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Axel Unterbeck on memory, cognition and the development of CNS drugs

Interviewed by Steve Carney

Axel Unterbeck,
President, Memory Pharmaceuticals

Axel Unterbeck, President, Director and Co-Founder of Memory Pharmaceuticals, has extensive experience in drug discovery, most notably with Bayer in the field of CNS research, being particularly involved in the discovery of drugs for Alzheimer's dementia, cerebral stroke and head trauma. His Bayer group was responsible for the development of the acetyl cholinesterase inhibitor, metrifonate, for the treatment of dementia, and BayX3702, a neuroprotective agent currently in Phase III clinical trials. Prior to his arrival at Bayer, Unterbeck was one of the team in the University of Cologne, Germany, led by Professors Müller-Hill and Beyreuther that in 1987 achieved the first full-length cloning of the human amyloid precursor protein. He received his MS/BS in Biology and Molecular Genetics from the University of Bonn, Germany, in 1982 and his PhD in 1986 from the Institute for Genetics in Cologne.

Could you give me some information about Memory Pharmaceuticals – size, structure, focus and company mission and objectives?
As you know, Memory Pharmaceuticals is focusing on the discovery and development of novel treatments for cognitive disorders associated with disease and aging. Our present pipeline includes multiple programmes targeting key central nervous systems indications including Alzheimer's disease and related disorders, schizophrenia and depression. We have presently four drug candidates in development, two in clinical trials and two compounds in non-clinical development. We presently have 83 employees in the company and we have been through an IPO in April of this year.

'It clearly showed our investors and pharmaceutical partners that we are competent on all levels'

In what way do you see Memory as being an attractive partner for collaborations and alliances with big Pharma?
We have applied a business and R&D model that really fits into large pharmaceutical strategies and thinking. Our drug discovery and development engine provides all the vital pieces of information of drug safety and efficacy, even before we enter clinical trials. So we were able to structure our first deal with Hoffman La Roche back in 2002, at a time when we had identified a first drug candidate targeting Alzheimer's disease in non-clinical development stages. The advantage was that we had fulfilled all the different criteria for meeting target profile, not only for us, but also for large pharmaceutical partners so we didn't have to scramble to add and generate additional data in order to satisfy the needs within the regulatory and pharmaceutical environment. We have developed compounds that clearly serve not only a highly unmet clinical need, but in many cases can fill gaps within big pharmaceutical pipelines, especially in the field of central nervous system R&D, which, as you know, has been subject to quite a few failures in the last decade. From a business point of view, we clearly achieved striking deals which were attractive for us, attractive for our investors and served as a validation of our R&D approaches. It clearly showed our investors and pharmaceutical partners that we are competent partners on all levels.

Who has been the biggest influence in your career?
That's an interesting question. Clearly Eric Kandel, our co-founder at Memory, is a mentor for myself. Within this company environment, he has been instrumental in terms of guiding our thinking in terms of scientific strategies, in terms of targets and pathways within the central nervous system from a pure R&D point of view. Prior to joining Memory Pharmaceuticals, I had been at Bayer for about 13 years. Without stating any

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names, during my time at Bayer I worked on both sides of the Atlantic, in Germany and the United States in central nervous system R&D. This was vital experience for my ability to operate both in large pharma and within small companies. This helped me to achieve what is visible now at Memory. Prior to joining the pharmaceutical arena, I worked at the Institute for Genetics in Cologne, Germany, with Professors Benno Müller-Hill and Konrad Beyreuther who, as you may know, is a key opinion leader in the field of Alzheimer's research. This period in my academic career in this field, was especially centred on Alzheimer's research and APP [amyloid precursor protein], and proved to be a decisive period in my life, in that it allowed me to really focus on central nervous disorders with particular emphasis on cognitive disorders.

'This is a totally novel approach for Alzheimer's disease'

Could you outline the benefits of your Phase I compound MEM1003 over existing L-channel modulators?

