Summary Report of Working Group 6 (WG6) meeting: Challenges in Technology transfer and industry/Regulatory issues

Report prepared by Rajeevkumar Raveendran Nair, Kavli Institute for Systems Neuroscience, NTNU, Norway

During the recent GenE-HumDi COST Action CA21113 2nd International Meeting in Cyprus (held in Limassol from April 8th to 10th, 2024), **Dr. Carsten W Lederer chaired the WG6 meeting on ''Challenges in Technology Transfer and Industry/Regulatory Issues''**. Participants at the meeting delved into crucial regulatory and industry challenges surrounding genome editing (GE) technologies. Carsten W Lederer provided an overview of WG6's objectives, focusing on key challenges and goals identified in an online survey of WG members and subsequent online discussions. Participants engaged in a comprehensive brainstorming session to explore regulatory and industry-related issues in GE.

Regulatory Challenges and Goals: In line with the CA21113 Technical Annex, one of the primary concerns identified was ensuring regulatory compliance in the preclinical models and methods used to evaluate the safety and efficacy of GE tools. Dr. Carsten W Lederer discussed the need to streamline regulatory guidelines to facilitate the clinical translation of GE technologies.

Technology Transfer and Industry Challenges and Goals: Dr. Carsten W Lederer highlighted challenges related to sourcing cost-effective GMP-grade GE materials and establishing guidelines for their production. There was also an emphasis on fostering intellectual property development and enhancing industry-academic collaborations in GE research. Beyond key points made in the Technical Annex and in line with the perceived needs of the GE field in the EU and with the wider aims of COST, he also pointed out the need to establish an entrepreneurial or industry mindset in early-stage researchers (ESRs) and to close the technology transfer and commercialization gap for inclusiveness target countries (ITCs).

Tasks for Regulatory Side and Technology Transfer & Industry

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On the Regulatory side, WG6 outlined several tasks to address regulatory challenges, including organizing an ATMP workshop, creating white papers with regulatory recommendations, and collaborating with other working groups such as WG3 and WG4 to determine the application-specific suitability of different models and methods. Moreover, there was a focus on developing international guidelines for GE clinical translation.

On the Technology Transfer & Industry side, WG6 identified tasks such as conducting market surveys, analyzing regulatory requirements for commercializing GE, and formulating guidelines for producing cost-effective GMP-grade GE products. Strategies for managing intellectual property rights were also pointed out as essential, with the corresponding need and motivation to involve more EU-based industry partners in the network.

Deliverables from WG6: The meeting addressed specific deliverables in future, encompassing peer-reviewed articles, regulatory guidelines, patent applications, industrial agreements, and documents for translating GE research into market-ready products.

There was a shared agreement in the meeting on the necessity for heightened industry and regulatory participation. In an EU environment, where few industrial partners exist in the GE field, this was emphasized as a critical step to breaking a vicious circle of academic achievements traditionally not readily being translated into commercial products and of business expertise in the GE field being rare. CA21113 might play a key role in amplifying and helping spread to ESRs and ITCs what little industry involvement is currently at its disposal. To this end, representatives of Platinum Supporter Maxcyte and of Miltenyi Biosciences both agreed to further involvement in future meetings to aid this goal. Overall, the meeting facilitated productive discussions and identified actionable steps to address regulatory and industry challenges in GE research. Moving forward, the group aims to achieve its deliverables and foster collaboration among stakeholders to advance GE technologies for the benefit of society.

Ahead of the Cyprus meeting, WG6 had engaged in discussions on various challenges through a web form survey. Participants offered insights into their areas of activity, with a significant majority from academic research. Conversations also revolved around delivery methodologies and platforms utilized across various research and clinical levels. Notably, the top-ranked individual challenge identified was ''Lowering product cost to allow inclusive access to patients''. Combining the survey feedback and grouping overlapping individual challenges rated as highly or extremely important, WG6 set as goal for the meeting to present and discuss the following four challenges, based on preparation of each topic by a dedicated WG member. Notably, Challenge #1 for WG6 was also independently identified under WG5 – Translation into the Clinic, and was

presented by representatives of both WGs, WG5 and WG6, to cover aspects corresponding to each respective WG:

Challenge #1 – Equity of patient access [Oliver Feeney / Alessia Cavazza]
Challenge #2 – Requirement for a separate pediatric regulatory framework [Alejandro Barquero]
Challenge #3 – Focus on safety of products and transparent reporting [Carla Fuster Garcia]
Challenge #4 – Harmonization of regulation and data [Lluis Montoliu]

After Dr. Carsten W Lederer's presentation, the selected WG members therefore took turns presenting these challenges, sparking lively discussions on the topics introduced, as summarized in the following.

