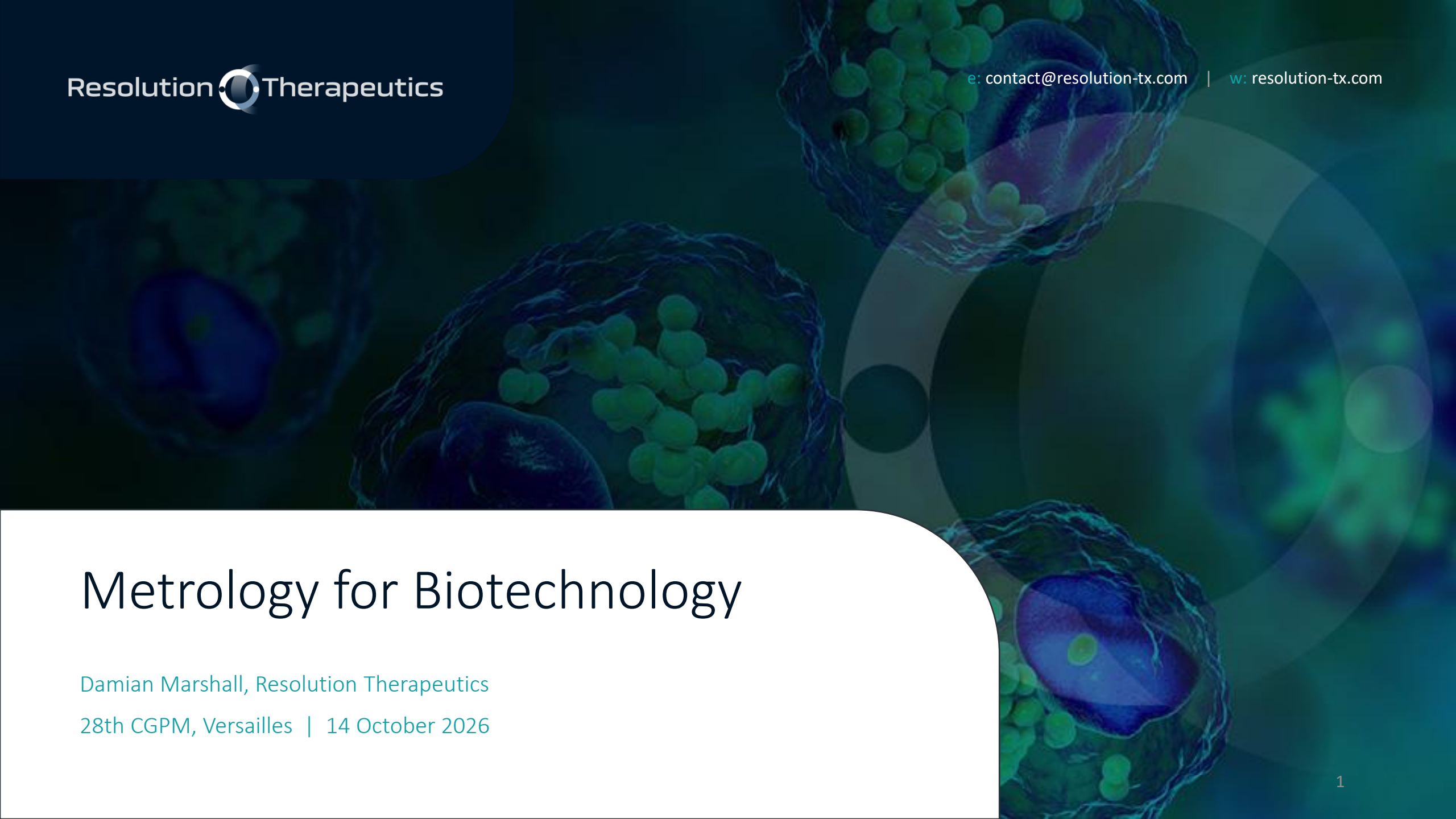

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Metrology for Biotechnology

Damian Marshall, Resolution Therapeutics

28th CGPM, Versailles | 14 October 2026

Biotechnology

Combining natural sciences and engineering to solve complex problems

The use of biology and living organisms to create products, tools and processes that solve human problems and improve life



