

转化医学通讯

GlobalIMD Newsletter

Diabetes

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● 推动新药测试的合作诊断

现在，制药公司想简单地把药品投放到市场是行不通的。监管机构和保险公司都要求制药公司明确指出哪些患者最有可能受益于这种药物，从而使其它病人免于经受不必要的副作用和承担不必要的费用。这些压力使得制药和诊断公司有时候尴尬地进行合作测试，这被称为合作诊断。据统计，2008年最多只有7个合作案例，2010年则至少达到25个，而仅2011年上半年有15个。

● 三分之一以上的临床实验医药外包

一份最新的报告指出，制药公司的临床试验目前超过三分之一都被外包了。著名的Kalorama Information调查公司有评论指出，在对过去几年的外包市场研究中，我们发现制造商对待医药外包的态度已经从“应该”转换为“必须”，近两年这一趋势在继续。

● 糖尿病的综合治疗和1型糖尿病患者的肾小球滤过率

肾小球滤过率（GFR）下降会导致终末期肾脏病，增加患心血管疾病的风险，严重可导致死亡。1型糖尿病患者是发生肾脏病的高危人群。在病程初期得到综合性治疗的1型糖尿病患者，相较于用传统方法治疗的，肾小球滤过率降低的长期风险明显偏低。

● 最新研究表明糖尿病会增加乳腺癌的发病率

● 通过成纤维细胞生长因子受体1的抗体介导激活改善2型糖尿病病情

重组成纤维细胞生长因子21（FGF21）用于临床治疗2型糖尿病及其他肥胖相关疾病的方法已经提出；该文章描述了一个替代的降糖策略，使用抑制抗-FGFR1（FGF受体1）的抗体（R1MAbs），模拟FGF21的代谢作用。

Science与GlobalIMD合作，首次推出Science专刊 - 临床和转化医学，全球发行

专业论文之二：

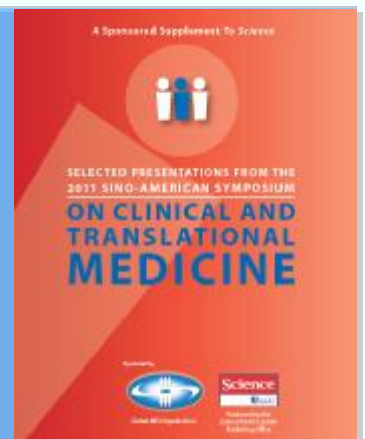
Global Outreach in Clinical Research by the NIH Clinical Center: Building Training Partnerships with China

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(内部资料, 仅供参考)





A Push to Tie New Drugs to Testing

From The New York Times

December 26, 2011

ChemGenex Pharmaceuticals found out the hard way how important it is to have a trustworthy companion.

The Food and Drug Administration last year rejected the company's drug to treat a subset of leukemia patients whose tumors had a particular genetic mutation. The main problem was not the drug itself, the agency said. Rather, ChemGenex had not specified a companion test that could reliably detect the mutation so that the drug could be given to the patients it is intended to help.

These days, it is often not enough for pharmaceutical companies simply to bring a drug to market. Regulators and insurers are also prodding the companies to develop tests to pinpoint which patients are most likely to benefit from a drug, thereby sparing other patients from needless side effects and expense.

The pressure has thrust drug and diagnostics companies into sometimes awkward partnerships aimed at developing such tests, which are called companion diagnostics. There were at least 25 such deals in 2010 and 15 in the first half of 2011, up from only seven in 2008, according to PricewaterhouseCoopers, a consulting firm.

"The tests are becoming almost gatekeepers to the drug," said M. Trevor Page, director of business development at Dako, a Danish diagnostics company.

The F.D.A. issued guidance to the industry on companion diagnostics in July, including its preference for having the test ready for approval at the same time as the drug. The following month, as if to show how it should be done, it approved two drugs and their accompanying tests.

One of the drugs, Pfizer's Xalkori for lung cancer, works wonders — but only for the roughly 5 percent of patients whose tumors have a particular chromosomal abnormality, as determined by a test from Abbott Laboratories.

The other drug, Zelboraf, from Roche and Plexxikon, can also produce remarkable improvements, but only for the roughly half of melanoma patients whose tumors have a particular mutation. The F.D.A. approved a test from Roche's diagnostics division to detect that mutation.

But the simultaneous approval of new drugs and tests is still rare. Before August, the only other dual approval was of Genentech's breast cancer drug Herceptin and Dako's test for the related HER2 protein in 1998. There are more than 70 other tests that guide drug use in some way, according to the Personalized Medicine Coalition, but they are rarely required and often developed well after the drug reaches the market.

