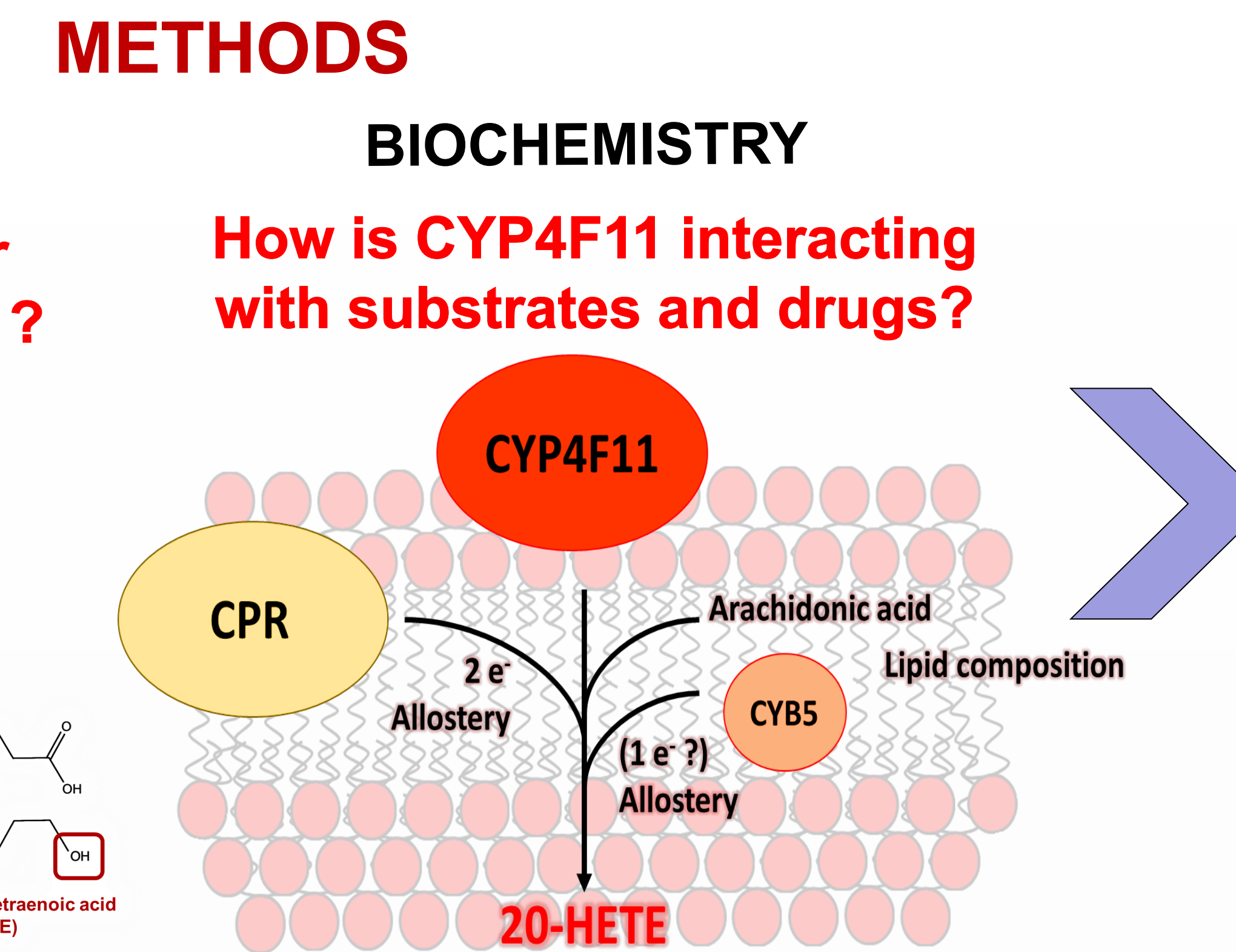
