AGX51, a potential anti-tumour therapy targeting ID proteins

Dr Benezra’s recent findings are the culmination of 30 years of basic and translational research. Back in 1989, ID (“Inhibitor of DNA binding”) proteins were identified as inhibitors of cell differentiation. Since then, ID proteins have been shown to play a critical role during normal embryonic and fetal development. As the foetus develops and cells differentiate to acquire different characteristics and carry out specific functions, it is important that a pool of stem cells (undifferentiated cells) keeps its stem-cell state and maintains its self-renewal capacity. This is, in part, taken care of by ID proteins, which inhibit cell differentiation.

In healthy adult tissues, ID protein expression is largely silenced, meaning that cells are mostly devoid of ID proteins. However, ID protein expression is reactivated in a variety of human cancers. Over-expression of ID proteins in cancer is often associated with more aggressive disease and an increased risk of metastasis. Recent evidence suggests these proteins are present in resting cancer stem cells which resist standard chemotherapies and may be responsible for disease recurrence.

**HOW ID BLOCKS DIFFERENTIATION**

The primary mechanism of action of ID proteins is to isolate, or ‘sequester’ other proteins by interacting with them. Dr Benezra and his team have focused on the protein-protein interactions between ID and E proteins. E proteins induce cell differentiation. As transcription factors, E proteins interact with DNA and promote the expression of specific genes that will give the cell specific characteristics and stall their growth. ID proteins bind to E proteins and, by doing so, prevent the formation of active transcription complexes and block E-protein-mediated gene expression. As a result, cell differentiation is inhibited.

**ID PROTEINS IN CANCER**

Oncogenic factors that promote proliferation and cancer activate different signalling pathways that lead, among other processes, to the over-expression of ID proteins. ID proteins are highly expressed in many solid tumours, including breast, pancreas, bladder, uterus, colon, stomach, nervous system, liver, ovary, prostate, kidney, oesophagus, lung and thyroid as well as in leukaemia. In all these cancer types, the presence of ID proteins is often associated with more aggressive disease and an increased metastatic potential, resulting in poor clinical outcomes.

Because ID proteins are over-expressed in cancer, Dr Benezra’s work applies the hypothesis that an anti-ID therapy could be an effective treatment for cancer.

**ID PROTEINS IN VISION LOSS**

In cancer, new blood vessels are formed to vascularise the tumour, and ID proteins were shown to be required in the newly formed vessels. Given these findings, Dr Benezra hypothesised that reducing ID protein levels would be protective not only in cancer, but also in ocular neovascularisation-related pathologies, where the pathologic formation of vessels is also involved. The contribution of ID proteins in this context had at the time not yet been explored.

Wet age-related macular degeneration (AMD) and retinopathy of prematurity (ROP) are two examples of neovascularisation-related pathologies affecting the eye. As a result, retinal function is impaired. AMD and ROP are the leading causes of vision loss in adults over 60 and premature babies, respectively.

The team led by Dr Benezra showed, in mouse models of AMD and ROP, that the genetic loss of ID proteins is associated with less ocular neovascularisation. This finding confirms that ID proteins are involved in these pathologies, and also suggests that ID proteins could be a therapeutic target: an anti-ID therapy could be an effective treatment also for AMD and ROP.

**AGX51: AN ID DEGRADER**

Together with Angiogenex, Inc., Dr Benezra has recently identified a small molecule, AGX51, which acts as an antagonist of ID proteins. AGX51 decreases cell growth and viability and is a strong candidate for anti-tumour therapy.

Over-expression of ID proteins in cancer is associated with more aggressive disease and an increased risk of metastasis. ID proteins bind to ID proteins. This binding prevents ID proteins from interacting with E proteins, and effectively allows E proteins to carry out their function as transcription factors. In the presence of AGX51, E proteins modulate gene expression, promote cell differentiation and inhibit cell growth.

In the meantime, the binding with AGX51 destabilises ID proteins, which in turn leads to ID degradation. The interaction between ID and E proteins was formerly considered to be impossible to inhibit. AGX51 is therefore a first-in-class compound that may be useful in the management of multiple diseases.

**ACTION OF AGX51**

Notably, Dr Benezra and his team have managed to describe the molecular mechanisms involved in the binding of AGX51 to ID proteins, and the subsequent sequence of events that leads to the degradation of ID proteins. In the absence of AGX51, ID and E proteins interact and form a complex called a dimer. The E protein is sequestered, unable to carry out its functions. AGX51 is a small molecule that can bind to a highly conserved region of ID proteins (a part of the structure that is very similar across all ID proteins). It’s important to note that in proteins, highly conserved regions are often important for folding, binding to other molecules, or for maintaining its structure.

The research team show that the interaction with AGX51 alters the ID protein structure, causing it to partially unwind. This structural change disrupts ID’s interaction with the E protein — allowing the E protein to be set free. The stabilised ID protein is then targeted for destruction by the cell. Importantly,
Behind the Research
Dr Robert Benezra

Research Objectives

Research in Robert Benezra’s Laboratory involves the analysis of molecular mechanisms that have direct application to cancer biology.

Detail

Bio

Robert Benezra, PhD is a Member of the Cancer Biology and Genetics Program at Memorial Sloan Kettering Cancer Center. His work over the past 30 years has identified the importance of ID proteins in foetal development and their reactivation in a variety of cancers. Recent targeting of ID proteins by small molecules with the help of Angiogenex, Inc., has led to the development of novel targeted therapies being readied for clinical application.

References


Personal Response

AGX51 holds exciting potential for patients. Can you tell us more about future plans and potential clinical trials for this anti-ID molecule?

We are currently amassing the safety and pharmacologic data required for filing an IND (investigational new drug) with the FDA as a prelude to a first-in-human clinical trial. Cancers that express ID in resting stem cells have high relapse rates and poor prognoses. These will be the first cancers we will be treating with our new oral formulations.

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