

*The Curative and Transformative Potential of Novel
Therapies for Rare Diseases in the
Age of Precision Medicine*

Christopher P. Austin, M.D.

Director, NCATS/NIH

EveryLife Scientific Workshop

September 12, 2017



Rare disease drug approvals are accelerating...



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2017 On Track to be a Record Breaking Year for Orphan Drug Approvals

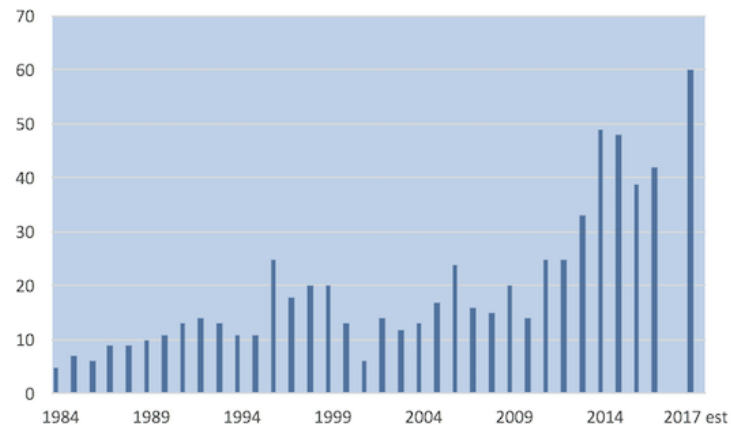
AUGUST 09, 2017

James Radke

It is only August but the U.S. Food and Drug Administration (FDA) is on track to set a record for orphan drugs approved this year. At last count, 42 orphan drugs have been approved between January 1, 2017 and August 9, 2017.

At their current pace, the FDA will approve more than 60 orphan drugs by the end of the year. That is 20% above their last record breaking period in 2014 (49 approvals) and 2015 (48 approvals).

Figure 1. Orphan Drug Approvals by the FDA per Year



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Gene therapy for rare diseases making strides...

NATURE BIOTECHNOLOGY | NEWS

First gene therapy approved

Nuala Moran

Nature Biotechnology 30, 1153 (2012) | doi:10.1038/nbt1212-1153

Published online 07 December 2012



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Article metrics

The first person to be administered a commercial gene therapy will be treated in Germany in the middle of 2013. The European Commission granted marketing authorization for Glybera (alipogene tiparvovec) for the treatment of the ultra-rare inherited disorder, lipoprotein lipase (LPL) deficiency, on November 2. The approval marks the beginning of a significant growth path for gene therapy, says Jörn Aldag, CEO of Glybera's developer, uniQure BV (formerly Amsterdam Molecular Therapeutics), based in Amsterdam. "The world has been watching very skeptically, questioning if a gene therapy could be approved at all. We have overcome all the barriers and now the European Medicines Agency (EMA) has validated Glybera and said it can be applied in [a] market environment." One of Europe's leading advocates for rare-disease patients, Alastair Kent, says he is "very pleased with the outcome." However, Kent, who is director of Genetic Alliance UK in London and president of the European Genetic Alliances' Network located in Amsterdam, cautions that it remains to be seen if this really will open up the gene therapy market. "We'll have to watch and wait, but hopefully EMA will be more confident about assessing risks and balances." uniQure is in the thick of negotiations with reimbursement bodies, trying to agree on a price for a one-off treatment that has lasting effects. The aim is to get a price comparable to the €250,000 (\$318,000)-a-year cost of enzyme replacement therapies for treating other rare metabolic disorders. While waiting on approval, the company has screened 319 patients, identifying 32 with the relevant mutation of the LPL gene. In all, Aldag estimates there are 400–500 patients in Europe, and he says Glybera will be profitable going forward. Now uniQure intends to engage with the US Food and Drug Administration, with the aim of launching Glybera in the US in 2014. More ambitiously still, over the next nine months the company will begin phase 1/2 trials of gene therapies in four other disorders.



uniQure
Jörn Aldag
uniQure CEO



Behind the scenes

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GSK statement about Ventolin HFA 200D Inhaler

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BUT...

Goodbye Glybera! The World's First Gene Therapy will be Withdrawn

FROM THE CLINIC

Evelyn Warner on 20/04/2017

The excitement about the therapy was undercut when it became clear Glybera would be a **commercial failure**. In October, it will officially be dead.

uniQure has announced that it will not go for the renewal of its marketing authorization for **Glybera** in Europe, which is set to expire in October this year. Since Glybera **missed approval** in the United States, this announcement marks the end of the road for the world's first gene therapy as it will be **withdrawn** in October.

