The neuroscience R&D group at Pfizer Inc., serving one of the big pharma’s five core therapeutic areas, has survived serial cuts and reorganizations to emerge a transformed unit. The group is noticeably streamlined, with a smaller therapeutic footprint and a mandate to unravel the biology underlying its chosen indications before moving compounds to the clinic. Pfizer will no longer pursue therapeutic areas such as depression or anxiety where new mechanisms have thus far failed to improve on existing therapies and address unmet medical need. Instead it will focus on legacy indications such as pain and schizophrenia, new indications such as neurodegenerative disease or autism, and orphan opportunities such as familial amyloid polyneuropathy, where it hopes to market Vyndaqel (tafamidis meglumine) (“When Is A Single Pivotal Trial “Robust” Enough? FDA’s Katz Offers Examples That Could Spell Trouble For Pfizer’s Vyndaqel” — “The Pink Sheet,” Jun. 4, 2012).

According to SVP and Head of PharmaTherapeutics R&D Rod MacKenzie, Pfizer’s persistence in neuroscience R&D is based on high unmet medical need, the insupportable cost of neurological disease to society, and Pfizer’s historical presence in these markets. Only a few years ago, Pfizer and its peers generated billions of dollars on CNS drugs of questionable efficacy whose mechanisms were poorly understood. Now it won’t invest in projects unless there is a strong scientific hypothesis.

Mackenzie said that with the hiring of Duke University neurobiology professor and Howard Hughes scholar Michael Ehlers as CSO in June 2010, Pfizer has taken a radically different approach in which molecular genetics and systems biology merge with an understanding of how circuitry works in the brain.

A Root-And-Branch R&D Strategy

A major reason for the “root-and-branch” revolution is the comparatively poor success rates and long development timelines for CNS drugs, according to the March/April issue of the Tufts CSDD Impact Report. “We’re at a point of inflection,” MacKenzie said, “where we need to take this moment to invest strongly. But not in the same way as we have in the past.”

A lot of industry’s historical failures were rooted in reliance on animal models that did not translate to human disease. Therefore, Pfizer is aiming to increase the amount of human biology in its datasets, and make stronger linkages, through human clinical pharmacology studies across a wide variety of neuro-functional domains.

The team is also trying to stratify patient populations, betting that in order to be successful in a specific pathway, it will need to identify biomarkers of response. Taking a page from the “precision medicine” playbook that worked so brilliantly in the case of its lung cancer therapy Xalkori (crizotinib), Pfizer neuroscience is trying to forge the same kind of tight genetic linkage in subsets of patients suffering from CNS disease, although it recognizes that the genetics of neurology are much less well described than the genetics underlying cancer.

In the new research paradigm, researchers start with symptom domains, for instance, inattention, distractibility, and executive dysfunction (referring to impairment of the mental processes involved in goal-directed activity). These symptoms are common to several indications, including schizophrenia, dementia, and depression, and they, in turn, correspond to cognitive domains, actual structures that can be imaged in the human brain. Cognitive domains might be working memory, goal-directed attention, performance monitoring. Moreover, the cognitive domains are served by a particular circuitry - in this case, the frontal parietal circuit.

Pfizer neuroscientists link symptoms with cognitive domains and link those domains with the neural circuitry, then they image it using technologies like positron emission tomography (PET) and functional magnetic resonance imaging (FMRI). “Now you first have to understand a lot of the circuitry,” MacKenzie explained, “and then you have to get into the circuitry, into the pathways, and then you get into the molecular targets. This provides a kind of stable platform for launching off into an indication.”

One consequence of this emphasis on neurobiology is how Pfizer is reconfiguring its R&D staff. Ehlers says he’s looking for scientists with strong skills in quantitative biology or the...
physical sciences. The idea is to build interdisciplinary teams with capabilities in biophysics, structural biology, electrophysiology, enzymology, bioinformatics, and human genetics.

The relocation of neuroscience research, along with cardio-metabolic research, from Groton, Conn., to a site licensed from MIT in Cambridge, Mass., is designed to place neuroscience research in close proximity to leading life science and IT firms in the area. MacKenzie and Ehlers hoped that this will promote valuable cross-talk between Pfizer scientists and their peers outside the company, and also that it will make it easier to hire in the interdisciplinary skill sets needed to build integrated research teams (“Pfizer Moves CNS And Cardio-Metabolic Research To Cambridge, Mass., Promotes Cross-Talk With Local Scientists” – “The Pink Sheet” DAILY, Jul. 3, 2012).

Another consequence is that this sort of profound change in the way research is done takes time to show results. “You can’t expect to turn this around in a year or two years,” MacKenzie said, “so it was a well considered decision to make this investment. We’re in it to win,” he said, and the company is committed for the long haul.

