Erythrocyte mediated enzyme replacement therapy

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Reader in Rare Diseases

PRESENTATION CONTEXT

Development of cell-based therapies for treatment rare inherited metabolic diseases- unmet clinical need

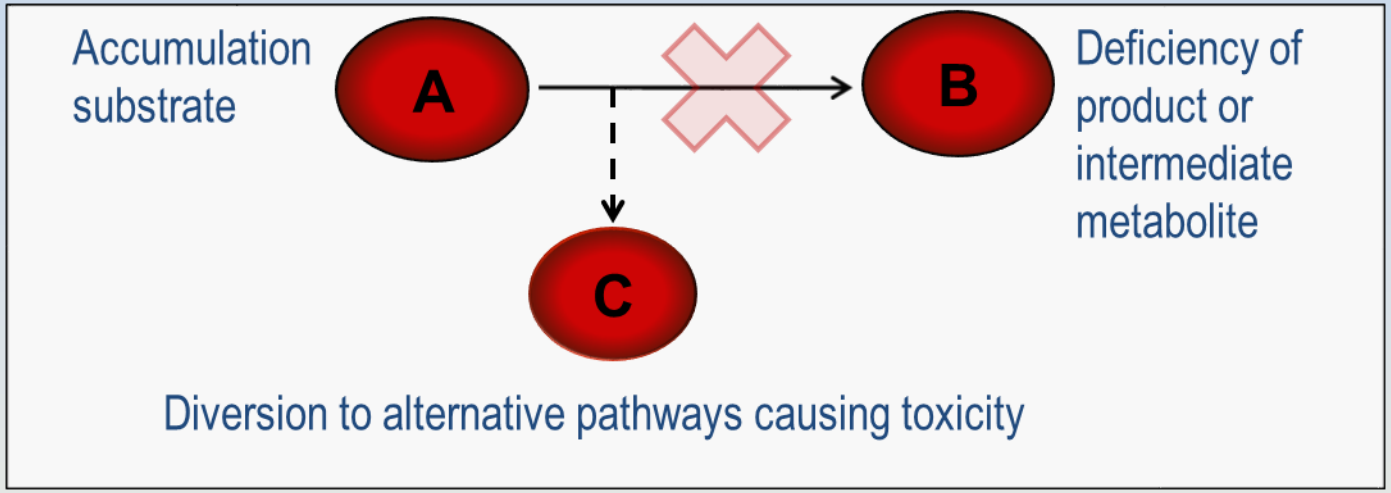
DEFINITIONS

Rare disease:

- European Union: affects < than 5 in 10,000 of the general population
- USA: affect fewer than 200,000 people (Japan < 50,000; Australia < 2,000)

Inherited metabolic disease (IMD):

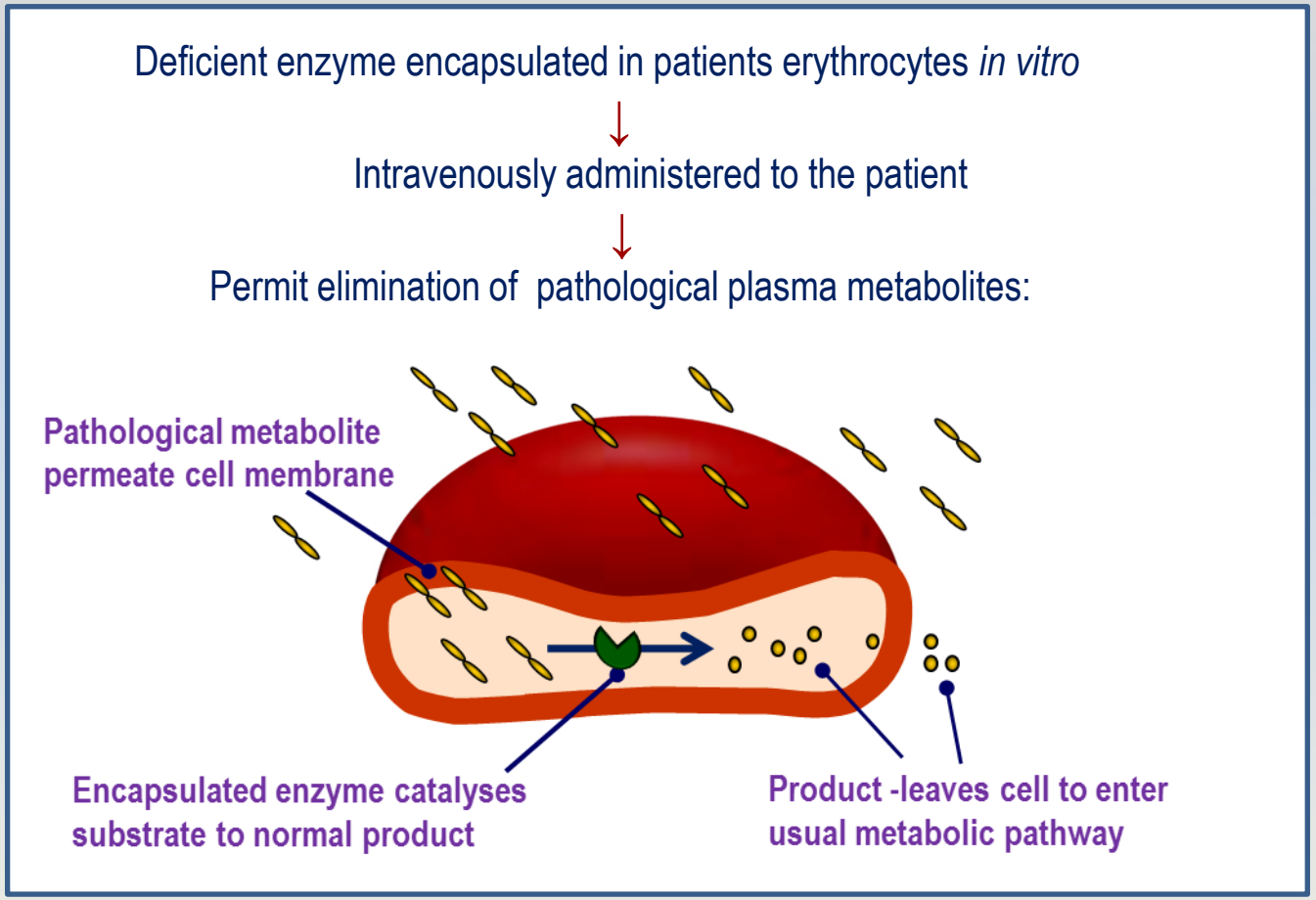
- a disorder where a single mutation in a gene causes a deficiency in a specific enzyme or transport protein → clinically significant block in a metabolic pathway
- Possible consequences:
- Therapeutic strategies
  - Substrate reduction
  - Product replacement
  - Gene product replacement
    - Gene therapy
    - Cell and organ transplantation
    - Enzyme replacement therapy (ERT)



