Metabolic and Inflammatory Disease R&D:
An Assessment of 5 Highly Promising Therapeutic Classes

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Executive Summary

The availability of the full sequence of the human genome and all the potential drug targets encoded therein provides a strong foundation for new drug research to be focused on the pursuit of specific targets. Although many of the targets identified have yet to be commercially exploited, there are a number of ways to validate their potential relevance as drug targets in the treatment of certain diseases. While not completely reliable, such validation provides a sound basis for the initiation of a specific target-based drug discovery program.

At any given time, a number of drug targets are attracting considerable interest from different pharmaceutical companies. The emergence of such targets as “hot topics” of research usually becomes apparent before the introduction of clinical candidates by a rapid increase in the level of patent activity directed toward such targets. This report seeks to identify targets falling into this category that are primarily of relevance to inflammatory or metabolic diseases and toward which few, if any, compounds directed at these specific targets have progressed into Phase II studies.

Although such extensive activity is indicative of corporate interest and perceived perception of the importance of certain targets, activity alone is no guarantee of commercial success. In the inflammation field the recent examples of lipoxygenase inhibitors and leukotriene antagonists highlight this point, with the more intensive activity directed at the former providing negligible commercial returns while the latter led to 3 successful products. With commercial success often achieved by either the first company to market a product directed at a new target or a fast follower, we have sought to identify the potentially successful players in each of 5 different areas.
The analogous example of dipeptidyl peptidase IV inhibitors is used to show that the first player (i.e., Novartis) in what becomes an intensively researched field is not always the first to succeed in getting a product to market. Merck’s sitagliptin (Januvia) was approved by the FDA for the treatment of type 2 diabetes in October 2006 and by the European Commission in March 2007.

The choice of chemokine antagonists, toll-like receptors, melanin-concentrating hormone (MCH) antagonists, melanocortin MC₄ agonists, and 11β-hydroxysteroid dehydrogenase inhibitors as the 5 topics of interest was based on an assessment of the levels of activity directed against various targets currently of considerable interest in creating new agents for the treatment of inflammatory, autoimmune, or metabolic disorders.

**Chemokine Antagonists**

Chemokine receptors are a family of 20 G protein–coupled receptors (GPCRs) that provide a large class of tractable drug targets for new anti-inflammatory drugs and, in certain instances, for the treatment of HIV infection or cancer. The inflammatory indications of greatest interest in this context are atherosclerosis, allergic rhinitis, asthma, chronic obstructive pulmonary disease (COPD), multiple sclerosis, and rheumatoid arthritis. To date, most of the industry’s interest in this class of receptors has focused on CCR1, CCR2, CCR3, CXCR1, CXCR2, and CXCR3 receptors for the treatment of inflammation and CCR5 and CXCR4 receptors for the treatment of HIV infection. In January 2007, 11 chemokine antagonists from 9 different companies were in clinical development for the treatment of inflammatory disorders, with 2 of these drugs, ChemoCentryx’s CCX-282 and Incyte’s INCB-3284, being the focus of high-value commercial deals with GlaxoSmithKline and Pfizer, respectively.

Many more chemokine antagonists are either in preclinical development or lead optimization, and most of the major pharmaceutical companies have current R&D efforts directed at chemokine receptor targets. A few specialist companies and some biotechnology companies have also shown considerable interest in this area. The most active companies are AstraZeneca, GlaxoSmithKline, and Schering-Plough. Although a number of chemokine antagonists have failed to progress beyond early Phase II clinical studies, reports of positive efficacy with some, for example, CCX-282 in treating Crohn’s disease, suggest that the promise of this approach may be realized provided that the appropriate target is chosen for the disease of interest.
Toll-like Receptors

Toll-like receptors (TLRs) form part of the host-defense pathway and a family of type I transmembrane proteins, with 10 human TLRs identified. One immunomodulatory drug, imiquimod (Aldura), was launched before it was shown to act via stimulation of specific TLRs. The different TLRs respond to certain lipopolysaccharides and/or oligonucleotide sequences and have a variety of functions, only some of which are currently well understood. Among these, the development of TLR-4 antagonists and TLR-7, TLR-8, and TLR-9 agonists has created the most interest to date, with considerable literature published on the TLR-2 receptor. Some TLR agonists are also of considerable interest as vaccine adjuvants rather than for direct use as therapeutics.

