Professor Mohamed El-Tanani
Anniversary Professor of Molecular Pathology and Cancer Therapeutics.
Director: Collaborative for Targeted Therapeutics and Diagnostics, University of Bradford.
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Ran GTPase Inhibitors: A novel class of Cancer Therapeutics

Background:

Researchers at the Institute of Cancer Therapeutics (ICT) at the University of Bradford have been investigating a novel biomarker in cancer, a protein called Ran-GTPase (Ran). Ran plays an important role in cancer development and progression and is overexpressed in various cancers with prognostic significance and its overexpression is correlated with increased aggressiveness of the cancer cells. Ran is a promising cancer therapeutic target; silencing Ran expression induces more apoptosis in cancer cells than normal cells. Ran silencing results in a selective killing effect on cancer cells with stronger activation of the PI3K/Akt/mTORC1 and MEK/ERK pathways; in contrast, loss of Ran in normal cells carries minimal effects. Ran overexpression may play a role in the metastatic development of breast and lung cancers.

Researchers have identified a correlation between survival rates of cancer patients with triple negative breast cancer (TNBC) and Non-Small Cell Lung Cancer (NSCLC) with the levels of Ran found in patient cancer cells. In addition, researchers found that suppressing this protein also causes cancer cells already resistant to the first-line and the latest targeted therapeutic treatments, gefitinib and osimertinib, to become re-sensitised to the drug.

Technology Overview:

Researchers have identified a novel peptide (NPP-1) and two small molecule therapeutics (MELT2014 & MELT2015 both repurposed drugs) that can inhibit Ran in cancer cells and have shown that NPP-1 is anti-proliferative and anti-migratory in breast and lung cell lines but not in a normal epithelial cell lines and it induces breast cancer cell apoptosis. NPP-1 is anti-tumorigenic in animal model systems. In addition MELT2014 was shown to significantly reduce gene expressions in MDA-MB-231 (TNBC cells) lowering levels of Ran, AK1, AKT2, pAKT, c-MYC and c-Met proteins. MELT2014 has also been shown to significantly reduce proliferating cell viability of MDA MB 231 and A549 (NSCLC cells) whilst having no effect on MCF10A normal mammary epithelial cells. In addition, in preclinical studies MELT2014 significantly reduces tumor volume (when compared to untreated) of MDA MB 231-luc xenografts in mice for both primary tumor (70-80%reduction) and metastatic deposits (80-90% reduction). Researchers have also shown that MELT2015 significantly sensitize the lung cancer drug resistance HCC827-GR5 to both tyrosine kinase inhibitors gefitinib and osimertinib through dysregulation of immune-target genes.

In addition, researchers at ICT have used multiple approaches to therapeutic development including conventional screening to identifying a class of NCE small molecule Ran Inhibitors (Hit to Lead programme) and discovery of Monoclonal Antibodies as Ran inhibitors. The team has a pipeline of lead candidates.

In conclusion:
NPP-1 & MELT2014 are:

- Anti-proliferative in breast and lung cell lines but not in a normal epithelial cell lines and it induces breast cancer cell apoptosis
- Anti-migratory against breast and lung cancer cells
- Anti-tumorigenic and anti-metastatic in animal model systems

And MELT2015 can sensitise TKI resistant NSCLC to TKIs

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Benefits:

Ran inhibitors represent a new class of cancer therapeutics that may be used as targeted treatments for cancer patients with unmet needs for example, TNBC, NSCLC with EGFRm+ with acquired resistance to TKIs and Breast Cancer and Lung Cancer Metastasis.

Potential Applications / Potential Markets:

The team at ICT are addressing the unmet needs of cancer patients focusing efforts on developing novel therapeutics for cancer types that currently have no targeted therapies:

- TNBC
- TKI resistant NSCLC
- Lung and breast cancer metastasis

Breast cancer (BC) incidence is ca. 1.4 million globally and increasing, of which TNBC accounts for ca. 15-20% of total BC and carries a poor prognosis, estimated incidence rates of TNBC 170,000 globally. Currently no approved targeted therapeutic is available and treatment is via chemotherapy only. The potential total market for targeted drugs for TNBC is c. $15billion. Lung Cancer is the most common cause of cancer deaths globally with incidence of 1.8 million. 85% of LC patients are affected by NSCLC, 50% express (EGFR) correlating with a poor prognosis. Sensitivity to Tyrosine Kinase Inhibitors (TKIs) e.g. Gefetinib correlated strongly with the presence of a specific activating EGFRm+. EGFRm+ is present in 10-15% of Caucasian patients and 50% of Asian patients. Patients become drug resistant to TKIs after 9 to 13 months. Resistance mechanisms are understood, most common is a secondary T790M mutation (50% of patients) treated by TAGRISSO (AZ). Treatment of patients that develop resistance via non-mutational pathways such as c-MET amplification is less well defined with no current targeted therapeutic available. Researchers have shown a correlation between Ran and c-Met. Forecast sales for TAGRISSO (AZ) $1.1 billion by 2020.

State of Development / Opportunity / Seeking:

UoB is seeking funding and collaboration, with the intention to set-up a spin-out company, to initially progress:

Stage 1: Novel Peptide development to Phase 1

Stage 2: Identify optimum use of MELT2014 & MELT2015 (repurposed drugs) in combination with known cancer therapeutics or in a novel formulation and progress to clinical trial stages

Stage 3: NCE development to Phase 1

Stage 4: Monoclonal antibodies to validate in vivo

IP Status:

Novel Nanoparticle Peptide (NPP-1) as a Ran inhibitor (Patent application submitted)
Two repurposed drugs MELT2014 & MELT2015 as Ran inhibitors (in combination with known cancer therapeutics or in a novel formulation) (Patent application submitted).

Recent News and conclusion:

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Recently we have been awarded a prestigious grant from Innovate UK to develop and validate Ran diagnostics in the blood of cancer patients. Consequently, we are looking for investor(s) or a pharmaceutical company to take it into the clinical market. Moreover, we are looking for investors in both diagnostics and therapeutics. Specifically, the diagnostics are very close to being released into the market and we estimate it to bring a large revenue within next 18-24 months on the condition that we receive sufficient funding from serious investor(s).