

A Decade of Innovation
in Rare Diseases

2005
2015





A Decade of Innovation in Rare Diseases

2 Introduction

The Orphan Drug Act: Crucial Incentives for Continued Advances against Rare Diseases

4 **Chronic Myelogenous Leukemia:** Scientific Advances Propel New Treatment Options for Patients

Spotlight: Neonatal-Onset Multisystem Inflammatory Disease

7 **Chronic Lymphocytic Leukemia:** New Era of Targeted Therapies

Spotlight: Mucopolysaccharidosis Type IVA

10 **Pulmonary Arterial Hypertension:** Slowing Progression and Keeping Patients Active

Spotlight: Homozygous Familial Hypercholesterolemia

13 **Hereditary Angioedema:** Putting Disease Management in the Hands of Patients

Spotlight: Huntington's Disease

16 **Cystic Fibrosis:** Attacking the Symptoms and the Cause

Spotlight: Gaucher Disease

19 Continued Progress for Patients with Rare Diseases

Introduction

Rare diseases are one of the most scientifically complex health challenges of our time. There are currently 7,000 known rare diseases, half of which affect children.¹

Although these conditions are defined in the United States as being rare because each affects fewer than 200,000 Americans, they are more common than the descriptor of “rare disease” suggests when combined.² Thirty million Americans, or 1 in 10, and an estimated 350 million people worldwide are living with a rare disease.^{3,4}

Unfortunately, rare diseases often are difficult to diagnose, and in many cases, few or no treatment options are available. Approximately 80% of rare diseases are caused by abnormalities in a person’s genes.⁵ These genetic abnormalities may be passed down from parents’ genes or

caused by mutations or changes to a person’s DNA during his or her lifetime.⁶ Because of the rarity of each disease itself, however, much remains unknown about the underlying causes and the clinical course of many rare diseases. Even within a particular rare disease, there can be many variations or subtypes resulting in different clinical manifestations and disease progression. There is an urgent need for continued research to map the genes responsible for rare diseases, identify genetic and other biologic anomalies that contribute to these conditions, and understand the natural history of rare diseases to inform the development of potential therapies.

RARE DISEASES by the numbers

RARE DISEASES AFFECT
30 MILLION
AMERICANS

THAT’S 1 IN 10



APPROXIMATELY
7,000
DIFFERENT RARE DISEASES
EXIST TODAY


THE FDA HAS APPROVED
NEARLY 500 ORPHAN DRUGS
SINCE THE PASSAGE OF
THE ORPHAN DRUG ACT



IN THE LAST 5 YEARS



OF ALL NEW DRUG
APPROVALS WERE FOR
RARE DISEASES


80% OF RARE
DISEASES
ARE GENETIC IN ORIGIN



APPROVED TREATMENTS
ARE AVAILABLE
FOR ONLY **5%** OF
ALL RARE DISEASES

THERE ARE
MORE THAN

450
MEDICINES
IN DEVELOPMENT
FOR RARE DISEASES

The development of drugs to combat these conditions is particularly challenging for several reasons. Knowledge gaps about the causes and clinical progression of a given rare disease make it difficult to determine the best strategy for targeting the condition and compound the inherent complexities of developing medicines. For example, clinical trials are an important part of the drug development process, but a lack of understanding of a disease can make it difficult to design and conduct clinical trials. Furthermore, the small patient populations in rare diseases often make it difficult to recruit a sufficient number of patients to participate in clinical trials and gain statistically significant results. This issue is particularly problematic when trying to address rare diseases that have a significant impact on children given that children comprise an even smaller percentage of the overall population.⁷

Despite the many scientific hurdles in the development of medicines to treat rare diseases, America's biopharmaceutical researchers have leveraged new technologies and the growing scientific understanding of many rare diseases to develop groundbreaking therapies over the past ten years. The Orphan Drug Act, first passed in 1983, has proven instrumental in this progress and continues to provide important incentives for the research and development of innovative new treatments for rare diseases (See sidebar: The Orphan Drug Act). Many of these medicines are transforming the treatment of diseases where few or no treatment options existed previously. In the last decade alone, more than 230 new orphan drugs were approved by the U.S. Food and Drug Administration (FDA).⁸

Yet, despite this remarkable progress, only 5% of rare diseases today currently have available treatment options and much work remains.⁹ A recent PhRMA report found there are currently more than 450 orphan drugs in development, offering patients more hope than ever before. A major area of this research targets rare cancers, accounting for more than one-third of all rare disease medicines in development. Other top research areas for rare diseases include genetic disorders, neurological conditions, infectious diseases, and autoimmune disorders.

This report seeks to highlight the significant progress made over the past decade in a broad range of disease areas, representing conditions that vary widely in terms of prevalence, availability of treatment options, and patient populations affected.¹⁰ Treatment advances covered in depth include those seen in chronic myelogenous leukemia, chronic lymphocytic leukemia, pulmonary arterial hypertension, hereditary angiodema, and cystic fibrosis. In addition, the report spotlights several rare diseases where major milestones have transformed treatment for patients.



The Orphan Drug Act: Crucial Incentives for Continued Advances against Rare Diseases

Biopharmaceutical research companies, academic researchers, patient groups, and others are applying the growing understanding of the causes of rare diseases to speed the development of new treatments for patients. The Orphan Drug Act of 1983 has been and continues to be an important force in driving treatment innovation for rare diseases.

The Orphan Drug Act created economic incentives to promote the development of new treatments for rare diseases, defined generally as those conditions affecting fewer than 200,000 people in the United States. The incentives include 7 years of market exclusivity, tax incentives for certain R&D costs, and user fee waivers.¹¹ Orphan drugs are also eligible for "fast track" FDA review, which expedites the review process.¹² As of December 31, 2014, the FDA had granted the orphan drug designation to 3,273 potential therapies.¹³

The Orphan Drug Act has been a great success, as demonstrated by the nearly 500 orphan drugs approved since its passage, with 233 of those approvals in the last decade alone.¹⁴ In contrast, the FDA had approved fewer than 10 orphan drugs in all of the 1970s before the Act was passed.¹⁵ Moreover, research demonstrates that most of the recent approvals have been for diseases with fewer than 10,000 patients demonstrating the research community's commitment to meeting the needs of small patient populations.¹⁶

Unprecedented scientific potential, combined with appropriate incentives, make this a promising time for many patients with rare diseases.



Chronic Myelogenous Leukemia (CML): Scientific Advances Propel New Treatment Options for Patients

Continued advances in the treatment of CML offer close to normal life expectancy for patients

QUICK FACTS

- CML is a rare form of blood cancer that most commonly affects adults in their 40s and 50s.¹⁷
- In patients with CML, abnormal blood cells (leukemia cells) crowd out normal white blood cells, red blood cells, and platelets, preventing the body from carrying out normal cellular and immune functions.¹⁸
- Approximately 5,900 cases of CML are diagnosed each year in the U.S.¹⁹

A Scientific Breakthrough Transforms the Treatment Of CML

A decade ago, the treatment of CML had been dramatically transformed by a new class of medicines known as tyrosine kinase inhibitors (TKIs).^{20,21} TKIs are targeted therapies developed to treat cancer at the cellular level by affecting biologic pathways specific to cancerous cells. Imatinib was the first TKI to be approved by the FDA in 2001 and was the

result of decades of research seeking to uncover the biological mechanisms associated with the “Philadelphia Chromosome”—an abnormality in chromosome 22 found in 95% of CML patients. This abnormality is caused when portions of chromosomes 9 and 22 break off and trade places. This results in the fusion of a gene on chromosome 9 with another gene

on chromosome 22, creating a “BCR-ABL” fusion gene. This fusion gene is associated with changes in protein tyrosine kinase activity that contribute to the growth and accumulation of leukemia cells in CML. Once researchers understood this biological pathway, they were able to develop a targeted treatment to inhibit the tyrosine kinase protein and stop the proliferation of leukemia cells.^{22,23}



Before the introduction of this novel medicine, only 30 percent of CML patients survived to 5 years after diagnosis. After the introduction of imatinib, the 5-year survival rate nearly tripled.^{24,25} Not only did imatinib dramatically improve survival rates and transform the treatment of CML, but it represented a complete paradigm shift in the treatment of cancer more broadly. Imatinib demonstrated that if researchers could understand the biological mechanisms contributing to cancer, then medicines could be specifically designed and targeted to interfere with these mechanisms. Ultimately, this meant that medicines could be targeted to treat cancer without harming healthy cells and thereby minimizing side effects. In cancer, where chemotherapy had been the primary mode of treatment, this was truly game-changing for patients.²⁶

The introduction of the first TKI had truly revolutionized treatment for CML patients a decade ago. However, there still remained a need for additional treatment options as imatinib did not work for everyone and in some cases, patients who may have responded initially to the drug developed resistance later on.²⁷

Spotlight: Neonatal-Onset Multisystem Inflammatory Disease

Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological cutaneous articular (CINCA) syndrome, is one of three types of rare, inherited autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS). CAPS are caused by mutations in the *CIAS1/NLRP3* gene. Of the three CAPS subtypes, NOMID is the most severe. The disease is extremely rare, with approximately 100 cases reported worldwide.ⁱ However, the actual prevalence of the disease is unknown because some symptoms of NOMID resemble those associated with other disorders, resulting in challenges in diagnosis. NOMID presents during infancy or early childhood and causes fever, rash, and disease of the joints and central nervous system.ⁱⁱ When left untreated, it can cause progressive hearing and vision loss, cognitive impairment, and joint deformity.