There are numerous economic, scientific and regulatory obstacles to developing companion diagnostics, executives and analysts say.

Often, scientists simply do not know what to test for to predict a drug's effectiveness, or they don't find out until near the end of the drug's clinical trials. And coordinating development and approval of a drug and a test — by two separate companies reviewed by two F.D.A. divisions — can raise the cost of drug development if not done well.

"This is like trying to choreograph a dance," said Dr. Mace L. Rothenberg, who runs cancer clinical trials for Pfizer.

Moreover, it is often a dance between a giant and a pixie, locked in an embrace but with a tendency to move in opposite directions.

Pharmaceutical companies can spend hundreds of millions of dollars to develop a drug, then can reap billions of dollars a year in sales with high profit margins. Diagnostic companies typically spend several million dollars to develop a test, with annual revenues also around that level, and low profit margins.

"You are really trying to get two very disparate industries to understand each other," said Mollie Roth, chief operating officer of Diaceutics, a consulting firm specializing in companion diagnostics.

For pharmaceutical companies, the risk is that a test can lower sales of their drugs by restricting use to a fraction of potential patients.

An often cited example of such a problem involved Selzentry, a Pfizer drug approved in 2007 to treat people with a certain subtype of H.I.V.

The test of a patient's virus, offered by Monogram Biosciences, cost about \$2,000, and all samples had to be sent to Monogram's laboratory in California. Analysts say the cost and inconvenience of the testing deterred use of Selzentry, especially since it was competing with drugs that could be used by all patients, with no need for testing.

"Top management still sees companion diagnostics as an obstacle between their product and the market," said Jorge Leon, a consultant to both drug and diagnostic companies.

Still, drug companies are embracing companion diagnostics because of pressures to control health spending. Also, in the rare cases where a test is available early in the drug's development, as was the case with Xalkori and Zelboraf, clinical trials can be made smaller and less costly by restricting them to patients most likely to benefit from the drug.

For diagnostic companies, there is a risk of developing a test in advance for a drug that may never reach the market.

For that reason, drug companies often have to pay all or part of the costs of developing the test. Pfizer, for instance, paid for Abbott to develop the companion test for Xalkori, said Stafford O'Kelly, president of Abbott's molecular diagnostics division.

He said that when it became evident that the F.D.A. would make a decision on Xalkori earlier than expected, Abbott had to work nights and weekends to get the test ready. "Rule No. 1 is that the diagnostic can never slow down the development of the therapeutic," he said.

Companion diagnostic developers have been pushing to share more in the bounty of a successful drug, perhaps via royalties on sales of the drug. But drug companies have resisted this.

"The value is in the combination, so why should one company get all the value?" said Mark R. Trusheim, an executive in residence at the Massachusetts Institute of Technology Sloan School of Management, who has studied the economics of companion diagnostics.

One reason the diagnostic companies do less well, Mr. Trusheim said, is that while drugs typically have market exclusivity because of patents and federal laws, tests often face instant competition.

Some laboratories at cancer hospitals, for instance, already have their own tests for the melanoma mutation that governs use of Zelboraf and are reluctant to switch to the approved test, which might be less convenient or more costly. Tests developed by a lab for its own use typically do not require F.D.A. approval.

To protect their investments, some developers of companion diagnostics want the name of the test to be specified in the label of the drug, arguing in part that unapproved tests might not be as accurate. Some pathologists oppose this.

The F.D.A. has so far taken a middle ground. The labels for Zelboraf and Xalkori state that an F.D.A.-approved test should be used. But they do not name the test, leaving open the possibility that additional tests can be approved.

Plexxikon, one of the developers of Zelboraf, said in comments submitted to the F.D.A. that linking a drug to a single approved test could allow a diagnostics company "to hold the entire drug development program hostage."

Plexxikon, which is owned by Daiichi Sankyo, is developing a drug aimed at a type of leukemia with a particular mutation. K. Peter Hirth, Plexxikon's chief executive, said that a company holding exclusive patent rights on the test for this mutation was "demanding incredibly high dollars in terms of upfront payments and support, which is prohibitive."

Jeffrey E. Miller, chief executive of the company in question, Invivoscribe, said his company's charges were reasonable considering the possible consequences of not having a validated companion test.

"The cost of developing the companion diagnostic," he said, "is trivial compared to the cost of a failed drug."



Pharma outsourcing over one third of trials

From Pharma Times Online

December 22, 2011

More than one third of clinical trials conducted by pharmaceutical companies are now being outsourced, a new report has found.

The shift is also accelerating in cost terms. The portion of global research and development expenditure outsourced to contract drug developers reached US\$36.6 billion in 2011, up by 6.6% from US\$31.8 billion in 2009, notes the report by Kalorama Information.