Red

Health

Medicines, vaccines, cell and gene therapies, diagnostics

Measurement: Dose, purity and potency of living medicines — the focus of this talk



Green

Agriculture and food

Pest-resistant and precision-bred crops; fermentation-made food

Measurement: Reference materials for GM content underpin the EU 0.9% labelling threshold



White

Industry and energy

Enzymes, bio-based chemicals and materials, biofuels

Measurement: Radiocarbon (^{14}C) measurement certifies how much carbon is bio-based



Grey

Environment

Bioremediation, wastewater treatment, environmental monitoring

Measurement: Wastewater PCR tracked SARS-CoV-2 spread across whole cities

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Biology is becoming a manufacturing technology

Biotechnology: innovation, growth and societal impact

Up to 60%

of physical inputs to the global economy could, in principle, be made biologically

McKinsey Global Institute, 2020

€2.7 tn

EU bioeconomy, employing 17.1 million people

European Commission, 2025

£2 bn

UK commitment to engineering biology over 10 years

UK Government, 2023

$15 bn

minimum federal investment over 5 years recommended for US biotechnology

US NSCEB, 2025

Beyond medicine

Fuel Microbes turn steel-mill exhaust gas into ethanol (~80 million litres a year, Belgium)

Food Precision-bred crops now regulated in England (2025)

Health Antibodies, vaccines, gene and cell therapies — the focus of this talk

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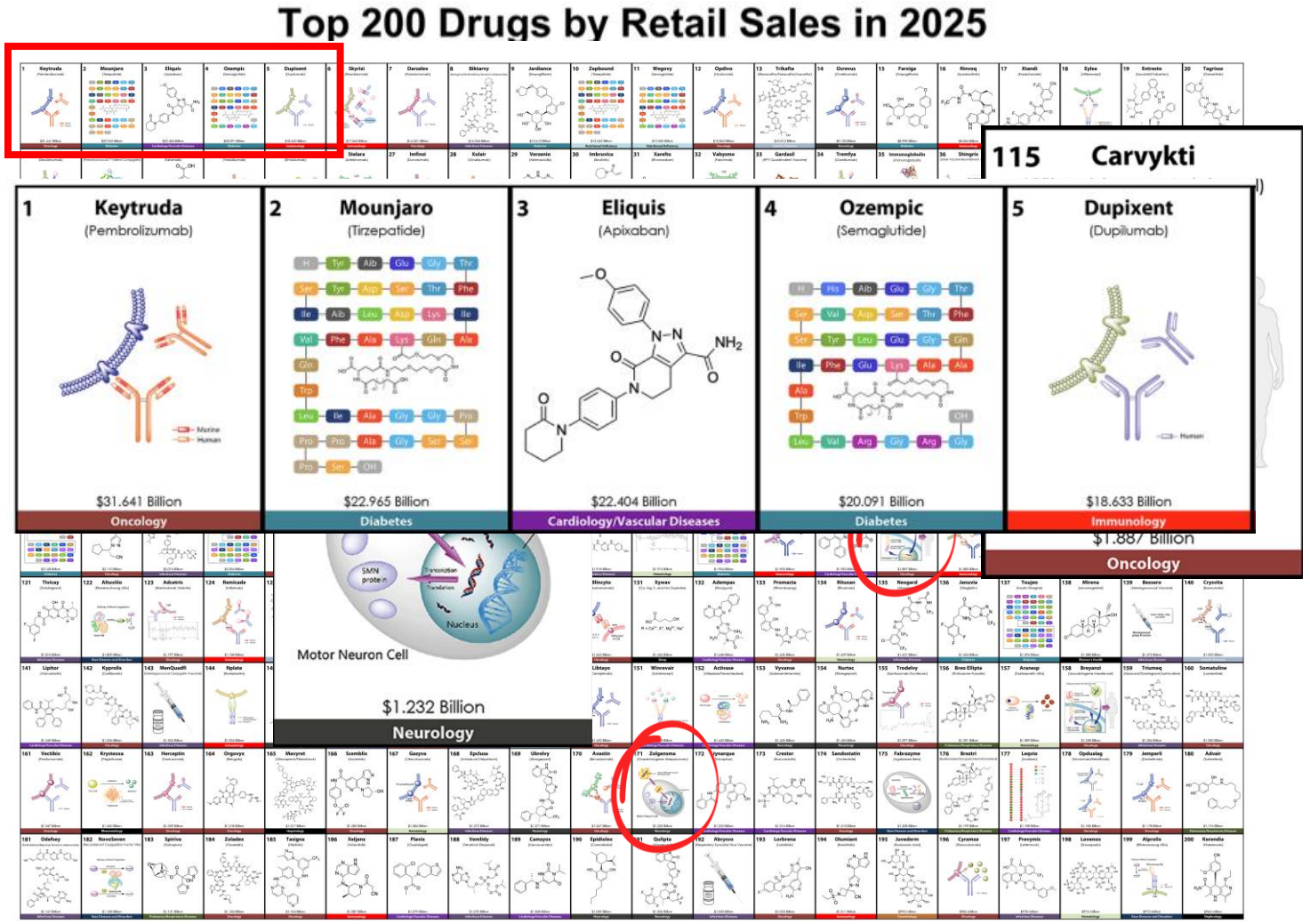
Medicines are becoming biological

