and observed a reversal of all symptoms in all patients.

**Impact**
Doctors have now established intravenous administration of macrophage-targeted glucocerebrosidase as an effective treatment for the symptoms of Type 1 and Type 3 Gaucher disease. For his research, Dr. Brady was awarded the National Medal of Technology and Innovation in 2008, the highest honor for achievement in science and technology bestowed by the U.S. President.

**Publications**

**2015: Repurposing existing drugs and discovering new antivirals for hepatitis C**

**Challenge**
Current therapies for the treatment of hepatitis C have improved substantially, but there are still serious limitations and unmet needs for patients, with cost being the most important barrier to effective clinical care.
Advance
IRP researchers, led by T. Jake Liang, M.D., developed a novel cell-based high-throughput assay to screen several small-molecule libraries. Through these efforts they identified a class of antihistamines and several novel compounds with the potential to act as potent hepatitis C virus (HCV) inhibitors in vitro and in vivo. These compounds have since been optimized by medicinal chemistry for preclinical development.

Impact
The discovery of approved antihistamine drugs with anti-HCV properties could facilitate the repurposing of these drugs for the treatment of hepatitis C. In the future it may also be possible to take novel compounds with higher potencies and better pharmacological properties and develop them into clinically-viable HCV drugs.

Publications


2014: Repurposed drugs to the rescue: Treating Zika

Challenge
In response to the health threat posed by the recent outbreak of Zika virus in Latin America and its recent spread to Puerto Rico and Florida, researchers have been working at a furious pace to learn more about the mosquito-borne virus. Considerable progress has been made in understanding how Zika might cause babies to be born with unusually small heads and other abnormalities, and in developing vaccines that may guard against Zika infection. Still, there remains an urgent need to find drugs that can be used to treat people already infected with the Zika virus.

Advance
IRP researchers led by Wei Zheng, Ph.D., and colleagues efficiently tested the effects of thousands of potential drug candidates on Zika-infected human cells in a matter of weeks by utilizing the high-tech, drug-screening robots and vast libraries of drug compounds available at the IRP. The initial screen generated a list of more than 100 compounds with potential promise for treating Zika infection and the team was able to narrow the list down to three lead candidates. Further investigation revealed that combination treatments also can offer protection against Zika virus.
**Impact**
The research team was able to identify lead compounds and combination treatments for continued drug development against Zika virus, which could aid in efforts to reduce the risks associated with Zika infection. The new work also demonstrates the promise of large-scale screens of existing drug compounds as a means to speed the discovery of new treatments to address many emerging infectious disease threats. To encourage other researchers around the world to pursue additional treatment strategies for Zika, the team made all of their data freely available to the scientific community.

**Publications**

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**2014: Revealing drug-resistant malaria’s genetic and molecular fingerprint**

**Challenge**
Resistance to artemisinin-based antimalarial drugs, the frontline treatment for malaria worldwide, has emerged in Cambodia and other countries of Southeast Asia. To monitor and prevent the spread of artemisinin-resistant parasites, researchers must be able to identify them accurately and quickly.

**Advance**
IRP researcher **Rick Fairhurst, M.D., Ph.D.**, was part of an international team that identified the first known genetic marker of artemisinin resistance in malaria parasites and subsequently characterized the molecular mechanism behind the resistance.

**Impact**
The ability to easily identify artemisinin-resistant parasites is a key step in preventing their spread to other malaria-endemic regions such as Africa. Further, understanding the resistance mechanisms will yield important clues for developing new malaria treatments.

**Publications**

2014: Simple new tool makes treatment for neglected tropical diseases safer

Challenge
Mass drug administration of ivermectin is a successful strategy to control the spread of debilitating parasitic diseases such as onchocerciasis, or river blindness, and lymphatic filariasis, also known as elephantiasis. Unfortunately, in areas where a particular parasitic worm called Loa loa is also prevalent, people carrying high levels of Loa loa larvae are at high risk of experiencing severe neurological side effects after ivermectin treatment.

Advance
By repurposing a hand-held automated cell counter, a team led by IRP researcher Thomas Nutman, M.D., worked with Central African and French colleagues to develop a portable, sensitive, and rapid tool to detect high blood levels of Loa loa larvae.

Impact
The cost-effective and highly mobile device enables health workers to identify Loa loa-infected people and potentially give them alternative therapies with less risk of neurological damage, while continuing mass ivermectin treatment campaigns to eliminate onchocerciasis and lymphatic filariasis in West and Central Africa.

Publications

2014: Testing a potential vaccine for the Chikungunya virus

Challenge
Chikungunya virus is transmitted by mosquitos, is endemic in Africa and South and Southeast Asia, and has recently emerged in the Caribbean, Central and South America. The virus causes joint pain and fever and sufferers have reported rash, muscle pain and joint swelling. No drugs or vaccines are currently available for treatment or prevention. However, a vaccine candidate was shown to provide non-human primates with protective immunity from infection and illness.

Advance
IRP researchers led by Julie Ledgerwood, D.O., tested the safety, tolerability, and immunogenicity of a virus-like particle (VLP) chikungunya virus vaccine in a phase 1 clinical trial in healthy adults.

Impact
The chikungunya VLP vaccine was immunogenic, safe, and well tolerated in the subjects tested—an essential initial step towards vaccine development to combat this rapidly emerging pathogen.
2013: Can fewer doses of HPV vaccine provide immunity?

Challenge
The human papillomavirus (HPV) vaccine is safe and effective, but completion rates of the recommended three-dose schedule are lower in low-income or difficult-to-treat populations. In 2011, IRP researchers reported that receiving two doses and even one dose of the vaccine did not alter the incidence of HPV 16/18 infection over a four-year study period. However, the precise strength and duration of vaccine response remained unknown.

Advance
IRP investigator Mahboobeh Safaeian, Ph.D., and colleagues confirmed that two or, in some cases, just one dose of the HPV 16/18 vaccine induced a robust and sustainable immune response as measured by antibody levels among women in the NCI Costa Rica Vaccine Trial. Although the women who received just one dose of the vaccine had lower antibody levels than participants who received all three doses, antibody levels remained stable up to 48 months after vaccination, and they were five times higher than levels in women who were unvaccinated but had antibodies from natural infection.

Impact
If confirmed, these findings could support modified vaccine administration schedules that may be cheaper, simpler, and more likely to be implemented around the world. Because long-term (more than 10 years) durability of antibody response and protection are needed, efforts to extend these findings beyond four years are underway.

Publications
2013: Candidate vaccine against RSV, a common childhood infection

**Challenge**
In the United States, respiratory syncytial virus (RSV) infection is the most common cause of bronchiolitis and pneumonia in children less than one year old [link](http://www.who.int/mediacentre/factsheets/fs117/en/) and the most common cause for hospitalization in children under five. Worldwide, it is estimated that RSV is responsible for nearly seven percent of deaths in babies aged one month to one year; only malaria kills more children in this age group [link]. No vaccine is currently available to prevent RSV infection.

**Advance**
Based upon their previous findings regarding the structure of a critical viral protein, IRP researchers led by Jason McLellan, Ph.D., Barney Graham, M.D., Ph.D., and Peter D. Kwong, Ph.D., developed an experimental vaccine to protect against RSV. When tested in animals, the candidate vaccine elicited high levels of RSV-specific antibodies.

**Impact**
IRP scientists continue to refine the vaccine and hope to launch early-stage human clinical trials of a candidate RSV vaccine as soon as clinical grade material can be manufactured, a process that takes about 18 to 24 months to complete.

**Publications**


2013: Developing a vaccine for all four dengue viruses

**Challenge**
Each year, dengue viruses infect 50-100 million people and cause 500,000 hospitalizations worldwide [23]. There are four distinct dengue viruses and, unfortunately, infection from one type does not provide long-term protection against the others. Instead, individuals can develop more severe symptoms upon infection by one of the other viruses. Thus, the ideal dengue vaccine would be tetravalent, i.e., offer protection against all four viruses.

**Advance**
In January 2013, IRP researchers at the National Institute of Allergy and Infectious Diseases (NIAID) and their colleagues successfully completed a Phase I clinical trial of a group of NIAID-developed tetravalent vaccines and selected one candidate, called TV003, for a Phase II trial [24]. In 90 percent of vaccine recipients, a single dose of TV003 induced immune responses against three or more dengue viruses.

