

# Homocystinuria

## Current and Novel Therapies

## Targeting the Homocysteine Pathway

Conventional management, enzyme replacement, gene therapy, proteostasis modulation, gut and liver directed strategies

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## SECTION 1

# The Clinical Problem

Why metabolic control in homocystinuria is still an unsolved therapeutic question

# Classical homocystinuria in one slide

**Autosomal recessive CBS deficiency.** Cystathionine beta-synthase converts homocysteine and serine into cystathionine using pyridoxal 5'-phosphate as cofactor; loss of function blocks the transsulfuration pathway.

**Biochemical consequence.** Homocysteine and methionine accumulate in blood and urine while cysteine falls, with loss of downstream glutathione and taurine synthesis.

**Multi-organ disease.** Ectopia lentis and high grade myopia, marfanoid habitus with scoliosis and osteoporosis, developmental delay and psychiatric disease, arterial and venous thromboembolism.

**Ocular involvement affects 90 percent** of poorly managed patients and is usually the earliest manifestation; thromboembolism remains the leading cause of morbidity and mortality.

- Related remethylation defects (MTHFR, methionine synthase, cobalamin disorders) raise homocysteine but keep methionine normal.

## DIAGNOSTIC BIOCHEMISTRY

Plasma total homocysteine above 100 micromol/l compared with under 15 micromol/l in health, with methionine typically 60 to 100 micromol/l. Normal methylmalonic acid excludes a remethylation defect and points to the transsulfuration block.

# Epidemiology: a rare disease with strong regional variation

| Population                      | Reported incidence    | Comment                                                                                |
|---------------------------------|-----------------------|----------------------------------------------------------------------------------------|
| Global estimate                 | 1 in 300,000          | Varies with mutation pattern and consanguinity                                         |
| Qatar                           | about 1 in 1,800      | Highest known incidence, driven by consanguineous marriage                             |
| Norway                          | 1 in 6,400            | Birth prevalence study                                                                 |
| Germany                         | 1 in 17,800           | Newborn screening survey                                                               |
| Kuwait and eastern Saudi Arabia | 1 in 43,000           | Regional screening programmes                                                          |
| Ireland                         | about 1 in 65,000     | Long established screened population                                                   |
| United States                   | 1 in 100,000 reported | Analyses suggest the true prevalence may be ten times higher because of underdiagnosis |

*More than 190 to 200 pathogenic CBS variants have been described; the gene maps to chromosome 21q22.3. Consanguinity and founder variants explain most of the geographic spread.*

# Treatment goal and monitoring

**The single governing principle in both reviews: keep plasma total homocysteine as close to the normal range as possible.**

Everything else is a means to that end.

**Responsiveness threshold.** Patients reaching tHcy below 50 micromol/l on pyridoxine alone are classified as responsive and usually show a milder clinical course.

**Routine monitoring.** Plasma tHcy as the primary marker, plus methionine and a full amino acid profile in patients on dietary restriction, to detect both loss of control and iatrogenic hypermethioninemia.

**Exclusion panel.** Serum B12 and folate rule out nutritional hyperhomocysteinemia; normal methylmalonic acid excludes cobalamin disorders.

**Emerging markers.** Cystathionine, methionine and S-adenosylmethionine are being evaluated to describe metabolic status more precisely than tHcy alone.

# Genotype determines the first therapeutic decision

| Variant                                | Geographic prevalence                   | Vitamin B6 response                | Residual CBS activity | Clinical severity                     |
|----------------------------------------|-----------------------------------------|------------------------------------|-----------------------|---------------------------------------|
| I278T                                  | Western Europe, North America, Far East | Responsive                         | Partial               | Mild to moderate                      |
| G307S                                  | Ireland and Australia                   | Non-responsive                     | Minimal to none       | Severe, early onset                   |
| p.R125Q, p.R266K, p.R336C, c.1224-2A>C | Global                                  | Variable to non-responsive         | Variable              | Variable, often severe                |
| MTHFR C677T                            | Global, especially Europe and Asia      | Not applicable (not classical HCU) | Thermolabile MTHFR    | Mild to moderate hyperhomocysteinemia |

### PRACTICAL CONSEQUENCE

Comprehensive genotyping and in vitro enzyme activity assays are unavailable in many clinical settings, so an empirical pyridoxine trial remains the standard way to classify a newly diagnosed patient.

