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CRISPR-Cas - transdisciplinary full work

Science, law, ethics, application and education

Thomas Schüller

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Author	Thomas Schüller, Syntagma Forschung, Wien · ORCID 0009-0003-9799-6747 · forschung@tschueller.com
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The parts remain freely accessible. The textbook edition combines them with syntax card, learning path and glossary into a study and working book and is updated with each new version of the work.

Contents

- Part 1: Main work

CRISPR-Cas — A Transdisciplinary Reference Work

- [CRISPR-Cas — A Transdisciplinary Reference Work](#)
 - [Verification caveat](#)
 - [Exclusions](#)
 - [Analytical axis: p/6](#)
- [PART A — SCIENCE, LAW, ETHICS](#)
 - [A1 Evolutionary basis](#)
 - [A2 Classification and mechanism](#)
 - [A3 Engineering and tool generations](#)
 - [A4 Delivery](#)
 - [A5 Off-target effects, safety, limitations](#)
 - [A6 Diagnostics](#)
 - [A7 Somatic clinical applications](#)
 - [A8 Germline](#)
 - [A9 Agriculture and animal breeding](#)
 - [A10 Gene drives and ecology](#)
 - [A11 Law and regulation, with emphasis on the EU and Austria](#)
 - [A12 Patents and economics](#)
 - [A13 Ethics, justice, philosophy of science](#)
 - [A14 Alternatives](#)
 - [A15 Bibliometrics and official figures](#)
 - [A16 AI-assisted discovery and design](#)
- [PART B — APPLICATION, EDUCATION, TOOLS, SAFETY](#)
 - [B1 Software](#)
 - [B2 Hardware](#)
 - [B3 DIY kits and community labs](#)
 - [B4 Education in Austria and the EU](#)
 - [B5 Safety guide, protective](#)
 - [B6 Handbook and training architecture](#)
 - [B7 Own tools — specification](#)
 - [B8 Physical kits from in-house manufacture](#)
 - [B9 Dissemination and funding models](#)
 - [B10 p/6 across all domains](#)
 - [Figures](#)
- [Conclusion](#)
 - [Diagram proposals](#)
 - [Templates and tools to be produced](#)
 - [Conflicts of interest](#)
 - [Research gaps](#)
 - [Legal traffic light for Austria](#)
 - [Consolidated sources](#)
 - [Change log](#)

CRISPR-Cas — A Transdisciplinary Reference Work

Verification caveat

No statement in this work carries the status “verified” in the sense of a completed individual check. Evidence is anchored to DOI, PMID or legal citation, per chapter where individual references are needed and otherwise collected in the consolidated source list; time-critical items (regulation, clinical programmes, patent proceedings) are stated as of 24 September 2026 and will age. Register figures (chapter A15) must be re-collected with a retrieval date before publication.

Exclusions

Military, weapons-related and defence applications are not a subject of this work in any form. Biosecurity and dual use, where touched on at all, are treated exclusively at the level of gene technology, release and employee protection law: facility requirements, safety levels, notification and authorisation duties, oversight, liability. A dedicated section on synthesis screening and biosecurity-specific reporting channels is not part of v0.2 and is reserved for a later version. Procedural, parameter, strain and method detail that would be operationally usable is excluded. The safety chapters (B5) are protective: containment, law, instruction.

This work is a domain instance of the master theorem FORSCH-0083. The guiding question in every chapter is: who bears the risk (ρ), who holds disposition (δ), and where do the two come apart? The asymmetry ρ≠δ is not an incidental finding in the CRISPR field but its recurring structure — from the origin of the microbial sequence resources, through the pricing of approved therapies, to the release decision on gene drives.

PART A — SCIENCE, LAW, ETHICS

A1 Evolutionary basis

State of knowledge

CRISPR-Cas is an adaptive immune system of prokaryotes. It operates in three phases: **adaptation** (Cas1-Cas2 acquires spacers from foreign DNA and integrates them into the CRISPR array), **expression** (transcription of the array and maturation into crRNA) and **interference** (crRNA-guided recognition and cleavage of the target). The **PAM** (protospacer adjacent motif) lies outside the target sequence and is absent from the organism’s own array; it is therefore the discriminating feature between self and non-self. **Primed adaptation** accelerates spacer acquisition against partially recognised invaders.

