CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Otto Heubner Centrum für Kinder- und Jugendmedizin

Initial Protocol Assistance – cureMILS

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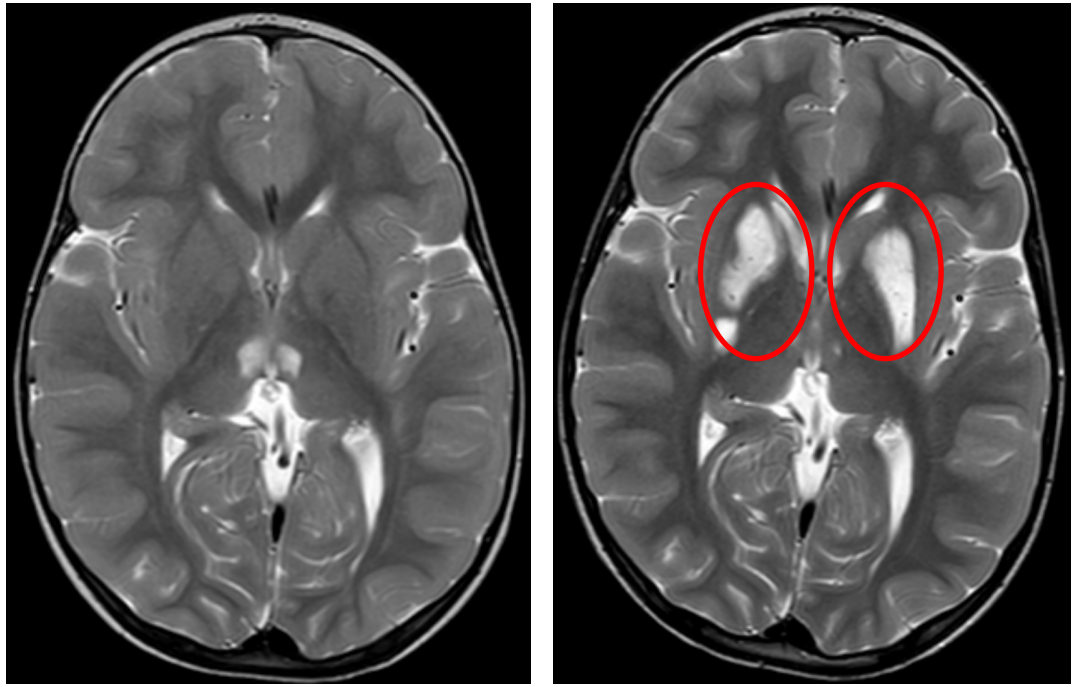
Initial meeting at 10.04.2024

Condition to be treated => Leigh Syndrome

- Maternally Inherited Leigh-Syndrome (MILS)
- Rare disease => 1:36,000 births
- Most frequent cause: mtDNA *MT-ATP6* mutations
- Symptoms: muscle weakness, basal ganglia and brain stem dysfunction, epilepsy, movement disorder, cardiomyopathy
- Presently no disease modifying treatment available
- No clear definition in the literature about the threshold degree of heteroplasmy
  => we chose 90%