In 2013, the FDA approved anakinra, originally approved for the treatment of rheumatoid arthritis, as the first and only therapy for NOMID.ⁱⁱⁱ Anakinra works by blocking the activity of the inflammation-causing interleukin-1 protein, which is overproduced in patients with NOMID.^{iv} Before approval of this treatment, an estimated 20% of children with NOMID would not reach adulthood.^v When diagnosed and treated, today's targeted treatments may allow many children with NOMID to live near-normal lives.^{vi}



A Decade Of Continued Advances Against CML

Today, an arsenal of additional targeted therapies is available for patients with CML, many of which are particularly effective in instances where mutations may have rendered imatinib ineffective. Researchers have identified more than 90 point mutations associated with the BCR-ABL gene, and among these, 40 have been biologically characterized.²⁸ Subsequent generation TKI medicines have been developed to treat many of these mutated forms of the BCR-ABL gene in patients resistant or intolerant to imatinib.²⁹ These second and third generation TKIs include dasatinib, nilotinib, bosutinib, and ponatinib.³⁰ By identifying the underlying genetic mutation that leads to drug resistance, physicians are able to identify the subsequent generation TKI that is most appropriate for the patient given his or her genetic profile. Researchers are also exploring use of TKIs in combination with other cancer-fighting agents.³¹

As knowledge of the underlying disease pathway has grown, researchers have also identified a new mechanism of action for combatting CML. In 2012, the FDA approved a new, first-in-class treatment called omacetaxine mepesuccinate, which was approved for the treatment of adult patients with chronic- or accelerated-phase CML with resistance and/or intolerance to two or more TKIs.³² This new medicine inhibits the synthesis of onco-proteins like BCR-ABL.³³ Because it does not require binding to BCR-ABL, it is not affected by mutations in the BCR-ABL gene that may cause resistance to TKI treatment.

The introduction of the first TKI nearly 15 years ago marked a transformational first step in the treatment of CML. The decade that followed, however, led to the development of medicines able to challenge genetic mutations and resistance to previous therapies, offering further survival gains for patients. Today, CML patients are living close to normal life spans thanks in large part to a greater understanding of the biological basis of this disease and continued development of targeted therapies to treat it.³⁴

CHRONIC MYELOGENOUS LEUKEMIA

Then: 2005

- Imatinib, the first tyrosine kinase inhibitor (TKI), revolutionized the treatment paradigm for patients, nearly tripling the odds of survival, by targeting cancer at the cellular level.
- But, some patients did not respond or could not tolerate imatinib. And still other patients, after initially responding to imatinib, developed resistance later on. For these patients there remained a substantial need for additional treatment options.

Now: 2015

- Additional targeted therapies are able to effectively treat many of the recently identified mutated forms of CML by disrupting signals that lead to cancer cell growth.
- A wide range of therapeutic options allows for more tailored treatment plans adapted to each patient's particular genetic profile.
- Today, CML patients are living close to normal life spans.



Chronic Lymphocytic Leukemia (CLL): New Era of Targeted Therapies

A new generation of targeted therapies improves quality of life and extends survival for patients

QUICK FACTS

- CLL is a rare form of blood cancer that typically progresses more slowly than acute types of leukemia.³⁵
- CLL affects an estimated 3 out of 100,000 people in the United States and most often occurs after middle age and is rarely found in children.^{36, 37}
- In patients with CLL, abnormal lymphocytes are produced and accumulate in the body. Lymphocytes are white blood cells that play an important role in helping the immune system fight infection. Accumulation of abnormal lymphocytes weakens the immune system.^{38, 39}
- As their immune system weakens, CLL patients may experience swelling of the lymph nodes, debilitating fatigue, and an increase in fever and infections.⁴⁰

CLL: A Form of Cancer Characterized by Compromised Immunity

CLL patients struggle to fight infection because abnormal lymphocytes—also referred to as leukemia cells in CLL—crowd out healthy blood cells. This suppresses the immune system and can pose challenges to using some types of medicines to treat CLL patients.⁴¹

Historically, chemotherapy has been the predominant first-line treatment for CLL. Although chemotherapy is effective for many patients, it can result in a variety of potential side effects, including suppression of the immune system.⁴² In CLL patients, who already have compromised immune

systems resulting from the nature of their disease, there was a significant need for additional treatment options that did not have some of these side effects.⁴³

A paradigm shift had already begun in cancer therapy over a decade ago, with a pivot toward medicines that specifically target cancer cells. In 2001, a targeted therapy for chronic myelogenous leukemia (CML) called imatinib generated excitement among CLL researchers because its success provided support for the concept that a medicine could be designed to interfere with the underlying biological processes causing a particular cancer. This success encouraged researchers who were embarking on a journey to understand the underlying biology driving cancer in CLL.⁴⁴

Targeted Therapies in CLL: Shifting Away from Traditional Chemotherapy

Over the last decade, a wide variety of treatment options have become available to CLL patients. These advances were primarily based on a greater understanding of the underlying biology of the disease, which enabled researchers to explore new areas beyond chemotherapy, including use of monoclonal antibodies (mAbs), tyrosine kinase inhibitors (like imatinib), and other targeted therapies, as well as other forms of treatment.⁴⁵

One of the first major advances happened in 2010, when the FDA approved a novel course of combination treatment that was shown to put many patients into remission for several years. The regimen, known by the acronym FCR, includes the use of two chemotherapy agents—fludarabine and cyclophosphamide—in combination with rituximab, a mAb that binds to the surface of cancer cells, making it easier for a patient's immune system to identify the cells and attack them.⁴⁶ Although this regimen is often considered first-line treatment, CLL patients who have severely weakened immune systems may not be able to tolerate chemotherapy-based regimens like FCR.⁴⁷ For this reason, additional treatment options were still very much needed.

New insight into the biological pathways of the disease has led to therapies that target the mechanisms by which CLL cells proliferate. For example, scientists discovered that a pathway called the B-cell receptor (BCR) pathway is abnormal in CLL, allowing for the survival and proliferation of CLL cells. Researchers have developed therapies that inhibit proteins involved in the BCR pathway, thus halting the progression and development of CLL.⁴⁸ Two oral medicines called BCR pathway inhibitors were approved in 2014 and have demonstrated long-lasting remission for patients with minimal side effects. The first, ibrutinib, targets Bruton's tyrosine kinase, a protein that is essential in the proliferation and survival of CLL cells.

Another BCR pathway inhibitor, idelalisib, acts by inhibiting a different part of the BCR pathway than that targeted by ibrutinib.⁴⁹ CLL patients today finally have treatment options that are free of the immunosuppression risks inherent of chemo-based therapy, thus providing improved survival and better quality of life.⁵⁰

Spotlight: Mucopolysaccharidosis Type IVA

Mucopolysaccharidoses (MPS) are genetic lysosomal storage diseases caused by the body's inability to produce specific enzymes. One in 25,000 babies born in the United States will have some form of MPS, but it is estimated that only 800 patients in the United States have mucopolysaccharidosis type IVA, also known as morquio A syndrome.^{vii} People with this rare disorder have a genetic mutation in the GALNS gene, which reduces the body's GALNS enzyme activity. The GALNS enzyme is essential to breaking down sugar molecules called mucopolysaccharides.^{viii} Mucopolysaccharides that are not completely broken down remain stored in cells and commonly cause musculoskeletal or respiratory dysfunction and significant limitations in mobility, endurance, and breathing.^{ix}

February 2014 marked a new era in treatment of the disease as the FDA approved the first treatment for Morquio A Syndrome. Elosulfase alfa works by replacing the missing GALNS enzyme and represents an important treatment advance as it addresses the condition on a cellular level to restore cell function. The drug has been shown to improve endurance, mobility, and overall quality of life for patients with the disease.^x

Importantly, the FDA recommends use of idelalisib in combination use with rituximab as a second-line therapy for patients who may not be able to take rituximab alone.⁵¹ Researchers believe the combination of BCR pathway inhibitors with monoclonal antibodies such as rituximab holds promise in eliciting even better treatment responses in patients.⁵² Initial studies indicate that the addition of rituximab to irubitinib may significantly affect survival in CLL. Looking forward, researchers are further energized by the potential of future combinations of BCR inhibitors and other targeted therapies.⁵³

“People have been waiting for drugs like these... I think what people like to envision for CLL is non-cytotoxic therapy. These new agents are going to raise a lot of interesting questions about potential combinations that in the long run may get us away from the use of cytotoxic chemotherapy entirely.”

