Using photoaffinity labelling to ‘fish’ for novel anti-inflammatory drug targets

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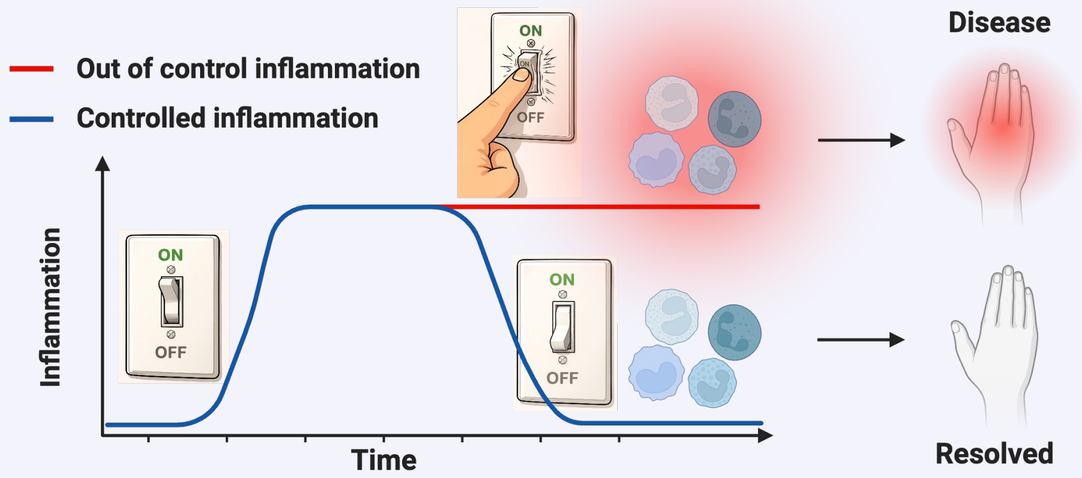
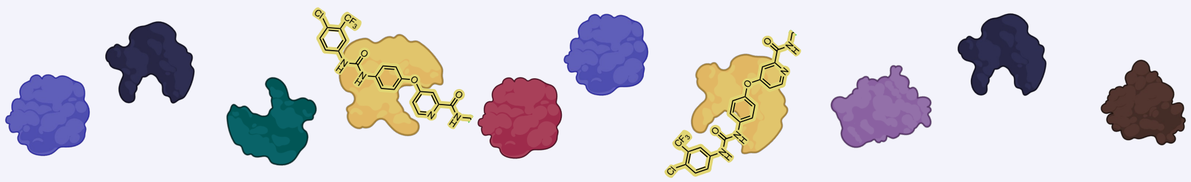
The problem: Out-of-control inflammation causes disease



Inflammation is essential for fighting infection and healing injury.