## SECTION 2

# Conventional Therapies

Pyridoxine, methionine restriction, betaine, folate and vitamin B12

# Pyridoxine (vitamin B6) supplementation

**First line wherever residual CBS activity exists.** B6 is converted to pyridoxal 5'-phosphate, the cofactor that CBS requires for catalysis.

**Empirical trial in every newly diagnosed patient,** typically starting at 100 to 500 mg per day with therapeutic monitoring of plasma tHcy and methionine.

**Genotype predicts the response.** I278T retains fractional enzyme function and responds; null variants such as G307S and the splice variant c.1224-2A>C do not.

**Biochemical response is not always clinical response.** Epigenetics, coexisting polymorphisms and nutrient status confound outcomes, and partial responders often need combination therapy.

- In responsive cases, pyridoxine is combined with vitamin D, folic acid and vitamin B12.

## SAFETY SIGNAL

Long term adherence is challenged by rising concern about peripheral neuropathy from chronic high dose pyridoxine. The dose should be the lowest that maintains biochemical control.

# Methionine-restricted diet

**Lifelong cornerstone applied regardless of genotype**, aimed at reducing methionine load using methionine free nutritional formulas with cysteine supplementation.

**Requires careful follow up of plasma amino acids** to maintain metabolic control, prevent protein malnutrition and secure normal growth in paediatric patients.

**Effective at lowering tHcy, but adherence is the limiting factor.** Poor palatability of the formulas drives long term non-compliance, especially in older children and adults.

**Diet alone is frequently insufficient** to prevent complications and usually requires adjunctive therapy.

- Qualitative patient research describes the diet as the dominant daily burden of living with the disease, which is why oral and gut directed agents are attractive.

## PRECLINICAL WORK AIMED AT THE DIET BURDEN

Two experimental strategies degrade methionine inside the gastrointestinal tract instead of restricting intake: an orally stable engineered methionine gamma-lyase (CDX-6512) and an engineered probiotic *E. coli* Nissle strain (SYNB1353). Both are covered later in this talk.

# Betaine (trimethylglycine)

**Mechanism.** Methyl donor for betaine-homocysteine methyltransferase, remethylating homocysteine back to methionine and bypassing the blocked CBS step.

**Standard adjunct in B6 non-responsive patients,** used together with dietary restriction.

**Efficacy in HCU.** In B6 unresponsive patients, individual mean reductions in plasma tHcy ranged from 47.4 to 105.0 micromol/l.

**Supporting data.** 6 g per day for 3 weeks significantly lowered homocysteine in healthy subjects ( $P = 0.030$ ); 1 g of betaine combined with low dose folic acid 400 micrograms, B6 8 mg and B12 6.4 micrograms produced a 10 percent reduction.

## TWO CAUTIONS

Prolonged therapy above 100 mg/kg/day in patients whose methionine intake is not adequately restricted has caused clinically relevant hypermethioninemia. Betaine also raises total cholesterol modestly, so monitoring is advised in patients at cardiovascular risk.

# Folate and vitamin B12

**Role.** Cofactors of the remethylation route: 5-methyltetrahydrofolate donates the methyl group, methionine synthase catalyses the reaction and methylcobalamin acts as cofactor.

**Most relevant in MTHFR, MTR and MTRR variants,** where insufficient folate or B12 directly elevates tHcy.

**Evidence.** A randomised trial in elderly participants taking daily folic acid 400 micrograms with vitamin B12 500 micrograms for two years showed marked reductions in tHcy.

**In classical HCU these vitamins are adjunctive and never curative;** they support the alternate pathway while the transsulfuration block persists.

## WHERE THE FOUR CONVENTIONAL PILLARS SIT TOGETHER

Pyridoxine addresses residual enzyme function, diet reduces substrate load, betaine and the folate and B12 axis push homocysteine back toward methionine. None of them replaces the missing enzyme.

# Limitations and challenges of conventional therapies

**Responsiveness to vitamin B6 varies** and cannot be predicted reliably where genotyping and enzyme activity assays are unavailable.

