Orchard Therapeutics

Overcoming the complex challenges associated with ex vivo gene therapies

Adrien Lemoine
VP Business Development & Operations

FIERCE WINNER

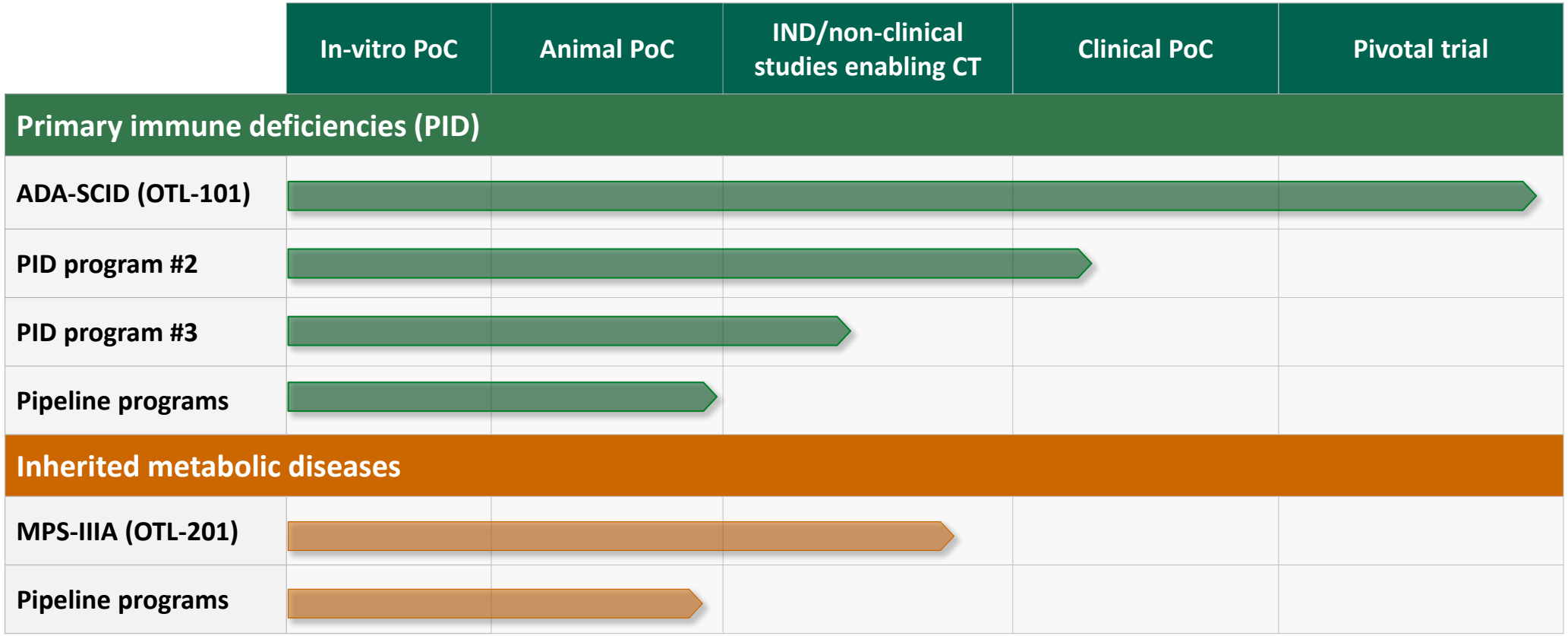
CIRM CALIFORNIA'S STEM CELL AGENCY

Orchard at a glance

Who we are	• Late-stage biotechnology company • Incorporated in September 2015 • Funding: £21m Series A; $19m grant from CIRM; ongoing Series B funding round • 2016 Fierce 15 company
Our mission	• To be a leading global, fully integrated company delivering innovative gene therapies that transform the lives of patients with rare disorders
Team	• A focused, entrepreneurial team experienced in the development, manufacture, commercialization and registration of advanced therapies for orphan diseases
Academic partners	• Scientific Advisory Board with leading experts and pioneers of gene therapy
Locations	• London (UK) • Foster City (California)