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Impact
The NIAID-developed dengue vaccine technology has been licensed by several companies in dengue-endemic regions of South America and Asia. Because it requires only a single dose, TV003 may offer a cost-effective approach to preventing dengue infections worldwide.

Publications

2013: Discovering a new hepatitis C gene—and its implications for precision medicine

Challenge
Hepatitis C viral (HCV) infection represents a serious threat to public health: up to 150 million individuals are infected worldwide, and as many as 85 percent will develop chronic hepatitis C. Up to five percent of those with chronic hepatitis C may eventually die from liver disease or cancer. Historically, individuals of African descent are less likely to respond to HCV treatment than patients of European or Asian ancestry, suggesting a genetic component to this treatment outcome.

Advance
IRP investigators Ludmila Prokunina-Olsson, Ph.D., and Thomas O’Brien, M.D., M.P.H., used RNA sequencing to uncover a new gene, Interferon lambda 4 (IFNL4), that affects the body’s ability to overcome HCV infection. Only individuals who carry a specific inherited genetic variant of IFNL4 can produce the IFN-λ4 protein, which is strongly associated with a reduced ability to clear the viral infection from the body.

Impact
The gene discovery may help researchers better understand why some people’s immune systems do not respond as strongly as others’ to clear HCV. In addition, the new genetic marker may better predict HCV treatment outcomes for African-American patients than currently available tests, offering a potential mechanism to improve care in this population and reduce existing health disparities.

Publications

2013: Investigational malaria vaccine found to be safe and protective

Challenge
Roughly 600,000 people die of malaria each year, most of them infants and children. Malaria transmits to humans through the bite of an infected mosquito, after which infectious malaria parasites travel to the liver, where they multiply and then spread throughout the body. Scientists and healthcare workers have made significant gains in characterizing, treating, and preventing malaria, but a vaccine has remained an elusive goal.

Advance
In a Phase I clinical trial, IRP investigators from the NIAID Vaccine Research Center, in collaboration with Sanaria Inc., the Walter Reed Army Institute of Research, and the Navy Medical Research Center, evaluated the safety and efficacy of a novel investigational malaria vaccine called PfSPZ. This vaccine includes live, but weakened, malaria parasites, called sporozoites, of the species Plasmodium falciparum—the most deadly of the malaria-causing parasites.

Impact
The study showed that a dose-dependent level of protection against malaria can be achieved when the PfSPZ vaccine is administered intravenously. While the results are promising, additional work is required to evaluate the vaccine in more people and to optimize the dose, schedule, and delivery to determine whether it confers long-lasting protection.

Publications

2013: Seeing the shape of hepatitis B’s action

Challenge
The World Health Organization estimates that the hepatitis B virus has infected two billion people around the world, and about 600,000 people die every year due to consequences of infection. A vaccine has existed since 1982, but there is no cure for already infected individuals, only complex and costly treatments.

Advance
IRP investigators led by Alasdair Steven, Ph.D., and Paul Wingfield, Ph.D., deciphered the atomic structure of the e-antigen protein, a key hepatitis B virus immune-regulator suspected in helping to establish chronic infection.
Impact
Revealing the complex structure of the e-antigen protein provides clues to how the hepatitis B virus eludes the immune system so successfully, which may lead to better treatments.

Publications

2012: Can we outwit the influenza virus with a universal vaccine?

Challenge
A master of disguise, the influenza virus presents unique strains, or versions, of itself each season through its ability to mutate, rendering vaccines developed for particular strains ineffective against new viruses. A universal influenza vaccine could provide people with broad and long-lasting flu protection. But researchers did not know if the presence of existing antibodies—formed in response to a bout with the flu or a vaccination—would interfere with the efficacy of a universal vaccine.

Advance
IRP researchers led by Gary J. Nabel, M.D., Ph.D., tested if a prime-boost vaccination schedule would be negatively affected by the presence of existing antibodies. They found that animals receiving a special prime-boost vaccine regimen were still able to produce broadly neutralizing antibodies, regardless of pre-existing immunity.

Impact
Further development and testing of a universal human influenza vaccine to provide broad and long-lasting protection against multiple influenza virus strains is underway. If successful, an approved universal influenza vaccine could save billions of dollars and, more importantly, millions of lives.

Publications

2012: Identifying a promising HIV vaccine target

Challenge
An important goal of HIV vaccine research is to identify what part of the virus to target. For decades, researchers have looked for regions of HIV that can induce antibodies able to neutralize multiple strains of the virus.

Advance
In late 2012, IRP researchers from the National Institute of Allergy and Infectious Diseases and their
colleagues reported the isolation of an antibody called 10E8 from an HIV-infected patient. The team found that the 10E8 antibody neutralizes approximately 98 percent of HIV strains tested, and they identified the specific part of the virus that 10E8 targets.

**Impact**

Unlike previously described HIV antibodies, 10E8 is not autoreactive—meaning it does not react to the body’s own cells—an important requirement for vaccines. This work suggests that an HIV vaccine that induces 10E8-like antibodies might be effective, offering hope for preventing an infection that has killed more than 25 million people worldwide. The 10E8 monoclonal antibody is now offered for commercial licensing applications via the NIH Office of Technology Transfer.

**Publications**


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**2012: Visualizing a viral infection as it happens**

**Challenge**

Retroviruses, such as the human immunodeficiency virus (HIV), initiate infection when the viral membrane fuses with host cells, a process mediated by viral proteins and cellular receptors. But scientists need a more detailed understanding of the mechanism in order to develop drugs that can impede the fusion.

**Advance**

IRP researchers led by Alasdair Steven, Ph.D., used cryo-electron tomography (cryo-ET), a technique that allows three-dimensional imaging of individual virus particles at molecular resolution, to visualize successive stages of virus-host cell fusion in a bird retrovirus model. They succeeded in viewing a specific “pre-hairpin” conformation of the interaction, a long hypothesized key intermediate of fusion that had never been directly visualized.

**Impact**

This discovery has informed many advanced investigations of fusion dynamics, including those of other retroviruses, such as HIV and the influenza virus, which infect by a similar mechanism.

**Publications**


2011: Understanding bacterial immune systems

Challenge
Bacteria have extremely diverse and rapidly evolving antivirus defense systems that remain poorly understood. Without more detailed characterization of these systems and the evolutionary dynamics of bacteria, doctors would continue struggling against the development and spread of antibiotic-resistant bacterial strains.

Advance
IRP researchers led by Eugene Koonin, Ph.D., developed an evolutionary classification of bacterial adaptive immunity systems. Koonin and colleagues then created a mathematical model of virus-host co-evolution that identifies conditions under which bacteria maintain or lose adaptive immunity.

Impact
Microbiologists quickly adopted the new classification of bacterial immunity systems as a framework for research in the field. Researchers can use the mathematical model of virus-host co-evolution to predict bacteriophage resistance and antibiotic resistance.

Publications


2010: Illuminating a path toward HIV vaccine development

Challenge
Since the discovery of the human immunodeficiency virus (HIV) in 1984, advances in antiretroviral therapy have helped control HIV progression around the world and, in several developed countries, turned a fatal illness into a chronic disease. But current therapies cannot entirely clear HIV from the body, highlighting the need for an effective vaccine.

Advance
Tongqing Zhou, Ph.D., and colleagues in the laboratory of Peter Kwong, Ph.D., identified a broadly neutralizing HIV antibody they called VRC01. Only about 20 percent of people can naturally generate these types of protective HIV antibodies. The researchers went on to map how the HIV virus co-evolved with broadly neutralizing antibodies in a single HIV-positive person.

Impact
By understanding the simultaneous evolution of HIV and its antibodies, scientists may eventually be able to create a blueprint for the development of an HIV vaccine that can induce broadly neutralizing HIV antibodies in the general population.
**Publications**

Press Release – NIH Scientists, Grantees Map Possible Path to an HIV Vaccine.


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**2010: Stopping Dengue in its tracks**

**Challenge**

Dengue virus is estimated to cause close to 400 million infections and half a million hospitalizations annually, the majority of which involve children. Due to the lack of effective therapies and vaccines and the increasing geographic range of the mosquitoes carrying the virus, this infectious tropical disease is a growing threat to global health and economies.

**Advance**

IRP researchers led by Leonid Chernomordik, Ph.D., focused on understanding how the dengue virus fuses with various organelles to deliver its RNA into human cells. The team discovered a series of cellular cofactors essential for the fusion process and successful dengue virus infection.

