Executive Summary

The diabetes market presents competitive, commercial, and regulatory challenges, but its size and breadth spur emerging biotechs to develop an ever-wider range of treatments and technologies.

- With fierce, entrenched market competition and high regulatory hurdles, type 2 diabetes isn’t a first-choice spot for most biotechs – or investors.
- Yet the prevalence and growth of this disease continues to attract new approaches, and new money.
- AstraZeneca’s lead in a $40 million funding round for PhaseBio and its once-weekly insulin is a reminder of incumbents’ need to fill portfolios and gain an edge.
- And for biotechs, even just a narrow slice of this multibillion-dollar market can mean handsome returns.

Type 2 diabetes isn’t an obvious spot for any aspiring biotech entrepreneur to invest hard-raised dollars. The highly competitive marketplace is dominated by Sanofi, desperate as $7 billion Lantus (insulin glargine) faces generic competition, Novo Nordisk AS, and Eli Lilly & Co., with AstraZeneca PLC chasing hard behind. The therapy mainstay remains insulin, discovered nearly 100 years ago, and now available in plenty of formats, including, most recently, inhaled. The newer glucagon-like-peptide-1 (GLP-1) agonists, including Novo’s leading $2 billion-a-year Victoza (liraglutide), are a valuable and expanding class; just this past January, Naia Ltd, launched with rights to a Phase I GLP-1 candidate for type 2 diabetes licensed from Amunix Operating Inc. [See Deal]

But since the arrival in Europe of the most recent new product category in type 2 diabetes, the oral sodium-glucose co-transporter-2 (SGLT-2) inhibitors in 2012,
validated new mechanisms of action have been few and far between. (See "The End Of Drug Innovation In Diabetes?" — IN VIVO, February 2015.) Pricing pressures and regulators’ scrutiny are intensifying in diabetes: Sanofi’s having to offer co-pay cards on its recently launched Lantus follow-on, Toujeo; FDA delayed approval of Novo’s "ultra" long-acting insulin Tresiba (insulin degludec) pending results of a cardiovascular outcomes trial.

Against this backdrop, it’s easy to see why the total private funding raised for companies focused primarily on diabetes drugs in the two years to March 2015 reached just $266 million, according to Informa’s Strategic Transactions, compared with over $2 billion for oncology. “It’s a double whammy: the probability of technical success with most novel mechanisms of action is low, and costs are high. That’s why investment [in diabetes] has been so much less” than in other sectors, explains Clay Thorp, general partner at Hatteras Venture Partners. (See also.)

Any biotech going beyond Phase II needs a large partner to fund late-stage trials and for commercialization. Yet partners want to see convincing late-stage data, in this field like no other, before committing their dollars. That means plenty of un-partnered Phase II assets, such as Oramed Pharmaceuticals Inc.’s oral insulin candidate or Biodel Inc.’s ultra-rapid-acting insulin. It also means languishing share prices. Plenty have crashed completely in diabetes – Tolerx Inc., Phenomix Corp, and most recently, Cebix Inc. Others, like DiaMedica Inc., CymaBay Therapeutics Inc., or private Rhythm Pharmaceuticals Inc., have quietly shelved their diabetes programs, or shifted them toward far narrower sub-populations and related metabolic complications.

“The capital markets reward oncology, orphan diseases, and specialty pharma plays,” concedes Jonathan Mow, CEO of private PhaseBio Pharmaceuticals Inc., whose lead program is a once-weekly formulation of insulin for type 2 diabetes that’s starting Phase II.

But although orphan diseases, with their narrow patient populations and lower regulatory hurdles, trump diabetes on most VCs’ wish lists, there remains a significant cohort of biotechs, such as PhaseBio, working on the disease. The arguments: this is a rapidly growing market where global drug sales could reach $80 billion by 2023, according to Decision Resources ($50 billion of which will come from G7 countries). Fewer contenders in the race leave bigger rewards for those who finish. And diabetes is a space that demands and embraces new technologies – not just insulin pumps and glucose monitors, but also more recently the customer-facing apps, devices, and services emerging from the red-hot digital health sector. As health and technology continue to merge, this will become a more important draw for investors. (See “Digital Health Investing: Bull Run Or Boom-And-Bust?” — START-UP, September 2014.) Medtronic PLC in March backed a $16.5 million Series B for technology firm Gloook, for instance, which aggregates and analyzes blood glucose and activity levels from across a range of devices onto a patient-friendly mobile app. (See "Medtronic Funds Diabetes App Firm To Help Target Pump-Monitor Systems"— "The Gray Sheet," Mar. 18, 2015.) Finally, diabetes, although associated with well-known risk factors and co-morbidities, is a heterogenous disease. Individuals face different risks and challenges in managing their condition. Insulin – a potent, effective, yet potentially dangerous drug if mis-administered – remains under-used. So there’s plenty of room, proponents argue, for an ever-wider range of treatments, technologies, and delivery forms. “There’s enough of a marketplace to support lots of different product opportunities,” says Mow.

