Selective Inhibitors of Genotoxic Stress Induced NFκB Pathway for Cancer Therapy

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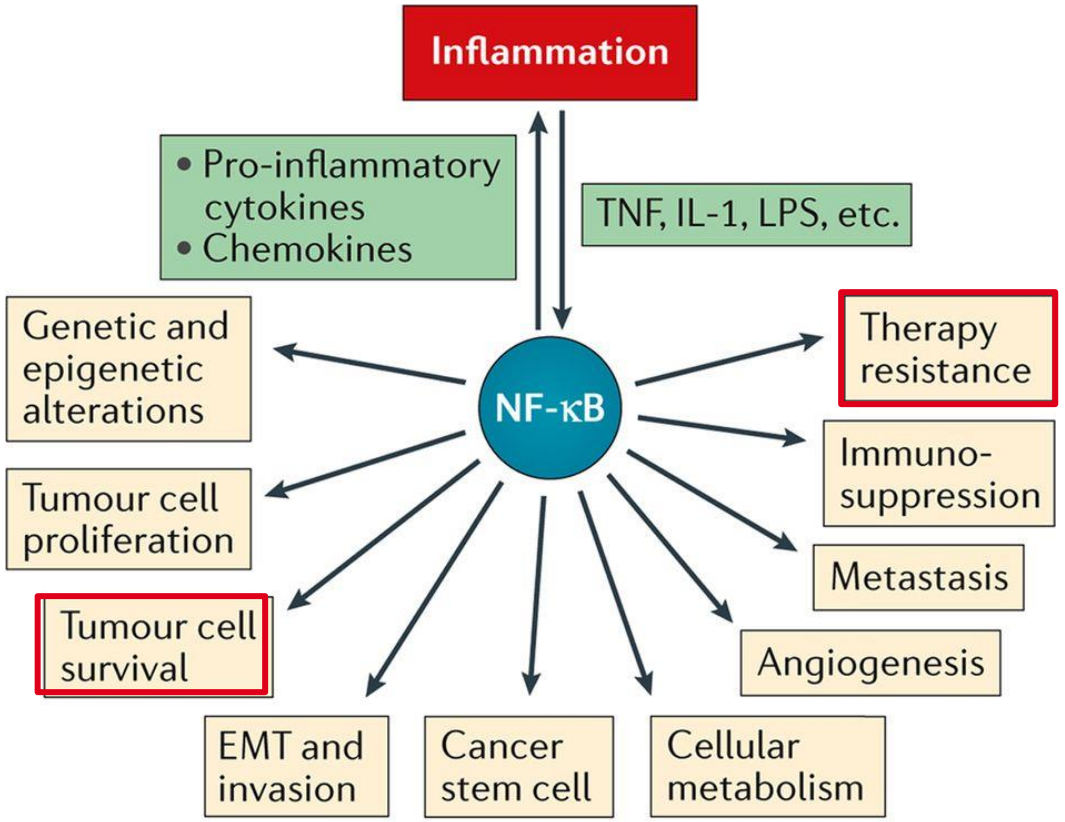
SPECIFIC NFκB TARGETING COULD OVERCOME CHEMOTHERAPEUTIC RESISTANCE -
A MAJOR BOTTLE NECK IN CANCER TREATMENT

- **Chemotherapeutic resistance** is a major hurdle in cancer treatment
- **High medical need:** 90% of failures in chemotherapy are due to metastasis of cancers related to chemotherapeutic resistance
- **Possible target**: The **NFκB pathway is a major regulator** that is activated upon DNA damage leading to tumor cell survival and thus therapeutic resistance
- So far, most **attempts to develop clinical NFκB pathway inhibitors failed due to widespread toxicity** caused by inhibiting NFκB´s versatile functions