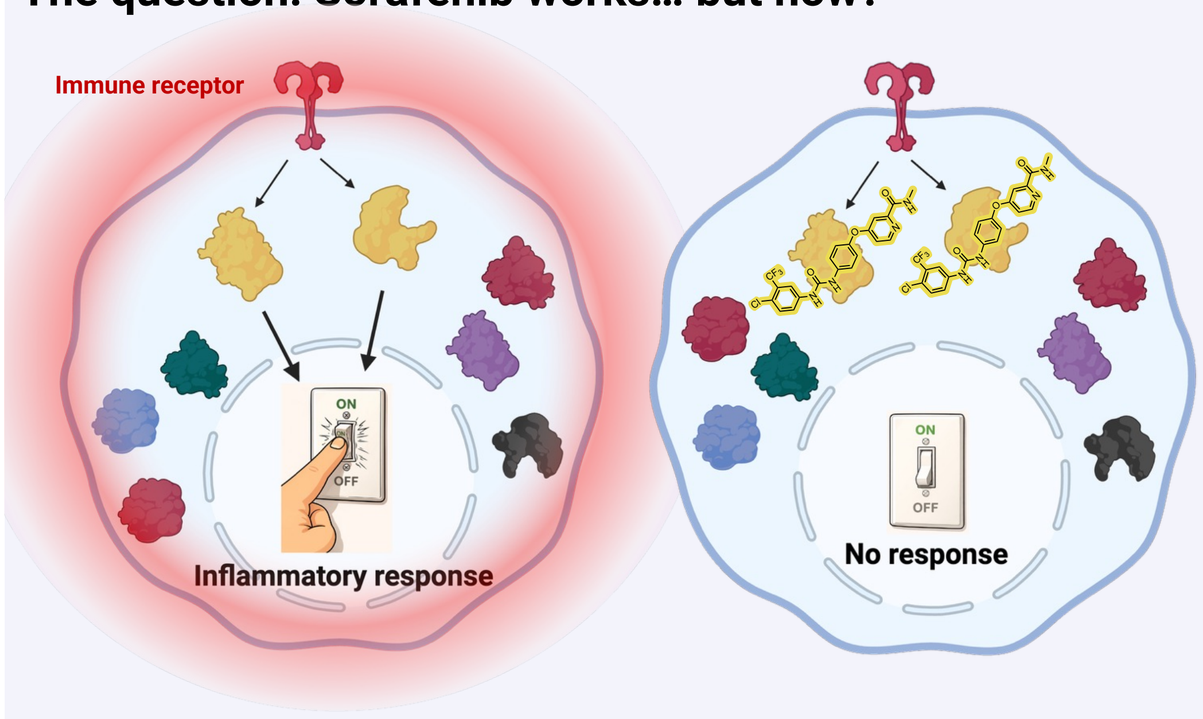
We want to fix **out-of-control** inflammation that causes severe disease.

The challenge: Finding the needles in the haystack!



There are **~10,000 different proteins** in the cell! Which do **sorafenib** target?

The question: Sorafenib works… but how?

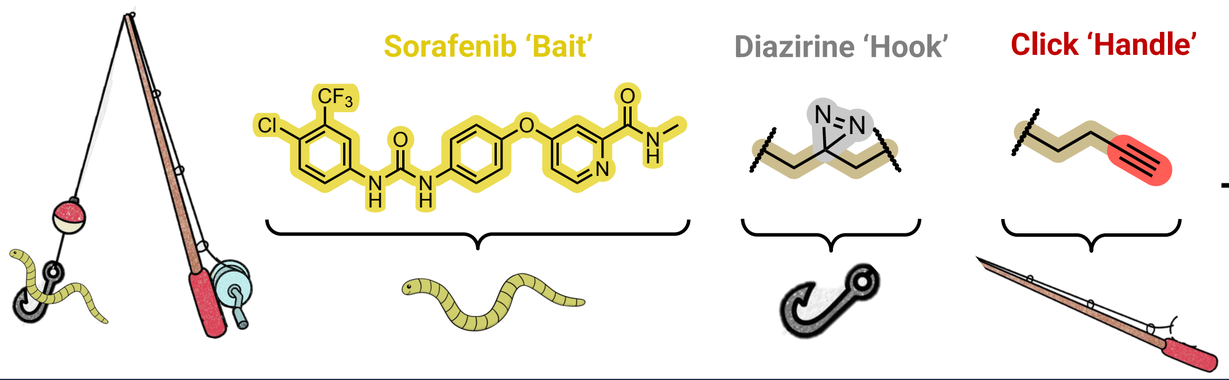


‘On-switch’ stuck **Sorafenib fixes the switch**

The cancer drug **sorafenib** blocks inflammatory ‘on-signals’, reversing out-of-control inflammation.

