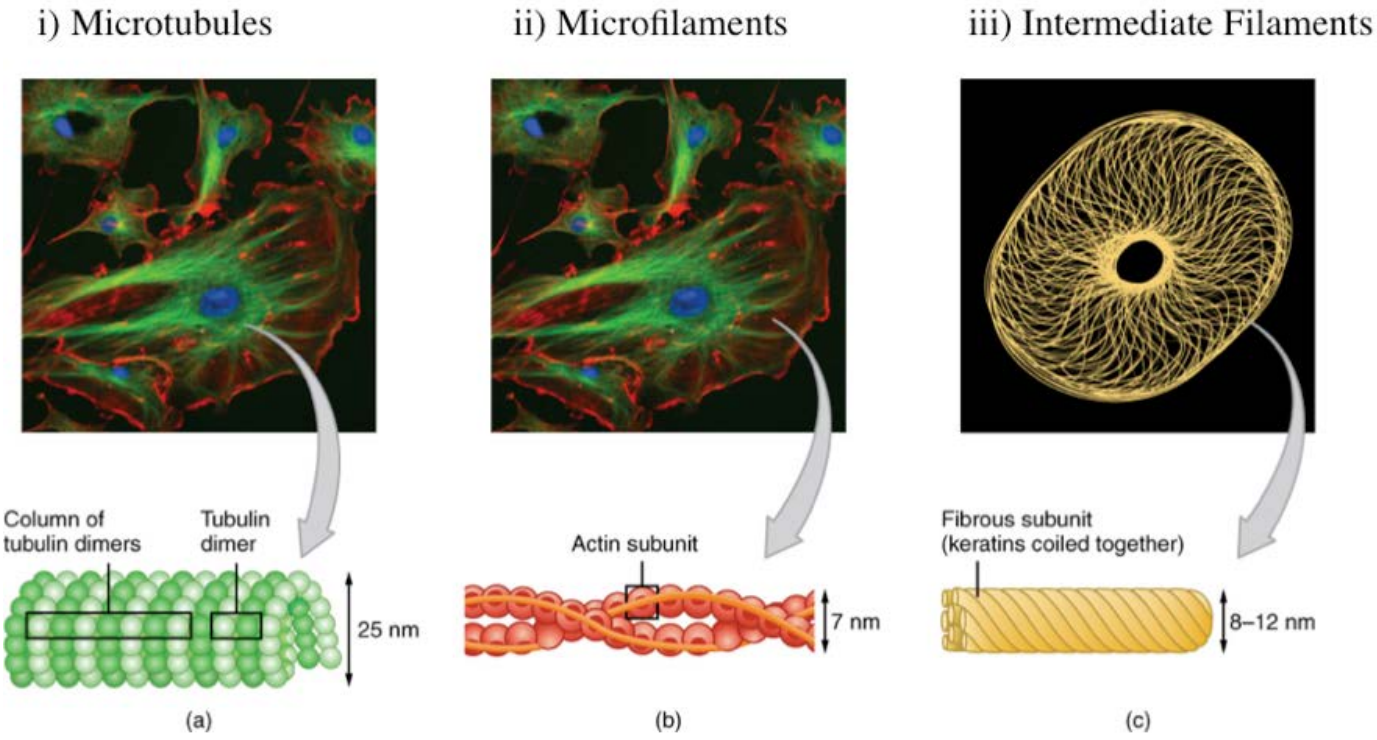
ANTI-TROPOMYOSINS DRUG TECHNOLOGY

This is a story of the cytoskeleton of the cancer cell and a new family of drugs designed to disrupt that crucial structure by targeting one of its key components, the protein tropomyosin.

The Cell Cytoskeleton

In the same way that a body needs a bony skeleton to provide an overall shape and strength, so a cell needs a physical support structure to provide shape and form. This is known as the cytoskeleton. All cells in our body have a cytoskeleton, which is comprised of three filaments systems, the actin microfilaments, the microtubule and the intermediate filaments.