Twelve TLR ligands are currently in clinical development as therapeutics or adjuvants for the treatment of viral infections, cancer, sepsis, allergic rhinitis, and myalgic encephalomyelitis, and several have now progressed to Phase III clinical development. Few major companies appear to have active research efforts directed against TLRs, with the exception of the TLR-4 antagonist programs at Eisai and Takeda. Other major companies (AstraZeneca, GlaxoSmithKline, Novartis, Pfizer, and sanofi-aventis) have established deals with the specialist companies that are currently the major players in this field. Anadys and Coley are the most significant of the latter and also the most successful in striking major collaborative deals.

11β-HSD1 Inhibitors

The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) catalyzes the interconversion of hormonally active cortisol and inactive cortisone. The more relevant form (as a drug target) appears to be 11β-HSD1, which plays a role in regulating hepatic glucose output via activation of gluconeogenic enzymes, and its inhibition is suggested to be relevant for the treatment of both type 2 diabetes and metabolic syndrome. Although the enzyme was well characterized in the 1960s, the first patents claiming 11β-HSD1 inhibitors only appeared in 2001; from 2004 onward, there has been a rapid expansion in the number of published patents claiming 11β-HSD1 inhibitors.

Only three 11β-HSD1 inhibitors (INCB-13739, AMG-221, and PF-915275) are currently in clinical development, but most major companies have filed patent applications claiming inhibitors of this enzyme. The most active patentees are Biovitrum and Incyte, with several other specialist companies also active. Merck appears to be the most active of the major companies, although no clinical candidate has
yet been identified. Two important commercial deals have been struck between major companies and biotechnology companies, with the deal between Amgen and the field leader Biovitrum the more significant. At present, all 3 of the inhibitors are being clinically developed for the treatment of type 2 diabetes, although there appears to be greater longer-term market potential in their development for the treatment of metabolic syndrome.

**MC Receptors**

The melanocortin (MC) receptors are a family of 5 closely related GPCRs that recognize several peptide ligands, of which the neuronally located MC4 receptor seems to provide the most pertinent therapeutic target. It appears to regulate energy homeostasis, and thus its specific stimulation represents a potential approach to the treatment of obesity, while specific antagonists may provide a treatment for cachexia. The MC4 receptor also appears to be involved in the regulation of sexual function, suggesting a new approach to the treatment of sexual dysfunction.

The period 2000 to 2006 has seen a steady increase in the level of patent activity on agents acting at MC receptors, and this has been accompanied by a steady increase in literature activity. Currently, only 2 MC agonists are in clinical development, Palatin’s bremelanotide for the treatment of sexual dysfunction and Action Pharma’s less specific agonist AP-214 for the treatment of acute respiratory distress syndrome (ARDS). These 2 companies are the most active specialist players in this field, while Eli Lilly, Merck, Novartis, and Roche are the most active major companies. Several other biotechnology companies play a significant role in this field. The only extant commercial deal of significance is one struck by Palatin with King Pharmaceuticals for the marketing and development of bremelanotide.

**MCH Receptors**

The MCH receptor MCH-1 is also a GPCR, and the effects of MCH on the stimulation of food intake appear to be via activation of this receptor. Thus, MCH-1 antagonists provide a potential means of treating obesity, an effect that has stimulated the growth in interest in this target since 2000, both in terms of patent applications and literature activity.
Three MCH-1 antagonists have currently reached Phase I development for the treatment of obesity, with several other identified compounds in preclinical development. Neurogen’s NGD-4715 appears to be the most significant of the 3 and is possibly the only one in active clinical development. A number of major companies are active in this field, with both Amgen and GlaxoSmithKline having progressed compounds to clinical development, while several specialist biotechnology companies (e.g., 7TM Pharma, Biovitrum, and Neurocrine) are also active players. MCH-1 antagonists appear to have been encompassed in 2 significant commercial deals, but have not been explicitly identified as a major focus of deals between Arena and Taisho or Abbott and Millennium.