Glybera was first approved in **October 2012** for hereditary **lipoprotein lipase deficiency (LPLD)**, a genetic disorder that uniQure acknowledges is "**ultra-rare**."

Indeed, only **about 1** person in a million suffers the disease, which manifests as pancreatitis, recurrent abdominal pain and eruptive fat-filled spots that result from very high triglyceride levels. Glybera provided a **one-off** solution by introducing copies of the relevant gene to produce the deficient lipase indefinitely; the longest term study has proven its efficacy for at least **six years**.

The company's **CEO, Matt Kapusta**, explained uniQure's move in a statement, remarking that "*Glybera's usage has been extremely limited, and we do not envision patient demand increasing materially in the years ahead.*" Moreover, Glybera's approval came with **hefty maintenance costs**: because of its purpose as an effective cure, uniQure was required by the European Commission to monitor patients over a long period of time, conduct a Phase IV clinical trial, undergo annual regulatory inspections and increase risk management precautions.



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CAR-T gene therapy targets rare cancers

U.S. Department of Health and Human Services

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FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

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For Immediate Release August 30, 2017

Release

This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.

Español

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said FDA Commissioner Scott Gottlieb, M.D. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving."

Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.

ALL is a cancer of the bone marrow and blood, in which the body makes abnormal lymphocytes. The disease progresses quickly and is the most common childhood cancer in the U.S. The National Cancer Institute estimates that approximately 3,100 patients aged 20 and younger are diagnosed with ALL each year. ALL can be of either T- or B-cell origin, with B-cell the most common. Kymriah is approved for use in pediatric and young adult patients with B-cell ALL and is intended for patients whose cancer has not responded to or has returned after initial treatment, which occurs in an estimated 15-20 percent of patients.

"Kymriah is a first-of-its-kind treatment approach that fills an important unmet need

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Antisense therapy for rare diseases

FDA Approves Spinraza for SMA

BY CURE SMA | PUBLISHED ON JANUARY 5, 2017

Like Share Tweet



On December 23, the FDA announced that it has approved Spinraza™ (nusinersen) to treat spinal muscular atrophy, making it the first-ever **FDA-approved therapy for SMA**.

We are thrilled to see our community's efforts culminate in the approval of **Spinraza**: not only the first-ever approved treatment for this disease, but also one that addresses the underlying genetic cause of SMA. This has been a story of all groups—families, researchers, companies and the FDA—working together as one community to reach this amazing milestone.

We are especially pleased that the sophisticated and rigorous clinical development plan that **Biogen** and **Ionis** chose to implement has resulted in a broad label that will now give so many patients access.

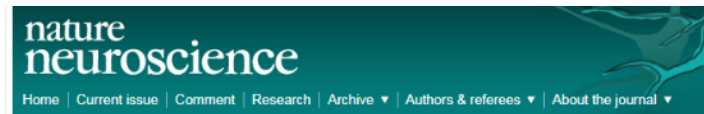
The approval from the FDA for all SMA—pediatric and adult—is the broadest possible label, with no restrictions—and this matches our core value at Cure SMA of being one united community for all ages and all types of SMA.

"Biogen is committed to continuing to work together with the SMA community as we embark on a future where there is now a treatment available for this devastating disease," said George A. Scangos, PhD, chief executive officer at Biogen. "The teams at Biogen and Ionis are grateful for the support we have received and we join Cure SMA and SMA families in celebrating this critical milestone for the community."

"There has been a long-standing need for a treatment for spinal muscular atrophy, the most common genetic cause of death in infants, and a disease that can affect people at any stage of life," said Billy Dunn, MD, director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research. "As shown by our suggestion to the sponsor to analyze the results of the study earlier than planned, the FDA is committed to assisting with the development and approval of safe and effective drugs for rare diseases and we worked hard to review this application quickly; we could not be more pleased to have the first approved treatment for this debilitating disease."

An Historic Moment for the SMA Community

This is an historic moment that our community has been working toward for decades. We extend our deepest gratitude to all our chapters, families, supporters, donors, and partners who have contributed to this milestone.



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NATURE NEUROSCIENCE | NEWS AND VIEWS

Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy

David R Corey

Nature Neuroscience **20**, 497–499 (2017) | doi:10.1038/nn.4508
Published online 13 February 2017

PDF Citation Rights & permissions Article metrics

Nusinersen (Spinraza) is a recently approved drug for treating spinal muscular atrophy. Approval of nusinersen may signal new opportunities for using antisense oligonucleotides as treatments for devastating neurological diseases.

