Current Status and Future Trends in Orphan Diseases: a Company Perspective

Carlo Incerti, M.D.

Head Global Medical Affairs

SANOFI GENZYME

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Rare Diseases – Strategic Considerations from a Company Perspective

- Molecular basis of several genetic diseases is well understood; validated drug targets lends to lower technical risks for success.
- If disease mechanism is well understood, drug development risk is reduced, with a rational and feasible clinical path (potential for a rapid POC in man).
- If disease mechanism is well understood *and* there is an outstanding unmet medical need, there is an increased probability of creating a transformative medicine.
- Transformative medicines are compelling from a value proposition standpoint (approval, pricing, reimbursement, penetration)
- Drug development is enhanced by the active participation of tripartite of patient organizations, academia/governments, and companies

Where We Are Today?

- **We know more about rare diseases today**
  - Eighty percent of rare diseases have identified genetic origins and fifty percent of rare diseases affect children
  - Many rare diseases, particularly those related to a genetic defect, can affect multiple organs and as a result they are represented in a highly complex and heterogeneous patient population
  - Diagnosis of rare diseases are often late in the course of disease

- **We know that treating rare disease is more than providing a medicine**
  - Getting to a timely and accurate diagnosis is essential
  - The development of diagnostic tools and training programs is important to ensure patients receive the benefits of treatment
  - The right treatment at the right dose at the right time is essential
  - Treating rare diseases must take a multi-disciplinary, collaborative and holistic approach

- **We better understand the challenges of developing and measuring outcomes of treatments for rare diseases**
  - Small and geographically dispersed populations present recruitment challenges for clinical trials
  - Low prevalence limits the ability to perform multiple studies
  - The heterogeneity of rare diseases pose challenges to uniform treatment paradigms and to study design
  - The slow progression of disease means measurable effect may take years
  - Surrogate endpoints are often more apparent than direct clinical outcomes in rare diseases

Evolution in rare diseases (1)

The past

- Most ultra-orphan diseases are slowly progressive, heterogeneous, genetic diseases
  - Poorly understood natural history
  - Experts are rare with few patients- “academic suicide”
- The knock-out mouse is often the animal model used
  - All mice will be identical
  - Disease progression is homogeneous
  - Human protein therapies provoke strong immune response

Future Trends

- Increasing interest in rare diseases from governments, academia, and industry
  - Patient organisations have a voice
  - Competition among academics, good career prospects
  - Competition in industry
- The knock-out mouse is still the animal model most used
  - Increasing use of iPSC from affected humans
  - Search for “curative” strategies such as gene therapy

Evolution in rare diseases (2)

The past	Future Trends
• The development pathway is unchartered and endpoints often do not exist or need disease-specific validation	• The development pathway remains unchartered and often still very long; • Endpoints often transposed (eg: 6 minute walk test); more disease-specific validation of assessments • Attempts to use biomarkers and surrogate endpoints
• The number of patients for trials are few	• Patients for trials are still few - more ex-EU and ex-US sites are now participating
• The cost of manufacturing and development and product quality as well as risk to patients are equivalent to other diseases	• The cost of manufacturing and development are still not very different than for more common diseases with multiple strategies under study to address this

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(Mol Gen Metab 2012; 367:1096)

Key factors for success: The right people

- Top scientists and clinicians knowledgeable about the disease
  - Elucidate the pathophysiology of the disease
  - Gather dependable natural history data on the disease
  - Generate an animal model for the disease
  - Assist in identifying relevant clinical endpoints and clinical trial design
  - Participate in complex and prolonged clinical trials and registries
- Active patient organisations
  - Translate the science advances into language patients understand
  - Encourage participation in natural history studies over several years
  - Assist clinicians, regulators, and payers in understanding what is important to the patient
  - Assist in identifying eligible patients for clinical trials, support retention (travel, lodging etc)
  - Patient support and education

Key factors for success: Continuous dialogue with the stakeholders

- Regulators and payers also require education on the disease and potential treatment
  - Increasing dialogue and willingness to accelerate development- Breakthrough therapy designation, scientific advice, SEED (Shaping European Early Dialogues) program
- General awareness of the disease with clinicians is also important
  - Publications in scientific journals on the natural history and clinical trial results is key