Its marketed CNS products, particularly in the areas of pain and schizophrenia, plus commercial pain assets gained in the King Pharmaceuticals acquisition, can help fund the novel research in the near term. And over the mid-term, late-stage label expansion trials for Lyrica (pregabalin) and Celebrex (celecoxib), or for near-to-market candidates from King Pharmaceuticals based on the mu-type opioid receptor, will help sustain the unit. But neuroscience will need to show results in the form of projects advancing through the clinic in the next five years if it is to prosper in Pfizer’s demanding “invest to win” business culture.

**The Neuroscience Pipeline**

Pfizer’s neuroscience clinical pipeline is heavily weighted toward pain, with indications spanning both acute and chronic pain. MacKenzie said pain is a substantial market that’s poorly served, primarily with reformulations of existing drugs for attributes such as convenience, abuse deterrence, extended half-life, and so forth. Pfizer is interested in these kinds of incremental improvements. But it’s also diving into novel disease-modifying mechanisms, particularly based on ion channels, and has sponsored original academic work showing genetic support for the role that ion channels play in pain states.

The neuroscience pipeline posted on Pfizer’s website in May shows 20 ongoing trials. Of the nine in registration or Phase III, seven are for various pain indications (eight if transthyretin familial amyloid polyneuropathy is considered a pain indication). Four of these late-stage trials are for new indications or a dosing improvement for the aging franchises Lyrica and Celebrex. Pfizer believes there is still revenue to be wrung from these workhorses, and is seeking expanded labels in peripheral and central neuropathic pain, or a controlled-release formulation (Lyrica) or a chronic pain indication (Celebrex). (A U.S. district court ruled on July 20th that Pfizer’s patents on Lyrica are “valid and infringed,” and gave the company exclusive rights to sell the drug until 2018. Pfizer sued the defendants, including Teva Pharmaceuticals USA and Sun Pharmaceutical Industries Ltd., for infringing Lyrica’s patents.)

Pfizer’s acquisition of King Pharmaceuticals in October 2010 accounts for two of the late-stage drugs, an abuse-resistant version of Remoxy (oxycodone) in registration, and an extended-release version of oxycodone-naltrexone in Phase III. Last July, Remoxy received its second of two “complete response” letters from FDA in less than three years, this time for manufacturing issues (“Remoxy’s “Complete Response” Letter Has No Clear Culprit But Many Suspects” – “The Pink Sheet” DAILY, Jun. 24, 2011).

Phases I and II show less of an emphasis on pain. Of 11 drugs, four are for pain, however the indications, targets, and therapeutic modalities are distinct from the late-stage pain pipeline. For instance, tanezumab, the anti-NGF (nerve growth factor) antibody that is still under an FDA clinical hold for osteoarthritis, is in Phase II for cancer pain. And PF-05089771, a small molecule against the novel Nav1.7 target, is in Phase II for acute pain, and in Phase I for chronic pain.

Other priority areas of focus in the neuroscience portfolio include schizophrenia (one drug in Phase II, two drugs in Phase I) and Alzheimer’s disease (bapineuzumab in two Phase III trials, and two earlier candidates in Phase I). Bapineuzumab, in late stage testing, has begun releasing results – the trial in ApoE4 carriers reported out on July 23 that it failed to hit its primary efficacy endpoints; the trial for ApoE4 non-carriers, which might have a better chance of success based on a Phase II trial in the same population, will be completed in August (“Bapineuzumab Failure Raises More Doubts About Beta Amyloid Approach In Alzheimer’s” – “The Pink Sheet” DAILY, Jul. 23, 2012). The Phase I Alzheimer’s drugs both came with Wyeth; they include PF-05236812, a passive immunotherapeutic antibody approach to clearing beta-amyloid, and PF-05212377, an oral 5-HT6 antagonist. Regarding ‘2377, Mackenzie said “we think we can get a cognitive benefit on top of donepezil. We’re also hoping to show some benefit on some of the mood scores.”

The schizophrenia candidates include a phosphodiesterase inhibitor, PF-02545920, in Phase II, and two Phase I compounds: PF-04958242, an AMPA glutamate receptor agonist being tested for both schizophrenia and sensorineural hearing loss, and PF-0518099, target unspecified. Vabicaserin (PF-05208769), a mixed serotonergic agent that originated with Wyeth, appeared in Pfizer’s February neuroscience pipeline as a Phase I candidate, but has since been dropped.

It is striking that projects further upstream in the pipeline, in Phases I and II, are almost entirely new molecular entities. There are also several “one-offs,” opportunistic compounds in which the group sees promise. These include PF-04427429, an antibody against calcitonin gene-related peptide (CGRP) in Phase I for chronic migraine, and PF-03049423, a compound in Phase II for recovery from ischemic stroke.
Pfizer's Neuroscience Acquisitions, 2006 to 2012