Subject terms: Nucleic-acid therapeutics • RNA

Progressive neurological diseases slowly rob patients of physical abilities and hope. Treatments are urgently needed, but traditional small molecule drug discovery is often difficult. An alternative approach is to use synthetic antisense oligonucleotides (ASOs) to modulate the expression of genes that influence disease. Recent data from phase 2 and phase 3 clinical trials^{1, 2} have demonstrated that nusinersen (Spinraza), an ASO drug, is effective for treating spinal muscular atrophy (SMA). The open question is whether this success can be translated to the control of other disease genes in the CNS.

SMA refers to several different motor neuron diseases³. SMA is most commonly associated with mutations in the survival motor neuron 1 (*SMN1*) gene. These mutations are the most frequent genetic cause of death in children, affecting one in ten thousand. The disease varies in severity, with many children beginning to meet developmental milestones until selective degeneration of spinal neurons halts progress and leads to an inevitable decline.

Fortunately, humans possess a second SMN gene, *SMN2*. *SMN2* and *SMN1* are related by an inverted gene duplication. *SMN2* contains a C-to-T mutation in exon 7 that redirects alternative splicing to exclude exon 7 and leads to an unstable mature protein that cannot substitute for mutant SMN1 (ref. 4). One potential therapeutic strategy is to identify agents to prevent this splicing event and thus increase the production of stable SMN protein to compensate for the loss of function of the *SMN1* gene.



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CRISPR is new but promising

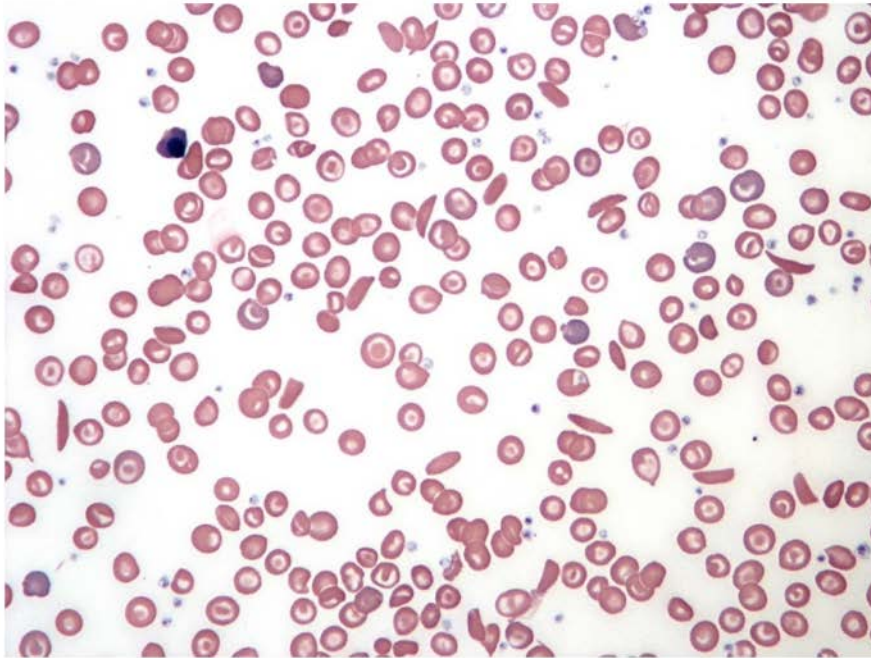
FierceBiotech

BIOTECH RESEARCH IT CRO MEDTECH

Research

CRISPR a potential cure for sickle cell disease

by Amirah Al Idrus | Oct 17, 2016 6:00am



Blood smear showing sickle cell disease—Courtesy of Keith Chambers

Sickle cell disease is caused by a mutation in the gene that codes for the protein beta-globin, a component of red blood cells. A group of physicians and researchers have used CRISPR/Cas9 editing to correct the mutation in stem cells taken from the blood of affected patients.

The team, from UC Berkeley, UC San Francisco Benioff Children's Hospital, Oakland Research Institute and the University of Utah School of Medicine, used CRISPR to fix the mutation in hematopoietic stem cells—cells that mature into red blood cells—that were taken from sickle cell patients, **according to a statement**. The edited cells produced healthy hemoglobin, which mutated cells do not make.