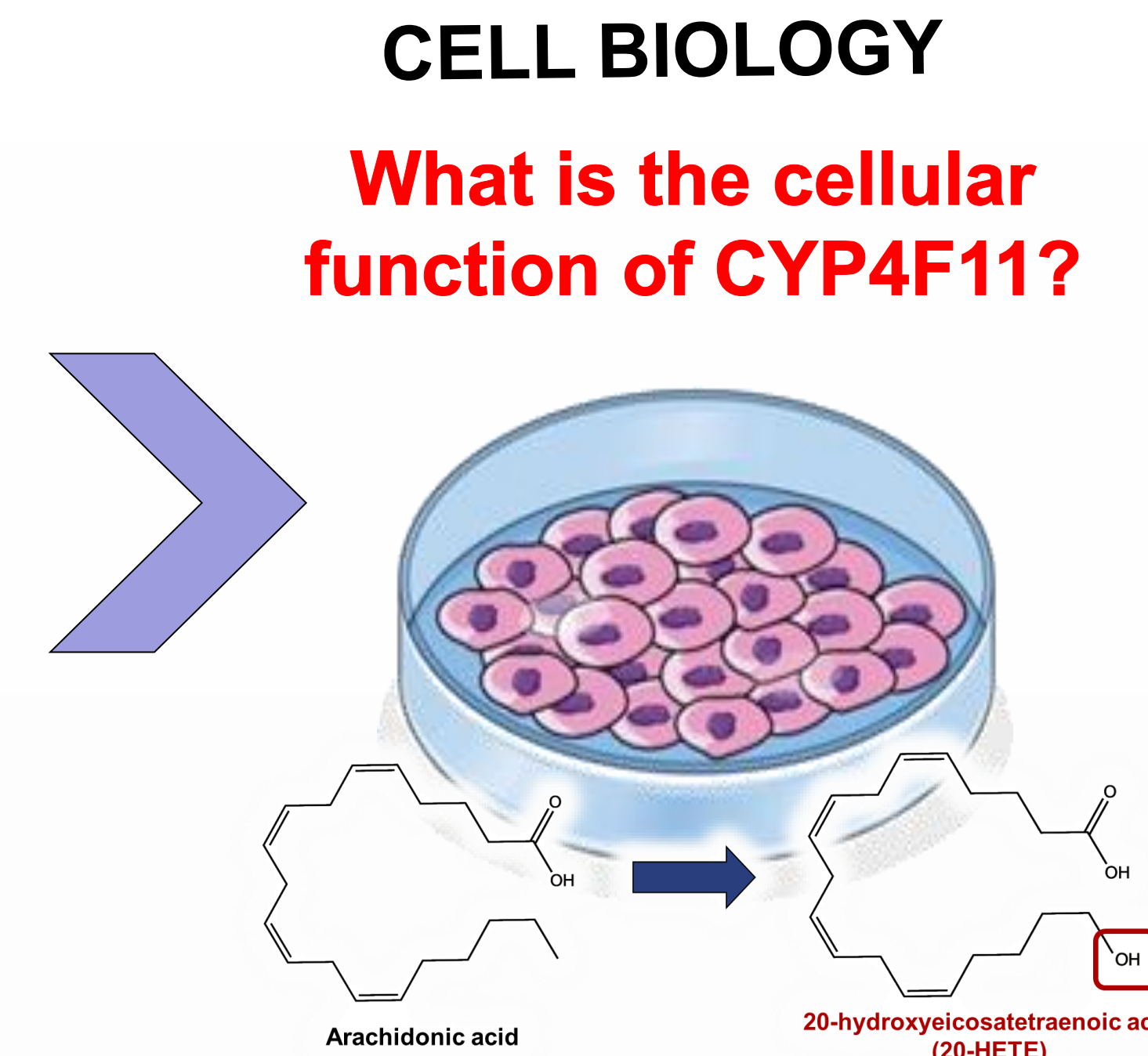