Indeed, when AstraZeneca’s venture arm in March 2015 led a $40 million round in PhaseBio, it served as a reminder that a competitive commercial market can be good news for aspiring start-ups.[See Deal] Hungry pharmaceutical players seeking to

Intarcia secures $225mm via royalty financing
Sanofi gets exclusive global rights to MannKind’s newly approved Afrezza diabetes treatment
Dance Biopharm raises $9.5mm through sale of convertible debt and warrants
Dance Biopharm seeks to go public; withdrawn
Midatech completes £32mm IPO in London
Emisphere, Novo Nordisk sign oral insulin deal
Transdermal drug delivery firm Zosano Pharma nets $46mm in IPO
Novo Nordisk to apply Zosano’s delivery system to Type II diabetes candidate
Adocia partners with Lilly on ultra-rapid insulin formulation; deal terminated, and then revived
Google partners smart lens technology with Novartis
Novartis teams up with diabetes start-up Semma Therapeutics
Semma brings in $44mm through first round
Merck could pay up to $500mm to buy SmartCells
build and defend valuable franchises need fresh offerings. AstraZeneca is the only major diabetes player lacking insulin in its portfolio, so its investment in PhaseBio has a strong strategic element (even though it has, as yet, no formal rights to the insulin program). There are plenty of other insulin contenders out there looking for a slice, or several, of this mega-market: new ultra-long-acting or ultra-rapid formulations, novel delivery routes, “smarter” glucose-responsive versions, cheaper variations.

Other groups like private Intarcia Therapeutics Inc, are seeking to cash in on new and improved formulations of GLP-1 agonists, which stimulate insulin release and induce satiety. Intarcia’s implant, inserted once- or twice-yearly for continuous subcutaneous delivery of exenatide, was the subject of an ex-US deal in November 2014 worth over $400 million up front and in near-term milestones from France’s Servier SA. [See Deal] That alliance – one of the largest ex-US biotech deals ever – shows it isn’t only the biggest drug firms that are interested in new diabetes programs (though several larger players allegedly fought for Intarcia’s Phase III asset, dissuaded perhaps by the biotech’s ambition to lead in the US on its own). And in late April, Intarcia raised an additional $225 million in a royalty financing.[See Deal]

Most type 2 diabetes R&D is centered around polishing up treatment mainstays like insulin and GLP-1, and, in devices, on developing new, improved, interconnected insulin pumps, glucose monitors, and adjacent technologies. But a few firms, such as Vitae Pharmaceuticals Inc, (with partner Boehringer Ingelheim GMBH), newly listed French group Poxel SA or start-up Numerate Inc., continue to take high-risk punts on novel mechanisms of action for type 2 diabetes – including, in the case of Germany’s Glycemicron AG, via functional foods. (See Exhibit 1.)

