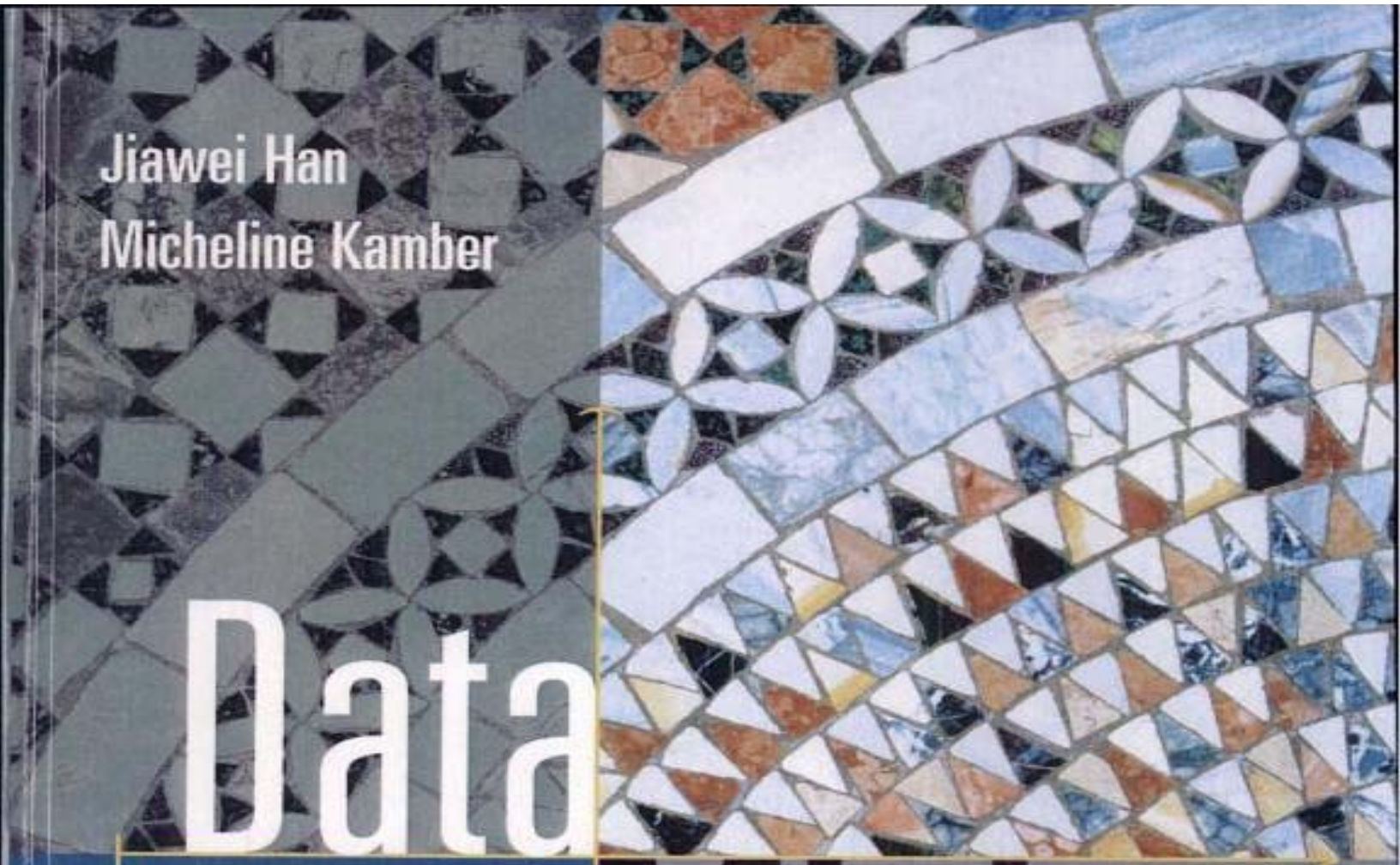
EXHIBIT A

Jiawei Han
Micheline Kamber



Data Mining

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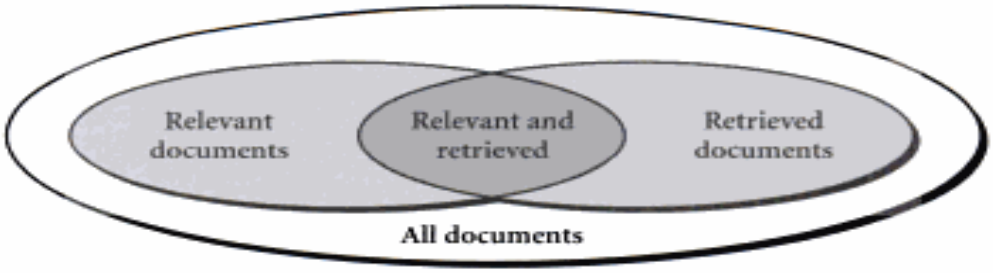

Figure 9.8 Relationship between the set of relevant documents and the set of retrieved documents.

unstructured documents, approximate search based on keywords, and the notion of relevance.

Basic Measures for Text Retrieval

"Suppose that a text retrieval system has just retrieved a number of documents for me based on my input in the form of a query. How can we assess how 'accurate' or 'correct' the system was?" Let the set of documents relevant to a query be denoted as $\{Relevant\}$, and the set of documents retrieved be denoted as $\{Retrieved\}$. The set of documents that are both relevant and retrieved is denoted as $\{Relevant\} \cap \{Retrieved\}$, as shown in the Venn diagram of Figure 9.8. There are two basic measures for assessing the quality of text retrieval:

- **Precision:** This is the percentage of retrieved documents that are in fact relevant to the query (i.e., "correct" responses). It is formally defined as

$$precision = \frac{|\{Relevant\} \cap \{Retrieved\}|}{|\{Retrieved\}|}. \tag{9.4}$$

- **Recall:** This is the percentage of documents that are relevant to the query and were, in fact, retrieved. It is formally defined as

$$recall = \frac{|\{Relevant\} \cap \{Retrieved\}|}{|\{Relevant\}|}. \tag{9.5}$$

Keyword-Based and Similarity-Based Retrieval

"What methods are there for information retrieval?" Most information retrieval systems support *keyword-based* and/or *similarity-based* retrieval. In **keyword-based information retrieval**, a document is represented by a string, which can be identified by a set of keywords. A user provides a keyword or an expression formed out of a set of keywords, such as *"car* **and** *repair shops"*, *"tea* **or** *coffee"*, or *"database systems* **but not** *Oracle"*. A good information retrieval system should

EXHIBIT B

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Ectopic expression of *seven-up* causes cell fate changes during ommatidial assembly

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SUMMARY

During *Drosophila* ommatidial development, a single cell is selected within the ommatidial cluster to become the R7 photoreceptor neuron. The *seven-up* gene has been shown to play a role in this process by preventing four other photoreceptor precursors, R3/R4/R1/R6, from adopting the R7 cell fate. The *seven-up* gene encodes a steroid receptor-like molecule that is expressed only in those four cells that require *seven-up* function in the developing *Drosophila* ommatidium. We have examined the functional significance of the spatially restricted expression of *seven-up* by misexpressing seven-up isoforms. As expected from the function that seven-up performs in R3/R4/R1/R6, ubiquitous expression of seven-up causes transformation of the R7 cell to an R1-R6 cell fate. In addition, depending on the timing and spatial pattern of expression, various other phenotypes are produced including the loss of the R7 cell and the formation of extra R7 cells. Ubiquitous expression of seven-up close to the morphogenetic furrow interferes with R8 differentiation resulting in failure to express the boss protein, the ligand for the sevenless receptor tyrosine kinase, and the R7 cell is lost consequently. Extra R7 cells are formed by recruiting non-neuronal cone cells as photoreceptor neurons in a *sevenless* and *bride of sevenless* independent way. Thus, the spatiotemporal pattern of *seven-up* expression plays an essential role in controlling the number and cellular origin of the R7 neuron in the ommatidium. Our results also suggest that *seven-up* controls decisions not only between photoreceptor subtypes, but also between neuronal and non-neuronal fates.

Key words: *Drosophila*, *seven-up*, steroid receptor, ommatidial assembly, cell fate

INTRODUCTION

How the diversity of neurons is generated during neurogenesis is one of the central questions in developmental biology. The compound eye of *Drosophila* offers an excellent model system for studying the genetic control of specification of neuronal identities. The *Drosophila* eye is a hexagonal array of ~800 ommatidia, or unit eyes, each containing 8 photoreceptor neurons, R1 through R8, and 12 non-neuronal accessory cells. Individual photoreceptor neurons can be uniquely identified by their morphology and the stereotyped position that they occupy (reviewed by Tomlinson, 1988; Ready, 1989). Since no lineage restrictions exist within the 20 cells that constitute an ommatidium, cells acquire their identity by responding to signals from neighboring cells within the ommatidium (Ready et al., 1976; Lawrence and Green, 1979; Wolf and Ready, 1991). A number of genes have been identified that are required for correct specification of cell fates during ommatidial assembly. Through mosaic analysis one can identify the cells in which a gene activity is required, and deduce its role in the cell-cell interactions that mediate cell fate decisions. Molecular features of the genes isolated so far are consistent with the proposed cell-cell interactions and induction mechanisms (reviewed by Banerjee and Zipursky, 1990; Hafen, 1991; Rubin, 1991)

The specification of the R7 neuron has been studied in the most detail and is at present the best understood (reviewed by Rubin, 1991). R7 is the UV-sensitive photoreceptor that synapses in a layer of the optic lobe distinct from all other photoreceptor neurons in each ommatidium (reviewed by Hardie, 1986). In normal development, the R7 neuron differentiates from a cell that occupies a fixed position in the ommatidial cluster, between R1 and R6. Several genes have been identified that are involved in selecting a single photoreceptor precursor as the R7 photoreceptor. Loss-of-function alleles of *sevenless* (*sev*), *bride of sevenless* (*boss*) and *seven in absentia* (*sina*) all transform the R7 precursor cell to a non-neuronal cone cell (Tomlinson and Ready, 1986, 1987b; Reinke and Zipursky, 1988; Carthew and Rubin, 1990). The *sevenless* gene encodes a receptor tyrosine kinase (Hafen et al., 1987; Bowtell et al., 1988; Basler and Hafen, 1988; Simon et al., 1989), whereas *boss* encodes a transmembrane protein that is expressed in the R8 cell and is the ligand for sev (Hart et al., 1990; Kramer et al., 1991). Genetic analyses indicate that the sev tyrosine

kinase acts through activation of the ras pathway (Simon et al., 1991; Fortini et al., 1992; Rogge et al., 1991; Bonfini et al., 1992; Gaul et al., 1992). Increased levels of ras activity in the cone cells achieved by either a ligand-independent allele of *sev* (Basler et al., 1991), ectopic expression of *boss* (Van Vactor et al., 1991), expression of activated *Ras1* (Fortini et al., 1992), or by reduction of the activity of *Gap1* (Gaul et al., 1992; Rogge et al., 1992; Buckles et al., 1992) all result in transformation of cone cells to R7 neurons. In contrast, loss-of-function alleles of *rough* (Tomlinson et al., 1988; Heberlein et al., 1991; Van Vactor et al., 1991) and *seven-up* (*svp*) (Mlodzik et al., 1990b) cause more than one photoreceptor precursor to adopt the R7 fate without affecting cone cell differentiation. In particular, loss of svp^+ function results in the cell autonomous transformation of four outer photoreceptor cells, R3/R4/R1/R6, towards R7-like cells (Mlodzik et al., 1990b).