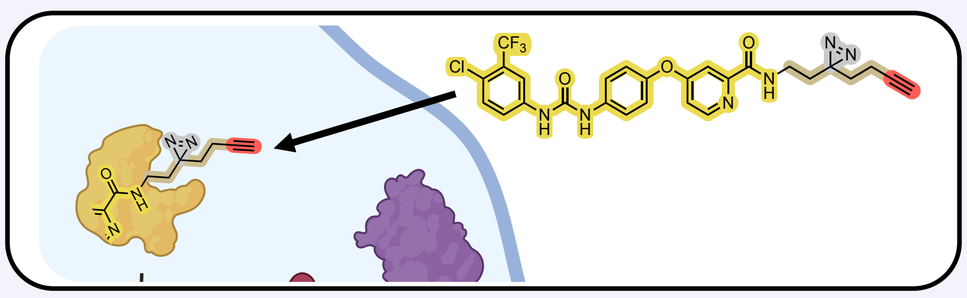
Identifying sorafenib’s **protein targets** may reveal how to **limit** inflammation.

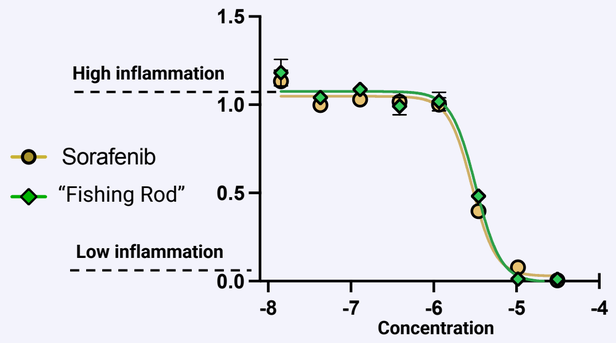
Our approach: Photoaffinity labelling (PAL) = Molecular fishing!



Component — How does it work? — Validation – how do we know it *has* worked?

Step 1: ‘Bait’ binds our protein targets

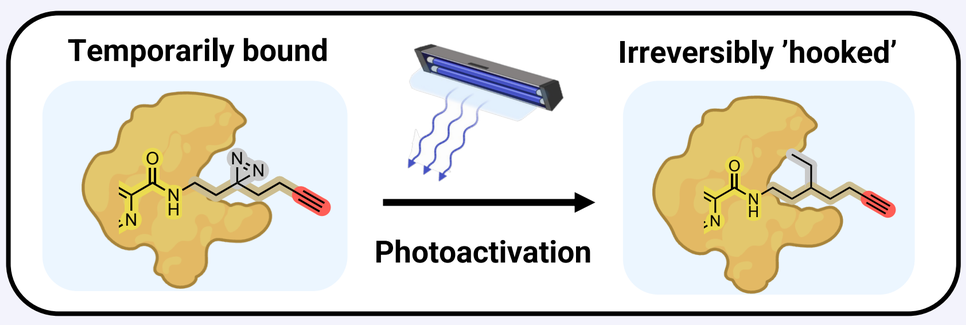


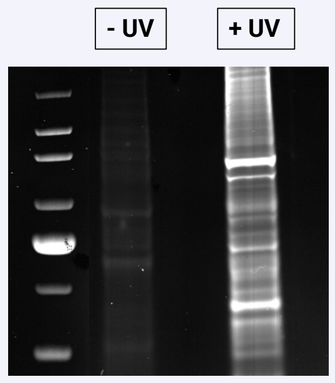


Behaves like sorafenib? ☑

Our rod has a similar effect on inflammation, so we can be certain it binds to the same proteins.

