New Drugs for the Treatment of Lymphoma

Luca Paoluzzi, MD[a], Yukiko Kitagawa, MD[a], Matko Kalac, MD[a], Jasmine Zain, MD[b], Owen A. O'Connor, MD, PhD[b,*]

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During the last decade the development of new drugs for the treatment of hematologic malignancies has come of age. Historically, most drugs developed for treatment of leukemias, lymphomas, and myeloma had already been proven in the solid tumor setting; rarely did the pharmaceutical industry set out to develop a new drug for a hematologic malignancy. This pattern changed when the drug imatinib showed that it was possible to nullify the pathognomic genetic lesion in chronic myelogenous leukemia (CML). Since the approval of imatinib for CML, a host of new drugs have emerged, some of which have a monofocal emphasis in the hematologic malignancies. Some of these drugs represent first-in-class molecules targeting unique biology influenced by conventional agents. Some are promising new chemical platforms modeled after more traditional agents, with the hope of improved efficacy and tolerability. Drugs such as bortezomib, vorinostat, thalidomide, and clofarabine have emerged as agents with proven activity in myeloma, mantle cell lymphoma (MCL), cutaneous T-cell lymphoma, and T-cell lymphoblastic leukemia. Despite their effects on a target theoretically important across many types of cancer, these agents have proven to have minimal activity in the solid tumors. Drugs targeting unique disease-specific pathways also have found potential applicability in treating malignancies such as CML (nilotinib), CD20-positive non-Hodgkin's lymphoma (NHL) (rituximab), follicular lymphoma (Bcl-2-targeted agents), and other B-cell neoplasia (splenic tyrosine kinase [Syk] inhibitors; IkB kinase inhibitors). Finally, many new drugs that represent improvements over older

[a] Herbert Irving Comprehensive Cancer Center, Columbia University, 1130 St. Nicholas Avenue, Room 216, New York, NY 10032, USA
[b] Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, The New York Presbyterian Hospital, Columbia University, 1130 St. Nicholas Avenue, Room 216, New York, NY 10032, USA
* Corresponding author. Lymphoid Development and Malignancy Program, Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons, The New York Presbyterian Hospital, Columbia University, New York, NY.
E-mail address: oo2130@columbia.edu (O.A. O'Connor).

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established agents have come of age, such as pralatrexate (a methotrexate derivative) in T-cell lymphoma, clofarabine (a nucleoside analogue) in T-cell acute lymphoblastic leukemia, lenalidomide (a new-generation immunomodulatory drug related to thalidomide) in myeloma and myelodysplastic syndrome, carfilzomib (a new-generation proteasome inhibitor) in myeloma, and a host of histone deacetylase inhibitors (mechanistically similar to vorinostat) in peripheral T-cell lymphoma, Hodgkin's disease, cutaneous T-cell lymphoma, and other hematologic malignancies. These examples demonstrate a new understanding that the hematologic malignancies are a fertile and productive arena for the development of innovative treatment strategies.

This article highlights some of these areas of innovative drug development, when possible emphasizing the biologic basis for the platform and linking this essential biology to the biochemical pharmacology. The article focuses on the many new targets including Syk, Bcl-2, and the phosphoinositide-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (**Table 1**).

Table 1
Examples of novel targeted approaches for the treatment of lymphoma

Mechanism	Drugs	Rationale
Inhibit antiapoptotic Bcl-2 family members	ABT-737/263 AT-101 GX015- Oblimersen	Silence the anti-apoptotic influence of Bcl-2, Bcl-xl, Bcl-w, and Mcl-1
Modulate proapoptotic family members and BH3-only proteins	Proteasome inhibitors (Bortezomib, PR-171)	Up-regulating derepression of pro-apoptotic family members will lead to induction of programmed cell death
Down-regulate cyclin D1 and related isoforms	Cyclin D1 antisense (ASDON) Histone deacetylase inhibitors (SAHA)	Down-regulating cyclin D1 and related isoforms will decrease the driving force for cells to transition from G1 into S phase, producing cell-cycle arrest
Increase cell-cycle–dependent kinase inhibitors such as p27/p21	Proteasome inhibitors HDACI	A relative increase in Cdk inhibitors will provide the "breaks" in cell-cycle proliferation, inducing cell cycle arrest
Inhibit pan–cell-cycle–dependent kinases	Flavopiridol AG-024322	Induce cell-cycle arrest
Inhibit selective cell-cycle–dependent kinases	PD-0332991 (cdk4/6) CINK4 (cdk4/6) Seliciclib (cdk2/1) BMS-387,032 (cdk2/1) PNU-252,808 (cdk2/1) PNU-252,808 (cdk2/1) NU6102, NU6140 (cdk2/1)	Inhibit specific phase transitions of cell-cycle progression
Inhibit protein translation and signaling pathways mediated through tyrosine kinase receptors and Ras	mTOR inhibitors (most derived from rapamycin, including temsirolimus), AKT inhibitor	Associated with a broad effect on cancer cell biology, including translation, NF-kB, transcription factors, and apoptosis