



T R A N S F O R M

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### **TransForm Discovers New Crystal Forms of HIV Protease Inhibitor Ritonavir**

*Article Published in PNAS Demonstrates TransForm's Expertise in Crystal Form Discovery*

**Lexington, MA, March 4, 2003**, --TransForm Pharmaceuticals Inc., today announced significant research findings that identify new crystal forms of the HIV protease inhibitor, Ritonavir (Norvir®). The work appears in the March 2003 edition of the Proceedings of the National Academy of Sciences (PNAS). Using their novel technology, TransForm's scientists identified several new forms of the well-known drug substance, one of which was a previously unknown polymorph, along with identifying novel, reproducible methods of preparing both the known and novel forms. A summary of the work was presented at the American Chemical Society ProSpectives meeting in February 2003 in Tampa, FL and later this month will be presented in a poster at the American Chemical Society National Meeting in New Orleans, LA.

“This study has further demonstrated the power of TransForm's technology in efficiently resolving a well-publicized problem with the HIV protease inhibitor, Ritonavir,” stated Edward Scolnick, M.D., President Emeritus, Merck Research Labs. “This example illustrates the importance of selecting the best product form the first time around. These findings provide new insights into the science of crystallizing compounds, and provide more opportunity for developing even better drugs or for improving marketed products.”

Ritonavir, an important drug used to treat HIV, garnered much attention in 1998 when a previously unknown, but thermodynamically more stable, polymorph of the drug unexpectedly appeared two years after its launch. This new form had less than 50% of the solubility of the original form, which could not be recovered despite considerable efforts. As a result, the drug failed the dissolution specifications approved by the FDA, and had to be withdrawn from the market pending reformulation of the newly discovered polymorph.

In their study of the compound, TransForm's scientists identified five forms of Ritonavir, including reported Forms I and II, and the discovery of three new forms, Forms III, IV and V. The scientists found these forms by performing over 2,000 crystallization experiments, utilizing multiple, and sometimes combined, crystallization methods over a six week period using CrystalMax™, TransForm's proprietary high-throughput crystallization system. CrystalMax™ includes proprietary experimental design and execution software, robotic dispensing and handling, high-throughput micro-analysis, and advanced data analysis and mining capabilities. Further details are discussed in the paper titled "*Elucidation of Crystal Form Diversity of the HIV Protease Inhibitor Ritonavir by High-Throughput Crystallization*" by Sherry L. Morissette, Stephen Soukasene, Douglas Levinson, Michael J. Cima, and Orn Almarsson, PNAS March 4, vol. 100, No. 5, pages 2180-2184. The work also appears on line at [www.pnas.org/cgi/doi/10.1073/pnas.0437744100](http://www.pnas.org/cgi/doi/10.1073/pnas.0437744100).

The application of CrystalMax™ represents a significant example of the importance of combining a deep understanding of chemistry with high throughput technology that enables reliable screening of polymorphs to select the most suitable solid form of a drug candidate for development. TransForm's ability to quickly and comprehensively identify the diversity of solid forms of a drug or drug candidate can have significant advantages in managing the product life cycle and in strengthening intellectual property protection.

"TransForm's high-throughput technology empowers its scientists to push the envelope in crystallization, and to explore a much broader experimental space than was previously possible," stated Michael Zaworotko, Ph.D., Professor and Chair, Department of Chemistry, University of South Florida in Tampa, Florida. "High-throughput screening is a significant complement to good chemistry. As the TransForm Ritonavir study demonstrates, the risk of failing to invest appropriately in this area can be significant and unforeseen, while the benefits can be considerable."

### **About TransForm**

TransForm is reinventing the pharmaceutical industry's approach to form and formulation, with a novel set of high-throughput, automated platform technologies, powered by state-of-the-art informatics and a scientific and managerial team with deep experience in pharmaceuticals. It uses these capabilities to optimize drug form and/or formulations, and increase the clinical and commercial value of pharmaceutical products, across the entire pharmaceutical value chain. In research and development, TransForm is working with partners such as Alza Corporation and Lilly, to help them make better candidate selection decisions, and reduces attrition and development time and cost. For later stage and marketed products, TransForm can help partners enhance product life cycle management by rapidly discovering novel forms and/or formulations to potentially improve bioavailability, broaden intellectual property protection and enable new dosage forms and/or combination products.

TransForm is also using these capabilities to develop its own proprietary product portfolio. TransForm, founded in late 1999 with initial technology from Millennium Pharmaceuticals (NASDAQ:MLNM), is a privately held company located in Lexington, Massachusetts. For more information, please visit our website at [www.transformpharma.com](http://www.transformpharma.com).