### EXHIBIT 1

**Selected Novel Drug Mechanisms In Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Mechanism</th>
<th>Stage Of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>Glucagon receptor antagonist. Glucagon works in the opposite way to insulin, raising blood sugar levels. This long-researched class has faced toxicity issues.</td>
<td>Phase II.</td>
</tr>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>Oxyntomodulin peptide: a biologic co-agonist of GLP-1 and the glucagon receptor. Potential to offer more potent weight loss than the GLP-1 agonists.</td>
<td>Phase II.</td>
</tr>
<tr>
<td>Vitae/Boehringer Ingelheim</td>
<td>11β HSD1 inhibitor. Inhibits the action of an enzyme that turns inactive cortisol into the stress hormone cortisol, associated</td>
<td>Phase II due to report in 1H 2015.</td>
</tr>
<tr>
<td>Company</td>
<td>Description</td>
<td>Status</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>-----------------------------------------------------------------------------------------------</td>
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<tr>
<td>CymaBay Therapeutics</td>
<td>Oral MBX 2982 targets G-protein coupled receptor 119. The compound stimulates insulin secretion from beta cells and GLP-1 release from the gut. Potential dual therapy with metformin or sitagliptin.</td>
<td>Completed four Phase I trials and one Phase II.</td>
</tr>
<tr>
<td>Poxel</td>
<td>Imeglimin, first in a new, tetrahydrotetrazine-containing class of oral agents called &quot;glimins.&quot; Increases muscle glucose uptake and insulin secretion; decreases glucose production in the liver.</td>
<td>Completed two Phase IIa trials, showing comparable efficacy to metformin with better safety/tolerability. Slated as safe treatment for sensitive populations (e.g., elderly, renal impaired).</td>
</tr>
<tr>
<td>Poxel</td>
<td>Direct AMP kinase activator; increases lipid oxidation and insulin-independent glucose uptake.</td>
<td>Lead optimization.</td>
</tr>
<tr>
<td>Numerate (raised $8 million in a Series C in June 2014, including Atlas Venture and Lilly Ventures)</td>
<td>Seeking selective long-chain FFA4 (free-fatty-acid) receptor agonists and dual acting FFA1 and 4 agonists. These mediate release of GLP-1 and insulin, adipocyte growth, and have anti-inflammatory effects.</td>
<td>Discovery. Numerate applies machine-learning algorithms to small-molecule drug design and discovery, focusing on targets where little data exist or where traditional structure-based design approaches are inadequate.</td>
</tr>
<tr>
<td>Glycemicon</td>
<td>Naturally occurring bile acid THBA, which inhibits retinoid orphan receptor gamma (RORγ). RORγ blocks the formation of fat cells leading to elevated blood sugar and insulin insensitive fat tissue. Modified probiotic that secretes GLP-1; shown in animals to convert intestinal cells into GLP-1.</td>
<td>Glycemicon is developing THBA as a medical food.</td>
</tr>
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</table>
Does Inhaled Insulin Get A Second Chance?

Right now, though, all eyes are on the launch trajectory of Sanofi’s inhaled insulin Afrezza, launched early in 2015. Developed by MannKind Corp., the drug was approved in June 2014 after five years and three attempts. Sanofi snapped up commercial rights two months later. But in early March 2015, analysts at Goldman Sachs downgraded MannKind’s stock and cut peak sales projections in half, as a result of poor initial sales. That fueled existing fears that Afrezza will suffer a similar commercial fate to Pfizer Inc.’s inhaled insulin, Exubera, withdrawn in 2008. That’s still a strong possibility, according to David Kliff, publisher of the Diabetic Investor, not least because of the recent upheaval in the top ranks of Sanofi management.

Still, that Afrezza is out there at all shows that at least some believe it’s worth persevering to offer patients a non-injected alternative. And even Goldman’s halved peak sales projection is still worth $1 billion: not another Lantus, maybe, but still a very valuable proposition, especially for smaller players.

Smaller players like private Dance Biopharm Inc., for instance. Set up in 2010 by John Patton, PhD, a co-founder of Inhale Therapeutics (now Nektar Therapeutics Inc.), the company behind Exubera, Dance is defiantly pursuing the “second generation” of inhaled insulin. Its liquid formulation of human insulin, Dance-501 (known as Adagio), is inhaled as a smooth mist from a silent electronic inhaler. The inhaler uses a vibrating mesh micropump technology developed by Ireland-based Aerogen Ltd. (a company carved out of Nektar in 2007), and is designed to look like a consumer electronic product.

Adagio’s advantage over Afrezza, say its proponents, is that it’s a liquid, whereas Afrezza is a powder formulation of human insulin. According to Adam Stern, CEO of SternAegis Ventures (part of banking group Aegis Capital Corp.), the liquid formulation allows cheaper manufacturing, requires no added excipients, and is going to be “easier for patients to appreciate.” Patton also points to data from German diabetes-focused clinical research organization Profil GMBH indicating strong consumer preference for the Aerogen technology over alternative devices. “Dance has a very unique second mover advantage,” asserts Stern, whose outfit led a $9.5 million private investment round in February 2015. He’s betting that the availability of inhaled insulins will prompt earlier, more widespread adoption. “Less than a quarter of diabetics are on insulin. Most would prefer an alternative to injection,” he contends.

Yet inhaled insulin divides opinion: some envision a world where inhaled eventually sidelined injected insulin, boosted by patient preference and convenience. Many more see it as an alternative treatment for a minority of patients with serious needle phobia.

