Incretin mimetics vie for slice of type 2 diabetes market

This February, New York–based Pfizer announced the acquisition of BioRexis Pharmaceutical, a biotech company in King of Prussia, Pennsylvania, with a strong product pipeline in type 2 diabetes, including long-acting agonists of glucagon-like peptide 1 (GLP-1) receptor, a key target in diabetes drug development. Pfizer is one of a number of companies looking for a piece of the growing worldwide market in diabetes. Indeed, inspired by the success of San Diego-based biotech Amylin with Byetta (exenatide), the only approved biotech diabetes drug (excluding insulin replacement therapy), other companies are striving to develop long-acting injectible GLP-1 mimetics as key components of drug regimens designed to stave off the need for insulin injections.

There are now over 30 drugs in nine classes available for the treatment of diabetes. The newest, Januvia (sitagliptin), from Whitehouse Station, New Jersey–based Merck, considered a sure-fire blockbuster, brought in an impressive $42 million for the company in its first partial quarter of sales, after its approval in October 2006 by the US Food and Drug Administration. Januvia represents the first drug to market that directly inhibits the enzyme dipeptidyl-peptidase 4 (DPP4). DPP4 inhibitors block the enzyme responsible for degrading GLP-1, which is released in the body at meal times, enhancing insulin secretion and helping to regulate appetite and food intake.

DPP4s and GLP-1s are new additions to a staged sequence of diabetes treatments, which usually start with lifestyle intervention plus an old, inexpensive oral drug, metformin. As the disease progresses (or if front-line treatment is ineffective) sulfonylurea drugs and glitizones (thiazolidinediones) are added to the regimen. DPP4s are emerging as the next step after the glitizones. London-based GlaxoSmithKline and the Basel-based pharma Novartis are also pursuing DPP4s, and biotech is now beginning to fill the gap between the end-of-the-line oral therapy and insulin with GLP-1 drugs, beginning with Byetta, the breakthrough injectible incretin mimetic derived from gila monster saliva.

Pfizer's move positions it to compete with the partnership between Amylin and Indianapolis, Indiana-based Eli Lilly that brought out Byetta. The success of Byetta (with fourth quarter sales of $137 million in 2006) proves that there is a market outside of small-molecule oral therapeutics in type 2 diabetes, and that patients are not particularly worried about the needle, especially when it's accompanied by salutary side effects such as weight loss. Nutley, New Jersey–based Roche, GlaxoSmithKline and Bagsvaerd, Denmark–based Novo Nordisk are also pursuing this new wave of diabetes protein therapeutics. The challenge in making a GLP-1 drug is being able to modify it to stay around longer in the body.

Big pharma's interest in novel targets for injectible biotech drugs to treat diabetes is at an all-time high, the result of increasing disease incidence and the deficiencies of current oral therapies.

Novo's Galvus (vildagliptin) is widely expected to be the next GLP-1 analog on the market. The company was sufficiently confident in the promise of their protein biologics that they recently discontinued all small-molecule development programs, thus placing all of their eggs in a biotech basket (News in Brief, p. 269).

The rapid marketplace uptake of Januvia shows that physicians are poised to try alternatives to the current oral drug regimens, which have not significantly improved on metformin. Indeed, just a few months after approval, the shine may already be wearing off Januvia. A review in the *New England Journal of Medicine* on February 1 by David Nathan compared the potency of Januvia unfavorably to older drugs such as insulin, the sulfonylureas and the biguanides. Additionally, he pointed out that the clinical trials supporting the approval of Januvia included a limited number of patients, whereas the drug has the potential to be used immediately by hundreds of thousands of people, setting the stage for a possible disastrous repeat of the approval and withdrawal of Rezulin (troglitazone), one of the glitazones, in 1997, over safety issues.

Potentially of greatest concern, however, are indications that DPP4 inhibitors could promote the growth and metastasis of tumors. David Kliff, publisher of the newsletter *Diabetic Investor*, says, "The problem with any diabetes drug is you're going to be on it for the rest of your life. If there is any connection between DPP4 inhibitors and cancer, I would hate to see six to eight months from now, patients getting cancer, and then all of a sudden Merck would have to pull the drug off the market. I'm not saying it's going to happen, but as we learned from Rezulin, sometimes where there's smoke, there's fire."

Given the consumer orientation of diabetes drug marketing and the massive sales forces big pharma details into the area, companies such as BioRexis are wise to find partners for their drug candidates. Indeed, even larger drug companies are finding this to be the case. Bristol-Myers Squibb recently partnered its phase 3 DPP4, saxagliptin, with London's AstraZeneca, a deal that also included codevelopment of a sodium glucose transporter inhibitor—another novel target for therapy. Cytokines, chemokines, ikappaB kinase, Jun N-terminal kinase and fatty acid binding protein are also being explored as potential targets for mono- and combination therapies.

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