New *sine qua non* for CMV

By Michael J. Haas, Senior Writer

Platelet-derived growth factor receptor- α has been a cancer target since the 2001 approval of **Novartis AG**'s leukemia drug Gleevec, an inhibitor of several Bcr-Abl tyrosine kinase receptors. Now, the pharma company and a trio of biotechs working on platelet-derived growth factor receptor- α may have had a new indication land in their laps, as a study by California researchers has shown that the receptor is a host factor for cytomegalovirus. The group suggests that disrupting the virus-receptor interaction could prevent CMV infection in transplant patients and pregnant women.¹

Although the cancer companies with anti-platelet-derived growth factor receptor- α (PDGFR- α) molecules declined to comment, infectious disease companies told *SciBX* it is not yet clear whether targeting PDGFR- α would be a feasible or safe strategy in the transplant and pregnancy settings.

CMV is a member of the herpes virus family that is present in about 50% of adults in the U.S. at any given time.² It is asymptomatic in most healthy adults, but its effects can be severe in immunocompromised individuals such as transplant patients, in whom active CMV infection can cause transplant failure, other organ failure and death. CMV also can cause congenital birth defects if a woman contracts the virus during or shortly before pregnancy. The pathways and mechanisms that drive active infection in these patient populations are not fully understood.

Moreover, there are no approved therapies to prevent or treat CMV infection during pregnancy. The only drugs marketed to prevent active CMV infection in transplant patients—**Roche**'s viral polymerase inhibitors ganciclovir and valganciclovir, a prodrug of ganciclovir—are associated with severe hematological and myelosuppressive side effects.

Despite the potential adverse events, demand for CMV antivirals is on the rise. Ganciclovir and valganciclovir posted combined sales of about \$255 million in 1H08, up 11% from about \$230 million in the same period in 2007.

The new CMV target was identified by Charles Cobbs through studies of the connection between the virus and brain tumors. Cobbs is a scientist at **California Pacific Medical Research Institute** and a neurosurgeon at the **University of California, San Francisco**.

In 2002, Cobbs and colleagues at the **Veteran Affairs Medical Center** found that a high percentage of glioblastoma multiforme (GBM)

tumors were infected with CMV.³ Five years later, Cobbs and a team at the **University of Alabama School of Medicine** found that CMV promoted glioma cell invasiveness by activating an unknown receptor.⁴

In a recent paper in *Nature*, Cobbs and his current team identified the receptor as PDGFR- α .

First, the team infected human embryonic lung fibroblasts with CMV and found that the virus activated PDGFR- α . They obtained similar results in two other cancer cell types—neuro-epithelial glioma cells and human umbilical vein endothelial cells (HUVECs)—indicating that CMV's activation of PDGFR- α is not cell specific.

The group further showed that blocking the receptor with Gleevec imatinib or **ImClone Systems Inc.**'s IMC-3G3, a humanized antibody against PDGFR- α , prevented CMV-induced activation of the receptor.

In human cells with small interfering RNA knockdown of PDGFR- α , and in murine Pdgfr- α knockout cells, the researchers showed that CMV depends on the receptor for viral entry, gene expression, production of infectious virus and activation of a downstream target—phosphoinositide 3-kinase (PI3K)—that ensures long-term virus survival.

Lastly, the team showed that inhibition of PDGFR- α with either its natural ligand (platelet-derived growth factor (PDGF)), Gleevec or IMC-3G3 prevented viral entry into human lung fibroblast cells. Additional studies in human and murine cells identified the viral envelope protein, CMV glycoprotein B, as the receptor's binding partner for viral entry.

Cobbs told *SciBX* these results demonstrate that PDGFR- α is an essential host factor in several stages of CMV's life cycle—and that inhibiting the virus-receptor interaction could be a new strategy to prevent infection in immunocompromised individuals.

One and only?

Companies contacted by *SciBX* agreed with Cobbs that the findings indicate PDGFR- α is an important cellular receptor for CMV. But they said the feasibility of targeting it would depend on whether other receptors play a role in CMV infection.

"CMV is the most prominent virus in organ transplantation and is associated with increased acute and chronic organ rejection," said Reinhard Schweitzer, director of medical marketing (immunology) at **Biotest AG**. He noted that because PDGFR- α is expressed on many cell types, "blocking this receptor may be a feasible strategy for preventing CMV adhesion and invasion."