Phages counter with **anti-CRISPR proteins (Acr)** that bind effectors, block DNA binding or inhibit nuclease activity. The result is continuing co-evolution.

CRISPR is only one module in the broader prokaryotic defence repertoire, which includes restriction-modification systems, abortive infection, CBASS, Thoeris, Gabija, retrons and Pycsar. These systems frequently cluster in genomic **defence islands** — a finding that itself serves as a search heuristic for new defence systems (work of the Sorek group).

Evolutionarily, the class 2 effectors derive from non-CRISPR ancestors: **IscB** and **TnpB** (OMEGA systems) are the compact forebears of Cas9 and Cas12 respectively; the eukaryotic **Fanzor** nucleases show that RNA-guided DNA cleavage is not confined to prokaryotes.

Open and contested points

The derivations Cas9←IscB and Cas12←TnpB are well supported. Less settled is the function of many derived CRISPR variants that no longer perform immune functions but instead carry out RNA-guided transposition or signalling; the classification literature notes this gap explicitly.

ρ/δ note

The sequence resource — microbes from soils, waters and thermal springs worldwide — is geographically widely distributed, largely outside the later centres of commercialisation. Disposition over its commodification (patents, products) lies elsewhere. This is the starting point of the DSI/Nagoya debate (A13) and the field’s first ρ/δ divergence, chronologically prior to any application.

Sources

Makarova KS, Wolf YI, Iranzo J et al., *Nat Rev Microbiol* 18:67-83 (2020), DOI 10.1038/s41579-019-0299-x — funding: US NIH/NLM intramural; interest: F. Zhang is a co-author and co-inventor on Broad patents. · Koonin EV, Makarova KS, *Phil Trans R Soc B* 374:20180087 (2019), DOI 10.1098/rstb.2018.0087.

A2 Classification and mechanism

State of knowledge

The Makarova/Koonin classification sorts these systems into **2 classes, 7 types and 46 subtypes** (as of 6 November 2025; in 2020 there were 6 types and 33 subtypes, in 2015 five types and 16 subtypes — the count grows with metagenomics). The 2025 revision introduces **type VII**, whose effector **Cas14** is a metallo-β-lactamase (β-CASP) nuclease; a C-terminal domain structurally resembles the C-terminus of Cas10, suggesting an evolutionary link to type III. **Class 1** uses multi-protein effector complexes, **class 2** a single large effector; the latter is what makes class 2 usable as a tool.

Mechanistically the effector first binds the PAM, then unwinds the duplex and forms an **R-loop** comprising an RNA-DNA heteroduplex and the displaced non-target strand. Specificity arises from PAM recognition and the seed region of the guide; mismatches distal to the PAM are tolerated more readily than proximal ones.

Comparison of types

Class/Type	Effector	Guide	Target	PAM/PFS	Cleavage product	Application profile
1 / I	Cascade + Cas3	crRNA	dsDNA	5′ PAM	processive degradation, long deletions	large deletions, diagnostics (CONAN)
1 / III	Cas10 complex (Csm/Cmr)	crRNA	RNA and transcription-coupled DNA	rPFS	Cas10 generates cyclic oligoadenylates (cOA)	cOA signalling to Csm6/Card1
1 / IV	Csf complex	crRNA	mostly DNA	—	mostly nuclease-free	plasmid-borne, competition
2 / II	Cas9	sgRNA	dsDNA	3′ NGG (SpCas9)	blunt double-strand break	standard tool, clinical use
2 / V	Cas12a/b/e/f/k	crRNA	dsDNA, collateral ssDNA	5′ TTTV (Cas12a)	staggered cut	diagnostics (DETECTR), CAST
2 / VI	Cas13a–d	crRNA	ssRNA	PFS	collateral RNA cleavage	diagnostics (SHERLOCK), RNA intervention
2 / VII	Cas14 (β-CASP)	crRNA	RNA	—	metallo-β-lactamase activity	newly described 2025, applications open

