Challenges of developing Cell and Gene Therapy products in Europe

Dr Sven Kili
VP & Head of Cell & Gene Therapy Development, Rare Disease Unit, GSK

The unmet need is overwhelming

Thirty percent of children with a rare disease will die before reaching their fifth birthday

"With some conditions that are common and maybe better understood, people can tell you what you are supposed to do, or set out 2 or 3 options, but basically it is not going to be too different – but with ADA SCID we found that every place seems to recommend something different… ***it leaves you feeling confused"***
ADA SCID Carer

I can't have her suffer any more. I would need something that is 100%...and proven beyond reasonable doubt
MLD Carer

"It was not so much a case of isolating him within our house, it was a case of isolating our house from everyone else…. no-one was allowed into our house if they were unwell" **ADA SCID Carer**

"We did not know what was wrong and I was begging*, but they kept switching us between doctors… I remember praying and begging doctors not to send us home. I knew something was wrong…my heart just knew. I think I felt gratitude when we got the diagnosis. Of course there is fear of not knowing about the condition, and we had no idea what was ahead of us."*
ADA SCID Carer

"She cannot do a whole lot, she cannot sit up, so we hold her – she loves to be held, so we hold her a lot. She has a little recliner we put her in, she lies on the couch by the window. In summer we take her outside a lot, we go for walks, we get in the pool"
MLD, Carer

The opportunity to help people is great

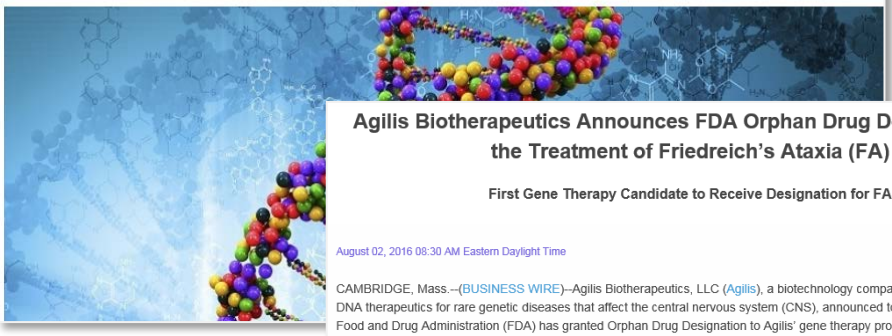
MolMed gains European conditional nod for ‘suicide gene’ drug

by *Ben Adams* | Jun 24, 2016 10:25am

Italian biotech MolMed has beer
its new drug that can help blood
stem cell transplants to help witl

BioMarin up on positive gene therapy data in hemophilia A

by *Stacy Lawrence* | Jul 27, 2016 4:32pm



Agilis Biotherapeutics Announces FDA Orphan Drug Designation for the Treatment of Friedreich’s Ataxia (FA)

First Gene Therapy Candidate to Receive Designation for FA

August 02, 2016 08:30 AM Eastern Daylight Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Agilis Biotherapeutics, LLC (Agilis), a biotechnology company advancing innovative DNA therapeutics for rare genetic diseases that affect the central nervous system (CNS), announced today that the United States Food and Drug Administration (FDA) has granted Orphan Drug Designation to Agilis' gene therapy product candidate, AGIL-FA, being developed for the treatment of Friedreich's ataxia (FA), an inherited degenerative neuromuscular disorder resulting in loss of
gilis is the first company to receive orphan
ar that Agilis has been granted orphan
es for AADC deficiency and Angelman

Spark Therapeutics Releases Positive Data On Most Advanced Product Candidate

R. Chandrasekaran , Benzinga Staff Writer | FOLLOW
July 01, 2016 9:55am | Comments

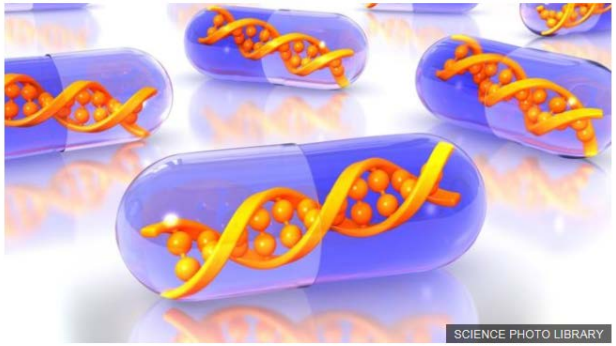
Stream Live From Benzinga Pro

Spark Therapeutics Inc ▲ONCE 4.28% revealed Friday the publication in "The Lancet" of long-term data from a first stage study of voretigene neparvovec (SPK-RPE65), its most advanced product candidate. Incidentally, the drug candidate received breakthrough therapy and orphan product status for the treatment of inherited retinal disease

