

WG 6 – Addressing Regulatory, Technological-transfer
and Industry Aspects in GenE-HumDi

Report from the Committee for
Advanced Therapies (CAT) Strategic

Review and Learning Meeting

20 April 2026 | Aliathon Resort, Paphos, Cyprus

**Organized by the Committee for Advanced Therapies (CAT) of
the European Medicines Agency with participation by GenE-
HumDi representatives**

*"Genome Editing to Treat Human Diseases" (GenE-
HumDi; COST Action CA21113)*

An EU-funded network connecting researchers and innovators across Europe and beyond



**Funded by
the European Union**

Report from the Committee for Advanced Therapies (CAT) Strategic Review and Learning Meeting

Strategic Review and Learning Meeting | Paphos, Cyprus | April 19–21, 2026

Location: Paphos, Cyprus

Dates: April 19–21, 2026

Context: Convened under the Cypriot Presidency of the Council of the EU

Introduction: Bridging Innovation and Regulation in Advanced Therapies

The Strategic Review and Learning Meeting (SRLM) of the Committee for Advanced Therapies (CAT) was convened in Paphos, Cyprus, from April 19 to 21, 2026, under the Cyprus Presidency of the Council of the European Union. Organised in collaboration with the Cyprus Pharmaceutical Services and CING, the meeting established a vital bridge between regulatory oversight and advanced therapy medicinal product (ATMP) innovation. This strategic alignment closely mirrors the core objectives of the COST Action CA21113 "Genome Editing to Treat Human Diseases" (GenE-HumDi). GenE-HumDi was established to connect genome-engineering innovators with specialists working in delivery science, disease modeling, genomic safety, clinical applications, and regulatory frameworks. As highlighted in the proceedings of GenE-HumDi's annual meeting, translating technological breakthroughs into stable, clinical solutions requires balancing editing efficiency with strict standards of genomic safety, reproducible manufacturing, and regulatory preparedness. The Paphos SRLM served as a crucial forum where academic researchers and CAT regulatory experts could align their translational ambitions, ensuring that the next generation of gene-editing therapies is guided by the harmonized principles of safety, durability, and universal patient accessibility.

Summary of the CAT Plenary and Overall SRLM Agenda

The overall proceedings of the CAT during this period consisted of its remote Plenary Meeting held on April 15–17, 2026, followed immediately by the in-person Strategic Review and Learning Meeting (SRLM) in Paphos on April 19–21, 2026. The remote plenary, chaired by Ilona Reischl-Kok and vice-chaired by Kieran Breen, addressed key regulatory evaluations and operational matters. Most notably, the CAT adopted a positive draft opinion recommending the granting of

a European marketing authorisation for Itvisma (onasemnogene abeparvovec, previously known as Zamzura) for treating 5q spinal muscular atrophy (SMA).

Additionally, the Committee managed complex post-authorisation evaluations, adopting requests for supplementary information and opinions for prominent CAR-T cell products, including Abecma, Breyanzi, Carvykti, Kymriah, and Tecartus/Yescarta. This included critical updates to monitoring guidelines for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) to enhance post-marketing patient safety. The CAT also advanced initial applications, adopting lists of questions for Zopapogene Imadenovec and discussing accelerated assessment pathways for Lunsotogene parvec.

Beyond product reviews, the Committee processed numerous ATMP scientific classification recommendations. Coordinator nominations were finalized for innovative treatments such as autologous venous grafts, human type I collagen, autologous platelet-rich plasma with mechanically processed adipose tissue, and allogeneic human umbilical cord-derived mesenchymal stromal cells. The Committee also adopted Day 30 scientific recommendations on ATMP classifications, including autologous adipose-derived stromal vascular fraction.

On administrative and procedural fronts, the CAT formally adopted its revised Rules of Procedure (RoP). It also participated in international cooperation activities, including an ATMP cluster teleconference with the US FDA, Health Canada, Swissmedic, and PMDA Japan.

Following the remote session, the physical SRLM in Paphos commenced on April 19 with a welcome reception at the Aliathon Resort. The core of the SRLM occurred on April 20, comprising an internal committee session in the morning, followed by guest lectures from leading neurological and hematological ATMP researchers, including three GenE-HumDi representatives in the afternoon, before concluding on April 21 with a final plenary wrap-up.

Presentations by GenE-HumDi Members 2026-04-20

Carsten W Lederer – Universal and mutation-specific advanced therapy development for erythroid blood disorders

Prof. Carsten Werner Lederer from the Department of Blood Disorder Genetics & Thalassemia (BDGT) at the Cyprus Institute of Neurology & Genetics presented on "Universal and mutation-specific advanced therapy development for erythroid blood disorders". Dr. Lederer contrasted classical gene addition therapies with advanced genome-editing technologies. Classical gene addition utilizing lentiviral vectors offers a permanent cure via proviral integration but carries significant limitations. These include a restricted packaging capacity of under 8.5 kb, challenges in achieving physiological expression, and inherent risks of insertional mutagenesis or non-physiological expression.