**Adherence to a low methionine diet is difficult**, so metabolic control deteriorates even under supervision and with vitamin support.

**Numerous patients never reach target tHcy levels** and therefore remain exposed to thromboembolic, ocular and skeletal risk.

**Long term outcomes of current interventions are inconsistent**, and there is limited capacity to reverse complications once established.

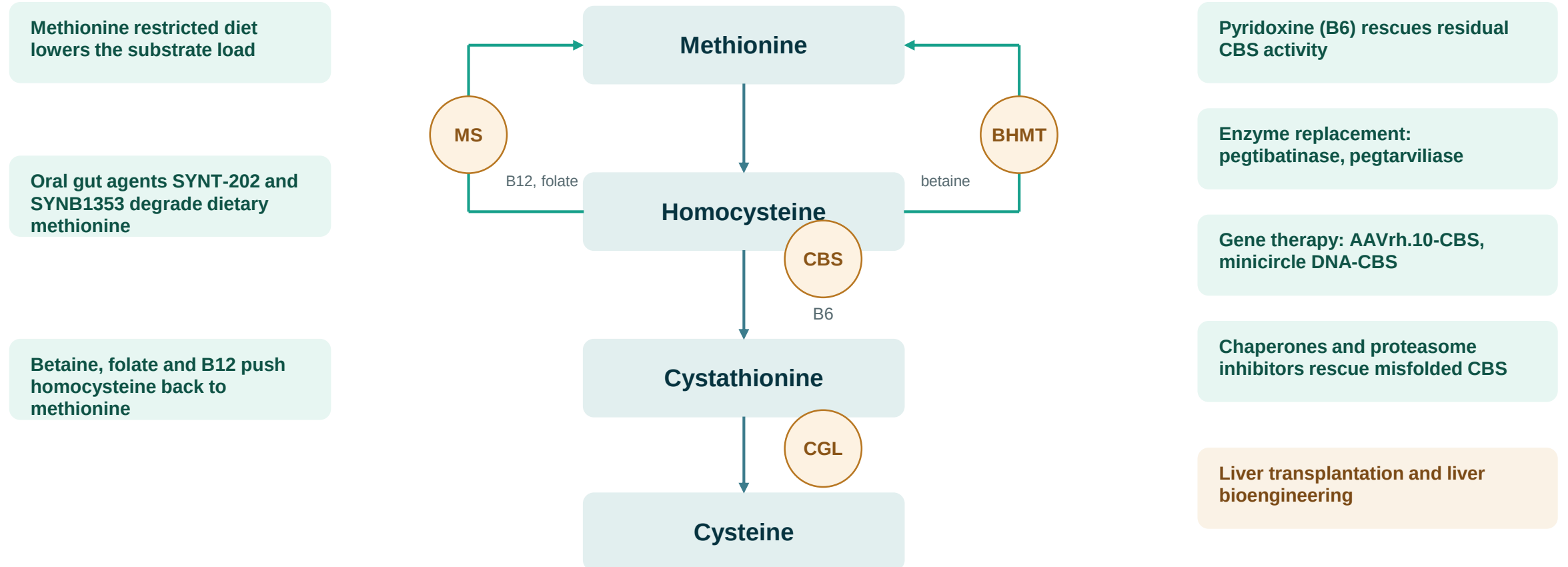
**This gap is the rationale for every novel strategy that follows.** The question is no longer how to lower homocysteine in responsive patients, but how to control it in those for whom diet and vitamins are not enough.

### SECTION 3

# Novel Therapeutic Approaches

Where each new intervention acts on the homocysteine pathway

# Where the therapies act



*Transsulfuration pathway shown vertically; remethylation routes shown as loops back to methionine.*

# Enzyme replacement therapy: the concept

**Mutation agnostic.** ERT delivers functional enzyme directly and therefore does not depend on residual endogenous CBS activity, unlike pyridoxine.

**The target protein.** Human CBS is a homotetramer of 551 amino acid subunits, each with three domains; it requires PLP for activity and binds a regulatory heme group through cysteine 52 and histidine 65.