Each of the 5 target classes considered in this report has the potential to provide high-revenue drugs, for the treatment of inflammatory disease, obesity, and metabolic syndrome. However, little or no clinical validation of this hypothesis has yet been produced by any of the targets. Only when comprehensive Phase II data are available will it be possible to more accurately assess which of these targets represent major commercial opportunities.
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**Chemokine Antagonists: Strong Evidence...Well Validated.**

*Q&A with Dr. Kris Vaddi, vice president, Preclinical Biology, Incyte, and Dr. Robert Newton, Drug Discovery Biology, Incyte* | 47

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**Thromboxane Antagonists**

The cardiovascular market also provided the stimulus for the development of thromboxane (TP receptor) antagonists as antiplatelet agents. The role of the unstable arachidonic acid metabolite thromboxane A₂ in the aggregation of platelets, and also in the constriction of vascular smooth muscle, suggested that blocking this response would provide a valuable new class of antiplatelet agents. Accordingly, most major companies initiated research efforts in this area, leading to extensive patent activity. There had been considerable success in identifying potent, orally active agents when it became apparent that the cardiovascular protective effects of aspirin were attributable to its interaction with platelets, leading to a specific inhibition of thromboxane A₂–induced aggregation of platelets. This discovery destroyed the commercial case for the development of thromboxane antagonists for the treatment of cardiovascular disease, because aspirin is available so cheaply. A number of companies continued to develop thromboxane antagonists for other indications, and 2 of them, Takeda’s domitroban (Bronica) and Bayer’s ramatroban (Baynas), were eventually launched for the treatment of asthma and allergic rhinitis, respectively; however, both are only available in Japan and neither generates significant sales revenues.

**Long-lived Efforts**

It is also possible to identify areas of research in which activity has been directed against a target for a prolonged period of time without any agent having successfully progressed through clinical development. Although most projects have only a finite lifetime before being stopped if success is not forthcoming, on some occasions the perceived potential returns from a project result in unusual longevity. Two projects in the anti-inflammatory field that fall into this category are p38 [mitogen-activated protein (MAP)] kinase inhibitors and PDE4 inhibitors.

**p38 MAP Kinase**

p38 MAP kinase is one of the pivotal kinases in the intracellular signaling cascade that regulates the response of most cells to stress and various other stimuli. Activation of the kinase results in the release of a plethora of inflammatory mediators, including cytokine, chemokines,
and prostaglandins, thus representing an obvious target for companies that seek to develop novel anti-inflammatory agents for the treatment of arthritis and other indications. Although a group at SmithKline Beecham had identified a series of compounds that inhibited the production of these mediators as early as 1984, it was only the identification of their molecular target as $\text{p38}\alpha$ kinase in 1994 that provided the major stimulus for activity in this area. Before this, the series of identified compounds had been described as acting as cytokine-binding proteins and the company had even trademarked the name CSAID (cytokine-specific anti-inflammatory drug) to cover them.

Activity in this area has been heavy since then, as highlighted by a number of reviews of patent activity in the past 10 years. It remains an area of intense activity, with some 70 patent applications of relevance published in 2006. Despite more than 20 years of research activity directed against the target, the pharmaceutical industry has so far succeeded in progressing only 1 agent to late-stage Phase II studies, Boehringer Ingelheim’s doramapimod, development of which appears to have been terminated due to lack of efficacy. Currently, 15 compounds with this mechanism of action are reported to be in clinical development in either Phase I or II studies. Many problems in developing agents that target this kinase have been reported, with toxicity, especially hepatotoxicity, a major issue and side effects also a problem. Most of the toxicity issues appear to be intrinsic to chemical classes investigated and not related to the target. There is thus sufficient incentive to continue pursuing this target.

**PDE4 Inhibitors**

The development of PDE4 inhibitors has had a more mixed record. They were first suggested to be of use in the treatment of asthma in the late 1980s, and it subsequently became apparent that they were effective anti-inflammatory agents and had the ability to relax airway smooth muscle. This resulted in the initiation of many research programs throughout the 1990s and a rapid increase in patent filings. By 1996, more than 50 applications per year were being published, and filings have continued at this high level since, with some 85 filings published in 2006. Despite this activity and many compounds having entered clinical development, no PDE4 inhibitor has yet been approved for clinical use.

