Neuropeptide patenting

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Neuropeptide patenting has increased rapidly during the 1990s, particularly in 1994; on average there are currently about two new cases per month. This special report describes the quantity and origin of patents relating broadly to neuropeptides and identifies the subset referring explicitly to modulators of neuropeptide Y.

This report is based on a search carried out on the Derwent WPI database, covering the period from 1963 to week 37 of 1996, based on the following text terms: neuropeptide, NPY, NP-Y, pancreatic polypeptide and peptide YY. From the resulting set of references, 165 patents referring to one or more of these concepts were identified, and data from the INPADOC database were merged in to provide additional detail for analysis. It should be noted that this study does not include unpatented compounds or patent applications that have been filed but not yet published. Inevitably the findings of the study are in part dependent on the breadth of the initial search strategy.

Growth in patenting

Neuropeptides were mentioned only very occasionally in patents before 1983, but there are now more than 20 cases published each year. This growth is shown graphically in Figure 1. Also indicated in Figure 1 are the subset of 36 cases, beginning in 1986, which refer explicitly to the neuropeptide Y (NPY) receptor and its modulation; these now account for about half of all neuropeptide patenting, and are discussed in more detail below.

Applicant countries

Applicants from 18 countries are actively patenting neuropeptides. The US contributes 41% of all inventions, followed by Japan at about half that level, and thereafter by Germany and the UK (Figure 2a). On a regional basis (Figure 2b), Europe is seen to fall roughly midway between North America and the rest of the world.

These data must be considered in the context of overall pharmaceutical industry patenting trends. Compared with a recent study of patenting in a related CNS area[1], the neuropeptide figures seem to attribute rather fewer patents to US applicants and more to Japanese than would be expected; also French applicants, contributing 3.5% here, would normally be expected to generate as many patents as Germany and the UK. However, the overall distribution is broadly as might be predicted for such a study. The US and Japanese contributions are somewhat exaggerated by domestic filings (see below for patenting policies).

Principal applicants

A total of 97 applicant names appear on the 165 neuropeptide patents in the analysis; those applicants appearing more than once (94 inventions in total) are listed in Table 1. Of the world's ten largest pharmaceutical companies,

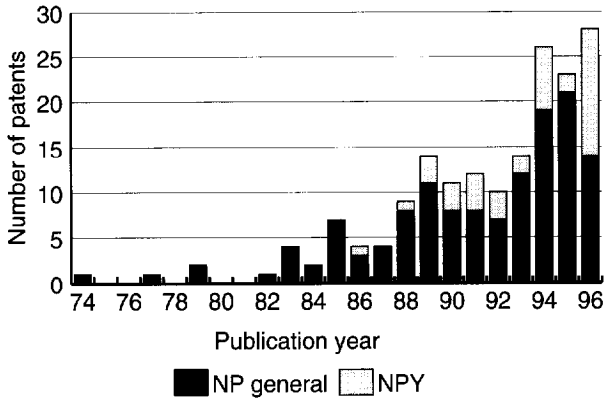

Figure 1. *Neuropeptide patenting from 1974 to 1996. The total for 1996 has been extrapolated from the figure for the first 37 weeks. NP, neuropeptide; NPY, neuropeptide Y.*

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  1359-6446/97/$17.00. PII: S1359-6446(96)10050-7

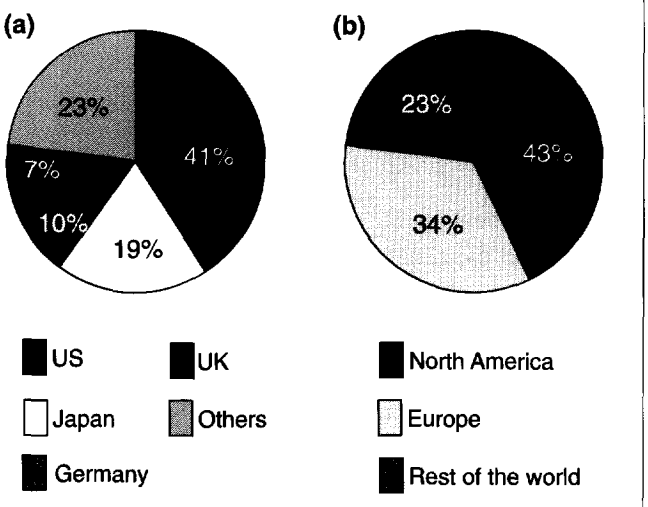

Figure 2. *Overview of the origin of neuropeptide patent applications (a) by country, and (b) by region.*