Healthcare is where biotechnology has the greatest impact today



2024

First year innovative biologics took a larger market share than innovative small molecules

4 out of 5

Four of the top 5 drug sales in 2025 were biological ($93.33 Bn)

Diverse medicines

Cell and Gene therapies are among the top selling drugs in 2025 (blockbuster status)

4,487

gene, cell and RNA therapies in development worldwide (Q2 2026)

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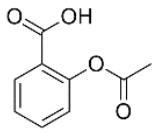
From molecules to living medicines

Each step adds orders of magnitude in size and complexity

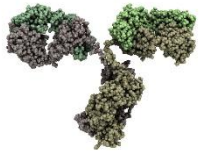


Small molecule

e.g. aspirin

~21 atoms

Fully defined structure

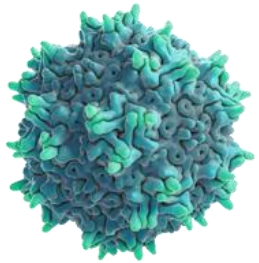


Antibody

MAb

~2 × 10^4 atoms

Defined sequence; variable sugars and folding

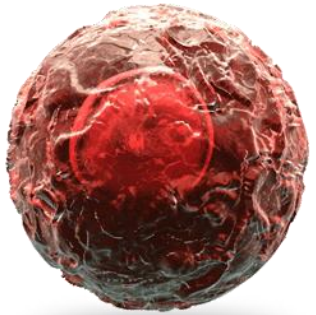


Viral vector

gene therapy (AAV)

~10^6 atoms

Some particles empty or partly filled



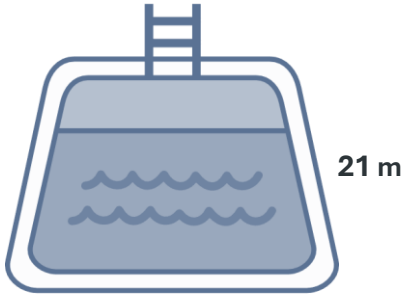
Cell therapy

e.g. CAR-T

~10^{14} atoms

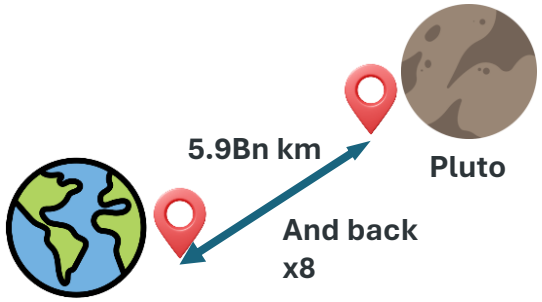
Alive; changes during manufacture and measurement