Side effects have been a major issue in the failure of PDE4 inhibitors to progress, with mechanism-related side effects due to different PDE4 isoforms, most notably the induction of emesis, leading to the
development of a good number of drugs being abandoned. Despite attempts to eliminate activity at the undesired isoform primarily responsible for this effect and the development of models to screen out such activity, only 2 PDE4 inhibitors succeeded in progressing beyond Phase II studies. A New Drug Application (NDA) was filed for GlaxoSmithKline’s cilomilast in December 2002 for its use in the treatment of chronic obstructive pulmonary disease (COPD), its development for the treatment of asthma having been terminated due to inadequate efficacy. Although deemed as approvable, an additional longer-term (6 or 12 months) Phase II study was requested by the FDA, apparently due to inconsistent efficacy. Although the company still listed cilomilast as approvable in 2006, it now appears unlikely to progress to the market.

Altana (Bad Homburg, Germany), in collaboration with Pfizer and Tanabe, developed roflumilast for the treatment of both asthma and COPD, but Pfizer terminated its involvement in July 2005 after the results of a Phase III study in COPD patients. Altana had already filed for European approval, in February 2004, for the use of roflumilast to treat both asthma and COPD, but subsequently withdrew the Marketing Authorization Application (MAA) in November 2005 after adding additional data. The MAA has yet to be resubmitted and the planned filing of an NDA in 2006 did not occur. Altana Pharma became part of Novo Nordisk in January 2007, and the latter has yet to indicate its intentions. Tanabe currently anticipates filing a Japanese regulatory submission in 2007.

1.4. Reasons for Failures

The above examples highlight some possible reasons why effective agents may fail to proceed to the market even when they are directed against a validated target and represent a novel therapeutic approach. Clearly, mechanism-related side effects can be a major problem and one that cannot always be circumvented, but side effects or toxicity that are inherent to the structure/structural class being developed are not necessarily indicative of an insurmountable problem. Some classes of target do seem to pose more problems in this regard than others; the nature of the transformation effected by the 5-lipoxygenase enzyme appeared to result in many specificity issues with the bulk of the inhibitors identified.

Other common issues, generally related to structure but independent of the desired activity, are hepatotoxicity due to interactions with P450 enzymes. Several P450 isoforms display very broad substrate specificity,
and this can pose a problem with agents, such as MAP kinase inhibitors, where the SAR of the 2 enzymes overlaps. Accordingly, many MAP kinase inhibitors have failed to progress for such a reason. Target specificity is another issue that has contributed to the problems of MAP kinase inhibitors, reflecting on the difficulty of modulating specificity when targeting drugs to a specific region of the desired target for which closely homologous regions are to be found in other targets.

Commercial factors are less commonly a cause of failure, with the thromboxane antagonists mentioned above representing the most extreme example of such issues. However, commercial reassessment of the prospects of a product, due to an improved understanding of the relevance of the target, may result in some projects being terminated, especially by the largest companies, which generally require greater returns from a product. The levels of such internal hurdle rates may be as high as $500 million in sales per year.

None of these potential problems should be regarded as a disincentive to pursue a specific target for the development of new drugs. Provided that the target is reasonably validated as relevant to the desired indication, there are good grounds for initiating a discovery project directed at that target. That such a process occurs concurrently in a number of companies is highlighted by the growth of activity directed against specific targets and leads to their emergence as hot topics for drug R&D.
CHI: Why are most 11β-HSD1 inhibitors currently being developed for the treatment of diabetes rather than, for example, metabolic syndrome?

Dr. Vicker: Essentially because of the superior clinical understanding, and clinical models, of type 2 diabetes.

Dr. Hollis: The FDA recently indicated that it does not regard metabolic syndrome as a registerable indication, and EU authorities have a similar attitude; therefore, studies in the component indications, such as type 2 diabetes, are required. In addition, there is scientific and commercial logic for pursuing type 2 diabetes. There is a logical endpoint, proximal to the point of intervention, and the endpoint should more quickly be achieved; this condition provides well-defined clinical endpoints such as Hb1Ac.

CHI: Do you consider 11β-HSD1 inhibitors to be of potential use in treating nonmetabolic disorders?

