

The Elephant Man and the Art of Jigsaw Puzzles

TALK OF SYSTEMS BIOLOGY HAS A WAY OF DRIFTING, QUITE RAPIDLY, INTO the abstract. I'm reminded of the preamble to Georges Perec's complex but engaging novel, *Life, A User's Manual*.



Although the idea of looking at the whole puzzle sounds daunting, it's essential that we get moving on it.

"The art of jigsaw puzzles seems of little substance, easily exhausted, wholly dealt with by a basic introduction to Gestalt: The perceived object... is not a sum of elements to be distinguished from each other and analyzed discreetly, but a pattern, that is to say a form, a structure... knowledge of the pattern and of its laws, of the set and its structure could not possibly be derived from discrete knowledge of the elements that compose it."

Certainly, this is a fine explanation of the thinking behind systems biology. The pieces of our particular puzzle—the interactions, pathways, and cells that decades of diligent research and more recent years of high throughput technology has massed—still exist largely in isolation. To quote Perec, "a puzzle piece means nothing – just an impossible question, an opaque challenge."

But such lofty language has done little to explain how systems biologists propose to do this. On page 52, H. Steven Wiley provides his expert view of the progress and promise of systems biology. Getting past the rhetoric and buzz of this often-denounced approach, he shows how systems biology is being done, and offers his predictions on where it could be executed. Although the idea of looking at the whole puzzle often sounds as daunting as it does intuitive, it's essential that we get moving on it. Here's an example of why:

On March 13th this year, six volunteers at the Northwick Park Hospital in London were given a first dose of the experimental drug TGN1412, an antibody to CD28 designed to treat B-cell chronic lymphocytic leukemia and rheumatoid arthritis. Mayhem ensued. Within five minutes, a "cytokine storm" equivalent to twenty times that endured during an influenza infection was unleashed. Fever, renal shutdown, respiratory failure, and cardiovascular collapse ensued. One account describes the ward as a "living hell." The patients began to shake and their heads became swollen, leading UK tabloids to dub these the "Elephant Man Trials."

The "elephant man" might have referred to the six wise blind men asked to describe an elephant, each one able to describe a piece but not the whole. The translational researchers described an antibody, TGN1412, that binds CD28, directly activating human T cells. Molecular immunologists know all about CD28, and numerous other molecules on the surface of lymphocytes that activate, coactivate and downregulate the response. Cell biologists and physiologists have information on lymphocyte populations, how they traffic around the body sniffing out foreign antigens, and how these antigens are presented in the lymphoid tissue. But no-one has the whole story.

That didn't stop the drug's developer, TeGenero, from claiming that TGN1412, was the "first universal T cell growth factor," one that would "therapeutically balance the immune system." The trial revealed that this was dangerous nonsense and that we are still profoundly ignorant of how the immune response operates as a system.

And this isn't an isolated case. With a whole raft of promising new monoclonals just about ready to go, and drug development drifting toward more complex biologically derived therapeutics it is imperative that we begin developing a more accurate way to predict systems-level responses. All stakeholders—patients, doctors, drug developers, and life scientists in general—should be watching to see what happens next, starting with the results from official UK investigation on TGN1412. Will regulators across the globe hold their nerve and introduce clear, easy-to-implement rules that prevent a recurrence of the disaster without dealing a knock-out blow to the whole sector?

It will be some time before the systems approach that Wiley and others are using to understand the fundamentals of the epidermal growth factor receptor system can inform such decisions. But as he shows, the approach has gone beyond mere buzz, taking us one step closer to leaving the rhetoric to philosophers. ■

A handwritten signature in black ink, appearing to read "Richard Gallagher". The signature is fluid and cursive, with a long, sweeping tail.

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