Global Trends in Access and their Impact on Orphan Drugs

- **The Perfect Storm**
  - The global recession has forced governments to reconcile budgetary challenges in a time when there is an increasing demand for health care services
  - Payers are increasingly questioning 'value' and demanding more evidence and greater certainty of clinical outcomes
  - Evaluation and reimbursement methodologies not aligned with the current technological challenges of diagnosing and treating rare diseases

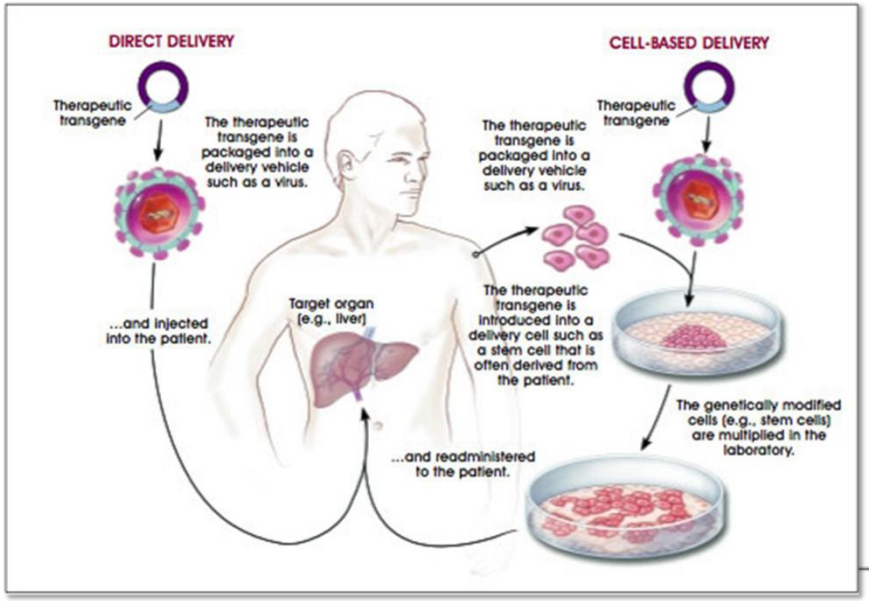
- **Evidentiary requirements tied to reimbursement can influence clinical program selection and increased investment in evidence generation**
  - Clinical Added Value of Orphan Drugs (EU)
  - Value Based Pricing (UK)
  - Increasing collaboration between regulators and payers through shared data

- **Diverse legislative and regulatory requirements for product designation, approval and reimbursement can influence patient access to orphan medicines**
  - Diverse health care systems with distinct definitions, criteria and requirements
  - Local clinical trial requirements
  - Varied access and reimbursement programs including special access schemes, managed entry agreements, decisions at high aggregate level versus local level

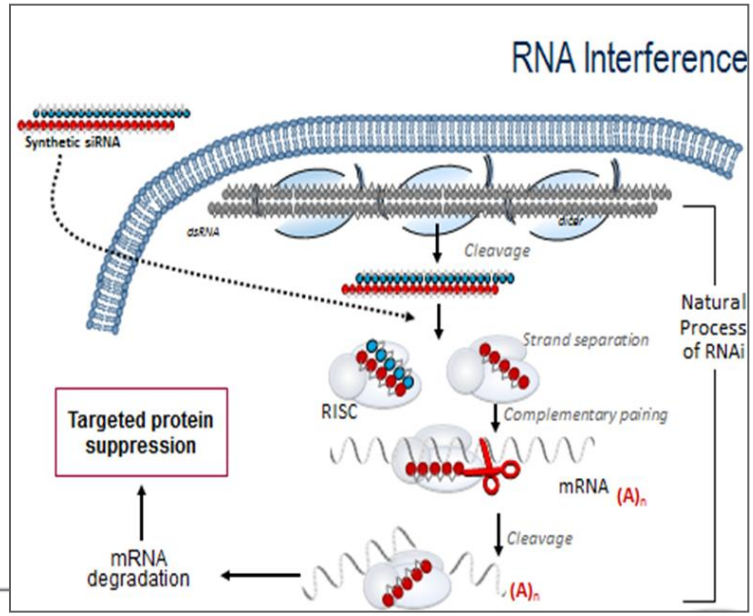
Scientific Considerations for the future

Will gene therapy, RNAi, or other new technologies like cell therapies be "the cure" of the future?

