Accelerating Single-Cell Analysis

Fifteen years ago, in the first important moments of a dawning field, scientists using microarrays carried out cell analysis in what now seem like rudimentary ways.

Say you wanted to know how certain genes operated in kidney development. You would, as S. Steven Potter, PhD, Director of the Gene Expression Core at Cincinnati Children's, explains, take a developing murine kidney sample, "mush it up," amplify its RNA , then see which genes were being expressed.

The results were not unlike the early glimpses astronomers had of far off objects in space. The blurry evidence shows something important out there, but with unclear images it was impossible to understand their origins or how they developed. Similarly, in analyzing kidney development using early methods of gene analysis, scientists like Potter could see particular genes expressed in the mush, but could not tell precisely which cells expressed the genes.

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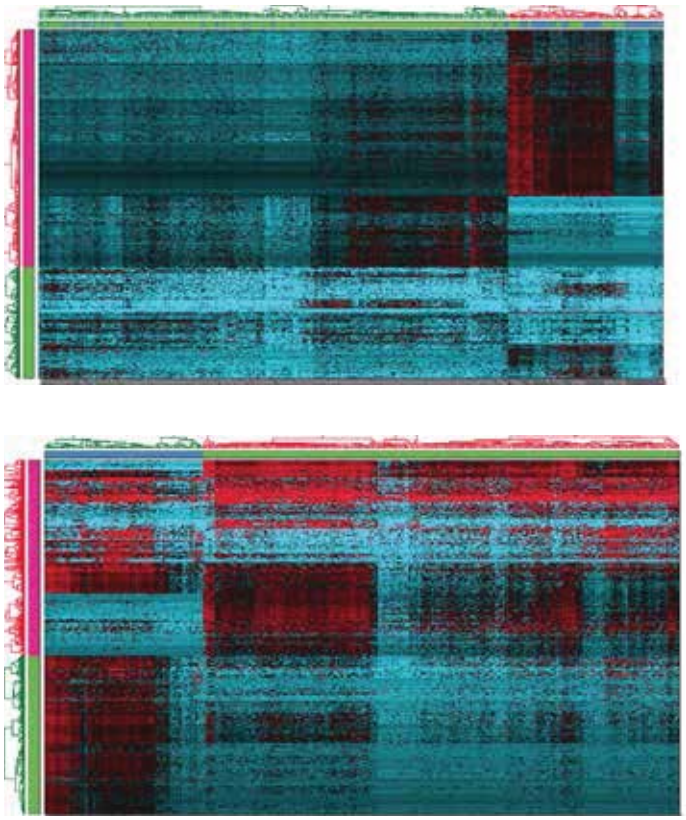
Such imperfect, noisy data makes it difficult to understand the normal development of complex organs with multiple cells types, and even harder to detect the points when development goes wrong and leads to congenital malformations and disease.

About five years ago, much better data began to emerge when it became possible for Gene Expression Core scientists to sequence one cell at a time. However, the work was incredibly labor intensive—imagine a project that begins with pipetting one cell at a time into tubes in order to analyze 23,000 genes.

Then two years ago, Cincinnati Children's purchased a $150,000 Fluidigm C1 System, which uses microfluidic chips to sequence up to 96 individual cells, simultaneously. This leap in



capability has supported a wave of important basic science projects at Cincinnati Children's including:

- A study led by Potter, recently published in *Development*, shows that developing kidney stem cells do not differentiate according to a single fated path, but prepare for a variety of developmental paths before committing to one.
- A project led by Potter and James Wells, PhD, Director of Basic Research in the Division of Endocrinology, is developing novel markers for cells in the human gut, defining their complete gene expression profiles for the first time. Their work is beginning to uncover intermediate states between stem cells and differentiated cells.
- Jeffrey Whitsett, PhD, Co-Director of Perinatal Institute, through the NIH-funded LungMap project, is using single cell analysis to better understand gene expressions that drive lung cell formation.

Two years ago, Cincinnati Children's purchased a $150,000 Fluidigm C1 System that can sequence up to 96 individual cells, simultaneously. This leap in capability has supported a wave of important basic science projects.

And more automation is coming. The Gene Expression Core is beta testing a new microfluidic chip for Fluidigm, which puts Cincinnati Children's among the first to be able to analyze 800 individual cells at a time.

Now, as researchers here analyze cell development across the kidneys, lungs, gut and immune system, they can obtain a staggeringly detailed series of snapshots along specific developmental pathways.

It is like moving from taking months to find the fuzzy dot of a single far-off galaxy to taking just a few days to see a collection of stars and planets within. With such dramatically improved maps, there is no telling what discoveries the next wave of explorers will make.