UT SOUTHWESTERN
MEDICAL CENTER

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September 18, 2025

Dear Colleagues,

It is my pleasure to provide this letter of support for Iris Medicine's application to the California Institute of Regenerative Medicine (CIRM) DISC0 program. I am a founding scientist of Iris Medicine and have been working with co-founder Dr. Blewett for the past several years. I've been involved in all major scientific decisions and have been receiving regular updates. I have known Dr. Zhang for the past two years and have been in frequent in person and online contact with him since he became the Chief Scientific Officer.

In 2004, surprising results appeared in separate Nature and Science articles claiming that double-stranded RNAs could activate gene expression. Like many others at the time, we were dubious about the quality of these results. Indeed, one paper was subsequently retracted as fraud. Nevertheless, I was working with Bethany Janowski at that time, an expert at transcriptional regulation who had discovered the ligand for the nuclear hormone receptor LXR during her graduate work and a new pathway for cholesterol transcriptional regulation during her postdoctoral work. We reasoned that duplex RNAs might act similarly to transcription factors and, rather than simply dismissing the nuclear RNAi hypothesis, we decided to experimentally test the potential of promoter targeted duplex RNAs.

To our surprise, we discovered that promoter-targeted duplex RNAs could act as ribonucleoprotein transcription factors. The RNA programs sequence-specific recognition while the protein Argonaute protects the RNA and facilitates binding. Bethany found that, just like some protein transcription factors, some promoter-targeted duplex RNAs inhibited gene expression when basal expression is high while RNAs to nearby sequences activated gene expression when basal expression was low. We observed that noncoding RNA transcripts that overlap gene promoters (not chromosomal DNA) are the molecular targets for activating small RNAs. We have recently reviewed nuclear RNAi, its mechanism, and its applications. [Johnson, K.C. and Corey, D.R. (2023) RNAi in cell nuclei: Potential for a new layer of biological regulation and a new strategy for therapeutic discovery. *RNA* **29**, 415-422].

The application of nuclear RNAi to therapeutic gene activation requires three things: 1) thoughtful choice of target genes; 2) an understanding of mechanism; and 3) a rigorous, skeptical approach to science. A "wishful" thinking approach that ignores the potential for confounding off-target effects is the surest recipe for wasted taxpayer dollars. I have observed Drs. Blewett and Zhang. They are exactly the right people to lead these experiments. They understand the value of rigor and the need to build a solid experimental foundation so that patients will have the best opportunity to benefit from clinical development.

These experiments will not be easy. It is essential to understand the "RNA landscape" at a gene target. Where does transcription start? Easy to determine for a TATA-box gene, not so

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easy for a TATA-less promoter. Where does transcription end? Are there opportunities to activate gene expression by modulating different splice variants? What is known about overlapping noncoding transcripts? These are not trivial questions to answer, but these answers are essential for any serious effort. This is where Dr. Gene Yeo comes in. He is a pragmatic innovator whose techniques succeed in the real world. I can report from first-hand experience that his newly discovered chimeric eCLIP technique for probing microRNA function is transformative, allowing active miRNA:target pairs to be readily identified. Indeed, a paper outlining our expertise was published earlier this month (Hofman, C.R., Hu, J., Bryl, R, Tse, V., and Corey, D.R. (2025). Nuclear argonaute:miR complexes recognize target sequences within chromatin-associated RNA and silence gene expression. *Nucleic Acids Research* **53**). Aside from the Yeo Lab itself, we are better positioned than almost any other academic lab to help with that aspect of the Iris research plan.

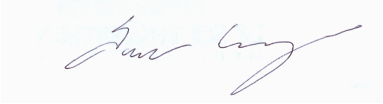
I pledge my full support for this project. I have been investigating the mechanism of nuclear RNAi and gene activation for over twenty years. We have successfully modulated the activity of several nuclear targets including progesterone receptor, LDL receptor, COX-2, PLA2G4A, frataxin, mutant C9orf72 ALS, and the mutant version of TCF4 responsible for Fuchs dystrophy. I look forward to sharing the lessons that we have learned with Drs. Yeo, Zhang, and Blewett. Our hard-earned experience will allow them to efficiently tackle the problem of activating disease relevant genes.

Indeed, we are now a bit ahead of the Iris team. Over the past two months, we have been using promoter-targeted RNAs to attempt activation of TCF4 as a potential treatment for Pitt Hopkins Disease (not to be confusing, mutations in TCF4 are responsible for two entirely different genetic diseases, it is a coincidence that both diseases intersect with my laboratory's mechanistic expertise). We are learning lessons about this difficult target and are happy to share them.

Finally, a bit about myself. I have been studying nucleic acids since my graduate work in the laboratory of Dr. Peter Schultz started in 1985. My laboratory at UT Southwestern has worked with many different types of nucleic acid chemistry and many different cellular nucleic acid targets. I have worked closely with companies like Ionis and Alnylam, work that has taught me important lessons about the value of rigorous science conducted with companies. I am Past-President of the Oligonucleotide Therapeutics Society and am currently the editor of Nucleic Acids Research responsible for (among other things) all work involving nucleic acid therapeutics. These experiences will help me be an effective resource.

In summary, I am excited by the important work proposed by the Iris team. I look forward to supporting it in every way possible. Please let me know if you have any questions or if there is any additional information that I can provide.

Sincerely,



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