Agentic AI Guided RNA Editing with CRISPR-Cas13

UCLA Emerging Scientists Program 2025

Pragyan Ramamoorthy

Senior, Dougherty Valley High School, San Ramon, CA

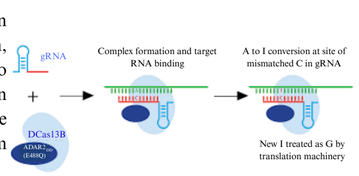
ABSTRACT

The **CRISPR-Cas13** system is a powerful tool for RNA editing, enabling correction of disease-related RNA sequences to restore functional proteins. Known for targeting single-stranded RNA like mRNA, Cas13 has opened opportunities for Nucleic Acid Therapeutics (NATs), which are drugs that use RNA to treat diseases by targeting gene expression. It shows strong potential against RNA viruses such as SARS-CoV-2, influenza, and HIV. Interest grew after the FDA approved HG202 in 2024, the first Cas13-based therapy for human trials. However, RNA editing remains complex and requires advanced skills in computation, molecular biology, and data analysis. This research explores how Agentic AI, powered by Model Context Protocol (MCP) servers, can simplify CRISPR-Cas13 experiments. These AI agents use large language models to plan experiments, design guide RNAs, minimize off-target effects, and streamline experimental workflows. MCPs allow the AI to interact with tools like Cas13design and REDIportal to provide accurate, context-aware guidance. The goal is to create a semi-autonomous Agentic AI prototype that supports RNA editing in research and commercial settings.

INTRODUCTION

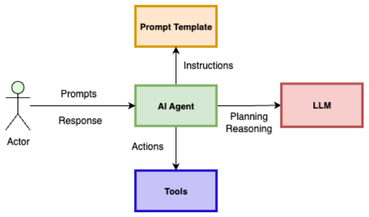
CRISPR is a gene-editing technology with different systems based on the Cas protein used. Cas9, the more well-known protien, edits DNA and forms permanent changes, requires a PAM sequence to function. Cas13 targets RNA, allowing for temporary changes in gene expression without altering the genome.

CRISPR-Cas13 system is made up of three main components: the crRNA (or guide RNA), the Cas13 protein, and the Deaminase Domain. The crRNA contains of two parts, a direct repeat and a guide sequence. The Cas13 protein acts as the core, holding the complex together. When base editing is needed, a deaminase domain is added to perform precise changes.



Together, these parts form a functional CRISPR-Cas13 complex capable of editing RNA accurately. Interest in Cas13 has grown significantly, especially after the FDA approved HG202 in November 2024, the first Cas13-based therapy cleared for human clinical trials.

Agentic AI



Agentic AI refers to systems that act independently, making decisions and taking actions to achieve goals with little human input. The agent itself coordinates and manages tasks. The large language model (LLM) is the brain that handles reasoning and planning. The prompt template tells the agent how to behave, including the steps it should take and the information it needs. Tools give the agent access to data sources and APIs.

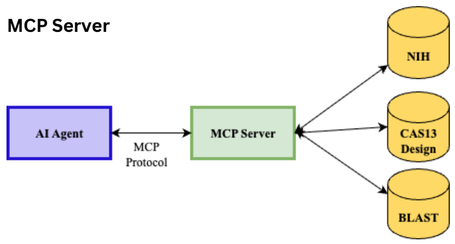
METHODOLOGY

- Research and capture end-to-end Cas13 experiment steps: this research is based on identifying various steps that are involved in CRISPR-CAS13 RNA editing. The steps are categorized in the following three phases. It is paramount for researchers to have a clear plan for these phases before setting foot in the lab.

- Identify the steps that Agentic AI can perform autonomously and identify data sources that can used in Cas13
- Develop an Agentic AI Prototype to demonstrate the hypothesis and publish code to Github for advancing the research.
- Capture results, learnings, conclusion, future considerations.

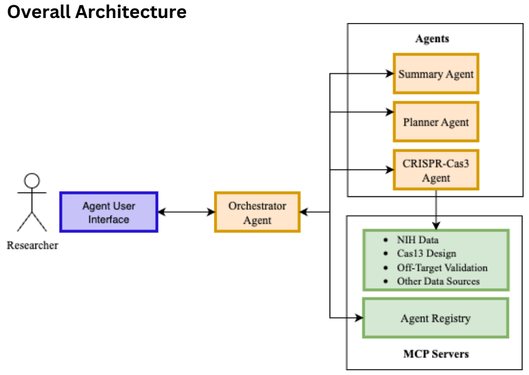
ARCHITECTURE

MCP Server



- MCP defines a standard way for applications (including AI models) to discover, access, and utilize contextual information, referred to as "tools", "resources", etc.
- Databases that are required for CAS13 experiment will have to be exposed through MCP protocol.