The predicted svp protein shares homology with members of the steroid receptor family (reviewed by Evans, 1988; Green and Chambon, 1988), suggesting that it acts as a ligand-responsive transcription factor (Mlodzik et al., 1990b). Two human homologues of *svp* have been identified that share extensive homology in both the DNA-binding domain and the ligand-binding domain (Miyajima et al., 1988; Wang et al., 1989; Ladias and Karathanasis, 1991). A striking aspect of *svp* expression is that, despite its apparent structure as a receptor, there is complete coincidence between the cells that express *svp* and those that require its function (Mlodzik et al., 1990b). This is in contrast to the sev receptor tyrosine kinase, which is required only in the R7 cell but is expressed in most photoreceptor precursors as well as cone cells (Tomlinson et al., 1987; Banerjee et al., 1987). The expression pattern of *sev* does not play a major role in restricting R7-forming potential, since ectopic expression of *sev* in all cells under heat-shock promoter does not cause other cells to adopt the R7 cell fate (Basler and Hafen, 1989a; Bowtell et al., 1989a). The restriction of *sev* activity is achieved by local presentation of its ligand, the boss protein by the R8 cell. There is also a restriction in the ability of sev-expressing cells to internalize the boss protein to the R7 precursor, but the significance of this restriction in controlling R7-forming potential is not clear (Kramer et al., 1990; Van Vactor et al., 1991; Cagan et al., 1992). The ligand for svp is not identified, nor its distribution known.

Here we have tested the functional significance of the *svp* expression pattern by analyzing the consequences of ectopic expression of *svp*. We observe a variety of cell fate transformations within an ommatidium including both the loss and gain of R7 cells. Our results indicate that the spatially restricted expression of *svp* plays an essential role in controlling the number of R7 cells that form within an ommatidium.

MATERIALS AND METHODS

Plasmid construction and P-element-mediated transformation

P-element constructs containing *hs-svp1* and *hs-svp2* genes were made by cloning a 1.7 kb *Eag*I fragment of pc162.1 and a 2.4 kb *Eag*I-*Cla*I fragment of pc162.2 (Mlodzik et al., 1990b), respectively, into the polylinker region of the CaSpeRhs vector (Thummel and Pirrotta, 1991). P-elements containing *sev-svp1* and *sev-svp2* genes were made by first inserting a 0.57 kb *Bam*HI fragment of CaSpeR-hs containing the trailer sequence of the *hsp70* gene into the *Bam*HI site of SE8/DM30 (Bowtell et al., 1989b) and then inserting the 2.9 kb *Eco*RI-*Cla*I fragment of pc162.1 and the 2.7 kb *Eco*RI-*Cla*I fragment of pc162.2, respectively, into the *Cla*I site located upstream of the *Bam*HI site in the SE8/DM30 vector. *sev-svpΔMlu* has an insertion of a stop codon linker (New England Biolabs) at the *Mlu*I site of *sev-svp2*, truncating the protein at residue 273. *sev-svpΔSal* has a deletion of a 1 kb *Sal*I-*Cla*I fragment truncating the protein 17 residues before the divergence point of the two isoforms.

Germ-line transformation was done using ry^{506} and w^{1118} as host strains and pπ25.7wc (Karess and Rubin, 1984) as a helper plasmid. Secondary jumps to new locations were made using a strain carrying a genomic source of transposase activity (Robertson et al., 1988).

Histology

Antibody stainings of imaginal discs were performed as described (Tomlinson and Ready, 1987a) except that in most cases the peripodial membrane was not removed. Affinity-purified rabbit antibody against BarH1/BarH2 proteins (Higashijima et al., 1992) was a kind gift of K. Saigo. Monoclonal antibody anti-boss1 (Kramer et al., 1991) was a generous gift of L. Zipursky. Monoclonal antibody against β-galactosidase was purchased from Promega. Monoclonal antibody against elav protein was made in the Rubin laboratory monoclonal antibody facility. Sections of adult retinae were made according to Tomlinson and Ready (1987a).

Marker strains

The following enhancer trap marker lines were used as cell-type-specific markers; BB02 (Hart et al., 1990) and rO156 (U. Gaul unpublished), which express β-galactosidase late in R8 differentiation, H214, which expresses β-galactosidase strongly in the R7 cell (Mlodzik et al., 1992), and rI533, an insertion in the *Gap1* gene (Gaul et al., 1992).

Generation of *svp* mutant clones by FLP-FRT mediated mitotic recombination

Clones homozygous for a null allele of *svp*, svp^{e22} (Mlodzik et al., 1990b), were made by mitotic recombination catalyzed by the FLP-FRT system (Golic and Lindquist, 1991). A 24 hour egg collection was taken from the crosses between males of w^{1118} hsFLP1/Y; 75AE svp^{e22}/*TM6B Hu, Tb* and females of w^{1118}; 75A *M*(3) w^{124}/*TM6B Hu Tb*. hsFLP1 has an insertion of the P[ry^+;*hsFLP*] element on the X-chromosome (Golic and Lindquist, 1989). 75A is an insertion of P[>w^{hs}>] element (> denotes an FRT site) at the base of 3R (Golic and Lindquist, 1991; K. Golic personal communication). 75AE has an excision of the w^{hs} gene catalyzed by FLP-mediated recombination from the 75A insertion and has one copy of FRT left. 40 hours after the end of the egg collection period, the vials containing larvae were submerged in a 37°C waterbath for 2 hours. Female $Tubby^+$ larvae were selected as wandering third instar and their discs were processed for antibody staining. $Tubby^+$ male siblings were used as controls that do not produce *svp* mutant clones. The *svp* mutant clones were visualized using an anti-BarH1/BarH2 antiserum as a molecular probe.

RESULTS

Ubiquitous expression of *svp* causes a variety of cell fate changes

Neuronal differentiation of the eye starts in the eye imaginal disc of the third instar larva as an indentation of the disc,

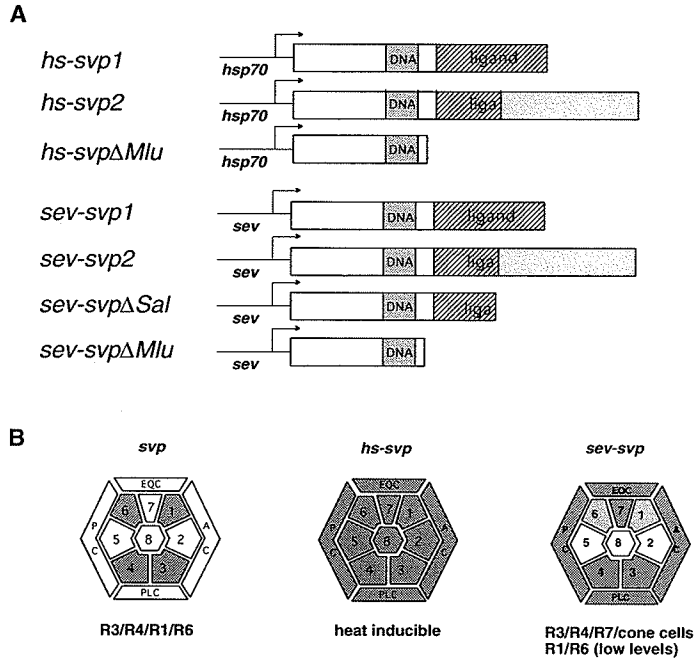

Fig. 1. Schematic structure and expression patterns of *svp* ectopic expression constructs. (A) cDNAs encoding the two isoforms of svp, as well as their truncated versions, were fused to the heat-inducible hsp70 promoter, and to the *sev* enhancer/promoter. DNA, region showing homology to the DNA-binding domain of steroid receptors; ligand, the putative ligand-binding domain. (B) Schematic representation of ommatidia with eight photoreceptor precursors (numbered 1 through 8) and four cone cells (AC, anterior cone cell; EQC, equatorial cone cell; PC, posterior cone cell; PLC, polar cone cell). Expression patterns of the endogenous *svp* gene (svp) and the two promoter fusions (hs-svp and sev-svp) are indicated by shading. Light shading of R1/R6 in sev-svp shows lower levels of expression compared to R3/R4/R7 and cone cells.

called the morphogenetic furrow, moves in a posterior-to-anterior direction. Pattern formation starts in the furrow as cells are recruited to form ommatidial clusters containing photoreceptor precursors (Tomlinson and Ready, 1987a; Wolf and Ready, 1991). From the morphogenetic furrow, rosettes of cells consisting of four to five core cells surrounded by a ring of 10-15 cells emerge with regular spacing. Each group of cells is then transformed into a precluster containing five postmitotic photoreceptor precursors, R8, R2, R5, R3 and R4. After a wave of mitosis, three more photoreceptor precursors R1/R6/R7 and four cone cells join the cluster successively. Each of the eight photoreceptor precursors and the cone cells occupies a stereotyped position within the cluster. Based on expression of neuron specific antigens, it has been inferred that photoreceptor precursors initiate neuronal differentiation in an invariant sequence; R8 initiates differentiation first, followed by R2/R5, R3/R4, R1/R6 and finally R7 (Tomlinson and Ready, 1987).

Since an eye disc contains ommatidial clusters at different stages of differentiation, it should be possible to identify the developmental stage that is sensitive to the ectopic expression of *svp* by applying a pulse of svp expression throughout the eye disc. Two classes of cDNAs, called type 1 and type 2, have been identified from the *svp* locus. Type 1 cDNA encodes a protein that shares homology with both the DNA-binding domain and the ligand-binding domain of steroid receptors, whereas type 2 cDNA diverges from type 1 in the middle of the putative ligand-binding domain (Mlodzik et al., 1990b). To express these two *svp* isoforms in all cells in the imaginal disc, we generated transformant lines that carry P elements containing *svp* cDNAs that were placed under the control of the heat-inducible hsp70 promoter (Fig. 1). Fusion genes employing type 1 and type 2 cDNAs will be called *hs-svp1* and *hs-svp2*, respectively.

When late third instar larvae carrying these fusion genes were exposed to a brief (1-2 hours) heat pulse, 5 to 20% of the animals failed to pupate or died as early pupae. Those that survived to adulthood had no obvious defects in external morphology, except that their eyes had a stripe of rough region running dorsoventrally. In retinal sections of such eyes, a stripe of ommatidia with abnormal numbers of photoreceptor cells was found, the stripe often being wider than the region of the rough exterior. The width of stripe with abnormal ommatidia was often more than 10 rows. Since a new row of ommatidia is produced approximately every 2 hours (Basler and Hafen, 1989b), if ubiquitous expression of svp affected a single developmental stage, we would have expected to see a relatively narrow stripe of abnormal ommatidia, e. g. one or two rows. The broadness of the affected region suggests either that the svp protein expressed under heat-shock control has a long perdurance, or that ectopically expressed svp interferes with multiple differentiation steps.

In retinal sections of wild-type eyes, three classes of photoreceptor cells can be distinguished by their morphology. The outer photoreceptor cells R1 through R6 have rhabdomeres of large diameter that project throughout the depth of the retina, whereas the two classes of central photoreceptor cells, R7 and R8, have rhabdomeres of small diameter, the former located in the apical retina, the latter in the basal retina. Within the stripe of abnormal ommatidia in heat-shocked *hs-svp* flies, ommatidia with different phenotypes were observed: these include loss of outer photoreceptor cells, loss of central photoreceptor cells, appearance of extra central photoreceptor cells and appearance of extra outer photoreceptor cells (Figs 2, 3). Ommatidia with different phenotypes appeared ordered in an anterior-to-posterior manner, forming narrow substripes within the broader stripe of abnormally constructed ommatidia (Fig. 3). For example, in a *hs-svp1* eye, loss of one or two outer photoreceptor cells was seen in the anteriormost region of the