Which side regulators – and payors – will fall is another matter. Dance-501 has completed a small Phase I trial among type 1 diabetics and a Phase II/III pharmacokinetic/pharmacodynamics trial among type 2 patients. Results from both will be presented at the American Diabetic Association (ADA) meeting in Boston in June 2015. Patton says European regulators have indicated that a year-long, 500-strong Phase III trial, with 250 patients in a comparator arm, will be sufficient for approval. FDA may prove more demanding, though – Afrezza’s long-awaited...
approval came with a boxed warning about acute bronchospasm in patients with asthma or chronic obstructive pulmonary disease, an associated Risk Evaluation and Mitigation Strategy (REMS), and post-marketing study requirements including around the risk of pulmonary malignancies. Inhaling a growth factor raises cancer concerns.

Meanwhile, payors are coming down hard on pricing for diabetes treatments, prompting aggressive discounting among established competitors. Goldman Sachs analysts estimate that Afrezza’s list price – originally double that of Sanofi’s rapid-acting injected equivalent, Apidra – has had to be slashed by 40% in order to get a look-in.

Afrezza’s bumpy journey has knocked Dance off balance, too: it withdrew an IPO filing in October 2014, as bankers got jittery in the build-up to Afrezza’s launch. [See Deal]

Now on the cusp of far larger Phase III trials, Dance needs a partner. Suitors are unlikely to line up before Afrezza’s fate is clearer. “Absolutely, Afrezza will be a benchmark,” Patton concedes. But he also warns that any new insulin takes a while to gain traction. “It’s a potent medicine. Historically, insulins have a bit of a lag before people embrace them.” The hope is that Dance can endure the wait.

Needle-Free, But Not Inhaled

AIM-listed Midatech Pharma PLC is avoiding both needles and pulmonary delivery with its trans-buccal formulation of insulin, currently in Phase II. The product is a stamp-sized strip that’s inserted into the mouth, onto the inside of the cheek. It contains human recombinant soluble insulin conjugated with carbohydrate-coated gold nanoparticles (GNPs). The resulting MidaForm-Insulin-PharmFilm, contained in the strip, was found in a Phase I trial to reach peak action faster than insulin aspart (Novo’s NovoLog/NovoRapid), with good safety and tolerability, according to CEO Jim Phillips. “The target product profile is that you pop a strip into your mouth just before eating,” he notes. “It’s like a breath-freshener strip.” The strip dissolves, rapidly releasing insulin directly into the bloodstream thanks to a steep osmotic gradient. The outer side of the strip (facing into the mouth cavity) is designed to prevent saliva from interfering with the insulin, while the fast, 24-hour turnover of the buccal membrane reduces the incidence of local effects such as lipodystrophy seen around insulin injection sites.

Midatech went public in December 2014, raising £32 million ($47.5 million) [See Deal] and claims it has sufficient resources to complete Phase II trials of the program, which sits within a 50-50 joint venture with US firm MonoSol Rx LLC. [See Deal] A Phase IIa trial in type 1 patients is underway, and two further US Phase IIb trials in type 1 and type 2 patients planned for 2016.

The joint venture, known as MidaSol Therapeutics LP, already has two large collaborators, according to Phillips (including a major international pharmaceutical company that signed up in March 2015 for a six-month investigation into needle-free delivery of one of its marketed diabetes drugs). [See Deal] Phillips claims there’s significant interest beyond. The data need to be good for interest to turn into licensing deals, though, given the failure rate in alternative insulin delivery. So far, safety looks promising: there are no ligands used to bind the insulin to the GNPs; instead it’s held electrostatically. The gold nanoparticles appear to be freely excreted by the kidneys once the payload is delivered. The company also hopes to expedite any eventual approval by pursuing the abbreviated 505(b)2 pathway in the US; Phillips claims they’re in early discussions with FDA.

Like Dance, Phillips claims Midatech’s program has the potential to make insulin
injections redundant: in theory, long-acting insulin could be included on the strip as well, in a fixed dose. The company also has a preclinical GNP-conjugated transbuccal GLP-1.

But unlike Dance, Midatech’s diabetes programs are a non-core legacy: the rest of its projects are focused on orphan or ultra-orphan diseases (such as targeted cancers) around which it plans to build its own commercial operations. Once Phase IIb trials have provided further data on the insulin’s speed of onset, duration of action, and long-term toxicology, the idea is to spin out the joint venture as a stand-alone diabetes company, or see it absorbed into a larger player.

