Genome-Scale CRISPR-Mediated Control of Gene Expression

Tech ID: 24613 / UC Case 2014-097-0

INVENTION NOVELTY

This invention is a novel method of controlling gene expression at genome scale using CRISPRi/a, which provides for highly specific and robust induction or repression of transcription.

VALUE PROPOSITION

While the catalog of mammalian transcripts and their expression levels in different cell types and disease states is rapidly expanding, an understanding of their function lags far behind. Tools to define the biological roles of both canonical and non-canonical transcripts and how quantitative differences in their expression define cellular states in normal development and in disease are needed. While RNAi-based reagents have been used for the knockdown of mRNA transcripts genome wide, these frequently have off-target effects. CRISPR technology offers a high-specificity genome-scale solution with a near-complete lack of off-target effects while providing strong repression or activation of gene expression.

This method of genome-wide transcription modulation provides the following advantages:

- A **robust** CRISPRi/a screening platform, showing very high reproducibility and activity with undetectable intrinsic toxicity
- **Control** of transcript levels for endogenous genes across a high dynamic range (up to ~1000-fold) reveals how gene dose controls function
- Mapping of **complex** pathways through complementary information provided by CRISPRi and CRISPRa
- CRISPRi provides **strong** (typically 90%–99%) knockdown of both protein coding and non-protein coding transcripts with minimal off-target activity
- CRISPRi is inducible and reversible, and can allow for the study of essential gene functions
- CRISPRa is a transformative technology for genome-scale mammalian gain-of-function screens, since previous approaches were plagued by numerous technical hurdles

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OTHER INFORMATION

KEYWORDS

CRISPR, Gene screening, Gene libraries, Gene expression

CATEGORIZED AS

- **Biotechnology**
  - Genomics
  - Other
- **Research Tools**
  - Screening Assays

RELATED CASES

2014-097-0, 2014-045-0, 2014-144-0

TECHNOLOGY DESCRIPTION

Inventors at UCSF have developed a method for high-specificity, genome-wide modulation of transcription of endogenous genes in human cells using CRISPRi/a. A saturating screen for activity of non-redundant small guide RNAs (sgRNAs) which modulate cellular susceptibility to a toxin was performed. From this, distinct rules were extracted for how and where either CRISPRi or CRISPRa maximally changes the expression of endogenous genes in human cells as well as for predicting off-target effects and providing an algorithm to design CRISPRi and CRISPRa genome-scale libraries targeting each gene with 6 or 10 sgRNAs. The libraries were validated by first screening for genes essential for cell growth or survival, and then by screening for genes that govern response to a specific toxin. These processes enrich for known categories of essential genes and provide comprehensive insights into the molecular mechanisms involved in response to the toxin. In addition, it can similarly be adapted to probe the mechanisms of resistance to cancer drugs and allow the identification of genes that regulate growth in normal and cancerous cells.

APPLICATION

- Systematically probe the biological roles of all genes within the genome in a single experiment

- Reveal mechanisms by which cancer cells develop resistance to anti-cancer drugs

- Reveal synthetic lethalities in cancer cells that guide strategies for combination therapies

- Identify cellular targets of new lead compounds and drugs

- Identify tumor suppressor genes that inhibit the growth of cancer cells

- Identify genes that regulate tissue development

- Gain new insight into host-pathogen interactions to reveal potential therapeutic targets

- Develop CRISPRi/a reagents with high-level specificity

LOOKING FOR PARTNERS

We are currently seeking partners to develop and commercialize this technology as a research tool for defining transcript function across the breadth of transcripts encoded by the human genome.

STAGE OF DEVELOPMENT

Preclinical

RELATED MATERIALS

▶ Gilbert LA et al. (2014) Genome-scale CRISPR-mediated control of gene repression and activation. Cell 159(3): 647-661

PATENT STATUS

Country	Type	Number	Dated	Case
Austria	Issued Patent	3169776	09/03/2025	2014-097
Belgium	Issued Patent	3169776	09/03/2025	2014-097

Bulgaria	Issued Patent	3169776	09/03/2025	2014-097
Germany	Issued Patent	3169776	09/03/2025	2014-097
Denmark	Issued Patent	3169776	09/03/2025	2014-097
Estonia	Issued Patent	3169776	09/03/2025	2014-097
European Patent Office	Issued Patent	3169776	09/03/2025	2014-097
Spain	Issued Patent	3169776	09/03/2025	2014-097
Finland	Issued Patent	3169776	09/03/2025	2014-097
France	Issued Patent	3169776	09/03/2025	2014-097
United Kingdom	Issued Patent	3169776	09/03/2025	2014-097
Italy	Issued Patent	3169776	09/03/2025	2014-097
Lithuania	Issued Patent	3169776	09/03/2025	2014-097
Luxembourg	Issued Patent	3169776	09/03/2025	2014-097
Latvia	Issued Patent	3169776	09/03/2025	2014-097
Malta	Issued Patent	3169776	09/03/2025	2014-097
Netherlands (Holland)	Issued Patent	3169776	09/03/2025	2014-097
Portugal	Issued Patent	3169776	09/03/2025	2014-097
Romania	Issued Patent	3169776	09/03/2025	2014-097
Sweden	Issued Patent	3169776	09/03/2025	2014-097
Slovenia	Issued Patent	3169776	09/03/2025	2014-097
Unitary Patent	Issued Patent	3169776	09/03/2025	2014-097
United States Of America	Issued Patent	11,254,933	02/22/2022	2014-097
Canada	Published Application			2014-097

Additional Patent Pending

DATA AVAILABILITY

Under NDA/CDA

ADDRESS

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