PIPADOR REVISION

MRCOG Part 1 Revision Notes

Gene Therapy

MOLECULAR BIOLOGY • LECTURE 98

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 98: Gene Therapy

Molecular biology • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

SOMATIC / SAFE	GERMLINE / RISK	EX VIVO	IN VIVO / AAV	EDITING / CAR-T

LEARNING OBJECTIVES — tick off as you go

- ☐ Distinguish somatic vs germline and ex vivo vs in vivo gene therapy.
- ☐ Compare viral and non-viral vectors.
- ☐ Describe the licensed products, including Casgevy and CAR-T.
- ☐ Explain CAR-T toxicity and the SMA treatment options.
- ☐ Counsel women about fertility, pregnancy and inheritance after gene therapy.

1 Principles

IN ONE LINE: *Add, silence or edit genes in a patient's own cells. Every licensed product is SOMATIC — the treated person is helped, but the disease variant is still passed on through their eggs or sperm.*

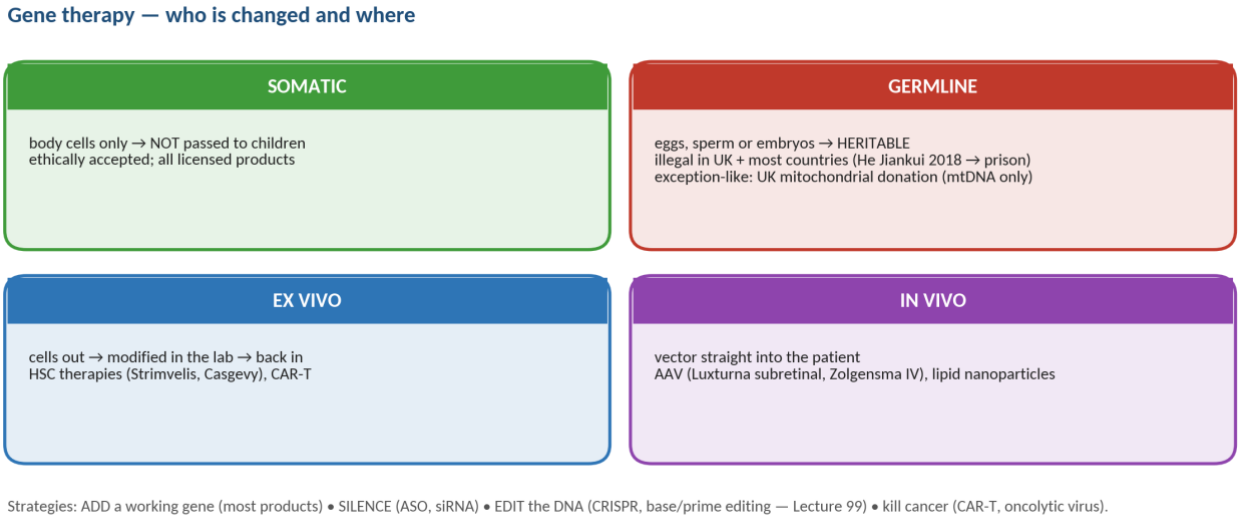


Figure 1. Somatic/germline and ex vivo/in vivo.

- **Setbacks that shaped the field**: Jesse Gelsinger (1999) died of an immune reaction to an adenoviral vector; early **X-SCID** trials with γ-retroviruses caused **leukaemia** (vector inserted next to the LMO2 oncogene) → safer lentiviral and AAV vectors, long-term follow-up.

2 Vectors

Choosing a vector — cell type, duration, payload size, safety

Vector	Genome	Capacity	Integrates?	Key points
γ-Retrovirus	RNA → DNA	~8 kb	YES	dividing cells only; early X-SCID trials → LEUKAEMIA (insertion near LMO2); Strimvelis
Lentivirus (HIV-based)	RNA → DNA	~8 kb	YES	dividing + non-dividing; safer integration; CAR-T, Lyfgenia, ex vivo HSCs
Adenovirus	dsDNA	~7.5–36 kb	no (episomal)	strong immunity, transient; Gelsinger death 1999; vaccines (ChAdOx1)
AAV	ssDNA	~4.7 kb	mostly no	long expression in non-dividing tissue; serotypes target organs; ~30–60% adults have neutralising antibodies; liver inflammation
HSV	dsDNA	up to ~150 kb	no	neurons; oncolytic T-VEC (melanoma)
Non-viral	LNP, naked DNA	large	no	lipid nanoparticles (patisiran, mRNA), electroporation — less efficient, low immunity

Figure 2. Vector comparison.