Basal ganglia necroses



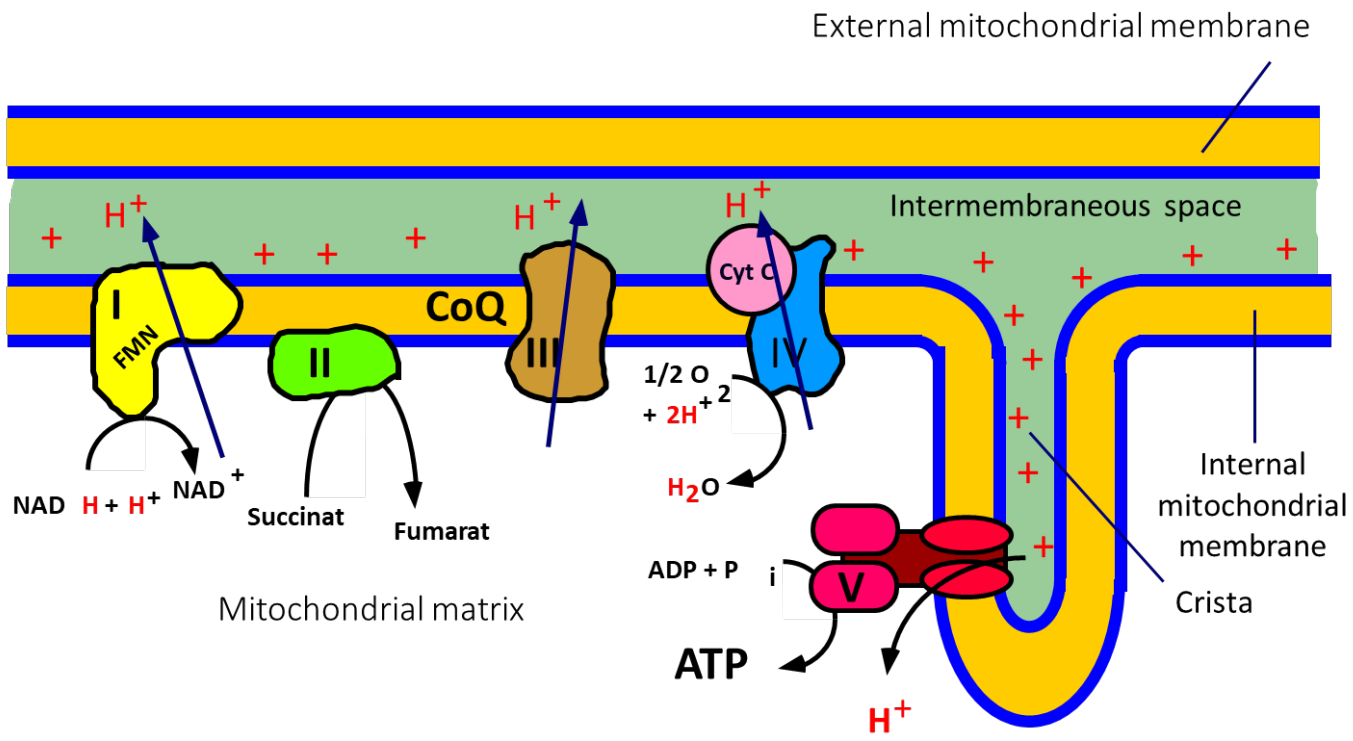
2 years

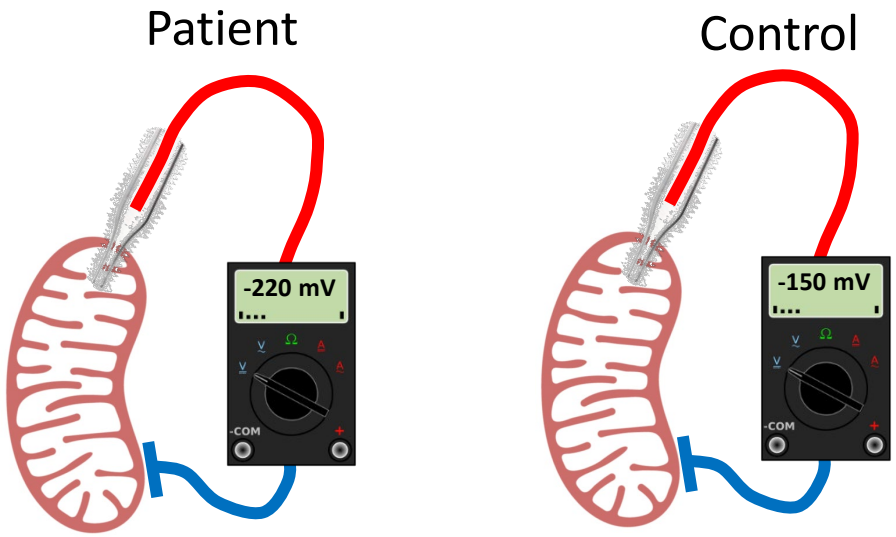
7 years

Screening test

The Screening Principle

=> Measurement of the mitochondrial membrane potential (MMP)