**Strength.** Biochemistry can be normalised quickly and predictably, independent of genotype.

**Structural weakness.** Chronic parenteral administration, immunogenicity risk typical of biologics, and high cost of goods restrict widespread adoption.

**Positioning.** ERT is expected to complement rather than fully replace diet and vitamin based care.

# Pegtibatinase (OT-58 / TVT-058)

**Molecule.** PEGylated recombinant human CBS catalytic core (residues 1 to 413) lacking the autoinhibitory regulatory domain, which yields a constitutively active, predominantly dimeric enzyme.

**Engineering.** A cysteine to serine substitution at position 15 prevents interdimer disulfide bonds and aggregation; five PEG chains of 20 kDa per subunit extend circulating half-life about tenfold.

**COMPOSE phase 1/2 (NCT03406611).** 1.5 mg/kg subcutaneously twice weekly in 32 participants with CBS deficient HCU.

**Tolerability.** Two episodes of mild injection site urticaria, resolved with temporary dose interruption and subsequent titration.

## EFFICACY SIGNAL

Mean relative reduction in total homocysteine of **67.1 percent** from baseline (97 to 32 micromol/l) across follow up at 6, 8, 10 and 12 weeks, holding levels below the clinically meaningful threshold of 100 micromol/l. In CBS deficient animals pegtibatinase also improved ocular and skeletal manifestations, reduced facial alopecia and enhanced hepatic glucose and lipid metabolism.

# Reading the pipeline over time

## BITTMANN ET AL, 2023

- COMPOSE ongoing in 32 participants, completion expected 2025; first results showed a 55 percent reduction of total homocysteine and good tolerance at 12 weeks.
- Pegtarviliase in an ongoing phase 1/2 multiple ascending dose trial, five cohort studies performed.
- CDX-6512 in pre-IND development after FDA orphan drug designation in January 2022.

## ALTHUBITY, 2026

- COMPOSE reported a 67.1 percent mean relative reduction in tHcy, with the dose and schedule confirmed.
- Pegtarviliase development discontinued in 2024 after interim phase 1/2 results and immunogenicity.
- CDX-6512 acquired and rebranded as SYNT-202 by Syntis Bio in 2024, still preclinical.

## TAKE HOME

When quoting this field, quote the trial, the dose and the date rather than the drug name alone. Two reviews three years apart already disagree on the headline number and on which programmes are still alive.

# Pegtarviliase (AGLE-177): an instructive failure

**Molecule.** Engineered cystathionine gamma-lyase variant (CGL-ILMDRGVS) carrying eight missense mutations, with about 60-fold higher affinity for homocysteine than wild type CGL and improved stability and circulation time.

**Preclinical.** Mice given 1, 3 and 10 mg/kg subcutaneously twice weekly from postnatal day 10 to 70 showed 30-day survival above 75 percent versus below 20 percent in controls, with resolution of liver steatosis and alopecia; 10 mg/kg lowered plasma tHcy by about 43 percent and brain tHcy by 87 percent.

**Phase 1/2 dose escalation (NCT05154890).** Weekly subcutaneous doses of 0.15, 0.45 and 1.35 mg/kg over 4 weeks produced tHcy reductions of 26.3 and 33.0 percent in cohorts 1 and 2.

**What went wrong.** Cohort 3 developed injection site reactions and rising tHcy, explained by anti-drug antibodies. Aeglea explored strategic alternatives in 2023 and clinical development was discontinued in 2024.

## LESSON FOR THE CLASS

The programme was stopped by immunogenicity, not by lack of potency. Any lifelong injectable enzyme for this disease will stand or fall on the antibody response.

# Oral enzyme therapy: CDX-6512, now SYNT-202

**Different logic.** A modified methionine gamma-lyase engineered to stay stable and active in the gastrointestinal tract, degrading dietary methionine locally instead of acting systemically.

**Engineering.** Artificial intelligence and machine learning guided directed evolution across 12 iterative rounds, with more than 27,000 variants screened under simulated gastric and intestinal conditions; the resulting enzyme resists gastric pH and intestinal proteases.