MNEMONIC / MEMORY HOOK

'AAV = Always Away from the genome (mostly); Lenti = Lands In the DNA' — AAV is mostly episomal; lentivirus integrates.

3 Licensed Products

Licensed gene therapies to know

Strimvelis	ADA-SCID ex vivo γ-retrovirus HSCs (Milan) — first EU ex vivo stem-cell gene therapy, 2016
Luxturna	RPE65 retinal dystrophy AAV2, SUBRETINAL injection, one-off — restores some vision
Zolgensma	SMA AAV9-SMN1, single IV infusion in infants (~£1.79 m list) — earlier = better (presymptomatic)
Casgevy	sickle cell, TDT β-thal CRISPR-edited own HSCs (BCL11A) — MHRA Nov 2023, world first
Lyfgenia	sickle cell lentiviral β-globin variant into HSCs — FDA (USA) 2023
Hemgenix / Roctavian	haemophilia B / A AAV5 factor IX / VIII to liver — years of factor; transaminitis, waning
CAR-T	B-cell cancers, myeloma ex vivo lentiviral T cells (see CAR-T figure)
Imlygic (T-VEC)	melanoma oncolytic HSV-1 with GM-CSF
Glybera	lipoprotein lipase deficiency first EU gene therapy (2012) — withdrawn 2017 (cost, low use)

Figure 3. Licensed gene therapies.

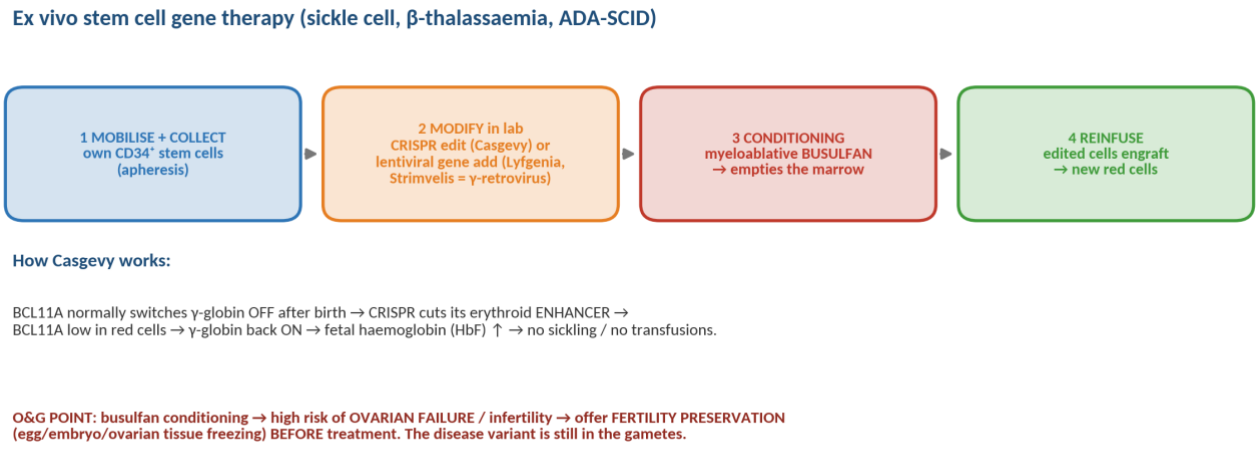


Figure 4. Ex vivo stem cell gene therapy and Casgevy.

- **Haemophilia AAV therapy** (Hemgenix, Roctavian): one infusion → years of factor production; liver enzyme rises need steroids; factor levels may wane; pre-existing AAV antibodies can exclude patients.

