Molecular targeted agents—where we are and where we are going

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Abstract

A total of 23 new cancer medicines or indication expansions were approved by the U. S. Food and Drug Administration in 2012. Among these, 12 are new molecular entities (NMEs)—new chemical or biological drugs approved for the first time for oncologic use—and 10 of these NMEs are molecular targeted agents. Among the 10 targeted agents, 4 are anti-angiogenesis agents and 2 are Bcr-Abl pathway inhibitors, targeting well established targets validated by previously approved agents such as bevacizumab (Avastin) or imatinib (Gleevec). Despite this progress, several questions remain: Do these newly approved agents provide sufficient treatment options to manage the broad spectrum of cancers we deal with in the clinic? Where will the next wave of new cancer drugs come from? Where should R&D efforts be invested to continue improve cancer treatment and management, especially for tumor types uniquely prevalent in China? This editorial and the review articles in this special issue of Chinese Journal of Cancer provide an in depth review of the progress and challenges in developing targeted cancer therapies, as well as an outlook of new research areas where near term breakthroughs are expected to overcome some of these challenges.

Key words Targeted agents, cancer

Based on the U.S. Food and Drug Administration (FDA) hematology/oncology approvals and safety notifications, 23 new cancer medicines or indication expansions were approved in 2012 (Table 1). Among these, only 12 are qualified as new molecular entities (NMEs)—new chemical or biological drugs approved for the first time for oncologic use. Furthermore, only 10 are molecular targeted agents. Two molecular targeted drugs that either attack a novel pathway or employ a new means to attack a known pathway are highlighted here.

New Agents That Target New Pathways or Have Novel Mechanisms of Action

Vismodegib (Erivedge)—smoothened receptor inhibitor of sonic hedgehog (SHH) signaling

Vismodegib, an inhibitor of smoothenened receptor, was discovered by Curis, a small biotech company in Cambridge, Massachusetts, USA, and developed by Roche/Genentech. It is the first compound targeting the sonic hedgehog (SHH) signaling pathway in cancer. The approved indication, basal cell carcinoma (BCC), is a small indication. However, the most convincing biological and preclinical evidence has been observed in BCC with a high frequency of mutations in PTCH1 or SMO, making BCC uniquely sensitive to SHH inhibitors. The approval was based on a single, international, single-arm, multi-center, open-label, 2-cohort trial conducted in 104 patients with either metastatic BCC (n = 33) or locally advanced BCC (n = 71). Treatment with 150 mg vismodegib per day orally resulted in objective response rate of 30% in patients with metastatic BCC and 43% in patients with locally advanced BCC, with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts[1]. On the other hand, SHH pathway antagonists have failed to show significant clinical activity in other solid tumors. This is likely because of a limited understanding of whether the SHH pathway functions as a key tumor driver in these other tumor types as it does in BCC.

Pertuzumab (Perjeta)—inhibitor of HER2 dimerization

HER2 pathway inhibition has been validated by the effectiveness of trastuzumab (Herceptin) as an effective means to treat patients with HER2-positive breast
### Table 1. Oncologic drugs and Indications approved by the U.S. Food and Drug Administration in 2012