In the same vein, the share of drug development expenses dedicated to in-house core activities declined from 74% to 62% over the last year.

"In past editions of our outsourcing market studies, we found that outsourcing moved from 'should' to 'must' for manufacturers," Kalorama Information comments. "This trend has only continued in the past two years."

Post-approval boom

The report on Outsourcing in Drug Development: The Contract Research (Clinical Trial) Market also identifies post-approval or Phase IIIb/IV studies as a fast-emerging "hot opportunity" for contract research organisations.

While the key objectives of post-approval trials are to satisfy regulatory commitments and extend knowledge about a product's efficacy, safety and effectiveness in actual-use settings, they have also evolved into "a powerful tool for companies to distribute their drug more broadly and for longer periods", Kalorama Information says.

Historically, Phase II-III trials were the first wave of clinical research operations to be outsourced, the market researchers point out.

However, growth in R&D spending on Phase I trials began to outpace Phases II-III in 2003, and Phase I remained the fastest-growing segment of drug development until around 2006. Today, growth in Phase I trials and Phases II-III is about equal, Kalorama Information adds.

Increasing complexity

Publisher Bruce Carlson puts the continuing trend towards R&D outsourcing down to the increasing complexity of regulatory requirements for drug development over the last 20 years, "requiring pharmaceutical companies to generate great quantities of more complex data to gain regulatory approval".

Many pharmaceutical and biotechnology companies "bring only a limited number of compounds to market and have relatively little experience dealing with the regulatory environment", Carlson adds.

"So they are outsourcing to companies that can take a drug through the regulatory process, and most importantly, reduce the time required to bring a drug to market."



Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

From N Engl J Med

December 22, 2011

Background

An impaired glomerular filtration rate (GFR) leads to end-stage renal disease and increases the risks of cardiovascular disease and death. Persons with type 1 diabetes are at high risk for kidney disease, but there are no interventions that have been proved to prevent impairment of the GFR in this population.

Methods

In the Diabetes Control and Complications Trial (DCCT), 1441 persons with type 1 diabetes were randomly assigned to 6.5 years of intensive diabetes therapy aimed at achieving near-normal glucose concentrations or to conventional diabetes therapy aimed at preventing hyperglycemic symptoms. Subse-

quently, 1375 participants were followed in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Serum creatinine levels were measured annually throughout the course of the two studies. The GFR was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula. We analyzed data from the two studies to determine the long-term effects of intensive diabetes therapy on the risk of impairment of the GFR, which was defined as an incident estimated GFR of less than 60 ml per minute per 1.73 m² of body-surface area at two consecutive study visits.

Results

Over a median follow-up period of 22 years in the combined studies, impairment of the GFR developed in 24 participants assigned to intensive therapy and in 46 assigned to conventional therapy (risk reduction with intensive therapy, 50%; 95% confidence interval, 18 to 69; P=0.006). Among these participants, end-stage renal disease developed in 8 participants in the intensive-therapy group and in 16 in the conventional-therapy group. As compared with conventional therapy, intensive therapy was associated with a reduction in the mean estimated GFR of 1.7 ml per minute per 1.73 m² during the DCCT study but during the EDIC study was associated with a slower rate of reduction in the GFR and an increase in the mean estimated GFR of 2.5 ml per minute per 1.73 m² (P<0.001 for both comparisons). The beneficial effect of intensive therapy on the risk of an impaired GFR was fully attenuated after adjustment for glycated hemoglobin levels or albumin excretion rates.

Conclusions

The long-term risk of an impaired GFR was significantly lower among persons treated early in the course of type 1 diabetes with intensive diabetes therapy than among those treated with conventional diabetes therapy. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; DCCT/EDIC ClinicalTrials.gov numbers, NCT00360815 and NCT00360893.)



Recent Diabetes Increases Breast Cancer Risk

From Internal Medicine News Digital Network

December 16, 2011

SAN ANTONIO – Diagnosis of diabetes within the prior 4 years was independently associated with breast cancer in a Swedish case-control study.

Dr. Håkan Olsson reported at the San Antonio Breast Cancer Symposium on all 2,724 women diagnosed with breast cancer in southern Sweden during 2005-2007 and 20,542 matched controls. He and his coworkers were interested in how the malignancy is related to diabetes, obesity, and serum lipid levels.

In a multivariate analysis adjusted for obesity, serum lipids, and other potential confounders, the breast cancer patients were 37% more likely than controls to have been diagnosed with diabetes during the previous 4 years. Yet diabetes diagnosed 4-10 years previously was not associated with a significant increase in breast cancer, said Dr. Olsson, professor of oncology and cancer epidemiology at Lund (Sweden) University.

