Evolution: Of X-Cells and X-Men

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Humans are obsessed with labels, constantly seeking to name and categorise unknowns, or 'X-things'. DNA sequencing has finally solved the identity of mysterious X-cells associated with tumours in marine fish, but how should we approach X in people?

Biology began as labelling. Early practitioners busied themselves collecting and naming the diversity of life, filling museums with lavish cases of specimens. Physics Nobel Laureate Ernest Rutherford deprecated this work as mere 'stamp collecting', but the labelling of organisms in a natural, systematic scheme of classification is in fact a grand hypothesis mapping out the evolutionary relationships of everything that ever lived. Indeed, it was the painstakingly careful labelling and describing of their extensive collections that led Darwin and Wallace to the grand organising principle of biology — evolution through natural selection. Sadly, taxonomy and systematics are now out of fashion and underfunded, despite the grand exercise being very far from finished. In this issue of *Current Biology*, Freeman *et al.* [1] finally give a name to an organism, the X-cell, which has defied labelling for a century.

Reports of idiosyncratic tumours on bottom-dwelling fish, such as cod, flatfish, catfish, dabs, croakers, and even the Antarctic icefish, go back almost 100 years. Cytology revealed that these tumours — variously referred to in the literature as papillomas, neoplasms, Geschwülste (growths or swellings), and xenomas — were made up of what were initially assumed to be aberrant fish cells. Indeed, much of this literature appeared in cancer journals — the underlying assumption being that these 'growths' were either carcinomas or virally transformed fish cells. Accordingly, Sefton Wellings, then head of the Pathology Department in the University of Oregon Medical School, established a registry for such fish tumours as part of the greater oncology effort to understand cancers in 'lower animals' [2].

Wellings and colleagues focused their electron microscope on flounder tumours and concluded that, while the structures might indeed be produced by unruly fish cells, their morphology perhaps suggested that they were an unknown type of unicellular parasite [3]. With a sense of drama they labelled them X-cells, daubing a large 'X' on each rogue cell in their images [3]. Wellings' X-cells have large, distinct nucleoli, mitochondria with cristae of a different shape from those in the mitochondria in *bona fide* fish cells, and a 0.5 μm coat of dense material — apparently some kind of wall [3]. In the ensuing years, researchers tried unsuccessfully to transmit X-cell disease to healthy fish, or to identify a virus associated with these cells. Notions of X-cells being parasites firmed when it was noted that they had far less DNA than a fish cell, produced isozymes not present in healthy fish tissue, and underwent a form of mitosis unlike that of fish cells [4]. Two decades later, a Japanese team was able to sequence a ribosomal RNA gene of an X-cell, elegantly localising it within the suspiciously unfishy cells in the xenoma [5]. Plugging the sequence into a gene tree showed — just as Wellings had suspected — that X-cells were indeed protozoa and not part of the fish. But the X-cell gene sequences proved unruly in phylogenetic trees, and the Japanese team was unable to ally them with any familiar group of protozoa — they were definitely protozoa, but not like any that had been seen before.

To divine exactly where X-cells belong in the wondrous radiation of protists, Freeman *et al.* [1] had to sequence 63 protein-coding genes from X-cells and add these to a global eukaryote tree. Thus, they finally found a home for X-cells, and what an interesting home it is. X-cells — which Freeman *et al.* [1] formally dub *Xcellia* and *Gadixcellia* (X-cells infecting cod, *Gadus*) — slot firmly into a large assemblage of protists known as Alveolata. The Alveolata have a unique 'triple' membrane (really just a normal cell membrane entirely underlain by a system of flattened membrane sacs known as alveoli) [6], and include familiar protists like ciliates, dinoflagellate algae (such as the zooxanthellae symbionts of corals), and parasites of humans and animals (such as malarias and *Toxoplasma*) [7]. More specifically, X-cells are sister to the alveolate subgroup perkinsids, which parasitise bivalve molluscs such as oysters. X-cells have finally been labelled, and they nestle amongst other aquatic parasites.

Pinning a label to X-cells, and placing them within a group of parasitic protists, solves a century-old mystery, but — like all science — the answer poses new questions. Perkinsids, dinoflagellates, and parasites like malaria and *Toxoplasma* have a relic plastid and were once photosynthetic before turning to parasitism [8–10]. Freeman *et al.* [1] found no hints of a plastid in X-cell DNA sequences, but there's a likely-looking candidate in Wellings' first image of an X-cell (Figure 1 in [3]), so watch this space. We also know nothing about how X-cell disease spreads, nor anything about the life cycle of these protists. Freeman *et al.* [1] note that disease is linked to bottom dwelling or sediment contact amongst hosts, and they also note that X-cells are vanishingly rare in the global plankton sequence surveys. A label is a good start, but there is still much to learn about X-cells.

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The naming of unknown quantities as 'X-things' originates in algebra, but has suffused through English-speaking culture in examples ranging from the colloquial 'X-factor' to the popular *X-Men* movies and comics. When defining something as '*x*', we create a label for that which cannot be labelled; something with a perceptible but unquantifiable difference. This urge to categorise manifests in the original daubing of X-cells, and now, finally, their X-factor has been identified. This labelling by Freeman *et al.* [1] provides us with an opportunity to consider why we need '*x*' in mathematics, science, and culture.

Pop culture examples like *X-Men* give us the everyday vernacular to discuss what it means to label things — and people — with '*x*'. *X-Men* also asks us to deal with the difficulties and dangers of our obsession with labelling. It's one thing for X-cells to yield up their X-factor, but when the world presents us with X-people, the urge to 'solve for *x*' becomes a deeply complex problem.

The X-Men are a group of 'mutants', all born with unique genetic mutations that manifest as superpowers — some easier to live with than others. In their universe, mutants are feared, hated, and hunted for their difference. Many cultural commentators identify how the X-Men work as a metaphor for marginalised groups labelled 'other' by society: racial and ethnic minorities, and people with disabilities, for example. The struggle between the X-Men and humanity represents the struggle around all that we do not understand, and the movies map out some of the problems when taxonomy collides with humanity.

In X-cells and *X-Men*, the shared language of '*x*' — the label of the un-label-able — is fundamental to how we understand the world, and how we navigate the unknown. Popular narratives like *X-Men* help society understand the complexity of margins and marginalisation as we explore them. This is why biologists approach '*x*' with curiosity, rather than as a problem. It's an inspiring thought that there will always be more '*x*' — more mysteries to discover, more difference to celebrate — in biology, and in ourselves.

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Neural Coding: Bumps on the Move

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By meticulously deconstructing the *Drosophila* head-direction neural circuit, two recent studies have revealed the mechanism of how the fly's body rotations are translated into a continuously updated internal compass representation.

We all have goals, for example when negotiating the way to work, or when trying to get that last triple-chocolate muffin for breakfast. To reach them, we have to move in a directed, planned manner; we have to know what we want and where we currently stand to be able to make up for the difference between the desired state of the world and the current state of the world. Your brain is in charge of all of this. For instance, it has to compute your body-orientation relative to the chocolate muffin and direct your legs to move over there and get it, quickly, before someone else does so and you have to settle for vanilla as your morning energy boost. Research on a handful of neurons