Open and contested points

Subtype boundaries are fluid and shift with each metagenomic survey; between 2020 and 2025 alone one type and thirteen subtypes were added. No robust application perspective exists for type VII so far. The therapeutic usability of type VI collateral activity in human cells is contested: diagnostically it is the mechanism of action, therapeutically a toxicity risk.

p/δ note

The classification work is openly published and freely reusable; disposition over the highest-performing effectors is patent-encumbered (A12). Open knowledge base and closed commercialisation sit directly adjacent.

Sources

Makarova KS, Shmakov SA, Wolf YI, Mutz P, Altae-Tran H, Beisel CL et al., “An updated evolutionary classification of CRISPR–Cas systems including rare variants”, *Nat Microbiol* 10(12):3346–3361 (6 Nov 2025), DOI 10.1038/s41564-025-02180-8 · Makarova et al. 2020, DOI 10.1038/s41579-019-0299-x · Koonin EV, Makarova KS, Zhang F, *Curr Opin Microbiol* 37:67–78 (2017), PMID 28605718.

A3 Engineering and tool generations

State of knowledge

Four development lines lead away from the SpCas9 base tool. **First**, more compact orthologues (SaCas9, CjCas9) for AAV packaging. **Second**, specificity and PAM variants: eSpCas9, SpCas9-HF1, HypaCas9, evoCas9, Sniper-Cas9 on the fidelity side; xCas9, SpCas9-NG, SpRY on the PAM side, approaching PAM-lessness. **Third**, catalytically altered versions: nickases (Cas9n) and dCas9 as a binding platform for CRISPRi/CRISPRa and epigenome editors. **Fourth**, editors without a double-strand break.

Base editing installs point mutations without a double-strand break: cytosine base editors (CBE, Komor et al. 2016) and adenine base editors (ABE, Gaudelli et al. 2017, later ABE8e), plus CGBE for transversions.

Prime editing (Anzalone et al. 2019) uses a Cas9 nickase plus reverse transcriptase with a pegRNA as template. Generations extend to **PE7**: Yan J et al., “Improving prime editing with an endogenous small RNA-binding protein”, *Nature* 628(8008):639–647 (2024), DOI 10.1038/s41586-024-07259-6, PMID 38570691 — the Adamson lab identified the RNA-binding La protein in genome-wide screens as the strongest mediator of prime editing and achieved a median 21.2-fold improvement over PEmax in U2OS cells with transiently expressed pegRNAs by fusing the N-terminal La domain to the editor (5.5-fold with epegRNAs, 2.3-fold in primary human T cells). **twinPE**, **PASTE** and **eePASSIGE** extend to gene-sized insertions; eePASSIGE (Pandey, Gao et al., *Nat Biomed Eng* 2024, DOI 10.1038/s41551-024-01227-1) uses a continuously evolved Bxb1 recombinase.

Epigenome editing (dCas9-DNMT3A, -TET1, -p300, CRISPRoff/CRISPRon) alters gene activity without sequence change, in part heritably across cell divisions and reversibly. **RNA editing** (REPAIR, RESCUE) works through dCas13. **CAST/INTEGRATE** and **bridge RNA recombinases** perform programmable insertion. **CRISPR screens** and **Perturb-seq** couple systematic perturbation with single-cell readout.