**Impact**

The finding explains a specific intracellular localization of dengue fusion and led to the development of broadly neutralizing antibodies that inhibit the early fusion stages of dengue virus infection. In addition, the team’s research yielded the first quantitative assays for screening these antiviral therapies, uncovering a new path towards the development of a vaccine against dengue virus.
2001: Identifying and understanding rare immune system diseases

Challenge
Primary immune deficiency diseases (PIDDs) are rare, difficult-to-manage disorders caused by inherited defects in cells of the immune system. They can result in increased risk of life-threatening infections, autoimmune diseases, and tumors. Understanding the molecular mechanisms underlying these immunodeficiencies is crucial to therapeutic decision-making and effective management of each disease.

Advance
For more than 30 years, IRP investigators at the National Institute of Allergy and Infectious Diseases (NIAID) have studied and developed new treatments for known PIDDs and worked to decipher immunodeficiencies of unknown etiology. In the last few years alone, IRP scientists identified:

- NEMO immunodeficiency, which leads to frequent bacterial and viral infections and abnormal teeth, hair, skin, and nails
- DOCK8 immunodeficiency, which can cause persistent skin infections, allergies, and cancer
- XMEN disease, characterized by persistent Epstein-Barr virus infections and magnesium deficiency
- PLAID, characterized by immune deficiency, autoimmunity, inflammatory skin disorders, and cold-induced hives

Impact
IRP researchers and their collaborators have made significant contributions to current understanding of PIDDs and to the treatment of patients affected by these devastating diseases. In 2007, NIAID opened a Primary Immune Deficiency Clinic at the NIH Clinical Center to provide a focus of IRP expertise for referring physicians and their patients. The clinic accepts patients with known or suspected PIDDs and offers treatment recommendations and, in some cases, a disease diagnosis.

Publications

2000: Discovering new tuberculosis drugs

Challenge
Current tuberculosis (TB) treatment regimens require people to take several antibiotic drugs for at least six months. The difficulty in adhering to these treatments has contributed to the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (Mtb), the bacterium that causes the disease.

Advance
In the late 1990s, IRP researchers led by Clifton Barry, Ph.D., tested more than 60,000 compounds related to the TB drug ethambutol. They identified several compounds that were effective against Mtb in the laboratory and collaborated with industry on further drug development. Animal studies revealed that a compound called SQ109 kills Mtb, including drug-resistant strains. Then in 2000, IRP scientists and collaborators reported the discovery of another potential TB drug, PA-824, that may be effective against latent TB infections.

Impact
Early human clinical studies indicated that SQ109 is safe, and additional clinical trials are currently underway to evaluate SQ109’s effectiveness. The FDA has granted SQ109 Orphan Drug and Fast Track status, which could help accelerate eventual FDA approval. PA-824 entered clinical trials in 2005, and initial results suggest that it is safe and effective. Follow-on trials will aim to determine if it too could be headed towards the pathway of approval and use within the TB armamentarium.

Publications


1995: In the fight against viral hepatitis A, vaccines save lives

**Challenge**
The hepatitis A virus causes contagious, acute inflammation of the liver. Prior to the discovery of a vaccine, an estimated 100 people died from it every year in the United States[^31]. With no treatments, creating a vaccine against the hepatitis A virus could reduce incidence of the disease and save lives[^32].

**Advance**
IRP researchers Robert Purcell, M.D., Albert Kapikian, M.D., Stephen Feinstone, M.D., and colleagues played a crucial role in developing the first licensed hepatitis A vaccine, from initial identification and characterization of the virus to the clinical trials that demonstrated protective efficacy[^33].

**Impact**
The discovery and development of hepatitis A vaccines were landmark moments for public health, providing nearly 100 percent of adults with protective levels of antibodies, and contributing to the decline of hepatitis A rates in the U.S. by 92 percent since 1995[^34].

**Publications**
NIAID’s Role in Hepatitis Research: [http://www.niaid.nih.gov/topics/hepatitis/Pages/default.aspx](http://www.niaid.nih.gov/topics/hepatitis/Pages/default.aspx)


[^32]: [http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general](http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general)
[^34]: [http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general](http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#general)
1991: Advancing early, rapid diagnosis of river blindness

Challenge
The eye and skin infection known as onchocerciasis, or river blindness, affects more than 18 million people worldwide[^35], mostly in rural African communities near streams and rivers. The disease is caused by the parasite *Onchocerca volvulus*, which is spread through the bite of an infected blackfly. The lack of a quick and inexpensive test to detect *O. volvulus* makes it difficult to track new infections and provide timely treatment.

Advance
During the early 1990s, IRP researcher Thomas Nutman, M.D. and collaborators identified Ov16, an *O. volvulus* protein that is abundant in the early stages of infection. The researchers found that antibodies against Ov16 can be detected in the blood of infected people up to one year before infection appears in the skin. This simple blood test showed promising results in initial field trials conducted in seven West African villages during late 1999 and early 2000.

Impact
In 2013, the investigators licensed the technology to the Program for Appropriate Technology in Health for the development of a rapid, noninvasive, and inexpensive diagnostic test that health care workers in resource-poor settings can use. By enabling early detection and treatment of river blindness, this test promises to aid efforts to eradicate the disease.

Publications


1989: Protecting at-risk children from a severe respiratory disease

Challenge
Respiratory syncytial virus (RSV) is a leading cause of bronchiolitis and pneumonia in children less than one year old[^36]. RSV infection can be life-threatening, especially for babies born prematurely or with health problems such as chronic lung disease or congenital heart disease[^37]. An effective means to prevent severe RSV disease was needed.

[^35]: http://www.who.int/gho/neglected_diseases/onchocerciasis/en/
[^36]: http://www.cdc.gov/rsv/about/faq.html
[^37]: http://www.cdc.gov/rsv/about/faq.html
**Advance**
IRP investigators Robert M. Chanock, M.D., Brian Murphy, M.D., and colleagues showed that giving anti-RSV antibodies to animals protected them from RSV infection. The researchers then developed a monoclonal antibody that neutralized RSV in animal models. The pharmaceutical company MedImmune licensed the monoclonal antibody, further developed it for human use, and conducted clinical trials showing that it could protect high-risk infants from severe RSV disease.

**Impact**
Following FDA approval in 1998, MedImmune marketed the RSV antibody Synagis® for prevention of severe RSV disease in high-risk infants. Monthly administration of Synagis during RSV season reduces RSV-related hospitalizations by an estimated 45 to 55 percent\(^3\). Because RSV is an important pediatric pathogen and an increasingly recognized cause of severe respiratory disease in chronically ill adults and the elderly, RSV vaccine research and development continues to be a high priority in the IRP.

**Publications**

Murphy BR, Sotnikov A, Paradiso PR, Hildreth SW, Jenson AB, Baggs RB, Lawrence L, Zubak JJ, Chanock RM, Beeler JA, et al. (1989). *Immunization of cotton rats with the fusion (F) and large (G) glycoproteins of respiratory syncytial virus (RSV) protects against RSV challenge without potentiating RSV disease*. *Vaccine*. 7(6), 533-40.

**1985: First detection and screening of the HIV virus**

**Challenge**
Early on in the acquired immunodeficiency syndrome (AIDS) epidemic, there was no way to test for the disease, and what we now know as the human immunodeficiency virus (HIV) had not yet been identified as its cause. However, a mysterious third member of the human T-cell leukemia retrovirus family (HTLV-III) had been newly discovered in AIDS patients. The lack of a diagnostic test for the virus that causes AIDS meant that healthcare professionals had no way of screening blood products for the disease or knowing if they had been unintentionally infected.

**Advance**
IRP researchers led by William Blattner, M.D., and Robert Gallo, M.D., pioneered the use of an enzyme-linked immunosorbent assay (ELISA) to detect antibodies against HTLV-III and showed a positive correlation between HTLV-III antibodies and progression to AIDS.

**Impact**
The new test’s high specificity and sensitivity meant that it quickly became the standard screening test for blood donors and populations at risk for AIDS. It was used to diagnose suspected AIDS cases and helped define the spectrum of diseases etiologically related to HTLV-III, later determined to be HIV.

**Publications**
1985: Hitting HIV hard with HAART therapy

Challenge
The human immunodeficiency virus (HIV), discovered in 1984, is a retrovirus that causes progressive failure of the immune system, resulting in the development of opportunistic infections and cancers (acquired immunodeficiency syndrome, or AIDS). Development of therapies is imperative to stop viral replication and progression of the disease.