Table 1. Applicants with two or more neuropeptide patents[a]

No. of patents	Country	Company/organization
12	Japan	Suntory Ltd
9	Germany	Hoechst Aktiengesellschaft (includes 4 Marion Merrell Dow)
8	US	USA (e.g. National Institute of Health)[b]
5	Sweden	Perstorp AB
5	Japan	Takeda Chemical Industry Ltd
4	US	Eli Lilly & Co.
4	US	The Salk Institute for Biological Studies[b]
4	Germany	Boehringer Ingelheim (includes 3 Thomae)
4	US	Merck & Co., Inc.
3	Australia	Garvan Institute of Medical Research[b]
3	US	Pfizer Inc.
3	US	Senetek plc
3	GB	The Wellcome Foundation Ltd
3	GB	Zeneca Ltd
2	Japan	Yamanouchi Pharmaceutical Co. Ltd
2	US	The Board of Trustees of the University of Illinois[b]
2	US	Research Foundation, The City University of New York[b]
2	France	Centre National pour la Recherche Scientifique (CNRS)[b]
2	GB	Queen Mary and Westfield College[b]
2	Japan	Kanegafuchi Chemical Industry Co. Ltd
2	US	University of Cincinnati[b]
2	US	Matrix Technologies, Inc.
2	US	Genentech, Inc.
2	US	The General Hospital Corporation
2	US	The Upjohn Company
2	US	E.I. Du Pont De Nemours and Co.

[a]71 Further applicants have one case each.
[b]Non-industrial source.

Roche, Bristol-Myers Squibb, American Home Products, SmithKline Beecham and Johnson & Johnson are all absent from the list, although Bristol-Myers Squibb do have a single case. More surprising, perhaps, is that Suntory, a far smaller company, heads the table; Perstorp and Senetek are clearly also taking a special interest in neuropeptides, as are the three non-industrial institutions appearing in the top half of Table 1. Several companies known to be actively studying neuropeptides do not appear on the list of applicants, for example Synaptic, Sanofi (SR120819A and related compounds) and Parke-Davis (PD160170). This may relate to the constraints of the study and search criteria as outlined above.

Patenting policy

The number of territories selected by an applicant when filing a particular patent application is generally a reliable indicator of that invention's perceived importance and hence its ultimate commercial potential. Approximately one-third of the neuropeptide cases in the study were filed only in the applicant's home country, including 22 Japanese (71% of all Japanese cases) and 20 US (29%); the remainder were German (mainly from non-corporate applicants), Soviet/Russian and Canadian. The Japanese domestic applications include 11 from Suntory, whose only internationally filed application is a recent filing in Europe claiming a recombinant technique.

At the other end of the spectrum are the PCT (Patent Cooperation Treaty) applications (also known as 'World Patents'), which designate all possible territories, now more than 80; these represent inventions in which the applicant has great confidence. Eight such cases stand out and are summarized in Table 2. Mention should also be made of an early Genentech case mentioning neuropeptides (EP1929); this patent is part of a group of ten interrelated cases covering basic recombinant technology.

Between the extremes of domestic filing and blanket territorial coverage

are applications with intermediate coverage, typically Europe, Japan, the US and possibly a few other territories such as Canada, Australia and South Korea; such coverage may be achieved either by direct application to regional and national patent offices, or via the PCT. A typical example is Merck's WO9623809 (Europe, Canada, Japan and USA), claiming cloning of the NPY receptor, technology that the company considers worthy of protection, but which currently has no direct commercial potential.

Table 2. Selected patents with broad territorial coverage

Patent	Company	Subject/application
WO9622305	Wellcome	*N*-Acylated peptide derivatives with neuropeptide Y receptor affinity
WO9614307	Pfizer	Substituted benzylamine NPY-Y1 ligands
WO9612489	Lilly	Bicyclic neuropeptide Y receptor antagonists
WO9518615[a]	Novo	Pyrrolidine and piperidine compounds used to treat neurogenic inflammation and pain
WO9417035	Thomae	Amino acid derivative NPY antagonists
WO9418161[a]	Merck	Selective beta 3 agonists for the treatment of diabetes and obesity
WO9311248a	Ciba-Geigy	Expression of protein by treating co-expressing neuropeptide with 7B2
WO9200290a	Upjohn	Anti-atherosclerotic 2-amino-6-phenyl-4H-pyran-4-one compounds are also ADP-induced platelet aggregation inhibitors