Comparison of editor classes

Class	Double-strand break	Achievable change	Repair pathway	Delivery burden	Clinical status (Sept 2026)
Nuclease (Cas9/Cas12)	yes	knock-out, HDR knock-in	NHEJ / MMEJ / HDR	moderate	approved (exa-cel)
Base editor (CBE/ABE)	no (nick)	point mutation, chiefly transitions	base excision, mismatch repair	large	phase 1–2 (VERVE-102, n=1 case)
Prime editor (PE2–PE7)	no (nick)	all point mutations, small indels	pegRNA-templated	very large	first clinical programmes
Epigenome (CRISPRoff/on)	no	reversible silencing/activation	no sequence change	large	preclinical
CAST / bridge recombinase	no	targeted large insertion	transposition/recombination	very large	preclinical

Open and contested points

The trade-off between efficiency and safety is unsettled: higher prime editing efficiency is in part bought with destabilised reverse transcriptase domains. Base editor off-targets at the RNA level and bystander edits within the target window vary by editor variant and remain the subject of ongoing methodological dispute.

p/δ note

Research tools are distributed broadly through Addgene and MTAs: the δ threshold for academic use is low. Therapeutic use of the same tools is patent- and capital-bound; the same technique therefore carries entirely different access barriers depending on context of use.

Sources

Yan J et al., *Nature* (2024), DOI 10.1038/s41586-024-07259-6, PMID 38570691 · Pandey S, Gao XD et al., *Nat Biomed Eng* (2024), DOI 10.1038/s41551-024-01227-1 — funding NIH, Gates Foundation, HHMI; interest: D. Liu is a co-founder of Prime Medicine, Beam Therapeutics and Editas.

A4 Delivery

State of knowledge

The carrier question determines reach, dosability and risk profile more strongly than the choice of editor.

Vector	Capacity	ex/in vivo	Immunogenicity	Repeat dosing	Tissue	Typical application
AAV	ca. 4.7 kb	in vivo	pre-existing anti-capsid antibodies	strongly impeded	eye, liver, CNS, muscle	EDIT-101 (subretinal)
Lentivirus	ca. 8–10 kb	ex vivo	integrating, insertional risk	not applicable	haematopoietic stem cells, T cells	CAR-T, Iovo-cel
LNP (mRNA)	large	in vivo	transient	possible	predominantly liver	nex-z, Verve-102
eVLP / VLP	protein/RNP	in vivo	low, short residence	open	variable	preclinical
RNP electroporation	RNP	ex vivo	minimal, short half-life	not applicable	cell product	Exa-cel manufacture

Open and contested points

LNPs allow titration and repetition but concentrate the dose in the liver — hepatotoxicity is therefore the central safety bottleneck of the in vivo line (see A7, MAGNITUDE). For AAV, pre-existing immunity to common serotypes excludes a relevant share of patients; robust, comparable prevalence figures across populations are lacking.

p/δ note

The move from ex vivo to in vivo shifts risk out of a controlled manufacturing step and into the patient’s body, while disposition over vector platform, dose and stopping criteria remains with the sponsor.

A5 Off-target effects, safety, limitations

State of knowledge

The off-target question is methodologically split between empirical assays and computational prediction.

Assay	Principle	Context	Sensitivity	Systematic limitation
GUIDE-seq	dsODN tag capture at break sites	living cells	high	requires efficient transfection
CIRCLE-seq / CHANGE-seq	cleavage of circularised genomic DNA	cell-free	very high	overestimates cellular off-targets
DISCOVER-seq	MRE11 ChIP at repair sites	cells and in vivo	high	captures only active repair
SITE-seq	biochemical digestion, affinity enrichment	cell-free	high	chromatin context absent
Digenome-seq	in vitro digestion plus whole-genome sequencing	cell-free	high	cost, depth
Prediction (CFD, Elevation, DeepCRISPR)	model on training data	in silico	variable	training-data bias, cell-type dependence

Beyond point off-targets, **on-target complications** are documented: large deletions, chromosomal translocations, chromothripsis, aneuploidy, a p53-mediated damage response (which disadvantages p53-intact cells relative to p53-deficient ones and is therefore selection-relevant), and mosaicism in early embryonic intervention. FDA and EMA have published guidance on genome-edited products requiring off-target characterisation.

