CHILDREN'S MEDICAL RESEARCH INSTITUTE

Jeans for Genes®

Dynamin II Inhibitors

Enhancing Immuno-Oncology Treatments

The Problem

Immuno-oncology is a fast-growing area of therapeutics which aims to treat cancers by tricking the body's immune system into selectively killing the cancer cells without damaging other cells in the body.

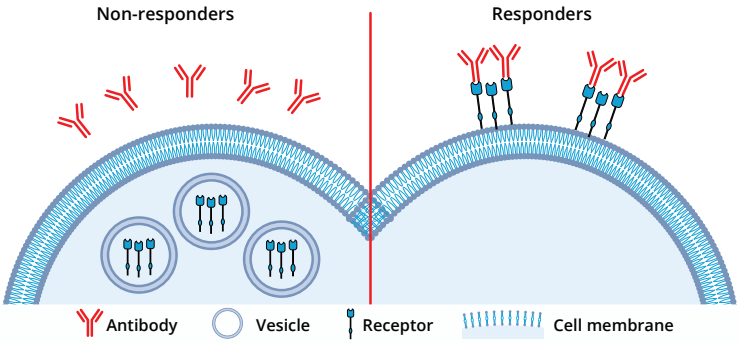
It relies on the use of monoclonal antibodies designed to bind to specific antigens/receptors which are present in large numbers in the cancer cells. Clinical trial results of such therapies have been mixed and can vary greatly between individuals, meaning that the overall response rate is low.

Current immuno-oncology response rates

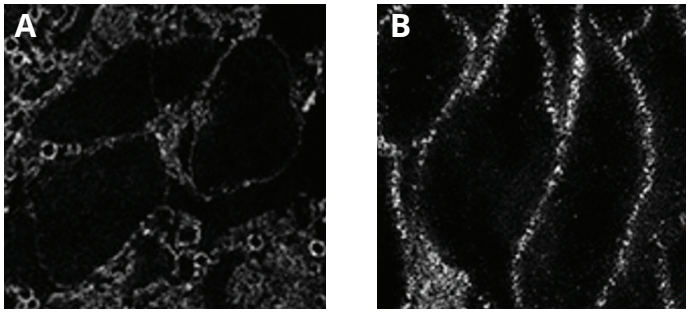
Therapy	Response Rate
Cetuximab (EGFR)	30% ORR
Atezolizumab (PD-L1)	23.5% ORR
Daratumumab (CD38)	29% PR, 3% CR
Nivolumab (PD-1)	40% ORR

***ORR** = Overall response rate **PR** = partial response **CR** = complete response*

One of the main reasons for this variability and poor response rate is that the receptors are often inside the cell rather than on the surface i.e. they are inaccessible to the antibody/therapy. In cetuximab studies, it has been clearly shown that, in non-responders, the EGF receptors are largely inside the cell, whereas in responding patients they are on the cell surface.



In non-responding patients, receptors are internalised in the cell. In responding patients, receptors cluster on the cell surface.

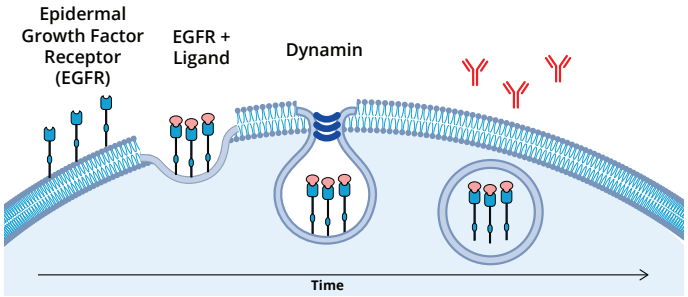


*Fluorescence imaging to demonstrate **(A)** the internalised receptors in cells of non responding patients and **(B)** cell surface receptors in responding patients.*

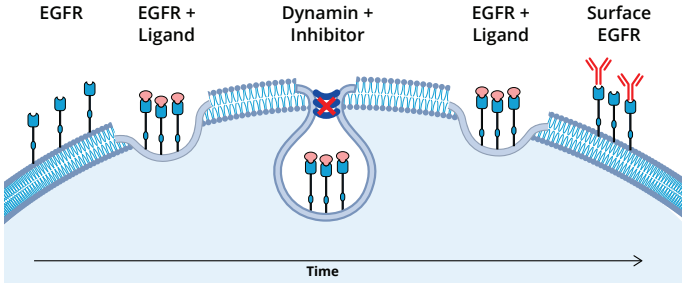
Our Solution

CMRI, in collaboration with University of Newcastle and University of Queensland, has developed proprietary technology with the potential to convert non-responding patients into responders. Our technology achieves this by inhibiting the process by which receptors become internalised. Consequently, large numbers of the required receptors segregate and cluster on the cell surface, making them readily available to the antibody/therapy.

In particular, we have designed a library of drugs to inhibit dynamin II, a key protein responsible for the internalisation of certain receptors. The technology includes a companion diagnostic to determine non-responders and several generations of small molecule libraries designed to inhibit dynamin II. Our approach is novel, proprietary, and there are no obvious competitors in the space.



