# Combination of CD20 targeted Engineered Toxin Body, MT-3724, with chemotherapy or IMiDs for the treatment of Non Hodgkin's Lymphoma

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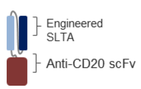
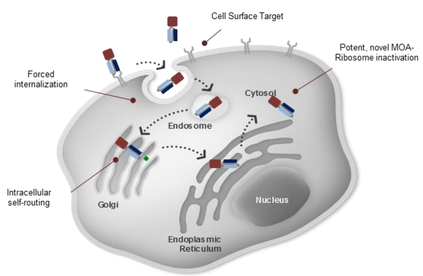
## Background

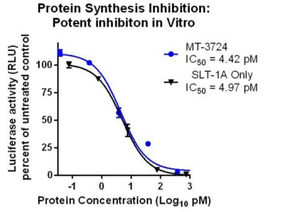
- MT-3724 specifically targets CD20 on lymphoma cells and directly kills target cells via enzymatic, irreversible destruction of ribosomes.
- The catalytic subunit derived from the A subunit from Shiga-like toxin and the scFv binding domain is specific for CD20.

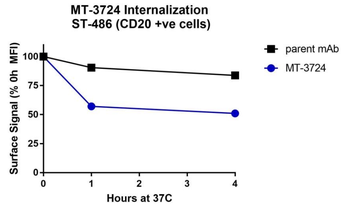


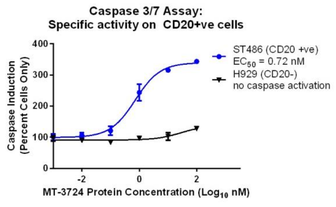

## MT-3724: Unique Mechanism of Action

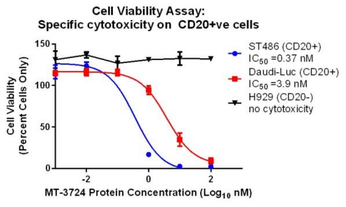
MT-3724 specifically targets and internalizes into CD20 expressing cancer cells, routes to ribosome and irreversibly and enzymatically inactivates ribosomes, leading to protein synthesis inhibition, ribotoxic stress, caspase activation and apoptosis.




- In vitro translation of luciferase is inhibited by SLTA or MT-3724 (Promega TnT Quick), measured by luciferase protein activity
- Cells are incubated at 4C with a saturating amount of mAb or MT-3724, excess washed off, cells placed at 37C, and surface expression measured by flow cytometry at 0, 1 and 4 hours later.

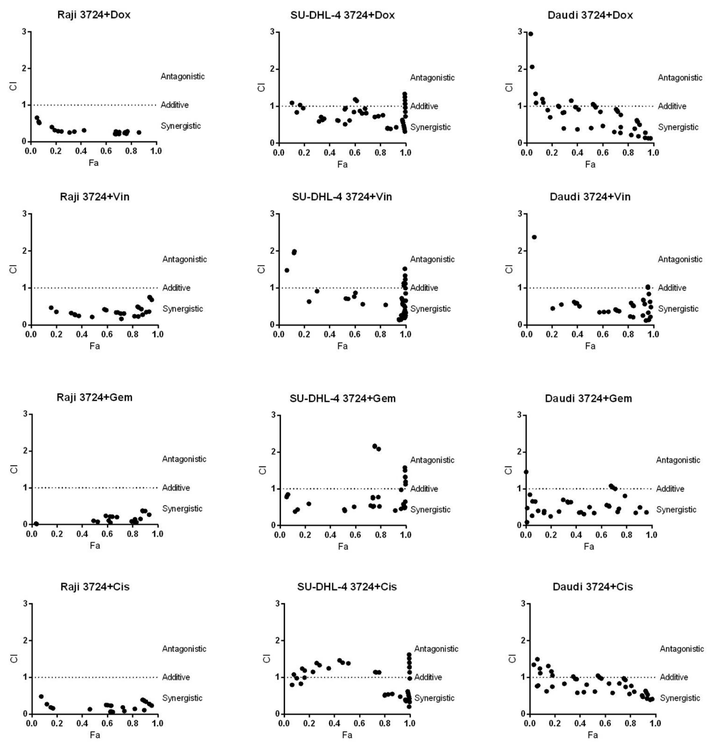



- Cells are incubated with a dilution series of MT-3724 and caspase activity is measured after 20 hours (Promega Caspase3/7-Glo)
- Cells are incubated with a dilution series of MT-3724 and cell viability is measured after 3 days (Promega Cell Titer-Glo)

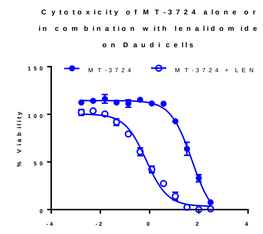
## Combination of MT-3724 with chemotherapy results in synergistic cytotoxicity in vitro

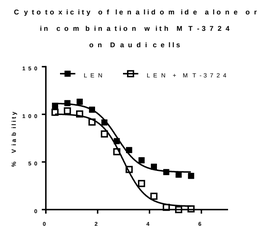
| Cell Line | Chemotherapy | | | | |
|---|---|---|---|---|---|
| | Doxorubicin | Vincristine | Gemcitabine | Bendamustine | Cisplatin |
| Raji | Synergistic | Synergistic | Synergistic | Not Reported | Synergistic |
| SU-DHL-4 | Predominantly Synergistic | Predominantly Synergistic | Predominantly Synergistic | Synergistic | Mixed |
| Daudi | Mixed | Predominantly Synergistic | Predominantly Synergistic | Synergistic | Mixed |
| HBL-1 | Synergistic | Predominantly Synergistic | Predominantly Synergistic | Synergistic | Predominantly Synergistic |

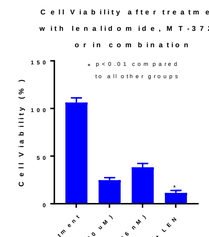



- Cells are incubated at 37C/5% CO2 with MT-3724, chemotherapeutic or a combination of the two an cell viability was measured after a three day incubation.
- Fraction Affected (Fa) represents the fractional response (cytotoxicity) measured in the presence of a given combination. Combination Index (CI) measures degree of drug interaction.
- CI and Fa plotted to graphically depict combinational responses observed

## Combination of MT-3724 with lenalidomide Significantly potentiates cytotoxicity in vitro




- Cells are incubated with lenalidomide or vehicle for 24 (left) or 48 (right) hours. Following this, MT-3724 was added and viability is measured after an additional 3 days (Promega Cell Titer-Glo).

## On-going Phase II clinical studies investigate MT-3724 as monotherapy and combination

| Study | Indication | Status | Next Milestone |
|---|---|---|---|
| Monotherapy | | | |
| Phase 2 | R-R DLBCL (2+ lines of therapy) | In-Progress | Potentially pivotal study |
| Combination | | | |
| Phase 2 GEMOX + MT-3724 | R-R DLBCL (2nd line SCT ineligible) | In-Progress | Data in 2019 |
| Phase 2 LEN+ MT-3724 | R-R DLBCL (2nd line SCT ineligible) | In-Progress | Data in 2020 |

## CONCLUSIONS

- **MT-3724 internalizes faster than the parent mAb containing same binding domain**
- **Combination of MT-3724 and chemo demonstrate synergistic cellular cytotoxicity**
- **Combination of MT-3724 and LEN demonstrate significantly greater potency against lymphoma cells than either agent alone**
- **MT-3724 alone or in combination with chemo or LEN under clinical investigation**

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