| Generic name       | Trade name | Mechanism of action                                                                 | Indication(s)                                                                                     | Approval date     | Manufacturer               |
|--------------------|------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------|---------------------------|
| Glucarpidase       | Voraxaze   | Toxic plasma methotrexate concentrations (>1 μmol/L) in patients with delayed        | Enzymatic inactivation of methotrexate                                                             | January 17, 2012  | BTG International Inc.    |
|                    |            | methotrexate clearance due to impaired renal function                               |                                                                                                  |                   |                           |
| Axitinib           | Inlyta     | Advanced renal cell carcinoma after failure of one prior systemic therapy           | Multiple TKI-VEGFR1/2/3, PDGFR, c-kit                                                            | January 27, 2012  | Pfizer                    |
| Vismodegib         | Erivedge   | Locally advanced or recurrent basal cell carcinoma                                  | Smoothened receptor inhibitor (hedgehog signaling)                                              | January 30, 2012  | Roche/Genentech/Curis     |
| Imatinib mesylate  | Gleevec    | Adjuvant treatment of adult patients following complete gross resection of Kit (CD117)-positive gastrointestinal stromal tumors (GIST); Label expansion to adjuvant treatment of GIST to 36 months | Multiple TKI-Bcr-Abl, c-kit, PDGFR-R                                                             | January 31, 2012  | Novartis                  |
| Everolimus         | Affinitor  | Renal angiomyolipoma (Tubular sclerosis complex-associated)                          | mTORi                                                                                           | April 26, 2012    | Novartis                  |
| Pazopanib          | Votrient   | Advanced soft tissue sarcoma patients who have received prior chemotherapy          | Multiple TKI-VEGFR1/2/3, PDGFR-a/b, c-kit                                                        | April 26, 2012    | GlaxoSmithKline           |
| Pertuzumab         | Perjeta    | Combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease | Anti-HER2-Inhibition of HER2 dimerization                                                       | June 8, 2012      | Roche/Genentech/Curis     |
| Cetuximab          | Erbitux    | Combination with FOLFIRI in first-line treatment of K-RAS mutation-negative (wild type), EGFR-expressing metastatic colorectal cancer | Anti-EGFR                                                                                       | July 9, 2012      | Eli Lilly/ImClone         |
| Carfilzomib        | Kyprolis   | Relapsed and refractory multiple myeloma                                            | Irreversible inhibition of 20S proteasome                                                        | July 20, 2012     | Onyx                      |
| Everolimus         | Affinitor  | Combination with exemestane in the treatment of hormone receptor-positive, HER2-negative breast cancer after failure of letrozole or anastrozole | mTORi                                                                                           | July 20, 2012     | Novartis                  |
| Ziv-aflibercept    | Zaltrap    | Combination with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) in the treatment of metastatic colorectal cancer resistant/progressed following an oxaliplatin-containing regimen | VEGF inhibitor (VEGF-A, VEGF-B, and PIGF)                                                       | August 3, 2012    | Regeneron/Sanofi Aventis  |
| Vincristine sulfate liposome injection | Marqibo    | Philadelphia-chromosome-negative acute lymphoblastic leukemia in second or greater relapse or progressed following two or more anti-leukemia therapies in adults patients | Tubulin inhibitor                                                                                 | August 9, 2012    | Talon Therapeutics         |
| Everolimus         | Affinitor  | Subependymal giant cell astrocytoma (Tubular sclerosis complex-associated)            | mTOR inhibitor                                                                                    | August 30, 2012   | Novartis                  |
| Enzalutamide       | Xtandi     | Metastatic castration-resistant prostate cancer previously treated with docetaxel    | Androgen receptor antagonist                                                                      | August 31, 2012   | Astellas/Medivation Pfizer |
| Bosutinib          | Bosulif    | Chronic, accelerated, or blast phase Philadelphia-chromosome-positive chronic myelogenous leukemia in adult patients | TKI-Bcr-Abl, Src family kinases (Src, Lyn, and Hck)                                              | September 5, 2012  | Pfizer                    |

(To be continued)
Table 1. Oncology drugs and indications approved by the U.S. Food and Drug Administration in 2012 (continued)

