

"A molecular wound response program associated with regeneration initiation in planarians" (2012), by Danielle Wenemoser et al. [1]

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In 2012, a team of scientists across the US conducted an experiment to find the mechanism that allowed a group of flatworms, [planarians](#) [3], to regenerate any body part. The group included Danielle Wenemoser, Sylvain Lapan, Alex Wilkinson, George Bell, and [Peter Reddien](#) [4]. They aimed to identify [genes](#) [5] that are expressed by planarians in response to wounds that initiated a regenerative mechanism. The researchers determined several [genes](#) [5] as important for tissue regeneration. The investigation helped scientists explain how regeneration is initiated and describe the overall regenerative mechanism of whole organisms.

The team included five individuals from various institutions. Danielle Wenemoser and Alex Wilkinson were from [Stanford University](#) [6] located in Palo Alto, California. Two others worked at the [Whitehead Institute](#) [7] for Biomedical Research at [Massachusetts Institute of Technology](#) [8] in Cambridge, Massachusetts. They were George Bell, who studied bioinformatics, and [Peter Reddien](#) [4]. Reddien studied tissue regeneration in planarians and utilized them as model organisms for regeneration in his research. Sylvain Lapan, who worked at [Harvard Medical School](#) [9] in Boston, Massachusetts, also contributed to the team.

The group identified [genes](#) [5] in planarians that tended to produce a lot of RNA, and ultimately proteins, when regeneration began. The group cut the rod-shaped planarians in half (transverse amputation) to help identify the [genes](#) [5] of interest. To tell whether or not a gene is activated, the researchers labeled the RNAs under investigation with fluorescent dyes and scanned the RNAs with a special microarray scanner. Genes that were particularly active generated a bright fluorescent area, whereas [genes](#) [5] that were less active yielded dimmer spots. That technique was performed with RNA isolated from amputated planarians at different times after amputations.

The group found that the first wave of genetic activity began thirty minutes to one hour after amputation. The initial wave of [genes](#) [5], referred to as wound-induced class 1 [genes](#) [5] (*W1*), produced proteins in the cells near the wound. Some of the *W1 genes* [5] continued to be expressed six hours post-injury whereas others showed transient expression lasting only one to three hours after the amputation. The researchers claimed that many of the *W1 genes* [5] share similarities to immediate early [genes](#) [5] (IEGs) in other organisms, which are typically quickly transcribed following a stimulus event, such as a chemical signal from a cell. Although scientists have shown that IEGs have many functions, the researchers noted the capability of those [genes](#) [5] to mediate long-term gene expression in tissues, suggesting *W1 genes* [5] serve a similar role.

Three hours after amputation, a second wave of [genes](#) [5] began to make products. The scientists divided the [genes](#) [5] into two categories, *W2* and *W3*, based on their different locations of expression. Like *W1 genes* [5], *W2 genes* [5] expressed under the outer layer of skin (epidermis) at the wound site, whereas *W3 genes* [5] expressed in the epidermis and beyond the wound site. The researchers showed that *W2 genes* [5] produce proteins important in genetic pathways that help structure body parts during regeneration. Specifically, the *Wnt1* and *Wntless genes* [5] help establish head-to-tail axes during regeneration. *W3 genes* [5] encode proteins responsible for remodeling the extracellular matrix, the tissue that provides structural support of cells in an organism. Through the identification of those three waves of [genes](#) [5], the research group expanded the list of wound-induced [genes](#) [5] in planarians from approximately five, to more than a hundred. Although the researchers recognized the gene groups present during amputation, they still hadn't detailed the initial regeneration mechanism.

The researchers performed different types of injuries, ranging from punctures to amputation. The researchers performed the injuries to determine whether simple wounds would cause expression of the same [genes](#) [5] that were activated in response to transverse amputation. *W1*, *W2*, and *W3 genes* [5] were all expressed in the planarians after both needle punctures and transverse amputations. *W3 genes* [5] produced proteins beyond twenty-three hours after both injury types. *W1* and *W2*, however, maintained expression past twenty-three hours only after injuries that required significant regeneration. The group concluded that a wound such as a needle puncture was sufficient to activate the [genes](#) [5] necessary for regeneration. Because each gene group produced RNA after injury, the researchers predicted that those [genes](#) [5] in the early response did not control the cells that would determine the identity of the missing tissue. Rather, the researchers hypothesized that the affected tissue may function to

determine the regenerated tissue identity later in the regenerative pathway.

The scientists also used [RNA interference](#)^[10] (RNAi) on the *W1* and *W2* [genes](#)^[5] to analyze the specific roles of the [genes](#)^[5]. RNAi is a technology that destroys specific RNA molecules to prevent a specified gene from producing RNA. The researchers inhibited both *W1* and *W2* [genes](#)^[5] with RNAi and observed wound healing in the planarians. After inhibiting the [genes](#)^[5], the researchers observed normal wound healing. The group inferred that many of the activated *W1* [genes](#)^[5] are redundant, or that they function similarly to *W2* and *W3* [genes](#)^[5] during regeneration. The group then focused on RNAi of an important immediate early gene in many organisms, the *W1* gene *fos-1*. They found that its inhibition led to impaired regeneration and asymmetry of the regenerated planarian tails. RNAi of *W2* [genes](#)^[5] resulted in regenerative mechanisms that displayed midline abnormalities, or abnormalities that occur on the median plane of symmetry. Common midline abnormalities can include a dysfunctional [central nervous system](#)^[11]. Based on the midline abnormalities noted with RNAi of *W1* and *W2* [genes](#)^[5], the researchers suggested that wound activated [genes](#)^[5] regulate the relative position of structures of the body, during regeneration. The researchers also claimed that the [genes](#)^[5] failed to cause other cells to differentiate. Therefore, they predicted that tissue around the planarian cells near the wounds determined the eventual identity, or cell type, of newly regenerated tissue.

The researchers tested whether or not proteins in planarian cells were necessary to regulate the [genes](#)^[5] that the researchers studied, as immediate early [genes](#)^[5] similar to *W1* [genes](#)^[5] typically activate before a cell synthesizes any new proteins. The researchers treated *W1*, *W2*, and *W3* [genes](#)^[5] with cycloheximide (CHX), a toxic chemical which hinders DNA translation and inhibits new protein synthesis. Due to the homology of *W1* [genes](#)^[5] with immediate early [genes](#)^[5], the researchers showed that those [genes](#)^[5] were expressed independently of new protein synthesis. Such evidence indicated that these [genes](#)^[5] are expressed rapidly after the injury and are the primary response in the regenerative mechanism. Scientists found that *W3* [genes](#)^[5] function normally without new protein synthesis, which the scientists did not predict given that those [genes](#)^[5] are expressed later than *W1* [genes](#)^[5], and would be more likely associated with protein synthesis. *W2* [genes](#)^[5], however, were significantly inhibited without new protein synthesis, indicating that the intermediate steps between wound detection and [induction](#)^[12] of *W2* is dependent on *de novo* protein synthesis.

The researchers found that although different wounds must perform different genetic responses to regeneration that are tailored to the appropriate tissue and wound type, the local tissue environment influences the specifics of those genetic responses.

Sources

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