— Susan O’Brien, M.D., The University of Texas MD Anderson Cancer Center

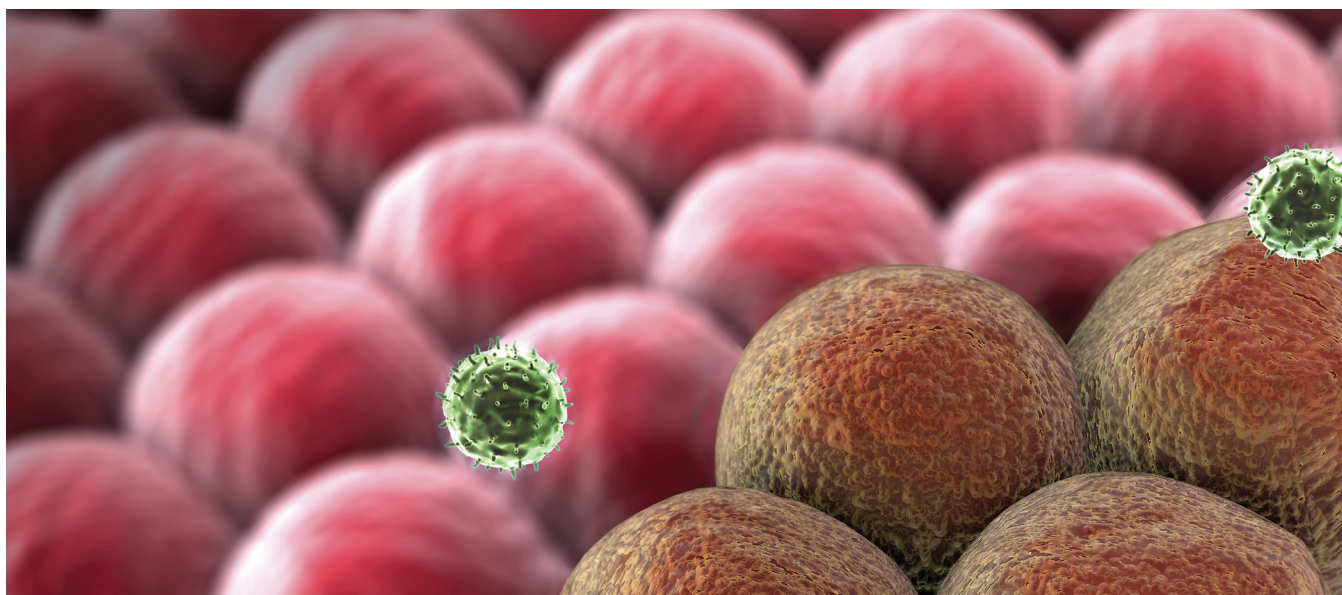
CHRONIC LYMPHOCYTIC LEUKEMIA

Then: 2005

- Chemotherapy was the predominant first-line treatment for patients with CLL.
- CLL patients already have very weak immune systems, making it sometimes difficult to tolerate chemotherapeutic regimens that may weaken the immune system further.
- For patients with immune systems unable to tolerate chemotherapy, additional treatment options with fewer side effects were very much needed.

Now: 2015

- New targeted therapies seek to treat the root cause of the disease, resulting in lasting remissions for many CLL patients and without the immunosuppression risks common with chemotherapy.
- The use of novel B-cell receptor (BCR) pathway inhibitors and targeted monoclonal antibodies like rituximab is expanding treatment options for all patients, even those with more compromised immune systems.





Pulmonary Arterial Hypertension (PAH): Slowing Progression and Keeping Patients Active

Improvements in PAH treatment enable patients to more effectively manage the disease

QUICK FACTS

- PAH is a chronic disease that increases stress on the heart as a result of thickening and narrowing of arteries in the lungs.⁵⁴
- PAH results in breathlessness, chest pain, dizziness, fainting, and swelling of the arms or legs. In serious cases, PAH can cause heart failure.⁵⁵
- An estimated 15-50 per 1 million people in the United States are affected by PAH.⁵⁶

Limited Treatment Options Relieved Symptoms, Did Little to Improve Activity Levels

PAH is a progressive condition where the blood vessels that carry blood from the heart to the lungs narrow, or become damaged or blocked. This makes it difficult for blood to flow, which increases pressure in the blood vessels and causes the heart to work harder. This eventually weakens the muscles in the heart and, in some cases, may lead to heart failure. Because of these changes, patients have difficulty breathing and maintaining normal activity levels.^{57, 58}

A decade ago, patients had limited treatment options and many required lung transplants as their condition worsened.⁵⁹ It was only in recent years that physicians have been able to distinguish PAH from a variety of other similar, but distinct, forms of hypertension, which is important in determining the most appropriate form of treatment.⁶⁰ Most treatment options for PAH have traditionally targeted the symptoms of the disease, rather than the direct cause of blood vessel swelling and constriction. Oxygen therapy and diuretics provided some

short-term relief by reducing shortness of breath and fluid build-up.^{61, 62} Patients were also given blood thinners to help prevent and reduce blood clots, as well as calcium channel blockers to open blood vessels in the heart. However, these medicines did not fully address the root causes of the condition or extend the lives of patients.^{63, 64}

As scientists and physicians learned more about the underlying causes of PAH, more targeted forms of treatment were developed. For example, scientists determined that levels of a naturally occurring vasodilator called prostaglandin tend to be lower in patients with PAH.⁶⁵ Vasodilators help reduce blood pressure by promoting smooth muscle relaxation in the heart. An early synthetic form of prostaglandin, called prostacyclin, was found to help PAH patients by enlarging blood vessels, thus decreasing blood pressure in the heart. This first generation of prostacyclin therapy was delivered through a semi-permanent IV on a continuous basis. For some patients, the route of administration was challenging, had a negative impact on quality of life, and was sometimes associated with potential life-threatening complications such as sepsis and blood clots.^{66, 67}

Breakthroughs Lead to Improved Quality of Life, Slower Disease Progression

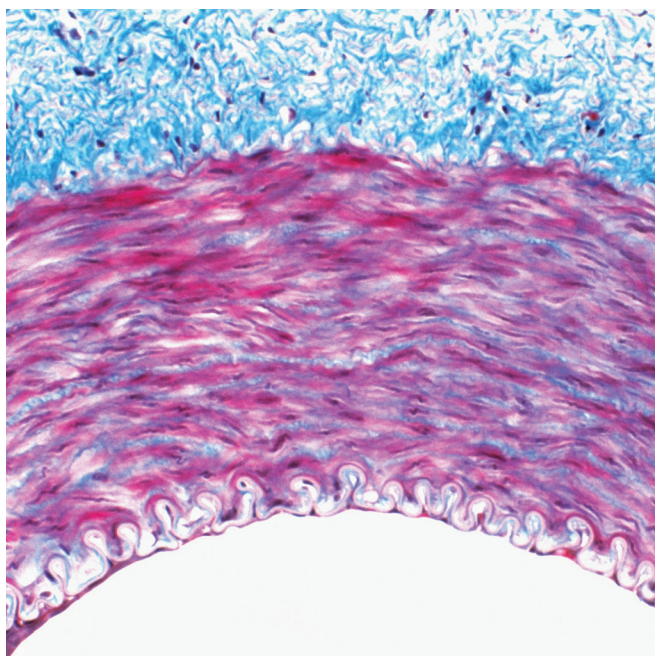
In the last decade, we have seen tremendous gains for patients with PAH. Continuing research and development has delivered several new medications, offering patients a variety of safer, more effective, and more convenient treatment options. The last decade also marked a substantial increase in our understanding of the causes of PAH, enabling biopharmaceutical researchers to apply that knowledge to the development of innovative treatments that combat the root cause of the disease.

Building on earlier advances, researchers learned that patients with PAH have an overabundance of endothelin-1 (ET-1), a peptide that causes blood vessels to constrict. A class of medicines called endothelin receptor antagonists (ERAs) marked an important advance in treating PAH by reducing the production of ET-1 and halting the constriction of blood vessels.⁶⁸ Ambrisentan, approved in 2007, is an ERA delivered intravenously or through injection.⁶⁹ Continued research and development led to the approval of an oral ERA, macitentan, in 2013, which was shown to slow disease progression and reduce morbidity from PAH.⁷⁰ These advances mark important milestones for patients, who now have a variety of treatment options that go beyond symptom management to address the underlying cause of PAH.

Spotlight: Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is an inherited genetic disorder affecting just 1 in 1 million Americans. HoFH patients lack the biological ability to remove low density lipoprotein cholesterol (LDL-C)—known as “bad cholesterol”—from the blood, leading to abnormally high levels of bad cholesterol in the body. The condition is rare, but extremely life-threatening for the few that inherit the disorder because it often leads to heart attack and death by age 30.^{xi, xii} Many patients with HoFH are treated with lipid-lowering therapies, as are other patients who aim to lower cholesterol levels. However, these treatments have generally not been sufficient to help HoFH patients achieve needed reductions in bad cholesterol—particularly those who have already experienced a cardiovascular event.^{xiii}

Two medicines were approved in recent years, providing important new options for managing this very serious condition. In combination with diet and other lipid-lowering treatments, both of these medicines have been found to significantly reduce bad cholesterol levels by as much as 50%. The FDA approved lomitapide, a once daily oral medication in 2012 and mipomersen sodium, a weekly injectable, in 2013. Both of the medicines work by impairing the creation of the lipid particles that lead to increased levels of LDL-C.^{xiv, xv} Prior to the availability of these new treatment options, patients often needed to try different treatment combinations to find the right course of therapy. These important advances reduce mortality and improve overall health by allowing patients to better manage their cholesterol levels.^{xvi}



Scientists also identified cyclic guanosine monophosphate (cGMP) as an effective drug target for PAH treatment, given that it regulates many cell functions, including vascular function and inflammation.⁷¹ Tadalafil, a once-daily oral treatment approved in 2009, inhibits a key enzyme that is known to break down cGMP.⁷² Decreasing the level of this enzyme leads to an increase in cGMP, enabling patients to breathe easier and maintain a higher level of physical activity.

In 2013, riociguat became the first approved treatment for PAH in a new class of drugs called soluble guanylate cyclase (sGC) stimulators. These molecules represent another way to increase the production of cGMP,⁷³ which helps relax the arteries and increase blood flow. As a result, blood pressure decreases, making it safer for patients to exercise and resume normal day-to-day activity.⁷⁴

Finally, researchers delved into important new ways for delivering synthetic forms of prostacyclins, which help enlarge blood vessels and reduce blood pressure. In 2009, an inhalable form of synthetic prostacyclin was approved, giving patients an easier, less invasive method for taking this type of treatment compared to earlier IV-administered methods.⁷⁵ In 2013, the FDA approved the first orally administered prostacyclin analogue.⁷⁶

For PAH patients, the past 10 years yielded novel therapies that not only manage symptoms but also slow disease progression—significant advances for a life-altering condition. In addition, research is underway exploring the use of medicines in combination earlier in the disease’s progression.⁷⁷

“This is the twelfth treatment for PAH, the third new therapy to be FDA approved in the last two months...To have this kind of advancement for PAH is extraordinary and speaks to the medical and research structure that has been built in this field.”