Orchard pipeline

Programs in primary immune deficiencies (PIDs) and inherited metabolic diseases



Building deep expertise in primary immune deficiencies and inherited metabolic diseases

PoC: Proof of Concept **IND**: Investigational New Drug **CT**: Clinical Trials

Challenge 1: the patient journey

OTL-101 illustration

Orchard therapeutics

Diagnosis of ADA-SCID

Treatment option evaluation:
- allogeneic HSCTs
- chronic ERT
- autologous GT

Prescription of autologous LV gene therapy

Bone marrow harvest

Hospitalization

Conditioning
(non-myeloablative Busulfan)

Gene therapy
(Day 0)

Initial follow-up
(in hospital, ~3-30 days)

Hospital discharge

Long-term patient follow-up (15 years)

Orchard therapeutics

Drug product manufacturing
- CD34+ stem cell isolation
- CD34+ purification
- Transduction with a lentivirus modified to implant a functional ADA transgene into the stem cells

Cryopreservation

Quality Control tests

Shipment
(dry LN2 shipping container)

Thawing

Patient-facing activities

Manufacturer of autologous LV gene therapy

Challenge 2: manufacturing a personalized GMP cell product

Orchard's platform illustration

Orchard therapeutics

Orchard therapeutics

Hospital

Drug product manufacturing facility

Lentiviral vector manufacturer

Collect blood or bone marrow

Thaw and infuse product

Ship tissue to manufacturing facility

PCT Cell Therapy Services, LLC
A Hitachi Group Company

Lonza

Isolate hematopoietic stem cells

Gene-modify HSCs with disease specific lentiviral vector

Cryopreserve HSC product

Ship cryopreserved product to hospital

OxfordBioMedica

Manufacture disease-specific lentiviral vector

Challenge 3: long term safety follow-up

Evolution and progress of the ex vivo gene therapy field

1970s: concept of gene therapy
- Replacing defective DNA with "good DNA"

1990: first patient treated: a 4 year old ADA-SCID treated with T-cell *ex vivo* GT

1993-2003: challenges for ex vivo GT research
- 2000s: some leukaemia and myelodysplasia cases with gamma-retrovirus vectors
- **2003: temporary FDA halt on using gamma-retrovirus vectors**

Development of safer vectors

Improved integration profiles

From 2000-2010: *ex vivo* GT major advances
- Metabolic disorders: **ALD**, **MLD**
- Primary immune deficiencies: **ADA-SCID**, **X-SCID**, **WAS**, etc.

Orchard Therapeutics established Nov 2015
- ***Ex vivo* lentivirus mediated GT**
- **ADA-SCID; MPS3-A**

2016: First *ex vivo* GT approved in EU
- **Strimvelis: ADA-SCID gamma-retrovirus mediated GT**

ADA-SCID: adenosine deaminase severe combined immunodeficiency
ALD: Adenoleukodystrophy
X-SCID: X-linked severe combined immunodeficiency
MLD: Metachromatic Leukodystrophy
WAS: Wiskott-Aldrich syndrome

The reward: strong efficacy and safety profile

Orchard therapeutics

Lentivirus-based gene therapy in ADA-SCID

- **48 patients treated as of end of June 2017, all alive**
  - In clinical study: 27 US, 10 UK
  - Compassionate Use/Early Access: 10 UK; 1 US
- 100% survival, follow-up 1 month to 5 years
- 98% (47/48) have stopped enzyme replacement therapy
- Safety profile continues to be favourable

The unique challenges of developing ex vivo gene therapy medicines are worth the reward!

Orchard therapeutics

Challenges → **Reward**

- Patient/family logistics
- GMP vector manufacturing
- Consistent transduction process
- Long term safety follow-up

- Bringing to the world one-off treatments that transform the lives of patients

Orchard Therapeutics

Bringing transformative gene therapies to patients with severe and life-threatening rare diseases

www.orchard-tx.com