Gene therapy drug approval granted to GSK

By Pallab Ghosh
Science correspondent, BBC News

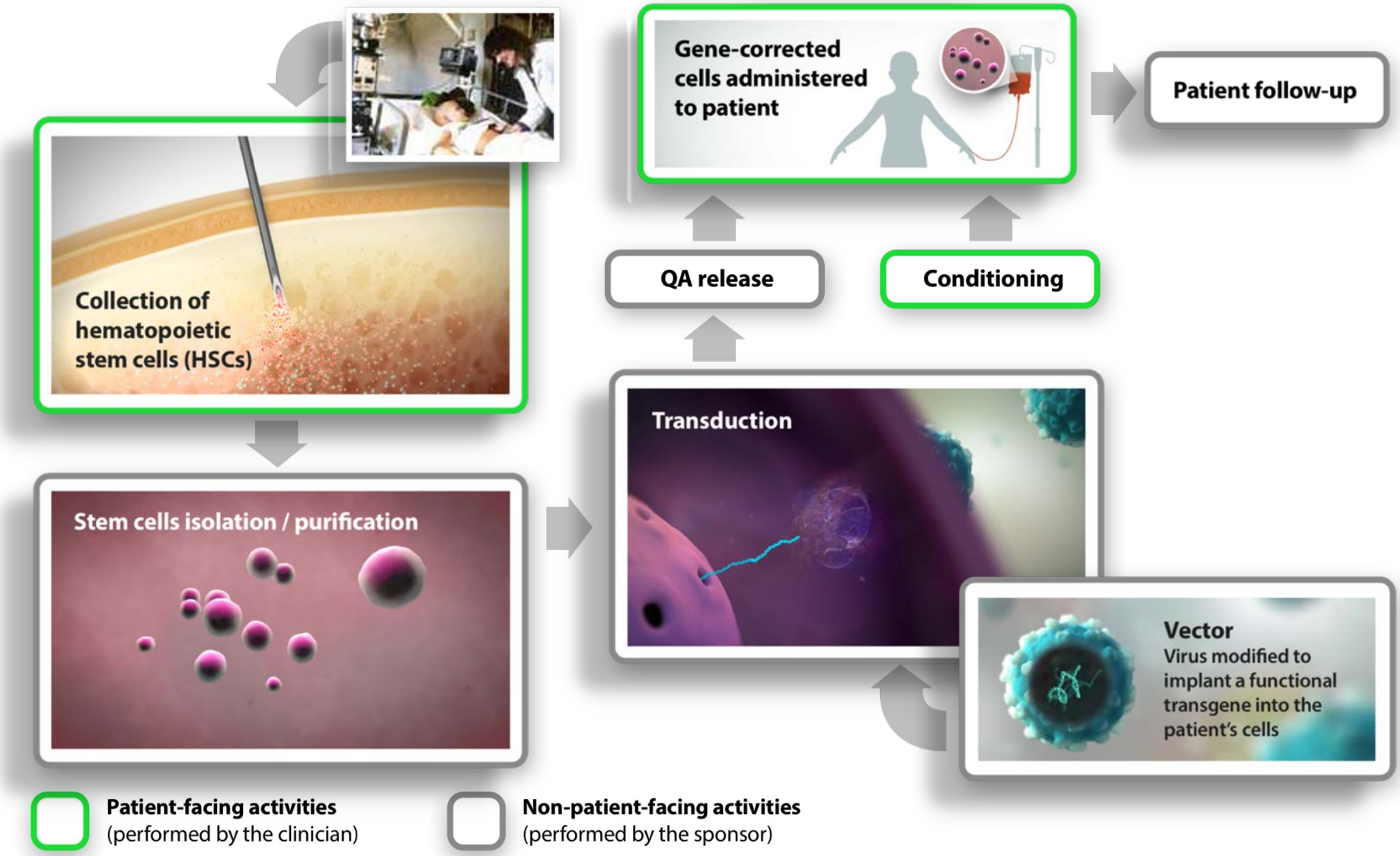
27 May 2016 | Science & Environment | Share



Regulators have given one of the world's largest drug companies approval to sell a new gene therapy.