Open and contested points

Whether computational prediction suffices for approval or empirical assays must be mandatory is not settled uniformly across regulators. Equally open: which assay combination constitutes a minimum standard, since the methods have systematically different

error directions (cell-free overestimates, cellular underestimates).

⚖️ note

The off-target risk is borne by the patient. Disposition over the choice, depth and interpretation of detection methods lies with the sponsor, controlled by the regulator. The patient has no access to this methodological choice and usually no sight of it.

A6 Diagnostics

State of knowledge

The collateral activity of types V and VI is diagnostically usable: after target binding the effector cleaves reporter nucleic acids non-specifically, producing a fluorescent or lateral-flow signal.

SHERLOCK (Cas13a; Gootenberg JS et al., *Science* 356:438–442 (2017), DOI 10.1126/science.aam9321) and **DETECTR** (Cas12a; Chen JS et al., *Science* 2018) combine this with isothermal pre-amplification (RPA or LAMP) and reach attomolar sensitivity at single-base resolution. **STOPCovid** was a simplified SARS-CoV-2 variant.

Clinical validation: Patchesung M et al., *Nat Biomed Eng* 4:1140–1149 (2020), DOI 10.1038/s41551-020-00603-x, report for the SHERLOCK SARS-CoV-2 assay a specificity of 100 % at a detection limit of 42 RNA copies per reaction. Across the full viral load range sensitivity is 96 % by fluorescence readout and 88 % by lateral flow; the frequently quoted 97 to 100 % applies only to samples within the detection limit.

Method	Sensitivity	Instrument need	Time	Single-base resolution
RT-PCR	very high	thermocycler	1–3 h	via probe design
LAMP	high	heat block	30–60 min	limited
SHERLOCK / DETECTR	very high (with pre-amplification)	heat block, lateral flow	30–60 min	yes

Open and contested points

The instrument advantage is offset by the need for pre-amplification; without it sensitivity drops markedly. Market penetration remained limited despite pandemic-era authorisations — the reasons (reagent supply chain, IP, reimbursement, competition from antigen tests) have not been conclusively studied.

⚖️ note

Point-of-care diagnostics promise a shift of disposition towards the user and the site of care. This is realised only where IP position and reagent supply permit it; otherwise disposition stays with the licence holder while the benefit is promised locally.

A7 Somatic clinical applications

State of knowledge

Casgevy / exa-cel (exagamglogene autotemcel; Vertex and CRISPR Therapeutics) is the first approved CRISPR therapy. Autologous haematopoietic stem cells are edited ex vivo at the *BCL11A* erythroid enhancer, reactivating fetal haemoglobin. Approvals: MHRA November 2023, FDA 8 December 2023 for sickle cell disease, then beta-thalassaemia, EU February 2024. The list price is **USD 2.2 million**. The lentiviral competitor **Lyfgenia / lovo-cel** (bluebird bio) is priced at USD 3.1 million and carries a boxed warning for haematological malignancy.

Real-world provision lags approval. Company figures (cited for source-finding only, not peer-reviewed) report for the year 2025 a global total of 147 first cell collections in patients with sickle cell disease or transfusion-dependent thalassaemia and 64 infusions. Causes include conditioning toxicity (myeloablative preparation with infertility risk), centre availability and reimbursement.