They also transplanted edited stem cells into mice, where they persisted four months after transplantation, suggesting that a potential therapy based on the approach would be long-lasting, according to the statement. The **results** are published in *Science Translational Medicine*.

NATURE METHODS | CORRESPONDENCE



Unexpected mutations after CRISPR–Cas9 editing *in vivo*

Kellie A Schaefer, Wen-Hsuan Wu, Diana F Colgan, Stephen H Tsang, Alexander G Bassuk & Vinit B Mahajan

Affiliations | Corresponding authors

Nature Methods 14, 547–548 (2017) | doi:10.1038/nmeth.4293

Published online 30 May 2017 | Updated online 14 June 2017 | Corrected online 25 July 2017

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Subject terms: DNA sequencing • Experimental models of disease • Genetic engineering • Genetics research • Translational research

At a glance



To the Editor:

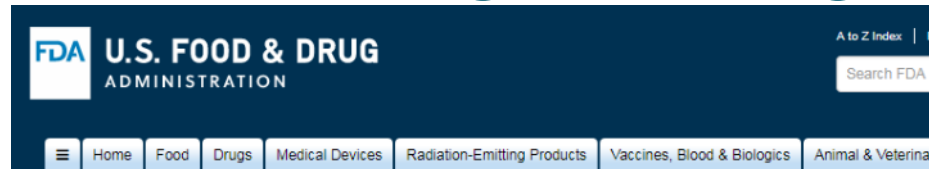
CRISPR–Cas9 editing shows promise for correcting disease-causing mutations. For example, in a recent study we used CRISPR–Cas9 for sight restoration in blind *rd1* mice by correcting a mutation in the *Pde6b* gene¹. However, concerns persist regarding secondary mutations in regions not targeted by the single guide RNA (sgRNA)². Algorithms generate likely off-target sites for a given gRNA, but these algorithms may miss mutations. Whole-genome sequencing (WGS) has been used to assess the presence of small insertions and deletions (indels)³ but not to probe for single-nucleotide variants (SNVs) in a whole organism. We performed WGS on a CRISPR–Cas9-edited mouse to identify all off-target mutations and found an unexpectedly high number of SNVs compared with the widely accepted assumption that CRISPR causes mostly indels at regions homologous to the sgRNA.

We tested four sgRNAs in cells then chose the sgRNA with the highest activity for *in vivo* targeting. DNA was isolated from two CRISPR-repaired mice (F03 and F05) and one uncorrected control¹. CRISPR–Cas9-treated mice were sequenced at an average depth of 50×, and the control was sequenced at 30×. Variant calls were confirmed by at least 23× sequencing coverage (Supplementary Tables 1 and 2). Multiple variant-calling software pipelines identified indels and



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But don't forget biologics...



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FDA News Release

FDA approves first treatment for a form of Batten disease

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For Immediate
Release

April 27, 2017

Release

The U.S. Food and Drug Administration today approved Brineura (cerliponase alfa) as a treatment for a specific form of Batten disease. Brineura is the first FDA-approved treatment to slow loss of walking ability (ambulation) in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency.

"The FDA is committed to approving new and innovative therapies for patients with rare diseases, particularly where there are no approved treatment options," said Julie Beitz, M.D., director of the Office of Drug Evaluation III in the FDA's Center for Drug Evaluation and Research. "Approving the first drug for the treatment of this form of Batten disease is an important advance for patients suffering with this condition."

CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), collectively referred to as Batten disease. CLN2 disease is a rare inherited disorder that primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms typically begin between ages 2 and 4. The initial symptoms usually include language delay, recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects essential motor skills, such as sitting and walking. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. Batten disease is relatively rare, occurring in an estimated two to four of every 100,000 live births in the United States.

Brineura is an enzyme replacement therapy. Its active ingredient (cerliponase alfa) is a recombinant form of human TPP1, the enzyme deficient in patients with CLN2 disease. Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a specific surgically implanted reservoir and catheter in the head (intraventricular



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...or small molecules, alone or in combination



September 28, 2016

U.S. Food and Drug Administration Approves ORKAMBI® (lumacaftor/ivacaftor) for Use in Children with Cystic Fibrosis Ages 6 through 11 who have Two Copies of the F508del Mutation

-Approximately 2,400 children ages 6 through 11 have two copies of the F508del mutation in the U.S.-

