BMB
reports

Mini Review

A new paradigm for cancer therapeutics development

*Soo-Youl Kim**

Cancer Cell & Molecular Biology Branch, Division of Cancer Biology, Research Institute, National Cancer Center, Goyang 410-769, Korea

The number of cancer patients has increased due to longer life spans and treatment has become a universal problem. Since molecular-targeted therapies were introduced as a new developmental strategy, certain targets have been examined hundreds of times, with developers overlapping their research efforts. We need to focus our energy and resources on novel drug candidate identification and optimization, in order to enhance the entry of early-stage drug candidates into the therapeutics pipeline. This presents a major opportunity for Korea to jump the decades-old development gap between our programs and those that are more advanced in other countries. Although this country does not have a specific center for validation and development of cancer therapeutics, we do have cutting-edge scientists performing research in many institutions. In this paper, I will review cancer drug development in Korea and suggest future directions, while urging colleagues to utilize their networking expertise so we can move toward a new paradigm of novel therapeutics development. An example of such efforts has begun with the Drug Development Consortium, which was described in the KSBMB chapter. This consortium was launched in 2010 by biochemists, chemists, cell and molecular biologists and pharmacologists. It is clear that effective cancer therapeutics will be developed more efficiently when we all strive for the same goal. [BMB reports 2010; 43(6): 383-388]

Early drug discovery

Every day we are presented with information about cancer and the threat it poses to our individual survival. Although anti-cancer therapies have improved patient survival, drug cytotoxicity has left painful memories of high failure rates and severe side effects along the route of drug development. In recent decades, targeted therapy has been widely accepted as the best approach to drug development, and candidates such as Herceptin (Her2 target, FDA approved in 1998) have achieved a global market with high clinical success rates and reduced side effects (1, 2) (Table 1).

Can you develop therapeutic drugs from the initial discovery of a novel molecule all the way through the pipeline to its eventual use in patients? If you have a large enough budget to drive your own idea from discovery to clinical trial, what kind of output can you expect? Haven't we all wondered why it has taken 40 years to develop Taxol (3) and 20 years for geldanamycin (4) Can we produce new cancer therapeutics in 5 years without knowing why global leaders require such a long drug development time? Novel targets require time for validation prior to clinical trials, which always end in a 'Yes' or 'No', without revision of the process during the trial. Thus, it is financially prudent to obtain as much in vitro data as possible for an efficient decision-making process.

When introducing a process for driving a drug candidate down the development pipeline, I would recommend that investigators start with novel targets. It is best to examine the value of a target via inhibition, using gene knockdown, knockout mice or siRNA treatments, prior to for screening target-specific inhibitors. Once screening has identified lead compounds, acute toxicity must be performed to determine the appropriate dosages to be examined. Next, candidate efficacy should be tested in different cell lines and animal models, including the hollow fiber assay and xenograft models. These examinations will determine where the greatest therapeutic benefits can be achieved with respect to type of cancer being treated and population of patients selected for study. *In vitro* validation platforms were introduced approximately two decades ago and are used commonly in the targeted-therapy process.

In the United States, the National Cancer Institute (NCI) uses a systemized development process for therapeutics. In April 1990, *in vitro* cell line screening was implemented in a fully operational form and it was followed by the *in vitro* cell line screening project (5-7). This project was designed to screen the potential anti-cancer activity of up to 3,000 compounds per year. The screen utilizes 60 different human tumor cell lines (NCI-60) representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate and kidney. The purpose is to identify synthetic compounds or natural products that show selective growth inhibition or cell killing activity, in particular tumor cell lines, and then to perform further evaluations of these compounds. Among the 60 cell lines in the screen, 12 were selected for the Hollow Fiber assay (8), which saves time and resources associated with animal experiments. In brief, a cell suspension is flushed into 1 mm (internal diam-

*Corresponding author. Tel: 82-31-920-2221; Fax: 82-31-920-2006;
E-mail: kimsooyoul@gmail.com

Received 23 May 2010

Keywords: Cancer therapeutics, Drug development

Table 1. Targeted drug list (Data monitor 2006)