Delivery of autologous gene therapy to the patient

Critical interface between clinician and manufacturer defines operating model more than logistics challenge of 'Hub and Spoke'



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GSK gene therapy program overview

- The strategic alliance with the Fondazione Telethon and Ospedale San Raffaele, acting through their joint Telethon Institute for Gene Therapy (TIGET) was established to research and develop autologous *ex vivo* gene therapy for rare genetic disorders

Indication	Stage
ADA deficiency (ADA-SCID)*	Approved
Metachromatic leukodystrophy (MLD)*	Ongoing trial in patients
Wiskott-Aldrich Syndrome (WAS)*	Ongoing trial in patients
Beta-thalassemia	Ongoing trial in patients
Mucopolysaccharoidosis type I (MPS type I)	Pre-clinical
Globoid-cell leukodystrophy (GLD)	Pre-clinical
Chronic granulomatous disorder (CGD)	Pre-clinical

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* Exclusively licensed to GSK

ADA SCID

Molecular and cellular pathology of ADA-SCID

- Absence of ADA leads to accumulation of deoxyadenosine triphosphate (dATP) and deoxyadenosine (dAdo)
- dATP inhibits
  - ribonucleotide reductase (DNA repair)
  - terminal deoxynucleotidyl transferase (VDJ recombination)
- dAdo inhibits
  - S-adenosylhomocysteine hydrolase (prevents lymphocyte activation)
- Profound lymphopenia
  - T cells
    - CD4 Helper, CD8, cytotoxic T cells
  - CD19 B-cells
  - CD16 NK-cells

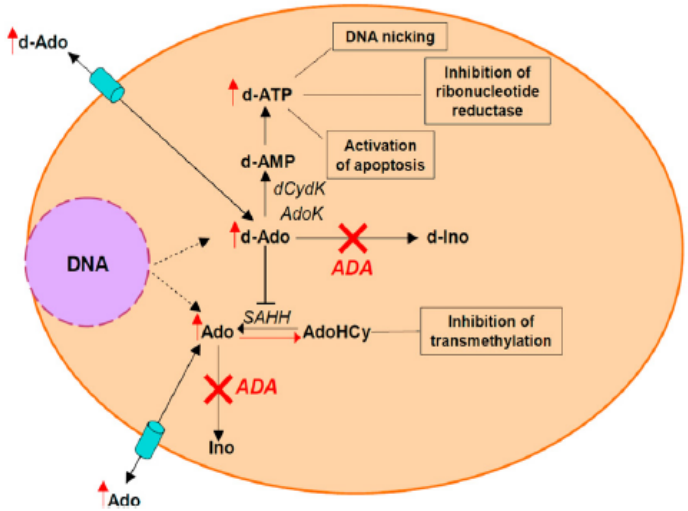


Fig. 1. Pathogenesis of ADA deficiency. The breakdown of DNA leads to recycling of deoxyadenosine and adenosine. In the absence of ADA, deoxyadenosine is converted to deoxyadenosine triphosphate and adenosine is converted to *S*-adenosylhomocysteine, both of whose substrates adversely affect several intracellular mechanisms. ADA, adenosine deaminase; ADCY, adenylyl cyclase; Ado, adenosine; AdoHCy, *S*-adenosylhomocysteine; AdoK, adenosine kinase; d-Ado, 2-deoxyadenosine; d-AMP, deoxyadenosine monophosphate; d-ATP, deoxyadenosine triphosphate; dCydK, deoxycytidine kinase; d-Ino, deoxyinosine; Ino, inosine; SAHH, *S*-adenosylhomocysteine hydrolase.

