modulate transcription of a target gene in a cell, specifically to modulate expression of genes without genetic modification.

SUMMARY

Methods and compositions of regulating expression of a target gene in a cell are provided. Aspects of the methods include contacting the cell with a compound having a first moiety covalently linked to a second moiety, wherein: (i) the first moiety exhibits specific binding to a first endogenous protein that binds to the target gene (or a region near the target gene, such as a promoter or a regulatory region) (ii) the second moiety exhibits specific binding to a second endogenous protein distinct from the first endogenous protein; and (iii) upon contacting the cell, the first endogenous protein and the second endogenous protein are spatially complexed to each other via the compound to yield a gain-of-function in the cell. In some embodiments, the gain-of-function is characterized by modulating expression of the target gene in a manner dependent on the presence of the second endogenous protein bound to the compound. Embodiments of the methods provide one or more beneficial features, including but not limited to: achieving the gain-of-function by utilizing less than about 50% of an amount of the first and/or second endogenous proteins present in the cell; mediation of the gain-of-function with an EC50 of less than about 1 micromolar; modulation of expression of the target gene in less than or equal to about 16 hours.

In a first aspect, the present invention provides a use of a chemical inducer of proximity (CIP) which couples B-cell lymphoma 6 (BCL-6) and either (a) a bromodomain and extra-terminal domain (BET) family protein or (b) a cyclin-dependent kinase (CDK), for the manufacture of a medicament for modulating a target gene in a cell.

In a second aspect, the present invention provides a chemical inducer of proximity (CIP) having the structure of:

A-B (Formula I); or

A-linker-B (Formula II),

wherein A comprises a first moiety exhibiting selective binding to B-cell lymphoma 6 (BCL-6), and

wherein B comprises a second moiety exhibiting selective binding to either:

(a) a bromodomain and extra-terminal domain (BET) family protein; or

(b) a cyclin-dependent kinase (CDK).

In a third aspect, the present invention provides a chemical inducer of proximity (CIP) which couples B-cell lymphoma 6 (BCL-6) and either (a) a bromodomain and extra-terminal domain (BET) family protein or (b) a cyclin-dependent kinase (CDK), for use as a medicament.

Accordingly, provided herein in one aspect is a compound of formula I:

BR – L – BC (I)

wherein:

BR is a ligand that specifically binds to bromodomain-containing protein 4 (BRD4);

BC is a ligand that specifically binds to B-cell lymphoma 6 (BCL-6) (or a homologue thereof); and

L is a linker,

or a pharmaceutically acceptable salt thereof.

In another aspect, provided herein is a method of treating a subject for a malignancy, the method comprising: administering to the subject an effective amount of a transcriptional chemical inducer of proximity (TCIP) which links BCL-6 and BRD4 to treat the subject for the malignancy.

In another aspect, provided herein is a pharmaceutical composition comprising: transcriptional chemical inducer of proximity (TCIP) for treating malignancy, the TCIP comprising a first ligand that specifically binds to BCL-6 and a second ligand that specifically binds to BRD4; and delivery vehicle.

In yet another aspect, provided herein is a method of treating a subject for Diffuse