**Regulatory.** FDA orphan drug designation for classical HCU granted in 2022.

**Efficacy in Tg-I278T CBS knockout mice.** A single oral dose of 148 mg/kg after a high protein meal lowered plasma tHcy by almost 50 percent within 4 hours; daily dosing over two weeks held tHcy at baseline while untreated controls rose by 39 percent.

**Non-human primates.** 370 mg/kg after a high protein meal produced a statistically significant, dose dependent fall in plasma methionine.

**Status.** Acquired and rebranded as SYNT-202 by Syntis Bio in 2024; no human data disclosed to date.

# Other enzyme candidates and the limits of ERT

**Erymethionase.** A methionine gamma-lyase preparation reported by Bittmann and colleagues as the first candidate to lower both homocysteine and methionine in plasma, which matters for restoring metabolic balance rather than a single analyte. Preclinical only.

**First-in-class framing.** Engineering and chemical modification of human CBS and CGL produced pegtibatinase (OT-58) and pegtarviliase (AEB-4104) as the first-in-class enzyme therapy candidates for HCU.

**Evidence maturity.** As of the 2023 review it was considered too early to draw scientific conclusions on CDX-6512 or erymethionase for treating patients; the 2026 review confirms that no human data have been released for the renamed programme.

## LIMITATIONS AND CHALLENGES OF ERT

Injectable agents such as pegtibatinase face lifetime adherence and immunogenicity hurdles. Oral agents such as SYNT-202 still require durable efficacy and safety data. Cost of goods and access considerations suggest ERT will complement, not replace, diet and vitamin based care. Lifelong substitution also means sustained cost to the health system and sustained compliance from parents in the early years.

#### SECTION 4

# Gene Therapy and Proteostasis

Durable genetic correction, and rescuing the enzyme the patient already has

# Gene therapy: AAVrh.10-CBS

**Design.** An AAVrh.10 vector delivers a functional human CBS gene under a cytomegalovirus early enhancer with chicken beta-actin promoter, targeting the hepatocytes where homocysteine is metabolised.

**Result in the l278T mouse model.** A single intravenous dose reduced plasma tHcy by about 97 percent within one week and sustained about 81 percent reduction one year after administration.

**Phenotype reversal,** including alopecia, skeletal defects and abnormal fat distribution.

**Why this serotype.** Pre-existing neutralising antibodies to AAVrh.10 are less prevalent than those to AAV2 or AAV8, which supports its suitability for liver directed applications.

**Clinical plausibility.** The durability of liver directed AAV expression seen in a human hemophilia B gene therapy trial supports long term transgene persistence.

# Minicircle DNA-CBS and the wider genome-level toolbox

**Minicircle vectors lack the bacterial backbone**, which raises transgene expression and lowers innate immune activation compared with conventional plasmids.

**Result.** A single liver targeted injection of MC.P3-hCBS in CBS deficient mice reduced plasma homocysteine by about 50 percent within one week, restored hepatic CBS activity around 34-fold and sustained metabolic correction beyond six months.

**Broader toolbox described by Bittmann:** mutation repair, gene editing with CRISPR-Cas9, adeno-associated gene transfer, minicircle DNA transfer and stabilised mRNA constructs optimised for translation.

**Delivery routes.** Non-viral methods (lipofection, electroporation, microinjection, calcium phosphate transfection) avoid viral risk but transfect less efficiently; viral vectors achieve high transfection rates yet carry a residual risk from recombination events.

## ADVANTAGES, LIMITATIONS AND CHALLENGES

Gene therapy addresses the genetic cause directly and offers durable correction from a single administration. Against that stand immune responses to viral vectors, dilution of the treatment effect as the liver grows in children, hepatic genotoxicity as a vector design consideration, and complex manufacturing.

# Pharmacological chaperones

**Rationale.** Most pathogenic CBS variants do not destroy the catalytic residues; they introduce structural perturbation, so the mutant protein aggregates and is degraded by the proteasome. Correcting misfolding raises the steady state level of enzyme and therefore of activity.

**Agents under study.** Glycerol, trimethylamine N-oxide and dimethyl sulfoxide restored activity in certain CBS mutants in cell and animal models. Bittmann adds betaine anhydrate, sorbitol, proline, aminolaevulinic acid, taurine, trehalose and 4-phenylbutyrate (Buphenyl).