| Generic name      | Trade name | Mechanism of Action                                                                 | Indication(s)                                                                 | Approval date       | Manufacturer    |
|-------------------|------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------|-----------------|
| Regorafenib       | Stivarga   | Metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGFR antibody, an anti-HER2 antibody, and, if KRAS wild-type, an anti-EGFR antibody | Dual inhibitor of VEGFR2 and Tie2, antiangiogenesis | September 27, 2012 | Bayer           |
| Paclitaxel, albumin-bound | Abraxane  | Combination with carboplatin for the initial treatment of locally advanced or metastatic non-small cell lung cancer | Albumin-bound paclitaxel, a mitotic inhibitor | October 11, 2012   | Celgene         |
| Pemetrexed        | Alimta     | Label expansion in maintenance setting treatment of locally advanced or metastatic non-small cell lung cancer | Folate antimetabolites           | October 17, 2012   | Eli Lily        |
| Rituximab         | Rituxan    | 90-minute infusion starting at cycle 2 for patients with non-Hodgkin lymphoma who did not experience a grade 3 or 4 infusion-related adverse reaction during cycle 1 | Anti-CD20          | October 19, 2012   | Roche/Genentech |
| Omacetaxine mepesuccinate | Synribo | Adult patients with chronic or accelerated phase chronic myeloid leukemia with resistance and/or intolerance to two or more tyrosine kinase inhibitors | Alkaloid, a protein translation inhibitor | October 26, 2012   | Teva            |
| Cabozantinib      | Cometriq   | Progressive metastatic medullary thyroid cancer                                      | Multiple TKI-RET, MET and VEGFR-2                                           | November 29, 2012   | Exelixis        |
| Abiraterone acetate | Zytiga    | Expanded indication in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer | Androgen receptor antagonist | December 10, 2012 | Janssen Biotech, Inc. |
| Ponatinib         | Iclusig    | Adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia that is resistant to imatinib and/or intolerance to prior tyrosine kinase inhibitor therapy, or Philadelphia-chromosome-positive acute lymphoblastic leukemia that is resistant or intolerant to prior tyrosine kinase inhibitor therapy | Bcr-Abl inhibitor | December 17, 2012 | ARIAD Pharmaceuticals, Inc. |

Source: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
New molecular entities that are conventionally defined as molecular targeted agents are italicized.

cancer. Pertuzumab, however, differs from trastuzumab in how it targets the HER2 pathway. Instead of directly inhibiting HER2 receptor homodimers, pertuzumab binds to the domain of HER2 involved in forming heterodimers, alters its conformation, and blocks binding to other HER family receptors, most notably HER3. Combination of these two HER2-targeting agents provides a complementary and more comprehensive blockade of HER2 signaling and results in greater antitumor activity than either agent alone. In a phase 3 registration trial, 808 patients with HER2-positive metastatic breast cancer were randomized to receive placebo plus trastuzumab plus docetaxel (control group) or pertuzumab plus trastuzumab plus docetaxel (pertuzumab group) as first-line treatment. The median progression-free survival (PFS) was 12.4 months and 18.5 months in the control and pertuzumab groups, respectively [hazard ratio (HR) for progression or death, 0.62; 95% confidence interval (CI), 0.51 to 0.75; P < 0.001]. Interim analysis of overall survival (OS) showed a strong trend in favor of the pertuzumab plus trastuzumab plus docetaxel regimen.

Remaining Challenges

The 23 approvals in 2012 are indeed an appreciable improvement from 18 in 2011 and 11 in 2010. However, the majority of the 10 molecular targeted NMEs approved
Progress in cancer targeted agents

Perspectives on Upcoming Breakthroughs in Anti-Cancer Therapy

Based on a review of active clinical development programs, some of the next wave of breakthroughs in oncology treatment are expected from the following areas in the near future.

Cancer immunotherapy

Immunotherapy turns off the inhibitory mechanism employed by tumor cells to evade host immuno-surveillance and restores the ability of cytotoxic T cells to destroy cancer cells. Cancer immunotherapy includes vaccines, adoptive T-cell transfer, immune cytokines, and immunomodulators, including check point antagonists such as cytotoxic T lymphocytes antigen 4 (CTLA-4) and programmed cell death protein 1 (PD1) or PD1 ligand (PDL1) inhibitors. The first major validation in this field occurred when ipilimumab (Yervoy), a monoclonal antibody against CTLA-4, was approved for the treatment of metastatic melanoma in 2011. Presently, multiple antibodies targeting PD1 are in active clinical development with promising data, marking the surge of immuno-oncology.