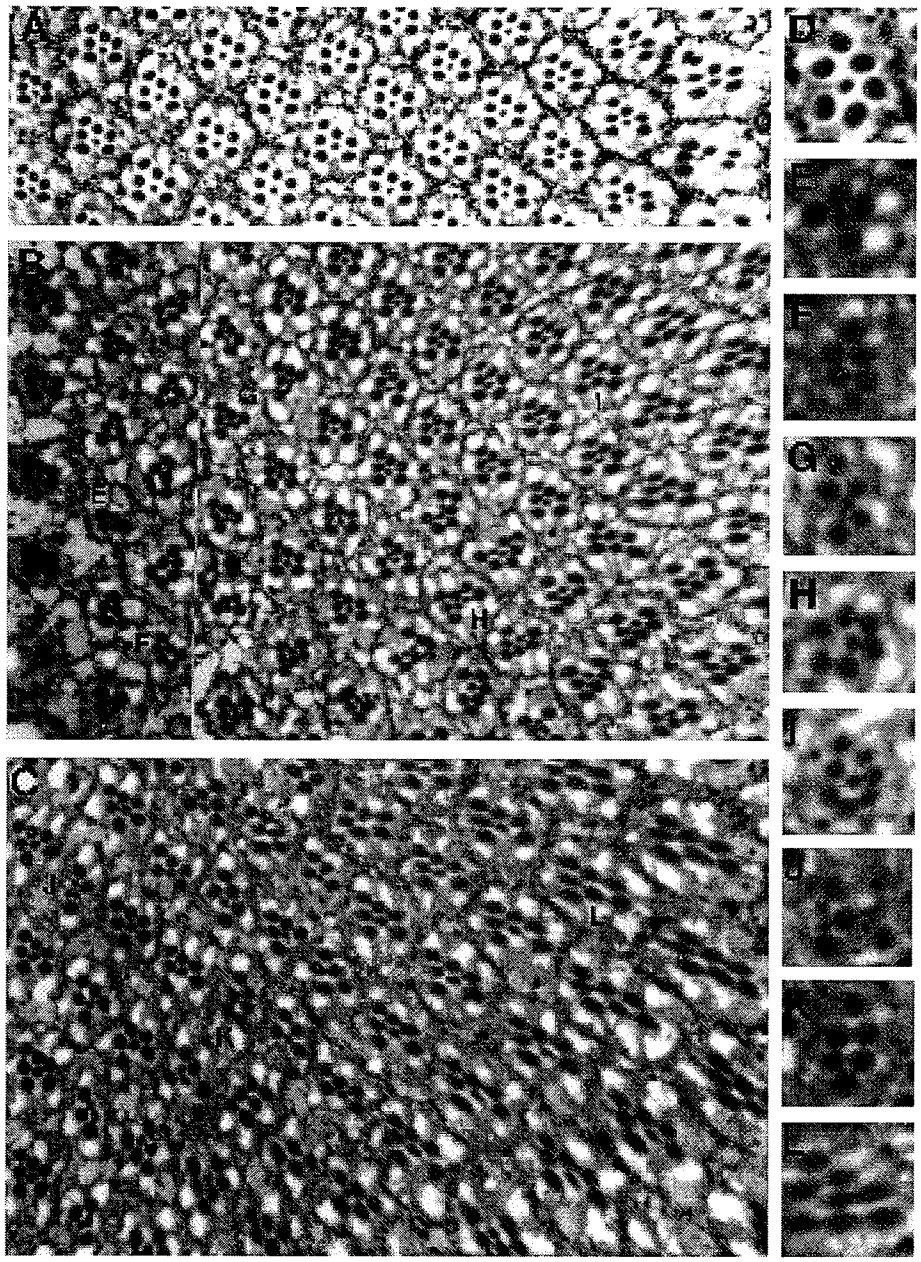

Fig. 2. Retinular phenotypes of heat-shocked *hs-svp* animals. (A) Wild type, (B) *hs-svp1*, (C) *hs-svp2*. Animals shown in B and C were heat shocked at 37°C for 2 hours as wandering third instar larvae. (A-C) Apical sections at the R7 level; (E-L) individual ommatidium corresponding to the labeled ommatidia in B and C, in basal sections at the R8 level. E lacks two outer photoreceptor cells without affecting R7 or R8; F and K lack both R7 and R8 yet contain six outer photoreceptor cells; G has an extra R7 and has a concomitant loss of an outer photoreceptor cell (class 2 in Fig. 3); H has an extra R7 with normal number of outer photoreceptor (class 1 in Fig. 3); I and L have a transformation of R7 to outer photoreceptor fate and J has reduced number of outer photoreceptor cell and contain extra central photoreceptor cells (class 2, in Fig. 3). A section of a wild-type ommatidia at the R8 level is shown in D.

stripe, partially overlapping a region of ommatidia that lacked the central photoreceptor cells R7 and R8. In the more posterior region of the affected stripe, ommatidia with extra central photoreceptor cells were present. This was followed by a row that contained mostly normal ommatidia, and further posterior was a region that lacked R7 but had an extra photoreceptor with the morphology of an outer photoreceptor cell (Figs 2B, 3D). Formation of substripes of ommatidia with specific phenotypes in a defined order suggests that each phenotype is caused by affecting a specific differentiation process that takes place in a stereotyped position in the developing eye imaginal disc. *hs-svp2* retinae also contained substripes of ommatidia with mutant phenotypes similar to those seen in *hs-svp1* retinae (Figs 2C, 3E-H). The order of specific substripes in *hs-svp2* retinae, however, differed from that in *hs-svp1* retinae (see for example the position of extra R7 phenotype, relative to that of the loss of R7 phenotype), indicating that superficially similar phenotypes are not necessarily caused by the same cellular mechanisms.

Ectopic expression of *svp* causes transformation of R7 to R1-R6 subtype

Previous analysis of loss-of-function phenotype of *svp* showed that *svp* prevents R3/R4/R1/R6 cells assuming the R7 cell fate (Mlodzik et al., 1990b). It is thus possible that ectopic expression of svp in the R7 precursor would prevent its differentiation and either transform it towards an

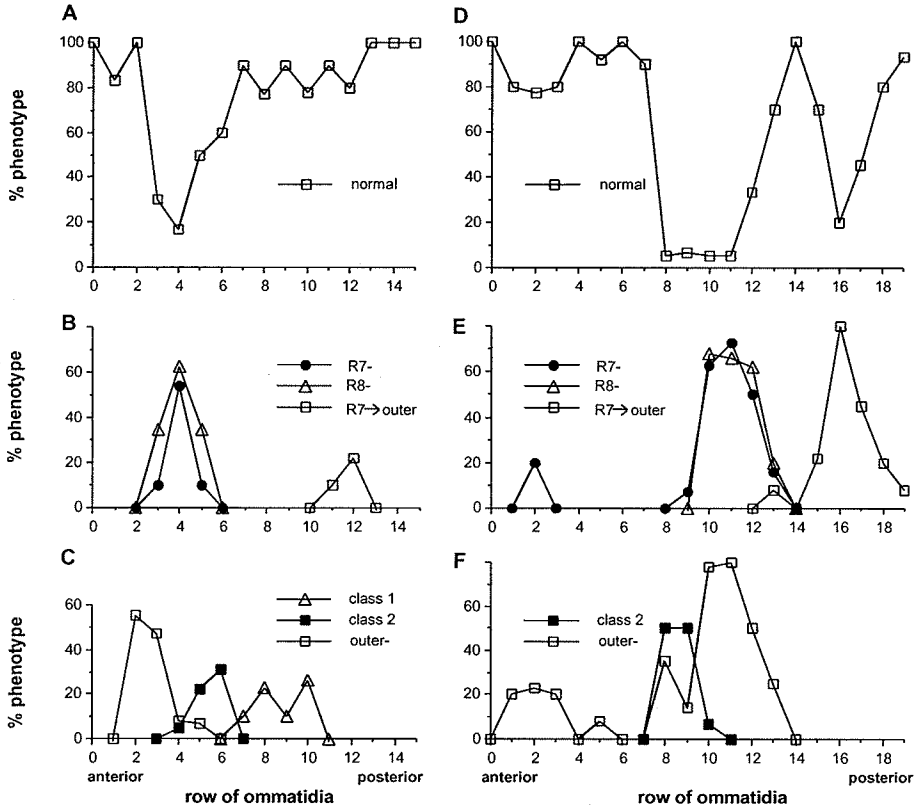

Fig. 3. A graphic representation of the *hs-svp* phenotypes. (A-C and D-F) Histograms representing specific phenotypes seen in the *hs-svp1* retina shown in Fig. 2B and the *hs-svp2* retina shown in Fig. 2C, respectively. Vertical axes show frequencies in percentage of ommatidia showing particular phenotypes among ommatidia in a given row. The position of row 0 is arbitrary. (A,D) Ommatidia with normal morphology. We define the stripe of affected ommatidia as rows 3 to 12 and rows 8 to 18 in retinae represented in A-C and D-F, respectively. Within this region, substripes of different phenotypes are observed. (B,E) Ommatidia lacking central photoreceptor cells (R7–, R8–. R7→outer). R7– (loss of R7) class and R8– (loss of R8) class are scored independently. These classes and R7→outer (transformation of R7 to outer photoreceptor cells) are mutually exclusive. Ommatidia exhibiting other phenotypes are depicted in C and F. Ommatidia that have extra R7-like cells are divided into two classes, class 1 and class 2. Class 1 ommatidia contain normal number (6) of outer photoreceptor cells, whereas class 2 ommatidia have reduced numbers of outer photoreceptor cells. Class 1 ommatidia were not found in *hs-svp2* retinae. Ommatidia that lack outer photoreceptor cells with one or no R7 are classified as outer–. Note that both outer– class and class 2 ommatidia have reduced numbers of outer photoreceptor cells. Ommatidia that show loss of central and outer photoreceptor cells are scored independently, as outer– and R7–, thus the total percentage does not necessarily add up to 100%. Anterior to the major stripe of affected ommatidia, *hs-svp2* retinae usually have a small number of ommatidia that lack outer photoreceptor cells with or without R7. This region (corresponding to rows 1 to 5 in D-F), although reproducibly seen, was not included in the row counts of the affected stripe. For each construct, we generated histograms from four to five animals that received identical heat-shock treatment. Although the peak height of specific phenotypes varied from eye to eye, the relative order of specific phenotypes was invariant among retinae carrying a given construct.

R3/R4/R1/R6 cell fate or cause the loss of the R7 cell. Indeed, we found substripes of ommatidia that show such phenotypes in heat shocked *hs-svp* retinae (Figs 2, 3).

The posteriormost region of the affected stripe in *hs-svp1* and *hs-svp2* retinae contained ommatidia that lacked a photoreceptor with normal R7 cell morphology in the apical sections at the level that R7 cell is present in wild-type ommatidia. Even in such abnormal ommatidia, the cell corresponding to R7 can be identified by comparison with flanking normally constructed ommatidia. The rhabdomere of the affected R7 cells (R7T) are larger than those of the normal R7 cells, resembling those of the outer photoreceptor cells. Moreover the R7T rhabdomere was not in its normal central position, but is located between those of R1 and R6. Serial sections revealed that the R7T rhabdomere indeed extended throughout the depth of the retina, as those of normal R1-R6 subtypes (Fig. 2B,C,I,L). These phenotypes are indistinguishable from those observed in flies that express the rough protein in the R7 cell, transforming R7 cell into R1-R6 subtype (Basler et al., 1990; Kimmel et al. 1990). We conclude that ectopic expression of svp, like that of rough, causes transformation of the R7 cell to outer photoreceptor cells. Since the width of the ommatidial rows with this specific phenotype was approximately two rows, the R7 cell must be sensitive to ectopic expression of svp for at least 4 hours.