**Mechanistic support.** Yeast expression systems for human CBS mutants show that chaperones promote correct assembly and tetramerization, which supports mutation specific therapeutic use.

**S-adenosylmethionine** is an allosteric activator binding the regulatory domain; about half of tested patients showed defective SAM activation linked to specific CBS mutations.

**Heme arginate** restored heme binding, improved tetramer formation and enhanced catalytic activity in several B6 resistant mutants.

*Limitation: most chaperones remain unvalidated in clinical trials, and responsiveness is mutation specific, so genotype guided selection will be required.*

# Proteasome inhibitors

**Principle.** Blocking proteasomal degradation stabilises CBS protein that is partially active but misfolded, so more enzyme survives to work.

**Bortezomib** increased hepatic CBS activity more than 20-fold and reduced plasma tHcy by 97 percent in a p.R266K mouse model.

**Carfilzomib** produced comparable biochemical benefit in preclinical HCU models, but its long term safety is not yet established.

**Main risk.** Systemic proteasome suppression. Liver targeted delivery strategies and dose minimisation are being explored to mitigate toxicity.

- Bittmann groups bortezomib with the probiotic approach as preclinical options that could act additively with chaperones by binding and stabilising CBS.

SECTION 5

# Gut, Liver and Definitive Therapy

Probiotic methionine consumption, liver bioengineering and transplantation

# Gut-directed probiotic therapy: SYN1353

**Design.** An engineered *Escherichia coli* Nissle strain expressing methionine gamma-lyase, which consumes methionine within the gastrointestinal tract and prevents its absorption and conversion to homocysteine.

**Pharmacological advantage.** Orally applied and not systemically absorbed, which lowers the risk of serious systemic side effects.

**Preclinical.** Reduced plasma homocysteine and methionine in mice and non-human primates without adverse events; Synlogic first shared these data in 2021.

**Clinical.** A phase 1 trial in healthy volunteers showed good tolerability and dose dependent methionine reduction. A phase 2 study in classical HCU (NCT05651054) is ongoing and efficacy data are pending.

**Platform precedent.** The same synthetic biotic approach was developed and taken into humans for phenylketonuria, which supports feasibility.

# Liver-directed bioengineering

**Concept.** Restore CBS activity within hepatic tissue without removing the whole dysfunctional liver, which would avoid the morbidity of transplantation.

**Liver organoids.** In vitro engineering of organoids with normal CBS enzyme activity, followed by later implantation into the patient.

**3D bioprinting.** Hepatocytes encapsulated in alginate methylcellulose with Matrigel form the shell lane while fibroblasts in alginate methylcellulose form the core lane; the fibroblasts act as supporting cells, stimulating hepatocyte markers such as albumin and increasing multicellular cluster size in co-culture.

**Cells for liver regeneration.** Transplantation of liver progenitor cells isolated from bone marrow is described as an alternative route to restoring the deficient enzyme.

**Status.** Experimental, with no patient data in HCU. Relevant as the long term alternative to whole organ transplantation rather than as current practice.

# Orthotopic liver transplantation

**Indication.** Severe pyridoxine non-responsive disease in which other options have failed. Transplantation restores CBS activity from the donor organ.

**Adult case.** A 24-year-old with cerebellar infarction and hypertension achieved normalised metabolic control after transplantation and required no drugs or restrictive diet afterwards.

**Paediatric case.** Methionine and homocysteine normalised at age 4 and remained stable for six years, in a patient with no complications before surgery, which supports early transplantation as a curative strategy.

**Cohort data.** Among 13 patients with classic HCU and 18 CBS variants, three B6 non-responders transplanted at ages 3, 8 and 8 years normalised methionine and total homocysteine within one week.

**Domino transplantation.** A recipient with cholangiocarcinoma who received a domino graft from a hyperhomocysteinemic donor was alive at one year with low homocysteine levels.

## BALANCE OF RISK

Surgical risk, lifelong immunosuppression, limited donor availability and graft versus host complications. Transplantation does not reverse established complications, so early diagnosis remains decisive and the procedure should be reserved for severe refractory disease.