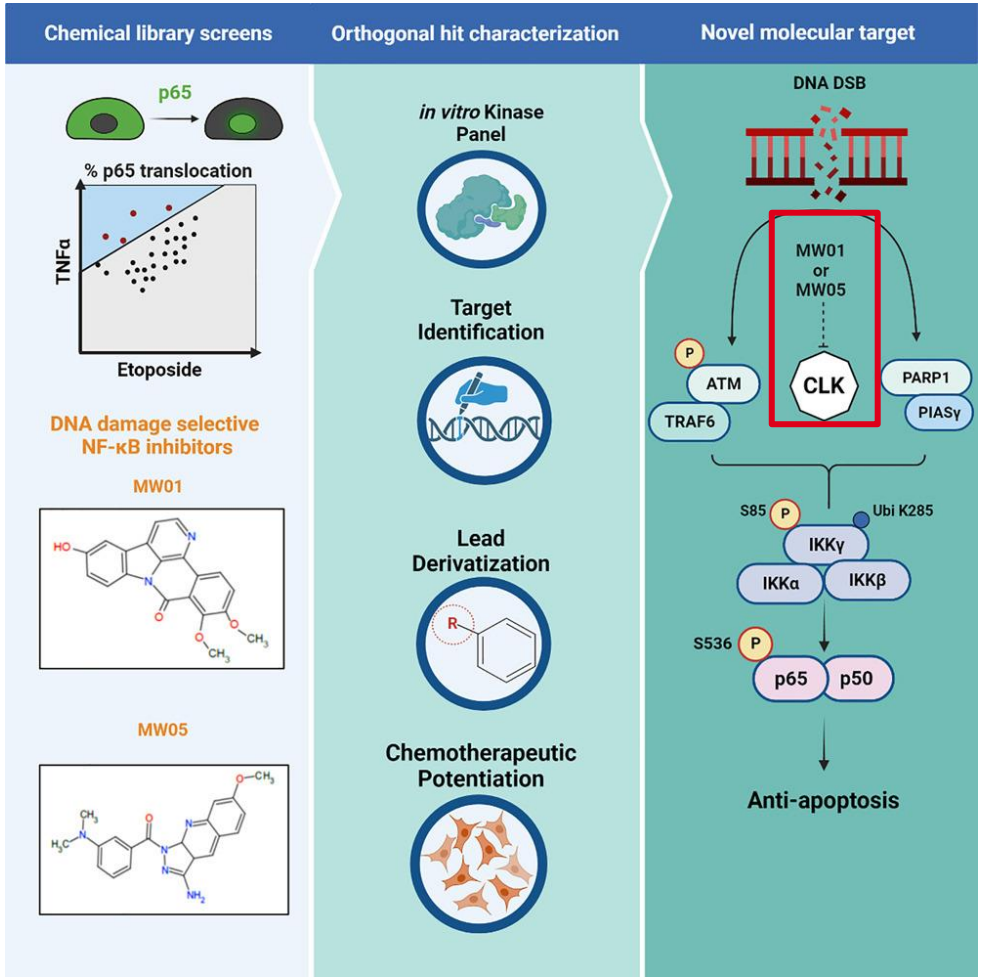


Selective NFκB pathway inhibitors are needed to overcome chemotherapeutic resistance