Theoretical defective metabolic pathway due an enzyme deficiency

ERYTHROCYTE- MEDIATED ENZYME REPLACEMENT THERAPY

- Autologous erythrocyte - carrier system for therapeutic enzymes
- Under development for > 20 years
- Approach:



Applicable to disorders where pathologically ↑ metabolite permeate erythrocyte membrane

- Scientific rationale: sustained ↓ accumulated metabolites arrest/ reverse progression of clinical disease

ADVANTAGES OF THERAPEUTIC APPROACH

Strategy

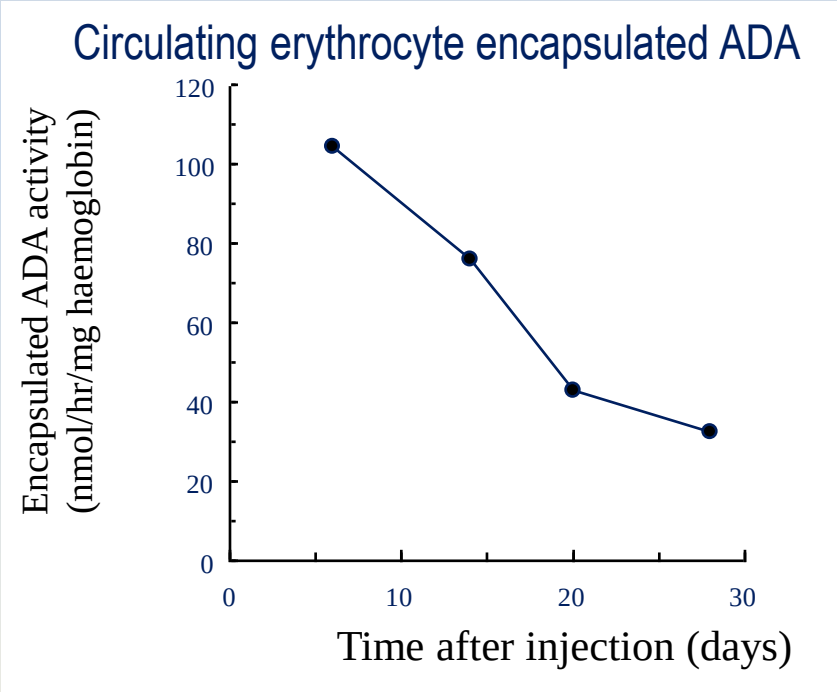
↑ enzyme activity
half-life

Majority licensed enzyme replacement therapies (ERT):

Short plasma half-life (mins - hours)

Frequent infusions: maintain therapeutic effective levels (cost implication)

Enzyme	Plasma $T_{1/2}$
Glucocerebrosidase (Gaucher disease)	18 mins
Galactosidase (Fabry disease)	1-2 hours
Adenosine deaminase (ADA deficiency)	< 30 mins
Pegadamase	72 hours
Erythrocyte encapsulated ADA	**12.5 days**



ADVANTAGES OF THERAPEUTIC APPROACH

Majority licensed enzyme replacement therapies (ERT):

Strategy:

↓ immunogenic reactions

↓ production anti-enzyme antibodies

- **Anti-enzyme antibody production →loss of therapeutic efficacy**
- **Allergic reactions**