The most likely explanation for the finding that only relatively recently diagnosed diabetes was linked to increased risk of breast cancer is that the diabetic hormonal milieu doesn't initiate breast tumors, but rather it promotes the growth of tumors that are already established but dormant. This would be analogous to the relationship between hormone replacement therapy and breast cancer, where the Early Breast Cancer Trialists' Collaborative Group has demonstrated that it's only present use, not past use, that increases the risk of malignancy, he observed.

Dr. Olsson and coworkers also looked at the relationship between diabetes and all other types of cancer among patients in the comprehensive regional cancer registry. They found that three other types of cancer in addition to breast cancer were associated with a significantly increased likelihood of prior diagnosis of diabetes compared to controls: pancreatic cancer, with a 2.36-fold increased rate; liver cancer, with a 3.43-fold increased odds; and colon cancer, with a 1.49-fold increase.

Dr. Olsson and coworkers also looked at the relationship between the antidiabetic medications metformin and glargine and cancer risk among all patients in the cancer registry, not just those with breast

cancer. Use of the long-acting insulin analog glargine, which is quite common among Swedish type 2 diabetic patients, was associated with a 2.88-fold increased overall cancer risk. In contrast, metformin use was associated with an 8% reduction in overall cancer risk, although this association didn't achieve statistical significance, unlike the relationship between glargine and overall cancer.

An association between glargine and increased cancer risk has also been noted in several other studies, according to Dr. Olsson.

In the southern Swedish breast cancer cohort, obesity after age 60 was independently associated with a 55% increased likelihood of breast cancer after controlling for diabetes and other factors in a multivariate analysis. However, obesity in women under age 60 was associated with a nonsignificant 41% reduction in breast cancer.

To Dr. Olsson's surprise, the investigators found that hypercholesterolemia was independently associated with a 27% reduction in the prevalence of breast cancer. In other words, significantly fewer breast cancer patients had a high cholesterol level compared with the general population. This is a novel finding that requires confirmation in other data sets, he added.

The relationship between metformin and breast cancer is under study in the large, prospective, phase III, double-blind, randomized [MA 32](#) clinical trial led by the National Cancer Institute of Canada Clinical Trials Group. More than 1,000 nondiabetic patients with early-stage breast cancer have been randomized to metformin or placebo. Key end points in the MA 32 study include overall and disease-free survival. Results are about 5 years off.

Dr. Olsson's study was funded by the Southern Sweden Health Care Region. He declared having no relevant financial relationships.



Amelioration of Type 2 Diabetes by Antibody-Mediated Activation of Fibroblast Growth Factor Receptor 1

From Sci Transl Med

December 14, 2011

Authors: Wu, Ai-Luen; Kolumam, Ganesh; Stawicki, Scott; Chen, Yongmei; Li, Jun; Zavala-Solorio, Jose; Phamluong, Khanhky; Feng, Bo; Li, Li; Marsters, Scot; Kates, Lance; van Bruggen, Nicholas; Leabman, Maya; Wong, Anne; West, David; Stern, Howard; Luis, Elizabeth; Kim, Hok Seon; Yansura, Daniel; Peterson, Andrew S.; Filvaroff, Ellen; Wu, Yan; Sonoda, Junichiro

Abstract:

Clinical use of recombinant fibroblast growth factor 21 (FGF21) for the treatment of type 2 diabetes and other disorders linked to obesity has been proposed; however, its clinical development has been challenging owing to its poor pharmacokinetics. Here, we describe an alternative antidiabetic strategy using agonistic anti-FGFR1 (FGF receptor 1) antibodies (R1MAbs) that mimic the metabolic effects of FGF21. A single injection of R1MAb into obese diabetic mice induced acute and sustained amelioration of hyperglycemia, along with marked improvement in hyperinsulinemia, hyperlipidemia, and hepatosteatosis. R1MAb activated the mitogen-activated protein kinase pathway in adipose tissues, but not in liver, and neither FGF21 nor R1MAb improved glucose clearance in lipotrophic mice, which suggests that adipose tissues played a central role in the observed metabolic effects. In brown adipose tissues, both FGF21 and R1MAb induced phosphorylation of CREB (cyclic adenosine 5'-monophosphate response element-binding protein), and mRNA expression of PGC-1 α (peroxisome proliferator-activated receptor- γ coactivator 1 α) and the downstream genes associated with oxidative metabolism. Collectively, we propose FGFR1 in adipose tissues as a major functional receptor for FGF21, as an upstream regulator of PGC-1 α , and as a compelling target for antibody-based therapy for type 2 diabetes and other obesity-associated disorders.



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