Perturbation of R8 development causes loss of R7

In addition to the transformation of the R7 cell to an outer photoreceptor cell described above, heat-shocked *hs-svp1* and *hs-svp2* retinae contained another substripe that lacked the R7 cell. This substripe was found two to five rows posterior to the anterior margin of the affected stripe (Figs 2, 3). Examination of basal sections revealed that most ommatidia that lacked R7 also were missing R8 (Figs 2,3). Of a total of 13 ommatidia arranged in a row in a heat-shocked *hs-svp1* retina, we found 7 ommatidia that lacked a central photoreceptor in apical sections, all of which also lacked the R8 in basal sections (Fig. 2). Two possibilities exist as to how the R7 cell was lost. First, expression of *svp* in the R7 precursor might have prevented its differentiation as a R7 neuron in a cell autonomous manner. Alternatively, since R8 is known to induce R7 differentiation by expressing boss on its surface (Kramer et al., 1991; Van Vactor et

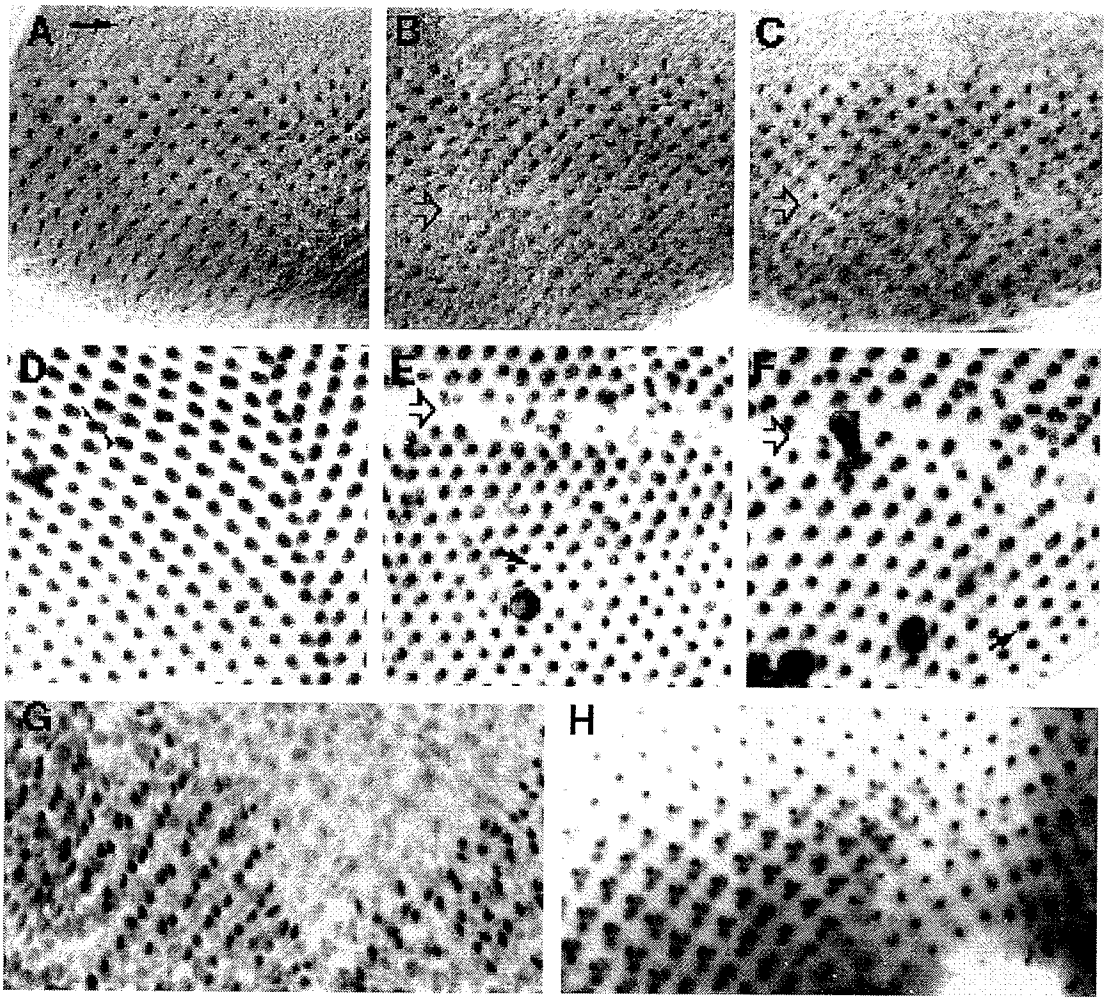

Fig. 4. Expression of R8-specific markers upon gain and loss of *svp* expression. (A-C) Anti-boss staining. (A) A wild-type disc. The morphogenetic furrow is indicated by an arrow. The boss staining can be first detected in row three and extends towards the posterior end of the disc. (B) *hs-svp1*; (C) *hs-svp2*. Discs from animals that had been heat shocked for 45 minutes at 37°C and chased at 22°C for 19 hours. The open arrow marks the position of the boss-negative stripe. (D-F) Histochemical detection of β-galactosidase activity of BB02 enhancer trap marker in 40 hour pupal eyes. Third instar larvae were heat shocked for 45 minutes and then reared at 22°C. (D) Wild type, (E) *hs-svp1* and (F) *hs-svp2*. BB02 expresses β-galactosidase in R8 (arrow) and R7 (arrowhead), with R8 having higher levels of expression. In heat-shocked *hs-svp* eyes, the regular ommatidial array is disrupted by a stripe of ommatidia that lack β-galactosidase expression. Most ommatidia within such a stripe (indicated by an open arrow) lack β-galactosidase expression in both R7 and R8. Further posterior (towards bottom of the figure) is a region that lacks staining of the R7 cell. An example of such ommatidia is indicated by an arrow. (G) A mosaic disc containing svp^{e22}, M^+ clone stained with an anti-BarH1 antibody. In the svp^+ region, BarH1 is expressed strongly in R1/R6, and weakly in all cells located basally in the disc (out of focus). In the svp^- region, R1/R6 do not express BarH1, whereas expression in the basal cells within the same clone is unaffected. At the boundary of svp^+ and svp^- regions, ommatidia with a single BarH1-expressing cell are present. This suggests that the effect of loss of *svp* on BarH1 expression is cell autonomous. (H) A disc containing svp^{e22}, M^+ clone stained with a mixture of anti-BarH1 and anti-boss antibodies. svp^- ommatidia can be identified as a region that does not express BarH1 in R1/R6 (slightly out of focus). boss expression is confined to a single cell in both svp^+ and svp^- ommatidia.

al., 1991), the loss of R7 could be a consequence of the loss of R8. We explored the latter possibility first by examining whether or not boss expression was affected by ectopic expression of *svp*. Following a 1 hour heat shock, third instar larvae were reared at 22°C for various periods and then stained with an anti-boss monoclonal antibody (Kramer et al., 1991). In wild-type larvae that were heat shocked, as well as in non-heat-shocked *hs-svp* animals, boss protein could first be seen in R8 three rows posterior to the morphogenetic furrow and remained detectable towards the posterior end of the eye disc (Kramer et al., 1991). When eye discs from *hs-svp* larvae were fixed 2 hours after heat shock, no abnormalities in boss expression were detected. However, a chase of 9 hours or longer resulted in appearance of a stripe of ommatidia where boss expression was absent or greatly reduced (Figs 4, 5). Since boss has an essential role in the induction of R7, we expect failure of R7 differentiation to occur in such ommatidia.

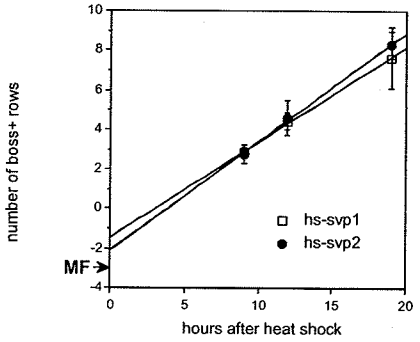

Fig. 5. Position of the boss-negative stripe in heat-shocked *hs-svp* animals after various recovery periods. The number of boss$^+$ ommatidia anterior to the boss-negative stripe was plotted against the chase period after the heat-shock treatment. Since anti-boss staining starts in row 3 in heat-shocked wild-type disc, the position of the morphogenetic furrow is marked at row −3.

The width of the boss-negative stripe was much narrower than the stripe of abnormally constructed ommatidia seen in retinal sections but correlated with the width of the substripe that lacks central photoreceptor cells. This means that there is a narrow developmental window in which ubiquitous expression of svp results in the loss of boss expression.

The induction of R7 through a boss-sev interaction takes place eight to ten rows behind the furrow (Basler et al., 1989; Mullins and Rubin, 1991; Hart et al., 1991). We wished to determine whether ectopic expression of *svp* causes an early defect in the initiation of boss expression and/or R8 differentiation, or if it causes a loss of boss expression at the time that the boss-sev interaction occurs. The distance between the morphogenetic furrow and the boss-negative stripe increased with longer chase periods; chases of 12 and 20 hours produced boss-negative stripes 7 and 11 rows posterior to the furrow respectively (Fig. 5). This meant that a new row of ommatidia was produced every 2 hours, indicating that there was no significant effect in advancement of the morphogenetic furrow after heat-shock treatment, at least between these two time points. Extrapolation of such data indicated that the time that *svp* expression affected boss expression is one to two rows behind the furrow, anterior to the position at which boss protein could first be detected (Fig. 5). We conclude that ectopic expression of *svp* results in a failure to initiate boss expression, and that proper expression of boss in such cells is never recovered following heat shock.

In order to determine whether ectopic expression of svp resulted in specific repression of boss expression or a general defect in R8 identity, we examined the behavior of enhancer trap marker lines that express β-galactosidase in the R8 cell. Two enhancer trap lines BB02 (Hart et al., 1990) and rO156 (Ulrike Gaul, personal communication) express β-galactosidase in R8 from row 10 on throughout imaginal disc development, independent of *boss* function. Third instar larvae carrying these marker genes, as well as *hs-svp1* and *hs-svp2* transgenes were heat shocked for 1 hour and stained for β-galactosidase activity in 40-hour-old pupae. With both *hs-svp1* and *hs-svp2*, there were one to two rows in which most ommatidia failed to express these R8 markers (Fig. 4D-F; and data not shown). With BB02, which expresses β-galactosidase also in R7 albeit at a lower level than R8, simultaneous loss of R8 and R7 was observed (Fig. 4E,F). Since multiple independent R8 markers showed loss of expression, it is likely that ubiquitous expression of *svp* isoforms resulted in a change in R8 identity.

To follow the fate of the affected R8 cell, we used the D120 line, which is an enhancer trap insertion in the *scabrous* gene (Mlodzik et al., 1990a). In this line, β-galactosidase expression starts in the R8 cell in the morphogenetic furrow, reflecting R8 specification (Mlodzik et al., 1990a; Baker et al., 1990). Although *scabrous* transcript and protein are expressed only in the morphogenetic furrow region, due to the stability of *lacZ* transcript and/or protein, β-galactosidase is detectable in R8 towards the posterior edge of the eye disc, thus serving as an excellent marker to follow R8 development. Larvae carrying the D120 insertion and either *hs-svp1* or *hs-svp2* genes were subjected to a 1 hour heat shock, and stained with anti-boss and anti-β-galactosidase antibodies after various chase periods. With 2 and 4 hours of chase, no abnormality in boss or β-galactosidase expression could be detected (data not shown). At 6 hours after heat shock, ommatidia that should have initiated boss expression failed to stain with boss antibody, yet all such ommatidia still contained R8 that expressed β-galactosidase (Fig. 6B,D). This means that the specification of the R8 precursor was normal and that the R8 cell was present despite its failure to initiate boss expression. With 11 hours of chase, the level of β-galactosidase in R8 in many of boss-negative ommatidia was either low or undetectable, although ommatidia further posterior still expressed β-galactosidase (Fig. 6D,E). Upon a 13 hour chase, all boss-negative ommatidia also failed to express β-galactosidase (data not shown). These results suggest that the R8 precursor undergoes cell death between 6 and 13 hours following the ectopic expression of *svp*.

Loss of *svp* function does not cause extra R8 formation

The finding that ectopic expression of *svp* interferes with R8 differentiation prompted us to examine whether *svp* suppresses R8 differentiation in normal development. We asked whether the loss of *svp* function results in expression of R8 traits in photoreceptor cells other than R8 itself. Due to embryonic lethality of *svp* mutants, clones that were genotypically mutant for *svp* were generated in the eye imaginal discs. We found that in *svp* clones the BarH1/BarH2 proteins, which are normally expressed in R1 and R6 (Higashijima et al., 1992), are not expressed, consistent with transformation of their fates (Fig. 4G). Within such *svp* mutant clones, expression of boss was still restricted to a single cell within each ommatidium (Fig. 4H). We conclude that although *svp* can suppress R8 differentiation, it is not utilized or not essential for restriction of R8 differentiation during normal ommatidial development.