# Comparison of treatment modalities, part 1

| Modality                          | Mechanism                                                                | Genotype association                                                    | Effectiveness                                                                        | Limitations and challenges                                                                    |
|-----------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Pyridoxine (B6)</b>            | Cofactor for CBS; enhances residual activity                             | Effective mainly in variants with residual activity such as p.Ile278Thr | Highly effective in responsive genotypes; lowers homocysteine and improves prognosis | Ineffective in non-responsive genotypes; responsiveness must be tested                        |
| <b>Betaine</b>                    | Remethylates homocysteine to methionine via BHMT, bypassing the CBS step | Effective in both responsive and non-responsive genotypes               | Reduces plasma homocysteine in non-responsive patients                               | Can raise methionine to toxic levels; requires careful monitoring                             |
| <b>Methionine-restricted diet</b> | Limits the precursor amino acid to reduce homocysteine production        | Applied universally, regardless of genotype                             | Reduces total homocysteine load; supportive in responsive and non-responsive cases   | Difficult compliance, especially in older children and adults; risk of nutritional deficiency |
| <b>Folic acid and B12</b>         | Cofactors for remethylation of homocysteine to methionine                | Useful in remethylation defects and mild elevation                      | Beneficial in MTHFR and cobalamin defects; adjunctive in CBS mutations               | Not curative for CBS deficiency; requires a combined approach                                 |

# Comparison of treatment modalities, part 2

| Modality                   | Mechanism                                         | Genotype association                                      | Effectiveness                                                 | Limitations and challenges                                                         |
|----------------------------|---------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------|
| Enzyme replacement therapy | Supplements the defective or absent CBS enzyme    | Under investigation for CBS deficient genotypes           | Potential to correct the enzymatic deficiency directly        | Not yet clinically available; enzyme delivery and immunogenicity remain challenges |
| Gene therapy               | Introduces a functional CBS gene into host cells  | Targeted at CBS null or severe mutation genotypes         | Preclinical studies show promise for long term correction     | Experimental; delivery vectors and sustained expression are hurdles                |
| Liver transplantation      | Provides normal CBS activity from the donor liver | Effective in CBS deficient patients with severe mutations | Can normalise homocysteine metabolism; curative in some cases | Invasive; limited to severe refractory cases; lifelong immunosuppression required  |

HOW TO READ THESE TWO TABLES TOGETHER

Conventional therapies are available everywhere but genotype dependent and adherence limited. Experimental therapies are genotype independent but not yet accessible. Transplantation is the only entry in the table that is both definitive and available today.

# The wider therapeutic landscape at a glance

| Category                                    | Agents and approaches                                                                                                                        | Status and comment                                                                                                                   |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <b>Supplemental and dietetic</b>            | Pyridoxine, vitamin D, folic acid, vitamin B12                                                                                               | Standard of care; the regimen differs between responsive and non-responsive patients                                                 |
| <b>Chaperones (small ligands)</b>           | Betaine anhydrate, sorbitol, proline, glycerol, aminolaevulinic acid, taurine, trehalose, 4-phenylbutyrate (Buphenyl)                        | Methyl donors and folding stabilisers that lower homocysteine; mostly experimental                                                   |
| <b>Proteasome inhibition and probiotics</b> | Bortezomib (Velcade), SYNB1353                                                                                                               | Both in preclinical or early clinical study as treatment options in HCU                                                              |
| <b>Enzyme replacement</b>                   | Pegtibatinase (OT-58), pegtarviliase, CDX-6512 / SYNT-202, erymethionase                                                                     | PEGylated recombinant enzyme given subcutaneously; oral gut restricted agents; erymethionase lowers both homocysteine and methionine |
| <b>Liver-directed therapy</b>               | 3D bioprinting and liver tissue engineering, organoids with normal CBS activity, bone marrow derived progenitor cells, liver transplantation | Transplantation is established but limited; bioengineering is future research                                                        |
| <b>Gene therapy</b>                         | Mutation repair, CRISPR-Cas9 editing, adeno-associated gene transfer, minicircle DNA vector transfer                                         | Studies in mice; a one-time approach would be desirable                                                                              |

# Personalized medicine and biomarkers

**Integrating genetic and metabolic profiling** allows treatment to be tailored to the molecular profile of the individual patient.