4 CAR-T Cells

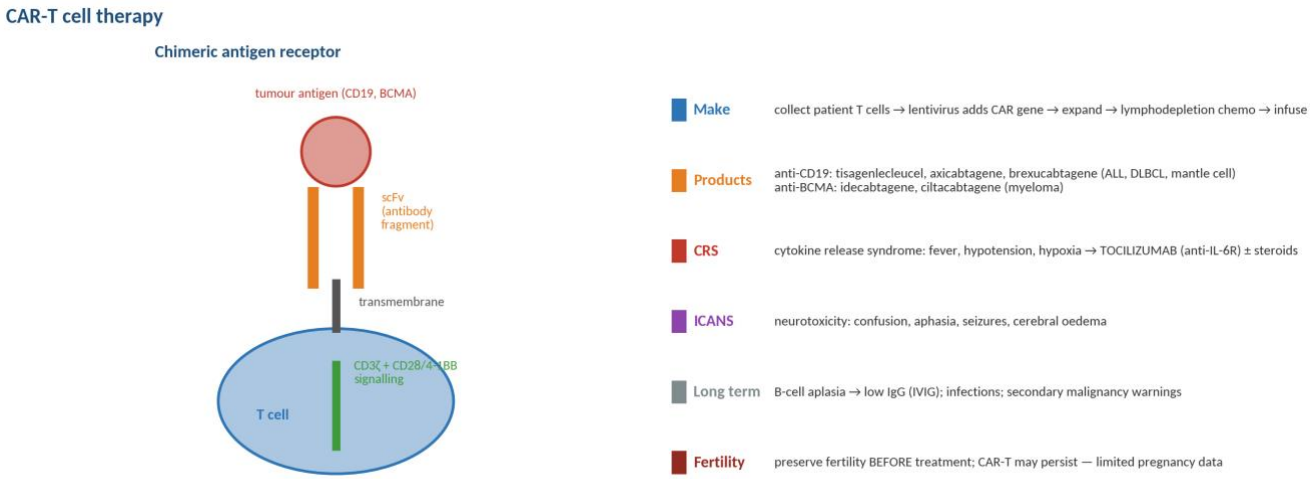


Figure 5. CAR-T cells.

5 Pregnancy, Fertility, Ethics and Regulation

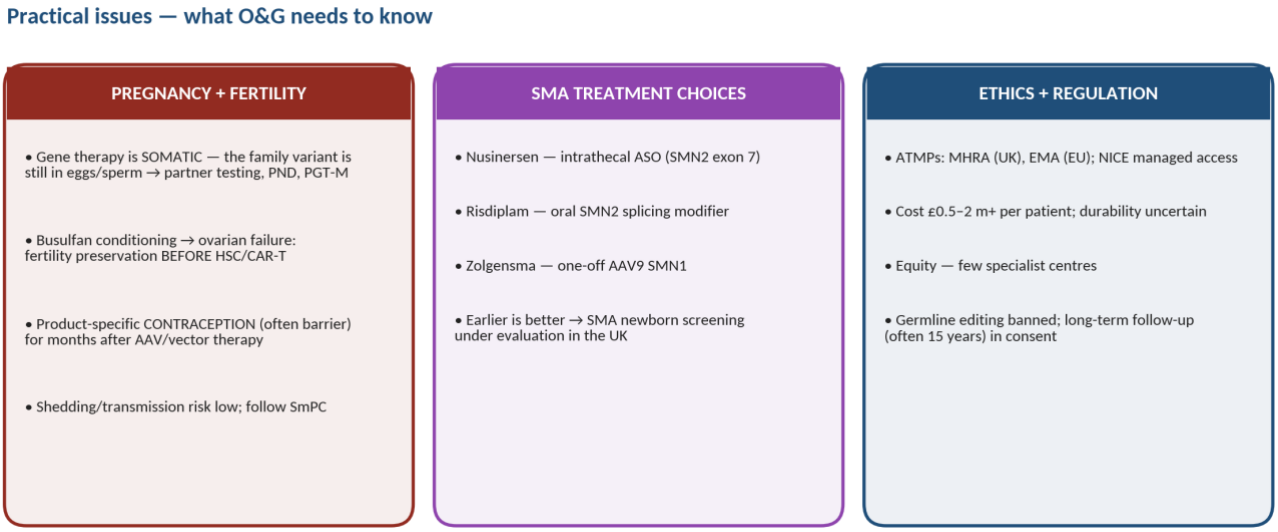


Figure 6. Practical issues.