[a]Non-core references

Core NPY patenting

Inventions referring explicitly to NPY and its modulation now account for a substantial proportion of all neuropeptide patenting. Such cases began to appear in the mid-1980s, the first two being from Perstorp, relating to compositions and use of the known NPY antagonist inositol triphosphate, which the company was at one time developing as α-trinositol. The early core patenting, concerned primarily with peptides, originated from Merrell Dow, US universities (University of California and University of Florida) and German companies (Boehringer Ingelheim, Hoechst and BASF). Apart from Perstorp's work, which was the subject of three further publications in 1992, the earliest patent reference to nonpeptide NPY antagonists seems to be Heumann's EP448765, in which the use of imidazolylalkyl guanidines is claimed. Heumann is not normally involved in drug discovery, but this early contribution to NPY antagonist patenting serves to emphasize that Germany, together with Sweden, was a focus of expertise in the field in the early 1990s.

The Garvan Institute of Medical Research (New South Wales, Australia) filed an application at the end of 1991, now published as WO9309227, in which the NPY-Y1 receptor was claimed. This fundamental technology probably underpins the agreement into which Bristol-Myers Squibb has entered with Garvan, who have a subsequent case covering peptide inhibitors of neuropeptide tyrosine pressor function. Apart from a Squibb case on general receptor protein technology filed at about the same time, Bristol-Myers Squibb appear to have no relevant patent property of their own, although a natural product (BMS192548) was at one stage reported to be under investigation as an NPY antagonist.

The Japanese contribution to the core NPY patenting is minimal, starting in 1994 with a peptide case from Yamanouchi, who published a similar case at the beginning of 1996. These cases, together with a more recent receptor cloning case from Japan Tobacco, are the only Japanese patents directly relating to NPY, and all three are Japan-only filings. Neither Suntory nor the National Institute of Health (NIH), ranked 1st and 3rd in Table 1, has core NPY patents, but Hoechst/Marion Merrell Dow (2nd) is well represented.

Other significant cases include three in 1994 from Thomae (WO9417035 and two domestic filings); their selective antagonist BIBP3226 is now reportedly under investigation by Amgen. During 1996 there have been internationally filed applications from Lilly, Pfizer, Wellcome and Merck, indicating that some of the industry's largest companies are now putting resources into NPY projects. There are reports of collaborative development work involving Lilly and Allelix, but the other patentees may not yet have progressed to that stage; Merck, for example, are claiming modified receptors in WO9614331 and WO9623809, which suggests that the infrastructure may now be in place for an effective screening programme. Wellcome claim acylated peptides in WO9622305, a more broadly filed follow-up to a 1994 publication from the same US-based team. Pfizer are known to have licensed from Neurogen the compound designated NGD-95-1, currently in Phase I trials for eating disorders, the first NPY modulator to progress beyond the preclinical stage.

Conclusion

Neuropeptide patenting has increased rapidly during the 1990s, particularly in 1994; on average there are currently about two new cases per month. Inventions relating specifically to NPY receptors and their modulation, which began to appear consistently in 1989, now account for approximately half of all neuropeptide patenting. The major contribution originates from the USA, although German companies were prominent before 1992; much of the patenting by Japanese companies is not international, and there is no direct evidence so far of development work in Japan. There is reasonable correlation between the retrieved patents and reported development activity, although a few candidate compounds appear to have no corresponding patent. Several companies with substantial patent applications in the field have no recognized lead compounds as yet, most notably Merck and Merrell Dow (now Hoechst Marion Roussell).

REFERENCE

1 Steele, P. (1996) *ID Research Alert* 1, 1–5

In short...

On the 4th of November, **Neuraxis**, a joint-venture by **Medeval** (Manchester, UK) and **Cerebrus** (Ascot, UK) was launched. Neuraxis specializes in the evaluation of CNS drug action and aims to provide clients with early evidence of the efficacy of their drugs, so helping them to focus their resources on potential winners. Neuraxis brings together Cerebrus' specialist knowledge of predictive pre-clinical biological models, Medeval's phase I contract research experience and the academic expertise in clinical psychiatry of the University of Manchester's Department of Psychiatry. The joint-venture management team consists of Professor J.F.W. Deakin (professor of psychiatry at the University of Manchester and President of the British Association for Psychopharmacology), Dr S. Toon (Managing Director of Medeval) and A. Smith (Chief Executive of Cerebrus).