Midatech isn’t alone in the non-injectable, non-inhaled insulin camp. Oramed’s ORM-0801 is about to initiate a Phase Ib trial in type 2 diabetics, but the Nasdaq-listed firm’s share price suffered after unconvincing results from a small, week-long placebo-controlled Phase Ila trial in early 2014. Oramed’s candidate encapsulates insulin with an absorption enhancer that allows it to cross the intestinal barrier, and with compounds to protect it from enzymatic degradation. But it’s intended as a new, earlier treatment option, not as a replacement for injections, making it a less compelling proposition. In November 2014, the group pulled in a $5 million lifeline from Chinese pharmaceuticals manufacturer Guangxi Wuzhou Pharmaceutical Co. Ltd.

Developing oral insulin has been slow and difficult for all. Novo’s oral basal insulin analog hasn’t yet reached Phase II, though the firm has shown its commitment to developing oral diabetes treatments. It has several oral pipeline candidates and plans to invest over $3.5 billion to open up a market estimated at more than $18 billion. Novo has hedged its bets across a variety of in-house and partner technologies for oral delivery; it has deals with Merrion Pharmaceuticals Ltd. and Emisphere Technologies Inc. [See Deal] (See “Novo Signs Up Another Oral Insulin Partner, Hedging Its Bets” — "The Pink Sheet" DAILY, Dec. 22, 2010.)

Further upstream, Zosano Pharma Corp., which netted $46 million at its January 2015 IPO[See Deal], is testing its transdermal microneedle patch system with Novo’s once-weekly GLP-1 candidate semaglutide. [See Deal] The technology allows fast, easy, pain-free systemic delivery via the skin.

**If Needles Are Needed, Weekly Better Than Daily**

The success or failure of inhaled insulin 2.0 and other needle-free insulins won’t affect the journey toward more convenient, longer-acting forms of the hormone. The idea is that fewer injections mean better compliance, thus better glucose control and fewer complications. Insulin leader Novo Nordisk’s Tresiba lasts up to 42 hours, allowing patients greater flexibility in the timing of daily doses. It was approved in Europe in early 2013, and the following year in combination with liraglutide as a once-daily injection, Xultophy. Tresiba could reach the US market this year following a resubmission, but it still leaves an open road for those, like PhaseBio, seeking to develop once-weekly insulin.

PhasedBio reckons its PE0139 could be the first once-weekly insulin to market. The candidate conjugates human insulin with an elastin-like polypeptide (ELP) “tail,” designed to increase half-life and stability. By changing the length of the tail (made of naturally occurring amino acids), the company claims it can “tune” a drug’s duration of action.

An advantage of the ELP technology over the well-known pegylation approach to extending duration of action, according to PhaseBio, is that when the compound is injected subcutaneously, the ELP tail reversibly hydrogen bonds to itself – or
coacervates – to become even more stable, with lower bioavailability. The result, according to CEO Jonathan Mow, is a very flat pharmacokinetic curve without the initial spike typical of an injectable drug – ideal for avoiding hypoglycemia that can result from too much insulin. The candidate can be stored at room temperature for up to a month, resulting in a profile that’s “really well matched to what we want insulin to do,” says Justin Klein, partner at New Enterprise Associates, the largest investor in PhaseBio.

PE0139 is currently up against gold-standard daily Lantus (as well as placebo) in a Phase IIa [four-week?] multiple ascending dose study. “Most doctors think in terms of units of Lantus, so we need some kind of mental exchange ratio” that they can use to understand the newer drug’s efficacy, explains co-founder Clay Thorp, a general partner at Hatteras, PhaseBio’s first investor. Data from the trial are expected during the first half of 2016. (PhaseBio’s ELP-conjugated GLP-1 agonist failed to show non-inferiority over Victoza in 2013. But insulin is a bigger molecule than GLP-1, notes Thorp, and therefore it remains stable for longer than GLP-1 agonists. And the GLP-1 program may still have potential in combination with the weekly insulin.)

PhaseBio’s hoping that by using human (native) insulin and naturally occurring amino acids, its compound should have a reduced risk of immunogenicity. This “increases our confidence that we’ll have a safe and predictable insulin as we get into bigger studies,” notes Klein. Engineered insulins such as Lantus rely on other compounds, like zinc, to force the insulin molecule into a shape that allows it to last longer.

Nasdaq-listed AntriaBio Inc. makes similar claims for its formulation of once-weekly human recombinant insulin – though it’s still preclinical. AB101 avoids new excipients, shows no initial bursts of insulin release, and shows near peak-less levels over the period. AntriaBio’s insulin is pegylated, but the company uses shorter than usual polyethylene glycol (PEG) chains. This allows the molecule to also be encapsulated into poly-lactic, poly-glycolic microspheres, further modifying and extending the insulin release profile. The degradable microspheres are slowly broken down by hydrolysis at the injection site.