Dr. Vicker: They may be of potential use for specific conditions such as hypertension, inflammation, osteoporosis, polycystic ovary syndrome, and Alzheimer’s disease, as well as diseases for which damping down of cortisol levels should be beneficial.

Dr. Hunter: The role of the enzyme in other conditions is currently less well validated.

CHI: Is there any significant risk of mechanism-related side effects?

Dr. Vicker: The enzyme’s involvement in the tight regulation of cortisol levels certainly suggests that it is possible. However, the use of tissue-specific agents and targeting diseases in which cortisol levels are elevated should minimize the risk.

Dr. Hunter: This target is selectively expressed in certain tissues and the effects are predominantly (exclusively?) intracellular, thus minimizing the risk of side effects. No evidence of such side effects has yet been seen, and monitoring the hypothalamic-pituitary-adrenal axis provides a means of identifying potential issues.
Metabolic Syndrome

Metabolic syndrome (or syndrome X) represents a condition that is seriously undertreated and for which the market is relatively undeveloped. In the absence of therapies specifically targeting the condition, patients rely on the use of agents that treat one or more of the concurrent symptoms of diabetes, hypertension, and obesity. Because the prevalence of the condition is currently estimated to be greater than 20% in US adults, it clearly represents a major market opportunity for any agent that can concurrently treat more than one of the underlying symptoms. A number of reviews have suggested that inhibition of $\beta$-HSD1 would be particularly beneficial in the treatment of this condition.38,39

Obesity

Obesity is currently a commercially undeveloped market. There is a clear need for effective therapeutics for the treatment of obesity that lack significant side effects. Such agents could expect to be widely used simply to treat obesity and also to reduce the risk of developing other medical problems, heart disease, type 2 diabetes, and metabolic syndrome as a consequence of being severely overweight. Obesity thus represents a major unmet medical need and provides significant market potential.

Although obesity forms a central element of metabolic syndrome, however, there is relatively little evidence to suggest that inhibition of $\beta$-HSD1 is likely to be an effective method of treating obesity.

CHI: Please comment on the current state of the art in other companies' development of $\beta$-HSD1 inhibitors.

Dr. Vicker: Merck appears to be the most advanced, with its compound probably ahead of Pfizer's and Incyte's. Both Roche and Amgen appear to have compounds at a less advanced stage, while the status of programs at AstraZeneca and Johnson & Johnson is uncertain. Abbott’s intense interest and filing of several process patents are suggestive of progress toward the clinic.

Dr. Hollis: Many other companies are pursuing this because it is a very attractive target. An extensive and large patent landscape has resulted from their efforts, with Incyte having contributed significantly to this.
Because there are many other, more direct, approaches to the potential treatment of obesity, it does not appear to be generally regarded as a desirable indication for which to develop 11β-HSD1 inhibitors.

Memory Disorders

The role of 11β-HSD1 in cognition is less well documented, but there are a number of suggestions that implicate the enzyme in the development of impaired memory and indicate that 11β-HSD1 inhibitors could be of value in treating aspects of this condition. How valuable such an approach could be would depend on the range of conditions that it would be suitable in treating, but the relative lack of treatments for such increasingly prevalent conditions indicates that there is significant market potential.

Some evidence of efficacy of this approach has been generated in both mice and humans using carbenoxolone and tends to substantiate the presumed role of the enzyme in the brain. One company, AGY Therapeutics (South San Francisco, CA), is pursuing this approach, having filed one patent application specifically relating to such a use of 11β-HSD1 inhibitors. Merck reported that it has explored the utility of some of its 11β-HSD1 inhibitors in animal models of cognitive function.

Inflammation

Because glucocorticoids are widely used in the treatment of inflammatory diseases, an enzyme that regulates endogenous levels of cortisol might be anticipated to play a key role in regulating the inflammatory response. There is limited evidence for the role of 11β-HSD1 in the development of inflammation, although it has recently been suggested that it does play such a role. In contrast, Bionetworks recently presented evidence to suggest that 11β-HSD2 is more significant in the development of inflammatory disease.