Early in phase 1 trials, BMS-936558, an anti-PD1 monoclonal antibody, showed promising efficacy with objective responses in 28% of patients with metastatic melanoma, 27% of patients with renal cell carcinoma, and 18% of patients with non-small cell lung cancer (NSCLC)\(^3\). Most importantly, many of the responses were durable, lasting for months to years. Currently, there are more than seven antibodies targeting PD1 or PDL1 in clinical development, with several in phase 3 trials. With encouraging efficacy in early phase clinical trials, these monoclonal antibodies are expected to be expedited through clinical development and to be an effective armament against cancer.

Other promising immunotherapies include the chimeric antigen (CAR) approach, particularly CD19 CAR for treating chronic lymphocytic leukemia (CLL) and lymphoma, and the bi-specific T-cell engagers (BiTEs) approach, including the use of blinatumomab (AMG103; Amgen/MicroMet). Blinatumoab, a bispecific antibody for CD19 x CD3, achieved high rate of complete response in patients with relapsed or refractory acute lymphoblastic leukemia.

Antibody-drug conjugates (ADCs)

The approval of brentuximab vedotin (Adcetris) for relapsed and refractory Hodgkin lymphoma and anaplastic large cell lymphoma in 2011 marks the recovery of ADCs from the market withdrawal of gemtuzumab ozogamicin (Mylotarg). The efficacy shown with trastuzumab emtansine (T-DM1) further validated the ADC approach as both efficacious and tolerable. Among 991 randomly assigned patients with HER2-positive advanced breast cancer, the median PFS was 9.6 months with T-DM1 vs. 6.4 months with lapatinib plus capeci-tabine. Moreover, the median OS at the second interim analysis was 30.9 months vs. 25.1 months in the respective treatment groups. The objective response rate was also higher for T-DM1 (43.6% vs. 30.8%)\(^4\). Under priority review, Kadcyla (T-DM1) was approved for HER2-positive metastatic breast cancer on February 26, 2013.

The success of T-DM1 further rejuvenated efforts in ADC development. There are now seven ADC programs in active clinical development stages for various cancer types at Roche/Genentech alone, with many ADCs being developed by other firms.

Novel inhibitors of critical targets/pathways

Cyclin-dependent kinase (CDK) inhibitors

Inhibitors against CDKs have been intensely studied and developed in various cancer types over the past 20 years, but these agents have shown little efficacy and substantial toxicity. The breakthrough came when PD 0332991 (Pfizer/Onyx), an inhibitor of CDK 4/6, was reported to have significant efficacy in first-line, post-menopausal, estrogen receptor (ER)-positive breast cancer patients. In a randomized phase 2 trial, adding PD 0332991 to letrozole (Femara, Novartis) increased median PFS from 7.5 months to 26.1 months compared
with letrozole alone (HR = 0.37, P < 0.001). ER positivity was the specific biomarker for ER-sensitive patients, independent of progesterone receptor (PR) status. Furthermore, CCND1 amplification and p16 expression were prospectively evaluated, but only ER status was predictive of activity[5].

**Bruton’s tyrosine kinase (BTK)**

BTK is an important cell signaling enzyme in hematopoietic cells such as B-cells. B-cell activation is driven by the B-cell receptor (BCR), and BTK is a crucial part of the BCR signaling pathway. BTK inhibitors act downstream of BCR by blocking BTK activity, thereby inhibiting proliferation, adhesion, and apoptosis in malignant B-cells. Ibrutinib (PCI-32765, Pharmacyclics/Johnson & Johnson) is an orally active, selective, and irreversible small molecule in clinical development in a variety of B-cell malignancies including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma. Robust results were reported in CLL/SLL. With a median follow-up of 17.5 months, PFS in the 420 mg dose cohort was 87.7% in the relapsed/refractory patient population. Moreover, the objective response rate in the 420 mg dose cohort was 81%, which included a 12% complete response rate, in treatment-naive patients age 65 years or older. Recently, Ibrutinib received FDA Breakthrough Therapy designation for MCL and Waldenström’s macroglobulinemia.

