# 482 HS206, TAK1 Selective Inhibitor

## Asset Overview

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|---|---|
| **Product Type** | Small Molecule |
| **Indication** | Oncology, Immunology |
| **Current Stage** | Lead identification / optimization |
| **Target(MoA)** | Transforming growth factor b-activated kinase 1 (TAK1) inhibitor |
| **Brief Description** | • A previously unreported TAK1 inhibitor that blocks TNFa dependent signaling<br>• High selectivity against TAK1 over all other known kinases expressed in the human genome<br>• In vitro data demonstrating the inhibitory potency against TAK1, as well as its ability to be well tolerated in mice in studies of MTD<br>• In cell-based assays, potent inhibition of cell proliferation of certain tumor lines including TNBC cells |
| **Organization** | Duke University |

## Differentiation

□ **TAK1 as a therapeutic target**

- TAK1 plays a key role in the signaling pathways of inflammation and cell survival
- TAK1 is activated by a number of proinflammatory signals (e.g., TNFa), resulting in the induction of key inflammatory and pro-survival genes
- TAK1 inhibition induces death of cancer cells and thus, TAK1 has emerged as a potential therapeutic target for cancer and inflammatory diseases
- Despite the increasing interest in TAK1 as a potential therapeutic target, academia and industry alike have failed to develop selective small molecule inhibitor targeting TAK1
- Previously identified inhibitors of TAK1 have not been advanced clinically, largely due to selectivity issues *in vivo*.

□ **Advantages**

- Inhibitors work by blocking TNFa signaling without impacting other cellular functions
- Highly selective for TNFa signaling and therefore could compete frontline anti-TNFa therapies on many levels, such as reducing cost and adverse side effects
- Small drug-like molecules that can be formulated for oral bioavailability

□ **TAK1 inhibitor pipelines**

- OM-101 (Kaplan Medical Center): Preclinical for proliferative itreoretinopathy (PVR)
- (Aclaris Therapeutics): Discovery for Neonatal Onset Multisystem Inflammatory Disease (genetic disorder) and pancreatic cancer
- (Astellas): Inactive (ovarian cancer)

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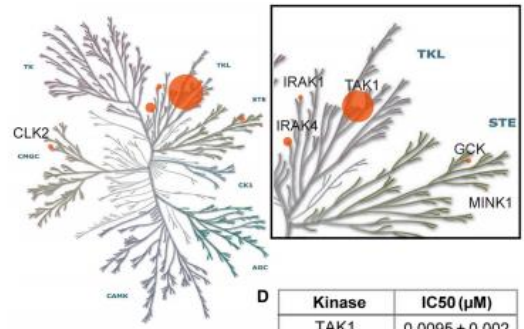
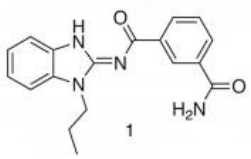
## Key Data

### Kinase selectivity of Takinib

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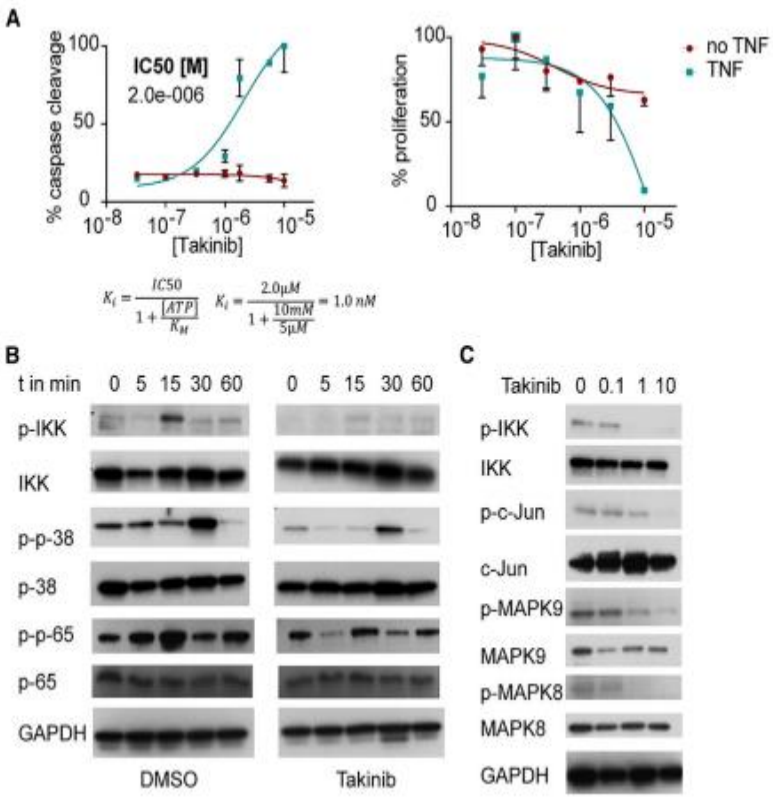
| Kinase | IC50 (μM) |
|---|---|
| TAK1 | 0.0095 ± 0.002 |
| IRAK4 | 0.12 ± 0.03 |
| IRAK1 | 0.39 ± 0.05 |
| GCK | 0.43 ± 0.04 |
| CLK2 | 0.43 ± 0.04 |
| MINK1 | 1.9± 1 |