Brand	Drug	Company	Class	Model of action	Approved indications	Year of first approval	Company reported sales in 2006 ($m)
Avastin	Bevacizumab	Genentech/Roche	Angiogenesis inhibitor	VEGF inhibitor (MAb)	Colorectal cancer, NSCLC,breast cancer	2004	$2,440
Erbitux	Cetuximab	ImClone Systems/ BMS/Merck Serono	Single-target signal transduction inhibitor	EGFR inhibitor cMAb	Colorectal cancer, head & neck cancer	2003	$1,100
Gleevec	Inmatinib	Novartis	Single-target signal transduction inhibitor	Abl TK inhibitor	CML, ALL, GIST	2001	$2,550
Herceptin	Trastuzumab	Genentech/Roche	Single-target signal transduction inhibitor	Her2 (ErbB2) inhibitor (cMAb)	Breast cancer	1998	$3,200
Iressa	Gefitinib	AstraZeneca	Single-target signal transduction inhibitor	EGFR TK inhibitor	NSCLC	2002	$237
Tarceva	Erlotinib	OSI/Genentech/ Roche	Single-target signal transduction inhibitor	EGFR TK inhibitor	NSCLC, pancreatic cancer	2004	$672
Targretin	Bexarotene	Ligand Pharmaceuticals	Single-target signal transduction inhibitor	Activator of retinoid X receptor subtypes	CTCL	1999	$9.9
Torisel	Temsirolimus	Wyeth	Single-target signal transduction inhibitor	mTOR inhibitor	RCC	2007	n/a
Vectibix	Panitumumab (ABX-EGF)	Amgen	Single-target signal transduction inhibitor	EGFR inhibitor (hMAb)	CRC	2006	$39
Nexavar	Sorafenib	Onyx/ Bayer schering	Multi-targeted inhibitor	PDGFR family, Flt-3, Kit, RET family, VEGFR2, VEGFR3, and Raf protein kinase family TK inhibitor	RCC	2005	$165
Sprycel	Dasatinib	Bristol-Myers Squibb	Multi-targeted inhibitor	Abl, Fyn, Src, Lck TK inhibitor	ALL, CML	2006	$25
Sutent	Sunitinib	Pfizer	Multi-targeted inhibitor	Flt-3, Kit, VEGFR2 and PDGF TK inhibitor	RCC, GIST	2006	$219
Tykerb	Lapatinib	GlaxoSmithKline	Multi-targeted inhibitor	EGFR & ErbB2 TK inhibitor	Breast cancer	2007	n/a
Velcade	Bortezomib	Millennium Pharmaceuticals	Cell cycle and apoptosis targeted agent	Reversible ubiquitin proteosome and nuclear factor kappa B inhibitor	MM, MCL	2003	$221
Zolinza	Vorinostat (SAHA)	Merck & Co	Epigenetic modulator	HDAC inhibitor	CTCL	2006	$1
Bexxar	Tositumomab	GlaxoSmithKline	Immuno-modulatory/ immuno-conjugated therapeutic	Radio-immuno-ther apeutic B-lymphocyte antigen CD20 modulator	NHL	2003	n/a
Campath/ Mabcampath	Alemtuzumab	Millennium Pharmaceuticals	Immuno-modulatory/ immuno-conjugated therapeutic	CD52 inhibitor (hMAb)	CLL	2001	n/a
Mylotarg	Gemtuzumabn ozogamicin	Wyeth Research	Immuno-modulatory/ immuno-conjugated therapeutic	CD33 directed immunotoxin (hMAb)	AML	2000	n/a
Ontak	Denileukin difitox	Ligand Pharmaceuticals	Immuno-modulatory/ immuno-conjugated therapeutic	Immuno-toxin IL-2 antagonist	CTCL	1999	$17
Rituxan/ MabThera	Rituximab	Biogen Idec/ Genentech/Roche	Immuno-modulatory/ immuno-conjugated therapeutic	B-lymphocyte antigen CD20 modulator (cMAb)	NHL (& RA)	1997	$4,800

eter) polyvinylidene fluoride hollow fibers with a molecular weight exclusion of 500 kDa. Three different tumor lines are prepared for each experiment and each mouse receives 3 intra-peritoneal implants (1 from each tumor line). Following fiber implantation, mice are treated daily with experimental agents and, on the day following the fourth treatment, fibers are collected and subjected to the stable endpoint MTT assay (Fig. 1).

