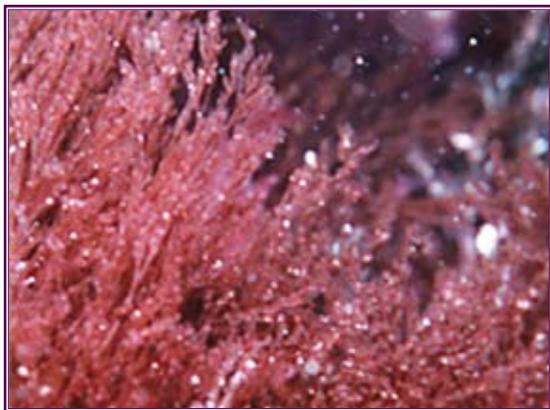


By Land or by Sea:

High-Yield Production of a Marine Anti-HIV Protein in Plants

Photo: D. Newman, NCI Natural Products Repository



Red algae *Griffithsia*, found off the coast of New Zealand, from which the HIV entry inhibitor griffithsin was isolated.

Although biomedical research has led to enormous progress in the prevention and treatment of disease, many would agree that developing countries have not yet reaped proportionate benefits, remaining caught in a cycle of poverty and disease. Drug development aimed specifically at providing medicines to those living in resource-poor areas has its own challenges—especially for the cost-effective production and widespread distribution of antiretroviral therapies to those living with HIV/AIDS.

In 2005, Barry O’Keefe, Ph.D., Associate Scientist in the Molecular Targets Development Program (MTDP) at CCR, and colleagues identified an antiviral protein that they named griffithsin (GRFT) after the red algae from which it was isolated. The research, performed in the MTDP, originated from a marine extract in NCI’s Natural Product Extract Repository (see “The Natural Products Repository: A National Drug Development Resource” in Vol. 2, No. 2 of *CCR connections*), which has collected hundreds of thousands of natural product extracts from around the world.

The ability of GRFT to restrict HIV entry into cells in quantities measured at a trillionth of a gram made it exponentially more potent than other inhibitors studied. The researchers licensed GRFT for prophylactic use against HIV but found that producing this “biologic” drug by the standard method of engineering *E. coli* bacteria to produce it did not yield large enough quantities of GRFT for use as a topical microbicide. So they set out to find a more cost-effective and higher-yield process of manufacturing the protein. Working with collaborator Kenneth Palmer,

Ph.D., and colleagues at the University of Louisville, the team found a solution.

In the April 14, 2009 issue of *The Proceedings of the National Academy of Sciences*, the researchers announced a breakthrough in the scalable manufacture of GRFT using a plant closely related to tobacco, *Nicotiana benthamiana*. They engineered the GRFT gene into tobacco mosaic virus, which they then used to infect the tobacco plants. Once the viral genes integrated into their hosts, the plants produced griffithsin (called GRFT-P). Twelve days after infection, harvest plants yielded about a gram of GRFT-P per plant. The researchers then developed a simple three-step purification process that produced about 99.5 percent pure material.

When tested against a panel of five antibody-based inhibitors of HIV entry, GRFT-P was shown to be effective against all three dominant clades of the virus, whereas each of the antibodies showed inactivity against a certain clade. “And even the most resistant strain to GRFT-P was still more sensitive than the most sensitive strain to any of the other agents,” said Dr. O’Keefe. “The potency is

really through the roof.” In addition, the researchers conducted safety and efficacy studies in animal models and human cervical explants, both with positive results. GRFT-P is also an extremely stable protein and can be shipped to many areas at room temperature without the need for refrigeration, a key advantage in resource-poor areas. It is currently being formulated into small sheets of film that women can use discreetly as an HIV control microbicide. “It’s amazing because you started with something from the ocean and then took it through bacteria, through a virus, and then to one of the oldest medicinally used plants—tobacco—which is now making something that fights HIV,” said Dr. O’Keefe. “And because it’s so temperature stable and such a robust protein, conceivably you can have something like that in a little foil packet on a street corner in Zimbabwe.”

To learn more about Dr. O’Keefe’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=okeefe>.