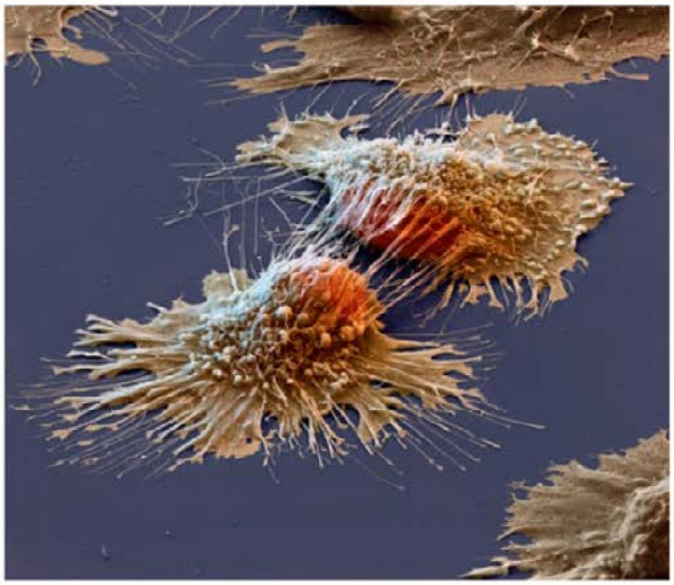
Adapted from: cnx.org/content/m46023/1.5/

All three systems play a role in numerous biological processes within the cell including cell growth, cell motility (or movement) and communication. More importantly these filaments systems are essential for cell survival.

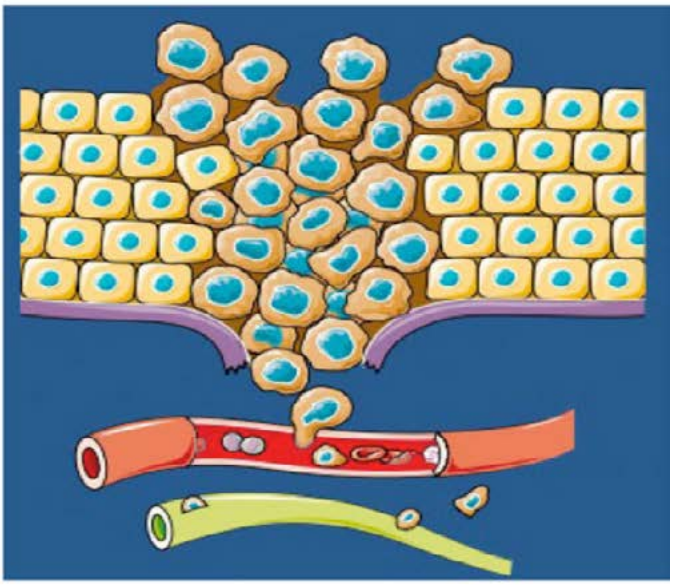
The Cell Cytoskeleton & Cancer

The cytoskeleton has a fundamental role in both cell division and cell movement, biological processes that are hijacked by the cancer cell to give them a survival advantage.

Cell division



Cell movement



Adapted from: repropedia.org and amandabauer.blogspot.com

For this reason researchers have spent many years looking at ways to target the cytoskeleton and in so doing, destroy the cancer cell.

Microtubules and Chemotherapy

Arguably the most effective and the most commonly used family of anti- cancer drugs over the past 40 years (and still is to this day) has been drugs that target the cytoskeleton of the cancer cell, or more particularly, the microtubules. Anti-microtubular drugs are the taxanes (paclitaxel, docetaxel) and the vinca alkaloids (vincristine, vinblastine). These drugs block the microtubules from forming the spindle, thereby preventing the cancer cell from dividing. The long-standing and widespread use of the taxanes and vinca alkaloids in chemotherapy validates the effectiveness of targeting the cytoskeleton of the cancer cell.