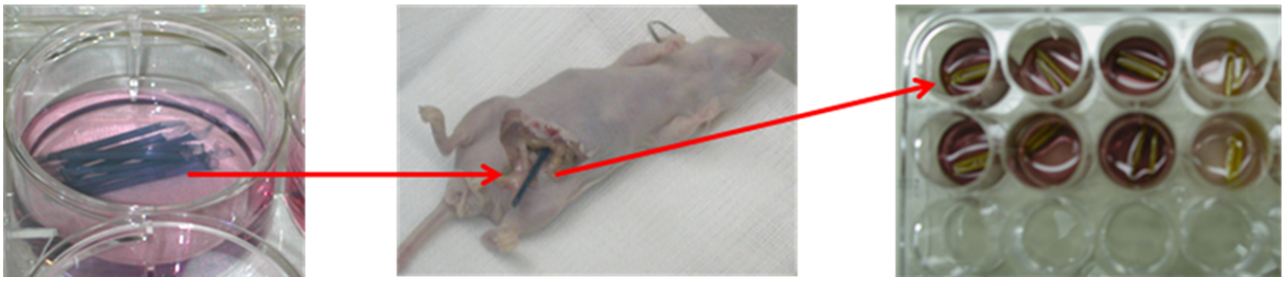

Fig. 1. Hollow fiber assay. Hollow fibers are implanted in mouse after filled with cancer cells. Fibers are collected and subjected to the MTT assay after treatment of anti-cancer drug candidates (photographed by Dr. Jaeheon Jeong).

For potentially cytotoxic anti-cancer agents to advance from the identification stage, through *in vitro* screens and into clinical development, efficacy must be demonstrated *in vivo* in one or more animal models of neoplastic disease. Following demonstration of activity in the NCI-60 cell line screen and the hollow fiber assay, compounds are examined for distal site anti-tumor activity in appropriate human tumor xenograft models in nude mice or, where relevant, in rodent tumor models. The specific tumor model employed depends on a number of factors including the sensitivity of individual tumor cell lines to the agent. Our group adopted a screening panel that includes 12 cell lines from the stomach and liver, as well as the NCI-60, and this new cell line panel was named NCC72, i.e., National Cancer Center 72. The Hollow fiber assay was established using 18 NCC cell lines and we have tested many xenograft models with drug candidates. For Korea, NCC represents the most efficient drug evaluation platform for cytotoxic and targeted therapies (Fig. 2).

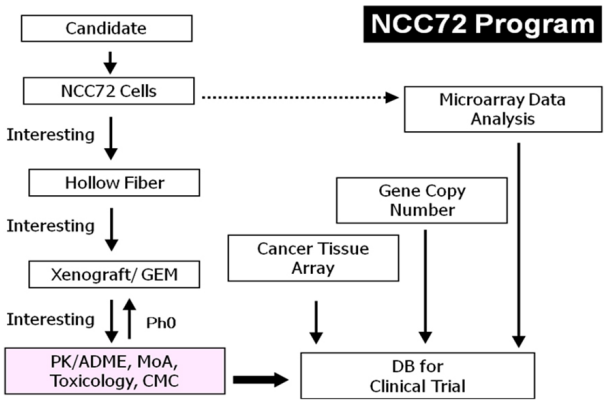

Fig. 2. The NCC72 program is being constructed by NCC pioneers including Drs. Hark-Kyun Kim, Kyeong-Man Hong, Seung-Hyun Oh, Seok-Hyun Kim, Yong-Nyun Kim, Chang-Hun Lee, Hye-Jin You, Sunshin Kim, Ho Lee and Soo-Youl Kim. This panel includes 12 cell lines from the stomach and liver, as well as the NCI-60 cell lines.

A new development process paradigm in the USA

The US Government drives the Developmental Therapeutics Program (DTP), which has played an important role in the discovery or development of 40 U.S.-licensed chemotherapeutic agents. On that list, paclitaxel is one of the most widely prescribed anti-cancer drugs on the market (9). Paclitaxel was first harvested by researchers with a National Cancer Institute (NCI) grant. A DTP contractor also formulated the drug for use in clinical trials. The DTP has been involved in the discovery or development of more than 70 percent of anti-cancer therapeutics on the market today. Although many academic and private-industry laboratories also are focused on drug discovery, financial and technical burdens, as well as lack of funding and infrastructure, present barriers that may keep promising therapeutic agents from reaching patients. The DTP successfully overcame therapeutic development barriers by supporting "high-risk" projects. The NCI's DTP is renowned for its success in taking late-stage preclinical drug candidates through the final steps of pre-clinical development and into initial clinical studies. To advance the NCI's mission of bringing novel therapies to patients, and to fully exploit NCI's expertise in the later stage of preclinical development, the Institute is now focusing efforts and resources on drug candidate identification and optimization to enhance the entry of early-stage drug candidates into the NCI therapeutics pipeline.

