

Discovery of a morphogen

TONY DURSTON*

*Hubrecht Laboratory, Netherlands Institute for
Developmental Biology, Utrecht, The Netherlands*

A new morphogen

In 1967, Theo Konijn, a young staff scientist at the Hubrecht Laboratory, and John Bonner of Princeton University and their colleagues, published a collaborative discovery which identified one of the first signal molecules (morphogen), regulating multicellular organisation during a developmental process (Konijn *et al.*, 1967, 1969).

This breakthrough was antedated by initial identifications of nerve growth factor and of epidermal growth factor in 1956 and 1962 respectively (Cohen and Levi-Montalcini, 1956; Cohen, 1962), but potential morphogens in early metazoan embryos were not identified until 1987 when b-FGF was identified as a putative regulator of mesoderm induction in the early *Xenopus* embryo (Slack *et al.*, 1987).

Using classical chemical separation methods, and a novel bioassay (see Fig. 2), these groups identified a chemoattractant for cells of the cellular slime mould *Dictyostelium discoideum* (purified initially from an *Escherichia coli* extract, see Konijn *et al.*, 1967) as 3'5' cyclic AMP (c-AMP).

These groups proceeded to demonstrate that c-AMP mediates a chemotactic aggregation process (Konijn *et al.*, 1969), via which *Dictyostelium* achieves multicellularity. They and others later showed that it regulates morphogenesis and patterned cell differentiation throughout the multicellular developmental cycle of this organism.

Weyer's turbine

Aggregating *Dictyostelium* cells show waves of chemotactic movement. These waves reflect the fact that *Dictyostelium* cells not only chemotact, but also relay c-AMP in an oscillatory fashion; secreting a c-AMP pulse in response to a c-AMP signal and then transiently entering an insensitive, adapted state. This property generates movement waves which are either expanding concen-



Fig. 1. Theo Konijn and Kees Weyer.

*Address for reprints: Hubrecht Laboratory, Netherlands Institute for Developmental Biology, Uppsalalaan 8, 3584 CT Utrecht, The Netherlands. FAX: +31-30-2516464. e-mail: tony@niob.knaw.nl

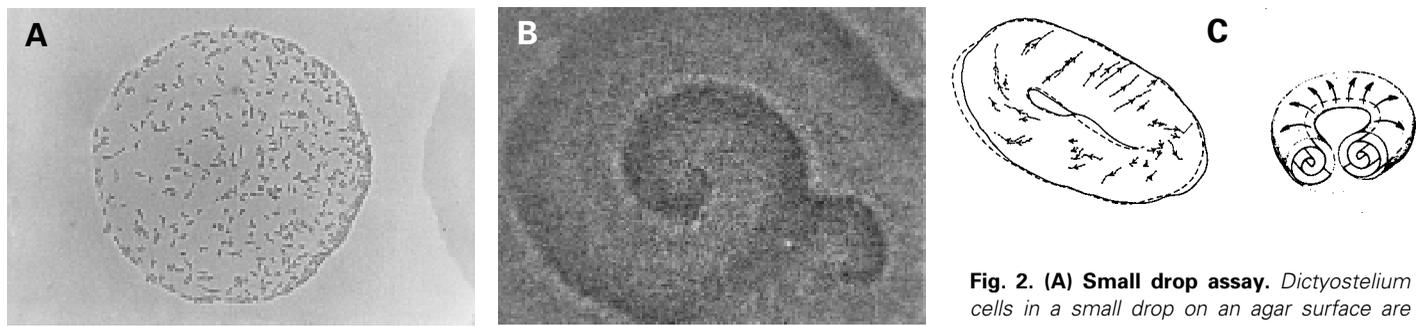


Fig. 2. (A) **Small drop assay.** *Dictyostelium* cells in a small drop on an agar surface are attracted towards a neighbouring drop of c-AMP (left). (By courtesy of T. Konijn). (B) **Spiral wave in a population of *Dictyostelium* cells.** (By courtesy of C.J. Weijer). (C) **Three dimensional spiral wave (torus scroll wave)** deduced from cell movement vectors in a doughnut shaped *Dictyostelium* aggregate (Durston *et al.*, 1978).

tric rings (initiated at a pacemaker cell) or expanding rotating spirals (initiated when a wavefront is broken). These are the mathematically predictable waveforms which occur in an isotropic two dimensional excitable medium: spirals are particularly important in *Dictyostelium* development. See below.