Effects of ectopic expression of *svp* in R7 and in cone cells

Experiments using *hs-svp* animals show that ubiquitous

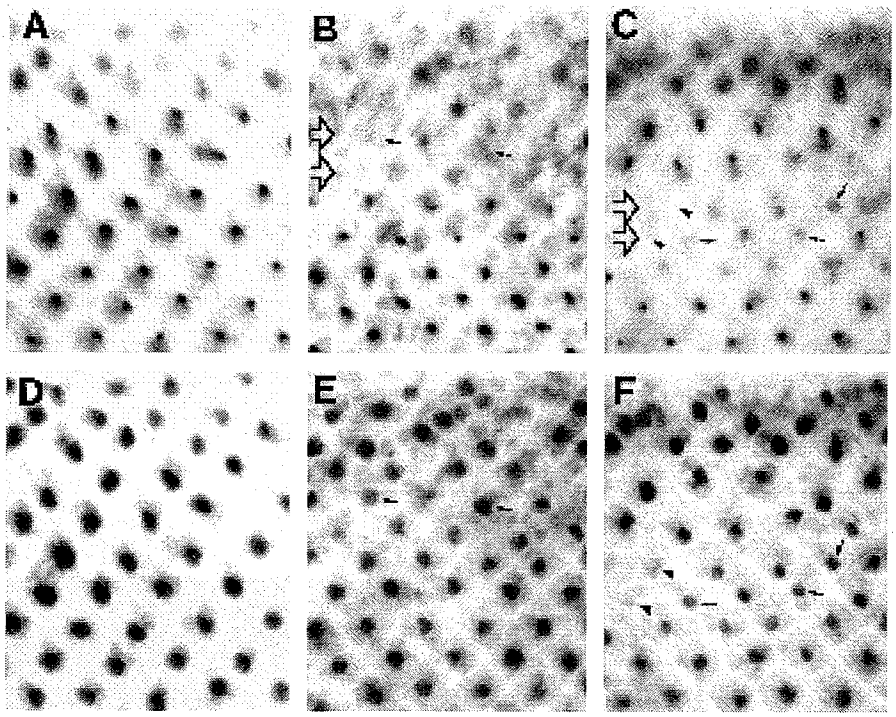

Fig. 6. The fate of the R8 cell in heat-shocked *hs-svp1* animals. Wild-type (A,D) or *hs-svp1* (B,C,E,F) third instar larvae were heat shocked for 1 hour and stained with a mixture of anti-boss and anti-β-galactosidase antibodies, 6 hours (A,B,D,E) or 11 hours (C,F) after the heat shock. The morphogenetic furrow is located at the top edge of the picture in all panels. (A-C) Focused apically to show boss expression, which is seen as small dots; (D-F) a more basal focal plane at the level of the R8 nuclei that express β-galactosidase. The faint round stainings seen in the apical focal plane are the out-of-focus images of the β-galactosidase-positive nuclei. The position of the boss-negative stripe is indicated by open arrows in B, C. Arrows indicate examples of ommatidia that fail to express boss, yet contain β-galactosidase-positive R8 nuclei. Arrowheads in C, F show ommatidia that express neither boss nor β-galactosidase, suggesting that the R8 cell has undergone cell death.

expression of svp causes transformation of R7 cell to outer photoreceptor cell fate at a specific stage during ommatidial development. To test if a similar phenotype is produced by specifically expressing svp in the R7 cell, transgenic animals that carry *svp* cDNAs under the control of *sev* regulatory elements were generated (Fig. 1). Sequences from the *sev* promoter and enhancer used in these fusion genes direct high levels of expression in R3/R4/R7 and in the cone cells and lower levels in R1/R6 (Bowtell et al., 1989b; Basler et al., 1990; Kimmel et al., 1990), thus achieving ectopic expression of *svp* in R7 and the cone cells. Seven lines carrying the *sev-svp1* gene and nine lines carrying the *sev-svp2* gene were examined for abnormality in ommatidial assembly. Six of the nine *sev-svp2* lines showed mild roughening of the eye with one copy of the transgene. Surprisingly, sections of such retinae revealed that the roughening is not caused by the loss or transformation of R7 cells. On the contrary, some ommatidia had an extra photoreceptor with R7-like morphology, i.e. rhabdomere of small diameter located apically (Fig. 7A). When the copy number of the construct was increased, we did observe a small number of ommatidia with extra outer photoreceptor cells and others that did not have an R7 cell with R8 present basally. The majority of abnormal ommatidia, however, had extra R7-like cells, the frequency of such ommatidia and the number of extra R7 cells increasing with the copy number of the *sev-svp* gene (Fig. 7A,B). To establish the identity of the extra photoreceptor cells, we used a reporter strain where the promoter of the *Rh4* rhodopsin gene, which is expressed exclusively in the R7 cells, has been fused to the *lacZ* gene (Fortini and Rubin, 1990). In *sev-svp2* retinae, extra photoreceptors expressed this R7 specific trait indicating that the extra cells have an R7 identity (Fig. 8A,B).

There are two possible mechanisms that could generate this phenotype. First, expression of *svp* in R7 may have affected its differentiation, but such an effect is compensated by R7 differentiation from other cells. Alternatively, R7 development may not have been affected in these transgenic animals and the phenotype is caused solely by the formation of extra R7 cells. The fate of the R7 precursor and the origin of the R7-like cells were examined using an enhancer trap line H214 that expresses β-galactosidase at high levels in the R7 cell in the eye imaginal disc (Mlodzik et al., 1992). In *sev-svp2* larval eye discs, not only the R7 cell but also the cone cells showed strong expression of β-galactosidase (Fig. 8D). We also observed expression of the neuron specific antigens elav (Robinow and White, 1991) and the 22C10 antigen (Zipursky et al., 1984) in the cone cells (Fig. 8G, and data not shown), establishing that cone cells were transformed to R7 cells in this genotype. In discs containing four copies of the *sev-svp2* transgene, some nuclei located basally in the disc also expressed elav (Fig. 8I). These may be uncommitted cells that have not yet been recruited to the ommatidial cluster. We conclude that svp type 2 protein expressed under the *sev* enhancer/promoter does not interfere with R7 differentiation, but rather transforms cone cells towards R7 cells. Despite this transformation, most *sev-svp2* ommatidia had four or more cone cells, as visualized with cobalt sulfide staining of pupal discs (data not

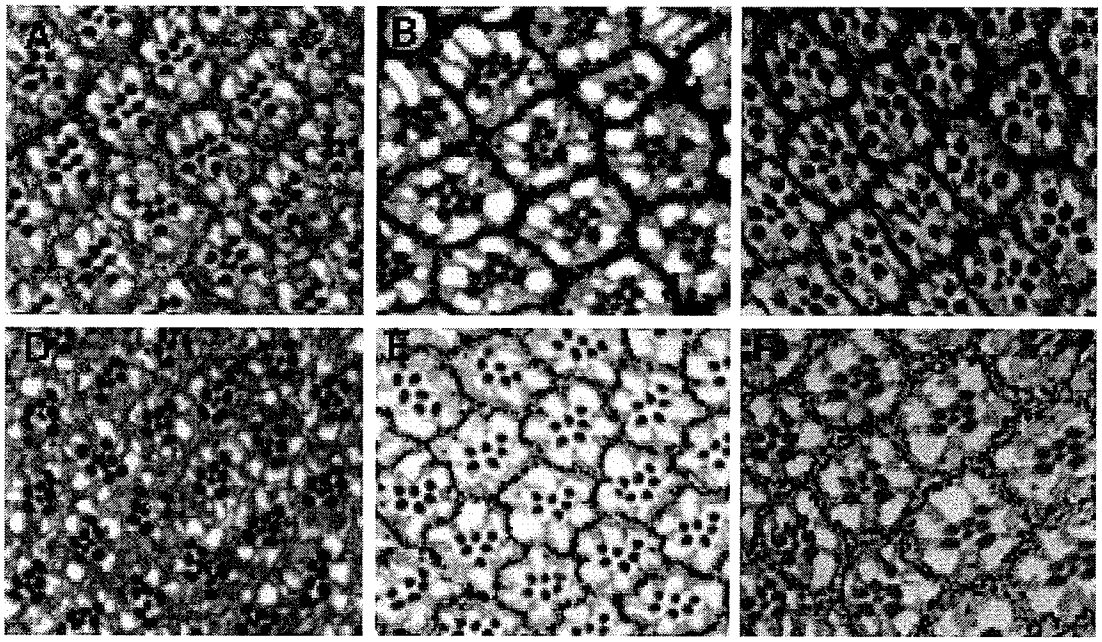

Fig. 7. Retinular phenotype of *sev-svp* animals. (A) *sev-svp2* one copy, (B) *sev-svp2* two copies, (C) *sev-svp1* three copies, (D) sev^{d2}; *sev-svp2* two copies, (E) $sina^{3}/sina^{1}$; *sev-svp2* two copies, (F) *sev-svpΔMlu* four copies. Sections are at the apical level where R7 is visible. Refer to Fig. 2A for a wild-type control. Animals shown in D and E carry *white* and *scarlet* mutations, respectively, and do not contain normal pigment granules.

shown). Thus, additional cells appear to be recruited to become cone cells when cone cells precursors enter the neuronal pathway. This is in agreement with other reports regarding the transformation of cone cell precursors (Basler et al., 1991; Gaul et al., 1992).

In contrast to *sev-svp2* lines, none of the *sev-svp1* lines showed any abnormality in ommatidial structure in single copy. When the copy number was increased to two or three, a phenotype similar to that seen in *sev-svp2* lines was observed (Fig. 7C). Thus the effect of *sev-svp1* appears to be weaker than that of *sev-svp2*.

sina, but not *sev* or *boss*, is required for *svp*-mediated cone cell transformation

Three genes, *sev*, *boss* and *sina*, are required for specification of the R7 precursor and in respective retinae all ommatidia lack the R7 cell. We examined whether these three genes are also required for the formation of R7 cells developing from the cone cells in *sev-svp2* lines. In the presence of the *sev-svp2* gene, many ommatidia contained one or two R7 cells even when *sev* or *boss* activity was removed (Fig. 7D, and data not shown). Such retinae contained ommatidia that expressed the *Rh4/lacZ* fusion gene, while in control eyes (*sev* or *boss* mutant alone) lacking R7, this R7 specific marker was never expressed (data not shown). On the contrary, in *sina*; *sev-svp2* animals no R7 cells formed, indicating that *sina* function is required for R7 differentiation in transformed cone cells (Fig. 7E).

To analyze the fate of the R7 precursor and the cone cells in *sev*; *sev-svp2* ommatidia, we examined expression of the H214 *lacZ* marker in larval eye discs. The cone cells expressed high levels of β-galactosidase as does the R7 cell in wild type, whereas the β-galactosidase level in the R7 precursor was low, if not undetectable, as in *sev* discs (Fig. 8E). This suggests that the R7 precursor failed to develop as the R7 cell in the absence of *sev*, whereas R7-like cells differentiating from the cone cells do not require *sev* activity. Indeed, in clusters that contained elav-positive cone cells, a majority of R7 precursors failed to express elav (Fig. 8H). To test whether the R7-like cells differentiating from cone cell precursors are functional R7 neurons, we tested the UV phototactic behavior of *sev*; *sev-svp2* animals. Animals in which the R7 precursor and the cone cells have switched their fates showed normal phototactic behavior, indicating that transformed cone cells have normal functional properties of the R7 neuron (Fig. 9).

Three genetic situations are known that cause transformation of cone cells into R7: ubiquitous expression of boss that results in activation of the *sev* pathway (Van Vactor et al., 1991) expression of a *boss*-independent form of *sev* (Basler et al., 1991) and reduction of *Gap1* activity (Gaul et al., 1992; Rogge et al., 1992; Buckles et al., 1992). Since in *sev-svp2* discs, cone cells differentiate into R7 in the absence of *boss* or *sev* function, it is unlikely that svp causes its effect by regulation of *boss* or *sev* expression and/or function. A possible target for *svp* is *Gap1*, which shows highly regulated expression that is confined to photoreceptor cells and cone cells posterior to the morphogenetic furrow (Gaul et al., 1992). Using an enhancer trap insert in *Gap1*, the rI533 line, we tested whether *sev-svp2* down-regulated *Gap1* expression in the cone cells. In *sev-svp2* discs, cone cells still expressed β-galactosidase (Fig. 8K), indicating that the effect of *sev-svp2* was not mediated by repression of *Gap1* transcription.