ADA-SCID, adenosine deaminase severe combined immune deficiency; DNA, deoxyribonucleic acid

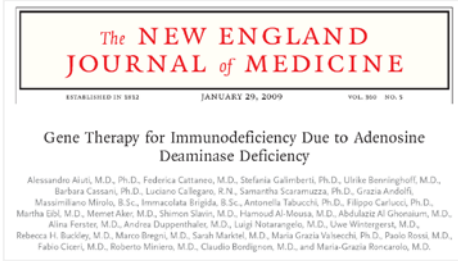
Autologous retroviral gene therapy for ADA-SCID: Clinical data overview

- 18 patient reported in MAA submission Q2 2014[1]:
  - All patients alive after a median follow-up of > 7 years (100% survival)
  - Soc (matched unrelated SCT) <70% survival.

- Immune reconstitution:
  - 15/18 patients free from the need for long-term enzyme replacement or rescue Stem Cell Therapy
  - Gradual and sustained improvement in T-cell counts

- Reduced rate of severe infections[2]:
  - Reduction from 1.1 event per person-year of observation before GT to 0.43 events per person-year of observation after GT (0-3 year data; n=12 pivotal study)

- Overall favourable safety and AE profile:
  - No deaths to date
  - No leukaemia
  - SAEs & AE's consistent with the disease and HSCT intervention

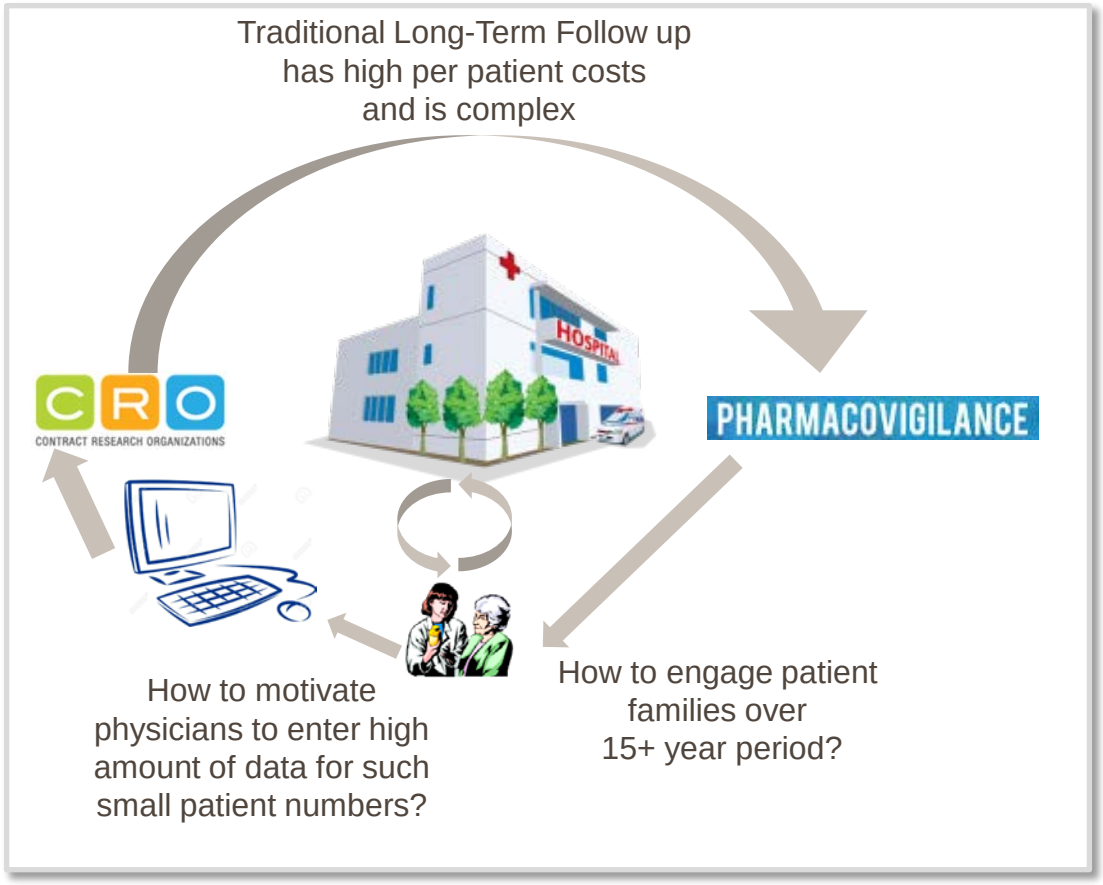

The NEW ENGLAND JOURNAL of MEDICINE

JANUARY 29, 2009

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

#1 including 12 patients treated in the pivotal study
#2 severe infection = infection requiring hospitalization or prolonging hospitalization
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency (NEJM, 2009)