The L-type calcium channel has been the target for a number of cardiovascular therapies. It goes way back to the first discovery, essentially from Bayer AG, of the compounds nitrendipine and nifedipine. These compounds came out of early cardiovascular research and led to the marketed compound, Adalat®. This is a class of drugs belonging to the chemical class of dihydropyridines. In particular, the dihydropyridines have been exceptionally successful, including the latest introduction to the market, which is Pfizer's amlodipine or Norvasc. This is one of the most successful antihypertensives to date, and continues to increase market share because of a unique safety and efficacy profile in cardiovascular use. So the advantage for us was that we knew the drug target very well and we have known the chemical class of dihydropyridines for more than 30 years in clinical practice. So this is an ideal starting point from a pure risk management point of view – to take a known drug target and a known chemical class which has been in man for some time. Now it turns out that L-type calcium channels are expressed in every excitable tissue. All muscle tissue, including skeletal muscle, cardiac muscle and smooth muscle in the vasculature expresses this channel, but also it is found in the central nervous system in key neuronal circuits, such as the human hippocampus, which is involved in learning and memory. There are distinct subtypes of this L-type calcium channel complex that reside within neurons and MEM1003 has been optimised towards this new target for and away from the channel subtypes found in the vasculature. So this is one answer to your question, the compound has been optimised for central nervous system use. As you know, calcium plays a very important role in the pathogenesis of Alzheimer's disease in addition to acute neurological disorders such as stroke and head trauma. Upon CNS injury, such as stroke and head trauma, but also in chronic indications, including Alzheimer's disease, there is an increase in intracellular calcium that can lead rapidly to apoptosis, necrosis and cell death. This has been very well documented over the last decade. Consequently, if you interfere with this deleterious calcium influx that, by the way, blocks all pathways known to be involved in long-term memory formation, one can restore normal physiological levels of calcium. This can have two consequences: one is to restore functions involved with memory formation (and we have shown this with MEM1003) and second, you can provide effective neuroprotection against injury driven by elevated calcium. Essentially, this provides protection against apoptosis, necrosis and cell death. We also know that the amyloid production cascade is driven by elevated calcium and you can modify the production of β-A4, the disease culprit in Alzheimer's disease, 1–42 can be modulated by this system as well. So there is an interesting combination of cognitive enhancement and neuroprotective properties from this approach.

'This is an ideal starting point from a pure risk management point of view'

Do you envisage your phosphodiesterase-4 (PDE-4) inhibitors being used solely as monotherapies or do you see a market for adjunct administration?

Yes, this is presently a question which is unclear. So far PDE-4 inhibitors have not been used as adjunct therapy, this is a totally novel approach for Alzheimer's disease. There have been developments in the PDE-4 arena in respiratory indications, such as in COPD [chronic obstructive pulmonary disease] and asthma, because it turns out that many PDE-4 inhibitors have useful anti-inflammatory properties in these diseases. There is one compound by Schering AG, called rolipram, which has been developed for depression in the past. It failed, however, due to emesis and nausea, which is one of the key challenges in the PDE-4 area. If you have non-specific, non-selective PDE-4 inhibitors, they end up with emetic properties. PDE-4 is a very complex enzyme family, having four different subtypes, a, b, c and d. They are expressed by four different genes, they are alternatively spliced, they have different expression patterns throughout the central nervous system and in the periphery, and it is clear that the safety and efficacy is guided by selectivity of compounds and potency. If you don't have selectivity for certain subtypes of PDE-4 and potent compounds, you, by definition, have strong liability with respect to emesis. This has hampered the field in the past. Coming back to your question, we see PDE-4 inhibitors as potential treatments for Alzheimer's disease and depression. We have two different compounds, the first compound, 1414, is now in Phase I clinical trials with our partner Roche, targeting Alzheimer's disease. Our objective here would be to target monotherapy in each case, but efficacy remains to be proven in clinical trials. Our objective in each programme is to target monotherapy first. As a fall back position if that cannot be achieved, we would think about combination therapy.