6.4. Possible Pitfalls

The potential pitfalls that may relate to the development of any 11β-HSD1 inhibitors are most likely to be due to an inability to demonstrate sufficient clinical efficacy despite extensive inhibition of the enzyme (Figure 6.1). The lack of homology to 11β-HSD2 suggests that specificity is unlikely to be a significant issue and that any observed side effects will either be compound specific, due to unanticipated selectivity issues, or mechanism related. The latter
may prove to be more of a problem if one attempts to develop agents for the treatment of memory disorders, when endocrine side effects might be observed, than for the converse problem with inhibitors developed for the treatment of diabetes or metabolic syndrome.

**Figure 6.1. SWOT Analysis for 11β-HSD1**

- **Strengths:**
  - Relevant target for several indications
  - Potential for directly targeting metabolic syndrome
  - Well-defined target, with selectivity unlikely to be a problem

- **Weaknesses:**
  - Mechanism-related side effects may become apparent
  - Risk of having effects other than for the desired indication

- **Opportunities:**
  - Major commercial opportunity in addressing unmet medical needs of metabolic syndrome
  - Significant potential for providing another class of agents for the treatment of type 2 diabetes

- **Threats:**
  - Many alternative approaches for the treatment of type 2 diabetes either available or in development.
  - Risk of not being able to show clear efficacy in treating metabolic syndrome

**Source: Norman Consulting**

The other risk, and one that appears to have been recognized by most of the companies currently developing 11β-HSD1 inhibitors, is that it is preferable to develop agents for a condition for which the clinical trial design is well established, and with clear endpoints, than for a condition for which there is no established clinical trial paradigm or clearly defined clinical endpoints.
Although 11β-HSD was first described in the 1960s, the area attracted relatively little interest in the period before 1970; no patents describing 11β-HSD1 inhibitors were published until 2001 (Figure 6.2). Biovitrum was the first company to file a patent application claiming such inhibitors, in May 2000, with 2 further filings in 2001 before Merck and AstraZeneca’s first filings in mid-2003. Some 21 filings from 8 different companies were published in 2004, and the rate of publication, and number of companies involved, exploded in 2006.

**Figure 6.2. Literature and Patent Activity in the 11β-HSD Field, 2000 to 2006**

![Literature and Patent Activity Graph]

Source: Norman Consulting

The literature activity in this area was fairly constant for most of the 1990s and then underwent an upsurge of interest after 2000, with the annual rate of publication of relevant papers tripling by 2005. There is no one paper that explains the upsurge in interest in what was a fairly well-documented target, although the increasing evidence for the role of the enzyme in regulating the development of metabolic syndrome may have been the driving force for this increase in literature activity. Although glycyrrhetinic acid was described as an 11β-HSD1 inhibitor as early as 1993, this disclosure provided no stimulus to the increase
in interest in this enzyme as a drug target. The concurrent upsurge in interest in the enzyme by pharmaceutical companies would appear to be attributable to the increasing understanding of its physiological role.

To date, only four 11β-HSD1 inhibitors are confirmed as having entered clinical development. Biovitrum’s BVT-3498 (AMG-311) entered clinical trials in 2002, and Phase I studies were completed by the end of October 2002 (Table 6.1). Phase II trials in patients with type 2 diabetes commenced in March 2003, and interim results were reported in 2004. Amgen acquired the rights to the program in September 2003, but development of BVT-3498 was stopped in 2004, with effort switched to backup compounds, of which AMG-221 has now entered clinical development. Although BVT-3498 was reported to be safe and well tolerated, no details of its efficacy have been published.

