

# Hereditary metabolic disorders / Bone marrow and organ transplantation, gene therapy

## Bone marrow transplantation

Bone marrow transplantation (BMT) - hematopoietic stem cells is a therapeutic option in treatment

- lysosomal diseases
- peroxisomal diseases

Lysosomal or peroxisomal disease affects at least blood vessels, but usually also affects other organs (often multisystem disease) → the idea was to try to treat BMT (an effort to eliminate at least one problem)

What does BMT solve?

1. metabolites that accumulate in the blood due to lysosomal or peroxisomal DMP and cause progression are not eliminated at all, after BMT they are at least blood levels able to reduce the concentration of these metabolites slightly and thus improve the condition
2. keeps active the production of healthy and intact blood cells and elements

first disorder treated with BMT → mucopolysaccharidosis I (MPS) = iduronidase deficiency, but after removing one complication, complications still persist that BMT does not solve - joint diseases, spinal deformities ... (so-called residual problems or disease) BMT must be performed in a small childhood, in order to prevent neurological impairment (it is reported that by the age of 18 months) the problem with such a transplant is that the child does not have sufficiently developed immunity, and therefore BMT can bring unfavorable results

Umbilical cord blood transplantation, which also contains stem hematopoietic stem cells, has promising results. other diseases in which BMT improves the condition are **MPS III** (heparan-N-sulfatase deficiency), **Krabbe disease** (galactosylceramidase deficiency), **X-ALD** (acyl-CoA transport disorder to lysosomes)

## Organ transplantation

- **Liver transplantation** - Liver transplantation improves the condition of eg the following diseases: **metabolic disorders of urea synthesis** (especially hyperammonaemia I, II and citrullinemia), **organic aciduria**, **severe glycogenosis disorders** (GDS I), **tyrosinemia I** (fumarate acetoacetylhydrolase deficiency). Liver transplants improve the condition, but as with BMT, residual disease does not resolve, transplantation is performed again as soon as possible and there is a relatively high risk of death (but even so it is better to do this and increase your chances of survival in certain diseases than doing nothing and often expecting 100% mortality in childhood or severe disorders)
- **Kidney transplantation** - Kidney transplantation improves the disease state in **cystinuria** (accumulation of cystine in the renal tubules, resorption disorder) and in **type I hyperoxaluria**.
- **Heart transplantation** - Heart transplantation could theoretically improve the condition in **Danon's disease** (deficiency of lysosomal transmembrane protein LAMP2)

## Pharmacological enzyme and gene therapy

- **Pharmacological enzyme therapy** = enzyme replacement therapy with ERT (enzyme replacement therapy), therapy in the treatment of lysosomal diseases, has not been successful for a long time because it was not known how to target the enzyme to lysosomes → it was discovered soon - the enzyme must be administered with mannose -6-phosphate label - ie a process similar to how the enzyme is transported from the ER to the lysosome - ie the enzyme is labeled M-6-P in the ER and this recognizes the M-6-P receptor (M6PR) and it directs the enzyme to lysosome, M6PR is recycled by returning the enzyme to the lysosome after transfer of the enzyme and is ready for further transport, or by targeting and incorporating into the cytoplasmic membrane - after recognizing the M6P tag, the EC occurring in (in our case recombinant enzyme) and directs it to the lysosome. ERT is used in treatment **Gaucher's disease** (beta-glucocerebrosidase deficiency), **Faber's disease** (alpha-galactosidase), **mucopolysaccharidosis I** (iduronidase deficiency), **mucopolysaccharidase IV** (galactose-6-sulfatase), **Pompe disease** (GDSII).
- **Financial issue of enzyme therapy**: for example, enzyme treatment of 1 patient with Gaucher disease (recombinant enzyme imiglucerase) costs \$ 550,000 per year and should be for life.
- **Gene therapy** - a nice idea, but currently, despite all the advances in biology and medicine, it is only a laboratory matter → the problem of how to transport a gene into the genome (finding a suitable vector - or carrier) - another viral vector is considered, another problem is so that production is optimal and non-toxic. Many diseases could be treated in the future with gene therapy, but especially DMP and malignant transformations etc.
- Conditions for gene therapy treatment
  - we need to **know the gene**, its correct sequence and its location and action (meaning) if the gene is non-functional - so it is not transcribed (ie its expression is suppressed) - then it is enough to insert the gene anywhere in the genome with a suitable vector

- if the gene is pathological and overexpressed, then the goal of gene therapy is to silence the **pathological gene** and insert the non-mutated gene into the genome, or **direct mutation repair** (the question is how?)
- the target bb must be selected. and select the appropriate vector
- **Execution of gene therapy**
  - assembly of genetic material (correct, non-mutated gene) that is intended for transport
  - selecting a **suitable vector**
    - **mechanical** - microneedle
    - **chemical** - interaction of chemical substances with the membrane, causing increased permeability and thus facilitated penetration of DNA through it or interaction of the substance with DNA, which transfers DNA to the cytosol
    - **viral** - the most promising, DNA injection as part of the viral genome
- **Disadvantages:** gene therapy is expensive and inefficient, technologically demanding and in case of accidental inclusion in the genome there is a risk of dysfunction of another normally functioning gene

## Links

- ws:Dědičné metabolické poruchy/Transplantace kostní dřeně a orgánů, genová terapie

## External links

- <http://www.genetika-biologie.cz/genova-terapie>
- [http://www.medicabaze.cz/index.php?sec=term\\_detail&tname=D%C4%9Bdi%C4%8Dn%C3%A9+metabolick%C3%A9+poruchy+-+l%C3%A9%C4%8Dba&termId=2611&h=transplantace+kostn%C3%AD+d%C5%99en%C4%9B#jump](http://www.medicabaze.cz/index.php?sec=term_detail&tname=D%C4%9Bdi%C4%8Dn%C3%A9+metabolick%C3%A9+poruchy+-+l%C3%A9%C4%8Dba&termId=2611&h=transplantace+kostn%C3%AD+d%C5%99en%C4%9B#jump)