Advance
Soon after HIV was found to be the cause of AIDS, IRP researchers Samuel Broder, M.D., Hiroaki Mitsuya, M.D., Ph.D., and Robert Yarchoan, M.D., demonstrated that certain nucleoside reverse transcriptase inhibitors had activity against HIV in the test tube, a discovery the team rapidly moved to test in clinical trials.

Impact
This research yielded the first drugs approved by the U.S. FDA for the treatment of HIV infection: zidovudine (AZT) in 1985, didanosine (ddI) in 1991, and zalcitabine (ddC) in 1992. These drugs became the foundation for highly active antiretroviral therapies (HAART), saving countless lives.

Publications

1984: Demonstration that HTLV-III is the causative agent of AIDS

Challenge
In 1982, doctors first used the term acquired immunodeficiency syndrome (AIDS) to describe a mysterious and often fatal disease of unknown cause. Researchers raced against the clock to understand what was causing more and more people to progressively lose their immune system function.

Advance
IRP researcher Robert Gallo, M.D., concurrently with researchers at the Pasteur Institute, showed that a retrovirus, dubbed HTLV-III—later renamed the human immunodeficiency virus (HIV)—is the virus that causes AIDS.

Impact
The discovery that HIV causes AIDS spurred development of a lab-based assay to detect antibodies created by the body in response to the virus, and therefore the exposure of infected individuals to the virus. In the years before effective treatments for AIDS were developed, diagnosis followed by public health initiatives aimed at restricting transmission of the virus were employed. Today, researchers are hot on the trail of an effective and safe HIV vaccine that might one day eradicate the deadly disease.

Publications
Popovic M, Sarngadharan MG, Read E, Gallo RC. (1984). Detection, isolation, and continuous production of
cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. *Science.* 224 (4648): 497–500.


1981: Discovery of the disease agent causing Lyme disease

**Challenge**

When Lyme disease was first identified in rural Connecticut in 1975, the cause of its rheumatoid arthritis-like symptoms was unknown. Physicians suspected a virus was behind the outbreak, but—without knowing its true agent—attempts at further understanding the pathogenesis and possible treatments of Lyme disease were unsuccessful.

**Advance**

In 1981, IRP researcher William Burgdorfer, Ph.D., at the National Institute for Allergy and Infectious Diseases (NIAID) Rocky Mountain Laboratories discovered spirochetes—a type of slim, spiral bacteria—in the midguts of deer ticks prevalent in the forests near where the infections were occurring. With further laboratory testing, he and colleagues at NIAID found that the bacteria, passed to humans via tick bites, were causing the mysterious Lyme disease, which is now recognized as the most common tick-borne illness in both the EU and USA.

**Impact**

The spirochete that causes Lyme disease was named after Dr. Burgdorfer—*Borrelia burgdorferi*—and since his seminal 1982 paper on its discovery more than 6,000 studies on clinical, epidemiological, and bacterial aspects of this disease have been published. With the knowledge that Lyme disease is carried by a bacterium, most patients treated with antibiotics can now achieve a full recovery.

**Publications**


1980: Discovery of the first human retroviruses

**Challenge**

In the 1970s, researchers knew retroviruses as the cause of some cancers in various animal species, but they had not been clearly defined as causative agents of any human diseases, including certain types of human cancers.
Advance
The discovery of T-cell growth factor—also known as interleukin-2—allowed researchers, including Robert Gallo, M.D., at the IRP to culture human T cells in vitro. Gallo’s team cultured two different T-cell lines from a patient with a cutaneous T-cell lymphoma and discovered that both cell lines continuously produced retrovirus particles. It was the first time that retroviruses had been observed in human cells.

Impact
This initial report of human retroviruses would lead the way towards eventual discovery and characterization of various cancer-causing viruses, including the HTLV-III retrovirus, later referred to as the human immunodeficiency virus (HIV) and identified as the cause of acquired immune deficiency syndrome (AIDS).

Publications

1974: Developing the first rotavirus vaccine

Challenge
Rotaviruses are the most common cause of severe childhood diarrhea worldwide. They are responsible for up to 500,000 deaths each year. To reduce their deadly effect, scientists needed to better understand the virus and apply that knowledge to developing a vaccine.

Advance
IRP researchers led by Albert Kapikian, M.D., first identified human rotavirus in the United States in 1974. The team defined the virus’ mode of transmission and pinpointed the proteins critical for triggering an immune response. Their efforts, in partnership with Wyeth-Ayerst Laboratories, led to the development, testing, and 1998 FDA approval of RotaShield, the first rotavirus vaccine.

Impact
While RotaShield is no longer in use, the researchers’ decades-long effort carried basic research results all the way through to the development of a vaccine. The knowledge derived from their process paved the way for the creation of second-generation rotavirus vaccines, which are now being licensed for use in low-income countries.

Publications

Further reading: http://www.niaid.nih.gov/topics/rotavirus/Pages/rotavirusVaccine.aspx

Further reading: https://www.cdc.gov/vaccines/pubs/pinkbook/rota.html
**2016: Dual antibody treatment suppresses HIV-like virus**

**Challenge**
While combination antiretroviral therapy (ART) has resulted in extraordinary reductions in viral load and rates of death in those affected by HIV, treatment must be maintained throughout the patient’s lifetime. Lifelong drug therapy can pose significant burdens and, according to the World Health Organization, only 46% of people living with HIV were receiving antiretroviral treatment in 2015.

**Advance**
IRP researcher led by Malcolm A. Martin treated 13 animals in the earliest stages of SHIV infection, a monkey version of HIV that expresses HIV surface molecules, with 3 infusions of 2 potent, broadly neutralizing HIV antibodies over a 2-week period. Six of these animals became elite controllers, with viremia at levels near or below the limit of standard detection methods with no additional drugs and four were able to achieve low levels of viremia. Viral loads temporarily increased following depletion of CD8+ cytotoxic T cells from elite controller animals suggesting that these cells were critical to maintaining viremia at low to undetectable levels in these animals.

**Impact**
Releasing patients from a lifetime of treatment would represent a major advance in the fight against HIV/AIDS. Although SHIV infections in monkeys differ from HIV-1 infections in several important ways, this novel immunotherapeutic approach holds significant promise to minimize the spread of HIV in the body thus allowing for the mobilization of a robust CD8+ T cell immune response and, ultimately, long term viral control.

**Publications**
2016: Treating fatigue: A novel and promising path forward

Challenge
Both Parkinson’s disease and the rare lysosomal disorder Gaucher disease need new therapeutic approaches and effective treatments that better address the root causes of the disorders.

Advance
Given that N-methyl-D-aspartate (NMDA) receptor antagonists, such as a low-dose ketamine, have well-documented rapid antidepressant effects in individuals with major depressive disorders, IRP researchers led by Leorey Saligan, Ph.D., R.N., C.R.N.P., and Carlos Zarate, M.D., hypothesized that similar anti-fatigue effects might also be present. In a randomized controlled trial of ketamine infusion for bipolar disorders, ketamine significantly lowered fatigue scores compared to placebo, and the effect remained significant after controlling for changes in non-fatigue depressive symptoms.

Impact
This study is the first to suggest that NMDA receptor inhibition is a potential therapeutic research target for fatigue, suggesting a novel potential role of the glutamatergic system. The results also validate the utility of the first clinician-administered fatigue questionnaire, the NIH-Brief Fatigue Inventory, to measure changes in fatigue symptoms in a clinical trial.

Publications

2015: Hepatitis C: Repurposing existing drugs and discovering new antivirals

Challenge
Treatments for hepatitis C virus (HCV) have improved substantially over the years, but serious limitations and unmet needs still exist for patients, with cost being the biggest barrier to effective clinical care.

Advance
IRP researchers led by T. Jake Liang, M.D., developed a novel cell-based high-throughput assay to screen several expansive small-molecule libraries, including a pharmaceutical collection, for activity against HCV. They identified a class of antihistamines and several novel compounds as potent HCV inhibitors in vitro and in vivo. The compounds have since been optimized by medicinal chemistry for preclinical development.