- Vertex revises ORKAMBI revenue guidance for 2016 -

BOSTON--(BUSINESS WIRE)-- [Vertex Pharmaceuticals Incorporated](#) (Nasdaq: VRTX) today announced that the U.S. Food and Drug Administration (FDA) approved ORKAMBI® (lumacaftor/ivacaftor) for use in children with cystic fibrosis (CF) ages 6 through 11 who have two copies of the *F508del* mutation. People with this mutation represent the largest population of those with CF, a rare, life-threatening disease. ORKAMBI is the first and only medicine to treat the underlying cause of CF for people with this mutation. It was previously approved by the FDA for use in people ages 12 and older with two copies of the *F508del* mutation. With today's approval, approximately 11,000 people with CF are eligible for treatment with ORKAMBI in the United States. ORKAMBI will be available for eligible children ages 6 through 11 in the United States as soon as possible. Vertex also today lowered its guidance for 2016 ORKAMBI revenues to a range of \$950 million to \$990 million.

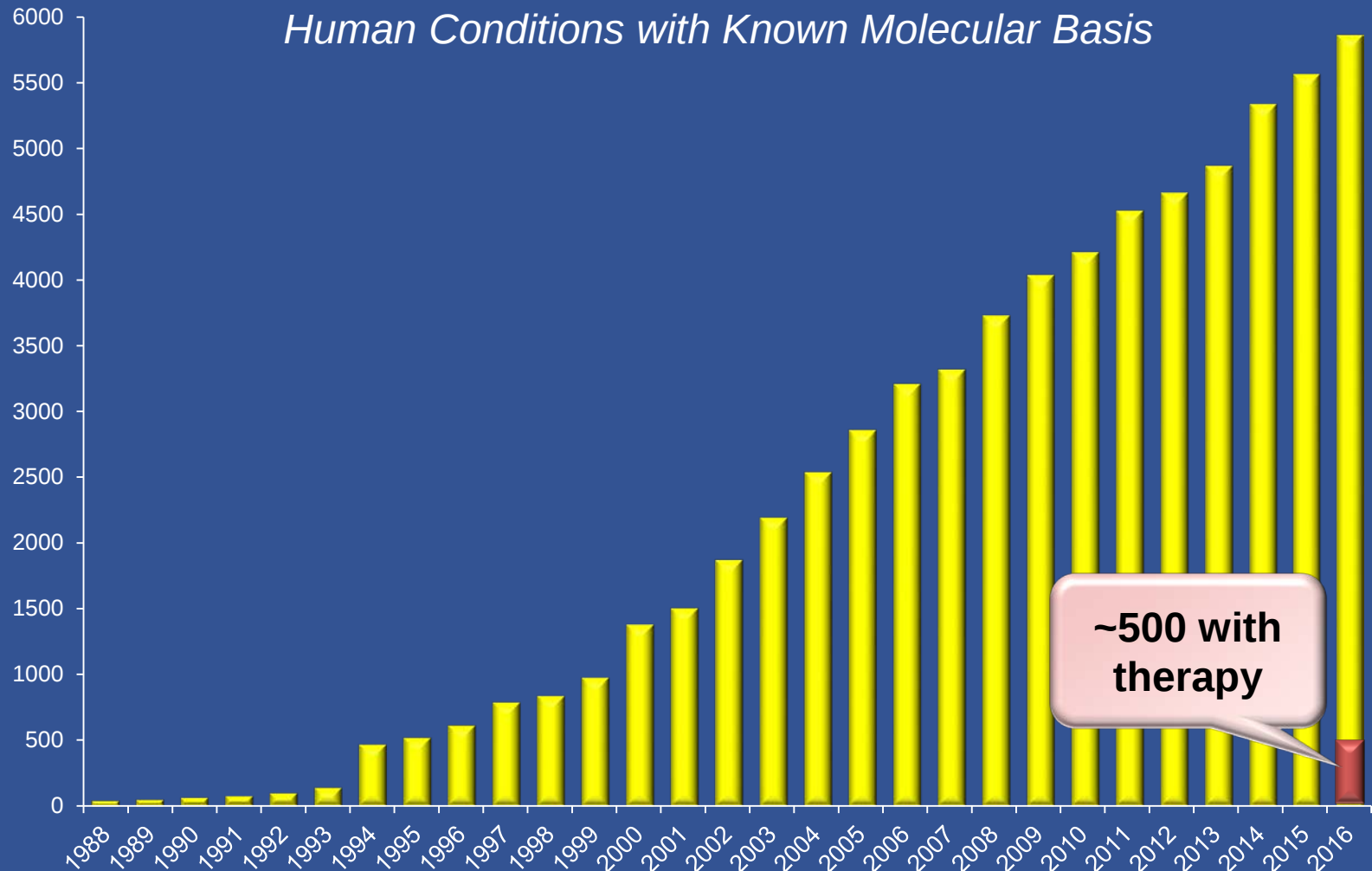
"The ability to treat children as young as six who have the most common form of the disease is an important milestone as we pursue our goal to develop medicines for all people with CF," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We believe it is important to treat the underlying cause of the disease as early as possible in these patients."

