Please read important disclosures beginning on page 3

ABX464 aggregates in solution above 0.16 µM (intrinsic solubility) and an autofluorescent shift marks its aggregate to crystal transition at 5 µM.

The claimed ABX464 (obefazimod) binding site on CBC is unsupported by its only cited proof, a UV Cross-Linking study an artifact of aggregation. Aggregation and crystallization artifacts may invalidate a number of Abivax's pivotal mechanistic claims.

Fluorescence Ratiometry and Dynamic Light Scattering

ABX464 (obefazimod), 8-chloro-N-[4-(trifluoromethoxy)phenyl]quinolin-2-amine

Abstract

Rationale

UV crosslinking studies are only valid for compounds assayed below their solubility limits and are usually used to identify a new potential binding site that is then characterized pharmacologically. The UV cross-linking study, reported in Campos 2015, is the sole evidence supporting a modulatory binding site on CBC. Vautrin 2019, “We have demonstrated that ABX464, by binding the CBC, ... induces the production of miR-124 from lncRNA-0599-205.” Vermeire 2023, “Binding of obefazimod at the interface between Cbp20 and Cbp80 of CBC stabilises the interaction between these two components and allows better interaction with microRNA biogenesis machinery [data in file].” Our searches turned up no traditional binding kinetics, saturability, reversibility or other traditional binding studies for the putative CBC binding site.

No positive or negative controls, as far as we could discern, were run in the UV cross-linking studies (no drug-free controls to assess spontaneous dimer association; no unrelated protein controls to assess a nonspecific aggregation effect; and no quantitation of drug in the protein bands). The assays were conducted at concentrations (0.1 to 50 µM) mostly above the drug’s aqueous solubility (0.16 µM) in a buffer where the only additions were the CBC subunits (CBC20 and CBC80). We reasoned that the drug would form aggregates and adsorb to almost any proteins in solution, under those conditions.

Methods

We reproduced the UV cross-linking study conditions reported by Campos 2015 figure 2d and measured drug aggregation in the cited UV crosslinking buffer by two methods: dynamic light scattering (DLS) to quantitate aggregates and fluorescence ratiometry to measure any shift in molecular ordering of the drug as concentrations increased.

1. Ratiometry: Emission spectra (excitation 350 nm, emission 400 to 650 nm) were acquired on a Shimadzu RF-6000 spectrofluorometer across 1 to 100 µM under three conditions: drug only; drug with bovine serum albumin (BSA, 1 mg/mL); and drug, BSA, and Triton (a control for reversibility).

2. DLS: DLS was conducted using the default settings on a Zetasizer instrument (dynamic light scattering, 90-degree detection, 25 °C). Each measurement returned the Z-average diameter,

polydispersity index (PdI), and derived count rate. Assay conditions were as described for ratiometry, above.

Results

The multiple high molecular weight smears observed on the published UV crosslinking gel are known aggregation artifacts (Campos 2015, figure 2d). We measured the aggregation of ABX464 under the same conditions in the absence of CBC subunits, to identify the concentrations where drug aggregation occurred. We found the drug had fully aggregated into particles and sunk to the bottom of the well at all concentrations tested (from 1 to 50 μM).

We determined that ABX464 is a charge-transfer fluorophore with intrinsic fluorescence from 400 to 650 nm, reported here for what we believe to be the first time. Autofluorescence is a property that is predicted to make ABX464 a candidate for phototoxicity, a toxicity Abivax has only reported for the metabolite, as far as we can locate. Autofluorescence also allowed us to follow the fluorescent character of the drug as a function of concentration.

We observed a concentration-dependent autofluorescent shift at (~5 μM), indicating a change in the drug's molecular ordering (aggregation or crystallization). As ABX464 increased from 1 to 5 μM, its emission shifted toward shorter wavelengths (a blue shift), sharply raising the 430/480 nm ratio. Pairing these results with the DLS studies that showed the drug fully aggregated at all concentrations tested (1 to 50 μM), we interpreted this as a transition from drug aggregate to the crystalline form of the drug. Abivax's formulation patent disclosed the crystal form (US 2024/0182422 A1). We showed that detergent (Triton X-100) progressively reversed the fluorescence shift, confirming that these observations were not the result of a solvatochromic artifact.

Conclusions

The 5 μM crystallization shift occurs at the same concentration (5 μM) used in nearly all of the published in vitro studies (Apolit 2023; Chebli 2017), so aggregation and crystallization artifacts may invalidate a number of Abivax's pivotal mechanistic claims; here we directly refute the CBC binding interaction as unsupported by the UV-crosslinking studies. Our findings indicate that the UV cross-linking of ABX464 to the cap-binding complex reported by Campos 2015, the sole support for the drug's proposed modulatory binding site, is due to a colloidal aggregation artifact. We have been unable to locate any other evidence that supports this claim.

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The principal individual responsible for the research, analysis, and preparation of this report is Gurkirat Kahlon, Founder and Chief Investment Officer of Scorpion Capital LLC.