Sponsor	Programme	Indication	Editor	Delivery	Phase / status Sept 2026
Vertex / CRISPR Tx	exa-cel (Casgevy)	sickle cell, beta-thalassaemia	Cas9 knock-out (BCL11A enhancer)	ex vivo, electroporation	approved
bluebird bio	lovo-cel (Lyfgenia)	sickle cell	lentiviral (not CRISPR)	ex vivo	approved, boxed warning
Intellia	nex-z (NTLA-2001)	ATTR amyloidosis	Cas9 knock-out (TTR)	LNP in vivo	phase 3 MAGNITUDE, resumed after hold (Mar 2026)
Intellia	lonvo-z (NTLA-2002)	hereditary angioedema	Cas9 knock-out (KLKB1)	LNP in vivo	phase 3 HAELO positive (27 Apr 2026), rolling BLA
Verve / Eli Lilly	VERVE-102	hypercholesterolaemia (PCSK9)	adenine base editor	GalNAc-LNP	phase 1 published, phase 2
Verve / Eli Lilly	VERVE-101	HeFH / ASCVD	ABE (PCSK9)	LNP	deprioritised
Verve / Eli Lilly	VERVE-201	refractory hypercholesterolaemia	ABE (ANGPTL3)	GalNAc-LNP	phase 1b
CRISPR Tx	CTX110 / CTX130	lymphoma / solid tumours	allogeneic Cas9 CAR-T	ex vivo	clinical
Great Ormond Street	base-edited CAR-T	T-ALL (Alyssa case)	base editor	ex vivo	single case, then trial
Excision Bio	EBT-101	HIV	multiplex Cas9	AAV	phase 1
YolTech	YOLT-101	heterozygous familial hypercholesterolaemia	adenine base editor (PCSK9)	LNP	phase 1 published (Mar 2026)
Editas	EDIT-101 (Brilliance)	LCA10 (CEP290)	Cas9	AAV subretinal	discontinued

MAGNITUDE safety event and resumption. A patient dosed with nex-z on 30 September 2025 in the ATTR cardiomyopathy trial developed grade 4 elevations of liver transaminases with raised total bilirubin; the event was reported on 24 October 2025. Intellia paused MAGNITUDE and MAGNITUDE-2 on 27 October 2025; the FDA imposed a clinical hold on 29 October 2025; the patient died on 5 November 2025. The FDA lifted the hold for MAGNITUDE-2 on 27 January 2026 and for MAGNITUDE on 2 March 2026. Both trials have since continued under additional conditions: enhanced monitoring of liver laboratory values, guidance on short-term steroid treatment where transaminases are elevated, and exclusion of patients with certain liver abnormalities, with recent cardiovascular instability, and with an ejection fraction below 25 % at screening. The evidence consists of company statements and trade reporting (cited for source-finding only); no peer-reviewed case report was available as of 24 September 2026. This is the most severe known safety event in an in vivo CRISPR trial, and the resumption under conditions is so far the only documented case in which such an event was translated into tightened trial conditions.

VERVE-102. Vafai SB, Täubel J, Ashdown T et al., “In Vivo Base Editing of PCSK9 with VERVE-102 for Hypercholesterolemia”, *N Engl J Med* 395(7):648–659 (13 August 2026), DOI 10.1056/NEJMoa2601283, PMID 42187087 (online 25 May 2026). Phase 1, 35 participants with at least 28 days of follow-up: dose-dependent mean LDL-C reduction of 9 to 62 %, PCSK9 reduction 51 to 88 %; no dose-limiting toxicity, no deaths; mild infusion-related reactions in 7 participants (20 %). Funded by Verve Therapeutics, a subsidiary of Eli Lilly since July 2025 — conflict of interest. The predecessor **VERVE-101** was deprioritised after transient grade 3 ALT elevation and thrombocytopenia in the 0.45 mg/kg cohort (reported April 2024); no dedicated peer-reviewed primary publication of the Heart-1 trial exists, the data derive from an AHA 2023 congress abstract and company statements. The only peer-reviewed item is an editorial: Horie T, Ono K, *Eur Heart J Cardiovasc Pharmacother* 10(2):89–90 (2024), DOI 10.1093/ehjcvp/pvad103.

Eli Lilly’s acquisition of Verve. Announced 17 June 2025: USD 10.50 per share in cash (about USD 1.0 billion) plus a contingent value right of up to USD 3.00 per share, totalling up to about USD 1.3 billion. Completed by tender offer, acquisition date 25 July 2025 per Lilly’s SEC filings (Form 10-Q/10-K FY2025); net payment less cash acquired USD 549.4 million. The central acquired IPR&D asset is VERVE-102.