Recent findings by Kees Weyer, who obtained his Ph.D. on *Dictyostelium* in the Hubrecht Laboratory in 1985, demonstrate the power of these relayed signals. The multicellular life cycle (developmental sequence) of *Dictyostelium* consists of a sequence of radially symmetrical structures, built on a cylindrical plan, which are each controlled by an apical organising region (tip).

Pursuing a line of work which was initiated in the Hubrecht Lab in the 1970s (Durston *et al.*, 1978; Weyer *et al.*, 1984), Weyer

showed that these structures are organised by a variant of the 3-D transformant of the spiral wave: the scroll wave (Siegert and Weyer, 1992; Steinbock *et al.*, 1993; Bretschneider *et al.*, 1999). He discovered that multicellular *Dictyostelium* structures contain

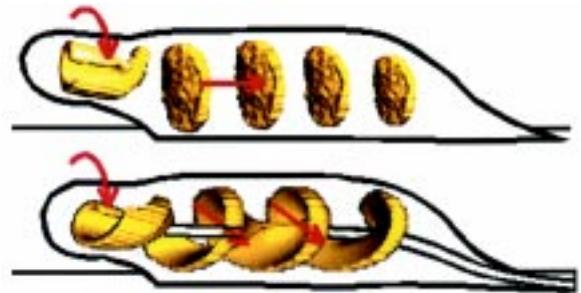


Fig. 4. Close up of two variants of the turbine wave in slugs of two different *Dictyostelium* species. (By courtesy of C.J. Weijer).

an axial scroll wave which is twisted. Twisting occurs because these later structures contain two basic cell types with different excitability properties: Weyer showed during his Ph.D. years that anterior (tip) cells are relatively excitable, with a high oscillation frequency (Weyer *et al.*, 1984). They therefore generate a rapidly rotating spiral. Posterior cells are less excitable, and generate a slower rotating spiral. The twist to the scroll generates a turbine waveform which ultimately breaks up into backward directed plane waves, powering forward chemotaxis and providing the driving force for morphogenesis.

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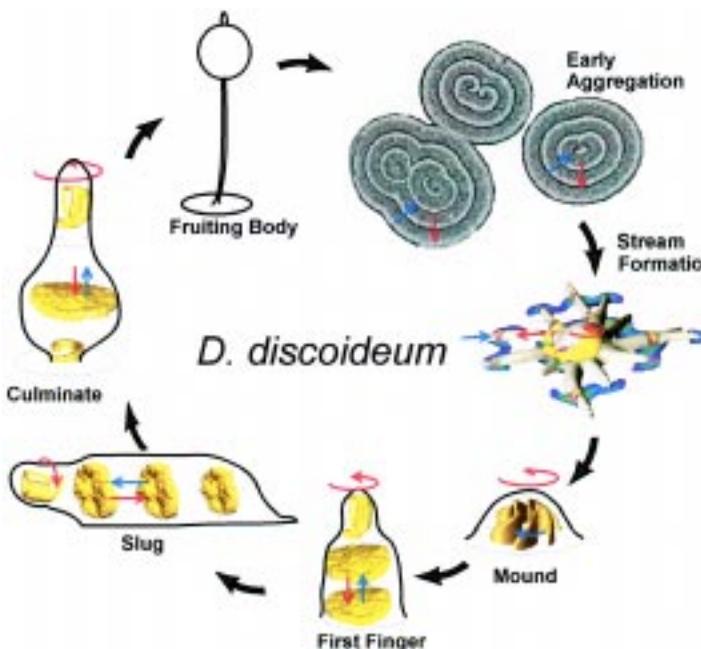


Fig. 3. Life cycle of *Dictyostelium* with spiral waveforms. The aggregating cells stream into mounds and these develop into cylindrical structures (first finger, slug), which contain a 3-dimensional spiral (scroll) wave. This scroll wave becomes twisted along its axis due to a frequency difference between anterior and posterior cell types (see text). The twisting provides a turbine effect which drives morphogenesis. Eventually, the structure becomes a fruiting body via mechanisms not discussed here. (By courtesy of C.J. Weijer).

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