According to the NCI, "there is an undisputed need for shorter drug development timelines, enhanced molecular targeted drug discovery, and more streamlined processes to assess anti-cancer drug action. Determination of safety, efficacy, and mechanism of action *in vivo*, should occur early in the drug development cycle and a process should be established to provide a rigorous, more effective, scientific basis for selecting potential clinical indications for new oncologic drugs. Recognizing these needs, the NCI is adopting a new strategic approach that focuses on identifying novel molecular targets and new molecules that exploit those targets to support the construction of an enhanced and robust drug discovery and development pipeline. This initiative is the new NCI-supported Chemical Biology Consortium; its goals are to "accelerate the

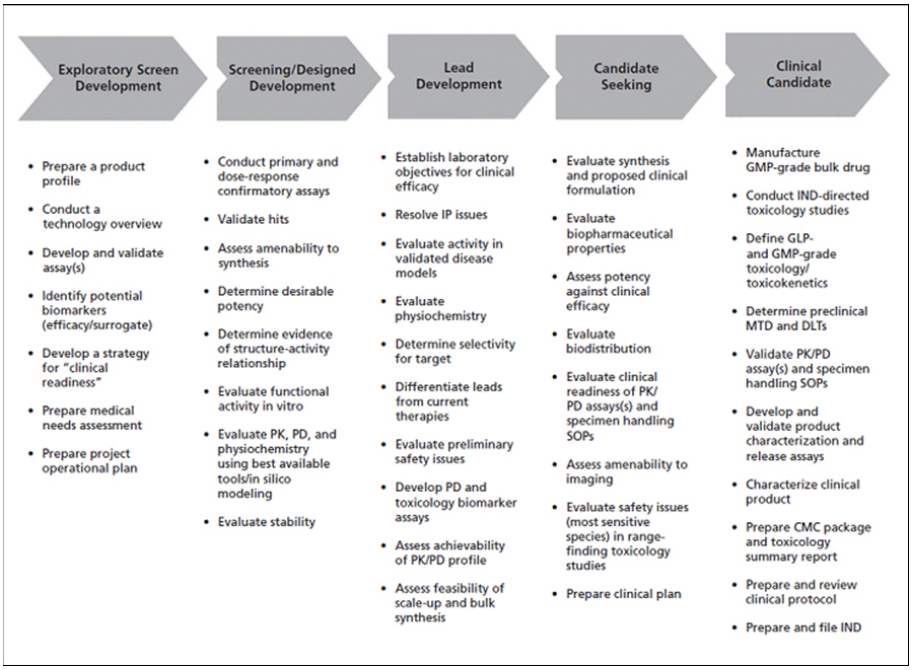

Fig. 3. CBC has 5 entry Gates. The Stage Gates represent milestones for the progression of a project through to the Execution Phase. The Stage Gates and accompanying Discovery Guidelines are blueprints for discovery projects to guide and inform discussions about the project as it progresses.

Discovery and Development of effective first-in-class targeted therapies by providing the proper environment to incubate new discoveries and facilitate their growth into full-scale oncologic drug development projects" (Fig. 3; http://dctd.cancer.gov/CurrentResearch/ChemicalBioConsortium.htm).

Drug development in Korea

Korean drug companies have developed two commercially-available anti-cancer drugs. Belotecan is made by CKD and mimics camtothecin-presenting topoisomerase I inhibitor activity (10). In 2003, belotecan was approved by the KFDA for ovarian cancer and NSCLC, and it was licensed to Johnson & Johnson. In 2007, Korea had approximately 10 candidates in clinical phases I & II, 15 candidates in the pre-clinical phase, and 20 candidates in screening. Although most of these candidates are small molecules, there has been an increasing interest in targeted antibodies, to match an expected increase in demand for these types of therapies (Table 1).