— Rino Aldrighetti, President and CEO, Pulmonary Hypertension Association⁷⁸

PULMONARY ARTERIAL HYPERTENSION

Then: 2005

- Standard of care was characterized by intravenous treatment aimed at reducing symptoms, not addressing root cause.
- Patients were required to limit physical activity to reduce their chances of a heart event.
- Patients were anxious of experiencing heart events or complications due to the lack of convenient and effective medications.

Now: 2015

- Inhaled and oral forms of prostacyclin treatment expand treatment options for patients.
- New treatments go beyond symptom management to treat the underlying cause of PAH.
- Patients are able to maintain active lifestyles with a reduced risk of serious heart events associated with PAH.



Hereditary Angioedema (HAE): Putting Disease Management in the Hands of Patients

Greater understanding of disease mechanisms yields effective and convenient treatment options for patients

QUICK FACTS

- HAE is a rare and potentially life-threatening inherited genetic disorder that causes edema (swelling) of the hands, feet, face, airways, and gastrointestinal tract.
- Gene mutations contribute to the development of HAE. Patients have one or more of these mutations, resulting in a variety of effects on the body, including impacting the body's ability to regulate blood-based systems involved in disease fighting, inflammatory response, and coagulation.
- As the condition is very rare, affecting 1 in 10,000 to 50,000 people, it is often under- or mis-diagnosed.⁷⁹

Historically, Options for Patients with HAE Were Limited to Treating Symptoms

HAE is a debilitating disease that causes edema in the body. Patients with HAE usually begin experiencing edema between ages 7 and 13 and have acute attacks of symptoms 6-11 times a year on average.⁸⁰ Patients who are not receiving

treatment may have an attack every 1-2 weeks. Most attacks occur spontaneously, meaning there is no trigger, although some may be triggered by factors such as anxiety, stress, dental procedures, or infections. Severe HAE attacks can

cause swelling of the throat, called laryngeal edema, as well as edema of the gastrointestinal tract. Laryngeal edema is particularly dangerous as it can cause death by asphyxiation in as many as 30% of people with HAE. Gastrointestinal edema can cause excruciating abdominal pain, nausea, vomiting, and diarrhea.^{81, 82}

Until recently, there were no medications available to specifically treat HAE, and patients often had to undergo surgeries to relieve severe symptoms.⁸³ Patients frequently received anabolic steroids to reduce the likelihood of an attack, but steroid use was accompanied by irreversible side-effects that were not well-tolerated, especially in female patients.⁸⁴ Anti-inflammatories were used to treat swelling, but were unable to address the root cause of HAE. Because of the limited number of treatment options, severe symptoms, including attacks, frequently led to hospitalizations, creating a significant physical, emotional, and economic burden on patients and their loved ones.⁸⁵



Novel Therapies Help Prevent or Lessen HAE Attacks

Today, patients have a range of treatment options when acute HAE attacks occur that were not available a decade ago. Better understanding of the underlying cause of HAE-induced inflammation has given scientists the keys to developing medicines that treat and prevent attacks at the source. Although available treatments do not cure this dangerous disorder, medicines provide important options to patients for reducing the severity of acute attacks.

Spotlight: Huntington's Disease

Huntington's disease (HD) is an inherited disorder that causes a progressive breakdown of nerve cells in the brain. Although patients with HD are born with the defective gene, symptoms generally do not appear until middle age—typically between the ages of 30 and 50. However, onset of HD can occur as young as the age of two. It is estimated that 1 in 10,000 Americans has the disease.^{xvii} HD has a significant effect on a person's functional abilities and usually results in movement, cognitive, and mental health disorders. Children developing HD rarely live to adulthood. Weakened HD patients generally succumb to pneumonia, heart failure, or other complications.^{xviii}

Chorea is a hallmark symptom of HD, characterized by involuntary movement that makes performing daily tasks difficult. Although there is no cure for Huntington's disease, recently approved treatments are helping patients manage symptoms and improve quality of life. The first treatment for HD, tetrabenazine, was approved by the FDA in 2008 and reduces involuntary movements by modifying chemical pathways in the brain. Tetrabenazine selectively inhibits vesicular monoamine transporter (VMAT)-2, a central nervous system enzyme, and depletes presynaptic dopamine, which lessens symptoms of chorea.^{xix} Lessening the burden of chorea for HD patients helps improve their overall quality of life and allows them to take part in normal daily activities.



HAE is most commonly caused by a defect in the genes that control a blood protein called the C1 inhibitor, which is important for controlling inflammation.⁸⁶ There are three types of HAE—types I, II, and III—each of which have similar signs and symptoms.⁸⁷ Typically, when the body is attacked by a pathogen or disease, the C1 inhibitor helps regulate proteins that control fluids released when the body fights an outside invader. For patients with the most common types of HAE, inadequate C1 inhibitor levels lead to an excess release of a peptide called bradykinin, which causes blood vessels to release fluids.⁸⁸ This influx of bradykinin leads to fluid build-up, dangerous swelling, and ultimately attacks of varying severity and duration.⁸⁹

Between 2008 and 2009, the FDA approved two intravenous C1 inhibitors containing human plasma that increase C1 inhibitor activity as a way to prevent HAE attacks.^{90, 91} In addition, the first injected HAE medicine, ecallantide, was approved in 2009.^{92, 93} Two years later, a self-administered injection that blocks bradykinin receptor sites and prevents the peptide from triggering fluid release was approved.⁹⁴ These medicines expanded treatment options for patients, allowing them to quickly treat an acute and potentially deadly HAE attack.

In 2014, the first plasma-free C1 inhibitor received approval as a self-injectable HAE treatment that decreases bradykinin production, which helps prevent swelling associated with fluid release.⁹⁵ In addition to being preventative, this medicine can be self-administered, giving patients the power to more conveniently manage their disease. This new medicine may also reduce complications from acute attacks. Self-injectable medicines such as these are offering HAE patients easier administration and allowing for more expedient action in cases of emergency.

Advances over the past decade have provided more effective options for managing HAE, thereby reducing patient and caregiver burden. As scientists continue to better understand the underlying causes of HAE, there is great potential for continued innovation that will revolutionize disease treatment and management.

HEREDITARY ANGIOEDEMA

Then: 2005

- Scientists had little knowledge of the underlying cause of HAE.
- No medications were approved in the U.S. specifically to treat HAE.
- Patients with HAE had limited options to relieve symptoms of an attack, and often were required to undergo invasive procedures to alleviate dangerous swelling.

Now: 2015

- New discoveries in the underlying cause of HAE have led to breakthroughs in both preventative and acute treatment options for patients.
- Several medications have been approved by the FDA in recent years to treat HAE by targeting the source of the disease.
- Patients are able to self-administer new injectable medications at home to halt acute HAE attacks.



Cystic Fibrosis (CF): Attacking the Symptoms and the Cause

Recent advances attack both the symptoms and root cause of cystic fibrosis and are transforming the lives of patients

QUICK FACTS

- CF is a life-threatening disease that primarily affects the lungs and digestive system.
- CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene which causes the body to produce thick, sticky mucus that clogs the lungs, pancreas, and other organs.⁹⁶
- An estimated 30,000 children and adults in the United States have CF, and each year 1,000 new cases are diagnosed.⁹⁷
- The life expectancy of a child with CF has doubled in the last 30 years due in part to treatment advances.⁹⁸

Step by Step Advances to Treat Symptoms of CF and Extend Life

In patients with CF the CFTR mutation causes an accumulation of thick, sticky mucus in parts of the body responsible for breathing and digesting food. In the lungs, this mucus blocks airways and results in a persistent cycle of inflammation, chronic bacterial infection, severe lung damage, and sometimes respiratory failure. In the pancreas, this mucus obstructs

the movement of digestive enzymes that are important for helping the body break down food and absorb nutrients.^{99, 100} Persistent coughing and wheezing, frequent lung infections, poor growth, slow weight gain, and difficulty moving bowels can make it hard for CF patients to remain active.¹⁰¹

Most patients with the disease are diagnosed as infants or in early childhood, and in the 1960s, life expectancy for most people with CF was just 10 years.¹⁰² Over the decades that followed, however, efforts to diagnose patients earlier and the development of comprehensive treatment programs that aggressively prevent and clear the buildup of mucus in the airways of CF patients helped to improve life expectancy.¹⁰³ By the 1990s, the FDA approved several medicines that could improve lung function for CF patients. These medicines included an inhaled antibiotic targeting *Pseudomonas aeruginosa*, the most common cause of infection for CF patients.¹⁰⁴

By 2004, with new treatments allowing better management of symptoms, life expectancy for patients with CF increased to the mid-30s.¹⁰⁵ Yet even with these advances, there was still substantial unmet medical need and opportunity to further extend and improve the lives of patients with CF.

