Metagenomi Presents New Data on Novel Gene Editing Systems at the 26th American Society of Gene + Cell Therapy (ASGCT) Annual Meeting

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– Company's metagenomics-derived gene editing toolbox shows activity, specificity, and translatability for broad use in genetic medicine development –

– Metagenomi's CRISPR associated transposase (CAST) systems designed for large, site-specific gene integrations reproducibly achieved programmable transposition into multiple endogenous sites in the human genome –

– First non-human primate data using MG29-1, a novel type V CRISPR system, shows POC for therapeutic gene knockdown –

Metagenomi, a genetic medicines company with a versatile portfolio of wholly owned, next-generation gene editing systems, presented new data for its gene editing programs during the 26th American Society of Gene + Cell Therapy (ASGCT) Annual Meeting. The presentations demonstrate enhanced efficiency of Metagenomi's proprietary type V and type II nucleases, first-in-class CAST systems for large, targeted DNA integration capabilities, and novel base editing systems. In addition, the Company presented proof of concept data in non-human primates, showcasing potential therapeutic translation of Metagenomi's lead novel nuclease technologies.

"As an industry, we are on the precipice of incredible advances in genomic medicine, but we need novel, efficient tools with editing capabilities beyond the current standard if we are to address the broadest spectrum of diseases," said Sarah Noonberg, Ph.D., M.D., Chief Medical Officer of Metagenomi. "The data we presented this week further validates the power of our metagenomics-based discovery approach in rapidly discovering and optimizing novel next-generation technologies that are highly targetable, specific and efficient. With a multitude of gene editing technologies, we can accelerate their translation to potentially curative therapies for a wide variety of important diseases."

The discoveries described in these presentations were enabled by Metagenomi's expertise in metagenomics and the Company's proprietary discovery platform. Metagenomi's discovery platform uses AI-enabled cloud computing to mine millions of sequences from diverse environments captured in its growing database, analyze their properties, and optimize novel systems for potential therapeutic applications.

Presentation Highlights

A Metagenomics-Derived Gene-Editing Toolbox Enables Efficient Genome Engineering with Nucleases and Base-Editors in Primary Cells and *In Vivo* (Oral, Abstract #256)

Current technologies are limited in ability to target various sites in the genome and can sometimes have off-target effects, which may affect the safety of potential therapeutics. Metagenomi is identifying and developing novel tools to overcome these limitations. Instead of focusing on a single or few isolated enzymes, Metagenomi has curated a library of type II nucleases with diverse PAM targets, and type V nucleases, which show increased specificity compared to existing type II systems, including Cas9. Company researchers have discovered entire families of editing systems and used chimeric methods to perform PAM-interacting domain (PID) swaps between family members, which rapidly and significantly increases the targeting density of the platform. In its totality, having a broad set of gene editing tools is important for targeting any location in the human genome.

Furthermore, researchers describe how Metagenomi has engineered one of its nucleases into an adenine base editor (ABE). This modified nuclease achieved up to 95% A-to-G conversion in cultured cells and ~50% conversion in mouse hepatocytes *in vivo*. In addition, there was no detectable pre-existing antibody immunity to Metagenomi's nucleases in a panel of serum samples from 48 randomly selected donors.

A Novel Type V CRISPR System with Potent Editing Activity in Mice and Non-Human Primates (Oral, Abstract #229)

Most gene editing tools are based on the spCas9 nuclease, which is a member of the type II family of CRISPR systems. Despite the observation that type V CRISPR systems exhibit higher specificity and a distinct PAM that enables access to genomic target sites not possible with Cas9, they have not been widely used for *in vivo* gene editing. In this presentation, Metagenomi researchers describe the first use of MG29-1, a novel type V system with minimal sequence identity to Cas12a/cpf1, to perform potent gene editing in primary human cells *in vitro*, as well as in mice and non-human primates (NHP) with high efficiency. This is the first report of NHP editing with a type V nuclease and demonstrates effectiveness for therapeutic gene knockdown.

The MG29-1 mRNA sequence was optimized with the addition of two potent human/NHP guide RNA spacers and the ingredients encased in a liver-targeted lipid nanoparticle (LNP) infused into NHPs, which resulted in on-target editing to as much as 55% of whole liver (estimated 75% of hepatocytes). There were no significant adverse effects or overproduction of inflammatory cytokines. Analyses for off-target effects revealed high specificity: no true off-target sites were detected.

Targeted Integration to Endogenous Sites in the Human Genome Using CRISPR-Associated Transposases Discovered from Natural Environments (Poster, Abstract #1429)

A substantial portion of genetic diseases are caused by simple loss of function, but integration of large segments of DNA into targeted sites has historically been a challenge. CRISPR associated transposases (CASTs) are a potential solution to this problem, as these systems have been shown to efficiently deliver large DNA portions into bacterial genomes.

Metagenomi's novel CAST system is capable of efficient transposition of a substantial DNA fragment (2.5 kilobases) *in vitro* into *E. coli* and mammalian cells. When delivered to mammalian cells, these CAST components are expressed in an active form and localized to the nucleus; researchers reproducibly achieved programmable transposition into multiple endogenous sites in the human genome. This provides proof of concept for potential therapeutic application – and a critical advancement for the gene editing field.

About Metagenomi
Metagenomi is a gene editing company committed to developing potentially curative therapeutics by leveraging a proprietary toolbox of next-generation gene editing systems to accurately edit DNA where current technologies cannot. Our metagenomics-powered discovery platform and analytical expertise reveal novel cellular machinery sourced from otherwise unknown organisms. We adapt and forge these naturally evolved systems into pow-

erful gene editing systems that are ultra-small, extremely efficient, highly specific and have a decreased risk of immune response. These systems fuel our pipeline of novel medicines. Our goal is to revolutionize gene editing for the benefit of patients around the world. For more information, please visit https://metagenomi.c.