Anti-cancer therapies are grouped by treatment method, i.e., chemotherapy, hormonal therapy, immunotherapy and targeted therapy, which includes small molecule and antibody treatments. Targets are grouped by mechanism such as angiogenesis, single-target signal transduction, multi-target signal transduction, cell cycle and apoptosis, immunomodulation, and epigenetic modulators. The most popular targets in drug development number less than 100 and include protein kinases (serine/threonine kinases, receptor tyrosine kinases, non-receptor tyrosine kinases), histone deacetylases (HDAC), protein phosphatases, farnesyl transferase, DNA-methyl transferases, telomerase, matrix metalloproteases, proteasomes, heat shock protein 90, mTOR, integrins, NF-kappaB, bcl-2, PARP, kinesin-like spindle protein, Wnt/beta-catenin, Hedgehog, STAT, toll-like receptors, endothelin receptor, Notch and CXCR4. The targets for antibody therapy are epithelial cell adhesion molecule, MUC-1, EGFR, CD20, carcino-embryonic antigen (CEA), HER2, CD22, CD33, Lewis Y, prostate-specific membrane antigen (PSMA), IGF1R, VEGF, VEGFR2, c-Met, integrin and CTLA-4 (11).

Although targeted therapy increases the risks associated with drug development, it offers a greater success rate than cytotoxic drug development. However, we can expect such development to generate a multitude of therapeutics targeting the same mechanisms, eventually resulting in a poor return on investment. Research into HDAC (histone deacetylase) is a prime example of this redundancy phenomenon. Cancer cells may contain high levels of HDAC to prevent apoptosis and, thus, HDAC inhibitors (HDI) can potentially stop cancer proliferation. HDIs have been shown to alter the activity of many transcription factors, including ACTR, cMyb, E2F1, EKLF, FEN 1, GATA, HNF-4, HSP90, Ku70, NFκB, PCNA, p53, RB, Runx, SF1 Sp3, STAT, TFIIE, TCF and YY1 (12). Interestingly, a patent search identified 354 registrations of HDIs since US FDA approval of Vorinostat (SAHA) for treatment of cutaneous T-cell lymphoma (CTCL; (13). Among these HDI 354 patents, 136 belonged to 10 pharmaceutical companies, including Merck

Table 2. Patents for HDAC inhibitors held by top 10 pharmaceutical companies (2007)

Rank	International patent Company	No. Pat
1	Novartis	29
2	Merck	15
3	Istituto di ricerche di biologia molecolarep angel	14
4	Methylgene INC.	13
5	Janssen pharmaceutica	12
6	Chondrogene limited	8
	Kalypsys INC.	8
8	Sloan kettering institute for cancer research	6
	Astellas pharma INC.	6
10	Astrazeneca	5
	Aton pharma INC.	5
	Board of regents the university of texas system	5
	Hoffmann la roche	5
	Topotarget UK LTD.	5
Total		136

and Novartis (Table 2). Thus, investing in novel drug discovery reduces the risk of developmental redundancy.

Suggestions for future drug development

We need networking among those with the greatest expertise, not more infrastructure, to organize a new drug development system. An integrated network of chemical biologists, molecular oncologists and compound-screening centers from government, academia and eventually from industry, must be established. I would like to call this the Drug Development Consortium (DDC) in Korea. We need to start this type of program immediately and without hesitation. The DDC must be centrally managed by volunteers with experience in developing research groups, to coordinate the selection of targets and screening of agents that interact with those targets. The DDC must use an iterative development process to design and optimize drug hits into lead compounds, explain failed clinical trial results and characterize mechanisms of action. No matter what happens to compounds in the development process, participation in the DDC program would bring the benefits of access to late-stage drug development resources and expertise (Fig. 4).

According to NCI, "CBC program participants will have an unparalleled opportunity to participate in a highly collaborative drug discovery partnership with the drug development group . Using state-of-the-art communication, data-sharing and project management tools, the CBC will effect a paradigm shift in the use of public-private partnerships to translate knowledge from leading academic institutions into ground-breaking new drug candidates for patients with cancer". An example of this type of program was launched in the U.S.A. in August 2009,