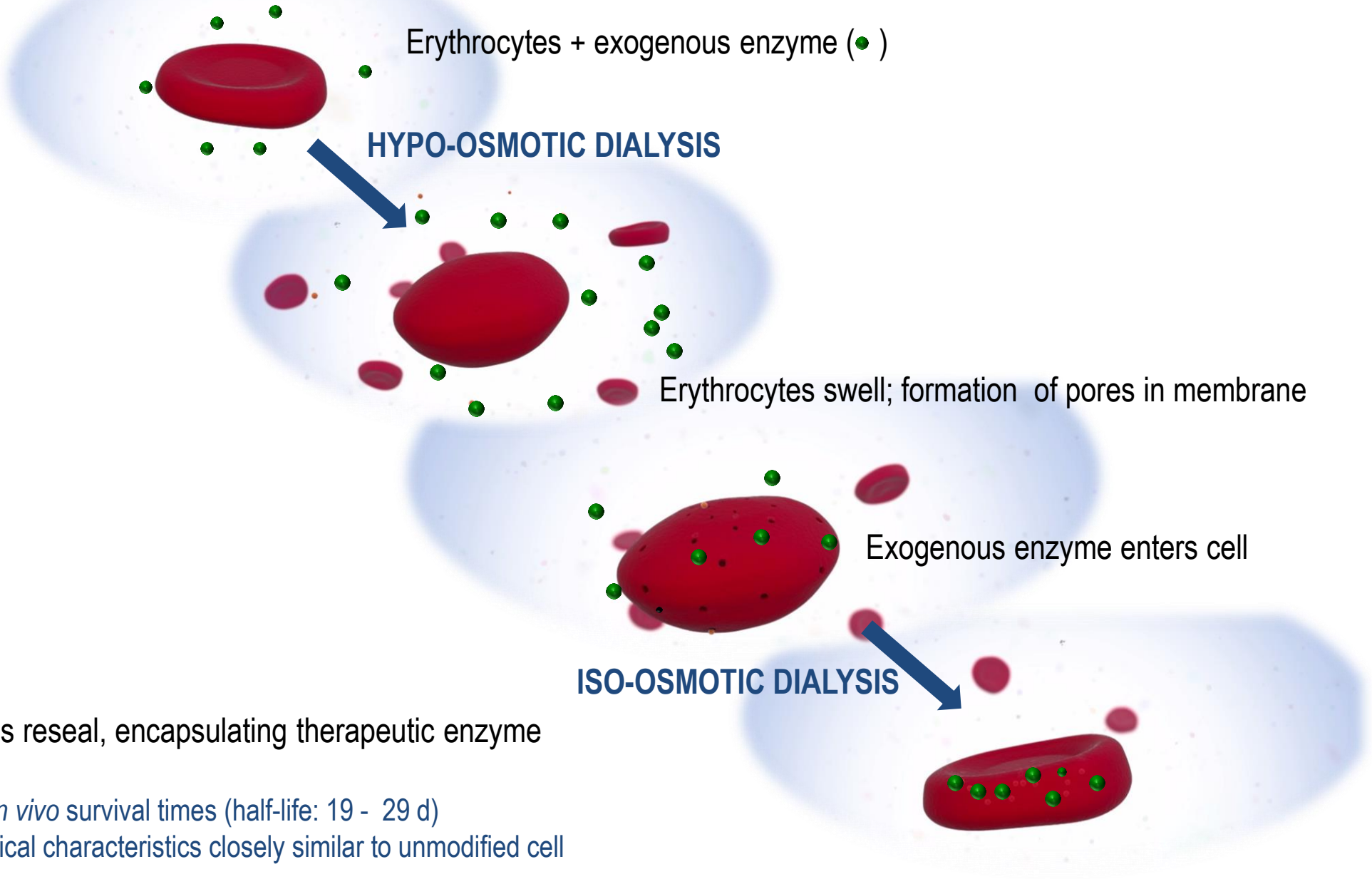
Disease	Enzyme	IgG positivity (%)	Allergic reactions
Fabry Disease	Agalsidase beta	70-80	√
Type 1 Gaucher disease	Imiglucerase	15	√
	Velaglucerase alfa	2	√
	Taliglucerase	53	√
Glycogen Storage Disease type II	Alglucosidase alfa	89	√ Severe
Mucopolysaccharidosis type I	Laronidase	97	√ Severe
Mucopolysaccharidosis type II	Idursulfase	51	√ Severe
Mucopolysaccharidosis type IVA	Elosulfase alfa	100	√ Severe
Mucopolysaccharidosis type VI	Galsulfase	98	√ Severe
Lysosomal acid lipase deficiency	Sebelipase alfa	57	√ Severe
Adenosine deaminase deficiency	Pegademase	59	√
Hypophosphatasia	Asfotase alfa	78	√

Nausea
Itching
Headache
Rash

Fever
Vomiting

Cardiac dysfunction
Anaphylaxis
Hypotension
Respiratory symptoms

ENCAPSULATION PROCESS



Erythrocytes reseal, encapsulating therapeutic enzyme

- Normal *in vivo* survival times (half-life: 19 - 29 d)
- Biochemical characteristics closely similar to unmodified cell