Impact
The discovery that approved antihistamine drugs have anti-HCV properties can facilitate repurposing of those compounds for HCV treatment more quickly than developing new drugs for testing and approval. Additionally, it may be possible to bring the novel compounds identified to have higher potencies and better pharmacological properties forward through testing into clinically-viable HCV drugs.
Publications


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2015: Sharper Images of Molecules Using Cryo-Electron Microscopy

Challenge
The molecular structure of numerous proteins cannot be determined using standard methods such as X-ray crystallography. New methods to determine protein structures are needed.

Advance
IRP researchers led by Sriram Subramaniam, Ph.D., developed groundbreaking new technology based on cryo-electron microscopy (cryo-EM) to determine the atomic structures of proteins. They have achieved resolutions which are comparable to X-ray crystallography, including on small proteins.

Impact
As new structures unfold at near-atomic resolution, the implications for drug discovery and development are revolutionary. Cryo-EM maps showing the contacts between small molecules and proteins will help explore questions such as why one drug is better than another or why certain drugs fail.

Publications

2015: Gaucher and Parkinson’s: Identifying one target for two diseases

Challenge
Both Parkinson’s disease and the rare lysosomal disorder Gaucher disease need new therapeutic approaches and effective treatments that better address the root causes of the disorders.

Advance
IRP researcher Ellen Sidransky, M.D., and colleagues at NCATS Chemical Genomics Center collaborated with Kansas University researchers to identify chemical chaperones—molecules that can help to stabilize or correct enzyme defects—for glucocerebrosidase (GCase), an enzyme missing in Gaucher disease that is essential for cells to break down cellular waste. The team then tested these chaperones in models of other diseases of cellular waste, including Parkinson’s disease. The chaperones rescue the cell’s ability to deal with noxious waste and prevent cellular degeneration.

Impact
The work now has been licensed to industry for further development with the aim of yielding new therapies for Parkinson’s disease and other neurological disorders. Researchers at NIH continue to explore this novel biology and its possible relevance to other diseases as well.

Publications


2014: Creating an artificial RNA receptor to deliver siRNA to Tumors

Challenge
Development of nontoxic, tumor-targetable, potent in vivo RNA delivery systems remains an obstacle to clinical applications of RNAi therapeutics.

Advance
IRP researchers led by Xiaoyuan (Shawn) Chen, Ph.D., developed an RNAi nanoplatform containing a molecular label, Zn(II)-DPA, and a tumor-targetable/drug-loadable hyaluronic acid nanoparticle. The delivery system works to target small-molecule drugs directly to tumors. Test nanoparticles loaded with doxorubicin—a standard cancer therapy—and aimed at the target RNA of the multidrug resistance 1 (MDR1) gene successfully suppressed tumor growth in an animal model.
Impact
The team’s design strategy offers a versatile, practical method for targeting RNA and chemotherapeutics to tumor cells and expands existing nanomaterial capabilities to further the field of drug and gene delivery.

Publications

2014: NLM Scrubber: Paving the road to “Big Data” by securing patient privacy

Challenge
Patients’ health data has the potential to transform how clinicians provide care and scientists conduct research—but ensuring patient privacy has been a major barrier. It is therefore critical that clinical records be effectively stripped of personally identifiable information (PII) before being shared.

Advance
IRP researchers led by Mehmet Kayaalp, M.D., Ph.D., developed a clinical text de-identification software tool called NLM Scrubber, which protects patient privacy better than any other freely available de-identification program.

Impact
Dr. Kayaalp’s NLM Scrubber tool means that the greater NIH research community will soon be able to access most data stored in electronic medical records (EMRs) without breaching patient privacy, an important step forward to realizing the promise of “Big Data” in healthcare.

Publications


**2014: Safer and faster prion disease detection**

**Challenge**
Creutzfeldt-Jakob disease (CJD) is an incurable, transmissible, and ultimately fatal neurodegenerative disorder. Currently, definitive diagnosis requires a biopsy or post-mortem sampling of brain tissue.

**Advance**
IRP researcher Byron Caughey, Ph.D., and colleagues collaborated with a team from the University of Verona to develop a less invasive and quicker test to diagnose CJD. The new technique involves gentle brushing of the nasal cavity to collect olfactory neurons connected to the brain. From a total of 43 CJD patients, the test correctly diagnosed 42 patients, and accurately showed negative results for all 43 non-CJD patients.

**Impact**
An easy-to-use diagnostic test will allow doctors to clearly differentiate CJD from other brain diseases and enhance the development of early treatments. With additional validation, this type of test has potential for use in both clinical and agricultural settings.

**Publications**

**2013: Protecting salivary glands from irradiation damage**

**Challenge**
Each year, more than 500,000 patients worldwide are treated for head and neck cancer. The current standard of care involves exposure to radiation that can damage salivary glands, leading to permanent dry mouth (xerostomia) that negatively affects oral health and overall quality of life.

**Advance**
IRP scientists led by Matthew Hoffman, B.D.S., Ph.D., showed that treating irradiated mouse fetal salivary gland tissues with the neurotrophic protein neurturin to restore parasympathetic function improves salivary gland regeneration.

**Impact**
The findings provide a new target and research direction for how salivary glands (and other sensitive organs) may be protected or regenerated in people undergoing extensive treatment for cancers.

**Publications**
2013: Visualizing chromosomal translocations in living cells

Challenge
When part of a chromosome breaks off and becomes attached to another chromosome—an abnormality called a chromosomal translocation—cells can quickly become uncontrolled, leading to excessive growth or cancer. However, because these events are very rare, it has been extremely difficult to study them.

Advance
IRP scientists led by Tom Misteli, Ph.D., used an experimental imaging system developed at the National Cancer Institute (NCI) to track fluorescently labeled chromosomes in thousands of mouse cells following induced breaks in their DNA. Though the vast majority of chromosomes reattached correctly, the researchers were able to capture time-lapse video of translocations, allowing them to visualize and identify several previously unknown distinct steps and proteins involved in the process.

Impact
Dr. Misteli’s new live-cell imaging technique now allows researchers to investigate rare chromosomal abnormalities. With a better understanding of how chromosomal translocations occur, there is potential to identify new therapeutic targets that might prevent the development of many types of cancer.

Publications

2013: Visualizing DNA repair in action

Challenge
DNA polymerase plays a central role in repairing damaged DNA, making this enzyme a key regulator of genome stability and likely protector against cancer and degenerative diseases. More information about DNA polymerase’s functions and interactions with other molecules is essential to better leverage genome repair mechanisms in developing new therapies.

Advance
IRP researchers led by Samuel H. Wilson, M.D., used a new time-lapse crystallography approach to capture and visualize real-time DNA polymerase activity during DNA synthesis and repair.

Impact
Dr. Wilson’s time-lapse snapshots provide novel insight into how DNA polymerase chooses the correct base when repairing DNA. The images also revealed specific features of the enzyme that are now considered therapeutic targets for regulating repair after stress-induced DNA damage.

Publications
2012: Medical radiation and cancer: minimizing the risk from CT scans

Challenge
Ionizing radiation is a known carcinogen. Many medical imaging tests employ ionizing radiation to capture detailed pictures of internal organs for diagnosing injury or disease. Radiation-related cancer risk from the scans is small at the individual level, however, small risks could result in a large number of future cancers in the total U.S. population. Because of the increasing use of computed tomographic (CT) scans in the U.S. (in 2007 the average was 70 million scans annually), it is important to discern which type of scans—and the ages at which they are given—contribute most to overall cancer risk.

Advance
IRP researchers led by Amy Berrington de Gonzalez, D.Phil., estimated that 29,000 future cancers could be related to CT scans performed in the U.S. in 2007 alone. They found that the largest contribution to cancer risk comes from the scans of the abdomen/pelvis, chest, head, and whole body.

Impact
Following the research results, the NIH Clinical Center updated its protocol to require documentation of the ionizing radiation dosage received for each CT scan, and professional groups in the U.S. and overseas have adjusted their guidelines, especially for pediatric use of CT. Between 2011 and 2013, CT procedure volume dropped 11% in the U.S., with about 10 million fewer scans.

Publications


2012: Understanding genetic recombination in a multi-cellular organism

Challenge
Genetic recombination is the defining phenomenon in genetics. It drives the evolution of genomes, yet it occurs at hotspots whose features are mostly unknown in organisms other than yeast. To better understand human disease, researchers needed to understand where and how recombination occurs in complex organisms.