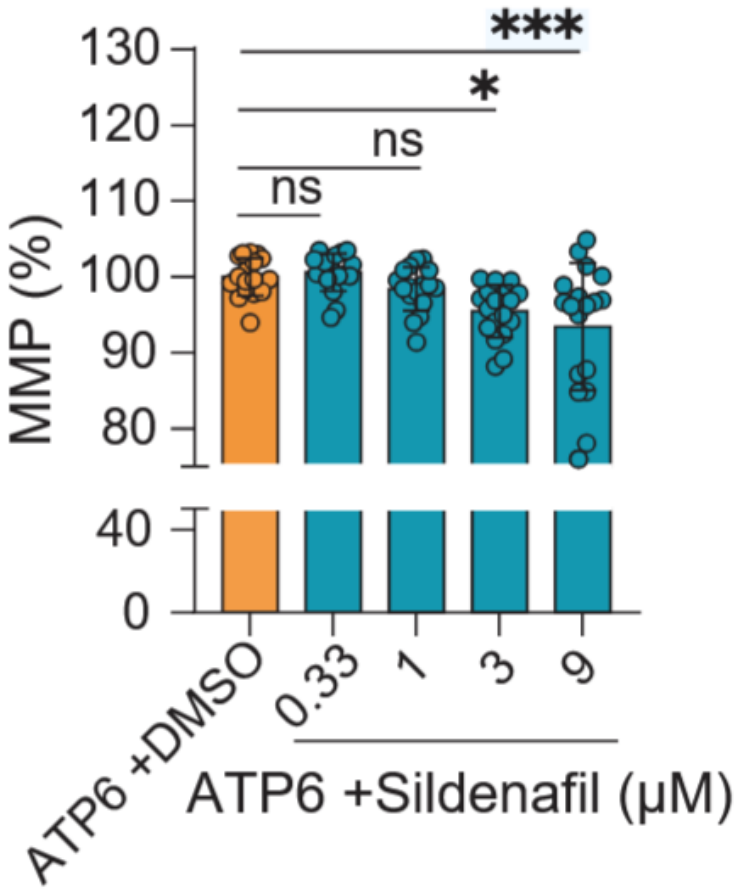


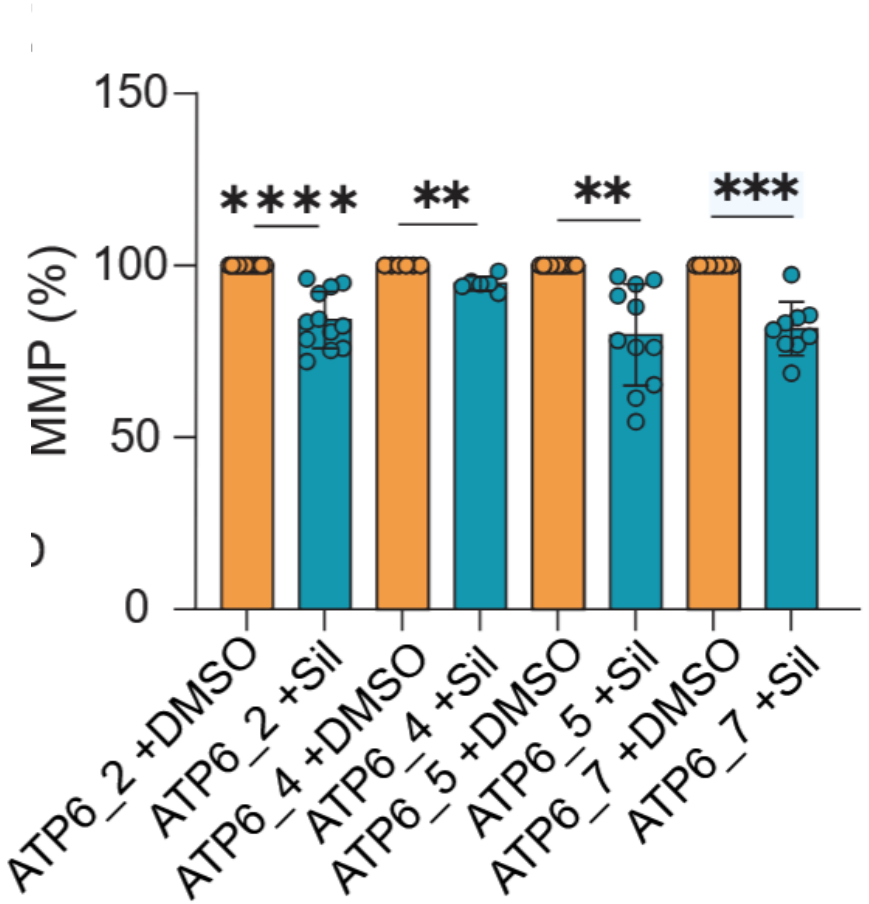


Potentiometric fluorescent dyes (TMRM)

Effect of Sildenafil on the mitochondrial membrane potential

=> Rising extracellular Sildenafil concentrations (confirmation in different patient lines)





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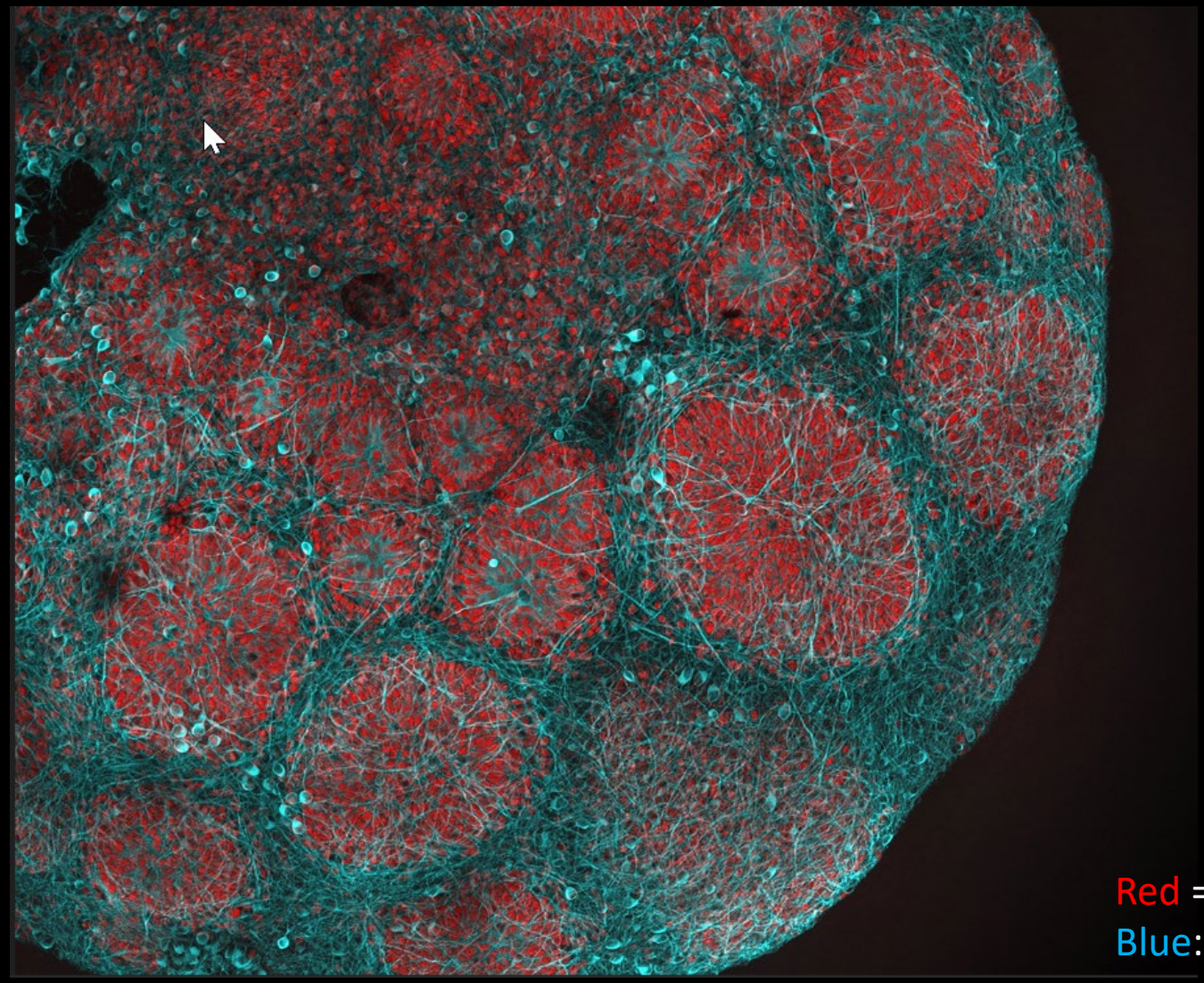
Effect of Sildeanfil on brain organoids

=> Normalization of calcium currents and intramitochondrial calcium concentrations