**Inhibitors of growth factor receptors and related signaling pathways**

Small and large molecules targeting receptor tyrosine kinases and downstream signaling components are in various stages of clinical development. In this issue, three review articles detail efforts to target insulin-like growth factor receptor (IGF-R)[6], mTOR[7], and the PI3K-AKT pathway[8]. Inhibitors of other pathways such as PARP and EGFR were described in past *Chinese Journal of Cancer (CJC)* issues[9,10].

**Fibroblast growth factor (FGF) and FGF receptor (FGFR)**

FGF/FGFR-mediated signaling drives tumor growth and angiogenesis. FGFR inhibitors have begun to show encouraging clinical outcomes in cancer, including durable partial responses. However, several major challenges of FGFR inhibitor development remain. These include the need to (1) better understand the predictive value of eight genetic alterations in FGFR, including copy number gains, activating mutations, and chromosomal translocations; (2) strategize and incorporate FGFR inhibitors into existing treatment regimens, such as EGFR inhibitor treatment in lung cancer and anti-VEGF therapy in renal cancer, to overcome or prevent FGFR-mediated recurrence or resistance; and (3) match isoform-specific FGFR inhibitors to tumor types exhibiting distinct, isoform-specific mechanisms of FGFR activation, e.g., FGFR1 amplification in breast cancer, FGFR2 amplification in gastric cancer, FGFR2 mutation in endometrial cancer, or FGFR3 mutation in bladder cancer.

**c-MET and hepatocyte growth factor (HGF)**

Because of its role in both tumor growth and metastasis, the MET axis is an attractive target for cancer therapy. Several MET pathway inhibitors are currently being studied, including (1) antibodies that compete and block the binding of HGF to MET, i.e., rilotumumab (AMG 102, Amgen) and ficituzumab (AV-299, AVEO); (2) antibodies that bind to MET, resulting in its degradation and subsequently to its inactivation, i.e., onartuzumab (MetMab, Roche); (3) selective MET receptor kinase inhibitors, e.g., tivantinib (ARQ 197, ArQuE); and (4) nonselective MET kinase inhibitors, e.g., crizotinib (Xalkori, Pfizer; approved for ALK-positive NSCLC due to its ALK inhibitory activity), cabozantinib (XL 184, Cometrix, Exelixis; approved for medullary thyroid cancer), and foretinib (GlaxoSmithKline). Although crizotinib and cabozantinib have been approved in lung and thyroid cancers, the role of MET inhibitors have played in their observed clinical efficacy is inconclusive because these agents are non-selective multi-kinase inhibitors. Furthermore, the phase 3 trials MARQUEE and ATTENTION, which were investigating the selective c-MET inhibitor tivantinib plus erlotinib in NSCLC, were recently discontinued due to lack of efficacy and safety concerns, respectively. The validation of c-MET/HGF pathway inhibition in cancer will have to wait for results from phase 3 trials of rilotumumab in advanced gastric cancer or onartuzumab and ficituzumab in NSCLC.

**New hormone treatments for prostate cancer**

Hormone treatment for prostate cancer has been revolutionized in the last two years. In April 2011, abiraterone (Zytiga, Johnson & Johnson/Cougar) was approved for castration-resistant prostate cancer. This agent is an oral antagonist of P450, which plays a key role in producing testosterone. In August 2012, enzalutamide (Xtandi, Medivation/Astellas), a new generation androgen receptor (AR) antagonist, was approved for the same indication. Although abiraterone and enzalutamide employ different mechanisms of action, both drugs demonstrated impressive OS benefits (4.6 and 4.8 months, respectively) in patients with late-stage prostate cancer. In addition, a more potent AR inhibitor, ARN-509 (Aragon), is in phase 2 development
and is purportedly more efficacious than enzalutamide.