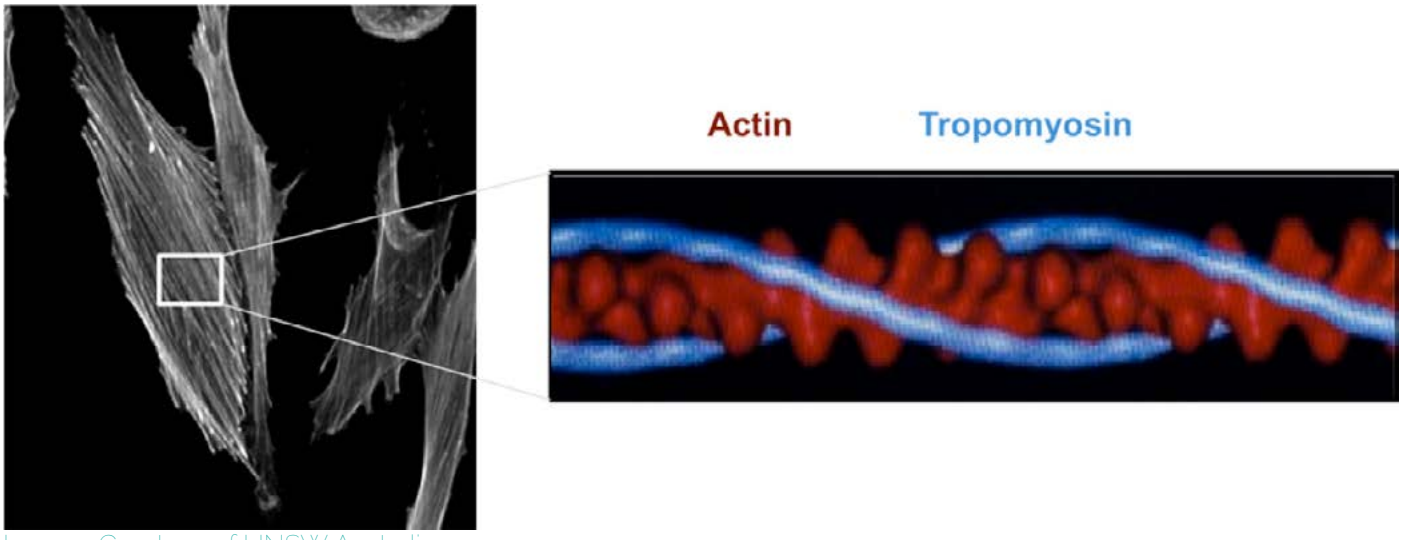
But it also has a downside, and that is that these drugs do not distinguish between the microtubules of cancer cells and non-cancer cells. All dividing cells in the body are equally affected, leading often to serious problems with the bone marrow (low red blood cell and white blood cell levels) and the lining of the gut (nausea, vomiting). These drugs also are very prone to the development of drug resistance mechanisms, meaning that their effectiveness often is limited to single use. They also have no effect on cancer stem cells.

But putting these negatives to one side, the taxanes and the vinca alkaloids continue to make a significant mark in chemotherapy some 50 years after their discovery in the bark of the Pacific yew tree (in the case of the taxanes) and the leaf of the Madagascar periwinkle bush (in the case of the vinca alkaloids) and have validated that targeting the cytoskeleton of a cancer cell is effective therapy.

Actin Microfilaments & Chemotherapy

The considerable success of anti-cancer drugs targeting the microtubule component of the cytoskeleton made it an obvious strategy to look at developing drugs that targeted the other cytoskeleton component... the actin microfilaments. However the current strategy has, to date, failed to generate any compounds that could be taken through to the clinic to treat cancer due to the unacceptably high level of toxicity.

Understanding this toxic hurdle requires an understanding of the nature of microfilaments. The actin microfilaments are constructed using two fundamental building blocks, proteins called actin and tropomyosin. Both actin and tropomyosin form polymers or strands that interlock together forming a "rope like" structure or actin filament (as shown below).



Images Courtesy of UNSW Australia

The actin microfilament has numerous roles in both muscle and non- muscle cells. In muscle cells, actin filaments are a fundamental component of the muscle sarcomere which is structure responsible for generating the force for muscle contraction. The actin filaments also have a role in non-muscle cells, in biological process such as cell movement cell division, cell communication and maintenance of cell structure. To date research has focused on developing compounds that target the actin building block that has proved unsuccessful as these compounds universally target all actin filaments including those important for contraction of the heart and diaphragm muscles. Therefore if targeting the actin microfilaments is going to be a successful therapeutic strategy its essential that we are able to discriminate between the actin filaments in the muscle and those in the cancer cells.

Two recent discoveries have demonstrated that it is possible to selectively target the actin cytoskeleton of a cancer cell by targeting the other core component of the actin microfilament, tropomyosin.

