Cell Journals Publishes BeyondSpring's New Data on Mechanism of Plinabulin to Mature Dendritic Cells, Leading to T-Cell Activation

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Novel Findings Published in Peer-Reviewed Cell Journals Chem and Cell Reports

NEW YORK, Oct. 08, 2019 (GLOBE NEWSWIRE) -- BeyondSpring Inc. (NASDAQ: BYSI), a global biopharmaceutical company focused on the development of innovative immuno-oncology cancer therapies, today announced that Cell Press publications *Chem* and *Cell Reports*, two peer-reviewed scientific journals, published new data that sheds light on the mechanism of action (MoA) of the Company's lead Phase 3 asset, Plinabulin, being developed in parallel for the treatment of cancer and prevention of chemotherapy-induced neutropenia.

In the *Chem* article, titled, "Structure, Thermodynamics and Kinetics of Plinabulin Binding to Two Tubulin Isotypes," [1] researchers utilizing x-ray crystallography and thermodynamics calculations demonstrated that Plinabulin as a NCE (new chemical entity) is differentiated from other tubulin-binding agents in both its binding site and the kinetics of the binding. The research also provides evidence that this binding may explain the beneficial efficacy and superior safety profile found with Plinabulin in the clinic, compared to other agents that bind to a nearby colchicine site in tubulin, such as C4AP (combretastatin-A4) or colchicine.

The lead authors of the *Chem* article include:

- Dr. Andrea Cavalli of Istituto Italiano di Tecnologia (IIT) and University of Bologna
- Dr. Michel Steinmetz of Paul Scherrer Institute (PSI) and the University of Basel
- Drs. Lan Huang, James R. Tonra and G. Kenneth Lloyd of BeyondSpring

In addition to the *Chem* publication, data on Plinabulin's ability to positively affect the body's immune mechanism was published in *Cell Reports*, titled, "GEF-H1 Signaling upon Microtubule Destabilization Is Required for Dendritic Cell Activation and Specific Anti-tumor Responses." [2] The *Cell Reports* article demonstrates that Plinabulin destabilizes microtubule and releases immune defense protein GEF-H1, a critical signaling protein for dendritic cell (DC) maturation, antigen cross-presentation and effective priming of CD8 T cells. In the absence of GEF-H1, anti-tumor immunity is hindered. Researchers noted that, in cancer patients, high expression of the GEF-H1 immune gene signature is associated with prolonged survival. Plinabulin is among the most potent tubulin targeted agents for maturing DCs. This highlights Plinabulin's potential as an ideal partner for combination immuno-oncology approaches seeking to overcome the limitations of checkpoints in treating certain cancers. This finding significantly contributes towards BeyondSpring's understanding of the durable anti-cancer effects demonstrated to date in nonclinical and clinical testing with Plinabulin.

The lead authors of the *Cell Reports* article include:

- Dr. Alfred Zippelius of University Hospital Basel and University of Basel
- Dr. Hans-Christian Reinecker of Massachusetts General Hospital, Harvard Medical School
- Dr. Abhishek Kashyap of University Hospital Basel and University of Basel and Massachusetts General Hospital, Harvard Medical School
- Dr. Michel Steinmetz of PSI and the University of Basel

"This journey from the 'bedside' back to the 'benchside' to uncover Plinabulin's mechanism represents more than five years of international collaborative work with leading institutions. We are grateful to our collaborators and this important recognition by the scientific community that Plinabulin is a first-in-class clinical asset for cancer treatment through an important immune mechanism," said Dr. Lan Huang, Chairman and Chief Executive Officer, BeyondSpring. "As a trained structural biologist, I am delighted to see another example where novel structure and novel binding

create a foundation for novel function. These papers validate our understanding of the mechanism of Plinabulin, which played a crucial role in selecting mechanism-targeted patients for our Phase 3 NSCLC study and providing a rationale for all of our clinical studies. This data confirms our understanding of Plinabulin's MoA, and combined with our clinical approach, we believe it can potentially increase our chances of success."