Dr. Oliver Feeney (& Heidi Howard in pre-meeting discussion)
Challenge #1: Equity of patient access
(For WG6: through lowered cost and fostering regional development).

Dr. Oliver Feeney addressed the challenge of 'Equity in Patient Access to Gene Editing Therapies'.

Understanding the Complexity of Equity in Patient Access: Dr. Oliver Feeney, focused on addressing the critical challenge of ensuring equity in patient access to GE-based therapies. He pointed out that equity of patient access is not only a moral imperative but also a complex issue involving ethical and distributive considerations. Key points highlighted include differentiating between 'equity,' 'equality,' and 'all things considered,' and balancing direct costs against future costs and other healthcare priorities. Stakeholder engagement emerged as a crucial aspect in addressing this complex issue.

Strategies to Reduce Costs and Increase Access: A range of strategies aimed at reducing costs and improving access to GE-based therapies were discussed. These included innovative payment models like fixed up-front and over-time payments, along with risk-sharing agreements and equity-based tiered pricing. Participants also discussed the potential of IP/patent pooling and incentivizing innovation to drive down costs. Challenges related to limited access due to manufacturing constraints were acknowledged, with proposed solutions including standardized platform technologies, data sharing initiatives, and the adoption of non-viral delivery methods. Dr. Oliver Feeney discussed the concept of distributed manufacturing models and point-of-care approaches, as means to address manufacturing challenges and enhance patient access.

Operational Challenges: The discussion delved into operational hurdles such as regional disparities in therapy access and the imperative for sufficient healthcare infrastructure and trained personnel.

Action Plan for Ensuring Equitable Access: The discussion outlined a comprehensive action plan to address the challenge of equitable patient access. This plan includes conducting a survey to gather insights from each European country, developing a working paper or white paper to consolidate findings and recommendations, and organizing a workshop with expert speakers to further explore potential solutions. By implementing these strategies, the group aims to promote fair and uniform access to gene editing therapies across Europe.

Suggested Solutions: Ahead of results from such an action plan, study and discussion of the topic already suggested as possible solution or remedial action that GenE-HumDi explores the following strategies. Firstly, the development of standardized platform technologies with detailed Standard Operating Procedures (SOPs) and affordable licenses can accelerate regulatory approval and reduce costs for new therapies. Additionally, facilitating data sharing can mitigate risks and streamline assay processes. Exploring non-viral delivery methods and *in vivo* techniques can enhance treatment accessibility and efficacy. Finally, establishing an international collaborative network of Centers of Excellence (CoE) combined with the establishment of point-of-care manufacturing facilities would help ensure efficient distribution of Advanced Therapy Medicinal Products (ATMPs) to patients in need. These initiatives collectively aim to advance the accessibility and effectiveness of gene editing therapies.

Dr. Alejandro Barquero

Challenge #2: Requirement for a separate pediatric regulatory framework (For higher-risk, higher-benefit unborn or pediatric patients).

Dr. Alejandro Barquero underscored the importance of the Pediatric Regulation, aimed at improving the availability of medicines for children and enhancing product information. Concerns were raised about the planned suppression of the legislation. Challenges in pediatric medicine are multifaceted, including limited treatment availability for children and rare diseases, often overlooked due to their individual rarity. While the Pediatric Regulation has addressed some of those challenges and advanced the development and accessibility of medications for children, concerns persist about its ability to address critical medical needs adequately. Moreover, despite the legislation's benefits, there are concerns about its inflexibility in adapting to scientific and technological advancements, its limitations in effectively addressing unmet medical needs, and its contribution to rising healthcare cost. While these factors highlight the

need for ongoing evaluation and potential revisions in legislation to ensure comprehensive and efficient pediatric healthcare, an outright abolishment of pediatric-specific consideration in treatment and in particular with regards to the therapeutic application of GE technology may worsen quality and access of care and cures for pediatric patients.