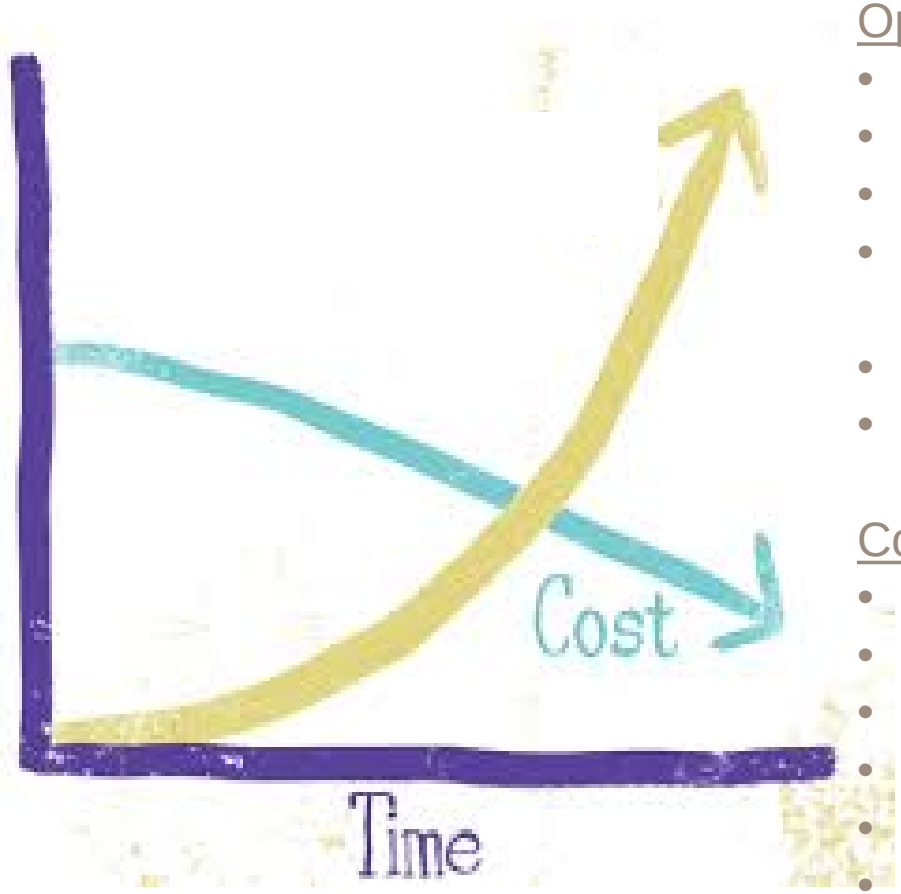
Paradigm shift is needed to establish cost effective and patient friendly long-term follow up



Need new solutions that:

- ✓Hold patient interest and engagement
- ✓Maintain safety monitoring
- ✓Drive down per patient costs
- ✓Reduce clinical site overhead
- ✓Improve patient retention
- ✓ Cater to changing needs of patients (e.g. moving countries, increased mobility)
- ✓ Increase capability to combine disease registries and product registries
- ✓ Meet Regulatory needs

Must advance opportunities to decrease cost of goods so to increase access to patients



Optimise Development

- Comparability - Academia → Industry
- Scale up – Manual → Auto
- Assay Development
- Manufacture location- global vs hub vs in hospital
- Logistics and transport – cross border
- Autologous vs Allo / ex-vivo vs in-vivo

Commercial Viability

- CoGs reduction – Global availability
- Cell Types
- Early Manufacturing development
- Biomarkers to support or predict efficacy
- Reproducibility & process
- Automation
- Manufacturing by design

Market Access Challenges

Challenges for Gene Therapies

Value should always be defined around the customer, and in a well-functioning health care system, the creation of value for patients should determine the rewards for all other actors in the system.

Michael E. Porter, Ph.D.

