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Targeting tumor metabolism to improve radio-sensitivity in non-small cell lung cancer (NSCLC)

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Lung tumor metabolism is severely altered involving enhanced levels of glucose uptake, glycolysis, lipogenesis and protein synthesis. These events are essential for the support of enhanced energy demands and increased need for ribonucleotides, proteins and membrane biogenesis that are required for rapid proliferation.

Combined treatment with cytotoxic therapy and metabolism modulating agents may improve outcomes in NSCLC. We observed that radiotherapy (RT) alone activates the metabolic stress sensor AMP-activated kinase (AMPK) within an Ataxia Telengiectasia Mutated (ATM) – AMPK – p53/p21cip1 pathway to mediate the RT-induced G2-M checkpoint and cytotoxicity. Further, inhibition of biosynthetic pathways and energy production through blockade of OxPhos inhibits tumor growth. In human NSCLC cells and xenografts, we combined RT with the anti-diabetic agent metformin, which blocks OxPhos complex I, and showed that metformin activates the ATM-AMPK-p53/p21cip1 axis and inhibits the Akt-mTOR pathway, tumor growth and angiogenesis and induces apoptosis and radio-sensitization.

Based on these observations and supporting retrospective clinical evidence from locally advanced lung cancer patients treated with Chemo-RT, we launched phase II studies combining metformin with chemo-RT. NRG-LU001 (NCT02186847) and OCOG ALMERA (NCT02186847) are on-going randomized phase II studies investigating whether targeting metabolism with metformin can improve progression free survival in stage III NSCLC.

In recent studies we observed that combined treatment with metabolism modulating agents can enhance anti-tumor activity in NSCLC. Combined treatment with Metformin and Salicylate, which activate AMPK through different mechanisms, mediated increased inhibition of clonogenic survival in part through AMPK and suppression of de-novo lipogenesis. Further, in earlier studies we showed that blockade of the cholesterol synthesis pathway with lovastatin (HMG-CoA reductase inhibitor) mediated activation of AMPK, suppression of the Akt-P13k pathways and radio-sensitization of NSCLC.

In current studies we observe that lovastatin also activates the ATM-AMPK-p53 axis, inhibit the Akt-mTOR pathway and mediate tumor suppression in an AMPK-dependent manner through suppression of de novo lipogenesis along both the mevalonate and the fatty acid synthesis pathways. Further, in retrospective clinical studies we find that in locally advanced NSCLC patients treated with Chemo-RT, statin treatment is associated with increased survival.

These observations suggest that targeting tumor metabolism is promising in NSCLC to improve outcomes of standard cytotoxic therapy. Completion of on-going trials with metformin will provide the first prospective evidence on this concept. We plan to investigate combinations of well-tolerated metabolism modulating agents that show promising pre-clinical activity in future rolling phase II studies.

OCOG-ALMERa: A phase II trial investigating the ability of metformin to chemo-radio-sensitize and prevent recurrence in locally advanced (LA) non-small cell lung cancer (NSCLC)*

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LA-NSCLC is frequently unresectable and is treated with concurrent chemo-radiotherapy (CRT), which is fairly toxic and provides poor disease control and overall survival. There is an urgent need to develop sensitizers to cytotoxic therapy that could improve the therapeutic ratio in this disease.

Preclinical studies from our group and others demonstrated that the biguanide metformin has activity in lung cancer and sensitizes lung cancer cells and tumors to radiotherapy and chemotherapy. Metformin is known to induce in cells a state of mild metabolic stress through blockade of the mitochondria OxPhos complex I. We showed that metformin alone triggers activation of the ATM-AMP-kinase-p53/p21cip1 pathway, inhibition of the radio-resistance Akt-mTOR pathway, radio-sensitizes NSCLC, enhances apoptosis and inhibits angiogenesis.

Metformin is an economical and effective anti-diabetic agent that is well-tolerated by non-diabetics too. Based on our pre-clinical results and additional supporting retrospective data from stage III NSCLC patients treated with chemo-radiotherapy, we launched a phase II clinical trial in locally advanced NSCLC combining metformin with concurrent CRT.