Proposed Solutions and Points for Discussion: In response to these challenges, participants in the meeting discussed the proposed significant revision of EU pharmaceutical legislation by the European Commission, which short of repealing implementations of the Pediatric Regulation altogether substantially weaken its role in ensuring special status of pediatirc treatments. Considerations included changing relevant parts of the rules from Regulations to (politically weaker) Directives, which provide more flexibility in national implementation but lower priority and consistency of pediatric developments across the EU. Concerns were voiced regarding the potential dissolution of the Pediatric Committee (PDCO) and the dispersion of pediatric competencies across non-pediatric working groups. Dr. Alejandro Barquero discussed the necessity for sponsors to submit Pediatric Investigational Plans (PIPs) for all innovative drugs and the lack of specificity regarding pediatric therapeutic needs. Additionally, the discussion addressed the need for flexibility in accommodating new technologies, such as gene therapy medicinal products (ATMPs), in pediatric drug development.

Addressing Ethical Concerns and Emerging Challenges: The discussion also highlighted emerging challenges, such as pediatric-based fetal care and treatments *in utero*, which currently fall outside the scope of existing pediatric legislation. Ethical considerations and potential hurdles in implementing regulatory frameworks for these innovative therapies were emphasized.

Overall, the discussion stressed the importance of reevaluating current regulatory frameworks to better meet the diverse medical needs of pediatric populations. By addressing these challenges and proposing innovative solutions, WG6 aims to contribute to the ongoing dialogue surrounding pediatric drug development and regulatory policy.

Dr. Carla Fuster Garcia
Challenge #3 Focus on safety of products and transparent reporting
(For WG: concerning definitions, regulation and attitudes, and not technological advances, which fall into the remit of WG4 instead).

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Dr. Carla Fuster Garcia facilitated a dynamic discussion on product safety and transparent reporting within the GE field. The conversation underscored the importance of transparency in GE discussions, emphasizing the need to communicate potential side effects without causing undue alarm among regulatory bodies. Highlighting the biological relevance of side effects, particularly regarding mutations in safe loci, emerged as a crucial aspect. The discussion acknowledged the varied benefits and risks associated with GE, emphasizing the necessity for thorough evaluation. The significance of incorporating patient input into regulatory decisions was recognized, although the ultimate authority to issue guidelines and approvals lies with regulatory bodies like the EMA and its CAT. Emphasizing the impact on patients' quality of life emerged as a pivotal factor, with substantial benefits potentially influencing regulatory decisions. Evaluating the potential for indels to cause new diseases was identified as a critical consideration, necessitating robust assays for off-target effects. The discussion also addressed challenges posed by population variation, particularly in selecting appropriate reference genomes. Current reference genomes may not adequately represent all populations, impeding safety and efficacy aspects e.g. of guide RNA designs for compatibility with different populations or ethnic groups. Balancing transparency with regulatory considerations emerged as essential for responsible GE development.

Moving forward, engaging regulatory bodies and patient organizations will be crucial to ensuring both safety and progress in GE. The discussion highlighted the need for ongoing collaboration and dialogue to navigate the complexities of GE research and development responsibly.

Dr. Lluis Montoliu

Challenge #4 Harmonization of regulation and data

(Across major economies, for assessment methods, GE tool classification, shared databases, based on more holistic analyses).

Dr. Lluis Montoliu delved into the intricate challenges of harmonizing regulation and data within the GE field. Several key points were highlighted for discussion, including the necessity of establishing uniform regulations for both on-target and off-target effects, considering the concept of the pangenome, and addressing the potential risks associated with germline transmission. Additionally, the discussion underscored the importance of harmonizing the classification of GE tools, aligning with other major economies, and establishing shared databases.

Key Points: One of the central challenges identified was the need to define acceptable levels of risk associated with on-target and off-target genetic noise. Participants discussed whether a generic or case-by-case approach should be adopted in

determining these thresholds. Questions were raised regarding the evaluation of on- and off-target effects against different reference genomes, underscoring the importance of comprehensive genomic analysis in assessing GE tools' safety and efficacy. Another point of contention was the significance of germline transmission risks, particularly in the context of regulatory agencies' concerns. The need for new nomenclature to classify various GE tools was also highlighted as an area requiring attention and discussion.