Red = neuronal precursor cells
Blue: neurons

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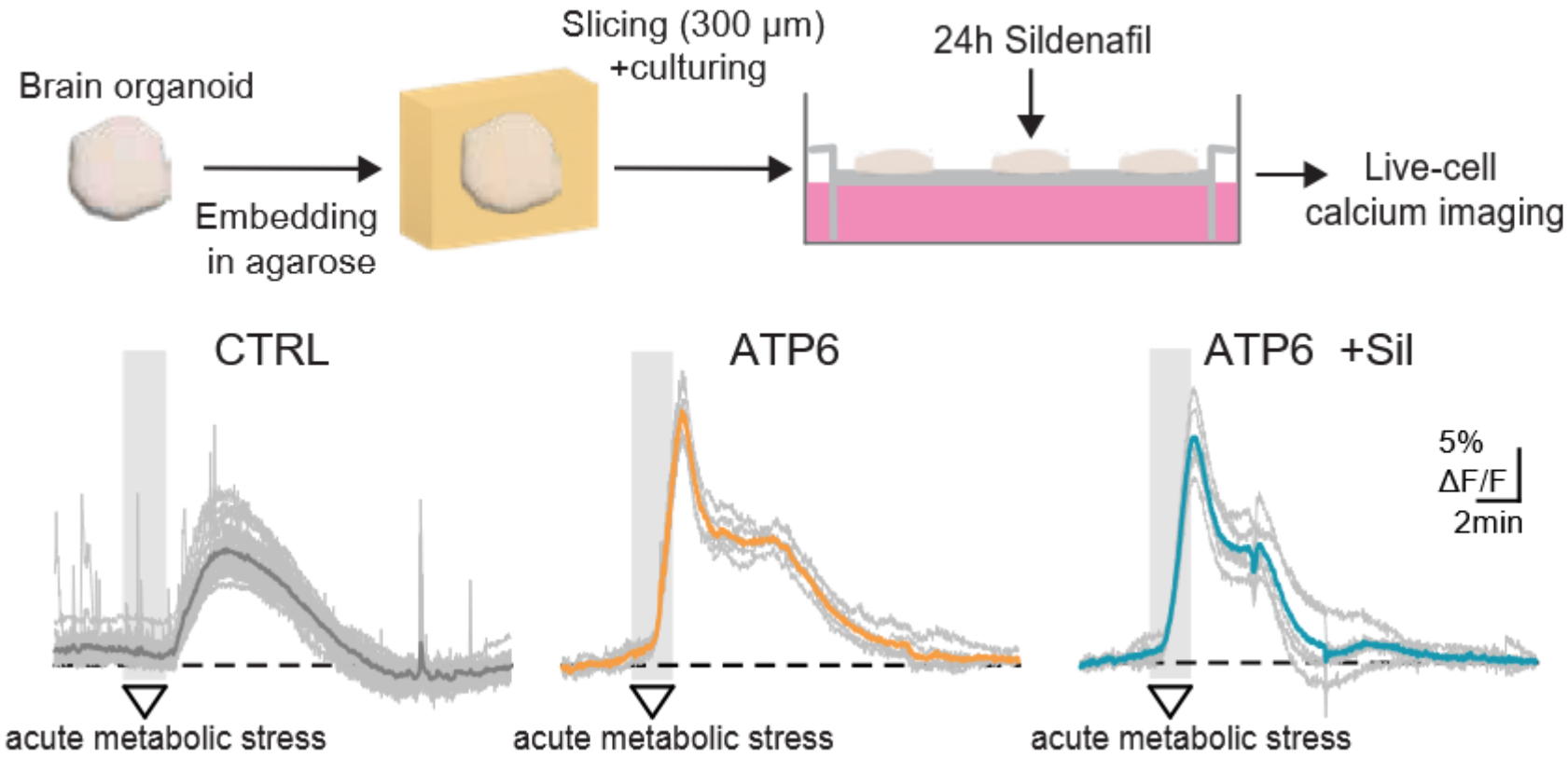