Advance
IRP researchers led by Rafael Daniel Camerini-Otero M.D., Ph.D., in collaboration with Galina Petukhova, Ph.D., of the Uniformed Services University of Health Sciences, constructed the first high-resolution, genome-wide physical map of recombination hotspots in a multi-cellular organism (the mouse).
**Impact**
The map revealed previously unknown molecular features at hotspots, as well as the mechanism for actively sequestering recombination away from functional genomic elements, such as promoters and enhancers. The recombination map has advanced our understanding of both how genetic recombination works in complex organisms and how it is initiated, giving additional insight into the role of genomic rearrangements in evolutionary processes leading to shifts in allele frequencies and the development of heritable genetic diseases.

**Publications**


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**2011: Advancing rapid detection of prion diseases**

**Challenge**
Prion diseases, such as Creutzfeldt-Jacob disease (CJD) in humans, scrapie in sheep, and mad cow disease in cattle, are difficult to diagnose, currently untreatable, and ultimately fatal. People and animals can be infected for years before symptoms appear. A faster and more practical prion diagnostic test that does not require cerebrospinal fluid sampling or brain tissue could simplify screening for prion diseases and allow earlier diagnostic confirmation to guide healthcare decision-making.

**Advance**
IRP scientists led by Byron Caughey, Ph.D., developed a prion blood test called enhanced Quaking-Induced Conversion (eQuIC), which uses an antibody to isolate abnormal prion protein from blood plasma and then amplifies it to enhance detection. The test is 10,000 times more sensitive for detecting variant CJD than previously described tests. The National Institute of Allergy and Infectious Diseases (NIAID) and its project partner, Swiss diagnostics firm Prionics AG, have applied for a patent on the eQuIC test.

**Impact**
eQuIC could be used by blood banks, hospitals, livestock operations, and rendering plants to screen for prion diseases in a far more efficient and less invasive manner than current diagnostic tools. Additionally, this concept of testing for abnormal proteins could eventually be applied to the diagnosis of other diseases, such as Alzheimer’s, Huntington’s, and Parkinson’s disease, but more research is needed and underway.

**Publications**
2011: Pioneering closed-chest hole-in-the-heart repair

Challenge
One of the most common congenital heart diseases is ventricular septal defect, or “hole-in-the-heart.” Current repair techniques require open-chest surgery and prolonged exposure to ionizing radiation to visualize the appropriate anatomy. Non-surgical interventions would reduce risks and improve recovery times.

Advance
IRP researcher Robert J. Lederman, M.D., and colleagues tested a pre-clinical MRI-guided, catheter-based, closed-chest intervention that provides enhanced image guidance, reduced radiation exposure, and reduced surgical risk.

Impact
If clinical trials continue to support development of MRI-guided treatments, pediatric patients with ventricular septal defect could avoid the risks associated with traditional surgical interventions in favor of a less invasive and safer procedure.

Publications

2011: Taking the random out of biopsy sampling

Challenge
Biopsy is currently the only way to confirm a diagnosis of prostate cancer. However, despite improvements in technology, prostate biopsy sampling remains a challenge, and cancerous lesions may be missed. Novel diagnostic tools are needed to ensure more accurate biopsies and better cancer detection rates.

Advance
IRP researchers Peter L. Choyke, M.D., Peter A. Pinto, M.D., Bradford Wood, M.D., and colleagues developed a combined magnetic resonance imaging (MRI) and ultrasound-guided prostate biopsy, a minimally invasive technique that allows for the detection of cancer at a far higher rate than current biopsy techniques.
Impact
Fusion MRI/ultrasound-guided biopsy has been shown in clinical trials to detect more instances of cancer than standard biopsies, consequently leading to more accurate diagnosis and more appropriate course of treatment for cancer patients.

Publications

2006: Inventing sharper and faster optical microscopes for live cell imaging

Challenge
Microscopes have traditionally evolved in tandem with medical research, and scientists today need new generations of microscopes to enable them to delve even deeper into the molecular mechanisms of disease.

Advance
IRP investigators, including Clare M. Waterman, Ph.D., Jennifer Lippincott-Schwartz, Ph.D., and Hari Shroff, Ph.D., have pioneered new imaging techniques and tools, such as fluorescent speckle microscopy (FSM), photoactivation localization microscopy (PALM), and inverted selective plane illumination microscopy (iSPIM), that provide dramatically clearer views of healthy and diseased live cells, their organelles, and the protein interactions within.

Impact
Through improved imaging, researchers around the world can now visualize complex developmental and disease progressions that previously could only be conjectured. The ability to visualize cellular organelles and macromolecules in such fine detail provides researchers with new tools to accelerate understanding of cellular function in health and disease.

Publications


2004: Developing a better way to monitor the size of slow growing, complex tumors

Challenge
There is currently no effective therapy for patients with peripheral nerve sheath tumors called plexiform neurofibromas resulting from neurofibromatosis type I (NF1), and surgery is only an option for a subset of patients with the disorder. Before 2004, there was not an accurate way to measure the growth of these tumors to track disease progression.

Advance
IRP researcher Brigitte Widemann, M.D., and colleagues developed a method called semi-automated volumetric MRI analysis to measure the tumors. The technique allows researchers to reproducibly and sensitively measure changes in tumor size and accurately define the time to disease progression or shrinkage as primary endpoints in clinical trials.

Impact
As a result of this study, semi-automated volumetric MRI analysis is now used nationwide to determine response in most clinical trials of therapies against neurofibromatosis type I and in preclinical trials of targeted agents for neurofibromas in animal models.

Publications


2002: Using adoptive cell transfer to treat advanced cancer

Challenge
Approximately 1.6 million people are diagnosed with cancer each year, and one third of those will die from the disease within five years41. In particular, patients with advanced, metastatic cancer face limited treatment options and low survival rates. Immunotherapy—the use of the patient’s own immune system to fight disease—may prove to be a new option.

Advance
IRP researcher Steven A. Rosenberg, M.D., Ph.D., and colleagues pioneered the use of adoptive cell transfer, an immunotherapy treatment in which infiltrating immune cells are removed from a tumor, activated in vitro, and then returned to the patient.

**Impact**
This approach has led to the regression of metastatic cancer in patients with melanomas, sarcomas, and lymphomas, in many cases resulting in long-term survival for people with complex and often refractive tumor types. Furthermore, these advances have helped to launch the field of immunotherapy for the treatment of cancer and chronic infection.

**Publications**


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**2000: Developing efficient modification of genomic DNA through recombineering**

**Challenge**
Traditional genetic engineering techniques use restriction enzymes to “cut” DNAs into fragments that are joined (“pasted”) with DNA ligase to produce new recombinant DNA. Though powerful and still very much in use today, these tools are too imprecise for biomedical researchers who need technologies that allow genetic changes to be made directly in genomic DNA with high fidelity and precision.

**Advance**
IRP scientists led by Donald Court, Ph.D., developed an *in vivo* recombineering (recombination-mediated genetic engineering) technique to create DNA constructs precise to the base pair. The new method utilizes homologous recombination to incorporate short pieces of synthetic single- or double-stranded DNA into the genome.

**Impact**
Recombineering has drastically changed the field of molecular biology and genetics by reducing both the cost and time involved in modifying genomic DNA and enabling the generation of transgenic animal models of great complexity. This has led to widespread functional genomic studies and an understanding of how genes are expressed and regulated.
**2000: From hormone to pharmaceutical: lipodystrophy**

**Challenge**

Lipodystrophy is a rare disease in which patients lack body fat and fat-derived hormones, such as leptin. Generalized lipodystrophy results in extreme forms of diabetes, insulin resistance, triglyceride elevation, and fatty liver disease, all of which complicate treatment and can lead to significant morbidity and mortality.

**Advance**

The first fat-derived hormone, leptin, was discovered in 1994. Since 2000, IRP researchers from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including Phillip Gorden, M.D., and Rebecca J. Brown, M.D., M.H.Sc., have treated more than 100 lipodystrophy patients with leptin replacement therapy, resulting in dramatic improvements in diabetes, lipid levels, and quality of life.

**Impact**

Based on these clinical studies, metreleptin (Myalept), the first recombinant leptin analog, was approved by the FDA in 2014 to treat patients with generalized lipodystrophy. Targeted treatment of leptin deficiency in lipodystrophy represents a major medical advance in the treatment of an unusual and otherwise difficult-to-treat disease.

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**Publications**


**1996: Dissecting good from bad with laser-capture microdissection**

**Challenge**
Due to the mixture of cell types in a tumor biopsy, the ability to separate the different cells in order to study them discretely has been a long-standing problem in research.