HYPOTHESIS

Could CYP4F11 be a new drug target for the treatment of lung cancer?

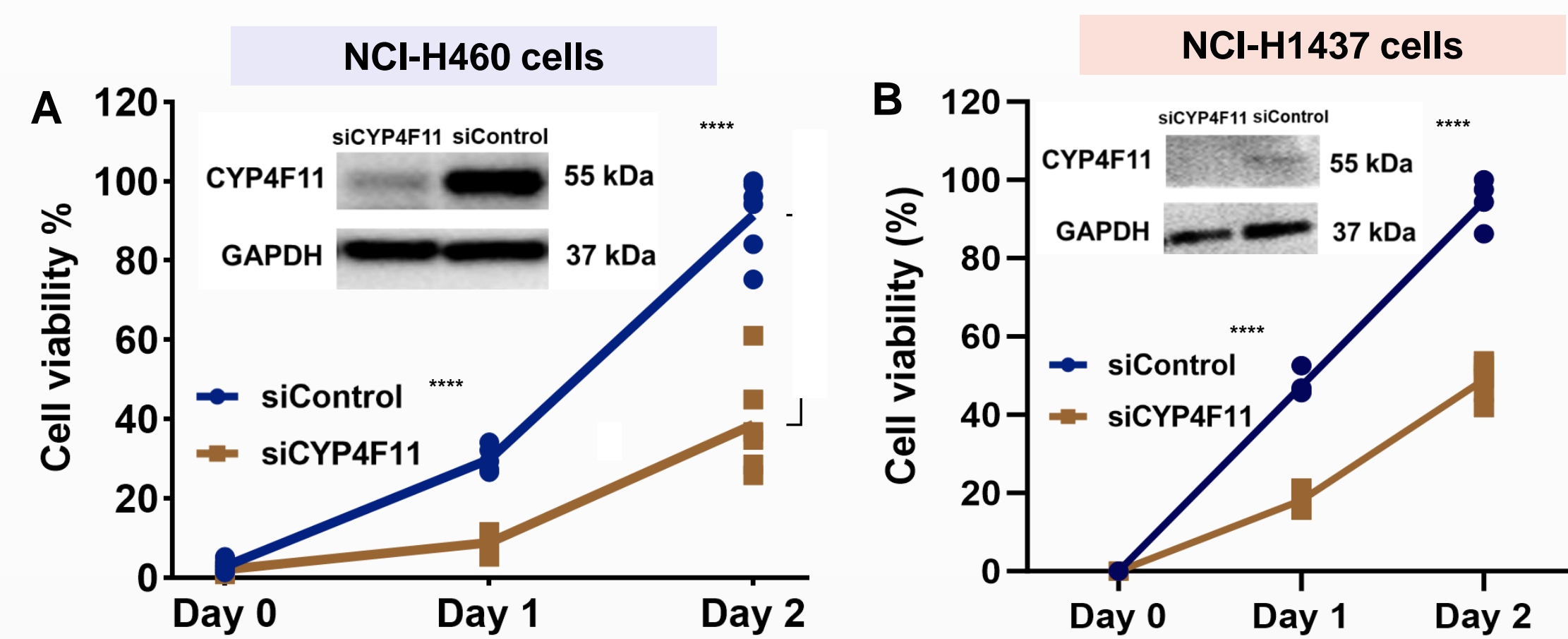


Understanding CYP4F11 function and interaction with drugs will accelerate its use as lung cancer drug target