What Is Value in Health Care? The New England Journal of Medicine; December 8, 2010

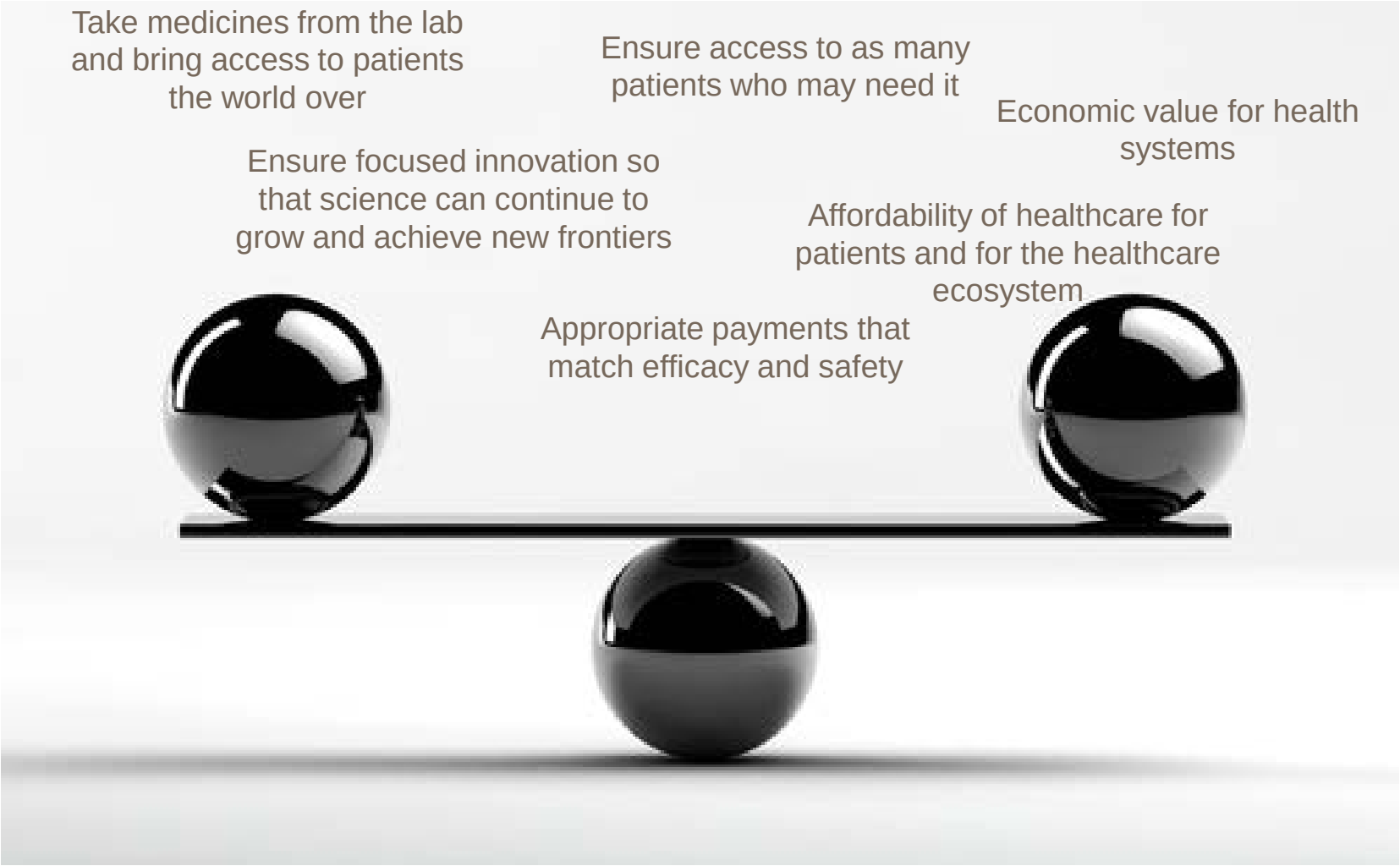
Stakeholders often have conflicting Goals

Achieving high value for the patients must become the overarching goal, leading to Improved performance and accountability of all stakeholders including payers, providers, patients and suppliers

Source: Personal communication Nazanin Mehin

Cell &Gene Therapies carry with them the potential promise of “intervention free survival”

Significant challenges exist to find a balance



Infrastructure for access and reimbursement significantly lags payer and producer intent

Lack of Infrastructure

+

One-time Treatments

+

Small populations

≠

Clear routes
for reimbursement

So why continue to focus on rare and ultra-rare diseases?

Source: businessinsider.com

Thank you