Direct or Cell-based Gene Therapy



RNA silencing either through synthetic conjugate or viral vector



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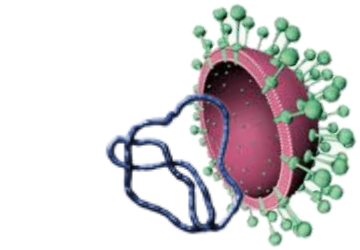
Significant Progress in Gene Therapy R&D; Evidence of Clinical Efficacy

Viral Vectors deliver a genetic payload



Gene expression

Vaccines


Infectious antigen


chimeric viruses


Inactivated or live attenuated


VLPs

Gene therapy


therapeutic protein

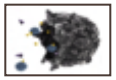

shRNA exon skipping


gene editing

Immuno-oncology


Oncology antigen


CAR/TCR


Oncolytic viruses immune adjuvants

Objective: Triggers an immune response

Objective: Correct a pathological pathway

Objective: Boost or redirect immunity

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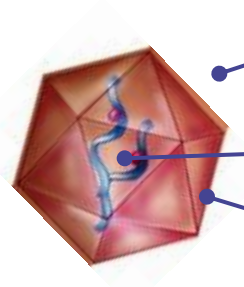
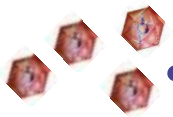
Progress the past 20 years



Viruses: from adeno to AAV; from retro to lenti (better safety profiles)

Improved **vector design** (increased safety and expression)

New **capsids** (targeted delivery and improved transduction)



Improvements in process **development and manufacturing** for higer yield, robustness, & purity - at scale (commercial capacity; decreased lot-to-lot variability)

Development of **analytics** to provide better quality control

Improved **clinical trial design**: delivery techniques, monitoring of safety signals, application of transient immuno suppressions