AstraZeneca’s investment has given PhaseBio’s team confidence that it will have a partner to undergo expensive Phase III trials and regulatory submission, even though the Big Pharma hasn’t actually signed on the dotted line to partner the program. AstraZeneca has no experience with insulin, but that’s better than teaming up with a player that may sideline a partners’ product in favor of its own, according to Mow. “If we can attract AstraZeneca to the table, then we know that this will be their insulin and they’d have a sole purpose in maximizing that product,” he argues. (Novo’s weekly insulin candidate in still in Phase I, according to the company’s web site; but once-weekly semaglutide, an injected GLP-1 agonist, is in Phase III, with recent positive Phase II results from an oral equivalent.)

Ultra-Rapid Insulin, Anyone?

While some attempt to draw out insulin’s duration of action as long as possible, others are trying to accelerate its effects. Many diabetics require mealtime insulin boosts, often on top of basal insulin, to cope with the sharp spike in blood sugar after eating. The rapid-acting insulins on the market don’t kick in immediately: Novo’s NovoRapid and Lilly’s Humalog take about 15 minutes, making it tricky to time the shots optimally, particularly in younger children.

The ideal ultra-rapid-acting insulin would be injected as a patient sits down to a meal, and still provide adequate blood glucose control. Novo’s ultra-fast version of aspart, FIAsp, is in Phase III trials, due to complete in June 2015.
France’s **Adocia SAS** is applying its *BioChaperone* technology to create ultra-rapid mealtime insulins, including *BioChaperone Lispro*, a faster version of Humalog. BioChaperone stabilizes and enhances the efficacy of therapeutic proteins by forming reversible physical complexes with polymers. These don’t modify the protein itself, but can alter its duration of action, enhance bioavailability, and protect against enzymatic degradation.

In September 2014, Adocia reported positive results for BioChaperone Lispro from a Phase Ila dose-response trial, showing faster onset of action and faster clearance from the blood relative to Humalog, and good tolerability. Three months later, Lilly paid $50 million up front for rights to develop and market the product, in a deal that marked an about-face for the Big Pharma. ([See "Adocia Targeting Insulin Combos After Ultra-Fast Insulin Deal With Lilly" — "The Pink Sheet" DAILY, Dec. 19, 2014.]) Lilly had in 2013 walked away from a research collaboration on the same program. [See Deal]In the more recent deal – which also gives Lilly rights to a concentrated formulation, well suited for patch-pumps – the larger partner committed $280 million in development and regulatory milestones, and $240 million if sales targets are met. The compound began a Phase Ib trial in January 2015, and could allow both type 2 and type 1 patients more flexibility in the timing of their mealtime injections and better glucose control than currently available insulins.

Adocia claims that low technology costs may allow the product to be priced at a similar level as Humalog. That may have been another important factor driving Lilly’s return: the Big Pharma has been the most aggressive of the big three on pricing. With partner Boehringer Ingelheim, its biosimilar version of Lantus, *Abasria*, was approved in Europe in September 2014, and has tentative US approval (via the 505(b)2 pathway) pending patent litigation from Sanofi.

Adocia is also seeking to play the value card in its insulin portfolio: *HinsBet* uses cheaper, human insulin in a fast-acting BioChaperone formulation whose speed of onset matches that of more expensive rapid-acting analog insulins (regular human insulin normally takes longer to kick in). This alternative to insulin analogs may find a receptive market in developing countries such as India, Mexico, and China where diabetes prevalence is growing.

HinsBet’s still un-partnered, like Biodel’s Phase II ultra-rapid-acting concentrated insulin, and tiny *Thermalin Diabetes LLC*’s ultra-concentrated rapid-acting *Fluorolog* for patients with high insulin resistance (though that’s still pre-IND). (See sidebar, "Partners Wait And See.")

### Can “Smart” Insulin Trump The Lot? Eventually, Maybe

**Novartis AG**’s July 2014 deal with Google to develop a "smart" contact lens that could potentially offer diabetics continuous, non-invasive blood glucose measurements caught the popular imagination – and provided a glimpse into a future of health-promoting "wearables." [See Deal] Others are pursuing a more ambitious goal still: glucose-responsive insulin that releases automatically according to blood sugar levels, without any need for measuring or monitoring at all. In other words, insulin so "smart" that it behaves almost as cleverly as pancreatic beta cells in healthy individuals. If it happens, smart insulin could trump current efforts to make insulin slower, faster, cheaper, and needle-free.
A watershed moment in the history of smart insulin was Merck’s 2010 purchase of SmartCells, whose preclinical candidate was based around technology from the Massachusetts Institute of Technology. [See Deal] The approach involved attaching a short chain of sugars to insulin to create a gel that releases insulin only when blood sugar reaches a specific concentration threshold.