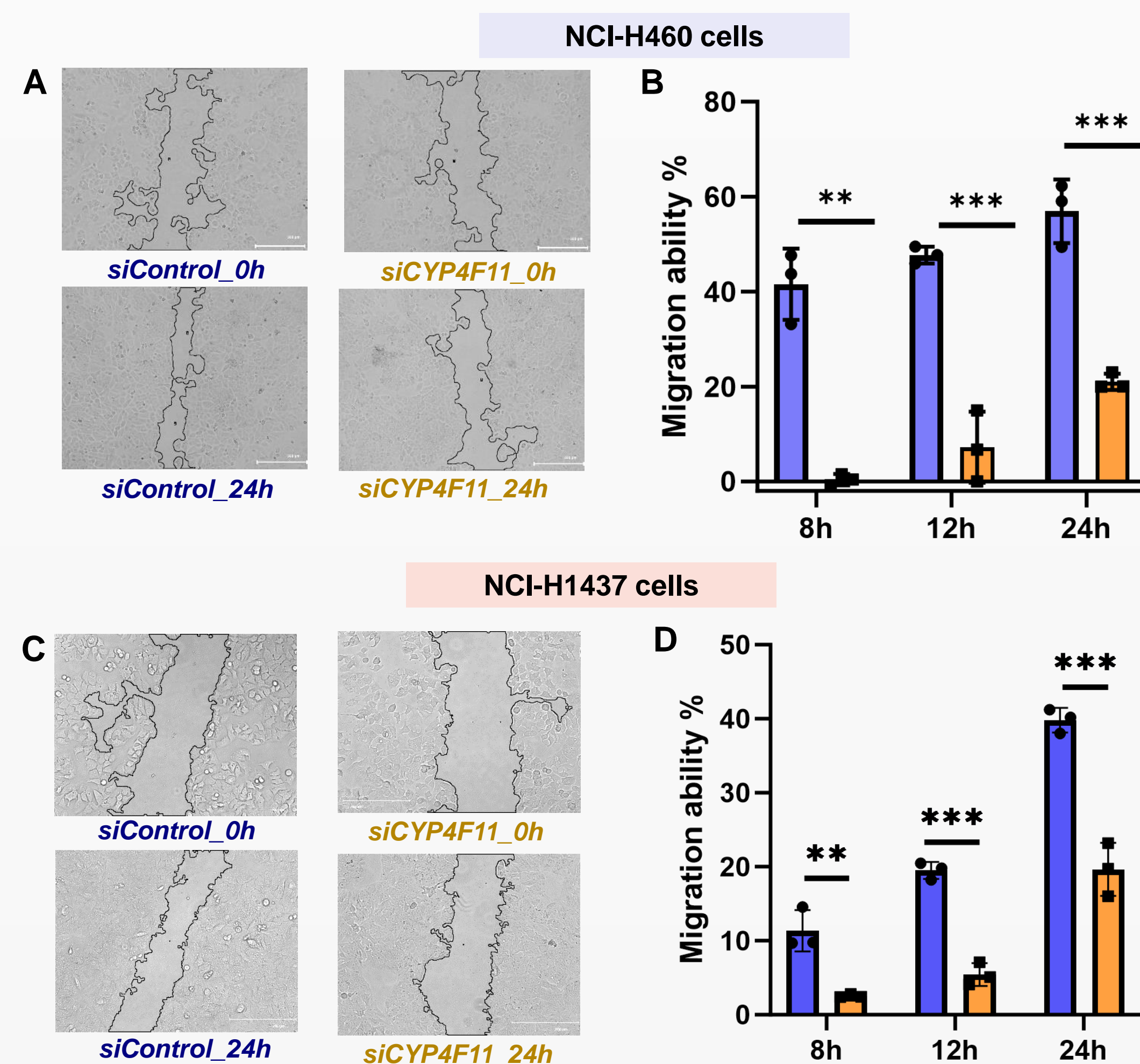
- Lung cancer is the leading cause of cancer-related death in the world.
- Cytochrome P450 4F11 (CYP4F11) which produces 20-HETE is highly expressed in patients with lung squamous cell carcinoma (TCGA analysis).
- 20-HETE is a known to promote cancer cell proliferation & migration.