Identification of **correct targets** for GT

... emerging clinical successes

APPROVED

GLYBERA® *(AAV gene therapy)*

IMVANEX® *(Genetic vaccine)*

IMLYGIC® *(Oncolytic virus)*

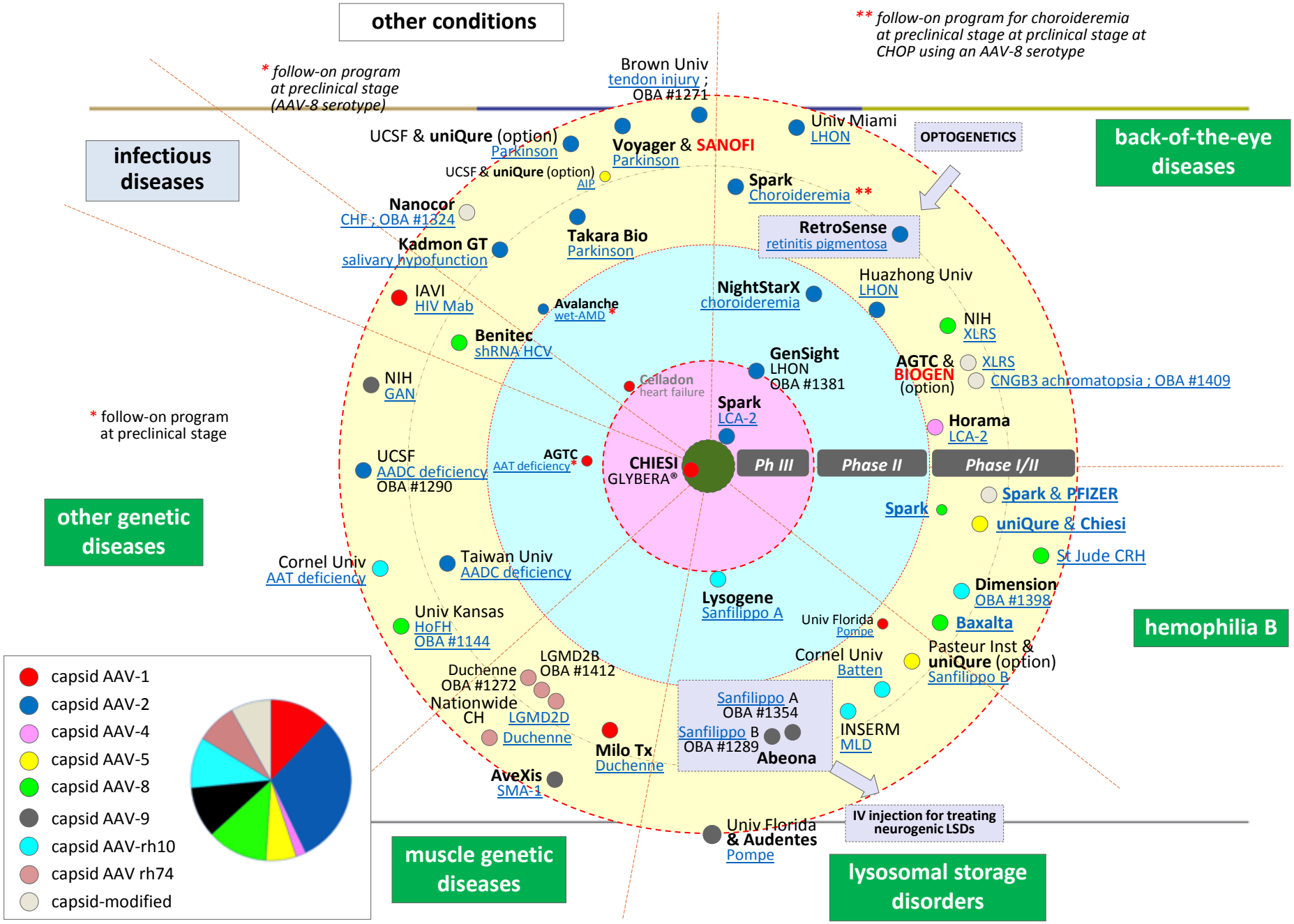
COMING SOON

Retinal dystrophies *(AAV gene therapy)*

dengue & ebola *(genetic vaccines)*

ADA-deficiency *(vgene-modified HSCs)*

Example of Competitive Landscape – AAV Gene Therapy



What will developing treatments for rare diseases look like in the future?

- Remote monitoring for Real World Efficacy data
  - Wearable devices
  - Web – based systems
- Newborn screening will soon identify many rare diseases with early treatment in order to prevent end-organ damage
- Long-term follow-up:
  - Registry is rapidly becoming the most commonly used instrument
    - academia, industry, government, patient association
  - Increasingly patient reported outcomes are being collected
    - Multiplicity of non-communicating databases
    - Still in infancy as validated tool to support approval

Conclusions

What worked in the past should be true for the future

- Know the pathophysiology and natural history of the disease well
  - Start a robust natural history **yesterday**, link Patient Reported Outcomes (PRO), assessments and common databases, look for predictive biomarkers
  - Early dialogue with regulators to get buy-in of paediatric development plans, end-points, and assessments
  - Newborn screening programs for rare diseases are increasing worldwide which should allow for earlier treatment and better outcomes
- Get the right stakeholders together
  - Patient Organisations, Academia/clinician experts, Industry
  - Validate the end-points for the disease - keep abreast of developments in technologies

Conclusion (cont.)
Improve diagnostics and monitoring

- Diagnostic Tests
- Screening Tests
  - Newborn
  - High Risk Populations
- Biomarker / Monitoring Assays
- Genotyping Assays (phenoptypic correlation)
- Special Tests (e.g. prognostic)

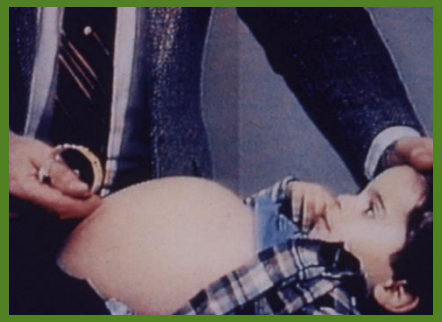
Conclusion (cont.)
Call to avoid creating “new orphans”

- Incentive to accelerate therapeutic developments (upstream investments)
- Understand and accept that a higher degree of uncertainty might persist when judging safety and efficacy data (downstream assessment)
- The real win is in optimizing health gains for each patients.

A lifetime commitment

"My mom was just tremendous and an amazing role model for me. I know the doctors told her that I was going to die but her perseverance, dedication and ability to work closely with Genzyme and search around the world to develop a treatment was amazing."

– Brian Berman, Type 1 Gaucher disease



1983

1991

2001

2011

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