If 1 atom = 1m









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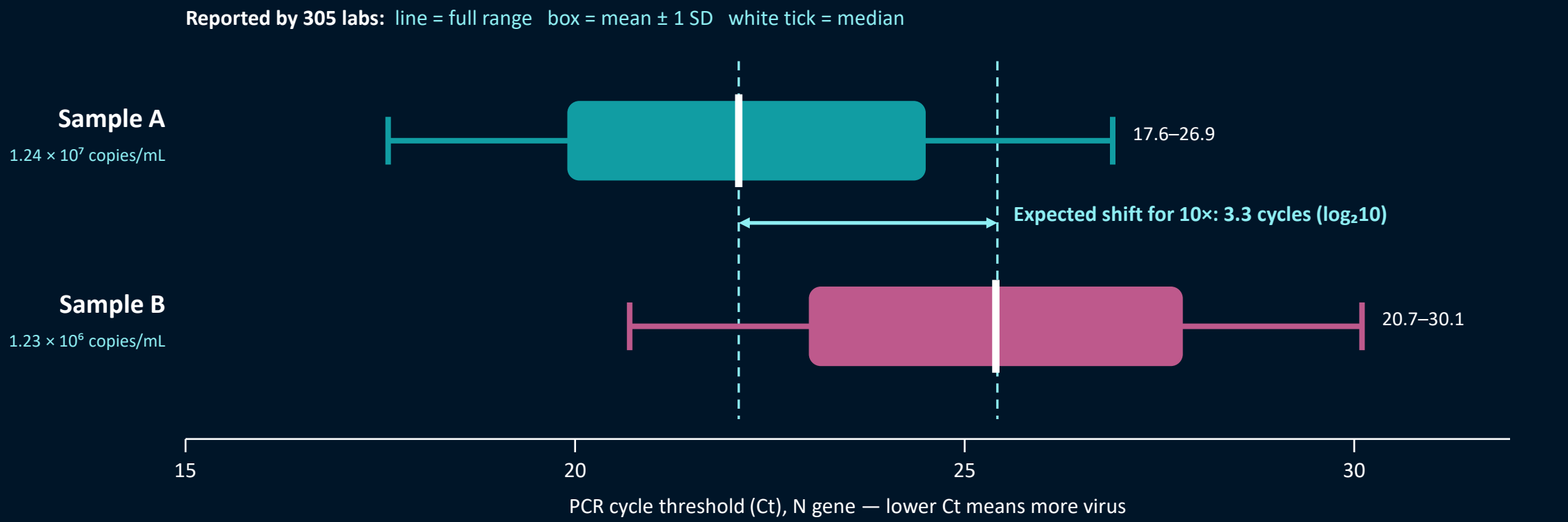
This complexity comes with measurement challenges

305 laboratories measured two SARS-CoV-2 samples, one with 10× less virus



3.3 cycles
difference between medians — exactly as expected

±2.3 cycles
1 SD between labs ≈ 5-fold in concentration

9 cycles
full range ≈ 600-fold: one Ct cannot identify the sample

dPCR
three NMIs assigned the true values by counting molecules

Kammel et al., PLoS ONE 2022; 17: e0262656, Table 2 (389 N-gene results per sample). Ranges as reported; verify before presenting.

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Why measuring biology is different

Four challenges in terms a metrologist will recognise



Defining the measurand

A “viable CAR-T cell” depends on the definition of viable, the marker used and the analysis rule.



Counting has unit one

Cell numbers and genome copies are SI-coherent counts — but only once the identity of the counted entity is fixed.



Potency is method-defined

Like Rockwell hardness, biological activity is defined by the procedure that measures it, not by an invariant property.



The artefact is alive

Products and reference materials change over time, so stable, long-lived reference artefacts are hard to make.