Second in vivo base editing programme. Alongside VERVE-102, a second peer-reviewed phase 1 publication on in vivo base editing of PCSK9 has been available since 3 March 2026: YOLT-101 (YolTech Therapeutics, China), *Nat Med* 32:1045–1051 (2026), DOI 10.1038/s41591-026-04254-4, trial registration NCT06458010. In six participants the highest dose group showed a 74.4 % reduction in PCSK9 and a 52.3 % reduction in LDL-C at 24 weeks, with no grade 3 or higher events and no detected off-target editing. An evidence base independent of Verve therefore exists, from a non-Western development programme.

Personalised n=1 therapy. Musunuru K, Grandinette SA, Wang X et al., “Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease”, *N Engl J Med* 392(22):2235–2243 (12 June 2025), online 15 May 2025, DOI 10.1056/NEJMoa2504747. The infant KJ Muldoon (born 1 August 2024) with severe CPS1 deficiency received a bespoke in vivo base editing therapy by LNP; first dose 25 February 2025, development took roughly six months, discharge on 3 June 2025. Funding: NIH Somatic Cell Genome Editing (U01TR005355, U19NS132301), R35HL145203 and others, Milky Way Research Foundation; partners IGI, Mass General Brigham, Danaher, Acuitas — interests accordingly.

Open and contested points

First, price and access: an ICER assessment placed the cost-effective threshold for exa-cel and lovo-cel jointly at roughly USD 1.35 to 2.05 million, which is below the USD 2.2 million list price; proponents point to single administration and avoided lifetime costs, critics to reimbursement barriers precisely among sickle cell patients. Second, the generalisability of n=1 platforms: the regulatory debate on bespoke therapies is open (Almendro-Vázquez/Kassim, *Clin Transl Med* 2025, DOI 10.1002/ctm2.70515 — author affiliation with Danaher). Third, whether LNP hepatotoxicity is class-wide or programme-specific; the MAGNITUDE case stands against an unremarkable VERVE-102 safety profile.

p/d note

The extreme case of the asymmetry. The patient bears lethal risk, conditioning consequences and exclusion from access. Disposition over manufacture, price, trial design, stopping decisions and data lies with sponsor and regulator. In sickle cell disease, which predominantly affects people of African descent and was historically underfunded, the price extends an existing inequality into the therapeutic era.

A8 Germline

State of knowledge

In late November 2018 He Jiankui announced the birth of CRISPR-edited twins (*CCR5* deletion, intended HIV resistance); a third child followed. The professional response was near-unanimous rejection: inadequate indication, mosaicism, unclear consent, no safety basis. In December 2019 He was sentenced in China to three years’ imprisonment for illegal medical practice.

Governance responses: the report of the international commission of NASEM and the Royal Society (2020), the WHO expert committee framework (2021), the ISSCR guidelines, and the Third International Summit in London (2023), which continued to classify heritable intervention as irresponsible.

Baylis F, Darnovsky M, Hasson K, Krahn TM, *CRISPR J* 3(5):365–377 (2020), DOI 10.1089/crispr.2020.0082, with a 2021 correction (DOI 10.1089/crispr.2020.0082.correx), mapped 106 states: 96 have relevant rules; the Oviedo Convention prohibits heritable germline modification for its parties.

Country	Reproductive germline modification	Basis
Austria	prohibited	Reproductive Medicine Act; Gene Technology Act (germline gene therapy impermissible)
Germany	prohibited, criminal offence	Embryo Protection Act §5
Switzerland	prohibited at constitutional level	Federal Constitution Art. 119; Reproductive Medicine Act
United Kingdom	clinically prohibited; embryo research licensed to 14 days	HFE Act 1990/2008, HFEA
USA	de facto prohibition via appropriations rider (FDA may not review applications)	Consolidated Appropriations Act
China	prohibited; tightened after the He case	2003 ethics guideline, Art. 336 Criminal Law, 2021 Civil Code
Japan	clinically prohibited by guideline	MEXT/MHLW guidelines

Open and contested points

Since 2024 private initiatives have appeared seeking to market embryo editing as prevention or enhancement; professional bodies