The approval is based on data from a previously announced open-label Phase 3 clinical safety study of ORKAMBI presented at the 39th European Cystic Fibrosis Society Conference in June 2016. These data will be presented at the 30th Annual North American Cystic Fibrosis Conference October 27-29 in Orlando, Florida.



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This is all cause for celebration, but...



Source: *Online Mendelian Inheritance in Man*, *Morbid Anatomy of the Human Genome*

How can we ramp up progress further?

NCATS Mission



To catalyze the generation of **innovative methods and technologies** that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.





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- Provide resource acceler
- Focus o process
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Discover



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Save the Date of Sept. 8, 2017!

Join us for the NCATS Toolkit for Patient-Focused Therapy Development: Demonstration and Dissemination Meeting

On Sept. 8, 2017, NCATS will launch a new, centralized online resource portal that will enable patient groups to make progress along the entire [translational science spectrum](#), no matter where they might be in that process. The [NCATS Toolkit for Patient-Focused Therapy Development: Demonstration and Dissemination Meeting](#) will take place from 9 a.m. to 4 p.m. ET on the NIH campus in Bethesda, Maryland. The event will enable the rare diseases and other patient communities to learn more about the toolkit, including how it can streamline their therapeutic development activities. Participants also will have the opportunity to provide input into how the toolkit can be refined, expanded and made even more useful.

Developed in collaboration with patients and rare disease advocates, the toolkit is a centralized online portal for resources and tools that will cover the broad therapy development landscape, including:

- How to establish a patient registry;
- How to drive patient-focused discovery and pre-clinical research and development;
- How to work with NIH and the Food and Drug Administration; and
- How to conduct post-market surveillance.

[Register now and learn more >](#)

[https://events-support.com/events/NCATS Toolkit Meeting](https://events-support.com/events/NCATS_Toolkit_Meeting)

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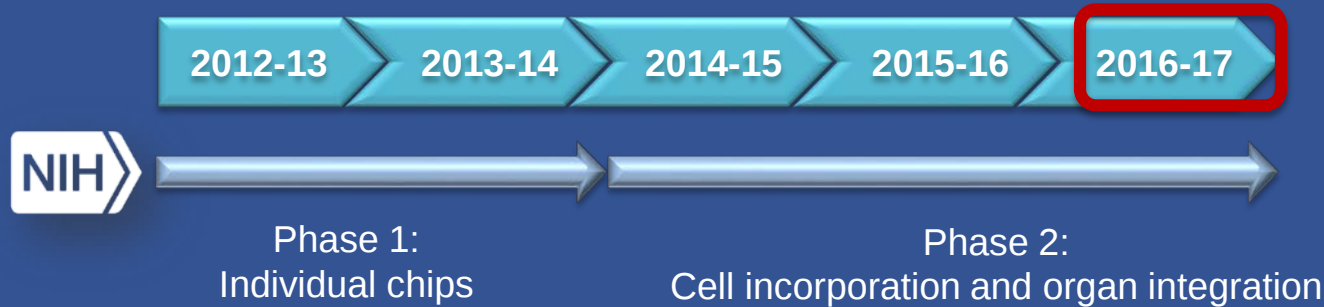
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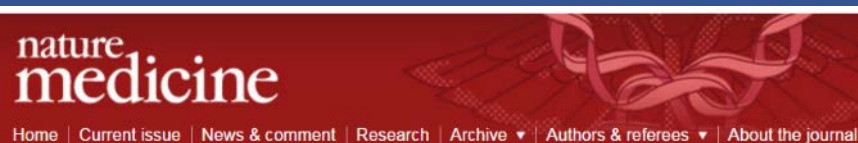
Human Tissue Chip Program

Goal: develop biochips to test for safe, effective drugs



■ Current focus:

- Integration (DARPA and NIH); insight/expertise (FDA); compound testing, validation
- Partnerships (MTA: GSK; Pfizer; AZ; MOU: IQ Consortium)
- Adoptions of the tech to the community