RESULTS

1. Impact of a CYP4F11 Knockdown on Proliferation and Migration in Lung Cancer Cells.

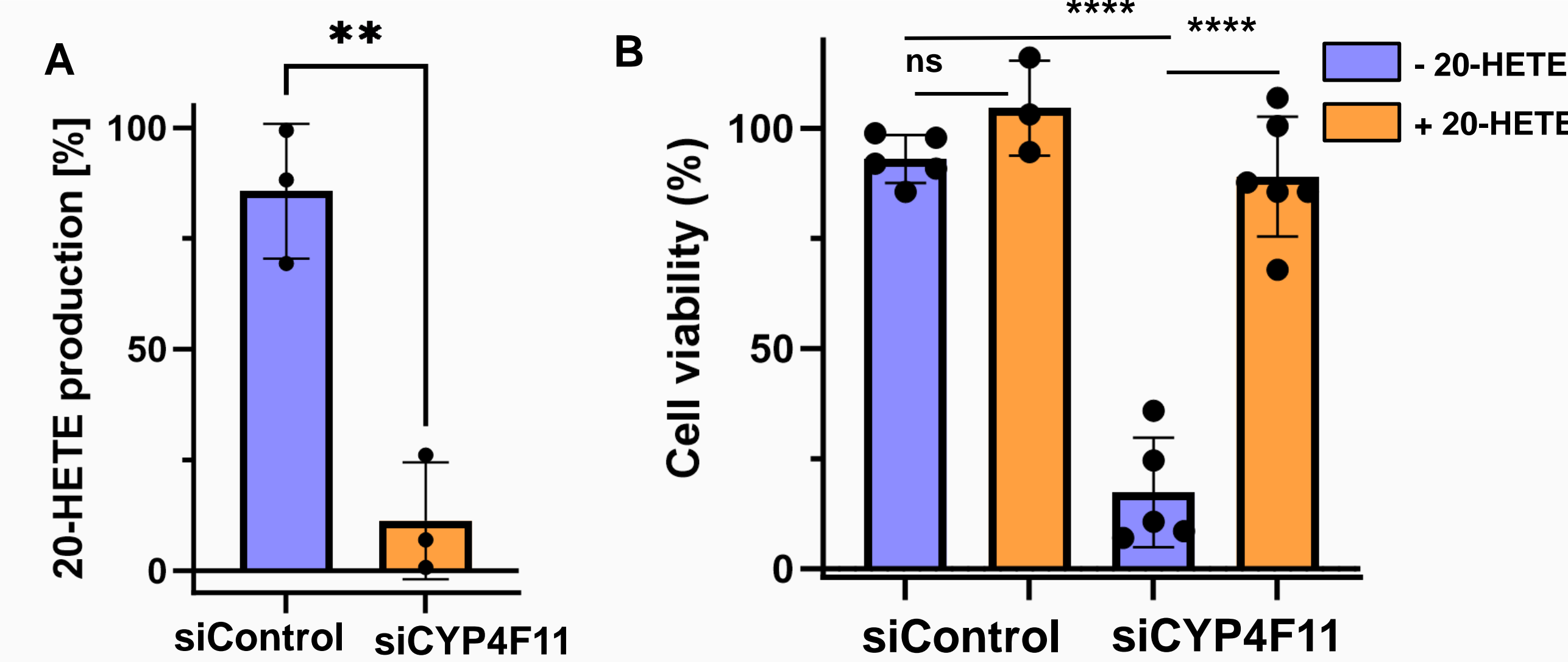


Transient knockdown of CYP4F11 attenuates the cell viability of the lung cancer cell lines NCI-H460 (A) and NCI-H1437 (B).