The SmartCells deal triggered a flurry of interest in the space. But Merck then went quiet for four years, announcing in 2014 that a Phase I trial was due to start in November that year and complete by July 2015.

Merck’s silence hasn’t dissuaded others from pursuing the smart insulin dream. (See Exhibit 2.) Early in 2015, researchers at MIT and the University of Utah published in the *Proceedings of the National Academy of Sciences* animal data from Ins-PBA-F, a once-daily “smart” insulin shown to respond more rapidly and effectively than Novo’s *Levemir* (insulin detemir) to changes in blood-sugar levels, and to stay in circulation for at least 10 hours. The glucose-responsiveness is mediated by the phenylboronic acid (PBA) attachment, which reversibly binds to glucose. When sugar levels are high, the sugar binds to the modified insulin and activates it.

**EXHIBIT 2**

**Selected Smart Insulin Approaches**

<table>
<thead>
<tr>
<th>Merck (SmartCells)</th>
<th>Insulin-lectin gel structure with competitive binding to glucose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensulin</td>
<td>Insulin-containing liposomes, linked by a boronic acid derivative that binds competitively and reversibly with glucose.</td>
</tr>
<tr>
<td>Glycostasis</td>
<td>Bi-directional approach (details under wraps), meaning insulin is released when blood sugar rises, but also taken back out of circulation when levels reduce.</td>
</tr>
<tr>
<td>Thermalin</td>
<td>Discovery stage glucose-responsive insulin, includes tailored carbohydrates that bind to sub-cutaneous lectins.</td>
</tr>
<tr>
<td>Biodel</td>
<td>Early preclinical work reported on a controlled-dissolution basal insulin that uses glucose-level-linked changing pH levels to determine release.</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Several patent applications filed around glucose-dependent insulins. Other work may be ongoing.</td>
</tr>
<tr>
<td>Cortendo AB</td>
<td>Orally-administered genetically modified</td>
</tr>
<tr>
<td>(BioPancreate)</td>
<td>probiotic; preclinical data reported in <em>Diabetes</em> in January 2015 suggest it may be able to reprogram upper intestinal endocrine cells into glucose-responsive insulin-secreting cells. The technology involves engineering a common strain of gut bacteria, <em>Lactobacillus</em>, to secrete GLP-1, which triggers insulin release in response to food. The technology was licensed from Cornell University by US-based BioPancreate, now a subsidiary of Sweden’s Cortendo. Cortendo’s ambitions lie in treating orphan endocrine diseases but it plans an IND submission later this year and is exploring out-licensing opportunities.</td>
</tr>
<tr>
<td>MIT/University of Utah</td>
<td>Phenylboronic acid (PBA) attached to long-acting insulin; PBA reversibly binds to glucose. When sugar levels are high, the sugar binds to the modified insulin and activates it. Ins-PBA-F is shown in animals to respond rapidly to changes in blood-sugar levels, and stay in circulation for at least 10 hours.</td>
</tr>
<tr>
<td>Academic literature</td>
<td>Microgels containing enzyme nano-capsules and human insulin; acid-degradable polymeric networks of insulin-loaded nano-particles and glucose-specific enzymes.</td>
</tr>
</tbody>
</table>

*Company web sites; US Patent Office; academic literature*

Meanwhile, four-year-old **Sensulin LLC** isn’t chemically modifying insulin at all. Instead, its *Agglomerated Vesicle Technology* packages unmodified human insulin into liposomes, and those liposomes are linked together by a derivative of boronic acid, which binds competitively, and reversibly, with glucose. So when blood sugar rises, the boronate linker binds sugar and the bond to the liposome depot is broken, releasing insulin. When sugar levels recede, the gates to the depot of lipid-encapsulated insulin close again. (See "Sensulin LLC" — *START-UP, November 2013*.)

CEO and co-founder Mike Moradi reckons that Sensulin’s technology has an advantage over both Merck and MIT – even though the liposomal approach hasn’t exactly lit up the drug therapy world (there are just a couple of liposome-based treatments out there, including cancer drug *Doxil* [doxorubicin]). That’s in part because the approach uses less linker than gel matrices, as well as using normal, unmodified human insulin. “With a gel matrix, every single insulin molecule has to be connected to its neighbor by a linker. In contrast, there might be just 10 linkers on the surface of a liposome containing far more insulin molecules,” he argues. Less linker may mean fewer safety concerns – and a novel release profile. “We have to be better or faster than Merck; hopefully both,” says Moradi.