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Two routes to comparability

SI traceability and WHO International Units coexist in medicine

SI-traceable CIPM MRA

SI unit — one, mole, kilogram

↓

Primary reference method — digital PCR, isotope dilution MS, qNMR

↓

Certified reference material from an NMI

↓

Laboratory result with stated uncertainty

Conventional World Health Organization

WHO International Standard — a physical vial of material

↓

1 International Unit (IU) defined by agreed activity of that vial

↓

Secondary and in-house standards

↓

Bioassay result in IU

Bridging is under way: WHO lentiviral vector reference reagents are assigned in copies, not IU; CCQM-K190 links NMI digital PCR values to the WHO SARS-CoV-2 RNA standard

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Where SI traceability reaches today

COUNT *How many?*	**Cells, vector genomes, capsids, RNA copies** SI route exists: digital PCR, cell counting (ISO 20391-1), calibrated flow cytometry	**Traceable**
COMPOSITION *What is it made of?*	**Identity, purity, full/empty capsids, sequence, sugars** Partly covered: reference materials and interlab studies; no CCQM key comparison yet for viral vectors	**Partly**
FUNCTION *Does it work?*	**Potency, viability, cell behaviour** No SI route: method-defined values, WHO units or product-specific references	**Conventional**

Clinical Effect

Count–composition–function framing from the CCQM Task Group on Gene Delivery Systems.

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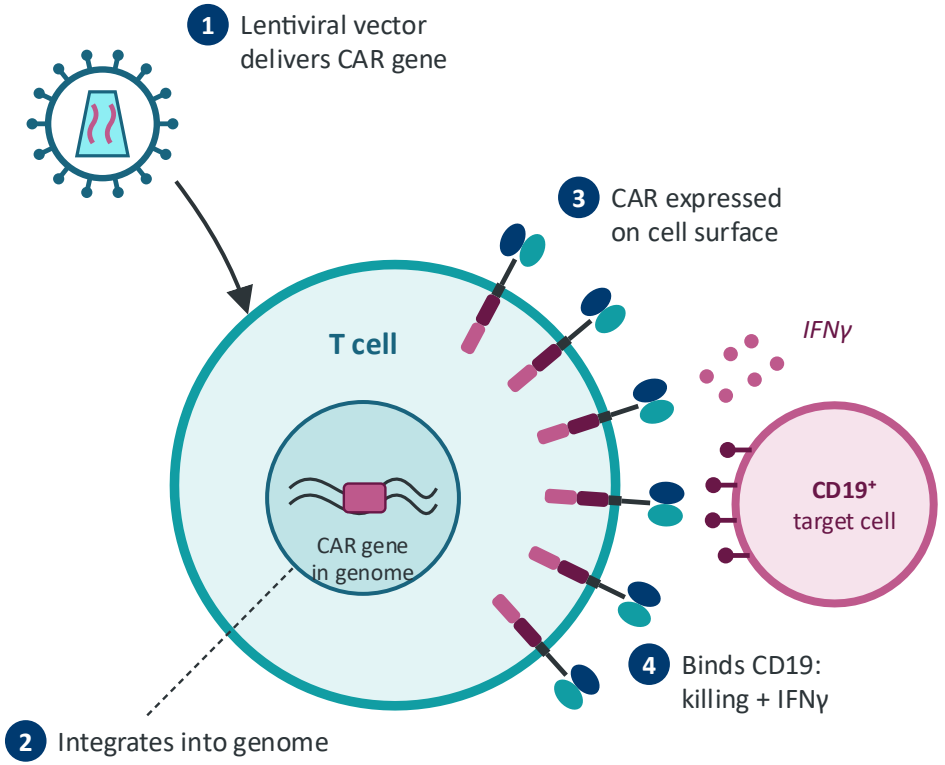
Potency testing of cell therapy products



Each step can be measured

Vector copy number	% CAR⁺ cells (flow)	IFNγ release
2 · COUNT	3 · COMPOSITION	4 · FUNCTION

KYMRIAH (2017)	YESCARTA (2017)	TECARTUS (2020)	CARVYKTI (2022)
CAR expression by flow cytometry	Cell viability	Cell viability	CAR expression on viable T cells
Production of IFNγ following CD19+ stimulation	Anti-CD19 CAR expression	Anti-CD19 CAR expression	Redacted
		Redacted	

Data adapted from – Simon et al (2025)
Analysis of the measurements used as potency tests for the 31 US FDA-approved cell therapy products – J. Transl. med