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NATURE MEDICINE | NEWS

Channeling chip power: Tissue chips are being put to the test by industry

Cassandra Willyard

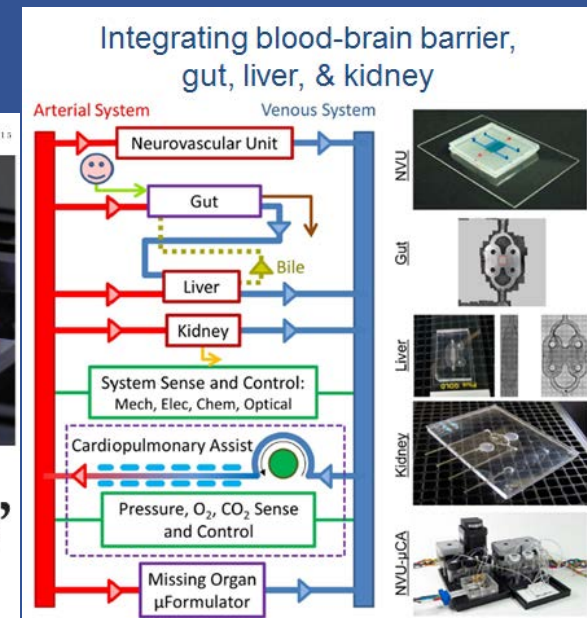
Nature Medicine 23, 138–140 (2017) | doi:10.1038/nm0217-138

Published online 07 February 2017



Miniature devices that mimic human organs could help to replace animals used in drug testing.

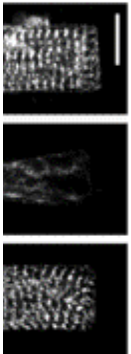
'Organs-on-chips' go mainstream



Barth Syndrome Heart on a Chip Model

ARTICLES

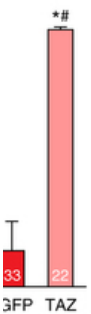
nature
medicine



Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies

Gang Wang^{1,14}, Megan L McCain^{2,14}, Luhan Yang^{2,3}, Aibin He¹, Francesco Silvio Pasqualini², Ashutosh Agarwal², Hongyan Yuan², Dawei Jiang¹, Donghui Zhang¹, Lior Zangi¹, Judith Geva¹, Amy E Roberts^{1,4}, Qing Ma¹, Jian Ding¹, Jinghai Chen¹, Da-Zhi Wang¹, Kai Li¹, Jiwu Wang^{5,6}, Ronald J A Wanders⁷, Wim Kulik⁷, Frédéric M Vaz⁷, Michael A Laflamme⁸, Charles E Murry⁸⁻¹⁰, Kenneth R Chien¹¹, Richard I Kelley¹², George M Church^{2,3}, Kevin Kit Parker^{2,13} & William T Pu^{1,13}

Study of monogenic mitochondrial cardiomyopathies may yield insights into mitochondrial roles in cardiac development and disease. Here, we combined patient-derived and genetically engineered induced pluripotent stem cells (iPSCs) with tissue engineering to elucidate the pathophysiology underlying the cardiomyopathy of Barth syndrome (BTHS), a mitochondrial disorder caused by mutation of the gene encoding tafazzin (*TAZ*). Using BTHS iPSC-derived cardiomyocytes (iPSC-CMs), we defined metabolic, structural and functional abnormalities associated with *TAZ* mutation. BTHS iPSC-CMs assembled sparse and irregular sarcomeres, and engineered BTHS 'heart-on-chip' tissues contracted weakly. Gene replacement and genome editing demonstrated that *TAZ* mutation is necessary and sufficient for these phenotypes. Sarcomere assembly and myocardial contraction abnormalities occurred in the context of normal whole-cell ATP levels. Excess levels of reactive oxygen species mechanistically linked *TAZ* mutation to impaired cardiomyocyte function. Our study provides new insights into the pathogenesis of Barth syndrome, suggests new treatment strategies and advances iPSC-based *in vitro* modeling of cardiomyopathy.