**Combination regimens**

**Targeted agent plus hormone treatment**

Adding the mTOR-targeting agent everolimus (Afinitor®) to hormone therapy, exemestane, significantly and dramatically prolonged PFS in relapsed hormone receptor-positive post-menopausal breast cancer. Because PFS nearly tripled (11.0 months vs. 4.1 months; HR = 0.36; P < 0.001), the results were regarded as practice-changing[13]. Afinitor is now approved in combination with exemestane to treat hormone receptor-positive, HER2-negative breast cancer after letrozole or anastrozole failure. With the solid phase 2 data and the initiation of a phase 2/3 trial (NCT01740427) of CDK inhibitor PD 0332991 in ER-positive patients, we expect a new era in breast cancer treatment that could have a significant impact on the future course of the disease. In addition to mTOR and CDK inhibitors, PI3K and AKT inhibitors are also ideal candidates to combine with hormone treatments in breast or prostate cancers.

**Targeted agent plus targeted agent**

The approval of vemurafenib (Zelboraf), a BRAF inhibitor developed by Roche/Plexxikon, transformed the treatment of patients with melanoma harboring BRAF V600E mutations. Although the BRAF inhibitor treatment resulted in impressive improvements in objective response rates (48% vs. 5%) and PFS (5.3 months vs. 1.6 months), the disease recurred in nearly all patients by eight months after the initiation of the treatment[12]. Resistance to BRAF inhibitors is associated with reactivation of the mitogen-activated protein kinase (MAPK) pathway. Concurrent attack of both signaling pathways by combining BRAF and MAPK kinase (MEK) inhibitors may therefore address the resistance. Early results with dabrafenib (GlaxoSmithKline), a selective BRAF inhibitor, and trametinib (GlaxoSmithKline), a selective MEK inhibitor, showed promising efficacy with tolerable toxicity at full monotherapy doses. The median PFS in the combination group was 9.4 months, as compared with 5.8 months in the monotherapy group (P < 0.001). Similarly, the objective response rate for combination therapy was 76%, as compared with 54% for monotherapy (P = 0.03) [13]. Phase 3 trial of this combination, COMBI-AD, is ongoing.

In addition, combining cancer immunotherapy with established treatment modalities, e.g., chemotherapy or radiotherapy, is also a viable strategy to provide further benefit to already impressive efficacy. One challenge in developing such combinations is rationally designing the most efficient and effective clinical testing strategy for dose optimization and scheduling to minimize toxicity and maximize efficacy. Moreover, minor subclones and evolutionary dynamics derived from tumor heterogeneity introduce further complexity. Indeed, the efficacy may be further impacted by the sequence and timing of combination therapy. Identifying the best way to integrate biomarkers into such a complex process presents yet another challenge. The review by Beckman et al.[16] provides insights into recently attempted approaches to address these challenges. With a carefully designed development strategy, combination therapies targeting critical tumor survival pathways are expected to become an important part of cancer treatment options in the near future.

**Perspectives on Oncological Drug Development in China**

**New regulatory approaches**

The recent approval of crizotinib by the China State Food and Drug Administration (SFDA) on February 25, 2013, merely 1.5 years after the U.S. FDA approval on August 26, 2011, marks an important milestone. Objective response rates of 51% and 61% were observed in two multi-center, single arm phase 1/2 clinical trials involving 255 patients with locally advanced or metastatic ALK-positive NSCLC, leading to accelerated approval by the U.S. FDA. The SFDA Center for Drug Evaluation (CDE) then granted special review to expedite the approval and availability of crizotinib in China.

Similarly, the U.S. FDA has recently developed and implemented the Breakthrough Designation pathway, established by the FDA Safety and Innovation Act (FDASIA) [15]. Passed in July 2012, FDASIA defines eligibility for the pathway as a product that is "intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints." On March 15, 2013, LDK378 (Novartis), currently in phase 2 trials, received FDA Breakthrough Therapy designation for ALK-positive NSCLC. LDK378 is an investigational selective inhibitor of ALK with positive early data in patients with ALK-positive NSCLC who have been previously treated with crizotinib.