Spotlight: Gaucher Disease

Gaucher disease is a genetic disorder that affects organs and tissue throughout the body. Between 1 in 50,000 to 100,000 people in the United States have some form of Gaucher disease. Type 1 is the most common form, affecting 6,000 Americans.^{xx, xxi} In patients with Type 1 Gaucher disease, mutations in the GBA gene prevent proper development of an enzyme that breaks down fatty substances.^{xxii} These fatty substances build up in the body, resulting in enlarged organs, particularly the liver and spleen. This buildup also results in bruising, clotting difficulties, fatigue, and weakening of the skeleton.^{xxiii} With appropriate treatment, type 1 Gaucher patients live close to normal life spans, making the availability of effective treatment options particularly important for successful disease management.^{xxiv}

A decade ago, available treatments for Type 1 Gaucher disease included enzyme replacement therapy (ERT) and substrate replacement therapy for patients unable to tolerate ERT. Although these treatments have proven to be important advances for patients suffering from Gaucher disease, patients today have a number of additional treatments available to them, offering different options for managing their disease.^{xxv}

- In 2010, the FDA approved velaglucerase alfa, the first alternative ERT for Gaucher patients in nearly 2 decades.
- The FDA approved taliglucerase alfa in 2012, the first approval of a drug produced by genetically engineered plant cells.^{xxvi, xxvii}
- And most recently in 2014, a new first-line oral therapy called eliglustat was approved as a long-term treatment for Type 1 Gaucher disease.^{xxviii} Eliglustat differs from ERT because rather than working by breaking down fatty deposits that build up in cells that cause the symptoms associated with the disease, eliglustat inhibits the accumulation of these fatty deposits in the first place.^{xxix} The availability of this medicine as a first-line oral treatment expands the treatment options for patients by providing an important alternative to intravenously administered medications.^{xxx}

The Last Decade: New Treatments Continue to Improve Survival and Quality of Life

Remarkable progress has been made over the past decade in both improving and extending the lives of patients with this debilitating disease. With earlier screening, improved treatments, and more comprehensive approaches to disease management, the median survival for a person with CF has increased to 37 years for women and 40 years for men. It is estimated that if mortality rates continue to improve along these lines, patients may live into their 50s.¹⁰⁶ Recent treatment advances are not just extending lives, but allowing CF patients to live healthier and more active lifestyles.

A key challenge for patients with CF is difficulty absorbing the necessary amounts of several important nutrients due to pancreatic insufficiency. In 2009, the first FDA-approved pancreatic enzyme replacement therapy (PERT) became available to CF patients to help digest and absorb food.^{107, 108} Although PERT had been used by patients prior to 2009, this approval marked the first treatment evaluated and assessed by the FDA. Since 2009, five additional pancreatic enzyme replacement therapies for CF have been approved in various formulations, providing a range of administration options for CF patients.^{109, 110} In 2010, the FDA also approved the first inhaled antibiotic for CF in more than a decade to treat respiratory tract infection, offering an additional, more convenient delivery system. The medicine is delivered via a portable nebulizer system in less than 3 minutes, reducing the burden for CF patients who often require 3 to 4 hours of breathing treatment daily.^{111, 112}

In addition to making advances in addressing the symptoms of the disease in recent years, researchers have made incredible progress in targeting the underlying causes of CF. The approval of ivacaftor in 2012 followed many decades of research seeking to identify and target the mutations in the CFTR gene that causes CF. This personalized medicine is from a class of medicines known as CFTR modulators and works by facilitating the proper flow of salt and water in and out of the cells lining the airways, leading to improved lung function.^{113, 114} The initial indication was limited to treating CF in patients who have a very specific mutation (G551D mutation). The FDA expanded the approval in 2014 after demonstrating effectiveness in patients with nine additional genetic mutations (R117H, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D).¹¹⁵ Today, the drug is in late-stage clinical trials for use both alone and in combination with another CFTR modulator to treat patients with the most common mutation found in CF patients.¹¹⁶

In the past decade, we have seen a revolution in the treatment and lives of CF patients. Patients today not only have a wide range of treatment options and strategies for managing their symptoms, but they also can look to a future where medicines are targeted specifically to the particular genetic mutations that cause their illness. New treatments on the horizon have the potential to not only continue to extend life expectancy, but also transform daily life for CF patients, allowing them to lead longer, healthier and more active lives.

CYSTIC FIBROSIS

Then: 2005

- Average life expectancy for CF patients was in the mid-30s.
- Although advances in treating and managing the disease had significantly improved life-expectancy for patients, more convenient treatment options were needed to better manage disease symptoms and further extend the lives of those with CF.
- Treatments were only able to address the symptoms of CF, but not the underlying cause of the disease.

Now: 2015

- Earlier screening and improved treatment contributed to an increase of life expectancy for patients. If mortality continues to decline at current rates, patients now may hope to live into their 50s.
- Improved delivery mechanisms for inhaled antibiotic breathing treatments are faster acting and can be delivered in less than 3 minutes with greater ease.
- FDA-approved pancreatic enzyme therapies aid with digestion and adsorption and help patients retain needed nutrients and maintain a healthier, more active lifestyle.
- For the first time, targeted therapies are available to address the underlying cause of CF, improving lung function for patients with a number of genetic sub-types.



Continued Progress for Patients with Rare Diseases

Over the past decade we have seen remarkable progress in the fight against rare diseases. In fact, in this period alone, more than 230 orphan drugs were developed by biopharmaceutical researchers and approved by the FDA.

The advances highlighted in this report demonstrate the many benefits new medicines have provided patients with rare diseases over the last decade. Scientific advances have transformed the lives of many patients by providing new treatment options which attack the underlying causes of orphan diseases or by providing a more effective means of fighting off disease complications and symptoms. For many patients suffering from a rare disease, new medicines have provided a treatment option where there had previously been none. Advances such as these made in recent years have come a long way in meeting the very diverse set of needs of patients with rare diseases, ultimately allowing many to live longer, more productive lives.

Even with this incredible progress however, just 5% of rare diseases have an available treatment option and much work remains to meet this significant unmet medical need.

Yet the development of therapeutic options for rare diseases is a challenging endeavor. Rare diseases are often complex and the underlying biological mechanisms that cause many of them are not well-understood. Additionally, the development of a medicine to target rare diseases can be further complicated by the small patient populations impacted by them. Enrolling patients in clinical studies and drawing conclusions about the

efficacy and safety of a treatment can also be challenging due to the small number of patients commonly involved.

Nevertheless, as researchers continue to build on recent breakthroughs and engage with the patient community, there is great promise for continued development of innovative medicines to treat rare disease and improve the lives of patients with these conditions. Advances in our understanding of the root causes of many diseases are enabling researchers to explore new targeted mechanisms for treatment. Policy and regulatory efforts to foster future research will be critical in overcoming the many scientific hurdles that are inherent of rare disease drug development and to continue transforming the lives of patients.

While there remains a significant need to develop new medicines for the many millions of patients currently lacking treatment options, the promise has never been greater.

References

1. Pariser, A; Yao, L. "Rare Diseases and Orphan Drugs." Pediatric Drug Development: Concepts and Applications. Edited by Mulberg, A, et al. 2013. 13:130-148. <http://onlinelibrary.wiley.com/book/10.1002/9781118312087>
2. National Institutes of Health. "Rare Diseases Clinical Research Network Fact Sheet." [http://report.nih.gov/nihfactsheets/Pdfs/RareDiseasesClinicalResearchNetwork\(ORDR\).pdf](http://report.nih.gov/nihfactsheets/Pdfs/RareDiseasesClinicalResearchNetwork(ORDR).pdf)
3. National Institutes of Health. "Rare Diseases Clinical Research Network Fact Sheet." [http://report.nih.gov/nihfactsheets/Pdfs/RareDiseasesClinicalResearchNetwork\(ORDR\).pdf](http://report.nih.gov/nihfactsheets/Pdfs/RareDiseasesClinicalResearchNetwork(ORDR).pdf)
4. The Global Genes Project. "RARE Diseases: Facts and Statistics." <http://globalgenes.org/rare-diseases-facts-statistics/>
5. The Global Genes Project. "RARE Diseases: Facts and Statistics." <http://globalgenes.org/rare-diseases-facts-statistics/>
6. National Institutes of Health: GeneEd. "Heredity/Inheritance Patterns." http://geneed.nlm.nih.gov/topic_subtopic.php?tid=5
7. U.S. Food and Drug Administration. "Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Disease." July 2014. <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/UCM404104.pdf>
8. U.S. Food and Drug Administration. Orphan Drug Designation and Approvals Database. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.
9. The Global Genes Project. "RARE Diseases: Facts and Statistics." <http://globalgenes.org/rare-diseases-facts-statistics/>
10. A Note on Methodology: Data in this report about the number of orphan drug designations and approvals are drawn from the U.S. Food and Drug Administration orphan drug product designation database. Data are current as of January 22, 2015.
11. U.S. Food and Drug Administration. "Orphan Drug Act, Relevant Excerpts." <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm>
12. U.S. Food and Drug Administration. "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics." May 2014. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>
13. U.S. Food and Drug Administration. Orphan Drug Designation and Approvals Database. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.
14. U.S. Food and Drug Administration. Orphan Drug Designation and Approvals Database. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.
15. U.S. Food and Drug Administration. Orphan Drug Designation and Approvals Database. <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.
16. Braun, M, et al. "Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years." Nature Reviews Drug Discovery. 2010. 9:519-522. <http://www.nature.com/nrd/journal/v9/n7/full/nrd3160.html>
17. National Organization for Rare Diseases. "Chronic Myelogenous Leukemia." <http://rarediseases.org/rare-disease-information/rare-diseases/byID/695/viewFullReport>