CLINICAL EXPERIENCE WITH ERYTHROCYTE-MEDIATED ERT

Disorder	Study type	Treatment
Adenosine deaminase deficiency	Compassionate use[1]	Single patient, 17 years Erythrocyte Encapsulated ADA: EE-ADA
Mitochondrial **N**euro**G**astro**I**ntestinal **E**ncephalomyopathy - **MNGIE** (thymidine phosphorylase deficiency)	Proof of concept[2]	One patient: Single dose Erythrocyte Encapsulated Thymidine Phosphorylase: EE-TP
	Compassionate evaluation[3]	Three patients: Escalating doses EE-TP

Compassionate use: unlicensed product made available to patient with severe disease and no available treatment

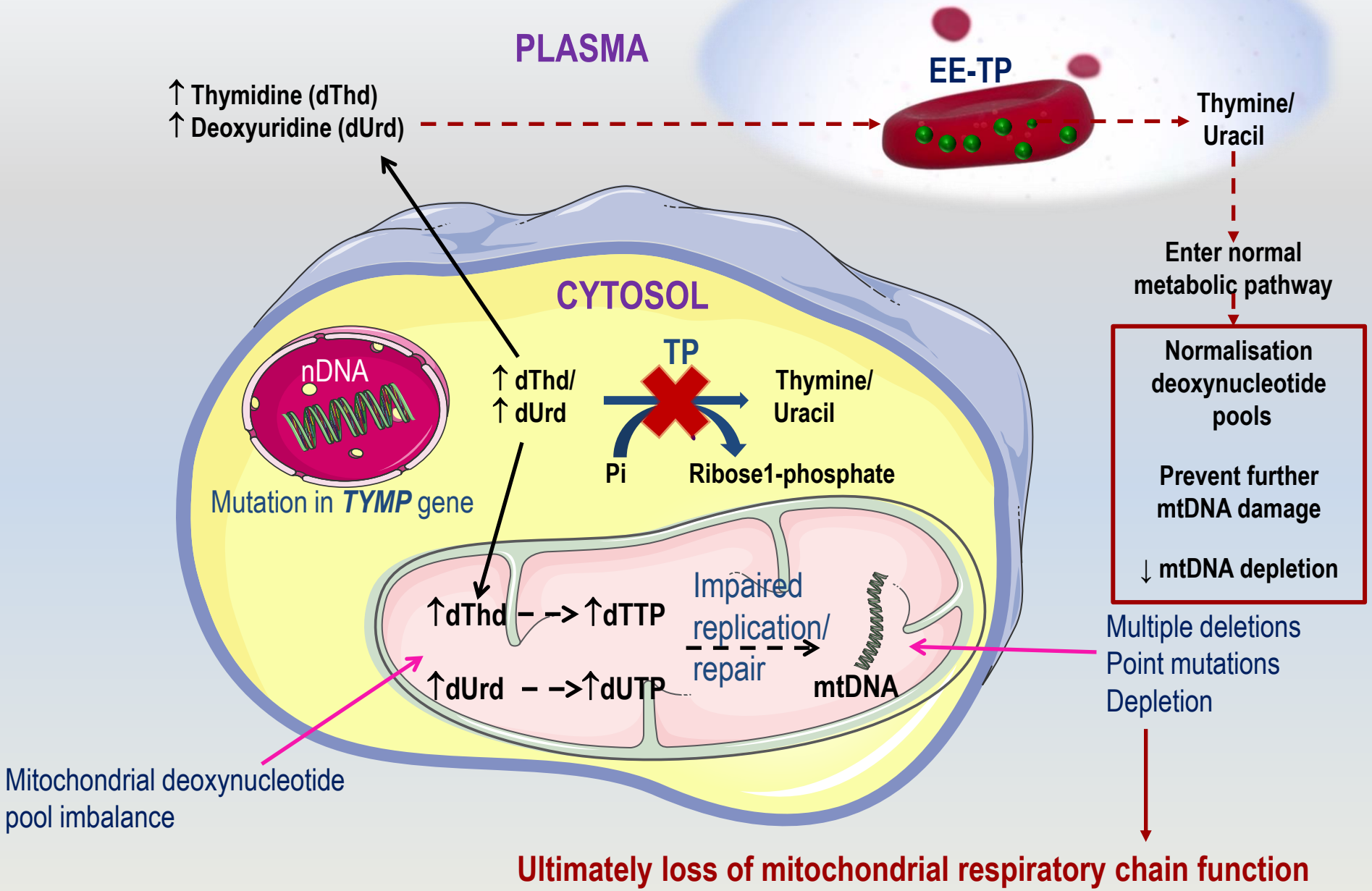
Manufacture: performed under a Specials licence held by St. George's Healthcare Trust Pharmacy according to the Rules and Guidance for Pharmaceutical Manufacturers 2007 (MHRA)

[1]Bax, B.E., Bain, M.D., Fairbanks, L.D., Webster, A.D.B., Ind, P.W., Hershfield, M.S. and Chalmers, R.A. (2007). *European Journal of Haematology,* 79, 338-348.