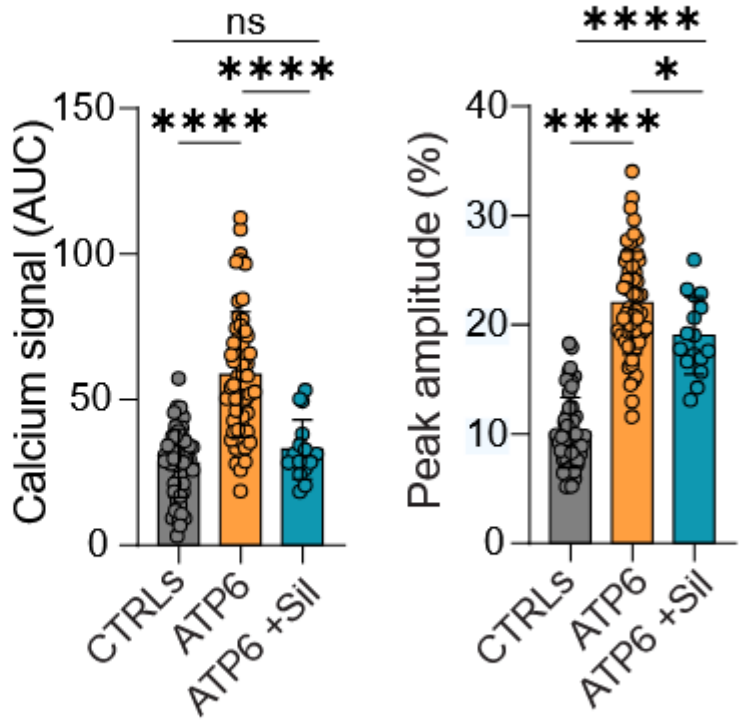

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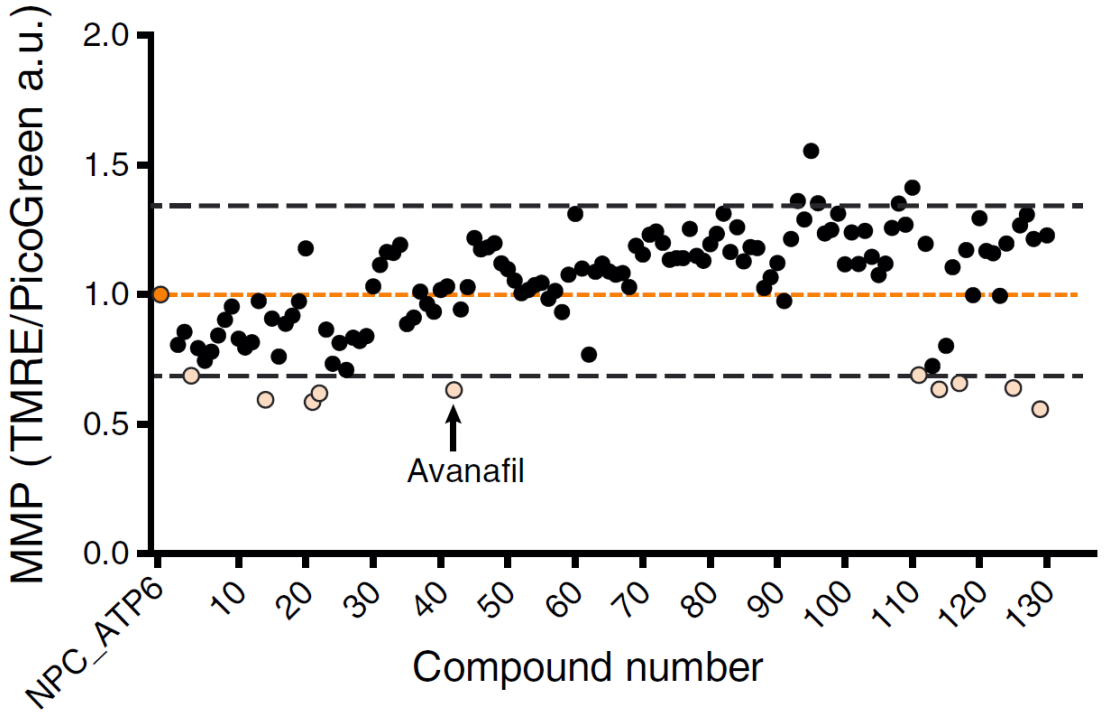
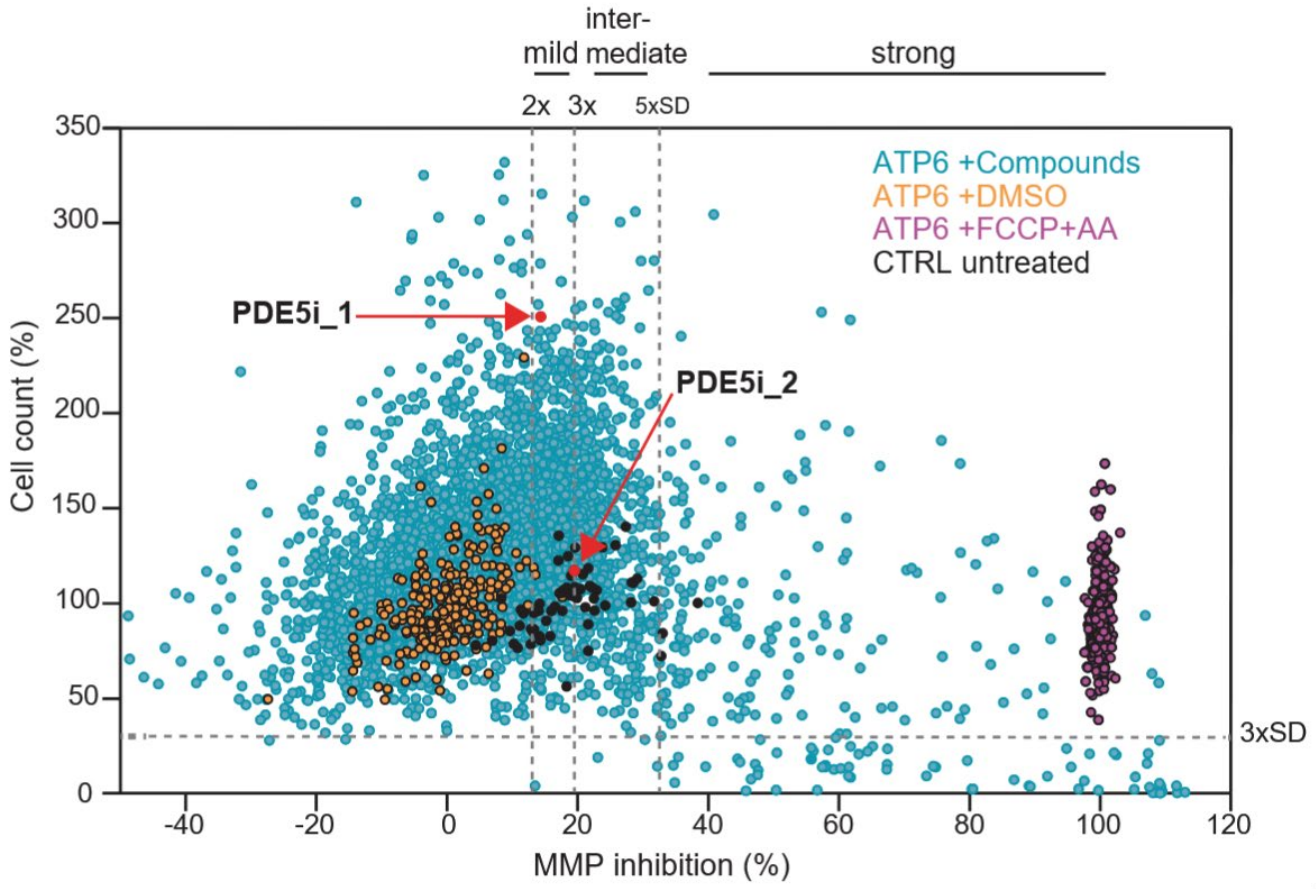
High content Screening