Nature Reviews | Immunology

Taniguchi & Karin, 2018

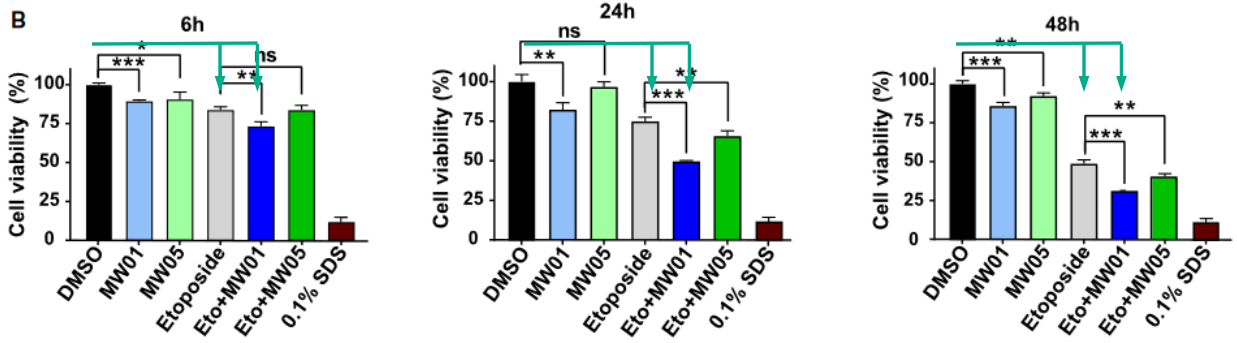
TWO NOVEL SELECTIVE INHIBITORS OF DNA DAMAGE-INDUCED NFKB-ACTIVITY

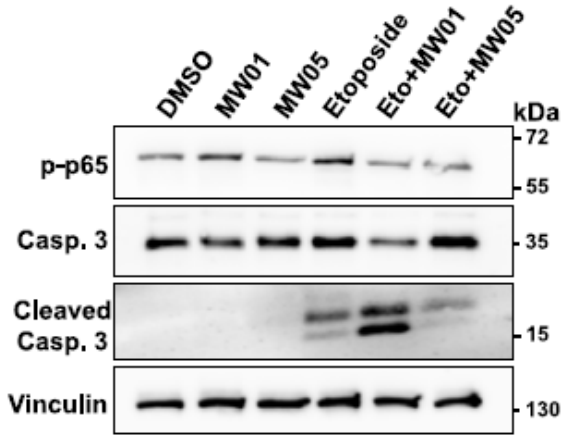


- Two novel lead compounds: MW01 and MW05
  - > **Selectively inhibit NFκB activation only following DNA damage**
- Drug targets: CLK2 and CLK4 (cdc-like kinases)
  - > **CLK2 and CLK4 act upstream of the general NFκB regulator IKK**
- Hit-to-Lead optimization started
  - > **30 derivatives are available for testing**

MW01 AND MW05 POTENTIATE CHEMOTHERAPY-INDUCED APOPTOSIS IN CANCER CELLS

MW01 and MW05 co-treatment with chemotherapeutic etoposide in U2-OS cells





The same effect was confirmed for co-treatment with cisplatin and irradiation.

- MW01 and MW05 synergize with known chemotherapeutics to kill cancer cells (IC50 ~ 1uM, specificity is increased with MW05)

  > Promising molecules for drug development as add-on therapy for chemotherapy and irradiation tumor therapy

  > Potential as stand-alone therapeutics depending on cancer types

Mucka et al., 2023

PRODUCT AND MARKET PERSPECTIVE

Type: Small molecule
Target: CLK2 and CLK4
MOA: Specific inhibition of DNA DSB induced NF-κB signaling and increase of apoptosis following chemotherapy and irradiation in cancer avoiding therapy resistance

Product strategies

1. **Add-on therapy** (chemotherapy, irradiation)
   Indication:
   > Cancer
   > Tumors with CLK2 / 4 expression

2. **Stand-alone therapy Indication:** Cancer
   Indications:
   > Cancers with high genetic instability
   > Tumors with BRCA1/2A mutation

Market

8 billion USD in 2023

6 billion USD of PARP Inhibitors

IP-Status

1st Inhibitor class with priority of 2017 (MW01)

> Patents granted in Europe (EP3538529B1), USA (US11028084B2), Australia (AU2017359276B2), Japan (JP2019535709A5)

2nd inhibitor class with priority of 2023 (MW05)

> Patent applications filed for nationalization in USA and Europe (PCT/EP2024/064219)

Mucka P, Lindemann P, Bosco B, Willenbrock M, Radetzki S, Neuenschwander M, Brischetto C, Peter von Kries J, Nazaré M, **Scheidereit C.** *CLK2 and CLK4 are regulators of DNA damage-induced NF-κB targeted by novel small molecule inhibitors.* **Cell Chem Biol. 2023 Jul 15:S2451-9456(23)00205-2. PMID: 37506701.**

Partnership opportunities

Open to different agreement opportunities including licensing and development

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