[2]Moran, N.F., Bain, M.D., Muqit, M. and Bax, B.E. (2008).*Neurology*. **71**, 686-688.

[3]Bax, B.E., Bain, M.D., Scarpelli, M., Filosto, M., Tonin P., and Moran, N. F. (2013).*Neurology.* **81**, 1269-1271.

METABOLIC DEFECT IN MNGIE AND TREATMENT WITH EE-TP



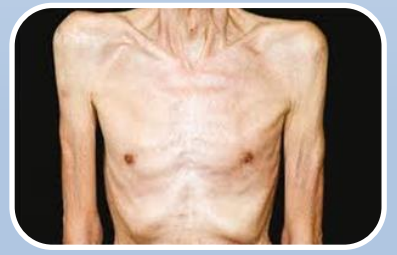
Ultra-rare estimated prevalence 1 in 1 million

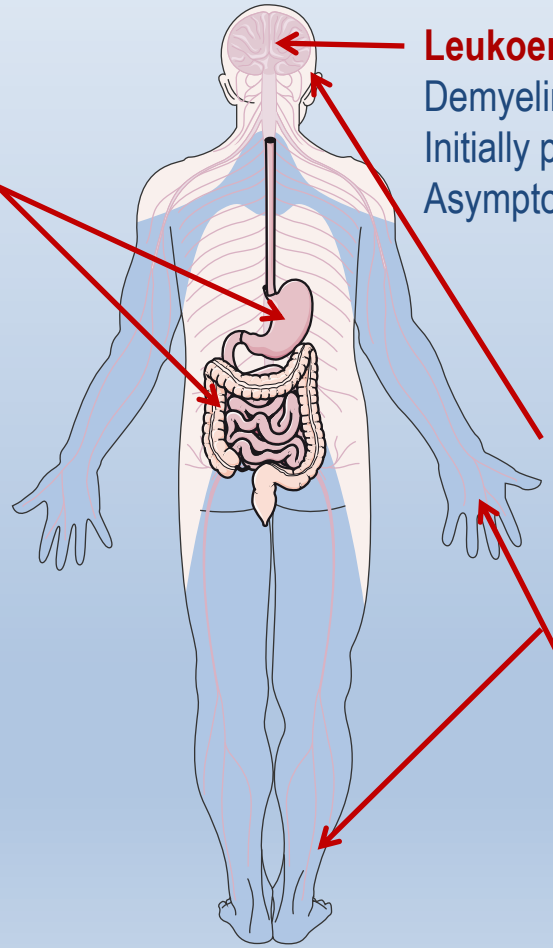
SYMPTOMS OF MNGIE

Manifests clinically as multi-systemic disease
Predominantly effects gastrointestinal and nervous systems

Gastrointestinal symptoms

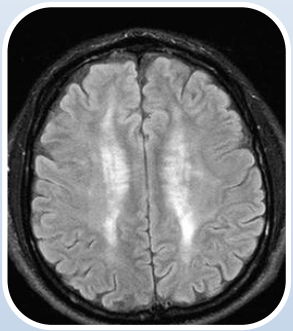
Severe gastrointestinal dysmotility
(dysfunction of muscles of GI tract)
Nausea/vomiting
Chronic abdominal pain
Premature satiety
↓
Malabsorption
Bacterial over-growth
Loss of muscle mass
Anorexia





Neurological symptoms

Leukoencephalopathy
Demyelination nerve fibres
Initially patchy →more confluent
Asymptomatic?



Ocular symptoms
Ptosis
Ophthalmoplegia
Loss of vision

Peripheral neuropathy
Numbness
foot drop
muscle weakness
hearing loss

MNGIE: UNMET CLINICAL NEED

Death average age 37 years

- combination nutritional/neuromuscular failure- high mortality

Allogeneic haematopoietic stem cell transplantation under investigation

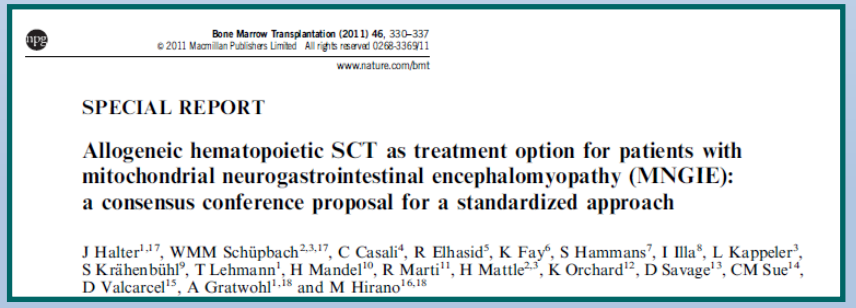
- high mortality risk (> 60%)
- limited by matched donor availability (< 30%)
- oligo-symptomatic: reluctant