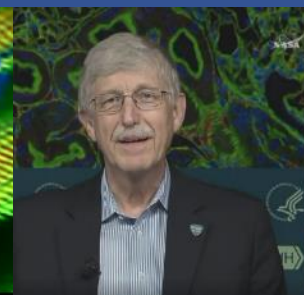
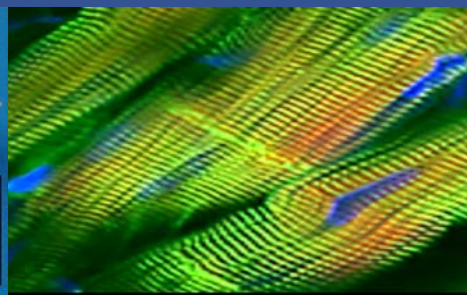
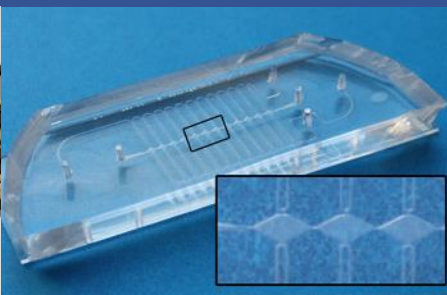
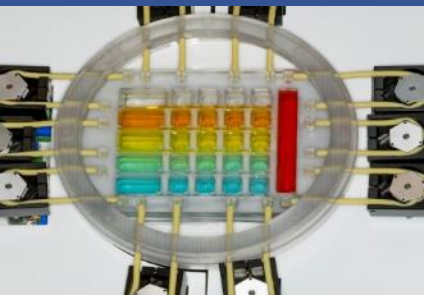
Genotype	WT	BTHS
	Galactose	Glucose



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Next Phase Tissue Chip Initiatives

- Tissue Chip Testing Centers (2016-2018)
 - Tech transfer and testing at 2 independent centers (Texas A&M and MIT)
- Tissue Chips for Disease Modeling (2017–2022)
 - Develop tissue chip models of human diseases, particularly rare
 - Using human primary or induced pluripotent stem cell sources
 - Use to test effectiveness of candidate therapeutics
- Tissue Chips in Space (2017–2021)
 - Partnership with Center for the Advancement of Science in Space (CASIS)
 - Adapt, refine chips for on-flight experiments at the International Space Station U.S. National Laboratory
 - To understand diseases (e.g. bone, muscle, aging) prevalent on earth and accelerated in space



International Rare Diseases Research Consortium (IRDiRC)

- ▶ Established 2011 to maximize global coordination and cooperation in rare disease research
 - ↳ 60 members from 20 countries in Europe, North America, Asia, Australia, Middle East
 - Funders
 - Companies
 - Patient Advocacy Groups
 - Scientists
 - ↳ Each funder supports its own research
- ▶ Guiding scientific and policy frameworks established
- ▶ 2011-2020 objectives achieved three years early:
 - ↳ 200 new therapies for rare diseases by 2020
 - ↳ Means to diagnose most rare diseases by 2020

Medical research: Next decade's goals for rare diseases

Christopher P. Austin & Hugh J. S. Dawkins

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Nature 548, 158 (10 August 2017) | doi:10.1038/548158c

Published online 09 August 2017

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Subject terms: Genetics • Medical research

The International Rare Diseases Research Consortium (IRDIRC) has in the past six years achieved its ambitious goals for 2020 — three years ahead of schedule (see *Nature* 472, 17; 2011). The consortium has now forged a further set of goals for 2017–27 to help the millions of people who have debilitating and lethal rare diseases.

Rare diseases were once considered medical curiosities of inscrutable phenotypic complexity and negligible public-health impact. The molecular basis of almost 6,000 rare disorders is now known. However, diagnosis of most of these conditions remains arduous, and less than 6% have approved treatments.

The new IRDIRC goals aim to achieve diagnosis within one year. Because diagnosis depends on a disorder being known, this will be accomplished through international coordination of unsolved cases. Other goals are to develop 1,000 new therapies, particularly for diseases with no approved treatment, and to create methods for assessing the impact of diagnoses and therapies on patients' well-being. (For details, see H. J. S. Dawkins *et al. Clin. Transl. Sci.*, in the press; and C. P. Austin *et al. Clin. Transl. Sci.*, in the press.)

The IRDIRC has nearly 50 organizations in 18 nations, with a combined yearly funding of more than US\$2 billion (see go.nature.com/2htbauh). New members are welcome to join this globally coordinated effort.

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Hugh J. S. Dawkins

IRDIRC Goals 2017–2027

VISION: Enable all people living with a rare disease to receive diagnosis, care, and therapy within one year of coming to subspecialty medical attention

GOAL 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline.

GOAL 2: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options.

GOAL 3: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

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