Die Screening-Plattform

=> Screening of n=300 / 5632 FDA/EMA approved drugs



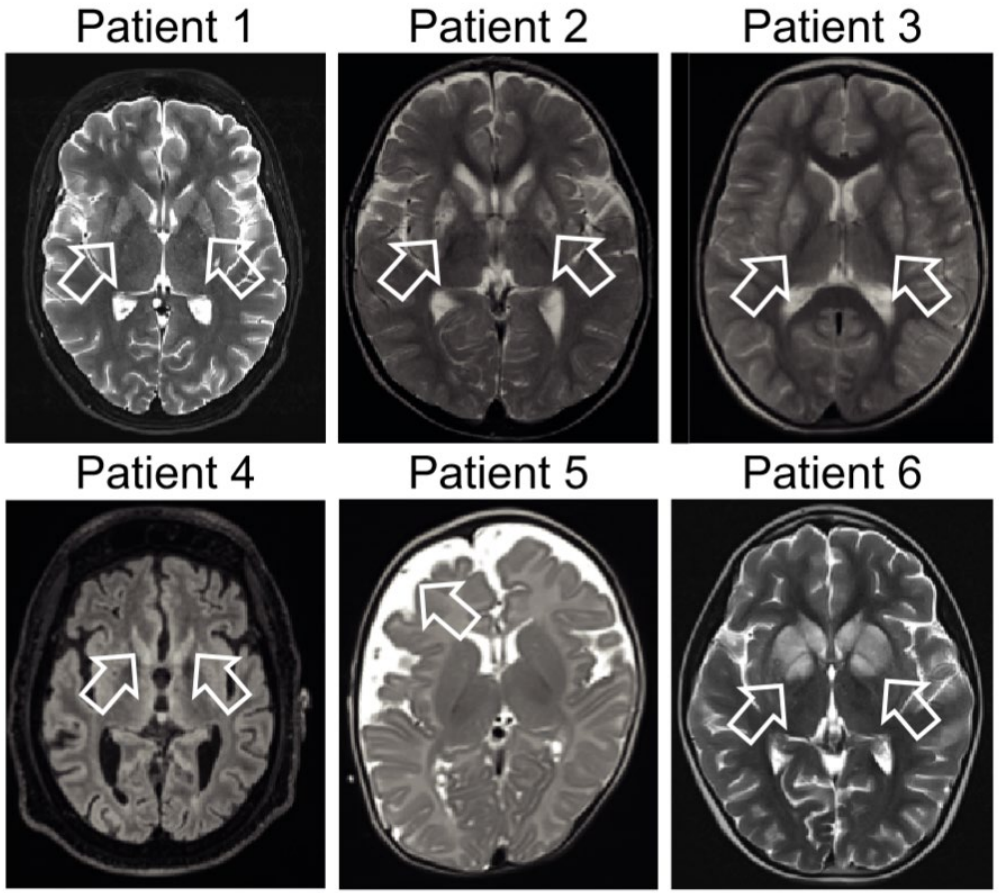


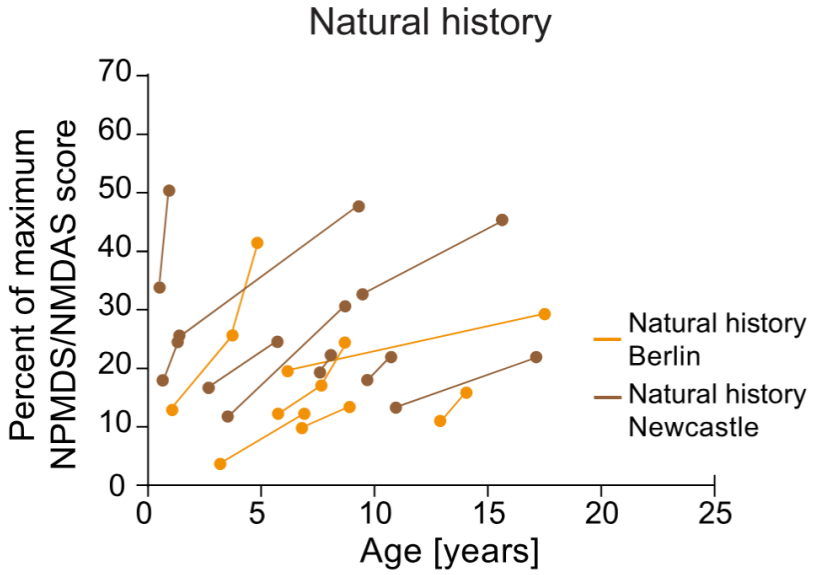
Lorenz *et al.* Cell Stem Cell 2017

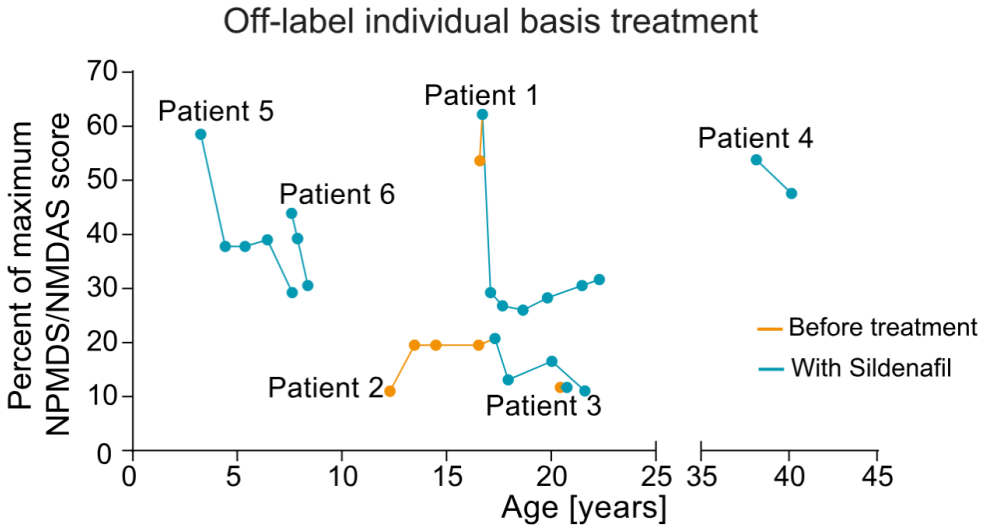
Zink *et al. Cell* 2026

Off-label compassionate use of Sildeanfil in 6 patients

=> Evaluation by the Newcastle Mitochondrial Disease Scales for Adults and Children







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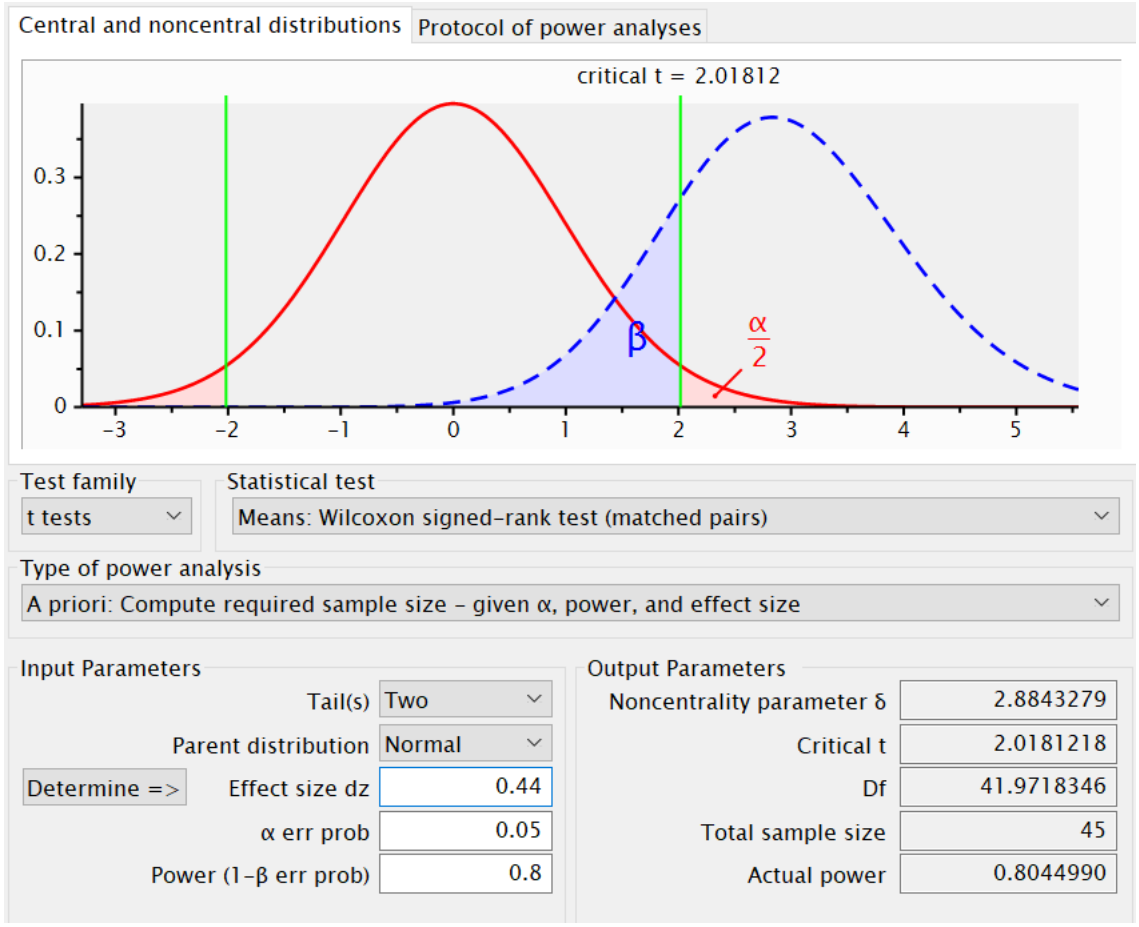
Primary endpoint (NPMDS)
=> Cohort size calculation



Age [y] #1	NPDMS #1	Age [y] #2	NPMDS #2	Delta age	Delta NPDMS	NPDMS/year
0,52	23,68	0,94	35,26	0,42	11,58	27,69
0,66	12,54	1,32	17,11	0,66	4,56	6,89
1,39	17,89	9,30	39,12	7,91	21,23	2,68
2,68	13,68	5,71	20,09	3,03	6,40	2,11
3,52	9,65	8,71	25,09	5,19	15,44	2,97
9,48	26,75	15,64	37,19	6,17	10,44	1,69
7,60	15,79	8,08	18,25	0,49	2,46	5,04
9,69	14,74	10,73	17,98	1,05	3,25	3,10
10,94	10,88	17,14	17,98	6,20	7,11	1,15
			Mean	**3,46**	**9,16**	**5,93**
			SD	**2,64**	**5,53**	**7,47**