Consensus proposal (Halter, 2011) for standardising SCT procedure

Restricted to patients:

without irreversible end-stage disease

with optimally matched donor



Bone Marrow Transplantation (2011) 46, 330–337

www.nature.com/bmt

SPECIAL REPORT

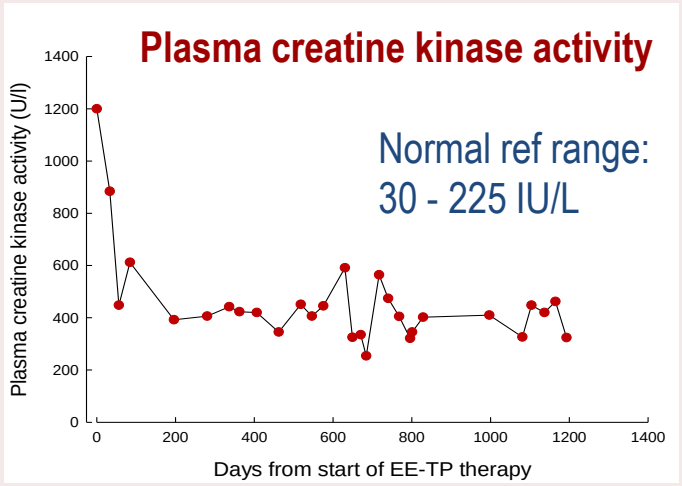
Allogeneic hematopoietic SCT as treatment option for patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a consensus conference proposal for a standardized approach

J Halter[1,17], WMM Schüpbach[2,3,17], C Casali[4], R Elhasid[5], K Fay[6], S Hammans[7], I Illa[8], L Kappeler[3], S Krähenbühl[9], T Lehmann[1], H Mandel[10], R Marti[11], H Mattle[2,3], K Orchard[12], D Savage[13], CM Sue[14], D Valcarcel[15], A Gratwohl[1,18] and M Hirano[16,18]

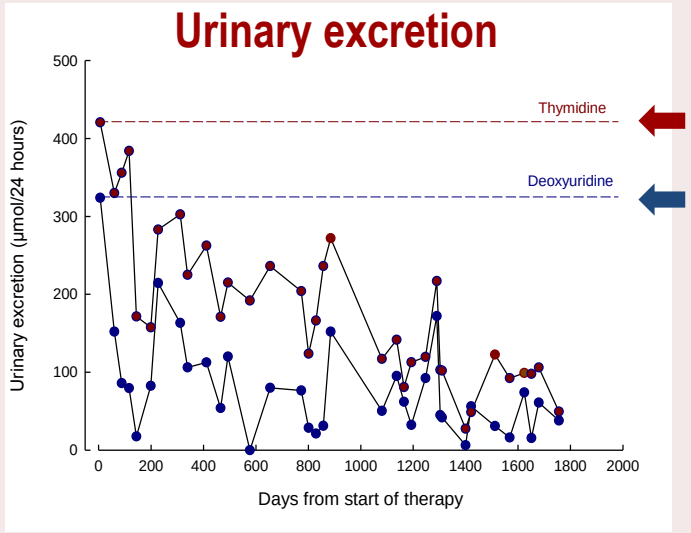
Majority patients ineligible: **critical requirement for alternative treatment strategy**

COMPASSIONATE STUDY METABOLITE DATA: PATIENT 3

Presentation age (yrs)	(♂) **26**
Symptoms • Peripheral neuropathy • External ophthalmoplegia • Intestinal dysmotility • Anorexia	 √ √ Minimal X
EE-TP Administration	28 yrs Dose escalated (IU/kg/4 weeks): **1-2**: 17.0 ± 0.5 **3-23**: 34.2 ± 1.1 **24-73**: 46.8 ± 1.1



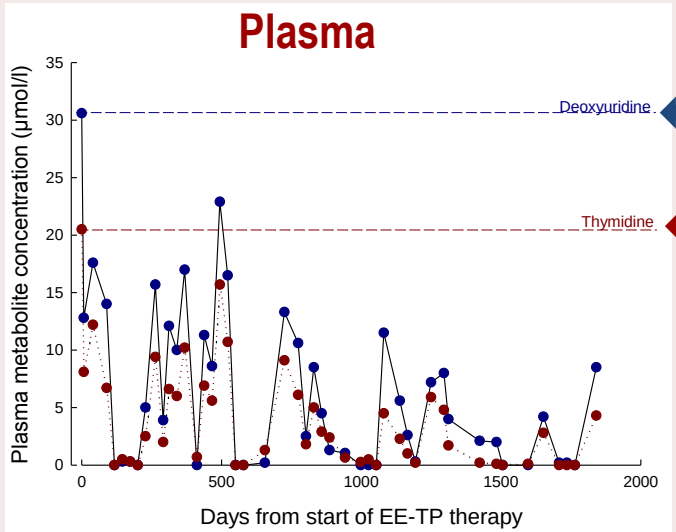
Muscle damage marker
Activity ↓ 1200 U/L pre-therapy to 320 U/L, 39 months