### Table 6.1. 11β-HSD1 Inhibitors in Clinical or Preclinical Development as of December 2006

<table>
<thead>
<tr>
<th>Drug</th>
<th>Developer</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCB-13739</td>
<td>Incyte</td>
<td>Type 2 diabetes</td>
<td>Phase II</td>
</tr>
<tr>
<td>AMG-221</td>
<td>Amgen</td>
<td>Type 2 diabetes</td>
<td>Phase I</td>
</tr>
<tr>
<td>PF-915275*</td>
<td>Pfizer</td>
<td>Type 2 diabetes</td>
<td>Phase I</td>
</tr>
<tr>
<td>BVT-3498</td>
<td>Biovitrum/Amgen</td>
<td>Metabolic syndrome</td>
<td>Discontinued</td>
</tr>
<tr>
<td>BX-1</td>
<td>Bionetworks</td>
<td>Rheumatoid arthritis</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Unidentified</td>
<td>Abbott</td>
<td>Type 2 diabetes</td>
<td>Preclinical</td>
</tr>
<tr>
<td>JNJ-25918646</td>
<td>Johnson &amp; Johnson</td>
<td>Metabolic syndrome</td>
<td>Preclinical</td>
</tr>
<tr>
<td>544</td>
<td>Merck</td>
<td>Type 2 diabetes</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Unidentified</td>
<td>Wyeth</td>
<td>Metabolic syndrome</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Unidentified</td>
<td>Takeda</td>
<td>Metabolic syndrome</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Unidentified</td>
<td>AstraZeneca</td>
<td>Metabolic syndrome</td>
<td>Preclinical</td>
</tr>
<tr>
<td>STX-1904</td>
<td>Ipsen</td>
<td>Metabolic syndrome</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

*Inferred to be an 11β-HSD1 inhibitor (see text).

**Note:** Abbott, Takeda, and Wyeth have all described preclinical efforts but have not yet publicly identified compounds by company code numbers.

**Source:** Norman Consulting
Incyte's INCB-13739 is also in clinical development. It is possible that some of the compounds described in Table 6.1 are also in early-stage clinical development. Both Merck and Pfizer have compounds identified as being in clinical development for the treatment of type 2 diabetes, although their mode of action has not yet been disclosed. In December 2006, Pfizer listed PF-734200 as being in Phase II studies and PF-915275 in Phase I, but it had reported in November 2006 that an unidentified 11β-HSD1 inhibitor (presumably PF-915275) was in Phase I clinical development, while Merck listed MK-0893, MK-0941, and MK-3887 as being in Phase I studies. MK-3887 entered clinical development in late 2006 and MK-0893 and MK-0941 in 2005.

INCB-13739

Incyte's INCB-13739 was the third 11β-HSD1 inhibitor to enter clinical development, with dose-escalation Phase I trials only commencing in June 2006, and in November a second Phase I study, in obese, insulin-resistant patients, was initiated. This study is described by Incyte as a Phase IIa study, and in January 2007 the company reported preliminary results showing that INCB-13739 produced complete inhibition of 11β-HSD1 in both adipose and liver tissue in 6 patients. A 28-day study is due to begin in the first quarter of 2007, while a 3-month study in type 2 diabetics is being planned, possibly starting in late 2007.

AMG-221

AMG-221 was the second development compound to emerge from the discovery program at Biovitrum. It entered clinical development in 2005 but has not yet been reported to have progressed to Phase II studies. At the end of September 2006, AMG-221 was still reported by Amgen to be in Phase I clinical development. No information on the tolerability of AMG-221 is available, and in a January 2007 presentation Biovitrum was unable to indicate when Phase II studies were scheduled to begin.

Preclinical Efforts

Table 6.1 also shows 8 companies as having 11β-HSD1 inhibitors in preclinical development. Three of these—AstraZeneca, Ipsen, and Takeda—have yet to present any details of their activity in this area.
Bionetworks is developing a derivative of the natural product
glycyrrhetinic acid, as BX-1, while the remaining companies shown in
the table have all described parts of their efforts in this area, many of
them in a session at the March 2006 American Chemical Society
(ACS) meeting.

In March 2006, the ACS Medicinal Chemistry section devoted a
session to 11β-HSD1 inhibitors. This featured presentations by Janssen,
Merck, Takeda, and Wyeth, with Pfizer and Merck also submitting
communications at the same meeting, while Abbott and Amgen/
Biovitrum presented details of their programs at the September
2006 meeting.

### 6.5. Active Major Companies

Fourteen major companies had published patent applications claiming
11β-HSD1 inhibitors by the end of 2006, as shown in Figure 6.3. Six of
these companies currently have 3 or fewer applications published. Both
applications from Bristol-Myers Squibb were published in late 2006 and
may be indicative of an ongoing effort, while all 3 published
applications from Eli Lilly appeared in mid-2006. Similarly, both
applications from Daiichi Sankyo and the solitary application from
Astellas appeared in 2006, with only 1 application from Novartis,
published in 2004, appearing to relate to a program that is unlikely
to be currently active.