'There is an interesting combination of cognitive enhancement and neuroprotective properties from this approach'

You have a significant history in Alzheimer's disease, can you point out what you think was your major contribution to the field?

I had the privilege, as I mentioned before, of working in the Institute for Genetics in Cologne with Benno Müller-Hill and Konrad Beyreuther. We published in 1987 in Nature, the full-length cloning of the amyloid

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precursor protein, which is involved in the pathology and cascade of events leading to Alzheimer's disease. We also located that gene on chromosome 21, which also links this protein and the pathology of Alzheimer's disease to Down's syndrome, trisomy 21. Down's syndrome, as you know, is caused by a triplication of this chromosome 21. What is interesting, is that Down's patients, in addition to their large list of clinical symptoms at birth, develop in their third decade of life, all characteristics of Alzheimer's disease. This provided a very interesting discovery, a link between Alzheimer's disease and Down's syndrome, the role of APP in Alzheimer's disease and more importantly, the mechanism by which β-A4 or Aβ 1–42, is generated out of this larger precursor molecule. This led to the discovery of the so-called secretases, the proteases that are involved in the cleaving of APP and generating, using β and γ cleavage sites flanking Aβ, the peptides which can aggregate with themselves, to form fibres and ultimately plaques. This was a seminal discovery because up to this time, it was totally unknown and unclear where amyloid was coming from in the human brain. People were speculating it might be an unconventional slow virus, such as in prion diseases, or that it might be caused by toxins such as aluminium, which was widely postulated in the 1960s, 1970s and 1980s. This, for the first time, demonstrated that amyloid is a product of an endogenous gene, a protein that is expressed in virtually every single neuronal tissue in the human brain and is produced by abnormal processing events that led to massive production of Aβ in Alzheimer's patients.

'Up to this time, it was totally unknown where amyloid was coming from in the human brain'

How do you view biomarker initiatives for diseases of cognitive impairment? Do you envisage a time when people will be treated prophylactically to prevent onset? In view of the size of the disease population, how will this be viewed by providers?

That is a very significant topic at this time, both in academia and in industry. As you know, there is a prodrome to Alzheimer's disease which is called MCI [mild cognitive impairment]. About 80% of this patient population converts to Alzheimer's disease within 7–8 years after the first clinical symptoms. So there is indeed a very significant interest in the recognition, the diagnosis of Alzheimer patients, ideally prior to the first onset of Alzheimer's disease. You can differentiate Alzheimer's disease from MCI using, for example, non-invasive imaging methods such as functional MRI [magnetic resonance imaging] and PET [positron emission tomography] scanning. These are two tools that have been developed to do exactly that. The early diagnosis of potential Alzheimer's patients may allow one to postpone the onset of the disease. Postponing the onset by as little as one year would be a significant achievement would have a very major impact on patients, care-givers and the economy in general. The figures quoted in the United States are in the order of US$100 billion spent per year on Alzheimer's disease, and if you can postpone the onset by just one year then you would have a very significant economic impact. The FDA, the NIH and other scientific and regulatory authorities have recognised this opportunity. If you can apply effective diagnostic tools, such as functional imaging, to identify Alzheimer's patients at a very early stage of the disease, this can lead at least to the delay of progression and in the best case, you may be able to halt the progression of the disease at an early stage and keep patients functional. Whether we can ever prevent this disease, I think that would be a very large stretch. Prevention is clearly a very long-term goal and I think will be very difficult to achieve. But if you can delay the progression, or postpone the onset, this would be wonderful.

Do you ever see a time when drugs will be developed that can reverse cognitive deficits?