421 µmol/24 hrs

324 µmol/24 hrs

General ↓ in excretion



30.6 µmol/l

20.5 µmol/l

Mid cycle concentrations D520:
< 10.7 µmol/l dThd
< 17.0 µmol/l dUrd

CLINICAL OUTCOME MEASURES: PATIENT 3

Disease rating scales

Scale	Pre-therapy	10 months	17 months	23 months	64 months
SF36 (health and well-being):					
Physical component (population mean 50 ± 10)	48.3	51.7	50.4	50.4	50.4
Mental component (population mean 50 ± 10)	59.7	58.1	60.0	58.5	60.0
Newcastle mitochondrial disease scale (normal = 0):					
I (general neurological functioning, 0 to 50)	4	3	3	4	4
II (system specific functioning, 0 to 45)	2	2	2	2	6
III (clinical assessment, 0 to 50)	11	11	11	11	11
MRC sum motor score (normal = 80)	56	68	74	74	74
Sensory sum score (normal = 0, maximum score = 64)	21	21	19	19	6
Overall neuropathy limitation scale: (0 = no disability, 12 = maximum disability)	3	3	3	3	4

Improvements noted only in: Sensory sum score and MRC sum motor score

Bilateral muscle power improvements in:

- wrist extension and first finger abduction
- knee flexion
- ankle dorsiflexion and great toe extension

Concluded: Other disease scales too coarse to reflect patient reported outcome gains
Carefully consider outcome measures for clinical trial

CLINICAL OUTCOME MEASURES: PATIENT 3

Clinical examination after 18 months revealed:

Improvement in:

- sensory ataxia (balance and gait)
- fine finger functioning
- in body weight, from 57.4 to 63.2 kg

Patient reported outcomes after 23 months:

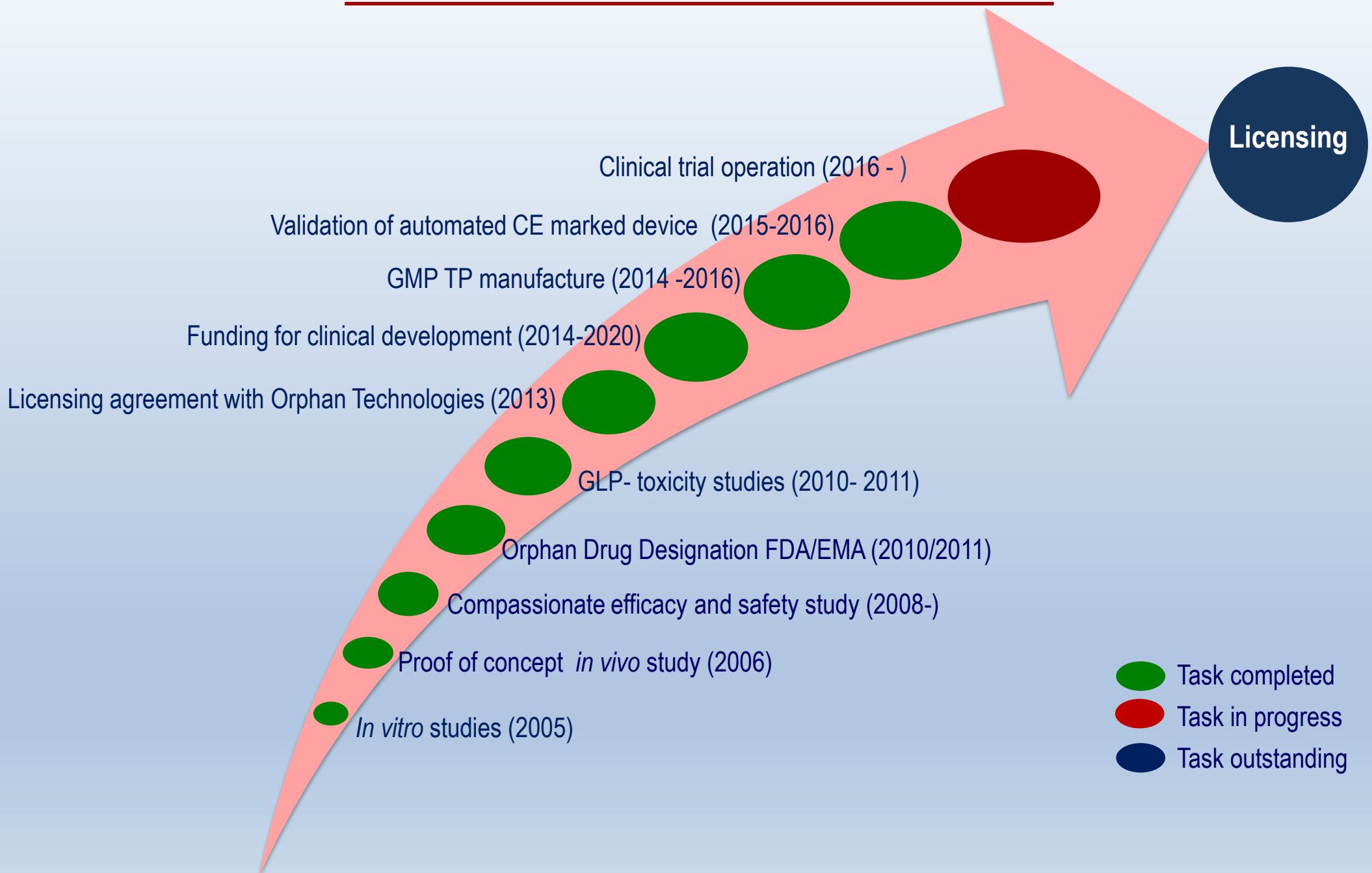
- Walk long distances (10 Km)
- Climb stairs without assistance
- Step on stool to reach high shelves
- Tie shoe laces
- Returned to weight training
- Returned to public performances as guitar player
- Feel sensation of sand on feet
- Previously reported numbness in hands and feet resolved