**Advance**
IRP scientists led by Michael R. Emmert-Buck, M.D., Ph.D., William M. Bonner, Ph.D., and Lance Liotta, M.D., Ph.D., invented laser-capture microdissection (LCM) to rapidly and precisely select specific cells from a biopsy sample. Using a low-energy laser beam and special transfer film, LCM enables researchers to isolate normal, precancerous, and cancer cells for analysis.

**Impact**
This novel technology provides a solution to the problem of isolation and purification of distinct cells within a given tissue sample. LCM has become a well-established research tool used throughout the world, and has been enhanced and expanded into many new biomedical applications.

**Publications**

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**1994: IL-15: Taking an immunotherapy from bench to bedside**

**Challenge**
Cytokines are a class of proteins that regulate signaling in the immune system. Since the 1970s, scientists have worked to better understand the large and complex family of cytokine molecules, in hopes of harnessing them to more effectively combat cancer and other diseases.

**Advance**
IRP researchers led by Thomas Waldmann, M.D., co-discovered the cytokine IL-15 and revealed its powerful role in triggering a cascade of tumor-fighting immune system cells. The lab demonstrated that IL-15's unique properties made it a potentially better immunotherapy than IL-2, a related protein in clinical use today.

**Impact**
Dr. Waldmann’s team then translated their observations from the research bench to the clinic by initiating the first clinical trials in humans using the cytokine as a cancer therapy. IL-15 is now being tested to treat patients with metastatic malignant melanoma and renal cell cancer. IL-15 has also shown promise in molecular vaccines, which could represent a major advance in treating cancer and autoimmune disorders such as AIDS.

**Publications**


Symptoms and Manifestations

2016: Improving detection and prevention of undiagnosed diabetes in African-descent populations

Challenge
Undiagnosed Type 2 Diabetes is often blamed on the combined effects of low health literacy, limited early symptoms, and a lack of access to care. However, an underappreciated factor specifically contributing to undiagnosed diabetes and health disparities among people of African descent is that traditional screening tests, such as fasting plasma glucose and hemoglobin A1c (A1C), have lower sensitivity as early markers of hyperglycemia, a hallmark sign of diabetes, than in the general population.

Advance
IRP researchers led by Anne Sumner, M.D., and David Sacks, M.D., demonstrated that the detection of hyperglycemia is markedly increased in African-descent populations by combining A1C, which is a non-fasting marker of glucose levels over time, with a novel non-fasting marker of glycemia: glycated albumin.

Impact
Earlier detection of hyperglycemia would likely reduced the prevalence of undiagnosed diabetes and improve the accuracy of statistics, leading to wiser public resource allocation and better health outcomes. The IRP team’s research justifies consideration for worldwide evaluation of glycated albumin as a diagnostic test for diabetes.

Publications
2016: The many faces of the autophagy machinery: LAP as a critical regulator of inflammation

**Challenge**
Genome-wide association studies (GWAS) have consistently highlighted autophagy machinery genes as risk loci for systemic lupus erythematosus (SLE), an autoimmune disease characterized by the recognition of, and reaction against, self-antigens. However to date, how the autophagy machinery functions in preventing SLE and other autoimmune pathologies has remained undetermined.

**Advance**
IRP researchers, led by Jennifer Martinez, Ph.D., discovered that LC3-associated phagocytosis (LAP), not canonical autophagy, was required to prevent the development of SLE in mice. They demonstrated that LAP exerts this protective effect by facilitating the efficient clearance of dying cells, preventing the production of inflammatory cytokines and the subsequent development of SLE symptoms.

**Impact**
The characterization of LAP as a critical regulator of inflammation in response to dying cells provides us with a greater understanding of the mechanisms underpinning the autoimmune reaction that is characteristic of SLE. In addition to gaining a greater understanding of how the disease develops, this discovery may lead to the development of anti-inflammatory therapeutics that specifically target LAP, while leaving the quality control mechanisms of canonical autophagy unaffected. Looking to the future, further GWAS analysis could lead to the identification of other autoimmune and autoinflammatory pathologies that are associated with LAP deficiencies.

**Publications**

2015: Traumatic brain injury: Linking a key protein to long-term complications

**Challenge**
Individuals with traumatic brain injury (TBI) are more likely to experience ongoing neurological complications such as post-concussive disorder (PCD), post-traumatic stress disorder (PTSD), and depression, and they are also more likely to develop chronic traumatic encephalopathy (CTE), a progressive brain degeneration that leads to dementia. However, there is currently no way to identify which people are at greatest risk for developing chronic symptoms from TBI.

**Advance**
IRP researchers led by Jessica Gill, Ph.D., R.N., hypothesized that a protein, tau, linked to Alzheimer’s and Parkinson’s diseases might play a role in post-TBI complications, but tau concentrations in the blood of patients who experience chronic symptoms or negative effects of TBI have proven difficult to measure.
Using a novel and ultra-sensitive technology, about 1,000 times more sensitive than conventional methods of measurement, the researchers were able to measure levels of tau months and years after military personnel had experienced TBI. The team found elevated tau levels in the blood samples of military participants with a history of TBI compared with participants who had never suffered a TBI, and the elevated tau levels were shown to be associated with chronic neurological symptoms.

**Impact**
This finding provides an insight into the underlying biology of TBI and could lead to new strategies for mitigating TBI’s debilitating symptoms. By using a new, ultrasensitive immunoassay technology, doctors and researchers can now more easily measure tau, clarify its role in long-term complications of TBI, and potentially use this information to better predict long-term outcomes and effective treatments.

**Publications**

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**2015: Designing a new method for live albumin labeling and lymphatic imaging**

**Challenge**
There is currently no non-invasive method for locating the sentinel lymph nodes (LNs), so named as the first lymph nodes likely to be reached from any cancer metastasis. Unable to examine LNs, doctors are hindered in accurate tumor staging and effective patient management.

**Advance**
IRP researchers, led by Xiaoyuan (Shawn) Chen, Ph.D., created a method to locate successfully the sentinel lymph nodes in three animal models: hind limb inflammation, orthotopic breast cancer, and metastatic breast cancer. In each model, the lymph nodes are distinguished by 18F-labeled Evans blue dye, a strong fluorescence signal and a high-intensity PET signal.

**Impact**
The new method’s excellent image quality, easy preparation, multimodality, and biosafety guarantee clinical translation to map sentinel lymph nodes and provide guidance during surgery.

**Publications**
2014: Finding new pathways in accelerated aging disorders

Challenge
Why does neurodegeneration develop in certain accelerated aging disorders, but not in others? Currently available treatments may slow disease progression, but the search continues for therapies that can halt or reverse the damage caused by neurodegenerative diseases.

Advance
IRP researchers led by Vilhelm A. Bohr, M.D., Ph.D., found an abnormality in the energy-supplying cell organelles called mitochondria across several accelerated aging disorders characterized by neurodegeneration. The team pinpointed the cause of the abnormality as a loss of central metabolites triggered by genome instability, and they demonstrated that adding the missing metabolites could restore proper function.

Impact
Dr. Bohr’s research highlights a new pathway that connects genome instability with mitochondrial dysfunction and provides new targets for developing therapeutic interventions for neurodegenerative diseases that currently have no cure.

Publications

2014: Identifying humans’ oldest animal relatives provides insights into the genetics of evolution

Challenge
Early evolution in animals and the molecular innovations that drove increased diversity (and complexity) is only partly understood. One of the main knowledge gaps relating to those early yet critical events was the lack of whole-genome sequencing data from the last non-bilaterian animal phylum without a sequenced genome: Ctenophora, or the comb jellies.

Advance
IRP researchers led by Andy Baxevanis, Ph.D., sequenced and analyzed the genome of a comb jelly, Mnemiopis leidyi, and found that comb jellies, which possess complex cell types such as neurons and muscle cells, are our oldest animal relatives—even predating the sponge, a simple animal without complex cell types. Interestingly, the group’s studies also show that a surprising number of genes implicated in human disease can be identified in the earliest animals, and that these early branching animal species may be ideal model organisms for investigating developmental processes inherent to all animals.