References:

1. La Sala, G, Olieric, N, Sharma, A, Viti, F, de Asis Balaguer Perez, F, Huang, L, Tonra JR, Lloyd GK, Decherchi, S, Diaz, JF, Steinmetz, MO and Cavalli, A (2019) Structure, Thermodynamics, and Kinetics of Plinabulin Binding to Two Tubulin Isotypes. *Chem* 5:1-18. https://www.cell.com/chem/fulltext/S2451-9294(19)30391-2

2. Kashyap, AS, Fernandez-Rodriguez, L, Zhao, Y, Monaco, G, Trefny, MP, Yoshida, N, Martin, K, Sharma, A, Olieric N, Shah, P, Stanczak, M, Kirchhammer, N, Park, S-M, Wieckowski, S, Laubil, H, Zagani, R, Kasenda, B, Steinmetz, MO, Reinecker, H-C and Zippelius, A (2019) GEF-H1 Signaling upon Microtubule Destabilization Is Required for Dendritic Cell Activation and Specific Anti-tumor Responses. *Cell Reports* 28: 3367-3380. https://www.cell.com/cell-reports/fulltext/S2211-1247(19)31105-2

About BeyondSpring
BeyondSpring is a global, clinical-stage biopharmaceutical company focused on the development of innovative immuno-oncology cancer therapies. BeyondSpring's lead asset, Plinabulin, is in a Phase 3 global clinical trial as a direct anticancer agent in the treatment of non-small cell lung cancer (NSCLC) and two Phase 3 clinical programs in the prevention of chemotherapy-induced neutropenia (CIN). BeyondSpring has strong R&D capabilities with a robust pipeline in addition to Plinabulin, including three immuno-oncology assets and a drug discovery platform using the ubiquitination degradation pathway. The Company also has a seasoned management team with many years of experience bringing drugs to the global market.

About Plinabulin
Plinabulin, BeyondSpring's lead asset, is a marine-derived small molecule that sequesters tubulin heterodimers in a differentiated manner from other agents in this class. Plinabulin is currently in late-stage clinical development to increase overall survival in cancer patients, as well as to alleviate chemotherapy-induced neutropenia (CIN). The anticancer benefits of Plinabulin have been associated with positive effects on antigen presenting cells and T-cell activation, as well as to the direct killing of cancer cells. Plinabulin's CIN data highlights the ability to positively affect the number of hematopoietic stem / progenitor cells (HSPCs), or lineage-/cKit+/Sca1+ (LSK) cells in mice. Effects on HSPCs could explain the ability of Plinabulin to not only treat CIN but also to reduce chemotherapy-induced thrombocytopenia and increase circulating CD34+ cells in patients.

Cautionary Note Regarding Forward-Looking Statements
This press release includes forward-looking statements that are not historical facts. Words such as "will," "expect," "anticipate," "plan," "believe," "design," "may," "future," "estimate," "predict," "objective," "goal," or variations thereof and variations of such words and similar expressions are intended to identify such forward-looking statements. Forward-looking statements are based on BeyondSpring's current knowledge and its present beliefs and expectations regarding possible future events and are subject to risks, uncertainties and assumptions. Actual results and the timing of events could differ materially from those anticipated in these forward-looking statements as a result of several factors including, but not limited to, difficulties raising the anticipated amount needed to finance the Company's future operations on terms acceptable to the Company, if at all, unexpected results of clinical trials, delays or denial in regulatory approval process, results that do not meet our expectations regarding the potential safety, the ultimate efficacy or clinical utility of our product candidates, increased competition in the market, and other risks described in BeyondSpring's most recent Form 20-F on file with the U.S. Securities and Exchange Commission. All forward-looking statements made herein speak only as of the date of this release and BeyondSpring undertakes no obligation to update publicly such forward-looking statements to reflect subsequent events or circumstances, except as otherwise required by law.

Media Relations:
Caitlin Kasunich / Amrita Singh
KCSA Strategic Communications
212.896.1241 / 212.896.1207
ckasunich@kcsa.com / asingh@kcsa.com

Investor Relations:
Stephen Kilmer
646.274.3580
stephen.kilmer@beyondspringpharma.com

Source: BeyondSpring, Inc.