But Schweitzer added that the effectiveness of blocking PDGFR- α would depend on "whether this specific pathway is the sole one, the dominant one or one of several mechanisms that CMV uses for viral entry."

He said "it would be interesting to learn how the receptor's expression is modulated under the special circumstances that follow organ transplantation," such as long-term immunosuppressive therapy and exposure to a high CMV load from either an infected transplant or reactivation of latent virus in the patient.

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—Reinhard Schweitzer,
Biotest AG

Biotest markets Cytotect, a hyperimmunoglobulin against CMV, in some European countries to treat CMV infection during organ transplantation. The drug is in a Phase III trial to treat CMV during pregnancy. The company expects to complete the trial in 1H09 and has Orphan Drug designation for the indication in the U.S. and EU.

Larry Smith, VP of vaccine research at **Vical Inc.**, said the specificity of PDGFR- α 's role in viral infection was unclear. "Several other CMV receptors have been reported, so targeting this single receptor may not suffice to prevent CMV infection and disease," he said.

These other receptors include dendritic cell-specific intracellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN; CD209) and tumor necrosis factor receptor 1.^{5,6}

In their *Nature* paper, the California Pacific team acknowledged that "these findings do not exclude a potentially important role for other co-receptors during [viral] internalization and expression," but they noted that their findings demonstrate that PDGFR- α is critical to the viral entry process.

Safety first

Even if targeting PDGFR- α is effective in preventing CMV infection in pregnant women and transplant patients, Ronald Moss, Vical's VP of clinical development, questioned the safety of the approach because the target has many functions in cell development. "That raises potential toxicity issues when targeting the receptor or its function in normal healthy subjects who are at risk of CMV infection," he said.

Consequently, he thought a vaccine that uses viral antigens would be a better way to prevent infection than a PDGFR- α inhibitor. "Vaccination of transplant patients prior to immunosuppression and vaccination of CMV-seronegative women of childbearing potential could prevent many of these cases" of CMV, he said.

Vical's DNA vaccine encoding phosphoprotein p65 and glycoprotein B is in a Phase II trial to prevent serious CMV infections in hematopoietic cell transplantation.

Moss noted it might be possible to target PDGFR- α safely in hematopoietic cell transplant recipients for a brief period of time. "But if that were feasible, one would question the advantages of this anticellular strategy compared to the more straightforward antiviral approach" of administering ganciclovir or valganciclovir, he said.

By contrast, Biotest's Schweitzer thinks vaccination is not the best strategy to protect transplant patients from CMV infection. "Active immunization is not a promising strategy in patients under intense

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—Larry Smith, Vical Inc.

immunosuppression," such as that received by transplant patients, he said.

Cobbs said it is too early to assess the potential side effects of targeting PDGFR- α in transplant patients or pregnant women.

But he did not think targeting PDGFR- α —for example, with Gleevec—would pose a threat to these patients.

"Gleevec isn't the first thing you'd want to give to pregnant women," Cobbs said. But he

noted that despite PDGFR- α 's involvement in cellular development, multiple studies have shown that the drug does not appear to harm fetuses.

Cobbs also noted that the drug is well tolerated in normal adults.

Maryam Khotani, patent and licensing counsel in California Pacific's Office of Technology Transfer and Intellectual Property Management, said the side effects of Gleevec and ImClone's mAb "are not any greater or worse than current antiviral therapies for CMV, and we haven't done any dosing studies yet."

Cobbs said his team is conducting *in vivo* studies to confirm their *in vitro* findings. He added that planned studies include elucidating the precise binding mechanism between PDGFR- α and its viral binding partner, CMV glycoprotein B.

Khotani said California Pacific has submitted U.S. and international patent applications for inhibition of the physical interaction between CMV and PDGFR- α and for inhibition of the activation or function of PDGFR- α itself.

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COMPANIES AND INSTITUTIONS MENTIONED

Biotest AG (Xetra:BIO), Dreieich, Germany
California Pacific Medical Research Institute, San Francisco, Calif.
ImClone Systems Inc. (NASDAQ:IMCL), New York, N.Y.
Novartis AG (NYSE:NVS; SWX:NOVN), Basel, Switzerland
Roche (SWX:ROG), Basel, Switzerland
University of Alabama School of Medicine, Birmingham, Ala.
University of California, San Francisco, Calif.
Veteran Affairs Medical Center, Birmingham, Ala.
Vical Inc. (NASDAQ:VICL), San Diego, Calif.