The approval of crizotinib reflects the desire and willingness of the China SFDA to take an evidence-based, yet flexible approach in reviewing and approving much needed, innovative drugs that will satisfy unmet medical needs in China.

**Programs for prevalent cancers in China**

Several cancer types, e.g., liver, esophageal,
nasopharyngeal, and gastric cancers, are uniquely prevalent in the Asia-Pacific region, including China. Drug development efforts at pharmaceutical companies in the West often do not focus on these cancer types. With the incidence climbing, there is an urgent need to organize research and development efforts to find solutions for these cancers. The U.S. Chinese Anti-Cancer Association (USCACA, www.uscaca.org) has recently formed an alliance with Xinxing Medical University to discover diagnostic and therapeutic means to manage esophageal cancer, which predominantly affects the population in the Henan province. The collaboration will establish a tissue bank enriched with esophageal cancer specimens. The center will apply genetics, genomics, and proteomics research tools to understand the underlying causes of esophageal cancer, and to discover and develop tools for early diagnosis of esophageal cancer. Meanwhile, collaborations are being formed with pharmaceutical companies, especially domestic Chinese companies, to develop treatments for this disease. A review by Bi et al. in this issue of CJC provides a detailed view of esophageal cancer from a molecular pathology perspective.

Clinical development programs

The successful development and ultimate approval of novel cancer medicines rely heavily on rationally devised and flawlessly executed clinical development strategy. USCACA has several initiatives to cultivate a solid platform for cancer drug development in China.

- In partnership with Fudan Cancer Hospital and South Texas Accelerated Research Therapeutics (START), a well-recognized research organization focusing on early phase cancer drug clinical development, USCACA facilitated the formation of START Shanghai, an internationally integrated research unit dedicated to early phase cancer drug trails. Now, cancer drugs can be tested in START centers in the U.S., Spain, and China simultaneously under the same standard and procedures.

- To further expand the early phase development excellence, USCACA and Jiangsu Hengrui Pharmaceutical Company established a scholarship program to support research staff from Chinese cancer hospitals to visit phase 1 research centers in the U.S. to compare and exchange best practices.

- Furthermore, USCACA has partnered with the Chinese Society for Clinical Oncology and SFDA scientists to explore innovative approaches supported by scientific and medical rationales to expedite clinical testing, review, and approvals of cancer drugs in China.

With the support of over 1,000 volunteers and our partner professional organizations, USCACA is confident that the next wave of breakthroughs in cancer drug development and cancer treatment will be coming from China to benefit our patients globally.

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Meeting Description

The Biennial Pathology Symposium of M. D. Anderson Cancer Center-Chinese Sister Institutions was first held in partnership with MD Anderson’s sister institute, Fudan University Shanghai Cancer Center in Shanghai in 2005. Pathology of the 21st Century (P21) is an international program at MD Anderson that has been held six times, in the United States and elsewhere. P21 emphasizes the use of innovative diagnostic tools for neoplastic disorders and new neoplastic entities and classification systems. As one of MD Anderson’s sister institutes in China, Sun Yat-sen University Cancer Center is honored to host this year’s combined pathology and P21 conference in China.

The main theme of this conference is novel approaches to the pathologic diagnosis and classification of tumors. The conference topics will cover a wide spectrum of neoplastic diseases, such as gynecologic tumors, gliomas, thyroid neoplasia, melanocytic lesions, neuroendocrine tumors, colorectal cancer, and prostate cancer. Particular attention will be given to molecular and cytogenetic testing in pathologic diagnosis and personalized therapy. Relevant topics, such as the application of and approach to immunohistochemical analyses in tumor pathology and the training of pathologists in the 21st century, will also be presented.

Conference Chairs

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  Sun Yat-sen University Cancer Center

• Ronald A. DePinho, M.D., Ph.D.
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