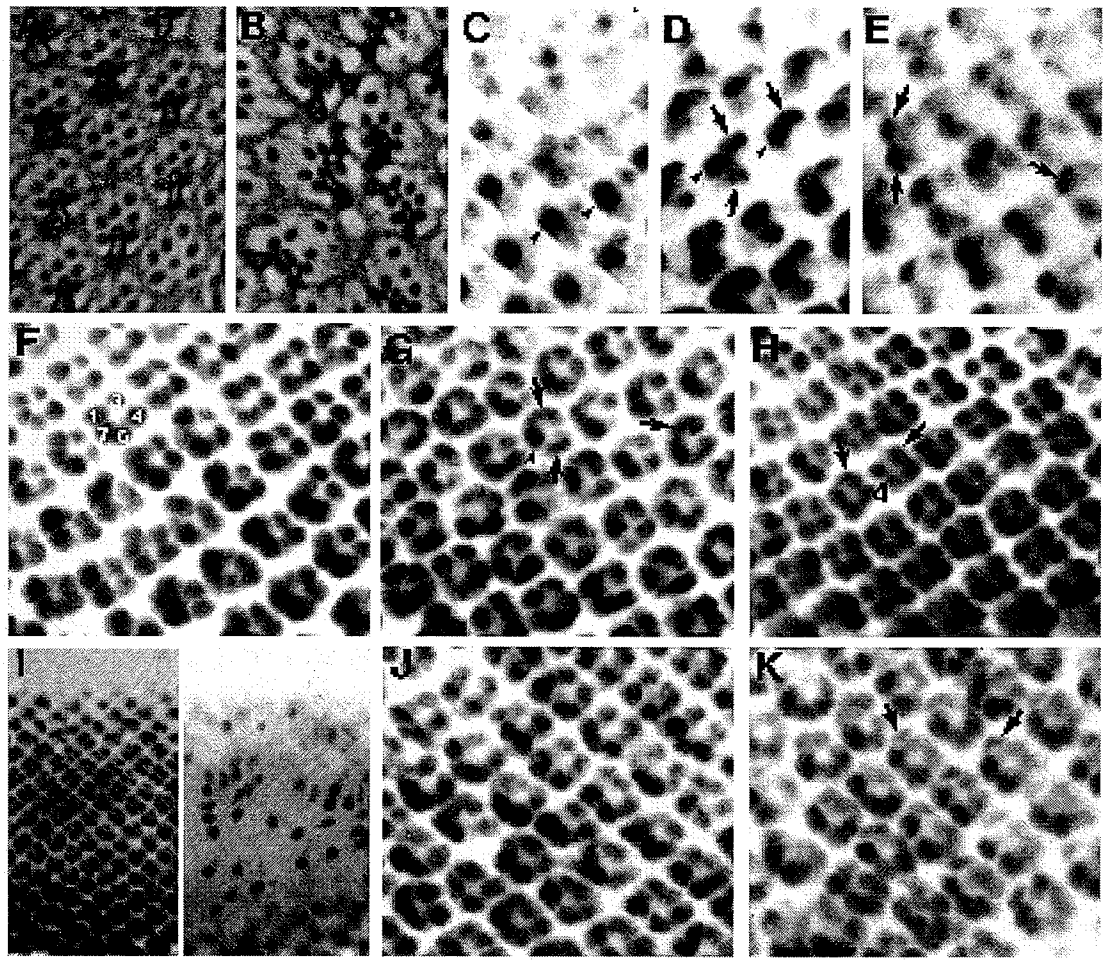

Fig. 8. Expression of cell specific markers in *sev-svp2* eyes. (A, B) Anti-β-galactosidase staining of retina carrying the *Rh4/lacZ* fusion gene, which is expressed in a subset of the R7 cells. (A) Wild type; (B) *sev-svp2* two copies; (C-E) anti-β-galactosidase staining of eye imaginal disc carrying the H214 enhancer trap marker; (C) wild type; (D) *sev-svp2* two copies and (E) sev^{LY3};*sev-svp2* two copies. The arrowhead shows the R7 precursor, arrows point to β-galactosidase-positive cone cells. (F-I) Anti-elav staining. (F) Wild type; photoreceptors are numbered in an ommatidium; R2/R5/R8 are not in this focal plane. (G) *sev-svp2* two copies. The arrowhead and the arrows show the R7 precursor and anti-elav-positive cone cells, respectively. (H) sev^{LY3}; *sev-svp2* 2 copies. Open triangle show the position of the R7 precursor, which fail to express elav. (I) *sev-svp2* four copies, stained with anti-elav. This is a composite photograph spliced approximately at the dorsoventral midline of the eye disc, with the left half focused on the photoreceptor precursor nuclei, and the right half focused on the $elav^{+}$ cells located basally. (J, K) Anti-β-galactosidase staining of eye discs carrying an enhancer trap insertion in the *Gap1* gene (rI533 line). (J) Wild type and (K) *sev-svp2* two copies. Some of the cone cells expressing β-galactosidase are indicated with arrows.

The putative ligand-binding domain is required for expression of the dominant phenotypes

The observation that both isoforms of *svp* cause similar phenotypes when ectopically expressed raised the possibility that ectopically expressed *svp* may not require the putative ligand-binding domain for its function. Since many of the steroid receptors function as ligand-independent transcriptional activators when their ligand-binding domain is deleted (reviewed in Evans, 1988), we tested whether truncated svp proteins lacking the ligand-binding domain could produce the same phenotype as that caused by svp type 1 and type 2 isoforms. Three constructs were made: *sev-svpΔMlu*, in which *sev* regulatory elements direct expression of a svp protein truncated shortly after the DNA-binding domain, *sev-svpΔSal*, where svp protein is truncated immediately before the point where type 1 and type 2 isoforms diverge, and *hs-svpΔMlu* where the same protein as *sev-svpΔMlu* would be produced under the heat inducible promoter (Fig. 1). Animals that carry up to four copies of either the *sev-svpΔMlu* or *sev-svpΔSal* genes were generated, but their ommatidia showed normal morphology in retinal sections. We also failed to detect any phenotype after heat shocking animals carrying the *hs-svpΔMlu* gene (Fig. 7F and data not shown). Thus C-terminal portions of both type 1 and type 2 isoforms are necessary for production of dominant phenotypes in these misexpression experiments. This requirement for the C-terminal portion could

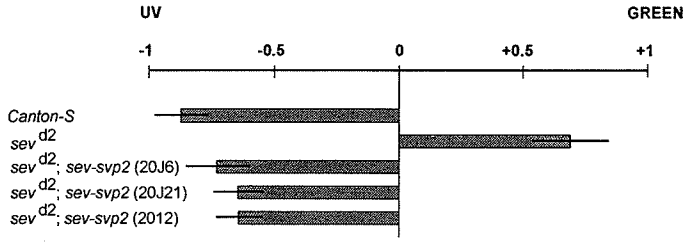

Fig. 9. Color choice preference for wild-type (Canton-S), sev^{d2} and sev^{d2}; *sev-svp2* flies. Flies were tested for the light color choice preference at 350 nm UV light and 550 nm green light. The phototactic value λ is calculated as follows:

$$\lambda = \frac{N(green)-N(UV)}{N(green)+N(UV)},$$

where N(green) and N(UV) are the numbers of flies attracted by green light and the UV light, respectively. Flies that lack functional R7 cells, unlike wild type, are attracted by the green light. Three independent lines carrying a single copy of the *sev-svp2* transgene were tested in sev^{d2} background. All show strong response to the UV light, indicating that the R7 cells that develop from cone cell precursors are functional and make proper connections in the medulla.

be in the activity of the svp protein, the production of the stable product, or both.

DISCUSSION

Within an ommatidium, three cell types are known to have the potential to develop as the R7 neuron: the R7 precursor, the cone cells and the precursors of R1 through R6. During wild-type development, however, the R7 precursor is the only cell that adopts the R7 fate. Cone cells are prevented from becoming R7 first because they are not in contact with R8 and are thus unable to activate the *sev* pathway through sev-boss interaction and, second, because expression of *Gap1* in cone cells reduces their intrinsic ras activity. R3/R4/R1/R6 are prevented from becoming R7 by the expression of the *svp* gene in these cells (Mlodzik et al., 1990b). Although svp^{+} function is normally not required in R2/R5, in *rough* mutant ommatidia *svp* is ectopically expressed in R2/R5 and is required to prevent them from becoming R7 (Heberlein et al., 1991). Our results of ectopic expression of the svp isoforms show that proper transcriptional regulation of *svp* expression is essential for the proper development of two other cell types that have potential to become the R7 neuron, the R7 precursor and the cone cells.

Since expression of *svp* is restricted to R3/R4/R1/R6, *svp* could act as a genetic switch between the R3/R4/R1/R6 neuronal type and the R7 type, in a manner similar to the homeotic selector genes. In such a case, one would expect ectopic expression of *svp* in the R7 cell to interfere with its differentiation, and possibly transform it towards the R3/R4/R1/R6 fate. Indeed, in both *hs-svp1* and *hs-svp2* animals, we found ommatidia in which the R7 cell was transformed to an outer photoreceptor fate. Curiously, we failed to observe similar transformation in animals carrying *sev-svp* transgenes, which express svp isoforms in the R7 cell under the control of the *sev* enhancer/promoter. There are a few possibilities that could explain this discrepancy. First, the R7 to outer photoreceptor transformation in *hs-svp* retinae may not be caused by ectopic expression in the R7 cell, but may be due to expression in other cells that influence the differentiation of the R7 precursor. Alternatively, under the *sev* enhancer/promoter control, the svp protein may not have been expressed in the R7 cell in the appropriate temporal pattern to effect this transformation. We favor the latter possibility because the stage that is susceptible to R7-to-outer photoreceptor transformation maps late in ommatidial assembly. In *hs-svp1* retinae, the substripe containing transformed R7 was located posterior to the substripe containing extra R7 cells, which is likely to correspond to the cone cell-to-R7 transformation seen in *sev-svp* retinae. Since expression in R7 directed by *sev* enhancer/promoter sequences ceases before expression in the cone cells does (Bowtell et al., 1989b), expression of svp in R7 may not have persisted long enough to cause transformation of the R7 cell. In addition, in the case of the *rough* gene that specifies the R2/R5 cell fate, its ectopic expression in R7 alone is sufficient to transform R7 to the outer photoreceptor fate (Basler et al., 1990; Kimmel et al., 1990) and no data thus far available suggest a requirement for an inductive signal controlling the photoreceptor subtype decision of the R7 cell.

Another phenotype caused by ectopic expression of svp that interferes with R7 differentiation is the loss of R7 seen in *hs-svp* retinae. It is unlikely that this phenotype is caused by ectopic expression in the R7 cell itself, for the following reasons. First, the loss of the R7 cell is usually accompanied by the loss of R8. Concomitant loss of R7 and R8 suggests that these two events are not caused by independent effects on R7 and R8. Second, ubiquitous expression of *svp* affects expression of the boss protein which serves as a ligand for the sev receptor tyrosine kinase. Since activation of sev is essential for the R7 precursor to assume a neuronal fate, the effect on boss expression can alone account for failure of R7 differentiation. Third, the ectopic expression of *svp* in R7 directed by the *sev* enhancer/promoter does not affect R7 differentiation. Taken together, these data strongly suggest that the loss of R7 caused by the ubiquitous expression of *svp* is due to the loss of the R8 cell. Whether the loss of R8 is caused by expression of *svp* in the R8 cell, or due to a nonautonomous mechanism, is not known.

Since R8 is believed to play a central role in initiating a series of induction steps (Tomlinson and Ready, 1987a), it is rather surprising that, in an ommatidium lacking R8, assembly proceeds with minor effects on the induction of outer photoreceptor cells. The sensitive period for the effect on R8 is quite early, one or two rows posterior to the morphogenetic furrow (Fig. 5). We show, however, that hs-svp does not affect specification of the R8 cell, as visualized by the expression of an enhancer trap insertion in the *scabrous* gene, and that the loss of R8 is likely to be caused by cell death that occurs between 6 and 13 hours after heat shock. Anterior to the stripe of ommatidia that have lost R8, there is another substripe consisting of ommatidia with different phenotypes (Figs 2, 3). This implies that there is yet another step in ommatidial assembly that *svp* can interfere with, which takes place prior to the effect on R8 differentiation and boss expression. Therefore, it is likely that the R8 cell

had already performed its function to induce other cells (e. g. R2/5) prior to the step that is affected by the ectopic expression of *svp*. Such a process must take place at or near the morphogenetic furrow, possibly prior to the formation of the 5-cell precluster (Banerjee and Zipursky, 1990).