18. National Cancer Institute. "Chronic Myelogenous Leukemia Treatment." <http://www.cancer.gov/cancertopics/pdq/treatment/CML/Patient/page1>
19. American Cancer Society. "What are the key statistics about chronic myeloid leukemia?" <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-key-statistics>
20. Pray, L. "Gleevec: the Breakthrough in Cancer Treatment." *Nature*. 2008. 1(1):37. <http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565>
21. American Cancer Society. "Targeted therapies for chronic myeloid leukemia." <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-treating-targeted-therapies>
22. Pray, L. "Gleevec: the Breakthrough in Cancer Treatment." *Nature*. 2008. 1(1):37. <http://www.nature.com/scitable/topicpage/gleevec-the-breakthrough-in-cancer-treatment-565>
23. American Cancer Society. "Targeted therapies for chronic myeloid leukemia." <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-treating-targeted-therapies>
24. American Cancer Society. "Cancer Facts and Figures 2012." <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2012/>
25. Druker, B, et al. "Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia." *New England Journal of Medicine*. 2006. 355(23):2408-17. <http://www.nejm.org/doi/full/10.1056/NEJMoa062867>
26. Cleveland Clinic. "Top 10 Medical Innovations of 2014." <http://health.clevelandclinic.org/2014/01/top-10-medical-innovations-for-2014/>
27. Assouline, S; Lipton, J. "Monitoring response and resistance to treatment in chronic myeloid leukemia." *Current Oncology*. 2001. 18(2):e71-e83. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070714/>
28. Medscape. "Mechanisms of Resistance, Common BCR-ABL Mutations, and Monitoring Response to Treatment of CML." <http://www.medscape.org/viewarticle/575913>
29. Breccia, M; Alimena, G. "Second-Generation Tyrosine Kinase Inhibitors (Tki) as Salvage Therapy for Resistant or Intolerant Patients to Prior TKIs." *Mediterranean Journal of Hematology and Infectious Disease*. 2014. 6(1): e2014003. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3894843/>
30. American Cancer Society. "Targeted therapies for chronic myeloid leukemia." <http://www.cancer.org/cancer/leukemia-chronicmyeloidcml/detailedguide/leukemia-chronic-myeloid-myelogenous-treating-targeted-therapies>
31. Bhamidipati, P, et al. "Management of imatinib-resistant patients with chronic myeloid leukemia." *Therapeutic Advances in Hematology*. 2013. 4(2): 103–117. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629755/>
32. U.S. Food and Drug Administration. "FDA approves Synribo for chronic myelogenous leukemia." October 26, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm325895.htm>
33. Nicolini, F et al. "Omacetaxine mepesuccinate for patients with accelerated phase chronic myeloid leukemia with resistance or intolerance to two or more tyrosine kinase inhibitors." *Haematologica*. 2013. 98(7): e78–e79. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3696599/>
34. Gambacorti-Passerini, C, et al. "Multicenter Independent Assessment of Outcomes in Chronic Myeloid Leukemia Patients Treated with Imatinib." *Journal of the National Cancer Institute*. 2011. 103(7): 553–61. <http://www.ncbi.nlm.nih.gov/pubmed/21422402>

35. American Cancer Society. "What is chronic lymphocytic leukemia?" <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcl/detailedguide/leukemia-chronic-lymphocytic-what-is-cl>
36. American Cancer Society. "What are the key statistics for chronic lymphocytic leukemia?" <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcl/detailedguide/leukemia-chronic-lymphocytic-key-statistics>
37. National Organization for Rare Diseases. "Chronic Lymphocytic Leukemia." <http://rarediseases.org/rare-disease-information/rare-diseases/byID/858/viewFullReport>
38. American Cancer Society. "What is chronic lymphocytic leukemia?" <http://www.cancer.org/cancer/leukemia-chroniclymphocyticcl/detailedguide/leukemia-chronic-lymphocytic-what-is-cl>
39. National Cancer Institute. "Chronic Lymphocytic Leukemia Treatment (PDQ®)." <http://www.cancer.gov/cancertopics/pdq/treatment/CLL/Patient/page1>
40. U.S. National Library of Medicine, Medline Plus. "Chronic lymphocytic leukemia (CLL)." <http://www.nlm.nih.gov/medlineplus/ency/article/000532.htm>
41. National Cancer Institute. "Chronic Lymphocytic Leukemia Treatment (PDQ®)." <http://www.cancer.gov/cancertopics/pdq/treatment/CLL/Patient/page1>
42. Cleveland Clinic. "2014 Cleveland Clinic Top 10 Medical Innovations of 2014." October 16, 2013. <http://my.clevelandclinic.org/about-cleveland-clinic/newsroom/releases-videos-newsletters/2013-10-16-cleveland-clinic-names-top-10-medical-innovations-for-2014>
43. Wendtner, CM. (April 25, 2012). Recent progress in the treatment of CLL. Medscape Multispecialty. <http://www.medscape.org/viewarticle/762258>
44. Cleveland Clinic. "2014 Cleveland Clinic Top 10 Medical Innovations of 2014." October 16, 2013. <http://my.clevelandclinic.org/about-cleveland-clinic/newsroom/releases-videos-newsletters/2013-10-16-cleveland-clinic-names-top-10-medical-innovations-for-2014>
45. National Cancer Institute. "Chronic Lymphocytic Leukemia Treatment (PDQ®)." <http://www.cancer.gov/cancertopics/pdq/treatment/CLL/Patient/page1>
46. U.S Food and Drug Administration. "FDA Approves Rituxan to Treat Chronic Lymphocytic Leukemia." February 18, 2010. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm201069.htm>
47. Wendtner, CM. (April 25, 2012). Recent progress in the treatment of CLL. Medscape Multispecialty. <http://www.medscape.org/viewarticle/762258>
48. Byrd, JC, et al. "Entering the Era of Targeted Therapy for Chronic Lymphocytic Leukemia: Impact on the Practicing Clinician." Journal of Clinical Oncology. 2014. 55.8262. <http://jco.ascopubs.org/content/early/2014/07/18/JCO.2014.55.8262.short?rss=1>
49. Cleveland Clinic. "Top 10 Innovations for 2014: #10 B-Cell Receptor Pathway Inhibitors." <http://summit.clevelandclinic.org/Top-10-Innovations/Top-10-for-2014/Top-10-Articles/10-B-Cell-Receptor-Pathway-Inhibitors.aspx>
50. Munch, J. "New Kinase Inhibitors Hold Promise for Chronic Lymphocytic Leukemia, Other B-Cell Malignancies." OncoLog. April 2014. 59(4). <http://www2.mdanderson.org/depts/oncolog/articles/14/4-apr/4-14-2.html>
51. U.S. Food and Drug Administration. "FDA approves Zydelyg for three types of blood cancers." July 23, 2014. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406387.htm>

52. Munch, J. "New Kinase Inhibitors Hold Promise for Chronic Lymphocytic Leukemia, Other B-Cell Malignancies." *OncoLog*. April 2014. 59(4). <http://www2.mdanderson.org/depts/oncolog/articles/14/4-apr/4-14-2.html>
53. Munch, J. "New Kinase Inhibitors Hold Promise for Chronic Lymphocytic Leukemia, Other B-Cell Malignancies." *OncoLog*. April 2014. 59(4). <http://www2.mdanderson.org/depts/oncolog/articles/14/4-apr/4-14-2.html>
54. American Lung Association. "Pulmonary Arterial Hypertension." <http://www.lung.org/lung-disease/pulmonary-arterial-hypertension/>
55. American Lung Association. "What are the Symptoms of Pulmonary Arterial Hypertension?" <http://www.lung.org/lung-disease/pulmonary-arterial-hypertension/symptoms-diagnosis.html>
56. Stringham, R; Shah, N. "Pulmonary Arterial Hypertension: An Update on Diagnosis and Treatment." *American Family Physician*. 2010. 82(4):370-377. <http://www.aafp.org/afp/2010/0815/p370.html>
57. Ruan, C, et al. "Prostacyclin Therapy for Pulmonary Arterial Hypertension." *Texas Heart Institute Journal*. 2010. 37(4): 391–399. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929860/>
58. Ruan, C, et al. "Prostacyclin Therapy for Pulmonary Arterial Hypertension." *Texas Heart Institute Journal*. 2010. 37(4): 391–399. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929860/>
59. American Lung Association. "What are the Symptoms of Pulmonary Arterial Hypertension?" <http://www.lung.org/lung-disease/pulmonary-arterial-hypertension/symptoms-diagnosis.html>
60. Simonneau, G, et al. "Updated Clinical Classification of Pulmonary Hypertension. *Journal of the American College of Cardiology*. 2009. 54(1): S43-S54. <http://www.sciencedirect.com/science/article/pii/S0735109709012169>
61. Nauser, T; Stites, S. "Diagnosis and Treatment of Pulmonary Hypertension." 2001. 63(9):1789-1799. <http://www.aafp.org/afp/2001/0501/p1789.html>
62. Humbert, M. "Treatment of Pulmonary Arterial Hypertension." *New England Journal of Medicine*. 2004. 351:1425-36. https://www.ttuhsu.edu/som/internalmedicine/pulm/education/core_pulm/pulm_htn_therapy_nejm_2004.pdf
63. Humbert, M. "Treatment of Pulmonary Arterial Hypertension." *New England Journal of Medicine*. 2004. 351:1425-36. https://www.ttuhsu.edu/som/internalmedicine/pulm/education/core_pulm/pulm_htn_therapy_nejm_2004.pdf
64. Nauser, T; Stites, S. "Diagnosis and Treatment of Pulmonary Hypertension." 2001. 63(9):1789-1799. <http://www.aafp.org/afp/2001/0501/p1789.html>
65. Ruan, C, et al. "Prostacyclin Therapy for Pulmonary Arterial Hypertension." *Texas Heart Institute Journal*. 2010. 37(4): 391–399. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929860/>
66. Higenbottam, T, et al. "Long term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension." *Heart*. 1998. 80(2): 151–155. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1728783/>
67. Taichman, D; Mandel, J. "Epidemiology of Pulmonary Arterial Hypertension." *Clinics in Chest Medicine*. 2007 28(1):1-22. [http://www.chestmed.theclinics.com/article/S0272-5231\(06\)00127-4/abstract](http://www.chestmed.theclinics.com/article/S0272-5231(06)00127-4/abstract)
68. Nazzareno, G, et al. "The endothelin system in pulmonary arterial hypertension." *Cardiovascular Research*. 2003. 61(2):227-237. <http://cardiovascres.oxfordjournals.org/content/61/2/227>
69. Nazzareno, G, et al. "Ambrisentan for the Treatment of Pulmonary Arterial Hypertension." *Circulation*. 2008. 117: 3010-3019. <http://circ.ahajournals.org/content/117/23/3010.full>