**Variant specific expectations.** Patients with p.I278T may show variable responses to B6, whereas p.R125Q and p.R266K variants require different therapeutic approaches.

**Early genetic workup,** including in asymptomatic individuals, supports accurate diagnosis and prompt tailored treatment.

**Monitoring.** Plasma tHcy remains the primary biochemical marker of metabolic control; cystathionine, methionine and SAM are under investigation as more informative markers of disease status.

**Stratification for emerging therapies.** Grouping patients by residual CBS activity or by the nature of the proteostatic defect may decide who receives chaperones, proteasome modulation, ERT or gene therapy.

# A stepwise approach in practice

1

## Confirm the diagnosis

Plasma tHcy with methionine, normal methylmalonic acid, B12 and folate to exclude nutritional and remethylation causes, genotyping where available

2

## Trial pyridoxine in every newly diagnosed patient

100 to 500 mg per day with monitoring; tHcy below 50 micromol/l on B6 alone defines a responsive patient

3

## Responsive patients

Pyridoxine with folic acid, vitamin B12 and vitamin D, plus moderate dietary control and lifelong monitoring

4

## Non-responsive patients

Methionine restricted, cysteine supplemented diet plus betaine, with methionine monitoring to avoid hypermethioninemia

5

## Persistent elevation despite optimal conventional care

Consider trial enrolment (pegibatinase, SYN1353) and discuss transplantation in severe refractory disease

6

## Lifelong surveillance in all groups

tHcy and amino acids, nutritional status, ophthalmology, bone health and thromboembolic risk assessment

## CONCLUSION

# Key messages

**Conventional care controls biochemistry in only part of the population** and rarely reverses established damage. That limitation, not novelty, is what drives the pipeline.

**Enzyme replacement gives mutation agnostic control** but demands lifelong administration and is defined by its immunogenicity risk, as the pegtarviliase programme showed.

**Gene therapy offers durable one-time correction in animal models**, with about 97 percent early and 81 percent one-year reduction of tHcy, and has not yet reached patients with HCU.

**Chaperones, proteasome inhibitors and gut directed agents** are attractive adjuncts that still need clinical validation, and their use will probably be genotype guided.

**Liver transplantation remains the only definitive option today**, reserved for severe refractory disease and unable to reverse existing complications.

**Early diagnosis through newborn screening remains the strongest determinant of outcome**, whichever therapy follows.

# Limitations of the evidence base

Both sources are **narrative rather than systematic reviews**, so study selection and emphasis reflect author judgment.

**Much of the novel therapy evidence is preclinical or early phase**, which limits conclusions on long term safety and efficacy.

**Some pipeline information derives from press releases and conference reports** and may change as further evidence emerges.

**Regional differences in prevalence, genotype distribution and consanguinity**, together with heterogeneity in CBS mutations and pyridoxine responsiveness, limit the generalisability of therapeutic expectations across populations.

- Where the two reviews disagree, as with the COMPOSE reduction figure, the more recent and more specific report should be preferred.

# Sources and trial identifiers

**Althubity AA.** Homocystinuria: advances in metabolic and molecular therapies targeting homocysteine pathways (Review). Mol Med Rep 2026;33:34. DOI 10.3892/mmr.2025.13745. Primary source for sections 5 to 10.

**Bittmann S, Villalon G, Moschuring-Alieva E, Luchter E, Bittmann L.** Current and novel therapeutical approaches of classical homocystinuria in childhood, with special focus on enzyme replacement therapy, liver-directed therapy and gene therapy. J Clin Med Res 2023;15(2):76-83. DOI 10.14740/jocmr4843.

**COMPOSE, pegtibatinase (TVT-058):** ClinicalTrials.gov NCT03406611.

**Pegtarviliase (ACN00177), multiple ascending dose study:** ClinicalTrials.gov NCT05154890.

**SYNB1353 phase 2 in classical homocystinuria:** ClinicalTrials.gov NCT05651054.

Prepared for presentation by **Dr. Daniel Zamanfar**. Content summarised and restructured from the two cited reviews; figures, doses and trial identifiers reflect what those reviews report through early 2025.