Step 2: UV-photochemistry ‘hooks’ our targets

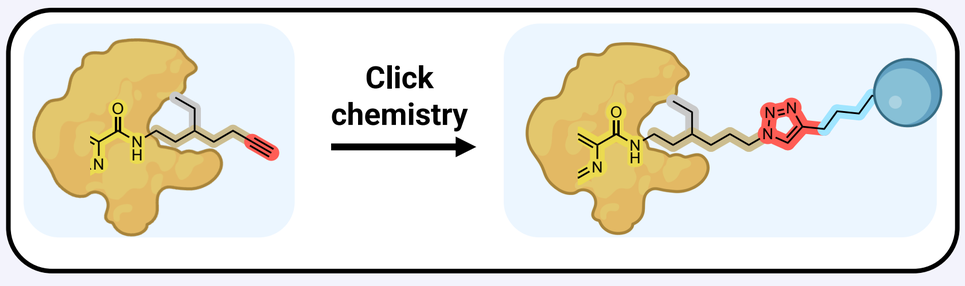


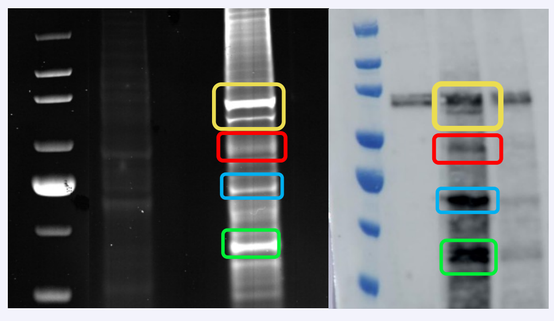


Targets ‘hooked’? ☑

Upon UV-activation, the ‘hook’ captures our proteins of interest.

Step 3: Click ’handle’ attached to the ‘reel’

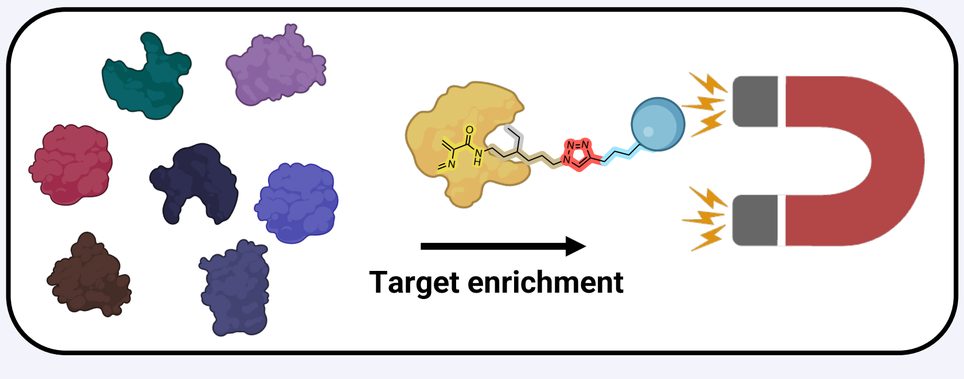




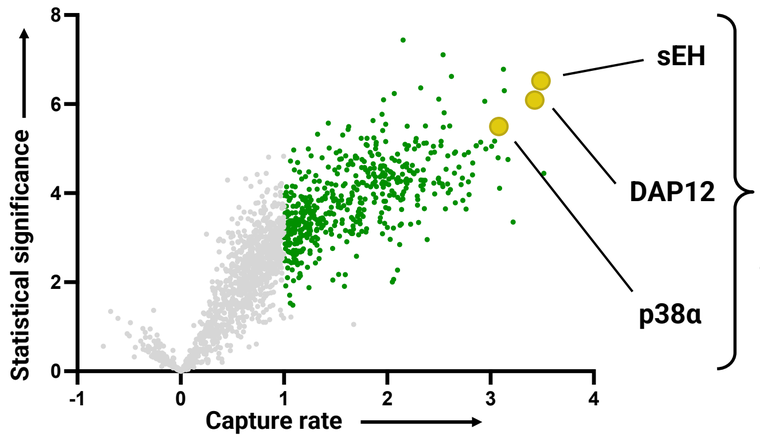
Reel attached? ☑

A consistent pattern between the images shows the reel attaching to ‘hooked’ target proteins.

Step 4: Magnets ‘reel in’ protein targets



The answer: Sorafenib targets multiple proteins



Our **molecular fishing rod** reeled in three inflammatory signalling proteins, each **blocked by sorafenib**.

Future work will investigate their potential as **drug targets** to treat **out-of-control inflammation.**