70. Pulido, T, et al. "Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension." New England Journal of Medicine. 2013. 369:809-818. <http://www.nejm.org/doi/full/10.1056/NEJMoa1213917>
71. Chen, C, et al. "Cyclic guanosine monophosphate signalling pathway in pulmonary arterial hypertension." Vascular Pharmacology. 2013. 58(3):211-8. <http://www.ncbi.nlm.nih.gov/pubmed/22982057>
72. U.S. Food and Drug Administration, http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022332s006lbl.pdf
73. U.S. Food and Drug Administration: News and Events. "FDA approves Adempas to treat pulmonary hypertension." October 8, 2013. Updated October 10, 2013. www.fda.gov/newsevents/newsroom/pressannouncements/ucm370866.htm
74. U.S. Food and Drug Administration: News and Events. "FDA approves Adempas to treat pulmonary hypertension." October 8, 2013. Updated October 10, 2013. www.fda.gov/newsevents/newsroom/pressannouncements/ucm370866.htm
75. U.S. Food and Drug Administration, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022387LBL.pdf
76. Hensley, S. "Drugmaker Names Pill After CEO Who Sought Daughter's Cure." NPR. December 24, 2013. <http://www.npr.org/blogs/health/2013/12/24/256839330/orenitram-united-therapeutics-names-pill-after-ceo-who-sought-daughters-cure>
77. Hoeper, M, et al. "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension." European Respiratory Journal. 2005. 26(5):858-863. <http://erj.ersjournals.com/content/26/5/858.short>
78. Pulmonary Hypertension Association. "New Pulmonary Hypertension Drug Approved!" (n.d.) <http://www.phassociation.org/PressRelease/122213>
79. U.S. Hereditary Angioedema Association. "What is HAE?" <http://www.haea.org/patients/what-is-hae/>
80. U.S. Hereditary Angioedema Association. "Hereditary Angioedema (HAE) Symptoms." <http://www.haea.org/patients/symptoms/>
81. U.S. Hereditary Angioedema Association. "Hereditary Angioedema (HAE) Symptoms." <http://www.haea.org/patients/symptoms/>
82. U.S. Food and Drug Administration. "Advisory Committee Briefing Document: Kalbitor® (ecallantide) For Acute Attacks of Hereditary Angioedema." January 2, 2009. <http://www.fda.gov/downloads/%E2%80%A6/ucm170334.pdf>
83. Agostoni, A. "Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond." Journal of Allergy and Clinical Immunology. 2004. 114(3 Suppl):S51-131. <http://www.ncbi.nlm.nih.gov/pubmed/15356535>
84. U.S. Hereditary Angioedema Association. "Do newly-approved treatments offer additional treatment options?" <http://www.haea.org/patients/treatments/>
85. U.S. Food and Drug Administration. "Advisory Committee Briefing Document: Kalbitor® (ecallantide) For Acute Attacks of Hereditary Angioedema." January 2, 2009. <http://www.fda.gov/downloads/%E2%80%A6/ucm170334.pdf>
86. U.S. Hereditary Angioedema Association. "What is HAE?" <http://www.haea.org/patients/what-is-hae/>
87. U.S. National Library of Medicine: Genetics Home Reference. "What is hereditary angioedema?" <http://ghr.nlm.nih.gov/condition/hereditary-angioedema>
88. U.S. Food and Drug Administration. "Advisory Committee Briefing Document: Kalbitor® (ecallantide) For Acute Attacks of Hereditary Angioedema." January 2, 2009. <http://www.fda.gov/downloads/%E2%80%A6/ucm170334.pdf>

89. U.S. National Library of Medicine: Genetics Home Reference. "What is hereditary angioedema?" <http://www.haea.org/patients/what-is-hae/>
90. U.S. Food and Drug Administration, <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM129918.pdf>
91. U.S. Food and Drug Administration, <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm186264.htm>
92. U.S. Food and Drug Administration, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/1252771b1.pdf
93. Cicardi, M, et al. "Ecallantide for the Treatment of Acute Attacks in Hereditary Angioedema." New England Journal of Medicine. 2010. 363:523-531. <http://www.nejm.org/doi/full/10.1056/NEJMoa0905079>
94. U.S. Food and Drug Administration, http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022150s0001b1.pdf
95. U.S. Food and Drug Administration, <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM405634.pdf>
96. Cystic Fibrosis Foundation. "Frequently Asked Questions." <http://www.cff.org/AboutCF/Faqs>
97. Cystic Fibrosis Foundation. "About CF" <http://www.cff.org/AboutCF/>
98. Cystic Fibrosis Foundation. "About CF" <http://www.cff.org/AboutCF/>
99. Cystic Fibrosis Foundation. "Frequently Asked Questions." <http://www.cff.org/AboutCF/Faqs/>
100. Syed, B; Hamad, B. "The cystic fibrosis drug market." Nature Reviews Drug Discovery. 2014. 13:721-722. <http://www.nature.com/nrd/journal/v13/n10/full/nrd4434.html>
101. Cystic Fibrosis Foundation. "About CF" <http://www.cff.org/AboutCF/>
102. Cystic Fibrosis Foundation. "Research Milestones." <http://www.cff.org/research/ResearchMilestones/>
103. Cystic Fibrosis Foundation. "Research Milestones." <http://www.cff.org/research/ResearchMilestones/>
104. Cystic Fibrosis Foundation. "TOBI®: Inhaled Antibiotic for CF" <http://www.cff.org/treatments/Therapies/Respiratory/TOBI/>
105. Cystic Fibrosis Foundation. "Patient Registry Annual Data Report 2014" http://www.cff.org/UploadedFiles/research/ClinicalResearch/PatientRegistryReport/2013_CFF_Patient_Registry_Annual_Data_Report.pdf
106. Mackenzie, T, et al. "Longevity of Patients With Cystic Fibrosis in 2000 to 2010 and Beyond: Survival Analysis of the Cystic Fibrosis Foundation Patient Registry." Annals of Internal Medicine. 2014. 161(4):233-241. <http://annals.org/article.aspx?articleid=1897099>
107. U.S. Food and Drug Administration. "Pancrelipase (marketed as Pancreaze, Creon and Zenpep) Information." <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm149334.htm>
108. Eurand. "Eurand Launches ZENPEP™ (pancrelipase) Delayed-Release Capsules." Press Release. November 30, 2009. <http://www.sec.gov/Archives/edgar/data/1119745/000111974509000008/pressrelease.htm>
109. U.S. Food and Drug Administration: News and Events. "FDA approves two new pancreatic enzyme products to aid food digestion." March 1, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm294143.htm>

110. U.S. Food and Drug Administration. "Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP)." May 17, 2012. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204745.htm>
111. Gilead: Press Releases. "U.S. Food and Drug Administration Approves Cayston(R) (Aztreonam for Inhalation Solution) for the Improvement of Respiratory Symptoms in Cystic Fibrosis Patients with Pseudomonas Aeruginosa." February 22, 2010. <http://www.gilead.com/news/press-releases/2010/2/us-food-and-drug-administration-approves-caystonr--aztreonam-for-inhalation-solution-for-the-improvement-of-respiratory--symptoms-in-cystic-fibrosis-patients-with-pseudomonas-aeruginosa>
112. Waknine, Y. "FDA Approves Inhaled Aztreonam for Cystic Fibrosis." Medscape. February 24, 2010. <http://www.medscape.com/viewarticle/717553>
113. U.S. Food and Drug Administration: News and Events. "FDA approves Kalydeco to treat rare form of cystic fibrosis." January 31, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm>
114. Vertex. "U.S. Food and Drug Administration Approves KALYDECO™ (ivacaftor) for Use in Eight Additional Mutations that Cause Cystic Fibrosis." February 21, 2014. <http://investors.vrtx.com/releasedetail.cfm?ReleaseID=827435>
115. Vertex. "U.S. Food and Drug Administration Approves KALYDECO® (ivacaftor) for Use in People with Cystic Fibrosis Ages 6 and Older Who Have the R117H Mutation." December 29, 2014. <http://investors.vrtx.com/releasedetail.cfm?ReleaseID=889027>
116. Syed, B; Hamad, B. "The cystic fibrosis drug market." Nature Reviews Drug Discovery. 2014. 13:721-722. <http://www.nature.com/nrd/journal/v13/n10/full/nrd4434.html>