ADVERSE REACTIONS TO EE-TP

Patient #	Adverse reaction	Duration	Pre-medication
1	X	NA	NA
2	• Coughing • Erythema of face and neck	**Cycles 1-17**: Transient: 5 mins of infusion **Cycles18→** Eliminated	**4 hours prior to infusion:** Oral dexamethasone 10 mg Oral chlorphenamine 4 mg **Prior to infusion:** IV chlorphenamine 10 mg IV hydrocortisone 100 mg
3	• Coughing • Erythema of face and neck	**Cycles 1-11**: Transient: 5 mins of infusion **Cycles 12 →** Eliminated **Cycles 68-73:** GMP material	**4 hours prior to infusion:** Oral dexamethasone 10 mg Oral chlorphenamine 4 mg **Prior to infusion**: IV chlorphenamine 10 mg IV hydrocortisone 100 mg Gradually reducing: Cycle 73: 4 mg Oral dexamethasone only
4	X	NA	NA

GMP preparation eliminated reactions → previous reactions against impurities, rather than enzyme

DEVELOPMENT PATHWAY OF EE-TP



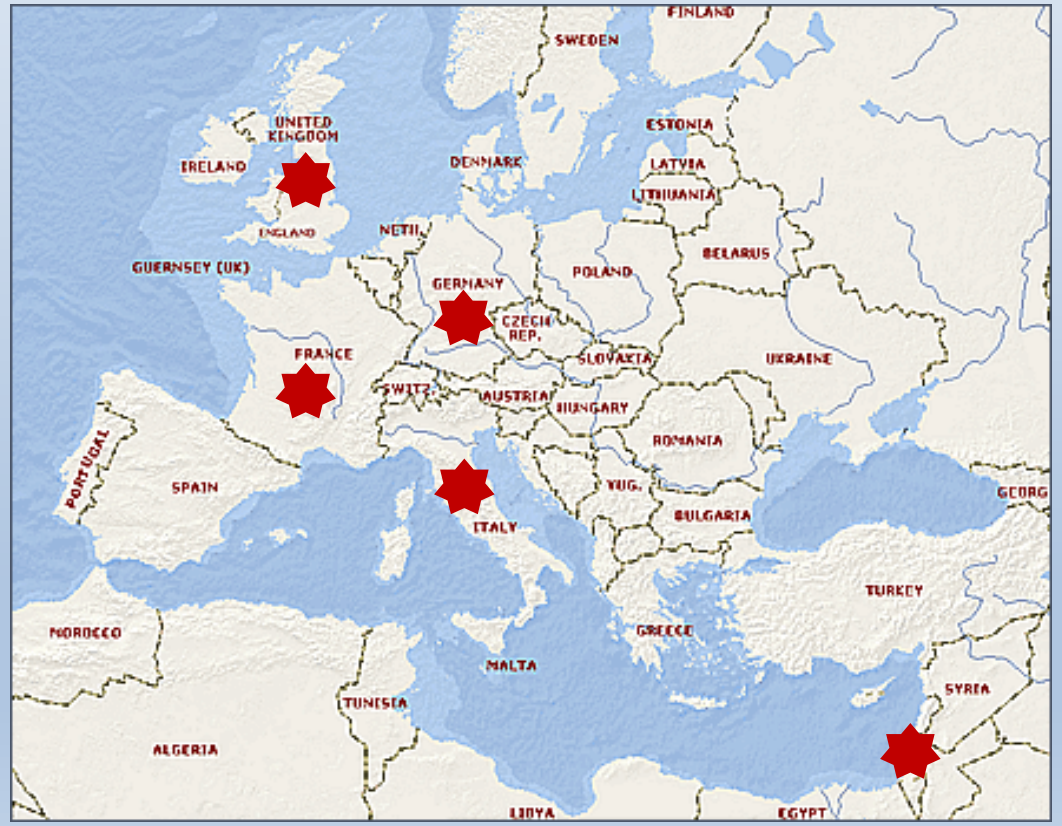
CLINICAL TRIAL OF EE-TP

Study Design

Multi-centre, open-label, multiple ascending dose, Phase II trial in 10 patients MNGIE (Q2 2017)

Principal investigator sites

Germany **France**
Italy **Israel**
UK



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Peter Mollison, Pharmacist

Commercial partner

Orphan Technologies

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Thomas Klopstock, Germany
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UNITED MITOCHONDRIAL DISEASE FOUNDATION
HOPE. ENERGY. LIFE.

Compassionate studies

MRC Medical Research Council

Preclinical studies and Clinical Development

Patients