SciBX
Science-Business eXchange

Interfering with integrins in atherosclerosis

By Tim Fulmer, Senior Writer

Researchers at **The University of North Carolina at Chapel Hill** have shown that a mAb targeting integrin $\alpha_v\beta_3$ blocks progression of atherosclerotic plaques in hyperglycemic pigs.[1] **Vascular Pharmaceuticals Inc.** has in-licensed the IP and is now developing a humanized version of the antibody with support from **Johnson & Johnson**.

The mechanisms that underlie vascular inflammation and drive atherosclerosis are fundamentally the same whether the disease occurs in diabetics or nondiabetics. In diabetes, however, hyperglycemia is thought to quicken progression of atherosclerosis and lead to more extensive disease that affects both the larger blood vessels and the organ microvasculature.[2]

In diabetes-associated atherosclerosis, vascular smooth muscle cells (VSMCs) and endothelial cells have been identified as key players in plaque formation, along with inflammatory cells such as macrophages.

David Clemmons, director of the Diabetes Center Of Excellence at the University of North Carolina at Chapel Hill, and others previously identified *in vitro* a molecular mechanism that helps explain how VSMCs could be driving the formation of atherosclerotic lesions in diabetics.[3–6]

Building on his previous work, Clemmons and his team have now shown *in vivo* that high glucose levels mimicking hyperglycemia lead to increased activation of integrin $\alpha_v\beta_3$ (CD51/CD61) on VSMCs, which in turn enhances the cells' responsiveness to insulin-like growth factor-1 (IGF-1). This results in excessive VSMC proliferation and migration, two processes that underlie formation of atherosclerotic lesions.

The researchers hypothesized that blocking that mechanism could stop or at least slow progression of atherosclerotic plaques.

However, directly targeting IGF-1 or its receptor, IGF1R (CD221), on VSMCs was out of the question because the receptor is highly expressed on tissues throughout the body. That left the option of indirectly targeting IGF-1 signaling by blocking upstream activation of integrin $\alpha_v\beta_3$, which is expressed on only three cell types: endothelium, smooth muscle and osteoclasts.

Using X-ray crystal structures of integrin $\alpha_v\beta_3$ as a guide, the researchers decided to target an eight-amino-acid stretch of the protein's extracellular domain, the C-loop, which is thought to confer ligand specificity.[7]

In cultured VSMCs, a mAb targeting the C-loop blocked activation of integrin $\alpha_v\beta_3$ by one of its ligands, vitronectin. The mAb also reduced downstream IGF-1 signaling.

Next, the team tested the therapeutic potential of the strategy by using the mAb to treat pig models of diabetes-associated atherosclerosis.

Local infusion of the C-loop-targeting mAb into the femoral artery led to a 65% reduction in atherosclerotic lesion area compared with infusion of a control antibody.

The findings were published in *Science Translational Medicine*.

Moving forward

Clemmons told *SciBX* that the next step is to humanize the antibody in preparation for testing in humans. That work is being carried out by Vascular Pharmaceuticals, which Clemmons founded in 2005.

"Once we've isolated an antibody variant with maximal affinity for the target and minimal immunogenicity, we'll continue with pharmacokinetics and pharmacodynamics studies of the mAb in rodents and pigs. Our hope is to start large-scale manufacture of the humanized version in June of this year," said Clemmons.

Clemmons did not disclose when Vascular Pharmaceuticals hopes to submit an IND to begin testing in humans. He did say the company hopes to raise series A funding during 2010 to fund development of the mAb through Phase IIa testing.

The biotech has already granted J&J first option on the antibody. In return, the pharma is helping fund the humanization work.

According to Clemmons, J&J first learned about his group's work through a cooperative program between the pharma and the University of North Carolina at Chapel Hill Office of Technology Development.

Vascular Pharmaceuticals has exclusively in-licensed patents covering the C-loop-targeting mAb from the university.

Fulmer, T. *SciBX* 3(9); doi:10.1038/scibx.2010.267
Published online March 4, 2010

REFERENCES

1. Maile, L. *et al. Sci. Transl. Med.*; published online Feb. 10, 2010; doi:10.1126/scitranslmed.3000476
   Contact: David Clemmons, The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
   e-mail: endo@med.unc.edu
2. Orasanu, G. & Plutzky, J. *J. Am. Coll. Cardiol*. **53**, S35–S42 (2009)
3. Jones, I. *et al. Proc. Natl. Acad. Sci. USA* **93**, 2482–2487 (1996)
4. Maile, L. *et al. Endocrinology* **148**, 2435–2443 (2007)
5. Mori, S. *et al. J. Diabetes Complications* **16**, 65–68 (2002)
6. Battacharyya, S. *et al. J. Biol. Chem*. **283**, 5699–5707 (2008)
7. Maile, L. *et al. Mol. Endocrinol*. **20**, 405–413 (2006)

COMPANIES AND INTITUTIONS MENTIONED

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
Vascular Pharmaceuticals Inc., Chapel Hill, N.C.