The effect size of 0.44 corresponds to a reduction of NPMDS by 50% (=2.9 NPDMS points/year)

=> min cohort size: 45

=> aimed at cohort size: 55 participants

cureMILS pivotal trial => overview

- Type of study: Pivotal trial
- Study medication: Sildenafil citrate
- Study duration: 2 phase study with interim analysis for 24 months
- Study individuals: n=27 female, n=27 male
- Inclusion criteria: Leigh syndrome
  + mutation in *MT-ATP6* (>90%)
  age 1-17 years
- Primary endpoint: safety, pharmacokinetics, efficacy (NPMDS)
- Secondary endpoints: PROMs, Goal attainment scaling (GAS)

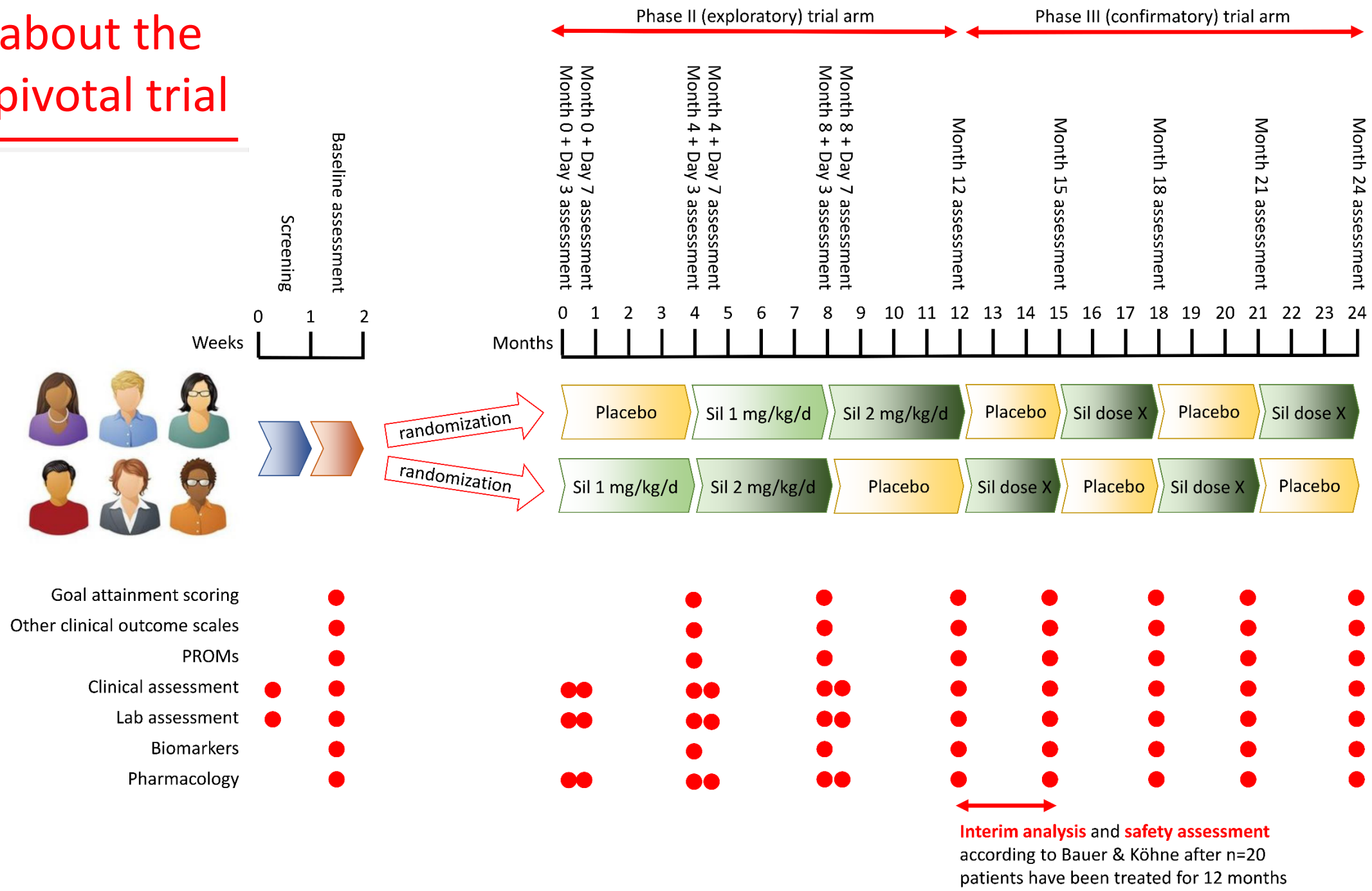
The study population

- children between 1-17 years of age
- patients with Leigh syndrome due to *MT-ATP6* mutations (>90% heteroplasmy)
- n=27 male and n=27 female children
- age groups should be evenly distributed

Dosing scheme

- Dose escalation scheme for sildenafil
  - first 12 months 1.0-2.0 mg/kg/d (dose escalation) *exploratory phase II*
  - second 12 months cross over between Sildenafil 2 mg/kg/d and Placebo each 3 months *confirmatory phase III*

Overview about the *cureMILS* pivotal trial



The next steps . . .

Pivotal II/III trial => cureMILS

- Safety in the patient group
- Measurement of efficacy for
  - Preventing metabolic crises
  - Improving the neurological outcome
- Endpoints
  - Newcastle score
  - PROMIS fatigue score
  - Motor scores GMFM88, MFG
  - Patient reported outcome measures
  - Goal attainment soring

Challenges

- Different course of the disease in different individuals
- Multicenter study (Europe-wide)
- Heterogeneous patient population