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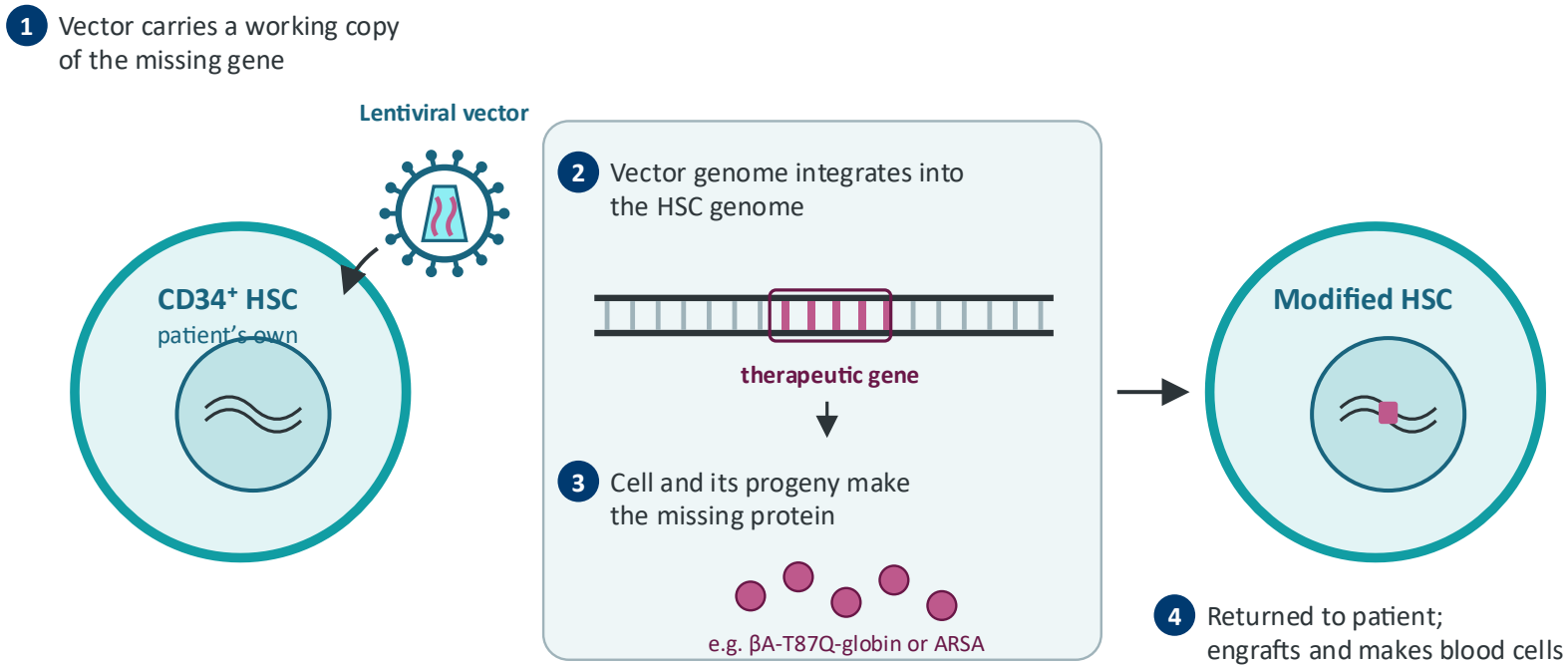
Potency testing of cell therapy products



Each step can be measured

Vector copy number, % LVV⁺ cells
COUNT

Transgene protein expression
COMPOSITION

Colony formation, ARSA activity
FUNCTION

zynteglo (2022)	libmeldy (2024)
Vector copy number (qPCR)	Cell viability
Percent LVV positive cells	Vector copy number
Redacted	Transduction efficiency
Redacted	transgene function (arylsulfatase A (ARSA) activity);
Colony forming cells	Redacted
βA-T87Q-globin quantitative protein expression	Redacted

Data adapted from – Simon et al (2025)
Analysis of the measurements used as potency tests for the 31 US FDA-approved cell therapy products – J. Transl. med