Dynamin is integral to the internalisation of cell surface receptors.



Inhibition of dynamin results in increased presence and clustering of cell surface receptors.

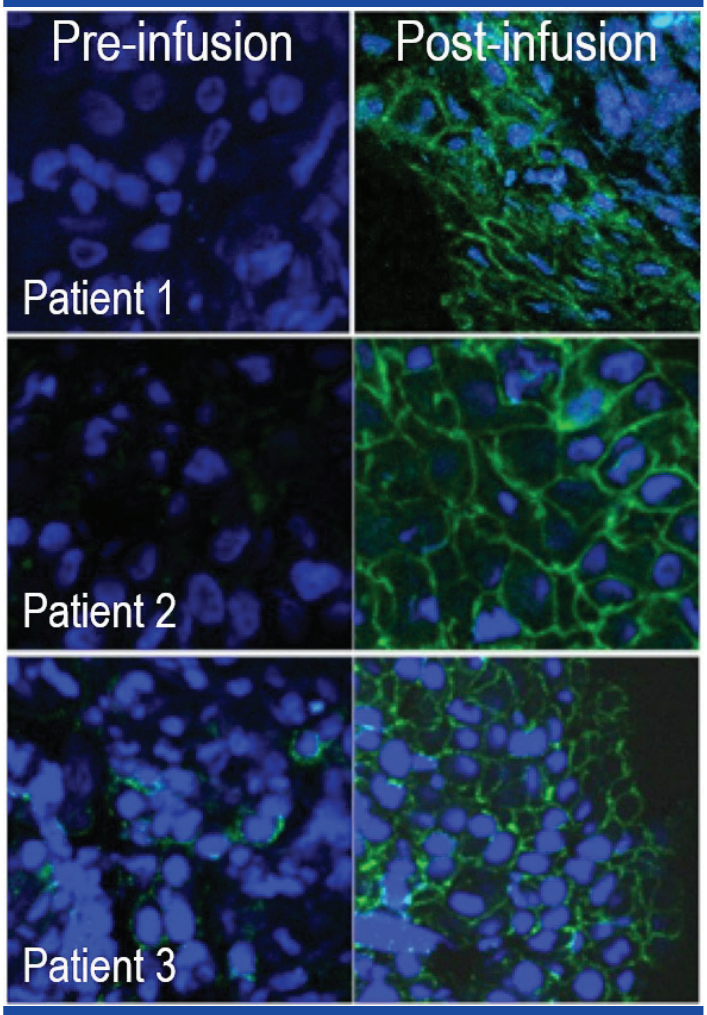
Clinical Trial

Prochlorperazine, an anti-psychotic drug which has been on the market for over 30 years, has been shown by our research team to have an off-target effect of inhibiting dynamin II with high potency. Following promising mouse studies and a pilot clinical investigation, a 10 patient phase 1b clinical trial is currently underway (Princess Alexandra Hospital, Brisbane) using prochlorperazine (a generic dopamine antagonist which is a potent dynamin II inhibitor) as an adjuvant therapy with cetuximab (an antibody targeting the EGFR). The clinical trial has recruited a mix of solid tumours, including triple negative breast cancer, HNSCC and some ACC's.

The clinical trial using re-purposed prochlorperazine is expected to provide proof of principle regarding the usefulness of dynamin inhibitors in enhancing immuno-oncology therapies. This in turn will add significant value to our dynamin II inhibitor new chemical entity (NCE) program.

Clinical Proof of Mechanism

A pilot clinical investigation of prochlorperazine in head and neck squamous cell carcinoma (HNSCC) patients demonstrated the capacity for dynamin inhibitors to increase tumour EGFR surface expression.



Patient biopsies of untreated HNSCC tumours before (left) and 90 min after (right) adminstration of 0.8mg/kg prochlorperazine. Staining with EGF-488 (green) shows cell surface EGFR clustering with confocal microscopy.

Seeking an industry partner or an investor into a NewCo for pre-clinical and clinical development of dynamin inhibitor drug candidates as immuno-oncology adjuvant therapy.

Our Competitive Advantages

NCE (New Chemical Entity) program

- First in class dynamin inhibitors
- Potency and specificity of new drugs
- Synthesis and scale-up capability

Reformulation adds significant value to the NCE program

- Prochlorperazine has been used clinically for 30 years
- Ability to demonstrate proof of principle that dynamin inhibitors are effective as an adjuvant to immuno–oncology therapies
- Market acceptance of reformulation will de-risk NCE program

The Market

The global mAb market is expected to reach $138.6bn by 2024. It is anticipated that multiple partnerships with mAb developers could be established.

Other Applications

The dynamin inhibitor program has wide application, and our scientists have produced strong data indicating potential uses in other indications such as epilepsy and infectious disease. Advancing the current program of work around immuno-oncology will also advance the potential in these other areas. It is envisaged that a pipeline of products will be developed around the various indications.

Please Contact

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