Impact
The use of comparative genomic techniques to study the comb jelly genome has shed light on what physical and structural features were present in the earliest animals, providing a new way of thinking...
regarding early animal evolution and evolutionary adaptation. These studies have also provided a solid foundation for looking beyond the traditional set of organisms currently used as experimental models, as basic biological discoveries arising from even our most distant animal relatives have great potential to give us keen insights about the human genome, as well as lay the groundwork for translational studies focused on specific human diseases.

**Publications**


**2013: Digging deeper into the basic principles of gene regulation**

**Challenge**

Transcription, the first step in determining which genes are expressed, is largely controlled by regulatory pieces of DNA. The global mapping of cellular regulatory elements—termed the ‘regulome’—has become possible thanks to advances in sequencing technologies, leading to important discoveries of how critical genes are regulated. However, researchers are still trying to chart how different regulatory elements interact, a critical piece in understanding gene transcription.

**Advance**

IRP researchers led by Rafael Casellas, Ph.D., generated maps depicting regulatory element interactions in both pluripotent embryonic stem (ES) cells and differentiated B lymphocytes. Unexpectedly, they found that genes with similar levels of expression in both cell types are often controlled by different regulatory elements, a finding that hints at the importance of tissue specificity in controlling gene expression.

**Impact**

The new interaction maps provide a rich resource for the scientific community, enabling the assessment of transcription regulation on a genome scale and allowing researchers to better study genes of therapeutic interest.

**Publications**

2012: Exposing “silent” heart attacks through novel imaging techniques

Challenge
Each year, about 1.2 million people in the U.S. have heart attacks, but not all heart attacks are visible with electrocardiography (EKG). Rapid and accurate methods to detect and manage “silent” heart attacks are needed to speed diagnosis and ensure timely treatment.

Advance
IRP scientists led by Andrew E. Arai, M.D., pioneered the use of non-invasive magnetic resonance imaging (MRI) to accurately detect and respond to unrecognized myocardial infarctions.

Impact
For the first time, physicians are able to detect, monitor, and treat heart attacks that patients may not even know had occurred. Early intervention in this type of cardiac damage can reduce the likelihood of subsequent cardiac events, including heart failure.

Publications

2012: Open your eyes to the power of image-based online searching

Challenge
Illustrations in medical literature contribute greatly to understanding complex biomedical concepts—for researchers, scientists, and the lay public alike. However, bibliographic databases are mostly text-based; hence the need for systems that deliver citations enriched by visual material, for example, radiographic images, photographs, sketches, graphs, or charts.

Advance
IRP researchers Dina Demner-Fushman, M.D., Ph.D., and Sameer Antani, Ph.D., led the development of Open-i (pronounced “open eye”), a novel open-access biomedical image search engine. In addition to image search capabilities, Open-i also provides outcome—or “take away”—statements extracted from a collection of 250,000 open access articles and 1 million illustrations in the biomedical literature hosted at the National Library of Medicine’s PubMed Central repository.

Impact
As the first production-quality system of its kind in the biomedical domain, Open-i enables medical professionals and the public to access both highly relevant visual information and key outcome statements from biomedical publications. Just a few months after public release, the site had more than 5,000 unique visitors per day and was ranked 382nd in the world (among 30 million Web sites).

42 https://irp.nih.gov/accomplishments/exposing-silent-heart-attacks-through-novel-imaging-techniques
Publications

2012: Visualizing coronary artery disease

Challenge
Coronary artery disease (CAD) is the most common type of heart disease and the leading cause of death in the United States, responsible for 400,000 deaths each year. Currently, no single test can detect CAD.

Advance
IRP researchers Khaled Abd-Elmoniem, Ph.D., and Ahmed Gharib, M.D., developed a more sensitive way to obtain images of the coronary vessel wall. The new technique is called "time-resolved acquisition of phase-sensitive dual-inversion recovery" (TRAPD) imaging and produces higher-quality results than conventional single-image methods.

Impact
TRAPD imaging provides better arterial wall visualization and quantitative assessments of coronary arteries, allowing for sensitive vessel wall thickness measurements that can distinguish CAD risk factors. The technique could eventually help identify individuals at risk for CAD and allow earlier access to treatments that relieve symptoms, reduce complications, and save lives.

Publications

2010: Finding independent roles for different cellular ESCRTs

Challenge
The cellular cleanup machinery includes a series of molecules called Endosomal Sorting Complex Required for Transport (ESCRTs) whose job it is to identify and flag proteins destined for liposomal processing and removal from the cell. How the ESCRT complexes assemble and function at a mechanistic level was poorly understood.

Advance
IRP researchers led by Dr. Jim Hurley reconstituted the ESCRT process and destruction of target proteins within the cell using a system of purified proteins and synthetic lipid vesicles. The team visualized the reaction using fluorescent ESCRT complexes and showed that each ESCRT plays a distinct and different role in the process. Their observations explained the ways ESCRTs direct protein flagging and transport to the cellular membrane, as well as the actual excision of the protein from within the structure—all without themselves being consumed within the reaction.
**Impact**
This study was one of the most complex reconstitutions of a membrane biology process ever undertaken, involving a total of 15 different proteins. It culminated in the discovery of the ESCRT bud neck assembly, which is now a target of further investigation.

**Publications**

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**2010: The Teaching Tool: A digital cervix for colposcopists**

**Challenge**
Colposcopy—examination of the cervix with a specialized microscope—is a widely used diagnostic technique for cervical cancer, a disease that affects nearly a quarter of a million women in the U.S. There is an ongoing need for effective knowledge assessment in this area, both for medical professionals in training and working clinicians seeking to advance their skills. Since colposcopy is image-based, an image-based assessment allowing for interaction with the images would be ideal.

**Advance**
IRP researchers led by Rodney Long, M.A., in collaboration with colleagues at the American Society for Colposcopy and Cervical Pathology (ASCCP), have developed the Teaching Tool, an interactive online assessment system for medical professionals in the field of colposcopy. This system uses cervicography images to simulate views of the uterine cervix as seen through a colposcope, and includes two assessment exams given by the ASCCP: one for medical professionals in training, and the other for established clinicians.

**Impact**
Since its release in 2010, the Teaching Tool has been used nationwide in more than 100 Resident Programs in Ob/Gyn and Family Practice, and at institutions such as the Mayo Clinic, Georgetown University, Baylor College of Medicine, and Duke University Medical Center. The tool has been used to give more than 1,000 exams to physicians in training and over 200 established medical professionals who use colposcopy in their practices.

**Publications**

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**2008: Diseases with no diagnosis: Providing relief for the rare and unknown**

**Challenge**
For individuals with rare and unknown diseases, there is no greater goal than an accurate diagnosis leading to possibilities of therapeutic relief. Doctors and scientists have long recognized the path to diagnosis as an opportunity to learn more about human disease. A program aimed at providing answers and insight could help both patients and researchers.
Advance
The NIH Undiagnosed Diseases Program (UDP) was established in 2008 and has since seen more than 150 patients a year. The success of the program is illustrated best through the discovery and diagnosis of rare disorders, such as when IRP researcher William A. Gahl, M.D., Ph.D., and colleagues uncovered a rare arterial calcification disease. By conducting clinical, radiographic and genetic studies in three families, the researchers eventually identified a novel gene mutation that causes a protein deficiency.

Impact
The UDP has received thousands of applications since opening, with approximately 10 percent of the program’s patients receiving a full diagnosis, and a further 30 percent gaining partial diagnosis. The researchers of the UDP continue to work tirelessly to discover the cause of those ailments still undiagnosed, along the way finding new biochemical, genetic and molecular pathways, and furthering our knowledge of human disease.

Publications
Press Release: NIH Launches Undiagnosed Diseases Program


1985: First electronic medical record to support clinical research

Challenge
As clinical trials become more complex, with patients often seeing multiple study professionals including specialists, pharmacists, nurses, and others, it has grown increasingly difficult to accurately track patient information and study results over time. A way to accurately record patient information in an accessible and secure database was needed.

Advance
NIH Clinical Center staff led by Thomas Lewis, M.D., adapted a first-in-class, hospital-wide electronic medical record (EMR), which allowed for the collection of data in an outpatient clinical trial. The EMR allowed researchers to structure data (fixed- and variable-length) that was automatically encoded after being entered directly by physicians and nurses at the time of patient contact, using procedures already familiar to them through routine patient care.

Impact
This novel hospital-based EMR was the first to be adapted in support of a clinical trial. By using an electronic data collection system, protocol data was improved in accuracy, completeness, and timeliness, at very low marginal costs.

Publications