Both the loss-of-function phenotype and the R7-to-outer photoreceptor transformation phenotype caused by hs-svp transgenes is consistent with the idea that *svp* acts by preventing R7 differentiation. It was thus unexpected that the ectopic expression of *svp* would cause the transformation of the cone cells towards R7 neurons. R7 differentiation from the cone cells caused by *sev-svp* transgene expression does not require the function of *boss* or *sev*, whereas it is completely suppressed by mutations in *sina*. Thus, ectopically expressed *svp* acts downstream of the sev receptor tyrosine kinase, but acts either upstream or in parallel to the *sina* gene. These epistatic relationships are similar to other conditions that cause the same cellular transformation, i.e., the expression of activated *Ras1* (Fortini et al., 1991) and the reduction in the *Gap1* activity (Gaul et al., 1992; Rogge et al., 1992; Buckles et al., 1992). Similarities in phenotypes and genetic relationships of *svp* and the activated ras pathway suggest that *svp* might act through ras to provide the potential to become a neuron. In support of this view, we have identified alleles of the *Ras1* gene among dominant suppressors of rough eye phenotype caused by the *sev-svp2* transgene (S. Kramer, F. Birkmeyer, M. M. and Y. H. unpublished). Although phenotypes caused by the loss of *svp* function indicate that *svp* is involved in a decision between two neuronal cell types, there is some evidence suggesting that *svp* plays a role similar to that of *sev* in providing neuronal fate per se. In ommatidia that are doubly mutant for *svp* and *sev*, not only R7 but also some of the outer photoreceptors fail to adopt a photoreceptor cell fate (Mlodzik et al., 1990b). Since *sev* is not required in R3/R4/R1/R6 in svp^+ ommatidia, it appears that the role that *svp* plays in R3/R4/R1/R6 is not simply to control their photoreceptor subtype, but also to decide between neuronal versus non-neuronal fate. Thus the role of *svp* appears different from that of the *rough* gene, which specifies a subtype of outer photoreceptors, but does not have the potential to induce neuronal development of cone cells (Kimmel et al., 1990; Basler et al., 1990). It should be noted, however, that many of the dominant phenotypes can be caused by both type 1 and type 2 isoforms, which differ in the putative ligand-binding domain. It is therefore possible that the phenotypes observed are generated in a ligand-independent way, due to a function that is at least in part different from the one that *svp* performs in R3/R4/R1/R6.

We have shown that spatially restricted expression of the *svp* gene is essential for execution of its normal function. This result is similar to those obtained with another *Drosophila* member of the steroid receptor gene family, the *tailless* gene (Steingrímsson et al., 1991) which, like svp, is expressed in the region of the embryo requiring its function. Ectopically expressed tailless appears to have the same function as the endogenous gene product, suggesting that either the tailless ligand is uniformly distributed, or the tailless function is ligand-independent. On the contrary, ubiquitous expression of the *ultraspiracle* gene, which is the *Drosophila* homolog of the retinoid X receptor and is likely to function as a heterodimer with the ecdysone receptor (Yao et al., 1992), do not interfere with normal development (Oro et al., 1992). These differences may reflect differences in strategies that steroid receptors utilize to regulate their functions, such as the distribution of the receptor itself, distribution of the ligand, or the distribution of the receptor's heterodimeric partner.

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EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

XEROX CORPORATION, Plaintiff, v. GOOGLE INC., YAHOO! INC., RIGHT MEDIA INC., RIGHT MEDIA LLC, YOUTUBE, INC., and YOUTUBE, LLC, Defendants.	)	C.A. No. 10-136-LPS-MPT

JOINT CLAIM CONSTRUCTION CHART

Pursuant to Paragraph 9 of the Court's February 15, 2011, Amended Scheduling Order, the parties respectfully submit this Joint Claim Construction Chart for U.S. Patent No. 6,778,979 (the "'979" Patent). A copy of the patent is attached to this chart as Exhibit A. In addition, the following documents from the prosecution history of the '979 Patent are attached as Exhibits B-F:

Exhibit B: March 24, 2003 Amendment and Remarks

Exhibit C: September 8, 2003 Amendment and Remarks

Exhibit D: January 23, 2004 Response and Request for Reconsideration

Exhibit E: April 23, 2004 Appeal Brief

Exhibit F: May 18, 2004 Notice of Allowability

Agreed Constructions

Claim Term or Issue	Agreed Construction
Antecedent Basis of Claim Terms	
"a query" / "the query" Claim 1: preamble; step (d) Claim 18: steps (b), (f) Claims 2, 19	"a query" and "the query" refer to the same query.
"a classification label from the organized classification of document content" / "the assigned classification label" Claim 1: steps (c), (d) Claim 18: steps (e), (f)	"a classification label from the organized classification of document content" and "the assigned classification label" refer to the same classification label.
"selected document content" / "the selected document content" Claim 1: preamble; steps (b), (c) Claim 18: steps (b), (d), (e) Claims 2, 19	"selected document content" and "the selected document content" refer to the same selected document content.
"an organized classification of document content" / "the organized classification of document content" Claim 1: steps (a), (c) Claim 18: steps (c), (e) Claims 5, 10	"an organized classification of document content" and "the organized classification of document content" refer to the same organized classification of document content"
"a set of entities" / "the set of entities" Claim 1: steps (b), (d) Claim 18: steps (d), (f)	"a set of entities" and "the set of entities" refer to the same set of entities.
Claim Terms	
"entity" Claim 1: steps (b), (d) Claim 18: steps (d), (f) Claim 2	something recognized in a document (e.g., a person's name, a location, a medical term, a graphics entity that may include image data, graphics data, audio data or video data) that can be in the form of an image, text, embedded data, HTML, etc.

Claim Term or Issue	Agreed Construction
"document" Claim 1: preamble; steps (a), (b), (c) Claim 18: steps (b), (c), (d), (e) Claims 2, 5, 10	an electronic (e.g., digital) or physical (e.g., paper) recording of information. In its electronic form, a document may include image data, audio data, or video data. Image data may include text, graphics, or bitmaps.
"organized classification of document content" Claim 1: steps (a), (c) Claim 18: steps (c), (e) Claims 5, 10	an organized set of categories that can be used to describe the subject matter of document content.
"defining an organized classification of document content" Claim 1: steps (a), (c) Claim 18: steps (c), (e)	setting an organized classification of document content.
"terms relating to context information surrounding the set of entities in the selected document content" Claims 2, 19	words or phrases that relate to the content surrounding the set of entities in the selected document content.
"the organized classification of document content is defined using a hierarchical organization" Claim 5	the organized classification of document content is defined using categories that are "parents" or "children" of other categories.
"article of manufacture" Claim 18	a computer program existent (permanently, temporarily, or transitorily) on any computer-usable medium such as on any memory device or in any transmitting device.

Disputed Constructions

Claim Term	Xerox's Proposed Construction	Defendants' Proposed Construction
"query" Claim 1: preamble; step (d) Claim 18: steps (b), (f) Claims 2, 19	a set of data specifying search criteria. Intrinsic Evidence: • col. 48, ln. 21-col. 52, ln. 29 • Figs. 38-41, and descriptions thereof • 1/23/04 Response and Request for Reconsideration, at 2-4 • 4/23/04 Xerox Appeal Brief, at 4-8	request for search results. Intrinsic Evidence: '979 Patent at: 3:2-33; 4:62-64; 5:1-3; 23:61-24:3; 26:58-67; 30:21-32; 30:43-56; 37:50-57; 40:18-23; 48:22-51; 48:63-49:16; 49:18-50:11; 50:42-44; 51:10-21; 51:22-52:29; 55:58-56:3; 62:62-63:2; Fig. 23; Fig. 24; Fig. 31; Fig. 38; Fig. 39; Fig. 40; Fig. 41; Fig. 46; Fig. 51. Claim 11. '979 Patent prosecution history: 3/24/03 Amendment at 4-5; 9/8/03 Amendment at 1-2, 5, 9-10; 1/23/04 Response and Request for Reconsideration at 1, 3-4; 4/23/04 Appeal Brief at 5-14; 5/18/04 Notice of Allowability at 2-3.
"selected document content" Claim 1: preamble; steps (b), (c) Claim 18: steps (b), (d), (e) Claims 2, 19	all or part of the content of a document in electronic form. Intrinsic Evidence: • col. 6, lns. 52-56 • col. 48, lns. 52-55 • col. 49, lns. 18-20 • col. 50, lns. 1-25 • col. 51, lns. 10-41 • Figs. 38, 39, and descriptions thereof • Claim 2 (col. 76, lns. 31-34) • 9/8/2003 Xerox Amendment and Remarks, at 2, 5, 7-10 • 4/23/2004 Xerox Appeal Brief, at 3-4	indefinite. Intrinsic Evidence: '979 Patent at: 3:6-10; 3:19-21; 3:26-28; 41:10-18.

Claim Term	Xerox's Proposed Construction	Defendants' Proposed Construction
"classification label" Claim 1: steps (a), (c), (d) Claim 18: steps (c), (e), (f)	a label in any format that identifies a category in the organized classification of document content. Intrinsic Evidence: • col. 41, ln. 52 – col. 42, ln. 34 • col. 43, ln. 14 – col. 45, ln. 63 • col. 48, ln. 21 – col. 50, ln. 11 • col. 51, ln. 22 – col. 52, ln. 29 • col. 59, lns. 24-65 • Claim 4 (col. 76, lns. 38-40) • Figs. 36, 38-41, and descriptions thereof	classifying word or phrase. Intrinsic Evidence: '979 Patent at: 3:2-33; 4:62-64; 41:53-60; 49:18-50:11; 51:34-51; 59:30-42; 60:52-55; Fig. 39.
"categorizing the selected document content using the organized classification of document content for assigning the selected document content a classification label" Claim 1: step (c) Claim 18: step (e)	determining the subject matter of the selected document content using one or more of the categories defining the organized classification of document content and assigning the corresponding classification label(s) to the selected document content. Intrinsic Evidence: • col. 41, ln. 52 – col. 46, ln. 67 • col. 48, ln. 21 – col. 50, ln. 11 • col. 51, ln. 22 – col. 52, ln. 29 • col. 59, lns. 24-65 • col. 60, lns. 52-55 • Figs. 36, 38-41, and descriptions thereof	using the organized classification of document content to categorize the selected document content and to assign to the selected document content a single classification label. Intrinsic Evidence: '979 Patent at: 4:58; 4:62-67; 40:66-41:9; 41:53-42:2; 42:29-34; 42:48-54; 45:41-53; 49:18-46; 50:3-11; 51:33-51; 52:15-29; Fig. 36; Fig. 38; Fig. 39; Fig. 40; Fig. 41. Claims 6, 9, 11, 20. '979 Patent prosecution history: 3/24/03 Amendment at 4-5; 9/8/03 Amendment at 1-2, 5, 9-10; 1/23/04 Response and Request for Reconsideration at 1, 3-4; 4/23/04 Appeal Brief at 5-14; 5/18/04 Notice of Allowability at 2-3.