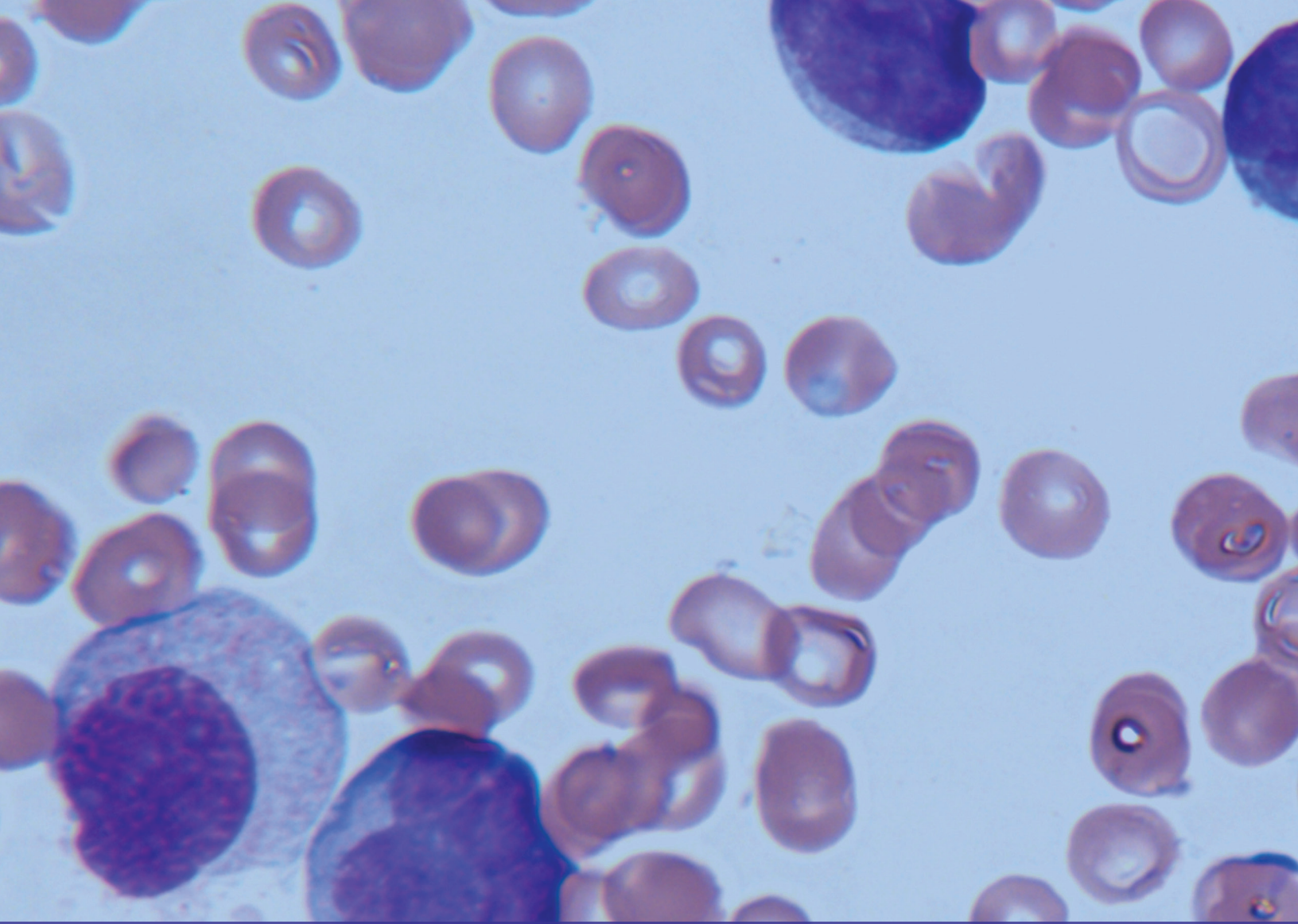
Spotlight References

- i. U.S. National Library of Medicine: Genetic Home Reference. "Neonatal onset multisystem inflammatory disease." <http://ghr.nlm.nih.gov/condition/neonatal-onset-multisystem-inflammatory-disease>
- ii. American College of Rheumatology. "Cryopyrin-Associated Autoinflammatory Syndromes (CAPS)." https://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Cryopyrin-Associated_Autoinflammatory_Syndromes_%28CAPS%29_%28Juvenile%29/
- iii. U.S. National Library of Medicine: Genetic Home Reference. "Neonatal onset multisystem inflammatory disease." <http://ghr.nlm.nih.gov/condition/neonatal-onset-multisystem-inflammatory-disease>
- iv. American College of Rheumatology. "Cryopyrin-Associated Autoinflammatory Syndromes (CAPS)." https://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Cryopyrin-Associated_Autoinflammatory_Syndromes_%28CAPS%29_%28Juvenile%29/
- v. Autoinflammatory Alliance. "NOMID/CINCA." <http://www.nomidalliance.org/nomid.php>
- vi. American College of Rheumatology. "Cryopyrin-Associated Autoinflammatory Syndromes (CAPS)." https://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Cryopyrin-Associated_Autoinflammatory_Syndromes_%28CAPS%29_%28Juvenile%29/

- vii. National Institute of Neurological Disorders and Stroke. "Mucopolysaccharidoses Fact Sheet." http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/detail_mucopolysaccharidoses.htm
- viii. National MPS Society. "MPS IV (Morquio Syndrome)." <http://mpsociety.org/mps/mps-iv-morquio/>
- ix. National Institute of Neurological Disorders and Stroke. "Mucopolysaccharidoses Fact Sheet." http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/detail_mucopolysaccharidoses.htm
- x. U.S. Food and Drug Administration. "FDA approves Vimizim to treat rare congenital enzyme disorder." February 14, 2014. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm386008.htm>
- xi. Kakaei, F, et al. "Liver Transplantation for Homozygous Familial Hypercholesterolemia: Two Case Reports." Transplant Proceedings. 2009. 41(7): 2939-41. [http://www.transplantation-proceedings.org/article/S0041-1345\(09\)01063-X/abstract](http://www.transplantation-proceedings.org/article/S0041-1345(09)01063-X/abstract)
- xii. National Human Genome Research Institute. "Learning About Familial Hypercholesterolemia." <http://www.genome.gov/25520184>
- xiii. P. Ziajka. "Management of Patients With Homozygous Familial Hypercholesterolemia." American Journal of Managed Care. November 29, 2013. http://www.ajmc.com/publications/supplement/2013/ad119_nov13_hofh/ad119_nov12_ziajka_s251to58/1
- xiv. U.S. Food and Drug Administration. "FDA approves new orphan drug for rare cholesterol disorder." December 16, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333285.htm>
- xv. U.S. Food and Drug Administration. News and Events: "FDA approves new orphan drug for rare cholesterol disorder." December 16, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333285.htm>
- xvi. Mary Louise Brumit. "Treating Homozygous Familial Hypercholesterolemia Isn't Easy, But It Can Be Successful." The Familial Hypercholesterolemia Foundation: News and Blog. January 28, 2013. <http://thefhfoundation.org/treating-homozygous-familial-hypercholesterolemia-isnt-easy-but-it-can-be-successful/>
- xvii. Huntington's Disease Society of America. "Fast Facts About HD." <http://www.hdsa.org/images/content/2/2/v2/22556/HDSA-FastFacts-2-7-14-final.pdf>
- xviii. Huntington's Disease Society of America. "Fast Facts About HD." <http://www.hdsa.org/images/content/2/2/v2/22556/HDSA-FastFacts-2-7-14-final.pdf>
- xix. U.S. Food and Drug Administration. "Briefing Document for Peripheral and Central Nervous System Advisory Committee." December 6, 2007. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4328b1-02-Prestwick.pdf>
- xx. U.S. National Library of Medicine: Genetic Home Reference. "Gaucher Disease." <http://ghr.nlm.nih.gov/condition/gaucher-disease>
- xxi. U.S. Food and Drug Administration. "FDA approves new orphan drug to treat a form of Gaucher disease." May 1, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302549.htm>
- xxii. U.S. National Library of Medicine: Genetic Home Reference. "Gaucher Disease." <http://ghr.nlm.nih.gov/condition/gaucher-disease>
- xxiii. U.S. National Library of Medicine: Genetic Home Reference. "Gaucher Disease." <http://ghr.nlm.nih.gov/condition/gaucher-disease>
- xxiv. N. Weinreb, P. Deegan, K.A. Kacena, P. Mistry, G. Pastores, P. Velentgas, S. vom Dahl. "Life Expectancy in Gaucher disease type 1." American Journal of Hematology. December 2008. 83(12). 896-900. <http://onlinelibrary.wiley.com/doi/10.1002/ajh.21305/abstract;jsessionid=AB4A992DF6ECA711162B5DD1F66B819.f01t04>

- xxv. National Gaucher Foundation, Inc. "FDA Approves Genzyme's Cerdelga™ (eliglustat) Capsules." <http://www.gaucherdisease.org/gaucher-disease-news/news208.php>
- xxvi. U.S. Food and Drug Administration, http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022575lbl.pdf
- xxvii. U.S. Food and Drug Administration. "FDA approves new orphan drug to treat a form of Gaucher disease." May 1, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302549.htm>
- xxviii. U.S. Food and Drug Administration, <http://www.accessdata.fda.gov/spl/data/7887c191-03db-4a18-9dea-b3907d0e9856/7887c191-03db-4a18-9dea-b3907d0e9856.xml>
- xxix. National Gaucher Foundation, Inc. "FDA Approves Genzyme's Cerdelga™ (eliglustat) Capsules." <http://www.gaucherdisease.org/gaucher-disease-news/news208.php>
- xxx. P. Kaplan. "Clinical potential of eliglustat tartrate in the treatment of type 1 Gaucher disease." Research and Reports in Endocrine Disorders. 4:1-8. May 14, 2014. www.dovepress.com/getfile.php?fileID=20049

Image Captions: Top: Close up of myelogenous leukemia cells, Getty Images @2015; Bottom Center: Cancer cell, Lymphocytes, Getty Images @2015; Bottom Right: Nerve cell attacked by virus, neurological disorder and genetic disease like parkinson disease, Huntington's disease, muscular dystrophy, Alzheimer's disease, multiple sclerosis, brain tumors., Shutterstock @2015



PhRMA
RESEARCH • PROGRESS • HOPE