Topic	Key points
Regulation	Gene therapies are ATMPs — MHRA (UK) / EMA (EU); NICE often via managed access. Research ethics through HRA specialist committees (the former GTAC role)
Germline	Heritable editing prohibited (HFE Act); He Jiankui (2018) imprisoned. Mitochondrial donation is the UK-licensed exception (changes mtDNA, not nuclear DNA)
Future	In vivo CRISPR (NTLA-2001 — ~90% fall in TTR in hereditary amyloidosis), base and prime editing, better AAV capsids, 'off-the-shelf' CAR-T
Counselling after treatment	Disease variant still in gametes → partner carrier testing, PND or PGT-M; pre-treatment FERTILITY PRESERVATION (busulfan); product-specific contraception after vector therapy

★ **PEARL**

Casgevy: CRISPR disrupts the BCL11A enhancer → fetal haemoglobin returns (UK, Nov 2023 — world first). Busulfan conditioning → offer fertility preservation first.

CAR-T toxicity: CRS → tocilizumab; ICANS. Gene therapy is somatic — the child can still inherit the variant.

6 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

~4.7 kb AAV capacity	**~8 kb** Lentivirus capacity	**30–60%** Adults with AAV antibodies	**1999** Gelsinger death
2016 Strimvelis (EU)	**Nov 2023** Casgevy (MHRA)	**~£1.79 m** Zolgensma list price	**~90%** TTR fall with in vivo CRISPR

HIGH-YIELD CHECKLIST

- ☐ Somatic (allowed) vs germline (banned); ex vivo vs in vivo.
- ☐ Add, silence, edit; CAR-T and oncolytic viruses.
- ☐ Retrovirus/lentivirus integrate; AAV mostly episomal (~4.7 kb); adenovirus immunogenic.
- ☐ Gelsinger (adenovirus); X-SCID leukaemia (γ-retrovirus).
- ☐ Strimvelis, Luxturna, Zolgensma, Casgevy, Lyfgenia (US), Hemgenix/Roctavian, Glybera.
- ☐ Casgevy: BCL11A enhancer → HbF.
- ☐ CAR-T: CD19/BCMA; CRS (tocilizumab), ICANS, B-cell aplasia.
- ☐ SMA: nusinersen, risdiplam, Zolgensma; early treatment.
- ☐ Fertility preservation before busulfan; variant still inherited; PGT-M.
- ☐ ATMPs: MHRA/EMA; NICE managed access; mitochondrial donation exception.

Self-assessment — cover the right-hand column

Question	Answer
Is germline gene therapy legal in the UK?	No
Which vector caused leukaemia in early X-SCID trials?	γ-Retrovirus (insertional mutagenesis)
Main limit of AAV vectors?	Small capacity (~4.7 kb) + pre-existing antibodies
Vector and route in Luxturna?	AAV2, subretinal injection
Vector in Zolgensma?	AAV9 carrying SMN1
How does Casgevy raise HbF?	CRISPR disrupts the BCL11A erythroid enhancer
Fertility issue with HSC gene therapy?	Busulfan conditioning → ovarian failure
Treatment for CAR-T cytokine release syndrome?	Tocilizumab (± steroids)
Can a treated parent pass on the disease variant?	Yes — gene therapy is somatic
UK regulator for gene therapy medicines?	MHRA (ATMPs)

7 References

- Frangoul H et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med 2021; MHRA approval of Casgevy, 2023.
- NICE HST15 (onasemnogene abeparvovec) and related technology appraisals.
- Gillmore JD et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis (NTLA-2001). N Engl J Med 2021.