Proposed Actions: To address these challenges, Dr. Lluis Montoliu proposed several actionable steps. These include suggesting acceptable minimum thresholds for on- and off-target effects, with careful consideration of their genomic locations to minimize potential risks. It was also suggested to conduct thorough genomic analyses of patient genomes to tailor GE approaches effectively. Furthermore, the discussion raised the question of whether dedicated registries for human GE are necessary, similar to those established by the World Health Organization (WHO) for human germline GE. It was recognized that Challenge #4 covers many aspects of GE and might benefit from separation into smaller, more readily addressable challenges. In this respect, data aspects of Challenge #3 represent one such sub-challenge within the wider need for GE harmonization, which owing to the substantial expertise among CA21113 participants in safety assessment technologies might be among those most readily tackled by the network.

In summary, Challenge # 4 underscores the importance of harmonizing regulations and data standards to ensure the safe and effective application of GE technologies. By addressing these challenges and implementing proposed actions, WG6 aims to contribute to the development of robust regulatory frameworks and data-sharing mechanisms that facilitate responsible GE research and clinical applications.

Dr. Carsten W Lederer presented the Outcomes of the WG6 meeting on challenges.

Challenging Access Disparities: Equity in Patient Access.

The discussion centered around the crucial issue of ensuring equity in patient access to gene editing therapies, with various aspects examined comprehensively. Diverse payment models were explored, including shifting from fixed upfront costs to variable payments based on outcomes, to enhance affordability and accessibility. Challenges related to GMP production and pricing bottlenecks were acknowledged, prompting considerations for cost-effective solutions. The discussion extended to the balance between centralized and distributed access to treatments, with a focus on optimizing access while maintaining expertise and quality standards. Strategies for promoting non-commercial manufacturing solutions and adopting non-viral or closed systems to reduce costs were discussed. Further, the importance of considering multiethnic representation in both the design and trials of gene editing therapies was emphasized to ensure inclusivity and effectiveness across diverse populations. To take actionable steps forward, the creation of a white paper is recommended, aimed at evaluating approaches and proposing recommendations for EU policymakers. Identifying potential authors and collaborators will be essential in this endeavor.

Requirement for a separate pediatric regulatory framework.

The discussion highlighted the distinct considerations surrounding pediatric healthcare, emphasizing that children are not merely small adults and necessitate tailored approaches in medical treatment due to susceptibility to organ damage. With the expiration of the EU Pediatric Regulation of 2007 looming, there was deliberation over the transition from regulation to directive, which would entail significant changes, including the dissolution of the Pediatric Committee and the absence of specific emphasis on pediatric needs. Concerns were raised about the potential lack of focus on pediatric healthcare, prompting an appeal for the reinstatement of a dedicated regulatory framework to address the unique requirements of pediatric patients effectively. An action plan is proposed, involving workshop coordination with regulatory bodies to discuss necessary regulatory changes, engagement with patient organizations and clinicians for comprehensive input, and the inclusion of small-drug manufacturers in crafting tailored solutions. Identifying potential authors and stakeholders will be crucial in driving these initiatives forward.

Focus on safety of products and transparent reporting.

The discussion highlighted the importance of transparency and the dissemination of information through various channels, such as publications versus press statements. This conversation also delved into the sub-aspect of harmonizing regulations to ensure

consistent reporting practices. Central to this discourse was the ongoing challenge of reconciling efficiency with safety and balancing thoroughness with the pace of progress in GE research. Participants emphasized the importance of prioritizing outcomes and results over methods and advocated for the establishment of clear thresholds based on existing data to guide regulatory decision-making processes effectively.

Harmonizing Regulation and Data: Toward Standardized Practices

Standardizing tool classifications to streamline regulatory processes, and ensuring uniformity in data collection and reporting are crucial steps in advancing GE technologies. There is a need to move towards holistic analyses that consider multiple factors for a more thorough evaluation. Achieving consensus on the data to collect and share is essential for standardized reporting practices. Systematic dissection of key aspects of harmonization is required to identify areas for improvement and establish uniform requirements for reporting across jurisdictions.