Overall Architecture



- Researchers will use a web interface that connects to the Orchestrator Agent (OA)
- The OA discovers tools and other agents depending on the user prompt.
- The OA works with the Planner agent to outline the plan and the autonomous tasks
- The OA calls the respective agents for each task
- CRISPR agent handles experiment-specific tools.
- The OA displays the Pre-Experiment plan

Pre-Experiment Planner Prompt Template

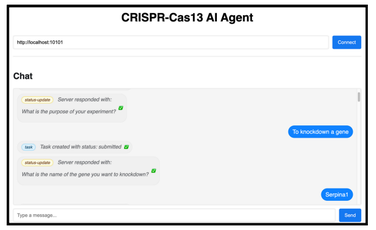
Prompt template contains predefined instructions for interacting with Large Language Models (LLMs) for planning the pre-experiment steps.

```
PLANNER_COT_INSTRUCTIONS =
'''
You are an ace CRISPR-Cas13 Pre-Experiment Planner.
You take the user input and create an experiment plan, break the experiment in to
actionable task.
You will include 3 tasks in your plan, based on the user request.
1. Gene Information Lookup.
2. Design Guide RNA.
3. Validate for Off-Target Effects.

Always use chain-of-thought reasoning before responding to track where you are
in the decision tree and determine the next appropriate question.

Your question should follow the example format below
{
   "status": "input_required",
   "question": "What is the purpose of your experiment?"
}
DECISION TREE:
1. Experiment Purpose
   -If unknown, ask for the experiment purpose
   -If known, proceed to step 2.
2. Gene Name
   - If unknown, ask for Gene Name.
   - If known, proceed to step 3.
3. Cas Variant
   - If unknown, ask for Cas Variant.
   - If known, proceed to step 4.

CHAIN-OF-THOUGHT PROCESS:
Before each response, reason through:
1. What information do I already have? [List all known information]
2. What is the next unknown information in the decision tree? [Identify gap]
3. How should I naturally ask for this information? [Formulate question]
4. What context from previous information should I include? [Add context]
5. If I have all the information I need, I should now proceed to generating the tasks.
'''
```

Prototype was built using A2A Protocol, Model Context Protocol, and Agent Development kit. For LLM, Gemini Flash 2.0 model was used. Source code for the prototype, artifacts, references, etc., can be found in the following QR code.

RESULTS

Prototype User Experience



[...]

Agent reasons and collects the necessary information for experiment planning. For example: purpose, gene name, cas protein, etc.

Upon collecting the information, the agent comes up with a list of autonomus tasks based on the instructions in the experiment planner prompt template and executes them.

CRISPR-Cas13 Pre-Experiment Plan

Autonomous Tasks Exectued

1. Lookup Gene information for Serpina1
2. Design Guide RNA for Serpina1 using Cas13b
3. Validate Guide RNA design for potential off-target effects

Gene Overview

- **Gene Name:** SERPINA1
- **Lastest Accession Number:** NM_000295.5
- **All Accession Numbers:** NM_000295.5, NM_001002235.3, NM_001002236.3, NM_001127700.2, NM_001127701.2, NM_001127702.2, NM_001127704.2, NM_001127705.2, NM_001127706.2, NM_001127707.2
- **Definition:** Homo sapiens serpin family A member 1 (SERPINA1), transcript variant 1, mRNA
- **Organism:** Homo sapiens
- **Taxonomy:** Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
- **Created Date:** 19-MAR-1999
- **Updated Date:** 29-APR-2025

Messenger RNA (mRNA)

- **Length:** 3006
- **Sequence(First 50 bases):**

```
CTCCTCAGCTTCAGGCACCACCACTGACCTGGGACAGTGAATCGACAATGCCGTCTTCTGTCT
CGTGGGGCATCCTCCTGCTGGCAGGCCTGTGCTGCCTGGTCCCTGGAGTTGGTATGATGTTCAA
GTTAGATAACAAAATGTTTATACCCATTAGAACAGAGAATAAATAGAA
CTACATTTCTTGCA
```

Guide RNA (Sample)

Guide RNA 1: crRNA807:845-867,GCCTCATAATAAGTGCCATACAG Guide RNA 2: crRNA809:847-869,TAGCCTCATAATAAGTGCCATAC Guide RNA 2: crRNA359:359-381,CTTCAATAGACACATCGGCCACA Guide RNA 3: TTTGA

Off-Target Validation

- **Status:** Pending

CRISPR-Cas13 Experiment Plan

[Pending]

CRISPR-Cas13 Post-Experiment Plan

CONCLUSION

- Agentic AI is viable to run select tasks autonomously to improve research efficiency and reduce barrier to entry.
- Access to databases is critical for agents to perform more autonomous tasks. Vast majority of the databases are proprietary and lack access through MCPs.
- Cas13 design is complex and there is not much information in the public domain about experiments conducted thus far.
- Thorough compliance and safety checks are required at every autonomous step.

FUTURE CONSIDERATIONS

- Expand Agentic AI capabilities to cover other phases of the CRISPR-Cas13 experiment planning.
- Work with government and educational institutions to democratize CRISPR-Cas13 research artifacts, educational modules, databases, etc., to enable research community.
- Work towards full automation of experiment steps through the use of robotics and other machinery.