In contrast, genome editing allows precise, DNA-level correction of genetic defects. While early editing methods relied heavily on double-strand break (DSB) repair pathways, Dr. Lederer noted

that precise correction via homology-directed repair (HDR) is highly inefficient in stem cells. Furthermore, NHEJ-based disruption, while efficient, is imprecise and carries safety risks, as DSBs can trigger genotoxicity, off-target mutations, and oncogenic translocations. This has driven the development of DSB-independent editing modalities, including base editors, prime editors, and epigenetic modifiers, which offer optimized efficiency with vastly reduced genotoxic risks.

For hemoglobinopathies (β -thalassemia and sickle cell disease), Dr. Lederer detailed therapeutic strategies aimed at breaking γ -globin repression to activate fetal hemoglobin (HbF) expression. Since γ -globin replaces defective β -globin and has anti-sickling properties, inducing HbF is highly therapeutic. This is achieved by deactivating repressors like BCL11A and ZBTB7A/LRF or disrupting their binding sites on the HBG promoter.

In Cyprus, both universal and mutation-specific strategies are being developed, with a focus on the highly prevalent *HBB*^{IVS1-110(G>A)} splicing mutation. Preclinical evaluations in patient-derived CD34+ hematopoietic stem and progenitor cells (HSPCs) compared disruption-based therapy to SpG SpG7 Adenine Base Editors (ABEs). In vivo trials in NBSGW mouse models demonstrated that SpG7 ABE mRNA achieved superior long-term repopulation and precision editing, resulting in correct HBB splicing and restoration of late-stage erythropoiesis. Additionally, the BDGT developed duplex DNA base editing targeting both the BCL11A enhancer and the HBG promoter. This dual-targeting strategy demonstrated remarkable superiority over Cas9 nucleases, inducing high levels of HbF while maintaining complete genomic integrity and avoiding off-target or chromosomal aberrations.

Karim Benabdellah – GenE-HumDi: Impact on Basic Research and Engaging the Next Generation (virtual)

Dr. Karim Benabdellah, Principal Investigator at the Department of Genomic Medicine at GENYO (Granada, Spain), delivered a talk entitled "GenE-HumDi: Impact on Basic Research and Engaging the Next Generation". Dr. Benabdellah gave a remote lecture in his capacity as the coordinator of the COST Action CA21113/21119 GenE-HumDi. He outlined the Action's multidisciplinary working group (WG) structure, which connects developers of novel editing tools (WG2) and delivery systems (WG3) with experts in genomic safety (WG4), clinical applications (WG5), and regulatory and societal impacts (WG6).

A central focus of Dr. Benabdellah's presentation was the critical contribution of the COST Action to academic research and scientific training across Europe. He emphasized that a significant portion of the Action's budget has been consistently dedicated to researcher mobility. By funding Short-Term Scientific Missions (STSMs) and Virtual Mobility Grants (VMGs)—under the coordination of Drs. Paula Rio and Fatma Zaher—the network has successfully overcome geographic barriers, enabling the seamless transfer of advanced technologies and specialized methodologies between international laboratories.

The tangible scientific impact of these mobility activities was illustrated by several collaborative STSM projects. These projects spanned cutting-edge investigations, including the in vitro

differentiation of epigenetically edited hematopoietic stem cells, optimizing Cas9-mediated precise repair in Fanconi anemia, and developing advanced computational screening platforms. Additionally, STSMs supported the application of advanced safety pipelines, such as using CAST-seq to analyze the off-target profiles of novel deep-ocean-derived Cas9 variants.

Beyond research stays, Dr. Benabdellah highlighted GenE-HumDi's regular training schools as major cornerstones for engaging the next generation of researchers. The inaugural training school in Granada in 2023 provided intensive, hands-on instruction in guide RNA design and experimental safety validation to young scientists. Subsequent training schools at Aarhus University and in Slovenia provided advanced education in in vivo delivery systems and clinical translation. This robust educational infrastructure assists in establishing scientific self-sufficiency, particularly in underrepresented Inclusiveness Target Countries (ITCs) and Near Neighbour Countries (NNCs). Fostering international, multidisciplinary collaboration at an early career stage ensures that future advanced therapy developers are thoroughly equipped with the technical skills and regulatory awareness necessary for successful clinical translation.

Claudio Mussolino – Enhancement of efficacy and safety for DSB-based precision repair

Dr. Claudio Mussolino, Group Leader in Genome and Epigenome Engineering at the University of Freiburg, presented on "Novel Tools for Precise Genome Editing and the University Model for IP Protection". Dr. Mussolino detailed innovative technologies engineered to overcome the genotoxic risks and inefficiencies associated with double-strand break (DSB) mediated genome editing. Approved gene-editing therapeutics currently rely on mutagenic NHEJ, which causes random insertions or deletions (indels). Conversely, precise editing via HDR is inefficient and carries intrinsic risks, as multiplex targeting often leads to catastrophic chromosomal translocations and genotoxic rearrangements.