The first is that whilst the actin protein is universal across all cell types there fortunately is a clear distinction between muscle tropomyosin and non-muscle tropomyosin. That discovery opened the door to the potential to develop anti-tropomyosin drugs that targeted non-muscle cells and that perhaps would have no more toxicity than drugs such as the taxanes.
However, it was the second discovery by scientists at the University of NSW Australia which opened this door of opportunity even wider. The breakthrough was the discovery that cancer cells are highly dependent on a particular type of tropomyosin for their survival

UNSW story. Chemotherapy hope for hard-to-treat childhood cancers. Open Link Here > Video Courtesy of UNSW Australia

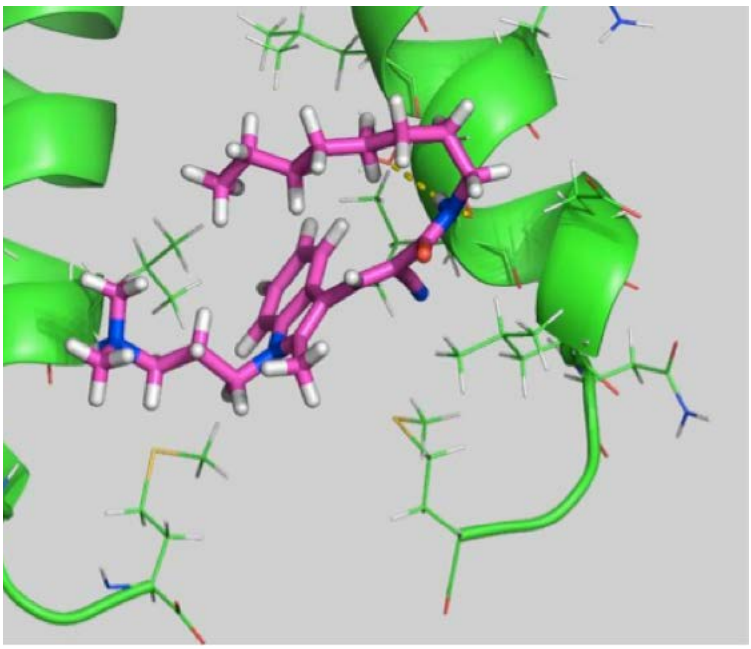
Interestingly, cancer cells in order to survive and thrive cleverly simplify and adapt their cell cytoskeleton. This results in them becoming very reliant on one particular tropomyosin building block, Tm5NM1 for biological processes such as cell division and survival. The reliance has proven to be an "Achilles heel" or vulnerability of the cancer cell.

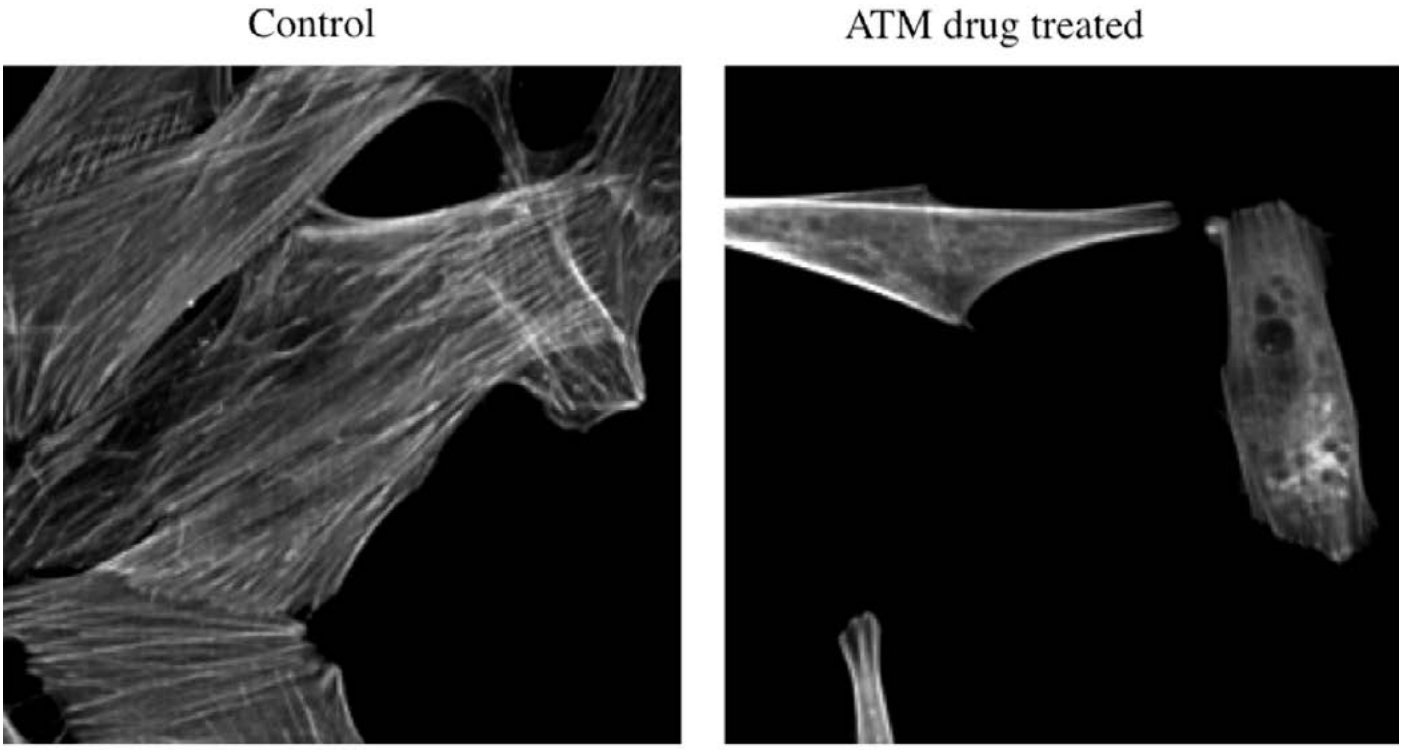
The anti-tropomyosin (ATM) drugs represent a novel class of anti-actin compounds that are able to discriminate and specifically target the actin cytoskeleton of tumor cells. This is an enormous step forward in developing anti-cancer agents that target a fundamental structure of a cancer cell.