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<th>Deal Date</th>
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<tr>
<td>7/1/2011</td>
<td>Pfizer pays $49.8 million for remainder of partner Icagen. Deal brings ion channel expertise with applications in pain, epilepsy, and inflammation. Pfizer discovered its Phase II Nav1.7 blocker PF-05089771 around 2007 and soon after the company sought collaborative help from sodium channel specialist Icagen and made an equity investment in the biotech; Pfizer subsequently acquired Icagen for their expertise in ion channel screening and biology.</td>
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<td>10/1/2010</td>
<td>Pfizer to acquire King for $3.56 billion, gains pain portfolio. Though not necessarily top sellers, Pfizer was particularly attracted to King’s pain relief products and strong sales force in that area. King’s pain portfolio includes Embeda (morphine), the Flector (diclofenac epolamine) patch, and recently launched Embeda (morphine sulfate/naltrexone hydrochloride), which is the first available opioid pain reliever designed to prevent misuse and abuse. In addition, King has two oxycodone compounds, Remoxy (licensed from Pain Therapeutics) and Acurox (from Acura), which have been held up in the approval process because the FDA has stated it wants further proof that they will cut down on dependency.</td>
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<tr>
<td>9/1/2010</td>
<td>Pfizer acquires FoldRx for undisclosed sum, bringing expertise in neurodegenerative diseases involving protein misfolding. FoldRx brought its lead candidate tafamidis meglumine for transthyretin amyloid polyneuropathy into Pfizer’s portfolio. The drug received a complete response letter in June after a mixed advisory committee review.</td>
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<tr>
<td>4/1/2006</td>
<td>Pfizer acquires Rinat Neuroscience, a specialist in protein engineering. Rinat was spun out of Genentech in 2001 with Genentech’s neuroscience assets. Rinat brought an Alzheimer’s program and tanezumab, the antibody targeting nerve growth factor.</td>
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Source: Elsevier’s Strategic Transactions

Pfizer declined to describe its preclinical neuroscience projects and even some Phase I candidates. However, MacKenzie confirmed that the pharma has a small but dedicated lab working on the basic biology of autism via internal efforts and academic collaborations. In an April 2012 article published in the journal Science Translational Medicine, researchers from the National Institute of Mental Health and Pfizer reported that an investigational inhibitor of mGlur5 (metabotropic glutamate receptor subtype 5) called GRN-529 improved social interactions and lessened repetitive behaviors in mice bred to display autism-like behavior. He also referred to some target work the neuroscience group is doing around cerebral amyloid angiopathy, a small-population, often fatal disease involving bleeds in the brain. The company also is investigating neurodegenerative diseases such as Parkinson’s via a collaboration with the Michael J. Fox Foundation for Parkinson’s Research focused on the LRRK2 gene, and also Huntington’s disease.

Accessing Assets and Platforms Via Business Development

Pfizer’s M&A record over the past five years brought the big pharma assets, platforms, and capabilities with direct relevance to neuroscience. The acquisition of Wyeth in 2009 brought CNS molecules in all phases, including bapineuzumab and early stage drugs to treat Alzheimer’s. It also brought biologics manufacturing capacity and R&D capabilities to supplement the Global Biotherapeutics Technologies group and the neurology-specific protein engineering expertise of Rinat Biosciences which Pfizer acquired in 2006.

The acquisition of FoldRx brought expertise in regulating protein misfolding with broad applications in neurodegenerative disorders including transthyretin amyloid polyneuropathy. FoldRx originated Pfizer’s Vyndaqel for that disorder. Moreover, FoldRx likely gave Pfizer neurosciences its beachhead in autophagy. Upregulating autophagy, and so degrading and removing misfolded proteins involved in neurodegeneration is a rising therapeutic approach.

The recent acquisition of Icagen supplemented Pfizer’s capabilities in ion channel regulation. In May 2011, Pfizer and Icagen joined with Yale School of Medicine to study the effect of selectively blocking Nav1.7 sodium channels with Pfizer’s compounds. Previous research has shown that patients with a rare genetic disorder called inherited erythromelalgia possess mutations of Nav1.7 channels resulting in severe chronic pain.

Finally, the King Pharmaceuticals acquisition brought assets and capabilities of another sort. King boasted an attractive portfolio of marketed and developmental pain products — largely based on opiates — and a strong commercial organization.

Pfizer neurosciences has been much less active on the licensing front. In the only recent deal, a 2009 collaboration with Adimab LLC, the antibody specialist looked to identify candidates against pain targets selected by Pfizer. MacKenzie said that neurosciences is looking for external opportunities, and that the ideal “sweet spot” is IND or Phase I. The reason, he explained, is that the pharma can then design the Phase II study, which is “what we do best.” As Pfizer continues to retool its internal portfolio, it recognizes the need to build it up. The challenge, MacKenzie said, is that “there are
relatively small numbers of very high-quality substrate out there, and we apply a very strong filter.”

And beyond commercial M&A and alliances, Pfizer is actively collaborating with disease foundations such as Michael J. Fox or Cure Huntington’s Disease. And although Pfizer’s CTI program is currently focused on biologics, MacKenzie said there is discussion within the R&D organization about how to involve small molecules. He predicts it will happen soon and it will “open up a whole variety of new potential investigators who might be involved with us, and that of course will hopefully end up going to the neuroscience group.”