### Effects on MBA-MB-231




(A) Cells were treated with titrations of Takinib in the presence or absence of TNF for 24 hr. Left: caspase-3/-7 activity was determined. Right: proliferation assay with Hoechst reagent was used to measure DNA content. (B) Time-course analysis of TNF signaling downstream of TAK1. Cells were treated with 10 uM Takinib and stimulated with TNF for the indicated time. Phosphorylated and total IKK, p-38, and p-65 were detected via western blot analysis. GAPDH was measured as a loading control. (C) Dose-dependent effects of TAK1 downstream signaling in TNF-activated cells.

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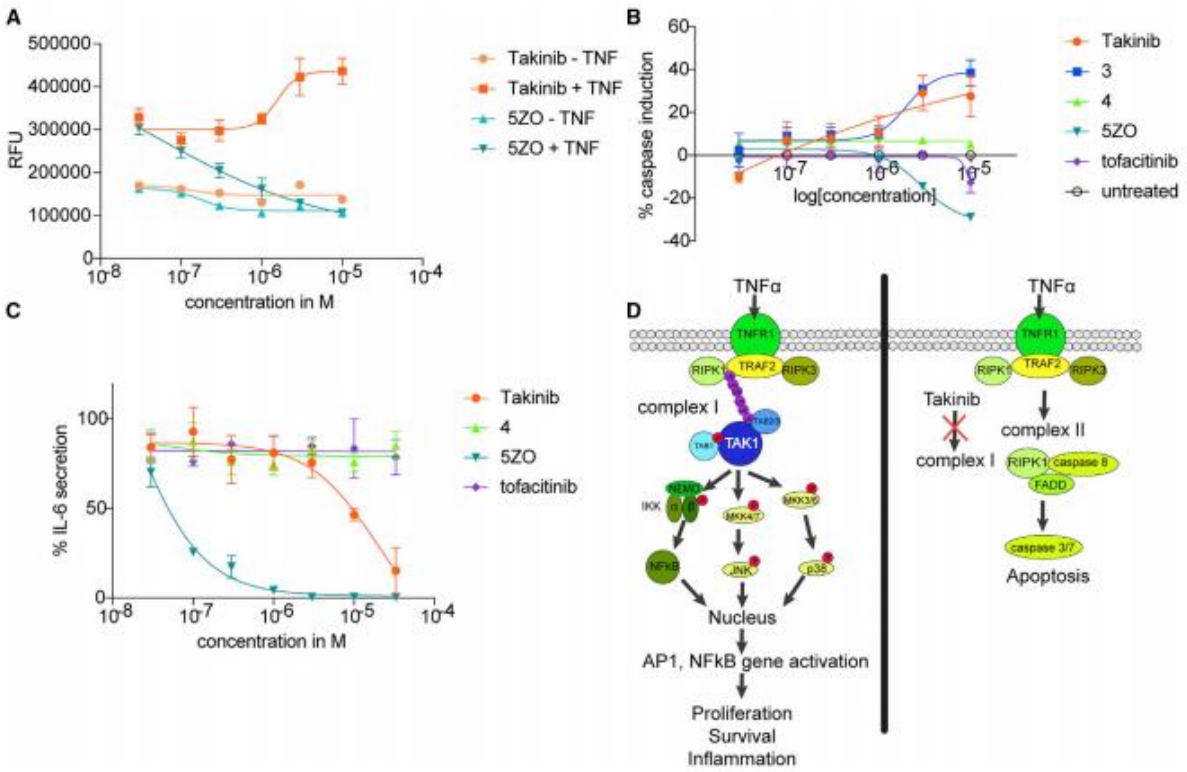
## Takinib induces apoptosis in RA FLS and reduces IL-6 secretion




(A) RA fibroblast-like synoviocytes (FLS) cells in the presence and absence of TNF were treated with titrations of Takinib and (5Z)- 7-oxozeaenol (5ZO, TAK1 biology research tool, MTKi) for 48 hr. Caspase-3/-7 activity was measured using the fluorogenic substrate (DEVD)2-R110. Data are expressed as relative fluorescence units (RFU) and normalized to yield % caspase induction. (B) Caspase induction after treatment with Takinib, 219, 220, 5ZO, or tofacitinib for 48 hr in the presence of TNF. (C) RA FLS were treated with indicated compounds and IL-6 secretion was measured using human IL-6 ELISA. (D) Proposed mechanism of Takinib induction of apoptosis through inhibition of complex 1 signaling.

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## Intellectual Property

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| **Patent No.** | US 10207998 B2 |
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| **Country** | US |

## Contact Information

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