**Glycostasis Inc.**, quietly incubating within the Pacific Northwest Diabetes Research Institute in Seattle for about three years, reckons its smart insulin approach may, too, have an edge. According to CEO John Mulligan, PhD, Glycostasis’ offering stands out in being bi-directional: not only is more insulin released when blood sugar rises, but when sugar levels reduce, insulin is taken back out of circulation again, thus avoiding the risks both of hypo- and hyperglycemia. “Most of the other [smart insulin] schemes are uni-directional, in the sense that they basically allow controlled release
of insulin; it’s essentially glucose-responsive dissolution of a depot,” he argues.

Glycostasis won’t provide more details for now about its technology, which it has licensed from PNDRI (where Mulligan is also an academic). But with proof of principle in hand, Mulligan has begun to talk to investors and potential corporate partners. Both Glycostasis and Sensulin (which has thus far survived on angel funds and grants, including from the Juvenile Diabetes Research Foundation [JDRF], a prolific supporter of research into treatments and cures for type 1 diabetes) need partners to step in.

Partnerships may be hard to come by at such an early stage – though some positive data from Merck’s program may help. The regulatory hurdles facing any glucose-responsive insulin will be as high as the potential rewards from such a treatment. Large trials will likely be required to prove that it’s sufficiently responsive to avoid both post-prandial hyperglycemia and the hypoglycemia that could result in the case of an over-supply of insulin. Determining levels of residual insulin from a prior dose could also be challenging, not least given daily variation in dietary habits and, thus, insulin demand. Tresiba’s delayed approval provides a warning that expensive cardiovascular outcomes trials may be required too.

For all the regulatory risk, self-regulating insulins, if they get to market, would represent a huge step forward in the treatment of diabetes. Educating patients on how to safely manage their insulin dosage is a challenge; too many fail to do so. Smart insulin would reduce or even eliminate that management challenge – yet still potentially achieve better outcomes. That could help reduce payor resistance to funding yet another new insulin.

Longer-acting, faster, cheaper and needle-free insulins will be available long before smart insulin. These may raise both the efficacy and cost-effectiveness hurdles for smart insulins.

Yet as long as diabetes remains one of the world’s most pressing health concerns, efforts to find more effective treatments will continue in biopharma and device R&D. So will social and community-focused prevention projects, urban planning, education, and more. Traditional biotech investors may continue to avoid diabetes, and larger partners may remain on the fence for longer than in other therapy areas. But for those, like Dance’s Patton, at the R&D coalface addressing the epidemic, “there’s no retreat and no surrender. No matter what happens, we’ll go forward.”

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Past failures and high development costs have made Big Pharma wary of partnering in diabetes, demanding convincing data and differentiation.

Past failures and high development costs have made Big Pharma wary, demanding convincing data and differentiation. Trial results for Biodel Inc.'s BIOD-531 (concentrated recombinant human insulin with excipients) reported in January 2015 showed better glucose control than HumalogMix and the high concentration Humulin U-500, among patients with severe insulin resistance requiring high doses. But Biodel’s dogged by the rejection of an earlier formulation at FDA in 2010. This time, Biodel is proceeding alone into a Phase IIb trial among those with moderate insulin resistance, and is setting up pivotal trials for 2016. But with shares languishing at just $1.30 (down from $21 in 2010), the company will need help. Its last fundraising was an $18.5 million follow-on public offering in June 2013.

And licensing products like Adocia SAS’s third diabetes program, BioChaperone Combo, that assemble marketed drugs from different sponsors may be more complicated, even with good data. Pre-mix products like Lilly’s HumalogMix or Novo Nordisk AS’s NovoMix combine slow- and fast-acting insulins in one convenient injection. But efficacy is traded off: typically, the rapid portions aren’t rapid enough, and the slow component doesn’t last long enough (plus they come in pre-set ratios and so aren’t suitable for many). The first Phase I trial of BioChaperone Combo suggested that it improved both the speed of onset of the rapid-acting insulin, and the duration of action of the basal element relative to HumalogMix. (The Chaperone technology allows glargine to become soluble at physiological pH, meaning it can be more easily combined with prandial insulin.) The pre-mix market is worth $2.4 billion.