Development of the ATM Technology

Using a model of the tropomyosin protein, Tm5NM1, we have been able to identify potential drug binding pockets and designed a range of small molecules capable of binding to those targets.

Shown in the image is the first in class ATM compound TR100 binding to the tail of Tm5NM1. The effect of the ATM binding to Tm5NM1 is to block the ability of this tropomyosin to bind together to form microfilaments. Due to such a heavy reliance by the cancer cell on Tm5NM1, taking away these filaments causes the structure of the cell to "collapse" resulting in the death of the tumor cell. This is shown below: neuroblastoma cancer cells have been treated with an ATM and have lost their internal structures (filaments) causing the cell to lose its shape and ultimately die.



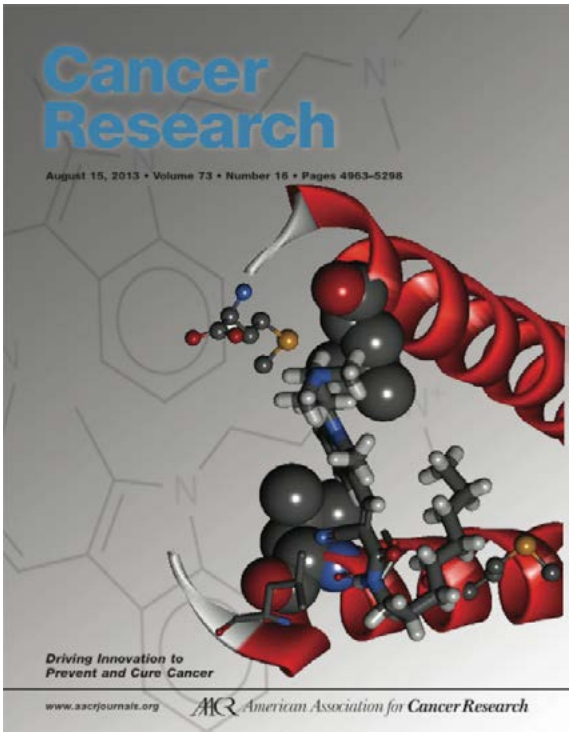


Images courtesy of UNSW Australia

ATM cell death animation Video (Courtesy of UNSW Australia)

A proof-of-concept study with the first generation compounds demonstrated that these ATM compounds have significant anti-cancer effect across a wide spectrum of human cancer cells both in the laboratory, with safety (particularly cardiac function) confirmed in animal studies.

This study was recently published in the Cancer Research Journal and also featured on the cover of the August edition.



Novogen and ATM Drugs

Novogen is building on that early work to design more powerful and more focused compounds. We have already identified two hit second generation compounds, and are already seeing encouraging evidence of even more powerful third-generation compounds. We are moving forward with our second-generation compounds and currently we are in the lead optimization phase. This development program is to be run in collaboration with the extensive network of universities, research institutions, charities and other biotech companies that Novogen has established globally.

Our clinical focus is four cancer types - neuroblastoma, melanoma, ovarian cancer and prostate cancer. Given that the target protein, Tm5NM1, is found in a number of cancer types, there is the possibility that the ATMs could be used for the treatment of a wide variety of cancers.