This needs to be seen in clinical trials, but we have shown (and our co-founder, Eric Kandel has shown) that in aging, you can observe in rodents, the identical deficits that you see in humans. That is, the impaired ability to form new long-term memories, that is, a lack of ability to switch short- to long-term memories. Short-term memory is defined as memories up to about three hours and everything beyond three hours is defined as long-term memory, ideally days and years. The step involved in switching from short- to long-term memory is called consolidation of long-term memory, and this is clearly where the prime deficit resides, not only in age-related memory impairment, but also in Alzheimer's patients. You see the same deficit in MCI patients, you see it in vascular dementia, but you see it also in aged rodents. That has given us a wonderful tool, an animal model, which basically mimics the deficit you see in man. This impairment in switching short- to long-term memory, which is a hippocampus-dependent function, has been shown by Eric Kandel and in our own hands to be capable of being reversed using experimental drugs.

'Prevention is clearly a very long term goal'

Have trophic factors also been shown to be active in these tests?

This is an interesting field, the so-called neurotrophic factors that are involved in these processes. Plastic changes that are needed to manifest long-term memory consolidation processes within neurons. In other words, to manifest synaptic connections such growth factors are involved, especially BDNF [brain-derived neurotrophic factor] but it has not been shown, to date, in a conclusive fashion, that one of these factors alone is sufficient to provide safe and beneficial effects long term. BDNF and other trophic factors are a consequence of gene regulation and if gene regulation is enhanced by cyclic AMP (cAMP) pathways, there are transcription factors such as CREB that are activated. Those transcription factors essentially trigger the transcription and translation of proteins, including neurotrophic factors, such as BDNF. These events are downstream of events that are triggered upstream by pathways, which can be modulated pharmacologically by using, for example, PDE-4 inhibitors to increase cAMP, or other approaches, such as G-protein-coupled receptor (GPCR) pathways capable of enhancing cAMP. cAMP enhancement is a very powerful way to trigger, in concert, all of the factors that are necessary to strengthen synaptic connections. Coming back to your question, one of those factors downstream of

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those transcription events is necessary, but not sufficient.

'I believe there is a significant gap in the CNS Pharmaceutical R& D pipelines in general, worldwide'

If you were a gambling man, where would you see the next blockbuster CNS drug coming from? What factors are blocking its development?

Well fortunately, I'm not a gambling man, I'm a very rational person and very cautiously optimistic even of programmes we are applying here in the company. But if I were to force myself into gambling mode, I believe there is a significant gap in the CNS Pharmaceutical R&D pipelines in general, worldwide. There are very few true innovations coming about, close to marketing and launching. There is a pipeline, clearly, of multiple approaches targeting Alzheimer's, and depression that is relatively thin. If you look at the Alzheimer's pipelines in Pharmaceutical companies, they are mostly focused on APP pathology. I would hope that in the near future we would at least be able to clarify the role of amyloid in disease. That is, to what extent those strategies related to the inhibition of production and aggregation of Aβ can lead to safe and efficacious drugs. So much resource is spent in this area, almost unilaterally, the sooner we get this answer, the better. If the answer is positive, this would be a clear blockbuster. It would help us as well because these compounds might delay progression; they may even postpone the onset by treating patients early, at the stage of MCI. They may in the best case even halt progression in early stage Alzheimer's patients. But those patients are still demented – they still have memory impairments, which need to be treated and this would be a very good case for us as well, because this is our focus. We could combine our drugs with amyloid inhibitors in order to treat the key clinical symptoms, which are memory and cognitive impairment. I think there is a lot of activity including Neurochem's Alzhemed™, vaccination approaches, γ- and β-secretases and if any of those compounds succeed, they would be true blockbusters. But there is a risk that they might not and that could change the entire landscape towards different players, including tau. In other areas, such as depression and schizophrenia, I think we are pretty much in the driving seat to come up with fully innovative methods, totally distinct from what has been done before. We would hope that within our PDE-4 inhibitor and our second programme with Roche, the nicotinic α7 receptor programme, we can provide new answers for the cognitive component in those diseases, which are presently untreatable.

Axel Unterbeck
Memory Pharmaceuticals,
100 Philips Parkway,
Montvale,
NJ 07645, USA
e-mail: info@memorypharma.com