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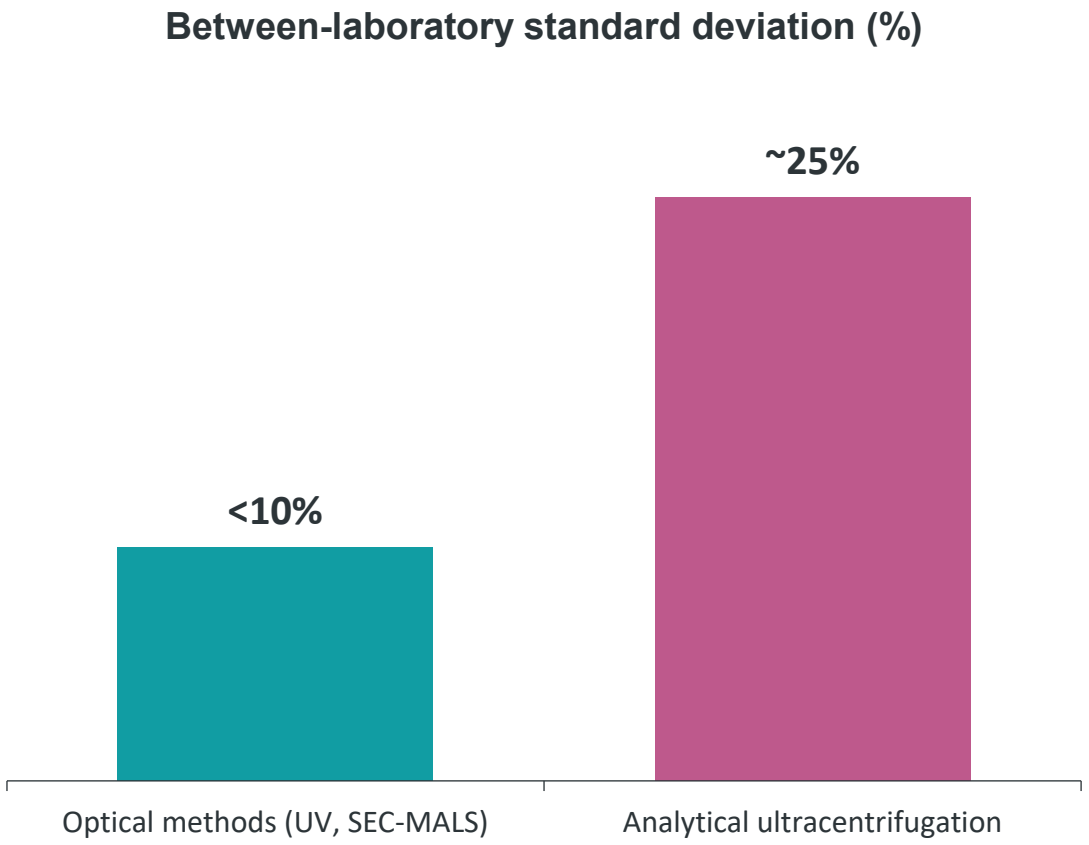
The “gold standard” was the least reproducible

Interlaboratory study of AAV full-to-total capsid ratio, 2024



Why it matters
The share of capsids that carry the gene affects the dose a patient receives

The surprise
Ultracentrifugation was widely treated as the reference method

Familiar territory
An interlab comparison exposed a hidden systematic effect

Next step
2026 AAV9 study tests a USP reference material as a common calibrant

Lehman et al., Human Gene Therapy 2024 (NIST, USP, NIIMBL); NIST news, Jul 2026. Optical-method value shown as an upper bound.

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Measurement gaps have real costs

Evidence from research, regulation and public health

36%

of an estimated $28 bn a year of irreproducible US preclinical research is attributed to biological reagents and reference materials

Freedman et al., PLoS Biol 2015 (estimate)

74%

of FDA complete response letters in 2020–24 cited quality or manufacturing issues (all drug types)

Pharma Manufacturing analysis, 2025

"…not agree that you have demonstrated that the attribute measured by the […] assay is associated with clinical outcomes."