Claim Term	Xerox's Proposed Construction	Defendants' Proposed Construction
"to restrict a search at the information retrieval system for information concerning the set of entities to the category of information in the information retrieval system identified by the assigned classification label" Claim 1: (d) Claim 18: (f)	the set of data specifying search criteria includes data items corresponding to one or more entities identified in the "automatically identifying" step and one or more classification labels assigned in the "automatically categorizing" step. Intrinsic Evidence: • col. 48, ln. 21 – col. 50, ln. 11 • col. 51, ln. 22 – col. 52, ln. 29 • Figs. 38-41, and descriptions thereof • 1/23/04 Response and Request for Reconsideration, at 2-4 • 4/23/04 Xerox Appeal Brief, at 4-8	to confine a search at the information retrieval system to the category of information identified by the assigned classification label, where the search seeks information concerning the set of entities. Intrinsic Evidence: '979 Patent at: 3:2-33; 4:62-67; 21:20-23; 40:66-41:9; 48:34-39; 48:66-49:3; 49:18- 50:11; 51:33-51; 51:64-52:11; 52:15-29; 59:56-59; Fig. 38; Fig. 39; Fig. 40; Fig. 41. Claims 2, 9, 19, 20. '979 Patent prosecution history: 3/24/03 Amendment at 4-5; 9/8/03 Amendment at 1-2, 5, 9-10; 1/23/04 Response and Request for Reconsideration at 1, 3-4; 4/23/04 Appeal Brief at 5-14; 5/18/04 Notice of Allowability at 2-3.
"characteristic vocabulary" Claim 10	one or more words or phrases that describe a class in the organized classification of document content. Intrinsic Evidence: • col. 48, ln. 21 – col. 49, ln. 67 • col. 51, ln. 22 – col. 52, ln. 29 • Fig. 36, 38, 40, and descriptions thereof	one or more words or phrases that describe the category of information corresponding to the class. Intrinsic Evidence: '979 Patent at: 4:58; 48:50-51; 48:63-49:6; 49:43-48; 51:34-39; 52:7-14; Fig. 36; Fig. 38; Fig. 40.

Claim Term	Xerox's Proposed Construction	Defendants' Proposed Construction
Order of steps	**Claim 1**: Step (a) must be performed before steps (c) and (d). Step (b) must be performed before the completion of step (d). Step (c) must be performed before the completion of step (d). **Claim 18**: Step (c) must be performed before steps (e) and (f). Step (d) must be performed before the completion of step (f). Step (e) must be performed before the completion of step (f). **Claim 2:** The step of Claim 2 must be performed during or after the completion of step (d) of Claim 1. **Claim 19:** The step of Claim 19 must be performed during or after the completion of step (f) of Claim 18. <u>Intrinsic Evidence</u>: • col. 41, ln. 52 – col. 42, ln. 34 • col. 43, ln. 14 – col. 45, ln. 63 • col. 48, ln. 21-col. 52, ln. 29 • col. 59, lns. 24-65 • col. 60, lns. 52-55 • Claim 2 (col. 76, lns. 31-34) • Figs. 36, 38-41, and descriptions thereof • 4/23/2004 Xerox Appeal Brief, at 8-10	**Claim 1:** Step (a) must be performed before steps (c) and (d). Step (b) must be performed before step (d). Step (c) must be performed before step (d). **Claim 18**: Step (c) must be performed before steps (e) and (f). Step (d) must be performed before step (f). Step (e) must be performed before step (f). **Claim 2:** The steps of claim 1 must be performed before the step of 2. **Claim 19:** The steps of claim 18 must be performed before the step of 19. <u>Intrinsic Evidence</u>: '979 Patent at: 4:60-67; 49:18-50:11; 51:23-52:14; Fig. 38; Fig. 39; Fig. 40.

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Dated: March 15, 2011

EXHIBIT D

#6/A WJR 3/26/03

Official

PATENT APPLICATION
Attorney Docket No. **D/A0A34**

CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office to Fax No. (703) 746-7239 on 3/24/03.

Typed or printed name of person signing this certificate
Thomas Zell

Signature: Thomas Zell

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Gregory T. Grefenstette et al.
Appl. No.: 09/683,235
Filed: 12/05/2001

Art Unit: 2172
Examiner: Isaac M. Woo

Title: **SYSTEM FOR AUTOMATICALLY GENERATING QUERIES**

Commissioner for Patents
BOX: NON-FEE AMENDMENT
Washington, D.C. 20231

AMENDMENT UNDER 37 C.F.R. 1.111

Sir:

In response to the Office Action of December 23, 2002, please amend the above-identified application as follows (An Appendix submitted herewith sets forth a marked up version of any prior pending paragraphs(s) and/or claim(s) with additions shown with underlining (e.g., new text) and deletions shown with a strikethrough (e.g., ~~delete text~~) under 37 C.F.R. 1.121(b)(1)(iii) and 37 C.F.R. 1.121(c)(1)(ii), respectively.):

A

In the Specification:

Please substitute the following paragraph(s) of the specification for their corresponding pending paragraphs(s) under 37 C.F.R. 1.121(b)(1):

1. Pending *Cross Reference To Related Applications* of the specification:

Priority is claimed from U.S. Provisional Application No. 60/311,857, filed August 13, 2001. Cross-reference is made to U.S. Patent Application Serial No. 09/543,962, entitled "Meta-Document And Method Of Managing", and U.S. Patent Application Serial No. 09/928,619 entitled "Fuzzy Text Categorizer", which are both hereby incorporated herein by reference. In addition, cross-reference is made to the following U.S. Patent Applications that (a) are concurrently filed with this patent application, (b) are assigned to the same assignee as this patent application, (c) are incorporated in this patent application by reference, and (d) claim priority to U.S. Provisional Patent Application Serial No. 60/311,857, filed August 13, 2001: U.S. Patent Application Serial No. 09/683,238, entitled "Meta-Document Management System With Personality Identifiers"; U.S. Patent Application Serial No. 09/683,239, entitled "Meta-Document Management System With Document Identifiers"; U.S. Patent Application Serial No. 09/683,240, entitled "Meta-Document Management System With Transit Triggered Enrichment"; U.S. Patent Application Serial No. 09/683,241, entitled "System For Propagating Enrichment Between Documents"; U.S. Patent Application Serial No. 09/683,242, entitled "Document-Centric System With Auto-Completion And Auto-Correction"; U.S. Patent Application Serial No. 09/683,237, entitled "System With User Directed Enrichment And Import/Export Control"; U.S. Patent Application Serial No. 09/683,236, entitled "Meta-Document Management System With User Definable Personalities".

2. Pending paragraph number 534:

The second action involves evaluating whether the personalities (i.e., $P_{1,1}$ to $P_{1,l}$) specified in the exported meta-document file are standard personalities. This second

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action is performed using properties that identify the personalities (e.g., name, creator, version number, unique identifier defined, for example, using the Digital Object Identifier standard, etc.). Standard personalities may, for example, be provided by software vendors and may be used by multiple systems. For all standard personalities, the exchange process matches the equivalent standard personalities from $P_{2,1}$ to $P_{2,n}$ to the personalities specified in the exported meta-document file. Identified matches are inserted into (or attached to) the new meta-document. Consequently, services and service providers associated with standard personalities are also inserted (or attached to), provided they correspond to services available at the importing meta-document server.

3. Pending paragraph number 535:

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The third action involves identifying "standalone services" that are specified outside a personality (i.e., $S_{1,1}$ to $S_{1,j}$). Similar to personalities, the third action matches standard services available at the importing meta-document server using properties that identify the services in the exported meta-document file. Subsequently at this third action, these identified services are inserted (or attached to) in the new meta-document file. Consequently, any local dictionaries and strategies associated with these services are also inserted (or attached to), provided they correspond to dictionaries and strategies available at the importing meta-document server.

REMARKS

The Office Action of December 23, 2002 has been carefully considered. Reconsideration of this application, as amended, is respectfully requested. Claims 1-20 are pending in this application. Of these, claims 1, 14, and 18 are independent claims.

This Amendment amends the specification to correct typographical errors and add patent application numbers of cross referenced patent applications that were not known at the time of filing and set forth as a comment in Applicant's transmittal letter.

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1. Response to Rejection Under 35 USC 103(a)

The Office Action on page 2 rejects claims 1-20 under 35 U.S.C. 103(a) as being unpatentable over Vu et al. (U.S. Patent No. 6,393,427, hereinafter referred to as Vu) in view of Myers et al. (U.S. Patent No. 6,374,274, hereinafter referred to as Myers). Applicant respectfully disagrees for the reasons discussed below.

Applicant's claimed invention is directed at a method, system, and article of manufacture for automatically generating a query, as described in detail in Applicant's specification in section F.3 (paragraph numbers 397-426). The system includes an entity extractor, a categorizer, and a query generator. The entity extractor identifies a set of entities in selected document content for searching information related thereto in an information retrieval system. The categorizer defines an organized classification of content with each class in the organization having an associated classification label that corresponds to a category of information in the information retrieval system.

Further in accordance with Applicant's invention, the categorizer assigns the selected document content a classification label from the organized classification of content. The query generator automatically formulates a query concerning the set of entities extracted by the entity extractor. In formulating the query, the query generator restricts the search at the information retrieval system to the category of information in the information retrieval system identified by the assigned classification label.

In contrast with Applicant's claimed invention, Vu discloses a method (operating on the client side) for constructing and maintaining (e.g., inserting and deleting documents from), a navigation tree based on existing document classifiers (see Col. 4, lines 19-21). The navigation tree is constructed adaptively to the size of the user's document collection on the client side from a classification tree returned from the existing document classifiers (see Col. 4, lines 29-31).

In further contrast with Applicant's claimed invention, Myers discloses a network database system with subscribing entities (e.g., user computers) that are authorized access to reliable sources of information. "Features that can be included in the system are customization of the documents to reflect sourcing by particular subscribers, automated formatting of the documents for storing in a network database, client access

facilitated by subscriber-maintained databases, and the avoidance of cookies remaining on clients' computer hard drives following document access." (see Abstract).

Applicant respectfully submits that neither Vu nor Myers taken singly or in combination discloses Applicant's invention set forth in independent claims 1, 14, and 18. In particular, the sections of Vu cited in the Office Acton at page 3, lines 3-7 that allegedly disclose the automatic formulation of a query as claimed by Applicant is not disclosed or suggested.

More specifically, the cited sections of Vu at page 3, lines 3-7 of the Office Action (i.e., col. 4, lines 55-67 to col. 5, lines 1-37) discloses a method for determining classification categories of a document that is introduced into a navigation tree. As set forth in col. 5, lines 6-14 of the cited section of Vu in the Office Action, keywords extracted from documents are used to query a classifier that determines what categories the documents belong to.

However, the Office Action fails to show that the cited section of Vu (i.e., col. 4, lines 55-67 to col. 5, lines 1-37) singly or in combination with Myers discloses or suggests Applicant's claimed invention in which a query is automatically formulated that restricts a search for information that concerns a set of entities identified in selected document content to a category of information at an information retrieval system, where the category, assigned to the selected document content, is identified by a classification label assigned from a classification of content where each classification label of the classification corresponds to a category in the information retrieval system.

Accordingly, Applicant respectfully submits that independent claims 1, 14, and 18 are patentably distinguishable over Vu taken singly or in combination with Myers. Insofar as claims 2-13, 15-17, and 19-20 are concerned, these claims depend from one of now presumably allowable independent claims 1, 14, and 18 and are also believed to be in allowable condition.

2. Fee Authorization And Extension Of Time

No additional fee is believed to be required for this Amendment. However, the undersigned Xerox Corporation attorney hereby authorizes the charging of any

necessary fees, other than the issue fee, to Xerox Corporation Deposit Account No. 24-0025. This also constitutes a request for any needed extension of time and authorization to charge all fees therefor to Xerox Corporation Deposit Account No. 24-0025.

3. Conclusion

In view of the foregoing remarks, reconsideration of this application and allowance thereof are earnestly solicited. In the event the Examiner considers a personal contact advantageous to the disposition of this case, the Examiner is hereby requested to call Attorney for Applicant(s), Thomas Zell.

Respectfully submitted,

Thomas Zell

Thomas Zell
Attorney for Applicant(s)
Registration No. 37,481
Telephone: 650-812-4282

Grenoble, France
Date: 3/24/03

APPENDIX

Marked Up Amended Paragraphs Of Specification:

This section of the Appendix sets forth a marked up version of the prior pending paragraphs(s) in the specification other than the claims with additions shown with underlining (e.g., new text) and deletions shown with a strikethrough (e.g., ~~delete text~~) under 37 C.F.R. 1.121(b)(1)(iii).

1. Pending *Cross Reference To Related Applications* of the specification:

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