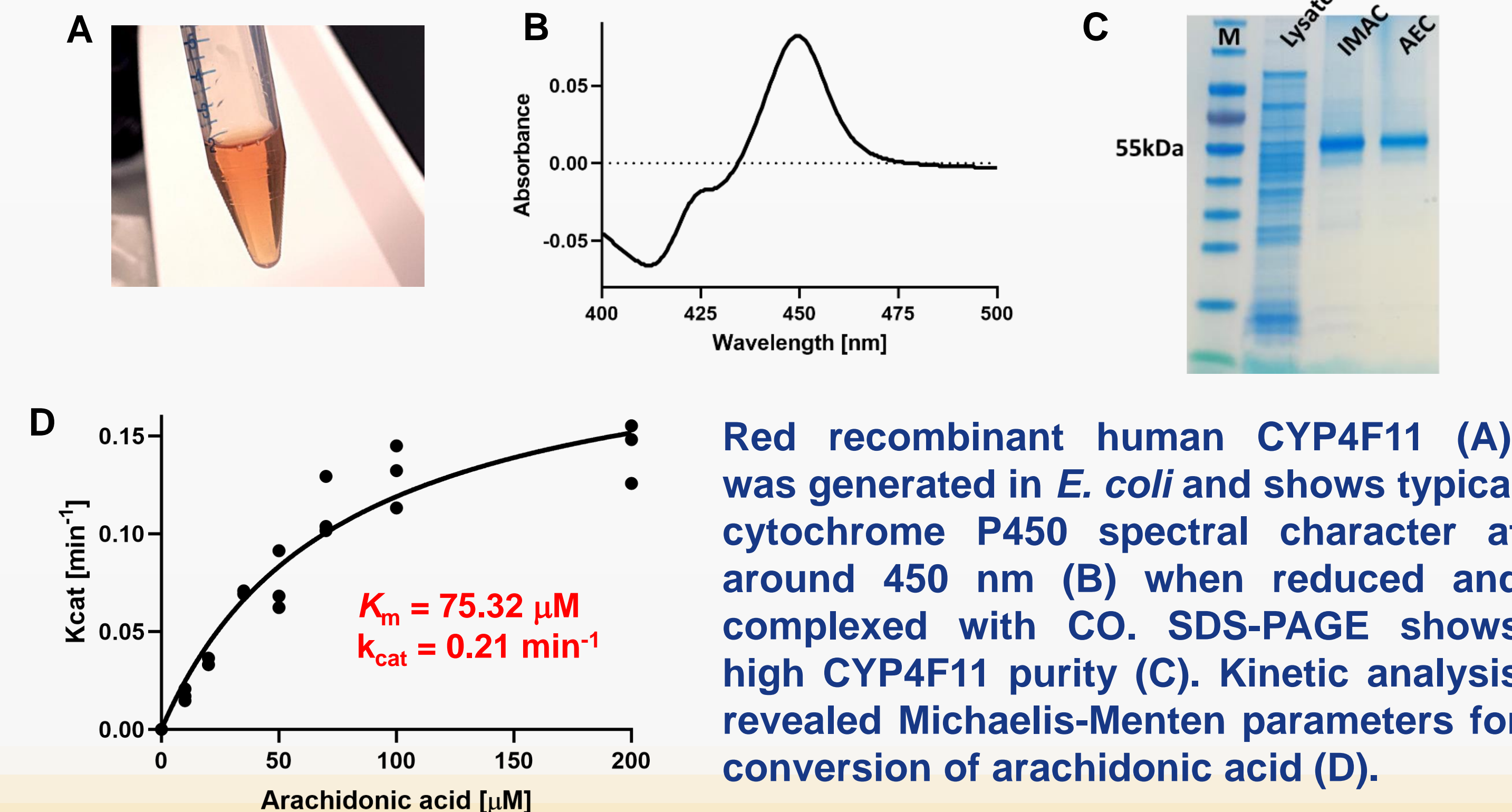
Transient knockdown of CYP4F11 attenuates the cell migration of the lung cancer cell lines NCI-H460 (A, B) and NCI-H1437 (C, D).

2. Addition of exogenous 20-HETE rescues cell proliferation of siCYP4F11 cells



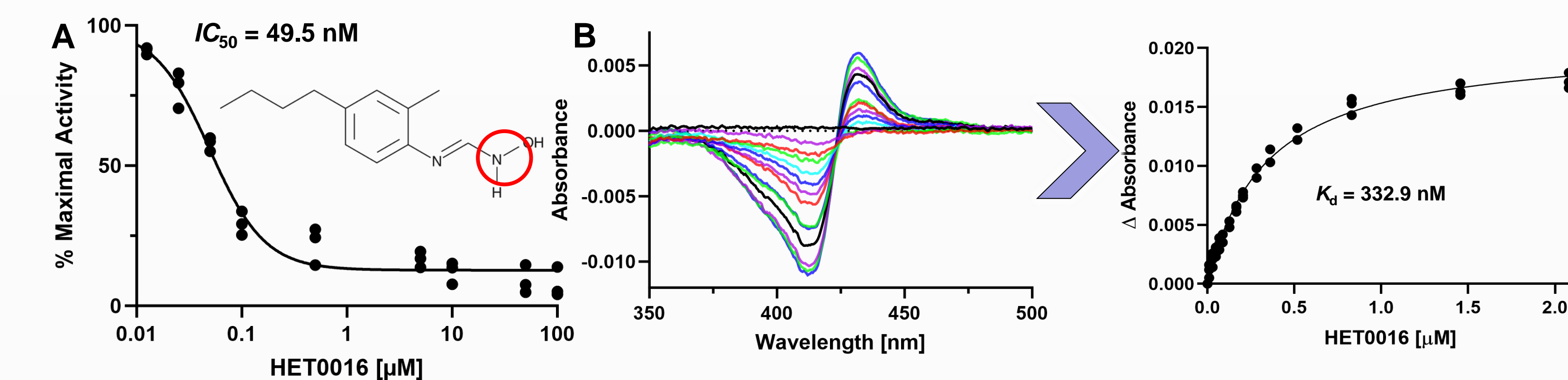
Generation of 20-HETE is significantly reduced in NCI-H460 siCYP4F11 cells compared to control cells (A). Addition of exogenous 20-HETE to siCYP4F11 rescues the cell proliferation up to the control cell level with no effect on control cells (B).