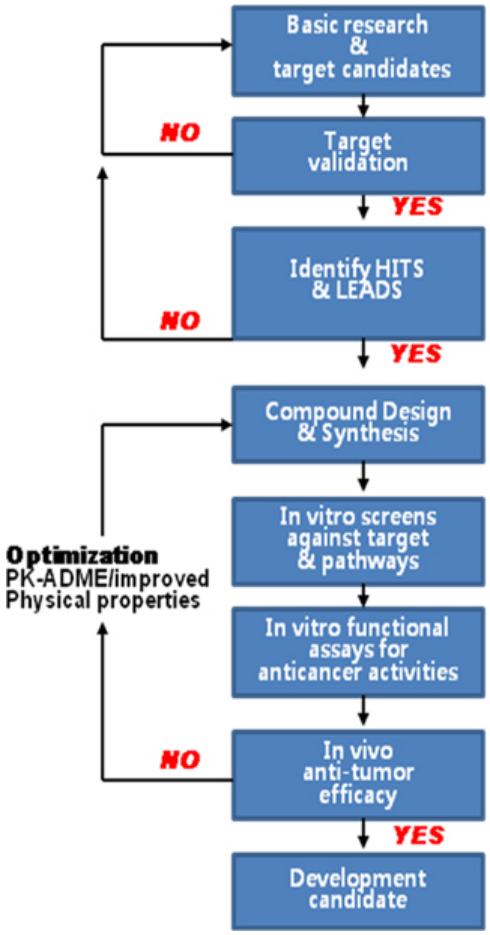

Fig. 4. The suggested function of Drug Development Consortium (DDC). We have multiple funding programs and projects supporting drug development. However, there are no funding sources or centers to incubate failed projects. To overcome the hurdles of novel therapeutics development, we need to access resources that support problem identification, as well as finding professional and efficient solutions to setbacks.

and billions of dollars have been invested in the CBC initiative (CBC, Fig. 3).

Acknowledgements

This work was supported by a research grant (NCC0810181) from the National Cancer Center in Korea.

REFERENCES

1. Slamon, D. and Pegram, M. (2001) Rationale for trastuzumab (Herceptin) in adjuvant breast cancer trials. *Semin. Oncol*. **28**, 13-19.
2. Sawyers, C. L. (2008) The cancer biomarker problem. *Nature* **452**, 548-552.
3. Kavallaris, M. (2010) Microtubules and resistance to tubu-

lin-binding agents. *Nat. Rev. Cancer* **10**, 194-204.
4. Fukuyo, Y., Hunt, C. R. and Horikoshi, N. (2010) Geldanamycin and its anti-cancer activities. *Cancer Lett.* **290**, 24-35.
5. Bates, S. E., Fojo, A. T., Weinstein, J. N., Myers, T. G., Alvarez, M., Pauli, K. D. and Chabner, B. A. (1995) Molecular targets in the National Cancer Institute drug screen. *J. Cancer Res. Clin. Oncol.* **121**, 495-500.
6. Smith, S. C., Baras, A. S., Lee, J. K. and Theodorescu, D. (2010) The COXEN principle: translating signatures of *in vitro* chemosensitivity into tools for clinical outcome prediction and drug discovery in cancer. *Cancer Res.* **70**, 1753-1758.
7. Monga, M. and Sausville, E. A. (2002) Developmental therapeutics program at the NCI: molecular target and drug discovery process. *Leukemia* **16**, 520-526.
8. Mi, Q., Pezzuto, J. M., Farnsworth, N. R., Wani, M. C., Kinghorn, A. D. and Swanson, S. M. (2009) Use of the in vivo hollow fiber assay in natural products anticancer drug discovery. *J. Nat. Prod.* **72**, 573-580.
9. Martin, V. (1993) Overview of paclitaxel (TAXOL). *Semin. Oncol. Nurs.* **9**, 2-5.
10. Crul, M. (2003) CKD-602. Chong Kun Dang. *Curr. Opin. Investig. Drugs* **4**, 1455-1459.
11. Palazzo, A., Iacovelli, R. and Cortesi, E. (2010) Past, Present and Future of Targeted Therapy in Solid Tumors. *Curr. Cancer Drug. Targets.* **10**, 433-461.
12. Drummond, D. C., Marx, C., Guo, Z., Scott, G., Noble, C., Wang, D., Pallavicini, M., Kirpotin, D. B. and Benz, C. C. (2005) Enhanced pharmacodynamic and antitumor properties of a histone deacetylase inhibitor encapsulated in liposomes or ErbB2-targeted immunoliposomes. *Clin. Cancer Res.* **11**, 3392-3401.
13. Duvic, M. and Vu, J. (2007) Vorinostat in cutaneous T-cell lymphoma. *Drugs Today (Barc)* **43**, 585-599.