FDA to a cell therapy developer on its potency assay, Aug 2023

The return can be large: standardising US cholesterol testing has an estimated benefit–cost ratio of about 4,470 : 1 (≈200 : 1 on conservative assumptions)

Mesoblast remestemcel-L complete response letter, 1 Aug 2023 (product later approved, Dec 2024). Hoerger et al., Prev Chronic Dis 2011.

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Who is doing what

Selected activities, mapped to count, composition and function

	NIST (USA)	UK: LGC and MHRA	Other NMIs and CCQM	Pharmacopoeias and ISO
Count	ISO 20391 cell counting; flow cytometry units (ERF); lentiviral copy-number material (2026)	LGC digital PCR reference methods; WHO lentiviral copy-number reagents (MHRA)	CCQM cell counting studies; NRC lentiviral vector material; CCQM-K190	ISO 16921-2:2026 viral vector quantification
Composition	NISTmAb RM 8671; AAV interlab studies; mRNA test material; Genome in a Bottle	AAV2 reference material (MHRA and CGT Catapult); BP guidance	CCQM-P244 RNA in lipid nanoparticles; PTB MetrINo nanotherapeutics	USP AAV8 empty/full standards; ISO AWI 26012 (AAV capsids)
Function	Flow assays for CAR-T identity and potency (in development)	WHO International Standards (MHRA makes >95%)	KRISS biopharma quality platform to 2030, with NIST	FDA draft potency guidance (2023); Ph. Eur. 5.32 (2026)

Not exhaustive. NIST, LGC, MHRA, BIPM/CCQM, EURAMET, KRISS, NRC, USP, ISO and EDQM sources; see speaker notes.

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NIST: a shared reference for an industry

From a reference molecule to a living reference material



NISTmAb
RM 8671

Open reference antibody; characterised by >100 collaborators; >10,000 units sold

ISO 20391
parts 1 and 2

NIST-led cell counting standards: qualify a method when no cell reference exists

NISTCHO
RM 8675

First living reference material: the cell line that makes NISTmAb

Viral vectors
RGTM 10268

Lentiviral copy-number test material; AAV9 interlab study with USP and NIIMBL

Delivered with industry: NIIMBL manufacturing institute and consortia for flow cytometry (17 organisations, 42 instruments), genome editing and mass spectrometry

NIST news releases 2016–2026; NIST VCAT updates, Jun 2025 and Jun 2026. Sales and collaborator figures are NIST-reported.

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A growing international effort

CCQM working groups and national programmes

CCQM (BIPM)

Gene Delivery Systems task group, 2025–27
viral vectors, vesicles, synthetic carriers; pilot study 2027

P244: RNA in lipid nanoparticles
substantial variation between NMIs

P260: T-cell immunophenotyping
new in 2026; relevant to CAR-T

Cell counting comparisons
and a request for a new calibration capability category for cells

KRISS Korea	~~₩~~39.7 bn biopharma quality platform to 2030, partnered with NIST
NRC Canada	Lentiviral vector reference material (~8,000 vials)
PTB Germany	Leads MetrINo nanotherapeutics project; chairs CCQM protein group
NIM China	Vice-chairs CCQM cell and protein groups

CCQM 31st meeting, Apr 2026; Kukinews, 23 Jun 2026; Manceur et al., 2025; EURAMET 22HLT04. Not exhaustive.

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What medicine developers need from metrology

Five priorities for the metrology community

Key comparisons for viral vectors and cell therapies
today led by pharmacopoeias and ISO rather than CCQM

A framework for function
potency and viability: definitions, uncertainty, links to the VIM revision on nominal properties

Recognised capabilities for cell measurements
a calibration and measurement capability (CMC) category in the KCDB

One system, not parallel ones
NMIs, WHO custodians, pharmacopoeias, regulators and industry, with sustained funding

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Living medicines need measurements we can trust

1. Biotechnology is becoming a core industrial technology — led by medicines
2. Counting is traceable today; function is not. That is the frontier
3. The metrology community already has the tools — and a role to play

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Thank you

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