To improve precision and safety, Dr. Mussolino's lab engineered HDR-CRISPR v.2.0, which incorporates a traffic light reporter to precisely measure repair outcomes, yielding a general decrease in on-target indels. To ease delivery and increase clinical viability, they developed CRISPR-PAL (HDR-CRISPR v.3.0). CRISPR-PAL utilizes Peptide Assisted Localization (PAL) to create a modular, easily deliverable system that outperforms fusion strategies. This approach achieved successful correction of the sickle cell disease mutation and significantly reduced genotoxic rearrangements, as validated by CAST-seq safety profiling.

Going beyond DNA cleavage, Dr. Mussolino showcased epigenome editing via Designer Epigenome Modifiers (DEMs). DEMs utilize TALE-based targeting domains fused to epigenetic effectors (like KRAB and DNMTs) to regulate gene expression. Epigenome editing is less invasive because it requires no DNA cleavage, thereby eliminating genotoxic risks and allowing multiplex gene targeting.

His laboratory demonstrated the therapeutic power of DEMs in primary human cells. They achieved sustained, long-term silencing of the HIV receptors CCR5 and CXCR4 in primary CD4+

T cells. Furthermore, they successfully applied DEMs for multiplex gene silencing in CAR T cells, inactivating the immune checkpoints PDCD1 and LAG3. The resulting "epiCAR T cells" maintained stable silencing, successfully resisted exhaustion, and demonstrated potent, repetitive tumor-killing capacity in long-term assays.

Finally, Dr. Mussolino discussed the intellectual property (IP) landscape, noting that Freiburg's model has secured granted patents for HDR-CRISPR in the US, and for DEMs in both the US and EU. He analyzed the institutional challenges of academic IP licensing and evaluated the strategic trade-offs of academic spin-offs versus licensing models in the highly competitive advanced therapies market.

Social Event and Discussions of EMA CAT – GenE-HumDi and community interactions

On the evening of April 20, 2026, SRLM delegates and guest speakers participated in a social event featuring a visit to the Archaeological Park of Kato Pafos and port, culminating in a dinner at the historic Hondros tavern. Set against the backdrop of ancient mosaics and the Mediterranean harbor, the informal setting of the Hondros tavern fostered a creative, productive dialogue between EMA members (in particular Ilona Reischl-Kok and Patrick Celis) and academic ATMP researchers from GenE-HumDi (specifically Carsten W Lederer and Claudio Mussolino). This regulatory-academic dinner discussion focused on bridging the translational gap through structured, early-stage collaboration.

The first discussion focused on establishing greater collaboration (a). Academic researchers highlighted that while networks like GenE-HumDi excel at basic technological development, they often hit a "translational wall" due to regulatory uncertainty. CAT members emphasized the value of the EMA's early-interaction support tools, such as the Innovation Task Force (ITF) briefing meetings and Scientific Advice. The group proposed creating a structured, informal liaison between GenE-HumDi working groups and the CAT to help academic developers integrate regulatory safety and CMC (Chemistry, Manufacturing, and Controls) requirements directly into their early preclinical designs.

The second topic addressed manuscript collaboration (b). To bridge the scientific-regulatory gap, the delegates discussed co-authoring joint consensus manuscripts and guidelines. Academic publications conventionally focus on editing efficiency and cellular potency. CAT members noted that integrating regulatory insights—such as the clinical importance of multiethnic genomic safety databases, pediatric Paediatric Investigation Plans (PIPs), and harmonized off-target profiling (such as GUIDE-seq and CAST-seq)—into these publications would significantly enhance their translational utility, also beyond the current GenE-HumDi COST Action.

Finally, they discussed future participation (c) in educational events. The roundtable proposed that CAT regulatory experts should actively participate as guest speakers in future GenE-HumDi events and post-GenE-HumDi networking events. Rather than treating regulatory approval as a

downstream hurdle, direct instruction on principles of GMP-compliant manufacturing, comparability testing, and safety profiling should be integrated into academic training. By teaching these regulatory principles to the next generation of researchers, academic laboratories can design their translational strategies with compliance built-in from day one, drastically accelerating the safe delivery of curative advanced therapies to patients.

Conclusion: Key Takeaways and Future Perspectives

The Paphos Strategic Review and Learning Meeting underscored that the transition of advanced therapies from technological breakthroughs to universally accessible medicines requires deep, early-stage integration between basic research and regulatory science. As demonstrated by the innovative base editors presented by CING and the genotoxicity-free epigenetic modifiers engineered at the University of Freiburg, academic laboratories are pioneering remarkably precise, next-generation editing technologies. However, scientific potency alone is insufficient for clinical success; it must be coupled with rigorous safety profiling, standardized off-target assessments, scalable GMP-compliant manufacturing, and proactive regulatory preparedness. Early and continuous collaborative dialogues, exemplified by the interactions between GenE-HumDi and the EMA CAT, are essential to demystifying the regulatory pathway for academic developers. Fostering these collaborative ties ensures that translational advanced therapies are designed with regulatory standards embedded from inception. This integrated approach is vital to bridging the gap between bench and bedside, ultimately accelerating the clinical translation of safe, effective, and universally affordable gene-edited medicines to meet critical unmet patient needs across Europe and globally.