3. Functional studies with human recombinant CYP4F11



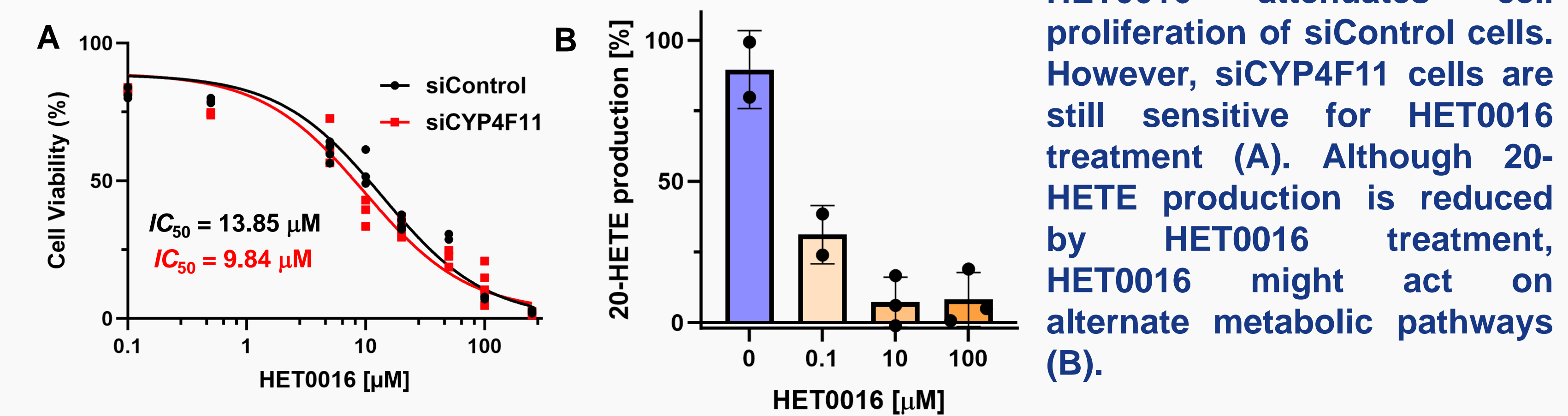
Red recombinant human CYP4F11 (A) was generated in *E. coli* and shows typical cytochrome P450 spectral character at around 450 nm (B) when reduced and complexed with CO. SDS-PAGE shows high CYP4F11 purity (C). Kinetic analysis revealed Michaelis-Menten parameters for conversion of arachidonic acid (D).

4. CYP4F11 binding and inhibition by HET0016



HET0016 is a pan-inhibitor of 20-HETE producing CY4 isoforms. HET0016 binds tightly to recombinant CYP4F11 (B) and very efficiently inhibits CYP4F11-mediated 20-HETE production (A).

5. HET0016 attenuates cell proliferation and 20-HETE production



HET0016 attenuates cell proliferation of siControl cells. However, siCYP4F11 cells are still sensitive for HET0016 treatment (A). Although 20-HETE production is reduced by HET0016 treatment, HET0016 might act on alternate metabolic pathways (B).

CONCLUSIONS

- CYP4F11 plays a pivotal role in lung cancer cells proliferation and migration associated with 20-HETE production and might be a new exciting target for cancer therapeutics.
- Although exhibiting off-target effects, HET0016 is a potential drug scaffold targeting CYP4F11 in lung cancer.

ACKNOWLEDGMENTS

UPMC HILLMAN CANCER CENTER

